Manganese catalysts in homogeneous oxidation reactions
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Chapter 2

Manganese Complexes as Homogeneous Epoxidation Catalysts

Abstract

The dinuclear manganese complex of \(N^1,N^1,N^3,N^3\)-tetrakis(2-pyridinylmethyl)-1,3-propanediamine (tptn) and in situ prepared complexes based on tptn derivatives are able to catalyse the oxidation of several alkenes to the corresponding epoxides. High turnover numbers (up to 900), using aqueous hydrogen peroxide as oxidant, were obtained in acetone and at ambient temperature.

2.1 Introduction

Selective oxidation of alcohols to aldehydes and the formation of epoxides from olefins are among the key reactions in organic chemistry. In the ongoing pursuit to develop environmental benign synthetic methodology there is currently great interest in new and more efficient catalytic versions of these oxidation reactions.\(^{1,2}\) Compared to catalytic methods that require oxidants like sodium hypochlorite (NaOCl) and ammonium periodates the use of hydrogen peroxide offers the advantage that it is a cheap, environmental friendly and a readily available reagent.\(^3\)

Manganese-based catalysts have been widely used for the oxidation of olefins to epoxides.\(^4\) Many reports have appeared on manganese porphyrins and salen complexes which are able to catalyse the epoxidation of olefins with high efficiency. As oxidants sodium hypochlorite or iodosylbenzene were used.\(^5\) Initial attempts using \(\text{H}_2\text{O}_2\) as oxidant for alkene epoxidation with porphyrin-based catalysts were unsuccessful due to dismutation of \(\text{H}_2\text{O}_2\) into \(\text{H}_2\text{O}\) and \(\text{O}_2\), leading to a fast depletion of the oxidant. Introduction of bulky groups on the porphyrin ligand allowed the use of aqueous hydrogen peroxide. Unfortunately, only low conversions were obtained,\(^5,7\) but the catalytic system was strongly improved by performing the oxidation reaction in the presence of large quantities of imidazole, acting as axial ligand. This catalytic system provides epoxide yields up to 99% (Scheme 1).\(^7\) The amount of axial ligand could be significantly reduced by the addition of a catalytic amount of carboxylic acid generating a biphasic system.\(^8\) Under the two-phase reaction conditions with the addition of a small amount of benzoic acid (0.04 equivalents) the reaction rate was enormously accelerated and high conversions in less than 15 min at 0°C could be obtained.

Carboxylic acids and nitrogen containing additives presumable facilitate the heterolytic cleavage of the \(\text{O} - \text{O}\) bond in the porphyrin manganese hydroperoxy intermediate resulting in a catalytically active manganese(V)-oxo intermediate.\(^9\) Homolytic cleavage of the \(\text{O} - \text{O}\) bond leads to the formation of hydroxyl radicals, resulting in unselective reactions, a serious problem using \(\text{H}_2\text{O}_2\) in metal-catalysed oxidation reactions.\(^4\) Furthermore, gradual improvement in the stereoselectivity of the oxidation of cis-stilbene was observed by increasing the number of \(\beta\)-halogen atoms on the porphyrin ligand.\(^10\) However, a general
disadvantage of manganese porphyrin chemistry is the difficulty of synthesising the ligands and the often tedious purification.

Scheme 1 Manganese porphyrin complex 2.1 as catalyst for epoxidation reactions.

The Jacobsen catalyst\textsuperscript{11} and the related Katsuki manganese salen catalyst\textsuperscript{12} are commonly applied for asymmetric epoxidation reactions. High yields and moderate to excellent enantioselectivities have been reported for oxidation of \textit{cis}-olefins with oxidants like iodosylarenes, sodium hypochlorite and molecular oxygen employing Mukaiyama conditions. Turnover numbers in the range of 35 to 40 were found.

Several attempts have been made to generate a related catalytic system that is capable of employing hydrogen peroxide as terminal oxidant, while maintaining the same activity and selectivity of the catalyst. Using imidazole or imidazole derivatives and carboxylates as axial ligands, high enantioselectivities but lower turnover numbers were observed.\textsuperscript{13} Imidazole groups were also covalently attached to the chiral salen ligands and with the corresponding catalysts enantiomeric excesses up to 64\% with \textit{H}_2\textit{O}_2 as oxidant were achieved.\textsuperscript{14}

Scheme 2 Manganese salen catalyst and catalytic cycle for epoxidation of indene.
Chapter 2

As oxidising intermediate a manganese(V)-oxo species was proposed\textsuperscript{15} which was confirmed by electrospray ionisation mass spectrometry (ES/MS).\textsuperscript{16} Subsequently an oxygen transfer from the manganese-oxo adduct to the alkene occurs as depicted in Scheme 2.

The tridentate macrocycle 1,4,7-triazacyclononane (tacn) and in particular 1,4,7-trimethyl-1,4,7-triazacyclononane (tmtacn) have been extensively studied as ligands in coordination chemistry.\textsuperscript{17} The manganese complexes have been investigated as enzyme models for superoxide dismutase, catalase and oxygen evolving processes in the photosystem II.\textsuperscript{18} Unilever Research reported in 1994 the manganese 1,4,7-trimethyl-1,4,7-triazacyclononane complex (Mn-tmtacn, Figure 1) as an excellent low temperature bleaching catalyst for stain removal and for the oxidation of catechol (a tea stain mimic) by H\textsubscript{2}O\textsubscript{2}.\textsuperscript{19,20}

In combination with H\textsubscript{2}O\textsubscript{2} it was also found that the dinuclear manganese complex is a highly active oxidation catalyst.\textsuperscript{21} High turnover numbers (more than 400) were obtained using styrene derivatives as substrates without notable catalyst degradation.\textsuperscript{22} After subsequent addition of substrate and oxidant to the reaction mixture the rate of oxidation remained constant indicating that the catalyst is extremely robust under the oxidation conditions.

\[
\text{Figure 1 Manganese tmtacn complex and free tmtacn ligand.}
\]

An improvement in reducing the catalase activity was found by performing the oxidation reactions in acetone at subambient temperatures, which effects a low steady state concentration of H\textsubscript{2}O\textsubscript{2} by trapping the latter with formation of a perhydrate.\textsuperscript{23,24,25} Using the optimised conditions the substrate scope of the catalyst was extended. Although the procedure is unsuitable for the epoxidation of electron deficient olefins, high turnover numbers up to 1000 have been reported for the conversion of several alkenes and styrenes to the epoxides by the \textit{in situ} prepared Mn-tmtacn complex using MnSO\textsubscript{4} (Scheme 3).\textsuperscript{23}

\[
\text{Scheme 3 Oxidation of styrene catalysed by in situ formed manganese complex in acetone.}
\]

Hydrogen peroxide decomposition by Mn-tmtacn complexes can also be suppressed by addition of oxalate\textsuperscript{26} or ascorbic acid\textsuperscript{27} as co-catalysts, or by anchoring the triazacyclononane ligand to a solid support (see Chapter 4 for more details concerning
methods to suppress catalase activity). Our group has shown that the Mn-tmtacn complex can also be employed as catalyst for the oxidation of substituted benzyl alcohols to the corresponding benzaldehydes with H$_2$O$_2$. No over-oxidation to carboxylic acids was observed.

Enantiomerically enriched epoxides have been obtained in some cases by using optically active derivatives of the tacn ligands. The manganese complexes were prepared in situ from chiral N-substituted tacn ligands with Mn(OAc)$_2$ giving enantioselectivities up to 43% for the epoxidation of styrene, cis-β-methylstyrene and chromene. Unfortunately, low turnover numbers were found with methanol as the reaction solvent which is not an ideal solvent because of substantial side reactions such as solvent oxidation and methanolysis of epoxides. Recently, a C$_3$-symmetric trispyrrolidine-1,4,7-triazacyclononane was developed and the corresponding dinuclear manganese complex was used in the catalytic epoxidation of vinylar enes with H$_2$O$_2$. Promising yields but low enantioselectivities were obtained using acetone as solvent.

Various successful attempts to fine-tune the catalyst selectivity have been made. Encapsulation of the Mn-tmtacn complex in zeolites increased the epoxidation selectivity. By immobilisation of the triazacyclononane ligand on an inorganic support a new group of active heterogeneous manganese tacn epoxidation catalysts were introduced. Improved selectivities were found but the conversions obtained were lower than with the homogenous catalysts.

