Catalytic Asymmetric Epoxidation of Enones Using La−BINOL−Triphenylarsine Oxide Complex: Structural Determination of the Asymmetric Catalyst

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Abstract: The catalytic asymmetric epoxidation of enones using the La−BINOL−Ph_3As═O complex generated from La(O-*i*-Pr)$_3$, BINOL, and Ph_3As═O in a ratio of 1:1:1 is described herein. Using 1−5 mol % of the asymmetric catalyst, a variety of enones, including a dienone and a *cis*-enone, were found to be epoxidized in a reasonable reaction time, providing the corresponding epoxy ketones in up to 99% yield and with more than 99% ee. The possible structure of the actual asymmetric catalyst has been clarified by various methods, including X-ray crystal structure analysis. This is the first X-ray analysis of an alkali-metal free lanthanoid−BINOL complex. Although La(binaphthoxide)$_2$(Ph_3As═O)$_2$ (**7**) was observed as the major complex in the complexes' solution, generated from La(O-*i*-Pr)$_3$, BINOL, and Ph_3As═O in a ratio of 1:1:1, the possible active species turned out to be the La−BINOL−Ph_3As═O complex in a ratio of 1:1:1. A probable reaction mechanism of the catalytic asymmetric epoxidation of enones is also proposed, suggesting that preferential formation of a heterochiral complex is the reason for asymmetric amplification. Moreover, the interesting role of La(O-*i*-Pr)$_3$ for accelerating the epoxidations while maintaining high ee's is discussed.

Introduction

Asymmetric epoxidation of olefins is one of the most important functional group manipulations in organic synthesis[1] due to the fact that enantiomerically enriched epoxides can be converted into various useful optically active synthetic intermediates. In 1980, Sharpless et al. reported the stoichiometric asymmetric epoxidation of allylic alcohols,[2a] a method which was later improved to a catalytic version by the addition of molecular sieves.[2b] 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] Moreover, asymmetric epoxidations of a wide range of olefins using optically active dioxiranes[4] and hydroperoxide[5] have been developed recently. Since the initial report by Juliá and co-workers,[6] catalytic asymmetric epoxidation of α,β-unsaturated ketones has been studied using several other methodologies such as asymmetric ligand−metal catalysis,[7] asymmetric phase transfer catalysis,[8] and polyamino acid catalysis.[6,9] A few years ago, we reported a general catalytic asymmetric epoxidation of enones using alkali-metal free lanthanoid−BINOL complexes.[10] These complexes were prepared from Ln(O-*i*-Pr)$_3$ and BINOL in a ratio of 1:1, providing the corresponding products in up to 95% yield and up to 94% ee. We speculated that this asymmetric induction might be induced by the multifunctinality of the asymmetric catalysts, where activation of both substrates (enone and peroxide) as well as control of their position is realized at the same time.

Despite excellent yields and enantiomeric excesses (ee's), this catalytic process is still unsatisfactory in terms of its rather low reactivity. Thus, we decided to overcome the drawback of our catalytic asymmetric epoxidation by tuning the reaction conditions. It is known that addition of triphenylphosphine oxide (Ph_3P═O) is effective for the enhancing the rate while maintain-

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(1) (a) *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley: New York, 2000. (b) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999. (c) Noyori, R. *Asymmetric Catalysis In Organic Synthesis*; John Wiley & Sons: New York, 1994.

(2) (a) Katsuki, K.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1992.

(3) Zhang, W.; Loebach, J. L.,; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801. (b) Irie, R.; Noda, K.; Ito, Y.; Matsumoto, N.; Katsuki, T. *Tetrahedron Lett.* **1990**, *31*, 7345. (c) Yamada, T.; Imagawa, K.; Nagata, T.; Mukaiyama, T. *Chem. Lett.* **1992**, 2231.

(4) (a) Curci, R.; Fiorentino, M.; Serio, M. R. *J. Chem. Soc., Chem. Commun.* **1984**, 155. (b) Wang, Z.-C.; Shi, Y. *J. Org. Chem.* **1997**, *62*, 8622. (c) Armstrong, A.; Hayter, B. R. *Chem. Commun.* **1998**, 621. (d) Yang, D.; Wong, M.-K.; Yip, Y.-C.; Wang, X.-C.; Tang, M.-W.; Zheng, Y.-C.; Cheung, K.-K. *J. Am. Chem. Soc.* **1998**, *120*, 5943. (e) Tian, H.; She, X.; Shu, L.; Yu, H.; Shi, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11551.

(5) Adam, W.; Rao, P. B.; Degen, H. G.; Saha-Möller, C. R. *J. Am. Chem. Soc.* **2000**, *122*, 5654.

(6) Juliá, S.; Masana, J.; Vega, J. C. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 929.

(7) (a) Enders, D.; Zhu, J.; Raabe, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1725. (b) Elston, C. L.; Jackson, R. F. W.; MacDonald, S. J. F.; Murray, P. J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 410. (c) Yu, H.-B.; Zheng, X.-F.; Lin, Z.-M.; Hu, Q.-S.; Huang, W.-S.; Pu, L. *J. Org. Chem.* **1999**, *64*, 8149. (d) For an impressive catalytic asymmetric epoxidation of cinnamate esters, see: Jacobsen, E. N.; Deng, L.; Furukawa, Y.; Martínez, L. E. *Tetrahedron* **1994**, *50*, 4323.

(8) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1998**, *39*, 1599. (b) Arai, S.; Tsuge, H.; Shioiri, T. *Tetrahedron Lett.* **1998**, *39*, 7563. (c) Corey, E. J.; Zhang, F. Y. *Org. Lett.* **1999**, *1*, 1287.

(9) For a recent review on this method, see: Porter, M. J.; Roberts, S. M.; Skidmore, J. *Bioorg. Med. Chem.* **1999**, *7*, 2145 and references therein.

(10) (a) Bougauchi, M.; Watanabe, S.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1997**, *119*, 2329. (b) Watanabe, S.; Kobayashi, Y.; Arai, T.; Sasai, H.; Bougauchi, M.; Shibasaki, M. *Tetrahedron Lett.* **1998**, *39*, 7353. (c) Watanabe, S.; Arai, T.; Sasai, H.; Bougauchi, M.; Shibasaki, M. *J. Org. Chem.* **1998**, *63*, 8090. (d) Daikai, K.; Kamaura, M.; Inanaga, J. *Tetrahedron Lett.* **1998**, *39*, 7321.

