

Asymmetric Catalysis and Amplification with Chiral Lanthanide Complexes

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I. Introduction

The importance of lanthanide reagents and catalysts in organic synthesis has been well-recognized since the pioneering works by Kagan and co-workers on the SmI_2 -promoted reactions¹ and by Luche and co-workers on the chemo- and stereoselective reduction of carbonyl compounds with the $\text{CeCl}_3/\text{NaBH}_4$ system.² Nonlinear effects (NLEs) in asymmetric catalysis, one of the most important conceptual findings in asymmetric synthesis, also originated in the work of Kagan and co-workers.³ Thanks to Kagan and other researchers, mechanistic, theoretical, and experimental studies on NLEs have advanced.⁴ The positive nonlinear effect ((+)-NLE), which is also called “asymmetric amplification”,⁵ is the convex deviation from the usually assumed linear relationship between the enantiopurity of the chiral ligand and that of the product. On the other hand, the concave deviation is called the negative nonlinear effect or (–)-NLE (Figure 1). Such phenomena (NLEs) have frequently been observed in various catalytic asymmetric reactions, especially using chiral metal complexes.⁶

The nonlinearities shown in Figure 1 may in principle arise by autoassociation or association

around a matrix of the initial chiral species, which produce diastereomeric perturbations. Mathematical treatments as well as mechanistic studies suggest that the NLEs observed in some catalytic asymmetric reactions come from the diastereomeric associations of chiral ligands in the catalytic cycles.⁴ From a practical point of view, such reactions in which asymmetric amplification can operate are highly favored because they may provide optically active products with high enantiomeric excesses (ee's) using a chiral ligand that is not enantiomerically pure.

The use of chiral lanthanide complexes as new catalysts in asymmetric synthesis is currently of intense interest. Lanthanides have partially filled 4f orbitals and almost empty 5d orbitals; in addition, the 4f electrons do not have a significant radial extension beyond the filled $5s^2 5p^2$ orbitals. Therefore, they are generally quite electropositive. In addition, because of their large ionic radii, in general they exhibit high coordination numbers such as 7, 8, or 9 to the maximum 12. These properties are highly advantageous for assembling various chiral and achiral ligands around the metal ions, thus creating an integrated chiral space in which the stereochemistry of the reaction may effectively be controlled; they also make NLEs likely to occur because they have a high capacity for ligand exchange and aggregation.

This paper briefly reviews recent progress (up to mid-2001) in the asymmetric reactions catalyzed by chiral lanthanide complexes (scandium, yttrium, and lanthanum will be included as lanthanides in this paper for brevity) since some important topics concerning asymmetric catalysis with chiral lanthanide metallocenes,⁷ lanthanide triflates-based chiral complexes,⁸ and chiral heterobimetallic lanthanide complexes⁹ as well as some discussion based on the coordination chemistry¹⁰ will be more precisely covered in other contributions to this issue, and special attention is focused upon the nonlinear effects (especially asymmetric amplification) observed in these reactions.

II. Chiral Complexes and Ligands

In Figures 2 and 3 are summarized the isolated chiral lanthanide complexes which have been efficiently used as catalysts and the chiral ligands employed for the in situ formation of the lanthanide complexes, which also worked as effective catalysts, respectively.



Junji Inanaga, born in Fukuoka in 1948, received his Ph.D. degree (Professor Masaru Yamaguchi) from Kyushu University in 1975 and then was appointed Research Associate there, where he had been engaged in the synthetic study of macrolides. Beginning in 1981 he spent two postdoctoral years at Indiana University (Professor Paul A. Grieco). He started his samarium chemistry in 1985 and was promoted to Associate Professor in 1989 at Kyushu University. In the same year he moved to the Institute for Molecular Science at Okazaki and then moved back to Kyushu University in 1993 as a starting IFOC member, where he was promoted to Professor in 2000. He held a Visiting Professorship at Universite Paris-Sud in 1994 and at Kyoto University in 1996. In 1987 he was awarded the Lectureship for Young Chemists, Chemical Society of Japan, and in 1988 the Progress Award in Synthetic Organic Chemistry, Japan. He was a recipient of the 1999 Shiokawa Award, the Rare Earth Society of Japan. His current research interests include new synthetic methods using lanthanides, chiral recognition, and asymmetric catalysis.



Hiroshi Furuno was born in Nagasaki, Japan, in 1971. He received his Ph.D. degree in 2000 from Kyushu University under the supervision of Professor Junji Inanaga. After spending a year as a Postdoctoral Fellow at Kyoto Institute of Technology, he was appointed Research Associate at IFOC in 2001. His research interest centers on the development of catalytic asymmetric synthesis using chiral rare-earth metal complexes.

III. Asymmetric Catalysis and Nonlinear Effects

A. Hetero-Diels–Alder Reaction

In 1983, Danishefsky and co-workers published a memorable paper reporting a chiral europium complex-catalyzed hetero-Diels–Alder reaction of benzaldehyde with the so-called Danishefsky's diene as the first example of a chiral lanthanide complex-catalyzed reaction (Scheme 1).¹¹ The catalyst (**1**), popularly used as a NMR shift reagent, was found to be effective for the reaction showing considerable



Tetsuji Hayano was born in 1976 in Fukuoka, Japan. He graduated from Fukuoka University, Faculty of Science, in 1999 and received his M.S. degree from Kyushu University in 2001 under the direction of Professor Junji Inanaga. In the same year he started his Ph.D. study under the guidance of Professor Inanaga on the development of novel chiral lanthanide complexes that can work as reusable heterogeneous catalysts in asymmetric synthesis.

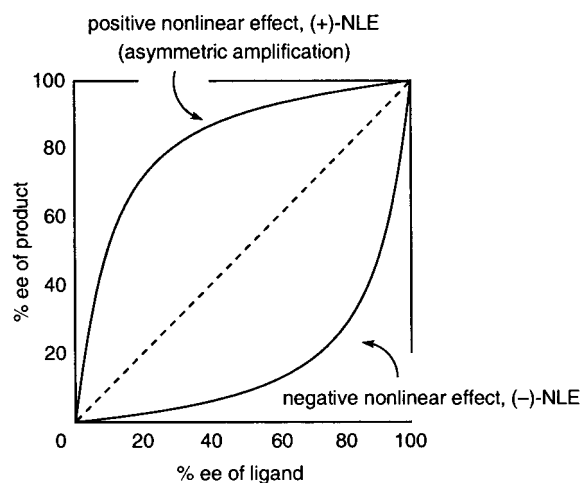
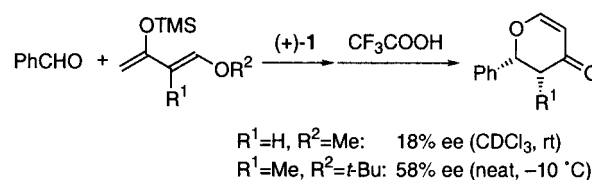


Figure 1.

enantioselectivity (58% ee). Schuring and co-workers prepared a polysiloxane-fixed europium complex (**3**) as a reusable polymeric catalyst, which showed comparable activity to the unsupported catalyst (**1**).¹² The europium complex (**1**) was employed also for the asymmetric hetero-Diels–Alder reaction of α -oxo esters with 1-methoxybutadiene, affording reasonable enantioselectivities.¹³

Scheme 1



Mikami et al. pointed out that the use of a lanthanide triflate/chiral ligand/base system could effectively promote the reaction of butyl glyoxylate with Danishefsky's diene in the presence of water to give the cycloadduct with up to 66% ee (Scheme 2).¹⁴ Interestingly, the enantioselectivity is highly depend-

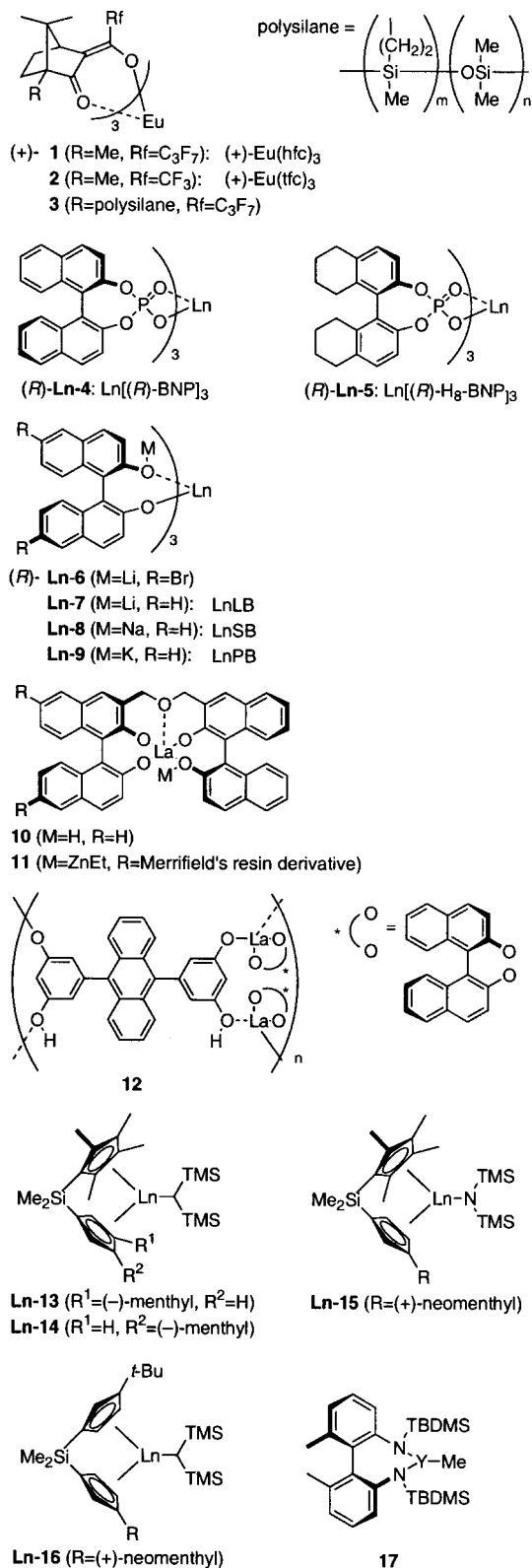
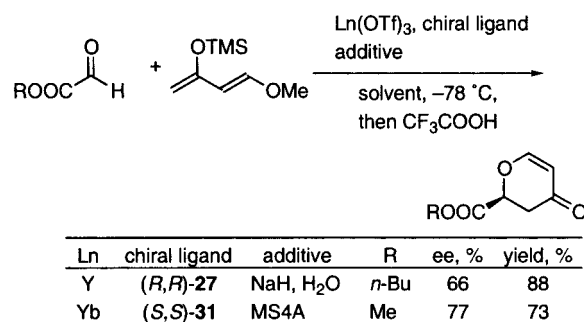