The mechanism of the Mn-tmtacn-catalysed epoxidation and alcohol oxidation has been the subject of much research. However, very little is known about the mechanisms or about the nature of the active intermediates in the catalytic systems. High-valent manganese, mono- or dinuclear manganese-oxo species and also radicals may all be involved. During the oxidation reactions often an induction period was observed, indicating that the original [Mn$_2$O$_3$(tmtacn)$_2$](PF$_6$)$_2$ complex is not the active catalytic species and has first to be converted to the active catalytic oxidation species. Recently, it was reported that the catalytic activity of Mn-tmtacn was significantly increased when it was pre-treated with excess of H$_2$O$_2$ prior to the addition of the substrate (benzyl alcohols). From the 16-line spectrum obtained form electron paramagnetic resonance spectroscopy (EPR) measurements it was inferred that the Mn$^{IV}$-Mn$^{IV}$ dimer was instantaneously reduced by H$_2$O$_2$ to a dinuclear Mn$^{III}$-Mn$^{IV}$ mixed-valent species in acetone. This mixed-valent species gradually changes to a Mn$^{II}$-species. EPR studies of the catalysts under comparable catalytic oxidation conditions using alkenes as substrates instead of alcohols showed again the mixed-valence Mn$^{III}$-Mn$^{IV}$ dimer. Based on EPR studies similar manganese species were reported during related phenol oxidation experiments. Barton proposed the formation of a Mn$^{V}$=O intermediate during the oxidation of 2,6-di-tert-butylphenol with Mn-tmtacn and hydrogen peroxide. From electrospray mass spectrometry (ES/MS) experiments the mononuclear Mn$^{V}$=O species could indeed be assigned. This species was also generated in oxidation reactions using a mononuclear Mn$^{IV}$-complex and from an in situ prepared Mn$^{II}$-complex from Mn(SO$_4$) and free tmtacn ligand. Despite the fact that various studies on the mechanism of the Mn-tmtacn
system have been performed, the mechanism of the oxidation reactions has not been firmly established.

### 2.2 Manganese complexes in oxidation catalysis

Drawbacks of the manganese 1,4,7-trimethyl-1,4,7-triazacyclononane catalysts are the difficult synthesis whereas modifications in the ligand structure are not easily accomplished due to lengthy and often tedious preparation. Furthermore, the sensitivity of the corresponding metal complexes to changes in the original tmtacn structure often leads to completely inactive manganese complexes. Therefore a major challenge is the design of novel dinucleating ligands featuring the three N-donor set (as for the tmtacn ligand) for each manganese site, retaining the high oxidation activity.

In this chapter we present high catalytic epoxidation activity for manganese complexes based on dinucleating ligands \( N,N,N',N' \)-tetrakis(2-pyridylmethyl)-1,2-ethanediamine (2a, tpen) and \( N,N,N',N' \)-tetrakis(2-pyridylmethyl)-1,3-propanediamine (2.2b, tptn) both featuring the three N donor set for each manganese site. The ligands 2.2a and 2.2b contain a two- and three-carbon spacer, respectively, between the three N-donor sets. Advantages of this type of ligands are the accessibility and the possibility to modify the ligand structure. The ligands and manganese complexes examined here were synthesised following literature procedures. Complexes of ligands 2.2a and 2.2b have been reported as mimics for the photosystem II (PS II). The hexadentate ligands were prepared by reaction of the corresponding diamines with an excess of 2-(chloromethyl)pyridine hydrochloride in dichloromethane under basic conditions. The crude products were purified by crystallisation with chemical yields up to 41%. The purification step was a modification of the method used by Toftlund and co-workers (Scheme 4).

\[
\begin{align*}
\text{H}_2\text{N} & \text{N} \quad \text{N} \quad \text{N} \\
n = 1, 2 \\
\text{NH}_2
\end{align*}
\]

\[
\begin{align*}
\text{Cl} & \text{N} \\
\text{Cl} \quad \text{N} \quad \text{N} \quad \text{N} \\
\text{CH}_2\text{Cl}_2, \text{NaOH}, 3\text{d, RT} \quad 35 - 41% \\
2.2a \quad n = 1 \\
2.2b \quad n = 2
\end{align*}
\]

**Scheme 4 Synthesis of hexadentate ligands.**

Preliminary screening in a number of different catalytic epoxidation reactions showed that complex 2.3 (Scheme 5) based on tpen, featuring a two-carbon spacer between the three N-donor sets in the ligand, was not reactive in oxidation reactions. In sharp contrast complex
2.4$^{37}$ (Mn$_2$O(OAc)$_2$tptn), based on tptn with a three-carbon spacer, is able to catalyse the oxidation of various alkenes to the corresponding epoxides.$^{38}$ Catalytic reactions were performed under a nitrogen atmosphere using 1.0 equivalent of complex 2.4, 1000 equivalents substrate and 1.0 ml of H$_2$O$_2$ (aq. 30%, 9.8 M, 9.8 equivalents with respect to substrate). The reaction conditions are summarised in Scheme 5. Samples for GC analysis were taken after 2h and 4h. During the oxidation reaction in acetone at room temperature gas bubbles developed rapidly when excess of oxidant was added. Evidently, part of the oxidant H$_2$O$_2$ decomposes to oxygen, similar to the reactions with Mn-tmtacn. An increase of the catalyst turnover number was obtained by performing the catalytic reactions in acetone at 0°C suppressing oxidant decomposition. Scheme 6 summarises the reactions catalysed by complex 2.4 and includes the catalytic oxidation of various alkenes. Several alkenes such as styrene, cyclohexene, trans-2-octene were converted to the corresponding epoxides in good yields. For the selected olefins generally up to 300 turnover numbers were found. Addition of a second aliquot of oxidant resulted in a considerable increase in epoxide yield after 4h (total t.o.n.’s up to 900 for cyclohexene). These results indicate that the catalyst is robust under the conditions used and is to a certain extent comparable with the Mn-tmtacn oxidation catalyst.

$$\text{C} = \text{C} \xrightarrow{\text{Mn catalyst (0.1 mol\%) \ H}_2\text{O}_2 \text{ (aq. 30\%) \ acetone, 0°C}} \text{C} = \text{C}$$

Mn catalysts:

\[2.3\]

\[(\text{ClO}_4)_2\]

\[2.4\]

\[(\text{ClO}_4)_2\]

**Scheme 5 Epoxidation reaction conditions and structures of manganese complexes.**

High selectivity is observed and it needs to be emphasised that in the epoxidation reaction of cyclic alkenes (especially for cyclohexene) besides the epoxides no allylic oxidation products were found. Excellent results were also found for internal alkenes *e.g.* entries 5 and 6 in Table 1, whereas slightly lower yields are found for terminal linear alkenes. In control experiments replacing the manganese tptn complex (2.4) with Mn(OAc)$_3$.3H$_2$O, strong peroxide decomposition and no epoxide formation was found. The data for the conversion of various alkenes to the corresponding epoxides are compiled in Table 1.
Scheme 6 Overview of oxidation reactions catalysed by manganese tptn and H$_2$O$_2$

Table 1 Oxidation of selected olefins with Mn$_2$O(OAc)$_2$tptn complex 2.4.$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product$^b$</th>
<th>t.o.n.$^c$ 2h</th>
<th>t.o.n.$^c$ 4h</th>
<th>t.o.n.$^c$ 2h</th>
<th>t.o.n.$^c$ 4h</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>298 K</td>
<td>298 K</td>
<td>273 K</td>
<td>273 K</td>
</tr>
<tr>
<td>1</td>
<td>styrene</td>
<td>styrene oxide</td>
<td>157</td>
<td>208</td>
<td>176</td>
<td>271</td>
</tr>
<tr>
<td></td>
<td></td>
<td>benzaldehyde</td>
<td>5</td>
<td>75</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td>cyclohexene</td>
<td>cyclohexene oxide</td>
<td>247</td>
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<td>328</td>
<td>868</td>
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<tr>
<td>3</td>
<td>cyclooctene</td>
<td>cyclooctene oxide</td>
<td>193</td>
<td>636</td>
<td>262</td>
<td>575</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cis-diol</td>
<td>49</td>
<td>93</td>
<td>61</td>
<td>48</td>
</tr>
<tr>
<td>4</td>
<td>cinnamyl alcohol</td>
<td>cinnamyl oxide</td>
<td>208</td>
<td>219</td>
<td>219</td>
<td>321</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cinnamyl aldehyde</td>
<td>69</td>
<td>85</td>
<td>70</td>
<td>86</td>
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<tr>
<td></td>
<td></td>
<td>benzaldehyde</td>
<td>22</td>
<td>47</td>
<td>21</td>
<td>46</td>
</tr>
<tr>
<td>5</td>
<td>trans-2-octene</td>
<td>trans-2-octene oxide</td>
<td>118</td>
<td>188</td>
<td>178</td>
<td>248</td>
</tr>
<tr>
<td>6</td>
<td>trans-4-octene</td>
<td>trans-4-octene oxide</td>
<td>97</td>
<td>148</td>
<td>153</td>
<td>210</td>
</tr>
<tr>
<td>7</td>
<td>1-decene</td>
<td>1-decene oxide</td>
<td>28</td>
<td>34</td>
<td>80</td>
<td>97</td>
</tr>
<tr>
<td>8</td>
<td>cis-β-methyl-styrene</td>
<td>cis-oxide</td>
<td>19</td>
<td>84</td>
<td>23</td>
<td>115</td>
</tr>
</tbody>
</table>

