Lanthanide Complexes in Multifunctional Asymmetric Catalysis

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Received October 23, 2001

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I. Introduction

Asymmetric catalysis has received considerable attention over the past few decades, and its contribution toward organic synthesis has become increasingly significant.[1] A wide variety of enantioselective chemical transformations are now performed with only catalytic amounts of chiral promoters, providing highly economic access to optically active compounds. Some of these enantioselective transformations can be applied to industrial production. Nonetheless, the performance of most artificial catalysts is still far from satisfactory in terms of generality and reactivity. On the other hand, enzymes catalyze a broad range of organic transformations under rather mild conditions, even though they are often specific for certain substrates. An advantage of enzymes over most artificial catalysts is that they often contain two or more active sites for catalysis (Figure 1b). The

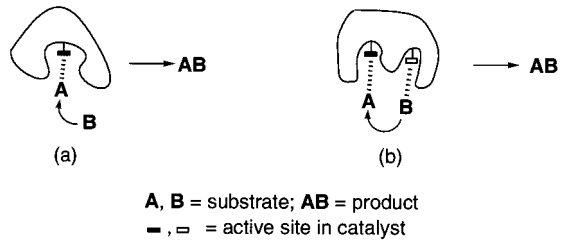
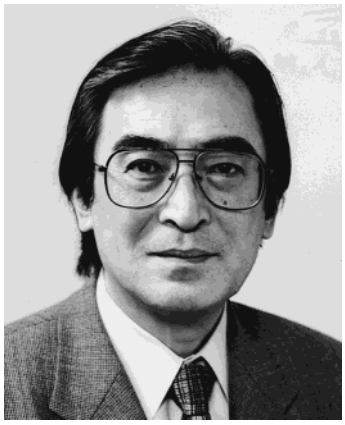


Figure 1. Catalysts with a single active site (a) and multifunctional catalysts (b).

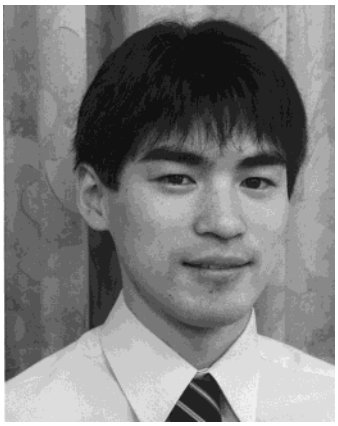
synergistic functions of the active sites make substrates more reactive in the transition state and control their positions so that the functional groups are proximal to each other. This concept of *multifunctional* catalysis is key to increasing the scope of natural and artificial catalysts.[2]

The development of asymmetric catalysis to date has been accomplished by employing various metal elements on the basis of the type of reaction targeted. While asymmetric catalysts containing p-block metal elements or d-block elements have been studied extensively,[1] the use of f-block elements (lanthanides and actinides) as metal components for asymmetric catalysts has not been studied until recently.[3] The utility of lanthanides for asymmetric catalysis was first demonstrated by Danishefsky et al.[4] Danishefsky et al. reported promotion of hetero Diels−Alder reactions by $Eu(hfc)_3$ with moderate enantiomeric excess (up to 58% ee). Several groups reported other examples of enantioselective catalytic cycloaddition.[5−10] Other lanthanide complexes were reported as catalysts in other enantioselective reactions such as Meerwein−Ponndorf−Verley (MPV) reductions,[11] hydrogenations,[12] hydrosilylations,[13] hydroaminations,[12] polymerizations,[14] and Mukaiyama aldol reactions.[15] These studies demonstrate the exceptional capability of lanthanides as Lewis acids.[16]

10.1021/cr010297z CCC: $39.75
Published on Web 05/24/2002



Masakatsu Shibasaki was born in 1947 in Saitama, Japan, and received his Ph.D. from The University of Tokyo in 1974 under the direction of the late Professor Shun-ichi Yamada before doing postdoctoral studies with Professor E. J. Corey at Harvard University. In 1977 he returned to Japan and joined Teikyo University as an associate professor. In 1983 he moved to Sagami Chemical Research Center as a group leader, and in 1986 took up a professorship at Hokkaido University, before returning to The University of Tokyo as a professor in 1991. He was a visiting professor at Philipps-Universität Marburg during 1995. He has received the Pharmaceutical Society of Japan Award for Young Scientists (1981), Inoue Prize for Science (1994), Fluka Prize (Reagent of the Year, 1996), the Elsevier Award for Inventiveness in Organic Chemistry (1998), the Pharmaceutical Society of Japan Award (1999), Molecular Chirality Award (1999), the Naito Foundation Research Prize for 2001 (2002), and ACS Award (Arthur C. Cope Senior Scholar Award) (2002). His research interests include asymmetric catalysis, including asymmetric Heck reactions and reactions promoted by asymmetric bifunctional complexes, and also the medicinal chemistry of biologically significant compounds.



Naoki Yoshikawa was born in 1974 in Niigata, Japan. He obtained his Master's degree in pharmaceutical sciences from The University of Tokyo in 1999, where he has worked on the development of direct catalytic asymmetric aldol reactions using multifunctional catalysts. He obtained his Ph.D. in 2002 under the supervision of Professor Masakatsu Shibasaki at The University of Tokyo, where he is currently working as a postdoctoral fellow of the Japan Science and Technology Corporation (JST).

Since the first report of a catalytic asymmetric nitroaldol reaction in 1992, Shibasaki et al. continued to develop the concept of *multifunctional* catalysis[17] wherein the catalysts exhibit both Lewis acidity and Brønsted basicity (Figure 2), using lanthanide complexes.[18] The synergistic effects of the two functions enable transformations that have never been possible using conventional catalysts employing only Lewis acidity. Furthermore, a variety of enantioselective transformations has been realized by carefully choosing the metal elements according to the type of the reaction, consistent with the above-mentioned concept. In particular, the development of heterobimetallic complexes[19−21] that contain a lanthanide[22] and alkali metal offer a versatile framework for asymmetric catalysts, because the property of the catalyst can be tuned dramatically according to the choice of alkali metal and further refined by choosing the proper lanthanide. This review focuses on the development of lanthanide multifunctional catalysts in a wide range of asymmetric reactions. For consistency, we classified the catalysts into six groups depending on the structure.

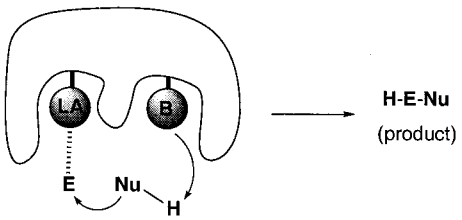


Figure 2. Multifunctional catalysts employing the synergistic function of a Lewis acid and a Brønsted base: LA = Lewis acid; B = Brønsted base; E = electrophile; Nu-H = nucleophile.

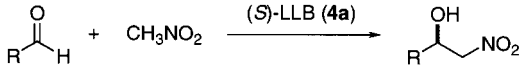
II. Heterobimetallic Catalysts Based on Lanthanide and Lithium (LnLB)

A. Catalytic Asymmetric Nitroaldol Reaction

1. Development of Heterobimetallic Complexes Based on Lanthanides and Alkali Metals

Shibasaki et al. were initially interested in utilizing the basic character of lanthanide alkoxides[23] in organic synthesis.[24] Aldol reactions, cyanosilylations of aldehydes, and nitroaldol reactions[25] were promoted by a catalytic amount of lanthanide alkoxides such as $La_3(O\text{-}t\text{-}Bu)_9$.[26] Furthermore, enantiomerically enriched nitroaldol adducts **3** were obtained with up to 90% ee (Scheme 1), when the catalyst (**4a**)

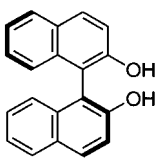
Scheme 1. First Catalytic Asymmetric Nitroaldol Reaction



1 **2a** **3**: up to 90% ee

was prepared from $La(O\text{-}t\text{-}Bu)_3$ (1 mol equiv), (*S*)-BINOL (**5a** in Chart 1, 1.5 mol equiv), LiCl (2 mol equiv), and H_2O (10 mol equiv). After detailed optimization, the method for catalyst preparation was improved to a more practical one that employs $LaCl_3 \cdot 7H_2O$ (1 mol equiv), $Li_2(S\text{-binol})$ (1 mol equiv), NaO-*t*-Bu (1 mol equiv),[27] and H_2O (4 mol equiv).[28] During efforts to elucidate the catalytic species, a series of

Chart 1. (*S*)-BINOL



5a

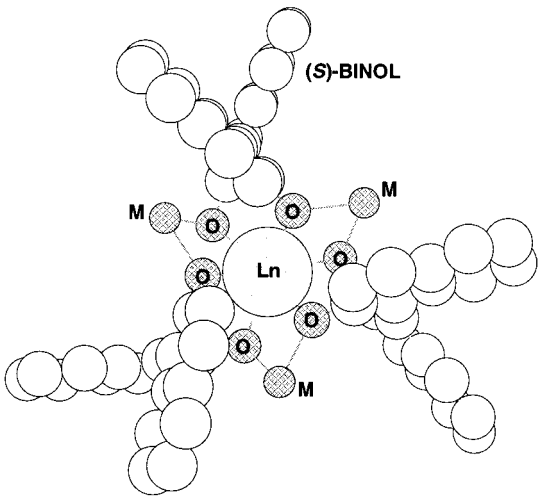
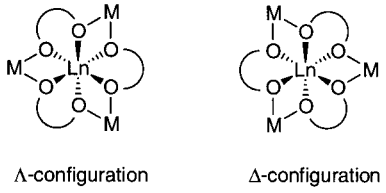


Figure 3. Structural framework of $M_3[Ln(binol)_3]$-type heterobimetallic complexes (LnMB).

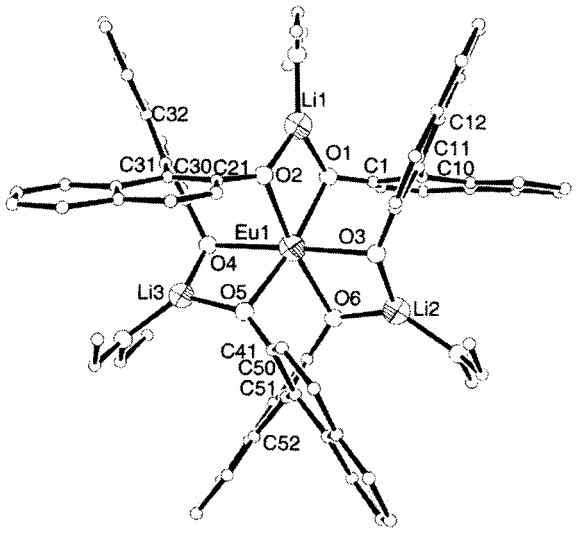
complexes containing lanthanide and an alkali metal were synthesized, and X-ray crystallographic analysis, elemental analysis, and mass spectroscopic studies of these samples revealed the formation of complexes bearing an interesting structural framework represented as $M_3[Ln(S\text{-binol})_3]$ (abbreviated as LnMB; Ln, lanthanide; M, alkali metal; B, BINOL; see Figure 3) with one molecule of H_2O coordinating to Ln.[29,30] Each complex has an asymmetric center at the central lanthanide metal and can exist as a mixture of diastereomers (Chart 2). Nevertheless,

Chart 2. Possible Configurations of $M_3[Ln(binol)_3]$-Type (LnMB) Complexes



every crystal possessed the Λ-configuration rather than the Δ-form when the complex was prepared from (*S*)-BINOL, indicating that the configuration at the center metal is strongly affected by the configuration of the BINOL. Thus, the catalyst (**4a**, $Li_3[La(binol)_3(H_2O)]$, LLB·H_2O) was prepared by treatment of $La(O\text{-}i\text{-}Pr)_3$[31] with Li(Hbinol) (3 mol equiv to La) and H_2O (1 mol equiv to La) in THF. Although this method produces the catalytic species in a high yield, an alternative method for catalyst preparation was investigated to make the catalyst more accessible, employing hydrated $LnCl_3$ as a widely available and much less expensive lanthanide source. As a result, an equivalently active catalyst (**4a**) was prepared from $LaCl_3{\cdot}7H_2O$, Li_2(binol) (2.7 mol equiv), and NaO-*t*-Bu (0.3 mol equiv) in THF.[32] All the preparative methods described above are considered to generate an identical catalytic species (**4a**). The catalytic activities of these complexes are maintained for several months under argon at ambient temperature, and special handling precautions are not necessary.

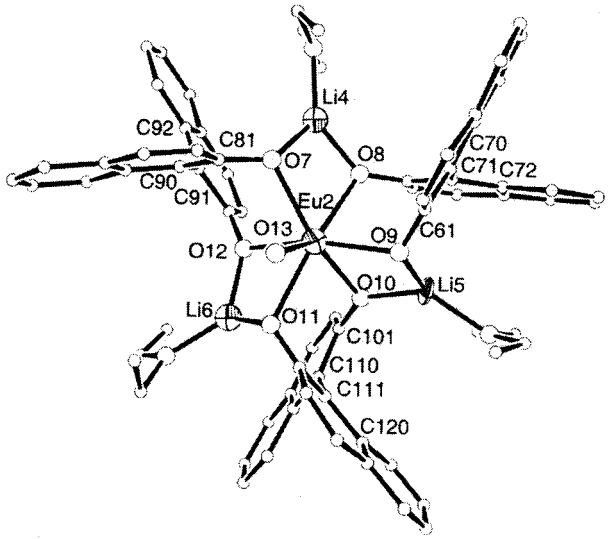
Aspinall et al. recently reported detailed structural studies of these complexes.[33] Whereas the crystal



Eu-**6**

Figure 4. X-ray crystal structure of $[Li(OEt)_2]_3[Eu(S\text{-binol})_3]$.

structures provided by Shibasaki et al. included one molecule of water coordinating to the central metal, Aspinall et al. succeeded in preparing anhydrous crystals of $M_3[Ln(binol)_3]$ (LnMB). Their procedure is to mix $Ln(N(SiMe_3)_2)_3$ and Li(Hbinol) in THF or Et_2O, cleanly affording $Li_3[Ln(binol)_3]$-type complexes. The resulting $HN(SiMe_3)_2$ was removed in vacuo, and the crystals were obtained from THF−petroleum ether solution. Using this procedure, Aspinall et al. determined the X-ray crystal structures of a series of complexes. The differences between the anhydrous (Eu-**6**, Figure 4) and aqua crystal structures (Eu-**7**, Figure 5) were also reported. The



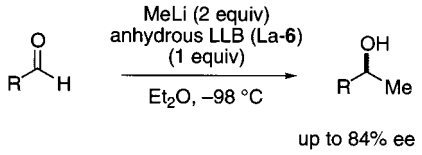
Eu-**7**

Figure 5. X-ray crystal structure of $[Li(OEt)_2]_3[Eu(S\text{-binol})_3(H_2O)]$.

