Chiral Metallosalen Complexes: Structures and Catalyst Tuning for Asymmetric Epoxidation and Cyclopropanation

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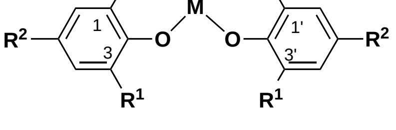
Received: July 2, 2001; Accepted: September 4, 2001

Abstract: Optically active metallosalens are currently one of the most widely used catalysts for asymmetric synthesis. This is mainly due to the following reasons: various salen [*N,N'*-ethylenebis(salicyldeneaminato)] ligands form complexes with many metal ions and the resulting metallosalens adopt versatile structures, therefore, metallosalens show a variety of catalytic performances. Thus, selection of a metal ion serving the aimed reaction and regulation of ligand conformation to be suitable for the reaction are indispensable for achieving metallosalen-catalyzed asymmetric reactions. Recently, several factors controlling ligand-conformation in metallosalens have been clarified. This article provides selected examples of tuning the structures of metallosalens in compliance to the aimed reaction, by taking asymmetric oxene or carbene transfer reaction as the instance.

Keywords: asymmetric catalysis; cyclopropanation; epoxidation; hydroxylation; metallosalen; sulfoxidation.

1 Introduction

Optically active metallosalen complexes **1** {the [*N,N'*-ethylenebis(salicyldeneaminato)] ligand is abbreviated as salen ligand in this review} have lately attracted considerable attention of synthetic organic chemists due to i) ease of their preparation: various metallosalen complexes can be synthesized simply by mixing diamine, salicyl aldehyde, and metal salt in an appropriate solvent, ii) easy construction of highly asymmetric coordination sphere, and iii) versatile catalytic performance.[1] Indeed, optically active metallosalen complexes bearing manganese,[2] chromium,[3,4a, b,5,6] vanadium,[1d,7] titanium,[8,9] cobalt,[10,11,12] ruthenium,[13] copper,[14] zinc,[15] and palladium[16] as the metal center have been synthesized and successfully applied to a variety of asymmetric reactions: epoxidation,[2] sulfoxidation,[1d,2a,8,17] C-H oxidation,[18,19] aziridination,[20,21,22] sulfimidation,[23] C-H amination,[24] cyclopropanation,[10,12,13] *S*-ylide formation,[25] Diels–Alder reaction,[26,27] hetero-Diels–Alder reaction,[28,29] hydrocyanation,[30] silylcyanation,[7,9,31] epoxide-ring opening,[5,11] aerobic oxidative coupling,[32] ymmetric catalysis of chiral metallosalen complexes can be realized not only by use of various metal ions but also by introduction of ligands of various structures and electronic nature. Especially, recent studies have revealed that metallosalen complexes are pliable and can adopt various conformations, depending on their metal centers and substituent(s) on the salen ligand and that the conformation of metallosalen complexes has a strong relation to their catalytic performance. Thus, clarifying the structural influence of metallosalen complexes on their catalytic performance is indispensable for designing a more efficient and more practical new metallosalen catalyst. In this article, we deal mainly with the relationship between the structures of metallosalen complexes [hereafter referred to as M(salen)s] and their

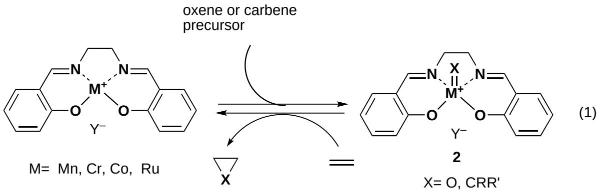


1: M = Mn, Cr, Co, Ti, Al, V, Ru

Tsutomu Katsuki was born in Saga, Japan, in 1946. He studied chemistry at Kyushu University, graduating in 1969, and received a doctoral degree in 1976 from the same university under the supervision of Professor M. Yamaguchi. He was a research associate at Kyushu University from 1971–1987. For two years from 1979–1980, he was a post-doctoral fellow with Professor K. B. Sharpless at Stanford University and Massachusetts Institute of Technology, at which time he and Professor Sharpless published their famous paper on the asymmetric epoxidation of allylic alcohols. He has been a full professor at Kyushu University since 1988. His current research interests are focused on asymmetric catalysis with organo-transition-metal complexes and the synthesis of natural products. His work has been recognized by the Inoue Science Award, the Synthetic Organic Chemistry Award, Japan, and the Molecular Chirality Award.

catalytic performances. As described above, the main catalytic performances of M(salen)s are i) oxene, nitrene, and carbene transfer and ii) Lewis acidity.[2] The relationship is discussed by taking oxene and carbene transfer reactions as examples. Catalytic performance of M(salen)s is also affected by other factors, which have been described in several reviews.[33]

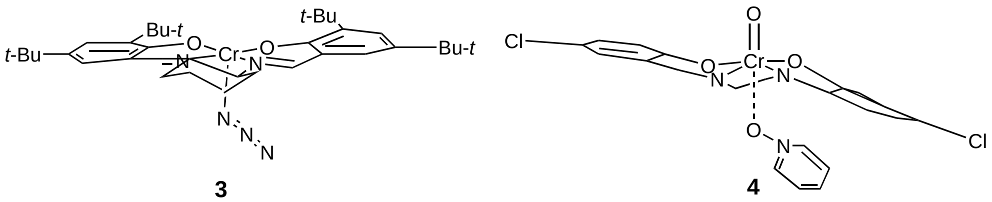
2 Ligand Conformation of M(salen)s



M(salen)s **1** possess two sp^3 carbons and a wide open space nearby C-3 and C-3′ that enable introduction of asymmetric carbons at C-8 and C-8′ and bulky and/or chiral substituents at C-3 and C-3′, respectively. Oxene and carbene transfer reactions have been considered to proceed through the corresponding oxenoid[1c,34] and carbenoid species **2**[35] (Equation 1). To transfer such species to a substrate with high enantio-face or -topos selectivity, the path of the incoming substrate and its orientation must be regulated strictly by the salen ligand. Ligands of most M(salen)s adopt non-planar stepped conformation, though the degree of their folding depends upon the metal ion used, its valency, the presence or the absence of an apical ligand, and the structure and electronic nature of salen ligands. For example, Cr(III)(salen)N_3 **3** has a nearly planar structure[4a] but Cr(V)(salen) **4** has a deeply folded non-planar one[1c] (Figure 1). The control of ligand-conformation and the choice of metal center are essential for achieving a desired catalytic performance with high enantioselectivity. Of various M(salen)s, Mn(salen)s are the most potent catalysts for oxene transfer (oxo transfer) reaction. Thus, we start this article with control of ligand conformation of achiral Mn(salen)s.

3 Mn(salen)-Catalyzed Epoxidation: Ligand Conformation and Enantioselectivity

M(salen)s have three single bonds in their ethylenediamine parts and M(salen)s can adopt a non-planar conformation, which affects their asymmetric induction. X-ray analyses of many M(salen)s have demonstrated that they can take various structures. As described in the preceding section, a cationic oxo-Cr(V)(salen) and its pyridine *N*-oxide adduct have been unambiguously determined to adopt non-planar structures by Kochi et al.[1c] The ligand of Al(salen) has also been reported to take a non-planar stepped-conformation.[36] On the other hand, simple chiral Mn(III)(salen)s bearing chirality only at their ethylenediamine part have been determined to adopt a nearly planar structure.[37] However, as the structures of the above-described oxo-Cr(V)(salen)[1c] indicate, the corresponding oxo-



3 **4**

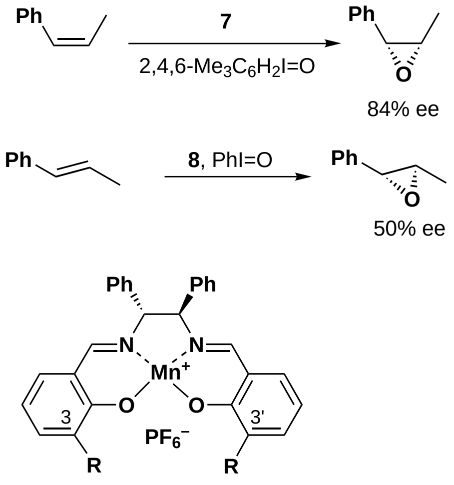
Figure 1. The structures of Cr(III)(salen)N_3 and O=Cr(salen)-pyridine *N*-oxide adduct.

