Asymmetric catalysis of metal complexes with non-planar ONNO ligands: salen, salalen and salan

Kazuhiro Matsumoto, Bunnai Saito and Tsutomu Katsuki*

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Chiral metal (M)–salen complexes are one of the most versatile asymmetric catalysts and the catalysis of *trans*-M(salen) complexes has been well cultivated. On the other hand, non-planar *cis*-β M(salen) complexes were recently found to show unique asymmetric catalysis that cannot be attained by *trans*-M(salen) complexes. Moreover, related non-planar M(salalen) and M(salan) complexes were also found to exert unprecedented asymmetric catalysis. This Feature Article summarizes the seminal studies on asymmetric catalysis of non-planar M(ONNO) complexes, full utilization of which will provide marked improvement in asymmetric synthesis.

1 Introduction

In the late 20th century, chemists witnessed remarkable advancement of catalytic asymmetric synthesis. Significant efforts have been devoted to the development of efficient catalysts and enormous numbers of metal- and organo-catalysts have been developed.[1] Among them, chiral metal–salen complexes have been established as one of the most versatile catalysts, due to the following features: ease of ligand preparation, high complexation ability of the ligand with a wide variety of metal (M) ions, and their structural diversity, which endow them with various catalytic performances.[2]

In an octahedral M(salen) complex, there are three potential configurations, *trans* (planar), *cis*-α and *cis*-β (Fig. 1). For the relatively rigid planarity of the salen skeleton, the ligand of *trans*-geometry is more stable than that of *cis*-geometry and the complexes usually adopt *trans*-configuration. For the same reason, salen ligands adopt a planar geometry in other types of coordination, such as square pyramidal complexes. Indeed, in most of the known M(salen) complexes, salen ligands have an almost planar geometry; despite this structural feature of the ligand, a chiral and/or sterically bulky group can be introduced nearby their donor atom(s) and set a highly asymmetric atmosphere around the metal center. Thus, the well-designed *trans*-M(salen) complexes serve as efficient catalysts for various asymmetric reactions such as atom-transfer reactions (epoxidation, aziridination, cyclopropanation, *etc.*), epoxide ring-opening reaction, 1,4-addition and so on.[2]

On the other hand, it is well known that M(salen) complexes can adopt a *cis*-configuration under certain conditions; *e.g.*, the coordination of a bidentate ligand forces a M(salen) complex to adopt a *cis*-configuration.[3] Although there are two *cis*-configurations (α and β), the *cis*-β one is generally more

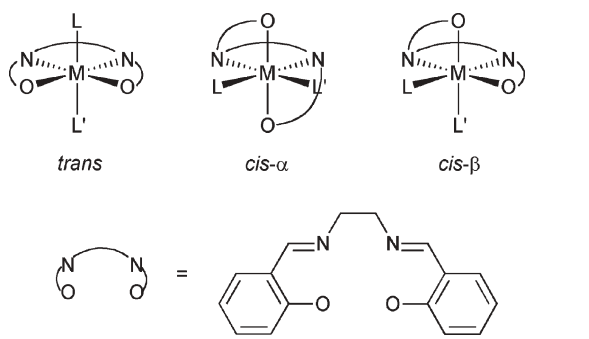


Fig. 1 Three potential configurations for an octahedral M(salen) complex.

Department of Chemistry, Faculty of Science, Graduate School, Kyushu University, Hakozaki, Higashi-ku, Fukuoka, 812-8581, Japan. E-mail: katsuscc@mbox.kyushu-u.ac.jp; Fax: +81 92 642 2607

Kazuhiro Matsumoto was born in Hiroshima, Japan, in 1980. He received his BS (in 2003) and MS (in 2005) in chemistry from Kyushu University. He is now a doctoral student under the supervision of Professor T. Katsuki, and a JSPS Research Fellow from 2005.

Bunnai Saito was born in Fukuoka, Japan in 1978. He obtained his PhD in 2006 from Kyushu University under the supervision of Professor Tsutomu Katsuki. He is currently working as a JSPS Postdoctoral fellow for Research Abroad with Professor Gregory C. Fu at Massachusetts Institute of Technology. His research interests are focused on metal catalyzed asymmetric synthesis and cross coupling reactions.

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

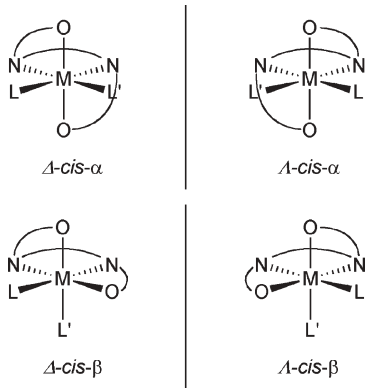


Fig. 2 Mirror-image isomers for *cis*-M(salen) complexes.

stable than the *cis*-α one and few stable *cis*-α M(salen) complexes are known.[4] Different from *trans*-complexes, the metal atom of *cis*-complexes is chiral (Δ or Λ) and the complexes are expected to be efficient asymmetric catalysts (Fig. 2). In addition, *cis*-complexes have two coordination sites in a *cis*-position. This is an inherent feature of *cis*-complexes and they can capture a bidentate ligand (ligand refers substrate or reagent) or two monodentate ligands. It is distinctive that, in *cis*-β M(salen) complexes, the ligands (L and L′) are non-equivalent and they differ in steric and electronic nature. These characteristics of *cis*-β M(salen) complexes offer advantages for constructing asymmetric catalysts. Actually, use of these characteristics of *cis*-β complexes remarkably expanded the scope of M(salen)-catalyzed asymmetric reactions. Moreover, the studies of *cis*-β M(salen) complexes set off those of the related complexes, half-reduced salen (salalen) and reduced salen (salan) complexes, which also enabled unprecedented asymmetric reactions (Fig. 3).

In this article, we describe the recent development of asymmetric catalysis of *cis*-β M(salen) and the related complexes, mainly with a central focus on the issues of our own interests.

