# Catalytic asymmetric carbon–carbon bond-forming reaction utilizing rare earth metal complexes

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<u>Abstract</u>: Novel optically active rare earth complexes have made possible a catalytic asymmetric nitroaldol reaction for the first time. Structural elucidation reveals that the complexes consist of one rare earth metal, three lithium atoms, and three BINOL units. Applications of the catalytic asymmetric nitroaldol reaction to syntheses of several β-blockers and *erythro*-AHPA have been also achieved. Although the lithium containing rare earth-BINOL complexes are not effective for Michael reactions, another lithium free lanthanum-BINOL complex prove to be quite effective in catalytic asymmetric Michael reactions to give adducts of up to 95% ee.

Recently we have found that rare earth alkoxides exhibit basic character, which can be utilized in aldol, cyanosilylation and nitroaldol reactions. (1) Furthermore, we have succeeded in preparing the optically active rare earth-BINOL complexes for the first time and demonstrating that they are useful basic catalysts for asymmetric nitroaldol reactions. (1,2) Typical results utilizing La-BINOL complex are shown in Scheme 1. These are the first examples of a catalytic asymmetric nitroaldol reaction.
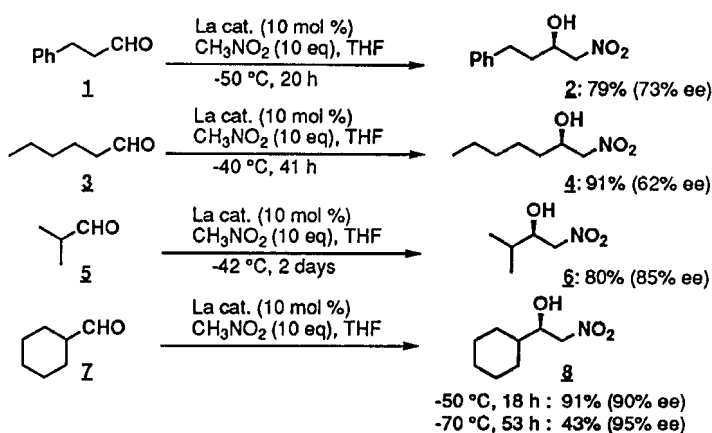
Scheme 1. La-BINOL complex catalyzed asymmetric nitroaldol reactions.

The La-BINOL complex and other rare earth-BINOL complexes are readily prepared starting from rare earth (La, Pr, Nd, Sm, Eu, Gd, Tb, Yb, and Y) trichlorides, di-Li salts of (S)-BINOL (1-2 mol equiv), NaOH (1 mol equiv), and H₂O (10 mol equiv). (3) The rare earth complexes are self assembled in THF and the solution can be directly used as an asymmetric catalyst. The addition of H₂O and NaOH is

essential to obtain nitroaldols in high optical purity. The role of H_2O and NaOH are considered to be as shown in Fig. 1.
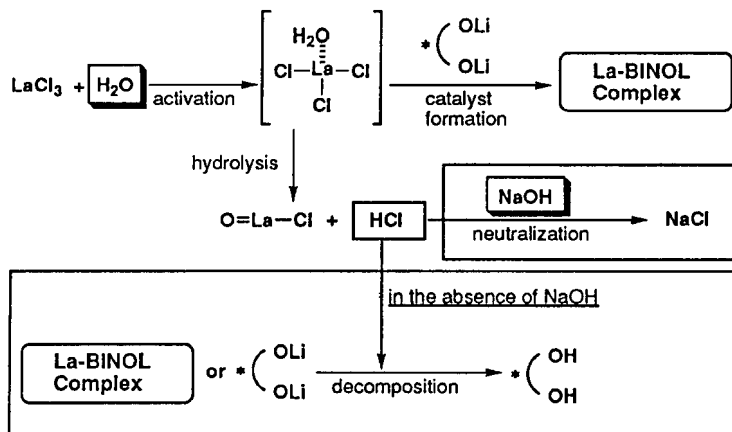

Fig. 1. Schematic view of the role of H_2O and NaOH in the optically active La complex formation.

