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Epoxidation of Strained Alkenes Catalysed by (1,2-dimethyl-4(1H)pyridinone-3-olate)$_2$Mn^{III}Cl

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Abstract

The mild epoxidation of strained alkenes using (DMPO)$_2$MnCl catalyst (DMPO = 1,2-dimethyl-4(1H)-pyridinone-3-olate) in the presence of various oxidants was studied. Hydrogen peroxide and monopersulfate were found to be the best oxidants when used with imidazole in acetonitrile at 4°C, with up to 94% conversion. Dismutation of hydrogen peroxide was also observed when used as an oxidant. The epoxidation using hydrogen peroxide or monoperoxysulfate appears to be mild and very selective for strained alkenes. A mechanism is proposed where imidazole is required for activation of the oxidant and where a detected Mn^V=O species is proposed as the active species. Competitive reaction between H$_2$O$_2$ and the substrate for the active species is proposed and homolytic vs heterolytic scissions of the O-O bond of the oxidant are discussed.

Keywords

Epoxidation, Manganese, Hydroxypyridinone

Introduction

Clean, high yielding catalysed epoxidation reactions of alkenes are of great importance, especially asymmetric ones.[1,2] Some of the most remarkable advances in this direction have been made using biomimetic or bio-inspired transition metal based catalysts that in essence aim to mimic the function of oxygenase enzymes, in particular the ones based on iron or manganese. The development of asymmetric epoxidations of alkenes by Mn-salen complexes is arguably the most successful endeavour in the field.[3] Of special interest are the systems that can use environmentally friendly oxidants such as O$_2$ or failing that, system that work with oxidants those by-products are environmentally friendly, such as hydrogen peroxide, peroxysulfates or linear alkyl peroxyacids.[4] Hydrogen peroxide has received special attention for its atom economy.[5]

Major developments in catalytic systems based on non-hemic Fe(II/III) complexes have been reported.[6] Two of the most noticeable achievements are probably the characterisation of the Fe(IV/V)=O active species and the identification of subtle effects of ligand structure and reaction conditions on the reactivity (e.g. epoxidation vs cis-dihydroxylation competition).[7] Numerous reviews have been published covering various aspects of the chemistry of these iron-based systems.[2,8] These highlighted the wide range of ligand structures investigated so far but also demonstrated that this

diversity merely applies to the overall structure of the ligand and that it does not actually extend much to the nature of the coordinating groups employed. The most representative and dominant families of ligands are based on nitrogen atoms in aliphatic amines and pyridine rings.

Non-hemic systems based on manganese are also known to be catalytically active in the epoxidation of alkenes using environmentally benign oxidants.[9] Various aspects of recent progresses have also been reviewed.[2,8,10] Interestingly, the same comments about ligand diversity can be made for these complexes; in fact and perhaps not surprisingly, strong similarities exist between the ligands in the iron-based and manganese-based complexes. The most commonly represented families of ligands in manganese complexes include derivatives of salen/salan, BPMEN, bipy and 1,4,7-triazacyclonane, again, nitrogen-rich ligands.

Not all but a significant number of biological systems that are involved in oxygen activation and oxidation reactions systems and that inspired these synthetic catalysts have coordinating environment that are more oxygen-rich than their models.[11] It is therefore surprising that ligands with coordinating oxygen atoms are not well represented in the aforementioned models, despite reports of the beneficial or even critically important effect on reaction outcomes of coordinating co-catalyst additives based on oxygen (e.g. carboxylic acids).[12]

It therefore appears to us that an underrepresented direction for further major advances may reside in the discovery of new coordinating groups, especially oxygen-rich ones that would fine tune the electronic property of the metal atoms, especially with respect to the high-valent active species formed. Towards filling that gap, we have been interested in the effect of hydroxypyridinones as ligands in oxidation catalyst. One interesting representative of this class of ligands is 1,2-dimethyl-3-hydroxy-4(1H)-pyridinone (DMHP) (Scheme 1). DMHP is a commercially available compound derived from naturally occurring food enhancer maltol in only one step[13] and whose coordination chemistry has attracted attention as model of bacterial siderophores or as a drug candidate.[14] However, involvement of DMHP or its analogues as ligands in catalysis is disappointingly scarce.[15] One key Mn[III] complex of DMHP however attracted our attention. Complex **1**, formulated as (DMPO)$_2$MnCl (DMPO being the deprotonated form of DMHP) was previously synthesised and its crystal structure described in the literature but no catalytic activity of any sort was reported by the authors.[16]
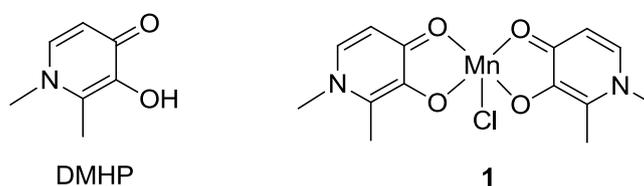
Scheme 1: 1,2-dimethyl-3-hydroxy-4(1H)pyridinone (DMHP) and complex **1**.

Interestingly, as observed by the authors, the coordination mode of the two bidentate ligands in that complex in the crystal structure is reminiscent of the coordination mode of salen ligands, i.e. the formation of a square planar pyramidal structure where chloride occupies an axial position. Moreover, the coordination mode of DMPO is also reminiscent of salen, porphyrin and acetylacetonate ligands, where one or two groups of one deprotonated heteroatom + one lone pair are the coordinating

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moieties. Contrary to these ligands that form a 6-membered ring with the metal, DMPO only forms a 5-membered ring. It occurred to us that the coordination mode of DMPO together with its idiosyncratic structural and electronic effect on the metal deserved attention as a new class of coordinating groups potentially leading to interesting and unexpected catalytic properties.

We wish here to report the activity of **1** as the first example of a new generation of catalyst that can perform the epoxidation of some alkenes in very high conversion and selectivity using hydrogen peroxide or monoperoxysulfate as the primary oxidant, and in a manner closely related to that of manganese porphyrin and manganese salen complexes. By comparing some features (conversion, selectivity, mechanism) of the epoxidation of alkenes with **1** and (salen)Mn^{III}, we herein want to show that the similarities and differences between the two systems strongly suggest that hydroxypyridinones could be a new class of coordinating groups, related to ubiquitous Schiff-bases, phorphyrins and acetylacetonate but those effect on the catalytic properties deserve more in-depth and widespread studies.

Results

A series of terminal oxidants were initially tested in order to ascertain the potential of **1** as an efficient epoxidation catalyst. When a primary oxidant was added to a mixture of complex **1**, imidazole as co-catalyst, and *cis*-cyclooctene in acetonitrile at 4°C, after 24 hours reaction time the formation of cyclooctene oxide in varying conversion was observed (Table 1).

Table 1: Epoxidation of *cis*-cyclooctene by **1** + imidazole and various oxidants in acetonitrile at 4°C.

Entry	Terminal Oxidant	Conversion to Epoxide/%[a]	Selectivity	Oxidant efficiency/%[i]
1	(Bu$_4$N)HSO$_5$[b]	94[c]	>99%	63
2	H$_2$O$_2$	74[d]	>99%	16
3	PhIO	36[f]	>99%	24
4	Urea.H$_2$O$_2$	20[f]	>99%	13
5	^{t}BuOOH	11[g]	69%	7
6	MPPH[h]	9	n.d.	6
7	NaIO$_4$	4[f]	>99%	3
8	Iodosylmesitylene	4[f]	>99%	3
9	KHSO$_5$[e]	0[f]	-	0
10	(Bu$_4$N)IO$_4$	0	-	0
11	Na$_2$CO$_3$.1.5H$_2$O$_2$	0[f]	-	0

[a] Conversion based on the substrate, determined by GC, reaction conditions: 4 mmol substrate, 0.2 mmol imidazole, 0.04 mmol catalyst, 10 mL acetonitrile, 6 mmol oxidant (except H$_2$O$_2$, 18 mmol), 24 hrs, 4°C [b] Formulated as 5 Bu$_4$N$^+$. 2 HSO$_5^-$. HSO$_4^-$. SO$_4^{2-}$, [c] 17% epoxidation was obtained in the blank reaction, [d] 18 mmol of H$_2$O$_2$ used, [e] Formulated as KHSO$_5$. ½ KHSO$_4$. ½ K$_2$SO$_4$, [f] Heterogeneous reaction where the oxidant is not entirely soluble, [g] cyclo-2-octenone was also detected in 5% conversion, [h] 2-Hydroperoxy-2-methyl-1-phenylpropane; [i] Percentage oxidant consumed leading to the epoxide.

Because of the ratio of substrate and catalyst used, the conversion percentage indicated also numerically corresponds to the turnover number (TON). The most effective oxidant tested was tetrabutyl ammonium monoperoxysulfate (TBAO) which showed excellent conversion of cyclooctene to the epoxide of 94% (TON = 94). The oxidant efficiency, defined herein as the percentage oxidant leading to epoxide is moderate to 63%, indicating that 37% of the peroxysulfate is decomposed by the catalyst in unproductive ways. Its potassium derivative ($KHSO_5$) showed no activity and this was ascribed to the lack of solubility of this oxidant in our acetonitrile solution. Hydrogen peroxide showed a very promising activity (when use in larger excess), to give 74% conversion, a percentage conversion that is not always easily achievable using (salen)Mn^{III} complexes.[1,17] However, it was also observed during the reaction a large amount of bubbling, presumably the formation of dioxygen via a catalase-like decomposition of the oxidant, which account for the low oxidant efficiency of only 16%.[18] Other related complexes such as (salen)Mn^{III} are also known to be prone to this type of unproductive decomposition of H_2O_2.[19,20]

It was noted that in all successful cases of *cis*-cyclooctene epoxidation (except in the presence of ^{t}BuOOH, see below), the reactions appeared very clean and the only detected product was the epoxide. Specifically, we particularly looked for the formation of cyclo-2-octenol, cyclo-2-octenone, and cis-cyclo-1,2-octanediol but these were not detected. The selectivity is therefore 100% within our detection limits. On the contrary, ^{t}BuOOH gave alongside the epoxide, 5% of cyclooctene-2-one, while cyclooctene-2-ol was not detected (Scheme 2). It can be suggested that *tert*-butyloxyl and/or *tert*-butylperoxyl radicals were generated and are responsible for the formation of this side-product via allylic hydrogen atom abstraction.[21]
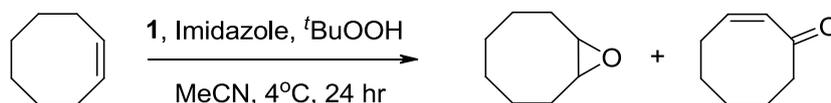
Scheme 2: Products of the oxidation of cis-cyclooctene by **1** and *tert*-butylhydroperoxide.

