Accounts

Asymmetric Catalysis of New Generation Chiral Metallosalen Complexes

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Chiral metallosalen complexes have been recognized as one of the most promising catalysts for various asymmetric reactions. The studies on asymmetric epoxidation catalyzed by chiral (salen)manganese complexes will be reviewed at first. The enantioselectivities have reached to the level as high as 90—99% ee for the epoxidation of conjugated *cis*-di- and trisubstituted olefins by developing the second generation of chiral salen ligands. Although it has been proven by Freichtinger and Plattner that epoxidation proceeds through an oxo species, the mechanism of asymmetric induction is still surrounded by controversy. However, our recent studies have clarified that the conformation of the salen ligand in oxo(salen)manganese(V) species plays a very important role in determining the direction of the olefin's access to the oxo species. This study led to the new finding that an achiral (salen)metal complex can be used as a chiral catalyst by regulating the conformation of achiral ligand. The appropriately modified (salen)manganese(III) complexes can also be applicable for asymmetric oxidation of enol ether derivatives, kinetic resolution of racemic allenes, enantioselective benzylic C–H oxidation, asymmetric desymmetrization of *meso*-heterocycles, and asymmetric oxidation of alkyl aryl sulfides. In the asymmetric aziridination of styrene derivatives by using PhI=NTs as a terminal oxidant, high enantioselectivity of up to 94% has been achieved by the further modification of the chiral (salen)manganese(III) complex. The chiral (salen)cobalt-(III) complex is a good catalyst for asymmetric cyclopropanation of styrene derivatives and asymmetric *S*-ylide formation from allyl aryl sulfides, in which the resulting *S*-ylides undergo [2,3]-Wittig rearrangement in situ to produce chiral 2-(phenylthio)pentanoate derivatives.

Development of efficient catalytic asymmetric reactions is the most challenging task in current synthetic chemistry; much effort has been devoted to create the chiral metal complexes of advanced asymmetric catalysis. As results, many brand-new ligands have been introduced in the last two decades and their combination with various metal ions has realized the syntheses of highly efficient asymmetric catalysts.[1] However, most ligands have only narrow applications and their use is limited to some specific reactions. Exceptionally, a few ligands such as dialkyl tartrate, binaphthol, semicollin (including bisoxazoline), and BINAP show wide applicability. Chiral salen ligand is one of such ligands and their metal complexes are now used as the catalysts for a variety of enantioselective reactions such as oxidations,[2] aziridination,[3] cyclopropanation,[4] Diels–Alder reaction,[5,6] addition of TMSCN to aldehydes,[7] and Strecker reaction[8] and for kinetic resolution of racemic epoxides.[9] In this article, we will discuss about asymmetric reactions, laying stress on asymmetric oxidations, using chiral metallosalen complexes of new generation and the mechanism of their asymmetric induction in the epoxidation.

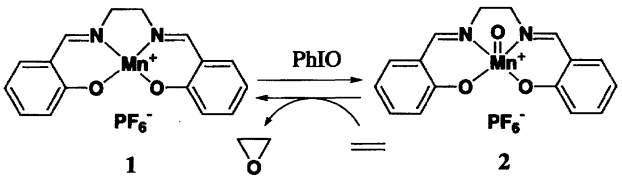
Chiral metallosalen complexes can be readily synthesized from metal salts and salen ligands which are prepared by simply mixing 1 mole of chiral ethylenediamine derivative and 2 moles of chiral or achiral salicylaldehyde derivative. Because porphyrin and metallosalen complexes have similar structures, the chemistry of metallosalen complexes has attracted the attention of chemists for long time. For example, (salen)cobalt complex was prepared by Pfeiffer, Tsumaki, et al. in 1933.[10] Its unique phenomena of adsorption and release of molecular oxygen had been studied extensively as the model compound of oxygen carrier in living bodies. In the mid-80s, metallosalen complexes were stepped on the stage of asymmetric synthesis. The recent development of metallosalen chemistry will be described by taking our own results as examples, for the most part.

1. Asymmetric Epoxidation

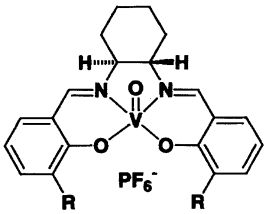
Epoxides are not only found in biologically active natural products, but also serve as versatile intermediates in organic synthesis because epoxides undergo various nucleophilic ring-opening reactions to give products of high synthetic use. A Ti(OPr-*i*)$_4$, dialkyl tartrate, and *t*-butyl hydroperoxide (TBHP) system introduced by Sharpless and

Katsuki provided the reliable method for asymmetric epoxidation of allylic alcohols and have been widely used in organic synthesis.[11] However, no general method for the epoxidation of isolated olefins was available. In 1986, two important papers on the oxidative catalysis of metallosalen complexes were published. i) Kochi et al. reported that cationic (salen)manganese(III) complex **1** (hereafter referred to as Mn-salen complex) is a good catalyst for epoxidation of simple olefins and that the epoxidation proceeds through oxo(salen)manganese(V) complex **2** (Scheme 1).[12] On the other hand, ii) Fujita et al., reported asymmetric oxidation of sulfides using chiral (salen)vanadium complex **3** as a catalyst (Chart 1), though enantioselectivity was moderate.[13] These two reports prompted the development of metallosalen catalyzed asymmetric epoxidation of simple olefins. To achieve high enantioselectivity in metal-catalyzed asymmetric reactions, construction of an asymmetric coordination sphere around metal ions is indispensable. Introduction of stereogenic carbons at the asterisked positions in metallosalen complexes **4** may constitute a chiral coordination sphere efficient for asymmetric catalysis (Chart 2), because these stereogenic centers are closely located to the metal center (For convenience sake, the numbering described in **4** is used in this article).

In 1990, Jacobsen group and our group reported Mn-salen catalyzed asymmetric epoxidation of unfunctionalized olefins. Jacobsen et al. reported asymmetric epoxidation by

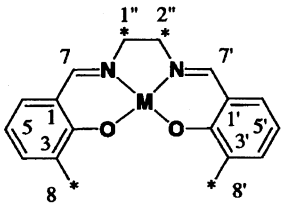


Scheme 1.



3a: R= *t*-Bu
3b: R= MeO

Chart 1. Compound **3**.



4

***= stereogenic center**

Chart 2. Compound **4**.

employing the catalysts **5** in which the stereogenic carbons reside only on the ethylenediamine moiety and the bulky *t*-butyl group is placed ortho to the phenoxide oxygen atom.[14] We reported asymmetric epoxidation using chiral Mn-salen complexes (*R*,*S*)-**6** bearing asymmetric centers at the ethylenediamine and aromatic moieties, respectively.[15] These complexes (**5** and **6**) show good level of enantioselectivity in epoxidation of conjugated *cis*-di- and trisubstituted olefins using iodosylbenzene[12] or sodium hypochlorite[16] as a terminal oxidant. Some typical examples are shown in Fig. 1. In the early stage of the study of chiral Mn-salen catalyzed asymmetric epoxidation, the steric repulsion between the substrate and the salen ligand had been assumed to play a major role in inducing asymmetry.[2] However, the study of epoxidation of 2-methyl-1,3-cyclohexadiene and 3-methylenecyclohexene cast a doubt on this assumption.[17] As the steric requirement of methyl group is larger than that of methylene group, the former substrate must show higher enantioselectivity than the latter one, if the assumption is correct. However, the results obtained were against this expectation. This result suggested that not only steric repulsion but also coulombic repulsion between the substrate and the salen ligand play important roles in asymmetric induction. Therefore, strengthening of these two repulsions was considered to be essential for further improvement of enantioselectivity in Mn-salen catalyzed epoxidation. However, Mn-salen complexes (**5** and **6**) which have sp^3 carbons at C8 and C8′ were not considered to be the best candidates for further improvement, because the substituents on the sp^3 carbons

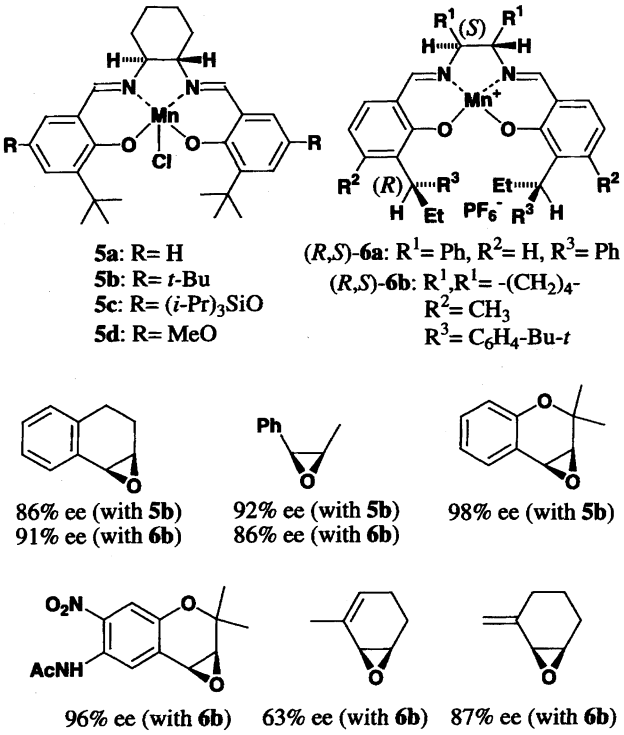
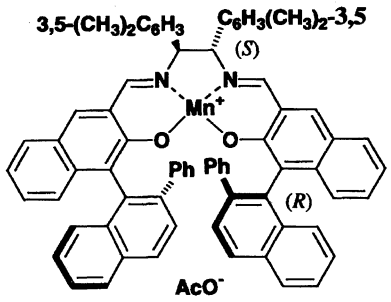


Fig. 1. Typical examples of asymmetric epoxidation of conjugated *cis*-olefins by using optically active Mn-salen complexes as catalysts.

direct away from the incoming olefins (For the discussion about an olefin's approach to a manganese-oxo bond, see the following sections).

