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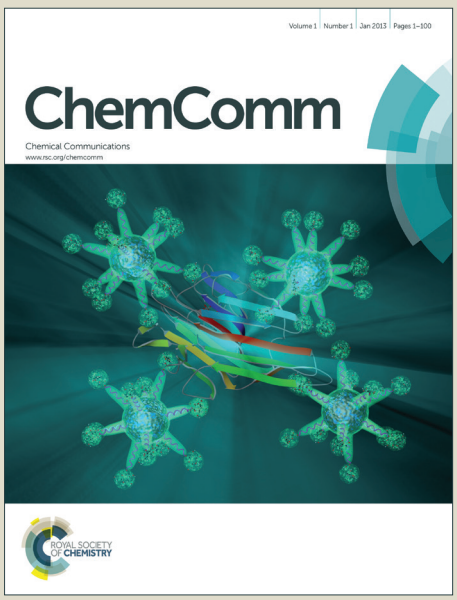

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ARTICLE

Biologically Inspired Non-Heme Iron-Catalysts for Asymmetric Epoxidation; Design Principles and Perspectives

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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Iron coordination complexes with nitrogen and oxygen donor ligands have have long since bee known to react with peroxides producing powerful oxidizing species. These compounds can b regarded as simple structural and functional models of the active sites of non heme iron depend oxygenases. Research efforts during the last decade have uncovered basic principles and structural coordination chemistry motifs that permit to control over the chemistry that evolves when these complexes react with peroxides, in order to provide powerful metal-based, but at the same time selective, oxidising agents. Oxidation methodologies with synthetic value are currently emerging f this approach. The current review focuses on asymmetric epoxidation, a reaction which has larg value in synthesis, and where iron/H_2O_2 based methodologies may represent not only a sustainable choice, but may also expand the scope of state-of-the-art oxidation methods. Basic principles th underlay catalyst design as well as H_2O_2 activation are discussed, whilst limitations and future perspectives are also reviewed.

Introduction

Iron is the most commonly found metal at the active site of metalloenzymes that participate in metabolic O_2 activation and oxygenation reactions. The fascinating oxidation properties of heme-based enzymes such as cytochrome P450's and peroxidases were rapidly recognized and served as a model for designing synthetic oxidation catalysts based on metalloporphyrins.[1-3] Besides hemes,[3-8] a growing number of iron dependent oxygenases are being discovered that do not rely on a heme-based active site, but instead contain iron centers ligated to imidazole and carboxylate (aspartate or glutamate) protein residues.[9-16] These enzymes can also reductively activate O_2 to form oxidizing species that engage in chemo, regio and stereoselective oxidations. Looking at the active site of these enzymes from the perspective of a coordination chemist, one can naïvely consider that their coordination structure should not differ substantially from the simple coordination complexes that can be prepared in a synthetic laboratory by combining iron salts, amines and carboxylic acids (See Figure 1).

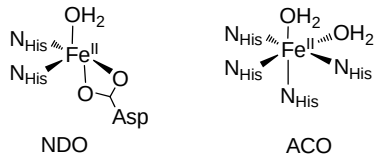

Figure 1. Schematic diagram of the active site of non-heme iron oxygen es naphthalene dioxygenase (NDO)[17] and apocarotenoid oxygenase (ACO), illustrating the presence of imidazol (histidine, N_{His}), carboxylate (aspartate, Asp) and water molecules in their first coordination sphere.

Continuing with this analogy, these simple compounds may b capable of performing challenging oxidation reactions, analogous to those occurring in the enzyme active sites. I enzymes, the use of O_2, a four electron oxidant, to perform tw electron oxidation reactions such as monoxygenations require a very precise controlled injection of protons and electron either from an electron transport chain or from a co-substrat This represents a significant challenge from a practical synthetic chemistry perspective that has prompted the development of coordination compounds that could use othe oxidants such as peroxides, peracids and hypervalent iodin reagents to generate metal based oxidizing species. Amon these, complexes that can catalytically utilise H_2O_2 to oxidiz organic substrates constitute the most interesting cases becaus of the benign nature of this oxidant. In this work we review th recent progress in the development of these ideas for designin non-heme catalysts for asymmetric epoxidation. Th

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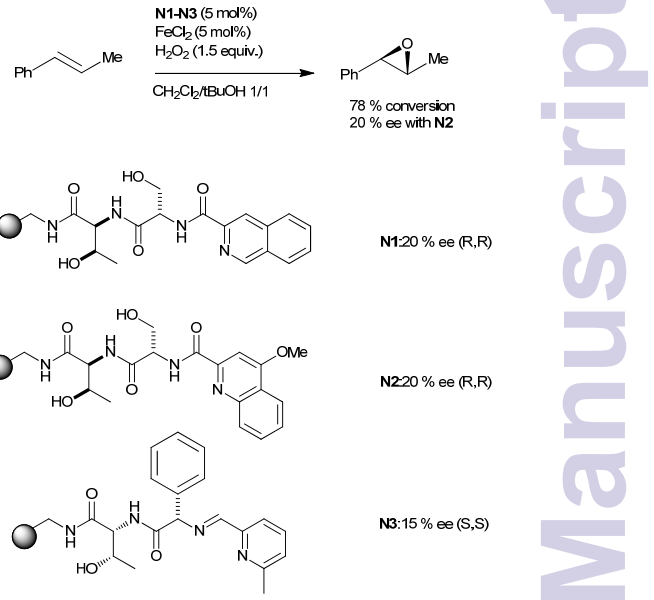
organization of the discussion is based on the oxidant employed. We pay particular attention to catalysts that use H_2O_2, whilst the few examples reported that use O_2 and relevant examples that rely in other oxidants such as peracids and iodosyl benzene are discussed later. To the best of our knowledge, iron catalyzed asymmetric epoxidation so far has only been documented with these oxidants. These oxidants We focus on asymmetric epoxidation because of the important role of this reaction in organic synthesis. Optically active epoxides are very interesting molecules because they are versatile synthons and high-potential precursors for more elaborated products that have significant interest in the pharmaceutical and chemical industries, amongst other fields.[19-22] Several methodologies for asymmetric epoxidation are already well established; however, iron-catalyzed epoxidation has been since long regarded as a potentially very attractive alternative because of the availability and low toxicity of this metal.[23-36] The delivery of an oxygen atom in a stereoselective manner constitutes a remarkable accomplishment in the frame of biologically inspired catalysis, because it requires exquisite control over the nature of the oxidant, calling for fine control of the mechanism of O-O activation (presumably via its lysis) when peroxides are employed. Nature employs sophisticated processes to control O-O lysis, and to discover simple conditions or reagents that can exert analogous control is therefore a scientifically remarkable goal, with important consequences in chemical synthesis. Consequently, it is not surprising that the reaction has received significant attention and has experienced rapid progress over the last decade.

Iron catalysts for asymmetric epoxidation employing H_2O_2.

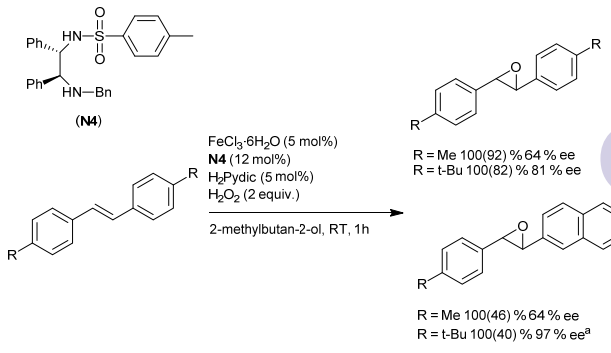
One of the main challenges of iron catalyzed asymmetric epoxidation with H_2O_2 is to avoid the Fenton reaction. This reaction generates highly reactive oxygen centered radicals, for which stereoselectivity could not be expected. Therefore, the design of selective oxidation reactions based on iron coordination compounds and H_2O_2 as oxidant requires the discovery of tools for governing the activation of this oxidant and the lysis of the O-O bond, so that metal based oxidants are formed, and production of oxygen centered radicals are avoided or at least minimized.

