Asymmetric Catalysis

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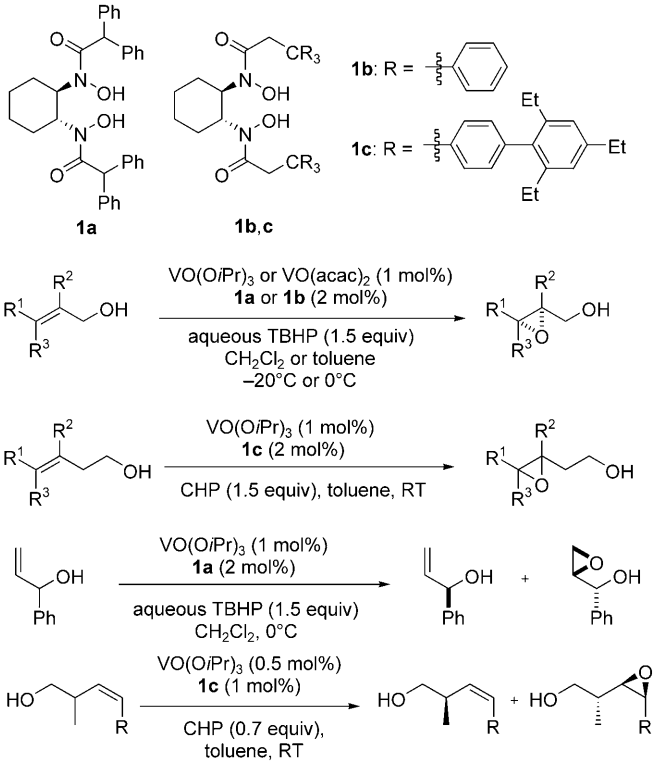
Vanadium-Catalyzed Enantioselective Desymmetrization of *meso* Secondary Allylic Alcohols and Homoallylic Alcohols**

*Zhi Li, Wei Zhang, and Hisashi Yamamoto**

Kinetic resolution of secondary allylic alcohols and homoallylic alcohols is one of the most important synthetic protocols used to provide enantiomerically enriched epoxides, especially those carrying several contiguous stereogenic centers. These chiral building blocks would 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 new bishydroxamic acid (BHA) ligands for the enantioselective vanadium-catalyzed asymmetric epoxidation and kinetic resolution of allylic alcohols and homoallylic alcohols (Scheme 1).[2,3]

However, the intrinsic problem of kinetic resolution is that the maximum yield is 50%, and half of the starting material turns out to be a by-product after the reaction. On the other hand, the desymmetrization of *meso* secondary allylic alcohols 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 of the starting material can participate in the reaction. Therefore, this approach should be more efficient than kinetic resolution in providing optically pure epoxy alcohols bearing at least two stereocenters.

Several *meso* secondary allylic alcohols have been successfully desymmetrized by using the Sharpless asymmetric epoxidation reaction,[1b,4] and this method has been applied in stereoselective natural product synthesis.[5] However, *cis*-substituted *meso* secondary allylic alcohols did not provide satisfactory enantioselectivities. Additionally, the catalyst loadings necessary for desymmetrization by Sharpless systems are usually high, often greater than a stoichiometric amount.[1b] Our vanadium/BHA catalyst system has several features that would facilitate this type of reaction, such as low catalyst loading, tolerance of aqueous peroxy oxidants, mild reaction conditions, and easy work-up procedures. By using our catalyst system, several typical *meso* secondary allylic alcohols such as *trans*- and *cis*-1,1-disubstituted and unsubstituted divinyl carbinols were all desymmetrized to give the corresponding epoxy allylic alcohols in high stereoselectivities and good yields (Table 1).



Scheme 1. Structures of BHA ligands **1a**–**1c**. Asymmetric epoxidation and kinetic resolution of allylic and homoallylic alcohols catalyzed by vanadium/BHA complexes. acac = acetylacetonate, CHP = cumene hydroperoxide, *i*Pr = 2-propyl, TBHP = *tert*-butyl hydroperoxide.

We used the optimized reaction conditions for the vanadium-catalyzed asymmetric epoxidation developed in our previous study, and then applied ligands **1a**–**c** and a 1.0 mol% catalyst loading to the desymmetrization reactions. As was found previously, ligand **1a** provided *trans*-substituted and 1,1-disubstituted substrates with excellent enantioselectivities (Table 1, entries 1–3), while **1b** was suitable for *cis*-substituted substrates (Table 1, entry 4). 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 the sterically more demanding ligand **1c** was used (Table 1, entry 5). The transformation for **3e** was more diastereoselective in the presence of CHP than in aqueous TBHP. The absolute configuration of

[*] Z. Li, Prof. Dr. H. Yamamoto
Department of Chemistry
The University of Chicago
5735 South Ellis Avenue, Chicago, IL 60637 (USA)
Fax: (+1) 773-702-0805
E-mail: yamamoto@uchicago.edu
Homepage: http://yamamotogroup.uchicago.edu/
Dr. W. Zhang
Department of Chemistry, Northwestern University
2145 Sheridan Road, Evanston, IL 60208 (USA)

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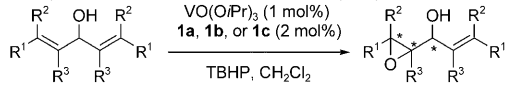
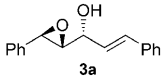
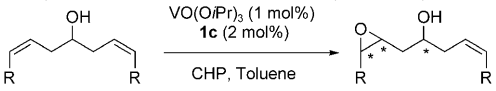
Table 1: Desymmetrization of *meso* secondary allylic alcohols.