Rare earth metals are generally regarded as a group of seventeen elements with similar properties, especially with respect to their chemical reactivity. However in the case of the above mentioned nitroaldol reaction, we have observed pronounced differences both in the reactivity and in the enantioselectivity among the various rare earth metals used. The unique relationship between ionic radius of rare earth metals and the optical purities of the nitroaldols is depicted in Fig. 2. For example, when benzaldehyde and nitromethane were used as a starting material, the Eu-(S)-BINOL complex gave (R)-2 in 72% ee (91% yield) in contrast to 37% ee (81% yield) in the case of the La-BINOL complex (-40 °C, 40 h). (3)

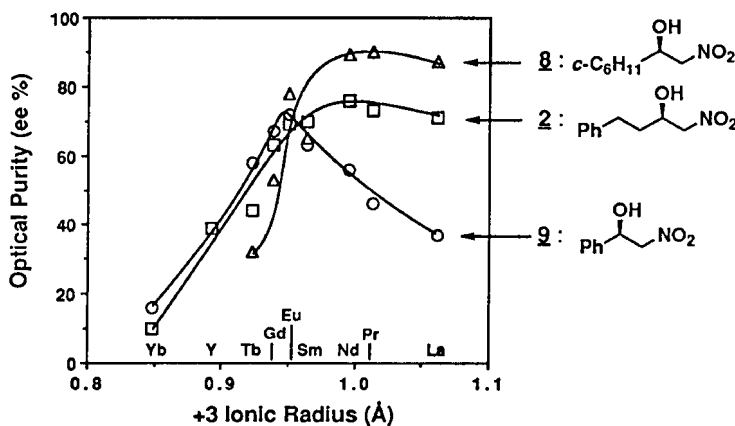Fig. 2. Effect of the ionic radii of rare earth metals on the optical purities of nitroaldol derivatives.

The relatively simple ^{13}C and ^1H NMR peak patterns of the La-BINOL catalyst suggest (4,5) either a simple structure for the catalyst or the magnetic equivalence of the BINOL moiety in case the catalyst has an oligomeric structure. With the exception of the La catalyst complex, an NMR study of all the other rare earth complexes provided little information on catalyst structure due to the paramagnetism of the rare earth elements.

By conventional EI- and FAB-MS methods, we could obtain only obscure spectra with complex fragment peaks. In contrast, the laser desorption/ionization time-of-flight mass spectrometry (LDI-TOF MS) (6,7) proved to be quite a powerful tool in the analysis of the structure of rare earth BINOL

complexes. By LDI-TOF MS method anionic and cationic species could be detected independently according to the measurement mode. In both anionic and cationic mode, tris-binaphthoxy mixed-metal complex of rare earth and Li came up as a candidate for the framework of the catalyst. Representative spectra in anionic mode were shown in Fig. 3. Although the LDI-TOF MS has a mass accuracy of about ±0.1%, (6) the proposed framework was strongly supported by the similarity of the mass spectra of the various rare earth complexes; since rare earth elements have their own atomic weight and isotope abundance distribution. The other BINOL-rare earth complexes also showed a peak pattern similar to La complex, suggesting that these rare earth complexes have fundamentally similar structures. Surprisingly no Cl atom containing fragment was detected.
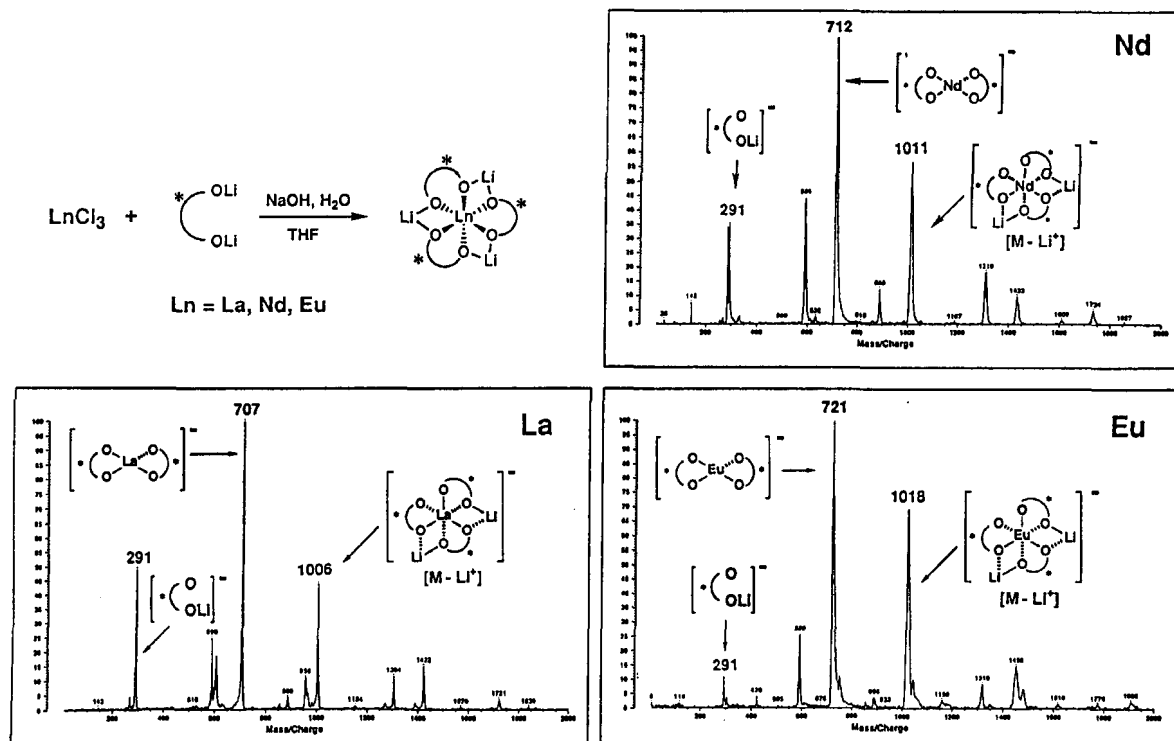

