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Mild Regiospecific Alcoholysis and Aminolysis of Epoxides Catalyzed by Zirconium(IV) oxynitrate

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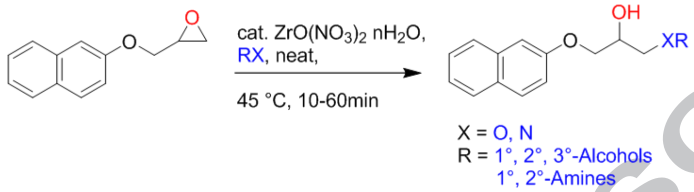
Sandip S. Shinde,* Madhukar S. Said, Trupti B. Surwase and Pradeep Kumar*



Mild regiospecific method has been developed for ring-opening of epoxides with various general alcohols and amines using zirconium(IV)oxynitrate as catalyst under solvent-free condition.

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Mild Regiospecific Alcoholysis and Aminolysis of Epoxides Catalyzed by Zirconium(IV) oxynitrate

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ABSTRACT

A regiospecific method for the ring-opening reaction of epoxides by the primary, secondary, tertiary alcohols, and aryl, aliphatic amines has been developed using non-toxic metal nitrate salt as a catalyst. The best results were obtained using zirconium(IV)oxynitrate among the various screened metal nitrate salts. The reported protocol works efficientyl both for styrene epoxide and aliphatic as well.

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Introduction

Epoxides represent an intrigue building block in bioscience and organic research due to their reactivity and versatility as an intermediate of numerous natural products.[1] Stereoselective epoxidation followed by regio-specific epoxide opening reactions are the key steps in construction of the polyketide skeleton. Recent ionophore polyketide biosynthesis of lasalocid, demonstrated that regioselective epoxide opening affords natural type mono- or di-epoxides in a sequential manner in enzyme catalyzed synthesis of Lasalocid.[2] In general, the ring opening of epoxide with alcohols requires either strongly acidic or basic conditions due to the poor nucleophilicity of alcohols.[3] Numerous methods have been developed to open the epoxide ring with amines or alcohols as a nucleophile in the presence of Lewis acids such as $BF_3.OEt_2$,[4] $Cu(BF_4)_2$,[5] $Fe(Cp)_2BF_4/PF_6$,[6] $Er(OTf)_3$,[7] and $Al(OTf)_3$[8] etc. However, many catalytic systems are associated with drawbacks such as tedious work-up procedure, long reaction time and disposal of hazardous chemicals, which prompted the organic researcher to develop a simple and environmentally benign methods.[9]

Zirconium salt is reported as a green catalyst in various organic transformation. [9, 10] Major attempts have focused on making various solid-supported catalyst including Zircono-silicate-nano material (Zr-Nano(PrTES)-ZSM-5),[11] sulphated-Y-Zr salt[12] as heterogeneous catalyst for the ring opening of epoxides with alcohols. However, these methods suffer from the tedious catalyst preparation, and also with their limited application to aryl alcohols only.

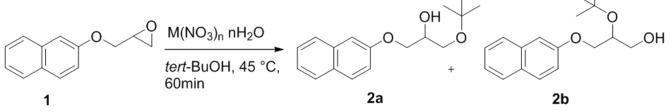
Recently, $Y(NO_3)_2$,[13] $ZrCl_4$[14] have been reported for epoxide opening with amines. More recently, $ZrO(NO_3)_2$ has been employed for ring opening reaction of epoxide in aprotic solvent conditions.[15] In addition, these metal nitrates are advantageous as they are heterogeneous redox catalyst in nature and have capability to activite the substrate by coordination with the oxygen.[16]

In continuation of our research interest on developing a more practical and new catalytic protocol for nucleophilic substitution reactions,[17] we herein report the epoxide opening reaction with a variety of alcohols and amines in the presence of various metal nitrates hydrates as catalyst.

Results and discussion,

The activity of various metal nitrates as a catalyst was examined for the ring opening of epoxides using 2-[(Naphthalen-2-yloxy)methyl]oxirane as a model substrate in *tert*-butanol (*t*-BuOH) solvent at 45 °C. The results are summarized in Table 1.

