Mn-salen catalyzed asymmetric epoxidation: search for new oxidation systems

Pekka Pietikäinen

University of Helsinki
Faculty of Science
Department of Chemistry
Laboratory of Organic Chemistry
P. O. Box 55, FIN-00014 University of Helsinki, Finland

ACADEMIC DISSERTATION

To be presented with the permission of the Faculty of Science of the University of Helsinki for public criticism in Auditorium A110 of the Department of Chemistry, A. I. Virtasen aukio 1, on June 1st, 2001 at 1 p.m.

Helsinki 2001
CONTENTS

ABSTRACT 3
PREFACE 4
LIST OF ORIGINAL PUBLICATIONS 5
ABBREVIATIONS 6

1. INTRODUCTION 7

2. Mn-SALEN CATALYZED ASYMMETRIC EPOXIDATION 9
   2.1. Background: oxo-based transition metal catalysis 9
   2.2. Chiral Mn(III)-salen complexes: steric and electronic effects on enantioselectivity 12
   2.3. Synthesis of chiral Mn(III)-salen complexes 18
   2.4. Epoxidation method: effects of the reaction conditions 19
      2.4.1. Choice of oxidant 19
      2.4.2. Axial ligand effects 25
   2.5. Substrate effects 27
   2.6. Mechanistic considerations 30

3. AIMS OF THE PRESENT STUDY 33

4. RESULTS AND DISCUSSION 34
   4.1. Synthesis of Mn(III)-Schiff base complexes 34
      4.1.1. Synthesis of symmetrical Mn(III)-salen complexes 34
      4.1.2. Synthesis of unsymmetrical Mn(III)-Schiff base complexes 35
   4.2. Asymmetric epoxidation with hydrogen peroxide 38
      4.2.1. Axial ligand effects 38
      4.2.2. Asymmetric epoxidation of various alkenes with H2O2 42
      4.2.3. Catalyst structure effects in asymmetric epoxidations with H2O2 43
   4.3. Asymmetric epoxidation with periodates 45
4.4. Asymmetric epoxidation with peroxymonosulfates

4.4.1. Effects of reaction conditions

4.4.2. Asymmetric epoxidation of various alkenes with peroxymonosulfates

4.4.3. Catalyst structure effects in asymmetric epoxidation with peroxymonosulfates

4.5. Asymmetric epoxidation with \textit{in situ} generated peroxyacids

4.5.1. Generation of the peroxyacids and the epoxidation procedure

4.5.2. Comparison with other oxidation systems utilizing H$_2$O$_2$

4.5.3. Possible catalytic routes for asymmetric epoxidation with peroxyacids

4.6. Asymmetric epoxidation catalyzed with unsymmetrical Mn(III)-Schiff base complexes

5. CONCLUSIONS AND FUTURE PERSPECTIVES

6. EXPERIMENTAL

7. REFERENCES AND NOTES

ORIGINAL PUBLICATIONS I-VII
During the last decade Mn(III)-salen complexes [salen = N,N'-bis(salicylidene)-ethylenediaminato] have emerged as efficient and practical catalysts for the asymmetric epoxidation of various unfunctionalized cis-disubstituted, tri- and tetrakisubstituted alkenes. The literature review of this thesis outlines the development of Mn-salen-based asymmetric epoxidation methodology. The essentials of Mn(III)-salen catalysis, such as design and synthesis of the salen ligand, the steric and electronic effects of catalyst structure on stereoselectivity, and the mechanism of asymmetric induction are surveyed. Also, other important aspects affecting the outcome of asymmetric epoxidation are covered including the effects of the oxidant and additives (axial ligands).

The present study describes the development of new oxidation systems based on chiral Mn-salen complexes. This development work included a systematic search for suitable stoichiometric oxidants and additives for asymmetric epoxidation, and the synthesis of Mn(III)-salen type catalysts. Several oxidants were investigated and found to be applicable to Mn-salen-based epoxidation: hydrogen peroxide, periodates, quaternary ammonium and phosphonium monopersulfates, and in situ generated peroxyacids. Moderate-to-high enantioselectivities in alkene epoxidation (ee up to 96 %), especially for electron-rich cis-disubstituted and trisubstituted olefins, were obtained with all oxidants. The presence of additives such as imidazoles, pyridines and amine-N-oxides was beneficial with all the oxidants. The effect of catalyst structure on the stereochemical outcome of the epoxidation was also studied.

Particular attention was paid to hydrogen peroxide due to its advantages over many other oxidants: high oxygen content, low price, ready availability, and environmental acceptability. A simple and practical epoxidation system involving oxidation-resistant carboxylate salts as additives was developed. A mechanistic basis for the role of these additives is proposed. Hydrogen peroxide was further utilized in the generation of peroxyacids in situ from carboxylic acid anhydrides, which increased reactivity and selectivity.

In addition to symmetrical Mn(III)-salen complexes, two novel non-C2-symmetric Mn(III)-Schiff-base complexes containing salicylaldehyde and 1-(2-hydroxyphenyl)ketone units were synthesized using a stepwise procedure. One of the two complexes was catalytically active in asymmetric epoxidation of various alkenes and showed moderate-to-good enantioselectivity, although it was lower than that obtained for analogous C2-symmetric salen-based catalysts. Possible reasons for the differences in reactivity and selectivity between these two types of catalysts are briefly discussed.
"Sed fugit interea, fugit inreparabile tempus"
(Time meanwhile flies, never to return)
Virgil (70-19 B. C.)

PREFACE

The experimental part of this study was carried out at the Laboratory of Organic Chemistry of the University of Helsinki during the years 1992-1998.

I am indebted to Professor Gösta Brunow for introducing me into the field of biomimetic oxidation chemistry and for his support and encouragement during the years of this work.

I am also grateful to Professor Tapio Hase, Head of the Organic Chemistry Laboratory, for placing the excellent research facilities of the Laboratory at my disposal.

I wish to thank Dr. Jorma Matikainen for running the mass spectra, Mr. Anssi Haikarainen (M.Sc.) for fruitful cooperation and Ms. Mia-Riitta Malmström for technical assistance. Thanks are extended to professors Tapio Hase and Markku Leskelä for reviewing the manuscript of the thesis and to Mr. Harri Salonen (BA) for revising the language.

I would like to express my warmest thanks to all my colleagues at the Laboratory of Organic Chemistry for valuable comments and for their friendship. Also refreshing moments spent with the members of the late (?) “Thursday Club” are gratefully appreciated.

This work was supported by the Technology Development Centre of Finland (TEKES) during the years 1992-1997, University of Helsinki, Research Foundation of Orion Corporation, and Orion Corporation Fermion, which I acknowledge with gratitude.

Finally, my sincerest appreciation goes to my parents, to my wife Tiina and to Enni, and Jeannette for their encouragement, patience, and love during all these years.

Espoo, March 2001
Pekka Pietikäinen
LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, referred to in the text by their Roman numerals (I-VII). Data published and discussed here for the first time are referred to as VIII.


### ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>Ar</td>
<td>aryl</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>t-Bu</td>
<td>tert-butyl</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>EI</td>
<td>electron impact</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>Eu(hfc)₃</td>
<td>tris[3-(heptafluoropropylhydroxymethylene)-(+)camphorato]europium(III)</td>
</tr>
<tr>
<td>FAB</td>
<td>fast atom bombardment</td>
</tr>
<tr>
<td>ImH</td>
<td>imidazole</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>MCPBA</td>
<td>m-chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>MMPP</td>
<td>magnesium monoperoxyphthalate</td>
</tr>
<tr>
<td>MS</td>
<td>mass spectrometry</td>
</tr>
<tr>
<td>N-MeIm</td>
<td>N-methylimidazole</td>
</tr>
<tr>
<td>NMO</td>
<td>N-methylmorpholine N-oxide</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>Oxone</td>
<td>potassium monopersulfate, 2KHSO₅·KHSO₄·K₂SO₄ triple salt</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>POHP</td>
<td>triphenylphosphine oxide-hydrogen peroxide adduct, Ph₃PO·½H₂O₂</td>
</tr>
<tr>
<td>PPNO</td>
<td>4-phenylpyridine N-oxide</td>
</tr>
<tr>
<td>i-Pr</td>
<td>iso-propyl</td>
</tr>
<tr>
<td>Py</td>
<td>pyridine</td>
</tr>
<tr>
<td>PyNO</td>
<td>pyridine N-oxide</td>
</tr>
<tr>
<td>salen</td>
<td>N,N′-bis(salicylidene)ethylenediamine dianion ligand</td>
</tr>
<tr>
<td>SPC</td>
<td>sodium percarbonate, Na₂CO₃·1½H₂O₂</td>
</tr>
<tr>
<td>UHP</td>
<td>urea-hydrogen peroxide adduct, urea·H₂O₂</td>
</tr>
</tbody>
</table>
1. INTRODUCTION

Epoxides are versatile intermediates in organic chemistry. The inherent polarity and strain of their three-membered ring makes them readily undergo stereospecific ring-opening reactions with nucleophiles to form 1,2-difunctional compounds. Optically pure epoxides with two contiguous stereogenic centers are particularly useful intermediates for the preparation of biologically and pharmaceutically active compounds.

The first attempts to prepare optically active epoxides were reported in 1965 and since then considerable attention has been paid to asymmetric epoxidation of olefins. Particularly, the use of chiral transition-metal complexes as epoxidation catalysts has received increased attention over the past two decades. The asymmetric epoxidation of allylic alcohols, discovered by Sharpless and Katsuki in 1980, which utilizes alkyl hydroperoxide together with titanium(IV)-dialkyltartrate catalyst, is a remarkable example of catalytic methods. This highly effective system has been widely used in organic synthesis and has been the subject of several review articles.

One of the recent challenges in asymmetric catalysis has been the achievement of high enantioselectivity in the epoxidation of unfunctionalized alkenes, that is alkenes with only hydrocarbon substituents. While the Sharpless epoxidation works efficiently with substrates capable of precoordinating with the catalyst, it is not suitable for the asymmetric epoxidation of unfunctionalized alkenes. The greatest difficulty in the selective epoxidation of alkenes bearing only hydrocarbon substituents is control of the olefin approach to the active oxidant, since selectivity is determined only through low-energy, non-bonded interactions between the catalyst and the substrate.

The most successful approach to achieving high selectivity in asymmetric epoxidation of unfunctionalized alkenes has involved a biomimetic strategy, utilizing chiral porphyrin- and salen-based transition metal complexes as catalysts (Figure 1). Metalloporphyrin epoxidation catalysts were initially developed as part of efforts to model the reactivity of biologically interesting metalloporphyrin-containing enzymes, such as cytochrome P 450s. Both classes of complexes are kinetically nonlabile and sterically well defined compounds with square-planar configuration, and therefore provide a feasible matrix for ligand design. The first reports of the use of porphyrin complexes as catalysts for epoxidation appeared in 1979 and the first example of asymmetric catalytic epoxidation with optically active metalloporphyrin was reported in 1983. Subsequently, several groups have reported the use of chiral metalloporphyrins as catalysts for the asymmetric epoxidation of unfunctionalized olefins. However, no truly synthetically useful epoxidation system based on chiral metalloporphyrins has been developed yet.
Unlike metalloporphyrins (1), salen complexes (2) have two potentially stereogenic sp\(^3\)-hybridized carbon atoms (asterisk) in the vicinity of the metal center. This closer proximity of the stereogenic centres to the metal binding site, compared to the chiral porphyrin ligands, allows better stereochemical control in the epoxidation step. The real breakthrough in transition-metal catalyzed asymmetric epoxidation of unfunctionalized alkenes was made in 1990 when two research groups, Jacobsen et al. and Katsuki et al., independently reported the use of optically active Mn(III)-salen complexes as epoxidation catalysts.\(^{12,13}\) Since then the salen-based catalysts have proven highly effective in enantioselective epoxidation of various classes of unfunctionalized olefins.

Mn-salen catalyzed asymmetric epoxidation, also known as the Jacobsen-Katsuki epoxidation, has been extensively reviewed since 1993.\(^{3,14-20}\) Most of the reviews have widely covered the essentials of Mn(III)-salen catalysis, such as design of the salen ligand, steric and electronic effects of the catalyst structure on stereoselectivity, and mechanism of the asymmetric induction. Also, effects of axial ligands and substrates in asymmetric epoxidation have been reported often. However, at the time the present study was started the effects of stoichiometric oxidants on the outcome of Mn(III)-salen catalyzed epoxidations had been studied much less.

The present study was undertaken in order to develop novel asymmetric epoxidation systems based on chiral Mn-salen complexes. This included the search for suitable stoichiometric oxidants and additives for asymmetric epoxidation, and the synthesis of new Mn(III)-salen type catalysts.

The literature review of this thesis outlines the development of salen-based asymmetric epoxidation methodology. The main emphasis is on the effects of oxidants, axial ligands, and general reaction conditions on the outcome of asymmetric epoxidation.
2. Mn-SALEN CATALYZED ASYMMETRIC EPOXIDATION

2.1. Background: oxo-based transition metal catalysis

General characteristics\textsuperscript{21,22}

Metalloporphyrins and metalloalens have common features with respect to their electronic structure and catalytic activity. The epoxidation of alkenes with these complexes is generally believed to proceed through oxo-metal species analogous to the oxoiron(V) intermediates participating in cytochrome P450-mediated oxidations.\textsuperscript{8}

Porphyrin- and salen-based transition metal complexes react with oxidants, such as iodosylarenines, sodium hypochlorite, and hydrogen peroxide, that are able to donate one oxygen atom (single oxygen atom donors) to form an oxo-metal species, which then relays the oxygen to the substrate. The concept of this widely accepted oxygen-rebound mechanism, introduced by Groves et al., is outlined in Figure 2.\textsuperscript{23}

![Figure 2. Transition metal-catalyzed asymmetric epoxidation of alkenes by oxygen rebound. LM= transition metal complex (L= porphyrin or salen), XO= oxygen atom donor (e.g. PhIO, NaOCl, O\textsubscript{2}/reductant, H\textsubscript{2}O\textsubscript{2}).](image)

Oxo transfer from metals to alkenes results in a net two-electron reduction of the metal complex (Figure 2). Therefore, only metals, such as Fe(III), Mn(III), Cr(III), and Ru(III), that are capable of shuttling between oxidation states are effective in oxo-transfer catalysis. Most of the studies with metalloporphyrins have been conducted with Fe(III) and Mn(III) as the metal center, mainly because of the relationship of these catalysts to biologically relevant metalloporphyrins.\textsuperscript{21,22}

In metalloporphyrin catalyzed epoxidations, alkenes are postulated to approach the metal-oxo bond from the side.\textsuperscript{24} This side-on approach model (Figure 3) and its variants account for the observation that olefin substitution significantly affects epoxidation efficiency. Generally, cis-olefins are observed to be more reactive substrates than trans-olefins. Cis-olefins also react with higher enantioselectivity in epoxidations catalyzed by chiral catalysts. Also cis-disubstituted olefins are better
substrates in transition-metal catalyzed epoxidations than 1,1-disubstituted olefins. These observations imply that the olefin substituents interact considerably with the catalyst plane during oxygen atom transfer. Epoxidation of alkenes by oxo-transfer occurs with varying degrees of stereospecificity depending on the metal center and the nature of the alkene substrate. While reactions catalyzed by Fe-porphyrins are mostly stereospecific affording cis-epoxides from the corresponding cis-alkenes, catalysis by Mn-porphyrins affords mixtures of cis- and trans-epoxides. Also, simple alkyl-substituted alkenes undergo epoxidation stereospecifically and conjugated olefins nonstereospecifically.

![Side-on approach model for oxygen transfer](image)

**Figure 3.** Side-on approach model for oxygen transfer showing the less hindered approach for (a) cis-alkenes than for (b) trans-alkenes. Dark line symbolizes the catalyst plane.

While the side-on approach model has received wide acceptance, the mechanism of oxygen transfer from the oxo-metal complex to the olefin double bond is controversial. Oxygen transfer from the oxo-metal species to the olefin has been proposed to occur via several different intermediates (Figure 4): (a) concerted transition state, (b) carbon radical, (c) carbocation, (d) π-radical cation, and (e) metallaoxetane. Mechanistic discussions concerning the oxygen transfer from the salen-Mn(V)=O complex to the alkene will be outlined in Section 2.6.

![Proposed intermediates](image)

**Figure 4.** Proposed intermediates for oxygen atom transfer.

Other important features that affect the outcome of the reaction include the nature of the axial ligand and the choice of the stoichiometric oxidant. The first oxidants reported to affect alkene epoxidation in the presence of metalloporphyrin derivatives were iodosylbenzene and related iodosylarene derivatives. A wide variety of other stoichiometric oxidants have been discovered to be effective oxygen atom donors in oxo-transfer reactions. These include NaOCl, alkyl hydroperoxides,
peroxyacids, amine N-oxides, potassium hydrogenpersulfate (Oxone), hydrogen peroxide, periodate, magnesium monoperoxyphthalate, and molecular oxygen with a stoichiometric reductant. NaOCl and PhIO have been studied particularly closely and used most widely in asymmetric catalytic epoxidations.\textsuperscript{11,14}

In natural cytochrome P450 systems the porphyrin ligand is protoporphyrin-IX with a thiolate residue of cysteine as the axial ligand.\textsuperscript{8} This proximal ligand is in part responsible for controlling the catalytic activity and selectivity of the enzyme.\textsuperscript{22} Not surprisingly, additional axial ligands, such as pyridines and N-substituted imidazoles, enhance the reaction rate and yield and also increase the stereoselectivity in metalloporphyrin-catalyzed epoxidations.\textsuperscript{8,22,27} These effects are especially prominent in reactions catalyzed by Mn(III)-porphyrins with NaOCl or H\textsubscript{2}O\textsubscript{2} as the stoichiometric oxidant.\textsuperscript{28,29}

**Mn(III)-salen complexes as epoxidation catalysts**

The analogy between metalloporphyrin- and salen-based epoxidations was revealed during the 1980’s in careful structural and kinetic studies by Kochi et al.\textsuperscript{30-33} At first their results showed that cationic chromium salen complexes were catalytically able to epoxidise alkenes in the presence of iodosylbenzene as stoichiometric oxidant.\textsuperscript{30-32} The active species in these reactions were identified as oxo-Cr(V) complexes and the structure of one such complex was determined by X-ray crystallography. Also the beneficial effect of added donor ligands on the reaction rate and epoxide yield was recognized.\textsuperscript{32} Subsequently Kochi et al. reported that also Mn(III)-salen complexes were capable of epoxidizing various alkenes with even higher efficiency.\textsuperscript{33} Oxo-manganese(V) species were postulated to be the active oxidants, although their physical characterisation was not possible due to their high reactivity. The existence of such species has recently been evidenced by tandem mass spectrometry.\textsuperscript{34} The selectivity of Mn(III)-salen complexes is the same as that observed for porphyrins: \textit{cis}-alkenes react faster than \textit{trans}-alkenes and electron-rich substrates faster than electron-poor substrates, indicating similar mechanistic pathways for porphyrin- and salen-catalyzed reactions. Also, epoxidation of \textit{cis}-alkenes with Mn-complexes is not stereospecific: a mixture of \textit{cis}-and \textit{trans}-epoxides is usually formed. Accordingly, Kochi et al. suggested that Mn(III)-salen catalyzed epoxidation takes place by way of a radical intermediate (Figure 4).\textsuperscript{33} Other metal-salen and related Schiff base complexes with Ni(II) and Fe(III) as the metal center have been subsequently studied.\textsuperscript{35-37}
2.2. Chiral Mn(III)-salen complexes: steric and electronic effects on enantioselectivity

Crucial factors in asymmetric epoxidation of unfunctionalized alkenes are the pathway and orientation of the approaching alkene to the active oxidant. Therefore, the attainment of high enantioselectivity relies on the steric and electronic properties of the substituents in the salen complex, in addition to the presence of disymmetric diimine moiety.\textsuperscript{14-18} Chart 1 (p. 15) and Chart 2 (p. 17) show various types of chiral Mn(III)-salen and closely related complexes that have been developed as epoxidation catalysts by several research groups since 1990.

