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# Iron catalyzed highly enantioselective epoxidation of cyclic aliphatic enones with aqueous H<sub>2</sub>O<sub>2</sub>

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Supporting Information Placeholder

**ABSTRACT:** An iron complex with a C<sub>1</sub>-symmetric tetradentate N-based ligand catalyze the asymmetric epoxidation of cyclic enones and cyclohexene ketones with aqueous hydrogen peroxide, providing the corresponding epoxides in good to excellent yields and enantioselectivities (up to 99 % yield, and 95 % ee), under mild conditions and in short reaction times. Evidence is provided that reactions involve an electrophilic oxidant, and this element is employed in performing site selective epoxidation of enones containing two alkene sites.

Introduction. Asymmetric epoxidation is a valuable reaction because chiral epoxides are versatile building blocks in synthetic organic chemistry.<sup>1-4</sup> Catalytic epoxidation methodologies based on iron complexes and peroxides (especially H<sub>2</sub>O<sub>2</sub>), which can be considered as biologically inspired, are interesting because of the availability and low environmental impact of these reagents.<sup>5-15,16</sup> Despite appealing, the approach is challenging because it requires the design of iron coordination complexes that can activate the O-O bond of peroxides to create selective metal based oxidants, and avoid the often facile production of hydroxyl radicals via the Fenton reaction.<sup>10,11,17,18</sup> Recent reports have disclosed successful examples where asymmetric epoxidation is accomplished, in some cases producing high levels of stereoselectivity (Figure 1).<sup>19-27</sup> Highly enantioselective epoxidation of difficult substrates such as β,β-disubstituted aromatic enones and α-alkyl styrenes, not accessible by other methods, have also been described.<sup>23,24</sup> However, a major limitation still resides at the fact that iron catalyzed asymmetric epoxidations have been limited in scope to olefins conjugated to aromatic rings,<sup>19-22,23,24-35</sup> and remains to be accomplished for aliphatic substrates. Particularly interesting are cyclic aliphatic enones. Cyclic α-epoxide enones are structures found in a number of natural products,<sup>36</sup> and are also valuable synthons that can be further elaborated into precious building blocks for organic synthesis.<sup>37</sup> However, their asymmetric epoxidation is notoriously difficult. Modest to good enantioselectivities have been obtained with chiral hydroperoxides,<sup>38,39</sup> poly(aminoacids) catalysts,<sup>40</sup> ammonium salt catalysts,<sup>41-43</sup> and metal based catalysts<sup>21,22,44,45</sup>, but excellent enantioselectivities have only been described by List and co-workers using cinchona alkaloid derived organocatalysts and hydrogen peroxide as oxidant. The main drawbacks of this system are the requirement of relatively high catalyst loadings (up to 10 %) and long reaction times (from 24 to 168 h). In addition, α and α' substituted enones are not valid substrates for the system. Highly enantioselective epoxidations that could improve these aspects will

be a competitive alternative. In this regard, an iron catalyzed H<sub>2</sub>O<sub>2</sub>-activation methodology was envisioned as a potential option because they commonly entail powerful, fast reacting oxidants.<sup>12</sup> On the other hand, the high reactivity of this kind of systems can be rapidly recognized as a challenging aspect for elaborating them into highly enantioselective catalysts.

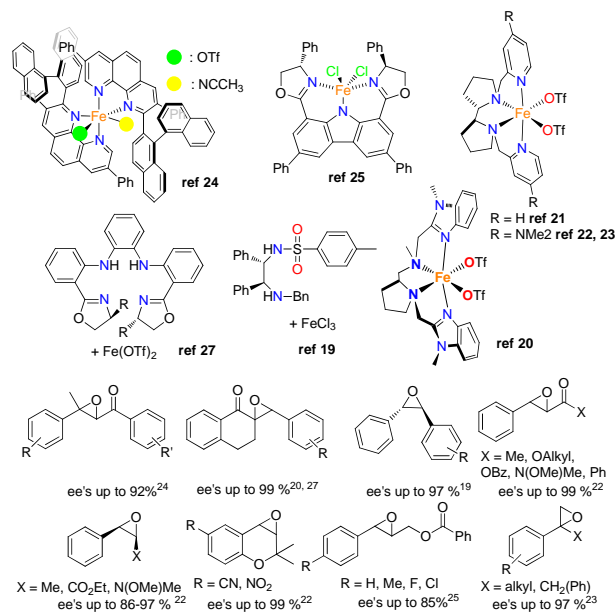


Figure 1. Representative examples of iron catalysts for asymmetric epoxidations, and current substrate scope.

