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$Y(NO_3)_3{\cdot}6H_2O$ catalyzed regioselective ring opening of epoxides with aliphatic, aromatic, and heteroaromatic amines

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Abstract

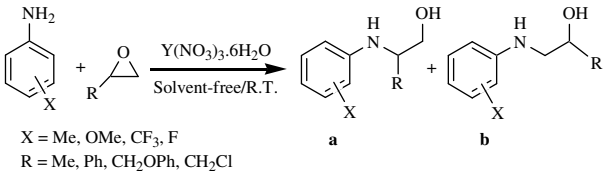
Yttrium nitrate hexahydrate [$Y(NO_3)_3{\cdot}6H_2O$] was found to be an efficient catalyst for selective ring opening of epoxides with aliphatic, aromatic, and heteroaromatic amines at room temperature under solvent-free conditions. The system tolerated a variety of hindered and functionalized epoxides/amines and afforded the desired β-amino alcohols at low catalyst concentration.

Keywords: Epoxides; Amines; 2-Amino alcohols; Yttrium nitrate hexahydrate; Regioselectivity

Amino alcohols constitute an important class of compounds having both chemical and biological applications. They are important pharmacophores present in various inhibitors and are used as building blocks for the synthesis of biologically active natural products, insecticidal agents and chiral auxillaries for asymmetric reactions.[1a–f] They act as starting materials for the synthesis of oxazolines which are useful in the polymer industry.[1g] Owing to their widespread applications, the synthesis of amino alcohols has received much attention in recent years.

Traditionally, 2-amino alcohols are prepared by heating an epoxide with an excess of amine at elevated temperature. The use of a high temperature leads to undesired side reactions and also limits the applicability towards temperature sensitive substrates. To overcome these drawbacks various promoters such as $ZnCl_2$,[2] ScOTf,[3] $MgBr_2{\cdot}OEt_2$,[4] bismuth salts,[5] $CoCl_2$,[6] $CuBF_4$,[7] DIPAT,[8] $Ti(OiPr)_4$,[9] $TaCl_5$,[10] $ZrCl_4$,[11] $Sm(OTf)_3$,[12] potassium dodecatungstocobaltate,[13] and aluminosilicate[14] have been employed for the above transformation. The use of non-conventional techniques such as microwave irradiation at elevated temperature has also been reported.[15] Recently, the use of $Al(OTf)_3$ (1 mol %) as catalyst in toluene at reflux has also been reported.[16] Although significant advances have been made in this area, low regioselectivity, longer reaction time, use of elevated temperature, high catalyst loading, toxic solvents and lower substrate compatibility limit their applications. Thus there is a need to develop an efficient catalytic protocol for ring opening of various epoxides with aliphatic, aromatic and heteroaromatic amines under ambient conditions.

In our previous study,[17] we introduced $Y(NO_3)_3{\cdot}6H_2O$, as a novel catalyst for Biginelli and aza-Michael reactions. The catalyst showed remarkable activity and reusability affording high yields of the desired products. The co-ordinating ability of $Y(NO_3)_3{\cdot}6H_2O$ along with its commercial availability prompted us to investigate its activity for ring opening of epoxides. We herein report a general protocol



Scheme 1. Aminolysis of epoxides under solvent-free conditions.

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Table 1
Influence of solvent and catalyst[a]

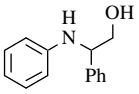
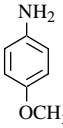
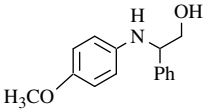
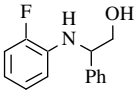
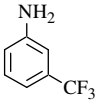
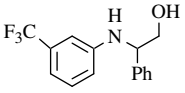
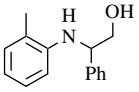
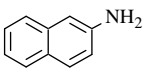
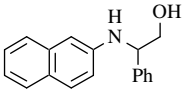
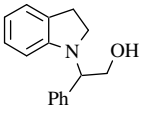
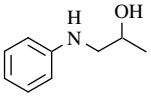
Entry	Solvent	Catalyst	Yield[b] (%)	Ratio[c] (**a**:**b**)
Influence of solvent				
1	Methanol	$Y(NO_3)_3{\cdot}6H_2O$	7	—
2	Tetrahydrofuran	$Y(NO_3)_3{\cdot}6H_2O$	12	—
3	Dichloromethane	$Y(NO_3)_3{\cdot}6H_2O$	10	—
4	Toluene	$Y(NO_3)_3{\cdot}6H_2O$	7	—
5	Water	$Y(NO_3)_3{\cdot}6H_2O$	5	—
6	None	$Y(NO_3)_3{\cdot}6H_2O$	92	84:16
Influence of catalyst				
7	None	$Cu(NO_3)_2.3H_2O$	42	73:27
8	None	$Zn(NO_3)_2{\cdot}6H_2O$	68	79:21
9	None	$Bi(NO_3)_3.5H_2O$	33	83:17
10	None	$Fe(NO_3)_3.9H_2O$	70	84:16
11	None	$La(NO_3)_3{\cdot}6H_2O$	91	78:22

