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Nickel-Catalyzed Regio- and Enantioselective Aminolysis of 3,4-Epoxy Alcohols

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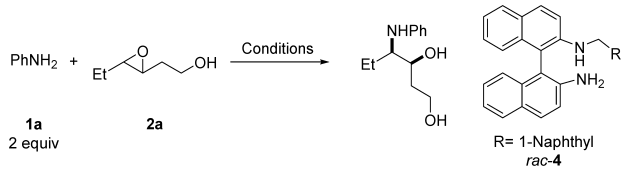
Supporting Information

ABSTRACT: The first catalytic regio- and enantioselective aminolysis of 3,4-epoxy alcohols has been accomplished. Under the catalysis of $Ni(ClO_4)_2 \cdot 6H_2O$, the C4 selective ring opening of various 3,4-epoxy alcohols proceeded in a stereospecific manner with high regioselectivities. Furthermore, with the Ni-BINAM catalytic system the enantioselective ring opening of 3,4-epoxy alcohols furnished various γ-hydroxy-δ-amino alcohols as products with complete regiocontrol and high enantioselectivities (up to 94% ee).

In recent years our group has developed various methods of asymmetric epoxidation of homoallylic alcohols furnishing direct access to highly enantioenriched 3,4-epoxy alcohols.[1] Regioselective and stereospecific ring opening of enantioenriched 3,4-epoxy alcohols with diverse nucleophiles could provide a straightforward entry to various chiral building blocks. For instance, a variety of optically active γ-hydroxy-δ-amino alcohols could be achieved through C4-selective aminolysis of enantioenriched 3,4-epoxy alcohols. δ-Amino alcohols are of pharmaceutical interest because they exhibit anesthetic activity and antagonist activity in calcium T-type channels.[2] Furthermore, δ-amino alcohols can serve as important synthetic intermediates for the synthesis of γ-amino acids.[3] Although regioselective ring opening of epoxy alcohols has been intensively studied in the last decades, good results have been obtained only in the cases of 2,3-epoxy alcohols.[4,5] In contrast, the regioselective aminolysis of 3,4-epoxy alcohols has remained elusive.[6] The challenge of this reaction lies in the control of the site preference of the nucleophilic attack through a relatively remotely located OH moiety as a directing group. Our group recently developed the first catalytic regioselective ring-opening reactions of 2,3-epoxy alcohols catalyzed by W salts.[7] Unfortunately, this protocol is not applicable to 3,4-epoxy alcohols (Scheme 1). Herein we report the first catalytic C4-selective ring-opening reaction of 3,4-epoxy alcohols with various amines as nucleophiles using $Ni(ClO_4)_2 \cdot 6H_2O$ as the catalyst. Moreover, the Ni–BINAM catalytic system turned out to be suitable for the enantioselective version of this ring-opening reaction.

For optimization of the reaction conditions, we used aniline (**1a**) and racemic *trans*-3,4-epoxyhexan-1-ol (**2a**) as standard substrates. Epoxide **2a** is a challenging substrate for regioselective ring-opening reaction because the substituents on the two sides of the epoxide demonstrate similar steric and electronic effects.

Scheme 1. Optimum Reaction Conditions for the Regioselective Ring Opening of *trans*-3,4-Epoxyhexan-1-ol with Aniline as the Nucleophile and Comparison with the Results Using the W System



Condition A: $W(OEt)_6$, 10 mol%, MeCN, 55 °C, 24 h — 45 %, C4:C3= 58:42

Condition B: $Ni(ClO_4)_2 \cdot 6H_2O$(20 mol%), *rac*-**4** (22 mol%), Chloroform, 55 °C, 24 h — 73 %, C4:C3> 95:5

