Manganese catalyzed *cis*-dihydroxylation of electron deficient alkenes with H_2O_2†

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A practical method for the multigram scale selective *cis*-dihydroxylation of electron deficient alkenes such as diethyl fumarate and *N*-alkyl and *N*-aryl-maleimides using H_2O_2 is described. High turnovers (>1000) can be achieved with this efficient manganese based catalyst system, prepared *in situ* from a manganese salt, pyridine-2-carboxylic acid, a ketone and a base, under ambient conditions. Under optimized conditions, for diethyl fumarate at least 1000 turnovers could be achieved with only 1.5 equiv. of H_2O_2 with *d*/*l*-diethyl tartrate (*cis*-diol product) as the sole product. For electron rich alkenes, such as *cis*-cyclooctene, this catalyst provides for efficient epoxidation.

Introduction

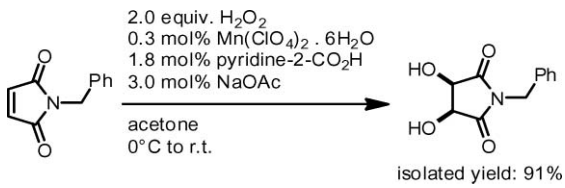
The selective and atom efficient *cis*-dihydroxylation of alkenes is a key transformation in synthetic organic chemistry,[1] with contemporary methods relying predominantly on stoichiometric oxidants, such as MnO_4^- and OsO_4,[1c,2] or transition metal based oxidation catalysts, in particular, ruthenium,[3,4] and osmium (asymmetric) dihydroxylation methods.[5]

Practical osmium free methods for *cis*-dihydroxylation of alkenes that avoid the need for excess amounts of oxidant are highly desirable, both in synthesis and for the large scale production of important building blocks, not least *N*-aryl and *N*-alkyl-maleimides.[6] Furthermore, the *cis*-dihydroxylation of electron deficient alkenes such as *N*-alkyl-pyrrole-2,5-diones remains a major challenge with the more reactive ruthenium based catalysts systems employing $NaIO_4$ providing one of the few effective routes available to the *cis*-diol products. For example 1-benzyl-1*H*-pyrrole-2,5-dione can be converetd to (*meso*)-*N*-benzyl-3,4-dihydroxy-2,5-pyrrolidinedione using 1.3 equiv. of $NaIO_4$ and 0.8 mol% of $Ru^{III}Cl_3$ in 73.3% yield.[6]

In recent years, considerable advances have been made in the development of atom-efficient and environmentally friendly catalytic *cis*-dihydroxylation methods employing H_2O_2,[1] most notably, in the use of iron pyridyl-amine complexes, by Que *et al.*,[7] manganese complexes by De Vos *et al.*[8] and Feringa *et al.*[9] and others[10] and ruthenium complexes by Che *et al.*[11] With the $[Mn^{III}_2O(RCO_2)_2(tmtacn)_2]^{2+}$ catalysts[12] we have reported recently,[9b–e] the *cis*-dihydroxylation of electron rich *cis*-alkenes was achieved with over 8000 turnovers to the *cis*-diol product of *cis*-cyclooctene and near complete atom efficiency in the oxidant H_2O_2. By contrast, this system shows little activity with electron deficient alkenes such as diethyl fumarate.

A key challenge, therefore, is to develop readily accessible methods based on simple catalysts, preferably prepared *in situ*, that are able to achieve similar efficiency in the *cis*-dihydroxylation for electron deficient alkenes.

In the present contribution we describe a readily accessible catalytic system based on manganese and H_2O_2 that is highly selective in the *cis*-dihydroxylation of electron deficient alkenes such as diethyl fumarate and *N*-alkyl-maleimides on a multigram scale (Scheme 1).



Scheme 1 *cis*-Dihydroxylation of 1-benzyl-1*H*-pyrrole-2,5-dione using the method described here.

The present system is based on a manganese source in combination with pyridine-2-carboxylic acid, a ketone and a base. With this method electron deficient alkenes can be converted quantitatively to the corresponding *cis*-dihydroxylation products. Furthermore, we show that for electron rich alkenes epoxidation dominates with the ratio between *cis*-diol and epoxide products showing a qualitative correlation between electron deficiency and the product distribution observed.

