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Unique asymmetric catalysis of *cis*-β metal complexes of salen and its related Schiff-base ligands

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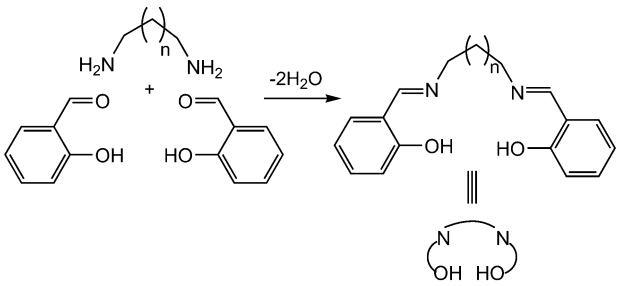
Complexes of chiral salen and its related tetradentate Schiff-base ligands adopt three different configurations, *trans, cis*-α and *cis*-β. Of these complexes, *trans*-complexes have been widely used as catalysts for various asymmetric reactions. However, recent studies have disclosed that *cis*-β metallosalen and its related complexes show unique asymmetric catalyses that cannot be achieved by *trans*-metallosalen complexes. The present article summarizes generation of *cis*-β metallosalen and its related complexes, their structural features, and their application to asymmetric syntheses.

1 Introduction

Aldehyde and primary amine condense to give Schiff-base. When aldehyde is a salicylaldehyde derivative and amine is a diamine derivative, the condensation produces N_2O_2-Schiff-base compound (**1**) that may form complexes with a variety of metals with elimination of two protons (Scheme 1). Hereafter, the deprotonated and metal-bound compound **1** is referred to as N_2O_2-Schiff base ligand. As various achiral and chiral salicylaldehyde and diamine derivatives are commercially or synthetically available, a wide variety of metal-N_2O_2-Schiff-base complexes have been synthesized at will. These complexes adopt mostly octahedral configuration, albeit with a few exceptions (*vide* infra), and they usually carry two ancillary ligands (X and Y).[1,2] Tetradentate Schiff-base ligands **1** are dianionic, and the ancillary ligands are anionic or neutral, depending on the valency of the central metal ion. When the complex bears a non-coordinating counter ion such as PF_6^- and ClO_4^-, a neutral ligand such as water or solvent is coordinated instead to the metal ion. The geometry of the N_2O_2-Schiff-base ligand depends on the structure of the diamine unit and the nature of the ancillary ligand and that of the central metal ion, as described in the following section. Needless to say, catalysis of metal-N_2O_2-Schiff-base complex is expected to vary with its configuration and the configuration can be regulated by adjusting the above-mentioned factors suitably. Despite this, the study on catalysis of metal-N_2O_2-Schiff-base complexes has been carried out exclusively with their *trans*-isomers **2**, however, recent studies disclosed that *cis*-β-isomers show unique catalyses that cannot be attained with other metal complexes. This account focuses on the chemistry of *cis*-β-metal-N_2O_2-Schiff-base complexes, which is a fertile but little explored territory with great potential. Although N_2O_2-Schiff-base compounds have been prepared from various diamines such as ethylene- ($n = 0$), propylene- ($n = 1$), tetramethylene-diamines ($n = 2$), and binaphthyldiamine, only metal complexes of *N*,*N*′-ethylenebis(salicylideneiminato) (hereafter denoted as salen ligand), *N*,*N*′-binaphthylbis(salicylideneiminato) and their related ligands are dealt with in this article, because studies on the catalysis of the complexes of other tetradentate Schiff-base ligands are limited.



Scheme 1

2 Conformations of metallosalen complexes

Studies of the catalysis of metallosalen complexes were undertaken with the complexes of first-row transition metals, such as chromium,[3] cobalt,[4,5] vanadium,[6] and manganese.[7] Due to the presence of two sp^3 carbons at the diamine unit, metallosalen complexes are endowed with high structural pliability, and metallosalen complexes exist as several stereoisomers

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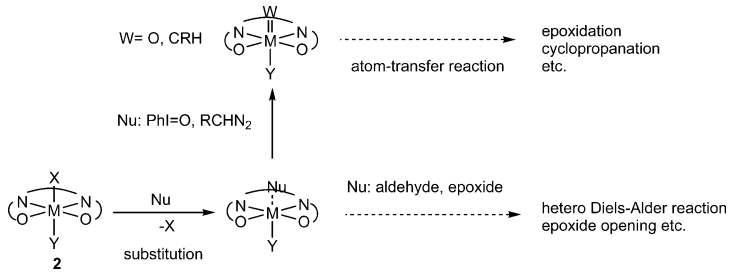


Scheme 2

(configurational and conformational isomers). Metallosalen complexes can take three configurations (*trans*, *cis*-β, and *cis*-α): two ancillary ligands occupy the apical positions in *trans*-isomer **2**, one equatorial and one apical positions in *cis*-β-isomer, and two equatorial positions in *cis*-α-isomer (Scheme 1). The above metallosalen complexes adopt *trans*-configuration when the ancillary ligands are monodentate. In general, the ancillary ligands of a *trans*-metallosalen complex can be readily substituted with a nucleophilic compound (Nu) that might be a reagent or a substrate (Scheme 2). The coordinated Nu is activated by the Lewis acidic metal ion or further transformed into an active species, depending on the nature of the nucleophilic compound. For example, treatment of a suitable metallosalen complex with Nu such as iodosylbenzene and diazo ester, generates an active oxene- (W = O) and a carbene–metal complex (W = CRH), respectively, *via* the corresponding addition compounds. These active species can undergo oxygen-, or carbon-atom transfer to a variety of substrates.[8,9] On the other hand, when the coordinated Nu is an aldehyde or an epoxide, it undergoes hetero Diels–Alder reaction or epoxide-opening reaction, respectively. Thus, various reactions can be catalyzed by *trans*-metallosalen complexes. If the salen ligand is chiral, these reactions proceed in an enantioselective manner (*vide infra*).

