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Catalytic Enantioselective Epoxidation of Homoallylic Alcohols by Chiral Zirconium Complexes

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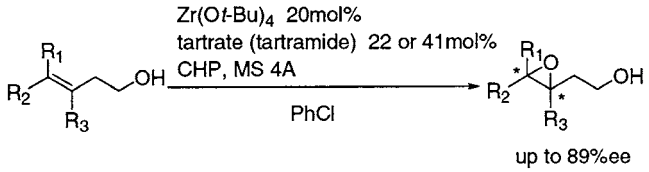
ABSTRACT



Catalytic enantioselective epoxidation of homoallylic alcohols using Zr(O*t*-Bu)$_4$ and tartrate ester (or tartramide) has been developed. In the Zr(O*t*-Bu)$_4$/diisopropyl tartrate-catalyzed epoxidation, the reverse of the enantiofacial preference was observed, depending on the Zr/ligand ratios of 1:1 or 1:2.

Asymmetric epoxidation of olefins is a powerful tool for the production of enantiomerically enriched epoxides that are versatile building blocks for the synthesis of natural products and biologically active substances. A variety of efficient methods have been developed.[1−6] The first practical asymmetric epoxidation was performed with allylic alcohols using *t*-BuOOH (TBHP) and stoichiometric amounts of Ti−tartrate complexes,[2] and afterward, the epoxidation was improved in a catalytic way.[3]

In contrast, when the Ti−tartrate−TBHP system was extended to the epoxidation of *homoallylic* alcohols, the rate of epoxidation was much slower and the enantiomeric purities of the resulting epoxides were lower, ranging from 27 to 55% ee.[7] Katsuki et al. also reported the asymmetric epoxidation of homoallylic alcohols using Zr(O*n*-Pr)$_4$ and tartramide derivatives: the ee of an epoxide from a cis-homoallylic alcohol was improved to 77% ee (25% yield), while other homoallylic alcohols gave poor results.[8] Here we report a *catalytic* asymmetric epoxidation of various homoallylic alcohols using chiral zirconium complexes.

Initially, we carried out the epoxidation of trans-3-hexen-1-ol (**1a**) with cumene hydroperoxide (CHP) using Zr(O*t*-Bu)$_4$ and tartrate ester (or tartramide). The epoxidation using stoichiometric amounts of Zr(O*t*-Bu)$_4$ and diisopropyl L-tartrate (DIPT) proceeded smoothly, and the corresponding epoxy alcohol (**2a**) was obtained in 78% yield with 88% ee in the short period of 1.0 h (Table 1, entry 1). Another combination of Zr(O*t*-Bu)$_4$ and dibenzyl L-tartramide (DBTA) also accelerated the reaction even at the lower temperature of −40 °C to give satisfactory results of 90% yield and 87% ee (Table 1, entry 2). Interestingly, the enantiofacial preference of the two reactions was opposite to that observed in the aforementioned epoxidation by Sharpless and Katsuki.[7,8]

(1) For recent reviews on highly enantioselective epoxidation of allylic alcohols, see: (a) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; Chapter 4.1. (b) Katsuki, T.; Martin, V. S. *Org. React.* **1996**, *48*, 1.

(2) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.

(3) Hanson, R.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922.

(4) For recent reviews on metal-catalyzed highly enantioselective epoxidation of unfunctionalized olefins, see: (a) Jacobsen, E. N. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; Chapter 4.2. (b) Collman, J. P.; Zhang, X.; Lee, V. J.; Uffelman, J. I. *Science* **1993**, *261*, 1404. (c) Katsuki, T. Coord. *Chem. Rev.* **1995**, *140*, 189. (d) Mukaiyama T. *Aldrichimica Acta* **1996**, *29*, 59.

(5) For recent reviews on asymmetric epoxidation of electron-deficient olefins, see: Porter, M. J.; Skidmore, *Chem. Commun.* **2000**, 1215.

