

# Tungsten-Catalyzed Regio- and Enantioselective Aminolysis of *trans*-2,3-Epoxy Alcohols: An Entry to Virtually Enantiopure Amino Alcohols\*\*

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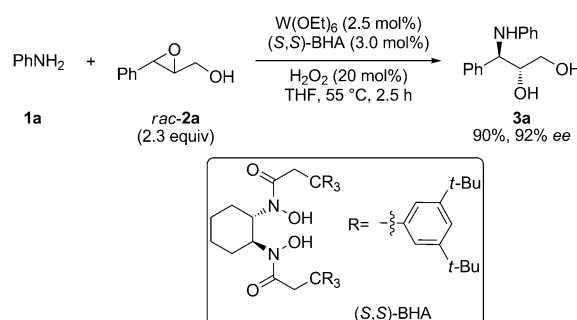
**Abstract:** The first catalytic enantioselective aminolysis of *trans*-2,3-epoxy alcohols has been accomplished. This stereospecific ring-opening process was efficiently promoted by a tungsten/bis(hydroxamic acid) catalytic system, furnishing various anti-3-amino-1,2-diols with excellent regiocontrol and high enantioselectivities (up to 95 % *ee*). Moreover, virtually enantiopure 3-amino-1,2-diols could be obtained by the sequential combination of two reactions that both involve the use of a chiral catalyst.

Substituted 3-amino-1,2-diols are a characteristic structural unit present in numerous biologically active compounds, such as leukotriene antagonists,<sup>[1]</sup> human carbonic anhydrase inhibitors,<sup>[2]</sup> and anti-inflammatory agents.<sup>[3]</sup> Furthermore, 3-amino-1,2-diols are also important synthetic intermediates of cardiovascular,<sup>[4]</sup> antibacterial,<sup>[5]</sup> and sedative agents,<sup>[6]</sup> selective norepinephrine reuptake inhibitors,<sup>[7]</sup> and drug candidates for the treatment of conditions that are ameliorated by monoamine reuptake.<sup>[8]</sup> Most of these biologically important molecules are required to be virtually enantiopure (>99.8 % *ee*, <0.1 % of the other enantiomer) for the pharmaceutical applications. Therefore, it is highly desirable to develop a direct catalytic approach to prepare enantioenriched 3-amino-1,2-diols starting from readily available precursors. Although the enantioselective ring opening of epoxides using various nucleophiles, such as azides,<sup>[9a,b]</sup> amines,<sup>[9c–h]</sup> water,<sup>[9i–m]</sup> alcohols,<sup>[9d,h,l,m]</sup> phenols,<sup>[9h,l–p]</sup> thiols,<sup>[9q,r]</sup> halides,<sup>[9s–v]</sup> and carbon nucleophiles,<sup>[9w–aa]</sup> has been intensively studied over the past decades, and tremendous progress has been achieved, excellent results are usually obtained with unfunctionalized terminal or *meso* epoxides, whereas the kinetic resolution of 2,3-epoxy alcohols is still elusive.<sup>[10,11]</sup> The challenge of this reaction lies not only in facial selectivity, but also in regiocontrol. Recently, our group reported the first

catalytic regioselective and stereospecific ring opening of 2,3-epoxy alcohols promoted by achiral tungsten salts.<sup>[12]</sup> As a continuation of our research in this field, we herein report the first enantioselective aminolysis of 2,3-epoxy alcohols with various amines as the nucleophiles using our tungsten/bis(hydroxamic acid) (W-BHA) catalytic system. Remarkably, this catalyst can promote both the epoxidation and the ring-opening reaction providing a new access to virtually enantiopure 3-amino-1,2-diols.

For the optimization of the reaction conditions, we used aniline (**1a**) and racemic *trans*-2,3-epoxycinnamyl alcohol (**2a**) as the standard substrates. After careful screening of the ligands, solvents, and temperature, we succeeded in establishing suitable reaction conditions for the kinetic resolution of 2,3-epoxy alcohols through enantioselective aminolysis (Scheme 1).<sup>[13]</sup>

The substrate scope of this reaction was then evaluated (Table 1). We first varied the structure of the amine: Diversely substituted anilines (**1a–k**), heterocyclic amines



**Scheme 1.** Optimized reaction conditions for the asymmetric ring opening of *trans*-2,3-epoxycinnamyl alcohol with aniline as the nucleophile.

