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Chromium– and Manganese–salen Promoted Epoxidation of Alkenes

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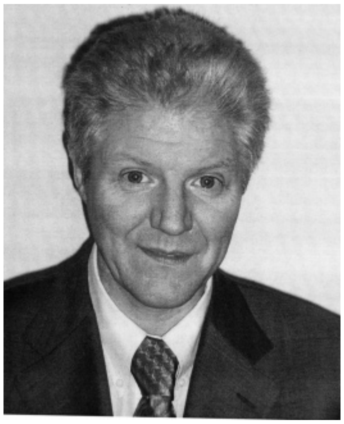
Eoghan McGarrigle was born in Dublin, Ireland. He studied chemistry at University College Dublin, where he obtained his B.Sc. degree in 1998. He carried out his doctoral studies under the supervision of Declan Gilheany and was awarded his Ph.D. degree for his thesis entitled "Chromium and manganese(salen)-mediated asymmetric alkene epoxidation" in 2003. Since then he has worked as a postdoctoral fellow in the group of Dr. Gilheany researching novel routes to P-chirogenic compounds.



Declan G. Gilheany was born in Tyrone, N. Ireland. He studied chemistry at Queens University Belfast and obtained his Ph.D. degree in 1983 under the supervision of Dr. B. J. Walker, having also been appointed temporary lecturer in organic chemistry during 1980–81. From there he became a lecturer in synthetic organic chemistry at St. Patricks College, Maynooth, Ireland. During 1988–90 he was a Fulbright Visiting Professor at Massachusetts Institute of Technology in the laboratory of Professor K. Barry Sharpless. He moved to his present position at University College Dublin in 1992. His main research interests lie in the area of catalytic asymmetric synthesis, especially asymmetric oxidation, structure and mechanism in organophosphorus chemistry, especially the applications of P-chiral compounds in catalysis, and synthesis of small and medium heterocycles.

1. Introduction

The first major breakthrough in asymmetric epoxidation (AE) using synthetic catalysts was realized by Katsuki and Sharpless in 1980.[1] They achieved enantiomeric excesses (ee's) greater than 90% in the titanium tartrate-based epoxidation of a variety of allylic alcohols. The highest ee previously recorded for an alkene was a mere 35%.[2] Subsequent development of this system led to a catalytic system for the AE of allylic alchohols.[3,4] The discovery and development of the reaction, now known as 'Sharpless epoxidation', was a significant factor in awarding one-half of the 2001 Nobel Prize in Chemistry to Prof. Sharpless for his work on asymmetric oxidation.[5]

A decade after the first published report on what would become known as Sharpless AE, the restriction that the alkene to be epoxidized must bear a pendant functional group (its main limitation) was satisfactorily overcome in a catalytic system. In 1990 Eric Jacobsen[6] and Tsutomu Katsuki announced their independently developed systems for the catalytic AE of unfunctionalized alkenes using manganese salen complexes.[7,8] The use of only nonbonding interactions between the substrate and catalyst broadens the potential scope of any catalyst, and with ee's greater than 90%, this work represented the next major breakthrough in catalytic AE.

Since these first reports of Mn(salen)-catalyzed AE[7,8] of unfunctionalized alkenes in 1990 the area of metal(salen)-mediated asymmetric reactions has expanded greatly. This is not only because of the utility of the method but also because it is mechanistically intriguing. The latter is true in terms of both its catalytic cycle and the mode of reaction of the active species. In addition, the reactions could be influenced by a number of other factors. All of this led to a large scope for study. Although the Mn(salen)-catalyzed AE reaction can be regarded as a mature subject, it remains (rightly) the subject of active research. Computational studies have added to the debate over the reaction mechanism on which a consensus on certain aspects has not yet been reached. Recent developments have reopened the debate over the identity of the active oxygen-transfer species, and the implications of these studies on previous mechanistic investigations will be included here. The lesser-known Cr(salen)-mediated AE will also be reviewed as it adds to the overall understanding of the field and offers insight into the mode of stereoselection and catalytic cycle.

In this review we will focus on the mechanism, catalytic cycle, intermediates, and mode of selectivity of Mn(salen)- and Cr(salen)-promoted AE of alkenes. We believe these systems provide many valuable lessons to anyone interested in developing catalytic asymmetric reactions. In addition to the fact that highly useful and selective systems have been developed, the plethora of different techniques that have been applied to this system (computational studies, X-ray crystallography, XANES, XAFS, EPR, electrospray-MS, cyclic voltammetry, NMR of paramagnetic compounds, UV−vis) demonstrate the versatility of the tool-kit of the practicing chemist.

Before starting the review of Mn(salen)- and Cr(salen)-promoted epoxidation, we note that there are many other competing methods for the catalytic and stoichiometric AE of alkenes.[9,10] We mention here leading references for some of the better known and more successful systems: chiral ketones,[11,12] Ru(salen),[13] and metal(porphyrin) complexes[14] are all capable of catalyzing the AE of unfunctionalized alkenes. Sharpless AE allows the epoxidation of allylic alcohols,[15,16] and a variety of methods exist for epoxidation of α,β-unsaturated carbonyl compounds.[17−21] In addition, biotransformation routes to epoxides have undergone substantial development.[22−24] There are also powerful catalytic systems that give access to enantiopure epoxides that are not alkene epoxidations. Jacobsen and co-workers developed extremely efficient metal−salen-catalyzed kinetic resolutions of racemic epoxides,[25] while Aggarwal and co-workers devised very elegant multicatalytic aldehyde epoxidations based on chiral sulfonium ylides.[26,27] Finally, the diol products from the extremely general asymmetric dihydroxylation (AD) reaction of Sharpless and co-workers can be efficiently converted to epoxides via halohydrin esters or via carbonates.[28,29]

We start by reviewing the Cr(salen)- and Mn(salen)-mediated achiral epoxidations that provided the basis for asymmetric variants. We then move on to detail the early work on Mn(salen)-catalyzed AE, concentrating on research from the groups of Jacobsen and Katsuki. The development of alternative ligand architectures and Katsuki's second-generation catalysts follows. The variety of stoichiometric oxidants and additives are then reviewed as well as the problem of production of *trans*-1,2-disubstituted epoxides and the various solutions to this so far offered. With these topics covered, research on the nature of the active species, the trajectory of substrate approach, and the mechanism of the reaction can be discussed in detail. Following this, the development of Cr(salen)-mediated AE will be reviewed in a similar manner so as to aid comparison between the two asymmetric systems.

1.1. Scope of Review

This review will comprehensively cover the development of Cr(salen)- and Mn(salen)-mediated AE with particular emphasis on recent progress (from 1999 to March 2004). Previous reviews are available.[30−41] Only monomeric, mononuclear, salen complexes having the general structure shown in Figure 1 will be included. Heterogenized/supported/polymeric catalysts (where the catalyst is bound to a solid support, imprinted in, encapsulated in, attached to, or part of a dimer, an oligomer, a polymer, or a dendrimer) will not be included—many of these aspects have been reviewed recently.[42−52] Any reference to papers containing such work are only to the part of that work which falls within the scope of the review and not to the whole body of work.

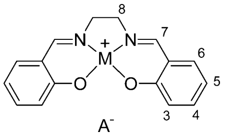


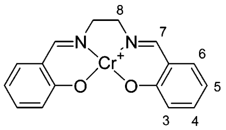
Figure 1. Metal(salen) complex (M = Cr, Mn; A = counterion).

2. Achiral Foundations

2.1. Achiral Cr(salen)-Catalyzed Epoxidations

In the mid-1980s Kochi and co-workers reported that Cr(salen) complexes were capable of catalyzing the epoxidation of unfunctionalized alkenes using PhIO as the stoichiometric oxidant (Chart 1 shows the complexes used, **1**−**8**).[53,54] The catalyst was used at 20 mol % with respect to (wrt) PhIO (the limiting reagent) and 1 mol % wrt alkene. Good yields were obtained for many alkenes, and from the outset it was noted that addition of oxygen-donor ligands such as pyridine *N*-oxide (PyO) and triphenylphosphine oxide (Ph_3PO) increased reaction rates. The effect of donor ligands on the related metal(porphyrin) epoxidizing systems was well known at this time.

Chart 1. Cationic Cr(salen) Complexes[a] Used in the Epoxidation of Alkenes by Kochi and Co-workers[53]



1: 3-8 = H
2: 8,8,8′,8′ = Me
3: 5,5′ = Cl
4: 7,7′ = Me
5: 7,7′ = Ph
6: 5,5′ = Cl, 8,8,8′,8′ = Me
7: 5,5′ = OMe, 8,8,8′,8′ = Me
8: 4,4′,6,6′ = OMe, 8,8,8′,8′ = Me

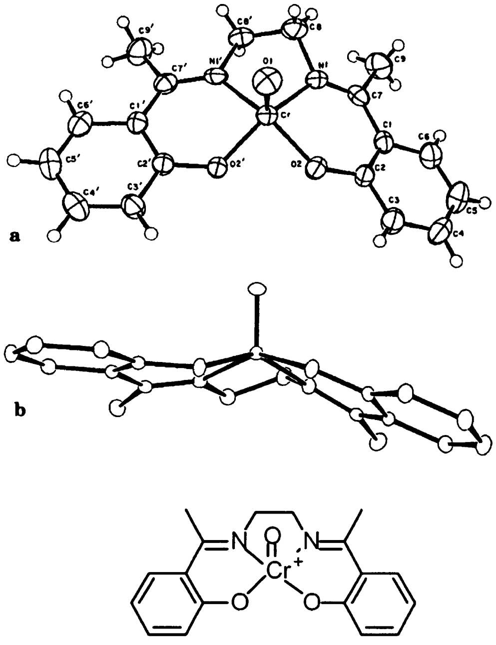
[a] The counterion was either PF_6^- or TfO^-.

Counterions such as chloride and trifluoroacetate formed strongly bound neutral adducts with the chromium salen complex, which rapidly decayed to unidentified chromium(III) products on oxidation. Thus, Kochi and co-workers concluded it was necessary to use cationic Cr(salen) complexes in order to effect oxygen transfer.

2.1.1. Nature of the Active Species

Kochi and co-workers showed that the active epoxidizing species was a chromium(V)−oxo species. The Cr^{III}(salen) complexes could be oxidized to oxo−Cr^{V}(salen) with either PhIO or *m*CPBA, but PhIO was used predominantly. This oxidation was accompanied by a color change from orange to dark green-black. The oxo−chromium complexes were characterized by IR, magnetic susceptibility, and ESR and shown to have a d^1 electron configuration characteristic of chromium(V) complexes. Oxo complexes bearing 5,5′-dinitro and 5,5′-dimethoxy were noted to be much less stable than other complexes—the lifetime of the oxo complex of a 5,5′-dinitro-substituted analogue of **2** was <10 min. Kochi and co-workers were able to isolate crystals of O═Cr(salen)$^+$ complexes suitable for X-ray analysis in two instances (Figure 2 shows one of these).[53−55] In the crystal structure the Cr atom is raised ~0.5 Å above the plane defined by the oxygen and nitrogen atoms of the salen ligand and has a square-pyramidal configuration with the oxo ligand occupying the apical position. This is in contrast to the Cr^{III}(salen) complexes where the chromium atom lies close to (<0.1 Å) the plane of the oxygen and nitrogen atoms.[56] In the O═Cr^{V}(salen) complexes the salen ligand adopts a stepped conformation similar to that found in Cr^{III}(salen) complexes. It was also noted that the chromium−oxygen bonds to the salen oxygen atoms were shorter than those in the Cr^{III}(salen) complexes by 0.11−0.14 Å.

The crucial observation was that the oxo complexes could be used as stoichiometric oxidants to oxidize alkenes and phosphines. The original Cr^{III}(salen) complex could be isolated almost quantitatively from the reaction, thus indicating a 1:1 stoichiometry between O═Cr(salen) and alkene. A concentration effect was noted: dilute solutions of the oxo complex (<0.02 M) gave higher yields of norbornene oxide



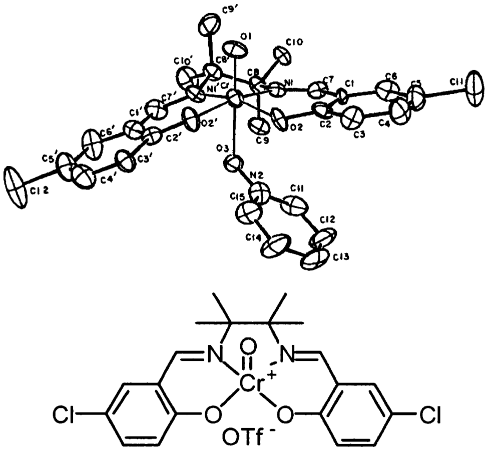
oxo-4

Figure 2. ORTEP diagram of the oxo−chromium(V) cation **oxo-4**: (a) top perspective; (b) side view with the hydrogen atoms removed for clarity. (Reprinted with permission from ref 55. Copyright 1985 American Chemical Society.)

$(>90\%)$ than more concentrated solutions (ca. 0.12 M, $\sim 60\%$ yield).

2.1.2. Effect of Additives and Ligand Structure

Donor ligands such as Ph_3PO, PyO, and water were shown to form 1:1 association complexes with the oxo species. Crystals suitable for X-ray analysis of one such complex were isolated (see Figure 3). The donor ligand was shown to occupy the vacant apical position in $O{=}Cr(salen)^+$, filling the octahedral coordination about Cr. IR studies indicated that the formation of a complex between the donor ligand and the O=Cr(salen) weakens the oxo−chromium bond for the crystallized adduct complex (ca. 0.2 kcal for PyO) even though the Cr=O bond length was shortened by only 0.01 Å. It was noted that the chromium atom was pulled back toward the plane of the ligand oxygen and nitrogen atoms by 0.27 Å and that the Cr−O single bonds lengthened by 0.03−0.04 Å. The latter change resulted in an increase in the distance between the two salen oxygen atoms, i.e., the bite angle of the ligand widened. The torsion angle at the ethylene bridge decreased from 42.4° to 36.6° on binding of PyO. This was accompanied by a decrease in the dihedral angle between the phenyl planes from 21.4° to 15.5° (the analogous angle in $Cr^{III}(salen)(H_2O)_2Cl$ reported by Mabbs and co-workers[56] is 17.3°). The pyridine ring was orientated away from the axial methylene substituent of the diamine backbone, suggesting a steric clash. Consistent with this, complexes having a tetramethylethylenediamine bridge showed substantially lowered adduct formation constants. Ph_3PO adducts were consistently less stable than their PyO counterparts, and water was the least effective by a large margin.



oxo-6 triflate

Figure 3. ORTEP diagram of the adduct of the oxo−chromium(V) cation from **oxo-6** triflate with PyO. (Reprinted with permission from ref 55. Copyright 1985 American Chemical Society.)

Addition of donor ligands led to increased rates and yields in the stoichiometric epoxidations. The increase in yield was in part attributable to suppressed side-product formation. The effect of donor ligands on rates showed a saturation effect which was explained by reversible binding of the ligand with the O=Cr(salen) complex. In the case of triethylphosphine oxide ($OPEt_3$) an inner-sphere complex of $[Cr^{III}(salen)(OPEt_3)_2]^+$ could be isolated after the reaction. Since its rate of incorporation into $Cr^{III}(salen)^+$ was found to be to be very slow, it was deduced that Et_3PO must have formed an inner-sphere complex with the oxo complex.

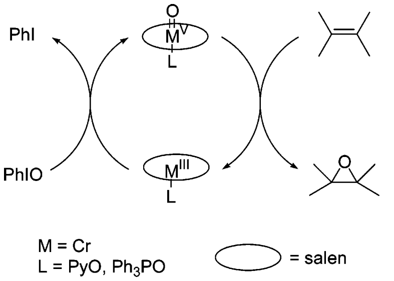
In catalytic epoxidations the effect of added donor ligand varied. Thus, addition of 0.5−1 equiv of PyO led to increased rates, but addition of more than 1 equiv led to deceleration. This was explained by the formation of $(PyO)_2Cr^{III}(salen)$, which is inactive to PhIO. Yields were increased slightly by addition of PyO.

Substituents on the salen ligand also affected the outcome of the reaction. Complexes bearing a tetramethylethylenediamine bridge gave higher conversions and less benzaldehyde as a side product than analogues derived from ethylenediamine. The former also had increased rates of reaction. The ability of ligand substituents to influence the reduction potentials of the $O{=}Cr(salen)^+$ complexes was also noted.[55]

2.1.3. Catalytic Cycle and Mechanism of the Reaction

On the basis of their experiments Kochi and co-workers postulated an oxygen rebound process for the catalytic cycle (see Scheme 1) similar to that proposed by Groves and co-workers[57] for metal(porphyrin)-catalyzed oxidations. The intermediacy of the O=Cr(salen) complex in the catalytic cycle is supported by the similarity of the products and side products obtained under catalytic conditions to those obtained from the reaction of alkenes with the isolated oxo complex (stoichiometric conditions). Kinetic experiments showed that the six-coordinate adducts formed between donor ligands and $O{=}Cr(salen)^+$ were much more reactive than their five-coordinate counterparts

Scheme 1. Cr(salen)-Catalyzed Epoxidation of Alkenes



(e.g., addition of 4-methylpyridine-*N*-oxide (100 equiv) increased the rate of norbornene epoxidation by 2 orders of magnitude), thus explaining the acceleration observed on addition of donor ligands. Due to the relatively slow ligand dissociation expected in chromium(III) complexes, the major chromium(III) species under catalytic conditions is expected to be Cr^{III}(salen)(L).

The mechanism of oxygen transfer proposed was electrophilic attack by the oxo−chromium complex on the double bond of the alkene. This was supported by a number of facts. Electron-rich alkenes were more reactive than electron-poor alkenes. Reactivity could be correlated with the substituent constants of a series of four substituted styrenes (using σ^+) and a series of three 5,5′-disubstituted complexes (using σ) (catalysts bearing electronegative 5,5′-chloro substituents were fastest). A Hammett correlation also existed between a series of 4 *p*-substituted pyridine *N*-oxides, but the slope was small, indicating only small changes in reactivity. This would be expected for coordination of donor ligand to the cationic chromium. In the presence of donor ligand no limiting rate due to saturation by alkene is observed, and therefore, precoordination of alkene to O=Cr(salen)$^+$ is absent or irrelevant under these conditions.

Analysis of the kinetics for the production of benzaldehyde from the reaction of styrene with O=Cr(salen)$^+$ in the presence of PyO and production of acetophenone from α-methylstyrene in the presence of picoline *N*-oxide led to the conclusion that at least one transient intermediate occurs after the rate-limiting step for oxidation. In the simplest case with styrene as substrate the intermediate forms either styrene oxide or, in the presence of PyO, a mixture of styrene oxide and benzaldehyde. The intermediate reacts with PyO to form benzaldehyde and formaldehyde with reduction of PyO and O=Cr(salen)$^+$. With α-methylstyrene as substrate the presence of an additional minor route to α-methylstyrene oxide was also implied from the kinetics.

Despite extensive mechanistic investigations Kochi and co-workers shied away from choosing a discrete structure for the intermediate. They recognized that the reaction showed some characteristics which would support a carbocationic intermediate such as **9,** but other characteristics indicated a closed intermediate. They proposed **10** and **11** as the two closest representative structures (see Figure 4), where the O−C$_\alpha$ bond must be sufficiently polarized (with some carbocation character) to allow (i) isomerization of *Z*-intermediates to *E,* (ii) rearrangements leading to phenylacetaldehyde from styrene, and (iii) attack by PyO leading to benzaldehyde formation.

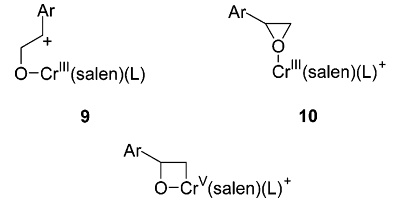


Figure 4. Structures tentatively proposed for reaction intermediate by Kochi and co-workers.[53]

2.1.4. Other Achiral Cr(salen)-Mediated Epoxidations

Only a handful of other reports on Cr(salen)-mediated achiral epoxidations have been published. Ganeshpure and Satish reported that the use of β-cyclodextrin as a phase-transfer agent, in the epoxidation of alkenes with PhIO catalyzed by [Cr(salen)(H_2O)$_2$]$^+$ in water/CH_2Cl_2, resulted in an increase in yields and rates.[58] Pasini and A. Cozzi reported the oxidation of styrene with a Cr(salen)/$NaNO_2$ system under both anaerobic and aerobic conditions.[59] Styrene oxide was detected, but yields were $<$1%. Adam et al. showed that 2-cyclohexenol is oxidized exclusively to 2-cyclohexenone by a Cr(salen) complex.[60] Koner et al. epoxidized norbornene with catalyst **1** and *tert*-butylhydroperoxide for comparison to immobilized versions.[61]

2.2. Mn(salen)-Catalyzed Achiral Epoxidations

Following their work on Cr(salen)-catalyzed epoxidations, Kochi and co-workers reported that Mn(salen) complexes also catalyzed the epoxidation of alkenes with PhIO as terminal oxidant.[62] The catalyst was used at 7 mol % wrt PhIO (the limiting reagent) and 3 mol % wrt alkene. They noted that the reaction was quicker than with Cr(salen) complexes and had a much broader substrate scope. Importantly, in sharp contrast to the Cr(salen) system, the relative reactivities of various substrates fell within a relatively narrow range (e.g., *E*- and *Z*-methylstyrene reacted at the same rate). However, irreversible degradation of the catalyst led to ever-decreasing concentration and so reduced the turnover.

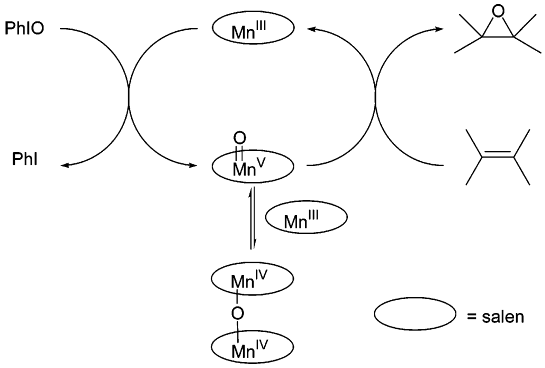
2.2.1. Nature of Active Species and Catalytic Cycle

Kochi and co-workers were unable to detect the species responsible for the epoxidation of alkenes. A transient species was detected, but it disappeared at a lower rate than the overall rate of epoxidation. To explain this and other experimental data they proposed an O=Mn^V(salen)$^+$ species as the reactive intermediate responsible for epoxidation and a μ-oxo−Mn^{IV}(salen) species as the detectable transient species (see Scheme 2). As can be seen, the catalytic cycle is similar to that proposed for Cr(salen) complexes.

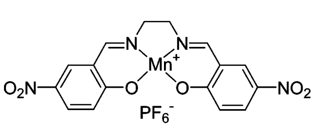
2.2.2. Effect of Additives and Ligand Structure

The redox properties of the Mn^{III}(salen)$^+$ complexes were strongly influenced by substituents on the salen,

Scheme 2. Catalytic Cycle for the Epoxidation of Alkenes Catalyzed by Mn(salen) Complexes Proposed by Kochi and Co-workers[62]



and the catalyst structure had a significant effect on yield with some substrates. The 5,5′-dinitro-substituted Mn(salen) **12** gave the best yields and was the most stereoselective in converting *Z*-alkenes to *cis*-epoxides and not *trans*-epoxides (*E*-alkenes were overwhelmingly converted to *trans*-epoxides in all cases).