Results and discussion

cis-Dihydroxylation of electron deficient alkenes

The catalyst is formed *in situ* by addition of a Mn^{II} salt and pyridine-2-carboxylic acid to acetone followed by addition of the substrate and then NaOAc (aq). The reaction mixture is then

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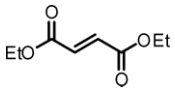
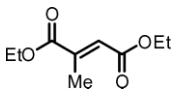
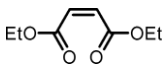
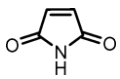
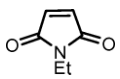
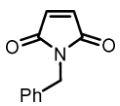
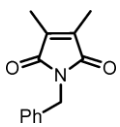
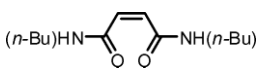
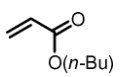
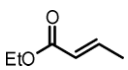
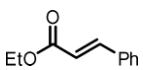
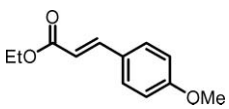
† Electronic supplementary information (ESI) available: Full details for reactions in Tables 1 and 2 with characterisation and spectra. See DOI: 10.1039/c0ob00102c

Table 1 *cis*-Dihydroxylation of alkenes by $Mn^{II}(ClO_4)_2$/pyridine-2-carboxylic acid/NaOAc/H_2O_2 in acetone

	Substrate	Conversion (%)[a]	Isolated yield (%)
1		100(>95%)[b]	91(95)[b]
2		>95	88
3		63	47[c]
4		100	98
5		100	>95
6		100	91
7		100	75
8		55	32
9		81	55[a,d]
10		<10	*cis*-diol:epoxide[a] 2 : 1
11		<10	*cis*-diol:epoxide[a] 1 : 1
12		<10	*cis*-diol:epoxide[a] 1 : 1

[a] Determined by Raman spectroscopy using the C=C stretching band at *ca.* 1600 cm^{-1} and by ^1H NMR spectroscopy. For detailed conditions and procedures see ESI. [b] In 2-butanone. [c] 25% and [d] 19% recovered starting material.

cooled in ice water and H_2O_2 is added either as a single batch or by syringe pump. Under optimized conditions, for diethyl fumarate at least 1000 turnovers could be achieved with only 1.5 equiv. of H_2O_2 with *d*/*l*-diethyl tartrate (*cis*-diol product) as the sole product.[13] Further oxidation of the *cis*-diol formed was not observed, even with excess H_2O_2.

A series of electron deficient alkenes together with conversions and isolated yields are shown in Table 1. The reaction conditions were optimized for each of the electron deficient alkenes examined using Raman spectroscopy to monitor conversion of the alkene (see for example section 6 of the ESI†) and ^1H NMR spectroscopy to determine product ratios. Isolation of *cis*-diol products was carried out using standard synthetic procedures (see ESI for detailed procedures). The optimum reaction conditions were found to be substrate specific but in general a 1 : 6 : 10 mixture of a Mn^{II} salt, pyridine-2-carboxylic acid and NaOAc provided good conversion and yield of the *cis*-diol products.

The present system is equally effective for mono-, di-, tri- and tetra-substituted electron deficient alkenes. For alkenes such as ethyl crotonate (Table 1, entries 10–12) low conversion and selectivity between *cis*-diol and epoxide products was observed. However overall good to excellent conversion was achieved with electron deficient *trans*-alkenes, such as diethyl fumarate and diethyl-2-methyl-fumarate, and cyclic *cis*-alkenes such as maleimide.

The reduced reactivity towards diethyl maleate and *N*,*N*′-dibutylmalediamide is surprising considering the fact that, *e.g.*, maleimide can be converted to the corresponding *cis*-diol product quantitatively (Table 1). Lowering the substrate concentration provided a modest improvement in conversion for diethyl maleate however a maximum conversion of only 63% was achieved in the present study.

