Manganese Catalysts in Homogeneous Oxidation Reactions

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Chapter 1

Introduction
Oxidation Catalysis

Abstract

The oxidation of organic compounds with high selectivity is of extreme importance in synthetic chemistry. Important oxidation reactions include the transformation of alcohols to either the corresponding carbonyl compounds or carboxylic acids, the oxidation of sulfides to sulfoxides and alkenes to epoxides and diols. The present introductory chapter is not intended to give a complete survey of all published work on oxidation catalysis but rather to give a background and summary of recent important developments in catalytic oxidation reactions. Included are biomimetic systems and new synthetically applicable oxidation procedures. In addition also the occurrence of several metal containing enzymes, which catalyse oxidative transformations in biological systems will be briefly discussed.

1.1 Biomimetic oxidation catalysis

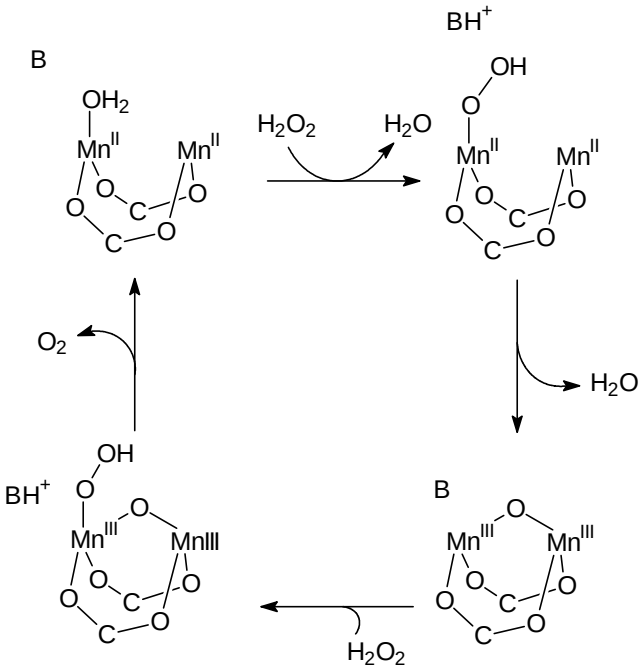
In Nature, many enzymes are present which are capable of catalysing oxidation reactions.[1] In a number of these reactions manganese or iron containing enzymes are involved. These enzymes are frequently studied by using model complexes which provide information on the nature and reactivity of the active site and about possible reaction mechanisms.[1] Based on these manganese or iron containing enzymes and on the related model complexes various oxidation catalysts have been evaluated.[2]

Manganese can frequently be found in the catalytic redox centre of several enzymes like superoxide dismutase,[3] catalase[4] and the oxygen evolving complex photosystem II.[5] Superoxide ($O_2^{\cdot -}$), a harmful radical for living organisms, is the product of single electron reduction of oxygen.[6] Due to the high toxicity it needs to be converted to less reactive species.[6] Superoxide dismutases are metalloenzymes which catalyse the dismutation of the superoxide ($O_2^{\cdot -}$) to oxygen (O_2) and hydrogen peroxide (H_2O_2).[7] The latter product can be degraded by catalase enzymes to water and oxygen (*vide supra*). Superoxide dismutase (SOD) enzymes can be classified into two major structural families; copper-zinc SOD and manganese or iron SOD.[6,8] Although SOD enzymes based on nickel also have been described, this class of enzymes has been less intensively studied.[9]

The active site of manganese SOD contains a mononuclear five-coordinate Mn^{III}-ion bound to three histidines, one aspartate residue and one water or hydroxide ligand. The mechanism of the catalytic conversion of superoxide to oxygen starts by binding of the superoxide radical anion to the Mn^{III}-monomer leading to the reduction to Mn^{II} and oxidation of superoxide into oxygen.[3,10] Subsequently the catalytic cycle is closed by binding of a second superoxide to the Mn^{II}-ion resulting in the oxidation of Mn^{II} and reduction of superoxide anion to H_2O_2.

In photosystem II (PS II), located in the thylakoid membrane of chloroplasts in green plants, algae and a number of cyanobacteria, two water molecules are oxidised to dioxygen.[5] PS II consists of light harvesting pigments, a water oxidation centre (WOC), and electron transfer components.[5] Based on many spectroscopic measurements it has been recognised that a tetranuclear Mn-cluster is the active catalyst for the oxygen evolution, which has been recently confirmed by the crystal structure of PS II.[11] However, the exact mechanism of the water oxidation has not been elucidated so far.

Catalases decompose hydrogen peroxide to water and oxygen and these manganese enzymes have been isolated from three different bacteria; *Lactobacillus plantarum,*[12] *Thermus thermophilus,*[13] *and Thermoleophilum album*.[4] X-ray crystallographic structure analysis[14] elucidated that these catalases contain a dinuclear manganese centre. During the catalytic process the dinuclear manganese active site cycles between the Mn^{II}_2- and Mn^{III}_2-oxidation states.[15] EPR,[16] NMR[17] and UV-Vis[17a] spectroscopic studies revealed that for the H_2O_2 disproportionation both Mn^{II}_2- and Mn^{III}_2-oxidation states are involved.[18] The proposed catalase mechanism is depicted in Scheme 1. H_2O_2 decomposition is initiated by the binding of H_2O_2 to the Mn^{III}-Mn^{III} dinuclear centre followed by reduction to the Mn^{II}-Mn^{II} intermediate and concomitant oxidation of the peroxide to O_2.[18,19] Subsequent binding of a second molecule H_2O_2 to the Mn^{II}-Mn^{II} species effects the reduction of H_2O_2 to H_2O and results in the oxidation of the Mn^{II}-Mn^{II} species, which closes the catalytic cycle.[3]



Scheme 1 *Proposed mechanism for manganese catalase.*

Many compounds containing a dinuclear manganese core encompassed by a variety of ligand types have been employed as catalase mimic complexes.[20] For example, Dismukes *et al.* reported the first functional catalase model which exhibit, high activity towards H_2O_2

decomposition; even after turnover numbers of 1000 no loss of H_2O_2 decomposition was observed.[21] The studied dinuclear Mn^{II}-complex is based on ligand **1.1** (Figure 1). EPR and UV-Vis spectroscopic investigations revealed, that under conditions of H_2O_2 decomposition both Mn^{III}-Mn^{III} and Mn^{II}-Mn^{II} oxidation states are present similar as observed for the natural manganese catalase enzymes.[19]

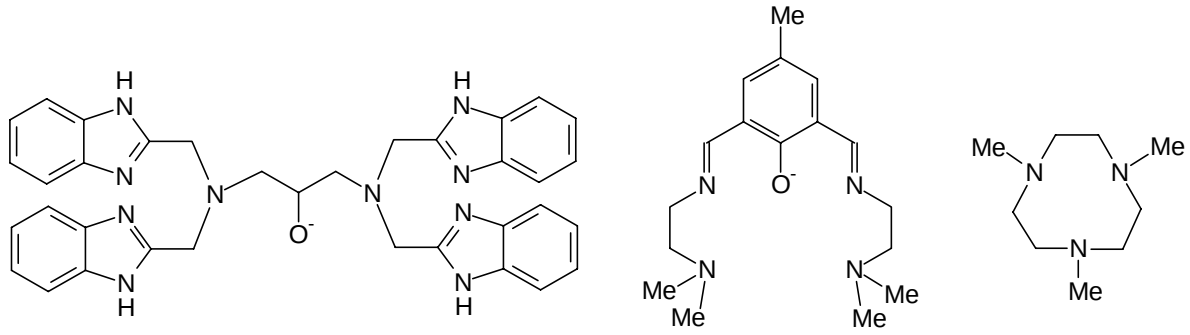
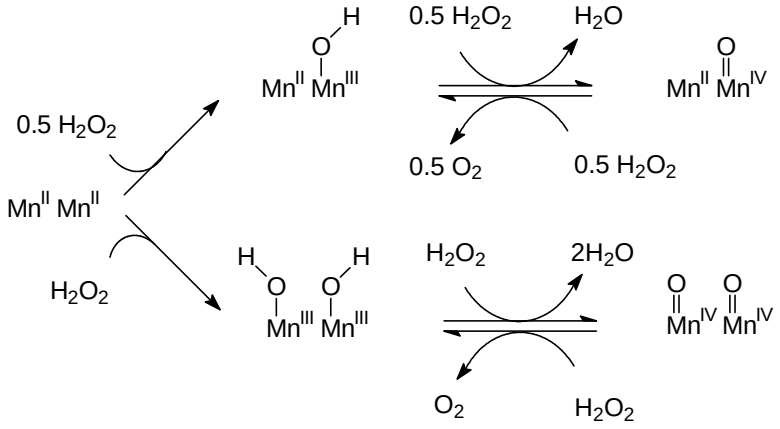


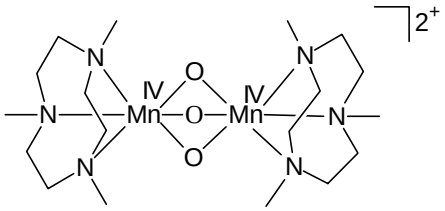
Figure 1 *Ligands studied in manganese catalase mimics.*

Sakiyama *et al.* explored various dinuclear manganese complexes as catalase mimics derived from 2,6-bis(*N*-[2-dimethylamino)ethyl]iminomethyl-4-methylphenolate) (**1.2**, Figure 1) and related ligands.[22] Several intermediates were detected using various spectroscopic studies during the H_2O_2 dismutase reactions. Employing UV-Vis, Mn-oxo species were detected and these measurements could be supported by mass spectrometry.[22] Using the latter technique signals for both mono- and di-Mn^{IV}-oxo intermediates could be assigned. Notably, the proposed mechanism is different from that for the manganese catalases and model compounds containing ligand **1.1** (Figure 1) as investigated by Dismukes. The formulated mechanism is depicted in Scheme 2.[22]



Scheme 2 *Proposed mechanism of H_2O_2 decomposition catalysed by Mn-complexes based on ligand **1.2**.*[22]

Manganese complexes of 1,4,7-triazacyclononane (tacn) or 1,4,7-trimethyl-1,4,7-triazacyclononane (tmtacn, **1.3**, Figure 1) ligands were originally synthesised by Wieghardt *et al.* and studied as models for the oxygen evolving centre of photosystem II and for manganese catalase.[23] Turnover numbers of the H_2O_2 decomposition as high as 1300 are readily reached.[23d] Recently, these complexes were also employed as bleaching-,[24] epoxidation-,[25] and alcohol oxidation[26] catalysts using H_2O_2 as oxidant. Turnover numbers in the range of 80 up to 1000 were observed. Bleaching processes of stains on textile in detergent industry have been studied intensively and the oldest bleaching procedures for laundry cleaning employ H_2O_2 and high temperatures.[19] Several catalysts are being investigated to attain low bleaching temperatures of 40 - 60^{o}C or to achieve effective bleaching under ambient conditions.[19] For example, manganese complexes from 1,4,7-trimethyl-1,4,7-triazacyclononane (**1.4**, Mn- tmtacn, Figure 2) complexes were extensively studied by Unilever Research as bleach catalysts for stain removal at ambient temperatures.[24,27] The Mn-tmtacn complex has been utilised in the brand detergent 'OMO Power'.[27] However, under laboratory conditions textile damage was discovered and the detergents were subsequently withdrawn from the market.[27]



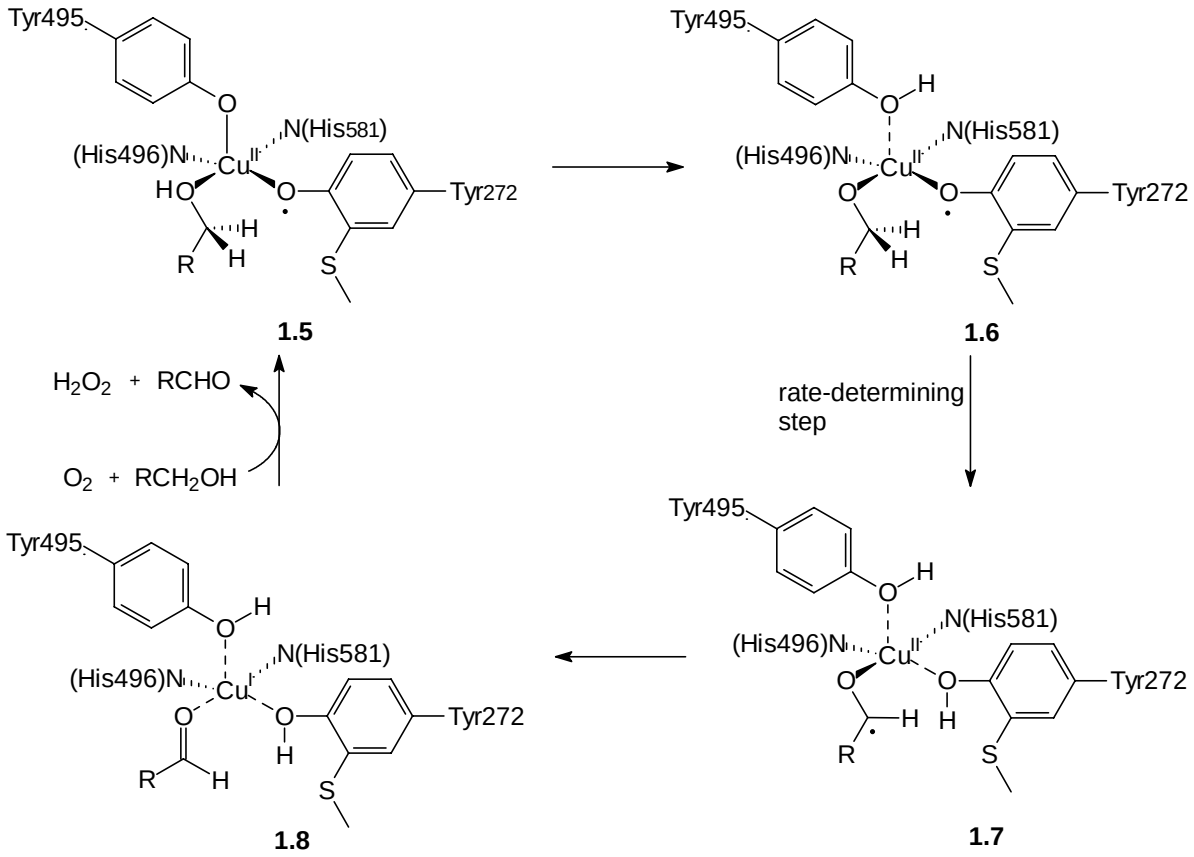
1.4

Figure 2 *Mn-tmtacn complex.*

In addition to the bleaching capacity of the Mn-tmtacn complex also epoxidation activity was described.[24,25b] Apart from high turnover numbers, it is essential to develop catalytic systems that employ H_2O_2 very efficiently, as many manganese or iron catalysts are known to be particularly effective in decomposition of H_2O_2 (*vide supra*). This can be suppressed by working in acetone or by addition of oxalate[28] or ascorbic acid[25c] as co-catalysts.

A variety of other metalloenzymes, containing iron or copper, are efficient oxidation catalysts.[29] Examples include the diiron containing enzyme methane monooxygenase (MMO) which selectively oxidises methane to methanol[30] and iron bleomycin, a metalloglycopeptide which degrades DNA oxidatively.[31,32] Another example is the mononuclear copper enzyme galactose oxidase (GOase) which catalyses besides the oxidation of galactose the conversion of benzylic, allylic and primary alcohols to the corresponding aldehyde compounds with oxygen as oxidant.[33] The active site of GOase consists of a mononuclear copper ion in a square pyramidal coordination geometry.[34] In this enzyme, at pH 7, the copper ion is coordinated to two histidine residues (His496, His581), a tyrosinate residue (Tyr272), a water molecule in the equatorial plane and to another tyrosinate (Tyr495) in the apical position.[34] For the oxidation of galactose and other primary alcohols a radical mechanism was

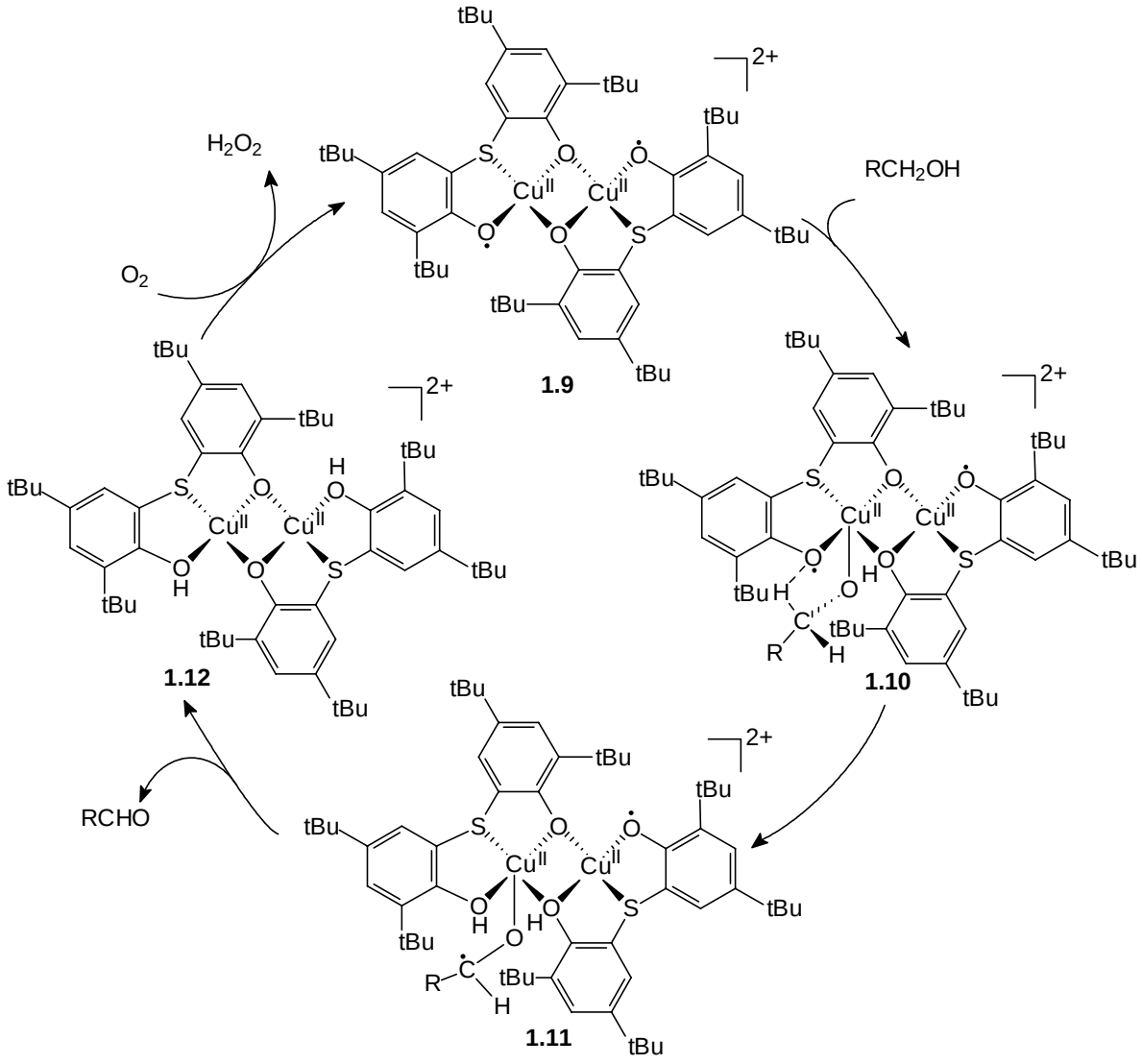
postulated.[35] This catalytic cycle starts with the binding of the substrate by replacing a H_2O molecule at the metal centre giving **1.5** as depicted in Scheme 3.[35]



Scheme 3 *Proposed reaction mechanism for galactose oxidase.*

Subsequently the alcohol is deprotonated, whereby the axial Tyr495 residue acts as a base (**1.6**).[35] In the rate-determining step a hydrogen atom is abstracted by the tyrosyl radical from the carbon atom of the alcohol giving a ketyl radical (**1.7**). By an intramolecular electron transfer to the Cu^{II}-ion radical **1.7** is oxidised to the aldehyde. Finally the starting Cu^{II}-tyrosyl radical intermediate is restored by the oxidation of the Cu^{I}-ion (**1.8**) and the tyrosine residue with O_2 whereby H_2O_2 is released.[35] Many functional GOase model complexes were developed and studied.[36] Stack *et al.* synthesised a number of copper complexes with diimine-diphenolate ligands.[37] Binaphthyl units were incorporated as backbone of the ligand changing a square-planar coordination geometry towards a tetrahedral geometry, which is preferred by Cu^{I}-ions. The synthesised non-planar copper complexes were found as catalysts or precursor catalysts in the oxidation of benzylic and allylic alcohols with O_2 as oxidant. At room temperature formation of the corresponding aldehyde compounds with the release of H_2O_2 were observed. Turnover numbers of 1300 were readily obtained.[37] Recently, the group of Wieghardt described a catalytic alcohol oxidation procedure using the ligand 2,2'-thiobis(2,4-di-*tert*-butylphenol).[38] The corresponding bis(phenolato) bridged dicopper(II) complex (**1.9**, Scheme 4) was found to be the catalytically active species.[38] Ethanol and benzyl alcohol were converted in 12h with yields

up to 63% (630 turnover numbers) in tetrahydrofuran under air at 20°C. No over-oxidation products or H_2O_2 disproportionation were detected. Secondary alcohols were oxidised to glycol coupling products with satisfactory yields.[38] This observation was explained by assuming that two alkoxides bind to the two copper ions and after C - C bond formation the two coordinated ketyl radicals recombine to yield the glycol products. The proposed catalytic cycle as given in Scheme 4 starts with the binding of an alcoholate ion to one of the Cu^{II}-ions in **1.9** at the axial position, followed by the rate-determining hydrogen abstraction step giving the ketyl radical **1.11**. In an intramolecular electron transfer step the ketyl radical is converted to the aldehyde. Finally the phenoxyl radicals **1.9** are regenerated by oxidation of the phenolate ligands by using O_2 which closes the catalytic cycle.[38] In contrast to the mechanism proposed for the model complexes studied by Stack *et al.* and for galactose oxidase, the catalytic active species described by Wieghardt *et al.* involves dinuclear copper(II) complexes and not copper(I) intermediates.[38]

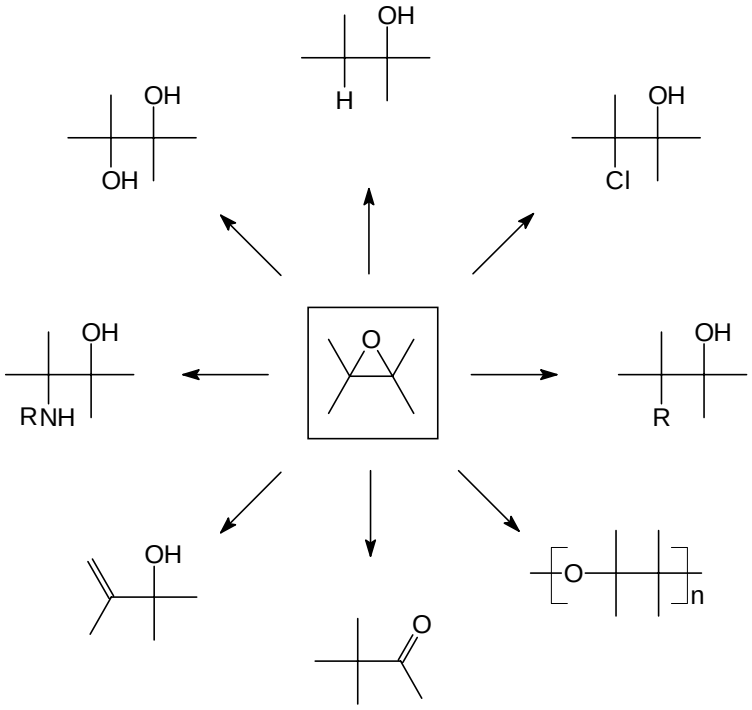


Scheme 4 *Mechanism for the catalytic oxidation of primary alcohols by dinuclear complex **1.9**, proposed by Wieghardt et al.*[38]

Another enzyme that has been widely studied is Tyrosinase (Tyr), which contains two copper atoms.[39] This enzyme catalyses the hydroxylation of phenols to catechols and the subsequent oxidation of these molecules to *o*-quinones. Extensive studies in this field have been made by the groups of Karlin[40] and Tolman.[41] Based on this research several bio-inspired copper catalysts have been developed. High turnover numbers and high selectivities were observed for the oxidation of alkanes, alkenes or alcohols and for oxidative coupling reactions including polymerisations.[42]

1.2 Catalytic epoxidation reactions

Epoxides are an important and versatile class of organic compounds and as a result the selective epoxidation of alkenes is a major area of research.[43] The epoxides can be transformed into a variety of functionalised products. For example reductions, rearrangements or ring-opening reactions with various nucleophiles give diols, aminoalcohols, allylic alcohols, ketones, polyethers etc. as depicted in Scheme 5.[43]



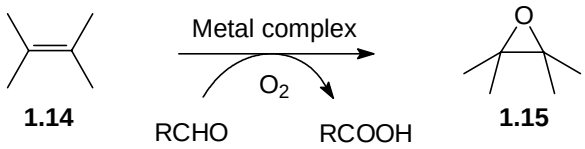
Scheme 5 *Possible conversions of epoxides (R = alkyl, aryl).*

The epoxidation reaction of olefins can be achieved by applying a variety of oxidants. Peroxycarboxylic acids are widely used stoichiometric reagents for epoxidation in industrial and academic research.[44] Other examples include: dioxiranes,[45] alkylhydroperoxides,[46] hydrogen peroxide,[46] hypochlorite,[47] iodosylbenzene[47] and oxygen.[48] With a few exceptions, most of the oxidants have the disadvantage that besides the oxidised products stoichiometric

amounts of waste products are formed which have to be separated from the epoxides. Main advantages of the use of oxygen (O_2) are the low costs and the absence of oxidant waste products. Therefore O_2 is among the most important oxidants for large-scale industrial application.[46] However, O_2 does not react spontaneously with *e.g.* alkenes and has to be activated with a suitable catalyst. With a heterogeneous epoxidation catalyst (Ag/Al_2O_3) and O_2 ethene can be oxidised on large scale to ethylene oxide.[49,50] After the adsorption of O_2 on the silver surface, O_2 is activated to convert ethene to ethene oxide.[49] The silver catalyst can transfer one oxygen atom and the remaining oxygen atom is removed by complete combustion with ethene to carbon dioxide and water.[49] High selectivities are mainly obtained for alkenes without α-hydrogen atoms. The scope of the aerobic epoxidation was extended by a ruthenium porphyrin complex, which is converted to a dioxoruthenium(VI) porphyrin catalyst.[51] Although both oxygen atoms were used for epoxidation, long reaction times and low turnover numbers were obtained.[51] However, using a ruthenium substituted polyoxometalate as an inorganic dioxygenase, high yields and selectivities were obtained in 2h.[52] Recently, a chiral dioxoruthenium porphyrin complex was synthesised resulting in epoxides with enantioselectivities in the range of 20 to 72% under aerobic conditions.[53]

1.3 Oxidation reactions with oxygen

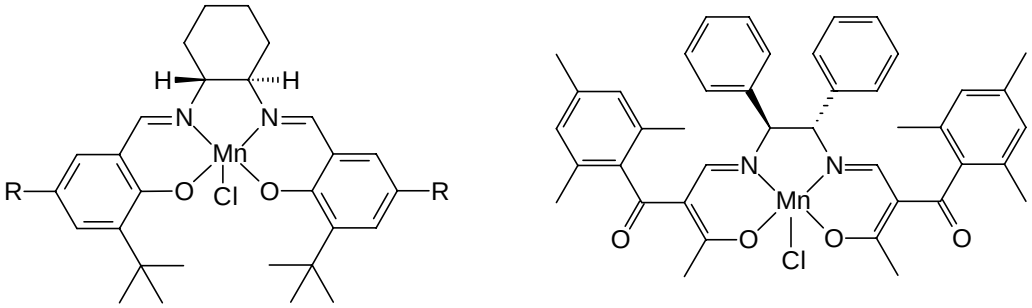
Various studies have been devoted to the aerobic oxidation of alkenes to the corresponding epoxides using transition metal complexes.[54] Mukaiyama *et al*. among others developed an epoxidation procedure catalysed by 1,5-disubstituted acetylacetonate nickel(II)[55] and oxovanadium(IV)[55b] complexes in the presence of primary alcohols as co-reagents. Using high temperatures (100°C) and high O_2 pressures (3 - 11 bar) yields up to 67% were obtained.[55] Switching from alcohols to aliphatic aldehydes as reductants allowed the use of milder conditions providing high epoxide yields for a variety of substrates.[56] In addition the concomitant co-oxidation of aldehydes to carboxylic acids has been observed as given in Scheme 6.[56,57]



Scheme 6 *Aerobic epoxidation in the presence of co-catalyst.*

Iron,[58] cobalt[59] and manganese[60] complexes were also effective catalysts utilising the Mukaiyama epoxidation conditions. The combined use of pivalaldehyde and O_2 was further exploited with chiral manganese(III) salen- (**1.16**)[60b] or aldiminatomanganese(III)[61] complexes (**1.17**) for the enantioselective olefin and sulfide[62] oxidation (Figure 3).

Satisfactory yields were only obtained by the use of relative high (4 - 8 mol%) catalyst loadings. Recently, these aerobic olefin epoxidations were extended to the use of polymer-bound[63] Mn-complexes and the use of perfluorinated solvents.[63a,64] The supported complexes combine the reactivity of homogeneous catalysts with the possibility to recycle the heterogeneous catalysts. However, some loss of activity was observed after recovering the catalyst due to leaching of the metal from the complexes.[63a]

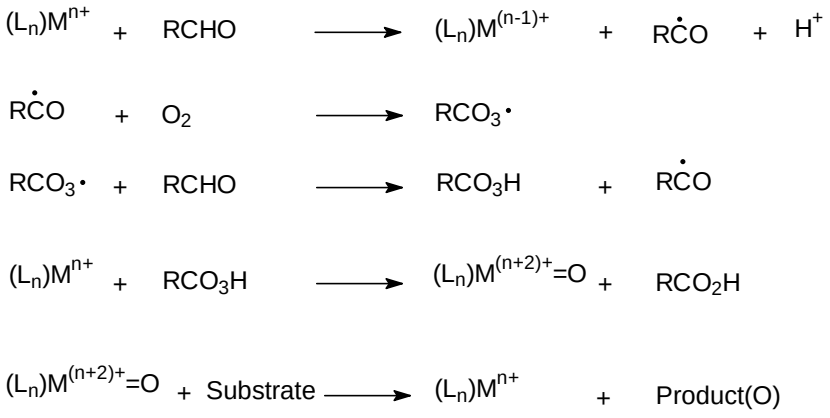


1.16 **1.17**

R = CH_3, *t*-Bu

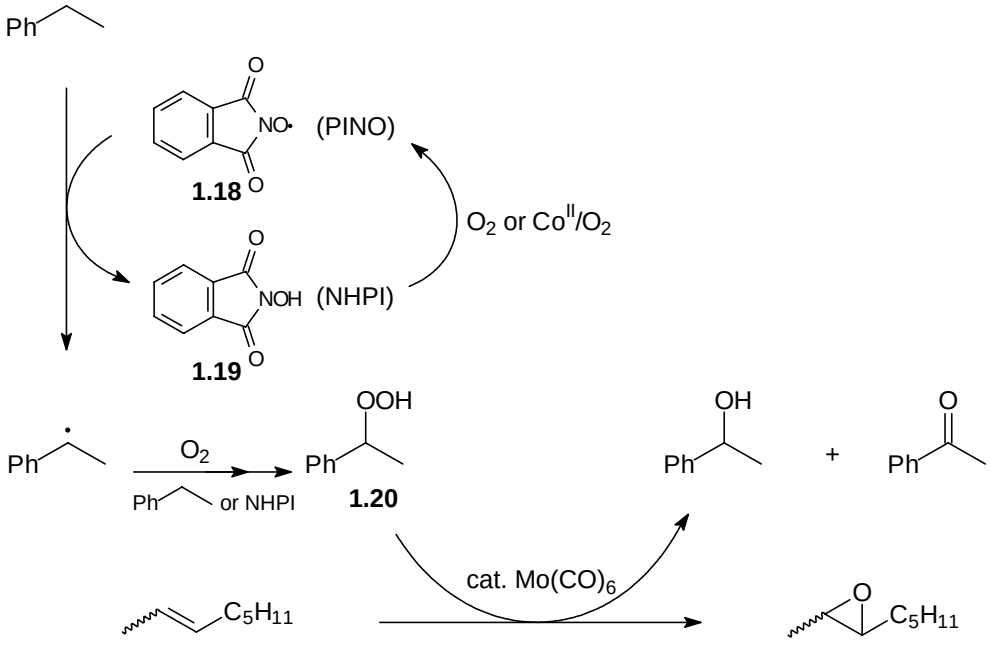
Figure 3 *Manganese(III) salen complex (**1.16**) and aldiminatomanganese(III) complex (**1.17**).*

The proposed mechanism for the metal complex-catalysed oxidation of substrates by O_2 in the presence of an aldehyde as co-oxidant is presented in Scheme 7.[65] The initiation starts with the conversion of the aldehyde to the corresponding acyl radical ($RC(O)^{\cdot}$) catalysed by the metal complex. Subsequently this radical reacts with O_2 producing an acylperoxy radical which can generate another acyl radical by reacting with a second aldehyde where upon it is converted to the peroxyacid. As reactive oxidation species a high-valent metal-oxo species $[(Ln)M^{(n+2)+}=O]$ is assumed, which is formed after reaction between the peroxyacid and the metal complex. Detailed mechanistic studies revealed that oxidation reactions can also proceed via intermediates other than high-valent metal-oxo intermediates *e.g.* by direct oxygen transfer from the acylperoxy radicals.[65]



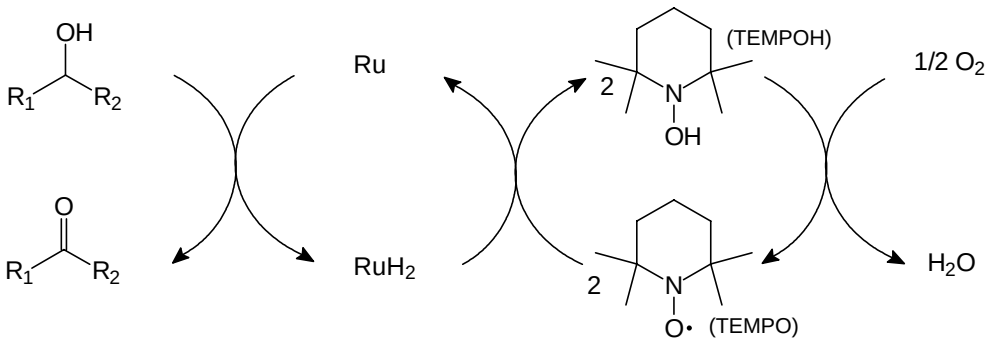
Scheme 7 *Proposed radical mechanism for the Mukaiyama reaction.*

Another catalytic aerobic oxidation method was developed by Ishii *et al.*[66] Employing *N*-hydroxyphthalimide (NHPI, **1.19**, Scheme 8) as a radical initiator a range of substrates *e.g.* alcohols[67a,b], sulfides[67c] or alkylbenzenes[67d] were oxidised with high conversions and selectivities. NHPI is commercially available or can be synthesised from phthalic anhydride (produced at large scale) and hydroxylamine.[66] In contrast to common radical chain reactions, the selectivities can be tuned by modifying NHPI by introducing substituents at the aryl functionality.[68] The cobalt salt/NHPI system catalyses the oxidation by generating a phthalimide *N*-oxyl radical (PINO, **1.18**).[69] Subsequently the PINO radical abstracts a hydrogen atom from an alkane. Trapping the alkane radical with O_2 affords alcohol or ketone compounds via alkyl hydroperoxides intermediate **1.20**. Recently, the alkylhydroperoxides were used as oxidants for the epoxidation of alkenes catalysed by molybdenum as shown in Scheme 8.[70] The $Mo(CO)_6$-catalysed alkene oxidations with *in situ* prepared hydroperoxides resulted in high yield and (stereo)selectivities. However, terminal alkenes such as 1-octene were converted with moderate yields to the corresponding epoxide.[70]



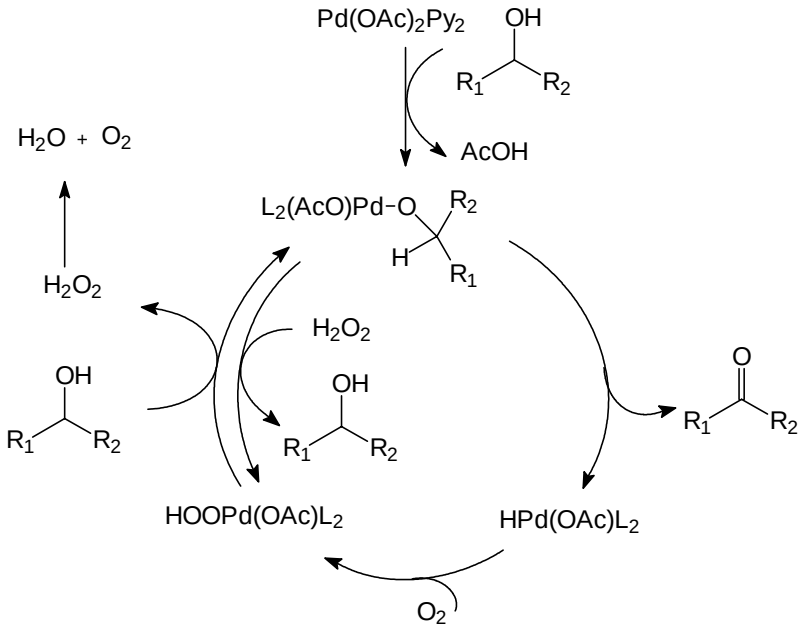
Scheme 8 *Epoxidation of alkenes using in situ generated hydroperoxides.*[70]

Another interesting example of selective metal-catalysed oxidation includes a system[71] which uses a combination of $RuCl_2(PPh_3)_3$ and the stable free radical 2,2',6,6'-tetramethylpiperidine *N*-oxyl (TEMPO, Scheme 9).[72] Employing this Ru-TEMPO catalytic mixture a variety of alcohols, both primary and secondary, could be oxidised into aldehydes and ketones with yields in the range of 68 - 100% and with high selectivities (>99%).[71] However, substrates containing heteroatoms (O, N, S) were found to be unreactive towards oxidation, presumably due to coordination to the metal centre and thereby inactivating the catalyst.



Scheme 9 *Proposed mechanism of $RuCl_2(PPh_3)_3$-TEMPO-catalysed oxidation of alcohols under aerobic conditions.*[72]

Careful studies of competition experiments revealed that this Ru-TEMPO system has a strong preference for primary *versus* secondary alcohols. In addition this observation is an indication that the mechanism involves a ruthenium centred dehydrogenation step with ruthenium hydrides as intermediates, whereby TEMPO acts as a hydrogen transfer mediator.[71] In contrast to the Ru-TEMPO alcohol oxidation catalysts, the mixed $Pd(OAc)_2$/ pyridine systems are suitable catalysts for the oxidation of both primary- and secondary-benzylic and aliphatic alcohols.[73,74] High selectivity and conversions are obtained for a wide scope of substrates. The Pd-based catalyst has also been found to be compatible with substrates containing different substituents including protecting groups. The proposed catalytic cycle proceeds via a Pd^{II}-alcoholate formed from the substrate and the starting Pd^{II}-pyridine complex (Scheme 10).[75] However, non-of these putative intermediates have been isolated or spectroscopically detected. Elimination of a Pd^{II}-hydride intermediate and subsequent reaction with O_2 gives a Pd^{II}-hydroperoxide species.



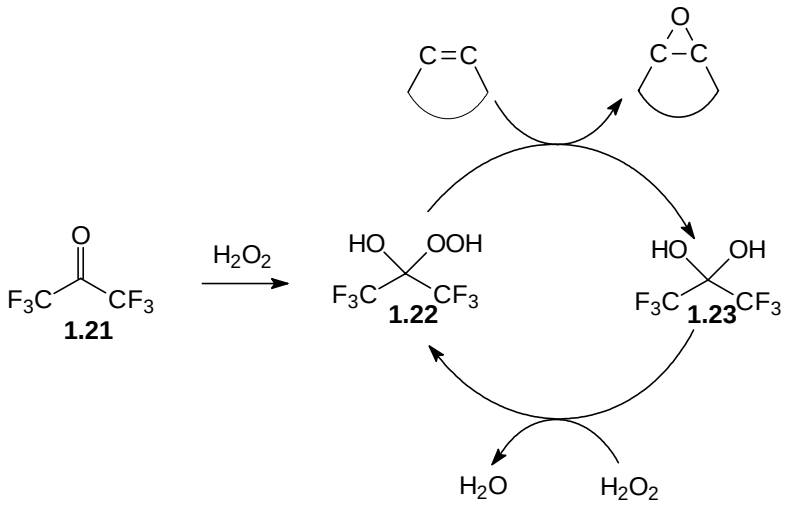
Scheme 10 *Proposed mechanism for Pd-catalysed alcohol oxidation.*[75]

This reactive peroxo species is converted to the Pd^{II}-alcoholate and simultaneous formation of H_2O_2 after ligand exchange with the alcohol. Subsequently H_2O_2 is decomposed by molecular sieves to H_2O and O_2.[75] Recently, the use of a complex of Pd^{II} and chiral sparteine was reported in an oxidative kinetic resolution procedure for secondary alcohols.[76] High enantiomeric excess (>99%) was observed for the oxidative resolution of a variety of benzylic and allylic alcohols employing 5 mol% of a Pd^{II}-source and 10 mol% of the chiral ligand.[76]

1.4 Oxidation reactions with (hydrogen) peroxide

The major drawback of the methods described by Mukaiyama[55] and Ishii[66] is the production of substantial amounts of organic waste. On the other hand, alkyl peroxides and particularly hydrogen peroxide as oxidants shows high atom efficiency. Therefore, these oxidants are attractive for industrial applications. Hydrogen peroxide has a high oxygen content and can be safely used in concentrations up to 60%.[46] As this oxidant is often partially destroyed by catalase type activity,[19] the development of novel synthetic methodologies employing H_2O_2 is a major challenge. It should be noted that, unselective side reactions might occur after the homolytic cleavage of H_2O_2 leading to hydroxyl radicals. Several attempts have been successfully made to suppress the unselective side reactions by fine-tuning the catalyst or optimising the reaction conditions.[77]

Widely employed stoichiometric non-metal organic oxidants are the peracid mCPBA[78] and the isolated dioxirane DMD.[79] A catalytic analogue constitutes the hexafluoroacetone perhydrate[80] and this perhydrate has been applied in epoxidation reactions,[80a,b] oxidation of substrates containing heteroatoms and[80c] aldehydes[81] and Baeyer-Villiger rearrangements.[80c]

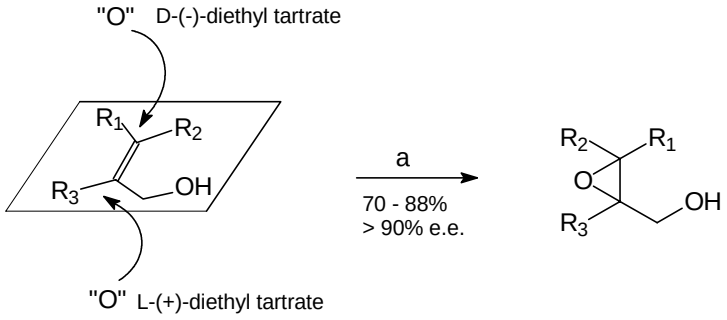


Scheme 11 *Epoxidation of alkenes catalysed by hexafluoroacetone.*

The highly electrophilic and therefore reactive hexafluoroacetone **1.21** (Scheme 11) reacts with H_2O_2 to give the perhydrate **1.22**, which is able to oxidise alkenes to the corresponding epoxides. Subsequently the catalytic cycle is completed by regeneration of the corresponding perhydrate from the hydrate **1.23**. Recently, the catalytic activity was improved by utilising perfluorinated ketones employing longer alkyl groups.[82]

1.4.1 Titanium-catalysed epoxidation reactions

Dialkyl tartrates have been successfully employed as chiral ligands in the titanium-based enantioselective epoxidation of allylic alcohols and the most efficient procedures involve *t*-butyl hydroperoxide (*t*-BuOOH) as the oxidant.[83] The hydroxyl moiety of the substrate has an activating and stereodirecting role by binding to the metal centre providing high enantioselectivities in the epoxidation reaction. The catalyst is an *in situ* prepared complex derived from titanium-*iso*-propoxide and the enantiomerically pure tartaric ethyl ester. Using 5 - 10 mol% of the titanium alkoxide and 10 - 20 mol% excess of the tartrate with respect to titanium-*iso*-propoxide high enantioselectivities (>90%) and yields (>80%) were obtained for a range of substituted allylic alcohols.[84] From spectroscopic data it was concluded that the titanium complex exists as a dimer in solution. Lowering the amount of catalyst led to a substantial decrease in enantiomeric excess and catalyst reactivity.

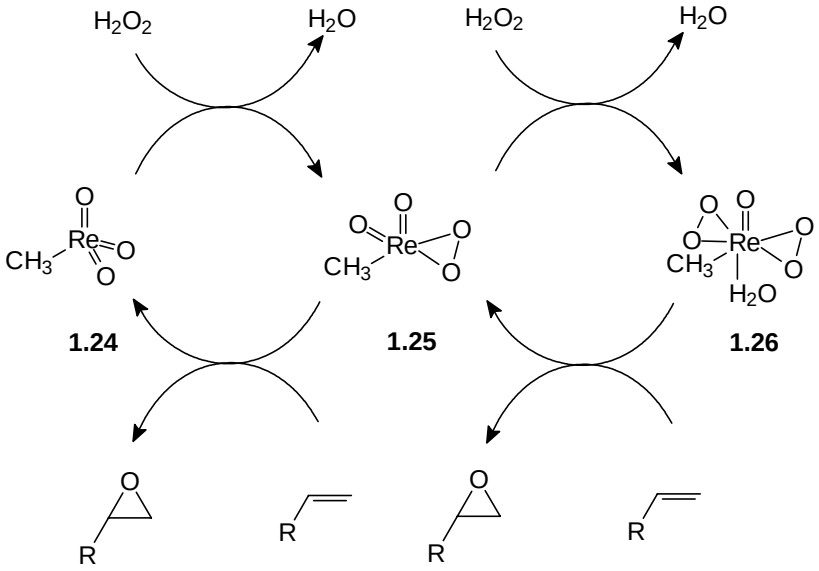


Scheme 12 *Sharpless epoxidation procedure; a. Ti(O-iPr)$_4$, t-BuOOH, CH_2Cl_2, -20^{o}C.*

1.4.2 Epoxidation reactions catalysed by rhenium complexes

Inorganic rhenium complexes like Re_2O_7 or ReO_3 were long considered to have negligible catalytic oxidation activity with H_2O_2.[54] Herrmann *et al.* discovered that organometallic oxorhenium(VII) species and especially methyltrioxorhenium[85] (**1.24**, MTO, Scheme 13) are efficient epoxidation catalysts.[86] The active catalyst is formed by reaction

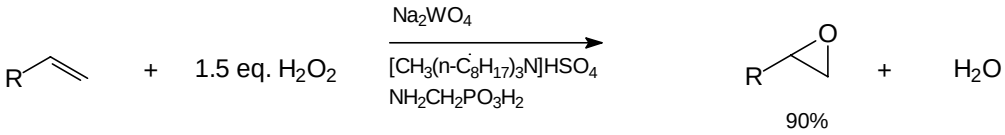
with H_2O_2, giving a monoperoxo rhenium complex **1.25** and the diperoxo complex **1.26**. The latter intermediate has been fully characterised by X-ray studies.[87,88,89] Disadvantages of the procedures were the restriction to use anhydrous H_2O_2 and the low yields for the formation of acid sensitive epoxides, due to the Lewis acidic character of the rhenium centre.[86] The catalytic oxidation of sensitive epoxides could be improved by employing an urea/H_2O_2 adduct,[90] however, long reaction times were required.[91] Addition of tertiary bases suppresses the epoxide ring-opening, but with a strong detrimental influence on the catalyst activity.[86] Sharpless *et al*. found an improvement in selectivity, without inhibition of the catalyst, by adding a large excess of pyridine with respect to the catalyst.[92a] Sensitive epoxides could be synthesised with only 1.5 equivalents of aqueous H_2O_2 even at low catalyst loadings.[92a,b] Higher catalyst loadings were necessary in the presence of bipyridine *N*,*N*'-dioxide as epoxide ring- opening suppressing agent.[93] Unreactive terminal alkenes could be converted to the corresponding epoxides by using less basic pyridine derivatives like 3-cyanopyridine.[94] In addition to the epoxidation reactions the conversion of 3-cyanopyridine to the corresponding *N*-oxide was observed.[95] Subsequently this feature was utilised for a scope of substrates on preparative scale.[95] Pyrazole was reported by Herrmann *et al.* as the most efficient additive and as active oxidation species a bis(peroxo)rhenium(VII)/pyrazole complex was proposed.[96] These results were, however, disputed by Sharpless *et al*. after a careful comparison of the obtained results.[97] Mechanistic investigations,[88] incorporating the positive pyridine effect,[98] showed that the additives minimise the MTO decomposition to perrhenate (ReO_4^-),[98a] thereby retaining high catalyst activity. Furthermore, the increased reaction rate was explained by the Brønsted basicity of pyridine increasing the HO_2^- concentration. HO_2^- is more nucleophilic and therefore more reactive with MTO compared to H_2O_2. Finally the basicity of pyridine and related additives lowers the concentration of hydronium ions and as a result reducing the sensitivity of epoxides towards decomposition by ring-opening.[98]



Scheme 13 *Catalytic epoxidation cycle of methyltrioxorhenium with H_2O_2.*

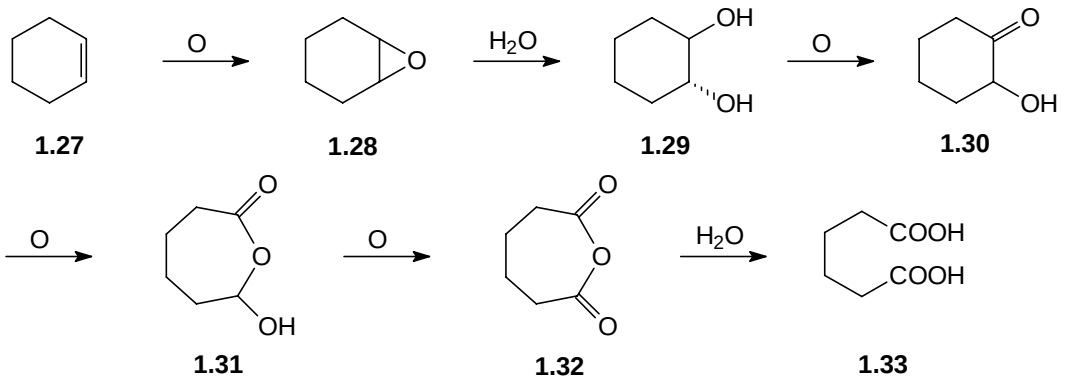
1.4.3 Tungsten-catalysed oxidation reactions

Payne and Williams reported in 1959 the epoxidation of olefins with H_2O_2, catalysed by sodium tungstate (Na_2WO_4).[99] Under phase-transfer conditions less reactive terminal olefins are also converted to the corresponding epoxides but unfortunately the epoxide yields did not exceed 53%.[100,101] The yields were strongly improved by adding a lipophilic phase-transfer catalyst and a heteropolyacid.[101] The use of chlorinated solvents was found to be necessary, defeating the environmental and economic benefits of aqueous H_2O_2. Noyori *et al.* disclosed a halide- and solvent-free epoxidation procedure.[102] High yields and t.o.n.'s in the range of 150 - 200 per W atom were observed for the epoxidation of alkenes catalysed by Na_2WO_4 (2 mol%) in the presence of (aminomethyl)phosphonic acid (1 mol%) and methyltri-*n*-octylammonium hydrogensulfate (1 mol%) as phase-transfer agent (Scheme 14).[102a] Slightly lower yields were achieved for the oxidation of functionalised olefins.[102b] Although the active oxidation intermediate is considered to be a peroxo tungsten complex, a detailed mechanism has yet to be elucidated.