(a) Experimental conditions, see experimental section and Scheme 5. (b) All products were identical to independently synthesised samples and identified by GC and $^1$H-NMR. (c) Turnover number in mole product per mole catalyst.
The oxidation of cis-β-methylstyrene with H$_2$O$_2$ in the presence of Mn$_2$O(OAc)$_2$tptn catalyst 2.4 gives in addition to the corresponding cis-epoxide also a considerable amount of trans-epoxide. Cis/trans isomerisation has been frequently observed in mechanistic studies using porphyrin and manganese salen catalysts and is usually attributed to the formation of a radical intermediate (a, Scheme 7) with a lifetime sufficient for internal rotation before ring closure via reaction path B providing the thermodynamically more stable trans-epoxide (b, Scheme 7). In case of a fast collapse of the radical intermediate (via reaction path A) retention of configuration will be observed.

Styrene epoxidation is often accompanied by the formation of a slight amount of benzaldehyde; a feature commonly observed during epoxidation reaction of this substrate. Cinnamyl alcohol also shows some cleavage and alcohol oxidation leading to benzaldehyde and cinnamyl aldehyde, respectively. In the presence of molecular oxygen the carbon radical species can react with oxygen generating a peroxy radical species (d) leading to a dioxetane (e) after ring closure. Subsequent cleavage of the dioxetane yields the by-product benzaldehyde (f).

![Scheme 7: Radical pathways to epoxides and fragmentation to benzaldehydes.](image)

### 2.3 Modified tptn and tpen ligands

Advantages of manganese catalysts based on ligands like tptn and tpen are the relatively facile synthesis compared with the synthesis of tmtacn ligands and corresponding complexes. In addition it can be envisaged that the hexadentate tptn ligand has a versatile
structure. Therefore changes in the overall structure can be easily applied giving the possibility for further optimisation and the enhancement of the catalytic activity. In addition to the influence of the spacer length the effect of the introduction of additional substituents at the 3- and at the 6-position of the pyridine rings will be described in this paragraph. Finally other coordinating groups were introduced on the alkylidene backbone and the effect of using pentadentate, tetradentate, tridentate ligands were examined during catalytic epoxidation reactions. The modified ligands are depicted in Figure 2. The synthesis and catalytic activity will be discussed in the next paragraphs.

![Figure 2 Structures of modified ligands.](image-url)
2.4 Synthesis of the ligands

Derivatives 2.7, 2.8 and 2.17 were prepared according to the general reaction procedure depicted in Scheme 8. The multistep synthesis started with a reductive amination of 2-pyridinecarboxaldehyde (or 6-methyl-2-pyridinecarbaldehyde for the synthesis of ligand 2.17) with ethylene- or propylenediamine giving compounds 2.18a, 2.18b and 2.18c, respectively, in good yield. Subsequently the corresponding aminal 2.19 was synthesised by reacting amine 2.18 with 2-pyridinecarboxaldehyde or 6-methyl-2-pyridinecarbaldehyde in diethyl ether according to the procedure of Girerd et al. Subsequently aminal 2.19 was reduced with NaBH₃CN in methanol resulting in amine 2.20. This amine gives the possibility to introduce new groups. These reaction steps proceed with satisfactory chemical yields and the products were obtained with high purity after work-up, making further purification unnecessary. Finally the amine can be benzylated using a reductive amination procedure (with NaBH(OAc)₃) to provide the target ligands 2.7, 2.8 and 2.17 with yields up to 72% after purification by column chromatography.

Scheme 8 Introduction of benzyl functionality via an aminal.

Ligands 2.11 and 2.12 were synthesised by a reductive amination reaction of N,N'-dimethylethylamine (or N,N'-dimethylpropylamine) and 2-pyridinecarboxaldehyde with NaBH(OAc)₃ in 1,2-dichloroethane. After purification by column chromatography the
yields were in the range of 61 - 65\% (Scheme 9). The synthesis procedure of ligand 2.13 started with the hydrogenation reaction with Pd/C of the \textit{in situ} formed imine derived from the condensation of 2-(aminomethyl)pyridine with 2-pyridinecarboxaldehyde. This was followed by the introduction of the methyl group using the procedure of Abdel-Magid \textit{et al.}\textsuperscript{42} to obtain the final product 2.13 in 80\% chemical yield.

\begin{center}
\includegraphics[width=0.8\textwidth]{scheme9.png}
\end{center}

\textbf{Scheme 9} Synthesis of ligands 2.11, 2.12 and 2.13.

Employing a Michael reaction under high pressure ligands 2.15 and 2.16 were synthesised (Scheme 10). Under a pressure of 15 kbar and at 50\degree C the starting amines were converted in 16h with 2-vinylpyridine to the final product with acetic acid as a catalyst. The high pressure reactions are depicted in Scheme 10. Side products as polyvinylpyridine were removed by column chromatography.

\begin{center}
\includegraphics[width=0.8\textwidth]{scheme10.png}
\end{center}

\textbf{Scheme 10} High pressure Michael reaction.
2.5 In situ prepared manganese complexes as homogeneous epoxidation catalysts

This paragraph summarises the catalytic oxidation activity of a number of different manganese catalysts based on the ligands given in Figure 2 (Paragraph 2.3). Typical catalytic reactions were performed at 0°C under a nitrogen atmosphere using acetone as solvent. The manganese catalysts based on ligands 2.5 - 2.14 and 2.17 were made by mixing 1 equivalent of the selected ligands with 1 equivalent of Mn(OAc)₃, followed by the addition of substrate and hydrogen peroxide. For preparing catalysts based on dinucleating ligands 2.15 and 2.16 2 equivalents of Mn(OAc)₃ and 1 equivalent of ligands were mixed prior to addition of substrate and oxidant. Several of the in situ formed complexes turned out as active oxidation catalysts for the conversion of a variety of alkenes to the corresponding epoxides.

Catalysts based on ligands 2.14, 2.15 and 2.16 were found to be inactive over a 4h time period for all selected substrates. Also inactive complexes were obtained by mixing 1 equivalent of Mn(OAc)₃ with the ligands 2.15 and 2.16. The catalyst based on ligand 2.11 resulted in low conversion and the substrate scope was limited to cyclohexene. Related ligand 2.12, containing a three-carbon spacer was useful for a broader scope of substrates. Generally turnover numbers for epoxide formation in the range of 162 to 573 were observed. Data for the conversion of various alkenes to the corresponding epoxides are compiled in Table 2 (ligands 2.5 - 2.10) and Table 3 (ligands 2.11 - 2.16). Noteworthy, complexes based on ligands 2.5 and 2.6 turned out to be very active and were also applicable to a number of different alkenes. Remarkably, in sharp contrast to the catalyst based on ligand 2.6 with the additional CH₃-groups on the 3-position, the complex based on ligand 2.17 with the CH₃-groups on the 6-position was completely inactive. However, catalysts based on ligands 2.9 and 2.10 display similar reactivities to 2.6. The reaction time profiles were followed for the oxidation of cyclohexene to cyclohexene oxide and are summarised in Figure 3 (containing results for manganese catalysts based on ligands 2.5 - 2.7), Figure 4 (based on ligands 2.8 - 2.10) and Figure 5 (based on ligands 2.11 - 2.13). Turnover numbers over 600 were reached and a dramatic decrease in induction time was obtained using the complexes based on ligands 2.5 and 2.6 compared with Mn₂O(OAc)₂tptn (2.4, Scheme 5).
### Table 2
Oxidation of selected alkenes to epoxides in the presence of manganese complex, in situ formed from Mn(OAc)$_3$.2H$_2$O and 0.1 mol % of ligand (2.5 - 2.10).a

