CHAPTER II

EXPERIMENTAL

2.1 General Procedures and Materials

2.1.1 Measurement

The weight of all chemical substrances was determined on a Metler Toledo electrical balance AB204-S. The injection volume of chemicals was used by micropipette Witeg Germany for 20-25 μL scale. Evaporation of solvents was carried out on a Bücchi Rotavapor R-200 equipped with a water aspirator model B-490. The magnetic stirrers were from Corning. The progress of the reaction was followed by thin layer chromatography (TLC) performed on Merck D.C. silica gel 60 F_{254} 0.2 mm. precoated aluminium plates cat. No. 1.05554 and visualized using UV light at 254 nm or one of the following dipping reagents: aq. $KMnO_4$, anisaldehyde, or PMA. Column chromatography was performed on silica gel 230-400 mesh for flash column chromatography. The chiral HPLC experiments were performed on Water 600^{TM} system equipped with gradient pump and Water 996^{TM} photodiode array detector; optionally alternate to Rheodyne 7725 manual sample loop (100 μl sample size for analytical scale). Chiral HPLC columns used for analysis of enantioselectivity were Daicel ChiralCel OD® (250 mm × 4.6 mm) and ChiralPak AD® (250 mm × 4.6 mm). ^{1}H and ^{13}C spectra were recorded on a Varian Mercury-400 plus NMR spectrometer operating at 400 MHz (^{1}H). The FIDs were processed and integrated after a base-line correction using Mestrec23 software from Mestrelab Research. Melting points were recorded on an electrothermal melting point

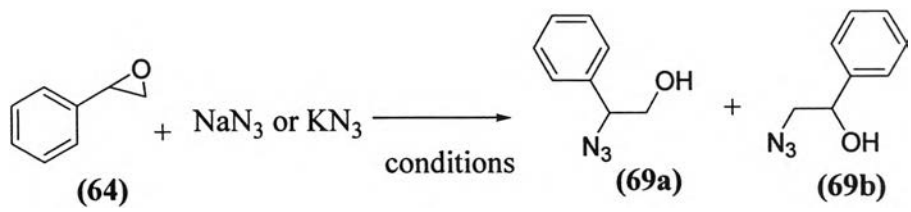
apparatus model 9100. Most of the reactions that required heating were performed in a screw-capped test tube in a heating block (a Biosan thermo-block).

2.1.2 Materials

All chemicals were purchased from Fluka, Merck or Aldrich Chemical Co.Ltd., and were used as received without any further purification except morpholine and *tert*-butylamine, which were distilled under ambient pressure. Commerical grade solvents were distilled before use in column chromatography. Solvents for reactions were reagent grade and used without purification. Nitrogen gas was obtained from TIG with 99.5% purity. HPLC grade hexane and 2-propanol for chiral HPLC experiments, obtained from J.T. Baker and Merck, respectively, were filtered through a membrane filter (0.5 m Millipore®-FH) before use. Each sample after dissolution in a suitable solvent was filtered through a Millex®-HV syringe filter unit prior to injection onto chromatography.

2.2 Synthesis of vicinal azido alcohols and phthalimido alcohols

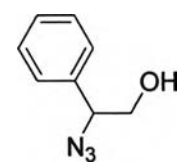
2.2.1 General procedure for synthesis of vicinal azido alcohols with and without phase transfer catalysts



(64) (69a) (69b)

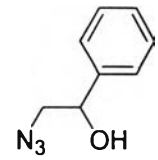
To a solution of NaN_3 (0.5 mmol, 32.5 mg or 1.5 mmol, 97.5 mg) or KN_3 (0.5 mmol, 28.1 mg) and/or a phase transfer catalyst (10 mol %) and in a solvent (1 mL or 125 μL) was added racemic styrene oxide (0.5 mmol, 58.8 μL) in a round bottom flask with a magnetic bar. A few experiments required a mixture of protic solvents at the ratio of 1:1

such as isopropanol:water and ethanol:water. The reaction was heated at an indicated temperature with continuous stirring until all styrene oxide was entirely converted to any product, as indicated by TLC, (SiO_2, 80/20 hexane/ethyl acetate). For TLC-monitoring the reaction in DMF or DMSO, the solvent must be first removed by adding a few drops of the reaction mixture to water and then extracting with ethyl acetate. Once the reaction was completed, the flask was allowed to cool down to room temperature. For the reaction performed in DMF or DMSO, the crude solution was first diluted with dichloromethane, and then washed with water about 5 times. For other volatile organic solvents, the solvent was directly evaporated; then, filtered through a short plug of silica gel filled in a dropper and eluted with dichloromethane. For mixture of protic solvents and alcohols such as ethanol:water, these crudes must be evaporated, and then the water phase extracted with water/dichloromethane in a separatory funnel. Afterwards, all these crudes must be dried by rotatory evaporation followed by a desiccating pump. After the crude NMR was obtained, the residues were subjected to flash chromatography on silica gel eluting with 98:2 hexane:ethyl acetate.