The formation of *tert*-butoxyl radicals via a homolytic scission of a Mn^{III}-OO-^{t}Bu adduct would be supported by the results of the cyclooctene epoxidation reaction performed using MPPH as a molecular probe for O-O bond scission.[22] Besides the 9% conversion of the substrate, the products of decomposition of MPPH were found by GC-MS to be 41% 2-methyl-1-phenyl-2-propanol, 43% benzaldehyde and 5% 1,2-diphenylethane (Scheme 3). Blank injection of MPPH in GC-MS gave only minor quantities of 2-methyl-1-phenyl-2-propanol.
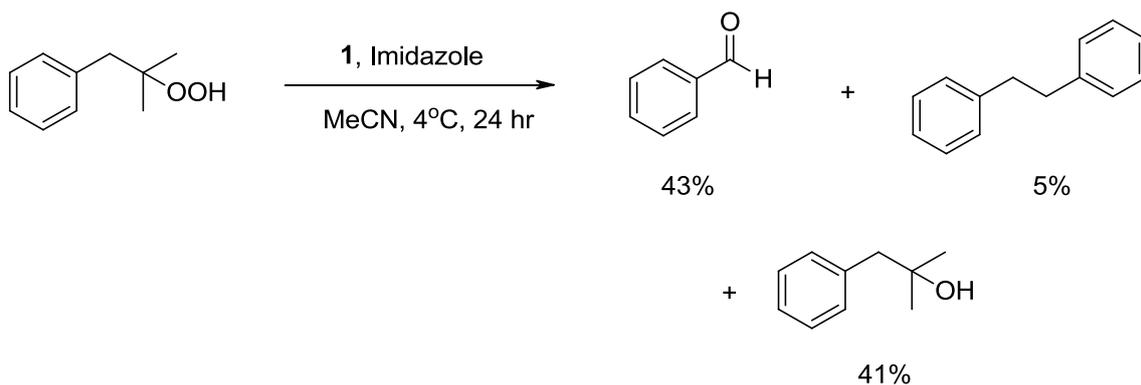
**Scheme 3:** Decomposition products of MPPH by **1** in acetonitrile.

Anhydrous sources of hydrogen peroxide (i.e. urea hydrogen peroxide and sodium percarbonate) achieved poor conversion, 20% and 0% respectively, and again this is attributed to the lack of solubility of the oxidant in the reaction medium. Common oxidants used in (salen)Mn^{III} catalysed epoxidations are the iodosylarenes and periodates. However, in our system only poor to moderate success was achieved even with more soluble analogues of these oxidants such as tetrabutyl ammonium periodate or iodosylmesitylene.

An attempt was made at using *meta*-chloroperoxybenzoic acid (mCPBA) as the oxidant. In the catalysed reaction, 67% epoxidation was obtained but the corresponding control without catalyst, 86% epoxidation was obtained. We cannot therefore demonstrate that the catalyst is actually activated by mCPBA. However, to account for the lower conversion in the catalysed reaction, it is clear that unproductive decomposition of the peroxyacid by the complex occurred.

Although hydrogen peroxide proved not as good an oxidant as TBAO, our focus was at first directed toward the former as it is in theory more atom efficient. To identify idiosyncrasies of catalyst **1** compared to (salen)MnCl type catalysts (complex (3,5-di-*t*bu-salen)MnCl (**2**) being used herein as an archetypal (salen)MnCl complex), epoxidation of various substrates were performed in our chosen reaction conditions (admittedly not in conditions optimised for (salen)MnCl type complexes) and the results are reported in Table 2.

Table 2: Conversion of epoxidation of various substrates with **1** or **2** + imidazole + H$_2$O$_2$ in acetonitrile, same reaction conditions as in Table 1, unless otherwise noted.

Entry	Substrate	Conversion to epoxide/%	
		(DMPO)$_2$MnCl (**1**)	(3,5-di-*t*bu-salen)MnCl (**2**)
1		74	47
2		78	90

Entry	Substrate	Conversion (1)	Conversion (2)
3		4	n.p.[a]
4		5[b]	43
5		4[c]	n.p.[a]
6		2	n.p.[a]
7		3(53[d])	n.p.[a]
8		0	n.p.[a]
9		80 (43% cis-epoxide, 57% trans-epoxide)	14 (65% cis-epoxide, 35% trans-epoxide)
10		25	28
11		2	n.p.[a]
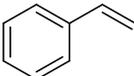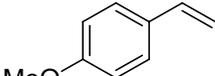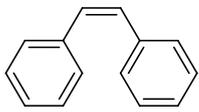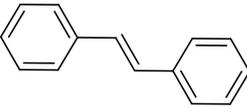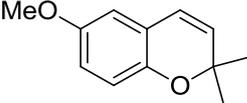
[a] Not performed, [b] Only the mono epoxide was detected, [c] Only the mono-epoxide of the endocyclic C=C bond (limonene 1,2-epoxide) was detected, no absolute stereochemistry of the epoxide was determined, [d] Batched addition of H_2O_2: addition over 30 minutes with vigorous stirring.

Table 2 indicates that some alkenes were efficiently converted to the epoxide by **1** whereas others were extremely poorly converted. It appears that only strained double bonds (entry 1, 2, 9) get epoxidised in good conversion and that other types of carbon-carbon doubles bonds are barely converted. This suggests that our catalyst has low reactivity and therefore has rather high selectivity, which is a desirable feature of catalytic systems. Epoxidation of cis-stilbene gave a mixture of 65% cis-epoxide and 35% trans-epoxide. On the contrary, epoxidation of trans-stilbene only gave trans-epoxide. Interestingly, that formation of cis and trans epoxide in the case of cis-stilbene seems to parallel what is usually found in (salen)Mn[III] complexes.[23] The conversions obtained are poor with regards to terminal alkenes, in contrast to (salen)Mn[III] system where no such substrate sensitivity is usually observed.[24] Traces of cyclo-2-heptenol and cyclo-2-heptenone side-products were observed in the epoxidation of cycloheptene (in contrast to cyclooctene where, as mentioned earlier, the corresponding oxidation products were not detected). Traces of adipic acid, cyclo-2-hexenol and cyclo-2-hexenone were detected when cyclohexene was epoxidised, showing that some minor side-reactions occurred. In all other cases selectivity was around 100%. When comparing reactivity of **1** and **2**, it is immediately obvious that striking differences emerge. Complex **2** gave better yield on some substrates (entries 2, 4 and 10) while much poorer yields on others (entries 1 and 9, including a

different cis/trans selectivity for the latter, see footnote e and f). This result strongly indicate that the DMHP ligand may be more suited than a salen one for some substrates and point to dramatic ligand effects that are not currently well understood but are critical for further catalyst developments.

Epoxidations of alkenes by **1** in the presence of tetrabutylammonium monoperoxysulfate ((Bu$_4$N)HSO$_5$) was also performed on various substrates and the results are reported in Table 3.

Table 3: Conversion of epoxidation of various substrates with **1** + imidazole + (Bu$_4$N)HSO$_5$ in acetonitrile, same reaction conditions as in Table 1.
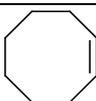
Entry	Substrate	Conversion to epoxide/%
1		94[a]
2		87
3		12[b]
4		69[c]
5		82
6		0
7		0
8		92
9		47[d]
10		26
11		38
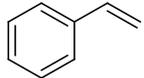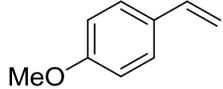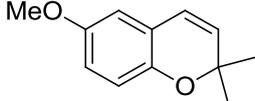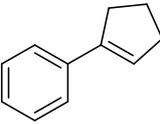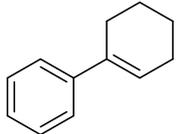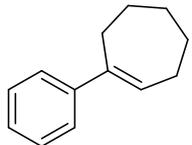
[a] 17% epoxidation was obtained in the blank reaction, [b] Cycloehexen-2-ol and cyclohexen-2-one were also detected, [c] Yield of the mono-epoxide given. 3% of diepoxide was also detected, [d] 37% of 1-phenyl-1,2-

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dihydroxycyclopentane were also detected. It was not checked if that diol formed from hydrolytic ring-opening of the epoxide during the reaction.

Table 3 shows that the use of TBAO also gave good conversions of strained alkenes and much poorer conversion on less trained carbon-carbon double bonds. It is very noteworthy that the conversion of precocene I (Table 3, entry 8) and 1,5-cyclooctadiene (Table 3, entry 4) in the presence of TBAO were so much higher than the ones in the presence of hydrogen peroxide (Table 2, entries 4 and 11) and a possible reason for this effect is discussed below. The large difference between the conversions observed for cyclohexene and norbornene (entries 3 and 5) seem to support our observations that only strained alkenes are epoxidised in good yield.

