VIP Asymmetric Epoxidation

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Titanium-Catalyzed Asymmetric Epoxidation of Non-Activated Olefins with Hydrogen Peroxide**

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Asymmetric epoxidation of olefins is a potent method for synthesizing enantioenriched epoxides that are high-utility intermediates. Thus, over the past few decades, extensive research efforts have been devoted to the development of catalytic asymmetric epoxidation,[1] and some excellent transition-metal catalysts based on titanium,[2] manganese,[3] vanadium,[4] and molybdenum[5] as well as organocatalysts such as chiral ketones[6] have been reported. However, these reactions require oxidants of lower atom-efficiency such as bulky alkyl hydroperoxides and oxones. From the viewpoint of green sustainability, the development of asymmetric epoxidation using aqueous hydrogen peroxide that is low-cost, highly atom-efficient, easy-to-handle, and ecologically benign (no production of hazardous waste), has been strongly desired in industry and academic research.[7]

Recently, we found that di-μ-oxo titanium(salalen) and di-μ-oxo titanium(salan) complexes serve as efficient catalysts for asymmetric epoxidation of olefins using aqueous hydrogen peroxide.[8] The epoxidation of conjugated olefins with the di-μ-oxo titanium(salalen) complex **1** (Figure 1) proceeded with high turnover numbers (up to 4600) as well as high to excellent enantioselectivity at room temperature. We also preliminarily examined epoxidation of 1-octene and obtained a high enantioselectivity of 82% *ee*.

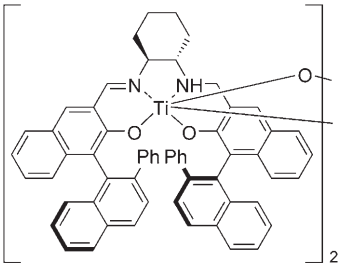

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Figure 1. Di-μ-oxo titanium(salalen) complex **1**.

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The development of asymmetric epoxidation of aliphatic olefins (non-activated olefins) with aqueous hydrogen peroxide is a high-priority issue; however, there are just a few catalysts for the reaction. Although a platinum catalyst was reported by Strukul and co-workers, it has been applied only to terminal olefins with no α branches.[9] Herein, we describe asymmetric epoxidation of non-activated olefins with aqueous hydrogen peroxide, which was achieved by using titanium(salalen) complex **1** and had a much wider substrate scope.

We first examined epoxidation of non-activated olefins at room temperature (Table 1). Yield was sharply sensitive to substrate concentration, and high yields were obtained at high concentration.[8a] A selectivity of 80% *ee* was observed in the epoxidation of non-branched terminal olefins, irrespective of the presence or absence of a functional group such as ester or ether and the length of the alkyl substituents (entries 2–5, Table 1). Reflecting the steric bulk of the alkyl substituent, epoxidation of vinylcyclohexane showed an improved enantioselectivity of 95% *ee* (entry 6, Table 1). *Z* Olefins are also favorable substrates and asymmetric epoxidation of non-branched *Z* olefins showed good enantioselectivity (entries 7–9, Table 1). Reactions of 1-cyclohexyl-1-alkenes also proceeded with good enantioselectivities of 73–81% *ee*, but the reactions were slow (entries 10 and 11, Table 1). Moreover, the epoxidation of (*Z*)-2,2-dimethyl-3-decene exhibited a high enantioselectivity of 97% *ee* yet was much slower (entry 12, Table 1). These results indicate that complex **1** can efficiently differentiate not only the alkyl group and the hydrogen atom but also methyl and methylene, methylene and methine, and methylene and quaternary carbons. While a good enantioselectivity of 70% *ee* was obtained in the epoxidation of (*Z*)-2-pentenyl benzyl ether, the reaction of (*Z*)-3-decene was poorly enantioselective, indicating that the differentiation of simple *n*-alkyl groups is difficult (entries 13 and 14, Table 1). It is also noteworthy that this asymmetric epoxidation is stereospecific and no isomerization was detected in the epoxidation of *Z* olefins by ^{1}H NMR analysis (entries 7–14, Table 1). Furthermore, low catalyst loading of 1–3 mol% is sufficient for the epoxidation. To our knowledge, this is the first example showing better than 70% *ee* in epoxidation of non-activated *Z* olefins using aqueous hydrogen peroxide.[10]

With these results, we investigated regio- and enantioselectivity of epoxidation of dienes that have terminal and internal double bonds. In electrophilic epoxidation, the more electron-rich C=C bond tends to be epoxidized preferentially. However, less electron-rich terminal C=C bonds were selectively epoxidized under the present conditions with good to high regioselectivity (Scheme 1). Although the detailed

