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Fe(PyTACN)-Catalyzed *cis*-Dihydroxylation of Olefins with Hydrogen Peroxide

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Abstract: A family of iron complexes with general formula [Fe(II)(^{R,Y,X}PyTACN)(CF_3SO_3)$_2$], where ^{R,Y,X}PyTACN = 1-[2′-(4-Y-6-X-pyridyl)methyl]-4,7-dialkyl-1,4,7-triazacyclononane, X and Y refer to the groups at positions 4 and 6 of the pyridine, respectively, and R refers to the alkyl substitution at N-4 and N-7 of the triazacyclononane ring, are shown to be catalysts for efficient and selective alkene oxidation (epoxidation and *cis*-dihydroxylation) employing hydrogen peroxide as oxidant. Complex [Fe(II)(^{Me,Me,H}PyTACN)(CF_3SO_3)$_2$] (**7**), was identified as the most efficient and selective *cis*-dihydroxylation catalyst among the family. The high activity of **7** allows the oxidation of alkenes to proceed rapidly (30 min) at room temperature and under conditions where the olefin is not used in large amounts but instead is the limiting reagent. In the presence of 3 mol% of **7**, 2 equiv. of H_2O_2 as oxidant and 15 equiv. of water, in acetonitrile solution, alkenes are *cis*-dihydroxylated reaching yields that might be interesting for synthetic purposes. Competition experiments show that **7** exhibits preferential selectivity towards the oxidation of *cis* olefins over the *trans* analogues, and also affords better yields and high [*syn*-diol]/[epoxide] ratios when *cis* olefins are oxidized. For aliphatic substrates, reaction yields attained with the present system compare favourably with state of the art Fe-catalyzed *cis*-dihydroxylation systems, and it can be regarded as an attractive complement to the iron and manganese systems described recently and which show optimum activity against electron-deficient and aromatic olefins.

Keywords: alkenes; *cis*-dihydroxylation; homogeneous catalysis; hydrogen peroxide; iron

Introduction

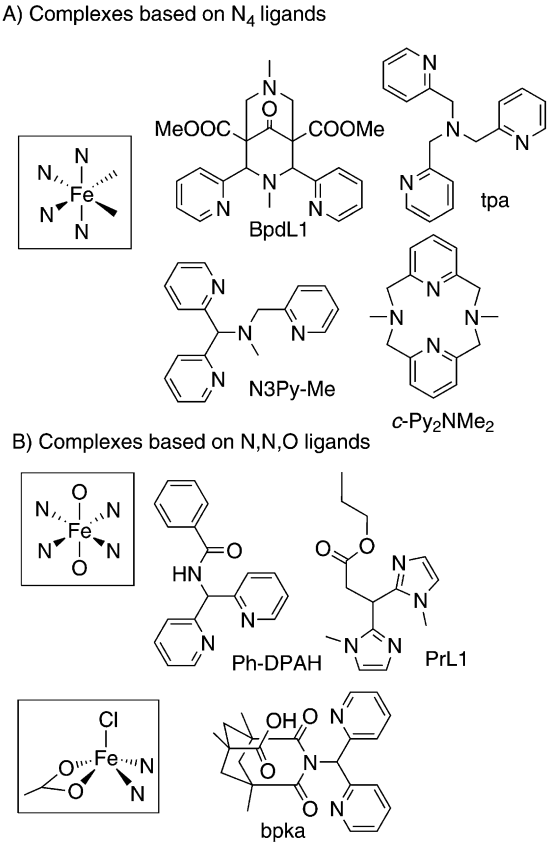
Olefin *cis*-dihydroxylation is an important reaction for organic synthesis because *syn*-diols are very useful synthons for a number of organic transformations. Notably, olefins constitute convenient feedstocks because of their readily availability from petroleum resources.[1,2] *cis*-Dihydroxylation reactions are commonly performed with stoichiometric amounts of MnO_4^-, and heavy metal oxides such as RuO_4 and OsO_4. Particularly reliable in terms of yields and selectivity are methodologies that rely on the latter metal. Outstanding and predictable stereoselectivities and yields can be routinely attained by using well-established *Cinchona* alkaloid ligands.[3,4] However, the toxicity and significant cost of OsO_4 pose serious drawbacks to the practical applicability of these reactions. Because of that, more convenient alternatives are actively pursued. Methodologies that employ catalytic amounts of OsO_4 in combination with sacrificial oxidants have been successfully developed,[5] and less toxic Ru[6–12] and Pd[13–19] catalyst-based methods have been studied, but obviously the most attractive solution will be to discover heavy-metal free reactions.[20–26] Towards this end, organic peroxides have been recently explored with promising results. In addition, a particularly appealing alternative is the development of catalytic methodologies that make use of first-row transition metal catalysts, and convenient oxidants such as peroxides. Along this line, selected Mn complexes have been recently described as highly active *cis*-dihydroxylation catalysts in combination

with H_2O_2 and Oxone.[27–31] Despite their obvious interest, so far these reactions have a rather limited substrate scope, and provide best yields and selectivity in the *cis*-dihydroxylation of electron-deficient olefins. Excellent enantioselectivities have been also very recently obtained in selected cases, by employing Oxone as oxidant.[30]