(69a)

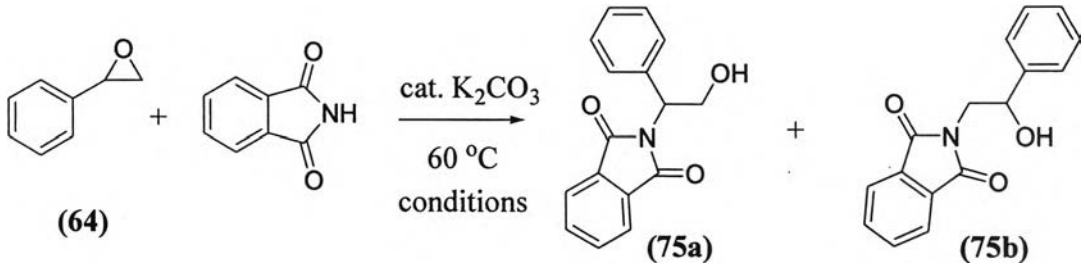
2-Azido-2-phenyl-ethanol (69a): light yellow liquid, R_f = 0.21 (SiO_2, 80/20 hexane/ethyl acetate), ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.98 (bs, 1H, O*H*), 3.79 (m, 2H, C*H*$_2$OH), 4.72 (dd, 1H, *J* = 6, 4.4 Hz, C*H*N_3), 7.35-7.46 (m, 5H, Ar*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 66.5 (*C*HN_3), 67.9 (*C*H$_2$OH), 127.2, 128.8, 129.0 (Ar)



(69b)

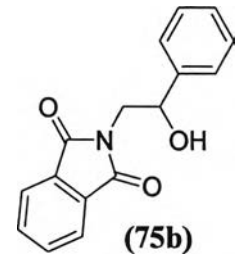
2-Azido-1-phenyl-ethanol (69b): yellow liquid, R_f = 0.33 (SiO_2, 80/20 hexane/ethyl acetate), ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.59 (bs, 1H, O*H*), 3.45 (dd, 1H, *J* = 4, 12.4 Hz, C*H*HN$_3$), 3.51 (dd, 1H, *J* = 8, 12.4 Hz, C*H*HN$_3$), 4.89 (dd, 1H, *J* = 4, 7.6 Hz, C*H*OH), 7.35-7.44 (m, 5H, Ar*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 58.0 (*C*H$_2$N$_3$), 73.4 (*C*HOH), 126.0, 128.2, 128.4 (Ar)

2.2.2 General procedure for synthesis of vicinal phthalimido alcohols



(64) **(75a)** **(75b)**

A dried and finely grounded potassium carbonate (5 mol %, 3.455 mg) and phthalimide (0.55 mmol, 82.9 mg) were suspended in the solvent (1 mL) in a screw-capped test tube. The test tube was heated in a heating block at 60 °C for 20 minutes and stirred intermittently. Then, racemic styrene oxide (0.5 mmol, 58.8 μL) was added into the tube with stirring. The reaction was checked for its completeness by TLC (SiO_2 70/30 hexane/ethyl acetate) under UV light and staining with PMA. After the reaction was complete, the crude product was isolated as described for the reaction with azide above. Then, the product was dried and prepared for ^{1}H NMR. The residues were subjected to flash chromatography on silica gel using a gradient elution from 90/10 to 70/30 hexane/ethyl acetate.



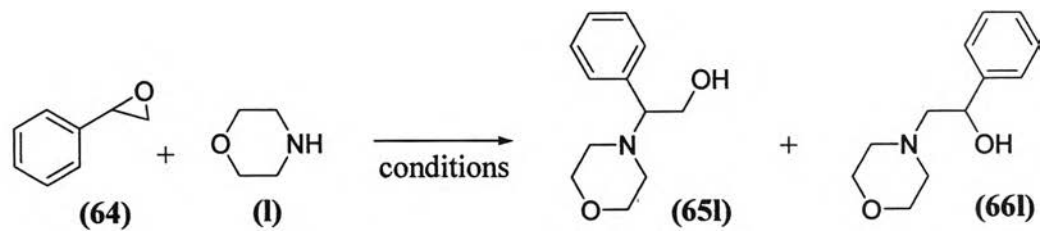
(75b)

***N*-(2-Hydroxy-2-phenyl-ethyl)-phthalimide (75b)**: white solid, mp. 208-210 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.64 (bs, 1H, O*H*), 2.88 (bs, 1H, O*H*), 3.98 (dd, 1H, *J* = 4, 14 Hz, C*H*HN), 4.06 (dd, 1H, *J* = 8.4, 14 Hz, C*H*HN), 5.10 (dd, 1H, *J* = 3.2, 8.4 Hz, C*H*OH), 7.29-7.51 (m, 5H, Ar*H*), 7.74-7.77 (m, 2H, *H* of phthalimide), 7.86-7.91 (m, 2H, *H* of phthalimide); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 45.8 (CH_2N), 72.4 (*C*HOH), 123.8, 126.0, 127.9, 128.5, 132.0, 134.1, 141.2 (Ar)

2.3 Synthesis of vicinal amino alcohols

2.3.1 General procedure of kinetics reaction for synthesis of vicinal racemic amino alcohols

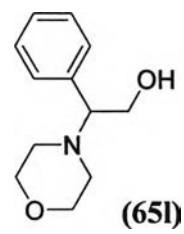
2.3.1.1 General procedure of kinetics reaction for synthesis of racemic vicinal amino alcohols with a variety of solvents in two different temperatures



(64) (l) (65l) (66l)

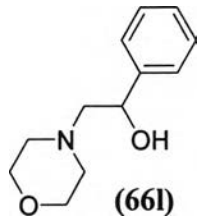
Racemic styrene oxide (0.75 mmol, 88.2 μL) and distilled morpholine (0.5 mmol, 44.4 μL) were added to the solvents (1 mL) in a screw-capped test tube. The temperature during the addition of each solvent in all the reactions was done at room temperature except for HFIP which required an external cooling. The test tubes were heated at 60 °C

by means of heating block or left at room temperature with occasional stirring. Monitoring the reaction progress was performed every 30 minutes by TLC eluting with 70/30 ethyl acetate/hexane and with $KMnO_4$ as a staining agent. The reactions in HFIP must be treated with sodium carbonate solution, and extracted with ethyl acetate to free the morpholine from its HFIP salt before the TLC. After the reactions were completed as indicated by the disappearance of the morpholine, they were quenched by cooling down in a cold water bath. Then, 5-6 drops of the reaction mixture were sampled to a test tube and dried by a stream of N_2 (g). The crude samples were directly analyzed by ^1H NMR. The isolated yields were obtained gravimetrically after column chromatography with a gradient of 60/40 hexane/ethyl acetate to 70/30 ethyl acetate/hexane. The identity and purity of the products were determined by ^1H NMR. The α/β ratio was also obtained gravimetrically, or by NMR if the separation was unsuccessful.



