Chapter 3

Tuning the selectivity of Mn-tmtacn by the use of carboxylic acid additives

The combination of \([\text{Mn}^\text{IV}_2\text{O}_3\text{(tmtacn)}]^2^+\) and carboxylic acids results in an effective system for the catalytic cis-dihydroxylation and epoxidation of alkenes using \(\text{H}_2\text{O}_2\) as terminal oxidant. Screening of a series of alkanoic and benzoic acids identified three most effective carboxylic acids. Trichloroacetic acid yields the most active system, while the selectivity of the reaction can be tuned towards either cis-dihydroxylation or epoxidation when 2,6-dichlorobenzoic or salicylic acid are employed, respectively. The combination of \([\text{Mn}^\text{IV}_2\text{O}_3\text{(tmtacn)}]^2^+/2,6\text{-dichlorobenzoic acid}\) is the most active Os-free cis-dihydroxylation catalyst reported to date.

Part of this chapter has been published:
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The Mn-tmtacn family of complexes were developed by Wieghardt and coworkers as model systems for the water splitting component of photosystem II (PS II, a Mn₄ cluster) and dinuclear manganese-based catalase enzymes in the late 1980’s (see Chapter 2, section 2.2.1). In 1994, Unilever scientists reported [MnIV₂O₃(tmtacn)₂]²⁺ (1) (Figure 3.1) as an excellent catalyst for clean and efficient low-temperature bleaching as well as its potential use as an epoxidation catalyst.¹ Since then, the Mn-tmtacn family of complexes have been studied extensively as oxidation catalysts² for both bleaching of laundry and for the oxidative transformations of a wide range of organic substrates: epoxidation, cis-dihydroxylation, sulfoxidation, C-H bond activation and benzyl alcohol oxidation (Figure 3.2).³⁴⁵

![Figure 3.1](image)

Figure 3.1 Ligands tmtacn, Me₄dtne, L₁ and SiO₂ immobilised tmtacn derivative, complex 1 and 2a and additives GMHA, chloral, L-ascorbic acid and oxalate.

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Whilst complex 1 can be employed as a catalyst, this complex exhibits catalase-type activity. This wasteful disproportionation of H$_2$O$_2$ is suppressed either by maintaining a low concentration of H$_2$O$_2$ during the reaction (either by slow addition of H$_2$O$_2$ or by working in acetone,\textsuperscript{1} utilising the formation of the corresponding perhydrate\textsuperscript{6,7}) or by the use of additives.\textsuperscript{5}

### 3.1 Suppressing catalase-type activity with additives

As early as 1994, Hage and coworkers reported that complex 1 and related complexes were effective in the epoxidation of styrene and 4-vinylbenzoic acid in an aqueous carbonate buffer at pH 8-9 with a large excess of H$_2$O$_2$ (100 equiv. with respect to substrate) as oxidant (Table 3.1, entry 1).\textsuperscript{3} Shortly after this, a seminal publication by De Vos et al. showed that with acetone as solvent and an excess of H$_2$O$_2$ (2 equiv. w.r.t. substrate) added slowly to a mixture of tmtacn and a manganese salt, the epoxidation of a series of alkene substrates could be achieved (entry 2).\textsuperscript{8} In a subsequent report oxalate-buffered aqueous CH$_3$CN enabled efficient epoxidation of a range of alkenes (entry 3).\textsuperscript{11} Similarly, Berkessel and coworkers reported the use of a mixture of ascorbic acid and sodium ascorbate in combination with tmtacn and Mn$^{2+}$ in a catalytic system capable of both epoxidation of alkenes and the oxidation of alcohols using excess H$_2$O$_2$ (entry 4).\textsuperscript{9} In a series of papers Shul’pin and coworkers reported the use of a large excess of acid additives such as acetic acid \textit{(e.g., 5000 equiv. w.r.t. 1)} to enhance the catalytic activity of the Mn-tmtacn system in CH$_3$CN using excess of H$_2$O$_2$ (2-3 equiv. w.r.t. substrate) giving either C-H bond activation of alkanes\textsuperscript{13} or epoxidation of alkenes\textsuperscript{10} (entry 5).

![Figure 3.2 Examples of catalytic oxidation reactions using Mn-tmtacn catalyst.\textsuperscript{11,12,13,14,15}](image)

\textsuperscript{1} Mixtures of H$_2$O$_2$ and acetone are potentially explosive, see also ref. [7].
Several other groups have also used additives in an attempt to improve the catalytic activity of Mn-tmtacn. Examples include the use of carboxylate buffers in combination with Mn-tmtacn for C-H bond activation, both at benzylic\textsuperscript{16} and at non-activated positions\textsuperscript{17} and the use of biphenols\textsuperscript{18} and Rose Bengal\textsuperscript{19} for the epoxidation of alkenes. Despite the recognition that additives are capable of enhancing the catalytic activity of Mn-tmtacn, their role was, at best, poorly understood\textsuperscript{1i}.

When De Vos \textit{et al.} attached a tacn derivative to a solid support to obtain a heterogeneous version of the Mn-tmtacn catalyst, surprisingly, \textit{cis}-dihydroxylation of alkenes was observed in addition to epoxidation\textsuperscript{20}. Although the \textit{cis}-diol/epoxide ratio was low (<0.64 for \textit{cis}-2-hexene), this was the first report on manganese-catalysed \textit{cis}-dihydroxylation.

| Table 3.1 Representative examples of Mn-tmtacn catalyzed epoxidations of alkenes employing \textit{H}_2\textit{O}_2 as oxidant. |
|---|---|---|---|---|---|---|
| Entry | Product | Catalyst / additive | Solvent | equiv. \textit{H}_2\textit{O}_2 | Yield | Ref. |
| 1 | \begin{tikzpicture} \node at (0,0) {\includegraphics[width=1cm]{image.png}}; \end{tikzpicture} | tmtacn + Mn\textsuperscript{2+} / - | acetone | 2 | 89% | [8] |
| 2 | tmtacn + MnSO\textsubscript{4} / oxalate buffer | CH\textsubscript{3}CN | 1.5 | >99% | [11] |
| 3 | tmtacn + Mn(OAc)\textsubscript{2} / sodium ascorbate | CH\textsubscript{3}CN | 2 | 97% | [9] |
| 4 | I / CH\textsubscript{3}CO\textsubscript{2}H | CH\textsubscript{3}CN | 2.6 | 80% \textsuperscript{c} | [10] |

\textsuperscript{a} With respect to (w.r.t.) substrate. \textsuperscript{b} pH 8. \textsuperscript{c} Calculated from the reported turnover number (t.o.n.) (see ref. 10).