Fig. 3. LDI-TOFMS spectra of La, Nd, and Eu BINOL complex in anion mode.

Although several attempts were made to obtain a X-ray grade crystal of a rare earth complex, these were largely unsuccessful. One reason for the low crystalline character of these rare earth complexes might be contamination due to soluble LiCl in the catalyst solution. Therefore we turned our attention to preparing the crystals under Li free conditions. Starting from rare earth (La, Pr, Nd, Sm, Eu, Gd, Tb, Dy, Er, Yb, and Y) trichlorides, di-Na salt of (*S*)-BINOL, NaO-*t*-Bu, and H$_2$O, (8) we were pleased to find that several of the rare earth complexes, with the exception of La, could be crystallized from THF. As shown in Fig. 4, X-ray crystallographic analyses have revealed that Eu, Pr, and Nd containing crystals have almost the same structure except for the distance of the atoms around the center rare earth metal. (9) For example the bond length between the rare earth metals and oxygens of BINOL were Eu-O: 2.286 and 2.312; Nd-O: 2.338 and 2.363; and Pr-O: 2.365 and 2.386 Å. These results suggest that small changes in the structure of catalyst (*ca.* 0.1 Å in bond length) cause a drastic change in the optical purity of nitroaldols produced. (3, 4)

All the above mentioned crystals were basic and acted as catalysts for the nitroaldol reaction. However, the nitroaldols thus obtained were mostly racemic mixtures. For example in the case of reaction of 3-phenylpropanal (**1**) with nitromethane at -40 °C, the results were as follows; Eu: 72% yield,
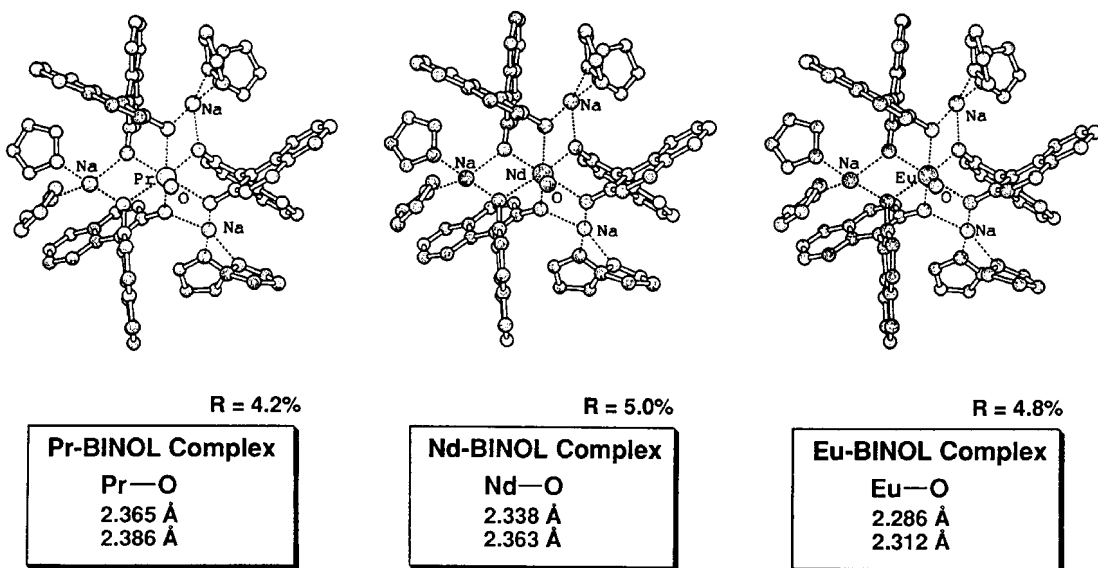