(65l)

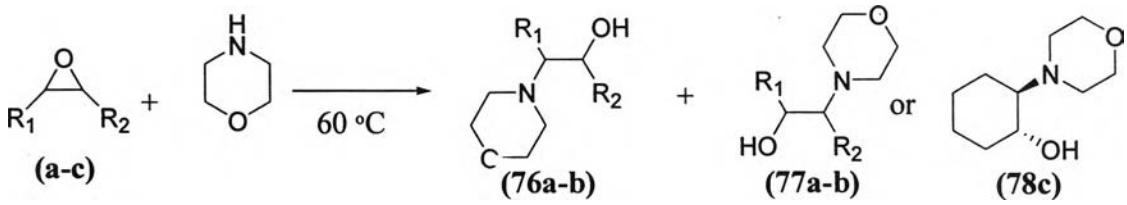
2-morpholin-4-yl-2-phenyl-ethanol (65l): orange oil, R_f = 0.11, ^1H NMR ($CDCl_3$, 400 MHz) δ 2.40 (t, 2H, *J* = 5.6 Hz, C*H*$_2$N), 2.53-2.59 (m, 2H, C*H*$_2$N), 2.79 (bs, 1H, O*H*), 3.61 (dd, 1H, *J* = 4.4, 8.4 Hz, C*H*HOH), 3.68-3.74 (m, 5H, *J* = 5.2 Hz, 1H of C*H*HOH and 4H of 2 C*H*$_2$O of morpholine), 3.96 (dd, 1H, *J* = 8.4, 10.8 Hz, C*H*Ph), 7.19-7.38 (m, 5H, Ar*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 50.0 (2 *C*H$_2$N of morpholine), 60.7 (*C*HN), 67.1 (2 *C*H$_2$O of morpholine), 70.6 (*C*H$_2$OH), 128.1, 128.4, 128.8, 135.8 (Ar)



(66l)

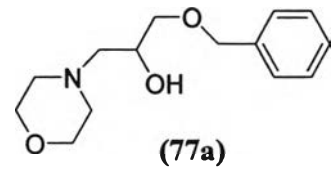
2-morpholin-4-yl-1-phenyl-ethanol (66l): white solid, mp. 83-84 °C,[80] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.48 (t, 2H, J = 10.0 Hz, CH_2N of morpholine), 2.58 (dd, 2H, J = 3.6, 12.4 Hz, NCH_2CHOH), 2.74 (t, 2H, J = 4.4 Hz, CH_2N of morpholine), 3.80 (m, 4H, 2 CH_2O of morpholine), 4.76 (dd, 1H, J = 3.6, 10.8 Hz, C*H*OH), 7.25-7.38 (5H, m, Ar*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 53.4 (2 *C*H_2N of morpholine), 66.6 (*C*H_2N), 67.0 (2 *C*H_2O of morpholine), 68.5 (*C*HOH), 125.8, 127.6, 128.4, and 141.8 (Ar)

2.3.1.2 General procedure of kinetics reaction for synthesis of racemic vicinal amino alcohols with a variety of solvents and oxiranes



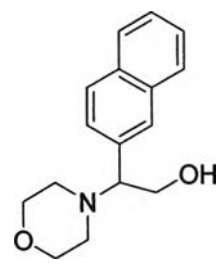
The reaction procedure and conditions for synthesis of aminolysis of other racemic oxiranes including benzyl glycidyl ether, β-naphthalene oxide, and cyclohexene oxide with morpholine were performed identically to the reaction of styrene oxide (0.75 mmol, 88.2 μL) and morpholine (0.5 mmol, 44.4 μL). Progress of the reactions was monitored by TLC using 60/40 ethyl acetate/hexane for benzyl glycidyl ether, 70/30 for naphthalene oxide, and 80/20 for cyclohexene oxide with $KMnO_4$ as a staining agent. ^{1}H NMR was also used to identify the products and to determine the ratio of isomers. The isolated yields were determined gravimetrically after column chromatography (SiO_2,

elution conditions: isocratic at 75/25 ethyl acetate/hexane for benzyl glycidyl ether; 80/20 to 50/50 hexane/ethyl acetate for naphthalene oxide; and isocratic at 70/30 ethylacetate/hexane for cyclohexene oxide. **(77a)**



(77a)