Monitoring of the percentage oxidation of cyclooctene by complex **1** in the presence of TBAO over time gave the results in Figure 1.
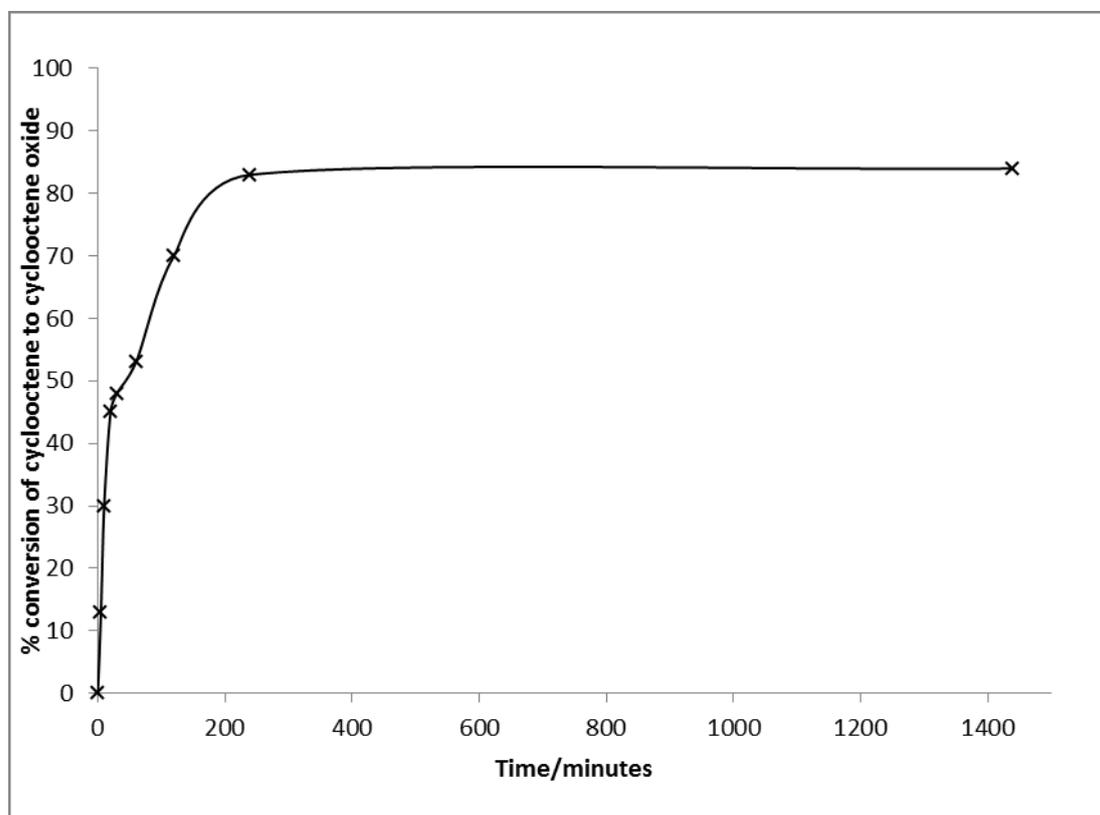
Figure 1: Conversion of cyclooctene to cyclooctene oxide by **1** and TBAO as a function of time. Reaction conditions as in Table 3.

As it can be seen, although all our reactions were performed for 24 hours, it would appear that the reaction is complete within about 4 hours, giving a turn-over frequency of 23.5 h^{-1}. The very quick drop in conversion rate can be explained by the simultaneous depletion in both substrate and oxidant and decomposition of the catalyst.

The effect of solvent and temperature on the epoxidation of *cis*-cyclooctene was investigated as it would be desirable in large-scale applications to move from acetonitrile to environmentally friendly solvents without the need for heating or cooling. The results are presented in Table 4.

Table 4: Epoxidation of *cis*-cyclooctene in various solvents and at various temperatures catalysed by **1** + Imidazole. Same reaction conditions as in Table 1 unless specified otherwise.

Entry	Solvent	Oxidant	Temperature/^{o}C	Conversion to epoxide/%[a]
1	Acetonitrile	H_2O_2	RT	12[b]
2	Acetonitrile	H_2O_2	4	78[c]
3	Acetonitrile	H_2O_2	-20	85 (93[d])
4	Ethanol	H_2O_2	4	39
5	Acetone	H_2O_2	4	31
6	Methanol	H_2O_2	4	13
7	Ethyl acetate	H_2O_2	4	0[b]
8	Dichloromethane	H_2O_2	4	0[b]
9	Water[e]	H_2O_2	4	0[b]
10	Acetonitrile	PhIO	RT	17%

[a] Conversion determined by GC after 24 hours reaction (except otherwise noted), [b] Vigorous dioxygen evolution observed, [c] Mild dioxygen evolution observed, [d] 48 hours reaction time, [e] unbuffered solution, biphasic system.

Acetonitrile was found to be by far the best solvent for the epoxidation. Disappointingly, the greenest solvents tested (ethanol, water, ethyl acetate) gave at best poor epoxidation results. In the case of ethyl acetate and dichloromethane (entry 7 and 8), poor conversion can be attributed to the poor solubility of the catalyst in the solvent combined to an observed faster dismutation of hydrogen peroxide. The reaction also seemed to provide more epoxide at lower temperature (entry 1, 2 and 3 for H_2O_2, entry 10 and Table 1, entry 3 for PhIO). In the case, of hydrogen peroxide, this appeared associated by much less vigorous bubbling, and therefore be associated with significant reduction of unproductive catalase-like decomposition of the oxidant. However, as expected, lowering the temperature also resulted in a much slower epoxidation reaction that appeared to require more than 24 hours to go to completion (entry 3).

The conversion of *cis*-cyclooctene to its epoxide as a function of the pH of the hydrogen peroxide solution used was measured and is presented in Figure 2.
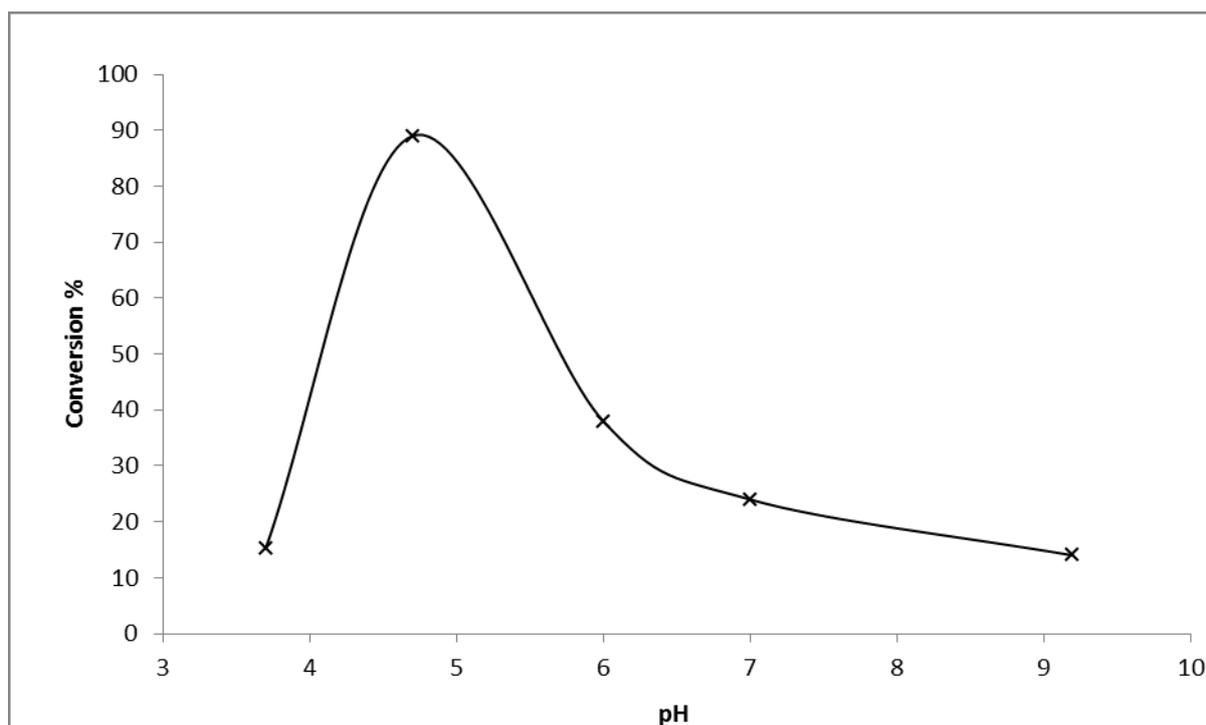
Figure 2: Conversion of cis-cyclooctene to its epoxide as a function of pH of the aqueous hydrogen peroxide solution. Reaction conditions were identical to those in Table 1.

We obtained an improved conversion at pH 4.7 of 88%. Higher pHs resulted in drastic reduction of conversion to the epoxide. Interestingly, a higher quantity of dioxygen bubbling was instead observed.

When imidazole (ImH) was omitted from the mixture in the presence of hydrogen peroxide, no epoxide was detected instead cyclooctene was recovered unreacted. Upon addition of a few equivalents of imidazole excellent epoxidation activity could be produced on cyclooctene. This is also a result that is analogous to observations made on some (salen)Mn^{III} complexes that were found to require a co-catalyst to efficiently activate the oxidant.[1,17b,25] In the reaction using monoperoxysulfate, the effect of the nature of the additive co-catalyst was also investigated and the results are reported in Table 5.

Table 5: Epoxidation of *cis*-cyclooctene with various additives by **1** + tetrabutylammonium monoperoxysulfate, same reaction conditions as in Table 1.

Entry	Co-catalyst	Conversion to epoxide/%
1	None	0
2	Imidazole	94
3	N-Methyl morpholine N-oxide	83
4	Pyridine	80
5	Sodium acetate	66
6	Quinoline	54
7	(L)-Histidine monohydrate monochloride	52

8	8-Hydroxyquinoline	45
9	Triethylamine	21
10	N-Methylimidazole	1
11	4-Phenylpyridine N-oxide	0

It would appear that numerous co-catalysts are capable of promoting the catalytic action of complex **1** in the presence of TBAO. Interestingly, the more environmentally friendly sodium acetate gave decent conversion and imidazole could also somewhat be replaced by histidine. Strikingly, although imidazole was found to be the best we tested, N-methylimidazole was found to be an extremely poor co-catalyst.