| R = 4.2% | R = 5.0% | R = 4.8% |

Pr-BINOL Complex	**Nd-BINOL Complex**	**Eu-BINOL Complex**
Pr—O	Nd—O	Eu—O
2.365 Å	2.338 Å	2.286 Å
2.386 Å	2.363 Å	2.312 Å

Fig. 4. Structure of rare earth-sodium-BINOL complexes.

3% ee (*S*) configuration; Nd: 83%, 7% ee (*R*); Pr: 80%, 9% ee (*R*)). On the other hand, only after they were stirred for 3 days with 3 equivalents of LiCl in THF, did the solutions prove to be efficient asymmetric catalysts (Eu: 84%, 70% ee; Nd: 71%, 68% ee; Pr: 84%, 73% ee). Again by applying the LDI-TOF MS method, all Li free crystals showed similar mass pattern (cf. Fig. 3) except that they contained Na instead of Li. Moreover, complete exchange of Na with Li, on addition of LiCl to the catalyst, was also observed with LDI-TOF MS.

The disclosed structure of the rare earth complexes led us to prepare the La-Li-BINOL complex (LLB) in a rationally designed procedure. (4) Namely, to a stirred suspension of mono-Li salt of (*S*)-BINOL, was added a THF solution of La(O-*i*-Pr)$_3$ (0.33 molar equiv) at room temperature. (10) This catalyst solution also gave almost the same LDI-TOF mass spectra as depicted in Fig. 3, and also showed excellent catalytic activity in the asymmetric nitroaldol reaction.

Nitroaldols are readily converted into β-amino alcohols and/or α-hydroxy carbonyl compounds. As an effective application of the LLB catalyzed nitroaldol reaction, convenient syntheses of three kinds of optically active β-blockers are presented in Scheme 2. (3, 11, 12)
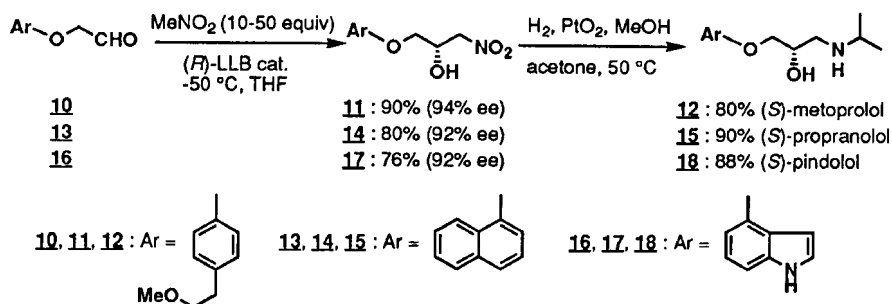
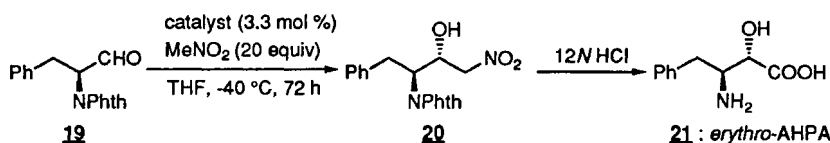Scheme 2. Catalytic asymmetric syntheses of β-blockers using (*R*)-LLB as a catalyst.