<table>
<thead>
<tr>
<th>Substrate</th>
<th>2.5</th>
<th>2.6</th>
<th>2.7</th>
<th>2.8</th>
<th>2.9</th>
<th>2.10</th>
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<td>636</td>
<td>209</td>
<td>582</td>
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<td>606</td>
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<td>cyclooctene</td>
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<td>678(26)</td>
<td>250</td>
<td>554</td>
<td>606(28)</td>
<td>635(58)</td>
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<tr>
<td>trans-2-octene</td>
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<td>95</td>
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<td>107</td>
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<td>228</td>
<td>327</td>
</tr>
<tr>
<td>1-decene</td>
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<td>65</td>
<td>0</td>
<td>135</td>
<td>77</td>
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<tr>
<td>cinnamylalcohol</td>
<td>192(32.66)</td>
<td>181(31.72)</td>
<td>0(52.67)</td>
<td>0(55.66)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

(a) Experimental conditions, see experimental section and Scheme 5. (b) All products were identical to independently synthesised samples and identified by GC and $^1$H-NMR. (c) Turnover number in mole product per mole catalyst. (d) Products: epoxide (cis-diol). (e) Products: epoxide (benzaldehyde, cinnamaldehyde).

### Table 3
Oxidation of selected alkenes to epoxides in the presence of manganese complex, in situ formed with Mn(OAc)$_3$.2H$_2$O and 0.1 mol% of ligand (2.11 - 2.16).a

<table>
<thead>
<tr>
<th>Substrate</th>
<th>2.11</th>
<th>2.12</th>
<th>2.13</th>
<th>2.14</th>
<th>2.15</th>
<th>2.16</th>
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<td>430</td>
<td>205</td>
<td>6</td>
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</tr>
<tr>
<td>cyclooctene</td>
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(a) Experimental conditions, see experimental section and Scheme 5. (b) All products were identical to independently synthesised samples and identified by GC and $^1$H-NMR. (c) Turnover number in mole product per mole catalyst.
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**Figure 3** Catalytic oxidation of cyclohexene to cyclohexene oxide using $\text{H}_2\text{O}_2$ and in situ prepared catalysts with: ■ Ligand 2.5, ● Ligand 2.6 and ▲ Ligand 2.7.

**Figure 4** Catalytic oxidation of cyclohexene to cyclohexene oxide using $\text{H}_2\text{O}_2$ and in situ prepared catalysts with: ■ Ligand 2.8, ● Ligand 2.9 and ▲ ligand 2.10.
The manganese catalyst prepared from ligand 2.6 performs efficiently and generally in less than 1h high conversions were found. After addition of the first aliquot of oxidant already 600 turnover numbers were found. By using the catalysts based on tptn this result was reached after 4h. Using ligand 2.5 (containing a two-carbon spacer) similar activities, however longer induction time was observed (see Figure 3). Manganese catalysts based on ligand 2.9, containing an ethyl moiety instead of the benzyl functionality (ligand 2.5) resulted in a dramatic increase in induction time. This indicates that additional functionalities have a significant influence on the reactivity, which is further supported by ligand 2.10 containing a furan group and the corresponding catalyst has again a short induction time period. Finally ligands 2.12 and 2.13 result in long induction time periods and low catalytic activity was found.

In the absence of ligand or Mn(OAc)$_3$, no oxidation products were observed, indicating that both components are required for catalytic activity. However, recently an efficient epoxidation procedure was developed using manganese (2+) salts without any organic ligand.$^{45}$ The reactions were performed in a hydrogen carbonate buffer and as active intermediate percarbonate (HCO$_4^-$) was proposed. No activity was found in buffers based on triethanolamine, phosphate, or borate.

Switching from acetone to methanol, diethyl ether, acetonitrile or dichloromethane resulted in zero conversion, thus acetone is the solvent of choice. Upon addition of acetic acid$^{46}$ only unreacted starting material was observed, although an efficient oxidation system...
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based on H$_2$O$_2$/Mn-tmtacn was found by addition of acetic acid for the oxidation of ethane, higher alkanes, alcohols and sulfides.$^{47}$

2.6 Conclusions

In conclusion, we have demonstrated that the Mn$_2$O(OAc)$_2$tpn (2.4) complex based on the dinucleating ligand tptn (2.2b) is a promising catalyst in catalytic epoxidation procedures using hydrogen peroxide as the terminal oxidant. Main advantages of the new catalytic system are the facile synthesis and possibility for ligand modification. In acetone and at ambient temperature the manganese complex of tptn is able to catalyse the selective oxidation of various alkenes such as styrene, cyclohexene, 2- and 4-octene to the corresponding epoxides with good yields. Turnover numbers higher than 300 were reached and are comparable with Mn-tmtacn systems. However, substantial epoxide yields could only be obtained with excess of oxidant using acetone as solvent; employing other solvents no conversion or oxidation products were found. Similar to Mn-tmtacn, small structural modifications have a large influence on the performance of complex 2.4. For instance, decreasing the three-carbon spacer of the hexadentate ligand tptn 2.2b to a two-carbon spacer containing ligand (2.2a) gives rise to the catalytically inactive complex 2.3.

The long induction period of catalyst 2.4 could be strongly reduced by employing pentadentate ligands and in particularly ligand 2.6. This observation might indicate that strong dinucleating ligands (such as ligand 2.2a and 2.2b) prevents the approach of H$_2$O$_2$ molecules to the metal core. Whereas increasing the spacer length or removing one of the pyridine moieties results in a metal centre with less steric constraints. As a consequence the corresponding complexes are faster converted to catalytically active species. The mechanism of this epoxidation method is not exactly known at the present, but in the case of the oxidation of cis-β-methylstyrene a considerable amount of the trans-epoxide is observed, which is generally accepted to involve radical intermediates.$^{39}$

2.7 Acknowledgements

Dr. Judith Kerschner and dr. Ronald Hage (Unilever Research) are gratefully acknowledged for providing complexes 2.3 and 2.4. Dr. Minze Rispens (University of Groningen) is gratefully acknowledged for providing several ligands described in this chapter. Drs. Vera Sprakel (University of Nijmegen) is acknowledged for creating the possibility to perform the high pressure Michael reactions at the University of Nijmegen.
2.8 Experimental section

General procedure and methods

All reagents were obtained from commercial suppliers and used without further purification unless otherwise noted. The solvents were distilled and dried before use, if necessary, using standard procedures. Reagents and starting materials were used as obtained from Aldrich, Acros Chimica or Fluka, but 2-pyridinecarboxaldehyde (Aldrich) was distilled prior to use. Aldrich silica gel Merckgrade 9385 (230 - 400 mesh) or Al₂O₃ were used for column chromatography. ¹H-NMR spectra were recorded on a Varian Gemini-200 (200 MHz) or a Varian Gemini-300 (300 MHz) spectrometer. Chemical shifts are denoted in δ-units (in ppm) relative to residual solvent peak (CHCl₃ = 7.27 ppm). ¹³C-NMR spectra (APT) were recorded on a Varian-200 (50.32 MHz) or a Varian-300 (75.48 MHz) spectrometer. Chemical shifts are denoted in δ-units (in ppm) relative to the solvent and converted to TMS scale using δ(CHCl₃) = 77.0 ppm. The splitting patterns are designated as follows: s (singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Mass spectra were obtained on a JEOL JMS-600H mass spectrometer (CI, EI) or a AEI MS-902 mass spectrometer operated by Mr. A. Kiewiet.

GC equipment and analysis

GC analyses were performed on a Hewlett Packard 6890 Gas Chromatograph equipped with an autosampler, using a HP-1 dimethyl polysiloxane column or a HP-5 5% phenylmethylsiloxane column. Calibration was performed using authentic samples of the alkene and epoxides and independent samples of further by-products. Conversions, yields and turnover numbers are the average of 2 - 3 runs (error ± 10%) and were determined using bromobenzene or 1,2-dichlorobenzene as internal standard, and calculated using the Chemstation software.

