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Opening of epoxides with aromatic amines promoted by indium tribromide: a mild and efficient method for the synthesis of β-amino alcohols

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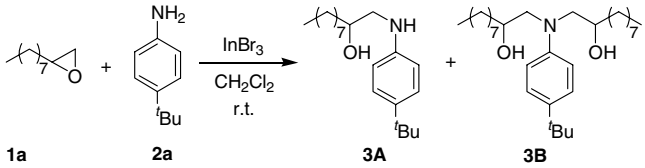
Abstract—A mild and efficient synthesis of β-amino alcohols by aminolysis of epoxides promoted by indium tribromide is described. The methodology is regio- and chemoselective and works well with independence of the epoxide or the aromatic amine used. In addition, the reaction can be carried out in a wide variety of undried solvents under air.

β-Amino alcohols are an important class of organic compounds due to their high occurrence in nature and their use as intermediates in the synthesis of natural products and pharmaceuticals.[1] The aminolysis of oxiranes is a classical route for the preparation of β-amino alcohols; however, there are some significant limitations arising from low nucleophilicity in the case of deactivated aromatic amines, steric factors in sterically bulky amines, and in some cases low boiling points when elevated temperatures are necessary.[2] Even though some of these drawbacks have been overcome with the use of a variety of catalysts,[3] there are still major limitations, such as the formation of bis-alkylated products[4] and low yields with highly hindered anilines.[5] Thus, there is a need for novel conditions and catalysts to carry out the title reaction under mild conditions that can tolerate a variety of functional groups.

Indium tribromide ($InBr_3$) has been found to be an efficient promoter for various transformations, such as, glycosidation,[6] thioacetylation, cyanation of ketones, conjugate addition reactions,[7] *C*-alkylation and sulfonylation of pyrroles and indoles,[8] palladium-catalyzed cross couplings,[9] Friedel–Crafts addition of indoles to epoxides,[10] and nucleophilic ring opening of aziridines.[11] In this context, the unprecedented use of $InBr_3$ in the aminolysis of epoxides together with its tolerance toward a variety of coordinating functional groups, prompted us to study its behavior to overcome the above mentioned limitations.

Therefore, we would like to report a mild, practical, and efficient method for the opening of epoxides with aromatic amines using $InBr_3$ to promote the reaction.

In order to find the best conditions, we first investigated the reaction of decenyl oxide **1a** with a primary aniline such as *p-tert*-butylaniline **2a** in dichloromethane[12] with different loadings of $InBr_3$ (Scheme 1). Thus, after stirring the reaction mixture for 12 h at room temperature β-amino alcohol **3A** was formed, together with variable amounts of the bis-alkylation product **3B** (Table 1). As shown in Table 1, the aminolysis of **1a** tolerated the use of $InBr_3$ in catalytic amounts; however, the best conversion and selectivity were achieved by using 1 equiv of $InBr_3$ (entry 6). When the reaction was carried out with less than an equimolecular amount of $InBr_3$, variable amounts of the undesired dimeric product **3B** were observed (entries 2–5).[13] Conversion was almost



Scheme 1.

Keywords: β-Amino alcohols; Aminolysis; Epoxides; Aromatic amines; Indium tribromide.
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Table 1. Aminolysis of decenyl oxide **1a** with *p-tert*-butylaniline **2a**

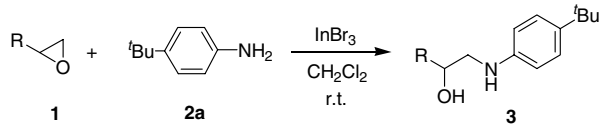
Entry	$InBr_3$ (mol%)	Conversion (%)[a]	**3A**:**3B** ratio[a]
1	5	21	100:0
2	10	43	94:6
3	25	65	98:2
4	50	93	96:4
5	75	94	99:1
6	100	92	100:0
7	0	0	—

[a] Conversion and ratios were determined by GCMS of the crude mixture.

Table 2. Study of the solvent effect in the aminolysis of epoxides promoted by $InBr_3$

Entry	Solvent	Conversion (%)[a]	**3A**:**3B** ratio[a]
1	$ClCH_2CH_2Cl$	93	100:0
2	$CHCl_3$	93	100:0
3	EtOAc	92	100:0
4	CH_2Cl_2	92	100:0
5	Toluene	90	100:0
6	CH_3CN	87	96:4
7	Et_2O	99	87:13
8	THF	94	87:13
9	H_2O	97	50:50
10	MeOH	52	100:0
11	DMF	5	100:0
12	Hexanes	58	100:0

[a] Conversion and ratios were determined by GCMS of the crude mixture.



