The First Catalytic Enantioselective Synthesis of *cis*-Epoxyketones from *cis*-Enones

Shizue Watanabe,[†,‡] Takayoshi Arai,[†] Hiroaki Sasai,*,[†] Masahiro Bougauchi,[‡] and Masakatsu Shibasaki*,[‡]

The Institute of Scientific and Industrial Research (ISIR), Osaka University, Mihogaoka, Ibaraki, Osaka 567-0047, Japan, and Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

The synthesis of optically active compounds is usually considered to be much more difficult than that of corresponding racemic compounds. Indeed, almost all developments of novel asymmetric reactions are based on the reactions for racemic compounds. However, in our recent studies on the development of enantioselective reactions utilizing rare earth and/or group 13 elements (Al or Ga) containing optically active complexes, we have found several multifunctional catalytic reactions in which these complexes not only activate both substrates in intermolecular reactions but also control the orientation of them.[1] The multifunctional catalyst can provide optically active compounds, which are difficult to synthesize even in a racemic form. This unique feature of the multifunctional catalyst is believed to be the result of a synergistic cooperation of metals in the asymmetric bimetallic complexes. This feature also seems to be present in the asymmetric epoxidation of *cis*-enones (*cis*-α,β-unsaturated ketones). We report here the first efficient synthesis of *cis*-epoxyketones from *cis*-enones by use of the catalyst ytterbium-(*R*)-3-(hydroxymethyl)-1,1′-bi-2-naphthol complex[2a] (Yb-3-CH₂OH-BINOL; Yb-**2**).

1: R = H
2: R = CH₂OH
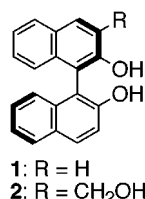
The stereoselective construction of *cis*-epoxyketones from acyclic *cis*-enones is difficult due to the tendency of *cis*-enones to afford the corresponding more stable *trans* derivatives during the oxidation process. For example, treatment of *cis*-**3** with TBHP in the presence of BuLi (10 mol %) provided a mixture of *cis*- and *trans*-epoxyketones in 8% and 43% yield, respectively (Table 1, entry 1).[3]

On the other hand, we were pleased to find that the Ln-**2** catalyst (Ln = Yb or La),[2a] prepared from Ln(O-*i*-Pr)₃ and **2** in a ratio of 1:1.4, gave *cis*-epoxides quite efficiently. TBHP seems to be a more appropriate oxidant than cumene

Table 1.   Representative Results for the Catalytic Asymmetric Epoxidation of *cis*-Enones
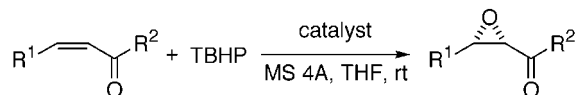
3: R¹ = C₅H₁₁, R² = CH₃   *cis*-**4**: R¹ = C₅H₁₁, R² = CH₃
5: R¹ = C₃H₇, R² = (CH₂)₂Ph   *cis*-**6**: R¹ = C₃H₇, R² = (CH₂)₂Ph
7: R¹ = C₅H₁₁, R² = C₃H₇   *cis*-**8**: R¹ = C₅H₁₁, R² = C₃H₇
9: R¹ = CH₃, R² = Ph   *cis*-**10**: R¹ = CH₃, R² = Ph
11: R¹ = C₃H₇, R² = Ph   *cis*-**12**: R¹ = C₃H₇, R² = Ph

entry	substrate	catalyst (mol %)	TBHP (equiv)	time (h)	cis-epoxide[a] y(%), ee (%)	trans-epoxide y (%), ee (%)[b]
1[c]	**3 → 4**	BuLi (10)	3	22	8, nd	43, nd
2[c]	**3 → 4**	La-**1**[d] (5)	1.5	72	31.5	<10, nd
3[c]	**3 → 4**	Yb-**1**[d] (5)	1.5	72	60, 4	<10, nd
4[c]	**3 → 4**	La-**2** (10)	3	72	58, 58	<10, nd
5	**3 → 4**	Yb-**2** (10)	3	72	74, 94	trace, nd
6[c]	**5 → 6**	Yb-**1**[d] (10)	3	146	56, 21	<10, nd
7	**5 → 6**	Yb-**2** (10)	3	146	78, 93	trace, nd
8[c]	**7 → 8**	Yb-**1**[d] (10)	3	127	75, 27	trace, nd
9	**7 → 8**	Yb-**2** (10)	3	127	80, 96	trace, nd
10	**9 → 10**	Yb-**2** (10)	3	81	60, 82	32, 10[e]
11	**11 → 12**	Yb-**2** (10)	3	96	51, 88	19, 58[e]