For diethyl fumarate and diethyl maleate a difference in maximum conversion (Table 1) and reaction rate was notable. Diethyl fumarate can be converted quantitatively to the *d*/*l*-diethyl tartrate within 60 min under optimised reaction conditions. For diethyl maleate by contrast only 20–30% conversion over several hours can be achieved using these conditions. In order to investigate the origin of these differences further a competition experiment in which a 1 : 1 mixture of diethyl fumarate and diethyl maleate was oxidised under conditions optimised for diethyl fumarate was performed (see Fig. 1 and ESI†). Under these conditions the conversion of diethyl maleate was 20% as expected. Surprisingly however only 90% conversion was achieved for diethyl fumarate (in the absence of diethyl maleate full conversion is achieved under these conditions). The fact that substantial conversion was

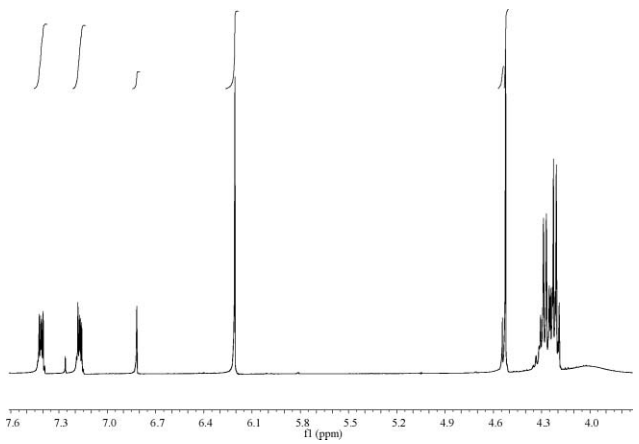


Fig. 1 ^1H NMR spectrum of reaction mixture (diluted in $CDCl_3$). Reaction conditions: $Mn(ClO_4)_2 \cdot 6H_2O$ (1.0 μmol), pyridine-2-carboxylic acid (3.0 μmol), NaOAc (30.0 μmol), 1,2 dichlorobenzene (as internal standard, 0.5 mmol), diethyl fumarate (0.5 mmol) and diethyl maleate (0.5 mmol) in acetone at 5 °C with single addition of H_2O_2 (1.5 equiv.). For Raman spectra and the full NMR spectrum see ESI. Diethylfumarate (6.8 ppm), diethylmaleate (6.2 ppm), *d*/*l*-diethyltartrate (4.52 ppm), *meso*-diethyltartrate (4.55 ppm).

Table 2 *cis*-Dihydroxylation and epoxidation of electron rich alkenes by $Mn^{II}(ClO_4)_2$/pyridine-2-carboxylic acid/NaOAc/H_2O_2 in acetone

	Substrate	Conversion (%)[a]	Yield
1	*cis*-cyclooctene	97	12% *cis*-diol (12%)[b] 72% epoxide (60%)[b] 12 α-hydroxy ketone (10%)[b]
2	cyclohexene	100	2% *cis*-diol 54% epoxide 14% α-hydroxy ketone 3% cyclohexenone
3	1-methyl-cyclohexene	100	8% *cis*-diol 64% epoxide
4	1-octene	82	9% *cis*-diol 35% epoxide 18% α-hydroxy ketone
5	styrene	100	4% *cis*-diol 75% epoxide 9% other
6	*trans*-β-methylstyrene	100	7% *cis*-diol 65% epoxide 12% α-hydroxy ketone
7	2-methyl-2-pentene	100	13% *cis*-diol 62% epoxide

[a] Determined by Raman spectroscopy and by ^{1}H NMR spectroscopy. For detailed conditions and procedures see ESI. [b] Isolated yields in parentheses.

achieved for both substrates confirms that catalyst inhibition by the substrates does not occur. Hence it is apparent that product inhibition (either from oxidation or hydrolysis products) of the diethylmaleate may be involved.[14] The stability of the substrate and products towards hydrolysis under the reaction conditions employed indicates that it is oxidation products which cause catalyst inhibition.

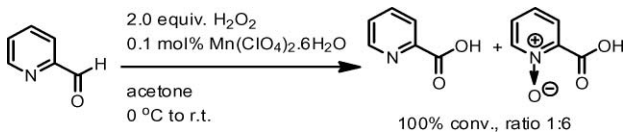
To investigate the possibility of primary oxidation products (*i.e. meso*- and *d*/*l*-diethyl-tartrate) being responsible for product inhibition, similar experiments were performed using a 1 : 1 mixture of diethyl fumarate and either *meso* or *d*/*l*-diethyl tartrate. In both cases full conversion of the diethyl fumarate was achieved. This confirms that the primary oxidation products are not responsible for catalyst inhibition.