To overcome the drawback of Mn-salen complexes of the first generation, a new Mn-salen complex **7** having a binaphthyl subunit was designed, in which the phenyl group on the naphthyl ring protrudes toward the incoming olefins (Chart 3).[18] The phenyl group is expected to increase both steric and coulombic repulsions between ligand and olefin. As expected, remarkably improved enantioselectivity has been realized in the epoxidation of conjugated *cis*-olefins with complex **7**. Some results are summarized in Table 1[18b,18c,18d] along with the highest %ee's reported by using Mn-salen catalysts of the first generation.[15c,19] Epoxidation of conjugated trisubstituted olefins also proceeds with high enantioselectivity (Table 2).[20]



7

Chart 3. Compound **7**.

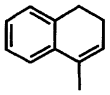
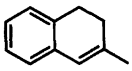
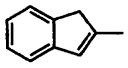
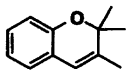
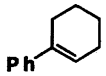
2. Mechanism of Asymmetric Induction by Mn-Salen Catalyst

The stereochemistry of the products (Fig. 1, Tables 1 and 2) can be explained by assuming that olefins approach a metal–oxo bond from its side so as to direct the bulky olefinic substituent away from the substituent at C3(3′) (Fig. 2, approach **a**).[2]

On the other hand, Jacobsen et al. have proposed that olefins approach the metal–oxo bond from the upside to avoid steric repulsion with 5′-*t*-butyl group when complex **5b** is used as the catalyst (approach **b**).[14b] However, *trans–cis* selectivity in the epoxidation of racemic 1-alkylindene with complex **8** as catalyst was found to be strongly dependent upon the presence or absence of 3(3′)-*t*-butyl groups (Scheme 2). 5(5′)-*t*-Butyl groups affect *trans–cis* selectivity to much smaller extent.[21] Such results suggested that olefins approach a metal–oxo bond along pathway **a** without being disturbed by 5(5′)-*t*-butyl groups.

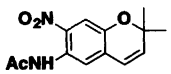
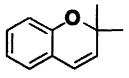
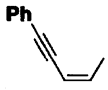
These seemingly conflicting experimental results can be rationalized by assuming that the salen ligands of oxo(salen)-

Table 2. Asymmetric Epoxidation of Trisubstituted Olefins with **7** as a Catalyst[a]

Entry	Substrate	Oxidant	Temp	Yield (%)	%ee	Confign.
1		PhIO	−20 °C	41	96	1*S*,2*R*
2		PhIO	−20 °C	48	92	1*S*,2*R*
3		NaClO	0 °C	91	88	—[b]
4		NaClO	0 °C	88	> 99	—[b]
5		PhIO	−20 °C	26	83	1*R*,2*R*

a) Reactions were carried out with **7** (0.025 mol amt.) in aqueous dichloromethane in the presence of NaOCl (5 mol amt.) and 4-phenylpyridine *N*-oxide (0.25 mol amt.) or acetonitrile in the presence of PhIO (2 mol amt.) and pyridin *N*-oxide (0.25 mol amt.). b) Absolute configuration has not been determined.

Table 1. Epoxidation of Conjugated *cis*-Olefins Using Mn-Salen Complex **7** as a Catalyst

Entry	Olefin	Oxidant	Solvent	Temp	Yield (%)	%ee	(%ee)[a]
1		PhIO	CH_3CN	0 °C	72	98	96[b]
2		PhIO	CH_3CN	−20 °C	60	> 99	98[c]
3		NaOCl	CH_2Cl_2	0 °C	55	98	88[c]
4		NaOCl	CH_2Cl_2	0 °C	80[d]	96(*trans*) 92(*cis*) (94)[e]	93(*trans*)[c] 58(*cis*) (81)[e]
5		NaOCl	CH_2Cl_2	−18 °C	82	93	64[f]

a) The highest %ee reported by using Mn-salen catalysts of the first generation. b) With Mn-salen complex **6b** (Ref. 15c). c) With Mn-salen complex **5b** (Refs. 19b and 19c). d) A mixture of *cis*- and *trans*-epoxides in a ratio of 2 : 1. e) The number in parentheses stands for the face selectivity. Face selectivity = $ee_{trans} \times \%trans + ee_{cis} \times \%cis$ (Ref. 19e). f) With Mn-salen complex **5c** (Ref. 19d).

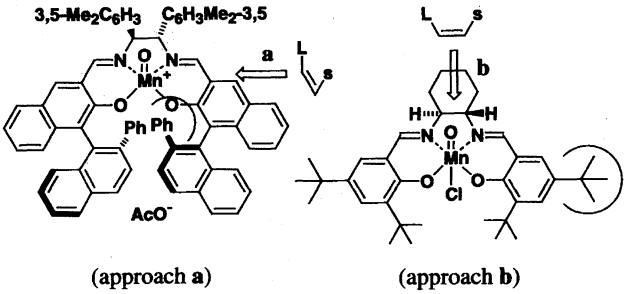
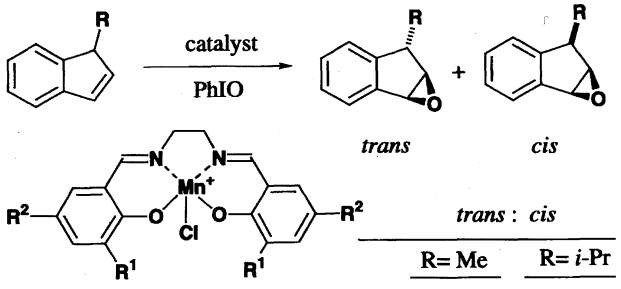


Fig. 2. Plausible approaching directions of olefins to the metal–oxo bond of optically active oxo(salen)manganese-(V) complexes.



	trans : cis	
	R= Me	R= *i*-Pr
8a	3.0 : 1	20 : 1
8b	5.7 : 1	83 : 1
8c	6.2 : 1	55 : 1

Scheme 2.

manganese(V) complexes take a non-planar stepped conformation (Fig. 3). In the epoxidation of 1-alkylindens using achiral Mn-salen complexes **8**, olefins approach the metal–oxo bond from the side of the downward benzene ring of the salen ligand. Therefore, steric repulsion between the substrate and 3- or 3′-*t*-butyl group plays an important role in determination of *trans–cis* selectivity.[2a,21] In contrast to the result that, achiral oxo(salen)manganese(V) complexes exist in an equilibrium mixture of two enantiomeric stepped conformers, chiral oxo(salen)manganese(V) complexes exist in one of the two stepped conformers due to the regulation by the chirality of the ethylenediamine part (vide infra). Olefins approach the metal–oxo bond beyond the downward benzene ring. *t*-Butyl group (R^2) introduced onto the upward benzene ring (B) effectively intercepts the undesired olefin's approach that leads to the formation of the minor enantiomer of epoxide, and enhances enantioselectivity. This explains why complex **5b** is a better catalyst than complex **5a**. Although the participation of oxo(salen)manganese(V) complex in Mn-salen catalyzed epoxidation has been proved,[22] its structure has not been determined. However, it is worth mentioning that X-ray analysis of oxo(salen)chromium(V) complex has demonstrated that it takes a non-planar stepped conformation.[23]

The assumption that the salen ligands of oxo(salen)-manganese(V) complexes are non-planar was also supported by the following studies.

Kochi et al. have reported that, in the epoxidation using Cr-salen complex as a catalyst, ligation of axial donor ligand accelerates the reaction rate.[23] Furthermore, we have discovered that the addition of donor ligand to the reaction medium of Mn-salen catalyzed epoxidation enhances its enantioselectivity.[24] Since then, most Mn-salen catalyzed epoxidation has been performed in the presence of donor ligands such as 4-phenylpyridine *N*-oxide.[2] Although the detailed mechanism of donor ligand effect is still unclear, the role of the donor ligand may be multifold. i) Reduction of the reactivity of metal–oxo species. ii) Conformational change of 3,3′-substituent of salen ligand. iii) Changing the geometry of metal–oxo species and the conformation of the basal salen ligand. iv) Further destabilization of the undesired diaxial conformation of oxo(salen)manganese(V) complexes (vide infra, Fig. 4). The third donor-ligand effect is strongly supported by the X-ray study of cationic oxo-(salen)chromium(V) complex and its donor-ligand adduct.[23] As discussed above, achiral oxo(salen)manganese(V) complexes are considered to exist in the equilibrium mixture of

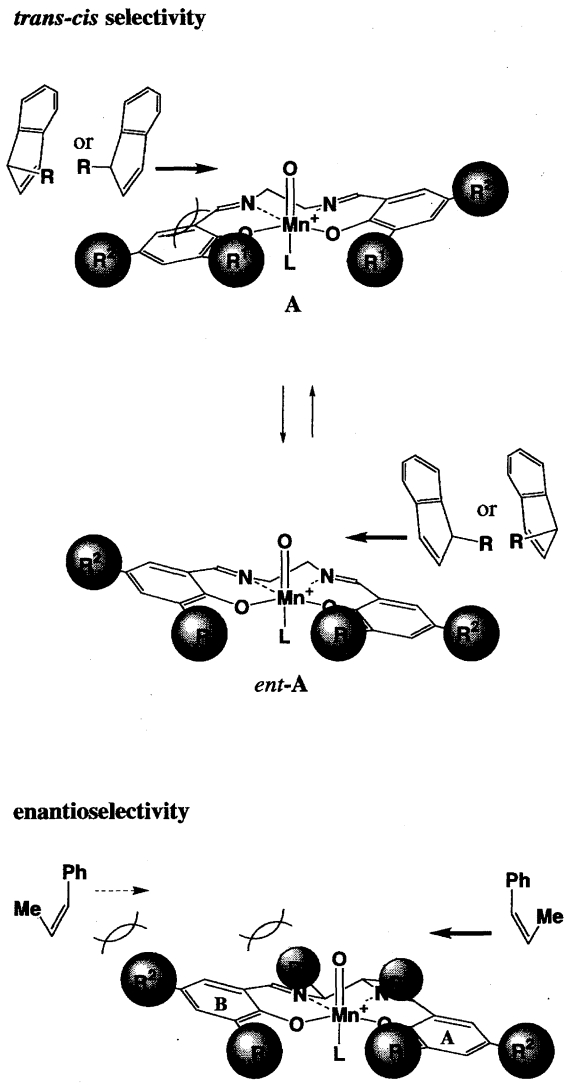


Fig. 3. An explanation of the diastereoselectivity and enantioselectivity in the epoxidation of 1-alkylindens by non-planar stepped conformation of oxo(salen)manganese(V) complexes.

