Non-Heme Iron Complexes for Stereoselective Oxidation: Tuning of the Selectivity in Dihydroxylation Using Different Solvents

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A new class of functional models for non-heme iron-based dioxygenases, including $[(N3Py\text{-}Me)Fe(CH_3CN)_2](ClO_4)_2$ and $[(N3Py\text{-}Bn)Fe(CH_3CN)_2](ClO_4)_2$ {N3Py-Me = [di(2-pyridyl)methyl]methyl(2-pyridyl)methylamine; N3Py-Bn = [di(2-pyridyl)methyl]benzyl(2-pyridyl)methylamine}, is presented here. NMR, UV and X-ray analyses revealed that six-coordinate low-spin Fe^{II} complexes with the pyridine N-atoms and the tertiary amine functionality of the ligand bound to Fe are formed. The two remaining coordination sites located *cis* to each other are occupied by labile CH_3CN groups that are easily exchanged by other ligands. We demonstrate that the reactivity and stereoselectivity of the complexes investigated depend on the choice of the solvent. The complexes have been examined as catalysts for the oxidation of both alkanes and olefins in CH_3CN. In this solvent alkanes are oxidized to alcohols and ketones and olefins to the corresponding *cis*-epoxides and *cis*-diols. In acetone as solvent a different reactivity pattern was found, with, as the most striking example, the *trans*-dihydroxylation of cis-olefins. ^{18}O-labeling studies in CH_3CN establish incorporation of ^{18}O from $H_2{}^{18}O_2$ and $H_2{}^{18}O$ in both the epoxide and the diol implicating an HO-Fe^{V}=^{18}O active intermediate originating from an $H_2{}^{18}O$-Fe^{III}OOH species. These results are in full agreement with mechanistic schemes derived for other dioxygenase model systems. Based on labeling studies in acetone an additional oxidation mechanism is proposed for this solvent, in which the solvent acetone is involved. This is the first example of a catalyst that can give *cis*- or *trans*-dihydroxylation products, just by changing the solvent.

Introduction

The catalytic oxidation of hydrocarbons using green oxidants like hydrogen peroxide or dioxygen is a topic of considerable interest.[1] Even though significant progress has been made, in particular with regard to epoxidation of alkenes using H_2O_2,[2−5] many challenges still remain. Among others, the hydroxylation of alkanes and the dihydroxylation of alkenes are highly interesting reactions from a synthetic point of view.

In nature an impressive variety of enzymes capable of performing these reactions with high selectivity under mild conditions exists. An important subset of this class of enzymes are the non-heme iron oxygenases, like, for example, methane monooxygenase,[6] which selectively oxidizes methane to methanol, the Rieske dioxygenases,[7,8] which are capable of stereospecifically dihydroxylating arenes, and iron-bleomycin, a metallo-glycopeptide that is capable of oxidative DNA cleavage,[9] but which can also oxidize a wide variety of organic substrates.[10]

The study of synthetic complexes that model the active site of these enzymes has been an important tool in the study of their functions. Some of these model complexes have proven to be very promising catalysts for the selective oxidation of organic substrates using H_2O_2 as the terminal oxidant. Stereoselective hydroxylation[11−14] epoxidation[4,14−16] and *cis*-dihydroxylation,[17−20] a reaction previously only available using osmium-,[21] ruthenium-[22] and manganese-based[23] catalysts, have been reported. Recently, even the first examples of enantioselective dihydroxylation have appeared in the literature.[24]

Recent studies have shed some light on the mechanism of these oxidation reactions. In the case of $[Fe(TPA)(CH_3CN)_2](ClO_4)_2$, a representative member of this class of catalysts, a strong and compelling case has been built in favor of the involvement of a formally HO-Fe^{V}O species that is formed by heterolysis of the O−O bond of a low spin Fe^{III}OOH intermediate.[13,20,25] This HO-Fe^{V}O species is postulated to be the active species responsible for the formation of both the epoxide and the *cis*-diol. The latter product is thought to be formed via a cyclic intermediate similar to reactions with $KMnO_4$.[15]

We have previously reported on the $[Fe(N4Py)(CH_3CN)](ClO_4)_2$ complex, which contains a pentadentate N ligand and reacts with H_2O_2 to form a well-defined and well-

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characterized $Fe^{III}OOH$ intermediate.[26−28] This intermediate was demonstrated to have an unusually weak O−O bond,[29,30] which is thought to be the reason for its high activity as an oxidation catalyst. Reactivity studies using a broad spectrum of mechanistic probes revealed that radical-type oxidizing species are involved and, consequently, a mechanism involving homolysis of the $Fe^{III}OOH$ species to give $Fe^{IV}O$ and ·OH was proposed.[31] This notion was later supported by calculations, which indeed showed homolysis to be the favored reaction pathway.[32] A strong effect of the solvent was observed. In acetone higher kinetic isotope effect (KIE) values of cyclohexane oxidation and higher C3/C2 ratios in adamantane oxidation were found compared to acetonitrile. This was attributed to the ability of acetone to act as an ·OH trap.

Following the TPA precedent we decided to redesign the N4Py ligand into a tetradentate ligand in order to obtain iron complexes capable of stereoselective oxidation. In this paper we present a new class of iron complexes with tetradentate ligands based on N4Py, in which one of the picolyl groups is replaced with a non-coordinating moiety like a methyl or a benzyl group (Figure 1). The properties of the corresponding iron complexes and their application as catalysts in oxidation reactions with H_2O_2 will be discussed, with particular emphasis on the effect of the solvent used, i.e. acetonitrile or acetone.

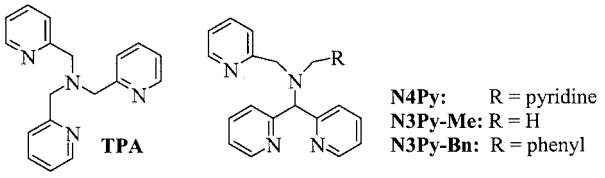


Figure 1. Ligands used for stereoselective epoxidation and *cis*-dihydroxylation of alkenes

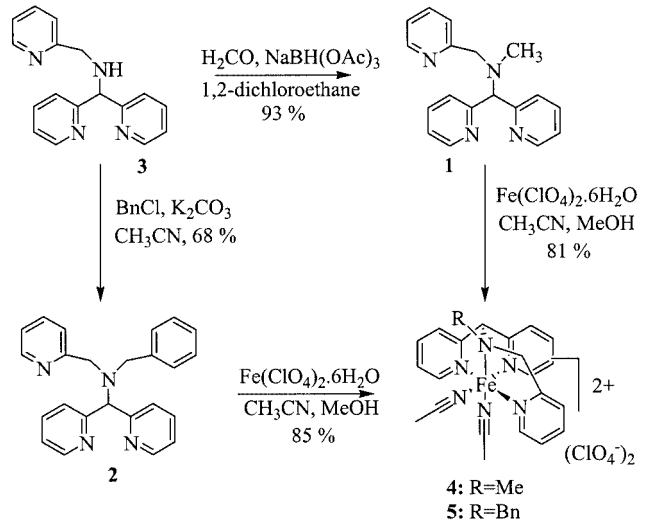
Results and Discussion

Synthesis and Properties of Iron Complexes

Ligands **1** and **2** were prepared from a common precursor, N3Py (**3**).[33] N3Py-Me was obtained in high yield by reductive amination with formaldehyde and $NaBH(OAc)_3$ (Scheme 1).[34] N3Py-Bn was prepared by alkylation of N3Py with benzyl chloride in the presence of K_2CO_3.