\section*{Aldehydes and carboxylic acids as additives}

\subsection*{Cis-dihydroxylation}

Previously, aldehydes were found to be effective in the suppression of the catalase type activity of I and allowed for good conversion of alkene substrates\textsuperscript{21,22}. Moreover, \textit{cis}-dihydroxylation was observed in addition to epoxidation (Scheme 3.1). Both GMHA and chloral hydrate (Figure 3.1 and Table 3.2, entries 1 and 2) provided the \textit{cis}-diol as the major product with cyclooctene as substrate, albeit with a low \textit{cis}-diol/epoxide ratio (1.2). Suppression of catalase-type activity was thought to be due to an equilibrium between the aldehyde and the corresponding perhydrate, thus maintaining a low effective \textit{H}_2\textit{O}_2 concentration in solution\textsuperscript{23}.

\textsuperscript{ii} The few mechanistic proposals given in literature will be discussed in Chapter 5.

\textsuperscript{iii} As will be shown in section 3.2.2, subsequent studies have indicated that this supposed perhydrate formation is likely to be incorrect. An alternative explanation for the role of the aldehyde additive was proposed to be coordination of the hydrate to a mononuclear manganese complex, however, evidence for the latter was inconclusive.
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Scheme 3.1 Catalytic oxidation of cyclooctene, employing 1 and an additive.

In this chapter a study of the major aspects of the catalytic oxidation of alkenes by 1 in the presence of additives, specifically carboxylic acids, will be described. In particular the role of additive concentration, possible involvement of peracids, solvents, competitive oxidation processes, catalyst selectivity and substrate scope will be explored.

3.2.2 Results

At the beginning of the research described in this thesis, the results obtained earlier with chloral hydrate were problematic with respect to reproducibility both in terms of activity and selectivity (Table 3.2, entries 1 and 2). The conversion obtained was lower (70%) than described previously (96%); however, the cis-diol/epoxide ratio increased from 1.2 to 2.4. This inconsistency in the outcome of the chloral-promoted reaction was puzzling. When the level of chloral hydrate was reduced from 25 to 1 mol% (entries 3 and 4), low conversion was observed. These results prompted an investigation into the role of the aldehyde additives played in the catalysis.

Although the relatively large amount of aldehyde needed could suggest the involvement of perhydrates, it opened the possibility that a contaminant in the aldehyde might be responsible for the observed activity instead of the aldehyde itself, as was inferred previously.21,22 Aldehydes are known to react, albeit slowly, during storage over prolonged periods and can contain (trace amounts of) the corresponding alcohol and carboxylic acid.23 While the use of trichloroethanol as additive did not result in alkene conversion, trichloroacetic acid was found to be active in combination with 1 (Table 3.2, entry 5). Importantly, the amount of CCl₃CO₂H could be reduced from 25 mol% to 1 mol% (w.r.t. substrate, i.e. 10 equiv. w.r.t. catalyst) with only a small decrease in reactivity (entries 5 and 6). When using 0.4 and 0.2 mol% of CCl₃CO₂H good conversion was obtained, although the use of 0.1 mol% CCl₃CO₂H resulted in a sharp drop in reactivity (entries 10 and 11).v

iv The (apparent) higher cis-diol/epoxide can be explained by the lower reactivity of the catalytic system in the second case (entry 3) compared to the one reported previously (entry 2, ref. [21] and [22]). The lower reactivity is evident from both the lower conversion and the higher mass-balance, suggesting less overoxidation of the cis-diol and thus a higher cis-diol/epoxide ratio (see also section 3.5).

v As will be discussed in Chapter 5, two carboxylate ligands are needed per manganese dimer to obtain the catalytically active species.
Table 3.2 Catalytic epoxidation and cis-dihydroxylation of cyclooctene.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Co-catalyst (mol%)</th>
<th>conv. (%)</th>
<th>mass bal.</th>
<th>cis-diol</th>
<th>epoxide</th>
<th>t.o.n.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>GMHA (25)\textsuperscript{e}</td>
<td>90</td>
<td>88</td>
<td>420</td>
<td>360</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Chloral hydrate (25)\textsuperscript{f}</td>
<td>88</td>
<td>80</td>
<td>370</td>
<td>310</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Chloral hydrate (25)</td>
<td>70</td>
<td>92</td>
<td>440</td>
<td>185</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Chloral hydrate (1.0)</td>
<td>3</td>
<td>104</td>
<td>20</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>CCl\textsubscript{2}CO\textsubscript{2}H (25)</td>
<td>96</td>
<td>77</td>
<td>325</td>
<td>405</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>CCl\textsubscript{2}CO\textsubscript{2}H (1.0)</td>
<td>91</td>
<td>78</td>
<td>440</td>
<td>245</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>HPF\textsubscript{6} (1.0)</td>
<td>3</td>
<td>100</td>
<td>10</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>(Et\textsubscript{4})N.OAc (1.0)</td>
<td>0</td>
<td>108</td>
<td>0</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>-</td>
<td>3</td>
<td>99</td>
<td>10</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>CCl\textsubscript{2}CO\textsubscript{2}H (0.2)</td>
<td>59</td>
<td>90</td>
<td>340</td>
<td>145</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>CCl\textsubscript{2}CO\textsubscript{2}H (0.1)</td>
<td>9</td>
<td>100</td>
<td>65</td>
<td>25</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a} Reaction conditions: I/cyclooctene/H\textsubscript{2}O\textsubscript{2} 1/1000/1300, H\textsubscript{2}O\textsubscript{2} added over 6 h, reported data after 7 h, general procedure A (see Appendix C). All values within +/- 10%. b) Based on substrate consumed. c) Mass balance [%] = unreacted alkene [%] + (cis-diol and epoxide products [%]). Deviation from 100% indicates loss through further oxidation of the cis-diol to the \(\alpha\)-hydroxyketone, see also ref. [21]. d) Turnover number. e) From ref. [21].

Having established that carboxylic acids, present in the aldehydes employed previously, are the active additive of the catalytic system, it was deemed important to examine which other components are essential to obtain an active catalytic system. When I alone is used, conversion was not observed (Table 3.3, entry 1). Similarly, activity is not observed when either the ligand tmtacn and manganese(III) acetate are mixed \textit{in situ} (Table 3.3, entry 2), the combination of I and tetraethylammonium acetate\textsuperscript{vi} (Table 3.2, entry 8) or the combination of I and a simple proton source such as HPF\textsubscript{6} (Table 3.2, entry 7) is used. When the tmtacn ligand was mixed \textit{in situ} with either manganese(II) perchlorate or manganese(III) acetate and the reaction was performed in the presence of CCl\textsubscript{2}CO\textsubscript{2}H, activity was observed (Table 3.3, entries 7 and 8). Ligand L1 (a linear variant of tmtacn) together with a Mn\textsuperscript{II} or Mn\textsuperscript{III} salt and CCl\textsubscript{2}CO\textsubscript{2}H gave no activity (Table 3.3, entries 9 and 10). From these results it is clear that the tmtacn ligand, Mn\textsuperscript{II}- or Mn\textsuperscript{III}-ions and a carboxylic acid are required to obtain a catalytically active system.