2 Asymmetric syntheses with *cis*-β M(salen) complexes as catalysts

cis-β M(salen) complexes are mainly provided by two approaches, use of dynamic ligand-structure change and introduction of a torsional subunit to salen ligand.[5] In the former approach, a *trans* M(salen) complex is transformed into a *cis*-β complex by coordination of a bidentate substrate or reactant. On the other hand, a typical example of the latter is the substitution of the ethylenediamine moiety with an axially chiral binaphthyldiamine one. In the strict sense, the latter complexes are not M(salen) complexes, but they are dealt with as such in this article because they are *cis*-β metal complexes of an ONNO-tetradentate ligand. For convenience' sake, they will be also referred to as M(salen) complexes.

In this section, we emphasize a focus on asymmetric catalyses of *cis*-β M(salen) complexes prepared in the above approaches.

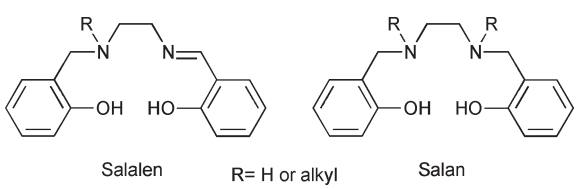
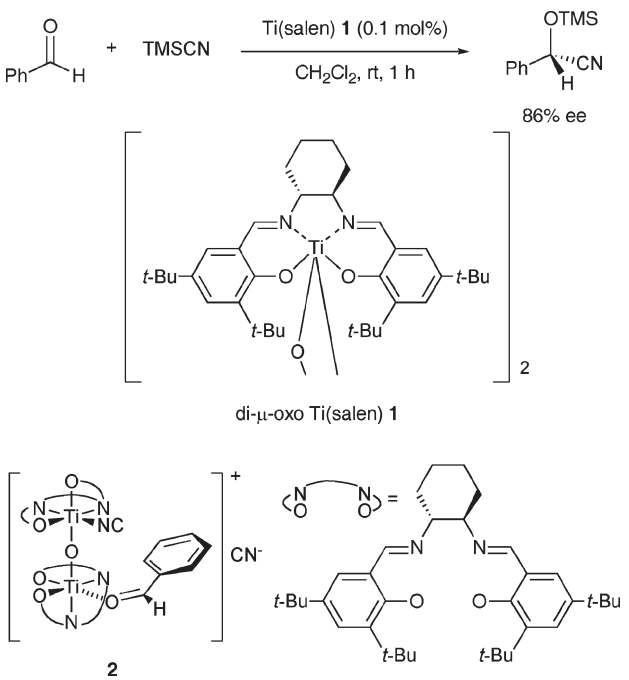


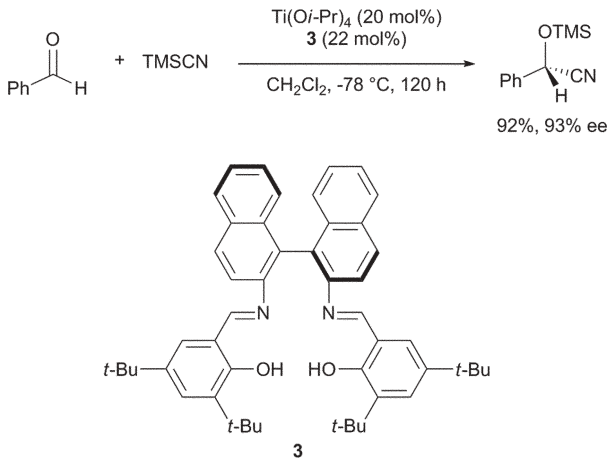
Fig. 3 Salalen and salan ligands.

2.1 Titanium-catalyzed asymmetric addition of cyanide to carbonyl compounds

Asymmetric addition of cyanide to carbonyl compounds is of considerable importance since the resultant cyanohydrins can be easily converted to various functional groups. Thus, much effort has been directed toward the development of this reaction and many effective catalysts have been introduced to date.[6] Among them, Ti(salen) complexes are highly promising catalysts for this reaction. Recently, two different types of *cis*-β Ti(salen) complex were found to serve as efficient catalysts. One is the di-μ-oxo Ti(salen) complex **1** where two bridging oxygen atoms are bound to the two titanium centers in a rectangular fashion (Scheme 1)[7] and the other is an *in situ* generated titanium complex of salen-ligand **3** derived from axially chiral 2,2′-diamino-1,1′-binaphthyl (Scheme 2).[8] Although high enantioselectivity has been obtained in both cases, di-μ-oxo Ti(salen) complex **1** is an attractive catalyst also from the viewpoint of substrate applicability and catalyst turnover. From the detailed kinetic analysis, the active species is considered to be *cis*-β-μ-oxo Ti-complex **2**, in which the salen ligands adopt *cis*-β conformation and the coordinating aldehyde and cyanide are placed in proximity.[9] Thus, the cyanide is transferred intramolecularly to the aldehyde in a highly enantioselective manner. It is noteworthy that both the cyanide and aldehyde are coordinated to the respective chiral titanium ions. This unique catalytic cycle is possible only when the salen ligand adopts a *cis*-β conformation. Moreover, complex **1** can be successfully used as the catalyst for addition



Scheme 1 Asymmetric cyanation of aldehydes catalyzed by di-μ-oxo Ti(salen) complex **1**.