(**1l** and **1m**), as well as secondary aromatic amines (**1n–u**) were reacted with **2a**. Generally, all of the reactions proceeded smoothly at 55 °C in the presence of the W-BHA catalytic system (2.5 or 5 mol %), providing the products **3a–u** in 71–95 % yield and 84–93 % *ee*. Remarkably, all of the reactions proceeded with complete regioselectivity in favor of the formation of the C3 regioisomers. Subsequently, we studied the substrate scope further by varying the structure of the 2,3-epoxy alcohols. For substituted *trans*-3-phenylglycidol, the reactions provided the products **3v–bb** in 78–95 % yield, with complete regioselectivity, and 90–95 % *ee*. Aliphatic *trans*-2,3-epoxy alcohols turned out to be less reactive and thus higher catalyst loadings (10 mol %) and longer reaction

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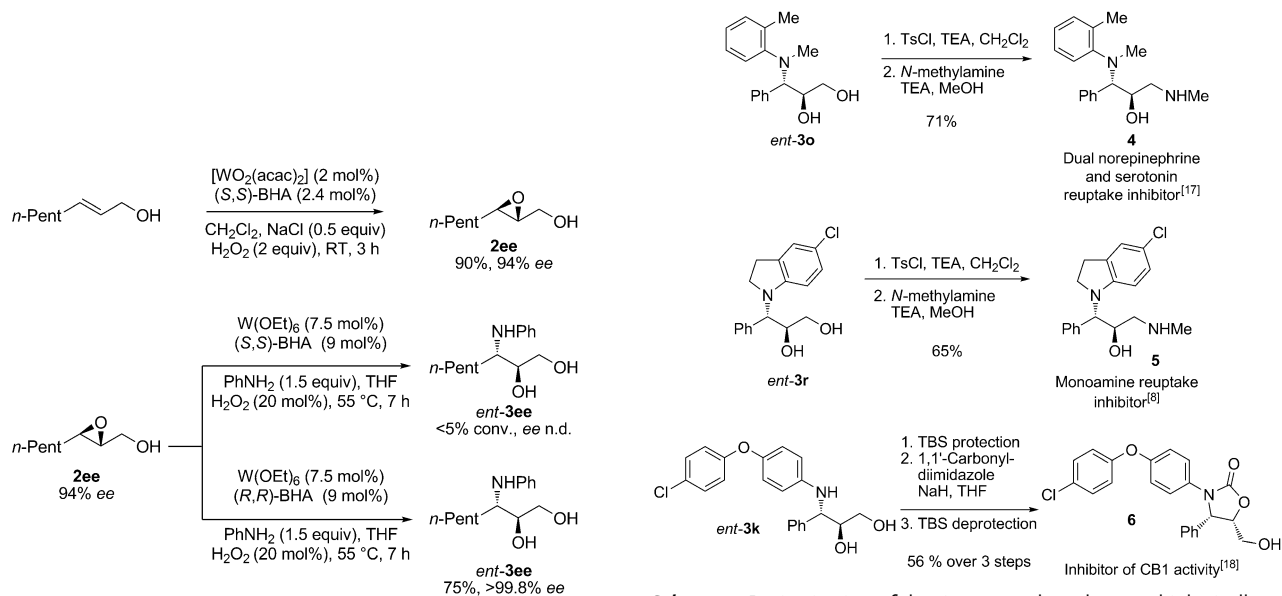
[\*\*] The Japan Science Promotion Foundation (JSP-ACT-C) and the National Institutes of Health (NIH, 2R01GM068433) are greatly appreciated for providing financial support. C.W. thanks the Alexander von Humboldt Foundation for his postdoctoral fellowship.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201408732>.

