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Water *vs.* Desiccant. Improvement of Yb-BINOL Complex Catalyzed Enantioselective Epoxidation of Enones

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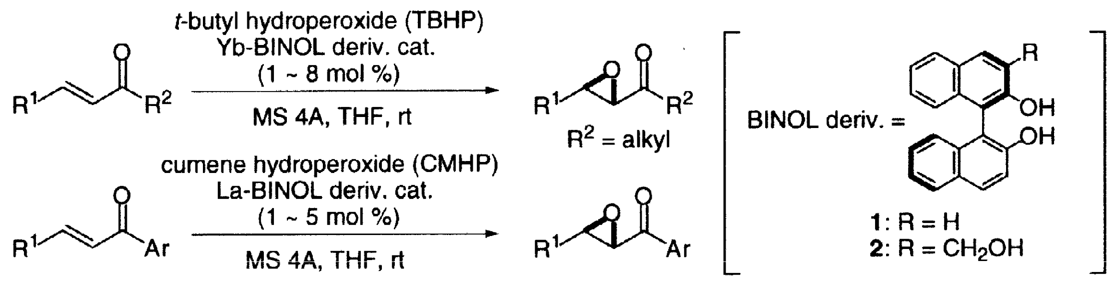
Abstract: The Yb-BINOL-complex-catalyzed enantioselective epoxidation of α,β-unsaturated ketones (enones) was greatly improved by addition of a small amount of water (ca. 5 equiv to Yb). Optimized conditions and a plausible mechanism of the role of water and molecular sieves in asymmetric epoxidation are also described.

Keywords: Asymmetric reactions, Catalysis, Epoxidation, Enones

We recently reported the general and practical catalytic enantioselective epoxidation of enones in the presence of Ln-BINOL derivative complexes (Ln = lanthanoid).[1a,2] As shown in Scheme 1, La-catalyst and Yb-catalyst can be used in a complementary manner for enantioselective epoxidation of aromatic and aliphatic substituted enones in up to 94% ee at room temperature. The Ln-BINOL derivative catalysts are readily prepared in situ by a mixing of Ln(O-*i*-Pr)$_3$[3] with (*R*)-1,1'-bi-2-naphthol (**1**: BINOL) and/or 3-hydroxymethyl-BINOL (**2**) in THF.[1] We have also revealed that addition of molecular sieves 4A (MS 4A) to the catalysis is effective to obtain the product in high yield. In this paper, we describe a highly improved method for the Yb-**1** complex promoted enantioselective epoxidation of enones in the presence of a small amount of water.



Scheme 1. Representative procedure of catalytic enantioselective epoxidation of enones promoted by Ln-BINOL derivative complexes.

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In the course of our study on the enantioselective epoxidation of enones, we found that yields and enantiomeric excesses of the products were much affected by an addition of water to the **Yb-1** catalysis. As shown in Figure 1, addition of ca. 5 mol equivalents of water to the **Yb-1** catalysis afforded epoxy ketone **4** in high enantiomeric excesses. In contrast, under the strictly dried conditions, optical purity of the product decreased to less than 25% ee. However, with a slow addition of 1 molar equivalent of Yb(O-*i*-Pr)$_3$ to **1**, a moderate ee of **4** was obtained.[4] The representative results are summarized in Table 1. Because of the significant effects of water on **Yb-1** catalyzed epoxidation of enones, we reinvestigated the molar ratio of Yb(O-*i*-Pr)$_3$ to **1**. After several attempts, we found that a 2:3 ratio of Yb(O-*i*-Pr)$_3$ and **1** gave the maximum ee in the presence of water (entry 3).

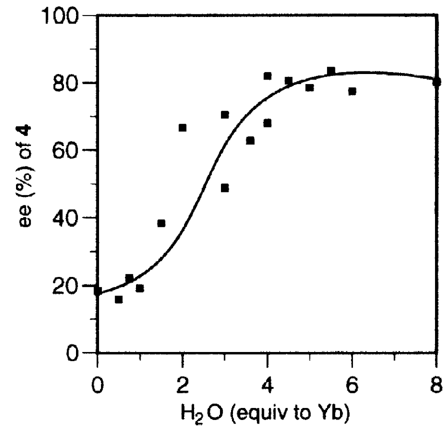
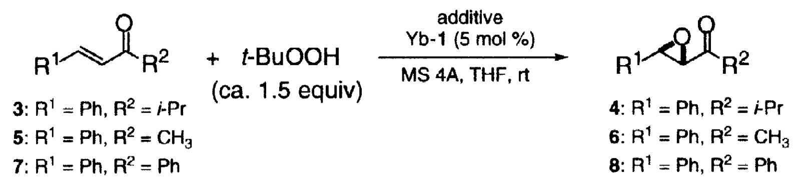


Figure 1. Effect of water on enantiomeric excess of **4**.

