

## Ring Opening of Epoxides by $Zn(OAc)_2$ / 1,7-Bis(2-Benzoic Acid)-1,4,7-Trioxaheptane (ZnBBATOH) as a New Catalyst

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### Abstract

We describe here the highly regioselective ring opening of epoxides with aromatic amines in the presence of a catalytic amount of  $Zn(OAc)_2$  and 1,7-bis(2-benzoic acid)-1,4,7-trioxaheptane in  $CH_2Cl_2$ . The yields of the amino alcohols are uniformly good and the recovered catalyst could be used in a new attempt without any purification.

**Key words:** Epoxide, ring opening, amines, zinc acetates, amino-alcohols.

### INTRODUCTION

The  $\beta$ -amino hydroxyl is a major class of functional group in many important biologically active natural and synthetic products and unnatural amino acids.<sup>1</sup> Several clinically useful skeletons, which exhibit a broad range of biological activities as anti-obesity drug<sup>2</sup> and anti-hypertensives agents,<sup>3</sup> contains the  $\beta$ -amino alcohol functionality. The classical method for the preparation of  $\beta$ -amino alcohol involves heating an epoxide in a protic solvent with excess amine. Although this non-catalytic reaction is satisfactory in many cases, it has a number of limitations. For example, the cleavage of epoxides by anilines using classical procedures is difficult.<sup>4</sup> The reaction required an excess of strong inorganic base or a long reaction time, or both and the yields of the corresponding secondary alcohols were low.<sup>5</sup> Recently, new methods using activators/promoters have been developed and used. These include Lewis acids such as  $BiCl_3$ ,<sup>6</sup>  $CeCl_3 \cdot 7H_2O$

$-NaI$ ,<sup>7</sup>  $TaCl_5$ ,<sup>8</sup>  $SmCl_3$ ,<sup>9</sup> diisopropoxyaluminium trifluoroacetate,<sup>10</sup>  $Cu(OTf)_2$ , or  $Sn(OTf)_2$ ,<sup>11</sup> and other activating agents such as alumina,<sup>12</sup> and trifluoroethanol, hexafluoro-2-propanol.<sup>13</sup> However, there are still some limitations with the literature methods; such as the failure of deactivated aromatic amines and some sterically hindered aromatic amines to open the epoxides, or still required of an excess of reagents and reflux temperature, and sluggish reactions. In conjunction with ongoing work in our laboratory on the macrocyclic crown ethers: synthesis,<sup>14</sup> formation of complexes,<sup>15</sup> and catalysis of regioselective ring opening of epoxides,<sup>16</sup> we found out that 1,7-bis(2-benzoic acid)-1,4,7-trioxaheptane (BBATOH) efficiently catalyzed the ring opening of epoxides with anilines under mild conditions with high regioselectivity. Recently, we prepared<sup>14a</sup> BBATOH and used it as a starting dicarboxylic acid material for the preparation of corresponding macrocyclic diamides. In this

