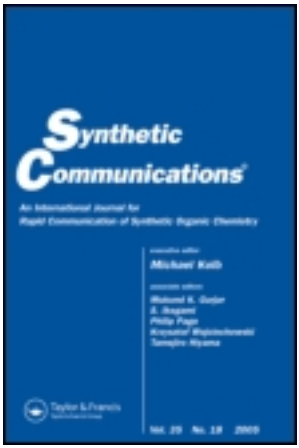

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Facile Synthesis of Aminoalcohols by Ring Opening of Epoxides Under Solvent Free Conditions

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ABSTRACT

The convenient cleavage of symmetrical and unsymmetrical epoxides with either aromatic or aliphatic amine under solvent free conditions is reported. The reactions were carried out in a sealed ampoule at 90°C to

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give regioselectively the corresponding β-amino alcohol in one pot in high yields.

Key Words: β-Aminoalcohols; Epoxide; Aromatic amines; Facile synthesis; Regioisomers.

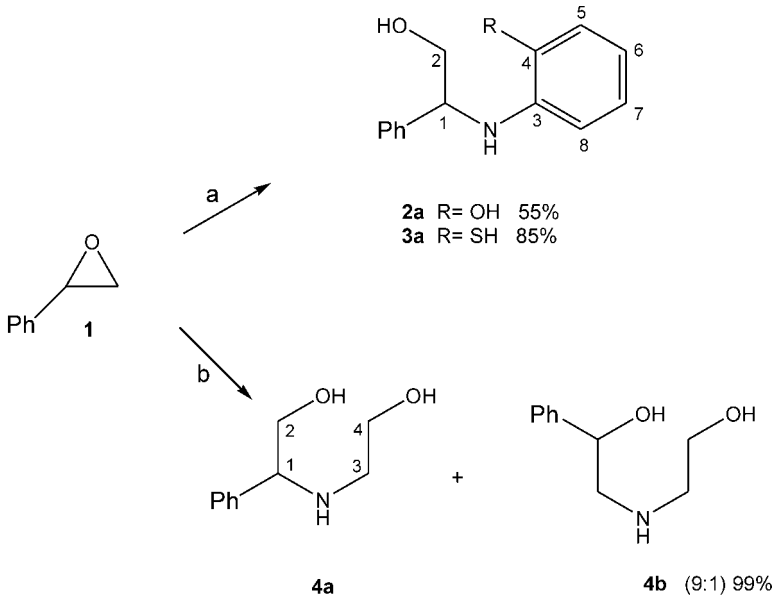
INTRODUCTION

The ring opening of epoxides is an attractive and easy route to achieve the synthesis of β-amino alcohols, which are of special interest in the fields of drugs and pharmaceuticals; they are also widely used in asymmetric synthesis as chiral auxiliaries.[1–7] The most common approach to accomplish the cleavage of epoxides involves the use of an epoxide in the presence of an excess of amine as nucleophile and of protic solvents.[8,9] Common routes for the ring opening epoxides described so far include Lewis acids[10] metal salts,[10–14] lanthanide halides,[15–17] triflates,[18,19] boranes,[20] heterogeneous catalysis,[21] fluoroalkyl alcohols,[22] ionic liquids,[23] and alumina.[24] On the other hand, the use of microwave irradiation has been recently reported for the epoxides opening either in the absence of catalyst[25] or in the presence of Montmorillonite K10 clay as catalyst.[26] However, most of these synthetic methods present different disadvantages such as the excess of amines, low yields by using deactivated aromatic amines, and lack of regio- and stereoselectivity when highly substituted epoxides are used. Additionally, many of the catalysts commonly employed are quite expensive. As part of our interest in the condensation reactions of β-amino alcohols with 1,2-dicarbonyls, we have reported the preparation and characterization of five- and six-membered heterocycles derived of β-amino alcohols and their application in the synthesis of optically pure piperazines.[27–29] In continuation with our studies we herein describe an efficient one pot preparation of amino alcohols by ring opening of a series of epoxides using aromatic and aliphatic amines as nucleophiles under solvent free conditions.

RESULTS AND DISCUSSION

The syntheses were achieved by treating equimolar ratios of 2-aminophenol, 2-aminothiophenol, or ethanolamine with a variety of epoxides. The reactions were carried out either in a sealed ampoule or in a Parr reactor at 90°C under solvent free conditions to yield the corresponding amino alcohols.

