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Vanadium-Catalyzed Enantioselective Desymmetrization of *meso*-Secondary Allylic Alcohols and Homoallylic Alcohols

Zhi Li,

Department of Chemistry, The University of Chicago, 5735 South Ellis Avenue, Chicago, IL 60637 (USA)

Dr. Wei Zhang, and

Department of Chemistry, Northwestern University, 2145 Sheridan Road, Evanston, IL 60208

Prof. Dr. H. Hisashi Yamamoto

Department of Chemistry, The University of Chicago, 5735 South Ellis Avenue, Chicago, IL 60637 (USA), Fax: (+1) 773-702-0805, Homepage: <http://yamamotogroup.uchicago.edu/>

H. Hisashi Yamamoto: yamamoto@uchicago.edu

Abstract

Vanadium-catalyzed epoxidation has extended substrate scope. In addition to various bis-allylic alcohols, bis-homoallylic alcohols can also be desymmetrized using our Vanadium-Bis-hydroxamic acid complexes.

Keywords

Asymmetric catalysis; epoxidation; desymmetrization; vanadium

Kinetic resolution of secondary allylic or homoallylic alcohols is one of the most important synthetic protocols to provide enantiomerically enriched epoxides, especially those carrying several continuous chiral centers. These chiral building blocks could be very useful for the asymmetric synthesis of natural products and biologically active substances. Many efficient protocols have been developed to satisfactorily mediate the kinetic resolution of allylic alcohols.^[1] Recently, we reported a new bis-hydroxamic acid (BHA) ligand for the enantioselective vanadium catalyzed asymmetric epoxidation as well as kinetic resolution of allylic and homoallylic alcohols (Scheme 1).^[2,3]

However, the intrinsic problem of kinetic resolution is that the maximum yield is 50%. Half of the starting material is considered undesired compound after the reaction. On the other hand, desymmetrization of *meso*-secondary allylic and homoallylic alcohols, which shares the same principle of facial discrimination of olefins with kinetic resolution, does not have this limitation because in theory all the starting material can participate in the reaction. Therefore, it should be more efficient than kinetic resolution in providing optically pure epoxy alcohols bearing at least two stereo centers.

Several *meso*-secondary allylic alcohols have been successfully desymmetrized by Sharpless Asymmetric Epoxidation reaction,^[1b, 4] and applied in stereo-selective natural product synthesis.^[5] However, *cis*-substituted *meso*-secondary allylic alcohol substrates could not

Correspondence to: H. Hisashi Yamamoto, yamamoto@uchicago.edu.

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provide satisfactory enantioselectivities. Additionally, catalyst loading for Sharpless system catalyzed desymmetrization was usually high, even higher than stoichiometric.^[1b] Our vanadium-BHA system has several features that would facilitate this reaction, such as low catalyst loading, tolerance of aqueous peroxy oxidants, mild reaction conditions and easy work-up procedures. Using our vanadium-BHA catalytic asymmetric epoxidation system, several typical *meso*-secondary allylic alcohols: such as *trans*-, *cis*-, unsym-, and unsubstituted divinyl carbinols, were all desymmetrized into corresponding epoxy allylic alcohols in high stereoselectivities and good yields (Table 1).

Since we had modified reaction conditions for the vanadium catalyzed asymmetric epoxidation in our previous study, we then applied ligands **1a–1c** to the desymmetrization reactions under the optimal conditions. 1.0 mol% catalyst loading was used. As we found in our previous study, ligand **1a** provided *trans*-substituted and unsym-substituted substrates with excellent enantioselectivities, while **1b** was suitable for *cis*-substituted substrates. The reactions also provided high diastereoselectivities and good yields. The simplest product in this category, 1,2-epoxy-4-penten-3-ol (**3e**) was generated with 95% *ee* when more bulky ligand, **1c**, was used. CHP was better than aqueous TBHP in facilitating the transformation for **3e**. The absolute configuration of epoxy alcohol **3e** was determined as (2*S*, 3*R*), by comparison with literature NMR data and optical rotation.^[6] Absolute configurations of epoxy alcohols **3a–d** were concluded from that of **3e** and kinetic resolution results of secondary allylic alcohols.^[2]

With these successful results in hand, we applied this catalyst system in the asymmetric epoxidation of *meso*-secondary homoallylic alcohols, which had been an unsolved problem of asymmetric synthesis (Table 2). Substrates bearing *cis*-substituents at the double bonds provided excellent yield and *ee*, while *trans*-counterparts did not proceed as satisfactorily.

Although our previous study showed that temperature does not significantly affect the enantioselectivity of homoallylic alcohol epoxidation,^[3] here a lower temperature (0°C) is necessary to achieve excellent *ee* values. As a result, the reaction time required was lengthened (Table 2, entries 5 and 6).