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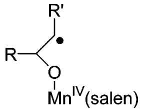
Kochi and co-workers reported that addition of pyridine or PyO (5−10 equiv wrt catalyst) led to increased yields with cyclooctene but had little or no effect on the yields of electron-rich alkenes such as *Z*-stilbene or *Z*-β-methylstyrene.[62] There was also no effect on the stereochemistry of the epoxide obtained, but formation of carbonyl side products was suppressed (similar results have since been reported by other workers[63,64]). Skarżewski et al. reported their results on the effects of additional ligands on Mn(salen) catalysts in 1995.[65] They found that the σ-donating power and the lipophilicity of the ligand both made positive contributions to the catalytic performance of the Mn(salen) catalyst. Their UV studies indicated that added *N*-oxides were bound to the Mn^{III}(salen) complexes. Increased amounts of *N*-oxide decreased the production of carbonyl side products in the epoxidation of styrene and changed the ratio of *cis*/*trans*-epoxide produced from *Z*-stilbene. Conductometric measurements showed that chloride counterion was displaced on addition of *N*-oxide and led to cationic complexes. The addition of *N*-oxides accelerated the decomposition of the species formed on addition of NaOCl to the Mn(salen) complex (thought to be a Mn^{IV}(salen)−μ-oxo dimer) and led to cationic species.

2.2.3. Mechanism of Oxygen Transfer

With regard to the mechanism of oxygen transfer from the proposed O=Mn^V(salen) species, a radical intermediate **13** was postulated to account for the observed reactivity (which included production of *trans*-epoxides from *Z*-alkenes, allylic oxidation of cyclohexene, attack on cyclohexane, and a Hammett ρ value of only −0.3 for a series of substituted styrenes).[62] To account for the production of certain side products, such as phenylacetaldehyde from styrene epoxidation (as seen in the Cr(salen) series), it was postulated that a cationic intermediate might arise in a minor pathway.[62]



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2.2.4. Alternative Stoichiometric Oxidants

Kochi and co-workers[66] subsequently reported the Mn(salen)-catalyzed oxidation of alkenes with alkyl hydroperoxides as terminal oxidants (4 mol % catalyst wrt oxidant and 2 mol % wrt alkene). The presence of pyridine bases or imidazole as cocatalysts was necessary for reasonable activity, while donor ligands such as PyO had no effect. A variety of alkenes were epoxidized under these conditions with reactivities lying in a narrow range (*E*-β-methylstyrene was just 10 times more reactive than 1-octene), as for the previously disclosed system using PhIO as terminal oxidant (see above). The two major products of the oxidation of cyclohexene were cyclohexene oxide and cyclohexenyl *tert*-butyl peroxide. Only production of the latter was suppressed by conducting the reaction in the presence of ionol (2,6-di-*tert*-butyl-*p*-cresol) as a radical inhibitor. Two pathways were deduced to be in operation. A free-radical process was responsible for the production of peroxides, while the production of epoxides was due to oxidation by an O=Mn(salen)$^+$ species. Pyridine and imidazole were implicated in the generation of this species, possibly functioning as both Brønsted bases and coordinating ligands. Dixit and Srinivasan reported similar results in their studies on the epoxidation of cyclohexene and cyclooctene with a Mn(salen) complex.[67]

2.2.5. Other Mn(salen)-Catalyzed Achiral Epoxidations

Oki and Hodgson crystallized and tested the efficiency of three complexes in the epoxidation of cyclohexene.[68] Antunes and co-workers reported the epoxidation of α-pinene and limonene.[69,70] Du and Yu reported the synthesis of Mn(salen) complexes where the two salicylaldehyde-derived moieties are different (labeled 'unsymmetrical' Mn(salen) complexes).[71,72] These complexes showed good activity in epoxidation reactions. Das and Cheng reported the crystal structure of a Mn(salen) bearing 3,3′-formyl substituents which demonstrated moderate activity as an epoxidation catalyst.[73] Qin and co-workers observed an increase in the epoxidation activity of Mn(salen) complexes bearing crown ethers on a diiminobenzene backbone.[74] The catalyst concentration has been shown to affect the selectivity for epoxide.[75]

Agarwal et al. reported evidence to suggest that substrate precoordination was not important in the epoxidation mechanism.[63] In 1989 Breslow et al. reported attempts to precoordinate substrates to Mn(salen) complexes modified with pyridyl groups in the presence of Cu^{2+} ions.[76] Substrates bearing pyridyl moieties to allow coordination to the catalyst via copper–pyridyl complexation showed dramatic increases in rates relative to noncoordinating substrates. Later studies using cyclodextrins to precoordinate the substrate were less successful.[77] Adam et al. reported evidence that demonstrates that precoordination is important in the epoxidation of allylic alcohols by Mn(salen) complexes.[60,78]

2.3. Summary and Outlook

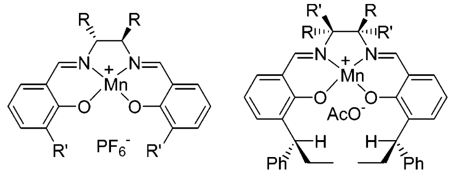
Kochi and co-workers demonstrated that both Cr(salen) and Mn(salen) complexes were effective catalysts for the epoxidation of alkenes with PhIO as terminal oxidant. In both cases the proposed active epoxidizing species was an $O{=}M^{V}(salen)^{+}$ complex, and in the chromium case this species could be isolated and used as a stoichiometric oxidant. The substituents on the salen ligand could be tuned to influence the reactivity of the metal–salen complexes. Additives such as PyO capable of acting as oxygen-donor ligands were shown to influence the reaction in both cases. An oxygen rebound mechanism was proposed for both systems. The alkene reacted with the metal–oxo species in both cases to form an intermediate. A build-up of positive charge on the alkene occurred with chromium, while in the manganese case a radical intermediate was proposed. Mn(salen) showed a broader substrate scope than Cr(salen). The use of alkylhydroperoxides as terminal oxidants with Mn(salen) was also reported. With this research reported, the stage was now set for an asymmetric variant to be discovered.

In light of the developing paradigm of 'ligand accelerated catalysis'[79] and their previous experiences working with Prof. Sharpless, it is not that surprising (in hindsight) that both Katsuki and Jacobsen saw the potential to develop an asymmetric version of the Kochi catalysts. These systems have the particularly attractive feature that the metal–ligand complex is not formed reversibly, as is the case in the Sharpless AE and AD systems. Thus, there is no background ligand-free reaction catalyzed by the metal, and the number of different metal complexes that can exist in solution is greatly reduced. Thus, the rate acceleration for any particular metal–ligand complex that is selective does not need to be so great in order to obtain reasonable enantioselectivities. In addition, stereogenic centers can be positioned much closer to the metal center than in the related porphyrin systems—this would be expected to improve the transfer of chiral information to the product. Finally, from a synthetic point of view, a wide range of metal-(salen) complexes is readily accessible and the ligand structure is easily varied.

3. Mn(salen)-Catalyzed Asymmetric Epoxidation

In 1990 Jacobsen and Katsuki independently reported Mn(salen)-catalyzed AEs of unfunctionalized alkenes using iodosylarenes (ArIO) as stoichiometric oxidants.[7,8] Before dealing with mechanistic aspects, it is appropriate to review how the field developed and what factors must be accounted for by a complete description of the reaction.

Chart 2. Some of the First Catalysts Developed by Jacobsen and Katsuki for the AE of Unfunctionalized Alkenes



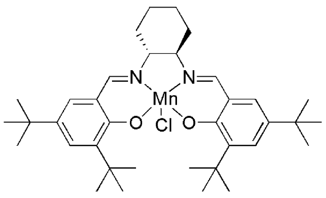
14: R = Ph, R' = H
15: R = Ph, R' = *t*Bu
18: R = Ph, R' = Me

16: R = Ph, R' = H
17: R' = Ph, R = H

3.1. Initial Results and Early Modifications

Using complexes **14** and **15** (1–8 mol %), Jacobsen and co-workers[7] reported that monosubstituted-terminal, trisubstituted, and *cis*-alkenes[80] were epoxidized in good to excellent ee (57–93%), while *trans*- and 1,1′-disubstituted-alkenes were epoxidized in low ee (20–33%). The 'side-on approach' model (see section 3.10), originally proposed by Groves for metal-(porphyrin) catalysts,[81,82] was used to rationalize the observed selectivity. Katsuki and co-workers[8] reported **16**–**18** as catalysts (9 mol %) for the AE of dihydronaphthalene and *E*- and *Z*-β-methylstyrene, Chart 2. The chirality of the diamine backbone controlled the sense of the ee in those cases where it was examined. Of Katsuki's catalysts, catalyst **17** gave the best enantioselectivities (40–50% ee). In the presence of added 2-methylimidazole, the result of 50% ee for the AE of *E*-β-methylstyrene represented the highest ee for a metal-catalyzed epoxidation of an unfunctionalized *E*-alkene. 2-Methylimidazole did not improve results with the other substrates. A radical mechanism, as previously proposed by Kochi,[62] was invoked[8] to account for the production of *trans*- and *cis*-β-methylstyrene oxide from *Z*-β-methylstyrene. The important influence of the substituents at the 3,3′-positions of the ligand on degree of enantioselectivity could be clearly seen in these initial reports. Iodosylarenes were used as the source of oxygen in these reports, but Jacobsen subsequently reported the use of bleach as stoichiometric oxidant, making the AE reaction more practical.[83]

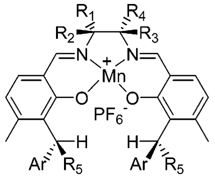
Reports detailing the effectiveness of complex **19** (now known as Jacobsen's catalyst)[84,85] in the catalytic AE of a range of *cis*-alkenes[80] (89–98%) followed.[86–90] Subsequently, its substrate scope has been shown to include conjugated *Z*-enynes (yielding predominantly *trans*-epoxides),[91] acyclic conjugated polyenes,[92] cyclic dienes,[93–96] heterocyclic enamines,[97,98] cinnamate esters,[99,100] conjugated trisubstituted alkenes,[87,101,102] enol ethers,[103,104] some tetrasubstituted conjugated alkenes,[105] and α-pinene.[69,106,107]



(R,R)-19

For some substrates only moderate,[108,109] unexpected,[110] or unsatisfactory[111–116] results have been

Chart 3



20: Ar = Ph, R_1, R_3 = Ph, R_2, R_4 = H, R_5 = Et
21: Ar = Ph, R_2, R_4 = Ph, R_1, R_3 = H, R_5 = Et
22: Ar = Ph, R_1, R_2, R_3, R_4 = H, R_5 = Et
23: Ar = Ph, R_1, R_2 = Me, R_3, R_4 = H, R_5 = Et
24: Ar = Ph, R_1, R_2, R_3, R_4 = Me, R_5 = Et
25: Ar = Ph, R_1, R_3 = Ph, R_2, R_4 = H, R_5 = Me
26: Ar = Ph, R_2, R_4 = Ph, R_1, R_3 = H, R_5 = Me
27: Ar = 4-t-BuC_6H_4, R_1, R_3 = H, R_2,R_4 = -$(CH_2)_4$-, R_5 = Et

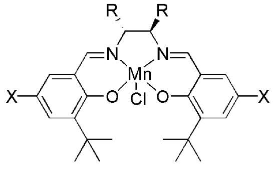
reported (see also section 3.6 for AE of *trans*-alkenes[80]). The poor performance of terminal alkenes such as styrene was overcome by the development of a low-temperature protocol[117,118] using *m*CPBA as oxidant (see section 3.5 for more detail). Section 5 shows representative epoxides which can be accessed by M(salen)-catalyzed AE. The ee of scalemic epoxide produced by Mn(salen)-catalyzed AE has been improved by subsequent kinetic resolution in some cases.[119,120] Attempts to use Jacobsen's catalyst and other Mn(salen) complexes in the kinetic resolution of various alkenes by diastereoselective epoxidation have met with moderate success[95,121−126] (better results have been obtained with other Mn(salen) catalysts,[127] see section 3.4). The ligand structure is now considered to be in the category of 'privileged'.[128] A stereochemical model for predicting the configuration of the major epoxide enantiomer formed has been detailed as well as an analysis of the substrate properties that should lead to high ee's.[100,101] Jacobsen's catalyst has been applied to the syntheses of a range of biologically active compounds[92,129−139] including Diltiazem and the side chain of Taxol.[99,100] Industrial requirements[133] prompted efforts to reduce the catalyst loading (see sections 3.7 and 3.8 for details). Industrially applicable syntheses of Jacobsen's catalyst have also been published,[140−142] and it is commercially available.[143,144]

Katsuki and co-workers continued their efforts to improve the catalyst by combining elements of chirality at the 3,3′-positions and the diimine backbone with groups at the 4,4′-positions (see Chart 3 for structural examples).[145−154] They were able to improve the enantioselectivity of their epoxidation catalysts with some substrates using **20** and **21**.[145−147] Using these catalysts (ca. 2 mol %) the sense of the ee of *cis*-epoxides was controlled by the chirality of the diamine backbone (as before); however, for *E*-alkenes the chirality at the 3,3′-positions was dominant. Catalysts **22**−**24**, bearing chirality at the 3,3′-positions only, were also capable of inducing moderate ee's.[148] Catalyst **23** showed very similar levels of asymmetric induction to **21** in the AE of *E*-stilbene and *E*-β-methylstyrene. For the AE of 1,2-dihydronaphthalene, **21** gave a considerably better ee than **22**−**24**. This reinforced the earlier observations on the contributions of the different elements of chirality to the sense asymmetric induction. Donor ligands were again shown to be capable of altering enantioselectivities and yields.[146,147] High ee's were achieved in the epoxidation of 2,2′-dimethylchromenes with catalysts **26** and **27**.[149−152,154] Catalyst **27** also gave the highest ee up to that time for an unfunctionalized *trans*-alkene[80] (*E*-stilbene gave *trans*-stilbene oxide in 62% ee).[150] This suggested that high ee's might be possible in the AE of *trans*-alkenes by the same Mn(salen) complex capable of generating high ee's in the AE of *cis*-alkenes.

3.2. Catalyst Tuning

In 1991 Jacobsen and co-workers reported on the electronic tuning of Mn(salen) catalysts for AE.[155] Using catalysts **28a**−**e** and **29a**−**e** for the AE of three *cis*-alkenes **30**−**32**,[80] they obtained a correlation between the ee obtained and the substituent constants of the 5,5′-substituents (σ_p) (see Figure 5 and Chart 4). In the most extreme case with 2,2-dimethylchromene **30** the ee varied from 22% using **28e** to 96% using **28a**. The ability to effect such dramatic changes in ee using simple changes in electronic

Chart 4



28: R = Ph;
29: R,R = -$(CH_2)_4$-

a: X = OMe
b: X = Me
c: X = H
d: X = Cl
e: X = NO_2
f: X = O*i*-Pr
g: X = O*t*-Bu
h: X = OTMS
i: X = OTES
j: X = OTIPS

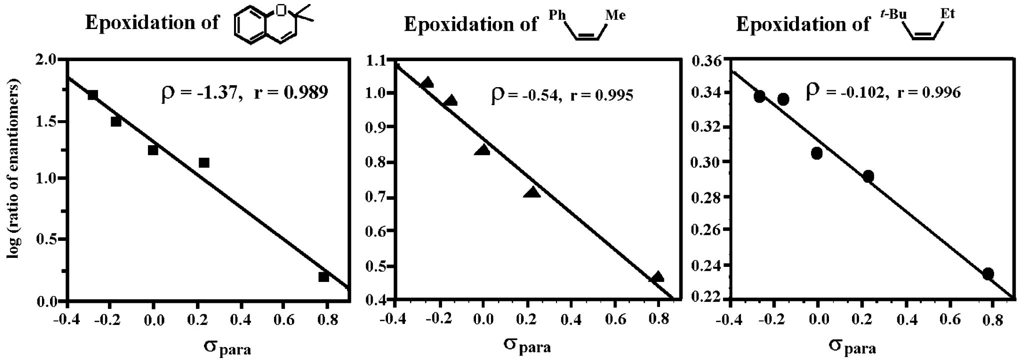
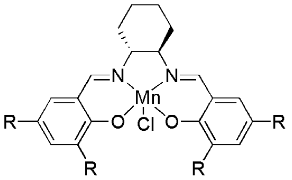


Figure 5. Hammett plots depicting enantiomeric composition of epoxides generated by oxidation of the indicated alkenes by catalysts **28a**−**e**: ee ranges 2,2-dimethylchromene **30**, 22−96%; *Z*-β-methylstyrene **31**, 49−83%; *Z*-2,2-dimethylhex-3-ene **32**, 26−37%. (Reprinted with permission from ref 155. Copyright 1991 American Chemical Society.)

structure of the catalyst is highly impressive. The results were rationalized using the Hammond postulate. Changing the 5,5′-substituent of the ligand altered the reactivity of the O═Mn(salen)$^+$ species responsible for oxo transfer to the alkene. According to the Hammond postulate the milder oxidant formed from **28a** will have a more product-like transition state (TS) than the more reactive oxidant formed from **28e**. A more product-like TS should have more nonbonded interactions between the substrate and the oxidant. In the absence of substrate precoordination to the catalyst and with oxo transfer to the substrate as the irreversible enantiodetermining step, the O═Mn(salen)$^+$ species formed from **28e** would be expected to be a more selective oxidant than the oxidant formed from **28a**. The evidence to support this rationalization was provided in 1998 in the form of detailed mechanistic studies.[156] Although in general a strategy which makes the catalyst less reactive would be detrimental to its practical use, it should be noted that the turnover-limiting step in this system is transfer of oxidant into the organic layer (see section 3.7 for details). Interestingly, these results predict that, on the basis of electronic effects only, methoxy substituents at the 5,5′-positions should induce higher enantioselectivity than *tert*-butyl ones. Since this is not the case,[36] one could infer that *tert*-butyl groups must have an added steric role at the 5,5′-positions, such as a blocking role suggested previously by Jacobsen and co-workers (see section 3.10). On the basis of computational studies, Cavallo and H. Jacobsen suggested that groups at the 5,5′-positions should only have an electronic effect on the first C−O bond-forming reaction.[157] It should be noted that in contrast to Jacobsen's results with **28** and **29**, Katsuki and co-workers[158,159] noted no improvement in ee on adding methoxy groups to their ligands (see section 4.2 for similar tuning studies in Cr(salen)-mediated AE).

Feichtinger and Plattner supported Jacobsen's analysis with their mass spectrometric studies on the stability of various O═Mn(salen) species.[160] Cavallo and H. Jacobsen recently published further computational studies on the effects of substituents at the 5,5′-positions on the salen ligand.[161] Their analysis concurs with that of Jacobsen and co-workers, finding that the calculated Mn═O bond strength and degree of formation of the first C−O epoxide bond correlated with the substituent constants, although it should be noted that they used σ^+_{para} and not σ_{para} in their Hammett correlations.

Further catalyst tuning by Jacobsen and co-workers led to the synthesis of a series of catalysts bearing bulky electron-donating groups in the 5,5′-positions, **28g**, **28j**, and **29f**−**j**.[93,101,105] Some of these gave improved enantioselectivity in the AE of cyclic dienes[93] and some conjugated trisubstituted and tetrasubstituted alkenes.[101,105] The epoxidation of some tetrasubstituted alkenes in high ee was achieved only by screening a range of Mn(salen) catalysts,[105] and no one catalyst proved optimum for all tetrasubstituted substrates, demonstrating that electronic tuning is not the only consideration. The groups of Kim[162] and Bu[163] have since used this strategy. The latter replaced the *tert*-butyl groups of Jacobsen's catalyst with *tert*-pentyl groups, resulting in catalyst **33**, which showed slightly improved enantioselectivities in the AE (10 mol % catalyst) of various alkenes (presumably as a result of steric and electronic effects).



33: R = *tert*Pentyl
34: R = Br
35: R = Cl

Meunier and co-workers[164,165] reported that yields obtained in epoxidations with Jacobsen's catalyst (using NaOCl or $KHSO_5$ as terminal oxidant) were higher than those obtained using tetra-halogenated complexes **34** and **35**, contrary to what would be expected from earlier work[62] (with PhIO as oxidant). Jacobsen's catalyst was suggested to be either more robust under the reaction conditions or more reactive. Similar results were obtained by Freire and co-workers[166] for a range of complexes but only when using NaOCl as oxidant—the opposite was true when using PhIO as oxidant, but the range of yields was smaller. Interpretation of the results of Freire and co-workers is complicated by the fact that some of the complexes were only partially soluble in the reaction medium and that not all complexes had the same counterion. Freire and co-workers suggest their results might support the operation of two mechanisms, each of which is favored by a different oxidant (see sections 3.8 and 3.8.2 for more on this topic). They also noted that the presence of bulky substituents on the diimine backbone usually improved yields, regardless of oxidant. This could be due, in part or in full, to a buttressing effect (see below) and/or prevention of catalyst degradation. In sharp contrast to the behavior of other Mn(salen) complexes, Plattner and co-workers[167] were unable to detect μ-oxo dimers involving Jacobsen's catalyst in the presence of donor ligand. We suggest here that the *tert*-butyl groups on Jacobsen's catalyst may be hindering the formation of μ-oxo dimers and so give rise to a higher effective concentration of catalyst in solution compared with other less bulky Mn(salen) complexes. The effect of buttressing groups in preventing the formation of μ-oxo dimers of oxo−ruthenium porphyrin complexes has been demonstrated.[168]

3.3. Mn(salen) Complexes with Alternative Architectures

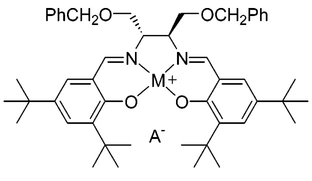
Since the first reports of Mn(salen)-catalyzed AE a range of Mn(salen) complexes has been reported, varying from the very simple to the complex. Burrows and co-workers reported some poor results with complexes bearing TBDMS groups at the 3,3′-positions.[169] Ahn and co-workers also studied the use of bulky groups at the 3,3′-positions and found that using groups bulkier than the *tert*-butyl group could improve the ee but if the group at the 3,3′-position was too big it could be detrimental to the ee.[170] Cheng et al. briefly reported results with 3,3′-methoxy-substituted complexes.[171] Poor results were reported with various unsubstituted and 4,4′-substituted homogeneous catalysts, some of which were later heterogenised.[165,172−175] Seebach and co-workers reported monomeric Mn(salen) complexes with dendritic salen ligands and noted that the dendritic branches did not affect catalytic performance in a negative way.[176] Pozzi and co-workers pioneered the synthesis of perfluorinated Mn(salen) complexes[177] and their testing in AE reactions under fluorous biphasic conditions.[178,179] Although early attempts had limited application, second-generation fluorous complexes showed improved scope and some recyclability.[180,181] Kureshy and co-workers introduced catalysts bearing tertiary amino side chains at the 5,5′-positions with the aim of introducing phase-transfer capabilities into the catalyst.[182−185] These showed very high yields and activity in AE with either urea−H_2O_2 or NaOCl as oxidants. With some chromenes ee's and yields of $>99\%$ can be achieved at loadings as low as 0.4 mol %. Murahashi et al.[186] reported the AE of 2,2′-dimethylchromene in 93% ee and 50% yield using a Mn(salen) complex bearing a binaphthyl strapping unit similar to those attached in some porphyrin systems.

In addition to Katsuki and co-workers (see section 3.1) several other groups have tested the effect of adding additional chirality at the 3,3′-position. Kim et al. claimed good preliminary results with catalysts synthesized by linking the 3,3′-positions via a chiral diimine to create a macrocyclic salen ligand with an extra 2-fold axis of symmetry.[187] Pedro and co-workers[188] reported that Mn(salen) complexes derived from a sesquiterpene salicylaldehyde derivative gave good yields but low ee's. Tang and co-workers obtained good results by attaching amino acid groups at the 3,3′-positions via an imino linkage.[189] They found that stereoinduction was controlled by the diimine backbone in the case of both *Z*- and *E*-substrates. Introduction of axial chirality into the salicylaldehyde part of the complex is discussed in section 3.4.