Herein we face some of these challenges by describing the first example of an iron catalyst that epoxidizes cyclic aliphatic enones in high yields and with good to excellent stereoselectivities, employing H<sub>2</sub>O<sub>2</sub> as oxidant. The optimum catalyst is C<sub>1</sub>-symmetric and contains a tetradentate ligand built in a

modular manner by combining a bulky picoline, a benzylimidazole ring, and a chiral bipyrrrolidine (catalyst **7**, Figure 2). Reactions are fast (30 min) and require relatively low catalysts loadings (1-3 mol%). Finally, it is shown that the current system operates via generation of an electrophilic oxidant, therefore differing mechanistically from asymmetric epoxidation methods described so far for this class of substrates, which operate via a Weitz–Scheffer<sup>46-51</sup> mechanism where nucleophilic oxidants account for the epoxidation reaction. We show that this element represents a valuable tool for performing site selective epoxidation of enones containing two alkene sites, with orthogonal selectivity with regard to Weitz–Scheffer epoxidation agents.

#### Results and discussion.

**Catalyst screening.** Our initial screening entailed epoxidation of cyclohexenone **S1**, employing different iron catalysts (details on the preparation, and characterization of the ligands and the complexes are collected in the supporting information) with tetradentate N-based ligands (1 mol %), hydrogen peroxide as oxidant (2.3 equiv.) and ethylhexanoic acid (2-eha, 1.4 equiv.) as additive necessary for helping in the controlled activation of the H<sub>2</sub>O<sub>2</sub> (Table 1).<sup>21,22</sup> Reactions were performed at -30°C by adding H<sub>2</sub>O<sub>2</sub> (during 30 min) via syringe pump to an acetonitrile solution of the substrate, the catalysts and 2-eha under air. Following H<sub>2</sub>O<sub>2</sub> addition, reactions were analyzed by gas chromatography to determine conversion, epoxide yield, and stereoselectivity. Results are collected in Table 1.

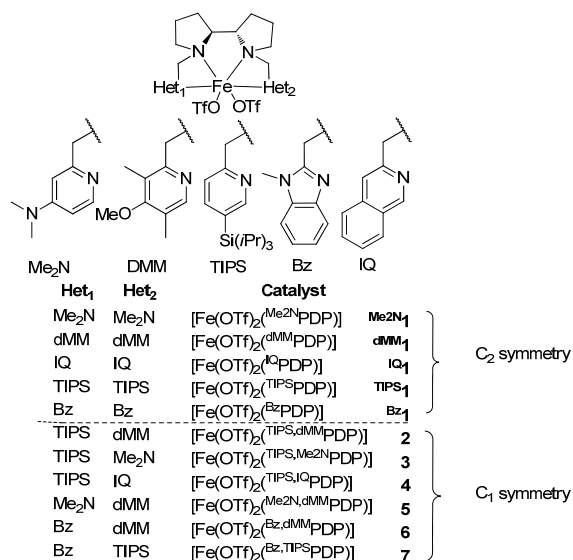


Figure 2. Schematic diagram of different catalysts employed.

Iron catalysts employed in the initial screening entailed C<sub>2</sub>-symmetric complexes containing tetradentate ligands based on a bis-pyrrolidine and two-heterocyclic amine binding units (Figure 2, Me<sub>2</sub>N<sub>1</sub>, dMM<sub>1</sub>, IQ<sub>1</sub>, TIPS<sub>1</sub> and Bz<sub>1</sub>, Table 1, entries 1-5). The heterocycles included electron-rich pyridines (entries 1-2, Me<sub>2</sub>N<sub>1</sub> and dMM<sub>1</sub>), bulky pyridines (entry 4, TIPS<sub>1</sub>), isoquinoline (entry 3, IQ<sub>1</sub>) and also N-methyl-benzylimidazole (entry 5, Bz<sub>1</sub>). We were quite pleased to observe that the complexes provided good to excellent ee's (from 72 to 88 % ee) in the epoxidation of