Steric effects

Following the results of Kochi et al, Jacobsen and Katsuki designed optically active Mn(III)-salen complexes as epoxidation catalysts.\textsuperscript{12,13} Representative examples of the Jacobsen-type (3-12) and Katsuki-type (13-21) catalysts are presented in Chart 1 (p. 15). The steric and electronic requirements for effective catalysis were recognized early on.\textsuperscript{38,39} Jacobsen et al. observed that incorporation of tert-butyl substituents at the C3- and C3’-positions of the salicylidene ligand is necessary for the attainment of high enantioselectivity (see Figure 5 and Chart 1 for numbering in salen complexes).\textsuperscript{12,38} Jacobsen rationalized these findings by using the side-on approach model proposed earlier (Figure 3) for the epoxidation reactions catalyzed by metalloporphyrins. Figure 5 shows the possible approaches of cis-alkene to a salen-Mn-oxo species.\textsuperscript{15}

![Figure 5](image-url) Possible side-on approaches to a salen-Mn-oxo intermediate. The oxo ligand is oriented out of the plane of the page.

Table 1 (p. 13) summarizes the epoxidation of (Z)-1-phenylprop-1-ene, a commonly employed model substrate for epoxidation systems, by different Mn(III)-salen catalysts. The effect of the substitution at the C3- and C3’-positions is illustrated by comparing the catalysts 3 and 4. The unsubstituted catalyst 3 shows very low
enantioselectivity, presumably because the olefin can approach the metal center easily from the sterically less hindered side remote from the stereogenic centers (pathways d-e in Figure 5). On the other hand, incorporation of bulky substituents at the C3- and C3'-positions (catalyst 4) improves selectivity dramatically by directing the olefin approach to the vicinity of the dissymmetric diimine bridge (paths a-b). The presence of groups larger than tert-butyl at the C3- and C3'-positions (e.g. 6, 18) generally have only slight positive or negative effects on epoxidation selectivity. Catalysts possessing bulky trialkylsilyl substituents at the C3- and C3'-positions (e.g. 22) exhibited significantly lower enantioselectivity compared with the related catalyst 4 (t-Bu groups at C3,C3'-positions), presumably because of the longer C-Si bond length compared with the C-C bond length.

Table 1. Asymmetric epoxidation of (Z)-1-prop-1-ene with different Mn(III)-salen complexes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>R,R</th>
<th>A</th>
<th>B</th>
<th>Oxidant</th>
<th>ee (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>Ph,Ph</td>
<td>H</td>
<td>H</td>
<td>NaOCl</td>
<td>&lt;10</td>
<td>14, 15</td>
</tr>
<tr>
<td>2</td>
<td>4,5</td>
<td>Ph,Ph</td>
<td>H, Me</td>
<td>t-Bu</td>
<td>Me₃PhIO⁺, NaOCl</td>
<td>84</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>Ph,Ph</td>
<td>Me</td>
<td></td>
<td>Me₃PhIO⁺</td>
<td>80</td>
<td>39</td>
</tr>
<tr>
<td>4</td>
<td>18</td>
<td>Ph,Ph</td>
<td>Ar</td>
<td></td>
<td>PhIO</td>
<td>89</td>
<td>45</td>
</tr>
<tr>
<td>5</td>
<td>22</td>
<td>Ph,Ph</td>
<td>H</td>
<td>Si(t-Bu)Me₂</td>
<td>NaOCl</td>
<td>53</td>
<td>41</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>(CH₂)₄</td>
<td>Me</td>
<td>t-Bu</td>
<td>NaOCl</td>
<td>80</td>
<td>40</td>
</tr>
<tr>
<td>7</td>
<td>11</td>
<td>(CH₂)₄</td>
<td>t-Bu</td>
<td>t-Bu</td>
<td>NaOCl</td>
<td>92</td>
<td>40</td>
</tr>
<tr>
<td>8</td>
<td>12</td>
<td>(CH₂)₄</td>
<td>OSi(i-Pr)₃</td>
<td>t-Bu</td>
<td>NaOCl</td>
<td>89</td>
<td>15, 78</td>
</tr>
<tr>
<td>9</td>
<td>7</td>
<td>Ph,Ph</td>
<td>OMe</td>
<td>t-Bu</td>
<td>NaOCl</td>
<td>83</td>
<td>51</td>
</tr>
<tr>
<td>10</td>
<td>9</td>
<td>Ph,Ph</td>
<td>NO₂</td>
<td>t-Bu</td>
<td>NaOCl</td>
<td>49</td>
<td>51</td>
</tr>
</tbody>
</table>

a) Iodosylmesitylene (2,4,6-Me-C₆H₃IO).
Concurrently with the work of the Jacobsen group, Katsuki et al. developed a series of Mn(III)-salen complexes 13-17 with four stereogenic centers, two at the dimine bridge and two at the C8- and C8’-positions. The conformation of the chiral substituents attached to the C8- and C8’-positions was found to have considerable influence on asymmetric induction. For example, increasing the size of the groups at the C8- and C8’-positions (4-tert-butylphenyl in 15 vs. Ph in 14) improved catalyst efficiency. Generally, these catalysts were not as efficient in the epoxidation of cis-alkenes as the synthetically more accessible Jacobsen-type catalysts. On the other hand, the Katsuki-type catalysts such as 16 exhibited higher enantioselectivity in the epoxidation of trans-alkenes. Katsuki et al. stated that the asymmetric induction of cis-alkenes is preferentially controlled by the chirality at the diimine bridge and that of trans-alkenes by the chirality at C8 and C8’ (catalyst 17). Katsuki et al. also synthesized Mn-salen complexes possessing axial chirality at the C3- and C3’-positions (18-21) resulting in improved epoxidation enantioselectivity.

The presence and properties of substituents on the C5- and C5’-positions of the salicylde ligand also have a significant, although generally less important, influence on epoxidation enantioselectivity. Generally, electron-donating (see next Section) or bulky substituents improve selectivity by blocking pathway c. For example, catalyst 11 with tert-butyl substituents at the C5- and C5’-positions afforded higher selectivity than the less hindered complex 10 (methyl at C5- and C5’-positions). However, further increase in the size of the C5,C5’-substituents has generally only a small effect on selectivity.

The structure of the diimine moiety also affects the asymmetric induction in epoxidation reactions and diverse effects have been observed depending on the catalyst type. Jacobsen et al. discovered that increasing the steric bulk on the diamine part (e.g. trans-1,2-dimesitylethylene diamine vs. trans-1,2-diphenylethylene diamine) afforded both decreased reactivity and poorer enantioselectivity. However, Katsuki et al. observed that catalyst 19 with bulky ethylenediamine-moiety was an especially effective catalyst. Interestingly, complex 30 with a tartrate-based backbone gave low to moderate enantioselectivity in epoxidations of various alkenes, but more significantly gave the opposite major enantiomer to that obtained using Jacobsen-type catalysts. This difference in enantiofacial selection was not explained. Also, Katsuki et. al. have reported a reversal in enantioselectivity by using catalyst 21 with a carboxylato group attached to the diimine moiety. This group coordinates to the metal center resulting in significant conformational changes in the salen structure and therefore reversed enantioselectivity.
Chart 1:

3: $R_1 = H \quad R_2 = H$
4: $R_1 = t$-Bu \quad R_2 = H
5: $R_1 = t$-Bu \quad R_3 = Me
6: $R_1 = 9$-methyl-9-fluorenyl \quad R_2 = Me
7: $R_1 = t$-Bu \quad R_3 = OMe
8: $R_1 = t$-Bu \quad R_2 = OSi($i$-Pr)$_3$
9: $R_1 = t$-Bu \quad R_2 = NO$_2$

10: $R = $ Me
11: $R = $ t-Bu
12: $R = OSi($i$-Pr)$_3$

13: $R_1 = Ph \quad R_2 = H \quad R_3 = Ph$
14: $R_1 = Ph \quad R_2 = Me \quad R_3 = Ph$
15: $R_1 = Ph \quad R_2 = Me \quad R_3 = 4$-t$-Bu$Ph$
16: $R_1, R_1 = (CH_2)_4 \quad R_2 = Me \quad R_3 = 4$-t$-Bu$Ph$
17: $R_1 = H \quad R_2 = Me \quad R_3 = 4$-t$-Bu$Ph$

18: $R_1 = Ph \quad R_2 = $ Me
19: $R_1 = 3,5$-Me$_2$Ph \quad R_2 = $ Ph
20: $R_1, R_1 = (CH_2)_4 \quad R_2 = $ Ph

21: $X = $ AcO$^-$, PF$_6$-

$^\dagger$ Only one of the two possible enantiomers for each catalyst is shown.
Electronic effects

The electronic effects of the substituents on the salicylidene ligand on the reactivity of the Mn(III)-salen complexes were studied already in the 1980's by Kochi et al. They showed that the presence of electron-withdrawing groups, such as -Cl or -NO₂ at C5- and C5'-positions, enhances the catalytic activity of the complex.\(^{32,33}\) Jacobsen et al. have unequivocally shown that the electronic nature of the substituent at the C5- and C5'-positions also strongly influences enantioselectivity.\(^{50}\) Complexes with electron-donating substituents show higher enantioselectivity than complexes possessing electron-withdrawing substituents (see Table 1). Electron-withdrawing substituents such as -NO₂ in 9 increase the reactivity of the catalyst, while substituents such as -OMe (catalyst 7) decrease the reactivity of the oxo-species. These findings were explained using the Hammond postulate. More reactive oxidant transfers oxygen via a more reactant-like transition state, with greater separation between substrate and catalyst and therefore poorer stereochemical communication. On the other hand, a milder oxidant would react via a more product-like transition state, resulting in more specific non-bonded interactions. However, Katsuki et al. have obtained somewhat different results with their catalysts. The introduction of -OMe substituent on the salicylide moiety was found to result in slightly diminished epoxidation enantioselectivity.\(^{51}\) This was explained by assuming that a metallaoxetane intermediate was involved in Mn(III)-salen catalyzed epoxidation.
Chart 2

22

23

24: \( R = \)

25: \( R = 2,4,6\)-trimethylphenyl

26: \( R_1 = R_2 = \text{Cl} \)

27: \( R_1 = \text{Et}, R_2 = \text{NO}_2 \)

28

29: \( R = \text{H} \)

30: \( R = t-Bu \)

31

32

33
2.3. Synthesis of chiral Mn(III)-salen complexes

The tetradeutate salen ligand (2, M= H₂) is very common in coordination chemistry; more than 2500 metal complexes of substituted salens have been described. The first optically active Mn(III)-salen complexes for asymmetric epoxidation were developed by Jacobsen et al. and Katsuki et al. in 1990, although chiral metal-salen complexes have been known for over 60 years. C₂-symmetric salen ligands can be prepared conveniently and with high yield by condensation of appropriately substituted 1,2-diamine with 2 equivalents of a salicylaldehyde derivative in ethanol (Scheme 1). The majority of the ligands are derived from chiral 1,2-diphenylethylenediamine or chiral trans-1,2-diaminocyclohexane. Salen complexes of all the first-row transition metals have been prepared and Mn(III) derivatives have been found to be the most efficient as epoxidation catalysts. Mn(III)-salen complexes are obtained by treating the ligand with excess Mn(OAc)₂·4H₂O in air. Also Mn(OAc)₃·2H₂O has been used in some cases. The intermediate Mn(III)-salen-OAc complex is usually converted to the Mn(III)-salen-Cl complex either with LiCl or aqueous NaCl. Other complexes with counterions such as PF₆⁻, ClO₄⁻, or BPh₄⁻ have been synthesized with less straightforward procedures. Jacobsen and co-workers have developed a practical large-scale procedure for the preparation of the most widely used chiral Mn(III)-salen catalyst. This catalyst is now also commercially available in both enantiomerically pure forms.

Scheme 1. Preparation of chiral Jacobsen-type Mn(III)-salen complexes: (i) EtOH/H₂O, reflux; (ii) Mn(OAc)₂·4H₂O (2 equiv.), air; (iii) LiCl or NaCl (aq.).

Following the development work of Jacobsen et al. and Katsuki et al., other research groups have synthesized various types of chiral Mn(III)-salen and closely related complexes (e.g. 22-33 in Chart 2). While these catalysts have many similarities both in structure and activity to the Mn(III)-salen complexes shown in Chart 1, they generally afford lower enantioselectivities compared with the Jacobsen- or Katsuki-type catalysts. Mukaiyama et al. developed the interesting Mn(III)-β-ketoimine complexes 24 and 25, which were found to be useful catalysts for asymmetric epoxidation when the combination of O₂ and an aldehyde was used as the...
In addition to chiral C$_2$ symmetric Mn(III)-salen catalysts, also a few optically active non-C$_2$ symmetric Mn(III)-Schiff base complexes have been synthesized for catalytic purposes. These include the pentadentate Mn-dihydrosalen complex 32, and the Mn-picolinamide-salicylidene complex 33.

2.4. Epoxidation method: effects of reaction conditions

Other important features in transition-metal catalyzed epoxidations, in addition to steric and electronic effects of the catalyst, that affect the outcome of the reaction, include the nature of the axial ligand and the choice of the oxidant. As for the general reaction conditions, asymmetric epoxidations are usually carried out in the presence of a catalytic amount of the Mn(III)-salen complex (1-10 mol.%) with 1-2 equivalents of a stoichiometric oxidant and axial ligand at temperatures varying from room temperature to –20 °C. In some cases even lower temperatures have been used. In general, enantioselectivity is enhanced as the reaction temperature is lowered. However, exceptions have been reported. The most common solvents are dichloromethane and acetonitrile but many other non-polar solvents are also applicable. A variety of stoichiometric oxidants are effective for Mn(III)-salen catalyzed epoxidations: PhIO, NaOCl, O$_2$/reductant, H$_2$O$_2$, peroxycids, KHSO$_5$, and dimethyldioxirane. The beneficial effect of axial ligands capable of coordinating to the metal center in porphyrins has been observed also in salen-catalyzed reactions.

2.4.1. Choice of oxidant

In principle, a variety of stoichiometric oxidants can be applied to catalytic oxidation reactions (Table 2). The factors that influence the choice of oxidant include active oxygen content, price, availability, selectivity, nature of the waste product, and ease of recycling. On this basis oxidants such as O$_2$/reductant and hydrogen peroxide would make ideal oxidants since they have high active oxygen contents and produce only water as a by-product. However, both molecular oxygen and hydrogen peroxide have been rarely used in enantioselective epoxidation, unlike iodosylbenzene and especially NaOCl, mainly because of the presence of competing reactions (i.e. low selectivity). Oxidant effects in metalloporphyrin-catalyzed reactions have been discussed in comprehensive reviews.
Table 2. Typical oxidants used in transition-metal catalyzed reactions

<table>
<thead>
<tr>
<th>Oxidant</th>
<th>Active oxygen (wt.%)</th>
<th>By-product</th>
</tr>
</thead>
<tbody>
<tr>
<td>O\textsubscript{2}/reductant</td>
<td>50.0</td>
<td>H\textsubscript{2}O</td>
</tr>
<tr>
<td>H\textsubscript{2}O\textsubscript{2}\textsuperscript{a}</td>
<td>47.0</td>
<td>H\textsubscript{2}O</td>
</tr>
<tr>
<td>NaOCl</td>
<td>21.6</td>
<td>NaCl</td>
</tr>
<tr>
<td>CH\textsubscript{3}CO\textsubscript{2}H</td>
<td>21.1</td>
<td>CH\textsubscript{3}CO\textsubscript{2}H</td>
</tr>
<tr>
<td>t-BuOOH</td>
<td>17.8</td>
<td>t-BuOH</td>
</tr>
<tr>
<td>KHSO\textsubscript{4}</td>
<td>10.5</td>
<td>KHSO\textsubscript{4}</td>
</tr>
<tr>
<td>MCPBA</td>
<td>9.3</td>
<td>m-Cl-C\textsubscript{6}H\textsubscript{4}CO\textsubscript{2}H</td>
</tr>
<tr>
<td>NaIO\textsubscript{4}</td>
<td>7.5</td>
<td>NaIO\textsubscript{3} (NaI)</td>
</tr>
<tr>
<td>PhIO</td>
<td>7.3</td>
<td>PhI</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Based on 100% H\textsubscript{2}O\textsubscript{2}.

Iodosylbenzene

Iodosylbenzene and other iodosylarenes were the first oxidants reported to effect alkene epoxidation in the presence of achiral or chiral metalloporphyrins.\textsuperscript{9,23,24} Although iodosylbenzene has certain disadvantages, such as costliness, low oxygen content, low solubility, and instability, which make it impractical in preparative use, it has been frequently used as terminal oxidant in mechanistic investigations.\textsuperscript{21,22} Kochi et al. employed PhIO in their pioneering studies with achiral Cr(III)- and Mn(III)-salen complexes.\textsuperscript{32-33} Also other achiral Mn(III)- and Fe(III)-Schiff base complexes have been studied as epoxidation catalysts with PhIO as the terminal oxidant.\textsuperscript{37,62} Also, the early studies of Jacobsen et al. and Katsuki et al. and later the mechanistic studies with chiral Mn-salens have been performed with iodosylarenes as oxidants.\textsuperscript{12-17}

NaOCl

Sodium hypochlorite (NaOCl) is considered an inexpensive and readily available oxidant with many applications in organic chemistry.\textsuperscript{63} It is used as an aqueous solution and is stable at alkaline pH. Since 1979, it has been used extensively as oxidant in reactions catalyzed by metalloporphyrins, including asymmetric epoxidations.\textsuperscript{22,64,65} Sodium hypochlorite has been used also as stoichiometric oxidant in epoxidations catalyzed by achiral Mn- and Ni-Schiff base complexes with low to moderate conversion.\textsuperscript{28,36}

In 1991 Jacobsen et al. developed an efficient asymmetric epoxidation procedure consisting of a two-phase system with an aqueous phase containing commercial bleach and an organic phase composed of a solution of substrate and catalyst in a suitable solvent.\textsuperscript{38} Usually a pyridine N-oxide derivative is added to
improve both catalyst turnover and enantioselectivity (see Section 2.4.2.). Reactions are typically conducted at 0 °C. Katsuki et al. later extended the temperature range to –18 °C by using NaOCl saturated with NaCl. Today, NaOCl is the most widely used terminal oxidant in asymmetric epoxidations catalyzed by Mn(III)-salen complexes. It has been used in many applications, some of which are industrially attractive. Table 1 (p. 13) and Table 3 (p. 22) show typical examples of the use of both PhIO and NaOCl as stoichiometric oxidants in Mn(III)-salen catalyzed epoxidations.