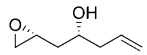
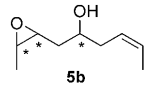


Entry[a]	Epoxy alcohol	Ligand	*T* [°C]	*t* [h]	d.r.	Yield [%][b]	*ee* [%][c]
1	 **3a**	**1a**	0	10	94:6	52	95
2	 **3b**	**1a**	0	12	95:5	60	95
3	 **3c**	**1a**	−10	96	99:1	62	95
4	 **3d**	**1b**	−10	96	87:13	73	97
5[d]	 **3e** (2*S*,3*R*)	**1c**	0	24	98:2	52	95

[a] All reactions were carried out in CH_2Cl_2 in the presence of 70% aqueous TBHP (1.2 equiv), unless otherwise indicated. [b] Yield of isolated product after chromatographic purification. [c] The d.r. and *ee* values were determined by HPLC or GC analysis on a chiral stationary phase, see the Supporting Information for details. [d] Reaction was carried out in CH_2Cl_2 in the presence of 88% CHP (1.2 equiv).

Table 2: Desymmetrization of *meso* secondary homoallylic alcohols.



Entry[a]	Epoxy alcohol	*T* [°C]	*t* [d]	d.r.	Yield [%][b]	*ee* [%][c]
1	 **5a** (2*R*,4*R*)	0	3	87:13	23	93
2		0	8	90:10	56	94
3		0	11.8	93:7	53	95
4[d]		0	5	92:8	51	97
5	 **5b**	RT	2	95:5	53	92
6		0	4	97:3	69	97

[a] All reactions were carried out in toluene in the presence of 88% CHP (1.2 equiv). [b] Yield of isolated product after chromatographic purification. [c] The d.r. and *ee* values were determined by HPLC or GC analysis on a chiral stationary phase, see the Supporting Information for details. [d] $VO(OiPr)_3$ (2 mol%) and **1c** (4 mol%) were used.

epoxy alcohol **3e** was determined as 2*S*,3*R* by comparison with NMR spectroscopic data and optical rotation data.[6] The absolute configurations of **3a**–**d** were assigned by comparison of the structures with that of **3e**, as well as from the kinetic resolution of secondary allylic alcohols.[2]

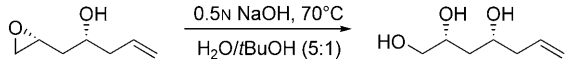
With these results in hand, we next applied this catalyst system to the asymmetric epoxidation of *meso* secondary homoallylic alcohols, which has been an unsolved problem in asymmetric synthesis (Table 2). Substrates bearing *cis* substituents on the double bonds provided excellent yields and *ee* values, while the reactions of the *trans* counterparts did not proceed 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) was necessary to achieve excellent *ee* values. As a result, the reaction time required was longer (Table 2, entries 5 and 6).

These substrates are typical examples of a "combination of enantiotopic groups and diastereotopic faces".[4b] Studies from Schreiber and co-workers showed that these reactions could provide higher stereoselectivities but lower yields after a longer reaction time.[4b,7] This observation is also applicable to our reaction. Here, the enantiotopic groups are the two double bonds, while the diastereotopic faces are the two faces of each double bond. As the reaction time for the desymmetrization of substrate **4a** increased, the *ee* values and diastereomeric ratios increased, while the yield reached a maximum after 8 days (Table 2, entries 1–3).

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

Stereospecific base-catalyzed epoxide hydrolysis of epoxy alcohol **5a** provided a 1,2,4-triol, the absolute configuration of which was established as 2*R*,4*R* (Scheme 2).[8] These results further support our previously described mechanism for the vanadium/BHA catalyst system.[3]



Scheme 2. Determination of the absolute configuration of **5a**.

To the best of our knowledge, the highly stereoselective synthesis of compound **5a** is the first time that this promising synthetic intermediate has been accessed.[9] Existing methods for the direct epoxidation of **4a** have only given poor conversions.[10–13] Indirect approaches include: preparation of a racemic mixture by iodo-lactonization,[14,15] a multiple-step synthesis using compounds, such as (−)-(*S*)-malic acid from the chiral pool,[16] or use of Jacobsen's method for the hydrolytic kinetic resolution of the racemic mixture.[9] Even though **5a** has been used in several academic and industrial syntheses, including preparation of a racemic mixture of the crucial intermediate of the famous medicine atorvastatin (Lipitor) used to control cholesterol levels, poor conversions are problematic.[9,14–16] Now that we have developed a highly stereoselective desymmetrization synthesis of **5a**, the above-mentioned procedures can be circumvented. We believe that more syntheses based on our approach will soon become available.

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

Experimental Section

Representative experimental procedure: $VO(OiPr)_3$ (2.5 μL, 0.0104 mmol) was added to a solution of **1a** (11.2 mg, 0.0210 mmol) in CH_2Cl_2 (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 sequentially added, and the mixture was stirred at the same temperature for 10 h (progress of the epoxidation was monitored by TLC). Saturated aqueous Na_2SO_3 was then added and the reaction mixture was stirred for 1 h at 0 °C before the reaction mixture was warmed to room temperature, extracted with Et_2O, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel to provide the epoxy alcohol **3a** (52 % yield, 95 % *ee*). Determination of the *ee* values for the epoxy alcohols is provided in the Supporting Information.

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