To address this challenging reaction, we first investigated a variety of metal salts as catalysts.[8] While in most cases the reactions proceeded with only low regioselectivities, $Ni(OTf)_2$ turned out to be the best catalyst, affording the product with moderately good regioselectivity (C4:C3 = 89:11). Further optimizations revealed that the use of 1,1′-dinaphthyl-2,2′-diamine (BINAM)-derived ligands had a crucial effect on the regiocontrol. After careful screening of ligands, solvents, and Ni salts we succeeded in establishing the optimum reaction conditions, under which the regioselectivity of the standard reaction was improved to an excellent level (Scheme 1).[8]

The substrate spectrum of this reaction was then evaluated (Scheme 2). First, diverse primary and secondary aromatic amines were reacted with various primary and tertiary aliphatic *trans*-3,4-epoxy alcohols under the optimum reaction conditions. Generally, all of the reactions proceeded smoothly at 55 °C to give the products **3a**–**k** in good yields (51–83%) with high regioselectivities (C4:C3 >95:5 to >99:1). One limitation of this method was observed in the case of an aliphatic *cis*-3,4-epoxy alcohol, which led to the formation of **3l** with relatively low regioselectivity.

Subsequently, we studied the use of aromatic and terminal 3,4-epoxy alcohols as precursors for the Ni-catalyzed regioselective ring-opening reaction, and the results are summarized in Scheme 3. It turned out that in most cases these reactions did not require the use of the BINAM-derivative *rac*-**4** as a ligand. Under the ligand-free conditions the products were obtained with complete regioselectivity. Only one exception was observed when an

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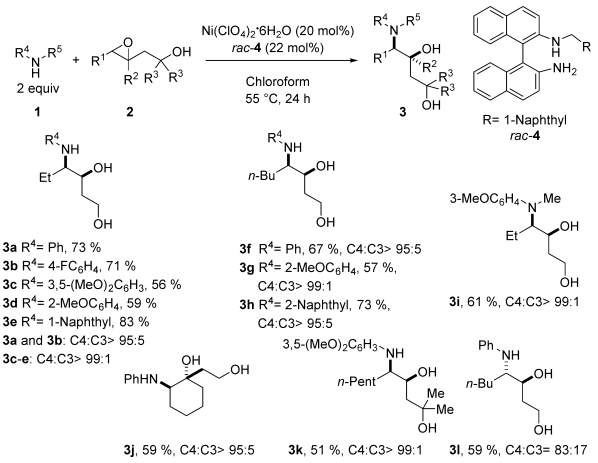
Scheme 2. Regioselective Ring-Opening Reactions of Aliphatic 3,4-Epoxy Alcohols with Various Amines as Nucleophiles[a−c]



[a]Unless otherwise specified, the ring-opening reactions were performed on a 0.25 mmol scale of racemic 3,4-epoxy alcohols **2** using 2.0 equiv of amines **1**, 20 mol % $Ni(ClO_4)_2{\cdot}6H_2O$, and 22 mol % racemic BINAM *rac*-**4** at 55 °C in 5 mL of chloroform. [b]Yields of the isolated products are shown. [c]All of the regiomeric ratios were determined by ^1H NMR spectroscopy.