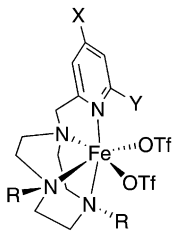
The family of Rieske oxygenases is a versatile group of bacterial iron-dependent enzymes that catalyze a wide array of oxidation reactions,[32–36] but their biotechnological interest remains in their capacity for catalyzing stereo- and enantioselective *cis*-dihydroxylation of arenes and olefins. The activity of these enzymes constitutes a source of inspiration for the development of synthetic methodologies and iron catalysts that are able to mediate the *cis*-dihydroxylation of olefins.[37] Inspired by these enzymes, the ability of iron complexes to catalyze these reactions was first described for the [Fe(II)(tpa)] family of complexes,[38–40] and rapidly extended to a series of iron complexes containing N-based ligands (Scheme 1).[41–44] Iron catalysts which contain ligands that combine N and O donor sites, and that are more closely related to the actual $His_2Carboxylate$-facial triad donor set present in the enzyme,[32,45] have been also explored (Scheme 1).[46–48]

The major drawback of these bioinspired catalysts is that they require the use of a large excess of substrate, and provide very modest turnover numbers (TONs) and substrate conversion. Therefore, an important goal in the field of bioinspired oxidation catalysis remains in the design of catalysts for performing *cis*-dihydroxylation reactions in a more practical manner. Research towards this target has been attempted with tpa-based systems with moderate to good yields and moderate selectivity towards *cis*-dihydroxylation *vs.* epoxidation.[49] In terms of yields and selectivities, state of the art Fe-catalyzed olefin *cis*-dihydroxylations were reported recently by Che and coworkers, who described a chemically robust complex $[Fe(III)(Cl)_2(c\text{-}Py_2NMe_2)]^+$ as an efficient catalyst in combination with Oxone as oxidant (Scheme 1). By using 0.7–3.5 mol% of catalyst loading, and Oxone (2 equivalents) as terminal oxidant, a range of alkenes was oxidized at room temperature with moderate to good yields and high chemoselectivities. Best yields were obtained in the *cis*-dihydroxylation of electron-poor alkenes.[50]

We have previously described a family of iron complexes based on a triazacyclononane ligand, [Fe(II)-$(CF_3SO_3)_2$(^{R,Y,H}PyTACN)] (where R = Me, *i*-Pr, Y = H, Me, **1**, **7**, **10** and **11**, Scheme 2) as models for non-heme iron-dependent oxygenases.[44,51] In the presence of a large excess of substrate with respect to the oxidant (10–100 milliequiv. H_2O_2 per equiv. of substrate) these complexes make an efficient use of the peroxide to mediate alkane and alkene oxidation reactions, suggesting that they are promising candidates to develop bioinspired oxidation catalysts with synthetic value.



Scheme 1. Representation of ligands used to prepared mononuclear iron (II) complexes to perform olefin oxidation. A) Complexes based on N_4 ligands and B) complexes based on N,N,O ligands.



R = CH_3	Y = H	X = H	[Fe(OTf)$_2$(^{Me,H,H}PyTACN)]	**1**
R = CH_3	Y = H	X = CH_3	[Fe(OTf)$_2$(^{Me,H,Me}PyTACN)]	**2**
R = CH_3	Y = H	X = Cl	[Fe(OTf)$_2$(^{Me,H,Cl}PyTACN)]	**3**
R = CH_3	Y = H	X = NO_2	[Fe(OTf)$_2$(^{Me,H,NO2}PyTACN)]	**4**
R = CH_3	Y = H	X = $N(CH_3)_2$	[Fe(OTf)$_2$(^{Me,H,NMe2}PyTACN)]	**5**
R = CH_3	Y = F	X = H	[Fe(OTf)$_2$(^{Me,F,H}PyTACN)]	**6**
R = CH_3	Y = CH_3	X = H	[Fe(OTf)$_2$(^{Me,Me,H}PyTACN)]	**7**
R = CH_3	Y = Cl	X = H	[Fe(OTf)$_2$(^{Me,Cl,H}PyTACN)]	**8**
R = CH_3	Y = CH_3	X = CH_3	[Fe(OTf)$_2$(^{Me,Me,Me}PyTACN)]	**9**
R = *i*-Pr	Y = H	X = H	[Fe(OTf)$_2$(^{iPr,H,H}PyTACN)]	**10**
R = *i*-Pr	Y = CH_3	X = H	[Fe(OTf)$_2$(^{iPr,Me,H}PyTACN)]	**11**

Scheme 2. Family of $[Fe(CF_3SO_3)_2(^{R,Y,X}PyTACN)]$ complexes studied as *cis*-dihydroxylation catalysts.

Herein, we describe the development of the family of [Fe(II)$(CF_3SO_3)_2$(^{Me,Y,X}PyTACN)] (Scheme 2) complexes as catalysts for the *cis*-dihydroxylation of olefins in yields that may be amenable for synthetic purposes, employing H_2O_2 as oxidant.