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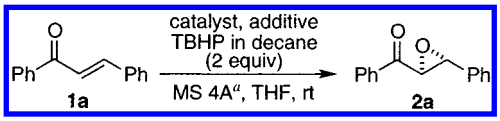
Table 1. Catalytic Asymmetric Epoxidation of Chalcone **1a** to Epoxy Ketone **2a** Using the La−BINOL Complex



entry	catalyst (mol %)	additives (mol %)	time (min)	yield (%)	ee (%)
1	La(O-*i*-Pr)$_3$ (10)		480	90	
2	La−(*R*)-BINOL (1:1) (10)		90	92	71
3	La−(*R*)-BINOL (1:1) (10)	Ph_3P═O (40)	30	98	97
4	La−(*R*)-BINOL (1:1) (10)	Ph_3P═O (30)	30	97	97
5	La−(*R*)-BINOL (1:1) (10)	Ph_3P═O (20)	30	94	95
6	La−(*R*)-BINOL (1:1) (10)	Ph_3P═O (10)	30	93	94
7	La−(*R*)-BINOL (1:1) (10)	Ph_3As═O (40)	60	92	85
8	La−(*R*)-BINOL (1:1) (10)	Ph_3As═O (30)	30	92	93
9	La−(*R*)-BINOL (1:1) (10)	Ph_3As═O (20)	30	96	95
10	La−(*R*)-BINOL (1:1) (10)	Ph_3As═O (10)	3	95	97
11	La(O-*i*-Pr)$_3$ (10)	Ph_3As═O (10)	480	64	

[a] MS 4A was not dried (1000 mg/mmol).

ing high ee's.[10d] However, addition of 3−6 equiv of Ph_3P═O to the La−BINOL complex is needed to enhance the reaction rate, and we became interested in finding new additives which might be more effective in terms of atom economy. Moreover, we hoped to determine the structure of an alkali-metal free lanthanoid−BINOL complex unequivocally by X-ray of the complex with the new additive. The structure of the alkali-metal free lanthanoid−BINOL complex had not been clarified, mainly due to the specific feature of lanthanoid metals.[11] In this article, we report a catalytic asymmetric epoxidation of enones using a novel multifunctional asymmetric catalyst, the La−BINOL−triphenylarsine oxide (Ph_3As═O) complex. This catalyst system exhibits much higher activity and selectivity compared to those of Ln−BINOL complexes, affording optically active epoxy ketones with broad generality in up to 99% yield and more than 99% ee. Furthermore, we report the first example of X-ray analysis of an alkali-metal free lanthanoid−BINOL−Ph_3As═O complex as well as a possible reaction mechanism of the catalytic asymmetric epoxidation of enones.

Results and Discussion

Catalytic Asymmetric Epoxidation of Enones Using the La−BINOL−Ph_3As═O Complex. Optimization of Reaction Conditions and Scope and Limitations of the Reaction. In an attempt to improve the catalytic asymmetric epoxidation of enones developed in our group[10a,b] and improved in Inanaga's group,[10d] we examined the reaction in detail using chalcone (**1a**) as a representative starting material. The results are summarized in Table 1. As previously reported, the catalyst (10 mol %) prepared from La(O-*i*-Pr)$_3$ and (*R*)-BINOL in a ratio of 1:1 gave the epoxide **2a** in 92% yield and 71% ee (Table 1, entry 2). On the other hand, the conditions developed by Inanaga using 40 mol % of Ph_3P═O gave rise to **2a** in 98% yield and 97% ee in a much shorter reaction time (30 min). However, as shown in entry 6 (Table 1), when the reaction was carried out in the presence of 10 mol % of Ph_3P═O, a slightly less satisfactory result was obtained. We examined the influence of many additives instead of Ph_3P═O on the catalytic asymmetric epoxidation, which would result in the formation of **2a** more efficiently, even in the presence of 10 mol % of an additive. As a result, we were pleased to find that the addition of Ph_3As═O (10 mol %) produced **2a** in 95% yield and 97% ee in only 3 min. Interestingly, different from the case of Ph_3P═O, the addition of 40 mol % of Ph_3As═O provided a less satisfactory result, giving **2a** in 92% yield and 85% ee (60 min). This difference could be explained by the fact that the Lewis basicity of Ph_3As═O is higher than that of Ph_3P═O.[12,13] From these results, we concluded that the complex generated from La(O-*i*-Pr)$_3$, (*R*)-BINOL, and Ph_3As═O in a ratio of 1:1:1 was the most effective asymmetric catalyst for the epoxidation of chalcone (**1a**).

Having developed the novel asymmetric catalyst for the asymmetric epoxidation of chalcone (**1a**), next we sought to explore the generality of this catalytic asymmetric reaction. Table 2 summarizes the use of the asymmetric catalyst generated from La(O-*i*-Pr)$_3$, (*R*)-BINOL, and Ph_3As═O in a ratio of 1:1:1 for the epoxidation of various substrates. As shown, almost all reactions proceeded to completion in reasonable reaction times when 5 mol % of the new catalyst was used at room temperature. Additionally, a slight improvement was achieved in almost all cases with the exception of enones **1e** and **1i** in terms of yield and ee. Aryl ketone type substrates such as **1a**−**c** were epoxidized smoothly and afforded the corresponding epoxy ketones in excellent yields and enantiomeric excesses (Table 2, entries 1−4). Particularly, epoxidation of **1a** proceeded quite efficiently, and the reaction was completed in 3 h, even with use of 1 mol % of the catalyst (Table 2, entry 2). This asymmetric catalyst system was also quite effective for alkyl ketone type substrates. In addition to the *tert*-butyl ketone derivative **1d** (Table 2, entry 5), excellent results were obtained also in the case of the enolizable enones **1e**−**i**[14] (Table 2, entries 6−10), which are generally difficult to epoxidize.[15] In particular, the epoxidation of **1f** proceeded with a big increase in terms of enantioselectivity (>99% ee, >200:1 enantioselectivity) relative to the previous result (94% ee, 32:1 enantioselectivity). Furthermore, we examined the epoxidation of other unique enones. We had already reported the catalytic asymmetric epoxidation of *cis*-enones using the Yb−3-hydroxymethyl−BINOL complex.[10c] It was found that the La−BINOL−Ph_3As═O complex also catalyzed the transformation of *cis*-enone **3** into *cis*-epoxy ketone **4**, but unfortunately the result was less satisfactory, and **4** was obtained in only 61% yield and 59% ee, together with less than 10% of the corresponding *trans*-epoxy ketone (Scheme 1a). We also tried the epoxidation of dienone **5**. The reaction was completed in 3 h with the use of 5 mol % of the catalyst and gave the product **6** in 95% yield and 96% ee with complete regioselectivity (Scheme 1b).[16] In this way, the new asymmetric catalyst system consisting of La(O-*i*-Pr)$_3$, BINOL, and Ph_3As═O in a ratio of 1:1:1 was found to have a broad generality for enones, affording the products in excellent yields and more than

(11) Although several catalytic asymmetric reactions using alkali-metal free lanthanoid−BINOL derivative complexes have been developed, the catalyst structures have not been unequivocally clarified yet. However, partial information has been obtained in some cases, see: (a) Kim, Y.-S.; Matsunaga, S.; Das, J.; Sekine, A.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 6506. (b) Furuno, H.; Hanamoto, T.; Sugimoto, Y.; Inanaga, J. *Org. Lett.* **2000**, *2*, 49. (c) Kobayashi, S.; Ishitani, H.; Araki, M.; Hachiya, I. *Tetrahedron Lett.* **1994**, *35*, 6325. (d) Kobayashi, S.; Araki, M.; Hachiya, I. *J. Org. Chem.* **1994**, *59*, 3758.

(12) Cruickshank, D. W. J. *J. Chem. Soc.* **1961**, 5486.

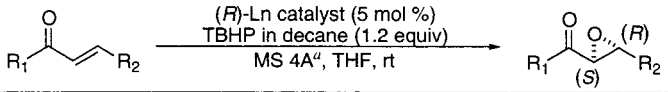
(13) When **1i** was used as a substrate, the different tendencies between the two additives were more noticeable. For the detailed data, see the Supporting Information.

