

Bismuth triflate-catalyzed mild and efficient epoxide opening by aromatic amines under aqueous conditions

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Abstract—Bismuth triflate catalyzes the ring opening of epoxides with aromatic amines under aqueous conditions. The reaction proceeds rapidly and affords the corresponding β -amino alcohols in excellent yields.

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Due to their ease of formation and wide reactivity with nucleophiles, epoxides are often used as starting materials and intermediates in organic synthesis. The nucleophilic opening of these epoxides has been studied extensively and there are several references to the opening of epoxides with alcohols, thiols, and amines,^{1–3} but aromatic amines have received less attention, perhaps because of their high affinity to Lewis acids. Therefore, we planned to develop an efficient catalytic ring opening reaction of *meso*-epoxides with anilines in water.

β -Amino alcohols are an important class of organic compounds, which have found much use in medicinal chemistry and organic synthesis.^{4,5} The classical synthesis of β -amino alcohols consists of heating an epoxide with an excess of amine at elevated temperatures.⁶ Since some functional groups may be susceptible to high temperatures, a variety of catalysts have been introduced for the cleavage of epoxides at room temperature.^{1,3,7–17} However, there are still some limitations with the existing methods; for example, deactivated amines fail to open these epoxides or still require high temperatures. Furthermore, many of the catalysts used are either corrosive or expensive. To overcome these limitations, we previously reported the use of BiCl_3 as an efficient catalyst for the nucleophilic opening of epoxides

with anilines. This method provides good yields of the corresponding *trans*- β -amino alcohols.¹⁸

Bismuth compounds have attracted recent attention due to their low toxicity,¹⁹ low cost, and good stability.^{20–22} Bismuth salts have been reported as catalysts for allylation of imines,²³ rearrangement of epoxides to aldehydes and ketones,²⁴ opening of epoxides,^{18,25,26} formation and deprotection of acetals,^{27–30} Friedel–Crafts reactions,^{31–34} Diels–Alder reactions,^{35,36} and intramolecular Sakurai cyclizations.^{37,38}

In this context, we have examined bismuth triflate as a Lewis acid for the opening of epoxides. Recently, great attention has been paid to the development of organic reactions in water. We wish to report our new method for epoxide opening using $\text{Bi}(\text{OTf})_3$ under aqueous conditions instead of BiCl_3 in an organic solvent. $\text{Bi}(\text{OTf})_3$ can be easily prepared from commercially available starting materials.^{39,40} We have already studied the use of BiCl_3 (10%) as an efficient catalyst for the nucleophilic opening of cyclohexene oxide with aniline in cyclohexane. Compared to BiCl_3 , $\text{Bi}(\text{OTf})_3$ is particularly attractive because it can be used in water.^{41,42} As it has been demonstrated that a water solution of $\text{Bi}(\text{OTf})_3$ is acidic,⁴³ it may be possible that the true catalyst is TfOH released from hydrolysis of $\text{Bi}(\text{OTf})_3$. However, the observation that TfOH is not as effective as $\text{Bi}(\text{OTf})_3$ to catalyze the epoxide opening (1 equiv aniline, 1 equiv cyclohexene epoxide, 10% TfOH, 25 °C, 7 h, 28%) suggests that a Lewis acid is likely involved in activating the epoxide. The corresponding *trans*- β -amino alcohol **3a** was obtained in good yield with BiCl_3 (Table 1, entry 1).¹⁸ When the reaction was run with $\text{Bi}(\text{OTf})_3$ (10%)

Keywords: bismuth; bismuth(III) triflate; epoxide; aromatic amine; beta-amino alcohol; aqueous conditions.

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Table 1. Bismuth(III) catalyzed epoxide opening with aromatic amines produced via Scheme 1

Entry	X	Solvent ^a	Yield (%) ^b
1	Cl	Cyclohexane	78
2	OTf	Cyclohexane	76
3	OTf	Et ₂ O	84
4	OTf	H ₂ O	83

^a Substrates **1** and **2** were mixed in 1:1 ratio with 10% BiX₃ at 25 °C.

^b Refers to yield of isolated product.

either in cyclohexane or diethyl ether, the β-amino alcohol was obtained in very similar yields (Table 1, entries 2 and 3). The ring opening reaction was finally studied in water (Table 1, entry 4) and the β-amino alcohol **3a** was isolated in a good yield (83%).

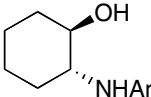
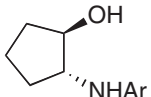
Encouraged by our results in the nucleophilic opening reaction catalyzed by 10% Bi(OTf)₃ in water, we studied the scope and limitations of this reaction with respect to the aniline and *meso*-epoxide employed in the process. The results are summarized in Table 2.