Table 1. Alcoholysis of 2-[(Naphthalen-2-yloxy)methyl]oxirane catalyzed by Metal Nitrates.[a]



Entry	$M(NO_3)$ (20 mol%)	**1**	Yield of **2a** (%)[b]	Selectivity ratio (%)[c] **2a**:**2b**	comments
1	-	100	-		
2	$Mg(NO_3)_2$ $6H_2O$	32	15	80:20	6% **2b**

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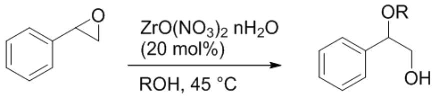
3	$Ca(NO_3)_2$ $4H_2O$	-	40	72:28	8% **2b**
4	$Ni(NO_3)_2$ $6H_2O$	32	58	89:11	trace 2-naphthol
5	$Cu(NO_2)_2$ $6H_2O$	28	62	93:7	trace 2-naphthol
6	$ZrO(NO_3)_2$ nH_2O	-	90	96:4	
7	$La(NO_3)_3$ H_2O	9	76	81:19	
8	$ZrO(NO_3)_2$ nH_2O (1 mol%)	6	53	88:12	
9	$ZrO(NO_3)_2$ nH_2O (0.5 equiv)		87	97: 3	
10[d]	$ZrO(NO_3)_2$ nH_2O	trace	82	96: 4	

[a]All reactions were carried out on a 1.0 mmol scale of epoxide with *t*-BuOH (3 mL) in the presence of 20 mol% $M(NO_3)n$ nH_2O at 45 °C for 60 min. [b]Isolated yield. [c]Selectivity determined by crude ^{1}H-NMR. [d]Reaction carried out in CH_2Cl_2 (3 ml) using 10 equiv of *t*-BuOH for 4h.

Reactions catalyzed by alkaline earth Mg and Ca nitrate hydrates, afforded **2a** with other regio-isomer **2b** in 6 to 8% respectively (entries 2-3). Same reaction without use of catalyst did not give any product and only starting material was recovered back (entry 1). Comparatively, the transition metal nitrates such as nickel, copper and zirconyl showed moderate to good conversion with high selectivity (entries 4-6). Reaction using nickel and copper nitrate consumed >50% of SM to afford 58 and 62 % yield of the desired product **2a** respectively with byproduct 2-naphthol detected in trace amount (entries 4-5). Zirconium(IV) oxynitrate showed higher conversion with 96% regioselectivity for product **2a** (entry 6). The reaction with less amount of zirconium (IV) oxynitrate (1 mol %), resulted in only moderate yield of product, even after prolonged reaction time (entry 8). Increase in the catalyst amount did not affect the regio-selectivity and yield of product significantly (entry 9). Co-solvent is known to be excellent media for epoxide opening with Lewis acid catalyst,[4] thus the same reaction was examined using *t*-BuOH (10 equiv) and CH_2Cl_2 as co-solvent. However, it took longer time (4h) to give the desired product **2a** in 82% yield with excellent regioselectivity (entry 10).

Table 2. Alcoholysis of Styrene Epoxide with various Alcohols Catalyzed by Zirconium (IV) oxynitrate.[a]



Entry	**R** (alcohols)	Time (min)	Yield (%)[b]
1	methanol	5	98
2	*n*-butanol	20	97
3	benzyl alcohol	20	94
4	allyl alcohol	20	96
5	*i*-propanol	30	94
6	*t*-BuOH	40	87
7	cyclohexanol	80	91

[a]All reactions were carried out under same reaction condition of entry 6 of table 1. [b]isolated yield

As illustrated in Table 2, the optimized conditions were further extended to the ring opening of styrene epoxide with various primary, secondary, and tertiary alcohols to examine the scope of $ZrO(NO_3)_2$ nH_2O as catalyst. These results prove that several derivatives of primary alcohols, such as benzylic, allylic and aliphatic, can easily be prepared following this approach. Similarly, compounds incorporating more hindered hydroxyl functionality can be also accessed through this mild and simple approach. Opening of styrene epoxide at benzylic position is favored due to the stable carbo-cation generated leading to the β-alkoxy alcohol as the major product.

