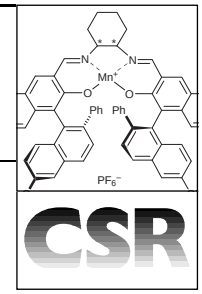
Utilisation of homogeneous and supported chiral metal(salen) complexes in asymmetric catalysis



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The first salen ligand and Cu complex were discovered in 1889, and gradually the potential catalytic activity of subsequent salen species has been recognised, particularly in the case of achiral salen complexes in oxidation reactions. The development of chiral salen metal complexes and catalysts in the last decade has however stimulated a very rapid growth in the chemistry and application of these species. The variety of asymmetric reactions in which particular chiral metal salen complexes are proving useful grows steadily, and there is no evidence of this growth slowing. This review summarises the key work and references on soluble chiral metal salen complex catalysts categorised according to the metal centre. It also describes the work to date on producing supported heterogeneous chiral analogues of some of these.

1 Introduction

Currently one of the most important synthetic ligand systems, especially in the context of asymmetric catalysis, are the tetradentate Schiff bases **1** known as salen (*N*,*N*′-bis(salicylaldehydo)ethylenediamine).† In 1889, while studying the effect of diamines on diketones, Combes prepared the first salen ligand **2** and its Cu complex.[1] Since then, salen derivatives and their metal complexes have been synthesised and characterised and gradually their value as catalysts has become recognised.[2] With the growth in interest in enantiomerically pure compounds for the pharmaceutical and agrochemical industries, it is perhaps not surprising that in the last decade attention has focused on chiral salen ligands, and in particular on the use of their optically pure metal complexes as asymmetric catalysts. Applications have grown rapidly and a broad range of asymmetric catalyses have now been described including oxidations, additions and reductions. It is therefore timely to review this expanding area.

† In this review, the terminology salen will be used to describe all the systems related to ligand **1**.

2 Homogeneous metal(salen) complexes

2.1 Manganese(salen) complexes

Various asymmetric reactions can be carried out using manganese(salen) complexes as catalysts.

2.1.1 Epoxidation of alkenes

2.1.1.1 Jacobsen's catalyst

In the early nineties, Jacobsen and his colleagues designed the chiral Mn(III)–Schiff base complex **3** which is currently the

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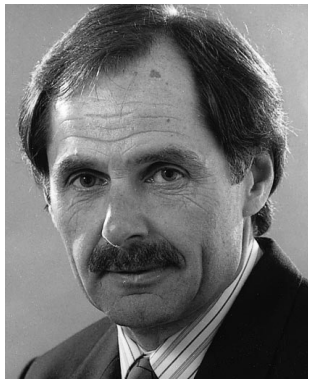

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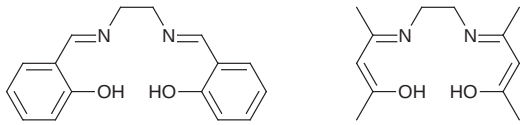

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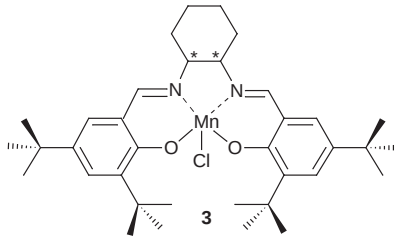
most efficient catalyst available for the enantioselective epoxidation of unfunctionalised olefins.[3] The catalyst was the result of a logical sequence of ligand modifications involving more than fifty complexes.

Enantioselective epoxidations of simple olefins using Jacobsen's catalyst give yields of up to 97% with an asymmetric induction as high as 98% enantiomeric excess depending on the substrate. The method typically involves 2 to 5 mole percent of catalyst in an organic solvent such as dichloromethane (Scheme 1). The source of oxygen used can be either an aqueous oxidant



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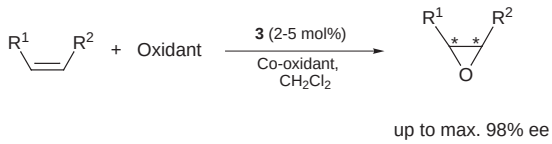


Scheme 1 Catalytic enantioselective epoxidation of simple olefins.

such as sodium hypochlorite or an organic peracid, for example *m*-chloroperbenzoic acid. In both cases, the presence of an additive has a significant effect on the catalysis rate, the yield and the enantioselectivity of epoxidation. Under aqueous conditions, 4-phenylpyridine *N*-oxide is the additive of choice whereas, in a non-aqueous system, *N*-methylmorpholine *N*-oxide appears to be most effective. The primary role of the additive is to avoid the formation of unreactive μ-oxo-Mn(IV) dimers.