the model substrate. However, the best stereoselection, delivered by the benzimidazole based catalyst Bz<sub>1</sub>, was accompanied by poor product yield (88% ee, 5% epoxide yield, entry 5). Systems based on two pyridine rings (entries 1-4), provide smaller stereoselectivities (72-84% ee) but good product yields (71-94%). C<sub>1</sub>-symmetric complexes (2-7) with distinct heterocyclic arms were subsequently considered (entries 6-12). Most interestingly, catalysts that combine a methyl-imidazole ring and either an e-rich pyridine (6, entry 10), or a bulky pyridine (7, entries 11-12) provided the corresponding epoxide with excellent enantioselectivities (88-90 ee). In the case of 7, the epoxide was obtained in a modest 55% yield that could be subsequently optimized to a good yield (86%) while retaining the high level of enantioselectivity by employing 3 mol% catalyst. Replacement of 2-eha by other carboxylic acids<sup>22,23</sup> did not produce an improvement in the stereoselectivity of the reaction.

**Characterization of the catalyst.** Structural characterization of **7** in the solid state was accomplished by single crystal X-ray diffraction analysis (Figure 3, and SI for crystallographic details). The structure corresponds to an octahedrally coordinated iron center, adopting a *cis-α* topological geometry, with the two heterocycles *trans* to each other and the two labile triflate anions *cis* to each other. The binding O atoms of the triflate ligands and the iron center define a plane roughly perpendicular to an hypothetical N<sub>py</sub>-N<sub>BzIm</sub> axis. Fe-N and Fe-O distances are ~ 2.1-2.2 Å, indicative of a high spin center. <sup>1</sup>H-NMR analyses in CD<sub>3</sub>CN indicate that the high spin state is retained in solution, being the number of signals consistent with its C<sub>1</sub> symmetry (see SI).

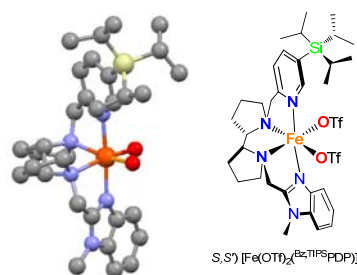
Table 1. Screening of the iron complexes in the asymmetric epoxidation reaction of 2-cyclohexenone

Entry	Catalyst	Conv(yield) % <sup>a</sup>	(ee)%
1	Me <sub>2</sub> N <sub>1</sub>	85(73)	75
2	dMM <sub>1</sub>	100(94)	84
3	IQ <sub>1</sub>	98(81)	72
4	TIPS <sub>1</sub>	87(71)	81
5	Bz <sub>1</sub>	26(5)	88
6	2	100(87)	85
7	3	90(72)	74
8	4	100(70)	75
9	5	99(80)	77
10	6	73(60)	88

11	7	67(55)	90
<sup>b</sup> 12	7	100(86)	90

Unless stated, reaction conditions are (*S,S'*)-catalyst (1 mol%), H<sub>2</sub>O<sub>2</sub> (2.3 equiv) and 2-eha (1.4 equiv.) in CH<sub>3</sub>CN at -30°C during 30 min. <sup>a</sup>Epoxide yields and substrate conversion determined by GC. Ee's determined by GC with a chiral stationary phase. The absolute configuration (*2R,3R*) of the epoxide was determined from its optical rotation, and by comparison from the literature.<sup>21 b</sup> 3 mol % of catalyst.

Figure 3. ORTEP diagram of the single crystal X-ray determined structure of (*S,S'*)-7 is shown. Triflate groups were omitted for clarity, except for the oxygen atoms directly bound to the iron center.

