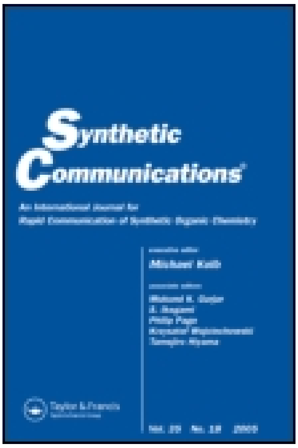


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

# $Mg(ClO_4)_2$, an Efficient Catalyst for Synthesis of β-Amino Alcohols by Ring Opening of Epoxides with Amines under Solvent-Free Conditions

Abbas Ali Jafari [a] & Moradgholi [a]
[a] Department of Chemistry, Faculty of Science, Yazd University, Yazd, Iran

Version of record first published: 02 Feb 2011.

To cite this article: Abbas Ali Jafari & Moradgholi (2011): $Mg(ClO_4)_2$, an Efficient Catalyst for Synthesis of β-Amino Alcohols by Ring Opening of Epoxides with Amines under Solvent-Free Conditions, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 41:4, 594-602

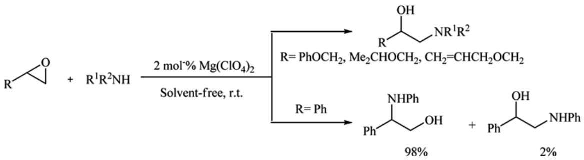
To link to this article: http://dx.doi.org/10.1080/00397911003629473

*Synthetic Communications*®, 41: 594–602, 2011
Copyright © Taylor & Francis Group, LLC
ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911003629473

# $Mg(ClO_4)_2$, AN EFFICIENT CATALYST FOR SYNTHESIS OF β-AMINO ALCOHOLS BY RING OPENING OF EPOXIDES WITH AMINES UNDER SOLVENT-FREE CONDITIONS

**Abbas Ali Jafari and Moradgholi**
*Department of Chemistry, Faculty of Science, Yazd University, Yazd, Iran*

## GRAPHICAL ABSTRACT



**Abstract** *Commercially available magnesium perchlorate is reported as an extremely efficient catalyst for the ring-opening reaction of epoxide with various primary and secondary amines, especially diphenyl amine, under solvent-free conditions at room temperature.*

**Keywords** Amines; β-amino alcohols; epoxides; $Mg(ClO_4)_2$; ring opening; solvent-free

## INTRODUCTION

Epoxides are versatile building blocks for the synthesis of many bioactive natural products. They are an ideal source for diversity because they can be opened with nucleophiles. They are well-known carbon electrophiles, and their ability to undergo regioselective ring-opening reactions contributes to their synthetic value.[1–4] Regioselective ring opening of epoxides with amines is an important reaction in organic and medicinal chemistry as the resultant β-amino alcohols are versatile intermediates. Thay have been used in biologically active natural products, synthetic amino acids, β-blockers, insecticidal agents, chiral auxiliaries, and oxazolines.[5,6] The classical synthesis of β-amino alcohols involves the heating of epoxide with an excess of amines at elevated temperature.[7] However, these conditions are not ideal, becuse epoxides are not tolerant with certain functional groups. Recently, various methods have been reported using metal salts,[8–13] metal triflates,[14–17] and some heterogeneous catalysts.[18–26] However, there are some limitations such as

Received October 25, 2009.

Address correspondence to Abbas Ali Jafari, Department of Chemistry, Faculty of Science, Yazd University, Yazd 89195-741, Iran. E-mail: Jafari@yazduni.ac.ir

longer reaction times, poor yields, use of expensive reagents in stoichiometric quantities, use of hazardous organic solvents, and poor regioselectivity.