Catalytic oxidation reactions (complexes)

Catalytic reactions with complex 2.3 or 2.4 were started by mixing 1.0 ml of a 1.0 mM stock solution of the manganese complex in acetone and 1.0 ml of a stock solution of 1.0 M of substrate and 0.5 M of internal standard at 0°C under a nitrogen atmosphere. After stirring for 2 min, excess of hydrogen peroxide (1.0 ml of 30% aq. H₂O₂, 9.8 M) was added. The progress of the reaction was monitored by GC, by taking a small sample of the reaction mixture and filtering over a short column of silica. To unequivocally establish the identity of the epoxides the retention times and spectral data were compared to those of commercially available and independently synthesised compounds.
Catalytic oxidation reactions (*in situ* experiments with ligands 2.5 - 2.17)

The same procedure as described for the catalytic reactions of the complexes 2.3 and 2.4 was followed with the ligands 2.5 - 2.14 and 2.17 except that the reactions were started by mixing 1.0 ml of a 1.0 mM stock solution of Mn(OAc)$_3$.2H$_2$O and 1.0 ml of a 1.0 mM stock solution of ligand (acetone was used as solvent). In the case of ligand 2.15 and 2.16 a 2.0 mM stock solution of Mn(OAc)$_3$.2H$_2$O was used. After stirring for 15 min substrate was added at 0°C under a nitrogen atmosphere. After stirring for 2 min excess of hydrogen peroxide (1.0 ml of 30% aq. H$_2$O$_2$, 9.8 M) was added. The progress of the reaction was monitored by GC.

**Synthesis of ligands**

Ligands 2.5, 2.6, 2.9, and 2.10 were synthesised by dr. Minze Rispens

2-Pyridinyl-N-(2-pyridinylmethyl)methanamine (2.22)

![2-Pyridinyl-N-(2-pyridinylmethyl)methanamine (2.22)](image)

To a solution of 2-pyridinecarboxaldehyde (5.0 g, 46.7 mmol) and 2-(aminomethyl)pyridine (5.1 g, 47.2 mmol) in methanol (100 ml) was added a catalytic amount of Pd/C (10%). After stirring for 24 h under a H$_2$ atmosphere (1 atm) the mixture was filtered over Celite. The solvent was evaporated under reduced pressure and the residue was purified by vacuum distillation at 140°C, 0.1 mm Hg, to give the product (4.9 g, 24.6 mmol, 53%) as a yellow oil.

$^1$H-NMR (300 MHz): δ 2.80 (br, 1H, NH), 3.89 (s, 4H, 2 x CH$_2$), 7.06 (m, 2H, Py), 7.26 (d, J = 7.69 Hz, 2H, Py), 7.55 (dt, J = 7.69, 1.83 Hz, 2H, Py), 8.46 (d, J = 4.76 Hz, 2H, Py). $^{13}$C-NMR (75 MHz): δ 52.2 (CH$_2$), 119.3 (CH), 119.7 (CH), 133.8 (CH), 146.7 (CH), 157.2 (C).

N-Methyl(2-pyridinyl)-N-(2-pyridinylmethyl)methanamine (2.13)

![N-Methyl(2-pyridinyl)-N-(2-pyridinylmethyl)methanamine (2.13)](image)

To a solution of 2.22 (0.90 g, 4.59 mmol) in 1,2-dichloroethane (40 ml) was added formaldehyde (37% solution in water, 0.45 ml, 6.0 mmol). NaBH(OAc)$_3$ (4.0 g, 18.9 mmol) was added in small portions. After stirring for 18 h at room temperature saturated aqueous NaHCO$_3$ (40 ml) was added and the 1,2-dichloroethane layer was separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 30 ml) and the combined organic layers were washed with 1 M NaOH (20 ml) and dried (Na$_2$SO$_4$). Evaporation of the solvent followed by column chromatography (Al$_2$O$_3$, akt. II - III, ethyl acetate/hexane/triethylamine 10:2:1) afforded 2.13 (0.78 g, 3.67 mmol, 80%) as a yellow oil.

$^1$H-NMR (300 MHz): δ 2.18 (s, 3H, CH$_3$), 3.65 (s, 4H, 2 x CH$_2$), 7.03 (m, 2H, Py), 7.39 (d, J = 7.69 Hz, 2H, Py), 7.54 (dt, J = 7.69, 1.83 Hz, 2H, Py), 8.42 (d, J = 4.77 Hz, 2H, Py). $^{13}$C-NMR (75 MHz): δ 41.2 (CH$_3$), 62.1 (CH$_2$), 120.4 (CH), 121.5 (CH), 134.9 (CH), 147.6 (CH), 157.7 (C). HRMS calcld. for C$_{13}$H$_{15}$N$_3$ 213.127, found 213.128.
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$N^1,N^1,N^2,N^2$-Tetrakis[2-(2-pyridinyl)ethyl]-1,2-ethanediamine (2.15)

A Teflon high-pressure capsule was filled with a solution of 1,2-ethanediamine (67 mg, 1.1 mmol), 2-vinylpyridine (0.60 g, 5.7 mmol) and acetic acid (0.23 mg, 3.8 mmol) in methanol (total volume 1.5 ml) and was kept at 50°C and 15 kbar for 16h. The resulting red solution was dissolved in CH$_2$Cl$_2$ (30 ml), washed with aqueous 1 M NaOH (30 ml) and washed with water (30 ml). The organic layers were dried over Na$_2$SO$_4$ and evaporated to leave a dark red oil. The oil was purified by column chromatography (Al$_2$O$_3$, akt. II - III, CH$_2$Cl$_2$/MeOH 97:3) to afford the pure product as a yellow oil (0.29 g, 0.61 mmol, 55%).

$^1$H-NMR (CDCl$_3$, 300 MHz): $\delta$ 2.53 (s, 4H, 2 x CH$_2$), 2.82 (s, 16H, 8 x CH$_2$), 6.99 (m, 8H, py) 7.44 (dt, 7.69, 1.83 Hz, 4H, Py), 8.41 (d, J = 4.03 Hz, 4H, Py). $^{13}$C-NMR (CDCl$_3$, 75 MHz): $\delta$ 33.6 (CH$_2$), 51.4 (CH$_2$), 51.9 (CH$_2$), 118.5 (CH), 120.9 (CH), 133.6 (CH), 146.6 (CH), 158.2 (C). HRMS calcd. for C$_{30}$H$_{36}$N$_6$ 480.300, found 480.301.

$N^1,N^1,N^3,N^3$-Tetrakis[2-(2-pyridinyl)ethyl]-1,3-propanediamine (2.16)

The same procedure as described for the preparation of ligand 2.15 was followed except that 1,3-propanediamine (83 mg, 1.1 mmol), 2-vinylpyridine (0.60 g, 5.7 mmol) and acetic acid (0.23 mg, 3.8 mmol) was used. The final product was purified by column chromatography (Al$_2$O$_3$, akt. II - III, CH$_2$Cl$_2$/MeOH 97:3) to afford the pure product as a yellow oil (0.28 g, 0.56 mmol, 51%).

$^1$H-NMR (CDCl$_3$, 300 MHz): $\delta$ 1.47 (q, J = 7.20 Hz, 2H, CH$_2$), 2.80 (s, 16H, 8 x CH$_2$), 6.99 (m, 8H, Py), 7.44 (dt, 7.69, 1.83 Hz), 8.41 (d, J = 4.76 Hz, 4H). $^{13}$C-NMR (CDCl$_3$, 75 MHz): $\delta$ 33.5 (CH$_2$), 49.4 (CH$_2$), 51.4 (CH$_2$), 118.4 (CH), 120.8 (CH), 133.6 (CH), 146.6 (CH), 158.3 (C). HRMS calcd. for C$_{31}$H$_{38}$N$_6$ 494.316, found: 494.316.