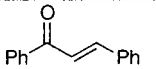
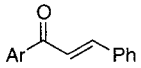
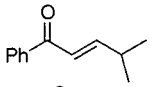
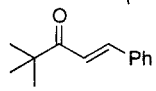
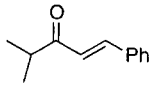
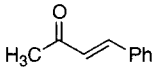
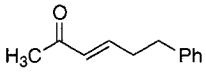
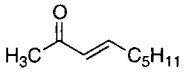
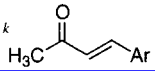
(14) Epoxy ketone **2i** can be converted into several natural coumarins efficiently. See: Nemoto, T.; Ohshima, T.; Shibasaki, M. *Tetrahedron Lett.* **2000**, *41*, 9569.

(15) A few successful examples using the polyleucine catalyst have been reported. See: Adger, B. M.; Barkley, J. V.; Bergeron, S.; Cappi, M. W.; Flowerdew, B. E.; Jackson, M. P.; McCague, R.; Nugent, T. C.; Roberts, S. M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3501.

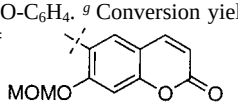
(16) The Yb−BINOL complex also catalyzes this reaction (5 mol % of the catalyst, 2 h, 87% yield, 93% ee). Watanabe, S. Ph.D. Thesis, The University of Tokyo, 1999.

Table 2. Catalytic Asymmetric Epoxidation of Various Enones **1a**−**i**

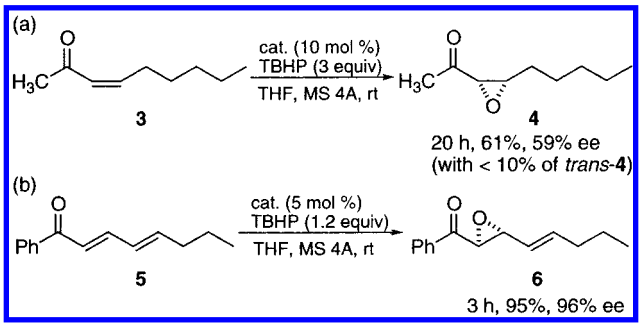


entry	enones	products	La-(*R*)-BINOL-Ph_3As=O complex time (h)	yield (%)	ee (%)	Ln-(*R*)-BINOL complex[b] time (h)	yield (%)	ee (%)	Yb-(*R*)-BINOL (2:3) complex[c] time (h)	yield (%)	ee (%)	La-(*R*)-BINOL-Ph_3P=O complex[d] time (h)	yield (%)	ee (%)
1		**1a** **2a**	0.25	99	96	7	93	91	1	99	81	0.5	99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

[a] MS 4A was not dried (1000 mg/mmol). [b] Reference 10a. [c] Reference 10b. [d] Reference 10d. [e] 1 mol % of the catalyst was used. [f] Ar = *o*-MOMO-C_6H_4. [g] Conversion yield. [h] 8 mol % of the catalyst was used. [i] 25 mol % of the catalyst was used. [j] 10 mol % of the catalyst was used. [k] Ar =



Scheme 1. Catalytic Asymmetric Epoxidation of *cis*-Enone **3** (a) and Dienone **5** (b) Using the La−(*R*)-BINOL−Ph_3As=O Complex



99% ee, even at room temperature.[17] It is obvious that reactions which proceed at room temperature have significant practical advantages compared to those that require low temperature for the induction of higher selectivity. Additionally, the simple chiral ligand, unmodified BINOL, makes this process more accessible.

Structural Determination of the La−BINOL−Ph_3As=O Complex. In contrast to some successful examples of structural determination of lanthanoid asymmetric catalysts,[18] little is known about the structure of alkali-metal free Ln−BINOL complexes.[11] First we made attempts to clarify their structures using NMR analysis. However, the ^{13}C NMR spectrum of the La−BINOL complex in THF was quite obscure. Additionally, asymmetric amplification was observed in the epoxidation. Thus,

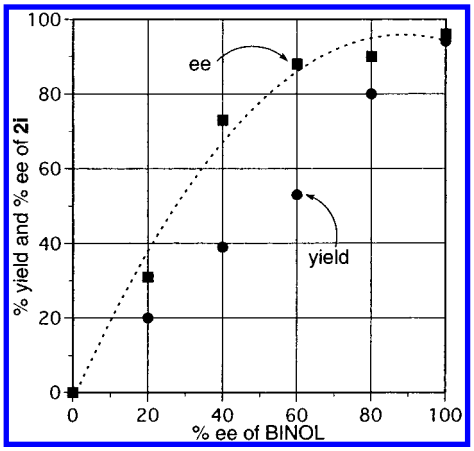


Figure 1. Nonlinear relationship between the enantiomeric purities of the product **2i** and BINOL.

(17) Epoxidations of **1a** and **1f** using 5 mol % of the Yb−(*R*)-BINOL−Ph_3As=O complex gave less satisfactory results, producing the corresponding epoxy ketones **2a** (1 h, 97%, 94% ee) and **2f** (10 h, 85%, 94% ee), respectively.

(18) Sasai, H.; Suzuki, T.; Itoh, N.; Tanaka, K.; Date, T.; Okamura, K.; Shibasaki, M. *J. Am. Chem. Soc.* **1993**, *115*, 10372.

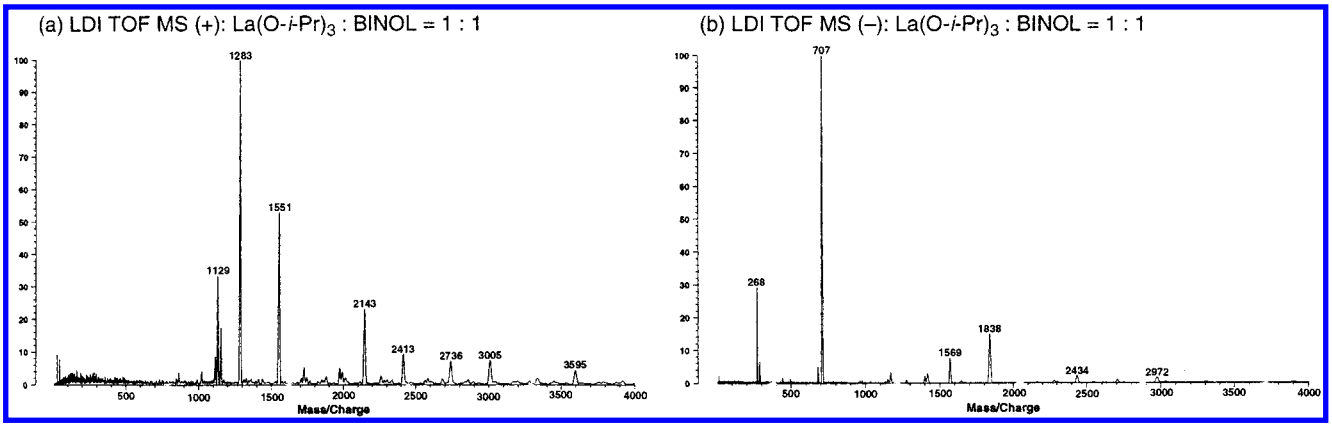


Figure 2. LDI TOF MS spectra of a complexes' solution generated from La(O-*i*-Pr)$_3$ and BINOL in a ratio of 1:1: (a) positive mode and (b) negative mode.

