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Vanadium-Catalyzed Asymmetric Epoxidation of Homoallylic Alcohols

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Catalytic asymmetric epoxidation of olefins is very useful for the synthesis of enantiomerically enriched epoxides, which are versatile building blocks for the synthesis of natural products and biologically active substances. There are many efficient protocols to mediate the epoxidation of allylic alcohols to provide satisfactory yields and enantioselectivities.[1] However, very limited catalyst systems can be used for the asymmetric epoxidation of homoallylic alcohols and those substrates in which olefin is located further from the hydroxy group. Sharpless asymmetric epoxidation, which was efficient for allylic alcohols, could not provide homoallylic alcohols with satisfactory enantioselectivities.[2,3] The protocol reported by our group, which used vanadium and α-amino acid-based hydroxamic acid ligands to perform the asymmetric epoxidation of homoallylic alcohols, was found to be efficient.[4,5] Unfortunately, however, the enantioselectivities of *trans* and *cis*-substituted olefins were not satisfactory. Thus, there has been no truly efficient catalytic asymmetric epoxidation of homoallylic alcohols reported. Recently, we reported a vanadium-catalyzed epoxidation of allylic alcohols with newly designed bishydroxamic acid (BHA) ligands (**1a** and **1b**),[6] which has the following features: (1) high enantioselectivity for a wide scope of allylic alcohols, (2) less than 1 mol % catalyst loading, (3) mild reaction conditions, and (4) use of aqueous *tert*-butyl hydroperoxide (TBHP) as an achiral oxidant instead of anhydrous TBHP[7−9] (Scheme 1). Herein, we report a new modified BHA ligand that is suitable for highly enantioselective vanadium-catalyzed epoxidation of homoallylic alcohols.

Initial experimental modification showed that cumene hydroperoxide (CHP) was better than TBHP to facilitate and complete the transformation, and toluene was used as solvent to inhibit cyclization of the produced epoxide to the corresponding tetrahydrofuran byproduct (Scheme 1), One mol % catalyst loading was enough to perform the reaction at room temperature. Reaction proceeded smoothly, and moderate enantioselectivity as well as good yield was achieved on **2a** when ligand **1b** was used (Table 1, entry 1). With this promising result in hand, new ligands based on **1b** were synthesized. The enantioselectivity was increased to 90% ee with **1c**. Finally, **1d**, which was introduced with a more hindered substituted phenyl group, was found to be excellent for the reaction; 96% ee was obtained on **2a**, while the rate of the reaction was also facilitated (Table 1).

The scope of the reaction was investigated with **1d** under the modified conditions. Gratifyingly, both *trans*- and *cis*-substituted epoxides were achieved with virtually complete enantioselectivities and satisfactory yields.

With the successful results of the asymmetric epoxidation of homoallylic alcohols, this catalyst system was applied to the kinetic resolution of these alcohols with outstanding selectivities (**4a, 4b**) (Scheme 2). Both the starting homoallylic alcohols and epoxy alcohols were obtained with satisfactory enantiopurity.[10] It should also be noted that this kinetic resolution gave us an opportunity to generate asymmetric carbon in a completely new scheme. In fact, starting homoallylic alcohols can be synthesized efficiently using preexisting chemistry of allylic anions.[11]

Scheme 1. Asymmetric Epoxidation of Allylic Alcohols and Homoallylic Alcohols by Vanadium and BHA Complexes

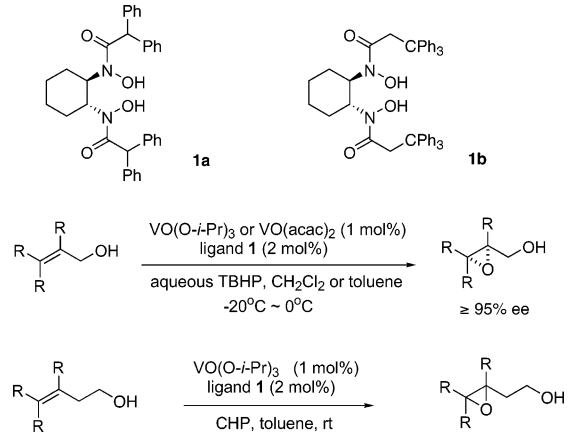
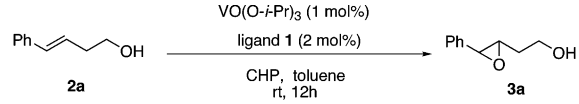
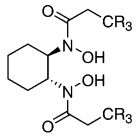
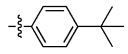
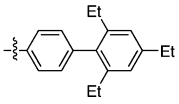


