Selective catalytic oxidations by palladium and manganese

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Chapter 5
Oxidation of alkenes with $\text{H}_2\text{O}_2$ by an *in situ* prepared Mn(II)/pyridine-2-carboxylic acid catalyst and the role of ketones in activating $\text{H}_2\text{O}_2$

A simple, high yielding catalytic method for the multigram scale selective epoxidation of electron rich alkenes using near-stoichiometric $\text{H}_2\text{O}_2$ under ambient conditions is reported. The system comprises of a Mn(II) salt (<0.01 mol%), pyridine-2-carboxylic acid (<0.5 mol%) and sub-stoichiometric butanedione. High T.O.N. (up to 300,000) and T.O.F. (up to 40 s$^{-1}$) can be achieved for a wide range of substrates with good to excellent selectivity, remarkable functional group tolerance and a wide solvent scope. It is shown that the formation of 3-hydroperoxy-3-hydroxybutan-2-one from butanedione, and $\text{H}_2\text{O}_2$ *in situ*, is central to the activity observed.

This chapter was published in part:
5.1 Introduction

The central role played by epoxides and (cis-)diols in all areas of synthetic organic chemistry, from total synthesis and materials science to bulk chemicals production, places the development of new methods for olefin oxidation at the centre of efforts to increase sustainability and reduce the environmental footprint of processes. In this regard considerable efforts have focused on replacing methods based on scarce and potentially toxic metals such as chromium, ruthenium and osmium with metals such as iron, titanium, manganese, tungsten and molybdenum. In addition to using environmentally benign and abundant metals, substituting terminal oxidants in particular Oxone, NaOCl, iodosylbenzenes and mCPBA, with more atom economic oxidants such as O₂ and especially H₂O₂ is a major challenge.

Ideally, catalytic oxidation methods based on efficient, safe and readily applicable ‘off the shelf’ components (i.e. in situ preparation) are desirable for the oxidation of alkenes with H₂O₂ for practical, economic and environmental reasons. Their relatively low toxicity and cost and the often high turnover numbers (T.O.N.s) that can be achieved, position manganese, iron, tungsten and molybdenum based catalysts at the focus of current attention. Notable examples are the ‘off the shelf’ systems based on molybdenum and tungsten oxides developed by Payne, Venturello and Noyori and coworkers and the methyltrioxorhenium (MTO) system developed by Herrmann and others. The tungsten and molybdenum systems have demonstrated remarkably high turn-over numbers (>2,000) and frequencies (> 10 s⁻¹) with H₂O₂ as terminal oxidant. Initial limitations imposed by the acidic conditions resulted in restrictions to their application in the formation of acid sensitive substrates and other substrates such as styrene; but, recently, modified conditions towards addressing this issue have been reported. In the case of the MTO systems good conversion and selectivity can be achieved for a range of alkene substrates in particular trans-alkenes albeit with relatively long reaction times (1- 20 h).

Alkene epoxidation and (cis-)dihydroxylation with manganese based catalysts has seen rapid progress in recent years also, not least in the recent reports by Lau and co-workers with (PPh₄)_2[Mn(IV)(N)(CN)₄] and with the manganese tri- and tetraaza-macrocycle based complexes developed by De Vos, Berkessel, Busch, Costas and our own groups. For methods based on manganese, however, the challenge is to activate H₂O₂ using similarly simple in situ prepared catalysts without producing hydroxyl radicals and avoiding strongly acidic or basic conditions. The systems reported by Hage et al. in NaHCO₃(aq) buffer and by Burgess and co-workers for the epoxidation of alkenes with MnSO₄ and aqueous NaHCO₃ with DMF or t-BuOH, albeit both requiring excess H₂O₂ (> 5 equivalents), are amongst the few in situ prepared manganese based procedures available to date.

The current challenge therefore is to develop methodologies that allow for efficient oxidation of alkenes (in terms of oxidant) with readily available catalyst systems under neutral conditions with good functional group tolerance and selectivity. Recently, we reported such a straightforward method, based on a Mn(II) salt (0.1 mol%), pyridine-2-carboxylic acid (PCA, 0.5 mol%) and H₂O₂ (2.0 equiv.), for the cis-dihydroxylation of electron deficient alkenes in acetone in excellent yields and selectivities.
addition the system showed moderate to good activity and selectivity in the epoxidation of electron rich alkenes.

The system, although effective, raised two important issues. Firstly, the requirement for a ketone to be used as (co-)solvent suggested that ketone-hydrogen peroxide adducts are involved in the reaction either as a reservoir, to reduce the steady state concentration of H$_2$O$_2$, or that these adducts are in fact involved in the oxidation directly.

Secondly, in contrast to the, e.g., largely aqueous tungsten based systems, the use of a combination of acetone and H$_2$O$_2$ presents a substantial risk of explosion and hence may prove unsuitable for routine use especially on medium and large scale. In our earlier report, we demonstrated that in acetonitrile similar reactivity could be achieved with 5 vol% of 1,1,1-trifluoroacetone, albeit being a ketone that is expensive and generates fluorinated waste. The combination of safety issues, cost and waste, in addition to solubility considerations and the drive for increased selectivity towards epoxidation of electron rich alkenes prompted us to explore other solvents and ketones.

Here we report a general and robust method for the epoxidation of simple and multifunctional alkenes with H$_2$O$_2$, catalysed by a combination of a Mn(II) salt, pyridine-2-carboxylic acid (PCA) and sub-stoichiometric 1,2-diketones, specifically butanedione in a wide range of solvents (Scheme 1). The use of sub-stoichiometric butanedione is cost effective and reduces the risks associated with H$_2$O$_2$ in combination with organic solvents considerably compared with the original acetone/H$_2$O$_2$ combination. Importantly, it enables a broad solvent scope, much higher reaction rates (completion reached within 10-20 min), unprecedented turnover frequencies (up to 40 s$^{-1}$) and extremely low catalyst loadings (< 0.01 mol% Mn(II)) at room temperature. The method is straightforward and provides high selectivity with good to excellent atom efficiency (Scheme 1).