Scheme 14 *Epoxidation catalysed by Na_2WO_4.*[102]

While aliphatic olefin substrates are efficiently converted to the corresponding epoxides, a low yield of 23% was observed for the oxidation of styrene. This disadvantage is attributed to the hydrolytic decomposition of the acid-sensitive epoxide, presumably at the aqueous/organic interface.[102b] This effect is a problem for epoxide synthesis, but it provides an opportunity for the direct oxidation of olefins to carboxylic acids. Cyclohexene can be directly oxidised to adipic acid catalysed by Na_2WO_4 with 4 equivalents of H_2O_2.[103] Adipic acid is an important industrial product and starting material for the synthesis of nylon-6,6.[103] The reaction involves four oxidation steps, during a one-pot conversion under organic solvent- and halide-free reaction conditions. The oxidation steps include olefin-, alcohol- and Baeyer-Villiger oxidation reactions (Scheme 15). Intermediates **1.28** to **1.30** were characterised by GC analysis and were independently converted to **1.33** under comparable oxidation conditions. The tungstate catalysed biphasic procedure developed by Noyori for the epoxidation of olefins can also be applied for the oxidation of sulfides to the corresponding sulfoxides and sulfones.[104] Omission of the (aminomethyl)phosphonic acid additive gives a suitable procedure for the selective oxidation of primary alcohols and secondary alcohols to the corresponding carboxylic acids or ketones, respectively.[105]

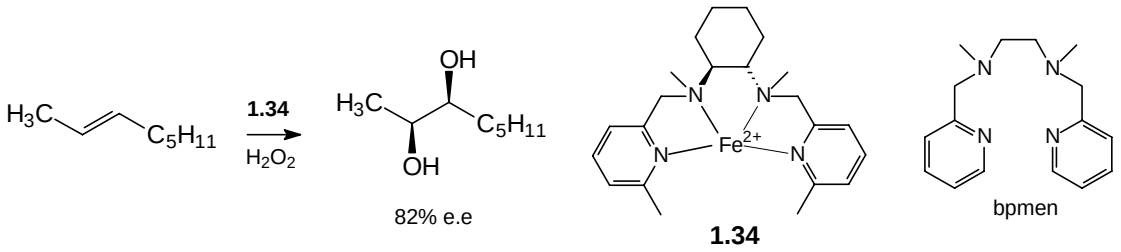


1.27 **1.28** **1.29** **1.30** **1.31** **1.32** **1.33**

Scheme 15 *Oxidation of cyclohexene to adipic acid with H_2O_2 using Na_2WO_4 catalyst.*[103]

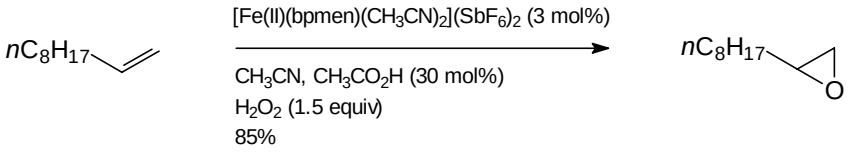
1.4.4 Iron-based epoxidation catalysts

A variety of iron porphyrin complexes are capable of catalysing oxidation reactions employing H_2O_2 as oxidant.[106] However, due to the often poor stability and difficult synthesis of these catalysts, the applicability is limited. Only a few non-heme iron complexes based on tetradentate nitrogen ligands are able to catalyse epoxidation reactions.[107] Que *et al.* studied intensively the non-heme iron epoxidation catalyst based on the tripodal tetradentate ligand tris(2-pyridylmethyl)amine (tpa).[107a] Interestingly, the introduction of additional CH_3-groups at the 6-position of the pyridine moieties was found to alter the course of olefin oxidation towards *cis*-dihydroxylation (for more details, see Chapter 4).[108] Recently, this research was extended by replacing the tripodal tetradentate ligand with a tetradentate bpmen[109] ligand containing an ethylenediamine backbone. The corresponding iron complexes showed similar oxidation activity as the complexes based on the tpa analogues.[108] Whereas the 6-methyl substituted [Fe-(6-Me_2-bpmen)(CF_3SO_3)$_2$][109] catalyst afforded the *cis*-diol as the major product. Thus as observed before in the Fe-tpa catalysts, the introduction of the 6-methyl substituents favours the pathway towards *cis*-dihydroxylation. Subsequently the ethylenediamine backbone was replaced by a chiral *trans*-cyclohexane-1,2-diamine backbone. The use of the corresponding chiral Fe-complex **1.34** as catalyst provided 2,3-octane-diol in 38% yield with an impressive 82% enantiomeric excess starting from *trans*-2-octene (Scheme 16).[110] Although the *cis*-diol yields and catalytic turnover numbers are still rather low (up to 10) this iron-based *cis*-dihydroxylation system has great potential for the future.



Scheme 16 *Enantioselective cis-dihydroxylation using chiral iron based catalyst **1.34**.*

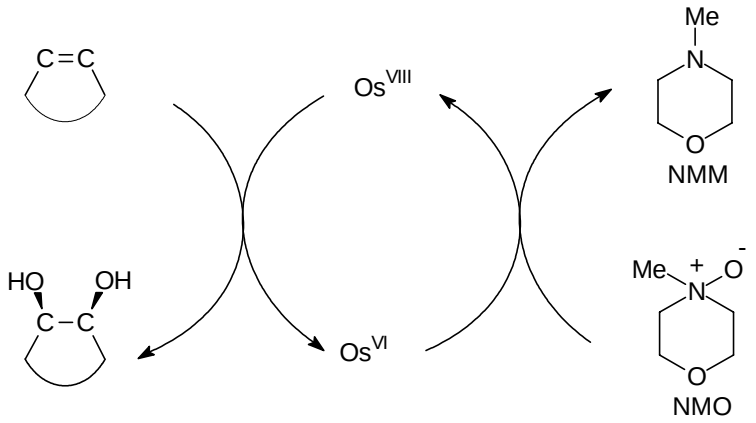
Jacobsen *et al.* made significant progress by fine-tuning the reaction conditions for the epoxidation of a number of olefins catalysed by the iron complex based on the bpmen ligand (Scheme 17).[111] Using 5 mol% of the mononuclear $[Fe^{II}(bpmen)(CH_3CN)_2](ClO_4)_2$[109] complex resulted in complete conversions of 1-decene, however, only modest selectivities towards epoxide due to over-oxidation were observed. Using SbF_6^- as anion and acetic acid as additive a strong improvement in the epoxide selectivities was found.[111] By employing only 1.5 equivalent of H_2O_2 yields in the range of 60 - 90% (t.o.n.'s up to 30) were obtained.



Scheme 17 O*xidation of 1-decene catalysed by iron(II) bpmen complex in the presence of acetic acid.*[111]

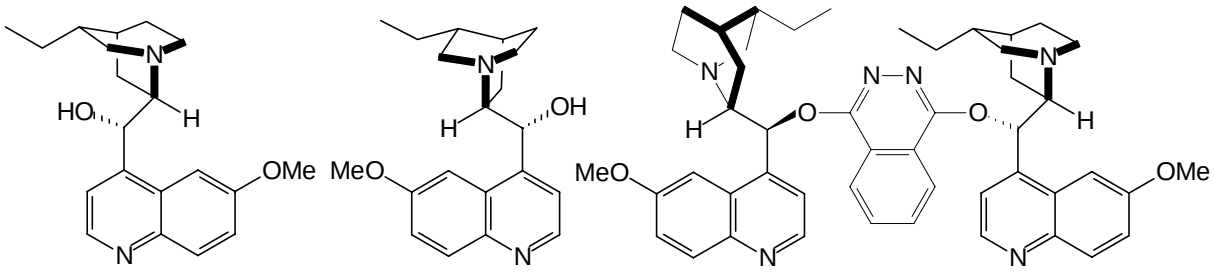
1.4.5 *cis*-Dihydroxylation catalysed by osmium tetroxide

The reaction of olefins with osmium tetroxide (OsO_4) is one of the most versatile procedures for *cis*-dihydroxylation.[112] However, when used in stoichiometric amounts, the high cost, the high toxicity and volatility of OsO_4 hamper the large scale application.[113] During the osmium-catalysed *cis*-dihydroxylation reaction osmium(VIII) is reduced to osmium(VI) upon reaction with the olefin. Catalytic amounts of OsO_4 can be employed by using a co-oxidant, which oxidises osmium(VI) back to the active reagent osmium(VIII). Synthetic suitable co-oxidants are *N*-methylmorpholine *N*-oxide (NMO, Scheme 18)[113] or potassium ferricyanide ($K_3[Fe(CN)_6]$).[114] A synthetic breakthrough was achieved by Sharpless *et al.* by the introduction of a catalytic asymmetric *cis*-dihydroxylation procedure.[115] The chiral catalytic system includes besides an osmium source, a co-oxidant like an amine oxide or $K_3[Fe(CN)_6]$.[114] This procedure represents one of the most impressive achievements of asymmetric catalysis.[112] The ligands studied by Sharpless *et al.* are based on dihydroquinidine (DHQD, **1.35**, Figure 4) and dihydroquinine (DHQ, **1.36**) and the chiral quinidine and quinine derivatives provide opposite enantiomers of the diols with approximately equal selectivity.



Scheme 18 *cis-Dihydroxylation catalysed by OsO_4.*[113]

Dihydroquinidine and dihydroquinine can both be attached to a phthalazine spacer providing $(DHQD)_2$-PHAL (**1.37**, Figure 4) which accelerates the rate of *cis*-dihydroxylation. These ligands have been intensively studied and to overcome the disadvantage of the release of free osmium during the homogeneous catalytic cycle several successfully immobilised OsO_4 catalysts have been prepared.[116] Mixtures of solid components of this catalytic system are commercially available as AD-mix (asymmetric dihydroxylation), wherein AD-mix-α contains $K_3[Fe(CN)_6]$ as the stoichiometric oxidant, $(DHQ)_2$-PHAL and a osmium(VI) source. The AD-mix-β contains the $(DHQD)_2$-PHAL ligand. By employing the AD-mix reagents alkenes can be converted into either enantiomer of the diol.

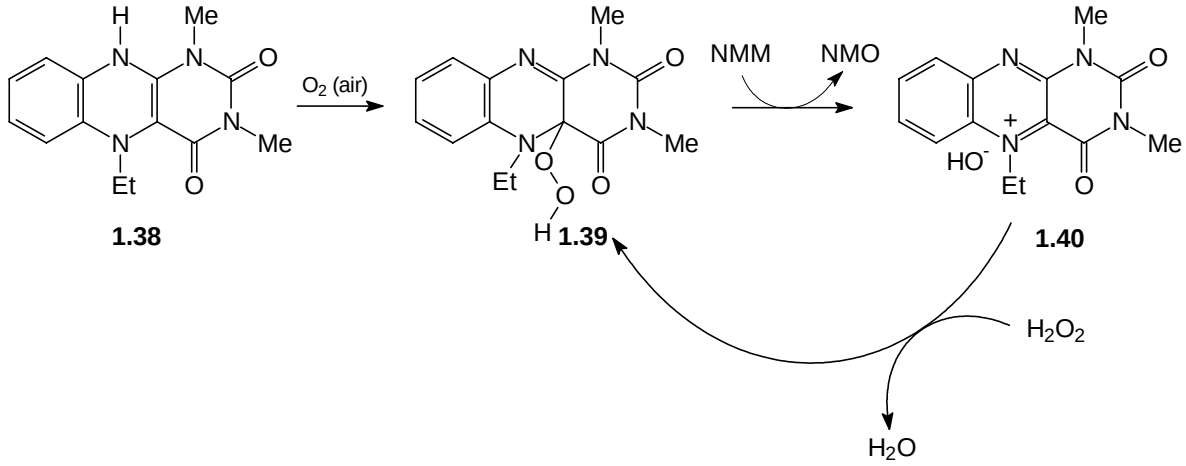


DHDQ (**1.35**) DHQ (**1.36**) $(DHDQ)_2$PHAL (**1.37**)

Figure 4 *Ligands studied in Sharpless cis-dihydroxylation reaction.*

For the reoxidation of osmium(VI) only a few procedures are available to date with H_2O_2 or O_2 as oxidant.[117] Unfortunately, in many cases lower yields were obtained due to over-oxidations. Recently, Beller *et al.* reported a method for aerobic osmium-catalysed *cis*-dihydroxylation of olefins.[118] Highly chemo- and enantioselective dihydroxylations using molecular oxygen and $K_2[OsO_2(OH)_4]$ (0.5 mol%) in the absence of any co-catalysts were obtained.[118] Other elegant osmium(VI) reoxidation systems, developed by Backväll *et al.* are based on Vanadyl acetylacetonate/H_2O_2[119] or a catalytic flavin/H_2O_2 system.[120] The mechanism of the latter catalytic oxidation is depicted in Scheme 19. The flavin

hydroperoxide **1.39** generated from flavin **1.40** and H_2O_2 recycles *N*-methylmorpholine (NMM) to the corresponding *N*-oxide (NMO), which subsequently reoxidises Os(IV) to OsO_4. Presumably flavin **1.38** acts as a precursor for the active catalysts; in the presence of air the intermediate **1.39** is formed. During the catalytic oxidation of NMM to NMO the cationic flavin **1.40** is produced which can by regenerated to the flavin hydroperoxide **1.39** with H_2O_2.[120]

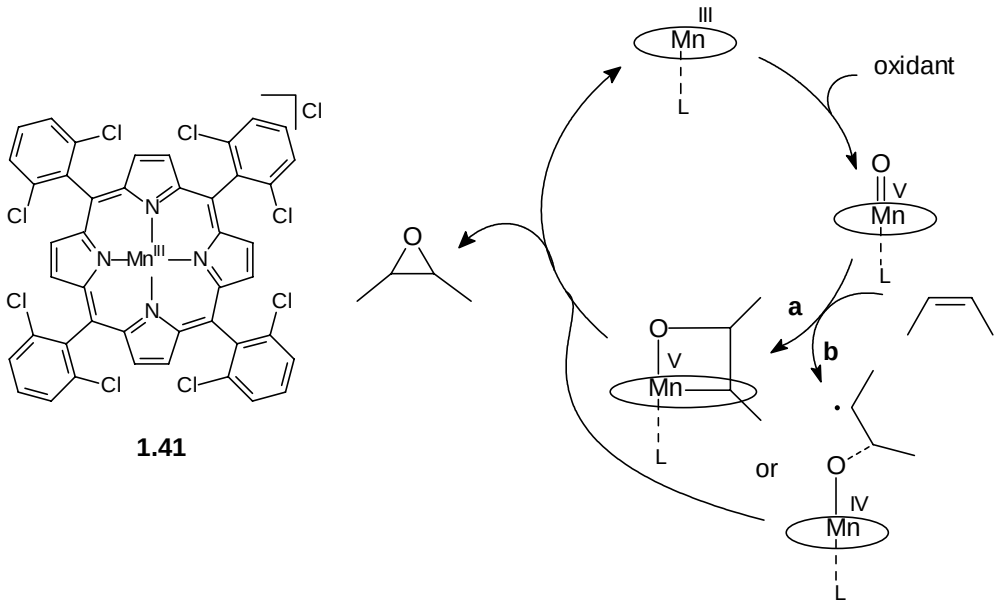


Scheme 19 *Catalytic reoxidation of NMO by flavin employing H_2O_2 as the terminal oxidant.*[120]

1.4.6 Oxidation reactions catalysed by manganese complexes

Manganese porphyrins and several other metal porphyrin complexes have been intensively studied as catalysts in epoxidation reactions of alkenes and the developments are summarised in several reviews.[47,48,121] A variety of oxidants such as iodosylarenes, alkylhydroperoxides, peracids, hypochlorites or hydrogen peroxide were employed.[47,48] The early porphyrin-based catalysts often showed rapid deactivation, due to oxidative degradation. More robust catalysts for olefin epoxidation and hydroxylation of alkanes were obtained after the introduction of halogen substituents.[122] Furthermore, the additional substituents or additives like pyridine or imidazole as axial ligands improved the catalysts activity and selectivity and allowed the use of H_2O_2 for the oxidation of a wide range of substrates.[123,124] The function of the axial coordinating additives has been proposed to favour the formation of oxomanganese(V) intermediates, which are presumed to be the actual oxidising species.[125] The catalytic epoxidation cycle of manganese porphyrin **1.41** starts with the conversion to the well established Mn^{V}-oxo species (Scheme 20).[77a,126] Subsequently the oxygen atom is transferred to the olefin via path **a** or **b** followed by release of the Mn^{III}-species and formation of the epoxide. The stepwise route **b** can give rotation around the

former double bond resulting in *cis*/*trans* isomerisation leading to *trans*-epoxides starting from *cis*-alkenes as observed experimentally.

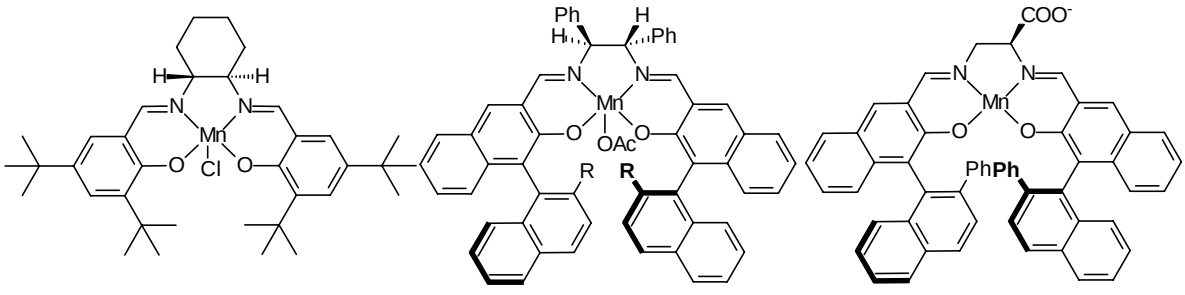


1.41

Scheme 20 *Manganese porphyrin **1.41** and the proposed catalytic epoxidation cycle.*[77,126]

1.4.7 Oxidation reactions catalysed by manganese salen complexes

After the first studies of chromium salen[127] catalysed epoxidation of olefins,[128] Kochi *et al.* reported the use of Mn-salen complexes as epoxidation catalysts.[129] A few years after the discovery of Kochi, the groups of Jacobsen[130a] and Katsuki[130b] independently described a breakthrough in this olefin epoxidation by the introduction of a chiral diamine functionality in the salen ligand (Figure 5).

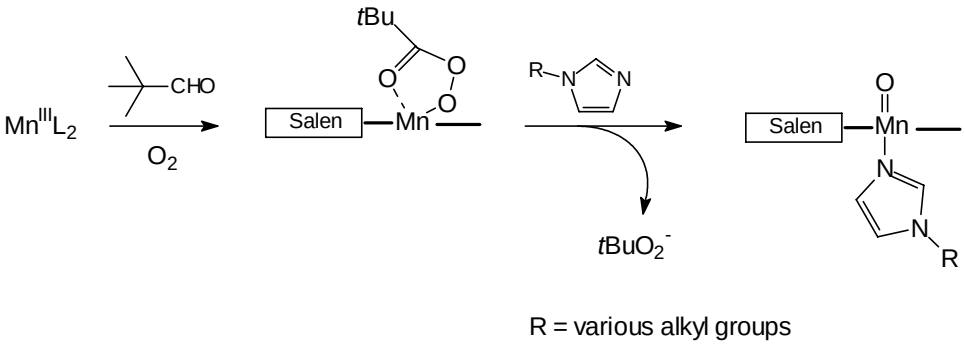


1.42 **1.43a** R = Me **b** R = Ph **1.44**

Figure 5 *Manganese complexes studied by the groups of Jacobsen (**1.42**) and Katsuki (**1.43**, **1.44**) in epoxidation reactions.*

Compared to chiral porphyrin manganese complexes,[131] the use of the Mn-salen catalysts results generally in e.e.'s up to 90% with yields exceeding 80%.[132] A wide range of oxidants including hypochlorite[132b], iodosylbenzene,[132b] or *m*-chloroperbenzoic acid (*m*-CPBA) can be applied.[133] Excellent e.e.'s are observed for epoxidation reactions of *cis*-alkenes catalysed by the Mn-salen complexes **1.42** and **1.43**, employing iodosylbenzene as oxidant. In sharp contrast the epoxidation of *trans*-olefins showed moderate selectivities (e.e. <60%), however, these results could be improved by the introduction of additional chiral groups at the 3'-position of the phenolate ring of the ligand. For the conversion of *trans*-stilbene e.e.'s up to 80% were reported using these modified salen ligands.[132] The oxidising species in the catalytic oxidation reaction is proposed to be a Mn^{V}-oxo intermediate,[133d,e] similar to the Mn-porphyrin catalyst (Scheme 20), and was confirmed by electrospray ionisation mass spectrometry.[134] Although high e.e.'s are obtained for a wide range of substrates the stability of the Mn-salen complexes is often a severe problem and turnover numbers are usually found in the range of 40 - 200. Recently, an extremely robust salen catalyst was reported by Katsuki.[135] It is based on a ligand with a carboxylic acid function attached to the diamine bridge (**1.44**, Figure 5). With this new catalyst 2,2-dimethylchromene was converted to the corresponding epoxide in 99% e.e. with iodosylbenzene as oxidant. Turnover numbers as high as 9200 after a 6h reaction time were reported.[135] Manganese salen systems employing H_2O_2 as oxidant are only catalytically active in the presence of additives like imidazole or derivatives thereof and carboxylic acids.[136] Under these special reaction conditions, low t.o.n.'s (<40) were observed and e.e.'s ranging from 60 - 96% have been reported. Berkessel *et al.* synthesised a half salen system with a covalently attached imidazole functionality. Using this new salen complex dihydronaphthalene was converted to the corresponding epoxide with H_2O_2 as oxidant in 72% yield and moderate e.e. (up to 60%). Employing this system the epoxidation reactions can be performed without further additives.[136d]

Mukaiyama *et al.* developed an aerobic epoxidation method employing Mn-salen complexes.[61e] He uses 2 equivalents of pivalaldehyde as the sacrificial reductant. Moderate yields were obtained for the oxidation of 1,2-dihydronaphthalenes to the corresponding epoxides. Remarkably, the epoxides were obtained with opposite configuration compared to reactions employing oxidants like hypochlorite, iodosylbenzene or H_2O_2.[61e] However, epoxides with the same configuration could be obtained by adding various *N*-alkyl imidazoles. Also the catalyst activity was significantly increased. These striking results were explained by suggesting that in the absence of additives an acylperoxo manganese intermediate is formed form O_2, pivalaldehyde and the Mn-salen complex leading to the (1*R*,2*S*)-olefin epoxide. By contrast after addition of the imidazole ligand the peroxo complex is converted to a Mn-oxo species, which is in accordance with the proposed Jacobsen/Katsuki epoxidation catalytic cycle, resulting in the (*1S*,2*R*) enantiomer (Scheme 21).[61e]



Scheme 21 *Aerobic epoxidation under Mukaiyama conditions and the proposed intermediates.*

1.5 Research objectives and outline of this thesis

The aim of the research described in this thesis is the design and development of new manganese containing oxidation catalysts. The catalysts should provide high selectivity towards the oxidation products employing hydrogen peroxide as the oxidant. Compared to catalytic procedures using oxidants like NaOCl or ammonium periodates, H_2O_2 offers the advantage that it is a cheap, environmentally benign and a readily available reagent. Since water is the only expected side product, catalytic oxidation methods employing this reagent are undoubtedly appealing. Much effort have also been devoted to the development of catalytic methods with high oxidant selectivity by suppressing the catalase type of H_2O_2 decomposition.

In the first three chapters selective epoxidation reactions are discussed. Chapters 5 and 6 describe the results of our efforts towards the oxidation of primary and secondary alcohols and the oxidation of sulfides, respectively. In the last chapter the concluding remarks and the future prospects are discussed. The summarised outline is depicted below:

Chapter 2: Manganese Complexes as Homogeneous Epoxidation Catalysts
This chapter deals with the synthesis of the hexadentate N^1,N^1,N^3,N^3-tetrakis(2-pyridinylmethyl)-1,3-propanediamine (tptn) ligand and several modified related ligands. The corresponding manganese complexes were studied as epoxidation catalysts.

Chapter 3: In Situ Prepared Manganese Complexes as Homogeneous Catalysts for Epoxidation Reactions with Hydrogen Peroxide
In this chapter the preliminary results are described of epoxidation reactions catalysed by *in situ* prepared complexes derived from ligands containing a N^1-(3-aminopropyl)-N^1-methyl-1,3-propanediamine backbone.

Chapter 4: Homogeneous cis-Dihydroxylation and Epoxidation of Olefins with High Hydrogen Peroxide Efficiency by Mixed Manganese/Activated Carbonyl Systems

A highly active and H_2O_2 efficient catalyst for the epoxidation of olefins is described in this section. Applying $[Mn_2O_3(tmtacn)_2](PF_6)_2$ in combination with several activated carbonyl compounds, like glyoxylic acid methylester methyl hemiacetal (gmha) or chloral, substantial amounts of *cis*-diols were obtained. Furthermore, on the basis of the results obtained with several mechanistic probes, a mechanism for both the epoxidation and *cis*-dihydroxylation reaction is proposed.

Chapter 5: Manganese Catalysts for Alcohol Oxidation

In this chapter new manganese complexes as catalysts for the oxidation of alcohols are described. Highly active and selective catalysts were found with excellent turnover numbers (up to 900) using aqueous H_2O_2 as oxidant at ambient temperatures. Electron paramagnetic resonance spectroscopy (EPR) and electrospray mass spectrometry (ES/MS) were used in mechanistic studies.

Chapter 6: New Ligands for Manganese-catalysed Selective Oxidation of Sulfides to Sulfoxides with Hydrogen Peroxide

In *Chapter 6* the oxidation of sulfides is discussed, for example methyl phenyl sulfide could be oxidised with little formation of side products. In addition chiral ligands were tested in the asymmetric sulfide oxidation, affording a series of different alkyl aryl sulfoxides.

Chapter 7: Summary, Conclusions and Future Prospects

Finally the overall conclusions and the future perspectives of the research described in this thesis will be given.

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Chapter 2

Manganese Complexes as Homogeneous Epoxidation Catalysts

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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.

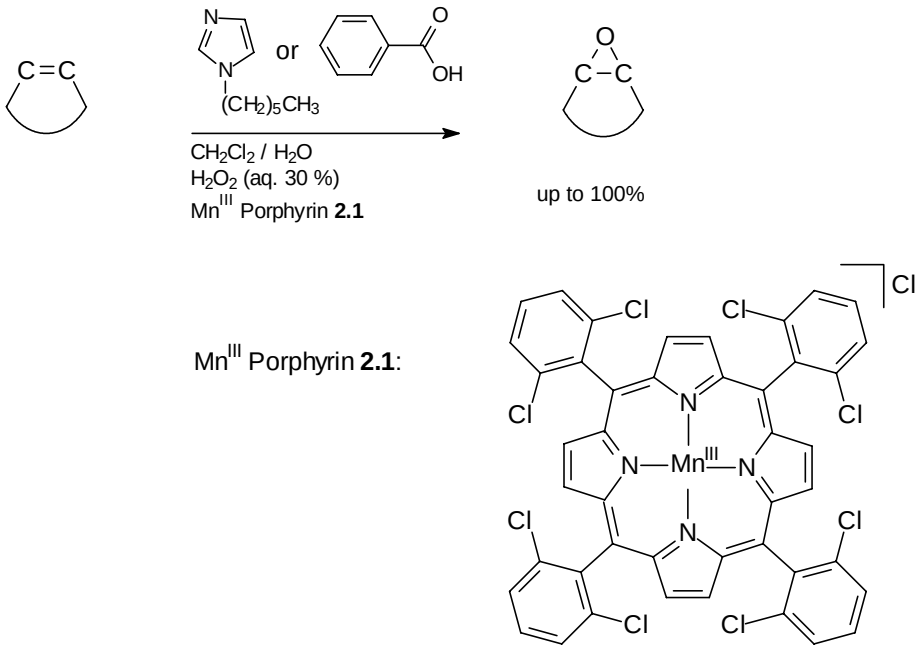
2.1 Introduction

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 H_2O_2 as oxidant for alkene epoxidation with porphyrin-based catalysts were unsuccessful due to dismutation of H_2O_2 into H_2O and 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,[6,7] 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^oC could be obtained.

Carboxylic acids and nitrogen containing additives presumable facilitate the heterolytic cleavage of the O - O bond in the porphyrin manganese hydroperoxy intermediate resulting in a catalytically active manganese(V)-oxo intermediate.[9] Homolytic cleavage of the O - O bond leads to the formation of hydroxyl radicals, resulting in unselective reactions, a serious problem using H_2O_2 in metal-catalysed oxidation reactions.[4a] Furthermore, gradual improvement in the stereoselectivity of the oxidation of *cis*-stilbene was observed by increasing the number of β-halogen atoms on the porphyrin ligand.[10] However, a general

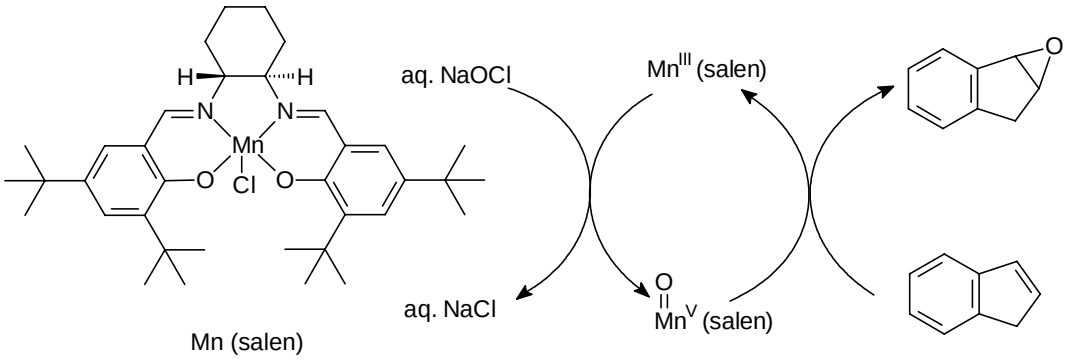
disadvantage of manganese porphyrin chemistry is the difficulty of synthesising the ligands and the often tedious purification.



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

The Jacobsen catalyst[11] and the related Katsuki manganese salen catalyst[12] are commonly applied for asymmetric epoxidation reactions. High yields and moderate to excellent enantioselectivities have been reported for oxidation of *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.[13] Imidazole groups were also covalently attached to the chiral salen ligands and with the corresponding catalysts enantiomeric excesses up to 64% with H_2O_2 as oxidant were achieved.[14]



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

As oxidising intermediate a manganese(V)-oxo species was proposed[15] which was confirmed by electrospray ionisation mass spectrometry (ES/MS).[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.[17] The manganese complexes have been investigated as enzyme models for superoxide dismutase, catalase and oxygen evolving processes in the photosystem II.[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_2O_2.[19,20]

In combination with H_2O_2 it was also found that the dinuclear manganese complex is a highly active oxidation catalyst.[21] High turnover numbers (more than 400) were obtained using styrene derivatives as substrates without notable catalyst degradation.[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.

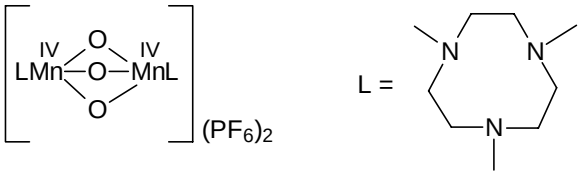
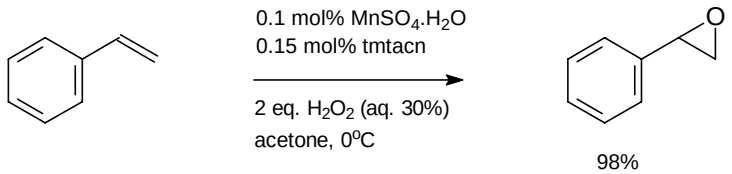


Figure 1 *Manganese tmtacn complex and free tmtacn ligand.*

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_2O_2 by trapping the latter with formation of a perhydrate.[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 *in situ* prepared Mn-tmtacn complex using $MnSO_4$ (Scheme 3).[23]



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[26] or ascorbic acid[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_2O_2.[28] 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.[29] 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 vinylarenes with H_2O_2. Promising yields but low enantioselectivities were obtained using acetone as solvent.[30]

Various successful attempts to fine-tune the catalyst selectivity have been made encapsulation of the Mn-tmtacn complex in zeolites increased the epoxidation selectivity.[31] By immobilisation of the triazacyclononane ligand on an inorganic support a new group of active heterogeneous manganese tacn epoxidation catalysts were introduced.[32] Improved selectivities were found but the conversions obtained were lower than with the homogenous catalysts.

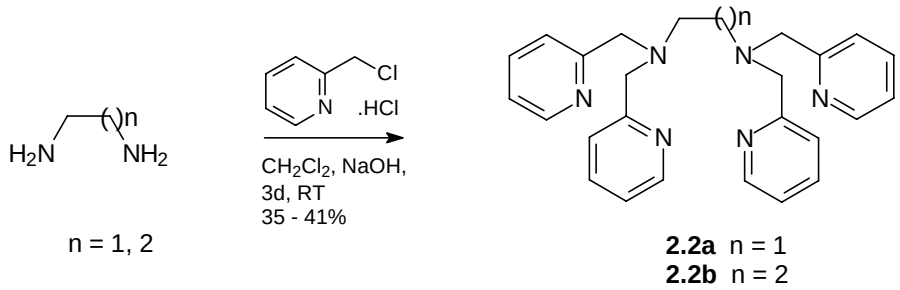
The mechanism of the Mn-tmtacn-catalysed epoxidation and alcohol oxidation has been the subject of much research. However, very little is known about the mechanisms or about the nature of the active intermediates in the catalytic systems. High-valent manganese, mono- or dinuclear manganese-oxo species and also radicals may all be involved. During the oxidation reactions often an induction period was observed, indicating that the original $[Mn_2O_3(tmtacn)_2](PF_6)_2$ 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_2O_2 prior to the addition of the substrate (benzyl alcohols).[28] 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_2O_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.[19,23] Based on EPR studies similar manganese species were reported during related phenol oxidation experiments.[33] 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.[34] From electrospray mass spectrometry (ES/MS) experiments the mononuclear Mn^{V}=O species could indeed be assigned.[35] This species was also generated in oxidation reactions using a mononuclear Mn^{IV}-complex[22] 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.[36] Furthermore, the sensitivity of the corresponding metal complexes to changes in the original tmtacn structure often leads to completely inactive manganese complexes.[28] 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.

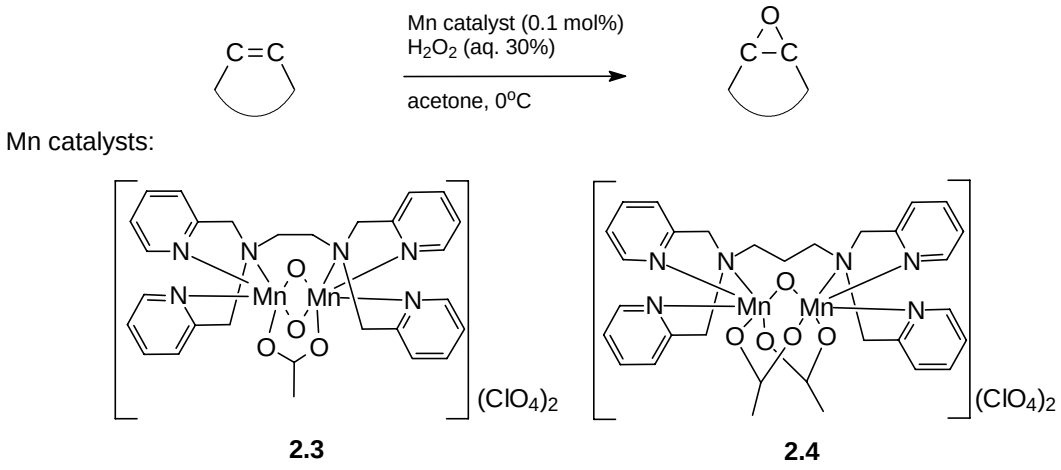
In this chapter we present high catalytic epoxidation activity for manganese complexes based on dinucleating ligands *N,N,N',N'*-tetrakis(2-pyridylmethyl)-1,2-ethane-diamine (**2a**, tpen) and *N,N,N',N'*-tetrakis(2-pyridylmethyl)-1,3-propanediamine (**2.2b**, tptn) both featuring the three N donor set 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.[37] Complexes of ligands **2.2a** and **2.2b** have been reported as mimics for the photosystem II (PS II).[37] 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).[37a]



Scheme 4 *Synthesis of hexadentate ligands.*

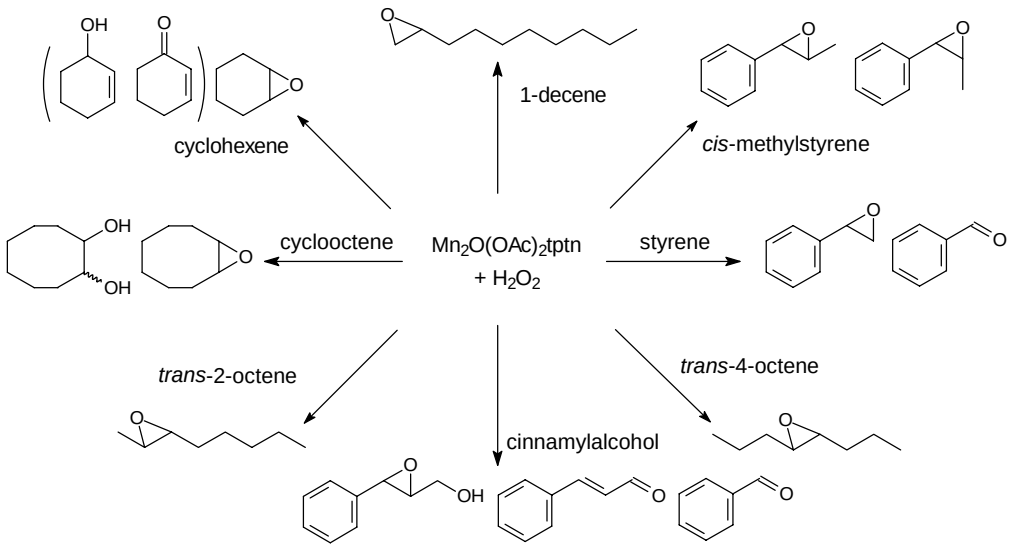
Preliminary screening in a number of different catalytic epoxidation reactions showed that complex **2.3**[37] (Scheme 5) based on tpen, featuring a two-carbon spacer between the three N-donor sets in the ligand, was not reactive in oxidation reactions. In sharp contrast complex

2.4[37] ($Mn_2O(OAc)_2$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_2O_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_2O_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^oC 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.



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 $Mn(OAc)_3.3H_2O$, 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_2O_2*

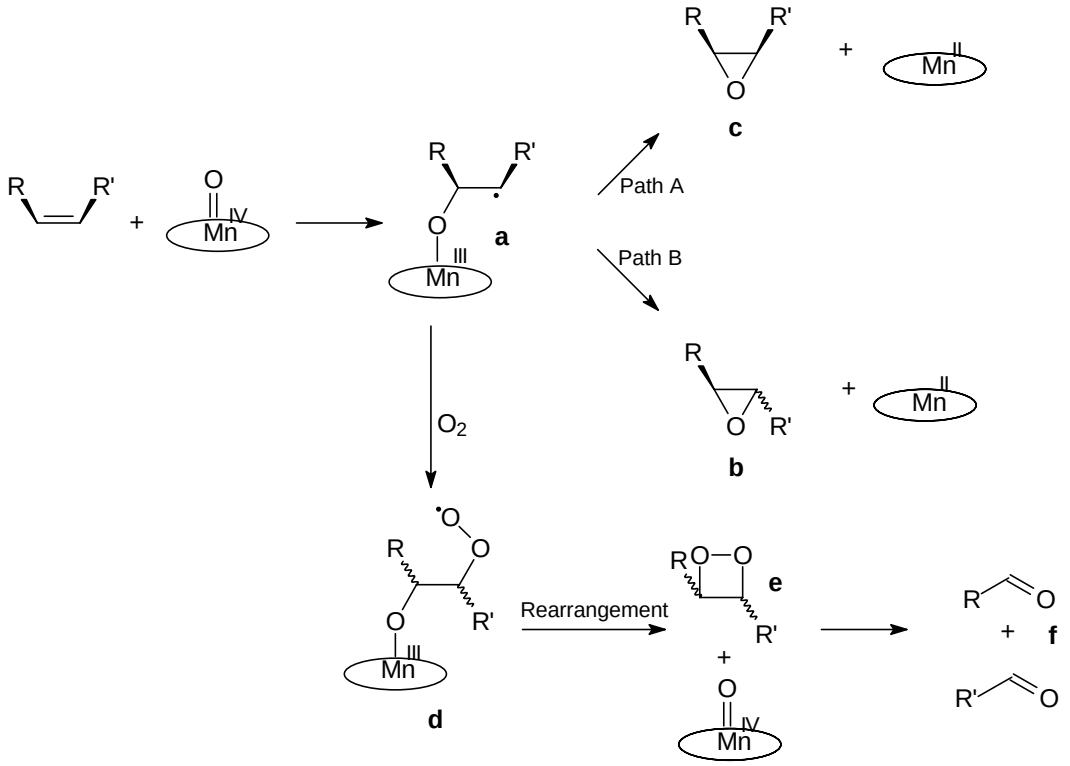
Table 1 *Oxidation of selected olefins with $Mn_2O(OAc)_2$tptn complex **2.4**.*[a]

Entry	Substrate	Product[b]	t.o.n.[c] 2h 298 K	t.o.n. 4h 298 K	t.o.n. 2h 273 K	t.o.n. 4h 273 K
1	styrene	styrene oxide	157	208	176	271
		benzaldehyde	5	75	2	14
2	cyclohexene	cyclohexene oxide	247	563	328	868
3	cyclooctene	cyclooctene oxide	193	636	262	575
		cis-diol	49	93	61	48
4	cinnamyl	cinnamyl oxide	208	219	219	321
	alcohol	cinnamyl aldehyde	69	85	70	86
		benzaldehyde	22	47	21	46
5	*trans*-2-octene	*trans*-2-octene oxide	118	188	178	248
6	*trans*-4-octene	*trans*-4-octene oxide	97	148	153	210
7	1-decene	1-decene oxide	28	34	80	97
8	*cis*-β-methyl-	*cis*-oxide	19	84	23	115
	styrene	*trans*-oxide	43	104	44	147

(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_2O_2 in the presence of $Mn_2O(OAc)_2$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).[39] 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.[40] Subsequent cleavage of the dioxetane yields the by-product benzaldehyde (**f**).



Scheme 7 *Radical pathways to epoxides and fragmentation to benzaldehydes.*

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.

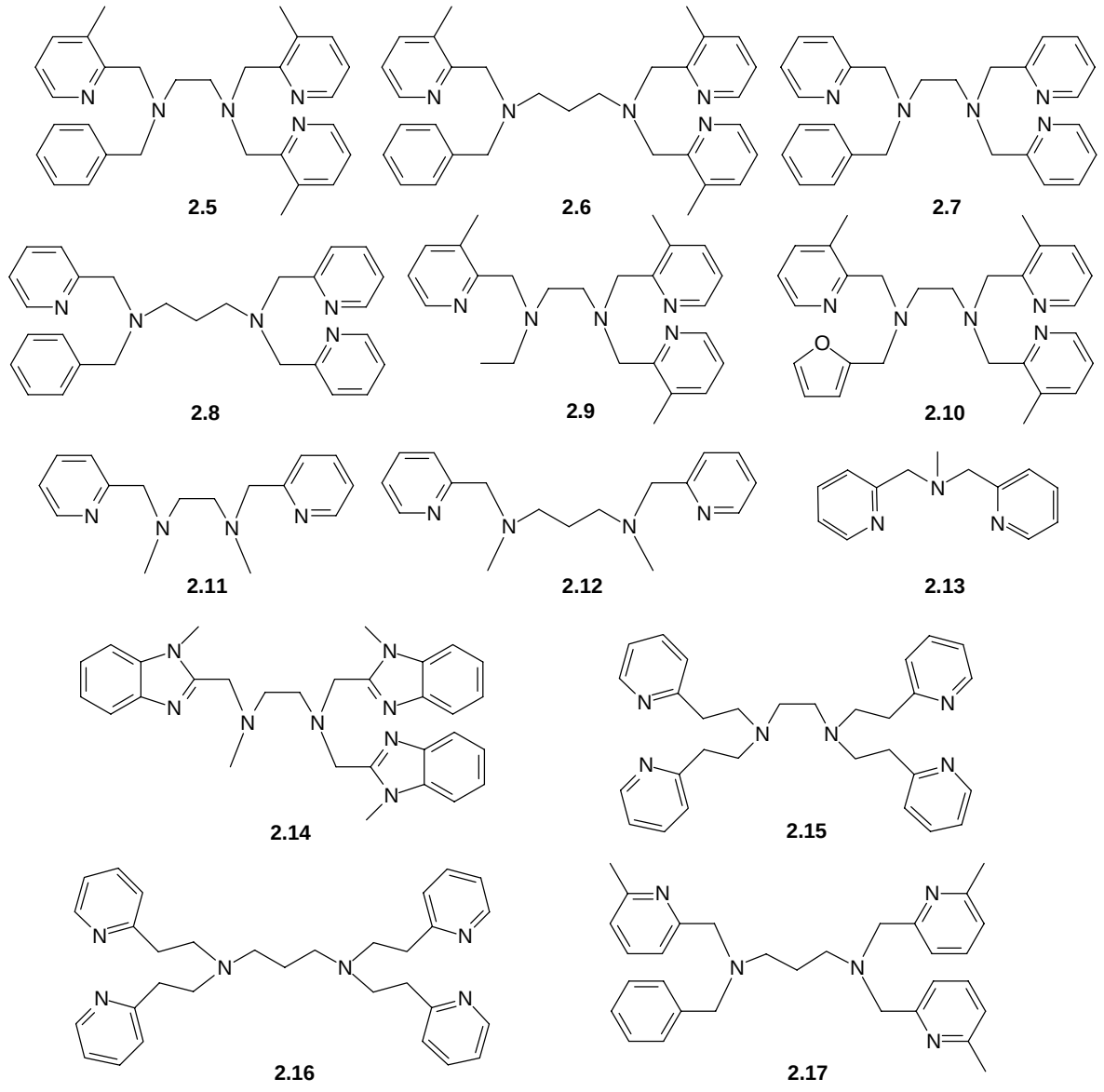
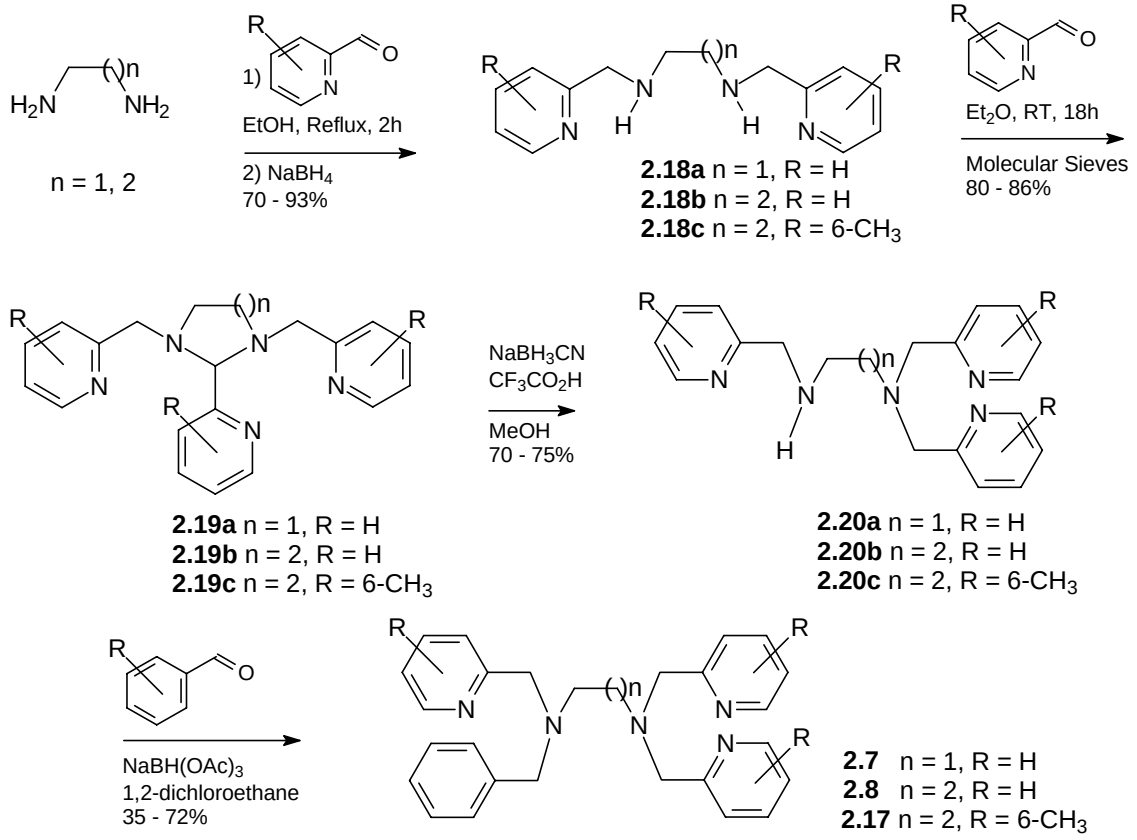


Figure 2 *Stuctures of modified ligands.*

2.4 Synthesis of the ligands

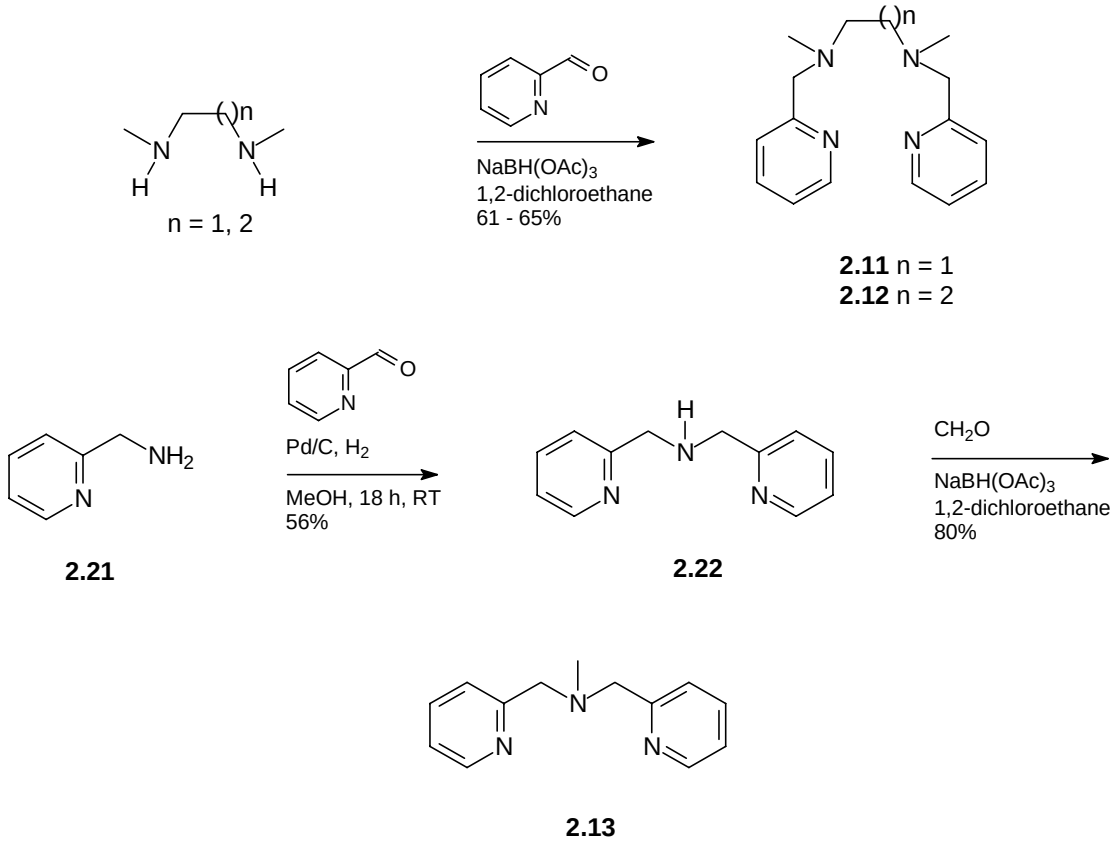
Derivatives **2.7**, **2.8** and **2.17** were prepared according to the general reaction procedure depicted in Scheme 8. The multistep synthesis started with a reductive amination of 2-pyridinecarboxaldehyde (or 6-methyl-2-pyridinecarbaldehyde for the synthesis of ligand **2.17**) with ethylene- or 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.*[41] Subsequently aminal **2.19** was reduced with $NaBH_3CN$ 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 $NaBH(OAc)_3$)[42] 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.*

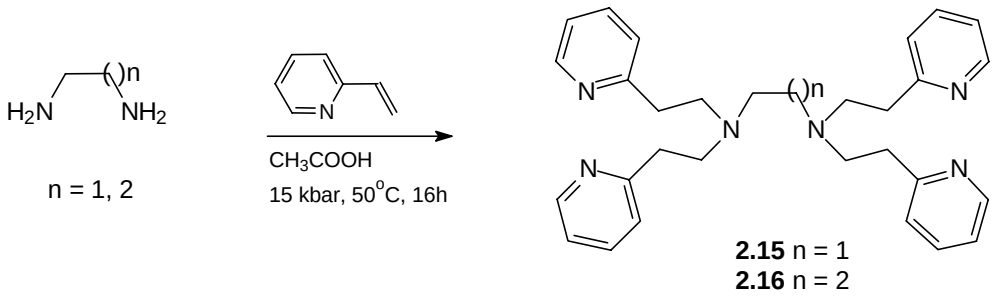
Ligands **2.11** and **2.12** were synthesised by a reductive amination reaction of *N,N'*-dimethylethylamine (or *N,N'*-dimethylpropylamine) and 2-pyridinecarboxaldehyde with $NaBH(OAc)_3$[42] in 1,2-dichloroethane. After purification by column chromatography the

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 *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 *et al.*[42] to obtain the final product **2.13** in 80% chemical yield.



