CHAPTER III

EXPERIMENTAL

3.1 General

Most chemicals and solvents were purchased from Aldrich, Fluka and J.T. Baker and were used as received. The progress of the synthetic reactions was followed by thin layer chromatography (TLC) on TLC aluminum sheets, silica gel F_{254} (Merck) and visualized under ultraviolet light at 254 nm. The alcohol products were purified by column chromatography, if necessary, and their structures were confirmed by ^{1}H-NMR spectroscopy (Varian Mercury Plus 400 at 400 MHz) using deuterated chloroform ($CDCl_3$, 99.8% D, Aldrich) as solvent.

All chromatographic separations were performed on an Agilent 6890 gas chromatograph (Agilent Technologies), equipped with a split/splitless injector and a flame ionization detector (FID). Gas chromatographic columns were 15 m long, 0.25 mm i.d. deactivated fused-silica capillary tubing (J&W Scientific). Analyte solutions were injected with a microsyringe (SGE) through a Microseal septum (Merlin Instrument Company).

3.2 Syntheses of racemic alcohols

Most of alcohol racemates used in this study were prepared from their corresponding ketones by sodium borohydride reduction in ethanol. Some chiral alcohols were acquired from previous synthesis by Iamsam-ang [27] and some were obtained commercially. Chiral alcohols and ketones used in this work are:

alcohols:

- 4-bromo-α-methylbenzyl alcohol (or 1-(4-bromophenyl)ethanol), 97% (Aldrich)
- 1-(4-chlorophenyl)ethanol, 98% (Aldrich)
- 1-cyclohexylethanol, 97% (Fluka)
- 2,6-difluoro-α-methylbenzyl alcohol (or 1-(2,6-difluorophenyl) ethanol), 97% (Aldrich)
- 2,2-dimethyl-1-phenyl-1-propanol, 99% (Aldrich)

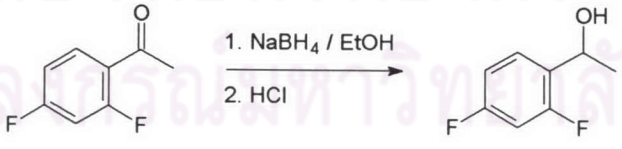
- α-ethylphenethyl alcohol (or 1-phenyl-2-butanol), 97% (Aldrich)
- β-ethylphenethyl alcohol (or 2-phenyl-1-butanol), 98% (Aldrich)
- 4-fluoro-α-methylbenzyl alcohol (or 1-(4-fluorophenyl)ethanol), 99% (Aldrich)
- indanol (or 1-indanol), ≥ 98% (Fluka)
- α-methyl-2-naphthalenemethanol (or 1-(2-naphthyl)ethanol), 98% (Aldrich)
- α-methyl-4-(trifluoromethyl)benzyl alcohol (or 1-(4-trifluoromethylphenyl)ethanol), 90% (Aldrich)
- 2-octanol, ≥ 96% (Fluka)
- 3-octanol, ≥ 95% (Fluka)
- 4-octanol, ≥ 98% (Fluka)
- 1-(pentafluorophenyl)ethanol, 97% (Fluka)
- 2-phenyl-2-butanol, 99% (Aldrich)
- 3-phenyl-1-butanol, 99% (Aldrich)
- (±)-1-phenylethanol, ≥ 98% (Fluka)
- 1-phenyl-1-propanol, 99% (Aldrich)
- 1-phenyl-2-propanol, 98% (Aldrich)
- 2-phenyl-1-propanol, 97% (Aldrich)
- 1,2,3,4-tetrahydro-1-naphthol, 97% (Aldrich)
- α-(trifluoromethyl)benzyl alcohol (or 2,2,2-trifluoro-1-phenylethanol), 98% (Aldrich)

ketones:

- 1-acetonaphthone, ≥ 96% (Fluka)
- benzylacetone, 96% (Fluka)
- 4-butylacetophenone, 95% (Aldrich)
- butyrophenone, ≥ 99% (Aldrich)
- deoxybenzoin, ≥ 98% (Fluka)
- 2,4-dichloroacetophenone, 96% (Fluka)
- 2,5-dichloroacetophenone, 98% (Aldrich)
- 3,4-dichloroacetophenone, 99% (Aldrich)

