Novel α-Amino Acid-Based Hydroxamic Acid Ligands for Vanadium-Catalyzed Asymmetric Epoxidation of Allylic Alcohols

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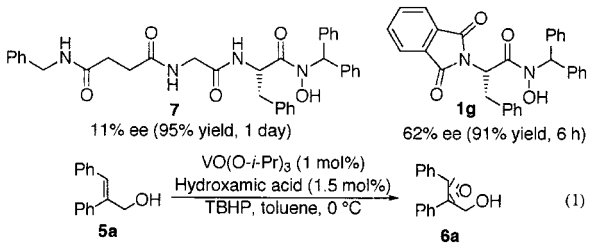
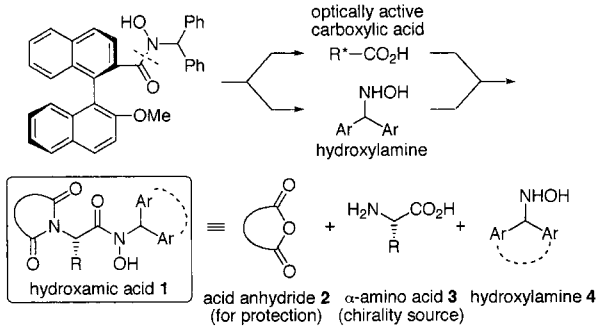
Received July 17, 2000

The development of novel effective chiral catalysts for enantioselective synthesis is a current topic of interest in synthetic organic chemistry.[1] Hydroxamic acids are good ligands for metal ions and are used as indicators for detecting metal ions.[2] In 1977, Sharpless and co-workers reported that hydroxamic acids are very resistant to oxidation and seem to bind well to molybdenyl and vanadium ions. They performed the asymmetric epoxidation of allylic alcohols in the presence of $VO(acac)_2$ and chiral hydroxamic acids.[3,4] However, catalysts of this type were not developed to a useful level, due to ligand deceleration along with dynamic ligand exchange processes in this system.[4] We recently described the vanadium-catalyzed asymmetric epoxidation of allylic alcohols using chiral binaphthyl-modified hydroxamic acids.[5] Our results suggested that several characteristics of the chiral vanadium complex play an important role in increasing the rate and enantioselectivity, i.e., the starting oxidation state of vanadium, the coordination ability of hydroxamic acids, and π-interaction or steric repulsion between the metal-binding site and oxidant. To improve this catalyst system, we planed to use combinatorial and related strategies[6] to identify effective vanadium-based catalysts for asymmetric epoxidation. For this purpose, our hydroxamic acid-bearing binaphthyl group can be reconstructed to novel α-amino acid-based hydroxamic acids suitable for the synthesis of a ligand library (Scheme 1). We report here that chiral α-amino acid-based hydroxamic acid ligands with a very simple structure are efficient catalysts for the asymmetric epoxidation of allylic alcohols.

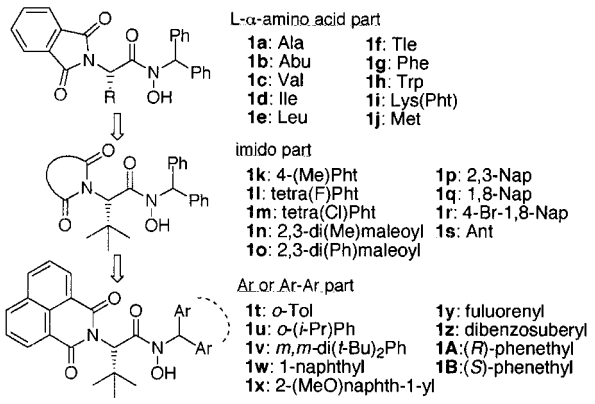
In a preliminary experiment, hydroxamic acid **1g** derived from phenylalanine gave better results than the peptide hydroxamic acid **7** in the asymmetric epoxidation of (*E*)-2,3-diphenyl-2-propen-1-ol (eq 1).[7] This reaction was also conducted in a water-free atmosphere, and a family of hydroxamic acids of this type were easily prepared from commercially available materials: a free α-amino acid was treated with appropriate carboxylic anhydride in DMF at 100 °C to give *N*-protected amino acid, which was transformed to acid chloride in the usual manner, and then treated with hydroxylamine to give the desired hydroxamic acid.[8] These features prompted us to optimize α-amino acid-based hydroxamic acids as ligands in the asymmetric epoxidation of allylic alcohols by using an iterative positional optimization approach, which involves screening one component of a ligand structure for selectivity, while holding the other units constant.[6]



