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Remarkable effect of tris(4-fluorophenyl)phosphine oxide on the stabilization of chiral lanthanum complex catalysts. A new and practical protocol for the highly enantioselective epoxidation of conjugated enones †

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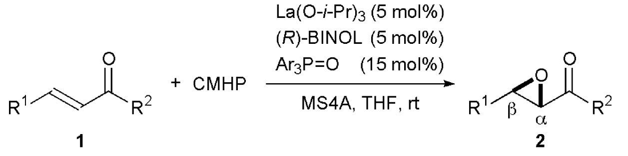
A new and efficient chiral catalyst system, lanthanum–chiral BINOL–tris(4-fluorophenyl)phosphine oxide–cumene hydroperoxide, was developed for the epoxidation of α,β-unsaturated ketones thus providing the corresponding epoxy ketones with excellent enantioselectivities (up to >99% ee) in good to excellent yields at room temperature.

The versatile utility of α,β-epoxy ketones as synthetic intermediates for various natural products, pharmaceuticals, and functional materials has attracted synthetic chemists to develop efficient and practical methods for the catalytic asymmetric epoxidation of conjugated enones and, in recent years, notable progress has been made.[1] Slightly later than Shibasaki's report on chiral La–BINOL complex-catalyzed asymmetric epoxidation,[2a] our report concerning the dramatic effects of triphenylphosphine oxide on lanthanum-catalyzed reaction, such as rate acceleration and a significant increase in enantioselectivity, appeared.[3a,4,5] The findings seemed to suggest that disaggregation of the oligomeric lanthanum complex by an appropriate achiral ligand is crucial for it to exert its high potential. Further study of the catalyst system allowed us to find a remarkable positive nonlinear effect (asymmetric amplification), from which we anticipated the self-organization of novel chiral lanthanum–BINOL–triphenylphosphine oxide–alkyl hydroperoxide (1 : 1 : 1 : 1) dinuclear peroxide-involved μ-complex as the active catalyst, and, as shown by the representative examples in Scheme 1, a variety of conjugated enones were successfully epoxidized in excellent enantioselectivities by using this catalyst system.[3b,3c,6] However, in the cases of slow-reacting substrates, competitive decomposition of the catalyst became a serious problem, resulting in low product yields. Therefore, exploring a more practical catalyst system generally applicable to a wide range of substrates, we carefully examined the substituent effect of various triphenylphosphine oxide derivatives on the catalytic ability of the resulting chiral lanthanum complex.



Ar=Ph: **1a/2a** (R^1=Ph, R^2=Ph); >99% ee (99%)
1b/2b (R^1=Ph, R^2=i-Pr); >99% ee (72%)
1c/2c (R^1=i-Pr, R^2=Ph); 98% ee (88%)

Scheme 1 Asymmetric epoxidation of conjugated enones catalyzed by the chiral La–BINOL–Ar_3P=O–CMHP complex.

Table 1 Effect of triarylphosphine oxides on the stability and activity of the lanthanum complex catalysts

$$\left\{\begin{array}{l} \text{La(O-}i\text{-Pr)}_3\ (5\ \text{mol\%}) \\ (R)\text{-BINOL}\ (5\ \text{mol\%}) \\ \text{Ar}_3\text{P=O}\ \ (15\ \text{mol\%}) \\ \text{MS4A, THF} \end{array}\right\} \xrightarrow[\text{2) stirring for 5 h, rt}]{\text{1) CMHP (160 mol\%)}} \xrightarrow[\text{rt, 1 h}]{\textbf{1a}} \textbf{2a}$$

Entry	Ar_3P=O	Yield (%)[a]	Ee (%)[b]
1	Ph_3P=O	67 (94)[c]	95 (>99)[c]
2	$(4\text{-MeO–}C_6H_4)_3P$=O	63	93
3	$(4\text{-Me–}C_6H_4)_3P$=O	44	92
4	$(3\text{-Me–}C_6H_4)_3P$=O	40	91
5	$(2\text{-Me–}C_6H_4)_3P$=O	13	59
6	$(4\text{-Cl–}C_6H_4)_3P$=O	71	96
7	$(4\text{-F–}C_6H_4)_3P$=O	81	98
8	$(4\text{-}F_3C\text{–}C_6H_4)_3P$=O	53	94

[a] Isolated yield. [b] Determined by HPLC using Daicel CHIRALCEL OB-H. [c] The catalyst was stirred at 0 °C for 5 h before adding **1a**.

