Short communication

Synthesis of β-aminoalcohols Catalyzed by ZnO

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Abstract

Zinc oxide (ZnO) catalyses the nucleophilic opening of epoxide rings by amines leading to the efficient synthesis of β-aminoalcohols. The reaction works well with aromatic and aliphatic amines in short reaction times and in the absence of any solvent. Exclusive *trans* stereoselectivity is observed for cyclic epoxides. Furthermore, the catalyst can be reused for several times without any significant loss of catalytic activity.

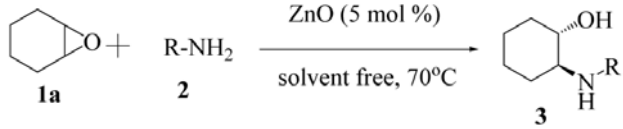
Keywords: ZnO, epoxides, amines, solvent-free conditions, β-aminoalcohols

1. Introduction

Epoxides are versatile synthetic intermediates and a variety of reagents are known for the epoxide ring opening.[1] The resulting products of epoxide aminolysis are important bioisosteres, which appear in several FDA approved drugs.[2] Opening of epoxides with amines developed in the past few years mainly involved monohaptic nucleophiles and the use of different catalysts such as metal triflates,[3] metal halides,[4] polymer supported catalysts,[5] montmorillonite K10,[6] metal salts,[7] and different reaction media such as fluoroalcohols,[8a] ionic liquids,[8b] and water[3b,c] or solvent-free conditions (SFC).[4c,9] Even though these procedures have considerably improved the scope of this reaction, they are associated with certain limitations. For example, metal triflates and halides either deactivated the Lewis acid catalyst as a consequence of the formation of a stable complex between the metal ion and the amine or require prolonged reaction times (of about 12 h). Only Zn(II) salts in acetonitrile[4b] were in some cases truly effective catalysts but they completely failed with bihaptic nucleophiles such as 2-picolylamine because the highly azaphilic Zn(II) cation forms a stable complex with the amine. Work-up with such Lewis acids, which are often used in stoichiometric quantities, is difficult due to the formation of emulsions. Furthermore, these catalysts are of no use with deactivated amines and are inconvenient for handling. In some cases reagents are expensive. Finally, hexafluoropropan-2-ol and [bmim]BF_4 were not effective in the aminolysis with alkyl amines.[8a,b] Therefore it seems highly desirable to find a simple, efficient, economical and inexpensive protocol for β-aminoalcohols synthesis via epoxide ring opening.

In the light of stringent and growing environmental regulations, the chemical industry needs to re-examine the most important synthetic processes and to develop more eco-compatible synthetic methodologies.[9] To this purpose heterogeneous catalysis plays a fundamental role, mainly due to its economic and environmental advantages (*i.e.* minimum execution time, low corrosion, waste minimization, recycling of the catalyst, easy transport and disposal of the catalyst).[10] Another important goal in green chemistry is represented by the elimination of volatile organic solvents, in fact solvent-free organic reactions make syntheses simpler, save energy, and prevent solvent waste, hazards, and toxicity.[11]

Of course the combination of heterogeneous catalysis with the use of solvent-free conditions represents a suitable way toward the so-called ideal synthesis. Because the revision of the fundamental synthetic reactions under solvent-free conditions (SFC) has been the subject of our research in recent years,[12] we have recently examined the catalytic activity of zinc oxide (ZnO) in organic synthesis.[13] ZnO is a non-toxic, inexpensive and non-hygroscopic white powder. It is an important material with a wide