One of the first examples in the literature describing the application of non porphyrinic iron catalysts and H_2O_2 in asymmetric epoxidation was reported by Jacobsen and co-workers, pursuing a combinatorial approach.[37] A large set of chiral peptides, devised as ligands was combined with multiple metal salts, resulting in a library of 5760 metal-ligand complexes that were tested for activity in the epoxidation of *trans*-*β*-methylstyrene as a model substrate. It was found that iron complexes provided the best yields of epoxide (up to 78% in the best case, using $FeCl_2$), although only modest enantioselectivities of up to 20 % ee were obtained (Scheme 1). The coordination structure of the catalyst was not established but it is possible to recognize a common N_2O triad with the best peptides, presumably forming a N_2OFeCl_2 complex.



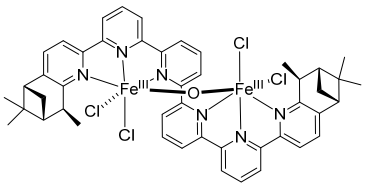
Scheme 1. Asymmetric epoxidation of *trans*-*β*-methylstyrene with peptide **N1-N3** ligands using H_2O_2 as oxidant.[37]

Beller and co-workers have developed iron based practical methods to epoxidize alkenes at room temperature and aerobic conditions. This example employs commercially available benchtop stable reagents: $FeCl_3 \cdot 6H_2O$ as metal source, in combination with pyridine-2,6-dicarboxylic acid and simple amines such as pyrrolidine, benzylamines or imidazoles to in situ assemble the catalyst, that activates H_2O_2 to epoxidize a wide array of alkenes.[38] A chiral version was designed through the use of a chiral 1,2-diphenyl-ethylene-1,2-diamine (Scheme 2, top, **N4**).[39] The system epoxidizes *trans*-stilbene derivatives with moderate to excellent yields and enantioselectivities (up to 92 % and 97 % ee, respectively, Scheme 2). Identification of the iron catalyst operating in these systems is difficult, and this fact translates into further difficulties to elucidate the reaction mechanism.[40] Nevertheless it is very interesting to notice that this system is built from the combination of carboxylic acids and amines, and therefore from a coordination chemistry point of view it can be regarded as a minimalistic approach towards a biomimetic non-heme catalyst.



Scheme 2. Asymmetric epoxidation of trans-stilbene derivatives using diamine **N4**, $FeCl_3 \cdot 6H_2O$, H_2O_2 and dipycolinic acid.[39a] 4 equiv. H_2O_2, 10 mol % H_2pydic, 1 mol % $FeCl_3 \cdot 6H_2O$, 24 mol % **N4**. Reaction at 10ºC

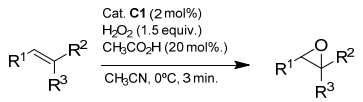
A system with improved definition, from the point of view of coordination chemistry, is a non heme iron catalyst based on a hexapyridine ligand containing pinene groups attached at two pyridine rings (Spp ligand), which in combination with two equivalents of $FeCl_2$ provides the diiron complex $[Fe^{III}_2(\mu\text{-}O)(Cl)_4(Spp)]$ (**C1**) (Figure 2). The complex epoxidizes styrenes with H_2O_2 in the presence of acetic acid. Up to 43 % ee was obtained for styrene in only 3 minutes (Table 1).[41] When peracetic acid was employed as oxidant, no epoxide product was observed, suggesting that the combination of hydrogen peroxide and acetic acid doesn't form peracetic acid in situ, which could be considered to be the final oxidant.



$[Fe^{III}_2(\mu\text{-}O)(Cl)_4(Spp)]$ **(C1)**

Figure 2. Proposed structure for $[Fe^{III}_2(\mu\text{-}O)(Cl)_4(Spp)]$ (**C1**)

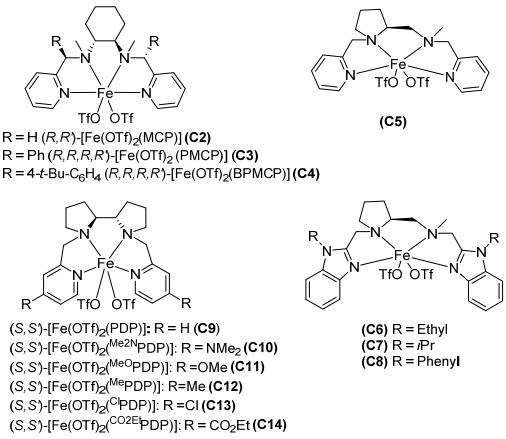
Table 1. Asymmetric epoxidation of styrene derivatives using cat **C1** and H_2O_2 as oxidant. [41]



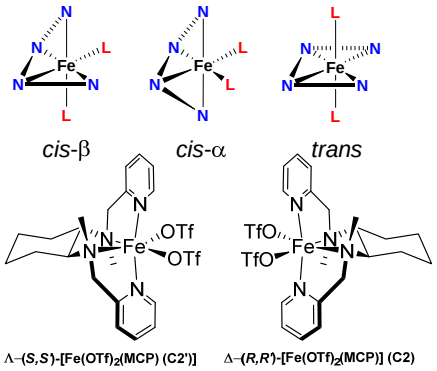
Entry	R^1	R^2	R^3	Conv/Yield (%)	ee (%)
1	Ph	H	H	100/95	43(*R*)
2[a]	*p*-MeO-C_6H_4	H	H	100/100	15 (*R*)
3[a]	*p*-Me-C_6H_4	H	H	100/100	30 (*R*)
4	Ph	Me	H	94/90	37 (*1R,2S*)
5	Ph	H	Me	62/62	40 (*1S,2R*)

[a]Using 1.2 mol% of catalyst.

Arguably the most successful family of iron catalysts developed so far for asymmetric epoxidation are those based on tetradentate ligands with a bis-amine-bis-pyridine (or related heterocycle) structure (Scheme 3). Upon binding to the metal, they form three five-membered ring chelate cycles, which confer high stability to the complexes. Unlike many other Fe based catalytic alkene epoxidation systems ample structural and spectroscopic information of the complexes in solid state and in solution exist. These ligands can bind to an octahedral metal center via three different topologies (Scheme 4). Of these, the *cis*-α topology has proven the most suitable so far for asymmetric epoxidation catalysts. This topology is C_2 symmetric, with the two pyridine donors *trans* to each other, and the two aliphatic diamines *cis*- to each other. This leaves two coordination sites at the iron site, which could be used to activate H_2O_2. The presence of two labile sites in relative *cis*-position also appears to be a crucial element in dictating the catalytic ability of this type of non-heme iron complex in hydrocarbon oxidation reactions.[42] Complexes that contain *trans*-labile sites appear to be much less active.[43] Octahedral coordination complexes with this type of ligand are chiral at the metal (Δ or Λ), and this chirality is in turn determined by the chirality of the aliphatic diamine part of the ligand. Thus chirality at the backbone is translated into a well-defined chiral space in the proximity of the labile coordination sites where H_2O_2 activation takes place.