**Oxygen/reductant**

The stoichiometry of a monooxygenase-mediated (e.g. cytochrome P450) oxidation with molecular oxygen requires two electrons and two protons to reduce the second oxygen atom to water. Therefore, a sacrificial reductant and a proton source are needed in addition to dioxygen. Many reducing agents have been used in oxygenations catalyzed by metalloporphyrins, such as borohydride, hydrogen and catalyst, zinc or electrons from an electrode.

There are also some examples where achiral Mn(III)-salen complexes have been used as catalysts in reactions conducted with molecular oxygen and reductant. In these cases, salen complexes were inferior to metalloporphyrins presumably because of the easy decomposition of the Mn complex.

On the other hand, Mukaiyama et al. have successfully developed methods for alkene epoxidation using molecular oxygen and pivalaldehyde in the presence of both achiral and chiral transition metal complexes. Katsuki et al. epoxidized unfunctionalized alkenes with this method using an achiral Ni(II)-Schiff base complex. Mukaiyama extended his method to enantioselective epoxidation using chiral Mn(III)-salen (e.g. 5) and related Mn(III)-β-ketoimine complexes (24-25) (see Chart 2). Moderate to high enantioselectivities were obtained in epoxidation of various benzocyclic alkenes (ee up to 92 %) with these systems (Table 3, entries 4 and 7). Interestingly, aerobic epoxidation with Mn(III)-β-ketoimine complexes was observed to produce epoxides with absolute configuration opposite to those observed in epoxidations employing oxidants such as PhIO and NaOCl. This was explained by assuming that the reactive species in aerobic epoxidation was an acyldperoxo-manganese complex, which epoxidizes alkenes with different enantiofacial selection than do salen-Mn(V)-oxo species.
Asymmetric epoxidation of \(-\)alkenes with various oxidants.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkene</th>
<th>Catal.</th>
<th>Oxidant</th>
<th>Additive</th>
<th>Temp. (°C)</th>
<th>Yield (%)</th>
<th>Ee (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>4</td>
<td>(\text{Me}_3\text{PhIO})</td>
<td>–</td>
<td>25</td>
<td>72</td>
<td>78</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>11</td>
<td>(\text{NaOCl})</td>
<td>PPNO</td>
<td>0</td>
<td>67</td>
<td>86</td>
<td>14</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>19</td>
<td>(\text{NaOCl})</td>
<td>PPNO</td>
<td>0</td>
<td>78</td>
<td>98</td>
<td>45c</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>24</td>
<td>(\text{O}_2/\text{-BuCHO})</td>
<td>–</td>
<td>RT</td>
<td>52</td>
<td>84</td>
<td>72</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>ent-8</td>
<td>MCPBA</td>
<td>NMO</td>
<td>-78</td>
<td>83</td>
<td>97</td>
<td>78</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>ent-11</td>
<td>(\text{NaOCl})</td>
<td>–</td>
<td>0</td>
<td>72</td>
<td>98</td>
<td>39</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>ent-11</td>
<td>(\text{O}_2/\text{-BuCHO})</td>
<td>N-OctIm(^a)</td>
<td>RT</td>
<td>37</td>
<td>92</td>
<td>72b</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>ent-5</td>
<td>(\text{KHSO}_3)</td>
<td>N-MeIm</td>
<td>0</td>
<td>82-86</td>
<td>84-95</td>
<td>90</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>16</td>
<td>(\text{H}_2\text{O}_2)</td>
<td>N-MeIm</td>
<td>RT</td>
<td>55</td>
<td>88</td>
<td>81</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>ent-11</td>
<td>DMD(^b)</td>
<td>N-MeIm</td>
<td>RT</td>
<td>55-78</td>
<td>15-93</td>
<td>92</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>ent-11</td>
<td>(\text{NaOCl})</td>
<td>–</td>
<td>RT</td>
<td>85</td>
<td>93(^d)</td>
<td>105</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(2:1)(^c)</td>
<td>(58)(^e)</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>19</td>
<td>(\text{NaOCl})</td>
<td>PPNO</td>
<td>0</td>
<td>80</td>
<td>96(^d)</td>
<td>45c</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(1:2)(^c)</td>
<td>(92)(^e)</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td></td>
<td>12</td>
<td>(\text{NaOCl})</td>
<td>PPNO</td>
<td>4</td>
<td>30</td>
<td>65</td>
<td>47</td>
</tr>
<tr>
<td>14</td>
<td></td>
<td>19</td>
<td>(\text{NaOCl})</td>
<td>PPNO</td>
<td>-18</td>
<td>37</td>
<td>88</td>
<td>66</td>
</tr>
<tr>
<td>15</td>
<td></td>
<td>11</td>
<td>(\text{NaOCl})</td>
<td>PPNO</td>
<td>0</td>
<td>(1:&gt;99)(^f)</td>
<td>34(^e)</td>
<td>106</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(69:31)(^f)</td>
<td>84(^d)</td>
<td></td>
</tr>
</tbody>
</table>

a) \(\text{N-octylimidazole}\). b) Dimethyldioxirane. c) Ratio of \(\text{trans}\) and \(\text{cis}\)-epoxides. d) ee of \(\text{trans}\)-epoxide. e) ee of \(\text{cis}\)-epoxide. f) Ratio of \(\text{trans}\) and \(\text{cis}\)-epoxides. Reaction was carried out in the presence of chiral quaternary salt.

Hydrogen peroxide and alkylhydroperoxides

Hydrogen peroxide is a particularly attractive oxidant with some obvious advantages: it is inexpensive, readily available and a mild reagent, with only water being formed as a by-product.\(^{61}\) The main problem in transition metal complex (metalloporphyrins, salen catalysts) catalyzed epoxidations with hydrogen peroxide is the homolytic cleavage of the weak O-O bond, which leads to a formation of radicals and therefore indiscriminate oxidation.\(^{21,22}\) This is the case also in oxidations with alkyl hydroperoxides. Another undesirable reaction is that of \(\text{H}_2\text{O}_2\) with the metal-oxo complex to produce molecular oxygen and water (dismutation). Nevertheless, hydrogen peroxide has been widely used as oxidant in epoxidations catalyzed by metalloporphyrins, especially with \(\text{Mn-porphyrins}\).\(^{73-76}\) The desired heterolytic bond
cleavage that produces the reactive metal-oxo species can be favoured by using
nitrogen heterocycle compounds,\textsuperscript{73,74} such as pyridines and imidazoles, or other
additives\textsuperscript{75,76} acting as acid-base catalysts or as axial ligands to the transition metal
catalyst.

Kochi et al. studied catalytic epoxidation reactions with \textit{tert}-butyl
hydroperoxide as oxidant with achiral Mn(III)-salen complexes in the presence of
pyridine or imidazole as the cocatalyst.\textsuperscript{77} Two concurrent reaction pathways were
identified, one leading to allylic substitution (homolytic route) and the other to olefin
epoxidation (metal-oxo route). Enantioselective epoxidation with \textit{tert}-butyl
hydroperoxide and a chiral Mn(III)-salen complex was found to be slow and low in
yield and to produce a mixture of by-products.\textsuperscript{78} Alkyl hydroperoxides have been also
used together with optically active vanadium- and titanium-salen complexes for the
asymmetric oxidation of sulfides to sulfoxides with moderate enantioselectivity.\textsuperscript{79}

Only very few examples exists in the literature of the use of hydrogen peroxide
as terminal oxidant in Mn(III)-salen catalyzed oxidations.\textsuperscript{55,80-82} Hydrogen peroxide
together with chiral Mn(III)-salen (e.g. 7) induced moderate enantioselection in
oxidation of various aryl alkyl sulfides to corresponding sulfides.\textsuperscript{80} Schweinkreis and
Berkessel introduced complex 32 as a catalyst in asymmetric epoxidation of 1,2-
dihyronapthalene with hydrogen peroxide, also with moderate enantioselectivity.\textsuperscript{55}
Katsuki et al. used catalyst 16 together with two cocatalysts, \textit{N}-methylimidazole and an
ammonium salt, for the epoxidation of chromene derivatives with H\textsubscript{2}O\textsubscript{2} or
bistrimethylsilylperoxide (Table 3, entry 9).\textsuperscript{81} Also, geraniol derivatives have been
enantioselectively epoxidized with hydrogen peroxide as oxidant.\textsuperscript{82}

\textbf{Peroxyacids}

\textit{m}-Chloroperoxybenzoic acid (MCPBA) is one of the most common peroxyacids
used at laboratory scale to perform various oxidation reactions. Because it is a
powerful epoxidation agent by itself, only few articles have been devoted to its use as
stoichiometric oxidant in metalloporphyrin-catalyzed olefin epoxidations.\textsuperscript{22,83} Peracids
have been used mainly for the preparation of metal-oxo complexes to model the high-
valent states of heme-containing enzymes. Only magnesium monoperophthalate
(MMPP) and peroxyacetic acid have been shown to be practical oxidants in Mn-
porphyrin-catalyzed epoxidation of simple alkenes.\textsuperscript{84,85}

Mukaiyama et al. used peracetic acid in Mn(III)-salen and Mn(III)-\textgreek{b}-ketoimine
catalyzed epoxidation of benzocyclic olefins with low to moderate
enantioselectivity.\textsuperscript{60d,72c} As with their aerobic oxidation system presented above,
acylperoxo-manganese complex was suggested as the reactive intermediate. Jacobsen
et al. have developed an efficient low temperature epoxidation system (-78 °C), that
consists of MCPBA and an excess of $N$-methylmorpholine $N$-oxide as additive (e.g. entry 5 in Table 3). Epoxidation of various unfunctionalized alkenes was shown to proceed with higher enantioselectivity than reactions conducted in the presence of aqueous bleach. Also MMPP was studied under similar conditions and it was found to be less efficient oxidant than MCPBA. Also other research groups have applied MCPBA/NMO and related systems in their studies. Although very high enantioselectivities are obtained with this method, it has rather limited practicability because of the demanding reaction conditions. Increasing the reaction temperature has been reported to cause decreased enantioselectivities.

**Other oxidants**

Other stoichiometric oxidants that have been applied in the asymmetric epoxidation of unfunctionalized alkenes catalyzed with Mn(III)-salen complexes include potassium monoperoxysulfate (KHSO$_5$, Oxone) and dimethyldioxirane. Oxone is a strong, inexpensive and versatile oxidising agent studied extensively in metalloporphyrin-catalyzed oxidations. Recently, it has found use as oxidant also in asymmetric epoxidations catalyzed by chiral ketones. The use of Oxone in asymmetric Mn(III)-salen catalyzed epoxidation of unfunctionalized alkenes has been described in two recent reports (e.g. entry 8 in Table 3). Moderate to good enantioselectivities were obtained in asymmetric epoxidation of electron-rich alkenes, particularly if a large amount (15 mol.%) of the catalyst was used.

Dimethyldioxirane is a reactive neutral soluble oxidant prepared from acetone and Oxone. It has been used mostly for the generation of unstable epoxides. Adam et al. have utilized dimethyldioxirane in asymmetric epoxidation of 2,2-dimethyl-2H-chromenes and isoflavones with Jacobsen-type catalysts. To achieve good enantioselectivity (ee >90%), a relatively high amount (>14 mol.%) of the catalyst had to be added to the epoxidation system (Table 3, entry 10).
2.4.2. Axial ligand effects

Kochi et al. observed in their kinetic and structural studies of metal-salen complex catalyzed epoxidations that the addition of a donor ligand such as pyridine N-oxide stabilizes oxo-metal intermediates via axial coordination resulting in enhanced reaction rate and epoxidation yield.\(^{32,33}\) Actually, Kochi et al. were able to isolate and characterize oxo-Cr(V) adduct with pyridine N-oxide as the axial ligand.\(^{30-32}\) Addition of pyridine N-oxide caused conformational changes in the salen structure and the Cr atom, which is displaced above the mean salen plane in the oxo-Cr(V) complex, was significantly pulled back by coordination with the axial ligand. Evidence that N-oxide additives function as axial ligands also in the case of Mn(III)-salen complexes was recently provided in a study in which a Mn(III) salen catalyst with a tethered N-oxide unit was synthesized and characterized by X-ray diffraction.\(^{94}\) The reactivity and selectivity of this catalyst was not affected by the presence of additional N-oxide.

Nitrogen heterocycle additives have a significant impact on the outcome of asymmetric epoxidation. Additives such as pyridine N-oxides, pyridines, or imidazoles influence the rate, yield, stereoselectivity, and enantioselectivity of Mn(III)-salen catalyzed epoxidation with a range of terminal oxidants.\(^{41b,86,94-99,103}\) The additive must be used in stoichiometric excess over the salen catalyst since it is oxidized along with the epoxidation. Katsuki et al. were the first to report donor ligand effects in asymmetric epoxidations conducted with PhIO as the oxidant. They found that donor ligands such as 2-methylimidazole and pyridine N-oxide derivatives increase enantioselectivity.\(^{41b,42,99}\) However, the addition of a donor ligand showed a negative effect in the epoxidation of trans-stilbene.\(^{41b}\) Katsuki et al. assumed that the donor ligand effect on enantioselectivity arose from a conformational change of the salen structure by coordination of the axial ligand.\(^{41b,99}\) In contrast to the findings of other groups,\(^{98}\) they also observed that the addition of a donor ligand did not increase the rate of epoxidation.\(^{51}\) Recently, Katsuki et al. have shown that chiral amine or N-oxide, which presumably acts as axial ligand, can induce enantioselectivity in epoxidations catalyzed by achiral Mn(III)-salen complex.\(^{100,101}\)

Jacobsen et al. have shown that 4-phenylpyridine N-oxide is an especially viable ligand in epoxidations conducted with NaOCl as oxidant, particularly for substrates that undergo epoxidation sluggishly with Mn(III)-based systems.\(^{95}\) They proposed that N-oxide additives affect the equilibria, wherein the active salen-Mn(V)=O complex undergoes reversible coupling with a Mn(III) complex to generate inactive µ-oxo dimer. Such µ-oxo dimers have previously been assumed to exist on the basis of kinetic\(^{33}\) and recently also MS studies.\(^{34}\) Pyridine N-oxide derivatives would assist the dissociation of unreactive µ-oxo dimers to reactive monomeric oxo-Mn(V) complexes.
Also other aromatic $N$-oxides have been found to be effective donor ligands in epoxidations utilizing NaOCl as oxidant.$^{96,97}$ Recently Hughes et al. showed in a comprehensive study that the $N$-oxides participate also in transporting the active oxidant HOCl into the organic layer in a NaOCl/organic solvent two-phase system.$^{102}$

Mukaiyama et al. have observed dramatic donor ligand effects in asymmetric epoxidations with their O$_2$/pivalaldehyde system.$^{72}$ Mn(III)-salen catalyzed epoxidation with molecular oxygen/pivalaldehyde in the presence of an axial ligand ($N$-alkylimidazole) was found to proceed with opposite enantioface selection than in the absence of the ligand.$^{72}$ They proposed that this difference in enantioface selection was due to the presence of different active species in the two cases. In the absence of a donor ligand, the reaction proceeds via a peroxyacylmanganese species that would directly epoxidize olefins while the same reaction in the presence of the ligand would proceed by way of oxo species.

There are also other possible modes of action for additive ligands. Nitrogenous bases may improve epoxide yield by lowering the Lewis acidity of Mn(III)-salen complexes and by suppressing undesired reaction pathways or by decreasing the contribution of the uncatalyzed epoxidation pathways.$^{33,51,86,98}$ Also, Jacobsen et al. observed in their MCPBA/NMO epoxidation system that NMO and MCPBA generate a 1:1 salt that is unreactive toward alkenes but oxidizes Mn(III)-salen complex.$^{86}$

2.5. Substrate effects

Asymmetric induction by chiral Mn(III)-salen catalysts is dependent also on the alkene substitution pattern. As an example, Figure 6 schematically shows substrate properties that favour high enantioselectivity in epoxidations with Jacobsen-type catalysts (e.g. 11).$^{15,95}$ These properties include: 1) an aryl, alkenyl, or alkynyl group conjugated to the alkene, 2) a cis double bond linkage, 3) a bulky group attached to the double bond, and 4) the presence of an allylic oxygen substituent. Tables 3 and 4 show some typical examples of the asymmetric epoxidation of various types of unfunctionalized alkenes with different Mn-salen catalysts.
Substrate properties favouring high enantioselectivity in epoxidations with the Jacobsen-type catalyst 11.

<table>
<thead>
<tr>
<th>Alkene</th>
<th>ee (%)</th>
<th>Properties</th>
<th>Alkene</th>
<th>ee (%)</th>
<th>Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Image" /></td>
<td>97</td>
<td>1, 2, 3, 4</td>
<td><img src="image2" alt="Image" /></td>
<td>88</td>
<td>1, 2</td>
</tr>
<tr>
<td><img src="image3" alt="Image" /></td>
<td>96</td>
<td>1, 2, 3, 4</td>
<td><img src="image4" alt="Image" /></td>
<td>72-85</td>
<td>1, 2, 4</td>
</tr>
<tr>
<td><img src="image5" alt="Image" /></td>
<td>93</td>
<td>1, 2, 3</td>
<td><img src="image6" alt="Image" /></td>
<td>78</td>
<td>1, 2</td>
</tr>
<tr>
<td><img src="image7" alt="Image" /></td>
<td>94</td>
<td>2, 3, 4</td>
<td><img src="image8" alt="Image" /></td>
<td>25</td>
<td>2, 3</td>
</tr>
</tbody>
</table>

Figure 6. Substrate properties favouring high enantioselectivity in epoxidations with the Jacobsen-type catalyst 11.

cis-Disubstituted alkenes

Cyclic and acyclic cis-disubstituted alkenes conjugated with aryl, alkenyl or alkynyl groups are generally very good substrates for Mn(III)-catalyzed epoxidation reactions. Especially high enantioselectivities have been achieved in the epoxidation of 2,2-dialkylchromene derivatives with all terminal oxidants (see Figure 6 and Table 3). Simple nonconjugated alkylsubstituted alkenes are generally observed to react slower than conjugated olefins and give both low yield and poor enantioselectivities (Figure 6). This difference in reactivity and selectivity between nonconjugated and conjugated alkenes has been explained by assuming that different epoxidation mechanisms are in operation (see Section 2.6.).

Epoxidation of 1,3-cycloalkadienes showes variable epoxide yields and enantioselectivities in most cases, although ee’s exceeding 90 % have been observed (Table 3, entries 13-14). Katsuki et al. explained these results to be controlled both by repulsive steric and π-π-repulsive electronic interactions between the alkene and Mn(III)-salen complex.
While the simple alkylsubstituted cis-alkenes are epoxidized with high stereoselectivity (high cis/trans ratio), reactions of conjugated cis-alkenes give a mixture of cis- and trans-epoxides (Table 3, entry 15 vs. 11, 12).\textsuperscript{14,15} Aryl-substituted alkenes afford cis-epoxides as predominant products, while conjugated dienes and enynes generally afford trans-epoxides.\textsuperscript{105} These results have been explained by assuming that the reaction proceeds via a radical intermediate (see Section 2.6. for mechanistic discussion).\textsuperscript{105} This phenomenon has been deliberately used in the synthesis of trans-epoxides from cis-alkenes.\textsuperscript{106} In addition, Jacobsen et al. found that the epoxidation of cis-alkenes in the presence of a chiral quaternary salt provides trans-epoxides preferentially (Table 3, entry 15). The mechanistic basis for this effect is not clear.\textsuperscript{107}

\textbf{Terminal alkenes}

Terminal alkenes, such as styrene, show unexpectedly low enantioselectivities under the usual reaction conditions. This has again been explained by the formation of radical intermediates, which in the case of disubstituted alkenes has lead to the formation of diastereomers, but in the case of monosubstituted alkenes to partial racemization since two enantiomers are formed.\textsuperscript{15,17,86,108} Recently, Jacobsen et al. solved this problem by using MCPBA as stoichiometric oxidant in the presence of excess NMO as additive at low temperature (-78 °C).\textsuperscript{78,86} The presence of NMO was indispensable since its absence in otherwise similar conditions produced racemic epoxide (Table 4, entry 2).