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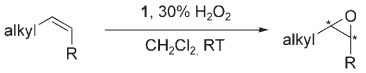
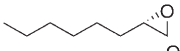
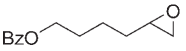
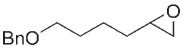
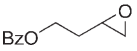
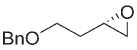
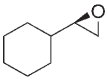
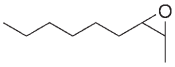
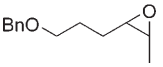
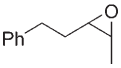
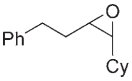
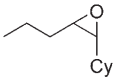
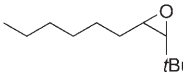
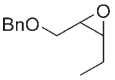
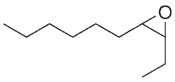
Table 1: Asymmetric epoxidation of non-activated olefins with titanium-(salalen) complex **1**.



R = H or alkyl

Entry	Product	Yield [%][a]	*ee* [%]
1[b]		85	82[c,d]
2[b]		70	81[e]
3[b]		75	81[e]
4[b]		69	81[f]
5[b]		70	79[d,g]
6[h]		72	95[d,i]
7[j]		85	74[k]
8[j]		99	71[f]
9[j]		90	77[g]
10[h]		60	73[c]
11[h]		49	81[i]
12[h]		19	97[k]
13[j]		77	70[c]
14[j]		53	11[g]

[a] Determined by ^{1}H NMR (400 MHz) analysis. [b] Conducted with 2 mol% of **1**; Bn = benzyl, Bz = benzoyl. [c] ^{1}H NMR analysis using a chiral shift reagent [Eu(hfc)$_3$]. [d] Absolute configuration was determined by comparison of the optical rotation with the literature value. [e] HPLC analysis (Daicel Chiralcel OB-H). [f] HPLC analysis (Daicel Chiralpak AS-H). [g] HPLC analysis (Daicel Chiralcel OD-H). [h] Conducted with 3 mol% of **1**; Cy = cyclohexyl. [i] GLC analysis (Chiraldex G-TA). [j] Conducted with 1 mol% of **1**. [k] GLC analysis (Spelco BETA-DEX-225).

reaction mechanism is unclear, these results suggest that complex **1** efficiently recognizes a difference in the steric bulk of the substituents and their substitution pattern.

In conclusion, we were able to demonstrate that Ti-(salalen)-catalyzed asymmetric epoxidation using aqueous hydrogen peroxide as the oxidant can be applied to a wide range of non-activated olefins and good to high enantioselectivity up to 97% *ee* was obtained. It was also inferred that the enantioface- and regioselectivity in this epoxidation are mainly dictated by a steric factor and the olefinic substitution pattern; terminal and *Z* olefins are selectively epoxidized. Mechanistic studies that might open a way for constructing a new catalyst for asymmetric epoxidation of non-activated olefins of wider scope are now in progress in our laboratory.

Experimental Section

Typical procedure for the epoxidation of 1-octene: Complex **1** (17.8 mg, 10 μmol) and 1-octene (83 μL, 0.5 mmol) were dissolved in dichloromethane (0.50 mL). The resulting mixture was stirred for 24 h at room temperature after 30% aqueous hydrogen peroxide (80 μL, 0.75 mmol) had been added. The solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel (pentane/Et_2O = 40:1) to give the corresponding epoxide. The *ee* value was determined by ^{1}H NMR spectroscopic analysis using a chiral shift reagent [Eu(hfc)$_3$] (hfc = 3-(heptafluoroproyplhydroxymethylene)-D-camphorate).

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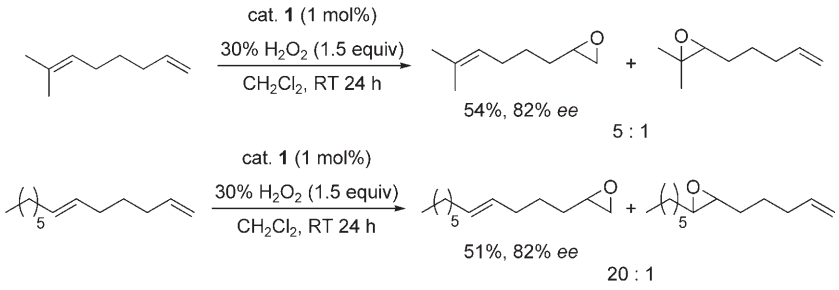

Scheme 1. Regio- and enantioselective epoxidation with the titanium(salalen) complex **1**.