The synthesis of Mn(salen) complexes where the two salicylaldehyde-derived moieties are different (labeled 'unsymmetrical' Mn(salen) complexes) has been claimed by several groups[71,190−193] (see section 4.4 for the Cr(salen) analogues). Pietikäinen and Haikarainen[192] reported the synthesis of unsymmetrical Mn(salen) complexes similar to the achiral unsymmetrical complexes of Yu and co-workers[71,72] (see section 2.2.5). These syntheses are confined to the use of an aromatic ketone rather than a salicylaldehyde as a source of one of the phenoxy moieties, and only moderate enantioselectivities were observed. Kim and Shin reported the synthesis of unsymmetrical complexes which were reported to give good to moderate enantioselectivities in the AE of styrene and α-methylstyrene.[190,194] The method of Lopez et al.,[195] which was used to synthesize the salen ligands, has been found to be unrepeatable by two independent groups,[196,197] and indeed, the reported characterization of the ligands[194] is not consistent with the structures given. Reger and Janda reported results obtained with an unsymmetrical Mn(salen) complex that were very close to those reported for symmetrical analogues.[198] Nielsen and Gothelf reported the synthesis of unsymmetrical *p*-acylthio-(phenylacetylene)-substituted salens from a diphenyldiamine backbone in low yield.[191] These were used to form Mn(salen) complexes, which were tested in the epoxidation of *Z*-β-methylstyrene, although no characterization for the Mn(salen) complexes was given. The ee's for the *cis*-epoxide were similar to those obtained with the symmetrical tetra-*tert*-butyl-substituted catalyst and those of the *trans*-epoxide slightly lower. The diastereoselectivities were slightly better (favoring *cis*-epoxide). Bigi et al. reported the use of an unsymmetrical complex (which was subsequently attached to a solid support) which gave slightly reduced ee and yield in the AE of 1-phenylcyclohexene.[193]

In addition to the diimine backbones derived from cyclohexanediamine and stilbene diamine, a variety of other diamine sources have been used. For further work on this topic by Katsuki and co-workers, see section 3.4, and for work by Jacobsen and co-workers, see section 3.6. Reddy and Thornton[199] synthesized a Mn(salen) complex with a pyrrolidine-based diimine backbone, which was shown to oxidize enol ethers giving α-hydroxy carbonyl compounds in moderate ee. Meunier and co-workers reported the synthesis of a Mn(salen) complexes with a 2,2′-diamino-1,1′-binaphthalene-derived diimine backbone which had poor activity as epoxidation catalysts.[165] Scott and co-workers also reported the synthesis Mn(salen) complexes from an axially chiral diamine[200] which showed poor activity in initial screening. X-ray crystallography showed that the highly nonplanar complexes adopted either a *cis*-β or a *cis*-α structure. Daly and Gilheany reported the attempted synthesis of metal(salen) complexes derived from enantiopure *trans*-cyclopentane- and cyclobutane-1,2-diamine (see section 4.4 for chromium analogues).[201] They hoped that by increasing the dihedral angle at the diimine backbone of the salen they could synthesize complexes with more deeply 'stepped' conformations, which might be more selective (see section 3.10 for more on catalyst conformations). Only the cyclopentane-derived salens gave a well-defined Mn(salen) complex. When compared to its cyclohexane analogue, a very slight increase and a slight decrease in ee were noted, respectively, with *E*- and *Z*-β-methylstyrene as substrates in AE reactions. Vogt et al. reported epoxidations of styrene ($<12\%$ ee) with salen-type complexes bearing a 1,2,2-trimethyl-1,3-diiminopentane backbone.[202]

Scheurer et al. reported the synthesis and use of M(salen) complexes with diimine backbones derived from L-tartaric acid of which **36** and **37** are examples.[203] They found that in the epoxidation of *Z*-alkenes, **37** displayed the opposite sense of enantioselectivity than that observed with cyclohexane diamine- or stilbene diamine-derived manganese catalysts with analogous stereochemistry on the diimine backbone. No reason was suggested for the reversal of stereochemistry observed from what might have been expected. Fuchs and co-workers described the synthesis and testing of similar catalysts which gave low ee's in the epoxidation of indene but did not mention the sense of the enantioselection.[204] Liao et al. reported that Mn(salen) complexes, with diimine backbones derived from succinic acid, give good yields in the epoxidation of dihydronaphthalene, but ee's were low.[205]



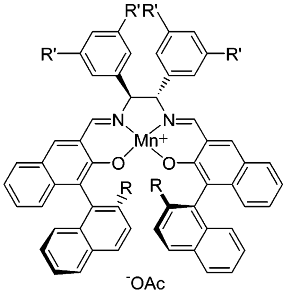
36: M = Cr; A = PF$_6$
37: M = Mn; A = Cl

Paul et al. reported the synthesis and preliminary testing of Mn(salen) complexes similar to Jacobsen's catalyst bearing an inositol-derived diamine backbone in 2002.[206] However, the catalysts showed poor selectivity and did not have the enhanced water solubility expected. In the same year Yan and Klemm reported their carbohydrate-based Mn(salen) complexes which also showed poor selectivities.[207,208] Recently, Ruffo and co-workers reported improved carbohydrate-based Mn(salen) catalysts.[209]

It can be seen that Mn(salen) complexes with a wide variety of structural motifs have been used in AE reactions, but ultimately very few of the catalysts in this section are significantly better than Jacobsen's catalyst. Some substructure 'families' may warrant further exploration, and some may warrant consideration in instances where commercially available Jacobsen's catalyst does not give rise to satisfactory results.

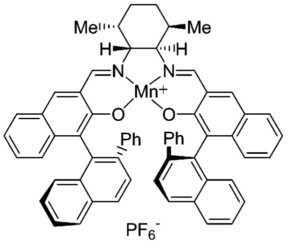
3.4. Katsuki's Second-Generation Catalysts

In 1993 Katsuki and co-workers introduced their second-generation catalysts bearing axial chirality at the 3,3′-positions (e.g., **38** and **39**).[210] Complex **39** (2.5 mol %) epoxidized *cis*-alkenes[80] in high ee (86−91%) in the presence of PyO. This new design motif was improved with the introduction of **40** and **41** for AE in the presence of PyO.[154,211,212] All catalysts (2.5 mol %) were designed on the basis of the proposed alkene approach to the metal−oxo bond along the Mn−N bond axis (see section 3.10 for more on approach trajectories). Record ee's in the AE of several *cis*-conjugated alkenes (up to 98% ee for some 2,2-dimethylchromene derivatives) were realized with **41**, thus supporting the approach hypothesis that informed the design. Its scope has been shown to include *cis*-enynes, conjugated trisubstituted alkenes,[213] enol ethers[214] (giving hydroxy acetals), and 1,3-dicycloalkadienes, and even some dialkyl-substituted *Z*-alkenes give moderate ee's.[158] Catalyst **41** has been applied to the synthesis of a variety of pheromones,[215,216] a quinaldic acid macrocyclic system (where Jacobsen's catalyst gave only poor results),[113] as well as some chiral bipyridine and biquinoline ligands.[217] Attempted kinetic resolutions (by epoxidation) have met with mixed results.[122,127] The successful AE of *trans*-alkenes[80] by second-generation catalysts[218] is discussed in section 3.6. Although complex **41** has been demonstrated to be a highly effective catalyst for AE, its availability remains a drawback to its widespread use. Section 5 shows representative epoxides which can be accessed by M(salen)-catalyzed AE.

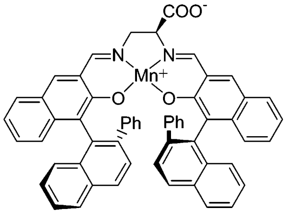


38: R, R' = H
39: R = Me, R' = H
40: R = Ph, R' = H
41: R = Ph, R' = Me

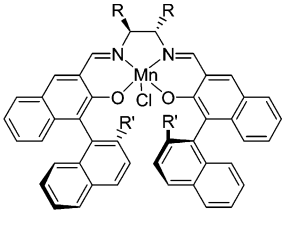
With **42** further rational improvements, based on the trajectory of alkene approach, were made (see section 3.10).[219] The more readily synthesized complex **43** gave unusually high turnover numbers (TONs) of up to 9200 and ee's up to 99% in the AE of several dimethylchromenes.[220] Prolonged reaction times were needed for some reactions, but the catalyst could be recycled and reused—demonstrating unusual stability under reaction conditions. The effectiveness of this catalyst has been rationalized in terms of the O=Mn(salen) species having a nonplanar salen conformation (see section 3.10).[221,222] Recently, Ahn et al. introduced **44** and **45** as efficient catalysts (4 mol %) for the AE of a variety of alkenes.[223] These complexes gave similar levels of enantioselectivity (in some cases higher) and yields as other second-generation catalysts but are synthetically slightly more accessible than, for example, **41** and **42**. Takata and co-workers reported similar binaphthyl-derived Mn(salen) complexes which give epoxides in very low ee, showing the importance of the appropriate choice of substituents and diamine.[224]



42



43


R' = -OOC-*t*-Bu
44: R = $-(CH_2)_4-$
45: R = Ph

3.5. Stoichiometric Oxidants

The main oxidants used in Mn(salen) AEs are iodosylbenzene (PhIO) and, the more practical, NaOCl (both of which had been used in metal(porphyrin) epoxidations). The NaOCl solution should have a high pH.[83,225] A variety of other oxidants have also been used. The usefulness of iodosylarenes is hampered by their insolubility in organic solvents, although use of soluble iodosylarenes has been reported recently.[226] Katsuki and co-workers[158] reported the use of NaOCl solutions at −18 °C by saturating them with NaCl to depress the freezing point (although lowering the reaction temperature does not always lead to higher ee's). Cao and Xi reported the use of $Ca(OCl)_2$ as terminal oxidant in the monophasic epoxidation of α-pinene using ethyl acetate or *t*-BuOH as solvent.[227] The use of LiOCl as terminal oxidant in AEs has been reported by Ahn and co-workers, and improved reaction rates relative to NaOCl were noted.[170] In most cases NaOCl is still the oxidant of choice; however, if, for example, a substrate or product is sensitive or water soluble, there are other viable options.

Mukaiyama and co-workers showed that molecular oxygen and peracetic acid can be used as the terminal oxidants in the AE of alkenes with Jacobsen's catalyst and related Mn(salen) complexes.[228] Pivaldehyde is required in the O_2 system, while unusually both oxidants require either *N*-methyl-imidazole (*N*-Me-Imd)[229] or PyO[230] (see section 3.7 for details of this).[106,107] Reasonable yields and ee's (60−92%) were reported. Variation of catalyst concentration had a significant effect on ee's.[230] The use of in-situ-generated peroxycarboxylic acids as terminal oxidants has also been reported.[231] Woodward and co-workers obtained ee's of up to 60% using a combination of Jacobsen's catalyst, molecular oxygen, and alkyl-2-oxocyclopentanecarboxylates.[232] Zsigmond et al. also reported the use of molecular oxygen as oxidant in a Mn(salen)-catalyzed oxidation of styrene, but epoxides were only minor products in their system.[233] Lee et al. reported preliminary results with a dichlorocarbene/molecular oxygen system as terminal oxidant.[234] Sobkowiak and co-workers reported a Mn(salen)/*t*-BuOOH/O_2-based system for the oxidation of cyclohexene in which epoxide is formed along with significant amounts of ketone and alcohol.[235] Electrochemical alkene epoxidation can be achieved using Mn(salen), usually with dioxygen as terminal oxidant.[236−241]

In the case of terminal alkenes such as styrene the pathway that leads to *trans*-epoxides from *Z*-alkenes was shown to give rise to enantiomeric leakage.[117] Suppression of this pathway was necessary to gain access to enantiopure epoxides from terminal alkenes. Jacobsen and co-workers reported that carrying out anhydrous epoxidations with Mn(salen) catalysts at −78 °C using *m*CPBA as oxidant and *N*-methylmorpholine-*N*-oxide (NMO) as an additive led to significant improvements in enantioselectivity for a range of alkenes including styrene derivatives.[117,118] These improvements were attributed to suppression of this pathway and an increase in the selectivity of the first C−O bond-forming step at lower temperatures. For styrene derivatives a catalyst bearing a stilbene diamine-derived diimine backbone was best in most cases. It should be noted that in this monophasic system the reaction is extremely rapid. Jacobsen and co-workers conservatively estimated $t_{1/2} = 30$ s for the epoxidation of indene.[156] In biphasic systems the rate-limiting step is transfer of oxidant into the organic layer (see section 3.7 for detail). They also tried magnesium monoperoxyphthalate, *tert*-butylhydroperoxide, and Oxone® as terminal oxidants, but these were too slow under the desired conditions (anhydrous solvent and low temperature). Katsuki and co-workers reported the use of bis(trimethylsilyl)peroxide with *N*-Me-Imd and NH_4PF_6 as additives.[152] Woodward and co-workers explained the inability of cumyl hydroperoxide to function as a terminal oxidant in terms of disproportionation of the hydroperoxide and formation of an inactive $[(salen)Mn^{III}OMn^{IV}(salen)]^+$ dimer.[144] Workers at Bristol-Myers Squibb have described the scale-up of Jacobsen's method taking into account safety issues concerning the use of *m*CPBA.[242]

Various successful H_2O_2-based systems, usually involving nitrogen heterocycles as additives, have been reported.[152,183,231,243−249] These can be particularly useful for sensitive epoxides. The use of carboxylate salts as additives[245] and certain solvent mixtures[231,244−248] has been reported to be advantageous in some of these H_2O_2-based systems. Kureshy et al. reported that with their urea−H_2O_2 (UHP) system the rate-limiting step is oxidation of the Mn(salen) species.[183]

Meunier and co-workers reported the bleaching of the catalyst by various oxidants, including $KHSO_5$,[164] over the course of the reaction. Gurjar et al. noted that acetonitrile/water is the best solvent system to use in conjunction with Oxone®.[250] Pietikäinen reported successful use of ammonium and phosphonium monoperoxysulfates which gave good yields of epoxides and ee's in excess of 90% in the AE of trisubstituted and *cis*-alkenes.[80,251,252] Adam and co-workers reported that dimethyldioxirane can be used as terminal oxidant in the AE of isoflavones and dimethylchromenes (up to 93% ee) using Jacobsen's catalyst in neutral conditions.[253−256] Other workers have also made use of dioxiranes.[139,202] In addition, Pietikäinen also reported the use of periodates as suitable oxidants.[257]

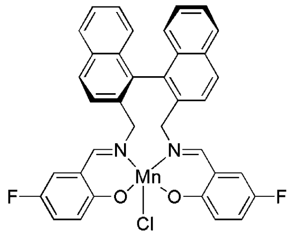
Several groups have drawn attention to the fact that the choice of terminal oxidant can significantly affect the yield and selectivity of the reaction. Jørgensen and co-workers showed that the regioselectivity and enantioselectivity in the mono-epoxidation of 1,3-dienes by Mn(salen) complexes are dependent on the choice of oxidant.[258,259] Katsuki and co-workers noted differences in ee and yield depending on whether NaOCl or PhIO was used.[213] Jacobsen and co-workers reported that choice of oxidant can affect the diastereoselectivity observed in the AE of *Z*-β-methylstyrene.[260] Linde et al. also noted different outcomes in the epoxidation of substrates that act as radical traps depending on choice of oxidant.[261] Adam et al. reported that the choice of counterion and oxidant can significantly affect the diastereoselectivity in the epoxidation of *Z*-stilbene.[262,263] For example, using **19** the ratios of *cis*/*trans*-epoxide were 29:71 and 75:25, respectively, with PhIO and NaOCl as terminal oxidants. The effects of oxidant choice were less pronounced when the Cl^- counterion was switched to nonligating ions such as PF_6^-, which led to more *cis*-epoxide. In a survey of several Mn(salen) catalysts Freire and co-workers[166] found that higher specificities (epoxide vs side products) and epoxide yields (significantly so in some cases) were obtained with PhIO rather than NaOCl, except with Jacobsen's catalyst, which gave higher yields with NaOCl. The effect of the diimine bridge on epoxide yield was also found to be slightly oxidant dependent. Collman et al. recently showed that the diastereoselectivity and enantioselectivity of an epoxidation depended on the source of oxygen and choice of counterion under some conditions but was independent of these factors under others.[264] The mechanistic implications of these results will be discussed in sections 3.8 and 3.9.

It would appear that, in some cases at least, the active epoxidation agent(s) varies depending on the terminal oxidant used. This may be due to participation of two or more competing oxygen-transfer agents in the epoxidation reaction (see section 3.8 for more on this topic). The preferred terminal oxidant in any given case will vary depending on such factors as substrate compatibility, time, scale, cost, convenience, safety, and environmental considerations.

3.6. Problem Substrates—*trans*-Alkenes

trans-Alkenes[80] are generally poor substrates with Mn(salen) and related systems; for example, *E*-stilbene undergoes epoxidation with **19** in 27% ee and in AEs catalyzed by **19** *E*-ethyl cinnamate reacts 25 times slower than *Z*-ethyl cinnamate giving epoxide in <30% ee.[100,265,266] This poor performance can be circumvented in some cases. Thus, *trans*-epoxides can be obtained in good ee and as the major isomer from the epoxidation of the *cis*-double bond of certain dienes and enynes.[91,92,153,211,212,267] In 1994 Jacobsen and co-workers noted that "If the side-on approach mechanism is correct and general, it is possible that *trans*-alkenes will always be poor substrates for catalysts bearing salen, porphyrin, and related tetradentate ligands".[266] They then reported that by adding cinchona alkaloid derivatives to the AE of *cis*-alkenes catalyzed by **29j** one could obtain *trans*-epoxides in up to 90% ee with good to excellent diastereoselectivity.

In a review chapter Jacobsen and Wu reported the use of catalysts **46** and **47** in the AE of *E*-β-methylstyrene.[36] Using the *m*CPBA/NMO protocol developed for low-temperature epoxidations, ee's of 86% and 83% were obtained with catalysts **46** and **47**, respectively, at −78 °C. To the best of our knowledge, no report explaining or elaborating on these results has appeared in the primary literature.



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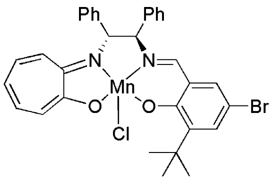

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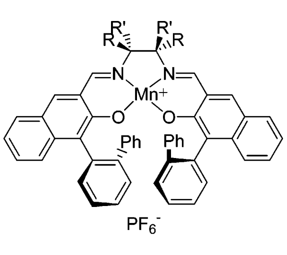
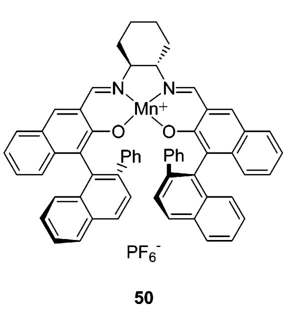
Katsuki and co-workers achieved ee's of ca. 60% for *trans*-alkenes by 1994[150,151,154] but more recently reported highly enantioselective second-generation Mn(salen) catalysts for the epoxidation of *trans*-β-substituted styrene derivatives.[218] The choice of catalyst **48** was optimum for β-alkyl styrene derivatives, while either **49** or **50** was best for β-unsaturated styrene derivatives such as stilbene. Enantiomeric excesses of >90% for β-alkyl-substituted and up to 88% for β-unsaturated styrene derivatives were possible when the temperature was reduced to −30 °C. These results have been rationalized by considering alkene approach over one of the basal naphthalene rings of an O=Mn(salen)$^+$ complex with a nonplanar, 'stepped' salen conformation (see section 3.10 for more on approach trajectories and conformations).



48: R',R' = -$(CH_2)_4$-; R, R = H
49: R,R = -$(CH_2)_4$-; R', R' = H



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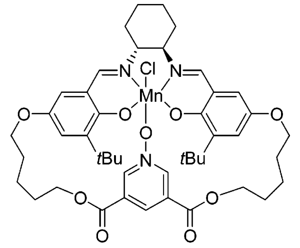
3.7. Effects of Added Donor Ligands

The ability of nitrogen- and oxygen-donor ligands to influence the outcome of metal(salen)-mediated epoxidations has been known since the initial work by Kochi and co-workers[53,62,66] (see sections 2.1.2 and 2.2.2). Added ligands such as PyO were proposed to coordinate to the metal center and thus affect the outcome of the reaction.[65] Over the past decade or so, however, a variety of effects have been reported and a number of different explanations for these effects have been proposed—these are described below.

Deng and Jacobsen reported that in the AE of *Z*-ethyl cinnamate catalyzed by Jacobsen's catalyst added 4-phenylpyridine *N*-oxide (4-PPNO) increased yield and selectivity by 10−15%.[99] They ascribed the improvements to suppression of a Lewis-acid-catalyzed conjugate addition of bleach and reduced catalyst decomposition (involving epoxide coordinating to Mn center). Improvements in rates and yields were noted in the AE of cyclic 1,3-dienes.[93] The effects of donor ligands were discussed in more detail in a later paper by Jacobsen et al.[100] They stated that in a screening of a wide range of potential donor ligands only the derivatives of pyridine *N*-oxides had beneficial effects on AE reactions catalyzed by Mn(salen) complexes. This class of donor ligands usually led to increased rates of epoxidation and total catalyst TONs. The effects were more pronounced for relatively unreactive substrates. They noted that the hypothesis that PyO derivatives act as axial ligands, as was the case in the Cr(salen)$^+$ systems investigated by Kochi (see section 2.1), was not consistent with the fact that, in general, the additives have little effect on either enantioselectivity of AE or *cis/trans*-epoxide ratios (when Clorox® was used as terminal oxidant donor ligand effects on ee were noted; however, these were attributed to suppression of Lewis acid catalysis by manganese species resulting from catalyst degradation. Such effects were not noted when 13% NaOCl was used as terminal oxidant). The effects on rate, yield, and catalyst lifetime were ascribed to the effect of PyO derivatives on the disproportionation of manganese μ-oxo dimers and on the stability of manganese species. Similar effects have been noted in the analogous Cr system (see section 4.7). However, since then Jacobsen and co-workers have modified their view. 4-PPNO was reported to have a slight yet consistently beneficial effect on enantioselectivity, reaction rate, and product yield in the case of trisubstituted alkenes.[101] Jacobsen and co-workers have given examples of 4-PPNO acting to significantly alter cis/trans ratios and ee's as well as rates and yield and used this fact in mechanistic arguments (see section 3.9).[260] They synthesized a Mn(salen) catalyst **51** with a built-in PyO module and produced evidence that the donor ligand must be bound to the complex during the formation of both C−O bonds. They also reported the use of NMO in their low-temperature AE reactions with *m*CPBA as terminal oxidant.[117] The suppression of direct epoxidation by *m*CPBA was considered to be a major role for NMO in this system. Talsi and co-workers later showed that NMO also coordinates the Mn^{III}(salen) and affects the reactivity of various complexes that arise on addition of oxidant.[268]



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Katsuki and co-workers found that added donor ligands affect the ee and yield obtained more often than not, but the effects were not always beneficial.[146,147] The effects were more noticeable with PF_6^- than AcO^- as counterion. They reported that PyO had no effect on the rate of AE of dihydronaphthalene and retarded the rate of AE of *E*-stilbene with a Mn(salen)$^+$ catalyst.[159] Katsuki and co-workers showed that reasonable ee's can be achieved in AE reactions catalyzed by achiral Mn(salen)$^+$ complexes carried out in the presence of chiral amines.[269,270] The low chemical yields and moderate ee's reported in their early communications have been improved upon using axially chiral 3,3′-dimethyl-2,2′-bipyridine *N,N′*-dioxides.[271] These results support the proposal that the donor ligand is bound to the Mn(salen) complex during the bond-forming steps (see section 3.10 for more).[272]

Complex **43**, with a built-in donor ligand group in the form of a carboxylate, was found to be particularly effective as a catalyst for AE.[220] The effectiveness of this catalyst and the variation of effect of donor ligands with catalyst structure have been rationalized in terms of an O═Mn(salen) species having a nonplanar salen conformation (see section 3.10 for more on catalyst conformation).[221,222] Calculations by Plattner, Wiest, and co-workers[167] also suggest that ligation of a donor ligand can alter the conformation adopted by the O═Mn(salen) complex. Katsuki and co-workers showed that apical ligands (including water) can affect the conformation adopted by the Mn^{III}(salen) complex in crystal structures of their second-generation catalysts.[221,222] Hutchings and co-workers found that added water had a slight effect on the yield and cis/trans ratio in the AE of *Z*-stilbene using **19** with PhIO as terminal oxidant.[273]

Workers at Smithkline Beecham found that in the AE of chromenes with Jacobsen's catalyst there was a small decrease in ee with time in the absence of donor ligand.[131] Adding *N*-oxide donor ligands was found to suppress this effect. It was proposed to do so by preventing catalyst decomposition to less selective oxidants. In addition, in the presence of some of these donor ligands rates were higher and the ee of the product did not fall off with lowered catalyst loading, as observed in the absence of donor ligands. Isoquinoline *N*-oxide was identified as the most suitable donor ligand for the reaction. Catalyst loadings as low as 0.4−0.1 mol % were capable of efficient epoxidations in the presence of isoquinoline *N*-oxide (ca. 10 mol %). This donor ligand also had the advantage that it could be easily removed in water washes.