\textsuperscript{vi} The combination of I/CH\textsubscript{3}CO\textsubscript{2}H is catalytically active, see Table 3.6, entry 1.
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Table 3.3 Product distribution following oxidation of cyclooctene catalyzed by 1, Mn\textsuperscript{II} and Mn\textsuperscript{III} salts in CH\textsubscript{3}CN, in the absence and presence of tmtacn.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol%)</th>
<th>CCl\textsubscript{3}CO\textsubscript{2}H (mol%)</th>
<th>Conv. (mol%)</th>
<th>T.O.N. cis-diol (%)</th>
<th>Mass. epoxide bal.(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{I} (0.1))</td>
<td>-</td>
<td>3</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>tmtacn (0.11)+1\textsubscript{M}(OAc\textsubscript{2})\textsubscript{2}H\textsubscript{2}O (0.1)</td>
<td>-</td>
<td>1</td>
<td>0</td>
<td>26</td>
</tr>
<tr>
<td>3</td>
<td>Mn(OAc\textsubscript{2})\textsubscript{2}H\textsubscript{2}O (0.1)</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>MnSO\textsubscript{4} (0.1)</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>MnSO\textsubscript{4} (0.2)</td>
<td>25</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Mn(ClO\textsubscript{4})\textsubscript{2}H\textsubscript{2}O (0.2)</td>
<td>25</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>tmtacn (0.11)+Mn(ClO\textsubscript{4})\textsubscript{2}H\textsubscript{2}O (0.1)</td>
<td>1</td>
<td>52</td>
<td>293</td>
<td>141</td>
</tr>
<tr>
<td>8</td>
<td>tmtacn (0.11)+Mn(OAc\textsubscript{2})\textsubscript{2}H\textsubscript{2}O (0.1)</td>
<td>1</td>
<td>71</td>
<td>402</td>
<td>204</td>
</tr>
<tr>
<td>9</td>
<td>(\text{L1} (0.22)+\text{Mn(ClO}_4\textsubscript{2})\textsubscript{2}H\textsubscript{2}O (0.2))</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>(\text{L1} (0.22)+\text{Mn(OAc}_3\textsubscript{2}H\textsubscript{2}O (0.2))</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

\textsuperscript{a) See general procedure A (see Appendix C). b) \(\text{L1} = \text{N}_2\text{N}_2\text{N'}\text{N''}\text{N'''}\text{-pentamethyldiethylenetriamine}\) (see Figure 3.1).

3.3 Peracids

Burgess,\textsuperscript{24} Stack,\textsuperscript{25} Que,\textsuperscript{26} and co-workers have demonstrated the use of Mn- and Fe-complexes in combination with peracids (either preformed or prepared \textit{in situ} from the corresponding acid and H\textsubscript{2}O\textsubscript{2}) in the epoxidation of alkenes. The combination of H\textsubscript{2}O\textsubscript{2} and carboxylic acids in the present system, raises the possibility of the involvement of \textit{in situ} formation of peracids.\textsuperscript{vii}

Table 3.4 Oxidation of cyclooctene.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Additive (mol%)</th>
<th>Conv. (%)</th>
<th>cis-diol (%)</th>
<th>t.o.n. epoxide</th>
<th>Mass. bal. (%)</th>
<th>Oxidant</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{I} (1))</td>
<td>(\text{CH}_3\text{CO}_2\text{H} (1))</td>
<td>14</td>
<td>78</td>
<td>36</td>
<td>98</td>
<td>\textsubscript{H}_2\textsubscript{O}_2\textsubscript{2}</td>
</tr>
<tr>
<td>2</td>
<td>(\text{I} (0))</td>
<td>-</td>
<td>97</td>
<td>26</td>
<td>919</td>
<td>97</td>
<td>\textsubscript{PAA}^a</td>
</tr>
<tr>
<td>3</td>
<td>(3\text{a} (0))</td>
<td>-</td>
<td>70</td>
<td>0</td>
<td>668</td>
<td>97</td>
<td>\textsubscript{PAA}^a</td>
</tr>
<tr>
<td>4</td>
<td>(3\text{b} (0))</td>
<td>-</td>
<td>85</td>
<td>0</td>
<td>838</td>
<td>99</td>
<td>\textsubscript{PAA}^a</td>
</tr>
<tr>
<td>5</td>
<td>(1 (1))</td>
<td>3-chlorobenzoic (1)</td>
<td>38</td>
<td>253</td>
<td>113</td>
<td>98</td>
<td>\textsubscript{H}_2\textsubscript{O}_2\textsubscript{2}</td>
</tr>
<tr>
<td>6</td>
<td>(1 (1))</td>
<td>3-chlorobenzoic (1)</td>
<td>74</td>
<td>6</td>
<td>715</td>
<td>98</td>
<td>\textsubscript{mCPBA}^c</td>
</tr>
<tr>
<td>7</td>
<td>(1 (1))</td>
<td>3-chlorobenzoic (1)</td>
<td>81</td>
<td>8</td>
<td>740</td>
<td>94</td>
<td>\textsubscript{mCPBA}^c</td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>-</td>
<td>91</td>
<td>0</td>
<td>899</td>
<td>99</td>
<td>\textsubscript{mCPBA}^c</td>
</tr>
<tr>
<td>9</td>
<td>(2\text{a (1)})</td>
<td>(\text{CCl}_3\text{CO}_2\text{H} (1))</td>
<td>10</td>
<td>0</td>
<td>21</td>
<td>92</td>
<td>\textsubscript{tBuOOH}^f</td>
</tr>
</tbody>
</table>

\textsuperscript{a) Employing 0.1 mol\% of catalyst (see general procedure A, Appendix C). b) Added by syringe pump over 6 h. c) See also ref. [25c]. d) No lag-period observed. e) Added as a 1.3 M solution in CH\textsubscript{3}CN. f) 1 equiv. of \textsubscript{tBuOOH} (70 w/w\% in H\textsubscript{2}O) added over 5 h, reported data after 7 h.}

\textsuperscript{vii} Stack and coworkers have also used a combination of tmtacn and a Mn\textsuperscript{II}-salt to oxidise 1-octene employing peracetic acid (PAA) (91% yield of the epoxide, see ref. [25c]).
The oxidation of cyclooctene was performed with both peracetic acid (PAA) and m-chloroperbenzoic acid (mCPBA) as oxidant in place of H$_2$O$_2$, to examine whether peracids are involved in the current system (Table 3.4). Whereas I and either acetic acid or 3-chlorobenzoic acid afforded a cis-diol/epoxide ratio of ~2:1 (vide infra, Table 3.6, entry 1 and 8), with peracetic acid (39% in CH$_3$CO$_2$H) or mCPBA, almost quantitative epoxidation is observed with formation of only minor amounts of cis-diol (~3%, Table 3.4, entry 1). It should be noted that in the absence of Mn-tmtacn both PAA and mCPBA give epoxidation of cyclooctene (84 and 90% yield, respectively, Table 3.4, entries 4 and 8), with slightly higher yields than in the presence of Mn-tmtacn (entries 3 and 7). Furthermore, with the alkyl peroxide tert-butylperoxide as oxidant, no significant conversion of cyclooctene was observed (entry 9).