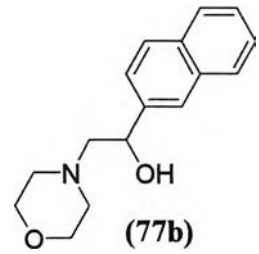
1-benzyloxy-3-morpholin-4-yl-propan-2-ol (77a): yellow oil, R_f = 0.09, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.39 (dd, 2H, *J* = 4 Hz for 1H of C*H*HN and *J* = 12.4 Hz for1H of C*H*HN of morpholine), 2.58-2.63 (m, 2H, CH_2N of morpholine), 3.20 (bs, 1H, O*H*), 3.45 (dd, 1H, *J* = 5.2, 9.2 Hz, OC*H*HCHOH), 3.50 (dd, 1H, *J* = 4.8, 9.2 Hz, OC*H*HCHOH), 3.66-3.73 (m, 4H, *J* = 8.4, 10.8 Hz, 2 CH_2O of morpholine), 3.93 (dddd, 1H, *J* = 3, 3.6, and 9.2 Hz, C*H*OH), 4.55 (AA', 2H, CH_2Ph), 7.25-7.34 (m, 5H, Ar*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 53.7 (2CH_2N of morpholine), 61.2 (CH_2N), 66.0 (2 CH_2O of morpholine), 72.5 (CH_2O), 73.5 (OCH_2Ph), 127.5, 128.4, 138.0 (Ar)



(76b)

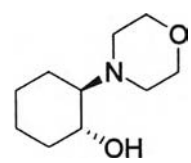
2-morpholin-4-yl-2-naphthalen-2-yl-ethanol (76b): orange oil, R_f = 0.21, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.57-2.66 (m, 2H, CH_2N of morpholine), 2.67-2.75 (m, 2H,CH_2N of morpholine), 3.76-3.81 (s, 4H, 2 CH_2O of morpholine), 3.84-3.92 (m, 2H, CH_2OH), 4.17 (dd, 1H, *J* = 7.6, 10.8 Hz, C*H*N), 7.40 (d, 1H, *J* = 8.4 Hz, γ-*H* of naphthyl), 7.50-7.53 (m, 2H, *H* of naphthyl), 7.72 (s, 1H, α-*H* of naphthyl), 7.81-7.84 (m,

3H, *H* of naphthyl); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 50.3 (2 *C*H_2N of morpholine), 61.0 (*C*HN), 66.3 (2 *C*H_2O of morpholine), 70.8 (*C*H_2OH), 123.8, 124.5, 126.4, 126.5, 127.6,127.8, 128.3, 128.4, 132.9, 133.2 (Ar)



(77b)

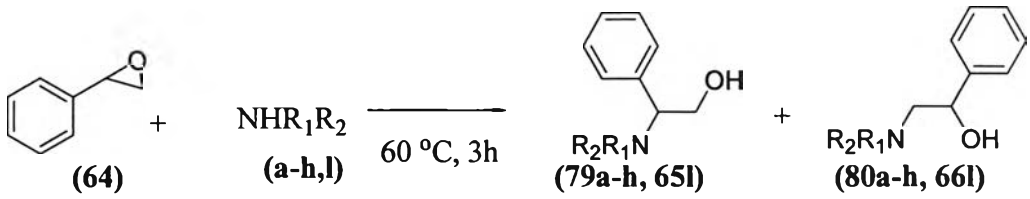
2-morpholin-4-yl-1-naphthalen-2-yl-ethanol (77b): light yellow-white solid, mp.108-110 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.50-2.61 (m, 2H, C*H*$_2$N of morpholine), 2.65 (dd, 2H, *J* = 3.6, 12.4 Hz, C*H*$_2$CHOH), 2.76-2.82 (m, 2H, C*H*$_2$N of morpholine), 3.74-3.84 (m, 4H, 2 C*H*$_2$O of morpholine), 4.96 (dd, 1H, *J* = 4.0, 10.0 Hz, C*H*OH), 7.46-7.49 (m, 3H, *H* of naphthyl), 7.80-7.88 (m, 4H, *H* of naphthyl); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 53.5 (2 *C*H_2N of morpholine), 66.5 (*C*H_2N), 66.9 (2 *C*H_2O of morpholine), 68.6 (*C*HOH), 123.8, 124.5, 125.6, 125.8, 127.6,127.8, 128.0, 132.9, 133.2, 139.0 (Ar)



(78c)

2-morpholin-4-yl-cyclohexanol (*trans*) (78c): orange oil, R_f = 0.21, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.07-1.27 (m, 4H, *H* of cyclohexanol), 1.64-1.69 (m, 1H, *H* of cyclohexanol), 1.73-1.82 (m, 2H, *H* of cyclohexanol), 2.05-2.10 (m, 1H, *H* of cyclohexanol), 2.16 (ddd, 1H, *J* = 3.2, 10.4, 10.8 Hz, C*H*N), 2.36-2.44 (m, 2H, C*H*$_2$N of morpholine), 2.66-2.73 (m, 2H, C*H*$_2$N of morpholine), 3.34 (ddd, 1H, *J* = 3.6, 10, 10.4 Hz, C*H*OH), 3.62-3.73 (m, 4H,2 C*H*$_2$O); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.2, 23.8, 25.3, 33.1 (*C* of cyclohexyl), 67.4 (2 *C*H_2N and *C*HN), 68.4 (*C*HOH), 70.4 (2*C*H_2O).

2.3.2 General procedure of reaction for synthesis of racemic vicinal amino alcohols from a variety of amines



(64) **(a-h,l)** **(79a-h, 65l)** **(80a-h, 66l)**

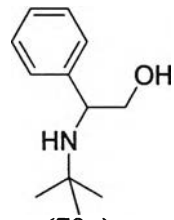
The racemic styrene oxide (0.5 mmol, 58.8 μL) and the amines (0.55 mmol, 1.25 mmol, or 2.5 mmol) depending on each type of amines were added to the solvent (1 mL) in a screw-capped test tube. The temperature during the addition of each solvent in all the reactions was done at room temperature except for HFIP which required an external cooling. After preparing for each experiment, all the test tubes must be heated at 60 °C in a heating block. All reactions were allowed to proceed for 3 h. The reactions with *tert*-butylamine and *p*-chloroaniline were also repeated with increasing the reaction time to overnight. The reaction mixtures were cooled and the crude ratio of isomers determined as described earlier. The isolated yields were determined gravimetrically after column chromatography.