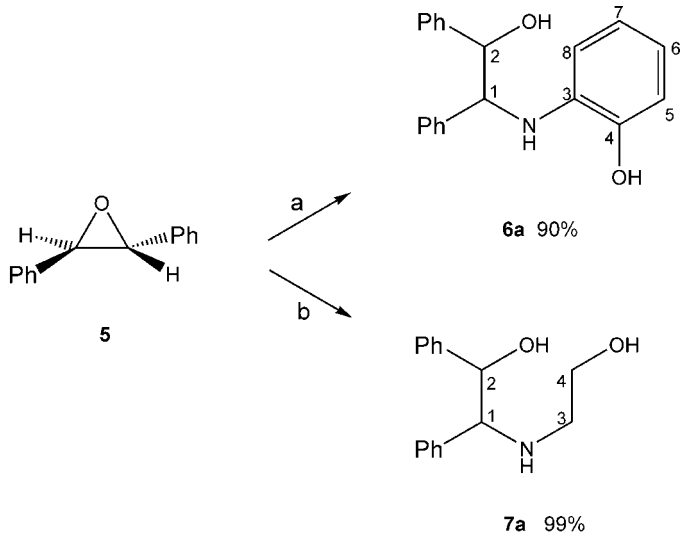
The reaction of 2-aminophenol and 2-aminothiophenol with styrene oxide afforded as main products the regioisomers **2a** and **3a**, respectively (Sch. 1).



Scheme 1. (a) 2-Aminophenol or 2-aminothiophenol and (b) ethanolamine.

For the reaction with *o*-aminophenol, however, the NMR spectrum of the crude mixture reaction showed signals for the two possible regioisomers in a 9 : 1 molar ratio which, after purification by crystallization from methylene chloride/hexane, led to the regioisomer **2a** as unique product. In both reactions the main product resulted from the attack of the amine at the more hindered carbon of the styrene oxide, which is in accordance with the literature.[11] On the other hand, the reaction with ethanolamine yielded a 3 : 1 mixture of regioisomers **4a** and **4b**. The major regioisomer **4a** was formed by the attack of ethanolamine at the benzylic carbon. Compound **4a** was also isolated by crystallization from methylene chloride/hexane.

The ring opening of *trans*-stilbene oxide with 2-aminophenol or ethanolamine under the above-mentioned conditions yielded, respectively, the amino alcohol **6a** or **7a** regioselectively in good yield (90–99%, Sch. 2). Crystalline amine hydrochloride of **7a** was obtained by adding HCl which in turn allowed us to establish the relative stereochemistry of **7a** by the x-ray diffraction analysis. Figure 1 shows its molecular perspective, and it is observed that the phenyl groups are syn orientated to each other. Unit cell parameters and basic information about data collection and structure refinement are summarized in Experimental section.



Scheme 2. (a) 2-Aminophenol and (b) ethanolamine.

Cyclohexene oxide reacted with 2-aminophenol, 2-amino-5-methyl-phenol, 2-amino-5-chloro-phenol, ethanolamine, and 2-amino-5-chlorobenzyl alcohol to give, respectively, the amino alcohols **9a**–**13a** in high yield (Sch. 3). All compounds showed the trans configuration as evidenced by J_{H-H} spin–spin coupling constants values. This selectivity is in accordance with previous

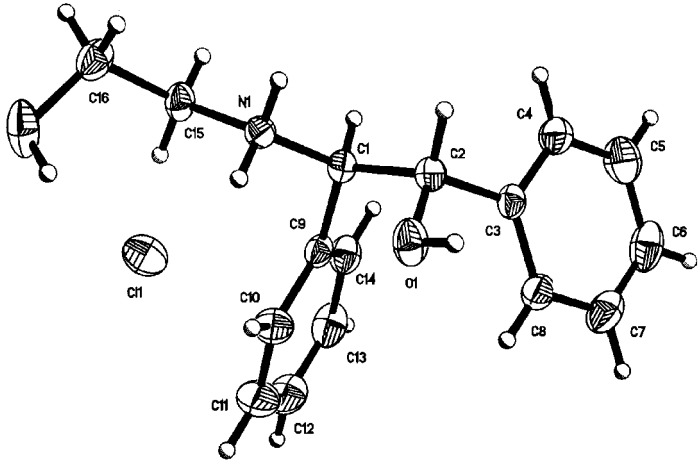
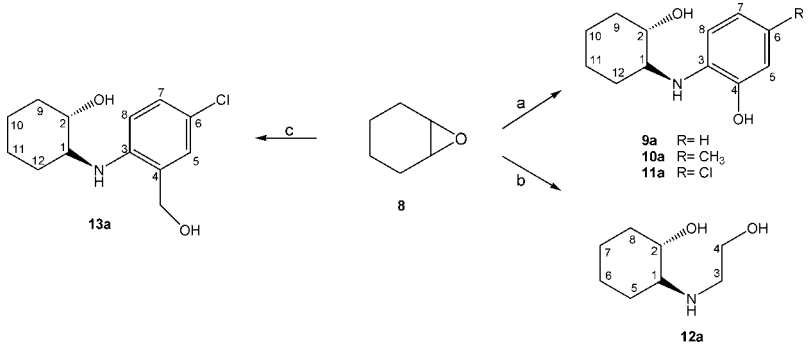


Figure 1. Molecular perspective for compound amine hydrochloride of **7a**.