Scheme 1. Design of an α-Amino Acid-Based Hydroxamic Acids as a Ligand



Scheme 2. Iterative Positional Optimization Approach



We developed a family of chiral hydroxamic acid ligands with a general structure of **1**, which consists of α-amino acid **3**, N^{α}-protecting group **2**, and hydroxylamine **4** (Scheme 2).[9] The enantioselectivities of epoxy alcohol **6a** obtained from asymmetric epoxidation in the presence of $VO(O\text{-}i\text{-}Pr)_3$ (1 mol %) and ligand **1** (1.5 mol %) at 0 °C for 6 h in toluene were investigated, and these results are shown in Figure 1.[7] In the first step, the source of chirality for ligand **1**, the amino acid moiety, was optimized. The selectivity of the product gradually increased with an increase in the steric hindrance of the side chain of the amino acid (from

(1) For a recent review, see: *Comprehensive Asymmetric Catalysis I−III*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999.

(2) Yale, H. L. *Chem. Rev.* **1943**, *33*, 209.

(3) (a) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1977**, *99*, 1990. (b) Sharpless, K. B.; Verhoeven, T. R. *Aldrichim. Acta* **1979**, *12*, 63. (c) Sharpless, K. B. *CHEMTECH* **1985**, *15*, 692. (d) Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1059.

(4) For recent reports on chiral vanadium-catalyzed epoxidation, see: (a) Bolm, C.; Luong, T. K. K.; Harms, K. *Chem. Ber./Recl.* **1997**, *130*, 887. (b) Bolm. C.; Kühn, T. *Synlett* **2000**, 899.

(5) (a) Murase, N.; Hoshino, Y.; Oishi, M.; Yamamoto, H. *J. Org. Chem.* **1999**, *64*, 338. (b) Hoshino, Y.; Murase, N.; Oishi, M.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* In press.

(6) (a) Kuntz K. W.; Snapper, M. L.; Hoveyda, A. H. *Curr. Opin. Chem. Biol.* **1999**, *3*, 313. (b) Shimizu, K. D.; Snapper, M. L.; Hoveyda, A. H. In *Comprehensive Asymmetric Catalysis I−III*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 3, 1389 and references therein.

(7) A representative procedure for the asymmetric epoxidation of **5a** in the presence of $VO(O\text{-}i\text{-}Pr)_3$ and hydroxamic acid **1g**: the hydroxamic acid ligand **1g** (30.0 mg, 0.063 mmol) was dissolved in toluene (4.2 mL). 10 μL of $VO(O\text{-}i\text{-}Pr)_3$ (0.042 mmol) was added, and the mixture was stirred for 1 h at room temperature while it turned light brown. The resulting solution was cooled to 0 °C, 78% *tert*-butylhydroperoxide (TBHP) (0.73 mL, 6.3 mmol) and allyl alcohol **5a** (883 mg, 4.2 mmol) were added, and the mixture was stirred for 6 h at 0 °C. Saturated aqueous solution of Na_2SO_3 was added, and the mixture was stirred for 1 h at 0 °C, allowed to warm to room temperature, extracted with ether, and dried over Na_2SO_4. The organic phase was concentrated under reduced pressure, and the residue was purified by column chromatography (ethyl acetate/hexane = 1:2) to give the epoxy alcohol **6a** (865 mg, 91%; 62% ee).

(8) See the Supporting Information for detailed experimental procedures.