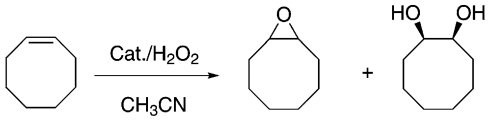
Results and Discussion

Catalyst Screening

Our previous studies with [Fe(II)-$(CF_3SO_3)_2$(^{Me,Y,X}PyTACN)] complexes have shown that N-methyl substituted TACN rings give rise to more active catalysts than those containing N-*i*-Pr substitutions.[44] Further optimization of this family of catalysts was devised by introducing modifications in the positions 4 and 6 of the pyridine ligand. Groups with different electronic properties were inserted in position 4 of the pyridine in order to study putative electronic effects in the catalytic activity. On the other hand, modifications in position 6 were presumed to mainly introduce steric effects, because this position is in close spatial proximity to the *cis*-available coordination sites, initially occupied by labile triflate ligands, and where oxidation of the substrate takes place. Taking these premises into consideration, the series of complexes shown in Scheme 2 was tested as catalysts in olefin oxidation. A first screening was performed by using a large excess of olefin (*cis*-cyclooctene (**S1**), (1 equiv.), and reduced amount of oxidant H_2O_2 (10–100 milliequiv.) added *via* syringe pump (30 min) to an acetonitrile solution of the catalyst (0.1 mol%). These conditions are commonly employed in the literature for iron-catalyzed *cis*-dihydroxylation reactions, and allow a fair comparison with our family of catalysts.[37] Under these conditions, the current set of iron complexes catalyzes the oxidation of the model substrate *cis*-cyclooctene to give a mixture of cyclooctene epoxide (**1E**) and *cis*-1,2-cyclooctanediol (**1D**) (Table 1, Scheme 2). The full family of complexes provides good to excellent conversion of the oxidant into the different olefin oxidation products (50 to 99%). Efficiencies attained by these complexes are among the highest reached with any non-heme iron catalyst under analogous conditions.[37,39–50,52–56]

The results on the catalytic activity of the series of complexes where substitution is introduced at position 4 of the pyridine (**1**–**5**) shows that the chemoselectivity towards epoxidation *vs.* *cis*-dihydroxylation is governed only to a minor extent by electronic effects imposed by the pyridine ring. The simplest catalyst **1** yields an equimolar mixture of epoxide and *syn*-diol. The catalysts with electron-withdrawing groups NO_2 and Cl (**3**, **4**) slightly favour the *cis*-dihydroxylation, while electron-donating groups enhance this selectivity to ratios **D/E** 2.3–2.6 (see catalysts **2** and **5**). These differences are lost at higher peroxide concentrations, and catalysts **1**, **2** and **4**, **5** uniformly provide nearly equimolar mixtures of epoxide and diol. Complex **3** appears to be an exception, showing a slight preference towards *cis*-dihydroxylation. On the other hand, a more substantial increase in the chemoselectivity towards the *syn*-diol product is observed both at low and high peroxide concentrations when the proton in the position 6 of the pyridine ligand is replaced by bulkier groups such as Me (**7** and **9**), or Cl (**8**). Fluorine-substituted complex **6** gives an equimolar mixture of epoxide and *syn*-diol. Most remarkable among the full series of complexes, catalyst **7** exhibited a high chemoselectivity towards the formation of the *syn*-diol product, while retaining a high efficiency in the use of H_2O_2. These results prompted us to investigate conditions where the substrate was the limiting reagent by using complex **7**.

Table 1. Oxidation of *cis*-cyclooctene (**S1**) with H_2O_2 catalyzed by the family of complexes [Fe(II)$(CF_3SO_3)_2$(^{Me,X,Y}PyTACN)].[a]



S1 **1E** **1D**

Catalyst	H_2O_2 (milliequiv.)	(TON)[b]	**1D**+**1E**[c]	**1D/1E**[d]
1	10	8	1.0
	100	99	1.0
2	10	9	2.6
	100	85	1.0
3	10	9	1.5
	100	85	2.1
4	10	8	1.5
	100	50	1.1
5	10	8	2.3
	100	69	1.4
6	10	7	0.8
	100	73	1.0
7	10	7	5.5
	100	86	6.2
8	10	8	2.5
	100	63	4.7
9	10	8	3.6
	100	81	3.5

[a] 1 equiv. of substrate was employed, catalyst concentration 1 mM (0.1 mol%). The reaction was performed by slow syringe pump addition over 30 min, of an acetonitrile solution of H_2O_2 into a solution of catalyst and substrate at room temperature.
[b] TON = turnover number (mol product/mol catalyst).
[c] **1D** stands for *syn*-cyclooctane-1,2-diol, and **1E** for cyclooctene epoxide.
[d] **1D/1E** = mols of diol/mols of epoxide.