- 2,4-difluoroacetophenone, 98% (Aldrich)
- 2,5-difluoroacetophenone, 98% (Aldrich)
- 3,4-difluoroacetophenone, 97% (Aldrich)
- 3,5-difluoroacetophenone, 97% (Aldrich)
- 2,4-dimethylacetophenone, 96% (Aldrich)
- 2,5-dimethylacetophenone, ≥ 97% (Fluka)
- 3,4-dimethylacetophenone, 98% (Aldrich)
- 4-ethylacetophenone, 97% (Aldrich)
- hexanophenone, 99% (Aldrich)
- isobutyrophenone, ≥ 97% (Fluka)
- 4-methylacetophenone, 95% (Fluka)
- 4-methylpropiophenone, 90% (Aldrich)
- 4-*tert*-butylacetophenone, 97% (Aldrich)
- 2,3,4,5-tetrafluoroacetophenone, 99% (Aldrich)
- β-tetralone, 98% (Aldrich)
- 2,4,5-trifluoroacetophenone, 99% (Aldrich)
- 2-(trifluoromethyl)acetophenone, 99% (Aldrich)
- 3-(trifluoromethyl)acetophenone, 99% (Aldrich)
- 4-(trifluoromethoxy)acetophenone, 98% (Aldrich)
- 1,1,1-trifluoro-3-phenyl-2-propanone, 96% (Aldrich)

The example of synthesis procedures of 1-(2,4-difluorophenyl)ethanol is described as follow.

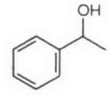
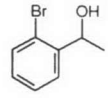
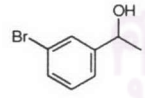
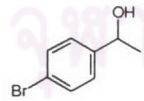
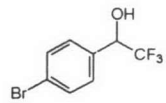
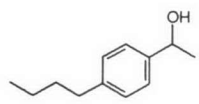


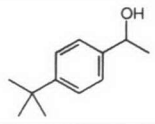
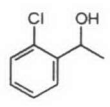
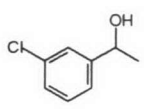
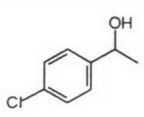
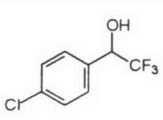
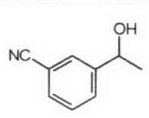
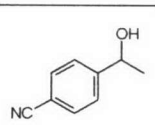
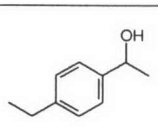
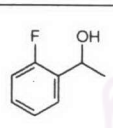
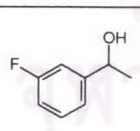
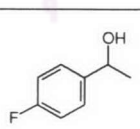
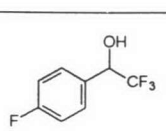
*1-(2,4-difluorophenyl)ethanol (**24F**)*: 2,4-Difluoroacetophenone (0.306 g, 2 mmol) and sodium borohydride ($NaBH_4$, 0.068 g, 1.8 mmol) were dissolved in 3-5 mL absolute ethanol. The mixture was refluxed for 3 hours before cooling down. The solvent was then removed by rotary evaporator to obtain viscous liquid with white precipitate. The liquid and precipitate wre redissolved in 2 M hydrochloric acid. Then the aqueous phase was extracted with dichloromethane. All organic layers were

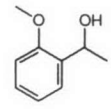
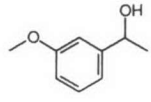
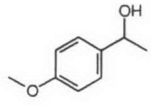
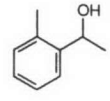
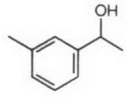
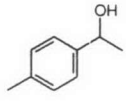
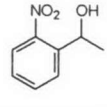
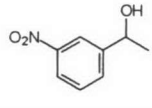
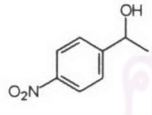
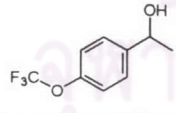
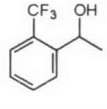
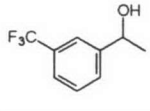
combined, dried with anhydrous sodium sulfate, and concentrated, yielding a colorless liquid of 1-(2,4-difluorophenyl)ethanol (**24F**) (0.247 g, 80.9%); $R_f = 0.22$ (dichloromethane-hexane 5:1); ^1H NMR ($CDCl_3$, 400 MHz): δ 1.54 (3H, d, $CHC\underline{H}_3$), 1.88 (1H, s, CHO<u>H</u>), 5.20 (1H, q, C<u>H</u>OH), 6.80 (1H, t, Ar<u>H</u>), 6.94 (1H, t, Ar<u>H</u>), 7.50 (1H, q, Ar<u>H</u>).