\textit{trans-Disubstituted alkenes}

Mn(III)-salen based catalysis has met only limited success in asymmetric epoxidation of \textit{trans}-substituted alkenes. As expected on the basis of the side-on approach, enantioselectivities are generally low to moderate and highly dependent on the Mn(III)-salen catalyst and reaction conditions.\textsuperscript{14-16} Only very recently have some reasonable results been obtained with a Mn(III)-salen based method (Table 4, entry 4).\textsuperscript{106} Also, chiral Cr(III)-salen complexes were recently found to be promising catalysts for the epoxidation of a \textit{trans}-alkene, (Z)-1-phenylprop-1-ene (Table 4, entry 5).\textsuperscript{109} An alternative useful route to \textit{trans}-epoxides has been developed by Jacobsen et al.\textsuperscript{107} The method involves Mn(III)-salen catalyzed epoxidation of \textit{cis}-alkenes in the presence of chiral alkaloid-derived salts.
Asymmetric epoxidation of various unfunctionalized alkenes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkene</th>
<th>Catal.</th>
<th>Oxidant</th>
<th>Additive</th>
<th>Temp. (°C)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>4</td>
<td>Me₃PhIO</td>
<td>–</td>
<td>5</td>
<td>75</td>
<td>57</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>Ar</td>
<td>ent-8</td>
<td>MCPBA</td>
<td>NMO</td>
<td>-78</td>
<td>83-88</td>
<td>80-86</td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>ent-3</td>
<td>Me₃PhIO</td>
<td>–</td>
<td>RT</td>
<td>(93)²</td>
<td>20</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>“</td>
<td>ent-20</td>
<td>PhIO</td>
<td>PPNO</td>
<td>-30</td>
<td>77</td>
<td>91</td>
<td>109</td>
</tr>
<tr>
<td>5</td>
<td>“</td>
<td>31</td>
<td>PhIO</td>
<td>Ph₃PO</td>
<td>RT</td>
<td>71</td>
<td>79</td>
<td>56</td>
</tr>
<tr>
<td>6</td>
<td>Ph⁺Ph</td>
<td>17</td>
<td>PhIO</td>
<td>–</td>
<td>RT</td>
<td>65</td>
<td>62</td>
<td>42</td>
</tr>
<tr>
<td>7</td>
<td>Ph⁺Ph</td>
<td>ent-11</td>
<td>NaOCl</td>
<td>PPNO</td>
<td>0</td>
<td>91</td>
<td>95</td>
<td>110</td>
</tr>
<tr>
<td>8</td>
<td>C₆Ph</td>
<td>ent-11</td>
<td>NaOCl</td>
<td>PPNO</td>
<td>0</td>
<td>69</td>
<td>93</td>
<td>110</td>
</tr>
<tr>
<td>9</td>
<td>“</td>
<td>19</td>
<td>PhIO</td>
<td>PyNO</td>
<td>-20</td>
<td>26</td>
<td>83</td>
<td>111</td>
</tr>
<tr>
<td>10</td>
<td>PhMe</td>
<td>ent-8</td>
<td>NaOCl</td>
<td>PPNO</td>
<td>0</td>
<td>90</td>
<td>90</td>
<td>112</td>
</tr>
<tr>
<td>11</td>
<td>PhMe</td>
<td>7</td>
<td>NaOCl</td>
<td>PPNO</td>
<td>0</td>
<td>37</td>
<td>35</td>
<td>112</td>
</tr>
</tbody>
</table>

a) Based on 76 % conversion of the starting alkene.

**Trisubstituted and tetrasubstituted alkenes**

Chiral Mn(III)-salen complexes have also been found to be highly selective catalysts for the enantioselective epoxidation of various acyclic and cyclic conjugated trisubstituted alkenes (Table 4, entries 7-9). This is somewhat surprising since trisubstituted alkenes should react with Mn(III)-salen complexes in the same way as trans-alkenes do, provided that transition-state geometries involving simple side-on approach of alkene to the metal center are in operation. Jacobsen et al. interpreted the high enantioselectivity observed for trisubstituted alkenes by using a skewed side-on approach model, while Katsuki et al. used a model involving both steric and electronic interactions.
Jacobsen et al. have also studied asymmetric epoxidation of various tetrasubstituted alkenes with different Mn(III)-salen complexes. The results (yield, ee) varied significantly, but high enantioselectivities (up to 96% ee) were attained with certain substrates (Table 4, entries 10-11). The observed selectivities could not be explained by the side-on approach model.

2.6. Mechanistic considerations

While the high efficiency of the Mn(III)-salen based asymmetric epoxidation method is widely acknowledged, the exact mechanism of the reaction has remained controversial. The existence of the key species in Mn(III)-salen catalyzed oxidations, the oxo-Mn(V) complex, has recently been confirmed by MS studies. It is also generally accepted that donor ligands such as N-oxides stabilize this oxo-Mn intermediate via axial coordination, and that the side-on approach of the alkene double bond parallel to the salen plane is operating. There remain three main mechanistic questions to be elucidated: (i) structure of the oxo-Mn(V) complex, (ii) trajectory of alkene approach, and (iii) mechanism of oxygen transfer from oxo-Mn(V) to the olefin double bond. These mechanistic controversies have been considered in detail in many reviews and hence will be only shortly outlined here.

The structures of many chiral Mn(III)-salen complexes have been determined by X-ray analysis and found to have near planar conformation. However, Katsuki et al. showed recently that certain Mn(III)-salen complexes have a shallow stepped non-planar structure. On the other hand, the structures of the oxo-Mn(V) species are not fully known and may to some extent differ from those of the Mn(III)-complexes. In fact, some research groups have proposed non-planar (bent, twisted, folded, or stepped) structures for the active catalyst while others hold to the planar model. Recently, Jørgensen et al. were able to synthesize a chiral nitrido-Mn(V)-salen complex, a nitrogen analogue of the oxo-Mn(V) species, from Mn(III)-complex and characterize it by X-ray diffraction. No severe deviations from near-planarity were observed.

Also, it is not fully clear what is the actual direction of the alkene approach to the metal centre in a Mn-oxo complex. Here again, different kinds of approach models have been proposed. Figure 7 summarizes the preferred trajectories of attack of alkenes on oxo-Mn(V) complexes. Jacobsen et al. proposed alternative approach models for 1,2-diaminocyclohexane-derived and 1,2-diphenylethylene-derived catalysts. Their model was based on steric effects assuming a planar oxo-species. Olefin approach a over the phenolic aromatic ring was proposed for
1,2-diphenylethylene-derived catalysts\(^\text{12}\) (e.g. 4 and 5) while another path (b) from the direction of the diimine bridge was proposed for 1,2-diaminocyclohexane-derived catalysts\(^\text{14,39}\) (e.g. 11) because of the presence of bulky \textit{tert}-butyl groups at the C5- and C5’-positions. Katsuki et al. favored another approach model for conjugated alkenes (path c along the N-Mn bond axis) due to steric and \(\pi-\pi\) interactions between the benzene ring of the salen ligand and the substituent on the alkene.\(^\text{43,104,118a}\) They have later refined this model and approach a was also thought possible based on a non-planar (folded) structure for the oxo-species.\(^\text{17,18,51,115,118b}\) Finally, Houk et al. suggested that the alkene could attack the salen metal center along path d, which has been presumed unlikely by other groups.\(^\text{116}\) This suggestion was based on the fact that there is a slight twist in the salen structure that results in an angle between the phenolic aromatic rings.\(^\text{114a}\) A common feature of all these models is that they can all reasonably well explain the stereochemical outcome of Mn(III)-salen catalyzed asymmetric epoxidation.\(^\text{20}\)

![Preferred directions of attack of alkenes on salen-Mn-oxo complexes.](image)

The most controversial mechanistic issue concerns the oxygen transfer from oxo-Mn(V) to the olefin double bond. In the case of Mn(III)-salen catalyzed asymmetric epoxidations three different mechanisms for oxygen transfer have been proposed (Figure 8): i) concerted pathway A, ii) pathway B proceeding via a radical intermediate, and iii) pathway C involving a manganaoxetane, see also Figure 4 in section 2.1.\(^\text{19,20}\)
Alkyl-substituted cis-alkenes react stereospecifically in Mn(III)-salen catalyzed epoxidation yielding exclusively the corresponding cis-epoxide. Therefore, epoxidation has been proposed to proceed by way of the concerted pathway A. Alternatively, epoxidation of conjugated cis-alkenes produces mixtures of cis- and trans-epoxides, the extent of the trans-epoxide depending strongly on the nature of the substrate. This lack of stereospecificity was explained by Jacobsen et al. by assuming pathway B via a radical intermediate, which allows C-C bond rotation to give both cis- and trans-configured epoxides. Cis/trans ratio of the epoxide from cis-alkene then correlates with the stability of the radical species. Also, Katsuki et al. suggested a radical mechanism in their early reports concerning the epoxidation of conjugated alkenes.

However, Norrby et al. have suggested the mechanistic pathway C proceeding via a reversibly formed manganaoxetane-intermediate based on calculations using MacroModel/MM3*. The enantioselectivity of the reaction was explained to arise from the energy difference between two competing metallaoxetane intermediates. Later they observed that in epoxidations of phenylsubstituted vinylcyclopropanes ("radical clocks"), no epimerization or cleavage of the cyclopropane occurred. Consequently, the reaction pathway B involving a radical intermediate was rejected. Experiments of Katsuki et al. supported the formation of metallaoxetanes, since a nonlinear relationship between enantioselectivity and temperature was found indicating the presence of a reversibly formed intermediate (metallaoxetane) in the reaction. However, Jacobsen et al. later criticized these experiments and observed a linear correlation of enantioselectivity and temperature over a wide temperature range (100
In addition, they contested the existence of metallaoxetanes as possible intermediates due to severe steric problems when using a Mn(III)-salen complex that had a strapped $N$-oxide axial ligand coordinated to manganese. In a very recent quantum chemical study based on density functional theory it was suggested that the formation of a manganaoxetane is less favored than the radical pathway.\textsuperscript{120}

In conclusion, the mechanistic discussion remains open and further studies towards an understanding of the mechanism of asymmetric epoxidation are needed. For example, one phenomenon introduced recently that may in part explain the mechanism is the spin crossover effect.\textsuperscript{121} Also, the presence of reactive species other than oxo-Mn(V) cannot be ruled out. In fact, Groves and Stern have shown that an oxo-Mn(IV) species can be formed along with the normal oxo-Mn(V) species in the oxidation of Mn(III)-porphyrin and that this species also performs alkene epoxidation, although with less diastereoselectivity.\textsuperscript{122} The existence and role of salen-Mn(IV)-oxo species has also been discussed recently.\textsuperscript{107,113b,123} It should also be noted that reaction conditions, such as oxidant, catalyst, additives, solvent, and even counter-ions,\textsuperscript{124} play a significant role in both stereo- and enantioselectivity, which renders results of the mechanistic studies elusive.

3. AIMS OF THE PRESENT STUDY

This research originally formed a part of TEKES’ (Technology Development Centre of Finland) Synthesis Technology Programme (1992-1997), which was aimed at evaluating new methods in chemical technology that would be of use to the chemical industry in Finland. The research project explored the possibility of using salen-type transition metal complexes for the production of fine chemicals.

The objectives of this thesis were:

1. To develop novel asymmetric epoxidation systems that are based on chiral Mn-salen complexes and utilize hydrogen peroxide as oxidant.\textsuperscript{I,III,VI}

2. To explore other possible oxidants to be used in Mn-salen catalyzed asymmetric epoxidations.\textsuperscript{II,IV,V}

3. To design and synthesize new Mn(III)-salen type complexes.\textsuperscript{VI,VII}
4. RESULTS AND DISCUSSION

The present study was undertaken to develop novel asymmetric epoxidation systems based on chiral Mn(III)-salen complexes. This work included the synthesis of chiral Mn(III)-salen type catalysts (Section 4.1.) and the search for suitable stoichiometric oxidants and axial ligands for asymmetric epoxidation (Sections 4.2. to 4.5.). Several oxidants were investigated: hydrogen peroxide, periodates (NaIO₄, Bu₄NIO₄), monopersulfates (Oxone, Bu₄NHSO₅, Ph₄PHSO₅), and in situ generated peroxyacids. Finally, asymmetric epoxidations catalyzed with new unsymmetrical Mn(III)-Schiff base complexes are presented in Section 4.6. Experimental details are reported in the original publications I-VII and in Section 6. The Mn(III)-salen complexes and alkene substrates included in this thesis are presented in Chart 3 (p. 37) and Figure 9, respectively.

![Figure 9. Alkene substrates included in this study.](image)

4.1. Synthesis of the Mn(III)-Schiff base complexes

4.1.1. Synthesis of symmetrical Mn(III)-salen complexes

The C₂-symmetric Mn(III)-salen complexes used in this study were conveniently synthesized using published procedures from commercially available achiral or chiral 1,2-diamines (1,2-diphenylethlenediamine, trans-1,2-diamino-cyclohexane) and appropriately substituted salicylaldehydes usually in ethanol. Subsequent treatment with Mn(OAc)₂·4H₂O and LiCl in air afforded the Mn(III)-complexes. Catalysts 36, 38 and 40 synthesized by this method are new compounds. Scheme 2 illustrates the synthesis route for the Mn(III)-salen complex 36.
Conditions: (i) SnCl₄, 2,6-lutidine, (CH₂O)ₙ, toluene, 95 °C, 5 h, yield 68 %. (ii) (S,S)-1,2-diphenylethylenediamine, EtOH, reflux 3 h, yield 91 %. (iii) Mn(OAc)₂·4H₂O, air, LiCl, EtOH, reflux 4 h, yield 96 %.

4.1.2. Synthesis of unsymmetrical Mn(III)-Schiff base complexes

In addition to the conventional C₂-symmetric Mn(III)-salen complexes, two new non-C₂-symmetric Mn(III)-complexes, 41 and 42, were synthesized as potential epoxidation catalysts. While the synthesis of symmetrical salen ligands is straightforward (e.g. Scheme 2), the unsymmetrical Schiff bases containing two different salicylaldehyde units are much less accessible and therefore, reports of the chiral unsymmetrical salen and related complexes have been scarce.¹²⁵-¹²⁷ Published methods involve the stepwise synthesis of non-C₂-symmetric salen ligands and related compounds via mono-imines. However, this method is generally unreliable and the mono-aldimines prepared from salicylaldehyde and 1,2-diamine are always contaminated with various amounts of the C₂-symmetric bis-imine even after attempted purification.¹²⁶,¹²⁸ The most reliable route for the preparation of non-C₂-symmetric salen ligands involves the use of statistical methods.¹²⁹

The new non-C₂-symmetric Schiff-base complexes 41 and 42 were synthesized using a stepwise procedure from appropriately substituted salicylaldehydes and 1-(2-hydroxyphenyl)ketones (Scheme 3). Aromatic ketones were chosen because they react considerably slower than salicylaldehydes with 1,2-diamines, allowing the selective preparation of mono-ketimines. The reactions proceeded smoothly in the presence of anhydrous Na₂SO₄ as drying agent and produced the chiral half-units 54 and 55 with over 60 % yield. The crude products were rapidly filtered through a short plug of neutralized silica gel to remove the unreacted diamine because attempted purification of the mono-ketimines by flash chromatography resulted in the formation of some of the starting ketones. However, attempts to prepare unsymmetrical Schiff-base ligands from trans-1,2-diaminocyclohexane were not successful, mixtures were instead obtained. Further reaction of the half-units 54 and 55 with the salicylaldehydes 56 and
lead to the formation of the unsymmetrical Schiff-base ligands 58 and 59. Finally, the Mn(III) complexes 41 and 42 were readily obtained from ligands 58 and 59 by the standard procedure using excess of Mn(OAc)$_2$·4H$_2$O and LiCl in air. Results of the asymmetric epoxidations catalyzed by the new complexes are presented in Section 4.6.

Scheme 3. Synthesis of the unsymmetrical Mn(III)-complexes 41 and 42. Conditions: 
(i) (R,R)-1,2-diphenylethylenediamine, Na$_2$SO$_4$, EtOH, reflux 20 h. 
(ii) Na$_2$SO$_4$, EtOH, reflux 3 h. 
(iii) Mn(OAc)$_2$·4H$_2$O, LiCl, air, EtOH, reflux 3 h.
Chart 3

34

ent-5: \( R_1 = t\text{-Bu} \quad R_2 = \text{Me} \)

ent-8: \( R_1 = t\text{-Bu} \quad R_2 = \text{OSi}(i\text{-Pr})_3 \)

35: \( R_1 = t\text{-Bu} \quad R_2 = t\text{-Bu} \)

36: \( R_1 = \text{C(Me)}_2\text{Ph} \quad R_2 = \text{Me} \)

37: \( R = \text{Br} \)

5: \( R = \text{Me} \)

10: \( R_1 = t\text{-Bu} \quad R_2 = \text{Me} \)

11: \( R_1 = t\text{-Bu} \quad R_2 = t\text{-Bu} \)

12: \( R_1 = t\text{-Bu} \quad R_2 = \text{OSi}(i\text{-Pr})_3 \)

39: \( R_1 = t\text{-Bu} \quad R_2 = \text{C(Ph)}_3 \)

40: \( R_1 = \text{C(Me)}_2\text{Ph} \quad R_2 = t\text{-Bu} \)

41

42

37
4.2. Asymmetric epoxidations with hydrogen peroxide$^{LIII,VIII}$

Hydrogen peroxide was chosen as stoichiometric oxidant for Mn(III)-salen catalyzed epoxidation due to its obvious advantages over many other oxidants: high oxygen content, low price, ready availability, and environmental acceptability. The only Mn(III)-salen based system for asymmetric epoxidation that utilizes hydrogen peroxide as terminal oxidant reported before this study was that of Schwenkreis and Berkessel. Their system involved a pentadentate chiral Mn(III)-dihydrosalen catalyst synthesized by a laborious route.$^{55}$ Also, concurrently with paper I, Katsuki et al. published their complex system that contained salen catalyst $^{16}$ and two cocatalysts, N-methylimidazole and an ammonium salt.$^{81}$ Both of these systems afforded moderate-to-good enantioselectivities in epoxidations of dihydronaphthalenes and 2,2-dimethylchromenes.

In this study, more straightforward epoxidation systems were developed that involve easily accessible Jacobsen-type catalysts and nitrogenous base or carboxylate salt cocatalysts.

