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.

β-Amino alcohols are important intermediates in the synthesis of a large number of biologically active natural and synthetic products1,2 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 catalysts6 and so despite the large number of methodologies7–11 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 catalyzed by Cu(BF₄)₂·xH₂O. Recently, Cu(BF₄)₂·xH₂O was employed as catalyst for the acetylation of phenols, thiols, alcohols and amines and for the formation of acylals.14

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

In order to understand the scope and limitations of this Cu(BF₄)₂·xH₂O 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(BF₄)₂·xH₂O. It was observed that the optimum amount of catalyst required for this process was 10 mol %. We evaluated the regioselectivity of the Cu(BF₄)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 data12a 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 SN₂ process.

To establish the generality of the methodology, various epoxides were treated with aniline and morpholine in the presence of Cu(BF₄)₂·H₂O and the results are shown in
Table 2. Ring-opening of various epoxides with amine alcohol catalyzed by Cu(BF$_4$)$_2$·xH$_2$O

<table>
<thead>
<tr>
<th>Entry</th>
<th>Epoxide</th>
<th>Product</th>
<th>Time (min)</th>
<th>Yield$^a$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>O</td>
<td>HN</td>
<td>5</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>O</td>
<td>OCH$_3$</td>
<td>10</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>Cl</td>
<td>NH$_2$</td>
<td>5</td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td>CH$_3$</td>
<td>NH$_2$</td>
<td>8</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>HN</td>
<td>O</td>
<td>10</td>
<td>96</td>
</tr>
<tr>
<td>6</td>
<td>Cl</td>
<td>HN</td>
<td>10</td>
<td>92</td>
</tr>
</tbody>
</table>

$^a$ Isolated yields of the corresponding amino alcohol.

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$_4$)$_2$·xH$_2$O (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$_2$O, dried (Na$_2$SO$_4$) 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.

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**References and notes**

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