3.4 Reactivity dependence on solvent

Several solvents other than CH$_3$CN were examined for the oxidation of cyclooctene catalysed by I/CCl$_3$CO$_2$H. In tBuOH/H$_2$O, THF and acetone conversion of cyclooctene was lower than that observed with CH$_3$CN (Figure 3.3 and Table 3.5). In both DMF and CH$_2$Cl$_2$ very low conversion was observed. The activity observed in several, quite different solvents (CH$_3$CN, acetone, tBuOH/H$_2$O and THF) indicates that coordination of organic solvents to the manganese complex is not critical to catalytic activity.

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viii Commercially available PAA (Fluka) used consists of 39% peracetic acid in acetic acid (45%) and contains up to 6% of H$_2$O$_2$. The formation of cis-diol can be attributed to the presence of H$_2$O$_2$ in commercially available PAA and, hence, allows for the formation of 3 (see also Chapter 4).

ix Complex 2a (see Chapter 4) was employed in this reaction as tBuOOH is not effective in reducing 1 under catalytic conditions.

x Overall the solvent dependence of the reactivity of I/CCl$_3$CO$_2$H correlates well with the stability of complex [Mn$^{III}$_2(μ-O)(μ-CCl$_3$CO$_2$)$_2$(tmtacn)$_2$]$^{2+}$ (2a) (Figure 3.3) under catalytic conditions (see Chapter 5 for details). That is, catalysis takes place only where 2a can be formed from 1 and is stable. In acetone, for example, the formation of 2a is very slow (by UV-Vis spectroscopy) and the resulting long lag-period is mainly responsible for the low conversion. In DMF, complex 2a is not stable and decomposes quickly (as determined by UV-Vis spectroscopy). It should be noted that the absence of activity or reduced activity observed in different solvents can, potentially, be due to competitive solvent oxidation which leads to a reduced efficiency in terms of cyclooctene conversion. However, catalytic activity towards alkene oxidation was observed only when 2a was present in solution.
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Figure 3.3 Solvent dependence of the oxidation of cyclooctene after 7 h by 1 (0.1 mol%) with CCl₃CO₂H (1 mol%) (see also Table 3.5).

Table 3.5 Product distribution dependence on solvent for the oxidation of cyclooctene catalyzed by 1 or MnSO₄ with CCl₃CO₂H (1 mol%).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol%)</th>
<th>Solvent</th>
<th>Conv. (%)</th>
<th>t.o.n. cis-diol</th>
<th>t.o.n. epoxide</th>
<th>Mass. bal. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 (0.1)</td>
<td>CH₃CN</td>
<td>91</td>
<td>440</td>
<td>245</td>
<td>78</td>
</tr>
<tr>
<td>2</td>
<td>1 (0.1)</td>
<td>tBuOH/H₂O (2:1 v/v)</td>
<td>39</td>
<td>225</td>
<td>90</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>1 (0.1)</td>
<td>THF</td>
<td>21</td>
<td>115</td>
<td>45</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>1 (0.1)</td>
<td>Acetone</td>
<td>53</td>
<td>175</td>
<td>140</td>
<td>78</td>
</tr>
<tr>
<td>5</td>
<td>1 (0.1)</td>
<td>DMF</td>
<td>20</td>
<td>0</td>
<td>5</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>MnSO₄ (1)</td>
<td>DMF</td>
<td>3</td>
<td>0</td>
<td>5</td>
<td>98</td>
</tr>
<tr>
<td>7</td>
<td>1 (0.1)</td>
<td>CH₂Cl₂</td>
<td>15</td>
<td>20</td>
<td>70</td>
<td>94</td>
</tr>
</tbody>
</table>

a) See general procedure A (Appendix C). b) 10 mol% CCl₃CO₂H.

3.5 Time course of the reaction

In the optimised reaction conditions for the catalytic oxidation of cyclooctene (100 mol%) a combination of 1 (0.1 mol%) and CCl₃CO₂H (1 mol%) is employed in CH₃CN at 0 °C. H₂O₂ (50% aq.) is added slowly by syringe pump addition over 6 h. When both substrate conversion and product formation are followed in time a significant lag-period is observed (phase I, Figure 3.4), after which cis-dihydroxylation and epoxidation begin simultaneously with both processes showing similar time dependence up to 4 h (phase II). Finally, towards the end of the reaction (phase III), the cis-diol concentration begins to level off and ultimately decreases. During the lag-period, i.e. phase I, the catalytically active species is formed as will be discussed in detail in Chapter 5.
Figure 3.4 Typical time course for product formation (cis-diol: triangles and epoxide: circles) and substrate consumption (cyclooctene: squares) under 'standard' conditions (see text for details) in the catalyzed oxidation of cyclooctene with H₂O₂ by 1/CCl₃CO₂H. Phase I - lag-period, Phase II - normal reactivity observed, Phase III - subsequent oxidation of cis-diol product is observed.

Figure 3.5 Catalytic oxidation of cyclooctene by a combination of 1 (0.1 mol%) and 2,6-dichlorobenzoic acid (3 mol%): a) extended addition of H₂O₂ (dotted lines) and b) maintaining pseudo-steady state levels of cyclooctene (solid lines).

Phase III of the reaction is intriguing as it appears that the cis-diol/epoxide selectivity of the catalyst decreases in time. This is not the case, however, and the apparent loss of the activity of the catalyst towards cis-diol formation is in fact due to further oxidation of the cis-diol product to the corresponding α-hydroxyketone. This is best exemplified in the
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case where a combination of 1 and 2,6-dichlorobenzoic acid (30 equiv. w.r.t. 1) is used (Figure 3.5, dotted lines). When the addition of oxidant (H₂O₂) is continued over a longer period, three observations can be made. First, the cyclooctene substrate is converted completely (after ca. 12 h). Secondly, the formation of the epoxide product is constant in time (after the initial lag-period) and its formation ceases when all cyclooctene has been consumed. Thirdly, the amount of cis-diol increases steadily during phase II. However, when most of the alkene substrate has been consumed the amount of cis-diol levels off and ultimately all cis-diol is oxidised. In an additional experiment the concentration of the cyclooctene substrate is held at a pseudo-steady state level (by addition of cyclooctene at approximately the same rate as it was consumed, Figure 3.5, solid lines). It is apparent that the epoxidation is unaffected and the epoxide is formed at a constant rate throughout the reaction. The formation of the cis-diol behaves initially in an identical manner as before. However, the amount of cis-diol increases throughout the reaction and after 40 h 2000 t.o.n.’s for cis-dihydroxylation are obtained. From these two experiments it can be concluded that the intrinsic (cis-diol/epoxide) selectivity of the catalyst is not altered over the 40 h of the reaction. In fact, the catalyst is very active and although it exhibits a preference for the oxidation of the alkene over the cis-diol, at low alkene concentration the cis-diol competes effectively with the alkene to be oxidised by the catalyst.xii Similar suppression of overoxidation is observed when 1-octene is used as substrate (Figure 3.6).