Scheme 3. (a) 2-Aminophenol, 2-amino-5-methyl-phenol, or 2-amino-5-chlorophenol, (b) ethanolamine, and (c) 2-amino-5-chlorobenzyl alcohol.

reports.[11–15,21,26] In addition, the structure of compound **9a** was analyzed by x-ray diffraction. Figure 2 shows a molecular perspective of **9a** in a chairlike conformation confirming the trans stereochemistry. It is also observed that the phenyl amine moiety and the hydroxyl group are in equatorial positions.

Moreover, the cleavage of ethylene and propylene oxides with 2-aminophenol was also carried out affording the corresponding aminoalcohols **14** and **15**. For the reaction with ethylene oxide a single compound **14a** was obtained in 99% yield (Sch. 4) whereas for propylene oxide a 3 : 1 mixture of regioisomers **15a** and **15b** was isolated. NMR data allowed to establish that the major product resulted from the attack of 2-aminophenol at the less substituted carbon.

In order to explore the stereoselectivity using a chiral inductor we treated *R*-(−)-2-phenylglycinol with *trans*-stilbene oxide for 12 hr at 90°C (Sch. 5). Under these conditions the reaction was not stereoselective and gave a mixture

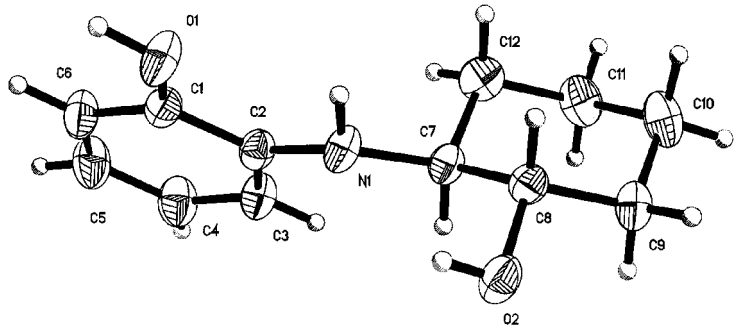
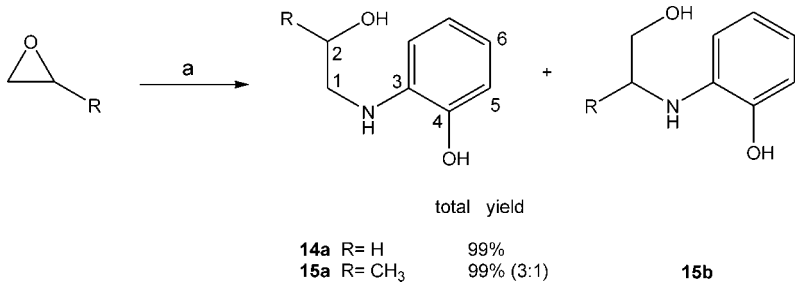


Figure 2. Molecular perspective of compound **9a**.



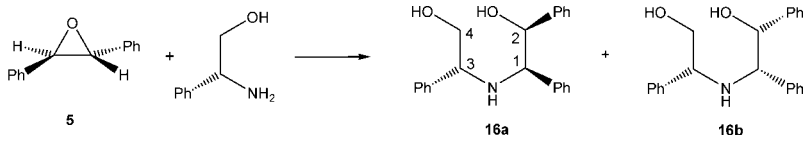
Scheme 4. (a) 2-Aminophenol.

of **16a** and **16b** in 99% yield (^{1}H NMR). Eventually, compound **16a** was isolated by crystallization from methylene chloride/hexane and its structure was established by x-ray diffraction (Fig. 3). The molecular perspective of **16a** shows that phenyl groups are on the same side and the relative configuration at C1 and C2 are *R* and *S*, respectively. Otherwise, compound **16b** was isolated and purified by addition of HCl giving the corresponding amine hydrochloride of **16b**.

In summary, we have described the convenient cleavage of symmetrical and unsymmetrical epoxides using aliphatic and aromatic amines under solvent free conditions. This novel synthetic method offers a convenient entry to β-aminoalcohols in high yield. The most important point of this study is that catalysts, amine excesses, or solvents are not required. The simplicity makes this approach interesting for further studies, and investigations with other chiral aminoalcohols are in progress.

EXPERIMENTAL

Amines and epoxides were obtained from Aldrich Chemical Co. ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL Eclipse + 300 spectrometer. Chemical shifts (ppm) are relative to $(CH_3)_4Si$. Coupling constants are quoted in Hz. Melting points were measured on Melt Temp II apparatus and are



Scheme 5. *R*-(−)-2-phenylglycinol.