Table 2. Oxidation of *cis*-cyclooctene (**S1**) using catalyst **7**: optimization of reaction conditions.[a]

Entry	Cat. (mol%):Oxidant (equiv.):H_2O (equiv.)	**1D** [%]	**1E** [%]	**1D/1E**	Conv[b] [%]	Oxidant
1	3:2:0	24	37	0.6	99	H_2O_2
2	3:1.2:15	42	9	4.7	75	H_2O_2
3	3:1.6:15	47	12	3.9	81	H_2O_2
4	3:2.5:15	46	14	3.3	87	H_2O_2
5	3:2:0	2	64	0.1	>99	H_2O_2/AcOH[c]
6	3:2:0	0	31	–	46	peracetic acid
7	1:2:[d]	0	9	–	13	Oxone
8	3:2:15	0.5	3.5	0.14	35	TBHP
9	3:2:5	31	17	1.9	99	H_2O_2
10	3:2:10	41	13	3.3	99	H_2O_2
11	**3:2:15**	**56**	**15**	**3.6**	**90**	**H_2O_2**
12	3:2:20	28	10	3.3	86	H_2O_2

[a] 1 equiv. refers to substrate, catalyst concentration 1 mM. The reaction was performed by slow syringe pump addition (15 min) of H_2O_2 to a solution of the catalyst (700 mM solution in CH_3CN), the substrate and water when required at 0 °C. Yield obtained by GC.
[b] Conv = substrate conversion.
[c] In the presence of 150 equiv. of acetic acid.
[d] Solvent used MeCN:H_2O (1:1) and the addition of 300 equiv. of $NaHCO_3$.

By employing 3 mol% of catalyst **7**, and 2 equiv. of H_2O_2 with respect to substrate (Table 2), *cis*-cyclooctene was converted into epoxide and diol in a combined 61% yield, with epoxide being the main product (37%). Other oxidants such as peracetic acid, TBHP and Oxone were also tested under analogous conditions, but none of them provided better yields. The combination of H_2O_2 and acetic acid provided the epoxide in 64% yield and only minor amounts of the diol. Because of that, H_2O_2 was retained as the oxidant of choice.

Interestingly, addition of water has a significant beneficial effect on the chemoselectivity of the reaction favouring *syn*-diol formation. When water was added, the ratio [diol]/[epoxide] increased considerably, and the *syn*-diol product **1D** was obtained with good yields (Table 2, entries 9–12). The optimum concentration of water necessary for *cis*-dihydroxylation was screened by using from 5 to 20 equiv. of water. The best catalytic results were obtained when 15 equiv. were used. Under these optimized conditions, *cis*-cyclooctene was oxidized to corresponding *syn*-diol **1D** (56%) and epoxide **1E** (15%).

By using these conditions (Table 2, entry 11), 3 mol% of catalyst, 2 equiv. of H_2O_2 with respect to the substrate, and 15 equiv. of water, in acetonitrile solution, some of the complexes were tested for the oxidation of *cis*-cyclooctene. Catalyst **7** remained as the most efficient for this type of reactions. Moreover, this screening confirmed our initial hypothesis that the only complexes that provide high chemoselectivity towards *cis*-dihydroxylation are those that have a bulky group in the 6 position of the pyridine; complexes **8** and **9** give moderate yields 57–64%, and chemoselectivity towards *syn*-diol as shown by diol/epoxide ratios of 3.4 and 3.3, respectively. On the other hand, complexes **1**, **3** and **6** give comparable or slightly inferior yields, (46–60%), but low diol/epoxide ratios (0.4–0.6) (Table 3).

Table 3. Oxidation of *cis*-cyclooctene (**S1**) applying different catalysts.[a]

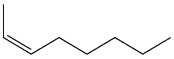
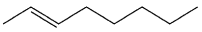
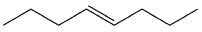
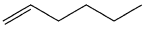
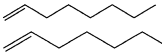
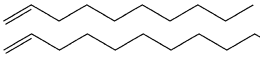
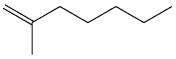
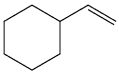
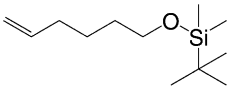
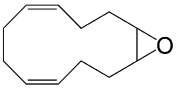
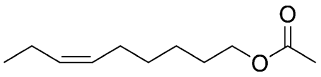
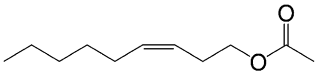
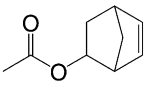
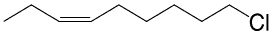
Catalyst	Yield **1D**+**1E** [%]	**1D/1E**	Conversion [%]
1	46	0.56	99
3	56	0.42	99
6	60	0.42	95
7	**71**	**3.6**	**90**
8	57	3.4	95
9	64	3.3	91

[a] All reactions were performed using 3 mol% of catalyst, 1 equiv. of substrate, 2 equiv. of H_2O_2 and 15 equiv. of water. Yield obtained by GC.