Figure 2. Isolated chiral lanthanide complexes.

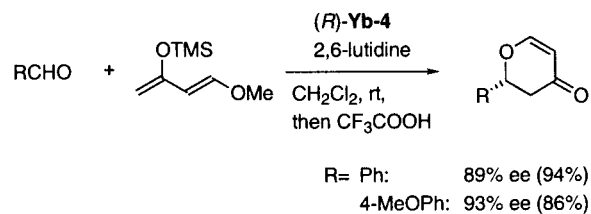
ent on the amount of water added. Qian and Wang reported that the same transformation could be best performed by the catalysis with a mixture of Yb(OTf)₃ and a chiral 2,6-bis[4'-isopropylloxazol-2-yl]pyridine (*i*-Pr-pybox) (**31**) in ether–dichloromethane mixed-solvent at –78 °C, affording up to 77% ee of the adduct.¹⁵

Scheme 2



In 1995, we prepared the 1:3 complexes of a series of trivalent lanthanide ions with a chiral binaphthyl phosphate ligand, Ln[(*R*)-BNP]₃ (**4**), and demonstrated that some of them effectively catalyzed the hetero-Diels–Alder reaction at room temperature, affording the products with good ee's (up to 70% ee).¹⁶ It was also shown that the addition of an equimolar amount of 2,6-lutidine to the ytterbium catalyst **Yb-4** further promoted the reaction under homogeneous conditions, suggesting deoligomerization of the complex, thus affording the cycloaddition products with enhanced enantioselectivities (up to 93% ee) (Scheme 3).¹⁷ The asymmetric induction was highly depen-

Scheme 3

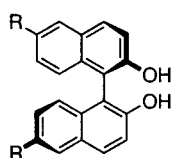


dent on the lanthanide ions used, either in the presence or absence of 2,6-lutidine; the ytterbium catalyst afforded the highest enantioselectivity as shown in Figure 4.^{16,18} Only ca. 0.07 Å difference (from Gd to Yb)¹⁹ brought about almost an 85% ee difference. Careful analysis of the ytterbium-catalyzed reaction showed that the enantioselectivity does not change throughout the reaction, suggesting the thermodynamic stability of the active catalyst (Figure 4).

In this reaction a remarkably high asymmetric amplification was realized as the first example in the metal/ligand = 1:3 system (Figure 5).²⁰ Catalysts prepared either by mixing Yb[(*R*)-BNP]₃ and Yb[(*S*)-BNP]₃ (Yb-catalyst **A**) or from enantiomerically impure Na–BNP and YbCl₃ (Yb-catalyst **B**) gave similar results.

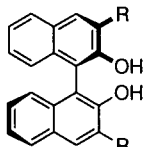
On the basis of some experimental results, Furuno et al. explained this phenomenon in terms of the autogenetic formation of the enantiopure homochiral ytterbium complex. For the formation of YbL₃, there are four possibilities in choosing three chiral ligands out of four: (L_R)₃, (L_R)₂L_S, L_R(L_S)₂, and (L_S)₃. From these four complexes, the heterochiral pairs such as Yb(L_R)₃ and Yb(L_S)₃ and/or Yb[(L_R)₂L_S] and Yb[L_R(L_S)₂] seem to irreversibly assemble forming thermodynamically very stable complexes that have almost no catalytic activity for the hetero-Diels–Alder reac-

BINOL Derivatives

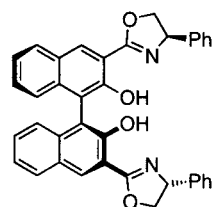
*(R)*- 18 (R=H): BINOL

19 (R=Br)

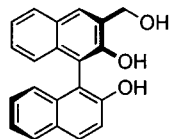
20 (R=Ph)

*(R)*- 21 (R=(CH₂)₂OMe)22 (R=CH₂NEt₂)

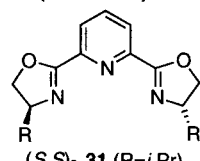
23 (R=9-anthryl)



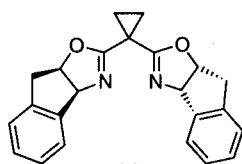
24

*(R)*-25

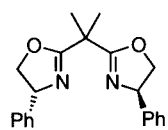
Bis(oxazoline)

*(S,S)*- 31 (R=*i*-Pr)32 (R=*t*-Bu)

33 (R=Ph)

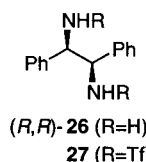


34

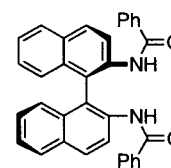


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Diamine Derivatives

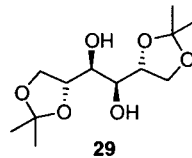
*(R,R)*- 26 (R=H)

27 (R=Trf)

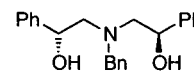


28

Diol and Aminodiol

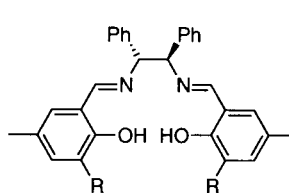


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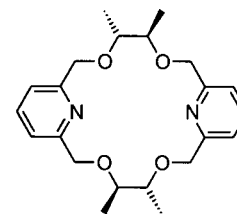


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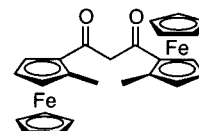
Miscellaneous



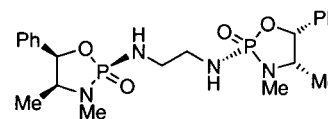
36 (R=adamantyl)



37



38



39

Figure 3. Chiral ligands for lanthanide complexes.

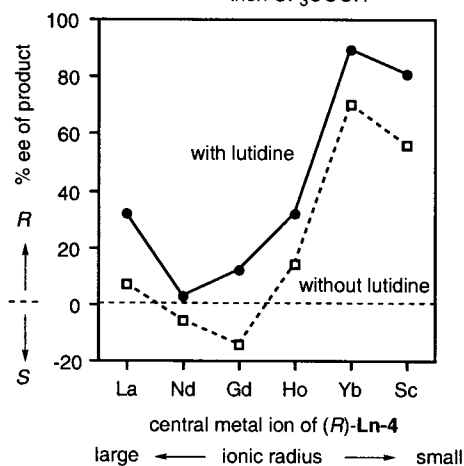
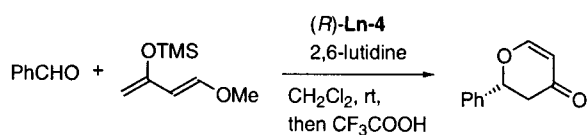
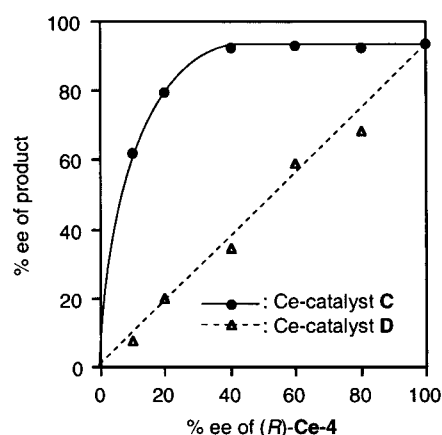
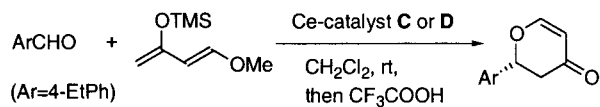
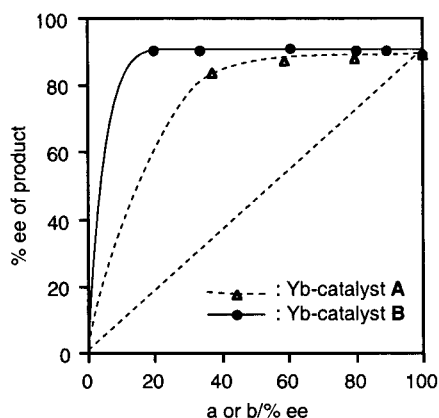
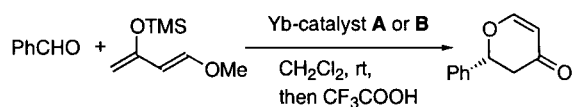


