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Copper(II) tetrafluoroborate-catalyzed ring-opening of epoxides by amines

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Abstract—Copper(II) tetrafluoroborate catalyzes efficiently the selective opening of epoxides by amines leading to the synthesis of β-amino alcohols. The reaction works well with aromatic and aliphatic amines in high yields under solvent-free conditions.

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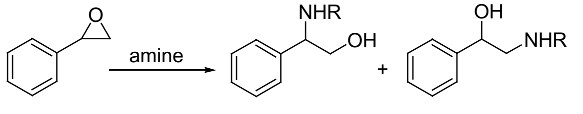
β-Amino alcohols are important intermediates in the synthesis of a large number of biologically active natural and synthetic products[1,2] including chiral auxiliaries.[3] The aminolysis of epoxides is the most common and practical method for the preparation of these compounds.[4] However, these methods require not only high reaction temperatures and long reaction times but also an excess of amine. In addition, these reactions can be accompanied by poor regioselectivity. In recent years, there has been significant interest in the ring-opening reactions of epoxides employing different amines. In order to overcome the shortcomings, a variety of air-sensitive catalysts have been described in the literature for epoxide ring-opening reactions at room temperature.[5] There are also reports where aliphatic amines have failed to react with epoxides in the presence of certain catalysts[6] and so despite the large number of methodologies[7–11] available for this purpose there is a demand for better catalysts. Very recently, a few reports appeared describing ring-opening reactions of epoxides under solvent-free conditions.[12] In continuation of our earlier efforts in this direction,[13] we report a mild, practical and efficient method for the opening of epoxides with different amines employing $Cu(BF_4)_2{\cdot}xH_2O$ under solvent-free conditions. Recently, $Cu(BF_4)_2{\cdot}xH_2O$ was employed as catalyst for the acetylation of phenols, thiols, alcohols and amines and for the formation of acylals.[14]



1 2 3

Scheme 1. Regioselectivity in the ring-opening of styrene oxide **1** with various amines catalyzed by $Cu(BF_4)_2{\cdot}xH_2O$.

In order to understand the scope and limitations of this $Cu(BF_4)_2{\cdot}xH_2O$ catalyzed methodology for the preparation of β-amino alcohols, various epoxides were treated with different amines under solvent-free conditions in the presence of $Cu(BF_4)_2{\cdot}xH_2O$. It was observed that the optimum amount of catalyst required for this process was 10 mol %. We evaluated the regioselectivity of the $Cu(BF_4)_2$ catalyzed epoxide ring-opening reaction with various amines using styrene oxide as a representative unsymmetric epoxide (Scheme 1). The reaction was found to be very fast and complete conversion took place in 5–10 min leading to a quantitative yield of the corresponding amino alcohol. The regioselectivity was determined by GC–MS and ^1H NMR data[12a] and the results are illustrated in Table 1.

The reaction of **1** with aromatic amines afforded the major regioisomer **2** by nucleophilic attack at the benzylic carbon. In the case of aliphatic amines, preferential attack at the terminal carbon of the epoxide may be explained in terms of an S_N2 process.

To establish the generality of the methodology, various epoxides were treated with aniline and morpholine in the presence of $Cu(BF_4)_2{\cdot}H_2O$ and the results are shown in

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Keywords: Copper(II) tetrafluoroborate; β-amino alcohols; Amines; Epoxides; Regioselectivity.

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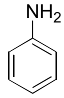
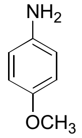
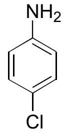
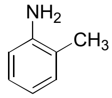
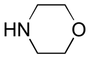
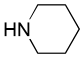
Table 1. Ring-opening of styrene oxide with various amines catalyzed by $Cu(BF_4)_2{\cdot}xH_2O$

Entry	Amine	Time (min)	Yield[a] (%)	Ratio (**2**:**3**)[b]
1		5	97	100:0
2		10	95	96:4
3		5	97	100:0
4		8	92	93:7
5		10	96	16:84
6		10	92	35:65

[a] Isolated yields of the corresponding amino alcohol.

[b] Determined by GCMS and ^{1}H NMR.

Table 2. It was observed that the corresponding amino alcohols were obtained in all cases in excellent yields. In the aminolysis of cyclohexene oxide with various amines, the resultant racemic 2-aryl/alkyl amino cyclohexanol was identified as the *trans*-diastereoisomer on the basis of NMR spectral data. Complete selectivity for nucleophilic attack at the less hindered carbon of the epoxide was observed in the reaction of glycidyl phenyl ether, propylene oxide and glycidyl *tert*-butyl ether. This process was also chemoselective as illustrated using epichlorohydrin, which resulted in the formation of the corresponding aminoalcohol by the nucleophilic attack at the terminal carbon of the epoxide.

In conclusion, we describe a mild and efficient catalyst for the opening of epoxides with amines. The mild reaction conditions, short reaction times, excellent regio-, diastereo-, and chemoselectivity and applicability to both aromatic and aliphatic amines make this a versatile method. The solvent-free conditions employed also make it environmentally friendly and potentially useful for industrial applications.

General procedure: To a magnetically stirred mixture of epoxide (1 mmol) and amine (1 mmol), $Cu(BF_4)_2{\cdot}xH_2O$ (0.10 mmol) was added and the reaction mixture was stirred at room temperature for the appropriate time. After completion of the reaction, the reaction mixture was diluted with Et_2O, dried (Na_2SO_4) and concentrated under reduced pressure to provide the crude product, which was purified by column chromatography to afford the pure β-amino alcohol. All compounds were fully characterized by IR, ^{1}H NMR, and mass spectra.

Acknowledgements

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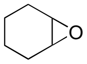
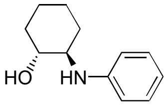
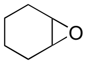
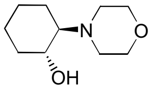
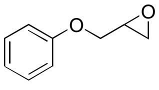
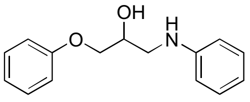
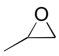
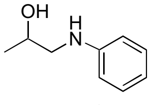
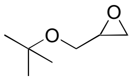
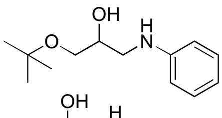
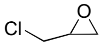
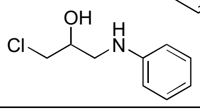
Table 2. Ring-opening of various epoxides with amines catalyzed by $Cu(BF_4)_2{\cdot}xH_2O$

Entry	Epoxide	Product	Time (min)	Yield[a] (%)
1			5	97
2			10	95
3			12	97
4			10	92
5			10	96
6			5	83

[a] Isolated yields of the corresponding amino alcohol.

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