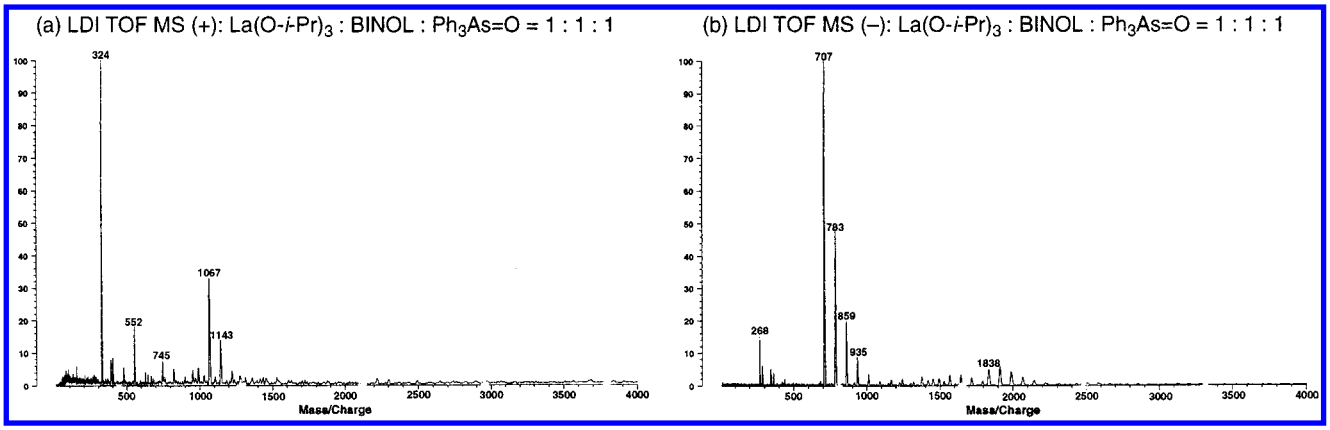


Figure 3. LDI TOF MS spectra of a complexes' solution generated from La(O-*i*-Pr)$_3$, BINOL, and $Ph_3As{=}O$ in a ratio of 1:1:1: (a) positive mode and (b) negative mode.

we concluded that the optically active lanthanoid complex should exist as an oligomer.

It is well known that oxygen ligands such as $Ph_3As{=}O$ and $Ph_3P{=}O$ have a high affinity to lanthanoid metals.[19] Thus, we expected that the newly developed asymmetric catalyst, the La−BINOL−$Ph_3As{=}O$ complex, would have a different structure, leading to the structural determination of the complex. Our investigation started with a comparison with the information that had been already obtained from the La−BINOL complex. First we measured the ^{13}C NMR spectrum of the La−BINOL−$Ph_3As{=}O$ (1:1:1) complex in THF. The obtained spectrum, however, was similar to that of the La−BINOL complex. Next, we examined if asymmetric amplification might be observed in the epoxidation using the La−BINOL−$Ph_3As{=}O$ complex. We investigated the reaction using enone **1i**,[20] and a positive nonlinear effect was observed, as shown in Figure 1. Moreover, it was of interest that a decrease in the reactivity was observed when BINOL with low enantiomeric excess was used. In particular, when (*rac*)-BINOL was used, no product could be obtained.[21] Unfortunately, at this stage, these results appeared to suggest that the chiral lanthanoid complex would have an oligomeric structure even in the presence of $Ph_3As{=}O$. Laser desorption/ionization time-of-flight mass spectrometry (LDI TOF MS) is often utilized for a structural analysis of organometallic complexes, and previously we succeeded in obtaining analyzable spectra of several lanthanoid complexes such as LnM_3tris(binaphthoxide) complex.[18,22] It has also been found that analyzable spectra can be obtained even in the case of alkali-metal free Ln−BINOL complexes (Ln = La or Yb).[23] The spectra of the complexes' solution generated from La(O-*i*-Pr)$_3$ and BINOL in a ratio of 1:1 are shown in Figure 2, and some peaks a molecular weight of the order of thousands are observed in both the positive and negative modes. Likewise, spectra of the complexes' solution generated from La(O-*i*-Pr)$_3$, BINOL, and $Ph_3As{=}O$ in a ratio of 1:1:1 are shown in Figure 3. In contrast to our expectation mentioned above, we could find only some small peaks which represent oligomers, and only one analyzable peak each was detected in the positive and negative modes.[24] The peak observed in the positive mode (MW 1067) corresponds to the molecular weight of the cationic complex described in Figure 4a, and the peak observed in negative mode (MW 707) corresponds to the molecular weight of the anionic complex described in Figure 4b. These data suggested that the monomeric La(binaphthoxide)$_2$($Ph_3As{=}O$)$_2$ complex (**7**) (Figure 4c) would be the major component in the solution generated from La(O-*i*-Pr)$_3$, BINOL, and $Ph_3As{=}O$ in a ratio of 1:1:1, and these results appeared to support our expectation that the

(19) Cotton, F. A.; Wilkinson, G.; Murillo, C. A.; Bochmann, M. *Advanced Inorganic Chemistry*, 6th ed.; John Wiley & Sons: New York, 1999; p 1108.

(20) The reactions were carried out using 25 mol % of the catalyst at room temperature and quenched after 6 h, except for the reaction using optically pure (*R*)-BINOL (2 h). For detailed data, see the Supporting Information.

(21) The results which were obtained for the reactions quenched after 6 h indicate that quenching the reactions after 2 h should lead to a negative nonlinear relationship.

(22) Yoshikawa, N.; Yamada, M. A. Y.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168.

(23) Watanabe, S. Ph.D. Thesis, The University of Tokyo, 1999.

(24) In the presence of $Ph_3As{=}O$, unknown peaks were observed every 76 units of molecular weight from the base peaks (1067 and 707), respectively.

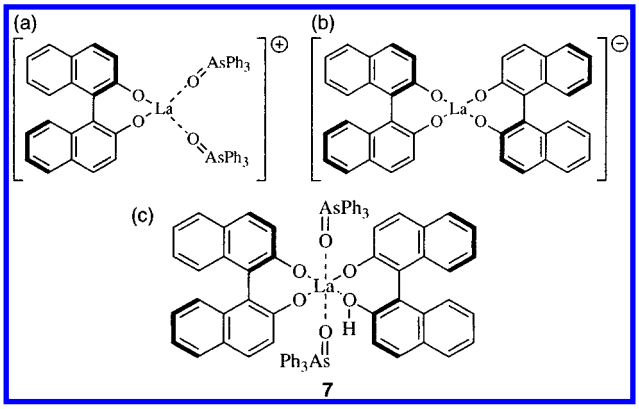


Figure 4. Structures corresponding to the molecular weight observed in positive mode (a) and negative mode (b) of LDI TOF MS and (c) the possible structure of the major complex in a complexes' solution generated from La(O-*i*-Pr)$_3$, (*R*)-BINOL, and $Ph_3As{=}O$ in a ratio of 1:1:1.