Figure 4.

tion. As a result, the enantiopure Yb complex based on an excess amount of the enantiomer, Yb(L_R)₃, would remain in solution as the real catalyst (Figure 6). This phenomenon turned out to be quite general within the lanthanide-metal ions with similar ionic radii such as that of the ytterbium ion.²⁰

Hayano et al. found that the CH₂Cl₂-soluble chiral cerium complex (C) prepared from ceric ammonium nitrate (CAN) and Na-(*R*)-BNP also affords high asymmetric amplification (Figure 7).²¹ Spectral (ESCA, ICP-MS) data of the catalyst indicated it to be the cerium(III) complex. Different from the case of the ytterbium catalyst, the oligomeric and CH₂Cl₂-insoluble cerium complex (D) also catalyzed the reaction. Interestingly, a linear relationship was observed in this case and the observed ee's of the product were linearly higher than those of the corresponding ligands of the catalysts (Table 1).²¹

Recently, Kambara et al. accomplished almost perfect enantioselectivity (99% ee) in the Y[(*R*)-H₈-BNP]₃ (5) catalyzed reaction without using 2,6-lutidine as an additive.²²



Preparative methods of optically impure Yb-catalyst

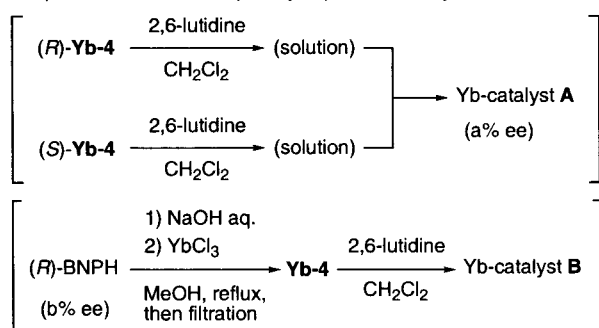


Figure 5.

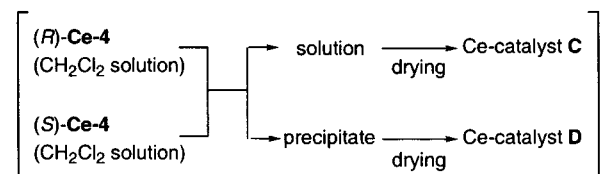


Figure 7.

and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) in the presence of molecular sieves 4A at 0 °C.²³ The reactions were carried out at -15 °C in the presence of additives to give the 8-hydroxyquinoline derivatives with high ee's (up to 91% ee). Whiting and co-workers also demonstrated that a chiral ytterbium complex prepared from Yb(OTf)₃, (1*R*,2*R*)-diphenylethylenediamine (**26**), and 2,6-lutidine nicely promoted the reaction of the *p*-anisidine-derived imine of methyl glyoxalate with Danishefsky's diene affording, after acidic workup, a 2,3-dehydro-4-piperidone derivative with 87% ee.²⁴ (Scheme 4)

Scheme 4

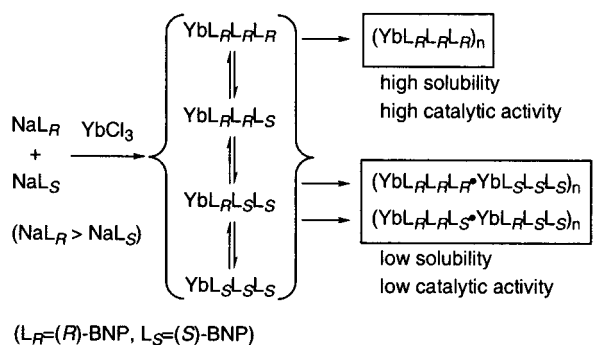
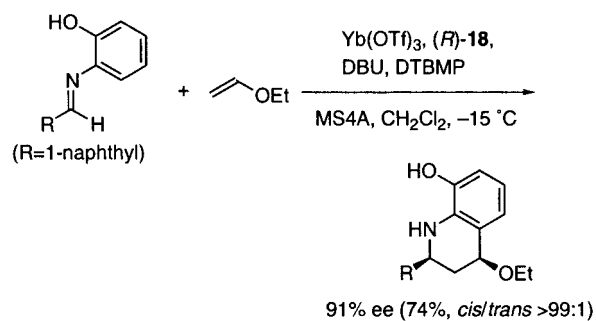
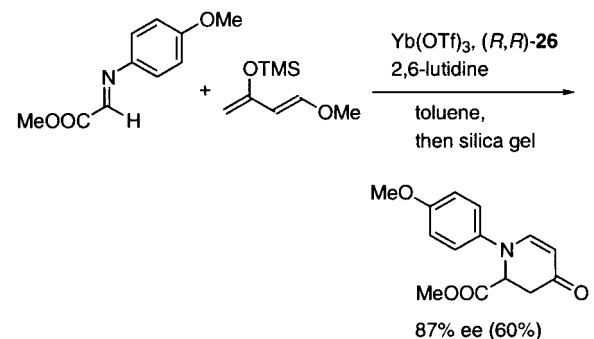


Figure 6.

Table 1.

entry	ee of catalyst (C or D), %	ee of (R)-18, %	
		for C	for D
1	10		5
2	20		10
3	40		18
4	50	96	
5	60	98	22
6	80	99	27

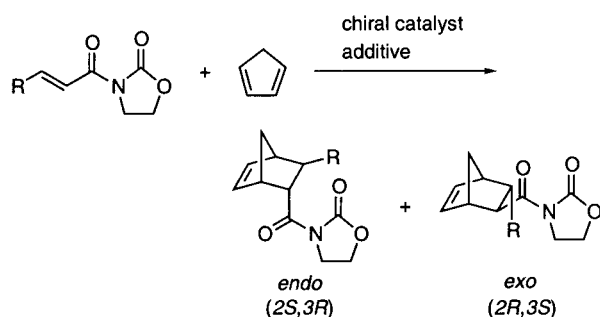
Ishitani and Kobayashi succeeded in the first catalytic asymmetric aza-Diels-Alder reaction of 2-hydroxyaniline-derived aldimines with electron-rich olefins by using a chiral ytterbium complex prepared in situ from Yb(OTf)₃, (*R*)-BINOL (**18**), DBU,



B. Diels–Alder Reaction

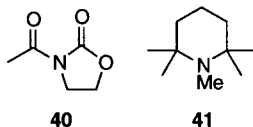
Kobayashi and co-workers realized a highly enantioselective Diels–Alder reaction by catalysis with in-situ-prepared chiral lanthanide complexes.²⁵ Either enantiomer can be selectively synthesized by modifying Ln(OTf)₃ with a single chiral source and a choice of achiral ligands. For example, the reaction of 3-(2-butenoyl)-1,3-oxazolidin-2-one preferably gave the *endo*-adduct (*endo*/*exo* = 89:11) with a (2*S*,3*R*) configuration in 93% ee when a catalyst prepared in situ from Yb(OTf)₃, (*R*)-BINOL (**18**), *cis*-1,2,6-trimethylpiperidine (TMP), and 3-acetyl-1,3-oxazolidin-2-one (**40**) was used. On the other hand, the (2*R*,3*S*) enantiomer was selectively obtained in 81% ee using a different catalyst prepared from Yb(OTf)₃, (*R*)-BINOL, 1,2,2,6,6-pentamethylpiperidine (**41**), and 3-phenylacetylacetone (PAA) (Scheme 5). The reversal of the enantiofacial selection

Scheme 5



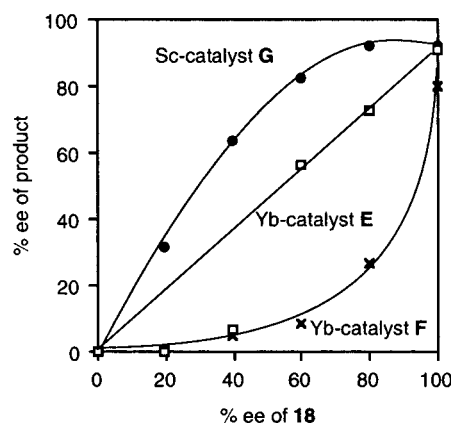
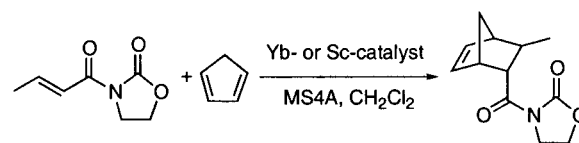
chiral catalyst, additive	R	ee, %	yield, %	<i>endo</i> / <i>exo</i>
Yb(OTf) ₃ , (<i>R</i>)- 18 , TMP, 40 ^a	Me	93	77	89:11
Yb(OTf) ₃ , (<i>R</i>)- 18 , 41 , PAA ^a	Me	<i>ent</i> -81	83	93: 7
Yb(OTf) ₃ , 28 , DIPEA	Me	<i>ent</i> ->98	97	91: 9
Sc(OTf) ₃ , (<i>S,S</i>)- 31 ^a	H	90	60	98: 2
12	Me	~75		<i>exo</i> -major
(<i>R</i>)- La-6	H	86	100	97: 3