TABLE 1

entry	catalyst	yield of 20 (%)	erythro (% ee) : threo
1	(*R*)-LLB	92	99 (96) : 1
2	(*S*)-LLB	96	74 (90) : 26
3	La(O-*i*-Pr)₃	52	89 (95) : 11
4	NaO-*t*-Bu	95	62 (65) : 38
5	LDA (1 equiv)	80	74 (49) : 26

Furthermore, diastereoselective catalytic asymmetric nitroaldol reaction of optically active α-amino-aldehydes with nitromethane proceed in a highly diastereoselective manner. A typical adduct, (2*S*, 3*S*)-3-phthaloylamino-2-hydroxy-1-nitro-4-phenylbutane was conveniently converted to (2*S*, 3*S*)-3-amino-2-hydroxy-4-phenylbutanoic acid (21: *erythro*-AHPA; phenylnorstatine), a component of the HIV protease inhibitor KNI-272 (Fig. 5). (13) As shown in Table 1, commonly used bases such as LDA and NaO-*t*-Bu gave the nitroaldol 20 with lower diastereo- and enantioselectivity.
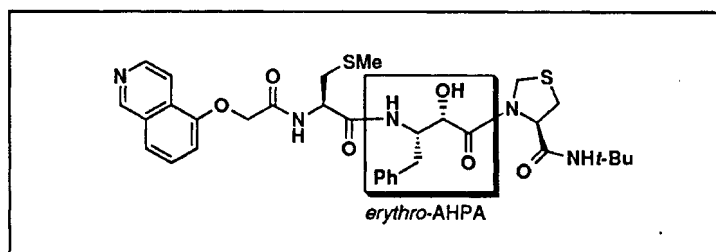
Fig. 5. KNI-272

In the case of a catalytic asymmetric Michael reaction which is another important carbon-carbon bond-forming reaction, LLB and other rare earth-Li-BINOL complexes have been found to be quite ineffective. For example, treatment of cyclopentenone (22) with dibenzyl methylmalonate (23) in the presence of 3 mol % of LLB gave the Michael adduct 24 of only 13% ee in 26% yield.

Therefore we focused on the preparation of a Li free La-BINOL complex which should form a structurally different La ester enolate from that generated with LLB. The Li free La ester enolate was expected to lead to Michael adducts with higher ees. Thus, to a stirred solution of La(O-*i*-Pr)₃ (10) (1.0 mmol) in anhydrous THF (5 mL) was added 1 mol equiv of (*S*)-BINOL at 0 °C, which resulted in rapid formation of a suspension. The white precipitate **I** (138 mg) thus obtained was immediately used for the Michael reaction as an asymmetric base catalyst. We were very pleased to find that treatment of dibenzyl methylmalonate (23) with cyclopentenone (22) (1.1 equiv) in anhydrous THF containing 10 mol % of the La-BINOL complex **I** at -20 °C for 48 h gave the Michael adduct 24 of 70% ee in 86% yield. (14)

Further studies were carried out to find a more effective catalyst in asymmetric Michael reactions. A possible mechanism for the above-mentioned Michael reaction is proposed in Fig. 6. Although the structure of the new La-BINOL complex **I** (15) was not unequivocally determined, it seemed likely that reaction of dibenzyl methylmalonate (23) with the La complex **I** would give the BINOL-La ester enolate **II** together with the La complex **III** consisting of La and the BINOL moiety in a molar ratio of 1:2. This

La ester enolate **II** would react with cyclopentenone (**22**), giving the La enolate **IV** in an enantioselective manner. Further reaction of this enolate **IV** with **23** would lead to the Michael adducts **V** together with the La ester enolate **II** due to the difference in their pKa values, thus making the catalytic cycle possible.
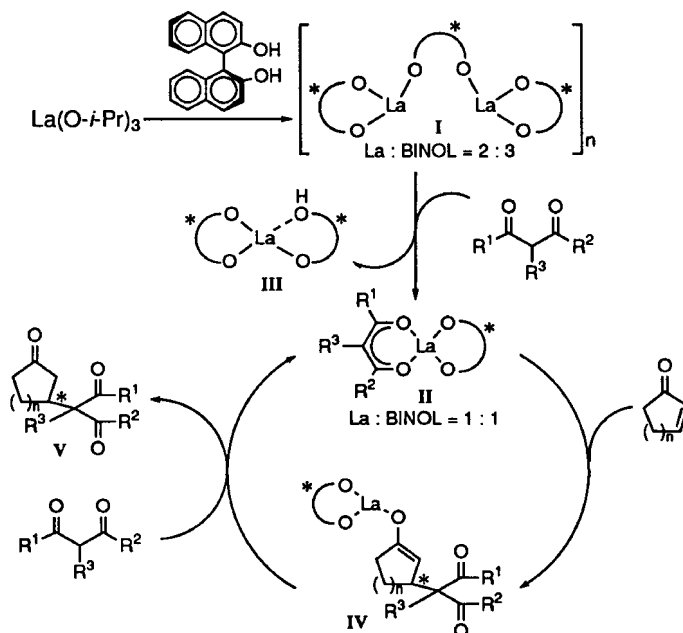