Scheme 1. Conversions and yields (isolated) obtained for the epoxidation of selected electron rich alkenes. Substrate final concentration was 0.5 M final concentration.

Furthermore, we demonstrate that the ketone used is catalytic in the reaction through the reversible formation of ketone-peroxide adducts. Through mechanistic studies we show that the primary limitation to the system is the competing oxidation of the ketone additive to carboxylic acids, which eventually leads to a loss in activity. The recognition of the ketone-hydrogen peroxide adduct as the actual oxidant presents considerable potential in the development of a new approach to oxidation catalysis.
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5.2 Results and discussion

5.2.1 General reaction conditions and optimisation

An initial screening of the oxidation of diethylfumarate and cyclooctene using stoichiometric amounts of ketones, with acetonitrile as solvent, identified butanedione[36] as a viable alternative to acetone or 1,1,1-trifluoroacetone, both in terms of cost, safety/toxicity and selectivity.

Initial screening showed that, with 0.5 equiv. of butanedione, 0.05 mol% Mn(II) and 0.5 mol% PCA, 95% conversion and 53% yield of cyclooctene oxide could be achieved (see Experimental section, table 3). cis-Diol and α-hydroxy-ketone by-products were obtained also. Surprisingly, increasing the amount of butanedione decreased both the conversion of cyclooctene and yield of epoxide. Higher turnover numbers (T.O.N. 9,500) and yield (80%) of the desired epoxide product was obtained by decreasing the concentration of Mn(II) to 0.01 mol%. Under these conditions full conversion was achieved within 15 min at room temperature (table 3, entry 3). For α-pinene similar optimisation indicated that the conditions optimum for cyclooctene were generally applicable (See table 4) for electron rich alkenes (with regard to electron deficient alkenes somewhat different conditions provided the best conversions and yields, see table 5, vide infra).

The dependence of conversion on the concentration of Mn(II) was examined further in the epoxidation of cyclooctene (Table 1). Similar yields (71% to 74%) were obtained even with only 0.001 mol% Mn(II) was used. Conversion decreased to 30% when 0.0001 mol% Mn(II), however this still represents a turnover number of 300,000 with respect to Mn(II).

Table 1. Effect of Mn(II) concentration on the epoxidation of cyclooctene. a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Mn(ClO₄)₂.6H₂O (mol %)</th>
<th>T.O.N.</th>
<th>Conversion (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.005</td>
<td>19,400</td>
<td>97</td>
<td>71</td>
</tr>
<tr>
<td>2</td>
<td>0.002</td>
<td>48,500</td>
<td>97</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>0.001</td>
<td>95,000</td>
<td>95</td>
<td>72</td>
</tr>
<tr>
<td>4</td>
<td>0.0005</td>
<td>130,000</td>
<td>65</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>0.0001</td>
<td>300,000</td>
<td>30</td>
<td>20</td>
</tr>
</tbody>
</table>

aConversion and yield was determined by Raman and ¹H NMR spectroscopy (+/- 3%, see Experimental section). Substrates were 0.5 M final conc.
The concentration of PCA could be reduced to 0.1 mol% with only a slight decrease in yield (see Experimental section, table 3, entry 4). Omission of either Mn(II), PCA or butanedione resulted in a complete loss of activity (table 3, entries 6-8).

Using conditions optimised for cyclooctene directly, the epoxide product of 1-methyl cyclohexene was obtained in high yield (90%), which indicated that with aliphatic alkenes this system performs well. Both aliphatic and aromatic alkenes were investigated under the reaction conditions optimised for cyclooctene also. Even without further optimisation, good to excellent conversion was observed for all cyclic alkenes examined, with typically 70% yield of the corresponding epoxide products. From a mechanistic perspective, the notable absence of significant allylic oxidation of cyclohexene indicates that hydroxyl radicals are not involved.\[39\]

\[\text{Mn(II) catalysed oxidation of alkenes with } \text{H}_2\text{O}_2\]

Scheme 2. Conversions and yields obtained for the epoxidation of electron rich alkenes using reaction conditions optimised for cyclooctene.

Conversion and yield was determined by Raman and $^1$H NMR spectroscopy (± 3%, see Experimental section). Substrate final concentration was 0.5 M. Isolated yields are indicated for selected substrates in parentheses.

For acyclic alkenes, good conversion was achieved with the highest yields for trisubstituted alkenes. 44% yield of epoxide product was obtained for 1-octene while for the gem-disubstituted alkene, 2,4-dimethyl-heptene, 80% yield of the epoxide product was obtained. Internal di-, tri- and tetra-substituted alkenes showed higher reactivity in general, with full conversion and 70-83% yield of the epoxide product (Scheme 1 and 9). As for styrene (Scheme 1), a set of aromatic alkenes were selectively oxidised to the corresponding epoxide (Scheme 2). Epoxidation of 2-carene and 3-carene (Scheme 2) showed full diastereoselectivity as in the oxidation of α-pinene (Scheme 1).
Although, the conditions optimised for the oxidation of cyclooctene provide generally good conversions and yields of the epoxide products, for several substrates, such as 1-octene and phenanthrene, incomplete conversion was observed, (Scheme 2). Variation in the concentration of butanedione, catalyst or H₂O₂ did not lead to improved results. However, by reducing the concentration of the substrate from 0.5 to 0.25 M but holding the concentration of all other components the same as in Scheme 2, higher conversion (90 and 85%, respectively) and yield of epoxide (60 and 68%, respectively) could be achieved. For α,β-unsaturated alkenes (Tables S5) in general lower conversions were achieved and selectivity was low with the cis-diol product as the major product.

