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Review

Mn-salen catalyst, competitor of enzymes, for asymmetric epoxidation

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Abstract

Asymmetric epoxidation of simple olefins using (salen)manganese(III) complexes as catalysts has made a great advances in the last half decade and now finds wide application in organic synthesis. In this article, we describe the scope of the reaction, and the principal achievements to date are presented in Tables. The mechanistic aspect of the reaction is also discussed briefly.

Keywords: (Salen)manganese(III) complex; Mn-salen catalyst; Oxo transfer reaction; Asymmetric epoxidation; Simple olefin

Contents

1. Introduction

Oxidation is one of the most important reactions for the metabolism of biotic substrates and many enzymes are known to catalyze various types of oxidation. Amongst such oxidizing enzymes, cytochrome P-450 has been most extensively studied, probably due to (i) its diverse presence in body, (ii) its multifold functions: P-450 participates in biosynthesis of steroid hormones, activation of vitamin D_3, metabolism of medicines, and so on, and (iii) easy availability. For example, the cytochrome P-450 camphor 5-exohydroxylase ($P\text{-}450_{CAM}$ from the soil bacterium *pseudomonus putida* is available in bulk and its structure has been established by X-ray analysis [1]. Cytochrome P-450 has an iron–porphyrin complex as the active site, wherein

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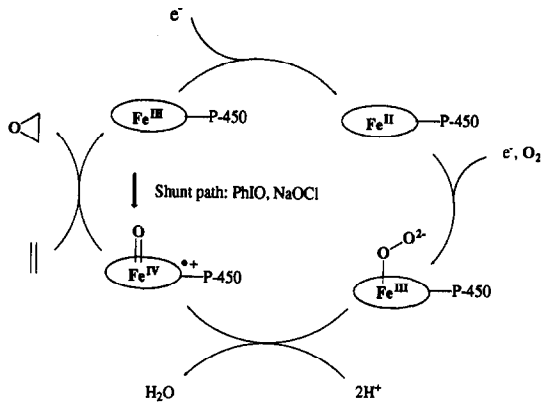
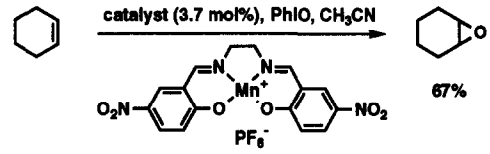


Fig. 1. Catalytic cycle of cytochrome P-450.

molecular oxygen is activated as a form of iron–oxo species and then transferred to the substrate. With this oxygen atom transfer reaction (hereafter referred to as oxo transfer reaction), the protein part of P-450 plays a very important role in electron and proton transfer as well as in the recognition of substrates. The general reaction mechanism of the P-450-catalyzed oxo transfer reaction has been disclosed by Groves et al., as shown in Fig. 1 [2]. Furthermore, Groves et al. reported that iron(III)–porphyrin complexes could be converted into the corresponding oxo species by treatment with an oxidant such as iodosylbenzene (shunt path, Fig. 1) [3]. This finding suggested that even simple iron(III) porphyrins bearing no protein carrier could be used as model compounds for the active site of cytochrome P-450. Since then, many metalloporphyrin complexes have been synthesized to reproduce the function of cytochrome P-450 in a flask and some well-designed optically active iron(III) and manganese(III) porphyrins have been found to be efficient catalysts for asymmetric epoxidation of simple olefins and oxidation of sulfides [4]. However, their scope is still rather limited [5–11].

On the other hand, metal complexes of [*N,N*-ethylenebis(salicyldeneaminato)] ligand (salen ligand) also aroused the interest of synthetic chemists as a model compound for the active site of cytochrome P-450, since they have features in common with metalloporphyrins with respect to their electronic structure and catalytic activity. To date, various metallosalen complexes such as (salen)manganese [12], (salen)chromium [13], and (salen)nickel complexes [14] have been synthesized and used for epoxidation of simple olefins but, among others, cationic (salen)manganese complexes are the most efficient as catalysts [12].



These salen-catalyzed epoxidations have also been postulated to proceed through the corresponding oxo metallosalen complexes **1** (Fig. 2). Actually Kochi et al. isolated the cationic oxo (salen)chromium(V) complex (**1**, M = Cr, X = OTf) and oxochromium(V) adduct with pyridine *N*-oxide as the axial ligand, and determined their structures unambiguously by X-ray diffraction [13]. The cationic oxochromium(V) complex has a roughly square pyramidal coordination in which the chromium atom is displaced 0.53 Å above the mean salen plane. The pyridine *N*-oxide adduct takes octahedral coordination and the chromium atom is displaced 0.26 Å above the mean salen plane. Both the oxochromium(V) species epoxidize olefins (Fig. 2) [13]. However, these two porphyrin and salen complexes differ from one another in structure (Fig. 3). Whereas the peripheral carbons of the porphyrin ligand are all sp^2, the salen ligand bears two sp^3 carbons at C1″ and C2″ which might be replaced with stereogenic carbons and, furthermore, sterically bulky and/or chiral substituents can be introduced at C3 and C3′ at

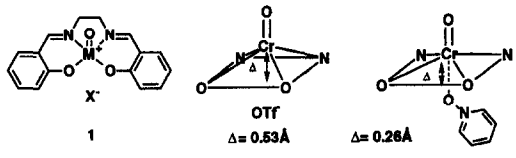


Fig. 2. The partial structure of oxo (salen)chromium(V) complex.

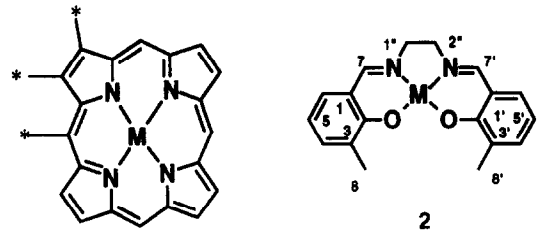


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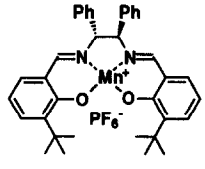
Fig. 3. The structural difference between metalloporphyrin and salen complexes.

need (for the sake of convenience, the numbering shown on the compound **2** is used for all the salen complexes described in this paper). These stereogenic centers reside proximately to the metal center and this renders the salen ligand a promising chiral template for the construction of asymmetric reaction sites. In fact, these types of optically active (salen)manganese(III) complexes (hereafter referred to as Mn-salen complexes) have been synthesized and found to serve as effective catalysts for asymmetric oxidation. Although preliminary aspects of Mn-salen catalyzed oxidation have been reviewed [15], the scope of the reaction is still extending rapidly and the deeper understanding on the reaction mechanism is now available. Accordingly, we summarize herein the recent advancement of Mn-salen catalyzed asymmetric epoxidation and the new aspects of the mechanistic study on the reaction.

2. Mn-salen catalyzed asymmetric epoxidation

2.1. Mn-salen catalysts and general experimental conditions for asymmetric epoxidation

In 1990, Jacobsen's and the author's groups reported asymmetric epoxidation with optically active Mn-salen epoxidation catalysts (**3** [16]a and **4** [16]b) which have stereogenic centers at C1″ and C2″ and sterically bulky and/or chiral substituents at C3 and C3′. With these catalysts and iodosylbenzene derivatives as terminal oxidants, moderate to good levels of enantioselectivity were achieved in the epoxidation of conjugated olefins. Since then, various modifications of Mn-salen catalysts have been made and much higher enantioselectivity has now been achieved. (For the rational design of optically active Mn-salen catalysts, see the previous reviews [15].) Among various modified Mn-salen catalysts, catalysts (**5** [17], **6** [18], **7** [19], **8** [20], and especially **9** [20]) seem to be most effective in terms of enantioselectivity.