cis-Dihydroxylation and epoxidation of electron rich alkenes

A series of electron rich alkenes is shown in Table 2. For all substrates examined the main product observed is the epoxide product. However, significant amounts of diol were formed in all cases. As has been noted for the $RuCl_3/NaIO_4$[3,6] and Ru^{III}tmtacn[11] systems, and to a lesser extent the Mn-tmtacn systems,[9] the diol produced is readily oxidised further to the α-hydroxy ketone and ultimately to C–C bond cleavage. The propensity for further oxidation of the *cis*-diol products results in reduced selectivity. Nevertheless, epoxidation was observed as the primary product in most cases, especially for electron rich alkenes such as *cis*-cyclooctene and styrene (Table 2, entries 1 and 5). Overall the substrate scope shows a qualitative correspondence between the *cis*-diol/epoxide ratio with the electron deficiency of the substrate. The extent of epoxidation of alkenes such as *cis*-cyclooctene (1 : 6 diol/epoxide) and ethyl crotonate (2 : 1 diol/epoxide) (see Tables 1 and 2) is comparable to the trends observed by Que and co-workers for Fe^{II} polypyridyl based catalysts.[15] This may indicate that selectivity is substrate, and not catalyst, controlled.

Catalyst composition

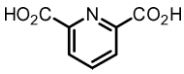
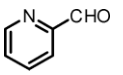
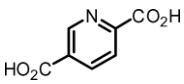
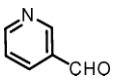
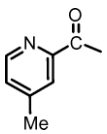
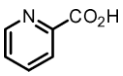
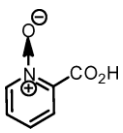
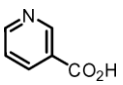
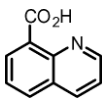
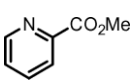
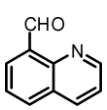
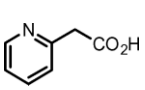
The catalyst system is sensitive to changes in catalyst composition. With picolinic-2-carboxaldehyde, which can be oxidized *in situ* (Scheme 2, see also ESI†), full conversion is observed



Scheme 2 Oxidation of pyridine-2-carboxaldehyde.

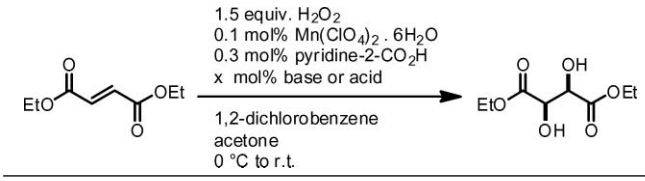
With other substituted pyridine carboxylic acids, *e.g.* pyridine-2,5-dicarboxylic acid, full activity was observed (Table 3). By contrast, for picolinic acid *N*-oxide or pyridine 2,6-dicarboxylic acid, activity was not observed (Table 3). This indicates that the co-catalyst is acting as a ligand to the Mn^{II} and that the *N*-oxide,

Table 3 Effect of molecular structure of the pyridyl ligand on efficiency towards the *cis*-dihydroxylation of diethyl fumarate

Ligand		Conversion (%)	Ligand		Conversion (%)
	A	0		B	0
	A	100		C	100
	A	0		D	100
	B	100		B	0
	D	0		D	0
	D	0		D	80
	D	100			

All reactions carried out in acetone at room temperature. Reaction conditions (Mn/ligand/NaOAc/H_2O_2, mol%): **A:** (0.1/0.1/1.2/400), **B:** (0.1/0.3/1.0/200). **C:** (0.1/0.3/1.2/800). **D:** (0.1/0.3/1.0/800). The oxidation of diethyl fumarate was monitored by following the intensity of the 1665 and 1648 cm^{-1} Raman bands (alkene stretching vibration), relative to the internal standard 1,2-dichlorobenzene (1575 cm^{-1}).

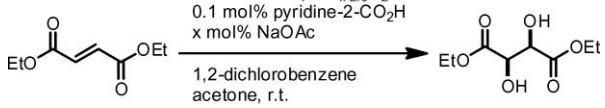
Table 4 Conversion of the diethyl fumarate with various bases and acid



Base or acid	Mol (%)	Conversion (%)
none	—	0
NaOAc	1.0	100
KOAc	1.0	100
NaOAc	20.0	100
NaOH	1.0	100
$NaHCO_3$	1.0	100
Na_2CO_3	1.0	100
NH_4OAc	1.0	70
AcOH[a]	1.0	0

The oxidation of diethyl fumarate was monitored by following the intensity of the 1665 and 1648 cm^{-1} bands (alkene stretching vibration). Relative to the internal standard 1,2-dichlorobenzene (1575 cm^{-1}).[a] Confirmed by ^1H NMR spectroscopy.

