

Catalytic Asymmetric Epoxidation of α,β -Unsaturated Ketones Promoted by Lanthanoid Complexes

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Catalytic asymmetric epoxidations are one of the most important asymmetric processes.¹ In 1980 Sharpless *et al.* reported a stoichiometric asymmetric epoxidation of allylic alcohols,^{2a} a method which was later improved to a catalytic process.^{2b} Moreover, catalytic asymmetric epoxidations of unfunctionalized olefins using salen–manganese complexes have been reported independently by Jacobsen *et al.*,^{3a} Katsuki *et al.*,^{3b} and Mukaiyama *et al.*^{3c,4} In striking contrast to these successful achievements, an efficient catalytic asymmetric epoxidation of enones *with broad generality* has not been developed.⁵ Quite recently, Enders and co-workers reported a very impressive and practical asymmetric epoxidation of enones using a stoichiometric amount of *N*-methylpseudoephedrine as a chiral source.⁶ In this Communication we report an efficient catalytic asymmetric epoxidation of enones using lanthanoid complexes, which is the first example of a catalytic process applicable to various enones.

We have succeeded in developing several kinds of hetero-bimetallic chiral catalysts such as LnM₃tris(binaphthoxide) complexes (LnMB), AlMBis(binaphthoxide) complexes (AMB), and GaMBis(binaphthoxide) complexes (GaMB) (Ln = lanthanoid, M = alkali metal, A = aluminium, Ga = gallium, B = BINOL (1) or its derivatives).⁷ Among them, LSB, ALB, and GaSB (L = lanthanum, S = sodium, L = lithium) have been found to be very useful for catalytic asymmetric Michael reactions.⁷ We envisioned that these chiral catalysts would be useful for the asymmetric epoxidation of enones using hydroperoxides such as *tert*-butyl hydroperoxide (TBHP) and cumene

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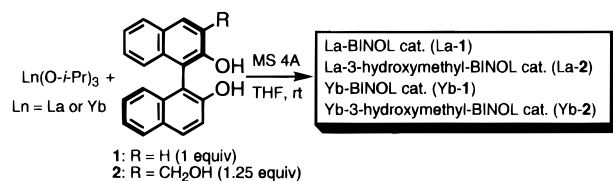
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Scheme 1. Preparation of Chiral Lanthanoid-BINOL Derivative Catalysts



hydroperoxide (CMHP).⁸ As expected, the reaction of **3** with TBHP (2 equiv)⁹ in the presence of LSB (10 mol %), generated from (*R*)-BINOL, in THF at room temperature for 10 h was found to give **4**¹⁰ with 83% ee¹¹ and in 92% yield. Unfortunately however LSB as well as ALB and GaSB was not useful for many other enones. Undeterred, we considered the possibility that an alkali metal free lanthanum complex of the type known to be effective for catalytic asymmetric Michael reactions¹² might also be useful in this case. The catalytic suspension of the La-BINOL complex was prepared from La(O-*i*-Pr)₃¹³ and (*R*)-BINOL (1 molar equiv) in the presence of MS 4A¹⁴ (Scheme 1). As expected it was found that treatment of **3** with TBHP (1.5 equiv) in the presence of 10 mol %¹⁵ of the La-BINOL complex (La-1) in THF at room temperature for 0.5 h afforded **4**¹⁰ with 62% ee¹¹ in 90% yield.^{16,17} Moreover, the use of CMHP instead of TBHP improved the asymmetric epoxidation, giving **4** with 83% ee in 93% yield^{18,19} (5 mol % of La-BINOL complex).¹⁵ In marked contrast to LSB this type of chiral lanthanum catalyst was found to be applicable to a range of enone substrates. Thus, **5** was converted to **6**¹⁰ with 86% ee¹¹ and in 93% yield, and **7** was transformed to **8**¹⁰ with 85% ee¹¹ in 85% yield (Table 1, entries 1, 4, and 6). After several attempts, we were pleased to find that the use of (*R*)-3-hydroxymethyl-BINOL (**2**) instead of **1** substantially improved the catalytic asymmetric epoxidations (Table 1, entries 2, 3, 5, and 7).^{20–22} Namely, **4**, **6**, and **8** were obtained with 91, 94, and 83% ee,¹¹ respectively, and in excellent yields.

In contrast to the results presented above, the enones shown in Table 1 (entries 8, 9, 10, and 11) were best converted to the corresponding epoxides by using the ytterbium complex generated from Yb(O-*i*-Pr)₃,¹³ (*R*)-**2**, and MS 4A¹⁴ in THF at 40 °C

(8) For the mechanism of epoxidations using hydroperoxides, see: Reed, K. L.; Gupton, J. T.; Solarz, T. L. *Synth. Commun.* **1989**, *19*, 3579–3587.

