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YCl_3-Catalyzed Highly Selective Ring Opening of Epoxides by Amines at Room Temperature and under Solvent-Free Conditions

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Received: 16 October 2017; Accepted: 6 November 2017; Published: 10 November 2017

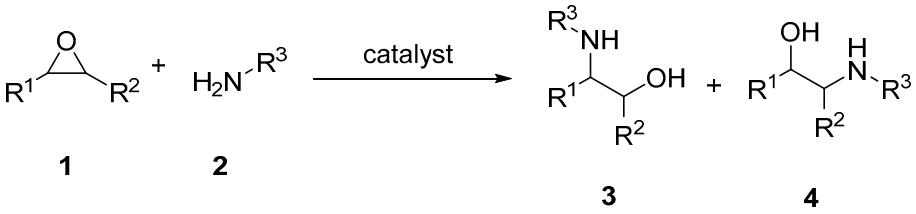
Abstract: A simple, efficient, and environmentally benign approach for the synthesis of β-amino alcohols is herein described. YCl_3 efficiently carried out the ring opening of epoxides by amines to produce β-amino alcohols under solvent-free conditions at room temperature. This catalytic approach is very effective, with several aromatic and aliphatic oxiranes and amines. A mere 1 mol % concentration of YCl_3 is enough to deliver β-amino alcohols in good to excellent yields with high regioselectivity.

Keywords: epoxides; β-amino alcohols; rare-earth metal catalysis; green chemistry

1. Introduction

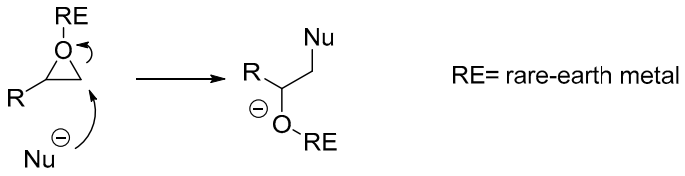
The *β*-amino alcohols are categorized as very useful chemical compounds due to their presence in numerous natural products, medicinally important molecules and ligands or chiral auxiliaries [1–3]. Other applications of these versatile compounds include their use as intermediates/precursors in the synthesis of cosmetics and daily-use products such as perfumes, hair dyes, and photo developers [4]. Moreover, β-amino alcohols are very useful precursors towards structurally complex and intriguing chemical compounds such as (multi-)cyclic organic compounds which can be obtained through rather facile chemical transformations or through synthesizing metalloorganic compounds via complexation with a metal center [5,6].

The simplest approach to the β-amino alcohols is the ring opening of epoxides with amines (Scheme 1) [7]. This approach is usually met with some limitations such as kinetically slow reactions that may be due to inefficient activation of epoxides and low regioselectivity. To overcome these issues, many new catalytic methods have been introduced using various catalysts, with aims to enhance the electrophilicity of epoxides through metallic coordination or H-bonding [8–26]. The *N*-alkylation of amines using cyclic carbonates is also an attractive approach to molecules under discussion [27,28]. Many methods for the synthesis of β-amino alcohols from epoxides or cyclic carbonates require a high reaction temperature, dry reaction conditions, and high catalyst loadings. The preparation of β-amino alcohols under solvent-free conditions and at room temperature is desirable and important due to environmental considerations.



Scheme 1. Aminolysis of epoxides for the synthesis of β-amino alcohols.

Rare-earth metals including lanthanides, scandium, and yttrium are being increasingly exploited in organic synthesis because of their unique reactivity and selectivity [29–37]. Rare-earth metals tend to be oxyphilic, in general, and exhibit a highly Lewis-acidic character. One work involving rare-earth Lewis acid catalysts such as YCl_3 demonstrated a highly efficient catalytic strategy towards the synthesis of cyclic carbonates via epoxide activation [38]. Similarly, we envisaged the Lewis-acidic activation of epoxide by Sc- and Y-based catalysts, thus making epoxide susceptible to nucleophilic attack by amines to produce β-amino alcohols (Scheme 2).



Scheme 2. Lewis-acidic activation of epoxide by YCl_3.

In this work, we report a simple, efficient, and environmentally friendly method using a rare-earth metal-based catalyst, YCl_3, for the ring opening of a library of epoxides by various amines under solvent-free conditions at room temperature. To the best of our knowledge, the ring-opening reaction of epoxide with amines catalyzed by YCl_3 has not been reported before.

