The Selective C-3 Opening of Aromatic 2,3-Epoxy Alcohols/Epoxides with Aromatic Amines Catalysed by β-Cyclodextrin in Water[1]

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Abstract: A simple and mild procedure has been developed for the first time for the C-3 selective ring-opening of aromatic 2,3-epoxy alcohols/epoxides with aromatic amines catalysed by β-cyclodextrin in water at room temperature to afford the corresponding β-aminoalcohols in excellent yields with high regioselectivity.

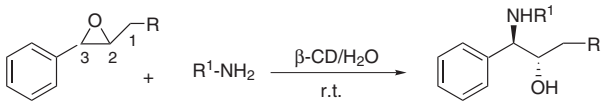
Key words: β-aminoalcohols, *trans*-2,3-epoxy alcohols, epoxides, aromatic amines, β-cyclodextrin, water

β-Aminoalcohols are versatile intermediates in the synthesis of biologically active natural products, unnatural aminoacids, β-blockers as well as insecticidal agents and chiral auxiliaries.[2] In continuation of the efforts to expand the synthetic utility of 2,3-epoxy alcohols their reactivities have been studied extensively with various nucleophiles.[3] The utility of these reactions is dependent on the regioselectivity at C-2 and C-3.[4,5] Ring-opening of epoxy alcohols with a wide variety of nucleophiles show different ratios of C-2 and C-3 isomers.[6] Regiocontrol is generally difficult to achieve in the ring-opening of substituted oxiranes and only a few direct and practical approaches to the ring-opening of substituted epoxides using amines as nucleophiles have been reported.[7]

One of the most straightforward synthetic procedures for the preparation of β-amino alcohols involves the ring-opening of epoxides with amines.[8] However, these reactions are generally carried out with large excess of the amines at elevated temperatures utilising expensive and stoichiometric amounts of reagents with extended reaction times and also entailing undesirable side reactions and low yields.[9] In view of these limitations there is still need for a widely applicable approach for the C-3 selective ring-opening of various substituted epoxides preferably using water as a solvent with a recyclable catalyst and minimising the use of harmful organic solvents as green chemistry becomes a central issue in both academic and industrial research in the 21st century.[10]

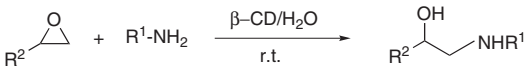
Our earlier expertise in the field of biomimetic modelling of organic chemical reactions involving cyclodextrins[11] prompted us to attempt the regioselective ring-opening of various substituted oxiranes with amines in the presence of β-cyclodextrin (β-CD) as this is one of the most useful synthetic transformations with a variety of applications.

Herein, we present the first highly regioselective aminolysis of *trans*-disubstituted aromatic epoxides/terminal epoxides with aromatic amines catalysed by β-cyclodextrin in water. This method provides facile and practical access to various β-amino alcohols (Scheme 1 and Scheme 2).



R = OH, OTBDMS, OTHP, COOMe, Br
R^1 = aryl

Scheme 1



R^1 = aryl; R^2 = Aryloxy, Phenyl

Scheme 2

In general, the reaction was carried out by the in situ formation of the β-CD complex of the epoxide in water followed by the addition of amine and stirring for 12 hours at room temperature to give the corresponding amino alcohol in impressive yields (80–92%). The reaction proceeds smoothly at room temperature without the formation of any by-products or rearrangements. In the presence of β-CD, ring-opening of *trans*-2,3-epoxy alcohols with aromatic amines (Table 1) yielded the C-3 opened product as the major isomer as detected by ^{1}H NMR spectroscopic analysis. This methodology is also compatible with functionalities such as OTBDMS, OTHP, CO_2Me, and Br. We have also examined the opening of terminal aromatic epoxides with aromatic amines (Table 2). These reactions are highly selective forming β-amino alcohols as the only products in excellent yields keeping intact functionalities such as methoxy and acetoxy. Selectivity was also observed with styrene epoxide where the amine attacks the terminal carbon. These cyclodextrin-mediated water-based reactions proceed under mild conditions without the need for organic solvents. The β-cyclodextrin can be easily recovered and reused. The compounds were characterised by spectroscopy, elemental analysis or otherwise compared with the known compounds.[7,8]

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Table 1 Synthesis of *anti*-β-Amino Alcohols from Epoxides in the Presence of β-CD