(9) The abbreviations for the components of hydroxamic acids are explained in the Supporting Information.

10.1021/ja002602o CCC: $19.00
Published on Web 10/04/2000

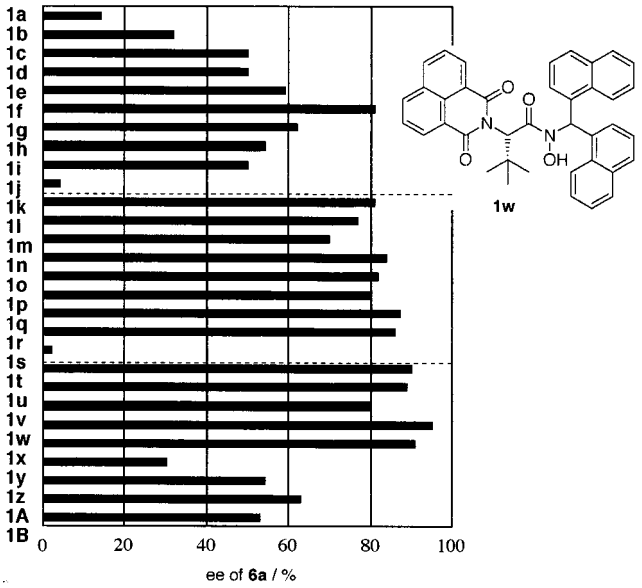


Figure 1. Enantioselectivities of epoxy alcohol **6a**.

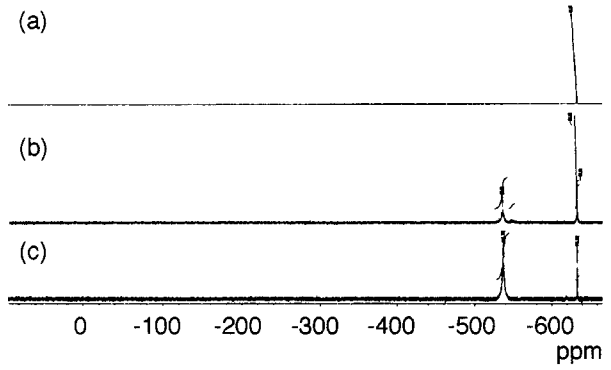


Figure 2. ^{51}V NMR spectra in benzene-d_6 at room temperature ($VOCl_3$, 0 ppm): (a) VO(O-*i*-Pr)$_3$, (b) VO(O-*i*-Pr)$_3$ and ligand **1w** (molar ratio, 1:1), and (c) VO(O-*i*-Pr)$_3$ and ligand **1w** (molar ratio, 1:1.5).

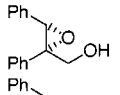
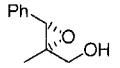
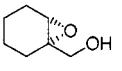
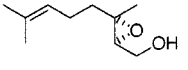
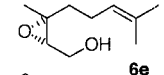
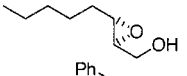
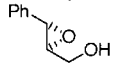
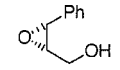
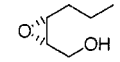
1a to **1f**), and the best result in this case was achieved using *tert*-leucine-derived hydroxamic acid **1f**. In the second step, the imido group was examined and optimized to 1,8-naphthalenedicarbonyl-protected hydroxamic acid **1q** (87% ee). Finally, the aryl groups near the metal-coordination site were changed. Interestingly, ligands that connected the phenyl groups gave low ee (**1y, z**). The best result was obtained using *N*-bis(1-naphthyl)methyl-substituted hydroxamic acid **1w** (entry 1, Table 1).[10] This reaction system was also tested to be conducted under an atmosphere of dry argon, and gave almost the same result (entry 2).