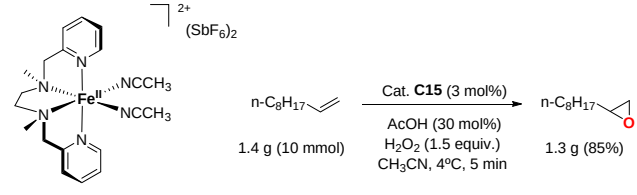


Scheme 3. Several examples of aminotetradentate iron complexes



Scheme 4. Top) Three possible topologies for iron complexes with linear tetradentate ligands. Bottom) Enantiomeric forms of the $[Fe(OTf)_2(mcp)]$ catalyst.

The ability of these kind of complexes to activate H_2O_2 and perform metal based oxidation of olefins was studied in detail in the mechanistic work reported by Que and co-workers.[43] In parallel, their use as aliphatic alkene epoxidation catalysts useful in preparative scale was described by Jacobsen and co-workers.[44] High epoxide yields (60-90%) were obtained in short reaction times in acetonitrile using 3 mol% $[Fe^{II}(men)(CH_3CN)_2](SbF_6)_2$, (**C15**) 1.5 equiv. of H_2O_2 and acetic acid as a key additive to ensure high product yields (Scheme 5).

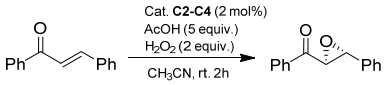


$[Fe^{II}(men)(CH_3CN)_2](SbF_6)_2$ **(C15)**

Scheme 5. Epoxidation of aliphatic alkenes using **C15** with hydrogen peroxide and acetic acid on gram scale

Initial use of (*R,R'*)-[Fe(OTf)$_2$(MCP)] (**C2**) in asymmetric epoxidation with H_2O_2 met with little success, with epoxidation of *trans*-2-heptene providing the corresponding epoxide in a modest 12% ee.[45] A more recent study by Sun and co-workers demonstrated improved activity in the epoxidation of *trans*-chalcones using **C2**. Additionally, the authors also studied more elaborated catalyst structures where aromatic groups were installed in pseudobenzylic positions (**C3-C4**, Figure 2). Reactions with catalyst **C4** were carried out using hydrogen peroxide and acetic acid, obtaining an improvement in both yield and enantioselectivities for *trans*-chalcone (up to 77 % ee compared with 54 % ee obtained with **C2** (Table 2)). The best enantioselectivity reported was 87 % ee, obtained when using the *para*-fluoro *trans*-chalcone substrate. Peracetic acid is also an efficient oxidant for use with these catalysts, but the yields and enantioselectivities of the resulting epoxides slightly decrease in comparison with those obtained with hydrogen peroxide and acetic acid are used. The principal limitation appears to be that the system appears to be applicable only for epoxidation of aromatic trans-α,β-enones.[46]

Table 2. Asymmetric epoxidation of *trans*-chalcone using catalysts **C2** – **C4** with H_2O_2 as oxidant[46]

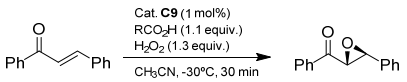


Entry	Cat	Yield/ee (%)
1	**C2**	47/54
2	**C3**	45/71
3	**C4**	47/72
4[a]	**C4**	53/77
5[b]	**C4**	57/55

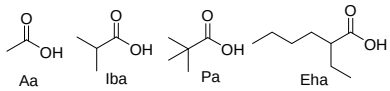
[a]At -15ºC. [b] 1.2 eq of AcOOH (8%) instead of H_2O_2/AcOH at room temperature

Bryliakov and co-workers explored the reactivity of (*S,S'*)-[Fe(OTf)$_2$(PDP)] (**C9**) (Scheme 3), an iron complex that was earlier pioneered by White in C-H oxidation reactions.[47] These studies showed that replacement of the cyclohexyldiamine by a bis-pyrrolidine backbone led to a catalyst with improved enantioselectivities in the epoxidation of chalcones. For example, the epoxidation of *trans*-chalcone improved from 54 % ee with 2 mol % of **C2** up to 71 % ee when 1 mol % of **C9** was used. Of significant interest, Bryliakov demonstrated that different alkyl carboxylic acids (CA) could be used in place of acetic acid, having an impact on the stereoselectivity of the epoxidation. The size of the carboxylic acid and enantioselectivities appear to be directly related. It was observed that the larger the substituent at the *alpha* carbon of the carboxylic acid, the higher the enantioselectivity, strongly suggesting that the carboxylic acid participates in defining the structure or electronic properties of the oxygen atom transfer (OAT) species. For instance, in the case of *trans*-chalcone enantioselectivity was improved up to 86 % ee using ethylhexanoic acid instead of acetic acid (Table 3).[48] This methodology was successfully applied to other substrates such as chromene derivatives, *trans*-cinnamate and styrene derivatives, but only moderate enantioselectivities were obtained in these cases.

Table 3. Asymmetric epoxidation of *trans*-chalcone using **C9** and different carboxylic acids. [48]

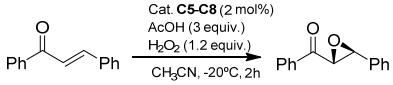


Entry	RCO_2H	Conv/Yield (%)	ee (%)
1	Aa	61/84	71
2	Iba	58/92	78
3	Pa	60/92	84
4	Eha	51/49	86



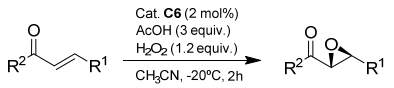
A proline derived diamine was more recently introduced by Sun and co-workers. This diamine differs from cyclohexadiamine and bipyrrolidine because it is not C_2-symmetric, and forms *cis*-α complexes with C_1 symmetry (Scheme 3, **C5**). Yields and enantioselectivities for the pyridyl based system **C5** remain moderate for *trans*-chalcone, (68 % yield and 56 % ee) but replacement of the pyridines by benzylimidazoles resulted in catalysts (Scheme 3, **C6-C8**) providing outstanding enantioselectivities for two kinds of substrates; *trans*-chalcones and tetralone derivatives which are epoxidized with up to 99 % yield, with 97 % ee and 99 % yield, with 98 % ee, respectively (Tables 4 and 5).[49]

Table 4. Asymmetric epoxidation of trans-chalcone using **C5**-**C8** catalysts with hydrogen peroxide and acetic acid. [49]

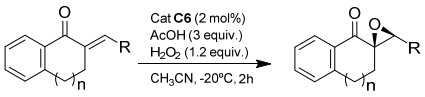


Entry	Cat	Yield/ee (%)
4	**C5**	68/56
5	**C6**	89/92
6	**C7**	90/88
7	**C8**	83/86

Table 5. Asymmetric epoxidation of *trans*-chalcones and trisubstituted enones derivatives using **C6** as catalyst[49]



Entry	R^1	R^2	Yield/ee (%)
1	*p*-Me-C_6H_4	Ph	90/91
2	*m*-Me-C_6H_4	Ph	99/95
3	*o*-Br-C_6H_4	Ph	96/94
4	Ph	*p*-Cl-C_6H_4	96/87
5	Ph	*o*-Cl-C_6H_4	78/91
6	Ph	*p*-MeO-C_6H_4	78/80

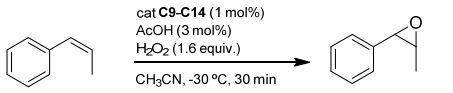


Entry	n	R	Yield/ee (%)
1	1	Ph	90/91
2	1	*p*-Me-C_6H_4	89/98
3	1	*m*-Me-C_6H_4	98/97
4	1	*o*-Me-C_6H_4	92/91
5[a]	2	Ph	78/85
6[b]	2	*p*-F-C_6H_4	86/93

[a]2 mol% of complex **C7**.
[b]CH_3CN (1.5 mL) and CH_2Cl_2 (1.0 mL) as solvent.