Table 2.1. Elution system of chromatography for each amine

entry	amines	elution system
1	*tert*-butylamine **(a)**	gradient from 75/25 to 100% ethyl acetate/hexane[a]
2	Cyclohexylamine **(b)**	isocratic at 85/15 ethyl acetate/hexane[a]
3	Benzylamine **(c)**	gradient from 60/40 to 25/75 hexane/ethyl acetate[a]
4	*m*-chloroaniline **(d)**	isocratic at 90/10 hexane/ethyl acetate[a]

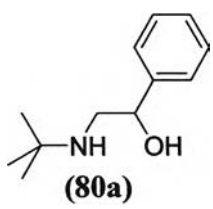
5	*N*-methyl aniline **(e)**	gradient from 93/7 to 80/20 hexane/ethyl acetate[a]
6	*N*-phenyl piperazine **(g)**	gradient from 80/20 to 50/50 hexane/ethyl acetate[a]
7	Morpholine **(l)**	gradient from 60/40 to 50/50 hexane/ethyl acetate[a]
8	Diethylamine **(h)**	gradient from 75/25 to 100 ethyl acetate/ hexane[a]
9	*p*-methoxyaniline **(f)**	gradient from 77/23 to 80/20 methylene chloride/hexane[b] and gradient from 90/10 to 80/20 hexane/ethyl acetate[c]

[a] by column chromatography; [b] by flash chromatography when the reaction was experimented in ethanol; [c] by column chromatography when the reaction was in trifluoroethanol



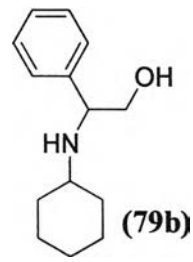
(79a)

2-*tert*-Butylamino-2-phenyl-ethanol (79a): yellow solid, mp. 61-62 °C,[44] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.05 (s, 9H, 3 C(C*H*$_3$)), 2.62 (bs, 2H, N*H* and O*H*), 3.30 (dd, 1H, *J* = 9.6, 10.0 Hz, C*H*H(OH)), 3.55 (dd, 1H, *J* = 4.4, 10.8 Hz, C*H*H(OH)), 3.87 (dd, 1H, *J* = 4.4, 9.6 Hz, C*H*Ar), 7.22-7.34 (m, 5H, Ar*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.3 (C(*C*H$_3$)$_3$), 51.5 (*C*(CH$_3$)$_3$), 58.7 (*C*HAr), 66.7 (*C*H$_2$OH), 126.7, 127.1, 128.5, 143.6 (Ar)



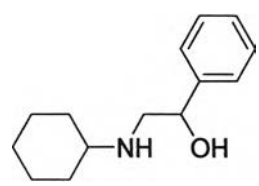
(80a)

2-*tert*-Butylamino-1-phenyl-ethanol (80a): yellow-white solid, mp. 86-87 °C,[44] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.1 (s, 9H, $3CH_3$), 2.64 (dd, 1H, J = 11.6 Hz C*H*H(NHC$(CH_3)_3$), 2.88 (dd, 1H, J = 3.2, 11.6 Hz, C*H*H(NHC$(CH_3)_3$), 3.30 (bs, 2H, N*H* and O*H*), 4.66 (dd, 1H, J = 3.2, 9.2 Hz, C*H*(OH)), 7.25-7.40 (m, 5H, Ar*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.5 (C($CH_3)_3$), 50.0 (CH_2(NHC$(CH_3)_3$), 50.5 ($C(CH_3)_3$), 72.0 (*C*HOH), 125.8, 127.3, 128.3, 142.9 (Ar)



(79b)

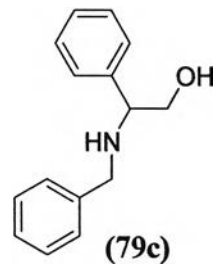
2-Cyclohexylamino-2-phenyl-ethanol (79b): yellow solid, mp. 106-108 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.75 (dd, 1H, J = 8.8, 11.6 Hz, C*H*H(NHCH_2Ph)), 2.90 (dd, 1H, J = 4, 11.6 Hz, C*H*H(NHCH_2Ph)), 2.92 (bs, 1H, N*H* or O*H*), 3.79 (d, 1H, J = 13.2 Hz, C*H*HPh), 3.84 (d, 1H, J = 13.6 Hz, C*H*HPh), 4.75 (dd, 1H, J = 4, 8.8 Hz, C*H*OH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 53.5 (CH_2(NHBn)), 56.5 (CH_2Ph), 71.8 (*C*HOH), 125.8, 127.1, 127.5, 128.1, 128.3, 128.5, 139.6, 142.5 (*C* of 2 Ar)



(80b)

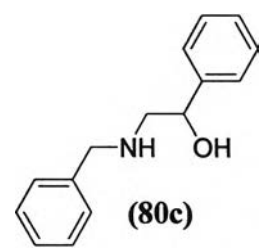
2-Cyclohexylamino-1-phenyl-ethanol (80b): yellow solid, mp. 68-70 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.10-1.25 (m, 5H, C*H* of cyclohexyl and N*H*), 1.56-1.62 (m, 1H, C*H* of cyclohexyl), 1.69-1.75 (m, 2H, C*H* of cyclohexyl), 1.89-1.97 (m, 3H, C*H* of cyclohexyl), 2.50-2.60 (m, 1H, C*H*NH of cyclohexyl), 2.76 (dd, 1H, J = 9.2, 11.6 Hz,