Complexation of the ligands **1** and **2** with $Fe(ClO_4)_2·6H_2O$ in methanol/acetonitrile resulted in the formation of red crystals, characterized as $[(N3Py\text{-}R)Fe(CH_3CN)_2](ClO_4)_2$, based on ^1H NMR and ES/MS analysis and confirmed by X-ray analysis for this complex with an *N*-methyl substituent (Figure 2).

The six-coordinate Fe^{II} center has a distorted octahedral geometry, with the iron bound to the three pyridine N atoms, the tertiary amine functionality of the ligand and two acetonitrile molecules, originating from the solvent used for crystallization. The open coordination sites, where acetonitrile molecules are bound, are located *cis* with respect to each other, as was expected. The $Fe-N_{ligand}$ distances vary from 1.909(8) Å for Fe1−N5 to 1.965(9) Å for Fe1−N3. These distances are similar to those found for other low-spin iron(II) complexes like $[(N4Py)Fe(CH_3CN)](ClO_4)_2$,[19] and $[(TPA)Fe(CH_3CN)_2](ClO_4)_2$.[35]



Scheme 1. Synthesis of ligands **1** and **2** and the corresponding iron(II) complexes **4** and **5**

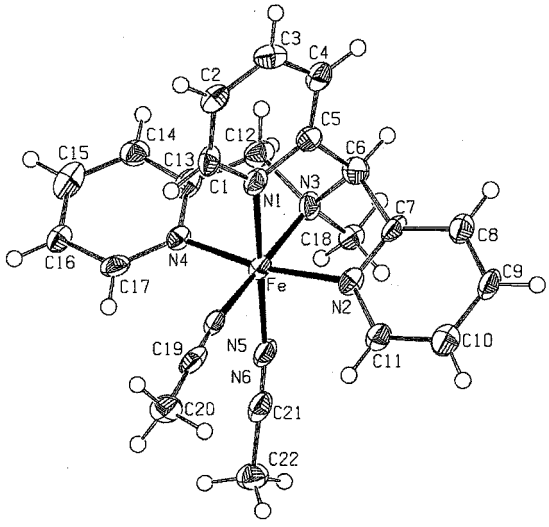


Figure 2. ORTEP plot of the cation of **4**

The ^1H NMR spectra in CD_3CN exhibit signals between $\delta = 0$ and 15 ppm, typical of a low-spin iron(II) complex. However, in contrast to the spectra of other low-spin iron(II) complexes like $[(TPA)Fe(CH_3CN)_2](ClO_4)_2$ and $[(N4Py)Fe(CH_3CN)_2](ClO_4)_2$,[28,35] which show very sharp signals, significant line broadening was observed for some of the signals of **4** and **5**. An example is the spectrum of **4** shown in Figure 3A. The line broadening is probably due to an equilibrium between the low-spin Fe^{II} bis-acetonitrile complex $[(N3Py\text{-}R)Fe(CH_3CN)_2]^{2+}$ and the paramagnetic high-spin Fe^{II} mono-acetonitrile complex $[(N3Py\text{-}R)Fe(CH_3CN)]^{2+}$, i.e. a reversible dissociation of one of the labile CH_3CN ligands. This was confirmed by the ^1H NMR

spectrum in [D_6]acetone, in which dissociation of acetonitrile is irreversible and results in signals in the δ = 0−180 ppm range, characteristic for a high-spin Fe^{II} complex (Figure 3B).[28] A similar solvent effect was found in the UV/Vis spectra of **4** in CH_3CN and acetone. In CH_3CN **4** exhibits a UV/Vis spectrum with absorption peaks at 352 ($\varepsilon = 5.3 \times 10^3$ $M^{-1}cm^{-1}$) and 428 nm ($\varepsilon = 4.3 \times 10^3$ $M^{-1}cm^{-1}$), whereas in acetone the complex exhibits an absorption peak at 331 nm ($\varepsilon = 4.2 \times 10^3$ $M^{-1}cm^{-1}$) with shoulders at 459 ($\varepsilon = 3.2 \times 10^2$ $M^{-1}cm^{-1}$) and 506 nm ($\varepsilon = 2.2 \times 10^2$ $M^{-1}cm^{-1}$), suggesting the formation of a different species in acetone.

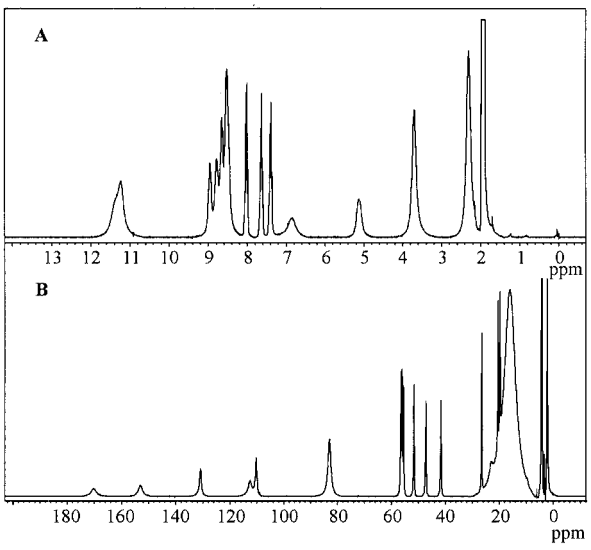


Figure 3. ^1H NMR spectrum of **4** (a) in CD_3CN and (b) in [D_6]-acetone

Cyclic voltammetry of **4** and **5** in CH_3CN showed one single quasi-reversible redox wave for the Fe^{II}/Fe^{III} couple at $E_{1/2}$ = 1180 mV (ΔE = 100 mV; i_a/i_p = 0.95) and 1200 mV vs. SCE (ΔE = 160 mV; i_a/i_p = 0.98), respectively. These values are significantly higher than those found for [(N4Py)Fe(CH_3CN)](ClO_4)$_2$ ($E_{1/2}$ = 1010 mV vs. SCE).[27] Apparently, in acetonitrile the low-spin iron(II) state is even more favored in the case of bis-acetonitrile complexes like **4** than mono-acetonitrile complexes like [(N4Py)-Fe(CH_3CN)](ClO_4)$_2$.

In acetone as solvent a different redox behaviour was observed for **4** (Figure 4). At a scan rate of 50 mV/s an oxidation wave was found at 1150 mV vs. SCE accompanied by a small reduction wave at 940 mV (i_a/i_p = 0.35) and a strong reduction wave at 350 mV vs. SCE. Increase of the scan rate leads to an increase of the reduction wave at 940 mV (i_a/i_p = 0.44 at 100 mV/s; i_a/i_p = 0.58 at 500 mV/s). When 600 mV vs. SCE was used as the vertex potential, i.e. without going through the oxidation at 1150 mV, no reduction wave was observed at 350 mV (Figure 4d). These results indicate that oxidation of the complex in acetone leads to an unstable species that decomposes to give a new species with a reduction potential at 350 mV.

