Catal Lett (2012) 142:794–802
DOI 10.1007/s10562-012-0814-4

Asymmetric Organocatalytic Efficiency of Synthesized Chiral β-Amino Alcohols in Ring-Opening of Glycidol with Phenols

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Received: 18 December 2011 / Accepted: 19 March 2012 / Published online: 11 April 2012

Abstract A series of novel chiral β-amino alcohols **3–5** and **7–10** were synthesized by regioselective ring opening of epoxides and chiral amines with a straightforward method in high yields (up to 99 %). Kinetic resolution of racemic glycidol with phenols was achieved by using chiral amino alcohols as organocatalysts. Amino alcohols **5, 8** and **10** exhibited the highest enantioselectivities with *p*-cresol, phenol, and *p*-methoxyphenol by 63, 65, 58 % ee, respectively. The moderate enantioselectivities were observed with catalyst **9b** towards all the nucleophiles (34–48 % ee). The ee values of the desired 3-aryloxy-1, 2-diols were determined by HPLC. This study presents an attractive tool for the synthesis of β-blockers and structurally complex molecules.

Keywords Epoxide ring opening · β-Amino alcohols · Kinetic resolution · Organocatalysts · 3-Aryloxy-1,2-propanediols

Electronic supplementary material The online version of this article (doi:10.1007/s10562-012-0814-4) contains supplementary material, which is available to authorized users.

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1 Introduction

Asymmetric organocatalysis with chiral organic Bronsted acids and bases is an important field of investigation in modern asymmetric synthesis [1]. This approach is very attractive due to its conceptual and experimental simplicity, the absence of hazardous heavy metal salts in reaction mixtures and extremely high efficiency of catalysis [2]. The use of chiral Bronsted acids as catalysts for asymmetric synthesis has recently become a particularly popular and productive field of research [3].

Amino alcohols that include both Bronsted acid and base are very important compounds for asymmetric synthesis. For example, chiral β-amino alcohols have been used in many reactions as catalysts such as asymmetric addition of organozinc reagents to ketones and aldehydes [4–7], asymmetric transfer hydrogenation [8, 9], reduction of ketones to alcohols [10, 11]. Furthermore, the asymmetric ring opening of epoxides by alcohol and thiol nucleophiles were also achieved with $Ti(i\text{-}OPr)_4$ and $Sc(OTf)_3$ mediated amino alcohols, respectively [12, 13]. On the other hand, amino alcohols can also serve as catalysts in their own right, that is, without any metal ion. Therefore, Russo and Lattanzi [14] used chiral amino alcohols as organocatalysts in the asymmetric epoxidation of α,β-enones up to 89 % ee. In addition, cinchonine-derived chiral quaternary ammonium salts and quinine have also been successfully employed as organocatalysts in the desymmetrization of meso-aziridines with benzenethiols [15, 16].

Enantiopure 3-aryloxy-1,2-propanediols are valuable targets for asymmetric synthesis as a result of their role as key synthetic intermediates in a variety of pharmaceutically (such as β-blockers) important compounds [17]. In principle, access to these building blocks may be provided by several routes, including asymmetric reduction of aryloxy ketone [18–20] or the ring opening of enantiopure

terminal epoxides with phenols [21–23]. Therefore, epoxides are versatile building blocks that have been extensively used in the synthesis of complex organic compounds. Their utility as valuable intermediates has further expanded with the advent asymmetric catalytic methods for their synthesis [24–27]. Terminal epoxides are the most important subclass of these compounds, but no general and practical methods were available for their synthesis in enantiomerically pure form.

The development of new methodologies, characterized by operational simplicity and the use of easily available catalysts, is the main target of modern organic synthesis. Hydrolytic kinetic resolution (HKR) developed by Jacobsen has emerged in recent times as a powerful tool to synthesize both terminal epoxides and their corresponding diols in highly enantiomerically pure form by using low loading of recyclable chiral cobalt-based salen complexes [28, 29]. The first phenolic kinetic resolution of terminal epoxides provided 3-aryloxy-1,2-propanediols were reported by Jacobsen et al. [30, 31]. The use of enzymes for the kinetic resolution of racemic substrates in order to afford enantiopure compounds in high enantiomerically pure form and good yields, has long been a popular strategy in synthesis [32–35]. The interest in the field of organocatalysts has increased greatly over the last few years [8]. Organocatalysts, by now, has definitely been maturated to a recognized third methodology, of potentially equal status to organometallic and enzymatic catalysis. They are usually robust, inexpensive, readily available and non-toxic.

In our previous study, it was found that chiral β-amino alcohols effectively catalyzed the asymmetric ring opening of glycidol with phenols [36]. To the best of our knowledge, this was the first example to have been reported in the literature. Therefore, it is still necessary to develop the structurally simple and effective organocatalysts for the activation of epoxides, which renders them to be more susceptible to nucleophilic attack under milder condition. Thus, in this study, we focused our attention on the synthesis of a new series of chiral β-amino alcohols as organocatalyst in the kinetic resolution of racemic glycidol with phenols to provide enantiomerically enriched 3-aryloxy-1,2-propanediols. Chiral β-amino alcohols **3–5, 7–10** were synthesized from chiral secondary amines **2** and **6** and appropriate epoxides in high regioselectivities and yields with a cost-effective and environmentally friendly process (Schemes 1,2). Enantiomeric excess (ee) of desired 3-aryloxy-1,2-propanediols were determined by HPLC.