![Figure 3.6](image)

**Figure 3.6** Catalytic oxidation of 1-octene by a combination of 1 (0.1 mol%) and 2,6-dichlorobenzoic acid (3 mol%): extended addition of H₂O₂ (dotted lines) and maintaining pseudo-steady state levels of 1-octene (solid lines).

---

xii H₂O₂ is being added at the same rate as under ‘standard’ conditions. As a consequence of the longer addition time, more oxidant than needed for single oxidation of the alkene substrate is being added, i.e. 5.2 equiv. of H₂O₂ w.r.t. substrate was added over a period of 21 h.

xiii Furthermore, the α-hydroxyketone formed is subject to further oxidation, ultimately giving suberic acid (see Appendix C).
3.6 Dependence of activity and selectivity on the carboxylic acid

Since CCl₃CO₂H was identified as an effective additive to i) suppress the catalase activity of I and ii) to enable I to act as both a cis-dihydroxylation and epoxidation catalyst, a series of alkanoic and benzoic acids were tested in combination with I, to identify more selective carboxylic acids, both for selective formation of cis-diol and selective formation of epoxide products. When comparing the activity and selectivity of different additives, it is, however, important to note the different phases during the reaction (Figure 3.4). Although all carboxylic acids examined promote oxidation of cyclooctene by I to both cis-diol and epoxide, the duration of the lag-period, the cis-diol/epoxide ratio and the conversion are dependent on the specific carboxylic acid employed. In order to compare the intrinsic activity and cis-diol/epoxide selectivity of the different additives it is important to take into account both the duration of the lag-period as well as the level of overoxidation. For example, for hexafluoroglutaric acid a lag-period of only 30 min is observed at 0 °C, while for CCl₃CO₂H the lag-period is 60-90 min and for 2,4,6-trichlorobenzoic acid a lag-period of almost 2 h was observed (Figure 3.7 and Table 3.6). Hence, the lag-period should be taken into account: i.e. low conversion after 7 h does not necessarily correspond to a low intrinsic activity. Furthermore, a very active system might appear non-selective towards cis-dihydroxylation, since due to the high activity substantial overoxidation occurs, resulting in a reduction of the amount of cis-diol observed after 7 h.

![Figure 3.7](image)

**Figure 3.7** Effect of different carboxylic acids on the lag-period for the cis-dihydroxylation of cyclooctene by I/H₂O₂.

Acetic acid, trichloroacetic acid, trifluoroacetic acid, glutaric acid and hexafluoroglutaric acid (Table 3.6, entries 1-5) all show a cis-diol/epoxide ratio of approximately 2, however, with CCl₃CO₂H and CF₃CO₂H higher conversion is observed than with CH₃CO₂H. The ditopic carboxylic acids examined (i.e. glutaric and hexafluoroglutaric acid) show similar selectivity with their mono-carboxylic acid counterparts (acetic and trifluoroacetic acid, respectively). For hexafluoroglutaric acid a shorter lag-period is observed compared with
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trifluoroacetic acid. For glutaric acid, however, the increased activity observed compared to acetic acid is surprising, when it is considered that glutaric acid exhibits a much longer lag-period (a rational for the latter observations is provided in Chapter 5).

For benzoic acid and its F-, Cl-, HO-, MeO- and Me- substituted analogs, activity towards both cis-dihydroxylation and epoxidation is observed. Indeed several inferences regarding the relative importance of steric and electronic effects towards reactivity and selectivity can be drawn from Figure 3.8 (see also Table 3.6). With the exception of 2,4,6-trimethyl- and 4-chlorobenzoic acid, for all substituted benzoic acids examined, an increase in reactivity compared with benzoic acid is observed. Comparison of ortho-, meta- and para-mono-substituted benzoic acids show only minor differences in selectivity, however, overall para-substitution results in a significant decrease in activity. A clear correlation between electronic parameters and either reactivity or selectivity is not observed for the benzoic acids. It should be noted, however, that the activity observed is affected significantly by the duration of the lag-period.

![Figure 3.8](image_url)

**Figure 3.8** Cis-dihydroxylation and epoxidation of cyclooctene by 1 (0.1 mol%) in the presence of (selected) chloro-, fluoro-, methyl-, methoxy-, and hydroxy-substituted benzoic acids (1 mol%). See also Table 3.6.

The selectivity of the reaction shows only moderate sensitivity to the position of the hydroxy group in the hydroxybenzoic acid series (*i.e.* meta-OH ~ ortho-OH, entries 22 and 21, Table 3.6). By contrast, steric demands at the 2- and 6-positions appear to be more important with regard to selectivity, with (bulky) 2,6-disubstituted benzoic acids providing consistently higher cis-diol/epoxide ratios without loss in activity, compared with their ortho-mono substituted analogs: both 2-chlorobenzoic acid and 2,4-dichlorobenzoic acid exhibit only a moderate cis-diol/epoxide ratio (entries 7 and 11), while 2,6-dichlorobenzoic acid is much more selective towards cis-dihydroxylation (entry 10). Furthermore, for the 2,6-difluorobenzoic acid promoted system (entry 15), the activity is comparable to the
Chapter 3

2,6-dichlorobenzoic acid promoted system, however, the selectivity observed was comparable to that with benzoic acid (entry 6). In the case of the 2,4,6-trimethylbenzoic acid (entry 14) promoted reaction the cis-diol/epoxide ratio is high also (~5), although in this case very low reactivity is observed. This suggests that while the activity is driven by both electronic and steric effects, the selectivity is dominated by steric factors with bulky substituents at both the 2- and 6-position favoring cis-dihydroxylation over epoxidation.xiii