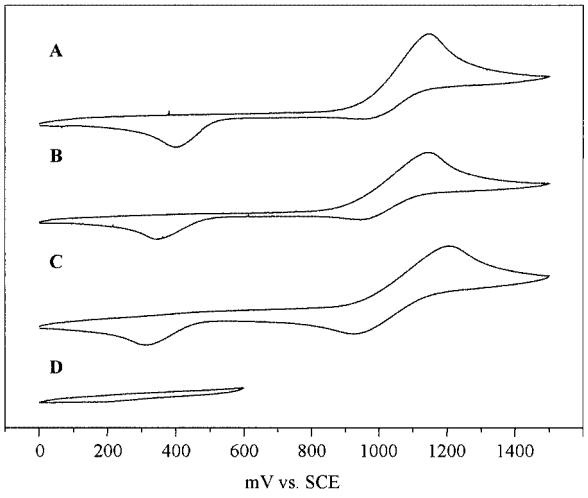
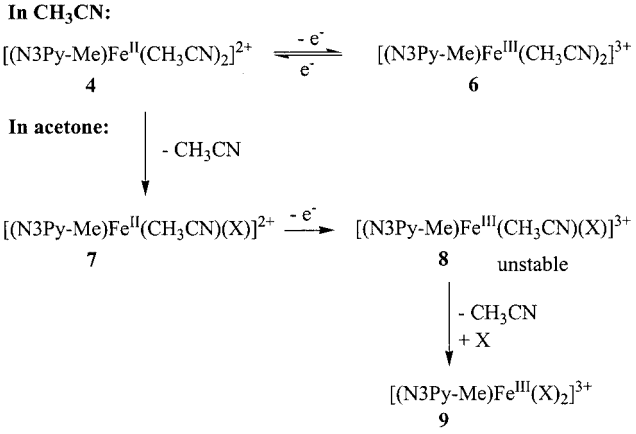


Figure 4. Cyclic voltammogram of 4 in acetone: (a) scan rate 50 mV/s; (b) Scan rate 100 mV/s; (c) scan rate 500 mV/s; (d) 600 mV used as vertex potential

Combined with the NMR spectroscopic data the results can be rationalized in the following manner (Scheme 2). In acetone loss of a labile acetonitrile ligand can occur affording **7**, which is assumed to have a redox potential of 940 mV. Oxidation of this complex will lead to the formation of the unstable mono-acetonitrile iron(III) complex **8**. Loss of the final acetonitrile ligand will result in the formation of an $[(N3Py\text{-}Me)Fe(X)]^{3+}$ species **9**, in which X can be acetone or water. This species will exhibit a different electrochemical behavior, presumably giving rise to the reduction wave at 350 mV.



Scheme 2. Redox behavior of **4** in CH_3CN and acetone

Catalytic Oxidation with N3Py Iron Complexes

Complexes **4** and **5** were tested in catalytic oxidations of both alkanes and alkenes. The results are summarized in Table 1 and 2. In view of the different properties of the complexes in acetone and acetonitrile (vide supra), combined with the fact that it is known from catalytic oxidation with [(N4Py)Fe(CH_3CN)](ClO_4)$_2$ that the solvent can have a pronounced effect on the observed reactivity and selectivity,[31] both solvents were employed in catalytic oxidation.

Table 1. Oxidation of alkanes by **4** and **5**; reactions performed under argon

Entry	Substrate	Products	Acetonitrile[a]		Acetone[a]	
			4	**5**	**4**	**5**
1	cyclohexane	cyclohexanol	7.9	8.1	8.8	5.7
		cyclohexanone	1.7	1.4	2.0	1.5
		A/K	4.6	5.8	4.4	3.8
2[b]	*cis*-1,2-dimethylcyclohexane	*trans*-1,2-dimethylcyclohexanol	2.3	2.7	4.8	4.1
		cis-1,2-dimethylcylcohexanol	0.4	0.6	1.8	1.9
		stereoselectivity (%)	85	73	82	68
3[b]	*trans*-1,2-dimethylcylohexane	*trans*-1,2-dimethylcyclohexanol	0.4	0.3	1.6	1.1
		cis-1,2-dimethylcylcohexanol	1.1	0.6	1.5	1.1
		stereoselectivity (%)	73	48	50	50
4	adamantane	1-adamantanol	13.1		13.3	
		2-adamantanol	2.5		1.1	
		2-adamantanone	1.3		0.5	
		tertiary/secondary	10.3		24.9	

[a] Turnover number = mol product/mol catalyst. [b] Secondary alcohols and ketones not quantified.

Table 2. Oxidation of alkenes by **4** and **5** with 50 equiv. H_2O_2; reactions carried out under air, unless noted otherwise

Entry	Complex	Substrate	Acetonitrile[a][b]				Acetone[a][c]			
			cis-epoxide	*trans*-epoxide	*meso*-diol	*rac*-diol	*cis*-epoxide	*trans*-epoxide	*meso*-diol	*rac*-diol
1	**4**	cyclooctene	14	–	22	1	17	–	0.2	4
2	**5**	cyclooctene	16	–	14	0	19	–	3	10
3	**4**	cyclohexene[d][e]	11[f]	–	13	0.7	0.8	–	0	2.4
4	**4**	*c*-stilbene	9[g]	0.7	8	0.6	7	3	6	7
		stereoselectivity (%)	93		93		70			54
5	**4**	*t*-stilbene	0[h]	8	0.5	7	0	6	11	3
		stereoselectivity (%)		>99		93		>99	79	
6	**4**	*c*-4-octene	19	1	17	1	11	3	0	1
		stereoselectivity (%)	95		94		79			>99
7	**4**	*t*-4-octene	2	4	1	1	2	6	1	1
		stereoselectivity (%)		67		50		75	50	
8	**4**	norbornene	36	–	*exo* 2 *endo* 1	2	2	–	*exo* 0 *endo* 1	43

[a] Turnover number = mol product/mol catalyst. [b] Reaction time 60 min. [c] Reaction time 30 min. [d] Reactions carried out under argon. [e] In acetone many other products were found, which were not identified. [f] 28 turnovers towards cyclohexenol and 7 turnovers towards cyclohexenone were observed. [g] 11 turnovers towards benzaldehyde were observed. [h] 13 turnovers towards benzaldehyde were observed.

Reactions were carried out under air, except in the case of substrates that are prone to undergo autoxidation in the presence of O_2, and an excess of substrate (1000 equiv.) was used to maximize turnover numbers. Hydrogen peroxide (50 equiv.) was introduced into the reaction mixture at 25 °C by syringe pump to reduce the loss of hydrogen peroxide due to catalase activity. Typical addition times are 60 and 30 min for acetonitrile and acetone, respectively. After the addition of H_2O_2 was complete the reaction mixture was stirred for another 5 min before a sample was taken and analyzed by GC.