(9) For obtaining anhydrous TBHP in toluene, see: Hill, J. G.; Rossiter, B. E.; Sharpless, K. B. *J. Org. Chem.* **1983**, *48*, 3608–3611.

(10) The absolute configurations were determined by transformation to the authentic samples (for **4**, **6**, **8**, **10**, and **14**) or determined by the Mosher method after transforming to the corresponding β -hydroxyketones (for **12** and **16**). See: Marsman, B.; Wynberg, H. *J. Org. Chem.* **1979**, *44*, 2312–2314.

(11) The ees of the epoxy ketones were determined by chiral stationary phase HPLC.

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(13) Purchased from Kojundo Chemical Co., Ltd., 5-1-28, Chiyoda, Sakato, Saitama 350-02, Japan (Fax: +81-492-84-1351).

(14) MS 4A was used after drying at 180 °C for 3 h under reduced pressure. Although the role of MS 4A is not clear at present, the reactions are accelerated by their addition.

(15) Based on the amount of Ln(O-*i*-Pr)₃.

(16) The use of other lanthanoids gave less satisfactory results.

(17) In the case of the Michael reactions reported in 12a, we observed that a 1:1 ratio of La(O-*i*-Pr)₃ and BINOL gave almost the maximum ee.

(18) Pure CMHP was obtained by the method in *Purification of Laboratory Chemicals*, 3rd ed.; Perrin, D. D., Armarego, W. L., Eds.; Pergamon Press: New York, 1988.

(19) The use of THF gave the best result (cf.: toluene, 62% ee in 96% yield; Et₂O, 47% ee in 78% yield; CH₂Cl₂, 45% ee in 93% yield).

(20) In the case of Ln-2 catalyst, a 1:1.25 ratio of Ln(O-*i*-Pr)₃ and **2** gave the maximum ee.

(21) Synthesized from (*R*)-BINOL in four steps. See Supporting Information.

(22) The use of (*R*)-3, 3'-dialkyl-BINOL (alkyl = CH₃ or CH₂CH₃), and (*R*)-3, 3'-dihydroxymethyl-BINOL gave less satisfactory results.

Table 1. Catalytic Asymmetric Epoxidations Using Alkali Metal Free Lanthanoid Complexes

$$\text{R}^1\text{-CH=CH-C(=O)-R}^2 + \text{ROOH} \xrightarrow[\text{MS 4A, rt, THF}]{(R)\text{-Ln cat.}} \text{R}^1\text{-CH(O)-CH(O)-C(=O)-R}^2$$

3, 4: R¹ = Ph, R² = Ph **11, 12:** R¹ = Ph, R² = *i*-Pr
5, 6: R¹ = *i*-Pr, R² = Ph **13, 14:** R¹ = Ph(CH₂)₂, R² = CH₃
7, 8: R¹ = Ph, R² = *o*-MOMOC₆H₄ **15, 16:** R¹ = CH₃(CH₂)₄, R² = CH₃
9, 10: R¹ = Ph, R² = CH₃

| entry | enone | epoxide | Ln cat. (mol %) | ROOH (1.5 eq) | time (h) | yield (%) | ee ^a (%) |
|-------|-------|---------|-----------------|---------------|----------|-----------|---------------------|
| 1 | 3 | 4 | La - 1 (5) | CMHP | 6 | 93 | 83 |
| 2 | 3 | 4 | La - 2 (5) | CMHP | 7 | 93 | 91 |
| 3 | 3 | 4 | La - 2 (1) | CMHP | 44 | 95 | 89 |
| 4 | 5 | 6 | La - 1 (5) | CMHP | 12 | 93 | 86 |
| 5 | 5 | 6 | La - 2 (5) | CMHP | 7 | 95 | 94 |
| 6 | 7 | 8 | La - 1 (5) | CMHP | 20 | 85 | 85 |
| 7 | 7 | 8 | La - 2 (5) | CMHP | 96 | 78 | 83 |
| 8 | 9 | 10 | Yb - 2 (5) | TBHP | 96 | 83 | 94 |
| 9 | 11 | 12 | Yb - 2 (8) | TBHP | 159 | 55 | 88 |
| 10 | 13 | 14 | Yb - 2 (8) | TBHP | 118 | 91 | 88 |
| 11 | 15 | 16 | Yb - 2 (8) | TBHP | 67 | 71 | 91 |

^a Absolute configurations were determined to be (α S, β R). See ref 10.

for 1 h (Scheme 1, Yb-2).²⁰ That is, treatment of **9** with TBHP (1.5 equiv) in the presence of 5 mol %¹⁵ of Yb-2 in THF at room temperature for 96 h was found to give **10**¹⁰ with 94% ee¹¹ in 83% yield. Gratifyingly, **12**, **14**, and **16** were obtained with 88, 88, and 91% ee, respectively, and in excellent yields. In contrast, the use of either Yb-1 catalyst or La-CMHP system afforded **10** with less satisfactory results.^{23,24} It seems likely that the difference in ionic radius between lanthanum and ytterbium as well as the difference in Lewis acidities accounts for the observed center metal effects.