Having demonstrated that **1** was an effective catalyst, using TBAO or hydrogen peroxide, but with a very selective efficacy on strained alkenes, we turned our attention towards a better understanding the mechanism of the reaction to draw parallel with (porphyrin)Mn^{III} and (salen)Mn^{III} systems, especially since there are still debates as to the latter's mechanism of action.[26]

Increasing the catalyst (and concomitant imidazole concentration in order to stay in a 1:4 ratio) had an adverse effect on the conversion of cyclooctene when using hydrogen peroxide, as shown in Figure 3. An increased formation of dioxygen due to Catalase-like activity was instead observed, suggesting two competing pathways that have a different dependency on the concentration of the catalyst (see below).
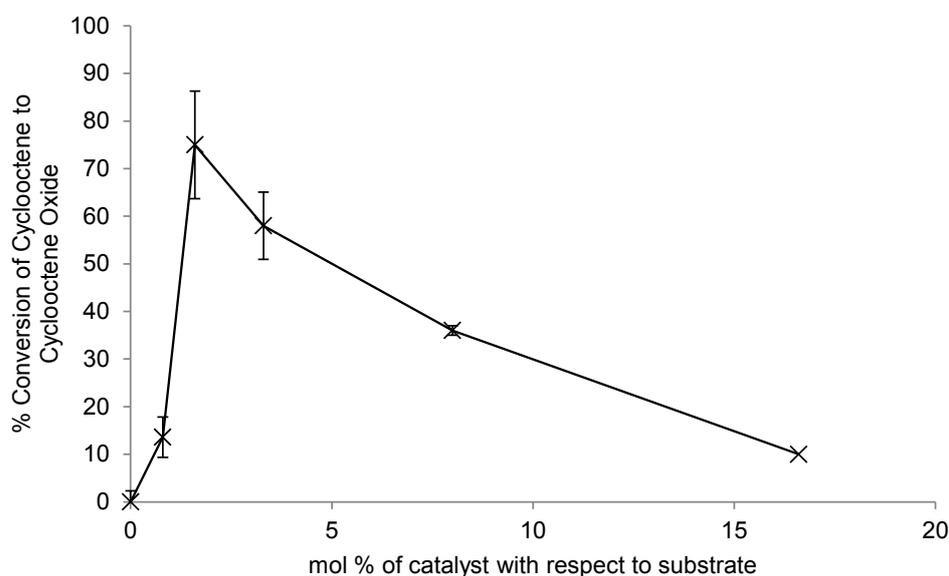

Figure 3: Percentage conversion of cis-cyclooctene to its epoxidation as a function of molar percentage of **1** ([Imidazole]/[**1**] kept constant at 4) in the presence of hydrogen peroxide. Other reaction conditions were the same as those described in the experimental section.

Our attention was then directed towards the effect of increasing amount of imidazole on the catalysis in the presence of hydrogen peroxide. It was observed that there was an optimum amount of imidazole required for best conversion, as shown in Figure 4. Four to five equivalents of Imidazole with respect to the catalyst were found to be best. Further addition of imidazole had a detrimental effect on the catalysis.
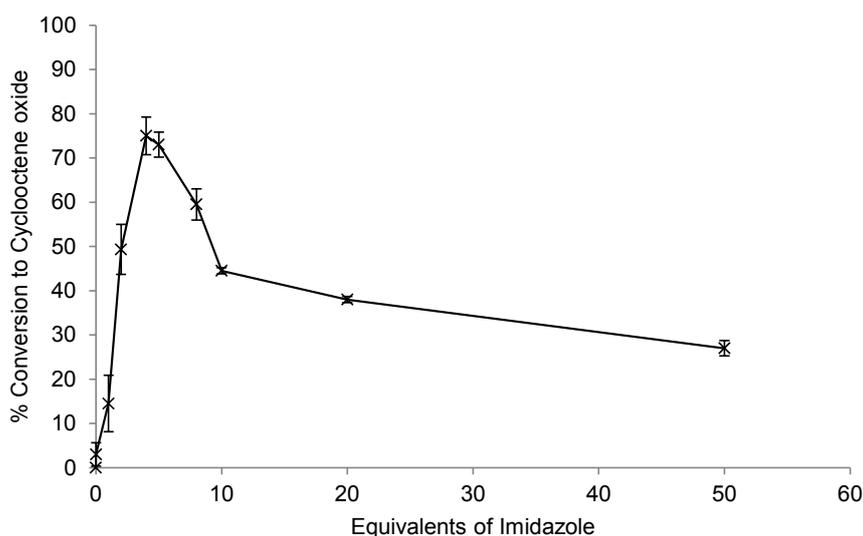

Figure 4: Conversion of cyclooctene to cyclooctene oxide as a function of the quantity of imidazole co-catalyst with respect to **1**, in the presence of hydrogen peroxide. Other reaction conditions were the same as those described in the experimental section.

Cyclic voltammetry of complex **1** was reported in the literature.[16] It was reported that the Mn^{III}/Mn^{IV} couple in **1** has a redox potential (quasi-reversible) of +0.54V vs NHE in acetonitrile. Upon addition of 5 equivalents of imidazole or sodium acetate, that couple is shifted to +0.26 V and +0.33 V respectively (data not shown). Moreover, addition of imidazole to complex **1** prompted a change in colour from browny/green to lime green and the associated change in the UV-vis spectra are presented in Figure 5. An insignificant shift of λ_{max} from 288 nm for **1** to 287 nm for **1** + 5 equivalents imidazole and 289 nm for **1** + 50 equivalents imidazole was observed but the addition of imidazole clearly had an hyperchromic effect. These observations suggest coordination of imidazole to the manganese centre do occur. It should be noted that this reaction is not instantaneous and an equilibration time was required before the colours fully developed. Due to the planar structure of the ligand metal complex, it is likely that imidazole binds axially to the manganese centre, a phenomenon well known in (salen)MnCl complexes.[27]
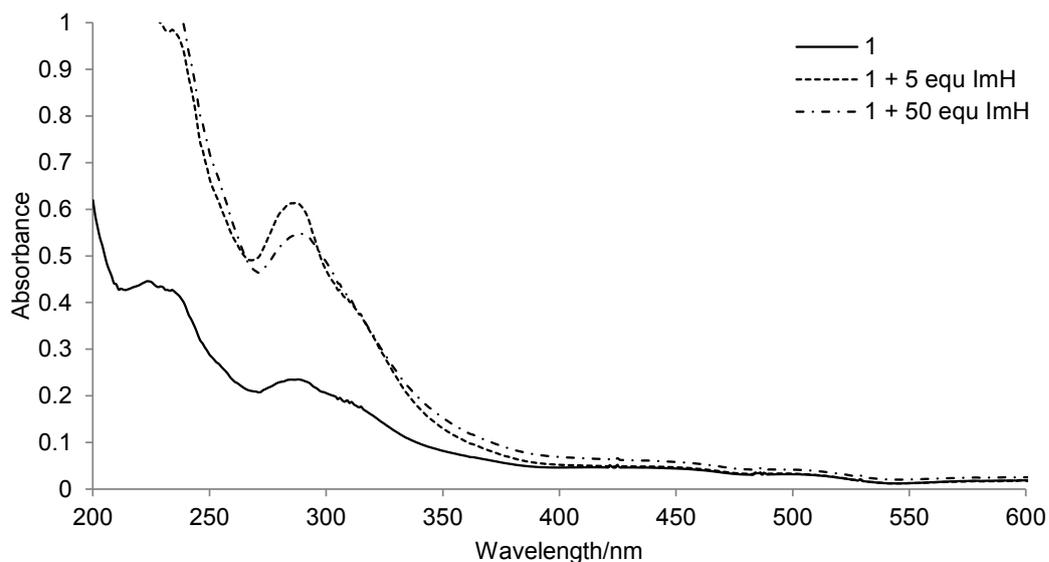
Figure 5: UV-Vis Spectra of complex **1**, and complex **1** with 5 and 50 equivalents of imidazole. [**1**] = 1.3 x 10^{-5} M in acetonitrile. Spectra corrected for the absorbance of unbound imidazole.

A nano-electrospray (nESI) MS study was performed on a mixture of **1** and imidazole (in a 1:4 molar ratio) in acetonitrile. The spectrum obtained is presented in Figure 6.
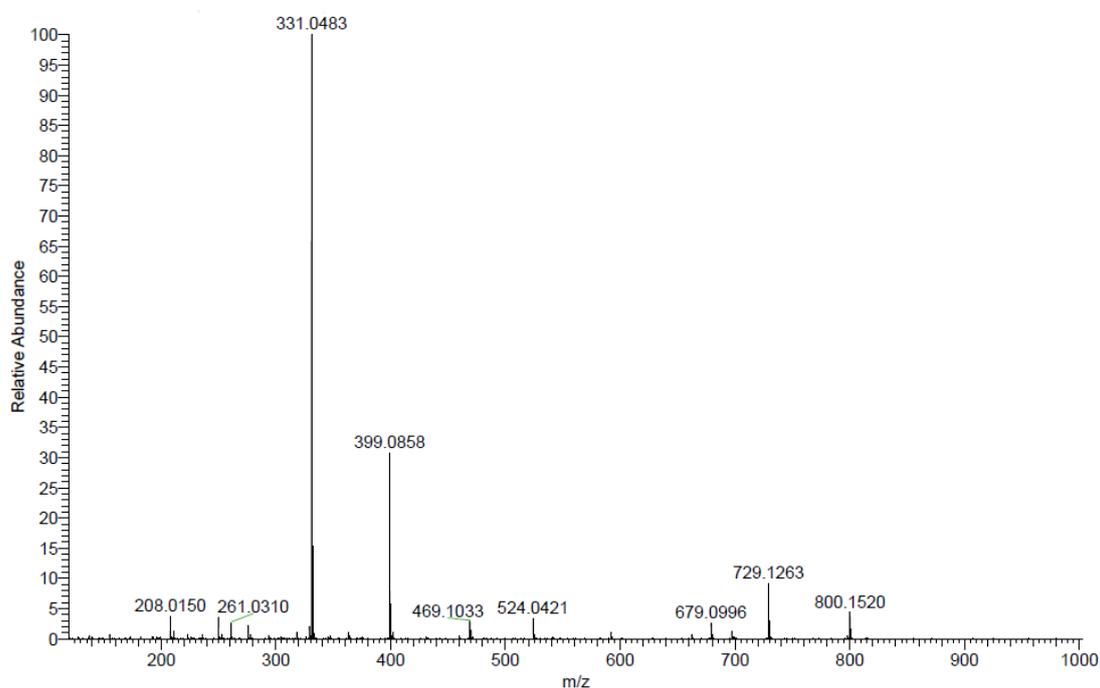

Figure 6: nESI-MS spectrum of **1** + imidazole in acetonitrile.