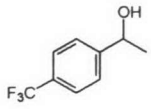
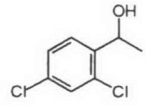
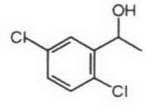
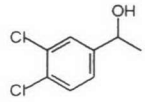
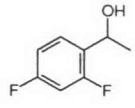
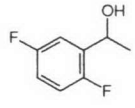
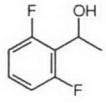
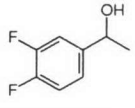
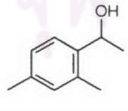
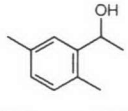
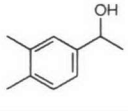
Other alcohols were synthesized with similar procedure. Further purification by column chromatography may be needed for some compounds. The yield of all synthesized alcohols was greater than 70%, except for **24Me**, **34Me** and **11** were obtained in 30-50%. The structures, abbreviations, and compound names for all alcohols used in this study are shown in table 3.1.

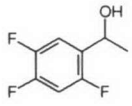
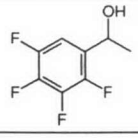
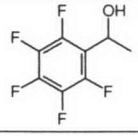
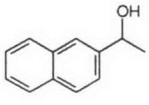
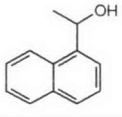
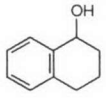
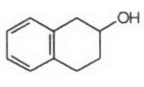
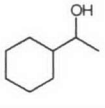
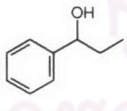
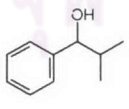
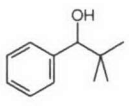
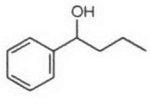
Table 3.1 Structure and abbreviation of all alcohol derivatives used in this study

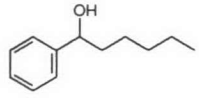
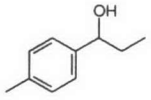
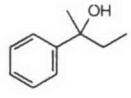
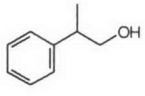
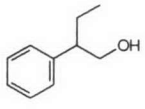
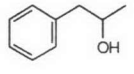
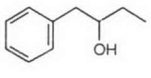
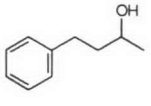
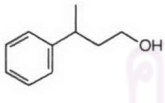
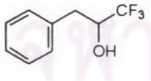
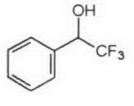
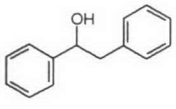
structure	abbreviation	compound
	**1**	1-phenylethanol (reference compound)
1-Phenylethanols with monosubstitution on aromatic ring		
	**2Br**	1-(2-bromophenyl)ethanol
	**3Br**	1-(3-bromophenyl)ethanol
	**4Br**	1-(4-bromophenyl)ethanol
	**F4Br**	2,2,2- trifluoro-1-(4-bromophenyl)ethanol
	**4Bu**	1-(4-butylphenyl)ethanol

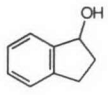
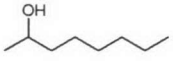
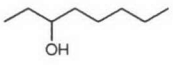
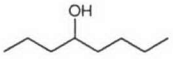
structure	abbreviation	compound
	**4tBu**	1-(4-*tert*-butylphenyl)ethanol
	**2Cl**	1-(2-chlorophenyl)ethanol
	**3Cl**	1-(3-chlorophenyl)ethanol
	**4Cl**	1-(4-chlorophenyl)ethanol
	**F4Cl**	2,2,2-trifluoro-1-(4-chlorophenyl)ethanol
	**3CN**	1-(3-cyanophenyl)ethanol
	**4CN**	1-(4-cyanophenyl)ethanol
	**4Et**	1-(4-ethylphenyl)ethanol
	**2F**	1-(2-fluorophenyl)ethanol
	**3F**	1-(3-fluorophenyl)ethanol
	**4F**	1-(4-fluorophenyl)ethanol
	**F4F**	2,2,2-trifluoro-1-(4-fluorophenyl)ethanol

structure	abbreviation	compound
	**2OMe**	1-(2-methoxyphenyl)ethanol
	**3OMe**	1-(3-methoxyphenyl)ethanol
	**4OMe**	1-(4-methoxyphenyl)ethanol
	**2Me**	1-(2-methylphenyl)ethanol
	**3Me**	1-(3-methylphenyl)ethanol
	**4Me**	1-(4-methylphenyl)ethanol
	**$2NO_2$**	1-(2-nitrophenyl)ethanol
	**$3NO_2$**	1-(3-nitrophenyl)ethanol
	**$4NO_2$**	1-(4-nitrophenyl)ethanol
	**$4OCF_3$**	1-(4-trifluoromethoxyphenyl)ethanol
	**$2CF_3$**	1-(2-trifluoromethylphenyl)ethanol
	**$3CF_3$**	1-(3-trifluoromethylphenyl)ethanol