**Table 1:** Asymmetric ring-opening reactions of *trans*-2,3-epoxy alcohols with various amines as the nucleophiles.<sup>[a]</sup>

| $  \begin{array}{c}  \text{R}^1\text{-N(R}^2\text{)} \\    \\  \text{H}  \end{array}  + \text{rac-2}  \xrightarrow[\text{THF, 55 }^\circ\text{C, 2.5-24 h}]{\text{W(OEt)}_6 \text{ (2.5-10 mol\%)} \\ \text{(S,S)-BHA (3-12 mol\%)} \\ \text{H}_2\text{O}_2 \text{ (20 mol\%)}}  \begin{array}{c}  \text{R}^1\text{-N(R}^2\text{)} \\    \quad   \\  \text{R}^5 \quad \text{R}^4 \\    \quad   \\  \text{HO} \quad \text{OH}  \end{array}  \quad \text{3a-jj}  $ |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <br><b>3a-k</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                  | <b>3a</b> R <sup>1</sup> =Ph 90%, 92% ee<br><b>3e</b> R <sup>1</sup> =3,5-(MeO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> 90%, 92% ee<br><b>3i</b> R <sup>1</sup> =2-naphthyl 88%, 92% ee                                                                                                                                                                                                                                                                                                             |
| <br><b>3b</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                    | <b>3b</b> R <sup>1</sup> =3,4-Me <sub>2</sub> C <sub>6</sub> H <sub>3</sub> 87%, 92% ee<br><b>3f</b> R <sup>1</sup> =4-BrC <sub>6</sub> H <sub>4</sub> 84%, 90% ee<br><b>3j</b> R <sup>1</sup> =4-NH <sub>2</sub> SO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> 82%, 84% ee                                                                                                                                                                                                                            |
| <br><b>3c</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                    | <b>3c</b> R <sup>1</sup> =4-MeOC <sub>6</sub> H <sub>4</sub> 91%, 92% ee<br><b>3g</b> R <sup>1</sup> =4-FC <sub>6</sub> H <sub>4</sub> 87%, 90% ee<br><b>3k</b> R <sup>1</sup> =4-(4'-ClC <sub>6</sub> H <sub>4</sub> )OC <sub>6</sub> H <sub>4</sub> 95%, 92% ee                                                                                                                                                                                                                                      |
| <br><b>3d</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                    | <b>3d</b> R <sup>1</sup> =2-MeOC <sub>6</sub> H <sub>4</sub> 85%, 90% ee<br><b>3h</b> R <sup>1</sup> =1-naphthyl 92%, 90% ee                                                                                                                                                                                                                                                                                                                                                                           |
| <br><b>3l</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                    | <b>3l</b> 94%, 86% ee                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <br><b>3m</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                    | <b>3m</b> 71%, 90% ee                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <br><b>3n-q</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                  | <b>3n</b> R <sup>1</sup> =Ph, R <sup>2</sup> =Me 86%, 91% ee<br><b>3o</b> R <sup>1</sup> =2-MeC <sub>6</sub> H <sub>4</sub> , R <sup>2</sup> =Me 84%, 90% ee<br><b>3p</b> R <sup>1</sup> =4-MeOC <sub>6</sub> H <sub>4</sub> , R <sup>2</sup> =Me 89%, 90% ee<br><b>3q</b> R <sup>1</sup> =4-MeOC <sub>6</sub> H <sub>4</sub> , R <sup>2</sup> =Bn 83%, 87% ee                                                                                                                                         |
| <br><b>3r</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                    | <b>3r</b> 85%, 92% ee                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <br><b>3s</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                    | <b>3s</b> 88%, 92% ee                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <br><b>3t</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                    | <b>3t</b> 83%, 93% ee                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <br><b>3u</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                    | <b>3u</b> 81%, 93% ee                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <br><b>3v-y</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                  | <b>3v</b> R <sup>1</sup> =Ph, R <sup>3</sup> =4-FC <sub>6</sub> H <sub>4</sub> 87%, 94% ee<br><b>3w</b> R <sup>1</sup> =4-MeOC <sub>6</sub> H <sub>4</sub> , R <sup>3</sup> =4-BrC <sub>6</sub> H <sub>4</sub> 95%, 90% ee<br><b>3x</b> R <sup>1</sup> =4-BrC <sub>6</sub> H <sub>4</sub> , R <sup>3</sup> =4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> 78%, 95% ee<br><b>3y</b> R <sup>1</sup> =4-BrC <sub>6</sub> H <sub>4</sub> , R <sup>3</sup> =4-BrC <sub>6</sub> H <sub>4</sub> 91%, 90% ee |
| <br><b>3z</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                    | <b>3z</b> 85%, 94% ee                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <br><b>3aa</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                   | <b>3aa</b> 79%, 92% ee                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <br><b>3bb</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                   | <b>3bb</b> 84%, 90% ee                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <br><b>3cc-gg</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                | <b>3cc</b> R <sup>1</sup> =4-BrC <sub>6</sub> H <sub>4</sub> , R <sup>3</sup> =Et 72%, 94% ee<br><b>3ee</b> R <sup>1</sup> =Ph, R <sup>3</sup> = <i>n</i> -Pent 77%, 94% ee<br><b>3gg</b> R <sup>1</sup> =Ph, R <sup>3</sup> =CH <sub>2</sub> Bn 70%, 92% ee                                                                                                                                                                                                                                           |
| <br><b>3dd</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                   | <b>3dd</b> R <sup>1</sup> =Ph, R <sup>3</sup> = <i>n</i> -Pr 84%, 92% ee<br><b>3ff</b> R <sup>1</sup> =Ph, R <sup>3</sup> = <i>n</i> -Hex 75%, 94% ee                                                                                                                                                                                                                                                                                                                                                  |
| <br><b>3hh</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                   | <b>3hh</b> 35%, 40% ee                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <br><b>3ii</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                   | <b>3ii</b> 31%, 74% ee                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <br><b>3jj</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                   | <b>3jj</b> 64%, 58% ee                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |