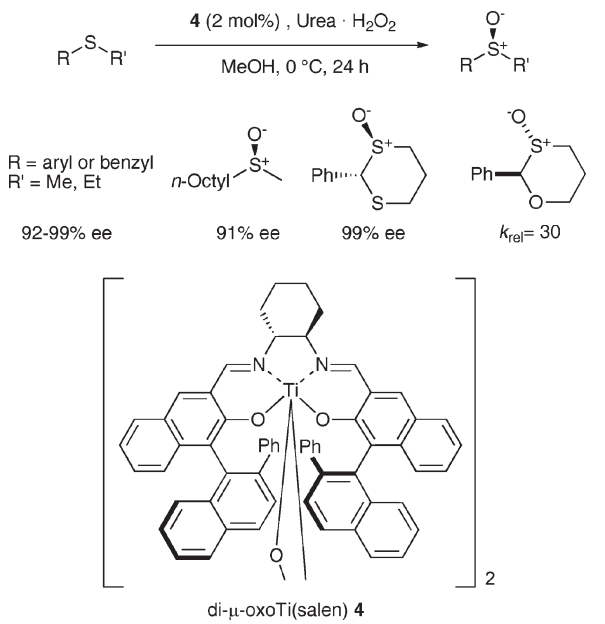
Scheme 2 Asymmetric addition of cyanide to aldehydes catalyzed by C_2-symmetric Schiff base system.

of TMSCN to aromatic ketones and ee values of up to 70% ee were obtained.[10]

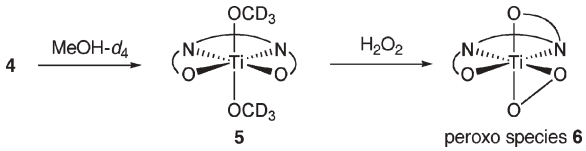
2.2 Titanium-catalyzed asymmetric sulfoxidation

Catalytic asymmetric sulfoxidation is the most straightforward and efficient method for preparation of optically active sulfoxides and a number of excellent asymmetric catalysts have been introduced for this reaction.[11] Taking into consideration the recent demand for an environmentally benign process, sulfoxidation with hydrogen peroxide as oxidant is a current topic of interest and several promising catalysts such as vanadium–Schiff base complexes have been introduced.[12]

Although di-μ-oxo Ti(salen) complexes **1** and **4** served as efficient catalysts for sulfoxidation using urea hydrogen peroxide adduct (UHP) as the terminal oxidant, complex **4** showed much superior enantioselectivity to **1** (Scheme 3).[13]



Scheme 3 Asymmetric oxidation of sulfides catalyzed by di-μ-oxo Ti(salen) complex **4**.



Scheme 4 A possible pathway for generating active peroxo species **6**.

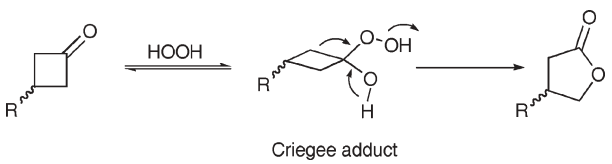
Not only aryl alkyl sulfides but also dialkyl sulfides are a good substrate for the oxidation and high to excellent enantioselectivity is achieved. Complex **4** also catalyzes oxidative desymmetrization of dithianes and oxidative kinetic resolution of racemic 1,3-oxathianes with high stereoselectivity.

^{1}H NMR study has disclosed that complex **4** is first converted to the corresponding *trans*-Ti(salen)$(OMe)_2$ complex **5**, coordination of hydrogen peroxide to which gives a *cis*-β peroxo species **6** that undergoes sulfoxidation (Scheme 4). The high asymmetric induction by complex **4** is attributed to participation of the peroxo species **6** of a concave shape that is formed by the *cis*-β salen ligand,[5] to which sulfides can approach only from one side due to the presence of a bulky 2-phenynaphthyl group.

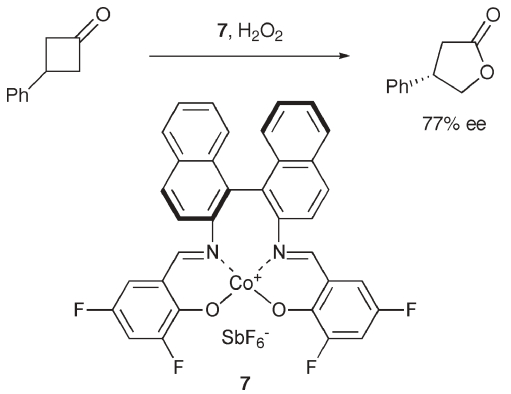
2.3 Asymmetric Baeyer–Villiger oxidation

Baeyer–Villiger oxidation of carbonyl compounds into esters (or lactones) has been widely used in organic synthesis.[14] This reaction consists of two steps: nucleophilic addition of a peroxy compound to a carbonyl compound giving a Criegee intermediate, and the subsequent migration of the α-carbon to the peroxy oxygen atom (Scheme 5). The rate-determining step of the reaction is the migration, which proceeds only when the C_α–C_{CO} bond is antiperiplanar to the O–O bond. Thus, regulating the conformation of the peroxy moiety is indispensable for achieving high enantioselectivity in the migration. For this purpose, a *cis*-β Co(salen) complex **7** was designed as the catalyst with the expectation that the Criegee intermediate could be coordinated to the cobalt ion as a bidentate ligand with a controlled conformation.[15] Indeed, the asymmetric Baeyer–Villiger oxidation using complex **7** proceeded with good enantioselectivity, while a *trans*-Co(salen) complex bearing the cyclohexanediamine unit gave the racemic product (Scheme 6).

Finally, highly enantiospecific and enantiomer-differentiating Baeyer–Villiger oxidations were achieved when Zr(salen)-$(OPh)_2$ complex **8** was used as the catalyst (Scheme 7).[16] While complex **8** has a *trans* geometry in the resting state, it tends to adopt a *cis*-β configuration and is easily chelated by a Criegee intermediate, partly due to d^0 electron configuration of the zirconium ion. This is the first example of chemocatalytic Baeyer–Villiger oxidation whereby a fast-reacting isomer gives an abnormal lactone stereospecifically. This phenomenon is



Scheme 5 Baeyer–Villiger oxidation.