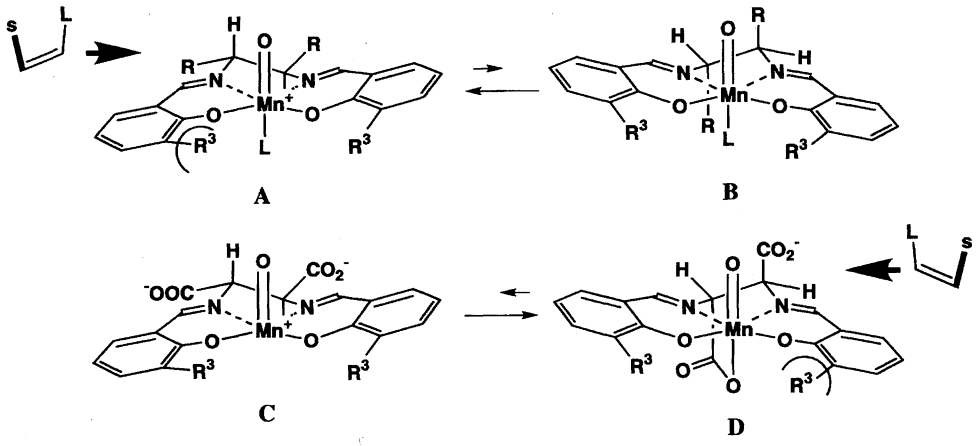
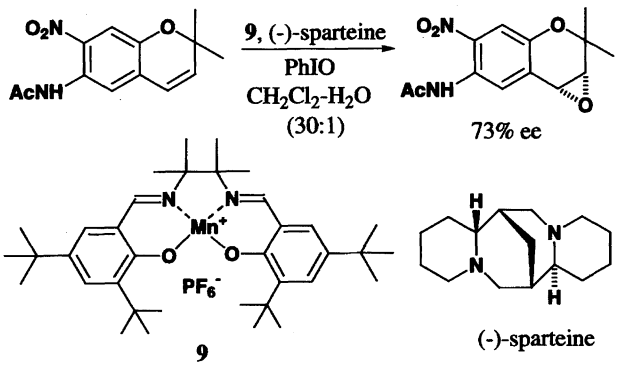


Fig. 4. The speculated non-planar conformation of the stepped oxo(salen)manganese(V) complexes by the influence of substituents on ethylenediamine moiety for asymmetric epoxidations.

enantiomeric conformers (**A** and *ent*-**A**, Fig. 3). If this equilibrium is shifted to one side by some means, the achiral Mn-salen complex should serve as a chiral catalyst. Considering the roles of axial donor ligand, authors have suggested that the equilibrium should be affected by the coordination of chiral donor ligand. Actually, a combination of achiral Mn-salen complex **9** and (−)-sparteine exhibits good enantioselectivity of 73%ee in epoxidation of 6-acetamido-2,2-dimethyl-7-nitro-2*H*-chromene (Scheme 3).[25] *To our knowledge, this is the first example of asymmetric reaction using an achiral metal complex as a chiral catalyst by regulating the conformation of achiral ligand.*

It has already been reported that a racemic catalyst serves as a chiral catalyst in the presence of an optically active agent which selectively depresses the catalytic activity of one enantiomer of the catalyst.[26] This type of optically active agent is called a chiral poison. Recently, the concept of chiral drugging which further activates catalytic activity of a chiral catalyst has been proposed.[27] The study shown here has demonstrated that an achiral catalyst can be used as a chiral catalyst, if the ligand-conformation of the catalyst is controlled by the addition of an optically active compound. The present asymmetric epoxidation using a combination of achiral Mn-salen complex **9** and (−)-sparteine would provide another new concept of chiral actualizer. A latent chirality of achiral catalyst is incarnated by an optically active agent, a chiral actualizer (in the present case, (−)-sparteine).[25] This concept will open a new avenue for the practical catalytic asymmetric reactions.



Scheme 3.

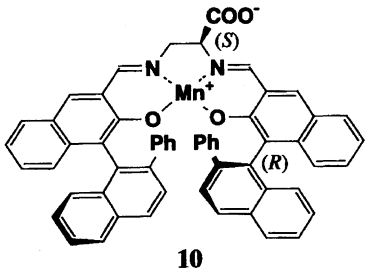
The discussion up to here strongly supports the idea that the direction of an olefin's approach to a metal–oxo bond is primarily dictated by the conformation of the basal salen ligand and the orientation of the olefin by the substituents on the ligand. In the oxo(salen)manganese(V) species derived from usual C_2-symmetric chiral Mn-salen complexes, the chirality sense of the conformation of the basal salen ligand is controlled by the chirality of the ethylenediamine moiety. The salen ligand folds in a manner such that the substituents (R) at the ethylenediamine part take a sterically favorable pseudo-equatorial orientation (Fig. 4, **A**). The diaxial conformation (**B**) is destabilized by steric repulsion between the substituent and axial ligands (oxo and axial donor ligands).

However, if the substituents at the ethylenediamine moiety are coordinating groups such as a carboxylato it can be coordinated to the metal ion in an axial orientation and it can cause inversion of the ligand conformation, because coordination stabilizes the otherwise unfavored diaxial conformation which will allow olefins to approach from the opposite direction (Fig. 4, **D**).[28] A salen-type manganese complex bearing an imidazole substituent at the C7 carbon have been synthesized by Berkessel; its C7-substituent was assumed to serve as the axial ligand. However, one of C=N bonds in the salen ligand is reduced to a C–N bond in the complex.[29] This endows Berkessel's complex with high conformational freedom. Effect of substituent coordination in Mn-salen complex had not been examined. For the study on substituent effect, however, a C_2-symmetric Mn-salen complex is not the desired one, because reversal of the conformation of usual C_2-symmetric salen complex forces the remaining substituent also to take axial orientation, which intercepts the olefin's approach along the desired pathway crossing over the downward benzene ring. Accordingly, a complex bearing a mono-substituted diamine moiety is considered to be the complex of choice for exploring the effect of substituent coordination.

Thus asymmetric epoxidation of 2,2-dimethyl-2*H*-chromenes with complex **10** having a mono-carboxylato

group on the ethylenediamine moiety as a catalyst was examined (Chart 4).[28] Complex **10** has a 2′-phenylnaphthyl group as a bulky C3-substituent. This has been proven to be highly effective for controlling the orientation of incoming olefins as discussed in the preceding section. Although the chirality sense of ethylenediamine moieties in **10** and **7** is opposite to each other, both the catalysts show the same sense of enantioselectivity, supporting our hypothesis of the ligand conformation (Table 3, Entries 2 and 3). Note that the configurations of ethylenediamine moieties in **10** and **7** are not identical, though both complexes have the same (*S*)-configuration due to the CIP-nomenclature system.

Differing from the epoxidation using usual Mn-salen complexes such as **5**—**7**, high enantioselectivity can be achieved in the present epoxidation without adding an axial ligand. Accordingly, the present reaction procedure is very simple. The catalyst can be recovered by column chromatography after the reaction and recycled for another run. Moreover, reduction of the amount of **10** from 2 mol% to 0.01 mol% maintains the high yield and high ee (> 98%ee), though prolonged reaction time is required at 0 °C (Entry 5). The turn-over number of the catalyst amounts to 9200 times. For the other substrates **11b**,**c**,**d**, (Chart 5), similar high enantioselectivity of greater than 90%ee is observed (Entries 6—11).



10

Chart 4. Compound **10**.

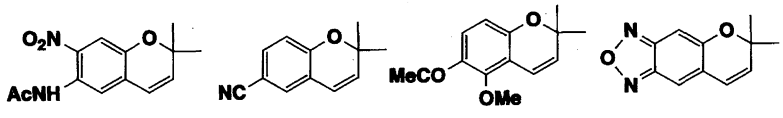
Our above studies support the hypothesis that the ligands of oxo(salen)manganese(V) complexes take a non-planar stepped conformation. Jacobsen's proposal on the olefin's approach (Fig. 2) is based on the hypothesis that the ligand of oxo(salen)manganese(V) complex has a planar structure. This hypothesis is predicated on the idea that the structure of (salen)manganese(III) complexes studied by X-ray diffraction is planar.[14a,30] However, it was also found that basal salen ligands are pliable and that some salen ligands actually take a non-planar stepped conformation (Fig. 5).[31] Although Mn-salen complex **12a** bearing two aqua ligands at axial sites takes a shallow stepped conformation, the complex **12b** bearing aqua and cyclopentene oxide ligands takes a more deeply bent conformation. On the other hand, it is known that the bond between manganese ion and the equatorial oxygen atom gets shorter as the oxidation state of manganese ion increases. The bond shortening is expected to further amplify the non-planarity of basal salen ligands. Therefore it is reasonable to assume that the salen ligands take a stepped-conformation, the chirality sense of which strongly affects the asymmetric induction by Mn-salen catalyst. A study on asymmetric Diels–Alder reaction using cationic Mn-salen complex also supports the non-planarity of the salen ligand.[5]

It is worth mentioning that the cyclopentyl group of the oxide ligand in complex **12b** exists in a sterically congested area and are very close to the phenyl (arrow 3) and the naph-

Table 3. Asymmetric Epoxidation of 2,2-Dimethyl-2*H*-chromene Derivatives Using **10** as a Catalyst[a]

Entry	Substrate	Catalyst	Catalyst mol%	Solvent	Temp °C	Time	Yield[b] %	ee[c] %	Confign.
1	**11a**	**10**	5	CH_2Cl_2	R.T.	2 h	92	96	3*S*,4*S*
2	**11a**	**7**[d]	2	CH_3CN	0	—	72	98	3*S*,4*S*
3	**11a**	**10**	2	CH_3CN	0	6 h	100	98	3*S*,4*S*
4	**11a**	**10**	0.2	CH_3CN	0	6 h	95	98	3*S*,4*S*
5	**11a**	**10**	0.01	CH_3CN	0	10 d	92	99	3*S*,4*S*
6	**11b**	**10**	2	CH_3CN	0	1 d	88	93	3*S*,4*S*
7	**11b**	**10**	0.01	CH_3CN	0	10 d	40	95	3*S*,4*S*
8	**11b**	**10**	2	CH_3CN	−20	20 h	96	96	3*S*,4*S*
9	**11c**	**10**	2	CH_3CN	0	1 d	84	83	3*S*,4*S*
10	**11c**	**10**	2	CH_3CN	−20	20 h	80	90	3*S*,4*S*
11	**11d**	**10**	2	CH_3CN	−20	20 h	86	97	3*S*,4*S*

a) All the reactions were carried out using 1-1.5 mol amt. of iodosylbenzene as a terminal oxidant. b) Isolated yield. c) The enantiomeric excesses of the epoxides were determined by HPLC analyses (column: Daicel Chiralcel OJ). d) The reaction was carried out in the presence of pyridin *N*-oxide (Ref. 18b).