Increasing the reaction to multigram scale for cyclooctene (1.1 to 5.5 g, 10-50 mmol) and trans-stilbene (9 g, 50 mmol) afforded essentially the same conversions and yields as on sub-gram scale (see Experimental section).

5.2.2 Oxidation of acid/base sensitive alkenes

The optimised reaction conditions described above are essentially neutral which makes the current method especially suitable for acid or base sensitive epoxide products such as α-pinene oxide and styrene oxide. For both these substrates (Scheme 1) excellent conversion and good yields (73% isolated yield) were achieved with the present system.

Scheme 3. Oxidation of α-pinene followed by in situ conversion to campholenic acid.

The natural product α-pinene is an important precursor to the flavour ingredient campholenic aldehyde (Scheme 3) and the preparation is carried out typically via the epoxide. α-Pinene oxide could be isomerised in situ to campholenic aldehyde with 20% final yield, in an overall one pot reaction by adding SiO₂ with gentle heating (Scheme 3).[40, 41, 42, 43] The present system allows the use of silica directly (i.e. without the need to modify it with other metal catalysts) which offers a considerable advantage over other methods.

5.2.3 Oxidation of conjugated and non-conjugated dienes

For non-conjugated dienes high regioselectivity was obtained compared to conjugated dienes, which showed only modest regioselectivity. In general, epoxidation of more substituted double bonds was preferred over less substituted double bonds. For limonene selectivity for the epoxidation of the internal alkene was observed. For citral, only one product was obtained, i.e. chemoselective epoxidation of the electron rich alkene without aldehyde oxidation (scheme 4).
Scheme 4. Epoxidation of substrates containing progressively dissimilar double bonds. For reaction conditions see Experimental section.

5.2.4 Oxidation of alkenes bearing multiple functional groups and allylic stereocentres

Selective oxidation of compounds with multiple oxidation sensitive centres, especially alcohols and aldehydes is a major challenge and is essential in achieving general applicability of any new method.\cite{44, 45, 46} Remarkably, for the unprotected homoallylic alcohol trans-2-decen-1-ol, the epoxide product was obtained in 61% yield (73% conversion) with only 10% of aldehyde. Indeed, in general, aldehydes and primary alcohols were stable under reaction conditions as shown for a series of bifunctional alkenes. For example, 3-vinyl benzaldehyde afforded the corresponding epoxide with 77% conversion and 66% yield (Scheme 5). β-citronellol showed good selectivity for epoxide product and the aldehyde was not observed after the reaction (Scheme 1).

For N-phenylcarbonyl-1,2-dihydro-quinoline-2-carbonitrile the corresponding epoxide product could be obtained in 65% isolated yield (\textit{vide infra}, Scheme 7).

Scheme 5. Oxidation of aldehyde and alcohol functionalised alkenes to the corresponding epoxide products. For reaction conditions see Experimental section. Yield determined by $^1$H NMR spectroscopy, isolated yield in parentheses.

Tolerance to protecting groups is a further characteristic of the present system. In the present study silyl based protecting groups were found to be unstable to reaction conditions as expected based on the sensitivity of such groups to H$_2$O$_2$. By contrast, hydrolytically sensitive acetyl and tert-butoxycarbonyl (Boc) protected alcohols were found to be stable under reaction conditions (Scheme 6).
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Scheme 6. Oxidation of protected allylic alkenes to the corresponding epoxide products. For details see section 5.4.6, yield determined by $^1$H NMR spectroscopy, isolated yield in parentheses.

Retention of configuration at the stereogenic centre of enantiopure acetyl protected allylic alcohol [isolated yield of epoxide 88%] upon epoxidation was observed, i.e. the epoxide product was obtained as only two of the four possible diastereomers (see section 5.4.6). This, together with the absence of allylic oxidation in the case of cyclohexene, (Scheme 2) provides strong evidence that species such as hydroxyl radicals are not formed in the reaction.

Stereochemical aspects. Stereochemistry presents a key challenge in modern synthetic chemistry. In the present system the influence of substrate on the stereochemical outcome of the reaction is evident for cyclic systems, especially terpenoids such as pinene and carenes (Schemes 1 and 2). For N-phenylcarbonyl 1,2-dihydro-quinoline-2-carbonitrile (Scheme 7) the corresponding epoxide product was obtained as a single diastereomer showing that stereochemical control by the substrate can be exerted for cyclic alkenes. This, together with the retention of stereochemistry in protected allylic alcohols makes the present system a versatile general method for the epoxidation of complex alkenes.

Scheme 7. Oxidation of N-phenylcarbonyl 1,2-dihydro-quinoline-2-carbonitrile to the corresponding diastereomerically pure epoxide product. For reaction conditions see Experimental section. Yield determined by $^1$H NMR spectroscopy.

cis-Dihydroxylation of electron deficient alkenes.

The catalysed cis-dihydroxylation of electron deficient alkenes such as diethylfumarate and succinimide was a major challenge in oxidation chemistry, until recently, when we demonstrated that clean conversion and excellent selectivity for the cis-diol product could be achieved using acetone as solvent. Under the present conditions using acetonitrile and butanedione, optimised for cyclooctene epoxidation, good conversion (74%) and full selectivity was observed for the cis-dihydroxylation of diethylfumarate...
Mn(II) catalysed oxidation of alkenes with H$_2$O$_2$

(Scheme 8 and Table 5). Increasing the relative amount of butanedione from 0.5 equiv. to 1.0/1.5 equiv. w.r.t. substrate allowed for full conversion. Surprisingly an increase in [Mn(II)] to 0.05 mol% resulted in a decrease in conversion (Table 5).