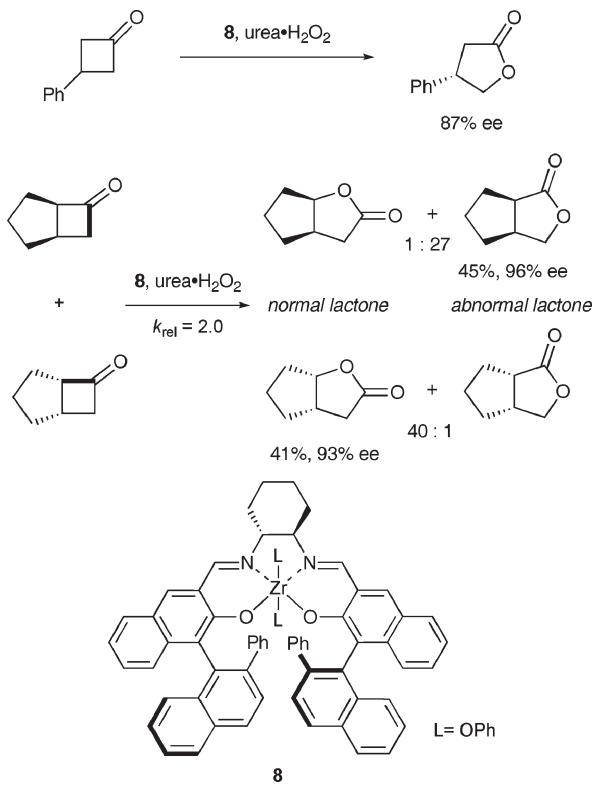
Scheme 6 Cobalt-catalyzed asymmetric Baeyer–Villiger oxidation.

opposite to the migratory aptitude (methine > methylene > methyl) well-known in Baeyer–Villiger reaction.

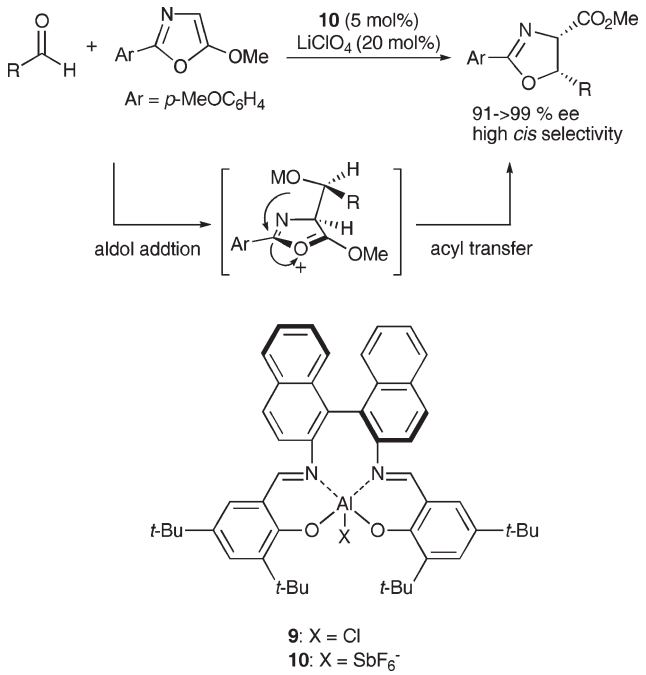
2.4 Aluminium-catalyzed asymmetric aldol type reaction

Optically active 2-oxazoline-4-carboxylates are important building blocks as masked β-hydroxy amino acids and several catalysts have been introduced for enantioselective synthesis of *trans*- and *cis*-2-oxazoline-4-carboxylates.[17] From the synthetic viewpoint, the *cis*-selective method is more convenient, since the *cis* compounds can be isomerized to their *trans* counterparts by base treatment.

Although the trigonal bipyramidal Al(salen) chloride complex **9** was catalytically less efficient, the corresponding cationic complex **10** was found to catalyze the addition of oxazole derivatives with aldehydes and the subsequent acyl



Scheme 7 Zirconium-catalyzed asymmetric Baeyer–Villiger oxidation.



Scheme 8 Al-catalyzed enantioselective aldol type reaction of aldehydes and 5-alkoxyoxazoles.

transfer to afford the desired *cis*-2-oxazoline-4-carboxylates in high diastereo- and enantio-selectivity (Scheme 8).[18] From X-ray crystal structure analysis, it was found that the complex exhibits a distorted octahedral Δ-*cis*-β configuration with two water molecules *cis*-coordinated to the aluminium ion.

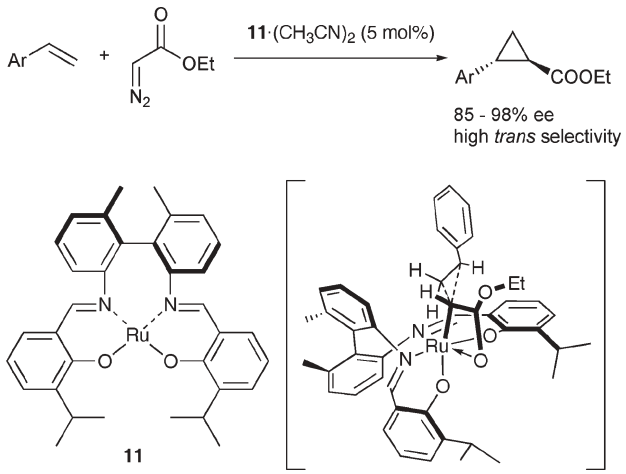
2.5 Ruthenium-catalyzed asymmetric cyclopropanation

Although considerable efforts have been made to develop new methods for the enantioselective synthesis of cyclopropanes, the most versatile and useful method is probably the metal-catalyzed enantioselective cyclopropanation of olefins with diazo compounds. M(salen) complexes are a competent catalyst for this type of reaction and both highly *trans*- and *cis*-selective cyclopropanation reactions have been achieved with suitably designed M(salen) complexes.[19] Of them, *cis*-β Ru(salen) complex **11** served as a highly efficient catalyst for *trans*- and enantioselective cyclopropanation (Scheme 9). Based on the DFT calculation, the carbenoid species formed by the addition of ethyl diazoacetate adopts a chelated structure where both carbene carbon and carbonyl oxygen atoms are bound to the ruthenium ion. Due to the *trans* influence, the species with the carbene carbon atom *trans* to the phenolate is much more reactive than that with the carbene *trans* to the imine. Eventually, the origin of this selectivity was attributed to the chiral-at-metal nature of the catalyst.