Table 1. Enantioselective epoxidation of enones by Yb-BINOL catalysts.



entry	enone	catalyst (Yb : **1**)[a]	MS 4A[b] (mg/mmol of enone)	additive (4.5 equiv to Yb)	time (h)	epoxide	yield (%), ee (%)[c,d]
1	**3**	**Yb-1** (1 : 1)	200	H_2O	48	**4**	83, 85
2	**3**	**Yb-1** (1 : 1)	200	–	48	**4**	81, 70
3	**3**	**Yb-1** (2 : 3)	200	H_2O	48	**4**	82, 93 (55, 88)
4	**3**	**Yb-1** (2 : 3)	200	–	48	**4**	67, 87
5	**3**	**Yb-1** (2 : 3)	–	–	48	**4**	5, 46
6	**3**	**Yb-1** (2 : 3)	200→0[e]	H_2O	48	**4**	trace
7	**3**	**Yb-1** (2 : 3)	0→200[f]	H_2O	48	**4**	48, 72
8	**3**	**Yb-1** (2 : 3)	1000	H_2O	48	**4**	62, 75
9	**5**	**Yb-1** (2 : 3)	200	H_2O	13	**6**	92, 94 (83, 94)
10	**7**	**Yb-1** (2 : 3)	200	H_2O	1	**8**	99, 81

a: Molar ratio of Yb(O-*i*-Pr)$_3$ and **1**. Yb(O-*i*-Pr)$_3$ was added slowly to **1**.

b: MS 4A (200 mg/1 mmol of enone) was used after drying at 180 °C for 3 h under reduced pressure.

c: The ees of the epoxy ketones were determined by chiral stationary phase HPLC. See reference 1a.

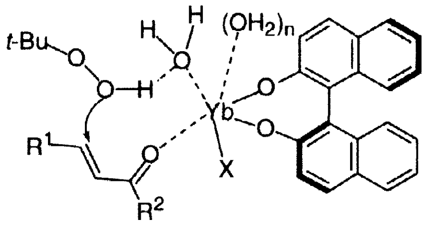
d: Yield and ee in parenthesis were obtained by use of **Yb-2** catalyst. See reference 1a.

e: MS 4A was filtered off from the catalyst solution and the filtrate was used as a catalyst.

f: After the preparation of the catalyst solution, MS 4A was added.

In contrast to the results of **Yb-1** catalysis, a 2:3 ratio of La(O-*i*-Pr)$_3$ and **1** afforded less reactive catalyst. Furthermore, **La-1** catalysis was not affected by the addition of water.

In our previous paper,[1a] we reported that the use of **2** in place of **1** is effective for preparing an efficient catalyst for enantioselective epoxidation. In contrast to the case of the **1**-derived catalyst, addition of water to the Ln-**2** catalyst caused deceleration of the catalyst turnover, although the optical purity of the products were still high. At present, the role of water can best be explained as that water molecules coordinate to the Yb atom(s) and thereby control the orientation of the hydroperoxides to form appropriate asymmetric environment for epoxidation.[5,6] A schematic drawing of this proposed mechanism is shown in Figure 2.[7] For Ln-**2** catalysis, 3-hydroxymethyl substituent seems to work as a mediator of the hydroperoxide, just as water molecules do in Ln-**1** catalysis. In the light of the effect of water in Yb-**1** as shown in Figure 2, we examined the use of a commercially available decane solution of TBHP,[8] which contained up to 4% water, as an oxidant. As expected, a good result was obtained for **4** (90% yield, 85% ee) without the further addition of water.



X = BINOL or other ligand

Figure 2. Plausible role of water as a mediator of TBHP and Yb-**1**.

Although MS 4A is usually considered to be a desiccant, it appeared that both water and MS 4A were required to promote efficient enantioselective epoxidation (entries 5-7). Indeed, when the Yb-**1** catalyst was prepared in the presence of MS 4A, and the MS 4A was filtered off from the catalysis, almost no epoxidation reaction took place (entry 6). In addition, when the Yb-**1** catalyst was prepared in the absence of MS 4A, and MS 4A was added simultaneously with the oxidant, the reaction proceeded to give the desired epoxide in 72% ee, though the yield was rather low (entry 7). Therefore MS 4A was found to be necessary at the epoxidation process in order to construct the catalytic cycle. However, addition of too much MS 4A resulted in a lowering both of yield and ee (entry 8). MS 4A seems to remove a small volume of water from the lanthanoid complex to form an unsaturated coordination environment on the metal thereby capable of making the coordination of enone easier to promote epoxidation.[9]

In order to confirm the proposed mechanism, we made several efforts to collect information on the structure of the Ln-**1** catalyst.[1,10] Measurement of the molecular weight of powder-dried La-**1** and Yb-**1**[11] revealed that these complexes have highly oligomeric structures but no proof for the role of water and MS 4A was obtained.[12,13] However, the attempt indicated that powder-dried Yb-**1** catalyst, which was prepared in the absence of MS 4A, can be stored more than a month without the loss of catalyst efficiency. That is, after the addition of MS 4A and water (4.5 equiv to Yb) to the powder-dried catalyst, 91% yield of epoxide **6** was obtained in 89% ee.[14]

In conclusion, Yb-**1** catalyst, prepared by a 2:3 ratio of Yb(O-*i*-Pr)$_3$ and BINOL, gave the maximum ee of the products by an addition of water in the presence of MS 4A. The powder-dried catalyst was also revealed to have the practical feature of long-term storability.