Janssen et al. observed a significant background reaction in the AE of 1-phenyl-1-cyclohexene catalyzed by Jacobsen's catalyst using NaOCl as terminal oxidant.[274] They attributed the beneficial effect of donor ligands to acceleration of the catalyzed reaction vs the uncatalyzed reaction and noted that decreasing the temperature may also be beneficial in this respect.

A number of other studies have also uncovered evidence that the donor ligand does not just function as an axial ligand during the oxidation step. Using a combination of UV−vis spectroscopy and conductance measurements, Woodward and co-workers[144] found that addition of ligands such as *N*-Me-Imd to Mn(salen)Cl led to formation of [Mn(salen)(*N*-Me-Imd)$_2$]Cl (see section 2.2.2 for similar studies on achiral Mn(salen) complexes by Skarżewski et al.[65]). Their electrospray MS experiments showed the presence of [Mn(salen)(*N*-Me-Imd)]$^+$ and [Mn(salen)(MeCN)]$^+$. Using EPR spectroscopy Campbell et al.[275] found that the addition of donor ligands to solutions of Jacobsen's catalyst resulted in the formation of a single species with well-defined geometry around the manganese center. Feth et al. also demonstrated loss of chloride from the inner coordination sphere of manganese on addition of 4-PPNO.[276] Thus, binding of donor ligands occurs prior to oxidation of the Mn^{III}(salen)$^+$ and displaces ligating chloride counterions. This contrasts with Cr^{III}(salen) complexes which do not tend to form adducts with donor ligands until addition of oxidant as they are kinetically inert (see section 2.1.2).[53]

Workers at Merck also examined the effects of *N*-oxide donor ligands on the AE of indene catalyzed by Jacobsen's catalyst.[277,278] In agreement with work by Skarżewski et al.[65] (see section 2.2.2), lipophilic *N*-oxide donor ligands provided rate enhancements. 4-(3-Phenylpropyl)pyridine-*N*-oxide (P$_3$NO) was found to be optimal for the epoxidation of indene. A catalyst loading of 0.25 mol % could be used to give indene oxide in 4 h without affecting the ee (88%) or yield (90%). They found that P$_3$NO suppressed catalyst decomposition and increased rates. They also noted that adding extra NaOH to the NaOCl solution obtained commercially led to increased stability of P$_3$NO and NaOCl. Thus, reduced amounts of hypochlorite solution could be used. In addition, it was found that P$_3$NO plays a role in transporting HOCl into the organic layer, where it acted as the major oxidant of Mn^{III} species. The turnover-limiting step for the epoxidation is oxidation of the Mn(salen) complex, and so the rate acceleration observed with P$_3$NO is due to increased HOCl concentration in the organic layer improving the rate of oxidation.

Feichtinger and Plattner studied the effect of additives such as PyO using mass spectrometry and found that the ligand rendered the O=Mn(salen) species more reactive.[160] In contrast to earlier achiral work, in their studies the additives were found to promote formation of dimeric μ-oxo Mn(salen) species (see section 3.8 for evidence of μ-oxo dimers in solution).

Chellamani and Harikengaram[279] suggested that PyO does not bind the oxo−Mn^V(salen) complex. However, this conclusion was based on the fact that addition of PyO did not change the absorption spectrum of a species which Kochi[62] had previously shown not to be directly responsible for oxygen transfer to alkene (its rate of decay in the presence of alkene was slower than the rate of epoxidation).

Mukaiyama and co-workers found that addition of *N*-Me-Imd changed the sense and degree of enantioselectivity in AEs catalyzed by Mn(salen) complexes with molecular oxygen or peracetic acid as terminal oxidant.[228,229] In the absence of *N*-Me-Imd, the sense of enantioselectivity was the opposite of that obtained with NaOCl or iodosylarenes and the enantioselectivity was low. Moderate to excellent ee's were obtained with added *N*-Me-Imd. PyO was later shown to act in the same way as *N*-Me-Imd.[230] The proposed role of the *N*-methylimidazole is to cause the conversion of an initially formed acylperoxo−Mn(salen) species into O=Mn(salen) (see section 3.9.5.2 for theoretical calculations). A similar role was proposed for NMO in a report on the use of in-situ-generated peroxycarboxylic acids and Mn(salen) complexes to carry out epoxidations.[231] Nitrogen heterocycles such as imidazole are also the additives of choice in many H$_2$O$_2$-based systems.[152,164,183,231,244,246−248] The imidazole was proposed to assist the conversion of a hydroperoxo−Mn(salen) species into O=Mn(salen).[152] The use of carboxylate salts as additives in H$_2$O$_2$-based systems has been reported.[183,245] 4-Methylpyridine was reported to assist in the solubilization of some Mn(salen) complexes in CH$_2$Cl$_2$.[164]

Collman et al.[264] demonstrated that the choice of donor ligand can influence the diastereoselectivity and enantioselectivity of epoxidation; for example, in the epoxidation of *Z*-stilbene, the relative amounts of *cis*- and *trans*-epoxides varied by as much as 50% with Jacobsen's catalyst, depending on choice of donor ligand. They also showed that in the AE of styrene the amount of phenylacetaldehyde produced (directly from styrene as a side product) depends on the donor ligand used. Evidence for the operation of two epoxidizing pathways in competition was demonstrated and the donor ligands shown to influence the dominance of one pathway over the other. Furthermore, with *N*-methylimidazole as donor ligand the outcome of the reaction was essentially independent of counterion and iodosylarene, the donor ligand completely dictating the selectivity. The mechanistic implications of this important study will be discussed in sections 3.8.2 and 3.9.

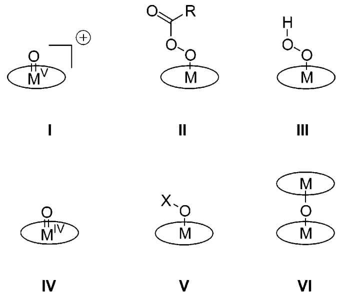
In summary, nitrogen- and oxygen-donor ligands (especially pyridine *N*-oxides and imidazole derivatives) can significantly affect the outcome of Mn(salen)-catalyzed AE. The rate, yield, enantioselectivity, and diastereoselectivity of the reaction can all be influenced as can catalyst stability (and thus TON). Depending on the terminal oxidant used, the donor ligand adopts different roles, but in all cases coordination by the donor ligand to the active Mn center is significant. This allows it to influence the reactivity and conformation of the active oxidant. In addition, coordination to Mn^{III}(salen) has been demonstrated to influence the species available for interaction with the terminal oxidant. Catalysts with built-in donor ligands have proved effective in AE, and the use of chiral nonracemic donor ligands with achiral Mn(salen) complexes for AE has been described. Pyridine *N*-oxides have been proposed to influence the stability of $((salen)Mn)_2O$ species. In biphasic systems with NaOCl as oxidant the donor ligand (preferably a lipophilic *N*-oxide) assists in phase-transfer processes. With PhIO as oxidant the donor ligand influences the competition between two different oxidants. With molecular oxygen and H_2O_2-based systems the donor ligand (either an imidazole or a carboxylate) is proposed to cause the conversion of acylperoxo− or hydroperoxo−Mn(salen) species to O=M(salen). NMO acts to suppress direct epoxidation of the substrate by *m*CPBA when it is used as terminal oxidant. As a consequence, the donor ligand plays a very important part in the whole AE process and should be chosen carefully.

3.8. Nature of the Active Species and the Catalytic Cycle

This is an area which has attracted a great deal of interest, and recent studies on the nature of the active species demonstrate that there are still some important issues in need of resolution. In addition, a full understanding of the roles of the various experimentally detected species in the catalytic cycle has not yet been achieved.

Studies of the catalytic cycle are complicated by the fact that the turnover can be limited by reoxidation of the Mn(salen) complex. This can manifest itself in two ways, the reoxidation reaction may be slow[183] and/or in biphasic systems the concentration of oxidant in the organic layer may be limiting[277,278] (see section 3.7 for more details). The epoxidation reaction itself can be extremely rapid.[156] Furthermore, when standard reaction conditions and catalysts are used, the Mn^{III}(salen) complex cannot be recovered and reused (in contrast to Cr^{III}(salen), see section 4.8). The pathway for decomposition of the complex has not been elucidated.[280−282] As a result of this decomposition, turnover numbers in the absence of donor ligands are generally of the order of hundreds or less (however there are exceptions,[186,220] see sections 3.3 and 3.4). Improvements in TONs resulting from added donor ligands, which can be as much as an order of magnitude, are discussed in section 3.7. Isolating the individual catalyst sites from each other in, for example, polymer matrixes has allowed some recycling,[50] suggesting that catalysts decompose by reacting with each other. Efforts to improve catalyst activity and stability through the use of inorganic supports,[46,47,49] ionic liquids,[283,284] and fluorinated media,[177,178,180,181,285] formation of supramolecular complexes,[286] building phase-transfer capability into the catalyst,[182,184,185] and synthesis of dimeric,[52,287] polymeric,[224,288] and dendritic[48,176] forms of Mn(salen) catalysts have all been reported.[289] The use of polymer-supported Mn(salen) and encapsulated Mn(salen) complexes has been reviewed.[44,50,51,290,291] These studies are either outside the scope of this review or are covered in section 3.3.

Chart 5. Species Proposed To Be Involved in the Catalytic Cycle (donor ligands omitted from some structures for clarity)



3.8.1. Experimental Detection of Entities Present in Solution

Until recently the intermediacy of an $O{=}Mn^{V}$-$(salen)^+$ **I** (see Chart 5) species as the major oxygen-transfer agent in the reaction was generally accepted. However, it is now clear that other potentially oxidizing species play a role, at least under certain conditions. The identities proposed for these species (see Chart 5) include acylperoxo−Mn(salen) (**II**),[228] hydroperoxo−Mn(salen) (**III**),[152] $O{=}Mn^{IV}$(salen) (**IV**),[292] and adducts[263,264] (**V**) such as PhIO−Mn(salen) and ClO−Mn(salen). In addition, a *μ*-oxo dimer (**VI**) has been proposed to act as a catalyst sink by Kochi and co-workers (see section 2.2.1). Studies have yet to reach a consensus on the nature of all the species present in the catalytic cycle.

The $O{=}Mn^{V}(salen)^+$ species was originally proposed by Kochi and co-workers (see section 2.2.1) by analogy to $O{=}Cr^{V}(salen)^+$. Although it was too unstable to isolate, they inferred the existence of an undetected species that was responsible for the epoxidation. A species was detected by UV, but its rate of decomposition was lower than the rate of epoxide formation, and so it was proposed to be a catalyst sink—a *μ*-oxo dimer (**VI**). Later, direct evidence for both an $O{=}Mn(salen)^+$ (**I**) and a *μ*-oxo dimer (**VI**) (with two PhIO ligands) was obtained by Plattner and co-workers from electrospray MS and MS-MS experiments.[160,293−295] The daughter ions of the $[PhIO(salen)Mn{-}O{-}Mn(salen)OIPh]^{2+}$ entity were $[PhIO(salen)Mn]^+$ and $[PhIO(salen)MnO]^+$. Nonligated *μ*-oxo dimer was not observed. In addition to PhIO, Et_3PO and *p*-cyano-*N*,*N*-dimethylaniline *N*-oxide served as good ligands in stabilizing the dimer. Interestingly, in contrast to other Mn(salen) complexes, they were unable to detect any dinuclear *μ*-oxo-bridged species when Jacobsen's catalyst (with triflate as counterion) was used.[167] Inspection of models led Wiest, Plattner, and co-workers to suggest that only nonplanar conformations would have steric clashes which would hinder formation of such dimers. The reactivity of the $O{=}Mn(salen)^+$ species toward alkenes and sulfides was examined by MS, and axial ligands and electron-withdrawing substituents on the salen were shown to increase the reactivity of the O=Mn(salen) species. Sabater et al. reported the synthesis of a $(salen)Mn^{III}{-}O{-}Mn^{IV}(salen)Cl$ species from the reaction of NaOCl with Mn^{III}(salen).[296] Laser flash photolysis of this species led to a transient intermediate, assigned to $O{=}Mn^{V}(salen)^+$, which was shown to react with alkenes.

Woodward and co-workers showed that many sources of Jacobsen's catalyst are contaminated with small amounts of Mn(salen)OH and that formation of the latter species is facile in the presence of hydroxide ions (as would be normal using buffered NaOCl as oxidant).[144] They also detected formation of a μ-oxo dimer when these samples of Jacobsen's catalyst containing small amounts of Mn(salen)OH were treated with cumyl hydroperoxide. The formation of the dimer, proposed to be a $Mn^{III}OMn^{IV}$ species, was accelerated by the presence of *N*-methyl imidazole. It was suggested that the inability of the $Mn^{III}OMn^{IV}$ species 'to form a manganese(IV) dimer on treatment with cumyl hydroperoxide is the reason for the lack of epoxidation activity in attempted catalysis'. Dimeric μ-oxo−Mn(salen) species containing manganese in a variety of oxidation states are known.[297−301]

Bryliakov et al. studied Mn(salen)-catalyzed AE with various oxidants using EPR and NMR spectroscopy.[268,302−305] With PhIO as oxidant, their results supported the presence of $[O{=}Mn^{V}(salen)]^{+}$ and two μ-oxo−Mn^{IV}(salen) dimers with different axial ligands (proposed to be PhIO and chloride). The μ-oxo−Mn^{IV}(salen) species were inactive toward styrene at −20 °C, but the proposed $[O{=}Mn^{V}(salen)]^{+}$ species was unstable and its concentration decreased rapidly in the presence of styrene. With *m*CPBA as oxidant, no species assignable to $[O{=}Mn^{V}(salen)]^{+}$ was detected. In this instance the major species at −70 °C were assigned to an unstable (salen)Mn^{III}OOCOAr (**II**), which decomposes to give $O{=}Mn^{IV}$(salen) (**IV**) (see Chart 5). If NMO is added (as in the Jacobsen system described in section 3.5) it ligates the two species and increases the rate of conversion of the acylperoxo complex (now **II**-NMO) into $O{=}Mn^{IV}$(salen)(NMO) (**IV**-NMO). The acylperoxo species (**II**) was much more reactive to styrene than $O{=}Mn^{IV}$(salen) (**IV**). However, in the presence of styrene the spectrum of NMO−Mn^{III}(salen) is unchanged on addition of *m*CPBA. Thus, the reaction with styrene is sufficiently rapid that appreciable amounts of the previously detected acylperoxo and $O{=}Mn^{IV}$ complexes do not arise. It was proposed that the active species in these conditions is the acylperoxo species and not $O{=}Mn^{V}$(salen). It should be noted that if this is the case, then both the Mn^{III}(salen)−acylperoxo species (**II**) and $O{=}Mn^{V}$(salen) (**I**) give rise to the same major enantiomer of epoxide. This has implications for the active species generated by Mukaiyama and co-workers in the absence of *N*-methyl-imidazole using their O_2/pivaldehyde system. It cannot be this Mn^{III}(salen)−acylperoxo species since it gives rise to the opposite major epoxide enantiomer to the $O{=}Mn^{V}$(salen) (see section 3.5 for details). In fact, Bryliakov et al. suggest that an unstable (salen)Mn^{IV}−acylperoxo species (**II**-*N*-Me-Imd) arises under Mukaiyama conditions but only when *N*-Me-Imd is present.[303,304] They were unable to detect an $O{=}Mn^{V}$(salen) species but did find evidence for an $O{=}Mn^{IV}$(salen) and a Mn^{II}(salen) species. The former decomposes in the presence of *N*-Me-Imd and was shown to give mixed-valent Mn^{III}/Mn^{IV} dimers ($g = 2$) in solution which were unreactive to alkenes and proposed to be $(\mu\text{-}O)_2$−Mn_2(salen)$_2$. We note that McAuliffe et al. previously isolated dimeric Mn(salen) complexes $[(\mu\text{-}O)_2Mn_2(salen)_2]$ and $[(\mu\text{-}O)(\mu\text{-}OH)Mn_2(salen)_2]$ and reported that the $Mn^{IV}Mn^{IV}$ dimers were EPR silent while the $Mn^{III}Mn^{IV}$ dimers gave broad signals ($g \approx 2$).[306] Bryliakov et al. proposed a possible catalytic cycle involving all these entities in the presence of *N*-Me-Imd. Species assigned as *N*-Me-Imd(salen)Mn^{IV}(OOCOR) were detected, but addition of alkene to solutions containing them produced epoxide of 0% ee, and so they cannot be the entity responsible for enantioselective epoxidation or its precursor.[304] Therefore, the entities in the O_2/pivaldehyde systems which give epoxide in nonracemic form in the presence or absence of *N*-Me-Imd with opposite senses of enantioselection remain undetected. Although no evidence for either the Mn^{III}−acylperoxo species (proposed by Bryliakov et al. to be the active oxidant in the *m*CPBA system) or the (salen)$Mn^{V}{=}O$ species (proposed as the active species under other conditions) was found, they are presumably potential oxidants in this system. On the basis of computational experiments, Khavrutskii et al. proposed an alternative explanation for the reversal in selectivity observed (see section 3.9.5 for more on computational studies). They found that different conformers of an O=Mn(salen) complex were accessible depending on whether *N*-Me-Imd was used or not (see section 3.10 for more on conformational details). Different approaches to these conformers might then result in the observed inversion in selectivity.[307,308]

Adam et al. independently reported EPR and ES-MS evidence for formation of $O{=}Mn^{V}$(salen) and several Mn^{IV} species from the reaction of $Mn^{III}(salen)^{+}$ and PhIO or NaOCl in the absence of substrate.[292] The structures for the Mn^{IV} complexes include $[ClO{-}Mn(salen)]^{+}$, $[HO{-}Mn(salen)]^{+}$, and $O{=}Mn^{IV}$(salen). Using PhIO as oxidant, chlorinated products were obtained when alkenes were added to these species. Such products are not observed in most cases under normal reaction conditions. In addition, $O{=}Mn^{IV}$(salen) was shown to generate epoxides in low ee via a radical intermediate. They concluded that Mn^{IV}(salen) species play, at most, a minor role under normal reaction conditions but may account for small amounts of product and byproducts. Evidence of an $O{=}Mn^{IV}$(salen) species capable of epoxidizing alkenes and a dimeric $Mn^{IV}{-}O{-}Mn^{IV}$ species has also been reported by Kureshy et al.,[184] who monitored the magnetic moment of reaction solutions over time.

Campbell et al. reported the application of dual-mode EPR to the study of Mn(salen) epoxidation using *m*CPBA and NaOCl as oxidant.[275] They showed that adding donor ligands to Mn^{III}(salen) led to a well-defined molecular geometry about the Mn center which was otherwise absent. Thus, the donor ligands bind to Mn^{III}(salen) and leave a single species available to oxidant (this may correspond to cleavage of dimeric species detected by Horwitz and co-workers[299]). A signal assigned to a $Mn^{III}Mn^{IV}$ dinuclear species (similar to that detected by Bryliakov et al.) arose only when epoxide was detectable. It was not visible in the absence of substrate or in the presence of substrate before epoxide was detectable (by TLC). It is not clear whether this is a reaction intermediate or a manganese byproduct of the epoxidation reaction.

In the same study Campbell et al.[275] also detected a signal at $g \approx 5$ which has also been reported by Adam et al. and Bryliakov et al. (who assigned it to L(salen)$Mn^{IV}{=}O$) and is present regardless of oxidant chosen. When NaOCl was used as oxidant, a Mn^{IV} species ($g \approx 4$) was detected and increased in concentration as the epoxidation neared completion. It was also visible in control experiments with no substrate present. Signals that might correspond to Mn^{V} species were detected but require further investigation. Finally, a radical species ($g \approx 2$) was noted only when the *m*CPBA/NMO system was used.[275] Hsieh and Pecoraro reported similar results from their EPR studies on reactions of *m*CPBA with Mn^{III}(salen) and related complexes.[309] In common with previous workers, they proposed formation of Mn^{IV}-Mn^{III} dinuclear species ($g \approx 2$) and a Mn^{IV} species ($g \approx 5$). The $Mn^{IV}Mn^{III}$ dinuclear species was suggested to arise from one-electron reduction of a dinuclear Mn^{IV} dimer. It was suggested that the reaction of $Mn^{V}{=}O$ with *m*-chlorobenzoate (*m*CB) gave a Mn^{IV}(OH) and an organic radical which then decarboxylates (CO_2 evolution was detected). This explains the radical detected by Campbell et al.

Recently, Feth et al. published the results of their investigations into high-valent Mn(salen) complexes using XANES, EXAFS, UV−vis, and Raman spectroscopy.[276] Their studies were conducted using *m*CPBA at room temperature without any added NMO, somewhat different from the conditions developed by Jacobsen and co-workers with this oxidant (see section 3.5). Oxidation of Jacobsen's catalyst produced a Mn^{IV}(salen) species with a Mn−O single bond (in addition to the bonds to the salen ligand); however, this was not a (salen)Mn^{IV}−μ-oxo dimer. In the absence of oxidant, they observed formation of a complex between the Mn^{III}(salen) and two axially ligated 4-PPNO moieties with displacement of chloride from the coordination sphere—similar observations have been made by others[144,275] (see section 3.7). The Mn^{IV}(salen) species is proposed to be a radical cation with a Mn−O single bond to *m*CPBA. The complex was observed to decay under certain conditions, and the resulting product was suggested to be a neutral $Mn^{IV}{=}O$ species, as previously proposed by Adam et al.[292] No evidence for an (salen)$Mn^{V}{=}O$ species was found. Epoxidation experiments to determine whether any of the species detected were active oxidants have yet to be reported.

From all the investigations (particularly the EPR ones) it is clear that the oxidant should be added to the reaction mixture after all the other components. The addition of donor ligand leaves only one Mn^{III} species available for oxidation rather than several. Furthermore, in the absence of substrate a larger number of EPR signals are detected when oxidant is added. It appears that 'the devil finds work for the idle oxidant'.

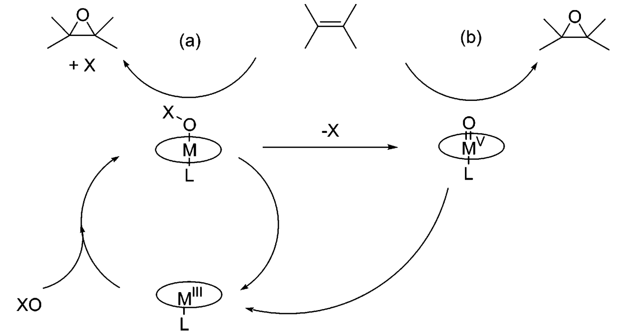
3.8.2. Recent Evidence for Multiple Oxidation Pathways/Multiple Oxidants

In the past few years evidence has emerged that strongly favors the presence of multiple oxidants or oxidation pathways in Mn(salen) catalyzed AE.

