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Remarkably High Asymmetric Amplification in the Chiral Lanthanide Complex-Catalyzed Hetero-Diels–Alder Reaction: First Example of the Nonlinear Effect in ML_3 System

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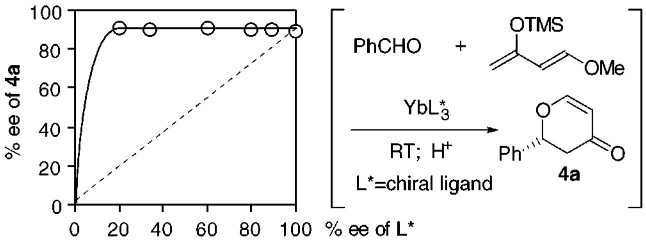
ABSTRACT



A remarkably high asymmetric amplification was realized in the Yb[(*R*)-BNP]$_3$-catalyzed hetero-Diels–Alder reaction as the first example in the metal/chiral ligand 1:3 system. The mechanism may be explained by the autogenetic formation of the enantiopure complex as the most active catalyst. The enantiomer-discriminative formation of homochiral ML_3 complexes is quite general within the lanthanide metal ions with similar ionic radii to that of the ytterbium ion.

Since the Kagan's first report regarding the positive nonlinear effect,[1] such an asymmetric amplification[2] has frequently been observed in various catalytic asymmetric reactions using chiral metal complexes.[3−5] However, most of them are limited within the range of Kagan's ML_2 (L = chiral ligand) model,[4] and a high degree of asymmetric amplification concerning the ML_3 system has never been reported although mathematical treatment allows one to expect considerable nonlinear effects in this system.[1,4c,d,6] We now report a remarkably high asymmetric amplification realized in the chiral lanthanide complex catalyzed hetero-Diels−Alder

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(1) Puchot, C.; Samuel, O.; Duñach, E.; Zhao, S.; Agami, C.; Kagan, H. B. *J. Am. Chem. Soc.* **1986**, *108*, 2353−2357.

(2) For the term "asymmetric amplification", see: Oguni, N.; Matsuda, Y.; Kaneko, T. *J. Am. Chem. Soc.* **1988**, *110*, 7877−7878.

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(4) For recent mechanistic studies, see: (a) Blackmond, D. G. *J. Am. Chem. Soc.* **1998**, *120*, 13349−13353. (b) Kitamura, M.; Suga, S.; Oka, H.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 9800−9809. (c) Brunel, J.-M.; Luukas, T. O.; Kagan, H. B. *Tetrahedron: Asymmetry* **1998**, *9*, 1941−1946. (d) Blackmond, D. G. *J. Am. Chem. Soc.* **1997**, *119*, 12934−12939.

(5) For recent examples on the asymmetric amplification, see: (a) Kanemasa, S.; Oderaotoshi, Y.; Sakaguchi, S.; Yamamoto, H.; Tanaka, J.; Wada, E.; Curran, D. P. *J. Am. Chem. Soc.* **1998**, *120*, 3074−3088. (b) Dosa, P. I.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 445−446 and references therein.

(6) Guillaneux, D.; Zhao, S.-H.; Samuel, O.; Rainford, D.; Kagan, H. B. *J. Am. Chem. Soc.* **1994**, *116*, 9430−9439. The possibility of nonlinear effect on the Danishefsky's Eu(hfc)$_3$-catalyzed hetero-Diels−Alder reaction has been examined.

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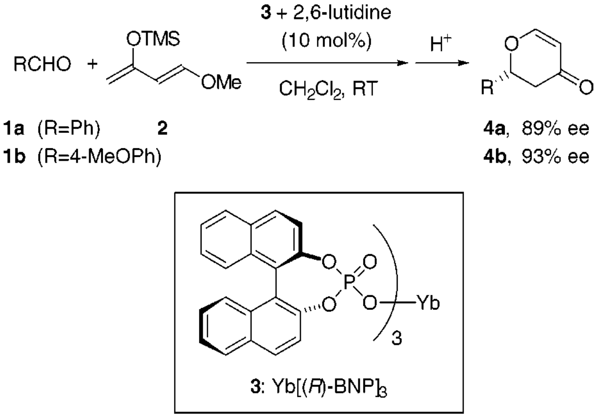
reaction[6] and also some interesting insights into the mechanism.