Mn(V)(salen)s that are the active species in Mn(salen)-catalyzed epoxidation[34,38] are also considered to adopt a non-planar structure. Indeed, the non-planarity of oxo-Mn(salen)s has been proven by the following experiments.[39] If a salen ligand adopts non-planar conformation, oxo-Mn(salen) bearing an achiral ligand must exist in a 1:1 equilibrium mixture of enantiomeric conformers (**5** and *ent*-**5**) (Scheme 1). Epoxidation with an achiral Mn(salen) as the catalyst gives a racemic epoxide, because these conformers are equally active and give enantiomeric epoxides, respectively. However, the epoxidation can be carried out in an enantioselective manner, if the equilibrium is shifted toward one conformer by some means. Cationic oxo-Mn(salen) is coordinated by an apical neutral ligand (L). If the apical ligand is chiral, the enantiomeric conformers become diastereomeric to each other and the equilibrium leans towards one conformer. Thus, cationic achiral Mn(salen) can be used as a chiral catalyst:[39] actually, epoxidation using achiral cationic Mn(salen) **6** as the catalyst showed high enantioselectivity of 82% ee in the presence of an optically active donor ligand, (+)-bipyridine *N,N′*-dioxide.[39c] Olefins approach the prevailing conformer over the downwardly-bent benzene ring, directing the bulkier substituent (R_L) away from the bulky 3- or 3′-substituent (R^1), to give the major enantiomers of epoxides. The presence of bulky 3- and 3′-substituents is indispensable for regulating the orientation of the incoming olefin. To our knowledge, this asymmetric epoxidation is the first example of an asymmetric reaction with an achiral catalyst modified by a chiral ligand.

Calculations also support the assumption that the ligand of oxo-Mn(salen) adopts a non-planar stepped conformation.[40] It is noteworthy that a calculation suggested that the ligand would be forced by binding of a bulky apical ligand to take the *cis*-conformation.[40c]

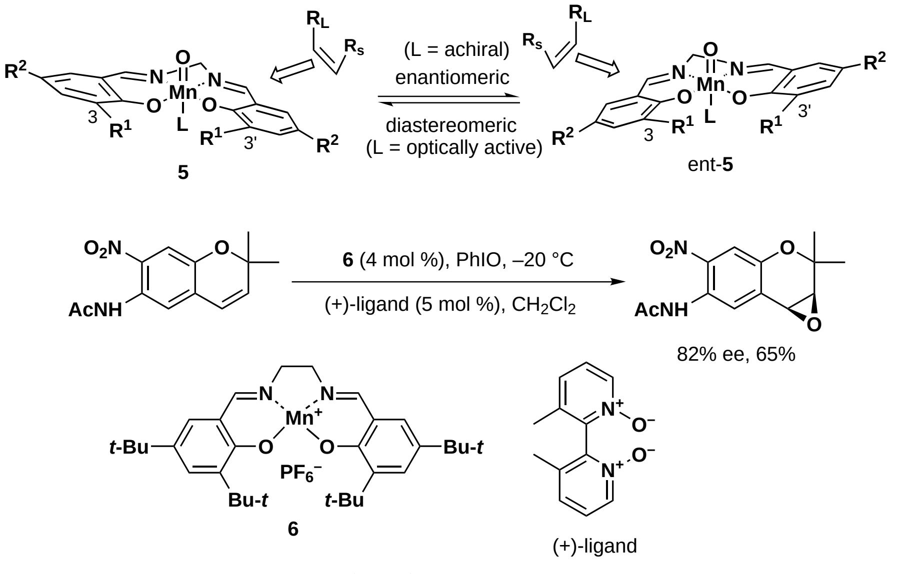
In 1990, Jacobsen's[41] and Katsuki's groups[42] independently reported asymmetric epoxidation using Mn(salen)s (**7** and **8**) which carry asymmetric carbons at the ethylene part and bulky and/or chiral substituents at C-3 and C-3′, as the catalyst (Scheme 2).

The oxo-Mn(salen)s derived from these C_2-symmetric chiral Mn(salen)s are also considered to adopt a non-planar conformation, in which the five-membered chelate ring formed between the manganese ion and ethylenediamine takes a half-chair conformation. Thus, oxo-Mn(salen)s should exist as an equilibrated mixture of two conformers (dieq- and diax-**9**) but the equili-



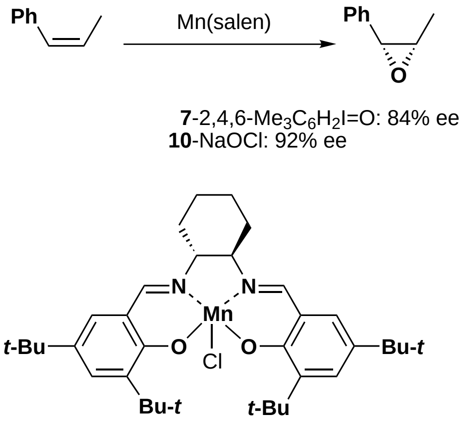
7: R= *t*-Bu, 8: R= (*S*)-Ph(Et)CH

Scheme 2. Early examples of Mn(salen)-catalyzed asymmetric epoxidation.



Scheme 1. Asymmetric epoxidation using achiral Mn(salen) as the catalyst.

brium is far shifted towards dieq-**9** to minimize steric repulsion between the substituents at the ethylenediamine unit and the apical ligands (Scheme 3). Thus, olefins approach dieq-**9** over its downward benzene ring, directing their bulkier olefinic substituent away from the 3′-substituent. This explains well the stereochemistry observed in the epoxidation with C_2-symmetric Mn(salen)s (Scheme 3). Furthermore, this ligand conformation suggests that the presence of a bulky substituent at C-5 blocks efficiently the undesired substrate approach over the upward benzene ring leading to the wrong enantiomer, while the 5′-substituent does not disturb the desired approach. Indeed, Mn(salen) **10** bearing 5- and 5′-*t*-butyl groups is a better catalyst than **7** (Scheme 4).[43] The coordination of a donor ligand to oxo-Mn(salen) causes not only conformational change of the salen ligand (*vide infra*) and change in geometry of oxo-Mn(salen) (*vide supra*),[1c,44a] but also reduction of reactivity of oxo-Mn(salen), and the addition of a donor ligand to the reaction mixture generally improves the enantioselectivity of the epoxidation[44] and chemical yield of epoxide.[1c] Thus, chiral Mn(salen)-catalyzed epoxidation has been generally performed in the presence of a donor ligand such as 4-phenylpyridine *N*-oxide, 4-dimethylaminopyridine *N*-oxide and 4-*t*-butylpyridine *N*-oxide.[33b,44,45]



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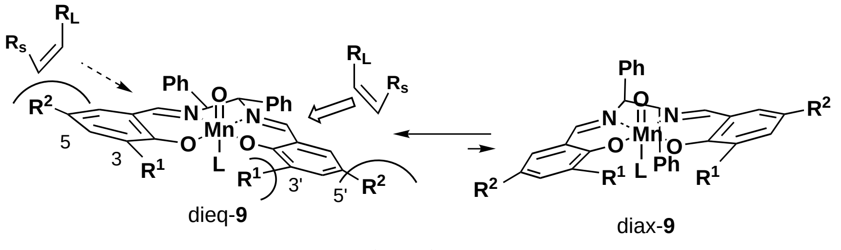
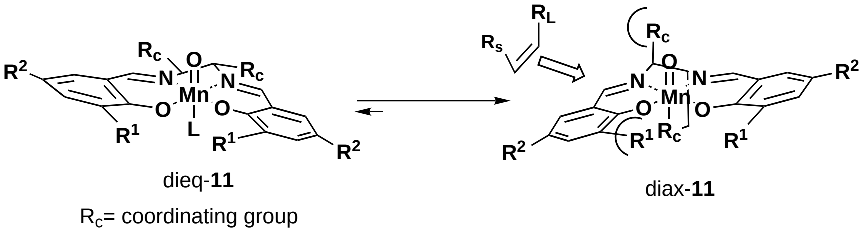
Scheme 4. Asymmetric epoxidation with 5,5’-disubstituted Mn(salen) **10.**

