*Asymmetric Catalysis*

# Enantioselective Epoxidation of Allylic Alcohols by a Chiral Complex of Vanadium: An Effective Controller System and a Rational Mechanistic Model**

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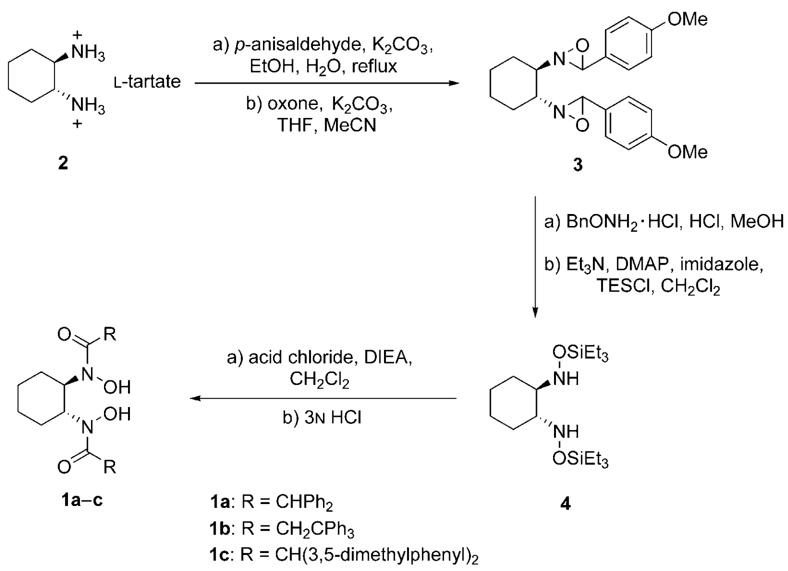
The asymmetric epoxidation of allylic alcohols by metal catalysts,[1] though a widely used synthetic method, could gain even more practical applications if the following were realized: 1) employment of a ligand designed to achieve high enantioselectivity for *Z* olefins, 2) catalyst loading of less than 1 mol %, 3) reaction temperatures of 0 °C to room temperature over a shorter time, 4) use of aqueous *tert*-butyl hydroperoxide (TBHP) as an achiral oxidant instead of anhydrous TBHP, and 5) simple workup procedures for small epoxy alcohols. Many important improvements have been made to the methodology developed by Sharpless and co-workers for the titanium tartarate catalyzed asymmetric epoxidation.[2–4] Nonetheless, each of these approaches fails to fulfil the above criteria.[1–5] Herein, we report our recent progress on all five fronts.

Recently, we developed a series of hydroxamic acid ligands and demonstrated that they were effective for the vanadium-catalyzed asymmetric epoxidation of allylic alcohols.[6,7] These results suggested that several structural features of the hydroxamic acid significantly enhanced the rate and enantioselectivity of the reaction. However, the ligand deceleration effect was still observed in these cases.[6–8] To exclude this effect, we planned to design a new $C_2$-symmetric bishydroxamic acid **1** that incorporated the following features: 1) an additional binding site with which **1** can chelate as a bidentate ligand to the metal center to complete the generation of a chiral vanadium/ligand complex more efficiently than the monohydroxamic acid and 2) an R group of the amide in **1** that is sufficiently large so the oxygen atom of the carbonyl group is directed towards the cyclohexane ring to minimize steric interaction and restrict its coordination with the metal center. Furthermore, the attachment of additional ligands to the vanadium center will also be restricted because of steric reasons. Thus, doubly or triply coordinated species, which are believed to be inactive, should not be generated from the bishydroxamic acid ligand, and consequently a ligand deceleration effect within the vanadium/**1** catalytic system should not be problematic.[8]

We devised a synthetic protocol for **1** from a readily available diamine tartrate salt (Scheme 1) so that the veracity of our hypothesis could be proved.[9] These reaction sequences can be carried out with satisfactory yields and without any purification to provide **4**, from which we have prepared an array of diverse ligands **1a–c**.



***Scheme 1.*** Preparation of bishydroxamic acid. DIEA = *N*,*N*-diisopropylethylamine, Bn = benzyl, DMAP = 4-dimethylaminopyridine, TESCl = triethylsilyl chloride.