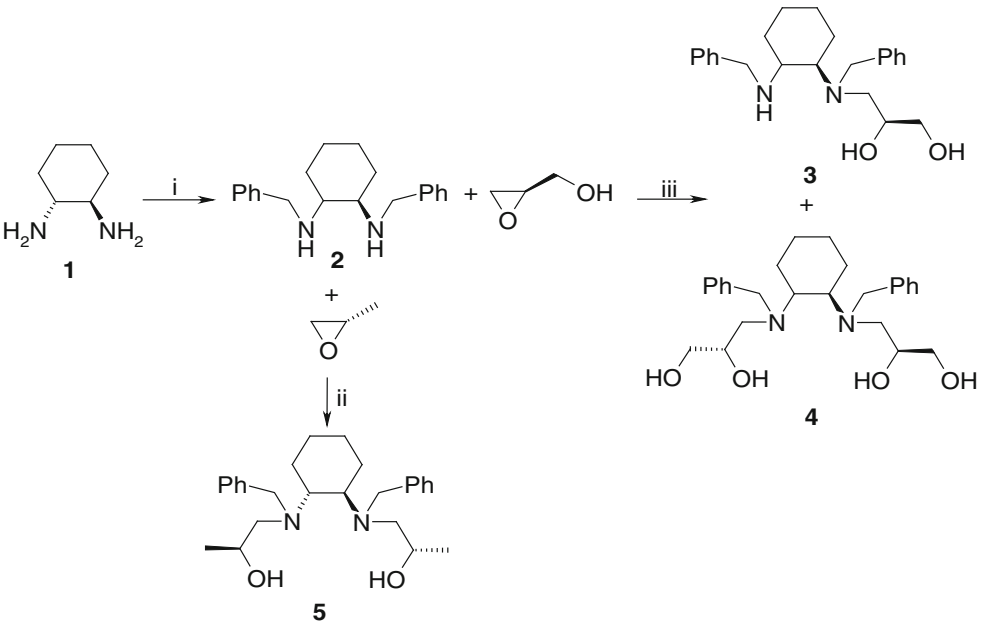
2 Results and Discussions

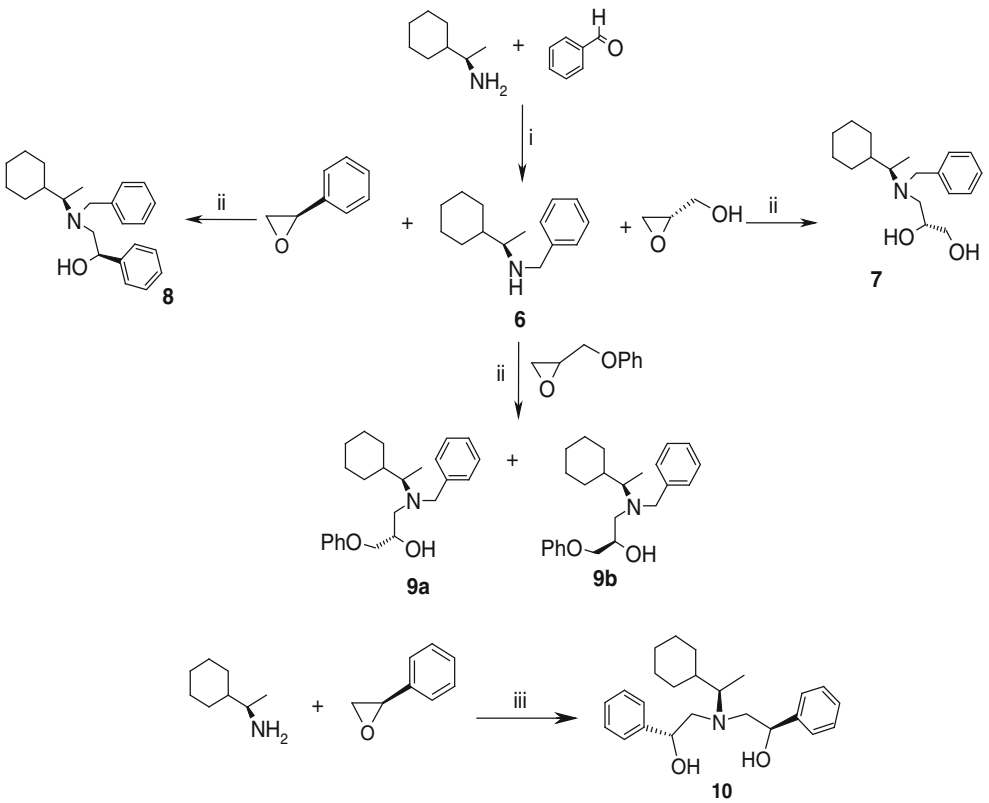
In this study, a series of novel chiral β-amino alcohols **3–5, 7–10** were synthesized and used as organocatalysts for enantioselective ring opening of glycidol with phenols. The regioselective ring opening of epoxides by amines is an important way for the preparation of β-amino alcohols [37, 38]. Thus, chiral β-amino alcohols were synthesized in the catalyst-free medium by regioselective ring opening of terminal epoxides with chiral amines **2** and **6** by using methanol as a solvent (Schemes 1,2). Chiral secondary amines **2** and **6** were synthesized by benzylation of *trans*-(1*R*,2*R*)-1,2-diaminocyclohexane obtained from classical resolution of *cis*/*trans* mixtures of 1,2-diaminocyclohexane and readily available (*R*)-cyclohexylethylamine, respectively. The ring opening reaction of (*R*)-glycidol with chiral amine **2** formed major regioisomeric products **3** and **4** in 33 and 35 % yields respectively. Chiral amino alcohol **5** was obtained from chiral amine **2** and regioselective ring opening of (*S*)-propylene oxide in 99 % yield.