Scheme 2.

quantitative when using above a half of equivalent of the Lewis acid (entries 4–6). The absence of $InBr_3$ resulted in no epoxide opening (entry 7), with starting materials recovered unreacted even after long reaction times (72 h). Thus, $InBr_3$ was required to promote the title reaction. By-product **3B** was the result of the aminolysis of the epoxide starting material with the more nucleophilic secondary amine **3A**; however, higher amounts of $InBr_3$ minimized the occurrence of **3B**, most likely by increasing the reaction rate.

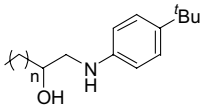
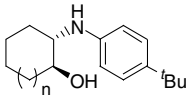
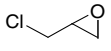
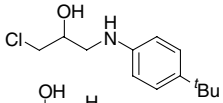
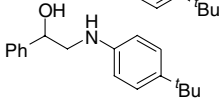
With this promising result in hand, we focused our attention on the study of scope and limitations of the title reaction with respect to the solvent and to the reactants, the aniline and the epoxide.

Thus, we examined the reaction in Scheme 1 in different non-dried undistilled solvents at room temperature, without any precaution to exclude moisture. The results are summarized in Table 2, and show that, high conversions were obtained with nearly all of the solvents used.

The best results were obtained in low-polar solvents such as dichloroethane, chloroform, dichloromethane, toluene, and ethyl acetate. The reaction was slower in MeCN and proceeded sluggishly in solvents such as MeOH, DMF, and hexanes; the latter probably due to the low solubility of the reactants. It is noteworthy that the yield of the reaction was not dependent on the nature of the solvent. However the occurrence of the by-product **3B** was dependent on the solvent used. For example, in coordinating solvents such as Et_2O and THF (entries 7 and 8) 13% of **3B** was formed. It is also interesting to note that when using water as a solvent the conversion was almost quantitative but a higher amount of bis-alkylation product **3B** was obtained (entry 9). This could probably be due to the strong coordinating and solvating ability of water, which would favor the high reactivity of the product **3B** to open the epoxide. From the above results we concluded that the title process is very versatile, since a great variety of different solvents can be used.

We next planned to evaluate the scope and limitations of the reaction with respect to the amine and the epoxide.

Table 3. Study of the aminolysis of different types of epoxides with *p-tert*-butylaniline **2a**[a]

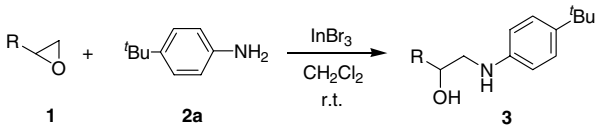
Entry	Epoxide		Amino alcohol		Yield (%)[b]
1		$n = 7$		**3a**	84
2		$n = 5$		**3b**	83
3		$n = 3$		**3c**	78
4		$n = 0$		**3d**	74
5		$n = 1$		**3e**	79
6				**3f**	65
7				**3g**	75

[a] All reactions were carried out according to the general procedure.
[b] Yields refer to isolated pure compounds after column chromatography.

Thus, aliphatic, aromatic, linear, and cyclic epoxides were reacted with *p*-*tert*-butylaniline **2a** in the presence of 1 equiv of $InBr_3$ using undistilled non-dried dichloromethane as solvent at ambient temperature (Scheme 2). In general, the methodology worked well independently of the nature of the epoxide, furnishing the corresponding β-amino alcohol in good yields (Table 3).

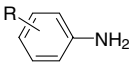
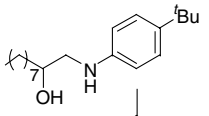
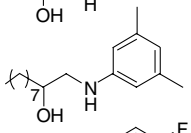
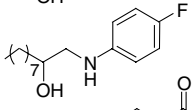
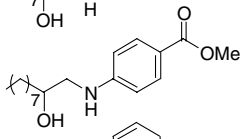
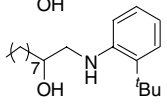
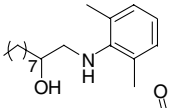
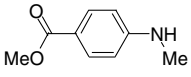
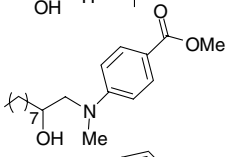
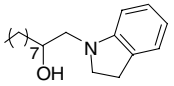
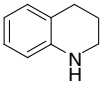
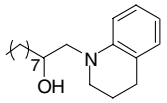
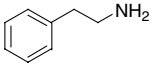
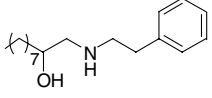
The reaction was completely regioselective since the only products isolated were those coming from the attack of the amine to the less substituted carbon (β) of the epoxide.[14] This selectivity was observed even for styrene oxide (entry 7), as opposed to similar examples previously reported in the literature.[15] In the case of cyclic oxides, the reaction worked well independently of ring-size, and gave exclusively the corresponding *trans*-β-amino alcohols.[16] The relative stereochemistry was determined based on the coupling constants of the peaks at 3.11 ppm (C*H*NHPh; ddd, J = 11.1, 9.1, and 4.0 Hz) and 3.34 ppm (C*H*OH; ddd, J = 9.7, 9.7, and 4.0 Hz) in their ^{1}H NMR spectra.[17] The process also proved to be chemoselective as was illustrated with epichlorohydrin (entry 6) resulting in a 65% yield of the amino alcohol corresponding to nucleophilic attack at the terminal carbon of the epoxide moiety.