^aMS4A was added.



is accounted for by the change in the coordination numbers. The coordination structure of the catalyst is affected by the ligands employed; more than two different complexes seem to be involved in the reaction as effective catalysts. This complexity was further ascertained by the observed diversity of the relationship between the enantiopurity of the chiral ligand and that of the product depending on the achiral ligands as well as metal ions of the catalysts used. For example, a (–)-NLE was observed in the catalysis with the chiral ytterbium complex (**E**) prepared in situ from Yb(OTf)₃, (*R*)-BINOL, TMP, and PAA, whereas the ytterbium catalyst (**F**) afforded an almost linear relationship, and the scandium catalyst (**G**) prepared from Sc(OTf)₃, (*R*)-BINOL, and TMP showed a (+)-NLE (Figure 8).^{25a,c}

Nakagawa and co-workers used an in-situ-prepared chiral complex composed of Yb(OTf)₃, 2,2'-bis-(acylamino)-1,1'-binaphthyl (**28**), and *N,N*-diisopropylethylamine (DIPEA) (1:1.2:2.4) for similar reactions



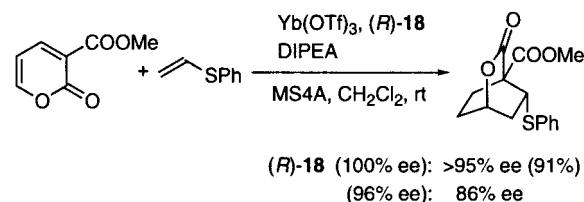
Yb-catalyst **E**: Yb(OTf)₃+(*R*)-**18**+TMP+**40**
 Yb-catalyst **F**: Yb(OTf)₃+(*R*)-**18**+TMP+PAA
 Sc-catalyst **G**: Sc(OTf)₃+(*R*)-**18**+TMP

Figure 8.

and achieved excellent enantioselectivities (up to >98% ee).²⁶ Fukuzawa et al. also examined the combined use of Sc(OTf)₃ and *i*-Pr-pybox (**31**) under various conditions and obtained the Diels–Alder adducts with fairly high enantioselectivities (up to 90% ee).²⁷ Aoyama and co-workers prepared a lanthanum-involved helical coordination polymer (**12**) from La(O-*i*-Pr)₃, (*R*)-BINOL, and anthracene-bis-resorcinol and demonstrated that it catalyzes the Diels–Alder reaction with moderate enantioselectivity (70% ee).²⁸ Shibasaki's lithium-containing heterobimetallic complex (*R*)-**La-6** was found to act as an effective Lewis acid catalyst for the Diels–Alder reaction, thus affording the product with up to 86% ee.²⁹

Markó and co-workers reported that the chiral catalyst composed of Yb(OTf)₃, (*R*)-BINOL (**18**), and DIPEA for the inverse electron-demand Diels–Alder reactions of 2-pyrone derivatives gave adducts in up to 95% ee (Scheme 6).³⁰ They also stated that a negative nonlinear effect was observed in this reaction.

Scheme 6

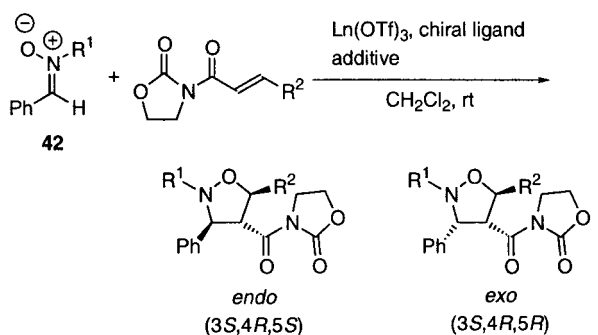


C. 1,3-Dipolar Cycloaddition

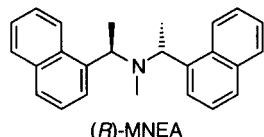
In 1997, Kobayashi's³¹ and Jørgensen's³² groups independently found that the complexes prepared from Yb(OTf)₃ and chiral ligands [(*R*)-BINOL (**18**) + amine or *i*-Pr-pybox (**31**), respectively] induced enantioselectivity in the 1,3-dipolar cycloaddition of nitrones (**42**) with activated olefins such as α,β -unsaturated alkenoyl oxazolidones. The corresponding

isoxazolidine derivatives were obtained in good ee's (up to 78% ee). Kobayashi and co-workers succeeded in improving the enantioselectivity (up to 96% ee) as well as diastereoselectivity (*endo/exo* = 99:1) by using an additional chiral amine base, *N*-methyl-bis[(*R*)-1-naphthylethyl]amine [(*R*)-MNEA].³³ Interestingly, the sense of enantioselectivity is switchable simply by changing the additive from molecular sieves 4A (MS4A) to a Nitron. Ohta and co-workers proposed a new complex between Sc(OTf)₃ and a chiral 3,3'-bis(2-oxazolyl)-BINOL (**24**) as an effective catalyst for the same reaction³⁴ (Scheme 7).

Scheme 7



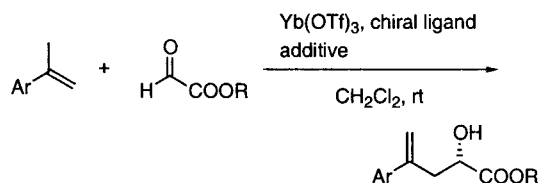
Ln	chiral ligand	additive	R ¹	R ²	ee, %	yield, %	<i>endo/exo</i>
Yb	(<i>R</i>)- 18	TMP, MS4A	Bn	Me	78	72	>99:1
Yb	(<i>S</i>)- 18	(<i>R</i>)-MNEA, MS4A	Bn	Me	<i>ent</i> -96	92	99:1
Yb	(<i>S</i>)- 18	(<i>R</i>)-MNEA, 42	Bn	Me	83	90	99:1
Yb	(<i>S,S</i>)- 31	MS4A	Ph	Pr	69	69	92:8
Sc	24	MS4A	Bn	Me	<i>ent</i> -83	86	92:8



D. Ene Reaction

Qian and co-workers used two types of chiral ytterbium complexes as catalysts of the asymmetric glyoxylate-ene reaction. One catalyst is a mixture of Yb(OTf)₃ and a 6,6'-disubstituted (*R*)-BINOL derivative (**19**),³⁵ and the other is a complex of Yb(OTf)₃ with Ph-pybox (**33**).³⁶ Moderate enantioselectivities were observed in both cases (Scheme 8).

Scheme 8



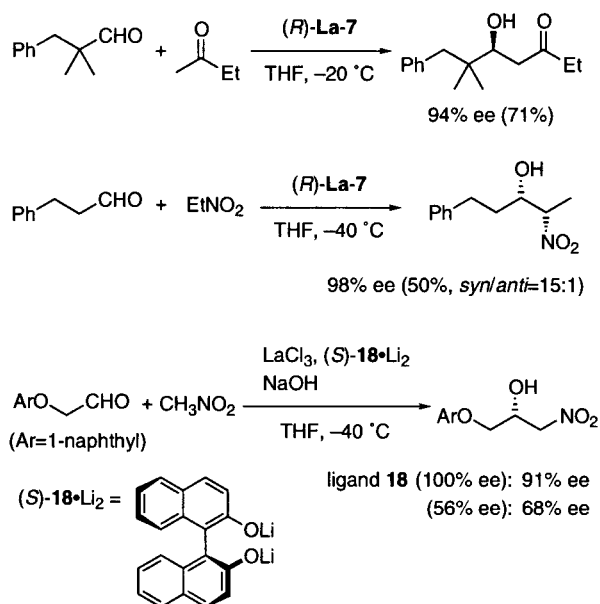
chiral ligand	additive	Ar	R	ee, %	yield, %
(<i>S</i>)- 19		Ph	Me	38	78
(<i>S,S</i>)- 33	MS4A	4-ClPh	Et	54	69

E. Aldol-Type Reaction

Great success in asymmetric aldol^{37,38} (up to 94% ee) and nitroaldol reactions^{37,39-42} (up to 98% ee) owes

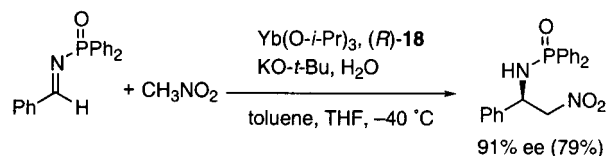
mainly to Shibasaki's outstanding work using the chiral heterobimetallic lanthanide complexes, lanthanide-alkali-metal-(*R*)-BINOL (LnMB), as catalysts. The details will be disclosed by Shibasaki et al. in this issue.⁹ Asymmetric amplification was reported for the reaction of nitromethane with α -naphthoxyacetaldehyde catalyzed by the chiral complex between LaCl₃·7H₂O, dilithium (*S*)-binaphthoxide, and NaOH; the nitroaldol product with 68% ee was obtained using 56% ee of the chiral ligand (Scheme 9).^{39a}

