cis-Dihydroxylation and Epoxidation of Alkenes by Manganese Catalysts - Selectivity, Reactivity and Mechanism
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Chapter 1

Enantioselective epoxidation and cis-dihydroxylation catalysts

The metal-catalysed enantioselective epoxidation and cis-dihydroxylation of alkenes is discussed. Special attention is given to typical reaction conditions employed, selectivities achieved, terminal oxidants used and the synthetic utility of these catalytic systems.

Sections 1.1.2-1.1.4 of this chapter have been adapted from: J. Brinksma, J. W. de Boer, R. Hage, B. L. Feringa, Manganese-based Oxidation with Hydrogen Peroxide, in: Modern Oxidation Methods, J.-E. Bäckvall (ed.), Wiley-VCH, Weinheim, 2004, pp. 295-326.
Chapter 1

An overview of the more synthetically useful enantioselective catalytic systems for both the epoxidation and cis-dihydroxylation of alkenes reported to date, is provided in this chapter. Typical reaction conditions, enantioselectivities achieved, terminal oxidants used and their synthetic utility are discussed briefly for each catalytic system. This chapter is not intended to afford a detailed and comprehensive overview of all aspects of the oxidation catalysts discussed, for this the reader is referred to the various excellent reviews mentioned in the individual sections. For epoxidation, the focus is mainly on first row transition-metal catalysts and as a consequence catalysts based on Re, Ru and W are not discussed. For cis-dihydroxylation both the Os- and Fe-based catalysts are discussed. The non-heme iron catalysts developed by Que et al. are discussed in more detail, due to their relevance to the Mn-tmtacn catalysts described in this thesis.

1.1 Epoxidation

1.1.1 Titanium

The Ti-catalysed asymmetric epoxidation of allylic alcohols was first reported by Sharpless et al. in 1980 (for V-catalysed epoxidations, see ref. [7]). Treatment of an allylic alcohol with tBuOOH in the presence of catalytic amounts of Ti IV(OiPr)4 and (S,S)- or (R,R)-dialkyltartrate affords the corresponding epoxides in high yield (50-90%) and with high ee (>90 %, Scheme 1.1). The most commonly used dialkyl tartrate ligands are diethyl- and diisopropyl tartrate, (S,S)- or (R,R)-DET and -DIPT, respectively. The catalyst is sensitive to H2O and anhydrous reagents and conditions should be used.10 The presence of molecular sieves generally enhances both the yield and ee of the reaction.

The catalytically active species is believed to be a Ti IV dimer containing two dialkyl tartrate ligands (Figure 1.1) and both the oxidant tBuOOH and the allylic alcohol coordinate to one of the Ti IV centres. The coordination of the allylic alcohol positions the substrate in such a way that the oxygen is delivered to one enantiotopic face of the alkene and this is key to the high ee’s observed for this reaction. A large number of both allylic and homoallylic alcohols have been used as substrates, showing the versatility of this epoxidation catalyst for (natural product) synthesis. The necessity for the presence of this alcohol functionality, however, limits this catalyst to this class of substrates.
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Figure 1.1 Active complex for Ti-tartrate catalysed epoxidation.8

Recently, Katsuki and coworkers reported a series of Ti-based catalysts which are not sensitive to H2O and which can use H2O2 as oxidant.13,14,15 The ligands used were derived from the well-known salen ligands where either one or both of the imine functionalities are reduced (i.e. salalen or salan ligands, respectively, Figure 1.2).

Figure 1.2 (TiIV(µ-O)(salalen))2 and (TiIV(µ-O)(salan))2 complexes.14,15

Typical reaction conditions employ 2-5 mol% of the Ti-dimer and a slight excess of H2O2 (30%) (1.01-1.5 equiv.) in CH2Cl2 at room temperature (Scheme 1.2).14,15 The yields are moderate to good (50-99%) and ee’s are typically between 75 and 99%. Substrates reported so far include aryl-substituted alkenes, such as styrene and 1,2-dihydronaphthalene, and aliphatic cis-alkenes.14,15 It is worth noting that several terminal alkenes could be converted to their corresponding epoxides with 70-85% ee. The active species is proposed to be a mononuclear TiIV-η2-OOH species based on CSI-MS (cold-spray ionisation mass-spectrometry) alone, where the TiIV centre acts as a Lewis acid to activate the peroxide.14

Scheme 1.2 Catalytic epoxidation by (TiIV(µ-O)(salalen))2 and (TiIV(µ-O)(salan))2 (left) and proposed catalytic active species (right).14,15
1.1.2 Mn-porphyrins
Both Fe\textsuperscript{III}- and Mn\textsuperscript{III}-porphyrins have been employed for the epoxidation of alkenes.\textsuperscript{16} These complexes are converted to their respective high-valent metal-oxo species by terminal oxidants such as iodosylbenzene and sodium hypochlorite (NaClO). Many chiral porphyrin derivatives have been prepared and moderate to good ee’s (up to 96%) have been obtained in several cases.\textsuperscript{17,18,19} The substrate scope tested is usually limited to styrene and a few derivatives thereof and best results are generally obtained with cis-alkenes such as cis-β-methylstyrene. However, while for high asymmetric induction during the interaction of the approaching alkene to the high-valent metal-oxo intermediate the chiral groups should be close to the metal-oxo moiety to afford a (rigid) chiral pocket, at the same time these groups should not be too close, since intramolecular oxidation (and finally inactivation) of the catalyst occurs.\textsuperscript{18} Catalyst stability is a serious issue with porphyrin-based oxidation catalysts, especially when the often tedious syntheses of the (chiral) porphyrin ligands are considered.