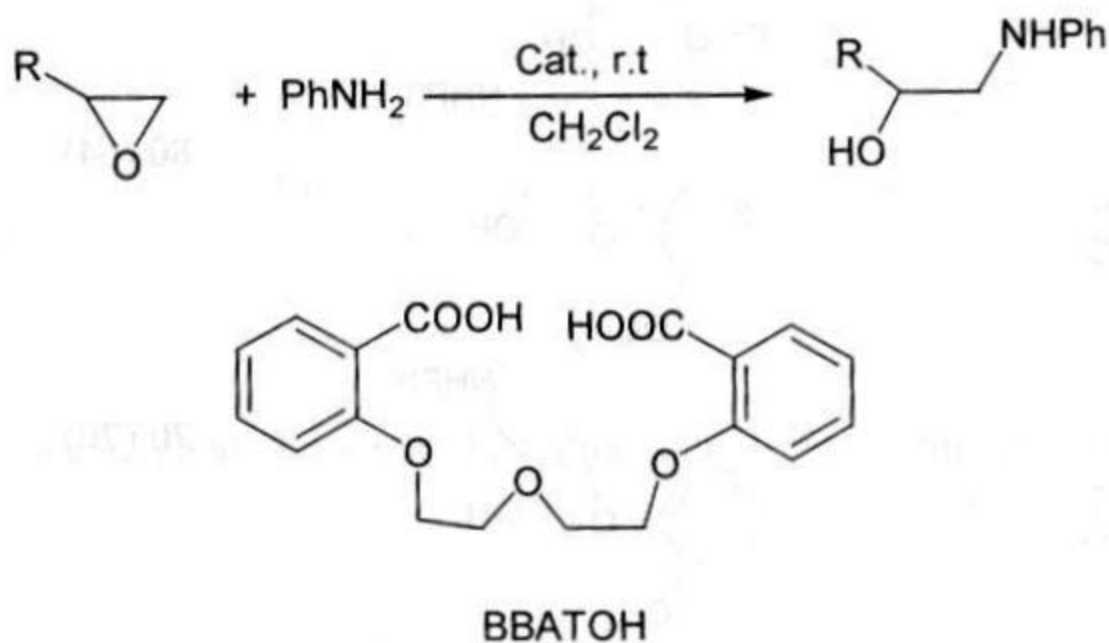
study, we wish to report the results of the reactions of some epoxides with anilines in the presence of a catalytic amount of  $Zn(OAc)_2$  and *BBATOH* (*ZnBBATOH*, for short), (Scheme 1, Table 1).

## RESULTS AND DISCUSSION

The results of the reactions of cyclohexene oxide with aniline in the presence of *ZnBBATOH* catalyst are summarized in Table 1 and are compared with the corresponding results obtained by other applied catalysts. In each case, cleavage of the epoxide ring occurs and upon simple workup, the corresponding amino alcohol was obtained. In comparison, the cleavage behavior of cyclohexene oxide with aniline in

the absence of catalyst is given in entries 1. As shown in Table 1, yields of ring opening with this methodology are quite good and (*ZnBBATOH*) is the more effective catalyst; *short reaction time and lower catalyst loading* (10 mol% versus 50 mol %) could be used. The catalyst was easily recovered and could be reused several times. Generally, the optimum amounts of the catalysts were found to be 0.1 mol per 1 mol of epoxide and aniline.

The results obtained with some representative epoxides in the presence of *ZnBBATOH* as the catalyst are summarized in Table 2. With the only exception of styrene oxide (entries 10-11), when unsymmetric epoxides were allowed to