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[2] For other catalytic asymmetric epoxidation of α,β-unsaturated carbonyl compounds, see: (a) Juliá S, Masana J, Vega JC. Angew. Chem. Int. Ed. Engl. 1980;19:929-931. (b) Kroutil W, Mayon P, Lasterra-Sánchez ME, Maddrell SJ, Roberts SM, Thornton SR, Todd CJ, Tüter M. Chem. Commun. 1996:845-846 and references cited therein. (c) Helder R, Hummelen JC, Laane RWPM. Wiering JS, Wynberg H. Tetrahedron Lett. 1976;1831-1834. (d) Colonna S, Gaggero N, Manfredi A, Spadoni M, Casella L, Carrea G, Pasta P. Tetrahedron 1988;44:5169-5178. (e) Colonna S, Manfredi A, Annunziata R, Gaggero N. J. Org. Chem. 1990;55:5862-5866. (f) Baccin C, Gusso A, Pinna F, Strukul G. Organometallics 1995;14:1161-1167. (g) Kumar A, Bhakuni V. Tetrahedron Lett. 1996;37:4751-4754. (h) Jacobsen EN, Deng L, Furukawa Y, Martinez LE. Tetrahedron 1994;50:4323-4334. (i) Lygo B, Wainwright PG. Tetrahedron Lett. 1998;39:1599-1602.

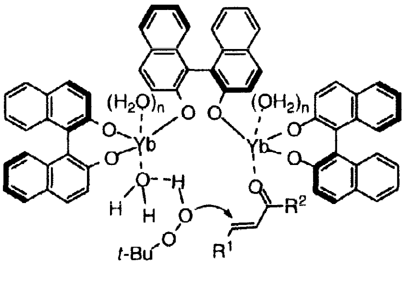
[3] Purchased from Kojundo Chemical Co., Ltd., 5-1-28, Chiyoda, Sakato, Saitama 350-0214, Japan (Fax:+81-492-84-1351).

[4] The reaction of $Yb(O\text{-}i\text{-}Pr)_3$ with **1** seems to be rather slow.

[5] For the multifunctionality of lanthanoid and/or aluminum complex, see: (a) Shibasaki M, Sasai H, Arai T. Angew. Chem. Int. Ed. Engl. 1997;36:1236-1256. (b) Sasai H, Arai T, Satow Y, Houk KN, 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.

[6] Catalytic asymmetric Michael reactions utilizing Ln-**1** catalyst proceed efficiently without the addition of water. Therefore, activation of enones by a water in the Ln-**1** catalysis would not have been a factor. Water may act as a scavenger of free Ln alkoxide moiety.

[7] The bimetallic transition state shown below is also feasible. A 2:3 ratio of Yb and **1**, and the fragment peak of LDI-TOF MS spectra of Yb-**1** complex support the bimetallic structure.



[8] Supplier: Aldrich Chemical Co., Inc. Milwaukee, WI 53233, USA.

[9] Due to the extremely high oxophilicity of lanthanoid element, complete removal of water from the catalyst would be impossible.

[10] Yttrium-BINOL complex (2:3) was prepared for the spectroscopic analyses of lanthanoid-BINOL complexes. Although Y-**1** catalyst gave 90% yield of **6** in 77% ee, ^1H- and ^{13}C-NMR spectra were obscure.

[11] Performed by KNAUER Vapor Pressure Osmometer.

[12] Catalyst solution was dried under reduced pressure for 12 h at room temperature and redissolved in THF. Molecular weights of La-**1** and Yb-**1** are 9.1×10^3 and 1.45×10^4, respectively.

[13] LDI-TOF MS spectra also support the oligomeric structure of Ln-**1** complexes.

[14] The general procedure of asymmetric epoxidation of **5** utilizing powder-dried Yb-**1** is as follows. After a mixture of MS 4A (48mg) and powder-dried Yb-**1** (7.84 mg, 0.012 mmol based on Yb employed) was dried under reduced pressure for 1 h at room temperature, THF (1.0 mL), a toluene solution of TBHP (3~4 M, 120 μL, 0.36~0.48 mmol), and a THF solution of water (1 M, 54 μL, 4.5 equiv to Yb) were added. The resulting suspension was stirred for an additional 10 min at room temperature. To this mixture was added enone **5** (0.24 mmol), followed by stirring for 24 h at room temperature.