3 Asymmetric syntheses with M(salalen) complexes

3.1 Synthesis of an optically active salalen ligand

As described above, *cis*-β metallosalen complexes show unique asymmetric catalysis that could not be obtained by the *trans* complexes. On the other hand, in 2004, Kol and co-workers reported an achiral hybrid salan/salen tetradentate



Scheme 9 Asymmetric cyclopropanation catalyzed by ruthenium complex **11**·$(CH_3CN)_2$.

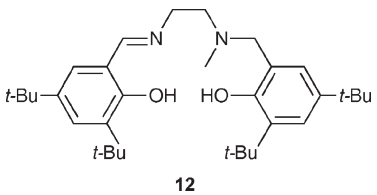
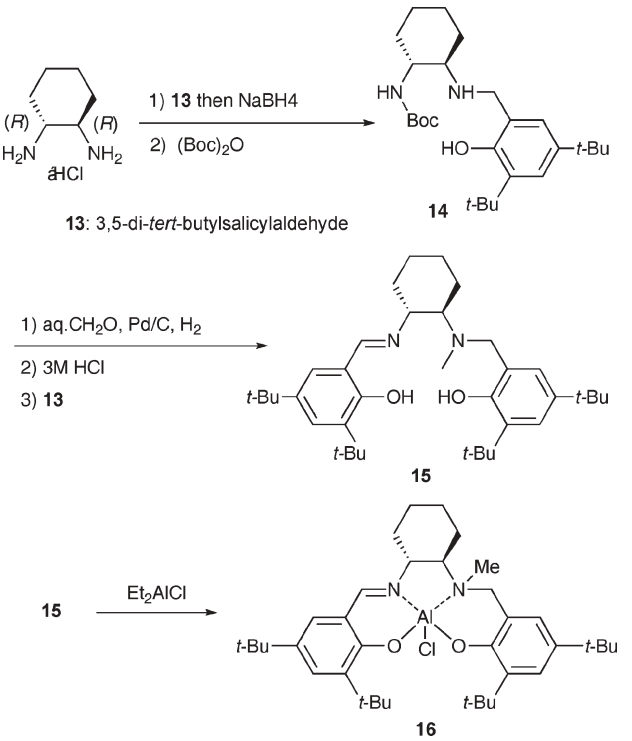


Fig. 4 Kol's salalen ligand.

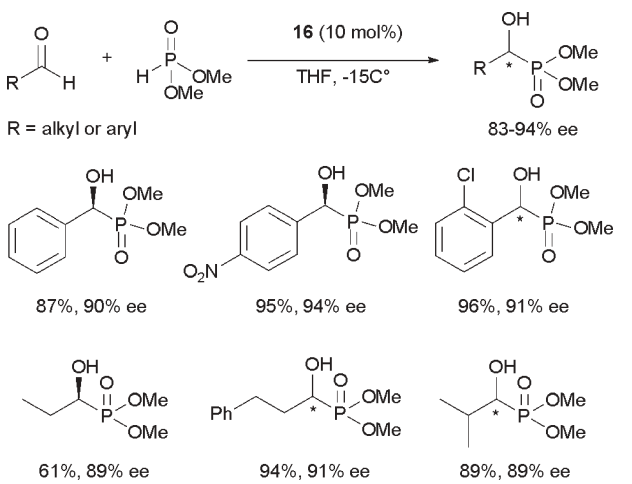


Scheme 10 Synthesis of optically active *N*-methyl salalen ligand **15** and Al(salalen) complex **16**.

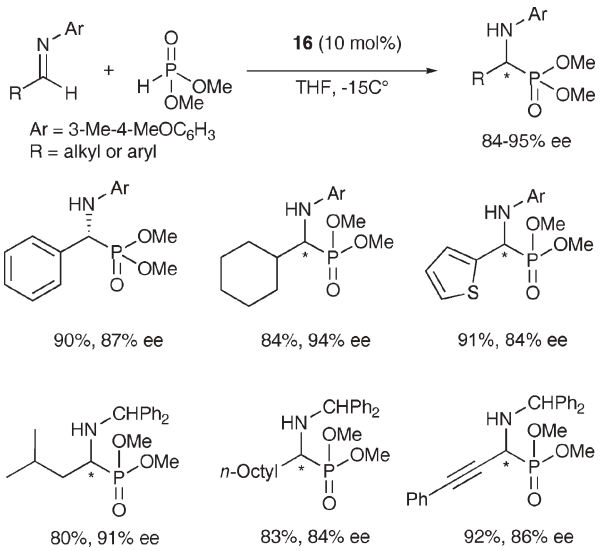
[ONN(Me)O]-type ligand **12** (salalen ligand) (Fig. 4).[20] Interestingly, X-ray crystal structure analysis has exhibited that the corresponding zirconium and titanium complexes adopt *cis*-β configuration. Therefore, we were intrigued with the asymmetric induction by an optically active salalen complex. Although Kol's reported procedure turned out to be ineffective for the synthesis of the optically active salalen ligand, the modular synthetic approach afforded the desired salalen ligand **15** in high yield (Scheme 10).[21] Furthermore, the corresponding penta-coordinated aluminium complex **16** was prepared in order to clarify the intrinsic asymmetry-inducing ability of this unique ligand. From X-ray crystal structure analysis, it has been disclosed that the complex adopts a distorted trigonal bipyramidal configuration and the methyl group on the nitrogen atom bound to the aluminium ion is *syn* to the chloro ligand.