Oxidation of Alkanes

Complexes **4** and **5** show a fair activity in the oxidation of cyclohexane in CH_3CN, with yields up to 19% based on hydrogen peroxide for complex **4** (Table 1, entry 1). These yields are slightly lower than those observed for $[(N4Py)Fe(CH_3CN)](ClO_4)_2$,[28] and $[(TPA)Fe(CH_3CN)_2](ClO_4)_2$,[36] and significantly lower than those found for $[(bpmen)Fe(CH_3CN)_2](ClO_4)_2$,[12,13] the most active non-heme iron cyclohexane oxidation catalyst known to date. The major product was cyclohexanol, with an alcohol/ketone (A/K) ratio of 3.8–5.8, significantly higher than those reported for radical chain autoxidation reactions (A/K ≈ 1).[37–39]

In acetone a similar reactivity and A/K ratio was obtained as in acetonitrile (Table 1, entry 1). However, one clear difference is seen with the KIE values for cyclohexanol formation, determined in a competition experiment between cyclohexane and $[D_{12}]$cyclohexane. In CH_3CN a k_H/k_D value of 3.5 was found for complex **4**, similar to the value observed for $[(TPA)Fe(CH_3CN)_2](ClO_4)_2$,[36] which was proposed to react via a formally Fe^VO species. Complex **5** gives a lower k_H/k_D value of 2.4. In acetone the k_H/k_D ratio increased significantly to 4.4 for **4** and 3.9 for **5**. The latter values are in the range of those typically observed in oxidations catalyzed by non-heme iron complexes using

tert-butyl hydroperoxide as oxidant,[40] which were demonstrated to proceed via alkoxy radicals.[36−38]

The oxidation of *cis*- and *trans*-1,2-dimethylcyclohexane to the corresponding tertiary alcohols was studied to assess the stereoselectivity of the oxidation reaction. Although several isomeric secondary alcohols were also formed, these were not quantified. In CH_3CN the oxidation of *cis*-1,2-dimethylcyclohexane afforded rather low yields of tertiary alcohols with 85% and 82% retention of configuration at the tertiary carbon (i.e. formation of *trans*-1,2-dimethylcyclohexanol) for complexes **4** and **5**, respectively (Table 1, entry 2). Using *trans*-1,2-dimethylcyclohexane low yields of the tertiary alcohols, with 73% and 50% retention of configuration (i.e. *cis*-dimethylcyclohexanol) were also found for **4** and **5** (Table 1, entry 3). For comparison, more than 99% retention of stereochemistry was observed with $[(TPA)Fe(CH_3CN)_2](ClO_4)_2$,[41] $[(bpmen)Fe(CH_3CN)_2](ClO_4)_2$ [12] and cytochrome P-450 models,[42] whereas a complete lack of stereoselectivity was observed for $[(N4Py)Fe(CH_3CN)](ClO_4)_2$ [31] and in free-radical autoxidation.[43]

In acetone higher yields of tertiary alcohols were obtained, but generally with a lower degree of stereoselectivity. In the case of *cis*-1,2-dimethylcyclohexane 73% and 68% retention of configuration (Table 1, entry 2), and in the case of *trans*-1,2-dimethylcyclohexane 48% and 50% retention of configuration were obtained (Table 1, entry 3) with **4** and **5**, respectively.

Adamantane as substrate was oxidized both at the secondary and tertiary carbons. Using **4** a tertiary/secondary ratio (normalized on a per hydrogen basis) of 10.3 was obtained in acetonitrile (Table 1, entry 4). In acetone this ratio increased to 24.9 (Table 1, entry 4). For TPA and related tetradentate nitrogen-donor ligands values between 15 and 33 have been reported in CH_3CN as solvent.[13] For comparison, tertiary/secondary ratios of about 2 have been found for oxidation of alkanes by ·OH,[11] values of 3.1−3.3 for $[(N4Py)Fe(CH_3CN)](ClO_4)_2$,[31] 9.5−10 for oxidations by *t*BuOOH utilizing catalysts like $[Fe_2O(bipy)_4(H_2O)_2](ClO_4)_4$ and $[FeCl_2(TPA)](ClO_4)$,[44,45] and 11−48 for oxidations with PhIO catalyzed by P-450 mimics.[46]

Oxidation of Alkenes

The oxidation of symmetrical alkenes in CH_3CN with H_2O_2, catalyzed by **4** and **5**, gave both epoxidation and *cis*-dihydroxylation products (Table 2). Based on the results with Fe-TPA complexes this would be expected for iron complexes with two open coordination sites *cis* to each other.[15] All reactions could be carried out under air, except with cyclohexene as substrate, since this led to a strongly increased formation of the allylic alcohol and ketone. This indicates involvement of autoxidation pathways under air.[47]

Cyclooctene as a substrate afforded a very clean reaction giving only the epoxide and the *cis*-dihydroxylation product, i.e. the *meso*-diol (Table 2, entries 1 and 2). A small preference for *cis*-diol formation was observed with **4** whereas **5** displayed a small preference for epoxide formation.

Cyclohexene as substrate also gave the epoxide and the *meso*-diol as main products (Table 2, entry 3). However, with this substrate allylic oxidation products — cyclohexenol (28 turnovers) and cyclohexenone (seven turnovers) — were also formed.

With *cis*-stilbene and *cis*-4-octene the *cis*-oxide and *meso*-diol were also formed as major products, with a stereoselectivity of 93−95% (Table 2, entries 4 and 6). With *trans*-stilbene the *trans*-oxide, was the only detectable epoxidation product (Table 2, entry 5). The *cis*-dihydroxylation product, i.e. *rac*-1,2-diphenylethanediol, was obtained with a stereoselectivity of 94%. Besides the oxides and diols substantial amounts of benzaldehyde were also formed with the stilbenes — 11 and 13 turnovers for *cis*- and *trans*-stilbene, respectively. With *trans*-4-octene and norbornene a preference for epoxidation was found. For both substrates the corresponding diols were only formed in small amounts.

In acetone as solvent a very different reactivity pattern was observed. Generally, more side-products were found compared to oxidations in CH_3CN as solvent. Using cyclooctene as substrate, the epoxide and the 1,2-diols were obtained as major products (Table 2, entries 1 and 2). However, in contrast to the results in CH_3CN now the *trans*-dihydroxylation product, i.e. *rac*-1,2-cyclooctanediol, was obtained as major product, with a selectivity of 95% in the case of complex **4.** Complex **5** showed a little bit lower selectivity towards *rac*-diol (76%), but a significantly increased yield.

Cyclooctene oxide is known to be very robust so it is unlikely that the *rac*-diol is formed by epoxide ring-opening.[48] Furthermore, when cyclooctene oxide was subjected to the standard reaction conditions no diol formation was observed, which demonstrates that the *rac*-diol is formed independently and is not a decomposition product from the epoxide. Thus, by changing the solvent from acetonitrile to acetone the stereochemical outcome of the dihydroxylation reaction is changed from *cis* to *trans.*

With *cis*- and *trans*-4-octene and *cis*- and *trans*-stilbene the epoxides were formed in similar amounts as for the reaction in CH_3CN, with the *cis*-epoxidation product as major product (Table 2, entries 4−7). Hence, the stereochemistry of epoxidation is not dependent on the solvent.