Due to the rotational freedom of the ethylenediamine unit, a *trans*-metallosalen complex can adopt several conformations. Typical conformations, stepped and umbrella, of a *trans*-metallosalen complex are shown in Fig. 1 (R = H). The conformation of the complex strongly depends on the conformation of a five-membered chelate ring formed between the metal ion and the ethylenediamine unit. The chelate ring can adopt half-chair, envelope and their distorted conformers. The chelate rings of *trans*-metallosalen complexes adopting stepped conformation generally exist in half-chair conformer and that of the complexes adopting symmetric umbrella conformation exist in envelope conformer (*vide infra*).[2,10] It is, however, noteworthy that most chiral metallosalen complexes substituted at C8 and C8′ adopt stepped conformation, because the half-chair conformer allows both substituents to take stable quasi-equatorial orientation (conformer **A**) (Fig. 1, R ≠ H).[10] Not only the chirality of C8 and C8′ carbons but also the conformation of the complex affects asymmetric induction by the metallosalen complex, as shown by the following examples. An achiral stepped metallosalen complex exists as an equilibrated mixture of enantiomeric conformers (**A** and **B**) (Fig. 1, R = H). The enantiomeric conformers become diastereomeric, when the apical ligand is replaced with a chiral ligand, and the equilibrium shifts to one side. Thus, an achiral metallosalen complex can serve as asymmetric catalyst in the presence of a chiral ligand. Indeed, an achiral manganese(salen) complex bearing bulky *tert*-butyl group at C3 and C3′ was found to serve as an effective catalyst for asymmetric epoxidation in the presence of an optically active ligand.[10]

Although the subject of this article is asymmetric catalysis of *cis*-β metallosalen complexes, asymmetric catalysis of *trans*-metallosalen complexes is briefly summarized for comparison.

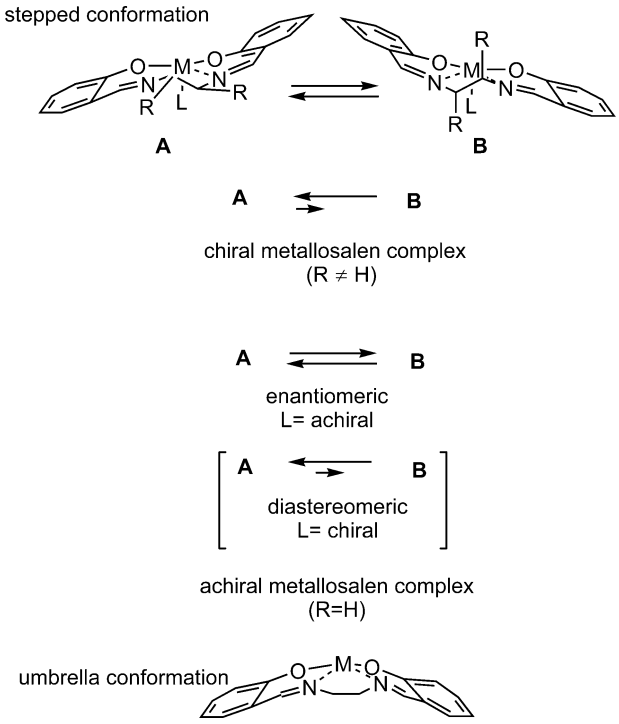


Fig. 1 Typical conformation of *trans*-metallosalen complexes.

Study on asymmetric catalysis of chiral metallosalen complexes began in the late seventies. In 1978, Nakamura and Otsuka *et al.*[5] reported asymmetric cyclopropanation using a chiral cobalt(salen) complex as the catalyst. More recently, Fujita *et al.* reported asymmetric sulfoxidation using a vanadium-(salen) complex as the catalyst.[6] Furthermore, based on the seminal study on the catalysis of manganese(salen) complexes by Kochi *et al.*,[7] Jacobsen *et al.* and Katsuki *et al.* independently disclosed that chiral manganese(salen) complexes are efficient catalysts for asymmetric epoxidation in 1990.[8,9] Highly asymmetric induction and catalytic performance of manganese(salen) complexes shown by these studies set off extensive studies on metallosalen-catalyzed asymmetric reactions. As a result, a wide variety of metallosalen complexes have so far been introduced and used as catalysts for various asymmetric reactions such as epoxidation, aziridination, cyclopropanation, C-H hydroxylation, C-H amination, sulfoxidation, sulfimidation, Diels–Alder reaction, epoxide-opening, Michael addition, *etc.*[9,11,12] Except for a few complexes, chiral metallosalen complexes used for these asymmetric reactions have several common structural features: (i) presence of substituents at C8 and C8′, (ii) presence of bulky and/or chiral substituents at C3 and C3′, and (iii) C_2-symmetric structure.[8,9] Two representative manganese(salen) complexes are shown in Fig. 2. Configurations of some chiral manganese-, cobalt-, chromium-, and ruthenium(salen) complexes used for these reactions have been determined unambiguously to be *trans* by X-ray diffraction analysis.[7,8,10,13] The proposed mechanism

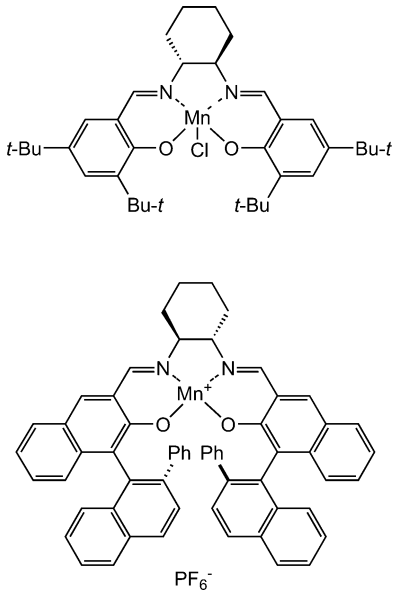
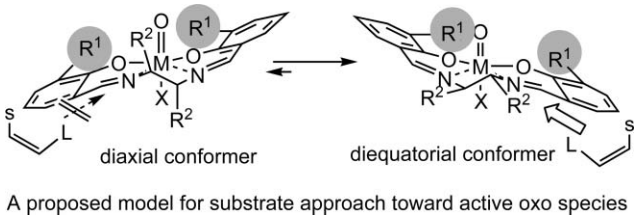