As early as 1997 Linde et al. carried out experiments with potential radical traps which led them to propose that two separate epoxidation pathways existed for the production of *cis*- and *trans*-epoxides from *Z*-alkenes.[261] These results are discussed in more detail in section 3.9.1 since at the time the possibility of multiple active oxygen-transfer species was not suggested. Later Linde et al.[310] reported the relative rates of epoxidation and *cis*/*trans*-epoxide ratios from epoxidation of a series of *para*-substituted *Z*-stilbenes with PhIO as terminal oxidant and noted that while the relative rates of formation of the *cis*-stilbene oxides were strongly dependent on substituents, no strong effect was found for *trans*-epoxide formation in the same reaction. To explain these and other results, they postulated separate pathways with no common transition state for the production of *cis*- and *trans*-epoxides from *Z*-alkenes. It was also found that both pathways involved asynchronous formation of the two C−O bonds. Their own radical trap results (see section 3.9.1) and the nonlinear enantioselectivity−temperature relationship observed by Katsuki et al. (see section 3.9.3) are accommodated by this proposal of separate pathways. The possibility that the separate pathways are due to oxidation by different oxidizing species was considered viable. In this context, $O{=}Mn^{V}$(salen) species in different spin states (see section 3.9.4 for more on spin states) could constitute different oxidizing species. It should be noted that although the theoretical results of Abashkin et al.[311] suggested that *trans*- and *cis*-epoxides could both arise from the same pathway, steric factors were not considered, and these would be expected to have a large effect on *Z*/*E*-isomerism. Added cinchona alkaloid derivatives probably bias the reaction toward one of these two pathways in the AE of *cis*-alkenes,[80] giving rise to the excellent diastereoselectivity observed (see section 3.6).[266] The detection of Mn(salen)OH impurities in commercial and synthetic samples of Jacobsen's catalyst complicates the interpretation of these studies, especially when considering results of reactions using NaOCl at high pH which should have increased amounts of Mn(salen)OH present.[144]

Adam et al.[263] described how using a range of oxidants in the epoxidation of *cis*-alkenes changed the ratio of *cis*/*trans*-epoxide. The fact that significantly different diastereoselectivities were observed with different oxidants caused them to propose that there is a second oxidation cycle operating in which the terminal oxidant is involved in substrate oxidation and that this is in competition with oxidation by $O{=}Mn^{V}$(salen). Scheme 3 shows their proposal for two competing mechanisms. Adam et al. also noted differences in diastereoselectivity with different counterions[262,263] but explained these in terms of the two-state reactivity hypothesis (see section 3.9.4). Freire and co-workers[166] also observed that the outcome of the reaction was oxidant dependent and proposed

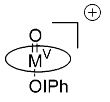
Scheme 3. Two Possible Reaction Pathways in the Mn(salen)-Catalyzed Epoxidation of Alkenes



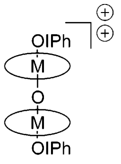
that their results could be interpreted in terms of the competing oxidation pathways suggested by Adam et al.

The dependency of the outcome of the reaction on the choice of oxidant and counterion was also examined by Collman et al. in a recent paper.[264] They tested three iodosylarenes and four different Mn(salen) complexes (differing only in counterion) and showed that diastereoselectivity and enantioselectivity depended heavily on the source of oxygen-donor ligand (none, PyO, Ph_3PO, or *N*-Me-Imd) and choice of counterion. Thus, for example, in the epoxidation of *Z*-stilbene, the *cis/trans*-epoxide ratio varied from 18:82 to 83:17 with Jacobsen's ligand with different counterions and iodosylarenes. The fact that the choice of iodosylarene makes a difference under certain conditions strongly suggests that it is involved in a species which transfers oxygen to the alkene. To explain their results Collman et al. proposed that two mechanisms are competing, one in which the iodosylarene is involved in the oxo-transfer species and the other (an $O{=}Mn^V(salen)^+$-derived species) where the iodosylarene is not present (see Scheme 3). Although Collman et al. propose a similar bifurcated mechanism to Adam et al., they suggest that the $O{=}Mn^V(salen)$ species is responsible for diastereoselective epoxidation of *Z*-stilbene to *cis*-stilbene oxide while the adduct with iodosylarene produces mainly *trans*-stilbene oxide—almost the very opposite to the suggestion of Adam et al. who propose that PhIO mostly yields $O{=}Mn^V(salen)$ and a nondiastereoselective pathway, while with NaOCl a concerted XO−Mn(salen) adduct pathway dominates. In addition, the effects of counterions are rationalized by Collman et al. in their model, whereas Adam et al. used the two-spin-state hypothesis to explain these (see section 3.9.4). Interestingly, although Collman et al. propose that with *N*-Me-Imd as donor ligand only one oxidant ($O{=}Mn^V(salen)$−*N*-Me-Imd) is acting (the outcome is independent of counterion and iodosylarene), under these conditions the yields, diastereoselectivities, and enantioselectivities are not at the extremes of the ranges demonstrated with variations in oxidant, donor ligand, and counterion. As such these conditions will probably not be the ideal conditions from a practical viewpoint

Finally, it is worth noting that $O{=}Mn^V(salen)^+$ has been proposed to act as a Lewis acid catalyst in asymmetric Diels−Alder reactions[312] and that both $O{=}Mn^V(salen)$−PhIO **VII** and [(PhIO) (salen)MnOMn(salen)(PhIO)]$^{2+}$ **VIII** species have been detected by Plattner and co-workers (see above). Thus, the PhIO moieties in these two species could also be competing oxidizing species under reaction conditions rather than a simple adduct with $Mn^{III}(salen)$.



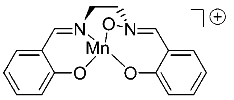
VII



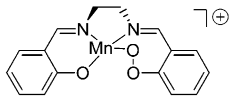
VIII

3.8.3. Recent Novel Proposals

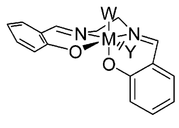
Several novel proposals concerning the catalytic cycle and active oxygen-transfer species have recently been made on the basis of computational studies. The merits of the calculations involved are discussed in section 3.9.5. Khavrutskii et al.[313] proposed that cationic species **52** and **53** might arise during the AE reaction. They noted that species analogous to **52** arise in porphyrin chemistry and that both structures would be indistinguishable from $O{=}Mn(salen)^+$ by mass spectroscopy. Furthermore, their studies on Mn(salen)−acylperoxo complexes suggest that cleavage of the O−O bond could lead to formation of structures such as **54a**,**b** as well as **52** and **53**.[307]



52



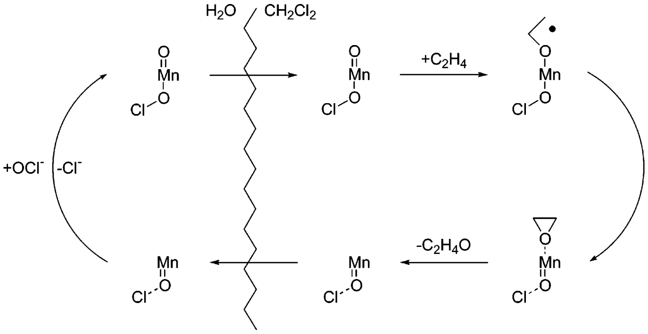
53



54a: W = oxo, Y = none
54b: W = none, Y = oxo

Cavallo and H. Jacobsen[314] recently suggested an alternative catalytic cycle in which the active species has a hypochlorite ligand trans to the oxo group and the manganese does not revert to Mn^{III} (see Scheme 4). Although only simple models were used for calculations, this scheme has several advantages when the spin state of the manganese is considered (see 3.9.4 for more on this). However, it is not yet clear how experimental observations such as the

Scheme 4. Catalytic Cycle Proposed by Cavallo and H. Jacobsen.



effects of donor ligands or evidence for multiple oxidants might be accounted for by this proposal.

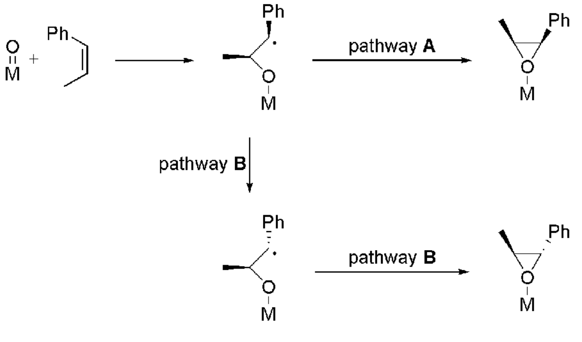
3.9. Mechanism of Oxygen Transfer to Alkene

The mechanism of Mn(salen)-catalyzed AE has been the source of much controversy[39,315] over the years, and a great deal of energy has been expended in efforts to understand the reactivity and selectivity observed. Concerted and stepwise reaction pathways have been proposed depending on the substrate. Radicals and metallaoxetanes have been proposed as intermediates in a stepwise reaction pathway. More recently, attention has focused on the spin state of the manganese center in the active species and the potential intermediates. With most oxidants an O=Mn^V(salen) species was believed to be the major oxidant transferring oxygen to alkenes, and most of the discussion with regard to the mechanism of the reaction has focused on oxygen transfer from this species. However, there is now substantial evidence suggesting that other oxygen-transfer species may intervene under certain reaction conditions (see section 3.8.2). Although much of the following discussion pertains to oxygen transfer by an O=Mn^V(salen) species, possible mechanisms involving other oxygen-transfer agents will be discussed as appropriate. Finally, since the nature of the terminal oxidant is important in determining the active oxygen-transfer species present, we will try to note which terminal oxidant was used where the outcome may be specific to the oxidant used.

3.9.1. Radical Intermediates

Since Mn(salen)-catalyzed AE is most effective for conjugated alkenes, most studies of active oxidants, catalytic cycle, and oxygen-transfer mechanism pertain to conjugated alkenes. With conjugated alkenes as substrates the reaction is not diastereoselective, i.e., mixtures of *cis*- and *trans*-epoxides are produced in the AE of *cis*-alkenes.[80] This makes it necessary to invoke a stepwise process with conjugated alkenes as substrates. Katsuki and co-workers[8] and later Jacobsen and co-workers[266,267] used a radical intermediate, as originally proposed by Kochi,[62] to rationalize the observed results. This was proposed to form irreversibly since no isomerized alkene is detected (see Scheme 5).[267] In this section we describe the experimental investigations that support the intermediacy of radicals. Computational studies on possible reaction intermediates will be described in section 3.9.5. We note at the outset that there is still uncertainty as to whether radical intermediates are exclusively involved when conjugated alkenes are substrates.

Scheme 5. Mechanism of Epoxidation of Conjugated Alkenes Involving an Irreversibly Formed Radical Intermediate



Dao et al.[316] appear to have intercepted the putative radical intermediate with TEMPO in a novel synthesis of alkoxyamines from styrenes, which has been successfully used by others[317] using either air or tBuOOtBu as oxidant to initiate the reaction.[318,319]

On the assumption that a common intermediate exists along the pathways leading to *cis*- and *trans*-epoxides from *cis*-conjugated alkenes (as in Scheme 5), Jacobsen and co-workers showed how the enantioselectivity of the major isomer obtained with *cis*-alkenes was being enhanced in the second C−O bond-forming step by different rates of partitioning of the diastereomeric radical intermediates (formed in the first step) into *cis*- and *trans*-epoxides (via pathway A and B in Scheme 5, respectively).[267] In essence the minor radical diastereomer formed in the first step was more likely to be converted into the minor diastereomer of epoxide, and thus, the ee of the epoxides was not completely determined in the first bond-forming step. This analysis does not extend to cases where there are multiple oxygen-transfer agents or separate pathways leading to diastereomeric epoxides (see section 3.8.2 and later in this section).

Z-Cinnamate esters with varied electronic and steric properties, **55a**−**i**, were used as substrates to probe the mechanism of the AE reaction by Jacobsen et al. using NaOCl as oxidant (see Figure 6).[100] The log of the ratio of *cis/trans*-epoxides obtained in the AE was correlated to the electronic properties of the substituents. They found a good correlation with σ values of the substituents rather than σ^+ and argued that this and the moderate influence of substituents on epoxidation rates supported a nonpolar intermediate rather than a cationic one. Subsequently, Linde et al. suggested that σ^+ is more suitable based on their Hammett correlations with unsymmetrical stilbenes where attack could be at either carbon of the alkene.[310] Jacobsen and co-workers also showed that substrates bearing electron-withdrawing groups (EWGs) yielded increased amounts of *trans*-product, which could be explained by their ability to stabilize the intermediate and so allow more isomerization before ring closure.[100] Unexpectedly, the ee's did not correlate with the substrate electronic properties. A provisional explanation that ‘the *cis*-cinnamate esters are not strictly isosteric since their distortion from planarity is expected to vary according to substituent’ was offered. The intermediate(s) formed could still be isosteric of course and so result in a correlation in the cis/trans partitioning.

Linde et al. found that conjugated alkenes **56a**−**c**, designed to be radical traps, gave epoxides **57a**−**c** to varying degrees depending on oxidant, Scheme 6.[261] With bleach as oxidant only **56c** gave products due to cyclopropyl ring opening (56% epoxide was formed vs 100% with **56a**,**b**), whereas with PhIO as oxidant epoxide accounted for 54−83% of material and ring-opened products accounted for the rest of the material. This was taken as strong evidence for the

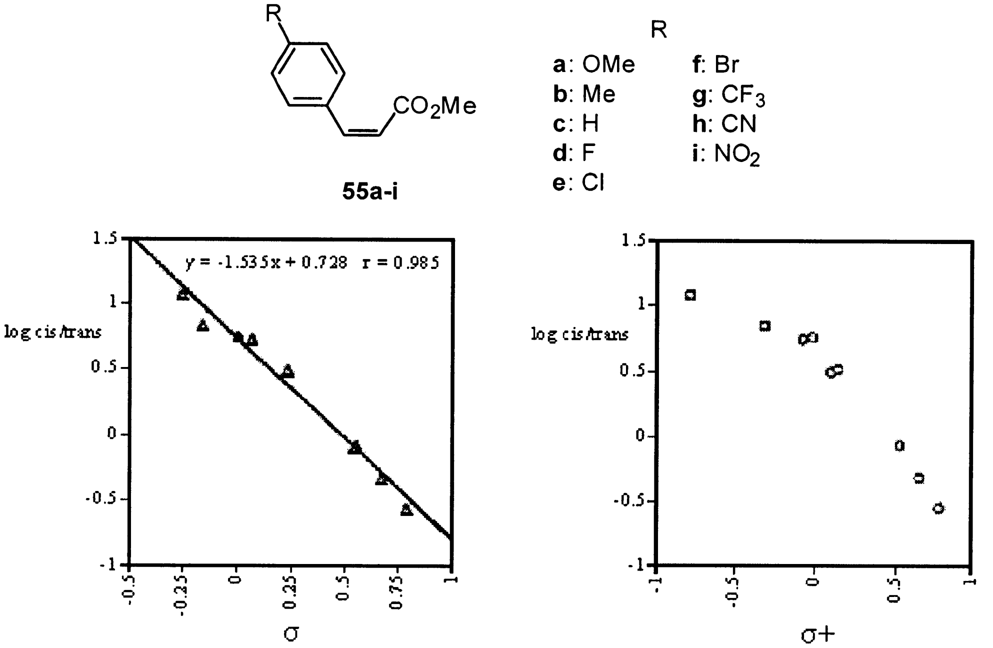
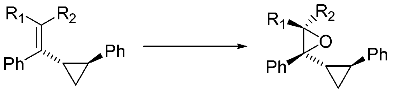


Figure 6. Plots of the log of the ratio of *cis*- and *trans*-epoxides from the AE of *Z*-methyl cinnamate derivatives **55a**–**i** against σ and σ^+. (Reprinted with permission from ref 100. Copyright 1994 Elsevier.)

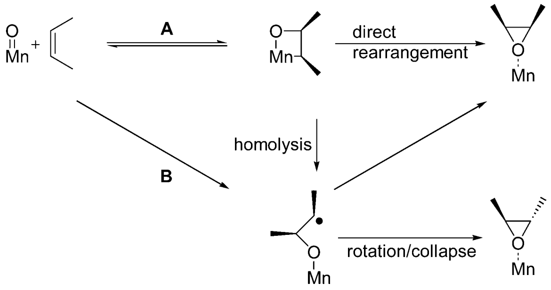
Scheme 6. Substrates Designed To Give Epoxides in the Absence of Radicals in the Mn(salen)-Catalyzed Epoxidation



56a-c **57a-c**

a: R_1,R_2 = H
b: R_1 = H, R_2 = Me
c: R_1 = Me, R_2 = H

Scheme 7. Proposed Mechanisms for the Mn(salen)-Catalyzed Epoxidation: (A) Reaction via a Metallaoxetane Intermediate; (B) Reaction via a Radical Intermediate



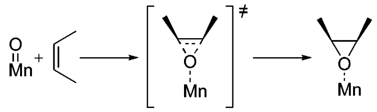
existence of a reaction pathway with no radical intermediates in addition to a reaction pathway involving a radical intermediate. The expectation is that any radical species generated will yield ring-opened products. Therefore, the absence of isomerized epoxide from the epoxidation of **56b**,**c** implies that isomerization occurs exclusively by radical pathways. This study was performed in the context of the possibility of a metallaoxetane intermediate (see section 3.9.3). The results are consistent with pathway **A** outlined in Scheme 7 but do not rule out the possibility that radicals are formed directly as in pathway **B**. In a later study Adam et al.[292] noted that **56a** gave complete conversion to epoxide from O=Mn^{IV}(salen) even though *Z*-stilbene yielded *trans*-stilbene oxide under the same conditions. Therefore, they concluded that the radical clock is rather slow (ring opening estimated at 3.6×10^8 s^{-1}, whereas the stilbene isomerization is estimated to be ca. 10^{11} s^{-1}). Thus, it is possible in the cases above that cyclopropyl ring opening is slower than direct C–O ring closing but faster than C–C bond rotation followed by ring closing—this scenario would also give rise to only nonisomerized epoxide and ring-opened products but does not invoke multiple pathways.[320]

3.9.2. Concerted Reaction

With nonconjugated alkenes radical intermediates would be considerably less stable, and in fact, a concerted pathway has been proposed by some workers.

Experiments by Jacobsen and co-workers with radical probe **58** as substrate and NaOCl as oxidant gave epoxide with no products of cyclopropyl ring opening, indicating that for nonconjugated alkenes a concerted mechanism was most likely (see Scheme 8).[321] In stark contrast, using a polymeric Mn(salen) complex, PhIO, and the nonconjugated alkene **59** designed to differentiate between cationic and radical intermediates Adam et al. ruled out cationic intermediates and proposed that radical intermediates intervene.[263] In later work on conjugated alkenes Adam[263] and Collman[264] argue that a concerted process due to one oxidant and a radical pathway due to a second oxidant are in competition (see section 3.8.2 for details).

Scheme 8. Concerted Mechanism for Epoxide Formation



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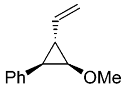

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3.9.3. Viability of Metallaoxetane Intermediates

In the mid-1990s Norrby et al. proposed that the reaction might proceed via reversible formation of a metallaoxetane followed by irreversible formation of a radical intermediate (see pathway A in Scheme 7).[322] They could account for the sense of selectivity and effects of substituents at the 3,3′- and 5,5′-positions and changes to the diimine bridge. The poor enantioselectivity observed with *trans*-alkenes[80] could also be explained. Nonlinear temperature effects on ee would be expected for their proposed mechanism.

Shortly afterward Katsuki and co-workers reported that there were nonlinear temperature effects on ee with PhIO as oxidant and used this to support the proposal of a metallaoxetane intermediate.[159] They detailed a mechanism similar to that of Norrby et al. in which a metallaoxetane is reversibly formed and one of the salen oxygens takes up an apical position with respect to manganese to accommodate the metallaoxetane. The metallaoxetane then breaks down irreversibly into either a radical intermediate (for conjugated alkenes) or an epoxide (for alkyl-substituted cases).

Adam et al. found that their results using Mn(salen) complexes and NaOCl for the oxidation of enol derivatives could be rationalized using a reaction pathway with a metallaoxetane intermediate.[103] In the AE of nonconjugated alkenes by Mn(salen)/H_2O_2 Brun and co-workers observed the formation of side products that could be easily rationalized if the reaction proceeded through metallaoxetane intermediates which then collapsed to give epoxides as major products.[323]

The viability of such oxametallacyclic intermediates in the catalytic cycle was strongly challenged by Jacobsen and co-workers.[156,260] The difficulty in explaining the effects of PyO derivatives was central to their arguments. They stated that addition of 4-PPNO affects the stereoselectivity in both C−O bond-forming steps using a range of oxidants. However, it should be noted that the differences in diastereoselectivity are very dependent on the terminal oxidant used, and with, for example, bleach as oxidant very little difference in the *cis*/*trans*-epoxide ratio of β-methylstyrene oxide is observed on addition of PyO (19 and 18, respectively). To support their arguments Jacobsen and co-workers synthesized complex **51** with a PyO moiety strapped on so that it cannot dissociate. This catalyst did not show changes in diastereoselectivity or enantioselectivity with added donor ligands, thus showing that these effects were derived from binding of the donor ligand to the metal center during the reaction. They argued that a metallaoxetane intermediate requires a heptacoordinate manganese center, which they considered unlikely. We note that heptacoordinate Mn^{II} species with ligand sets similar to salens have been characterized by Bailey et al.[324] and Gou et al.[325]

Contrary to the results of Katsuki and co-workers (see above), Jacobsen and co-workers[156] observed a linear Eyring correlation over a wide temperature range (ee increased as temperature decreased with three out of four substrates); however, it should be noted that they used *m*CPBA as oxidant in this study to give a wide range of temperatures. Using Jacobsen's catalyst and NaOCl as oxidant, Pericàs and co-workers later reported that ee's increased with temperature in the epoxidation of 9-ethylidenefluorene.[102] Although they do not comment on it themselves, an Eyring plot of their results is in fact linear (four data points, $R^2 = 0.985$).[326] A similar, positive correlation has also been noted by Jacobsen and co-workers in one other instance.[156] Pozzi and co-workers also found ee's were improved by increasing temperature under fluorous biphasic conditions.[180,181]

A heptacoordinate manganese center in the metallaoxetane was also necessary to explain how chiral amines would induce enantioselectivity in AE reactions catalyzed by achiral $Mn(salen)^+$ complexes in this mechanism (see section 3.7 for details).[269−271] The effectiveness of complex **43**, which would have a hexacoordinate O═Mn(salen), does not sit well with this mechanism either. In later computational studies[327−329] (see section 3.9.5) a role for a metallaoxetane intermediate was not ruled out completely but radical intermediates were favored by most calculations. More recently, evidence of multiple oxidants and/or oxidation pathways allows nonlinear temperature effects to be rationalized without metallaoxetanes, but equally donor ligand and oxidant effects can also be explained by changing partitioning between competing pathways/oxidants (see sections 3.8.2 and 3.9.1).

3.9.4. Relevance of Spin States

There has been considerable discussion in the literature of the influence that the spin states of manganese might have on the course of the epoxidation reaction. A substantial amount of this discussion has been on the basis of theoretical calculations, and we note at the outset that the quality of these calculations is probably not sufficient to draw firm conclusions (see section 3.9.5). However, the issue is intriguing and may ultimately provide helpful insight into the course of these reactions.

The spin issue arises because the most stable electronic configuration of Mn^{III} in the salen N_2O_2 ligand environment has all four d electrons unpaired—a quintet state[275,302]—whereas when a Mn^V atom is placed in a similar environment, its two d electrons can only have singlet or triplet arrangements. On first sight, therefore, there must be a spin-crossing event during the reaction; however, it is not strictly correct to ignore the oxo moiety in Mn^V═O, and its inclusion in the analysis allows a quintet possibility. A further consideration is that deviation from a strictly planar N_2O_2 ligand arrangement has been suggested for the Mn^V═O species by a number of workers in attempts to explain stereoselection in these systems (see section 3.10 for conformational possibilities). Indeed, a slight deviation form planarity can be seen in the X-ray crystal structure determination of Jacobsen's catalyst.[330,331] If the distortion of the N_2O_2 plane were to approach the tetrahedral

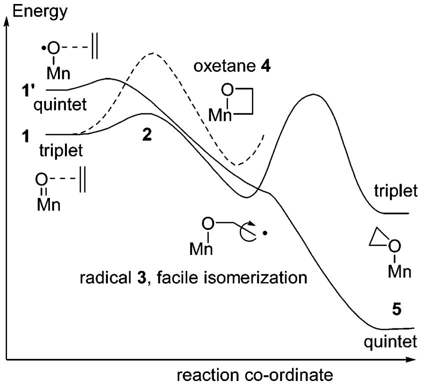


Figure 7. Reaction profiles calculated by Linde et al.[327] (Reprinted with permission from ref 327. Copyright 1999 American Chemical Society.)

arrangement, then the singlet state would be favored for the Mn^{III} species.