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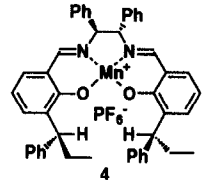

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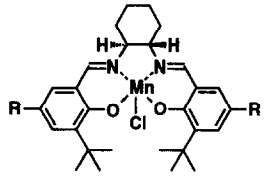
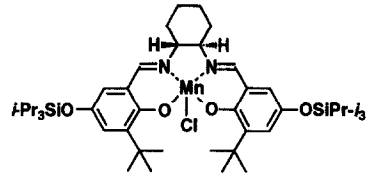


5, a: R= *t*-Bu, b: R= Me



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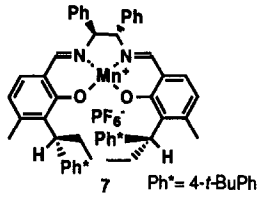
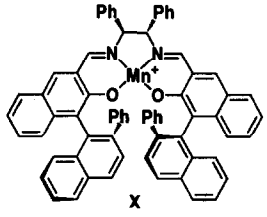
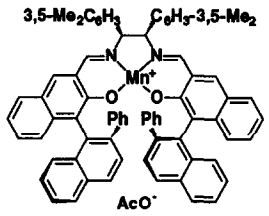


7 Ph*= 4-*t*-BuPh



8, a: X=AcO⁻, b: X= PF_6^-



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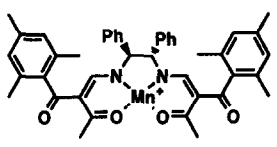
By using these catalysts, high enantioselectivity has been achieved in the epoxidation of conjugated mono-, *cis*-di-, tri-, and tetrasubstituted olefins. Besides iodosylbenzene, aqueous sodium hypochlorite [21], hydrogen peroxide [22], bistrimethylsilyl peroxide [22]b, molecular oxygen [23], and peracid [24,25] can also be used as a terminal oxidant. However, some oxidants require an appropriate additive. In the case of hydrogen peroxide or bistrimethylsilyl peroxide, the co-existence of *N*-alkylimidazole is indispensable. The reaction of the peroxide with Mn(III)-salen complex gives a peroxy species [RO–O–M^{III}] (R = H or Me_3Si) that does not effect oxygen transfer. The heterolytic O–O bond cleavage of the peroxy species giving an active oxo manganese species is essential for oxo transfer reaction and this bond cleavage is promoted by the coordination of a strong donor ligand such as *N*-methylimidazole to manganese ion [22]. Mukaiyama and co-workers have reported that molecular oxygen can also be used as a terminal oxidant in combination with pivalaldehyde [23]. With this system, it has been proposed that the reaction of molecular oxygen with Mn-salen complex in the presence of an aldehyde provides highly reactive acylperoxy Mn-salen species [RCO_2–O–Mn^{III}] which epoxidize olefins directly. However, the same reaction in the presence of the donor ligand such as *N*-alkylimidazole is considered to proceed by way of oxo species [26]. This has been supported by the fact that the sense of enantioface selection observed in the absence of the donor ligand is opposite to that observed in the presence of the donor ligand. Furthermore, β-diketoiminato–manganese(III) complex (**10**) which is structurally related to Mn-salen complex has also been found to be a useful catalyst for simple conjugated olefins, when the combination of molecular oxygen and an aldehyde is used as an oxidant [27]. Epoxidation with *m*-chloroperbenzoic acid (*m*-CPBA) can be carried out in the presence of *N*-methylmorpholine *N*-oxide [24,25]. *N*-Methylmorpholine *N*-oxide depresses the undesired epoxidation with free *m*-CPBA. Although there is no description about active species in this reaction, it seems reasonable to postulate that acylperoxy species is an active species also in this reaction in analogy with Mukaiyama's reaction. This may also be supported from the fact that epoxidation with oxo species at −78°C is very slow [28], while the epoxidation with *m*-CPBA is fast even at −78°C [24].



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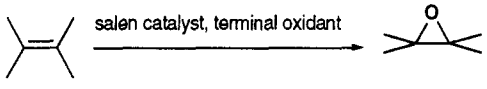
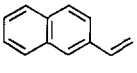
The author and co-workers found that asymmetric induction by Mn-salen catalyst is affected by the donor ligand added to the reaction medium [29,30]. Donor ligands such as 2-methylimidazole and pyridine *N*-oxide derivatives, especially 4-*N*,*N*-dimethylaminopyridine *N*-oxide [19] and 4-phenylpyridine *N*-oxide [31], bring about the enhancement of enantioselectivity. However, the addition of a donor ligand shows negative effect in the epoxidation of *trans*-stilbene [29]. The effect of a donor ligand on enantioselectivity is considered to be attributable to the change of the structure of the salen ligand by coordination of the ligand [30]. In connection with this, the reaction using hydrogen peroxide usually shows slightly diminished enantioselectivity as compared with the reaction using iodosyl benzene or aqueous sodium hypochlorite in the presence of pyridine *N*-oxide derivatives, probably because *N*-methylimidazole is a less effective axial ligand in terms of enantioselectivity enhancement. Besides increasing enantioselectivity, the addition of a donor ligand improves the yield of the epoxide in most cases, because coordination of a donor ligand to manganese ion depresses the Lewis acidity [28] of oxo Mn-salen complexes and prevents the decomposition of acid sensitive epoxide. Ligand-free cationic oxo Mn-salen species often decompose acid-sensitive epoxides under the reaction conditions even at low temperature.

Mn-salen catalyzed epoxidation can be carried out in various solvents such as acetonitrile, dichloromethane, ethyl acetate, and ether at varied temperature (25°C ~ −40°C). However, the reaction is very slow at the temperature as low as −78°C [28], except when using *m*-CPBA as an oxidant [24]. In general, enantioselectivity is enhanced, as the reaction temperature becomes

Table 1
Asymmetric epoxidation of monosubstituted olefins using (salen)manganese(III) complexes as catalysts



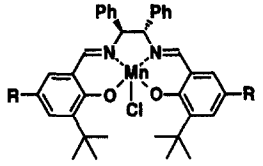
Entry	Substrate	Catalyst	Solvent	Oxidant	Temp.	Yield (%)	% ee	Confign	Ref.
1		**9**	CH_2Cl_2	NaOCl[a]	-18 °C	5	70	-	[33]
2		**11a**	CH_2Cl_2	*m*-CPBA[b]	-78 °C	88	86	-	[24]
3	"	**9**	CH_3CN	PhIO	-24 °C		26	-	[32]
4		**11a**	CH_2Cl_2	*m*-CPBA[b]	-78 °C	83	85	-	[25]
5		**11c**	CH_2Cl_2	*m*-CPBA[b]	-78 °C	83	80	-	[25]
6		**11a**	CH_2Cl_2	*m*-CPBA[b]	-78 °C	85	82	-	[25]
7		**11a**	CH_2Cl_2	*m*-CPBA[b]	-78 °C	85	82	-	[25]
8		**10**	C_6H_6	O_2[c]	rt	49	48	-	[27]

a) Aqueous NaOCl saturated with sodium chloride was used.
b) Reaction was carried out in the presence of excess *N*-methylmorpholine *N*-oxide.
c) Reaction was carried out in the presence of pivalaldehyde.

lower. However, some reactions show the maximum enantioselectivity at some temperature (vide infra) [32].

2.2. The scope and limitation of Mn-salen catalyzed asymmetric epoxidation

Epoxidation of simple olefins with highly efficient Mn-salen catalysts is summarized in Tables 1–5. Substrates are classified according to substitution pattern and entries are in the order of increasing number of carbon atoms in the substrate in each class. In general, olefins bearing functional groups such as ether, ester, amide, nitro, acetal, silyl ether, nitrile, and acetylenic groups can be successfully epoxidized without interference from these functional groups. However, sulfides and allylic alcohols are oxidized to the corresponding sulfoxides and aldehydes under the usual reaction conditions.

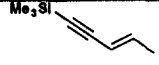
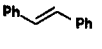
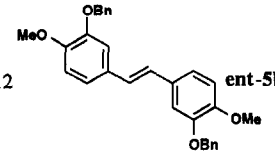


11, a: R= OSi(Pr-*i*)$_3$, b: R= Me, c: R= OMe

2.2.1. Monosubstituted olefins

Epoxidation of olefins conjugated with unsaturated groups usually shows higher enantiose-

Table 2
Asymmetric epoxidation of *trans*-disubstituted olefins using (salen)manganese(III) or (salen)-chromium(III) complexes as catalysts

Entry	Substrate	Catalyst	Solvent	Oxidant	Temp.	Yield (%)	% ee	Confign	Ref.
1		**5a**	CH_2Cl_2	NaOCl		23 (2:1)[a]	46[b]	-	[34]
2		**7**	CH_3CN	PhIO		61	9	1*R*,2*R*	[19]
3	"	**ent-5a**	CH_2Cl_2-MeOH	H_2O_2		34	47	1*R*,2*R*	[15c]
4	"	**4**	CH_2Cl_2[c]	PhIO	rt	32	56	1*R*,2*R*	[19]
5	"	**12**	CH_2Cl_2[d]	PhIO	rt	-	83	1*R*,2*R*	[35]
6		**5a**	CH_2Cl_2	NaOCl	-	-	25	1*S*,2*S*	[36]
7	"	**8b**	CH_3CN	PhIO	rt	37	67	1*R*,2*R*	[37]
8	"	**8b**	"	"	0 °C	30	73	1*R*,2*R*	[37]
9	"	**8b**	"	"	-20 °C	37	77	1*R*,2*R*	[37]
10	"	**8b**	"	"	-40 °C	17	81	1*R*,2*R*	[37]
11	"	**7**	"	"	rt	65	62	1*R*,2*R*	[19]
12		**ent-5b**	CH_2Cl_2	2,4,6-$Me_3C_6H_2IO$	5 °C	-	30	1*R*,2*R*	38

a) Product is a mixture of *trans*- and *cis*-epoxides. Numbers in parentheses are a ratio of *trans*- and *cis*-epoxides.
b) The number stands for the e.e. of *trans*-epoxide.
c) Reaction was carried out in the presence of 2-methylimidazole.
d) Reaction was carried out in the presence of triphenylphosphine oxide.
e) Data taken from Refs. [34] (entry 1) and [38] (entry 12).

lectivity than non-conjugated olefins in Mn-salen catalyzed epoxidation. The epoxidation of conjugated olefins with oxo Mn-salen species involves reversible metallaoxetane formation and irreversible radical formation steps and, through these enantio- and diastereoselective steps, high enantioselectivity is realized (see the next section about the reaction mechanism).