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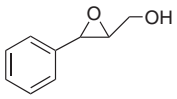
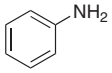
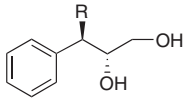
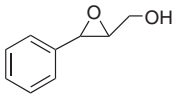
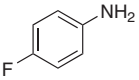
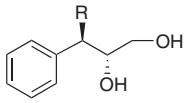
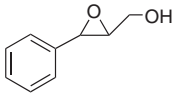
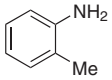
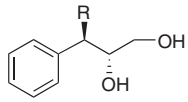
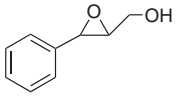
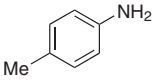
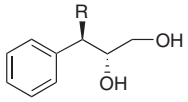
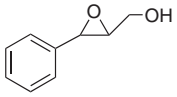
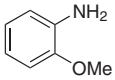
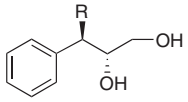
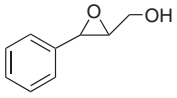
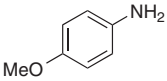
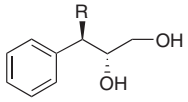
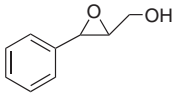
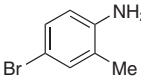
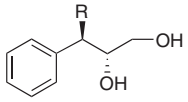
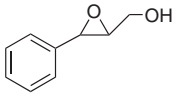
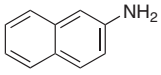
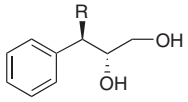
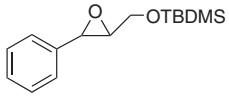
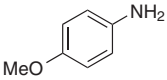
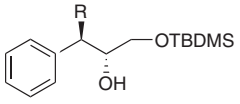
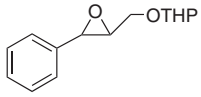
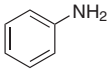
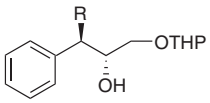
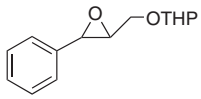
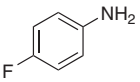
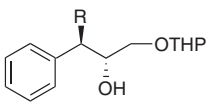
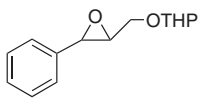
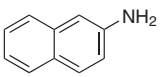
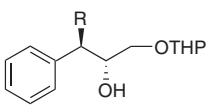
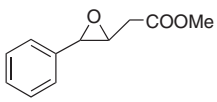
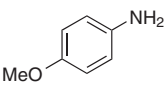
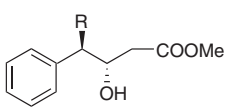
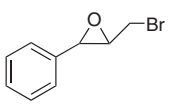
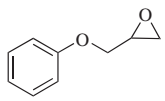
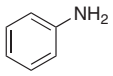
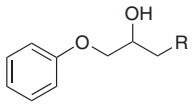
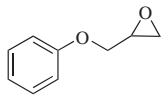
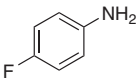
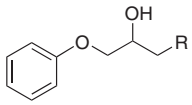
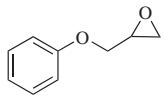
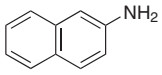
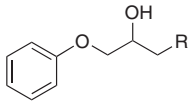
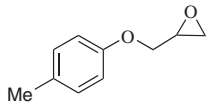
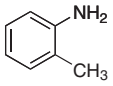
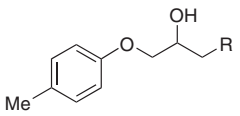
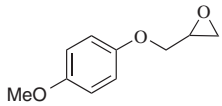
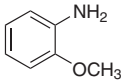
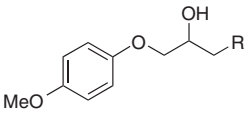
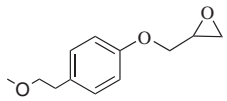
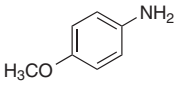
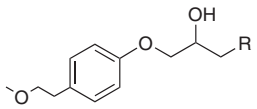
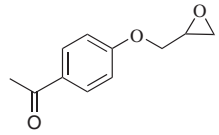
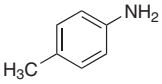
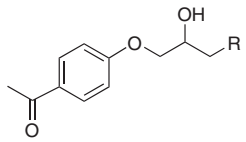
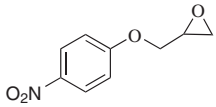
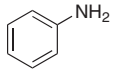
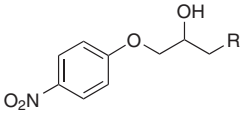
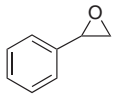
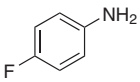
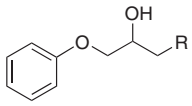
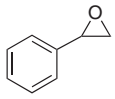
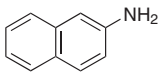
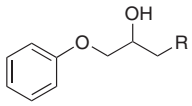
1				92	99–101
2				90	60–62
3				88	103–105
4				92	105–107
5				86	68–70
6				90	Oil
7				86	103–105
8				84	Oil
9				88	Oil
10				90	Oil
11				88	Oil
12				82	Oil
13				80	104–106
14				82	110–112