It was Linde et al. who showed that considerations of spin might assist in the interpretation of the experimental results.[327] Their argument is illustrated in Figure 7. If, for example, the $Mn^V{=}O$ species reacts only from the triplet state and there is only one transition state on the quintet surface as shown in Figure 7, then the timing of the spin crossover could affect the outcome of the reaction. Thus, if the crossover occurs before the energy well corresponding to the radical species, then there will be no opportunity for rotation around the C−O bond leading to the other diastereomer of product and there will be no ring opening of a radical trap. Conversely, if crossover occurs after the formation of the radical, then both of these effects will be observed. This analysis is certainly elegant and enables reconciliation of the contradictory results from the radical-trapping experiments. It is also part of an emerging paradigm of the effect of spin state on reactivity.[332−334]

The question arises as to how realistic Figure 7 is as a representation of the potential-energy surfaces of the reaction. A number of possible sources of invalidation of the analysis in Figure 7 have been found.[311,328,329,335] First, the energy gaps between the quintet, triplet, and singlet spin states and even their energy ordering may not be as shown in Figure 7. Second, while the potential-energy surface (PES) for the triplet probably does follow the course shown in Figure 7, the PES for the quintet may not and may even have a second transition state. There seems to be some measure of agreement that the presence of an anionic basal ligand (e.g., the chloride in Jacobsen's catalyst) may lead to the latter outcome.[263,311,320,328,335,336] Finally, there is the possibility that the reaction may react on both quintet and triplet and indeed singlet[311] manifolds so that the timing of crossover may be irrelevant or, at best, only one of several factors.

Experimental evidence supporting the dependence of the diastereoselectivity on the spin state of the oxidant has come from Adam et al.[262,263] They noted that with some oxidants ligating counterions such as Cl^- led to increased amounts of *trans*-epoxides forming from *Z*-substrates when compared to nonligating counterions such as PF_6^- and explained their results in terms of the varying participation levels of the different $Mn^V{=}O$ spin states in cationic $Mn^V{=}O(salen)^+$ and neutral $Mn^V{=}O(salen)Cl$ as calculated in the computational studies of Linde et al. and Abashkin et al., respectively.[311,327] However, Collman et al. proposed an alternative explanation for the effect of counterions based on multiple oxidants (see section 3.8.2) and state 'further experimental results are needed to justify the computational results'.[264]

It is noted here that, as of yet, there has been very little study of the effect of the choice of oxidant on the $Mn^V{=}O$ spin-state distribution. (salen)$Mn^V{=}O$ is suggested to be lower in energy as a triplet than a quintet by many calculations,[328] but Mn^{III}(salen) is known to be in a quintet.[275,302] This could be crucial since the reaction of alkene with $Mn^V{=}O$ might be sufficiently rapid that a thermodynamic equilibrium between the different spin states would not be established. If different oxidants gave rise to different kinetic distributions it could explain the dependence of the diastereoselectivity on terminal oxidant without requiring a second oxidation cycle involving Lewis-acid-catalyzed activation of the terminal oxidants proposed by Adam et al. and Collman et al. Similarly, donor ligands could affect this partitioning between different spin states. However, Linde et al. suggest that multiple oxidants must be in rapid equilibrium under catalytic conditions since the product distribution is affected significantly by the electronic properties of the substrate.[310]

3.9.5. Theoretical Calculations

There have now been a substantial number of computational studies performed on manganese salen complexes and their epoxidation reactions.[157,160,161,167,259,261,294,307,308,311,313,314,322,327−329,335−343] Some of these calculations were undertaken expressly to address the spin issue described in the last section, while others focused more on the nature of the reactive intermediate (if any) in the reaction. However, there is, at present, no consensus description of either the spin of the reactant $Mn^V{=}O$ species or the nature of the reaction intermediate. Almost all calculations suggest that the triplet state is lower in energy than the quintet, but the singlet state may be lower, and there is some measure of agreement that any intermediate will be radical in character and that metallaoxetanes are probably not involved in the reaction.[311,327−329,335]

3.9.5.1. Calculational Methodology. Khavrutskii et al.[313] set out a clear comparison of most of the calculations to date. At the present time several difficulties attend the production of useful theoretical results in this system, most of which can be expected to be resolved as future computing power increases. We enumerate here the main issues that have reduced the usefulness of the calculations. We emphasize strongly our belief that theoretical calculations can give substantial insight into these reactions, insight that may never be available from any other source.

(i) The choice of calculational method. In recent years, the density functional theory (DFT) type of calculation has replaced the more traditional Hartree−Fock (HF) method, and indeed, most of the calculations reported on metal–salen systems have used DFT methods. However, within the DFT family there are a number of different options. The very popular B3LYP is a so-called *hybrid* method (in the sense that it has aspects of HF incorporated), whereas the method known as BP86 is a so-called *pure* method. Both methods have been used for metal–salen calculations, and it is clear that they have different outcomes. In particular, there can be very substantial differences in the spin-state energies computed by the two methods with the B3LYP method favoring the higher spin states. Thus, where the quintet is the ground state, its stability appears to be enhanced when calculated using B3LYP.[311,329] Such effects are to be expected to a certain extent because of the presence of the HF component in the hybrid method.[313] Conversely, using the BP86 method results in de-emphasis of the importance of the quintet state[313,335] to the extent that the known quintet resting state of Mn^{III} is not quite reproduced, being found to be degenerate[311] with the triplet at some levels of calculation.[161,328,329,335,339,340] At this time it is not clear which method gives more reliable results. We note that workers have compared the methods and chosen either one[313,327,336,340] or the other[311,328,329,335] as best, both on reasonable grounds in particular, comparison to very high level CASSCF calculations.[343] In this context we note that similar difficulties have been found on other transition-metal processes involving potential spin crossings. It seems likely that the appropriate methodology will depend on the system being studied, in some cases best with BP86 and other cases requiring approximately 15% exact exchange.[334]

We also note that where there is a check against physical properties (spin density by ESR, geometrical parameters of Mn^{III}(salen) complexes,[328] and Mn–nitrido complexes,[313] known Mn^{V}–oxo crystal structures[340]) this has also not produced clarity. The spin density of the starting Mn^{III} species is known and can be reproduced correctly by both types of calculations at an appropriate level.[161,313,327–329,335,336,340] We also note that the B3LYP calculations have reproduced the observed spin densities for the analogous Cr^{III} and Cr^{V}=O species (see section 4.9.3), but the BP86 method has not been applied in this case. Khavrutskii et al. showed that B3LYP correctly predicts the ground state of O=Mn^{IV}(salen) and nitrido–Mn(salen) species in addition to calculating geometrical parameters which correspond very well with experimental values for crystal structures of nitrido Mn(salen) complexes.[313]

(ii) Inadequacy of the basis sets and geometry optimization procedures used.[335] It has now been many years since one of the authors noted,[344,345] in the context of phosphorus chemistry, that at least triple-ζ plus polarization basis sets with full geometry optimization plus some correlation in HF calculations are required for reliable results in ground-state properties. These requirements must apply with greater force in the area of the reactivity of transition-metal complexes. Most of the calculations to date fall short on some or all of these grounds.

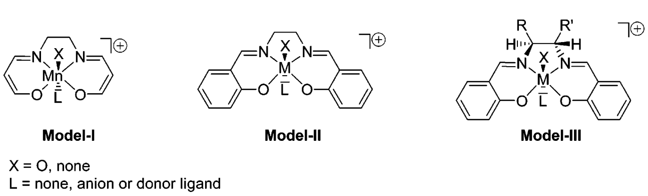


Figure 8. Model systems for calculations.

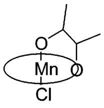
(iii) Choice of model system used. At the present time it is not possible to perform extensive calculations using, for example, Jacobsen's catalyst. It is necessary to use a model system, which entails compromise on the reliability of the results but holds out the promise of insight into the reaction. We distinguish three levels of model system (see Figure 8) that have been, or could be, used. Models I and II have been used to date, the former more often. Model III has rarely been used.[157,338,339]

Model I (the acacen ligand) is the most truncated ligand system which stills maintains a similarity to the catalysts used in practice. We consider this model to be unsatisfactory in two respects. First, it is electronically unlike salen in the absence of the benzene rings. It has been quite some time since the ameliorating electronic influence of benzenoid annelation was recognized in simple calculations on hydrocarbons.[346] Therefore, it is not possible to be confident about calculated energy differences between, for example, triplet and quintet spin states with this model. A subsidiary point is that Katsuki's ideas (see section 3.10 for detail) about the interaction of the benzene rings with the conjugating group on the substrate cannot be addressed at all. Second, the steric properties of, for example, the cyclohexane backbone in Jacobsen's catalyst, especially the twist it imparts to the rest of the ligand (section 3.10 for proposals on conformations), cannot be modeled by the ethylene bridge. This makes the calculated molecular structures difficult to take seriously, and it also has implications for the relative energies of spin states if the twist promotes a tetrahedral distortion to the N_2O_2 ligand set (see above). For these reasons we consider Model II to be the minimum which should now be used to study the system. Ideally Model III with full geometry optimization would be used, but we recognize that the computing power necessary may not be available at the present time.

3.9.5.2. Novel Ideas Generated by Computational Studies. Recent computational studies have introduced novel ideas on how the AE reaction might proceed.

Abashkin and Burt[339] propose that one of the oxygen atoms of the salen ligand participates in the reaction by stabilizing a singlet reaction pathway through the formation of a five-membered ring (**60**), which should give only *cis*-epoxides from *Z*-alkenes. The feasibility of this intermediate was established using calculations based on Model III, so their proposal has significant merit. They further propose that this reaction pathway is in competition with one involving a triplet radical intermediate, and they are able to rationalize the experimental observations. However, comparison of the energies of the two competing pathways had to be carried out with Model

I, reducing its persuasiveness. Also, they make no comment as to how the ultimate quintet Mn^{III} species is formed. This proposal has substantial predictive power regarding the influence of the substituents on the salen rings and should be testable experimentally.



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An even more intriguing proposal which avoids the necessity for a spin change in the reaction has been put forward by Cavallo and H. Jacobsen.[314] In their proposed catalytic cycle (Scheme 4) Mn^{III} plays no part, and therefore, the arguments in relation to spin states are void. Using the BP86 method with Model I they showed that the reaction could proceed on the triplet surface. The fact that the calculational method is less than persuasive does not detract from the elegance of the proposal. It too carries substantial predictive power, which should be testable by various catalysis experiments. It is unclear how the effects of donor ligands, especially in catalyst **51** (see section 3.7), or the results suggesting multiple active oxidants (see section 3.8.2) might be accounted for in this model.

Using Model II and B3LYP Khavrutskii et al. considered several other potential oxidants such as the imine−oxo and peroxo species **52** and **53** and two forms of $Mn^V{=}O$ **54a** and **54b**, where at least one of the phenolic O atoms adopts an axial position in a pseudo-octahedral manganese coordination sphere resulting in so-called 'bent' complexes. Their calculations indicated that **52** was lower in energy than $O{=}Mn^V$(salen) species (see section 3.8.3 also).[313] In the case where the stoichiometric oxidant is an organic peracid or the combination of O_2 and aldehyde there have been suggestions that species other than $Mn^V{=}O$ could be oxygen-transfer agents in the absence of donor ligand (see section 3.8 for details). Khavrutskii et al. suggest that O−O cleavage of quintet Mn^{III}−acylperoxo species might lead to N−oxo species **52**[308] as well as **53** and **54,** although the latter are higher in energy. In the triplet state **54b** is favored. Alternatively, they suggest that a spin-crossing event could take place from the quintet to triplet surface where O−O bond cleavage is easier. O−O cleavage is most likely to occur prior to epoxidation as the energies for epoxidation by acylperoxo complexes are too high.[307] They also calculated that cationic Mn^{IV}−acylperoxo species should be stable to O−O cleavage and, therefore, detectable experimentally (see section 3.8.1 for details).[340] Finally, the O−O cleavage from acylperoxo species **II** (see Chart 5) with ligated donor ligand is calculated to be facile. Thus, addition of a coordinating ligand could switch the products of O−O cleavage from an equatorial Mn=O bond to an axial Mn=O bond, which might explain the reversal in selectivity noted on addition of donor ligands to AE reactions where either peracetic acids or O_2/pivaldehyde are used.[307]

3.9.6. Outlook on Mechanism

The growing evidence for the existence of multiple oxidants or oxidation pathways has changed the debate on the mechanism of the reaction. It is no longer necessary to interpret all results in terms of an $O{=}Mn^V$(salen) species as active oxidant. The questions now are (a) what are the active species present and (b) what sort of pathway is involved when each species acts? Linde et al. suggested that with PhIO or NaOCl as oxidant a nonradical pathway exists for alkenes which is in competition with a radical pathway.[261,310] Their experiments do not distinguish whether two oxygen-transfer species compete or one oxygen-transfer species allows both pathways. Adducts formed between the terminal oxidant and the Mn(salen) species are proposed to be in competition with $O{=}Mn^V$(salen) as oxygen-transfer agents. Adam et al. proposed that XO−Mn(salen) adducts are mostly found with oxidants such as bleach and follow a concerted pathway, while oxidants such as PhIO mostly give $O{=}Mn^V$(salen), which in turn gives a radical intermediate and a higher ratio of *trans*/*cis*-epoxide.[263] However, Collman et al. suggest that oxidants such as ArIO lead to a mixture of XO−Mn(salen) adducts and $O{=}Mn^V$(salen), and their interpretation of the evidence supports the opposite mechanisms (to Adam's proposals) for these two types of species (see section 3.8.2).[264] These latest results have to be reconciled with earlier mechanistic studies including radical-trapping attempts and Eyring plots. Eyring plots with PhIO as oxidant were nonlinear, whereas with *m*CPBA and NaOCl linear plots were obtained. This seems to be more in agreement with Collman's proposals and suggests that the latter systems may yield a single oxidant, $O{=}Mn^V$(salen). Radical-trapping experiments gave more ring-opened products (due to radical trapping) when PhIO was used as oxidant than with NaOCl, suggesting there is less opportunity for formation of *trans*-epoxide from *cis*-alkenes from the $O{=}Mn^V$(salen) species than from the adduct species, which is also in line with Collman's proposals. Further research in this area should help to clarify these issues.

3.10. Conformation of O=Mn(salen) and Trajectory of Alkene Approach

To understand how Mn(salen) catalysts achieve such high selectivity in the AE of alkenes we must know the identity and conformation of the active oxygen-transfer species and the trajectory of approach of the alkene to this species. Most of the work on the latter two items assumes that the identity of the active species is $O{=}Mn^V$(salen), and so the discussion in this section is mostly confined to this entity. In light of recent studies showing that other oxygen-transfer entities can be involved, it is clear there is a need for more research in this particular area. For a detailed discussion on controlling the conformation of metallosalen complexes in general, the reader is referred to a review by Katsuki.[31]

Due to the fact that $O{=}Mn^V$(salen) cannot be isolated, it is necessary to infer its structure indi-

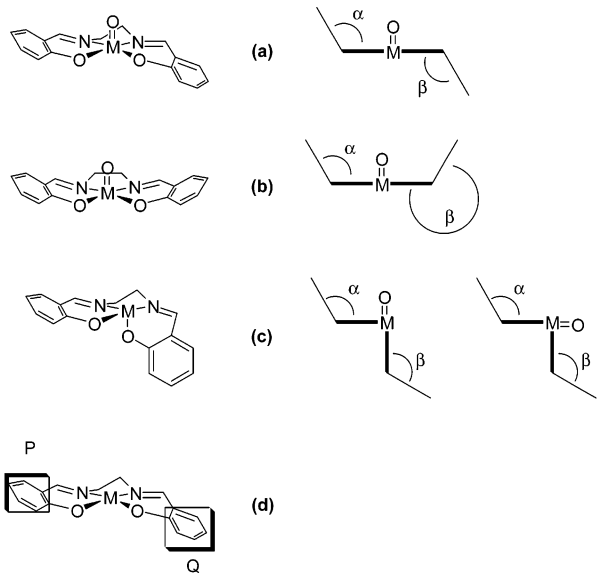


Figure 9. Conformations of M(salen) complexes: (a) 'stepped' or 'folded', (b) 'bowl-shaped' or 'umbrella', (c) 'bent', and (d) 'twisted'.

rectly. Simple Mn^{III}(salen) complexes have been crystallized,[260,330,331] and relatively flat ligand structures have been found which raises the question 'how do such flat molecules impart such high selectivity?'. As early as 1994 Feringa et al. suggested that the slight twist observable in crystal structures of Mn^{III}(salen) species could be important in the oxygen-transfer step.[330] Subsequently, it has been proposed by a number of workers that in fact the active Mn species is not so flat, and various conformational modes have been suggested.[31,39,157,161,167,322,330,338,347] Three principal nonplanar conformations (see Figure 9) have been proposed for the oxo complex: (a) stepped, sometimes called 'folded', (b) bowl-shaped, and (c) bent. In addition, there is the possibility of having a twist in each of these conformations, as described by the dihedral angle between the planes of the salicylidene rings (planes P and Q in Figure 9d). The angles α and β between the planes of the salicylidene rings and the least-squares plane of the N_2O_2 of the salen ligand determines whether and to what degree the complexes have stepped or bowl conformations. The bent conformation, on the other hand, is distinct with one of the salen oxygens in an apical position.

Complexes with stable Mn^{V}−oxo[348] bonds[349−351] have been isolated, and these may serve as a guide to structural details. They show Mn−oxo bond lengths of 1.55−1.56 Å with a square-pyramidal geometry, and they are diamagnetic. However, the ligands are tetraanionic, the Mn−oxo bond is a formal triple bond, and the complexes are stable in contrast to O=Mn^{V}(salen). Thus, any analogies between the two should be made cautiously. Nitrido−Mn^{V}(salen) complexes (formal N≡Mn triple bonds) have been isolated,[352−355] and manganese−heteroatom bond lengths of 1.51−1.56 Å have been reported. Jorgensen and co-workers argue that nitrido−manganese salen complexes can be used as structural models for O=Mn(salen) complexes. In the nitrido salen complexes, which are diamagnetic, the Mn atom is raised ca. 0.48 Å out of the least-squares plane of salen O and N atoms. O=Cr^{V}(salen) complexes show similar bond lengths and displacement from the plane (~0.53 Å).[53−55] Jorgensen and co-workers noted that the chirality of the diimine bridge is transmitted throughout the salen conformation.[337] However, the twist is smaller than that in the chromium−oxo case. Calculations suggest that the nitrido species should be less reactive than the manganese−oxo species due to a weaker bond and lower lying unoccupied MOs in the latter complex, which is indeed the case.[354]

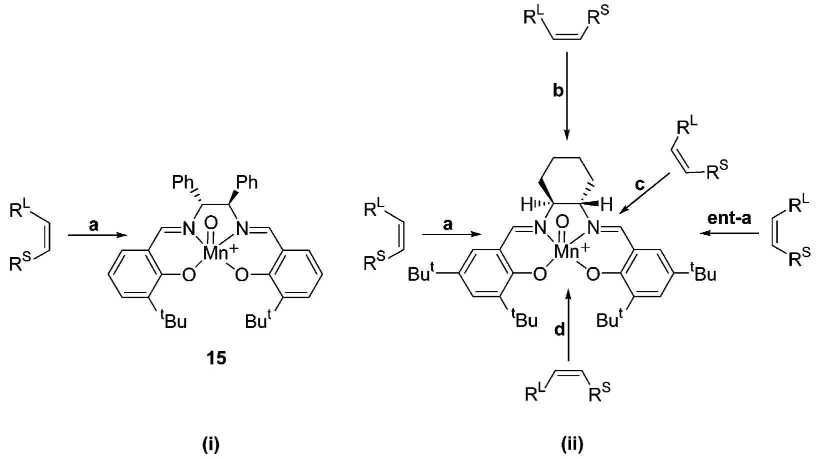
Various computational studies on O=Mn^{V}(salen) predict the distance of Mn out of the N_2O_2 plane and Mn−O bond to vary with spin state; for example, distances of 0.52, 0.40, and 0.25 Å above the plane and Mn−O bond lengths of 1.55, 1.62, and 1.68 Å were predicted by Khavrutskii et al. for the singlet, triplet, and quintet states, respectively.[313] Binding of imidazole was also predicted to increase the Mn−O bond length (0.5−0.16 Å). Calculations by Plattner, Wiest, and co-workers found 'bowl'-shaped and stepped conformations in unsubstituted O=Mn(salen)(Me$_3$NO) complexes (see Figure 9).[167,294] The relative energies of the conformations were sufficiently similar to allow them to postulate that these could be in rapid equilibrium. Also, the triplet to quintet gap was lowered by an axial ligand, making the triplet state the ground state in the stepped conformations. Interestingly, the step was accentuated by the presence of the ligand. It was also noted that incoming substrate should destabilize the bowl-shaped conformation, while a bulky *N*-oxide would destabilize the stepped conformation. This was suggested as an explanation for the detrimental effect of bulky *N*-oxides on ee. Stronger ligand binding led to weakening of the Mn=O bond, which should lead to increased reactivity. However, it should be noted that these theoretical studies were carried out with a salen ligand which did not have any substituents on the ethylenediamine backbone or on the salicylaldehyde-derived part (Model II in section 3.9.5.1). For the reasons outlined in section 3.9.5, they should therefore be treated with caution. Cavallo and H. Jacobsen suggest that even an axial anionic ligand such as Cl$^-$ will induce folding in the complex.[161]

Lipkowitz and Schefzick investigated how different structural changes in the conformation of the ligand affect Avnir's continuous chirality measure (CCM).[341] They found that the chirality content of the Mn(salen) complex could be increased most by increasing the twist and step size in the complex. They were unable to assess how the CCM relates to the ee of epoxide obtained with a given complex due to the debate over spin states (see section 3.9.4).

Katsuki and co-workers supplied strong experimental evidence that O=Mn(salen) complexes have nonplanar conformations available in solution. This was based around achiral complex **61** which, when oxidized, has potential conformers that can be enantiomeric (**oxo-61a** and **oxo-61b**, see Scheme 9). They showed that addition of nonracemic chiral amines and amine oxides could induce ee's in AE reactions (up to 82% ee).[269−271] This is most easily explained by postulating that the addition of chiral ligands

Scheme 9. Equilibrium between Achiral Mn(salen) Complexes in the Presence of a Nonracemic Ligand

Scheme 10. Proposed Trajectories of Alkene Approach to O=M(salen)$^+$



renders the reactivity of the two conformers unequal. Crystallographic studies by Katsuki and co-workers also showed that some Mn^{III}(salen) complexes can have nonplanar structures.[221,222,356] The sense of the enantioselectivity obtained in AE reactions using complex **43** was also explained in terms of a stepped structure.[220]

Many approach trajectories have been proposed to explain the degree and sense of enantioselectivity obtained with various catalysts (see Scheme 10).[39] All of these are to a greater or lesser extent side-on approaches (see Figure 10). A side-on approach by the alkene to the metal−oxo species allows a favorable orbital overlap and was previously accepted for porphyrin complexes.[81,82] The angle between the M=O bond and the new C−O bond(s) is close to 90° in a side-on approach proper. Success with *trans*-alkenes[80] in the Cr(salen) system (see section 4.1) and with, for instance, tri- and tetrasubstituted cases with Mn(salen) have necessitated some modifications.[100,101,105] These include slightly larger approach angles or stepped conformations of the complex.[157]

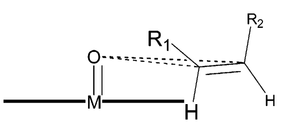


Figure 10. "Side-on" approach.