1a 2 3

Scheme 1

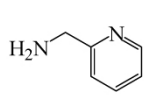
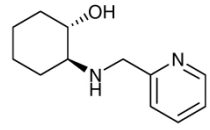
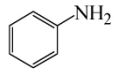
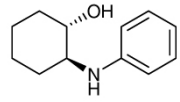
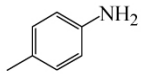
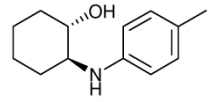
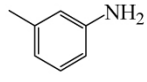
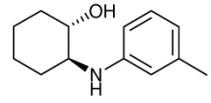
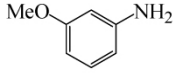
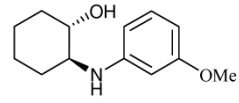
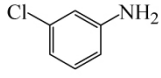
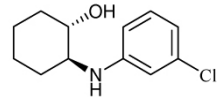
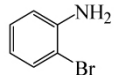
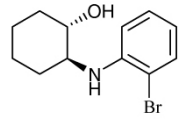
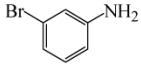
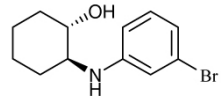
ranging application as a catalyst for a number of organic syntheses. So, we wish to report here some efficient ZnO-catalyzed preparations of β-aminoalcohols under solvent-free conditions by conventional heating in an oil bath (Scheme 1). Furthermore, ZnO can be re-used up to five times.

2. Results and Discussion

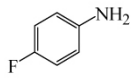
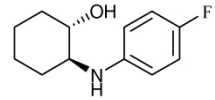
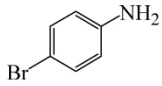
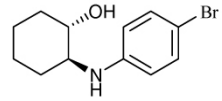
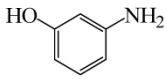
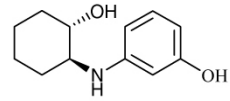
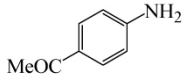
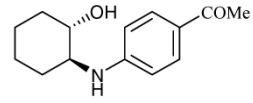
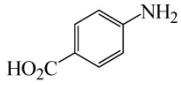
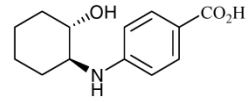
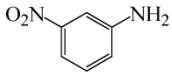
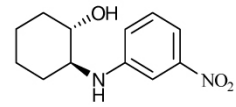
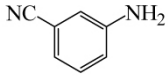
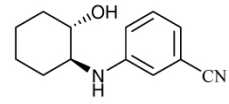
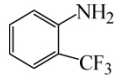
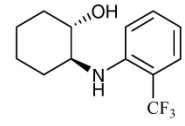
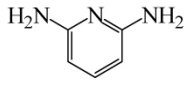
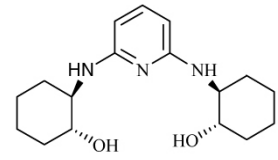
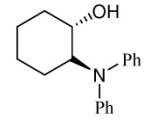
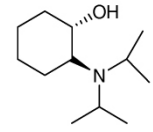
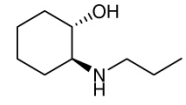
In order to delineate the standard operating conditions, cyclohexene oxide (7-oxabicyclo[4.1.0]heptane, **1a**) (1 mmol) was treated with 2-picolylamine (**2a**) (1 mmol) under solvent-free conditions in the presence of a catalytic amount of ZnO (5 mol%) at 70 °C in an oil bath. Complete conversions took place in 2 h leading to a quantitative yield of the 2-(2-picolylamine)cyclohexanol (**3a**). The catalyst was recovered by filtration after diluting the reaction mixture with ethyl acetate and was reused repeatedly without any significant loss of catalytic activity.

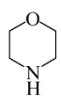
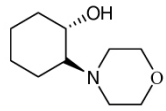
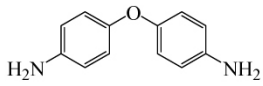
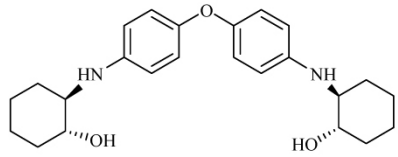
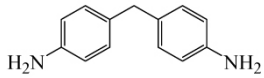
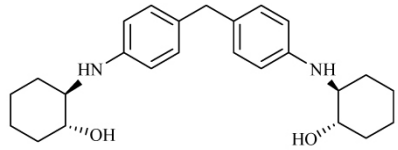
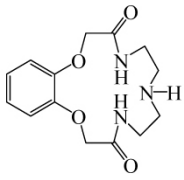
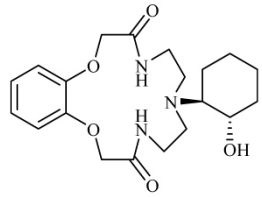
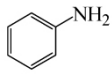
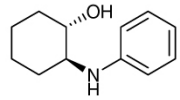
The inexpensive and commercially available catalyst ZnO could now be applied under optimized conditions for the reaction of **1a** with variously substituted aromatic and aliphatic amines (Table 1). The reaction protocol is simple and does not require dry glassware and reagents. This is very important for scaling-up the process. The final amino