C*H*HNH), 2.95 (dd, 1H, *J* = 3.2, 11.6 Hz, C*H*HNH), 4.64 (bs, 2H, N*H* and O*H*), 4.81 (dd, 1H, *J* = 3.2, 9.6 Hz, C*H*OH, 7.22-7.38 (m, 5H, Ar*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.9, 25.7, 32.3, 32.5 (*C* of cyclohexyl), 53.7 (*C*H_2N), 56.9 (*C*HN), 71.2 (*C*HOH), 125.8, 127.5, 128.4, 142.5 (*C* of Ar)



(79c)

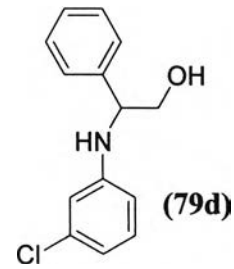
2-Benzylamino-2-phenyl-ethanol (79c): yellow oil, mp. 68-69 °C,[31] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.70 (bs, 2H, N*H* and O*H*), 3.57 (dd, 1H, *J* = 9.2, 10.4 Hz, C*H*HOH), 3.59 (d, 1H, *J* = 13.2 Hz, PhC*H*HNH), 3.70 (dd, 1H, *J* = 4.4, 11.2 Hz, C*H*HOH), 3.76 (d, 1H, *J* = 12.4 Hz, PhC*H*HNH), 3.83 (dd, 1H, *J* = 4 and 9.6 Hz, C*H*(Ph)CH_2OH), 7.24-7.40 (m, 10H, Ar*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 51.1 (*C*H_2(Ph)NH), 63.8 (*C*H(Ph)CH_2OH), 66.7 (*C*H_2OH), 127.2, 127.4, 127.7, 128.3, 128.5, 128.7, 139.8, 140.2 (C in 2 Ar)



(80c)

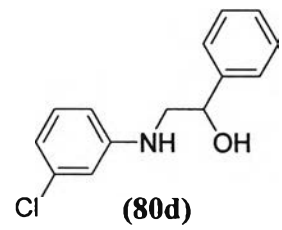
2-Benzylamino-2-phenyl-ethanol (80c): orange solid, mp. 114 °C,[81] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.75 (dd, 1H, *J* = 8.8, 11.6 Hz, C*H*H(NHCH_2Ph)), 2.90 (dd, 1H, *J* = 4, 11.6 Hz, C*H*H(NHCH_2Ph)), 2.92 (bs, 1H, N*H* or O*H*), 3.79 (d, 1H, *J* = 13.2 Hz, C*H*HPh), 3.84 (d, 1H, *J* = 13.6 Hz, C*H*HPh), 4.75 (dd, 1H, *J* = 4, 8.8 Hz, C*H*OH); ^{13}C

NMR ($CDCl_3$, 100 MHz) δ 53.5 (*C*H_2(NHBn)), 56.5 (*C*H_2Ph), 71.8 (*C*HOH), 125.8, 127.1, 127.5, 128.1, 128.3, 128.5, 139.6, 142.5 (C in 2 Ar)



(79d)

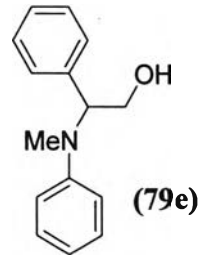
2-(3-Chloro-phenylamino)-2-phenyl-ethanol (79d): brown oil, R_f = 0.09, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.72 (dd, 1H, *J* = 7.2, 11.2 Hz, C*H*HOH), 3.90 (dd, 1H, *J* = 4.4, 11.2 Hz, C*H*HOH), 4.44 (dd, 1H, *J* = 4.4 and 7.2 Hz, C*H*Ph), 6.43 (dd, 1H, *J* = 1.6, 8.4 Hz, p-*H* to Cl of 3Cl-aniline), 6.57 (s, 1H, o-*H* to Cl of 3Cl-aniline), 6.67 (dd, 1H, *J* = 1.6, 8 Hz, p-*H* to NH of 3Cl-aniline), 7.01 (t, 1H, *J* = 8 Hz, m-*H* to NH of 3Cl-aniline), 7.28-7.38 (m, 5H, Ar*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 59.7 (*C*HPh), 67.1 (*C*H_2OH), 112.0 (*C*N of 3Cl-aniline), 113.6, 117.8, 126.6, 127.8, 128.9, 130.2, 134.8, 139.4 (C of 3Cl-aniline and Ar), 148.4 (*C*Cl of 3Cl-aniline)



(80d)

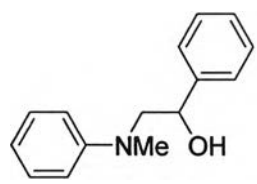
2-(3-Chloro-phenylamino)-1-phenyl-ethanol (80d): brown oil, R_f = 0.13, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.90 (bs, 2H, N*H* and O*H*), 3.29 (dd, 1H, *J* = 8.8, 13.2 Hz, C*H*HN), 3.39 (dd, 1H, *J* = 4, 13.2 Hz, C*H*HN), 4.93 (dd, 1H, *J* = 4, 8.8 Hz, C*H*OH), 6.55 (dd, 1H, *J* = 1.6, 8.8 Hz, p-*H* to Cl of 3Cl-aniline), 6.65 (s, 1H, o-*H* to Cl and NH of 3Cl-aniline), 6.71 (dd, 1H, *J* = 1.6, 8.8 Hz, p-*H* to NH of 3Cl-aniline), 7.08 (t, 1H, *J* = 8 Hz, m-*H* to NH of 3Cl-aniline), 7.32-7.41 (m, 5H, Ar*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 51.6