To clearly see the stabilizing effect of achiral ligands, a mixture of La(O–i–Pr)$_3$, (R)-BINOL, a triarylphosphine oxide[7] and excess cumene hydroperoxide (CMHP) was stirred for 5 h at room temperature prior to the epoxidation of chalcone (**1a**). The yields and enantioselectivities of **2a** obtained are summarized in Table 1. In all cases, both chemical yields and enantioselectivities are significantly decreased when they are compared with the case of Scheme 1 where the aging time of the catalyst was less than 30 min.[3b] The results suggest that the active catalyst gradually oligomerized under the conditions probably through the ligand exchange with excess CMHP, although it was found to be rather slow at 0 °C (*cf.* entry 1). Among the phosphine oxides examined, tris(4-fluorophenyl)phosphine oxide was the most effective, thus giving **2a** with 98% ee in 81% yield even under such unfavorable conditions (entry 7). It is interesting to note that the results also indicate that the *para*-substituents of triarylphosphine oxides do not significantly affect the enantioselectivity but rather the chemical yield. Their bulkiness seems to be more responsible for the thermodynamic stability of the complexes than their electronic effects; the smaller and less-donating *para*-substituent appears to be the better (*cf.* entries 1–3 and 6–8).

Fig. 1 shows the decay curves of the enantiomer excess (ee) and chemical yield of **2a** as the function of the aging time of the catalyst containing tris(4-fluorophenyl)phosphine oxide or triphenylphosphine oxide, respectively, as the achiral ligand. The superiority of the former is apparent.

Thus, a new chiral La–BINOL–tris(4-fluorophenyl)phosphine oxide–CMHP catalyst system was successfully applied

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† Electronic supplementary information (ESI) available: HPLC analysis of **2**, ^{1}H NMR data for **3** and **4**, and crystal data for **5**. See http://www.rsc.org/suppdata/ob/b4/b405882h/

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Table 2 The La–(*R*)-BINOL–tris(4-fluorophenyl)phosphine oxide–CMHP complex-catalyzed epoxidation of **1** to give **2** (Ar = 4-F-C_6H_4 in Scheme 1)

Entry	R^1	R^2	**1/2**	Time (min)	Yield (%)[a]	Ee (%)[b,c]
1[d]	Ph	Ph	**1a/2a**	90 (90)[e]	98 (77)[e]	98 (98)[e]
2	Ph	4-MeO-C_6H_5	**1d/2d**	15	98	98
3[f]	Ph	*i*-Pr	**1b/2b**	120	89	>99
4	Ph	*t*-Bu	**1e/2e**	30	97	>99
5	4-MeO-C_6H_4	Ph	**1f/2f**	15	93	>99
6	3,4-$(MeO)_2$-C_6H_3	Ph	**1g/2g**	20	89	>99
7	4-NC-C_6H_4	Ph	**1h/2h**	15	92	>99
8	4-O_2N-C_6H_4	Ph	**1i/2i**	20	94	>99
9	3-O_2N-4-F-C_6H_3	Ph	**1j/2j**	20	98	>99
10	*i*-Pr	Ph	**1c/2c**	40	99	98
11	4-F-C_6H_5	*t*-Bu	**1k/2k**	20	91	99
12	PhC(O)	Ph	**1l/2l**	180	85	94 (>99)[g]
13	EtOC(O)	Ph	**1m/2m**	120	88	92 (>99)[g]

[a] Isolated yield. [b] Determined by HPLC using chiral column (Daicel CHIRALCEL OB–H for **2a**,**c**, CHIRALCEL AS for **2b**,**e**,**h**,**k**, and CHIRALPAK AD for **2d**,**f**,**g**,**i**,**j**,**l**,**m**). [c] Absolute configurations of the epoxy ketones **2a**–**f**,**i** and **2l** are determined to be α*S*,β*R* and α*S*,β*S*, respectively, by comparing their HPLC retention times and/or optical rotations with the literature data,[4b,8] and those of **2g**,**h**,**j**,**k** are tentatively assigned based on the similarity of their optical rotations. The absolute configuration of **2m** was determined to be α*S*,β*S* by the X-ray crystallographic analysis of the (−)-menthyl carbonate **5** obtained according to Scheme 2 (Fig. 2). [d] 0.5 mol% of the catalyst was used. [e] Triphenylphosphine oxide was used in place of tris(4-fluorophenyl)phosphine oxide. [f] The substrate was added last (*cf.* typical procedure). [g] Ee after one recrystallization.