![Figure 1.3 Example of chiral porphyrin epoxidation catalyst.\textsuperscript{20}](image-url)

Without additives, the use of H\textsubscript{2}O\textsubscript{2} as oxidant leads to homolytic cleavage of the O-O bond of the intermediate hydroperoxo complex, resulting in the formation of hydroxyl radicals and as a consequence non-selective oxidation of the substrate occurs.\textsuperscript{16} However, when a nitrogen containing heteroarene such as imidazole coordinates axially to the Mn\textsuperscript{III}-porphyrin, heterolytic cleavage of the O-O bond is promoted, yielding the catalytically active Mn\textsuperscript{V}=O intermediate.\textsuperscript{21} Although excess H\textsubscript{2}O\textsubscript{2} (3-5 equiv.) was required, good yields (85-99%) have been obtained for the epoxidation of several alkenes using [Mn\textsuperscript{III}(TDCPP)Cl] 1.1 (TDCPP: tetra-2,6-dichlorophenylporphyrin, Figure 1.4).\textsuperscript{22} The amount of imidazole used can be lowered to 1 equiv. with respect to (w.r.t.) the manganese porphyrin when also a small amount (1 equiv. w.r.t. catalyst) of carboxylic acid is used.\textsuperscript{23} When both the imidazole and carboxylic acid were attached to the manganese porphyrin (1.2) (Figure 1.4 and 1.5) up to 1000 t.o.n.’s have been obtained for several substrates, including cyclooctene and p-chlorostyrene, using 2 equiv. of H\textsubscript{2}O\textsubscript{2} w.r.t. substrate (Figure 1.5).\textsuperscript{24,25} A few examples of chiral porphyrins employing H\textsubscript{2}O\textsubscript{2} are known, however, the ee’s obtained are low (ca. 30%).\textsuperscript{26,27}
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Figure 1.4 Mn-porphyrins used for the catalytic epoxidation of alkenes employing H₂O₂ as terminal oxidant.

\[ \text{R}^1 = \text{alkyl, aryl} \]
\[ \text{R}^2 = \text{alkyl, H} \]

Figure 1.5 Epoxidation of alkenes catalysed by Mn-porphyrin 1.2 (see Figure 1.4).

As structural and functional mimics for porphyrin containing enzymes, such as cytochrome P450, both Fe- and Mn-containing metalloloporphyrins are useful models to gain insight into the intriguing chemistry exhibited by these biologically relevant systems.
However, despite progress made, the tedious synthesis and purification of the (chiral) porphyrin ligands and the (generally) high catalyst loadings required, render these Fe- and Mn-porphyrins less practical as epoxidation catalysts for (asymmetric) chemical synthesis.

1.1.3 Mn-salen

Following the initial report by Kochi on the use of Mn-salen complexes as epoxidation catalysts, the groups of Jacobsen and Katsuki reported the incorporation of a chiral diamine functionality in the salen ligand (Figure 1.6) affording enantioselective epoxidation catalysts. The use of the Mn-salen catalysts results generally in good to excellent ee’s (>90%) and yields (>80%) for the epoxidation of cis-disubstituted and trisubstituted alkenes employing iodosylbenzene as oxidant. Trans-alkenes give, generally, lower ee’s, although several Mn-salen derivatives are known to give good ee’s (up to 80%) for a number of trans-alkenes also. Although high ee’s can be obtained, the stability of the Mn-salen complexes is often a problem and t.o.n.’s are usually in the range of 40-200. A robust Mn-salen catalyst was introduced by Katsuki et al. based on ligand 1.5 with a carboxylic acid functionality attached to the diamine bridge (Figure 1.6) and up to 9200 t.o.n.’s have been obtained using iodosylbenzene as oxidant.

The catalytically active species is proposed to be a Mn\textsuperscript{V}=O intermediate, as was confirmed by electrospray ionisation mass spectrometry. An extensive discussion of the stereoselectivity, mechanism and scope of this asymmetric epoxidation is beyond the scope of this chapter. Despite the fact that there is consensus on the nature of the active species (i.e. a Mn\textsuperscript{V}-oxo intermediate), some controversy remains on the exact way the enantioselection takes place. Three key issues can be distinguished: i) the catalyst structure (i.e. if the salen ligand is planar, bent or twisted), ii) the trajectory of the approach of the reacting alkene, and iii) the mode of oxygen transfer from the Mn\textsuperscript{V}=O intermediate to the alkene (involving a concerted pathway, a stepwise radical pathway or a metallaoxetane intermediate).