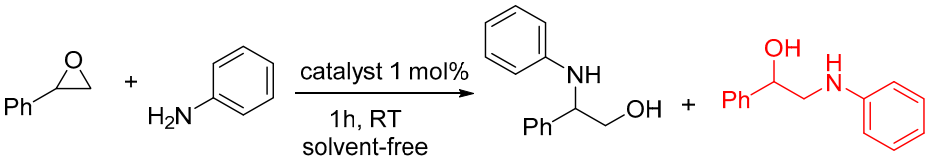
2. Results and Discussion

Initially, we screened the ring-opening reaction of styrene oxide (**1a**) as the model substrate with aniline (**2a**) as the model nucleophile at room temperature. The conversion and regioselectivity were calculated based on ^{1}H-NMR of crude reaction mixture, and the results are summarized in Table 1. In the absence of a catalyst, only traces of corresponding β-amino alcohol were observed. In the presence of 1 mol % YCl_3 as a catalyst, we were delighted to see a more than 90% conversion of **1a**, producing both possible regioisomers, **3aa** and **4aa** (Table 1, entry 2). The result indicates that the reaction proceeded smoothly with high regioselectivity (**3aa**:**4aa**, 93:7). After 3 h of reaction, 1 mol % loading of YCl_3 gave a 100% conversion of **1a** under solvent-free conditions (Table 1, entry 6). Under identical reaction conditions, $ScCl_3$ gave an 82% conversion of 1a with 92% regioselectivity towards **3a** (Table 1, entry 3).

We tried a higher catalyst loading (5 mol %) for both YCl_3 and $ScCl_3$ and found no noticeable effect on regioselectivity of the reaction; however, an increase in rate of substrate conversion was noted (Table 1, entries 4 and 5). Adding the solvent to the reaction had a negative effect on the catalytic activity of Lewis acids. When $CHCl_3$ was used as the reaction solvent with 1 mol % YCl_3 and at room temperature, only a 50% conversion of **1a** was noted after a 1 h reaction time (Table 1, entry 7), and it took more than 12 h to achieve full conversion of the epoxide under these conditions. It is worth noting that, when 5 mol % YCl_3 was used with and without the solvent ($CHCl_3$), the aminolysis of **1a** was slightly slower in the presence of a solvent, further confirming that the highest efficiency of YCl_3 can be achieved under solvent-free conditions (Table 1, entry 8). Full conversion of **1a** was noticed after 2 h using 5 mol % YCl_3 in $CHCl_3$, while under a solvent-free condition, 100% conversion was noted after

1 h. Similarly, a 5 mol % loading of $ScCl_3$ also gave a lower conversion of **1a** (88%) in the presence of $CHCl_3$ (Table 1, entry 9) compared to solvent-free conditions (100%) (Table 1, entry 5).

Table 1. Optimization studies for the aminolysis of styrene oxide (**1a**).



1a **2a** **3aa** **4aa**

Sr. No.	Catalyst	Conversion (%)	3aa:4aa Ratio (%)
1	None	NR	-
2	YCl_3	90	93:7
3	$ScCl_3$	82	92:8
4 [a]	YCl_3	100	93:7
5 [b]	$ScCl_3$	100	92:8
6 [c]	YCl_3	100	93:7
7 [d]	YCl_3	50	94:6
8 [e]	YCl_3	87	94:6
9 [f]	$ScCl_3$	88	93:7
10	$NbCl_5$	82	87:13
11	$ZrCl_4$	75	87:13
12	$ZnCl_2$	traces	nd
13	$Nb(OEt)_5$	85	82:18

[a] 5 mol % YCl_3; [b] 5 mol % $ScCl_3$; [c] 3 h; [d] $CHCl_3$ as reaction solvent; [e] 5 mol % YCl_3 and $CHCl_3$ as reaction solvent; [f] 5 mol % $ScCl_3$ and $CHCl_3$ as reaction solvent. NR = No Reaction; nd = not determined.