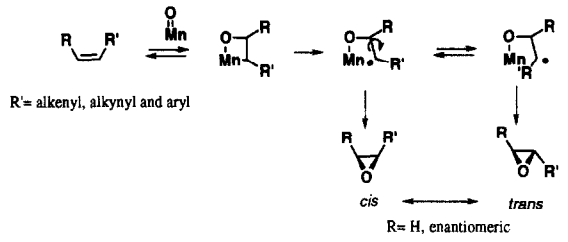


Fig. 4. Participation of radical intermediates.

Table 3
Asymmetric epoxidation of *cis*-disubstituted olefins using (salen)manganese(III) complexes as catalysts

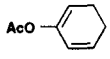
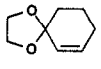
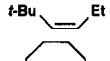
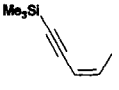
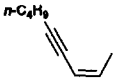
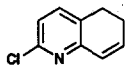
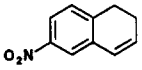
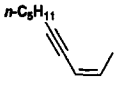
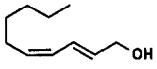
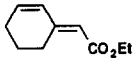
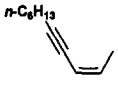
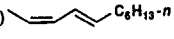
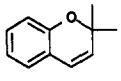
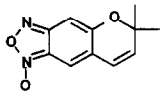
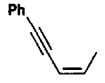
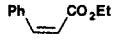
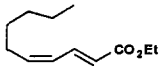
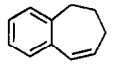
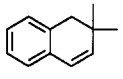
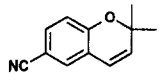
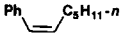
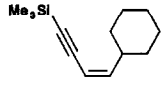
Entry	Substrate	Catalyst	Solvent	Oxidant	Temp.	Yield (%)	% ee	Confign	Ref.
1		**9**	CH_2Cl_2	NaOCl[a,b]	-18 °C	82	93	(1*S*,2*R*)	[33]
2	"	**6**	Et_2O	NaOCl[b]	4 °C	45	64	-	[18]
3		**6**	EtOAc	NaOCl[b]	4 °C	35[c]	71	-	[18]
4		**6**	Et_2O	NaOCl[b]	4 °C	30	65	-	[18]
5	"	**9**	CH_2Cl_2	NaOCl[a,b]	-18 °C	68	88	-	[33]
6		**6**	Et_2O	NaOCl[b]	4 °C	32	90	-	[18]
7		**6**	EtOAc	NaOCl[b]	4 °C	47[d]	68	-	[18]
8		**7**	CH_3CN	PhIO	rt	10	87	-	[39]
9		**9**	CH_2Cl_2	NaOCl[b]	-18 °C	54	94	-	[33]
10		**5a**	CH_2Cl_2	NaOCl	4 °C	63	94	-	[17]
11		**6**	chlorobenzene	NaOCl[e]	4 °C	-(69:31)[f]	84[g]	-	[40]
12		**9**	CH_2Cl_2	NaOCl[b]	-18 °C	40	82	-	[33]
13		**5a**	CH_2Cl_2	NaOCl	rt	84 (2.5:1)[f]	90[g] (78)[h]	3*R*,4*R*	[31]
14		**7**	CH_2Cl_2	NaOCl		36	86	1*S*,2*R*	[19]
15	"	**5a**	CH_2Cl_2	NaOCl	4 °C	81	92	1*S*,2*R*	[17]
16	"	**9**	CH_2Cl_2	NaOCl		16	90[i]	1*S*,2*R*	[20c]
17	"	**6**	chlorobenzene	NaOCl[e]	4 °C	80 (95:5)[f]	81[g]	1*S*,2*S*	[40]
18	"	**10**	C_6H_6	O_2[j]	rt	28 (37:63)[f]	80[i]	1*R*,2*S*	[27]
19	"	**11a**	CH_2Cl_2	*m*-CPBA[k]	-78 °C	71	98	-	[25]
20		**9**	CH_2Cl_2	NaOCl[a,b]	-18 °C	23	82	1*S*,2*R*	[33]

Table 3 (continued)

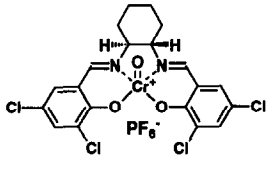
21		**9**	CH_2Cl_2	NaOCl	0 °C	55	98	-	[20c]
22	"	**5a**	CH_2Cl_2	NaOCl		80	88	-	[15c]
23	"	**11a**	CH_2Cl_2	*m*-CPBA[k]	-78 °C	89	96	-	[25]
24		**9**	CH_2Cl_2	NaOCl[b]	0 °C	80[l]	(83)[h]	2*R*	[41]
25		**8a**	CH_2Cl_2	NaOCl[b]	0 °C	77	96	7*R*,8*S*	[42]
26		**4**	CH_3CN	PhIO	rt	93	49	1*R*,2*S*	[16b]
27	"	**5b**	fluorobenzene	O_2[m]	rt	78	63	1*S*,2*R*	[23]
28	"	**7**	CH_2Cl_2	NaOCl[n]	rt	38	91	1*S*,2*R*	[19]
29	"	**3**	CH_3CN	Me_3PhIO	25 °C	72	78	1*R*,2*S*	[16b]
30	"	**5a**	CH_2Cl_2	NaOCl	0 °C	67	86	1*S*,2*R*	[15c]
31	"	**8a**	"	"	0 °C	96	93	1*S*,2*R*	[20a]
32	"	**9**	CH_2Cl_2	NaOCl[b]	0 °C	78	98	1*S*,2*R*	[20c]
33	"	**13**	CH_2Cl_2	NaOCl[b]	0 °C	78	91	1*R*,2*S*	[43]
34	"	**14**	CH_2Cl_2	NaOCl[b]	0 °C	78	97	1*R*,2*S*	[43]
35		**5b**	fluorobenzene	O_2[m]	rt	43	43	-	[23]
36		**ent-9**	CH_2Cl_2	NaOCl[b]	0 °C	100[l]	(86)[h]	2*S*	[41]
37		**ent-5a**	CH_2Cl_2	NaOCl[b]	0 °C	16 (2.3:1)[f,o]	83[g]	-	[44]
38		**ent-5a**	CH_2Cl_2	NaOCl[b]	0 °C	58	77[g]	-	[44]
39		**5a**	CH_2Cl_2	NaOCl	rt	65 (1.6:1)[f]	90[g] (72)[h]	3*R*,4*R*	[31]
40		**ent-5a**	CH_2Cl_2	NaOCl[b]	0 °C	50 (1.1:1)[f]	92[g]	-	[44]
41		**ent-5a**	CH_2Cl_2	NaOCl	4 °C	72	98	3*R*,4*R*	[17]

However, in the case of monosubstituted olefins, the radical formation leads to racemization (Fig. 4, R = H). Thus, the reaction of this class of substrates provides unexpectedly low enantioselectivity under usual conditions (Table 1, entry 3). Jacobsen and co-workers ingeniously solved this problem by using *m*-CPBA as a terminal oxidant (vide supra) and attained high enantios-

Table 3 (continued)