2.1.1.2 Mechanism

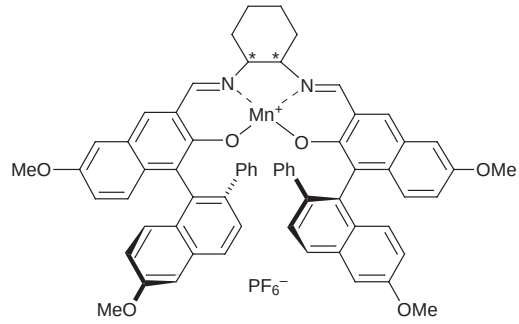
The question of mechanism remains a very active topic with continuing debate amongst the leading groups. It is generally agreed that the initial complex **3** is oxidised to a reactive oxo-Mn(V)salen complex. The latter has not been isolated and characterised but related species with other metal centres are known. While **3** is almost certainly planar, the oxo species has been postulated as planar, bent and twisted (folded) by different researchers. Interestingly whereas many transition metal complex catalysed reactions of alkenes invoke co-ordination of the alkene at the metal centre, this is not envisaged with this system. Instead the alkene is viewed as approaching the oxo oxygen atom directly followed by oxygen transfer to form the epoxide. Considerable discussion has taken place regarding how this transfer is achieved and various mechanisms have been proposed: concerted; stepwise *via* a carbocation; stepwise *via* a radical; [2 + 2] cycloaddition leading to a metallaoxetane; electron transfer and charge transfer. The latter two mechanisms are difficult to sustain since they cannot adequately account for the very high stereocontrol observed in these catalyses. Radical intermediates and the involvement of a metallaoxetane are also now not favoured for the Mn system — but the debate remains. Stereocontrol is seen as arising as a result of the specific trajectory of approach of the alkene to the oxo-Mn(V)salen complex with interaction of the alkene substituents with the ligand ultimately controlling the stereochemistry and in this case the enantioselectivity of the catalyst. Detailed arguments have been presented regarding the trajectory by those favouring a planar, bent or twisted structure for the oxo complex and substrate structure dependence is important in these arguments.

It is worth emphasising that the active Mn complex has a great tendency to form a μ-oxo-Mn(IV)dimer which is inactive and prevents the catalytic cycle continuing. As mentioned earlier the primary role of the *N*-oxide co-oxidant appears to be co-ordination to monomeric Mn centres such that dimer formation is inhibited. To maximise this benefit and optimise catalytic turnover the experimental procedures reported in the literature need to be carefully reproduced.

A very detailed and critical discussion of all key publications to date in this area appears in a seminal article published by Gilheany and co-workers[4] which appeared during the processing of the present review.

2.1.1.3 Katsuki's complexes

Shortly before Jacobsen's group published their key findings, Katsuki and his colleagues had developed[5] another set of complexes. The main difference in the ligand design was the introduction of two extra stereogenic axes in place of the bulky tertiary alkyl groups in the C-3 and C-3′ positions of the aryl groups. Using these interesting complexes such as **4,** Katsuki



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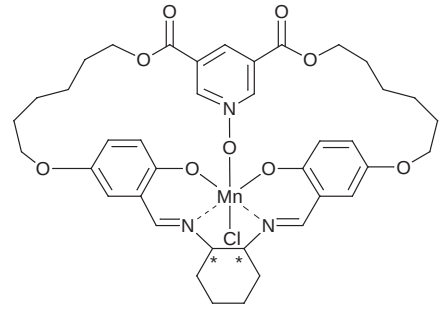
studied the enantioselective epoxidation of unfunctionalised olefins but observed lower asymmetric induction than Jacobsen. The group also first showed[6] that a donor ligand such as *N*-methylmorpholine *N*-oxide improves the enantioselectivity of the system. More recently, Jacobsen demonstrated the importance of these additives with the Mn(salen) complex **5** in



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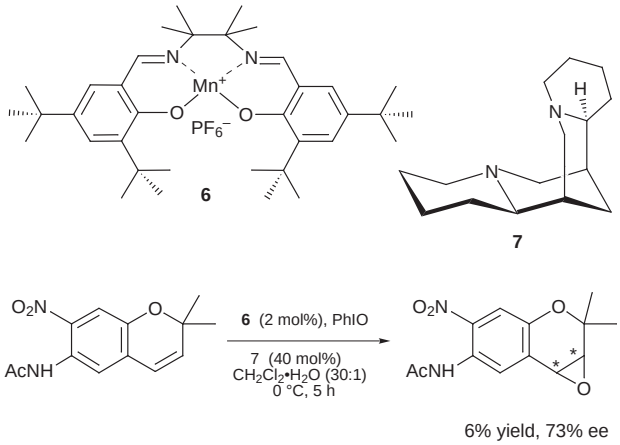
which the 'additive' is present intramolecularly as part of the ligand structure.[7]

Katsuki and his colleagues also examined[8] the epoxidation of 2,2-dimethylchromene derivatives using achiral Mn(salen) complexes in the presence of chiral additives. Epoxidation of 6-acetoamino-7-nitro-2,2-dimethylchromene gave only modest yields (5–65%) and enantioselectivities (with up to 73% ee) (Scheme 2). The best asymmetric induction occurred with

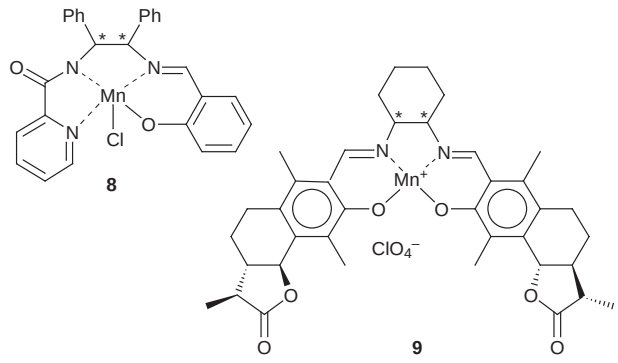


Scheme 2 Epoxidation of 2,2-dimethylchromene derivatives.

catalyst **6** using (−)-sparteine **7** as an axial chiral ligand and iodosylbenzene as oxidant at 0 °C in a methylene chloride–water solvent system.