Fig. 6. Possible mechanism for the catalytic asymmetric Michael reaction promoted by alkali metal free La-(S)-BINOL complex.

The above-mentioned mechanistic consideration suggested that the intermediary La ester enolate **II**, the real asymmetric catalyst, would be more effectively prepared starting with La(O-i-Pr)3, dibenzyl methylmalonate (**23**), and BINOL. This indeed proved to be the case. The BINOL-La ester enolate **II**, for use as an asymmetric base catalyst was first prepared as follows (Scheme 3).
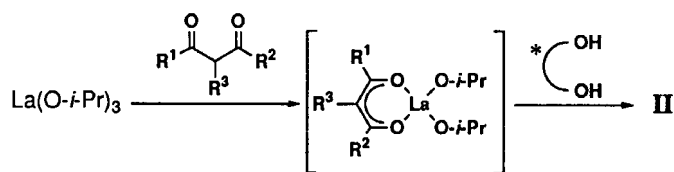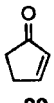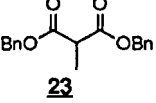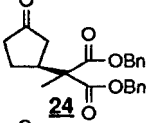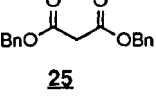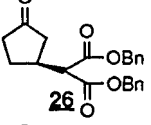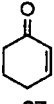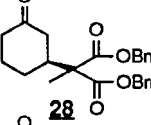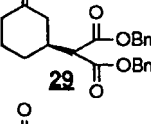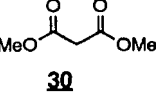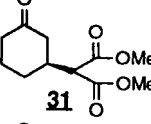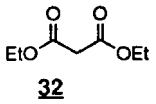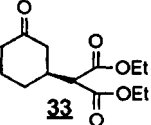
Scheme 3

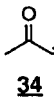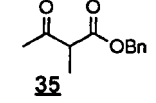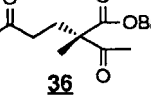To a stirred solution of La(O-i-Pr)3 (0.1 mmol) in THF (0.5 mL), dibenzyl methylmalonate (**23**) (0.1 mmol) in anhydrous THF (1.0 mL) was gradually added at 0 °C, and the resulting solution was stirred at 0 °C for 0.5 h. In this instance no precipitate was observed. To this La ester enolate solution was then added (S)-BINOL (0.1 mmol) in THF (1.0 mL) at 0 °C, and the whole solution was further stirred for 0.5 h at the same temperature. This THF solution was directly used as an asymmetric base catalyst. Thus to a stirred solution of the above-prepared ester enolate **II** was successively added dibenzyl methylmalonate (**23**) (0.9 mmol) and cyclopentenone (**22**) (1.0 mmol) at -20 °C and the whole reaction mixture was stirred for 60 h at the same temperature. This afforded the Michael adduct **24** of 90% ee in 75% yield. It was further observed that the asymmetric ester enolate catalyst **II**, which was prepared through removal of THF and i-PrOH, followed by a re-addition of THF (1.0 mL), showed better reactivity and gave **24** of 95% ee in 97% yield. (14) To the best our knowledge this is the best example
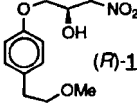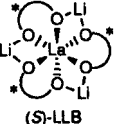
of a catalytic asymmetric Michael reaction. (16) Using the procedure described above various substrates were further subjected to a catalytic asymmetric Michael reaction. The results summarized in Table 2 showed that various Michael adducts were obtained in good enantiomeric excesses, ranging from 62% to 95% ee, and in excellent yields.