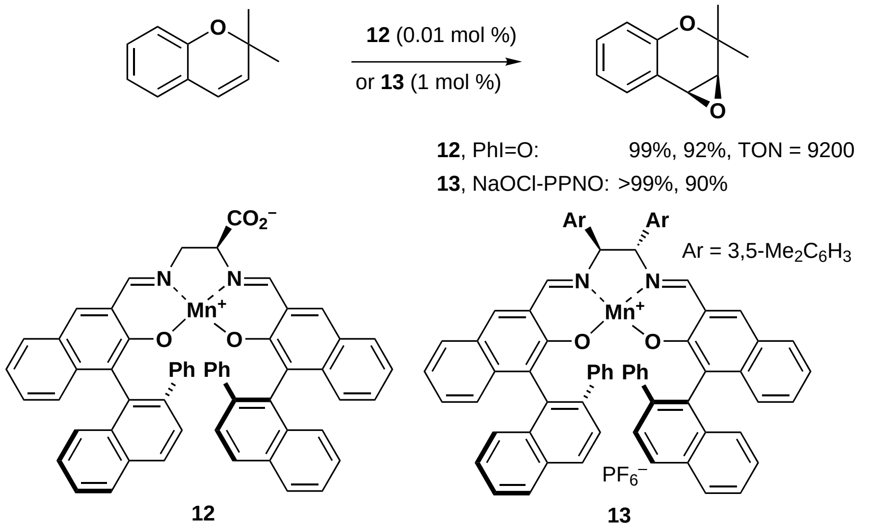
Despite the above description, a diaxial conformer (diax-**11**) may participate in epoxidation, when the substituents at the ethylenediamine unit are coordinating groups (R_C): an axially oriented substituent coordinates to the manganese ion with the inversion of the ligand conformation (Scheme 5). Accordingly, olefins approach the Mn = O bond from the opposite side (*cf.* Scheme 3). However, the diax-**11** is not expected to be a suitable catalyst for epoxidation, because another uncoordinated substituent (Rc) also takes axial orientation and disturbs the desired approach of olefins. From this analysis, non C_2-symmetric Mn(salen) bearing one coordinating substituent at the ethylenediamine unit is expected to be a promising catalyst. Indeed, non-symmetric Mn(salen) **12** bearing one carboxylate group has been found to be as equally efficient as catalyst for the epoxidation of 2,2-dimethylchromene as the C_2-symmetric Mn(salen) **13** (Scheme 6).[46] It is noteworthy that, though the chirality of the ethylenediamine units in **12** and **13** is opposite to each other, the sense of asymmetric induction by **12** and **13** is identical, reflecting the reversal of ligand conformation in **12.** Use of non-symmetric **12** brings about another synthetic advantage of high turn-over number (9200).[46] Different from epoxidations using usual Mn(salen)s as catalysts, the epoxidation with **12** is performed in the absence of donor ligand. Therefore, the regenerated Mn(III)(sa-



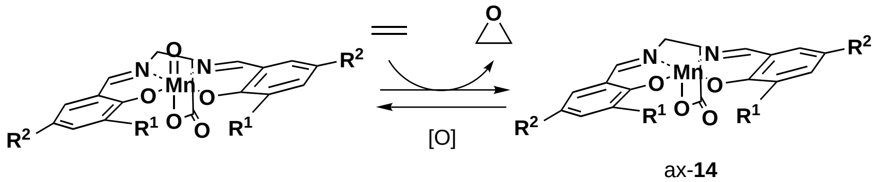
Scheme 3. Conformational equilibration of chiral oxo Mn(salen)s.



Scheme 5. Conformation of oxo Mn(salen) bearing a coordinating group.



Scheme 6. Catalysis of non-symmetric Mn(salen) **12** and of symmetric Mn(salen) **13.**

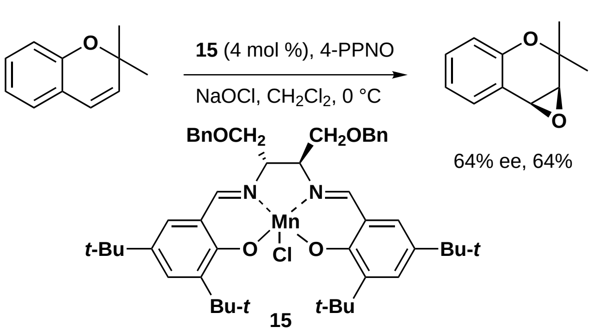


Scheme 7. Catalytic cycle of the epoxidation with Mn(salen) bearing a coordinating group.

len) (ax-**14**) always bears an open apical site and is readily reoxidized to the corresponding oxo-Mn(salen), improving turn-over number (Scheme 7).

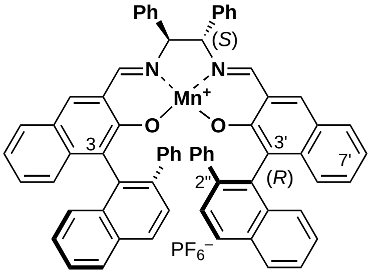
Mosset and his coworker have reported that the sense of asymmetric induction by Mn(salen) **15** bearing a tartrate-derived diamine unit is opposite to that by **7** and **8** (Scheme 8).[47] This reversal of asymmetric induction may be attributed also to the participation of diaxial conformer. Probably due to the presence of the non-coordinated axial benzyloxymethyl group, however, the enantioselectivity observed is sub-standard (*cf.* Scheme 5).

The benzylic position of 3- and 3′-substituents of the so far described Mn(salen)s except for the complexes (**12** and **13**) is an sp^3 carbon and the substituents on the benzylic carbon project away from incoming olefins. Therefore, the orientation of incoming olefins is not controlled sufficiently by such a substituent as the *t*-butyl group. On the other hand, the 2”-phenylnaphthyl group introduced at the 3- and 3′-carbons of **12**, **13**, **16**, and **17** protrudes its 2”-phenyl group close to the approaching path of olefins (Figure 2) and regulates their orientation more efficiently, achieving high enantioselectivity (Table 1).

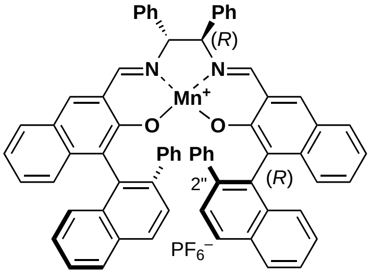


Scheme 8. Asymmetric epoxidation with Mn(salen) **15**.

As discussed above, the whole ligand-conformation of simple chiral oxo-Mn(salen)s is mainly dictated by the conformation of the five-membered chelate ring that is determined by the chirality at the ethylenediamine part, although the natures of the substituent(s) on the salen ligand and of the apical ligand also affect it to some extent. Interestingly, however, X-ray diffraction analyses of diastereomeric **16** and **17** have disclosed that they have a considerably different ligand conformation from each other (Figure 3). This result suggests that the ligand conformation of cationic Mn(salen)s such as **16** and **17** possessing a binaphthyl unit is not determined by a single factor, the conformation of the five-membered ring, but by several, at least two, factors.[52] A combination of these factors determines the conformation of Mn(salen)s of this type. The detailed analysis of the structures of **16** and **17** has revealed that the interaction between the 2“-phenylnaphthyl group and the apical



16



17

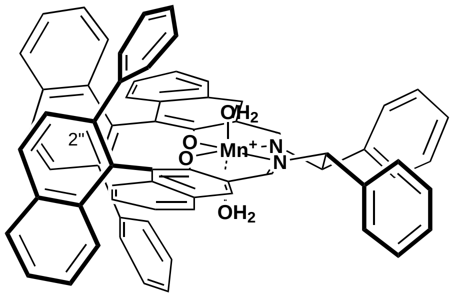
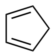
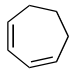
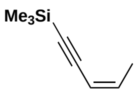
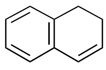
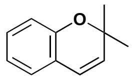
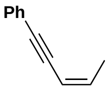
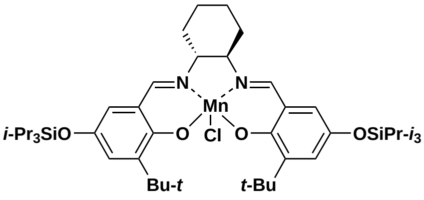


Figure 2. The side view of **16** $\cdot 2\,H_2O$ from the C-7′ side.

Table 1. Asymmetric epoxidation of *cis*-conjugated olefins with Mn(salen)s as catalysts.

Entry	Substrate	Catalyst	Oxidant	Temp.(°C)	Yield (%)	% ee	Configuration	Ref.
1		**13**	NaOCl	– 18	82	93	1*S*,2*R*	[48]
2		**18**	NaOCl	4	45	64	–	[49]
3		**13**	NaOCl	– 18	54	94	–	[48]
4[a]	 Me3Si	**10**	NaOCl	rt	84	78	3*R*,4*R*	[50]
5		**13**	NaOCl	0	78	98	1*S*,2*R*	[51]
6		*ent*-**10**	NaOCl	0	67	86	1*S*,2*R*	[2b]
7	 O	**13**	NaOCl	0	75	99	3*S*,4*S*	[51]
8		**10**	NaOCl	4	72	98	3*R*,4*R*	[43]
9[a]	 Ph	**13**	NaOCl	0	80	94	3*R*,4*R*	[51]
10		*ent*-**10**	NaOCl	rt	85	81	3*R*,4*R*	[50]

[a] Product is a mixture of *trans*- and *cis*-epoxides. The % ee stands for the face selectivity: face selectivity = ee (*trans*) × % (*trans*) + ee (*cis*) × % (*cis*). Configuration given here is that of *trans*-epoxide.