Cumulative experimental evidence indicates that the substituents at the C\textsubscript{2}-symmetric diimine bridge and bulky substituents at the 3,3’-positions play an important role in governing the trajectory of side-on approach of the olefin, and thus in the asymmetric induction. With the five-membered chelate ring (comprising the ethylenediamine and the
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Mn\(^{V}\)-ion) being non-planar, the approach of the alkene over the downwardly bent benzene ring of the Mn-salen along one of the Mn-N bonds can be envisioned (Figure 1.7). The largest substituent of the alkene (R\(_L\)) is then pointing away from the 3,3'-substituents and this governs the stereochemical outcome of the reaction between the Mn\(^{V}=O\) intermediate and the alkene.\(^{31,32,35}\)

![Figure 1.7 Model rationalizing the stereocontrol in Mn-salen epoxidation.\(^{31c}\)](image)

The typical oxidants used are hypochlorite (ClO\(^-\)), iodosylbenzene or \(m\)-chloroperbenzoic acid (\(m\)CPBA).\(^{31,36}\) However, considerable effort has been devoted to the use of H\(_2\)O\(_2\) in combination with Mn-salen catalysts. Promising results have been reported for certain substrates, although low turnover numbers (generally around 20-50) were obtained with H\(_2\)O\(_2\) as terminal oxidant. When employing H\(_2\)O\(_2\), the presence of additives such as imidazole (derivatives) or carboxylates is required.\(^{37,38,39,40}\) The role of these additives is attributed to preventing O-O bond homolysis leading to non-selective oxidation pathways and destruction of the catalyst.

Berkessel and coworkers developed a chiral dihydrosalen ligand with a covalently attached imidazole group.\(^{37,38}\) With the corresponding Mn-salen complex \(1.6\), \(1,2\)-dihyronaphthalene was converted to the corresponding epoxide with moderate ee (up to 64%) using a dilute (1\%) aqueous solution of H\(_2\)O\(_2\) as oxidant.

![Figure 1.8 Chiral Mn-salen catalysts.\(^{37,38,39}\)](image)

1.6

1.7 \(\text{Ph}^+ = 4\)-t-butylphenyl
Using Mn-salen \(1.7\) together with \(N\)-methylimidazole as an axial ligand, Katsuki and coworkers obtained up to 95\% \(ee\) for the epoxidation of substituted chromenes with 10 equiv. of \(\text{H}_2\text{O}_2\) (30\% aq.) as oxidant.\(^\text{39}\) It should be noted, however, that only a very limited number of substrates were reported (\(ee\)’s ranging from 88-98\%). With carboxylate salts or carboxylic anhydrides in combination with either aqueous \(\text{H}_2\text{O}_2\) or UHP (urea-
\(\text{H}_2\text{O}_2\)), respectively, moderate to excellent \(ee\)’s (55-99\%) have been obtained for the epoxidation of several \(cis\)-alkenes.\(^\text{40,41,42}\)

### 1.1.4 Mn-salts

Burgess and coworkers have reported a very simple, yet effective, system for the epoxidation of alkenes employing \(\text{H}_2\text{O}_2\) as oxidant mediated by a Mn\(^{\text{II}}\)-salt in the presence of NaHCO\(_3\) buffer.\(^\text{43,44,45}\) Although HCO\(_3\)\(^-\) is known to activate \(\text{H}_2\text{O}_2\) for the epoxidation of various alkenes,\(^\text{46}\) the presence of a Mn-salt strongly increases both the yield and the rate of the reaction.\(^\text{44}\) Peroxycarbonate (HCO\(_4\)\(^-\)) is formed \textit{in situ} under reaction conditions from NaHCO\(_3\) and \(\text{H}_2\text{O}_2\) as observed by \(^{13}\text{C}\) NMR (Figure 1.9). It is believed that a manganese \(\eta^2\)-peroxycarbonate \([\text{Mn}^{\text{II}}-\eta^2\text{-HCO}_4\]\(^+)\) species is formed.\(^\text{44}\) Whether the manganese ion acts as a Lewis acid to activate HCO\(_4\)\(^-\) or a Mn\(^{\text{IV}}\)=O intermediate is formed, is not known and neither is the nuclearity of the active species.

\[ \text{H}_2\text{O}_2 + \text{HCO}_3^- \rightarrow \text{HCO}_4^- + \text{H}_2\text{O} \]

\[ \text{Mn}^{\text{II}} \rightarrow \text{Mn}^{\text{IV}} \]

**Figure 1.9** Typical reaction conditions (top) and proposed mechanism for the epoxidation of alkenes by Mn\(^{\text{II}}\)/NaHCO\(_3\) (bottom).\(^\text{43,44,45}\)

Typical conditions employ MnSO\(_4\) (1 mol\%), 0.2 M NaHCO\(_3\) buffer (pH 8.0) and 10 equiv. of \(\text{H}_2\text{O}_2\) (30\%) and either DMF or \(\text{tBuOH}\) is used as an organic co-solvent (Figure 1.9).\(^\text{44}\) In the presence of various additives the excess of \(\text{H}_2\text{O}_2\) used can be lowered and at the same time, the yields of the epoxide product are increased. The screening of a large number of
additives indicated that CH₃CO₂Na (6 mol%) was the best additive when t-BuOH was used as co-solvent and salicylic acid (4 mol%) with DMF as co-solvent. In the latter case the amount of H₂O₂ required for near quantitative conversion of the substrate could be lowered to 2-5 equiv., depending on the substrate. The yield of epoxide product is typically between 55-99% and a wide range of alkenes can be employed as substrate, although terminal aliphatic alkenes are not reactive and cis-alkenes yield a mixture of cis- and trans-products. Since no (chiral) ligands are involved, only racemic products are obtained in the case of prochiral substrates.

1.1.5 Metal-free epoxidation catalysts

Enantioselective epoxidation of alkenes can also be accomplished using metal free catalysts. Both oligopeptides (Juliá-Colonna epoxidation) and chiral ketones (forming chiral dioxiranes as the oxygen transferring species) have been used as organocatalysts for epoxidation.

