

A Brief Review on Synthesis of β -amino Alcohols by Ring Opening of Epoxides

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ABSTRACT

β -amino Alcohols are the versatile intermediates in the preparation of many biologically active compounds as well as in pharmaceutical industry. The synthesis of these structures is achieved by various routes but the simplest way is ring opening of epoxide by an amine. There are several difficulties in making these molecules viz reaction conditions, role of catalyst, stereo effects etc. This review focuses on ring opening of epoxides under different conditions to achieve amino alcohols.

INTRODUCTION TO β -AMINO ALCOHOLS COMPOUNDS

β -amino alcohols are the versatile intermediates for many organic compounds in the making of natural and synthetic originated biologically active compounds ^[1,2]. They are widely used as β -blockers, insecticidal agents, and chiral auxiliaries ^[3].

The most common class of naturally occurring compounds containing β -amino alcohol subunit are hydroxy amino acids. For example, the vancomycin ^[4] class of antibiotics contains an aryl serine moiety (**Figure 1**) and the antifungal agent spingofungin (**Figure 2**) contains a hydroxyl amino acid moiety in the polar head group. Another group of naturally occurring biologically active products is the cyclic amino alcohols, like quinines that are used in the treatment of malaria. One important class of cyclic amino alcohols is the polyhydroxylated alkaloids, also known as aza-sugars, e.g. castanospermine ^[5] that was found to be a potent inhibitor of α - and β -glucosidases. Peptidomimetics constitutes a large group of synthetically produced pharmacologically active amino alcohols, most commonly Renin and HIV-1 protease inhibitors, for example Saquinavir.

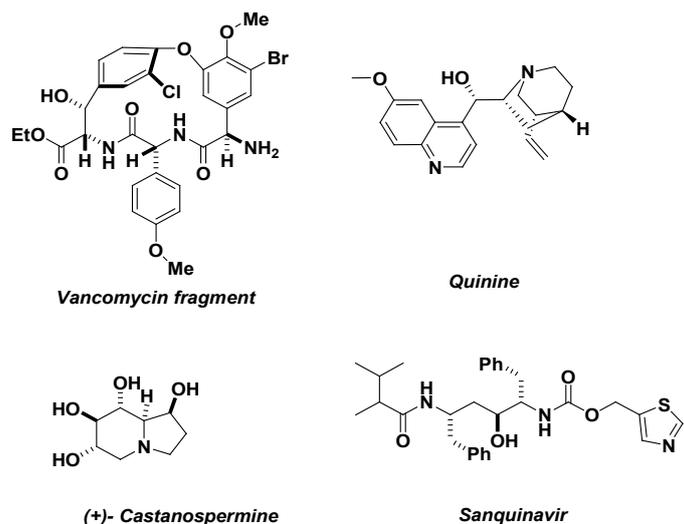


Figure 1. Biologically active amino alcohols.

2-aminoalcohols represent a broad range of β -adrenergic blockers widely used in the management of cardiovascular disorders [6], including hypertension [7], angina pectoris, cardiac arrhythmias, and also other disorders [8-10] related to the sympathetic nervous system. The versatility of this transformation is recognized well as it constitutes the key step for synthesis of β_2 -adrenoceptor agonists [11-14], novel anti-HIV agents [15], 4-demethoxydaunomycin [16], protein kinase C inhibitor balanol [17], glycosidase inhibitor [18], antimalarial agents [19], liposidomycin B class of antibiotics [20], naturally occurring brassinosteroids [21], taxoid side chain [22], diverse heterocycles, for example, benzodiazepinones/benzoxazines/benzoxazepinones [23] and indoles [24] a vast range of biologically active natural and synthetic products [25,26], unnatural amino acids [27-32], and chiral auxiliaries [33,34].

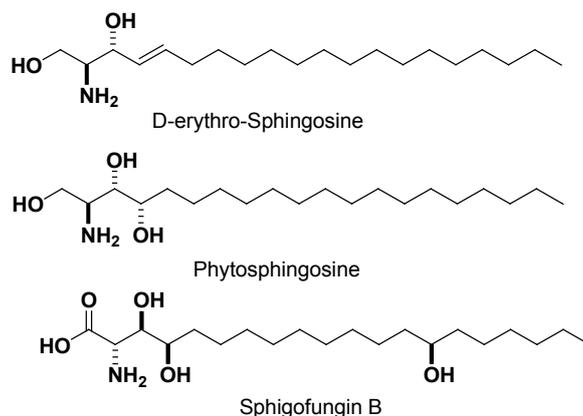


Figure 2. Various Sphingoid Bases.

β -Amino alcohols also play an important role as chiral ligands and chiral auxiliaries in asymmetric catalysis, most commonly derived from natural sources. The amino alcohols are generally derivatized to improve their chelating ability or to increase their steric directing effect [35]. **Figure 3** depicts common β -amino alcohol derivatives used in asymmetric synthesis [36].

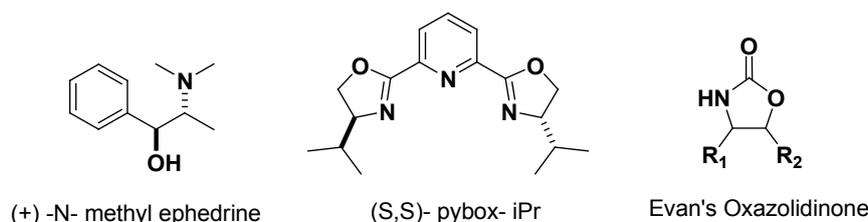


Figure 3. Examples of β -Amino Alcohol-containing Chiral Ligands and Auxiliaries.

There are a few methods for synthesizing racemic mixtures of β -amino alcohols (both enantiomers present). Enantiomerically pure β -amino alcohols are available only through reductions of amino acids, kinetic resolution of racemic mixtures of amino alcohols, or chromatographic methods.

1, 2-Amino alcohols can either be prepared so that a chiral center is created in the reaction, or derived from a compound

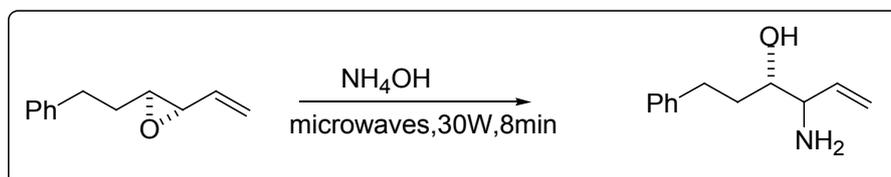
that already contains a stereogenic center. In the latter case, amino acids are natural compounds that are also readily available. The method of choice is often reduction of the parent amino acid. The reduction of amino acids to the corresponding amino alcohols is economically feasible only for the naturally occurring L-amino acids. On the other hand, nucleophilic additions to an imine and oxime chemistry can also be used to provide amino alcohols [37,38].

The only synthetic methodologies available for the direct synthesis of amino alcohols in high yields are the amination of chiral epoxides and the asymmetric hydrogenation or reduction of prochiral-amino ketones. In turn, this also demands a stereoselective method to open the epoxide ring. There are number of means to achieve this with simple alkenes. With unsymmetrical epoxides, the regioselectivity can be controlled through reagent choice [39]. Nucleophilic attack tends to prefer reaction at the least hindered center with concurrent inversion, as observed with primary and secondary amines [40-42].

Here in this review, we would like to present the various approaches to achieve β -Amino Alcohols by ring opening of epoxides. It consists of ring opening of epoxide by conventional methods and solvent free methods.

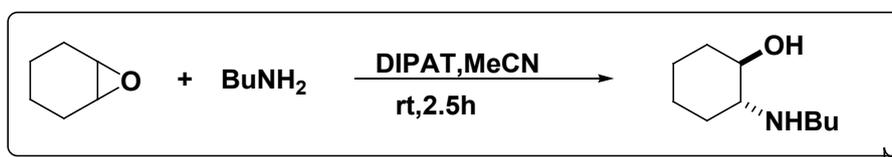
EARLIER APPROACHES FOR THE SYNTHESIS OF β -AMINO ALCOHOLS BY EPOXIDE RING OPENING

Lindstrom et al. [43] reported Di- and trisubstituted vinyl epoxides in NH_4OH under microwave irradiation affording the corresponding vicinal aminoalcohols in high yields. The reaction is stereospecific and highly regioselective for addition at the allylic carbon (**Scheme 1**).



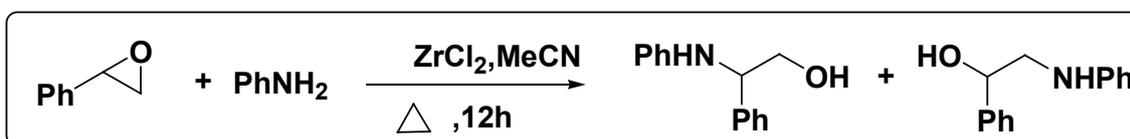
Scheme 1. Stereospecific reaction of vicinal amino alcohols.

Aminolysis of symmetrical as well as unsymmetrical epoxides using various amines in the presence of diisopropoxy aluminium trifluoroacetate (DIPAT) as a new promoter yielding 1,2-amino alcohols in excellent yields at room temperature with good to excellent selectivities were achieved by Akamanchi et al. [44] (**Scheme 2**).



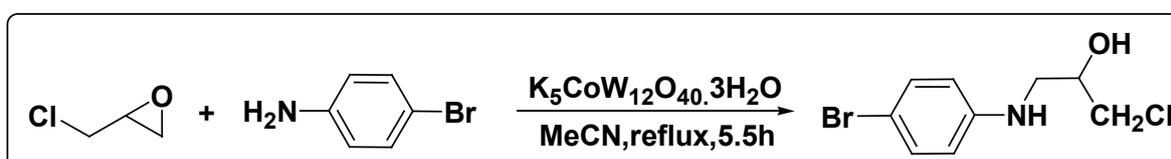
Scheme 2. Aminolysis of symmetrical as well as unsymmetrical epoxides using various amines in the presence of diisopropoxy aluminium trifluoroacetate (DIPAT).

