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$ZrCl_4$ as a new and efficient catalyst for the opening of epoxide rings by amines

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Abstract—Zirconium(IV) chloride catalyses the nucleophilic opening of epoxide rings by amines leading to the efficient synthesis of β-amino alcohols. The reaction works well with aromatic and aliphatic amines in short times at room temperature in the absence of solvent. Exclusive *trans* stereoselectivity is observed for cyclic epoxides. Aromatic amines exhibit excellent regioselectivity for preferential nucleophilic attack at the sterically less hindered position during the reaction with unsymmetrical epoxides. However, in case of styrene oxide, selective formation of the benzylic amine was observed during the reactions with aromatic amines.

β-Amino alcohols are versatile intermediates in the synthesis of a vast range of biologically active natural and synthetic products,[1] unnatural amino acids,[2] and chiral auxiliaries for asymmetric synthesis.[3] The nucleophilic opening of epoxides with amines constitutes a well recognised route for the synthesis of β-amino alcohols.[4] The classical approach,[5] involving heating epoxides with amines, works less well with poorly nucleophilic amines. Moreover, the lack of appreciable regioselectivity, the requirements for high temperature (which poses problems in dealing with sensitive epoxides), and the need for an excess of amine in the classical methods of β-amino alcohol synthesis have led to the necessity for activation of the epoxides so as to increase their susceptibility to nucleophilic attack by amines. The various methodologies developed for this purpose include the use of alumina,[6] metal amides,[7] metal alkoxides,[8] metal triflates,[9] transition metal halides,[10] alkali metal perchlorates,[11] rare earth metal halides,[12] silica under high pressure,[13] and montmorillonite clay under microwave irradiation.[14] However, these methodologies suffer from one or more disadvantages such as long reaction times, elevated temperatures, moderate yields, use of air and/or moisture sensitive catalysts, requirement of stoichiometric amounts of catalyst, costly reagents/catalysts, potential rearrangement to allylic alcohols,[15] potential hazards in handling pyrophoric/moisture sensitive reagents in the preparation of the catalyst, and in most of the cases being applicable to aromatic amines only. Therefore, the development of a better catalyst for the activation of epoxides rendering them more susceptible to nucleophilic attack under milder conditions is in high demand.

Considering the widespread applications of the resultant β-amino alcohols, we felt that a catalyst of choice should be one that is easily available and less costly, less toxic, and operable under environmentally friendly conditions so as to fulfill the 'triple bottom line'[16] philosophy of green chemistry. We reasoned that the high abundance of zirconium in the earth's crust[17] should make zirconium(IV) compounds less costly. Since zirconium, in its normal quadrivalent state displays no redox properties but can attain a covalency maximum up to 8 and displays low toxicity,[18] Zr(IV) compounds should be ideal for catalytic applications. Accordingly, Zr(IV) derivatives are finding increasing commercial use in catalysis.[19] Recently, zirconium sulfophenyl phosphate has been introduced as a heterogeneous catalyst in the preparation of β-amino alcohols via opening of epoxide rings with amines.[20] However, this methodology was not applicable to aliphatic amines and even with aromatic amines the reactions were carried out for a prolonged period (2–22 h). Therefore, we planned to employ various Zr(IV) derivatives to evaluate their catalytic efficiency in carrying out the ring-opening reaction of epoxides with amines and

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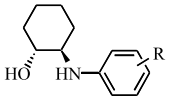
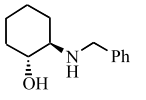
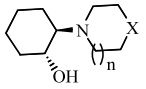
found that $ZrCl_4$ acts as an excellent catalyst for the desired transformation.

In order to delineate the standard operating conditions, cyclohexene oxide **1** (2.5 mmol) was treated with aniline (2.5 mmol) at room temperature under solvent-free conditions in the presence of $ZrCl_4$ (5 mol%). Complete conversion took place in 15 min leading to a quantitative yield of the resultant 2-phenylaminocyclohexanol, identified as the *trans* isomer with characteristic ^1H NMR signals appearing at δ 3.13 (ddd, 1H, $J=10.0$, 10.1, and 3.9 Hz) for the C**H**NH and at 3.33 (ddd, 1H, $J=10.5$, 10.4, and 4.2 Hz) for the C**H**OH protons and a ^{13}C NMR signal at δ 60 for the **C**HNH carbon.[9e,11] The catalyst was recovered by filtration after diluting the reaction mixture with Et_2O and was reused repetitively without any significant loss of catalytic activity. To evaluate the generality, reactions of **1** were carried out with various aromatic and aliphatic amines under the catalytic influence of $ZrCl_4$ and excellent results were obtained (Table 1). The reaction proceeded well with both aromatic and aliphatic amines.