We also compared the catalytic activity of four transition metal-based Lewis acid catalysts $NbCl_5$, $ZrCl_4$, $ZnCl_2$, and $Nb(OEt)_5$ (Table 1, entries 10–13). When used under solvent-free conditions at room temperature, 1 mol % $NbCl_5$, $Nb(OEt)_5$, and $ZrCl_4$ gave conversions of 82%, 85%, and 75%, respectively, after a 1 h reaction time with a decrease in regioselectivity when compared to tested rare-earth based catalysts. The change in counter anion in the case of $Nb(OEt)_5$ did not result in any considerable change or enhancement in catalytic activity towards aminolysis. Moreover, to our surprise, $ZnCl_2$ gave almost no conversion under identical reaction conditions, even when reaction time was prolonged to 5 h. Figure 1 shows the proton nuclear magnetic resonance (^{1}H-NMR) spectra for the aminolysis reaction of **1a** with **2a** for all tested catalysts under identical reaction conditions. Comparatively, YCl_3 as a catalyst seemed to be the best choice amongst the tested series of catalysts considering the higher conversion of epoxide and higher regioselectivity (Figure 1 and Table 1).

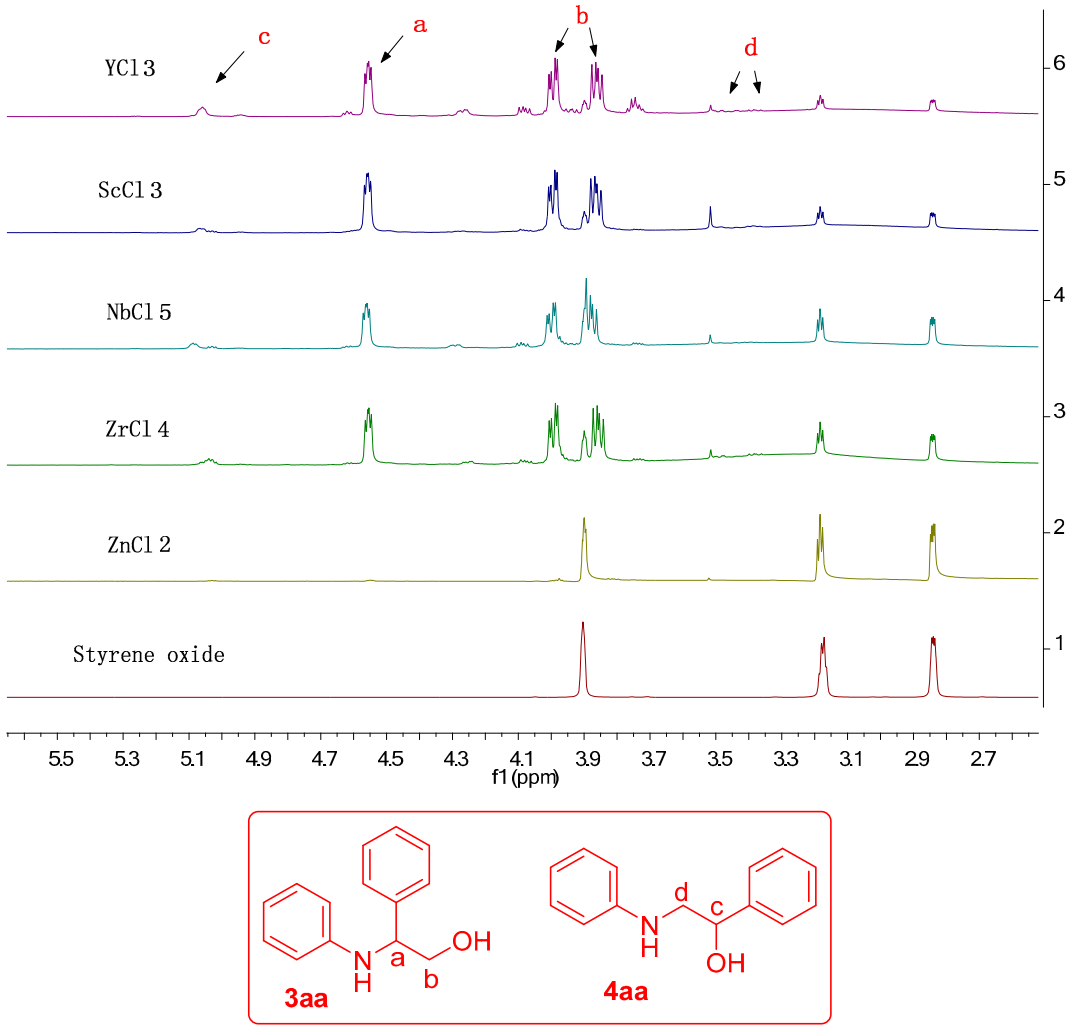
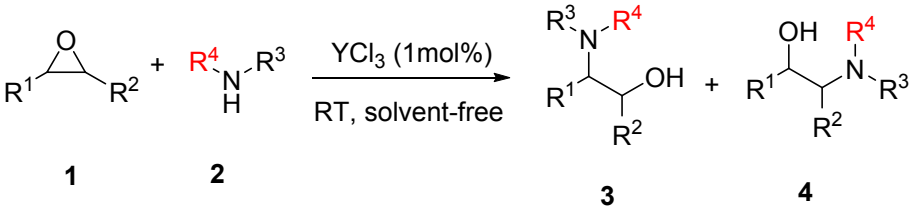