Table 1: ZnO catalyzed synthesis of β-aminoalcohols by condensation reaction of **1a** with amines (**2**)

Entry	Substrate		Product		Time (h)	Yield[b,c] (%)
1		**2a**		**3a**	2	98
2		**2b**		**3b**	3	98
3		**2c**		**3c**	3.5	92
4		**2d**		**3d**	2	93
5		**2e**		**3e**	1	90
6		**2f**		**3f**	4	92
7		**2g**		**3g**	3.5	90
8		**2h**		**3h**	1	90

[a] All products were characterized by ^{1}H NMR, IR and mass spectral data which were found to be identical with those described in ref. 3,4; for compound **3a** see 3d, for **3b**,**c**,**f**,**u** see 4c, for **3d** see 6, for **3e** see 14, for **3h** see 4a, for **3j** see 4g, for **3n** see 3c, for **3s** see 15, and for **3t** see 16. [b] A racemic aminocyclohexanol was obtained. [c] Yields for the isolated compounds. [d] Reaction was carried out on 100 mmol scale.

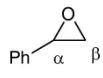
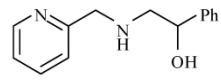
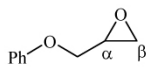
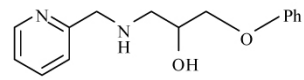
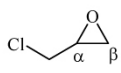
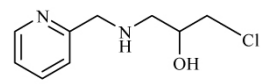
Entry	Substrate		Product		Time (h)	Yield[b,c] (%)
9		**2i**		**3i**	2	95
10		**2j**		**3j**	3	98
11		**2k**		**3k**	2	90
12		**2l**		**3l**	3	93
13		**2m**		**3m**	4.5	85
14		**2n**		**3n**	36	50
15		**2o**		**3o**	30	50
16		**2p**		**3p**	6	80
17		**2q**		**3q**	4	70
18	PhNHPh	**2r**		**3r**	30	50
19	$(CH_3)_2CHNHCH(CH_3)_2$	**2s**		**3s**	3	85
20	$CH_3CH_2CH_2NH_2$	**2t**		**3t**	4	94

Entry	Substrate		Product		Time (h)	Yield[b,c] (%)
21		**2u**		**3u**	2	90
22		**2v**		**3v**	3	90
23		**2w**		**3w**	3	90
24		**2x**		**3x**	4	80
25		**2b**		**3b**	6	90[d]

alcohols were isolated with high purity (> 99%) and in good yields (50–98%).

The results summarized in Table 1 reveal that excellent yields were obtained with aromatic and aliphatic amines and in each case the resulting racemic 2-aryl/alkylaminocyclohexanol was obtained with exclusive *trans* diastereoselectivity as detected by ^{1}H NMR spectroscopic analysis. Primary and secondary amines react very rapidly. Aniline and its derivatives with electron donating substituents also react quite fast. However, anilines with electron withdrawing substituents, as well as sterically hindered anilines, react very slowly, and aminolysis required prolonged reaction times. The most important contribution is probably the success in the aminolysis of cyclohexene epoxide with diphenylamines (entries 17, 22, 23). This represents the first catalytic method for the synthesis of β-aminoalcohols derived from diarylamines. These products can be useful for preparation of macrocyclic

Table 2: ZnO-catalyzed ring opening of 1,2-epoxides **1b–d** with 2-picolylamine (**2a**) under solvent-free conditions

Entry	**1,2-Epoxide**		**Product**		**Time (h)**	**Yield[a] (%)**
1		**1b**		**3y**	2	96[b]
2		**1c**		**3z**	3	95
3		**1d**		**3a'**	1	93

[a] Yields for the isolated compounds. [b] ^{1}H NMR, IR and mass spectral data were found to be identical with those described in ref. 3d.

compounds. The conversion of aniline into 2-aryl/alkylaminocyclohexanol on a 100 mmol scale (entry 25) proceeded just as well as the 1 mmol reaction.