The role of $ZrCl_4$ in catalysing the opening of epoxide rings with amines may be realised through the catalytic cycle depicted in Figure 1. Coordination of Zr^{4+} with the epoxide oxygen (**TS-I**) renders the epoxide susceptible to nucleophilic attack by the amine leading to **TS-II**/**TS-IIa** followed by protonolysis (via intramolecular proton transfer involving **TS-IIa** or intermolecular proton transfer involving **TS-II**) leading to the formation of the amino alcohol and liberation of the catalyst.

Table 1. Reactions of **1** with various amines in the presence of $ZrCl_4$[a]

Entry	Amine	Product[b]	Yield (%)[c]
			
1	R = H	R = H	100
2	R = 2-OMe	R = 2-OMe	100
3	R = 4-Me	R = 4-Me	100
4	R = 4-Cl	R = 4-Cl	95
5			92
			
6	X = CH_2, n = 0	X = CH_2, n = 0	96
7	X = CH_2, n = 1	X = CH_2, n = 1	100
8	X = O, n = 1	X = O, n = 1	100

[a]Cyclohexene oxide (2.5 mmol) was treated with the amine (2.5 mmol) in the presence of $ZrCl_4$ (5 mol%) at room temperature under nitrogen in the absence of solvent for 15 min. [b]The ^1H and ^{13}C NMR analyses confirmed the *trans* stereochemistry of the product. [c]Isolated yields of the corresponding amino alcohol.

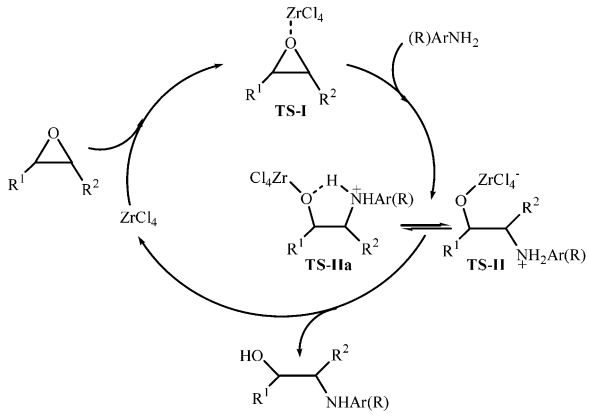


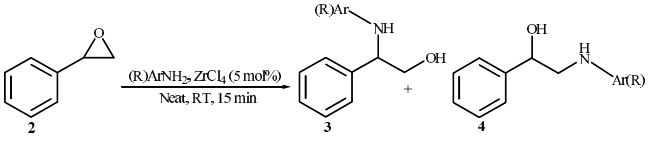
Figure 1. Catalytic cycle during the $ZrCl_4$-catalysed opening of epoxide rings with amines.

The DSC endotherm of the recovered catalyst was found to be identical with that of an authentic sample of $ZrCl_4$ indicating that no ligand exchange takes place during the reaction. The exclusive formation of the *trans* amino alcohol suggests that the initially formed intermediate (**TS-I**) is weakly polar and no distinct charge accumulation on the epoxide carbons takes place.

We next planned to evaluate the regioselective outcome of the $ZrCl_4$-catalysed epoxide opening reaction with various amines using styrene oxide **2** as a representative unsymmetrical epoxide (Scheme 1) and the results are summarised in Table 2.

In all cases the corresponding amino alcohols were obtained in excellent yields. The two isomers could not be separated by column chromatography. On each occasion, the regioselectivity was determined by GC–MS and ^1H NMR. In the MS, the regioisomer **3** exhibited a daughter ion at m/z (M^+–31) due to the loss of CH_2OH and the diagnostic feature in the mass spectra of **4** was the ion peak at m/z (M^+–106) arising from the loss of PhCHO.