[a] Absolute configurations of the major enantiomer were determined to be (α*S*,β*S*) other than entries 3, 6, 8 (α*R*,β*R*). [b] nd: Not determined. [c] The starting material was retained. [d] Prepared from Ln(O-*i*-Pr)₃ and **1** in a ratio of 1:1. [e] Absolute configurations of the major enantiomer were determined to be (α*S*,β*R*).

hydroperoxide (CMHP).[4] It is noteworthy that the reaction proceeds at room temperature without special care to remove moisture. As shown in Table 1, the Yb-**2** catalyst gave *cis*-epoxyketone of a higher ee than the La-**2** catalyst and/or the BINOL (**1**) derived catalysts. By use of the Yb-**2** catalyst, aliphatic *cis*-enones were converted into *cis*-epoxyketones in a highly enantioselective manner (93−96% ee).[5,6] The absolute configuration of the β-position of *cis*-epoxyketones was determined to be *S* when (*R*)-Yb-**2** was utilized. This was in direct contrast to what was seen in the epoxidation of the corresponding *trans*-enones, in which the major enantiomer was (α*S*, β*R*).[2a] Attempts to prepare racemic authentic samples with Ln(O-*i*-Pr)₃ resulted in the formation of a mixture of *cis*- and *trans*-epoxyketones, suggesting the importance of the multifunctional character of the Yb-**2** catalyst.[2a,7] For aromatic *cis*-enones, which isomerize readily to *trans*-enones, 10 mol % of the Yb-**2** catalyst was effective to obtain *cis*-epoxides, though a small amount of *trans*-epoxyketones were also formed.[8] We also examined asymmetric epoxidation of trisubstituted enone (CH₃)₂C=CHCOPh

† Osaka University.
‡ The University of Tokyo.

(1) (a) Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1236−1256. (b) Sasai, H.; Arai, T.; Satow, Y.; Houk, K. N.; Shibasaki, M. *J. Am. Chem. Soc.* **1995**, *117*, 6194−6198. (c) Arai, T.; Sasai, H.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 441−442. (d) Gröger, H.; Saida, Y.; Sasai, H.; Yamaguchi, K.; Martens, J.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 3089−3103. (e) Emori, E.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 4043−4044.

(2) (a) Bougauchi, M.; Watanabe, S.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1997**, *119*, 2329−2330. (b) Sasai, H.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1994**, *116*, 1571−1572.

(3) Furthermore, use of KF−Al₂O₃ and TBHP, or NaOH (10 mol %) and H₂O₂, did not afford *cis*-epoxyketones.

(4) CMHP was effective for the epoxidation of *trans*-enones promoted by either the La-**1** or La-**2** catalyst (see ref 2a). However, it appeared that epoxidation of *cis*-enones using CMHP was quite slow.

(5) Measurements of enantiomeric excess were performed by stationary phase chiral HPLC. See Supporting Information.

(6) The absolute configurations were determined by Mosher method after transforming to the corresponding β-hydroxyketones (for **4**, **6**, **8**, **10**) or determined by transformation to the authentic sample (for **12**).

(7) By use of 10 mol % of Ln(O-*i*-Pr)₃, the following results were obtained. La(O-*i*-Pr)₃: *cis*-**6**: *trans*-**6** = 66:18 (rt, 11 h); *cis*-**10**: *trans*-**10** = 60:32 (rt, 2 h); *cis*-**12**: *trans*-**12** = 68:23 (rt, 4 h), Yb(O-*i*-Pr)₃: *cis*-**10**: *trans*-**10** = 51: 34 (rt, 29 h).

(8) Recently, we have revealed that a 2:3 ratio of Yb(O-*i*-Pr)₃ and BINOL (**1**) was an efficient catalyst (Yb-**1**) for the epoxidation of *trans*-enones in the presence of both water and MS 4A. See, Watanabe, S.; Kobayashi, Y.; Arai, T.; Sasai, H.; Bougauchi, M.; Shibasaki, M. *Tetrahedron Lett.* **1998**, *39*, 7353−7356. However, the Yb-**1** catalyst gave the *cis*-epoxyketones very slowly.