Fig. 2 Representative structures of chiral manganese(salen) complexes.

for asymmetric induction by these *trans*-metallosalen complexes is explained by taking epoxidation using a chiral manganese(salen) complex as an example (Scheme 3).[8,9] A putative intermediate, an oxo Mn(salen) complex, has been



Scheme 3

considered to adopt a stepped conformation. Although the oxo Mn-complex can adopt diaxial and diequatorial conformers, the latter one is far more favored (*vide supra*) and olefins can approach the oxo Mn-complex from the downwardly-bent benzene ring, directing their bulkier substituent (L) away from the C3-substituent (R^1), without causing steric repulsion with the C8-substituent. Thus, epoxidation occurs enantiofaceselectively.[10] Needless to say, ease of generation of an active species and its reactivity are dependent on the metal ion used, and use of a suitable metal ion in accordance with the reaction is essential for achieving high enantioselectivity and good chemical yield. For detailed discussion about catalysis of *trans*-metallosalen complexes, see appropriate reviews.[9–12]

A *trans*-metallosalen complex provides coordination site(s) available for a monodentate-reagent or substrate, but it is not necessarily a suitable catalyst, when a reagent or substrate is multidentate. As described in Scheme 1, a metallosalen complex can adopt another octahedral *cis*-β configuration, in which two ancillary ligands are *cis* to each other. The *cis*-β complex (**3**) can be a good catalyst for the reaction with a bidentate substrate or reagent (Fig. 3). Besides, some metallosalen complexes preferentially adopt *cis*-β configuration with or without a bidentate ancillary ligand (X–Y): (i) complexes of some second or third-row transition metals such as zirconium, hafnium[14] and ruthenium can take *cis*-β configuration without a bidentate ligand (*vide infra*). (ii) Chiral metallosalen complexes having a substituent at C7 and C7′ adopt *cis*-β configuration to avoid the steric repulsion between the substituents at C7 and C8 (and C7′ and C8′). It is noteworthy that metal

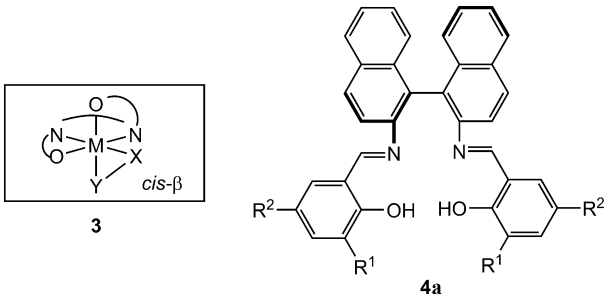
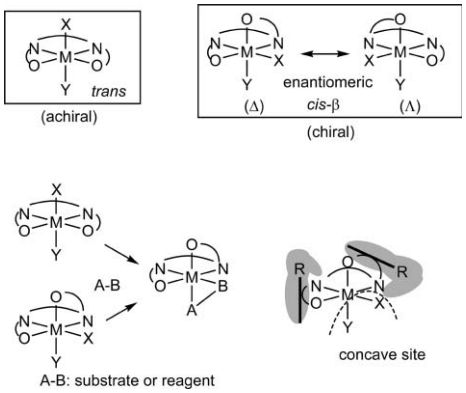


Fig. 3 Structure of *cis*-β-complexes coordinated by a bidentate ligand and an example of tetradentate Schiff base ligand derived from axially chiral diamine.

complexes of tetradentate Schiff-base ligands derived from axially chiral diamines such as 2,2′-diamino-1,1′-binaphthyl (for **4a**) and 2,2′-diamino-6,6′-dimethyl-1,1′-biphenyl (for **4b**) can also adopt *cis*-β configuration.[15,16] These *cis*-β complexes also serve as catalysts for the reactions of bidentate substrates or reagents. Some complexes of the ligand derived from 2,2′-diamino-6,6′-dimethyl-1,1′-biphenyl can take another *cis* complex, *cis*-α complex, but they have not been dealt with in this article, because their use in asymmetric reaction is limited.[16]

The fact that the first coordination sphere of those complexes is chiral is another feature of these *cis*-β complexes beneficial to construction of an asymmetric reaction site and a highly sophisticated asymmetric reaction site might be constructed by combining the chiralities of the first coordination sphere and of the substituent(s) on the basal salen ligand. For example, a suitably substituted *cis*-β ligand provides a unique reaction site of concave-type that should enable chiral recognition (Scheme 4). Thus, a chiral *cis*-β metallosalen complex and its



Scheme 4

related complexes are expected to show unique catalysis which cannot be attained with a *trans*-metallosalen complex. The scope of metallosalen-catalyzed reactions should be further expanded by using *cis*-β-metallosalen complexes as catalysts. As discussed above, a *trans*-metallosalen complex can be transformed into the corresponding *cis*-β complex, when it is exposed to a bidentate ligand. Therefore, it is important to consider the possibility that *trans*-metallosalen complexes participate in a reaction with *cis*-β conformation, when the substrate or reagent can be a bidentate ligand. In the following sections are described representative examples of the *cis*-β-complexes of salen and its related Schiff-base ligands and their characteristic catalysis.