Table 3.6 Cis-dihydroxylation and epoxidation of cyclooctene - influence of carboxylic acids.a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Carboxylic acid (mol%)</th>
<th>Conv. (%)</th>
<th>t.o.n.b</th>
<th>Mass bal. (%)</th>
<th>Lag-period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>cis-diol</td>
<td>epoxide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>acetic acid (1.0)</td>
<td>14</td>
<td>78</td>
<td>36</td>
<td>1.5 h</td>
</tr>
<tr>
<td>2</td>
<td>glutaric acid (0.5)</td>
<td>38</td>
<td>207</td>
<td>104</td>
<td>2-3 h</td>
</tr>
<tr>
<td>3</td>
<td>CCl_3CO_2H (1.0)</td>
<td>91</td>
<td>440</td>
<td>245</td>
<td>60-90 min</td>
</tr>
<tr>
<td>4</td>
<td>trifluoroacetic acid (1.0)</td>
<td>90</td>
<td>296</td>
<td>251</td>
<td>30-45 min</td>
</tr>
<tr>
<td>5</td>
<td>hexafluoroglutaric acid (0.5)</td>
<td>92</td>
<td>315</td>
<td>256</td>
<td>15-30 min</td>
</tr>
<tr>
<td>6</td>
<td>benzoic acid (1.0)</td>
<td>21</td>
<td>110</td>
<td>60</td>
<td>&gt;2h</td>
</tr>
<tr>
<td>7</td>
<td>2-chlorobenzoic acid (1.0)</td>
<td>29</td>
<td>165</td>
<td>80</td>
<td>&gt;2h</td>
</tr>
<tr>
<td>8</td>
<td>3-chlorobenzoic acid (1.0)</td>
<td>38</td>
<td>253</td>
<td>113</td>
<td>N/A</td>
</tr>
<tr>
<td>9</td>
<td>4-chlorobenzoic acid (1.0)</td>
<td>16</td>
<td>88</td>
<td>42</td>
<td>&gt;2h</td>
</tr>
<tr>
<td>10</td>
<td>2,6-dichlorobenzoic acid (1.0)</td>
<td>36</td>
<td>320</td>
<td>21</td>
<td>&gt;1.5 h</td>
</tr>
<tr>
<td>11</td>
<td>2,4-dichlorobenzoic acid (1.0)</td>
<td>21</td>
<td>128</td>
<td>47</td>
<td>&gt;2h</td>
</tr>
<tr>
<td>12</td>
<td>2,3,6-trichlorobenzonic acid (1.0)</td>
<td>42</td>
<td>362</td>
<td>30</td>
<td>1.25 h</td>
</tr>
<tr>
<td>13</td>
<td>2,4,6-trichlorobenzonic acid (1.0)</td>
<td>24</td>
<td>197</td>
<td>16</td>
<td>2-3 h</td>
</tr>
<tr>
<td>14</td>
<td>2,4,6-trimethylbenzoic acid (1.0)</td>
<td>9</td>
<td>40</td>
<td>8</td>
<td>&gt;2h</td>
</tr>
<tr>
<td>15</td>
<td>2,6-difluorobenzonic acid (1.0)c</td>
<td>47</td>
<td>301</td>
<td>103</td>
<td>1.5 h</td>
</tr>
<tr>
<td>16</td>
<td>2,4-difluorobenzonic acid (1.0)c</td>
<td>43</td>
<td>268</td>
<td>106</td>
<td>2 h</td>
</tr>
<tr>
<td>17</td>
<td>3,4-difluorobenzonic acid (1.0)c</td>
<td>34</td>
<td>206</td>
<td>82</td>
<td>&gt;1.25 h</td>
</tr>
<tr>
<td>18</td>
<td>3,5-difluorobenzonic acid (1.0)c</td>
<td>33</td>
<td>194</td>
<td>82</td>
<td>2 h</td>
</tr>
<tr>
<td>19</td>
<td>2-methoxybenzoic acid (1.0)</td>
<td>47</td>
<td>244</td>
<td>158</td>
<td>2 h</td>
</tr>
<tr>
<td>20</td>
<td>4-methoxybenzoic acid (1.0)</td>
<td>26</td>
<td>137</td>
<td>83</td>
<td>&gt;2h</td>
</tr>
<tr>
<td>21</td>
<td>2-hydroxybenzoic acid (1.0)</td>
<td>64</td>
<td>225</td>
<td>320</td>
<td>1.25 h</td>
</tr>
<tr>
<td>22</td>
<td>3-hydroxybenzoic acid (1.0)</td>
<td>69</td>
<td>260</td>
<td>325</td>
<td>1.5 h</td>
</tr>
<tr>
<td>23</td>
<td>4-hydroxybenzoic acid (1.0)</td>
<td>46</td>
<td>219</td>
<td>170</td>
<td>&gt;2 h</td>
</tr>
<tr>
<td>24</td>
<td>5-bromosalicylic acid (1.0)</td>
<td>62</td>
<td>252</td>
<td>296</td>
<td>N/A</td>
</tr>
</tbody>
</table>

a) Employing 1 (0.1 mol%), see also general procedure A (Appendix C).
b) Turnover number. c) MnIII_2 bis(carboxylato) complexes 17-20 used instead of 1 (see Figure 4.2, Chapter 4).

3.7 Me₄dtne

In order to get an indication of the relative importance of the dinuclear structure of 1, a related manganese-dimer was tested for catalytic activity as well. The complex [MnIIIIV_2(µ-O)_2(µ-CH_3CO_2)(Me₄dtne)]²⁺ is based on the ethylene-bridged tmtacn type

xiii The electron withdrawing/donating nature of the various acids is inferred from the redox potentials of the bis(carboxylato) complexes, see Chapter 4, Table 4.1.
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...ligand, Me₄dtne. Its reactivity was tested on cyclooctene using selected carboxylic acids (Table 3.7). As with the combination 1/CH₃CO₂H low activity is observed with [Mn<sup>III,IV</sup>₂(µ-Ø)₂(µ-CH₃CO₂)(Me₄dtne)]<sup>2+</sup> in combination with CH₃CO₂H (entry 1). However, when CH₃CO₂H is replaced by CCl₃CO₂H, the conversion increases to 31% and a cis-diol/epoxide ratio of 1:1 is obtained (entry 2). The use of both 2,6-dichlorobenzoic acid and salicylic acid results in low conversion (7 and 8%, respectively) and both acids give a cis-diol/epoxide ratio of 0.7 (entries 3 and 4).<sup>xiv</sup>

Table 3.7 Catalytic oxidation of cyclooctene by [Mn<sup>III,IV</sup>₂(µ-Ø)₂(µ-CH₃CO₂)(Me₄dtne)]<sup>2+</sup> (0.1 mol%) at 0 °C.<sup>a</sup>

<table>
<thead>
<tr>
<th>Entry</th>
<th>acid (mol%)</th>
<th>Conv. (%)</th>
<th>t.o.n. (cis-diol)</th>
<th>epoxide</th>
<th>mass. bal. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>acetic acid (1)</td>
<td>3</td>
<td>0</td>
<td>6</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>trichloroacetic (1)</td>
<td>31</td>
<td>154</td>
<td>150</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>2,6-dichlorobenzoic (3)</td>
<td>7</td>
<td>37</td>
<td>50</td>
<td>101</td>
</tr>
<tr>
<td>4</td>
<td>salicylic acid (1)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>8</td>
<td>38</td>
<td>58</td>
<td>102</td>
</tr>
</tbody>
</table>


3.8 Substrate scope

3.8.1 Alkenes

From the screening of a range of carboxylic acids, three carboxylic acids stand out: CCl₃CO₂H is one of the most active additives, while overoxidation of the cis-diol is limited. 2,6-Dichlorobenzoic acid exhibits the highest selectivity for cis-dihydroxylation and salicylic acid gives the epoxide as the main product. These three acids were employed in the oxidation of a series of alkenes representing key structural classes (Table 3.8).