4.2.1. Axial ligand effects

Nitrogen heterocycles as axial ligands$^{LIII}$

Asymmetric epoxidation of unfunctionalized alkenes with hydrogen peroxide was studied in the presence of various nitrogen heterocycle ligands. Results of the asymmetric epoxidation of 1,2-dihydronaphtalene ($^{44}$), a frequently used alkene substrate, are summarized in Table 5.

The presence of a nitrogen heterocycle as an axial ligand was essential for a successful reaction (entry 1). Generally, amine N-oxides were found to be more efficient ligands than the other nitrogen heterocycles, giving higher enantioselectivities. However, pyridine N-oxide, which has been successfully used in epoxidations with PhIO gave poor conversion (entry 2).$^{99}$ 4-Dimethylaminopyridine together with benzoic acid co-catalyst worked well, although the effect of benzoic acid was only marginal. The chiral Mn(III)-salen complexes ent-$^{5}$ and $^{11}$ afforded similar or better enantioselectivities than the systems of Schwenkreis and Berkessel and Katsuki; catalyst ent-$^{5}$ was slightly more selective than catalyst$^{11}$.

In all reactions unbuffered 30 % hydrogen peroxide was used as the oxidant. Diluted (1.5 %) oxidant in similar conditions only produced a 22:78 mixture of epoxide and alkene (determined by $^{1}$H NMR). This contrasts with the results of Schwenkreis and Berkessel who obtained similar alkene conversions irrespective of the concentration of $\text{H}_2\text{O}_2$.$^{55}$ In addition, only a relatively small excess of $\text{H}_2\text{O}_2$, less
than 3 equivalents, was needed to accomplish complete reactions compared with the 6-10 equivalents used by other research groups.\textsuperscript{55,80}

Table 5. Asymmetric epoxidation of 1,2-dihydronaphthalene (44) with H\textsubscript{2}O\textsubscript{2} and various axial ligands\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catal.</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Additive (mol. equiv.)</th>
<th>Isol. yield (%)</th>
<th>ee (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>34</td>
<td>22</td>
<td>4</td>
<td>-</td>
<td>(31:69)\textsuperscript{b}</td>
<td>-</td>
<td>I</td>
</tr>
<tr>
<td>2</td>
<td>34</td>
<td>22</td>
<td>4</td>
<td>PyNO (0.4)</td>
<td>(53:47)\textsuperscript{b}</td>
<td>-</td>
<td>I</td>
</tr>
<tr>
<td>3</td>
<td>34</td>
<td>22</td>
<td>2</td>
<td>DMAP (0.125) + PhCO\textsubscript{2}H (0.125)</td>
<td>62 (58)\textsuperscript{c}</td>
<td>-</td>
<td>I</td>
</tr>
<tr>
<td>4</td>
<td>34</td>
<td>22</td>
<td>2</td>
<td>imidazole (0.4)</td>
<td>64</td>
<td>-</td>
<td>I</td>
</tr>
<tr>
<td>5</td>
<td>34</td>
<td>22</td>
<td>2</td>
<td>N-Melm (0.4)</td>
<td>67</td>
<td>-</td>
<td>I</td>
</tr>
<tr>
<td>6</td>
<td>ent-5</td>
<td>22</td>
<td>2</td>
<td>imidazole (0.7)</td>
<td>56</td>
<td>59</td>
<td>I</td>
</tr>
<tr>
<td>7</td>
<td>ent-5</td>
<td>22</td>
<td>2</td>
<td>N-Melm (0.7)</td>
<td>59</td>
<td>60</td>
<td>I</td>
</tr>
<tr>
<td>8</td>
<td>ent-5</td>
<td>2</td>
<td>1.25</td>
<td>N-Melm (0.6)</td>
<td>51</td>
<td>64</td>
<td>III</td>
</tr>
<tr>
<td>9</td>
<td>ent-5</td>
<td>2</td>
<td>1.5</td>
<td>t-BuPy (0.6)</td>
<td>60</td>
<td>59</td>
<td>III</td>
</tr>
<tr>
<td>10</td>
<td>ent-5</td>
<td>2</td>
<td>2</td>
<td>NMO (0.4)</td>
<td>74</td>
<td>69</td>
<td>III</td>
</tr>
<tr>
<td>11</td>
<td>ent-5</td>
<td>2</td>
<td>1.5</td>
<td>PPNO (0.4)</td>
<td>61</td>
<td>69</td>
<td>III</td>
</tr>
<tr>
<td>12</td>
<td>11</td>
<td>22</td>
<td>4</td>
<td>DMAP (0.5) + PhCO\textsubscript{2}H (0.25)</td>
<td>50</td>
<td>48</td>
<td>I</td>
</tr>
<tr>
<td>13</td>
<td>11</td>
<td>22</td>
<td>22</td>
<td>imidazole (0.7)</td>
<td>51</td>
<td>50</td>
<td>I</td>
</tr>
<tr>
<td>14</td>
<td>11</td>
<td>22</td>
<td>22</td>
<td>N-Melm (0.7)</td>
<td>53</td>
<td>52</td>
<td>I</td>
</tr>
</tbody>
</table>

\textsuperscript{a) Ratio of alkene: H\textsubscript{2}O\textsubscript{2}: catalyst= 1: 2.3: 0.025 (entries 1-5); 1: 2.5-3: 0.5 (entries 6-14). b) Ratio of epoxide and alkene determined by \textsuperscript{1}H NMR. c) Yield without PhCO\textsubscript{2}H.}

Carboxylate salts as cocatalysts in asymmetric epoxidation with H\textsubscript{2}O\textsubscript{2}\textsuperscript{III}

The oxo-based transition-metal catalyzed epoxidation systems utilizing nitrogen heterocycles as axial ligands suffer from either the oxidative destruction of the heterocyclic cocatalyst or the relative complexity of the systems. Interestingly, Mansuy et al. discovered that a simple ammonium salt, such as ammonium acetate, alone acts as a very efficient cocatalyst for the metalloporphyrin-catalyzed epoxidation of simple alkenes by H\textsubscript{2}O\textsubscript{2}.\textsuperscript{76} Also, bases such as sodium carbonate have been shown to promote the porphyrin-catalyzed epoxidation without requiring any other additive.\textsuperscript{75}

In this study the effects of various carboxylate salts (NH\textsubscript{4}OAc, NH\textsubscript{4}O\textsubscript{2}CH, NaOAc, and PhCO\textsubscript{2}Na) and an inorganic base (NaHCO\textsubscript{3}) were compared to those of typical nitrogenous ligands shown in the previous section; results are presented in
Table 6. Carboxylate salts were generally more efficient cocatalysts than the nitrogenous bases presented in Table 5 and both higher yields of epoxides and higher ee’s were obtained. The only exception was NMO, which gave results comparable to those of the carboxylates. Also, the amount of the salt (NH₄OAc) could be reduced from 40 mol-% to 20 mol-% without any significant effect on the yield or ee of the epoxide. In general, enantioselectivity was enhanced slightly as the reaction temperature was lowered. Most of the reactions were performed with 30 % aq. hydrogen peroxide but anhydrous urea-H₂O₂ was an equally good oxidant. This is in contrast with the results of Schwenkreis and Berkessel, who obtained a very low epoxide yield in asymmetric epoxidation of 44 with catalyst 11 using UHP as oxidant.55

Table 6. Asymmetric epoxidation of 1,2-dihydronaphthalene (44) with H₂O₂ and catalyst ent-5 in the presence of different carboxylate salts⁴

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cocatalyst (mol. equiv.)</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Isol. yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NH₄OAc (0.4)</td>
<td>RT</td>
<td>1.25</td>
<td>73</td>
<td>61</td>
</tr>
<tr>
<td>2</td>
<td>''</td>
<td>2</td>
<td>1.25</td>
<td>73</td>
<td>67</td>
</tr>
<tr>
<td>3</td>
<td>NH₄OAc (0.2)</td>
<td>2</td>
<td>1.25</td>
<td>70</td>
<td>66</td>
</tr>
<tr>
<td>4ᵇ</td>
<td>NH₄OAc (0.4)</td>
<td>2</td>
<td>1</td>
<td>68</td>
<td>67</td>
</tr>
<tr>
<td>5</td>
<td>''</td>
<td>-18</td>
<td>4</td>
<td>73</td>
<td>68</td>
</tr>
<tr>
<td>6</td>
<td>NH₄O₂CH (0.4)</td>
<td>2</td>
<td>1.25</td>
<td>65</td>
<td>68</td>
</tr>
<tr>
<td>7</td>
<td>NaOAc (0.4)</td>
<td>2</td>
<td>1</td>
<td>68</td>
<td>69</td>
</tr>
<tr>
<td>8</td>
<td>PhCO₂Na (0.4)</td>
<td>2</td>
<td>1.25</td>
<td>69</td>
<td>67</td>
</tr>
<tr>
<td>9</td>
<td>NaHCO₃ (0.2)</td>
<td>2</td>
<td>1</td>
<td>62</td>
<td>66</td>
</tr>
<tr>
<td>10</td>
<td>PhCO₂H (0.2)</td>
<td>2</td>
<td>2.5</td>
<td>(19:81)c</td>
<td>-</td>
</tr>
</tbody>
</table>

a) Ratio of alkene: H₂O₂: cocatalyst; ent-5= 1: 2.5-3: 0.4-0.6: 0.05. b) Reaction was performed using urea-H₂O₂ (3 mol. equiv.) as oxidant. c) Epoxide: alkene ratio analyzed by ¹H NMR.

Possible roles of the cocatalyst in the asymmetric epoxidation with H₂O₂

The exact role of the carboxylate additives in transition-metal catalyzed oxidation reactions is not fully clear. Figure 10 shows possible catalytic cycles for alkene epoxidations with hydrogen peroxide in the presence of additives. Nitrogenous additives most likely act as ligands to the salen metal catalyst and as bases via intermediates (a), (b) and (d).⁷²ᵇ Alternatively, they may assist dissociation of unreactive µ-oxo dimers to reactive monomeric oxo complexes.⁹⁵ Nitrogenous bases may also improve epoxide yield by lowering the Lewis acidity of Mn(III) complexes.
In the case of carboxylate additives two different roles are possible. First, analogously with the nitrogenous additives, they can act as buffers promoting the formation of HO$_2^-$ from H$_2$O$_2$, which facilitates the formation of the hydroperoxy complex (b) from Mn(III)-salen (c).\textsuperscript{73,74} In fact, the apparent pH of 30 \% H$_2$O$_2$ (8.9 M) was raised from pH 2.6 to approximately pH 6 when the carboxylates were dissolved in H$_2$O$_2$ in the same proportions as used in the epoxidation reactions. Moreover, the use of carboxylic acid in place of the corresponding acid salt resulted in dramatic retardation of the reaction rate (Table 6, entry 10). The importance of the basicity of the cocatalyst was further pointed out by the fact that also NaHCO$_3$ as an additive gave satisfactory results (entry 9). Similar results have been obtained in reactions catalyzed by Mn-porphyrins.\textsuperscript{74,75}

![Figure 10. Possible roles of axial ligand (L) and carboxylate in epoxidation with H$_2$O$_2$ catalyzed by Mn(III)-salen complexes.](image)

Another possibility is that the reaction sequence from Mn(III)-salen (a) to the active oxidant, salen-Mn(V)=O (d), proceeds via a peroxyacylmanganese species (e). A similar catalytic route was proposed for the Mn-porphyrin catalyzed epoxidation of alkenes with H$_2$O$_2$ in the presence of a lipophilic nitrogen heterocycle ligand and a carboxylic acid cocatalyst.\textsuperscript{74} Reactions involving DMAP and benzoic acid probably proceed by this path (Table 5, entries 3 and 12). Also, the reaction of molecular oxygen with Mn(III)-salen complexes in the presence of an aldehyde has been assumed to provide a peroxyacylmanganese species.\textsuperscript{72} It was suggested that this active species, in the absence of an axial ligand, directly epoxidizes olefins, but the same reaction in the presence of the ligand (e.g. N-alkylimidazole) would proceed by way of oxo species. This was supported by the fact that the enantioface selection observed in the absence of the axial ligand is opposite to that observed in the presence of the axial ligand. In our experiments the same enantioface selection without any inversions was observed with all the additives indicating that the same active oxidant (d) was produced.
In addition, the possibility of carboxylates acting as axial ligands on the salen complexes cannot be ruled out. Very recently, Katsuki et al. showed that a Mn-salen complex with a tethered carboxylate group in proximal position was active without added donor ligand.\(^49\) On the other hand, results obtained in the presence of NaHCO\(_3\), which is presumably not capable of functioning as ligand to the salen metal, indicate that basicity alone is a *sufficient* property of additives in salen-catalyzed epoxidations with hydrogen peroxide.

**4.2.2 Asymmetric epoxidation of various olefins with H\(_2\)O\(_2\)**

Various disubstituted and trisubstituted alkenes were enantioselectively epoxidized with hydrogen peroxide and generally the highest yields and selectivities were obtained using either catalyst 5 or 11. Results are summarized in Table 7.

**Table 7. Asymmetric epoxidation of various alkenes with H\(_2\)O\(_2\)\(^a\)**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkene</th>
<th>Catal.</th>
<th>Additive</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Isol. yield (%)</th>
<th>ee (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>43</td>
<td>ent-5</td>
<td>NH(_4)OAc</td>
<td>2</td>
<td>2</td>
<td>63</td>
<td>75</td>
<td>III</td>
</tr>
<tr>
<td>2</td>
<td>45</td>
<td>ent-5</td>
<td>&quot;</td>
<td>2</td>
<td>1.25</td>
<td>70</td>
<td>85</td>
<td>III</td>
</tr>
<tr>
<td>3</td>
<td>&quot;</td>
<td>ent-11</td>
<td>&quot;</td>
<td>2</td>
<td>1.5</td>
<td>71</td>
<td>87</td>
<td>III</td>
</tr>
<tr>
<td>4</td>
<td>47</td>
<td>ent-11</td>
<td>&quot;</td>
<td>2</td>
<td>1.25</td>
<td>90</td>
<td>91</td>
<td>III</td>
</tr>
<tr>
<td>5</td>
<td>48</td>
<td>5</td>
<td>&quot;</td>
<td>2</td>
<td>2</td>
<td>(36:52)(^b)</td>
<td>-</td>
<td>VIII</td>
</tr>
<tr>
<td>6</td>
<td>&quot;</td>
<td>5</td>
<td>NMO</td>
<td>2</td>
<td>3</td>
<td>42 (49)(^c)</td>
<td>86</td>
<td>VIII</td>
</tr>
<tr>
<td>7</td>
<td>49</td>
<td>34</td>
<td>N-MeIm(^d)</td>
<td>22</td>
<td>3</td>
<td>56</td>
<td>-</td>
<td>I</td>
</tr>
<tr>
<td>8</td>
<td>&quot;</td>
<td>ent-5</td>
<td>&quot;</td>
<td>22</td>
<td>4</td>
<td>49</td>
<td>42</td>
<td>I</td>
</tr>
<tr>
<td>9</td>
<td>&quot;</td>
<td>11</td>
<td>&quot;</td>
<td>22</td>
<td>4</td>
<td>51</td>
<td>47</td>
<td>I</td>
</tr>
<tr>
<td>10</td>
<td>50</td>
<td>ent-11</td>
<td>NH(_4)OAc</td>
<td>-18</td>
<td>4</td>
<td>84</td>
<td>96</td>
<td>III</td>
</tr>
<tr>
<td>11</td>
<td>51</td>
<td>ent-11</td>
<td>&quot;</td>
<td>2</td>
<td>4</td>
<td>90</td>
<td>96</td>
<td>VIII</td>
</tr>
<tr>
<td>12</td>
<td>52</td>
<td>5</td>
<td>&quot;</td>
<td>2</td>
<td>18</td>
<td>73</td>
<td>83</td>
<td>VIII</td>
</tr>
<tr>
<td>13</td>
<td>53</td>
<td>5</td>
<td>&quot;</td>
<td>-18</td>
<td>5</td>
<td>74</td>
<td>83</td>
<td>VIII</td>
</tr>
<tr>
<td>14</td>
<td>&quot;</td>
<td>ent-11</td>
<td>&quot;</td>
<td>2</td>
<td>1.5</td>
<td>72</td>
<td>83</td>
<td>VIII</td>
</tr>
</tbody>
</table>

\(^{a}\) Molar ratio of alkene: H\(_2\)O\(_2\): salen= 1: 3-5: 0.2-0.4: 0.05. \(^{b}\) Ratio of epoxide and alkene, cis/trans-ratio of the epoxide 7:1. \(^{c}\) Yield in parenthesis is calculated from the reacted olefin, cis/trans ratio of the epoxide 15:1. \(^{d}\) 0.7 mol. equiv. N-MeIm was used.
Particularly promising results (ee >90 %) were obtained with 2,2-dialkyl-
chromene 47 and with the trisubstituted alkenes 50 and 51. The epoxidation of (Z)-1-
prop-1-ene, while giving high enantioselectivity, showed variable levels of
stereoselectivity depending of the additive used. In this case NMO was a considerably
more effective additive than NH₄OAc, affording both higher conversion and cis-trans
ratio of the corresponding epoxide. The origin of this difference in reactivity and
stereoselectivity between these additives is not clear, although it may indicate that they
have different roles during the catalytic cycle as discussed in the previous section.

Hydrogen peroxide was used also for the epoxidation of a trans-alkene, (E)-1-
prop-1-ene (49) (entries 7-9). Generally, trans-alkenes react much slower and with
lower selectivity than cis-alkenes in metal complex-catalyzed epoxidations.14-16
Accordingly, the yield of the trans-epoxide was only moderate and trace amounts of
the allylic oxidation product 1-phenylpropan-2-one were detected (¹H NMR).
However, the ee’s obtained for the asymmetric epoxidation of 49 are among the
highest reported for epoxidation of trans-alkenes with Jacobsen-type catalysts.41

4.2.2. Catalyst structure effects in asymmetric epoxidation with H₂O₂

Different 1,2-diphenylethanediamine- and 1,2-diaminocyclohexane-derived
catalysts were studied to determine the steric and electronic requirements for effective
catalysis. The results of catalyst structure effects in asymmetric epoxidation of various
alkenes with H₂O₂ are summarized in Table 8.

Incorporation of t-Bu substituents at the C3- and C3'-positions of the salen
complex is necessary for attainment of high enantioselectivity in asymmetric
epoxidation.14,15,38 Consequently, catalyst 38 with t-Bu groups at C4- and C4'-positions
appropriately showed low enantioselectivity in the epoxidation of alkene 44 (entry 2).
Also, introduction of substituents larger than t-Bu at the C3- and C3'-positions (catalyst
40 with -C(Me)₂Ph groups) resulted in considerably lower enantioselectivity (entries 3
and 8). Similar although not as pronounced effects have been reported also by
Jacobsen et al. (see Table 1, p. 13).39,46,47

Jacobsen et al. have also shown that Mn(III)-salen catalysts bearing electron-
donating or bulky groups at the C5- and C5'-positions exhibit higher asymmetric
induction than those bearing electron-withdrawing groups.50 While bulky electron-
donating -OSi(i-Pr)₃ substituents at the C5- and C5'-positions of the salicylide ligand in
catalysts ent-8 and 12 attenuated the reactivity of the catalyst as shown by longer
reaction times (entries 1, 4 and 7), the effect on enantioselectivity was small. On the
other hand, introduction of an electron-withdrawing Br-substituent in the salicylide
ligand (catalyst 37) resulted in a faster reaction and lower enantioselectivity (entry 5).
These findings are well in accordance with the results presented in Table 1 (p. 13). While tuning the size of the groups attached to the C5- and C5'-positions on the salicylide moiety had only a small effect on enantioselectivity in epoxidation of benzocyclic alkene 45, the effect was more pronounced in the case of the sterically demanding trisubstituted alkenes 52 and 53 (entries 9-14). t-Bu was the optimal substituent and both larger and smaller substituents resulted in lower selectivity. The significant effect exerted by the trimethylphenyl group on enantioselectivity is presumably due to its ability to block all sides of the catalyst making the side-on approach of the alkene more difficult.