[a] Reaction conditions: aniline = 1.2 mmol; styrene oxide = 1 mmol; solvent = 1 ml, time = 1 h.
[b] Yield determined by GC.
[c] Ratios determined by GC–MS analysis.

for aminolysis of aliphatic/aromatic epoxides with a wide variety of amines under solvent-free conditions (Scheme 1).

Initially, the ring opening of styrene oxide with aniline was chosen as a model and the role of various solvents and catalysts on the reaction system was investigated. Solvents such as water, toluene, tetrahydrofuran, methylene dichloride, and methanol (Table 1, entries 1–5) provided low yields of the desired product (5–12%), while the same reaction under solvent-free conditions afforded a 92% yield within 1 h. The high reaction rate observed could be attributed to the fact that, under solvent-free conditions, the concentration of catalyst is greater leading to rate enhancement as compared to the same reaction in the presence of solvent. Further, the effect of various metal nitrates on the reaction system was examined (Table 1, entries 6–11). $Y(NO_3)_3{\cdot}6H_2O$ and $La(NO_3)_3{\cdot}6H_2O$ provided excellent yields of the desired product within a short reaction time (1 h). However, since $Y(NO_3)_3{\cdot}6H_2O$

Table 2
Ring opening of epoxides with aliphatic and aromatic amines[a]

Entry	Amine	Epoxide	Product[b]	Time (h)	Yield[c] (%)	Ratio[d] (**a**:**b**)
1				1	92 (81)	84:16
2				1	91	85:15
3				3	89	87:13
4				3	90	89:11
5				1	92	83:17
6				4	88 (82)	90:10
7				1	91	90:10
8				3	75	0:100

(*continued on next page*)

Table 2 (*continued*)

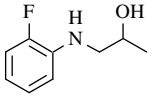
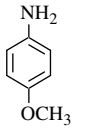
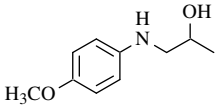
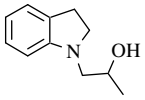
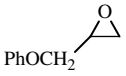
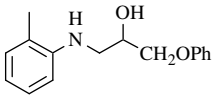
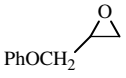
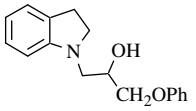
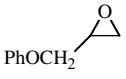
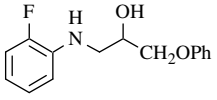
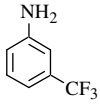
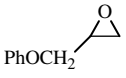
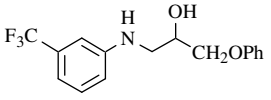
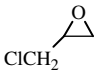
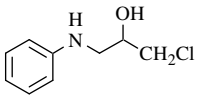
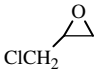
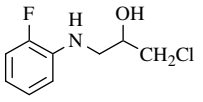
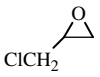
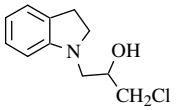
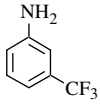
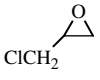
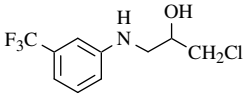
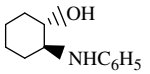
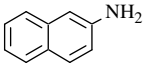
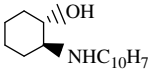
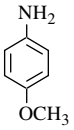
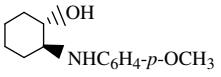
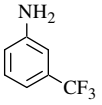
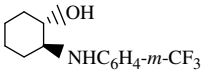
Entry	Amine	Epoxide	Product[b]	Time (h)	Yield[c] (%)	Ratio[d] (**a**:**b**)
9				3	81 (77)	0:100
10				3	72	0:100
11				3	83	17:83
12				3	90	0:100
13				3	92	1:99
14				5	86	1:99
15				3	85	2:98
16				4	84	0:100
17				4	82	0:100
18				4	83	0:100
19				4	81	0:100
20				7	90	—