Scheme 8. Oxidation of electron deficient alkenes to their cis-diol products. For details see section 7. In all cases only a single product was formed. Yield determined by $^1$H NMR spectroscopy. Substrates were 0.5 M final conc..

5.2.5 Solvent dependence and scope

Although acetonitrile is the solvent of choice in the present study, the ability to use a wider range of solvents is important both for safety and economic reasons and to overcome solubility limitations that may be encountered with certain substrates. Using the conditions optimised in acetonitrile, the solvent scope for the oxidation of cyclooctene and diethylfumarate (which yields the cis-diol product exclusively) was examined. In general, in alcohols, good conversion and yields were obtained albeit slightly lower than obtained in acetonitrile (Table 2). Remarkably, in acetone and butanone, using only 0.01 mol% of Mn(II), conversion was not observed without 2,3-butanedione within 2 h.

Table 2. Solvent dependence of the epoxidation of cyclooctene

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Conversion (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acetone</td>
<td>90</td>
<td>68</td>
</tr>
<tr>
<td>2</td>
<td>Butanone</td>
<td>85</td>
<td>58</td>
</tr>
<tr>
<td>3</td>
<td>tert-BuOH</td>
<td>65</td>
<td>55</td>
</tr>
<tr>
<td>4</td>
<td>CH$_3$CN</td>
<td>95</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>Methanol</td>
<td>90</td>
<td>62</td>
</tr>
<tr>
<td>6</td>
<td>Ethanol</td>
<td>70</td>
<td>45</td>
</tr>
</tbody>
</table>

5.2.6 Mechanistic considerations

Several mechanistically relevant observations can be made based on the substrate scope. The degree of retention of configuration of cis-/trans- 2-heptene (Scheme 9) is relatively low. For cis-2-heptene, 75% of the epoxide product was obtained as a mixture of cis-2-
heptene oxide and trans-2-heptene oxide (2:1) (Scheme 9). By contrast, trans-2-heptene provided 45% trans-2-heptene oxide and only 9% cis-2-heptene oxide. This indicates that the epoxidation of alkenes is not a concerted reaction but is instead stepwise. It should be noted though that the heptane-1,2-diol that was formed as a minor product was in both cases the result of cis-dihydroxylation only. Essentially the same results were obtained with both cis- and trans-1-methylstyrene and cis- and trans-stilbene.

Scheme 9. Oxidation of cis-/trans-2-heptene, 1-methyl-styrene and stilbene. For conditions see Experimental section. Yields determined by $^1$H NMR spectroscopy. Note that the trans-dihydroxylation products were not observed in any of the examples.

The absence of significant allylic oxidation, for example, for cyclohexene, indicates that the low retention of configuration observed for 2-heptene is not due to a radical oxidation pathway involving hydroxyl radicals however. Furthermore, the diastereoselectivity observed for the epoxidation of 1-benzoyl-1,2-dihydro-2-quinolinecarbonitrile and the absence of racemisation for (S)-4-phenylbut-3-en-2-yl acetate requires, however, that if a stepwise mechanism is involved then the rate of the step, prior to which rotation can occur, is generally fast.

5.2.7 Role of ketone in the catalytic reaction

Although our initial objective was to find safer alternatives to acetone as solvent, we discovered that butanedione was an active ketone for the manganese catalytic oxidation of alkenes sub-stoichiometrically. Indeed at low Mn(II) loadings the requirement for butanedione to be present, even when acetone is used as solvent, indicated that the ketone was involved directly in the reaction and not simply acting as (co)solvent. Indeed,
the full conversion observed with sub-stoichiometric amounts of butanedione means that it is involved in the oxidation directly and is therefore catalytic. Furthermore, the broad solvent scope and the absence of activity when butanedione was omitted, together with the increased activity that allows for the use of low Mn(II) (<0.01 mol%) and PCA (<0.05 mol%) catalyst loadings, with much shorter reaction times than in acetone alone, hinted that hydrogen peroxide/butanedione adducts (i.e. 3-hydroperoxy-3-hydroxybutan-2-one) could be involved. UV/Vis and Raman spectroscopic analysis of the reaction mixture confirmed that the diketone reacts immediately (<10 s) with H₂O₂ in a 1:1 ratio, manifested in the decrease and blue shift in both the carbonyl stretch (1722 cm⁻¹) in the Raman spectrum (Figure 1) and the absorption band at 417 nm in the UV/vis absorption spectrum of the reaction mixture (Figure 2).

Figure 1. Changes in the Raman spectrum (upper spectrum 1500-1800 cm⁻¹ region, lower spectrum 500-1100 cm⁻¹ region), λ_exct = 785 nm, of the reaction mixture during the epoxidation of cyclooctene. The conditions used are those stated in Scheme 3. Spectra at prior to (purple) and t = 1 (blue), 5 (green), 20 (grey) and 30 (orange) min after addition of H₂O₂. (1,2-DCB : 1,2-dichlorobenzene)

Figure 2. Changes in the (a) UV/vis absorption spectrum of the reaction mixture 1 min after addition of H₂O₂ and after 35 min. (b) absorbance of the butanedione at 417 nm over time. Conditions used are those stated in Figure 1.

That the changes observed are due to the formation of a mono-hydroperoxyacetal (Scheme 10) is supported by the 1:1 stoichiometry required to see a complete loss in the
Chapter 5

intensity of both the 1722 cm$^{-1}$ Raman band and the 417 nm UV/Vis absorption band (Figure 2). With 1 equiv. of H$_2$O$_2$ with respect to substrate, the 1722 cm$^{-1}$ Raman band and the 417 nm absorption began to recover after approximately 66% of the H$_2$O$_2$ was consumed (i.e. <1 equiv. of H$_2$O$_2$ with respect to butanedione remained). This is consistent with the formation of 1:1 adduct of H$_2$O$_2$ and butanedione (Scheme 10).[40]

\[
\begin{align*}
H_2O_2 & \quad + \quad \text{ketone} \\
& \quad \xrightarrow{\text{reaction}} \quad \text{ketone} + \text{hydroperoxyl alcohol}
\end{align*}
\]

Scheme 10. Reaction between ketones and H$_2$O$_2$.