(6) For recent reviews on chiral ketone-catalyzed asymmetric epoxidation, see: (a) Denmark, S. E.; Wu, Z. *Synlett* **1999**, 847. (b) Frohn, M.; Shi, Y. *Synthesis* **2000**, 1979.

(7) Bryant, E. R.; Sharpless, K. B. *J. Org. Chem.* **1984**, *49*, 3707.

(8) Ikegami, S.; Katsuki, T.; Yamaguchi, M. *Chem. Lett.* **1987**, 83.

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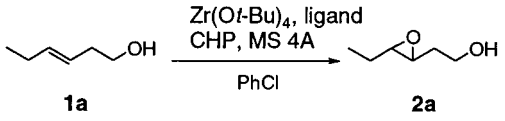
Table 1. Asymmetric Epoxidation of Homoallylic Alcohols



1a 2a

entry	ligand[a] [Zr/ligand] (equiv)	temp (°C)	time (day)	yield[b] (%)	ee (% ee)[c] (absolute configuration)[d]
1	DIPT [1.0/1.2]	0	1.0 h	78[e]	88 (3*S*,4*S*)
2	DBTA [1.0/1.2]	−40	0.5 h	90[e]	87 (3*S*,4*S*)
3	DIPT [1.0/2.1]	0	1.0 h	18[e]	66 (3*R*,4*R*)
4	DIPT [0.2/0.22]	0	1	92[e]	78 (3*S*,4*S*)
5	DIPT [0.2/0.22]	−40	1	90	82 (3*S*,4*S*)
6	DBTA [0.2/0.22]	−40	1	92	87 (3*S*,4*S*)
7	DIPT [0.2/0.41]	0	5	86	71 (3*R*,4*R*)
8	DBTA [0.2/0.41]	0	4	85	73 (3*S*,4*S*)

[a] (L)-Form. [b] Isolated yield. [c] Determined by chiral HPLC after isolation as triphenylmethyl ether. [d] Determined by comparison of optical rotation (ref 7). [e] Determined by ^{1}H NMR using triphenylmethane as an internal standard.

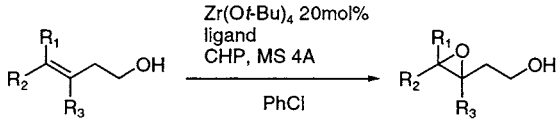
These intriguing results encouraged us to attempt a *catalytic* asymmetric epoxidation. After surveying catalytic conditions, proper preparation of the active catalyst was essential for optimal rates and selectivities. The catalyst should be prepared by mixing Zr(O*t*-Bu)$_4$ and DIPT (DBTA) in chlorobenzene in the presence of molecular sieves 4A (MS 4A) at 20 °C for 1 h before adding homoallylic alcohol and CHP. The mixing period is critical for the success of the reaction.[9] A catalytic epoxidation using Zr(O*t*-Bu)$_4$ and DBTA in a 1:1 ratio[10] afforded the highest yield and asymmetric induction (92% yield, 87% ee; Table 1, entry 6).

There were two significant findings. First, a catalyst from a 1:1 mixture[10] of Zr(O*t*-Bu)$_4$ and DIPT afforded (3*S*,4*S*)-**2a** in 78% ee, while that from a 1:2 mixture[10] produced the opposite enantiomer with a (3*R*,4*R*)-configuration in 71% ee (Table 1, entries 4 and 7).[11] The enantiofacial preference was dependent on the Zr:DIPT ratio.[12,13] Second, the presence and the type of molecular sieves also influenced the yield and enantiomeric excess of **2a**. For example, in a 1:2 catalytic system of Zr(O*t*-Bu)$_4$ and DIPT, no epoxidation of **1a** occurred without molecular sieves, and MS 4A (Na-zeolite A) were the molecular sieves of choice (MS 4A, 71% ee; MS 5A, 62% ee; MS 3A, 32% ee). Molecular sieves probably play a key role in promoting the exclusive formation of the active catalyst.[14]

