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A powerful, practical and chemoselective synthesis of 2-anilinoalkanols catalyzed by $Bi(TFA)_3$ or $Bi(OTf)_3$ in the presence of molten TBAB

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Abstract—A facile and efficient synthesis of β-amino alcohols by ring opening of epoxides with anilines in good to excellent yields in the presence of catalytic amounts of $Bi(TFA)_3$ or $Bi(OTf)_3$ via the use of molten tetrabutylammonium bromide (TBAB) as an ionic liquid is described. In addition, the observed chemoselectivity can be considered as a noteworthy advantage of this method.

Epoxides are versatile intermediates in organic chemistry and their reactions with different nucleophiles have been the subject of extensive studies. Ring opening of epoxides with excess amounts of amines is the most common method for the synthesis of β-amino alcohols, which are an important class of compounds in pharmaceutical and organic chemistry. Some of these compounds are used as starting materials for the preparation of oxazolines, which have been widely explored as protecting groups.[1] These amino alcohols are also used as insecticidal agents and as chiral ligands in asymmetric synthesis.[2] Recently, Cho et al. proposed the formation of the 2-anilinoalkanol as an intermediate in the ruthenium-catalyzed synthesis of indoles.[3] Furthermore, β-amino alcohols are a major functional group in natural products such as sphingosine that demonstrate physiological activities.[4] Thus the development of facile and environmentally friendly synthetic methods towards β-amino alcohols, constitutes an active area of investigation in organic synthesis.

Although, aminolysis reactions of epoxides are typically catalyzed by transition metal salts,[5] new catalytic systems are continuously being explored in the search for improved efficiencies and cost effectiveness. In this context, Lewis acids such as $Ca(OTf)_2$,[6] alumina,[7] zirconium sulfophenyl phosphonate,[8] $CeCl_3$,[9] diisopropoxyaluminium trifluoroacetate,[10] $TaCl_5$[11] and LiOTf[12] have been reported as catalysts. Recently, it has been found that epoxides can be converted into β-amino alcohols using anilines in the presence of $[Bmim]BF_4$ as an ionic liquid.[13] However, these methods often involve the use of expensive reagents,[4,8,11,13] extended reaction times,[6,13] drastic reaction conditions,[11] give mixtures of regioisomers,[6,7,9] unsatisfactory yields,[7] especially with aliphatic epoxides and entail undesirable side reactions due to polymerization or rearrangement of oxiranes.[6,10,11] Acid-catalyzed ring opening of epoxides with anilines is limited and requires careful control of the acidity to prevent side reactions. Therefore, the introduction of new and efficient methods for this transformation is still in demand.

Because of the volatile and toxic nature of many organic solvents, ionic liquids are emerging as effective solvents for 'green' processes.[14] These solvents are nonflammable, nonvolatile, easy to handle and possess high thermal stability.[15] However, the high cost of most conventional room temperature ionic liquids and apprehension about their toxicity[13] have led us to explore the use of more benign salts in the molten state as practical alternatives. Recently, molten tetrabutylammonium bromide was used as a low toxic and cost-effective ionic liquid in a number of useful synthetic transformations.[16] In addition, the applications of $Bi(TFA)_3$ and $Bi(OTf)_3$ as environmentally friendly reagents for organic synthesis have been extensively investigated.[17] Due to our interest in the use of Bi(III) salts,[18] we have reported that

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Keywords: Ionic liquid; Anilines; Ring opening; Epoxides; Chemoselectivity; Epoxides; Bi(III) salts.

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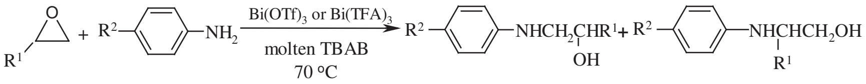


Scheme 1.

$Bi(TFA)_3$ and $Bi(OTf)_3$ are extraordinarily efficient catalysts for the conversion of epoxides to thiiranes[19] and 1,3-dioxolanes.[20] Unlike many Lewis acids, $Bi(TFA)_3$ and $Bi(OTf)_3$ are relatively stable, nontoxic, easy to handle and insensitive to air and moisture. We now report a facile and efficient method for the ring opening of epoxides with anilines catalyzed by $Bi(TFA)_3$ or $Bi(OTf)_3$ in molten tetrabutylammonium bromide at 70 °C (Scheme 1). Different classes of epoxides carrying activated and deactivated groups were reacted with aniline, *p*-methylaniline and *p*-bromoaniline in molten TBAB in the presence of catalytic amounts of the Bi(III) salts. These reactions were performed under moderate conditions to produce the corresponding β-amino alcohols in good to excellent yields. The results are shown in Table 1. The high reactivity and selectivity are similar to those observed in the case of strong Lewis acids.[8–11]

Table 1. Ring opening of epoxides with aromatic amines and $Bi(TFA)_3$ or $Bi(OTf)_3$ in the presence of molten TBAB