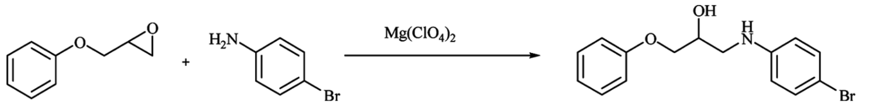
Since the beginning of the new century, green chemistry[27,28] has become a major driving force in organic chemistry with pressure to develop environmentally benign synthetic routes to materials. Performing reactions under solvent-free conditions with solid catalysts could enhance their efficiency from an economic as well as an ecological point of view, so solvent-free chemical reactions have received much attention. These reaction conditions offer several advantages in preparative procedures such as environmental compatibility, simplification of workup, formation of cleaner products, enhanced selectivity, reduction of by-products and waste products, and improved reaction rates. Therefore, there is a need to develop new methods for the synthesis of β-amino alcohols using less hazardous solvents, or better, those that do not need solvents at all. In addition, there is further scope to search for better catalysts in terms of operational simplicity.

Magnesium perchlorate has emerged as a potential catalyst in various organic transformations[29–31] because of its high catalytic activity, availability, and economic viability. In this investigation, we report the catalytic potential of $Mg(ClO_4)_2$ for the synthesis of β-amino alcohols at room temperature under solvent-free conditions.

## RESULTS AND DISCUSSION

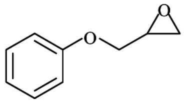
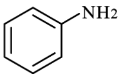
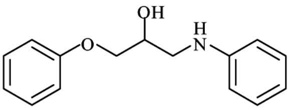
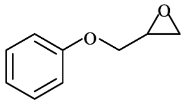
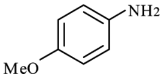
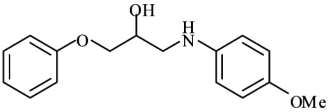
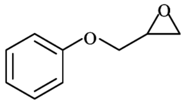
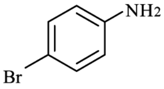
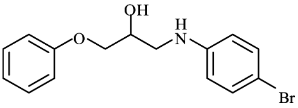
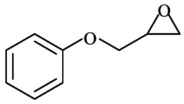
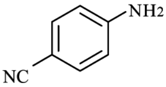
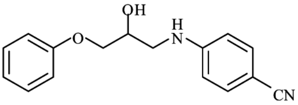
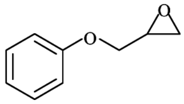
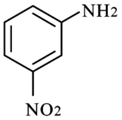
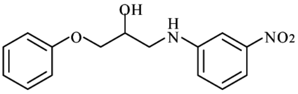
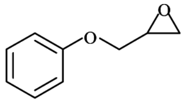
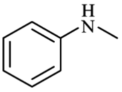
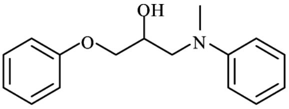
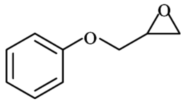
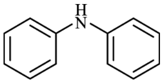
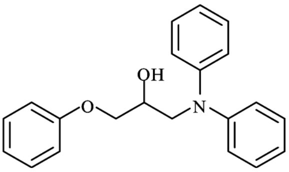
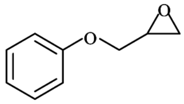
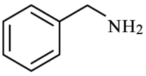
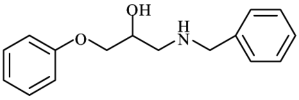
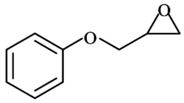
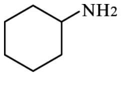
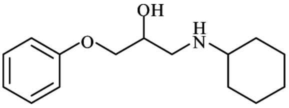
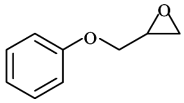
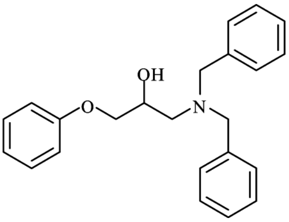
To determine the best experimental conditions, the reaction of phenyl glysidyl ether (2 mmol) with 4-bromo-aniline (2.1 mmol) in the presence of a catalytic amount of $Mg(ClO_4)_2$ in different solvents was the model reaction (Table 1). We observed that the reaction did not proceed properly in solvent and that the desired product, 1-(4-bromophenylamino)-3-phenoxypropan-2-ol, was obtained in less than 80% yield even after 24 h. In addition, because of the current challenges for developing solvent-free and environmentally benign protocols,[13] we have studied the reaction under solvent-free conditions in the presence of this catalyst. We have found that solvent-free conditions were extremely suitable and efficient in which a lesser amount of $Mg(ClO_4)_2$ (0.01 g, 2 mol%) was sufficient to complete the reaction in a very short