3 Representative examples of *cis*-β-complexes of salen and its related Schiff-base ligands

The *cis*-β-structure of a metallosalen complex is usually verified by spectroscopic analyses. If the isomer gives a single crystal,

X-ray analysis is the most reliable method for determination of its structure. The structure of an isomer in solution can be determined by NMR analysis. For example, signals for its imino protons are useful for the diagnosis of the *cis*-β structure: two protons at the imino carbons in a C_1-symmetric *cis*-β-isomer show different chemical shifts, while the chemical shifts of those protons in a C_2-symmetric *trans*-isomer are identical. The IR and CD spectra can also be used for diagnosing *cis*-β-structure. The *cis*-β-structure of metallosalen complexes in the following discussions has been determined mostly by X-ray and/or NMR analyses. For the determination of the structure of each complex, refer to the original paper cited. In this section are given some typical examples of *cis*-β-metallosalen complexes and complexes of N_2O_2-binaphthyl and its related Schiff-base ligands. Examples are categorized based on the central metal.

Simple achiral Co(salen) complexes adopt *trans*-configuration with stepped or umbrella ligand-conformation[2] and chiral Co(salen) complexes mostly with planar or slightly stepped ligand-conformation.[12] Co(salen) complexes, however, take *cis*-β-configuration, when they are treated with a bidentate ligand such as acetylacetonate (acac) and oxalate (ox). For example, a Co^{III}(salen)(acac) complex has been determined to approximate octahedral configuration and the salen ligand to adopt *cis*-β-configuration unambiguously by X-ray analysis (Fig. 4).[17] It is noteworthy that, even if a *trans*-metallosalen

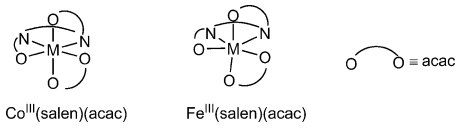


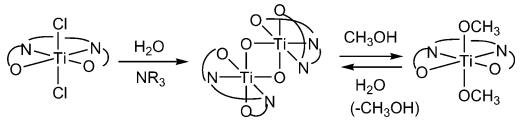
Fig. 4 The structures of the first coordination spheres of Co^{III}(salen)-(acac) and Fe^{III}(salen)(acac).

complex is achiral, the resulting *cis*-β complex is chiral (Scheme 3). Okawa *et al.* have reported that a Co^{III}(salen) complex gives Λ-*cis*-β-Co^{III}(salen) in preference to Δ-*cis*-β-Co^{III}(salen)(*l*-moba), when the Co^{III} complex is treated with H(*l*-moba) in methanol (*l*-moba = *l*-menthyloxy-3-benzoylacetone).[18]

Achiral non-substituted Fe^{III}(salen) complexes also adopt *trans*-configuration with stepped or umbrella conformation,[2] and Fe^{III}(salen) complexes bearing a bidentate ligand like acac or catecholate adopt *cis*-β-configuration.[19,20] It is noteworthy that the structures of these *cis*-β isomers are distorted-octahedral, while the structure of the Co^{III}(salen)(acac) complex is approximately octahedral (Fig. 4). This difference in structures of *cis*-β-Co^{III}- and Fe^{III}(salen) complexes has been attributed to difference in ligand field stabilization energy: the stabilization energy of the Co^{III}-complex is larger than that of the Fe^{III}-complex.[20] Later, Morgenstern-Badarau *et al.* has claimed that the distorted-octahedral structure of the Fe^{III}(salen)(ox) complex is attributed to the constraint by oxalate chelation, based on X-ray analysis:[21] the $Fe–O_{(ax)}$ bond is slightly (*ca.* 0.08 Å) longer than the $Fe–O_{(eq)}$ bond being *trans* to N atom.

Simple achiral and chiral Cr^{III}(salen)X complexes (X = Cl, N_3, *etc.*,) adopt *trans*-configuration.[4,12] Along with other metallosalen complexes, *trans*-Cr^{III}(salen)X complexes are converted into the corresponding *cis*-β-complexes in the presence of a bidentate ligand. For example, [Hpip]Cr^{III}(salen)(ox) (Hpip = piperidium ion) takes octahedral configuration and its salen ligand adopts *cis*-β geometry.[22] X-ray analysis of an ox-bridged dinuclear Cr^{III}(salen)(ox)Cu(acpy) complex (acpy = *N*-acetylacetonylidene-*N*-(2-pyridylethyl)aminate) has also demonstrated that the geometry of the salen ligand is non-planar *cis*-β geometry.[23]

Ti(salen)X_2 complexes (X = Cl, OR, alkyl) usually adopt *trans*-configuration. However, the Ti^{IV}(salen)Cl_2 complex is converted into the corresponding di-μ-oxo Ti(salen) complex, in which the bridging di-μ-oxo moiety serves as a bidentate ligand and the salen ligand adopts *cis*-β geometry, upon its treatment with H_2O in the presence of an amine (Scheme 5).[24]

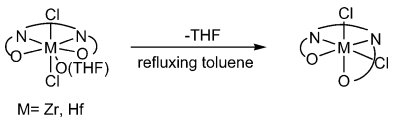


Scheme 5

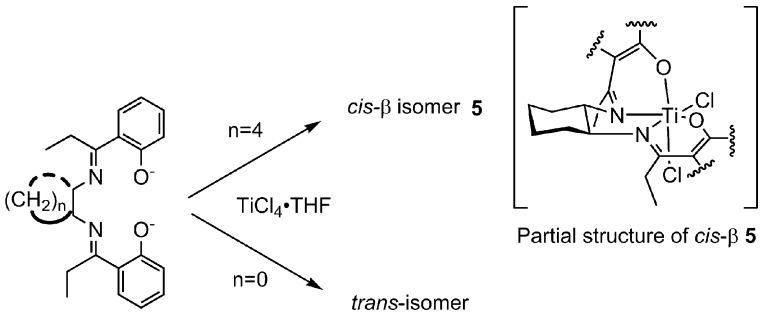
On the other hand, the di-μ-oxo Ti complex is converted into a *trans*-Ti(salen)$(OMe)_2$ complex, upon being dissolved in methanol.[25] These results suggest that configuration of the Ti(salen) complex can be controlled by choosing reaction conditions suitably.