A series of amino alcohols has been prepared by a novel zinc-catalyzed nucleophilic opening of epoxide rings by amines was published by Reedijk et al. [45] (**Scheme 3**).



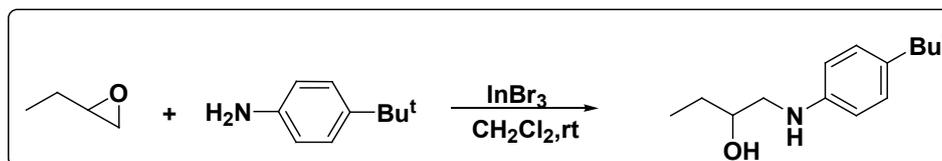
Scheme 3. A series of amino alcohols has been prepared by a novel zinc-catalyzed nucleophilic.

Rafiee et al. [46] reported (**Scheme 4**) Aminolysis of epoxides using various amines catalyzed by potassium dodecatungstocobaltate trihydrate in a convenient and efficient method with good selectivities.



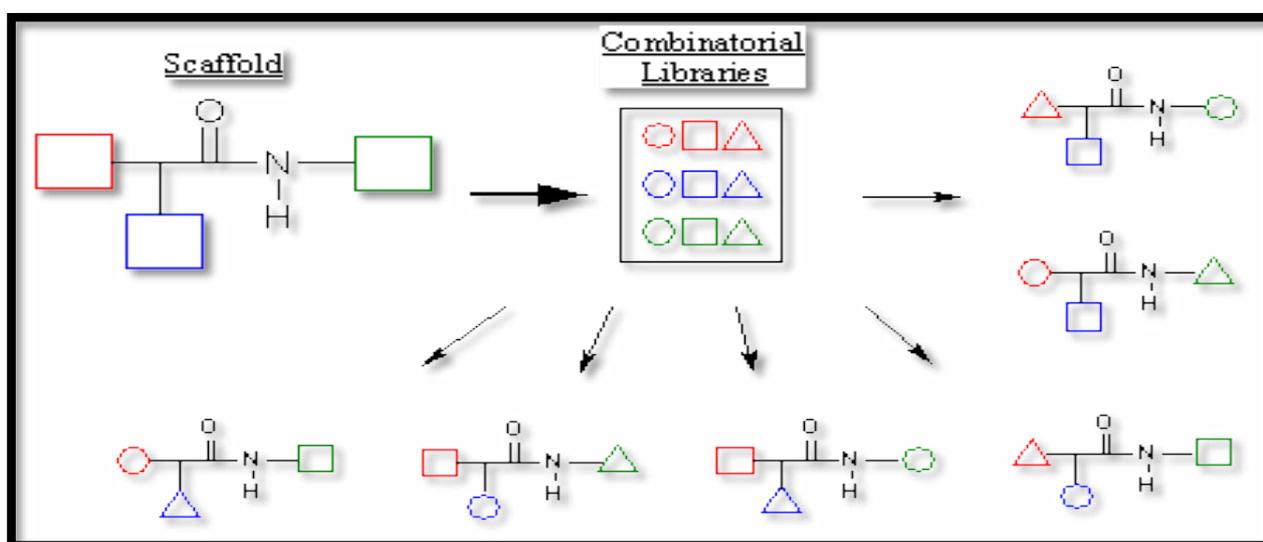
Scheme 4. Aminolysis of epoxides using various amines catalyzed by potassium dodecatungstocobaltate trihydrate.

A mild and efficient synthesis of β -amino alcohols by aminolysis of epoxides promoted by indium tribromide is described by Navarro et al. [47] This methodology is regio- and chemoselective and works well with independence of the epoxide or the aromatic amine used (**Scheme 5**).



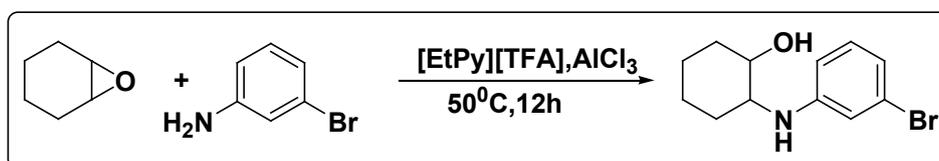
Scheme 5. A mild and efficient synthesis of β -amino alcohols by aminolysis of epoxides promoted by indium tribromide.

Heteropoly acid was found to be an effective and efficient catalyst for the ring opening reaction of epoxides with various aromatic amines to produce the corresponding β -amino alcohols in moderate to excellent yields in water (**Scheme 6**). This method was reported by Saidi et al. [48] which provides a new and efficient protocol in terms of mild reaction conditions, clean reaction profiles, small quantity of catalyst, and simple work-up procedure.



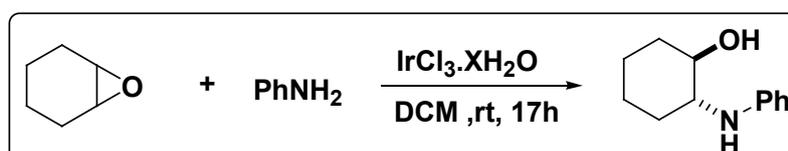
Scheme 6. Various aromatic amines to produce the corresponding β -amino alcohols in moderate to excellent yields in water.

Malhotra et al. [49] reported aminolysis of epoxides by using the ionic liquid 1-ethylpyridinium trifluoro acetate ([EtPy][TFA]) as reaction medium (**Scheme 7**). These reactions went smooth under mild conditions without any catalyst to afford corresponding β -aminoalcohols in high conversions. Moreover, further enhancement in the conversions was observed when AlCl_3 was used as Lewis acid catalyst.



Scheme 7. Aminolysis of epoxides by using the ionic liquid 1-ethylpyridinium trifluoro acetate ([EtPy][TFA]) as reaction medium.

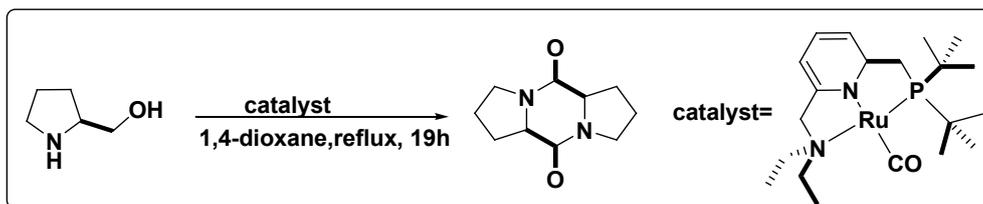
Peddinti et al. [50] described the ring opening of epoxides by aryl, heterocyclic, or aliphatic amines under mild conditions using Iridium trichloride catalyst (**Scheme 8**). The reactions proceed at room temperature to afford the corresponding β -amino alcohols in excellent yields. In general, the aminolysis of cyclopentene oxide is faster than that of cyclohexene oxide in the presence of iridium trichloride as a catalyst.



Scheme 8. The ring opening of epoxides by aryl, heterocyclic, or aliphatic amines under mild conditions using Iridium trichloride catalyst.

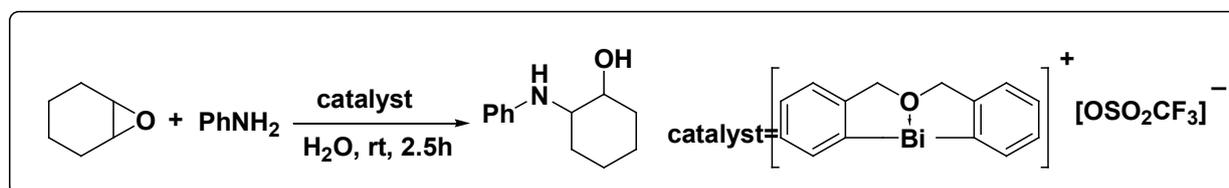
Milstein et al. [51] selected Ru-pincer-complex as catalyst which determines, if peptides or pyrazines are formed from β -amino

alcohols. Use of PNN complex leads to linear poly (alanine) or to cyclic dipeptides, depending on the R group (**Scheme 9**). With the PNP complex, pyrazines are formed. These reactions are homogeneously catalyzed under neutral conditions and are environmentally benign.



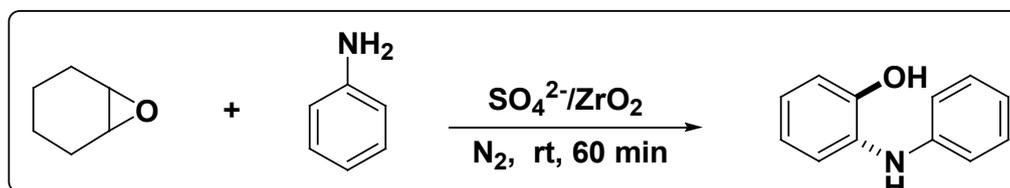
Scheme 9. PNN complex leads to linear poly (alanine) or to cyclic dipeptides, depending on the R group.

Yin et al.^[52] used an air-stable organobismuth triflate complex with a novel 5, 6, 7, 12-tetrahydrodibenzo[c,f]-[1,5]oxabismocine framework. The organobismuth framework is cationic, and the complex shows relatively strong Lewis acidity ($0.8 < \text{Ho} < 3.3$). It was found to exhibit high catalytic activity towards the ringopening reaction of epoxides in aqueous media with aromatic amines at room temperature (**Scheme 10**). This catalyst shows good stability, recyclability and reusability. The catalytic system affords a simple and efficient method for the synthesis of β -amino alcohols.



