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Zinc-catalyzed aminolysis of epoxides

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Abstract—A series of amino alcohols has been prepared by a novel zinc-catalyzed nucleophilic opening of epoxide rings by amines.

Epoxides are an important class of synthons which have found much use in synthetic organic chemistry.[1–3] Thus, the nucleophilic ring opening of the oxirane ring is often employed for the preparation of sophisticated bioactive molecules.[4] β-Amino alcohols[5] were typically obtained from opening of epoxides with an excess of amines at elevated temperatures. Since very high temperatures may be inappropriate for certain functional groups, a variety of air-sensitive, expensive or specific catalysts have been described in the literature to perform epoxide opening at room or low temperatures.[6–10] However, it has been reported that aliphatic amines failed to react with epoxides in the presence of cobalt,[6] rhodium,[9] or copper[10] catalysts. The use of titanium tetraisopropoxide allowed the aminolysis of epoxides by alkylamines in a pressure reactor.[7] Finally, the intramolecular aminolysis of epoxides catalyzed by diethylaluminium chloride has been performed under an argon atmosphere.[8]

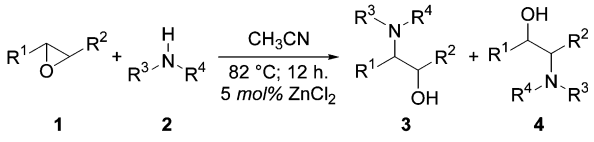
In this paper, a much more simple and effective catalytic route for the synthesis of β-amino alcohols under aerobic conditions is described. The reaction of both an aliphatic or an aromatic amine with an epoxide, in the presence of low-cost zinc(II) chloride as catalyst, leads to the formation of the corresponding regioisomeric β-amino alcohols **3** and **4** (Scheme 1).

Typically, 5 mmol of the amine were reacted with 5 mmol of the epoxide in acetonitrile at 82°C under air for 12 h. The nucleophilic addition is catalyzed by the presence of 5 mol% zinc(II) chloride which is very easy to handle. Several amines and epoxides were employed and the results are reported in Table 1.[11,12]

Three aminolyses of styrene oxide even led to total conversions (entries 1–3). Furthermore, the ring openings were highly regioselective with **3**:**4** ratios ranging from 80:20 to 93:7. At this point, it should be mentioned that no reaction was observed between aniline and styrene oxide in the absence of zinc(II) chloride. Only 40% of β-amino alcohol was obtained when benzylamine was used, probably because of a combination of steric hindrance and its lower nucleophilicity (entry 4). This may also explain the poor regioselectivity (59:41) of this addition. At first sight, the result obtained with 2-(aminomethyl)pyridine was surprising where no conversion of the epoxide could be detected (entry 5). This may be due to co-ordination of the zinc by the pyridine (see Fig. 1).

Indeed, pyridine-containing ligands may be used in order to fine-tune the properties of the zinc catalyst. Furthermore, the utilization of chiral ligands may allow the enantioselective opening of the oxiranes.

The use of ethyl 3-phenylglycidate as the epoxide for reaction with the same nucleophilic amines gave only moderate yields, but with very high regioselectivities (entries 6–8). The low reactivities observed may be due to the chelating properties of ethyl 3-phenylglycidate which reduce the activation of the oxirane ring by the



Scheme 1. Zinc-catalyzed aminolysis of epoxides.

Keywords: ring opening; aminolysis; epoxide; zinc catalyst.
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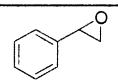
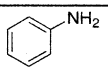
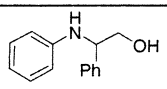
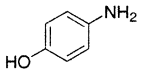
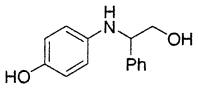
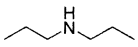
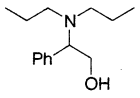
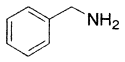
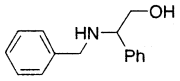
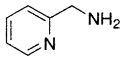
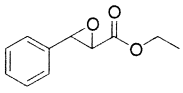
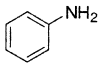
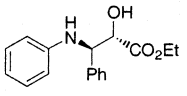
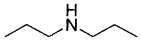
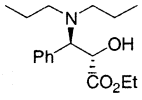
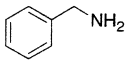
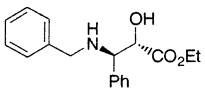
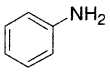
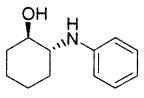
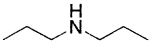
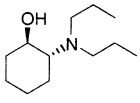
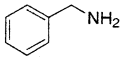
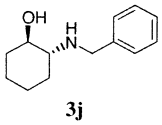
Table 1. β-Aminoalcohols produced via Scheme 1

Entry	1	2	3[12]	Ratio 3:4[a]	Yield %[b]
1			 **3a**	93:7	100
2			 **3b**	89:11	100
3			 **3c**	80:20	100
4			 **3d**	59:41	40
5			No Reaction	-	-
6			 **3e**	91:9	40[c]
7			 **3f**	89:11	44
8			 **3g**	90:10	26
9			 **3h**	-[e]	76[d]
10			 **3i**	-[e]	53
11			 **3j**	-[e]	63

[a]The ratio was determined by Gas Chromatography (GC). See Scheme 1 for **3** and **4**.

[b]The yield was determined by GC, with 2-bromotoluene as an internal standard.

[c]The yield is 96% after a reaction time of 3 days.

[d]71% conversion when the reaction was performed with $ZnBr_2$ as catalyst; 85% with $Zn(ClO_4)_2$.