TABLE 2. Catalytic asymmetric Michael reactions promoted by
Li free La-(S)-BINOL ester enolate II (10 mol %)

entry	enone	Michael donor	product	temp. (°C)	time (h)	yield (%)	ee (%)
1	22	23	24	-20	60	97	95
2	22	25	26	-20	72	96	92
3	27	23	28	0	84	83	87
4	27	25	29	-10	84	94	92
5	27	30	31	-10	84	100	75
6	27	32	33	-10	84	97	78
7	34	35	36	-50	48	86	62

In conclusion two types of asymmetric La-BINOL complexes are now available; namely LLB which is quite effective in catalytic asymmetric nitroaldol reactions, and a Li free BINOL-La ester enolate complex II that is very effective in catalytic asymmetric Michael reactions. Very interestingly, the two complexes complement each other in their ability to catalyze asymmetric nitroaldol and asymmetric Michael reactions (Table 3). Elucidation of the structure of the complex II and mechanistic studies are in progress.

TABLE 3. Comparison of the catalytic behavior of La-BINOL complexes

Catalyst	Michael	Nitroaldol
Alkali Metal Free La (S)-BINOL Complex	(S)-24 — 97%, 95% ee (-20 °C, 60 h)	(R)-11 — 48%, 6% ee (-10 °C, 72 h)
(S)-LLB	(R)-24 — 26%, 13% ee (-40 °C, 60 h)	(R)-11 — 90%, 94% ee (-50 °C, 62 h)

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6. Performed by Shimadzu/Kratos KOMPACT MALDI III apparatus.

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8. The molar ratio was 1:2:1:11, respectively. See reference 3.

9. Crystal data for the rare earth BINOL complexes: $EuNa_3C_{60}H_{36}O_6 \cdot 6THF \cdot H_2O$, space group $P6_3$, $a = 15.279$ (2) Å, $b = 15.279$ (2) Å, $c = 18.454$ (8) Å; $\alpha = 90.00$ (0)°, $\beta = 90.00$ (0)°, $\gamma = 120.00$ (0)°, $Z = 6$, The structure was solved by direct methods and refined to $R(F) = 0.048$, $R_w(F) = 0.056$. $NdNa_3C_{60}H_{36}O_6 \cdot 6THF \cdot H_2O$, space group $P6_3$, $a = 15.295$ (1) Å, $b = 15.295$ (1) Å, $c = 18.459$ (2) Å; $\alpha = 90.00$ (0)°, $\beta = 90.00$ (0)°, $\gamma = 120.00$ (0)°, $Z = 6$, The structure was solved by direct methods and refined to $R(F) = 0.050$, $R_w(F) = 0.049$. $PrNa_3C_{60}H_{36}O_6 \cdot 6THF \cdot H_2O$, space group $P6_3$, $a = 15.309$ (2) Å, $b = 15.309$ (2) Å, $c = 18.452$ (8) Å; $\alpha = 90.00$ (0)°, $\beta = 90.00$ (0)°, $\gamma = 120.00$ (0)°, $Z = 6$, The structure was solved by direct methods and refined to $R(F) = 0.042$, $R_w(F) = 0.048$.

10. Purchased from Soekawa Chemical Co., Ltd., Tokyo, Japan.

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15. The ^{13}C NMR spectrum of this catalyst was quite obscure; in general, rare earth complexes exist as oligomers.

16. For catalytic asymmetric Michael reactions, see: (a) M. Sawamura, H. Hamashima, and Y. Ito, *J. Am. Chem. Soc.* **114**, 8295 (1992). (b) M. Yamaguchi, T. Shiraishi, and M. Hirama, *Angew. Chem. Int. Ed. Engl.* **32**, 1176 (1993). (c) D. J. Cram, and G. D. Y. Sogah, *J. Chem. Soc., Chem. Commun.* **1981**, 625-627. (d) M. Takasu, H. Wakabayashi, K. Furuta, and H. Yamamoto, *Tetrahedron Lett.* **29**, 6943 (1988). (e) S. Aoki, S. Sasaki, and K. Koga, *Tetrahedron Lett.* **30**, 7229 (1989). (f) R. Helder, and H. Wynberg, *Tetrahedron Lett.* **1975**, 4057. (g) A. Sera, K. Takagi, H. Katayama, H. Yamada, and K. Matsumoto,. *J. Org. Chem.* **53**, 1157 (1988). (h) T. Yura, N. Iwasawa, K. Narasaka, and T. Mukaiyama, *Chem. Lett.* **1988**, 1025. (i) B. E. Rossiter, and N. M. Swingle, *Chem. Rev.* **92**, 771 (1992) and references cited therein.