Table 1. Effect of solvent during the $Mg(ClO_4)_2$-catalyzed ring-opening reaction of phenyl glysidyl ether (2 mmol) with 4-bromo-aniline (2.1 mmol) at room temperature



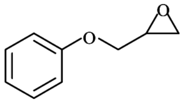
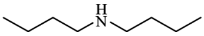
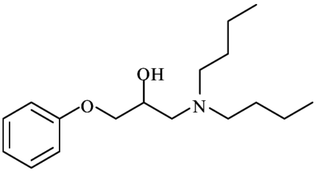
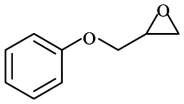
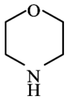
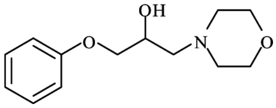
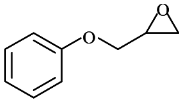
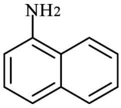
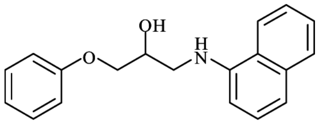
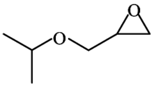
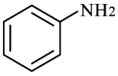
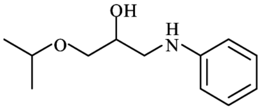
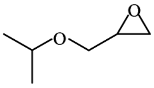
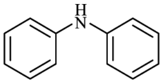
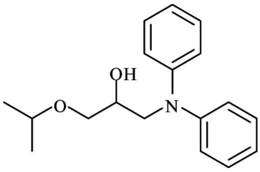
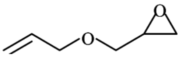
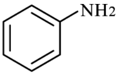
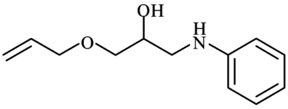
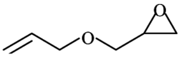
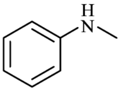
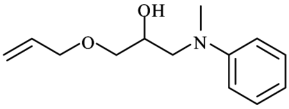
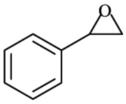
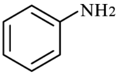
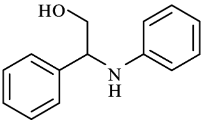
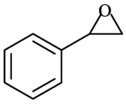
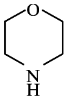
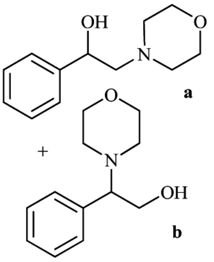
| Entry | Solvent | Cat. (mol%) | Time | Yield (%) |
|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | 5 | 24 h | 80 |
| 2 | $CH_3CN$ | 5 | 24 h | 50 |
| 3 | *n*-Hexane | 5 | 24 h | 60 |
| 4 | EtOH | 5 | 24 h | 65 |
| 8 | Solvent-free | 5 | 5 min | 90 |
| 6 | Solvent-free | 2 | 15 min | 93 |
| 7 | Solvent-free | 1 | 1 h | 90 |
| 5 | Solvent-free | — | 24 h | NR |