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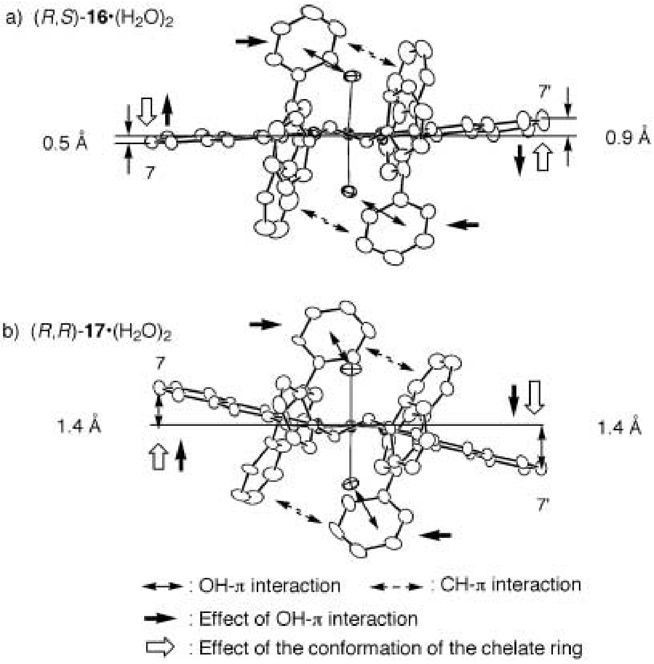

a) (*R*,*S*)-**16**•(H_2O)$_2$

b) (*R*,*R*)-**17**•(H_2O)$_2$

Figure 3. X-ray structures (back views) of complexes, **16** and **17**.

ligand plays an important role in determination of the ligand conformation. Manganese ions of cationic Mn(salen)s are generally coordinated by a neutral ligand such as water or alcohol at their apical sites, depending on their preparation and recrystallization conditions. The 2”-phenyl groups on the 3- and 3′-substituents are located close to the apical ligands, and can attractively interact with them through OH-π interaction (Figure 3).[52] If this attractive interaction works synergetically with the effect caused by the chelate ring conformation, the salen ligand is expected to be more deeply folded than the ligand of simple Mn(salen). However, the ligand is expected to be less folded when two effects cancel each other out. Since Mn(salen)s, **16** and **17**, are diastereomeric at the ethylenediamine part, the effect of the chelate ring conformation should work in opposite directions. On the other hand, the OH-π interaction works in the same direction in **16** and **17**, because they have the same binaphthyl structure. Thus, these two diastereomers adopt different ligand conformations. Complex **17** in which the two factors work synergetically adopts a deeply folded stepped conformation as expected, while complex **16** takes a slightly folded one (Figure 3).[52] These results further suggest that introduction of the apical ligand which cannot interact attractively with the 2″-phenyl ring reduces the folding of the ligand in **17** and increases it in **16.** In accord with this discussion, replacement of one aqua ligand with the cyclopentene oxide ligand increases the ligand folding in **16** but decreases it in **17.**[52] Thus, the ligand conformation of Mn(salen)s such as **16** and **17** can be modulated by carefully choosing the apical ligand and this endows them with diverse catalytic performances. It is noteworthy that the outer benzene rings of the naphthalene moieties in the basal salen ligand contribute to the blockage of the undesired substrate approach as a 5 (or 5′)-*t*-butyl group in **10** does (*cf.* Scheme 3). Epoxidation with **13** as the catalyst is well effected in the presence of 4-phenylpyridine *N*-oxide. Although the effect of a donor ligand is multifold, the addition of 4-phenylpyridine *N*-oxide changes the ligand conformation of **13** favorably for epoxidation. Mn(salen)s possessing chiral binaphthyl or its related structure are hereafter referred to as second-generation Mn(salen)s. Mn(salen)s bearing neither binaphthyl nor its related structure are referred to as the first-generation Mn(salen)s, the conformation of which is determined mainly by the chirality at the diamine unit.

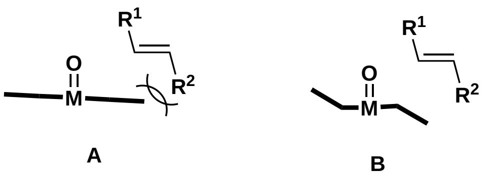
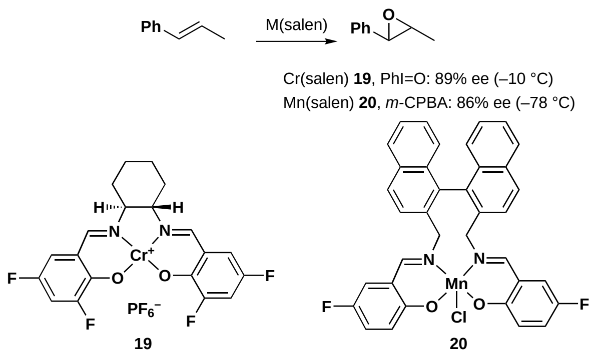


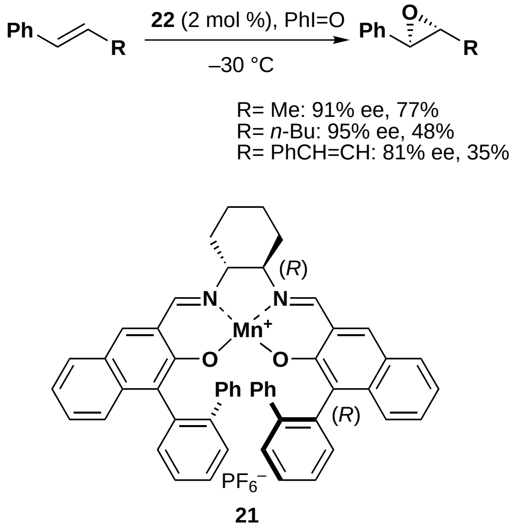
Figure 4. The approach of *trans*-olefins.

Despite the above description, epoxidation of *trans*-olefins with Mn(salen)s shows sub-standard enantioselectivity, probably because one of two olefinic substituents interacts with the salen ligand to destabilize the desired orientation of incoming olefins (Fig. 4, **A**). Thus, a deeply folded oxo-M(salen) **B** is expected to become a better catalyst for epoxidation of this class of olefins. Recently, Cr(salen) **19**[3] and Mn(salen) **20**[33b] bearing electron-withdrawing groups have been found to be efficient catalysts for *trans*-β-methylstyrene (Scheme 9). Oxo-Cr(salen) derived from **19** may have a folded salen ligand as expected from Kochi's report.[1c] Introduction of a binaphthyldiamine unit may cause deformation of the salen ligand of **20**. However, the scope of the reaction with them has not been fully studied.

As discussed above, second-generation (*R*,*R*)-Mn(salen) adopts a deeply folded conformation. Therefore, it is expected to be a good catalyst for epoxidation of *trans*-


Cr(salen) **19**, PhI=O: 89% ee (–10 °C)
Mn(salen) **20**, *m*-CPBA: 86% ee (–78 °C)

Scheme 9. Asymmetric epoxidation of *trans*-β-methylstyrene.



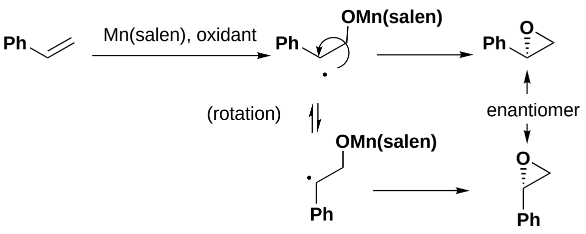
Scheme 10. Asymmetric epoxidation of conjugated *trans*-olefins.

olefins. Indeed, the modified second-generation (*R*,*R*)-Mn(salen) **21** is an efficient catalyst for epoxidation of *trans*-olefins (Scheme 10).[53] Complex **21** has been determined to adopt a deeply folded structure similar to **17.**

4 Ru(salen)-Catalyzed Epoxidation

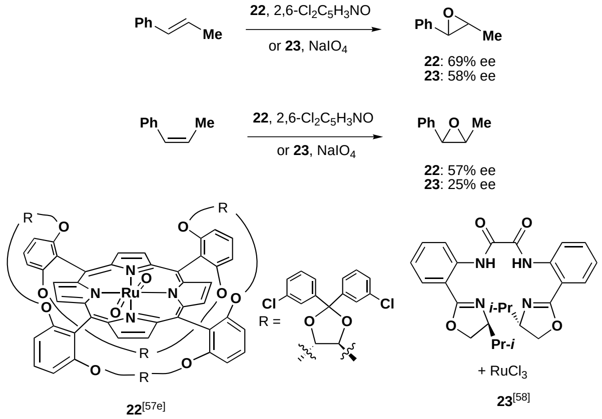
Styrene and its derivatives are another type of poor substrates for Mn(salen)-catalyzed epoxidation. Epoxidation of conjugated olefins proceeds via a radical intermediate (Scheme 11)[1e,42] and the rotation of the resulting C-C bond in the radical intermediate causes racemization in the reactions of styrenes. Jacobsen et al. solved this problem by performing the reaction at − 78 °C by using *m*-chloroperbenzoic acid as the terminal oxidant in the presence of *N*-methylmorpholine *N*-oxide.[54] Low temperature freezes the rotation of the C-C bond. Still, it is impossible to obtain high enantioselectivity in the reaction at room temperature.