Figure 1. Comparative analysis of ^{1}H-NMR spectra of crude mixtures of regioselective ring-opening reaction of styrene oxide (**1a**) with aniline (**2a**) using different metal catalysts to give (**3aa**) and (**4aa**). The regioisomer (**3aa**) forms predominantly, as can be observed from spectra. The letters a, b, c, and d indicate the peaks or peak region corresponding to protons on carbons indicated by a, b, c and d in chemical structures of **3aa** and **4aa**. Reaction conditions: **1a** (1 equiv.), **2a** (1 equiv.), catalyst (1 mol %), RT, 1 h.

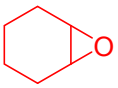
The most convenient and economically friendly reaction conditions—1 mol % YCl_3, no solvent, and room temperature—were then applied to overnight reactions of structurally diverse epoxides and various amines as nucleophiles. The results are summarized in Table 2. The results showed that the aminolysis of **1a** proceeds efficiently with aromatic amines such as aniline (**2a**), 3-methoxyaniline (**2b**), and 4-chloroaniline (**2c**) (Table 2, entries 1–3), giving a 100% conversion of **1a** with excellent regioselectivity, while the presence of a strong electron-withdrawing nitro group in 4-nitroaniline (**2d**) showed a negating effect on the reaction, giving only a 13% conversion of **1a** in an almost equimolar mixture of **3ad** and **4ad** regioisomers (Table 2, entry 4).

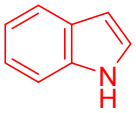
Table 2. Ring-opening of epoxides with amines catalyzed by YCl_3.

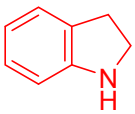


1a: R^1=Ph, R^2=H
1b: R^1=CH_2Cl, R^2=H
1c: R^1=Me, R^2=H
1e: R^1=CH_2=CH_2, R^2=H
1f: R^1=CO_2Me, R^2=Me

2a: R^3=Ph, R^4=H
2b: R^3=3-OMe-C_6H_5, R^4=H
2c: R^3=4-Cl-C_6H_5, R^4=H
2d: R^3=4-NO_2-C_6H_5, R^4=H