2.1.1.4 Other manganese-based systems

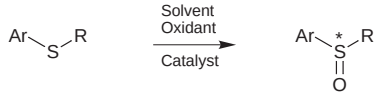
Zhao's laboratory synthesised[9] the hybrid Mn–picolinamide–salicylidene **8**. These non-symmetrical catalysts generated moderate asymmetric induction (31–74% ee) in the epoxidation of dihydronaphthalene though higher turnover numbers than with **4** were possible.



Pedro *et al.*[10] using complex **9** in conjunction with iodosylbenzene, in the presence of molecular oxygen and pivalaldehyde, epoxidised various unfunctionalised olefins. The yields obtained were generally high (78–99%) however the asymmetric induction was poor (5–10% ee).

2.1.2 Oxidation of sulfides

Jacobsen showed[11] that the Mn(salen) complex **3** is an effective catalyst for asymmetric oxidation of sulfides (Scheme 3) as well



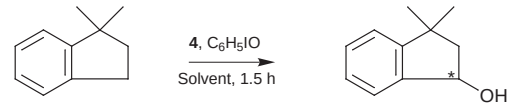
Scheme 3 Asymmetric oxidation of prochiral alkyl aryl sulfides.

as for the epoxidation of conjugated olefins. Reactions were carried out with 2–3 mol% of catalyst in acetonitrile using unbuffered hydrogen peroxide as the stoichiometric oxidant to yield sulfoxides in good yield (84–95%) but with only modest enantiomeric excesses (34–68%).

Subsequently Katsuki, using complex **4,**[12] managed to oxidise in an asymmetric fashion a range of alkyl aryl sulfides with up to 94% ee. The oxidation proceeded using an equimolar amount of iodosylbenzene and 1 mol% of the catalyst. The enantioselectivity of the reaction was found to be affected by the solvent.

2.1.3 Hydroxylation

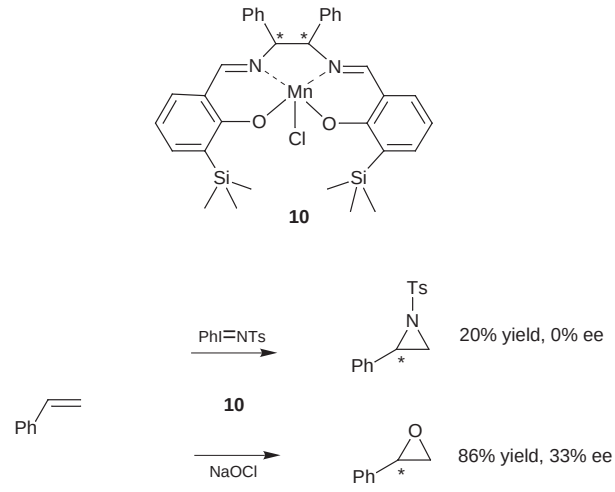
In 1996, Katsuki showed[13] that the chiral substituents at the C-3 and C-3′ positions of the aryl groups of the Mn(salen) complex such as in **4** enabled asymmetric benzylic hydroxylation (with up to 64% ee) to be carried out using iodosylbenzene as oxidant in solvents of high polarity (*e.g.* chlorobenzene, Scheme 4).



Scheme 4 Asymmetric hydroxylation of 1,1-dimethylindane.

2.1.4 Aziridination

Burrows and his co-workers investigated[14] the use of the chiral Mn(salen) complex **10** as a catalyst in the aziridination, as well as the epoxidation, of olefins. Typically, the former reaction involved formation of the *N*-tosyl-2-phenylaziridine derivative by reacting styrene with tosyliminoiodobenzene in the presence of 5 mol% of complex **10**. Unfortunately not only was the yield modest (20%) but no asymmetric induction was observed (Scheme 5). However the epoxidation of styrene carried out in



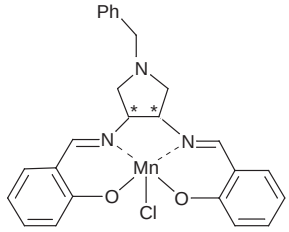
Scheme 5 Styrene oxidation catalysed by chiral Mn(salen) complexes.

methylene chloride with bleach as oxidant resulted in a good yield (86%) with moderate asymmetric induction (33% ee) using this same complex.

2.1.5 Oxidation of ketone silyl enol ether

Thornon *et al.* reported[15] that complexes **3** and **11** catalysed the oxidation of a range of ketone silyl enol ethers to give α-hydroxyketones using iodosylbenzene as oxidant in acetonitrile at room temperature (Scheme 6). The reactions proceeded in

good to excellent yield (70–94%) combined with moderate asymmetric induction (14–62%).