42	"	**5a**	C_6H_6	O_2[p]	rt	37	92	-	[26]
43	"	**9**	CH_3CN	PhIO[q]	-20 °C	60	>99	3*S*,4*S*	[20c]
44	"	**9**	CH_2Cl_2	NaOCl[b]	0 °C	75	99	3*S*,4*S*	[20c]
45		**7**	CH_3CN	PhIO		63	94	3*S*,4*S*	[19]
46	"	**9**	CH_3CN	PhIO		72	97	3*S*,4S	[20b]
47		**5a**	CH_2Cl_2	NaOCl	rt	85 (2:1)[f]	93[g] (81)[h]	3*R*,4*R*	[31]
48	"	**9**	CH_2Cl_2	NaOCl[b]	0 °C	80 (2:1)[f]	96[g] (94)[h]	3*R*,4*R*	[20c]
49	"	**13**	CH_2Cl_2	NaOCl[b]	0 °C	75 (1:1.2)[f]	91[i] (94)[h]	3*R*,4*S*	[43]
50	"	**14**	CH_2Cl_2	NaOCl[b]	0 °C	70 (1:3.5)[f]	97[i] (95)[h]	3*R*,4*S*	[43]
51		**ent-5a**	CH_2Cl_2	NaOCl[b]	4 °C	56 (13:87)[f]	95-97[i]	1*R*,2*R*	[45]
52	"	**5a**	CH_2Cl_2	*m*-CPBA[k]	-78 °C	0	-	-	[25]
53		**ent-5a**	CH_2Cl_2	NaOCl[b]	0 °C	81 (9:1)[f]	87[g]	-	[44]
54		**5b**	fluorobenzene	O_2[m]	rt	52	77	1*S*,2*R*	[23]
55	"	**10**	C_6H_6	O_2[j]	rt	57	79	-	[27]
56	"	**11a**	CH_2Cl_2	*m*-CPBA[k]	-78 °C	83	97	-	[25]
57		**5b**	fluorobenzene	O_2[m]	rt	80	72	-	[23]
58		**ent-5a**	CH_2Cl_2	NaOCl	4 °C	96	97	3*R*,4*R*	[17]
59	"	**6**	CH_2Cl_2	*m*-CPBA[k]	-78 °C	91	97	-	[25]
60		**10**	C_6H_6	O_2[j]	rt	40 (12:88)[f]	80[i]	-	[27]
61		**5a**	CH_2Cl_2	NaOCl	rt	65 (5.2:1)[f]	98[g] (93)[h]	3*R*,4*R*	[31]

electivity in the epoxidation of styrene derivatives (entries 2, 4–7).



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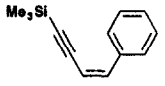
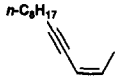
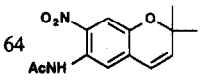
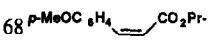
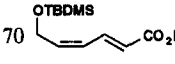
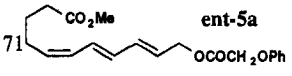
2.2.2. *trans-Disubstituted olefins*

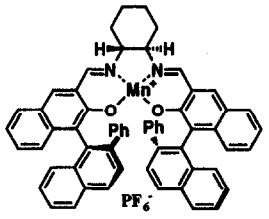
In the case of *trans*-disubstituted olefins, Mn-salen catalyzed epoxidation has achieved only limited success (Table 2). Enantioselectivity observed is only moderate to good and dependent on the Mn-salen catalyst and the reaction conditions used. For example, the highest enantioselectivity in the Mn-salen catalyzed epoxidation of *trans*-β-methylstyrene was ob-

Table 3 (continued)

62		**5a**	CH_2Cl_2	NaOCl	rt	34 (1:1)[f]	35[g] (35)[h]	-	[31]
63		**ent-9**	CH_2Cl_2	NaOCl[b]	0 °C	84[l]	(90)[h]	2*S*	[41]
64		**7**	CH_3CN	PhIO	rt	78	96	-	[19]
65	"	**9**	CH_2Cl_2	NaOCl[b]	0 °C	80	>99	3*S*,4*S*	[20c]
66	"	**13**	CH_2Cl_2	NaOCl[b]	0 °C	77	98	3*R*,4*R*	[43]
67	"	**14**	CH_2Cl_2	NaOCl[b]	0 °C	63	>99	3*R*,4*R*	[43]
68		**6**	chlorobenzene	NaOCl[e]	4 °C	- (89:11)[f]	86[g]	2*S*,3*S*	[40]
69		**6**	chlorobenzene	NaOCl[e]	4 °C	- (>96:4)[f]	90[g]	1*S*,2*S*	[40]
70		**ent-5a**	CH_2Cl_2	NaOCl[b]	0 °C	58 (7.3:1)[f]	83[g]	-	[44]
71		**ent-5a**	CH_2Cl_2	NaOCl[b]	0 °C	62 (8:1)[f]	82[g]	5*S*,6*S*	[44]

a) Aqueous NaOCl saturated with sodium chloride was used.
b) Reaction was carried out in the presence of 4-phenylpyridine *N*-oxide.
c) The product is 4-acetoxy-2-cyclopentenone.
d) The product is 4-hydroxy-2-cyclohexenone.
e) Reaction was carried out in the presence of *N*-benzylated quinine salt.
f) Product is a mixture of *trans*- and *cis*-epoxides. Numbers in parentheses are a ratio of *trans*- and *cis*-epoxides.
g) The number stands for the e.e. of *trans*-epoxide.
h) The number in parentheses stands for the face selectivity. Face selectivity = ee*trans* × %*trans* + eecis × %*cis* [46].
i) The number stands for the e.e. of *cis*-epoxide.
j) Reaction was carried out in the presence of pivalaldehyde.
k) Reaction was carried out in the presence of excess *N*-methylmorpholine *N*-oxide.
l) Product is a mixture of *trans*- and *cis*-epoxides but the ratio of two isomers has not been determined.
m) Reaction was carried out in the presence of pivalaldehyde and *N*-methylimidazole.
n) Reaction was carried out in the presence of 4-(*N*,*N*-dimethylamino)pyridine *N*-oxide.
o) The allylic alcohol was oxidized to the corresponding aldehyde.
p) Reaction was carried out in the presence of pivalaldehyde and *N*-octylimidazole.
q) Reaction was carried out in the presence of pyridine *N*-oxide.
r) Data taken from Refs. [41] (entries 24, 36, 63), [42] (entry 25), [44] (entries 37, 40, 53, 70, 71) and [45] (entry 51).

served when the catalyst **4** was used in the presence of 2-methylimidazole (entry 4), but the highest one in the epoxidation of *trans*-stilbene was observed when the catalyst **8b** was used at low temperature in the absence of donor ligand (entries 7–10) [37]. Quite recently, epoxidation of *trans*-β-methylstyrene with chiral Cr-salen complex **12** was found to show good enantioselectivity, though the scope of the reaction was not reported (entry 5) [35].



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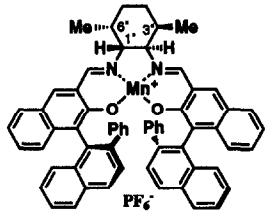

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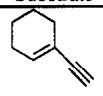
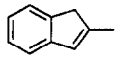
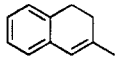
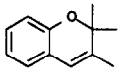
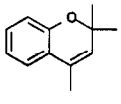
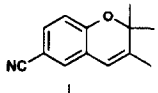
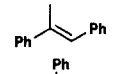
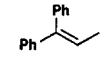
2.2.3. *cis*-Disubstituted olefins

Conjugated *cis*-disubstituted olefins are generally good substrates for Mn-salen catalyzed epoxidation and high enantioselectivity up to > 99% e.e. has been achieved, except for simple 1,3-cycloalkadienes (Table 3). Epoxidation of simple 1,3-cycloalkadienes with most Mn-salen catalysts shows only moderate enantioselectivity probably due to the poor electrostatic repulsion between the unsaturated olefinic substituent and the salen ligand (vide infra) [39]. However, the epoxidation with Mn-salen catalyst **9** that has an electron-rich phenyl substituent in the space over the salen-benzene ring shows good to excellent level of enantioselectivity, especially when the reaction is carried out at depressed temperature (−18°C), using aqueous sodium hypochlorite saturated with sodium chloride as a terminal oxidant (entries 1, 5, 9, and 12) [33]. Although epoxidation of dialkyl-substituted olefins usually shows insufficient enantioselectivity [39] except for that of 3,3-ethylenedioxycyclohexene (entry 10) [17], epoxidation of (Z)-1-cyclohexyl-1-propene with **9** under the above reaction conditions shows good enantioselectivity of 82% e.e. (entry 20) [33].