cis-β Complexes so far discussed carry an ancillary bidentate ligand. However, Ti(salen) complex **5** possessing substituents at C7, C7′, C8, and C8′ autonomously adopts *cis*-β configuration to avoid steric repulsion between substituents at C7 (C7′) and C8 (C8′) (Scheme 6). This result indicates that a metallosalen complex can adopt an otherwise unstable *cis*-β complex, when substantial steric repulsion is caused by introducing substituents on the salen ligand. The Ti(salen) complex only substituted at C7 and C7′ adopts *trans*-configuration.[26]

Different from the salen complexes of first-row transition metals discussed above, Zr- and Hf(salen) or -(acen) complexes adopt seven-coordinated pentagonal bipyramidal configuration.[14] One solvent molecule such as tetrahydrofuran is coordinated to the metal ions at their equatorial position (Scheme 7). Upon heating in toluene, however, the complexes



Scheme 7



Scheme 6

lose tetrahydrofuran and adopt octahedral complexes with chlorides in *cis* positions. This indicates that *cis*-β Zr- and Hf-complexes are more stable than the corresponding *trans*-complexes, when the complexes take octahedral configuration.

On the other hand, Ru(salen) complexes mostly adopt *trans*-configuration with an almost planar or a distorted stepped ligand conformation to various extents, depending on the structure of the salen ligand and the nature of the apical ligand.[10,13,27] However, it has recently been reported that treatment of a cationic *trans*-Ru(salen)(NO)(H_2O) complex with acetonitrile gives the corresponding *trans*-Ru(salen)-(NO)(CH_3CN) complex which, however, is slowly converted into its *cis*-β isomer.[28] This means that the *cis*-β isomer bearing CH_3CN as the ligand is thermodynamically more stable than the corresponding *trans*-isomer. It is noteworthy that no formation of a pentagonal bipyramidal Ru-complex which violates the 18-electron rule has been reported.

In contrast with metallosalen complexes, complexes of N_2O_2-tetradentate Schiff-base ligands bearing an axially chiral diamine such as **4** prefer *cis*-configuration to *trans*-configuration, because the seven-membered chelate ring formed from a metal ion and the diamine takes a twist-boat conformation due to the large dihedral angle between the two naphthalene rings. Depending on the central metal ion, the dihedral angle ranges from 74° to 88°. As described before, *cis*-β configuration is chiral (Δ or Λ), and the configuration of the complex is Δ, when the ligand carries an (*R*)-binaphthyl unit (Fig. 5).[15] Ligand **4b** bearing 2,2′-diamino-6,6′-dimethylbiphenyl

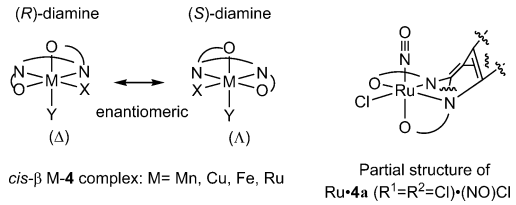


Fig. 5 The first coordination spheres of metal-**4** complexes.

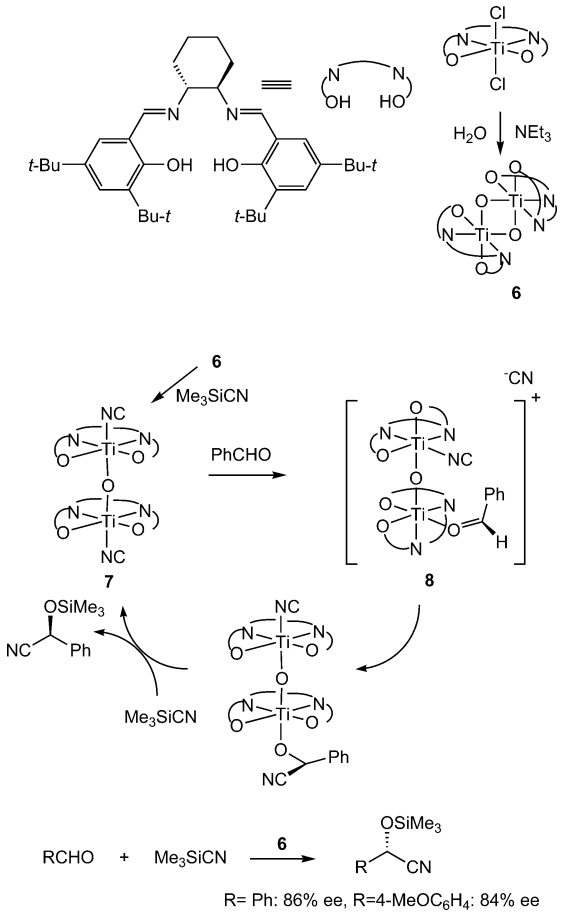
as a diamine unit is structurally similar to **4a** but is a little more flexible. Thus, complexes of **4b** can adopt either configuration, *cis*-β *and cis*-α (see, Fig. 1), depending on the central metal ion.[16] For example, the zirconium complex adopts *cis*-α configuration, while the ruthenium complex adopts *cis*-β configuration.

4 Typical asymmetric reactions using *cis*-β complex as catalyst

Some asymmetric reactions that clarify unique catalysis of *cis*-β complex are described in this section.