Recently, we synthesized the 1:3 complexes of a series of trivalent rare earth metal ions with chiral ligands, RE[(*R*)-BNP]$_3$ (RE = rare earth; BNP = 1,1′-binaphthyl-2,2′-diyl phosphate), as isolable chiral Lewis acids which effectively catalyze the hetero-Diels–Alder reaction of aldehydes with the Danishefsky diene **2**[7–10] (Scheme 1).

Scheme 1. Yb[(*R*)-BNP]$_3$-Catalyzed Hetero-Diels–Alder Reaction of Aldehydes with the Danishefsky's Diene



Further investigation allowed us to find a remarkably high positive nonlinear effect as the first example in ML$_3$ system. Thus, when solutions of enantiopure Yb[(*R*)-BNP]$_3$ and Yb-[(*S*)-BNP]$_3$ complexes containing 2,6-lutidine were mixed in different ratios (method I) and the resulting suspension was used as a catalyst (**A**) for the reaction of **1a** with **2**, a notable asymmetric amplification was observed (Figure 1). Very interestingly, the catalysts (**B**) prepared from the chiral ligands with various ees according to the method II further promoted the amplification, e.g., by using only 20% ee of the chiral ligand, the product **4a** with a 90% ee was obtained. The results strongly suggest that the active catalyst generated from an enantiomerically impure ligand has the same structure as that of the catalyst prepared from the enantiopure ligand.

To gain an insight into the mechanism of the present highly positive nonlinear effect, we carried out the reactions shown in Scheme 2. The ytterbium complex (**Yb-5**) was prepared from 50% ee of the ligand (*R*/*S* 75:25), and the once-isolated complex was treated with 2,6-lutidine in dichloromethane. Separation of the CH$_2$Cl$_2$-soluble part (complex **6**) from the insoluble part (complex **7**) by centrifugation (**6**/**7** 41:59) followed by LiAlH$_4$ reduction of each part afforded the corresponding BINOLs with 98 and 7% ee, respectively. In addition, while the complex **6** did catalyze the reaction of **1a** with **2** giving **4a** (90% ee) in 98% yield, the complex **7** hardly promoted the reaction under the same reaction

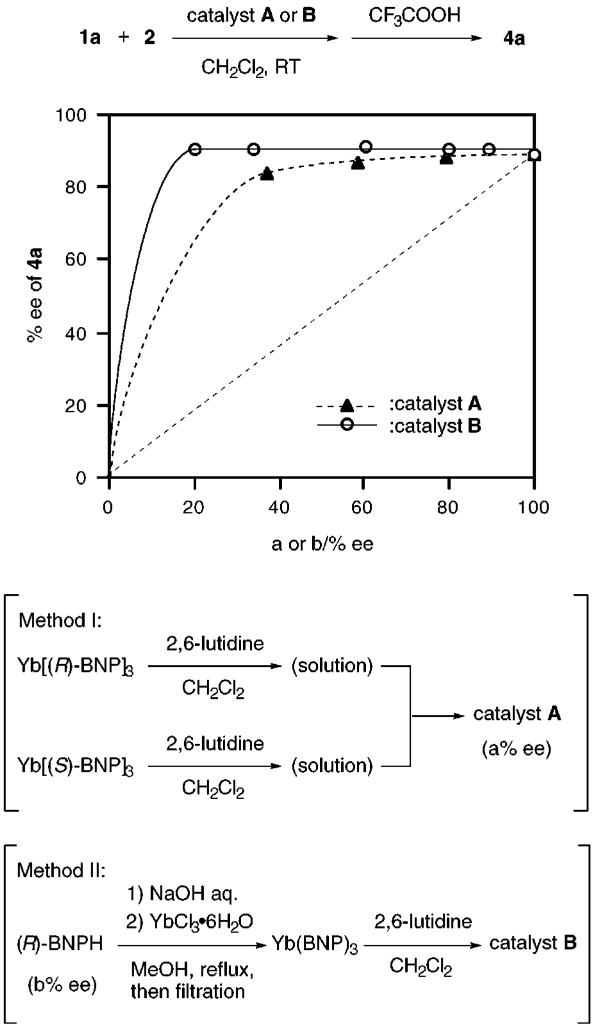
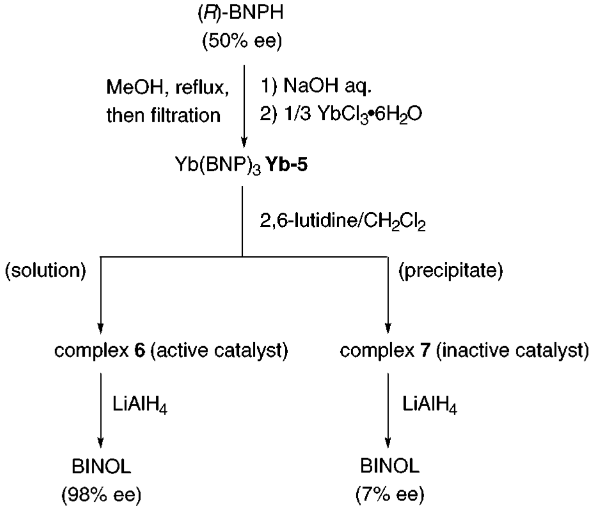