With both *cis*- and *trans*-stilbene only small amounts of diol were found. However, substantial amounts of the corresponding acetonides were obtained, which are the products of the reaction of the diols with the solvent to form an acetal. Similar amounts of acetal were found by independent reaction of the corresponding diol under the same reaction conditions, indicating strongly that the acetonide is derived from the diol. When the acetonides are taken into account *cis*-stilbene gives the *trans*-dihydroxylation products — the *meso*-diol — as the main product and *trans*-stilbene affords mainly the corresponding *cis*-dihydroxylation products, i.e. the *rac*-diol.

With norbornene as substrate the main product was found to be *rac*-norbornanediol (Table 2, entry 8). When

the epoxide was tested under these reaction conditions no diol formation was observed, again suggesting that the diol is not formed as a decomposition product of the epoxide. With cyclohexene as substrate many products were formed, including low yields of cyclohexene oxide and *rac*-1,2-cyclohexanediol (Table 2, entry 3). No evidence for *cis*-dihydroxylation products was found. However, many of the side-products that were formed have not been identified up to now, except the allylic oxidation products cyclohexenol (11 turnovers) and cyclohexenone (one turnover), which makes it difficult to compare the results for this substrate.

The most remarkable feature of the reactions in acetone is the fact that, in all cases, the *rac*-diol is the preferred product. For *cis*-alkenes like norbornene, cyclooctene, cyclohexene, and *cis*-stilbene, this amounts to a *trans*-dihydroxylation reaction. This is the first example of a catalyst that can give both *cis*- and *trans*-dihydroxylation just by changing the solvent. Catalytic *cis*-dihydroxylation is mostly achieved by OsO_4 complexes in the presence of a stoichiometric oxidant like $K_3Fe(CN)_6$ or *N*-methylmorpholine *N*-oxide.[21] *trans*-Diols are usually prepared from alkenes in two steps: first epoxidation followed by epoxide ring-opening.[49]

Labeling Studies

To obtain more information on the mechanism of the epoxidation and dihydroxylation reaction ^{18}O labeling experiments were performed. The oxidation of cyclooctene in acetonitrile was monitored by using 10 equivalents of a 2% solution of $H_2{}^{18}O_2$ in $H_2{}^{16}O$ under a N_2 atmosphere Table 3). Analysis was performed by GC/CI-MS. Only 50% of the epoxide contained ^{18}O. For the *meso*-diol predominantly the singly labeled product was found. In a complementary experiment using a 2% solution of $H_2{}^{16}O_2$ in $H_2{}^{18}O$ 28% of the epoxide contained an ^{18}O atom. For the *cis*-diol the main product was again singly labeled *cis*-cyclooctanediol. When a solution of 1% $H_2{}^{18}O_2$ in a 1:1 mixture of $H_2{}^{16}O$ and $H_2{}^{18}O$ was used, both singly and doubly labeled *cis*-cyclooctanediols were formed. These observations lend support to a proposed catalytically active species in which both oxygen atoms from hydrogen peroxide and water are present. Further evidence for such a mechanism was obtained by examining the incorporation of labeled oxygen as a function of concentration of water in the reaction mixture. The results are shown in Figure 5.

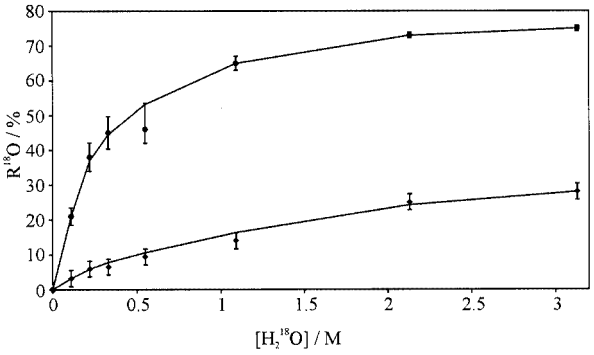


Figure 5. Incorporation of ^{18}O from $H_2{}^{18}O$: • diol; ◆ epoxide

At low concentration there is a more or less linear relationship between the concentration of water and the degree of incorporation of ^{18}O into the diol. At higher concentrations the extent of oxygen incorporation relative to the enhanced concentration decreases. This result is indicative of a pre-equilibrium between water and the active species of the catalyst. Similar results were found for the model systems $[(bpmen)Fe(CH_3CN)_2](ClO_4)_2$, $[(TPA)Fe(CH_3CN)_2](ClO_4)_2$, and several Fe-TPA derivatives for the oxidation of alkanes and alkenes.[50] Based on the cumulative data, which are in accordance with $[(TPA)Fe(CH_3CN)_2](ClO_4)_2$, the same mechanism for the oxidation in CH_3CN is proposed as was postulated for the oxidation with $[(TPA)Fe(CH_3CN)_2](ClO_4)_2$ (Scheme 3). In this mechanism the active $(HO)Fe^{V}{=}O$ species **13** is formed by heterolysis of the peroxide bond in intermediate **12**.

These labeling experiments were repeated in acetone, using *cis*-stilbene as substrate since it gives higher yields of *trans*-dihydroxylation products than cyclooctene. Here, incorporation of ^{18}O-oxygen into both epoxides and diols was investigated. The results are summarized in Table 4.

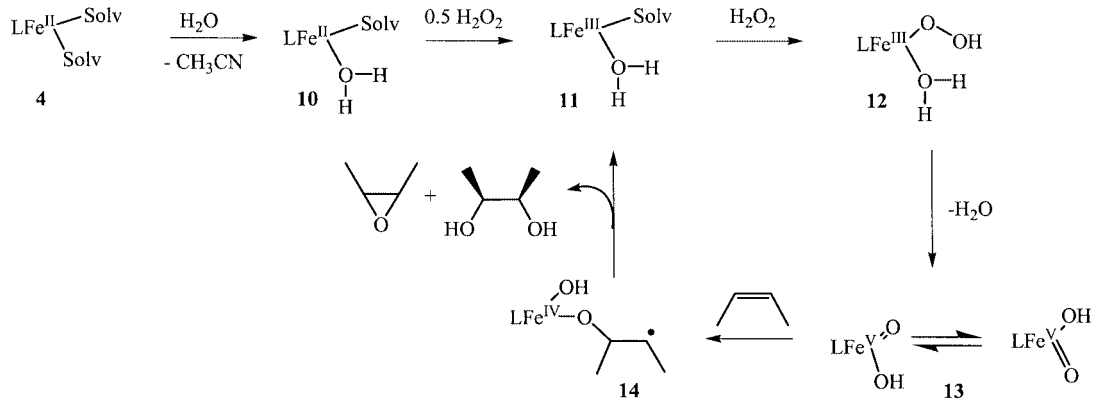
Even though a different substrate was used for the labeling studies and the level of ^{18}O incorporation is generally lower than in CH_3CN, the same pattern as in CH_3CN is discernible for the epoxidation and *cis*-dihydroxylation.