Costas and co-workers studied the impact of modifying the electronic properties of tetradentate aminopyridine ligands on the catalytic properties of the corresponding iron complexes with the aim to discover fundamental elements that could affect the H_2O_2 activation mechanism. A series of catalysts of general formula (*S,S'*)-[Fe(OTf)$_2$(^{X}PDP)] were prepared and studied as epoxidation catalysts (**C10**-**C14**) (Scheme 3).[50] Taking *cis*-*β*-methylstyrene as a model substrate, the complexes were tested as epoxidation catalysts, providing a dependence between product yields and stereoselectivities with the electron-donating nature of the ligand. For example, in the case of the epoxidation of *cis*-*β*-methylstyrene, as the electron donating properties of the ligand increase along the **C10**-**C14** series, enantioselectivity improved from 16% ee to 62% ee and yields from 13% to 87%. Interestingly, in the case of **C10**, the complex containing the most electron donating ligand, chemoselectivity and stereoselectivity of the epoxidation reaction remained unaltered when acetic acid was used in only catalytic amounts (1.5 equiv. with respect to the iron catalyst). Instead, less electron rich catalysts such as **C14** experience important erosion in yield when acetic acid loading is decreased (Table 6). Since in the case of catalyst **C10** carboxylic acids can be used in catalytic amounts, the range of examples that can be explored has virtually no limit. Among a series of CA's explored, *S*-Ibuprofen (S-Ibp) and 2-ethylhexanoic (2-eha) acid displayed the best enantioselectivities in the epoxidation of a wide array of substrates. A Hammet analysis by plotting the log(ee) vs Hammett parameters of the electronic groups in the catalyst showed a linear correlation with four different substrates, showing that the stereoselectivity is consistently improved as the catalyst becomes more electron rich.

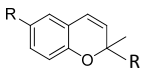
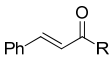
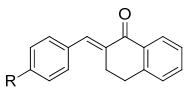
Table 6. Asymmetric epoxidation of *cis*-*β*-methylstyrene using (*S,S'*)-[Fe(OTf)$_2$(^{X}PDP)].[a]



Entry	Catalyst	Conv.(Yield) %	ee (%)
1	**C14**	31(13)	21
2	**C13**	32(15)	16
3	**C9**	49(26)	19
4	**C12**	31(17)	30
5	**C11**	38(26)	38
6[a]	**C10**	100(87)	62
7[a,b]	**C10**	100(85)	61
8[a,b]	**C14**	44(22)	19

[a]2 mol% of catalyst. [b]140 mol % of acetic acid

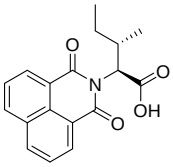
Table 7. Substrate scope for the asymmetric epoxidation using **C10**, H_2O_2 and S-Ibp or 2-eha as carboxylic acid co-ligand. [50]

Entry	Substrate	CA	Conv.(Epox. Isol. Yield, %)	ee (%)
1	 R = Me	S-ibp	100(97)a	86
2[a]	R = CO2Et	*S*-ibp	91	97
3[a]	R = C(O)N(OMe)(Me)	*S*-ibp	84	95
4	 R= CN	2-eha	95	99(*3R,4R*)
5	R = NO_2	2-eha	97	99(*3R,4R*)
6	 R = OMe			
7	R = O*i*Pr	2-eha	94	97(*2R,3S*)
8	R = Me	2-eha	60	94
9	R = N(OMe)(Me)	2-eha	95	99
10	R = Ph	2-eha	99	98(*2R,3S*)
11	R = *p*-CF_3-C_6H_4	2-eha	94	97(*2R,3S*)
12	 R = H	2-eha	94	90(*2R,3S*)

13	R = Me	2-eha	97	97(*2R,3S*)
14	R = *t*Bu	2-eha	96	95

[a]5 mol % catalyst, and 3 equiv of H_2O_2.

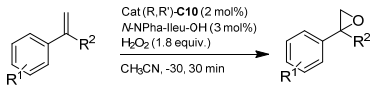
Further studies by the same authors showed that catalyst **C10** tolerates protected amino acids instead of carboxylic acids as co-ligands. This was regarded as a significant step forward towards the design of biologically inspired oxidation catalysts since amino acids constitute the natural ligands in non-heme iron dependent oxygenases.[51, 52] Amino acids were found to promote the activation of hydrogen peroxide by **C10** catalyzing the epoxidation of challenging substrates realizing good to excellent yields and stereoselectivities. A wide screening of N-protected amino acids was performed with the two enantiomeric forms of **C10** looking for matching-mismatching effects resulting from the combination of the chirality of the catalyst with the chirality of the aminoacid. Most remarkable is the ability of this system to stereoselectively epoxidize terminal aromatic olefins. Highly enantioselective epoxidation of this type of substrate is notoriously difficult.[53-57] After testing several amino acid derivatives, and N-protecting groups, the best result in terms of yield and enantioselectively was obtained using *N*-NPha-Ileu-OH (Figure 3). Several examples of terminal olefinic substrates are were summarized in Table 8.[58]



N-NPha-Ileu-OH

Figure 3. Amino acid *N*-NPha-ILeu-OH employed in catalytic asymmetric epoxidation of α-alkyl substituted styrenes.

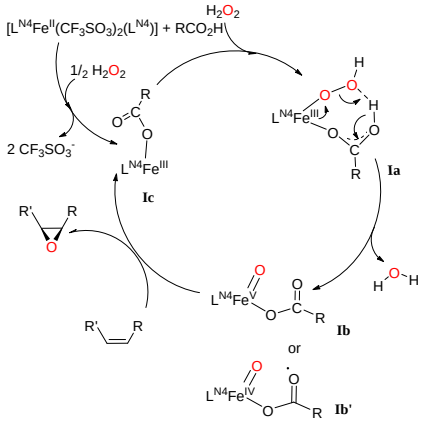
Table 8. Asymmetric epoxidation using (*R,R'*)-**C10**, H_2O_2 and *N*-NPha-ILeu-OH as additive. [58]



Entry	R^1	R^2	Yield/ee (%)
1	Cl	Me	90/63
2	H	Et	78/80
3	H	$CH_2O(Ac)$	80/83
4	H	$CH_2(Ph)$	70/80
5	H	*i*Pr	60/91
6	*p*-Cl	*i*Pr	87/92
7	*m*-Cl	*i*Pr	90/97
8	*H*	*t*-Bu	85/91
9	*p*-F	*t*-Bu	85/96
10	*o*-Cl	*t*-Bu	57/92

Role of acetic acid and active species in non-heme iron oxidation catalysis

The role of carboxylic acids in the above described reactions needs to be fully understood. AcOH has long been recognized to play a beneficial role in Mn catalyzed oxidation reactions.[49, 57, 59, 60] Interestingly, Jacobsen and co-workers[61] discovered that $[Fe^{II}(men)(CH_3CN)_2](SbF_6)_2$ (**C15**, scheme 5) catalyzed epoxidations of aliphatic alkenes also significantly benefit from the presence of this acid. Mechanistic studies directed to elucidating its role were performed by Que *et al* using $[Fe^{II}(OTf)_2(men)]$ (**C15'**) and $[Fe^{II}(OTf)_2(tpa)]$ (**C16**) (tpa = *tris*-(2-pydidylmethyl)amine) which served as prototypical cases of iron epoxidation catalysts with tetradentate ligands and two *cis* labile coordination sites.[62] The mechanism that emerged is shown in Scheme 6.