In the Juliá-Colonna enantioselective epoxidation oligopeptides are used as catalyst, usually poly-leucine or poly-alanine, for the epoxidation of α,β-unsaturated ketones and -esters employing H₂O₂ as terminal oxidant under basic conditions. Although high ee’s have been obtained (up to 99%), the very basic conditions used and the limited substrate scope are drawbacks of this system.

The combination of catalytic amounts of (chiral) ketones and potassium peroxomonosulfate (i.e. Oxone: 2KHSO₅·KHSO₄·K₂SO₄) results in the formation of (chiral) dioxiranes, which in turn are capable of enantioselective epoxidation of alkenes. Many chiral ketones have been used successfully by Shi and coworkers, including binaphthyl derivatives and carbohydrate derived ketones as depicted in Figure 1.10.⁴⁹,⁵⁰

![Figure 1.10 Chiral ketones.](image)

The ketone interacts with potassium peroxomonosulfate forming a dioxirane (Figure 1.11). This dioxirane subsequently oxidizes the alkene to the corresponding epoxide, regenerating the free ketone.⁵⁰ The oxidant used most often is KHSO₅. The substrates most commonly employed are both trans- and trisubstituted alkenes, however, good results with cis- and terminal alkenes have been obtained also.⁴⁹,⁵⁰,⁵¹ Both yields (>70%) and ee’s (>90%) obtained are usually good. The catalyst loading is typically high (10-30 mol%) and excess KHSO₅ is used (1.1-5 equiv.). Especially the latter is a major drawback for large scale applications since Oxone is far from being an atom-efficient oxidant, even in cases where only 1 equiv. is needed.
Recently, H$_2$O$_2$ has been successfully applied as terminal oxidant in the presence of a nitrile (CH$_3$CN is then often used as (co-)solvent). It is believed that H$_2$O$_2$ and CH$_3$CN form a peroximidic acid \textit{in situ}, which is in turn responsible for the regeneration of the dioxirane from the ketone.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure11.png}
\caption{Typical reaction conditions (top) and proposed catalytic cycle (bottom) for dioxirane-based epoxidation.}
\end{figure}

1.2 \textit{Cis}-dihydroxylation

The two textbook examples of stoichiometric reagents for the \textit{cis}-dihydroxylation of alkenes are OsO$_4$ and KMnO$_4$. Although OsO$_4$ is the most reliable reagent and affords the highest yields and selectivities of the \textit{cis}-diol, its (large-scale) application is limited since it is an expensive and very toxic reagent. Various methods that are catalytic in OsO$_4$ have been developed and employ secondary oxidants such as H$_2$O$_2$, chlorates (ClO$_3$), or N-methylmorpholine N-oxide (NMO) in stoichiometric amounts, although the use of H$_2$O$_2$ often results in lower chemoselectivity. The use of KMnO$_4$ often partially results in C-C bond cleavage as side reaction, and yields of the desired \textit{cis}-diol product usually do not exceed 50%.

1.2.1 Os-catalyzed \textit{cis}-dihydroxylation

The best known and well-established catalysts for the enantioselective \textit{cis}-dihydroxylation of alkenes were developed by Sharpless and coworkers. They reported the first catalytic asymmetric dihydroxylation (AD) reaction in 1988. Using catalytic amounts of OsO$_4$ and
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Ligands based on the cinchona alkaloids dihydroquinine (DHQ) or dihydroquinidine (DHQD), enantioselective cis-dihydroxylation of virtually all classes of alkenes can be accomplished.\textsuperscript{58,59,60} Over the years many cinchona-based alkaloids have been tested and it is apparent that the nature of the substituent at the C9 position of the ligand is the most important factor for attaining high ee.\textsuperscript{58} The three ligand classes depicted in Figure 1.12 are complementary and together serve all substitution patterns of alkenes (i.e. primary, 1,1'-disubstituted, cis-1,2-disubstituted, trans-1,2-disubstituted, tri- and tetra-substituted alkenes). Yields are usually high (>75%) and ee’s are good to excellent (80-99%).\textsuperscript{58}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure1.12.png}
\caption{Cinchona alkaloid derived ligands used in the Os-catalyzed cis-dihydroxylation (Alk* = cinchona alkaloid).\textsuperscript{59}}
\end{figure}

\begin{scheme}
\centering
\includegraphics[width=\textwidth]{scheme1.3.png}
\caption{Typical reaction conditions employing AD-mix-α.\textsuperscript{61}}
\end{scheme}

Several reoxidants of the Os catalyst have been employed, e.g. NMO or potassium ferricyanide (K₃Fe(CN)₆). Premixes are commercially available\textsuperscript{62} at present, making this Os-based catalytic method a convenient procedure for lab-scale enantioselective cis-dihydroxylation. The commercial premixes, known as AD-mix-α and AD-mix-β, contain the non-volatile Os source K₂OsO₂(OH)₆, K₃Fe(CN)₆, K₂CO₃ and the ligand (DHQ)₂PHAL or (DHQD)₂PHAL, respectively (Scheme 1.3).\textsuperscript{58,61}

Recent developments include the use of more environmentally benign reoxidants for the Os catalyst, such as H₂O₂\textsuperscript{63} or O₂,\textsuperscript{64} and efforts to attach the Os catalyst to a solid support.\textsuperscript{65} However, despite the fact that the Os-catalyzed cis-dihydroxylation of alkenes affords
excellent enantioselectivities and yields for a wide range of alkenes, the practical utility, particularly on a large-scale, is severely hampered by the cost and, especially, the high toxicity associated with Os.