structure	abbreviation	compound
	**4CF$_3$**	1-(4-trifluoromethylphenyl)ethanol
1-Phenylethanols with disubstitution on aromatic ring		
	**24Cl**	1-(2,4-dichlorophenyl)ethanol
	**25Cl**	1-(2,5-dichlorophenyl)ethanol
	**34Cl**	1-(3,4-dichlorophenyl)ethanol
	**24F**	1-(2,4-difluorophenyl)ethanol
	**25F**	1-(2,5-difluorophenyl)ethanol
	**26F**	1-(2,6-difluorophenyl)ethanol
	**34F**	1-(3,4-difluorophenyl)ethanol
	**35F**	1-(3,5-difluorophenyl)ethanol
	**24Me**	1-(2,4-dimethylphenyl)ethanol
	**25Me**	1-(2,5-dimethylphenyl)ethanol
	**34Me**	1-(3,4-dimethylphenyl)ethanol

structure	abbreviation	compound
Other alcohols		
	**triF**	1-(2,4,5-trifluorophenyl)ethanol
	**tetraF**	1-(2,3,4,5-tetrafluorophenyl)ethanol
	**pentaF**	1-(pentafluorophenyl)ethanol
	**2**	1-(2-naphthyl)ethanol
	**3**	1-(1-naphthyl)ethanol
	**4**	1,2,3,4-tetrahydro-1-naphthol
	**5**	1,2,3,4-tetrahydro-2-naphthol
	**6**	1-cyclohexylethanol
	**7**	1-phenyl-1-propanol
	**8**	2-methyl-1-phenyl-1-propanol
	**9**	2,2-dimethyl-1-phenyl-1-propanol
	**10**	1-phenyl-1-butanol

structure	abbreviation	compound
	**11**	1-phenyl-1-hexanol
	**12**	1-(4-methylphenyl)propanol
	**13**	2-phenyl-2-butanol
	**14**	2-phenyl-1-propanol
	**15**	2-phenyl-1-butanol
	**16**	1-phenyl-2-propanol
	**17**	1-phenyl-2-butanol
	**18**	4-phenyl-2-butanol
	**19**	3-phenyl-1-butanol
	**20**	1,1,1-trifluoro-3-phenyl-2-propanol
	**21**	2,2,2-trifluoro-1-phenylethanol
	**22**	1,2-diphenylethanol

structure	abbreviation	compound
	**23**	1-indanol
	**2oct**	2-octanol
	**3oct**	3-octanol
	**4oct**	4-octanol

3.3 Preparation of capillary columns

Capillary gas chromatographic columns were prepared by statically coating [28] deactivated fused silica tubing (15 m × 0.25 mm i.d., J&W Scientific) with stationary phase solution in dichloromethane (0.4% w/v) to obtain 0.25 μm film thickness. Two beta-cyclodextrin derivatives used in this study were received from Professor Gyula Vigh (Texas A & M University). Two chiral columns were prepared and contained identical derivatized cyclodextrin concentration of 0.20 molal in polysiloxane OV-1701. All columns were conditioned at 200-230°C until a stable baseline was observed and the performance of each column was determined by means of Grob test [29-30]. Three types of stationary phases used in this study are:

- polysiloxane OV-1701 (7% phenyl, 7% cyanopropyl, 86% dimethyl polysiloxane, Supelco) was used as reference stationary phase and as diluent for the two solid cyclodextrin derivatives
- 30.0% heptakis(2,3-di-*O*-methyl-6-*O*-*tert*-butyldimethylsilyl)cyclomalto-heptaose (or BSiMe) in OV-1701
- 32.8% octakis(2,3-di-*O*-methyl-6-*O*-*tert*-butyldimethylsilyl)cyclomalto-octaose (or GSiMe) in OV-1701

3.4 Gas chromatographic analyses

The average linear velocity of hydrogen carrier gas was adjusted to 50 cm/sec. A split injector with 100:1 split ratio and flame ionization detector were maintained at 250 °C. Each alcohol derivative was dissolved in acetone to obtain a concentration of ~10-20 mg/mL. Approximately 0.1-0.5 μL of solution was injected. Column efficiency was checked regularly in the temperature range of 160-200 °C with *n*-alkanes (retention factor, $k' \geq 5$; efficiency > 3000 plates/m). In addition, enantioselectivity values of the two chiral columns were checked with represented compounds to verify their performance.

Thermodynamic measurements were performed isothermally in a temperature range of 60-230°C with 10-20 °C intervals. Each sample solution was injected at least in duplicate on three columns. Retention factors and enantioselectivities of all analytes were calculated from obtained chromatograms. Thermodynamic parameters were determined by means of van't Hoff approach.