3.2 Al(salalen)-catalyzed asymmetric hydrophosphonylation of aldehydes and aldimines

Various chiral α-hydroxy and amino phosphonic acids are biologically active compounds that are attracting increased interest in pharmaceutical and medicinal chemistry. The addition of phosphites to aldehydes (or aldimines), namely hydrophosphonylation (Pudovic reaction), is one of the most straightforward approaches toward the synthesis of α-hydroxy (or amino) phosphonates and several asymmetric catalysts have been introduced for this reaction.[22,23] For achieving high enantioselectivity, use of an asymmetric metal complex possessing two vacant sites which are simultaneously coordinated by both the substrate and phosphite is considered to be desirable. Since complex **16** carries an open vacant site together with the chloro ligand in a *cis*-position, we expected that the chloro ligand would be replaced by nucleophilic phosphite preferentially and an aldehyde (or aldimine) also coordinates with the aluminium ion, allowing the hydrophosphonylation to proceed in an intramolecular manner. Indeed, complex **16** served as an efficient catalyst for asymmetric hydrophosphonylation of aldehydes: not only aromatic but also aliphatic aldehydes were successfully converted to the corresponding α-hydroxy phosphonates in good yields with high enantioselectivity. Moreover, high enantioselectivities were attained in the reaction of aliphatic aldehydes, irrespective of the presence or absence of branching (Scheme 11).[21] In



Scheme 11 Al-catalyzed asymmetric hydrophosphonylation of aldehydes.



Scheme 12 Al-catalyzed asymmetric hydrophosphonylation of aldimines.

addition, the same complex catalyzed the hydrophosphonylation of various aldimines.[24] However, enantioselectivity and yields of these reactions were affected by an N-protecting group of aldimines and the use of a suitable group was crucial for achieving high enantioselectivity: a 4-methoxy-3-methylphenyl group is the best such group for aromatic and α-branched aliphatic aldimines, while a diphenylmethyl group is the best for non-branched aliphatic aldimines (Scheme 12).[24]

Transition state models for the reactions have been proposed as described in Fig. 5, based on the stereochemistry of the reaction and the relationship between the enantiomeric excesses of complex **16** and of the product. The geometry of aldimines bearing a bulky N-group is usually *E* and the reactions of aldehyde and aldimines should show the sense of enantioface selection opposite to each other. Indeed the

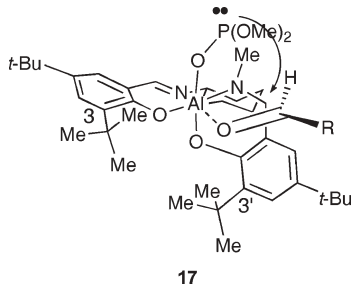


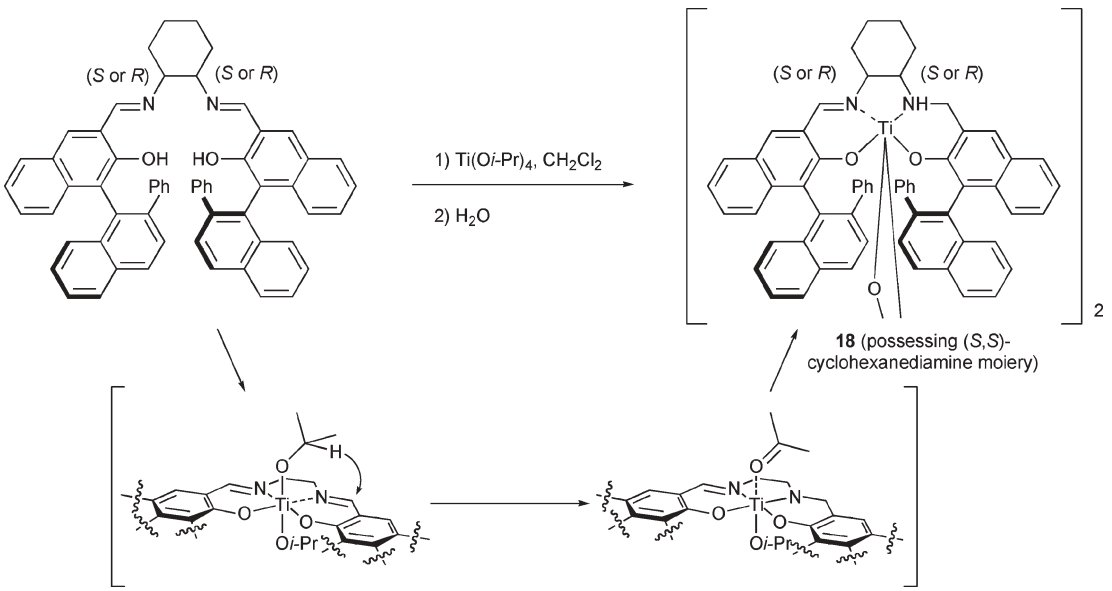
Fig. 5 Proposed transition state model for Al(salalen)-catalyzed hydrophosphonylation.

configurations of the products derived from benzaldehyde and benzaldines are *S* and *R*, respectively (Schemes 11 and 12).[21,24]

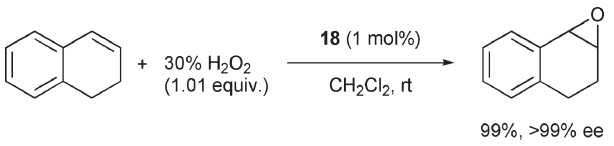
3.3 Ti(salalen)-catalyzed asymmetric epoxidation

As mentioned above, the di-μ-oxo Ti(salen) complex **4** is an efficient catalyst for oxidation of sulfides. However, the *cis*-β peroxo species **6** derived from **4** was found to be not active enough for epoxidation of olefins.