Some mono- or disubstituted allylic alcohols were enantiomerically epoxidized in good to high selectivity in the presence of optimized ligand **1w** (Table 1). Disubstituted allylic alcohols, except the 3-*cis*-substituted one, were epoxidized with excellent enantioselectivities and yields (**6a**−**c**). Even though **1w** was optimized for a particular substrate, it was an effective catalyst for a range of disubstituted allylic alcohols, and gave products with moderate-to-high enantioselectivity and yield (**6d**,**e**). The reactions of monosubstituted allylic alcohols in asymmetric epoxidation require a longer reaction time and give the corresponding epoxy alcohols with 76−87% ee.

The best catalyst identified by the above screening, **1w**, was also effective as a low-loading catalyst (0.1 mol %), but with a slight loss of selectivity (entry 3). This constitutes the first example of high enantioselectivity in vanadium-catalyzed asymmetric

(10) This ligand is a colorless crystal that is suitable for X-ray crystal structure analysis. The results of this analysis are shown in the Supporting Information.

Table 1. The Asymmetric Epoxidation of Various Allylic Alcohols in the Presence of VO(O-*i*-Pr)$_3$ (1 mol %) and Hydroxamic Acid **1w** (1.5 mol %)[a]

entry	epoxy alcohol **6**	time (h)	yield (%)[b]	ee (%)[c]
1	 **6a**	6	96	95
2[g]		6	93	96
3[h]		15	99	86
4[i]		6	98	91
5	 **6b**	6	97	95
6	 **6c**	5	82	93[d]
7	 **6d**	6	95	81[d]
8	 **6e**	3	97	78[d]
9	 **6f**	70	94	83[d]
10	 **6g**	80	58[e]	87
11	 **6h**	1 week	71[f]	76
12	 **6i**	24	80	82[d]

[a] All reactions were carried out at 0 °C in the presence of 1.5 equiv of *tert*-butylhydroperoxide and 1 mol % of vanadium catalyst prepared in situ by mixing VO(O-*i*-Pr)$_3$ and ligand **1w** (V/ligand 1:1.5) unless otherwise noted. [b] Isolated yield by column chromatography. [c] Determined by HPLC analysis with a chiral column (Chiral OD-H) unless otherwise noted. [d] Determined by GLC analysis with a chiral stationary phase column (β-TA). [e] The aldehyde was obtained in 9% yield as a byproduct. The allyl alcohol was recovered in 8% yield. [f] The allyl alcohol was recovered in 21% yield. [g] The reaction was conducted under an atmosphere of dry argon. [h] 0.1 mol % of VO(O-*i*-Pr)$_3$ and 0.15 mol % of **1w** were used. [i] 1.1 mol % of **1w** was used.

epoxidation with high reactivity. To understand the structure of the catalyst, a ^{51}V NMR experiment was performed (Figure 2). When hydroxamic acid **1w** in benzene-d_6 was treated with an equimolar amount of VO(O-*i*-Pr)$_3$ at room temperature, two peaks were observed at −537 and −633 ppm, as shown in Figure 2b. The peak at −537 ppm increased when the amount of **1w** was increased (the ratio of integration of these peaks is 95:5 (−537 ppm/−633 ppm) with the addition of 1.5 equiv of ligand, Figure 2c). This peak can be assigned to VO(O-*i*-Pr)$_2$(L) (L = hydroxamate of **1w**). This observation suggests that 1:1 complexation of vanadium and ligand was effective, and this would positively affect the enantioselectivity.

These results show that chiral amino acid-based hydroxamic acids identified from libraries can be effective asymmetric catalysts for the epoxidation of allylic alcohols, especially disubstituted allylic alcohols. The mild reaction conditions, e.g., reasonable temperature (0 °C), low degree of catalytic loading (1mol % of vanadium), and halogen-free solvent (toluene), extend the scope of this process. Experiments are in progress to identify effective asymmetric catalysts for other important reactions using this positional optimization strategy.

Acknowledgment. The authors thank Dr. Masataka Oishi for his useful suggestions. Y.H. acknowledges a JSPS Fellowship for Japanese Junior Scientists.

Supporting Information Available: Experimental details for preparing hydroxamic acid ligand **1** and the asymmetric epoxidation of allylic alcohol **5**, and spectroscopic data for **1** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA002602O