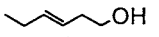
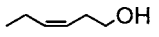
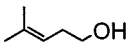
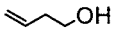
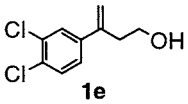
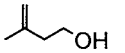
The reversed enantioselection could be ascribed to the differences in the structure of the zirconium complexes between 1:1 and 1:2 Zr(O*t*-Bu)$_4$/DIPT mixtures. To elucidate the structure of the complexes, we analyzed the Zr/tartrate complexes by ^{1}H and ^{13}C NMR, but their peaks in the NMR spectra were too obscure to be assigned. Analyses by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI TOF MS) showed the presence of a trimeric zirconium complex from a 1:1 mixture and that of a monomeric complex from a 1:2 mixture. In addition, the use of a 1:1 Zr(O*t*-Bu)$_4$/DIPT catalyst showed a linear relationship between the optical purities of DIPT used and product **2a,** whereas the epoxidation using a 1:2 mixture exhibited a nonlinear relationship.[15]

Under optimized catalytic conditions, representative homoallylic alcohols of different patterns were applied to the

Table 2. Catalytic Asymmetric Epoxidation of Homoallylic Alcohols



1 2

substrate	method[a]	yield (%)[b]	ee (%)[c]	abs. config.[d]
 **1a**	A	92	87	3*S*, 4*S*
	B	86	71	3*R*, 4*R*
 **1b**	A	93	72	3*S*, 4*R*
	B	45	49	3*R*, 4*S*
 **1c**	A	95	47	3*S*
	B	93	59	3*R*
 **1d**	A	55 (94)[e]	78	3*S*
	B	15 (25)[e]	82	3*R*
 **1e**	A	98	73	3*R*
	B	93	89	3*S*
 **1f**	A	83 (98)[f]	74	3*S*
	B	78 (96)[f]	86	3*R*

[a] Method A: Zr(O*t*-Bu)$_4$/(L)-DBTA = 0.20 equiv/0.22 equiv, reaction temp = −40 °C, reaction time = 1 day. Method B: Zr(O*t*-Bu)$_4$/(L)-DIPT = 0.20 equiv/0.41 equiv, reaction temp = 0 °C, reaction time = 3−5 days. [b] Isolated yield. [c] Determined by chiral HPLC after transformation to triphenylmethyl ether. [d] Determined by comparison of optical rotation and chiral HPLC (refs 7, 10, and 18). [e] Determined by ^{1}H NMR using triphenylmethane as an internal standard. [f] Determined by ^{1}H NMR using diphenylmethane as an internal standard.

(9) Experimental details are provided in Supporting Information.

(10) In this paper, we referred to Zr/ligand ratios (or mixtures) of 0.2/0.22 and 0.2/0.41 as 1:1 and 1:2, respectively.

(11) Diethyl tartrate, dibenzyl tartrate, and dibenzyl tartramide were unusable as ligands in the 1:2 system.

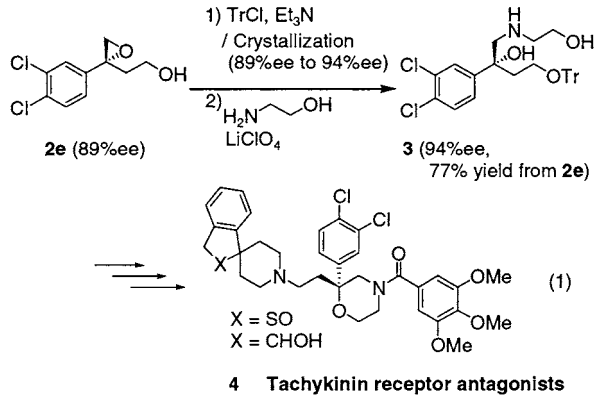
(12) It has been reported that enantiofacial selectivities were reversed between 1:1 and 2:1 (not 1:2) ratios of Ti/tartramide in the epoxidation of allylic alcohols: Lu, L. D.; Johnson, R. A.; Finn, M. G.; Sharpless, K. B. *J. Org. Chem.* **1984**, *49*, 728.