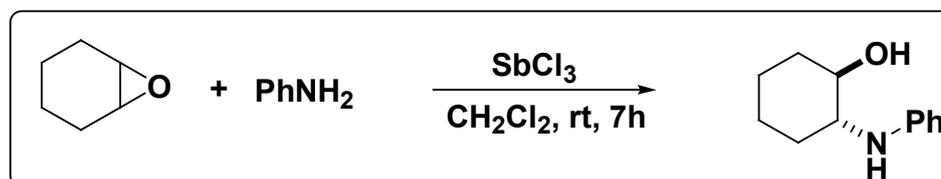
Scheme 10. Catalytic activity towards the ringopening reaction of epoxides in aqueous media with aromatic amines at room temperature.

The catalytic efficacy of sulfated zirconia was investigated by Reddy et al.^[53] towards the opening of epoxide rings by aromatic amines under solvent-free conditions to selectively synthesize various β -amino alcohols with high regioselectivity (**Scheme 11**). Interestingly, the $\text{SO}_4^{2-}/\text{ZrO}_2$ catalyst was found to exhibit an excellent catalytic activity for the reaction.



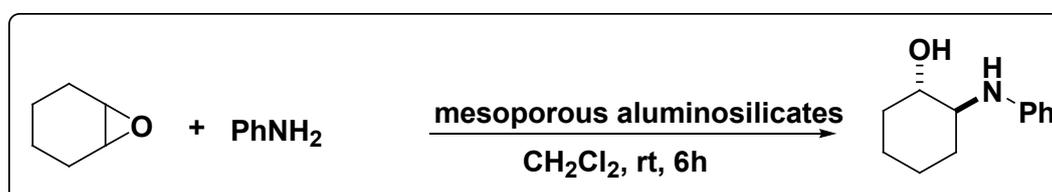
Scheme 11. Aromatic amines under solvent-free conditions to selectively synthesize various β -amino alcohols with high regioselectivity.

A mild and convenient ring opening of epoxides with aniline and its derivatives takes place at room temperature in the presence of antimony trichloride as catalyst to afford the corresponding β -amino alcohols in good yields was achieved by Peddinti et al.^[54] (**Scheme 12**).



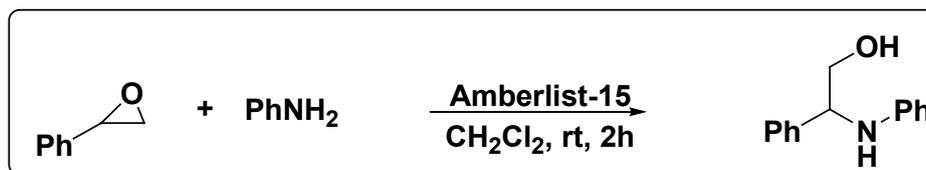
Scheme 12. Antimony trichloride as catalyst to afford the corresponding β -amino alcohols.

Graham et al.^[55] reported (**Scheme 13**) mesoporous aluminosilicates as efficient catalyst for the ring-opening reactions of a range of epoxides with aromatic amines to produce β -substituted alcohols in high yields under mild reaction conditions.



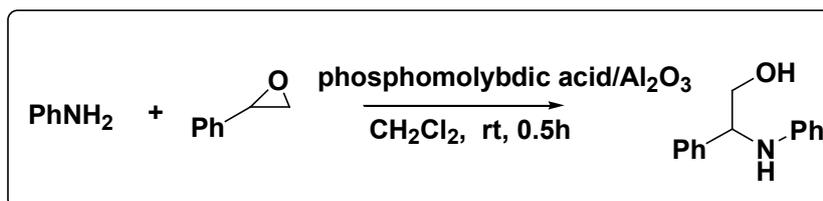
Scheme 13. Mesoporous aluminosilicates as efficient catalyst for the ring-opening reactions.

Satyanarayana et al. ^[56] published Oxiranes ring-opening reaction with amines catalyzed by Amberlist-15 under mild reaction conditions (**Scheme 14**). The reactions were carried out at room temperature to afford the corresponding β -amino alcohols in excellent yields and high regioselectivity.



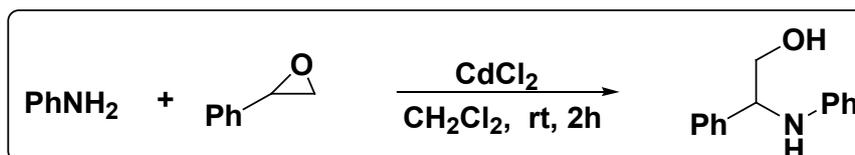
Scheme 14. Oxiranes ring-opening reaction with amines catalyzed by Amberlist-15 under mild reaction conditions.

Epoxides ring-opening reaction were studied by Kumar et al. ^[57] with various amines catalyzed by solid acid containing phosphomolybdic acid-neutral alumina under mild reaction conditions (**Scheme 15**). All the reactions were carried out at room temperature to afford the corresponding β -amino alcohols in excellent yields and with high regioselectivity.



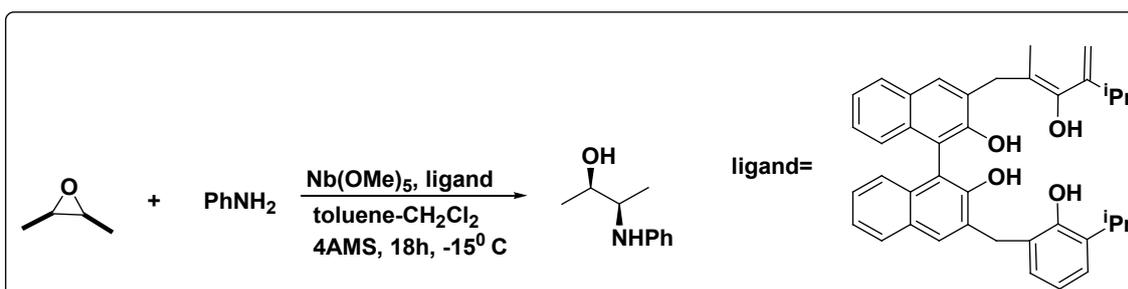
Scheme 15. Various amines catalyzed by solid acid containing phosphomolybdic acid-neutral alumina under mild reaction conditions.

Leelavathi et al. ^[58] reported epoxides ring-opening reactions using CdCl_2 -catalyzed with aromatic amines in mild reaction conditions (**Scheme 16**), affording the corresponding 2-amino alcohols with high regioselectivity.



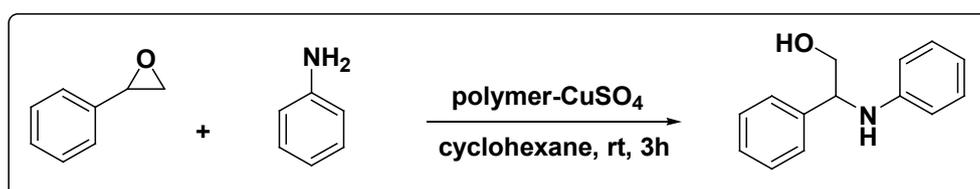
Scheme 16. Ring-opening reactions using CdCl_2 -catalyzed with aromatic amines in mild reaction conditions.

Kobayashi et al. ^[59] described molecular recognition in the desymmetrization of *meso* epoxides with anilines is displayed by a Lewis acid catalyst (**Scheme 17**) formed from Niobium (V) methoxide and a novel tetradentate binol derivative. The catalyst has a remarkable ability to distinguish between different *meso* epoxides.



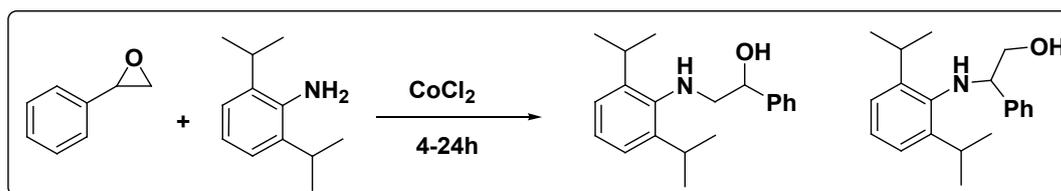
Scheme 17. Molecular recognition in the desymmetrization of *meso* epoxides with anilines is displayed by a Lewis acid catalyst.

Tammishetti et al. reported an efficient and mild method for synthesis of β -aminoalcohols by aminolysis of epoxides (**Scheme 18**) using an alkylamine functional, insoluble and cross-linked polymer support ^[60]. A polymer metal complex of this polymer and copper sulphate was then prepared which is used as a heterogeneous catalyst.



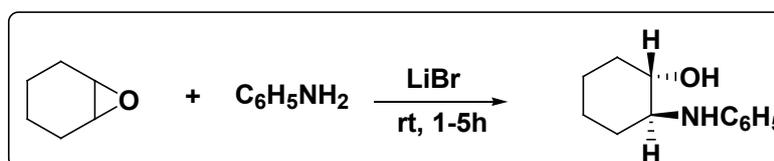
Scheme 18. A polymer metal complex of this polymer and copper sulphate.

CoCl_2 has been used as a mild and effective catalyst by Sundararajan et al.^[61] for regioselective ring opening of oxiranes with anilines to synthesize β -amino alcohols in good yields (**Scheme 19**).



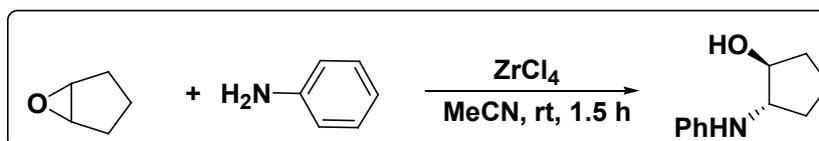
Scheme 19. Regioselective ring opening of oxiranes with anilines to synthesize β -amino alcohols.