Table 5 Effect of variation in equivalents of base on reactivity of the present system under conditions where the ratio of Mn^{II} to pyridine-2-carboxylic acid is 1 : 1



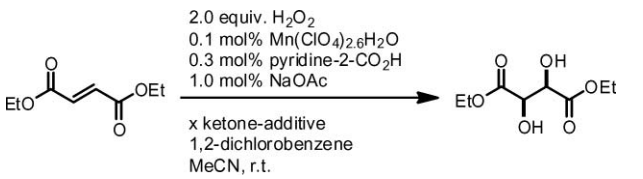
Mol% of NaOAc	Conversion (%)
0	0
0.1	0
0.2	22
0.3	32
0.5	46
1.0	72
2.0	31

The oxidation of diethyl fumarate was monitored by following the intensity of the 1665 and 1648 cm^{-1} bands (alkene stretching vibration). Relative to the internal standard 1,2-dichlorobenzene (1575 cm^{-1}).

although it can be formed under reaction conditions (Scheme 1), is not involved in the oxidation catalysis. A notable observation is that for quinoline-8-carboxylic acid no conversion was observed in contrast to quinoline-8-carbaldehyde for which 80% was observed. In this case the very limited solubility of the quinoline-8-carboxylic acid in the reaction mixture is almost certainly the reason for the difference in reactivity, emphasising the point that the conversion achieved is highly dependent on the initial formulation of the reaction mixture.

The system is relatively insensitive to the nature of the base employed with, *e.g.*, NaOAc, $NaHCO_3$ and NaOH or $Mn(OAc)_2$ providing comparable results (Table 4). The insensitivity in terms of activity or selectivity to variation in the base employed indicates that the catalyst is not dependent on acetate as a ligand. Furthermore, the number of equivalents of base employed does not affect the reaction significantly provided that it is in excess with respect to the pyridine-2-carboxylic acid and Mn^{II}.

Table 6 *cis*-Dihydroxylation of diethyl fumarate in acetonitrile with various ketones



Ketone	Amount	Conversion (%)
none	—	0
CH_3COCH_3	10 vol (%)	20
CH_3COCH_3	0.3 equiv.	0
CF_3COCH_3	30 vol (%)	100
CF_3COCH_3	20 vol (%)	>95
CF_3COCH_3	10 vol (%)	>95
CF_3COCH_3	5 vol (%)	>95
CF_3COCH_3	0.3 equiv	90
CF_3COCF_3	10 vol (%)	0
CF_3COCH_3 (in MTBE)	10 vol (%)	>95
CCl_3COCCl_3	10 vol (%)	0

The oxidation of diethyl fumarate was monitored by following the intensity of the 1665 and 1648 cm^{-1} bands (alkene stretching vibration) relative to the internal standard 1,2-dichlorobenzene (1575 cm^{-1}). In all cases *d*/*l*-diethyl-tartrate was the sole product observed.

Notably when a 1 : 1 ratio of pyridine-2-carboxylic acid/Mn^{II} is employed (Table 5) the system is highly sensitive to the number of equivalents of base added with a 1 : 1 ratio being optimum. This indicates that the base serves mainly to deprotonate pyridine-2-carboxylic acid and allows the catalyst to form. For the pyridine based ligands (Table 3) that do not bear a carboxylic acid residue, the addition of base is still necessary to ensure the deprotonation of the pyridine in the acetone/water mixture and furthermore is required in order to achieve a significant reaction rate and conversion.

By contrast, in the absence of added base or where acid, *e.g.*, acetic acid, is added prior to addition of H_2O_2, conversion was not observed (Table 4). However, once the reaction had commenced addition of acetic acid resulted in a decrease in reaction rate and conversion but did not inhibit the reaction fully (see ESI†).