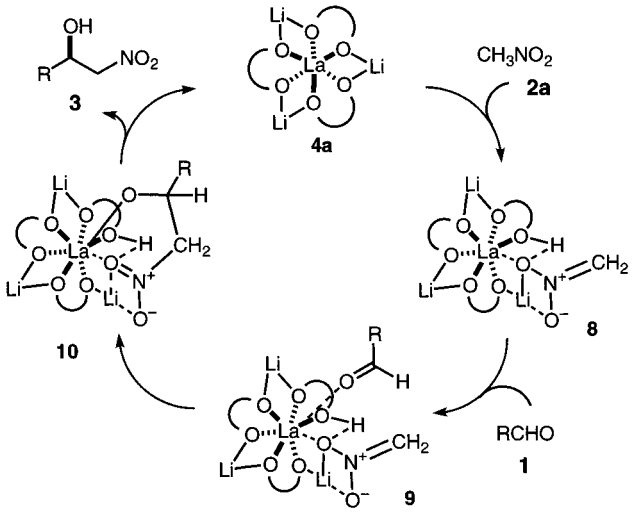
anhydrous crystals (La-**6**) mediated the enantioselective addition of alkyllithiums to aldehydes with up to 84% ee (Scheme 2).

A plausible catalytic cycle for the enantioselective nitroaldol reaction is described in Scheme 3. In this

Scheme 2. Enantioselective Alkylation of Aldehydes Mediated by Anhydrous LLB (La−6)



Scheme 3. Proposed Mechanism for the Catalytic Asymmetric Nitroaldol Reaction[a]

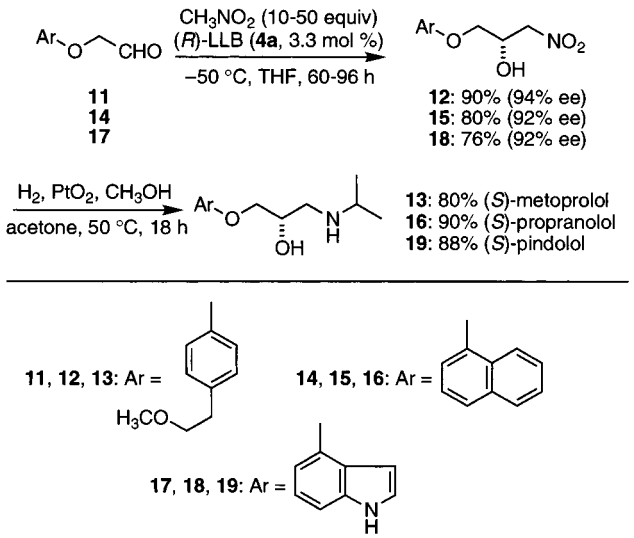


[a] H_2O is omitted for clarity.

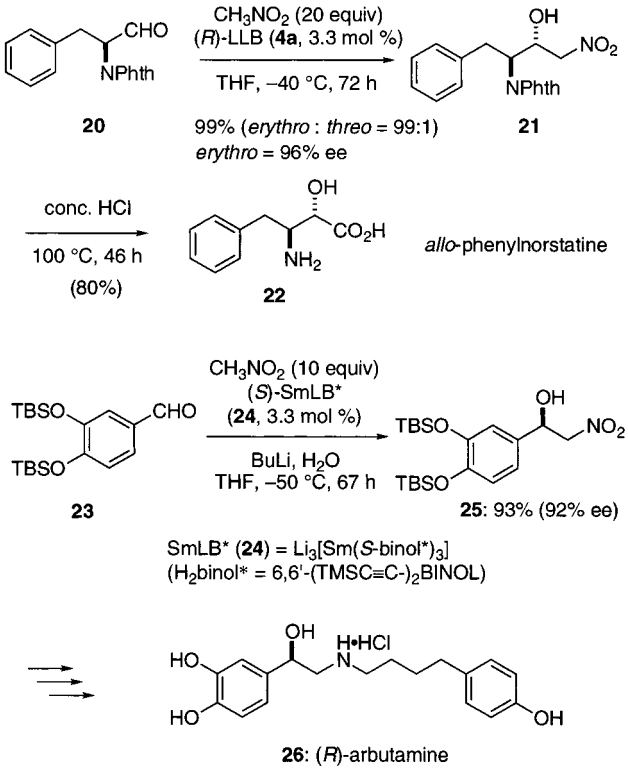
reaction, it is likely that the lanthanum metal in LLB (**4a**) acts as a Lewis acid to activate the aldehyde, and the lithium binaphthoxide moiety functions as a Brønsted base to deprotonate the nitromethane to give a lithium nitronate (**8**).[34]

The catalytic asymmetric nitroaldol reaction was successfully applied to the synthesis of a variety of optically active β-hydroxy nitroalkanes, and the utility of this method was demonstrated in the catalytic asymmetric synthesis of β-blockers (Scheme 4),[35] *allo*-phenylnorstatine (Scheme 5),[36] and (*R*)-arbutamine (Scheme 5).[30] A tandem inter−intramolecular catalytic asymmetric nitroaldol reaction was also reported.[37]

Scheme 4. Catalytic Asymmetric Synthesis of β-Blockers Using (*R*)-LLB (4a) as a Catalyst

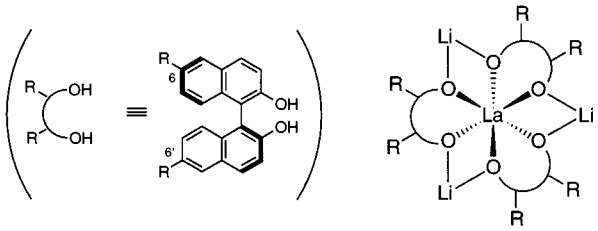


Scheme 5. Catalytic Asymmetric Synthesis of *allo*-Phenylnorstatine and Arbutamine



Moreover, the diastereoselective variant of this reaction was achieved by developing a new complex (**4e**) prepared from 6,6′-bis(triethylsilylethynyl)-BINOL (**5e**) (Chart 3).[38] Various nitroalkanes and nitroethanol were applicable, giving the corresponding *syn*-adducts with high levels of diastereo- and enantioselectivity. The results are summarized in Table 1.[39] The observed *syn*-selectivity can be explained by Newman projections that are depicted in Figure 6. This method was applied to the synthesis of *threo*-dihydrosphingosine (**30**) (Scheme 6).

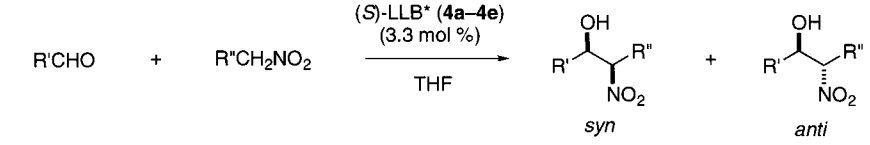
Chart 3. Heterobimetallic Complexes 4 Prepared from 6,6′-Disubstituted BINOLs 5



2. Effects of Lanthanides

Lanthanides have a distinctive feature referred to as “lanthanide contraction”. The ionic radius of an

Table 1. Diastereo- and Enantioselective Nitroaldol Reactions



1a: R' = $PhCH_2CH_2$
1b: R' = $CH_3(CH_2)_4$
2b: R" = Me
2c: R" = Et
2d: R" = CH_2OH
3a: R' = $PhCH_2CH_2$, R" = Me
3b: R' = $PhCH_2CH_2$, R" = Et
3c: R' = $PhCH_2CH_2$, R" = CH_2OH
3d: R' = $CH_3(CH_2)_4$, R" = CH_2OH

entry	aldehyde	nitroalkane	catal	time (h)	temp (°C)	products	yield (%)	*syn*:*anti*	ee of *syn* (%)
1	**1a**	**2b**	**4a**	75	−20	**3a**	79	74:26	66
2	**1a**	**2b**	**4b**	75	−20	**3a**	80	74:26	65
3	**1a**	**2b**	**4c**	75	−20	**3a**	77	84:16	90
4	**1a**	**2b**	**4d**	75	−20	**3a**	72	85:15	92
5	**1a**	**2b**	**4e**	75	−20	**3a**	**70**	**89:11**	**93**
6	**1a**	**2b**	**4e**	115	−40	**3a**	21	94:6	97
7	**1a**	**2c**	**4a**	138	−40	**3b**	89	85:15	87
8	**1a**	**2c**	**4e**	138	−40	**3b**	**85**	**93:7**	**95**
9	**1a**	**2d**	**4a**	111	−40	**3c**	62	84:16	66
10	**1a**	**2d**	**4e**	111	−40	**3c**	**97**	**92:8**	**97**
11	**1b**	**2d**	**4a**	93	−40	**3d**	70	87:13	78
12	**1b**	**2d**	**4e**	93	−40	**3d**	**96**	**92:8**	**95**

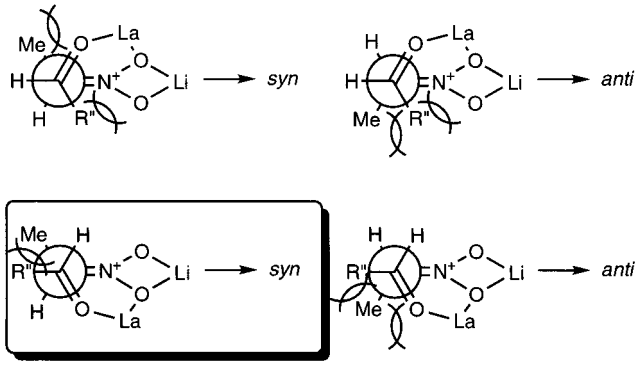
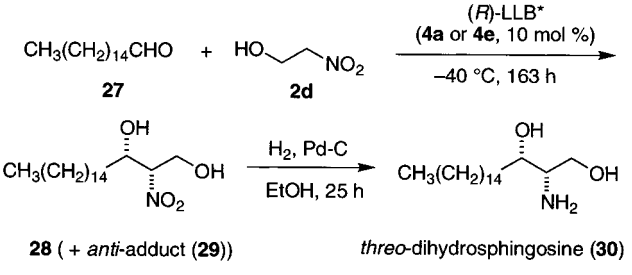


Figure 6. Newman projections of intermediates for the diastereoselective nitroaldol reaction.

Scheme 6. Catalytic Asymmetric Synthesis of *threo*-Dihydrosphingosine



cat = **4e**: 78% (*syn* / *anti* = 91:9), *syn*: 97% ee
cat = **4a**: 31% (*syn* / *anti* =86:14), *syn*: 83% ee

octacoordinated trivalent lanthanide element decreases as the atomic number of the lanthanide increases from 1.16 Å in La to 0.98 Å in Lu.[40,41] This phenomenon was clearly illustrated using a catalytic asymmetric nitroaldol reaction.[42] As shown in Figure 7, the optical purity of nitroaldols **3e**−**g** that were obtained by using the heterobimetallic catalysts (LnLB) depended on the ionic radius of the lanthanides in the catalyst. Moreover, the best lanthanide differed according to the substrates used in the reaction. These results indicate an advantage of the use of lanthanides for the asymmetric catalyst,

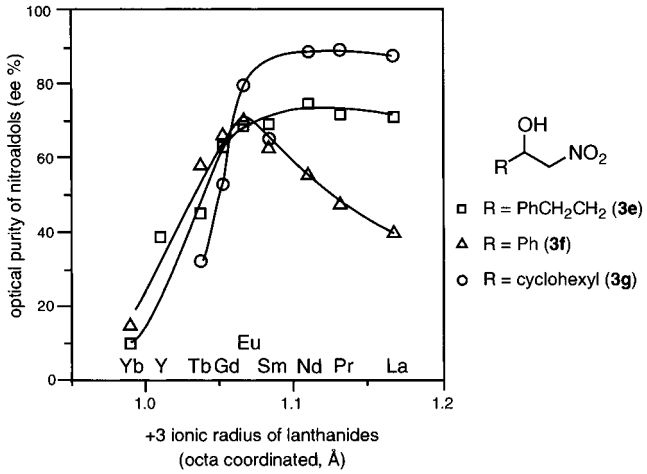


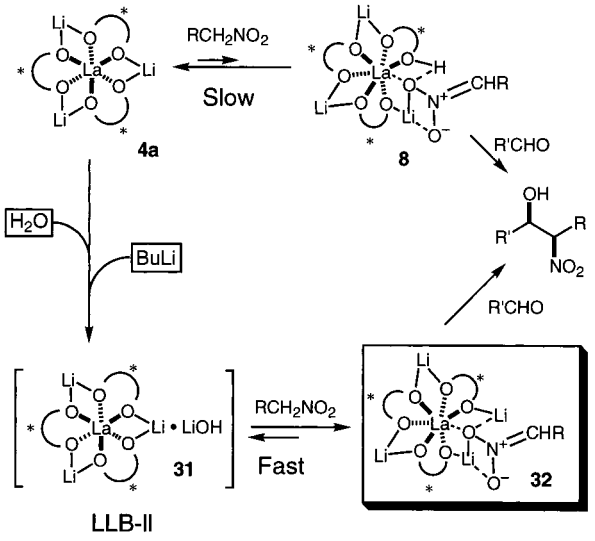
Figure 7. Effects of the ionic radii of lanthanide on the optical purity of nitroaldol adducts.

because the reaction can be optimized simply by choosing the lanthanide based on the substrate.