Three major peaks can be observed, at m/z 331.0483, 399.0858, 729.1263 and 800.1520. The peak at m/z 331.0483 can be assigned to [(DMPO)$_2$Mn]+ (expected m/z 331.0491). More importantly, a peak at m/z 399.0858 was also detected. This accurate mass measurement and the isotope pattern

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match very well with the expected value for $[(DMPO)_2Mn^{III}(ImH)_1]^+$ complex (Figure 7). nESI mass spectrum of a mixture of complex **1** and sodium acetate in acetonitrile failed to identify any similar adduct that would be formulated as $[(DMPO)_2Mn^{III}OAc]$ and would therefore be neutrally charged.
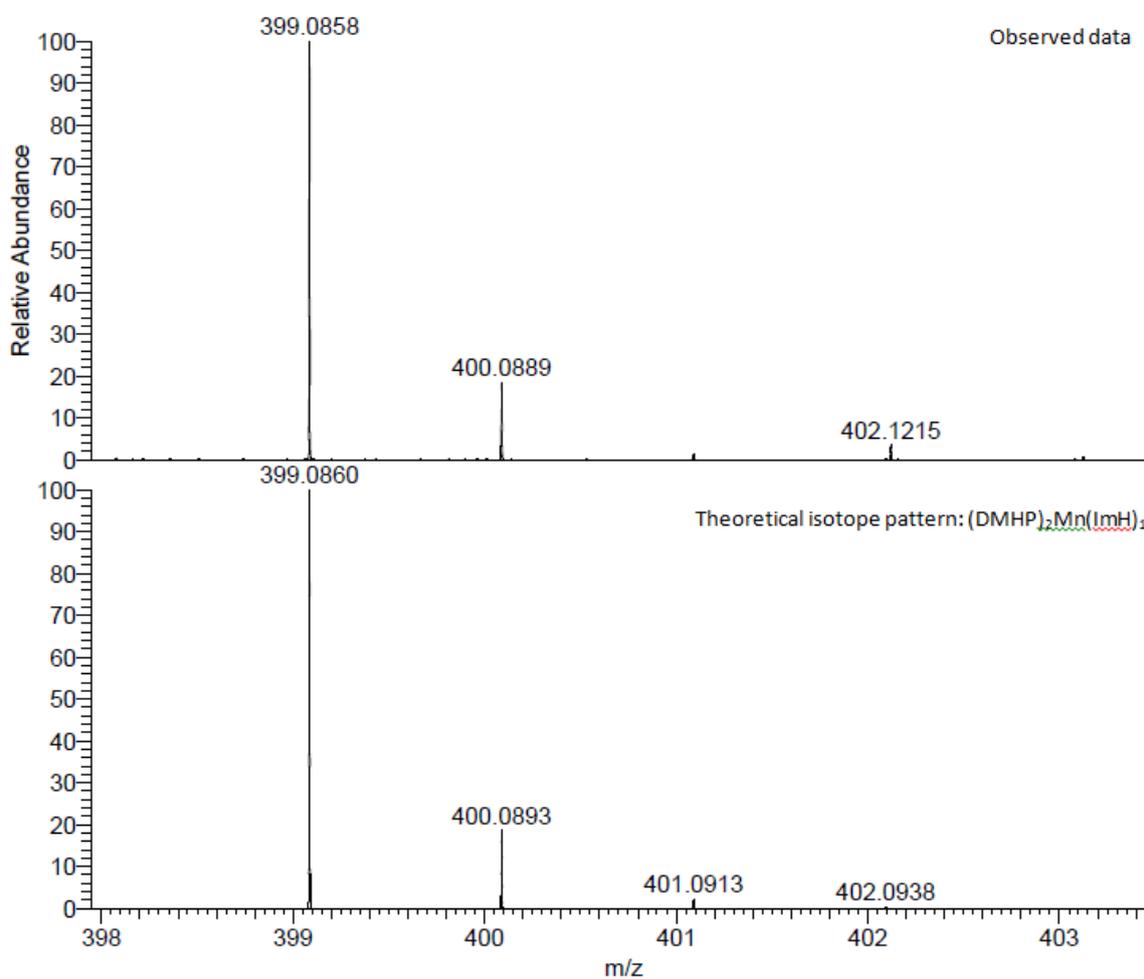

Figure 7: Detected m/z peak for $[(DMPO)_2Mn(ImH)_1]^+$ (top) and its theoretical isotope pattern (bottom).

Interesting is the detection of a peak at m/z 729.1263 that appears to match the isotope pattern of a species formulated as $[(DMPO)_4Mn_2(Im)_1]^+$ (Figure 8).
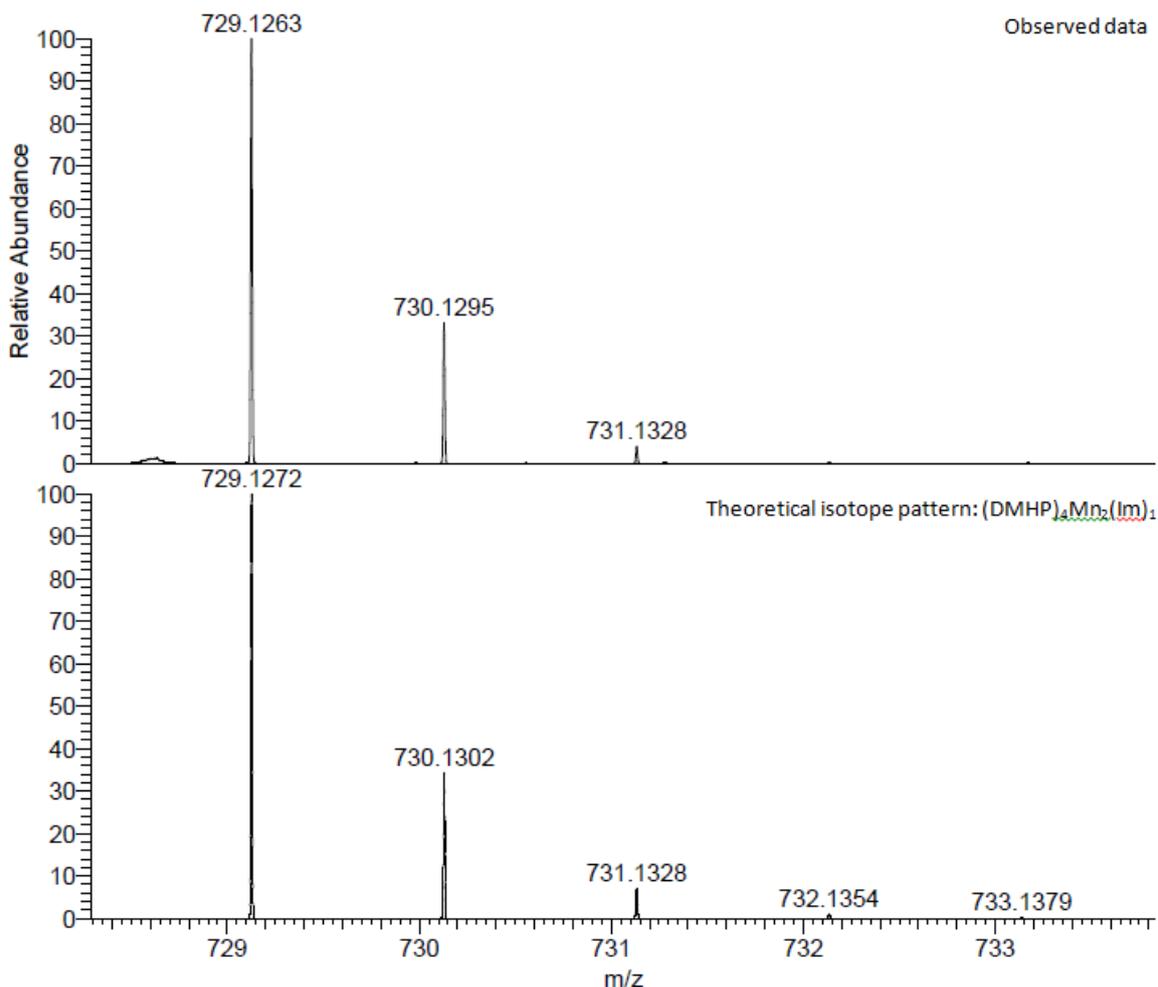
Figure 8: Detected m/z peak for $[(DMPO)_4Mn_2(Im)_1]^+$ (top) and its theoretical isotope pattern (bottom).