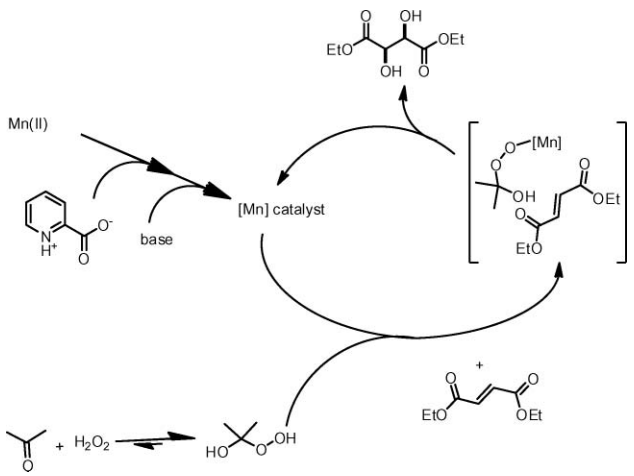
Solvent dependence

Acetone is the solvent of choice in the present study. However, the catalysis proceeded equally well in 2-butanone (Table 1, entry 1). Initial screening of the reaction conditions for solvent tolerance indicated that activity is observed only in ketone based solvents. Notably, the system is tolerant to some co-solvents (Table 6), for example in acetonitrile 20% conversion was obtained with 10 vol% acetone. Furthermore, electron deficient ketones such as 1,1,1-trifluoroacetone can be employed (5 vol%) in acetonitrile providing full conversion (Table 6). This indicates that the ketone may play a role directly in the catalysis over and above its role as a solvent, for example through the intermediacy of ketone-peroxide adducts such as that proposed by Que and coworkers.[16] Notably sub-stoichiometric amounts of CF_3COCH_3 provided 90% conversion. In this case ^{19}F NMR spectroscopy indicated the formation of species other than the ketone. For the hexahalo-acetones however no conversion was observed (Table 6).

Overall, however, the use of acetone or 2-butanone is preferred over more electron deficient ketones due to convenience, cost and environmental reasons. The presence of significant amounts of water in the reactions employing acetone as solvent reduces potential hazards associated with the combination of acetone and H_2O_2 significantly. In addition the activity of this system with 2-butanone allows for oxidation of less hydrophilic substrates.

Mechanistic considerations

The effect of variation in the parameters, *i.e.* solvent, co-catalyst and base on the conversion observed provides some insight into the reaction mechanism (Scheme 3). The first observation is the importance of the order of addition of the reaction components. Addition of the base, *e.g.*, NaOAc, prior to addition of the manganese salt and pyridine-2-carboxylic acid results in formation of a precipitate and reduced or no reactivity. Furthermore, replacement of the pyridine-2-carboxylic acid with pyridine-2-carboxaldehyde shows full activity while the corresponding *N*-oxide shows no activity.



Scheme 3

The system is relatively insensitive to the nature of the base employed (Table 4). The presence of a ketone in the reaction is essential as demonstrated in the reactivity observed in acetonitrile and MTBE (Table 6). The equilibrium between H_2O_2 and ketones is well established and essentially all H_2O_2 in acetone or 2-butanone solution is present as the hydrogen peroxide/ketone adduct.[16,17] This adduct is likely to be directly involved in the catalytic cycle as no activity (and importantly no decomposition of H_2O_2) is observed in acetonitrile in the absence of added ketone.

The selectivity observed, *i.e.* electron deficient alkenes undergo predominantly *cis*-hydroxylation, electron rich alkenes undergo epoxidation mainly, indicates that the substrate may determine how the O–O bond is cleaved.

An important question arises as to the nature of the manganese species that engages in activation of the peroxide to oxidise the alkene. One possibility is the formation of a high valent manganese-oxo species through heterolysis of the acetone peroxy O–O bond. The relatively slow reaction rate even in the presence of excess H_2O_2 could suggest that Lewis acid activation of the coordinated oxygen atom of the acetone H_2O_2 adduct by the Mn(II) centre is important however. In such a case the oxygen atom of the peroxide that is coordinated to the Mn(II) ion would be rendered electrophilic in terms of its interaction with the alkene. For electron poor alkenes addition of this oxygen atom may be assisted by nucleophilic attack on the neighbouring carbon atom by the –OH group of the acetone peroxide adduct. Such a mechanism could rationalise the difference in selectivity observed for electron rich and electron deficient alkenes.

