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Tungsten-Catalyzed Regio-, and Enantioselective Aminolysis of *trans*-2,3-Epoxy Alcohols-New 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 our W-bishydroxamic acid catalytic system furnishing various *anti*-3-amino-1,2-diols as products in excellent regiocontrol and high enantioselectivities (up to 95 % *ee*). Moreover, virtually enantiopure 3-amino-1,2-diols could be obtained through combined asymmetric routes.

Keywords

Ring opening; Kinetic resolution; Regioselective; Amino alcohols; Tungsten-catalysis

3-Amino-1,2-diol is a characteristic structural unit present in numerous biologically active compounds such as leukotriene-antagonist,^[1] human carbonic anhydrase inhibitor,^[2] and anti-inflammatory agents.^[3] Furthermore, 3-amino-1,2-diols are also important synthetic intermediates of cardiovascular,^[4] antibacterial,^[5] sedative agents,^[6] selective norepinephrine reuptake inhibitors^[7] and drug candidates to treat conditions ameliorated by monoamine reuptake^[8]. Most of these biologically important molecules are required to be virtually enantiopure (>99.8 % *ee*, <0.1% enantiomer) for the pharmaceutical applications. Thus it is highly desirable to develop a direct catalytic approach to prepare enantioenriched 3-amino-1,2-diols starting from readily available precursors. Although enantioselective ring-opening of epoxides using various nucleophiles, such as azide,^[9a,b] amines,^[9c-h] water,^[9i-m] alcohols,^[9d,h,l,m] phenols,^[9h,l-p] thiols,^[9q,r] halides,^[9s-v] and carbon nucleophiles^[9w-aa] has been intensively studied in the past decades and tremendous progress has been achieved, excellent results are usually obtained in the case of unfunctionalized terminal or *meso* epoxides, while kinetic resolution of 2,3-epoxy alcohols is still elusive.^[10,11] The challenge of this reaction remains 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 W-salts.^[12, 13] As a continuation of our research in this field, we report the first asymmetric aminolysis of 2,3-epoxy alcohols with various amines as nucleophiles using our W-bishydroxamic acid (W-BHA) catalytic system. Remarkably, this catalyst can promote both epoxidation and ring-opening reaction providing a new access to virtually enantiopure 3-amino-1,2-diols.

For optimization of the reaction conditions, we used aniline (**1a**) and racemic *trans*-2,3-epoxy cinnamyl alcohol (**2a**) as standard substrates. After careful screening of ligands, solvents and temperature we succeeded in establishing the optimum reaction conditions for the kinetic resolution of 2,3-epoxy alcohols through enantioselective aminolysis (Scheme 1).^[14]

The substrate spectrum of this reaction was then evaluated (Table 1). We first varied the structure of the amines: diverse substituted anilines **1a–k**, heterocyclic amines **1l** and **1m**, as well as secondary aromatic amines **1n–u** were reacted with **2a**. Generally, all the reactions proceeded smoothly at 55 °C under the catalysis of 2.5 or 5 mol% W-BHA providing the products **3a–u** in 71–95 % yield and 84–93 % *ee*. Remarkably, all the reactions proceeded with complete regioselectivity in favor of the formation of C-3-regioisomers. Subsequently, we studied the substrate scope further by varying the structure of 2,3-epoxy alcohols. In the cases of substituted *trans*-3-phenylglycidol all the reactions provided the products **3v–bb** in 78–95 % yield, complete regioselectivities and 90–95 % *ee*. Aliphatic *trans*-2,3-epoxy alcohols turned out to be less reactive and thus higher catalyst loading (10 mol%) and longer reaction time (7 or 24 h) were required to achieve good conversions. In these cases the reactions yielded the products **3cc–gg** in 70–84 % yield, high regioselectivities (C3:C2 > 95:5) with excellent asymmetric induction (92–94 % *ee*). Remarkably, all the C-3-regioisomers of **3cc–3gg** could be easily separated from the corresponding minor C-2-regioisomers through column chromatography. One limitation of this method was observed in the cases of *cis*-, trisubstituted and terminal 2,3-epoxy alcohols which led to low yields (31–64 %) and enantioselectivities (40–74 % *ee*).

Since 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 in good enantioselectivities.^[15]

Recently, our group developed a W-catalyzed enantioselective epoxidation of allylic alcohols using the same BHA as ligand.^[16] 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 required catalysts for epoxidation and ring-opening may be enantiomers. Indeed, the enantioenriched **2ee** provided by the W-catalyzed epoxidation employing (*S,S*)-BHA barely reacted with aniline under the catalysis of (*S,S*)-BHA-W, but reacted smoothly with (*R,R*)-BHA-W catalyst to furnish **3ee** almost exclusively (>99.8 % *ee*, Scheme 2).

These amazing results open a new entry to synthesize virtually enantiopure compounds through a combined asymmetric routes consisting of an initial asymmetric reaction followed by a kinetic resolution process of the resulting functional group.^[17] Remarkably, in general >99.8% ee would be rather difficult to achieve except enzymatic transformations. By implementation of our strategy a variety of virtually optically pure amino alcohols (up to > 99.8 % ee) have been successfully prepared and the results are summarized in Table 2. It is noteworthy that compound **3j** is reported to be a human carbonic anhydrase IX (hCA IX) inhibitor.^[2]

As an illustration of the utility of this method, three biologically active compounds **4**,^[18] **5**^[8] and **6**^[19] have been readily synthesized through derivatization of the ring-opening products *ent*-**3o**, *ent*-**3r** and *ent*-**3k** (Scheme 3).