Asymmetric addition of trimethylsilyl cyanide to aldehydes

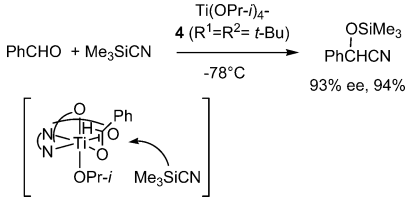
Cyanohydrin and its trialkylsilyl derivatives are highly useful building blocks and many transition metal-mediated asymmetric hydrocyanation or silyl cyanation reactions have been reported. Chiral transition metal complexes serve as Lewis acids and activate aldehydes with differentiation of their enantiofaces. Thus, cyanide attacks aldehydes enantioface-selectively to give optically active cyanohydrins. Di-μ-oxo Ti(salen) complex **6** has been found to show a highly efficient and unique catalysis for asymmetric silyl cyanation (Scheme 8), making the most of the characteristic of the Ti(salen) complex that *trans*- and *cis*-β-isomers can be interconverted easily (*vide supra*).[24] The treatment of **6** with Me_3SiCN gives *trans*-μ-oxo Ti(cyanide) complex **7**. A weakly bound apical cyanide ligand in **7** is displaced with aldehyde to give *cis*-β-μ-oxo Ti complex **8** and the aldehyde and the cyanide are placed close to each other



Scheme 8

and react in an intramolecular fashion with enantioselectivity higher than 80% ee even at room temperature. This intramolecular trimethylsilyl cyanation becomes possible only when a *cis*-β salen complex participates in the reaction.

The *cis*-β Ti-**4a** ($R^1 = R^2 = t$-Bu) complex also serves as an efficient catalyst for timethylsilyl cyanation.[29] High enantioselectivity of 93% ee has been attained in the reaction of benzaldehyde at −78 °C (Scheme 9). In this reaction, aldehyde



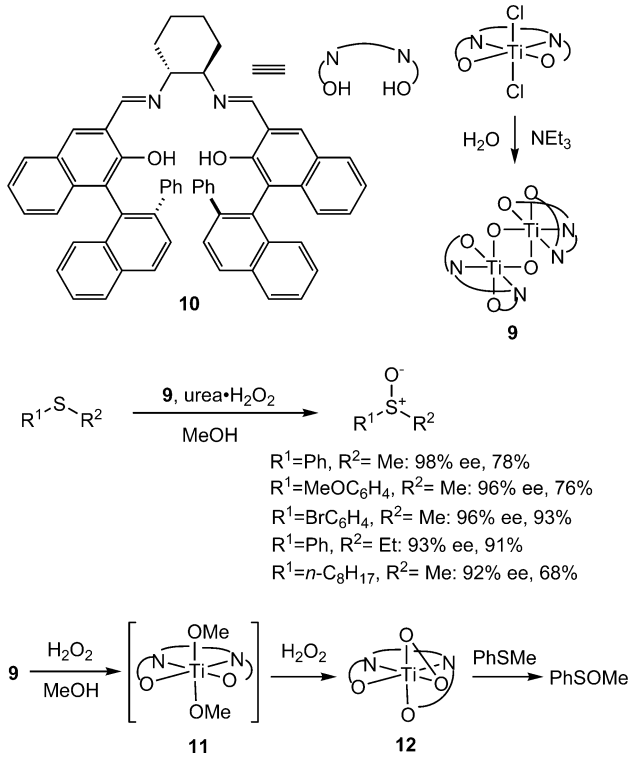
Scheme 9

is coordinated to the Ti ion and trimethylsilyl cyanide attacks the aldehyde from the sterically less-hindered side in an intermolecular fashion.

Asymmetric sulfoxidation

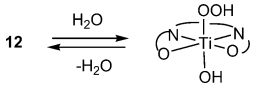
Asymmetric sulfoxidation is the most convenient method for preparation of optically active sulfoxides and many excellent methods have so far been developed for this purpose. Still, there is room for improvement in atom efficiency of the terminal oxidant. Thus, sulfoxidation with hydrogen peroxide as the terminal oxidant has recently received wide attention and several promising catalysts like vanadium-Schiff base and metallosalen complexes have been reported.[30] Of these

complexes, di-μ-oxo Ti complex **9** bearing the salen ligand **10** is a highly efficient catalyst for sulfoxidation using urea·hydrogen peroxide adduct as the oxidant (Scheme 10).[31] The complex **9**



Scheme 10

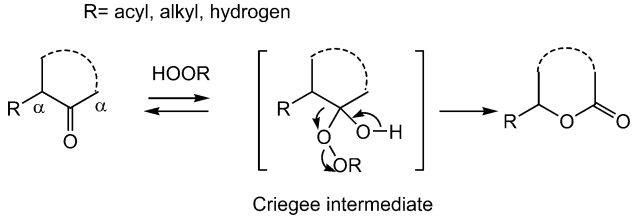
can be prepared from the corresponding Ti(salen)Cl_2 complex, according to Belokon's procedure (Scheme 5). This sulfoxidation is carried out in methanol and, as described in Scheme 5, the complex **9** is first converted into the corresponding *trans*-Ti(salen)$(OMe)_2$ complex **11**. However, alkoxide exchange on the titanium ion is rapid and hydrogen peroxide, a bidentate ligand, interacts with **11** to give *cis*-β peroxo Ti(salen) complex **12**, in which the peroxo moiety is placed in the chiral concave site (see also Scheme 4). Thus, oxidation of a wide range of sulfides proceeds with high enantioselectivity.[31] The participation of *cis*-β peroxo complex **12** has been established by ^{1}H NMR study. Though commercial 30% hydrogen peroxide is more desirable as the oxidant than the urea·hydrogen peroxide adduct, use of the former somewhat reduces enantioselectivity, presumably due to the fact that water brings about the opening of the peroxo ring, albeit slowly, to give a *trans*-hydroperoxo hydroxo Ti(salen) complex (Scheme 11). Its hydroperoxo moiety should have high conformational freedom, and it catalyzes less selective sulfoxidation.