**Table 8.** Catalyst structure effects in asymmetric epoxidations with H2O2

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkene</th>
<th>Catal.</th>
<th>A</th>
<th>B</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>44</td>
<td>ent-8</td>
<td>t-Bu</td>
<td>OSi(i-Pr)3</td>
<td>5</td>
<td>54 (63)c</td>
<td>64</td>
<td>III</td>
</tr>
<tr>
<td>2</td>
<td>&quot;</td>
<td>38</td>
<td>4-t-Bu</td>
<td>4-t-Bu</td>
<td>4</td>
<td>55</td>
<td>23</td>
<td>VIII</td>
</tr>
<tr>
<td>3</td>
<td>&quot;</td>
<td>40</td>
<td>C(Me)2Ph</td>
<td>t-Bu</td>
<td>2</td>
<td>56</td>
<td>43</td>
<td>VIII</td>
</tr>
<tr>
<td>4</td>
<td>45</td>
<td>ent-5</td>
<td>t-Bu</td>
<td>Me</td>
<td>1.25</td>
<td>70</td>
<td>85</td>
<td>III</td>
</tr>
<tr>
<td>5</td>
<td>&quot;</td>
<td>37</td>
<td>t-Bu</td>
<td>Br</td>
<td>1</td>
<td>71</td>
<td>67</td>
<td>III</td>
</tr>
<tr>
<td>6</td>
<td>&quot;</td>
<td>ent-11</td>
<td>t-Bu</td>
<td>t-Bu</td>
<td>1.5</td>
<td>71</td>
<td>87</td>
<td>III</td>
</tr>
<tr>
<td>7</td>
<td>&quot;</td>
<td>12</td>
<td>t-Bu</td>
<td>OSi(i-Pr)3</td>
<td>6</td>
<td>54 (75)c</td>
<td>89</td>
<td>III</td>
</tr>
<tr>
<td>8</td>
<td>&quot;</td>
<td>40</td>
<td>C(Me)2Ph</td>
<td>t-Bu</td>
<td>1.5</td>
<td>74</td>
<td>77</td>
<td>III</td>
</tr>
<tr>
<td>9</td>
<td>52</td>
<td>ent-11</td>
<td>t-Bu</td>
<td>t-Bu</td>
<td>18</td>
<td>57</td>
<td>79</td>
<td>VIII</td>
</tr>
<tr>
<td>10</td>
<td>&quot;</td>
<td>10</td>
<td>t-Bu</td>
<td>Me</td>
<td>18</td>
<td>69</td>
<td>71</td>
<td>VIII</td>
</tr>
<tr>
<td>11</td>
<td>&quot;</td>
<td>37</td>
<td>t-Bu</td>
<td>Br</td>
<td>5</td>
<td>78</td>
<td>76</td>
<td>VIII</td>
</tr>
<tr>
<td>12</td>
<td>53</td>
<td>ent-11</td>
<td>t-Bu</td>
<td>t-Bu</td>
<td>1.5</td>
<td>72</td>
<td>83</td>
<td>VIII</td>
</tr>
<tr>
<td>13</td>
<td>&quot;</td>
<td>12</td>
<td>t-Bu</td>
<td>OSi(i-Pr)3</td>
<td>18</td>
<td>(23:73)d</td>
<td>-</td>
<td>VIII</td>
</tr>
<tr>
<td>14</td>
<td>&quot;</td>
<td>39</td>
<td>t-Bu</td>
<td>C(Ph)3</td>
<td>1</td>
<td>67</td>
<td>57</td>
<td>VIII</td>
</tr>
</tbody>
</table>

a) Molar ratio of alkene: H2O2: NH4OAc: catalyst= 1: 3-5: 0.2-0.4: 0.05. b) R,R = Ph,Ph for catalysts ent-5, ent-8, 37, and 38. R,R= (CH2)4 for catalysts 10, ent-11, 12, 39, and 40. c) Yield in parenthesis is calculated from the reacted olefin. d) Ratio of epoxide and alkene.
4.3. **Asymmetric epoxidations with periodates**

The periodates NaIO$_4$ and Bu$_4$NIO$_4$ have been shown to be capable of acting as single oxygen atom donors in metalloporphyrin-catalyzed reactions including epoxidations, although not many have been published.$^{130,131}$ Recently, various simple alkenes were epoxidized with high yields; epoxidations were catalyzed by a Mn(III)-porphyrin with NaIO$_4$ and Bu$_4$NIO$_4$ as oxidants and imidazole as axial ligand.$^{131}$ Because metalloporphyrins and salen complexes have similar catalytic activities and reaction pathways it was anticipated that also periodates would be suitable oxidants for salen-catalyzed epoxidations.

Therefore, the periodates NaIO$_4$ and Bu$_4$NIO$_4$ were used in the enantioselective epoxidation of alkene substrates 44, 46 and 49 catalyzed by the Jacobsen-type salen complexes ent-5 and 11 in the presence of imidazole as donor ligand. Results of the epoxidations are summarized in Table 9. The reactions were complete in 3-6 hours at room temperature and longer reaction times were found to reduce slightly both the yield and enantioselective excess of the epoxide (e.g. entry 2). Lowering the reaction temperature from 22 °C to 4 °C resulted in reduced reactivity and a slight increase in enantioselectivity (entry 4).

Suitable oxidant/catalyst combinations were found for each of the alkene substrates. In the epoxidation of 1,2-dihydronaphthalene (44) the yield of the epoxide was independent of the periodate oxidant used. However, epoxidations with Bu$_4$NIO$_4$ proceeded with higher asymmetric induction than epoxidations with NaIO$_4$ (entry 1 vs 2, entry 5 vs 6). Oxidations catalyzed by the salen complex ent-5 afforded 5-15 % higher yields of epoxide than those catalyzed by catalyst 11 (e.g. entry 3 vs 6), but the optical yields were similar.

As expected, epoxidation of (E)-1-phenylprop-1-ene (49), a trans-alkene, proceeded with substantially lower enantioselectivity than that of 1,2-dihydronaphthalene (entries 7-11). Nevertheless, the enantioselectivity obtained for the epoxidation of 49 with this system compares favourably with the results obtained by other systems.$^{12,14-15}$ Epoxidation of 49 catalyzed by 11 afforded 10 % higher yields of epoxide than by epoxidation with catalyst ent-5. However, yield and ee were not dependent on the oxidant (e.g. entry 8 vs 10).

Finally, a reaction system using BuNIO$_4$ as terminal oxidant was applied to the epoxidation of 2,2-dimethylchromene (46) (entries 12-15). 2,2-Dialkylchromenes have earlier been epoxidized with particularly high enantioselective with catalyst 11 using NaOCl as oxidant. Here both catalysts ent-5 and 11 produced the corresponding epoxide with good enantioselectivity, although selectivity was lower than that obtained with Jacobsen’s NaOCl-method.$^{39,103}$ However, the new epoxidation system presented
here, which offers mild reaction conditions, has been used by other research groups in the epoxidation of various unfunctionalized alkenes.48,53

Table 9. Asymmetric epoxidation of unfunctionalized alkenes with periodates\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkene</th>
<th>Catal. ( (M+IO_4^-) )</th>
<th>Oxidant</th>
<th>Time (h)</th>
<th>Isol. yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ent-5</td>
<td>Na\textsuperscript{b}</td>
<td>24</td>
<td>45</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>&quot;</td>
<td>Bu\textsubscript{4}N</td>
<td>24</td>
<td>48</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>&quot;</td>
<td>&quot;</td>
<td>3</td>
<td>55</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>&quot;</td>
<td>&quot;</td>
<td>24\textsuperscript{c}</td>
<td>52</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>11</td>
<td>Na\textsuperscript{b}</td>
<td>6</td>
<td>40</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>&quot;</td>
<td>Bu\textsubscript{4}N</td>
<td>3</td>
<td>40</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>ent-5</td>
<td>Na\textsuperscript{b}</td>
<td>6</td>
<td>51</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>&quot;</td>
<td>Bu\textsubscript{4}N</td>
<td>3</td>
<td>53</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>11</td>
<td>Na\textsuperscript{b}</td>
<td>6</td>
<td>60</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>&quot;</td>
<td>Bu\textsubscript{4}N</td>
<td>3</td>
<td>63</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>&quot;</td>
<td>&quot;</td>
<td>24\textsuperscript{c}</td>
<td>69</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>ent-5</td>
<td>Bu\textsubscript{4}N</td>
<td>3</td>
<td>82</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>&quot;</td>
<td>&quot;</td>
<td>18\textsuperscript{c}</td>
<td>78</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>11</td>
<td>&quot;</td>
<td>3</td>
<td>79</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>&quot;</td>
<td>&quot;</td>
<td>18\textsuperscript{c}</td>
<td>64</td>
<td>84</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a} See paper II for reaction conditions. Molar ratio of alkene: oxidant: ImH: catalyst= 1: 2.5: 0.75: 0.06. b) 0.06 mol. equiv. of Bu\textsubscript{4}NBr was used as phase transfer catalyst. c) Reaction was performed at 4 °C.
4.4. Asymmetric epoxidations with peroxymonosulfates\textsuperscript{IV, V}

Oxone is a strong, inexpensive and versatile oxidising agent that has been studied in metalloporphyrin-catalyzed oxidations and used also in Mn(III)-salen catalyzed epoxidations.\textsuperscript{88} It is an efficient oxygen donor but has some disadvantages: it is insoluble in organic solvents, buffering is needed due to its acidity, and it rapidly bleaches metal catalysts and donor ligands during oxidation reactions. The monopersulfates \textit{Bu}_4\text{NHSO}_5 and \textit{Ph}_4\text{PHSO}_5 are solids easily prepared from Oxone.\textsuperscript{132-134} Unlike Oxone, they are readily soluble in various organic solvents. Also they have also been used in oxidations catalyzed by various transition-metal complexes but not with Mn(III)-salen complexes.\textsuperscript{133-135} Results here show that the Mn(III)-salen catalyzed asymmetric epoxidation of simple alkenes is efficiently conducted with these monopersulfates as alternatives for Oxone.

4.4.1. Effects of reaction conditions

First, the epoxidation of a simple model substrate, 6,7-dihydro-5\textit{H}-benzocycloheptene (45), was conducted in acetonitrile under different reaction conditions by using the typical Jacobsen-type catalyst 5 (ent-5) (results in Table 10) together with \textit{Bu}_4\text{NHSO}_5 as oxidant and NMO as additive. Reactions were conducted also in \textit{CH}_2\textit{Cl}_2, which resulted in longer reaction times, but the yield and ee of the epoxide were practically identical in both solvents. The reaction proceeded smoothly at 2 °C and lowering the temperature to -18 °C increased the yield but had practically no effect on the ee of the epoxide (entry 2). Further lowering of the temperature resulted in retardation of the reaction rate (entry 3) and a slight increase in ee. At -74 °C the reaction remained incomplete even after a prolonged reaction time.

Using an aromatic amine \textit{N}-oxide, picoline \textit{N}-oxide, in place of NMO gave equally good yield and ee (entry 5). Imidazole, however, was not as effective donor ligand giving lower yield and enantioselectivity (entry 6). The reason is presumably the tendency of imidazole to degrade in the presence of many oxidants, e.g. KHSO\textsubscript{5}.\textsuperscript{88} Also, when the epoxidation was performed using a substoichiometric amount of the \textit{N}-oxide additives the ee of the epoxide was slightly reduced (entry 4).
Table 10. Asymmetric epoxidation of 6,7-Dihydro-5H-benzocycloheptene (45) with Bu₄NHSO₅ and catalyst 5/ent-5.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Isol. yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NMO (1.0)</td>
<td>2</td>
<td>1</td>
<td>59</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td>NMO (1.0)</td>
<td>-18</td>
<td>1.5 (2.5)</td>
<td>72</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>NMO (1.0)</td>
<td>-46</td>
<td>5</td>
<td>57 (80)</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>NMO (0.25)</td>
<td>-18</td>
<td>1.75</td>
<td>74</td>
<td>84</td>
</tr>
<tr>
<td>5</td>
<td>PicNOe (1.0)</td>
<td>2</td>
<td>1</td>
<td>72</td>
<td>89</td>
</tr>
<tr>
<td>6</td>
<td>ImH (1.0)</td>
<td>2</td>
<td>1</td>
<td>67</td>
<td>80</td>
</tr>
</tbody>
</table>

a) Molar ratio of alkene: oxidant: ent-5 = 1: 1.6: 0.03-0.07. b) Reaction was conducted in CH₂Cl₂. c) Yield in parentheses is calculated from the reacted olefin. d) Ratio of epoxide to alkene. e) PicNO= picoline N-oxide.

4.4.2. Asymmetric epoxidation of various alkenes with monopersulfates

Bu₄NHSO₅ has previously been reported to cause catalyst deactivation when used with metalloporphyrins. It was assumed that Bu₄NHSO₅ present as an impurity inhibits epoxidation of olefins by Bu₄NHSO₅. The mechanism of this action is not known yet. Ph₄PSO₅ was presumed to react more selectively with metalloporphyrins than Bu₄NHSO₅. Therefore, various di- and trisubstituted aromatic alkenes were epoxidized by using both monopersulfates as oxidants together with NMO and catalyst ent-5 (Table 11).

All the reactions proceeded smoothly and both oxidants gave almost identical yields and ee’s with most of the substrates. The epoxide yields and enantioselectivities were fully comparable with the results obtained with the widely used oxidants NaOCl and PhIO (see Table 3, p. 22). Only the epoxidation of indene (43) and 1,2-dihydonaphthalene (44) gave somewhat moderate ee’s (entries 1, 2 and 4). The corresponding epoxides are very sensitive compounds and partial epoxide ring opening with subsequent kinetic resolution or other competing reactions are a possibility.

The epoxidation of (Z)-1-phenyl-propene produced the corresponding epoxide with a stereoselectivity (cis/trans= 7-9, entries 8 and 9) comparable with the results obtained earlier with Jacobsen-type catalysts. Here, the use of Ph₄PSO₅ resulted in a slightly lower yield than that achieved with Bu₄NHSO₅ but equal stereoselectivity.
Asymmetric epoxidation of various alkenes with monopersulfates and catalyst ent-5°

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkene</th>
<th>Oxidant</th>
<th>Time (h)</th>
<th>Isol. yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>43</td>
<td>Bu₄NHSO₅</td>
<td>1</td>
<td>75</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>&quot;</td>
<td>Ph₄PHSO₅</td>
<td>1</td>
<td>78</td>
<td>75</td>
</tr>
<tr>
<td>3ᵇ</td>
<td>44</td>
<td>KHSO₅</td>
<td>1.25</td>
<td>30</td>
<td>61</td>
</tr>
<tr>
<td>4</td>
<td>&quot;</td>
<td>Bu₄NHSO₅</td>
<td>1</td>
<td>74</td>
<td>74</td>
</tr>
<tr>
<td>5</td>
<td>45</td>
<td>Ph₄PHSO₅</td>
<td>1.25</td>
<td>78</td>
<td>91</td>
</tr>
<tr>
<td>6</td>
<td>47</td>
<td>Bu₄NHSO₅</td>
<td>1.25</td>
<td>86</td>
<td>91</td>
</tr>
<tr>
<td>7</td>
<td>&quot;</td>
<td>Ph₄PHSO₅</td>
<td>1.5</td>
<td>86</td>
<td>89</td>
</tr>
<tr>
<td>8</td>
<td>48</td>
<td>Bu₄NHSO₅</td>
<td>1</td>
<td>72 (8.3:1)ᶜ</td>
<td>87ᵈ</td>
</tr>
<tr>
<td>9</td>
<td>&quot;</td>
<td>Ph₄PHSO₅</td>
<td>1.25</td>
<td>66 (9.4:1)ᶜ</td>
<td>89ᵈ</td>
</tr>
<tr>
<td>10</td>
<td>50</td>
<td>Bu₄NHSO₅</td>
<td>1</td>
<td>97</td>
<td>93</td>
</tr>
<tr>
<td>11</td>
<td>&quot;</td>
<td>Ph₄PHSO₅</td>
<td>1</td>
<td>98</td>
<td>91</td>
</tr>
</tbody>
</table>

a) Reactions were performed at -18 °C. Molar ratio of alkene: oxidant: NMO: ent-5= 1: 1.6: 1: 0.07. b) Reaction was performed at 2 °C. c) Ratio of cis- and trans-epoxide. d) ee of the cis-epoxide.

The reaction system presented here offers mild reaction conditions, as illustrated by a comparison of the epoxidation of 1,2-dihydronaphthalene (44) by Oxone and by Bu₄NHSO₅ (entry 3 vs 4).⁸⁻¹⁰ Ammonium and phosphonium monopersulfates might find more general use since they are readily soluble unlike oxidants such as Oxone and PhIO and offer mild reaction conditions.

4.4.3. Catalyst structure effects in asymmetric epoxidations with monopersulfates

The electronic and steric effects of substituents on different 1,2-diphenylethlenediamine- and 1,2-diaminocyclohexane-derived catalysts were studied in the epoxidation of alkene 45 with Bu₄NHSO₅ (Table 12). In almost all cases the 1,2-diphenylethlenediamine-derived catalysts afforded considerably better yields and ee’s than the corresponding 1,2-diaminocyclohexane-derived complexes. However, with other oxidants (e.g. H₂O₂) the two types of catalysts usually give comparable yields and ee’s in the epoxidation of various alkenes (see also Table 1, p. 13).¹⁻³ The reason for this difference is not clear. It is possible that 1,2-diaminocyclohexane-derived complexes are partially deactivated or decomposed during the catalytic cycle by some unknown mechanism.¹³³ In fact, when epoxidation of alkene 44 was conducted in a two-phase system using aqueous Oxone as the oxidant, catalyst 11 was completely
bleached during the reaction (as indicated by TLC and disappearance of the colour of
the catalyst). However, the 1,2-diphenylethylenediamine-derived complex ent-5 was
able to catalyze the reaction, although with low yield (Table 11, entry 3).