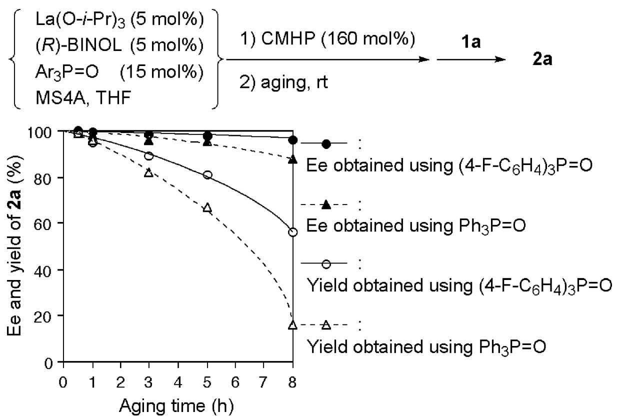
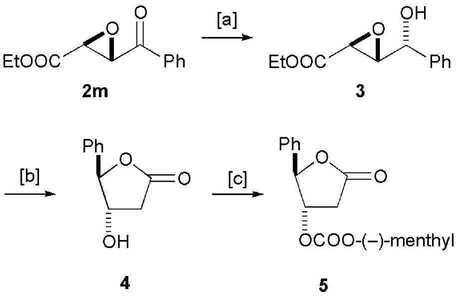


Fig. 1 Effect of triphenylphosphine oxide and tris(*p*-fluorophenyl)phosphine oxide on the stability of the active catalyst.

to the epoxidation of a variety of α,β-unsaturated ketones (Table 2).‡ Generally, the corresponding epoxy ketones were obtained in excellent enantioselectivities with higher yields in shorter reaction times than the cases employing the triphenylphosphine oxide-containing catalyst. This tendency became more obvious when the amount of the catalyst was decreased; *e.g.*, no drawback was observed in the reaction using 0.5 mol% catalyst bearing tris(4-fluorophenyl)phosphine oxide whereas the corresponding reaction using the triphenylphosphine oxide-containing catalyst ended in decrease of the yield (*cf.* entry 1 in Table 2). The acid-labile products **2f** and **2g** could be isolated in high yields by using triethylamine as a co-eluent (1 vol%) (entries 5 and 6). The protocol could also be successfully applied to the epoxidation of cross-conjugated enones such as **1l** and **1m** (entries 12 and 13). A two-step conversion of **2m** to 2-deoxy-D-ribonic γ-lactone derivative (**4**) is demonstrated in Scheme 2. The absolute configuration of **4** was determined by the X-ray crystallographic analysis of the corresponding menthyl carbonate **5** (Fig. 2) which was derived from (−)-(1*R*,2*S*,5*R*)-menthyl chloroformate.[9]

In conclusion, we have succeeded in developing a highly efficient catalyst system which hardly loses its activity at room temperature. The present finding would be of much help in designing new chiral lanthanide catalysts that can be recovered and reused. We are now exerting efforts to develop such reusable chiral catalysts.



Scheme 2 The conversion and configuration determination of **2m**. *Reagents*: [a] $Zn(BH_4)_2$, 96% (92% de); [b] $(PhSe)_2$, $NaBH_4$, EtOH, 72%; [c] (−)-menthyl chloroformate, pyridine, 95%.

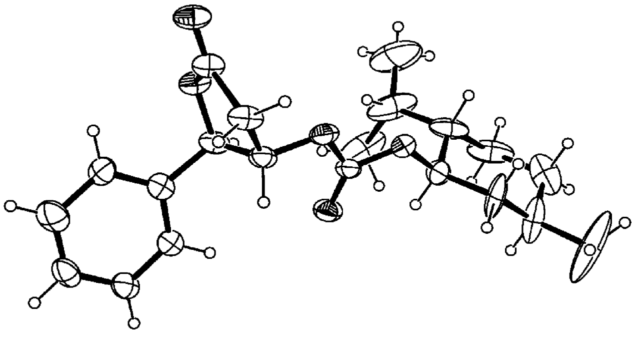


Fig. 2 The ORTEP drawing of **5** (30% probability level).