5.3 Conclusions

In conclusion, a practical, fast and readily implemented method for selective epoxidation of electron rich alkenes with H$_2$O$_2$ and an in situ prepared catalyst system was established which can achieve high turnover numbers (up to 300,000). Importantly, the tolerance to other oxidation sensitive functional groups, the mild conditions (i.e. between 0 °C and r.t.) and solvent scope make this system highly competitive with stoichiometric oxidants such as mCPBA. The system is especially suited to epoxidation of electron rich alkenes and shows good to excellent selectivity in the epoxidation of dienes and bifunctional substrates. In the case of electron deficient alkenes the method can show exceptional selectivity and activity in their cis-dihydroxylation. The preliminary mechanistic study has focused on the role of butanedione and indicates that further optimisation of the system should focus on overcoming the oxidation of the ketone as a competing reaction.

5.4 Experimental

5.4.1 Materials and Methods

UV/Vis absorption spectra were recorded at room temperature in 1 mm pathlength quartz cuvettes using an AnalytikJena Specord600. Raman spectra were recorded using a Perkin Elmer Raman Flex equipped with a fibre optic probe ($\lambda_{exc}$ 785 nm). For both Raman and $^1$H NMR spectroscopy 1,2-dichlorobenzene was employed as internal standard. EPR spectra were recorded using a Bruker at room temperature using a liquid cell and at 77 K using 2 mm.

Caution. The drying or concentration of solutions that potentially contain H$_2$O$_2$ should be avoided. Prior to drying or concentrating, the presence of H$_2$O$_2$ should be tested for using peroxide test strips followed by neutralisation on solid NaHSO$_3$ or another suitable reducing agent. When working with H$_2$O$_2$, suitable protective safeguards should be in place at all times.
Mn(II) catalysed oxidation of alkenes with H₂O₂

**Caution.** Butanedione has been linked with lung disease upon exposure to vapours. It should be handled in a properly ventilated fumehood and exposure to vapours should be avoided.

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 H₂O₂ employed can affect the outcome of the reaction where sequestrants are present as stabilisers.¹ H NMR (400.0 MHz) and ¹³C NMR (100.6 MHz) spectra were recorded on a Varian Avance 400. Chemical shifts are relative to ¹H NMR CDCl₃ (7.26 ppm), DMSO-d₆ (2.5 ppm), CD₃CN (1.94 ppm), ¹³C NMR CDCl₃ (77 ppm).

5.4.2 Optimisation of conditions for catalytic oxidation of cyclooctene, α-pinene and diethyl fumarate

Table 3. Optimisation of conditions for the epoxidation of cyclooctene

<table>
<thead>
<tr>
<th>Entry</th>
<th>Mn(ClO₄)₂·6H₂O (mol %)</th>
<th>Pyridine-2-COOH (mol %)</th>
<th>butanedione (equiv.)</th>
<th>Conv. (°)</th>
<th>Yieldb,c (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.05</td>
<td>0.5</td>
<td>0.5</td>
<td>95</td>
<td>53</td>
</tr>
<tr>
<td>2</td>
<td>0.05</td>
<td>0.5</td>
<td>1.5</td>
<td>95</td>
<td>56</td>
</tr>
<tr>
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<td>0.01</td>
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<td>0.5</td>
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<td>0.01</td>
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<td>0.5</td>
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<td>70</td>
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<tr>
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<td>15</td>
</tr>
<tr>
<td>6</td>
<td>----</td>
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<td>7</td>
<td>0.05</td>
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</tr>
<tr>
<td>8</td>
<td>0.05</td>
<td>0.5</td>
<td>----</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* Determined by ¹H NMR and Raman spectroscopy. b Yields determined by ¹H NMR using 1,2-dichlorobenzene as internal standard. c The side products were the corresponding cis-diol and α-hydroxyl ketone.
Table 4. Optimisation of conditions for the epoxidation of α-pinene

<table>
<thead>
<tr>
<th>Entry</th>
<th>Mn(ClO₄)₂·6H₂O (mol %)</th>
<th>Pyridine-2-COOH (mol %)</th>
<th>Butanedione (equiv.)</th>
<th>Conversion* (%)</th>
<th>Yieldb,c (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.05</td>
<td>0.5</td>
<td>0.5</td>
<td>86</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>0.05</td>
<td>0.5</td>
<td>1.5</td>
<td>85</td>
<td>45 (43)</td>
</tr>
<tr>
<td>3</td>
<td>0.01</td>
<td>0.5</td>
<td>0.5</td>
<td>95</td>
<td>80 (73)</td>
</tr>
<tr>
<td>4</td>
<td>0.01</td>
<td>0.1</td>
<td>0.5</td>
<td>80</td>
<td>47</td>
</tr>
<tr>
<td>5</td>
<td>0.01</td>
<td>0.1</td>
<td>3.0</td>
<td>35</td>
<td>15</td>
</tr>
<tr>
<td>6</td>
<td>0.05</td>
<td>0.5</td>
<td>3.0</td>
<td>28</td>
<td>12</td>
</tr>
</tbody>
</table>

* Determined by ¹H NMR and Raman spectroscopy. b Yields determined by ¹H NMR using 1,2-dichlorobenzene as internal standard. c The side products were the corresponding cis-diol and α-hydroxyl ketone products and rearrangement products.