Table 2 (*continued*)

Entry	Amine	Epoxide	Product[b]	Time (h)	Yield[c] (%)	Ratio[d] (**a**:**b**)
21				7	92 (89)	—
22				7	91 (88)	—
23				7	90	—

[a] Reaction conditions: amine = 3 mmol; epoxide = 2.5 mmol; $Y(NO_3)_3{\cdot}6H_2O$ = 0.025 mmol.
[b] Only the major regioisomer is shown.
[c] Yields determined by GC. Yields in parentheses are of isolated products.
[d] Ratios determined by GC–MS analysis.

afforded high regioselectivity towards the major isomer (2-anilino-2-phenylethanol), it was used for further study.

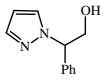
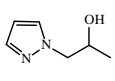
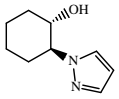
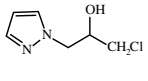
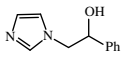
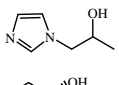
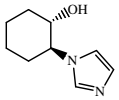
Thus using $Y(NO_3)_3{\cdot}6H_2O$ (1 mol %) as the catalyst, the ring opening of various aliphatic/aromatic epoxides with structurally and electronically different amines was studied under ambient conditions (Table 2, entries 1–23).[18] The reaction of aniline with styrene oxide provided a combined yield of 92% [2-(phenylamino)-2-phenylethanol + 2-(phenylamino)-1-phenylethanol] with excellent regioselectivity towards the major isomer, up to 84%.

The structure of the major isomer was confirmed by GC–MS (base peak at M^+-31) and ^1H NMR (dd, $\delta = 3.65$ ppm, benzylic proton) indicating attack at the benzylic position.[19] Anilines with electron-donating and electron-withdrawing groups such as Me, OMe, CF_3, F (entries 2–5) were well tolerated under the present catalytic system.The aminolysis of styrene oxide with bulky 2-naphthyl amine proceeded efficiently to give 88% yield (entry 6). Indoline also reacted smoothly with styrene oxide within a short reaction time (entry 7).

In order to explore the generality of the protocol, we turned our attention towards the ring opening of aliphatic epoxides such as propylene oxide, phenyl glycidyl ether, epichlorohydrin, and cyclohexene oxide (entries 8–23). Excellent yields of the desired amino alcohols were obtained with a reversal of regioselectivity indicating attack at the less substituted carbon of the epoxide. The probable reason may be that in styrene oxide the positive charge on oxygen appears to be localized on the more highly substituted benzylic carbon leading to the major product. Whereas in case of aliphatic epoxides steric factors predominate over electronic factors thereby facilitating the attack at the less hindered carbon atom of the epoxide ring.[3]

The reaction of propylene oxide with amines such as aniline, 2-fluoroaniline, *p*-anisidine and indoline afforded good yields with complete regioselectivity (entries 8–11).

Table 3
Ring opening of epoxides with heteroaromatic amines[a]

No.	Heterocycle	Product[b]	Yield[c] (%)	Ratio[d] (**a**:**b**)
1[e]			92	59:41
2			86	7:93
3			88	—
4			81	3:97
5			90	26:74
6			83	10:90
7			90	—

[a] Reaction conditions: heterocycle = 1.2 mmol; epoxide = 1 mmol; $Y(NO_3)_3{\cdot}6H_2O$ = 0.025 mmol; time = 24 h.
[b] Only the major regioisomer is shown.
[c] Yields determined by GC.
[d] Ratios determined by GC–MS analysis.
[e] $Y(NO_3)_3{\cdot}6H_2O$ = 3 mol %; time = 8 h.

Chemoselective aminolysis of epichlorohydrin was observed, with desired product resulting from attack at the less substituted carbon on the epoxide ring (entries 16–19). The ring opening of cyclohexene oxide was also successfully achieved giving 90–92% yields of the desired amino alcohols (entries 20–23).