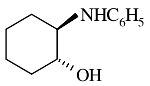
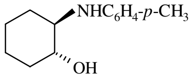
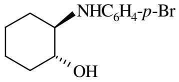
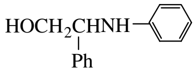
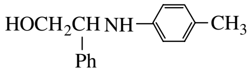
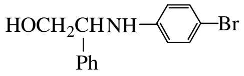
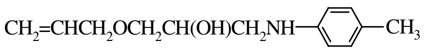
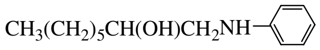
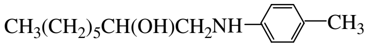
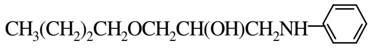
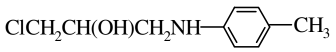
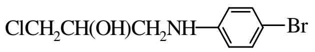
Entry	Products[a]	Yield (%)[b]/mmol of Bi(III) salt/time (min)	
		$Bi(TFA)_3$	$Bi(OTf)_3$
1		68/0.05/45	78/0.02/45
2		70/0.05/55	76/0.02/35
3		67/0.07/55	80/0.03/60
4		90/0.03/15	96/0.01/15
5		93/0.03/15	95/0.01/15
6		90/0.04/15	92/0.01/15
7		82/0.05/30	84/0.02/15
8		86/0.05/20	90/0.01/15
9		90/0.06/20	92/0.02/25
10		84/0.05/45	85/0.02/25
11		80/0.05/45	80/0.01/20
12		78/0.06/45	79/0.02/45
13		81/0.06/45	86/0.03/60

Table 1 (*continued*)

Entry	Products[a]	Yield (%)[b]/mmol of Bi(III) salt/time (min)	
		Bi(TFA)$_3$	Bi(OTf)$_3$
14		83/0.06/60	87/0.02/60
15		78/0.07/60	82/0.03/60
16		80/0.05/45	90/0.02/45
17		85/0.05/45	88/0.02/30
18		80/0.06/45	83/0.03/55
19		83/0.05/50	86/0.02/45
20		90/0.05/45	93/0.02/30
21		80/0.06/60	85/0.03/60

[a] All products were characterized by ^{1}H NMR, ^{13}C NMR, IR and mass spectroscopy.

[b] Isolated yields.

The reactions of cyclohexene oxide as a model compound with anilines in the presence of these catalysts proceeded readily in short times (35–60 min) and with good yields (Table 1, entries 1–3).

The reactions of styrene oxide with aromatic amines (Table 1, entries 4–6) under acidic conditions gave the corresponding β-amino alcohols, in which the aromatic amines in contrast to the other oxiranes attack the α-carbon of the epoxide ring in high yield and excellent regioselectivity.

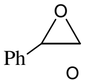
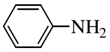
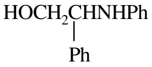
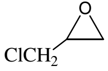
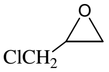
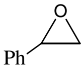
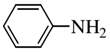
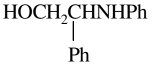
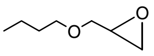
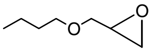
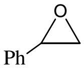
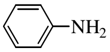
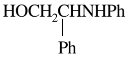
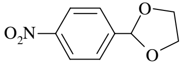
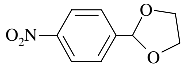
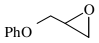
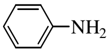
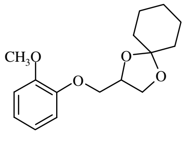
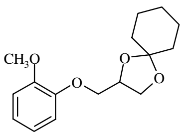
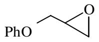
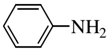
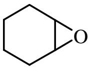
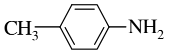
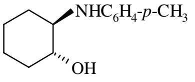
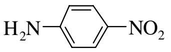
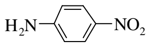
A variety of epoxides were converted to the products with high efficiency and chemoselectivity in the presence of functional groups such as PhO–, RO–, ClCH$_2$– and allyl ether. The presence of weak electron-donating or electron-withdrawing groups such as CH$_3$ or Br on the aromatic ring of aniline did not make any difference in this reaction. Furthermore, stronger examples such as *p*-nitroaniline and 1,2-diaminobenzene or aliphatic amines did not produce the corresponding β-amino alcohols under the same reaction conditions. This may be due to the weaker nucleophilicity of *p*-nitroaniline or high basicity and strong complexation of the amines with these catalysts. This type of behavior was also previously reported with metal triflates as catalysts.[5a,b,12] Also it was found that Bi(OTf)$_3$ (0.01–0.03 mmol) was a more effective catalyst than Bi(TFA)$_3$ (0.03–0.07 mmol).