Jacobsen proposed that with complex **15** approach **a** was favored. With complexes bearing cyclohexane diamine-derived backbones, Jacobsen and co-workers proposed a trajectory of approach over the diimine bridge to explain the results they observed (approach **b** in Scheme 10).[86,331] Katsuki and co-workers are responsible for substantial development of this topic and produced compelling evidence to support their proposals. They originally proposed that the alkene approaches along the N−Mn bond[151,154] (approach **c** in Scheme 10, R_L is usually conjugated with the alkene in their proposal) and used this hypothesis to design improved catalysts.[158,211,212] They argued that approach **b** cannot account for the exceptionally high ee's observed with *cis*-alkenes[151] or the effects of chirality at the 3,3′-positions.[159] They showed how their proposed trajectory explains the sense and degree of asymmetric induction obtained using a combination of steric interactions and π,π-repulsive interactions.[153] It is noteworthy that they did not need to modify their explanation to account for the selectivity observed with trisubstituted alkenes.[213] They used **42** and **50** to distinguish between the approach suggested by Jacobsen and their own proposal. One would expect Jacobsen's approach to give epoxides with the same configuration from both catalysts. In fact, **42** and **50** gave epoxides of the opposite configuration, which is in line with Katsuki's approach.[219]

Katsuki and co-workers have since modified their position slightly.[159] Evidence that the salen ligand is stepped (see Figure 9a) in O=Mn(salen)$^+$ leads to approach **ent-a** being favored. They note that all their previous arguments hold for approach **ent-a** if the ligand is stepped. In such a conformation the 5,5′-substituents would not block approach **ent-a**. Katsuki and co-workers used the suggestion that the complexes are stepped to different degrees to explain why different diastereomers of their second-generation catalysts (bearing axial chirality at the 3,3′-positions) are more suitable for the AE of different substrates.[357] Their arguments are based on differing contributions of enthalpy and entropy to the enantioselection obtained with different diastereomers of the catalysts. The approach proposed by Katsuki explains the results obtained in the AE of *trans*-alkenes[80,218] in the oxidation of enol derivatives[103] and in attempted kinetic resolutions using Mn(salen) complexes.[122,126]

H. Jacobsen and Cavallo carried out computational studies on the trajectory of approach.[157] Their results support pathway **ent-a** as proposed by Katsuki. According to their calculations the main function of the diimine backbone is to confer rigidity to the nonplanar ligand conformation, and bulky 3,3′-substituents are necessary to block approach **d.** They suggest a reason for the lack of success obtained with a *trans*-1,2-diamino-1,2-dimethylcyclohexane-derived complex. They also suggest that the lack of success with nonconjugated alkenes is due to the absence of regiospecificity in the first C−O bond-forming step.

Houk et al. published a computational study where they proposed that the alkene approaches the catalyst from the side of the two phenolic oxygens (approach **d**).[338] They noted that there was a twist between the planes of the salicylaldehyde-based parts of Mn(salen) complexes in all structures recorded in the Cambridge Crystallography Database at that time. This twist was controlled by the diamine backbone. A strength of their proposed approach is the way that it can explain the observed selectivity for catalysts with diimine backbones derived from either stilbene diamine or cyclohexane diamine.

Khavrutskii et al. proposed that when using O_2/pivaldehyde in the absence of donor ligands a bent complex can arise (see Figure 9c).[307] They note that this complex might have a different favored approach by alkene and thus allow an alternative explanation for the reversal of enantioselection observed in these systems when donor ligands are added (see sections 3.8.3 and 3.9.5.2).

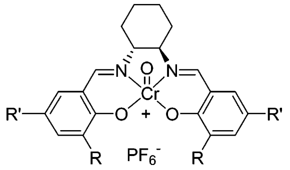
4. Asymmetric Epoxidation with Cr(salen) Complexes

Although Kochi's discovery of Cr(salen)-mediated epoxidation preceded Mn(salen)-catalyzed epoxidation (see sections 2.1 and 2.2), it has been less studied to date. This is largely due to the greater practical potential of Mn(salen) systems in terms of activity and substrate scope. However, such studies are worthwhile, both in themselves and also for the potential insights they may give on the manganese analogues. In this context, it is especially noteworthy that the stoichiometric variant of the epoxidation reaction is available in the case of chromium (the proposed active species can be isolated and reacted with alkene in the absence of terminal oxidant, see section 2.1). This gives the (relatively rare) opportunity to study stereoselectivity issues separate from catalysis issues. In attempting to draw analogies between chromium and manganese, we must be mindful to weigh all the factors involved to ensure that any insights are meaningful. For this reason, this section has been structured to aid the direct comparison of the two systems.

4.1. Initial Results and Early Modifications

When Bousquet and Gilheany[358] first reported the AE of alkenes mediated by Cr(salen) complexes such as **62**−**65** (Chart 6) it was immediately clear that there were significant differences between the chromium and manganese systems—*trans*-alkenes[80] were epoxidized at higher rates and with greater selectivity than their *cis*-counterparts; for example, *E*-β-methylstyrene was epoxidized diastereoselectively to *trans*-epoxide in up to 83% ee by **63,** while using the same conditions *Z*-β-methylstyrene gave *cis*-epoxide in 59% ee in addition to *trans*-epoxide as a minor product.[359] This called into question whether the side-on approach mechanism could be applied to Cr(salen) systems and suggested that it would be possible to design Mn(salen) systems that could epoxidize these substrates with high selectivity too (this possibility has been realized, see section 3.6). We note that the configuration of products obtained from *Z*-β-methylstyrene was the opposite of that obtained with the analogous manganese salen systems, while those from *E*-β-methylstyrene were the same.

Chart 6. O=Cr(salen)$^+$ Complexes Used in the Initial Report by Bousquet and Gilheany



62: R, R′ = H
63: R, R′ = Cl
64: R =H, R′ = Cl
65: R, R′= *t*-Bu

Two other features made the chromium system attractive for further study. First, slightly lower ee's were reported using catalytic (10 mol %) rather than stoichiometric conditions, demonstrating that the intrinsic selectivity of the catalytic system was not being achieved. This raised the question of whether the same could be true of the manganese variant. Second, additives such as phosphine oxides and amine *N*-oxides had substantial effects on rate and selectivity (±30% ee), allowing for the possibility of improving the system through ligand-accelerated catalysis independent of the salen ligand.

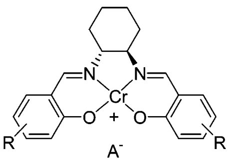
4.2. salen Ligand Tuning in O=Cr^{V}(salen) Epoxidations

Subsequent stoichiometric studies showed that, in common with the manganese systems, substituents at the 3,3′-positions played a crucial role in enabling high enantioselectivity.[39,360,361] However, complexes having chloro (**63**) or *tert*-butyl (**65**) substituents at both the 3,3′- and 5,5′-positions gave lower ee's than those bearing chloro (**66**) or *tert*-butyl (**67**) substituents at the 3,3′-positions only, Chart 7.[360] This is in contrast to the results of Jacobsen and co-workers, who found that *tert*-butyl groups at the 5,5′-positions were beneficial and halogen groups were detrimental to the ee obtainable (see sections 3.1 and 3.2). Out of nine complexes bearing non-hydrogen 3,3′-substituents surveyed by Ryan et al., eight gave ee's of >80% in the stoichiometric epoxidation of *E*-β-methylstyrene when combined with a suitable additive.[360] In contrast to Mn(salen) systems, EWGs were found to be the best substituents for the 3,3′-positions.[360] Thus, complex **68a** bearing trifluoromethyl groups at the 3,3′-positions was capable of epoxidizing *E*-β-

Chart 7

66: R = 3-Cl; A = PF_6
67: R = 3-*t*-Bu; A = PF_6
68a: R = 3-CF_3; A = NO_3
68b: R = 3-CF_3; A = BARF

BARF = [B(bis-3,5-CF_3-phenyl)$_4$]



R = 3-Br-5-X; A = PF_6

69a: X = t-Bu
69b: X = OMe
69c: X = Et
69d: X = Me
69e: X = H
69f: X = Br

methylstyrene in 92% ee and 45% yield in stoichiometric mode,[361] a record ee at the time for a nonenzymatic metal-mediated epoxidation of an unfunctionalized *E*-alkene.

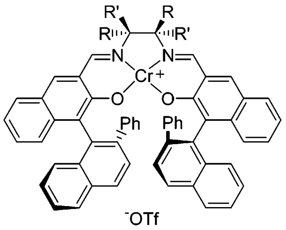
As expected from the work of Kochi and co-workers, yields and reaction times were found to vary substantially with different salen ligand substituents. In stoichiometric mode the shortest reaction times (<1 h) and highest yields (up to 48%) were recorded for halogen-bearing salen complexes.[360] Electron-donating alkyl substituents increased the reaction time dramatically (to 7−10 days for **67**). Lower yields were accounted for in the most part by unreacted alkene.[360] It was subsequently demonstrated (see section 4.8) that 50% is the maximum yield that can be expected from the stoichiometric reaction.

In 2001 O'Mahony et al. reported the results of an extensive survey of all the ring substituents of the salen ligand in Cr(salen)-mediated AE.[362] They found that 6,6′-substitution improved ee's in the absence of 3,3′-substitution. Substitution of the 4,4′- and 5,5′-positions with halogens was always detrimental to the ee obtained. Unfortunately, although 3,3′-substitution had previously been shown to be beneficial, the effects of 3,3′- and 6,6′-substitution were not cooperative. These results were rationalized in terms of competition between two different modes of approach by substrate (analogous to approaches **c** and **d** in Scheme 10) (see section 4.10). Electronic tuning of the 5,5′-substituents of a series of 3,3′-dibromo-substituted complexes[363] **69a**−**f** did not yield linear Hammett plots such as those reported by Jacobsen and co-workers with Mn(salen) complexes (see section 3.2). The existence of multiple oxidation pathways was suggested as a possible rationale for the unexpected nonlinearity. Synthetically accessible complex **69a** yielded *trans*-*β*-methylstyrene oxide in up to 90% ee, demonstrating that a bulky *tert*-butyl group could be beneficial in some cases. Complex **69a** gave higher ee's than electronically similar catalysts **69c** and **69d,** suggesting that the *tert*-butyl groups have beneficial steric effects (as noted in the manganese case, see section 3.2)

Cr(salen) complexes with various counterions have been used in epoxidations. Hexafluorophosphate and triflate are the most commonly reported. Scheurer et al. reported no reaction with a triflate counterion.[203] Daly et al. tried a variety of nonnucleophilic counterions and reported that nitrate was best[361] but not in all instances.[362] Kochi and co-workers[53,55] reported that chloride ions led to decomposition of the oxo−chromium species, although Bryliakov and Talsi[364] reported that the epoxidation of *E*-*β*-methylstyrene with the chloride analogue of **65** gives rise to epoxide in 37% yield and 41% ee.

4.3. Katsuki's Second-Generation Catalysts

Imanishi and Katsuki reported the use of second-generation-type Cr(salen) complexes **70** and **71** as AE catalysts (2 mol %).[365] Using **70** ee's of up to 78% and 70%, respectively, were reported with 2,2-dimethylchromenes and *p*-substituted styrenes as substrates (see also section 4.6). Epoxidations in ACN with **70** and **71** yielded epoxides with the opposite sense of asymmetric induction, showing that the diimine backbone was dictating the sense of induction. Complicated effects were noted in connection with the choice of solvent—these will be discussed in section 4.8.

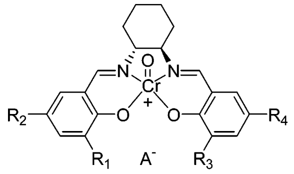


70: R = Ph
71: R' = Ph

4.4. Cr(salen) Complexes with Alternative Architectures

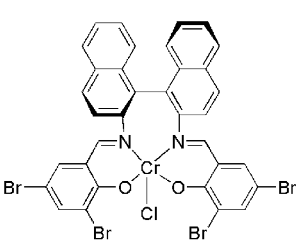
Daly et al. reported the synthesis of 'unsymmetrical' Cr(salen) and the analogous oxo−Cr(salen) complexes (**72**−**75**) with ligands in which the C_2-symmetry of the ligand was broken by use of two different salicylaldehyde moieties (see section 3.3 for manganese analogues).[196] It had been argued that if the derived oxo−Cr^V(salen) complexes were nonplanar, the C_2-symmetry of the Cr^{III}(salen) precursor might not be required, and thus, it was postulated that these new complexes might offer a way of improving their performance in AE reactions (note that nonplanar $Cr^{III}(salen)^+$ complexes can still have C_2-symmetry, see section 4.10). However, each unsymmetrical complex exhibited lower enantioselectivity than either of the corresponding symmetrical analogues. On the other hand, the effect of added Ph_3PO was particularly dramatic, raising ee's by 27−46%. The explanation proposed as the simplest for the observed effects was that two diastereomeric complexes (for instance, **72** and **73**), formed by introduction of the oxo ligand react with different selectivities and rates. Since the reaction with alkene was incomplete, the contribution by the two complexes was unequal.

Scheurer et al. reported the synthesis and use of M(salen) complexes with diimine backbones derived from L-tartaric acid of which **36** and **37** are examples.[203] In contrast to the results of Gilheany and co-workers, with **36** they obtained the same stereochemistry as with **37** in the AE of 2,2-dimethyl-



72: R_1,R_2 = Cl, R_3 = *t*-Bu, A = NO_3
73: R_1 = *t*-Bu, R_3,R_4 = Cl, A = NO_3
74: R_1,R_2 = *t*-Bu, R_3 = Cl, A = PF_6
75: R_1 = Cl, R_3,R_4 = *t*-Bu, A = PF_6

chromene (in low ee). No rational was proposed for the observed stereochemistry. Schuster et al. reported the diastereoselective epoxidation of α-pinene using **65** and its stilbene diamine-derived analogue with molecular O_2 as terminal oxidant.[106,107] Zhou et al. reported the use of **76** with a diimine backbone bearing axial chirality.[366] Moderate ee's (ca. 60%) were obtained in the AE of 4-chlorostyrene and *Z*-*β*-methylstyrene in toluene using PhIO as oxidant.



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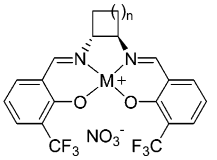
In 2003 Daly and Gilheany reported attempts to synthesize metal(salen) complexes (e.g., **77a**,**b**) with diimine backbones derived from enantiopure *trans*-cyclopentane-1,2-diamine and *trans*-cyclobutane-1,2-diamine (see section 3.3 for manganese analogues).[201] They hoped that by increasing the dihedral angle at the diimine backbone of the salen they could synthesize complexes with more deeply stepped conformations (see section 4.10). Only the cyclopentane-derived salen gave a well-defined Cr(salen) complex (**77b**), and it gave a slightly lower ee in the AE of *E*-*β*-methylstyrene than **68a**.



77: M = Cr
a: n = 1
b: n = 2

4.5. Stoichiometric Oxidants

In contrast to the Mn(salen) system where a huge variety of terminal oxidants are viable (see section 3.5), PhIO is used almost exclusively in the Cr(salen) AE. Gilheany and co-workers[358,361] noted that bleach gave considerably poorer ee's than PhIO and speculated that this might be due to the presence of chloride ions in solution (see section 4.2). Interestingly, the sense of enantioinduction was reversed (see section 4.9.4 for discussion and section 3.5 for oxidant-induced changes in configuration in Mn(salen)-promoted AE).[361] H_2O_2 and *n*BuNHSO$_5$ failed to give appreciable yields of epoxide (<5%).[361] Bryliakov and Talsi[364] reported that *m*CPBA produced the (salen)-Cr^V=O and should be a suitable oxidant but noted that the background reaction probably would not allow enantioselection. NMO had been used to suppress background oxidation by *m*CPBA in the Mn(salen) AE (see section 3.5), but Scheurer et al. already reported that NMO/*m*CPBA is not viable in Cr(salen) AE.[203] Schuster et al. briefly reported the Cr(salen)-catalyzed diastereoselective epoxidation of α-pinene with molecular O_2 as terminal oxidant.[107] Low yields were obtained in achiral epoxidations using Cr(salen)/*tert*-butylhydroperoxide[61] and Cr(salen)/$NaNO_2$.[59] Brandt et al. speculated that the heavy iodine atom in PhIO might facilitate the spin change from the quartet Cr^{III}(salen) to the doublet O=Cr^V(salen) (see section 4.9.3), and therefore, oxidants other than PhIO perform badly in the system.[370]

4.6. Problems with Substrates—Only *trans*-Alkenes?

The reported substrate scope of Cr(salen)-mediated AE is limited. Gilheany and co-workers concentrated much of their efforts on the epoxidation of *E*-*β*-methylstyrene in an attempt to understand the dramatic selectivity difference between Cr(salen) and Mn(salen) complexes. Imanishi and Katsuki[365] reported the AE of 2,2-dimethylchromenes and styrenes in up to 78% and 70% ee, respectively, using **70** (see section 4.3). The latter are promising ee's given that a low-temperature (−78 °C) protocol is required to obtain high ee's with terminal alkenes using Mn(salen)-catalyzed AE (see section 3.5). *E*-*β*-Methylstyrene is the only other substrate reported to have been epoxidized in >70% ee. Several conjugated *cis*- and *trans*-alkenes[80] have been epoxidized in 60−70% ee.[39] In addition, Schuster et al. report the diastereoselective epoxidations of α-pinene in >70% de.[106,107]

4.7. Effects of Added Donor Ligands

From the first discovery of Cr(salen)-mediated AE it was clear that added donor ligands could have dramatic effects on the outcome of the reaction.[358] The donor ligand is thought to act by forming an adduct with the O=Cr^V(salen) complex, thus altering the reactivity and conformation of the complex (see section 2.1.2). Ph_3PO has been found to be the most consistent additive in improving the ee obtained,[39,360−363,367,368] but there are notable effects from a wide variety of other additives such as phosphine sulfides, amine oxides, sulfoxides, and even carbonyl compounds. Essentially any compound containing an oxo moiety has some effect. The effects of donor ligands are greatest when either the 3,3′- or 5,5′-position, or both, is substituted.[362] The ability of additives to improve the ee is greatest with the least selective catalysts and smallest with the most selective catalysts. It was noted that this ‘ceiling effect’ is not just a result of the nonlinear relationship between % ee and $\Delta\Delta G^‡$.[361] It has been proposed that the beneficial effects of salen substitution and additive were working in concert, and it was speculated that both types of change were pushing the oxo−Cr(salen) complex toward an optimum conformation.

In addition to varying effects on ee and yield, Imanishi and Katsuki reported one instance where the addition of donor ligand changes the actual sense of the ee obtained in the AE of a 2,2′-dimethylchromene derivative.[365] This result will be discussed in terms of competing epoxidation pathways in section 4.9.

The strong donor ligand effect observed with unsymmetrical Cr(salen) complexes[196] was proposed to arise due to selective binding of Ph_3PO to one of the diastereomeric oxo complexes and either increase selectivity or reactivity of that complex (note that there is incomplete reaction between O=Cr(salen) and the alkene).

Gilheany and co-workers noted that bulky donor ligands were less effective and the effects of donor ligands on rates were lower than expected from the work of Kochi and co-workers on achiral systems (see section 2.1.2).[368] The fact that the effects on ee reached a maximum at substoichiometric quantities (with respect to O=Cr(salen)) and that the expected binding constants are low suggest that the role, or more probably roles, of the donor ligand is more complex than previously suggested (see below).

Additives with extended π-systems also have large effects[367] (±20% ee), and it was speculated that these might be due to interference with $\pi-\pi$ interactions between the incoming substrate and the salen ligand aromatic rings in a manner analogous to that proposed for manganese by Katsuki (see section 3.10).

Using EPR spectroscopy and complexes with chloride counterions, Bryliakov and Talsi showed that addition of a donor ligand such as DMF changes the equilibrium ratio between different Cr^V species in solution.[364] Addition of donor ligands (D) decreased the concentration of the proposed dimeric species and led to an increase in monomeric $DCr^V{=}O$(salen). The $Cr^V{=}O$(salen) species also showed greater stability against decomposition (in the absence of substrate) when ligated. Similar roles have been proposed for donor ligands in Mn(salen) AE systems (see section 3.7).

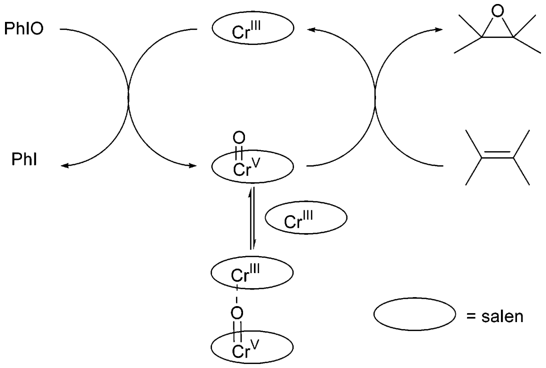
4.8. Nature of the Active Species and the Catalytic Cycle

Kochi and co-workers showed that Cr^{III}(salen) reacts with PhIO to give an $O{=}Cr^V$(salen) species which can be isolated and was shown to epoxidize alkenes (see section 2.1.1). However, another epoxidizing species has been suggested as a possibility by various groups. Both a PhIO−(salen)Cr^{III} adduct[361,365] and a (salen)$Cr^{IV}{=}O$ entity[361] have been considered as potential oxygen-transfer agents. If oxygen transfer to alkene takes place exclusively from $O{=}Cr^V$(salen), then the selectivity of a given complex should be the same under catalytic and stoichiometric conditions. The sense of enantioselectivity would be expected to remain constant in different solvents also. These two expectations are not fulfilled. It is also noteworthy that, in contrast to the Mn(salen) systems, the Cr(salen) catalyst can be recycled and reused without loss of selectivity or reactivity.[360] Efforts to improve the performance of Cr(salen) complexes by heterogenizing them have met with some success but are beyond the scope of this review.[61,366]

The catalytic cycle cannot just follow the simple oxygen rebound scheme first proposed by Kochi (see Scheme 1). Gilheany and co-workers noted that the yield in stoichiometric reactions (<50%) was lower than that in catalytic reactions.[360,361] They proposed[361] that in the stoichiometric mode Cr^{III}(salen) generated during the reaction reacts with $O{=}Cr^V$(salen) to produce Cr^{IV}salen−μ-oxo dimers similar to those proposed in manganese systems (see section 2.2.3). This would reduce the amount of epoxide that can be produced by acting as a chromium(V) sink. The excess PhIO under catalytic conditions prevents this from occurring. Experimental evidence in support of this hypothesis was given, including electrospray mass spectrometry experiments and yield data from stoichiometric reactions to which either extra Cr^{III}(salen) or extra oxo−Cr^V(salen) was added.

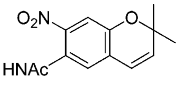
Bryliakov and Talsi[364] recently presented EPR and ^2H studies that support the presence of a mixed-valence binuclear L(salen)Cr^VOCr^{III}(salen)L species (where L = Cl or solvent) in reaction mixtures rather than the $[Cr^{IV}(salen)]_2$−μ-oxo dimer. This binuclear species was shown to be present even in solutions exposed to >1 equiv of PhIO with respect to Cr(salen), although increasing the amount of PhIO present did shift the equilibrium toward the monomeric $Cr^V{=}O$ species. Bryliakov and Talsi suggest that it acts solely as a reservoir for the active (salen)$Cr^V{=}O$ species. We note that the half-life of this binuclear species was shown to be lower in the presence of substrate, but this does not imply that it is an active catalyst since the degree of disproportionation to monomeric $O{=}Cr^V$(salen) might be expected to increase in the presence of substrate. A revised catalytic cycle is shown in Scheme 11. Note the similarity with its manganese equivalent (Scheme 2).