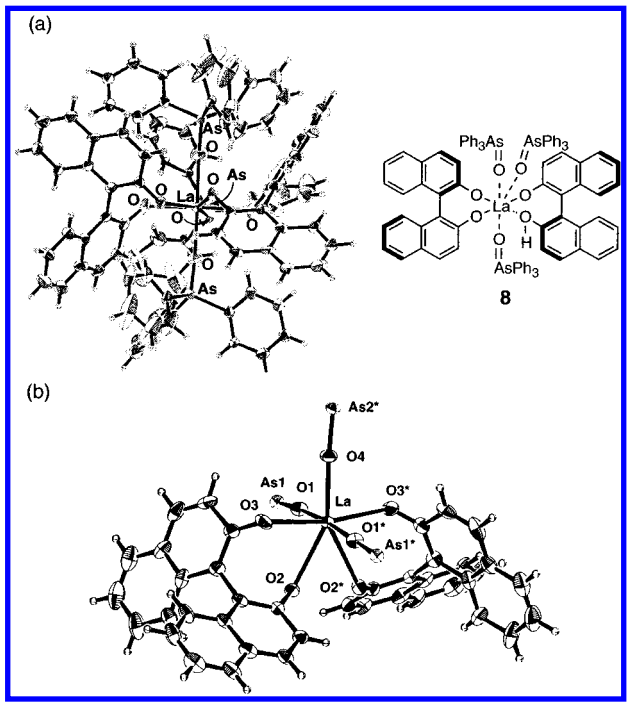


Figure 5. X-ray structure of La(binaphthoxide)$_2$($Ph_3As{=}O$)$_3$ **8** (a). Triphenyl moieties of the triphenylarsine oxides are omitted for clarity (b). Selected bond lengths (Å): La−O(1), 2.365(5); La−O(1*), 2.365(5); La−O(2), 2.684(6); La−O(2*), 2.684(6); La−O(3), 2.437(5); La−O(3*), 2.437(5); La−O4, 2.391(8).

stable complex is formed by coordination of $Ph_3As{=}O$ to the lanthanum metal. At this stage we expected that the complex stabilized by the coordination of $Ph_3As{=}O$ could crystallize, and after several attempts we were pleased to get X-ray-grade crystal from the complexes' solution generated from La(O-*i*-Pr)$_3$, BINOL, and $Ph_3As{=}O$ in a ratio of 1:1:3, containing an excess amount of $Ph_3As{=}O$ relative to the best ratio for the asymmetric epoxidation. The X-ray crystal structure analysis is shown in Figure 5. The crystal structure turned out to be La(binaphthoxide)$_2$($Ph_3As{=}O$)$_3$ (**8**) (Figure 5a) with a pentagonal bipyramidal structure (Figure 5b). To the best of our knowledge, this is the first X-ray crystal structure analysis of an alkali-metal free lanthanoid−BINOL complex. Considering the distance between the La atom and the oxygen atoms of $Ph_3As{=}O$, it can be expected that the ligands should coordinate strongly and contribute to the stability of the active species.

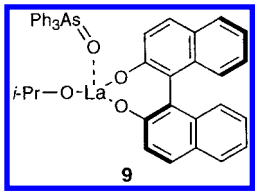
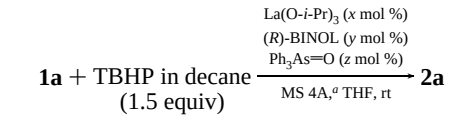


Figure 6. Speculated active species in a complexes' solution generated from La(O-*i*-Pr)$_3$, (*R*)-BINOL, and $Ph_3As{=}O$ in a ratio of 1:1:1.

Table 3. Catalytic Asymmetric Epoxidation of **1a** to Epoxy Ketone **2a** Using La−(*R*)-BINOL−$Ph_3As{=}O$ Complexes



entry	La(O-*i*-Pr)$_3$ (*x* mol %)	(*R*)-BINOL (*y* mol %)	$Ph_3As{=}O$ (*z* mol %)	time (min)	yield (%)	ee (%)
1	10	20	10	72	95	96
2	10	20	20	72	93	92
3	10	20	30	90	92	95
4	10	10	10	3	95	97

[a] MS 4A was not dried (1000 mg/mmol).

Furthermore, the X-ray crystal structure strongly suggests that the lanthanum complex should exist not as an oligomeric species, but as a monomeric species in the solution. In conclusion, our speculation that **7** would be the major component in the solution generated from La(O-*i*-Pr)$_3$, BINOL, and $Ph_3As{=}O$ in a ratio of 1:1:1 should be reasonable. In striking contrast to the case of $Ph_3As{=}O$, no X-ray-grade crystals were obtained in the presence of $Ph_3P{=}O$.

Effect of Excess La(O-*i*-Pr)$_3$ on the La(binaphthoxide)$_2$-($Ph_3As{=}O$)$_2$ Complex. At first, the results shown in Table 1 encouraged us to speculate that La−BINOL−$Ph_3As{=}O$ complex **9** (Figure 6) should exist in the complexes' solution generated from La(O-*i*-Pr)$_3$, BINOL, and $Ph_3As{=}O$ in a ratio of 1:1:1 and might function as the most effective species. However, the major component in the complexes' solution turned out to be **7**. Moreover, the crystal prepared from the complexes' solution generated from La(O-*i*-Pr)$_3$, BINOL, and $Ph_3As{=}O$ in a ratio of 1:1:3 proved to be **8** by X-ray crystal structure analysis. These facts again made us question if the ratio of the three components used (La−BINOL−$Ph_3As{=}O$ = 1:1:1) was the best one. To solve this problem, we carried out detailed investigations on the ratio of the three components. At first we examined the effect of the amount of $Ph_3As{=}O$ relative to La−BINOL complex obtained in a ratio of 1:2. The results are shown in Table 3 (entries 1−3). For all conditions, a lower reactivity than under the best conditions (entry 4) was observed, with the ee values remaining unchanged in all cases. Table 4 summarizes the results obtained by changing the ratio of La(O-*i*-Pr)$_3$ and BINOL. During these investigations, the relative amount of $Ph_3As{=}O$ to that of BINOL was kept constant because of the fact that the ratio 1:1:1 was apparently superior to the other ratio using more than 1 equiv of $Ph_3As{=}O$ to BINOL (see Table 1). As a result, an increase in the yield was observed proportional to a decrease in the ratio of BINOL relative to La(O-*i*-Pr)$_3$. In contrast, no change was observed with respect to the enantiomeric excess, except for the result in entry 1. Moreover, we carried out the epoxidation of **1d** using La−BINOL−$Ph_3As{=}O$ complex generated in a ratio of 1:1:0.5. As a result, a decrease in the reactivity was observed when less than 1 equiv of $Ph_3As{=}O$ was used (Scheme 2). All these results supported our conclusion that the La−BINOL−$Ph_3As{=}O$ complex generated in a ratio of 1:1:1 should be the best one

Table 4. Catalytic Asymmetric Epoxidation of **1a** to Epoxy Ketone **2a** Using La−(*R*)-BINOL−Ph_3As=O Complexes in a Ratio of *x*:*y*:*z*

1a + TBHP in decane (1.2 equiv) → **2a**
La(O-*i*-Pr)$_3$ (*x* mol %), (*R*)-BINOL (*y* mol %), Ph_3As=O (*z* mol %), MS 4A,[a] THF, 25 °C, 15 min

entry	La(O-*i*-Pr)$_3$ (*x* mol %)	(*R*)-BINOL (*y* mol %)	Ph_3As=O (*z* mol %)	ratio (*x*:*y*:*z*)	yield (%)	ee (%)
1	5	20	20	0.5:2:2	29	80
2	5	10	10	1:2:2	57[b]	95
3	5	8.3	8.3	1.2:2:2	71[b]	96
4	5	7.1	7.1	1.4:2:2	79[b]	94
5	5	6.3	6.3	1.6:2:2	82[b]	95
6	5	5.6	5.6	1.8:2:2	88[b]	94
7	5	5	5	2:2:2	98[b]	96
8	5	4	4	2.5:2:2	77	96
9	5	3.3	3.3	3:2:2	68	96

[a] MS 4A was not dried (1000 mg/mmol). [b] Yields refer to the average of isolated yields for three or four runs.