1.2.2 Fe-catalyzed cis-dihydroxylation and epoxidation

Iron based complexes have been employed successfully for the oxidation of alkenes employing H₂O₂ as oxidant. In a series of papers, Que and coworkers have reported on their extensive investigations of a family of non-heme Fe complexes containing tri- and tetradeutate ligands such as TPA, BPMEN and Ph-DPAH (Figure 1.13). These complexes both catalyze the hydroxylation of alkanes and the epoxidation and/or cis-dihydroxylation of alkenes, and they are functional models for non-heme iron containing enzymes such as Rieske dioxygenases. This is a class of enzymes involved in the biodegradation of arenes by catalysing the cis-dihydroxylation of an arene double bond and contain the 2-His-1-carboxylato facial triad motif, a common feature for many dioxygen activating mononuclear non-heme Fe containing enzymes.

![Figure 1.13 TPA, BPMEN and Ph-DPAH (derived) ligands.](image)

While investigating the reactivity of a series of Fe¹¹ containing complexes based on the TPA family of ligands, Que and coworkers found that these complexes are capable of cis-dihydroxylation of alkenes, in addition to epoxidation, albeit with low t.o.n.'s (Scheme 1.4). Comparison with the reactivity of related Fe-complexes showed that the presence of two labile sites cis to one another is a prerequisite for cis-dihydroxylation activity of these Fe complexes. That is, if the two labile sites are trans or if only one labile site is present, only epoxidation is observed. While the catalyst based on the ligand TPA favors cis-dihydroxylation over epoxidation only slightly (Table 1.1, entry 3), the introduction of two or more Me substituents at the 6-position of the ligand results in catalysts which strongly favors cis-dihydroxylation over epoxidation. Differences between both catalysts are also observed when comparing the results of ¹⁸O labelling experiments. While for Fe-TPA one of the oxygens in the cis-diol product originates from H₂O₂ (and the other from H₂O), both oxygens of the cis-diol product of the Fe-(6-Me₃TPA) catalyzed reaction originate from H₂O₂.
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\[
\begin{array}{c}
R_1^1 R_3^1 \quad 1 \text{ equiv. Fe-complex} \\
R_2^1 R_4^1 \
1000 \text{ equiv. H}_2\text{O}_2 \\
\text{CH}_3\text{CN, r.t.}
\end{array}
\]

Scheme 1.4 Cis-dihydroxylation and epoxidation of alkenes by Fe-based catalysts employing H\textsubscript{2}O\textsubscript{2} as oxidant.\textsuperscript{77}

Table 1.1 Selected examples for catalytic oxidation of cyclooctene by Fe catalysts.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>t.o.n. (\text{cis-diol} )</th>
<th>(\text{epoxide} )</th>
<th>cis-diol/epoxide</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>([\text{Fe}^{II}(\text{BPMEN})(\text{CH}_3\text{CN})_2]^{2+})</td>
<td>0.9(2)</td>
<td>7.5(6)</td>
<td>1:8</td>
<td>[77]</td>
</tr>
<tr>
<td>2</td>
<td>([\text{Fe}^{II}(6-\text{Me}_2\text{-BPMEN})(\text{OTf})_2]^{2+})</td>
<td>6.2(1)</td>
<td>1.5(1)</td>
<td>4:1</td>
<td>[77]</td>
</tr>
<tr>
<td>3</td>
<td>([\text{Fe}^{II}(\text{TPA})(\text{CH}_3\text{CN})_2]^{2+})</td>
<td>4.0(2)</td>
<td>3.4(1)</td>
<td>1.2:1</td>
<td>[77]</td>
</tr>
<tr>
<td>4</td>
<td>([\text{Fe}^{II}(6-\text{Me}_2\text{-TPA})(\text{CH}_3\text{CN})_2]^{2+})</td>
<td>4.9(6)</td>
<td>0.7(6)</td>
<td>7:1</td>
<td>[77]</td>
</tr>
<tr>
<td>5</td>
<td>([\text{Fe}^{II}(6-\text{Me}_2\text{-TPA})(4-\text{Me}-\text{benzoato})]^{+})</td>
<td>5.0(6)</td>
<td>0.5(1)</td>
<td>10:1</td>
<td>[77]</td>
</tr>
<tr>
<td>6</td>
<td>([\text{Fe}^{II}(6-\text{Me}_3\text{-TPA})(\text{benzoato})]^{+})</td>
<td>6.1(4)</td>
<td>0.5(1)</td>
<td>12:1</td>
<td>[77]</td>
</tr>
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<td>7</td>
<td>([\text{Fe}^{II}(6-\text{Me}_2\text{-TPA})(3-\text{NO}_2\text{-benzoato})]^{+})</td>
<td>6.7(3)</td>
<td>0.4(1)</td>
<td>17:1</td>
<td>[77]</td>
</tr>
<tr>
<td>8</td>
<td>([\text{Fe}^{II}(\text{Ph-DPAH})_2]^{2+})</td>
<td>7.0(6)</td>
<td>0.5(1)</td>
<td>14:1</td>
<td>[78]</td>
</tr>
<tr>
<td>9</td>
<td>([\text{Fe}^{II}(\text{TPA})(\text{OTf})_2]^{2+})</td>
<td>5.9</td>
<td>4.3</td>
<td>1.4:1</td>
<td>[89]</td>
</tr>
<tr>
<td>10</td>
<td>([\text{Fe}^{II}(\text{TPA})(\text{OTf})_2]^{2+})</td>
<td>0.8</td>
<td>13.1</td>
<td>1:16</td>
<td>[89]</td>
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</tbody>
</table>