Scheme 11

Asymmetric Baeyer–Villiger oxidation

Carbonyl compounds are converted into ester or lactone by treatment with peroxide such as peracid and hydrogen peroxide (Scheme 12). This conversion known as Baeyer–Villiger oxidation is of high synthetic value and has been widely used in various organic syntheses. The reaction starts with nucleophilic attack of a peroxy compound to the carbonyl compound giving



Scheme 12

a Criegee intermediate, followed by [1,2]migration of the α-carbon to an electrophilic oxygen in the peroxy moiety. Of the two α-carbons, the more substituted one is more nucleophilic and migrates preferentially. Thus, the migratory aptitude of α-carbon is in the order of methine > methylene > methyl. Baeyer–Villiger oxidation was discovered more than one hundred years ago, but the study of its asymmetric version started recently. In 1994, Bolm and Strukul independently reported metal-catalyzed asymmetric Baeyer–Villiger oxidation.[30] Since then, several metal catalysts have been introduced but there is considerable room for improvement in enantioselectivity. On the other hand, biological Baeyer–Villiger oxidation proceeds in an excellent, mostly complete, enantioselective manner. The rate-determining step in Baeyer–Villiger oxidation is migration of the α-carbon to the peroxy oxygen. Therefore, control of the migration is essential for achieving enantioselectivity. The migration proceeds only when the σ-orbital of the C–C bond between α and carbonyl carbons can overlap sufficiently with the σ*-orbital of the peroxy O–O bond. Consequently, regulating the conformation of the peroxy moiety to allow σ*-orbital to interact selectively with one of the two σ-orbitals is indispensable for highly stereoselective Baeyer–Villiger oxidation. Especially, the selective σ-σ* interaction is crucial for asymmetric Baeyer–Villiger oxidation of prochiral ketones, in which the migratory aptitude of both α-carbons is equal. In biological Baeyer–Villiger oxidations, the Criegee intermediate has been considered to form a hydrogen bond with the protein around the active site, so that its peroxy conformation is regulated to allow selective σ,σ*-interaction (Fig. 6).

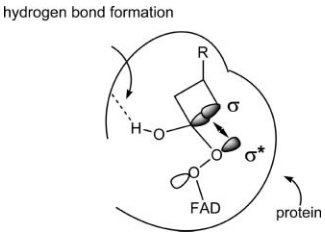
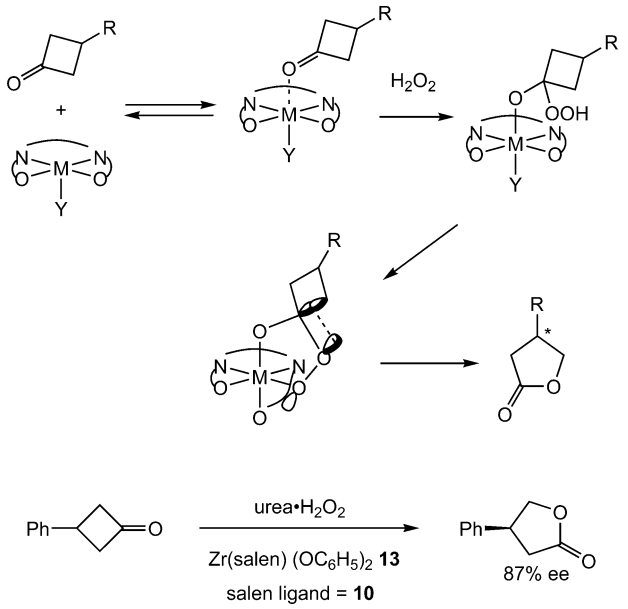


Fig. 6 Schematic model for enzymatic control of stereoelectronic demand in Baeyer–Villiger oxidation.

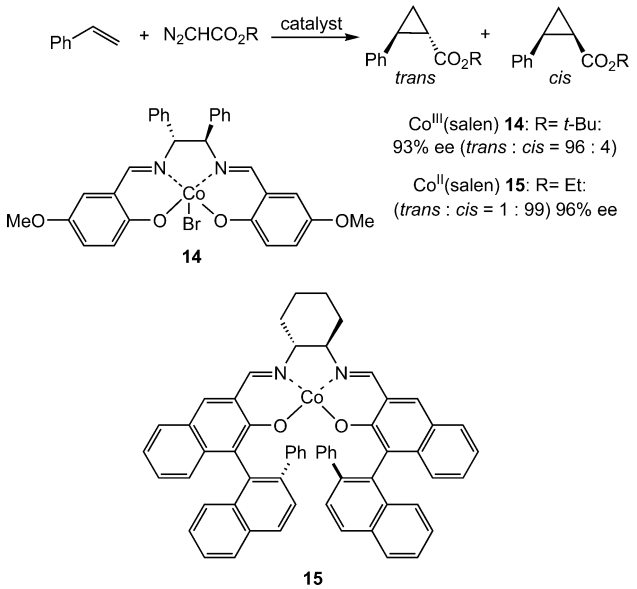
The Criegee intermediate generated in Scheme 12 is a bidentate ligand when the peroxy compound is hydrogen peroxide (R = H). Thus, the intermediate can make a chelate with *cis*-β metallosalen complexes and its rearrangement is expected to occur in an enantioselective manner if the conformation of the chelate is regulated to enable selective σ,σ*-interaction by the chirality of the *cis*-β salen ligand (Scheme 13). Indeed, it was found that the *cis*-β Co(salen) complex was a superior catalyst for asymmetric Baeyer–Villiger oxidation to the *trans*-Co(salen) complex.[32] Furthermore, Zr(salen) complex **13** bearing **10** as the ligand was revealed to be a better catalyst for the oxidation.[33] In view of the nature of the Zr(salen) complex that tends to adopt *cis*-β configuration, this result is acceptable (*vide supra*).