B. Second-Generation Heterobimetallic Catalysts: Self-Assembly of Heterobimetallic Complexes and Reactive Nucleophiles

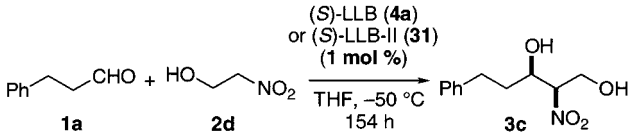
Although catalytic asymmetric nitroaldol reactions promoted by heterobimetallic complexes were highly stereoselective, most cases required a long reaction time even with relatively high catalyst loadings of 3−10 mol %. To achieve a more efficient catalysis, a novel strategy to accelerate the reactions was necessary. A possible mechanism of catalytic asymmetric nitroaldol reactions is shown at the top of Scheme 7. Because many attempts to detect intermediate **8** were unsuccessful, the concentration of **8** seemed to be rather low in the reaction mixture. The low concentration was attributed to the presence of an acidic OH group in the proximity of lithium nitronate, because the nitronate could be protonated by the OH group to give the nitroalkane and LLB (**4a**). To avoid

Scheme 7. Proposed Mechanism for the Catalytic Asymmetric Nitroaldol Reaction Promoted by LLB or LLB-II



this undesirable pathway, a catalytic amount of base (1 mol equiv to La) was added to remove the proton from **8**. Consequently, second-generation LLB (LLB-II, **31**), prepared from LLB (**4a**), H_2O (1 mol equiv to La), and BuLi (0.9 mol equiv to La), efficiently accelerated catalytic asymmetric nitroaldol reactions, even with a reduced catalyst loading (1 mol %) (Scheme 8).[43] The self-assembly of LLB (**4a**) and

Scheme 8. Acceleration of Nitroaldol Reaction by LLB-II



(*S*)-LLB (**4a**) : yield trace

(*S*)-LLB + H_2O + BuLi: yield 76% (*syn*/*anti* = 94/6), 96% ee (*syn*)
(LLB-II, **31**)

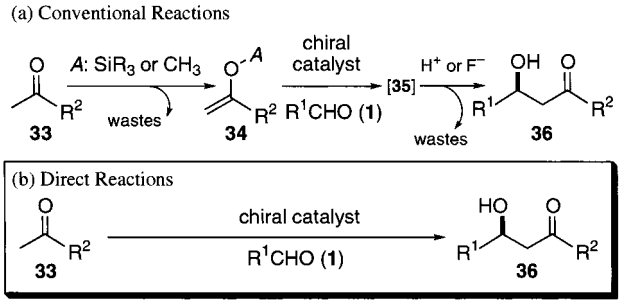
lithium nitronates was thought to readily occur to form complex **32**, because the optical purity of nitroaldols was not deteriorated. This strategy for acceleration was applied to several heterobimetallic complexes, making the reactions more practical.[44]

C. Direct Catalytic Asymmetric Aldol Reactions of Unmodified Ketones with Aldehydes

1. Methyl Ketones as Nucleophiles: Catalysis by LLB and Heteropolymetallic Complexes

The aldol reaction has gained wide acceptance as a remarkably useful synthetic tool because of the following features.[45] First, a C−C bond is easily formed between aldehydes and ketones, which are commonly available materials in organic synthesis. Second, one or two stereogenic centers are constructed simultaneously. Third, the resulting aldol adducts are also synthetically versatile compounds. Diastereo- and enantioselective aldol reactions have been performed with excellent chemical yield and stereoselectivity using catalytic amounts of chiral

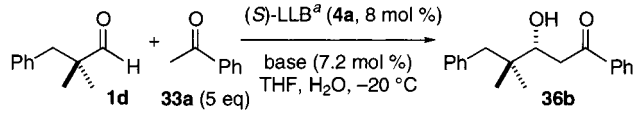
Scheme 9. Aldol-Type Addition of Latent Enolates and Direct Aldol Reaction of Unmodified Ketones



promoters.[46] Most cases, however, required the conversion of donor substrates into more reactive species (**34**, Scheme 9), such as enol silyl ethers or ketene silyl acetals (Mukaiyama-type aldol addition reaction), using no less than stoichiometric amounts of silicon atoms and bases (Scheme 9a). From an atom-economic perspective,[47] such stoichiometric amounts of reagents, which give rise to wastes such as salts, should be excluded from the procedures. Thus, direct catalytic asymmetric aldol reaction, which employs unmodified ketone **33** as a nucleophile, emerged as the next target (Scheme 9b). Other chemists have directed considerable attention to this field, which is reflected in the increasing number of publications.[48−52] In the earliest stages of the investigation, the subject appeared to be very challenging,[53] because the formation of enolates from the ketones is generally much less favorable than that from nitroalkanes, due to their high pK_a values (nitroalkanes ∼ 10, ketones ∼ 17 in H_2O).

Existing heterobimetallic multifunctional catalysts ($Li_3[La(binol)_3]$ (**4a**), $Na_3[La(binol)_3]$ (vide infra), $K_3[La(binol)_3]$ (vide infra), $Li[Al(binol)_2]$,[54] and $Li[Ga(binol)_2]$)[55] were first screened in the reaction of pivalaldehyde with acetophenone as model substrates. $Li_3[La(binol)_3]$ (**4a**, LLB)[56] catalyzed the reaction to afford the aldol adducts with up to 94% ee.[57] Other complexes such as $Na_3[La(binol)_3]$ and $K_3[La(binol)_3]$ had much lower reactivity and selectivity. Despite the high selectivity, the catalytic activity of **4a**,[56] however, was rather low, requiring at least 20 mol % catalyst loading and anhydrous reaction conditions. It was eventually determined that the addition of catalytic amounts of bases greatly enhances the catalytic activity.[58] For example, the reaction between **1d** and **33a** reached completion after 18 h to afford the product (**36b**) in 83% yield and 85% ee, when potassium bis(trimethylsilyl)amide (KHMDS) (0.9 mol equiv to La) and H_2O (2 mol equiv to La)[59] were added (Table 2, entry 4).[39] In contrast, there was no product formation in the absence of the additives after the same reaction time (entry 1). Because the catalytic species is likely to consist of three kinds of metals (La, Li, and K) as discussed below, the catalyst (**37**) was called a "heteropolymetallic catalyst". Table 3 summarizes the results of aldol reactions of various substrates tested.[39] The aldol products were obtained from α,α-disubstituted aldehydes with a range of 76−93% ee. Interestingly, α-monosubstituted or α-unsubstituted aldehydes, which possess (an) acidic proton(s) at the α-position,

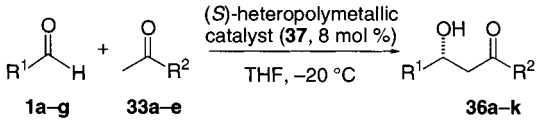
Table 2. Direct Catalytic Asymmetric Aldol Reactions of 1d with 33a under Various Conditions



entry	base	H_2O (equiv to La)	time (h)	yield (%)	ee (%)
1			18	trace	
2	KHMDS	0	18	83	58
3	KHMDS	1	18	89	79
4	KHMDS	2	18	83	85
5[b]	KHMDS	2	33	71	85
6	KHMDS	4	18	67	89
7	LHMDS	2	5	22	80
8	NHMDS	2	5	28	86
9	KHMDS	2	5	74	84

[a] LLB was prepared without addition of H_2O. See ref 56. [b] (*S*)-LLB, 3 mol %; KHMDS, 2.7 mol %.

Table 3. Direct Catalytic Asymmetric Aldol Reactions Promoted by Heteropolymetallic Asymmetric Complex 37



1c: R^1 = *t*-Bu
1d: R^1 = $PhCH_2C(CH_3)_2$
1e: R^1 = $BnOCH_2C(CH_3)_2$
1f: R^1 = *i*-Pr
1g: R^1 = Et_2CH
1a: R^1 = $PhCH_2CH_2$
1b: R^1 = *n*-C_5H_{11}

33a: R^2 = Ph
33b: R^2 = CH_3
33c: R^2 = Et
33d: R^2 = 3-NO_2-C_6H_4
33e: cyclopentanone

entry	aldehyde (R^1)	ketone[a] (R^2) (equiv)	aldol	time (h)	yield (%)	ee (%)
1	**1c**	**33a** (5)	**36a**	15	75	88
2	**1d**	**33a** (5)	**36b**	28	85	89
3	**1d**	**33b** (10)	**36c**	20	62	76
4[b]	**1d**	**33c** (15)	**36d**	95	72	88
5	**1e**	**33a** (5)	**36e**	36	91	90
6[c]	**1e**	**33a** (5)	**36e**	24	70	93
7[d]	**1f**	**33a** (5)	**36f**	15	90	33
8[e]	**1f**	**33d** (3)	**36g**	70	68	70
9[f]	**1g**	**33d** (3)	**36h**	96	60	80
10[e,g]	**1b**	**33d** (5)	**36i**	96	55	42
11[h]	**1a**	**33d** (3)	**36j**	31	50	30
12	**1d**	**33e** (5)	**36k**	99 (*syn*:*anti* = 93:7)	95	76/88 (*syn*/*anti*)

[a] Excess ketone was recovered after the reaction. [b] H_2O: 8 mol %. [c] 5.7 mmol (**1e**) scale. [d] Reaction at −30 °C. [e] Reaction at −50 °C. [f] Catalyst (**37**): 15 mol %; −45 °C. [g] Catalyst (**37**): 30 mol %. [h] Reaction at −40 °C.

resist enolization under the reaction conditions, without isolation of self-condensation products of aldehydes.

Because the KOH, generated from KHMDS and H_2O, dissolves in THF upon addition of LLB ($Li_3[La(binol)_3]$), it was postulated that the KOH could interact with any part of LLB. An analysis by laser desorption/ionization/time-of-flight mass spectra (LDI-TOF mass) suggested that the metal exchange between Li (of LLB) and K (from KOH) occurs in the catalyst solution. Nonetheless, it was believed that the real catalytic species retains the LLB framework ($Li_3[La(binol)_3]$) with KOH coordinating to the center

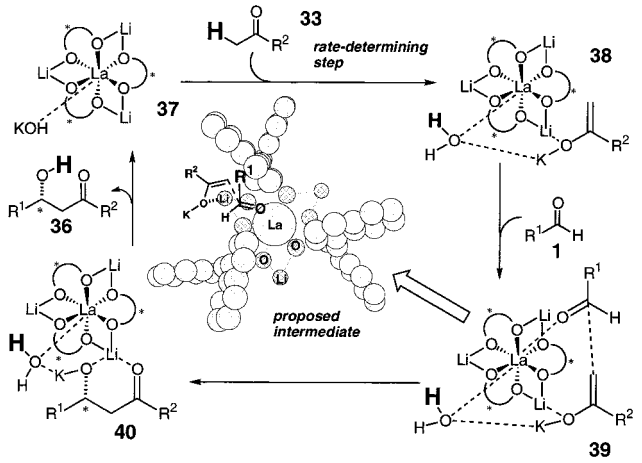


Figure 8. Working model for direct catalytic asymmetric aldol reactions promoted by heteropolymetallic complex **37**.

metal of LLB, because $K_3[La(binol)_3]$ complex (LPB; vide infra) that was separately prepared afforded a racemic aldol adduct. A plausible reaction mechanism is described in Figure 8, in which the ketone is deprotonated by KOH and the aldehyde is activated and fixed by the lanthanum ion. A kinetic study using aceto-d_3-phenone indicated a significant isotope effect ($k_H/k_D = 5$), proving that the rate-determining step lies at the formation of an enolate.[60] The coordination of aldehydes to the center metal of the catalyst was confirmed by NMR study. An upfield shift of formyl hydrogen in pivalaldehyde was observed by addition of 20 mol % of PrLB ($Li_3[Pr(binol)_3]$, **41**),[61] whereas there was no shift after the addition of $Li_2(binol)$ (Figure 9).

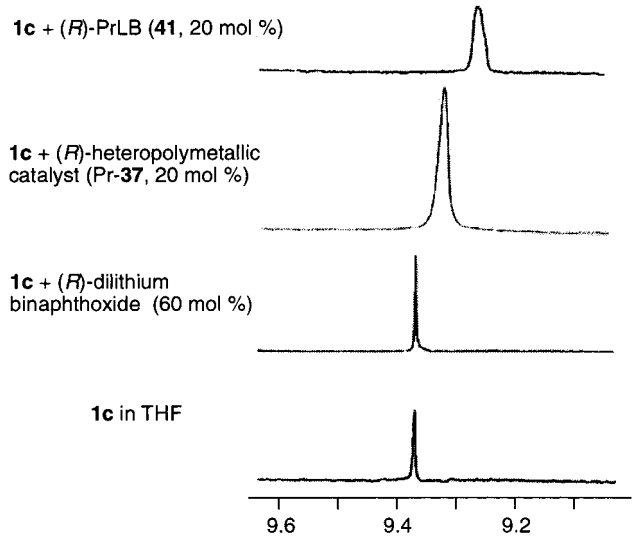


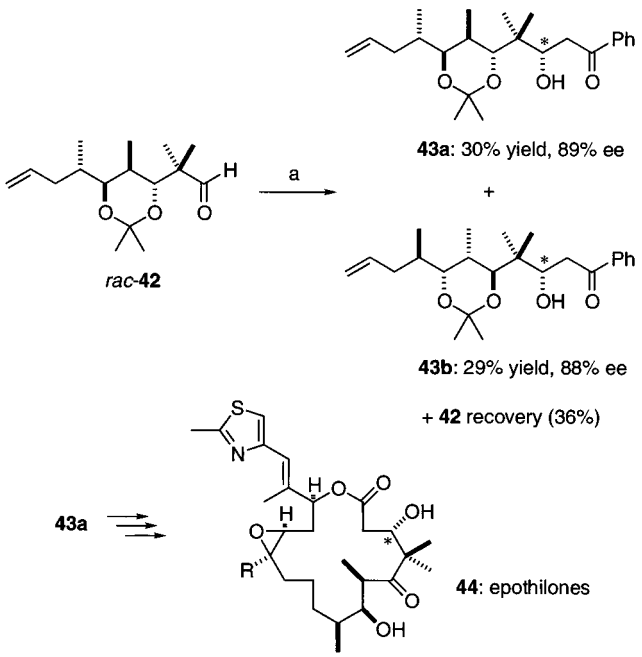
Figure 9. Chemical shift (ppm) of the formyl hydrogen in **1c**. (*R*)-Heteropolymetallic catalyst (Pr−**37**) was prepared from $Pr(O\text{-}i\text{-}Pr)_3$ instead of $La(O\text{-}i\text{-}Pr)_3$.

The direct aldol reaction has been applied to the resolution of racemic aldehyde **42** by using heteropolymetallic catalyst **37** in an enantioselective total synthesis of epothilones (**44**) (Scheme 10).[62]

2. 2-Hydroxyacetophenones as Nucleophiles

When Shibasaki et al. began to develop the diastereoselective variant of the direct aldol reaction, a

Scheme 10. Catalytic Resolution of Racemic Aldehyde 42 by Heteropolymetallic Asymmetric Complex 37 in the Enantioselective Total Synthesis of Epothilones



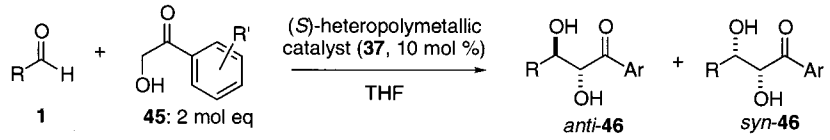
(a) Acetophenone (**33a**), (*R*)-heteropolymetallic catalyst (**37**), THF, –20 °C.

serious limitation emerged that methylene ketones such as propiophenone do not afford any products.[63] This indicates that the active site in the catalyst bears the least space for two substrates (methyl ketone and aldehyde), thus enabling high levels of enantiocontrols. This might be the reason that any substitution at the α-position of the ketone with an alkyl group, even with a methyl group, inhibited the reactions.

Hence, a direct aldol reaction of 2-hydroxyacetophenones (**45**) was investigated (Table 4), because the hydroxyl group was thought to facilitate the interaction of the ketone (**45**) with the catalyst (**37**). The preliminary reaction was performed in the presence of heteropolymetallic catalyst **37** using α,α-disubstituted aldehydes, which proved to be the most suitable class of aldehydes in the reaction with methyl ketones **33** (i.e., acetophenone, acetone, etc.). The products, however, were obtained with only poor enantiomeric excess. In contrast, α-unsubstituted aldehydes gave unexpectedly excellent results as described in Table 4.[64] Moreover, the reactions proceeded *anti*-selectively, providing a valuable approach to the catalytic asymmetric synthesis of *anti*-1,2-diols.[65−68] Although the diastereoselectivity needs to be improved for practical use, excellent enantioselectivity was achieved for most of the *anti*-aldol adducts obtained (Table 4).