Finally, the reaction was carried out using different aromatic amines (Scheme 3). As can be seen from Table 4, the process worked well for all types of aromatic amines independently of their electronic and steric nature, giving good to excellent yields together with complete regio- and chemoselectivity. Thus, anilines carrying



Scheme 3.

Table 4. Opening of epoxide **1a** with different types of aromatic amines **2**[a]

Entry	Amine	R	2	Amino alcohol	3	Yield (%)[b,c]
1		*p*-^{t}Bu	**2a**		**3a**	84
2		*m*,*m*′-di-Me	**2b**		**3h**	62
3		*p*-F	**2c**		**3i**	65
4		*p*-CO_2Me	**2d**		**3j**	79
5		*o*-^{t}Bu	**2e**		**3k**	93
6		*o*,*o*′-di-Me	**2f**[c]		**3l**	81
7			**2g**[c]		**3m**	79
8			**2h**[c]		**3n**	96
9			**2i**[c]		**3o**	85
10			**2j**		**3p**	0

[a] All reactions were carried out following the general procedure.
[b] Yields refer to isolated pure compounds after column chromatography.
[c] Reaction was carried out using 5 mol% of $InBr_3$ during 12 h.

highly deactivating groups such as *p*-fluoroaniline (entry 3) or *p*-carboxymethylaniline (entry 4) gave very reasonable yields under the generally mild conditions used for activated anilines. Sterically hindered amines such as *o*-*tert*-butylaniline (entry 5) and *o*,*o*′-dimethylaniline (entry 6) gave the corresponding β-amino alcohols in excellent yields and selectivities at room temperature.[18] It is noteworthy that in the case of *N*-alkylated anilines the reaction worked well using 5 mol% of $InBr_3$.

In the same way, secondary hindered amines such as indoline (entry 8), 1,2,3,4-tetrahydroquinoline (entry 9), and *p*-carboxymethyl-*N*-methylaniline (entry 7) gave products with very good yields and complete regioselectivities. To the best of our knowledge, there are no literature precedents of epoxide opening with the latter types of amines. As it had been previously noticed in the literature with other Lewis acid promoters,[14] aliphatic amines failed to give the desired β-amino alcohol (entry 10). The lack of reactivity of aliphatic amines toward aminolysis of epoxides has been reported to be due to the stronger complexation with the catalyst as a consequence of their higher basicity.

In summary, we have described a mild, versatile, and efficient method for the opening of epoxides with aromatic amines using indium tribromide as reaction promoter. This method is applicable to a variety of epoxides and aromatic amines, especially deactivated and highly hindered amines, as well as other nitrogen heterocycles; therefore, this procedure can be regarded an attractive alternative to existing methods for the preparation of β-amino alcohols.

Typical experimental procedure. A solution of epoxide **1** (1 mmol) and amine **2** (1 mmol) in a non-dried solvent (14 mL) at room temperature was treated with indium tribromide (1 equiv). The mixture was stirred until total disappearance of starting materials (TLC, GCMS) prior to being quenched by the addition of a saturated solution of ammonium chloride (60 mL), extracted with dichloromethane (60 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (100–200 mesh) using a mixture of *n*-hexanes and ethyl acetate as eluent. β-Amino alcohols **3** were fully characterized according to their data of ^{1}H NMR and mass spectra.

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13. The dimeric product **3B** was isolated after column chromatography and identified by MS and NMR.
14. Similar behavior has been observed using other Lewis acids: (a) Reddy, L. R.; Reddy, M. A.; Bhanumathy, N.; Rao, K. R. *Synthesis* **2001**, *6*, 831–832; (b) Reddy, L. R.; Reddy, M. A.; Bhanumathy, N.; Rao, K. R. *New J. Chem.* **2001**, *25*, 221–222.
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17. The same pattern has been observed before. See, for example: Chandrasekhar, S.; Ramachandar, T.; Prakash, S. J. *Synthesis* **2000**, *13*, 1817–1818, and references cited therein.
18. This type of anilines gave very low yields when using other catalyst systems such as $Cu(OTf)_2$ and $Sn(OTf)_2$. See, for example: Ref. 5.