Encouraged by the above results, we next investigated the ring opening of epoxides with heterocyclic amines such as pyrazole and imidazole (Table 3, entries 1–7). There are very few reports in the literature for the ring opening of epoxides with heterocyclic amines.[20] These methods require high temperature and pressure. The products obtained are of pharmaceutical importance and thus a milder protocol was desired for the synthesis of such hetero-amino alcohols. Initially, we studied the ring opening of various epoxides such as styrene oxide, propylene oxide, epichlorohydrin and cyclohexene oxide with pyrazole and excellent results were obtained. The reaction of pyrazole with styrene oxide and propylene oxide afforded 92% and 86% yields, respectively (entries 1 and 2). The ring opening of cyclohexeneoxide and epichlorohydrin with pyrazole afforded the desired amino alcohol in good yields (entries 3 and 4). The aminolysis of these epoxides was next investigated with imidazole which gave excellent yields in the range of 83–90% under ambient conditions (entries 5–7). Thus, the catalyst $Y(NO_3)_3{\cdot}6H_2O$ enabled efficient coupling of heteroaromatic amines with various epoxides providing excellent yields of desired products.

In summary, the first example of selective ring opening of aliphatic/aromatic epoxides with aliphatic, aromatic and heteroaromatic amines catalyzed by $Y(NO_3)_3{\cdot}6H_2O$ under ambient conditions is described. The protocol offers several advantages such as low catalyst loading (1 mol %), high reaction rate, solvent-free conditions and wider substrate compatibility making it an important addition to previously reported methods.

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18. *General procedure for aminolysis of epoxides*: A mixture of amine (1.2 equiv), epoxide (1 equiv) and $Y(NO_3)_3{\cdot}6H_2O$ (1 mol %) was stirred at room temperature. The progress of the reaction was monitored using a gas chromatograph (Chemito 1000). After completion, the product was isolated by silica gel chromatography usingchloroform/methanol as eluent.
19. *Spectral data of selected products*: Table 2, entry 4: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) $\delta = 3.65$ (dd, $J = 7.1$ Hz, $J = 11.1$ Hz, 1H), 3.84 (dd, $J = 3.8$ Hz, $J = 11.1$ Hz, 1H) 4.39 (dd, $J = 4$ Hz, $J = 6.9$ Hz, 1H), 6.55 (d, $J = 8$ Hz, Ar 1H), 6.71 (s, Ar 1H), 6.80 (d, $J = 7.7$ Hz, Ar 1H), 7.05 (t, $J = 7.8$ Hz, Ar 1H), 7.16–7.26 (m, Ar 5H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) $\delta = 60.1$, 67, 110.5, 114.1, 116.5, 122.5, 126.1, 126.7, 127.7, 128.8, 129.6, 139.5, 147.4. MS (EI, 70 eV): 281 (9) (M^+), 250 (100), 172 (28). MS/MS *analysis (−ve ESI* mode): calcd for (M−1) = 280.26, found (M−1) = 280.07. Table 2, entry 9: $\delta = 1.22$ (d, $J = 6.2$ Hz, 3H), 2.98 (dd, $J = 8.4$ Hz, $J = 12.9$ Hz, 1H) 3.16 (dd, $J = 3.3$ Hz, $J = 12.8$ Hz, 1H) 3.95–4.05 (m, 1H), 6.60–6.99 (m, Ar 4H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) $\delta = 20.7$, 51.3, 66.2, 112.8, 114.7, 118.5, 124.6, 136.3, 150.2. MS/MS *analysis (+ve ESI* mode): calcd for (M+1) = 170.19, found (M+1) = 170.07. MS (EI, 70 eV): 169 (25) (M^+), 124 (100), 77 (20). Table 2, entry 23:$\delta = 1.01$–1.04 (m, 1H), 1.2–1.4 (m, 3H), 1.6–1.76 (m, 2H), 2.05 (m, 2H), 3.11 (ddd, $J = 4$ Hz, $J = 9.75$ Hz, $J = 10.1$ Hz, 1H), 3.33 (ddd, $J = 4$ Hz, $J = 9.75$ Hz, $J = 10.1$ Hz, 1H), 6.80 (d, $J = 8.1$ Hz, Ar 1H), 6.87 (s, Ar 1H), 6.92 (d, $J = 7.7$ Hz, Ar 1H), 7.22 (t, $J = 7.7$ Hz, Ar 1H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) $\delta = 24.1$, 24.6, 31.4, 33.4, 59.7, 74.3, 110.1, 114.2, 116.8, 122.5, 126.1, 129.7, 148.1. MS/MS *analysis (−ve ESI* mode): calcd for (M−1) = 258.26, found (M−1) = 258.13. MS (EI, 70 eV): 259 (46) (M^+), 216 (12), 200 (100), 174 (33).
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