[a] Only one regioisomer could be detected by ^{1}H NMR spectroscopy analysis.
[b] Isolated yields.
[c] Not corrected.

Table 2 Synthesis of β-Amino Alcohols from Epoxides in the Presence of β-CD

Entry	Substrate	Amine (*R*)	Product	Yield (%)[a]	Mp (°C)[b]
1				92	59–61
2				90	52–54
3				86	62–64
4				90	65–67
5				88	60–62
6				89	56–58
7				85	85–87
8				82	131–133
9				86	57–59
10				82	55–57

[a] Isolated yields.
[b] Not corrected

These reactions do take place with α-CD as well with the same regioselectivity and stereochemistry; however, β-CD was chosen as the catalyst since it is inexpensive and easily accessible. These reactions do not proceed in the absence of cyclodextrin. The C-3 selectivity in the reaction of *trans*-2,3-epoxy alcohols with aromatic amines in the presence of β-CD in water has been postulated and confirmed as follows: the role of CD appears to be not only to activate the epoxides but also form a CD–epoxide complex through hydrogen bonding. These studies were undertaken with *trans*-epoxy cinnamyl alcohol as a representative example. A comparison of the ^{1}H NMR spectra (D_2O) of β-CD, β-CD–*trans*-epoxy cinnamyl alcohol complex and freeze-dried reaction mixtures of the β-CD complex of *trans*-epoxy cinnamyl alcohol with amines at 6 hours and 12 hours was undertaken. There is a clear upfield shift of H_3 (0.028 ppm) and H_5 (0.036 ppm) protons of β-cyclodextrin in β-CD–*trans*-epoxy cinnamyl alcohol complex as compared to β-CD indicating the formation of inclusion complex of epoxide with β-CD.[12] However, it is observed from the spectra of the reaction mixtures of β-CD–epoxide complex and amines at 6 hours and 12 hours that these complexes apart from retaining the upfield character of H_3 and H_5 protons with subtle changes, there is also an upfield shift of the H_6 proton of 0.030 ppm at 6 hours and 12 hours, indicating the complexation of the

amine from the primary face side of the cyclodextrin. From these ^{1}H NMR spectroscopy studies it can be concluded that, while the epoxide is still being retained in the cavity, amine complexes from the primary side of cyclodextrin (Figure 1) to attack at C-3 of the epoxy alcohol resulting in high regioselectivities.

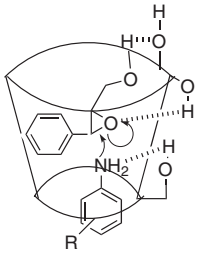


Figure 1

Thus, it has been shown for the first time that amino alcohols can be obtained with high regioselectivity from easily accessible oxiranes and inexpensive amines in the presence of β-cyclodextrin in water. This methodology describes a simple, convenient and highly efficient method for the synthesis of amino alcohols. The notable features of this method are cleaner reaction profiles, high yields and operational simplicity. Above all, these reactions are carried out in water. This methodology will be a useful addition to the modern synthetic methodology with the ever-growing demand for eco-conscious chemical processes and increasing interest in green chemistry.

General Procedure

β-Cyclodextrin (1 mmol) was dissolved in H_2O (15 mL) at 60 °C, epoxide (1 mmol) dissolved in acetone (1 mL) was added slowly with stirring and cooled to r.t. Amine (1.0 mmol) was then added and stirring was continued at r.t. After completion of the reaction the organic material was extracted with EtOAc, the organic phase was separated, filtered and washed with brine. The organic phase was then dried (Na_2SO_4), filtered and the solvent was removed under vacuum. The crude product was purified by silica gel column chromatography using EtOAc–*n*-hexane (2:8) as eluent.

Acknowledgment

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