Catalysts **7** and **8** were obtained by aminolysis reaction of (*R*)-glycidol and (*R*)-styrene oxide with amine **6** by yields 99 and 65 %, respectively. Surprisingly, it was observed that selective ring opening of racemic phenyl glycidyl ether could be achieved with chiral amine **6** to give complete conversion to the diastereomer pair of **9a** and **9b,** which was efficiently separated by column chromatography. Catalyst **10** was also obtained with chiral amine **6** and two equivalent ratios of (*R*)-styrene oxide at a high regioisomeric yield (69 %). The low regioselectivities obtained in the case of compounds **8** and **10** arising from more electrophilic character of benzylic carbon of styrene oxide when compared with other epoxides. It was shown that amines **2** and **6** exhibited a preference for nucleophilic attack at terminal or achiral carbon of epoxides as a S_N2 reaction to give corresponding chiral β-amino alcohols with retention of configuration on stereogenic center as reported previously [37, 38]. Therefore, this method provided an easy and efficient route to the corresponding chiral β-amino alcohols without using any catalyst and excess amounts of amine dealing with thermally sensitive epoxides due to the side reactions.

We have demonstrated that the chiral β-amino alcohols are efficient enantioselective organocatalysts for kinetic resolution of racemic glycidol with phenols [36]. However, the enantioselectivities of amino alcohol organocatalysts were obtained drastically different with respect to the phenol nucleophiles. We also showed that the reaction conditions have a strong influence on the yield and enantioselectivity of the reaction; no significant reactions occurred when performed at the room temperature to the studied temperature (50 °C). The higher temperatures and further reaction periods lead to higher yields but lower enantioselectivities [36]. Encouraged by these observations, we aimed to practically route to synthesise of chiral β-amino alcohols as efficient organocatalysts. Therefore, *p*-methoxyphenol, *p*-cresol (*p*-methylphenol) and phenol

Scheme 1 Reactions and conditions: *i* **1** PhCHO, MeOH, reflux, 2 h. **2** $NaBH_4$, reflux. *ii* MeOH, 40 °C. *iii* MeOH, rt

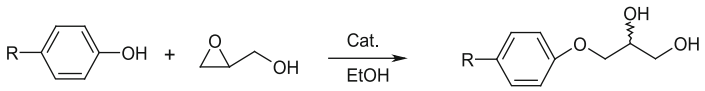


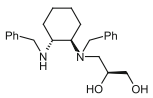
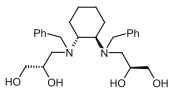
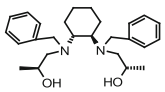
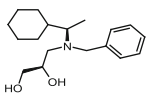
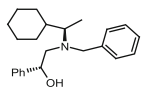
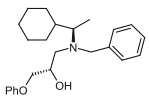
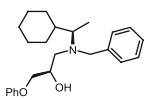
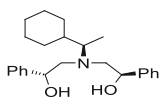


Scheme 2 Reactions and conditions: *i* **1** MeOH, reflux, 3 h. **2** $NaBH_4$, rt, 2 h. *ii* MeOH, 50 °C. *iii* MeOH, 70 °C

were chosen as oxygen nucleophiles due to the convenient determination of ee values of desired 3-aryloxy-1,2-diol adducts by HPLC. However, in general, reactions of epoxides with oxygen nucleophiles are rather difficult, and therefore, the epoxide ring opening with phenolic oxygen nucleophiles is quite challenging (pKa value of Ar-OH ≈ 10) when compared with glycidol and ethanol. All the reactions were performed with 10 mol % of amino alcohol organocatalysts in ethanol at 50 °C and the results were summarized in Table 1.

Table 1 Catalytic asymmetric ring opening of glycidol with phenols



Catalysts			(R)	Product		
No	Structure	Config.		Yield[b] (%)	ee[c] (%)	Config.[d]
3		*R,R,S*	MeO–	40	16	*R*
			Me–	45	Racemic	–
			H–	36	Racemic	–
4		*S,R,R,S*	MeO–	60	37	*R*
			Me–	54	63	*R*
			H–	50	33	*R*
5		*S,R,R,S*	MeO–	55	32	*S*
			Me–	52	16	*S*
			H–	57	26	*S*
7		*R,R*	MeO–	48	14	*R*
			Me–	45	Racemic	-
			H–	40	22	*R*
8		*S,R*	MeO–	63	51	*S*
			Me–	63	7	*S*
			H–	55	65	*S*
9a		*S,R*[a]	MeO–	75	20	*S*
			Me–	68	5	*S*
			H–	70	10	*S*
9b		*R,R*[a]	MeO–	80	44	*R*
			Me–	76	34	*R*
			H–	66	48	*R*
10		*S,R,S*	MeO–	45	58	*S*
			Me–	65	9	*S*
			H–	52	54	*S*