Scheme 9



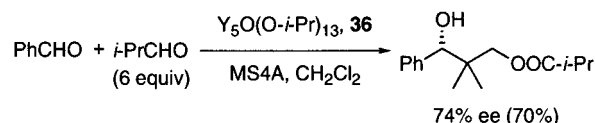
The catalytic asymmetric nitro-Mannich-type reaction was best effected by another kind of lanthanide heterobimetallic complex composed of Yb(O-*i*-Pr)₃, KO-*t*-Bu, and (*R*)-BINOL (1:1:3) to give the desired product with up to 91% ee (Scheme 10).⁴³

Scheme 10



The first catalytic enantioselective aldol-Tishchenko reaction between aromatic aldehydes and 2-methylpropanal (6 equiv) was realized by Morken and co-workers using the yttrium complex prepared from Y₅O(O-*i*-Pr)₁₃ and a chiral salen ligand (**36**) to give the corresponding β -acyloxy alcohols with up to 74% ee (Scheme 11).⁴⁴

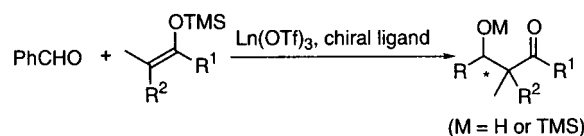
Scheme 11



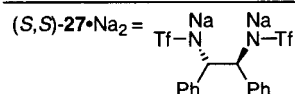
For the Mukaiyama aldol reaction, use of lanthanide triflates in combination with chiral ligands

was found to be effective, producing up to 82% ee (Scheme 12).^{45,46}

Scheme 12



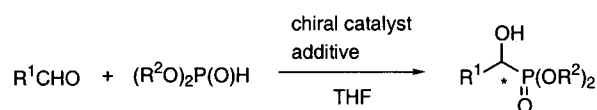
Ln	chiral ligand	R ¹	R ²	result
Yb	(<i>S,S</i>)- 27 •Na ₂	OEt	Me	49% ee (84%)
Ce	37	Ph	H	82% ee (<i>syn/anti</i> =93:7)



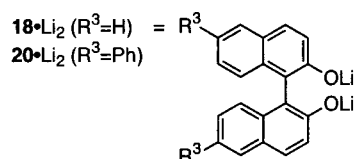
F. Hydrophosphonylation and Hydrophosphination of Aldehydes and Imines

Shibasaki-type chiral heterobimetallic lanthanide complexes were found to be quite effective also for the enantioselective hydrophosphonylation and phosphination of aldehydes and imines. Thus, the corresponding α -hydroxy phosphonates and α -amino phosphonates, which are biologically or pharmaceutically important compounds, were obtained in high enantioselectivities. Shibuya et al.⁴⁷ and Spilling et al.⁴⁸ independently reported the chiral lanthanum complex (composed of **18**•Li₂, NaO-*t*-Bu, and H₂O) catalyzed reaction of aldehydes for which Shibuya pointed out a significant effect of the electron-donating *para*-substituents of benzaldehyde on the enantioselectivity.⁴⁹ Thus, the highest enantioselectivity (95% ee) was attained by Shibasaki et al. in the reaction of *p*-dimethylaminobenzaldehyde.⁵⁰ Qian et al. also examined the influence of the substituents at the 3,3'- and 6,6'-positions of BINOL as a constituent of the chiral lanthanide complex.⁵¹ (Scheme 13)

Scheme 13



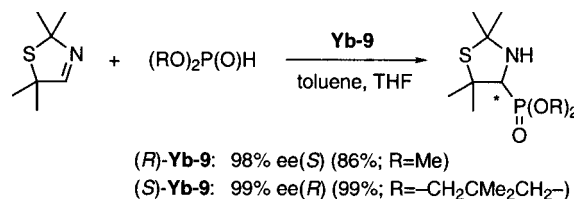
chiral catalyst, additive	R ¹	R ²	ee, %	yield, %
LaCl ₃ , (<i>R</i>)- 18 •Li ₂ , NaO- <i>t</i> -Bu, H ₂ O	4-MeOPh	Et	82(<i>S</i>)	91
LaCl ₃ , (<i>R</i>)- 18 •Li ₂ , NaO- <i>t</i> -Bu, H ₂ O	PhCH=CH	Me	41(<i>S</i>)	73
LaCl ₃ , (<i>S</i>)- 20 •Li ₂ , NaO- <i>t</i> -Bu, H ₂ O	4-MeOPh	Et	74(<i>R</i>)	89
(<i>R</i>)- La-7	4-MeOPh	Et	82(<i>S</i>)	95
(<i>R</i>)- La-7	4-Me ₂ NPh	Me	95(<i>S</i>)	88



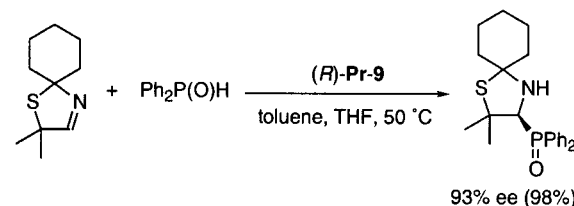
The research chemists of the Shibasaki's and Martens' groups actively investigated the enantioselective hydrophosphonylation^{52,53} and phosphination⁵⁴ of acyclic and cyclic imines and found that LnK₃(*R*)-BINOL]₃ (**Ln-9**) complex is superior to the corresponding lithium (**Ln-7**) or sodium (**Ln-8**) complexes

as a catalyst. Thus, almost perfect enantioselectivity was attained in the reaction of 2,2,5,5-tetramethyl-3-thiazoline using **Ln-9** as a catalyst (Schemes 14 and 15).

Scheme 14



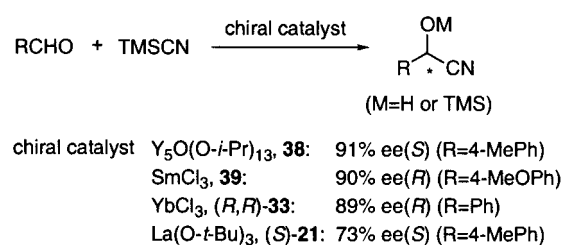
Scheme 15



G. Silylation of Aldehydes

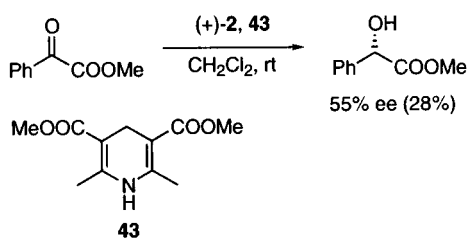
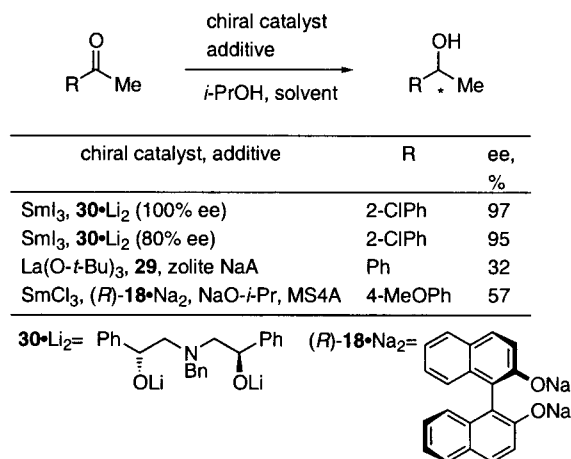
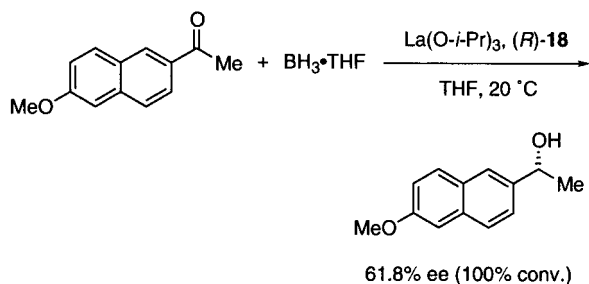
In 1996, Abiko and Wang reported the first chiral yttrium complex-catalyzed asymmetric silylcyanation of aldehydes that requires only 0.2 mol % of the catalyst prepared in situ from Y₅O(O-*i*-Pr)₁₃ and a ferrocene-derived C₂-chiral 1,3-diketone ligand (**38**).⁵⁵ Aromatic aldehydes were converted to the corresponding cyanohydrins with high enantioselectivities (up to 91% ee). As an effective catalyst system for the same transformation, Fang et al. proposed a combination of SmCl₃ and a chiral bis-phosphoramidate ligand (**39**)⁵⁶ and Aspinall and Greeves et al. successfully used LnCl₃ in combination with Phpybox (**33**).⁵⁷ Qian et al. reported that an in-situ prepared complex from La(O-*t*-Bu)₃ and a chiral BINOL derivative (**21**) in a 2:3 ratio was also effective.⁵⁸ (Scheme 16)