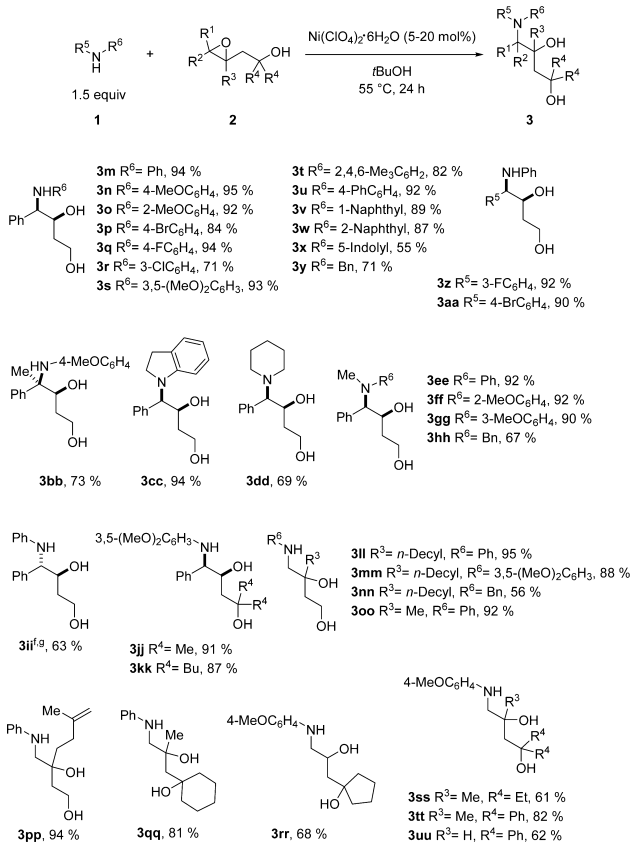
aromatic *cis*-epoxy alcohol was employed as the substrate. In this case, the product **3ii** was obtained with high regioselectivity only in the presence of the ligand *rac*-**4**. Furthermore, aliphatic amines were found to be less reactive than their aromatic analogues. Thus, in these cases a higher catalyst loading (20 mol %) was required to achieve good yields.

In order to find out whether these Ni-catalyzed ring-opening reactions proceed in a stereospecific manner, we conducted the reaction with enantioenriched (98% ee) *trans*-3,4-epoxyhexan-1-ol (**2a**) as the precursor and **1a** as the nucleophile under the same reaction conditions as used for the racemic epoxide. To our delight, the product was furnished with identical enantiomeric excess in comparison to its epoxide precursor, indicating the stereospecificity of this Ni-catalyzed reaction.[8]

Although highly enantioselective epoxidations of homoallylic alcohols are well-developed, the chiral ligands employed for these reactions are generally onerous to prepare, requiring multiple steps starting from commercially available materials.[1] Therefore, kinetic resolution of readily available racemic 3,4-epoxy alcohols by enantioselective ring opening utilizing a simple ligand is still of enormous interest. To achieve this goal, we first tested the [Co(salen)] and [Cr(salen)Cl] complexes, which are successful catalysts for the kinetic resolution of terminal, *meso*-, and aromatic epoxides.[9] However, both complexes failed to provide the product in high efficiency and excellent asymmetric induction.[10] Moreover, our W−bis(hydroxamic acid) catalytic system, which could promote highly enantioselective aminolysis of 2,3-epoxy alcohols,[7b] also was not applicable to 3,4-epoxy alcohols, giving the product with only low enantioselectivity.[10]

After obtaining these results, we decided to find or design a suitable ligand for the Ni-catalyzed kinetic resolution of 3,4-epoxy alcohols. Initially, a large number of privileged chiral ligands were screened, but in most cases the products were obtained either in racemic form or with very low enantioselectivities.[10] Only in the case of BINAM as the ligand did the reaction provide the product with moderately good enantiomeric excess (Table 1, entry 1). Encouraged by this result, we prepared

Scheme 3. Regioselective Ring-Opening Reactions of Aromatic and Terminal 3,4-Epoxy Alcohols with Various Amines as Nucleophiles[a−e]



[a]Unless otherwise specified, reactions were performed on a 0.25 mmol scale of racemic 3,4-epoxy alcohols **2** using 1.5 equiv of amines **1** and 5−20 mol % $Ni(ClO_4)_2{\cdot}6H_2O$ at 55 °C in 2.5 mL of *t*-BuOH. [b]Unless otherwise specified, the products were obtained with complete regioselectivity (C4:C3 > 99:1). [c]Catalyst loadings: 5 mol % $Ni(ClO_4)_2{\cdot}6H_2O$ for **3m−s**, **3u**, **3w**, **3z**, **3aa**, **3cc**, **3ee−gg**, **3jj−mm**, **3oo**, and **3pp**; 10 mol % $Ni(ClO_4)_2{\cdot}6H_2O$ for **3t**, **3x**, **3bb**, and **3qq-uu**; 20 mol % $Ni(ClO_4)_2{\cdot}6H_2O$ for **3y**, **3dd**, **3hh**, and **3nn**. [d]Yields of isolated products are shown. [e]All of the regiomeric ratios were determined by ^1H NMR spectroscopy. [f]C4:C3 > 95:5. [g]The reaction was performed with 10 mol % $Ni(ClO_4)_2{\cdot}6H_2O$ and 12 mol % *rac*-**4** in 5 mL of chloroform.