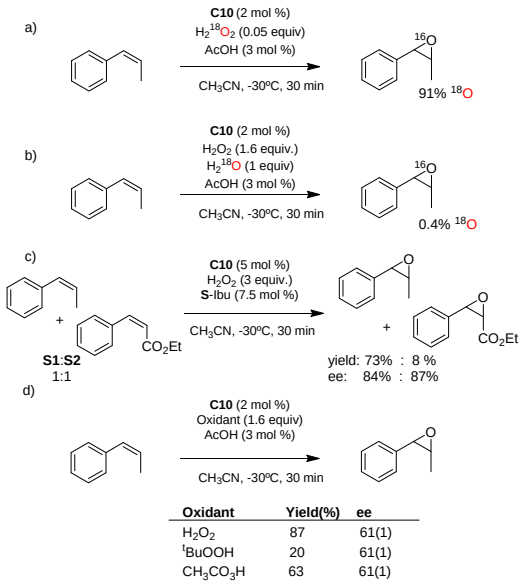


Scheme 6. Proposed mechanism for epoxidation reaction using aminotetradentate iron complexes

It was concluded that AcOH binds at the ferric center and facilitates heterolytic O-O cleavage in a hydroperoxoiron(III) species (**Ia**), forming a high valent $Fe^{V}(O)(AcO)$ oxidant (**Ib**) via a carboxylic acid assisted pathway.[62] Subsequently, **Ib** is then responsible for the O-atom delivery to the olefin. The involvement of the $Fe^{V}(O)(OAc)$ oxidant was also evidenced by the formation of a minor *cis*-hydroxyacetoxylated product in olefin oxidation by $[Fe^{II}(OTf)_2(tpa)]$ (**C16**) in the presence of acetic acid.[63]

This mechanistic scenario serves to accommodate all the experimental observations described so far with the (*S,S'*)-$[Fe(OTf)_2(^{X}PDP)]$ series of catalysts (Scheme 3, **C9-C14**). Isotopic labelling analysis showed that the oxygen atom transferred to the olefin originates from H_2O_2 (Scheme 7, a). Competitive oxidation of pairs of olefins showed preferential oxidation of the most electron rich substrate, providing evidence of an electrophilic character of the oxidant (Scheme 7, b). Of significant interest, epoxidations using tert-butylhydroperoxide (TBHP) or peracetic acid instead of H_2O_2 provided the epoxide with the same level of stereoselectivity (Scheme 7, c), demonstrating a common OAT species, irrespective of the terminal oxidant. The dependence between the ee outcome and the nature of the CA also provides strong evidence of its participation in the oxidizing species. Furthermore, this mechanistic scheme also provides a frame to rationalize the impact of the electronic properties of the ligand in the activation of H_2O_2 and in the stereoselectivity of the OAT event. It was rationalized that the powerful electron donating ability of the electron-rich pyridine exerts a "push" effect that synergistically combines with the "pull" of the

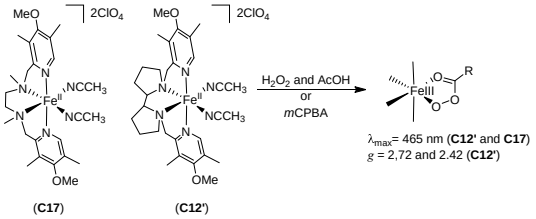
carboxylic acid, facilitating O-O heterolysis. This mechanism resembles that operating in cytochrome P450.[64] The electron-donating properties of the ligand also serve to provide stabilization to the highly electrophilic high valent oxo-iron species **Ib**. As the electrophilic iron-oxo species is attenuated, the transition state of the OAT reaction becomes more product like, with a closer olefin/iron-oxo contact that favors stereochemical differentiation.[65]



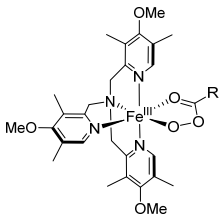
Oxidant	Yield(%)	ee
H_2O_2	87	61(1)
^tBuOOH	20	61(1)
CH_3CO_3H	63	61(1)

Scheme 7. A) Isotopic labelling analysis. b) Competitive oxidation. c) Different oxidants tested

Direct observation and elucidation of reaction intermediates in these systems is challenging because of their high reactivity and paramagnetic nature, which complicates and often precludes spectroscopic characterization. An EPR study by Talsi and co-workers proposed that high valent species $LFe^V(O)$ (L = (S,S')-PDP) could be[48] identified as a rhombic S= ½ system with EPR values of g = 2.66, 2.42 and 1.71 from the reaction of **C9** with H_2O_2 in the presence of acetic acid (7.5-15 equiv. with respect to the catalyst) in a CH_2Cl_2/CH_3CN mixture at −70 °C. The EPR parameters of these species resemble those earlier observed from the reaction of **C15** and **C16** with either 30% H_2O_2/AcOH, peracetic acid or *m*CPBA.[66, 67] The decay of these species was accelerated by the addition of cyclohexene, resulting in the formation of cyclohexene oxide. However, further spectroscopic analysis was precluded because these signals accounted for only ~ 10% of the total iron content of the samples. This assignment was later challenged by Que, Rybak-Akimova and co-workers who observed a S = 1/2 species with very similar EPR parameters when $[Fe(^{DMM}PDP)(CH_3CN)_2](ClO_4)_2$ (**C12'**) and $[Fe(^{DMM}men)(CH_3CN)_2](ClO_4)_2$ (**C17**) were reacted with H_2O_2/AcOH or peracids. The authors were also able to connect these EPR spectroscopic features with a band in the UV-Vis spectrum at λ_{max} = 465 nm, proposing that these species are ferric acylperoxide complexes.[68] Furthermore, reaction of $[Fe(OTf)_2(^{DMM}tpa)]$ (**C18**) with either 70% H_2O_2 (10 equiv.) in the presence of 200 equiv of AcOH, mCPBA or peracetic acid in acetonitrile at -40 ºC produced a metastable species which was characterized by EPR (g = 2.58, 2.38 and 1.72) and UV-Vis (λ_{max} = 460 nm)(Figure 4). These intermediates were prepared with sufficient purity to allow their characterization by different spectroscopic techniques. The combination of EPR, Mossbauer, and ESI led to the conclusion that these species should be better formulated as (L-Fe^{III}-OOC(O)R) (L = ligand, R = CH_3 or C_6H_4-3-Cl) and not Fe^V(O)(OAc). Thus these species may not be the OAT agents but instead precursors of a yet unobserved high valent oxidant that is the OAT agent. Consistently, ferric-acylperoxide species proved kinetically not competent for reacting with olefins. Moreover, DFT calculations suggest that these species evolve via rate determining O-O cleavage to form two possible electromers formulated as $Fe^V(O)(O_2C\text{-}Ar)$ or $Fe^{IV}(O)(\cdot O_2C\text{-}Ar)$, that act as the active oxidant.[69]



Scheme 8. Synthesis of acylperoxoiron(III) complexes from reaction of $[Fe(^{DMM}men)(CH_3CN)_2](ClO_4)_2$ (**C17**) and $[Fe(^{DMM}PDP)(CH_3CN)_2](ClO_4)_2$ (**C12'**) with H_2O_2/AcOH or peracids.[68]



[TPA-Fe^{III}(OOC(O)R)] (R = CH_3 or C_6H_4-3-Cl)

Figure 4. Proposed structure of the acylperoxoiron(III) complex formed in reaction of $[Fe(OTf)_2(^{DMM}TPA)]$ (**C18**) with peracids or with H_2O_2/AcOH.