Chakraborti^[62] reported Lithium bromide as an inexpensive and efficient catalyst for the opening of epoxide rings by amines, and this provides an environmentally friendly method for the synthesis of β -amino alcohols (**Scheme 20**). Aromatic and aliphatic amines react with cycloalkene oxides to exclusively form *trans*-2-(aryl/alkylamino) cycloalkanols in high yields. Non-styrenoidal, unsymmetrical alkene oxides undergo selective nucleophilic attack at the sterically less hindered carbon atom by aniline. The chelation effect of the Li^+ ion enables selective opening of the epoxide ring in 3-phenoxypropylene oxide in the presence of styrene oxide.



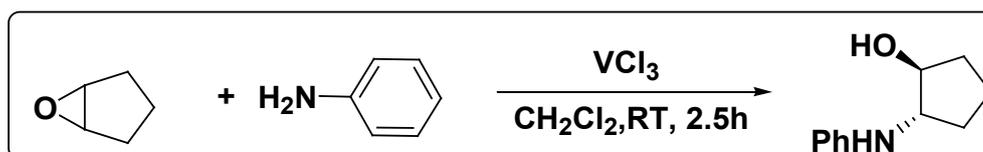
Scheme 20. Lithium bromide as an inexpensive and efficient catalyst for the opening of epoxide rings by amines.

Venkateswarlu et al.^[63] used Zirconium (IV) chloride catalyst for the ring opening of epoxides with anilines to afford the corresponding β -amino alcohols in acetonitrile at ambient temperature was discussed (**Scheme 21**).



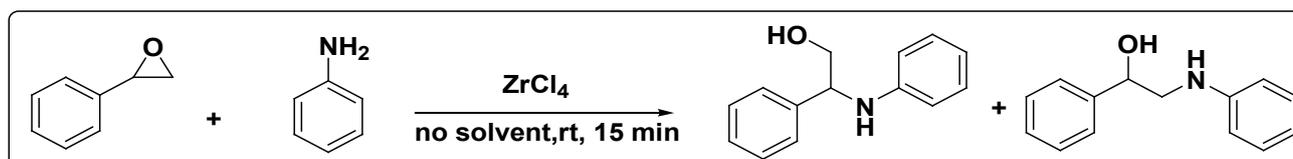
Scheme 21. Zirconium (IV) chloride catalyst for the ring opening of epoxides with anilines.

Vanadium (III) chloride^[64] was found to catalyze the cleavage of epoxides with aromatic amines in an efficient way to afford the corresponding β -amino alcohols in very good yields (**Scheme 22**). The reactions are completely anti-stereoselective, highly regioselective and proceed at room temperature.



Scheme 22. Anti-stereoselective reactions of Vanadium (III) chloride.

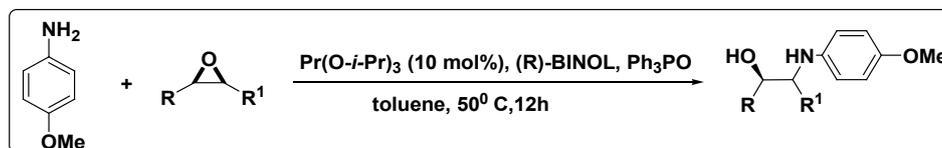
Zirconium (IV) chloride^[65] catalyses the nucleophilic opening of epoxide rings by amines leading to the efficient synthesis of β -amino alcohols (**Scheme 23**). The reaction works well with aromatic and aliphatic amines in short times at room temperature in the absence of solvent. Exclusive *trans* stereoselectivity is observed for cyclic epoxides. Aromatic amines exhibit excellent regioselectivity for preferential nucleophilic attack at the sterically less hindered position during the reaction with unsymmetrical epoxides. However, in case of styrene oxide, selective formation of the benzylic amine was observed during the reactions with aromatic amines.



Scheme 23. Zirconium (IV) chloride catalyses the nucleophilic opening of epoxide rings by amines leading to the efficient synthesis of β -amino alcohols.

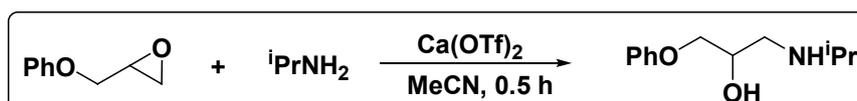
Formal synthesis of 4-demethoxydaunomycin was achieved using a catalytic asymmetric ring opening reaction of *meso*-

epoxide as a key step. The epoxide opening reaction was promoted by 10 mol% of Pr-(R)-BINOL-Ph₃PO complex^[66] to give the β-amino alcohol (**Scheme 24**) in 80% yield with 65% enantiomeric excess (ee).



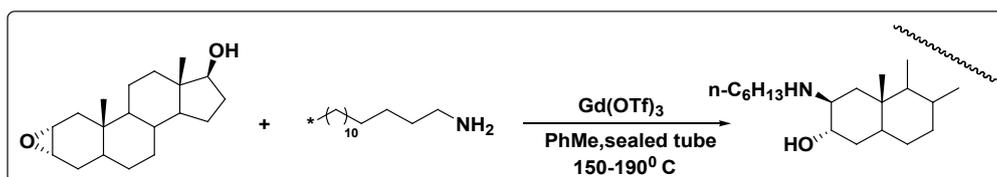
Scheme 24. The epoxide opening reaction was promoted by 10 mol% of Pr-(R)-BINOL-Ph₃PO complex^[54] to give the β-amino alcohol.

Cepanec et al.^[67] described aminolysis of epoxides catalyzed by calcium trifluoromethanesulfonate under mild reaction conditions. This method is efficient in the synthesis of wide variety of β-amino alcohols with high regio- and stereoselectivity (**Scheme 25**).



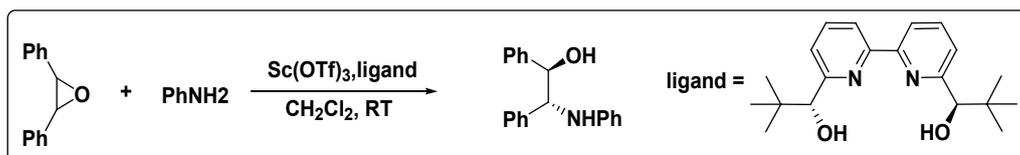
Scheme 25. Aminolysis of epoxides catalyzed by calcium trifluoromethanesulfonate under mild reaction conditions.

The opening of hindered 2,3 α-steroidal epoxide with primary and secondary amines was performed by D. Poirier et al.^[68] with a catalytic amount of Gd(OTf)₃ in toluene in a sealed tube at high temperature (**Scheme 26**). This method is much more efficient (48-97% yields) than the older classical one (0-64% yields) using a large excess of amine.



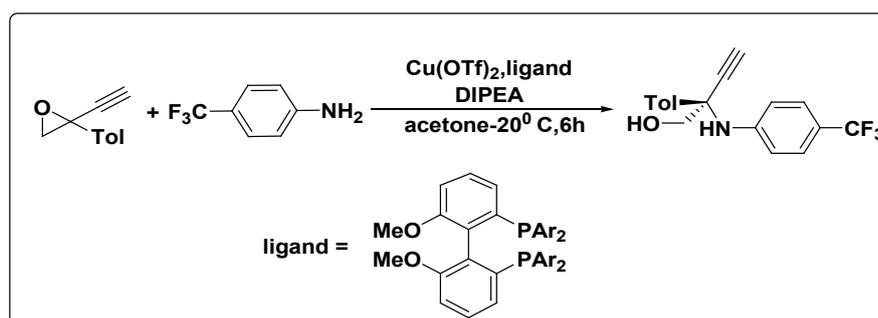
Scheme 26. The opening of hindered 2,3 α-steroidal epoxide with primary and secondary amines.

Schneider et al.^[69] proposed the scandium-bipyridine-catalyzed enantio-selective addition of anilines and O-alkyl hydroxylamines to meso-epoxides has been optimized and extended to a broad range of epoxides and amines (**Scheme 27**). Whereas aromatic meso-epoxides generally furnished the corresponding 1, 2-amino alcohols in excellent enantioselectivities, aliphatic meso-epoxides only gave rise to moderate enantioselectivities in the aminolysis.



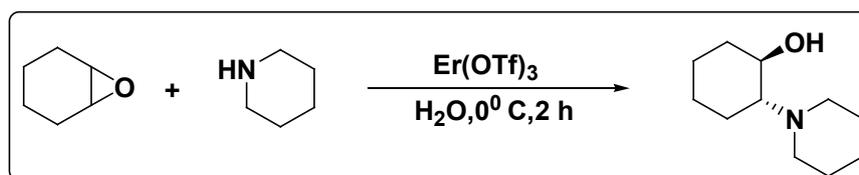
Scheme 27. Scandium-bipyridine-catalyzed enantio-selective addition of anilines and O-alkyl hydroxylamines to meso-epoxides.

Nishibayashi et al.^[70] proposed enantioselective copper-catalyzed ring-opening reactions of racemic ethynyl epoxides with amines using (R)-DTBM-MeO-BIPHEP as a chiral ligand have been found to give the corresponding amino alcohols in high yields with up to 94% ee (**Scheme 28**). This methodology may provide a novel synthetic approach to optically active amino alcohols, the structures of which are widely found in many natural products, biologically active compounds, and chiral ligands.



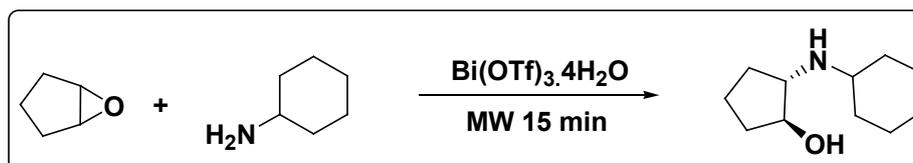
Scheme 28. Enantioselective copper-catalyzed ring-opening reactions of racemic ethynyl epoxides with amines using (R)-DTBM-MeO-BIPHEP.

$\text{Er}(\text{OTf})_3$ is proposed as a highly efficient and reusable catalyst by Procopio et al. [74] for the opening of epoxides in water with aliphatic as well as aromatic amines leading to the synthesis of β -amino alcohols (**Scheme 29**).