**Scheme 1**

**Table 1.** Ring Opening of Cyclohexene Oxide with Aniline

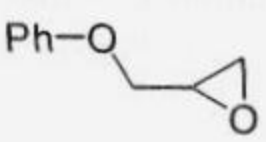
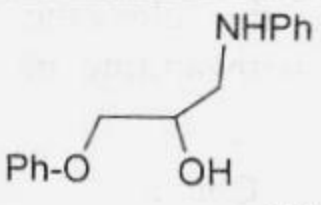
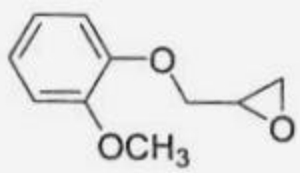
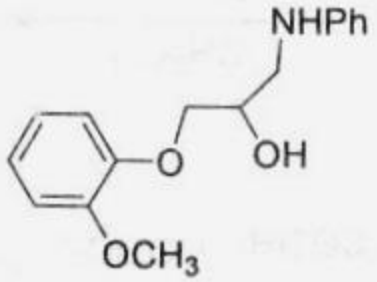
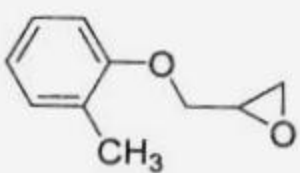
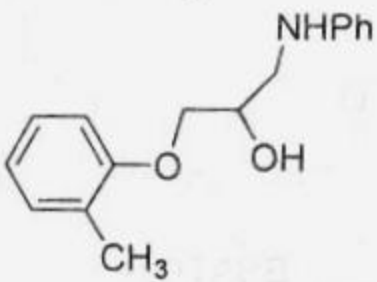
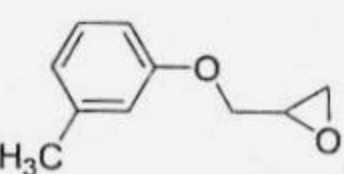
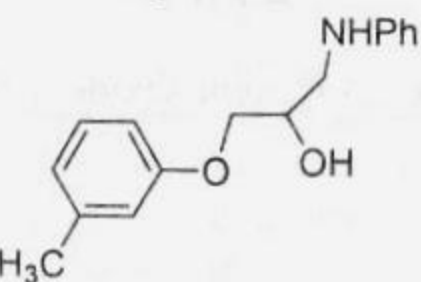
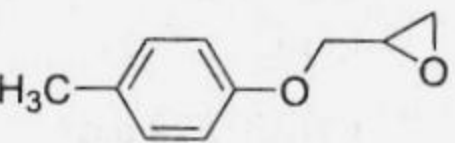
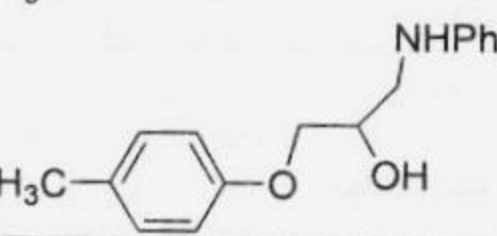
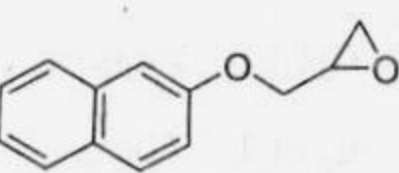
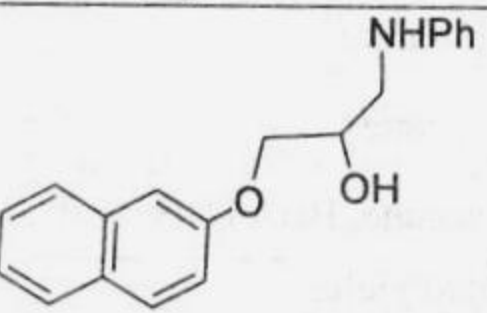
Entry	Catalyst	Catalyst (mol %)	Reaction conditions	Yield (%) <sup>a, ref</sup>
1	-	-	$CH_2Cl_2$ / 7 days	0
2	Zinc tartarate	10	$CH_2Cl_2$ / 28 days	53 <sup>17</sup>
3	Zinc tartarate	50	$CH_2Cl_2$ / 7 days	95 <sup>17</sup>
4	Zinc acetate	10	$CH_2Cl_2$ / 7 days	40
5	Zinc acetate, BBATOH	10	$CH_2Cl_2$ / 7 days	96

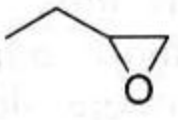
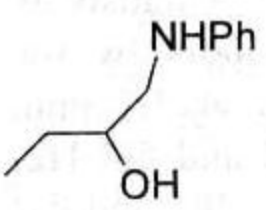
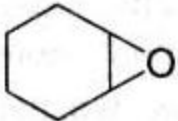
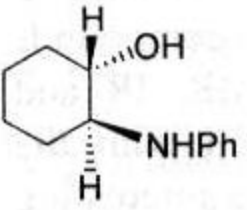
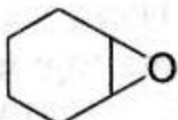
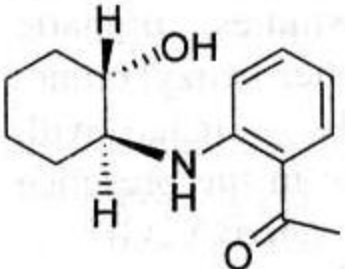
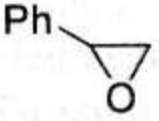
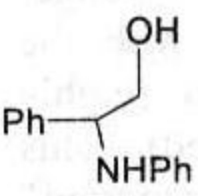
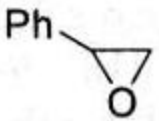
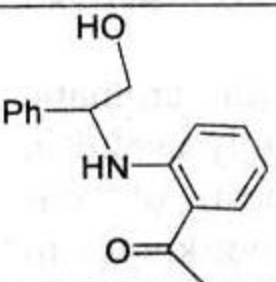
<sup>a</sup> Yields refer to isolated yield.