1d= 

2e= 

2f= 

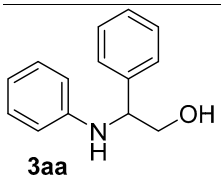
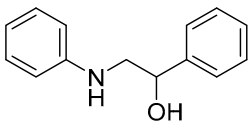
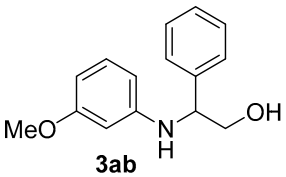
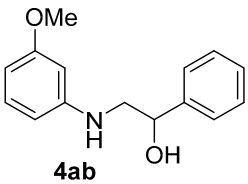
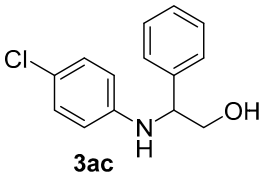
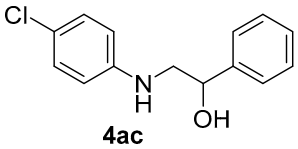
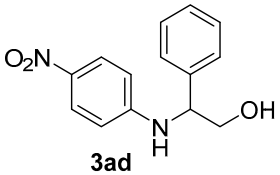
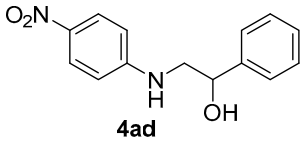
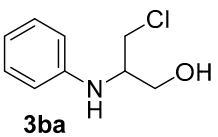
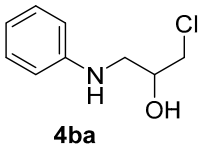
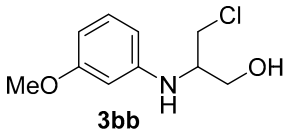
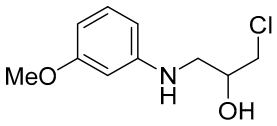
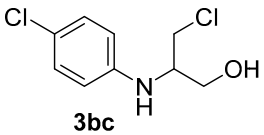
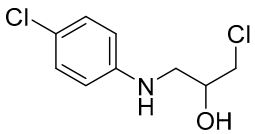
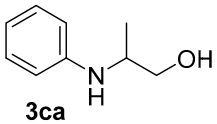
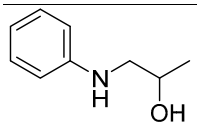
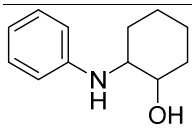
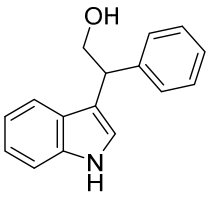
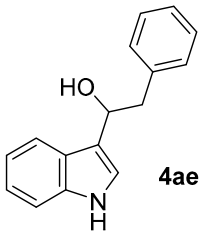
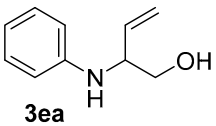
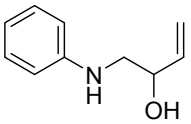
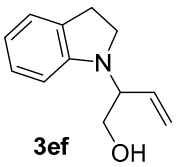
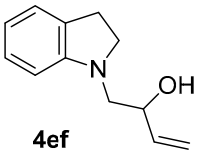
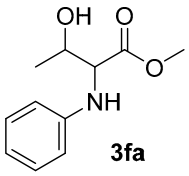
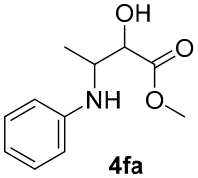
Sr. No.	Epoxide 1	Amine 2	3	4	Epoxide Conversion [a] and 3:4 Ratio [b] (%)
1	1a	2a	 **3aa**	 **4aa**	100 93:7
2	**1a**	2b	 **3ab**	 **4ab**	100 >99:<1
3	**1a**	2c	 **3ac**	 **4ac**	100 98:2
4	**1a**	2d	 **3ad**	 **4ad**	13 50:50
5	1b	**2a**	 **3ba**	 **4ba**	100 19:81

Table 2. *Cont.*

Sr. No.	Epoxide 1	Amine 2	3	4	Epoxide Conversion [a] and 3:4 Ratio [b] (%)
6	**1b**	**2b**	 **3bb**	 **4bb**	70 <1:>99
7	**1b**	**2c**	 **3bc**	 **4bc**	100 2:98
8	1c	**2a**	 **3ca**	 **4ca**	100 70:30
9	1d	**2a**			100 -
10	**1a**	2e	 **3ae**	 **4ae**	30 93:7
11	1e	**2a**	 **3ea**	 **4ea**	75 83:17
12	**1e**	2f	 **3ef**	 **4ef**	100 82:18
13	1f	**2a**	 **3fa**	 **4fa**	100 0/100

[a,b] Based on ^{1}H-NMR of crude reaction mixture.

We also carried out aminolysis of epichlorohydrin (**1b**), an interesting molecule with applications in polymer chemistry with different amines. When reacted with **2a** and **2c**, it showed full conversion and moderate results with respect to regioselectivity (Table 2, entries 5 and 7). On the other hand, reaction with **2b** resulted in poor conversion of **1b** and lower regioselectivity (Table 2, entry 6).

Unlike **1a**, **1b** gave **4** as a major regioisomer. This shift in regioselectivity can be attributed to the nucleophilic attack of amine at less hindered site of the epoxide ring (S_N2 mechanism). Propylene oxide (**1c**) was also successfully tested for YCl_3-catalyzed aminolysis with **2a** to give 100% conversion (Table 1, entry 7). We also investigated the preparation of β-amino alcohols from a cyclic epoxide, cyclohexene oxide (**1d**) using **2a** as nucleophilic amine; the corresponding reaction gave full conversion of **1d** (Table 2, entry 9). The reaction of **1a** with indole (**2e**), a very commonly studied heterocyclic amine due to its structural features and biological importance [39–44], gave only a 30% conversion of **1a** (Table 2, entry 5) but, interestingly, 91% regioselectivity (Table 2, entry 10). Since the most reactive position of **2e** is C3, the C3-attack is favored to give **3ae** and **4ae**.