Scheme 2. Catalytic Asymmetric Epoxidation of **1d** to Epoxy Ketone **2d** Using La−(*R*)-BINOL−Ph_3As=O (1:1:1) Complexes

1d + TBHP in decane (1.5 equiv) → **2d**
La(O-*i*-Pr)$_3$ (x mol %), (*R*)-BINOL (y mol %), Ph_3As=O (z mol %), MS 4A, THF, rt

catalyst	result
• La cat. (x:y:z = 10:10:10)	: 1 h, 93%, 99% ee
• La cat. (x:y:z = 10:10:5)	: 2.5 h, 88%, 99% ee

and promotes the reaction most efficiently. Consequently, the information obtained from the above investigations allowed us to make the following deductions:

(i) No change in the enantiomeric excess was observed for all conditions (Tables 3 and 4) except for entry 1 (Table 4). From this fact, we can speculate that the same complex should exist under all conditions and function as the most active and effective catalyst.

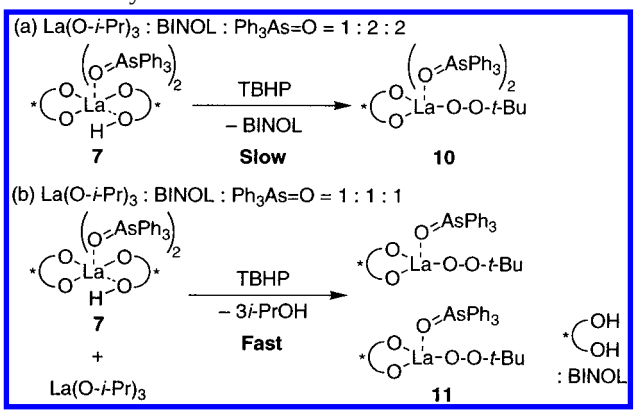
(ii) In contrast to the ee values, the reactivity was obviously different in each case. This fact appeared to suggest that the generation rate of the most active catalyst might be different in each case.

(iii) Although the La−BINOL−Ph_3As=O complex generated in a ratio of 1:1:1 was the best one for the epoxidation, the major component existing in the solution would be the 1:2:2 complex **7**.

The above-mentioned experimental information prompted us to propose the mechanism shown in Scheme 3. In the complexes' solution generated from La(O-*i*-Pr)$_3$, BINOL, and Ph_3As=O in a ratio of 1:2:2, **7** exists as the major complex.[25] The complex **7** reacts with TBHP to afford the La−BINOL−Ph_3As=O complex **10**, and **10** promotes the reaction. On the other hand, in the complexes' solution generated from La(O-*i*-Pr)$_3$, BINOL, and Ph_3As=O in the best ratio (1:1:1), **7** is formed similarly to the complexes' solution generated from La(O-*i*-Pr)$_3$, BINOL, and Ph_3As=O in a ratio of 1:2:2. However, 1 equiv of the excess La(O-*i*-Pr)$_3$ should remain in the reaction medium. Therefore, the excess La(O-*i*-Pr)$_3$ reacts with TBHP and also **7** to afford La−BINOL−Ph_3As=O complex **11** in a ratio of 1:1:1, and the resulting complex would function as the most active and effective catalyst. It seems that excess

(25) The corresponding complexes could be observed by LDI TOF MS in the complexes' solution generated from La(O-*i*-Pr)$_3$, BINOL, and Ph_3As=O in a ratio of 1:2:2.

Scheme 3. Proposed Mechanism for the Generation of the Active Catalyst



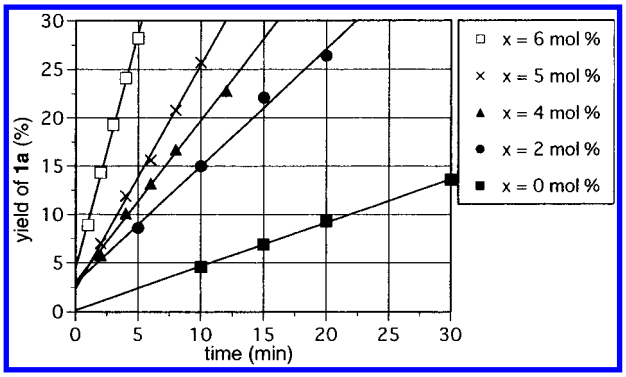


Figure 7. Kinetic experiments of the epoxidations using 6 mol % of the La−(*R*)-BINOL−Ph_3As=O complex in a ratio of 1:2:2 with *x* mol % of La(O-*i*-Pr)$_3$.

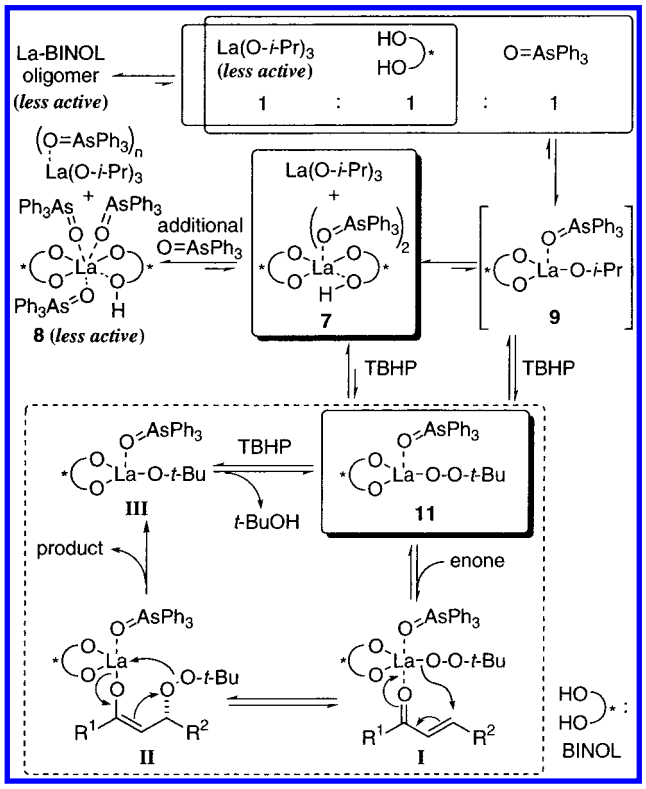
La(O-*i*-Pr)$_3$ plays a key role in facilitating the transformation of **7** to **11**. To prove our assumption, we made many attempts to detect the 1:1:1 complex under various preparative conditions for the catalysts using several methods in the presence or absence of TBHP. Unfortunately, however, we could not detect any complexes directly.[26] This may be due to the fact that rapid a equilibrium might be reached between several complexes in the solution. To get experimental evidence for the beneficial effect of excess La(O-*i*-Pr)$_3$, we measured initial rates of the epoxidations of **1a** using 6 mol % of the 1:2:2 complex **7** accompanied with 0−1 equiv (0−6 mol %) of excess La(O-*i*-Pr)$_3$ as the additive.[27] As shown in Figure 7, an increase in the initial rate for the reaction was observed upon the addition of La(O-*i*-Pr)$_3$ to **7**. Considering the result shown in Table 4 and the fact that La(O-*i*-Pr)$_3$ itself is not an effective catalyst for the epoxidation (Table 1), this result obviously supports the assumption discussed above.[28] From these results, it is obvious that the presence of an excess of La(O-*i*-Pr)$_3$ to the 1:2:2 complex **7** should be essential for faster formation of the most active species. In other words, these results suggested that the transformation of **7** to **11** can be facilitated by the presence of an excess of La(O-*i*-Pr)$_3$, and the 1:1:1 complex **11** should be

(26) In the presence of TBHP, a significant decrease in the peak corresponding to the anionic complex (MW 707, Figure 4b) was observed in the (−)-LDI TOF MS spectrum of the complexes' solution generated from La(O-*i*-Pr)$_3$, BINOL, and Ph_3As=O in a ratio of 1:1:1, suggesting that the lanthanum metal should have one BINOL unit as a ligand in the reaction medium.