react in the presence of ZnBBATOH, the ring opening takes place in a completely regioselective fashion, the attack at the less substituted oxirane carbon affording the desired compound as the only product. However, when styrene oxide was used in  $\text{CH}_2\text{Cl}_2$ , two regioisomer were formed in 60:40 ratios. This observed reverse regioselectivity could be

attributed to ionic nature of styrene oxide reactions. This is more confirmed by the observation that the reaction of sterically hindered aromatic amine, for example, 2-acetylaniline, with styrene oxide the ring opening takes place in a completely regioselective fashion, by attack at the benzylic carbon.

Table 2. Ring Opening of Various Epoxides with Amines Catalyzed by ZnBBATOH in  $\text{CH}_2\text{Cl}_2$ .

Entry	Epoxides	Major Product	Yield % of product (Isolated) <sup>a</sup>
1			75 (60)
2			80 (64)
3			70 (70)
4			70 (62)
5			70 (66)
6			75 (63)

7			70 (65)
8			100 (65)
9			100 (62)
10			60 (50)
11			100 (73)

<sup>a</sup> Isolated yield of pure product after column chromatography [(peterelium ether/ EtOAc(9: 1)).

The stereoselectivity of the aminolysis reactions was *anti* as demonstrated by the reaction of cyclohexane oxide with 2-acetylaniline which gave exclusively corresponding *trans* amino alcohols by the coupling constants of the peaks at 3.3 ppm (CHNHAr) (ddd,  $J = 12.5, 10.2$  and  $5.4$  Hz) and 3.5 ppm (CHOH) (ddd,  $11.5, 9.1$  and  $4.2$  Hz) in <sup>1</sup>H-NMR spectra. All the compounds are fully characterized by <sup>1</sup>H-NMR, IR and mass spectral data by comparison with the known compounds.<sup>10-12, 17, 18</sup> It is interesting to note that in the above studies, aliphatic amines such as *n*-butyl amine, benzylamine, and *iso*-propylamine failed to react with epoxides at room temperature in the presence of a catalytic amount of ZnBBATOH in CH<sub>2</sub>Cl<sub>2</sub>. This may be due to stronger complexation of aliphatic amines with the catalyst due to their higher basicity (highly exothermic reactions were observed). This type of behavior was also previously reported<sup>6, 9, 11</sup> with metal catalysts.

The cleavage of epoxides with aromatic amines is unique and will be highly useful in organic synthesis. To the best of our knowledge, the above catalyst is not known to be used as a catalyst in ring opening reactions of epoxides. A variety of chiral derivatives of BBATOH can be complexed with zinc acetate for asymmetric version of the reaction which is in progress in our laboratory.