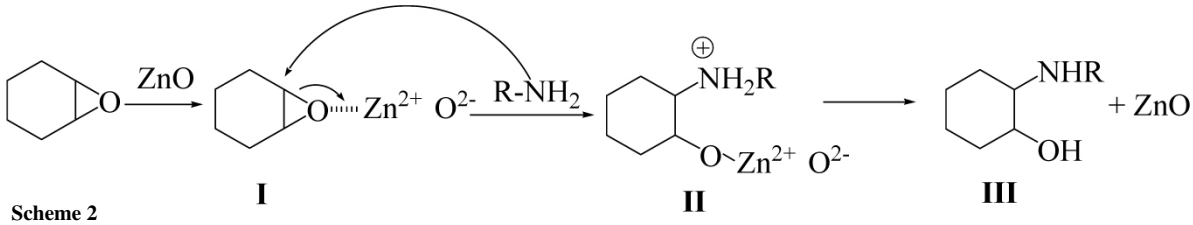
Then, ZnO catalyzed conditions were extended to a variety of 1,2-epoxides (Table 2). All the reactions were fast and completely β- or C_2-regioselective. Excellent chemoselectivity was achieved with epichlorohydrin (entry 3, Table 2) resulting in 93% yield of the aminoalcohol corresponding to the nucleophilic attack at the terminal carbon of the epoxide moiety. No product arising from nucleophilic displacement of the chlorine could be detected through MS analysis of the reaction mixture.

The re-usability and catalytic activity of ZnO was studied in this system. The catalyst can be so easily separated by dispersing the reaction mixture in ethyl acetate, so that the recovery and re-use of ZnO could be very convenient. As shown in Table 3, the yields of 2-(2-picolylamine)cyclohexanol (**3a**) only slightly decreases after the re-use of ZnO for five times.

Table 3: Re-use of ZnO

Number of use	Yield (%)	Recovery of ZnO (%)
1	98	96
2	94	95
3	92	95
4	92	93
5	90	90

Structurally, the ZnO crystal is described schematically as a number of alternating planes composed of four-fold coordinated O^{2-} and Zn^{2+} ions. As shown in Scheme 2, we propose the following mechanism for the reaction: first, ZnO activates the epoxide with its Lewis acid site (Zn^{2+}) to give intermediate **I** and this is followed by a nucleophile (amine) attack to **I** to give **II** and **III**, respectively.



Scheme 2

3. Experimental

Progress of the reactions was monitored by the use of silica gel polygrams SIL G/UV 254 plates. IR spectra were recorded on Perkin Elmer 781 and on Impact 400 D Nicolet FTIR spectrometers. NMR spectra were recorded on Bruker DPX 250 MHz instrument and mass spectra on Shimadzu QP 1100 EX spectrometer using EI 70 eV modes. Microanalyses were performed on a Perkin Elmer 240-B microanalyzer.

3. 1. General Procedure

A mixture of ZnO (5 mol %, 0.04 g), amine (1 mmol) and 1,2-epoxide (1 mmol) were heated and stirred in an oil bath at 70 °C. The progress of the reaction was monitored by TLC (eluent: *n*-hexane : EtOAc = 80 : 20). After the reaction was complete, ethyl acetate (2 × 10 mL) was added to the reaction mixture and ZnO was removed by filtration. The organic solvent was then evaporated and the crude product was obtained. This was further purified by column chromatography. The structures of the products were confirmed by ^{1}H NMR, ^{13}C NMR and comparison with authentic samples obtained commercially or prepared by reported methods.

2-(3-Toluidino)cyclohexanol (3d):[6] Oily liquid. ^{1}H NMR ($CDCl_3$) δ 7.02 (1H, s), 6.39–6.60 (3H, m), 3.46 (2H, brs, NH, OH), 3.19–3.27 (1H, m), 3.02–3.08 (1H, m), 2.21 (3H, s), 2.00–2.05 (2H, m), 1.61–1.69 (2H, m), 1.17–1.35 (4H, m); ^{13}C NMR ($CDCl_3$) δ 21.5, 23.7, 25.0, 31.0, 33.4, 59.9, 75.6, 111.5, 115.6, 118.5, 128.7, 139.0, 148.0; MS *m/z* 205 [M^+]. Anal. Cald. for $C_{13}H_{19}NO$: C, 76.06; H, 9.33. Found: C, 76.03; H, 9.30.