(27) The reactions were carried out according to the general conditions for kinetic experiments. For the general conditions and the numerical data for plots in Figure 7, see the Supporting Information.

(28) Moreover, epoxidation of **1a** using 10 mol % of the crystal **8** afforded **2a** in 71% yield and 67% ee. But addition of 1 equiv of La(O-*i*-Pr)$_3$ to **8** increased both the reactivity and the selectivity (1.5 h, 95%, 78% ee).

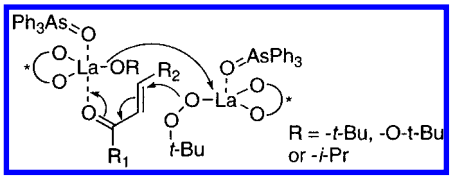
Scheme 4. Proposed Mechanism for the Epoxidation of Enones Catalyzed by the La−(*R*)-BINOL−Ph_3As=O Complex



the actual catalyst. Thus, we can now conclude that the use of La(O-*i*-Pr)$_3$, BINOL, and Ph_3As=O in a ratio of 1:1:1 gives rise to the best catalytic system in the present asymmetric epoxidation. In addition, it can be expected that the existence of an excess of La(O-*i*-Pr)$_3$ should cause a very fast equilibrium to be reached between the complexes in the solution generated from La(O-*i*-Pr)$_3$, BINOL, and Ph_3As=O in a ratio of 1:1:1. This may also be the reason for the ^{13}C NMR result mentioned above.

Proposed Mechanism of the Catalytic Asymmetric Epoxidation of Enones Using the La−BINOL−Ph_3As=O Complex. On the basis of the assumed most active catalyst, we propose the reaction mechanism shown in Scheme 4. The 1:2:2 complex **7** (precatalyst),[29] which is the major component in the solution generated from La(O-*i*-Pr)$_3$, BINOL, and Ph_3As=O in a ratio of 1:1:1, reacts with an excess of La(O-*i*-Pr)$_3$ and TBHP to afford the 1:1:1 complex **11** (active catalyst) in the reaction medium.[30] However, if an excess amount of Ph_3As=O exists in the reaction medium, less active species **8** is formed in part, leading to a decrease in the reactivity. Activation of the enone by coordination to the lanthanum metal of **11** followed by Michael addition of lanthanum peroxide, which should be on the same metal (transition state **I**), affords chiral lanthanum enolate intermediate **II**. Subsequent formation of the epoxy ketone followed by dissociation from the lanthanum complex gives the lanthanum *tert*-butoxide complex **III**. Finally, the reaction of **III** with TBHP regenerates the active catalyst **11**. In the proposed mechanism, we showed only one lanthanum complex, activating both enone and TBHP. However, unfortunately, we cannot completely exclude a mechanism in which several lanthanum complexes participate at the moment. Another possible reaction mechanism is outlined in Scheme 5. The enone is activated by one active complex, and at the same time, lanthanum peroxide, which is the other active complex, attacks the enone. To confirm whether a mechanism catalyzed by one complex is more plausible or not, we carried out kinetic studies. Unfortunately, we were not able to obtain clear results. However, as a result of our investigations on the influence of other solvents, it was found that the ee's of the products did not depend on the polarity of the reaction medium.[31] These results seem to support a mechanism catalyzed by one complex.

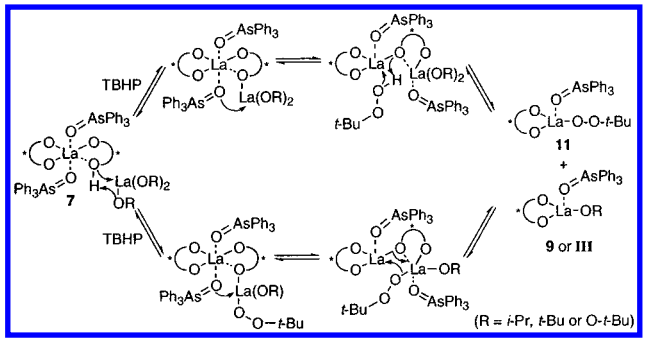
Scheme 5. Reaction Mechanism with Several La Complexes Participating



As mentioned above (Figure 1), we observed asymmetric amplification in the present epoxidation. Moreover, the reaction did not proceed well when (*rac*)-BINOL was used. We believe that these results can be explained as follows. The complexes' solution generated from La(O-*i*-Pr)$_3$, (*rac*)-BINOL and Ph_3As=O in a ratio of 1:1:1 provided the same LDI TOF MS spectra as those using optically pure BINOL, indicating that a 1:2:2 complex should be formed as the major complex in the solution. Therefore, we expected that the stability of the La[(*R*)-binaphthoxide][(*S*)-binaphthoxide](Ph_3As=O)$_2$ complex [(*R*,*S*)-**7**] might be much higher than that of **7**, leading to the low reactivity and the observed asymmetric amplification.[32] To obtain experimental proof which supports our speculation, we carried out the experiments shown in Scheme 6.[11b] The 1:2:2 complex was prepared from BINOL with 50% ee, and the resulting solution was allowed to stand at room temperature. After 1 day, a white precipitate was observed. Separation followed by hydrolysis of the white precipitate and the supernatant with aqueous HCl gave the corresponding BINOL with 2% and 68% ee, respectively. Moreover, the ratio of BINOL and Ph_3As=O isolated from the white powder and the supernatant was almost 1:1, respectively.[33] From these results, it is obvious that some heterochiral complex, which likely exists as (*R*,*S*)-**7**, is formed in the solution, having lower solubility than the corresponding homochiral complex (*R*,*R*)-**7**. Further-

(29) The possibility that La(binaphthoxide)$_2$(Ph_3As=O) complex might be the efficient active precatalyst to **11** cannot be excluded because (+)-LDI TOF MS data showed that a small amount of La(binaphthoxide)$_2$-(Ph_3As=O) complex existed in the reaction medium.

(30) Following is the proposed mechanism for the transformation of **7** to **11**.

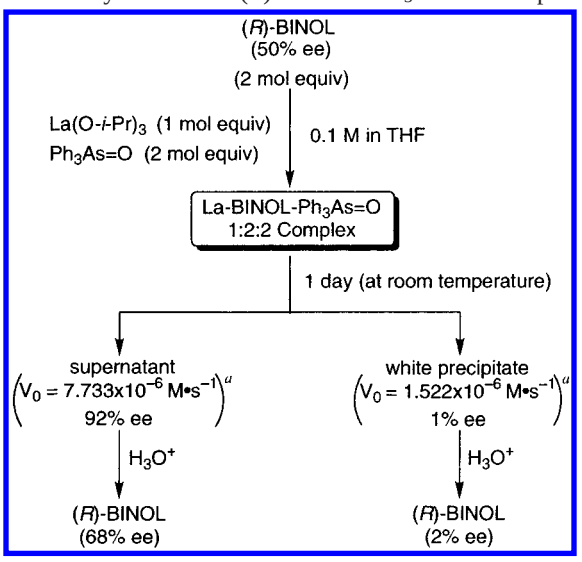


(31) Epoxidations of **1a** using 10 mol % of the La−(*R*)-BINOL−Ph_3As=O complex proceeded similarly in other solvents such as DME (30 min, 94%, 96% ee), benzene (10 min, 93%, 96% ee), and toluene (10 min, 95%, 95% ee).