Table 5. Optimisation of conditions for the cis-dihydroxylation of diethyl fumarate

<table>
<thead>
<tr>
<th>Entry</th>
<th>Mn(ClO₄)₂·6H₂O (mol %)</th>
<th>Butanedione (equiv.)</th>
<th>Conversion* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.01</td>
<td>0.5</td>
<td>74</td>
</tr>
<tr>
<td>2</td>
<td>0.01</td>
<td>1.0</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>0.01</td>
<td>1.5</td>
<td>full</td>
</tr>
<tr>
<td>4</td>
<td>0.05</td>
<td>0.5</td>
<td>61</td>
</tr>
<tr>
<td>5</td>
<td>0.05</td>
<td>1.0</td>
<td>78</td>
</tr>
<tr>
<td>6</td>
<td>0.05</td>
<td>1.5</td>
<td>89</td>
</tr>
</tbody>
</table>

* Determined by ¹H NMR and Raman spectroscopy. Only the cis-diol product was formed.

5.4.3 Procedures for catalytic oxidation of alkenes described in schemes 1, 2, 4-7 and 9 and characterisation of products

General procedure: To a solution of Mn(ClO₄)₂·6H₂O (0.01 mol %, 0.0361 mg) and pyridine-2-carboxylic acid (0.5 mol %, 0.123 mg) in acetonitrile was added the alkene (1 mmol) to give a final concentration of the substrate of 0.5 M, NaOAc (aq. 0.6 M, 1 mol %, 16.7 μl) and 2,3-butanedione (0.5 equiv. 43.5 μl) to give a final volume of 2 ml. The solution was stirring in an ice/water bath before addition of H₂O₂ (50 wt. %, 1.5 equiv., 85 μl). The solution was stirred for 1 h.

After 1 h, brine (10 ml) was added and the reaction mixture was extracted with dichloromethane. The combined organic layers were washed with brine. The product was dried over Na₂SO₄ (anhyd.), filtered, and the dichloromethane was removed in vacuo. 1,2-Dichlorobenzene was employed as internal standard for Raman and ¹H NMR.
Mn(II) catalysed oxidation of alkenes with H$_2$O$_2$

The products were isolated by flash column chromatography on silica gel 230-400 or neutral aluminium oxide 70-230.

**Note:** For some reactions CD$_3$CN was used as solvent with analysis after the reaction carried out by $^1$H NMR spectroscopy directly.

Cyclooctene oxide Isolated by flash column chromatography on neutral aluminium oxide 70-230 (pentane/ether = 9:1, Rf = 0.6). The title compound was obtained as colourless solid (91.5 mg, 0.73 mmol, 73%).

At 1.1 gram (10 mmol) scale, the oxidation of cyclooctene using the same procedure provided cyclooctene oxide as a colourless solid (881 mg, 7.0 mmol, 70%).

At 5.5 gram (50 mmol) scale, the oxidation of cyclooctene using the same procedure provided full conversion with cyclooctene oxide obtained as a colourless solid (4.23 g, 33.5 mmol, 67%). (side products: 15% diol, 7% alpha-hydroxyl ketone)$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 2.87-2.81 (m, 2H), 2.12-2.06 (m, 2H), 1.60-1.30 (m, 8H), 1.25 (m, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 55.5, 26.5, 26.3, 25.5.

$\alpha$-pinene oxide The procedure used was as for the catalysed oxidation of cyclooctene.

The product was isolated by flash column chromatography over neutral aluminum oxide (pentane/ether = 99:1, Rf = 0.6). The title compound was obtained as colourless oil (111 mg, 0.73 mmol, 73%).

On a 680 mg (5 mmol) scale $\alpha$-pinene was converted to $\alpha$-pinene oxide to yield a colourless oil (540 mg, 3.55 mmol, 71%).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.04 (dd, $J$ = 4.1 Hz, 1.1, 1H), 2.02-1.86 (m, 4H), 1.73-1.68 (m, 1H), 1.60 (d, $J$ = 9.4 Hz, 1H), 1.33 (s, 3H), 1.28 (s, 3H), 0.93 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 60.3, 56.8, 45.0, 40.5, 39.7, 27.6, 26.6, 25.8, 22.3, 20.1; HRMS (ESI+) calc. for C$_{10}$H$_{17}$O (M+H)$^+$ 153.1265, found 153.1274.
Styrene oxide. The procedure used was as for the catalysed oxidation of cyclooctene. The product was isolated by flash column chromatography over neutral aluminium oxide (pentane/ether = 85:15, Rf = 0.5). The title compound was obtained as colourless oil (87.5 mg, 0.73 mmol, 73%).

\[ \text{H NMR (400 MHz, CDCl}_3\text{)} \delta 7.41-7.28 (m, 5H), 3.87 (t, J=2.7 Hz, 1H), 3.15 (dd, J = 5.5 Hz, 4.1, 1H), 2.81 (dd, J = 5.5 Hz, 2.5, 1H); \]

\[ \text{C NMR (101 MHz, CDCl}_3\text{)} \delta 137.6, 128.9, 128.5, 128.1, 127.9, 125.4, 52.3, 51.1. \]

Citronellol epoxide The procedure used was as for the catalysed oxidation of cyclooctene. The product was isolated by flash column chromatography over neutral aluminium oxide (pentane/ether = 30:70, Rf = 0.5). The title compound was obtained as colourless oil (117 mg, 0.68 mmol, 68%).

\[ \text{H NMR (400 MHz, CDCl}_3\text{)} \delta 3.65 (m, 2H), 2.68 (t, J = 6.3 Hz, 3H), 1.74-1.36 (m, 7H), 1.28 (s, 3H), 1.24 (s, 3H), 0.89 (d, J=6.5, 3H); \]

\[ \text{C NMR (101 MHz, CDCl}_3\text{)} \delta 64.6, 64.6, 60.8, 58.4, 58.3, 39.7, 39.5, 33.7, 33.6, 29.3, 29.1, 26.4, 26.1, 24.8, 19.6, 19.4, 18.6, 18.6; \]

HRMS (ESI+) calc. for C_{10}H_{21}O_2 (M+H)+ 173.1536, found 173.1527.