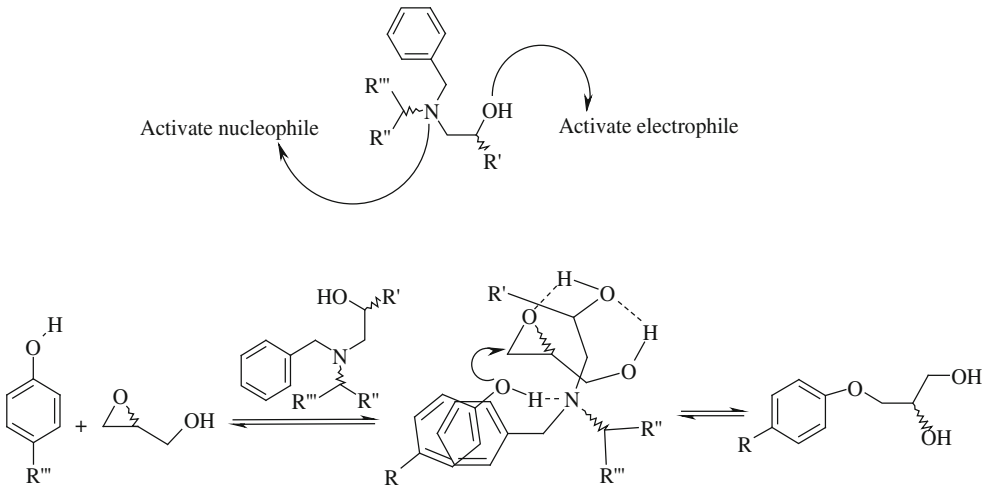
Reactions run in absolute ethanol at 55 °C for 24 h

[a] Absolute configurations **9a** and **9b** were determined by the reaction of **6** and (*S*)-glycidyl phenyl ether which was found to be enantiopure form of **9a**

[b] Isolated yields after thin layer chromatography on silica gel

[c] Determined by chiral HPLC analysis on Chiralcell OD column

[d] Major enantiomer was determined according to the enantiomerically pure chromatograms of corresponding 3-aryloxydiols on HPLC



Scheme 3 Proposed H-bonding-mediated cooperative catalysis mechanism of the reaction

Pioneering studies of Wynberg [39] and then followed by Wang [16] proposed that the natural cinchona alkaloids are bifunctional catalysts utilizing both the tertiary amine and the hydroxyl group to activate and orient the nucleophile and electrophile, respectively, thus achieving optimum asymmetric catalysis. Prompted by these results and our efforts for epoxide transformations, we believe that the chiral amino alcohols, upon interaction with both a nucleophile and electrophile through the suitable atoms of the catalyst, may form a rigid pocket around the activated nucleophile or electrophile, thereby allowing them to function as efficient organic catalysts. As shown in Scheme 3, the possible mechanism of the reaction involves the activation of the glycidol ring followed by attack of activated phenol by hydrogen bond formation with the catalyst.

Considering the values in Table 1, it can be noted that catalyst **3** with secondary amine unit, exhibits low conversion and enantioselectivities (16 % ee only for *p*-methoxyphenol). This is probably due to the preference only; Lewis-base catalysed reaction to the acid catalysed via –NH– unit of the catalyst **3**. Catalyst **4** showed better conversion and enantioselectivities than the catalysts **3** and **5** especially with *p*-cresol nucleophile by 63 % ee for *R* enantiomer of 3-(*p*-methylphenoxy)-1,2-propanediol which was found to be the highest among the other catalysts. Such different stereochemical outcomes were also obtained with a previously report [16]. This selectivity may be explained by electronic and steric effect of methyl substituent on *p*-cresol and catalyst's characteristics. The *p*-cresol is more sterically hindered than phenol, whereas weaker nucleophile than the methoxyphenol. The appropriate orientation of catalyst **4** with *p*-cresol involving π–π interactions between aromatic moiety of nucleophile and benzyl substituent of amine group of catalyst leads to energetically differentiated transition state of racemic glycidol. Catalyst **5** favoured to form the *S* isomers of products with low enantioselectivities (16–32 % ee). This may be due to the low steric hindrance of methyl substituents on alcohol functional groups.

Non symmetric catalysts **7**–**9** were selected due to their structurally simplicity and to employed their enantioselectivity on the reaction. Catalyst **7**, bearing hydroxymethylene substituent on the alcohol stereogenic center exhibited low enantioselectivity (22 % ee for phenol). On the other hand, catalyst **8** showed a good enantioselectivity with *p*-methoxyphenol and phenol nucleophiles, by 51 and 65 % ee for *S* enantiomer of desired products, respectively. This indicates that the phenyl group is an appropriate substituent on the stereogenic center of alcohol for these catalysts. Catalyst **10** was chosen to investigate the scope and limitations of phenyl substituent on selectivity of the reaction. The catalyst **10** showed similar stereochemical outcomes with the catalyst **8** (Table 1). It can be stated that the further alcohol functionality was not found to be effective on the enantioselectivity of the reaction.