11a **11b** **11c** **11d**

Chart 5. Compounds **11**.

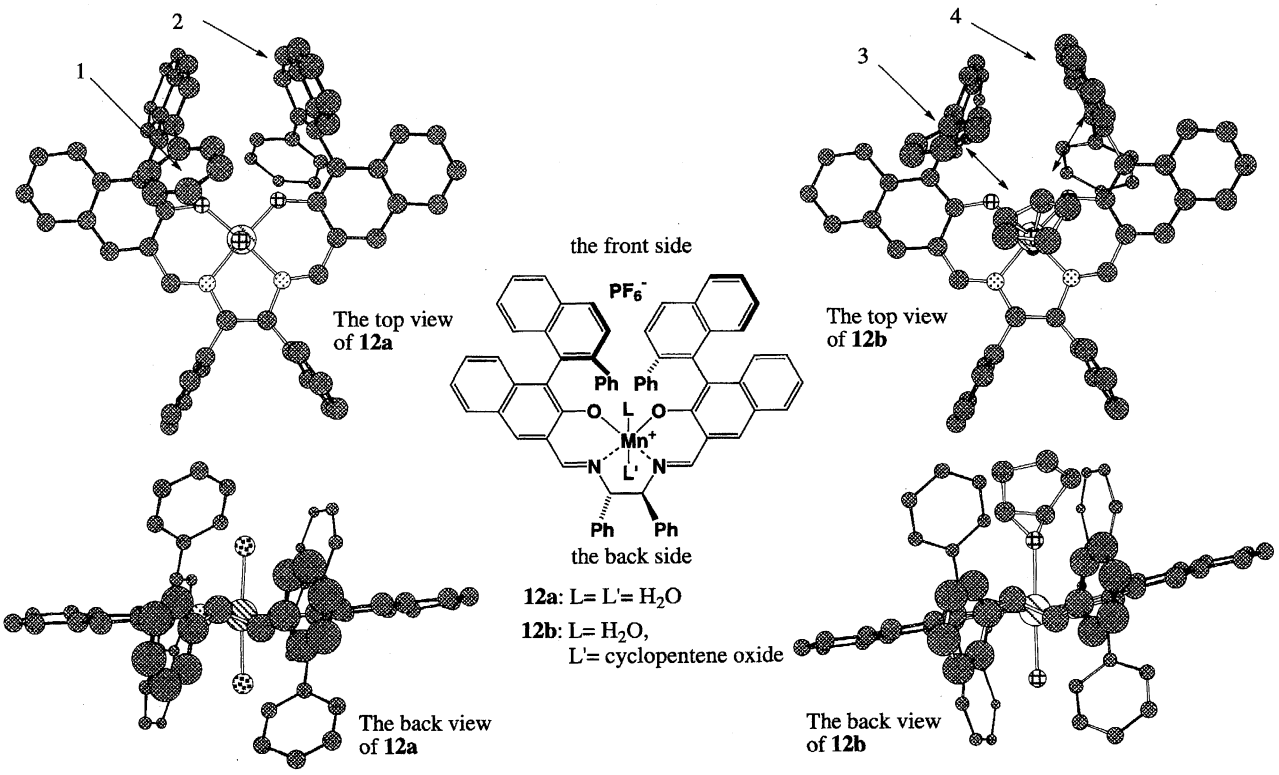


Fig. 5. Supporting information of the non-planar stepped conformation oxo(salen)manganese(V) complex from the X-ray analyses of (salen)manganese(III) complexes, **12a** and **12b**.

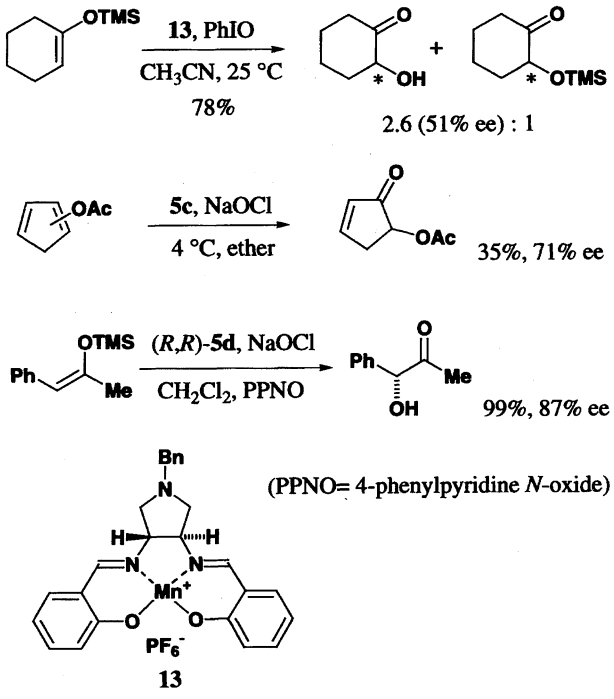
thyl (arrow 4) groups, suggesting that there is some kind of interaction between cyclopentyl group and the aryl rings such as C–H π interaction. This may suggest that Mn-salen catalysts of second generation have some ability to recognize substrates.[31]

There is controversy about the mechanism of metal–oxo bond with olefins. A non-linear relationship between enantioselectivity and reaction temperature which suggests participation of a reversibly formed metallaoxetane intermediate was observed by our group.[32] Norrby and Åkermark have also proposed participation of metallaoxetane intermediate.[33] However, a kinetic isotope effect on osmium tetraoxide catalyzed dihydroxylation which had also been proposed through a metallaoxetane intermediate,[34] has recently been demonstrated to be incompatible with metallaoxetane intermediate.[35]

In the course of our study on asymmetric induction by Mn-salen catalyst, another substrate approach along the axis of metal-nitrogen bond in a (salen)manganese complex was proposed, based on the assumption that the salen ligand had a planar structure. Although our study disclosed that the assumption is not correct, the possibility that substrates approach the manganese–oxo bond along the metal–nitrogen bond axis would not be excluded.

3. Asymmetric Oxidation of Enol Ether Derivatives

Reddeppa Reddy and Thornton have reported asymmetric oxidation of trimethylsilyl enol ethers using complex **13** (Scheme 4). This reaction gives a mixture of α-hydroxy ketone and its silyl ether but enantioselectivity



Scheme 4.

varies with substrates used, ranging from 15 to 62%.[36] Jacobsen and co-workers have reported that oxidation of enol- and dienol acetates using complex **5c** shows moderate enantioselectivity.[19] Furthermore, Fell et al. have reported that oxidation of conjugated silyl enol ether using **5d** shows high enantioselectivity.[37] The study on the stereochemistry

of the last reaction supports our another hypothesis that olefins approach a metal–oxo bond along the metal–nitrogen bond axis.

In the oxidation of enol ethers using **7** as the catalyst, the enantiomeric excesses of the resulting α-hydroxy ketones were found to depend upon the reaction time, suggesting that partial epimerization of the unstable α-hydroxy ketones took place during the reaction. α-Hydroxy ketone is not the primary product of this reaction but is derived from the intermediary epoxy ether by attack of water. Therefore, α-hydroxy acetal which was stable to the reaction conditions was expected to be produced if the reaction was carried out in an alcoholic solvent. Actually, α-hydroxy acetals were obtained with constant and high enantioselectivity even in the oxidation of simple enol ethers (Table 4).[38] In alcoholic solvents, the solvent competes with a donor ligand in coordination to a metal center and therefore no donor ligand effect (see the previous section) can be expected in the present reaction. It is worth mentioning that high enantioselectivity was realized in the oxidation of simple enol ethers without adding any donor ligand.

4. Kinetic Resolution of Racemic Allenes

Oxidation of allenic compounds generally provides complex mixtures. However, oxidation of racemic allenes with optically active oxidants or catalysts occurs in an enantiomer-differentiating manner. Thus, this type of reaction is expected to be a useful method for obtaining optically active allenes, but the efficiency of this oxidative kinetic resolution still remains insufficient. Thus, the kinetic resolution of racemic allenes was studied by using Mn-salen complexes as a catalyst. First, the resolution of racemic 1-phenyl-1,2-propadiene using **7** as a catalyst was examined. This reaction proceeds smoothly at −40 °C and the relative reaction rate (k_{rel}) was calculated to be 10 (Fig. 6).[39] Furthermore, the kinetic resolution of 1,3-diarylallenes proceeded with a relative reaction rate as high as 18—23 (Table 5, Entries 1—4), except for the substrates bearing electron-donating substituents at aryl

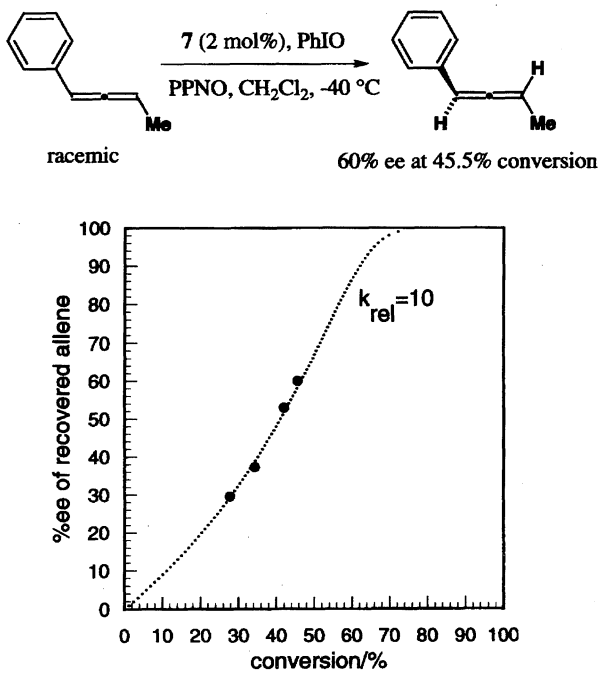


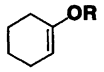
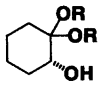
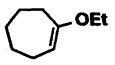
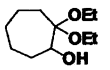
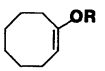
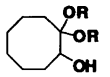
Fig. 6. Kinetic resolution of racemic 1-phenyl-1,2-butadiene using complex **7** as a catalyst. The relative reaction rate of the enantiomers was estimated to be 10 by comparing the experimental data (large dots) with theoretically calculated data (small dots) described in the graph.

ring (Table 5, Entries 5 and 6). The lower enantioselectivity observed in the latter two substrates is probably because introduction of electron-donating group such as methyl and methoxy groups enhances the level of HOMO of the substrates and therefore the transition state in these reactions shifts earlier, reducing the specific interaction between the substrates and the salen ligand.