$N^1,N^1,N^2,N^2$-Tetrakis(2-pyridinylmethyl)-1,2-ethanediamine (2.2a)

To a solution of 2-(chloromethyl)pyridine hydrochloride (24.4 g, 148.7 mmol) in CH$_2$Cl$_2$ (50 ml) was dropwise added 5 M NaOH (50 ml) under N$_2$ at 0°C. After stirring for 1h 1,2-ethanediamine (2.0 g, 33.3 mmol) was added. The mixture was stirred vigorously and after 4d the mixture was extracted with CH$_2$Cl$_2$ (3 x 150 ml) and the combined organic layers were dried (Na$_2$SO$_4$). After evaporation of the solvent under reduced pressure the residue was purified by crystallisation from cyclohexane giving the pure product (5.0 g, 11.8 mmol, 35%).
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$^1$H-NMR (300 MHz): $\delta$ 2.70 (s, 4H, 2 x CH$_2$), 3.71 (s, 8H, 4 x CH$_2$), 7.05 (m, 4H, Py), 7.39 (d, $J = 7.69$ Hz, 4H, Py), 7.45 (m, 4H, Py), 8.42 (d, $J = 4.39$ Hz, 4H, Py). $^{13}$C-NMR (75 MHz): $\delta$ 49.9 (CH$_2$), 58.3 (CH$_2$), 119.3 (CH), 120.2 (CH), 133.8 (CH), 146.5 (CH), 157.3 (C). HRMS calcd. for C$_{26}$H$_{28}$N$_6$ 424.237, found 424.236.

$^{N_1,N_1,N_3,N_3}$-Tetrakis(2-pyridinylmethyl)-1,3-propanediamine (2.2b)

The same procedure as described for the preparation of ligand 2.2a was followed except that 2-(chloromethyl)pyridine hydrochloride (22.0 g, 134.1 mmol) and 1,3-propanediamine (2.0 g, 22.2 mmol) was used. The final residue was purified by crystallization from cyclohexane giving the pure product (4.0 g, 9.1 mmol, 41%).

$^1$H-NMR (300 MHz): $\delta$ 1.74 (q, $J = 7.69, 7.32, 6.96$ Hz, 2H, CH$_2$), 2.48 (t, $J = 7.33$ Hz, 4H, 2 x CH$_2$), 3.68 (s, 8H, 4 x CH$_2$), 7.11 (m, 4H, Py), 7.34 (d, 4H, Py), 7.51 (m, 4H, Py), 8.42 (d, $J = 4.03$ Hz, 4H). $^{13}$C-NMR (75 MHz): $\delta$ 24.5 (CH$_2$), 52.2 (CH$_2$), 60.2 (CH$_2$), 121.6 (CH), 122.6 (CH), 136.2 (CH), 148.8 (CH), 159.8 (C). HRMS calcd. for C$_{27}$H$_{30}$N$_6$ 438.253, found 438.252.

$^{N_1,N_2}$-Bis(2-pyridinylmethyl)-1,2-ethanediamine (2.18a)

To a solution of 1,2-ethanediamine (1.5 g, 25 mmol) in methanol (25 ml) was added 2-pyridinecarboxaldehyde (5.7 g, 52.5 mmol) and the mixture was heated under reflux for 3h. After cooling to room temperature and NaBH$_4$ (2.7 g, 70 mmol) was added in small portions. After stirring for 16h at room temperature the solution was acidified to pH 1 - 2 using a 4 M HCl-solution and the mixture was stirred for an additional 0.5h. The solution was brought to pH 14 using a NH$_3$-solution (12.5% in water), extracted with CH$_2$Cl$_2$ (3 x 50 ml) and the combined organic layers were dried (Na$_2$SO$_4$). After evaporation of the solvent under reduced pressure the product was obtained as a yellow oil (4.5 g, 18.8 mmol, 75% yield).

$^1$H-NMR (300 MHz): $\delta$ 2.07 (br, 2H, NH), 2.73 (s, 4H, 2 x CH$_2$), 3.82 (s, 4H, 2 x CH$_2$), 7.05 (m, 2H, Py), 7.22 (m, 2H, Py), 7.54 (m, 2H, Py), 8.45 (m, 2H, Py). $^{13}$C-NMR (75 MHz): $\delta$ 46.5 (CH$_2$), 52.6 (CH$_2$), 119.3 (CH), 119.7 (CH), 133.9 (CH), 146.6 (CH), 157.3 (C).

$^{N_1,N_3}$-Bis(2-pyridinylmethyl)-1,3-propanediamine (2.18b)

The same procedure as described for the preparation of compound 2.18a was followed except that 1,3-propanediamine (2.8 g, 37.8 mmol), 2-pyridinecarboxaldehyde (8.1 g, 75.7 mmol) and NaBH$_4$ (4.0 g, 105 mmol) was used to afford the product as a yellow oil (7.0 g, 26.5 mmol, 70% yield).
$^1$H-NMR (300 MHz): $\delta$ 1.70 (q, $J = 6.78$ Hz, 2H, CH$_2$), 2.68 (t, $J = 6.96, 6.59$ Hz, 4H, 2x CH$_2$), 2.89 (br, 2H, NH), 3.82 (s, 4H, 2x CH$_2$), 7.06 (m, 2H, Py), 7.51 (m, 2H, Py), 7.55 (m, 2H, Py), 8.43 (m, 2H, Py). $^{13}$C-NMR (75 MHz): $\delta$ 27.2 (CH$_2$), 45.5 (CH$_2$), 52.5 (CH$_2$), 119.4 (CH), 119.8 (CH), 133.9 (CH), 146.7 (CH), 156.8 (C).

$N^1,N^3$-Bis[(6-methyl-2-pyridinyl)methyl]-1,3-propanediamine (2.18c)

The same procedure as described for the preparation of compound 2.18a was followed except that 1,3-propanediamine (0.25 g, 4.17 mmol), 6-methyl-2-pyridinecarbaldehyde (1.0 g, 8.26 mmol) and NaBH$_4$ (0.44 g, 11.5 mmol) was used to afford the product as a yellow oil (1.1 g, 3.87 mmol, 93% yield).

$^1$H-NMR (300 MHz): $\delta$ 1.42 (q, $J = 6.96$ Hz, 2H, CH$_2$), 2.47 (s, 6H, CH$_3$), 2.70 (t, $J = 6.96$ Hz, 4H, 2x CH$_2$), 3.80 (s, 4H, 2x CH$_2$), 3.80 (s, 4H, 2x CH$_2$), 6.99 (d, $J = 7.57$ Hz, 2H, 2x CH, Py), 7.04 (d, $J = 7.57$ Hz, 2H, 2x CH, Py), 7.45 (t, $J = 7.57, 7.81$ Hz, 2H, 2x CH, Py). $^{13}$C-NMR (75 MHz): $\delta$ 22.3 (CH$_3$), 26.4 (CH$_2$), 45.5 (CH$_2$), 52.1 (CH$_2$), 120.3 (CH), 122.0 (CH), 136.4 (CH), 157.3 (C), 161.0 (C).

2-[(2-(2-Pyridinyl)-3-(2-pyridinylmethyl)-1-imidazolidinyl)methyl]pyridine (2.19a)

A solution of 2.18a (3.8 g, 15.9 mmol) and 2-pyridinecarboxaldehyde (1.7 g, 15.9 mmol) in diethyl ether (10 ml) was stirred at room temperature with CaCl$_2$ protection. The reaction mixture was stirred for 16h and the white precipitate was recovered after filtration and washed with diethyl ether to afford the pure product (4.5 g, 13.8 mmol, 86%).

$^1$H-NMR (300 MHz): $\delta$ 2.69 (m, 2H, CH$_2$), 3.26 (m, 2H, CH$_2$), 3.60 (d, $J = 14.3$ Hz, 2H, CH$_2$), 3.89 (d, $J = 14.3$ Hz, 2H, CH$_2$), 4.22 (s, 1H, CH), 7.03 (m, 2H, Py), 7.14 (m, 1H, Py), 7.29 (d, $J = 7.69$ Hz, 2H, Py), 7.51 (dt, $J = 7.60, 1.59$ Hz, 2H, Py), 7.64 (dt, $J = 7.69, 1.46$ Hz, 1H, Py), 7.83 (d, $J = 8.05$ Hz, 1H, Py), 8.40 (d, $J = 4.76$ Hz, 2H, Py) 8.45 (d, $J = 5.12$ Hz, 1H, Py). $^{13}$C-NMR (75 MHz): $\delta$ 48.8 (CH$_2$), 56.4 (CH$_2$), 86.7 (CH), 119.3 (CH), 120.3 (CH), 120.5 (CH), 120.7 (CH), 133.7 (CH), 134.2 (CH), 145.9 (CH), 146.3 (CH), 156.6 (C), 158.4 (C).
2-(2-Pyridinyl)-1,3-bis(2-pyridinylmethyl)hexahydropyrimidine (2.19b)

The same procedure as described for the preparation of compound 2.19a was followed except that 2.18b (6.0 g, 22.8 mmol) and 2-pyridinecarboxaldehyde (2.4 g, 22.8 mmol) was used to afford the product as a white solid (6.5 g, 19.0 mmol, 83% yield).