Figure 1. The asymmetric amplification observed in the hetero-Diels–Alder reaction of **1a** with **2** by the catalyst **A** or **B**.

Scheme 2. Correlation between Catalytic Activity and Optical Purity of the Yb–BNP Complex



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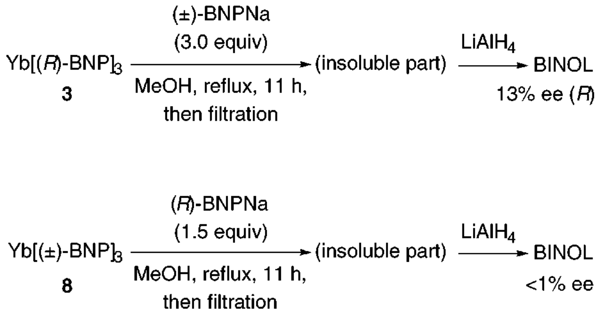
[7] Inanaga, J.; Sugimoto, Y.; Hanamoto, T. *New J. Chem.* **1995**, *19*, 707–712.

[8] Hanamoto, T.; Furuno, H.; Sugimoto, Y.; Inanaga, J. *Synlett* **1997**, 79–80.

conditions (<1% yield). These results clearly indicate that the active catalyst **6** is composed entirely of the enantiopure ligands, whereas the inactive **7** is made up with almost a 1:1 mixture of enantiomers.

The experiments shown in Scheme 3 indicate how easily the ligands of the complex **3** can be exchanged by sodium salt of the opposite enantiomer, giving the heterochiral complex, whereas the complex **8** prepared from racemic BNPH hardly gives rise to such a ligand exchange reaction under similar conditions. These results demonstrate the remarkable thermodynamic stability of the heterochiral complex.

Scheme 3. Attempted Ligand Exchange Reactions of **3** and **8**



Taking all these facts into consideration, we propose the origin of the present asymmetric amplification as shown in Figure 2. For the formation of YbL_3, there are four possibilities in choosing three chiral ligands: $(L_R)_3$, $(L_R)_2L_S$, $L_R(L_S)_2$, and $(L_S)_3$. From these four complexes, the heterochiral pairs such as $Yb(L_R)_3$ and $Yb(L_S)_3$ and/or $Yb[(L_R)_2L_S]$ and $Yb[L_R(L_S)_2]$ seem to irreversibly assemble, forming the thermodynamically very stable complexes which have almost no catalytic activity for the hetero-Diels–Alder reaction. As a result, the enantiopure Yb complex based on excess amount of the enantiomer, $Yb(L_R)_3$, would remain in solution as the real catalyst.[11]