About one third of the label is built into the epoxide when $H_2{}^{18}O_2$ is used and about 40% incorporation is found when $H_2{}^{18}O$ is used. Also, in the case of the *cis*-diol the main fraction is singly labeled by $H_2{}^{18}O_2$. With $H_2{}^{18}O$ about one third of the product contains a single labeled oxygen, whereas with a combination of $H_2{}^{18}O_2$ and $H_2{}^{18}O$

Table 3. Incorporation of ^{18}O into the oxidation products of cyclooctene in acetonitrile[a]

Product	$H_2{}^{18}O_2$ in H_2O	H_2O_2 in $H_2{}^{18}O$	$H_2{}^{18}O_2$ in $H_2{}^{18}O/H_2O$ (1:1)
epoxide, labeled	50 (7)	28 (1)	53 (4)
cis-diol, not labeled	3 (1)	23 (1)	3 (1)
cis-diol, single labeled	94 (1)	76 (1)	37 (1)
cis-diol, double labeled	3 (1)	1 (1)	60 (1)

[a] Margins of error in parentheses.



Scheme 3. Proposed mechanism for the catalytic oxidation by N3Py-MeFe$(ClO_4)_2(CH_3CN)_2$ in acetonitrile

Table 4. Incorporation of ^{18}O into the oxidation products of *cis*-stilbene in acetone[a]

Product	$H_2{}^{18}O_2$ in H_2O	H_2O_2 in $H_2{}^{18}O$	$H_2{}^{18}O_2$ in $H_2{}^{18}O/H_2O$ (1:1)
cis-epoxide, labeled	32 (1)	40 (1)	49 (6)
trans-epoxide, labeled	21 (1)	17 (5)	23 (5)
cis-diol, not labeled	10 (2)	70 (5)	15 (1)
cis-diol, single labeled	67 (8)	29 (5)	42 (4)
cis-diol, double labeled	23 (10)	1 (1)	43 (4)
trans-diol, not labeled	19 (8)	70 (3)	29 (1)
trans-diol, single labeled	63 (6)	17 (6)	49 (1)
trans-diol, double labeled	18 (2)	13 (3)	22 (1)

[a] Margins of error in parentheses.

about 40% of the product is singly labeled and 43% doubly labeled. Taken together the data suggest that the epoxide and the *cis*-diol are formed by the same mechanism as with CH_3CN as solvent, involving a catalytically active species in which oxygen atoms from both hydrogen peroxide and water are present.

The labeling data for the *rac*-diol are somewhat harder to interpret. One complication is the fact that the *rac*-diol was obtained in two forms, the "free" diol and the acetonide. Since the acetonide is a secondary product, derived from the diol, only the free diol was considered in the experiments. In the experiment with $H_2{}^{18}O_2$ 63% of the product contains a single label whereas roughly equal amounts of non-labeled and doubly labeled diol were found. This appears to suggest that at least one oxygen of the diol comes from H_2O_2. The use of $H_2{}^{18}O$ resulted mainly in a product without a label whereas the experiment with $H_2{}^{18}O_2$ and $H_2{}^{18}O$ gave only a marginally higher amount of doubly labeled product. Thus, the second oxygen in the *trans*-diol does not have a clear origin and can stem from multiple sources like H_2O_2, H_2O or, most probably, the solvent acetone.

Since the experiments were performed under an inert atmosphere, incorporation of oxygen from O_2 can be excluded.

Mechanistic Interpretation

N3Py-R Fe complexes (**4** and **5**) are clearly very promising catalysts for stereoselective catalytic oxidation with H_2O_2. The reactivity profile in acetonitrile, not unexpectedly, is very characteristic of an iron complex with two *cis* open coordination sites: stereoselective hydroxylation of alkanes and stereoselective epoxidation and dihydroxylation of alkenes. The reactivity pattern of alkane oxidation, including the observed KIE values in cyclohexane oxidation, the 3:2 ratio in adamantane oxidation and the high degree of stereoselectivity in the oxidation of *cis*- and *trans*-1,2-dimethylcyclohexane observed with **4** and **5** is strongly reminiscent of those reported for other iron complexes of tetradentate N ligands like [(TPA)Fe$(CH_3CN)_2$]$(ClO_4)_2$ [36] and [(bpmen)Fe$(CH_3CN)_2$]$(ClO_4)_2$.[12] Furthermore, the oxidation of alkenes gives rise to the corresponding epoxides and *cis*-dihydroxylation products with high stereoselectivity. These results are also similar to what was reported for [(TPA)Fe$(CH_3CN)_2$]$(ClO_4)_2$ in CH_3CN.[15,36] These findings suggest that a common mechanistic pathway for these complexes exists. A mechanism involving heterolysis of the O−O bond of a low-spin $Fe^{III}OOH$ intermediate **12** to give a formally $Fe^{V}O$ species **13** is proposed, similar to that for [(TPA)Fe$(CH_3CN)_2$]$(ClO_4)_2$-catalyzed hydroxylation[12][50a]

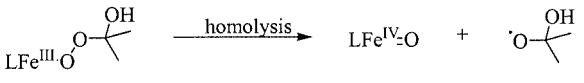
and *cis*-dihydroxylation (Scheme 3).[15,17] Addition to a double bond presumably produces a radical species **14** that is too short lived to isomerize and thus rapidly reacts with the coordinated OH to form the *cis*-diol. The same mechanism is expected to apply to the N3Py-R complexes discussed here. This is clearly supported by the labeling experiments.

The oxidation results obtained in acetone as solvent are quite different from those in CH_3CN, and it is hard to rationalize them in a single mechanistic proposal. Based on the results it is more likely that several competing pathways exist.

Based on the labeling studies it appears that an active species similar to that proposed in the mechanism in CH_3CN, resulting from heterolysis of a $Fe^{III}OOH$ intermediate, is responsible for the formation of epoxide and *cis*-diol. The fact that the second O atom in the product is clearly not only derived from water molecules is presumably caused by scrambling with the solvent.

However, from the data it is clear that this cannot be the sole pathway. In particular, the fact that *rac*-diols are an important product of the oxidation of alkenes suggests that another mechanistic pathway exists as well. Furthermore, the higher KIE in the oxidation of cyclohexane and the stronger preference for oxidation at tertiary carbons in adamantane suggest the presence of a more selective oxidizing species but could also indicate the presence of alkoxy-type radicals (vide supra). The lower stereoselectivity in the hydroxylation of *cis*- and *trans*-1,2-dimethylcyclohexane, alkene epoxidation and alkene dihydroxylation, combined with the fact that generally more side products are formed in acetone than in CH_3CN as solvent, are certainly more indicative of the involvement of radical species.