Substrate Scope

Next, the substrate scope of the catalytic *cis*-dihydroxylation was investigated under the optimized conditions in the presence of complex **7**. Best yields were obtained when terminal or *cis* aliphatic olefins were used as substrates (Table 4, substrates **S1**, **S2**, **S5**–**S8**). In these cases the *syn*-diol product was obtained in 25–56% yield, and diol/epoxide ratios range from 1.8 to 3.6. On the other hand, when the system was applied in the oxidation of *trans* olefins such as *trans*-2-octene (**S3**), *trans*-4-octene (**S4**), and the 1,1-disubstituted olefin 2-methyl-heptene (**S9**), the epoxide product was obtained preferentially. Noteworthy, besides epoxide and diol, 2-hydroxy ketone products were also identified as oxidation products in some of the reactions. The latter products are most likely originat-

Table 4. Substrate scope.[a]

Substrate		Conversion	Yield [%]		D/E	Yield [%]
			D	**E**		
	**S1**	94[b]	56	15	3.6	71
	**S2**	92[b]	56	26	2.2	82
	**S3**	80	9	25	0.4	34
	**S4**	66	4	17	0.2	21
	**S5**	85	35	20	1.8	55
	**S6**	68	37	14	2.6	51
	**S7**	56	35	12	2.9	47
	S8	51	33	12	2.8	46
	**S9**	66	7	39	0.2	49
	**S10**	68	21	21	1	42
	**S11**	-.	22	26	0.9	48
	**S12**	75[c]	25	13	1.8	38
	**S13**	77	31; 25[d]	9; 3[d]	3.4	40
	**S14**	89	43	23	2.0	66
	**S15**	80	34	22	1.5	56
	**S16**	80	9	35	0.3	44
	**S17**	76	38; 38[d]	22; 22[d]	1.7	60

[a] 1 equiv. of substrate, 3 mol% catalyst (1 mM). The reaction was performed by slow syringe pump addition (15 min) of 2 equiv. of H_2O_2 (700 mM solution in CH_3CN) to a solution of the catalyst, the substrate and 15 equiv. of H_2O at 0 °C.
[b] Hydroxy ketone yields for substrates *cis*-cyclooctene (**S1**) and *cis*-2-octene (**S2**) are 6% and 5%, respectively; in the other cases are $<5\%$.
[c] Alcohol product resulting from deprotection is obtained in 20% yield.
[d] Isolated yields.

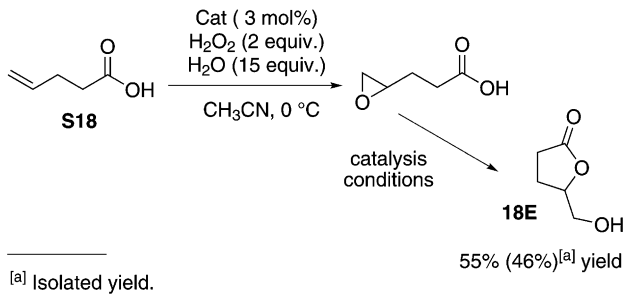
ing from overoxidation of the originally formed *syn*-diol. On the other hand, aromatic olefins are not suitable substrates for the system. Oxidation of *cis*-β-methylstyrene gives a mixture of products, and the same occurs when an aromatic enone such as methyl cinnamate was employed as substrate. The latter substrate is oxidized very efficiently and selectively by the $[Fe(III)(Cl)_2(c\text{-}Py_2NMe_2)]^+$ system recently described by Che et al.[50] Moreover, this catalyst can oxidize the diester dimethyl fumarate giving 99% of *syn*-diol product, but our catalyst **7** is not capable of oxidizing this olefin, presumably because it is deactivated by the two ester groups. Because of this different catalytic behaviour it is very likely that both systems differ fundamentally in the nature of the active oxidation species involved. In the case of the $[Fe(III)(Cl)_2(c\text{-}Py_2NMe_2)]^+$ complex, a *cis*-Fe(V)(O)(OH) and/or *cis*-$Fe(V)(O)_2$ is proposed to be the active catalytic species.[50] The oxidizing species proposed for catalyst **7** on the basis of isotopic labelling analysis is described as Fe(V)(O)(OH).[44] At present it is not possible to ascertain the basis for the distinct electronic preference exhibited by both species. On the other hand, precedents for electrophilic and nucleophilic preferences in iron-based *cis*-dihydroxylation catalysis has been previously documented for the Fe(TPA) family of complexes, suggesting that they may arise from distinct spin states.[57]

Functional groups are tolerated to a different extent. Olefins containing epoxide (**S13**) and siloxane

(**S12**) functionalities are oxidized towards the corresponding *syn*-diol in yields close to 30%. When the olefin substrate contains an ester moiety, the yields depend on the distance between the olefin and the ester group. Moderate yields (approx 45%) are obtained when the olefin is distant to the ester group (**S14**), but drops to 34% as the ester is closer to the olefinic sites (**S15**). Nevertheless, chemoselectivity towards *cis*-dihydroxylation appears to be highly dependent on the nature of the substrate; norbornene-2-yl acetate (**S16**) is oxidized with a poor chemoselectivity towards the diol, yielding a low **D/E** ratio (Table 4). A halide moiety is reasonably tolerated, hence 1-chloro-*cis*-non-9-ene (**S17**) was oxidized in 59% combined yield (38% diol and 22% epoxide). Terminal olefins in linear alkenes afford relatively good yields of *cis*-diol. The possibility that part of this diol will originate from epoxide ring opening was therefore investigated. When 1,2-octene epoxide was submitted to catalytic conditions, catalyst:epoxide:H_2O_2:H_2O (3:100:200:150), the epoxide product was recovered in 80% yield and no formation of *syn*-diol product was observed. Because of that we concluded that the diol also comes exclusively from a *cis*-dihydroxylation reaction for these classes of substrates.