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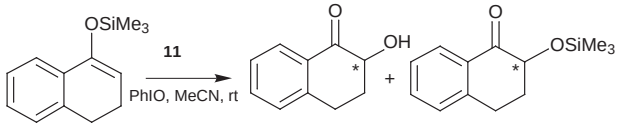


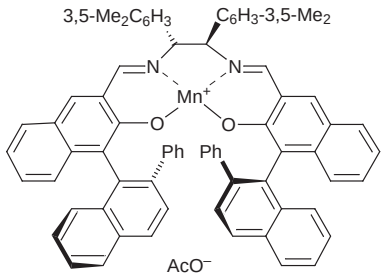
0.8 : 1, hydroxy ketone : silyloxy ketone
72% yield (total products)
62% ee (isolated alcohol)

Scheme 6 α-Oxidation of ketone silyl enol ethers.

Later, Waldemar and his co-workers showed[16] that **3** also catalyses the asymmetric oxidation of silyl ketene acetals in high enantioselectivity (up to 81% ee for α-hydroxy ketones and up to 57% ee for α-hydroxy esters). The same group also reported the strong dependence of yield and enantioselectivity on the type of oxygen donor, the pH of the aqueous bleach medium, the additive and the substitution pattern of the enol substrate.

2.1.6 Kinetic resolution of racemic allenes

While oxidising a racemic mixture of 1-phenylbuta-1,2-diene with complex **12**, Katsuki and his colleagues were able to generate some enantiomerically enriched 1-phenylbuta-



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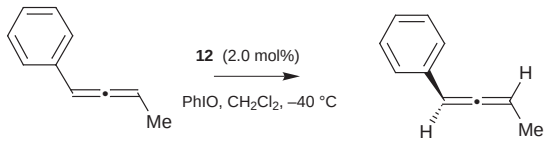


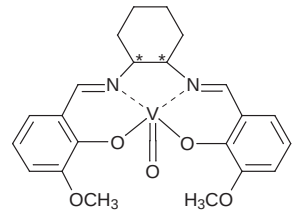
60% ee at 45.5% conversion

Scheme 7 Kinetic resolution of racemic 1-phenylbuta-1,2-diene.

1,2-diene (60% ee at 45.5% conversion) (Scheme 7).[17]

2.2 Vanadium(salen) complexes

Fujita reported[18] the first example of asymmetric oxidation using the V(IV)salen complex **13** and to some extent this molecule offers precedence for the proposed oxo-Mn(v)salen intermediate in catalyses employing Jacobsen's catalyst. The catalyst allowed the enantioselective oxidation (40% ee) of methyl phenyl sulfide to be achieved with cumene hydroperoxide in methylene chloride (Scheme 8).



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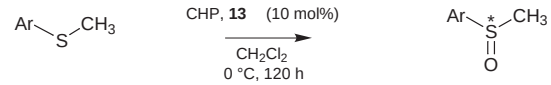


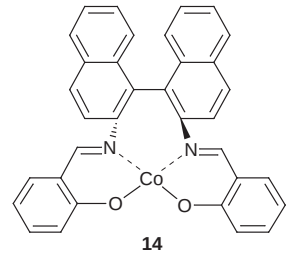
96% yield, 40% ee

Scheme 8 Asymmetric oxidation of methyl phenyl sulfide.

2.3 Cobalt(salen) complexes

2.3.1 Hydroxylation

Nishinaga *et al.* described[19] the hydroxylation of styrene using the optically active Co(salen) complex **14** to produce 1-phenylethanol in modest yield (30% isolated) and enantiomeric excess (38% ee) (Scheme 9).



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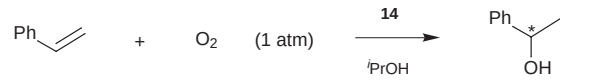


30% yield, 38% ee

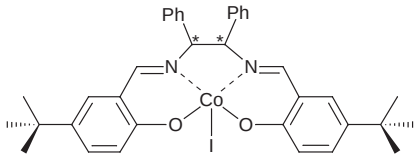
Scheme 9 Asymmetric hydroxylation of styrene.

2.3.2 Cyclopropanation

Katsuki found[20] that the Co(salen) complex **15** catalysed the asymmetric cyclopropanation of styrene with *tert*-butyl diazoacetate (Scheme 10). The reaction showed high *trans*-selectivity (*trans* : *cis*, 95:5) together with good enantioselectivity (75% ee). In this case there is good evidence confirmed by quantitative modelling studies that the Co(v)salen carbenoid intermediate complex has a folded structure, and that this controls the enantioselectivity of the catalysis.[20] This also adds weight to the argument that the intermediate arising with Jacobsen's Mn catalyst is folded.

2.3.3 Epoxide ring opening

Jacobsen *et al.* described[21] the asymmetric nucleophilic ring-opening of *meso* epoxides using benzoic acid in the presence of



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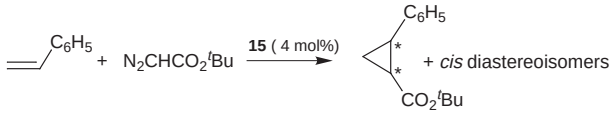
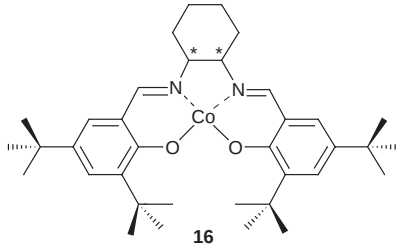


76% yield, 75% ee, (*trans*:*cis*) (95:5).