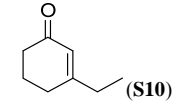
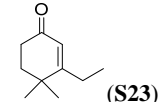
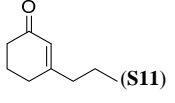
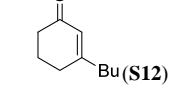
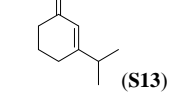
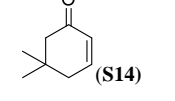
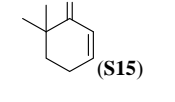
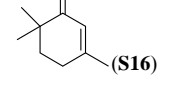
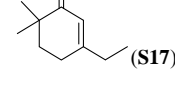
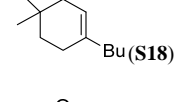
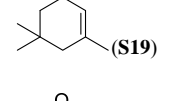
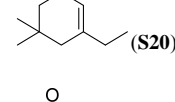
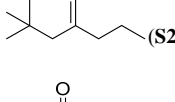
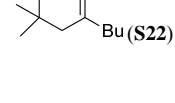


**Substrate scope.** The substrate scope in the asymmetric epoxidation of a series of cyclic aliphatic enones (Table 2) catalyzed by 7 was determined using the optimized conditions. In first place, it was observed that epoxidation of 2-cyclopentenone, a substrate that is recognized as particularly challenging,<sup>36</sup> proceeds with excellent yield and enantioselectivity (Table 2, entry 1), but a slight erosion of stereoselectivity was observed when the enone ring was enlarged up to 7 and 8 member rings (84% and 81 % ee, respectively, entries 3 and 4). Substitutions in the two sides of the cyclic enone produced different effects in the level of enantioselectivity of the reactions. In general, substitutions at the olefinic side ( $\alpha$  and  $\beta$ ) decrease ee's, while substitutions at the opposite side ( $\alpha'$  and  $\beta'$ ) lead to important improvement. For example, alkyl substitution at the  $\alpha$  position of 5 and 6-member ring enones caused a significant decrease in ee's (62-65% ee, entries 5-6), that could be partially rescued by employing 2 as catalyst (for S5 75% yield and 76 % ee, and for S6 81 % yield and 75% ee). Also, for tert-butyl group in  $\alpha$  position the reaction didn't take place (entry 7, S7). Although the current ee values leave room for improvement, it should be stated that the current catalysts constitute the first ones that provide good enantioselectivities for these substrates.  $\beta$ -alkylated cyclic enones gave also slightly lower enantioselectivities in comparison with the parent cyclic unsubstituted enones (see entries 8-13); isopropyl and ethyl  $\beta$ -substitution in 2-cyclohexenone provided the more modest ee's (66 and 70 % ee, entries 13 and 10, respectively) while  $\beta$ -alkyl substituted 2-cyclohexenones with methyl, propyl and butyl chains are epoxidized with high enantioselection (entries 9, 11 and 12, 80-84% ee). Most interestingly, the introduction of a *gem*-dimethyl group at positions  $\alpha'$ ,  $\beta'$  or  $\gamma$  results in a very substantial improvement of the enantioselectivities. Particularly outstanding enantioselectivities were obtained for substrates with *gem*-dimethyl substitution in position  $\alpha'$  (entries 15-18, 90-95% ee). This is a particularly relevant result since there is no alternative method for the

asymmetric epoxidation of this type of substrates. Substitution at position  $\beta'$  also provided high enantiomeric excesses (between 85 and 91% ee, entries 14, 19-22). Of notice, natural product isophorone (entry 19) was epoxidized in 71% isolated yield and 89% ee. Substitution at position  $\gamma$  also enhanced enantioselectivity (92% ee, entry 23), although in this case the epoxide was obtained in a modest 35% isolated yield. The relatively modest yields of epoxides bearing bulky and rigid substituents in close proximity to the olefinic site (entries 12 and 22) suggest that steric hindrance may be limiting these reactions.