various BINAM derivatives and investigated them as ligands for this ring-opening reaction. Interestingly, with an N,N′-disubstituted BINAM as the ligand, both the yield and asymmetric induction diminished dramatically (entries 2 and 3). In contrast, the reactions employing an N-monoalkylated BINAM derivative as the ligand all afforded the product with relatively high enantioselectivity (entries 4−13), while the best result concerning both yield (based on aniline) and enantiomeric excess was obtained in the case of *N*-(naphthylmethyl)-BINAM (*S*)-**4** as the ligand (entry 4). Moreover, the results also indicated that the alkyl or benzyl substituent plays a crucial effect on the asymmetric induction, since the change of benzyl to either phenyl or amide resulted in total loss of the facial selectivity (entries 14 and 15). Finally, after careful screening of solvents and Ni salts, we succeeded in establishing the optimum reaction conditions, under which the product was obtained in excellent yield and enantioselectivity (entry 16).[10] The ligand (*S*)-**4** was simply prepared in a single step starting from commercially

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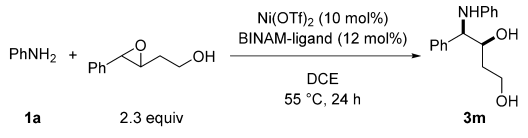
Table 1. Ligand Screening for the Enantioselective Ring Opening of *trans*-3,4-Epoxy Homocinnamyl Alcohol with Aniline as the Nucleophile[a]



4: R^2= CH_2-1-naphthyl
5: R^2= Bn
6: R^2= CH_2-3,5-$(CF_3)_2C_6H_3$
7: R^2= CH_2-3,5-(*t*Bu)$_2C_6H_3$
8: R^2= CH_2-3,5-$(OMe)_2C_6H_3$
9: R^2= CH_2-4-*t*BuC_6H_4
10: R^2= CH_2-2,4,6-$Me_3C_6H_2$
11: R^2= CH_2-2-naphthyl
12: R^2= CH_2-1-Pyrenyl
13: R^2= CH_2*c*-Hex
14: R^2= Ph
15: R^2= C=OPh
16: R^1= H
17: R^1= Bn
18: R^1= Ph

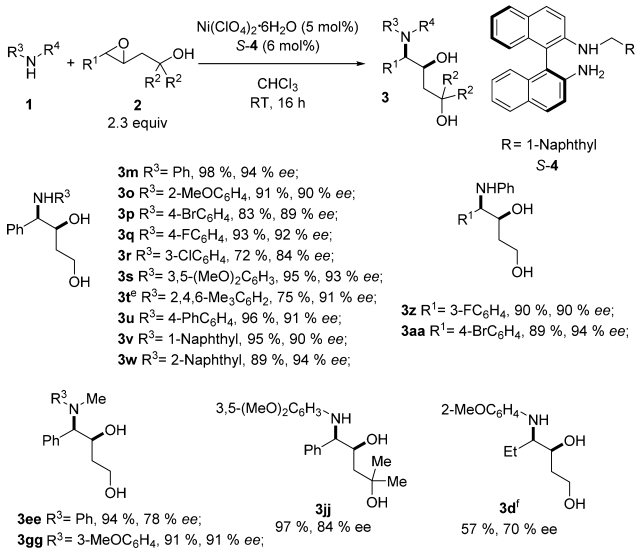
entry	ligand	yield (%)[b]	ee (%)[c]
1	**16**	60	66
2	**17**	21	18
3	**18**	23	0
4	**4**	90	85
5	**5**	89	77
6	**6**	88	55
7	**7**	86	78
8	**8**	81	76
9	**9**	85	78
10	**10**	75	76
11	**11**	78	73
12	**12**	89	85
13	**13**	87	78
14	**14**	23	0
15	**15**	25	0
16[d]	**4**	**98**	**94**
17[e]	**4**	49[f]	89