Scheme 16



H. Reduction of Carbonyl Groups

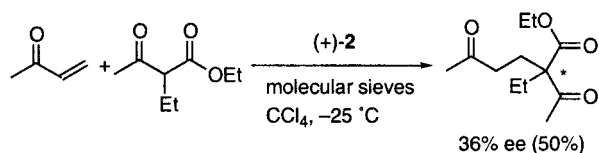
The chiral lanthanide complex-catalyzed enantioselective reduction of carbonyl compounds has been examined in the following three reactions: the reduction with NADH models (Scheme 17),⁵⁹ the Meerwein–Ponndorf–Verley reduction (Scheme 18),^{60–62} and the borane reduction (Scheme 19).⁶³ Particularly noteworthy in terms of enantioselectivity is the work of Evans et al.; a samarium complex prepared in situ from SmI₂ and (*R*)-styrene oxide-derived C₂-chiral amino diol (**30**) catalyzed the Meerwein–Ponndorf–Verley reduction of aryl methyl ketones in high

Scheme 17**Scheme 18****Scheme 19**

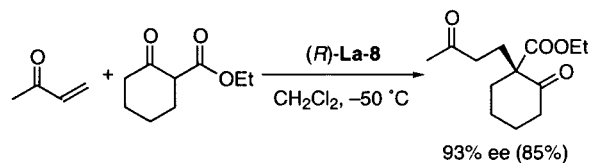
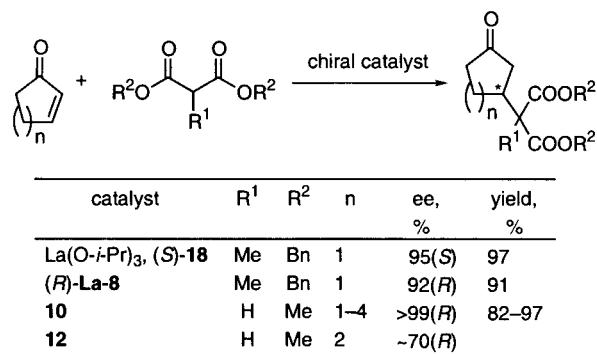
enantioselectivities (up to 97% ee) (Scheme 18).⁶⁰ A significant effect of the lanthanide-metal size on the enantioselectivity was observed. Thus, the complexes of yttrium, terbium, samarium, and neodymium showed higher selectivities than those of scandium, lutetium, and lanthanum. Asymmetric amplification was also observed: When 80% ee of the chiral ligand was used, the reduction product was formed in 95% ee, which is the same selectivity obtained using the enantiopure ligand.

I. Michael-Type Reaction

In 1993, Scettri and co-workers applied a shift reagent, (+)-Eu(tfc)₃ (**2**), as a catalyst to the Michael addition of 1,3-dicarbonyl compounds to methyl vinyl ketone observing modest enantioselectivities (Scheme 20).⁶⁴

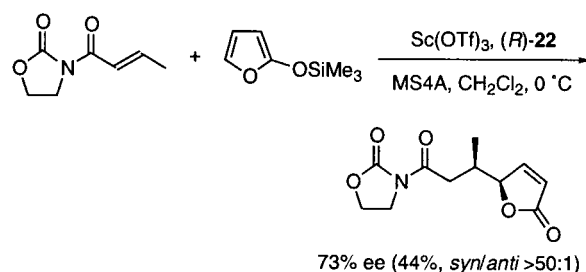
Scheme 20

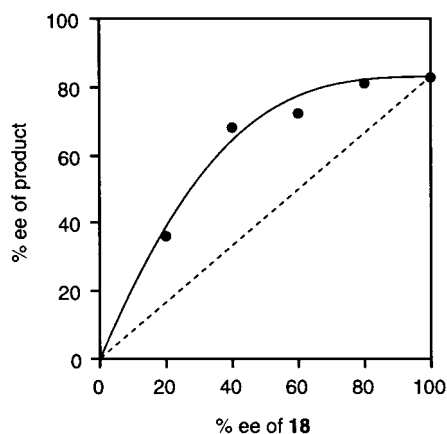
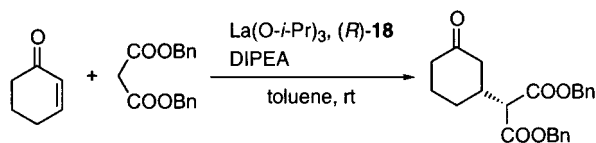
Intensive studies by Shibasaki and co-workers produced excellent results. Thus, very high enantioselectivities (up to 99% ee) were realized in the Michael reaction of various 1,3-dicarbonyl compounds with α,β -unsaturated carbonyl compounds by using $\text{La(O-}i\text{-Pr)}_3/(S)\text{-BINOL}$,⁶⁵ $\text{LaNa}_3[(R)\text{-BINOL}]_3$ (**La-8**),^{66,67} or La-linked-bisBINOL (**10**)⁶⁸ complexes. They also succeeded in immobilizing the latter complex by attaching it to a polymer having a polystyrene backbone (**11**).⁶⁹ The effect of the immobilization on the enantioselectivity was found to be small; good enantioselectivities (over 80% ee) were ensured. Another heterogeneous polymeric catalyst is Aoyama's helical coordination polymer (**12**), which gave the addition product of dimethyl malonate to 2-cyclohexenone in ca. 70% ee^{28,70} (Scheme 21).

Scheme 21

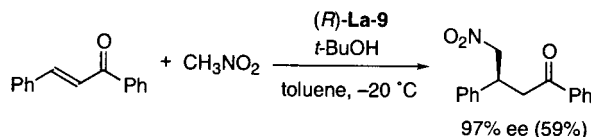
We found that a novel complex composed of $\text{La(O-}i\text{-Pr)}_3$, (*R*)-BINOL, and DIPEA (1:3:3) is as effective as the corresponding heterobimetallic complexes for the Michael addition reaction of dibenzyl malonate to cyclohexenone. Furthermore, a notable asymmetric amplification was observed in the reaction catalyzed by the lanthanide-amine-BINOL (LAB) system as shown in Figure 9.⁷¹

The Michael reaction of 2-(trimethylsilyloxy)furan with oxazolidinone enolates was examined by Katsumi and co-workers. The scandium complex prepared from Sc(OTf)_3 and a BINOL derivative (**22**) showed a high diastereoselectivity but with a modest enantioselectivity (73% ee) (Scheme 22).⁷²

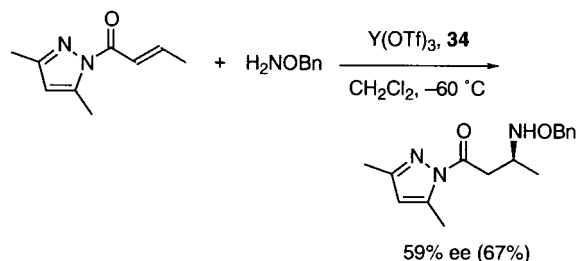
Scheme 22

**Figure 9.**

Shibasaki's $\text{LaK}_3[(R)\text{-BINOL}]_3$ complex (**La-9**) was found to catalyze the Michael addition of nitromethane to conjugated enones with high enantioselectivities (up to 97% ee) (Scheme 23).⁷³

Scheme 23

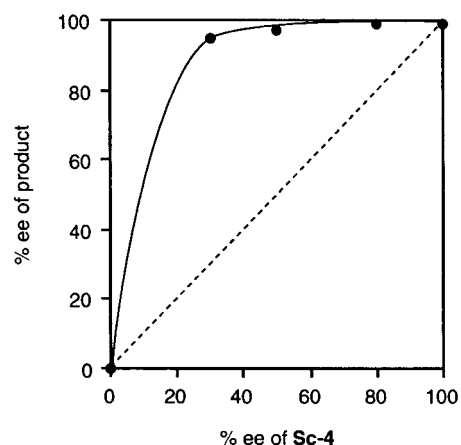
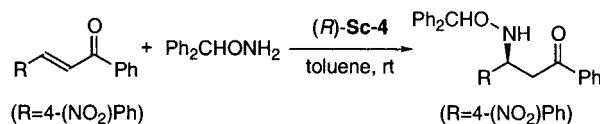
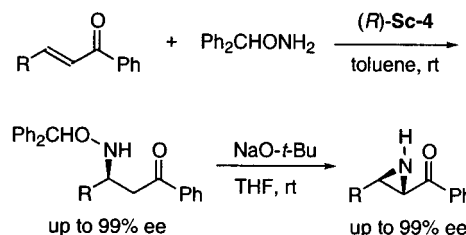
Enantioselective conjugate addition of *O*-benzylhydroxylamine to α,β -unsaturated pyrazole amides using a $\text{Ln}(\text{OTf})_3$ -bisoxazoline (**34**) complex was reported by Sibi et al. to give the desired products with moderate enantioselectivities (Scheme 24).⁷⁴

Scheme 24

Recently, we found that the $\text{Sc}[(R)\text{-BNP}]_3$ complex (**Sc-4**) was a quite effective catalyst for the addition reaction of nitrogen nucleophiles to conjugated enones; the enantioselective addition reaction of *O*-diphenylmethylhydroxylamine to various conjugated enones was accomplished at room temperature with almost complete enantioselectivities (up to >99% ee) (Scheme 25), and as shown in Figure 10, a significant asymmetric amplification was observed in this reaction.⁷⁵ The Michael adducts thus obtained can be cleanly converted to the corresponding α -keto aziridines by catalysis with $\text{NaO-}t\text{-Bu}$ or $\text{La}(\text{O-}i\text{-Pr})_3$.