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°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.



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^oC 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.[43] 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 CH_3-groups on the 3-position, the complex based on ligand **2.17** with the CH_3-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[44] 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 $Mn_2O(OAc)_2$tptn (**2.4**, Scheme 5).

Table 2 *Oxidation of selected alkenes to epoxides in the presence of manganese complex, in situ formed from $Mn(OAc)_3.2H_2O$ and 0.1 mol % of ligand (**2.5** - **2.10**).*[a]

Turnover numbers[c] after 4 h for ligands **2.5** - **2.10**						
Substrate[b]	**2.5**	**2.6**	**2.7**	**2.8**	**2.9**	**2.10**
cyclohexene	569	636	209	582	589	606
cyclooctene[d]	697(15)	678(26)	250	554	606(28)	635(58)
trans-2-octene	166	167	95	506	227	189
trans-4-octene	295	323	107	481	228	327
1-decene	175	65	0	135	77	41
cinnamylalcohol[e]	192(32,66)	181(31,72)	0(52,67)	0(55,66)	0	0

(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, cinnamylaldehyde).

Table 3 *Oxidation of selected alkenes to epoxides in the presence of manganese complex, in situ formed with $Mn(OAc)_3.2H_2O$ and 0.1 mol% of ligand (**2.11** - **2.16**).*[a]

Turnover numbers[c] after 4 h for ligands **2.11** - **2.16**						
Substrate[b]	**2.11**	**2.12**	**2.13**	**2.14**	**2.15**	**2.16**
cyclohexene	157	430	205	6	0	0
cyclooctene	0	573	213	0	0	0
trans-2-octene	0	162	93	0	0	0
trans-4-octene	44	177	68	0	0	0
1-decene	0	0	0	0	0	0
cinnamylalcohol	0	0	0	0	0	0

(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.

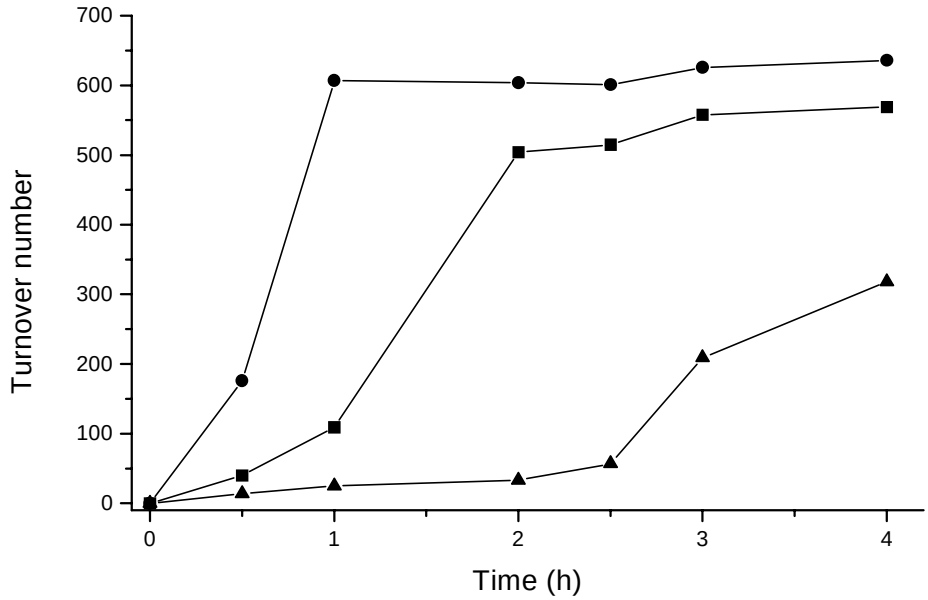


Figure 3 *Catalytic oxidation of cyclohexene to cyclohexene oxide using H_2O_2 and in situ prepared catalysts with*: ■ *Ligand* ***2.5***, ● *Ligand* ***2.6*** *and* ▲ *Ligand* ***2.7***.

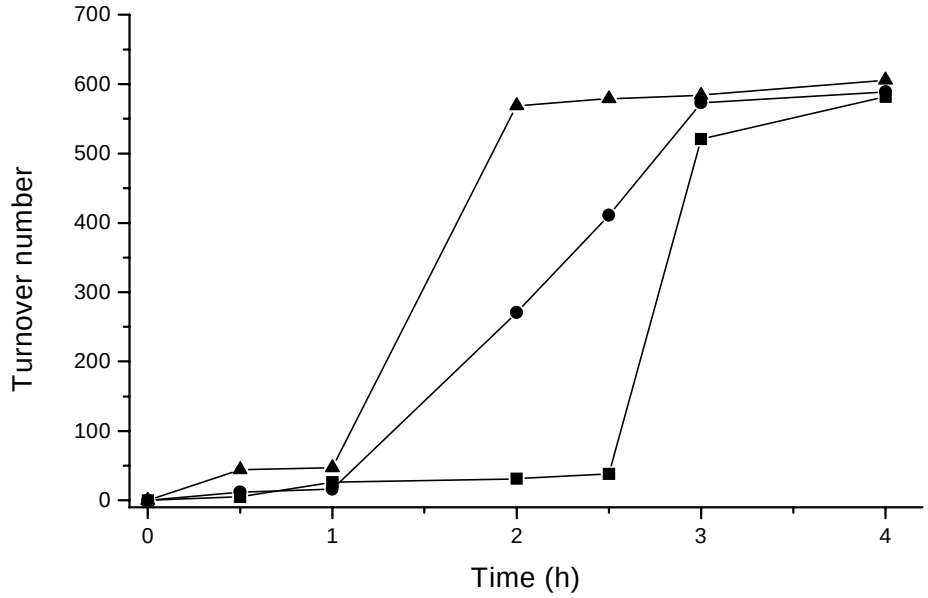


Figure 4 *Catalytic oxidation of cyclohexene to cyclohexene oxide using H_2O_2 and in situ prepared catalysts with:* ■ *Ligand* ***2.8***, ● *Ligand* ***2.9*** *and* ▲ *ligand* ***2.10***.

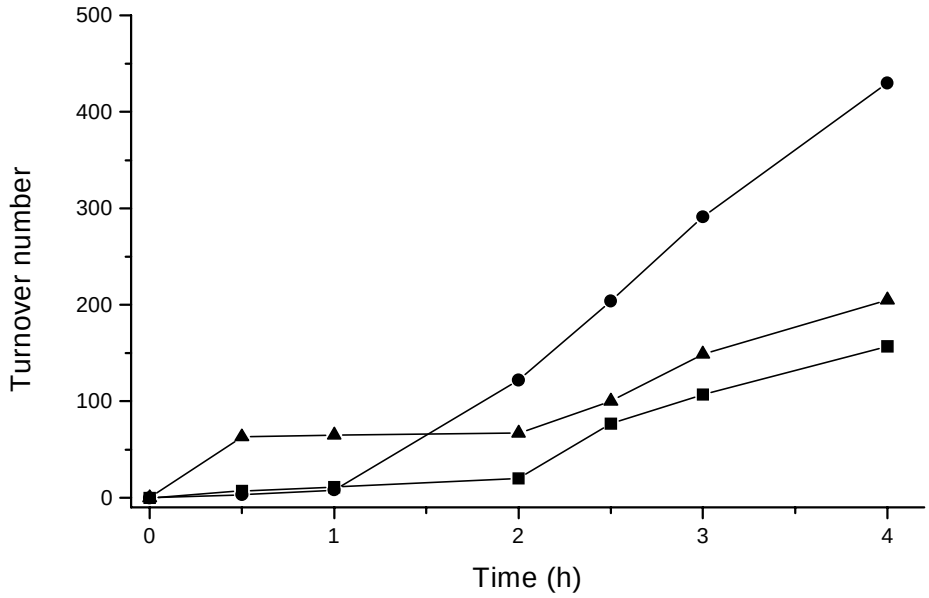


Figure 5 *Catalytic oxidation of cyclohexene to cyclohexene oxide using H_2O_2 and in situ prepared catalysts with:* ■ *Ligand* ***2.11***, ● *Ligand* ***2.12***, ▲ *Ligand* ***2.13***.

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

based on H_2O_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 $Mn_2O(OAc)_2$tptn (**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_2O_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 Al_2O_3 were used for column chromatography. ^{1}H-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 ($CHCl_3$ = 7.27 ppm). ^{13}C-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 ($CHCl_3$) = 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 $\pm$ 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^{o}C under a nitrogen atmosphere. After stirring for 2 min, excess of hydrogen peroxide (1.0 ml of 30% aq. H_2O_2, 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.

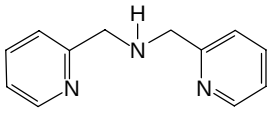
Catalytic oxidation reactions (*in situ* experiments with ligands 2.5 - 2.17)

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 $Mn(OAc)_3.2H_2O$ 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 $Mn(OAc)_3.2H_2O$ was used. After stirring for 15 min substrate was added at 0^{o}C under a nitrogen atmosphere. After stirring for 2 min excess of hydrogen peroxide (1.0 ml of 30% aq. H_2O_2, 9.8 M) was added. The progress of the reaction was monitored by GC.

Synthesis of ligands

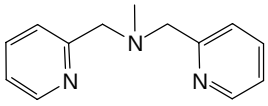
Ligands **2.5**, **2.6**, **2.9**, and **2.10** were synthesised by dr. Minze Rispens[48]

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



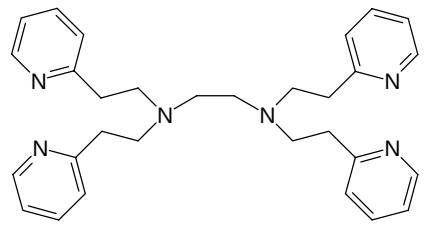
To a solution of 2-pyridinecarboxaldehyde (5.0 g, 46.7 mmol) and 2-(aminomethyl)pyridine (5.1 g, 47.2 mmol) in methanol (100 ml) was added a catalytic amount of Pd/C (10%). After stirring for 24h under a H_2 atmosphere (1 atm) the mixture was filtered over Celite. The solvent was evaporated under reduced pressure and the residue was purified by vacuum distillation at 140^{o}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)**



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 18h 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_2Cl_2 (3 x 30 ml) and the combined organic layers were washed with 1 M NaOH (20 ml) and dried (Na_2SO_4). Evaporation of the solvent followed by column chromatography (Al_2O_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 calcd. for $C_{13}H_{15}N_3$ 213.127, found 213.128.

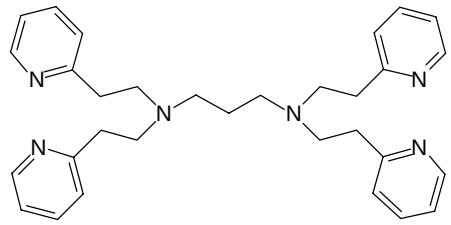
N^1,N^1,N^2,N^2-Tetrakis[2-(2-pyridinyl)ethyl]-1,2-ethanediamine (2.15)



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_2Cl_2 (30 ml), washed with aqueous 1 M NaOH (30 ml) and washed with water (30 ml). The organic layers were dried over Na_2SO_4 and evaporated to leave a dark red oil. The oil was purified by column chromatography (Al_2O_3, akt. II - III, CH_2Cl_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): δ 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): δ 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.

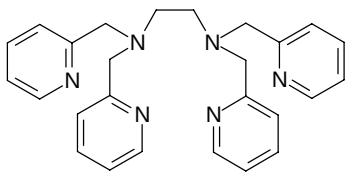
N^1,N^1,N^3,N^3-Tetrakis[2-(2-pyridinyl)ethyl]-1,3-propanediamine (2.16)



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_2O_3, akt. II - III, CH_2Cl_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): δ 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): δ 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.

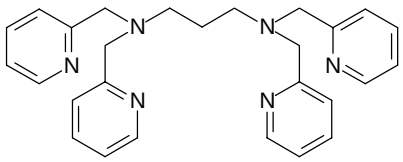
N^1,N^1,N^2,N^2-Tetrakis(2-pyridinylmethyl)-1,2-ethanediamine (2.2a)



To a solution of 2-(chloromethyl)pyridine hydrochloride (24.4 g, 148.7 mmol) in CH_2Cl_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_2Cl_2 (3 x 150 ml) and the combined organic layers were dried (Na_2SO_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%).

^{1}H-NMR (300 MHz): δ 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): δ 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.

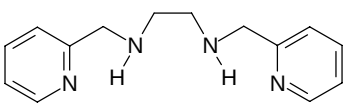
N^1,*N*^{1},*N*^{3},*N*^{3}-Tetrakis(2-pyridinylmethyl)-1,3-propanediamine (2.2b)



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): δ 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): δ 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.

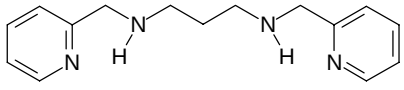
N^1,*N*^{2}-Bis(2-pyridinylmethyl)-1,2-ethanediamine (2.18a)



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_2Cl_2 (3 x 50 ml) and the combined organic layers were dried (Na_2SO_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): δ 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): δ 46.5 (CH_2), 52.6 (CH_2), 119.3 (CH), 119.7 (CH), 133.9 (CH), 146.6 (CH), 157.3 (C).

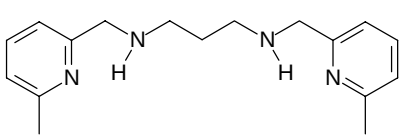
N^1,*N*^{3}-Bis(2-pyridinylmethyl)-1,3-propanediamine (2.18b)



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-pyridinecarbox-aldehyde (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).

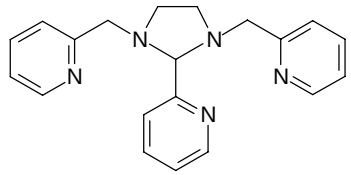
^{1}H-NMR (300 MHz): δ 1.70 (q, J = 6.78 Hz, 2H, CH_2), 2.68 (t, J = 6.96, 6.59 Hz, 4H, 2 x CH_2), 2,89 (br, 2H, NH), 3. 82 (s, 4H, 2 x CH_2), 7.06 (m, 2H, Py), 7.51 (m, 2H, Py), 7.55 (m, 2H, Py), 8.43 (m, 2H, Py). ^{13}C-NMR (75 MHz): δ 27.2 (CH_2), 45.5 (CH_2), 52.5 (CH_2), 119.4 (CH), 119.8 (CH), 133.9 (CH), 146.7 (CH), 156.8 (C).

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



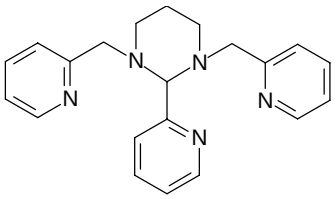
The same procedure as described for the preparation of compound **2.18a** was followed except that 1,3-propanediamine (0.25 g, 4.17 mmol), 6-methyl-2-pyridine-carbaldehyde (1.0 g, 8.26 mmol) and $NaBH_4$ (0.44 g, 11.5 mmol) was used to afford the product as a yellow oil (1.1 g, 3.87 mmol, 93% yield).
^{1}H-NMR (300 MHz): δ 1.42 (q, J = 6.96 Hz, 2H, CH_2), 2.47 (s, 6H, CH_3), 2.70 (t, J = 6.96 Hz, 4H, 2 x CH_2), 3.80 (s, 4H, 2 x CH_2), 3.80 (s, 4H, 2 x CH_2), 6.99 (d, J = 7.57 Hz, 2H, 2 x CH, Py), 7.04 (d, J = 7.57 Hz, 2H, 2 x CH, Py), 7.45 (t, J = 7.57, 7.81 Hz, 2H, 2 x CH, Py). ^{13}C-NMR (75 MHz): δ 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): δ 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): δ 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).

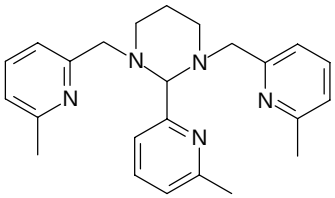
2-(2-Pyridinyl)-1,3-bis(2-pyridinylmethyl)hexahydropyrimidine (2.19b)



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}H-NMR (300 MHz): δ 1.50 (m, 1H, CH_2), 1.89 (m, 1H, CH_2), 2.24 (dt, J = 2.56 Hz, 2H CH_2), 2.97 (m, 2H, CH_2), 3.27 (d, J = 14.6 Hz, 2H, CH_2), 3.53 (d, J = 14.6 Hz, 2H, CH_2), 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}C-NMR (75 MHz): δ 25.0 (CH_2), 52.4 (CH_2), 60.5 (CH_2), 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).

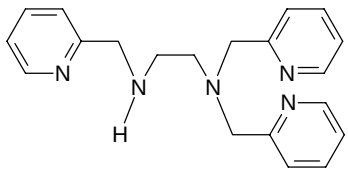
2-(6-Methyl-2-pyridinyl)-1,3-bis[(6-methyl-2-pyridinyl)methyl]hexahydropyrimidine (2.19c)



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}H-NMR (300 MHz): δ 1.61 (m, 1H, CH_2), 2.03 (m, 1H, CH_2), 2.40 (complex, 11H, 2H, CH_2, 9H, 3 x CH_3), 3.06 (m, 2H, CH_2), 3.33 (d, J = 15.1 Hz, 2H, CH_2), 3.60 (d, J = 15.1 Hz, 2H, CH_2), 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}C-NMR (75 MHz): δ 23.2 (CH_2), 24.4 (CH_3), 49.8 (CH_2), 54.2 (CH_2), 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).

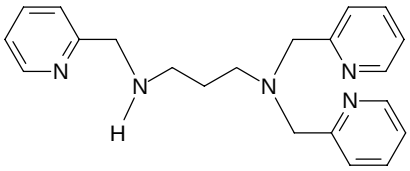
***N*^{1},*N*^{1},*N*^{2}-Tris(2-pyridinylmethyl)-1,2-ethanediamine (2.20a)**



To a solution of aminal **2.19a** (1.0 g, 3.04 mmol) in MeOH (50 ml) was added $NaBH_3CN$ (0.19 g, 3.02 mmol) and CF_3CO_2H (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_2Cl_2 (3 x 50 ml) and the combined organic layers were dried (Na_2SO_4). Evaporation of the solvent afforded **2.20a** (0.70 g, 2.13 mmol, 70%) as a yellow oil.

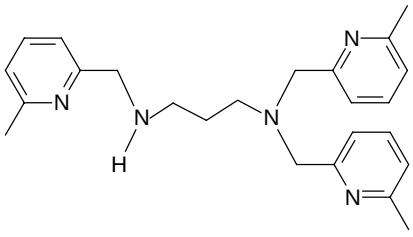
^{1}H-NMR (300 MHz): δ 2.40 (br, 1H, NH), 2.70 (s, 4H, 2 x CH_2), 3.75 (s, 6H, 3 x CH_2), 7.16 (m, 4H, Py), 7.52 (m, 5H, Py), 8.46 (m, 3H, Py). ^{13}C-NMR (75 MHz): δ 44.2 (CH_2), 51.6 (CH_2), 52.5 (CH_2), 58.1 (CH_2), 119.2 (CH), 119.4 (CH), 120.4 (CH), 120.7 (CH), 133.7 (CH), 133.8 (CH), 146.4 (CH), 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)



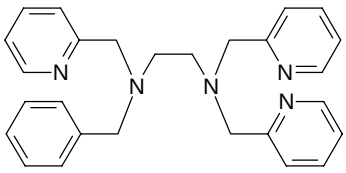
The same procedure as described for the preparation of compound **2.20a** was followed except that **2.19b** (1.0 g, 2.92 mmol), $NaBH_3CN$ (0.18 g, 2.90 mmol) and CF_3CO_2H (0.44 ml, 5.74 mmol) was used to afford the product as a yellow oil (0.74 g, 2.13 mmol, 73% yield).
^{1}H-NMR (300 MHz): δ 1.71 (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), $NaBH_3CN$ (0.20 g, 3.10 mmol) and CF_3CO_2H (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).

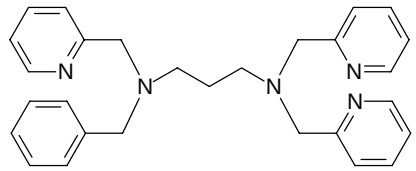
N^1-Benzyl-*N*^{1},*N*^{2},*N*^{2}-tris(2-pyridinylmethyl)-1,2-ethanediamine (2.7)



To **2.20a** (0.70 g, 2.10 mmol) in 1,2-dichloroethane (25 ml) was added benzaldehyde (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

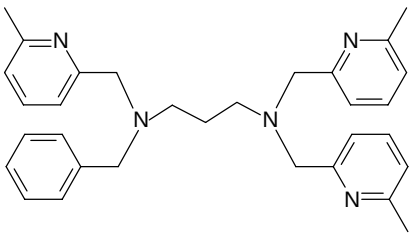
by extraction with CH_2Cl_2 (3 x 50 ml). The combined organic layers were dried (Na_2SO_4) and the solvent evaporated under reduced pressure to afford the crude product. The oil was purified by column chromatography (Al_2O_3, akt. II - III, ethyl acetate/hexane/triethylamine 10/4/1) to afford the pure 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_2O_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_2), 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.

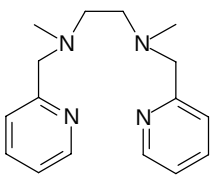
N^1-Benzyl-N^1,N^3,N^3-tris[(6-methyl-2-pyridinyl)methyl]-1,3-propanediamine (2.17)



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_2O_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

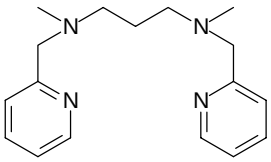
(CH_2), 61.1 (CH_2), 119.9 (CH), 120.0 (CH), 121.7 (CH), 121.8 (CH), 127.3 (CH), 128.6 (CH), 129.3 (CH), 137.1 (CH), 140.0 (C), 157.7 (C), 157.8 (C), 160.0 (C), 160.3 (C).

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



To a solution of *N*,*N'*-dimethylethylenediamine (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_2Cl_2 (3 x 30 ml) and the combined organic layers were washed with 1 M NaOH (20 ml) and dried (Na_2SO_4). Evaporation of the solvent followed by column chromatography (Al_2O_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): δ 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): δ 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_2O_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): δ 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): δ 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.

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Chapter 3

In Situ Prepared Manganese Complexes as Homogeneous Catalysts for Epoxidation Reactions with Hydrogen Peroxide

Abstract

*Based on N^1-(3-aminopropyl)-N^1-methyl-1,3-propanediamine (**3.3**) several heptadentate and pentadentate ligands have been synthesised and used for manganese-catalysed epoxidation reactions. High turnover numbers (up to 700) were obtained in acetone at ambient temperature using aqueous hydrogen peroxide.*

3.1 Introduction

The catalytic centres of many dinuclear metalloenzymes contain bridging carboxylate units.[1] Examples of enzymes with dinuclear metal cores include manganese catalases[2] and proteins that employ metal ions to activate molecular oxygen.[3] Ligands with carboxylate moieties and the corresponding metal complexes have been successfully studied as model compounds for dinuclear metalloenzymes.[4] Carboxylate bridged biomimetic complexes are typically formed in solution by self-assembly. However, the dinuclear complexes are often not stable and dissociate into mononuclear species.[4] The use of multidentate ligands can enhance the stability. Besides the efforts to synthesise multidentate dinucleating ligands incorporating bridging carboxylate units, a variety of nitrogen bridging ligands were synthesised to overcome dissociation problems.[5] Recently, Lippard *et al.* prepared a range of ligands based on 1,8-naphthyridine including several dinuclear metal complexes (Figure 1).[6]

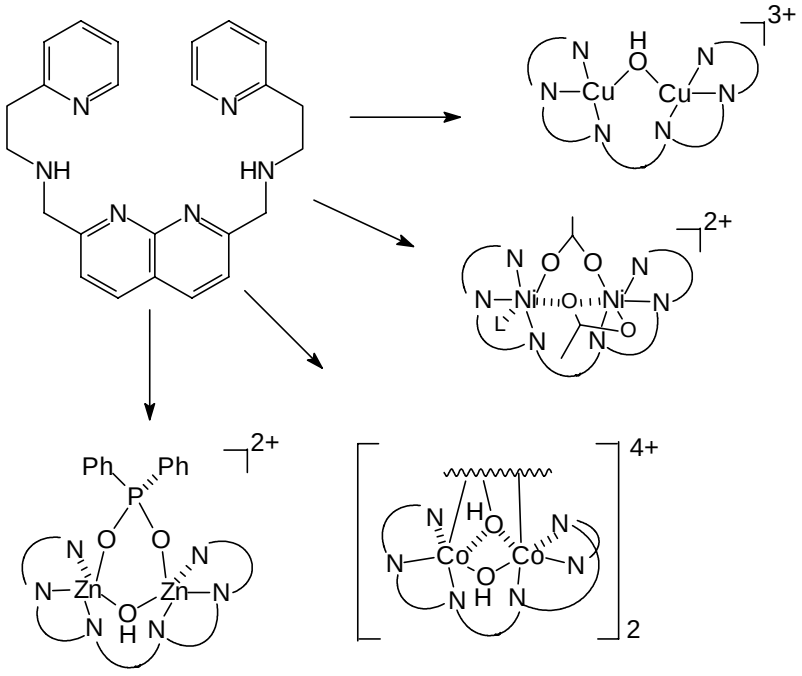
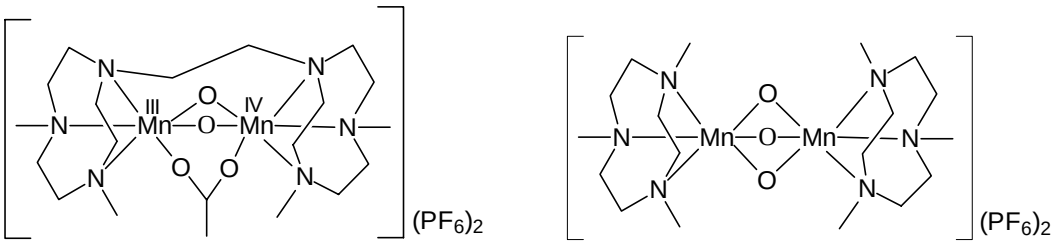


Figure 1 *Novel naphthyridine based dinucleating ligand.*[7]

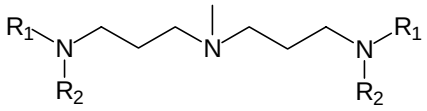
Dinuclear copper(II), zinc(II), nickel(II), and tetranuclear cobalt(II) complexes were obtained as shown in Figure 1. The metallocomplexes were used to mimic the physical and biological properties of a variety of metalloproteins.[7,8] These model compounds showed enhanced stability compared to the initial carboxylate-based model systems. For example the dinuclear zinc(II) derivative was successfully used to mimic metallohydrolases, by catalysing the transesterification of 2-hydroxypropyl-4-nitrophenylphosphate, a model substrate for RNA.[9] Urease, an enzyme that catalyses the hydrolysis of urea and small amide substrates, was modelled by the dinuclear nickel complex.[10] The activity and selectivity of catalysts are largely influenced by the nature of the ligands. For example, studying the bleaching capacity of Mn-complexes based on tacn ligands (see also Chapter 2) revealed higher bleach performance with the ethylene bridged dinuclear Mn-complex **3.1** compared to catalyst **3.2** (Figure 2).[11] At high temperature this effect appears to be related to the stability of this mixed-valence Mn-species.



3.1 **3.2**

Figure 2 *Manganese complexes based on tmtacn as bleaching catalysts.*

Although solvent and temperature conditions can also have a large influence on the catalyst turnovers, fine-tuning of steric and electronic requirements by introduction of different substituents in the ligands is often essential to accomplish efficient oxidation activity. From the results of the epoxidation reactions described in the previous chapter it is evident that a number of related ligands can provide a variety of active manganese epoxidation catalysts. Several modifications in the overall structure were introduced and studied. Influences like *e.g.* spacer length, additional substituents at pyridine rings or the introduction of other functional groups attached to the alkyl backbone were examined during catalytic epoxidation reactions and proved to have a strong influence on activity.[12] In this chapter we describe the synthesis and catalytic activity of manganese oxidation catalysts based on ligands synthesised from N^1-(3-aminopropyl)-N^1-methyl-1,3-propanediamine (**3.3**). The general structure of the backbone is depicted in Figure 3.



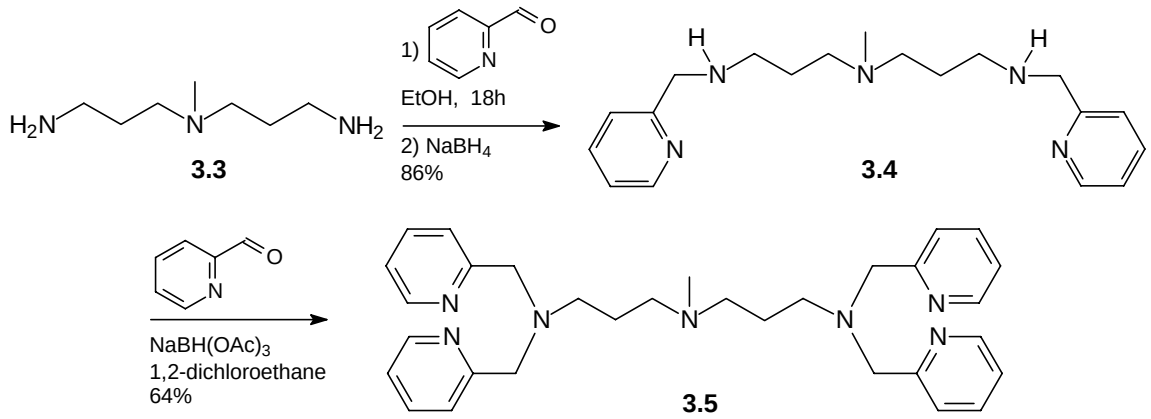
3.3

Figure 3 *General structure for the ligands described in this chapter*.

3.2 Synthesis of the ligands

The two primary amine functionalities of triamine **3.3** are available for the introduction of modifications by reactions like alkylation or reductive amination reactions.[13] Introduction of alkyl groups on the primary amine can be accomplished by formation of the corresponding imine followed by reduction to the corresponding secondary amine. Although the imines are often easily isolated, they can also be reduced in a one-pot procedure. Several reducing agents can be applied in the reductive amination of aldehydes and ketones including borane-pyridine[14] and zinc-acetic acid.[15] However, the most general and frequently used reagents are sodium borohydride ($NaBH_4$),[16] sodium triacetoxy borohydride ($NaBH(OAc)_3$)[17] or hydrogen in the presence of a metal catalyst.[18] Recently, a new and mild method was developed using decaborane ($B_{10}H_{14}$) as reducing agent with methanol as solvent.[19]

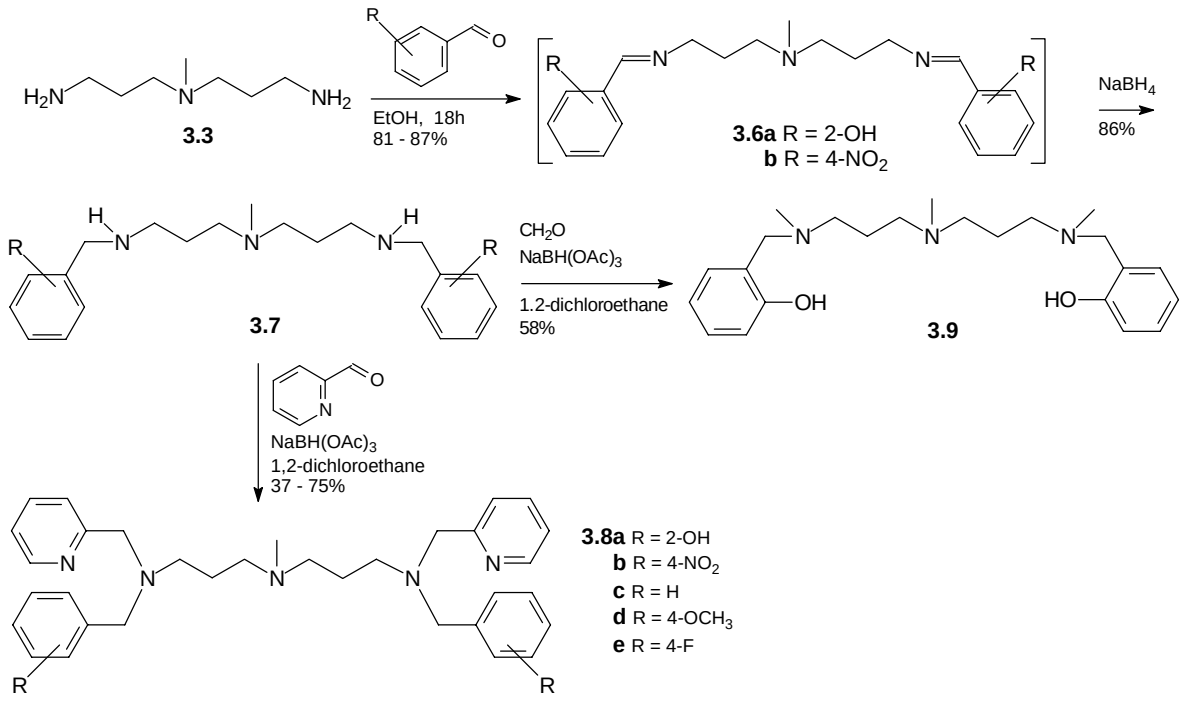
Subsequently the secondary amine can be further alkylated via a second reductive amination applying reducing agents such as sodium cyanoborohydride ($NaBH_3CN$)[20] or $NaBH(OAc)_3$.[17] The latter reagent eliminates the risk of residual hydrogen cyanide in the product after the work-up procedures by employing $NaBH_3CN$. Relying on the successful reductive amination procedures using $NaBH_4$ and $NaBH(OAc)_3$ described in Chapter 2, heptadentate ligand **3.5** was obtained in satisfactory yields using a two step synthesis as given in Scheme 1. As the crude reaction mixtures of the first alkylation step contained only minor impurities according to ^{1}H-NMR, they were used without further purification. The most indicative resonances in the ^{1}H-NMR ($CDCl_3$) spectra of **3.4** and **3.5** appear at 3.81 ppm and 8.46 ppm, which are assigned to the CH_2-pyridine moieties and pyridine ortho-hydrogen atoms after alkylation of triamine **3.3**, respectively.



Scheme 1 *Synthesis of heptadentate ligand **3.5**.*

Next the pentadentate ligands **3.8a - e** were synthesised as depicted in Scheme 2. Imines **3.6a** and **3.6b** crystallised spontaneously and were reduced with $NaBH_4$ to the corresponding amines (**3.7a** and **3.7b**) after isolation and characterisation. Compounds **3.7c - 3.7e** were obtained using the same synthesis method as used for **3.7a** and **3.7b** except that the

imines were reduced *in situ*. Subsequently amines **3.7a - 3.7e** were converted to ligands **3.8a - 3.8e** by a second reductive amination reaction with 2-pyridinecarboxaldehyde and purified by column chromatography with moderate to satisfactory yields. In some cases low yields were found after tedious and often difficult purification using column chromatography.[21] Probably this is due to hydrogen bonding of the amines to the stationary phase resulting in tailing on SiO_2 or Al_2O_3. Ligand **3.9** was obtained after methylation of **3.7a** by a reductive amination with formaldehyde and $NaBH(OAc)_3$ in 58% yield, following the synthesis procedure of Abdel-Magid *et al*.[17b,c]



Scheme 2 *Synthesis of pentadentate ligands **3.8a** - **3.8e** and **3.9**.*

3.3 In situ prepared manganese complexes as homogeneous epoxidation catalysts

Typical catalytic reactions were performed at 0°C under a nitrogen atmosphere using acetone as solvent. The manganese catalyst based on ligand **3.5** was made by mixing 1 equivalent of ligand with 2 equivalent of $Mn(OAc)_3$, followed by addition of substrate and oxidant (H_2O_2). The catalyst based on the heptadentate ligand **3.5** resulted in high epoxidation activity for the conversion of several alkenes such as cyclohexene, cyclooctene, *trans*-2-octene, *trans*-4-octene or 1-decene, as major product the corresponding epoxide was found. The results are summarised in Table 1 and the reaction time profile is given in Figure 4. For the selected olefins generally up to 300 turnover numbers were found. Addition of a second aliquot (1 ml of 30% aq. H_2O_2, 9.8M, 9.8 equivalents with respect to substrate) of

oxidant resulted in a considerable increase in epoxide yield after 4h (total t.o.n.'s over 600, for cyclooctene). It needs to be emphasised that during the epoxidation reaction of cyclic alkenes (especially for cyclohexene) besides the epoxides almost no allylic oxidation products were observed. In control experiments by omission of ligand strong peroxide decomposition and no epoxide formation was seen, as discussed in Chapter 2. Satisfactory results were also found for internal alkenes *e.g.* entries 3 and 4, whereas slightly lower yields are found for terminal linear alkenes.

Table 1 *Oxidation of selected alkenes to epoxides in the presence of Mn-complex, in situ formed from 0.2 mol% $Mn(OAc)_3.2H_2O$ and 0.1 mol % of ligand **3.5**.*[a]

Entry	Substrate	Product[b]	t.o.n.[c] 2h 273 K	t.o.n.[c] 4h 273 K
1	cyclohexene	cyclohexene oxide	484	558
2	cyclooctene	cyclooctene oxide	299	668
		cis-diol	24	56
3	*trans*-2-octene	*trans*-2-octene oxide	262	436
4	*trans*-4-octene	*trans*-4-octene oxide	234	367
5	1-decene	1-decene oxide	169	325

(a) Experimental conditions, see experimental section. (b) All products were identical to independently synthesised samples as identified by GC and ^{1}H-NMR. (c) Turnover numbers in mole product per mole catalyst.

For screening the complexes based on ligands **3.8a - 3.8e** and **3.9**, 1 equivalent of $Mn(OAc)_3$ was used. In sharp contrast to **3.5**, the catalysts based on the ligands **3.8a - 3.8e** and **3.9** turned out to be completely inactive during catalytic epoxidation reaction. No oxidation products but only starting material was found after 4h reaction time. In addition preliminary experiments employing 1 equivalent of ligands **3.8** and 2 equivalents $Mn(OAc)_3$ showed no oxidation products.

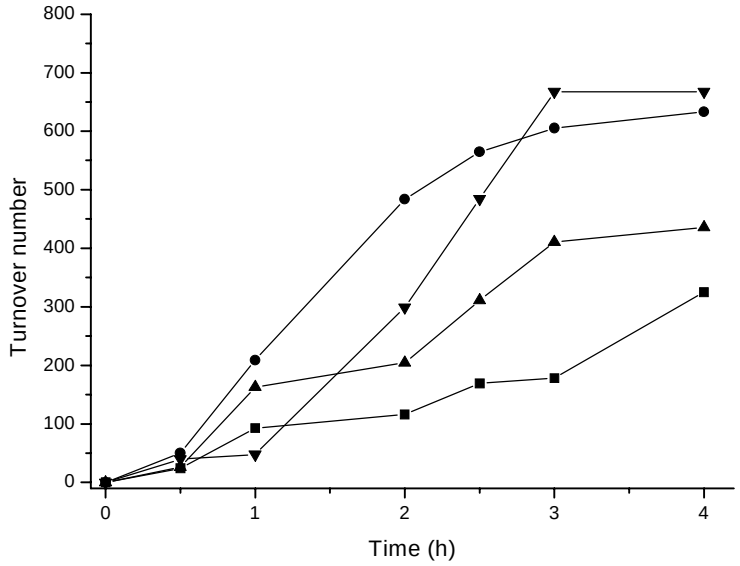
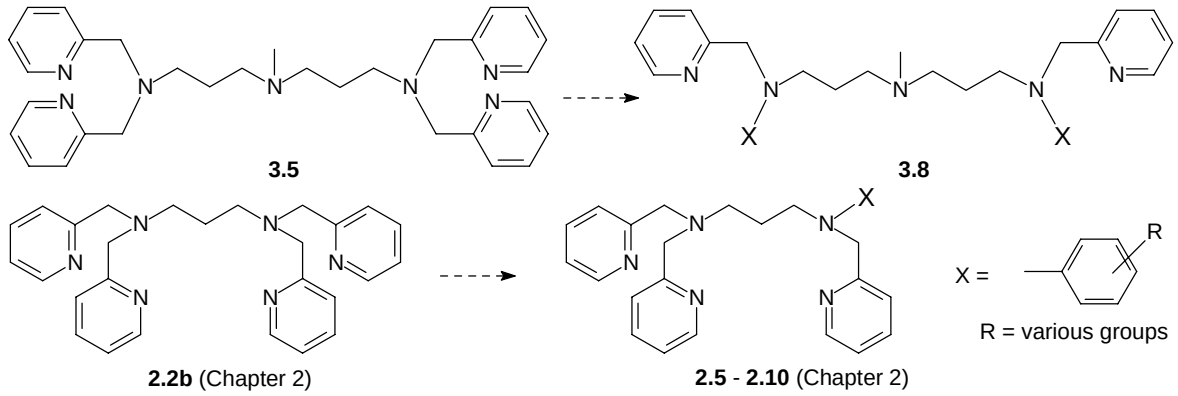


Figure 4 *Time course of the catalytic oxidation of different alkenes to the corresponding epoxides by using H_2O_2 and in situ prepared Mn-catalysts based on ligand **3.5**. ■ 1-decene, ▲ trans-2-octene, ● cyclohexene, ▼ cyclooctene.*

3.4 Discussion and conclusions

Several ligands were synthesised from N^1-(3-aminopropyl)-N^1-methyl-1,3-propanediamine (**3.3**). Although satisfactory yields were found and a number of different substituents were introduced, the *in situ* prepared manganese catalysts from the pentadentate ligands (**3.8a** - **3.8e**) turned out to be unreactive. However, the manganese catalyst prepared *in situ* from heptadentate ligand **3.5** was found to be a very active epoxidation catalyst. Turnover numbers of 300 could be readily reached for the oxidation of several alkenes and the oxidation activity is in some extent comparable to the extensively studied oxidation catalyst Mn-tmtacn[22] or Mn-tptn.[23] Using cyclooctene as substrate, besides epoxide formation also *cis*-diol (56 t.o.n.'s) was found as a side product. Similar amounts of diol were found by employing tptn-based complexes (Chapter 2; for more details about *cis*-dihydroxylation, see Chapter 4).

As already was discussed in Chapter 2, it is clear that structural modifications have large influences on the activity of the catalyst. Switching from heptadentate ligands **3.5** to pentadentate ligands **3.8** resulted in inactive epoxidation catalysts (Scheme 3).



Scheme 3 *Structural modifications of ligands.*

These results are in sharp contrast to the results obtained with the pentadentate modified tptn ligands **2.2b** described in Chapter 2 (for example, see ligands **2.5 - 2.10**, Chapter 2). The main difference of the active manganese catalysts based on pentadentate ligands **2.5 - 2.10** described in Chapter 2 and the ligands presented in this chapter are the number of pyridine functionalities. Employing the *in situ* prepared Mn-complexes using the ligands **2.11 - 2.13**, containing two pyridine groups, indeed some oxidation activity was observed. However, long induction periods were observed. This might indicate that at least three pyridine moieties are necessary to achieve active epoxidation catalysts.

3.5 Experimental section

General procedure and methods

For general information see Chapter 2.

GC equipment and analysis

GC analyses were performed as described in Chapter 2.

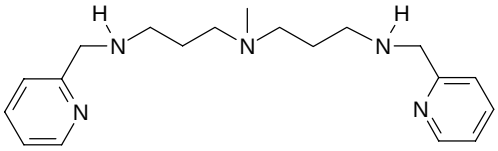
Catalytic oxidation reactions

Catalytic reactions with ligand **3.5** were started by mixing 1.0 ml of a 2.0 mM stock solution (in acetone) of $Mn(OAc)_3.2H_2O$ and 1 ml of a 1.0 mM stock solution of ligand. After stirring for 15 min 1.0 ml of a stock solution of 1.0 M of substrate and 0.5 M of internal standard at 0^oC under a nitrogen atmosphere were added. After stirring for 2 min, excess of hydrogen peroxide (1.0 ml of 30% aq. H_2O_2, 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. After 2h a second aliquot of oxidant (1.0 ml) was added and the catalytic reaction was stirred for another 2h. To establish the identity of the epoxides unequivocally the retention times and spectral data were compared to those of commercially available and

independently synthesised compounds. The same procedure as described for the catalytic reactions of the *in situ* prepared complex **3.5** was followed with the ligands **3.8a** - **e** and **3.9** except that the reactions were started by mixing 1.0 ml of a 1.0 mM stock solution of $Mn(OAc)_3.2H_2O$ and 1 ml of a 1.0 mM stock solution of ligand.

Synthesis of the ligands

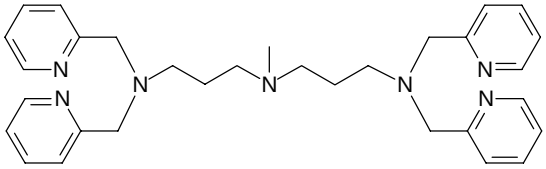
***N*-Methyl-*N*,*N*-bis{3-[(2-pyridinylmethyl)amino]propyl}amine (3.4)**



To a solution of 3,3'-diamino-N-methyldipropylamine (**3.3**, 1.0 g, 6.90 mmol) in ethanol (50 ml) was added 2-pyridinecarboxaldehyde (1.64 g, 15.2 mmol). After stirring for 16h at room temperature $NaBH_4$ (1.0 g, 26.3 mmol) was added in small portions. After stirring for 2h at room temperature the reaction mixture was acidified to pH 1 - 2 using a 4 M HCl-solution and stirred for another 0.5h. After the solution was brought to pH 14 using an aqueous NH_3-solution (12.5% in water), the mixture was extracted with CH_2Cl_2 (3 x 50 ml). The organic layers were dried (Na_2SO_4) and the solvent evaporated under reduced pressure to afford the product as a red oil (1.96 g, 6.0 mmol, 87% yield) which was directly used for the synthesis of **3.5** without further purification.

^{1}H-NMR (300 MHz): δ 1.62 (q, J = 7.14 Hz, 4H, 2 x CH_2), 2.12 (s, 5H, CH_3, 2 x NH), 2.32 (t, J = 7.32 Hz, 4H, 2 x CH_2), 2.60 (t, J = 6.95 Hz, 4H, 2 x CH_2), 3.81 (s, 4H, 2 x CH_2), 7.06 (m, 2H, Py), 7.55 (m, 2H, Py), 8.46 (d, J = 4.4 Hz, 2H, Py). ^{13}C-NMR (75 MHz): δ 28.3 (CH_2), 42.8 (CH_3), 48.8 (CH_2), 55.9 (CH_2), 56.6 (CH_2), 122.4 (CH), 122.8 (CH), 136.9 (CH), 149.8 (CH), 160.5 (C). MS (EI^+): m/z 327.

***N*,*N*-Bis{3-[bis(2-pyridinylmethyl)amino]propyl}-*N*-methylamine (3.5)**

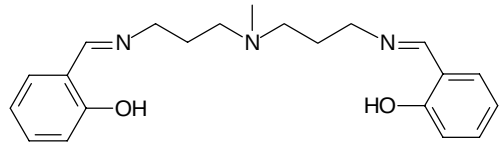


To a solution of **3.4** (1.0 g, 3.05 mmol) in 1,2-dichloroethane (50 ml) was added 2-pyridinecarboxaldehyde (0.68 g, 6.4 mmol). During 1h $NaBH(OAc)_3$ (1.30 g, 12.2 mmol) was added in small portions. After stirring for 24h at room temperature an aqueous saturated solution of $NaHCO_3$ was added and the mixture was stirred for another 0.5h. The mixture was extracted with CH_2Cl_2 (3 x 50 ml). The organic layers were dried over Na_2SO_4 and the solvent evaporated to leave a dark red oil. The oil was purified by chromatography (Al_2O_3, akt. II - III, ethyl acetate/hexane/triethylamine 10:4:1) to afford the product as a yellow oil (0.99 g, 1.95 mmol, 64%).

^{1}H-NMR (300 MHz): δ 1.65 (q, J = 7.20 Hz, 4H, 2x CH_2), 2.09 (s, 3H, CH_3), 2.25 (t, J = 7.51 Hz, 4H, 2x CH_2), 2.52 (t, J = 7.14 Hz, 4H, 2x CH_2), 3.78 (s, 8H, 4x CH_2), 7.11 (t, J = 6.05 Hz, 4H Py), 7.49 (d, J = 7.69 Hz, 4H, Py), 7.61 (dt, J = 1.46, 6.96 Hz, 4H, Py), 8.49 (d, J =

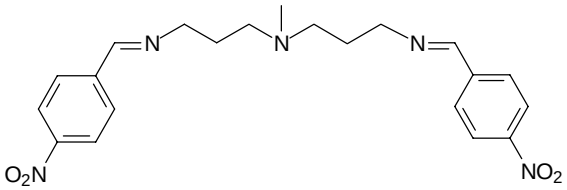
4.40 Hz, 4H, Py). ^{13}C-NMR (75 MHz): δ 22.8 (CH_2), 40.1 (CH_3), 50.9 (CH_2), 53.9 (CH_2), 58.9 (CH_2), 120.4 (CH), 121.4 (CH), 134.9 (CH), 147.5 (CH), 158.2 (C). HRMS calcd. for $C_{31}H_{39}N_7$ 509.327, found 509.327.