In parallel with the study of the Al(salalen) complex, the present authors developed another approach to M(salalen) complexes: the transformation of Ti(salen) complexes to the corresponding di-μ-oxo Ti(salalen) complexes *via* Meerwein–Ponndorf–Verley reduction (Scheme 13).[25] The transformation was carried out in the following sequence: (i) mixing Ti(O*i*-Pr)$_4$ and the salen ligand to give the Ti(salen)(O*i*-Pr)$_2$ complex that spontaneously underwent intramolecular Meerwein–Ponndorf–Verley reduction of one of the imines with the apical isopropoxide group on the titanium atom, and (ii) the treatment of the resultant complex with water to give the di-μ-oxo Ti(salalen) complex **18**. In the complex, salalen ligands adopt a *cis*-β conformation and the absolute configuration of the metal centers was proved to be (Λ,Λ) from the X-ray crystal structure.



Scheme 13 Synthesis of di-μ-oxo Ti(salalen) complex **18** *via* Meerwein–Ponndorf–Verley reduction.



Scheme 14 Asymmetric epoxidation of 1,2-dihydronaphthalene with Ti(salalen) complex **18**.

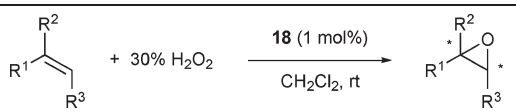
Ti(salalen) complex **18** could catalyze oxidations of not only sulfides but also olefins. What is the most striking is the results obtained for epoxidation. The epoxidation of 1,2-dihydronaphthalene in the presence of 1.01 equivalent of aqueous hydrogen peroxide proceeded with almost complete enantioselectivity in a quantitative yield (Scheme 14).[25,26] Various cyclic and acyclic conjugated olefins were converted to the corresponding epoxides with high to excellent enantioselectivity (Table 1). Even in the epoxidation of styrene, 93% ee was achieved. The epoxidation was stereospecific and no formation of *trans*-epoxides was observed in the epoxidation of *cis*-olefins. Moreover, a non-activated olefin, 1-octene, was also a good substrate for the epoxidation and 82% ee was obtained.

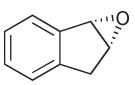
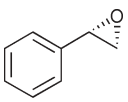
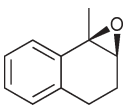
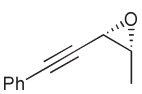
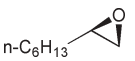
Although the reaction mechanism is unclear, the peroxotitanium species activated by an intramolecular hydrogen bonding with the amino proton has been proposed to be the active species, on consideration of the difference in catalysis between Ti(salen) and Ti(salalen) complexes (Fig. 6).

4 Asymmetric syntheses with M(salan) complexes

M(salan) complexes are tetrahydro derivatives of M(salen) complexes and they are structurally more flexible than M(salen) and M(salalen) complexes. Salan ligands bind to a metal atom in a non-planar arrangement, and a *cis*-α configuration is dominant in an octahedral coordination.

Table 1 Asymmetric epoxidation of olefins catalyzed by Ti(salalen) complex **18**



Entry	Product	Yield (%)	Ee (%)
1[a]		87	99
2		90	93
3		75	95
4[a]		64	88
5[b]		70	82

[a] AcOEt was used as the solvent. [b] 3 mol% of **18** was used.

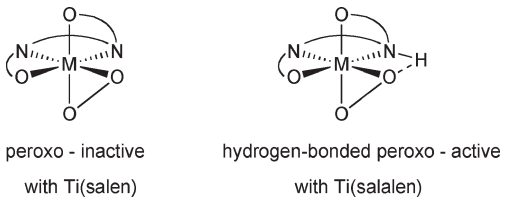


Fig. 6 Proposed active species for the titanium-catalyzed oxidation and their activity for epoxidation.

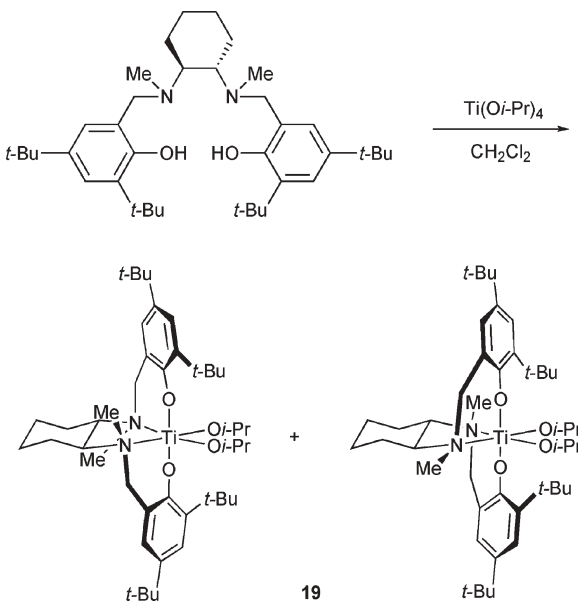
However, the *cis*-α isomer can be equilibrated with the *cis*-β and *trans* isomers. Thus, due to difficulty in control of their stereochemistry, there are few reports on asymmetric catalysis of M(salan) complexes. For example, Walsh and co-workers reported that treatment of Ti(O*i*-Pr)$_4$ with a salan ligand gave a diastereomeric mixture **19** (Scheme 15).[27] However, M(salan) complexes should be as attractive as other analogues, if their stereochemistry can somehow be regulated.

4.1 Vanadium-catalyzed asymmetric oxidation of sulfides

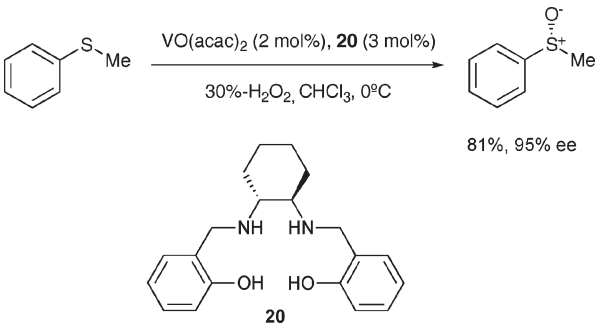
Vanadium-tridentate Schiff base complexes are efficient catalysts for oxidation of sulfides using aqueous hydrogen peroxide, and good to high enantioselectivity has been achieved with several Schiff base complexes as catalyst.[12] On the other hand, Zhu and co-workers have reported that asymmetric sulfoxidation with a VO(acac)$_2$/salan **20**/aqueous hydrogen peroxide system shows high enantioselectivity, though good substrates are limited to some alkyl aryl sulfides and *tert*-butyl alkyl sulfides (Scheme 16).[28] It is noteworthy that a VO(acac)$_2$/corresponding salen/aqueous hydrogen peroxide system is much less effective for asymmetric sulfoxidation.