**Table 2.** Ring opening of epoxides with various amines catalyzed by $Mg(ClO_4)_2$ under solvent-free conditions at room temperature

| Entry | Epoxide | Amine | Product[a] | Time | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 |  |  |  | 4 min | 97 |
| 2 |  |  |  | 4 min | 90 |
| 3 |  |  |  | 15 min | 93 |
| 4 |  |  |  | 7 h | 96 |
| 5 |  |  |  | 60 min | 97 |
| 6 |  |  |  | 15 min | 98 |
| 7[c] |  |  |  | 120 min | 81 |
| 8 |  |  |  | 5 h | 87 |
| 9 |  |  |  | 150 min | 80 |
| 10 |  | $(PhCH_2)_2NH$ |  | 30 min | 97 |

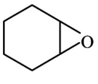
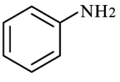
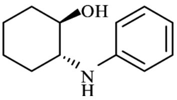
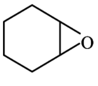
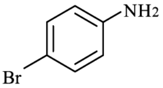
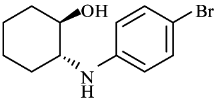
(*Continued*)

**Table 2.** Continued

| Entry | Epoxide | Amine | Product[a] | Time | Yield[b] (%) |
|---|---|---|---|---|---|
| 11 |  |  |  | 4.5 h | 83 |
| 12 |  |  |  | 45 min | 96 |
| 13 |  |  |  | 90 min | 89 |
| 14 |  |  |  | 6 min | 93 |
| 15[c] |  |  |  | 120 min | 74 |
| 16 |  |  |  | 5 min | 93 |
| 17 |  |  |  | 30 min | 93 |
| 18 |  |  |  | 8 min | 98 |
| 19 |  |  |  | 180 min | 97[d] |

(*Continued*)

**Table 2.** Continued

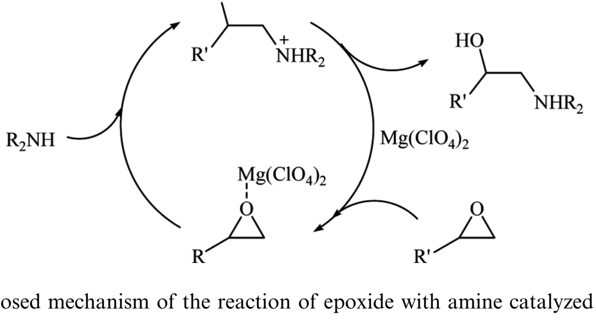
| Entry | Epoxide | Amine | Product[a] | Time | Yield[b] (%) |
|---|---|---|---|---|---|
| 20 |  |  |  | 30 min | 92 |
| 21 |  |  |  | 45 min | 89 |

[a] All the products were fully characterized by the usual spectroscopic techniques.
[b] Yields refer to isolated yield.
[c] 10 mol% $Mg(ClO_4)_2$ was used.
[d] The ratio of a/b was 54/46.

time (15 min) with excellent regioselectivity. In the absence of the catalyst, a similar reaction did not proceed under solvent-free conditions (Table 1, entry 5) even after 24 h. The results of this study are summarized in Table 1.

After this success, we employed similar reaction conditions to the ring opening of phenyl glysidyl ether with different aromatic and aliphatic amines. All reactions proceeded well in excellent yields with excellent regioselectivity, which the epoxide rings were opened from the less-hindered site in the appropriate reaction times. This type of ring opening shows that steric hindrance plays a major role in the ring-opening reactions. The results of this investigation are summarized in Table 2 (entries 1–13). Primary and secondary amines react very rapidly. Aniline and its derivatives with electron-donating substituents also react quite fast. However, aminolysis of epoxides by anilines with electron-withdrawing substituents and sterically hindered anilines required prolonged reaction times.