In summary, we developed the first catalytic asymmetric aminolysis of 2,3-epoxy alcohols, which was efficiently promoted by the W-BHA catalytic system. This kinetic resolution method demonstrated a broad substrate scope and was applicable to various amines and a variety of *trans*-2,3-epoxy alcohols. Furthermore, the sequential reaction of epoxidation/ ring-opening (kinetic resolution) provides a new route to prepare virtually enantiopure products for pharmaceutical use.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.

Optimum reaction conditions for the asymmetric ring-opening of *trans*-2,3-epoxy cinnamyl alcohol with aniline as nucleophile.

Scheme 2.

Investigation of the Ligand-effect on the Outcome of the Ring-opening Reaction.

Scheme 3.

Derivatization of the ring-opening products to biologically active compounds in optically pure form.

Table 1

Kinetic resolution by ring-opening reactions of *trans*-2,3-epoxy alcohols with various amines as nucleophiles.

[a–d]

1 + **rac-2** (2.3 equiv.) → **3a-jj**

W(OEt)₆ (2.5-10 mol%), (S, S)-BHA (3-12 mol%), H₂O₂ (20 mol%), THF, 55 °C, 2.5-24 h

3a R¹ = Ph
 90 %, 92 % ee

3b R¹ = 3,4-Me₂C₆H₃
 87 %, 92 % ee

3c R¹ = 4-MeOC₆H₄
 91 %, 92 % ee

3a-k

3d R¹ = 2-MeOC₆H₄
 85 %, 90 % ee

3e R¹ = 3,5-(MeO)₂C₆H₃
 90 %, 92 % ee

3f R¹ = 4-BrC₆H₄
 84 %, 90 % ee

3g R¹ = 4-FC₆H₄
 87 %, 90 % ee

3h R¹ = 1-Naphthyl
 92 %, 90 % ee

3i R¹ = 2-Naphthyl
 88 %, 92 % ee

3j R¹ = 4-NH₂SO₂C₆H₄
 82 %, 84 % ee

3k R¹ = 4-(4'-Cl-C₆H₄)OC₆H₄
 95 %, 92 % ee

3l, 94 %, 86 % ee

3m, 71 %, 90 % ee

3n-q

3n R¹ = Ph, R² = Me
 86 %, 91 % ee

3o R¹ = 2-MeC₆H₄, R² = Me
 84 %, 90 % ee

3p R¹ = 4-MeOC₆H₄, R² = Me
 89 %, 90 % ee

3q R¹ = 4-MeOC₆H₄, R² = Bn
 83 %, 87 % ee

3r, 85 %, 92 % ee

3s, 88 %, 92 % ee

3t, 83 %, 93 % ee

3u, 81 %, 93 % ee

3v-y

3v R¹ = Ph, R³ = 4-FC₆H₄
 87 %, 94 % ee

3w R¹ = 4-MeOC₆H₄, R³ = 4-BrC₆H₄
 95 %, 90 % ee

3x R¹ = 4-BrC₆H₄, R³ = 4-NO₂C₆H₄
 78 %, 95 % ee

3y R¹ = 4-BrC₆H₄, R³ = 4-BrC₆H₄
 91 %, 90 % ee

3z, 85 %, 94 % ee

3aa, 79 %, 92 % ee

3bb, 84 %, 90 % ee

3cc R¹ = 4-BrC₆H₄, R³ = Et
 72 %, 94 % ee

3ff R¹ = Ph, R³ = *n*-Hex
 75 %, 94 % ee

3dd R¹ = Ph, R³ = *n*-Pr
 84 %, 92 % ee

3gg R¹ = Ph, R³ = CH₂Bn
 70 %, 92 % ee

3ee R¹ = Ph, R³ = *n*-Pent
 77 %, 94 % ee

3hh, 35 %, 40 % ee

3ii, 31 %, 74 % ee

3jj, 64 %, 58 % ee

3cc-gg

3hh, 35 %, 40 % ee

3ii, 31 %, 74 % ee

3jj, 64 %, 58 % ee

[a] Unless otherwise specified, reactions were performed on a 0.25 mmol scale of amines **1** using 2.3 equiv. racemic *trans*-2,3-epoxy alcohols (**2**) and x mol% W(OEt)₆, 1.2x mol% BHA and 20 mol% H₂O₂ (30 %) at 55 °C in 2.5mL THF.

[b] For catalyst loading and reaction time, see Supporting Information (SI): Page 4.

[c] Yields of the isolated products.

[d] All enantiomeric excesses were determined by HPLC-analysis on chiral stationary phase.

Table 2

Synthesis of virtually enantiopure compounds through combined asymmetric routes.^[a–h] ^[a] For detailed reaction conditions, see SI page 16–17.^[b] Yields of the isolated products.

[c] All enantiomeric excesses were determined by HPLC-analysis on chiral stationary phase.

[d] (S, S)-BHA was employed.

[e] 5 mol% $\text{WO}_2(\text{acac})_2$ and 5.5 mol% BHA were used.

[f] (R, R)-BHA was employed.

[g] 1.5 Equiv aniline was used.

[h] 1.5 Equiv epoxide was used.