Table 4
Asymmetric epoxidation of trisubstituted olefins using (salen)manganese(III) complexes as catalysts

Entry	Substrate	Catalyst	Solvent	Oxidant	Temp.	Yield (%)	% ee	Confign	Ref.
1		**11b**	CH_2Cl_2	NaOCl[a)]	0 °C	61	86	-	[36]
2		**9**	CH_2Cl_2	NaOCl[a)]	-20 °C	91	88	-	[47]
3		**ent-6**	CH_2Cl_2	NaOCl[a)]	0 °C	75	86	1*S*,2*S*	[36]
4		**9**	CH_3CN	PhIO[a)]	-20 °C	48	92	1*S*,2*R*	[47]
5		**9**	CH_3CN	PhIO[a)]	-20 °C	41	96	1*S*,2*R*	[47]
6		**9**	CH_2Cl_2	NaOCl		88	>99	-	[47]
7		**ent-5a**	CH_2Cl_2	NaOCl	0 °C	51	97	3*R*,4*R*	[34]
8	"	**9**	CH_2Cl_2	NaOCl[a)]		63	89	-	[47]
9		**ent-5a**	CH_2Cl_2	NaOCl[a)]	0 °C	69	93	1*S*,2*S*	[36]
10	"	**9**	CH_2Cl_2	NaOCl[a)]		26	83	1*R*,2*R*	[47]
11		**ent-5a**	CH_2Cl_2	NaOCl	0 °C	82	>98	3*R*,4*R*	[34]
12		**ent-5a**	CH_2Cl_2	NaOCl[a)]	0 °C	87	88	1*S*,2*S*	[36]
13		**ent-5a**	CH_2Cl_2	NaOCl[a)]	0 °C	91	95	*S*	[36]

a) Reaction was carried out in the presence of 4-phenylpyridine *N*-oxide.

Reaction of acyclic conjugated *cis*-disubstituted olefins gives a mixture of *cis* and *trans* epoxides probably through a radical intermediate (Fig. 4, R ≠ H). In this connection, Jacobsen and co-workers have recently found that the reaction in the presence of a quaternary ammonium salt provides *trans*-epoxide preferentially (entries 11, 17, 68, and 69) [40]. Although the role of the ammonium salt in these reactions has not been clarified, this provides an alternate procedure for obtaining optically active *trans*-epoxides. In contrast to this, they have reported that epoxidation with *m*-CPBA in the presence of *N*-methylmorpholine *N*-oxide at −78°C provides *cis*-epoxides exclusively with excellent enantioselectivity (entry 19) [25]. However, under these conditions, epoxidation of α,β-unsaturated ester does not proceed, differing from the reaction using aqueous NaOCl as an oxidant (entries 51 and 52).

2.2.4. *Trisubstituted olefins*

Conjugated trisubstituted olefins are also good substrates for Mn-salen catalyzed epoxidation (Table 4) [34,36,47].

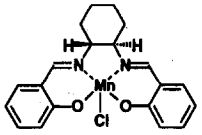


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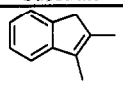
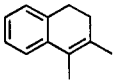
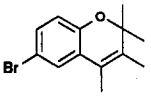
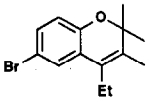
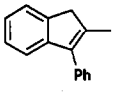
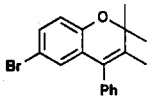
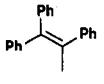
Table 5
Asymmetric epoxidation of tetrasubstituted olefins using (salen)manganese(III) complexes as catalysts

Entry	Substrate	Catalyst	Solvent	Oxidant	Temp.	Yield (%)	% ee	Config	Ref.
1		**ent-11c**	CH_2Cl_2	NaOCl[a)]	0 °C	37	35	1*R*,2*S*	[48]
2		**11c**	CH_2Cl_2	NaOCl[a)]	0 °C	45	65	1*S*,2*R*	[48]
3	"	**11b**	CH_2Cl_2	NaOCl[a)]	0 °C	-	38	-	[48]
4		**11b**	CH_2Cl_2	NaOCl[a)]	0 °C	84	96	3*S*,4*R*	[48]
5		**11b**	CH_2Cl_2	NaOCl[a)]	0 °C	81	97	3*S*,4*R*	[48]
6		**15**	CH_2Cl_2	NaOCl[a)]	0 °C	-	19	-	[48]
7	"	**ent-6**	CH_2Cl_2	NaOCl[a)]	0 °C	90	90	-	[48]
8		**ent-5a**	CH_2Cl_2	NaOCl[a)]	0 °C	-	4	-	[48]
9	"	**15**	CH_2Cl_2	NaOCl[a)]	0 °C	72	81	-	[48]
10		**15**	CH_2Cl_2	NaOCl[a)]	0 °C	12	46	*R*	[48]

a) Reaction was carried out in the presence of 4-phenylpyridine *N*-oxide.

2.2.5. Tetrasubstituted olefins

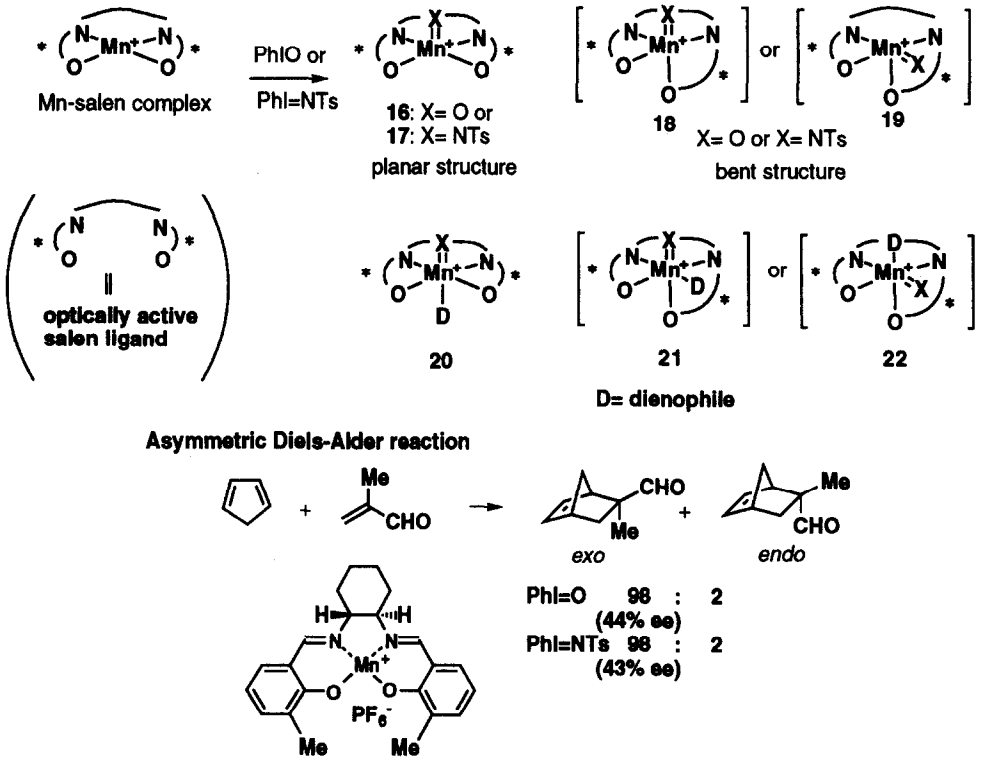
Some conjugated tetrasubstituted olefins also show high enantioselectivity in Mn-salen catalyzed epoxidation (Table 5, entries 4, 5, 7 and 9) but the enantioselectivity seems strongly dependent upon the catalyst used (cf. entries 6 and 7, and entries 8 and 9) [48].

3. The mechanism of one oxygen atom transfer and of asymmetric induction by Mn-salen catalyst

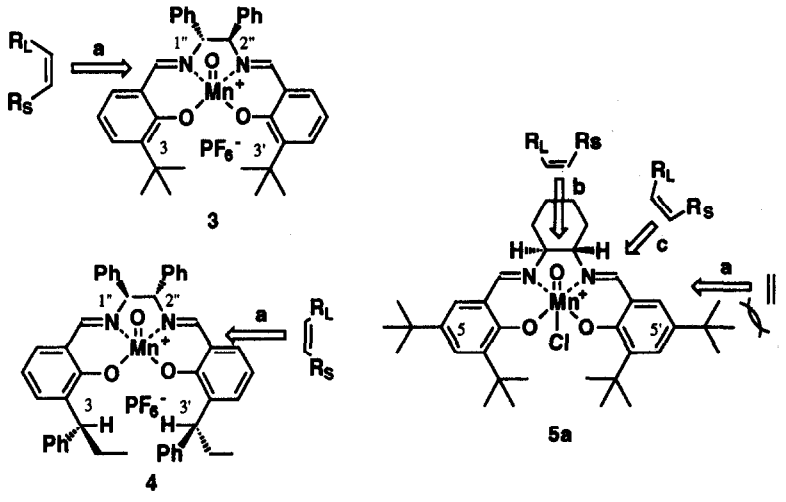
Although excellent levels of enantioselectivity have been achieved in Mn-salen catalyzed epoxidation of simple olefins, there is still a controversy on its reaction mechanism, especially about the mechanism of oxo transfer from the putative oxo (salen)manganese(V) species to olefins. Here we briefly review the mechanisms proposed to date.