Scheme 10 Asymmetric cyclopropanation of styrene.

the Co(salen) complex **16**. The reaction proceeded well (96% isolated yield) with good asymmetric induction (93% ee) (Scheme 11).



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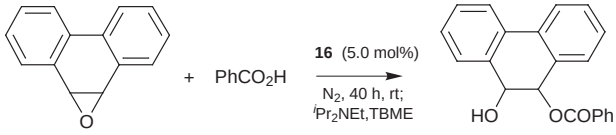
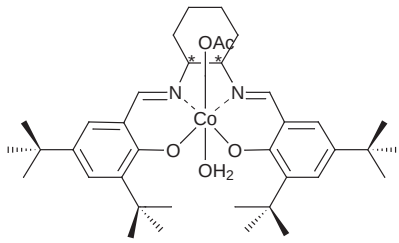


96% yield, 93% ee

Scheme 11 Asymmetric ring-opening of a *meso* epoxide.

2.3.4 Hydrolytic kinetic resolution

Jacobsen also discovered[22] that the Co(salen) complex **17** was active in the hydrolytic kinetic resolution of racemic epoxides which enables access to terminal epoxides and diols in high enantiomeric purity (Scheme 12). The organic solvent-free



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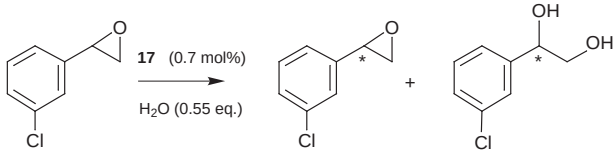


racemic 45% yield, 99% ee 45% yield, 91% ee

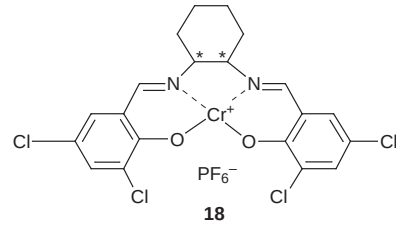
Scheme 12 Hydrolytic kinetic resolution of racemic epoxides.

method was carried out in the presence of water at room temperature over a 48 h period. Once the resolution was completed, the epoxide was easily isolated by partitioning the two products between pentane and water. Removal of the solvent followed by distillation of the pentane layer separated the enriched epoxide and the reusable catalyst **17**.

2.4 Chromium(salen) complexes

2.4.1 Epoxidation

Gilheany[23] reported that the Cr(salen) complex **18** catalysed asymmetric epoxidation of unfunctionalised *trans* olefins in higher enantiomeric excess than the corresponding *cis* isomers. For instance, (*E*)-β-methylstyrene was epoxidised in 83% ee whereas its *Z* isomer reacted with only 56% ee (Scheme 13).



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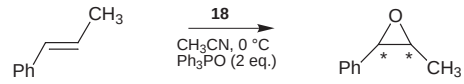
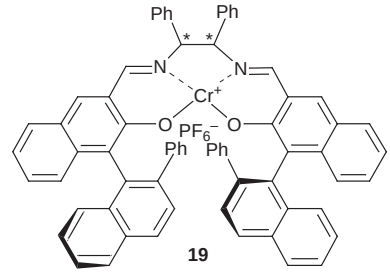


Scheme 13 Asymmetric epoxidation of (*E*)-β-methylstyrene.

Katsuki examined[24] the epoxidation of conjugated alkenes using Cr(salen) complexes. The system typically generated a modest asymmetric induction. However, a strong relationship was found between the solvent, the donor ligand used and the stereochemistry arising in the reaction. For instance, as shown in Scheme 14 and Table 1, reaction of 6-acetamido-7-nitro-



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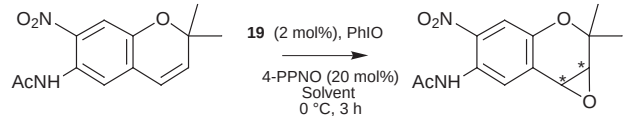


Scheme 14 Asymmetric epoxidation of 6-acetamido-7-nitro-2,2-dimethylchromene.

Table 1 Solvent effect

Solvent	Yield (%)	Ee (%)	Configuration
CH_3CN	10	78	3*R*,4*R*
Toluene	23	23	3*S*,4*S*

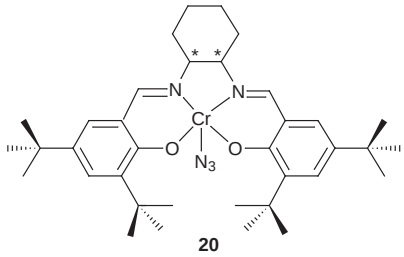
2,2-dimethylchromene in acetonitrile, using complex **19** as a catalyst and iodosylbenzene as terminal oxidant along with 4-phenylpyridine *N*-oxide as an activator, generated the corresponding epoxide in 78% ee with a (3*R*,4*R*) configuration.