The reaction was carried out by adding Bi(OTf)₃ to a mixture of epoxide and amine in an aqueous solution at room temperature (Scheme 1). The optimum amount of Bi(OTf)₃ was found to be 10 mol%. The biphasic reaction mixture was stirred at room temperature for 7–24 h to give the corresponding *trans*-β-amino alcohols in

good yields (Table 2). The procedure worked well with anilines bearing a variety of substituents (Scheme 2, Table 2). Cyclohexene oxide was treated with amines such as *p*-methylaniline (entry 3) to isolate the corresponding β-amino alcohols in good yields. Sterically more hindered anilines such as *o*-methylaniline also led to the alcohols in good yield (entry 2). The corresponding β-amino alcohol was also produced efficiently when less nucleophilic amines like *p*-trifluoromethylaniline were used in the same conditions (entry 4). Electron rich amines like *p*-methoxyaniline afforded the product in good yield as well (entry 5). In some cases where the starting materials precipitated out of the reaction mixture, the ring opening reaction was studied in a micellar solution of sodium dodecyl sulfate (SDS)⁴⁴ and the product could be obtained with a substantially improved yield. The use of *p*-trifluoromethylaniline and *p*-bromoaniline as nucleophiles led to good yields of the amino alcohols using 40% SDS in water (Table 2, entries 4 and 6). However, it should be pointed out that the addition of 40% SDS did not afford the β-amino alcohol with a better yield for cases where SDS was not necessary.

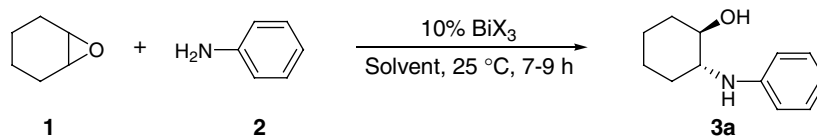
The same method was also effective for the opening reaction of cyclopentene oxide affording the corresponding β-amino alcohols (entries 7–10) albeit with lower yields (62–69%) after longer reaction times (21–24 h). Aliphatic amines have also been employed using these

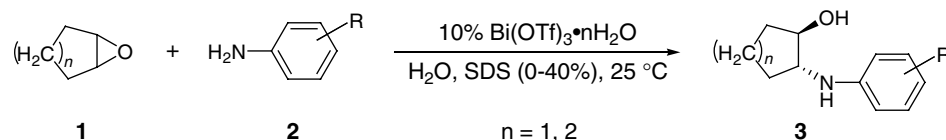
Table 2. Bismuth triflate catalyzed epoxide opening with aromatic amines produced via Scheme 2

Entry		<i>t</i> (h)	Additive	Amino alcohol	Yield (%) ^{a,b}
1	3a	7	—		83
2	3b	9	—	Ar = <i>o</i> -CH ₃ C ₆ H ₄	86
3	3c	9	—	Ar = <i>p</i> -CH ₃ C ₆ H ₄	84
4	3d	8	40% SDS	Ar = <i>p</i> -CF ₃ C ₆ H ₄	79
5	3e	9	—	Ar = <i>p</i> -CH ₃ OC ₆ H ₄	77
6	3f	8	40% SDS	Ar = <i>p</i> -BrC ₆ H ₄	84
7	3g	24	40% SDS		68
8	3h	24	40% SDS	Ar = <i>o</i> -CH ₃ C ₆ H ₄	62
9	3i	21	—	Ar = <i>p</i> -CH ₃ C ₆ H ₄	63
10	3j	23	—	Ar = <i>p</i> -CF ₃ C ₆ H ₄	69

^a Substrates **1** and **2** were mixed in 1:1 ratio with 10% Bi(OTf)₃ at 25 °C.

^b Refers to yield of isolated product. All products have been previously reported in the literature.

**Scheme 1.**



Scheme 2.

conditions. The β -amino alcohols were obtained in good yields (1 equiv piperidine, 1 equiv cyclohexene epoxide, 10% $\text{Bi}(\text{OTf})_3$, 25 $^\circ\text{C}$, 24 h, 74%; 1 equiv cyclohexylamine, 1 equiv cyclohexene epoxide, 10% $\text{Bi}(\text{OTf})_3$, 40% SDS, 25 $^\circ\text{C}$, 18 h, 78%).

The general procedure for the $\text{Bi}(\text{OTf})_3$ -catalyzed epoxide opening can be described as follows. To a mixture of epoxide **1** (1 mmol) and amine **2** (1 mmol) in water (1 mL) was added $\text{Bi}(\text{OTf})_3$ (0.10 mmol) at 25 $^\circ\text{C}$ for 7–9 h (21–24 h for the opening of cyclopentene oxide). The resulting biphasic mixture of liquids was magnetically stirred. In the case where the reagents were precipitated, SDS (40%) was added. The reaction mixture was quenched by the addition of aqueous sodium hydrogen carbonate, extracted with ether, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum (rotary evaporator). The residue was purified by column chromatography on silica gel using hexanes/ethyl acetate as eluent. All the compounds were fully characterized by IR, ^1H NMR, and ^{13}C NMR by comparison with the known compounds.¹⁸

In summary, we have found that the opening of epoxides proceeds smoothly with various anilines and a catalytic amount of $\text{Bi}(\text{OTf})_3$ under aqueous conditions. This method offers several advantages including aqueous and mild reaction conditions, low catalyst loading (10%), and no formation of by-products.

Acknowledgements

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