1,2-Epoxyoctane The procedure used was as for the catalysed oxidation of cyclooctene. The product was isolated by flash column chromatography over neutral aluminium oxide (pentane/ether = 98:2, Rf = 0.5). The title compound was obtained as colourless oil (52.5 mg, 0.41 mmol, 41%).

\[ \text{H NMR (400 MHz, CDCl}_3\text{)} \delta 2.89 (m, 1H), 2.74 (q, 1H), 2.45 (q, 1H), 1.53-1.27 (m, 10H), 0.88 (t, 3H); \]

\[ \text{C NMR (101 MHz, CDCl}_3\text{)} \delta 52.3, 47.1, 32.4, 31.7, 29.0, 25.9, 22.5, 14. \]
**Mn(II) catalysed oxidation of alkenes with H$_2$O$_2$**

2-Methyl-2-(2-methylpentyl)oxirane The procedure used was the same as for the catalysed oxidation of cyclooctene. The product was isolated by flash column chromatography over silica gel (pentane/ether = 97:3, Rf = 0.5). The title compound was obtained as a colourless oil (102 mg, 0.72 mmol, 72%).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 2.52-2.45 (m, 2H), 1.73-1.40 (m, 2H), 1.26-1.18 (m, 7H), 1.09-0.97 (m, 1H), 0.88-0.79 (m, 6H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 56.0, 55.9, 54.3, 53.7, 44.2, 44.1, 39.7, 39.1, 30.0, 29.8, 20.7, 20.6, 20.0, 19.8, 19.5, 14.1; HRMS (ESI+) calc. for C$_9$H$_{19}$O (M+H)$^+$ 143.14285, found 143.14304;

At 9 gram (50 mmol) scale, the oxidation of stilbene using the same procedure provided 85% conversion with stilbene oxide obtained as a colourless solid (6.24 g, 31 mmol, 63.5 %). (side products: 15% diol, 3% alpha-hydroxyl ketone).

$^1$H NMR spectrum in CDCl$_3$ of the purified product obtained by multi-gram oxidation of trans-stilbene

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.49-7.40 (m, 10H), 3.96(s, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 137.2, 128.6, 128.4, 125.6, 62.9.
Figure 3. $^1$H NMR spectrum in CDCl$_3$ of the crude product obtained by oxidation of phenanthrene.
Mn(II) catalysed oxidation of alkenes with H₂O₂

Figure 4. 1H NMR spectrum in CD₃CN with 1,2-DCB as internal standard of the reaction mixture obtained by oxidation of 2-carene

1H NMR (400 MHz, CDCl₃) δ 2.82 (s, 1H), 2.30 (m, 1H), 2.13 (dd, J = 9.0 Hz, 7.2), 1.55 (m, 2H), 1.24 (s, 3H), 0.99 (s, 3H), 0.71 (s, 3H), 0.50 (m, 1H). 13C NMR (101 MHz, CDCl₃) δ 58.1, 55.8, 27.7, 23.3, 23.0, 19.1, 15.9, 14.5, 13.8.

The procedure used was as for the catalysed oxidation of cyclooctene. The product was isolated by flash column chromatography over neutral aluminium oxide (pentane/ether = 96:4, Rf = 0.5). The title compound was obtained as colourless oil (68 mg, 0.45 mmol, 45%).

3-carene oxide The procedure used was as for the catalysed oxidation of cyclooctene. The product was isolated by flash column chromatography over neutral aluminium oxide (pentane/ether = 96:4, Rf = 0.5). The title compound was obtained as colourless oil (68 mg, 0.45 mmol, 45%).
Figure 5. $^1$H NMR spectrum in CDCl$_3$ with 1,2-DCB as internal standard of the crude product obtained upon oxidation of dec-2-en-1-ol.

3-(Oxiran-2-yl)benzaldehyde The procedure used was as for the catalysed oxidation of cyclooctene. The product was isolated by flash column chromatography over neutral aluminium oxide (pentane/ether = 81:19, Rf = 0.6). The title compound was obtained as colourless oil (90 mg, 0.61 mmol, 61%).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 10.02 (s, 1H), 7.83 (m, 2H), 7.54 (m, 2H), 3.95 (t, $J$ = 2.6 Hz, 1H), 3.20 (dd, $J$ = 5.3, 4.1, 1H), 2.82 (dd, $J$ = 5.4, 2.5, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 191.9, 139.0, 131.3, 129.5, 129.2, 126.6, 51.7, 51.2; HRMS (ESI+) calc. for C$_9$H$_9$O$_2$ (M+H)$^+$ 149.05971, found 149.05980.

Chapter 5
Mn(II) catalysed oxidation of alkenes with H₂O₂

(1aS*,2S*,7bR*)-3-Benzoyl-1a,2,3,7b-tetrahydrooxireno[2,3-c]quinoline-2-carbonitrile.

The reactions procedure was the same as for the oxidation of cyclooctene. The product was isolated by flash column chromatography over silica gel (Dichloromethane, Rf = 0.5). The title compound was obtained as white solid (180 mg, 0.65 mmol, 65%).