\(^1\text{H-NMR (300 MHz): } \delta 1.50 \text{ (m, 1H, CH2), 1.89 (m, 1H, CH2), 2.24 (dt, J = 2.56 Hz, 2H CH2), 2.97 (m, 2H, CH2), 3.27 (d, J = 14.6 Hz, 2H, CH2), 3.53 (d, J = 14.6 Hz, 2H, CH2), 3.99 (s, 1H, CH), 6.99 (t, J = 6.32 Hz, 2H, Py), 7.08 (dt, J = 6.23, 1.47, 0.74 Hz, 1H, Py), 7.69 (d, J = 7.69 Hz, 2H, Py), 7.50 (dt, J = 7.69, 1.47 Hz, 2H, Py), 7.59 (dt, J = 7.69, 1.46 Hz, 1H, Py), 7.84 (d, J = 8.06 Hz, 1H, Py), 8.36 (d, J = 4.39 Hz, 2H, Py), 8.47 (d, J = 4.76 Hz, 1H, Py). \(^{13}\text{C-NMR (75 MHz): } \delta 25.0 \text{ (CH2), 52.4 (CH2), 60.5 (CH2), 88.9 (CH), 122.2 (CH), 123.1 (CH), 123.8 (CH), 124.1 (CH), 136.8 (CH), 137.4 (CH), 148.9 (CH), 149.0 (CH), 160.3 (C), 162.3 (C).}

2-(6-Methyl-2-pyridinyl)-1,3-bis[(6-methyl-2-pyridinyl)methyl]hexahydropyrimidine (2.19c)

The same procedure as described for the preparation of compound 2.19a was followed except that 2.18c (1.1 g, 3.87 mmol) and 6-methyl-2-pyridinecarbaldehyde (0.47 g, 3.88 mmol) was used to afford the product as a white solid (1.2 g, 3.09 mmol, 80.0 % yield).

\(^1\text{H-NMR (300 MHz): } \delta 1.61 \text{ (m, 1H, CH2), 2.03 (m, 1H, CH2), 2.40 (complex, 11H, 2H, CH2, 9H, 3 x CH3), 3.06 (m, 2H, CH2), 3.33 (d, J = 15.1 Hz, 2H, CH2), 3.60 (d, J = 15.1 Hz, 2H, CH2), 4.11 (s, 1H, CH), 6.98 (m, 3H, Py), 7.31 (d, J = 7.81 Hz, 2H, Py), 7.50 (m, 3H, Py), 7.70 (d, J = 7.32 Hz, 1H, Py). \(^{13}\text{C-NMR (75 MHz): } \delta 23.2 \text{ (CH2), 24.4 (CH3), 49.8 (CH2), 54.2 (CH2), 83.0 (CH), 120.0 (CH), 120.5 (CH), 121.5 (CH), 121.7 (CH), 135.2 (CH), 136.1 (CH), 156.1 (C), 162.2 (C), 165.7 (C).}

N\(^1\),N\(^1\),N\(^2\)-Tris(2-pyridinylmethyl)-1,2-ethanediamine (2.20a)

To a solution of aminal 2.19a (1.0 g, 3.04 mmol) in MeOH (50 ml) was added NaBH\(_2\)CN (0.19 g, 3.02 mmol) and CF\(_3\)CO\(_2\)H (0.46 ml, 5.98 mmol). The solution was stirred at room temperature with CaCl\(_2\) protection for 18h. A 15% NaOH-solution (30 ml) was added and after stirring for 3h the solution was extracted with CH\(_2\)Cl\(_2\) (3 x 50 ml) and the combined organic layers were dried (Na\(_2\)SO\(_4\)). Evaporation of the solvent afforded 2.20a (0.70 g, 2.13 mmol, 70%) as a yellow oil.
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$^1$H-NMR (300 MHz): δ 2.40 (br, 1H, NH), 2.70 (s, 4H, 2 x CH 2), 3.75 (s, 6H, 3 x CH 2), 7.16 (m, 4H, Py), 7.52 (m, 5H, Py), 8.46 (m, 3H, Py). $^{13}$C-NMR (75 MHz): δ 44.2 (CH 2), 51.6 (CH 2), 52.5 (CH 2), 58.1 (CH 2), 119.2 (CH), 119.4 (CH), 120.4 (CH), 120.7 (CH), 133.7 (CH), 133.8 (CH), 146.4 (CH), 146.7 (CH), 157.1 (C), 157.5 (C). HRMS calcd. for C_{20}H_{23}N_{5} 333.195, found 333.196.

$N^1,N^1,N^3$-Tris(2-pyridinylmethyl)-1,3-propanediamine (2.20b)

The same procedure as described for the preparation of compound 2.20a was followed except that 2.19b (1.0 g, 2.92 mmol), NaBH$_3$CN (0.18 g, 2.90 mmol) and CF$_3$CO$_2$H (0.44 ml, 5.74 mmol) was used to afford the product as a yellow oil (0.74 g, 2.13 mmol, 73% yield).

$^1$H-NMR (300 MHz): δ 1.71 (q, J = 6.95 Hz, 2H, CH 2), 1.95 (br, 1H, NH), 2.56 (m, 4H, 2 x CH 2), 3.72 (s, 4H, 2 x CH 2), 3.77 (s, 2H, CH 2), 7.11 (m, 4H, Py), 7.49 (m, 5H, Py), 8.44 (m, 3H, Py). $^{13}$C-NMR (75 MHz): δ 24.9 (CH 2), 45.4 (CH 2), 50.0 (CH 2), 52.9 (CH 2), 57.9 (CH 2), 119.3 (CH), 119.6 (CH), 120.3 (CH), 133.8 (CH), 146.4 (CH), 146.7 (CH), 157.3 (C), 157.5 (C). HRMS calcd. for C_{21}H_{25}N_{5} 347.210, found 347.211.

$N^1,N^1,N^3$-Tris[(6-methyl-2-pyridinyl)methyl]-1,3-propanediamine (2.20c)

The same procedure as described for the preparation of compound 2.20a was followed except that 2.19c (1.2 g, 3.09 mmol), NaBH$_3$CN (0.20 g, 3.10 mmol) and CF$_3$CO$_2$H (0.48 ml, 6.26 mmol) was used to afford the product as a yellow oil (0.90 g, 2.31 mmol, 75% yield).

$^1$H-NMR (300 MHz): δ 1.69 (q, J = 6.96 Hz, 2H, CH 2), 2.42 (s, 6H, 2 x CH$_3$), 2.43 (s, 3H, CH$_3$), 2.52 (t, 6.96 Hz, 2H, CH$_2$), 2.59 (t, J = 6.96 Hz, 2H, CH$_2$), 3.68 (s, 4H, 2 x CH$_2$), 3.78 (s, 2H, 2 x CH$_2$), 6.89 (t, 8.06 Hz, 2H, 2 x CH, Py), 6.99 (d, J = 7.33 Hz, 1H, Py), 7.26 (d, J = 7.69 Hz, 2H, 2 x CH, Py), 7.41 (t, J = 7.51 Hz, 4H, 4 x CH, Py). $^{13}$C-NMR (75 MHz): δ 21.9 (CH$_3$), 24.2 (CH$_2$), 45.4 (CH$_2$), 50.0 (CH$_2$), 52.9 (CH$_2$), 58.1 (CH$_2$), 116.5 (CH), 116.9 (CH), 118.7 (CH), 118.8 (CH), 119.0 (CH), 134.0(CH), 154.9 (C), 155.3 (C), 156.7(C),156.9(C).

$N^1$-Benzyl-$N^1,N^2$-tris(2-pyridinylmethyl)-1,2-ethanediamine (2.7)

To 2.20a (0.70 g, 2.10 mmol) in 1,2-dichloroethane (25 ml) was added benaldehyde (0.24 g, 2.31 mmol). During 1h NaBH(OAc)$_3$ (1.34 g, 6.29 mmol) was added in small portions. After stirring for 24h at room temperature a saturated solution of NaHCO$_3$ (30 ml) was added, followed
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by extraction with CH$_2$Cl$_2$ (3 x 50 ml). The combined organic layers were dried (Na$_2$SO$_4$) and the solvent evaporated under reduced pressure to afford the crude product. The oil was purified by column chromatography (Al$_2$O$_3$, akt. II - III, ethyl acetate/hexane/triethylamine 10/4/1) to afford the pure product as a yellow oil (0.31 g, 0.73 mmol, 35% yield).