As for cyclooctene, for cis-2-heptene either the cis-diol is obtained as the major product when using 2,6-dichlorobenzoic acid or the cis-epoxide when salicylic acid is used (Table 3.8). Furthermore, retention of configuration (RC)<sup>27</sup> for both the cis-diol (RC >96%) and epoxide (RC >95%) is observed, indicating that the reaction between the alkene and the activated catalyst proceeds via a concerted pathway. Trans-heptene on the other hand gives lower conversion and the very poor mass-balance indicates that competing processes are taking place. For the terminal alkenes styrene and 1-octene epoxidation is observed to be the major process even with CCl₃CO₂H or 2,6-dichlorobenzoic acid. The same holds for cyclopentene and cyclohexene where the epoxide is observed as the major product. The general trend that 2,6-dichlorobenzoic acid favors cis-dihydroxylation and salicylic acid...

<xsup>xiv</xsup> A possible explanation for the similar selectivity observed for the reaction promoted by 2,6-dichlorobenzoic and salicylic acid, respectively, is that the corresponding carboxylates are too sterically demanding to replace the µ-acetate ligand in [Mn<sup>III,IV</sup>₂(µ-Ø)₂(µ-CH₃CO₂)(Me₄dtne)]<sup>2+</sup>. While in the case of 1 (containing two tmtacn ligands) replacement of two µ-ØO bridges by two (sterically demanding) carboxylates can be facilitated by increasing the Mn-Mn separation, this would not be possible in the complex with the ethylene-bridged ligand Me₄dtne.
favors epoxidation holds for these substrates. It should be noted that both for cyclopentene and cyclohexene only minor amounts of allylic oxidation products were observed. While high conversion is achieved with electron-rich alkenes, electron-deficient alkenes (i.e., dimethyl-maleate and -fumarate) show low conversion, indicating that the catalyst is electrophilic in character.

Table 3.8 Cis-dihydroxylation and epoxidation of various alkenes.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>2,6-dichlorobenzoic acid (3 mol%)</th>
<th>CCl₃CO₂H (1 mol%)</th>
<th>salicylic acid (1 mol%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mass bal. (conv.)</td>
<td>mass bal. (conv.)</td>
<td>mass bal. (conv.)</td>
</tr>
<tr>
<td>cyclooctene</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cis-diol</td>
<td>525</td>
<td>445</td>
<td>85%</td>
</tr>
<tr>
<td>epoxide</td>
<td>75</td>
<td>225</td>
<td>85%</td>
</tr>
<tr>
<td>cis-2-heptene</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>erythro/threo-diol</td>
<td>440 / 10</td>
<td>295 / 5</td>
<td>70%</td>
</tr>
<tr>
<td>cis/trans-epoxide</td>
<td>125 / 5</td>
<td>330 / 10</td>
<td>72%</td>
</tr>
<tr>
<td>trans-2-heptene</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>erythro/threo-diol</td>
<td>0 / 85</td>
<td>0 / 240</td>
<td>72%</td>
</tr>
<tr>
<td>cis/trans-epoxide</td>
<td>10 / 90</td>
<td>15 / 285</td>
<td>67%</td>
</tr>
<tr>
<td>cyclohexene</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cis-diol</td>
<td>110</td>
<td>70</td>
<td>75%</td>
</tr>
<tr>
<td>epoxide</td>
<td>400</td>
<td>570</td>
<td>76%</td>
</tr>
<tr>
<td>2-cyclohexen-1-ol</td>
<td>25</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>2-cyclohexen-1-one</td>
<td>135</td>
<td>35</td>
<td>80%</td>
</tr>
<tr>
<td>cyclopentene</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cis-diol</td>
<td>305</td>
<td>190</td>
<td>75%</td>
</tr>
<tr>
<td>epoxide</td>
<td>360</td>
<td>460</td>
<td>76%</td>
</tr>
<tr>
<td>2-cyclopenten-1-one</td>
<td>85</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>1-octene</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>diol</td>
<td>125</td>
<td>115</td>
<td>76%</td>
</tr>
<tr>
<td>epoxide</td>
<td>295</td>
<td>200</td>
<td>80%</td>
</tr>
<tr>
<td>styrene</td>
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<td></td>
</tr>
<tr>
<td>diol</td>
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<td>71%</td>
</tr>
<tr>
<td>epoxide</td>
<td>770</td>
<td>615</td>
<td>87%</td>
</tr>
<tr>
<td>dimethylmalate</td>
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<td></td>
</tr>
<tr>
<td>meso-/DL-diol</td>
<td>0 / 0</td>
<td>0 / 0</td>
<td>98%</td>
</tr>
<tr>
<td>cis/trans-epoxide</td>
<td>0 / 0</td>
<td>0 / 0</td>
<td>99%</td>
</tr>
<tr>
<td>dimethylfumarate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>meso-/DL-diol</td>
<td>0 / 15</td>
<td>0 / 105</td>
<td>96%</td>
</tr>
<tr>
<td>cis/trans-epoxide</td>
<td>0 / 0</td>
<td>0 / 0</td>
<td>96%</td>
</tr>
</tbody>
</table>

a) See general procedure B and C in Appendix C. All values +/- 10%. b) Based on substrate consumed. c) Turnover number. d) Isolated yield cis-cyclooctane diol: 46%. e) Reaction conditions: 1/alkene/H₂O₂ 1/500/650, see also general procedure D in Appendix C. Under these conditions, using CCl₃CO₂H as additive, cyclooctene gives: 79% conversion, 122 t.o.n. epoxide, 166 t.o.n. cis-diol (mass-balance: 78%).

The discrepancy in the mass balance is due to further oxidation of the cis-diol to the α-hydroxyketone, see also ref. [21]. g) Multiple (minor) oxidation side products observed by GC. h) Benzaldehyde is the major oxidation side product.
3.8.2 Benzyl alcohol oxidation and C-H bond activation

Previously, Mn-tmtacn based catalysts were found to be active in the oxidation of benzylalcohols to their corresponding aldehydes in acetone (and to the carboxylic acids when excess H$_2$O$_2$ was used). Furthermore, overoxidation of the cis-cyclooctanediol to the corresponding α-hydroxyketone (at high conversion of cyclooctene, Figure 3.5) and the formation of a number of (unidentified) by-products in trace amounts in the catalytic oxidation of trans-heptene (Table 3.8) were observed. Therefore, the current system was tested for activity for both alcohol oxidation and C-H bond activation.