[a]Unless otherwise specified, the ring-opening reactions were performed on a 0.25 mmol scale of **1a** using 2.3 equiv of racemic epoxy homocinnamyl alcohol, 10 mol % $Ni(OTf)_2$, and 12 mol % BINAM **4**–**18** at 55 °C in 5 mL of dichloroethane. [b]Yields of the isolated products based on **1a**. [c]Determined by HPLC analysis on a chiral stationary phase. [d]The reaction was performed with 5 mol % $Ni(ClO_4)_2{\cdot}6H_2O$ and 6 mol % (*S*)-**4** in 5 mL of chloroform at room temperature. [e]The reaction was performed on a 0.50 mmol scale of racemic epoxy homocinnamyl alcohol using 0.55 equiv of **1a** with 5 mol % $Ni(ClO_4)_2{\cdot}6H_2O$ and 6 mol % (*S*)-**4** in 5 mL of chloroform at room temperature. [f]Yield of the isolated products based on the epoxide.

available BINAM and 1-(bromomethyl)naphthalene. Moreover, we also conducted the kinetic resolution with 0.55 equiv of aniline, and the reaction afforded both the product (89% ee) and the remaining epoxide (90% ee) with high enantioselectivity at 52% convertion (entry 17). The selectivity factor was determined to be 32.9.[11]

After establishing the optimum reaction conditions, we started to evaluate the scope of the enantioselective aminolysis of 3,4-epoxy alcohols, and the results are displayed in Scheme 4. Generally, the reactions between aromatic epoxy alcohols and aniline derivatives furnished the products with high enantioselectivities. Notably, the tertiary epoxy alcohol, which is not accessible through asymmetric epoxidation in an enantioselective manner, also turned out to be a suitable substrate for this kinetic resolution reaction, giving the product with good enantioselectivity. Relatively low enantiomeric excess was obtained with an aliphatic epoxide as the precursor.

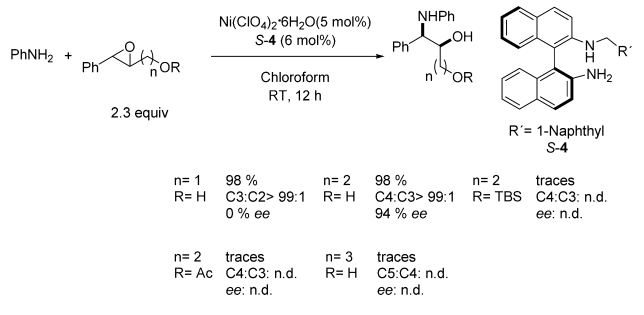
Scheme 4. Enantioselective Aminolysis of 3,4-Epoxy Alcohols[a–d,12]



[a]Unless otherwise specified, the ring-opening reactions were performed on a 0.25 mmol scale of amines **1** using 2.3 equiv of racemic 3,4-epoxy alcohols **2**, 5 mol % $Ni(ClO_4)_2{\cdot}6H_2O$, and 6 mol % (*S*)-**4** at room temperature in 5 mL of chloroform. [b]Yields of the isolated products based on the amines used. [c]All of the reactions afforded the products with complete regioselectivity, as determined by ^1H NMR spectroscopy. [d]All of the enantiomeric excesses were determined by HPLC analysis on a chiral stationary phase. [e]10 mol % $Ni(ClO_4)_2{\cdot}6H_2O$ and 12 mol % (*S*)-**4** were used. [f]The reaction was performed at 55 °C using 20 mol % $Ni(ClO_4)_2{\cdot}6H_2O$, and 22 mol % (*S*)-**4**.