More recently, Talsi *et al* have described the detection by EPR spectroscopy of a highly reactive intermediate in the reaction of dimeric iron complexes $[Fe^{II}_2(\mu\text{-}OH)_2(L)_2]^{4+}$, L = TPA* or ^{DMM}men, with H_2O_2/AcOH or peracetic acid in 1.2 CH_2Cl_2/CH_3CN mixtures at -75 to -85 ºC. The resulting intermediate is characterized by a rhombic set of g values (2.07, 2.00 and 1.96) characteristic of an S =1/2 system. These species accumulate in only 1-2% and are reactive towards olefins even at -85ºC. The authors proposed this to be a Fe^V(O) species on the basis of comparison with the literature. The limited accumulation of this intermediate precluded further spectroscopic characterization.[70]

Iron asymmetric epoxidation catalysts that use O_2.

The most abundant and economical oxidant is O_2, and therefore represents the most desirable oxidant. However, controlled activation of O_2 is extremely difficult and iron catalyzed epoxidation methodologies employing O_2, and exhibiting potential synthetic value are scarce.[71, 72] Not surprisingly, asymmetric methods are almost unknown. The first example using aerobic conditions was described in 1989, and involved the non-heme iron complex of PYML-6 (**C19**) (Figure 5, left).[73]

The reaction between iron complex, O_2, mercaptoethanol as a reducing agent and *cis*-*β*-methylstyrene as a substrate, produced *cis* epoxide with 51% ee and only traces of *trans* epoxide. In contrast, epoxidation of *trans*-*β*-methylstyrene yielded a racemic epoxide mixture,. but if the reducing agent was changed to sodium L-ascorbate, racemic *trans* epoxide was obtained as the major product from the epoxidation of the *cis* alkene. Only trace amounts of *cis* epoxide were formed, showing a drasticerosion of stereochemistry. The system can operate using hydrogen peroxide as oxidant, however a slight erosion of enantioselectivity (45% ee) and yields were observed for *cis*-*β*-methylstyrene.

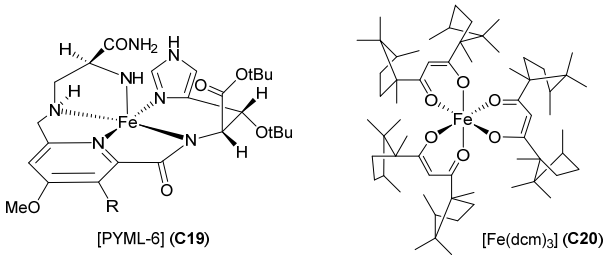


Figure 5. Iron catalysts that employ O_2 to perform asymmetric epoxidation.

More recently, You and co-workers developed a chiral *β*-diketone-iron(III) complex ($Fe(dcm)_3$) (**C20**) (dcm = tris(d,d-dicampholylmethanato; Figure 5, right) that is able to epoxidize styrene derivatives using dioxygen and excess 2-ethylbutyraldehyde as a sacrificial co-substrate. After 10 hours excellent yields (up to 91%) and enantioselectivities (up to 86% ee) were obtained.[74] No mechanistic studies were reported for this system.

Iron asymmetric epoxidation catalysts using peracids and PhIO

Despite the fact that H_2O_2 is a very attractive oxidant, its use in asymmetric epoxidation is challenging because it requires activation and efficient control of the O-O lysis. Consequently, other oxidants have been also explored, for example, peracids, whereby heterolytic O-O cleavage is favored by the electron-withdrawing effect of the peracid carbonyl moiety. Peracids are electrophilic oxidants that can directly epoxidize olefins without the aid of a catalyst and therefore, the background reaction must be minimized. A second type of oxidants is oxo-donors like iodosylbenzene, which have been successfully employed in heme catalyzed oxidation reactions, and that avoid the problem of O-O lysis control. One of the first examples of iron catalyzed asymmetric epoxidation employing peracids was reported by Menage and co-workers who described a non-heme oxo-bridged diiron complex $[Fe^{III}_2(\mu\text{-O})(bpp)_4(H_2O)_2]^{4+}$ (**C21**) with chiral bypiridine ligands (**N5**) (Figure 6).[75] The catalyst was tested for the epoxidation of alkenes and high efficiencies were obtained, with up to 850 TON. However, enantioselectivities remained moderate, ranging from 9–63% ee (Table 9).

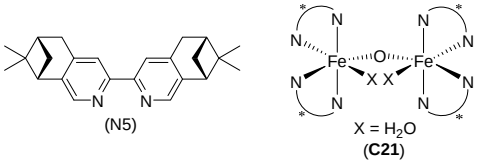
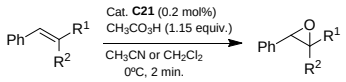


Figure 6. Structure of diiron complex $[Fe^{III}_2(\mu\text{-O})(bpp)_4(H_2O)_2]^{4+}$ (**C14**)

Table 9. Asymmetric epoxidation of different olefins using **C21** as catalyst and peracetic acid as oxidant. [75]



Entry	R^1	R^2	Conv/Yield (%)	ee (%)
1[a]	H	H	84/60	15(R)
2[b]	Ph	H	67/67	0
3[a]	Me	H	86/48	24(1R,2S)
4[b]	H	Me	100/74	15
5[a]	CO_2Me	H	70/35	63
6[b]	$CO_2(i\text{Pr})$	H	nd/nd	19
7[b]	CO_2Ph	H	92/66	56(2R,3S)

[a]Reacton in CH_2Cl_2. [b]Reaction in CH_3CN.

A breakthrough was described by Yamamoto who designed a mononuclear iron catalyst bearing phenanthroline ligands derivatized with binaphthyl moieties (**C22**) (Figure 7).[76, 77] In catalytic reactions, the catalyst was prepared in situ, but it could be also isolated and fully characterized by different methods, including X-ray diffraction analysis. The resulting complex bears structural similarities to the mcp type of catalysts (Scheme 3), adopting a C_2 symmetric octahedral structure with two *cis*-labile coordination sites. The catalyst epoxidizes *β*,*γ*-disubstituted enones with stereoretention and high enantioselectivity using peracetic acid as terminal oxidant. *m*CPBA also proved to be a valid oxidant, but unfortunately H_2O_2 was found not to be. The substrate scope of this system is particularly interesting because alternative methods for highly stereoselective epoxidation of this kind of substrate are lacking. Selected results highlighting the scope of this catalyst system are shown in Table 10. Intermolecular competitive studies between electron-rich and electron-poor olefins showed a 2.4 preference for the electron-rich olefin, implying the generation of an electrophilic oxidant. To demonstrate the importance of the resulting chiral epoxides, they were further transformed into *β*-ketoaldehydes and 2-isoxazolidines maintaining excellent enantioselectivities.

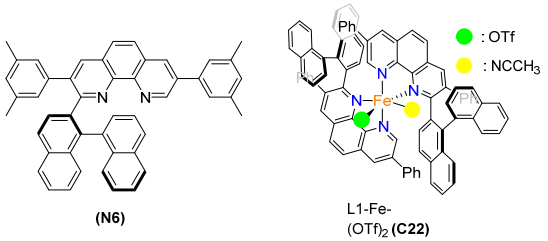
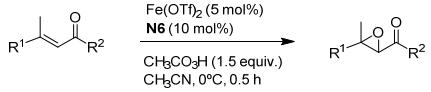


Figure 7. Ligand **N6** and the corresponding iron complex.