The spectrum seems to indicate that the imidazole is deprotonated, and would therefore suggest a structure where an imidazolate anion is bridging the two manganese atoms. Based on rare but known complexes where imidazolate bridged manganese atoms in dinuclear complexes[28], we can propose the possible existence of dinuclear complexes whose structure depicted in Scheme 4.
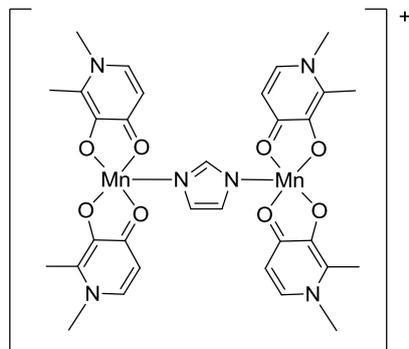
Scheme 4: Proposed structure for $(DMPO)_4Mn_2(Im)_1$.

The mass and isotope pattern of the peak at m/z 800.1520 (data not shown) matches the formula $[(DMPO)_5Mn^{III}_2]^+$ (expected m/z 800.1531) and is present too in the nESI spectrum of complex **1** in acetonitrile without other additives. The exact origin of this peak has not been studied further.

nESI mass spectrum of the reaction mixture shortly after addition of hydrogen peroxide clearly showed the formation of a species formulated as $[(DMPO)_3Mn(III)H]+$ (m/z detected at 470.1110, expected at 470.1118) and the release of free DMHP ligand (detected as $DMHP+H^+$), indicating decomposition of the complex. More interestingly, the mass spectrum also clearly showed the formation of the hydroperoxo adduct (Figure 9, m/z = 432.0835) but with a weak intensity, possibly related to its unstable nature. Interestingly, this adduct is formulated as $(DMPO)_2(ImH)_1Mn(IV)OOH$, i.e. with a Mn^{IV} species and with the imidazole still bound.
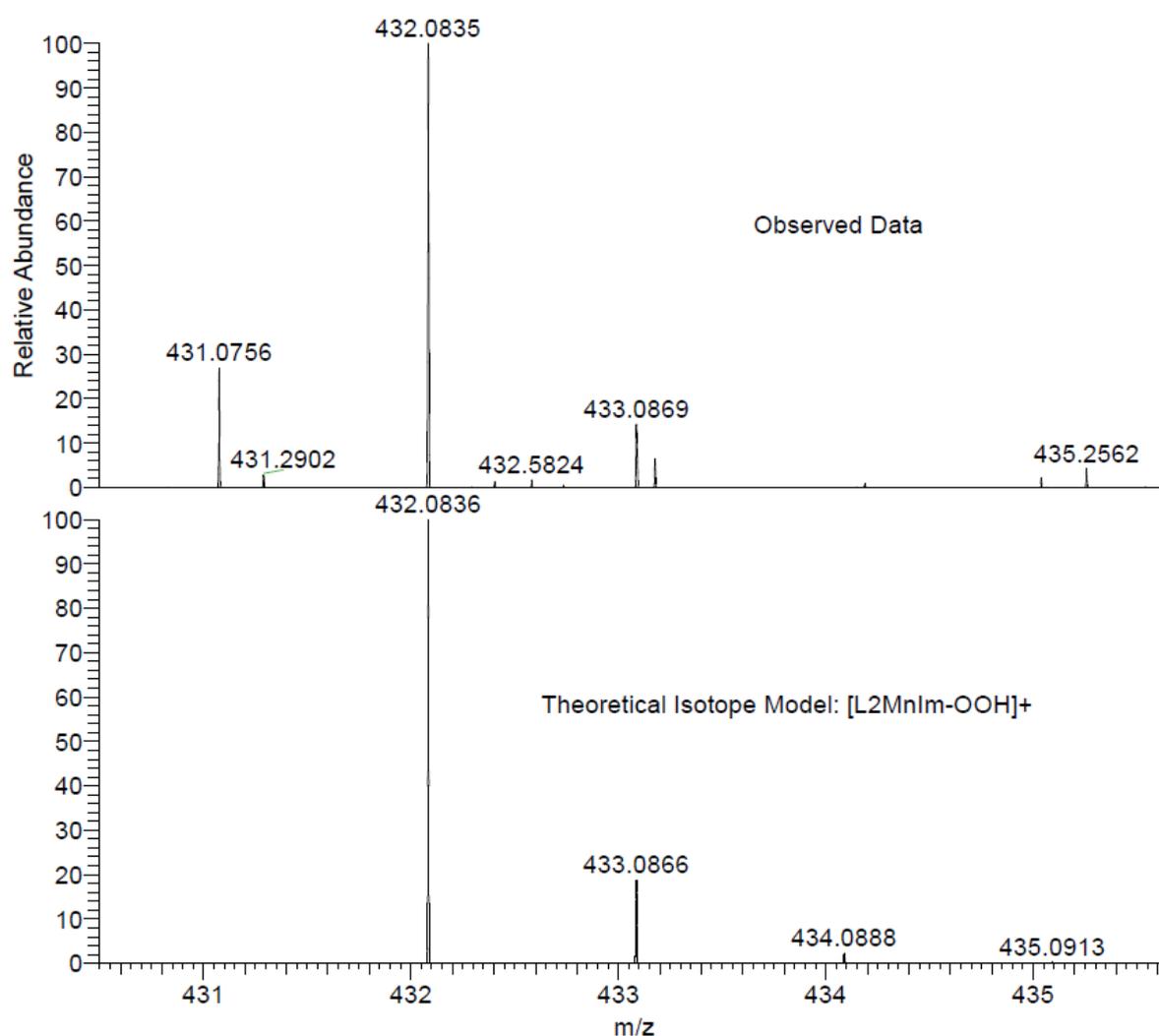
**Figure 9:** Detected m/z peak for $[(DMPO)_2(Im)_1Mn(IV)(OOH)]^+$ (top) and its theoretical isotope pattern (bottom).

In the case of monoperoxysulfate used as the oxidant, nESI mass spectrometry of a mixture of **1**, imidazole and $Bu_4N.KHSO_5$ in methanol, gave a moderately intense peak at m/z 347.0426 that was ascribed to a $[L_2Mn(V)O]+$ species (expected 347.0434).
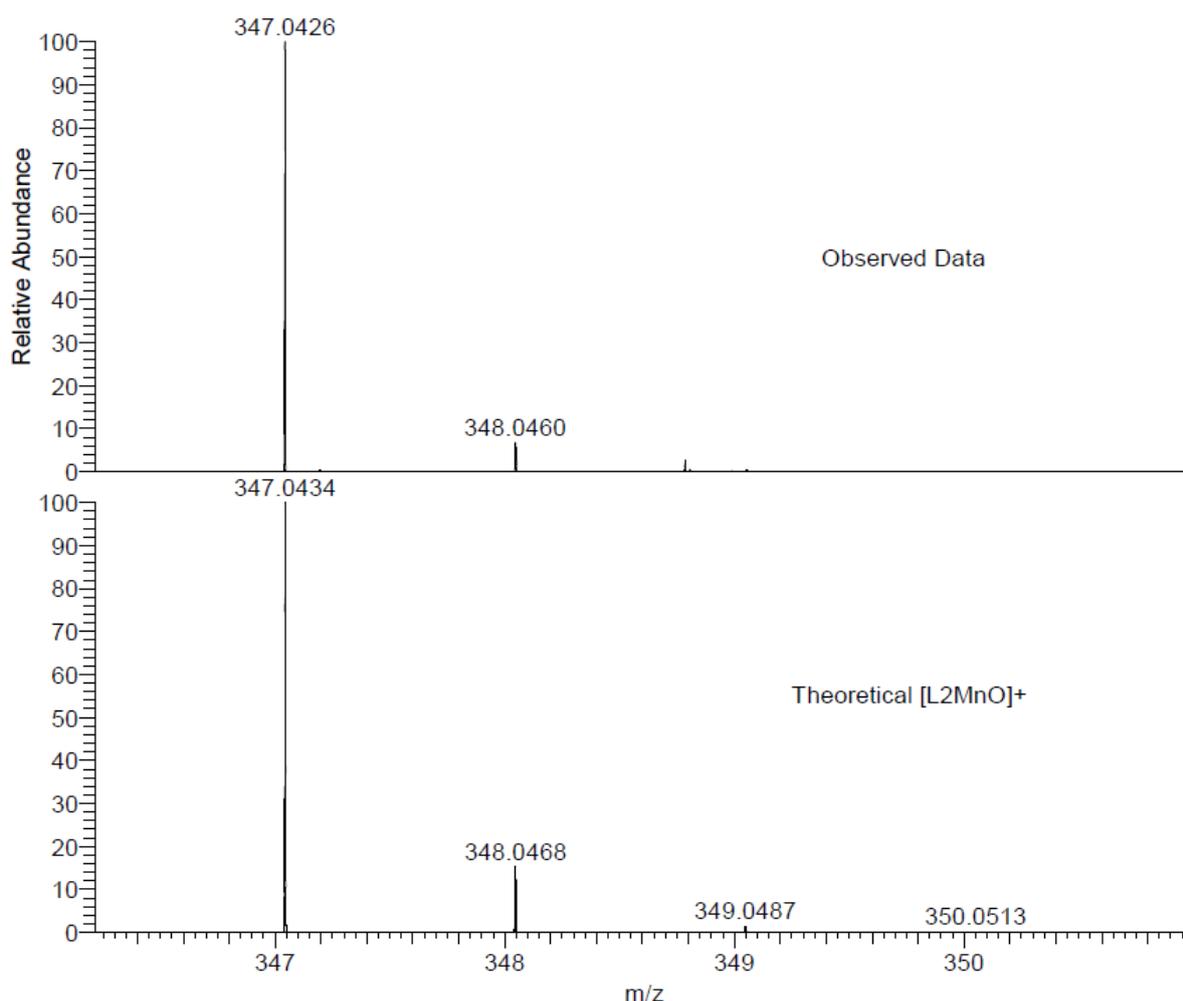
Figure 10: Detected m/z peak for [(DMPO)$_2$Mn(V)O]$^+$ (top) and its theoretical isotope pattern (bottom).