Table 2. Substrate scope of aliphatic cyclic enones in asymmetric epoxidation reaction with 7 as catalyst

Entry	Substrate	Isol. yield (%)	(ee)%
1	(S2)	75	90
2	(S1)	75	90
3	(S3)	66	84
4	(S4)	99	81
<sup>a</sup> 5	(S5)	100(84)	65
<sup>a</sup> 6	(S6)	100(82)	62
7	(S7)	-	-
<sup>a</sup> 8	(S8)	92(71)	76
<sup>a</sup> 9	(S9)	100(80)	80

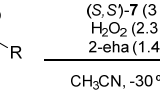
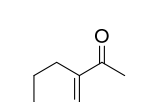
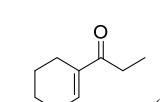
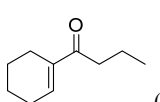
10		81	70	<sup>b</sup> 23		35	92
11		75	82				
12		80	84				
<sup>a</sup> 13		40(30)	66				
14		63	90				
15		72	92				
16		78	90				
17		65	95				
18		74	95				
19		71	89				
20		82	85				
21		78	91				
22		73	85				

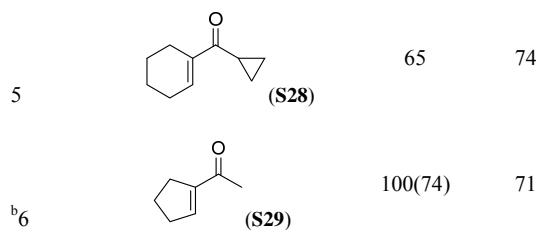
Unless stated, reaction conditions are (*S,S'*)-**7** (3 mol%), H<sub>2</sub>O<sub>2</sub> (2.3 equiv) and 2-eha (1.4 equiv.) in CH<sub>3</sub>CN at -30°C during 30 min. <sup>a</sup> Substrate conversion and epoxide yields (in parenthesis) determined by GC. <sup>b</sup>10 mol% catalyst. Ee's determined by GC with a chiral stationary phase.

Remarkably, cyclohexene-1-ketones were also epoxidized in good yields and excellent enantioselectivities. Optimum stereoselectivities were obtained with different alkyl chains (87-92 % ee, Table 3, entries 1-3). For branched groups, such as tert-butyl and cyclopropyl the enantioselectivities decreased slightly (entries 4 and 5), and a significant decrease in enantioselectivity was also obtained for the 5 membered cyclopentene rings (entry 6). Of interest is the observation that the epoxidation of the cyclopropyl derived substrate produces the epoxide without detectable amounts of cyclopropane ring opening products.

The relevance of the levels of enantioselectivity obtained with **7** can be best estimated when reactions are placed into context with the methodologies reported in the literature (Scheme 1). For comparison, a single example exists in the literature where the related allylic alcohol is epoxidized with excellent ee's by using Sharpless epoxidation, then followed by the oxidation of the alcohol to the ketone using CoCl<sub>2</sub> (Scheme 1, a).<sup>52</sup> On the other hand, direct epoxidation of the ketone has been performed with modest enantioselectivity using a chiral hydroperoxide (Scheme 1, b).<sup>38</sup> To the best of our knowledge, this is the first example of a catalytic methodology that can epoxidize this kind of olefins with excellent ee's.

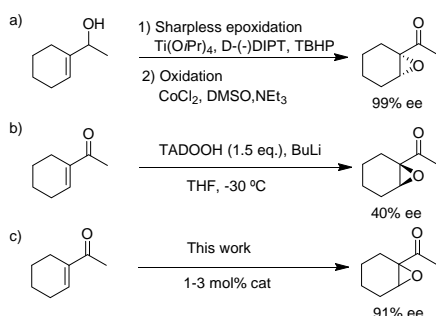
Table 3. Substrate scope with **7** as catalyst

Entry	Substrate	Isol. yield (%)	(ee)%
1		98	91
<sup>a</sup> 2		77	87
<sup>a</sup> 3		80	92
4		88	80



Unless stated, reaction conditions are (*S,S'*)-**7** (3 mol%), H<sub>2</sub>O<sub>2</sub> (2.3 equiv) and 2-eha (1.4 equiv.) in CH<sub>3</sub>CN at -30°C during 30 min. <sup>a</sup> 4 mol % catalyst. <sup>b</sup> Epoxide yields and substrate conversion determined by GC for numbers in parenthesis. Ee's determined by GC with a chiral stationary phase.