Table 12. Catalyst structure effects in asymmetric epoxidation with Bu₄NHSO₅

![Catalyst structure diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catal.</th>
<th>R,R₂</th>
<th>R₁</th>
<th>R₂</th>
<th>Time (h)</th>
<th>Isol. yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1ᵇ</td>
<td>ent-5</td>
<td>Ph,Ph</td>
<td>t-Bu</td>
<td>Me</td>
<td>1.5</td>
<td>72</td>
<td>90</td>
</tr>
<tr>
<td>2ᵇ</td>
<td>35</td>
<td>Ph,Ph</td>
<td>t-Bu</td>
<td>t-Bu</td>
<td>1.25</td>
<td>78</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>ent-8</td>
<td>Ph,Ph</td>
<td>t-Bu</td>
<td>OSi(i-Pr)₃</td>
<td>3.5</td>
<td>62</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>36</td>
<td>Ph,Ph</td>
<td>C(Me)₂Ph</td>
<td>Me</td>
<td>3</td>
<td>70</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>(CH₂)₄</td>
<td>t-Bu</td>
<td>Me</td>
<td>3.5</td>
<td>60</td>
<td>74</td>
</tr>
<tr>
<td>6</td>
<td>ent-11</td>
<td>(CH₂)₄</td>
<td>t-Bu</td>
<td>t-Bu</td>
<td>2.5</td>
<td>52</td>
<td>72</td>
</tr>
<tr>
<td>7</td>
<td>39</td>
<td>(CH₂)₄</td>
<td>t-Bu</td>
<td>C(Ph)₃</td>
<td>3</td>
<td>49</td>
<td>60</td>
</tr>
<tr>
<td>8</td>
<td>40</td>
<td>(CH₂)₄</td>
<td>C(Me)₂Ph</td>
<td>t-Bu</td>
<td>1.5</td>
<td>66</td>
<td>83</td>
</tr>
</tbody>
</table>

a) Reactions were performed at 2 °C. Molar ratio of 45: Bu₄NHSO₅: NMO: catalyst = 1: 1.6: 1: 0.07. b) Reaction was performed at −18 °C.

Introduction of bulky electron-donating OSi(i-Pr)₃ groups at the C5- and C5’-positions of the salicylde ligand attenuated the reactivity of the catalyst as expected, but at the same time both enantioselectivity and yield of the epoxide were also lower than in reactions catalyzed by ent-5 (entry 1 vs. 3). This differs somewhat from the results obtained with H₂O₂ as the oxidant where the difference in selectivity between catalysts ent-5 and ent-8 was not so pronounced (see Table 7, p. 45). Increasing the size of the substituents at the C5- and C5’-positions of the 1,2-diaminocyclohexane-derived catalysts from methyl (6) and tert-butyl (5) to triphenylmethyl (7) resulted in considerably decreased enantioselectivity (entries 5-7). Similar effects have been observed also with hydrogen peroxide (p. 44).

Increasing the size of the substituents at the C3- and C3’-positions had variable effects. Introduction of bulky C(Me)₂Ph groups on the C3- and C3’-positions of the 1,2-diphenylethylenediamine-derived salen ligand (catalyst 36) resulted in decreased
asymmetric induction compared with the results obtained with catalyst ent-5 as could
be expected on the basis of earlier results.\textsuperscript{III,137} On the other hand, the 1,2-
diaminocyclohexane-derived catalyst 40 bearing C(Me)$_2$Ph groups at the C3- and C3'-
positions was found to be more reactive and selective than catalyst ent-11 bearing t-Bu
substituents (entry 5 vs 8). The reason for this reversed difference in reactivity and
enantioselectivity between catalysts ent-11 and 40 is not fully clear. A possible
explanation could be that catalyst 40 is more stable than the less hindered catalyst ent-
11 towards the oxidative degradation induced by the monopersulfate oxidant during
the catalytic cycle.

4.5. **Epoxidations with in situ generated peroxyacids\textsuperscript{VI}**

While H$_2$O$_2$ is a very practical oxidant in Mn(III)-salen catalyzed asymmetric
epoxidation, as shown in the previous section, higher enantioselectivities are in some
cases desirable. The MCPBA/NMO system introduced by Jacobsen et al. offers high
enantioselectivity but lacks practicability because of the strict reaction conditions (low
reaction temperature, large excess of NMO).\textsuperscript{78,86} However, other peroxyacids used in
Mn(III)-salen catalyzed epoxidations, MMPP and peroxyacetic acid, afford lower
selectivity than MCPBA/NMO.\textsuperscript{60d,72c,78,86} Therefore, an effort to combine the good
properties of H$_2$O$_2$ and MCPBA was made in this study by using in situ generated
peroxyacids as oxidants.

Alkenes are epoxidized with peroxycarboxylic acids generated in situ from
aqueous H$_2$O$_2$ or more preferably from anhydrous urea-H$_2$O$_2$ (UHP) and from
anhydrides such as acetic anhydride and trifluoroacetic anhydride,\textsuperscript{138-140} phthalic
anhydride,\textsuperscript{141,142} and particularly maleic anhydride.\textsuperscript{142-145} Peroxyacetic acid generated
from excess acetic anhydride and 30 % H$_2$O$_2$ has been used in Mn-porphyrin catalyzed
epoxidation of unfunctionalized alkenes.\textsuperscript{85} UHP is an easy-to-handle solid source of
anhydrous H$_2$O$_2$, an alternative to concentrated hydrogen peroxide for use in various
oxidation reactions including Mn(III)-salen catalyzed epoxidations.\textsuperscript{III,56,138,139} Also
other anhydrous adducts of hydrogen peroxide, triphenylphosphine oxide-H$_2$O$_2$
(Ph$_3$PO·½H$_2$O$_2$, POHP) and sodium percarbonate (Na$_2$CO$_3$·1½H$_2$O$_2$, SPC) have been
used as H$_2$O$_2$ donors.\textsuperscript{140}

**4.5.1. Generation of the peroxyacids and the epoxidation procedure**

The unfunctionalized benzocyclic alkenes 43-45 were enantioselectively
epoxidized with peroxycarboxylic acids formed in situ from anhydrous adducts of
H₂O₂ and carboxylic acid anhydrides (maleic, phthalic, and acetic anhydride) together with Mn(III)-salen complexes and N-methylmorpholine N-oxide (NMO) additive. For comparison purposes also peroxylauric acid was tested as a possible alternative for MCPBA. The typical epoxidation procedure showing maleic anhydride and UHP is outlined in Scheme 4. The results are summarized in Table 13.

The peroxyacids were prepared using a slight excess of the anhydride over H₂O₂ to obtain peroxyacids essentially free of H₂O₂, which was further ascertained by using CH₂Cl₂-DMF mixture as the reaction medium. This was done because reaction of maleic anhydride with concentrated H₂O₂ in the presence of small amounts of water-miscible solvents of high dielectric constant (e.g. DMF) has been reported to effect rapid and complete formation of peroxymaleic acid.

The epoxidation reactions (eq. (2) in Scheme 4) were very facile and the rate of epoxidation was strongly dependent on the presence of NMO. Although the reaction could be conducted even with substoichiometric amounts of the additive (0.2 mol.% was enough to induce complete reaction), its absence resulted in significant retardation of the epoxidation (incomplete reaction after 24 h). Also, epoxidation in the absence of Mn-salen complexes was negligible under the usual reaction conditions, indicating a large rate difference between the catalyzed and uncatalyzed reactions.

The efficiencies of the different carboxylic anhydrides and H₂O₂ adducts with catalysts ent-11 and 12 were tested using alkene 45 as substrate (entries 1-7). Particular attention was paid to maleic anhydride since it may be used in non-buffered systems unlike acetic or trifluoroacetic anhydrides. Also, peroxymaleic acid has been observed to be more reactive than most peroxyacids with the exception of trifluoroper oxyacetic acid. Here, the highest chemical yields were obtained using maleic or acetic anhydrides. Reactions performed with UHP/phthalic anhydride or peroxylauric acid afforded lower yield, although comparable ee values were obtained.

Scheme 4. Typical epoxidation procedure utilizing in situ generated peroxymaleic acid.
in all cases. Enantioselectivity in oxidations with peroxymaleic acid was independent of the H$_2$O$_2$ adduct used (entries 1 and 2). However, reactions performed using POHP were faster and produced higher chemical yields than epoxidations induced by UHP. The slight difference in reactivity can be attributed to the higher solubility of POHP in organic solvents. Lowering the reaction temperature from 2 °C to –18°C had a marginal positive effect on the yield and ee of the epoxides, however, reaction temperatures below –18 °C were not beneficial for the reaction. In the case of the less soluble UHP/MA system the reactions were impractically slow at –70 °C. Reactions conducted using phthalic anhydride started to slacken when the temperature was decreased below 0 °C.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkene</th>
<th>Catal.</th>
<th>Oxidant$^b$</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Isol. yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>45</td>
<td>ent-11</td>
<td>UHP/MA</td>
<td>2</td>
<td>1.5</td>
<td>71</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>&quot;</td>
<td>ent-11</td>
<td>POHP/MA</td>
<td>2</td>
<td>0.5</td>
<td>81</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>&quot;</td>
<td>ent-11</td>
<td>&quot;</td>
<td>-18</td>
<td>0.75</td>
<td>81</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>&quot;</td>
<td>12</td>
<td>&quot;</td>
<td>-18</td>
<td>1.5</td>
<td>73</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>&quot;</td>
<td>ent-11</td>
<td>UHP/PA</td>
<td>2</td>
<td>4</td>
<td>54</td>
<td>87</td>
</tr>
<tr>
<td>6</td>
<td>&quot;</td>
<td>ent-11</td>
<td>UHP/Ac$_2$O</td>
<td>-18</td>
<td>0.5</td>
<td>80</td>
<td>89</td>
</tr>
<tr>
<td>7</td>
<td>&quot;</td>
<td>ent-11</td>
<td>peroxyauric acid</td>
<td>-18</td>
<td>2.75</td>
<td>66</td>
<td>91</td>
</tr>
<tr>
<td>8</td>
<td>44</td>
<td>ent-5</td>
<td>UHP/MA</td>
<td>-18</td>
<td>1</td>
<td>70</td>
<td>73</td>
</tr>
<tr>
<td>9</td>
<td>&quot;</td>
<td>ent-5</td>
<td>POHP/MA</td>
<td>-70</td>
<td>1</td>
<td>69 (72)$^c$</td>
<td>66</td>
</tr>
<tr>
<td>10</td>
<td>43</td>
<td>ent-11</td>
<td>UHP/MA</td>
<td>2</td>
<td>0.5</td>
<td>41</td>
<td>73</td>
</tr>
<tr>
<td>11</td>
<td>&quot;</td>
<td>ent-5</td>
<td>&quot;</td>
<td>-18</td>
<td>0.5</td>
<td>50</td>
<td>80</td>
</tr>
<tr>
<td>12</td>
<td>&quot;</td>
<td>ent-8</td>
<td>&quot;</td>
<td>-18</td>
<td>1.25</td>
<td>40</td>
<td>81</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkene</th>
<th>Catal.</th>
<th>Oxidant$^b$</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Isol. yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>45</td>
<td>ent-11</td>
<td>UHP/MA</td>
<td>2</td>
<td>1.5</td>
<td>71</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>&quot;</td>
<td>ent-11</td>
<td>POHP/MA</td>
<td>2</td>
<td>0.5</td>
<td>81</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>&quot;</td>
<td>ent-11</td>
<td>&quot;</td>
<td>-18</td>
<td>0.75</td>
<td>81</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>&quot;</td>
<td>12</td>
<td>&quot;</td>
<td>-18</td>
<td>1.5</td>
<td>73</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>&quot;</td>
<td>ent-11</td>
<td>UHP/PA</td>
<td>2</td>
<td>4</td>
<td>54</td>
<td>87</td>
</tr>
<tr>
<td>6</td>
<td>&quot;</td>
<td>ent-11</td>
<td>UHP/Ac$_2$O</td>
<td>-18</td>
<td>0.5</td>
<td>80</td>
<td>89</td>
</tr>
<tr>
<td>7</td>
<td>&quot;</td>
<td>ent-11</td>
<td>peroxyauric acid</td>
<td>-18</td>
<td>2.75</td>
<td>66</td>
<td>91</td>
</tr>
<tr>
<td>8</td>
<td>44</td>
<td>ent-5</td>
<td>UHP/MA</td>
<td>-18</td>
<td>1</td>
<td>70</td>
<td>73</td>
</tr>
<tr>
<td>9</td>
<td>&quot;</td>
<td>ent-5</td>
<td>POHP/MA</td>
<td>-70</td>
<td>1</td>
<td>69 (72)$^c$</td>
<td>66</td>
</tr>
<tr>
<td>10</td>
<td>43</td>
<td>ent-11</td>
<td>UHP/MA</td>
<td>2</td>
<td>0.5</td>
<td>41</td>
<td>73</td>
</tr>
<tr>
<td>11</td>
<td>&quot;</td>
<td>ent-5</td>
<td>&quot;</td>
<td>-18</td>
<td>0.5</td>
<td>50</td>
<td>80</td>
</tr>
<tr>
<td>12</td>
<td>&quot;</td>
<td>ent-8</td>
<td>&quot;</td>
<td>-18</td>
<td>1.25</td>
<td>40</td>
<td>81</td>
</tr>
</tbody>
</table>

a) Molar ratio of alkene: UHP: anhydride: NMO: catalyst= 1: 1.6-2: 2-3.5: 2-3.5: 0.05-0.07.$^vi$ b) MA= maleic anhydride, PA= phthalic anhydride. c) Yield in parentheses is for the reacted alkene.

The benzocyclic alkenes 43 and 44 were epoxidized with equal efficiency using both POHP and UHP as the source of H$_2$O$_2$. With these alkenes the highest selectivities were obtained using 1,2-diphenylethylene-derived complexes as catalysts. Epoxidation of indene (43) was very facile but at the same time the chemical yield was only moderate compared with some other reaction systems.$^{III-V}$ It is possible that the highly sensitive indene epoxide reacts with maleic acid resulting in epoxide ring opening; other sensitive epoxides have behaved similarly with maleic acid.$^{143,145}$
4.5.2. Comparison with other oxidation systems utilizing H$_2$O$_2$

The experimental results obtained with peroxyacids were compared with those reported earlier that were obtained employing aqueous H$_2$O$_2$ and UHP as oxidants. In general, 3-5 % higher enantioselectivities were obtained using in situ generated peroxyacids than were obtained using hydrogen peroxide. Moreover, epoxidations proceeded considerably faster: with peroxyacids reaction times were usually less than 1 h, while reactions conducted using H$_2$O$_2$ took 2-4 h to reach completion. These differences in enantioselectivity and reactivity are illustrated in Mn(III)-salen (ent-5) catalyzed epoxidation of 1,2-dihydronaphthalene (44) with aqueous H$_2$O$_2$, anhydrous H$_2$O$_2$ adducts, and peroxymaleic acid (Table 14). All the oxidants with the exception of Na$_2$CO$_3$⋅1.5H$_2$O$_2$ (SPC) gave similar epoxide yields, but peroxymaleic acid afforded up to 8 % higher enantioselectivity. The very low reactivity of SPC is presumably due to its low solubility in the solvent system. Similar differences in reactivity between UHP and SPC have been reported before.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant</th>
<th>Time (h)</th>
<th>Isol. yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30% H$_2$O$_2$ or UHP or POHP</td>
<td>2-3</td>
<td>70-74</td>
<td>65-69</td>
</tr>
<tr>
<td>2</td>
<td>Na$_2$CO$_3$⋅1.5H$_2$O$_2$</td>
<td>6</td>
<td>traces</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>UHP/maleic anhydride$^b$</td>
<td>0.75</td>
<td>70</td>
<td>73</td>
</tr>
<tr>
<td>4</td>
<td>UHP/Cl$_3$CCN$^c$</td>
<td>1.5</td>
<td>70</td>
<td>72</td>
</tr>
</tbody>
</table>

$^a$ Molar ratio of 44: H$_2$O$_2$ adduct: NMO: ent-5 = 1: 2.8: 1: 0.05. $^b$See Table 12. $^c$ Molar ratio of 44: UHP: Cl$_3$CCN: NMO: ent-5 = 1: 2.8: 4: 1: 0.05.

In addition to the carboxylic anhydrides, other derivatives capable of generating activated oxidants in situ with H$_2$O$_2$ were tested. All the systems studied, namely benzoyl imidazole, ethyl chloroformate and cyanoformate, nitrites (benzonitrile, trichloroacetonitrile), and formamide generally produced unsatisfactory results. The only exception was trichloroacetonitrile, which in epoxidation of alkene 44 gave results similar to those obtained with maleic anhydride.
4.5.3. Possible catalytic routes for asymmetric epoxidation with peroxycacids

While the enantiomeric excesses obtained here are reasonably high they sometimes fall short of the selectivities obtained with the MCPBA/NMO system introduced by Jacobsen et al.\textsuperscript{78,86} Also, the temperature dependence is somewhat different. Here, decreasing the reaction temperature considerably below $-18\,^\circ\text{C}$ did not improve the ee's in contrast to the case of MCPBA where lowering the temperature to $-74\,^\circ\text{C}$ is highly favourable to the attainment of high enantioselectivity.\textsuperscript{78,86} Usually much lower enantioselectivity is obtained with MCPBA when epoxidation is conducted at higher temperatures.\textsuperscript{48,86,87} In addition, NMO plays different roles in the MCPBA/NMO system than other axial ligands. Jacobsen et al. observed that NMO and MCPBA generate a 1:1 salt that is unreactive toward alkenes but oxidizes the Mn(III)-salen catalyst.\textsuperscript{86} Furthermore, excess NMO is critical in preventing the uncatalyzed epoxidation pathways that take place in the absence of the additive.\textsuperscript{78,86}

Based on these differences in reactivity and selectivity, it is reasonable to assume that the oxidation method introduced here might operate with a different mechanistic pathway than the Jacobsen's system. Figure 11 presents one possible catalytic route for asymmetric epoxidation with peroxycacids. In the case of \textit{in situ} generated peroxycacids, the reaction sequence from salen-Mn(III) (a) to salen-Mn(V)=O (e), which is the actual active oxidant, most likely proceeds via a peroxacylmanganese species (b).\textsuperscript{117} A similar pathway has been proposed for the Mn-porphyrin catalyzed epoxidation of alkenes with $\text{H}_2\text{O}_2$ in the presence of nitrogen heterocycle ligands and carboxylic acid cocatalysts (see also Figure 10, p. 41).\textsuperscript{74} An alternative sequence involves peroxycylic intermediate (b) as the active species without the presence of the oxo compound (e).\textsuperscript{17} The Mn-salen catalyzed epoxidation with molecular oxygen/pivalaldehyde (or peroxycetic acid) has been proposed to provide, in certain conditions, salen-Mn(III)-O-OCOR as the active oxidant which directly epoxidizes alkenes.\textsuperscript{60d,72c} Likewise, acylperoxoiiron(III) porphyrin species from Fe(III)-porphyrins and MCPBA have been suggested as potent oxidants for olefin epoxidations especially at low temperatures.\textsuperscript{150} Therefore, the presence of (b) as active species in Mn-salen catalyzed epoxidation with MCPBA/NMO seems a reasonable assumption,\textsuperscript{17} although the exact mechanistic role of NMO in this reaction system is not clear.\textsuperscript{78,86} In addition, the involvement of other reactive species, e.g. salen-Mn(IV)=O, which might affect the stereoselectivity in the reaction cannot be ruled out.\textsuperscript{107,113b,123}
The viability of the unsymmetrical complexes 41 and 42, prepared as shown in Section 4.1., as catalysts in the asymmetric epoxidation of typical unfunctionalized alkenes (44, 45 and 48) was studied and the results were compared with those obtained with analogous symmetrical salen catalysts (results in Table 15).