5. Asymmetric Benzylic Oxidation (Enantioselective C–H Oxidation)

C–H oxidation is the most fundamental method for direct functionalization of organic compounds, but there is no re-

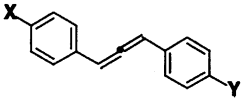
Table 4. Asymmetric Oxidation of Enol Derivatives Using Mn-Salen Catalyst **7** as a Catalyst[a]

Entry	Substrate		Solvent	Oxidant mol amt.	Product		Yield %	ee %	Confign.
1		R = Me	MeOH	PhIO (1.0)		R = Me	38	85	*R*
2		R = Et	EtOH	PhIO (2.0)		R = Et	58	89	*R*
3			EtOH	PhIO (2.0)			55	81	—[b]
4		R = Me	MeOH	PhIO (1.0)		R = Me	60	83	—[b]
5		R = Et	EtOH	PhIO (2.0)		R = Et	68	88	—[b]

a) All the reactions were carried out at 0 °C in the absence of donor ligand. b) Configuration has not been determined.

Table 5. Kinetic Resolution of 1,3-Diarylallenes Using **7** as a Catalyst[a)]

Entry	Substrate		Conversion	%ee of	k_{rel}
	X	Y	%	unreacted allene	
1	CF_3	CF_3	57.0	92.6	19±1
2	Cl	Cl	57.8	92.7	18±1
3	H	H	59.5	96.3	19±1
4	H	Cl	59.7	98.7	23±1
5	CH_3	CH_3	77.8	97.3	6±1
6	MeO	MeO	83.3	60.6	2.0±0.2



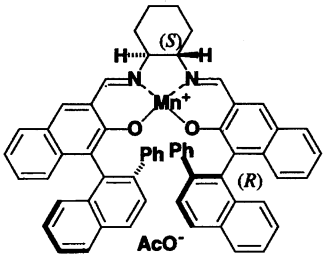
a) All the reactions were carried out with **7** (2 mol%) as a catalyst and PhIO (1 mol amt.) as a terminal oxidant in the presence of 4-phenylpyridine *N*-oxide in CH_2Cl_2 at −40 °C.

liable method available for this purpose. In 1990, Groves and Viski have reported that asymmetric benzylic oxidation using optically active iron–porphyrin complex as a catalyst proceeds with moderate enantioselectivity (up to 72%ee).[40)] Study on the kinetic isotope effect suggests that this reaction proceeds via a radical intermediate.[41)] (Salen)manganese(III) complexes also catalyze C–H oxidation and kinetic resolution of racemic dihydronaphthalene oxide has been examined, though the relative reaction rate is modest.[42)]

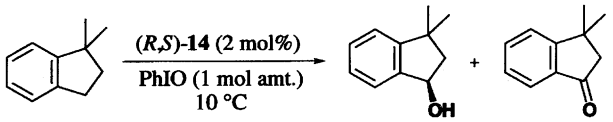
Asymmetric benzylic oxidation using complex (*R,S*)-**14** as a catalyst and 1,1-dimethylindan as a substrate was examined in our laboratory.[43)] The enantioselectivity of the reaction was found to depend on the viscosity of solvent and reaction time (Table 6).[44)] Use of a solvent of high viscosity such as chlorobenzene and longer reaction time improved enantioselectivity, suggesting participation of a radical intermediate and of enantiomer-selective oxidation of the resulting benzylic alcohols. The solvent of high viscosity constituting a stout solvent cage represses radical decay which causes partial racemization, and the longer reaction time increases alcohol conversion to ketone. However, suppression of radical decay by a solvent cage was considered to be imperfect.

To suppress radical decay more efficiently, a new Mn-salen complex of concave type **15** (Chart 6) was designed as shown in Fig. 7, in order to cover up the metal center by the bulky silyl group. Results of benzylic oxidation of various substrates with these complexes are shown in Table 7.[44)] As expected, enantioselectivity in hydrogen atom abstraction step increases up to 84%ee and subsequent kinetic resolution further improves the enantiomeric excess to 90%ee (Entries 1 and 3). Oxidation of other substrates also showed good to high enantioselectivity (Entries 6—12). It is noteworthy that the initial oxidation rate of 1,1-dimethylindan with **15a** and **15b** is ca. 6—7 times faster than that with **16** of Jacobsen type (Chart 7), even though the coordination spheres of **15a** and **15b** are much more congested than that of **16** (Entries 1, 2, and 5). Since it is reasonable to consider that the mechanism of hydroxylation by these catalysts should be the same, these results suggest that there is some attractive

Table 6. Asymmetric Hydroxylation of 1,1-Dimethylindan Using (*R,S*)-**14** as a Catalyst

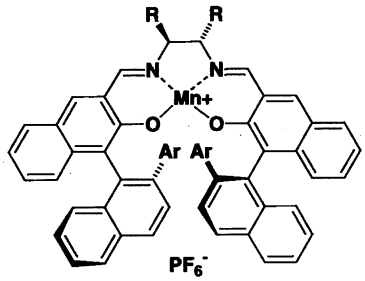


(*R,S*)-**14**



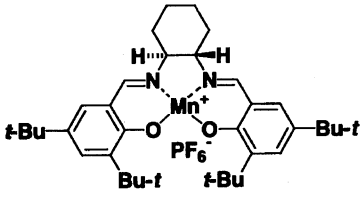
Entry	Solvent	Time	%ee	Yield (%)[a)]	Alcohol/Ketone
1	CH_3CN	5 min	31	7	26
2	CH_3CN	1.5 h	39	18	4
3	AcOEt	5 min	44	8	16
4	AcOEt	1.5 h	50	17	4
5	C_6H_5Cl	5 min	53	2	11
6	C_6H_5Cl	1.5 h	61	7	3

a) Yield of a mixture of alcohol and ketone.



15a: Ar= 4-[*t*-Bu(C_6H_5)$_2$Si]C_6H_4
R= 3,5-$(CH_3)_2C_6H_3$
15b: Ar= 4-[*t*-Bu(C_6H_5)$_2$Si]C_6H_4
R,R= $(CH_2)_4$

Chart 6. Compounds **15**.



16

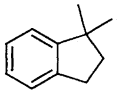
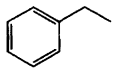
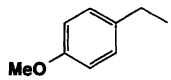
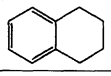
Chart 7. Compound **16**.

interaction between substrates and the salen ligands in **15a** and **15b**, as suggested by X-ray analysis of **12b**.

6. Desymmetrization of *meso*-Heterocycles

Desymmetrization of symmetrical compounds such as *meso*-compounds by enantiotopic selective C–H oxidation

Table 7. Asymmetric Benzylic Hydroxylation Using Mn-Salen Complexes (**15a** and **15b**) as Catalysts[a)]

Entry	Substrate	Catalyst	Temp	Time	%ee	Yield (%)[b)]	Confign.
1		**15a**	−20 °C	10 min	84	4.8 (Trace)	*R*
2		**15b**	−20 °C	10 min	70	4.0 (0.15)	*R*
3		**15a**	−20 °C	20 h	90	24.5 (10.2)	*R*
4		**15b**	−20 °C	20 h	81	16.6 (11.9)	*R*
5		**16**	−20 °C	10 min	14	0.7 (0.2)	*R*
6		**15b**	−30 °C	10 min	65	2.1 (Trace)	*R*
7		**15b**	−30 °C	12 h	78	6.4 (3.3)	*R*
8		**15a**	−30 °C	12 h	64	2.0 (4.4)	*R*
9		**15b**	−30 °C	10 min	83	1.8 (Trace)	*R*
10		**15b**	−30 °C	24 h	87	13.0 (10.5)	*R*
11		**15a**	−30 °C	12 h	77	7.2 (11.1)	*R*
12[c)]		**15b**	−30 °C	12 h	77	22.0 (6.2)	*R*

a) Reactions were carried out in chlorobenzene by using 2 mol% of catalyst and iodosylbenzene as a terminal oxidant unless otherwise noted. b) Yields were determined by GLC analysis using *p*-dichlorobenzene as an internal standard. The number in parentheses is the yield of ketone. c) Reaction was carried out with 3 mol% of catalyst.

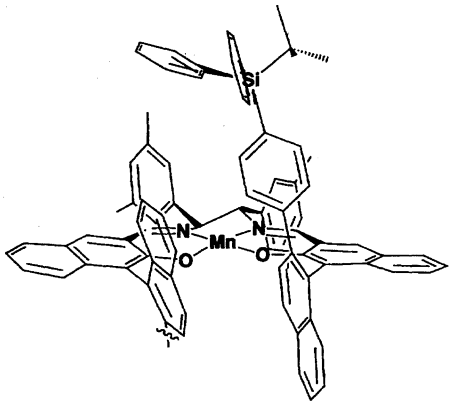
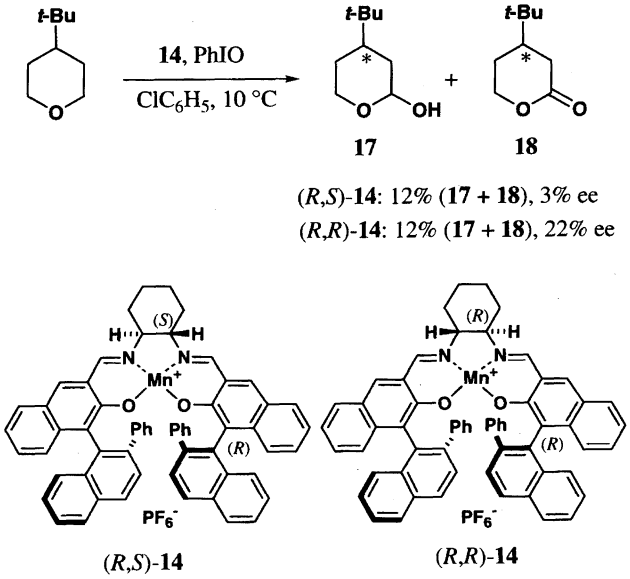


Fig. 7. The structure of **15a** drawn on the basis of the X-ray structure of **12a**. All the hydrogen atoms, counter anion, and the left bottom part of the ligand were omitted for clarification. The conformation of *t*-butyldiphenylsilyl moiety was optimized by using TRIPOS-SYBYL on an IRIS Indigo 2.