To extend the scope of reaction and examine the efficacy of $ZrO(NO_3)_2$ nH_2O, the alcoholysis was carried out with various epoxides using different alcohols as shown in Table 3. It is noteworthy that in case of naphthyloxy, phenyloxy substituted epoxide reactions; ring opening takes place from less substituted side of epoxide to afford the corresponding α-alkoxy alcohols in excellent yield (entries 1-5). However, *tert*-alcohol slightly took longer time than primary alcohols but the regio-selectivity was not affected. Linear alkyl substituted substrates provided moderate yield (38-52%) of desired α-alkoxy alcohols (entires 6-8), which could probably be due to the competition of mechanistic pathway for such type of aliphatic nucleophilic epoxide ring opening.[18] Further we carried out the ring opening reactions on internal epoxides such as cyclopentyl and cyclohexyl epoxides with primary secondary and tertiary alcohols, the reaction resulted in exclusive formation of the trans-products in quantitative yield (entries 9-12).

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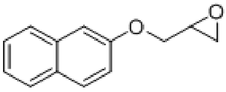
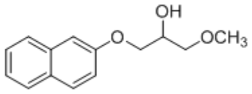
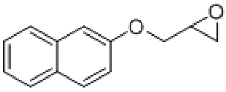
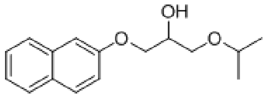
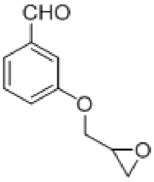
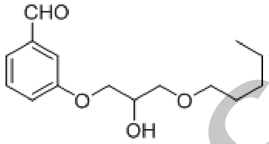
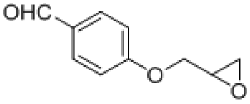
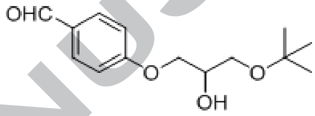
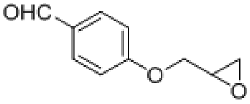
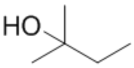
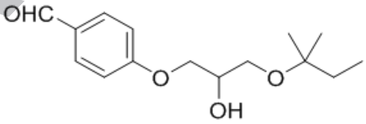
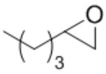
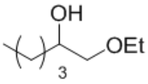
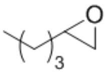
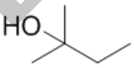
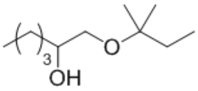
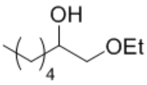
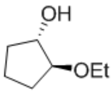
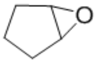
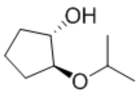
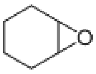
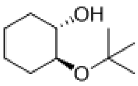
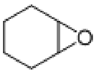
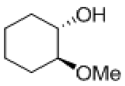
Table 3. Alcoholysis of Epoxides Catalyzed by Zirconium (IV) oxynitrate at 45°C.[a]

Entry	Epoxised	Alcohol	Time(min)	product	Yield[b]
1		MeOH	20		86
2		*i*-propanol	40		84
3		*n*-pentanol	30		90
4		*t*-BuOH	50		86
5			55		83
6		EtOH	13h		44
7			21h		38
8		EtOH	14h		52
9		EtOH	50		94
10		*i*-propanol	120		83
11		*t*-BuOH	120		96
12		MeOH	60		98

[a] Unless otherwise indicated, all reactions were carried out on a 1.0 mmol scale of **SM** under same condition of entry 6 of Table 1.
[b] Isolated yield.