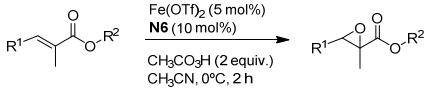
Table 10. Asymmetric epoxidation of *β,β*-trisubstituted chalcones derivatives using Fe(OTf)2, **N6** as ligand and peracetic acid as oxidant.[76, 77]



Entry	R^1	R^2	Yield/ee (%)
1	Ph	Ph	80/91
2	Ph	p-Me-C_6H_4	77/92
3	Ph	o-Me-C_6H_4	61/92
4	Ph	m-Me-C_6H_4	67/90
5	Ph	*p*-CF_3-C_6H_4	70/89
6	n-C_3H_7	Ph	20/50

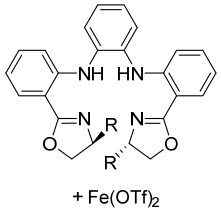
This system is also competent for epoxidizing trisubstituted *α,β* unsaturated esters, providing epoxidic products with high enantioselectivities, although only in moderate yields in most cases (Table 11).[77]

Table 11. Asymmetric epoxidation trisubstituted *α,β* unsaturated esters derivatives using Fe(OTf)2, **N6** as ligand and peracetic acid as oxidant.[77]



Entry	R^1	R^2	Yield/ee (%)
1	Ph	C$(CH_3)_2$(*t*-Bu)	69/95
2	*p*-Me-C_6H_4	C$(CH_3)_2$(*t*-Bu)	65/93
3	*m*-Me-C_6H_4	C$(CH_3)_2$(*t*-Bu)	24/94
4	*o*-Br-C_6H_4	C$(CH_3)_2$(*i*Pr)	16/93
5	p-Cl-C_6H_4	C$(CH_3)_2$(*i*Pr)	64/94
6	1-naphthyl	C$(CH_3)_2$(*i*Pr)	62/98

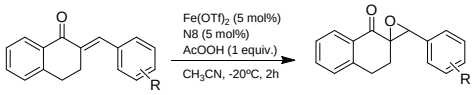
A different type of iron catalysts based on N-based tetradentate ligands, in this case inspired by porphyrins, have been recently described by Gao and co-workers. These ligands do contain pyridines, but instead they bear chiral oxazoline moieties (Figure 8). The catalyst epoxidizes di and trisubstituted electron deficient olefins with high enantioselectivities, using peracetic acid or *m*CPBA as terminal oxidant (Table 13).[78] However, the catalyst was found not to be operative with peroxides. After testing several ligands with different bulky groups, it was found that those containing *i*Pr groups (**N7-N14**) performed optimally. A Hammet analysis indicated that the active oxidant species has electrophilic character.



N7: R = Ph N11: R = ^{s}Bu
N8: R = *i*Pr N12: R = ^{t}Bu
N9: R = Bn N13 R = Et
N10: R = ^{i}Bu N14: R = Me

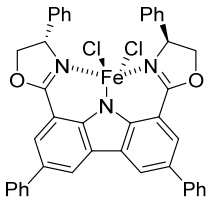
Figure 8. Structure of N7-N14 ligands

Table 13. Asymmetric epoxidation of trisubstituted enones derivatives using ligand N8.[78]



Entry	R	Yield/ee (%)
1	H	93/85
2	*o*-F	90/92
3	*m*-F	90/89
4	*p*-F	90/87
5	*o*-,*m*-Cl	82/94
6	*o*-,*p*-Cl	81/97
7	*o*-Br,*p*-Cl	80/99

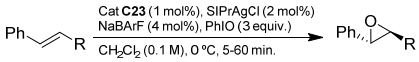
Recently, Nakada and co-workers reported on the development of an iron catalyst with a tridentate ligand based on a carbazole central unit and chiral oxazolines (**C23**) (Figure 9).[79] The combination of the iron-chloride catalyst, iodosylbenzene as oxidant, NaBArF and SIPrAgCl (SIPr = N,N′-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene) as additives, resulted in highly asymmetric epoxidation of (E) alkenes. Both SIPrAgCl and NaBArF are were found to be necessary for the reaction to occur. EPR analysis of a sample taken during catalysis shows an isotropic signal centered at g = 2.0, indicative of an intermediate with a S = ½ electronic structure. By analogy to CpdI in heme systems, the authors propose that the intermediate should be described as a Fe^{IV}(O) species bearing a π-cation radical ligand (Scheme 9).



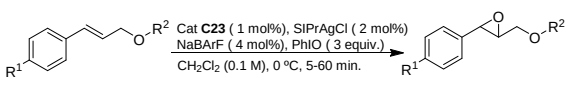
(C23)

Figure 9. Structure of new bioinspired porphyrin iron complex **C23.**

Table 12. Asymmetric epoxidation of trans-stilbene and cinnamyl alcohol derivatives.

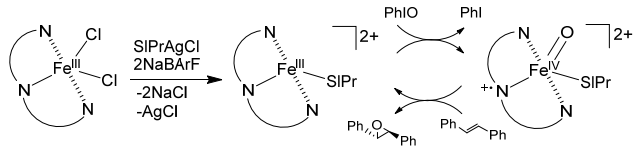


Entry	R	Yield/ee (%)
1	p-Me-C_6H_4	61/84
2	p-F-C_6H_4	58/92
3	p-Cl-C_6H_4	60/92
4	p-OMe-C_6H_4	51/49
5	1-naphthyl	40/97
6	2-naphthyl	45/93



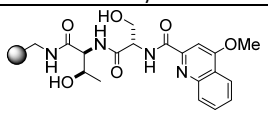
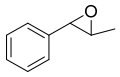
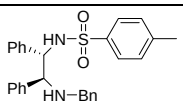
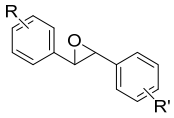
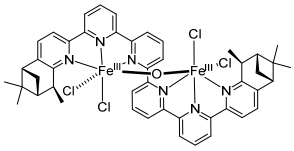
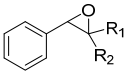
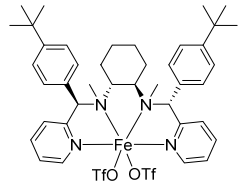
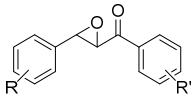
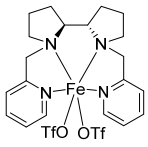
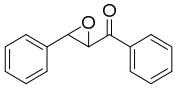
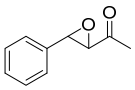
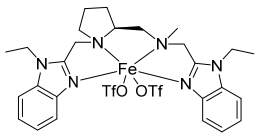
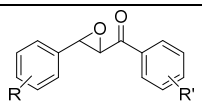
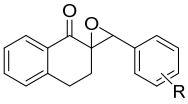
Entry	R^1	R^2	Yield/ee (%)
1	H	C(O)(Ph)	93/79
2	Me	C(O)(Ph)	76/85
3	F	C(O)(Ph)	69/84
4	Cl	C(O)(Ph)	61/74
5	H	CH_2(OMe)	90/76
6	H	CH_2(1-naphthyl)	39/83