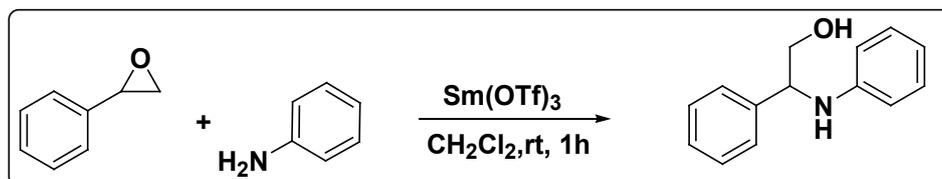
Scheme 29. $\text{Er}(\text{OTf})_3$ is proposed as a highly efficient and reusable catalyst.

Ollevier et al. [72] reported microwave irradiation, neat mixtures of epoxides and amines afforded smoothly the corresponding 2-amino alcohols in the presence of a catalytic amount of $\text{Bi}(\text{OTf})_3 \cdot 4\text{H}_2\text{O}$ (**Scheme 30**). A wide variety of aliphatic amines were reacted with cycloalkene oxide, styrene oxide, and stilbene oxide. The reaction proceeded rapidly and afforded the 2-amino alcohols in high up to quantitative yields.



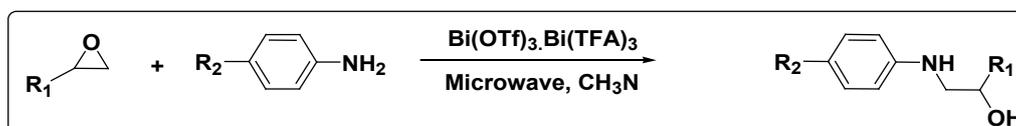
Scheme 30. Microwave irradiation, neat mixtures of epoxides and amines afforded smoothly the corresponding 2-amino alcohols in the presence of a catalytic amount of $\text{Bi}(\text{OTf})_3 \cdot 4\text{H}_2\text{O}$.

Yadav et al. [73] proposed rapid ring opening reaction of oxiranes with amines catalyzed by samarium triflate under mild reaction conditions (**Scheme 31**). The reactions were carried out at below room temperature to afford the corresponding β -amino alcohols in excellent yields and high regioselectivity. This protocol has been applied for the synthesis of various β -blockers.



Scheme 31. Rapid ring opening reaction of oxiranes with amines catalyzed by samarium triflate under mild reaction conditions.

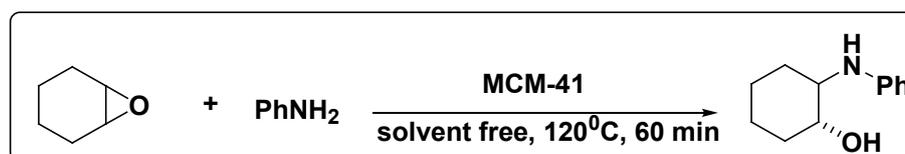
A facile and environmentally friendly methodology was described by Khosropour et al. [74] for the ring opening of epoxides with anilines (**Scheme 32**) has been developed in the presence of catalytic amounts of Bismuth (III) triflate or Bismuth (III) trifluoroacetate using microwave-assisted heating.



Scheme 32. Catalytic amounts of Bismuth (III) triflate or Bismuth (III) trifluoroacetate using microwave-assisted heating.

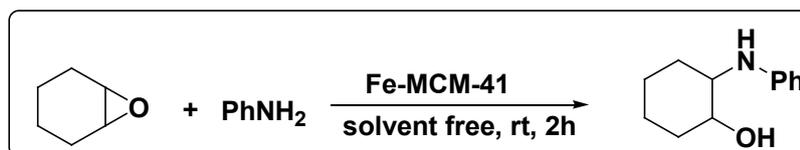
SOLVENT FREE SYNTHESIS OF β -AMINO ALCOHOLS

Bakhtiari et al. [75] synthesized β -amino alcohols in high yields [75] by reaction of epoxides with amines in the presence of MCM-41 as a green and reusable catalyst under solvent-free conditions (**Scheme 33**).



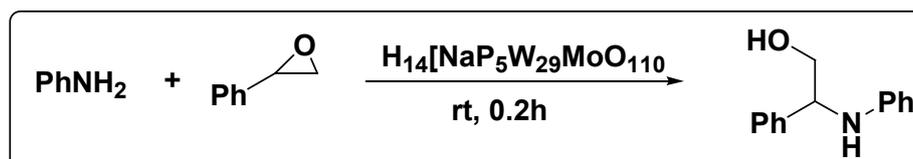
Scheme 33. Amines in the presence of MCM-41 as a green and reusable catalyst under solvent-free conditions.

A highly efficient method for the aminolysis of epoxides in the presence of a catalytic amount of Fe-MCM-41 is reported by Heravi et al. [76] (**Scheme 34**). An important advantage of this catalyst is the ease of separating it from the reaction mixture, as well as the fact that it could be recycled a number of times.



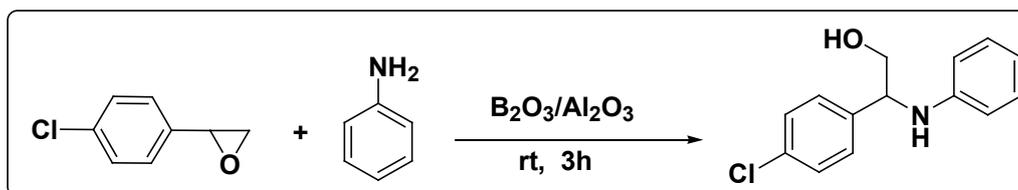
Scheme 34. A highly efficient method for the aminolysis of epoxides in the presence of a catalytic amount of Fe-MCM-41.

Heravi et al. [77] developed a simple and efficient method for the synthesis of β -amino alcohols by ring opening of epoxides in the presence of a catalytic amount of $H_{14}[NaP_5W_{29}MoO_{110}]$ at room temperature under solvent-free conditions. The reaction works well for both aromatic and aliphatic amines and it was presented in **Scheme 35**.



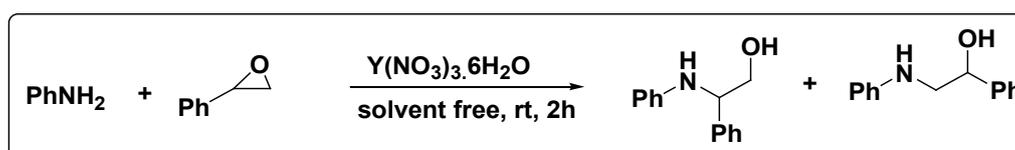
Scheme 35. Simple and efficient method for the synthesis of β -amino alcohols by ring opening of epoxides in the presence of a catalytic amount of $H_{14}[NaP_5W_{29}MoO_{110}]$.

A convenient and efficient procedure for the solvent-free synthesis of β -amino alcohols has been achieved by Wu et al. [78] via $B_2O_3-Al_2O_3$ -promoted highly regioselective ring opening of epoxides with aromatic amines in good to excellent yields at room temperature (**Scheme 36**). Additionally, the catalyst can be recycled without affecting the catalytic property.



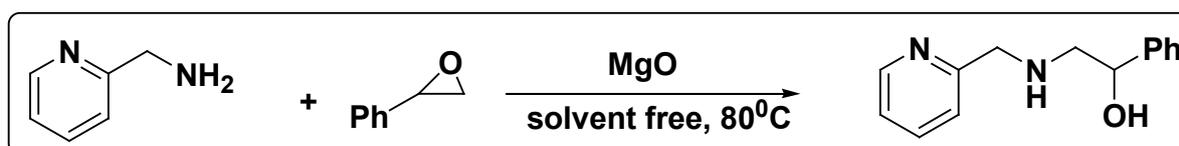
Scheme 36. $B_2O_3-Al_2O_3$ -promoted highly regioselective ring opening of epoxides with aromatic amines.

Bhanage et al. [79] used Yttrium nitrate hexahydrate $[Y(NO_3)_3 \cdot 6H_2O]$ as an efficient catalyst for selective ring opening of epoxides with aliphatic, aromatic, and heteroaromatic amines at room temperature under solvent-free conditions (**Scheme 37**). The system tolerated a variety of hindered and functionalized epoxides/amines and afforded the desired β -amino alcohols at low catalyst concentration.



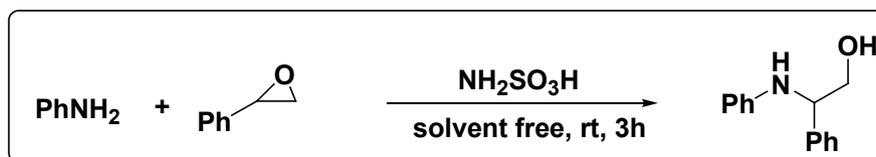
Scheme 37. Yttrium nitrate hexahydrate $[Y(NO_3)_3 \cdot 6H_2O]$ as an efficient catalyst for selective ring opening of epoxides with aliphatic, aromatic, and heteroaromatic amines.

MgO catalyzed efficiently the ring opening of epoxides with a range of aromatic and aliphatic amines to produce β -substituted alcohols in high yields under solvent-free conditions (**Scheme 38**). Exclusive trans stereoselectivity is observed for cyclic epoxide by Hosseini-Sarvari et al. [80].



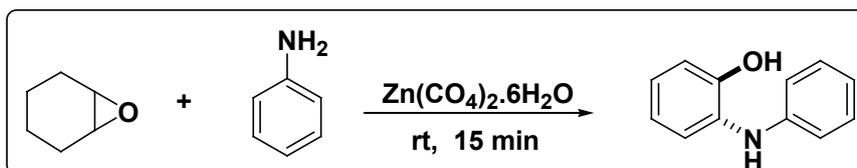
Scheme 38. MgO catalyzed efficiently the ring opening of epoxides with a range of aromatic and aliphatic amines.