As expected, the use of a complex of vanadium with ligand **1** provided epoxy alcohols both in good yields with high enantioselectivities (Table 1).[9] The catalyst **5a**, derived from vanadium and **1a**, invariably induced excellent enantioselectivities during the epoxidation of *trans*-disubstituted and -trisubstituted allylic alcohols. The most gratifying aspect of this catalytic system was the excellent enantioselectivity observed during the epoxidation of *cis*-substituted allylic alcohols with catalyst **5b**, which was derived from vanadium and **1b.** It is of note that 1) the slow reactivity of some substrates were surmounted by performing the epoxidation at 0 °C or room temperature without significant loss of enantioselectivity, 2) the catalyst loading could be as low as 0.2 mol %, 3) all the reactions were performed in air and in the presence of aqueous TBHP; the use of anhydrous TBHP increased neither the yield nor the enantioselectivity.[9] Also as expected, the negative effect of a dynamic ligand exchange was not observed in the vanadium/bishydroxamic acid catalytic system. The high reactivity of the vanadium/ligand complex was maintained, even if the ratio of ligand/vanadium was increased to more than 3:1.[9]

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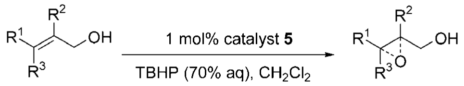
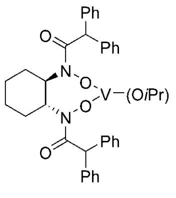
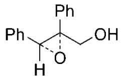
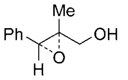
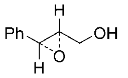
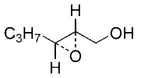
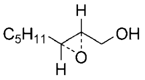
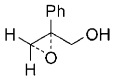
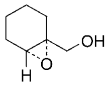
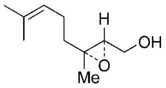
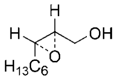
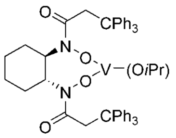
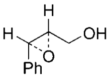
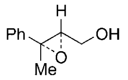
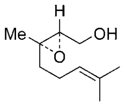
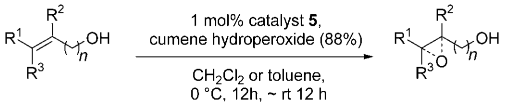
*Table 1:* Enantioselective epoxidation of allylic alcohols

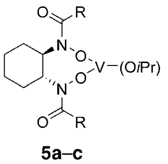
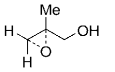
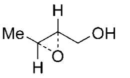
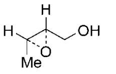
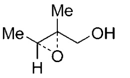
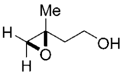


| Catalyst | Product | *T* [°C] | *t* [h] | Yield [%] | *ee* [%] |
|---|---|---|---|---|---|
|  **5a** |  | −20 | 48 | 91 | 97 |
| |  | −20 | 48 | 84 | 97 |
| |  | −20 | 60 | 53 | 97 |
| |  | −20 | 72 | 56 | 95 |
| |  | −20 | 72 | 51 | 95 |
| |  | 0 | 48 | 73 | 95 |
| |  | −20 | 48 | 79 | 95 |
| |  | −20 | 48 | 68 | 95[a] |
| |  | 0 | 72 | 60 | 95 |
|  **5b** |  | −20 | 120 | 24 | 97 |
| |  | −20 | 48 | 64 | 96 |
| |  | −20 | 48 | 62 | 95 |

[a] Catalyst was **5c**.

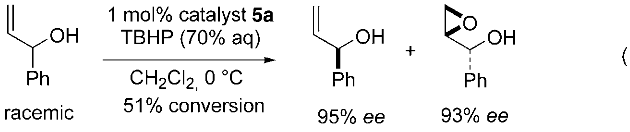
*Table 2:* Enantioselective epoxidation of small allylic alcohols



| | Catalyst | Product | Yield [%] | *ee* [%] |
|---|---|---|---|---|
|  **5a–c** | **5c** |  | 78 | 97 |
| | **5a** |  | 50 | 93 |
| | **5b** |  | 71 | 92 |
| | **5a** |  | 68 | 95 |
| | **5c** |  | 73 | 94 |

This method was applied to the asymmetric synthesis of small epoxy alcohols, which is a long-standing problem in asymmetric oxidation. Thus, after the reaction, the product was extracted with water to give the enantiopure epoxy alcohols (Table 2).[2,9]