Low enantioselectivity of catalyst **7** led us to prepare catalyst **9a** and **9b** which bearing more sterically hindered group on the alcohol stereogenic center. The inductive electron withdrawing effect of phenoxy unit on the catalysts **9a** and **9b** makes them to exhibit a good reactivity. **(*R*,*R*)-9b** showed better enantioselectivities than **(*S*,*R*)-9a** by an appropriate orientation of chiral substituents on the stereogenic center of alcohol group. The selectivities of *p*-methoxyphenol, *p*-cresol (*p*-methylphenol) and phenol nucleophiles with **9b** were found to be 44, 34 and 48 % ee values of (*R*)-3-aryloxy-1,2-propanediols, respectively. The substituents and configuration of alcohol group of catalysts **9a** and **9b** were found to be closely relevant to the stereochemical outcomes of the reaction. In generally, the

configurations of obtained 3-aryloxy-1,2-propanediol products were found to be relevant with the configuration of employed catalysts as shown in Table 1. Steric and electronic effects of substituent on the phenols were found to have significant influence on the yield and the enantioselectivities of 3-aryloxy-1,2-propanediols.

It was shown that the catalysts could be synthesized from readily available starting materials, usually less expensive and applied in less-demanding reaction conditions. Moreover, the absence of a transition metal makes this type of reaction an attractive tool for the synthesis of pharmaceuticals, such as β-blockers, in which compounds, the presence of hazardous metallic traces are inadmissible in the final product. In this strategy, these factors contribute to superior atom efficiency, allowing the direct synthesis of structurally complex molecules.

3 Conclusions

In conclusion, we have described a straightforward synthesis of series chiral β-amino alcohols in high yield and regioselectivities. β-amino alcohols were employed as an efficient organocatalysts for the enantioselective ring opening of glycidol with phenols, giving rise to the 3-aryloxy-1,2-propanediols in moderate yield and enantioselectivities. Although the control of enantioselection of the reaction is modest, future modifications of the system based on mechanistic understanding may improve the stereochemical performance of the catalysts.

4 Experimental

4.1 Reagents and General Methods

All chemicals were of reagent grade unless otherwise specified. (*R*)-cyclohexylethylamine, (*R*)-glycidol, (*R*)-styrene oxide and (*S*)-propylene oxide were purchased from Fluka. Silica Gel 60 (Merck, 0.040–0.063 mm) and silica gel/TLC-cards (F254) were used for flash column chromatography and TLC. All reactions were carried out under an N_2 atmosphere with a dry solvent under anhydrous conditions, unless otherwise noted. Optical rotations were taken on a Perkin Elmer 341 model polarimeter. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker AV-400 High Performance Digital FT-NMR Spectrometer. The chemical shifts (*d*) and coupling constants (*J*) are expressed in parts per million and hertz. The elemental analyses were obtained with CARLO-ERBA Model 1108 apparatus. Enantiomeric excesses were determined by HPLC system (BioRad Pomp and UV detector, Daicel Chiral Cell-OD column).

4.2 Synthesis

*4.2.1 (R,R)-1,2-Diaminocyclohexane (**1**)*

(*R*,*R*)-1,2-Diaminocyclohexane **1** was isolated from isomeric mixture of *cis*- and *trans*-1,2-diaminocyclohexane according to the method reported earlier [40]. (*R*,*R*)-1,2-Diaminocyclohexane L-tartrate: yield 39 %, $[\alpha]_D^{20}$: +11.6 (c 1, H_2O) Ref. [40] +11.6 (c 1, H_2O). (*R*,*R*)-1,2-Diaminocyclohexane: yield 95 %, $[\alpha]_D^{20}$: −19.8 (c 1, 1 M HCl), Ref. [40] −20 (c 1, 1 M HCl).

*4.2.2 (R,R)-N,N′-Dibenzyl-1,2-diaminocyclohexane (**2**)*

This compound was synthesized as a described method [41] by using (*R*,*R*)-1,2-diaminocyclohexane **1** (1.5 g, 13.16 mmol) was dissolved in anhydrous MeOH (8.0 ml) and heated to reflux. Benzaldehyde (2.67 ml, 26.32 mmol) was added dropwise over a period of 2 min, and the mixture was stirred at reflux temperature for 30 min. The solution was allowed to cool to room temperature and sodium borohydride (1.05 g, 27.60 mmol) was added portion wise. After the vigorous effervescence had subsided the mixture was heated to reflux for 15 min. The reaction was then quenched by the addition of water (8 ml) and the aqueous phase was extracted with DCM (3 × 15 ml). The separated organics were dried over potassium carbonate, filtered and the solvent evaporated to give the diamine **2** as a waxy solid (3.86 g, 99 %). $[\alpha]_D^{20}$: −79.7 (c 2.5, $CHCl_3$), [41] −80 (c 2.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.50–7.20 (m, 10H), 3.98 (d, 2H, $J = 13.2$ Hz), 3.75 (d, 2H, $J = 13.2$ Hz), 2.40–2.30 (m, 2H), 2.24 (d, 2H, $J = 13.2$ Hz), 2.15 (bs, 2H), 1.85–1.81 (m, 2H), 1.36–0.130 (m, 2H), 1.15–1.1 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 141.01, 128.38, 128.19, 126.79, 60.90, 50.89, 31.56, 25.08.