To study the directing effect of the hydroxyl group, we first performed the Ni-catalyzed reaction using unfunctionalized epoxides, including *trans*-1-phenylpropylene oxide, *trans*-2,3-epoxyoctane, and stilbene oxide as substrates. In each case, only a trace of product was formed. Furthermore, *trans*-epoxy cinnamyl alcohol, OAc- and OTBS-protected *trans*-epoxy homocinnamyl alcohol, and *trans*-epoxy bis(homocinnamyl) alcohol were employed as substrates for the kinetic resolution reaction. The results (Scheme 5) revealed that the presence of the OH moiety and its relative position with respect to the epoxide ring are crucial for both the reactivity and the facial selectivity of this ring-opening reaction. On the basis of these results, we can conclude

Scheme 5. Comparison of Enantioselective Ring Opening of *trans*-Epoxy Homocinnamyl Alcohol and its Analogues



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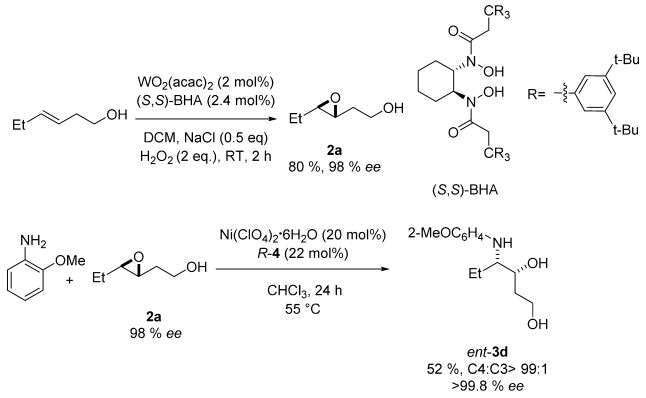
that the OH moiety plays a significant role as a directing group for the Ni-catalyzed ring-opening reaction.

Furthermore, as demonstrated in Scheme 6, a virtually enantiopure amino alcohol, *ent*-**3d**, was readily prepared through

Scheme 6. Synthesis of a Virtually Enantiomerically Pure Compound through Combined Asymmetric Routes



combined asymmetric routes consisting of an initial W-catalyzed asymmetric epoxidation followed by a Ni-catalyzed enantioselective ring opening (kinetic resolution).

In conclusion, we have developed the first regioselective aminolysis of 3,4-epoxy alcohols. Under the catalysis of commercially available $Ni(ClO_4)_2{\cdot}6H_2O$, various 3,4-epoxy alcohols with different substitution patterns were successfully reacted with diverse amines to furnish a variety of γ-hydroxy-δ-amino alcohols as products with high to complete regioselectivities. Furthermore, the enantioselective aminolysis of aromatic 3,4-epoxy alcohols was efficiently promoted by the Ni−BINAM catalytic system, generally affording the products with high enantioselectivities.

■ ASSOCIATED CONTENT

Supporting Information

Representative experimental procedures and necessary characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(10) For details of the optimization of the reaction conditions for the kinetic resolution, see pp 27−30 in the SI.

(11) For details of the determination of the selectivity factor for this kinetic resolution reaction, see p 34 in the SI.

(12) The absolute configuration of the major enantiomer of ring-opening product **3d** obtained through the kinetic resolution was assigned to be (3*S*,4*R*) by comparison of its HPLC data with those for the same compound obtained through the simple Ni-catalyzed ring opening of (3*R*,4*R*)-3,4-epoxyhexan-1-ol under the assumption that the Ni-catalyzed ring-opening process of 3,4-epoxy alcohols proceeds via an S_N2-type reaction pathway. The stereochemistries of other ring-opening products were assigned by analogy assuming a common reaction pathway. For details, see pp 35, 36, 155, and 157 in the SI.

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