[a] Unless otherwise specified, all reactions were performed with amine **1** (0.25 mmol), racemic *trans*-2,3-epoxy alcohol **2** (2.3 equiv), W(OEt)<sub>6</sub> (*x* mol%), BHA (1.2*x* mol%), and H<sub>2</sub>O<sub>2</sub> (30%, 20 mol%) at 55 °C in THF (2.5 mL). For catalyst loadings and reaction times, see the Supporting Information, p. 4. Yields of isolated products are given. All *ee* values were determined by HPLC analysis on a chiral stationary phase. Bn = benzyl.


**Scheme 3.** Derivatization of the ring-opened products to biologically active compounds in optically pure form. TBS = *tert*-butyldimethylsilyl, TEA = triethylamine, Ts = *para*-toluenesulfonyl.

times (7 or 24 h) were required to achieve good conversions. In these cases, the reactions yielded the products **3cc–gg** in 70–84% yield, with high regioselectivities (C3/C2 > 95:5), and with excellent asymmetric induction (92–94% *ee*). Remarkably, all of the C3 regioisomers of **3cc–3gg** could be easily separated from the corresponding minor C2 regioisomers through column chromatography. Limitations of this method were revealed by the reactions of *cis*-disubstituted, trisubstituted, and terminal 2,3-epoxy alcohols, which led to low yields (31–64%) and enantioselectivities (40–74% *ee*; **3hh–3jj**).

As the ring-opening process is a kinetic resolution of racemic 2,3-epoxy alcohols, we selected two reactions to determine the *s* factors. In both cases, the recovered 2,3-epoxy alcohols were obtained with good enantioselectivities.<sup>[14]</sup>

Recently, our group developed a tungsten-catalyzed enantioselective epoxidation of allylic alcohols using the same BHA as the ligand.<sup>[15]</sup> Thus, we tested the possibility of combining the epoxidation and the ring-opening reaction in a one-pot procedure. Unfortunately, the results were not promising at all.

This observation suggested that the catalysts required for epoxidation and ring opening may be enantiomers. Indeed, the enantioenriched **2ee** provided by the tungsten-catalyzed epoxidation employing (S,S)-BHA barely reacted with aniline in the presence of (S,S)-BHA-W, but reacted smoothly with the (R,R)-BHA-W catalyst to furnish **3ee** almost exclusively (> 99.8% *ee*, Scheme 2).