With regard to the differences in maximum conversion observed (Table 1) overall the data suggests that it is secondary oxidation products which are responsible for catalyst inhibition. It should be noted that the addition of acids after the reaction has commenced slows but does not halt conversion. Hence, in the case of electron rich alkenes (Table 2), secondary oxidation products although formed will not inhibit that catalyst significantly (*vide supra*). For the α,β-unsaturated substrates (Table 1), however, the secondary oxidation products are likely to include oxalate monoester type species, which may sequester the manganese efficiently and thereby reduce or halt conversion. The qualitative correlation between the rate of conversion of the substrate and the maximum conversion supports this conclusion. For substrates such as maleimide and diethyl fumarate the further oxidation of the *cis*-diol product is not competitive and hence good conversion and selectivity is observed. For less reactive substrates the further oxidation of the *cis*-diol product becomes significant and hence secondary oxidation products form, which can inhibit the reaction, before full conversion.

Conclusions

Overall, the substrate scope for *cis*-dihydroxylation obtained with Mn^{II}/pyridine-2-carboxylic acid is complimentary to the $[Mn^{IV}_2O_3(tmtacn)_2]^{2+}$ based systems we reported recently[9b,c] (*vide supra*) and extends the scope of alkenes that can be converted with high turnover numbers to *cis*-diols using 1st row transition metals and H_2O_2.[18] Importantly, the system presented here is most effective for substrates that, to date, have proven most challenging, even for osmium based reagents. The *in situ* preparation of the catalyst from readily available reagents together with its ease of application (equally well from mg to multi-gram scale reactions, see ESI†) and using H_2O_2 makes this an excellent alternative to the $RuCl_3/NaIO_4$ based *cis*-dihydroxylation method for substrates such as maleimides.[6]

In conclusion, we have demonstrated that the catalyst system Mn^{II}/pyridine-2-carboxylic acid/NaOAc in acetone or 2-butanone can achieve high turnover *cis*-dihydroxylation of, in particular, electron deficient *trans*-alkenes. From a broader perspective these results demonstrate, as shown by Burgess and co-workers for epoxidation previously,[19] that relatively simple ligand/metal systems hold remarkable potential in achieving synthetically useful selective oxidative transformations. Importantly, in the present study we have shown that even at room temperature high turnover numbers and reaction rates can be achieved. Future studies will be directed to identifying the catalytically active species involved in the reaction and in applying the system to other oxidative transformations.

Experimental section

All reagents are of commercial grade and used as received unless stated otherwise. Hydrogen peroxide was used as received as a 50% wt. solution in water; note that the grade of H_2O_2 employed can affect the reaction where sequestrants are present as stabilizers. The synthesis and characterization of diethyl-2-methylfumarate,[20] *N*,*N*-dibutylmalediamide, 1-benzyl-1*H*-pyrrole-2,5-dione and 1-benzyl-3,4-dimethyl-1*H*-pyrrole-2,5-dione are described as ESI. NMR spectra were recorded at ^{1}H- (500 or 400.0 or 201.0 MHz) and ^{13}C-NMR (100.6 or 50.0 MHz). Chemical shifts are denoted relative to the residual solvent absorption (^{1}H: $CDCl_3$ 7.26 ppm, DMSO-d_6 2.50 ppm, CD_3OD 3.31 ppm, acetone-d_6 2.05 ppm; ^{13}C: $CDCl_3$ 77.0 ppm, DMSO-d_6 39.5 ppm, CD_3OD 49.0 ppm). Raman spectra were recorded using a fibre optic equipped dispersive Raman spectrometer (785 nm, Perkin Elmer RamanFlex). Temperature was controlled using a cuvette holder equipped with a custom made fibre optic probe holder (Quantum Northwest). 1,2-Dichlorobenzene was employed as internal standard for Raman spectroscopy.

Caution

The drying or concentration of acetone solutions that potentially contain hydrogen peroxide should be avoided. Prior to drying or concentrating, the presence of H_2O_2 should be tested for using peroxide test strips followed by neutralisation on solid $NaHSO_3$ or another suitable reducing agent. When working with H_2O_2, especially in acetone, suitable protective safeguards should be in place at all times.[17]

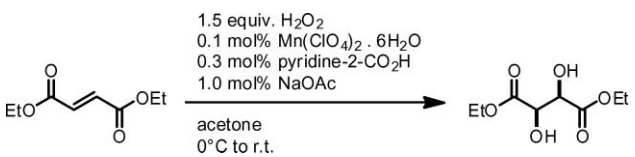
Caution

Perchlorate salts are potentially explosive in combination with organic solids and solvents. In the present study manganese(II) acetate or manganese(II) sulfate was found to give essentially identical reactivity and should be used above 2 gram reaction scales.