Application of sulfamic acid as an efficient and green catalyst for the ring opening of epoxides by aliphatic and aromatic amines under solvent-free conditions is described by Kamal et al. [81]. In this process, the use of basic neutralization agent was not required due to the intrinsic zwitterionic property of sulfamic acid (**Scheme 39**).



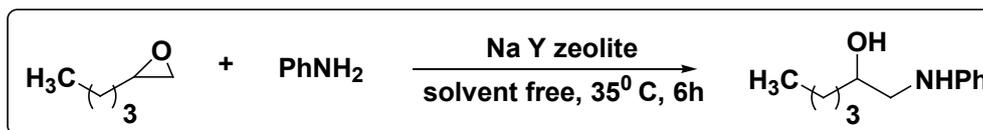
Scheme 39. Application of sulfamic acid as an efficient and green catalyst for the ring opening of epoxides by aliphatic and aromatic amines.

Chakraborti et al.^[82] used commercially available Zinc(II) perchlorate hexahydrate $[\text{Zn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}]$ as a new and highly efficient catalyst for opening of epoxide rings by amines affording 2-amino alcohols in high yields under solvent-free conditions and with excellent chemo-, regio-, and stereoselectivities (**Scheme 40**). For unsymmetrical epoxides, the regioselectivity was influenced by the electronic and steric factors associated with the epoxides and the amines. Zinc(II) perchlorate hexahydrate was found to be the best catalyst compared to other metal perchlorates. The counter anion modulated the catalytic property of the various Zn(II) compounds that followed the order $\text{Zn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O} > \text{Zn}(\text{BF}_4)_2 > \text{Zn}(\text{OTf})_2 > \text{ZnI}_2 > \text{ZnBr}_2 > \text{ZnCl}_2 > \text{Zn}(\text{OAc})_2 > \text{Zn}(\text{CO}_3)_2$ in parallelism with the acidic strength of the corresponding protic acids (except for TfOH).



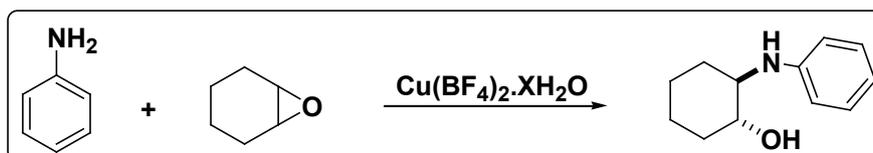
Scheme 40. Zinc(II) perchlorate hexahydrate $[\text{Zn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}]$ as a new and highly efficient catalyst for opening of epoxide rings by amines.

Na Y zeolite was used as a recyclable catalyst by Kureshy et al.^[83] for the ring opening of epoxides using aliphatic and aromatic amines as nucleophile under solvent-free conditions to give the corresponding β -amino alcohols in high yields (**Scheme 41**).



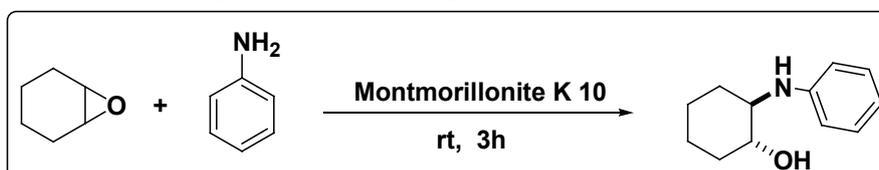
Scheme 41. Na Y zeolite was used as a recyclable catalyst.

Kamal et al.^[84] used Copper(II) tetrafluoroborate as efficient catalyst for the selective opening of epoxides by amines leading to the synthesis of β -amino alcohols (**Scheme 42**). The reaction works well with aromatic and aliphatic amines in high yields under solvent-free conditions.



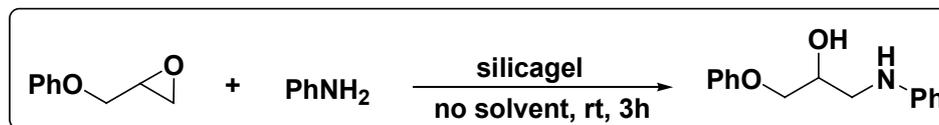
Scheme 42. Copper (II) tetrafluoroborate as efficient catalyst for the selective opening of epoxides by amines leading to the synthesis of β -amino alcohols.

Montmorillonite K 10 efficiently catalyses the opening of epoxide rings by Chakraborti et al.^[85]. Amines with excellent regio- and diastereo-selectivities under solvent-free conditions at room temperature afford an improved process for synthesis of 2-amino alcohols (**Scheme 43**). Reaction of cyclohexene oxide with aryl/alkyl amines leads to the formation of trans-2-aryl/alkyl amino cyclohexanols. For unsymmetrical epoxides, the regioselectivity is controlled by the electronic and steric factors associated with the epoxide and the amine. Selective nucleophilic attack at the benzylic carbon of styrene oxide takes place with aromatic amines, whereas, aliphatic amines exhibit preferential nucleophilic attack at the terminal carbon. Aniline reacts selectively at the less hindered carbon of other unsymmetrical epoxides. The difference in the internal strain energy of the epoxide ring in cycloalkene oxides and alkene oxides led to selective nucleophilic opening of cyclohexene oxide by aniline in the presence of styrene oxide. Due to the chelation effect, selective activation of the epoxide ring in 3-phenoxy propylene oxide takes place in the presence of styrene oxide leading to preferential cleavage of the epoxide ring in 3-phenoxy propylene oxide by aniline.



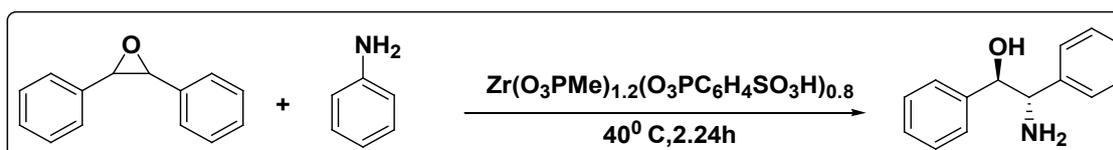
Scheme 43. Montmorillonite K 10 efficiently catalyses the opening of epoxide rings.

Silica gel (60-120 mesh) efficiently catalyzes the opening of epoxide rings by amines at room temperature under solvent-free conditions providing an easy method as reported by Chakraborti et al.^[86] for the synthesis of 2-amino alcohols. Aromatic and aliphatic amines react with cyclohexene oxide with exclusive formation of the *trans*-2-aryl/alkylaminocyclohexanols in high yields (**Scheme 44**).



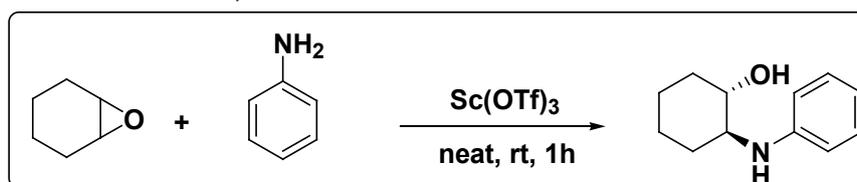
Scheme 44. Silica gel (60-120 mesh) efficiently catalyzes the opening of epoxide rings.

A convenient method for the ring opening of epoxides by aromatic amines, catalysed by zirconium sulfophenyl phosphonate^[87] in solvent-free conditions, is described and presented in **Scheme 45**.



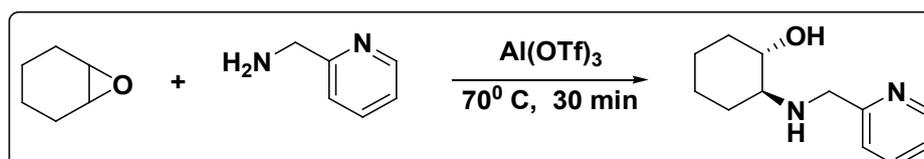
Scheme 45. A convenient method for the ring opening of epoxides by aromatic amines, catalysed by zirconium sulfophenyl phosphonate.

A simple and efficient method has been developed by De et al.^[88] for the synthesis of β -amino alcohols by ring opening of epoxides in the presence of a catalytic amount of $\text{Sc}(\text{OTf})_3$ at room temperature under solvent-free conditions (**Scheme 46**). The reaction works well with both aromatic and aliphatic amines.



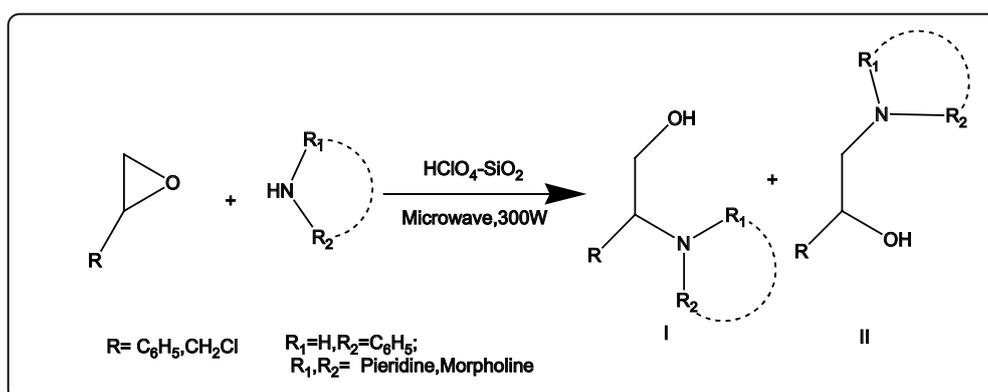
Scheme 46. The synthesis of β -amino alcohols by ring opening of epoxides in the presence of a catalytic amount of $\text{Sc}(\text{OTf})_3$.