Examination of the stereochemistry of the aldol products (**46**) revealed that the configuration at the *β*-position of the major diastereomer (*anti*-**46**, "a" in Figure 10) is opposite to that of aldol product **36b** from acetophenone (**33a**) ("c" in Figure 10).[58] More-

Table 4. Diastereo- and Enantioselective Direct Catalytic Aldol Reaction of 2-Hydroxyacetophenones with Aldehydes: Catalytic Asymmetric Synthesis of *anti*-1,2-Diols



1h: R = $C_6H_5(CH_2)_3$
1b: R = *n*-C_5H_{11}
1i: R = *trans*-3-nonenyl
1j: R = 2-methylpropyl
1a: R = $C_6H_5(CH_2)_2$

45a: R' = H
45b: R' = 2-MeO
45c: R' = 3-MeO
45d: R' = 4-MeO
45e: R' = 2,5-$(MeO)_2$
45f: R' = 2-Me
45g: R' = 4-Me

46a: R = $C_6H_5(CH_2)_3$, R' = H
46b: R = *n*-C_5H_{11}, R' = H
46c: R = *trans*-3-nonenyl, R' = H
46d: R = 2-methylpropyl, R' = H
46e: R = $C_6H_5(CH_2)_2$, R' = H
46f: R = $C_6H_5(CH_2)_3$, R' = 2-MeO
46g: R = $C_6H_5(CH_2)_3$, R' = 3-MeO
46h: R = $C_6H_5(CH_2)_3$, R' = 4-MeO
46i: R = $C_6H_5(CH_2)_3$, R' = 2,5-$(MeO)_2$
46j: R = $C_6H_5(CH_2)_3$, R' = 2-Me
46k: R = $C_6H_5(CH_2)_3$, R' = 4-Me
46l: R = *n*-C_5H_{11}, R' = 4-Me
46m: R = *trans*-3-nonenyl, R' = 4-Me

entry	aldehyde	ketone	products	temp (°C)	time (h)	yield (%)	dr (*anti*:*syn*)	ee (%) (*anti*/*syn*)
1	**1h**	**45a**	**46a**	−50	24	84	84:16	95/74
2	**1h**	**45a**	**46a**	−50	40	78	78:22	92/70
3	**1b**	**45a**	**46b**	−50	24	84	74:26	94/84
4	**1i**	**45a**	**46c**	−50	28	90	72:28	94/83
5	**1j**	**45a**	**46d**	−50	24	86	65:35	90/83
6	**1a**	**45a**	**46e**	−50	24	89	69:31	95/87
7	**1h**	**45b**	**46f**	−40	35	69	76:24	95/74
8	**1h**	**45c**	**46g**	−40	35	82	77:23	95/83
9	**1h**	**45d**	**46h**	−40	35	50	81:19	98/79
10	**1h**	**45e**	**46i**	−40	35	42	74:26	80/41
11	**1h**	**45f**	**46j**	−40	35	75	77:23	84/57
12	**1h**	**45g**	**46k**	−40	35	90	83:17	97/85
13	**1h**	**45g**	**46k**	−40	13	90	82:18	96/83

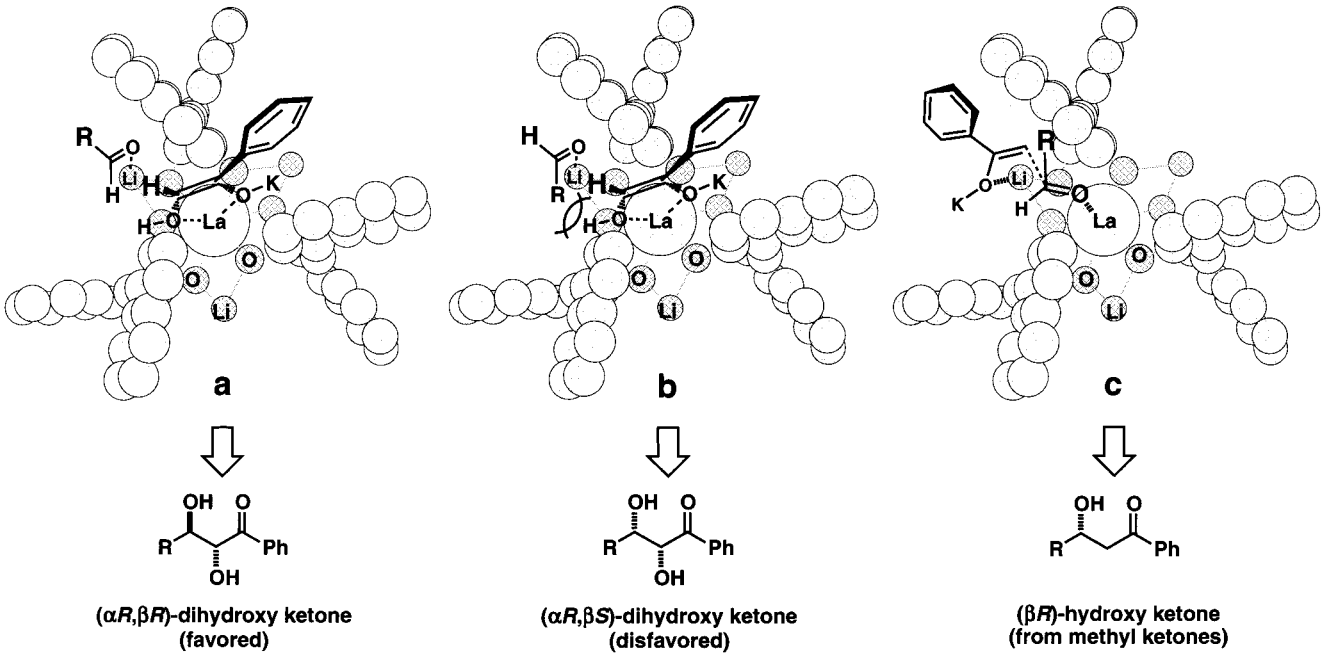


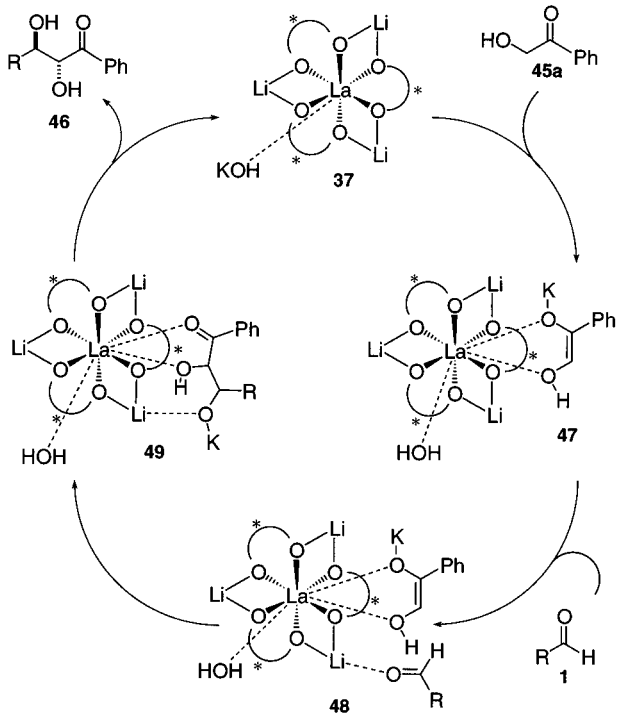
Figure 10. (a) Favored transition state for the formation of 1,2-diols. (b) Disfavored transition state. (c) Proposed transition state for the aldol reaction of acetophenone.

over, an identical configuration (*R*) was expressed at the α-position both of *anti*- and of *syn*-products (**46**) for all direct aldol reactions examined, suggesting that the aldehyde (**1**) attacks the *Re*-face of the (*Z*)-enolate for the formation of both diastereomers ("a" and "b" in Figure 10). The configuration of the *β*-position, meanwhile, would depend on a direction in which the enolate−LLB complex approaches the aldehyde, namely the differentiation of the enantioface of the *aldehyde* ("a" vs "b" in Figure 10).

As discussed in section II.C.1, the direct aldol reaction of acetophenone (**33a**) is promoted by the synergistic functions of the heteropolymetallic catalyst (**37**), wherein the lanthanum ion acts as a Lewis acid to activate the aldehyde and the KOH functions as a Brønsted base to generate an enolate from the ketone. On the basis of this mechanism and the above-described stereochemistry of the products (**46**), the following catalytic cycle (Scheme 11) can be postulated for the present system. First, 2-hydroxyacetophenone coordinates to the lanthanum metal of the catalyst (**37**) in a bidentate fashion and is deprotonated by KOH at the α-position. The resulting potassium enolate then forms a chelate complex (**47**) with the lanthanum metal of LLB. The priority of the ketone (**45**) for the coordination to the lanthanide center metal over that of the aldehyde (**1**) can be explained by the possible capability of the ketone (**45**) to form a stable complex with Lewis acids such as a lanthanum ion. Avoiding the resulting sterically crowded lanthanide center, the aldehyde subsequently coordinates to the lithium metal and is then attacked by the enolate, affording an alkoxide−LLB complex (**49**) via intermediate **48** (see also Figure 10). The resulting alkoxide−LLB complex (**49** in Scheme 11) is then protonated by H_2O to produce the dihydroxy ketone, and the catalyst (**37**) is regenerated.

Although the stereochemistry of the enolates from **45** is not evident, the formation of (*Z*)-enolates seems

Scheme 11



predominant for the following reasons. First, the chelate complex (vide supra) can be formed only from (*Z*)-enolate. Second, the formation of an enolate would be facilitated by a strong interaction between the ketone and the catalyst through a bidentate coordination with the hydroxyl and carbonyl group of **45**.

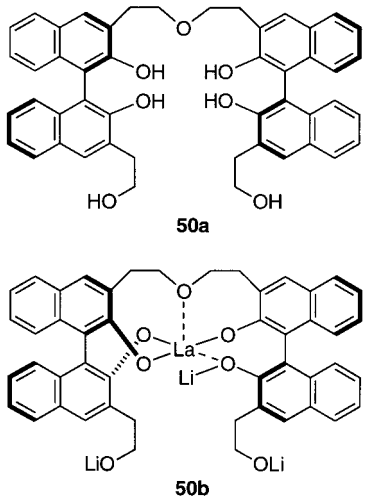
The reaction mechanism of the present system is different from that proposed for the direct aldol reaction of acetophenone (**33a**). In the latter system, the *aldehyde* coordinates to the center metal of (*S*)-LLB, and the enolate selectively attacks the *Re*-face

of the aldehyde ("c" in Figure 10). On the other hand, the *ketone* (**45**) coordinates to the center metal in the present system. Moreover, the present system is most effective for α-unsubstituted aldehydes rather than for substituted aldehydes. This tendency is in striking contrast to the case of acetophenone, wherein α,α-disubstituted aldehyde is the most suitable substrate, and suggests a difference between the transition state for the present system and that for the previous system.

3. Catalysis by a Lanthanide Complex with Lithium Alkoxides

Having established the concept of Lewis acid−Brønsted base multifunctional catalysts, Shibasaki et al. developed a novel multifunctional catalyst bearing a structural framework that is different from the conventional one. To enhance the catalytic activity, they attempted to introduce metal alkoxide as a strong Brønsted base into the catalyst. Thus, a novel ligand **50a** (Chart 4) was synthesized, and catalyst

Chart 4

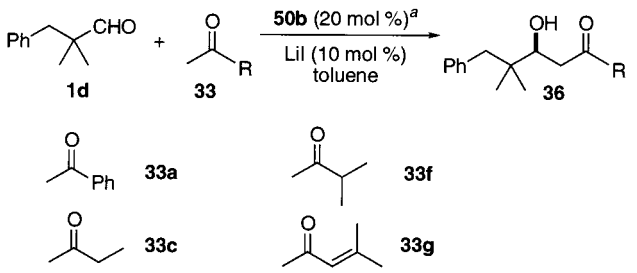


50b (a possible structure) was prepared by treatment of the ligand (**50a**) with La(O-*i*-Pr)$_3$ (1 mol equiv to **50a**) and BuLi (3 mol equiv to **50a**). The catalyst (**50b**) promoted the aldol reaction of less acidic dialkyl ketones as well as an aromatic ketone with moderate enantiomeric excess (Table 5).[69] Moreover, substantial deceleration of the reaction was observed when the catalyst was prepared from typical-group metals or d-block metals in place of lanthanoid or with reduced amounts of BuLi, indicating that the reaction was promoted by the cooperation of lanthanum and lithium.

III. Heterobimetallic Catalysts Based on Lanthanide and Sodium (LnSB)

As mentioned in the Introduction, the choice of the appropriate metal element on the basis of the type of the reaction significantly influences the efficiency of the catalysis in terms of both reactivity and selectivity. This is also the case in multifunctional catalysis by lanthanide complexes, which are summarized in the following sections.

Table 5. Direct Aldol Reaction Catalyzed by La−Li−Alkoxide Complex 50b



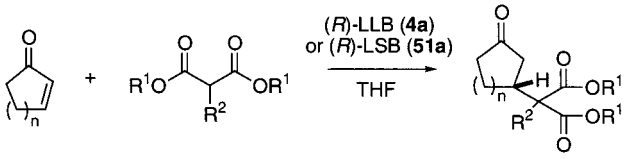
entry	ketone (mol equiv)	temp (°C)	product	time (h)	yield (%)	ee (%)
1	**33a** (2)	−30	**36b**	4	70	67
2	**33c** (5)	−20	**36d**	14	71	40
3	**33f** (5)	−20	**36l**	71	62	45
4	**33g** (5)	−30	**36m**	50	66	60
5	**33g** (5)	−20	**36m**	14	70	52

[a] BuLi provided by Aldrich was used for catalyst preparation.

A. Michael Additions of Malonates

While the structure of $Li_3[La(binol)_3]$ (LLB, **4a**) was investigated, another heterobimetallic complex consisting of La, Na, and BINOL ($Na_3[La(binol)_3]$, LSB, **51a**) was synthesized according to a procedure similar to that for LLB. The structure of LSB (**51a**) was determined by X-ray crystallographic analysis.[29] While LLB (**4a**) was ineffective for a Michael reaction,[70] LSB (**51a**) proved to be a suitable catalyst for this type of reaction.[71,72] Substituted or unsubstituted malonates reacted with α,β-unsaturated ketones to give the Michael adducts in excellent yield and enantiomeric excess. The results are summarized in Tables 6 and 7.