\textsuperscript{a) Conditions: catalyst:H}_2\text{O}_2: \text{cyclooctene} 1:10:1000 in \text{CH}_3\text{CN.} \ b) Also 0.2(1) turnover number trans-diol observed. c) Conditions: catalyst:H}_2\text{O}_2: \text{cyclooctene} 1:14.5:500 in \text{CH}_3\text{CN.} \ d) In the presence of \text{CH}_3\text{CO}_2\text{H (100 equiv. w.r.t. to catalyst).} \n
When either \([\text{Fe}^{II}(\text{TPA})\text{or Fe}^{II}(6-\text{Me}_3\text{TPA})\) were used as a catalyst in the oxidation of a series of electron-deficient alkenes, only \textit{cis}-dihydroxylation and not epoxidation of these electron-deficient alkenes was observed.\textsuperscript{80} Competition experiments between electron-rich (cyclooctene and 1-octene) and electron-deficient alkenes (\textit{tert}-butyl acrylate and dimethyl fumarate) showed that class A catalysts (represented by Fe-TPA) form an electrophilic oxidant, while class B catalysts (represented by Fe-6-Me_3-TPA) form a nucleophilic oxidant.\textsuperscript{80} Another promising system is based on the ligand Ph-DPAH (Figure 1.13).\textsuperscript{78} Excellent selectivities for \textit{cis}-dihydroxylation were obtained for a range of both electron-rich and electron-deficient alkenes under limiting oxidant conditions (catalyst:oxygen:alkene 1:10:1000) (see, for example, entry 8, Table 1.1).

The species \([\text{Fe}^{III}(\text{TPA})(\eta^1\text{-O}_2\text{H})]^{2+}\) has been observed at \(-40^\circ\text{C}\) when \([\text{Fe}^{II}(\text{TPA})]^{2+}\) was treated with \text{H}_2\text{O}_2 in \text{CH}_3\text{CN.}\textsuperscript{69} It should be noted, however, that species observed at low temperatures do not necessarily relate to the intermediates effecting oxidation catalysis at room temperature.\textsuperscript{79} Careful analysis of both product distribution, \(^{18}\text{O}\) labelling studies\textsuperscript{77,73,76,81,82} and DFT calculations\textsuperscript{83,84} has led to the proposed mechanisms for \textit{cis}-dihydroxylation and epoxidation catalysed by the Fe-TPA and Fe-BPMEN family of complexes depicted in Figure 1.14. The most extensively studied and best representative for the ‘class A’ catalysts is \([\text{Fe}^{II}(\text{TPA})]^{2+}\) (water-assisted pathway, \(wa\), Figure 1.14, upper part) (other examples of this class include catalysts based upon the ligands TPA, 6-Me-TPA and BPMEN).\textsuperscript{85} The low-spin Fe\textsuperscript{III} centre in \([\text{Fe}^{III}(\eta^1\text{-O}_2\text{H})(\text{TPA})]^{2+}\) weakens the O-O bond. Water coordinates to the site \textit{cis} to the end-on bound hydroperoxo ligand and forms a hydrogen bond with the non-bonded oxygen atom of the \(\eta^1\text{-O}_2\text{H}\) ligand. This results in the
proposed formation of a \{Fe^V=O(OH)\} intermediate via heterolytic cleavage of the O-O bond and loss of water. If this \{Fe^V=O(OH)\} species reacts quickly with the alkene to afford the cis-diol product, this fits well with the labelling results,\(^{77,85}\) provided that no oxygen exchange with solvent H\(_2\)O and the Fe\(^V\) intermediate occurs. The oxygen incorporated in the epoxide product originates mainly from H\(_2\)O\(_2\) (90 %), with a minor percentage originating from H\(_2\)O (9 %).\(^{77}\) In order to fit with the observed \(^{18}\)O incorporation in the epoxide product, it is required that oxygen exchange between solvent H\(_2\)O and the \{Fe^V=O(OH)\} is much slower than reaction with the alkene. The limited oxo-hydroxo tautomerisation, required for the only partial incorporation of H\(_2\)O in the epoxide product, is rationalised by the different \textit{trans} ligands to the oxo and hydroxo ligands, respectively, resulting in non-equivalent coordination sites.\(^{85}\)

The complexes that show the highest selectivity for cis-dihydroxylation, ‘class B’ catalysts containing more than one Me substituent at the 6-position of the ligand (e.g. 6-Me\(_2\)-TPA, 6-Me\(_3\)-TPA and 6-Me\(_2\)-BPMEN), are best represented by [Fe\(^{IV}\)(6-Me\(_3\)-TPA)]\(^{2+}\).\(^{77}\) This catalyst is proposed to react via a non-water-assisted (\textit{nwa}) pathway (Figure 1.14, lower part).\(^{73}\) The Fe\(^{III}\)\(\eta^1\)-OOH intermediate formed initially is proposed to convert to the species Fe\(^{III}\)\(\eta^2\)-OOH containing a side-on bound hydroperoxo group. The latter species is proposed to either react with the alkene directly or the O-O bond is cleaved first, to afford a Fe\(^{V}\)(=O)(OH) intermediate, which then reacts with the alkene.\(^{77,76}\) It should be noted that neither the proposed Fe\(^{III}\)\(\eta^2\)-OOH, nor the Fe\(^{V}\)(=O)(OH) intermediate have been observed spectroscopically and their involvement is inferred solely from \(^{18}\)O labelling studies.\(^{76,85}\)