€H NMR (400 MHz, CDCl₃) δ 7.53-7.51 (dd, J = 7.5, 1.1 Hz, 1H), 7.4-7.34 (m, 3H), 7.27-7.23 (m, 2H), 7.19-7.16 (t, J = 7.5 Hz, 1H), 7.08-7.03 (t, J = 7.6 Hz, 1H), 6.54-6.52 (d, J = 8.0 Hz, 1H), 6.27 (d, J = 2.4 Hz, 1H), 4.29-4.27 (dd, J = 3.8 Hz, 2.6, 1H), 4.15 (d, J = 4.0 Hz, 1H); €C NMR (101 MHz, CDCl₃) δ 170.1, 135.2, 133.6, 131.3, 130.1, 129.1, 128.3, 126.8, 126.4, 124.0, 114.8, 59.4, 51.0, 41.5; HRMS (ESI+) calc. for C₁₇H₁₂N₂O₂ (M+Na)⁺ 299.07910, found 299.07887; The stereochemistry of 1-benzoyl-1,2-dihydro-2-quinolinecarbonitrile oxide was determined by €H-NMR spectroscopic analysis. The coupling constants[51] of protons Hₐ, Hₕ and Hₐc (see Scheme) indicate that the CN group is trans to the epoxide moiety.
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Figure 6. $^1$H and $^{13}$C NMR spectra in CDCl$_3$ of the isolated product from the oxidation of 1-benzoyl-1,2-dihydro-2-quinolinecarbonitrile. Only one diastereoisomer pair formed.
Mn(II) catalysed oxidation of alkenes with H₂O₂

Figure 7. $^1$H NMR spectrum in CDCl₃ with 1,2-DCB internal standard of the crude product obtained upon oxidation of cis-heptene.
Figure 8. $^1$H NMR spectrum in CDCl$_3$ with 1,2-DCB internal standard of the crude product obtained upon oxidation of trans-heptene.
Figure 9. $^1$H NMR spectrum in CDCl$_3$ of the reaction mixture obtained upon oxidation of cis-1-methylstyrene.
Figure 10. $^1$H NMR spectrum in CDCl$_3$ of the reaction mixture obtained upon oxidation of trans-1-methylstyrene.
**Oxidation of conjugated and non-conjugated dienes – Scheme 4**

\[
\begin{align*}
\text{Mn(II) catalysed oxidation of alkenes with } H_2O_2
\end{align*}
\]

**Figure 11.** $^1$H NMR spectrum in CD$_3$CN with 1,2-DCB internal standard of the reaction mixture obtained upon oxidation of citral.

**5.4.4 Procedure for catalytic oxidation of $\alpha$-pinene followed by in situ isomerisation and product characterisation**

**Procedure:** After epoxidation of $\alpha$-pinene (1 mmol, 158 μl) by the procedure described for cyclooctene, silica gel 230-400 (150 g) was added to the reaction mixture, which was then stirred at 40°C for 1 h. The silica gel was removed by filtration and the solvent was removed in vacuo. Campholenic aldehyde was obtained as yellow oil (30 mg, 0.2 mmol, 20 %)
Figure 12. $^1$H and $^{13}$C NMR in spectrum in CDCl$_3$ of the product campholenic aldehyde obtained from $\alpha$-pinene.
5.4.5 Procedures for the catalytic oxidation of electron deficient alkenes

Oxidation of electron deficient alkenes to their cis-diol products. In all cases only a single product was formed.

The alkene (1 mmol, final conc. 0.5 M), aqueous NaOAc (0.6 M, 16.7 μl, final conc. 5 mM) and 2,3-butanedione (130.5 μl, final conc. 0.75 M) were added to a solution of Mn(ClO₄)₂ (final conc. 0.05 mM) and pyridine-2-carboxylic acid (2.5 mM) in CH₃CN to give a final volume of 2 ml. The solution was stirred in an ice water bath and H₂O₂ (50 wt. %, 1.5 equiv. 85 μl) was added as a single portion and the solution stirred for 1 h. After 1 h, brine (10 ml) was added and the reaction mixture was extracted with dichloromethane. The combined organic layers were washed with brine. The product was dried over Na₂SO₄ (anhyd.), filtered, and the dichloromethane was removed in vacuo.

5.4.6 Retention of chirality in allylic alkenes

Figure 13. ¹H NMR spectrum in CDCl₃ of the crude product obtained by the oxidation of (S)-4-phenylbut-3-en-2-yl acetate.
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**Figure 14.** HPLC chromatogram (Chiralpak AD-H : Heptane/i-Propanol = 98/2, 216nm) of the product obtained by the oxidation of racemic 4-phenylbut-3-en-2-yl acetate (together with 4-phenylbut-3-en-2-yl acetate) also showing all four stereoisomers.

**Figure 15.** HPLC chromatogram (Chiralpak AD-H : Heptane/i-Propanol = 98/2, 216nm) of the product obtained by the oxidation of (S)-4-phenylbut-3-en-2-yl acetate showing only two of the four potential stereoisomers.
5.5 Bibliography

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[31] The system was discovered as a result of our mechanistic studies into a wide range of manganese oxidation catalysts based on polypyridyl ligands in which we found that ligand oxidation to form PCA in situ occurred prior to the onset of oxidation catalysis. D. Pijper, P. Saisaha, J. W. de Boer, R. Hoen, C. Smit, A. Meetsma, R. Hage, R. P. van Summeren, P. L. Alsters, B. L. Feringa, W. R. Browne, Dalton Trans. 2010, 39, 10375-10381.

[32] The system operated with neat acetone or butanone, or in acetonitrile with 1,1,1-trifluoroacetone as co-solvent.


[37] It should be noted that reduction of butanedione/H2O2 adducts (i.e. 3-hydroperoxy-3-hydroxybutan-2-one) is facile as manifested in its decomposition to acetic acid under reaction conditions. This is in stark contrast to acetone and butanone peroxyacetals, which do not decompose readily during work up and hence present a substantial risk of crystallisation during work-up.


[48] Conversion was not observed in diethyl carbonate, tetrahydrofuran, water, ethyl acetate, methyl tert-butyl ether, dichloromethane or dichloroethane, primarily due to phase separation and insolubility.