(CH_2N), 72.3 (CHOH), 111.9 (*C*N of 3Cl-aniline), 113.2, 118.1, 125.8, 128.2, 128.6, 130.2, 135.0 (C of 3Cl-aniline and Ar), 141.6 (*C*Cl of of 3Cl-aniline)



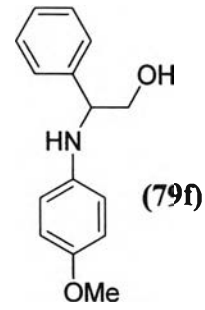
(79e)

2-(Methyl-phenyl-amino)-2-phenyl-ethanol (79e): blue oil, R_f = 0.33, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.73 (s, 3H, NC*H*$_3$), 4.09-4.18 (ABX, 2H, *J* = 5.2, 11.6 Hz, C*H*$_2$OH), 5.09 (dd, 1H, *J* = 6.4, 8.4 Hz, C*H*Ph), 6.82 (t, 1H, *J* = 7.6 Hz, *H* of NAr), 6.96 (d, 2H, *J* = 8.8 Hz, *H* of Ar), 7.26-7.34 (m, 7H, 2 Ar*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 32.4 (*C*H$_3$), 61.6 (*C*HN), 64.9 (*C*H$_2$OH), 115.0, 118.6, 127.2, 127.6, 128.4, 129.2, 137.3, 150.6 (*C* of 2 Ar)



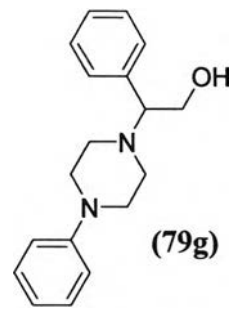
(80e)

2-(Methyl-phenyl-amino)-1-phenyl-ethanol (80e): blue oil, R_f = 0.26, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.71 (s, 3H, O*H*), 2.95 (s, 3H, NC*H*$_3$), 3.45 (dd, 1H, *J* = 3.6, 14.8 Hz, C*H*HN), 3.53 (dd, 1H, *J* = 8.4, 14.8 Hz, C*H*HN), 5.01 (dd, 1H, *J* = 3.6, 8.4 Hz, C*H*OH), 6.82 (t, 1H, *J* = 6.8 Hz, *H* of NAr), 6.90 (d, 2H, *J* = 7.6 Hz, *H* of Ph), 7.20-7.40 (m, 7H, 2 Ar*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 38.8 (*C*H$_3$), 62.1 (*C*H$_2$N), 71.6 (*C*H$_2$OH), 112.1, 114.2, 125.8, 127.8, 128.5, 129.3, 142.0, 149.5 (*C* of 2 Ar)



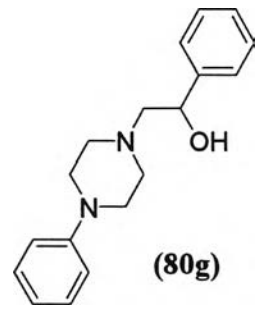
(79f)

2-(4-Methoxy-phenylamino)-2-phenyl-ethanol (79f): brown oil, R_f = 0.18, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.69 (s, 3H, OC*H*$_3$), 3.74 (dd, 1H, *J* = 3.2, 10.8 Hz, C*H*HOH), 6.82 (t, 1H, *J* = 7.6 Hz, *H* of NAr), 3.92 (dd, 1H, *J* = 4, 10.8 Hz, C*H*HOH), 4.43 (dd, 1H, *J* = 4, 6 Hz, C*H*Ph), 6.53-6.57 (AA'BB', 2H, *J* = 8.8 Hz, *H* of Anisidine), 6.68-6.72 (AA'BB', 2H, *J* = 8.8 Hz, *H* of Anisidine), 7.28-7.39 (m, 5H, Ar*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 55.5 (*C*HN), 61.9 (*C*H_2OH), 66.8 (OCH_3), 114.4, 115.0, 126.2, 127.3, 128.7 (*C* of 2 Ar)



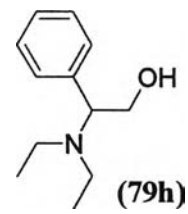
(79g)

2-Phenyl-2-(4-phenyl-piperazin-1-yl)-ethanol (79g): pink-white solid, mp. 110-112 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.55-2.60 (m, 2H, C*H*$_2$N of piperazine), 2.73-2.80 (m, 2H, C*H*$_2$N of piperazine), 3.11 (bs, 1H, O*H*), 3.16-3.26 (m, 4H, 2 C*H*$_2$NPh), 3.72-3.79 (AA'X, 2H, *J* = 5.6, 6 Hz, C*H*$_2$OH), 4.05 (dd, 1H, *J* = 8, 8.8 Hz, C*H*N), 6.85-6.92 (m, 3H, o- and p-*H* of N-Ph), 7.24-7.41 (m, 7H, Ar*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 49.3 and 49.5 (4 *C*H_2N of piperazine), 60.6 (*C*HN), 70.2 (*C*H_2OH), 116.1, 119.9, 128.0, 128.4, 128.9, 129.1, 135.6, 151.1 (*C* of 2 Ar)