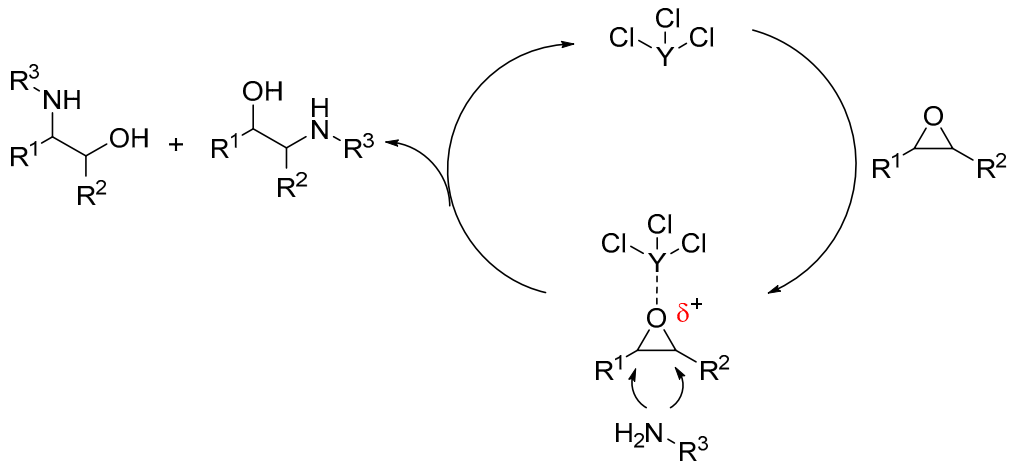
Butadiene monoxide (**1e**) is an important epoxide substrate considering its current and potential applications in polymer chemistry [45,46]. When subjected to aminolysis with **2a** and indoline (**2f**), it gave 75% and 100% conversions, respectively (Table 2, entries 11 and 12) with moderate regioselectivity. The resultant β-amino alcohols could be used to develop novel polymeric materials with numerous applications through simple polymerization processes. To further test the potential of our catalytic approach, we tried a novel epoxide, **1e**, as a challenging substrate bearing electron-withdrawing ester functionality. Interestingly, aminolysis of **1e** with **2a** gave full conversion of **1e**, further establishing the potential of rare-earth based catalysts for aminolysis of epoxides. Moreover, **1e** gave **4ea** as the only product, indicating the nucleophilic attack of **1a** at less hindered sites, similarly following the trend of **1b** bearing a chloromethyl substituent.

Finally, we compared the activity of our present catalytic system with that of some of the previously reported catalysts used for the synthesis of β-amino alcohols under solvent-free conditions and at room temperature. These results are summarized in Table 3 for the reaction of **1a** and **2a** as the model reaction. These results indicate that some of these reactions involved the use of complex catalysts for the activation of epoxide and higher catalyst loading, and some systems required longer reaction time. Our rare-earth based metal catalyst (YCl_3), however, demonstrates better catalytic efficiency for the synthesis of β-amino alcohols.

Table 3. Data regarding the solvent-free aminolysis of styrene oxide (**1a**) with aniline (**2a**).

Sr. No.	Catalyst	Cat. Loading (mol %), Temperature (°C)/Time (h)	Conversion (%)	Ref.
1	$(Et_4N)_2[MnL^2Cl]$	1 25/4	99	[47]
2	$[Co(L^1)Cd(OH_2)_2(NO_3)]\cdot H_2O$	1 r.t./4	98	[48]
3	$[(L^2(H_2))Zn(NO_3)_2]$	2 30/4	98	[49]
4	Nano Fe_3O_4	10 r.t./20	83	[50]
5	YCl_3	1 25/3	100	This work

The plausible mechanism of the reaction involves the activation of the epoxide ring by Lewis-acidic and oxyphilic YCl_3 (Scheme 3). The catalyst activates the epoxide ring through interaction with the oxygen atom of the epoxide, making the epoxide ring more vulnerable to nucleophilic attack by amines. Interestingly, the nucleophilic attack was found to be regioselective for most of the substrates.



Scheme 3. A plausible mechanism for the ring-opening reactions of epoxides with amines catalyzed by YCl_3.

The nucleophilic attack at sterically hindered site indicates the dominance of the electronic effect (S_N1-type mechanism) over the steric effect due to the possible stabilization of intermediate carbocation in resonance with substituents such as the phenyl ring or the double bond. On the other hand, the results obtained for **1b** and **1e** indicate that the nucleophilic attack occurs at less hindered site of the epoxide ring (S_N2 mechanism).