Finally, the method was also applied to the kinetic resolution of a secondary allylic alcohol. As expected, both the epoxy alcohol and the allylic alcohol were isolated with high enantioselectivities [Eq. (1)].[9]



(1)

To explain the reaction enantioselectivity, we have proposed a possible intermediate during the epoxidation[10] (Figure 1). If **1a** is divided into four sections, as indicated by the circle in Figure 1, it is seen that the second and fourth quadrants of **1a** (corresponding to the shaded sections) are more crowded than the first and third quadrants (corresponding to the unshaded quarters) because of the structural features of the chiral cyclohexyl bishydroxamic acid (Figure 1a), especially when the vanadium center is introduced. [VO(O*i*Pr)$_3$] coordinates with **1a** by displacement of two *i*PrOH units with two hydroxy groups from the bishydroxamic acid (Figure 1b). Another *i*PrOH unit of [VO(O*i*Pr)$_3$] is then displaced by TBHP, which occupies the less-crowded third quadrant. Finally, when the allylic alcohol forms, it will coordinate with the vanadium center through its oxygen atom from the top. During the reaction, the oxygen atom of TBHP is spiro overlapped with the olefin and attacks it from the bottom. Steric bulk at the α position of the carboxylate group, which is greater in the case of **1a**, plays an important role and is suitable for *trans*-substituted allylic alcohols as the sub-

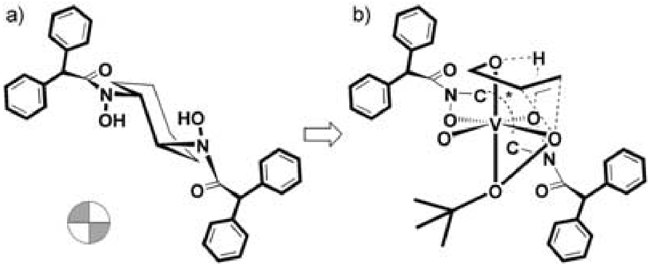


*Figure 1.* Postulated model of the epoxidation of allylic alcohols catalyzed by the vanadium/**1a** complex. a) Chiral cyclohexyl bishydroxamic acid **1a** and b) the proposed reaction intermediate. The circle represents the division of the bishydroxamic acid into quarters to explain its stereochemistry. The shaded sections of the circle represent the parts of the bishydroxamic acid in bold.

strate. On the other hand, the additional flexibility of **1b** allows the *cis*-substituted allylic alcohols enough space to fit into the chiral pocket, thus resulting in high selectivity.

In conclusion, we have developed a new catalytic system for the asymmetric epoxidation of allylic alcohols. Investigations into the mechanism and further applications of bishydroxamic acid ligands in asymmetric catalysis is in progress.

## Experimental Section

Representative experimental procedure: [VO(O*i*Pr)$_3$] (0.0025 mL, 0.0104 mmol) was added to a solution of **1a** (11.2 mg, 0.0210 mmol) in $CH_2Cl_2$ or toluene (1 mL), and the reaction mixture was stirred for 1 h at RT. The resulting solution was cooled to 0°C, and 70% aqueous TBHP (0.22 mL, 1.59 mmol) and α-phenylcinnamyl alcohol (220 mg, 1.05 mmol) were added. The mixture was stirred at the same temperature for 12 h. The process of epoxidation was monitored by TLC. Saturated aqueous $Na_2SO_3$ was added, and the reaction mixture was stirred for 1 h at 0°C. The reaction mixture was then allowed to warm to RT, extracted with $Et_2O$, dried over $Na_2SO_4$, and concentrated under reduced pressure. The remaining residue was purified by flash column chromatography on silica gel to provide the epoxy alcohol (93%, 94% *ee*). Determination of the *ee* values of the epoxy alcohols is provided in the Supporting Information.

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**Keywords:** asymmetric catalysis · chirality · epoxidation · ligand design · vanadium

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[9] See the Supporting Information for detailed experimental procedures.

[10] For a mechanistic study on an oxidation mediated by a vanadium/hydroxamic acid system, see: a) K. P. Bryliakov, E. P. Talsi, *Kinet. Catal.* **2003**, *44*, 334–346; b) K. P. Bryliakov, E. P. Talsi, T. Kühn, C. Bolm, *New J. Chem.* **2003**, *27*, 609–614.