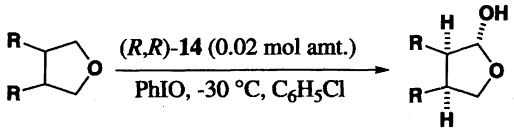
Scheme 5.

is an important strategy for creating new chiral centers. Although biological reactions of this type are well known, there is no successful precedent in the reaction using molecular catalysis. Since the Mn-salen complexes were found to be effective catalysts for asymmetric oxidations, as shown in the previous sections, the asymmetric desymmetrizations of prochiral tetrahydropyran, *meso*-tetrahydrofurans and *meso*-pyrrolidines were examined by using the complexes.

Oxidation of 4-*t*-butyltetrahydropyran with (*R*,*S*)- and (*R*,*R*)-**14** was first examined (Scheme 5). Oxidation occurred selectively at the carbon α to the oxygen atom, giving a mixture of lactol **17** and lactone **18** irrespective of catalysts used.[45)] Interestingly, (*R*,*R*)-**14** showed better enantioselectivity than (*R*,*S*)-**14**, differing from the above described epoxidation and benzylic oxidation. The slow reaction is probably ascribed to the dihedral angle between α-C–H σ bond and n-orbital on the oxygen atom. The n–σ interaction facilitates hydrogen atom abstraction. However, 4-*t*-butyltetrahydropyran exists in chair conformer and the dihedral angle is as large as 60°.

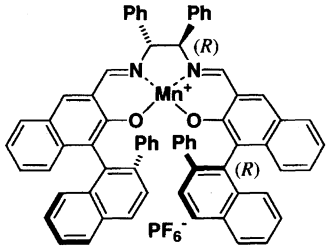
As the next step of the analysis, the oxidation of *meso*-tetrahydrofurans which were expected to have smaller dihedral angles was examined next (Scheme 6). As expected, the reaction proceeded smoothly even at −30° and showed higher enantioselectivity (up to 90%ee) when (*R*,*R*)-**14** was used as a catalyst.[45b)]

Desymmetrization of *meso*-pyrrolidine derivatives was also examined (Scheme 7).[46)] Enantioselectivity of the reaction was dependent on an *N*-protecting group of substrates, solvent, and catalyst. In accord with desymmetrization

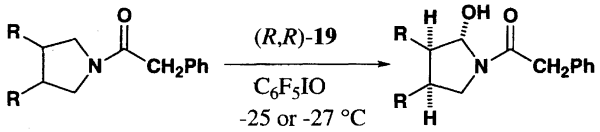


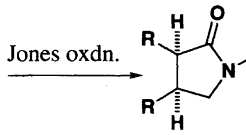
R=Me: 41%, 89% ee
R,R=$(CH_2)_3$: 59%, 82% ee
R,R=$(CH_2)_4$: 61%, 90% ee

Scheme 6.



(*R*,*R*)-**19**





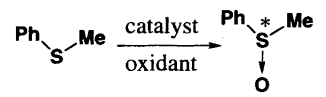
R=Me: 49%, 84% ee
R,R=$(CH_2)_3$: 48%, 76% ee
R,R=$(CH_2)_4$: 48%, 75% ee

Scheme 7.

of *meso*-tetrahydrofurans, (*R*,*R*)-Mn-salen catalyst showed better enantioselectivity than (*R*,*S*)-catalyst and (*R*,*R*)-**19** showed slightly better enantioselectivity than (*R*,*R*)-**14**. Acetonitrile was the solvent of choice for this reaction. Among the substrates examined, the pyrrolidines protected with phenylacetyl group showed the highest enantioselectivity. Under these optimized conditions, good to high enantioselectivity (up to 84%ee) was realized

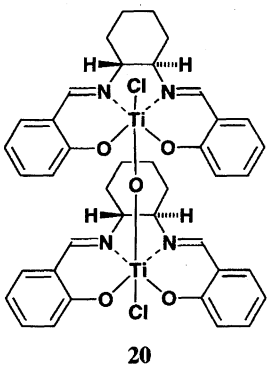
7. Asymmetric Oxidation of Alkyl Aryl Sulfides

As described in the beginning of this article, Fujita and co-workers have first reported asymmetric oxidation of sulfides using chiral (salen)vanadium complexes **3** as catalysts. In that study, they have also reported that introduction of electron-donating alkoxy groups at C3(3′) instead of bulky *t*-butyl groups enhances enantioselectivity.[13] Taking advantage of this electron-donating substituent effect, Jacobsen et al. have examined oxidation of sulfides using complex **5d** as the catalysts, but only slightly improved enantioselectivities have been observed, though good chemical yield has been realized.[47] Later, Fujita et al. reported that μ-oxobis-[(salen)titanium] complex **20** was a more effective catalyst (Scheme 8).[48] However, since TBHP slowly oxidizes sulfides even in the absence of catalyst, use of a large amount



Catalyst	Oxidant	Yield(%)	%ee
3a	CHP	70	10
3b	CHP	96	40
5d	H_2O_2	90	47
20	TBHP	89	63

CHP= 1-methyl-1-phenylethyl hydroperoxide



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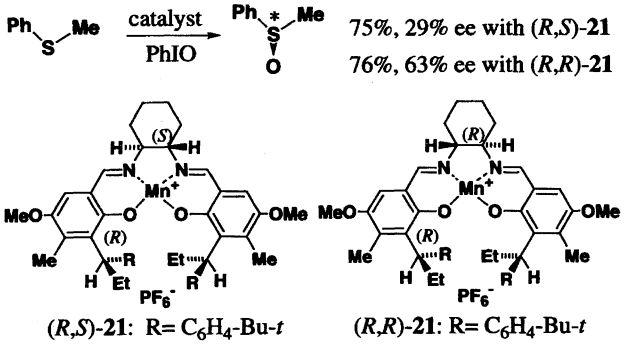
Scheme 8.



75%, 29% ee with (*R*,*S*)-**21**
76%, 63% ee with (*R*,*R*)-**21**

(*R*,*S*)-**21**: R= C_6H_4-Bu-*t* (*R*,*R*)-**21**: R= C_6H_4-Bu-*t*

Scheme 9.

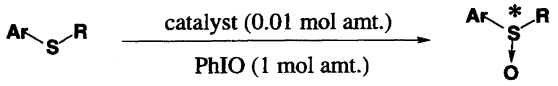
of the catalyst (0.2 mol amt.) is indispensable.

Methoxy derivative (*R*,*S*)-**21** of (*R*,*S*)-**6b** was synthesized and employed for the oxidation of methyl phenyl sulfide (Scheme 9).[49] To our disappointment, (*R*,*S*)-**21** showed only modest enantioselectivity. However, it was found that (*R*,*R*)-**21** exhibited considerably better enantioselectivity. Accordingly, methoxy derivatives of Mn-salen complexes of the second generation [(*S*,*R*)-**22** and (*S*,*S*)-**22**] were synthesized and examined (Table 8).[50] As expected, (*S*,*R*)-**22** showed high enantioselectivity of 81%ee (Entry 1) [Although (*S*,*R*)-**22** and (*S*,*S*)-**22** are methoxy derivatives of (*R*,*R*)-**7** and (*R*,*S*)-**7** respectively, their stereochemical nomenclatures are not identical to those of the parent complexes due to the sequence rule of IUPAC nomenclature]. Asymmetric oxidation of other alkyl aryl sulfides using (*S*,*R*)-**22** as the catalyst showed moderate to high enantioselectivity. In particular, the substrates bearing an electron-withdrawing group showed high enantioselectivity (up to 94%ee, Entries 3, 4, 5, and 9).

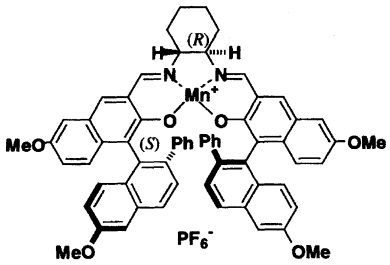
8. Asymmetric Aziridination

Aziridines are nitrogen equivalents of epoxides and are useful intermediates for the synthesis of compounds containing nitrogen functionalities. As described in Section 1, an oxo transfer reaction (oxene transfer reaction) via oxo metal (metal oxenoid) species is the most useful method for the synthesis of epoxides. Likewise, nitrene transfer reaction via metal nitrenoid species is a useful method for the synthesis of aziridines.[51] Burrows et al. examined aziridination of styrene using Mn-salen complexes **23** as the catalysts and PhI=NTs as the aziridinating agent (Scheme 10). This reaction provided the corresponding aziridine, but no enan-

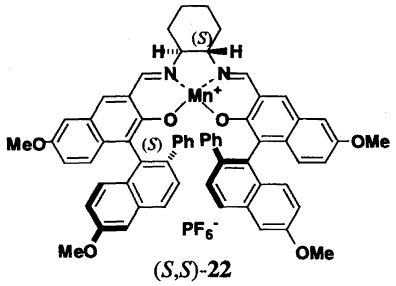
Table 8. Asymmetric Oxidation of Alkyl Aryl Sulfides Using Mn-Salen Complexes as Catalysts