3. Materials and Methods

All chemicals were obtained from commercial vendors and used without further purification. Styrene oxide was purchased from TCI Chemicals Co. Ltd., Tokyo, Japan. 1,2-propylene oxide, cyclohexene oxide epichlorohydrin, 4-nitroaniline and 4-chloroaniline were purchased from Merck, Darmstadt, Germany. Butadiene monoxide was purchased from Alfa Aesar, Ward Hill, MA, USA. Aniline was purchased from Panreac AppliChem, Darmstadt, Germany. Indole, indoline and 3-methoxyaniline were purchased from Acros Organics, Geel, Belgium.

All reactions were performed in vials. The reaction progress was routinely monitored by ^{1}H-NMR and analytical thin-layer chromatography (TLC) using a pre-coated silica gel glass plates. The products were identified and analyzed using IR, ^{1}H-NMR, and ^{13}C-NMR. The IR spectra were recorded on a Frontier FT-IR spectrometer (PerkinElmer Inc., Waltham, MA, USA). The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker Ascend^{TM} 600 MHz spectrometer (Bruker Co., Billerica, MA, USA) using $CDCl_3$ as a reference solvent. The mass analysis data was obtained from Compact mass spectrometer (Bruker Co., Billerica, MA, USA).

3.1. General Procedure

In a general procedure, epoxide (1 mmol) and amine (1 mmol) were placed in a vial equipped with a magnetic stirrer and plastic cap. The mixture was stirred at room temperature in the presence of YCl_3 (1 mol %) without solvent. After the reaction, the crude mixture was purified by column chromatography using silica gel as stationary phase. All products were identified by spectroscopic studies and by comparison with the previously described physical and spectroscopic data of the β-amino alcohols.

3.2. Spectroscopic Data

All β-amino alcohols are known except for **3ab**, **3ea**, **3ef**, **4ef**, and **4fa**, which are new compounds, whose spectroscopic data are given below.

2-((3-methoxyphenyl)amino)-2-phenylethan-1-ol (3ab, Table 2, Entry 2). ^{1}H-NMR (600 MHz, $CDCl_3$): δ = 3.57 (s, 3H), 3.61 (m, 1H), 3.79 (dd, *J* = 11.1, 3.8 Hz, 1H) 4.37, (t, *J* = 5.4 Hz, 1H), 6.02 (s, 1H),

6.09 (d, *J* = 8.0 Hz, 1H), 6.14 (d, *J* = 8.2 Hz, 1H), 6.90 (t, *J* = 8.1 Hz, 1H), 7.15 (t, *J* = 6.9 Hz, 1H), 7.22 (m, 4H). ^{13}C-NMR (MHz, CDCl3): δ = 55.2, 60.1, 67.4, 100.1, 103.2, 107.1, 126.9, 127.8, 129.0, 130.1, 140.3, 148.9, 160.8. MS (APCI): *m*/*z* calculated for $[M + 1]^+$: 244.1332 Found: 244.1323 FT-IR (ATR): 3394, 1609, 1598, 1492, 1450, 1304, 1210, 1036, 908, 827, 751, 729, 701, 687.

1-(phenylamino)but-3-en-2-ol (3ea, Table 2, Entry 11). ^{1}H-NMR (600 MHz, $CDCl_3$): δ = 3.62 (dd, *J* = 10.7, 6.3 Hz, 1H), 3.77 (dd, *J* = 10.8, 3.8 Hz, 1H), 4.02 (d, *J* = 4.0 Hz, 1H), 5.24 (d, *J* = 10.4 Hz, 1H), 5.31 (d, *J* = 17.2 Hz, 1H), 5.80 (m, 1H), 6.65 (d, *J* = 7.8Hz, 2H), 6.72 (t, *J* = 7.1 Hz, 1H), 7.16 (t, *J* = 7.5 Hz, 2H). ^{13}C-NMR (MHz, CDCl3): δ = 57.9, 65.1, 70.7, 114.1, 117.6, 118.3, 129.4, 136.6, 147.5. MS (APCI): *m*/*z* calculated for C10H14NO $[M + 1]^+$: 164.0169 Found: 164.1064 FT-IR (ATR): 3388, 1598, 1500, 1433, 1416, 1316, 1067, 1028, 992, 922, 872, 746, 690.