The spin-state of the intermediate Fe\(^{III}\)\(\eta^1\)-OOH species, low-spin for class A and high-spin for class B catalysts, respectively, is proposed to be key to the differences observed between both classes of catalyst by controlling the mode of O-O bond cleavage in the Fe\(^{III}\)\(\eta^1\)-OOH intermediate.\(^{76}\)

\[\text{Fe}^{III} \text{OOH} \rightarrow \text{Fe}^V \text{O} + \text{H}_2\text{O} \]

\[\text{Fe}^{III} \text{OOH} \rightarrow \text{Fe}^{V}=\text{O} \text{OH} \rightarrow \text{cis-diol} \]

\[\text{Fe}^{III} \text{OOH} \rightarrow \text{Fe}^{V} \text{OOH} \rightarrow \text{Fe}^{V}=\text{O} \text{OH} \rightarrow \text{cis-diol} \]

\[\text{Fe}^{III} \text{OOH} \rightarrow \text{Fe}^{V} \text{OOH} \rightarrow \text{Fe}^{V}=\text{O} \text{OH} \rightarrow \text{cis-diol} \]

**Figure 1.14** Proposed mechanism for Fe-catalyzed oxidation of alkenes.\(^{77,76,80,85}\)

In the majority of reports on the Fe-TPA and Fe-BPMEN family of catalyst so-called limiting oxidant conditions are used. That is, the catalyst:oxidant:substrate ratio is typically 1:10:1000 and the oxidant H\(_2\)O\(_2\) added slowly over time. This favors the study of the chemistry and reactivity of these complexes since both catalyst and oxidant decomposition are limited. However, these limiting oxidant conditions hamper the practical utility of this
fascinating family of catalysts severely, since maximum turnover numbers are only 10 (up to 30 t.o.n. for a few selected examples, see e.g. ref. [77] and [78]) and as a consequence substrate conversion is usually limited to 1-3 %.

There are, however, two studies reported where limiting substrate conditions are used, i.e. where excess H₂O₂ is used and thus full conversion of substrate is possible. Jacobsen and coworkers employed 3 mol% of the complex [Fe^{II}(BPMEN)(CH₃CN)₂](SbF₆)₂ as catalyst for the epoxidation of several mono- and di-alkyl substituted alkenes in CH₃CN (Scheme 1.5). In the presence of 30 mol% of CH₃CO₂H (vide infra) overoxidation was suppressed and the amount of H₂O₂ used could be lowered to 1.5 equiv. w.r.t. substrate. Under these conditions (catalyst:oxidant:substrate 1:50:33) full conversion of the alkene was obtained and the corresponding epoxides were isolated in 61-90%. Around the same time, Que et al. reported the use of Fe-catalysed oxidation of alkenes under limiting substrate conditions also (catalyst:oxidant:substrate 1:137:34) (Scheme 1.5). Interestingly, in addition to epoxidation, cis-dihydroxylation was observed as the dominant process, as under the limiting oxidant conditions reported earlier. Employing the complex [Fe^{II}(5-Me₃-TPA)(CH₃CN)₂]^{2+} cis-diol/epoxide ratios in the range of 1.5-4.3 were obtained for several alkyl substituted alkenes and the cis-diols were obtained with 45-67% yield. Unfortunately, however, the catalysts affording the highest cis-diol/epoxide ratios (4-7:1) under limiting oxidant conditions (i.e. 6-Me₂-TPA, 6-Me₃-TPA and 6-Me₂-BPMEN) were not very active under these limiting substrate conditions and less than 6% combined yield of products was obtained. It should be noted that even under these limiting substrate conditions the catalyst loading is still high (3 mol%) and the t.o.n.’s that can be achieved is thus limited to 34.

As mentioned above, Jacobsen et al. employed complex [Fe^{II}(BPMEN)(CH₃CN)₂]^{2+} (3 mol%) as catalyst for the epoxidation of alkenes employing H₂O₂ as oxidant and the presence of the additive CH₃CO₂H (30 mol%) suppressed overoxidation of the epoxide product and allowed for an increased addition rate of H₂O₂. When the mononuclear complex [Fe^{II}(BPMEN)(CH₃CN)₂]^{2+} was treated with H₂O₂ in the presence of CH₃CO₂H in CH₃CN the carboxylato bridged dinuclear complex [Fe^{II}(µ-O)(µ-CH₃CO₂)(BPMEN)]^{2+} was isolated. Although in the presence of CH₃CO₂H the latter dinuclear Fe^{II} complex
exhibited the same catalytic activity as the mononuclear complex,\(^1\) (spectroscopic) evidence was not provided as to whether this dinuclear complex or a mononuclear complex is present during catalysis.

Stack and coworkers reported on the epoxidation activity of the \(\mu\)-oxo bridged dinuclear complex \([\text{Fe}^{III}\{\mu-(\mu-O)(H_2O)(\text{phen})\}]^{4+}\) employing peracetic acid (PAA) as oxidant.\(^8\) Good conversions (87-100\%) and high isolated yields (86-90\%) were reported for a range of alkenes, however, PAA and not H\(_2\)O\(_2\) is used as oxidant, limiting the atom-efficiency of this reaction.