On the other hand, many ruthenium complexes serve as catalysts for various oxidations[55] and efforts have been directed to the development of Ru-catalyzed asymmetric epoxidation. Thus far, chiral ruthenium-Schiff base,[56] ruthenium-porphyrin **22**,[57] ruthenium-tetradentate bisamide **23**,[58] and ruthenium-pybox complexes[59] have been used as the catalyst and moderate to good levels of enantioselectivity (up to 77% ee[57b] for *cis*-olefins, 76% ee[57d] for *trans*-olefins, and 83% ee for *p*-chlorostyrene[57e]) have been achieved. Besides, some ruthenium complexes showed a unique asymmetric catalysis that cannot be attained by Mn(salen)s: some reactions are stereospecific and *trans*-olefins are better substrates for the reactions than the isomeric *cis*-olefins (Scheme 12).[57d, e,58]

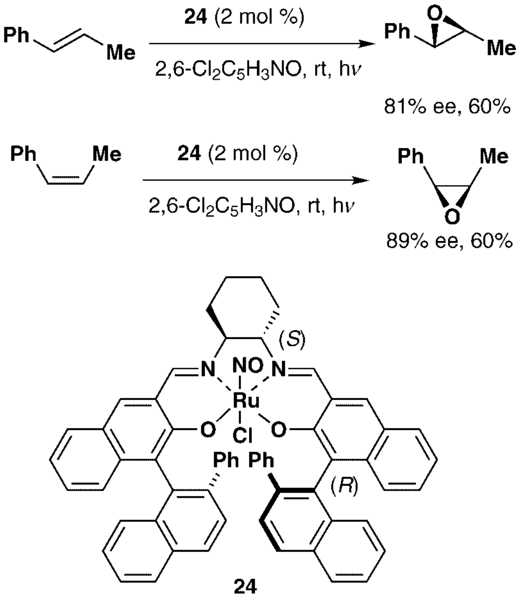


Scheme 11. Stereochemical scramble by participation of a radical intermediate.

The advantages of ruthenium-catalyzed epoxidation have been further extended by introducing (nitrosyl)ruthenium complex **24** bearing a second-generation (*R*,*S*)-salen ligand (Scheme 13). Although complex **24** is coordinatively saturated and catalytically inactive, irradiation of visible light makes the complex active by

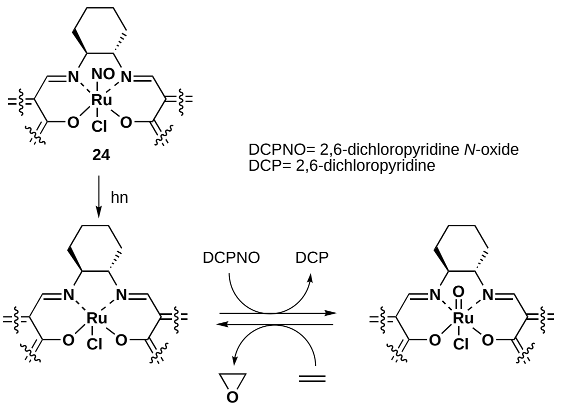


Scheme 12. Ruthenium-mediated asymmetric epoxidation.



Scheme 13. Stereospecific epoxidation using Ru(salen) as catalyst.

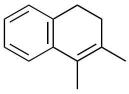
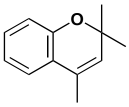
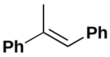
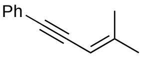
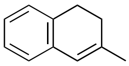
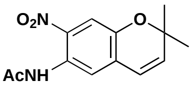
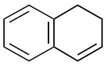
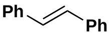
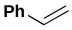
promoting dissociation of the apical nitrosyl ligand (Scheme 14).[60] Dissociation of the apical nitrosyl ligand by irradiation has recently been proved by spectroscopic study of achiral (ON)Ru(salen) complex.[61] In accord with this, irradiation of **24** in the presence of 2-naphthol has been found to give 1-nitro-2-naphthol (*vide infra*).[62] Thus, the complex **24** catalyzes stereospecific epoxidation with high enantioselectivity under irradiation: the epoxidation of both *cis*- and *trans*-olefins gives the corresponding *cis*- and *trans*-epoxides, respectively (Scheme 13).[60] 2,6-Dichloropyridine *N*-oxide or tetramethylpyrazine *N,N*′-dioxide[63] is the terminal oxidant of choice for this reaction (Scheme 14). Some other examples of epoxidation with **24** are summarized in Table 2. All the olefins are epoxidized with high



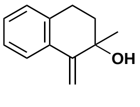
DCPNO= 2,6-dichloropyridine *N*-oxide
DCP= 2,6-dichloropyridine

Scheme 14. Proposed reaction pathway for (ON)Ru(salen)-catalyzed epoxidation.

Table 2. Asymmetric epoxidation of conjugated olefins using **24** as a catalyst.

Entry	Substrate	Time [h]	Yield [%]	% ee	Configuration[f]
1[a]		28	32[b]	82	–
2[a]		16	54[c]	97	3*S*
3[a]		17.5	83 (2)[d]	86	–
4[a]		18	56	80	–
5[a]		22	74	88	1*S*,2*R*
6[e]		20	59	97	3*S*,4*S*
7[e]		2	51 (5)[d]	87	1*S*,2*R*
8[a]		40	64	85	1*R*,2*R*
9[a]		7	30 (2)[d]	83	*S*
10[a]		14	63 (7)[d]	71	*S*

[a] Reaction was carried out in dioxane with a halogen lamp as a light source.
[b] Allylic alcohol **25** (10%) and diol **26** (3%, 73% ee) were also produced.
[c] Product was a mixture of allylic alcohol **27** (54%, 97% ee) and enone **28** (4%).
[d] The number in parentheses is the yield of the corresponding ketone or aldehyde.
[e] Reaction was carried out in benzene under incandescent light.
[f] Structures of compounds **25**–**28**:



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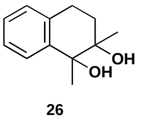

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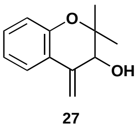

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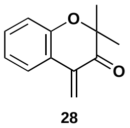

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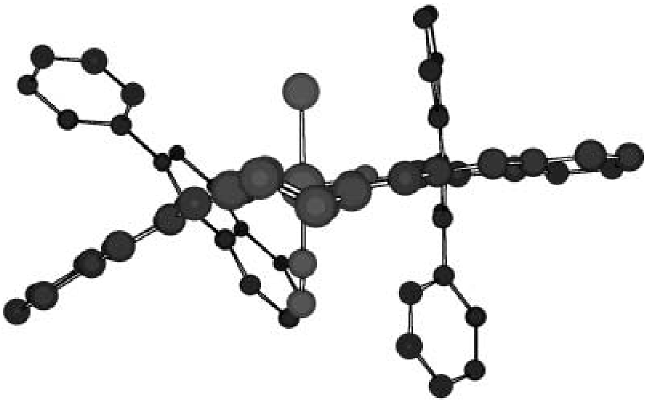

Figure 5. The view of **24** from the cyclohexane side.

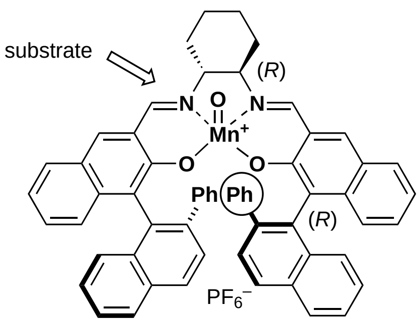

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Figure 6. Substrate-approaching path and location of 2“-substituent.

enantioselectivity, irrespective of their substitution pattern. However, the resulting coordinatively unsaturated Ru(salen) species is a Lewis acid and some acid-sensitive epoxides slowly rearrange into the corresponding allylic alcohols, ketones or aldehyde under the reaction conditions, reducing enantiomeric excesses of the epoxides (entries 1–3, 7, 9, and 10).