Scheme 11. Revised Catalytic Cycle (donor ligands omitted for clarity)



Decreases in selectivity on going from stoichiometric mode to catalytic mode have been noted by Gilheany and co-workers;[39,358,361] for example, with **68a** as catalyst in the AE of E-β-methylstyrene, the ee obtained in stoichiometric mode was higher than that in catalytic (10 mol %) mode (90% vs 82% in the absence of donor ligand).[361] Decreasing the catalyst loading further also decreased the ee. When NaOCl was used as oxidant the sense of enantioselectivity was opposite to that observed with PhIO as oxidant.[361] A second active species was proposed to be present under catalytic conditions. Catalyst decomposition to less selective species over the course of the reaction was discounted as the ee remains constant.

Imanishi and Katsuki[365] reported that in the AE of 2,2-dimethylchromenes **78** and **79** with complexes **70** and **71** the stereochemistry of the major epoxide enantiomer depended on the solvent used; for example, when alkene **78** was epoxidized by complex **71** (2 mol %) in acetonitrile (ACN) the (3*S*,4*S*)-epoxide was obtained in 42% ee and 2% yield. However, when the same reaction was run in toluene the (3*R*,4*R*)-epoxide was obtained in 46% ee and 14% yield! Similarly, with **70** epoxides of the opposite configuration were favored depending on whether CH_3CN or toluene was used, and the addition of 4-phenylpyridine-*N*-oxide (4-PPNO) (20 mol %) had different effects in the two solvents. In ACN it had a beneficial effect on ee but resulted in lowered yields, while in toluene both ee's and yields were reduced. With chlorobenzene as solvent the configuration of the major epoxide isomer changed when 4-PPNO was used and yields were lower. Two possibilities were considered to explain these strange results: (i) there were different dominant active species depending on the solvent used or (ii) the reaction proceeds through different intermediates depending on the choice of solvent (see section 4.9).



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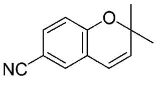

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A Cr(salen)−PhIO adduct was suggested by Imanishi and Katsuki[365] as a possible active species that might compete with O=Cr(salen). Previously, an iron−porphyrin−PhIO adduct was reported to epoxidize alkenes.[369] They hoped that *N*-Me-Imd might convert such an adduct to a chromium−oxo species since such a conversion had been proposed for manganese acylperoxo and hydroperoxo manganese species (see section 3.7). However, the addition of *N*-methylimidazole did not change the configuration of the major epoxide isomer obtained in ACN or toluene. It was also reported that the use of pentafluoroiodosylbenzene instead of PhIO gave the oxo complexes of the iron porphyrins and not the PhIO adducts.[369] However, the use of pentafluoroiodosylbenzene instead of PhIO gave the same sense and 'similar' levels of enantioselectivity in toluene and ACN with *p*-chlorostyrene as substrate. Unfortunately, the reaction was not carried out in stoichiometric mode, and so the possibility of a Cr(salen)−PhIO adduct was not ruled out completely. Imanishi and Katsuki favored the proposal that different reactive intermediates were favored depending on the solvent, see section 4.9.

Ordinarily AEs with chromium complexes proceed with good diastereoselectivity, that is, epoxidation of *trans*-alkenes[80] gives *trans*-epoxide and cis gives cis as the major product. The intermediacy of (salen)-Cr^{IV}=O was proposed to explain the unusual 1:1 ratio of *trans*- and *cis*-epoxide and low enantioselectivity observed when **68b** was used in the AE of *E*-*β*-methylstyrene. The BARF ([B(bis-3,5-CF_3-phenyl)$_4$]) counterion is known to be susceptible to one-electron oxidation, and calculations supported the proposal.[370]

4.9. Mechanism of Oxygen Transfer

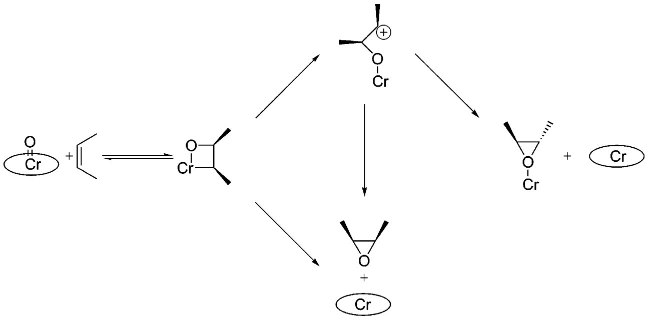
Most of the discussion in relation to the mechanism of oxygen transfer to alkene has been based on electrophilic attack of an O=Cr^V(salen) species (or an O=Cr^V(salen)D species where D is a donor ligand) on the alkene. In the achiral variant Kochi and coworkers established that a discrete intermediate exists along the reaction pathway after the rate-determining step (see section 2.1.3). Additionally, any mechanistic rationale should allow for the production of mixtures of *trans*- and *cis*-epoxides from conjugated *Z*-alkenes and perhaps the reversal in the sense of enantioinduction observed by Katsuki and Imanishi on changing solvent. Using Cr(salen)Cl complexes Bryliakov and Talsi[364] showed that reaction of [Cr^V=O(salen)D] with substrate displays pseudo-first-order kinetics and self-decay pathways not involving substrate also exist.

The existence of a radical intermediate along the reaction pathway would explain the production of *trans*-epoxides from *Z*-alkenes. However, Kochi observed a correlation with σ^+ in the epoxidation of a series of *para*-substituted styrenes, suggesting that a cationic intermediate (which could also explain the isomerization) participates.

4.9.1. Viability of Metallaoxetane Intermediates

To explain the unusual solvent effects they observed (see section 4.8), Imanishi and Katsuki proposed that the reaction proceeded through a cationic intermediate in ACN (as originally proposed by Kochi, section 2.1.3), but in less polar solvents such as toluene the only intermediate involved was a metallaoxetane (see Scheme 12). According to this hypothesis styrene derivatives might be epoxidized in higher ee if a metallaoxetane was the only intermediate since it would not be prone to epimerization (this has been used to explain the low ee's obtained for the epoxidation of styrene derivatives with Mn(salen) complexes under standard conditions, see section 3.5). This expectation was borne out with ee's of up to 50−70% being obtained in toluene in Cr(salen)-catalyzed epoxidations of styrene derivatives at 0 °C. These results suggested that with further tuning Cr(salen) complexes could be more suitable

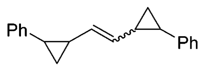
Scheme 12. Proposed Reaction Mechanism Involving Metallaoxetane Intermediates



catalysts for the epoxidation of styrene derivatives than their manganese counterparts (high ee's are reported for Mn(salen) complexes at −78 °C using *m*CPBA as oxidant,[117,118] see section 3.5). At the very least, these results suggest the participation of intermediates where free rotation about the C−C bond can be limited. The main problem with proposing a metallaoxetane intermediate is the same as for the manganese cases (see section 3.9.3)—it necessitates a seven-coordinate species.[53] Katsuki and Imanishi preferred this explanation to the hypothesis that there were different dominant active species depending on the solvent used (see section 4.8 for discussion of this proposal).

4.9.2. Use of Substrates as Reaction Probes

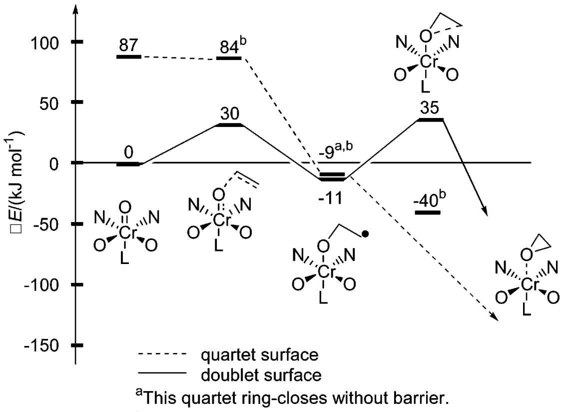
The results of experiments using radical traps in the Cr(salen)-catalyzed AE reaction were recently reported.[370] Using alkenes **56a** and **80** no epoxide was detected in the products of the reaction with catalyst **62** under catalytic or stoichiometric conditions. Unfortunately, it was also shown that the epoxide of **56a** was not stable under reaction conditions. However, the distributions of the reaction products from the breakdown of the epoxide and from the AE reaction were different, strongly suggesting the breakdown of a reaction intermediate. Thus, in accord with the report of Kochi and co-workers, this was strong evidence of the existence of a stepwise pathway for the reaction. Unfortunately, owing to the limits placed on the design of the traps by the substrate scope of the reaction, the results did not show conclusively that a stepwise pathway was the only viable pathway for the production of epoxide (cf. the results of Linde et al. with radical traps in Mn(salen)-catalyzed epoxidations, see section 3.9) nor do the traps distinguish between a cationic and radical intermediate.



80

4.9.3. Spin States and Theoretical Calculations

In conjunction with their experimental study, Brandt et al. carried out a DFT study of the Cr(salen)-mediated epoxidation reaction. The reader is referred to section 3.9.5 for a critical assessment of methods used in computational studies on M(salen) systems and the reliability of results. Using B3LYP and Model I their calculated ground spin states for $Cr^{III}(salen)^+$ and $O{=}Cr^{V}(salen)^+$ of quartet and doublet, respectively, were in good agreement with experimental values established by Kochi and co-workers[53] and Bryliakov et al.[371] This provided further validation for the calculations carried out on $Mn(salen)^+$ systems using the same methods (see section 3.9.5.1). In contrast to the proposal of Kochi and co-workers (see section 2.1), their calculations suggest a radical intermediate rather than a cationic one (see Figure 11). The first C−O bond is formed on the doublet PES, giving rise to the radical intermediate. Two possibilities then exist: the second C−O bond formation takes place followed by spin crossing to the quartet surface or a spin crossover to the quartet PES is then followed by barrierless collapse to the Cr^{III}(salen)−epoxide complex. The probability for spin crossover before the second bond formation event is considered to be quite high as judged by the small energy differences between the two PESs at this point. This is supported experimentally by the relatively low (compared with Mn(salen)) quantities of *trans*-β-methylstyrene oxide that arise in the epoxidation of *Z*-β-methylstyrene by Cr(salen) complexes. The coordination of donor ligand was calculated to lower the energy of activation for the addition of ethene to the $O{=}Cr(salen)^+$ model, which explains the increase in rates noted when donor ligands are used. Second, in the transition state the salen ligand has a different calculated conformation and is closer to the substrate when donor ligand is coordinated. This accounts for the increased enantioselectivity observed with donor ligands. In close analogy with the work of Wiest and co-workers on O=Mn(salen) (see section 3.10), the study found two different possible conformations for the $O{=}Cr(salen)^+$ species. It was speculated that the difference in substrate selectivity between the manganese and chromium systems might be due to differences in conformational preferences of the respective complexes for the stepped or bowl conformations. In addition, the calculations support the following explanation for the high amounts of *trans*-β-methylstyrene oxide from the AE of *Z*-β-methylstyrene with **68b**: a one-electron reduction of the BARF counterion takes place, and the resulting $Cr^{IV}{=}O$ species (which has a triplet ground state) reacts with alkene to form a radical intermediate which is stable on the triplet and quintet PESs, and so C−C bond rotation has more time than usual to take place. Finally, Brandt et al. suggested the poor performance of some oxidants may be linked to spin-state issues.



aThis quartet ring-closes without barrier.

bVertical excitation from the doublet surface.

Figure 11. PES calculated by Brandt et al. (Reprinted with permission from ref 370. Copyright 2002 Wiley.)

4.9.4. Evidence for Multiple Oxidation Pathways

Multiple oxidation pathways have been proposed as possible explanations for various results.[361,363,365] The fact that the sense of enantioinduction with a given catalyst changed either by changing the reaction solvent[365] or the oxidant[361] could be explained by the existence of two competing reaction pathways. Also, the lower selectivities observed in catalytic reactions compared with stoichiometric reactions might be explained in this manner. Multiple oxidation pathways have also been proposed as a possible reason for the nonlinearity observed in Hammett plots (see section 4.2).[363] The experimental evidence has already being detailed in sections 4.9.1, 4.8, and 4.2. Although these results might be explained by two competing active oxidants, evidence as to the nature of such a species is lacking. In addition, it is difficult to envisage how the enantioselectivity of the product could be constant with time if the multiple oxidants proposal were true. Whereas bifurcation of the reaction pathway after the rate-determining step can easily explain the constant ee during the reaction, and in fact, in the presence of some additives Kochi noted formation of byproducts in this manner.

4.9.5. Summary of Mechanistic Studies

Although the existence of O═Cr^V(salen) as an epoxidizing species and mixed-valent dimeric species as a catalyst sink are in accordance with all the evidence, other aspects of the reaction mechanism remain unclear. Katsuki's proposal of a metallaoxetane species which can decompose either directly to epoxide or via a cationic intermediate is consistent with the observed experimental evidence, while computational studies, on the other hand, support the formation of a radical species. The main objection to metallaoxetane species is the formation of a seven-coordinate intermediate, while proposed radical intermediates are not in agreement with Kochi's substrate studies and do not seem to explain the reversed enantioselectivities and decreased catalytic ee's that have led to proposals of multiple oxidation pathways.

4.10. Trajectory of Alkene Approach and Conformation of O═Cr(salen)

Bousquet and Gilheany noted that a side-on approach (see Figure 10) by alkene to a planar O═Cr(salen)$^+$ complex could not explain the selectivity observed.[358] However, a nonplanar O═Cr(salen) complex can accommodate such an approach.[39] Experiments with unsymmetrical complexes[196] led to the suggestion of stepped as opposed to bent conformation (see Figure 9). This is in agreement with crystal structures of achiral O═Cr(salen) complexes (see section 2.1). An attempt to increase the step using a cyclopentane diimine-derived complex was unsuccessful, although this may have been due to a loss of conformational rigidity.[201] Calculations[370] support proposals that coordinating donor ligands affect the conformation of the O═Cr(salen) species and thus the observed selectivity. Gilheany and co-workers originally favored approach over the 3,3′-positions of the complex (as proposed by Houk for Mn(salen), see Scheme 10) to rationalize the observation that although the 3,3′-positions needed to bear substituents, halogens gave better selectivity than bulky groups such as *tert*-butyl. Subsequently, they admitted the possibility of approach along the Cr−N bond (as proposed by Katsuki for Mn(salen), see section 3.10) to account for noncooperative effects between the substituents at the 6,6′- and 3,3′-positions.[362]

5. Comparison and Summary of Cr(salen)- and Mn(salen)-Promoted AE

Highly enantioselective M(salen) catalysts have been developed for the AE of a wide variety of alkenes. Chart 8 shows representative epoxides which can be accessed by Mn(salen)-catalyzed AE. For small-scale use, commercially available Mn(salen) catalyst **19** (Jacobsen's catalyst) has been demonstrated to be very effective for a broad range of conjugated alkenes. The second-generation Mn(salen) catalysts introduced by Katsuki and coworkers have surpassed Jacobsen's catalyst in terms of selectivity and activity, but they are not as synthetically accessible, and this has limited their application. *trans*-Epoxides can be accessed in high ee from *cis*-alkenes using **19** or from *trans*-alkenes using Cr(salen) or specific second-generation Mn(salen) catalysts.

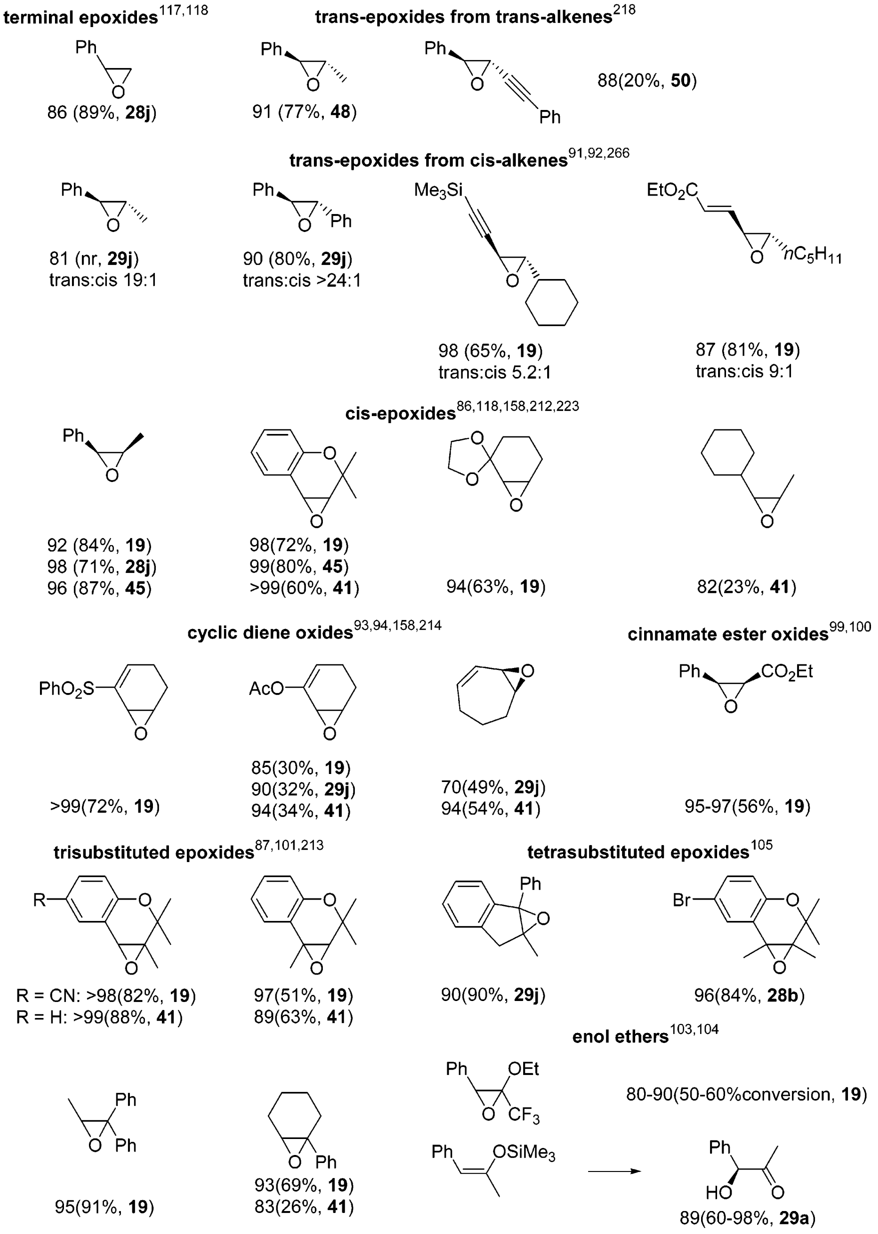
A wide variety of oxidants can be used with Mn(salen), but sodium hypochlorite is most commonly used. This has the advantage of being relatively inexpensive and, once reduced, environmentally benign. To date, the choice of oxidant with Cr(salen) is restricted. In both systems the choice of oxidant can affect the yield, specificity, de (particularly with Mn), and ee (particularly with Cr).

Added donor ligands such as PyO can have dramatic effects on AEs catalyzed by M(salen) complexes. The catalyst stability, rate, ee (especially with Cr), and de (especially with Mn) of the epoxidation can be influenced. Coordination of these additives to the metal center is the principal way in which they exert their influence. In the case of Mn(salen)-catalyzed AE with NaOCl as oxidant there is an added role for these additives as phase-transfer catalysts. In both Cr and Mn systems the addition of a donor ligand can reverse the sense of enantioinduction under some reaction conditions. Chiral nonracemic donor ligands can induce good ee's with achiral Mn(salen) catalysts. In a recent study a donor ligand rendered the outcome of the reaction independent of the choice of counterion and iodosylarene.

A wide variety of spectroscopic techniques have been used to probe the catalytic cycle. The number and nature of M(salen)-derived species present is highly dependent on the conditions used. There is significant room for improvement of the recyclability and TON of the catalysts. A greater understanding of the deactivation and decomposition pathways would be of use in this respect.

There remain substantial unresolved issues in relation to the mechanism of M(salen)-catalyzed epoxidations. The importance of the spin state of the metal in determining the outcome of the reaction has been examined by theoretical studies with some experimental support. Advances in computational methods should help to clarify this issue. Oxygen transfer to alkene is from a (salen)M^V═O species in some cases; however, this is not the only active species. In Mn(salen)-catalyzed AE radical intermediates intervene in the formation of *trans*-epoxides from conjugated *Z*-alkenes. However, there is evidence that a completely separate pathway, with no radical intermediates, exists and by which, for in-

Chart 8. Representative Products Which Can Be Accessed by Mn(salen)-Catalyzed AE[a]



[a] References are given for each product class. The % ee obtained is given below each structure along with the yield and catalyst used in parentheses; nr = not reported.

stance, *cis*-epoxides can be formed from *Z*-alkenes. There is now firm evidence supporting the participation of multiple competing oxygen-transfer species under standard conditions in both the Cr and Mn system. Adducts formed between the M(salen) complex and terminal oxidants such as PhIO are the most likely candidates at the present time in the Mn system. A consensus on the relative selectivities of these adducts and $O{=}M^V$(salen) has not been established. Computational studies have led to several alternative proposals for the nature of the oxidant. Choice of reaction conditions, especially terminal oxidant and donor ligands, can influence the relative degree of participation of the competing oxidants and thus the outcome of the reaction.

For the case of $O{=}Mn^V$(salen) as the oxygen-transfer species, many different approach trajectories for substrates have been suggested. The balance of evidence in Mn(salen)-catalyzed AE suggests that, for most complexes, the substrate approaches over the aromatic ring of the salen ligand to some extent. There is nearly full agreement that the degree of nonplanarity of the conformation of these complexes plays an important role in determining the exact trajectory. For other potential oxygen-transfer species the substrate approach trajectory has hardly been explored.

In conclusion, there is a large scope for increased understanding of the mechanistic possibilities which should lead to further improvements in catalyst design and/or reaction conditions.

6. Abbreviations Used

AD	asymmetric dihydroxylation
AE	asymmetric epoxidation
BARF	[B(bis-3,5-CF_3-phenyl)$_4$]
B3LYP	Becke three-parameter hybrid functional combined with Lee–Yang–Parr correlation method

BP86	Becke−Perdew 1986
CCM	continuous chirality measure
DFT	density functional theory
DMF	*N,N'*-dimethylformamide
ee	enantiomeric excess
ESR	electron spin resonance
ES-MS	electrospray mass spectrometry
EPR	electron paramagnetic resonance
EWG	electron-withdrawing group
EXAFS	extended X-ray absorption fine structure
HF	Hartree−Fock
*m*CPBA	*m*-chloroperbenzoic acid
N-Me-Imd	*N*-methyl-imidazole
NMO	*N*-methyl-morpholine-*N*-oxide
PES	potential-energy surface
PyO	pyridine-*N*-oxide
4-PPNO	4-phenylpyridine-*N*-oxide
P_3NO	4-(3-phenylpropyl)pyridine-*N*-oxide
TBDMS	*tert*-butyldimethylsilyl
TEMPO	tetramethylpiperidine *N*-oxide
TES	triethylsilyl
TIPS	triisopropylsilyl
TMS	trimethylsilyl
TON	turnover number
TS	transition state
wrt	with respect to
XANES	X-ray absorption near-edge structure

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8. Note Added in Proof

The reader is referred to the following article: Xia, Q.-H.; Ge, H.-Q.; Ye, C.-P.; Liu, Z.-M.; Su, K.-X. Advances in Homogeneous and Heterogenous Catalytic Asymmetric Epoxidation. *Chem. Rev.* **2005**, *105*, 1603 (next article in this issue). submitted for publication. We thank Prof. Xia for the opportunity to read this article in advance of its publication. The reader will find many other catalytic asymmetric epoxidation systems reviewed, including dimeric and heterogenous Mn(salen) and Cr(salen) systems which were outside the scope of the present review.

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