β -Amino alcohols N-2-pyridylmethyl substituted have been prepared in excellent yields under mild conditions by the first Lewis acid-catalyzed aminolysis of 1,2-epoxides with the bidentate amine 2-picolylamine with use of 5 mol % of $\text{Al}(\text{OTf})_3$ under solvent-free conditions was reported by L. Vaccaro et al.^[89] (**Scheme 47**).



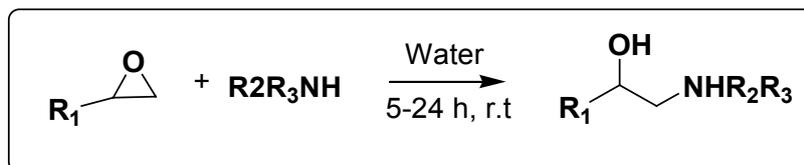
Scheme 47. First Lewis acid-catalyzed aminolysis of 1,2-epoxides with the bidentate amine 2-picolylamine.

Murthy et al.^[90] have reported the synthesis of β -Amino alcohols were achieved by the ring opening of epoxides in presence of a reusable perchloric acid supported silica matrix ($\text{HClO}_4\text{-SiO}_2$) surface in a microwave under solvent free conditions (**Scheme 48**).



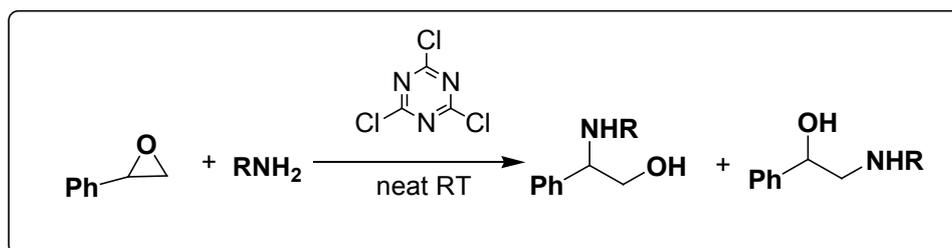
Scheme 48. Per chloric acid supported silica matrix ($\text{HClO}_4\text{-SiO}_2$) surface.

Saidi et al.^[91] have stated that aminolysis of a variety of epoxides by aliphatic and aromatic amines in water, in the absence of any catalyst with high yields, is reported. β -amino alcohols were formed under mild conditions with high selectivity and in excellent yields (**Scheme 49**).



Scheme 49. Aminolysis of a variety of epoxides by aliphatic and aromatic amines in water, in the absence of any catalyst.

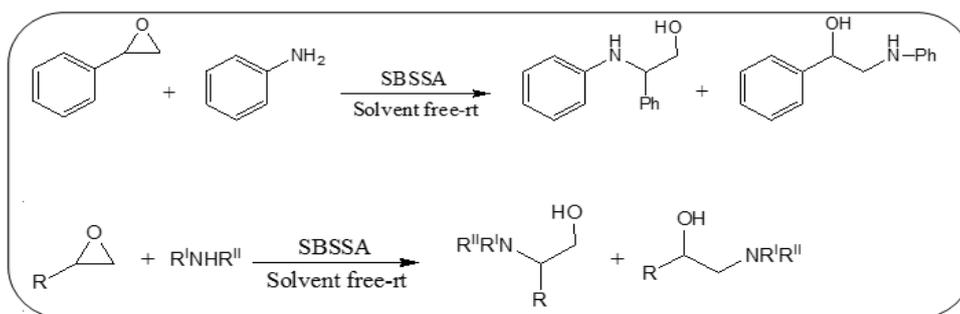
The 2,4,6-trichloro-1,3,5-triazine (cyanuric chloride) catalyzed synthesis of β -amino alcohols by aminolysis of epoxide under solvent free condition is described by Kamble et al.^[92] (**Scheme 50**).



Scheme 50. The 2,4,6-trichloro-1,3,5-triazine (cyanuric chloride) catalyzed synthesis of β -amino alcohols by aminolysis.

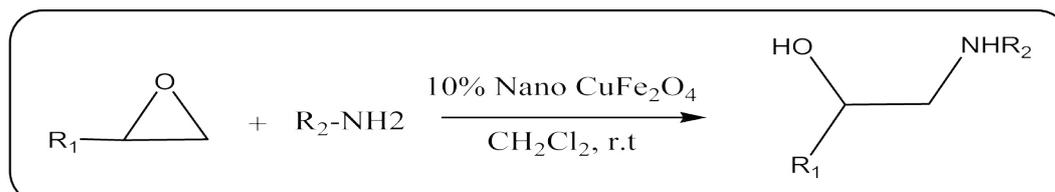
Readily synthesized chiral sulfinamide based organocatalyst enables an asymmetric ring-opening (ARO) reaction of *meso* epoxides with anilines in high yields of with excellent enantioselectivity at room temperature. A probable mechanism for the catalytic ARO reaction is envisaged by ¹H and ¹³C NMR experiments.

Tajbakhsh et al.^[93] reported a recyclable and reusable catalyst Silica-bonded S-sulfonic acid (SBSSA) for the synthesis of β -amino alcohols. A regioselective β -amino alcohols with high yields was achieved by the reaction of epoxides with several amines under solvent free conditions at room temperature (**Scheme 51**).



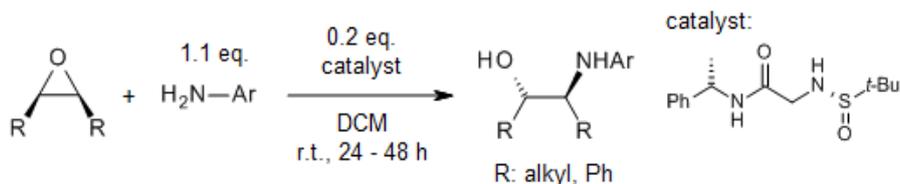
Scheme 51. A recyclable and reusable catalyst Silica-bonded S-sulfonic acid (SBSSA) for the synthesis of β -amino alcohols.

Baghbanian et al.^[94] developed a simple and efficient method for the synthesis of β -amino alcohols by regioselective ring opening of epoxides with amines using CuFe_2O_4 nanoparticles as a heterogeneous recyclable catalyst at room temperature in high yields (**Scheme 52**).



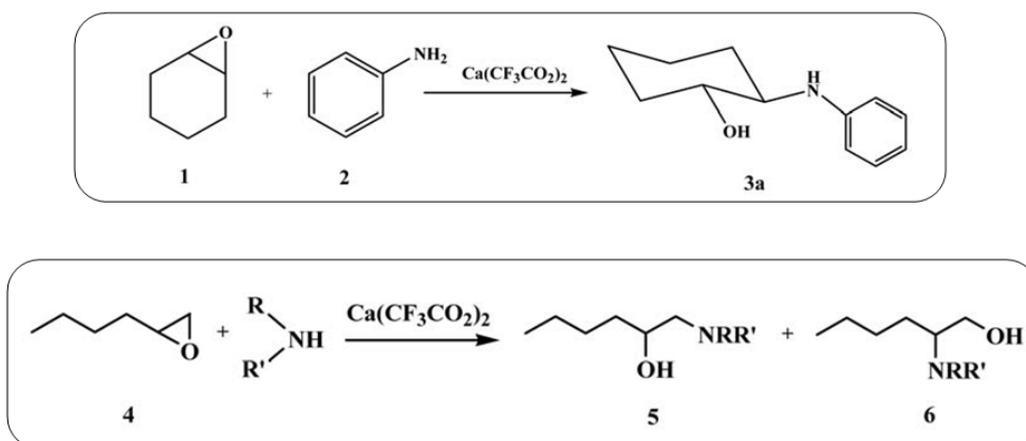
Scheme 52. Regioselective ring opening of epoxides with amines using CuFe_2O_4 nanoparticles.

Kureshy et al.^[95] achieved high yield (up to 95%) of chiral β -amino alcohols with excellent enantioselectivity (up to 99%) in 24-30 h at room temperature under optimized reaction conditions. In the process they synthesized a chiral sulfinamide based organocatalyst from readily available starting materials and used for the asymmetric ring-opening (ARO) reaction of *meso* epoxides with anilines. A probable mechanism for the catalytic ARO reaction is envisaged by ¹H and ¹³C NMR experiments (**Scheme 53**).



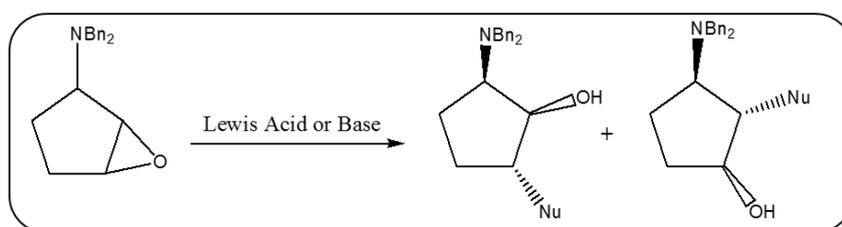
Scheme 53. A probable mechanism for the catalytic ARO reaction is envisaged by ^1H and ^{13}C NMR experiments.

The selective ring-opening of epoxide's by amines leading to the synthesis of β -aminoalcohols was achieved by Ali et al.^[96] by using $\text{Ca}(\text{CF}_3\text{CO}_2)_2$ an efficient catalyst. The reaction works well with various aromatic and aliphatic amines under solvent-free conditions. Corresponding β -aminoalcohols were obtained in excellent yields with high regioselectivity. This is an improved and efficient, sustainable and environmentally friendly process for the synthesis of β -aminoalcohols by the aminolysis of 1,2-epoxides (**Scheme 54**).