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Notes and references

‡ Typical procedure (entry 4 in Table 2): To a mixture of La(O-*i*-$Pr)_3$ (6.4 mg, 0.02 mmol) and well-dried MS 4 Å (40 mg) was added a solution of (*R*)-BINOL (5.8 mg, 0.02 mmol) and tris(4-fluorophenyl)phosphine oxide (19.9 mg, 0.06 mmol) in dry THF (1 ml) under argon, and the mixture was stirred at room temperature for 1 h. After the addition of CMHP (3.1 mg, 0.02 mmol) and stirring of the resulting mixture for 30 min, a solution of enone **1e** (75.3 mg, 0.4 mmol) in THF (1 ml) was added. To the mixture was added dropwise CMHP (94.4 mg, 0.62 mmol) over 30 min. After additional stirring for 30 min, silica gel (*ca.* 100 mg) was added, and the whole mixture was filtered through Celite. The eluate was concentrated and the residue

was passed through a short column of NH-silica[10] with a mixture of hexane–AcOEt (4 : 1) as an eluent to leave (*R*)-BINOL on the column. The crude product thus obtained was purified by column chromatography on silica gel to give epoxy ketone **2e** (73.2 mg, 97%), the optical purity of which was determined to be >99% ee by HPLC analysis (Daicel CHIRALCEL AD).

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4 A similar catalyst system using triphenylarsine oxide in place of triphenylphosphine oxide has been extensively and successfully studied: (*a*) T. Nemoto, T. Ohshima and M. Shibasaki, *Tetrahedron Lett.*, 2000, **41**, 9569; (*b*) T. Nemoto, T. Ohshima, K. Yamaguchi and M. Shibasaki, *J. Am. Chem. Soc.*, 2001, **123**, 2725; (*c*) T. Kinoshita, S. Okada, S.-R. Park, S. Matsunaga and M. Shibasaki, *Angew. Chem., Int. Ed.*, 2003, **42**, 4680; (*d*) T. Ohshima, T. Nemoto, S. Tosaki, H. Kakei, V. Gnanadesikan and M. Shibasaki, *Tetrahedron*, 2003, **59**, 10485 and references cited therein.

5 For other lanthanide-catalyzed epoxidations of conjugated enones, see: (*a*) R. Chen, C. Qian and J. G. de Vries, *Tetrahedron*, 2001, **57**, 9837; (*b*) D. Jayaprakash, Y. Kobayashi, T. Arai, Q.-S. Hu, X.-F. Zheng, L. Pu and H. Sasai, *J. Mol. Catal. A*, 2003, **196**, 145.

6 The protocol was successfully applied to large-scale experiments (*e.g.*, 80 kg scale; 90% chemical yield, 98% ee): private communication from Mr T. Kagawa (Tosoh Corporation, Japan).

7 In order to minimize the possible destabilization of the lanthanum complex catalyst due to the competitive coordination of CMHP and the product (epoxy ketone) to the metal ion, 15 mol% of triarylphosphine oxides were used in these experiments. Actually, in the case where *tert*-butyl hydroperoxide (TBHP) was employed in the epoxidation of chalcone, the use of 15 mol% of triphenylphosphine oxide [La/(*R*)-BINOL/Ph_3PO = 1 : 1 : 3] afforded the product with 96% ee in 99% yield whereas the use of 5 mol% of it [La/(*R*)-BINOL/Ph_3PO = 1 : 1 : 1] gave a slightly worse result (93% ee, 91% yield; unpublished).

8 (*a*) W. Krouti, M. E. Lasterra-Sánchez, S. J. Maddrall, P. Mayon, P. Morgan, S. M. Roberts, S. R. Thornton, C. J. Todd and M. Tüter, *J. Chem. Soc., Perkin Trans. 1*, 1996, 2837; (*b*) B. Lygo and P. G. Wainwright, *Tetrahedron*, 1999, **55**, 6289; (*c*) W. Adam, P. B. Rao, H.-G. Degen and C. R. Saha-Möller, *J. Am. Chem. Soc.*, 2000, **122**, 5654.

9 Crystal data for **5**: $C_{21}H_{28}O_5$, M = 360.43, monoclinic, a = 9.685(8), b = 8.592(6), c = 23.185(13) Å, V = 1928(2) Å^3, T = 93(2) K, space group $P12_11$, Z = 4, Mo–Kα radiation, λ = 0.71075 Å, 15474 reflection measured, 4675 unique (R_{int} = 0.0893), $wR(F^2)$ = 0.2872. CCDC reference number 224162. See http://www.rsc.org/suppdata/ob/b4/b405882h/ for crystallographic data in.cif or other electronic format.

10 Purchased from Fuji Silysia Chemical Ltd., Japan.