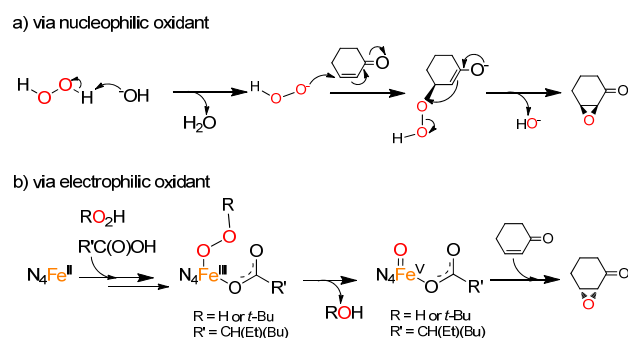
**Scheme 1.** Examples in the literature for epoxidation of 1-acetyl-1-cyclohexene



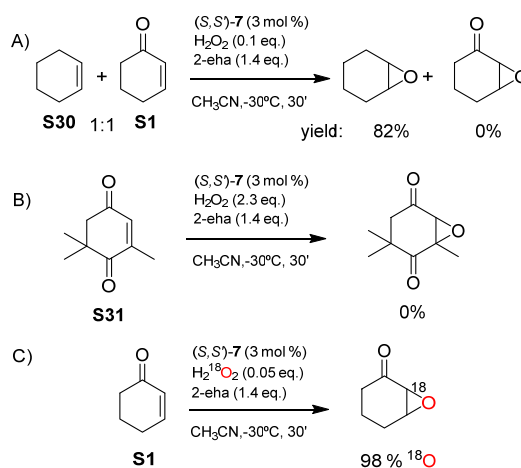
**Mechanistic studies.** Asymmetric epoxidation of cyclic enones has been so far performed via nucleophilic attack of peroxide agents at the olefinic site, activated via formation of an imine/iminium from reaction between the ketone moiety and a primary/secondary amine organocatalyst. This can be regarded as a variant of the Weitz–Scheffer epoxidation mechanism, where a basic peroxide is responsible for the initial attack at the β-carbon of the unsaturated carbonyl compound (Scheme 2a).<sup>46-51</sup> On the other hand, activation of H<sub>2</sub>O<sub>2</sub> by iron catalysts is most commonly leading to electrophilic oxidants, and this has proven the case for the enantioselective epoxidation of aromatic enones with **1**.<sup>21,22,53-56</sup> Nevertheless, examples for nucleophilic behavior have been also documented for related catalysts in olefin oxidation reactions.<sup>57</sup> Mechanistic studies were therefore performed to address this question. Evidence for the presence of an electrophilic oxidant was gathered by competitive epoxidation of a mixture of cyclohexene (**S30**) and 2-cyclohexenone (**S1**) under oxidant limiting conditions, observing that the epoxidation only takes place at the more electron-rich olefin (Scheme 3a). Likewise, the more electron-deficient enone **S31** could not be epoxidized (Scheme 3b).

Further mechanistic studies indicate the reaction mechanism of these iron catalysts is highly reminiscent of the one operating in P450<sup>58,59</sup> and in non-heme iron dependent oxygenases such as the family of Rieske oxygenases.<sup>60,61</sup> In first place isotopic analysis shows that hydrogen peroxide is the exclusive source of oxygen atoms that end up in the epoxide (Scheme 3c), discarding water and atmospheric O<sub>2</sub> as alternative sources. Indeed,

reactions with O<sub>2</sub> as the sole oxidant do not produce the epoxide. In addition, the use of *tert*-butyl hydroperoxide instead of hydrogen peroxide in the catalytic oxidation of 2-cyclohexenone yields the epoxide in 50 % of yield and 91 % ee (compare with 75% yield and 90% ee with H<sub>2</sub>O<sub>2</sub>). The virtually common stereoselectivity irrespective of the oxidant employed constitutes strong evidence that a common oxygen atom transfer agent is formed with both oxidants. Therefore, the sum of the experimental observations are consistent with a mechanistic scheme early proposed for structurally related catalysts<sup>23</sup> where the carboxylic acid (2-eha) assists the cleavage of the O–O bond, forming a carboxylate bound high valent Fe=O species, which is highly electrophilic and performs the oxygen atom transfer reaction (Scheme 2b).