Further, to generalize this methodology, allyl and isopropyl glysidyl ether (as electron-deficient epoxides), styrene oxide (as an aromatic substituted epoxide), and cyclohexene oxide were treated with various amines in the presence of 2 mol% $Mg(ClO_4)_2$ under these conditions (Table 2, entries 14–21). When cyclohexene oxide was treated with anilines (entries 20 and 21), *trans* β-hydroxy substituted amine products were obtained in excellent yields. The reaction of styrene oxide with aniline



**Scheme 1.** Proposed mechanism of the reaction of epoxide with amine catalyzed by $Mg(ClO_4)_2$.

**Table 3.** Comparison of the ring-opening reaction of phenyl glysidyl ether with aniline catalyzed by $Mg(ClO_4)_2$ and some other reported catalyst

| Entry | Cat. (mol%) | Solvent | Temp. (°C) | Time (min) | Yield (%) | Ref. |
|---|---|---|---|---|---|---|
| 1 | $H_2NSO_3H$ (10) | — | rt | 90 | 90 | 25 |
| 2 | Montmorillonite K10 (30 mg) | — | rt | 180 | 100 | 26 |
| 3 | NaY zeolite (50 mg) | — | 35 | 300 | 95 | 21 |
| 4 | $Cu(BF_4)_2$ (10) | — | rt | 12 | 97 | 12 |
| 5 | $SnCl_4$ (5) | — | 50 | 600 | 91 | 11 |
| 6 | $Bi(OTf)_3$ (2) | Molten TBAB | 70 | 15 | 84 | 23 |
| 7 | $ZrCl_4$ (5) | — | rt | 15 | 100 | 9 |
| 8 | $FeCl_3 \cdot 6H_2O$ (5) | — | 50 | 720 | 88 | 11 |
| **9** | **$Mg(ClO_4)_2$ (2)** | — | **rt** | **4** | **97** | — |

proceeded well, and the epoxide ring was opened from the more hindered cite with excellent regioselectivity in a short reaction time. In the case of the reaction of styrene oxide with morpholine, because of the steric effect, the mixture of two products was produced in 54/46 ratio (Table 2, entry 19). The ring-opening reaction from the more hindered site of styrene oxide indicates the carbocationic character of the intermediate during the progress of the reaction. The results of this study are tabulated in Table 2. The regioselectivity was determined by $^1H$ and $^{13}C$ NMR.

The possible mechanism of the reaction involved activation of the epoxide ring and is presented in Scheme 1. $Mg(ClO_4)_2$ activated the epoxide ring through coordination with oxygen of epoxide to increase the susceptibility of the epoxide ring to nucleophilic attack of the nitrogen atom.

This protocol is versatile; both aromatic and aliphatic amines could be employed in contrast to a large number of reports that describe the epoxide opening only by aromatic amines. The most important contribution is probably the success in the aminolysis of epoxide with diphenylamine for the synthesis of new β-amino alcohols derived from diarylamine in good yields (Table 2, entries 7 and 15).

To show the merit of $Mg(ClO_4)_2$ in comparison with the other catalysts used for a similar reaction, we have tabulated some of the results in Table 3. As is evident from the results, the required ratio for most catalysts used for this purpose is >2 mol% and the required reaction times are much longer (12 h).

## CONCLUSION

In conclusion, the present procedure provides an efficient methodology for the synthesis of β-amino alcohols via ring-opening reaction of epoxide with amine. The notable advantages offered by this method are the use of relatively cheap commercially available $Mg(ClO_4)_2$, short reaction time, applicability to both aromatic and aliphatic amines, good yields of products, excellent regioselectivity, and solvent-free conditions.

## EXPERIMENTAL

### General Remarks

Chemicals were purchased from Merck and Fluka Chemical Companies. All the products are known and were characterized by comparison of their physical data with those reported in the literature. Infrared (IR) spectra were run on a Shimadzu model 8300 Fourier transform (FT)–IR spectrophotometer. NMR spectra were recorded on a Bruker Avance DPX 250- or 500-MHz instrument. The purity of the products and the progress of the reactions were monitored by thin-layer chromatography (TLC) on silica-gel polygram SILG/$UV_{254}$ plates.