## EXPERIMENTAL

All materials and solvents were obtained from Merck chemical company (Germany) and Fluka (Switzerland). IR spectra were recorded on a Shimadzu -IR 470 spectrophotometer. <sup>1</sup>H NMR spectra were recorded on Bruker-80 and 100 MHz instruments using tetramethylsilane (TMS) as an internal standard. Mass Spectra were determined on a Shimadzu GCMS-QP 1000 EX instrument at 70 eV. Elemental analyses were performed at the Research Institute of Petroleum Industry of Iran. Columns chromatography was carried out on short columns of silica gel 60 (230-400 mesh) in glass columns (2-3 cm diameter) using 15-30 g of silica gel per 1 g of crude mixture. BBATOH was obtained according to literature.<sup>14a</sup>

## Cleavage of Epoxides with Aromatic Amines: General Procedure

Zn(OAc)<sub>2</sub> · 2H<sub>2</sub>O (0.2 mmol) and 1,7-bis(2-benzoic acid)-1,4,7-trioxaheptane (BBATOH) (0.2 mmol) were mixed in a flask and then, epoxide (2 mmol), aniline (2 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (10 mL) were added to the catalyst and the mixture was stirred for 7 days at room temperature. The catalyst was filtered off and washed with CH<sub>2</sub>Cl<sub>2</sub> (10 mL). The filtrate was washed with water (2 x 15 mL), passed through anhyd MgSO<sub>4</sub> and the solvent was distilled off to give the respective amino alcohol. These were further purified by column chroma-tography [silica gel, peterelium ether / EtOAc (9 : 1)]. Physical properties of the products thus obtained were in good agreement with reported data.<sup>10-12, 17, 18</sup>

Spectral data of some of the representative compounds are given below.

1-(2-Methoxy-phenoxy)-3-phenylamino-propan-2-ol (Table 2, entry 2): viscous liquid. IR (neat):  $\nu = 3500, 3400, 1250, 1120$  cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 3.2-3.4$  (m, 2H),  $3.4-3.7$  (m, 2H),  $3.8$  (s, 3H),  $3.9-4.3$  (m, 3H),  $6.5-6.8$  (m, 3H),  $6.9$  (s, 4H),  $7.0-7.3$  (m, 2H).

MS :  $m/z$  273 (M<sup>+</sup>).

Anal Calcd for C<sub>16</sub>H<sub>19</sub>NO<sub>3</sub>: C, 70.31, H, 7.01, N, 5.12. Found C, 70.35, H, 7.04, N, 5.32.

1-Phenylamino-3-*o*-tolylloxy-propan-2-ol (Table 2, entry 3): viscous liquid.

IR (neat):  $\nu = 3450, 1250, 1120$  cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 2.2$  (s, 3H),  $2.8-3.4$  (m, 2H),  $3.4-3.7$  (m, 2H),  $3.7-4.4$  (m, 3H),  $6.3-6.9$  (m, 5H),  $6.9-7.3$  (m, 4H).

MS :  $m/z$  257 (M<sup>+</sup>).

Anal Calcd for C<sub>16</sub>H<sub>19</sub>NO<sub>2</sub>: C, 74.68, H, 7.44, N, 5.44. Found C, 74.71, H, 7.50, N, 5.48.

1-Phenylamino-3-*m*-tolylloxy-propan-2-ol (Table 2, entry 4): viscous liquid.

IR (neat):  $\nu = 3500, 3400, 1250, 1150$  cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 2.3$  (s, 3H),  $3.0$  (b, 2H),  $3.1-3.6$  (m, 2H),  $3.8-4.4$  (m, 3H),  $6.4-6.8$  (m, 5H),  $6.9-7.3$  (m, 4H).

MS :  $m/z$  257 (M<sup>+</sup>).

Anal Calcd for C<sub>16</sub>H<sub>19</sub>NO<sub>2</sub>: C, 74.68, H, 7.44, N, 5.44. Found C, 74.70, H, 7.47, N, 5.47.

1-Phenylamino-3-*p*-tolylloxy-propan-2-ol (Table 2, entry 5): viscous liquid.

IR (neat):  $\nu = 3550, 3400, 1240, 1100$  cm<sup>-1</sup>.

$^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta = 2.2$  (s, 3H), 3.0 (b, 2H), 3.1-3.6 (m, 2H), 3.8-4.44 (m, 3H), 6.6-6.9 (m, 5H), 7.0-7.3 (m, 4H).