2-(3-Methoxyphenylamino)cyclohexanol (3e):[14] Oily liquid. ^{1}H NMR ($CDCl_3$) δ 7.06 (1H, s), 6.21–6.31 (3H, m), 3.73 (3H, s), 3.33 (2H, brs, NH, OH), 3.27 (1H, ddd, *J* = 4.0, 5.7, 4.4 Hz), 3.08 (1H, ddd, *J* = 4.0, 5.7, 4.4 Hz), 2.05–2.11 (2H, m), 1.65–1.73 (2H, m), 1.02–1.65 (4H, m); ^{13}C NMR ($CDCl_3$) δ 23.9, 24.9, 30.9, 32.6, 55.1, 59.9, 73.1, 100.3, 103.1, 107.2, 130.0, 149.3, 160.7; MS *m/z* 221 [M^+]. Anal. Cald. for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65. Found: C, 70.52; H, 8.63.

2-(2-Bromophenylamino)cyclohexanol (3g): Oily liquid. ^{1}H NMR ($CDCl_3$) δ 7.40–7.46 (1H, m), 7.16–7.18 (1H, m), 6.74–6.85 (1H, m), 6.56–6.60 (1H, m) 3.20 (2H, brs, NH, OH), 4.19–4.35 (1H, m), 3.38–3.41 (1H, m), 2.04–2.10 (2H, m), 1.67–1.74 (2H, m), 1.13–1.43 (4H, m); ^{13}C NMR ($CDCl_3$) δ 24.0, 24.4, 31.5, 32.7, 59.7, 74.1, 112.9, 118.3, 123.4, 128.3, 132.5, 144.9; MS *m/z* 270 [M^+]. Anal. Cald. for $C_{12}H_{16}BrNO$: C, 53.35; H, 5.97. Found: C, 53.33; H, 5.95.

2-(3-Bromophenylamino)cyclohexanol (3h):[4a] Oily liquid. ^{1}H NMR ($CDCl_3$) δ 6.93–6.99 (1H, m), 6.75–6.79 (2H, m), 6.53–6.58 (1H, m), 4.15 (2H, brs, NH, OH), 3.42 (1H, m), 3.25–3.30 (1H, m), 2.98–3.03 (2H, m), 1.64–1.73 (2H, m), 1.01–1.31 (4H, m); ^{13}C NMR ($CDCl_3$) δ 24.4, 24.6, 31.6, 33.1, 56.9, 73.9, 115.7, 117.8, 120.4, 124.3, 129.8, 148.4; MS *m/z* 270 [M^+]. Anal. Cald. for $C_{12}H_{16}BrNO$: C, 53.35; H, 5.97. Found: C, 53.31; H, 5.96.

2-(4-Fluorophenylamino)cyclohexanol (3i): Oily liquid. ^{1}H NMR ($CDCl_3$) δ 6.84–6.91 (2H, m), 6.63–6.69 (2H, m), 3.67 (2H, brs, NH, OH), 3.30–3.34 (1H, m), 2.88–3.01 (1H, m), 2.07–2.10 (2H, m), 1.70–1.75 (2H, m), 1.04–1.35 (4H, m); ^{13}C NMR ($CDCl_3$) δ 23.9, 24.5, 31.2, 33.3, 58.4, 73.0, 115.1 (d, J_{CF} = 37.5 Hz), 116.5 (d, J_{CF} = 6.3 Hz), 143.4, 156.4 (d, J_{CF} = 239.0 Hz); MS *m/z* 209 [M^+]. Anal. Cald. for $C_{12}H_{16}FNO$: C, 68.88; H, 7.71. Found: C, 68.85; H, 7.70.

2-(3-Hydroxyphenylamino)cyclohexanol (3k): Oily liquid. ^{1}H NMR ($CDCl_3$) δ 7.06 (1H, s), 6.18–6.27 (3H, m), 4.68 (3H, brs, NH, OH, Ar-OH), 3.26–3.29 (1H, m), 3.01–3.04 (1H, m), 1.99–2.02 (2H, m), 1.59–1.65 (2H, m), 1.18–1.26 (4H, m); ^{13}C NMR ($CDCl_3$) δ 25.4, 26.2, 31.2, 33.4, 62.9, 72.3, 105.7, 109.2, 111.7, 130.4, 143.3, 148.2; MS *m/z* 207 [M^+]. Anal. Cald. for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27. Found: C, 69.42; H, 8.27.