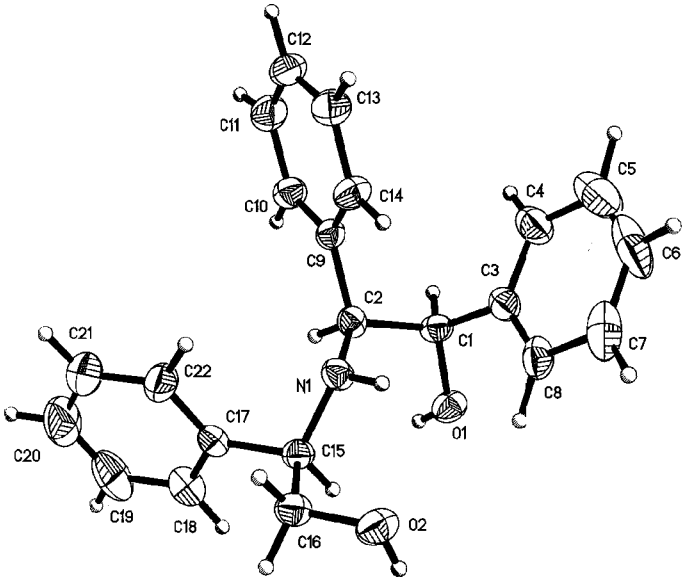


Figure 3. Molecular perspective of compound **16a**.

uncorrected. Elemental microanalyses were performed by Galbraith Laboratories, Inc. Mass spectra were obtained with a JEOL JMS-AX505 HA mass spectrometer. Optical rotations were measured on a JASCO DIP-360 digital polarimeter $[\alpha]_D^{20}$ values are given in deg cm^{-2} g^{-1}. The x-ray crystallographic studies were done on a Bruker Smart Apex CCD diffractometer $\lambda_{(Mo-K\alpha)} = 0.71073$ Å, graphite monochromator, $T = 293$ K, $\omega - 2\theta$ scan, range $1.5 < \theta < 25^\circ$. Corrections were done for Lorentz and polarization effects. The structures were solved by direct methods (Shelxs 86); all nonhydrogen atoms were refined anisotropically, by full least squares, (SHELXL-97)[30] Hydrogen atoms bound to carbon atoms were inserted at calculated position with isotropic temperature factor 1.2 times the U_{iso} of the parent carbon atom. Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC nos. 225262, 225263, and 225264 for compounds **7a**, **9a**, and **16a**, respectively.

Crystal data: Compound **7a** ($C_{16}H_{20}ClNO_2$). MW = 293.78, $a = 7.945$ (1) Å, $b = 6.821$ (1) Å, $c = 28.561$ (2) Å, $\beta = 95.604$ (2)°, $V = 1540.4$ (3) Å^3, space group $P2_1/n$, $Z = 4$, $\rho_{calc} = 1.267$ g/cm^3, 11,989 reflections collected, 2727 independent reflections, No. of variables 193, final $R = 0.037$, $R_w = 0.081$.

Crystal data: Compound **9a** ($C_{12}H_{17}NO_2$). MW = 227, a = 10.4 17 (1) Å, b = 10.607 (1) Å, c = 20.652 (1) Å, $\alpha = \beta = \gamma = 90^\circ$, V = 2281.9 (3) Å^3, space group *Pbcn*, $Z = 8$, $\rho_{calc} = 1.207\,g/cm^3$, 17,399 reflections collected, 2017 independent reflections, No. of variables 145, final $R = 0.051$, $R_w = 0.087$.

Crystal data: Compound **16a** ($C_{22}H_{23}NO_2$). MW = 333, a = 11.817 (1) Å, b = 5.818 (1) Å, c = 14.109 (1) Å, β = 108.946 (2)°, V = 917.2 (2) Å^3, space group $P2_1$, $Z = 2$, $\rho_{calc} = 1.207\,g/cm^3$, 7611 reflections collected, 3245 independent reflections, No. of variables 318, final $R = 0.039$, $R_w = 0.047$.

General Procedure

The corresponding amine and the appropriate epoxide were heated at 90°C either in a type Parr reactor or in a sealed ampoule for the time indicated for each compound. After completion of the reaction, the reaction mixture was cooled and extracted with methylene chloride (3 × 30 mL), the solvent was removed, and the oil residue was crystallized from a mixture hexane–methylene chloride.