Catalyzed oxidations

Example reactions for the *cis*-dihydroxylation of diethyl fumarate and maleimide. For entries 2–9 (Table 1) and 1–7 Table 2 see ESI.†

cis-Dihydroxylation of diethyl fumarate



$Mn(ClO_4)_2{\cdot}6H_2O$ (3.6 mg, 10 μmol), pyridine-2-carboxylic acid (3.7 mg, 30 μmol) and diethyl fumarate (1.64 g, 9.33 mmol) were dissolved in acetone (20 mL) and the mixture was stirred at 0 °C. After addition of 167.0 μL of 0.6 M (aqueous) NaOAc (0.1 mmol, 1.0 mol%), H_2O_2 (50 wt% in water, 0.85 mL, 15.0 mmol, 1.5 equiv.) was added in one portion. The mixture was stirred for 16 h, allowing the temperature to rise to r.t. Excess solid $NaHSO_3$ was added to the reaction mixture to remove residual peroxides if present (verified using peroxide test-strips). The salts were removed by filtration, washed several times with acetone, after which the acetone was removed *in vacuo*, giving the product as a colourless oil (1.78 g, 8.62 mmol, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.52 (d, J = 3.7 Hz, 2H), 4.33–4.26 (m, 4H), 3.43 (s, 2H), 1.33–1.28 (m, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.6, 72.0, 62.5, 14.1; HRMS (ESI+) calc. for $C_8H_{14}O_6$ $(M+Na)^+$ 229.0688, found 229.0683; elemental analysis (calc. for $C_8H_{14}O_6$) C 45.75% (46.60%), H 6.90% (6.84%).

Competition experiment in the oxidation of diethyl fumarate and dimethyl maleate

1.0 mL of a stock solution in acetone (20 mL) of $Mn(ClO_4)_2{\cdot}6H_2O$ (7.3 mg, 20 μmol) and pyridine-2-carboxylic acid (7.5 mg, 60 μmol) was added to a solution of 1,2 dichlorobenzene (56 μL, 0.5 mmol), diethyl fumarate (88 mg, 0.5 mmol) and diethyl maleate (88 mg, 0.5 mmol) in acetone (1 mL). After addition of 17.0 μL of 0.6 M (aqueous) NaOAc (2.5 μmol, 1.0 mol%), the mixture was cooled to 5 °C and H_2O_2 (50 wt% in water, 85 μL, 0.15 mmol, 1.5 equiv.) was added in one portion. Excess solid $NaHSO_3$ was added to the reaction mixture to remove residual peroxides if present (verified using peroxide test-strips). The ^{1}H NMR spectrum of the crude reaction mixture was received after dilution in $CDCl_3$ with 1,2-dichlorobenzene as internal reference. From the integrals it is estimated that conversion of diethyl fumarate is 90% while for diethyl maleate the conversion is 20%. With regard to the product distribution, integration of the absorption at *ca.* 4.5 ppm shows a product distribution of 5 : 1 for the *cis*-diol products of diethyl fumarate and diethyl maleate respectively.

Acknowledgements

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12 Tmtacn is *N*,*N'*,*N''*-trimethyl-1,4,7-triazacyclononane.

13 Under the reaction conditions employed, the epoxide (diethyl oxirane-2,3-dicarboxylate) was found to be fully stable and did not undergo ring opening, precluding this as being a route to formation of the *cis*-diol products.

14 With excess H_2O_2 (10 equiv.) monomethoxyoxalic acid was formed which could be expected to sequester manganese ions.

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18 For the heterogenised Mn-tmtacn catalysts of De Vos and coworkers[8] and our own results[9] using $[Mn^{IV}_2O^3(tmtacn)_2]^{2+}$ with carboxylic acids, in which the active $[Mn^{III}_2O(RCO_2)_2(tmtacn)_2]^{2+}$ catalysts form *in situ*, a strong preference for the *cis*-dihydroxylation of electron rich *cis*-alkenes was observed. The latter system is highly active with over 8000 turnovers to the *cis*-diol product of cyclooctene and near complete atom efficiency in the oxidant H_2O_2[9].

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