At the end of the reaction, a brown solid, insoluble in acetonitrile was always recovered and proved unable to catalyse further epoxidation. We have not been able to characterise this amorphous residue. Based on the above mentioned MS analysis and previous literature reports on (salen)Mn[III] and (porphyrin)Mn[III] systems, it may be composed of free ligand, (DHMP)$_3$Mn species and possibly various μ-oxo species.[29]

Discussion

With regard catalytic activity, we have here demonstrated that DMHP is a suitable ligand of Mn[III] complexes to form a catalyst capable of epoxidising some alkenes with excellent selectivity and efficiency using oxidants that give the most environmentally friendly decomposition products. As demonstrated, the epoxidations have some unique features, in particular relatively clean and selectivity for strained alkenes that make them stand out when compared to (salen)Mn[III] or (porphyrin)Mn[III] complexes. It was not obvious that DMHP as a ligand would allow the complex to be catalytically active, especially with regard to the sensitivity of the reaction to the substrate, oxidant and

co-catalyst. It can be noted that most active Mn(III) epoxidation catalyst in the literature contain nitrogen as coordinating groups, for example in salen, porphyrins and various other systems based for example of macrocyclic polyaza ligands.[2] To the best of our knowledge, DMHP falls into a group of very rare oxygen-rich ligands that provide catalytically active complexes. This is especially true when considering that in the presence of sodium acetate, an oxygen-only coordination is expected around the metal. This shows that further studies of hydroxypyridinones as alternative ligands in system containing salen, porphyrins, acetylacetonate, etc. are a worthy endeavour.

Because active species involved in Mn-catalysed oxidation reactions are relevant to enzymatic systems, not least Catalase-like reaction and in the photosystem, it is also worth discussing the data giving insights into the mechanism of action of complex **1** to try and extract key features illustrating the idiosyncrasies provided by the ligand. Results of the epoxidation of cyclooctene with **1** seem to indicates that (beside obvious solubility issues) not all commonly studied oxidants are capable of activating (DMPO)$_2$MnCl. This observation should be contrasted to (salen)Mn^{III} that appears to be easily activated with a wider range of oxidants, although in yields that are known to be variable. Similarly, (salen)Mn^{III} appears to be capable of epoxidising a wider range of substrates than complex **1**. It was reported that the Mn^{III}/Mn^{IV} couple in **1** has a redox potential (quasi-reversible) of +0.54V vs NHE in acetonitrile[16] while that of (salen)Mn^{III} in acetonitrile was reported to be +1.29 V vs NHE.[30] We can therefore extrapolate that the (DMPO)$_2$Mn$^{IV/V}$ redox potential of **1** is also much lower than the one of (salen)Mn$^{IV/V}$. It can then be proposed that the higher propensity of DMPO to stabilise higher oxidation states compared to salen make the activated complex less reactive and therefore more selective. It is interesting to note the large difference in reactivity between small cyclic alkenes (Table 2, entry 3) and larger ones (Table 2, entry 1 and 2). This result is not unprecedented, it was indeed also observed for a (salen)Cr^{III} complex that is known to be less reactive than its Mn^{III} counterpart.[31] Substrate selectivity means that complex **1** is not as versatile an epoxidation catalyst as (salen)Mn^{III} but this can also be a blessing in disguise if epoxidation selectivity is to be achieved on structurally complex substrates that could have several carbon-carbon double bonds present. Furthermore, the proposed higher stability of the active species resulting from **1** may in the future allow their isolation and characterisation. This could help further understand the mechanism of formation and reactivity of numerous high-valent oxo manganese systems previously studied.

The observation of selectivity against double-bond strain has elsewhere also been rationalised by a concerted mechanism for the insertion of the oxygen atom into the double bond (Scheme 5 involving a putative Mn^{V}=O species discussed below) [32] where release of strain in the double bond lead to drastic difference in reactivity.[33] This concerted mechanism would also be responsible for the formation if *cis* and *trans* epoxide from cis-stilbene as was indeed observed with **1** and with (salen)Mn^{III} complexes.[30,34] Moreover, the lower reactivity of **1** is expected to give a higher ratio of *trans*-epoxide compared to complex **2**, as observed in Table 2, entry 9.
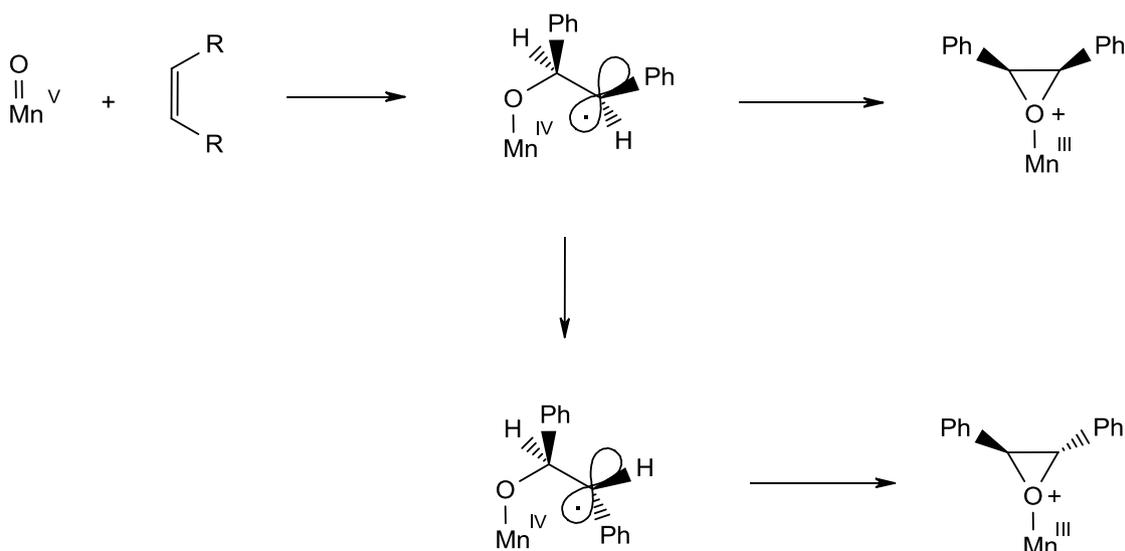
Scheme 5: Proposed mechanism for the stepwise insertion of the oxygen atom via formation of a radical intermediate.

The effect of added co-catalysts in epoxidation by (salen)Mn[III] complexes is well known.[3a] It has been suggested that the role of added co-catalysts is to act as Brønsted bases, helping the formation of the active species but the effect we observed of buffered solutions of hydrogen peroxide (alkaline pH) on epoxidation and amount of catalase-like decomposition seem to contradict this observation.[18] Our UV-Vis spectrophotometry, cyclic voltammetry and nESI-MS studies indicate that imidazole binds the complex in acetonitrile solutions. By analogy with studies performed on (salen)MnCl, we propose that the chloride anion is displaced by the added co-catalyst, thus leaving one coordination site on the metal for the oxidant. The fact that optimum conversion was obtained with 4 equivalents of imidazole suggests the binding equilibrium of the co-catalyst is not thermodynamically favourable in the reaction conditions. It has been proposed that excess imidazole can cause an increase in the catalase-like decomposition of hydrogen peroxide by (salen)Mn[III] complexes.[35] However, remarkably, we instead observed that excess imidazole reduced catalase-like decomposition of H_2O_2.[18] This effect therefore cannot be the cause of the reduction in conversion. The decrease of catalytic activity of **1** upon addition of larger amount of imidazole could instead be caused by the formation of a bis-imidazole complex, in effect saturating the coordination sphere of the metal (Scheme 6). Formation of these bis adducts have been proposed to occur with (salen)Mn[III] and (porphyrin)Mn[III] complexes.[36]
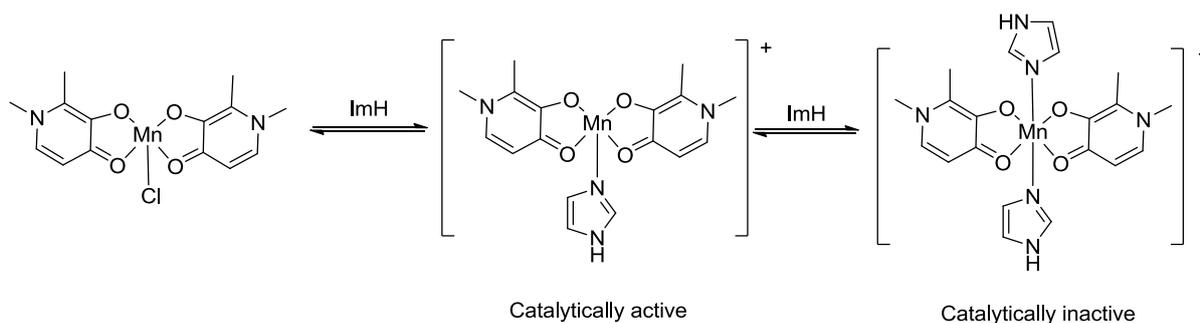
Scheme 6: Proposed equilibriums between **1** and imidazole.

Attempts at identifying the bis-imidazole adduct by nESI-MS or at isolating them were however unsuccessful and pending further work, this proposal relies only on UV-Vis and reactivity data. We also considered the possibility of one or two DMPO ligands being removed by imidazole to give inactive $(DMPO)Mn(ImH)_n$ or $Mn(ImH)_n$ complexes respectively but no evidence for these was forthcoming either in our MS experiments. To explain the said decrease in oxidation activity, it is also possible to consider that imidazole, when present in large amount, starts to compete against the alkene as a substrate but attempts to identify products of imidazole oxidation also failed (oxidations of imidazole were observed in Mn(Porphyrin) systems[37]). Finally, Imidazole could affect the pH of the reaction, and hence at high concentrations, will have an effect akin to the one observed in Figure 2. Further work is will investigate to role of the added co-catalyst in more detail.