2-[({3-[(3-{[(*Z*)-(2-Hydroxyphenyl)methylidene]amino}propyl)(methyl)amino]propyl}-imino) methyl]phenol (3.6a)



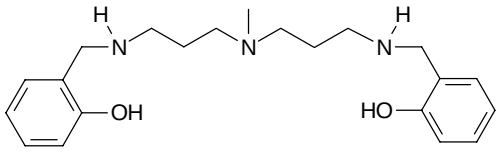
To a solution of 3,3'-diamino-N-methyldipropyl-amine (**3.3**, 10.0 g, 68.8 mmol) in ethanol (100 ml) was added salicylaldehyde (17.7 g, 145.1 mmol). After stirring for 16h at room temperature the solvent was evaporated under reduced pressure. The pure product (21.2 g, 60.1 mmol, 87% yield) was obtained as a yellow solid after crystallisation from ethanol.
^{1}H-NMR (300 MHz): δ 1.80 (q, J = 6.96 Hz, 4H, 2 x CH_2), 2.38 (t, J = 7.14 Hz, 4H, 2 x CH_2), 3.57 (t, J = 6.78 Hz, 2 x CH_2), 6.84 (m, 4H, Ar), 7.21 (m, 4H, Ar), 8.28 (s, 2H, 2 x CH), 13.53 (br, 2H, 2 x OH). ^{13}C-NMR (75 MHz): δ 29.1 (CH_2), 42.7 (CH_3), 55.7 (CH_2), 55.8 (CH_2), 117.6 (CH), 119.0 (CH), 119.3 (CH), 131.7 (CH), 132.7 (CH), 151.6 (CH), 161.9 (C), 165.5 (C).

***N*-Methyl-*N*-(3-{[(*E*)-(4-nitrophenyl)methylidene]amino}propyl)-*N*-(3-{[(*Z*)-(4-nitrophenyl)methylidene]amino}propyl)amine (3.6b)**



The same procedure as described for the preparation of ligand **3.6a** was followed except that 3,3'-diamino-N-methyldipropylamine (2.0 g, 13.8 mmol) and 4-nitrobenzaldehyde (4.4 g, 29.0 mmol) were used. The pure product (4.6 g, 11.2 mmol, 81% yield) was obtained as a yellow solid after crystallisation from ethanol.
^{1}H-NMR (300 MHz): δ 1.89 (q, J = 7.14 Hz, 4H, 2 x CH_2), 2.25 (s, 3H, CH_3), 2.46 (t, J = 7.14 Hz, 4H, 2 x CH_2), 3.70 (t, J = 6.59 Hz, 4H, 2 x CH_2), 7.86 (d, J = 8.79 Hz, 4H, Ar), 8.25 (d, J = 8.78 Hz, 4H, Ar), 8.36 (s, 2H, CH). ^{13}C-NMR (75 MHz): δ 25.9 (CH_2), 39.7 (CH_3), 52.8 (CH_2), 57.3 (CH_2), 121.3 (CH), 126.1 (CH), 139.2 (C), 146.4 (C), 156.2 (CH). MS (EI^+): m/z 411.

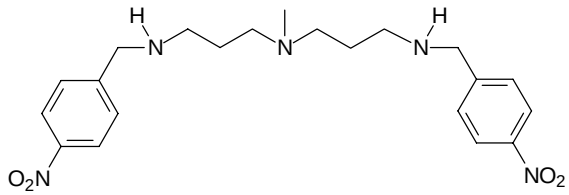
2-[({3-[{3-[(2-Hydroxybenzyl)amino]propyl}(methyl)amino]propyl}amino)-methyl]phenol (3.7a)



To a solution of **3.6a** (2.0 g, 5.66 mmol) in ethanol (50 ml) was added $NaBH_4$ (0.43 g, 11.3 mmol) in small portions. After stirring for 2h at room

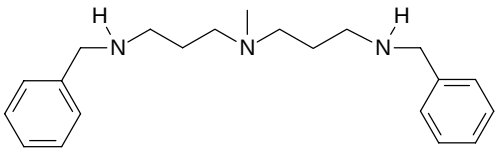
temperature the reaction mixture was acidified to pH 1 - 2 using a 4 M HCl-solution and stirred for another 0.5h. After the solution was brought to pH 14 using an aqueous NH_3-solution (12.5% in water), the mixture was extracted with CH_2Cl_2 (3 x 50 ml). The organic layers were dried (Na_2SO_4) and the solvent evaporated under reduced pressure to afford the product as a colourless oil (1.33 g, 3.74 mmol, 66% yield).
^{1}H-NMR (300 MHz): δ 1.68 (q, J = 6.78 Hz, 4H, 2 x CH_2), 2.17 (s, 3H, CH_3), 2.38 (t, J = 6.78 Hz, 4H, 2 x CH_2), 2.69 (t, J = 6.59 Hz, 4H, 2 x CH_2), 3.93 (s, 4H, 2 x CH_2), 6.78 (m, 4H, Ar), 6.96 (d, J = 6.95 Hz, 2H, Ar), 7.15 (m, 2H, Ar). ^{13}C-NMR (75 MHz): δ 27.4 (CH_2), 42.6 (CH_3), 48.1 (CH_2), 53.2 (CH_2), 56.8 (CH_2), 116.9 (CH), 119.5 (CH), 123.0 (C), 128.9 (CH), 129.2 (CH), 158.9 (C). MS (EI^+): m/z 357.

_N_-Methyl-_N,N_-bis{3-[(4-nitrobenzyl)amino]propyl}amine (3.7b)



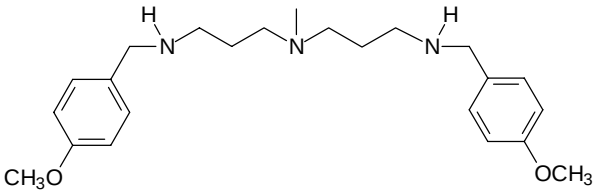
The same procedure as described for the preparation of compound **3.7a** was followed except that **3.6b** (1.0 g, 2.43 mmol) and $NaBH_4$ (0.37 g, 9.72 mmol) were used to afford the product as a red oil (0.9 g, 2.17 mmol, 89% yield).
^{1}H-NMR (300 MHz): δ 1.62 (q, J = 6.96 Hz, 4H, 2 x CH_2), 2.14 (s, 3H, CH_3), 2.33 (t, J = 7.14 Hz, 4H, 2 x CH_2), 2.58 (t, J = 6.96 Hz, 4H, 2 x CH_2), 3.80 (s, 4H, 2 x CH_2), 7.42 (d, J = 8.79 Hz, 4H, Ar), 8.10 (d, J = 8.79 Hz, 4H, Ar). ^{13}C-NMR (75 MHz): δ 28.2 (CH_2), 42.8 (CH_3), 48.7 (CH_2), 53.8 (CH_2), 56.7 (CH_2), 124.2 (CH), 129.1 (CH), 143.3 (C), 148.9 (C). MS (EI^+): m/z 415.

_N_-Methyl-_N,N_-bis(3-phenylpropyl)amine (3.7c)



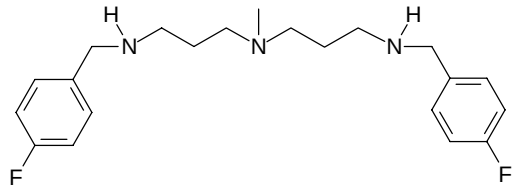
The same procedure as described for the preparation of compound **3.4** was followed except that 3,3'-diamino-N-methyldipropylamine (**3.3**, 5.0 g, 34.4 mmol), benzaldehyde (7.7 g, 72.6 mmol) and $NaBH_4$ (2.6 g, 68.8 mmol) were used. The pure product (9.6 g, 29.5 mmol, 86% yield) was obtained as a as colourless oil.
^{1}H-NMR (300 MHz): δ 1.62 (q, J = 7.14 Hz, 4H, 2 x CH_2), 1.91 (br, 2H, NH), 2.14 (s, 3H, CH_3), 2.32 (t, J = 7.14 Hz, 4H, 2 x CH_2), 2.60 (t, J = 6.96 Hz, 4H, 2 x CH_2), 3.71 (s, 4H, 2 x CH_2), 7.32 (m, 10H, Ar). ^{13}C-NMR (75 MHz): δ 28.1 (CH_2), 42.8 (CH_3), 48.6 (CH_2), 54.6 (CH_2), 56.8 (CH_2), 127.5 (CH), 128.7 (CH), 128.9 (CH), 140.9 (C). MS (EI^+): m/z 325.

_N_-(4-Methoxybenzyl)-_N_-{3-[{3-[(4-methoxybenzyl)amino]propyl}(methyl)amino]propyl}amine (3.7d)



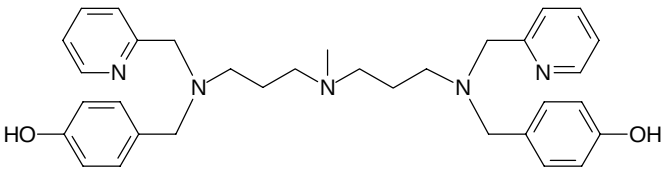
The same procedure as described for the preparation of compound **3.4** was followed except that 3,3'-diamino-N-methyldipropylamine (2.0 g, 13.8 mmol), 4-methoxybenzaldehyde (3.8 g, 27.9 mmol) and $NaBH_4$ (1.0 g, 26.3 mmol) were used. The pure product (2.7 g, 7.0 mmol, 51% yield) was obtained as a white solid after precipitation from CH_2Cl_2/pentane.
^{1}H-NMR (CD_3OD, 300 MHz): δ 1.72 (q, J = 7.14 Hz, 4H, 2 x CH_2), 2.14 (s, 3H, CH_3), 2.41 (t, J = 6.96 Hz, 4H, 2 x CH_2), 2.88 (t, J = 6.96 Hz, 4H, 2 x CH_2), 3.67 (s, 2 H, 2 x NH), 3.94 (s, 4H, 2 x CH_2), 6.86 (d, J = 8.79 Hz, 4H, Ar), 7.29 (d, J = 8.79 Hz, 4H, Ar). ^{13}C-NMR (CD_3OD, 75 MHz): δ 25.0 (CH_2), 39.7 (CH_3), 45.4 (CH_2), 50.9 (CH_2), 52.7 (CH_3), 53.6 (CH_2), 111.2 (CH), 126.8 (CH), 130.0 (C), 156.0 (C). MS (EI^+): m/z 385.

_N_-(4-Fluorobenzyl)-_N_-{3-[{3-[(4-fluorobenzyl)amino]propyl}(methyl)amino]propyl}-amine (3.7e)



The same procedure as described for the preparation of compound **3.4** was followed except that 3,3'-diamino-N-methyldipropylamine (2.0 g, 13.8 mmol), 4-fluorobenzaldehyde (3.6 g, 29.0 mmol) and $NaBH_4$ (1.0 g, 26.3 mmol) were used. The organic layers were dried (Na_2SO_4) and the solvent evaporated under reduced pressure to afford the pure product as a colourless oil (4.1 g, 11.3 mmol, 82% yield).
^{1}H-NMR (300 MHz): δ 1.60 (q, J = 6.96 Hz, 7.32, 4H, 2 x CH_2), 1.68 (br, 2H, NH), 2.13 (s, 3H, CH_3), 2.31 (t, J = 6.95 Hz, 7.33, 4H, 2 x CH_2), 2.57 (t, J = 6.96 Hz, 4H, 2 x CH_2), 3.67 (s, 4H, 2 x CH_2), 6.94 (m, 4H, Ar), 7.21 (m, 4H, Ar). ^{13}C-NMR (75 MHz): δ 25.0 (CH_2), 39.8 (CH_3), 45.4 (CH_2), 50.8 (CH_2), 53.6 (CH_2), 112.4 (CH), 112.7 (CH),127.0 (CH), 127.1 (CH) 133.6 (C), 160.9 (C). MS (EI^+): m/z 361.

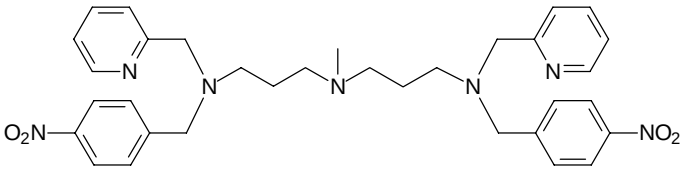
2-{[{3-[{3-[(2-Hydroxybenzyl)(2-pyridinylmethyl)amino]propyl}(methyl) amino] propyl}(2-pyridinylmethyl)amino]methyl}phenol (3.8a)



The same procedure as described for the preparation of ligand **3.5** was followed except that **3.7a** (2.0 g, 5.9 mmol), 2-pyridinecarboxaldehyde (1.3 g, 12.1 mmol) and $NaBH(OAc)_3$

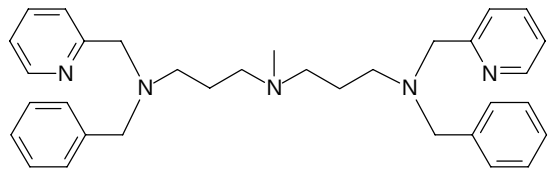
(4.7 g, 22.2 mmol) was used. The product was purified by chromatography (Al_2O_3, akt. II - III, ethyl acetate/hexane/triethylamine 10/4/1) to afford pure **3.8a** as a yellow oil (1.2 g, 2.2 mmol, 38%).
^{1}H-NMR (300 MHz): δ 1.58 (q, J = 7.32 Hz, 4H, 2 x CH_2), 1.98 (s, 3H, CH_3), 2.11 (t, J = 7.14 Hz, 4H, 2 x CH_2), 2.46 (t, J = 7.51 Hz, 4H, 2 x CH2), 3.68 (s, 4H, 2 x CH_2), 3.72 (s, 4H, 2 x CH_2), 6.72 (m, 4H, Ar), 6.91 (m, 2H, Ar), 7.08 (m, 4H, Ar), 7.22 (d, J = 8.05 Hz, 2H), 7.57 (dt, J = 1.46, 7.69 Hz, 2H, Ar), 8.49 (d, J = 4.76 Hz, 2H). ^{13}C-NMR (75 MHz): δ 24.7 (CH_2), 42.4 (CH_3), 52.3 (CH_2), 55.9 (CH_2), 58.3 (CH_2), 60.1 (CH_2), 116.8 (CH), 119.6 (CH), 122.9 (C), 122.9 (CH), 123.9 (CH), 129.3 (CH), 129.7 (CH), 137.3 (CH), 149.8 (CH), 128.2 (C), 158.3 (C). HRMS calcd. for $C_{33}H_{41}N_5O_2$ 539.326, found 539.326.

_N_-Methyl-_N_,_N_-bis{3-[(4-nitrobenzyl)(2-pyridinylmethyl)amino] propyl}amine (3.8b)



The same procedure as described for the preparation of ligand **3.5** was followed except that **3.7b** (0.9 g, 2.2 mmol), 2-pyridinecarboxaldehyde (0.51 g, 4.8 mmol) and $NaBH(OAc)_3$ (1.4 g, 6.6 mmol) was used. The product was purified by chromatography (Al_2O_3, akt. II - III, ethyl acetate/hexane/triethylamine 10/4/1) to afford pure **3.8b** as a yellow oil (0.70 g, 1.17 mmol, 53%).
^{1}H-NMR (300 MHz): δ 1.60 (q, J = 7.32 Hz, 4H, 2 x CH_2), 2.06 (s, 3H, CH_3), 2.20 (t, J = 7.32 Hz, 4H, 2 x CH_2), 2.43 (t, J = 7.33 Hz, 4H, 2 x CH_2), 3.63 (s, 4H, 2 x CH_2), 3.68 (s, 4H, 2 x CH_2), 7.09 (t, J = 6.05 Hz , 2H, Ar), 7.42 (m, 6H, Ar), 7.58 (dt, J = 7.60, 1.66 Hz, 2H, Ar), 8.08 (d, J = 8.42 Hz, 4H, Ar), 8.45 (d, J = 4.39 Hz, 2H, Ar). ^{13}C-NMR (75 MHz): δ 22.4 (CH_2), 39.5 (CH_3), 50.0 (CH_2), 53.0 (CH_2), 55.5 (CH_2), 57.8 (CH_2), 119.5 (CH), 120.2 (CH), 120.9 (CH), 126.7 (CH), 133.9 (CH), 144.4 (C), 145.2 (C), 146.5 (CH),156.9 (C). MS (CI): m/z 598 (M + 1).

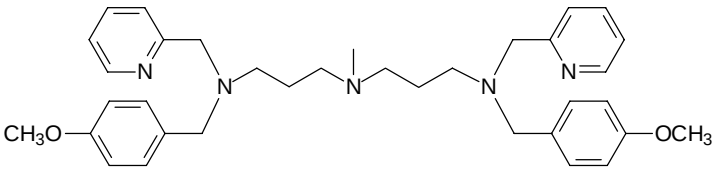
_N_-Benzyl-_N_-{3-[{3-[benzyl(2-pyridinylmethyl)amino]propyl}(methyl)amino]-propyl}-_N_-(2-pyridinylmethyl)amine (3.8c)



The same procedure as described for the preparation of ligand **3.5** was followed except that **3.7c** (2.0 g, 6.13 mmol), 2-pyridinecarboxaldehyde (1.44 g, 13.5 mmol) and $NaBH(OAc)_3$ (3.9 g, 18.4 mmol was used. The final product was obtained by chromatography (Al_2O_3, akt. II - III, ethyl acetate/hexane/triethylamine 10/4/1) to afford pure **3.8c** as a yellow oil (2.33 g, 4.59 mmol, 75%).

^{1}H-NMR (300 MHz): δ 1.59 (q, J = 7.32 Hz, 4H, 2 x CH_2), 2.06 (s, 3H, CH_3), 2.20 (t, J = 7.69 Hz, 4H, 2 x CH_2), 2.41 (t, J = 7.14 Hz, 4H, 2 x CH_2), 3.55 (s, 4H, 2 x CH_2), 3.66 (s, 4H, 2 x CH_2), 7.31 (m, 18H, Ar, Py), 8.43 (d, J = 5.12 Hz, 2H, Py). ^{13}C-NMR (75 MHz): δ 22.4 (CH_2), 39.6 (CH_3), 49.7 (CH_2), 53.2 (CH_2), 56.2 (CH_2), 57.8 (CH_2), 119.2 (CH), 120.2 (CH), 124.3 (CH), 125.7 (CH), 126.3 (CH), 133.8 (CH), 137.0 (C), 146.3 (CH), 158.0 (C). HRMS calcd. for $C_{33}H_{41}N_5$ 507.336, found 507.336.

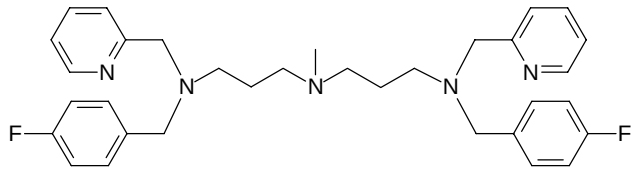
_N_-(4-Methoxybenzyl)-_N_-{3-[{3-[(4-methoxybenzyl)(2-pyridinylmethyl)amino]propyl}-(methyl)amino]propyl}-_N_-(2-pyridinylmethyl)amine (3.8d)



The same procedure as described for the preparation of ligand **3.5** was followed except that **3.7d** (1.0 g, 2.6 mmol), 2-pyridinecarboxaldehyde (0.61 g, 5.7 mmol) and $NaBH(OAc)_3$ (1.7 g, 8.0 mmol) was used. The product was purified by chromatography (Al_2O_3, akt. II - III, ethyl acetate/hexane/triethylamine 10/4/1) to afford pure **3.8d** as a yellow oil (0.64 g, 1.1 mmol, 43%).

^{1}H-NMR (300 MHz): δ 1.58 (q, J = 7.32 Hz, 4H, 2 x CH_2), 2.06 (s, 3H, CH_3), 2.22 (t, 7.51 Hz, 4H, 2 x CH_2), 2.39 (t, J = 7.14 Hz, 4H, 2 x CH_2), 3.48 (s, 4H, 2 x CH_2), 3.64 (s, 4H, 2 x CH_2), 3.72 (s, 6H, 2 x OCH_3), 6.77 (d, J = 8.42 Hz, 4H, Ar), 7.05 (t, J = 6.04 Hz, 2H , Ar), 7.20 (d, J = 8.43 Hz, 4H, Ar), 7.44 (d, J = 8.05 Hz, 2H, Ar), 7.55 (dt, J = 7.69, 1.47 Hz, 2H, Ar), 8.42 (d, J = 4.03 Hz, 2H, Ar). ^{13}C-NMR (75 MHz): δ 25.4 (CH_2), 42.7 (CH_3), 51.6 (CH_2), 52.6 (CH_2), 55.8 (CH_3), 56.3 (CH_2), 58.5 (CH_2), 60.6 (CH_2), 114.1 (CH), 122.3 (CH), 123.3 (CH), 130.5 (CH), 132.0 (C), 136.9 (CH), 149.3 (CH), 159.1 (C), 161.2 (C). HRMS calcd. for $C_{35}H_{45}N_5O_2$ 567.357, found: 567.356.

_N_-(4-Fluorobenzyl)-_N_-{3-[{3-[(4-fluorobenzyl)(2-pyridinylmethyl)amino]propyl}-(methyl)amino]propyl}-_N_-(2-pyridinylmethyl)amine (3.8e)

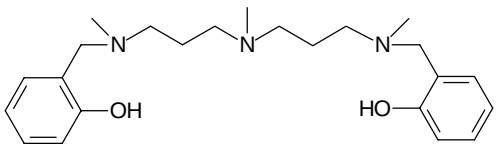


The same procedure as described for the preparation of ligand **3.5** was followed except that **3.7e** (2.0 g, 5.5 mmol), 2-pyridinecarboxaldehyde (1.2 g, 11.2 mmol) and $NaBH(OAc)_3$ (3.2 g, 15.1 mmol) was used. The final product was purified by chromatography (Al_2O_3, akt. II - III, ethyl acetate/hexane/triethylamine 10/4/1) to afford pure **3.8e** product as a yellow oil (1.1 g, 2.0 mmol, 37%).

^{1}H-NMR (300 MHz): δ 1.58 (q, J = 7.32 Hz, 4H, 2 x CH_2), 2.06 (s, 3H, CH_3), 2.19 (t, J = 7.51 Hz, 4H, 2 x CH_2), 2.39 (t, J = 7.33 Hz, 4H, 2 x CH_2), 3.50 (s, 4H, 2 x CH_2), 3.65 (s, 4H,

2 x CH_2), 6.91 (t, J = 8.61 Hz, 4H, Ar), 7.07 (t, J = 6.04 Hz, 2H, Ar), 7.24 (m, 4H, Ar), 7.42 (d, J = 7.69 Hz, 2H, Ar), 7.56 (dt, 7.69, 1.47 Hz, 2H, Ar), 8.44 (d, J = 4.39 Hz, 2H, Ar). ^{13}C-NMR (75 MHz): δ 25.5 (CH_2), 42.7 (CH_3), 52.7 (CH_2), 56.3 (CH_2), 58.4 (CH_2), 60.7 (CH_2), 115.4 (CH), 115.7 (CH), 122.4 (CH), 123.2 (CH), 130.7 (CH), 130.8 (CH), 136.9 (C), 149.4 (CH), 160.8 (C), 164.0 (C). HRMS calcd. for $C_{33}H_{39}N_5F_2$ 543.317, found: 543.317.

2-{[{3-[{3-[(2-Hydroxybenzyl)(methyl)amino]propyl}(methyl)amino]propyl}(methyl)-amino]methyl}phenol (3.9)



To **3.7a** (1.00 g, 2.83 mmol) in 1,2-dichloroethane (50 ml) was added formaldehyde (0.90 g, 11.3 mmol, 37% in water). During 1h $NaBH(OAc)_3$ (2.4 g, 11.2 mmol) was added in small portions. After stirring for 16h at room temperature an aqueous saturated solution of $NaHCO_3$ (50 ml) was added to the reaction mixture and stirring was continued for another 0.5h. The mixture was extracted with CH_2Cl_2 (3 x 50 ml). The organic layers were dried over Na_2SO_4 and the solvent evaporated under reduced pressure to afford the pure product as a colourless oil (0.63 g, 1.64 mmol, 58% yield).
^{1}H-NMR (300 MHz): δ 1.64 (q, J = 7.32 Hz, 4H, 2 x CH_2), 2.11 (s, 3H, CH_3), 2.21 (s, 6H, 2 x CH_3), 2.25 (t, J = 7.32 Hz, 4H, 2 x CH_2), 2.43 (t, J = 7.51 Hz, 4H, 2 x CH_2), 3.62 (s, 4H, 2 x CH_2), 6.74 (m, 4H, Ph), 6.89 (d, J = 6.59 Hz, 2H, Ph), 7.10 (dt, J = 7.33, 1.46 Hz, 2H, Ph). ^{13}C-NMR (75 MHz): δ 22.3 (CH_2), 38.7 (CH_3), 39.5 (CH_3), 52.6 (CH_2), 52.9 (CH_2), 58.9 (CH_2), 113.5 (CH), 116.4 (CH), 119.4 (C), 125.8 (CH), 125.8 (CH), 126.1 (CH), 155.5 (C). HRMS calcd. for $C_{23}H_{35}N_3O_2$ 385.273, found: 385.273.

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Chapter 4

Homogeneous *cis*-Dihydroxylation and Epoxidation of Olefins with High Hydrogen Peroxide Efficiency by Mixed Manganese/Activated Carbonyl Catalyst Systems

Part of this chapter has been published: Brinksma, J.; Schmieder; L.; Van Vliet, G.; Boaron, R.; Hage, R.; De Vos, D. E.; Alsters, P. L.; Feringa, B. L. *Tetrahedron Lett.* **2002**, *43*, 2619 - 2622.

Abstract

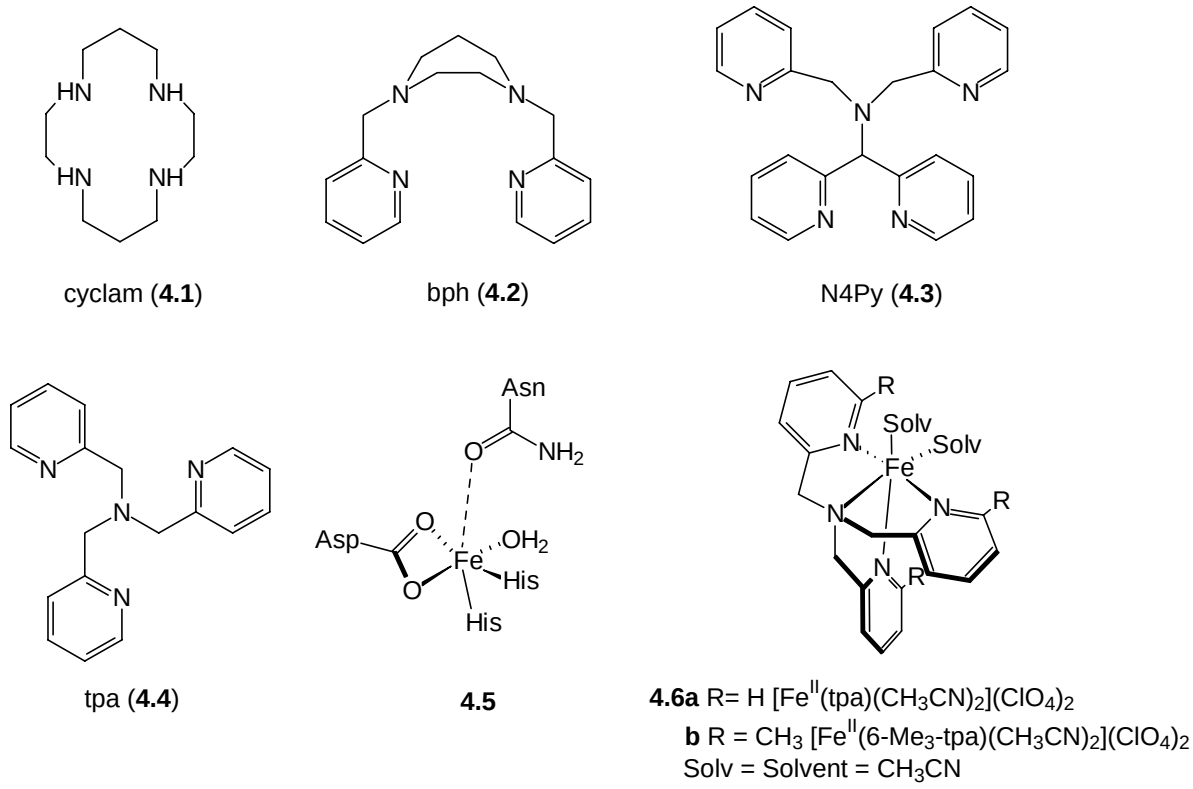
The use of $[Mn_2O_3(tmtacn)_2](PF_6)_2$ (tmtacn = 1,4,7-trimethyl-1,4,7-triazacyclononane) in combination with glyoxylic acid methyl ester methyl hemiacetal (gmha) results in a highly active and hydrogen peroxide efficient catalyst for the epoxidation of olefins. This is the first homogeneous catalytic cis-dihydroxylation system with hydrogen peroxide and with turnover numbers up to 420 for cis-diol formation.

4.1 Introduction

For economic and environmental reasons, catalytic olefin oxidations based on oxygen or hydrogen peroxide are preferred over traditional stoichiometric oxidations, *e.g.* epoxidation with peracids and *cis*-dihydroxylation with permanganate.[1] Whereas currently several catalytic methods are available for catalytic epoxidation with aqueous H_2O_2 (most successfully with Re-, W-, and Mn-based catalysts),[2] high turnover numbers for *cis*-dihydroxylation reactions are only achieved with osmium.[3] However, the high cost and toxicity of osmium hamper large scale application and provide a strong incentive to develop benign Fe- or Mn-based *cis*-dihydroxylation catalysts. Que *et al.* recently reported the first *cis*-dihydroxylation reaction with H_2O_2 as oxidant catalysed by a non-heme iron complex.[4] Although this system shows good *cis*-diol selectivities, turnover numbers are rather low (up to 22).

4.2 Iron and manganese complexes as epoxidation- and *cis*-dihydroxylation catalysts

Iron porphyrin complexes are potent catalysts for epoxidation reactions using H_2O_2 as oxidant.[5] However, disadvantages of these complexes like the poor stability under the reaction conditions and the difficult synthesis of the ligands limit their applicability. Non-heme iron complexes based on tetradentate nitrogen ligands like cyclam[6] (**4.1**, Figure 1), bph (**4.2**), tpa (**4.4**) and derivatives of tpa are able to catalyse epoxidation reactions.[4,7] These ligands leave two open coordination sites on the metal. Depending on whether these open sites are located *cis* or *trans* to each other, different type of selectivity was observed. Complexes with *trans*-open coordination sites like $[Fe(cyclam)(CH_3CN)_2](OTf)_2$ and $[Fe(bph)(CH_3CN)_2](ClO_4)_2$, catalyse the epoxidation of alkenes with H_2O_2 as terminal oxidant.[4,7b] Complexes with two *cis*-open coordination sites like $[Fe(tpa)(CH_3CN)_2](ClO_4)_2$ (**6a**) and $[Fe(6\text{-}Me_3\text{-}tpa)(CH_3CN)_2](ClO_4)_2$ (**4.6b**) catalyse besides the epoxidation of alkenes also the *cis*-dihydroxylation reaction.[4] Employing $[Fe(6\text{-}Me_3\text{-}tpa)(CH_3CN)_2](ClO_4)_2$, containing two *cis*-coordinated acetonitrile molecules, as catalyst, the *cis*-diol was observed as the major product.



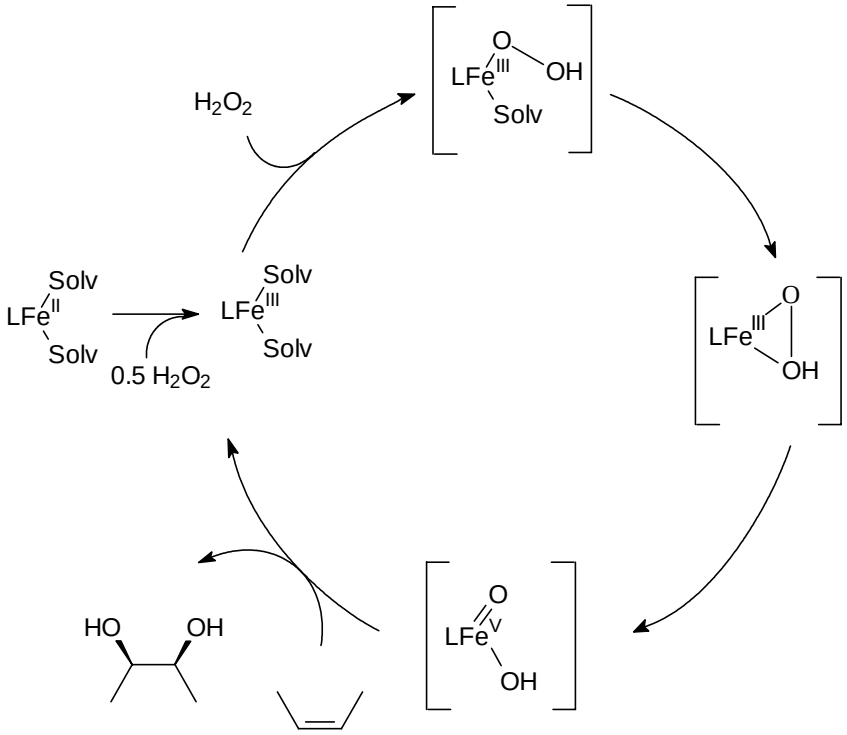
cyclam (**4.1**) bph (**4.2**) N4Py (**4.3**)

tpa (**4.4**) **4.5**

4.6a R= H $[Fe^{II}(tpa)(CH_3CN)_2](ClO_4)_2$
b R = CH_3 $[Fe^{II}(6\text{-}Me_3\text{-}tpa)(CH_3CN)_2](ClO_4)_2$
Solv = Solvent = CH_3CN

Figure 1 *Ligands **4.1** - **4.4** used for epoxidation and cis-dihydroxylation of alkenes, mono-nuclear Fe^{II}-centre of naphthalene 1,2-dioxygenase **4.5** and synthetic model complexes **4.6**.*

From labeling studies with ^{18}O it was concluded that the oxygen atoms in the *cis*-diol products are exclusively delivered from the oxidant H_2O_2, making the catalyst a useful model for the bacterial enzyme Rieske dioxygenases. These group of enzymes catalyses enantiospecifically the *cis*-dihydroxylation of arene or alkene substrates, with incorporation of both atoms of dioxygen.[8] Recently, the crystal structure of naphthalene 1,2-dioxygenase was published (mononuclear Fe-centre **4.5**, Figure 1). It appeared to contain a mononuclear non-heme Fe^{II}-centre coordinated by two histidines and a bidentate aspartate group with two *cis*-sites available for exogenous ligands.[9] As active intermediate for the oxidation of the substrates to diols a Fe^{III}-peroxo species was proposed, formed after binding of O_2 to the Fe^{II}-centre and accepting an electron from the Rieske cluster.[8,10] The mechanism that was proposed for the Rieske dioxygenases model complex $[Fe(6\text{-}Me_3\text{-}tpa)(CH_3CN)_2](ClO_4)_2$ is given in Scheme 1 and involves an $Fe^{III}(OOH)$ species similar as found in oxidation reactions with related iron complexes like $[Fe^{II}(tpa)(CH_3CN)_2](ClO_4)_2$ and $[Fe^{II}(N4Py)(CH_3CN)](ClO_4)_2$.[11] However, the latter complex does not catalyse the *cis*-diol formation. From this difference in reactivity of the tpa and N4-Py (**4.3**, Figure 1) based iron complexes, it was concluded that an $Fe^{III}(\eta^1\text{-}OOH)$ intermediate is not responsible for *cis*-dihydroxylation and it was postulated that this species reacts via a transition state with the hydroperoxide bound in an η^2-fashion.[4] For the formation of an $Fe^{III}(\eta^2\text{-}OOH)$ species a metal centre with two labile sites in *cis*-position at the metal centre is required to allow *cis*-dihydroxylation with H_2O_2 as oxidant.



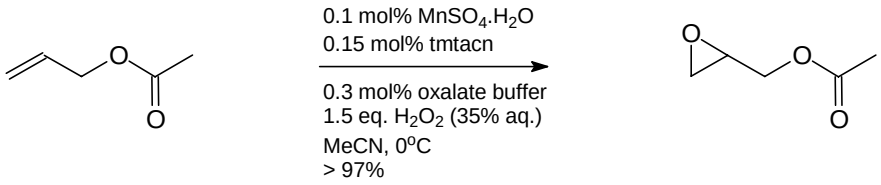
Scheme 1 *Proposed mechanism for the cis-dihydroxylation reaction of alkenes by [Fe(6-Me$_3$-tpa)(CH$_3$CN)$_2$](ClO$_4$)$_2$ and H$_2$O$_2$.*[4]

This intermediate could undergo heterolysis of the O - O bond giving a high-valent iron oxo intermediate with features resembling OsO_4, MnO_4^- and RuO_4, which are all oxidants that can give *cis*-dihydroxylation.[12]

Industrial applications not only put economic and environmental constraints on the oxidant, but also on the catalyst. Fe- or Mn-based catalysts are highly attractive for commercial application, because they are non-toxic and inexpensive. Although the complex using [Fe(6-Me$_3$-tpa)(CH$_3$CN)$_2$](ClO$_4$)$_2$ shows good *cis*-diol selectivities, the catalyst has a rather low activity.[4] Apart from a high turnover, there is a need to develop catalytic systems that employ H_2O_2 very efficiently, as many Mn- or Fe-catalysts are known to induce efficient decomposition of H_2O_2. This can be suppressed by working in acetone,[13] however, this solvent is not acceptable for large-scale applications because of the risk of formation of explosive cyclic peroxides.

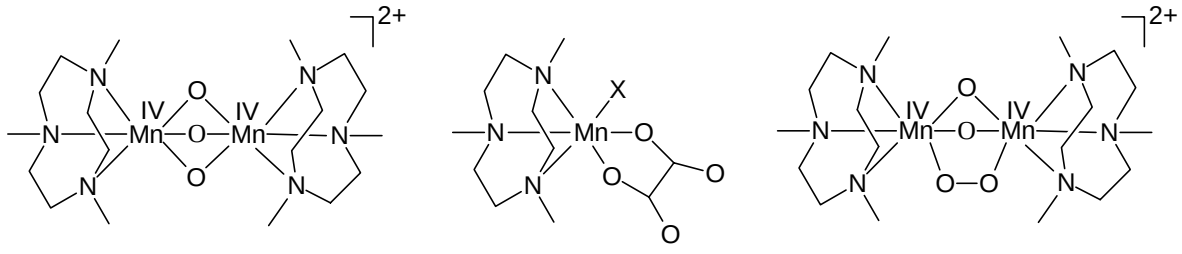
Recently, several research groups found that oxidant decomposition by manganese 1,4,7-trimethyl-1,4,7-triazacyclononane ([Mn$_2$O$_3$(tmtacn)$_2$](PF$_6$)$_2$, Mn-tmtacn, **4.7**, Figure 2) complexes can be suppressed by addition of co-catalysts.[14,15] De Vos and co-workers found a greatly enhanced epoxidation activity of the *in situ* prepared Mn-tmtacn complex after addition of a catalytic amount of oxalate buffer.[14] Besides oxalic acid, several other bi- or polydentate ligands like diketones or diacids also favour epoxidation over oxidant decomposition, using the Mn-tmtacn complex. Employing this mixed catalytic system, electron deficient olefins, especially terminal olefins (for example 1-hexene or allyl acetate,

Scheme 2) are converted into the corresponding epoxides in high yields with acetonitrile as solvent.[14]



Scheme 2 *Selective epoxidation of allyl acetate in the presence of an oxalate buffer.*

In addition to the efficient use of oxidant, the isomerisation of *cis*- and *trans*-alkenes was strongly reduced in the presence of the oxalate buffer. The epoxidation of 2-hexenes was found to be completely stereospecific (>98%) using only 1.5 equivalents of the oxidant. Compared with the earlier procedures using acetone,[13a] in which the tmtacn catalyst produced as much as 34% of *trans*-epoxide starting from *cis*-2-hexene, this new system represents a significant improvement. Although the precise role of the oxalate co-catalyst is not known to date, De Vos postulated the formation of a Mn-tmtacn/oxalate species (**4.8**, Figure 2)[16] related to known analogous Cu^{2+}- and Cr^{3+}-structures.[17] It has been suggested that, the addition of a catalytic amount of the bidentate oxalate co-catalyst impedes the formation μ-peroxo-bridged dimers **4.9**, and as a result the catalase type activity of oxidant decomposition is suppressed.[16,18]

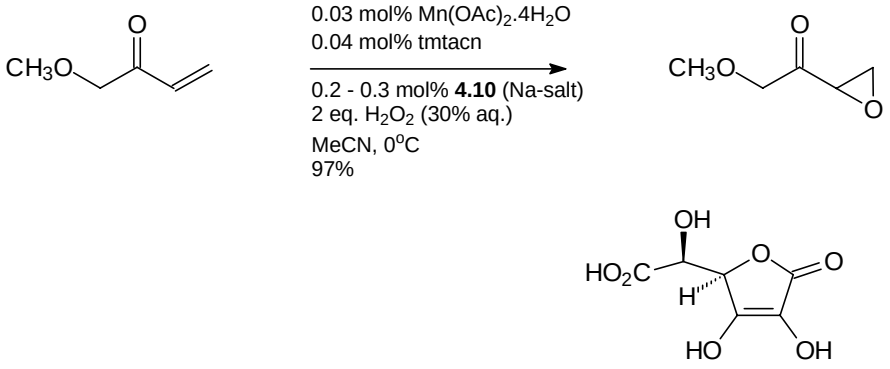


4.7 **4.8** **4.9**

Figure 2 *Mn-tmtacn and proposed structures for Mn-tmtacn/oxalate oxidation catalyst (X = activated "O" to be transferred.[16]*

Related to the Mn-tmtacn oxalate buffer system compounds like ascorbic acid (**4.10**, Scheme 3) or squaric acid were used by Berkessel and Sklorz resulting in a further improvement of the epoxidation reaction catalysed by the Mn-tmtacn complex.[15] The original aim was to obtain enantiomerically enriched epoxides, but the chiral co-ligands did not induce enantioselectivity in the epoxidation. Up to date, the exact role of ascorbic acid as co-catalyst remains unclear. The oxidant efficiency of this catalytic system is the highest reported so far. Almost quantitative yields for the conversion of a range of substrates and with retention of olefin configuration were achieved employing catalysts loading of only 0.03

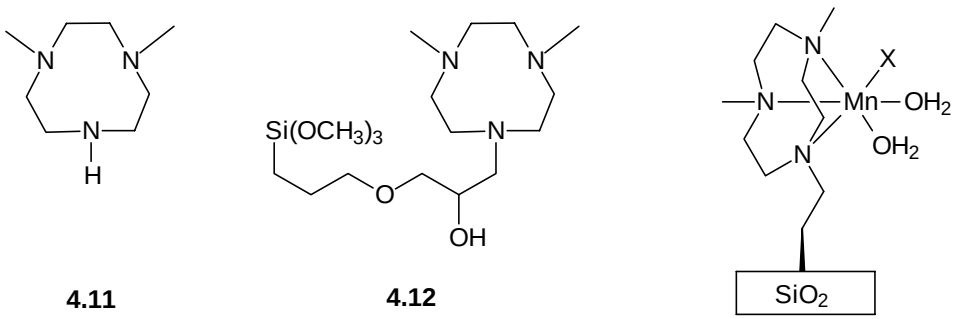
mol%. The catalytic oxidation procedure was also suitable for the oxidation of 2-pentanol providing the corresponding ketone (2-pentanone) in high chemical yield and with high oxidant efficiency.



4.10

Scheme 3 *Epoxidation in the presence of ascorbic acid (**4.10**).*

Suppressing the oxidant decomposition was also achieved by anchoring the triazacyclononane (tacn) ligand to a solid support.[16] The heterogenisation procedure of the tacn ligand started with the conversion of dimethyl tacn (dmtacn, **4.11**, Figure 3) to the silylated compound **4.12** with 3-(glycidyloxy)propyltrimethoxysilane followed by immobilisation on a SiO_2 surface and subsequently metalation of the new heterogenised ligand with $MnSO_4.H_2O$. Remarkably, during alkene oxidation with this new heterogenised catalyst substantial amounts of *cis*-diol were formed besides the expected epoxide. However, the catalyst activity with respect to *cis*-diol formation is still modest (10 - 60 mol *cis*-diol/mol Mn). Control experiments with dmtacn (**4.11**) resulted in strong peroxide decomposition and no oxidation products were obtained. A single sufficient long-lived species (**4.13**, Figure 3) was postulated as active intermediate for both epoxidation and *cis*-dihydroxylation. This intermediate contains two labile coordination sites (*e.g.* H_2O next to X, the activated oxygen, which might be inserted into the olefin.[16]

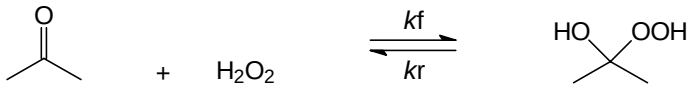


4.11 **4.12** **4.13**

Figure 3 *Structures of dmtacn (**4.11**), heterogenised ligand **4.12** and the proposed epoxidation/cis-dihydroxylation active structure **4.13** (X = activated "O" to be transferred).*[16]

4.3 Suppressing catalase activity by activated carbonyl co-catalysts

Recently, the catalytic properties of the $[Mn_2O_3(tmtacn)_2](PF_6)_2$ complex have been extensively studied and this complex was found to be one of the most efficient catalysts to date.[2f,13a,b,14,15] Oxidation activity is mainly observed at ambient temperature and using acetone as solvent, while switching to other solvents resulted in strong oxidant decomposition. The oxidation characteristics of the Mn-tmtacn complex in acetone were explained by a mechanism involving the nucleophilic addition of H_2O_2 to acetone, resulting in the formation of 2-hydroperoxy-2-hydroxypropane (hhpp, **4.14**) as depicted in Scheme 4.[19] Most probably, due to the reduction of the H_2O_2 concentration in acetone the epoxidation reaction is favoured over oxidant decomposition. Therefore it is proposed that at low temperature hhpp is serving as an oxidant reservoir, which gradually releases H_2O_2 maintaining a low oxidant concentration.[20]



4.14 (hhpp)

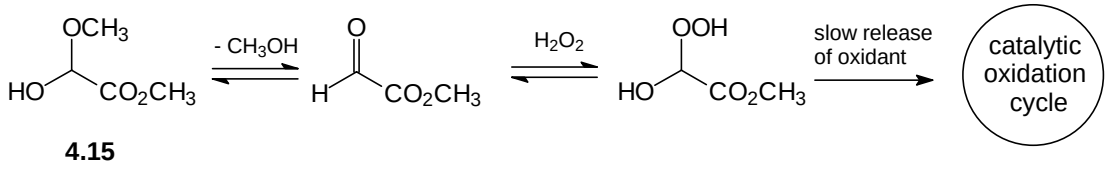
Scheme 4 *Reaction of acetone with H_2O_2.*

Unfortunately the combination of acetone and H_2O_2 can also give the formation of explosive cyclic peroxides and therefore this solvent is not acceptable for industrial applications involving H_2O_2. Addition of catalytic amounts of co-catalysts strongly enhances the catalytic features of Mn-tmtacn complexes for epoxidation reactions and an important finding is that acetone is not required for efficient H_2O_2 consumption.[14,15]

Therefore a challenge is the design of novel Mn-tmtacn/co-catalytic systems retaining the high oxidation activity in solvents like acetonitrile. Based on the successful oxidation results reported in acetone utilising the Mn-tmtacn complex, we reasoned that *activated* ketones or aldehydes with electron-withdrawing substituents such as α-keto esters may facilitate the formation of perhydrates and suppress the decomposition of oxidant similar to hhpp in acetone. This approach provides the possibility to take advantage of other solvents and maintain the high oxidant efficiency comparable with results using acetone as solvent.[13]

In this paragraph, the catalase suppressing activity of the co-catalyst glyoxylic acid methyl ester methyl hemiacetal (gmha, **4.15**, Figure 4) is described.

In Figure 4 the proposed equilibrium reactions of gmha with H_2O_2 are depicted. These formulated reactions and the slow release of oxidant to the oxidation cycle are based on the analogous equilibrium reaction of H_2O_2 with acetone.[19]



4.15

Figure 4 *Proposed equilibrium reactions of glyoxylic acid methylester methyl hemiacetal (gmha,* ***4.15****) with* H_2O_2.

To investigate the inhibition of oxidant decomposition in acetonitrile by Mn-complexes in the presence of gmha, the amount of oxygen that evolved as a function of the time was measured.[21] The inhibition of H_2O_2 disproportionation was determined by reacting Mn-tmtacn with oxidant in the presence of the additive (gmha) but in the absence of a substrate. Over a long period of time the Mn-tmtacn/gmha catalytic system possesses hardly any catalase activity and almost no decomposition of H_2O_2 to oxygen was detected. Control experiment in the absence of gmha resulted in strong peroxide decomposition. The results are summarised in Figure 5.

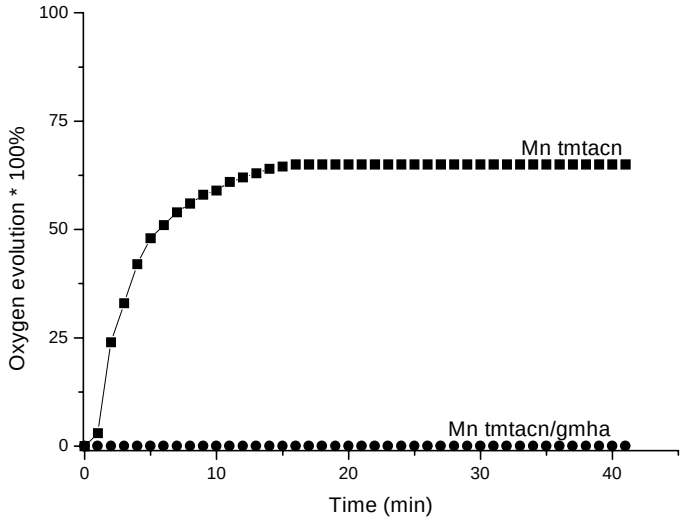


Figure 5 *Effect of gmha on the catalase activity of the* $[Mn_2O_3(tmtacn)_2](PF_6)_2$ *(Mn-tmtacn) complex in acetonitrile.*

4.4 Catalytic oxidation of cyclooctene by $[Mn_2O_3(tmtacn)_2](PF_6)_2$/gmha system

Preliminary oxidation experiments with the mixed Mn-tmtacn/gmha system were performed by adding H_2O_2 (only 1.3 equivalents with respect to the substrate) over a 3h addition period to a mixture of alkene, Mn-tmtacn (0.1 mol%) and gmha (225 mol%) at 0°C. Samples for GC analysis were taken after 4h. The use of acetonitrile as the solvent for the oxidation of cyclooctene resulted in a 50% yield (500 t.o.n.'s) of cyclooctene oxide. Surprisingly, the additive gmha not only suppresses oxidant decomposition very efficiently, but also imparts *cis*-dihydroxylation activity on the manganese catalyst achieving 15% yield of *cis*-cyclooctane diol. Data of the results of the conversion of cyclooctene to the corresponding epoxide and *cis*-diol, employing different solvents, are collected in Table 1.

A blank reaction without gmha**,** gave no conversion of cyclooctene in acetonitrile. Although almost complete conversion was obtained by using gmha (entry 3) as solvent, unfortunately no (detectable) products could be analysed (complex mixture). The influence of a range of different solvents on the mixed Mn-tmtacn/gmha catalytic system was examined using the previously described conditions.