The wide scope of the epoxidation catalyzed by **24** is attributable to its unique structure, a distorted stepped-conformation, the left part of which largely declines downwards (Figure 5).[64] This structure is considered to be retained in the intermediary oxo species. Thus, both *cis*- and *trans*-olefins can approach it with the desired orientation.[60b]

5 Enantiotopic-Selective C-H Oxidation: Desymmetrization of *meso*-Heterocycles

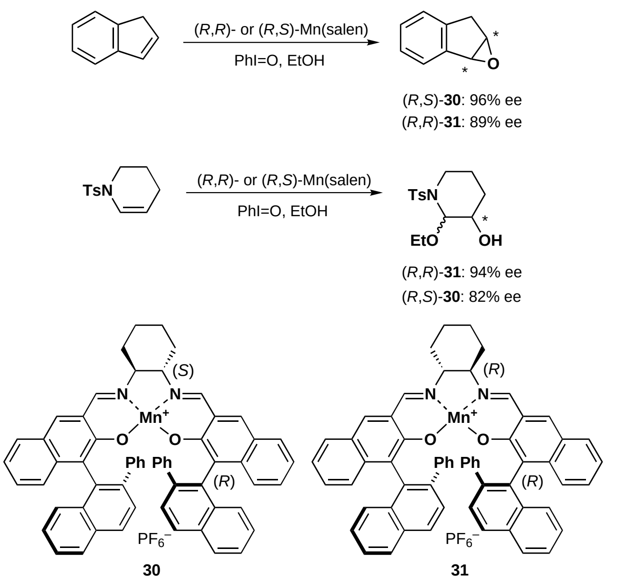
Mn(salen)s catalyze hydroxylation of C-H bonds at benzylic carbons[18] and at carbons α to heteroatoms such as oxygen and nitrogen atoms in an enantioselective manner.[19] It is noteworthy that asymmetric benzylic oxidation is well effected by using a modified (*R*,*S*)-Mn(salen)s as the catalyst,[18b, c,33a] while asymmetric C-H oxidation at the carbons α to heteroatoms is better performed by using (*R*,*R*)-Mn(salen)s as the catalyst in the absence of a donor ligand.[19] As shown in Figures 3b, (*R*,*R*)-Mn(salen) has a deeply folded structure and substrates approach the corresponding oxo-Mn(salen) **29** from downward side. The orientation of the substrate is controlled by the 2“-phenyl group (the encircled one) that is pulled toward the metal center by OH-π and CH-π interactions (Figures 3 and 6).[52] Replacing the remaining aqua ligand with a neutral donor ligand causes the shift of the 2”-phenyl away from the metal center and weakens the regulation of the orientation, reducing enantioselectivity. Thus, the reaction with (*R*,*R*)-Mn(salen) is well effected in the absence of a donor ligand.

Enantioselectivity of the asymmetric reaction is given by the Eyring equation:

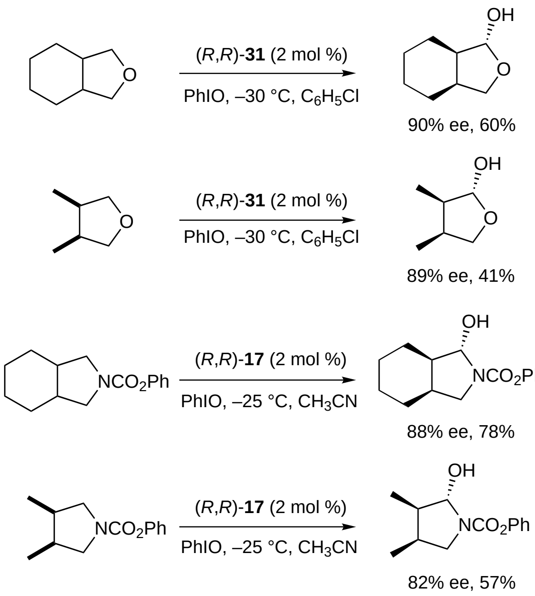
$$\ln(k_R/k_S) = -\Delta\Delta H^{\ddagger}/RT + \Delta\Delta S^{\ddagger}.$$

Enthalpy- and entropy-dependence of enantioselectivity in second-generation Mn(salen)-catalyzed oxidation varies with substrate and catalyst used.[65] As expected from the structures of (*R*,*S*)- and (*R*,*R*)-Mn(salen)s (Figure 3), the incoming substrate interacts with the 2″-phenyl group of (*R*,*S*)-Mn(salen) at an early stage of the reaction, while the substrate interacts with the 2″-phenyl group of (*R*,*R*)-Mn(salen) at later stage (see also Figure 6). This indicates that the reactions with (*R*,*S*)-Mn(salen)s are more enthalpy-dependent than the reactions with (*R*,*R*)-Mn(salen)s and that entropy factors play a more important role in enantio-differentiation in the latter reaction. This consideration is compatible with the results obtained in the oxidation of substrates of different nucleophilicity with (*R*,*S*)- and (*R*,*R*)-Mn(salen)s as the catalyst:[65] since the distance between a substrate and the O = Mn bond at the transition state becomes longer as the substrate gets more nucleophilic, the oxidation of the substrate of higher nucleophilicity is expected to become less enthalpy-dependent and to become better effected by (*R*,*R*)-Mn(salen)s. Indeed, epoxidation of indene is better performed with (*R*,*S*)-Mn(salen) **30**, while the oxidation of more nucleophilic *N*-protected tetrahydropyridine is better effected with (*R*,*R*)-Mn(salen) **31** (Scheme 15). The analysis using Eyring equation has disclosed that stereocontrol in the latter reaction is mainly governed by entropic factors.[65]

On the other hand, study on kinetic isotopic effect has indicated that Mn(salen)-catalyzed oxidation of heterocycles proceeds through one-electron transfer.[65] It has been reported that the electron-transfer reaction can occur at a longer distance than formation of the charge-transfer complex.[66] This explains why (*R*,*R*)-Mn(salen)s are suitable catalysts for oxidative desymmetrization of *meso*-heterocycles: the reaction through a transition state at long distance is less enthalpy-dependent and the use of (*R*,*R*)-Mn(salen)s is essential for achieving high enantioselectivity in such reactions. Indeed, good to high levels of enantioselectivity have



Scheme 15. Epoxidation of indene and *N*-tosyltetrahydropyridine with Mn(salen)s **30** and **31**.

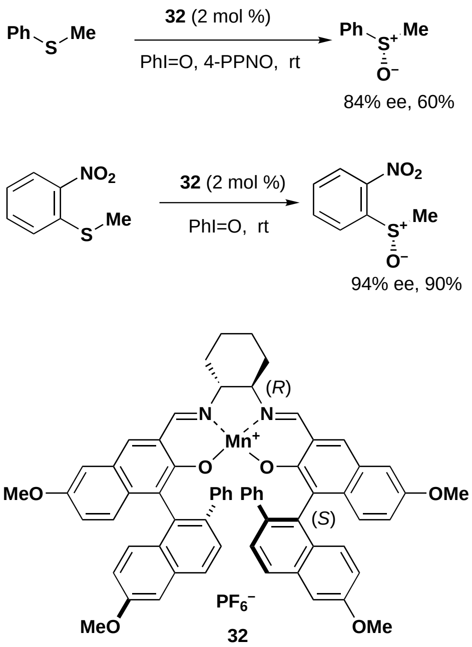


Scheme 16. Desymmetrization of *meso*-heterocycles with (*R*,*R*)-Mn(salen) as catalyst.

been achieved in desymmetrization of *meso*-furans and -pyrrolidines with (*R*,*R*)-Mn(salen)s (**31** or **17**) as the catalyst (Scheme 16).[19] In contrast, desymmetrization with first-generation Mn(salen) shows only modest enantioselectivity.[19b]

6 Asymmetric Sulfoxidation using Hydrogen Peroxide

Sulfoxides are versatile chiral building blocks for organic synthesis and much effort has been directed toward asymmetric oxidation of sulfides. As the results, many high enantioselective methodologies have been reported to date,[67] but several problems remained unsolved: i) insufficient enantioselectivity in the reactions using an atom-efficient oxidant such as hydrogen peroxide, and ii) the limited scope of the reaction. As expected from asymmetric epoxidation using second-generation Mn(salen)s as the catalyst, asymmetric oxidation of sulfides with a modified Mn(salen) **32** also shows good to high enantioselectivity (Scheme 17).[68] However, low atom-efficient iodosylbenzene is used as the oxidant in this reaction.



Scheme 17. Mn(salen)-catalyzed asymmetric sulfoxidation.

Prior to the above study, Fujita et al. had reported V(salen)- and Ti(salen)-catalyzed asymmetric sulfoxidations using *t*-butyl hydroperoxide (TBHP) as the oxidant.[1d,8] Jacobsen et al. have also reported asymmetric sulfoxidation using a combination of Mn(salen) and hydrogen peroxide.[69] These reactions are considered to proceed through alkylperoxo and hydroperoxo intermediates, respectively. However, the conformation of the alkylperoxo or the hydroperoxo moiety of intermediary active species is not sufficiently controlled and the reactions show sub-standard enantioselectivity: since the salen ligands of those complexes adopt square planar geometry, the hydroperoxo or the alkylperoxo group at the apical site should be a mono-dentate ligand and have conformational freedom (Figure 7). Different from this, an M(salen) adopting a *cis*-β-structure is expected to afford the corresponding peroxo species in which the configuration of the peroxo moiety is fixed as described in Figure 7. Recently, Belokon' et al. have reported that a di-μ-oxo(salen)titanium complex, which serves as an efficient catalyst for asymmetric hydrocyanation, has a *cis*-β dimer structure **33**.[9] Since