These substrates are typical examples of ‘combination of enantiotopic groups and diastereotopic faces’.^[4b] Studies from Schreiber proved that these reactions could provide higher stereoselectivities but lower yields in longer reaction time.^[4b, 8] This is applicable in our reaction as well. Enantiotopic groups are the two double bonds, while diastereotopic faces are two faces of each double bond. Given longer reaction time, substrate **4a** underwent desymmetrization with constantly increasing *ee*% and diastereomeric ratio, while the yield had a peak value at about 200hrs. (Table 2, entries 1–3)

In order to decrease the reaction time while retaining high enantioselectivity and acceptable yield of product **5a**, we attempted to apply 2 mol% catalyst loading to the system. The combination of lower temperature and higher catalyst loading provided the best result of this study. (Table 2, entry 4).

Stereospecific base-catalyzed epoxide ring hydrolysis of epoxy alcohol **5a** provided a 1, 2, 4-triol of which the absolute configuration has been established (Scheme 2).^[7] Therefore, the absolute configuration of **5a** was determined as (2*R*, 4*R*). These results further supported our previous mechanism hypothesis on the vanadium-BHA catalyzed epoxidation.^[3]

To the best of our knowledge, our highly stereoselective synthesis of compound **5a** is the first time this very promising synthetic intermediate has been accessed.^[9] Existing direct epoxidation methods of **4a** can only provide poor conversion.^[10–13] Indirect approaches

include either compromising with its racemic mixture obtained by iodo-lactonization,^[14, 15] synthesizing via multiple steps from chiral pool compounds such as (–)-(*S*)-malic acid,^[16] or use of Jacobsen's hydrolytic kinetic resolution of the racemic mixture.^[9] This is true even though **5a** has been used in several academic and industrial syntheses, including the racemic mixture of the crucial intermediate of the famous cholesterol control medicine atorvastatin, i.e. Lipitor®.^[9, 14–16] Now that we have developed a highly stereoselective desymmetrical synthesis of compound **5a**, all those procedures can be circumvented. Thus, we believe more syntheses based on our progress will soon become available.

In conclusion, we have successfully applied our vanadium-BHA catalyst system to the highly enantioselective desymmetrization of *meso*-secondary allylic and homoallylic alcohols. Further studies focusing on improvements of the catalytic conditions are in progress.

Experimental Section

Representative experimental procedure: [VO(O^{*i*}Pr)₃] (2.5 μL, 0.0104 mmol) was added to a solution of **1a** (11.2 mg, 0.0210 mmol) in CH₂Cl₂ (0.5 mL), and the reaction mixture was stirred for 1 h at RT. The resulting solution was cooled to 0°C, and (1*E*, 4*E*)-1,5-diphenylpenta-1,4-dien-3-ol (**2a**) (250 mg, 1.06 mmol) and 70% aqueous TBHP (0.17 mL, 1.23 mmol) were added sequentially. The mixture was stirred at the same temperature for 10 h. The process of epoxidation was monitored by TLC. Saturated aqueous Na₂SO₃ 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 Et₂O, dried over Na₂SO₄, and concentrated under reduced pressure. The remaining residue was purified by flash column chromatography on silica gel to provide the epoxy alcohol **3a** (52%, 95% *ee*). Determination of the *ee* values of the epoxy alcohols is provided in the Supporting Information.

Acknowledgments

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Scheme 1.
 Asymmetric Epoxidation and Kinetic Resolution of Allylic and Homo-allylic Alcohols
 Catalyzed by Vanadium-BHA Complexes

Scheme 2.
Absolute Configuration Determination of **5a**

Table 1

Desymmetrization of *meso*-Secondary Allylic Alcohols

entry ^[a]	epoxy alcohol	ligand	temp, time	<i>dr</i> , %yield ^[b] , % <i>ee</i> ^[c]
1	3a	1a	0°C, 10h	94:6, 52, 95
2	3b	1a	0°C, 12h	95:5, 60, 95
3	3c	1a	−10°C, 96h	99:1, 62, 95
4	3d	1b	−10°C, 96h	87:13, 73, 97
5 ^[d]	3e, (2 <i>S</i> , 3 <i>R</i>)	1c	0°C, 24h	98:2, 52, 95

^[a] All entries were carried out in CH₂Cl₂ in the presence of 1.2 equiv. of TBHP 70% aqueous solution unless otherwise indicated.

^[b] Isolated yield after chromatographic purification.

^[c] *Dr.* and *ee.* values were determined by chiral HPLC or chiral GC and the detailed information was provided in the supporting information.

^[d] Reaction was carried out in CH₂Cl₂ in the presence of 1.2 equiv. of 88% CHP.

Table 2Desymmetrization of *meso*-Secondary Homo-allylic Alcohols

entry ^[a]	epoxy alcohol	temp, time	<i>dr</i> , %yield ^[b] , % <i>ee</i> ^[c]
1		0°C, 72h	87:13, 23, 93
2		0°C, 192h	90:10, 56, 94
3		0°C, 284h	93:7, 53, 95
4 ^[d]		0°C, 120h	92:8, 51, 97
5		rt, 48h	95:5, 53, 92
6		0°C, 96h	97:3, 69, 97

^[a] All entries were carried out in toluene in the presence of 1.2 equiv. of 88% CHP.^[b] Isolated yield after chromatographic purification.^[c] *Dr.* and *ee.* values were determined by chiral GC and the detailed information was provided in the supporting information.^[d] 2 mol% VO(O^{*i*}Pr)₃ and 4 mol% ligand **1c** was used.