Table 1 *Effect of solvents on the oxidation of cyclooctene.*[a]

Entry	Solvent	Epoxide[b]		*cis*-Diol[b]	
		yield(%)	t.o.n.[c]	yield(%)	t.o.n.[c]
1	MeCN	50	500	15	150
2	EtOAc	22	220	0	0
3	gmha	0	0	0	0
4	THF	11	110	1	10
5	Acetone	37	370	6	60
6	NMP[d]	7	70	0	0
7	CH_2Cl_2	2	20	0	0

(a) Experimental conditions, 0.1 mol% $Mn_2O_3(tmtacn)_2(PF_6)_2$ in the presence of gmha (225 mol%) see also experimental section. (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 determined by GC. (d)1-Methyl-2-piperidone.

Table 1 shows clearly that switching from acetonitrile to other solvents, renders a system devoid of any or only little catalytic activity. From the (solvent) screening experiments, acetonitrile was selected as solvent for further optimisation. The initial results of the effects of various reaction parameters on the oxidation of cyclooctene as substrate, catalysed by the mixed Mn-tmtacn/gmha system are collected in Table 2. In all investigated reactions, the exclusion of air was not necessary.

The optimisation of the Mn-tmtacn/gmha catalyst started with the systematic examination of the rate of oxidant addition. Using 225 mol% of the additive gmha and 0.1 mol% of Mn-tmtacn complex a small but distinct increase in *cis*-diol yield was observed by increasing the time of H_2O_2 addition to 6h (Table 2, entry 1 - 3). A further fine-tuning of the Mn-tmtacn/gmha *cis*-dihydroxylation catalyst was achieved by lowering the concentration of gmha (entry 4 - 7). Using 25 mol% of the additive and increasing the time of oxidant addition to a 6h period the *cis*-cyclooctane diol was discovered as the major product starting from cyclooctene (entry 7). Besides 42% of *cis*-diol, corresponding to 420 t.o.n.'s, 36% (360 t.o.n.'s) of epoxide was formed. It has to be emphasised that this is the first observation of a homogeneous manganese-catalysed *cis*-dihydroxylation reaction.

Table 2 *Effect of the concentration of gmha and rate of oxidant addition for the oxidation of cyclooctene.*[a]

Entry	gmha	Oxidant	Epoxide		*cis*-Diol[b]	
	(mol%)	addition (h)	yield (%)	t.o.n.[c]	yield (%)	t.o.n.[c]
1	225	1.5	46	460	32	320
2	225	3	42	420	26	260
3	225	6	47	470	37	370
4	90	1.5	44	440	22	220
5	90	3	46	460	22	220
6	90	6	47	470	22	220
7	25	6	36	360	42	420
8	0	1.5	0	0	0	0
9	0	3	0	0	0	0
10	0	6	0	0	0	0

(a) Experimental conditions, 0.1 mol% $[Mn_2O_3(tmtacn)_2](PF_6)_2$, see also experimental section. (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 determined by GC.

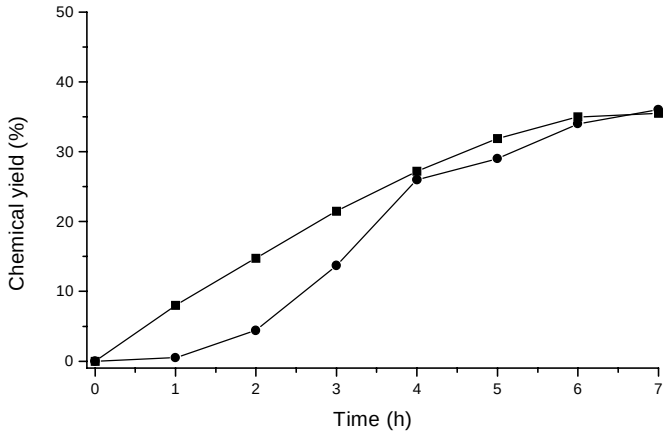
During control experiments (Table 2, entry 8 - 10) with omission of gmha or $[Mn_2O_3(tmtacn)_2](PF_6)_2$ catalyst, no oxidation products in acetonitrile were found, proving that both the additive and manganese catalyst are essential for the formation of active species.

High catalyst efficiency was maintained by lowering the catalyst loadings and as little as 0.015 mol% of the catalyst was sufficient to achieve high yields for the conversion of cyclooctene to both cyclooctene oxide and *cis*-cyclooctane diol. Using this extremely low catalyst loading, total catalyst turnover numbers of more than 6000 were obtained and to the best of our knowledge, the efficiency of the Mn-tmtacn/gmha system is the highest one reported so far for oxidations employing Mn-tmtacn complexes. Although the time course profiles of the oxidation of cyclooctene showed the appearance of a longer induction period at low catalyst loading (Figure 6), the yields of cyclooctene oxide and *cis*-cyclooctane diol are almost not affected. High turnover numbers were obtained without noticeable catalyst degradation. The same oxidation activity was observed after adding a fresh aliquot of cyclooctene and oxidant after 6h of the experiment as described in Table 3 (entry 2). This procedure could be repeated without loss of activity, indicating that the catalyst is quite robust under the oxidation conditions. Unfortunately, when the gmha concentration was lowered to 4 mol%, a strong decrease in catalytic activity was observed. The effects of catalyst loading on the Mn-tmtacn/gmha system and the time profiles of the oxidation of cyclooctene are summarised in Table 3 and Figure 6, respectively.

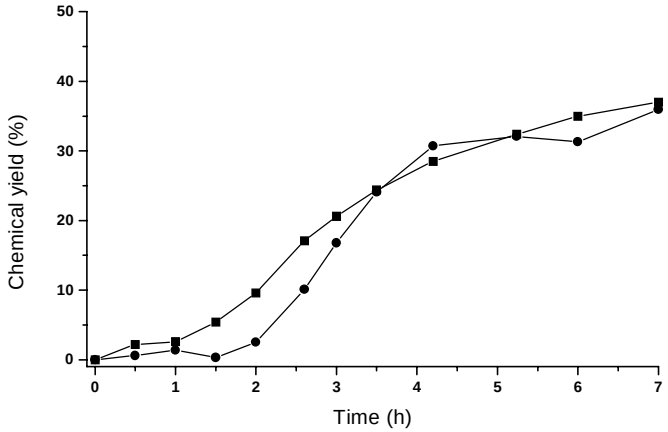
Table 3 *Effects of the Mn-tmtacn and gmha concentration on the oxidation of cyclooctene.*[a]

Entry	Mn-tmtacn (mol%)	gmha (mol%)	Epoxide yield (%)	*cis*-Diol[b] yield (%)
1	0.1	25	36	42
2	0.05	25	36	35
3	0.05	4	6	8
4	0.025	25	37	36
5	0.015	25	40	40
6	0.007	25	20	6

(a) Experimental conditions, see experimental section. (b) All products were identical to independently synthesised samples and identified by GC and ^{1}H-NMR.



(a)



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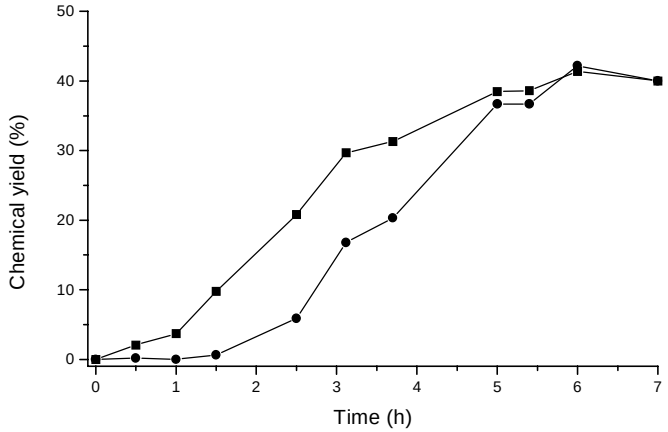


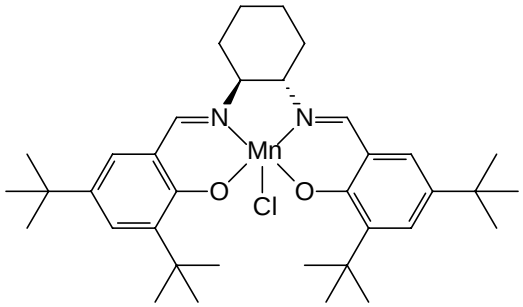
(c)

Figure 6 *Time profile of the oxidation of cyclooctene by H_2O_2 with Mn-tmtacn (a, 0.05 mol%, b, 0.025 mol%, c, 0.0125 mol%) and gmha (25 mol%); ■ epoxide; ● cis-diol.*

4.5 Effects of additives on the oxidation of cyclooctene catalysed by the mixed $[Mn_2O_3(tmtacn)_2](PF_6)_2$/gmha system

In the previous paragraph preliminary oxidation experiments were described with the mixed Mn-tmtacn/gmha oxidation catalyst. Using only a slight excess of H_2O_2 high turnover numbers (up to 420) to *cis*-diol were observed besides the formation of epoxide (360 t.o.n.'s).[22] In this section we describe the attempts to increase the selectivity of this homogeneous *cis*-dihydroxylation reaction by adding a number of other additives in the presence or absence of the initially used additive gmha.

A number of additives have been successfully used by several research groups to improve the manganese salen-catalysed epoxidation reactions employing H_2O_2 as oxidant. The manganese salen complexes have been extensively studied as catalysts for the oxidation of olefins to the corresponding epoxides, especially by the research groups of Jacobsen[23] and Katsuki[24]. In general, epoxide yields can be obtained above 80% and e.e.'s usually exceed 90%. The catalysts can be used with a wide range of oxidants *e.g.* hypochlorite,[25] iodosylbenzene,[25] or *m*-chloroperbenzoic acid (*m*-CPBA)[26]. However, manganese salen systems employing H_2O_2 as oxidant are only catalytically active in the presence of additives like imidazole or derivatives thereof and carboxylic acids.[27]

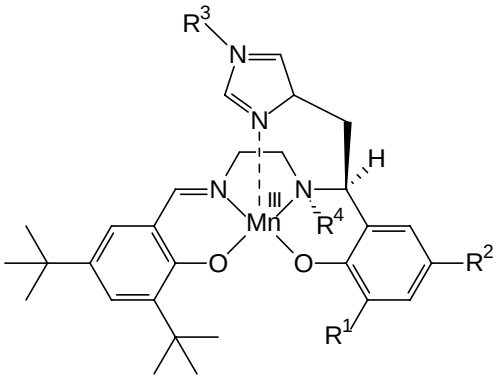


4.16

Figure 7 *Manganese salen complex used for epoxidation reactions.*

The exact role of the additives during the catalytic cycle is not clear. Nitrogen heterocycles are believed to act as ligands to the salen metal catalyst and can favour the heterolytic bond cleavage producing the reactive metal-oxo species.[25,28] A severe problem during oxidation reactions catalysed by metal complexes with H_2O_2 is the homolytic cleavage of the O - O bond, which leads to destructive radical pathways.[28b,29] Another possible mode of action of the nitrogen heterocycle additives is to assist the dissociation of unreactive μ-oxo dimers to reactive monomeric-oxo complexes.[30] The co-catalysts may also improve the epoxide yield by lowering the Lewis acidity of the Mn^{III}-complexes.[31] Manganese salen complexes containing a covalently attached imidazole group which can function as an axially coordinating group were synthesised by Schwenkreis and Berkessel.[32] In this case additives are unnecessary and the novel pentadentate salen Mn-complexes have been reported to

catalyse epoxidation reactions using H_2O_2 as oxidant.[32] Oxidants other than H_2O_2 can be used as well. Furthermore, pyridine *N*-oxides have been used as additives in manganese salen-catalysed epoxidations.[27b,33] They have a favourable effect on reaction rate, *cis*/*trans* ratio and are thought to act as axial ligands. This proposal was supported by a study of a catalyst tethered with pyridine *N*-oxide. From the X-ray crystal structure of this Mn^{III}-complex, it became clear that the *N*-oxide group is axially coordinated, opposite to the chloride counter ion (Figure 8).[33]



R^1, R^2, R^3, R^4 = H, alkyl, alkoxy

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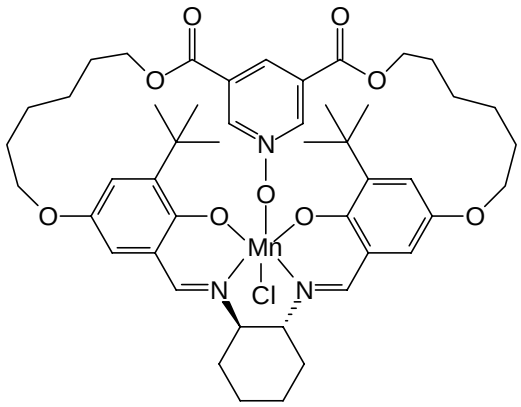


4.18

Figure 8 *Mn-salen complex **4.17** with an internal axial ligand and Mn-salen complex **4.18** with a tethered pyridine N-oxide moiety.*

Based on the beneficial effects of a range of additives on the oxidation reaction catalysed by manganese salen complexes described in literature, we made a number of attempts to increase the *cis*-dihydroxylation selectivity of our Mn-tmtacn/gmha catalyst. Using the optimised reaction conditions as described in the previous paragraphs several additives were tested in the presence of 25 mol% gmha using cyclooctene as the model substrate. The results are listed in Table 5. Carboxylates can act as bases and promote the formation of HO_2^- which facilitate the formation of a hydroperoxy complex.[27c] Unfortunately, employing the inorganic base $NaHCO_3$ (Table 5, entry 1) a dramatic decrease in conversion and low product yields were found. This observed result is in sharp contrast with observations for the salen-based Mn-complexes.[27c] Sterically demanding amines like *t*-butylamine (25 mol%, entry 2) showed a negative effect on the *cis*-dihydroxylation reaction. However, by lowering the additive (*t*-butylamine) amount to only 1 mol% (entry 3) high epoxide and *cis*-diol selectivities were observed. Although upon the addition of a catalytic amount of CF_3SO_3H (entry 4) or pyridine *N*-oxide (entry 5) conversions over 90% were easily reached, the selectivities to cyclooctene oxide or *cis*-cyclooctane diol formation were not enhanced. The positive effect of a catalytic amount of CF_3SO_3H as co-catalyst was successfully employed in our group for the oxidation of primary and secondary alcohols

catalysed by a non-heme dinuclear iron complex.[34] In summary, our attempts to increase the *cis*-diol selectivity by addition of base or acid resulted in some cases (entry 4 and 5) in a increase in conversion, which led, however, to a dramatic decrease of selectivity.

Table 5 *Effects of additives on the epoxidation and cis-dihydroxylation of cyclooctene catalysed by the mixed $[Mn_2O_3(tmtacn)_2](PF_6)_2$/gmha system.*[a]

Entry	Additive	Conversion (%)	Epoxide[b]		*cis*-Diol[b]	
			yield(%)	t.o.n.[c]	yield (%)	t.o.n.[c]
1	$NaHCO_3$	26	9	90	5	50
2	*t*-butylamine	21	3	30	0	0
3	*t*-butylamine[a]	53	27	270	21	210
4	CF_3SO_3H	99	36	360	14	140
5	pyridine-*N*-oxide	93	36	360	20	200
6	-----[d]	90	36	360	42	420

(a) Conditions: 10 mmol cyclooctene, 5 mmol 1,2-dichlorobenzene (internal standard), 10 μmol Mn-complex, 2.5 mmol gmha (25 mol %), 2.5 mmol additive (entries 1 and 2), 100 μmol additive (entries 3 and 4), 192 μmol additive (entry 5), 13 mmol H_2O_2 (aq. 50%, 6h addition period), in 10 ml MeCN at 0^oC. Samples were taken 1h after complete addition of oxidant and identified by GC. (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) Only in the presence of 25 mol% gmha, experimental conditions: see Table 7 and experimental section.

In addition to gmha, a few other carbonyl compounds were tested as co-catalysts (25 mol%) for the oxidation of cyclooctene with H_2O_2 (1.3 equivalents with respect to cyclooctene) catalysed by 0.1 mol% of the Mn-tmtacn complex. In the presence of glyoxylic acid hydrate (Table 6, entry 1, Figure 9) the epoxide was formed in 84% yield and remarkably, *cis*-diol formation was almost completely suppressed. Modest *cis*-diol yields ($\leq$25%) and predominant formation of the epoxide were obtained with diethyl ketomalonate (entry 2) or 2-ketoglutaric acid (entry 3) as the co-catalysts. Furthermore the use of additives containing alcohol moieties (entry 4 - 7), replacing gmha as co-catalyst, was unsuccessful giving only low conversions and yields. However, *cis*-diol formation (37% yield) predominated over epoxide (31%) formation in the presence of chloral hydrate (entry 8). Minor amounts of 2-hydroxycyclooctanone were also found due to oxidation of the formed diol. Thus, a variety of carbonyl compounds with an adjacent electron withdrawing group are

able to reduce oxidant decomposition by Mn-tmtacn and to impose *cis*-dihydroxylation activity on the manganese catalyst, albeit with varying *cis*-diol/epoxide ratios.

Table 6 *Influence of carbonyl compounds on the epoxidation and cis-dihydroxylation reaction of cyclooctene catalysed by* $[Mn_2O_3(tmtacn)_2](PF_6)_2$.[a]

Entry	Additive	Conversion (%)	Epoxide[b]		*cis*-Diol[b]	
			yield (%)	t.o.n.[c]	yield (%)	t.o.n.[c]
1	glyoxylic acid hydrate	100	84	840	<2	<20
2	diethyl ketomalonate	97	36	360	18	180
3	2-ketoglutaric acid	99	65	650	25	250
4	*t*-butanol	0	0	0	0	0
5	2-pyrrolidinone	5	1	10	0.2	2
6	formaldehyde	20	2	20	2	20
7	2,3,4,5,6-pentafluorobenzyl alcohol	24	2.5	25	3.4	34
8	chloral hydrate	88	31	310	37	370
9	gmha	90	36	360	42	420

(a) Conditions: 10 mmol cyclooctene, 5 mmol 1,2-dichlorobenzene (internal standard), 10 μmol Mn-complex, 2.5 mmol (25 mol%) additive, 13 mmol (aq. 50%) H_2O_2 6h addition period), in 10 ml MeCN at 0°C. Samples were taken 1h after complete addition of oxidant and analysed by GC. (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.

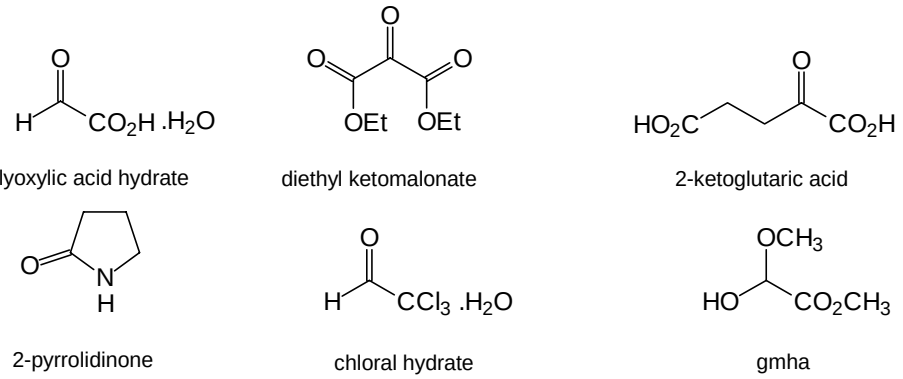
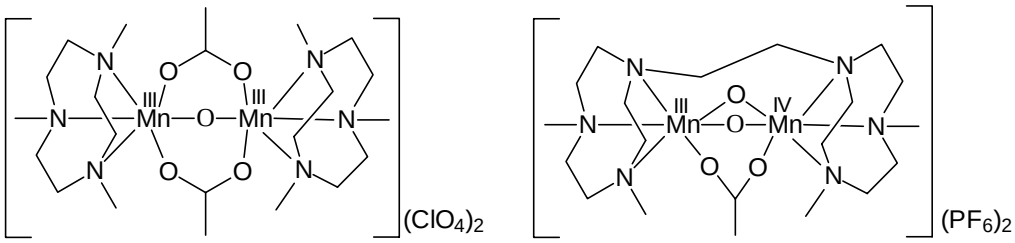


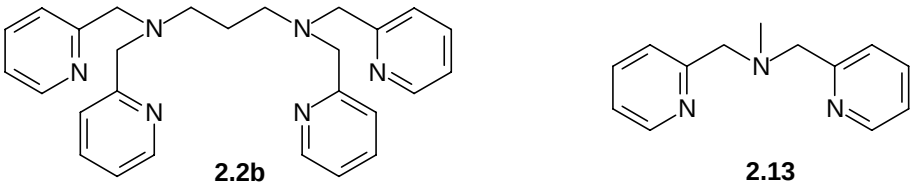
Figure 9 *The additives listed in Table 6.*

4.6 Mn-complexes related to Mn-tmtacn

In addition to the manganese complex based on the tmtacn ligand, two other Mn-tacn complexes were used in combination with the additive gmha (25 mol%) employing 0.1 mol% of manganese complex and acetonitrile as solvent. The manganese complexes depicted in Figure 10 comprise a dinuclear Mn^{III}-complex (**4.19**) and a mixed-valent Mn^{III}-Mn^{IV} complex (**4.20**). The complexes **4.19** and **4.20** were also studied in our group as catalyst for the oxidation of substituted benzyl alcohols to the corresponding aldehydes.[35] Although the bridged tacn-based manganese complex resulted in some conversion it provided only 90 t.o.n.'s to benzaldehyde.[35] Compound **4.19** did not display any activity towards benzyl alcohol oxidation.[13b,35] Both complexes turned out to be virtually unreactive for the oxidation of cyclooctene with gmha as co-catalyst and only starting material could be recovered. Besides the manganese complexes **4.19** and **4.20**, the well established manganese salen epoxidation catalyst **4.16** (Figure 7) was studied in the presence of 25 mol% gmha for the oxidation of cyclooctene with H_2O_2 in acetonitrile, but was found to be unreactive. Ligands **2.2b** and **2.13**, containing a 3N-donor set like the free tacn ligand were used and converted *in situ* to the corresponding manganese complex by mixing the ligand with $Mn(OAc)_3$. Despite the fact that the *in situ* prepared complexes were found to be active epoxidation catalysts for a number of alkenes in acetone with H_2O_2 as oxidant,[36] no oxidation products could be obtained in acetonitrile in combination with gmha.



4.19 **4.20**



2.2b **2.13**

Figure 10 *Mn-complexes and ligands **2.2b** and **2.13** used for the oxidation of cyclooctene in the presence of gmha.*

4.7 Scope of the $[Mn_2O_3(tmtacn_2)](PF_6)_2$/gmha-catalysed oxidations of olefins

A range of olefins has been subjected to the epoxidation/*cis*-dihydroxylation procedure with the mixed Mn-tmtacn/gmha system to study the scope of the oxidation. Catalytic oxidation reactions were performed by gradually adding aqueous 50% H_2O_2 in 6h to a mixture of alkene, Mn-tmtacn catalyst (0.1 mol%), and gmha (25 mol%) in acetonitrile at 0^oC. Under these reaction conditions, the presence of gmha as the co-catalyst enables high conversions with only a 30% excess of oxidant with respect to the substrate. Results of the oxidation experiments of a variety of substrates are given in Table 7. The oxidant efficiency is drastically improved compared to previous manganese systems using a larger excess of oxidant.[13] For example, the $Mn_2O(OAc)_2$tptn epoxidation catalyst described in Chapter 2 provided only high olefin conversions by using 8 equivalents of oxidant.[13b] Besides oxidation reactions catalysed by Mn-tmtacn in the presence of gmha, experiments were performed in an oxalate buffer (0.3 mol%) under the conditions as described by De Vos *et al*.[14] In most cases the conversions were significantly lower than those obtained with gmha (25 mol%) as co-catalyst and 1.3 equivalents of H_2O_2 using the present substrates. For similar experiments with a larger excess of oxidant, see reference 13. In particular, styrene (Table 7, entry 8) afforded a high yield of styrene oxide in the presence of gmha, whereas the use of oxalate (0.3 mol%) resulted in only modest conversion of styrene (Table 8, entry 8). When a mixture of gmha (25 mol%) and oxalate (0.3 mol%) was used as the co-catalyst system, the epoxide yields even surpassed those obtained with the Mn-tmtacn/gmha catalytic system, and high epoxide yields at complete conversion were obtained for the non-sterically hindered alkenes (Table 9; entries 1 - 3, 6 and 8). Figure 11 shows the time profiles of the epoxidation of cyclooctene in the presence of gmha, oxalate and the results of the use of a mixture of gmha/oxalate as additives.

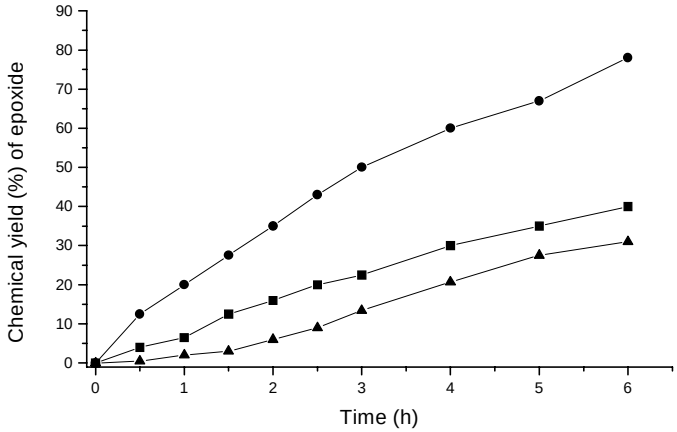


Figure 11 *Time profile of the epoxidation of cyclooctene in the presence of gmha (▲), oxalate (■) and a mixture of oxalate/gmha (●).*

Table 7 Oxidation of selected olefins with the $[Mn_2O_3(tmtacn)_2](PF_6)_2$ complex[a] and gmha as co-catalyst.

Entry	Substrate	Conversion (%)	Product[b]	Yield (%)	t.o.n.[c]
1	cyclopentene	97	epoxide	61	610
			cis-diol	26	260
			cyclopentenone	8	80
2	cyclohexene	88	epoxide	59	590
			cis-diol	9	90
			2-cyclohexenone	8	80
3	cyclooctene	90	epoxide	36	360
			cis-diol	42	420
			2-HO-cyclooctanone	22	220
4	norbornylene	95	*exo*-epoxide	54	540
			exo-cis-diol	18	180
5	*trans*-2-hexene	77	*trans*-epoxide	21	210
			cis-epoxide	5	50
			RR/*SS*-diol	15	150
			RS/*SR*-diol	0	0
6	*cis*-2-hexene	93	*cis*-epoxide	45	450
			trans-epoxide	4	40
			SR/*RS*-diol	28	280
			RR/*SS*-diol	1	10
7	*cis*-stilbene	82	*cis*-epoxide	26	260
			trans-epoxide	20	200
			meso-hydrobenzoin	4	40
			hydrobenzoin	4	40
8	styrene	97	epoxide	86	860
			$Ph(CH)(OH)CH_2OH$	6	60
			$PhC(O)CH_2OH$	1	10

(a) Experimental conditions, see experimental part. (b) All products were identical to independently synthesised samples and identified by GC and ^{1}H-NMR. (c) Turnover number = mole product per mole catalyst.

Table 8 Oxidation of selected olefins with the $[Mn_2O_3(tmtacn)_2](PF_6)_2$ complex[a] and oxalate as co-catalyst.

Entry	Substrate	Conversion (%)	Product[b]	Yield (%)	t.o.n.[c]
1	cyclopentene	92	epoxide	77	770
			cis-diol	0	0
			cyclopentenone	10	100
2	cyclohexene	73	epoxide	61	610
			cis-diol	0	0
			2-cyclohexenone	7	70
3	cyclooctene	52	epoxide	41	410
			cis-diol	0	0
			2-HO-cyclooctanone	0	0
4	norbornylene	59	*exo*-epoxide	36	360
			exo-*cis*-diol	0	0
5	*trans*-2-hexene	37	*trans*-epoxide	24	240
			cis-epoxide	0	0
			RR/*SS*-diol	0	0
			RS/*SR*-diol	0	0
6	*cis*-2-hexene[d]	80	*cis*-epoxide	64	640
			trans-epoxide	2	20
			SR/*RS*-diol	1	10
			RR/*SS*-diol	0	0
7	*cis*-stilbene	32	*cis*-epoxide	11	110
			trans-epoxide	15	150
			meso-hydrobenzoin	1	10
			hydrobenzoin	1	10
8	styrene	44	epoxide	38	380
			$Ph(CH)(OH)CH_2OH$	0	0
			$PhC(O)CH_2OH$	0	0

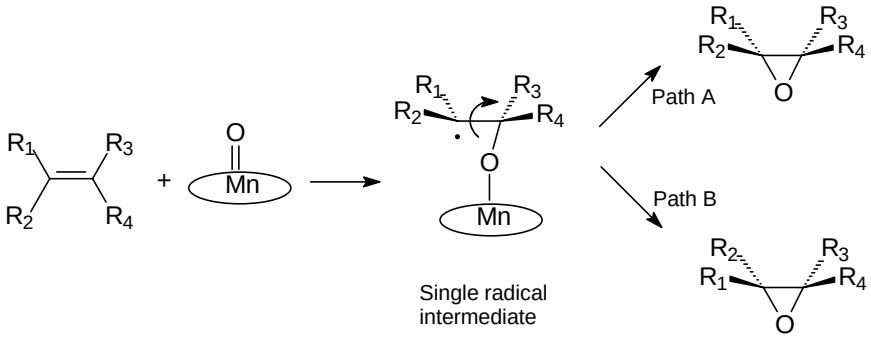
(a) Experimental conditions, see experimental part. (b) All products were identical to independently synthesised samples and identified by GC and ^{1}H-NMR. (c) Turnover number = mole product per mole catalyst. (d) Reaction run on 32 mmol scale.

Table 9 Oxidation of selected olefins with the $[Mn_2O_3(tmtacn)_2](PF_6)_2$ complex[a] and gmha and oxalate as co-catalysts.

Entry	Substrate	Conversion (%)	Product[b]	Yield (%)	t.o.n.[c]
1	cyclopentene	100	cyclopenteneoxide	86	860
			cis-cyclopentanediol	0	0
			cyclopentenone	10	100
2	cyclohexene	100	cyclohexene oxide	82	820
			cis-cyclohexanediol	0	0
			2-cyclohexenone	8	80
3	cyclooctene	100	cyclooctene oxide	84	840
			cis-cyclooctane diol	6	60
			2-hydroxy-1-cyclo-octanone	8	80
4	norbornylene	88	*exo*-epoxide	53	530
			exo-cis-diol	6	60
5	*trans*-2-hexene	93	*trans*-2-hexene oxide	55	550
			cis-2-hexene oxide	3	30
			RR/*SS* hexanediol	9	90
			RS/*SR* hexanediol	0	0
6	*cis*-2-hexene	100	*cis*-2-hexene oxide	82	820
			trans-2-hexene oxide	3	30
			SR/*RS* hexanediol	1	10
			RR/*SS* hexanediol	0	0
7	*cis*-stilbene	77	*cis*-stilbene oxide	26	260
			trans-stilbene oxide	16	160
			meso-hydrobenzoine	3	30
			hydrobenzoine	2	20
8	styrene	100	styrene oxide	86	860
			phenyl-1,2-ethanediol	5	50
			α-hydroxyacetophenone	3	30

(a) Experimental conditions, see experimental part. (b) All products were identical to independently synthesised samples and identified by GC and ^{1}H-NMR. (c) Turnover number = mole product per mole catalyst.

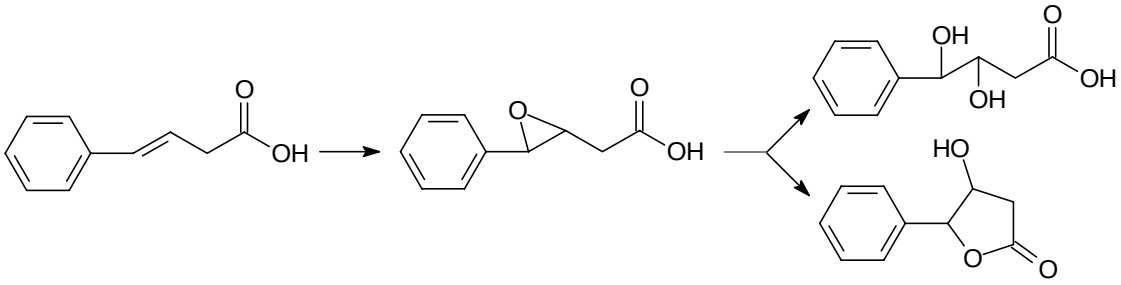
Substantial amounts of *cis*-diols were formed next to the epoxides when *only* gmha was present as the co-catalyst. The epoxide/*cis*-diol ratio depends strongly on the alkene structure. The highest amount of *cis*-diol was found for cyclooctene (Table 7, entry 3), which afforded the *cis*-diol as the main product (42%, 420 t.o.n.'s) besides the epoxide (36%, 360 t.o.n.'s). Minor amounts of 2-hydroxycyclooctanone were also found due to oxidation of the formed diol. The ring size of cycloalkenes has a profound influence on the epoxide/*cis*-diol ratio (Table 7, entries 1 - 4). For these cyclic olefins, almost no *trans*-diol could be detected (ratio *cis*-diol/*trans*-diol >99.5/0.5). *cis*-Diol formation is also observed for aliphatic acyclic alkenes (Table 7, entries 5 and 6). Yields of diol are significantly lower for *trans*-2-hexene (entry 5) than from *cis*-2-hexene (entry 6), but the epoxide/*cis*-diol ratio was similar for both substrates. The aryl-substituted alkenes (entry 7 and 8) yield nearly exclusively epoxide under these conditions. Limited *cis*/*trans* isomerisation is observed in the epoxide formation of *cis*-2-hexene (entry 6). The *cis/trans* isomerisation points to epoxidation via a Mn-oxo species, with formation of epoxides from C-centred radical intermediates with a lifetime sufficient for some C - C bond rotation prior to reaction to the epoxide.[37] The possible radical pathways are schematically depicted in Scheme 5. In case of long-lived radical, rotation can occur before ring-closure leading to the isomerised epoxide (path B). On the other hand in case of a fast collapse of the radical intermediate retention of configuration (via path A) can be found.[38] In line with this mechanism, olefins that form a relatively long-lived radical intermediate, such as *cis*-stilbene (Table 7, entry 7), show substantial loss of configuration in epoxide. These results stem from extensive studies on the epoxidation of styrene using porphyrins[39] or the Jacobsen catalyst (**4.16**).[37]



Scheme 5 *Radical pathways leading to the formation of epoxides.*

No diols were formed on replacing the substrate by an epoxide, thus excluding epoxide hydrolysis. Additional proof for this is found in the fact that the epoxide concentration does not decrease over time in the oxidation reactions. A decrease in the amount of epoxide during the reaction could point to epoxide hydrolysis. This conclusion is further supported by the time course profile of the Mn-tmtacn/gmha-catalysed oxidation of cyclooctene, which shows that both epoxide and diol increase progressively with time (Figure 6, section 4.4). Epoxide hydrolysis was observed by Kerschner *et al.* using a mononuclear Mn-tmtacn complex ($[Mn^{IV}(tmtacn)(OMe)_3](PF_6)$).[40] This complex was found to catalyse the

oxidation of different olefins with H_2O_2 in buffered aqueous solution at room temperature. Several products were obtained starting from styrylacetic acid and besides the epoxide also diols and lactones were observed.[40] However, the diol formation was explicitly attributed to the result of epoxide hydrolysis (Scheme 6), although no experiments were conducted to support this assumption. The observed lactone can be the result of an intramolecular ring opening of the epoxide by the carboxylic acid anion (originating from the buffer) or by dehydration of the diol.



Scheme 6 *Epoxidation of styrylacetic acid and hydrolysis reaction of the epoxide.*[40]

4.8 Mechanistic considerations

In order to obtain more information about the nature of the mixed Mn-tmtacn/gmha oxidation, the reaction mixtures were probed by electron paramagnetic resonance spectroscopy (EPR) and electrospray mass spectroscopy (ES/MS). Further mechanistic information was obtained by isotope labeling experiments using $H_2{}^{18}O_2$. ES/MS is a valuable technique for the investigation or identification of relatively short-lived intermediates in both organic and aqueous solution.[41] This mild ionisation method minimises fragmentation of ions and has been successfully employed in many mechanistic studies of oxidation reactions catalysed by, for example, manganese salen complexes[42] and iron complexes of tpa[43], N4Py[44] and derivatives thereof.[45]

Initial attempts to monitor the oxidation reactions catalysed by the Mn-tmtacn complex with electrospray mass spectrometry (ES/MS) started with the study of the oxidation of cyclooctene under the standard reactions conditions as described in the previous paragraphs. The ES/MS spectrum of the Mn-complex in acetonitrile in the absence of substrate, gmha and oxidant shows characteristic signals with m/z 645 (base peak) and m/z 250, assigned to $[L_2Mn^{IV}{}_2(\mu\text{-}O)_3(PF_6)]^+$ and $[L_2Mn^{IV}{}_2(\mu\text{-}O)_3]^{2+}$, respectively (L = 1,4,7-trimethyl-1,4,7-triazacyclononane). On addition of cyclooctene and oxidant (in the absence of gmha), after 30 min a new peak appeared with m/z 250.5 assigned to $[L_2Mn^{III}Mn^{IV}(\mu\text{-}O)_2(\mu\text{-}OH)]^{2+}$. After another 30 min the spectrum showed the appearance of a peak at m/z 172 due

to free ligand, $[LH]^+$ (*ca.* 10% intensity of the base peak at m/z 250). The latter detected signal increased significantly to *ca.* 50% intensity relative to the base peak m/z 250 after 20h. It needs to be emphasised that no oxidation products were found in the absence of the additive gmha, even over a long reaction time period in acetonitrile. Furthermore, under these conditions, the UV-spectra of the Mn-tmtacn complex showed no change in the characteristic absorbances[46] over a long time. Following the oxidation reaction by ES/MS under catalytic conditions by gradually adding aqueous, 50% H_2O_2 in 6h to a mixture of alkene, Mn-tmtacn catalyst (0.1 mol%), and gmha (25 mol%) in acetonitrile at 0^oC the spectra changed considerable and a new clear signal appeared at m/z 368. Interestingly, the intensity of this peak increased progressively by time and this signal was tentatively assigned to a Mn-tmtacn/*cis*-cyclooctane diol ($MnLC_8H_{14}O_2$) complex.

The oxidation of cyclooctene catalysed by the mixed Mn-tmtacn/gmha system was studied by electron paramagnetic resonance spectroscopy (EPR). Due to the strong antiferromagnetic coupling the Mn-tmtacn complex gives no EPR signal. However, upon mixing with H_2O_2, 16-line spectra with A values of 78 G were reported and attributed to Mn^{III}-Mn^{IV} mixed-valence complexes (Figure 12).[47] These dinuclear species were reported during the catalytic oxidation of alcohols[13b] to the corresponding carbonyl compounds, and during epoxidation reactions starting from alkenes.[13a]

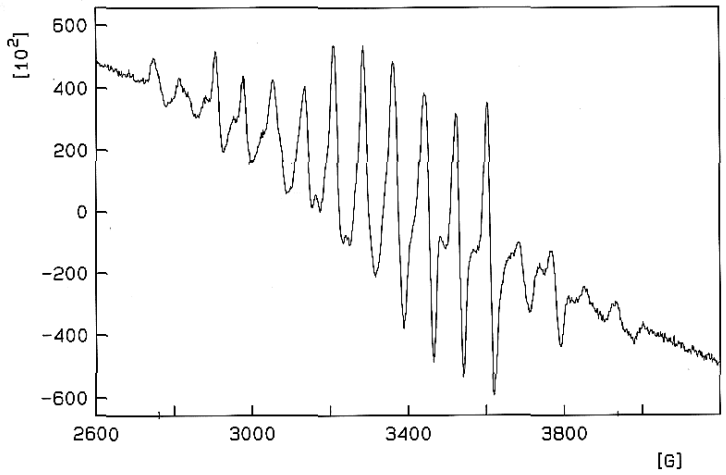


Figure 12 *A dinuclear Mn^{III}-Mn^{IV} mixed-valence complex.*

Samples of the catalytic *cis*-dihydroxylation reaction mixture at 0^oC were taken in acetone and frozen to 77K for EPR studies. After 0.5h the EPR spectrum displayed an intensive signal at 1400 G with an A value of 72 G (Figure 13), indicating that a mononuclear Mn^{IV}-species[40] may take part in the catalytic cycle. Furthermore, the obtained EPR spectrum is accompanied by a much less intensive 6-line EPR signal, typical for a mononuclear Mn^{II}-species.

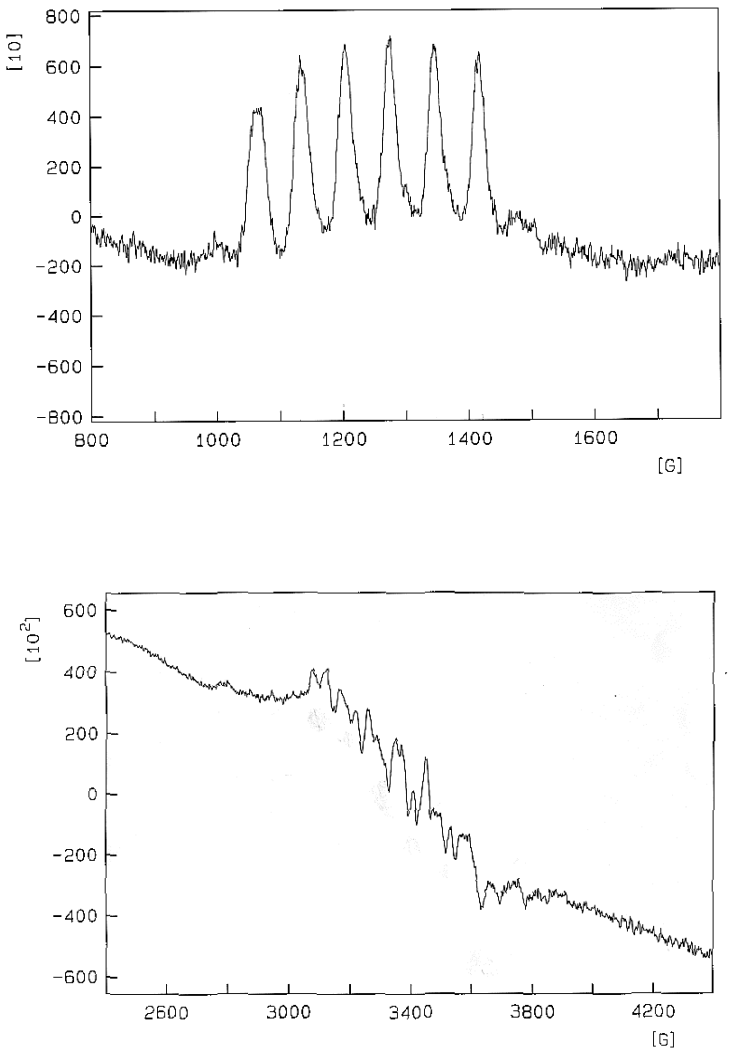


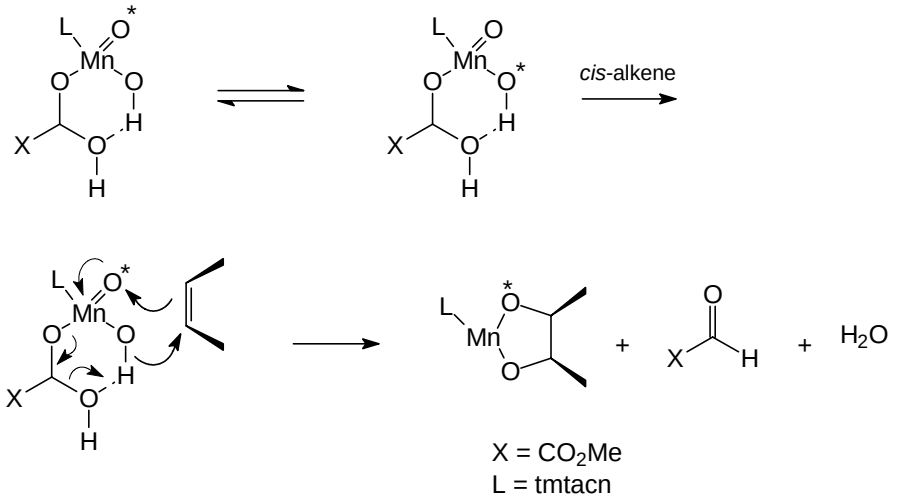
Figure 13 *Electron paramagnetic resonance spectra of Mn-tmtacn/gmha in the presence of cyclooctene and H_2O_2.*

4.9 Proposed mechanism

Isotope labeling experiments with ^{18}O provided further insight into the source of the oxygen atoms that are incorporated into the *cis*-diol. Oxidation of cyclooctene with $H_2{}^{18}O_2$ afforded mainly singly labeled *cis*-diol (>95% ^{18}O incorporation). Single incorporation was also observed by the complementary experiment with $H_2{}^{16}O_2$ and labeled $H_2{}^{18}O$. From the labeling studies we conclude that one oxygen atom in the *cis*-diol product is derived from H_2O_2 and the other oxygen is likely delivered by H_2O. The labeling experiments yielded >85% incorporation of ^{18}O in the epoxide, showing that the epoxide mainly originates from the peroxide. A mechanism, which accounts for the mixed label in the diol product, is presented in the next paragraph. In contrast, Que reported for a non-heme iron-catalysed *cis*-

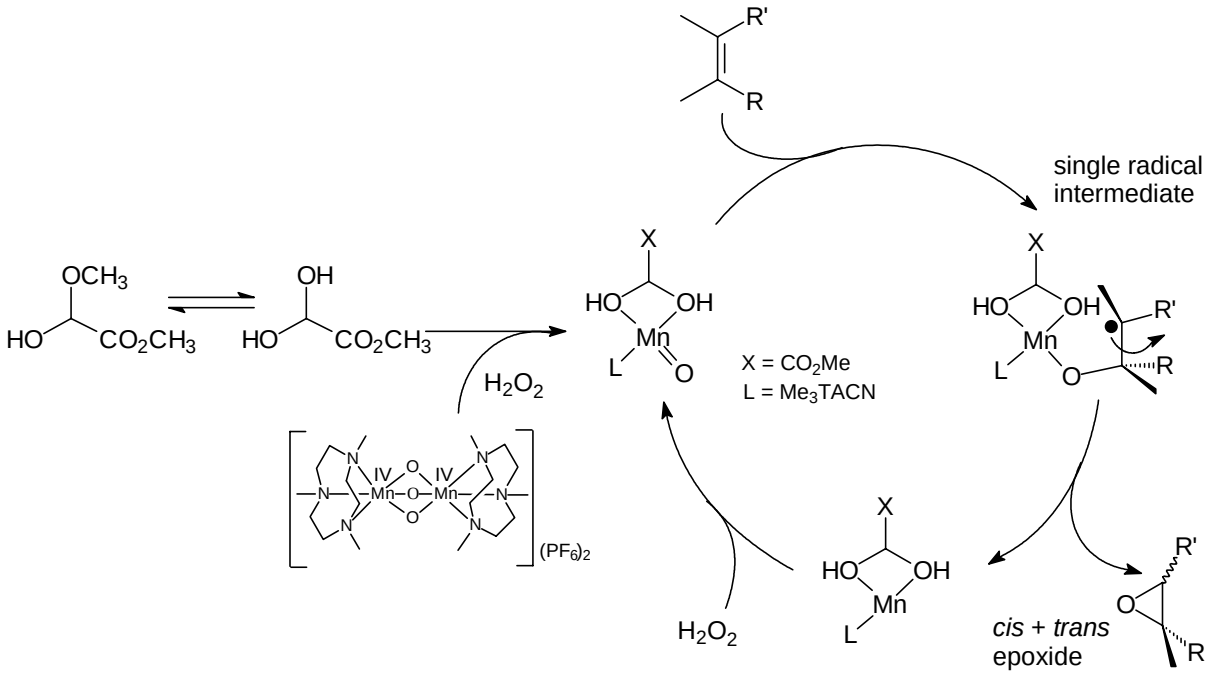
dihydroxylation reaction in which both oxygen atoms were delivered exclusively for the oxidant into the *cis*-diol.[4a]

Since *cis*-diol formation through Mn-tmtacn-catalysed epoxide hydrolysis (paragraph 4.7) can be excluded (*vide supra*), we propose that the *cis*-diol is formed by reaction of the alkene with a manganese oxo-hydroxo species. Like in the case of oxalate, hydrated activated carbonyl compounds[48] might break down the catalase active[18] dinuclear manganese tmtacn complex $[Mn_2O_3(tmtacn)_2](PF_6)_2$) into a mononuclear manganese species via complexation to the manganese centre. *cis*-Diol formation from a manganese oxo-hydroxo species with a coordinated hydrated carbonyl ligand could be induced through a hydrogen bonded six-membered ring transition state via a concerted pathway as depicted in Scheme 7. Reoxidation of the manganese centre with H_2O_2, release of the diol from manganese, and finally hydration of the carbonyl compound closes the catalytic cycle.



Scheme 7 *Proposed cis-dihydroxylation mechanism catalysed by Mn-tmtacn/gmha system.*

As active intermediate for the epoxidation reaction, we propose a mononuclear Mn-oxo species formed from the dinuclear Mn-tmtacn complex similar as described previously for the *cis*-dihydroxylation reaction. This mononuclear species reacts with the alkene to the single radical intermediate, which subsequently reacts to the epoxide with concomitant elimination of the carbonyl co-catalyst. After release of the epoxide the manganese centre is reoxidised with the oxidant and the catalytic epoxidation cycle is closed for another turnover as summarised in Scheme 8.



Scheme 8 *Proposed catalytic cycle for the epoxidation with the mixed Mn-tmtacn/gmha system.*

4.10 Conclusions

In conclusion, the use of activated carbonyl compounds like gmha and chloral hydrate in combination with the manganese complex based on tmtacn ($[Mn_2O_3(tmtacn)_2](PF_6)_2$) results in a highly active and H_2O_2 efficient epoxidation system. Turnover numbers up to 860 were readily achieved and only a slightly excess of oxidant was necessary to obtain high conversions. Besides being efficient in epoxidation this new catalytic system also provides to the best of our knowledge the most active osmium-free homogeneous catalyst for *cis*-dihydroxylation. Up to 420 turnover numbers for *cis*-diol formation were found starting from cyclooctene. Compared with the anchored Mn-tacn catalyst, the present homogeneous Mn-tmtacn/activated carbonyl compound system is much more accessible, since both the manganese complex and several activated carbonyl compounds like gmha have large scale applications.

4.11 Acknowledgements

Ing. Lizette Schmieder and dr. Paul L. Alsters (DSM Fine Chemicals) are gratefully acknowledged for creating the possibility to join the Mn-tmtacn/gmha *cis*-dihydroxylation project and DSM Fine Chemicals Austria for supply of gmha. Dr. D. Schipper (DSM Food

Specialities) for NMR experiments on the gmha/50% H_2O_2 experiments. Prof. dr. Dirk E. De Vos (Centre for Surface Chemistry and Catalysis, Katholieke Universiteit Leuven) is acknowledged for providing several substrates (and corresponding oxidation products). Dr. Ronald Hage (Unilever Research Vlaardingen) is acknowledged for assistance with recording several EPR spectra.

4.12 Experimental section

General procedure and methods

For general information, see Chapter 2. $H_2{}^{18}O$ (97% ^{18}O-enriched) and $H_2{}^{18}O_2$ (90% ^{18}O-enriched, 2% solution in $H_2{}^{16}O$) were obtained from ICON (Services USA). CH_3CN was pretreated by refluxing over CaH_2. N^1,N^2-Dimethyl-N^1,N^2-bis(2-pyridinylmethyl)-1,2-ethanediamine (ligand **2.13**), N^1,N^1,N^3,N^3-tetrakis(2-pyridinylmethyl)-1,3-propanediamine (ligand **2.2b**) have been synthesised according to the procedure described in Chapter 2. The complex $Mn_2O_3(tmtacn)_2(PF_6)_2$ was obtained as a gift from Unilever Research Vlaardingen.

GC Equipment and analysis

GC analyses were performed as described in Chapter 2. EPR spectra were recorded at Unilever Research Laboratory on a Bruker ECS 106 instrument at 77K. The electrospray mass experiments were performed at room temperature at a Micromass ZMD 2000, ESIC(+) Vcone = 20V and Vcap = 3.25kV connected to a Alliance 2690 HPLC system, at the analytical department of the University of Groningen.