One possibility for radical species to be formed is through the formation of an iron-acetonylperoxy intermediate (**15**), by reaction of the iron center with the hydrogen peroxide adduct of acetone, followed by homolysis of the O−O bond to generate an $Fe^{IV}O$ complex (**1**) and an acetonyloxy radical species **17** (Scheme 4). Iron-alkylperoxo complexes have been demonstrated to be particularly predisposed to undergo O−O bond homolysis.[51]



15 **16** **17**

Scheme 4. Proposed formation of radical species by homolysis of the O−O bond of a iron-acetonyl peroxy species

Such radical species could also explain the formation of *rac*-diols: analogous to the proposal for TMP-Fe complexes (TMP = tetramesitylporphyrin),[52] the $Fe^{IV}O$ species could add to the double bond, leaving a carbon radical intermediate that is sufficiently long-lived to undergo isomerization to the thermodynamically more stable *trans* form before formation of either the epoxide, which explains the reduced stereoselectivity in acetone, or the *rac*-diol by reaction with another oxygen radical species.

Conclusions

In this paper we have presented a new class of tetradentate N-ligands for application in iron-catalyzed oxidations using H_2O_2: N3Py-R, with R being Me or Bn. Compared to the parent ligand of this class of catalysts, TPA, the N3Py-R ligands presented here have the added advantage that the R group can be readily modified, for example by the introduction of chiral groups for use in catalytic asymmetric oxidations.

The electrochemistry, NMR features and UV/Vis spectra of the N3Py-Fe complexes are solvent dependent. In acetone the labile acetonitrile ligands are rapidly displaced, presumably by the solvent, leading to the formation of a high-spin complex with different spectroscopic and electrochemical behaviour.

In both solvents good oxidation activity with H_2O_2 as sacrificial oxidant was found, but the reactivity, and in particular the selectivity, are strongly solvent dependent.

Not surprisingly the reactivity pattern in acetonitrile is quite similar to that of $[(TPA)Fe(CH_3CN)_2](ClO_4)_2$. The N3Py-Fe complexes are capable of stereoselective hydroxylation, epoxidation and *cis*-dihydroxylation. Mechanistic studies support a mechanism similar to that described for TPA-Fe, involving formally $Fe^{V}O$ species.

A major finding reported in this paper is the very different reactivity pattern observed in acetone, a solvent never reported for $[(TPA)Fe(CH_3CN)_2](ClO_4)_2$. The most striking example is the oxidation of alkenes to give the corresponding epoxides and the *rac*-diol as the main products. Mechanistic studies revealed that most likely more than one competing mechanistic pathway is available in acetone. Besides the heterolysis of a tentative $Fe^{III}OOH$ intermediate to give formally $Fe^{V}O$ species — the dominant mechanism in CH_3CN — a pathway involving $Fe^{IV}O$ species and acetonyloxo radicals, formed by homolysis of an intermediate iron-acetonylperoxy species, is proposed. The $Fe^{IV}O$ species may be responsible for the formation of *trans*-diols, following the TMP-Fe precedent.

The work described here constitute the first examples of a new generation of iron-based oxidation catalysts that can give either *cis*-dihydroxylation or *trans*-dihydroxylation of alkenes, simply by switching from CH_3CN to acetone as solvent.

Experimental Section

General Information: Commercially available chemicals were used without further purification unless noted otherwise. $H_2{}^{18}O_2$ (90% ^{18}O-enriched, 2% solution in $H_2{}^{16}O$) and $H_2{}^{18}O$ (95% ^{18}O-enriched) was obtained from ICON Services Inc. N3Py[33] and *cis*-4-octene[53] were prepared according to literature procedures.

^1H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini 300 spectrometer at ambient temperature (^1H at 300 MHz and ^{13}C

at 75 MHz). Chemical shifts (in ppm) are referenced to the residual protic solvent peaks. X-band EPR spectra were obtained at liquid nitrogen temperature on a Bruker ECS106 instrument or at liquid helium temperatures on a Bruker E500 equipped with an Oxford Instruments ESR-10 cryostat. UV/Vis spectra were recorded on a Hewlett Packard 8453 diode array spectrophotometer, using a cell equipped with a home-built temperature-control device. Electrochemical studies were carried out with a PAR 273A potentiostat in acetonitrile with 0.1 M tetrabutylammonium perchlorate as the supporting electrolyte. Cyclic voltammograms (CV) were obtained by using a three-component system consisting of a glassy carbon working electrode, a platinum wire auxiliary electrode and a saturated calomel reference electrode. Mass spectra were recorded on a NERMAG R 3010 triple quadrupole mass spectrometer (Nermag, Argenteuil, France) equipped with a home-built atmospheric-pressure ionization source. GC analyses were performed on a Hewlett Packard 6890 Gas Chromatograph using a HP-1 dimethyl polysiloxane column or a HP-5 5%-phenyl methyl siloxane column, or a Hewlett Packard 5890 II Gas Chromatograph using a CP-wax 52 CB column or a CP-wax 57 CB column.

Caution: Perchlorate salts are potentially explosive and should be handled with care.

Crystallographic Studies. Crystal Structure Determination of 4: $(C_{22}H_{24}FeN_6)^{2+}\cdot(ClO_4^-)_2$, M_r = 627.22, triclinic, $P\bar{1}$, a = 10.504(8), b = 11.685(9), c = 12.449(9) Å, α = 77.20(1)°, β = 65.71(1)°, γ = 66.34(1)°, V = 1272.7(17) Å^3, Z = 2, D_x = 1.637 gcm^{-3}, λ(Mo-K_α) = 0.71073 Å, μ = 8.63 cm^{-1}, F(000) = 644, T = 90 K, $GooF$ = 0.970, $wR(F^2)$ = 0.2377 for 4307 reflections and 355 parameters and $R(F)$ = 0.0856 for 2378 reflections obeying $F_o \geq 4.0\ \sigma(F_o)$ criterion of observability.

The asymmetric unit consists of three moieties, a cationic Fe complex and two ClO_4^- anions. Crystals were obtained by recrystallization from a mixture of acetonitrile and pentane. The crystals were very fragile: contact with a glass fiber caused damage as crystal cracks. The recorded frames showed (broad) anisotropic mosaicity and duplicated reflections. A red parallelepiped-shaped crystal with the dimensions of 0.220 × 0.150 × 0.120 mm mounted on a glass fiber was aligned on a Bruker[54] SMART APEX CD diffractometer (Platform with full three-circle goniometer). The diffractometer was equipped with a 4 K CCD detector set 6.0 cm from the crystal. The crystal was cooled to 90 K using the Bruker KRYOFLEX low-temperature device. Intensity measurements were performed using graphite-monochromated Mo-K_α radiation from a sealed ceramic diffraction tube (SIEMENS). Generator settings were 50 kV/40 mA.