Scheme 13

Asymmetric cyclopropanation

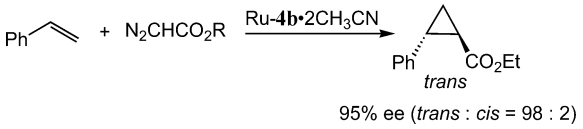
As described in Scheme 2, several metallosalen complexes can react with a diazo compound, especially α-diazo ketone or ester, to give the corresponding carbene–metal complexes that undergo cyclopropanation. Thus, much effort has been directed toward asymmetric cyclopropanation using chiral *trans*-metallosalen complexes as catalysts. As a result, both *trans*- and *cis*-selective cyclopropanation reactions have been achieved in highly enantioselective manner with the metallosalen catalysts suitably designed by tuning valency of the metal ion, *trans*-effect of the apical ligand, electronic nature of the substituent(s) on the salen ligand and structure of the salen ligand, respectively (Scheme 14).[11] Furthermore, a ruthenium



Scheme 14

complex of **4b** (Ru-**4b**·$2CH_3CN$) that adopts *cis*-β structure has been reported to provide a unique reaction site for *trans*-selective cyclopropanation (Scheme 15).[34]

Based on DFT calculation, the ester group of the carbene intermediate derived from an α-diazo ester has been considered to coordinate with the ruthenium ion (Fig. 7).[34] Consequently,



Scheme 15

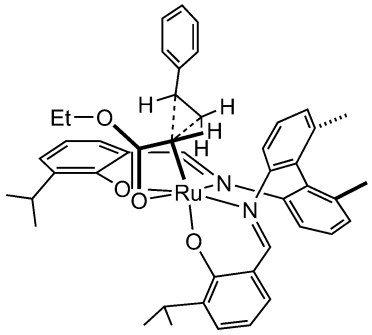
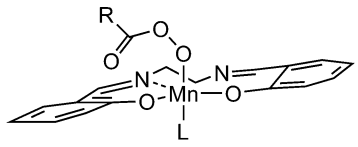


Fig. 7 Proposed structure for Carbene-Ru-**4b** intermediate.

the conformation of the carbene moiety is fixed to block one enantioface of the moiety by a benzene ring of the biphenyl group. The orientation of the incoming olefin is also controlled by the ligand **4b** to show *trans*-selectivity. Thus, the cyclopropanation proceeds in a highly enantio- and *trans*-selective manner. It is noteworthy that the face control by chelate formation is possible only when a *cis*-β metal complex is used as the catalyst.

Finally, it should be mentioned that the structure of some metallosalen complexes bearing a latent bidentate ligand might be necessary to be reviewed. Mn(salen)-mediated asymmetric epoxidation using a mixture of molecular oxygen and aldehyde originally introduced by Mukaiyama and Yamada has been proposed to proceed *via* a *trans*-acylperoxo Mn(salen) species,[35] but recent studies, especially a density functional study, have suggested participation of *cis*-β-acylperoxo Mn(salen) species (**C** or **D**) (Fig. 8).[36,37]



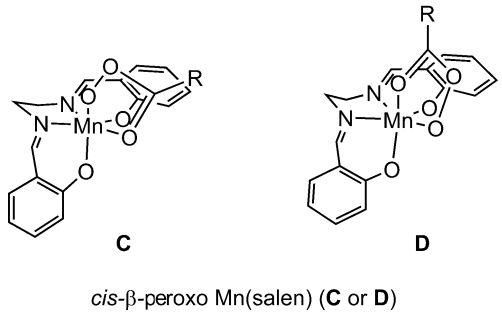


Fig. 8 Possible conformations for acylperoxo Mn(salen) species.

Conclusion

In this article, we have described that *cis*-β metallosalen and its related complexes provide efficient reaction sites for the asymmetric reaction of a bidentate substrate or reagent. Moreover, a metallosalen complex of *cis*-β geometry can be

ligated by a bidentate apical ligand such as μ-oxo ligand and provides another useful reaction site for the reaction between the precoordinating substrate and reagent, as exemplified by asymmetric silyl cyanation using a di-μ-oxo Ti(salen) complex as catalyst. These reaction sites cannot be provided by *trans*-metallosalen complexes and the use of *cis*-β metallosalen and its related complexes have expanded the scope of metallosalen and its related chemistry. Furthermore, it deserves comment that this type of reaction site should be used for the reaction between a precoordinating substrate and reagent: the precoordinated substrate and reagent are expected to react intramolecularly in a highly asymmetric atmosphere. There are many examples of the reaction between precoordinated substrate and reagent. Thus, we can expect further future extension of this area of chemistry. Some metallosalen complexes, $Mo(salen)(O)_2$ and $Ru(salen)(CO)_2$, bearing a specific ancillary ligand are known to adopt *cis*-β configuration, but they were not dealt with in this article, because little study has been done regarding their asymmetric catalysis. Finally, an unexplored but promising aspect of the catalytic performance of metallosalen complexes is briefly described. Two principal functions of catalyst are strict molecular recognition and satisfaction of stereoelectronic demand of a desired reaction. Some excellent catalysts can exercise well two functions simultaneously. However, most catalysts do one function well but another function less efficiently. On the other hand, metallosalen complexes can adopt two different configurations, *trans* and *cis*-β, which are interchangeable by appropriately choosing reaction conditions. As we described in this review, *trans*-metallosalen complexes can distinguish enantio-faces or -toposes effectively, while some *cis*-β metallosalen complexes can regulate orbital-interaction suitably for a desired reaction. These results suggest a possibility of designing a new catalyst that can exercise molecular recognition with some configuration and enable the orbital interaction necessary for the reaction with different configuration. It is known that many enzymes accomplish their sophisticated biocatalysis with appropriate change of their structures. Creation of such enzyme-like new catalysts is a subject of future investigation in the study of asymmetric catalysis of not only metallosalen complexes but also other structurally flexible complexes.

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