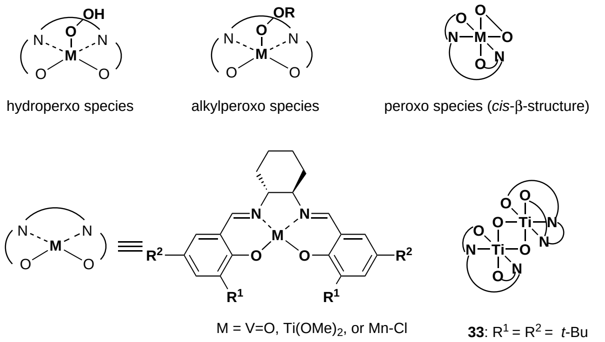
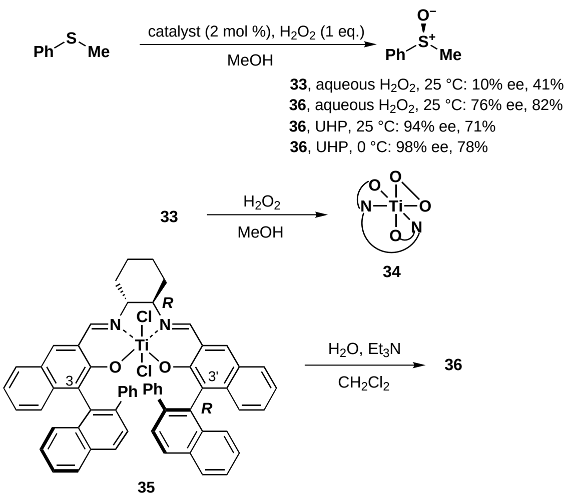


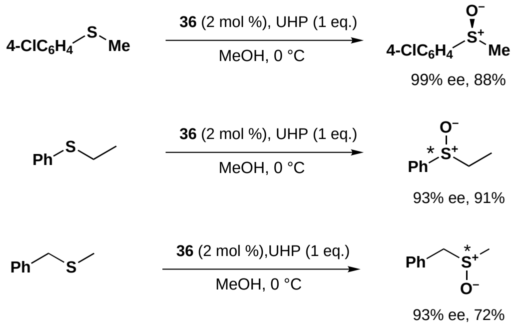
Figure 7. Planar alkyl- and hydro-peroxo species and non-planar peroxo species (*cis*-β structure).



Scheme 18. Ti(salen)-catalyzed asymmetric sulfoxidation.

alkoxide exchange on the titanium ion is rapid, treatment of the di-μ-oxo(salen)titanium complex **33** with alcoholic hydrogen peroxide is expected to give with retention of the *cis*-β structure the corresponding peroxo species **34** which undergoes highly enantioselective sulfoxidation (Scheme 18).[17]

Against expectations, however, sulfoxidation with **33** as the catalyst shows only modest enantioselectivity (Scheme 18). This suggests that control of the orientation of incoming sulfides by **34** is not sufficient. On the other hand, a di-μ-oxo(salen)titanium complex **36** derived from second-generation Ti(salen) **35** shows the expected high enantioselectivity when urea · hydrogen peroxide (UHP) is used as the oxidant. Use of Ti(salen) **35** itself as the catalyst shows only modest enantioselectivity under the same reaction conditions. The oxidation with **36** as the catalyst can be applied to various sulfides (Scheme 19).[17] Lately, it has been disclosed that complex **36** is converted in methanol to planar Ti(salen) bearing two apical methoxido ligand and the planar Ti(salen) reacts with hydrogen peroxide to give the desired peroxo species.[17b]



Scheme 19. Asymmetric sulfoxidation using Ti(salen) **36** as catalyst.

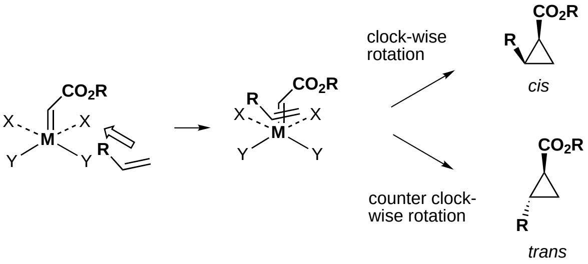
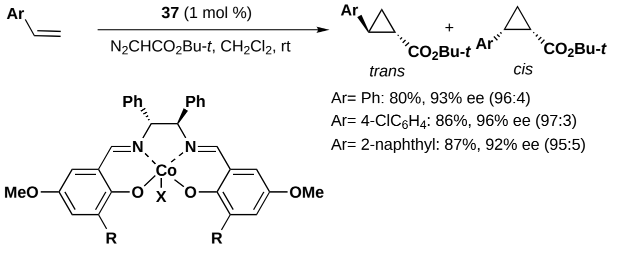


Figure 8. Proposed reaction pathway for metallosalen-catalyzed cyclopropanation.

7 M(salen)-Catalyzed Asymmetric Cyclopropanation

Metallosalen complexes are useful catalysts not only for oxene transfer but also carbene transfer.[70] Olefins are considered to approach an intermediary (carbene)M-(salen) along the M-N or M-O bond axis with an orientation perpendicular to the M-C bond, rotating clockwise or counter-clockwise to give the cyclopropane adduct (Figure 8).[71] Therefore, the substrate approach and the sense of the substrate rotation must be controlled concomitantly to achieve high diastereo- and enantioselective cyclopropanation. Furthermore, different from an oxene atom, the carbene atom carries substituent(s) on it and its orientation also influences the stereochemistry of cyclopropanation. Accordingly, the control of the orientation of the substituent on the carbene atom is another subject for asymmetric cyclopropanation.

The Co(III)(salen) **37** bearing no substituent at C-3 and C-3′ shows high *trans*- and enantioselectivity (Scheme 20).[10] 3,3′-Substituted Co(III)(salen)s such as **38** show no catalytic activity. The intermediary (carbene)Co(salen) species is considered to adopt a stepped-conformation and the ester group on the carbene atom lies above the downwardly-bent salen ligand. Olefins approach along the Co-O bond axis and rotate counter-clockwise to avoid steric repulsion between the ester group and the olefinic substituent. The presence of 3′- and 3-substituents hampers the desired approach and the rotation of the olefin, respectively



37: R = H, X = Br, **38**: R = *t*-Bu, X = Br or I

Scheme 20. Co(III)(salen)-catalyzed *trans*-selective cyclopropanation.

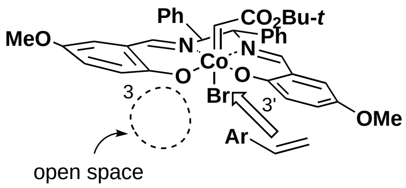


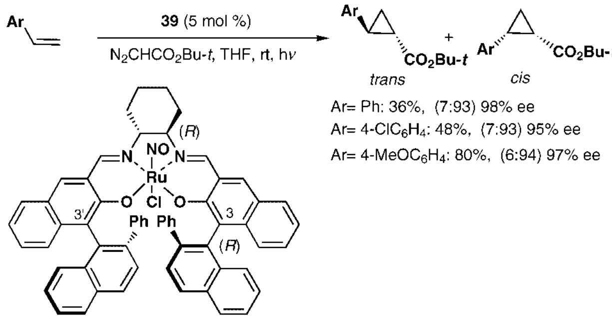
Figure 9. A possible explanation for *trans*-selective cyclopropanation.

(Figure 9). It is noteworthy that the presence of 5,5′-methoxy and apical bromo groups exerts favorable electronic and *trans* effects on enantioselectivity.[10a]

On the other hand, the opposite *cis*-selectivity should be realized if either the approach or the rotation is reversed: i) the approach along the same Co-O bond with clockwise rotation, ii) the approach along the Co-N bond axis with counter-clockwise rotation, and iii) the approach along another Co-N bond axis with clockwise rotation. The first possibility can be realized, if the counter-clockwise rotation is disfavored by introducing 3- and 3′-substituents. As discussed above, however, the presence of the substituents at C-3 and C-3′ blocks the substrate-approaching path. Therefore, some device which hampers the counter-clockwise rotation without blocking the path is required.

The Ru-O bond of Ru(salen) is *ca.* 0.2 Å longer than the Co-O bond of Co(III)(salen). Furthermore, one of the 3- and 3′-substituents of second-generation Ru(salen) largely inclines outward (see Figure 5) thereby leaving the wide open space above C-3 or C-3′. Thus, it is expected that the first possibility is realized by using second-generation Ru(salen)s as the catalysts. Indeed, cyclopropanation using (*R*,*R*)-Ru(salen) **39** exhibits high *cis*- and enantioselectivity (Scheme 21).[13] This reaction is also performed under the irradiation of visible light to promote the dissociation of the apical ligand.

The reaction with complex **40** bearing no chirality at the ethylenediamine part also shows good *cis*-selectivity as well as high enantioselectivity (Scheme 22). This result supports that the chirality of the binaphthyl units exerts a central role in the manifestation of *cis*- and enantioselectivity.[13c]



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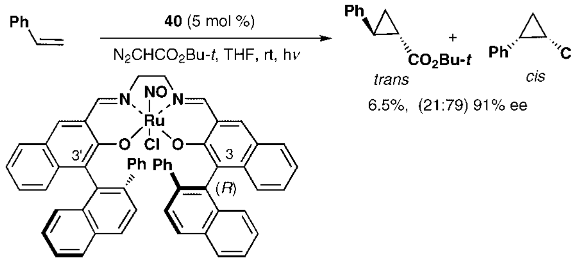
Scheme 21. Ru(salen)-catalyzed *cis*-selective cyclopropanation.