Table 6. Michael Reaction: Enantioselection on Acceptors



52a: n = 2
52b: n = 1

53a: R^1 = Bn, R^2 = H
53b: R^1 = Bn, R^2 = Me
53c: R^1 = Me, R^2 = H

54a: n = 2, R^1 = Bn, R^2 = H
54b: n = 2, R^1 = Bn, R^2 = Me
54c: n = 2, R^1 = Me, R^2 = H
54d: n = 1, R^1 = Bn, R^2 = Me

entry	enone	Michael donor	product	catal	temp (°C)	time (h)	yield (%)	ee (%)
1	**52a**	**53a**	**54a**	LSB (**51a**)	rt	12	98	85
2	**52a**	**53a**	**54a**	LLB (**4a**)	rt	12	78	2
3	**52a**	**53b**	**54b**	LSB (**51a**)	0	24	91	92
4	**52a**	**53c**	**54c**	LSB (**51a**)	rt	12	98	83
5	**52b**	**53b**	**54d**	LSB (**51a**)	−40	36	89	72

B. Conjugate Additions of Thiols

The success in the Michael reaction led to the examination of other nucleophiles in place of malonates. Because thiols undergo a similar type of conjugate addition reaction, investigations were focused on the catalytic asymmetric conjugate addition

Table 7. Michael Reaction: Enantioselection on Donors

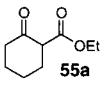
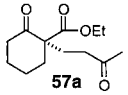
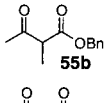
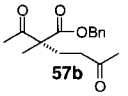
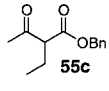
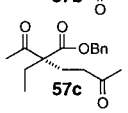
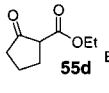
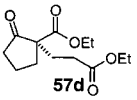
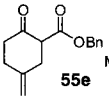
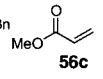
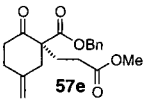
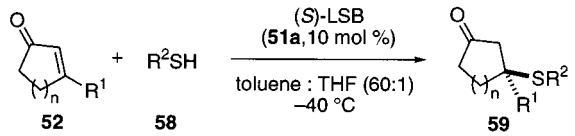
Michael donor	Michael acceptor	product	cat ((*R*)-**51a**) amount (mol %)	time (h)	yield (%)	ee (%)
 **55a**	 **56a**	 **57a**	5	19	89	91
 **55b**	**56a**	 **57b**	5	16	93	83
 **55c**	**56a**	 **57c**	5	16	98	89
 **55d**	 **56b**	 **57d**	20	18	97	84
 **55e**	 **56c**	 **57e**	20	93	69	89

Table 8. Catalytic Asymmetric Conjugate Addition of Thiols to Enones



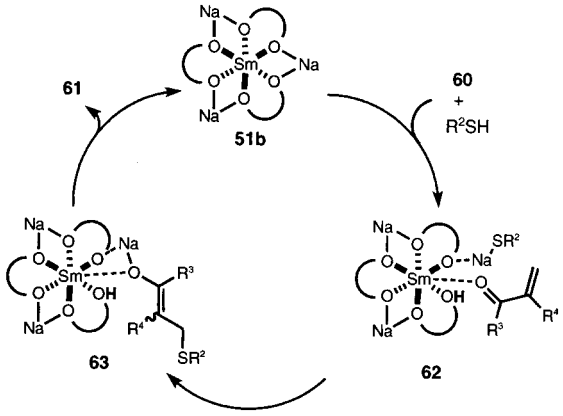
52 **58** **59**

enone	R^2	product	time	yield (%)	ee (%)
$n = 2$, R^1 = H (**52a**)	4-*t*-BuPh (**58a**)	**59a**	20 min	93	84
52a	Ph (**58b**)	**59b**	20 min	87	68
52a	$PhCH_2$ (**58c**)	**59c**	14 h	86	90
$n = 1$, R^1 = H (**52b**)	**58c**	**59d**	4 h	94	56
$n = 3$, R^1 = H (**52c**)	**58c**	**59e**[a]	41 h	87	83
$n = 2$, R^1 = Me (**52a**)	**58c**	**59f**[a,b]	43 h	56	85

[a] 20 mol % of catalyst was used, and toluene was used as solvent. [b] Reaction at −20 °C.

of thiols to α,β-unsaturated carbonyl compounds.[73] Heterobimetallic complexes containing sodium (Na_3-[Ln(binol$_3$)], LnSB, **51**) efficiently promoted the addition of thiols including benzyl mercaptan to α,β-unsaturated thioesters as well as α,β-unsaturated ketones. In particular, LSB (Na_3[La(binol$_3$)], **51a**) and SmSB (Na_3[Sm(binol)$_3$], **51b**) had excellent performance, giving the products with up to 93% ee (Tables 8 and 9).[39,74,75] The chirality in products **61** (Table 9)[39] should be generated at the protonation step. Namely, catalytic asymmetric protonation using a heterobimetallic complex was achieved.[76] The proposed mechanism is shown in Scheme 12. The reaction was applied to the total synthesis of epothilones, together with a direct aldol reaction.[62]

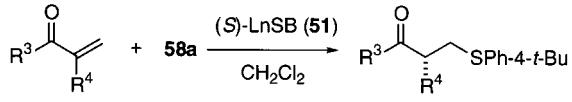
Scheme 12. Proposed Mechanism for Catalytic Asymmetric Protonation in the Conjugate Addition of Thiols



IV. Heterobimetallic Catalysts Based on Lanthanide and Potassium (LnPB): Hydrophosphonylations, Hydrophosphination, and Michael Addition of Nitromethane

The synthesis of acyclic and cyclic α-amino phosphonic acids is an important topic in modern pharmaceutical chemistry, and several methods for stereoselective synthesis of α-amino phosphonic acid derivatives have been reviewed.[77] Shibasaki et al. recently demonstrated an efficient approach to catalytic asymmetric synthesis of these biologically interesting compounds[78] by means of hydrophosphonylation of imines using heterobimetallic multifunctional catalysts. Different from the above cases, heterobimetallic complexes containing potassium (K_3-

Table 9. Catalytic Asymmetric Protonations in Conjugate Additions of Thiols

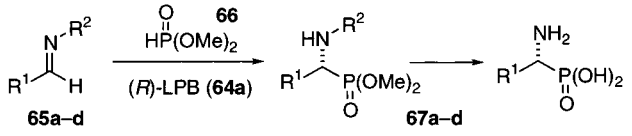


60a–e **61a–e**

enone									
R^3	R^4	no.	product	Ln	catal (mol %)	temp (°C)	time (h)	yield (%)	ee (%)
EtO	Me	**60a**	**61a**[a]	La (**51a**)	20	−20	48	44	75
EtO	Me	**60a**	**61a**	La (**51a**)	20	−20	48	50	82
EtS	Me	**60b**	**61b**	La (**51a**)	20	−78	2	93	90
EtS	Me	**60b**	**61b**	La (**51a**)	10	−78	8	90	88
EtS	Me	**60b**	**61b**	Sm (**51b**)	10	−78	7	86	93
EtS	Me	**60b**	**61b**	Sm (**51b**)	2	−78	6	89	88
EtS	*i*-Pr	**60c**	**61c**	Sm (**51b**)	10	−78	7	78	90
EtS	$PhCH_2$	**60d**	**61d**	Sm (**51b**)	10	−78	7	89	87
EtS	Ph	**60e**	**61e**	Sm (**51b**)	10	−93	1	98	84

[a] Toluene was used as solvent.

Table 10



65a, **67a**: R^1 = *i*-Pr, R^2 = DAM
65b, **67b**: R^1 = *i*-Pr, R^2 = $CHPh_2$
65c, **67c**: R^1 = Et, R^2 = $CHPh_2$
65d, **67d**: R^1 = C_5H_{11}, R^2 = $CHPh_2$

DAM = $CH(C_6H_4$-*p*-$OCH_3)_2$

entry	imine	product	catal amt (mol %)	time (h)	yield (%)	ee (%)
1	**65a**	**67a**	10	96	70	96
2	**65b**	**67b**	5	143	82	92
3	**65c**	**67c**	20	70	80	91
4	**65d**	**67d**	20	87	87	85

[Ln(binol)$_3$], LnPB, **64**) were effective, whereas lithium- or sodium-based complexes (Li_3[Ln(binol)$_3$] or Na_3[Ln(binol)$_3$]) were less effective. Dialkyl phosphites reacted with acyclic imines in the presence of the LPB catalyst (K_3[La(binol)$_3$], **64a**)[79] and with cyclic imines in the presence of the YbPB catalyst (K_3[Yb(binol)$_3$], **64b**),[80−82] affording the corresponding α-amino phosphates with high enantiomeric excess (Table 10 and Scheme 13).[83] The reaction of diphenylphosphine oxide with cyclic imines was catalyzed by PrPB (K_3[Pr(binol)$_3$], **64c**) as well (Table 11).[84] On the other hand, the enantioselective hydrophosphonylation of aldehydes was efficiently catalyzed by a lithium-based catalyst (LLB, **4a**), even at −78 °C (Table 12).[85−87] These results indicate that the best catalyst can be obtained simply by selecting the appropriate combination of metals.

The LPB complex (K_3[La(binol)$_3$], **64a**) also promotes the enantioselective Michael addition of nitromethane to chalcones. In this system, the addition of *t*-BuOH was essential to obtain a high chemical yield and enantioselectivity (Scheme 14).[88]

Scheme 13. Hydrophosphonylation of Cyclic Imines

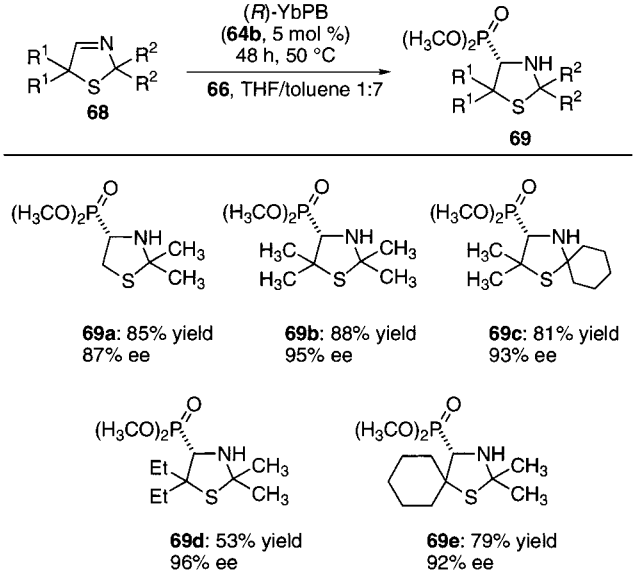
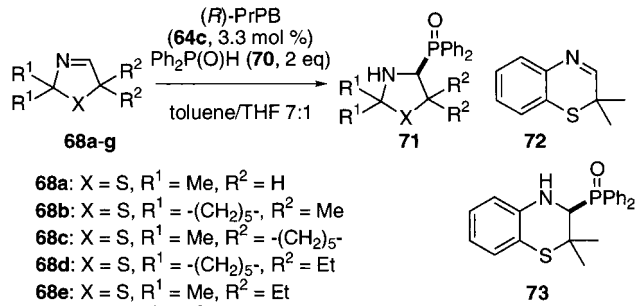


Table 11. Catalytic Asymmetric Addition of Diphenylphosphine Oxide to Cyclic Imines

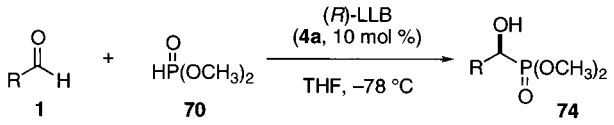


68a: X = S, R^1 = Me, R^2 = H
68b: X = S, R^1 = -$(CH_2)_5$-, R^2 = Me
68c: X = S, R^1 = Me, R^2 = -$(CH_2)_5$-
68d: X = S, R^1 = -$(CH_2)_5$-, R^2 = Et
68e: X = S, R^1 = Me, R^2 = Et
68f: X = S, R^1 = R^2 = Me
68g: X = CH_2, R^1 =Me, R^2 = H

entry	imine	product	yield (%)	ee (%)
1	**68a**	**71a**	98	91
2	**68b**	**71b**	98	93
3	**68c**	**71c**	95	92
4	**68d**	**71d**	98	81
5	**68e**	**71e**	76	82
6	**68f**	**71f**	50	92
7[a]	**68g**	**71g**	63	75
8	**72**	**73**	72	82

[a] Reaction at room temperature.

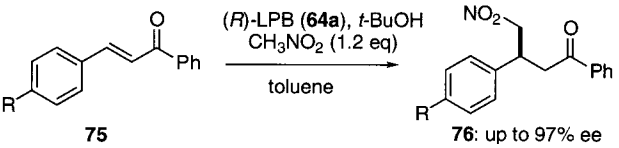
Table 12. Enantioselective Hydrophosphonylation of Aldehydes



1k, **74a**: R = Ph
1l, **74b**: R = 4-NO_2-C_6H_4
1m, **74c**: R = 4-Cl-C_6H_4
1n, **74d**: R = 4-CH_3-C_6H_4
1o, **74e**: R = 4-CH_3O-C_6H_4
1p, **74f**: R = 4-$(CH_3)_2N$-C_6H_4
1q, **74g**: R = (*E*)-PhCH=CH
1r, **74h**: R = (*E*)-$PhCH=C(CH_3)$
1s, **74i**: R = (*E*)-$CH_3(CH_2)_2CH=CH$
1b, **74j**: R = $CH_3(CH_2)_4$

entry	aldehyde	product	time (h)	yield (%)	ee (%)
1	**1k**	**74a**	8	88	79
2	**1l**	**74b**	12	85	36
3	**1m**	**74c**	8	80	63
4	**1n**	**74d**	7	93	78
5	**1o**	**74e**	8	87	93
6	**1p**	**74f**	12	88	95
7	**1q**	**74g**	8	90	84
8	**1r**	**74h**	8	94	92
9	**1s**	**74i**	8	63	75
10	**1b**	**74i**	8	88	61

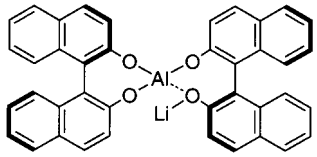
Scheme 14. Catalytic Asymmetric Michael Addition of Nitromethane to Enones



V. Other Heterobimetallic Complexes Containing Lanthanides

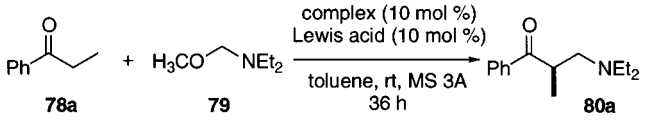
Having achieved direct aldol reaction of unmodified ketones with aldehydes (section II.C), Shibasaki et al. attempted to extend the use of unmodified ketones as nucleophiles in the reaction with imines, namely the Mannich-type reaction.[89−93] Among various het-

Chart 5. Li[Al(*R*-binol)$_2$] ((*R*)-ALB)



77

Table 13. Direct Catalytic Asymmetric Mannich-Type Reactions Using Unmodified Ketone: Effects of Lewis Acids

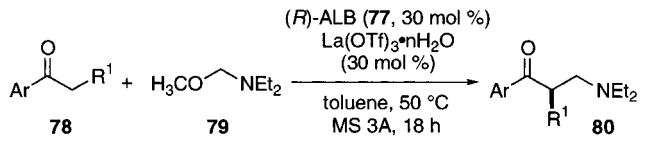


78a **79** **80a**

entry	complex	Lewis acid	yield (%)	ee (%)
1	(*R*)-LLB (**4a**)[a]		12	25
2	(*R*)-LLB (**4a**)[a]	La(OTf)$_3$·*n*H$_2$O	18	9
3	(*R*)-LLB (**4a**)[a]	Yb(OTf)$_3$·*n*H$_2$O	23	0
4	(*R*)-ALB (**77**)		6	16
5	(*R*)-ALB (**77**)	Sc(OTf)$_3$·*n*H$_2$O	66	2
6	(*R*)-ALB (**77**)	Yb(OTf)$_3$·*n*H$_2$O	55	10
7	(*R*)-ALB (**77**)	La(OTf)$_3$·*n*H$_2$O	53	30
8		La(OTf)$_3$·*n*H$_2$O	35	

[a] See ref 94.