1-(indolin-1-yl)but-3-en-2-ol (3ef, Table 2, Entry 12). ^{1}H-NMR (600 MHz, $CDCl_3$): δ = 3.02 (m, 4H), 3.17 (q, *J* = 8.0 Hz, 1H), 3.29 (q, *J* = 8.8 Hz, 1H), 3.53 (q, *J* = 8.0 Hz, 1H), 4.37 (s, 1H), 5.22 (d, *J* = 10.5 Hz, 1H), 5.39 (d, *J* = 17.2 Hz, 1H), 5.92 (m, 1H), 6.55 (d, *J* = 7.9 Hz, 1H), 6.70 (t, *J* = 7.3 Hz, 1H), 7.08 (dd, *J* = 18.0, 7.6 Hz, 2H). ^{13}C-NMR (MHz, CDCl3): δ = 29.0, 54.9, 57.4, 70.7, 107.7, 116.4, 118.7, 124.8, 126.9, 127.6, 138.3, 152.8. MS (APCI): *m*/*z* calculated for $[M + 1]^+$: 190.1226 Found: 190.1226 FT-IR (ATR): 3399, 1603, 1489, 1268, 1235, 1050, 992, 922, 743, 715.

2-(indolin-1-yl)but-3-en-1-ol (4ef, Table 2, Entry 12). ^{1}H-NMR (600 MHz, $CDCl_3$): δ = 2.98 (m, 2H), 3.35 (q, *J* = 9.4 Hz, 1H), 3.45 (q, *J* = 6.0 Hz, 1H), 3.80 (m, 2H), 4.19 (q, *J* = 7.02 Hz, 1H) 5.25 (dd, *J* = 20.0, 14.1 Hz, 2H), 5.77 (m, 1H), 6.53 (d, *J* = 7.9 Hz, 1H), 6.67 (t, *J* = 7.3 Hz, 1H), 7.06 (m, 2H). ^{13}C-NMR (MHz, CDCl3): δ = 28.6, 47.4, 60.2, 62.2, 108.2, 119.5, 124.8, 124.5, 130.5, 132.5, 151.4. MS (APCI): *m*/*z* calculated for $[M + 1]^+$: 190.1226 Found: 190.1222 FT-IR (ATR): 3380, 1606, 1486, 1461, 1254, 1050, 1025, 922, 743, 712.

Methyl 3-hydroxy-2-(phenylamino)butanoate (3fa, Table 2, Entry 13). ^{1}H-NMR (600 MHz, $CDCl_3$): δ = 1.08 (d, *J* = 6.5 Hz, 3H), 3.82 (s, 3H), 3.93 (m, 1H), 4.42 (d, *J* = 1.3 Hz, 1H), 6.66 (d, *J* = 8.2 Hz, 2H), 6.72 (t, *J* = 7.3 Hz, 1H), 7.17 (t, *J* = 7.7 Hz, 1H). ^{13}C-NMR (MHz, CDCl3): δ = 14.4, 51.5, 52.9, 71.6, 114.3, 118.4, 129.6, 146.7, 174.3. MS (APCI): *m*/*z* calculated for $[M + 1]^+$: 210.1124 Found: 210.1122 FT-IR (ATR): 3388, 1732, 1601, 1500, 1433, 1254, 1212, 1126, 1075, 1017, 749, 690.

4. Conclusions

In summary, we have demonstrated a new, simple, highly efficient, and environmentally friendly method for the synthesis of β-amino alcohols using a rare-earth metal catalyst, YCl_3. This catalytic strategy provides β-amino alcohols with high selectivity and in good to excellent yields under solvent-free conditions at room temperature. Various epoxides and amines could be successfully employed under these conditions to give corresponding β-amino alcohols. Mechanistic studies and asymmetric catalytic versions of this method are under investigation in our laboratory. We also have commenced studies for further expansion of our approach to carry out novel transformations based on rare-earth metal catalysis; new findings will be reported in due time.

Acknowledgments: R.R.S. is thankful to National Research Council of Thailand for an NRCT Foreign Researcher award. R.R.S., and W.N. are thankful to Vidyasirimedhi Institute of Science and Technology for research facilities and financial support for this work. R.A.K. and A.A. extend their appreciation to the Deanship of Scientific Research at King Saud University for funding this work through research group no. RG-1438-006.

Author Contributions: R.R.S. conceived and designed the experiments; W.N. performed the experiments and provided the spectroscopic data in the paper; R.R.S. and W.N. analyzed the data; R.A.K. and A.A. gave suggestions while the paper was written. R.R.S. wrote the paper.

Conflicts of Interest: The authors declare no conflict of interest.

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