Although we have not succeeded in determining the structure, it was found that an almost 1:1 ratio of Ln(O-*i*-Pr)₃ (Ln = La or Yb) and **1** gave the maximum enantiomeric excesses (Figure 1).²⁵ The ¹³C-NMR spectrum of La-1 was quite obscure, suggesting that both the chiral Yb-1 catalyst and the La-1 catalyst exist as oligomers. Moreover, we have succeeded in obtaining asymmetric amplification of the catalytic asymmetric epoxidation (Figure 2). We believe that the oligomeric structure of these lanthanoid-BINOL catalysts may play a key role in these catalytic asymmetric epoxidations of enones. That is, a Ln-alkoxide moiety in the catalysts appears to act as a Brønsted base, activating a hydroperoxide moiety so as to make possible a Michael reaction, and at the same time another Ln metal ion seems to act as a Lewis acid, both activating and controlling

(23) In the case of Yb catalysis, the use of CMHP caused decrease in yields and ees of the epoxides obtained.

(24) Using Yb-1 catalyst, the following ees and yields were obtained (TBHP, 5 mol % of the catalyst). **10**, 88% ee (94% yield); **12**, 83% ee (84% yield); **14**, 53% ee (87% yield); **16**, 67% ee (83% yield).

(25) The structure **i** is tentatively proposed. The unequivocal structural determination is currently under investigation.

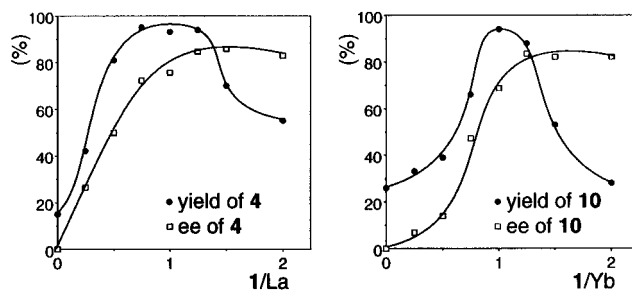
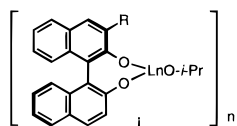


Figure 1. Influence of the ratio of Ln(O-*i*-Pr)₃ and **1** on yield and ee. Left: epoxidation of **3** catalyzed by La-1 catalyst. Right: epoxidation of **9** catalyzed by Yb-1 catalyst.

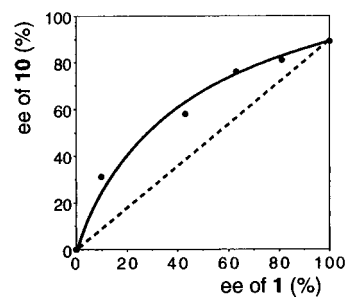


Figure 2. Asymmetric amplification in the epoxidation of **9** catalyzed by Yb-1 catalyst.

the orientation of the enone.²⁶ Such a mechanism, analogous to those for enzymatic methods, may explain why various epoxides can be synthesized with good enantiomeric excesses even at room temperature.

The general procedure is as follows: A THF solution of (*R*)-BINOL (2.5 mL, 0.25 mmol) or (*R*)-3-hydroxymethyl-BINOL (3.1 mL, 0.31 mmol) was added to a THF suspension (25 mL) of MS 4A (1.0 g). To this stirred suspension was added La-(O-*i*-Pr)₃¹³ (0.25 mmol, 1.25 mL) or Yb(O-*i*-Pr)₃ (0.25 mmol, 2.5 mL) in THF at room temperature. After stirring for 0.5–1 h at room temperature (for La) or 40 °C (for Yb), to the resulting THF suspension was added the enone (5.0 mmol) and a toluene solution of the hydroperoxide (2.1 mL, 7.5 mmol) at room temperature. After stirring for the time shown in Table 1 at room temperature, the reaction mixture was treated with saturated NH₄Cl aqueous. The epoxide was further purified by flash chromatography on silica gel.

In conclusion, we have succeeded in developing an efficient and general method for the catalytic asymmetric epoxidation of enones using lanthanoid complexes. It is noteworthy that this catalytic asymmetric epoxidation can be carried out at room temperature using 1–8 mol % of a chiral catalyst to give epoxides with good enantiomeric excesses. Further studies are in progress.

Supporting Information Available: Experimental procedures, ¹H, ¹³C NMR, IR, and mass spectral data for the products (27 pages). See any current masthead page for ordering information and Internet access instructions.

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(26) Considering the mechanism of epoxidations using a hydroperoxide, the activation of an enone by the same lanthanoid atom appears to be precluded.