Que and coworkers reported the \textit{in situ} formation of PAA from CH\(_3\)CO\(_2\)H and H\(_2\)O\(_2\) catalysed by either Fe(TPA) or Fe(BPMEN) complexes during the catalytic epoxidation and \textit{cis}-dihydroxylation of alkenes.\(^8\) That is, these Fe-based catalysts both catalyse the formation of PAA (from CH\(_3\)CO\(_2\)H and H\(_2\)O\(_2\)) and subsequently catalyse the oxidation of the alkene by activating PAA. The \textit{in situ} formation of PAA was inferred from an extensive range of control reactions and comparison of t.o.n. and \textit{cis}-diol/epoxide ratios using either PAA or H\(_2\)O\(_2\) in the presence or absence of CH\(_3\)CO\(_2\)H and/or H\(_2\)O. With increasing CH\(_3\)CO\(_2\)H concentration the selectivity towards epoxidation is improved at the expense of \textit{cis}-dihydroxylation (Table 1.1, entries 9 and 10), in line with the results reported by Jacobsen \textit{et al.}\(^8\) (vide supra).

Thus, Que \textit{et al.}\(^8\) proposed that the role of CH\(_3\)CO\(_2\)H is in the \textit{in situ} formation of PAA. However, Jacobsen \textit{et al.}\(^8\) reported that the carboxylato-bridged dinuclear complex \([\text{Fe}^{III}\{\mu-(\mu-\text{CH3CO2})(\text{BPMEN})\}]^{3+}\) is an active catalyst for the epoxidation of alkenes employing H\(_2\)O\(_2\). On the other hand, Que \textit{et al.}\(^8\) have reported that this same complex is not active. It should be noted, however, that the conditions used by Jacobsen employed (excess) CH\(_3\)CO\(_2\)H, while Que \textit{et al.} employed otherwise similar conditions, however, CH\(_3\)CO\(_2\)H was absent. Furthermore, Que \textit{et al.} have found small, yet significant, effects of the carboxylato anion (4-methylbenzoato, benzoato or 3-nitrobenzoato) on the observed selectivity for the \textit{cis}-dihydroxylation and epoxidation activity of the complex \([\text{Fe}^{II}(6-\text{Me2-TPA})(\text{RCO2})]\)\(^4\) (Table 1.1, entries 5-7).\(^7\) Also, upon treatment with H\(_2\)O\(_2\) the complex \([\text{Fe}^{II}(\text{BPMEN})(\text{CH3CN})]\)\(^2\) has been reported to hydroxylate benzoic acid, forming the complex \([\text{Fe}^{III}(\text{BPMEN})(\text{salicylato})]\)\(^+\).\(^9\) The role of carboxylic acid in the catalytic epoxidation and \textit{cis}-dihydroxylation of alkenes by this series of Fe-based catalysts is intriguing and deserves further exploration.

The introduction of a chiral backbone in the BPMEN ligand afforded the chiral catalysts \([\text{Fe}^{III}(\text{BPMCN})(\text{CH3CN})]\)\(^2\) and \([\text{Fe}^{II}(6-\text{Me2-BPMCN})(\text{CH3CN})]\)\(^2\) (Figure 1.13).\(^9\) These complexes constitute the first enantioselective \textit{cis}-dihydroxylation catalysts based on Fe and ee’s up to 82\% were obtained. Interestingly, the ee increases upon raising the temperature (for \textit{trans}-2-heptene 40, 79 and 88\% ee at 0, 30 and 50\°C, respectively), suggesting that two active species are present, probably with two different BPMCN conformations, and one of them is favoured at increased temperature.\(^9\) Despite being a promising alternative for the Os based \textit{cis}-dihydroxylation catalysts (see section 1.2.1), the substrate scope reported so far is rather limited and, moreover, only catalysis under limiting

\(^1\) That is selective epoxide formation under limiting substrate conditions.
oxidant conditions (catalyst:oxidant:alkene 1:20:1000) has been reported (up to 11 t.o.n.’s for cis-diol).

1.3 Summary and conclusions

Although many enantioselective epoxidation catalysts have been developed, the terminal oxidants used are generally not atom-efficient (e.g. BuOOH, NaClO or iodosylbenzene). The catalytic systems employing H₂O₂ either do not show enantioselectivity or have only a limited substrate scope when H₂O₂ is used as oxidant. Furthermore, catalyst loadings are generally high and catalyst stability is often limited, especially when H₂O₂ is used as oxidant.

Regarding (enantioselective) cis-dihydroxylation, the only synthetically useful catalysts are based on Os, which is both expensive and toxic. Moreover, these Os-based catalysts generally employ oxidants such as NMO or K₃Fe(CN)₆, and not H₂O₂. Que and coworkers developed a promising family of catalysts based on Fe. However, here turnover numbers are low (often under oxidant limiting conditions) and these systems are not synthetically useful yet. It is therefore desirable to develop robust catalytic systems that show high enantioselectivity and employ H₂O₂ as oxidant.

1.4 References

5 See section 1.2.2 for relevant references.
Enantioselective epoxidation and cis-dihydroxylation catalysts

66 van den Berg, T. A. (University of Groningen) 2003, personal communication.