The combination of 1 and either 2,6-dichlorobenzoic acid, CCl$_3$CO$_2$H or salicylic acid resulted in good conversion of benzyl alcohol (69-100%) with benzoic acid being the major product (Table 3.9). Catalytic oxidation of cyclooctane using 1/CCl$_3$CO$_2$H provided 52% conversion of the substrate and cyclooctanone was found as the major product. Using the same system, n-octane was partly oxidized to a complex mixture of various alcohols and ketones.

Table 3.9 Catalytic oxidation of benzylalcohol, cyclooctane and n-octane.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>2,6-dichlorobenzoic acid$^a$</th>
<th>CCl$_3$CO$_2$H$^b$</th>
<th>salicylic acid$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(conv.)</td>
<td>Mass</td>
<td>(conv.)</td>
</tr>
<tr>
<td>benzylalcohol</td>
<td>(100%)</td>
<td>79%</td>
<td>(69%)</td>
</tr>
<tr>
<td>benzaldehyde</td>
<td>0</td>
<td>305</td>
<td>410</td>
</tr>
<tr>
<td>benzoic acid</td>
<td>785</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cyclooctane</td>
<td>(52%)</td>
<td>82%</td>
<td></td>
</tr>
<tr>
<td>cyclooctanol</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cyclooctanone</td>
<td>310</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n-octane</td>
<td>(21%)</td>
<td>(n.d.)</td>
<td>(n.d.)</td>
</tr>
<tr>
<td>alcohol / ketone</td>
<td>(n.d.)</td>
<td>(n.d.)</td>
<td>(n.d.)</td>
</tr>
</tbody>
</table>

a) Reaction conditions: 1/substrate/H$_2$O$_2$ 1/1000/1800, H$_2$O$_2$ added over 7 h, reported data after 8 h, see general procedure C in Appendix C. All values +/- 10%.
b) Reaction conditions: 1/substrate/H$_2$O$_2$ 1/1000/1300, H$_2$O$_2$ added over 6 h, reported data after 7 h, see general procedure B in Appendix C. c) Based on substrate consumed. d) Turnover number.

3.9 Summary

The complex [Mn$_2$O$_3$(tmtacn)$_2$]$^{2+}$ (1) itself does not show catalytic activity in the oxidation of organic substrates with H$_2$O$_2$ as oxidant; in fact it catalyses the decomposition of H$_2$O$_2$ (catalase type activity). However, carboxylic acid additives such as CCl$_3$CO$_2$H suppress catalase-type activity. Examination of a range of carboxylic acids confirmed that both the

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$^{15}$ In their paper, Hage et al. did not describe the use of additives. However, 1 was used as epoxidation catalyst under basic aqueous conditions using a carboxylate buffer.
Chapter 3

activity and the selectivity of the catalyst can be tuned by the use of the appropriate carboxylic acid. CCl\textsubscript{3}CO\textsubscript{2}H was identified as providing the most active system. The most selective additive for \textit{cis}-dihydroxylation is 2,6-dichlorobenzoic acid, while the use of salicylic acid results in the highest preference for epoxidation.

Based on the results of the reactions performed with peracids (PAA and \textit{m}CPBA) and the lack of activity of Mn\textsubscript{II} and Mn\textsubscript{III} salts with trichloroacetic acid and H\textsubscript{2}O\textsubscript{2}, it can be excluded that \textit{cis}-dihydroxylation arises from the \textit{in situ} formation of peracids. For epoxidation, involvement of peracids formed \textit{in situ} cannot be excluded completely. However, it is unlikely since i) the combination of Mn-salts and acids do not result in epoxidation and ii) in the absence of CCl\textsubscript{3}CO\textsubscript{2}H the complex 2a gives the same \textit{cis}-diol/epoxide ratio as in the presence of CCl\textsubscript{3}CO\textsubscript{2}H (see Chapter 5, Figure 5.5 and Table 5.1).

The catalytic oxidation of a series of alkenes representing key structural classes revealed that reaction between the active catalyst and the alkene substrate occurs via a concerted pathway (section 3.8.1). Comparison between electron-rich and electron-poor substrates showed that the catalyst is electrophilic in nature with the highest selectivities for \textit{cis}-dihydroxylation observed for electron-rich \textit{cis}-alkenes.

The system 1/2,6-dichlorobenzoic acid (>2000 t.o.n. for \textit{cis}-1,2-cyclooctanediol) is the most active Os-free \textit{cis}-dihydroxylation catalyst reported to date. However, this very high activity of the present system was found to be its Achilles’ heel as exemplified by the oxidation of several of the substrates. Besides \textit{cis}-dihydroxylation and epoxidation, the catalytic system is also capable of alcohol oxidation and C-H bond activation. In general, the activated catalyst prefers to oxidise (electron-rich) alkenes. However, when the alkene concentration becomes low (\textit{e.g.} at high conversion of cyclooctene, Figure 3.5) or is not accessible (\textit{e.g.} \textit{trans}-2-heptene, Table 3.8), the catalyst will oxidise alcohols or C-H bonds, respectively. Overoxidation can be circumvented by maintaining pseudo-steady state concentrations of substrate.

Thus, the use of carboxylic acids suppresses the catalase activity of 1 and instead a very active and selective oxidation catalyst is obtained, of which the selectivity can be tuned towards either \textit{cis}-dihydroxylation or epoxidation by the use of the appropriate carboxylic acid additive. Furthermore, the combination 1/carboxylic acid results in a very H\textsubscript{2}O\textsubscript{2} efficient catalyst and nearly all H\textsubscript{2}O\textsubscript{2} is used in oxidation events (see also Chapter 5, Figure 5.9).

These results are promising, but raise several questions. First of all, the considerable lag-period, during which catalytic activity is not observed, is not understood. Moreover, the observations described in this chapter do not explain the role of the carboxylic acids in controlling activity and selectivity. Neither has the catalytically active species been identified. These issues will be addressed in Chapter 5, however, to understand the present catalytic system it is essential to understand first the complexes involved. In the next chapter the ligand exchange and redox chemistry of several Mn-tmtacn complexes relevant to catalysis will be explored.
3.10 References

27 RC (retention of configuration) = 100% × (A – B)/(A + B) where A = yield of product with retention of configuration and B = yield of epimer: Fujita, M.; Costas, M.; Que, Jr., L. J. Am. Chem. Soc. 2003, 125, 9912-9913.