General oxidation procedure with the Mn-tmtacn/gmha system

To a solution of $[Mn_2O_3(tmtacn)_2](PF_6)_2$ (31.6 mg, 0.04 mmol), gmha (1.20 g, 10.0 mmol), substrate (40 mmol) and 1,2-dichlorobenzene (internal standard, 2.94 g, 20.0 mmol) in acetonitrile (40 ml) was added H_2O_2 using a syringe pump (3.0 ml of 50% aq., 52 mmol) in 6h at 0^oC. Samples were taken 1h after complete addition of oxidant.

General oxidation procedure with the Mn-tmtacn/oxalate system

To a solution of $[Mn_2O_3(tmtacn)_2](PF_6)_2$ (31.6 mg, 0.04 mmol), oxalate buffer[14] (1.4 ml of a solution of 0.32 g (2.39 mmol) sodium oxalate and 0.30 g (2.38 mmol) oxalic acid hydrate in 28 ml H_2O), substrate (40 mmol) and 1,2-dichlorobenzene (internal standard, 2.94 g, 20.0 mmol) in acetonitrile (40 ml) was added H_2O_2 (3.0 ml of 50% aq., 52 mmol) in 6h at 0^oC. Samples were taken 1h after complete addition of oxidant.

General oxidation procedure with the Mn-tmtacn/oxalate/gmha system

To a solution of $[Mn_2O_3(tmtacn)_2](PF_6)_2$ (31.6 mg, 0.04 mmol), oxalate buffer[14] (1.4 ml of a solution of 0.32 g (2.39 mmol) sodium oxalate and 0.30 g (2.38 mmol) oxalic acid hydrate in 28 ml H_2O), gmha (1.20 g, 10.0 mmol), substrate (40 mmol) and 1,2-dichlorobenzene (internal standard, 2.94 g, 20.0 mmol) in acetonitrile (40 ml) was added H_2O_2 (3.0 ml of 50% aq., 52 mmol) in 6h at 0^oC. Samples were taken 1h after complete addition of oxidant.

Isotope labeling experiments with ^{18}O

Essentially the same procedure was used as described above, except that the reactions were performed on a 0.1 mmol substrate (cyclooctene) scale using labeled H_2O_2 or H_2O. The labeled products were identified by GC/MS (CI).

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6 Abbreviations used: cyclam = 1,4,8,11-tetraazacyclotetradecane; bph = 1,4-bis(2-pyridinyl-methyl)-1,4-diazepane; tpa = tris(2-pyridylmethyl)amine; 6-Me_3-tpa = *N*,*N*,*N*-tris[(6-methyl-2-pyridinyl)methyl]amine; N4Py = *N*,*N*-bis(2-pyridylmethyl)-*N*-bis(2-pyridyl)methyl- amine.

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48 GMHA is an equilibrium mixture, which also contains some hydrated methyl glyoxylate. NMR experiments showed that formation of peroxyhydrate from GMHA and aqueous H_2O_2 is very slow.

Chapter 5

Manganese Catalysts for Alcohol Oxidation

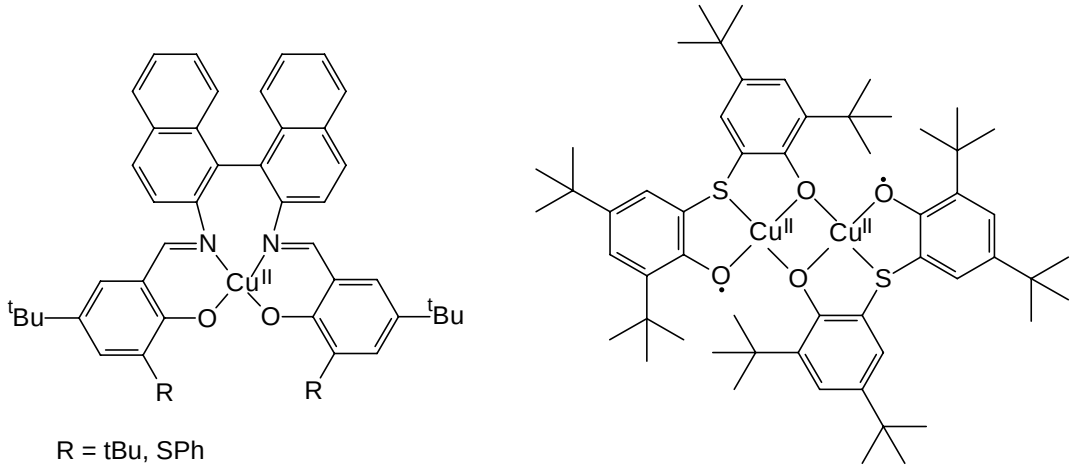
Part of this chapter has been published: Brinksma, J.; Rispens, M. T.; Hage, R.; Feringa, B. L. *Inorg. Chim. Acta* ***2002*** *(accepted for publication).*

Abstract

*In this chapter new manganese complexes and their use as catalyst in the oxidation of alcohols is described. The in situ prepared manganese complexes based on ligands **2.2 - 2.8** were applied in the catalytic oxidation of alcohols to aldehydes or ketones. Highly active and selective catalysts were found with excellent turnover numbers (up to 900) using aqueous hydrogen peroxide as oxidant at ambient temperatures. Electron paramagnetic* resonance *spectroscopy (EPR) and electrospray mass spectrometry (ES/MS) indicated that dinuclear species may be involved in the catalytic oxidations. Comparing the rate of oxidation of benzyl-d_7 alcohol with that of benzyl alcohol by the different catalysts yielded isotope effects (k_H/k_D) of 2.2 - 4.3. Although the exact nature of the oxidising species has not been elucidated, these results indicate that hydroxyl radicals are not involved in these processes.*

5.1 Introduction

The oxidation of alcohols to the corresponding carbonyl compounds is a key reaction in organic synthesis.[1] Many traditional procedures are based on strong oxidising (metal-based) reagents like $KMnO_4$, MnO_2, SeO_2, RuO_4 or chromium(VI) compounds.[2] Recently, a number of catalytic alcohol oxidation methods using cheap and environmental friendly oxidants like oxygen or hydrogen peroxide have been reported.[3] Stack *et al.* reported a mimetic system (complex **5.1**, Figure 1)[4] for the mononuclear copper enzyme galactose oxidase (GOase), which catalyses the aerobic oxidation of benzylic and allylic alcohols to the corresponding carbonyl compounds with the formation of H_2O_2.[5] The studied Cu-model complexes are based on diimine diphenolate ligands containing a binaphthyl backbone unit to enforce a non-square planar geometry preferred by the Cu^{II}-ion.[4] Furthermore, the substituents on the phenolate moieties are necessary in order stabilise the Cu^{I}-phenoxyl radical species. Benzyl alcohol and 1-phenyl ethanol are readily converted to the corresponding carbonyl compounds with the concomitant formation of H_2O_2, using O_2 as oxidant at room temperature. Under neat reaction conditions turnover numbers over 1000 were readily achieved. When the catalytic oxidation experiments where performed in acetonitrile, the reactions occur however, much less efficiently. Another attractive GOase model based on a novel dinuclear Cu^{II}-phenoxyl radical species was described by the group of Wieghardt (**5.2**, Figure 1).[6] High yields could be obtained for the conversion of primary and secondary alcohols. In addition to aldehydes, ketones and/or 1,2-diols were also formed (formed by oxidative C - C coupling). In all cases the reduction product is H_2O_2.[6] More details about reaction mechanisms have been discussed in Chapter 1.

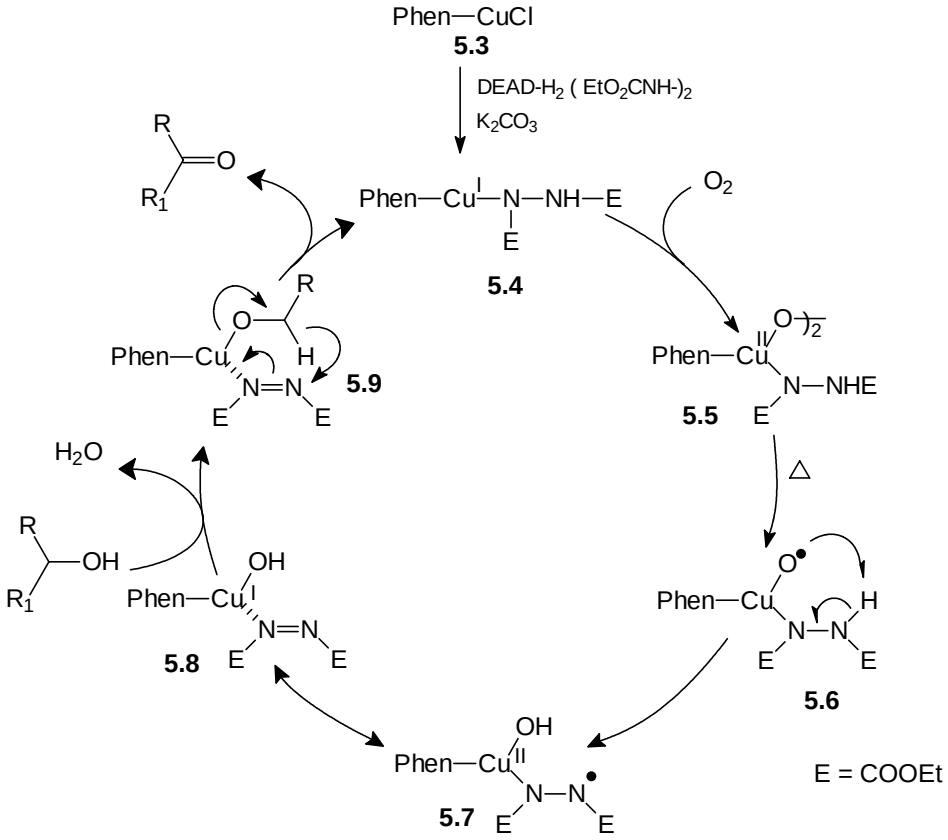


5.1 **5.2**

Figure 1 *Structural models for the galactose oxidase enzyme (GOase).*[4,6]

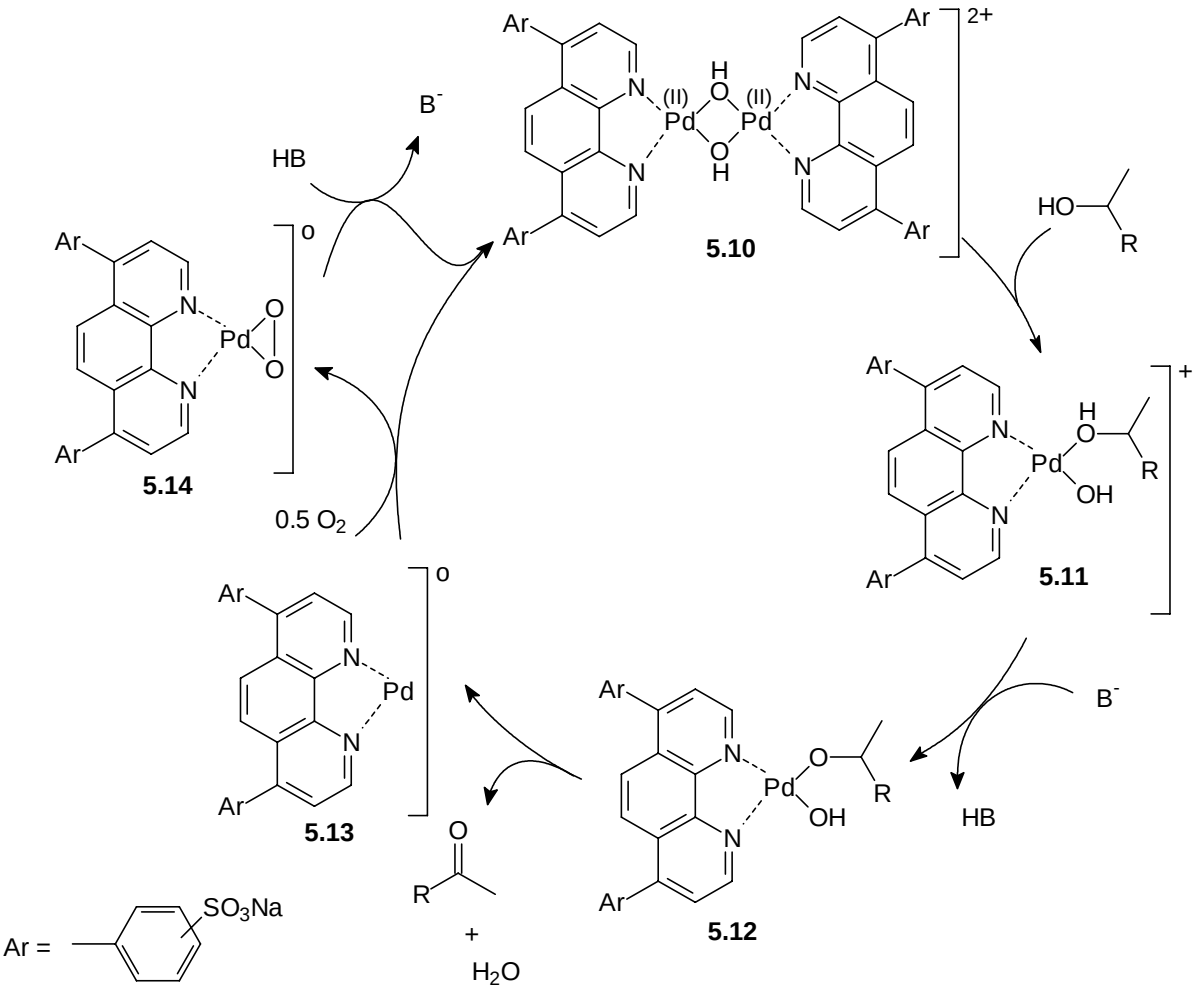
Another selective catalyst for oxidation of alcohols to the corresponding carbonyl compounds on a multigram scale employing O_2 as oxidant was disclosed by Markó *et al.*[7] High conversions and yields were obtained with high tolerance to a variety of functional groups using a 5 mol% phenanthroline Cu^{I}-complex and 5 mol% of a dialkylazodicarboxylate as a hydrogen transferring agent. Oxygen could also be replaced by air after intensive efforts to optimise the catalytic oxidation reaction.[8] Although evidence for a number of postulated intermediates was not obtained, a dehydrogenation mechanism was proposed as given in Scheme 1. Mechanisms involving an oxo transfer process were excluded, because sulfides and alkenes were found to be inert towards oxidation using this procedure.[8] The envisioned mechanism involves the conversion of the copper complex (CuCl.Phen, Phen = 1.10-phenanthroline, **5.3**) to complex **5.4** by the addition of diethylhydrazinodicarboxylate (DEAD-H_2) as the co-catalyst and base. In the presence of O_2, complex **5.4** is subsequently converted to the μ^2-peroxo bis copper(II) intermediate **5.5**. Upon heating, homolytic O - O bond cleavage provides the copper oxy radical **5.6**, followed by intramolecular hydrogen atom abstraction generating radical **5.7** (= azo-substituted copper(I) hydroxyl species **5.8**). Ligand exchange and release of H_2O leads to species **5.9**. Subsequently intramolecular hydride shift and elimination of the carbonyl compound closes the catalytic cycle. The role of the azo additives is besides to transfer hydrogen atoms also believed to stabilise several reactive copper intermediates formed in this catalytic cycle *e.g.* complex **5.8**.[8b]

Sheldon *et al.* recently reported a water soluble palladium(II) bathophenanthroline complex.[9] This Pd-system is a stable and recyclable catalyst for the selective oxidation of terminal olefins to the corresponding 2-alkanones, under neutral, copper and chloride free conditions.[9] The same catalyst also proved to be suitable for the oxidation of alcohols using O_2 as oxidant.[3b]



Scheme 1 *Proposed mechanism for the oxidation of alcohols by the Cu-phenanthroline complex (**5.3**).*[8]

High conversions with high selectivities for both primary and secondary alcohols to the corresponding carbonyl compounds was obtained. However, high temperatures and pressures were necessary (100°C, 30 bar air pressure). As the catalyst precursor a dinuclear Pd-intermediate **5.10** (Scheme 2) containing two bridging hydroxy ligands was postulated.[10] Upon addition of the substrate it presumably converts into mononuclear species **5.11**. Next, the carbonyl compound and water are released after β-hydride elimination. The postulated zero-valent Pd-species **5.13** is subsequently oxidised with O_2 to a Pd-peroxide intermediate **5.14**. The latter species reacts with one equivalent of the Pd^0-species **5.13** to give the starting Pd-dimer **5.10**. Using this water soluble palladium(II) bathophenanthroline catalyst, a wide scope of substrates can be oxidised, including primary and secondary allylic, benzylic and aliphatic alcohols. Turnover numbers of 400 were achieved with yields exceeding 90% for the conversion of secondary alcohols. For the oxidation of primary alcohols longer reaction times were necessary and lower turnover numbers were observed. An attractive feature of this water-soluble catalytic system is the possibility to re-use the Pd-complex maintaining high reactivity and selectivity.[10]



Scheme 2 *Catalytic cycle proposed for alcohol oxidation using a water-soluble Pd-complex.*[3b]

5.2 Oxidation of primary and secondary alcohols with Mn-complexes

The dinuclear manganese(IV) complex $[(Mn_2O(tmtacn)_2](PF_6)_2)$[11,12,13] was studied as catalyst for *e.g.* the oxidation of a range of substituted benzylic alcohols to benzaldehydes.[14]. Turnover numbers in the range of 80 up to 1000 were readily reached with high selectivities employing H_2O_2 as oxidant. From the 16-line spectrum obtained from EPR experiments, it was concluded that the Mn-tmtacn complex is reduced to a dinuclear Mn^{III}-Mn^{IV} mixed-valent species in the presence of oxidant. Ultimately a 6-line spectrum was obtained, indicative of mononuclear Mn^{II}-species.[14]

In the course of our studies on novel ligands featuring three N-donor sets for each Mn-centre in dinuclear Mn-complexes we explored the dinucleating ligands[15] *N,N,N',N'*-tetrakis(2-pyridylmethyl)-1,2-ethanediamine (tpen, **2.2a**) and *N,N,N',N'*-tetrakis(2-pyridyl-methyl)-1,3-propanediamine (tptn, **2.2b**, Figure 2) in catalytic epoxidation reactions.[16]

Advantages of this type of ligand are their easy accessibility and the possibility for ligand modification as described in Chapter 2. Screening the corresponding dinuclear manganese complexes in a number of different catalytic epoxidation reactions showed that the complexes based on tpen (**2.2a**) were unreactive**,** in sharp contrast to the Mn-complexes based on tptn (**2.2b**), containing a two-carbon or a three-carbon spacer, respectively.[16b,c]

In this chapter the use of tpen (**2.2a**), tptn (**2.2b**) and related ligands **2.5 - 2.8** in Mn-catalysed oxidation of a variety of primary and secondary alcohols employing H_2O_2 as oxidant will be discussed.

It will be shown that several *in situ* prepared complexes with $Mn(OAc)_3$ based on tptn (**2.2b**) and tptn-derivatives are active and selective catalysts for the oxidation of a number of substituted primary benzyl alcohols to benzaldehydes and secondary alcohols to the corresponding ketones.

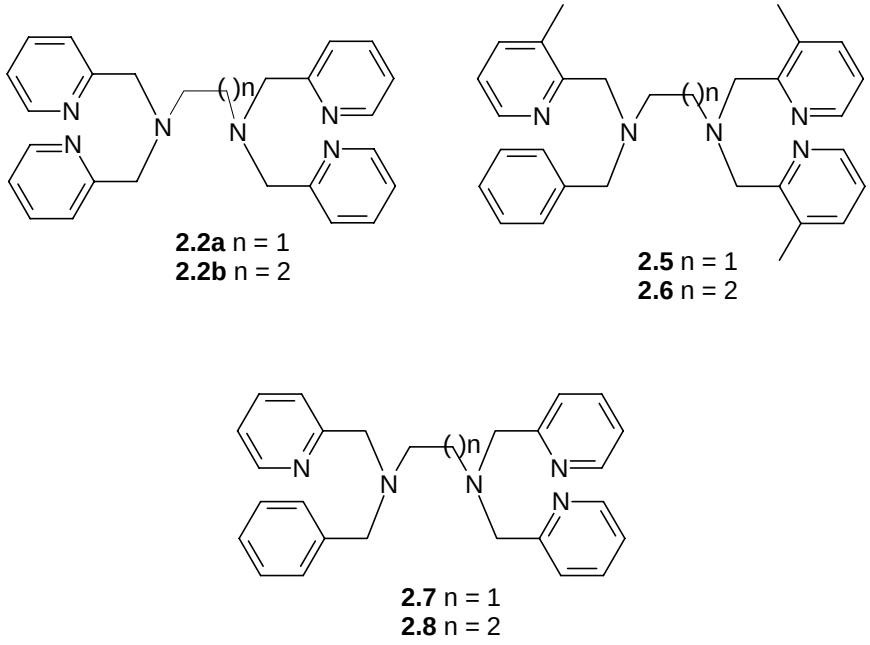
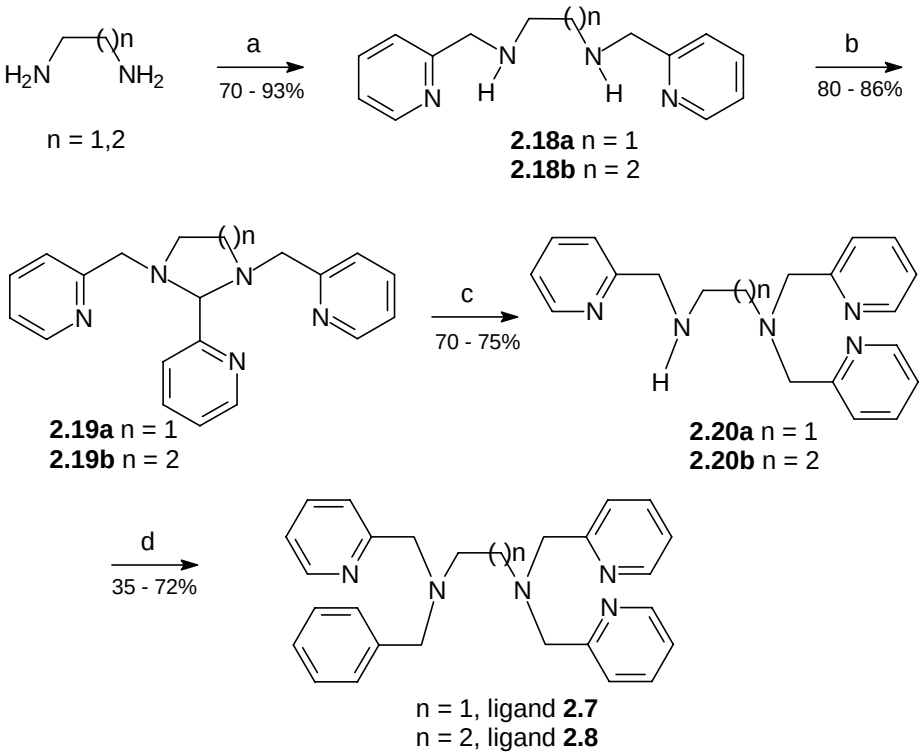


Figure 2 *Ligands used for the manganese-catalysed alcohol oxidation.*

5.3 Synthesis of ligands

The ligands **2.2a** and **2.2b** (Figure 2) were synthesised according to several (slightly modified) literature procedures[15] and the corresponding manganese complexes were studied as epoxidation catalysts.[16] Ligands **2.5** and **2.6** were provided by dr. Minze Rispens. Ligands **2.7** and **2.8** were prepared as described in Chapter 2. The general synthesis route is summarised in Scheme 3.



(a) MeOH, 2-pyridinecarboxaldehyde, $NaBH_4$. (b) Et_2O, 2-pyridinecarboxaldehyde, molecular sieves 4Å. (c). CH_3OH, $NaBH_3CN$, CF_3CO_2H. (d) 1,2-dichloroethane, benzaldehyde, $NaBH(OAc)_3$.

Scheme 3 Synthesis of ligands **2.7** and **2.8**.

5.4 Catalytic oxidation experiments

Catalysts prepared *in situ* from $Mn(OAc)_3$ and ligands **2.2 - 2.8** (Figure 2) were examined as catalysts in the oxidation of a number of substrates utilising H_2O_2 as oxidant.[17] The alcohol oxidation experiments were performed at 0^oC under a nitrogen atmosphere using acetone as solvent. The manganese catalysts based on ligands **2.2a**, **2.2b** were made by mixing 1 equivalent of the selected ligands with 2 equivalents of $Mn(OAc)_3$, followed by addition of substrate (1000 equivalents). For the preparation of catalysts based on ligands **2.5 - 2.8**, 1 equivalent of Mn-salt was used. The reactions were initiated by addition of oxidant and were monitored by GC. The results (turnover numbers and selectivities) for the oxidation of various alcohol substrates to the corresponding carbonyl compounds are summarised in Table 1. The *in situ* prepared Mn-catalyst based on tpen (ligand **2.2a**) resulted in an unreactive oxidation catalyst, similar results were obtained during epoxidation experiments.[18] However, the *in situ* prepared Mn-catalyst based on ligand **2.2b** (tptn) provided a highly active and selective alcohol oxidation catalyst.

Table 1 *Oxidation of selected alcohols with in situ prepared Mn catalysts based on ligands **2.2b** – **2.8**.*[a]

		Turnover numbers after 4h (t.o.n.)[c] and selectivity (%) with ligands **2.2b – 2.8**									
	Substrate[b]	**2.2b**	Sel.[d]	**2.5**	Sel[d]	**2.6**	Sel[d]	**2.7**	Sel[d]	**2.8**	Sel[d]
1	benzyl alcohol	326	95	331	99	303	99	127	95	293	95
2	4-methoxybenzyl alcohol	201	80	270	75	291	75	97	80	255	80
3	4-chlorobenzyl alcohol	449	99	392	99	414	99	127	99	308	99
4	4-trifluoromethylbenzyl alcohol	329	70	317	70	258	70	173	90	352	90
5	4-fluorobenzyl alcohol	233	90	240	80	248	70	21	99	231	88
6	2,5-dimethoxybenzyl alcohol	90	99	71	99	63	99	63	99	72	99
7	cyclohexanol	363	95	583	85	593	80	486	80	595	70
8	cycloheptanol	849	85	808	99	688	99	735	90	894	90
9	1-octanol	108	85	53	90	46	90	53	85	63	70
10	2-octanol	680	95	664	85	480	95	298	95	555	95
11	*sec*-phenylethyl alcohol	657	90	793	90	715	95	400	70	593	70

(a) Conditions, see experimental section. (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 ligand. (d) Selectivity in mole aldehyde (or ketone) per mole converted substrate.

The conversion of benzyl alcohol (entry 1) resulted in the selective formation of benzaldehyde with 326 turnover numbers. Subsequently a range of *para*-substituted benzyl alcohols were screened, achieving high t.o.n.'s in the range of 201 (Table 1, 4-methoxybenzyl alcohol, entry 2) to 449 (4-chlorobenzyl alcohol, entry 3). Although substrates with electron-donating substituents such as 4-methoxybenzyl alcohol (entry 2) react less efficiently compared to substrates containing electron-withdrawing groups like 4-trifluoromethyl benzylalcohol (entry 4), rather small effects on the catalysis (t.o.n.'s) were found. However, a distinct steric effect was observed as *ortho* substituted substrates react more sluggishly and in fact 2,5-dimethoxybenzyl alcohol (entry 6) was found to be virtually unreactive. High conversions were also obtained when secondary alcohols were oxidised. For example, the oxidation of cyclohexanol (entry 7) resulted in 363 t.o.n.'s and also for cycloheptanol (entry 8) excellent results (894 t.o.n.'s) were found with selectivities up to 99% to the corresponding ketones. For 4-trifluoromethyl benzylalcohol lower selectivities were observed (entry 4). Perhaps over-oxidation to benzoic acid takes place, however, this was not quantified. Other secondary alcohols like 2-octanol (entry 10) and *sec*-phenylethylalcohol (entry 11) were selectively transformed to the corresponding ketones with high conversions. Although the oxidation of secondary alcohols proceeds with satisfactory conversions, the *in situ* prepared complexes gave only low conversions in the oxidation of 1-octanol (entry 9).

The Mn-complex prepared *in situ* using ligand **2.7** (Figure 2) resulted in dramatically lower t.o.n.'s for the oxidation of some substrates. With the substituted benzyl alcohols (entry 1 - entry 6) only low t.o.n.'s were reached, typically between 21 (entry 5) and 173 (entry 4), whereas employing secondary alcohols generally higher conversions were observed. However, the results with ligand **2.7** are inferior compared to those with the Mn-catalyst based on ligand **2.2b**. Higher t.o.n.'s were reached by using the *in situ* prepared complex of ligand **2.8**, containing a three-carbon spacer, and the observed results are comparable with the Mn-complex based on ligand **2.2b**.

Suitable oxidation catalysts were also found by employing the Mn-complexes based on ligand **2.5** or ligand **2.6**, resulting in high conversions and selectivities for primary and secondary alcohols. Generally the results even surpasses those found for ligand **2.2b**, achieving turnover numbers easily over 700. In addition preliminary experiments with $Mn(ClO_4)_2$ resulted in only slightly lower conversions compared to $Mn(OAc)_3$.

Addition of a second amount of H_2O_2 (1 ml of a 30% solution in water, 9.8 equivalents with respect to substrate) resulted in some cases (ligand **2.2b** and **2.7**) in a considerable increase in aldehyde or ketone yield, indicating that the catalysts are robust under the conditions used. In a control experiment in which the ligand was omitted, strong peroxide decomposition and no oxidation products were found. In the absence of the manganese salt only substrate and no oxidation products were found.

The reaction time profiles were followed for the oxidation of cyclohexanol to cyclohexanone and the results are summarised in Figure 3. Turnover numbers up to 600 were easily reached for the Mn-complexes. Following the time course of the oxidation of cyclohexanol, a remarkable decrease in induction time was obtained for the complexes based on ligands **2.5** and **2.6**, containing additional methyl groups at the 3-position of the pyridine

rings, compared to the Mn-complexes based on ligands **2.7** or **2.8**. The striking influence of the additional methyl groups on the reactivity could be a result of either electronic or steric properties of the ligands; perhaps pointing to a change in coordination of the ligand as has been observed for Fe-tpa[19] complexes.[20] Notably, Mn-complexes derived from ligands related to **2.5** and **2.6** but with CH_3-groups at the 6-position, were found to be completely inactive during alcohol oxidation experiments. Similar results were observed during epoxidation studies as discussed in Chapter 2.

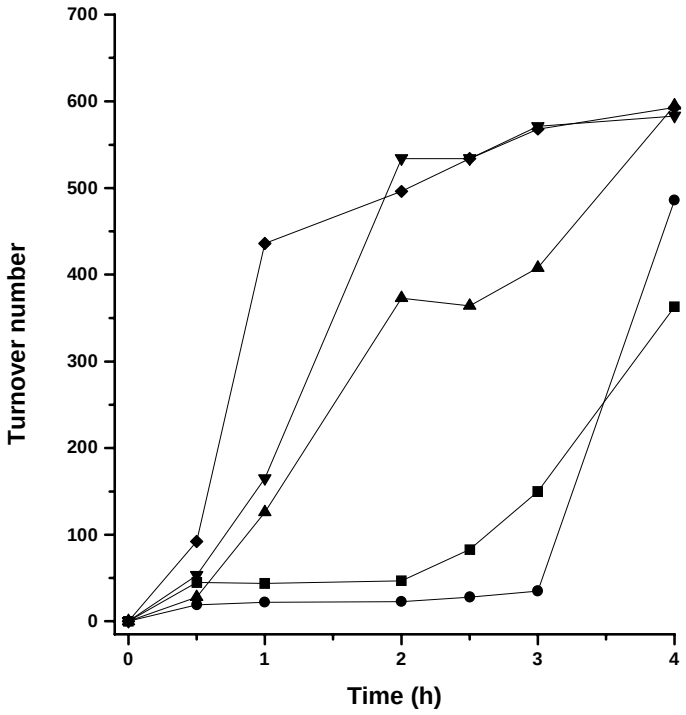


Figure 3 Time profile of the oxidation of cyclohexanol with Mn-complexes prepared *in situ* with ligands **2.2b** - **2.8**:
■ ligand **2.2b**, ▼ ligand **2.5**, ◆ ligand **2.6**, ● ligand **2.7**, ▲ ligand **2.8**.

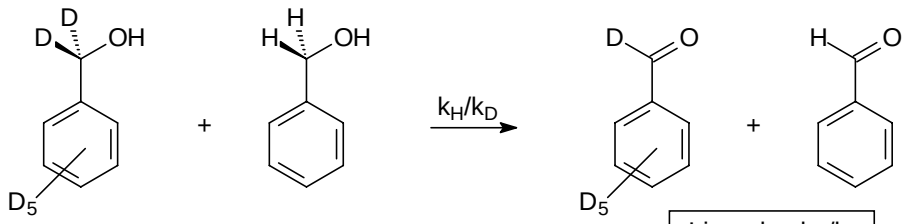
Hodgson *et al.* investigated the effects of methyl groups at the pyridine rings of bispicen[21] ligands (*e.g.* **2.18a**, Scheme 3) on the redox potentials of the corresponding manganese complexes.[22] Structural studies revealed that the methyl groups at the 6-position are in close proximity of the metal center and therefore impose severe steric constraints.[22] Furthermore, from electrochemical studies (cyclic voltammetry) showed that the difference in electrochemical properties between parent and methylated is entirely due to steric factors.[22]

Based on the research of Hodgson, we tentatively propose that the additional methyl groups at the 6-postion in our ligand system prevent the approach of a H_2O_2 molecule to the metal core, resulting in unreactive oxidation catalysts. On the contrary introduction of a methyl functionality at the 3-postions or increasing the spacer length, facilitates the reaction

with H_2O_2. However, additional research is necessary to elucidate the origin of these effects and to establish the relation between the effect of the methyl groups in the ligands and the observed enhanced reactivity.

5.5 Primary kinetic isotope effect

Primary kinetic isotope effects have been extensively studied in order to obtain more insight into oxidation mechanisms.[23] The primary kinetic isotope (k_H/k_D) data found for many alcohol oxidation reactions by high-valent transition metal complexes usually indicate the involvement of an association/dissociation equilibrium of the alcohol to the metal complex prior to hydride or hydrogen transfer.[23] The values of the kinetic isotope effects observed for the oxidation of benzyl alcohol catalysed by the manganese complexes based on ligands **2.2b**, **2.5 - 2.8** were determined by competition experiments between benzyl alcohol and benzyl-d_7 alcohol (Scheme 4). Values in the range of k_H/k_D 2.2 to 4.3 were observed, and these values ($k_H/k_D \geq 2$) strongly indicate that cleavage of the (benzylic) C-H bond is involved in the rate determing step.[4] Higher values were found for the Cu-based galactose oxidase models studied by the groups of Stack ($k_H/k_D = 5.3$)[4] and Itoh ($k_H/k_D = 6.8$).[24] A primary kinetic isotope value of 7.7 was found for galactose oxidase itself by Maradufu *et al*.[25] Similar values ($k_H/k_D = 4.0$) were found in our group for the oxidation of primary and secondary alcohols using a non-heme dinuclear iron catalyst.[26] A k_H/k_D value of 3.8 was calculated for the oxidation of alcohols by the $[Mn_2O(tmtacn)_2](PF_6)_2$ catalyst.[14b] Based on the competition experiments it can be concluded that hydroxyl radicals are not involved in these processes, as due to the high reactivity of these radicals a much lower isotopic effect would be expected.[26] Generally, isotope effect values of 1 - 2 are associated with radical oxidation reactions.[27] In agreement with this, no indications for hydroxylation of aromatic rings for the various substrates employed, as listed in Table 1, have been obtained. Furthermore, no hydroxylation of benzene, which is also a substrate for hydroxylation using OH radicals,[28] has been observed under the same conditions.



Ligand	k_H/k_D
2.2b	3.2
2.5	3.1
2.6	3.4
2.7	2.2
2.8	4.3

Scheme 4 *Competition experiments used for isotope effect determination.*

5.6 EPR and ES/MS experiments

The catalytic alcohol oxidation reactions were investigated by electron paramagnetic resonance spectroscopy (EPR). Initial experiments involved the *in situ* preparation of the Mn-complexes using ligands **2.2a, 2.2b** and **2.5 - 2.8**, under the same conditions as employed for the catalytic oxidation reactions (see paragraph 5.4). Samples of the catalytic oxidation reaction mixture at 0^oC were taken in acetone and frozen to 77K for EPR studies. After mixing the ligands and $Mn(OAc)_3.2H_2O$ for 15 min no EPR signals were obtained at 77K, which may be caused by the formation of EPR-silent Mn^{III}-species or antiferromagnetically coupled Mn^{IV}-Mn^{IV} species. After addition of substrate (cyclohexanol) and oxidant (1.0 ml of 30% aq. H_2O_2, 9.8 equivalents with respect to substrate) samples were immediately frozen to 77K for EPR analysis. Mixing ligand **2.6** with $Mn(OAc)_3.2H_2O$ yields immediately after addition of H_2O_2 a strong 16-line signal with an A value of 78 G (Figure 4). Only weak 16-line signals were detected for the complexes based on ligands **2.2b** and **2.8**. For the complexes prepared with ligands **2.2a**, **2.5** and **2.7** no EPR signals were detected. After 30 min the complexes derived from ligands **2.5** and **2.7** starts as well to display weak 16-line EPR signals comparable with catalysts prepared from ligands **2.2b** and **2.8**. However, after 90 min incubation at 0^oC now also strong signals were obtained for the *in situ* prepared complexes based on ligands **2.2b**, **2.5**, **2.7**, **2.8**, whilst the intensity for the ligand **2.6** system remained constantly high. The obtained characteristic 16-line spectra represent mixed-valence Mn^{III}-Mn^{IV} complexes with an A value of 78 Gauss.[29] After a reaction period of 4h, however, only the complexes based on ligands **2.2b** and **2.7** still displayed a weak Mn^{III}-Mn^{IV} EPR signal (roughly 10% of the intensity observed after 90 min). The manganese complexes based on ligands **2.5**, **2.7**, **2.8** showed a 6-line EPR signal with an A value of 108 Gauss, typical for a mononuclear Mn^{II}-species.[14] In sharp contrast to ligands **2.2b**, **2.5 - 2.8**, complexes with ligand **2.2a** (tpen) remained EPR silent over the entire 4h reaction period.

Using electrospray mass spectroscopy (ES/MS) resulted in the observation of mainly mononuclear complexes after mixing the ligands **2.2a**, **2.2b**, **2.5 - 2.8** with $Mn(OAc)_3.2H_2O$. Upon mixing ligand **2.2a** with the Mn-salt, the ES/MS spectrum showed prominent peaks at m/z 425 and m/z 538, corresponding to protonated ligand **2.2a** ($[HL]^+$) and a mononuclear complex identified as $[LMn(OAc)]^+$, respectively. Similar species were obtained by preparing the complex *in situ* from ligand **2.2b**, resulting in signals at m/z 439 and m/z 552. However, after mixing ligand **2.7** with $Mn(OAc)_3$ signals for mononuclear complexes (m/z 537) were observed. Using ligand **2.8** containing a three-carbon spacer, a base peak of m/z 438 was found which was assigned to the free ligand. Mixing ligand **2.5** and **2.6** resulted in peaks at m/z 579 and at m/z 593 assigned to mononuclear species with the general structure $[LMn(OAc)]^+$. After addition of substrate and H_2O_2 to the *in situ* prepared Mn-complexes we found for the complex based on ligand **2.2a** a base peak (at m/z 538), which was assigned to $[LMn(OAc)]^+$.

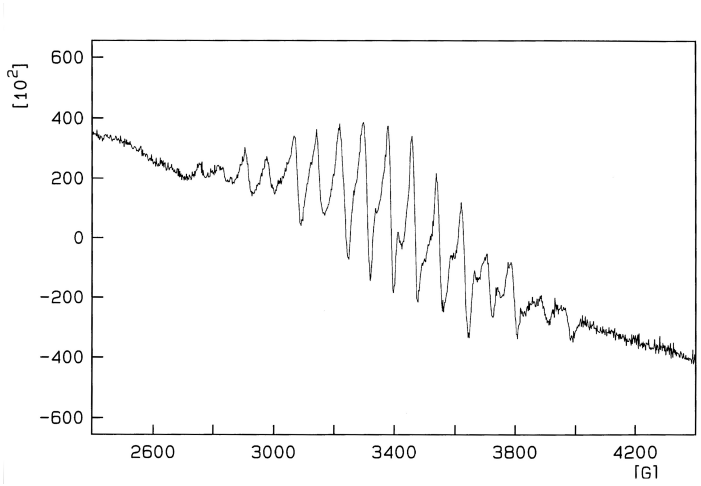


Figure 4 *Electron paramagnetic resonance spectrum of in situ prepared manganese complex based on ligand **2.6** immediately after addition of cyclohexanol and oxidant.*

For the complexes based on ligand **2.2b**, **2.6** and **2.8** signals at m/z 683, 724 and 682 were detected, corresponding to species like $[LMn^{II}_2(OAc)_2(OH)]^+$. It is noted that this is *not* the species observed with EPR. Whilst most Mn^{III}-Mn^{IV} species studied so far are magnetically strongly coupled due to two bridging oxygen atoms,[30] dinuclear manganese(II) complexes with acetato bridges exhibit weak coupling and consequently exhibit very different EPR spectra.[31] Although EPR experiments showed also dinuclear complexes after mixing ligands **2.5** and **2.7** with $Mn(OAc)_3.2H_2O$, these results could not be confirmed by the ES/MS experiments, perhaps due to redox chemistry or other side reactions in the mass spectrometer.

5.7 Conclusions

In conclusion, we have demonstrated that the *in situ* prepared manganese complex based on tptn (ligand **2.2b**) and the related ligands **2.5** - **2.8** are promising catalysts in a new alcohol oxidation procedure using H_2O_2 as the terminal oxidant. Main advantages of this 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 alcohols to the corresponding aldehydes or ketones, with H_2O_2 as oxidant.

For the selected *in situ* prepared Mn-complexes based on the discussed ligands, generally turnover numbers up to nearly 900 were found. Preliminary screening experiments of different catalytic alcohol oxidation reactions showed that the *in situ* prepared manganese complex with the tpen **2.2a** was unreactive, similar to ligand characteristics in previously described epoxidation studies.[16b,c] The tptn-based modified ligands **2.7** and **2.8**, containing a two-carbon spacer and a three-carbon spacer, respectively, were found to provide moderate

(complex based on ligand **2.7**) to active catalysts (based on ligand **2.8**), although long induction periods were observed. Using *in situ* prepared complexes based on ligand **2.5** and ligand **2.6** excellent results were found and most remarkably, the induction period was strongly reduced particularly with complexes derived from ligand **2.6**.

This may be linked with the observation that ligand **2.6** yields a strong 16-line EPR signal immediately after mixing the ligand with Mn-salt, H_2O_2 and substrate. Therefore we tentatively assign dinuclear species as being involved in the oxidation reactions. It needs to be emphasised that for the other ligands much longer induction times were observed before the oxidation reactions have been initiated. Furthermore, also longer incubation periods were necessary before strong 16-line EPR signals were detected.

ES/MS monitoring experiments also gave to some extent indications for the formation of dinuclear Mn-intermediates. The ligands with the three-carbon spacer yield in all cases much quicker active catalysts (showing shorter lag phases) than the two-carbon analogues, likely connected with a faster formation of dinuclear species.

Comparing the rate of oxidation of benzyl-d_7 alcohol with that of benzyl alcohol by the different catalysts showed isotope effects (k_H/k_D) of 2.2 - 4.3 and these results indicate that hydroxyl radicals are not involved in these processes. However, we cannot conclude which species exactly is involved in the oxidation reactions, *e.g.* high-valent Mn=O species or Mn-OOH species. Based on the EPR experiments of the reaction mixtures we tentatively propose that by mixing the ligands with Mn-salts, subsequent addition of H_2O_2 gives rise to the formation of dinuclear Mn-species, which could be the intermediate precursors of the active intermediates for the oxidation of alcohols. During the oxidation reactions, these complexes are ultimately converted to mononuclear Mn^{II}-species.

5.8 Acknowledgements

Dr. Minze Rispens (University of Groningen) is gratefully acknowledged for providing several ligands described in this chapter. Dr. Ronald Hage (Unilever Research Vlaardingen) is gratefully acknowledged for helpful discussions and for the assistance with recording several EPR spectra.

5.9 Experimental section

General procedure and methods

For general information, see Chapter 2.

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 alcohols and carbonyl compounds and independent samples. Conversions, yields and turnover numbers are the average of 2 - 3 runs (error $\pm$10%) and were determined using bromobenzene as internal standard and calculated using the Chemstation software.

ES/MS and EPR experiments

The electrospray mass (ES/MS) experiments were performed at room temperature at a Micromass ZMD 2000, ESIC(+) Vcone = 20V and Vcap = 3.25kV connected to a Alliance 2690 HPLC system, at the analytical department of the University of Groningen.
EPR experiments were carried out at Unilever Research Vlaardingen, using a Bruker ECS 106 at 77K.

Catalytic oxidation reactions

Catalytic alcohol oxidation reactions were started by mixing 1.0 ml of a stock solution of $Mn(OAc)_3.2H_2O$ in acetone and 1.0 ml of a stock solution of ligand **2.2b** (or **2.2a**). After stirring for 15 min, 1.0 ml of a stock solution of substrate and bromobenzene (internal standard) were added. After stirring for 2 min, excess of oxidant (1.0 ml of 30% aq. H_2O_2) was added. The concentrations of $Mn(OAc)_3$, ligand **2.2b** (or **2.2a**), substrate, hydrogen peroxide and internal standard were 2 mM, 1 mM, 1M, 9.8 M and 0.5 M, respectively. 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 establish the identity of the alcohols and carbonyl compounds unequivocally, the retention times and spectral data were compared to those of commercially available or independently synthesised compounds. The same procedure as described for the catalytic reactions with **2.2b** was followed with ligands **2.5** - **2.8** except that a 1M stock solution of $Mn(OAc)_3.2H_2O$ was used.

Determination of primary kinetic isotope effect (k_H/k_D) for the catalytic oxidation of benzyl alcohol and benzyl-d_7 alcohol

For determination of the k_H/k_D values, the same procedure as used in the previous described catalytic oxidation experiments was followed except that 1.0 ml of a stock solution (conc. 1 M) of benzyl alcohol, *p*-methylbenzyl alcohol and of bromobenzene (conc. 0.5 M, internal standard) were used. Another solution, using benzyl-d_7 alcohol, *p*-methylbenzyl alcohol and bromobenzene (internal standard) was also prepared and used as substrate.

The amounts of alcohols before and after the oxidation reaction were determined by GC analysis. The k_H/k_D value was determined using the following the equations:[32]

$k_H / k_{Me} = \log (H_f / H_i) / \log (Me_f / Me_i)$ (1)

$k_D / k_{Me} = \log (D_f / D_i) / \log (Me_f / Me_i)$ (2)

then , k_H/k_D = (eq 1) /(eq 2)

H_f and H_i are final and initial quantities of benzyl alcohol.

D_f and D_i are final and initial quantities of benzyl alcohol d_7.

Me_f and Me_i are final and initial quantities of *p*-methylbenzyl alcohol.

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18 See Chapter 2.

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Chapter 6

New Ligands for Manganese-Catalysed Selective Oxidation of Sulfides to Sulfoxides with Hydrogen Peroxide

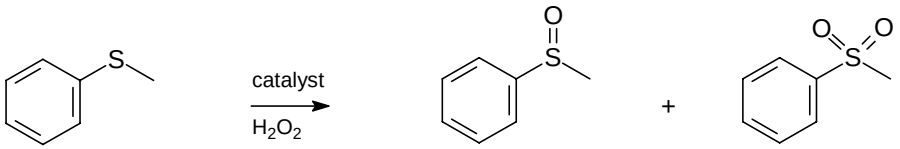
Part of this chapter has been published: Brinksma, J.; La Crois, R.; Feringa, B. L.; Donnoli, M. I.; Rosini, C. *Tetrahedron Lett.* **2001**, *42*, 4049 - 4052.

Abstract

A number of manganese complexes have been used in catalytic oxidation of sulfides to sulfoxides with hydrogen peroxide at 0°C in acetone. Chemical yields of a series of different alkyl aryl sulfoxides are obtained in the range of 48 to 55%, and turnover numbers up to 250 were found, while the formation of sulfones is almost suppressed. In addition the use of chiral ligands resulted in chiral Mn-catalysts affording a series of different alkyl aryl sulfoxides with 50% yield and with enantioselectivities up to 18%.

6.1 Introduction

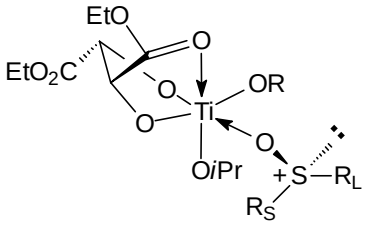
The selective catalytic oxidation of sulfides to sulfoxides has been a challenge for many years, due to the importance of sulfoxides as intermediates in organic synthesis.[1] The use of hydrogen peroxide as oxidant has been extensively studied.[2] The undesired sulfone is a common by-product in sulfide oxidation reactions with H_2O_2 and its formation has to be suppressed (Scheme 1).



Scheme 1 *Possible products of the oxidation of methyl phenyl sulfide.*

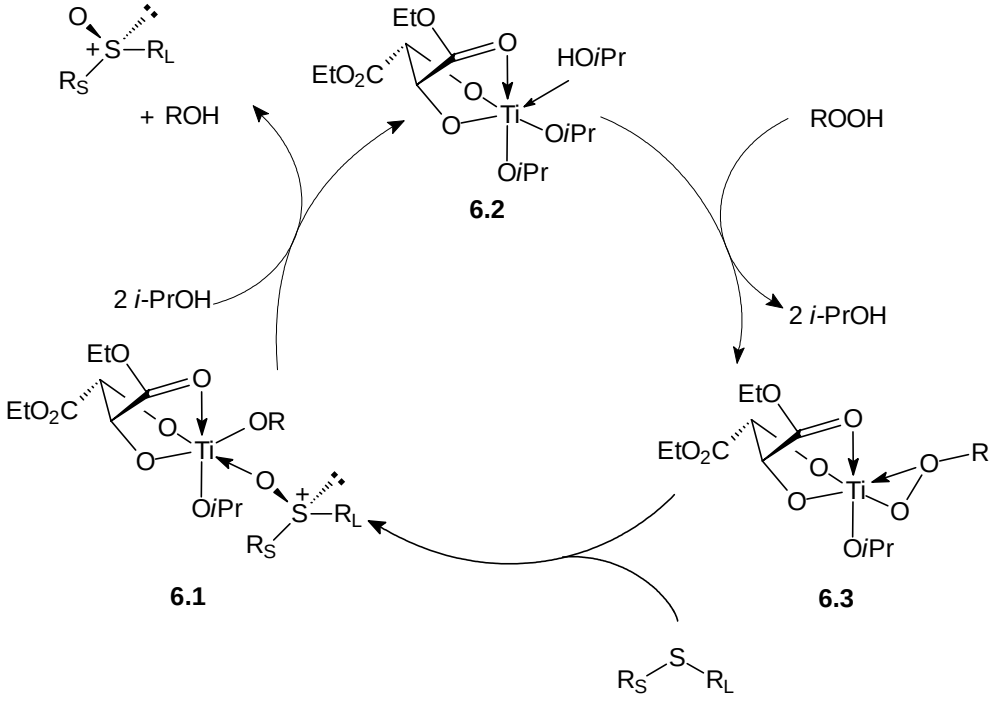
Much effort has been devoted also to the development of catalytic methods for the preparation of optically active sulfoxides owing to their importance as chiral ligands[3], and bioactive products.[4] Kagan[5] and Modena[6] observed that the use of diethyltartrate and titanium tetra isopropoxide (Ti(O*i*-Pr)$_4$) and hydroperoxides as oxidant yields enantiomeric excesses exceeding 90% in the oxidation of aromatic thioethers. Initially Kagan employed the standard Sharpless reagent[7] but discovered only racemic sulfoxide. After modification of this system by adding one equivalent of water a dramatic improvement of enantioselectivity was obtained for a range of sulfides and sulfone formation was avoided. The process was made catalytic by adding molecular sieves (4Å) before the formation of the catalyst.[8] The molecular sieves presumably acts as a moisture scavenger and therefore control the amount of water present in the reaction mixture. However, the role of the molecular sieves is at present unclear. Recently, the use of water was replaced by 2-propanol, which resulted in the opportunity to further decrease the catalyst loading and using cumylhydroperoxide as oxidant sulfoxides were obtained with yields in the range of 75 - 95%.[9]

The active species in the catalytic cycle is proposed to be a monomeric titanium complex (Figure 1).[3] The monomeric titanium compound is coordinated to two isopropoxide moieties and bound in a tridentate fashion to one diethyl tartrate. The overall catalytic cycle is given in Scheme 2; this mechanism is based on titanium complexes attached to minimally one isopropoxide ligand. High enantiomeric excesses are mainly obtained for the oxidation of sulfides containing substituents with substantially different sizes.