1-{4-[(2-Hydroxycyclohexyl)amino]phenyl}ethenone (3l): solid; m.p. 79 °C. ^{1}H NMR ($CDCl_3$) δ 7.76 (2H, d, *J* = 3.2 Hz), 6.56 (2H, d, *J* = 3.2 Hz), 4.30 (2H, brs, NH, OH), 3.43–3.55 (1H, m), 3.24–3.28 (1H, m), 2.48 (3H, s), 2.07–2.12 (2H, m), 1.69–1.79 (2H, m), 1.18–1.34 (4H, m); ^{13}C NMR ($CDCl_3$) δ 23.9, 24.2, 24.6, 31.4, 33.5, 58.9, 74.2, 112.1, 113.6, 130.8, 152.3, 196.6; MS *m/z* 233 [M^+]. Anal. Cald. for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21. Found: C, 72.06; H, 8.20.

4-(2-Hydroxycyclohexylamino)benzoic acid (3m): solid; m.p. 167 °C. ^{1}H NMR ($CDCl_3$) δ 7.85 (2H, d, *J* = 2.3 Hz), 6.62 (2H, d, *J* = 2.3 Hz), 5.29 (1H, s, CO_2H), 4.94 (2H, brs, NH, OH), 3.23–3.43 (2H, m), 1.95–2.10 (2H, m), 1.69–1.85 (2H, m), 1.02–1.47 (4H, m); ^{13}C NMR ($CDCl_3$) δ 24.2, 24.4, 30.3, 32.9, 61.2, 74.2, 113.7, 118.3, 132.2, 151.5, 171.1; MS *m/z* 235 [M^+]. Anal. Cald. for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28. Found: C, 66.32; H, 7.25.

2-(3-Cyanophenylamino)cyclohexanol (3o): Oily liquid.^{1}H NMR ($CDCl_3$) δ 6.96 (1H, m), 6.80 (2H, d, *J* = 1.4 Hz), 6.54–6.59 (1H, m), 3.32 (2H, brs, NH, OH), 3.30–3.32 (1H, m), 3.05–3.07 (1H, m), 2.06–2.07 (2H, m), 1.66–1.72 (2H, m), 1.16–1.33 (4H, m); ^{13}C NMR ($CDCl_3$) δ 23.7, 24.7, 31.3, 33.5, 59.5, 74.3, 111.2, 116.0, 118.2, 121.1, 124.9, 129.9, 148.3; MS *m/z* 216 [M^+]. Anal. Cald. for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46. Found: C, 72.13; H, 7.45.

2-[2-(Trifluoromethyl)phenylamino]cyclohexanol (3p): Oily liquid. ^{1}H NMR ($CDCl_3$) δ 7.16–7.35 (2H, m), 6.52–6.81 (2H, m), 4.10–4.27 (1H, m), 3.23–3.30 (1H, m), 3.19 (2H, brs, NH, OH), 1.88–1.92 (2H, m), 1.52–1.57 (2H, m), 1.07–1.15 (4H, m); ^{13}C NMR ($CDCl_3$) δ 24.2, 24.5, 31.2, 33.4, 55.9, 59.5, 121.4 (q, J_{CF} = 257.9 Hz), 113.3 (q, J_{CF} = 37.7 Hz), 116.9 (2×q, J_{CF} = 12.5 Hz), 126.4 (q, J_{CF} = 4.6 Hz), 132.9, 145.9 (q, J_{CF} = 4.6 Hz); MS *m/z* 259 [M^+]. Anal. Cald. for $C_{13}H_{16}F_3NO$: C, 60.22; H, 6.22. Found: C, 60.20; H, 6.20.