3.1. The structure of oxo Mn-salen complex

No oxo metallosalen complex has been isolated except for oxo Cr-salen complexes in which salen ligands take square planar coordination as described in the Section Section 1 [13]. Although the structures of oxo Mn-salen complexes have not been determined yet, it seems reasonable that the salen ligand in the oxo Mn-salen complex also takes square planar geometry. This assumption was supported by the experiment of oxo Mn-salen catalyzed Diels–Alder reaction. Oxo Mn-salen and *N*-tosylimino Mn-salen complexes (**16** and **17**) serve not only as oxidizing agents but also as Lewis acid catalysts. In general, the oxidation (epoxidation and aziridination) proceeds at usual reaction conditions but, below −70°C, these complexes serve mainly as a Lewis acid catalyst and do not oxidize olefins. Thus, the author and co-worker examined the Mn-salen catalyzed Diels–Alder

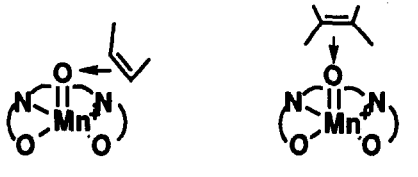


Scheme 1. .



Scheme 2.

reaction with these complexes (**16** and **17**) as catalysts and found that **16** and **17** showed the same level of enantioselectivity and *exo / endo* ratio (Scheme 1). If the salen ligand takes a bent structure (**18** or **19**), dienophile must coordinate *cis* to the ligand **X** (**21** or **22**) and, therefore, exchange of the ligand X from oxygen atom to *N*-tosylimino group should affect enantioselectivity and *exo / endo* ratio of the reaction. However, this is not the case as described above. On the other hand, if the salen ligand takes square planar geometry like **16** and **17**, the ligand **X** and dienophile occupy two distant axial positions as shown in **20**, respectively, and the exchange of the ligand (**X**) little affects on enantioselectivity [28,32]. This is the case observed.



side-on approach top-on approach

Fig. 5. Olefin's approach to oxo metal species.

3.2. Approach of olefins to the oxo Mn-salen complex

In porphyrin-catalyzed epoxidation reactions, olefins are considered to approach the metal–oxo bond from its side and parallel to the porphyrin ring (so called side-on approach, Fig. 5) [49]. This side-on or skewed side-on [36] approach has also been considered to be applicable to the salen-catalyzed epoxidation, because of the structural similarity between porphyrin and salen complexes [1]. However, a top-on approach has recently been proposed for the epoxidation of tetrasubstituted olefins for steric reason [48].

With the side-on or skewed side-on approach, three pathways (**a**, **b**, and **c**) for the incoming olefin have been proposed (Scheme 2). In the early stages of the author's and Jacobsen's studies, Mn-salen complexes (**3** and **4**) were introduced based on the hypothesis that olefins ap-

[1] For example, Jorgensen explained the stereochemistry observed in the epoxidation using (salen)manganese and manganese prophyrin catalysts, with the same transition state model [50].

proach along the pathway **a** between nitrogen and oxygen atoms, orienting their bulkier olefinic substituent away from C3(3′)-substituent to avoid the steric repulsion with C3(3′) substituent [16].

However, Jacobsen and co-workers have proposed a different pathway in the epoxidation with modified Mn-salen complex **5a** in which 5,5′-*t*-butyl groups stand in the pathway **a**. Although strong steric repulsion between the 5(5′)-substituent and the incoming olefin along the pathway **a** is expected, **5a** catalyzes the epoxidation smoothly and exhibits high enantioselectivity. Based on this result, Jacobsen and co-workers proposed pathway **b** passing between two nitrogen atoms, wherein the larger substituent on the incoming olefin has been considered to be directed away from C2″ axial hydrogen atom [17]. Our recent results, however, cast some doubt on this proposal. Complex **14** bearing axial methyl groups at C3″ and C6″ carbons is expected to show an opposite sense of asymmetric induction to that observed with complex **13**, as long as olefins approach along the pathway **b**. This is not the case. Both **13** and **14** show the same sense of asymmetric induction (Table 3, entries 33, 34, 49, and 50) [43].

Although only steric repulsion is considered as the factor controlling the orientation of the incoming olefin in the above discussions, enantioface selectivity of some substrates cannot be rationalized by considering only steric factors. In general, *cis*-β-methylstyrene exhibits better enantioselectivity than (Z)-1-cyclohexyl-1-propene, though the bulkiness of the cyclohexyl group is roughly equal to that of the phenyl group. 4-Cyclohexyl-1-trimethylsilyl-3-buten-1-yne is a better substrate than 4-phenyl-1-trimethylsilyl-3-buten-1-yne (Table 3, entries 61 and 62) [31]. These stereochemistries seem strange at first, but they can be rationalized by considering both the steric and π-electronic repulsions between the salen ligand and the olefinic substituent [39,51]. The incoming olefin along the pathway **a** or **c** feels different electronic atmospheres at each side of the pathway, because a π-electron-rich salen benzene ring exists at one side of the pathway and a cyclohexane ring bearing no π-electron exists at the other side. The repulsive π–π electron interaction between the benzene ring of salen ligand and the unsaturated olefinic substituent cooperates with steric repulsion to direct the olefinic substituent away from C3′ substituent as well as the salen-benzene ring [39]. Thus, olefins bearing sterically bulky and π-electron-rich substituents at one terminal carbon show high enantioselectivity. As described above, the pathway **a** in the epoxidation with catalyst **5a** was denied due to the presence of 5,5′-*t*-butyl groups. Accordingly only the pathway **c** seemed to give a rational explanation on the mechanism of asymmetric induction [51]. The above discussion are all based on the assumption that the salen ligand of the oxo species takes a planar structure (Fig. 6), however, some experimental results suggest that salen ligands do not take a planar structure, but a folded structure. X-ray analysis of the pyridine *N*-oxide adduct of oxo the Cr-salen complex has shown that the salen ligand takes a folded structure (**23**, M = Cr, L = pyridine *N*-oxide) [13]. Quite recently, the salen ligand of a structurally related cationic $Al(H_2O)_2$-salen

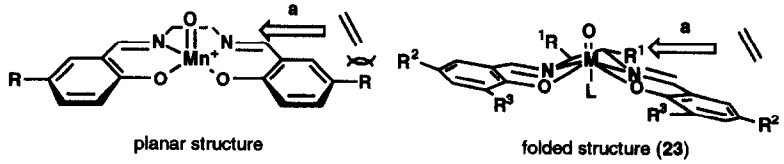
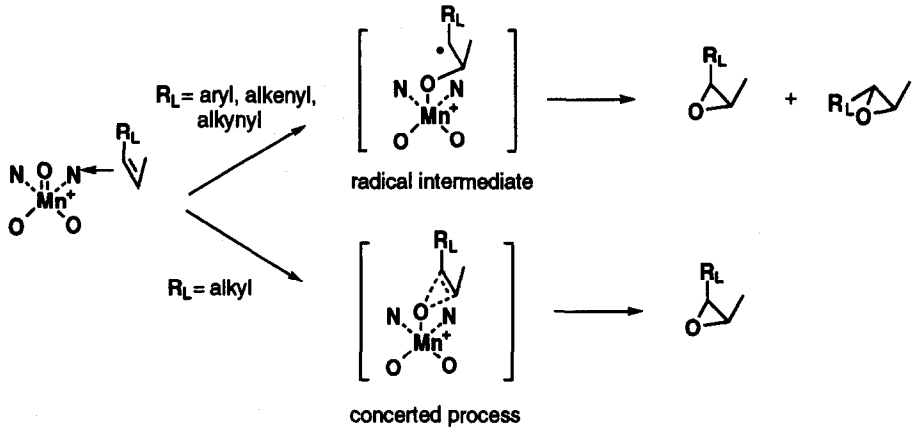


Fig. 6. The structures of salen ligand and olefin's approach.