These amazing results open a new entry to virtually enantiopure compounds by combining a first asymmetric reaction with a kinetic resolution process of the resulting functional group.<sup>[16]</sup> Remarkably, *ee* values of > 99.8% are generally rather difficult to achieve unless an enzyme is employed as the catalyst. By implementation of our strategy, a variety of virtually optically pure amino alcohols (up to > 99.8% *ee*) were successfully prepared, and the results are summarized in Table 2. It is noteworthy that compound **3j** was reported to be a human carbonic anhydrase IX (hCA IX) inhibitor.<sup>[2]</sup>

As an illustration of the utility of this method, the three biologically active compounds **4**,<sup>[17]</sup> **5**,<sup>[8]</sup> and **6**<sup>[18]</sup> were readily synthesized through derivatization of the ring-opening products **ent-3o**, **ent-3r**, and **ent-3k** (Scheme 3).

In summary, we have developed the first catalytic enantioselective aminolysis of 2,3-epoxy alcohols, which was efficiently promoted by a tungsten/bis(hydroxamic acid) catalytic system. This kinetic resolution method featured a broad substrate scope and was applicable to various amines and a variety of *trans*-2,3-epoxy alcohols. Furthermore, the sequential reaction process combining epoxidation and ring opening (kinetic resolution) provides a new route for the preparation of virtually enantiopure products of pharmaceutical interest.

**Table 2:** Synthesis of virtually enantiopure compounds through combined asymmetric routes.<sup>[a–c]</sup>

|                                                                                                                                              |                                                                                                                                                                |
|----------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                              |                                                                                                                                                                |
| <b>Step 1:</b>                                                                                                                               |                                                                                                                                                                |
| <br><b>2a</b><br>87%, 94% <i>ee</i>                                                                                                          | <br><b>2aa</b><br>87%, 84% <i>ee</i>                                                                                                                           |
| <br><b>2hh</b> <sup>[d]</sup><br>92%, 95% <i>ee</i>                                                                                          | <br><b>2ii</b><br>88%, 90% <i>ee</i>                                                                                                                           |
| <br><i>ent-2a</i> <sup>[d,e]</sup> R=Ph, 87%, >94% <i>ee</i><br><i>ent-2ee</i> <sup>[d]</sup> R=n-Pent, 90%, >94% <i>ee</i>                  |                                                                                                                                                                |
| <b>Step 2:</b>                                                                                                                               |                                                                                                                                                                |
| <br><b>3a</b> R <sup>4</sup> =Ph<br>91%, >99.8% <i>ee</i><br>x=2.5, 2.5 h                                                                    | <br><b>3g</b> R <sup>4</sup> =4-FC <sub>6</sub> H <sub>4</sub><br>87%, >99.8% <i>ee</i><br>x=2.5, 5 h                                                          |
| <br><b>3j</b> R <sup>4</sup> =4-NH <sub>2</sub> SO <sub>2</sub> C <sub>6</sub> H <sub>4</sub><br>75%, >99.8% <i>ee</i><br>x=5, 7 h           | <br><i>ent-3k</i> <sup>[f]</sup> R <sup>4</sup> =4-(4-ClC <sub>6</sub> H <sub>4</sub> )OC <sub>6</sub> H <sub>4</sub><br>95%, >99.8% <i>ee</i><br>x=2.5, 2.5 h |
| <br><i>ent-3o</i> <sup>[f]</sup> R <sup>4</sup> =2-MeC <sub>6</sub> H <sub>4</sub> , R <sup>5</sup> =Me<br>82%, >99.3% <i>ee</i><br>x=5, 7 h | <br><b>3p</b> R <sup>4</sup> =4-MeOC <sub>6</sub> H <sub>4</sub> , R <sup>5</sup> =Me<br>90%, >99.8% <i>ee</i><br>x=2.5, 5 h                                   |
| <br><b>3q</b> R <sup>4</sup> =4-MeOC <sub>6</sub> H <sub>4</sub> , R <sup>5</sup> =Bn<br>81%, >99.8% <i>ee</i><br>x=5, 7 h                   | <br><i>ent-3r</i> <sup>[f]</sup><br>94%, >99.8% <i>ee</i><br>x=2.5, 5 h                                                                                        |
| <br><i>ent-3ee</i> <sup>[g]</sup><br>75%, >99.8% <i>ee</i><br>x=7.5, 7 h                                                                     | <br><i>ent-3hh</i> <sup>[f,h]</sup><br>64%, >98.5% <i>ee</i><br>x=10, 24 h                                                                                     |
| <br><b>3ii</b> <sup>[f]</sup><br>38%, >99.2% <i>ee</i><br>x=10, 24 h                                                                         | <br><b>3aa</b><br>74%, >99.0% <i>ee</i><br>x=10, 7 h                                                                                                           |