(32) At first, we examined crystallization of the heterochiral complex (*R*,*S*)-**7** extensively. However, a crystal for X-ray analysis could not be obtained.

(33) For the detailed experimental data for Scheme 6, see the Supporting Information.

Scheme 6. Correlation between Catalytic Activity and Optical Purity of the La−(*R*)-BINOL−Ph_3As=O Complex



[a] Epoxidation of **1a** using 6 mol% of the supernatant or using the white precipitate treated with 6 mol% La(O-*i*-Pr)$_3$. The reactions were carried out at 0 °C, and ee's of the product were determined after completion of the reactions.

more, we carried out the epoxidations of **1a** using the white precipitate and the supernatant in the presence of 1 equiv of La(O-*i*-Pr)$_3$ as the additive.[34] While the reaction using the supernatant gave the product in 92% ee with a moderate initial rate (7.733×10^{-6} M s^{-1}), the reaction using the white precipitate proceeded more slowly (1.522×10^{-6} M s^{-1}), affording the product in 1% ee. The results clearly suggested that the transformation of (*R*,*S*)-**7** to **11** should be much slower, even in the presence of La(O-*i*-Pr)$_3$, than that of (*R*,*R*)-**7** due to the low solubility of the heterochiral complex. On the basis of these data, it is difficult to make conclusions about the stability of the La[(*R*)-binaphthoxide][(*S*)-binaphthoxide](Ph_3As=O)$_2$ complex [(*R*,*S*)-**7**]. However, it can be emphasized that preferential formation of the heterochiral complex might be the reason for the asymmetric amplification and the decrease in the reactivity.

Conclusion

We have succeeded in improving catalytic asymmetric epoxidations of enones using the novel asymmetric catalyst, the La−BINOL−Ph_3As=O complex. This catalyst system is quite effective for several *trans*-enones, including a dienone, yielding products in up to 99% yield and more than 99% ee. Moreover, we have carried out detailed investigations on the structural determination of the La−BINOL−Ph_3As=O complex, including the first X-ray crystal structure analysis of an alkali-metal free lanthanoid−BINOL complex. The La−BINOL−Ph_3As=O complex in a ratio of 1:2:2 (**7**) was observed as the major component in the complexes' solution generated from La(O-*i*-Pr)$_3$, BINOL, and Ph_3As=O in the best ratio (1:1:1). However, the La−BINOL−Ph_3As=O complex generated in a ratio of 1:1:1 (**11**) turned out to be the most active and effective catalyst. Furthermore, preferential formation of the heterochiral complex, likely La[(*R*)-binaphthoxide][(*S*)-binaphthoxide](Ph_3As=O)$_2$, [(*R*,*S*)-**7**], was found to be the reason for asymmetric amplification. Finally, we have clarified the possible reaction mechanism of the epoxidation on the basis of various experimental results. Further studies are currently underway.

Experimental Section

General Procedure for the Catalytic Asymmetric Epoxidations of Enones Using the La−(*R*)-BINOL−Ph_3As=O Complex. To a mixture of (*R*)-BINOL (7.2 mg, 0.025 mmol), triphenylarsine oxide (8.1 mg, 0.025 mmol), and MS 4A [500 mg; MS 4A was not dried (1000 mg/mmol of starting material)] in dry THF (2.5 mL) was added a solution of La(O-*i*-Pr)$_3$ (0.125 mL, 0.025 mmol, 0.2 M solution in THF) at room temperature. [La(O-*i*-Pr)$_3$ was purchased from Kojundo Chemical Laboratory Co., Ltd., 5-1-28, Chiyoda, Sakado-shi, Saitama 350-0214, Japan (fax ++(81)-492-84-1351).] After the mixture was stirred for 1 h at the same temperature, TBHP (0.12 mL, 0.6 mmol, 5 M solution in decane) was added. After the mixture was stirred for 30 min, enone **1f** (73.1 mg, 0.5 mmol) was added directly, and the mixture was stirred at room temperature. After 6 h, the reaction was quenched by addition of 2.5% aqueous critic acid solution (5 mL) at 0 °C and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4. After concentration in vacuo, the residue was purified by flash column chromatography (SiO_2, hexane/ethyl acetate 50:1) to give epoxy ketone **2f** (74,9 mg, 92%, 99.2% ee) as a colorless oil. The IR, ^{1}H NMR, ^{13}C NMR, and mass spectra were identical with those of an authentic sample.[10a] $[\alpha]^{25}_D$ +102 (*c* 1.0 $CHCl_3$). The enantiomeric excess of **2f** was determined by chiral stationary-phase HPLC analysis (Daicel Chiralpak AD, *i*-PrOH/hexane 2/98, flow rate 1.25 mL/min, t_R = 10.7 min (3*R*,4*S*)-isomer and 11.9 min (3*S*,4*R*)-isomer, detection at 254 nm).

Preparation of the Crystal of La-bis[(*R*)-binaphthoxide]tris-(triphenylarsine oxide) (8) for X-ray Analysis. To a stirred mixture of (*R*)-BINOL (28.6 mg, 0.1 mmol) and triphenylarsine oxide (96.6 mg, 0.3 mmol) in THF (0.5 mL) was added a solution of La(O-*i*-Pr)$_3$ (0.5 mL, 0.1 mmol, 0.2 M solution in THF). After the reaction mixture was stirred for 1 h, the solution was concentrated to 0.125−0.15 M and kept at room temperature under argon. After 24 h, an X-ray-grade crystal of La-bis[(*R*)-binaphthoxide]tris(triphenylarsine oxide) (**8**) was grown.

Data for 8: collected at −100 °C, $C_{98}H_{80}O_9As_3La$ = 1765.37, clear, prism, crystal system trigonal, lattice type primitive, *a* = 17.6048(6) Å, *c* = 26.653(1) Å, *V* = 7153.9(5) Å^3, $P3_221$,[35] *Z* = 3, *D* = 1.229 g/cm^3, $R(F)$ = 0.054, $R_w(F)$ = 0.082, GOF = 1.85. Hydrogen atoms were included but not refined. THF × 1 and H_2O × 1 were incorporated in the crystal. For data collection and solution and refinement of the structure, see the Supporting Information.

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Supporting Information Available: Enantiomeric excess analysis of the epoxy ketones **2a**−**h**, **4**, and **6**; experimental procedures and spectral and analytical data for all new compounds for the synthetic pathway to **1i**; their ^{1}H NMR and ^{13}C NMR spectra; detailed results of catalytic asymmetric epoxidation of **1i** to **2i** using La−BINOL complexes; general conditions for the kinetic studies and experimental data of Figures 1 and 7 and Scheme 6; and an X-ray crystallographic file (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(34) The concentration of the 1:2:2 complex in the supernatant was calculated from the ee values of BINOL contained in the white precipitate and the supernatant, respectively.

(35) The space group is $P3_221$ in the case of La-bis[(*S*)-binaphthoxide]-tris(triphenylarsine oxide).