2-(2-Hydroxy-1-phenyl-ethylamino)-phenol (2a).[31] From 2 g (18.4 mmol) of 2-aminophenol and 2.2 g (18.8 mmol) of styrene oxide, 2.36 g (55%), yellow pale solid, mp 142–145°C; time 3 hr; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.4–3.5 (1H, m, CH_2) 3.6–3.7 (1H, m, CH_2), 4.2–4.3 (1H, m, CH), 6.1 (1H, dd, J = 1.3, 7.5, H-8), 6.4 (2H, m, H-6, H-7), 6.7 (1H, dd, J = 1.5, 7.4, H-5), 7.3–7.4 (4H, m, H-arom); ^{13}C NMR: (74 MHz, DMSO-d_6) δ: 59.6 (C-1), 66.0 (C-2), 111.7 (C-8), 113.9 (C-5), 116.7 (C-6), 119.9 (C-7), 127.3 (C-m), 127.4 (C-p), 128.8 (C-o), 137.3 (C-3), 142.6 (C-i), 144.9 (C-4); MS m/z (%): [M^+ 229 (10)], 198 (100), 120 (10), 109 (5); IR ν_{max} (KBr): 3485 (NH), 3370 (OH) cm^{-1}.

2-(2-Mercapto-phenylamino)-2-phenyl-ethanol (3a). From 1.16 g (9.32 mmol) of 2-aminothiophenol and 1.06 g (9.32 mmol) of styrene oxide, 2.36 g (85%), yellow solid, mp 152°C; time 3 hr; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.64–3.70 (1H, m, H-2a), 3.70 (1H, m, H-2b), 4.06 (1H, t, J = 7.4, H-1), 6.44 (1H, td, J = 7.5, 1.5, H-6), 6.72 (1H, d, J = 8.0, H-8), 7.18 (1H, td, J = 7.5, 1.5, H-7), 7.10 (1H, d, J = 7.7, H-5), 7.26 (5H, m, H-arom); ^{13}C NMR (74 MHz, DMSO-d_6) δ: 54.4 (C-1), 64.5 (C-2), 114.9 (C-8), 115.2 (C-4), 116.8 (C-6), 127.6 (C-p), 128.7 (C-m, C-o), 130.4 (C-7), 137.0 (C-5), 140.8 (C-i), 150.7 (C-3); MS m/z (%): [$M^+ + 1$, 245 (38)], 215 (25), 125 (100); IR ν_{max} (KBr): 3366 (NH), 3251 (OH). Anal. calcd. for $C_{14}H_{15}NOS$: C, 68.60; H, 6.12; N, 5.71; S, 13.04. Found: C, 68.14; H, 6.15; N, 5.67; S, 13.28.

2-(2-Hydroxy-ethylamino)-2-phenyl-ethanol (4a). From 0.5 mL (8.8 mmol) of ethanolamine and 1 mL (8.8 mmol) of styrene oxide, 1.58 g (99%, 3 : 1); time 3 hr; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.3 (2H, bs, OH), 2.8 (4H, m,

H-2, H-4), 3.7 (2H, t, $J = 5.1$, H-3), 4.7 (1H, dd, $J = 3.7, 8.8$, H-1), 7.2 (5H, m, H-arom); ^{13}C NMR (74 MHz, $CDCl_3$) δ: 51.1 (C-1), 57.1 (C-3), 64.9 (C-4), 72.1 (C-2), 126.4 (C-m), 127.3 (C-p), 128.5 (C-o), 145.1 (C-i); MS m/z (%): [$M^+ + 1$, 182 (2)], 132 (8), 105 (8), 91 (5), 74 (100). IR ν_{max} ($CDCl_3$): 3607, 3443 cm^{-1}. Anal. calcd. for $C_{10}H_{16}NO_2Cl$: C, 65.93; H, 8.79; N, 7.69. Found: C, 65.13; H, 8.25; N, 8.04.

2-(2-Hydroxy-ethylamino)-1-phenyl-ethanol (4b). White solid, mp 94°C; time 3 hr; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.79 (4H, m, H-1, H-3), 3.6 (2H, t, $J = 5.1$, H-4), 4.8 (1H, dd, $J = 4.2, 11.01$, H-2), 7.4 (5H, m, H-arom); ^{13}C NMR (74 MHz, $CDCl_3$) δ: 49.0 (C-3), 60.7 (C-1), 64.7 (C-4), 66.8 (C-2), 125.9 (C-m), 127.5 (C-p), 128.7 (C-o), 140.0 (C-i); MS m/z (%): [$M^+ + 1$, 182].