The structure was solved by Patterson methods (DIRDIF) and refined with SHELXL against F^2 of all reflections. Non-hydrogen atoms were refined freely with anisotropic displacement parameters. Hydrogen atoms were refined in rigid mode. Checking for higher symmetry and structure calculations were performed with the PLATON package.
CCDC-213726 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

***N*-[Di(2-pyridinyl)methyl]-*N*-methyl-*N*-(2-pyridinylmethyl)amine (N3Py-Me, 1):** Formaldehyde (37% solution in water, 0.45 mL, 6.0 mmol) was added to a solution of **3** (1.262 g, 4.59 mmol) in 1,2-dichloroethane (35 mL). $NaBH(OAc)_3$ (3.92 g, 18.5 mmol) was added in small portions. After stirring for 7 h at room temperature saturated $NaHCO_{3(aq)}$ (35 mL) was added and the 1,2-dichloroethane layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with 1 N NaOH (20 mL) and brine (20 mL), dried (Na_2SO_4) and the solvent removed in vacuo to give **1** (1.235 g, 4.27 mmol, 93%) as a slightly yellow oil. ^{1}H NMR ($CDCl_3$): δ = 2.19 (s, 3 H), 3.72 (s, 2 H), 4.96 (s, 1 H), 7.14 (m, 3 H), 7.71 (m, 6 H), 8.56 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 40.32 (q), 61.04 (t), 77.87 (d), 121.76 (d), 122.10 (d), 122.92 (d), 123.21 (d), 136.29 (d), 136.43 (d), 148.86 (d), 149.22 (d), 159.37 (s), 160.59 (s) ppm. MS (CI): m/z = 291 [M + 1].

***N*-Benzyl-*N*-[di(2-pyridinyl)methyl]-*N*-(2-pyridinylmethyl)amine (N3Py-Bn, 2):** A mixture of benzyl chloride (0.46 mL, 3.8 mmol), **3** (740 mg, 2.7 mmol) and K_2CO_3 (370 mg, 2.7 mmol) in CH_3CN (20 mL) was stirred under an argon atmosphere. The mixture was heated under reflux overnight and benzyl chloride (0.23 mL, 1.9 mmol) was again added. After heating under reflux for 24 h the solvent was evaporated and water (20 mL) was added to the residue. The product was extracted with ethyl acetate (3 × 30 mL) and the combined ethyl acetate layers were washed with brine (15 mL) and dried (Na_2SO_4). Evaporation of the solvent followed by column chromatography (Alox. neutral, akt. I, ethyl acetate/hexane/triethylamine, 10:6:1) afforded **2** (670 mg, 1.83 mmol, 68%) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ = 3.79 (s, 2 H), 3.90 (s, 2 H), 5.30 (s, 1 H), 7.14 (m, 4 H), 7.29 (m, 2 H), 7.40 (m, 2 H), 7.66 (m, 6 H), 8.48 (m, 1 H), 8.56 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 54.93 (t), 56.47 (t), 71.24 (d), 121.62 (d), 121.90 (d), 122.60 (d), 123.75 (d), 126.77 (d), 128.14 (d), 128.70 (d), 136.11 (d), 136.23 (d), 138.94 (s), 148.81 (d), 149.15 (d), 160.04 (s) ppm. MS (CI): m/z = 367 [M + 1].

[(N3Py-Me)Fe(CH$_3$CN)$_2$](ClO$_4$)$_2$ (4): A solution of $Fe(ClO_4)_2\cdot 6H_2O$ (250 mg, 0.69 mmol) in CH_3CN (3 mL) was added to a solution of **1** (198 mg, 0.68 mmol) in MeOH (3 mL). The dark-red solution was placed in an ethyl acetate bath and after 3 days **4** (344 mg, 0.55 mmol, 81%) was isolated as dark-red crystals. ^{1}H NMR (CD_3CN): δ = 3.68, 5.12, 6.83, 7.40 (m, 1 H), 7.63 (m, 1 H), 8.02 (m, 1 H), 8.52, 8.65, 8.77, 8.95, 11.21 ppm. $C_{22}H_{24}Cl_2FeN_6O_8$: calcd. C 42.13, H 3.86, N 13.40; found C 41.98, H 3.78, N 13.27. UV/Vis (in CH_3CN): λ_{max} (ε) = 352 nm (5288 M^{-1}cm^{-1}), 428 (3261).

[(N3Py-Bn)Fe(CH$_3$CN)$_2$](ClO$_4$)$_2$ (5): Following the procedure as for **4**, starting from **2** (95 mg, 0.26 mmol) and $Fe(ClO_4)_2\cdot 6H_2O$ (105 mg, 0.29 mmol), **5** (152 mg, 0.22 mmol, 85%) was obtained as dark red crystals. ^{1}H NMR (CD_3CN): δ = 2.82, 4.44, 5.84, 6.98 (m, 3 H), 7.35 (m, 1 H), 7.49 (m, 3 H), 8.02 (m, 1 H), 9.40, 9.50, 9.64, 9.72, 9.79, 9.96, 10.78, 13.17 ppm. ES/MS: m/z = 521 [M − $(ClO_4)^-$ − 2(CH_3CN)]$^+$, 231.5 [M − 2(ClO_4)$^-$ − (CH_3CN)]$^{2+}$.

Catalytic Oxidations: All experiments were carried out under air, unless noted otherwise, in a water bath thermostatted at 25 °C. In a typical procedure cyclohexane (0.19 mL, 1000 equiv.) was added to a solution of **9** (8.75 × 10^{-4} M, 2 mL) and a known amount of bromobenzene (internal standard) in acetone. The reaction was started by syringe pump addition of 1 M H_2O_2 (88 μL, 50 equiv.) over 30 min. After the addition was complete the reaction mixture was stirred for an additional 5 min. An aliquot (1 mL) was taken from the reaction and filtered through a small silica column. The silica was thoroughly washed with diethyl ether or diethyl ether/10% methanol. The sample was concentrated to a volume of 2 mL by passing an Ar stream over the solution and then analyzed by GC.

Kinetic Isotope Effect Determination: Essentially the same procedure was used as described above, but now a mixture of cyclohexane and [D_{12}]cyclohexane was used (ratio cyclohexane/[D_{12}]cyclohexane varied from 1:1 to 1:4). The KIE was determined by comparing the turnover numbers for cyclohexanol and [D_{11}]cyclohexanol (determined by GC using the CP-wax 52 CB column) and corrected for relative concentration of cyclohexane and [D_{12}]cyclohexane.

Labeling Experiments: In a typical procedure cyclooctene (0.23 mL, 1000 equiv.) was added to a solution of **4** ($8.75 \cdot 10^{-4}$ M, 2 mL) in acetonitrile under a N_2 atmosphere. The reaction was started by syringe pump addition of $H_2{}^{18}O_2$ (10 equiv., 30 μL of 2% $H_2{}^{18}O_2$ in $H_2{}^{16}O$, diluted with 220 μL acetonitrile) over 60 min. After the addition was complete the reaction mixture was stirred for an additional 5 min. The reaction mixture was filtered through a small silica column. The silica was thoroughly washed with diethyl ether or diethyl ether/10% methanol. The sample was concentrated to a volume of 2 mL by passing an Ar stream over the solution and then analyzed by GC/CI-MS.

In the $H_2{}^{18}O$ experiment, $H_2{}^{16}O_2$ (50% in $H_2{}^{16}O$, 2 μL) and $H_2{}^{18}O$ (90%, 48 μL) were dissolved in acetonitrile (50 μL) and used for the oxidation as mentioned above.

In the $H_2{}^{18}O_2/H_2{}^{18}O$ experiment, $H_2{}^{18}O_2$ (2% in $H_2{}^{16}O$, 25 μL) and $H_2{}^{18}O$ (90%, 25 μL) were dissolved in acetonitrile (50 μL) and used for the oxidation as mentioned above.

Acknowledgments

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