2-({6-[(2-Hydroxycyclohexyl)amino]pyridin-2-yl}amino)cyclohexanol (3q): Oily liquid. ^{1}H NMR (DMSO-d_6) δ 7.24–7.41 (2H, m), 6.97 (1H, t, *J* = 1.5 Hz), 5.50–5.70 (4H, m), 5.36 (4H, brs, NH, OH), 2.30–2.48 (4H, m), 1.42–1.55 (4H, m), 1.04–1.27 (8H, m); ^{13}C NMR (DMSO-d_6) δ 23.7, 24.2, 31.1, 34.1, 56.0, 73.3, 95.1, 138.4, 158.3; MS *m/z* 305 [M^+]. Anal. Cald. for $C_{17}H_{27}N_3O_2$: C, 66.85; H, 8.91. Found: C, 66.82; H, 8.90.

2-(Diphenylamino)cyclohexanol (3r): Oily liquid. ^{1}H NMR ($CDCl_3$) δ 6.67–7.32 (10H, m), 4.13–4.54 (1H, m), 3.02–3.23 (1H, m), 3.01 (1H, brs, OH), 2.34–2.48 (2H, m), 1.72–1.84 (2H, m), 1.12–1.34 (4H, m); ^{13}C NMR ($CDCl_3$) δ 24.4, 25.9, 32.1, 33.4, 60.2, 74.1, 119.2, 120.6, 126.2, 146.4; MS *m/z* 267 [M^+]. Anal. Cald. for $C_{18}H_{21}NO$: C, 80.86; H, 7.92. Found: C, 80.84; H, 7.90.

2-(Diisopropylamino)cyclohexanol (3s):[15] Oily liquid. ^{1}H NMR ($CDCl_3$) δ 3.56–3.73 (1H, m), 3.42–3.60 (2H, m), 3.34–3.39 (1H, m), 3.37 (1H, brs, OH), 1.14–2.25 (20H, m); ^{13}C NMR ($CDCl_3$) δ 19.3, 23.7, 23.8, 29.9, 32.9, 46.5, 67.5, 72.8; MS *m/z* 199 [M^+]. Anal. Cald. for $C_{12}H_{25}NO$: C, 72.31; H, 12.64. Found: C, 72.30; H, 12.61.

2-(Propylamino)cyclohexanol (3t):[16] Oily liquid. ^{1}H NMR ($CDCl_3$) δ 4.56 (2H, brs, NH, OH), 4.31–4.33 (1H, m), 4.13 (2H, dd, *J* = 7.2, 7.2 Hz), 3.60–3.61 (1H, m), 2.18–2.27 (2H, m), 2.04–2.08 (3H, s), 1.72–1.78 (2H, m), 1.22–1.33 (6H, m); ^{13}C NMR ($CDCl_3$) δ 14.1, 21.0, 24.1, 24.5, 30.9, 33.1, 60.4, 72.7, 87.0; MS *m/z* 157 [M^+]. Anal. Cald. for $C_9H_{19}NO$: C, 68.74; H, 12.18. Found: C, 68.72; H, 12.10.

2-(4-{4-[(2-Hydroxycyclohexyl)amino]phenoxy}anilino)cyclohexanol (3v): Oily liquid. ^{1}H NMR ($CDCl_3$) δ 6.78 (4H, d, *J* = 8.8 Hz), 6.59 (4H, d, *J* = 8.8 Hz), 3.44 (4H, brs, NH, OH), 3.29 (2H, ddd, *J* = 8.9, 3.6, 9.8 Hz), 2.99 (2H, ddd, *J* = 8.9, 3.6, 9.8 Hz), 2.01–2.03 (4H, m), 1.68–1.80 (4H, m), 1.00–1.36 (8H, m); ^{13}C NMR ($CDCl_3$) δ 24.3, 24.8, 32.4, 33.3, 60.8, 74.0, 115.0, 119.0, 143.4, 150.2; MS *m/z* 396 [M^+]. Anal. Cald. for $C_{24}H_{32}N_2O_3$: C, 72.70; H, 8.13. Found: C, 72.70; H, 8.10.

2-(4-{4-[(2-Hydroxycyclohexyl)amino]benzyl}anilino)cyclohexanol (3w): Oily liquid. ^{1}H NMR ($CDCl_3$)

δ 6.80 (4H, d, *J* = 5.9 Hz), 6.43 (4H, d, *J* = 5.9 Hz), 3.90–3.98 (2H, m), 3.59 (2H, s), 3.44 (4H, brs, NH, OH), 2.88–3.15 (2H, m), 0.84–1.87 (16H, m); ^{13}C NMR ($CDCl_3$) δ 20.8, 24.2, 30.8, 31.3, 40.0, 60.3, 73.8, 114.2, 129.4, 143.2, 146.0; MS *m/z* 394 [M^+]. Anal. Cald. for $C_{25}H_{34}N_2O_2$: C, 76.10; H, 8.69. Found: C, 76.10; H, 8.67.