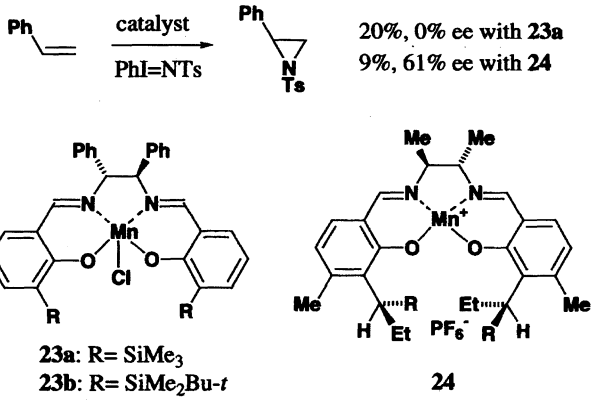
Entry	Sulfide Ar, R	Catalyst	Solvent	Additive	Temp	Time h	Yield %	ee %	Confign.
1	C_6H_5, Me	(*S*,*R*)-**22**	C_6H_5Cl	4-PPNO	R.T.	2	98	81	*S*
2	C_6H_5, Me	(*S*,*S*)-**22**	C_6H_5Cl	None	R.T.	2	91	39	*R*
3	*o*-$O_2NC_6H_4$, Me	(*S*,*R*)-**22**	CH_3CN	None	R.T.	2	94	94	—
4	*p*-$O_2NC_6H_4$, Me	(*S*,*R*)-**22**	CH_3CN	None	−20 °C	2	49	86	—
5	*o*-BrC_6H_4, Me	(*S*,*R*)-**22**	CH_3CN	None	0 °C	2	68	87	—
6	*p*-BrC_6H_4, Me	(*S*,*R*)-**22**	$C_2H_5CO_2Et$	4-PPNO	−20 °C	4	24	79	—
7	*p*-$CH_3OC_6H_4$, Me	(*S*,*R*)-**22**	C_6H_5Cl	4-PPNO	−20 °C	4	38	64	*S*
8	C_6H_5, Et	(*S*,*R*)-**22**	C_6H_5Cl	4-PPNO	R.T.	2	63	75	—
9	*o*-$O_2NC_6H_4$, Et	(*S*,*R*)-**22**	CH_3CN	None	R.T.	4	40	89	—



(*S*,*R*)-**22**



(*S*,*S*)-**22**

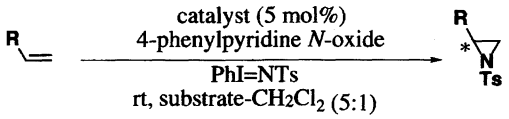


Scheme 10.

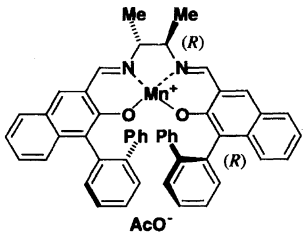
tioselectivity was observed.[52] We also examined asymmetric aziridination using complex **6** as a catalyst but enantioselectivity was poor, as was the chemical yield of aziridine. However, enantioselectivity of the reaction was found to be affected by the substituents at the ethylenediamine moiety and complex **24** showed moderate enantioselectivity of 61%ee, though chemical yield was still low (Scheme 10).[3a] The low reactivity is ascribed to the fact that intermediary metal nitrenoid in aziridination has a *p*-tolylsulfonyl group at the nitrene atom, differing from metal oxenoid which has no substituent at the oxene atom. *N*-*p*-Tolylsulfonyl group disturbs olefin's approach and its orientation affects enantioselectivity of the reaction. The steric bulkiness of the substituents at ethylenediamine moiety is considered to affect the orientation of *N*-substituent. To further enhance the reaction rate, steric hindrance by *N*-substituent must be overcome by some means.

During the study of epoxidation of 1-alkylindenes, we happened to find that catalytic activity of complex **7** is 2—3 times higher than those of **8b** and **8c**.[21] This suggests that the salen ligand of new generation accelerates the reaction through an attractive interaction between ligand and substrate, as discussed in Section 2. Thus aziridination of styrene derivatives was examined using complex **7** as a catalyst.

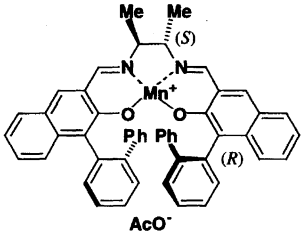
Table 9. Asymmetric Aziridination of Styrene Derivatives Using Mn-Salen Complexes as Catalysts



Entry	Substrate	Catalyst	Yield (%)	%ee	Confign.
1	Styrene	**7**	60	8	*S*
2	Styrene	(*R*,*R*)-**25**	76	94	*S*
3	*p*-Chlorostyrene	(*R*,*R*)-**25**	70	86	—
4	*p*-Methylstyrene	(*R*,*R*)-**25**	75	81	—
5	Indene	(*R*,*R*)-**25**	10	50	—
6	Styrene	(*R*,*S*)-**25**	25	13	*S*



(*R*,*R*)-**25**



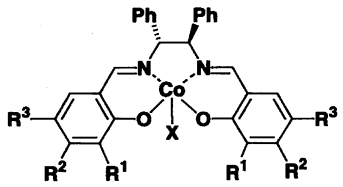
(*R*,*S*)-**25**

rene was examined with complex **7** as a catalyst (Table 9).[3b] Although chemical yield of aziridine was improved remarkably as expected, enantioselectivity was diminished (Entry 1). Low enantioselectivity was considered to be ascribed to the undesired orientation of the *p*-tolylsulfonyl group. To adjust it, we modified complex **7** to (*R,R*)-**25**; then high enantio selectivity (up to 94%ee) together with good chemical yield (Entries 2—4) was realized.[3b] Again, 2,3-diaminobutane was the best auxiliary for the ethylenediamine part though the best C3(3′)-substituent was not 2-phenylnaphthyl but biphenyl group. However, the good substrates for the present reaction seem to be limited to styrene derivatives (Entry 5). On the other hand, (*R,S*)-**25** showed poor catalytic activity and enantioselectivity (Entry 6).

9. Asymmetric Cyclopropanation

From the results of asymmetric oxene and nitrene transfer reactions, carbene transfer reaction such as cyclopropanation was expected to be performed in a highly enantioselective manner by using metallosalen complex as a catalyst. In 1978, Nakamura and Otsuka reported cyclopropanation using chiral (salen)cobalt(II) complex as a catalyst, though enantioselectivity was low.[53] On the other hand, we found that an axial ligand affects asymmetric induction in epoxidation by Mn-salen catalyst to a large extent. This prompted us to examine asymmetric cyclopropanation using (salen)cobalt(III) complex as a catalyst which carried an anionic ligand as an axial ligand.

We first examined cyclopropanation of styrene with *t*-butyl 2-diazoacetate in the presence of iodo(salen)cobalt(III) complex **26** (hereafter abbreviated as Co-salen (**I**) complex) that carried *t*-butyl group at C3 and C3′ (Chart 8).[4] Contrary to our expectation, complex **26** did not catalyze the desired cyclopropanation (Table 10, Entry 1). Co-salen (**I**) complex **27** having methyl group at C3 and C3′ also showed very poor

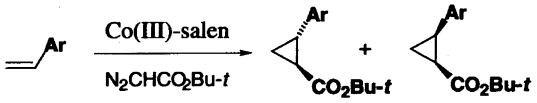


26: R^1= *t*-Bu, R^2=H, R^3= H, X= I
27: R^1= Me, R^2=H, R^3= H, X= I
28: R^1= H, R^2=H, R^3= H, X= I
29: R^1= H, R^2= *t*-Bu, R^3= H, X= I
30: R^1= H, R^2= H, R^3= *t*-Bu, X= I
31: R^1= H, R^2=H, R^3= H, X= Br
32: R^1= H, R^2= *t*-Bu, R^3= H, X= Br
33: R^1= H, R^2= H, R^3= *t*-Bu, X= Br
34: R^1= H, R^2= H, R^3= OMe, X= Br
35: R^1= H, R^2= H, R^3= OMe, X= I

Chart 8. Compounds **26**—**35**.

catalytic activity (Entry 2). However, it was found that Co-salen (**I**) complex **28** bearing no substituent at C3 and C3′ catalyzed cyclopropanation and gave a *trans*-isomer preferentially, though enantioselectivity was moderate (Entry 3). Although there have been many excellent methods for asymmetric cyclopropanation reported,[54] most of them gave a considerable amount of *cis*-isomer together with *trans*-isomer, except for Nishiyama's method which shows high enantioselectivity as well as high *trans*-selectivity.[55] This reaction was the second example that showed high *trans*-selectivity. Introduction of bulky *t*-butyl group at C4(4′) (**29**) or C5(5′) (**30**) did not affect either enantioselectivity and *trans*-selectivity (Entries 4 and 5). Therefore, we tried to improve asymmetry-inducing ability of the catalyst by changing the electronic nature of the ligand. The effect of replacing the axial iodide of the complex with a bromide was expected to work well since a bromide ligand might lower the activity

Table 10. Asymmetric Cyclopropanation of Styrene Using Co(III)-Salen Complexes as Catalysts



Entry	Substrate R	Catalyst	Yield %	*trans* : *cis*	%ee (*trans*)	%ee (*cis*)
1	C_6H_5	**26**	0	—	—	—
2	C_6H_5	**27**	—[a]	—	—	—
3	C_6H_5	**28**	79	95:5	64 (1*S*,2*S*)	51 (1*S*,2*R*)
4	C_6H_5	**29**	76	98:2	73 (1*S*,2*S*)	—
5	C_6H_5	**30**	76	95:5	75 (1*S*,2*S*)	—
6	C_6H_5	**31**	83	95:5	66 (1*S*,2*S*)	82 (1*S*,2*R*)
7	C_6H_5	**32**	85	96:4	89 (1*S*,2*S*)	93 (1*S*,2*R*)
8	C_6H_5	**33**	55	94:6	83 (1*S*,2*S*)	42 (1*S*,2*R*)
9	C_6H_5	**34**	80	96:4	93 (1*S*,2*S*)	91 (1*S*,2*R*)
10	4-Cl-C_6H_4	**34**	86	97:3	96[b]	—
11	2-Naphthyl	**34**	87	95:5	92[b]	—

a) The formation of only a trace amount of the product was detected by TLC analysis. b) Absolute configuration has not been determined.

of carbenoid species due to its weaker *trans*-effect as compared with an iodide ligand. As expected, Co-salen (Br) complexes **31**—**33** showed better enantioselectivity than the corresponding Co-salen (**I**) complexes **28**—**30** (Entries 6—8). To further improve the enantioselectivity, the substituent of the salen ligand was modified. As discussed in the previous sections, introduction of electron-donating group into salen ligand improves enantioselectivity.[13,47,49,50] Thus, cyclopropanation using complex **34** bearing electron-donating methoxy group at C5 and C5′ was examined and high enantioselectivity of 93%ee was achieved without decaying high *trans*-selectivity (Entry 9). Asymmetric cyclopropanation of other styrene derivatives also showed high enantioselectivity as well as high *trans*-selectivity (Entries 10 and 11).