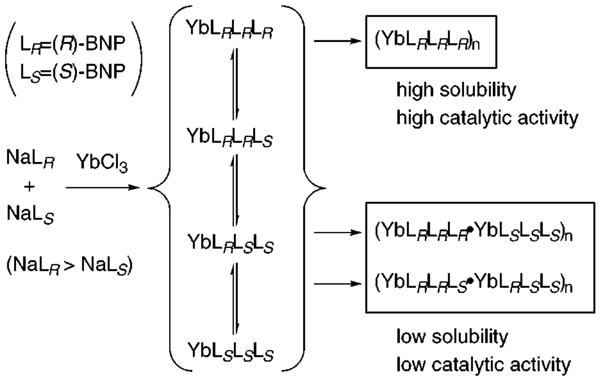
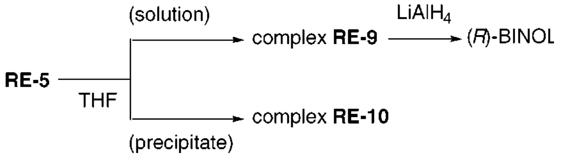


Figure 2. A possible chirality-discrimination process for the formation of the ytterbium complex.

This phenomenon (autogenetic formation of the enantiopure ytterbium complex) was also confirmed by use of THF instead of 2,6-lutidine/dichloromethane and turned out to be quite general within the lanthanide metal ions with similar ionic radii to that of the ytterbium ion, e.g., Nd, Gd, and Ho (Table 1).

Table 1. Correlation between the THF-Soluble Complex **RE-9** and Optical Purity of the Ligand[a]



entry	RE	**RE-9**:**RE-10**	ee of (*R*)-BINOL, %[b]
1	La	3:97	
2	Ce	3:97	
3	Nd	36:64	99
4	Gd	37:63	98
5	Ho	41:59	97
6	Yb[c,d]	46:54[e]	98
7	Sc	54:46	64

[a] **RE-5** prepared from 50% ee (*R*)-ligands was used. [b] BINOL derived from **RE-9**. Determined by HPLC using DAICEL CHIRALPAK AD. [c] Elementary analyses of **Yb-9** and **Yb-10** were carried out. **Yb-9.** Calcd for $C_{64}H_{46}O_{14}P_3Yb$ [$=Yb(BNP)_3\cdot H_2O\cdot THF$]: C, 58.90; H, 3.55. Found: C, 58.62; H, 3.63. **Yb-10.** Calcd for $C_{60}H_{38}O_{13}P_3Yb$ [$=Yb(BNP)_3\cdot H_2O$]: C, 58.45; H, 3.11. Found: C, 58.67; H, 3.02. [d] The hetero-Diels–Alder reaction of **1a** with **2** catalyzed by **Yb-9** or **Yb-10** in the presence of 2,6-lutidine in dichloromethane afforded **4a** with 88% ee (94% chemical yield) or 1% ee (8%), respectively. [e] **Yb-10** was reduced by $LiAlH_4$ and the corresponding (*R*)-BINOL was obtained in 5% ee.

In conclusion, an extremely high asymmetric amplification was observed in the Yb[(*R*)-BNP]$_3$-catalyzed hetero-Diels–Alder reaction and the unique enantiomer-discriminative process in the formation of homochiral ML_3 complex was revealed. These findings would lead to a new phase in the area of asymmetric catalysis with chiral metal complexes, especially lanthanide ones.

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(11) Because of the difficulty in making a good crystalline of the Yb complex suitable for X-ray analysis, we cannot discuss here in detail about the possible chirality (Δ or Λ) of the metal center of the complex.

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Supporting Information Available: A typical experimental procedure for the asymmetric amplification of the enantioselective hetero-Diels–Alder reaction and the determination of the optical purity of the component ligand of the complex **Yb-9** (see Table 1). This material is available free of charge via the Internet at http://pubs.acs.org.

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