Scheme 3.

complex has also been reported to have a similar folded structure [52]. Examination of the stereochemistry of Co-salen catalyzed asymmetric cyclopropanation has also suggested that the salen ligand of Co(V)-salen carbenoid complex takes a folded structure and that the non-symmetrically folded salen ligand strongly influences the enantioselectivity of the reaction [53]. Although no oxo Mn-salen complex has been isolated, these findings suggest that the salen ligand also has a folded structure. If so, 5′-substituent does not interfere with the approach of olefins along the pathway **a**. Actually, the stereochemistry observed in most Mn-salen catalyzed epoxidation can also be explained by the pathway **a** [32].

3.3. Mechanism of one oxygen atom transfer from oxo Mn-salen complex to olefins

However, there is still controversy on the mechanism of oxygen atom transfer from oxo species to the incoming olefin. One suggestion is that the incoming olefin attacks the electrophilic oxygen atom in a side-on manner and then one electron transfers from the olefin to the oxo bond to give a radical intermediate, when the substrate bears a radical stabilizing group

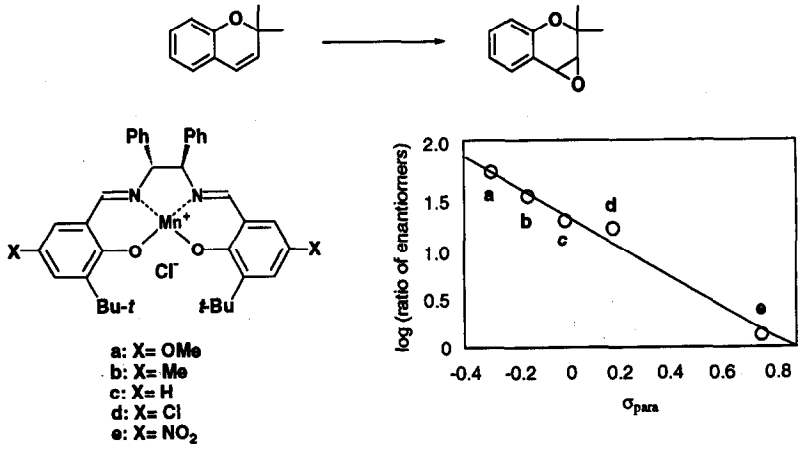
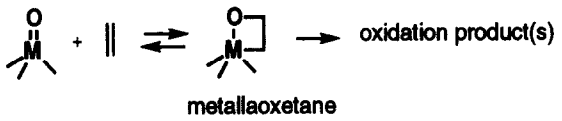


Fig. 7. Electronic effect of substituent on enantioselectivity.



Scheme 4. Sharpless' proposal on the mechanism of oxidation with oxo metal species.

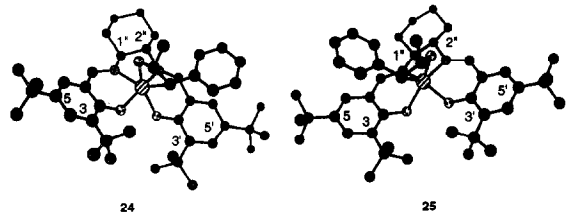
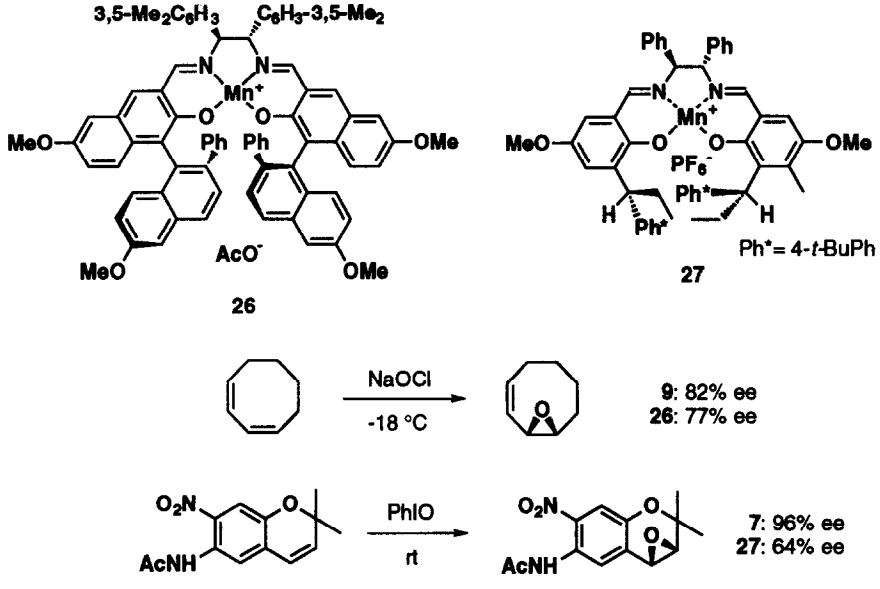


Fig. 8. The two metallaoxetane intermediates found in calculation.

(Scheme 3). This proposal has long been accepted for Mn-salen catalyzed epoxidation [12,15]. On the other hand, alkylsubstituted olefins have been considered to be epoxidized in a concerted process from the following observation by Jacobsen et al. [54]. Epoxidation of *trans*-2-phenyl-1-vinylcyclopropane gives the corresponding epoxide and no product of cyclopropane cleavage is detected. If a radical intermediate intervenes, the product of cyclopropane cleavage should be detected, since the rate of rearrangement of a secondary phenylcyclopropyl radical is very fast ($> 10^{10}$ s^{-1}). These two scenarios seem to be compatible with Jacobsen's observation that Mn-salen complexes with an electron-donating group at C5 and C5′ show higher asymmetric induction than that with an electron-withdrawing group (Fig. 7) [55]. The electronic effect of substituents corresponds well with the σ-value of substituents. This electronic effect has been attributed to the change in the reactivity of the oxo species. The electron-donating substituent decreases the reactivity of the oxo species and the reaction with less reactive oxo species proceeds via a more product-like transition state, resulting in more specific non-bonded interactions and better enantioselectivity.

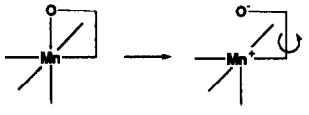
In 1977, Sharpless and co-workers proposed that the reaction of oxo metal species and olefins reversibly gives a metallaoxetane intermediate which is converted to oxidation product(s) (Scheme 4) [56], and recently they demonstrated that the asymmetric dihydroxylation using chirally modified osmium tetroxide as a catalyst proceeds through a metallaoxetane intermediate



Scheme 5.

by analyzing the relationship between reaction temperature and enantioselectivity (vide infra) [57].

Norrby and Åkermark have recently proposed that Mn-salen catalyzed epoxidation proceeds by way of a metallaoxetane intermediate (Fig. 4) based on the calculation using Macromodel/MM3 [58]. According to their model, the enantioselectivity of the reaction can be explained by the energy difference between two diastereomeric metallaoxetane intermediates (**24** and **25**). Intermediate **24** giving the major enantiomer of the epoxide is more stable than **25** by 11 kcal/mol (Fig. 8, The figure was kindly provided by Dr. P.-O. Norrby.). They have pointed out a possibility that the *cis–trans* isomerization observed during the epoxidation of *cis*-alkenes is attributable to a rotation around the carbon–carbon single bond of the intermediate brought by the heterolysis of metal oxygen bond.