2-(2-Hydroxy-1,2-diphenyl-ethylamino)-phenol (6a). From 2 g (18.4 mmol) of 2-aminophenol and 3.7 g (18.8 mmol) of *trans*-stilbene oxide, 5.13 g (90%), yellow pale solid, mp 130°C; time 5 hr; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 4.6 (1H, d, $J = 4.5$, H-1), 5.1 (1H, d, $J = 4.7$, H-2), 6.4 (1H, m, H-8), 6.6-6.7 (3H, m, H-7, H-6, H-5), 7.1–7.3 (10H, m, H-arom); ^{13}C NMR (74 MHz, DMSO-d_6) δ: 64.5 (C-1), 77.3 (C-2), 114.6 (C-8), 114.8 (C-5), 118.9 (C-6), 121.4 (C-7), 126.8 (C-m′), 127.7 (C-p′), 128.0 (C-m), 128.1 (C-p), 128.3 (C-o′), 128.4 (C-o), 135.4 (C-i′), 138.6 (C-3), 140.0 (C-i), 144.7 (C-4); MS m/z (%): [$M^+ + 1$, 305 (1)], 198 (100), 120 (20); IR ν_{max} ($CHCl_3$): 3603 (NH), 3411 (OH). Anal. calcd. for $C_{20}H_{19}NO_2$: C, 78.68; H, 6.22; N, 4.59. Found: C, 77.10; H, 6.42; N, 4.47.

2-(2-Hydroxy-ethylamino)-1,2-diphenyl-ethanol (7a). From 0.77 mL (12.7 mmol) of ethanolamine and 2.5 g (12.7 mmol) of *trans*-stilbene oxide, 3.25 g (99%), white solid, mp 100°C; time 3 hr; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.30 (1H, bs, NH), 2.56–2.59 (2H, m, H-3) 3.50–3.54 (2H, m, H-4), 3.85 (1H, d, $J = 5.8$, H-1), 4.82 (1H, d, $J = 5.8$, H-2), 7.14–7.24 (10H, m, H-arom); ^{13}C NMR (74 MHz, DMSO-d_6) δ: 48.9 (C-3), 61.4 (C-4), 68.7 (C-1), 77.1 (C-2), 126.9 (C-p), 127.7 (C-m′), 127.8 (C-p), 128.2 (C-o), 128.3 (C-o′), 139.2 (C-i′), 140.7 (C-i); MS m/z (%): [$M^+ + 1$, 258 (2)], 198 (5), 178 (5), 165 (7), 150 (100) 132 (10), 118 (18), 105 (30), 91 (28); IR ν_{max} ($CDCl_3$): 3607 (NH), 3443 (OH). Anal. calcd. for $C_{16}H_{19}NO_2$: C, 74.70; H, 7.39; N, 5.44. Found: C, 74.51; H, 7.51; N, 5.38.

2-(2-Hydroxycyclohexylamino)-phenol (9a).[32] From 2 g (18.4 mmol) of 2-aminophenol and 1.85 mL (18.8 mmol) of cyclohexene oxide, 3.46 g (90%), pale yellow solid, mp 127°C; time 3 hr; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.05–1.33 (4H, m, H-cyclohex), 1.55–1.68 (2H, m, H-cyclohex), 1.85–1.88 (2H, m, H-cyclohex), 2.91 (1H, ddd, $J = 4.3, 9.2, 12$, H-1), 3.30 (1H, ddd, $J = 3.5, 9.2, 12$, H-2), 6.58–6.71 (4H, *m*, H-arom); ^{13}C NMR (74 MHz, DMSO-d_6) δ: 24.4 (C-10), 24.5 (C-11), 31.5 (C-9), 34.6 (C-12), 58.8 (C-1), 72.4 (C-2), 110.7 (C-8), 113.9 (C-5), 116.1 (C-6), 120.1

(C-7), 137.8 (C-3), 144.7 (C-4); MS m/z (%): [M^+ 207 (90)], 148 (100), 120 (50), 109 (25).

2-(2-Hydroxy-5-methyl-cyclohexylamino-phenol) (10a). From 1 g (8.12 mmol) of 2-amino *m*-cresol and 0.8 mL (8.12 mmol) of cyclohexene oxide, 1.54 g (86%), yellow pale solid, mp 140°C; time 3 hr; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.0–1.1 (1H, m, H-cyclohex), 1.25–1.40 (4H, m, H-cyclohex), 1.67–1.78 (2H, m, H-cyclohex) 2.06–2.24 (3H, m, H-cyclohex), 2.25 (3H, s, $-CH_3$), 2.99 (1H, ddd, $J = 4.3$, 9.2, 12, H-1), 3.37 (1H, ddd, $J = 3.5$, 9.2, 12, H-2), 4.14 (bs, NH), 6.15–6.61 (4H, m, H-arom); ^{13}C NMR (74 MHz, $CDCl_3$) δ: 21.5 (C-13), 24.4 (C-10, C-11), 32.2 (C-9), 34.7 (C-12), 58.8 (C-1), 72.4 (C-2),111.6 (C-8), 113.8 (C-5), 116.3 (C-6), 128.5 (C-7), 136.7 (C-3), 142.0 (C-4); MS m/z (%): [M^+, 221 (100)], 162 (82), 134 (78), 123 (48). Anal. calcd. for $C_{13}H_{19}NO_2$: C, 70.58; H, 8.59; N, 6.33. Found: C, 69.79; H, 8.70; N, 6.20.