J. Epoxidation of Conjugated Enones

Catalytic asymmetric epoxidation is another important asymmetric process. Shibasaki and co-work-

**Figure 10.****Scheme 25**

ers successfully carried out the highly enantioselective catalytic epoxidation of conjugated enones using lanthanide complexes prepared from $\text{La}(\text{O-}i\text{-Pr})_3$ and (*R*)-BINOL (**18**) or (*R*)-3-hydroxymethyl-BINOL (**25**) to give the corresponding epoxy ketones with up to 94% ee.⁷⁶ The latter catalyst system, $\text{Yb}(\text{O-}i\text{-Pr})_3$ /**25**, was found to be quite effective also for the epoxidation of cis enones (up to 96% ee).⁷⁷ The asymmetric amplification observed in the Yb -(*R*)-BINOL complex-catalyzed epoxidation of benzalacetone is shown in Figure 11, which suggests that some aggregation of the catalyst exists.^{76b}

From the experiments dealing with the $\text{Ln}[(R)\text{-BNP}]_3/2,6$ -lutidine complex-catalyzed hetero-Diels-Alder reaction (section A), we noticed that the addition of an external ligand to the chiral lanthanide complex was quite effective not only for solubilizing the catalyst but also for enhancing the stereoselectivity, which suggests the importance of coordinative saturation of the lanthanide with appropriate ligands to deoligomerize the polymeric complexes. On the basis of the above idea, we examined the effect of a variety of additives for the La -(*R*)-BINOL complex-catalyzed asymmetric epoxidation of chalcone with *tert*-butyl hydroperoxide (TBHP) as an oxidant.⁷⁸ Some selected results are shown in Table 2. Among the additives tested, triphenylphosphine oxide gave the best result of 96% ee and showed a notable ligand-acceleration of the reaction rate.

It was also found that cumene hydroperoxide (CMHP) is the oxidant of choice. When CMHP was used in place of TBHP, the enantioselectivity was

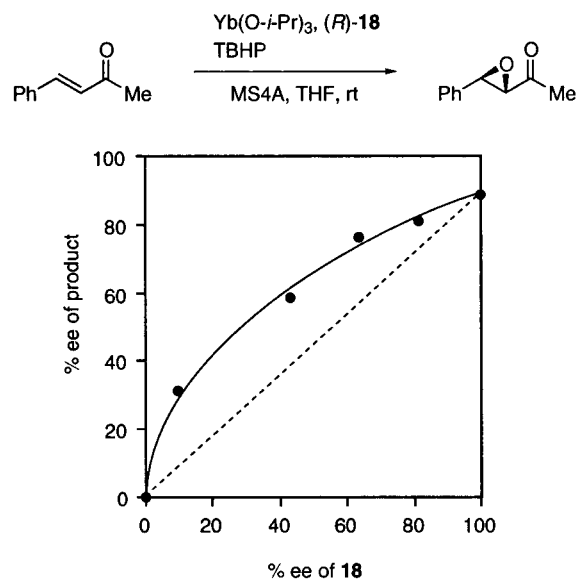


Figure 11.

Table 2.

entry	additive	time, h	ee, %	yield, %
1	none	3.0	73	89
2	lutidine <i>N</i> -oxide	3.0	74	96
4	<i>n</i> - $\text{Bu}_3\text{P}=\text{O}$	3.0	73	88
5	$\text{Ph}_3\text{P}=\text{O}$	0.5	96	99
6	(<i>p</i> -tolyl) $_3\text{Pd}=\text{O}$	1.0	94	95
7	(<i>o</i> -tolyl) $_3\text{Pd}=\text{O}$	1.5	73	96
8	(Me_2N) $_3\text{P}=\text{O}$	1.5	86	99

Table 3.

entry	R ¹	R ²	time, h	ee, %	yield, %
1	Ph	Ph	0.2	>99	99
2	Ph	Me	3.0	>99	90
3	Ph	<i>i</i> -Pr	4.0	>99	72
4	Ph	<i>t</i> -Bu	3.0	99	93
5	<i>i</i> -Pr	Ph	3.0	98	88
6	$\text{Ph}(\text{CH}_2)_2$	Me	1.0	86	60

further raised to over 99% ee and the amount of the catalyst can be reduced to 0.5 mol % without a serious decrease in the enantioselectivity.⁷⁹ This method is applicable to a wide range of substrates, as can be seen from some examples in Table 3. In addition, all of the reagents required for this asymmetric epoxidation are commercially available and the low reaction temperatures usually required to attain a high enantioselectivity are not necessary, thus making the protocol highly practical.

As expected from the above results, a very high asymmetric amplification was observed in the epoxidation of chalcone with CMHP using the $\text{La}(\text{O}-i\text{-Pr})_3/(\text{R})\text{-BINOL}/\text{Ph}_3\text{PO}$ (1:1:3) system (Figure 12).⁷⁹ Using only 40% ee of the ligand, one can attain more than 99% enantioselectivity.

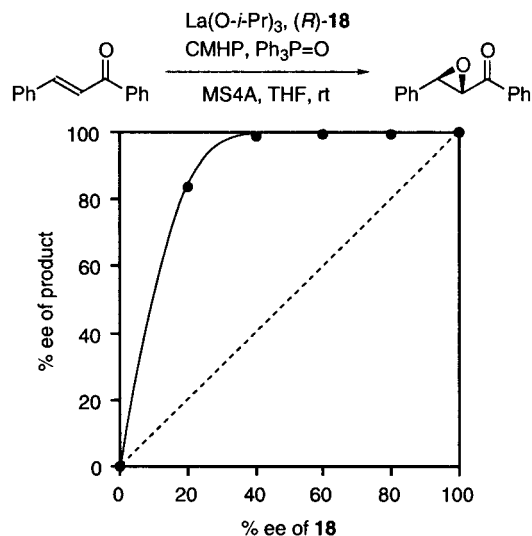


Figure 12.

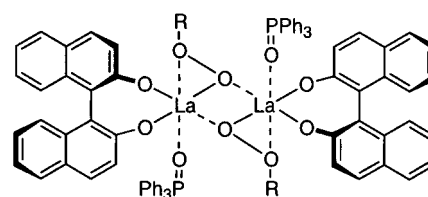


Figure 13.

This result strongly suggests that the active catalyst may not be monomeric and may have a particular structure that hardly changes during the reaction because of its thermodynamic stability. This was further supported by the fact that the use of (*R*)-3,3'-di(9-anthryl)-BINOL (**23**) in place of (*R*)-BINOL (**18**) in preparing the catalyst system showed the opposite sense of enantioselection and that neither positive nor negative nonlinear effects were observed in the epoxidation, suggesting a monomeric structure of the catalyst due to steric bulkiness of the 3,3'-anthryl groups.⁸⁰ Thus, a homochiral dimeric complex like a binuclear μ -complex, composed of $\text{La}/(\text{R})\text{-BINOL}/\text{Ph}_3\text{PO}/\text{ROOH} = 1:1:1:1$ (Figure 13), is tentatively proposed as an active catalytic species for the reaction; one of the lanthanum ions may work as a Lewis acid to activate the substrate, and the peroxide attached to the other lanthanum ion might be delivered as an active oxidant, thus controlling the stereochemistry of the epoxidation. Actually, the epoxidation of chalcone with CMHP using the preformed catalyst system, $\text{La}(\text{O}-i\text{-Pr})_3/(\text{R})\text{-BINOL}/\text{Ph}_3\text{PO}/\text{CMHP}$ (1:1:1:1), afforded the expected epoxide with 99% ee.⁷⁹ The present protocol is so convenient and effective that it can be successfully applied to large-scale experiments (e.g., 30 kg scale; 90% chemical yield, >98% ee).⁸¹

Shibasaki and co-workers also pointed out that the effectiveness of additives such as water^{76b} and triphenylarsine oxide.⁸² From the LDI-TOFMS spectrum of the complex, the $\text{La}(\text{O}-i\text{-Pr})_3/(\text{R})\text{-BINOL}/\text{Ph}_3\text{AsO}$ (1:1:1) structure was suggested. They successfully applied the catalyst to the synthesis of natural products^{82a} and claimed that triphenylarsine oxide is superior to triphenylphosphine oxide as an additive with respect to the reaction rate and the stoichiometry.^{82b}

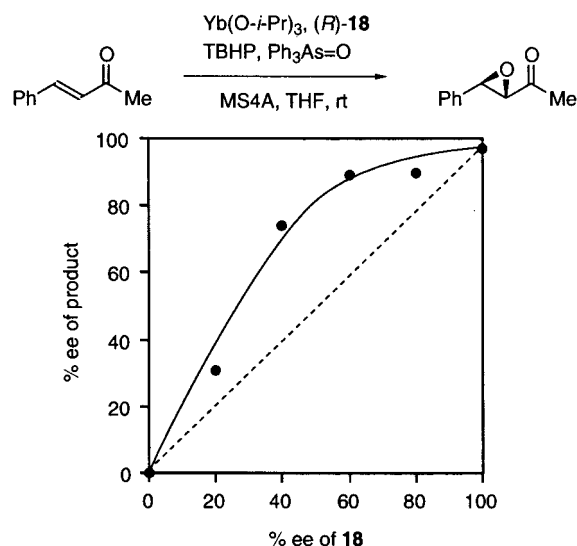


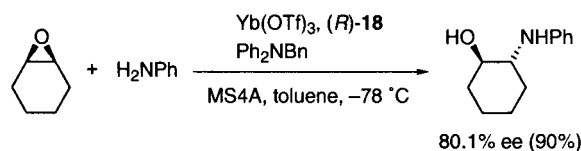
Figure 14.