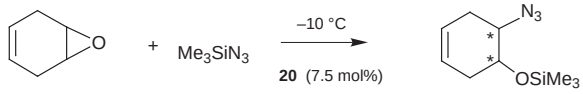
When the reaction was carried out in a less polar solvent, under the same conditions, the opposite enantiomer was generated with 23% ee.

In the case of these Cr(salen) species pyridine *N*-oxide adducts of the oxo derivative have been isolated and their solid state structure characterised by X-ray crystallographic analysis. Interestingly the salen ligand adopts a folded conformation.[25]

2.4.2 Epoxide ring opening

The ring-opening of cyclohexa-1,4-diene monoepoxide was carried out by Jacobsen's group[26] under solvent free conditions in presence of 7.5 mol% of **20** and azidotrimethylsilanolate to produce the azido silyl ether in 92% enantiomeric excess (Scheme 15).



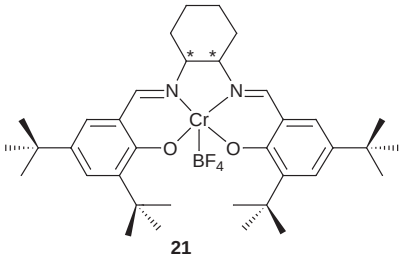


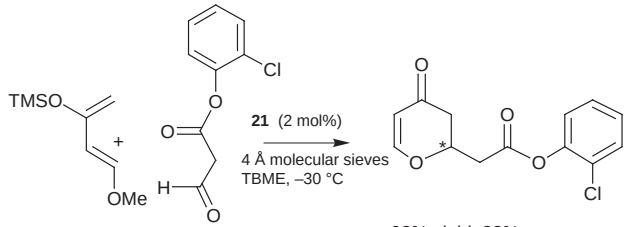
95% yield, 92% ee

Scheme 15 Asymmetric ring-opening of cyclohexa-1,4-diene monoepoxide.

2.4.3 Hetero-Diels–Alder reactions

Jacobsen's laboratory has also achieved[27] the asymmetric hetero-Diels–Alder reaction between [(2-chlorobenzoyl)oxy]-acetaldehyde and 1-methoxy-3-[(trimethylsilyl)oxy]buta-1,3-diene in the presence of 2 mol% Cr(salen) **21** using a non-coordinating ethereal solvent at −30 °C in the presence of dried 4 Å molecular sieve (Scheme 16). The asymmetric induction





92% yield, 83% ee
67% yield, 99% ee (recryst.)

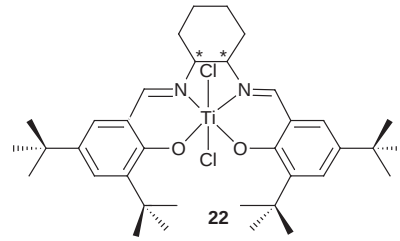
Scheme 16 Asymmetric hetero-Diels–Alder reaction.

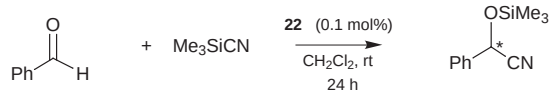
was in excess of 83% (99% after recrystallisation). The nature of the catalyst's counterion was reported to have a dramatic effect on both the yield and enantioselectivity of the reaction.

2.5 Titanium(salen) complexes

2.5.1 Trimethylsilylcyanation of aldehyde

North and his colleagues used[28] the optically active Ti(salen) catalyst **22** in the enantioselective trimethylsilylcyanation of benzaldehyde in dichloromethane at room temperature producing (*S*)-2-phenyl-2-trimethylsilyloxyacetonitrile in 86% ee (Scheme 17).



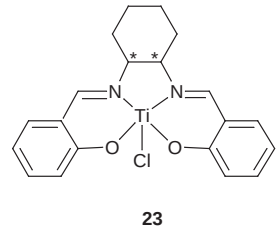


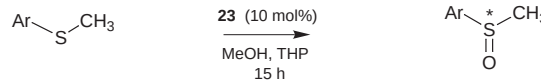
100% yield, 86% ee

Scheme 17 Enantioselective trimethylsilylcyanation of benzaldehyde.

2.5.2 Oxidation of sulfide

Nakajima and his co-workers reported[29] that chiral Ti(salen) complex **23** catalysed the oxidation of methyl phenyl sulfide to the sulfoxide in good yield (98%) and enantioselectivity (62% ee) with triphenylmethyl hydroperoxide as the oxidant at 0 °C (Scheme 18).





98% yield, 62% ee

Scheme 18 Asymmetric oxidation of methyl phenyl sulfide.