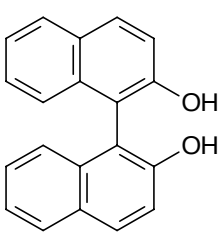
6.1

Figure 1 *Proposed active monomeric titanium intermediate.*[3]



Scheme 2 *Proposed catalytic mechanism for enantioselective sulfide oxidation.*

After the discovery of Kagan and Modena a number of publications related to this research followed based on chiral diols.[10] Several chiral ligands with alcohol moieties are given in Figure 2.



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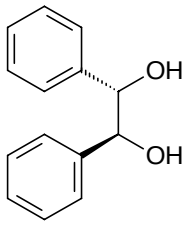

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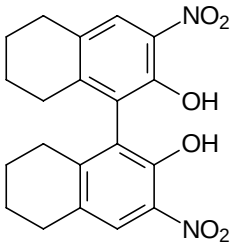

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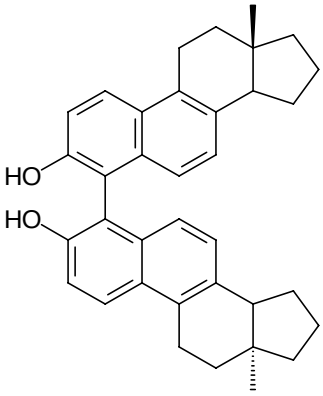

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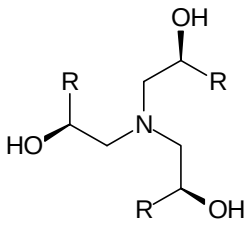


6.8b R = Me
c R = Ph
d R = *t*-Bu

Figure 2 *Chiral diol and triol ligands in titanium-catalysed sulfide oxidation.*

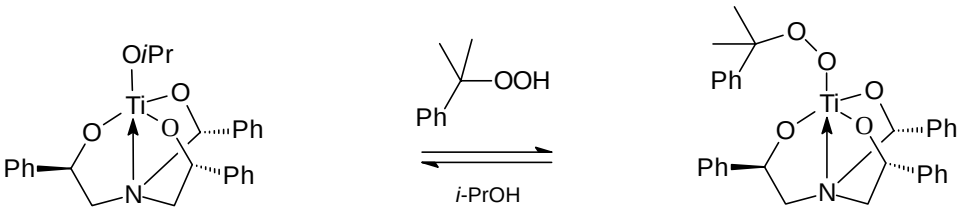
Titanium complexes based on *R*-(+)-binaphthol (**6.4**) gave optically active sulfoxides with high enantiomeric excesses using *tert*-butyl hydroperoxide (*t*BuOOH) as stoichiometric oxidant.[11] In general the *para*-substituted phenyl benzyl sulfides result in low enantioselective excesses using titanium catalysts.[5a] However, Rosini *et al*. obtained good conversion and e.e.'s for *para*-substituted phenyl benzyl sulfides by using only 0.05 equivalent of a chiral titanium complex derived from (*S*)-diphenyl ethan-1,2-diol (**6.5**).[10b,12]

Reetz *et al*. published the use of (*R*)-3,3'-dinitrooctahydrobinaphthol (**6.6**) as chiral ligand. The nitro groups proved to be of major importance since the enantiomeric excesses dropped from 86% to 10% when octahydrobinaphthol was used with cumyl hydroperoxide as oxidant.[13] Remarkably, the reversed absolute stereochemistry of the product was observed using the Reetz procedure using ligand **6.6**. Reversal of chiral induction was also found upon fluorine substitution at the 5,5'-, 6,6'-, 7,7'- and 8,8'-positions of binaphthol.[14]

The yield was further improved by using bissteroidal diol **6.7** ligands using *t*BuOOH as oxidant in THF with 1 to 3 equivalents of water.[15] Interestingly, the stereogenic centres in the steroid backbone of the ligand determined the absolute configuration of the product.

Nugent and Harlow introduced a different approach based on C_3-symmetrical triol amines **6.8** (Scheme 2).[16] The C_3-symmetrical triol amines were converted to titanium complexes **6.9** by addition of a stoichiometric amount of trialkanolamine to a solution of Ti(O*i*-Pr)$_4$ in dichloromethane. After reaction with cumyl hydroperoxide the monomeric

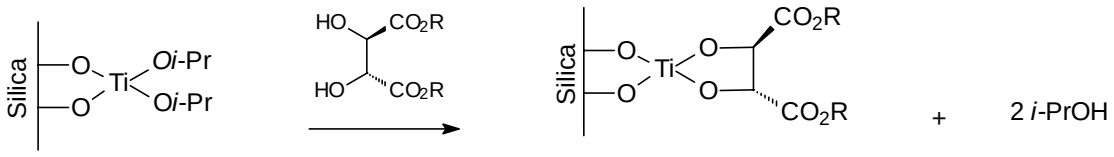
titanium peroxide **6.10** was obtained and completely characterised by electrospray ionisation and NMR spectroscopy studies[17] and used as catalyst of the oxidation of alkyl aryl sulfides resulting in moderate e.e.'s (Scheme 3).[18]



6.9 **6.10**

Scheme 3 *Formation of monomeric titanium peroxide.*

In only a few cases has H_2O_2 been utilised as terminal oxidant for oxidation reactions with titanium-based catalysts. Titanium derivatives supported on silica have been investigated as catalysts in these oxidation reactions (Scheme 4).[19] Mayoral *et el.* initially used the titanium supported silica catalyst **6.11** with *t*BuOOH but found higher sulfoxide/sulfone selectivity when H_2O_2 was employed.[20] After recovery of the catalyst similar activity, but an increase in selectivity with H_2O_2 was found caused by modification of the titanium centres by the large excess of water (aqueous H_2O_2 was used). The excess of water probably hydrolyses the isopropoxy groups to hydroxy groups and therefore polar diethyl tartrate groups were coordinated to the catalyst giving catalyst **6.12a**. The introduction of diethyl tartrate resulted in a reduction of the catalytic activity but an increase in sulfoxide/sulfone selectivity with *t*BuOOH, while the catalytic activity was almost not affected when H_2O_2 was used. Again the recovered catalyst gave an increase in selectivity, which points to a new structure after the recovery. The change of the IR carbonyl band after the oxidation reaction suggested hydrolysis of the ester groups and therefore tartaric acid groups were introduced. Oxidation results using *t*BuOOH with catalyst **6.12b** were found to be very similar to those with the tartrate **6.12a** catalyst but the reaction with H_2O_2 results in excellent chemoselectivity to sulfoxide; however, only low enantioselectivity (13%) was obtained.[20]

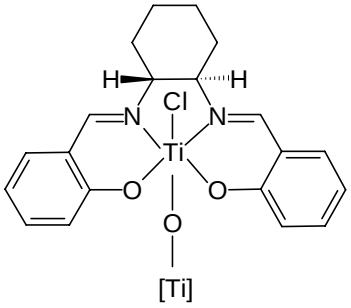


6.11

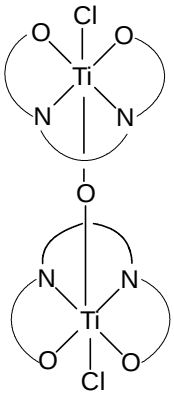
6.12 a R = Et
b R = H

Scheme 4 *Titanium derivatives supported on silica.*

Fujita employed chiral titanium Schiff base complexes in the asymmetric sulfide oxidation chemistry.[21] Starting from the C_2-symmetrical salen ligand the titanium complex **6.13** was synthesised by reacting titanium tetrachloride ($TiCl_4$) with the Schiff base ligand in wet pyridine. The structure was confirmed by X-ray and was elucidated as a μ-oxo dinuclear structure in dichloromethane, but in methanol a mononuclear species was found. The complex catalyses the asymmetric oxidation of methyl phenyl sulfide to the corresponding oxide, however, only with organic hydroperoxides like triphenylmethyl hydroperoxide, 1-methyl-1-phenylethylhydroperoxide or *tert*-butyl hydroperoxide. With 4 mol% of titanium catalyst sulfoxides were obtained with enantioselectivities up to 53%.



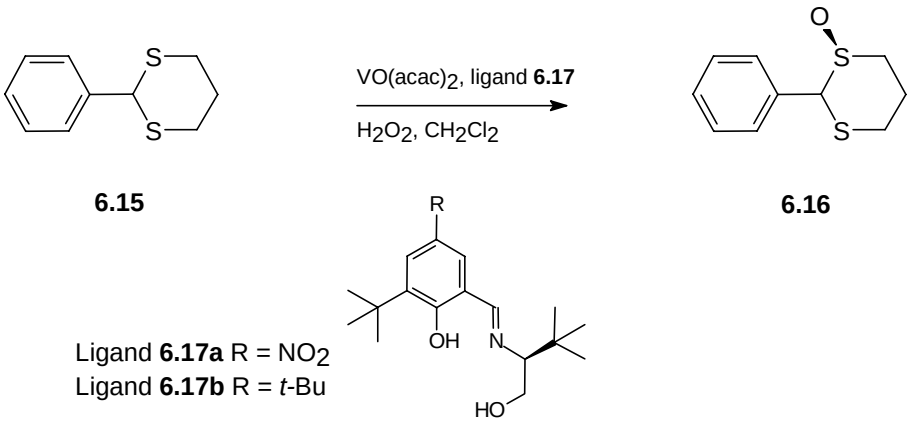
6.13



6.14

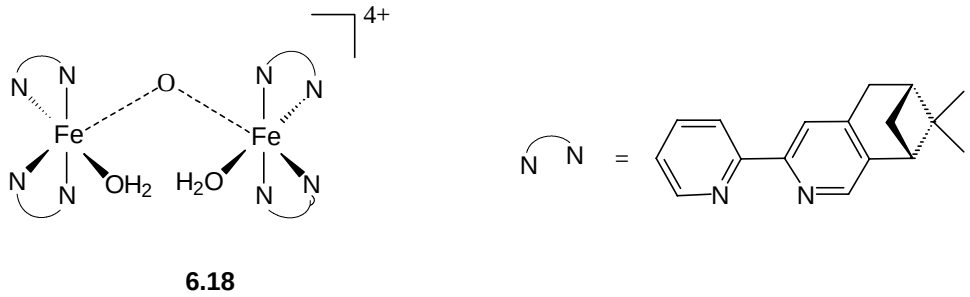
Figure 3 *Chiral titanium schiff base complexes.*

Besides manganese and titanium salen derived complexes, oxovanadium(salen) compounds were studied as catalysts for the oxidation of a range of different sulfides. In the presence of 4 mol% of vanadium complex sulfoxides in good yields but with moderate e.e.'s in the range of 20 - 40% were obtained employing organic hydroperoxides.[22,23] Vanadium Schiff base catalysts were introduced by the group of Bolm and prepared *in situ* from $VO(acac)_2$ and the Schiff bases.[24,25] Various sulfides and dithianes have been oxidised with only 0.01 mol% of catalyst loading. Using aqueous H_2O_2 enantioselectivities were obtained in the range of 53 - 70%. The dithiane **6.15** given in Scheme 5 was converted to the corresponding sulfoxide **6.16** with an e.e. of 85% with aqueous H_2O_2 using ligand **6.17b**. Remarkably, during the oxidation at room temperature and under air conditions only traces of sulfone were detected. By further exploiting the ligands, *tert*-butyl disulfide was oxidised to *tert*-butyl *tert*-butanethiosulfinate with 91% e.e. and 94% yield.[26]



Scheme 5 *Vanadium-based Schiff base catalyst.*

Iron catalysts for sulfide oxidation reactions have been reported, for the first time by Fontecave *et al.*, describing a highly robust non-heme iron complex **6.18** (Figure 4).[27] The complex contains a chiral pinene modified 2,2'-bipyridine ligand[28] and was used for oxidation of cyclohexane, linear alkanes as well as epoxidation of alkenes and sulfides at room temperature with H_2O_2.[29] Remarkably, the catalytic activity of the complex remained constant after multiple use (up to 50 times) after the recovery of the complex. High yields and e.e.'s between 18 and 40% were reached and, importantly, no over-oxidation to sulfone occurred. The results with this bipyridine system are comparable to that of the chiral iron binaphthalene tetraphenylporphyrin but the latter catalytic system needs oxidants like alkyl hydroperoxides or iodosylbenzene.[30]

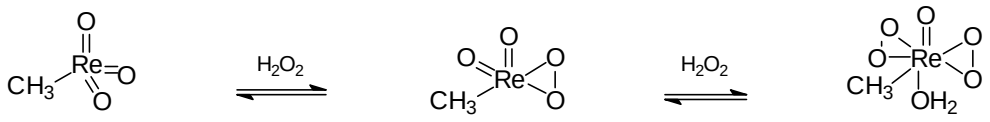


6.18

Figure 4 *Dinuclear iron complex of a chiral bipyridine ligand.*

Methyltrioxorhenium (CH_3ReO_3, MTO, **6.19**, Scheme 6) has been established as a versatile oxygen transfer catalyst for a variety of oxidation reactions like epoxidation, hydroxylation of olefins and sulfide oxidation with H_2O_2.[31,32] A wide range of sulfide substrates can be oxidised in the presence of a catalytic amount of MTO although long reaction times in the range of 19 to 192h in dichloromethane or chloroform were necessary. Upon switching to acetonitrile a striking solvent effect was observed. For example, the MTO-catalysed oxidation of methyl phenyl sulfide was completed in 10 min as compared to 36h in

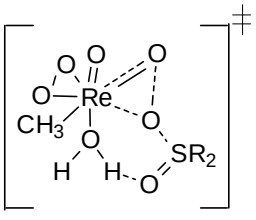
chloroform using 2 - 3 mol% of catalyst with chemical yields up till 92%.[33] The activation of H_2O_2 is based on the interaction with methyltrioxorhenium yielding an equilibrium mixture of two potential catalytic active peroxorhenium compounds, the mono- and diperoxo complexes **6.20** and **6.21**, respectively.[34] The diperoxo compound **6.21** has been structurally characterised by X-ray crystallography.[35]



6.19 **6.20** **6.21**

Scheme 6 *Activation of H_2O_2 by MTO.*

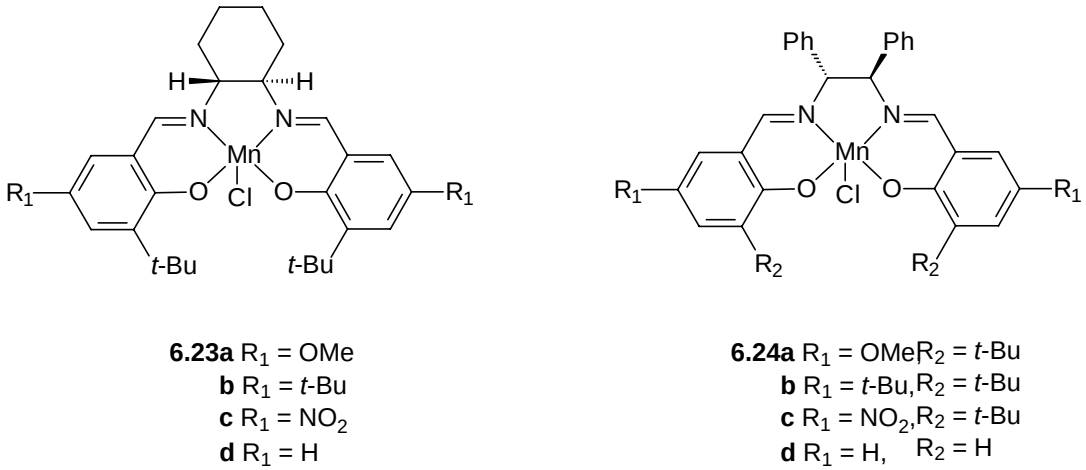
In aqueous solution the water molecule remains coordinated to the diperoxo compound **6.21** which was concluded from ^{1}H-NMR experiments performed in d^8-THF at 55^{o}C. For the monoperoxo complex **6.20** no indicative ^{1}H signals for H_2O were obtained, implying water is not coordinated or the coordination is exceptionally labile.[36] From kinetic studies it was confirmed that H_2O_2 converts MTO to the 1:1 and 2:1 rhenium peroxide complexes.[37,38] The second step involves the reaction of the peroxides **6.20** or **6.21** with the substrate. From the oxidation results of a broad range of substrates it was found that the relative reaction rate depends strongly on the identity of the substrates and solvents. Increasing the electron donating ability of the substrate resulted in an increase of reaction rate. The use of substrates with electron withdrawing substituents resulted in a rate decrease. Based on this electronic effect it was proposed that the sulfur atom of the substrate attacks as a nucleophile the peroxo group of the 1:1 complex **6.20**. Increasing the hydrogen peroxide concentration resulted in sulfone which was explained by the fact that **6.21** contains a water molecule which can allow hydrogen bond formation to the oxo group of the sulfoxide giving a six-membered ring, which facilitates the conversion to the sulfone (Figure 5).



6.22

Figure 5 *Transition state for sulfone formation with diperoxo MTO complex.*

Jacobsen studied the sulfide oxidation catalysed by the well established manganese(III) salen complexes.[39] For the epoxidation reactions with the salen complexes sodium hypochlorite was used as oxidant.[40] It turned out that sodium hypochlorite was too reactive for the oxidation of sulfides but employing iodosylbenzene as oxygen atom transfer source no over-oxidation was obtained. Disadvantages of iodosylbenzene are the poor solubility, low oxygen atom efficiency and high cost for practical application. By changing to H_2O_2 high chemical yields and identical enantiomeric excesses (range of 34 - 68%) compared with iodosylbenzene were obtained. Using acetonitrile as solvent and 2 - 3 mol% of catalyst with 6 equivalents of oxidant the formation of sulfone was minimised.[41] Ligands with bulky-substituents at the 3,3'- and 5,5'-positions resulted in the highest enantioselectivity (Figure 6). The enantioselectivity of the sulfide oxidation is in general lower than that of the epoxidation using these catalysts. Ligand **6.23b** emerged as most selective for the oxidation of a variety of substrates. Complexes of ligands with electron-withdrawing substituents were found to be less enantioselective. For example complex **6.23c** containing a nitro substituted ligand did not induce enantioselectivity; presumably this effect is attributed to the greater reactivity of catalyst **6.23c**.



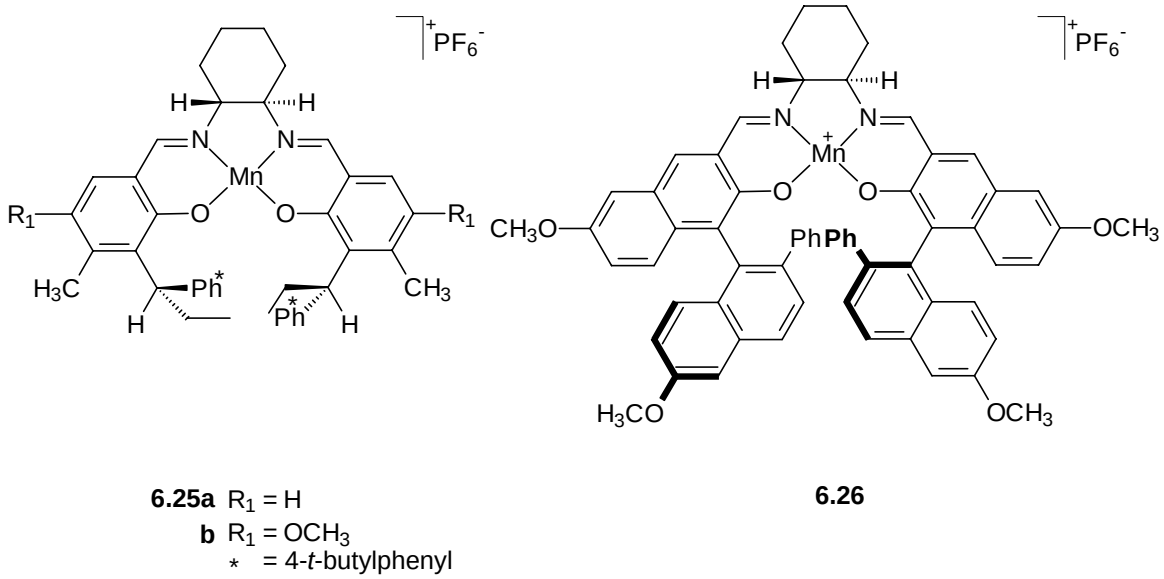
6.23a R_1 = OMe
b R_1 = *t*-Bu
c R_1 = NO_2
d R_1 = H

6.24a R_1 = OMe, R_2 = *t*-Bu
b R_1 = *t*-Bu, R_2 = *t*-Bu
c R_1 = NO_2, R_2 = *t*-Bu
d R_1 = H, R_2 = H

Figure 6 *Manganese(III) salen complexes for sulfide oxidation.*

Katsuki *et al.* used similar manganese salen complexes for sulfide oxidation as Jacobsen *et al.*[42,43] Although in the Jacobsen procedure the preferred oxidant was H_2O_2 it resulted in lower yields and more over-oxidation than using the related Katsuki complexes employing H_2O_2 as oxidant.[42,43] The reasons for this difference are still not clear. The successful epoxidation catalyst **6.25a** (Figure 7) was used for the oxidation of methyl phenyl sulfide by iodosylbenzene as oxidant and resulted in good yields of sulfoxide (67%), whereas sulfone formation (30%) was found to be the minor oxidation reaction.[44] However, only an e.e. of 3% was obtained. By introducing an electron-donating methoxy group (complex **6.25b**) an increase of e.e. (29%), although still moderate, was reached. Considerably higher e.e.'s were found by using the diastereomer of **6.25b**. The addition of pyridine-*N*-oxide and lowering the temperature to -20^{o}C resulted in a further improvement. The best results were

achieved with substrates containing electron-withdrawing substituents.[44] Finally the catalytic system was fine-tuned by introducing axial chirality in the ligand giving **6.26**. With this catalyst also aryl ethyl sulfides could be oxidised with high yield and selectivity; these substrates showed poor conversion with the initially studied systems.[45] Recently, Katsuki and Saito synthesised di-μ-oxo titanium complexes starting from the salen ligands **6.25** and **6.26** and the complexes were found to serve as efficient catalysts for asymmetric oxidation of various sulfides using H_2O_2 or the urea-hydrogen peroxide adduct as oxidants.[46] Enantioselectivities as high as 94% were observed[46] and as active intermediate a monomeric peroxo titanium species was proposed based on MS and NMR studies.[47]



6.25a R_1 = H
b R_1 = OCH_3
* = 4-*t*-butylphenyl

6.26

Figure 7 *Katsuki complexes for sulfide oxidation.*

6.2 Synthesis of ligands

Considering that one might expect that a good epoxidation catalyst can also work as a promoter of the oxidation of thioethers, we describe here the use of several catalysts for the sulfide oxidation that were highly active in the oxidation of benzylic alcohols[48] and in the conversions of olefins to epoxides[49,50] with H_2O_2. In preliminary research the Mn-tmtacn complex (**6.27**, Figure 8)[51] and the manganese salen complex **6.28**[52] were tested as catalysts in the sulfide oxidation. The ligand and corresponding complex were initially designed as a catalyst for homogeneous epoxidation reactions with H_2O_2 as oxidant. However, complex **6.28** turned out to be inactive in oxidation experiments with styrene as substrate using acetone as solvent.[52] Also after addition of *p*-cresol as an axial ligand the Mn-salen complex remained inactive as epoxidation catalyst.[52] The ligands **2.2a**, **2.2b**, **6.29** - **6.31** were used for

the *in situ* formation of the manganese complexes. In addition, preliminary results on the possibility of inducing enantioselectivity in the ligands are described in this section.

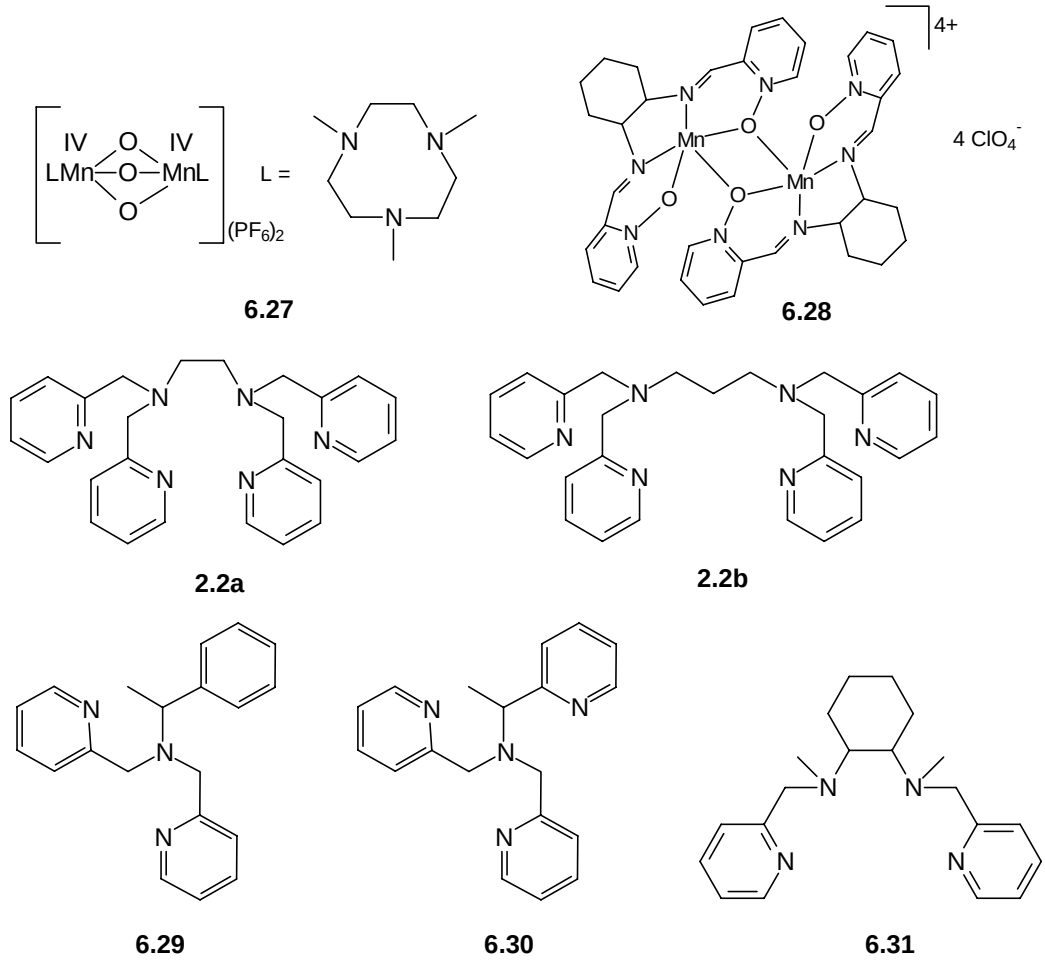
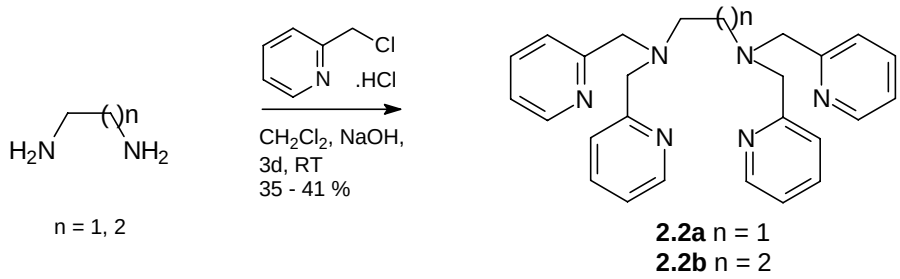


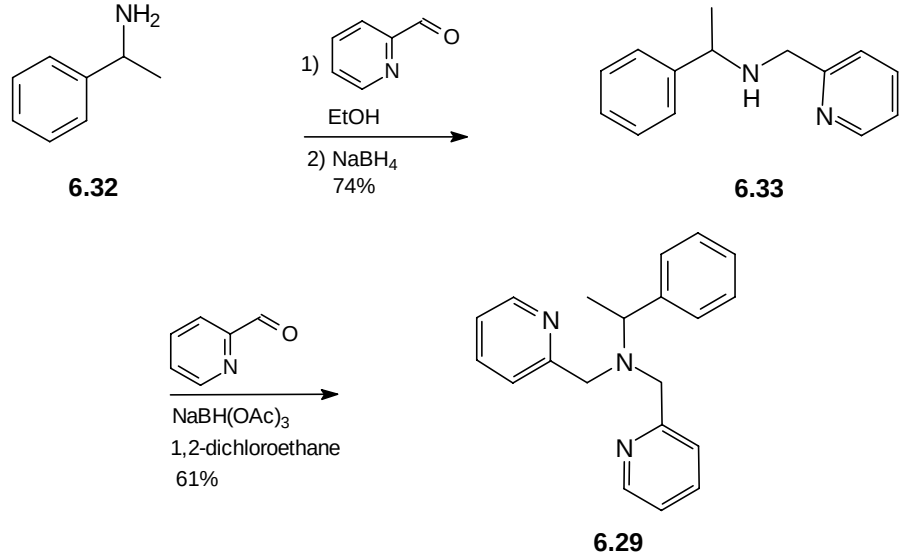
Figure 8 *Manganese complexes and ligands for the in situ formation of manganese catalysts for sulfide oxidation.*

The hexadentate ligands N^1,N^1,N^2,N^2-tetrakis(2-pyridinylmethyl)-1,2-ethanediamine (tpen, **2.2a**) and N^1,N^1,N^3,N^3-tetrakis(2-pyridinylmethyl)-1,3-propanediamine (tptn, **2.2b)** were prepared as described in Chapter 2, by reaction of the corresponding diamines with an excess of 2-(chloromethyl)pyridine hydrochloride in dichloromethane under basic conditions. The synthesis is depicted in Scheme 7. The corresponding manganese complexes were used as epoxidation catalyst for various substrates.



Scheme 7 *Synthesis of hexadentate ligands.*

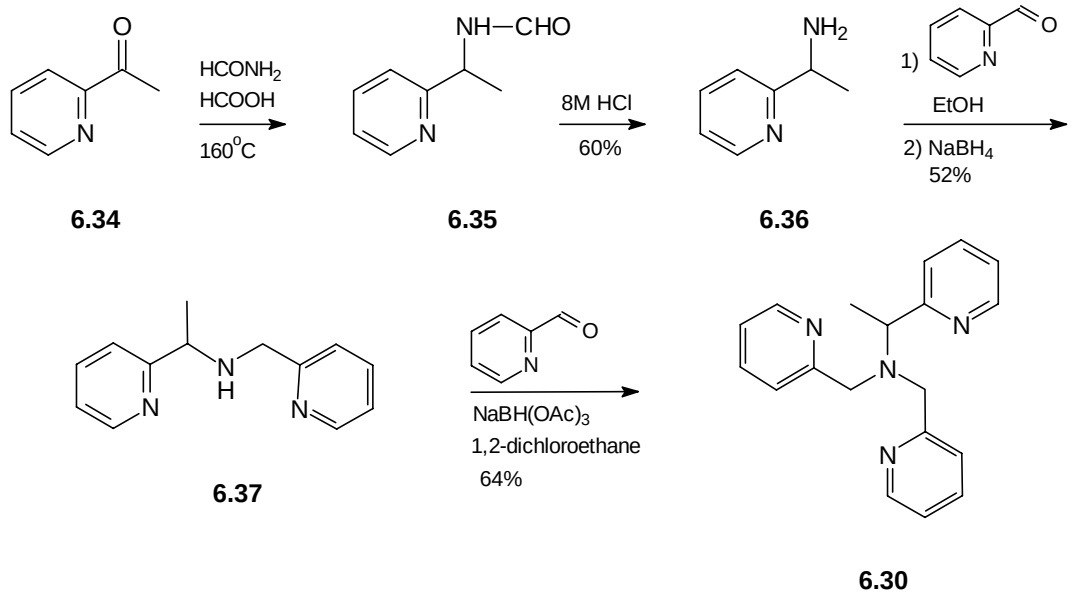
The synthesis procedure of ligand **6.29** (racemic) started with a condensation reaction of dl-α-phenylethylamine (**6.32**) with 2-pyridinecarboxaldehyde followed by reduction with sodium borohydride ($NaBH_4$) to yield amine **6.33** in 74% yield. ^{1}H-NMR spectra of the crude reaction product showed no impurities and therefore no further purification was performed. Typical resonances in the ^{1}H-NMR ($CDCl_3$) spectra appear around 3.70 ppm for to the single CH_2 pyridine protons and an indicative signal at 3.77 ppm for the CH proton. Subsequently, the amine **6.33** could be condensed with 2-pyridinecarboxaldehyde and was reduced *in situ* with sodium triacetoxyborohydride ($NaBH(OAc)_3$)[53] in 1,2-dichloroethane giving **6.29** in 61% chemical yield after purification by vacuum distillation or column chromatography (Scheme 8).



Scheme 8 *Reductive amination reactions.*

Ligand **6.30** (racemic) was synthesised following the same method as for compound **6.29** except that 1-(2-pyridinyl)-1-ethanamine (**6.36)** was used. 1-(2-Pyridinyl)-1-ethanamine was synthesised by a Leuckart reaction. In this procedure 2-acetylpyridine (**6.34**) reacts with formamide in formic acid to *N*-formyl-pyridylamine (**6.35**) followed by hydrolysis in a solution of hydrochloric acid to the corresponding amine **6.36** (Scheme 9). Using this method the amine was obtained in 60% chemical yield after purification by vacuum distillation; it

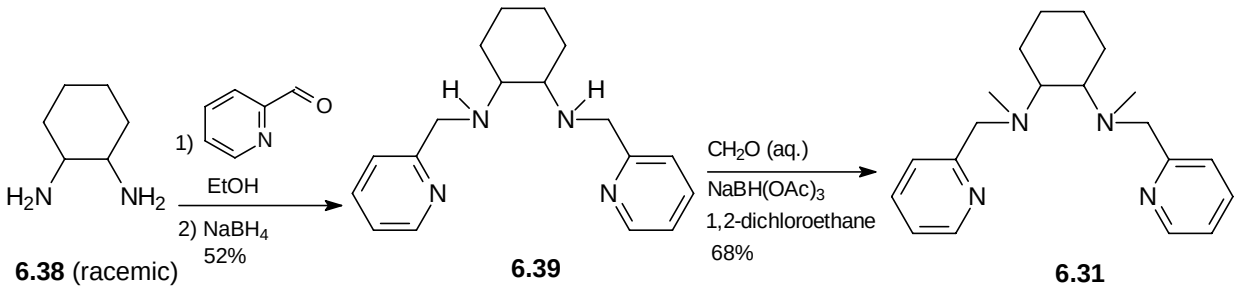
was converted into ligand **6.30** in two steps as described before. The pyridylamine **6.36** can be resolved with tartaric acid according to Van der Haest *et al*.[54]



6.34 **6.35** **6.36** **6.37** **6.30**

Scheme 9 *Synthesis of pyridylethylamine (**6.36**) via a Leuckart reaction and condensation to ligand **6.30**.*

The previous synthesis method for ligands **6.29** and **6.30** was also followed to prepare ligand **6.31**, which was obtained pure after column chromatography. The reaction procedure is depicted in Scheme 10.



6.38 (racemic) **6.39** **6.31**

Scheme 10 *Synthesis of ligand **6.31**.*

6.3 Catalysis

Since several manganese salts catalyse oxidation reactions with H_2O_2, first the oxidation of methyl phenyl sulfide with H_2O_2 in the presence of 0.2 mol% $Mn(OAc)_3 \cdot 2H_2O$ was examined. Different solvents, the effect of temperature and the amount of oxidant were investigated and the results are collected in Table 1.

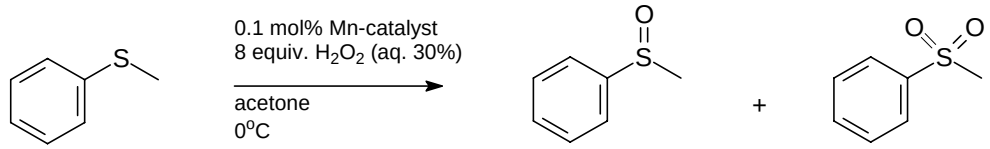
Table 1 *Oxidation of methyl phenyl sulfide with H_2O_2 (30% in water) in the presence 0.2 mol% $Mn(OAc)_3 \cdot 2H_2O$ at 0°C.*

Entry	Solvent	Oxidant[a]	t.o.n. 2h[b,c] Sulfoxide (Sulfone)	t.o.n. 4h Sulfoxide (Sulfone)	t.o.n. 6h Sulfoxide (Sulfone)	Sulfide not reacted after 6h (%)
1	acetone	2	14 (0)	15 (0)	16 (0)	94
2	acetone	8	56 (53)	61 (62)	73 (78)	70
3	acetonitrile	2	20 (5)	20 (5)	20 (5)	94
4	acetonitrile	8	98 (51)	115 (149)	126 (181)	32
5[d]	dichloromethane	8	21 (19)	27 (36)	35 (70)	75

(a) Equivalent oxidant with respect to substrate. (b) Turnover number in mole product per mole catalyst. (c) All products were identical to independently synthesised samples and identified by GC. (d) Room temperature.

The oxidation of the test substrate, methyl phenyl sulfide, catalysed by $Mn(OAc)_3 \cdot 2H_2O$ is almost completely suppressed in acetone and acetonitrile at 0°C using 2 equivalents of H_2O_2. Only 6% of methyl phenyl sulfide was converted to the sulfoxide after 6h in both solvents, possibly due to catalase type of oxidant decomposition. When, under the same conditions, excess (8 equivalents) of oxidant was used 30% (in acetone) and 68% (in acetonitrile) of sulfide was converted into a mixture of sulfoxide and sulfone. From these results we decided to employ acetone as reaction solvent to test different Mn-complexes as sulfide oxidation catalysts.

The dinuclear manganese(IV) complex **6.27** (Figure 8) based on the tmtacn ligand[55,56], (used as catalyst in the selective oxidation of sulfides to sulfones with periodic acid in pyridine[57]) and complex **6.28** were used as catalyst in the sulfide oxidation reactions. Furthermore the dinucleating ligands *N,N,N',N'*-tetrakis(2-pyridylmethyl)-1,2-ethanediamine (**2.2a**, tpen) and *N,N,N',N'*-tetrakis(2-pyridylmethyl)-1,3-propanediamine (**2.2b**, tptn) were used for the *in situ* catalyst formation. Finally the three and four N-donor ligands **6.29**, **6.30** and **6.31** were explored in the catalytic sulfide oxidation chemistry. Typical catalytic reactions were performed at 0°C under a nitrogen atmosphere using 1 equivalent of catalyst, 1000 equivalents of substrate and 8 equivalents of oxidant with respect to the substrate. The experimental conditions and the possible oxidation products of methyl phenyl sulfide are summarised in Scheme 11.



Scheme 11 *Possible products of oxidation of methyl phenyl sulfide and experimental conditions***.**

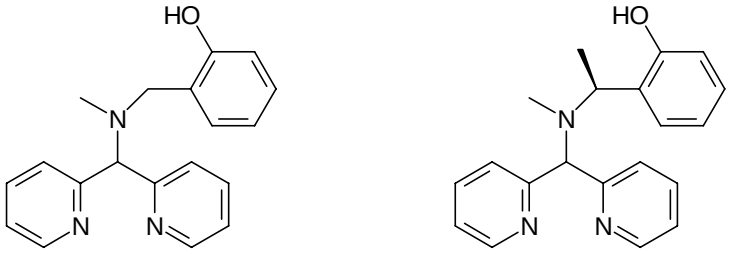
The complexes and in the *in situ* formed catalysts turned out to be active in sulfide oxidation. For instance, the dinuclear manganese complex $[Mn_2O_3(tmtacn)_2](PF6)_2$ (**6.27**) is efficient in the oxidation of methyl phenyl sulfide and generally resulted in full conversion in 1h. Unfortunately, besides the desired sulfoxide, over-oxidation to sulfone was observed. Manganese complexes based on tpen (**2.2a**) and tptn (**2.2b**) were also found to be active, however, also with the dinucleating ligands over-oxidation was found. The dinuclear manganese(II) complex **6.28** and the *in situ* formed complexes based on the ligands **6.29, 6.30** and **6.31** were found to be less reactive in the sulfide oxidation. Turnover numbers for sulfoxide formation in the range of 49 to 574 were observed but besides the sulfoxide in most cases, sulfone was formed by over-oxidation of the substrate. For sulfone production turnover numbers over 300 were easily reached. The results of the preliminary oxidation experiments are compiled in Table 2.

Table 2 *Catalytic oxidation of methyl phenyl sulfide.*[a]

Entry	Complex or Ligand[b]	t.o.n.[c] 2h Sulfoxide (Sulfone)	t.o.n. 4h Sulfoxide (Sulfone)	t.o.n. 6h Sulfoxide (Sulfone)
1	**6.27**	574(395)[c]	n.d.	n.d.
2	**6.28**	150 (245)	163 (285)	198 (364)
3	**2.2a**	330 (220)	342 (343)	357 (464)
4	**2.2b**	349 (222)	563 (342)	n.d.
5	**6.29**	49 (69)	51 (95)	55 (105)
6	**6.30**	51 (82)	70 (114)	107 (177)
7	**6.31**	146 (173)	167 (179)	179 (219)

(a) Employing 8 equiv. of H_2O_2 (30% in water) in the presence of complex or catalyst formed *in situ* by reacting $Mn(OAc)_3{\cdot}2H_2O$ with ligand at 0^oC. (b) See Figure 8. (c) Turnover number in mole product per mole catalyst. (d) Result after 1h.

Based on the oxidation results with complex **6.27** and Mn-complexes derived from ligands **2.2a** and **2.2b** (all featuring three N-donor sets) and because of the successful use of manganese salen complexes containing two N-donor and two O-donor sets as catalysts for the oxidation of a broad range of different sulfides with high selectivity,[41] we decided to use the new ligand 2-{[[di(2-pyridinyl)methyl](methyl)amino]methyl}phenol[58] (**6.40**, Figure 9), featuring a three N-donor and one O-donor ligand in order to minimise over-oxidation as was obtained by Jacobsen *et al.* employing salen ligands.[41]



6.40 (*S*)-**6.41**

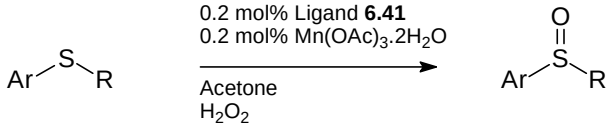
Figure 9 *Ligands with nitrogen and oxygen donor functionalities.*

A synthetic route to ligand **6.40** and the chiral analogue ligand (*S*)-**6.41** was developed in our group and these molecules were studied as ligands in the catalytic epoxidation with H_2O_2 as oxidant.[58] The catalysts were formed *in situ* with $Mn(ClO_4)_2.6H_2O$ and oxidation reactions were performed in acetone at 0^oC. A broad scope of substrates (styrene, dihydronaphthalene, 1-decene, *trans*- and *cis*-ß-methylstyrene and cinnamyl alcohol) were oxidised to the corresponding epoxides with yields in the range of 14 - 80%. Using the chiral analogue enantioselectivities of 3 - 12% were induced.[58]

The manganese sulfide oxidation catalyst, formed *in situ* by reacting the new ligand **6.40** with $Mn(OAc)_3{\cdot}2H_2O$, was used for the oxidation of methyl phenyl sulfide as test substrate and already after 2h, 247 turnover numbers to the sulfoxide and 58 turnover numbers to sulfone were obtained. This result implies an increase in selectivity compared with the former tested catalysts.

In order to improve the catalytic system the oxidant was added over a 1h period but unfortunately only a negligible effect on the conversion was found. The use of $Mn(ClO_4)_2{\cdot}6H_2O$ instead of $Mn(OAc)_3{\cdot}2H_2O$ caused an increase in over-oxidation to sulfone, whereas switching from acetone to acetonitrile or dichloromethane as solvent resulted in a dramatic decrease in conversion. Therefore it was concluded that the best conditions for ligand **6.40** are acetone as the solvent, a reaction temperature of 0^oC with 8 equivalents of H_2O_2. Subsequently we decided to test ligand (*S*)-**6.41**, a chiral version of ligand **6.40**, reasoning that we should obtain sulfoxides with conversions comparable with those obtained using ligand **6.40**, but in optically active form. The results of oxidations of several substrates using this new ligand (*S*)-**6.41** are presented in Table 3.

Table 3 *Oxidation of sulfides with different Aryl (Ar) and Alkyl (R) groups using Mn-catalysts based on ligand (S)-**6.41**[a]*



Entry	Ar	R	Yield Sulfoxide (%)[b]	e.e.[c]	Absolute Configuration[d]
1	Ph	Me	55	18	*R*
2	*p*-MeC_6H_4	Me	50	8	*R*
3	*p*-$MeOC_6H_4$	Me	48	5	*R*
4	Ph	CH_2Ph	50	5	*R*
5	2-Naphthyl	Me	52	6	*R*
6	1-Naphthyl	Me	52	7	*R*

(a) Reaction conditions, see experimental section. (b) Isolated yield after column chromatography (SiO_2, EtOAc). (c) Determined by HPLC on a Daicel Chiralcel OB-H column. (d) Determined by Daicel Chiralcel OJ column. (d) Determinated by comparison with literature values.[10b]

Employing the catalyst formed *in situ* by reacting the enantiopure ligand (*S*)-**6.41** with $Mn(OAc)_3{\cdot}2H_2O$, sulfoxides are obtained in yields ranging from 48 to 55%. It seems that the structure does not affect the chemical yield of the reaction. An important feature is that only minor amounts of by-products resulting from over-oxidation were found. Using (*S*)-**6.41** always sulfoxides with the (*R*)-configuration and e.e.'s up to 18% (methyl phenyl sulfide) were obtained. Increasing the amount of catalyst from 0.2 mol% to 2 mol% did not improve the enantioselectivity.

6.4 Discussions and conclusions

The oxidation of aryl sulfides using manganese catalysts has been investigated and various ligands have been tested. The catalytic oxidation reactions were performed in acetone at 0^oC in order to suppress catalase activity and under those conditions a minor amount of unselective oxidation by manganese salts was observed.

The Mn-tmtacn complex **6.27** yields an active catalyst for sulfide oxidation reactions. With 8 equivalents of H_2O_2 the catalyst performed very efficiently in the oxidation of methyl phenyl sulfide and resulted in full conversion in 1h using only 0.1 mol% of catalyst. High

turnover numbers (up to 574) to sulfoxide were easily reached but unfortunately over-oxidation to the undesired sulfone was always observed. Manganese complexes formed *in situ* by reacting $Mn(OAc)_3.2H_2O$ with the hexadentate ligands tpen (**2.2a**) and tptn (**2.2b**), resulted in an active catalytic system, however, again oxidation to sulfone was found. By using the dinuclear complex **6.28** and the corresponding *in situ* formed complexes based on the ligands **6.29, 6.30** and **6.31** in most cases active catalysts were obtained. Unfortunately in general also sulfones were detected beside the desired product. Because of the successful use of the Jacobsen salen sulfide oxidation catalysts[41] containing two N-donor and two O-donor sets, the new ligand 2-{[[di(2-pyridinyl)methyl](methyl)amino]methyl}phenol (**6.40**) featuring a three N-donor and one O-donor was employed. Based on the structural similarities of ligand **6.40** and the salen-based ligands, we anticipated to obtain high activity and selectivity as was observed by Jacobsen *et al*. employing manganese salen catalysts.[41] The structure of the ligand and the chiral analogue **6.41** are depicted in Figure 9.

Using the complex formed *in situ* from ligand **6.40** with $Mn(OAc)_3{\cdot}2H_2O$ and methyl phenyl sulfide as test compound, high activity was observed. The manganese complex based on ligand **6.40** is a promising catalyst for the oxidation of methyl phenyl sulfide using H_2O_2: with a low amount of catalyst (0.2 mol%) we obtained the corresponding sulfoxide with 55% chemical yield, with minor formation of sulfone. Besides methyl phenyl sulfide a range of substrates was successfully oxidised to the corresponding sulfoxide as major product. Enantioselectivities up to 18% were observed with yields up to 55%. In conclusion the Mn-complexes based on ligand **6.40** and **6.41** are active catalysts for the oxidation of sulfides to sulfoxides with H_2O_2 as terminal oxidant.

6.5 Acknowledgement

Irene Donnoli is gratefully acknowledged for performing the catalytic experiments described in this chapter. Dr. René La Crois and dr. Alette Ligtenbarg are acknowledged for providing ligands **6.40**, **6.41** and complex **6.28**.

6.6 Experimental section

General procedure and methods

For general information see Chapter 2. The described sulfide substrates and the corresponding sulfones and sulfoxides were obtained from Aldrich and Acros or synthesised according to the literature.[10b]

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% phenylmethyl-siloxane column. Calibration was performed using authentic samples of the sulfide and sulfoxides and independent samples of further by-products. Conversions, yields and turnover numbers were determined using bromobenzene as internal standard, and calculated using the Chemstation software.

Catalytic oxidation reactions (complexes)

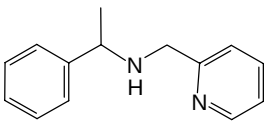
Catalytic reactions with complex **6.27** or **6.28** were started by mixing 1.0 ml of a 1.2 mM stock solution of the manganese complex in acetone and 1.0 ml of a stock solution of 1.2 M of substrate and 0.5 M of bromobenzene (internal standard) at 0^{o}C under a nitrogen atmosphere. After stirring for 2 min, excess of oxidant (1.0 ml of 30% aq. H_2O_2, 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 establish the identity of the sulfoxides unequivocally the retention times and spectral data were compared to those of commercially available and independently synthesised compounds.

Catalytic oxidation reactions (*in situ* experiments)

The same procedure as described for the catalytic reactions of the complexes **6.27** and **6.28** was followed with the ligands **2.2a**, **2.2b**, **6.29** - **6.31**, **6.40** and **6.41** except that the reactions were started by mixing 1.0 ml of a 2.4 mM stock solution of $Mn(OAc)_3.2H_2O$ and 1.0 ml of a 1.2 mM stock solution of ligand **2.2a** (or **2.2b**). In the case of ligand **6.29** - **6.31**, **6.40** and **6.41** a 2.4 mM stock solution was used. After stirring for 15 min, substrate was added, at 0^{o}C under a nitrogen atmosphere. After stirring for 2 min, excess of oxidant (1.0 ml of 30% aq. H_2O_2, 9.8 M) was added. The progress of the reaction was monitored by GC.