*4.2.3 (2S)-3-{Benzyl[(1R,2R)-2-(benzylamino)cyclohexyl]amino}propane-1,2-diol (**3**)*

(*R*)-glycidol (241 mg, 3.26 mmol) was added to a solution of (*R*,*R*)-*N*,*N*′-dibenzyl-1-2-diaminocyclohexane (500 mg, 1.63 mmol) in methanol (3 ml) and stirred at room temperature for 24 h. The solution was concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (*n*-hexane/EtOH/TEA = 6/1/0.5), to afford **3** (200 mg 33 %) as a colourless oil. $[\alpha]_D^{20}$: −61.5 (c 2.5, $CHCl_3$). IR: 3326, 3031, 2933, 2858, 1452, 1380, 1240, 1105, 1079, 1041, 738 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.35–7.22 (m, 10H), 3.79–3.55 (m, 7H), 3.42-3.37 (m, 2H), 2.74–1.72 (m, 8H), 1.25–1.03 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 140.10, 140.04,

128.87, 128.44, 128.37, 128.22, 69.28, 64.44, 62.43, 56.93, 52.00, 48.98, 31.66, 25.51, 25.08, 23.52. Anal. Cald. for $C_{23}H_{32}N_2O_2$: C, 74.96; H, 8.75; N, 7.60. Found: C, 74.88; H, 8.66; N, 7.71.

4.2.4 *(2S)-3-{Benzyl[(1R,2R)-2-{benzyl[(2S)-2,3-dihydroxypropyl]amino}cyclohexyl]amino}propane-1,2-diol (**4**)*

(*R*)-Glycidol (241 mg, 3.26 mmol) was added to a solution of (*R*,*R*)-*N*,*N*′-dibenzyl-1-2-diaminocyclohexane (500 mg, 1.63 mmol) in methanol (3 ml) and stirred at room temperature for 24 h. The solution was concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (*n*-hexane/EtOH/TEA = 6/1/0.5), to afford **4** (250 mg, 35 %) as a colourless oil. $[\alpha]_D^{20}$: −54.2 (c 2.5, $CHCl_3$). IR: 3367, 3030, 2943, 2864, 1456, 1377, 1331, 1252, 1113, 1080, 1030, 914, 749, 702 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.03–7.33 (m, 10H), 3.92–3.30 (m, 10H); 2.95–2.71 (m, 4H); 2.48–2.21 (m, 4H); 1.95–1.81 (m, 4H); 1.42–1.14 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 138.25, 128.59, 128.31, 127.37, 68.96, 65.19, 58.25, 52.16, 25.63, 24.14, 22.01. Anal. Cald. for $C_{26}H_{38}N_2O_4$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.61; H, 8.69; N, 6.26.

4.2.5 *(1R,2R)-N,N′-Dibenzyl-N,N′-bis(ethan-(1-(S)-methyl)-1-ol)-trans-diaminocyclo-hexane (**5**)*

(*S*)-1,2-Epoxypropane (118 mg, 2.0 mmol) was added to a solution of (*R*,*R*)-*N*,*N*′-dibenzyl-1-2-diaminocylohexane **2** (250 mg, 0.82 mmol) in methanol (3 ml) and stirred at 40 °C in an oil bath equipped with contact thermometer for 24 h. The solution was concentrated under reduced pressure to give product **5** (340 mg, 99 %) as a colourless oil. IR: 3384, 3031, 2923, 2858, 1953, 1882, 1812, 1600, 1452, 1296, 1388, 1336, 1253, 1132, 1060, 964, 746 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.36–7.15 (m, 10H), 5.92 (bs, 2H), 3.74 (d, 2H, $J = 12.8$ Hz), 3.49–3.40 (m, 4H), 2.70–2.60 (m, 4H), 2.40–2.34 (m, 2H), 2.00–1.90 (m, 2H), 1.80–1.60 (m, 2H), 1.20–0.9 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 139.78, 129.61, 128.23, 127.21, 65.89, 64.31, 59.83, 56.92, 25.97, 25.03, 21.78. Anal. Cald. for $C_{26}H_{38}N_2O_2$: C, 76.06; H, 9.33; N, 6.82. Found: C, 75.98; H, 9.39; N, 6.77.

4.2.6 *(R)-N-benzyl-cyclohexylethylamine (**6**)*

According to the same procedure as that of **2**, the product **6** was prepared starting from (*R*)-cyclohexylethylamine (1 ml, 6.82 mmol), benzaldehyde (6.95 ml, 6.82 mmol) and sodium borohydride (272 mg, 7.15 mmol) to obtain **6** (1.42 g, 96 as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.38–7.29 (m, 5H), 3.89 (d, 1H, $J = 13.2$ Hz), 3.75 (d, 1H, $J = 13.2$ Hz), 2.58–2.51 (m, 1H), 1.82–1.71 (m, 6H), 1.44–1.14 (m, 4H), 1.09–1.01 (m, 5H). Anal. Cald. for $C_{15}H_{23}N$: C, 82.89; H, 10.67; N, 6.44. Found: C, 82.80; H, 10.59; N, 6.51.