For entry 6, direct benzylic oxidation is observed

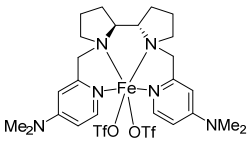
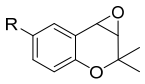
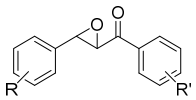
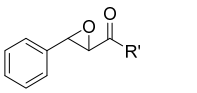
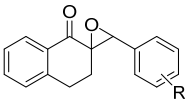
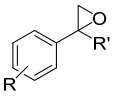
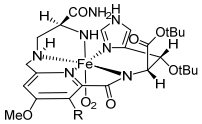
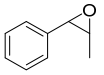
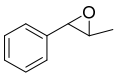
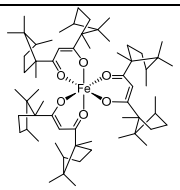
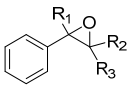


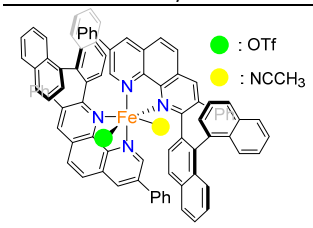
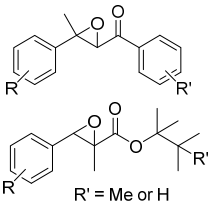
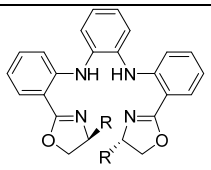
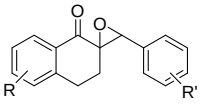
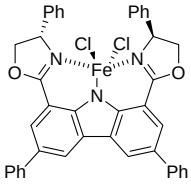
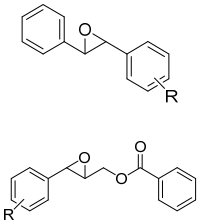
Scheme 9. Proposed mechanism for **C23** catalyst

Table 13. Summary of iron catalysts and several olefins oxidized

Catalyst	Additive/Oxidant	Epoxide product	Range of yield and ee (%)	[Ref]
 **(N2)** + $FeCl_2$	-/H_2O_2		conv 78 % ee 20 %	[37]
 **(N4)** + $FeCl_3{\cdot}6H_2O$	H_2pydic/H_2O_2		yield 40-94 % ee 10-97 %	[39]
 $[Fe^{III}_2(\mu\text{-}O)(Cl)_4(Spp)]$ **(C1)**	AcOH/H_2O_2		R_1= Me, R_2= H, 90 (37) % R_1= H, R_2= Me, 62 (40) %	[41]
 (*R,R,R,R'*)-[Fe(OTf)$_2$(BPMCP)] **(C4)**	AcOH/H_2O_2		yield 40-90 % ee 69-87 %	[46]
 (S,S')-[Fe(OTf)2(PDP)] **(C9)**	2-eha/H_2O_2	 	98 (86) % 51 (62) %	[48]
 **(C6)**	AcOH/H_2O_2	 	yield 78-99 % ee 74-97 % yield 72-98 % ee 87-98 %	[49]

[a]Yield based on additive

Catalyst	Additive/Oxidant	Epoxide product	Range of yield and ee (%)	[Ref]
 (*S*,*S*')-[Fe-(OTf)$_2$(^{Me2N}PDP)]: **(C10)**	S-Ibp/H_2O_2	 R = Me, CO_2Et, N(OMe)Me	yield 84-97 % ee 86-97 %	
		 R = CN, NO_2	yield 95-97 % ee 99 %	
	2-eha/H_2O_2		yield 94-99 % ee 97-98 %	[50]
		 R = Me, OMe, OEt, O*i*Pr, OBz, N(OMe)Me	yield 60-95 % ee 91-99 %	
			yield 94-97 % ee 90-97 %	
	NPha-Ileu-OH/H_2O_2	 R' = Me, Et, *i*Pr, *t*Bu, CH_2(Ph)	yield 52-94 % ee 50-97 %	[58]
 PYML-6 (**C19**)	2-mercaptoethanol/O_2		yield 2 % ee 51 %[a]	[73]
			yield 2 % ee 0 %[a]	
 Fe(dcm)3 (**C20**)	2-ethylbutyradehyde/O_2		R_1= H, R_2= H, R_3= H, 90 (78) % R_1= H, R_2= H, R_3= Me, 79 (85) % R_1= H, R_2= Me, R_3= H, 91 (48) % R_1= Me, R_2= H, R_3= H, 51 (55) % R_1= H, R_2= Ph, R_3= H, 62 (58) %	[74]

Catalyst	Additive/Oxidant	Epoxide product	Range of yield and ee (%)	[Ref]
 : OTf : $NCCH_3$ Ph = 3,5 Me-Ph **(C22)**	-/AcOOH	 R' = Me or H	yield 45-88 % ee 89-92 % yield 24-69 % ee 93-99 %	[76, 77] [77]
 + $Fe(OTf)_2$ R = *i*Pr	-/AcOOH or mCPBA		yield 33-94 % ee 73-99 %	[78]
 **(C23)**	SIPrAgCl, NaBArF/PhIO		yield 40-61 % ee 49-97 % yield 42-93 % ee 74-85 %	[79]

Conclusions and Overview

The field of biologically inspired oxidation catalysis has experienced major advances over the last ten years. Non heme iron coordination complexes aimed at mimicking the activity of iron dependent oxygenases are being incorporated into the tools of synthetic organic chemistry. Asymmetric epoxidation constitutes one of the reactions where the progress of the field has been very significant. Reports in the early years of the 21st century focused mainly on the mechanistic aspects of olefin oxidation reactions at non heme iron sites, and provided foundations that selected iron complexes able to mediate olefin epoxidation via metal based mechanisms. Since then, catalysts that mediate asymmetric epoxidation with good product yields and high levels of stereoselectivity have been described in few cases. Table 13 collates some representative examples that serve to provide an overview of the field, the scope, experimental conditions and limitations of the reported systems. A perusal of this table shows that these catalysts have so far a rather limited scope, focused primarily on chalcones. However, some systems are starting to show promising results towards more challenging classes of substrates such as terminal styrenes and *β,β*-trisubstituted chalcones. In contrast, interesting substrates such as aliphatic alkenes, are efficiently oxidized by iron epoxidation systems, but incorporation of stereoselectivity is still lacking. Regarding the oxidant, important steps have been made towards controlling the activation/breakage of the O-O bond of peroxides, most specifically H_2O_2, and as a result this oxidant is increasingly being incorporated in iron catalyzed asymmetric epoxidations. Comprehension of the mechanisms of catalyst deactivation is also becoming necessary, to develo even more efficient catalysts. So far, iron catalysts successful in asymmetric epoxidation rarely exceed 100 TON. Finall models for understanding the origin of the stereoselectivity are also required for rationalizing which elements of the catalys need to be changed/elaborated in order to increase the substrate scope. So far successful catalysts are very much focused o octahedral iron complexes with tetradentate N-based ligands. In this regard, the impact of the nature of carboxylic acids in defining the stereoselectivity of the reactions performed with this class of complexes can potentially extend their versatility. Alternative carboxylic acids may be employed to design nove asymmetric epoxidation systems, extending substrate scope without the need of further catalyst development. Finall structurally simpler ligand frameworks that could enable analogous control of the activation of H_2O_2, and provide good stereoselectivities will be also quite interesting from a practic organic synthesis point of view. Knowledge gained from these models will be very important to the fundamental future o epoxidation catalyst development in order to aid broadening o the substrate scope.

Acknowledgements

We acknowledge help from Dr Christopher Whiteoak in proofreading the manuscript and providing valuable suggestions. We acknowledge financial support from the European Researc Council (ERC-2009-StG-239910), MINECO of Spain (CTQ2012-37420 C02-01/BQU, CSD2010-00065), and Generalitat de Catalunya (2014 SGR 862). X.R. and M.C. thank ICREA-Academia awards.

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