[1] a) A. Berkessel, H. Gröger, *Asymmetric Organocatalysis*, Wiley-VCH, Weinheim, **2005**; b) T. Katsuki in *Comprehensive Coordination Chemistry II*, *Vol.* 9 (Ed: J. McCleverty), Elsevier Science, Oxford, **2003**; c) T. Katsuki in *Catalytic Asymmetric Synthesis*, 2nd ed. (Ed: I. Ojima), Wiley-VCH, New York, **2000**; d) E. N. Jacobsen, M. H. Wu in *Comprehensive Asymmetric Catalysis* (Eds: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**.

[2] a) T. Katsuki, K. B. Sharpless, *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976; b) T. Katsuki, V. S. Martin, *Org. React.* **1996**, *48*, 1–299.

[3] a) W. Zhang, J. L. Loebach, S. R. Wilson, E. N. Jacobsen, *J. Am. Chem. Soc.* **1990**, *112*, 2801–2803; b) R. Irie, K. Noda, Y. Ito, N. Matsumoto, T. Katsuki, *Tetrahedron Lett.* **1990**, *31*, 7345–7348.

[4] a) W. Zhang, A. Basak, Y. Kosugi, Y. Hoshino, H. Yamamoto, *Angew. Chem.* **2005**, *117*, 4463–4465; *Angew. Chem. Int. Ed.* **2005**, *44*, 4389–4391; b) W. Zhang, H. Yamamoto, *J. Am. Chem. Soc.* **2007**, *129*, 286–287.

[5] A. U. Barlan, A. Basak, H. Yamamoto, *Angew. Chem.* **2006**, *118*, 5981–5984; *Angew. Chem. Int. Ed.* **2006**, *45*, 5849–5852.

[6] a) Y. Shi, *Acc. Chem. Res.* **2004**, *37*, 488–496; b) D. Yang, *Acc. Chem. Res.* **2004**, *37*, 497–505.

[7] a) S. Juliá, J. Masana, J. C. Vega, *Angew. Chem.* **1980**, *92*, 968–969; *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 929–931; b) S. Colonna, H. Molinari, S. Banfi, S. Juliá, J.

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Masana, A. Alvalez, *Tetrahedron* **1983**, *39*, 1635 – 1641; c) P. Pietikäinen, *Tetrahedron Lett.* **1994**, *35*, 941 – 944; d) A. Berkessel, M. Frauenkron, T. Schwekreis, A. Steinmetz, G. Baum, D. Fenske, *J. Mol. Catal. A* **1996**, *113*, 321 – 342; e) P. Pietikäinen, *Tetrahedron* **1998**, *54*, 4319 – 4326; f) S. Arai, H. Tsuge, T. Shioiri, *Tetrahedron Lett.* **1998**, *39*, 7563 – 7566; g) L. Shu, Y. Shi, *Tetrahedron* **2001**, *57*, 5213 – 5218; h) R. I. Kureshy, N. H. Kahn, S. H. R. Abdi, S. Singh, I. Ahmed, R. S. Shunkla, R. V. Jasra, *J. Catal.* **2003**, *219*, 1 – 7; i) M. K. Tse, C. Dobler, S. Bhor, M. Klawonn, W. Magerlein, H. Hugl, M. Beller, *Angew. Chem.* **2004**, *116*, 5367 – 5372; *Angew. Chem. Int. Ed.* **2004**, *43*, 5255 – 5260; j) M. Marigo, J. Franzén, T. B. Poulsen, W. Zhuang, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 6964 – 6965.

[8] a) K. Matsumoto, Y. Sawada, B. Saito, K. Sakai, T. Katsuki, *Angew. Chem.* **2005**, *117*, 5015 – 5019; *Angew. Chem. Int. Ed.* **2005**, *44*, 4935 – 4939; b) Y. Sawada, K. Matsumoto, S. Kondo, H. Watanabe, T. Ozawa, K. Suzuki, B. Saito, T. Katsuki, *Angew. Chem.* **2006**, *118*, 3558 – 3560; *Angew. Chem. Int. Ed.* **2006**, *45*, 3478 – 3480; c) K. Matsumoto, Y. Sawada, T. Katsuki, *Synlett* **2006**, 3545 – 3547.

[9] M. Colladon, A. Scarso, P. Sgarbossa, R. A. Michelin, G. Strukul, *J. Am. Chem. Soc.* **2006**, *128*, 14006 – 14007.

[10] D. Mikame, T. Hamada, R. Irie, T. Katsuki, *Synlett* **1995**, 827 – 828.

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