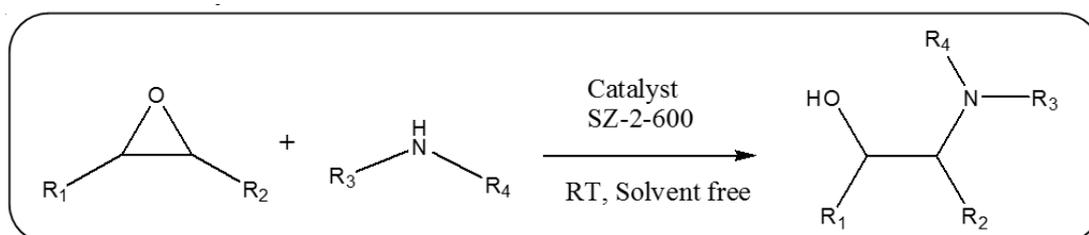
Scheme 54. The selective ring-opening of epoxide's by amines leading to the synthesis of β -aminoalcohols was achieved by using $\text{Ca}(\text{CF}_3\text{CO}_2)_2$.

Larin et al.^[97] reported the optimal conditions for regio- and stereoselective epoxide ring opening of N,N-disubstituted 1,2-epoxy-3-aminocyclopentanes by different nucleophilic reagents. The substituents on the nitrogen atom in the epoxide precursor and the orientation of the oxirane ring are crucial for the reaction outcome (**Scheme 55**).



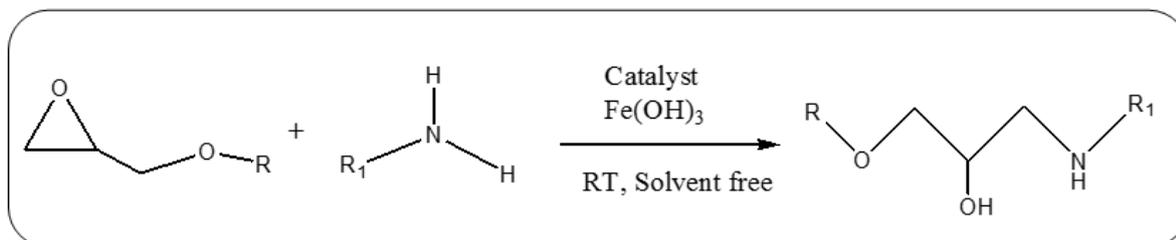
Scheme 55. The optimal conditions for regio- and stereoselective epoxide ring opening of N,N-disubstituted 1,2-epoxy-3-aminocyclopentanes by different nucleophilic reagents.

Single-step and two-steps synthetic procedure for the synthesis of sulfated zirconia (SZ) was developed by Bajaj et al.^[98]. These SZ materials were then employed as solid acid catalysts for the aminolysis of different aliphatic/aromatic terminal, aryloxy and *meso*epoxides with aromatic and aliphatic amines under ambient conditions. Amongst the catalyst prepared, SZ-2-600 prepared in two-steps and 600°C calcined was found to be the most efficient catalyst to give β -amino alcohols in up to 98% yield and >99% regioselectivity. The SZ catalyst was successfully recycled and reused up to six catalytic runs with intact efficiency (**Scheme 56**).



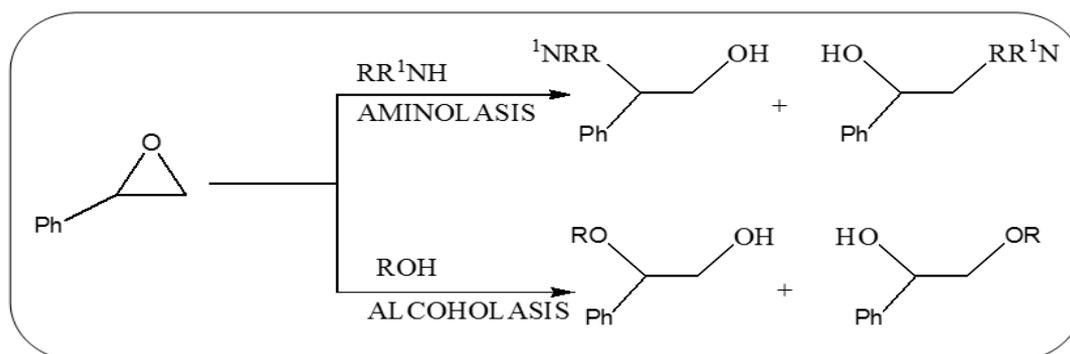
Scheme 56. Single-step and two-steps synthetic procedure for the synthesis of sulfated zirconia (SZ).

An efficient and environmentally benign heterogeneous catalysts for the epoxide ring opening reaction of various aryloxy, terminal and *meso* epoxides with aromatic and aliphatic amines under solvent free condition at room temperature was achieved by Bajaj et al.^[99] using Iron hydroxide-Fe(OH)₃ and iron oxides (Fe₃O₄ and Fe₂O₃) catalysts. The nano-sized Fe(OH)₃ (IH-1) showed better catalytic activity to give the product β-amino alcohols in excellent yield (up to □96%) and high regioselectivity in 10–360 min. The catalyst was successfully recycled and reused eight times with no loss in catalytic activity (**Scheme 57**).



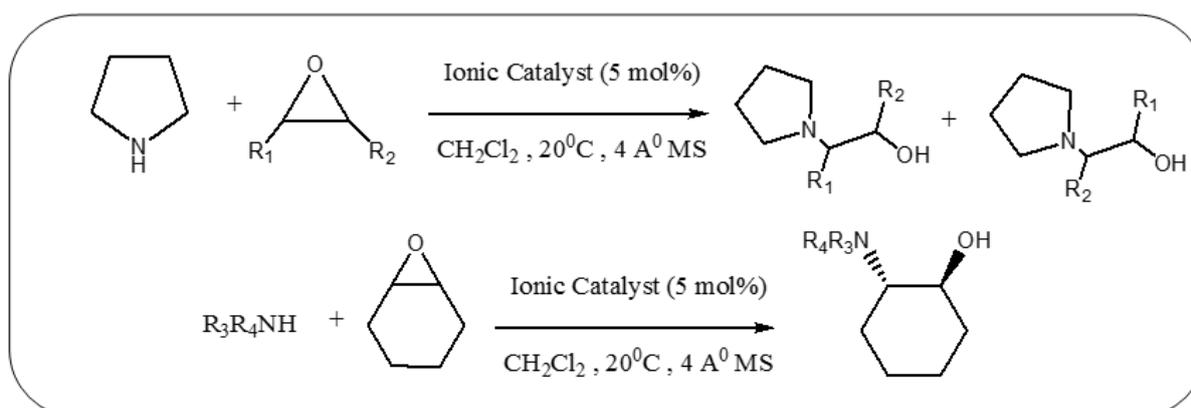
Scheme 57. Aryloxy, terminal and *meso* epoxides with aromatic and aliphatic amines under solvent free condition was achieved by using Iron hydroxide-Fe(OH)₃ and iron oxides (Fe₃O₄ and Fe₂O₃) catalysts.

The catalytic activity of naturally occurring Montmorillonite clay modified by acid treatment is reported for the reactions of epoxides with nucleophiles such as amines and alcohols at ambient temperature and solvent-free condition were described by Dutta et al.^[100] The solid acid catalyst acts as reusable and exhibits significantly higher catalytic activities than known catalysts for the opening of the oxirane ring with nitrogen (aromatic as well as aliphatic amines) and oxygen (aromatic as well as aliphatic alcohols). A wide range of β-amino alcohols and β-alkoxy alcohols were synthesized with high epoxide conversion of excellent regioselectivity. They reported the modified catalyst is recycled up to five times without significant loss in conversion and selectivity (**Scheme 58**).



Scheme 58. The reactions of epoxides with nucleophiles such as amines and alcohols at ambient temperature and solvent-free.

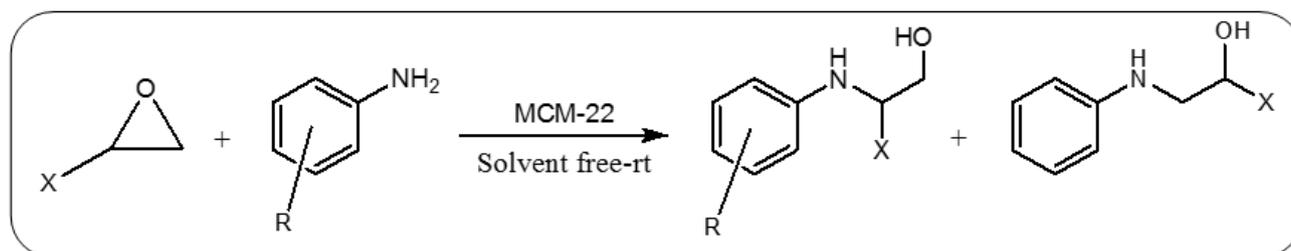
Different β-amino-alcohols were synthesized in satisfying conversion (50-80%) in 24 h, under mild conditions Supramolecular ionic organocatalysts and a metal-based catalyst was achieved by Bibal et al.^[101]. They investigated the ring-opening of epoxides by amines, without any artifice to enhance conversion (i.e., solvophobic effect, extended reaction time, heating, excess of amine, high catalyst loading) (**Scheme 59**).



Scheme 59. Under mild conditions Supramolecular ionic organocatalysts and a metal-based catalyst was achieved.

Sakthivel et al.^[102] synthesized β-amino alcohols at room temperature employing microporous MCM-22 zeolite as catalyst in an eco-friendly manner without using any solvent. The zeolite MCM-22 showed promising activity for the conversion of primary

and secondary amines into β -amino alcohols under mild reaction conditions (**Scheme 60**). The catalytic activity remains intact for three recycles ^[103,104].



Scheme 60. The zeolite MCM-22 showed promising activity for the conversion of primary and secondary amines into β -amino alcohols under mild reaction conditions.

CONCLUSION

In this review article, we have demonstrated the importance of amino alcohols in biological applications and the various methods to synthesize β -amino alcohols. The review is focused on the developments in synthesizing the β -amino alcohols in the last 20 years.

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