The unsymmetrical Schiff base complex 41 was found to be catalytically active and to induce moderate-to-good enantioselectivity (ee 44-79 %). Also, the benzocyclic alkenes (44, 45) produced the corresponding epoxides with almost equal yield with both catalyst 41 and symmetrical catalysts ent-5 and 11. However, the catalytic activity of 41 was lower than the activity of ent-5 or 11, as indicated by longer reaction times. Also, the ee’s achieved by using 41 were generally lower than those obtained with the symmetrical complexes. Interestingly, epoxidation of 45 with Bu₄NHSO₅ and 41 afforded higher ee than the reaction catalyzed with 11. This is in accordance with our earlier observation that 1,2-diphenylethylenediamine-derived salens (e.g. ent-5) show higher asymmetric induction than their 1,2-diaminocyclohexane-derived counterparts (e.g. 11) in epoxidations conducted with Bu₄NHSO₅ as the oxidant.

The results are not surprising since almost all the unsymmetrical Schiff-base complexes studied to date have shown diminished enantioselectivity in asymmetric epoxidations compared with the analogous C₂-symmetric catalysts. The diminished enantioselectivity of 41, and other unsymmetrical Schiff-base complexes, could be explained by the formation of diastereomeric Mn(V)-oxo species (A and B),
which may differ in stability and reactivity, and may have different selectivity during alkene epoxidation.\textsuperscript{54,126,151} Also, the presence of the ethyl group in the 2-hydroxypropiophenone unit can change the steric environment of the catalyst 41, thereby leading to decreased asymmetric induction compared with the symmetrical catalysts.

![Image of molecular structures A and B](image)

**Table 15.** Asymmetric epoxidation catalyzed with symmetrical and unsymmetrical Mn(III)-Schiff base complexes\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkene</th>
<th>Catal.</th>
<th>Oxidant</th>
<th>Additive</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>44</td>
<td>41</td>
<td>Bu₄NIO₄</td>
<td>ImH</td>
<td>22</td>
<td>6</td>
<td>47 (69)\textsuperscript{b}</td>
<td>48</td>
</tr>
<tr>
<td>2</td>
<td>&quot;</td>
<td>ent-5</td>
<td>&quot;</td>
<td>&quot;</td>
<td>22</td>
<td>3</td>
<td>55</td>
<td>64</td>
</tr>
<tr>
<td>3</td>
<td>&quot;</td>
<td>41</td>
<td>NaOCl</td>
<td>PyNO</td>
<td>2</td>
<td>6</td>
<td>40</td>
<td>44</td>
</tr>
<tr>
<td>4</td>
<td>&quot;</td>
<td>ent-5</td>
<td>&quot;</td>
<td>&quot;</td>
<td>2</td>
<td>2.5</td>
<td>49</td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td>&quot;</td>
<td>11</td>
<td>&quot;</td>
<td>&quot;</td>
<td>2</td>
<td>2.5</td>
<td>45</td>
<td>73</td>
</tr>
<tr>
<td>6</td>
<td>45</td>
<td>41</td>
<td>Bu₄NHSO₅</td>
<td>NMO</td>
<td>-18</td>
<td>4</td>
<td>68</td>
<td>79</td>
</tr>
<tr>
<td>7</td>
<td>&quot;</td>
<td>ent-5</td>
<td>&quot;</td>
<td>&quot;</td>
<td>2</td>
<td>1.5</td>
<td>59</td>
<td>89</td>
</tr>
<tr>
<td>8</td>
<td>&quot;</td>
<td>11</td>
<td>&quot;</td>
<td>&quot;</td>
<td>2</td>
<td>2.5</td>
<td>52</td>
<td>72</td>
</tr>
<tr>
<td>9</td>
<td>48</td>
<td>41</td>
<td>Bu₄NHSO₅</td>
<td>NMO</td>
<td>-18</td>
<td>5</td>
<td>47\textsuperscript{c}</td>
<td>50\textsuperscript{d}</td>
</tr>
<tr>
<td>10</td>
<td>&quot;</td>
<td>ent-5</td>
<td>&quot;</td>
<td>&quot;</td>
<td>-18</td>
<td>1</td>
<td>72\textsuperscript{e}</td>
<td>87\textsuperscript{d}</td>
</tr>
</tbody>
</table>

\textsuperscript{a) See ref. VII for reaction conditions. b) Yield calculated from the reacted alkene. c) A mixture of cis- and trans-epoxides (4.6:1). d) ee of the cis-epoxide. e) A mixture of cis- and trans-epoxides (8.3:1).}

While complex 41 was catalytically active, the complex 42 with a tethered imidazole group showed no catalytic activity with any of the substrates and oxidants, with or without added donor ligands. The inactivity of catalyst 42 is most likely due to intermolecular coordination, contrary to the desired intramolecular coordination,\textsuperscript{55} of the tethered imidazole moiety of one complex with the metal center of another catalyst molecule. This eventually results in the occupation of most of the coordination sites, which renders the catalyst inactive.
5. CONCLUSIONS AND FUTURE PERSPECTIVES

Presently, chiral Mn(III)-salen complexes are presumably the most efficient and practical catalysts for the asymmetric epoxidation of various cis-disubstituted, and tri- and tetrasubstituted alkenes. This thesis extends the scope of this method by introducing new oxidants and additives to be used in conjunction with Jacobsen-type catalysts.

It was shown that hydrogen peroxide together with simple carboxylate salts is able to promote the asymmetric epoxidation of various alkenes in a straightforward manner with high yield and enantioselectivity.\textsuperscript{I,III} The obvious good properties of hydrogen peroxide together with the high oxidation resistance and low price of carboxylates makes this a particularly practical epoxidation system that might be amenable to large-scale syntheses.\textsuperscript{III} Hydrogen peroxide was further utilized in the generation of peroxyacids \textit{in situ} from carboxylic anhydrides, which increased reactivity and selectivity.\textsuperscript{VI} Also, oxidants such as \text{Bu}_4\text{NIO}_4, \text{Bu}_4\text{NHSO}_5, and \text{Ph}_4\text{PHSO}_3 might find more general use since they are readily soluble in organic solvents unlike the frequently used oxygen donors \text{KHSO}_5 and, particularly, \text{PhIO}.\textsuperscript{II,IV,V}

The Mn-salen based asymmetric epoxidations conducted with different oxidant/catalyst combinations are summarized in Table 16 and compared with the currently most widely used Jacobsen’s \text{NaOCl} system. The new oxidation systems developed here give chemical yields, and stereo- and enantioselectivities that are fully comparable with those of earlier systems, which utilize \text{NaOCl}, \text{PhIO} or \text{O}_2/\text{aldehyde} as oxidant with most of the alkene substrates studied.

Although there has been great progress in Mn-salen based asymmetric epoxidation during the last decade there still remain great challenges including the finding of good catalysts for highly enantioselective epoxidation of \textit{trans}-alkenes and simple alkyl-substituted olefins. In fact, systems based on \textit{in situ} generated chiral dioxiranes may be better suited for asymmetric epoxidation of unfunctionalized \textit{trans}-alkenes.\textsuperscript{89} Also further development of oxidant systems that would offer milder reaction conditions are needed since the susceptibility of the Mn-salen catalysts towards oxidative degradation is the major limiting factor of the method.

The great success of soluble chiral Mn(III)-salen complexes has recently given rise to several attempts to build heterogenous systems by the attachment of these catalysts to insoluble solid supports.\textsuperscript{152} The main objectives of such studies have been to facilitate catalyst separation and reuse and to increase catalyst stability. The results obtained so far have been somewhat disappointing, but further development is anticipated.
Table 16. Comparison of the different epoxidation systems presented in this study

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkene</th>
<th>Catal.</th>
<th>Oxidant</th>
<th>Additive</th>
<th>Yield (%)</th>
<th>ee (%)</th>
<th>Ref.</th>
<th>ee (%) NaOCl</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Alkene" /></td>
<td>ent-5</td>
<td>H₂O₂</td>
<td>NH₄OAc</td>
<td>73</td>
<td>68</td>
<td>III</td>
<td>86ᵃ</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2" alt="Alkene" /></td>
<td>ent-5</td>
<td>Bu₄NIO₄</td>
<td>ImH</td>
<td>52</td>
<td>69</td>
<td>II</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="Alkene" /></td>
<td>ent-5</td>
<td>Bu₄NHSO₅</td>
<td>NMO</td>
<td>74</td>
<td>74</td>
<td>VIII</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td><img src="image4" alt="Alkene" /></td>
<td>ent-5</td>
<td>PMA</td>
<td>NMO</td>
<td>70</td>
<td>73</td>
<td>VI</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td><img src="image5" alt="Alkene" /></td>
<td>ent-5</td>
<td>H₂O₂</td>
<td>NH₄OAc</td>
<td>75</td>
<td>89</td>
<td>III</td>
<td>92ᵇ</td>
</tr>
<tr>
<td>6</td>
<td><img src="image6" alt="Alkene" /></td>
<td>ent-5</td>
<td>Bu₄NHSO₅</td>
<td>NMO</td>
<td>72</td>
<td>90</td>
<td>V</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td><img src="image7" alt="Alkene" /></td>
<td>ent-5</td>
<td>PMA</td>
<td>NMO</td>
<td>73</td>
<td>92</td>
<td>VI</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td><img src="image8" alt="Alkene" /></td>
<td>ent-5</td>
<td>H₂O₂</td>
<td>NH₄OAc</td>
<td>63</td>
<td>75</td>
<td>III</td>
<td>88ᵃ</td>
</tr>
<tr>
<td>9</td>
<td><img src="image9" alt="Alkene" /></td>
<td>ent-5</td>
<td>Bu₄NHSO₅</td>
<td>NMO</td>
<td>78</td>
<td>75</td>
<td>V</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td><img src="image10" alt="Alkene" /></td>
<td>ent-5</td>
<td>PMA</td>
<td>NMO</td>
<td>72</td>
<td>87</td>
<td>VI</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td><img src="image11" alt="Alkene" /></td>
<td>ent-5</td>
<td>H₂O₂</td>
<td>NMO</td>
<td>49</td>
<td>86</td>
<td>VIII</td>
<td>84ᵉ</td>
</tr>
<tr>
<td>12</td>
<td><img src="image12" alt="Alkene" /></td>
<td>ent-5</td>
<td>Bu₄NHSO₅</td>
<td>NMO</td>
<td>72</td>
<td>87</td>
<td>V</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td><img src="image13" alt="Alkene" /></td>
<td>ent-5</td>
<td>H₂O₂</td>
<td>N-MeIm</td>
<td>51</td>
<td>47</td>
<td>I</td>
<td>20ᵈ</td>
</tr>
<tr>
<td>14</td>
<td><img src="image14" alt="Alkene" /></td>
<td>ent-5</td>
<td>Bu₄NIO₄</td>
<td>ImH</td>
<td>69</td>
<td>54</td>
<td>II</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td><img src="image15" alt="Alkene" /></td>
<td>ent-5</td>
<td>Bu₄NIO₄</td>
<td>ImH</td>
<td>78</td>
<td>85</td>
<td>II</td>
<td>98ᵉ</td>
</tr>
<tr>
<td>16</td>
<td><img src="image16" alt="Alkene" /></td>
<td>ent-11</td>
<td>H₂O₂</td>
<td>NH₄OAc</td>
<td>90</td>
<td>91</td>
<td>III</td>
<td>91ᶠ</td>
</tr>
<tr>
<td>17</td>
<td><img src="image17" alt="Alkene" /></td>
<td>ent-5</td>
<td>Bu₄NHSO₅</td>
<td>NMO</td>
<td>86</td>
<td>91</td>
<td>V</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td><img src="image18" alt="Alkene" /></td>
<td>ent-11</td>
<td>H₂O₂</td>
<td>NH₄OAc</td>
<td>84</td>
<td>96</td>
<td>III</td>
<td>95ᵍ</td>
</tr>
<tr>
<td>19</td>
<td><img src="image19" alt="Alkene" /></td>
<td>ent-5</td>
<td>Bu₄NHSO₅</td>
<td>NMO</td>
<td>97</td>
<td>93</td>
<td>V</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td><img src="image20" alt="Alkene" /></td>
<td>ent-11</td>
<td>H₂O₂</td>
<td>NH₄OAc</td>
<td>90</td>
<td>96</td>
<td>VIII</td>
<td>92ᵍ</td>
</tr>
</tbody>
</table>

a) Ee’s observed using the same catalyst under optimized bleach conditions, from ref. 14.  
b) Using catalyst 4, from ref. 78.  
c) From refs. 38 and 39.  
d) Using catalyst 4, from ref. 12.  
e) From refs. 38 and 103.  
f) Mukaiyama’s conditions: O₂/t-BuCHO, N-octylimidazole, from ref. 72.  
g) From ref. 110.
6. EXPERIMENTAL

Detailed descriptions of the general experimental procedures can be found in the original publications I-VII.

6.1. Materials

1,1,2-Triphenylethene (51) was prepared by Grignard reaction from benzophenone and benzylchloride with subsequent dehydration. 1,1-Diphenyl-3-methylbut-1-ene (52) and 1,1,3-triphenylpropene (53) were prepared by Grignard reaction with bromobenzene and subsequent dehydration from ethyl 3-methylbutanate and ethyl 3-phenylpropanate, respectively.

6.2. Synthesis of Mn(III)-salen complexes

6.2.1. [N,N’-Bis(3-tert-butyl-5-methylsalicylidene)ethylene diamine]chloromanganese(III) (34).

Catalyst 34 was synthesized from the corresponding salen ligand according to the published procedure. Brown powder, yield 98%, mp >300 °C. IR (neat): 2960, 2948, 2910, 2867, 1610, 1542, 1438, 1409, 1389, 1336, 1291, 1264, 1233, 1208, 817, 777 cm⁻¹. MS (EI) m/z 496 (M)⁺, 461 (M-Cl)⁺.

6.2.2. [(S,S)-N,N’-Bis(4-tert-butylsalicylidene)-1,2-diphenylethlenediamine]-chloromanganese(III) (38).

4-tert-Butyl-2-hydroxybenzaldehyde. The aldehyde was prepared from 3-tert-butylphenol according to the procedure of Casiraghi et al. The product was purified by dry column flash chromatography (eluent hexane-ethyl acetate). Yellowish oil, yield 31 %. ¹H NMR δ 1.32 (9H, s), 7.00 (2H, d, J=1.8 Hz), 7.05 (1H, dd, J= 8.1 and 1.8 Hz), 7.48 (1H, d, J= 8.1 Hz), 9.84 (1H, s), 11.01 (1H, s). ¹³C NMR δ 31.2, 36.0, 114.8, 118.0, 118.9, 133.7, 162.0, 162.2, 196.2. MS (EI) m/z (rel. int): 178 (M⁺, 6 %), 163 (71), 162 (29), 139 (52), 112 (31), 87 (40), 86 (26), 75 (100), 74 (37).

(S,S)-N,N’-Bis(4-tert-butylsalicylidene)-1,2-diphenylethlenediamine. Yellowish crystals from EtOH, yield 93 %, mp 202.5-203 °C. ¹H NMR δ 1.27 (18H, s), 4.73 (2H, s), 6.84 (2H, dd, J= 1.8 and 8.1 Hz), 6.99 (2H, J= 1.8 Hz), 7.08 (2H, J= 8.1 Hz), 7.18 (10H, m), 8.28 (2H, s), 13.3 (2H, s). ¹³C NMR δ 31.4, 35.4, 80.5, 114.4, 116.6, 116.7, 127.9, 128.3, 128.7, 131.7, 140.2, 157.0, 161.1, 166.0. MS (EI) m/z 532 (M)⁺.
Mn(III)-salen complex 38. Catalyst 38 was prepared from the corresponding salen ligand using the published procedure (solvent ethanol-acetonitrile). Brown powder, yield 92 %, mp 273-275 °C. IR (neat): 3064, 3029, 2958, 2901, 2865, 1600, 1515, 1408, 1381, 1295, 1218, 1199, 1091, 960, 700, 669, 652, 614 cm⁻¹. MS (FAB) m/z 585.0 (M-Cl)+.

6.3. Epoxidation procedures

6.3.1. Epoxidation of the trisubstituted alkenes 51-53 with H₂O₂

Epoxidations, purifications and analyses of the trisubstituted alkenes 51-53 were performed using the general procedure in publication III.

¹H NMR and MS data of the obtained epoxides

1,1,2-Triphenyloxirane. Solid, mp 73 °C (lit. mp 75-76 °C). ¹H NMR δ 4.36 (1H, s), 7.02-7.40 (15H, m). HRMS (EI) m/z: calcd for C₂₀H₁₆O 272.1201, found 272.1212.

1,1-Diphenyl-3-methyl-1-buteneoxide. Oil, solidifies on standing. ¹H NMR δ 0.93 (3H, d, J= 5.9 Hz), 1.08 (3H, d, J= 5.3 Hz), 1.13 (1H, m), 3.10 (1H, d, J= 8.6 Hz), 7.26-7.46 (10H, m). HRMS (EI) m/z: calcd for C₁₇H₁₈O 238.1358, found 238.1348.

1,1,3-Triphenyl-1-propeneoxide. Oil, solidifies on standing. ¹H NMR δ 2.71 (2H, m), 3.68 (1H, t, J= 6.1 Hz), 7.13-7.49 (15H, m). HRMS (EI) m/z: calcd for C₂₁H₁₈O 286.1358, found 286.1344.

6.3.2. Epoxidation of 1,2-dihyronaphthalene (44) with KHSO₅ (Table 11).

To a cooled (2 °C) solution of 44 (66 mg, 0.51 mmol), 4-tert-butylpyridine (37 mg, 0.27 mmol), Bu₄NBr (10 mg, 0.03 mmol), and catalyst ent-5 (17.5 mg, 0.027 mmol) in CH₂Cl₂ (1.5 ml) was added a precooled solution of KHSO₅ (0.2 M, 5 ml) in phosphate buffer (pH 7.0). The mixture was stirred at 2 °C for 75 min and then diluted with CH₂Cl₂. Phases were separated and the organic phase was washed with water and saturated NaCl solution, dried over Na₂SO₄, and concentrated. Flash chromatography (eluent hexane-EtOAc) afforded the epoxide, yield 22 mg (30 %). The ee of the epoxide was determined to be 61 % by ¹H NMR analysis in the presence of Eu(hfc)₃.

6.3.3. Epoxidation of 1,2-dihyronaphthalene (44) with UHP/Cl₃CCN (Table 14).

Solid UHP (1.4 mmol as H₂O₂) was added in two roughly equal portions in 20 min to a cooled solution of 44 (65 mg, 0.50 mmol), NMO (175 mg, 1.49 mmol), Cl₃CCN (0.2 ml, 2.0 mmol), and catalyst ent-5 (16.5 mg, 0.025 mmol) in MeOH-CH₂Cl₂ (1.5 ml). The mixture was stirred at 2 °C for 1.5 h and treated as above, yield 51 mg (70 %), ee 72 %.
7. REFERENCES AND NOTES


30. references therein.
Soc. 1998, 120, 948.


64


137. A 10-15 % decrease in ee was observed when epoxidation of 44 was conducted with NaOCl/PyNO and catalyst 36 or 40 compared with the reaction using catalyst ent-5 or 11: Pietikäinen, P.; Brunow, G. Spring Meeting in Synthetic Chemistry, Turku, Finland, 11-12 May 1995, p. 43.