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An efficient method for the ring opening of epoxides with aromatic amines catalyzed by bismuth trichloride

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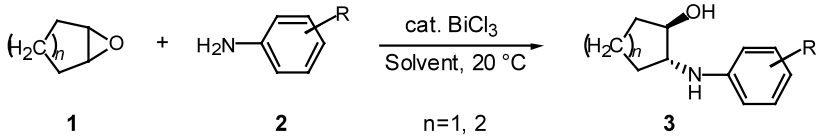
Abstract—We describe here the nucleophilic opening of epoxides with aromatic amines in the presence of a catalytic amount of $BiCl_3$. The mild reaction conditions and the low toxicity of bismuth salts make this procedure particularly attractive for the synthesis of β-amino alcohols. © 2002 Elsevier Science Ltd. All rights reserved.

Due to their ease of formation and wide reactivity with nucleophiles, epoxides are used as starting materials and intermediates in organic synthesis. The nucleophilic opening of these epoxides has been studied extensively since it provides a suitable route to the formation of C–C, C–N, C–O or C–S σ-bonds. There are several references to the opening of epoxides with alcohols, thiols and amines, 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 aniline derivatives.

β-Amino alcohols are an important class of organic compounds, which have found much use in medicinal chemistry and organic synthesis.[1,2] The classical synthesis of β-amino alcohols consists of heating an epoxide with an excess of amine at elevated temperatures.[3] 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.[4–17] However, there are still some limitations with the literature methods; for example, deactivated amines fail to open up these epoxides or still require high temperatures. Furthermore, many of the catalysts used are either corrosive or expensive. To overcome these limitations, we report herein a mild and efficient method for the nucleophilic opening of *meso*-epoxides with anilines catalyzed by bismuth(III). The corresponding *trans*-β-amino alcohols are obtained in good yields using bismuth chloride as a catalyst.

Due to the interest in the use of bismuth compounds as environmentally friendly reagents for organic synthesis,[18,19] we undertook a study of the utility of bismuth chloride as a catalyst for the opening of epoxides with aromatic amines. Bismuth compounds have attracted recent attention due to their low toxicity,[20] low cost, and good stability. Bismuth salts have been recently reported as catalysts for rearrangement of epoxides to aldehydes and ketones,[21] opening of epoxysilanes,[22] cleavage of epoxides with alcohols,[23] acylation of alcohols,[24,25] formation of acetals,[26,27] deprotection of acetals,[28,29] Friedel–Crafts acylations and sulfonylations,[30–33] Diels–Alder reactions,[34] aza-Diels–Alder reactions,[34–37] and intramolecular Sakurai cyclizations.[38,39]

The reaction was carried out by adding bismuth trichloride to a mixture of epoxide and amine in a suitable solvent at room temperature (Scheme 1). The optimum



1 **2** **3**

Scheme 1.

Keywords: bismuth; bismuth(III) chloride; epoxide; aromatic amine; beta-amino alcohol; catalysis.

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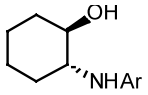
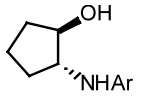
ratio of bismuth trichloride was found to be 10%. The reaction mixture was stirred at room temperature for 6–24 h to give the corresponding *trans*-β-amino alcohols in good yields (Table 1).

The best results were obtained using 0.1 equiv. of $BiCl_3$ and 1.1 equiv. of the aniline. The procedure works well with differently substituted anilines (Scheme 1, Table 1). In the first place, we examined the reaction of cyclohexene oxide with aniline and 0.1 equiv. $BiCl_3$ at 20°C to give the corresponding β-amino alcohol **3a** in 84% yield (entry 4). This success encouraged us to exploit the generality of this reaction by opening that epoxide with various amines. For example, cyclohexene oxide was treated with amines such as *o*-methylaniline (entry 5), *p*-methylaniline (entry 6), *o*-methoxyaniline (entry 8), *p*-methoxyaniline (entry 9) to isolate the corresponding alcohols in good yields. Sterically more hindered anilines such as *o*-methylaniline or *o*-methoxyaniline led to the alcohols still in good yields. Electron deficient amines like *p*-trifluoromethylaniline led also to the corresponding β-amino alcohol in good yield (entry 7). Cyclopentene oxide also afforded the β-amino alcohols in good yield (entries 11–14). The isolated yields for the amino alcohols were in the range of 65–85%. Except for entries 1 and 3 where dichloromethane or diethyl ether were chosen, cyclohexane was usually the solvent of choice. Among various solvents tested, it was indeed found to be the best solvent for the epoxide opening. Bismuth chloride is insoluble in common organic solvents and is used in cyclohexane as a suspension.