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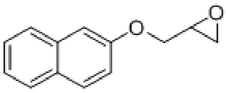
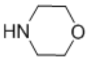
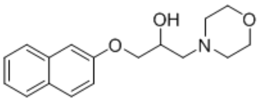
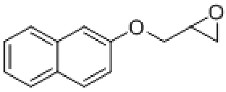
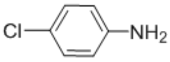
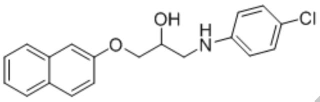
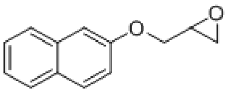
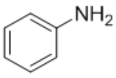
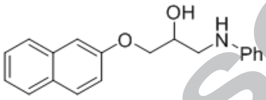
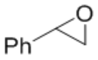
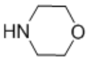
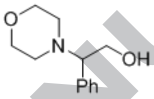
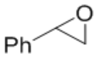
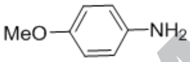
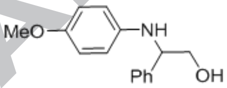
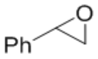
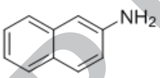
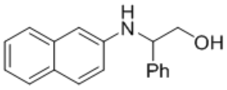
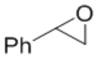
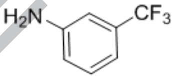
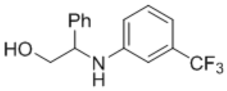
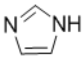
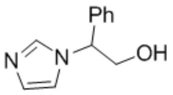
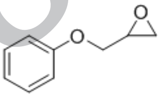
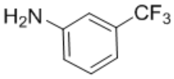
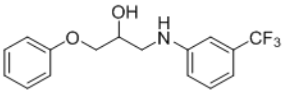
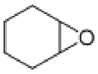
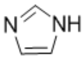
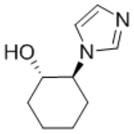
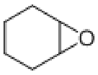
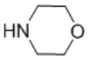
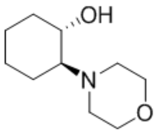
Table 4. Aminolysis of Epoxides Catalyzed by Zirconium(IV) Oxynitrate.[a]

Entry	Epoxide	Amine	Product	Yield(%)[b]
1				86
2				87
3				82
4				91
5				94
6				83
7				82
8				91
9				78
10				93
11				97

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[a] Unless otherwise indicated, all reactions were carried out on 1.0 mmol scale of **SM** with amine (1. 5 mmol) stirring at 45°C for 20 min.

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Table 4 shows the extended scope of this protocol for ring opening of epoxide with amines, such as aryl and cyclic amine at 45 °C for 20min. In the reaction of epoxide with aryl amine, morpholine. the nucleophilic addition occurred from the less-subsituted side, affording selectively β-hydroxy amine products (entries 1-3). In contrast, the reaction of styrene epoxide with morpholine or other aryl amines afforded β-amino alcohols as single regio-selective products (entries 4-8). The results obtained with respect to regioselectivity are in agreement with earlier report of zirconium phosphonate catalyzed ring opening of epoxides.[19] Notably, ring opening of epoxide was found to be more efficient and general with diverse range of the cyclic and heterocyclic amines such as morpholine, aniline, 2-amino naphthalene and imidazole efficiently leading to the corresponding amino alcohol in excellent yield. the cyclohexene epoxide was also successfully converted to *trans*-β-hydroxy amine in quantitative yield (entry 10-11). From the experiment, it is evident that, in case of aliphatic epoxides steric effect predominates over electronic-controlled factor thereby facilitating the attack at the less hindered carbon atom of the epoxide ring. Overall, the epoxide ring opening with amine and alcohol indicates that $ZrO(NO_3)_2\ nH_2O$ has shown best catalytic activity with wide substrate scope as compared to the previously reported bismuth triflate[20] or Zr-silicate-nano particles.[1]

Conclusion

An efficient ring-opening of epoxides by variety of alcohols and amines is developed using zirconium oxynitrate hydrated salt as catalyst. We believe this will present a better environmentally benign protocol and should find widespread application in green chemical reactions.

General procedure of alcoholysis and amynolysis: A mixture of styrene epoxide (120 mg, 1.0 mmol) and *t*-butyl alcohol (3 ml) [or morpholine (0.5 mL)] and $ZrO(NO_3)_2\ nH_2O$ (46 mg, 20 mol%). The mixture was heated under stirring at 45 °C. The progress of reaction was monitored by GC-MS and TLC. After completion, the reaction mixture was concentrated under the reduced pressure. Then crude product was purified using column cromatography (20% ethyl acetate:pet ether, rf 0.6) to afford 168.7 mg (87 %) of 2-*tert*-butoxy-2-phenylethanolas a white solid. obs mp 76-78 °C, reported mp 77-79 °C; [6] ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.39–7.28$ (m, 5H), 4.65 (dd, $J = 8.05, 4.39$ Hz, 1H), 3.56–3.50 (m, 2H), 1.21 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) 28.7, 67.8, 74.8, 75.1, 126.3, 127.2, 128.1, 142.2; HRMS (EI) calcd for $C_{12}H_{18}O_2$ (M+) 194.3068, found 194.3066.

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References and notes

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† Electronic Supplementary Information (ESI) available: [^{1}H and ^{13}C NMR of new compounds spectral data].

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