A cautious note is that the mass balance shows substantial losses in some of the reactions. In the case of the most volatile olefins, this may be an important contributing factor, but in the case of substrates such as 1-*tert*-butyldimethylsilyloxy-5-hexene (**S12**) and 1,5-cyclododecadiene-9,10-oxide (**S13**), mass loss is indicative of important, unidentified side reactions. Indeed GC-MS analysis of crude reaction mixtures revealed the presence of multiple oxidation products in small amounts, preventing proper characterization.

Carboxylic acids are not compatible with the *cis*-dihydroxylation activity of a terminal olefin. In the oxidation of the pentanoic acid (**S18**), as observed in the presence of acetic acid, the formation of the *syn*-diol product was precluded, and the oxidation was diverged towards formation of the epoxide, which under the catalytic conditions provided the corresponding lactone 5-(hydroxymethyl)dihydrofuran-2(3*H*)-one (**18E**), in 55% yield (Scheme 3).



[a] Isolated yield.

Scheme 3. Catalytic oxidation of 3-pentenoic acid (**S18**).

cis- and *trans*-olefins behave quite differently in these catalytic reactions. Hence, further information to explain this difference was sought by means of competition experiments. Competitive oxidation of an equimolar mixture of *cis*-2-octene (**S2**) and *trans*-2-octene (**S3**) led to quantitative conversion of the *cis*-isomer, while 50% of the *trans*-isomer remained unreacted. Moreover, *cis*-2-octene oxidation occurred preferentially towards the diol product (**2D**) (diol/epoxide ratio = 3), while *trans*-2-octene oxidation afforded only minor amounts of the diol (**3D**) (4%). The reaction exhibited a poor mass balance, and epoxide (**3E**) was obtained in modest 14% yield (Scheme 4, A).

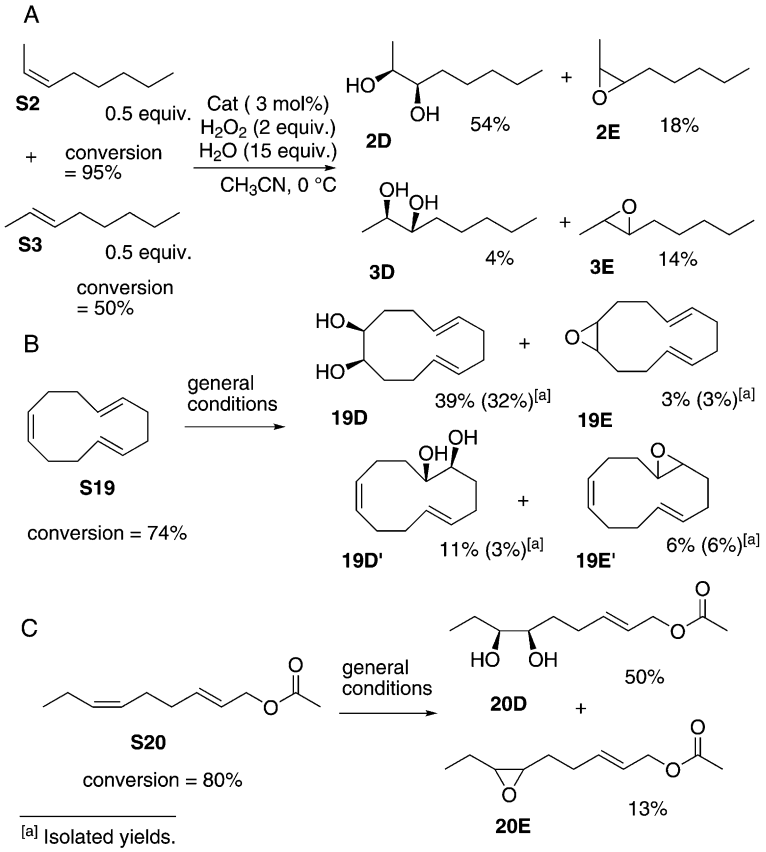
A second competitive experiment was performed with the substrate *trans-trans-cis*-1,5,9-cyclododecatriene (**S19**) where *trans*- and *cis*-olefin sites are present in the same substrate in a relative 2:1 ratio. *cis*-Dihydroxylation took place preferably in the *cis*-olefin, giving a 39% of the *syn*-diol product (**19D**), and only 11% of *syn*-diol resulting from *cis*-dihydroxylation at the *trans*-olefin site (**19D′**). However, the epoxidation occurred with similar relative reactivity. Interestingly, oxidation of this substrate gave an excellent overall ratio diol/epoxide = 5 (Scheme 4, B).

Oxidation of (2*E*,6*Z*)-nona-2,6-dienyl acetate (**S20**) further underlines the preference of the catalyst to oxidize *cis*-double bounds. In this case we also have to take into account that the *trans*-olefin is deactivated because of the proximity to the electron-withdrawing acetate group. The corresponding *syn*-diol resulting from selective *cis*-dihydroxylation at the remote *cis*-site was obtained in 50% yield (**20D**), along with 13% of the corresponding epoxide (**20E**). Products arising from oxidation of the proximal *trans*-olefinic site were not formed (Scheme 4, C).