[a] For detailed reaction conditions, see the Supporting Information, pp. 16–17.  
 [b] Yields of the isolated products. [c] All *ee* values were determined by HPLC analysis on a chiral stationary phase. [d] (S,S)-BHA was employed. [e] [WO<sub>2</sub>(acac)<sub>2</sub>] (5 mol%) and BHA (5.5 mol%) were used. [f] (R,R)-BHA was employed. [g] Aniline (1.5 equiv). [h] Epoxide (1.5 equiv).

Received: September 2, 2014  
 Published online: October 19, 2014

**Keywords:** amino alcohols · kinetic resolution · regioselectivity · ring opening · tungsten

- O. Rachlin, D. Kirstein, Patent WO9719925A1, **1997**.
- A. Thiry, A. Delaen, L. Goossens, R. Houssin, M. Ledecq, A. Frankart, J.-M. Dogné, J. Wouters, C. T. Supuran, J.-P. Hénichart, B. Masereel, *Eur. J. Med. Chem.* **2009**, *44*, 511–518.
- M. Berger, H. Rehwinkel, E. May, H. Schaecke, Patent WO2010009814A1, **2010**.
- P. M. Manoury, J. L. Binet, J. Rousseau, F. M. Lefevre-Borg, I. G. Cavero, *J. Med. Chem.* **1987**, *30*, 1003–1011.
- a) C.-L. J. Wang, W. A. Gregory, M. A. Wuonola, *Tetrahedron* **1989**, *45*, 1323–1326; b) W. A. Gregory, D. R. Brittelli, C.-L. J. Wang, M. A. Wuonola, R. J. McRipley, D. C. Eustice, V. S. Eberly, P. T. Bartholomew, A. M. Slee, M. Forbes, *J. Med. Chem.* **1989**, *32*, 1673–1681.