(13) Inversion of enantiofacial selection was also observed in stoichiometric systems of entries 1 and 3 in Table 1.

epoxidation by the use of a combination of Zr(O*t*-Bu)$_4$ with DIPT or DBTA (Table 2). In most of the examples, the corresponding epoxy alcohols were obtained in good yields and with sufficiently high enantioselectivity for practical use. Low isolated yields of **2d** and **2f** were due not to poor catalysis of the Zr/tartrate but to the physical properties of the products and technical problems when isolating the products from their complex reaction mixture. The epoxy alcohols in question are soluble in water and have low boiling points.

It is noteworthy that the enantiofacial selection led by a 1:1 complex of Zr/(L)-DBTA was always opposite to that led by a 1:2 complex of Zr/(L)-DIPT for all the substrates. The following tendencies were also observed. (1) By method A, oxygen was added from the back of the homoallylic alcohol when drawn in the orientation shown in Table 2. On the contrary, oxygen was delivered from the front of **1** by method B. (2) Epoxidations of trisubstituted, terminal, or 1,1-disubstituted homoallylic alcohols (**1c**, **1d**, **1e**,[17] and **1f**) by a 1:2 Zr/DIPT system proceeded with higher enantioselectivity but with slower rates and slightly lower yields than those by a 1:1 system. Regarding disubstituted alkenols (**1a** and **1b**), a Zr/DBTA system gave higher synthetic and optical yields.

Asymmetric epoxidation product (3*R*)-**2e** is a key intermediate for the synthesis of tachykinin receptor antagonists **4**, which are expected to be of therapeutic use in a wide variety of chromic diseases (eq 1). Epoxide (3*R*)-**2e**, which had been prepared by method B using (D)-DIPT, was protected with triphenylmethyl chloride and Et_3N, followed by an addition of aminoethanol to yield **3** in good yield (77% yield from **2e**) and with high enantiomeric purity. Compound **3** was transformed into **4**.[12]



In summary, we developed a general catalytic system for the asymmetric epoxidations of homoallylic alcohols using Zr(O*t*-Bu)$_4$ and tartrate ester or tartramide in which the enantiofacial selectivity was reversed depending on the Zr/ligand ratio. Further studies on the mechanistic aspects of the catalytic system are underway.

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Supporting Information Available: Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) (a) Terada, M.; Matsumoto, Y.; Nakamura, Y.; Mikami, K. *J. Mol. Catal. A* **1998**, *132*, 165. (b) Terada, M.; Matsumoto, Y.; Tanaka, M.; Nakamura, Y.; Mikami, K. *Microporous Mesoporous Mater*. **1998**, *21*, 461. (c) Terada, M.; Matsumoto, Y.; Nakamura, Y.; Mikami, K. *Inorg. Chim. Acta* **1999**, *296*, 267.

(15) For recent reviews on nonlinear effects in asymmetric synthesis, see: Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed.* **1998**, *37*, 2922.

(16) Behnke, D.; Hennig, L.; Findeisen, M.; Welzel, P.; Muller, D.; Thormann, M.; Hofmann, H. J. *Tetrahedron* **2000**, *56*, 1081.

(17) Compound **1e** was easily prepared by the carbonyl-ene reaction: Okachi, T.; Fujimoto, K.; Onaka, M. *Org. Lett.* **2002**, *4*, 1667.

(18) Absolute configuration of **2e** was determined by comparing the chiral HPLC spectrum after transformation to compound **3**: (a) Takemoto, T.; Nishi, T. *Tetrahedron Lett.* **2000**, *41*, 1785. (b) Nishi, T.; Ishibashi, K.; Takemoto, T.; Nakajima, K.; Fukazawa, T.; Iio, K.; Mukaiyama, O.; Yamaguchi, T. *Bioorg. Med. Chem. Lett*. **2000**, *10*, 1665.