7-(2-Hydroxycyclohexyl)-5,6,7,8,9,10-hexahydro-2*H*-1,13,4,7,10-benzodioxatriazacyclopentadecine-3,11(4*H*,12*H*)-dione (3x): Oily liquid. ^{1}H NMR ($CDCl_3$) δ 8.03 (2H, s, NH), 6.96–7.01 (2H, m), 6.85–6.91 (2H, m), 4.51 (4H, s), 4.32 (1H, brs, OH), 3.49 (4H, t, *J* = 5.4 Hz), 3.33–3.36 (1H, m), 3.18–3.20 (1H, m), 2.92–2.96 (4H, t, *J* = 5.4 Hz), 1.96–2.02 (2H, m), 1.69–1.80 (2H, m), 1.25–1.30 (4H, m); ^{13}C NMR ($CDCl_3$) δ 24.0, 24.8, 32.1, 32.7, 38.0, 47.3, 66.8, 73.2, 120.0, 122.0, 165.0, 168.1, 168.6; MS *m/z* 391 [M^+]. Anal. Cald. for $C_{20}H_{29}N_3O_5$: C, 61.36; H, 7.47. Found: C, 61.33; H, 7.45.

1-Phenoxy-2-[(2-pyridylmethyl)amino]-1-ethanol (3z): Oily liquid. ^{1}H NMR ($CDCl_3$) δ 8.20–8.43 (1H, m), 7.50–7.78 (1H, m), 7.03–7.16 (4H, m), 6.71–6.84 (3H, m), 5.60 (2H, brs, NH, OH), 3.78–4.05 (5H, m), 2.70–2.88 (2H, m); ^{13}C NMR ($CDCl_3$) δ 53.2, 59.0, 68.9, 70.0, 114.5, 121.0, 122.2, 122.8, 129.3, 137.0, 148.9, 158.4, 158.6; MS *m/z* 258 [M^+]. Anal. Cald. for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02. Found: C, 69.75; H, 7.01.

1-Chloro-3-[(2-pyridylmethyl)amino]-2-propanol (3a'): Oily liquid. ^{1}H NMR ($CDCl_3$) δ 9.07 (1H, d, *J* = 5.9 Hz), 7.70 (1H, d, *J* = 5.9 Hz), 7.27–7.32 (2H, m), 5.61 (2H, brs, NH, OH), 3.97–4.01 (2H, m), 3.54 (2H, s), 2.76–3.01 (3H, m); ^{13}C NMR ($CDCl_3$) δ 46.5, 54.2, 54.3, 70.2, 122.7, 122.9, 135.0, 148.6, 169.1; MS *m/z* 200 [M^+]. Anal. Cald. for $C_9H_{13}ClN_2O$: C, 53.87; H, 6.53. Found: C, 53.86; H, 6.52.

4. Conclusions

In conclusion, we have described a novel and highly efficient solvent-free protocol for the synthesis of β-aminoalcohols using non-toxic and inexpensive ZnO powder. Our method is superior to other existing methods as: *(i)* there is no need for toxic and waste-producing Lewis acids, *(ii)* work-up is simple, *(iii)* the reaction procedure does not require any specialized equipment, *(iv)* zinc oxide powder can be re-used and *(v)* solvent-free conditions are appropriate.

5. Acknowledgment

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6. References

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Povzetek

Povzetek: Cinkov oksid (ZnO) katalizira nukleofilno odpiranje epoksidnih obročev z amini, kar predstavlja učinkovito sintezo β-aminoalkoholov. Reakcija dobro poteka z aromatskimi in alifatskimi amini s kratkimi reakcijskimi časi in brez dodatkov topila. Pri cikličnih epoksidih reakcija poteka z izključno *trans* stereoselektivnostjo. Katalizator je možno večkrat ponovno uporabiti brez občutnejših izgub katalitske aktivnosti.