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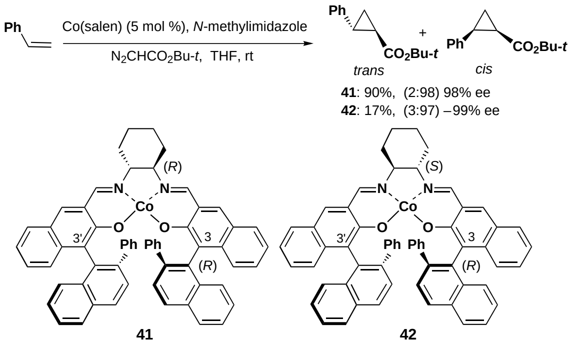
Scheme 22. Cyclopropanation with (ON)Ru(salen) bearing no chirality at the diamine moiety.

The second and third possibilities have also been examined. When olefins approach along an M-N bond axis directing their substituent away from the ester group, their rotation leading to a *tans*-isomer causes severe steric repulsion with the salen ligand. Thus, an M(salen) that provides a path along an M-N bond axis is expected to show high *cis*-selectivity. The Co(II)-O bond length is roughly equal to the Mn(III)-O bond length and it is expected that the structures of second-generation Co(II)(salen)s (**41** and **42**) are also similar to those of second-generation Mn(salen)s (**30** and **31**) in which 3,3′-(2-phenyl)naphthyl groups are parallel to each other and perpendicular to salen ligands (Figure 3), thus the path along Co-O bond axis is considered to be blocked. Different from Co(III)(salen)s, Co(II)-(salen)s does not lose their catalytic activity even if substituents are present at C-3 and C-3′, suggesting that (carbene)Co(IV)(salen)s allow substrates to approach them along a Co-N bond axis. Thus, in accord with the above assumption, both (*R*,*R*)-**41** and (*R*,*S*)-**42** show high *cis*-selectivity together with excellent enantioselectivity, although (*R*,*S*)-**42** is catalytically less active (Scheme 23).[12] The reason why the path along a Co-N bond axis is available for (carbene)Co(IV)(salen)s is unclear at present. It is noteworthy that (*R*,*R*)-Co(salen) **42** and (*R*,*R*)-Ru(salen) **39** induce an opposite sense of asymmetry to each other, although they carry the same second-generation (*R*,*R*)-salen ligand. This also indicates that olefins approach the metal-carbenoid species derived from **39** and **41** from different sides, respectively.

In these reactions, olefins are considered to approach the intermediary carbenoid species [(*R*,*R*]-**43** and (*R*,*S*)-



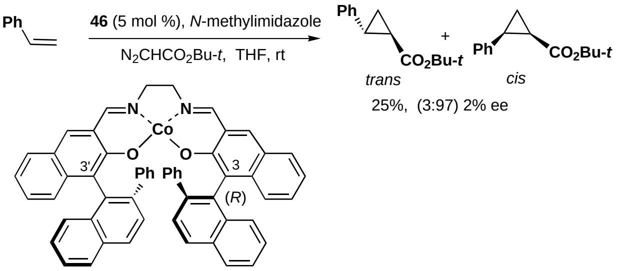
Scheme 23. Co(II)(salen)-catalyzed *cis*-selective cyclopropanation.

44] along the Co-N bond axis from the downwardly bent naphthalene side and rotate counter-clockwise and clockwise, respectively, to avoid the repulsion between the salen ligand and the olefinic substituent, giving enantiomeric *cis*-cyclopropane adducts in a highly enantioselective manner (Figure 10).[12b] However, the olefin approaching toward (*R*,*S*)-**44** suffers steric repulsion with the 2″-phenyl group and the reaction with **42** is slower than that with **41**. Cyclopropanation of various olefins by using **41** as the catalyst also proceeds with high *cis*- and enantioselectivities as well as good yields.[12] It is noteworthy that diethyl diazoacetate can be used for this reaction as equally efficient as *t*-butyl diazoacetate, without decaying stereoselectivity.[12b]

Salen ligand conformation is regulated by the chirality at the diamine part. Thus, a carbenoid species **45** derived from Co(salen) **46** bearing no chirality at the diamine part exists in an equilibrated mixture of (*R*,*R*)-type and (*R*,*S*)-type conformers [(*R*,*R*)- and (*R*,*S*)-**45**] (Figure 10). This equilibrium is considered to lean against (*R*,*S*)-**45** because the repulsion between the 2”-phenyl group and the ester group in (*R*,*R*)-**45** is larger than that between the naphthyl ring and the carbenoid ester in (*R*,*S*)-**45.** However, olefins can approach (*R*,*R*)-**45** more easily than (*R*,*S*)-**45.** Thus, the reaction with **46** as the catalyst is considered to be high *cis*- and low enantioselective. Actually, the reaction with **46** show high *cis*-selectivity and poor enantioselectivity (Scheme 24).

8 Conclusion

In this article, we have discussed how ligand-structure of metallosalens influences on their catalytic performances. Needless to say, however, the catalytic performances are affected not only by ligand structure but also



Scheme 24. Cyclopropanation with Co(II)(salen) bearing no chirality at the diamine moiety.

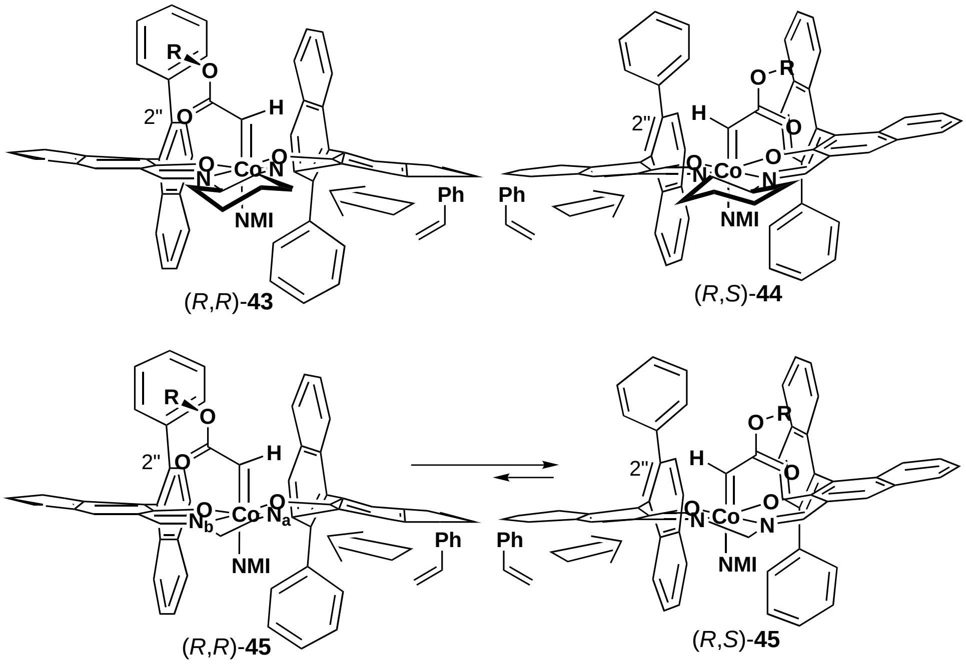


Figure 10. The proposed substrate-approach toward (carbene)Co(IV) species.

other factors. Some such examples are enumerated below: the electronic nature of the substituent(s) on the salen ligand has influence on the catalytic performance as shown by Fujita et al.[8] and studied later in detail by Jacobsen et al.[72] In well-designed reaction systems, multiple (usually two) M(salen)s participate cooperatively and show high enantioselectivity, as exemplified by enantioselective ring-opening reactions of epoxides.[4] Aggregated M(salen)s through a weak Lewis acidic metal ion also show unique catalysis: an enantioselective Nozaki – Hiyama reaction is catalyzed by Cr(salen)s in the presence of manganese ion that combines two Cr(salen)s.[73] A similar phenomenon has been observed in the asymmetric synthesis of α-amino acids by using a Cu(salen) as the phase transfer catalyst.[14] A dinuclear Ti(salen) complex ligated by a μ-oxo bridge serve as an efficient catalyst for addition of trimethylsilyl cyanide to ketones.[9] A dimeric homochiral Co(salen) and Mn(salen) connected by a covalent bond serves as the efficient catalyst for enantioselective ring-opening reactions of epoxides[4b] and epoxidation with urea · hydrogen peroxide as the oxidant.[74] Furthermore, nature of an apical ligand[38,44,75] and the valency of manganese ion of oxo Mn(salen)[75] have an influence on the catalytic performance.

Although M(salen)s are already one of the most widely used chiral catalysts in asymmetric synthesis, these findings will promote the construction of so far undeveloped new M(salen)s and further expand the scope of M(salen) chemistry.

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