Considerable asymmetric amplification was also observed (Figure 14), and the formation of a heterochiral complex as an ineffective catalyst was suggested for the phenomenon. Furthermore, they demonstrated that the protocol is applicable to the epoxidation of α,β -unsaturated pyrazol amides, thus affording up to 93% ee.⁸³

K. Ring-Opening Reaction of Meso Epoxides

Asymmetric ring opening of cyclohexene oxide with aniline was achieved by Hou and co-workers.⁸⁴ They used a catalyst system, $\text{Yb}(\text{OTf})_3/(\text{R})\text{-BINOL}/\text{Ph}_2\text{NBn}$, for the reaction and obtained the corresponding *trans*-1,2-amino alcohol with 80% ee (Scheme 26).

Scheme 26



Schaus and Jacobsen reported that the asymmetric ring opening of *meso* epoxides with cyanotrimethylsilane (TMSCN) can be catalyzed by the chiral ytterbium complex prepared in situ from YbCl_3 and a chiral Ph-pybox (**33**), yielding the β -trimethylsilyloxy nitrile ring-opened products with good enantioselectivities (83–92% ee).⁸⁵ The reaction exhibits a second-order kinetic dependence on the catalyst concentration and a first-order dependence on the epoxide concentration, consistent with a bimetallic pathway involving simultaneous activation of the epoxide and cyanide. This was further supported by the observation of a notable positive nonlinear effect (Figure 15).

L. Hydrogenation, Hydroamination, and Hydrosilylation of Olefins

Marks and co-workers prepared various chiral lanthanide metallocenes (**13–16**) bearing (–)-menthyl or (+)-neomenthyl substituents on one of the two

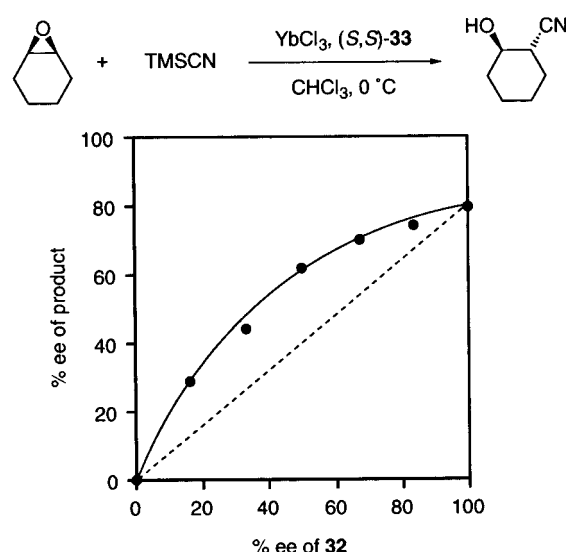
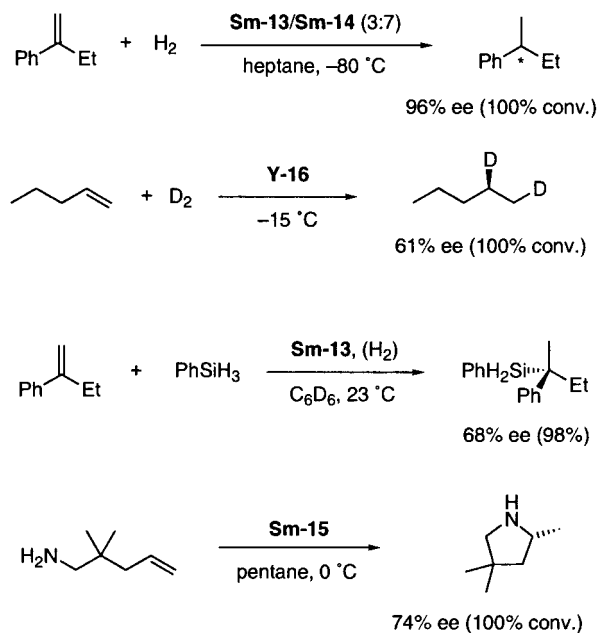


Figure 15.

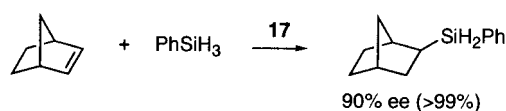
cyclopentadienyl rings connected with dimethylsilyl group and successfully used them for enantioselective olefin hydrogenation (up to 96% ee)⁸⁶ and hydrosilylation (up to 68% ee)⁸⁷ of 1,1-disubstituted ethenes and also for intramolecular hydroamination (up to 74% ee)^{86b,88} (Scheme 27). Detailed discussion on this subject is given by Molander et al. in this issue.⁷

Scheme 27



Recently, Tilley et al. demonstrated that the chiral ytterbium hydride generated in situ from [(*S*)-DADMB]- $\text{YMe}(\text{thf})_2$ (**17**) (DADMB = 2,2'-bis-(*tert*-butyldimethylsilylamido)-6,6'-dimethylbiphenyl) works as an efficient catalyst for the enantioselective hydrosilylation of norbornene (90% ee) (Scheme 28).⁸⁹

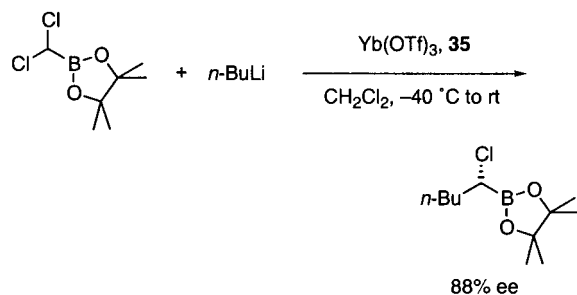
Scheme 28



M. Miscellaneous

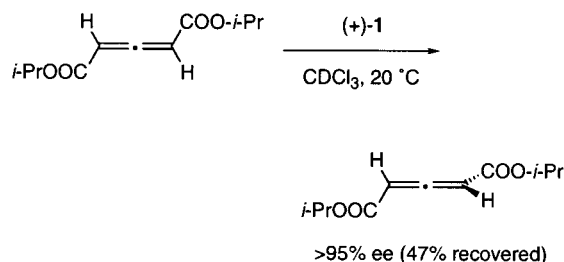
An efficient enantiotopic displacement of *pro-R* or *pro-S* chlorides on an sp^3 carbon center with an alkyl group, which proceeds through Matteson's homologation process, was attained by Jadhav and Man using $\text{Yb}(\text{OTf})_3$ as a most effective Lewis acid in combination with a chiral bisoxazoline ligand (**35**) to afford the corresponding alkylation product with 88% ee (Scheme 29).⁹⁰

Scheme 29



Naruse et al. reported that the europium complex (**1**) is exceptionally effective for the enantiomeric enrichment of allenedicarboxylates. For example, diidopropyl penta-2,3-dienedioate with over 95% ee was recovered at the sacrifice of the opposite enantiomer when the substrate was treated with a stoichiometric amount of (+)-**1** in deuteriochloroform at 20 °C for 9 days (Scheme 30).⁹¹ The enantiomeric enrichment does not seem to proceed in a catalytic manner.

Scheme 30



IV. Conclusions

Chiral lanthanide complexes prepared either *in situ* or as isolable forms have been shown to effectively catalyze a variety of reactions with high enantioselectivities. In all cases, lanthanide ions work as a Lewis acid, thus gathering various chiral and achiral ligands, substrates, and, in some cases, reagents. They hardly lose their Lewis acidity even, in some cases, in the presence of water, amines, or amino alcohols, although in such circumstances most traditional Lewis acids lose their activities by hydrolysis or through the complete occupation of their coordination sites. The lanthanides provide various ionic radii continuously within the range of, e.g., in the case of hexacoordinates, 1.032 (La^{3+}) to 0.861 (Lu^{3+}) or to 0.745 Å (Sc^{3+}); therefore, fine-tuning of transition structures is often possible by choosing an appropriate lanthanide ion for the chiral lanthanide catalysts. However, in many cases exact coordination

numbers and structures of the active chiral lanthanide catalysts have not yet been fully determined and the issues remain to be clarified soon to provide a guiding principle for designing new chiral lanthanide complexes as efficient catalysts.

A large number of examples of NLEs have been accumulated over the past 15 years. NLEs are now recognized as a ubiquitous phenomenon in asymmetric reactions, especially in enantioselective catalysis. This is also true for the catalysis with chiral lanthanide complexes. Thus, notable asymmetric amplifications, (+)-NLEs, have been observed in a variety of reactions. Such NLEs can be explained in terms of the self-organization, aggregation, and/or self-assemblies of the chiral complexes that may arise in given reactions. The remarkably high asymmetric amplifications observed in the lanthanide complex-catalyzed reactions may be responsible for the large coordination number of the lanthanide ions, which is advantageous for the rapid ligand exchange and also for the aggregation of the heterochiral complexes to generate certain thermodynamically stable complexes with very poor catalytic activity. Asymmetric amplification is highly advantageous from a practical viewpoint because it allows the convenient use of enantiomerically impure chiral ligands without purification.

V. Acknowledgments

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VI. References

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