- [6] R. Giani, E. Marinone, G. Melillo, M. Borsa, G. C. Tonon, *Arzneim.-Forsch.* **1988**, *38*, 1139–1141.
- [7] A. T. Vu, S. T. Cohn, P. Zhang, C. Y. Kim, P. E. Mahaney, J. A. Bray, G. H. Johnston, E. J. Koury, S. A. Cosmi, D. C. Deecher, V. A. Smith, J. E. Harrison, L. Leventhal, G. T. Whiteside, J. D. Kennedy, E. J. Trybulski, *J. Med. Chem.* **2010**, *53*, 2051–2062.
- [8] C. Y. Kim, P. E. Mahaney, E. J. Trybulski, P. Zhang, E. A. Terefenko, C. C. McComas, M. A. Marella, R. D. Coghlan, G. D. Heffernan, S. T. Cohn, A. T. Vu, J. P. Sabatucci, F. Ye, Patent US20050222148A1, **2005**.
- [9] a) L. E. Martínez, J. L. Leighton, D. H. Carsten, E. N. Jacobsen, *J. Am. Chem. Soc.* **1995**, *117*, 5897–5898; b) J. F. Larrow, S. E. Schaus, E. N. Jacobsen, *J. Am. Chem. Soc.* **1996**, *118*, 7420–7421; c) G. Bartoli, M. Bosco, A. Carlone, M. Locatelli, M. Massaccesi, P. Melchiorre, L. Sambri, *Org. Lett.* **2004**, *6*, 2173–2176; d) C. Schneider, A. R. Sreekanth, E. Mai, *Angew. Chem. Int. Ed.* **2004**, *43*, 5691–5694; *Angew. Chem.* **2004**, *116*, 5809–5812; e) K. Arai, M. M. Salter, Y. Yamashita, S. Kobayashi, *Angew. Chem. Int. Ed.* **2007**, *46*, 955–957; *Angew. Chem.* **2007**, *119*, 973–975; f) K. Arai, S. Lucarini, M. M. Salter, K. Ohta, Y. Yamashita, S. Kobayashi, *J. Am. Chem. Soc.* **2007**, *129*, 8103–8111; g) B. Plancq, T. Ollevier, *Chem. Commun.* **2012**, *48*, 3806–3808; h) D. E. White, P. M. Tadross, Z. Lu, E. N. Jacobsen, *Tetrahedron* **2014**, *70*, 4165–4180; i) M. Tokunaga, J. F. Larrow, F. Kakiuchi, E. N. Jacobsen, *Science* **1997**, *277*, 936–938; j) S. E. Schaus, B. D. Brandes, J. F. Larrow, M. Tokunaga, K. B. Hansen, A. E. Gould, M. E. Furrow, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 1307–1315; k) L. Zhao, B. Han, Z. Huang, M. Miller, H. Huang, D. S. Malashock, Z. Zhu, A. Milan, D. E. Robertson, D. P. Weiner, M. J. Burk, *J. Am. Chem. Soc.* **2004**, *126*, 11156–11157; l) J. M. Ready, E. N. Jacobsen, *J. Am. Chem. Soc.* **2001**, *123*, 2687–2688; m) J.-M. Ready, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2002**, *41*, 1374–1377; *Angew. Chem.* **2002**, *114*, 1432–1435; n) T. Iida, N. Yamamoto, S. Matsunaga, H.-G. Woo, M. Shibasaki, *Angew. Chem. Int. Ed.* **1998**, *37*, 2223–2226; *Angew. Chem.* **1998**, *110*, 2383–2386; o) J. M. Ready, E. N. Jacobsen, *J. Am. Chem. Soc.* **1999**, *121*, 6086–6087; p) S. Matsunaga, J. Das, J. Roels, E. M. Vogl, N. Yamamoto, T. Iida, K. Yamaguchi, M. Shibasaki, *J. Am. Chem. Soc.* **2000**, *122*, 2252–2260; q) T. Iida, N. Yamamoto, H. Sasai, M. Shibasaki, *J. Am. Chem. Soc.* **1997**, *119*, 4783–4784; r) Z. Wang, W. K. Law, J. Sun, *Org. Lett.* **2013**, *15*, 5964–5966; s) S. E. Denmark, P. A. Barsanti, K.-T. Wong, R. A. Stavenger, *J. Org. Chem.* **1998**, *63*, 2428–2429; t) B. Tao, M. M.-C. Lo, G.-C. Fu, *J. Am. Chem. Soc.* **2001**, *123*, 353–354; u) X. Pu, X. Qi, J. M. Ready, *J. Am. Chem. Soc.* **2009**, *131*, 10364–10365; v) J. A. Kalow, A. G. Doyle, *J. Am. Chem. Soc.* **2010**, *132*, 3268–3269; w) N. Oguni, Y. Miyagi, K. Itoh, *Tetrahedron Lett.* **1998**, *39*, 9023–9026; x) S. E. Schaus, E. N. Jacobsen, *Org. Lett.* **2000**, *2*, 1001–1004; y) F. Bertozzi, P. Crotti, F. Macchia, M. Pineschi, B. L. Feringa, *Angew. Chem. Int. Ed.* **2001**, *40*, 930–932; *Angew. Chem.* **2001**, *113*, 956–958; z) B. Trost, C. Jiang, *J. Am. Chem. Soc.* **2001**, *123*, 12907–12908; aa) M. Bandini, P. G. Cozzi, P. Melchiorre, A. Umani-Ronchi, *Angew. Chem. Int. Ed.* **2004**, *43*, 84–87; *Angew. Chem.* **2004**, *116*, 86–89.