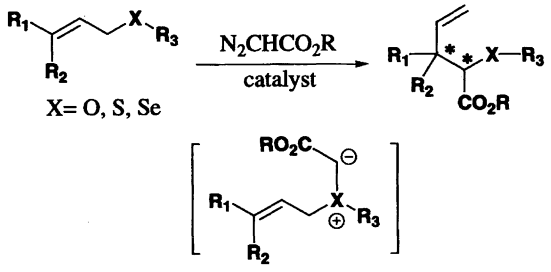
As discussed in Section 1, the ligands of the intermediary oxo Mn(V)-salen complexes take a non-planar stepped conformation and the non-planarity of the salen ligand played a very important role in asymmetric induction by Mn-salen catalyst. Although the mechanism of asymmetric induction by Co(III)-salen catalyst is unclear at present, we assume that the ligand of the intermediary Co(V)-salen carbenoid species also had a non-planar structure, as shown in Fig. 8, which was drawn by using TRIPOS-SYBYL on an IRIS Indigo 2. Differing from the oxygen atom of oxo Mn(V)-salen species, the carbenoid carbon of Co(V)-salen species carries a bulky *t*-butoxycarbonyl group on it, which is considered to protrude over the downward benzene ring **A** in Fig. 8. In Mn(III)-salen catalyzed epoxidation, olefins are considered to approach metal–oxo bond, passing over the downward benzene ring.[32] In the present reaction, however, this pathway is blocked by the carbenoid ester group. Thus we assumed that styrene would approach the carbenoid carbon from the front side (Fig. 8), directing its phenyl group away from the ester group to give (1*S*,2*S*)-isomer in preferential amount. This assumption is compatible with the observation that the Co(III)-salen complexes bearing C3(3′)-substituents show no or very poor catalytic activity. C3(3′)-Substituents probably interfere with the incoming olefins.

10. Asymmetric *S*-Ylide Formation and Its [2,3]-Wittig Rearrangement

Carbon–carbon bond formation introducing asymmetric center(s) provides a very efficient method for the construction of sterically complex molecules. One such reaction is the asymmetric [3,3]- or [2,3]-sigmatropic rearrangement which has been widely used in the synthesis of various natural products. However, this type of reaction is a self-immolative asymmetric synthesis[56] wherein the chirality in the substrate is transferred into the product while the original chirality is decayed, and examples of catalytic and enantioselective sigmatropic rearrangement are still rare. A few years ago, Doyle et al. reported that the reaction of allyl ether and diazoacetate in the presence of $Rh_2(OAc)_4$ proceeded with moderate to good diastereoselectivity (79 : 21—97 : 3), giving the corresponding [2,3]-Wittig rearrangement products by way of the intermediary oxonium ylides (Scheme 11, X = O).[57] Later, Uemura et al. reported the asymmetric version of this reaction using allylic sulfides or selenides as substrates in the presence of Cu(I)-2,2′-methylenebis(oxazolines) or Rh_2(5*S*-MEPY)$_4$ (MEPY : methyl 2-pyrrolidone-5-carboxylate) (Scheme 11, X = S or Se).[58] Those reactions proceeded with modest enantioselectivity (up to 41%ee).

As discussed in the previous sections, we have demonstrated that Mn-salen complexes are effective catalysts for asymmetric epoxidation and oxidation of sulfides, and that Co-salen complex is an effective catalyst for asymmetric cyclopropanation. In analogy with the catalysis by Mn-salen complexes, Co(III)-salen complexes were expected to catalyze *S*-ylide formation in an enantioselective manner. Thus, the stereoselective rearrangement of the *S*-ylide which is derived from allyl aryl sulfides and α-diazoacetates in situ was examined in a catalytic and enantioselective manner.

Cinnamyl phenyl sulfide was first employed as a substrate and treated with *t*-butyl diazoacetate in the presence of optically active Co(III)-salen complex as the catalyst.[60] In common with asymmetric cyclopropanation, Co-salen complex **26** bearing a *t*-butyl group at C3 and C3′ showed no catalytic activity for *S*-ylide formation. Thus, *S*-ylide formation with



Scheme 11.

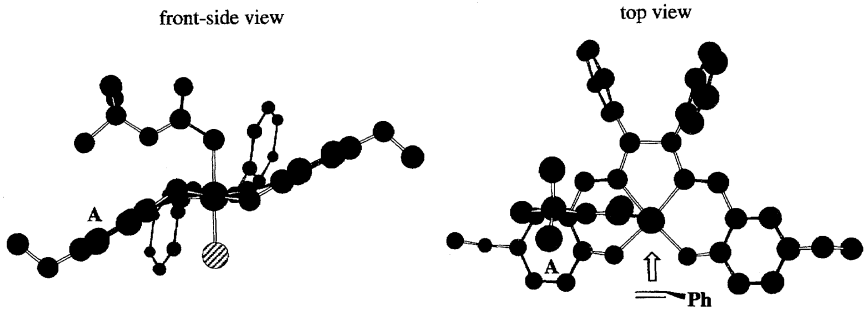
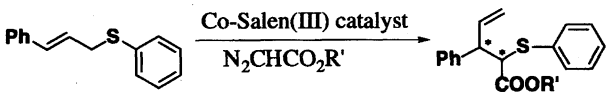


Fig. 8. The front side and top views of carbene Co(V)-salen complex derived from the corresponding Co(III)-complex (**34**).

Table 11. Co-Salen Catalyzed Asymmetric [2,3]-Sigmatropic Rearrangement



Entry	Catalyst	R′	Yield (%)	*anti* : *syn*	%ee[a]
1	**30**	*t*-Bu	74	83:17	47
2	**33**	*t*-Bu	86	83:17	43
3	**34**	*t*-Bu	81	85:15	64
4	**35**	*t*-Bu	64	82:18	50
5	**34**	(−)-Menthyl	68	93:7	74[b]

a) The enantiomeric excess of the *anti*-isomer unless otherwise noted. b) The diastereomeric excess of the *anti*-isomer.

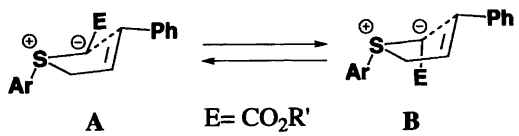
Co-salen catalysts (**30**, **33**, **34**, and **35**) bearing no 3,3′-substituent was examined and catalyst **34** was found to show the best enantioselectivity of 64%ee (Table 11). Although enantiomeric excess of the rearrangement products was dependent on the catalysts used, diastereomer ratio (the ratio of *anti*- and *syn*-isomers) was not affected by the catalysts (Entries 1—4). This observation strongly suggests that the intermediary *S*-ylide is not coordinated to the catalyst. Therefore, differentiation of the enantiotopic lone pair electrons on the sulfur atom is dictated by the chirality of the Co-salen complex, but diastereoselectivity is determined by the difference in the potential energy of the two transition states, **A** and **B**, in Scheme 12. To further improve both enantioselectivity and diastereoselectivity, (−)-menthyl diazoacetate was employed as the diazo compound, expecting matched double diastereo differentiation. Both the enantioselectivity in *S*-ylide formation and the *syn–anti* ratio of the product were improved to 74%ee and 93 : 7, respectively, as expected (Entry 5). This means that the sense of asymmetric induction by the (−)-menthyl moiety matches to that by the Co-salen catalyst **34**.

Next 3-methyl-2-butenyl phenyl sulfide and geranyl phenyl sulfide were employed as substrates for the reaction. Both sulfides were converted to the rearrangement products in good stereoselectivities as shown in Scheme 13. The undesired combination of (−)-menthyl diazoacetate and *ent*-**34**, which is the enantiomer of **34**, showed low selectivity of 8%de as expected.

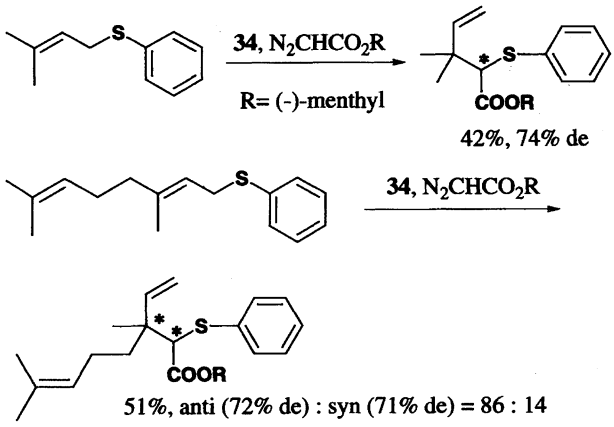
After we had published our results, Doyle et al. reported an excellent [2,3]-Wittig rearrangement via *O*-ylide by using his modified chiral rhodium catalyst.[59]

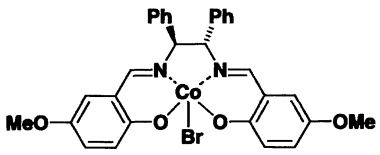
Conclusion

Chiral metallosalen complexes have now been demonstrated to serve as efficient catalysts for a wide variety of asymmetric reactions. However, our understanding of the mechanism of asymmetric induction by chiral metallosalen complexes is still immature and further study is required for acquiring more knowledge on the catalysis of metallosalen complexes, which should enable the cultivation of new fields of asymmetric synthesis. Furthermore, deep understanding of their catalysis will also contribute to comprehension of the mechanisms of many biological reactions catalyzed by metal–enzymes.



Scheme 12.





ent-**34**

Scheme 13.

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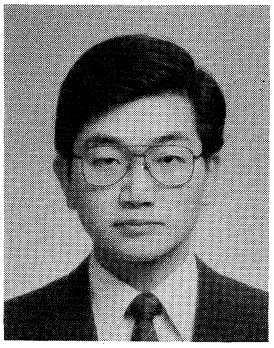

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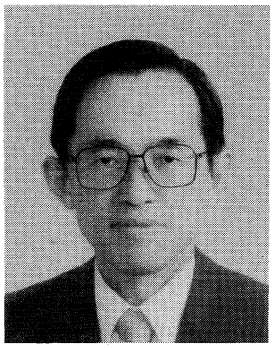

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