MS :  $m/z$  257 ( $\text{M}^+$ ).

Anal Calcd for  $\text{C}_{16}\text{H}_{19}\text{NO}_2$ : C, 74.68, H, 7.44, N, 5.44. Found C, 74.72, H, 7.46, N, 5.47.

*1-(Naphthalene-2-yloxy)-3-phenylamino-propan-2-ol* (Table 2, entry 6): viscous liquid.

IR (neat):  $\nu = 3430, 1260, 1240, 1150\text{ cm}^{-1}$ .

$^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta = 3.1$ -4.6 (m, 7H), 6.6-7.0 (m, 2H), 7.0-7.5 (m, 6H), 7.5-7.8 (m, 4H).

MS :  $m/z$  293 ( $\text{M}^+$ ).

Anal Calcd for  $\text{C}_{19}\text{H}_{19}\text{NO}_2$ : C, 77.79, H, 6.53, N, 4.77. Found C, 77.82, H, 6.55, N, 4.80.

*1-[2-(2-Hydroxy-cyclohexylamino)-phenyl]-ethanone* (Table 2, entry 9): semi solid.

IR (neat):  $\nu = 3400, 3300, 1630, 1240, 1160\text{ cm}^{-1}$ .

$^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta = 1.2$ -1.5 (m, 4H), 1.6-1.9 (m, 2H), 1.9-2.3 (m, 2H), 2.45 (bs, 1H, OH), 2.54 (s, 3H), 3.30 (ddd, 1H,  $J_1 = 12.5\text{ Hz}$ ,  $J_2 = 10.2\text{ Hz}$ ,  $J_3 = 5.4\text{ Hz}$ ), 3.50 (ddd, 1H,  $J_1 = 11.5\text{ Hz}$ ,  $J_2 = 9.1\text{ Hz}$ ,  $J_3 = 4.2\text{ Hz}$ ), 6.6 (t, 1H,  $J = 8\text{ Hz}$ ), 6.9 (d, 1H,  $J = 8\text{ Hz}$ ), 7.3 (dt, 1H,  $J_1 = 8\text{ Hz}$ ,  $J_2 = 1.5\text{ Hz}$ ), 7.7 (dd,  $J_1 = 8\text{ Hz}$ ,  $J_2 = 1.5\text{ Hz}$ ), 8.9 (d, 1H,  $J = 6.5\text{ Hz}$ ).

MS :  $m/z$  233 ( $\text{M}^+$ ).

Anal Calcd for  $\text{C}_{14}\text{H}_{19}\text{NO}_2$ : C, 72.07, H, 8.21, N, 6.00. Found C, 72.30, H, 8.4, N, 6.15.

*1-[2-(2-Hydroxy-1-phenyl-ethylamino)-phenyl]-ethanone* (Table 2, entry 11): semi solid.

IR (neat):  $\nu = 3400, 3300, 1630, 1240, 1160\text{ cm}^{-1}$ .

$^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta = 2.5$  (s, 3H), 3.0 (b, 1H), 3.8-4.06 (m, 2H), 4.6 (dd, 1H,  $J_1 = 12\text{ Hz}$ ,  $J_2 = 5.5\text{ Hz}$ ), 6.4-6.6 (m, 2H), 7.0-7.4 (m, 6H), 7.8 (dd, 1H,  $J_1 = 8.7\text{ Hz}$ ,  $J_2 = 1.7\text{ Hz}$ ), 9.52 (d, 1H,  $J = 6\text{ Hz}$ ).

MS :  $m/z$  255 ( $\text{M}^+$ ).

Anal Calcd for  $\text{C}_{16}\text{H}_{19}\text{NO}_2$ : C, 75.27, H, 6.71, N, 5.49. Found C, 75.50, H, 6.75, N, 5.52.

## ACKNOWLEDGEMENTS

We are thankful to Sistan and Baluchestan University for the partial support of this work.

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