- [10] For reviews on the regioselective ring opening of 2,3-epoxy alcohols, see: a) R. M. Hanson, *Chem. Rev.* **1991**, *91*, 437–475; b) P. C. A. Pena, S. M. Roberts, *Curr. Org. Chem.* **2003**, *7*, 555–571.
- [11] For examples of the regioselective ring opening of 2,3-epoxy alcohols with stoichiometric promoters, see: a) M. Caron, K. B. Sharpless, *J. Org. Chem.* **1985**, *50*, 1557–1560; b) C. H. Behrens, K. B. Sharpless, *J. Org. Chem.* **1985**, *50*, 5696–5704; c) S. Y. Ko, K. B. Sharpless, *J. Org. Chem.* **1986**, *51*, 5413–5415; d) M. Caron, P. R. Carlier, K. B. Sharpless, *J. Org. Chem.* **1988**, *53*, 5185–5287; e) M. Onaka, K. Sugita, H. Takeuchi, Y. Izumi, *J. Chem. Soc. Chem. Commun.* **1988**, 1173–1174; f) T. K. Chakraborty, G. V. Reddy, *Tetrahedron Lett.* **1991**, *32*, 679–682; g) M. Canas, M. Poch, X. Verdaguier, A. Moyano, M. A. Pericàs, A. Riera, *Tetrahedron Lett.* **1991**, *32*, 6931–6934; h) M. Chini, P. Crotti, L. A. Flippin, C. Gardelli, E. Giovani, F. Macchia, M. Pineschi, *J. Org. Chem.* **1993**, *58*, 1221–1227; i) R. Martín, G. Islas, A. Moyano, M. A. Pericàs, A. Riera, *Tetrahedron* **2001**, *57*, 6367–6374; j) M. Sasaki, K. Tanino, M. Miyashita, *Org. Lett.* **2001**, *3*, 1765–1767; k) M. Sasaki, K. Tanino, A. Hirai, M. Miyashita, *Org. Lett.* **2003**, *5*, 1789–1791; l) M. Pastó, B. Rodríguez, A. Riera, M. A. Pericàs, *Tetrahedron Lett.* **2003**, *44*, 8369–8372; m) Y. Tomata, M. Sasaki, K. Tanino, M. Miyashita, *Tetrahedron Lett.* **2003**, *44*, 8975–8977; n) K. Surendra, N. S. Krishnaveni, K. R. Rao, *Synlett* **2004**, 506–510.
- [12] C. Wang, H. Yamamoto, *J. Am. Chem. Soc.* **2014**, *136*, 6888–6891.
- [13] For details on the optimization of the reaction conditions, see the Supporting Information, p. 3.
- [14] For details on the determination of the *s* factors and the absolute stereochemistry of the amino alcohols, see the Supporting Information, p. 18.
- [15] C. Wang, H. Yamamoto, *J. Am. Chem. Soc.* **2014**, *136*, 1222–1225.
- [16] For a review on combined asymmetric synthesis, see: a) L. Fransson, C. Moberg, *ChemCatChem* **2010**, *2*, 1523–1532; for selected examples, see: b) T. R. Hoye, J. C. Suhadolnik, *J. Am. Chem. Soc.* **1985**, *107*, 5312–5313; c) S. L. Schreiber, T. S. Schreiber, D. B. Smith, *J. Am. Chem. Soc.* **1987**, *109*, 1525–1529; d) W. R. Roush, J. A. Straub, M. S. VanNieuwenhze, *J. Org. Chem.* **1991**, *56*, 1636–1648; e) M. I. Klauck, S. G. Patel, S. L. Wiskur, *J. Org. Chem.* **2012**, *77*, 3570–3575; f) S. Xu, C.-T. Lee, G. Wang, E.-i. Negishi, *Chem. Asian J.* **2013**, *8*, 1829–1835.
- [17] A. T. Vu, S. T. Cohn, E. A. Terefenko, W. J. Moore, P. Zhang, P. E. Mahaney, E. J. Trybulski, I. Goljer, R. Dooley, J. A. Bray, G. H. Johnston, J. Leiter, D. C. Deecher, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2464–2467.
- [18] H. Liu, X. He, D. Philipps, X. Zhu, K. Yang, T. Lau, B. Wu, Y. Xie, T. N. Nguyen, X. Wang, Patent WO2008076754A2, **2008**.