$^1$H-NMR (300 MHz): δ 2.66 (m, 4H, 2 x CH$_2$), 3.52 (s, 2H, CH$_2$), 3.65 (s, 2H, CH$_2$), 3.70 (s, 4H, 2 x CH$_2$), 7.05 (m, 3H), 7.19 (m, 5H), 7.39, (m, 3H), 7.51 (m, 3H), 8.42 (m, 2H, Py, 1H, Ar). $^{13}$C-NMR (75 MHz): δ 49.4 (CH$_2$), 49.8 (CH$_2$), 56.2 (CH$_2$), 58.1 (CH$_2$), 58.3 (CH$_2$), 119.2 (CH), 119.3 (CH), 120.1 (CH), 120.2 (CH), 124.4 (CH), 125.7 (CH), 126.2 (CH), 133.8 (CH), 136.7 (C), 146.3 (CH), 146.5 (CH), 157.3 (C), 157. (C). HRMS calcd. for C$_{27}$H$_{29}$N$_{5}$ 423.242, found 423.242.

$N^1$-Benzyl-$N^1$,N$^3$,N$^3$-tris(2-pyridinylmethyl)-1,3-propanediamine (2.8)

The same procedure as described for the preparation of compound 2.7 was followed except that 2.20b (0.74 g, 2.07 mmol), benzaldehyde (0.24 g, 2.31 mmol) and NaBH(OAc)$_3$ (1.34 g, 6.29 mmol) was used to afford, after purification by column chromatography (Al$_2$O$_3$, akt. II - III, ethyl acetate/hexane/triethylamine 10:2:1), the pure product as a yellow oil (0.48 g, 1.10 mmol, 53%).

$^1$H-NMR (300 MHz): δ 1.72 (q, J = 7.14 Hz, 2H, CH$_2$), 2.41 (t, J = 7.14 Hz, 2H, CH$_2$), 2.49 (t, J = 7.32 Hz, 2H, CH$_2$), 3.61 (s, 2H, CH$_2$), 3.61 (s, 2H, CH$_2$), 3.69 (s, 4H, 2 x CH$_2$), 7.04 (m, 3H), 7.17 (m, 5H), 7.34 (d, J = 8.06 Hz, 3H), 7.52 (m, 3H), 8.42 (m, 3H). $^{13}$C-NMR (75 MHz): δ 22.1 (CH$_3$), 49.4 (CH$_2$), 49.9 (CH$_2$), 56.1 (CH$_2$), 57.6 (CH$_2$), 57.9 (CH$_2$), 119.2 (CH), 119.3 (CH), 120.2 (CH), 120.3 (CH), 124.3 (CH), 125.6 (CH), 126.3 (CH), 133.8 (CH), 136.9 (C), 146.2 (CH), 146.4 (CH), 157.4 (C), 157.8 (C). HRMS calcd. for C$_{28}$H$_{31}$N$_{5}$ 437.258, found 437.257.

$N^1$-Benzyl-$N^1$,N$^3$,N$^3$-tris[(6-methyl-2-pyridinyl)methyl]-1,3-propanediamine (2.17)

The same procedure as described for the preparation of compound 2.7 was followed except that 2.20c (0.90 g, 2.31 mmol), benzaldehyde (0.90 g, 2.50 mmol) and NaBH(OAc)$_3$ (1.50 g, 6.93 mmol) was used to afford, after purification by column chromatography (Al$_2$O$_3$, akt. II - III, ethyl acetate/hexane/triethylamine 10:2:1), the pure product as a yellow oil (0.80 g, 1.67 mmol, 72%).

$^1$H-NMR (300 MHz): δ 1.77 (q, J = 7.14 Hz, 2H, CH$_2$), 2.62 (complex, due to overlap 13H, 3 x CH$_3$, 2 x CH$_2$), 3.45 (s, 2H, CH$_2$), 3.64 (s, 2H, CH$_2$), 3.73 (s, 4H, 2 x CH$_2$), 6.90 - 7.51 (complex, 14H). $^{13}$C-NMR (75 MHz): δ 24.9 (CH$_3$), 52.5 (CH$_2$), 52.9 (CH$_2$), 59.1(CH$_2$), 60.8
(CH$_2$), 61.1 (CH$_2$), 119.9 (CH), 120.0 (CH), 121.7 (CH), 121.8 (CH), 127.3 (CH), 128.6 (CH), 129.3 (CH), 137.1 (CH), 140.0 (C), 157.7 (C), 157.8 (C), 160.0 (C), 160.3 (C).

$N^1,N^2$-Dimethyl-$N^1,N^2$-bis(2-pyridinylmethyl)-1,2-ethanedianime (2.11)

To a solution of $N,N'$-dimethylethlyenediamine (1.0 g, 11.3 mmol) in 1,2-dichloroethane (25 ml) was added 2-pyridinecarboxaldehyde (2.54 g, 23.7 mmol). NaBH(OAc)$_3$ (7.22 g, 33.9 mmol) was added in small portions. After stirring for 18h at room temperature saturated aq. NaHCO$_3$ (40 ml) was added and the 1,2-dichloroethane layer was separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 30 ml) and the combined organic layers were washed with 1 M NaOH (20 ml) and dried (Na$_2$SO$_4$). Evaporation of the solvent followed by column chromatography (Al$_2$O$_3$, akt. II-III, ethyl acetate/hexane/triethylamine 10:2:1) afforded 2.11 (1.86 g, 6.89 mmol, 61%) as a yellow oil. 

$^1$H-NMR (300 MHz): $\delta$ 2.17 (s, 6H, 2 x CH$_3$), 2.55 (s, 4H, 2 x CH$_2$), 3.58 (s, 4H, 2 x CH$_2$), 7.04 (m, 2H, Py), 7.31 (m, 2H, Py), 7.51 (m, 2H, Py), 8.43 (m, 2H, Py). $^{13}$C-NMR (75 MHz): $\delta$ 40.4 (CH$_3$), 53.0 (CH$_2$), 61.7 (CH$_2$), 119.4 (CH), 120.5 (CH), 133.8 (CH), 146.5 (CH), 156.9 (C). HRMS calcd. for C$_{16}$H$_{22}$N$_4$ 270.184, found 270.184.

$N^1,N^3$-Dimethyl-$N^1,N^3$-bis(2-pyridinylmethyl)-1,3-propanediamine (2.12)

The same procedure as described for the preparation of compound 2.11 was followed except that $N,N'$-dimethylpropylenediamine (1.0 g, 9.78 mmol), 2-pyridinecarboxaldehyde (2.20 g, 20.5 mmol) and NaBH(OAc)$_3$ (6.2 g, 29.3 mmol) was used to afford the product after purification by column chromatography (Al$_2$O$_3$, akt. II - III, ethyl acetate/hexane/triethylamine 10:2:1) to afford 2.12 as a yellow oil (1.81 g, 6.36 mmol, 65%). 

$^1$H-NMR (300 MHz): $\delta$ 1.67 (q, J = 7.32 Hz, 2H, CH$_2$), 2.15 (s, 3H, CH$_3$), 2.38 (t, J = 7.32 Hz, 2H, CH$_2$), 7.04 (m, 2H, Py), 7.29 (m, 2H, Py), 7.53 (m, 2H, Py), 8.43 (m, 2H, Py). $^{13}$C-NMR (75 MHz): $\delta$ 22.7 (CH$_2$), 40.0 (CH$_3$), 53.2 (CH$_2$), 61.4 (CH$_2$), 119.3 (CH), 120.5 (CH), 133.8 (CH), 146.4 (CH), 157.0 (C). HRMS calcd. for C$_{17}$H$_{24}$N$_4$ 284.200, found 284.199.

2.9 References

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43 The in situ prepared Mn-complexes based on 2.2a and 2.2b ligands by mixing Mn(OAc)$_3$ with the ligands provided comparable results as obtained with the complexes 2.3 and 2.4.

44 The obtained profiles are similar for other substrates, but not given for clarity.


47 The authors of this procedure also noted that it can not be excluded that in some cases the substrate oxidations occur via H$_2$O$_2$ derivatives e.g. peroxy acids.