### General Procedure for the Reactions of Epoxide with Amine Catalyzed by $Mg(Clo_4)_2$ Under Solvent-Free Conditions

$Mg(ClO_4)_2$ (4.5 mg, 2 mol%) was added to a magnetically stirred mixture of epoxide (2.0 mmol) and amine (2.1 mmol) under solvent-free conditions for the appropriate reaction time (Table 2). The progress of the reaction was monitored by TLC. After completion of the reaction, 10 mL of an organic solvent ($Et_2O$ or EtOAc) were added to the reaction mixture, and the organic layer was washed with 10 mL of water and dried over anhydrous $Na_2SO_4$. Evaporation of the solvent under diminished pressure resulted in almost-pure products in good to excellent yields (Tables 2). For further purification (especially entries 7, 13, and 15 of Table 2), the collected products were purified by column chromatography on silica gel eluted with EtOAc / petroleum ether to afford the highly pure products.

### Selected Spectral Data for New Compounds

**1-Diphenylamino-3-phenoxy-propan-2-ol (Table 1, Entry 7).** $^1H$ NMR (500 MHz, $CDCl_3$): 7.36–7.32 (m, 6H), 7.15 (dd, $J_1 = 8.6$ Hz, $J_2 = 1.0$ Hz, 4H), 7.06–7.03 (m, 3H), 6.95 (dd, $J_1 = 8.6$ Hz, $J_2 = 1.0$ Hz, 2H), 4.42–4.38 (m, 1H), 4.14–4.06 (m, 3H), 4.02 (dd, $J_1 = 15.0$ Hz, $J_2 = 7.1$ Hz, 1H), 2.56 (br, 1H, OH) ppm; $^{13}C$ NMR (125.8, $CDCl_3$): 158.9, 148.7, 130.0, 129.9, 122.4, 121.8, 121.7, 115.1, 70.1, 68.5, 55.6 ppm; IR (KBr): $\nu = 3452$, 3060, 2925, 1589, 1495, 1456 $cm^{-1}$. $C_{21}H_{21}NO_2$ (319.40): calcd. C, 78.97; H, 6.63. Found: C, 78.85; H, 6.56.

**1-Diphenylamino-3-isopropoxy-propan-2-ol (Table 1, Entry 15).** $^1H$ NMR (500 MHz, $CDCl_3$): 7.37–7.34 (m, 4H), 7.17 (d, $J = 7.7$ Hz, 4H), 7.05 (t, $J = 7.3$ Hz, 2H), 4.17–4.13 (m, 1H), 4.01 (dd, $J_1 = 14.9$ Hz, $J_2 = 6.4$ Hz, 1H), 3.90 (dd, $J_1 = 14.9$ Hz, $J_2 = 6.5$ Hz, 1 H), 3.66–3.60 (m, 2H), 3.53 (dd, $J_1 = 9.5$ Hz, $J_2 = 5.5$ Hz, 1H), 2.78 (br, 1H, OH), 1.24 (t, $J = 6.1$ Hz, 6H) ppm; $^{13}C$ NMR (125.8, $CDCl_3$): $\delta = 148.8$, 129.8, 122.0, 121.7, 72.7, 70.1, 68.9, 55.5, 22.5; IR (KBr): $\nu = 3452$, 3060, 2925, 1589, 1495, 1456 $cm^{-1}$. $C_{18}H_{23}NO_2$ (285.38): calcd. C, 75.76; H, 8.12. Found: C, 75.23; H, 8.05.

## ACKNOWLEDGMENT

The authors are thankful to the Research Council of Yazd University for financial support.