Table 14



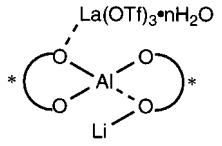
78 **79** **80**

entry	ketone Ar	ketone R^1	ketone no.	product	yield (%)	ee (%)
1	Ph	CH_3	**78a**	**80a**	65	40
2	Ph	C_2H_5	**78b**	**80b**	69	34
3	4-$CH_3OC_6H_4$	CH_3	**78c**	**80c**	76	31
4	2-naphthyl	CH_3	**78d**	**80d**	61	44
5	6-CH_3-2-naphthyl	CH_3	**78e**	**80e**	69	44

erobimetallic complexes, encouraging results were achieved with LLB (**4a**, Li$_3$[La(binol)$_3$])[94] and ALB (Li[Al(binol)$_2$])[54] (**77**, Chart 5) (Table 13, entries 1 and 4). After many trials attempting to improve the reaction, significant effects of Lewis acids as additives were discovered. The reactivity and selectivity were greatly improved by addition of La(OTf)$_3$·*n*H$_2$O to ALB (**77**). While the product was obtained in only 6% yield in the absence of La(OTf)$_3$·nH$_2$O, a moderate yield (53%) was achieved using ALB−La(OTf)$_3$ as a catalyst (Table 13, entry 7). Moreover, enantiomeric excess also improved from 16% to 30%. Table 14 summarizes the results using several unmodified ketones. The structure of the catalytic species was speculated to be **81** (Chart 6) based on LDI-TOF MS data.

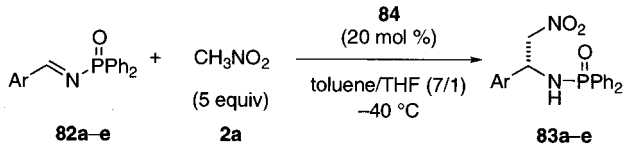
In 1999, Shibasaki et al. first reported a catalytic asymmetric nitro-Mannich-type reaction[95] by developing Yb−K−BINOL complexes.[96] Although a conventional composition of Yb, K, and BINOL (1:3:3) afforded only modest results, fine-tuning of the procedure for catalyst preparation revealed a much more effective catalyst with the composition of 1:1:3. This novel catalyst promoted the reaction of nitromethane with several *N*-phosphinoylimines to afford the desired products with up to 91% ee (Table 15). A proposed structure of the catalyst is shown in Chart 7.

Chart 6



81

Table 15. Catalytic Asymmetric Nitro-Mannich-Type Reactions

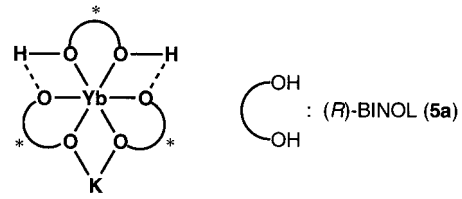


82a–e **2a** **83a–e**

entry	Ar	imine	product	time (h)	yield (%)	ee (%)
1	Ph	**82a**	**83a**	60	79	91
2	4-Cl-C_6H_4	**82b**	**83b**[a]	60	93	87
3	*p*-tolyl	**82c**	**83c**[a]	168	85	89
4	2-furyl	**82d**	**83d**[a]	168	57	83
5	2-thiophenyl	**82e**	**83e**[a]	168	41	69

[a] The absolute configuration was tentatively assigned.

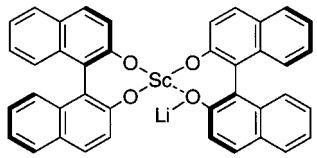
Chart 7. Proposed Structure of the Catalyst for the Nitro-Mannich-Type Reaction



84

Vallée et al. recently examined the possibility of activating HCN[97] for an asymmetric Strecker reaction[98,99] with the aid of the Brønsted basicity of the heterobimetallic multifunctional catalysts. Because existing heterobimetallic catalysts gave unsatisfactory results, they investigated two new heterobimetallic complexes containing Ti(III) or Sc(III), based on the M(III)−BINOL−lithium structure. The Sc−Li catalyst (Li[Sc(binol)$_2$]) (**85**, Chart 8) promoted

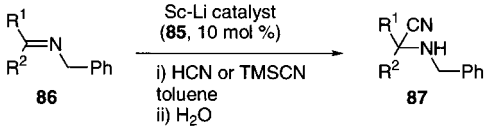
Chart 8. Vallée's Sc−Li−BINOL Complex



85

asymmetric hydrocyanation of ketimines as well as that of aldimines using TMSCN or HCN as a cyanide source, giving the amino nitriles with moderate to

Table 16. Strecker-Type Reactions Catalyzed by Sc−Li Catalyst 85



86a, 87a: R^1 = Ph, R^2 = H
86b, 87b: R^1 = 2-naphthyl, R^2 = H
86c, 87c: R^1 = Ph, R^2 = Me

entry	imine	product	CN source	temp (°C)	time (h)	yield (%)	ee (%)
1	**86a**	**87a**	TMSCN	−20	1	50	95
2	**86a**	**87a**	TMSCN	−20	3	80	91
3	**86a**	**87a**	TMSCN	−20	9	>95	88
4	**86a**	**87a**	TMSCN	−20	96	>95	85
5	**86a**	**87a**	HCN	−40	1	55	75
6	**86a**	**87a**	HCN	−40 to 0	4	95	81
7	**86b**	**87b**	TMSCN	−20	3	45	65
8	**86b**	**87b**	HCN	0	1	60	71
9	**86b**	**87b**	HCN	−20	1	80	86
10	**86c**	**87c**	TMSCN	−20	1	20	55
11	**86c**	**87c**	TMSCN	−20	3	42	50
12	**86c**	**87c**	TMSCN	−20	6	70	45

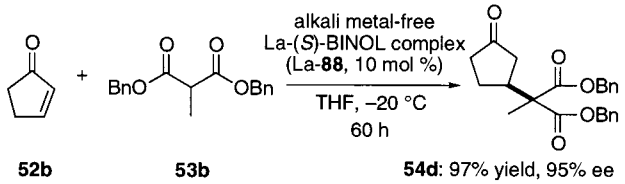
excellent enantiomeric excess (Table 16). The reaction mechanism, however, has not yet been clarified.

VI. Alkali-Metal-Free Lanthanide Complexes

A. Development of a Lithium-Free Lanthanum−BINOL Complex: A Catalytic Asymmetric Michael Reaction

While efforts to develop an efficient catalyst for the Michael reaction led to the discovery of LSB (**51a**), another strategy to achieve an asymmetric Michael reaction had been already launched.[70] Because preliminary attempts to utilize the heterobimetallic complex containing lanthanum and lithium (Li_3[Ln(binol)$_3$]) gave rise to the formation of Michael adducts with poor yield and poor enantiomeric excess, early studies focused on the preparation of a lithium-free lanthanum−BINOL complex that could form a structurally different enolate intermediate. As a result, a suspension (La−**88**) was formed upon mixing La(O-*i*-Pr)$_3$ and (*S*)-BINOL (**5a**, 1 mol equiv to La) that possessed catalytic activity toward a Michael reaction. Further optimized procedures gave Michael adducts in excellent yield with good to excellent enantiomeric excess (up to 95% ee) (Scheme 15).[100]

Scheme 15. Catalytic Asymmetric Michael Reaction Promoted by an Alkali-Metal-Free Lanthanum Complex



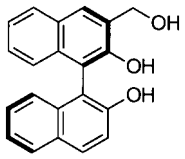
52b **53b** **54d**: 97% yield, 95% ee

B. Catalytic Asymmetric Epoxidations of α,β-Unsaturated Carbonyl Compounds

During successful development of C−C bond-forming reactions in asymmetric catalysis, attention was also directed to heteroatom−carbon bond-forming reactions due to the growing need of methods for stereoselective synthesis of highly functionalized molecules. A typical example is the catalytic asymmetric epoxidation of olefins,[101] which is discussed in this section.

As discussed in sections III and VI.A, Shibasaki et al. succeeded in developing two types of catalysts, namely LSB (**51a**) and alkali-metal-free La−BINOL complex (La−**88**), for catalytic asymmetric Michael addition of malonates to enones and hypothesized that these types of catalysts would also be effective for the asymmetric Michael-type addition of hydroperoxides to enones, leading to the formation of optically active epoxides.[102] As expected, chalcone reacted with *tert*-butyl hydroperoxide (TBHP) in the presence of LSB (**51a**, 10 mol %) and gave the corresponding α,β-epoxy ketone in 92% yield with 83% ee. This catalyst (**51a**), however, was applicable to only a limited range of enones. In contrast, an alkali-metal-free La−BINOL complex (La−**88**), which is another effective catalyst for Michael additions of malonates to enones, furnished optically active α,β-epoxy ketones from a wide range of *trans*-enones with excellent enantiomeric excess when cumene hydroperoxide (CMHP) was used as an oxidant. Moreover, the use of 3-(hydroxymethyl)-BINOL (**89**, Chart 9)

Chart 9

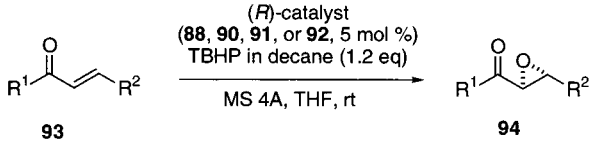


89

as a ligand gave better results (Table 17A).[103] Further optimization revealed that the best lanthanide metal depended on the substrate. Whereas La was the best metal for chalcone-type substrates, complexes prepared from Yb(O-*i*-Pr)$_3$ (Yb−**88** or **90**) exhibited better catalytic activity for aliphatic substrates using TBHP as an oxidant (Table 17A,B).[103,104] The catalysts (La−**88** and Yb−**88**) were also applicable to *cis*-enones, affording the corresponding *cis*-epoxides with high enantiomeric excess (Table 18).[105]

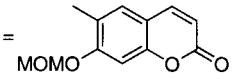
Despite excellent enantioselectivity, there remained one major drawback. For certain types of substrates, the reaction required a long time to complete the conversion of the substrates even with a relatively high catalyst loadings of 5−8 mol %. In 1998, Inanaga et al. reported that the catalytic activity of **88** was enhanced by the addition of $Ph_3P{=}O$ (Table 17C).[106] The phosphine oxide, however, had to be added in excess amount with respect to the lanthanum metal to obtain sufficient reactivity. Shibasaki et al. reported the enhancement of the catalytic activity with minimal additives.[107,108] As discussed below, those attempts led to precise determination of the structure of the alkali-metal-free lanthanum−BINOL complex (**88a**), which was for a long time unknown. The initial investigations were performed using chalcone as a model substrate, and

Table 17



93 **94**

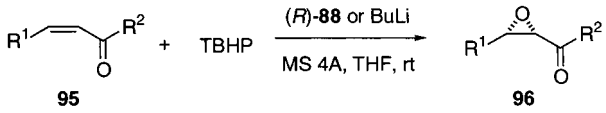
93b, **94b**: R^1 = *o*-MOMO-C_6H_4, R^2 = Ph
93c, **94c**: R^1 = Ph, R^2 = *i*-Pr
93d, **94d**: R^1 = *t*-Bu, R^2 = Ph
93e, **94e**: R^1 = *i*-Pr, R^2 = Ph
93f, **94f**: R^1 = CH_3, R^2 = Ph
93g, **94g**: R^1 = CH_3, R^2 = CH_2CH_2Ph
93h, **94h**: R^1 = CH_3, R^2 = C_5H_{11}
93i, **94i**: R^1 = CH_3, R^2 = Ar

Ar = 

			A: Ln−BINOL (**88**)[a]			B: Yb−BINOL (2:3) (**90**)[b]			C: La−BINOL−Ph_3P=O (**91**)[c]			D: La−BINOL−Ph_3As=O (**92**)[d]		
entry	enone	epoxide	time (h)	yield (%)	ee (%)	time (h)	yield (%)	ee (%)	time (h)	yield (%)	ee (%)	time (h)	yield (%)	ee (%)
1	**93a**	**94a**	7	93	91[e,g]	1	99	81	0.5	99	96	0.25	99	96
2	**93a**	**94a**	44	95	89[e,g]							3	97	89
3	**93b**	**94b**	20	85	85[e]							4	91	95
4	**93c**	**94c**	7	95	94[e,g]				1	89	93	1.5	95	94
5	**93d**	**94d**										7	94	98
6	**93e**	**94e**	159	55	88[f,g,h]	48	82	93	12	67	96	8	72	95
7	**93f**	**94f**	96	83	94[f,g]	13	92	94	6	92	93	6	92	>99
8	**93g**	**94g**	118	91	88[f,g,h]				1	92	87	1.5	98	92
9	**93h**	**94h**	67	71	91[f,g,h]							1.5	89	95
10[f]	**93i**	**94i**	15	68	83[f]	48	65	85	2.5	98	97	2	94	96

[a] See ref 103. [b] H_2O (4.5 mol equiv to Yb) was added. See ref 104. [c] See ref 106. [d] See ref 107. [e] Ln = La (**88a**). [f] Ln = Yb (**88b**). [g] 3-(Hydroxymethyl)-BINOL (**89**, 1.25 mol equiv to La) was used as a ligand. [h] Catalyst: 8 mol %. [i] Catalyst: 25 mol %.