4.2.7 *3-[N-Benzyl((R)-1-cyclohexylethyl)amino]-(R)-propane-1,2-diol (**7**)*

To a solution of (*R*)-*N*-benzyl-1-cyclohexylethylamine **6** (1.42 g, 6.53 mmol) in methanol (5 ml) was added (*S*)-glycidol (518 mg, 7.0 mmol) and stirred at 50 °C in an oil bath equipped with contact thermometer for 24 h. The solvent was evaporated and then excess glycidol was removed by kugelruhr distillation apparatus to give 1.90 g (99 %) of compound **7** as colourless oil. $[\alpha]_D^{20}$: −30.3 (c 2.5, $CHCl_3$). IR: 3370, 3031, 2927, 2844, 1457, 1382, 1079, 1029, 741 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.30–7.21 (m, 5H), 3.78 (d, 1H, $J = 13.6$ Hz), 3.61–3.29 (m, 5H), 3.54 (d, 2H, $J = 6.8$ Hz), 2.44–2.36 (m, 1H), 2.18 (d, 1H, $J = 12.8$ Hz), 1.75–1.64 (m, 4H), 1.45–1.35 (m, 1H), 1.30–1.10 (m, 4H), 1.01 (d, 3H, $J = 6.8$ Hz), 0.92–0.80 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 140.07, 129.03, 128.42, 127.18, 69.19, 64.78, 62.79, 54.95, 54.57, 41.04, 31.52, 30.53, 26.52, 26.43, 26.33, 11.56. Anal. Cald. for $C_{18}H_{29}NO_2$: C, 74.18; H, 10.03; N, 4.81. Found: C, 74.11; H, 10.09; N, 4.74.

4.2.8 *2-[N-Benzyl-((R)-1-cyclohexylethyl)amino]-(S)-1-phenylethanol (**8**)*

(*R*)-Phenyl oxirane (720 mg, 6.0 mmol) was added to the solution of (*R*)-*N*-benzyl-cyclohexylethylamine **6** (1.30 g, 5.96 mmol) in methanol (5 ml). The solution was stirred at 50 °C in an oil bath equipped with contact thermometer for 24 h. The solvent was evaporated and excess phenyl oxirane was removed by kugelrohr distillation apparatus. The crude product was purified by silica-gel column chromatography (Petroleum ether/EtOAc/TEA = 8.5/1/0.5), to afford **8** (1.3 g, 65 %) as a colourless oil. $[\alpha]_D^{20}$: −185.0 (c 2.5, $CHCl_3$). IR: 3448, 3070, 3031, 2927, 2850, 1953, 1882, 1810, 1606, 1496, 1452, 1382, 1336, 1247, 1201, 1066, 1035, 746 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.50–7.34 (m, 10H), 4.79 (dd, 1H, $J_1 = 3.6$ Hz, $J_2 = 3.2$ Hz), 4.01 (d, 1H, $J = 13.6$ Hz), 4.00 (bs, 1H), 3.51 (d, 1H, $J = 13.6$), 2.76–2.57 (m, 3H), 2.37 (d, 1H, $J = 12.8$ Hz), 1.87–1.77 (m, 4H), 1.60–1.45 (m, 1H), 1.45–1.25 (m, 3H), 1.12 (d, 3H, $J = 6.4$ Hz), 1.04–0.95 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 142.45, 139.44, 129.23, 128.48, 128.26, 127.36, 127.19, 125.96, 69.18, 59.02, 57.98, 54.04, 40.73, 31.14, 30.64, 26.50, 26.41, 26.21, 10.21. Anal. Cald. for $C_{23}H_{31}NO$: C, 81.85; H, 9.26; N, 4.15. Found: C, 81.79; H, 9.32; N, 4.09.

4.2.9 2-[N-Benzyl((R)-1-cyclohexylethyl)amino]-(S)-1-phenoxyethanol (**9a**) and 2-[N-Benzyl((R)-1-cyclohexylethyl)amino]-(R)-1-phenoxyethanol (**9b**)