4.2 Titanium-catalyzed asymmetric epoxidation

As mentioned above, Ti(salalen) complex **18** is an excellent catalyst for asymmetric epoxidation of olefins. However, the



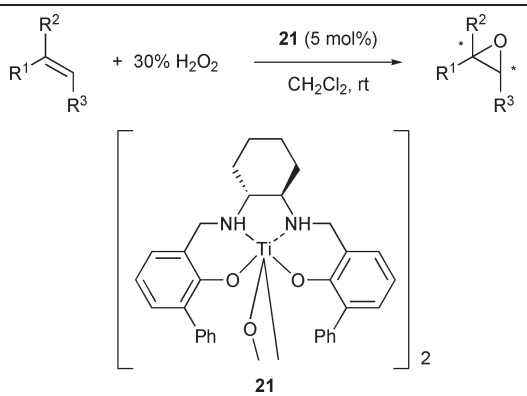
Scheme 15 An example of structure diversity in M(salan) complexes.



Scheme 16 V(salan)-catalyzed asymmetric sulfoxidation.

complex has a complicated and unique structure and its synthetic method *via* Meerwein–Ponndorf–Verley reduction is specific for this particular complex and poorly applicable to other salalen complexes. We had proposed that the active species in the epoxidation is a peroxotitanium complex hydrogen-bonding with the amine proton (*vide supra*). According to this proposal, we focused attention on Ti(salan) complexes. It was expected that the peroxo species derived from the complexes could also be activated by an intramolecular hydrogen bonding with the amine proton. In addition, preparation of salan ligands and their titanium complexes is simple.

Table 2 Asymmetric epoxidation of olefins catalyzed by Ti(salan) complex **21**



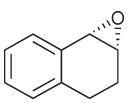
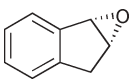
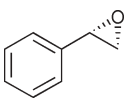
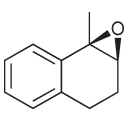
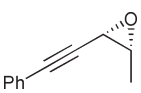
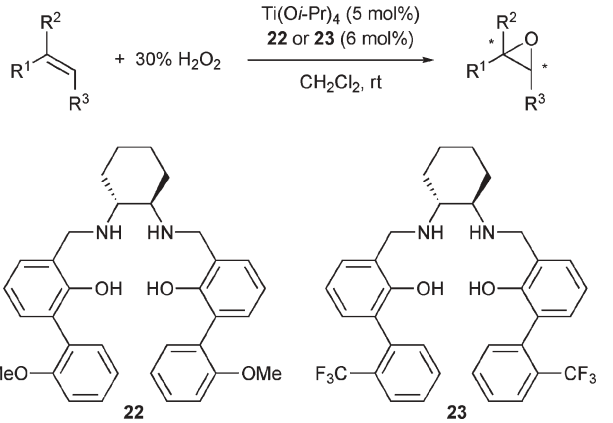
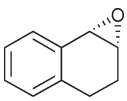
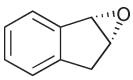
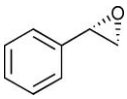
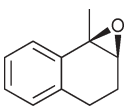
Entry	Product	Yield (%)	Ee (%)
1		87	96
2		72	95
3		47	82
4		55	95
5		69	90

Table 3 Titanium-catalyzed asymmetric epoxidation of olefins



Entry	Product	Yield (%)	Ee (%)
1 (with **22**)		89	98
(with **23**)		93	98
2 (with **22**)		86	98
(with **23**)		77	98
3 (with **22**)		68	89
(with **23**)		80	87
4 (with **22**)		81	96
(with **23**)		71	93
5 (with **22**)		84	94
(with **23**)		92	96

Di-μ-oxo Ti(salan) complexes were prepared from Ti(O*i*Pr)$_4$ and the salan ligands that were prepared by reduction of the corresponding salen ligands with sodium borohydride. Various Ti(salan) complexes were prepared in this way and complex **21** bearing a phenyl group at C3 and C3′ positions showed good catalytic performance for asymmetric epoxidation (Table 2).[29] Various olefins were epoxidized with high to excellent enantioselectivity.

Although asymmetric induction by Ti(salan) complex **21** is slightly inferior to that by Ti(salalen) complex **18** and higher catalyst loading of **21** is necessary to give satisfactory yield, its accessibility offers a large advantage. Moreover, the Ti(salan) complex prepared *in situ* from Ti(O*i*-Pr)$_4$ and the salan ligand shows a catalytic performance comparable with the isolated di-μ-oxo Ti(salan) complex **21**.

We further investigated the effects of an aryl group at the C3 and C3′ positions with the *in situ* protocol.[30] It was found that the introduction of an *ortho*-substituted aryl group led to an improvement in both yield and enantioselectivity (Table 3).

Conclusion

This article describes recent expansion of the catalysis of M(ONNO) complexes, which was brought about mainly by

suitable use of non-planar M(salen), M(salalen) and M(salan) complexes, appropriate regulation of their dynamic structural behavior, and suitable and timely activation of the active species. Although the number of M(ONNO) complexes used so far is rather limited, some reactions such as epoxidation could be achieved in a highly enantioselective manner with satisfactory atom efficiency and under ecologically benign conditions. We believe that there is still further room for improvement of catalytic performances of M(ONNO) complexes, which will allow realization of ideal reactions in terms of stereoselectivity, atom economy and ecological benignity.

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