Table 18



95 **96**

95a, **96a**: R^1 = C_5H_{11}, R^2 = CH_3
95b, **96b**: R^1 = C_3H_7, R^2 = $(CH_2)_2Ph$
95c, **96c**: R^1 = C_5H_{11}, R^2 = C_3H_7
95d, **96d**: R^1 = CH_3, R^2 = Ph
95e, **96e**: R^1 = C_3H_7, R^2 = Ph

entry	substrates	catal (mol %)	TBHP (equiv)	time (h)	*cis*-**91:** yield (%), ee (%)	*trans*-**91:** yield (%), ee (%)
1	**95a** → **96a**	BuLi (10)	3	22	8, nd	43, nd
2	**95a** → **96a**	La−**88** (5)[a]	1.5	72	31, 5	<10, nd
3	**95a** → **96a**	Yb−**88** (5)[a]	1.5	72	60, 4[b]	<10, nd
4	**95a** → **96a**	La−**88** (10)[c,d]	3	72	58, 58	<10, nd
5	**95a** → **96a**	Yb−**88** (10)[c,d]	3	72	74, 94	trace, nd
6	**95b** → **96b**	Yb−**88** (10)[c]	3	146	56, 21[b]	<10, nd
7	**95b** → **96b**	Yb−**88** (10)[c,d]	3	146	78, 93	trace, nd
8	**95c** → **96c**	Yb−**88** (10)[c]	3	127	75, 27[b]	trace, nd
9	**95c** → **96c**	Yb−**88** (10)[c,d]	3	127	80, 96	trace, nd
10	**95d** → **96d**	Yb−**88** (10)[c,d]	3	81	60, 82	32, 10[e]
11	**95e** → **96e**	Yb−**88** (10)[c,d]	3	96	51, 88	19, 58[e]

[a] Prepared from Ln(O-*i*-Pr)$_3$ and ligand (**5a** or **89**) in a ratio of 1:1.4. [b] The opposite enantiomer was obtained. [c] Prepared from Ln(O-*i*-Pr)$_3$ and ligand (**5a** or **89**) in a ratio of 1:1. [d] Ligand **89** was used. [e] Absolute configuration was determined to be (αS,βR).

the results are summarized in Table 19. As indicated in entries 2 and 3, Inanaga's conditions successfully shortened the reaction time from 90 to 30 min. The reaction was also performed under the same conditions except for the reduced amount of Ph_3P=O (10−30 mol %) (entries 4−6), and there was a slightly decreased yield and enantiomeric excess. The screening of many additives revealed that the addition of Ph_3As=O was very effective for the enhancement of the catalytic activity, even with reduced amounts (entries 7−10). The reaction was completed in only 3 min, giving the product in 95% yield and 97% ee when 10 mol % of Ph_3As=O was added (entry 10). Table 17D summarizes the effectiveness of the catalyst system (**92**) including Ph_3As=O in comparison with other catalysts (**88**, **90**, and **91**).

Having established an efficient and general catalyst system (**92**), Shibasaki et al. next focused on the reaction mechanism. Since the discovery of the alkali-metal-free lanthanum−BINOL catalysts (**88**, **90**, and **91**), little information has been obtained concerning the catalyst structure. Although analysis of the catalyst solution by ^{13}C NMR suggested that the catalysts might exist as oligomers, the structure (**97**) shown in Chart 10 arose as a candidate for the catalytic species on the basis of LDI-TOF mass

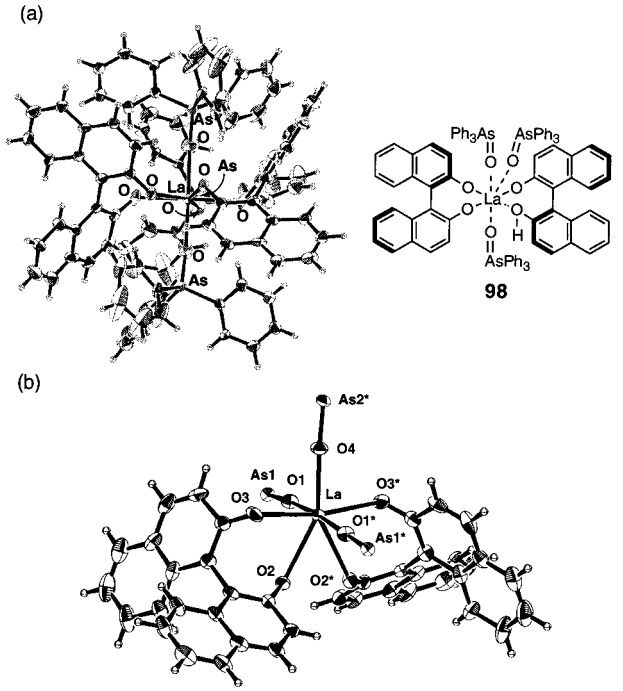
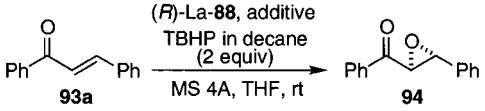


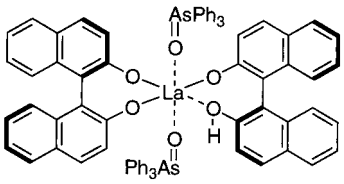
Figure 11. (a) X-ray structure of La(binaphthoxide)$_2$(Ph_3As=O)$_3$. (b) Phenyl moieties of the Ph_3As=O omitted for clarity. Selected bond lengths (Å): La−O(1), 2.365(5); La−O(1*), 2.365(5); La−O(2), 2.684(6); La−O(2*), 2.684(6); La−O(1), 2.635(5); La−O(1*), 2.635(5); La−O(2), 2.684(6); La−O(2*), 2.684(6); La−O(3), 2.437(5); La−O(3*), 2.437(5); La−O(4), 2.391(8).

Table 19. Effects of Additives on the Epoxidation Promoted by La−BINOL Complex (La−88)



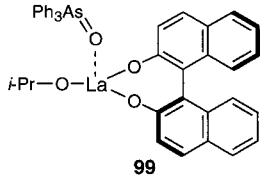
entry	catal (mol %)	additive (mol %)	time (min)	yield (%)	ee (%)
1	La(O-*i*-Pr)$_3$ (10)	none	480	90	
2	La−**88** (1:1) (10)	none	90	92	71
3	La−**88** (1:1) (10)	Ph_3P=O (40)	30	98	97
4	La−**88** (1:1) (10)	Ph_3P=O (30)	30	97	97
5	La−**88** (1:1) (10)	Ph_3P=O (20)	30	94	95
6	La−**88** (1:1) (10)	Ph_3P=O (10)	30	93	94
7	La−**88** (1:1) (10)	Ph_3As=O (40)	60	92	85
8	La−**88** (1:1) (10)	Ph_3As=O (30)	30	92	93
9	La−**88** (1:1) (10)	Ph_3As=O (20)	30	96	95
10	La−**88** (1:1) (10)	Ph_3As=O (10)	3	95	97
11	La(O-*i*-Pr)$_3$ (10)	Ph_3As=O (10)	480	64	

Chart 10. Possible Structure of the Major Complex in the Catalyst Solution Generated from La(O-*i*-Pr)$_3$, (*R*)-BINOL, and Ph_3As=O in a Ratio of 1:1:1



97

Chart 11. Speculated Active Species in the Catalyst Solution Generated from La(O-*i*-Pr)$_3$, (*R*)-BINOL, and Ph_3As=O in a Ratio of 1:1:1

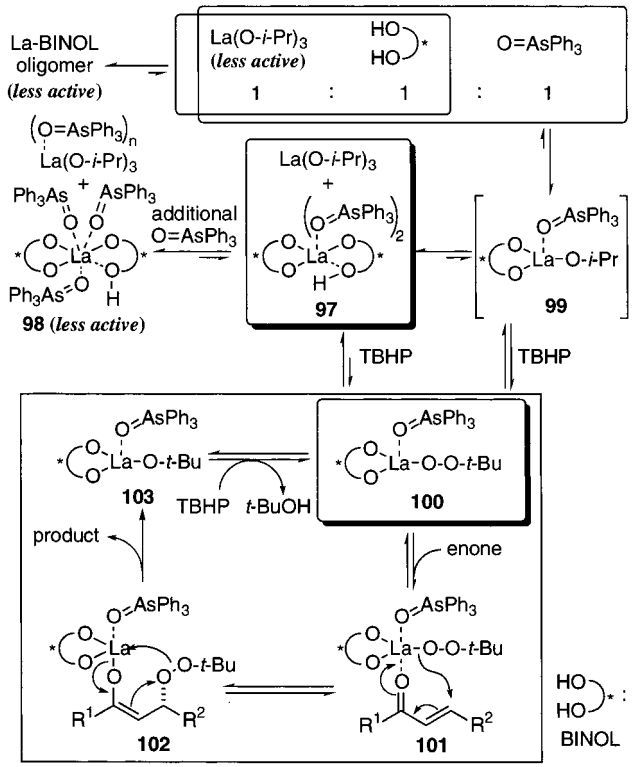


99

spectra. Moreover, an X-ray grade crystal was obtained from the mixture of La(O-*i*-Pr)$_3$, BINOL, and Ph_3As=O (1:1:3), and analysis revealed the structure shown in Figure 11. The structure consisted of a lanthanum ion, BINOL, and Ph_3As=O in a ratio of 1:2:3. These studies strongly supported structure **98** as the major component in the catalyst solution. It was still believed, however, that the real catalytic species would bear a different structure (**99**) as shown in Chart 11, because the use of the crystal itself as a catalyst produced less satisfactory results. The addition of La(O-*i*-Pr)$_3$ to the solution of the crystal improved the result.

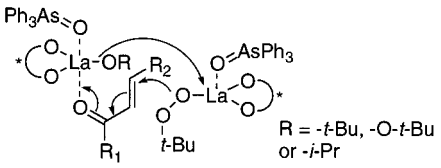
The proposed reaction mechanism is described in Scheme 16, wherein the lanthanum alkoxide moiety

Scheme 16. Proposed Mechanism for the Epoxidation of Enones Catalyzed by La−BINOL−Ph_3As=O Complex 92



functions as a Lewis acid to activate the enone and as a Brønsted base to activate the peroxide. Excess La(O-*i*-Pr)$_3$ in the catalyst solution promotes the transformation of component **97** into the catalytic species **100**, thereby accelerating the catalytic cycle. Another mechanism in which two molecules of the La complex participate is also possible, albeit less plausible (Chart 12).

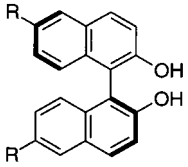
Chart 12. Proposed Intermediate in Which Several La Complexes Participate



104

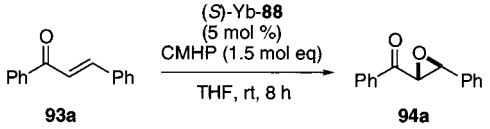
Qian and de Vries et al. recently investigated the effects of the structure of ligands on asymmetric epoxidation.[109] A series of 6,6′-disubstituted BINOLs (**5f**−**k**, Chart 13) were synthesized, and their effectiveness was evaluated in the reaction of chalcone (**93a**) using CMHP as an oxidant. The catalysts were prepared from Yb(O-*i*-Pr)$_3$ and a ligand (**5f**−**k**) in a ratio of 1:1. A catalyst prepared from substituted ligand **5f**−**k** gave the product (**94a**) with an enantiomeric excess better than that afforded by the BINOL catalyst when the reaction was performed without additives (Table 20).

Chart 13



5a: R = H
5f: R = Br
5g: R = Ph
5h: R = *p*-MeC$_6$H$_4$
5i: R = *p*-MeOC$_6$H$_4$
5j: R = *p*-F$_3$CC$_6$H$_4$
5k: R = 1-naphthyl

Table 20. Effects of Substituents on BINOL



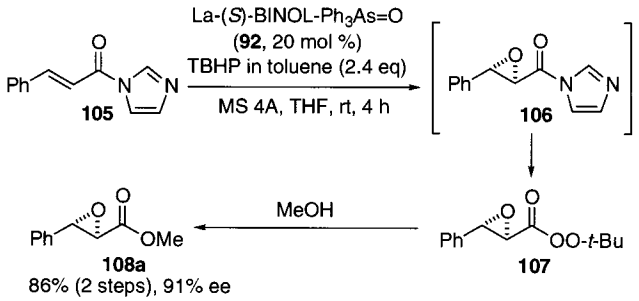
93a 94a

entry	ligand	yield (%)	ee (%)
1	**5a**	95	44
2	**5f**	76	62
3	**5g**	91	95
4[a]	**5g**	91	97
5	**5h**	78	70
6	**5i**	86	83
7	**5j**	88	89
8	**5k**	84	63

[a] Reaction was carried out at 0 °C for 36 h.

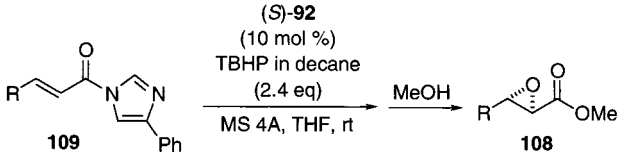
The reaction was very recently extended to catalytic asymmetric synthesis of α,β-epoxy esters.[110,111] Cinnamic acid imidazolide **105** was oxidized by TBHP in the presence of La−BINOL−Ph$_3$As=O (**92**) as a catalyst (10 mol %) to afford peroxy ester **107**, which was readily converted into methyl ester **108a** upon treatment with MeOH (Scheme 17). The system showed a good generality with regard to the substrates, and the products (**108**) were obtained with high enantiomeric excess from a wide range of α,β-unsaturated carboxylic acid imidazolides **109** after treatment with MeOH (Table 21).

Scheme 17. Catalytic Asymmetric Epoxidation of Cinnamic Acid Imidazolide 105 Using La−(*S*)-BINOL−Ph$_3$As=O Complex 92



86% (2 steps), 91% ee

Table 21. Catalytic Asymmetric Epoxidations of Various α,β-Unsaturated Carboxylic Acid 4-Phenylimidazolides



109a, **108a**: R = Ph
109b, **108b**: R = 4-Cl-C$_6$H$_4$
109c, **108c**: R = 4-Br-C$_6$H$_4$
109d, **108d**: R = 4-MeO-C$_6$H$_4$
109e, **108e**: R = PhCH$_2$CH$_2$
109f, **108f**: R =
109g, **108g**: R =
109h, **108h**: R =
109i, **108i**: R =
109j, **108j**: R =

entry	imidazolide	epoxide	time (h)	yield (%)	ee (%)
1	**109a**	**108a**	3.5	86	92
2[a]	**109a**	**108a**	12	73	85
3	**109b**	**108b**	5	91	93
4[b]	**109c**	**108c**	4	86	89
5	**109d**	**108d**	6	80	91
6	**109e**	**108e**	1	86	83
7	**109f**	**108f**	2	93	86
8	**109g**	**108g**	1.5	92	79
9	**109h**	**108h**	2	85	82
10	**109i**	**108i**	4	81	81
11	**109j**	**108j**	4	72	88

[a] Catalyst: 5 mol %. [b] 4-Methylimidazolide was used.

VII. Related Lanthanide Complexes

A. La-Linked-BINOL Complex

Catalysts that are easily handled and reusable are preferable from a practical point of view. A major strategy to attain such a goal is to develop polymer-supported catalysts.[112] Most attempts to immobilize catalysts onto polymers, however, led to a deterioration in the reactivity and selectivity. In contrast, fundamentally stable catalysts could be recycled without immobilization.[113] Although the catalysts described in this review are relatively stable to air and moisture in comparison with conventional Lewis acids, most attempts to recycle the catalysts failed.