We have observed that bubbling of the reaction mixture occurred with hydrogen peroxide and that was ascribed to a catalase-like decomposition of the oxidant. Numerous manganese complexes are known to catalyse dismutation of hydrogen peroxide in a catalase-like manner.[38] The most commonly encountered catalase mimics require two atoms of manganese to decompose one molecule of hydrogen peroxide, either by being dinuclear or mononuclear with a 2:1 reaction stoichiometry.[20] If applicable to **1**, such a Metal:H_2O_2 stoichiometry would explain the observed dependence of the conversion on the concentration of **1** (Figure 3), when higher concentration of catalyst could favour competing catalase-like decomposition over epoxidation. Furthermore, the higher conversion of styrene obtained with slow addition of hydrogen peroxide compared to the conversion obtained when all the oxidant is added at once (Table 2, entry 7) also seems to indicate that the decomposition of hydrogen peroxide is indeed performed by the active species responsible for epoxidation and that a competition therefor exists between epoxidation and H_2O_2 decomposition. Also, the higher yield of precocene I and 1,5-cyclooctadiene epoxidation using TBAO (Table 3, entry 8 and 4 respectively) compared to hydrogen peroxide (Table 2, entries 4 and 11) noted above could be explained by that competition. In the case of hydrogen peroxide, relatively rapid decomposition of the active species prevents epoxidation of the unreactive substrates. In the case of TBAO, this active species decomposition by the oxidant does not exist, giving the more unreactive substrate time to be converted. We can therefore propose that this decomposition reaction proceeds via two one-electron reductions of H_2O_2 by the active species as proposed elsewhere.[39]

A large body of work has investigated the nature of the active species in related manganese catalysts, $Mn^{IV}=O$ and/or $Mn^{V}=O$ being proposed more commonly, especially since these have a wider relevance to manganese based enzymes.[8a] In catalysed oxidation, the nature of the active species can also vary depending on the oxidant used. In the case of alkylhydroperoxides as oxidants, MPPH has been used as a mechanistic probe to differentiate between homolytic and heterolytic scission of the O-O bond in the corresponding Mn-OOR adduct.[22] We have herein obtained evidence using MPPH that products coming from homolytic and heterolytic scissions did form. However, extrapolating this result to an hydrogen peroxide adduct is not straightforward: for the homolytic vs heterolytic scission of the O-O bond of an hydroperoxide adduct, it has been reported that what is applicable to alkyl hydroperoxides may not be applicable to H_2O_2 and that the type of scission can sometimes be pH dependent.[40] It was elsewhere reported that that heterolytic scission of the O-O bond was common for (hydroperoxido)manganese(III) complexes.[19c,41]

In the case of hydrogen peroxide as the oxidant, we have observed by mass spectrometry a species detected as $[(DMPO)_2(ImH)Mn(IV)OOH]^+$. Our mixture could therefore contain the hydroperoxo adduct as detected. This type of species has frequently been proposed as part of the catalytic cycle of related complexes and it has been detected unambiguously by mass spectrometry in some cases.[42a,9j,9k,42b] Alternatively, we could propose the formation in solution of a η^2 side-on peroxo complex that we detected as its protonated form. These are also known for Mn^{IV} complexes.[43]
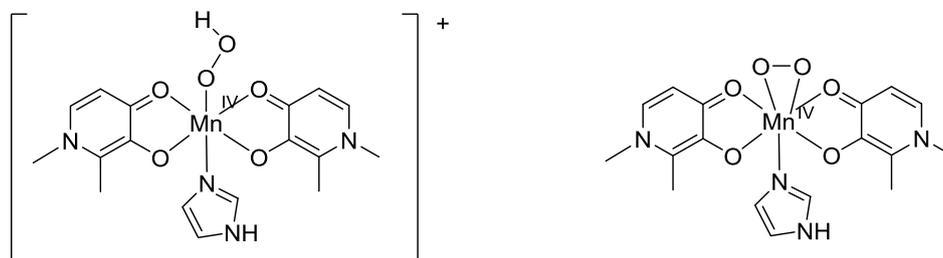
Scheme 7: Possible structures for the species detected at m/z 432.0835.

The involvement of $Mn^{V}=O$ species as the oxidising agent has also been proposed.[44] Direct proof of the formation of $Mn^{V}=O$ has been reported for the reaction of Iodosylbenzene with (salen)Mn^{II}.[45] In the case of monoperoxysulfate as an oxidant, we observed a $Mn^{V}=O$ species by nESI mass spectrometry. The cyclic voltammetry results indicate that DMPO has a much higher stabilising effect on high oxidation states than salen, for which $Mn^{V}=O$ species were detected. It is therefore reasonable to consider that $Mn^{V}=O$ are thermodynamically at least as accessible with DMHP as with salen. Finally, the successful epoxidation of cyclooctene with PhIO (Table 1, entry 3), a 2-electron oxidant is more easily explained by formation of a $Mn^{V}=O$ species, thus strengthening the likelihood of its formation and involvement in the catalytic cycle.

It is also interesting to know whether imidazole is still bound to the manganese atom during the whole catalytic cycle or is released at some stage after formation of the hydroperoxo adduct to allow the active species to be formed. Reports of (salen)Mn^{III} complexes where the axial ligand is covalently bound to the ligand and therefore cannot be released seem to suggest their presence during the whole catalytic cycle is not detrimental to activity.[34c] The observation of a [(DMPO)$_2$(ImH)$_1$Mn(IV)-OOH]+ and [(DMPO)$_2$Mn(V)O]+ species suggests that in our case, imidazole is released at some stage before or simultaneously to the formation of the Mn^V=O active species.

Based on the results discussed above, we suggest the mechanism described in Scheme 8. Considering that both hydrogen peroxide and TBAO gave very similar oxidation profiles, we propose that they follow a very similar mechanism and that the detection of the species formulated as [(DMPO)$_2$(ImH)Mn(IV)OOH]$^+$ and [(DMPO)$_2$Mn(V)O]$^+$ indicate the presence of various intermediates in the overall common catalytic cycle. Two pathways to the active species are proposed, one from a Mn(III)-OOH adduct that undergoes an heterolytic scission of the O-O bond (that would explain the formation of 2-methyl-1-phenyl-2-propanol when MPPH was used as the oxidant. This pathway may be specific to MPPH or common to all ROOH oxidants used), one involving the Mn^{IV}-OOH species that would undergo an homolytic scission of the O-O bond. We propose here that these two pathways lead to the same active species. In the case of Mn(salen) complexes however, numerous studies suggested the existence of competing pathways with varying active species.[26] Using the main two oxidants studied herein, competition between the epoxidation, dismutation (in the case of hydrogen peroxide only) and degradation reactions explain the selectivity observed for strained alkenes. Strained substrates would react with the active species much faster than unstrained ones[46], hence would compete favourably against dismutation of H$_2$O$_2$ and complex degradation. Unstrained alkenes would react so slowly that dismutation and degradation predominate.

Scheme 8: Proposed mechanism for the epoxidation of alkenes.

Conclusions

We have for the first time identified that a previously known Mn[III] complex can be used as a new class of epoxidation catalyst using monoperoxysulfate or hydrogen peroxide as the primary oxidant. Critically, this complex is formed from a unique type of coordinating group whose impact on the properties of metal complexes is not fully understood. The most striking feature of our system is its ability to perform very selective and clean epoxidation reactions on strained carbon-carbon double bonds. To the best of our knowledge, these results are at almost unprecedented levels for a biomimetic Mn[III] catalyst. Furthermore, these reactions are accessible using the oxidants that give the most environmentally friendly decomposition products.

The mechanism of the epoxidation reaction appear to have close similarities to that of the well-known (salen)Mn[III] and (porphyrin)Mn[III] systems but some key differences exists that deserve further investigation. These could lead to development of new classes of industrially viable catalysts but could also to shed light on the mechanism of Mn-based epoxidations in general. Moreover, the unique nature of the coordination group, and the impact it has on reactivity (demonstrated herein) should also

inspire further studies aiming to replace salen, porphyrins and acetylacetonate type ligands in other fields of catalysis, well beyond oxidation reactions.

Further work aimed at confirming the proposed mechanism of the epoxidation reaction and at optimising the reaction with hydrogen peroxide and with monopersulfate are well advanced in our laboratory and will be published in due course.

Experimentals

Complex **1** was synthesised as described.[16] Hydrogen peroxide was 30% w/v in water, tBuOOH was 70% in water. Iodosylbenzene and MPPH were prepared by literature methods.[47,48] Limonene 1,2-epoxide was prepared according to Wilkinson et al.[49] 1-phenyl-cyclopentene, 1-phenyl-cyclohexene and 1-phenyl-cycloheptene were synthesised by Grignard reaction of Bromobenzene on the corresponding cyclic ketone followed by dehydration in toluene with p-toluenesulfonic acid.[50]

Typical reaction procedure: Complex **1** (0.04 mmol), the substrate (4 mmol, 100 equivalents), imidazole (0.16 mmol, 4 equivalents) were solubilised in acetonitrile (10 mL) at 0°C and left to stir for 10-15 minutes. Then, 6 mmol (150 equivalents) of oxidant were added (except H_2O_2: 18 mmol, 450 equivalents were used). The mixture was then incubated at 4°C for 24 hours, after which it was diluted with 10 mL water and extracted once with 10 mL diethyl ether. Bromobenzene was then added to the organic phase and the mixture was analysed by GC/MS. All reported conversions are an average of at least 3 repeats.

All nESI analyses were in acquired positive ion mode on a Thermofisher LTQ Orbitrap XL spectrometer with an Advion NanoMate infusion system. Samples were dissolved in MeOH or MeCN. The NanoMate spray potential = +1.45kV, with an infusion flow rate of 0.25 µL/min. The Orbitrap capillary temperature = 200°C, the capillary voltage = +30V, and the tube lens voltage = +150V.

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