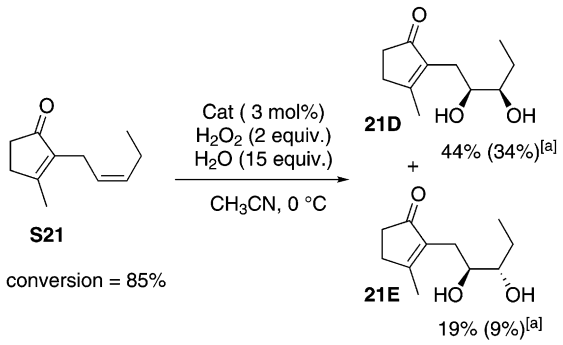
An interesting target for selective *cis*-dihydroxylation represents the natural product *cis*-jasmone (**S21**), which was oxidized in relatively good yield (**21D**) (44%). In this case, the side product obtained was the *anti*-diol 19% (**21E**), originating from the opening of the epoxide ring during work-up (Scheme 5).

Time Course Analysis

The selectivity towards the *syn*-diol product in reactions where the substrate is the limiting reagent is substantially smaller than that obtained with small amounts of H_2O_2 and large excess of substrate. To shed light onto this difference, a time course analysis of the oxidation of *cis*-cyclooctene was performed. The study shows that the *syn*-diol is formed with very high selectivity within the first 20 min of the reaction (Table 5). In this period, epoxide is obtained in minor amounts and *syn*-diol/epoxide ratios are high (6.5–8.3), comparable to the ratios observed under condi-



Scheme 4. Competitive oxidation experiments. Yields obtained by GC.



Scheme 5. Catalytic oxidation of *cis*-jasmone (**S21**).

Table 5. Time course analysis using *cis*-cyclooctene.[a]

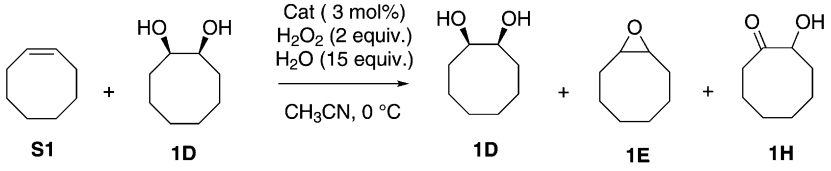
Time (min)	**1D** [%]	**1E** [%]	**1D**/**1E**
10	25	3	8.3
20	47	7	6.5
30	51	16	3.2

[a] 1 equiv. of *cis*-cyclooctene, catalyst concentration 1 mM and oxidant concentration 700 mM. The reaction was performed by slow syringe pump addition (30 min) of H_2O_2 to a solution of the catalyst and the substrate at room temperature. Samples were taken every 10 min.

tions of limiting amounts of H_2O_2. After 30 min, the reaction slowed down and the epoxidation reaction became more important, erasing the **1D**/**1E** ratio.

Based on these observations, we assume that *syn*-diol products can reversibly bind to the iron site, because of the formation of a five-membered chelate iron glycolate (or hydrogen glycolate species). Previous studies have shown that two *cis*-labile sites are required for Fe-catalyzed efficient *cis*-dihydroxylation reactivity. In agreement with this an increased concentration of *cis*-diol would then block the iron site, shutting down the *cis*-dihydroxylation reactivity. In favour of this interpretation, product release appears also to be the rate-determining step in the catalytic cycle of naphthalene dioxygenase, an enzyme of the Rieske oxygenase family that catalyzes the *cis*-dihydroxylation of naphthalene.[58] In our catalytic system, the excess of H_2O_2 in the absence of two available *cis* sites at the iron catalyst may lead to epoxidation reactions, for which multiple paths may exist,[39,56] but also results in oxidation of the metal-bound diol towards the corresponding 2-hydroxy ketone. In order to test this idea, we performed the oxidation of *cis*-cyclooctene (**S1**) in the presence of different amounts of *syn*-

Table 6. Catalytic oxidation of *cis*-cyclooctene **S1** in the presence of different equivalents of *syn*-cyclooctane-1,2-diol.[a]



Olefin [equiv.]:*syn*-diol [equiv.]	**1D**[b] [%]	**1E** [%]	**1H** [%]	**1D/1E**
1:0	56	15	6	3.6
0.7:0.3	37	18	12	2
0.5:0.5	0	22	29	–

[a] The reaction was performed by slow syringe pump addition (15 min) of H_2O_2 to a solution of the catalyst, the substrate and *syn*-diol at 0 °C.

[b] Difference yield of *syn*-diol expressed as the difference $\Delta[\mathbf{1D}] = [\mathbf{1D}]_{\text{after reaction}} - Y[\mathbf{1D}]_0$.

cyclooctane-1,2-diol **1D** (Table 6). Indeed, when a mixture of 70 equiv. of *cis*-cyclooctene and 30 equiv of the *syn*-diol **1D** was subjected to standard oxidation conditions, only a minor increase of the *syn*-diol was observed (37%) but epoxide **1E** and 2-hydroxy ketone **1H** products were formed in larger amount (18 and 12%, respectively). Even more revealing was the oxidation of an equimolar mixture of *cis*-cyclooctene (**S1**) and *syn*-diol **1D**. The reaction resulted in no further increase in the concentration of diol, but epoxide **1E** and hydroxy ketone **1H** products were formed in 22 and 29% relative yields. In conclusion, product release from the ferric glycolate species represents most likely the rate-determining step of the reactions. Interestingly, this interpretation also offers a reasonable interpretation for the beneficial role of water in the chemoselectivity towards the *cis*-dihydroxylation reaction. Water may enhance product release by favouring the hydrolytic cleavage of the ferric glycolate species, thus disfavouring epoxidation and diol-bound over-oxidation paths. Based on this conclusion, we had the idea to improve the *cis*-dihydroxylation by removing the *syn*-diol from the reaction mixture.