The author and co-workers independently found experimental proofs that Mn-salen catalyzed epoxidation proceeds through a reversibly formed intermediate (Scheme 5): epoxidation of some substrates using our catalysts (**26** and **27**) modified with an electron-donating methoxy group gave a lower enantioselectivity than that using the unmodified parent catalysts (**9** and **7**). Epoxidations of 1,3-cyclooctadiene with **26** and of 6-acetamido-2,2-dimethyl-7-nitrochromene with **27** showed lower enantioselectivity than those with **9** and **7**, respectively. In addition to this, we also found that epoxidation of 1,3-cyclooctadiene with **9** showed maximum enantioselectivity at 0°C (Fig. 9) [32]. In most asymmetric reactions, enantioselectivity increases, as the reaction temperature is decreased. This is true if the reaction proceeds through only one transition state, and the observed linear relationship between enantioselectivity and reaction temperature is expressed by Eyring's equation:

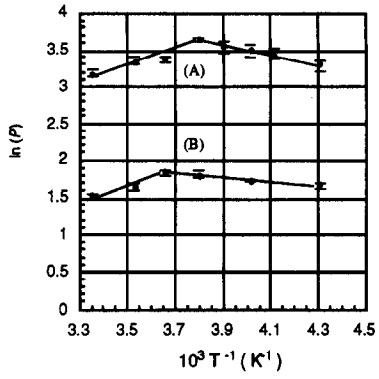


Fig. 9. Non-linear relationship between enantioselectivity and temperature.

$$\ln(P) = -\frac{\Delta\Delta H^{\neq}}{RT} + \frac{\Delta\Delta S^{\neq}}{R}$$

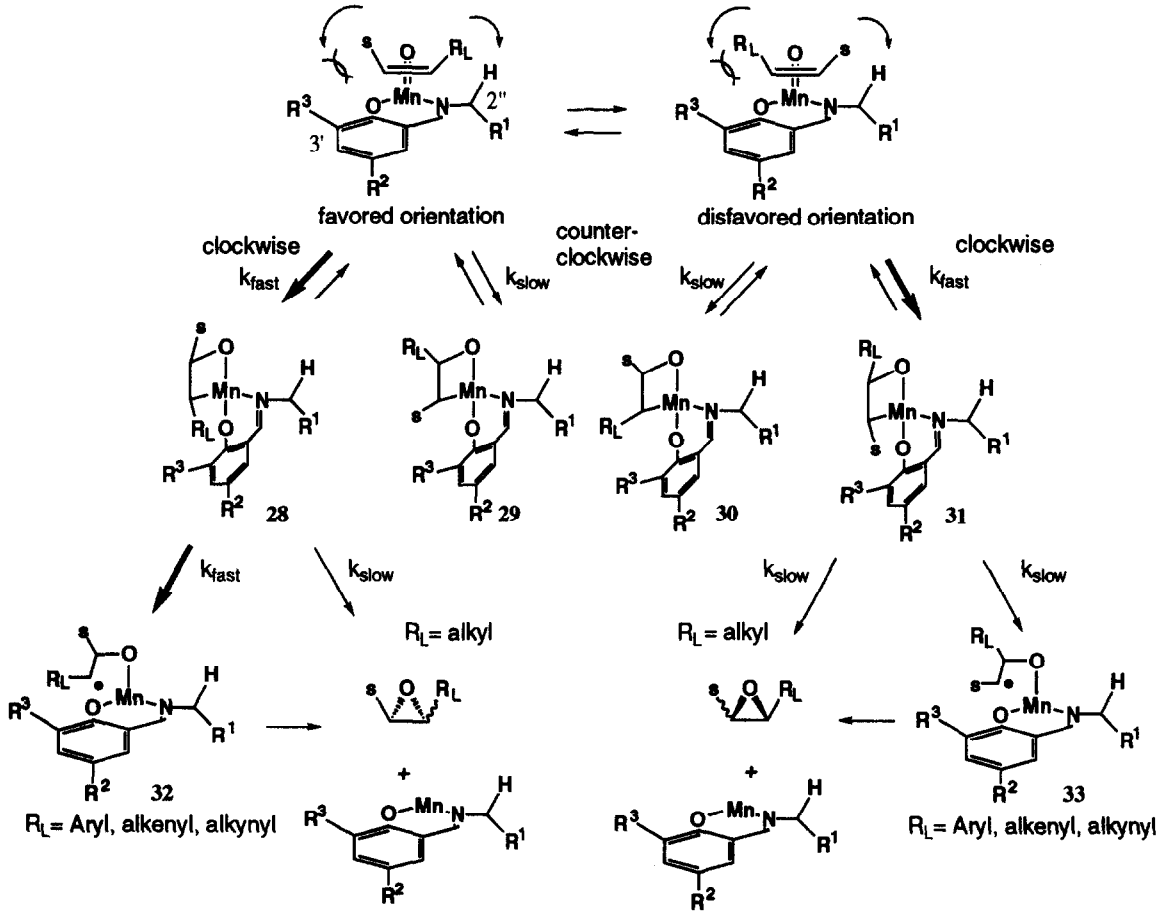
$$P = \frac{I\ (\text{major enantiomer of epoxide})}{I'\ (\text{minor enantiomer of epoxide})}$$

'enantioselectivity' in this equation is expressed by $\ln(R/S)$. In contrast to this, Scharf and co-workers have demonstrated that a reaction which involves reversible formation of diastereomeric intermediates and irreversible transformation of the intermediates to a product or another intermediate has a possibility to show non-linear relationship between enantioselectivity and reaction temperature [59]. Scharf's proposal explains our findings reasonably well and suggests the presence of the reversibly formed diastereomeric intermediates in Mn-salen catalyzed epoxidation. Assuming the metallaoxetane intermediate as the reversibly formed intermediate gives a reasonable explanation to our observations.

Although the epoxidation of conjugated *cis*-olefins provides a mixture of *cis*- and *trans*-epoxides, the epoxidation of *cis*-dialkylsubstituted olefin is slow but stereospecific to give the corresponding *cis*-epoxide exclusively [39]. This is compatible with Jacobsen's report on the epoxidation of *trans*-2-phenyl-1-vinylcyclopropane [54]. These results probably suggest

that the intermediary metallaoxetane decomposes quickly to a radical intermediate in the epoxidation of conjugated olefins, while the metallaoxetane intermediate is converted slowly but directly to the epoxide in the reaction of non-conjugated olefins [32].

Considering the above arguments, the author and co-workers have proposed a new reaction mechanism for Mn-salen catalyzed epoxidation including metallaoxetane and radical intermediates in tandem (Scheme 6) [32]: Olefins approach the oxo–metal bond from its side probably along the pathway **a** (Fig. 6), directing their bulky and π-electron-rich substituent away from the C3′-substituent to minimize steric and electronic repulsions. Though coordination of the olefin to the metal ion followed by oxygen atom insertion with rotation may provide four possible metallaoxetane intermediates (**28**, **29**,**30**, and **31**) [56], the pathway to the intermediates **29** and **30** (counter-clockwise rotation) is considered to be disfavored by the steric repulsion between the olefinic substituent and the C3′-substituent. The salen ligand in the resulting metallaoxetanes (**28** and **31**) takes a bent form in which one of the phenolic oxygen atom coordinates at axial site, since the oxygen and carbon atoms of the metallaoxetane coordinate at axial and equatorial coordination site, respectively. That the salen ligand takes a bent form seems to be justifiable, since most of the salen ligands in Cr-, Fe-, and Co-salen complexes



Scheme 6. The oxo Mn-salen complex (**23**, Fig. 6, M = Mn) is viewed from its right-hand side and the left-half of the complex is omitted for clarification. Donor ligand attached to Mn-salen and oxo Mn-salen complexes is also omitted for clarification.

having a divalent ligand such as oxalate or acetylacetonate take a bent form [60]. The unstable metallaoxetane (**28**) bearing a radical stabilizing group on the carbon proximal to manganese ion rapidly collapses to a radical intermediate (**32**), while the metallaoxetane (**31**) bearing alkyl group at the carbon proximal to manganese ion is slowly transformed into epoxides as discussed above. Thus enantioface selection performed in metallaoxetane formation step is further enhanced by the second diastereoselective metallaoxetane cleavage process, since the metallaoxetane formation is reversible [56]. Accordingly, olefins bearing a radical stabilizing group such as aryl, alkenyl, or alkynyl group show excellent levels of enantioselectivity. In the case of alkyl-substituted olefins, both the intermediates (**28** and **31**) collapse slowly to the corresponding epoxides and diastereoselective cleavage can not be expected. Thus, olefins bearing only alkyl substituents show moderate enantioselectivity [32].

Quite recently, the polymer-bound optically active Mn-salen complex was synthesized and applied to the epoxidation of conjugated olefins. However, the enantioselectivity observed with this complex was considerably lower than that with monomeric Mn-salen complex [61]. The unexpectedly low enantioselectivity was attributed to steric reasons and/or certain microenvironmental effect associated with the macromolecular system [61], but the restriction on the structural change of the salen ligand by anchoring to a solid polymer may also influence on the enantioselectivity.

4. Conclusion

Studies on salen-catalyzed epoxidation started in the search for stereoselective oxo transfer reaction comparable to the biological process catalyzed by cytochrome P-450 and a fairly good level of enantioselectivity has been achieved in the epoxidation of conjugated olefins to date, though further improvement is required in the epoxidation of simple olefins. Many new findings obtained in these studies also shed light on the mechanisms of oxo transfer reaction and of asymmetric induction. However, our knowledge on the structures of catalytically active oxo Mn-salen species and their reactivity is still immature and further study is required for the future development of Mn-salen catalyzed oxo transfer reaction.

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