2-(5-Chloro-2-hydroxy-cyclohexylamino)-phenol (11a). From 1 g (6.8 mmol) of 4-chloro 2-aminephenol and 0.8 mL (6.8 mmol) of cyclohexene oxide, 1.17 g (65%), brown oil; time 3 hr; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.0–1.07 (1H, m, H-cyclohex), 1.24–1.37 (4H, m, H-cyclohex), 1.65–1.75 (2H, m, H-cyclohex), 1.95–2.12 (3H, m, H-cyclohex), 3.01 (1H, ddd, $J = 4.3$, 9.2, 12.0, H-1), 3.37 (1H, ddd, $J = 3.5$, 9.2, 12.0, H-2), 5.26 (1H, bs, NH), 6.46 (2H, m, H-7, H-8), 6.63 (1H, s, H-5); ^{13}C NMR (74 MHz, $CDCl_3$) δ: 24.3, 24.9, 31.2, 33.4, 60.0 (C-1), 74.3 (C-2), 113.1 (C-8), 115.7 (C-5), 117.8 (C-6), 125.6 (C-7), 137.0 (C-3), 143.5 (C-4); MS m/z (%): [M^+, 256 (90)].

2-(2-Hydroxy-ethylamino)-cyclohexanol (12a).[33] From 1.2 mL (19.8 mmol) of ethanolamine and 2 mL (19.8 mmol) of cyclohexene oxide, 3.1 g (99%), yellow oil; time 3 hr; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.9–1.1 (4H, m, H-cyclohex), 1.1–1.5 (2H, m, H-cyclohex), 1.82–1.97 (2H, m, H-cyclohex), 2.58–2.61 (2H, m, H-3), 3.60–3.64 (2H, m, H-4), 2.81 (1H, ddd, $J = 4.3$, 9.2, 12.0, H-1), 3.60 (1H, ddd, $J = 3.5$, 9.2, 12.0, H-2), 5.2 (1H, bs, NH); ^{13}C NMR (74 MHz, $CDCl_3$) δ: 24.6 (C-6, C-7) 29.9 (C-5), 34.2 (C-8), 48.2 (C-3), 60.8 (C-4), 63.1 (C-1), 73.28 (C-2); MS m/z (%): [M^+, 159 (10)], [$M^+ + 1$, 160 (18)], 128 (100), 110 (45), 100 (85), 81 (40); IR ν_{max} ($CHCl_3$): 3370 (NH), 3250 (OH), 2932, 2859 (CH_2).

2-(5-Chloro-2-hydroxymethyl-phenylamino)-cyclohexanol (13a). From 0.53 g (3.36 mmol) of 2-amino-4chloro-benzylalcohol and 0.34 mL (3.36 mmol) of cyclohexene oxide, 0.70 g (80%), white solid, mp 90°C; time 3 hr; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.00–1.15 (1H, m, cyclohex), 1.20–1.41 (4H, m, cyclohex), 1.62–1.80 (2H, m, cyclohex), 2.00–2.12 (3H, m), 3.09 (1H, ddd, $J = 3.5$, 9.0, 12.5, H-1,) 3.37 (1H, ddd, $J = 3.7$, 9.0, 12.5, H-2), 4.50 (2H, s, H-13), 6.69 (1H, d, $J = 6.0$, H-8), 6.99 (2H, dd, $J = 2.3$, 8.7, H-5, H-7); ^{13}C NMR: (74 MHz, $CDCl_3$) δ: 24.3 (C-11),

24.8 (C-10), 31.5 (C-9), 33.5 (C-12), 59.6 (C-13), 63.9 (C-1), 74.5 (C-2), 113.3 (C-8), 117.2 (C-6), 121.5 (C-4), 126.3 (C-5), 128.9 (C-7), 146.0 (C-3). Anal. calcd. for $C_{13}H_{18}NO_2Cl$: C, 61.08; H, 6.69; N, 5.51. Found: C, 59.42; H, 6.81; N, 6.04.

2-(2-Hydroxy-ethylamino)-phenol (14a). From 2 g (18.3 mmol) of 2-aminophenol and 0.9 mL (18.3 mmol) of ethylene oxide, 2.9 g (99%), brown oil; time 1 hr; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.03 (2H, m, H-1), 3.50 (2H, m, H-2), 5.70 (1H, bs, NH), 6.79–6.87 (2H, m, H-6, H-8), 6.99–7.08 (2H, m, H-5, H-7); ^{13}C NMR (74 MHz, $CDCl_3$) δ: 57.4 (C-1), 59.6 (C-2), 115.7 (C-8), 120.3 (C-5), 123.4 (C-6), 126.5 (C-7), 137.0 (C-3), 153.5 (C-4); IR ν_{max} ($CHCl_3$): 3339 (OH), 2952 (CH_2).