## REFERENCES

1. Parker, R. E.; Isaacs, N. S. Mechanisms of epoxide reactions. *Chem. Rev.* **1959**, *59*, 737–799.
2. Bonini, C.; Righi, G. Regio- and chemoselective synthesis of halohydrines by cleavages of oxiranes with metal halides. *Synthesis* **1994**, 225–238.

3. Rao, A. S.; Paknikar, S. K.; Kirtane, J. G. Recent advances in the preparation and synthetic applications of oxiranes. *Tetrahedron* **1983**, *39*, 2323–2367.
4. Smith, J. G. Synthetically useful reactions of epoxides. *Synthesis* **1984**, 629–656.
5. Ager, D. J.; Prakash, I.; Schaad, D. R. 1,2-Amino alcohols and their heterocyclic derivatives as chiral auxiliaries in asymmetric synthesis. *Chem. Rev.* **1996**, *96*, 835–875.
6. Bose, D. S.; Narsaiah, A. V. An efficient asymmetric synthesis of (*S*)-atenolol: Using hydrolytic kinetic resolution. *Bioorg. Med. Chem.* **2005**, 627–630.
7. Deyrup, J. A.; Moyer, C. L. 1,2,3-Oxathiazolidines heterocyclic system. *J. Org. Chem.* **1969**, *34*, 175–179.
8. Reddy, L. R.; Reddy, M. A.; Bhanumati, N.; Rao, K. R. Cerium chloride–catalysed cleavage of epoxides with aromatic amines. *Synthesis* **2001**, 831–832.
9. Chakraborti, A. K.; Kondaskar, A. $ZrCl_4$ as a new and efficient catalyst for the opening of epoxide rings by amines. *Tetrahedron Lett.* **2003**, *44*, 8315–8319.
10. Firouzabadi, H.; Iranpoor, N.; Khoshnood, A. Aluminum tris (dodecyl sulfate) trihydrate $Al(DS)_3 \cdot 3H_2O$ as an efficient Lewis acid–surfactant-combined catalyst for organic reactions in water: Efficient conversion of epoxides to thiiranes and to amino alcohols at room temperature. *J. Mol. Catal. A: Chem.* **2007**, *274*, 109–115.
11. Zhao, P. Q.; Xu, L. W.; Xia, C. G. Transition metal–based Lewis acid – catalyzed ring opening of epoxides using amines under solvent-free conditions. *Synlett* **2004**, 846–850.
12. Kamal, A.; Ramu, R.; Azhar, M. A.; Khanna, G. B. R. Copper(II) tetrafluoroborate–catalyzed ring-opening of epoxides by amines. *Tetrahedron Lett.* **2005**, *46*, 2675–2677.
13. Maheswara, M.; Rao, K. S. V. K.; Do, J. Y. Regioselective ring opening of epoxides with amines using $Zn(ClO_4)_2$–$Al_2O_3$ as a heterogeneous and recyclable catalyst. *Tetrahedron Lett.* **2008**, *49*, 1795–1800.
14. Ollevier, T.; Lavie-Compin, G. Bismuth triflate–catalyzed mild and efficient epoxide opening by aromatic amines under aqueous conditions. *Tetrahedron Lett.* **2004**, *45*, 49–52.
15. Procopio, A.; Gaspari, M.; Nardi, M.; Oliverio, M.; Rosati, O. Highly efficient and versatile chemoselective addition of amines to epoxides in water catalyzed by erbium(III) triflate. *Tetrahedron Lett.* **2008**, *49*, 2289–2293.
16. Mancilla, G.; Femenıa-Rıos, M.; Macıas-Sanchez, A. J.; Collado, I. G. $Sn(OTf)_2$-catalysed regioselective styrene oxide ring opening with aromatic amines. *Tetrahedron* **2008**, *64*, 11732–11737.
17. Ollevier, T.; Nadeau, E. Microwave-enhanced bismuth triflate–catalyzed epoxide opening with aliphatic amines. *Tetrahedron Lett.* **2008**, *49*, 1546–1550.
18. Curini, M.; Epifano, F.; Marcotullio, C. M.; Rosati, O. Zirconium sulfophenyl phosphonate as a heterogeneous catalyst in the preparation of β-amino alcohols from epoxides. *Eur. J. Org. Chem.* **2001**, 4149–4152.
19. Danafar, H.; Yadollahi, B. $(TBA)_4PFeW_{11}O_{39} \cdot 3H_2O$-catalyzed efficient and facile ring-opening reaction of epoxides with aromatic amines. *Catal. Commun.* **2009**, *10*, 842–847.
20. Hosseini-Sarvari, M.; Sharghi, H. Sulfamic acid – catalyzed ring opening of epoxides with amines under solvent-free conditions. *J. Iran. Chem. Soc.* **2008**, *5*, 384–393.
21. Kureshy, R. I.; Singh, S.; Khan, N. H.; Razi Abdi, S. H.; Suresh, E.; Jasra, R. V. Efficient method for ring opening of epoxides with amines by NaY zeolite under solvent-free conditions. *J. Mol. Catal. A: Chem.* **2007**, *264*, 162–169.
22. Reddy, Y. V.; Saraswathy, M.; Rao, B. V.; Shekaram, T. Polymer-supported copper sulphate – promoted aminolysis of epoxides with aromatic amines. *Catal. Commun.* **2006**, *7*, 466–471.
23. Khodaei, M. M.; Khosropour, A. R.; Ghozati, K. A powerful, practical, and chemoselective synthesis of 2-anilinoalkanols catalyzed by $Bi(TFA)_3$ or $Bi(OTf)_3$ in the presence of molten TBAB. *Tetrahedron Lett.* **2004**, *45*, 3525–3529.