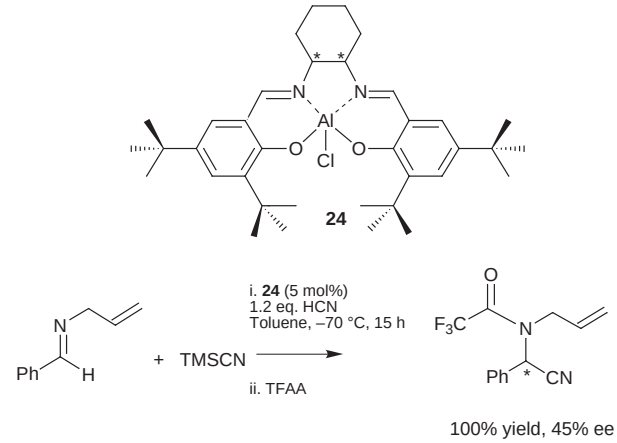
2.6 Aluminium(salen) complexes

2.6.1 Addition of hydrogen cyanide to imines

Jacobsen and his colleagues described[30] the first example of a metal catalysed enantioselective Strecker reaction using chiral Al(salen). The reaction of *N*-allyl benzaldimine was completed within 15 h at – 70 °C in the presence of a catalytic amount of complex **24** and HCN (Scheme 19, 91% yield, 95% ee).

3 Supported metal(salen) complexes

The large range of catalytic processes now involving soluble chiral metal(salen) complexes makes the development of their



Scheme 19 Addition of hydrogen cyanide to *N*-allyl benzaldimine.

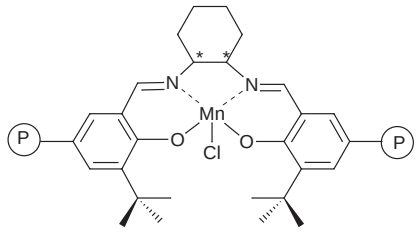
heterogeneous counterparts very attractive. Early work on supported systems focussed on achiral complexes.[31] While these results provide a useful strategic guide in terms of the immobilisation chemistry, the more recent work on chiral complexes is more relevant to this review and is now described according to the type of support involved.

3.1 Organic supports

With regard to organic supports both insoluble and soluble polymers have been studied.

3.1.1 Cross-linked polymer supports

The synthesis of the first polymer-supported chiral Mn(salen) complexes along with their application as recyclable asymmetric catalysts was reported independently by Sivaram *et al.*[32] and Minutolo *et al.*[33] Monomeric Jacobsen-type units (containing two polymerisable vinyl groups) were copolymerised with styrene and divinylbenzene to yield the corresponding crosslinked polymers **25–27** as a monolithic compact block.



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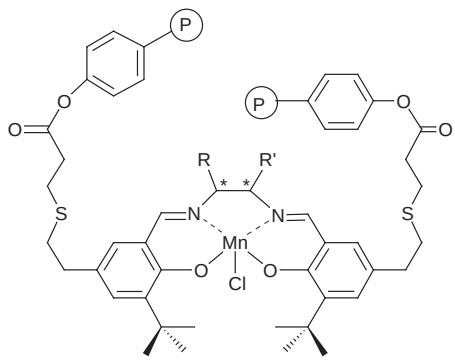
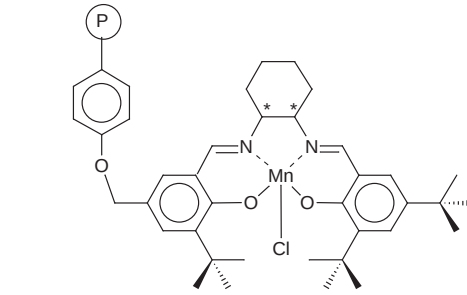


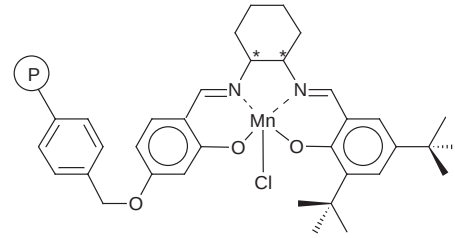
26 R and R' = -$(CH_2)_4$-
27 R = R' = Ph

Whereas the insoluble Jacobsen's catalyst **25** epoxidised unfunctionalised alkenes in good yields (65–72%), but low enantioselectivity (1–26% ee), the heterogeneous catalysts containing a spacer arm between the active site and the polymeric backbone **26** and **27** induced better enantioselectivity (14–62% ee). In all cases, reactions were performed with an excess of iodosylbenzene as the oxygen source and without additives. The poorer enantiomeric purity obtained relative to that found with the homogeneous systems may be well explained by the structure of these immobilised catalysts. The ligands as developed by both the Indian and Italian groups are attached by both ligand aromatic rings to the support, and the resultant Mn complex may be forced to adopt a flatter geometry compared to that of the homogeneous counterpart. This resultant rigid system may well be responsible for the poor asymmetric induction observed and the better results obtained with complexes **26** and **27** which are more flexible tend to confirm this.