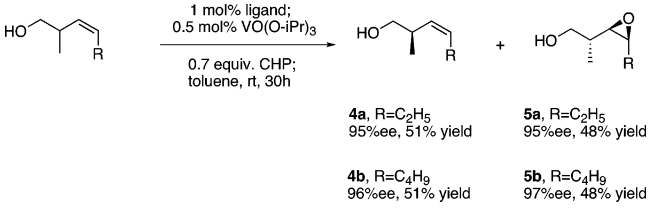
Table 1. Screening of Ligands



entry[a]	ligand	%yield[b], %ee[c]
1	**1b** R = 	52, 71
2	 **1c** R = 	56, 90
3	**1d** R = 	61, 96

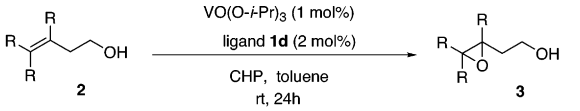
[a] All reactions were carried out in toluene in the presence of 1.5 equiv of cumene hydroperoxide (CHP) (88%) unless otherwise indicated. [b] Isolated yield after chromatographic purification. [c] Enantiomeric excess values were determined by chiral HPLC (AD-H), and the detailed information is provided in the Supporting Information.

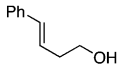
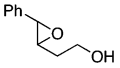
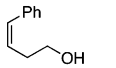
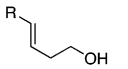
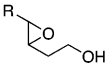
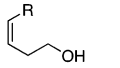
Scheme 2. Kinetic Resolution of Homoallylic Alcohols



10.1021/ja067495y CCC: $37.00

Table 2. Scope of Substrates



entry[a]	HAA	epoxy alcohol		%yield[b], %ee[c], config.	
1	 **2a**		**3a**	90,	96
2	 **2b**		**3b**	85,	99
3	 **2c-e**		**3c, R=C_2H_5**	85,	93 *(3R, 4R)*
4			**3d, R=C_5H_{11}**	89,	96
5			**3e, R=C_6H_{13}**	92,	98
6	 **2f-i**		**3f, R=C_2H_5**	92,	95 *(3R, 4S)*
7			**3g, R=C_3H_7**	90,	97
8			**3h, R=C_4H_9**	91,	99
9			**3i, R=C_5H_{11}**	90,	99

[a] All reactions were carried out in toluene in the presence of 1.5 equiv of cumene hydroperoxide (CHP) (88%) unless otherwise indicated. [b] Isolated yield after chromatographic purification. [c] Enantiomeric excess values were determined by either chiral HPLC or chiral GC, and the detailed information is provided in the Supporting Information.

The absolute configurations of **3c** and **3f** were determined as (3*R*,4*R*) and (3*R*,4*S*), respectively, by comparison of reported optical rotation.[2b,3b,12]In summary, we have designed a new chiral bishydroxamic acid ligand, which has been shown to be excellent for the vanadium-catalyzed asymmetric epoxidation and kinetic resolution of homoallylic alcohols. Further studies focusing on broader application of our chiral vanadium−hydroxamic acid complexes to wider scope are ongoing.

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Supporting Information Available: Representative experimental procedures and spectral data for **1c** and **1d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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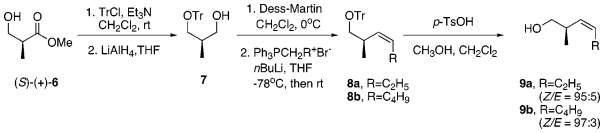

(10) (a) Enantiomeric excess values were determined by chiral GC analysis, and the detailed information is provided in Supporting Information. The absolute configurations of **4a** and **4b** were determined as (*R*) and (*R*), respectively, by comparison of retention times (GC analysis) of the absolute configuration known compounds (**9a**, **9b**), which were prepared by the following reported sequence: Ehrlich, G.; Kalesse, M. *Synlett* **2005**, *4*, 655. Detailed information is provided in Supporting information. (b) For the stereoselective epoxidation of homoallylic alcohols, see: Mihelich, E. D.; Daniels, K.; Eickhoff, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 7690.

(11) Kende, A. S.; Toder, B. H. *J. Org. Chem.* **1982**, *47*, 167.

(12) To explain these enantioselectivities, as well as those of kinetic resolutions, we proposed a possible model of the asymmetric epoxidation of homoallylic alcohol catalyzed by the complex of vanadium and ligand **1d**, which is provided in the Supporting Information.

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