24. Bhanushali, M. J.; Nandurkar, N. S.; Bhor, M. D.; Bhanage, B. M. $Y(NO_3)_3 \cdot 6H_2O$-catalyzed regioselective ring opening of epoxides with aliphatic, aromatic, and heteroaromatic amines. *Tetrahedron Lett.* **2008**, *49*, 3672–3676.
25. Kamal, A.; Prasad, B. R.; Reddy, A. M., Khan, M. N. A. Sulfamic acid as an efficient and recyclable catalyst for the ring opening of epoxides with amines and anilines: An easy synthesis of β-amino alcohols under solvent-free conditions. *Catal. Commun.* **2007**, *8*, 1876–1880.
26. Chakraborti, A. K.; Kondaskar, A.; Rudrawar, S. Scope and limitations of montmorillonite K-10 – catalysed opening of epoxide rings by amines. *Tetrahedron* **2004**, *60*, 9085–9091.
27. Tanaka, K.; Toda, F. Solvent-free organic synthesis. *Chem. Rev.* **2000**, *100*, 1025–1074.
28. Varma, R. S. Solvent-free organic syntheses using supported reagents and microwave irradiation. *Green Chem.* **1999**, 43–55.
29. Bhagat, S.; Chakraborti, A. K. An extremely efficient three-component reaction of aldehydes/ketones, amines, and phosphites (Kabachnik–Fields reaction) for the synthesis of α-aminophosphonates catalyzed by magnesium perchlorate. *J. Org. Chem.* **2007**, *72*, 1263–1270.
30. Wu, J.; Sun, W.; Xia, H.-G.; Sun, X. A facile and highly efficient route to α-amino phosphonates via three-component reactions catalyzed by $Mg(ClO_4)_2$ or molecular iodine. *Org. Biomol. Chem.* **2006**, *4*, 1663–1666.
31. Bartoli, G.; Bosco, M.; Dalpozzo, R.; Marcantoni, E.; Massaccesi, M.; Rinaldi, S.; Sambria, L. Mg(ClO4)2 as a powerful catalyst for the acylation of alcohols under solvent-free conditions. *Synlett* **2003**, 39–42.