For reactions with aromatic amines, the benzylic proton of **3** and **4** appeared $\sim\delta$ 4.5 and 5.0, respectively, in the ^1H NMR. During the reaction with aniline, the GC–MS revealed the product to be a mixture of **3** and **4** in a ratio of 92:8 on the basis of the daughter ions at m/z 213–31 and 213–106 corresponding to **3** and **4**, respectively. The signals at δ 3.6–4.0 (m, 4H), 4.48–4.51 (m, 1H), 6.4–7.5 (m, 10H) in the ^1H NMR of the product could be assigned to 2-phenylamino-2-phenylethanol **3**[8b] and the values at δ 3.1–3.4 (m, 2H),



Scheme 1. Regioselectivity in the epoxide ring opening of styrene oxide **2** with various amines catalysed by $ZrCl_4$.

Table 2. Reactions of **2** with various amines in the presence of $ZrCl_4$[a]

Entry	Amine	Yield (%)[b]	Ratio **3**:**4**[c]
			
1	R = H	98	92:8
2	R = 2-OMe	100	100:0
3	R = 2-Cl	98	100:0
4	R = 4-Me	100	100:0
5	R = 4-Cl	95	100:0
6		96	22:78
7		92	39:61
8		98	40:60
9		94	45:55

[a]Styrene oxide (2.5 mmol) was treated with the amine (2.5 mmol) in the presence of $ZrCl_4$ (5 mol%) at room temperature under nitrogen in the absence of solvent for 15 min. [b]Isolated yields of the corresponding amino alcohols.[c]Determined by GCMS and ^1H NMR analyses of the product.

4.60 (bs, 2H), 4.89–4.97 (m, 1H), 6.5–7.8 (m, 10H) to 2-phenylamino-1-phenylethanol **4**. A 92:8 ratio could be determined for **3**:**4** taking into consideration the integral values of the corresponding benzylic protons.

The benzylic proton of **3** and **4**, arising from the reactions using aliphatic amines, appeared at $\sim\delta$ 3.9 and 4.7, respectively. The ratio of the two regioisomeric products was determined by GC–MS and ^1H NMR (based on the methine and methylene proton signals corresponding to **3** and **4**) and by comparison with the reported values (in the case of the product obtained with piperidine,[21] and benzylamine[11]).

Selective formation of the regioisomeric product **3** arising from nucleophilic attack at the benzylic carbon of **2** was observed during the reactions with aromatic amines (entries 1–5). Aliphatic amines exhibited a preference for nucleophilic attack at the terminal carbon and the best selectivity (22:78) was observed in the case of benzylamine (entry 6). A moderate selectivity in favour of attack at the non-benzylic position was observed for pyrrolidine, piperidine, and morpholine (entries 7–9). The preference for the formation of **3** during the reaction with aromatic amines may be accounted for by the fact that the phenyl group in **2** assists in the stabilization/accumulation of carbocationic character at the benzylic carbon in **TS-I**. Thus, aromatic amines, being less nucleophilic, react selectively at the benzylic carbon of **2**. The preference for reaction at the terminal carbon of **2** by the aliphatic amines may be explained due to the increased nucleophilicity of aliphatic amines, compared to that of aromatic amines, favouring a more S_N2 process.

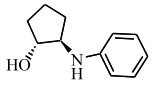
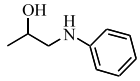
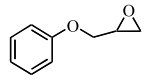
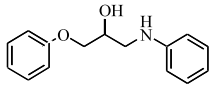
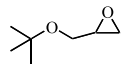
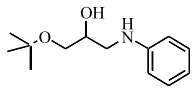
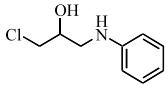
Finally, to claim $ZrCl_4$ as a general catalyst for the activation of epoxides for nucleophilic attack by amines, different epoxides were treated with aniline in the presence of $ZrCl_4$ (5 mol%) and the results are summarised in Table 3.

Quantitative yields of the corresponding amino alcohols were obtained in the reaction of cyclopentene oxide, propylene oxide, glycidyl phenyl ether, and glycidyl *tert*-butyl ether (entries 1–4). A *trans* stereospecificity was observed in the cleavage of the epoxide ring during the reaction of cyclopentene oxide. Completely selective nucleophilic attack at the sterically less hindered terminal carbon of the epoxide moiety in propylene oxide, glycidyl phenyl ether, and glycidyl *tert*-butyl ether was observed.