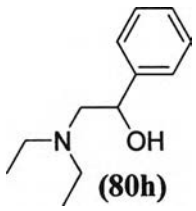
(80g)

1-Phenyl-2-(4-phenyl-piperazin-1-yl)-ethanol (80g): orange-white solid, mp. 110-111 °C,[82] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.59-2.62 (AA'X, 2H, J = 5.6 Hz, CH_2N), 2.64-2.70 (m, 2H, CH_2N of piperazine), 2.91-2.98 (m, 2H, CH_2N of piperazine), 3.22-3.33 (m, 4H, 2 CH_2NPh), 4.84 (dd, 1H, J = 4.8, 8.4 Hz, C*H*OH), 6.91 (t, 1H, p-*H* of N-Ph), 6.96 (d, 2H, o-*H* of N-Ph), 7.27-7.45 (m, 7H, Ar*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 49.2 and 53.1 (4 *C*H_2N of piperazine), 66.2 (*C*H_2N), 68.7 (*C*HOH), 116.2, 120.0, 125.8, 127.6, 128.4, 129.2, 141.8, 151.0 (*C* of 2 Ar)



(79h)

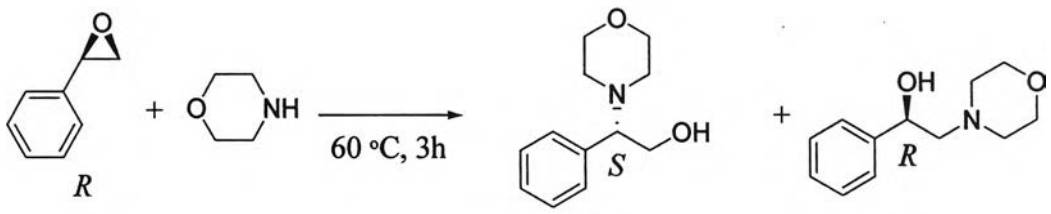
2-Diethylamino-2-phenyl-ethanol (79h): yellow oil, R_f = 0.16, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.08 (t, 1H, J = 7.2 Hz, 2 CH_3), 2.29 (dq, 2H, J = 6.8, 13.2 Hz, CH_2N of diethylamine), 2.75 (dq, 2H, J = 6.8, 13.2 Hz, CH_2N of diethylamine), 3.65 (dd, 1H, J = 3.2, 8.8 Hz, C*H*N), 3.91-3.99 (AA'X, 2H, J = 10.4, 21.6 Hz, CH_2OH), 7.19-7.36 (m, 5H, Ar*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.6 (2 *C*H_3), 43.2 (2 *C*H_2N of diethylamine), 60.4 (*C*HN), 64.5 (*C*H_2OH), 127.9, 128.3, 128.9, 177.7 (*C* of Ar)



(80h)

2-Diethylamino-1-phenyl-ethanol (80h): yellow oil, R_f = 0.09, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.08 (t, 1H, *J* = 6.8 Hz, 2 C*H*$_3$), 2.46 (dd, 2H, *J* = 10.8, 12.4 Hz, C*H*$_2$N), 2.55-2.66 (m, 3H, *J* = 3.2 Hz for C*H*$_2$N and *J* = 7.2 Hz for C*H*$_2$N of diethylamine), 2.75 (dq, 2H, *J* = 6.8, 13.2 Hz, C*H*$_2$N of diethylamine), 4.66 (dd, 1H, *J* = 3.2, 10.8 Hz, C*H*OH), 7.26-7.39 (m, 5H, Ar*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.8 (2 *C*H$_3$), 46.8 (2 *C*H$_2$N of diethylamine), 61.8 (*C*H$_2$N), 69.2 (*C*HOH), 125.8, 127.4, 128.3, 142.5 (*C* of Ar)

2.3.3 General procedure for stereospecific synthesis of optically active vicinal amino alcohols with different protic solvents



(62) **(81a)** **(81b)**

The optically active (*R*)-styrene oxide (0.5 mol, 58.4 μL) and the distilled morpholine (0.55 mmol, 49.0 μL) were added to the solvent (1 mL) in a screw-capped test tube. The temperature during the addition of each solvent in all the reactions was done at room temperature except for HFIP which required an external cooling. After preparing for each experiment, all the test tubes must be heated at 60 °C in a heating block. All reactions were allowed to proceed for 3 h. The reaction mixtures were cooled and the crude ratio of isomers determined as described earlier. The identity and purity of the products were determined by ^{1}H NMR. The isolated yields were obtained and

determined gravimetrically after column chromatography with a gradient of 60/40 hexane/ethyl acetate to 70/30 ethyl acetate/hexane. Both α and β pure regioisomers of each experiment were identified for % *ee* by chiral column chromatography. Chiral HPLC columns used for analysis of enantiomeric purity were Daicel ChiralCel OD® and ChiralPak AD®. The conditions of using chiral column chromatography to determine the *ee* of both pure α and β regioisomers were shown in Table 2.2. Racemic products of each α and β regioisomer had been identified for their retention time of (*R*) or (*S*) enantiomer by such conditions of this table before each pure α and β regioisomer was analyzed by the chiral HPLC.

Table 2.2. The conditions of chiral column chromatography for determining enantiomeric purity of pure α and β regioisomers

type of pure regioisomer	chiral HPLC column	conditions		
		mobile phase	flow rate (mL/min)	λ_{abs}(nm)
α	ChiralCel OD®	Hexane/*i*-PrOH (90/10)	0.5	205
β	ChiralPak AD®	Hexane/*i*-PrOH (90/10)	0.5	210