Table 1. Bismuth trichloride catalyzed epoxide opening with aromatic amines produced via Scheme 1

Entry		Solvent[a]	Amino alcohol	Yield (%)[b]
				
1	**3a**	CH_2Cl_2 (1 M)	Ar = Ph	78
2	**3a**	C_6H_{12} (1 M)	Ar = Ph	78
3	**3a**	Et_2O (1 M)	Ar = Ph	72
4	**3a**	C_6H_{12}	Ar = Ph	84
5	**3b**	C_6H_{12}	Ar = *o*-CH_3Ph	68
6	**3c**	C_6H_{12}	Ar = *p*-CH_3Ph	69
7	**3d**	C_6H_{12}	Ar = *p*-CF_3Ph	85
8	**3e**	C_6H_{12}	Ar = *o*-OCH_3Ph	70
9	**3f**	C_6H_{12}	Ar = *p*-OCH_3Ph	65
10	**3g**	C_6H_{12}	Ar = *p*-BrPh	74
				
11	**3h**	C_6H_{12}	Ar = Ph	76
12	**3i**	C_6H_{12}	Ar = *o*-OCH_3Ph	56
13	**3j**	C_6H_{12}	Ar = *p*-CH_3Ph	69
14	**3k**	C_6H_{12}	Ar = *p*-BrPh	73

[a] Substrates **1** and **2** were mixed in 1.1:1 ratio with 0.1 equiv. $BiCl_3$ at 20°C; concentration was 2 M except 1 M for entries 1, 2, and 3.

[b] Refers to yield of isolated product. All products (except that from entry 7) have been previously reported in the literature.

The *trans* stereochemistry of the β-amino alcohols was determined from the coupling constants of the C–H protons α to the heteroatoms in the ^{1}H NMR spectra. For example, the *trans* stereochemistry of the compound **3c** was assigned from the coupling constants of the peaks at 3.31 ppm (ddd, $J = 10.5$, 9.2, 4.1 Hz, C<u>H</u>-NHAr) and 3.31 ppm (ddd, $J = 10.5$, 9.7, 4.4 Hz, C<u>H</u>-OH) in the ^{1}H NMR spectrum.[12]

The general procedure for the β-amino alcohol synthesis can be described as follow. To a mixture of epoxide **1** (1 mmol) and amine **2** (1.1 mmol) in the solvent (0.5 mL) was added anhydrous $BiCl_3$ (0.10 mmol) at 20°C for 7–11 h (20–24 h for the opening of cyclopentene oxide).

It was quenched by the addition of aqueous sodium hydrogen carbonate, extracted with dichloromethane, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum (rotary evaporator). The residue was purified by column chromatography on silica gel using chloroform as eluent. All the compounds were fully characterized by IR, ^{1}H NMR, and ^{13}C NMR by comparison with the known compounds.[40]

In summary, we have demonstrated a novel, mild and efficient method for the ring opening of *meso*-epoxides with aromatic amines using bismuth trichloride as a catalyst. To the best of our knowledge, the above catalyst is not known to catalyze epoxide opening reaction with aromatic amines. This method is compatible with deactivated and sterically hindered aromatic amines. Advantages of this method include low toxicity and low cost of the Lewis acid catalyst, and insensitivity of the Lewis acid to air and moisture.

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40. All of the obtained β-amino alcohols are known compounds to which the spectroscopic data were compared, except **3d** (entry 7): IR (neat): $\nu = 3385$ cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.40$ (d, $J = 8.8$ Hz, 2H), 6.72 (d, $J = 8.8$ Hz, 2H), 3.75 (d, $J = 8.8$ Hz, 1H), 3.40 (m, 1H), 3.22 (m, 1H), 2.34 (s, 1H), 2.12 (m, 2H), 1.78 (m, 2H), 1.37 (m, 3H), 1.12 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 150.79$, 126.85, 125.08 (q, $J = 270.0$ Hz), 119.57 (q, $J = 32.7$ Hz), 113.17, 74.76, 59.59, 33.62, 31.71, 24.97, 24.39.