Racemic glycidyl phenyl ether (1.9 g, 12.66 mmol) was added to a solution of (*R*)-*N*-benzyl-1-cyclohexylethylamine **6** (2.22 g, 11.75 mmol) in methanol (10 ml) and stirred at 50 °C in an oil bath equipped with contact thermometer for 24 h. The solvent was evaporated and then excess glycidyl phenyl ether was removed by kugelruhr distillation apparatus. Diastereomer pair was separated by silica-gel column chromatography (petroleum ether/ethyl acetate/triethyl amine = 85/10/5), to afford a higher R_f value (0.65) of **9a** (2.1 g 49 %) as a colourless oil. $[\alpha]_D^{20}$: −76.8 (c 2.5, $CHCl_3$). IR: 3460, 3063, 3030, 2934, 2857, 1600, 1496, 1458, 1380, 1298, 1247, 1047, 752 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.39–7.27 (m, 7H), 6.99–6.90 (m, 3H), 4.10–4.00 (m, 1H), 3.99–3.95 (m, 1H), 3.89–3.84 (m, 2H), 3.65 (bs, 1H), 3.40 (d, 1H, $J = 13.6$ Hz), 2.70–2.47 (m, 3H), 2.24 (d, 1H, $J = 13.2$ Hz), 1.77–1.65 (m, 4H), 1.50–1.30 (m, 1H), 1.30–1.11 (m, 3H), 1.06 (d, 3H, $J = 6.8$ Hz), 0.90–0.80 (m, 2H). ^{13}C NMR (400 MHz, $CDCl_3$): δ (ppm) 158.83, 139.54, 129.41, 129.17, 128.50, 127.20, 120.83, 114.53, 70.40, 65.84, 59.28, 54.11, 52.36, 40.80, 31.11, 30.69, 26.52, 26.43, 26.21, 10.24. Anal. Cald. for $C_{19}H_{31}NO$: C, 78.84; H, 10.79; N, 4.84. Found: C, 78.92; H, 10.88; N, 4.90. The diastereomer **9b** (2.1 g 49 %) with lower R_f value (0.40) was also obtained as a colourless oil. $[\alpha]_D^{20}$: −40.8 (c 2.5, $CHCl_3$). IR : 3445, 3063, 3038, 2928, 2857, 1600, 1498, 1456, 1250, 1047, 758 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.34–7.26 (m, 8H), 6.08–6.84 (m, 2H), 3.96–3.93 (m, 1H), 3.84–3.80 (m, 1H), 3.76–3.74 (m, 2H), 3.44 (d, 1H, $J = 13.2$ Hz), 2.79–2.73 (m, 1H), 2.67–2.63 (m, 1H), 2.46–2.41 (m, 1H), 2.24 (d, 1H, $J = 13.2$ Hz), 1.77–1.65 (m, 4H), 1.50–1.35 (m, 1H), 1.30–1.10 (m, 3H), 1.06 (d, 3H, $J = 6.4$ Hz), 0.92–0.80 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 158.70, 140.26, 129.39, 128.36, 127.06, 120.84, 114.41, 70.33, 67.94, 62.49, 55.02, 54.39, 41.09, 31.54, 30.56, 26.56, 26.46, 26.28, 11.24. Anal. Cald. for $C_{19}H_{31}NO$: C, 78.84; H, 10.79; N, 4.84. Found: C, 78.94; H, 10.79; N, 4.94. In order to the determination of absolute configurations of diastereomers pair (*R*)-*N*-benzyl-1-cyclohexylethylamine **6** and (*S*)-glycidyl phenyl ether was reacted as usual manner. The optical rotation of purified diastereomer was measured to give **9a** by $[\alpha]_D^{20}$: -76.8 (c 2.5, $CHCl_3$).

4.2.10 N-(R)-1-Cyclohexylethyl-3-aza-(S,S)-1,5-diphenyl-1,5-pentanediol (**10**)

(*R*)-Styrene oxide (1.04 g, 8.66 mmol) was added to the solution of (*R*)-N-benzyl-1-cyclohexylethylamine **(6)** (500 mg, 3.94 mmol) in methanol (5 ml). The solution was stirred at 70 °C in an oil bath equipped with contact thermometer for 24 h. Solvent evaporated and excess (*R*)-styrene oxide was removed by kugelrohr distillation apparatus. The crude product was purified by silica-gel column chromatography (Petroleum ether/EtOAc/TEA = 8.5/1/0.5), to afford **10** (1 g, 69 %) as a colourless oil. $[\alpha]_D^{20}$: −119.6 (c 2.5, $CHCl_3$). IR : 3396, 3062, 3028, 2916, 2851, 2662, 2357, 2336, 1947, 1888, 1604, 1493, 1447, 1373, 133151242, 1062, 966, 912, 753 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.45–7.32 (m, 10H), 4.76 (dd, 2H, $J_1 = 4.4$, $J_2 = 4.0$), 4.97 (bs, 2H), 2.69–2.61 (m, 4H), 2.52–2.45 (m, 2H), 1.88–1.75 (m, 4H), 1.43–1.26 (m, 4H), 1.00 (d, 3H, $J = 6.8$), 0.96(m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 142.72, 128.41, 127.52, 126.06, 70.96, 61.53, 58.45, 40.57, 31.03, 30.85, 26.72, 26.54, 26.38, 11.14. Anal. Cald. for $C_{24}H_{33}NO_2$: C, 78.43; H, 9.05; N, 3.81. Found: C, 78.37; H, 9.11; N, 2.71.

4.2.11 General Procedure for the Ring Opening of Glycidol

A solution of glycidol (0.66 mol), phenol or phenol derivatives (0.33 mol) and catalyst (0.033 mol) was dissolved in absolute ethanol (1 ml). The mixture was stirred at constant temperature (50 °C) for 24 h. The solvent was evaporated and the desired 3-aryloxy-1,2-propanediols was purified by silica-gel TLC plate (EtOAc/*n*-hexane = 2/1). Ee values were determined by HPLC analysis (Biorad pump, Daicel® chiralcel OD column, UV-detector 254 nm, ethanol: *n*-hexane = 1: 9, flow rate: 1 ml min^{-1}). Retention times for (*R*) and (*S*) of 3-(*p*-methoxyphenoxy)-, 3-(*p*-methylphenoxy)- and 3-phenoxy-1,2-propanediol were found to be 8 and 10, 13 and 17 and 9 and 17 ± 1 min, respectively.

Acknowledgments We thank the Research Project Council of Dicle University (DÜBAP-08-FF-13) and the Scientific and Technological Research Council of Turkey (TUBİTAK) (Project no: 110T468) for their financial support.

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