**Scheme 2.** Mechanistic scenarios for the asymmetric epoxidation of a cyclic enone. A) Nucleophilic Weitz–Scheffer epoxidation mechanism and B) Electro-



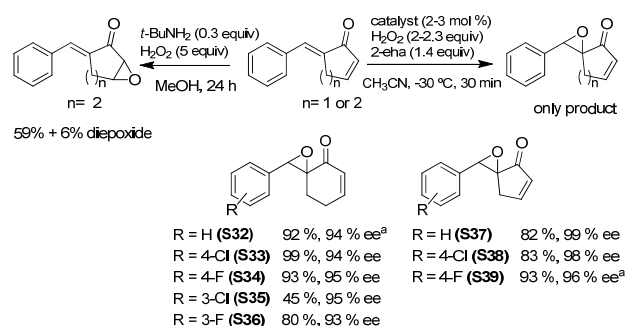
philic oxidation via a high valent iron oxo species.<sup>22</sup>

**Scheme 3.** (a) Competitive epoxidation experiment of cyclohexene (**S30**) and 2-cyclohexenone (**S1**), (b) the epoxidation of electron deficient olefin **S31** and (c) epoxidation of **S1** using H<sub>2</sub><sup>18</sup>O<sub>2</sub>

**Regioselective epoxidation of diolefins.** The electrophilic character of the active species can indeed find utility in the oxidation of substrates bearing olefinic moieties with

distinct electronic properties. Thus, substrates **S32**–**S39** were subjected to oxidation under standard conditions using  $\text{Me}_2\text{N}^1$  or **7**, providing the product resulting from epoxidation at the more e-rich site in excellent yields and stereoselectivities Scheme 4, right, 94–99% ee). Instead, epoxidation with basic hydrogen peroxide (*t*-Bu-NH<sub>2</sub> and H<sub>2</sub>O<sub>2</sub>) provided preferential oxidation at the cyclic aliphatic enone (59 % yield, along with 6% of a diepoxide, Scheme 4 left more details SI). Therefore, asymmetric epoxidation with these iron catalysts is orthogonal with enamine catalysis.

Scheme 4. Asymmetric epoxidation of dienones with  $\text{Me}_2\text{N}^1$  or **7** as catalysts (right) and with basic H<sub>2</sub>O<sub>2</sub> (left)



Unless stated, reaction conditions are (*S,S*)- $\text{Me}_2\text{N}^1$  (2 mol%), H<sub>2</sub>O<sub>2</sub> (2 equiv) and 2-eha (1.4 equiv.) in CH<sub>3</sub>CN at -30°C during 30 min. <sup>a</sup> (*S,S*)-**7** (3 mol%), H<sub>2</sub>O<sub>2</sub> (2.3 equiv) and 2-eha (1.4 equiv.) in CH<sub>3</sub>CN at -30°C during 30 min. <sup>b</sup> Ee's determined by HPLC with a chiral stationary phase.

**Conclusion.** In conclusion this work describes high yield and highly enantioselective epoxidation of cyclic enones with a C<sub>1</sub> symmetric iron coordination complex that combines a bulky pyridine and a benzylimidazole in its structure. Reactions are performed in short reaction times, employing aqueous hydrogen peroxide as oxidant. These features make this system a compelling alternative to methodologies with cinchona alkaloid organocatalysts, in some cases complementing its substrate scope. Furthermore, this work constitutes the first example where highly enantioselective (>90% ee) epoxidation of non aromatic substrates with iron catalysis is described, and also the first example of an enantioselective electrophilic oxidation of this challenging class of substrates. This element confers the system with an orthogonal selectivity with regard to enamine catalysis that can find use in the site selective enantioselective epoxidation of polyene substrates. Finally, the design of C<sub>1</sub> symmetric complexes where the electronic and steric properties of distinct heterocycles are combined constitutes a novel aspect in the design of this class of catalysts. Further studies will be devoted to extend the development of this class of catalysts in order to improve enantioselectivities and to expand their application to oxidation of other families of challenging substrates.

**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. "This material is available free of charge via the Internet at <http://pubs.acs.org>."

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