In order to evaluate the intermolecular chemoselectivity of the reagents, competitive reactions were carried out and the results are summarized in Table 2. It is interesting to note that acid-sensitive groups such as acetals and ketals were stable under these reaction conditions (Table 2, entries 3 and 4). Furthermore, in this competitive reaction aliphatic amines and *p*-nitroaniline did not give the desired product and were completely recovered. Such selectivity has not been reported previously and could be considered as a useful practical achievement in epoxide ring opening reactions.

In conclusion, the present procedure demonstrates the successful use of TBAB as a reaction media for the regio- and chemoselective ring opening of epoxides with anilines using 1–3 mol % of bismuth(III) triflate or 3–7 mol % of bismuth(III) trifluoroacetate as catalysts. The notable features of this procedure are clean reaction profiles, improved yields, enhanced rates and simplicity in operation, which make it a useful and attractive process for the synthesis of β-amino alcohols. Moreover, nonhydroscopic, inexpensive and nontoxic catalysts and solvents for this transformation are other noteworthy advantages of this method. The highly catalytic nature of these reagents and their wide applicability should make this procedure an attractive alternative to existing methods for the preparation of β-amino alcohols.

General procedure: To a mixture of epoxides (1 mmol) and anilines (1 mmol) in molten TBAB (0.5 mmol) was added Bi(TFA)$_3$ (0.03–0.07 mmol) or Bi(OTf)$_3$) (0.01–0.03 mmol). The reaction mixture was stirred at 70 °C for the appropriate time according to Table 1. The progress of the reaction was followed by GLC or TLC. After completion, the reaction was washed with 0.5 N HCl (25 mL) and extracted. The mixture was extracted with CH$_2$Cl$_2$ (3 × 10 mL) and the combined organic

Table 2. Competitive ring opening of epoxides with aromatic amines in the presence of $Bi(TFA)_3$–TBAB and $Bi(OTf)_3$–TBAB

Entry	Epoxide	Anilines	Products	Yield (%)/Time (min)	
				$Bi(TFA)_3$	$Bi(OTf)_3$
1			 $HOCH_2\underset{Ph}{\underset{\mid}{C}}HNHPh$	82(25)[a]	90(20)[b]
				100	100
2			 $HOCH_2\underset{Ph}{\underset{\mid}{C}}HNHPh$	80(25)[a]	88(25)[b]
				100	100
3			 $HOCH_2\underset{Ph}{\underset{\mid}{C}}HNHPh$	82(30)[a]	86(25)[b]
				100	100
4			$PhOCH_2CH(OH)CH_2NHPh$	76(45)[c]	81(25)[d]
				100	100
5			$PhOCH_2CH(OH)CH_2NHPh$	77(45)[c]	80(25)[d]
		$H_2NCH_2CH_2CH_2CH_3$	$H_2NCH_2CH_2CH_2CH_3$	100	100
6				69(65)[c]	73(45)[d]
				100	100

[a] 0.03 mmol of $Bi(TFA)_3$.

[b] 0.01 of $Bi(OTf)_3$.

[c] 0.05 mmol of $Bi(TFA)_3$.

[d] 0.02 of $Bi(OTf)_3$.

layers dried with Na_2SO_4. The solvent was evaporated and the crude product purified by chromatography on a silica-gel plate or silica-gel column to afford the pure β-amino alcohols in 68–96% yields.[21]

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21. Selected spectroscopy data: Compound **2** (Table 1, entry 2): viscous liquid, IR (NaCl, cm^{-1}) 3618–3104 (NH and OH), 1603, 1502, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.09 (m, 1H), 1.47 (m, 3H), 1.72 (m, 2H), 2.09 (m, 2H), 2.33 (s, 3H), 3.14 (ddd, 1H, $J = 11.2, 11.2, 6.2$ Hz), 3.31–3.53 (m, 1H), 3.89 (br s, 2H), 6.78–7.02 (m, 4H, Ar–H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 24.7, 25.4, 31.4, 31.8, 33.6, 60.9, 74.8, 115.2, 119.3, 129.8, 147.7. Anal. Calcd for $C_{13}H_{19}NO$: C, 76.06; H, 9.33; N, 6.82. Found: C, 76.35; H, 9.11; N, 6.61. Compound **10** (Table 1, entry 10): viscous liquid; IR (NaCl, cm^{-1}) 3510–3115 (NH and OH), 3009, 1598, 1500, 1068, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.15 (dd, $J = 9.9$, 10 Hz, 2H), 3.26 (dd, $J = 5.1$, 7.2 Hz, 2H), 3.52 (m, 2H), 3.81 (br s, 1H), 4.08 (d, $J = 9.1$ Hz, 2H), 5.23 (d, $J = 12.4$ Hz, 2H), 5.98 (m, 1H), 6.62 (d, $J = 10.2$ Hz, 2H), 7.15 (d, $J = 10.04$ Hz, 2H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 47.4, 69.4, 72.8, 73.9, 113.9, 117.9, 118.5, 129.7, 134.7, 142.7. Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.30; H, 8.39; N, 6.68.