Synthesis of ligands

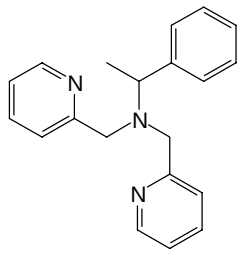
1-Phenyl-*N*-(2-pyridinylmethyl)-1-ethanamine (6.33)



To dl-α-phenylethylamine (**6.32**, 4.0 g, 33.1 mmol) in ethanol (50 ml) was added 2-pyridinecarboxaldehyde (4.4 g, 36.1 mmol). After stirring for 16h at room temperature $NaBH_4$ (5.0 g, 132.4 mmol) was added in small portions. Using 4 M HCl the reaction mixture was acidified to pH 1 - 2, after stirring for 2h at room temperature. The reaction mixture was stirred for another 0.5h, brought to pH 14 with a NH_3-solution (12.5% in water) and the mixture was extracted with CH_2Cl_2 (3 x 100 ml). The combined organic layers were dried (Na_2SO_4) and

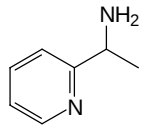
the solvent evaporated under reduced pressure to afford the pure product as a colourless oil (5.2 g, 24.5 mmol, 74% yield).
^{1}H-NMR (300 MHz): δ 1.36 (d, J = 6.59 Hz, 3H, CH_3), 2.50 (br, 1H, NH), 3.69 (s, 2H, CH_2), 3.77 (q, J = 6.59 Hz, 1H, CH), 7.19 (m, 7H, Py and Ph), 7.52 (dt, J = 7.69, 1.83 Hz, 1H), 8.49 (d, J = 4.76 Hz, 1H, Py). ^{13}C-NMR (75 MHz): δ 21.9 (CH_3), 50.6 (CH_2), 55.5 (CH), 119.3 (CH), 119.9 (CH), 124.3 (CH), 124.4 (CH), 125.9 (CH), 133.8 (CH), 142.9 (C), 146.8 (CH), 157.3 (CH).

1-Phenyl-*N*,*N*-bis(2-pyridinylmethyl)-1-ethanamine (6.29)



To 1-phenyl-*N*-(2-pyridinylmethyl)-1-ethanamine (**6.33**, 1.0 g, 4.7 mmol) in 1,2-dichloroethane (50 ml) was added 2-pyridine-carboxaldehyde (0.55 g, 5.2 mmol). During 1h $NaBH(OAc)_3$ (4.5 g, 21.2 mmol) was added in small portions. After stirring for 24h at room temperature a saturated solution of $NaHCO_3$ (25 ml) was added, followed by extraction with CH_2Cl_2 (3 x 100 ml). The combined organic layers were dried (Na_2SO_4) and the solvent evaporated under reduced pressure to afford the crude product. The oil was purified by column chromatography (Al_2O_3, akt. II - III, ethyl acetate/hexane/triethylamine 10:4:1) to afford the product as a yellow oil (0.87 g, 2.87 mmol, 61% yield).
^{1}H-NMR (300 MHz): δ 1.42 (d, J = 6.59 Hz, 3H, CH_3), 3.78 (m, 5H, CH and 2 x CH_2), 7.32 (m, 6H, Py and 5H, Ar), 8.43 (d, J = 4.76 Hz, 2H, Py). ^{13}C-NMR (75 MHz): δ 13.4 (CH_3), 54.9 (CH_2), 57.0 (CH), 120.3 (CH), 121.2 (CH), 125.4 (CH), 126.4 (CH), 126.6 (CH), 134.8 (CH), 141.2 (C), 147.3 (CH), 159.2 (C). HRMS calcd. for $C_{20}H_{21}N_3$ 303.174, found: 303.173.

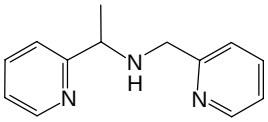
1-(2-Pyridinyl)-1-ethanamine (6.36)[54]



A solution of 2-acetylpyridine (**6.34**, 25.0 g, 0.21 mmol) in formic acid (30 ml) was added to formamide (135 g, 3.0 mol) at 160°C in 30 min. Subsequently an additional amount of formic acid (30 ml) was introduced and the mixture was stirred at 160°C for 90 min. After cooling, a concentrated aq. KOH-solution (250 ml) was added and the mixture was extracted with CH_2Cl_2 (5 x 100 ml). The solvent of the combined organic layers was evaporated and the crude product was heated to reflux in 8 M HCl (150 ml) for 6h. After cooling, the mixture was extracted with ether (2 x 100 ml). The aqueous layer was made alkaline by the addition of a concentrated aq. KOH solution and extracted with CH_2Cl_2 (5 x 150 ml). The organic layers were combined and dried (Na_2SO_4). After evaporation of the solvent under reduced pressure the residue was purified by bulb to bulb distillation at 160°C, 40 mm Hg to afford the pure product (15.0 g 123 mmol, 60% yield).
^{1}H-NMR (300 MHz): δ 1.32 (d, J = 6.96 Hz, 3H, CH_3), 1.70 (br, 1H, NH), 4.04 (q, J = 6.78 Hz, 1H, CH), 7.04 (m, 1H, Py), 7.19 (d, J = 8.06 Hz, 1H, Py), 7.53 (m, 1H, Py), 8.45 (d, J =

4.76 Hz, 1H, Py). ^{13}C-NMR (75 MHz): δ 25.0 (CH_3), 53.0 (CH), 120.6 (CH), 122.3 (CH), 137.1 (CH), 149.7 (CH), 166.4 (C).

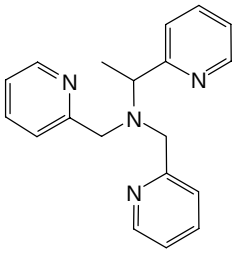
1-(2-Pyridinyl)-*N*-(2-pyridinylmethyl)-1-ethanamine (6.37)



To racemic 1-(2-pyridyl)ethylamine (**6.36**, 2.0 g, 17.0 mmol) in ethanol (50 ml) was added 2-pyridinecarboxaldehyde (2.1 g, 18.7 mmol). After stirring for 16h at room temperature $NaBH_4$ (2.6 g, 68.0 mmol) was added in small portions. After stirring for 2h at room temperature, the reaction mixture was acidified to pH 1 - 2 using 4 M HCl. The reaction mixture was stirred for another 0.5h. The solution was brought to pH 14 with a NH_3-solution (12.5% in water) and the mixture was extracted with CH_2Cl_2 (3 x 50 ml). The combined organic layers were dried (Na_2SO_4) and the solvent evaporated under reduced pressure to afford the crude product. The residue was purified by vacuum distillation at 140^{o}C, 0.05 mm Hg, affording the pure product (1.9 g, 8.92 mmol, 52% yield).

^{1}H-NMR (300 MHz): δ 1.39 (d, J = 6.59 Hz, 3H, CH_3), 2.36 (br, 1H, NH), 3.73 (s, 2H), 3.89 (q, J = 6.60 Hz, 1H, CH), 7.08 (m, 2H), 7.21 (m, 1H), 7.32 (d, J = 7.69 Hz, 1H), 7.57 (m, 2H), 8.49 (m, 2H). ^{13}C-NMR (75 MHz): δ 12.8 (CH_3), 55.1 (CH_2), 58.6 (CH), 120.3 (CH), 120.4 (CH), 121.1 (CH), 134.5 (CH), 134.8 (CH), 147.3 (CH), 147.4 (CH), 159.0 (C), 160.4 (C).

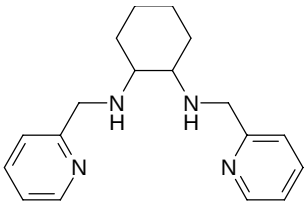
1-(2-Pyridinyl)-*N*,*N*-bis(2-pyridinylmethyl)-1-ethanamine (6.30)



To **6.37** (2.0 g, 9.39 mmol) in 1,2-dichloroethane (50 ml) was added 2-pyridinecarboxaldehyde (1.1 g, 10.3 mmol). During 1h $NaBH(OAc)_3$ (9.96 g, 47.0 mmol) was added in small portions. After stirring for 24h at room temperature a saturated solution of $NaHCO_3$ (50 ml) was added, followed by extraction with CH_2Cl_2 (3 x 100 ml). The combined organic layers were dried (Na_2SO_4) and the solvent evaporated under reduced pressure to afford the crude product. The oil was purified by column chromatography (Al_2O_3, akt. II - III, ethyl acetate/hexane/triethylamine 10:4:1) to afford the product as a yellow oil (1.83 g, 6.02 mmol, 64% yield).

^{1}H-NMR (300 MHz): δ 1.47 (d, J = 6.59 Hz, 3H, CH_3), 3.68 (d, J = 15.0 Hz, 2H, CH_2), 3.89 (q, J = 14.7 Hz, 2H, CH_2), 3.97 (d, J = 6.83 Hz, 1H, CH), 7.04 (m, 3H, Py), 7.50 (m, 6H, Py), 8.40 (d, J = 4.76 Hz, 2H, Py), 8.48 (d, J = 4.76 Hz, 1H, Py). ^{13}C-NMR (75 MHz): δ 14.9 (CH_3), 57.3 (CH_2), 60.7 (CH), 122.3 (CH), 122.4 (CH), 123.2 (CH), 123.5 (CH), 136.6 (CH), 136.9 (CH), 149.4 (CH), 161.1 (C), 162.5 (C). HRMS calcd. for $C_{19}H_{20}N_4$ 304.169, found 304.169.

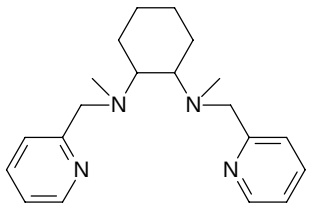
N^1,N^2-Bis(2-pyridinylmethyl)-1,2-cyclohexanediamine (6.39)



To a solution of 1,2-cyclohexanediamine (2.0 g, 18.7 mmol) in EtOH (50 ml) was added 2-pyridylcarboxaldehyde (4.20 g, 39.3 mmol). After stirring for 16h at room temperature $NaBH_4$ (2.6 g, 68.0 mmol) was added in small portions at 0°C. Subsequently the reaction mixture was stirred for another 2h at room temperature. Using 4 M HCl the reaction mixture was acidified to pH 1 - 2 and stirring was continued for another 0.5h. The solution was brought to pH 14 with a NH_3-solution (12.5% in water) and the resulting mixture was extracted with CH_2Cl_2 (3 x 100 ml). The combined organic layers were dried (Na_2SO_4) and the solvent evaporated under reduced pressure to leave a dark yellow oil. The oil was purified by column chromatography (Al_2O_3, akt. II - III, CH_2Cl_2/MeOH/Et_3N 8:1:1) to afford the pure product (3.0 g, 10.1 mmol, 54% yield) as a yellow oil.

^{1}H-NMR (300 MHz): δ 1.17 (br, 4H), 1.68 (br, 2H), 2.08 (br, 2H), 2.36 (br, 2H), 3.79 (d, J = 14.28 Hz, 2H, CH_2), 3.98 (d, J = 14.28 Hz, 2H, CH_2), 7.20 (t, J = 6.23 Hz, 1H, Py), 7.40 (d, J = 7.69 Hz, 1H, Py), 7.69 (dt, J = 5.86, 1.83 Hz, 1H, Py), 8.36 (d, J = 4.39 Hz, 1H, Py). ^{13}C-NMR (75 MHz): δ 24.7 (CH_2), 31.3 (CH_2), 52.3 (CH_2), 61.1 (CH), 121.6 (CH), 122.1 (CH), 136.2 (CH), 148.9 (CH), 160.6 (C).

N^1,N^2-Dimethyl-N^1,N^2-bis(2-pyridinylmethyl)-1,2-cyclohexanediamine (6.31)



To a stirred solution of **6.39** (2.5 g, 8.6 mmol) in 1,2-dichloroethane (50 ml) was added formaldehyde (aq. 37%, 1.8 ml, 23.8 mmol). During 1h $NaBH(OAc)_3$ (5.5 g, 25.7 mmol) was added in small portions. After stirring for 24h at room temperature a saturated solution of $NaHCO_3$ (50 ml) was added, followed by extraction of the mixture with CH_2Cl_2 (3 x 100 ml). The combined organic layers were dried (Na_2SO_4) and the solvent evaporated under reduced pressure to afford the crude product. The oil was purified by column chromatography (Al_2O_3, akt. II - III, ethyl acetate/hexane/triethylamine 10:4:1) to afford the product as a yellow oil (2.3 g, 7.1 mmol, 82% yield).

^{1}H-NMR (300 MHz): δ 1.16 (m, 4H), 1.71 (m, 2H), 1.93 (m, 2H), 2.23 (s, 6H, 2 x CH_3), 2.61 (m, 2H), 3.73 (d, J = 14.64 Hz, 2H, CH_2), 3.86 (d, J = 14.64 Hz, 2H, CH_2), 7.07 (m, 2H, Py), 7.53 (m, 4H, Py), 8.44 (d, J = 4.76 Hz, 2H, Py). ^{13}C-NMR (75 MHz): δ 22.3 (CH_2), 23.4 (CH_2), 34.1 (CH_3), 57.9 (CH_2), 62.0 (CH), 119.0 (CH), 120.3 (CH), 129.5 (CH), 133.7 (CH), 146.1 (CH), 148.5 (C), 158.9 (C). HRMS calcd. for $C_{20}H_{28}N_4$ 324.231, found: 324.232.

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Chapter 7

Summary
Conclusions and Future Prospects

Abstract

In this chapter the most important results described in the previous chapters are summarised and a number of suggestions for future research will be discussed. Finally, the prospects of the manganese catalysts, which were investigated in the course of the studies described in this thesis, are presented.

7.1 Introduction

Selective oxidation reactions like the oxidations 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 oxidations.[1] Compared to catalytic methods that require oxidants like NaOCl and ammonium periodates the use of H_2O_2 offers the advantage that it is a cheap, environmentally friendly and a readily available reagent.[1] Since water is the only expected by-product, synthetic applications of this reagent are undoubtedly appealing, provided efficient catalysis is accomplished.

Recently, a number of metal complexes have been found to be suitable catalysts for selective epoxidation reactions with H_2O_2 as oxidant.[2] It was also found that the dinuclear manganese(IV) complex based on the *N,N',N"*-1,4,7-trimethyl-1,4,7-triazacyclononane (tmtacn) ligand is a highly active oxidation catalyst using H_2O_2.[3]

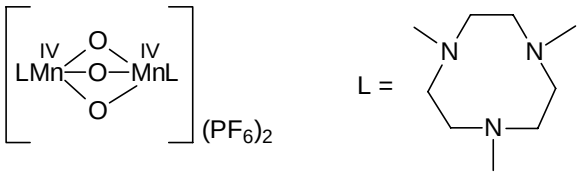
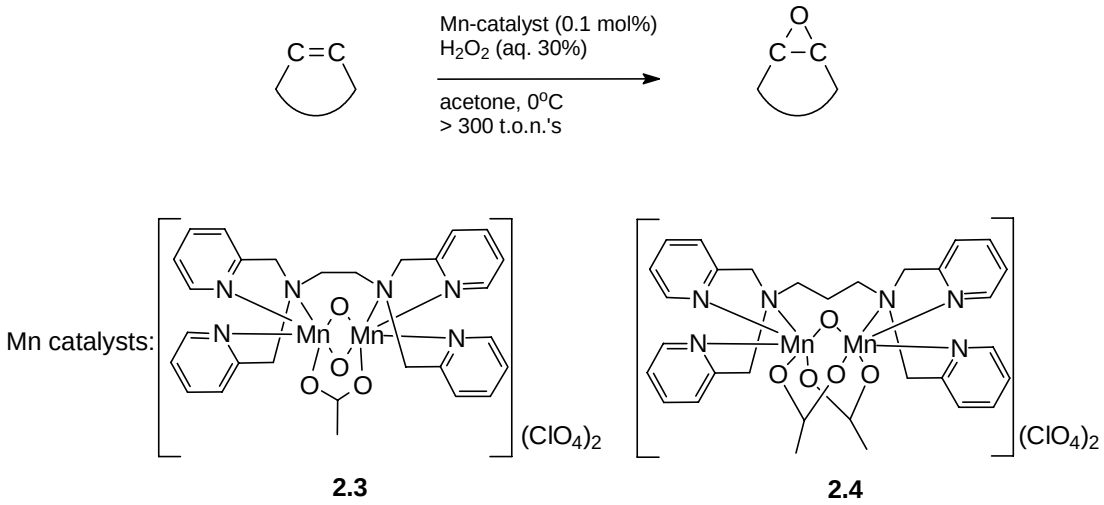


Figure 1 *Manganese complex based on the ligand tmtacn.*

Synthesis and modifications of the tmtacn ligand are, however, not easily accomplished due to lengthy and tedious preparation. Furthermore, the sensitivity of the corresponding metal complexes to changes in the tmtacn structure often leads to completely inactive Mn-complexes.[4] Consequently the design of novel dinucleating ligands featuring the three N-donor set for each Mn-site and retaining the high oxidation activity is a challenge. The research presented in this thesis explored and developed several new manganese based oxidation catalysts employing H_2O_2 as oxidant. The most important achievements will be surveyed in the following paragraphs.

7.2 Manganese complexes and homogeneous epoxidation catalysts

In Chapter 2 and Chapter 3 the catalytic epoxidation activity for manganese complexes based on the dinucleating ligands *N,N,N',N'*-tetrakis(2-pyridylmethyl)-1,2-ethanediamine (tpen), *N,N,N',N'*-tetrakis(2-pyridylmethyl)-1,3-propanediamine (tptn), both featuring the three N-donor set for each manganese site similar as the tmtacn ligand, is reported. Advantages of this type of ligand are the accessibility and the possibility to modify the ligand structure. Preliminary screening in a number of different catalytic epoxidations showed that complex **2.4**, based on tptn with a three-carbon spacer, is highly active oxidation catalyst employing H_2O_2 as oxidant in acetone at ambient temperature (Scheme 1).[5] Various alkenes like styrene, cyclohexene and 2-octene were converted into the corresponding epoxides with good yields. High turnover numbers exceeding 300 can be readily reached.[5]



Scheme 1 *Epoxidation reaction conditions and manganese complexes **2.3** and **2.4**.*

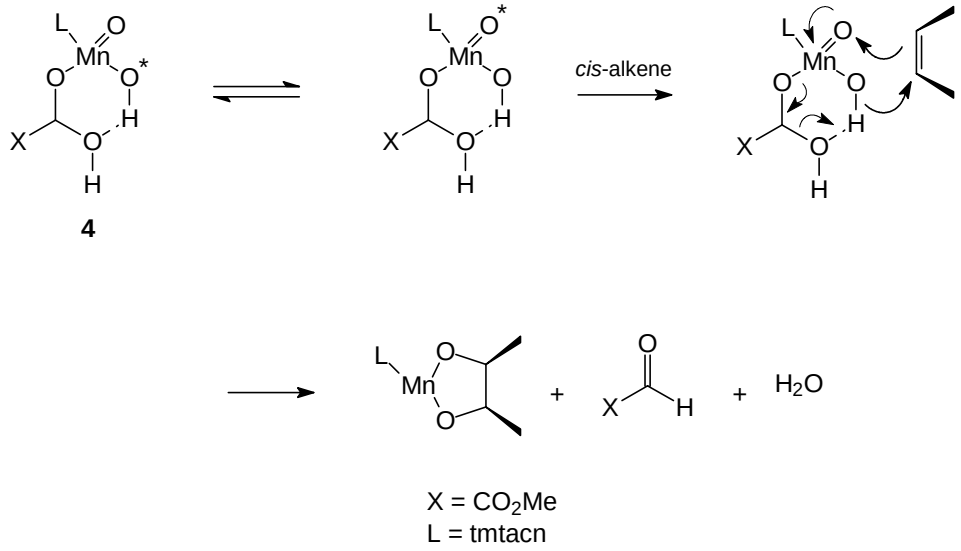
Small structural modifications of **2.4** led to large changes in it's catalytic activity, comparable to results obtained with Mn-tmtacn. For example, using a two-carbon spacer as present in complex **2.3**, the Mn-complex was found to be completely inactive. Mn-catalysts prepared from modified ligands containing additional CH_3-moieties at the 3-position of the pyridine groups, led to a remarkable reduction of the induction period for the oxidation. The mechanism of this epoxidation method is not known at the present, however, by studying the oxidation of *cis*-β-methylstyrene a considerable amount of the *trans*-epoxide is observed, which is generally pointing to a pathway involving radical intermediates.[6]

7.3 Homogeneous epoxidation and *cis*-dihydroxylation

Although several methods are available for catalytic epoxidations with aqueous H_2O_2,[1] high turnovers for *cis*-dihydroxylation are only achieved using osmium catalysts.[7] However, the high cost and toxicity of Os hamper large scale application and provide a strong incentive to develop benign Fe- or Mn-based *cis*-dihydroxylation catalysts. Que *et al.* recently reported the first *cis*-dihydroxylation with H_2O_2 catalysed by a non-heme iron complex.[8] Recently, Mn-complexes based on tmtacn and the complexes presented in Chapter 2 and 3 were found to be highly active in catalytic oxidation. However, many Mn- or Fe-catalysts are known to be particularly effective in decomposition of H_2O_2. This can be suppressed by performing the reactions in acetone,[3d] or by using oxalate[9a] or ascorbic acid[9b] as co-catalysts, or by anchoring the tacn ligand to a solid support.[9c] Chapter 4 describes the challenge related to the efficient use of H_2O_2 employing activated aldehyde compounds like glyoxylic acid methyl ester methyl hemiacetal (gmha) as co-catalysts in combination with the Mn-tmtacn complex (Figure 1).[10] Acetonitrile was employed as solvent. Surprisingly, this solvent not only strongly suppresses H_2O_2 decomposition by the Mn-catalyst, but also imparts a high homogeneous catalytic *cis*-dihydroxylation activity.[10] Catalytic alkene oxidation in the presence of the hemiacetal (25 mol%) gives oxidation that competes so favourably with oxidant disproportionation, that only a slightly excess (1.3 equivalents) of H_2O_2 is necessary to obtain full conversions. The oxidation is even more efficient when a mixture of gmha (25 mol%) and oxalate (0.3 mol%)[9a] was used as the co-catalyst system. The epoxide yields even surpassed those obtained with the Mn-tmtacn/gmha catalytic system, and high epoxide yields at complete conversion were obtained for non-sterically hindered alkenes. The most interesting achievements of this research is that significant amounts of *cis*-diols besides the epoxides are formed when *only* gmha was present as the co-catalyst. The highest amount of *cis*-diol was found for cyclooctene, which afforded the *cis*-diol as the main product (42%, 420 t.o.n.'s) besides the epoxide (36%, 360 t.o.n.'s). Minor amounts of 2-hydroxycyclooctanone were also found due to oxidation of the diol. Limited *cis*/*trans* isomerisation is observed in the epoxide formation of *cis*-2-hexene. The *cis/trans* isomerisation points to epoxidation via a Mn-oxo species, with formation of epoxides from C-centered radical intermediates with a lifetime sufficient for some C - C bond rotation prior to reaction to the epoxide.[11] In line with this mechanism, olefins that form a relatively long-lived radical intermediate, such as *cis*-stilbene, show substantial loss of configuration in the epoxide.

Based on the cumulative data presented in this chapter, a Mn-oxo-hydroxo species was proposed as the reactive *cis*-dihydroxylation intermediate. Like in the case of oxalate, hydrated activated carbonyl compounds[12] might convert the catalase active oxo-bridged Mn-tmtacn complex [13] into mononuclear Mn-species. Intermediate **4**, containing an internal H-bond with gmha, is proposed to induce *cis*-dihydroxylation (Scheme 2). Reoxidation of the Mn-center with H_2O_2, release of the diol from Mn, and hydration of the carbonyl compound closes the catalytic cycle. To the best of our knowledge this is the most active osmium-free

homogeneous catalyst for *cis*-dihydroxylation (t.o.n.'s up to 420). However, the precise requirements for the ligand and the role of gmha to achieve *cis*-dihydroxylation exclusively are not known to date. Ligand and co-catalyst modification possibly by combinatorial methods can improve the *cis*-diol selectivity. An example would be the covalent attachment of gmha or ultimately chiral gmha analogues, aiming to induce enantioselective *cis*-dihydroxylation.



Scheme 2 *Proposed cis-dihydroxylation mechanism catalysed by Mn-tmtacn/gmha system.*

7.4 Manganese catalysts for alcohol oxidation

Several *in situ* prepared complexes with $Mn(OAc)_3$ based on tptn- and tptn-derivatives turned out to be also active and selective catalysts for the oxidation of a number of substituted primary benzyl alcohols as well as secondary alcohols to the corresponding carbonyl compounds.[14] For the selected *in situ* prepared Mn-complexes based on the ligands **2.2b**, **2.5** - **2.8** (Figure 2), generally high activity and selectivity were found (t.o.n.'s up to 900). Preliminary screening in a number of different catalytic alcohol oxidation reactions showed that the *in situ* prepared manganese complex with **2.2a** was unreactive, similar to ligand characteristics in previous described epoxidation studies. The tptn-based modified ligands **2.7** and **2.8**, containing a two-carbon spacer and a three-carbon spacer, respectively, were found to form moderate (complex based on ligand **2.7**) to active catalysts (based on ligand **2.8**), however, long induction periods were observed. Using *in situ* prepared complexes based on ligand **2.5** and ligand **2.6** excellent results were found and most remarkably, the induction period was strongly reduced. This may be linked with the observation that ligand **2.6** yields a strong 16-line EPR signal immediately after mixing the ligand with $Mn(OAc)_3$, H_2O_2 and substrate and therefore dinuclear species are most probably

involved in the oxidation reactions. The catalysts based on the ligands with the three-carbon spacer yield in all cases much higher reactivity (shorter lag phases) than the two-carbon analogues, likely connected with a faster formation of dinuclear species. The primary kinetic isotope effects (k_H/k_D) for the Mn-catalysed oxidation of benzyl alcohol and benzyl-d_7 alcohol observed are in the range of 2.2 to 4.3. These values, strongly indicate that cleavage of the (benzylic) C-H bond is involved in the rate-determing step.[15] Based on these results it can be concluded that hydroxyl radicals are not involved in these processes, as due to the high reactivity of these radicals a much lower isotopic effect would be expected.[16] In agreement, no indications for hydroxylation of aromatic rings for the various substrates have been obtained. Furthermore, no hydroxylation of benzene, which is also a substrate sensitive to hydroxylation, has been observed under the same conditions.[17] However, we cannot conclude which species exactly is involved in the oxidation reactions, *e.g.* high-valent Mn=O species or Mn-OOH species.

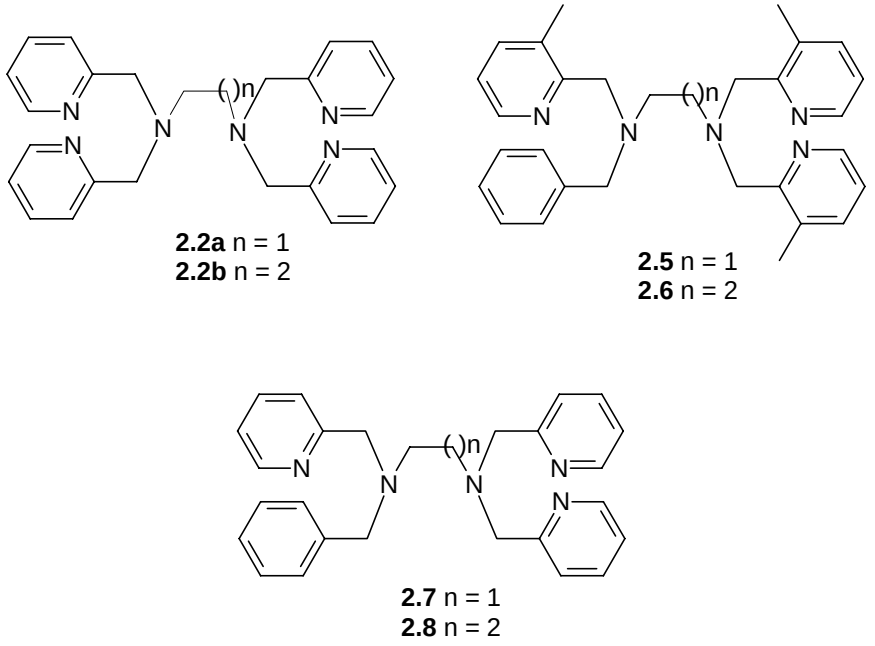
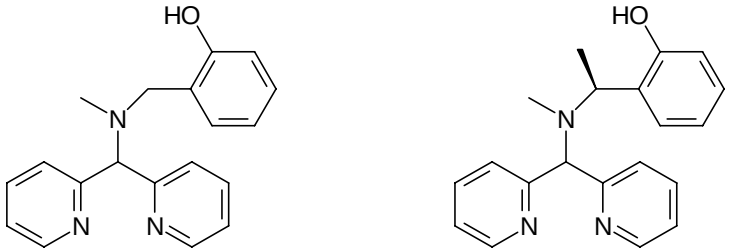


Figure 2 *Ligands used for the manganese-catalysed alcohol oxidation.*

7.5 Oxidation of Sulfides to Sulfoxides

The selective catalytic oxidation of sulfides to sulfoxides has been a challenge for many years, owing to the importance of sulfoxides as intermediates in organic synthesis.[18] The undesired sulfone is a common by-product in sulfide oxidation using H_2O_2 as oxidants and its formation has to be suppressed. Much effort has been devoted to the development of catalytic methods for the preparation of optically active sulfoxides owing to their importance as chiral ligands, and bioactive products.[18] Since the first reports of Kagan[19] and Modena,[20]

who used diethyl tartrate and Ti(O*i*-Pr)$_4$ and hydroperoxides as an oxidant yielding e.e.'s higher than 90%, a number of publications related to this research followed with variable results.[21] Considering that one could expect that a good olefin or alcohol oxidation catalyst can also work as a promoter of the oxidation of thioethers, Mn-tmtacn and a number of *in situ* formed complexes that were highly active in the oxidation of benzylic alcohols to aldehydes and of olefins to epoxides with H_2O_2 were screened as sulfide oxidation catalysts. In addition, Chapter 6 describes the preliminary results on the possibility of inducing enantioselectivity using optically active Mn-complexes. The complexes and *in situ* formed catalysts turned out to be active in sulfide oxidation. For instance the dinuclear manganese complex based on tmtacn performs efficiently in the oxidation of methyl phenyl sulfide and generally resulted in full conversion in 1h. Unfortunately, besides the desired sulfoxide, oxidation to sulfone was observed. Manganese complexes based on tptn and tpen were also found to be active. However, also over-oxidation to sulfone was found. Employing the novel ligand **6.40** (Figure 3), which was intensively used for epoxidation studies in our group,[22] slightly over-oxidation to sulfone was observed. Ligand **6.40** was utilised because of the similarity to the salen ligands[23] containing two N-donor and two O-donor sets. Subsequently ligand **6.41**, a chiral version of ligand **6.40**, was explored for the oxidation sulfoxides and yields ranging from 48 to 55 % with e.e.'s up to 18% were achieved.[24]



6.40 **6.41**

Figure 3 *Ligands with nitrogen and oxygen donor functionalities.*

7.6 Final conclusions and future prospects

This final paragraph presents the general discussion for the manganese catalysts described in this thesis. A number of manganese complexes have already shown the value as potentially efficient oxidation catalysts. The complexes based on tptn were found to be promising catalysts in catalytic epoxidation procedures using H_2O_2 as the terminal oxidant. The derived manganese complexes were also applicable for catalytic alcohol and sulfide oxidation reactions. Based on comparable activity for the *in situ* prepared catalysts employing different substrates and preliminary mechanistic investigation, it might be that the oxidation reactions proceed via similar oxidation intermediates. Main advantages of the new catalytic system are the facile synthesis and possibilities for ligand modification. In acetone and at

ambient temperature the manganese complex of tptn is able to catalyse the selective oxidation of various alkenes to the corresponding epoxides, which give high activity (t.o.n.'s up to 900) as obtained with the Mn-tmtacn catalyst. But a real challenge remains the development of a Mn-catalyst capable of enantioselective epoxidation of olefins employing H_2O_2 as oxidant, since most of the efficient and highly enantioselective catalysts known to date make use of NaOCl as oxidant, whereas t.o.n.'s in the range of 35 to 40 were found.[25] On account of the promising epoxidation results obtained with tptn and the modified tptn ligands, it can be considered to use these ligands as a starting point to synthesise catalysts capable of asymmetric epoxidation employing environmentally friendly oxidants like H_2O_2. For example, the introduction of chirality in the backbone (spacer) of the ligands or the introduction of chiral moieties at the periphery of the pyridine groups can provide an interesting new class of tptn based ligands. However, small structural changes can have a profound effect on the activity and therefore the mechanism of these Mn-oxidation catalysts derived from tptn type of ligands deserve to be explored in detail as well.

For most of the oxidation reactions, an excess of oxidant is necessary, presumably due to a catalase type of H_2O_2 decomposition. Using a number of activated carbonyl compounds like gmha in combination with Mn-tmtacn a highly active and H_2O_2 efficient epoxidation system was developed. On top of this, the system showed excellent *cis*-dihydroxylation activity (up to 420 t.o.n.'s). In view of the fact that toxic and expensive osmium is the only catalyst that can be used for this conversion, this is a very promising development.

Although this field of Mn-catalysed *cis*-dihydroxylation is in a preliminary stage and furthermore the present mixed Mn-tmtacn/gmha procedure does not lead to full conversions to *cis*-diol, this challenging new research field provides a very promising development. However, with additional studies, the future will see the advent of a new generation of *cis*-dihydroxylation procedures based on manganese that can be used in synthetic organic chemistry using environmental friendly oxidants. Looking at the versatility of the additive gmha and the striking effect of this additive on the oxidation behaviour of Mn-tmtacn towards *cis*-dihydroxylation it can be recommended to focus on the design and synthesis of new co-catalysts. Design and screening of the influence of the new gmha related compounds could possibly be performed by a combinatorial approach. A challenging strategy might be the covalent attachment of gmha or gmha analogues, aiming to improve the *cis*-diol selectivity at low catalyst loading. A closely related and ultimate task is the design and synthesis of chiral gmha analogues for asymmetric *cis*-dihydroxylation catalysed by Mn-complexes. In conclusion several of the Mn-catalysts described in this thesis have the potential to become one of the most important oxidation catalysts of the future.

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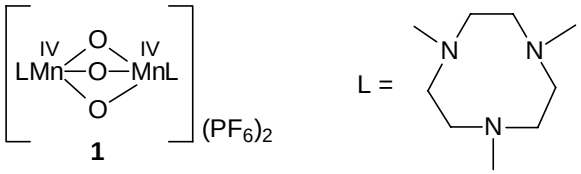
Samenvatting

Mangaan Katalysatoren voor Homogene Oxidatie Reacties

Introductie

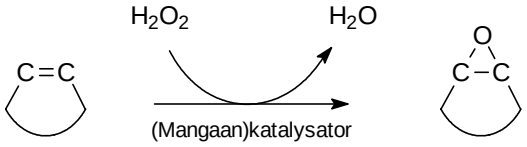
Veel essentiële functies in organismen worden vervuld door enzymen die mangaan bevatten. Enzymen zijn verbindingen die (bio)chemische reacties katalyseren en tijdens de omzetting van de uitgangsstoffen (substraten) verandert de katalysator (het enzym) niet. Efficiënte katalysatoren kunnen in zeer kleine hoeveelheden een uitgangstof volledig omzetten tot het gewenste product.

Om de werking van enzymen te kunnen bestuderen kan gebruik gemaakt worden van enzymmodellen. De modellen bestaan vaak uit twee onderdelen namelijk één of meerdere metaalatomen, bijvoorbeeld mangaan of ijzer, en een organisch molecuul, het ligand, dat gebonden is aan het metaalcentrum. De gekatalyseerde reactie vindt plaats op het metaalcentrum en door gebruik te maken van verschillende liganden kunnen de katalytische eigenschappen worden beïnvloed. De modellen kunnen ook een uitgangspunt zijn voor de ontwikkeling van nieuwe oxidatiekatalysatoren. Mangaancomplexen (**1**, Figuur 1) gebaseerd op macrocyclische-triamine (tmtacn) liganden zijn intensief gebruikt als enzymmodel, bijvoorbeeld voor het enzym *catalase*, een enzym dat het voor cellen schadelijke waterstofperoxide omzet tot water en zuurstof. Het mangaancomplex werd tevens intensief bestudeerd als bleekkatalysator in wasmiddelen door Unilever Reseach. Behalve actief te zijn in bleekprocessen is dit complex ook zeer effectief toe te passen als katalysator in andere oxidatie reacties, zoals epoxidatie en alcoholoxidaties.



Figuur 1 *Mangaancomplex gebaseerd op het ligand tmtacn.*

Epoxiden kunnen via veel verschillende syntheseprocedures gemaakt worden, daarnaast kunnen deze verbindingen ook als interessante bouwstenen dienen om andere moleculen te kunnen synthetiseren. Een veel gebruikte methode om epoxiden te maken is de oxidatie van alkenen. Voor deze oxidatie reactie is een groot aantal methoden bekend, gebruik makende van een scala van traditionele oxidanten. Helaas produceren de meeste van deze traditionele synthese routes, naast het gewenste epoxide, veel ongewenste bijproducten. Daarom hebben zuurstof (O_2) of waterstofperoxide (H_2O_2) als oxidant de voorkeur omdat water in principe het enige bijproduct is ("green chemistry"). Dit maakt deze oxidanten bovendien bijzonder aantrekkelijk voor industriële applicaties. Daar H_2O_2 niet uit zich zelf reageert met de alkenen is een katalysator nodig. Een katalytische oxidatie reactie van een alkeen met H_2O_2 is gevisualiseerd in Schema 1.



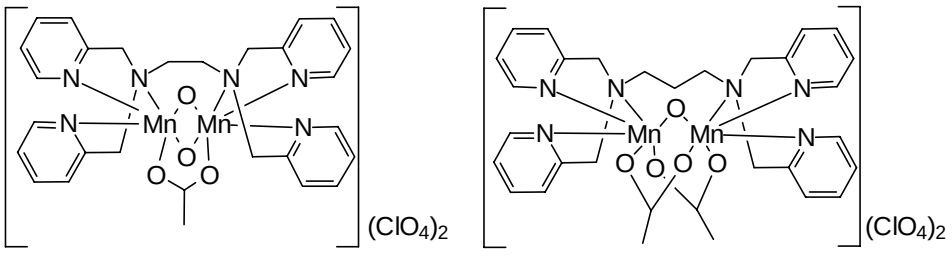
Schema 1 *Epoxidatie met H_2O_2 als oxidant.*

Doelstelling van het onderzoek

Het doel van het in dit proefschrift beschreven onderzoek is het ontwerp en de synthese van nieuwe homogene oxidatiekatalysatoren. Het onderzoek was gebaseerd op het actieve en veel bestudeerde Mn-tmtacn complex (**1**, Figuur 1). Een nadeel van het ligand tmtacn is de moeilijke synthese; daarnaast zijn modificaties doorgaans niet eenvoudig te introduceren. Daarom is in eerste instantie onderzoek verricht naar actieve complexen gebaseerd op liganden die net als het tmtacn ligand drie stikstof-donoren bevat, maar nu ook eenvoudig te synthetiseren en te veranderen zijn. Vervolgens zijn de effecten van deze veranderingen op de (ep)oxidatie katalyse verder bestudeerd.

Mangaancomplexen als homogene epoxidatiekatalysator

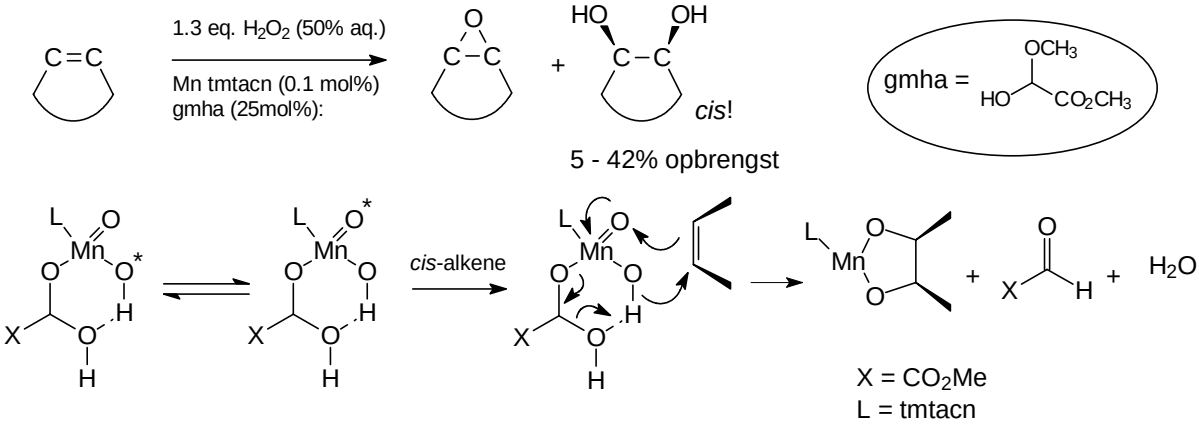
De katalytische oxidatie eigenschappen van verschillende mangaan complexen zijn beschreven in de hoofdstukken 2 en 3. De mangaan complexen **2.3** en **2.4** (Figuur 2), gebaseerd op de liganden tpen en tptn, respectievelijk, zijn intensief bestudeerd als katalysator voor epoxidatie reacties. Een scala van verschillende alkeen-substraten werd hiervoor gebruikt. Zowel goede selectiviteit als reactiviteit werd gevonden voor complex **2.4**. Complex **2.3**, met 1-koolstof atoom minder in de brug, was inactief als epoxidatie katalysator. Zoals uit eerder werk al was gebleken kunnen kleine aanpassingen in de structuur grote gevolgen hebben op de reactiviteit. Met de introductie van extra methyl-substituenten aan de pyridinegroepen kon de reactietijd daarentegen aanmerkelijk gereduceerd worden.



Figuur 2 *Mangaancomplexen gebruikt voor epoxidatie reacties.*

Homogene epoxidatie en *cis*-dihydroxylatie reacties

De in hoofdstuk 2 en 3 beschreven epoxidatie-katalysatoren hebben als nadeel dat er een overmaat aan H_2O_2 nodig is om hoge conversies te verkrijgen. De reden hiervan is dat de complexen naast oxidatie activiteit ook *catalase*-activiteit vertonen; d.w.z. ontleding van het H_2O_2 naar water en zuurstof. Het voorkomen van H_2O_2 ontleding is een belangrijke uitdaging om efficiënte oxidatiekatalyse te verkrijgen. In hoofdstuk 4 is het onderzoek beschreven om de *catalase*-activiteit te onderdrukken met behulp van co-katalysatoren. Door het hemiacetal gmha (Schema 2) als co-katalysator (25 mol%) te gebruiken in combinatie met het Mn-tmtacn complex konden oxidatie reacties uitgevoerd worden met slechts een minimale overmaat aan H_2O_2 (1.3 equivalenten). De oxidatiereactie kan nog efficiënter worden gemaakt door aan het gmha/Mn tmtacn systeem een oxalaat-buffer toe te voegen. Het meest interessante aspect van deze ontdekking is dat naast epoxide-producten ook significante hoeveelheden *cis*-diolen worden gevormd, wanneer gmha als enig additief wordt gebruikt. Deze *cis*-diolen kunnen normaal alleen op bijzonder lastige wijze en via milieu onvriendelijke methoden gemaakt worden.



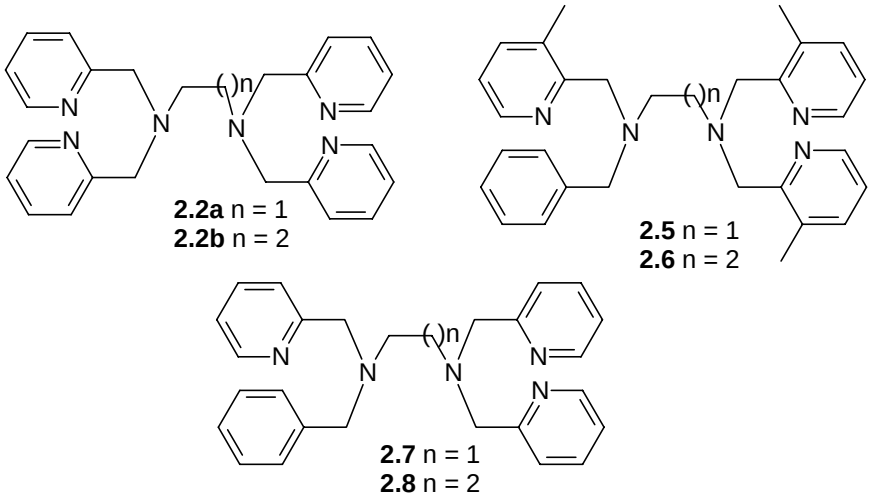
Schema 2 *Mn-tmtacn gekatalyseerde cis-dihydroxylering reactie en voorgestelde mechanisme.*

Gebaseerd op de resultaten beschreven in hoofdstuk 4 wordt een Mn-oxo-hydroxo deeltje voorgesteld als het reactieve *cis*-dihydroxylering-intermediair. Het hemiacetal gmha zet het *catalase* actieve Mn-tmtacn om in een mono-nucleair Mn-deeltje, zoals weergegeven in Schema 2.

Mangaankatalysatoren voor alcohol- en sulfide-oxidatie

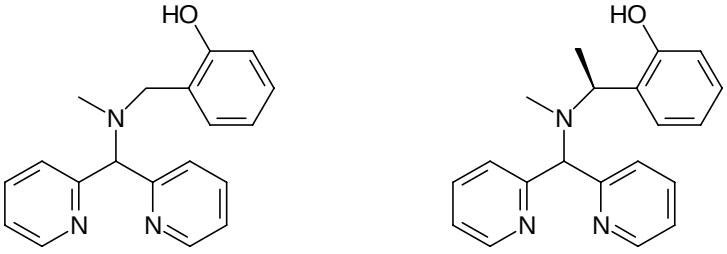
In hoofdstuk 5 zijn de resultaten weergegeven van een studie naar de meest actieve mangaan epoxidatie-katalysatoren voor alcohol oxidatie reacties met H_2O_2 als oxidant. De

complexen werden *in situ* gesynthetiseerd en zijn gebaseerd op de liganden zoals weergegeven in Figuur 3 en gebruiken $Mn(OAc)_3$ als mangaanzout. Voor de *in situ* geprepareerde complexen uitgaande van de liganden **2.2b**, **2.5 - 2.8**, werden hoge activiteiten (300 - 900 turnover nummers) en selectiviteiten (80 - 99%) gevonden. Het complex gebaseerd op tpen (ligand **2.2a**) bleek echter niet reactief te zijn, en overeenkomstige waarnemingen werden gedaan tijdens eerdere epoxidatie-reacties. De tptn-derivaten zoals, liganden **2.7** en **2.8**, met een 2-koolstof en 3-koolstof brug tussen de twee liganden, leverden matige (ligand **2.7**) tot actieve (ligand **2.8**) katalysatoren op. Goede resultaten werden met de liganden **2.5** en **2.6** behaald, en ook werd de reactietijd aanmerkelijk verkort. Het actieve intermediair is tot dusver niet bekend maar hydroxyl-radicalen als actieve deeltjes kunnen zeer waarschijnlijk uitgesloten worden op grond van data verkregen met onder andere spectroscopische methoden.



Figuur 3 *Enkele bestudeerde liganden.*

In hoofdstuk 6 wordt de activiteit van een aantal *in situ* gemaakt complexen, gebaseerd op eerder beschreven liganden, beschreven voor de oxidatie van sulfides naar sulfoxides. Daar sulfoxides belangrijke bouwstoffen in de organische chemie zijn is de selectieve katalytische oxidatie van sulfides naar sulfoxides van groot belang. Een probleem is de oxidatie van sulfoxides naar de overeenkomstige sulfonen. Veel onderzoek is gedaan om de vorming van deze vaak ongewenste producten te voorkomen. Er van uitgaande dat goede oxidatiekatalysatoren voor alkeen- en alcoholsubstraten ook toepasbaar zijn voor de conversie van sulfides, zijn de meest actieve liganden getest voor deze klasse van substraten. De meest succesvolle resultaten zijn verkregen met de liganden **6.40** and **6.41**. Goede conversies van sulfides naar sulfoxides en slechts kleine hoeveelheden van sulfonen werden gevonden met de complexen gebaseerd op ligand **6.40**. Vervolgens werd ligand **6.41**, een chirale versie van ligand **6.40,** bestudeerd voor de oxidatie van sulfides, waarbij opbrengsten tot 55% en enantioselectiviteiten tot 18% werden gevonden.



6.40 **6.41**

Figuur 4 *Liganden gebruikt in sulfide oxidatiereacties.*

Conclusies

Zoals aan het begin van deze samenvatting beschreven, was het doel van dit onderzoek de synthese van nieuwe liganden met als toepassing mangaangekatalyseerde oxidatiereacties. Er kan geconcludeerd worden dat een aantal veel belovende systemen gedurende het onderzoek ontwikkeld zijn. De bestudeerde op mangaan gebaseerde complexen, beschreven in dit proefschrift kunnen gebruikt worden als katalysator voor zowel de oxidatie van alkenen en alcoholen maar zijn ook toepasbaar voor de oxidatie van sulfides. De gevonden resultaten zoals opbrengsten en activiteiten (meer dan 900 turnover nummers), zijn op veel punten vergelijkbaar met het zeer actieve en intensief bestudeerde tmtacn complex. Maar een interessant voordeel ten opzichte van het tmtacn ligand is dat de tptn liganden relatief eenvoudig structureel te veranderen zijn. Door deze modificaties konden de katalytische oxidatie eigenschappen positief beïnvloed worden. Zo is bijvoorbeeld de reactietijd aanmerkelijk gereduceerd, door de introductie van additionele methyl-substituenten aan pyridinegroepen. Deze actieve oxidatiekatalysatoren zijn bijzonder geschikt als basis voor vervolgonderzoek, te denken valt aan de introductie van chirale-substituenten. Dit leidt tot de grote uitdaging van enantioselective-epoxidatie reacties met H_2O_2 als oxidant. De chiraliteit zou bijvoorbeeld geïntroduceerd kunnen worden in de *backbone* van de liganden of via de pyridinegroepen.

Hoewel de beschreven mangaan gebaseerde oxidatiesystemen actief zijn met H_2O_2, is helaas wel een grote overmaat nodig van dit aantrekkelijke oxidant. Het gebruik van geactiveerde aldehydes zoals gmha als co-katalysator in combinatie met het Mn-tmtacn complex heeft geleid tot een bijzonder H_2O_2 efficiënt oxidatiesysteem, met slechts een kleine overmaat aan oxidant werden hoge conversies verkregen. Interessant was ook de vorming van significante hoeveelheden *cis*-diol uitgaande van alkeen-substraten. Ook al geeft deze methode nog geen volledige selectiviteit naar *cis*-diolen, het is een goede stap in de richting naar alternatieven voor de traditionele dihydroxylering-procedures gebaseerd op het zeer giftige osmium. Kortom, gezien de enorme veelzijdigheid, goede toegankelijkheid en stabiliteit kunnen deze mangaankatalysatoren na vervolgonderzoek, de katalysatoren van de toekomst worden.

List of Publications

New manganese catalysts for alcohol oxidation.
Brinksma, J.; Rispens, M. T.; Hage, R.; Feringa, B. L. *Inorg. Chim. Acta.* **2002**, *accepted for publication, in press*.

Homogeneous cis-dihydroxylation and epoxidation of olefins with high H_2O_2 efficiency by mixed manganese/activated carbonyl catalyst system.
Brinksma, J.; Schmieder, L.; Van Vliet, G.; Boaron, R.; Hage, R.; De Vos, D. E.; Alsters, P. L. Feringa, B. L. *Tetrahedron Lett.* **2002**, *43*, 2619 - 2622.

New ligands for manganese catalysed selective oxidation of sulfides to sulfoxides with hydrogen peroxide.
Brinksma, J.; La Crois, R.; Feringa, B. L.; Donnoli, M. I.; Rosini, C. *Tetrahedron Lett.* **2001**, *42*, 4049 - 4052.

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Brinksma, J.; Hage, R.; Kerschner, J.; Feringa, B. L. *Chem. Commun.* **2000**, 537 - 538.

Rheology and thermotropic properties of bis-urea-based organogels in various primary alcohols
Brinksma, J.; Feringa, B. L.; Kellogg, R. M.; Vreeker, R.; Van Esch, J. *Langmuir* **2000**, *16*, 9249 - 9255.

Dinuclear manganese complexes as catalysts for oxidation with hydrogen peroxide
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