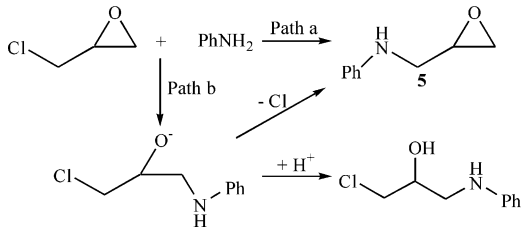
Excellent chemoselectivity was achieved with epichlorohydrin (entry 5) resulting in an 81% yield of the amino alcohol corresponding to nucleophilic attack at the terminal carbon of the epoxide moiety. No product arising from nucleophilic displacement of the chlorine could be detected through GC–MS analysis of the reaction mixture. Nucleophilic attack on epichlorohydrin generally results in the formation of a new methyloxirane **5**. The reaction, in principle, may proceed via two distinct pathways: (i) direct displacement of chlorine (path a) or (ii) initial attack on the epoxide (path b) followed by protonation of the amino alcohol or extrusion of the chlorine atom to give **5** (Scheme 2).[22] It is anticipated that the chlorine atoms in $ZrCl_4$ make the central metal sufficiently electrophilic so as to hold the negative charge of the alkoxide generated after the nucleophilic attack on the metal complexed epoxide. Thus, the free alkoxide anion is not available for subsequent elimination of the chloride anion.

In conclusion, $ZrCl_4$ is a new, highly efficient, and reusable catalyst for the opening of epoxides with amines leading to the synthesis of β-amino alcohols.

Table 3. Reaction of various epoxides with aniline in the presence of $ZrCl_4$[a]

Entry	Epoxide	Product[b]	Yield (%)[c]
1			100[d]
2			100
3			100
4			100
5			81

[a]The epoxide (2.5 mmol) was treated with aniline (2.5 mmol) in the presence of $ZrCl_4$ (5 mol%) at room temperature under nitrogen in the absence of solvent for 15 min. [b]Determined by GCMS and $^1H/^{13}C$ NMR. [c]Isolated yields of the corresponding amino alcohol. [d]The ^1H and ^{13}C NMR analyses established the *trans* stereochemistry of the product.



Scheme 2. Reaction of epichlorohydrin with a nucleophile.

The specific advantages are that the reactions are carried out under mild conditions in short times, with excellent stereo-, regio-, and chemoselectivity, and work for aromatic and aliphatic amines. The low cost and lack of appreciable toxicity of $ZrCl_4$[23] are consistent with increasing environmental concerns.[24] The solvent-free reaction conditions employed in the present method will make it 'environmentally friendly' and potentially useful for industrial applications.

Typical procedure: 2-(phenylamino)cyclohexanol: $ZrCl_4$ (0.03 g, 5 mol%) was added to a magnetically stirred mixture of **1** (0.25 mL, 2.5 mmol) and aniline (0.225 mL, 2.5 mmol) at room temperature under nitrogen. After completion of the reaction (15 min, TLC), the reaction mixture was diluted with Et_2O (15 mL) and the precipitated catalyst was separated by decantation of the supernatant ethereal solution. The catalyst was washed with Et_2O (10 mL) and the combined ethereal solutions were dried (Na_2SO_4) and concentrated in vacuo to afford 2-(phenylamino)cyclohexanol (0.475 g, 100%), mp 57–59°C (lit.[9e] 58–59°C); ^1H NMR ($CDCl_3$) δ 1.03–1.42 (m, 4H), 1.72–1.78 (m, 2H), 2.10–2.16 (m, 2H), 2.8–3.0 (m, 2H, D_2O exchangeable), 3.13 (ddd, 1H, $J=3.9$, 10.0, 10.1 Hz), 3.33 (ddd, 1H, $J=4.2$, 10.4, 10.5 Hz), 6.7–7.2 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 24.27, 25.02, 31.62, 33.15, 60.17, 74.55, 114.40, 118.38, 129.34, 147.81; EIMS (m/z) 191 (M^+).

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