[e]Only one species.

zinc catalyst (Fig. 2). The coordination of the carbonyl group of the ester function probably decreases the Lewis acidity of the zinc salt. This was confirmed by the total conversion reached after a reaction time of 3 days (entry 6), demonstrating the poorer catalytic activity of the zinc complex.

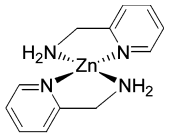


Figure 1. Likely coordination of 2-(aminomethyl)pyridine to zinc.

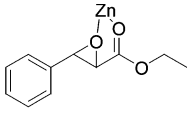


Figure 2. Chelating ability of ethyl 3-phenylglycidate

Finally, three aminolyses were performed on an aliphatic epoxide, namely cyclohexene oxide (entries 9–11). Good yields were achieved (53–76%), taking into account that aliphatic epoxides are less reactive than the aromatic ones. In addition, the aminolysis of cyclohexene oxide by aniline was achieved using other zinc salts as catalysts, i.e. zinc(II) bromide and zinc(II) perchlorate under the same experimental conditions (Table 1, entry 9). $ZnBr_2$ led to 71% conversion while 85% of the epoxide was opened with $Zn(ClO_4)_2$. Further investigations are currently in progress to improve these catalytic activities.

In summary, a simple and regioselective zinc-catalyzed aminolysis of aromatic or aliphatic epoxides performed under air is reported with good to very high yields. The use of 2-(aminomethyl)pyridine as the nucleophilic amine showed the possibility of catalyzing the ring opening by a zinc/pyridine-containing ligand complex. Consequently, the reaction involving bipyridine-derived ligands is currently under investigation and the resulting fine-tuning of the catalyst is expected to allow optimization of the activity, especially in the case of ethyl 3-phenylglycidate. Furthermore, enantioselective zinc-catalyzed aminolysis is now being studied.

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11. **General procedure**: A mixture of the epoxide (5 mmol), the amine (5 mmol), 2-bromotoluene (5 mmol, 855 mg; internal GC standard), and zinc chloride (0.25 mmol, 34 mg) in acetonitrile (20 mL) was stirred under reflux under air for 12 h. After this reaction time, the reaction mixture was filtered under reduced pressure over a small quantity of silica. The filtrate was concentrated in vacuo and analyzed by GC and ^1H NMR.
12. **3a**: δ 3.74 (dd, $J=11.0$, 7.8 Hz, 1H), 3.92 (dd, $J=11.0$, 4.4 Hz, 1H), 4.52 (dd, $J=7.8$, 4.4 Hz, 1H), 6.5–7.5 (m, 10H) ppm; **3b**: δ 3.5–3.9 (m, 2H), 3.45 (dd, $J=6.7$, 4.1 Hz, 1H), 6.9–7.4 (m, 9H) ppm; **3c**: δ 0.95 (t, $J=7.0$ Hz, 6H), 1.2–1.4 (m, 8H), 3.78 (dd, $J=11.0$, 7.7 Hz, 1H), 3.90 (dd, $J=10.8$, 4.7 Hz, 1H), 4.52 (dd, $J=7.7$, 4.7 Hz, 1H), 6.7–7.2 (m, 5H) ppm; **3d**: δ 3.55 (dd, $J=10.6$, 8.6 Hz, 1H), 3.59 (d, $J=12.9$ Hz, 1H), 3.7 (dd, $J=10.6$, 4.3 Hz, 1H), 3.77 (d, $J=12.9$ Hz, 1H), 3.82 (d, $J=4.3$ Hz, 1H), 7.0–7.6 (m, 10H) ppm; **3e**: δ 1.16 (t, $J=9.0$ Hz, 3H), 3.8–4.1(m, 3H), 4.2 (q, $J=9.0$ Hz, 2H), 4.65 (d, $J=6.8$ Hz, 1H), 6.9–7.5 (m, 10H) ppm; **3f**: δ 0.91 (t, $J=7.0$ Hz, 6H), 1.10–1.4 (m, 7H), 2.2–2.4 (m, 4H), 3.45 (d, $J=13.8$ Hz, 1H), 4.09 (d, $J=13.8$ Hz, 1H), 4.18 (q, $J=9.0$ Hz, 2H), 4.65 (d, $J=11$ Hz, 1H), 7.28–7.40 (m, 5H) ppm; **3g**: δ 1.15 (t, $J=8.9$ Hz, 3H), 3.35 (d, $J=13.9$ Hz, 1H), 3.9 (d, $J=13.9$ Hz, 1H), 4.11 (d, $J=6.7$ Hz, 1H), 4.22 (q, $J=8.9$ Hz, 2H), 4.85 (br s, 1H), 7.25–7.43 (m, 10H) ppm; *trans*-**3h**: δ 1.0 (m, 1H), 1.34 (m, 3H), 1.76 (m, 2H), 2.1 (m, 2H), 2.80 (ddd, $J=10.6$, 9.8, 3.8 Hz, 1H), 3.3 (ddd, $J=9.9$, 9.8, 4.6 Hz, 1H), 6.75 (m, 3H), 7.1 (m, 2H) ppm; *trans*-**3i**: δ 0.90 (t, $J=7.2$ Hz, 6H), 1.1–1.4 (m, 7H), 1.6–1.8 (m, 4H), 2.12 (m, 1H), 2.2–2.4 (m, 4H), 3.31 (m, 1H), 4.07 (s, 1H) ppm; *trans*-**3j**: δ 1.08 (m, 1H), 1.34 (m, 3H), 1.40 (s, 2H), 1.79 (m, 2H), 2.1 (m, 2H), 2.85 (ddd, $J=10.4$, 9.7, 3.8 Hz, 1H), 3.3 (ddd, $J=9.9$, 9.7, 4.5 Hz, 1H), 7.06 (m, 5H) ppm.