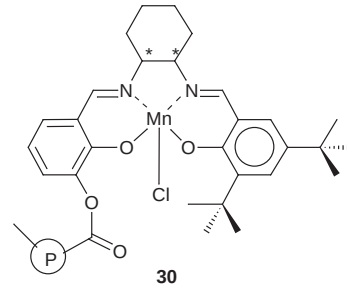
Sherrington and his colleagues have reported[34] a series of polymer-supported complexes **28–30** where the Mn(salen)Cl



28
para



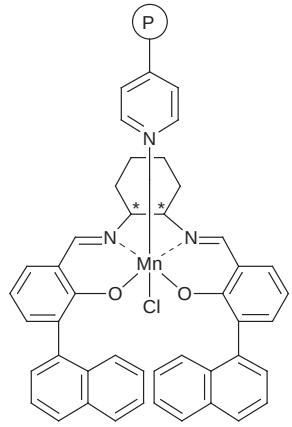
29
meta



30
ortho

moiety was immobilised in a pendant fashion by only one of its aromatic rings to poly(styrene) and poly(methacrylate) resin beads of various morphologies. The attachment was achieved at different positions on the aromatic group relative to the hydroxy functional group (*ortho*, *meta* and *para*). Whereas complexes **29–30** exhibited modest enantioselectivity (0–7%), the Mn-(salen)Cl-containing polymer **28** allowed the epoxidation of 1-phenylcyclohexene with enantioselectivity in the range of 61–91%.

Kureshy developed[35] the polymer-based chiral Mn(salen) complex **31**. Copolymerisation of styrene, divinylbenzene and 4-vinylpyridine generated highly crosslinked (50%) porous beads loaded with pyridine ligand at 3.8 mmol g^{-1}. Oddly, once functionalised with metal complex, the polymer was reported to



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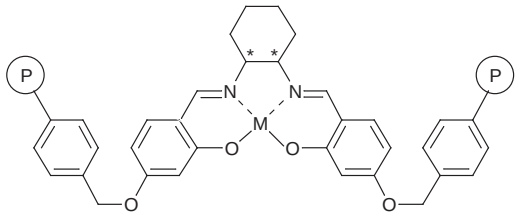
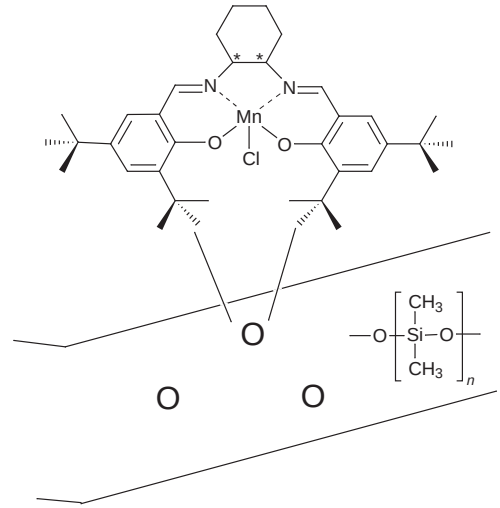


32 M = Ir, Co, Ru



Scheme 20 Immobilisation of Mn(salen) complex into a siloxane elastomer network.

contain only 10 μmol g^{-1} of active sites. The results obtained in the enantioselective epoxidation of styrene derivatives were encouraging, being in the range of 16–46% ee. The reactions were carried out in presence of iodosylbenzene without any additives in dichloromethane.

Lemaire and his colleagues reported[36] the use of metal(salen) complexes (where metal = Ir, Co, Ru) **32** in the asymmetric transfer hydrogenation of acetophenone. The asymmetric induction generated using Ir(salen) was good, with enantiomeric excesses in the range of 21–70%. However, both the Co and Ru complexes were inactive.

3.2 Inorganic supports

Two types of inorganic material have been used as a support. They are siloxane and zeolite-based.

3.2.1 Siloxane material

Vankelecom *et al.* proposed[37] an inorganic support for the immobilisation of Jacobsen's catalyst. The catalyst was occluded by steric restrictions in an elastomeric type polydimethylsiloxane membrane (Scheme 20). This chiral catalytic membrane was reported to allow regeneration of the heterogeneous complex which gave essentially the same catalytic activity, product, and enantiomeric selectivity as in the homogeneous case. Little recycling data were specified however.

3.2.2 Zeolites

Bein reported[38] the insertion of a Mn(salen) complex into a zeolite. These heterogeneous catalysts generated good asymmetric inductions with up to 88% ee for *cis*-β-methylstyrene. The group also proved that the epoxidation took place inside the cage of the zeolite.

Corma encapsulated[39] a chiral Mn(salen) complex inside the supercage of a zeolite-Y. The resulting system exhibited similar catalytic activity to the same complex under homogeneous conditions using bleach as oxidant in methylene chloride (*e.g.* 74% ee was obtained in the asymmetric epoxidation of ethyl cinnamate). Neither recycling experiments nor leaching studies were reported.

4 The future

There seems little evidence that the expansion in the applications of chiral metal(salen) complex catalysts is slowing up, and undoubtedly new catalytic processes will continue to emerge. Bearing in mind the scope that exists for changing the metal centre and the detailed ligand structure, it is perhaps not surprising that such versatility exists in the catalytic processes available. Potentially the chiral metal(salen) complexes could emerge as the single most important group of asymmetric catalysts in technological as well as scientific terms. This makes the target of producing supported heterogeneous analogues, of comparable activity and selectivity, an important one. Such species, if also capable of re-use or continuous operation, would in turn further improve the importance of this group of asymmetric catalysts, and offer a more cost effective use of these species in a larger number of circumstances. It seems that this area of catalysis will remain a fertile one for scientific research and development for some time to come.

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