Iterative Catalytic Oxidation

To our delight, an improved methodology in terms of product yields and selectivity could be derived by performing the oxidation reaction at substoichiometric conversion levels, and separating the diol product from the reaction mixture. After the first peroxide addition, the catalytic solution was loaded onto a silica gel column, and the *syn*-diol product was removed from the solution. The recovered substrate was subjected to a second addition of catalyst and H_2O_2. This allows us to substantially increase the product yields and in some cases also to improve the ratio of diol/epoxide (Table 7).

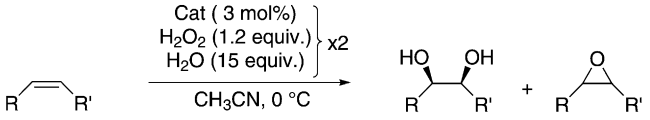
Under these conditions, aliphatic olefins are oxidized towards the corresponding *cis*-diols in improved yields ranging from 19 to 60% and diol/epoxide ratios between 1 and 6.7. To the best of our knowledge for all the substrates collected in Table 7, these numbers represent the most efficient iron-based system in terms of *syn*-diol product yield described to date.

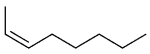
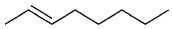
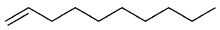
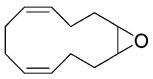
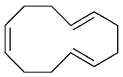
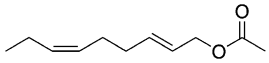
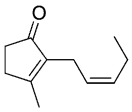
Conclusions

The present work describes an active and selective iron catalyst that performs the *cis*-dihydroxylation of aliphatic olefins in yields that become interesting for synthetic purposes simply by using H_2O_2 as green oxidant. The selectivity towards *syn*-diol product obtained with our catalyst is determined by the nature of the alkene. Best yields and selectivities are obtained when *cis*-olefins are oxidized. On the other hand, *trans*-olefins are oxidized with comparable epoxide:diol ratios. Notably, small differences among the structures of the active iron complexes can dramatically change the selectivity of the oxidations. Pure electronic modifications in the electron-donating nature of the PyTACN ligand result in catalysts exhibiting quite similar chemoselectivities in olefin oxidation. On the other hand, the introduction of a bulky group at position 6 of the pyridine reverses the selectivity towards the preferential formation of the *syn*-diol product.

For aliphatic substrates, reaction yields attained with the present system compare favourably with those of state of the art Fe-catalyzed *cis*-dihydroxylation systems, and because of that it can be regarded as an attractive complement. That is not the case for electron-deficient and aromatic olefins, which are most conveniently oxidized with the highly active systems recently described by Che.[50] This somewhat different substrate scope is surprising given the similarities of the first coordination sphere FeN_4 of both cata-

Table 7. Catalysis using two iterative catalytic oxidations.



Substrate		Conversion	Yield [%]		D/E	Yield [%]
			D	E		
	**S1**[a]	96	60	11	5.7	71
	S6[a]	73	53	20	2.7	73
	**S2**[a]	98	56	26	2.2	82
	**S3**[a]	69	19	19	1	38
	**S7**[a]	75	40	16	2.6	56
	**S13**[b]	94	33	5[a]	–	38
	**S19**[b]	96	53	21	2.5	73
	**S20**[b]	88	56	17	3.3	73
	**S21**[b]	90	45	7[c]	6.7	52

[a] GC yield.
[b] Isolated yields.
[c] *trans*-Diol product originated from the ring opening of the epoxide product.

lysts, but at the same time it hints at the possibility of developing novel catalysts with alternative substrate scope. Efforts towards this goal are currently being undertaken in our laboratory.

Experimental Section

Typical Catalytic Oxidation Procedure

A 15-mL vial was charged with catalyst (1.5 μmol, 3 mol%), alkene (50 μmol, 1 equiv.), CH_3CN (1.5 mL) and a magnetic stir bar. The vial was placed on an ice bath and stirred. 13.5 μL of water were added (750 μmol, 1500 mol%) and 143 μL of a 700 mM (100 μmol, 2 equiv.) H_2O_2 solution (diluted in acetonitrile from a 35% H_2O_2 aqueous solution) were delivered by syringe pump over 15 min at 0 °C. After syringe pump addition, the solution was stirred for 30 min at 0 °C.

An internal standard was added at this point. The iron complex was removed by passing the solution through a short path of silica followed by elution with 2 mL of AcOEt. Finally, the solution was subjected to GC analysis.

Full experimental details of iterative addition protocol and products characterization are collected in the Supporting Information.

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