Because catalysts are often decomposed through ligand exchange, initial studies to develop reusable catalysts were focused on connecting two or more BINOL units in multifunctional catalysts. After synthesis of many linked-BINOLs,[114] ligand **110**,

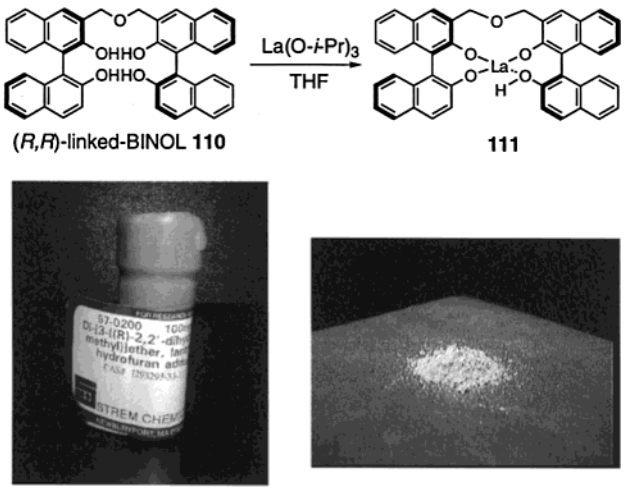
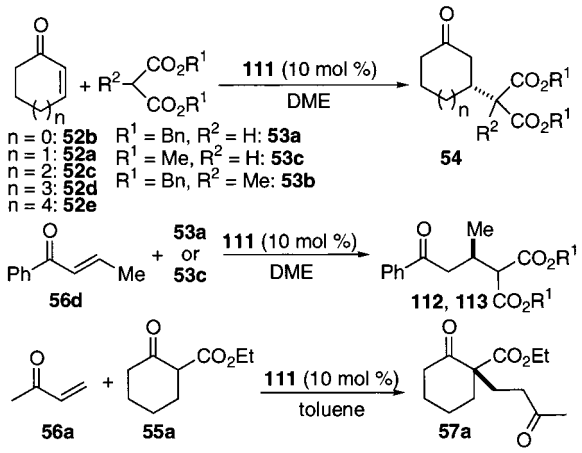


Figure 12. Air-stable powdered (*R*,*R*)-La-linked-BINOL complex **111**, which has no deliquescent properties.

Table 22. Catalytic Asymmetric Michael Reactions Promoted by (*R*,*R*)-La-Linked-BINOL 111

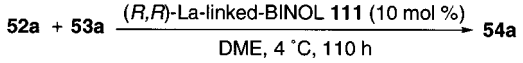


entry	acceptor	donor	temp (°C)	time (h)	product	yield (%)	ee (%)
1	**52b**	**53a**	4	85	**54d**	85	>99
2	**52b**	**53c**	4	85	**54e**	96	>99
3	**52a**	**53a**	rt	72	**54a**	94	>99
4	**52a**	**53a**	4	85	**54a**	98	>99
5	**52a**	**53c**	rt	72	**54c**	95	>99
6[a]	**52a**	**53b**	rt	84	**54b**	84	98
7	**52c**	**53a**	4	85	**54f**	96	>99
8	**52c**	**53c**	4	85	**54g**	97	>99
9[a]	**52d**	**53c**	rt	96	**54h**	82	99
10	**52d**	**53a**	4	120	**54i**	61	82
11	**56d**	**53a**	−40	56	**112**	97	78
12	**56d**	**53c**	−40	56	**113**	95	74
13	**56a**	**55a**	−30	36	**57a**	97	75

[a] The reaction was carried out in DME/THF (9/1).

which bears an ether moiety, proved to construct an effective asymmetric catalyst (Figure 12). Asymmetric Michael additions of malonates to α,β-unsaturated ketones were promoted by catalyst **111**, which was prepared from La(O-*i*-Pr)$_3$ and **110**, to give the adducts in good to excellent yield with excellent enantiomeric excess (Table 22).[115] Moreover, activity of the catalyst was preserved, even after being kept under air for 4 weeks. After completion of the reaction, the catalyst was precipitated upon addition of pentane at 0 °C. The Michael adduct was isolated from the supernatant, and powdered catalyst was

Table 23. Asymmetric Michael Reaction Using Recycled Catalyst



	cycle			
	1	2	3	4
yield (%)[a]	82	94	68	50
ee (%)	>99	>99	99	98

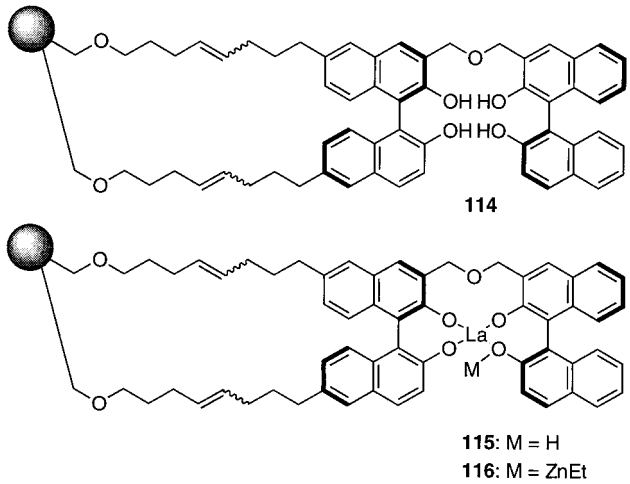
[a] Isolated yield.

obtained by drying the precipitate under reduced pressure. This recovered catalyst was reused several times, giving the product with higher than 98% ee, although the catalytic activity was slightly less (Table 23).[116]

B. Immobilized La-Linked-BINOL Complexes

Although the immobilization of asymmetric catalysts offers various advantages,[112] random attachment of ligands onto a polymer often gives rise to poor yield or poor selectivity, especially when the catalyst is constructed with two or more ligands,[117] because random immobilization prevents the formation of catalysts in a desired structure. Shibasaki et al. were encouraged by the development of a La-linked-BINOL complex (**111**) to explore a general method for immobilizing their multifunctional catalysts consisting of two or more BINOLs, because the linkage in **110** would control the relative position of the two BINOLs so that the formation of the desired catalytic species is facilitated. Thus, a polymer-supported linked-BINOL (**114**, Chart 14) was synthesized,[118] and

Chart 14

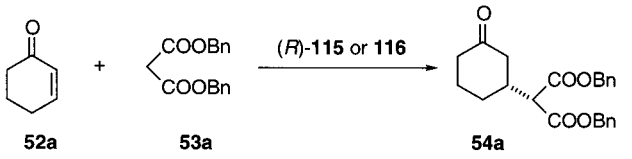


several types of asymmetric complexes were prepared from this ligand. The utility of the complexes was evaluated in catalytic Michael addition of malonate **53a** (Table 24). Although the selectivity and reactivity were deteriorated compared with nonsupported catalyst (**111**), the immobilized catalysts (**115** and **116**) gave the product (**54a**) with up to 78% ee.[119]

C. Ln–Ln Homobimetallic Complex

While most catalysts discussed in the sections above are likely to offer the synergistic effects of a

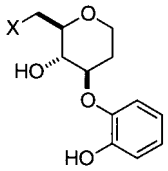
Table 24. Michael Reaction Promoted by Immobilized Catalysts



52a 53a 54a

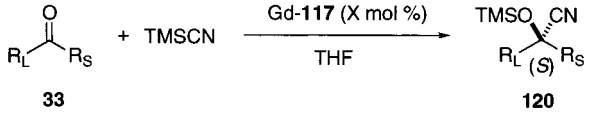
entry	catal (mol %)	solvent	temp (°C)	time (h)	yield (%)	ee (%)
1	**111** (10)	THF	0	45	53	85
2	**115** (20)	THF	rt	72	45	66
3	**115** (50)	DME	rt	87	56	78
4	**116** (20)	THF	rt	72	72	66

Chart 15



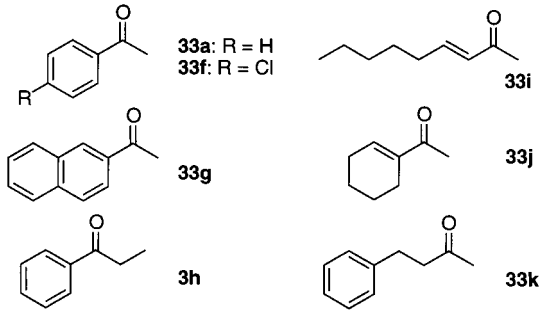
118: X = $Ph_2P(O)$
119: X = Ph_2CH

Table 25. Enantioselective Cyanosilylation of Ketones Catalyzed by Gd−117



33 120

Gd-**117** = Gd(O-*i*-Pr)$_3$ + **118** (2 mol eq to Gd)

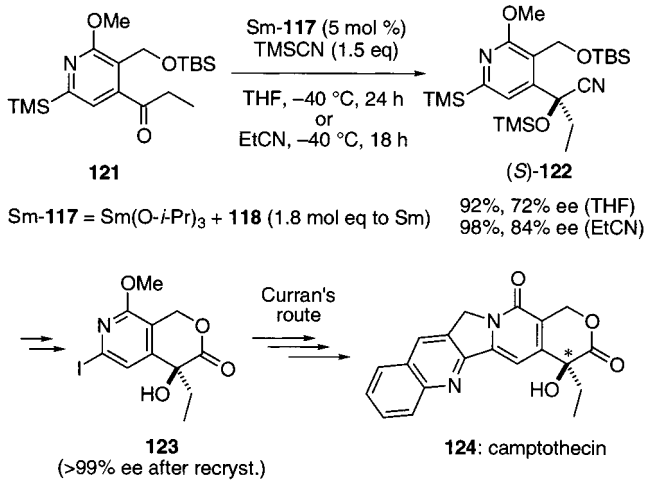


entry	ketone	product	Gd (mol %)	temp (°C)	time (h)	yield (%)	ee (%)
1	**33a**	**120a**	5	−40	2	92	92 (*S*)
2[a]	**33a**	**120a**	10	−30	36	85	92 (*R*)
3	**33f**	**120b**	5	−60	55	89	89
4	**33g**	**120c**	5	−60	24	95	87
5	**33h**	**120d**	5	−60	14	93	97
6	**93f**	**120e**	10	−60	14	97	86
7	**33i**	**120f**	15	−60	18	87	80
8	**33j**	**120g**	15	−60	4	95	89
9	**33k**	**120h**	5	−60	1	90	62

[a] Reaction using a Ti catalyst. See ref 122.

Lewis acid and a Brønsted base, a different mode of catalysis is presented in this section. In contrast to the nucleophilic substrates mentioned above, trimethylsilyl cyanide (TMSCN)[97] can be activated by a Lewis base[120−124] or by transmetalation.[125] If the trimethylsilyl group in TMSCN is replaced with an electronically more positive metal, the nucleophilicity of the cyanide group is increased. Shibasaki et al.

Scheme 18. Catalytic Enantioselective Synthesis of Camptothecin



121 (*S*)-122

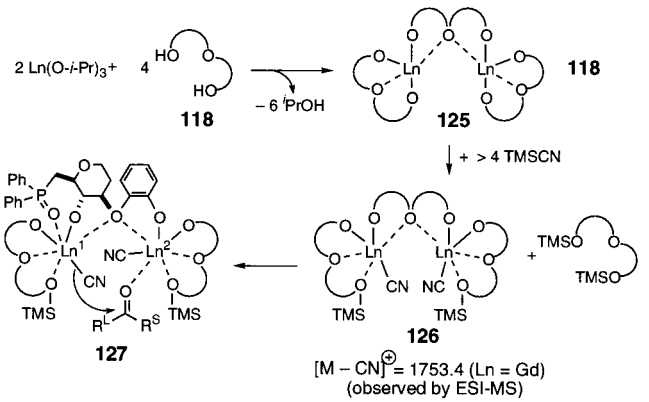
Sm-**117** = Sm(O-*i*-Pr)$_3$ + **118** (1.8 mol eq to Sm)

92%, 72% ee (THF)
98%, 84% ee (EtCN)

123 (>99% ee after recryst.) **124**: camptothecin

achieved a catalytic asymmetric cyanosilylation of ketones by employing this mode of activating the cyanide. The catalyst (Gd−**117**) was prepared from Gd(O-*i*-Pr)$_3$ and novel ligand **118** (Chart 15), which bears a phosphine oxide moiety, after evaporation of the solvent together with *i*-PrOH. The catalyst system (Gd−**117**) furnished cyanohydrins with good to excellent enantiomeric excess from a wide range of ketones (Table 25),[126] providing a valuable method for construction of quaternary carbon centers.[127] The utility of this method was demonstrated in a catalytic enantioselective synthesis of camptothecin by using samarium as a lanthanide,[126,128] as shown in Scheme 18. The reaction mechanism was proposed as shown in Scheme 19, based on analysis by ESI-MS, kinetic

Scheme 19. Working Model of the Catalyst Structure and the Reaction Mechanism for Enantioselective Cyanosilylation of Ketones



studies, and labeling experiments using TMS^{13}CN. In this mechanism, a catalytically active complex **126** is generated from the precatalyst and TMSCN in the reaction mixture. A key to the efficient catalysis is the synergistic effect of the two Gd metals in the catalyst. One Gd metal activates the cyanide by forming a more polarized Gd−CN bond (Ln^1−CN in Scheme 19) from TMSCN, and the other (Ln^2 in Scheme 19) activates the aldehyde by its Lewis acidity. The following experiment proved that the phosphine oxide moiety in **118** was essential to this reaction. The use of **119** as a ligand led to much

slower reactions, and the cyanohydrins (**120**) were obtained with less than 10% ee. The phosphine oxide moiety, hence, should facilitate formation of the Ln−CN bond and stabilize the active 2:3 complex (**126**), together with activating the resulting Ln−cyanide (see **127**). As was the case in several other reactions, the choice of lanthanide influenced the optical purity of the product.[129]

VIII. Conclusions

Lanthanide-based multifunctional complexes constitute a significant part of enantioselective catalysis. Nonetheless, their scope is still evolving. For example, the rate-determining step in the direct aldol reaction still lies at the deprotonation of the ketone even after acceleration by the addition of KOH, and the development of the direct aldol reaction of esters remains unsolved. In contrast to most conventional Lewis acid catalysis, enantioselective reactions discussed herein are promoted mainly by the Brønsted basicity of the catalysts, while the Lewis acidity assists the catalysis by controlling the position of the electrophiles as well as activating them. Therefore, further modification of the base moieties in the catalysts by rational design is necessary to increase the scope of catalysis.

Lanthanides are characterized by their ability to accommodate larger numbers of ligands.[130] Accordingly, they are less prone to coordinative saturation and might allow for construction of structurally sophisticated complexes. These features make lanthanides attractive metals as a component of asymmetric catalysts. Nevertheless, their high coordinating numbers often cause the formation of oligomeric complexes, making it difficult to elucidate the structure. The rational design of lanthanide-based multifunctional catalysts necessarily involves a novel framework of ligands that efficiently generate desired catalytic species in a stable form.

IX. Nomenclature for Catalysts

BINOL	2,2′-dihydroxy-1,1′-binaphthyl
H_2binol	2,2′-dihydroxy-1,1′-binaphthyl
LLB	$Li_3[La(binol)_3]$
Ln	lanthanide
LnMB	$M_3[Ln(binol)_3]$
LPB	$K_3[La(binol)_3]$
LSB	$Na_3[La(binol)_3]$

X. Acknowledgment

The work from our group mentioned in this review was realized through the efforts of many co-workers, whose names are cited in the references.

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CR010297Z