(**13**). The Yb-**2** catalyst (10 mol %) was also effective, giving 78% of corresponding epoxide **14** in 87% ee (120 h).[9]

In the absence of TBHP, treatments of *cis*-enones by base catalysts, including Yb-**2**, afforded *trans*-enones.[10] This fact indicates the possibility of isomerization of *cis*-enones to *trans*-enones in Yb-**2**-catalyzed epoxidation. If the *trans*-epoxyketones were only obtained from *trans*-enones generated via isomerization of *cis*-enones, the ee of the *trans*-epoxyketone should be as high as that obtained from *trans*-enones as a starting material.[2a,11] However, the *trans*-epoxyketones obtained from *cis*-enones have low optical purity. These results clearly indicate that two kinds of pathways to afford *trans*-epoxyketones are involved in the epoxidation of *cis*-enones. The proposed mechanism for *trans*-epoxyketones from *cis*-enones is shown in Scheme 1.

The epoxidation of enones by hydroperoxides proceeds via conjugate addition of peroxide anion to enones.[12] In the intermediary enolate II, single bond rotation between the α and β position occurs to form *trans*-epoxyketone through the enolate IV. Meanwhile, isomerization of *cis*-enones to *trans*-enones competes with this pathway. Although the structural elucidation of the Yb-**2** catalyst is extremely difficult,[2,8] the amphoteric ytterbium atom(s) in the catalyst could control the orientation of *cis*-enone and the peroxide anion to furnish *cis*-epoxide, avoiding the side reactions that form *trans* derivatives.

In conclusion, *cis*-epoxyketones were obtained for the first time in high enantiomeric excess by use of the Yb-**2** catalyst

Scheme 1. Proposed Mechanism for the Epoxidation of *cis*-Enones
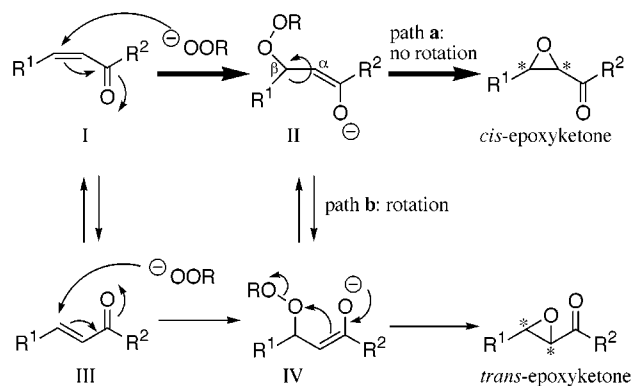
at room temperature. The synthetic value of optically pure epoxides has been widely recognized.[13] Synthetic applications of the epoxidation of *cis*-enones are in progress.

Supporting Information Available: Experimental procedures, ^{1}H and ^{13}C NMR, IR, and mass spectral data for the *cis*-enones and epoxyketones (31 pages).

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(9) Yield and ee of **14** using another catalyst: La-**1** (5 mol %, 92 h); 46% (42% ee), Yb-**1** (5 mol %, 97 h); 75% (8% ee); La-**2** (10 mol %, 190 h); 51% (27% ee).

(10) Treatment of **5** in the presence of 10 mol % of Yb-**2** at room temperature for 78 h gave *cis*- and *trans*-**5** in a ratio of 6:1.

(11) Treatment of *trans*-**9** and *trans*-**11** with Yb-**2** catalyst (10 mol %) gave *trans*-**10** and *trans*-**12** in 80% ee (87% yield) and 71% ee (81% yield), respectively.

(12) Reed, K. L.; Gupton, J. T.; Solarz, T. L. *Synth. Commun.* **1989**, *19*, 3579−3587.

(13) Recent application of epoxyketones for organic synthesis. See: (a) Gillmore, A. T.; Roberts, S. M.; Hursthouse, M. B.; Abdul Malik, K. M. *Tetrahedron Lett.* **1998**, *39*, 3315−3318. (b) 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**, 3501−3507. (c) Alcaraz, L.; Macdonald, G.; Ragot, J. P.; Lewis, N.; Taylor, R. J. K. *J. Org. Chem.* **1998**, *63*, 3526−3527. For *cis*-α,β-unsaturated esters. See: (d) Jacobsen, E. N.; Deng, L.; Furukawa, Y.; Martínez, L. E. *Tetrahedron*, **1994**, *50*, 4323−4334.