2-(2-Hydroxy-propylamino)-phenol (15a). From 1.70 g (15.6 mmol) of 2-aminophenol and 1.1 mL (15.6 mmol) of propylene oxide, yield 99%, white solid; time 1 hr; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.11 (3H, d, $J = 1.8$, CH_3), 2.69 (1H, dd, $J = 10.6$, 13.4, H-1a), 3.13 (1H, dd, $J = 12.0$, 13.6, H-1b), 3.85 (2H, m, H-2), 6.90 (m, H-arom); ^{13}C NMR (74 MHz, $CDCl_3$) δ: 20.2 (CH_3), 64.8 (C-1) 66.2 (C-2), 116.3 (C-8), 119.9 (C-5), 122.2 (C-6), 125.8 (C-7), 137.4 (C-3), 152.8 (C-4); MS m/z (%): [M^+, 167], 155 (15), 133 (13), 122 (100), 95 (20); IR ν_{max} ($CHCl_3$): 3602 (NH), 3424 (OH). Anal. calcd. for $C_9H_{13}NO_2$: C, 64.67; H, 7.78; N, 8.38. Found: C, 64.00; H, 8.59; N, 8.20.

2-(2-Hydroxy-1-methyl-ethylamino)-phenol (15b). Yellow solid ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.07 (3H, d, $J = 1.8$, CH_3), 2.93 (1H, dd, $J = 9.6$, 13.2, H-2a), 3.03 (1H, dd, $J = 9.6$, 13.0, H-2b), 3.8 (1H, m, H-1), 7.07 (5H, m, H-Ar); ^{13}C NMR (74 MHz, $CDCl_3$) δ: 20.7 (CH_3), 62.0 (C-1), 65.3 (C-2), 116.0 (C-8), 120.6 (C-5), 124.2 (C-6), 126.7 (C-7), 138.3 (C-3), 153.7 (C-4); MS m/z (%): [M^+ 167].

(1′*R*,1*S*,2*R*)-2-(2′-Hydroxy-1′-phenyl-ethylamino)-1,2-diphenyl-ethanol (16a). From 1 g (7.28 mmol) of (*R*)-(−)-2-phenylglycinol and 1.43 g (7.28 mmol) of *trans*-stilbene oxide, white solid, mp 140°C, $[\alpha]_D^{20} = -0.064$ (C = 2.24, $CHCl_3$); time 12 hr; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.54 (1H, dd, $J = 4.4$, 10.4, H-3), 3.68–3.75 (2H, m, H-4), 3.91 (1H, d $J = 5.1$, H-1), 4.98 (1H, d, $J = 5.1$, H-2), 7.0–7.59 (H-arom); ^{13}C NMR (74 MHz, $CDCl_3$) δ: 61.6 (C-3), 66.0 (C-4), 66.2 (C-1), 75.9 (C-2), 126.7, 127.2, 127.5, 127.6, 127.7, 128.0, 128.1, 128.3, 128.7, 139.4 (C-i), 140.1 (C-i), 140.9 (C-i); MS m/z (%): [$M^+ + 1$, 334 (2)], 302 (10), 284 (5), 256 (100), 194 (12), 121 (15), 106 (78); IR ν_{max} (film): 3064 (NH), 3033 (OH). Anal. calcd. for $C_{22}H_{27}NO_2$: C, 79.20; H, 6.90; N, 4.20. Found: C, 78.74; H, 7.02; N, 4.12.

(1′*R*,1*R*,2*S*)-2-(2′-Hydroxy-1′-phenyl-ethylamino)-1,2-diphenyl-ethanol hydrochloride (16b). $[\alpha]_D^{25} = -0.013$ (C = 1.8, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.92 (1H, dd, $J = 4.4$, 10.4, H-3), 4.11 (3H, m, H-4,

H-1), 5.43 (1H, d, $J = 5.1$, H-2), 6.91–7.45 (15H, H-Ar); ^{13}C NMR (74 MHz, $CDCl_3$) δ: 61.1 (C-3), 65.4 (C-4), 66.9 (C-1), 77.6 (C-2), 127.2, 127.4, 127.5, 127.6, 127.7, 128.0, 128.1, 128.3, 128.7, 139.3 (C-i), 139.9 (C-i), 140.9 (C-i); IR ν_{max} (film): 3064 (NH), 3033 (OH).

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