CHAPTER II
EXPERIMENTAL

2.1 General

All reactions were performed in oven-dried glasswares. The weight of all chemical substances was determined on a Mettler AE200 electrical balance. Melting points were recorded on a Fisher-Johns melting point apparatus and were uncorrected. Evaporation of solvents was carried out on a Büchi Rotavapor R-114 equipped with a Büchi B-480 Waterbath. The progress of the reactions was followed by Thin Layer Chromatography (TLC) performed on Merck D.C. silica gel 60 F_{254} 0.2 mm precoated aluminium plates and visualized using either UV light (254 nm), iodine, or 2,4-DNP reagent. Column chromatography was performed on 230-400 mesh silica gel for flash column chromatography or activated neutral aluminium oxide 90 (Activity I).

Normal phase high performance liquid chromatography (HPLC) experiments were performed on a Gilson HPLC system equipped with an 803C manometric module, a 303 pump and a 112 uv/vis detector. A Daicel Chiralcel OD® column (cellulose tris(3,5-dimethylphenyl carbamate) on a 10 μm silica gel substrate, 250 mm × 4.6 mm) was used in attempts for the separation of enantiomers. Gas chromatographic (GC) experiments were performed on a Shimadzu GC-14B gas chromatograph equipped with a flame ionization detector (FID) (model c-R8A chromatopac shimadzu) using a 30 m×0.25 μm DB™-1(100% dimethylpolysiloxane) capillary column.

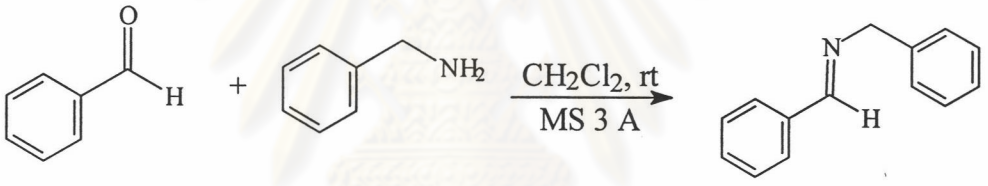
IR spectra were recorded on a Nicolet Impact 410 Fourier Transform Infrared Spectrometer. Proton (^{1}H) and carbon (^{13}C) nuclear magnetic resonance (NMR) spectra were recorded on a Bruker ACF200 spectrometer operating at 200 MHz (^{1}H) and 50 MHz (^{13}C) in $CDCl_3$ (unless otherwise stated). Chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane (TMS) or using the residual protonated solvent signal as a reference. Coupling constants (*J*) are proton-proton coupling unless otherwise noted and are reported in Hertz (Hz).

2.2 Materials

All chemicals were purchased from Fluka, Merck or Aldrich Chemicals Co., Ltd. and were used as received without further purification. Commercial grade solvents for column chromatography were distilled before use. Solvents for reactions were AR grade and dried with activated 3 Å molecular sieves. HPLC grade hexanes and 2-propanol for HPLC experiments on a chiral column, obtained from J.T. Baker and Merck, respectively, were filtered through a membrane filter (0.5 μm Millipore®-FH) before use. Each sample was filtered through a Millex®-HV syringe filter unit prior to injection on to the chromatograph. High purity nitrogen gas, hydrogen gas, and air for GC experiments were obtained from TIG.

2.3 Synthesis of imines

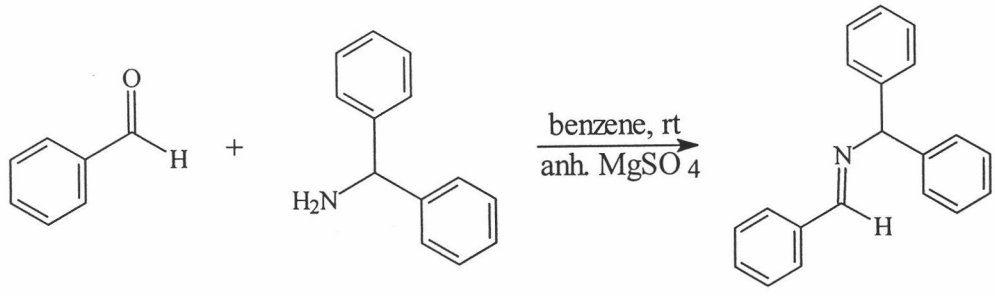
2.3.1 Synthesis of *N*-Benzylidene benzylamine (42)



42

Imine **42** was prepared according to the method by Jacobsen *et al.*[30] To a 25 mL round bottom flask was added activated 3 Å molecular sieves and 5 mL dichloromethane. To this solution, benzylamine (0.55 mL, 5 mmol) was added followed by slow syringe addition of benzaldehyde (0.51 mL, 5 mmol). When the starting materials disappeared, the sieves were removed by filtration. The sieves were washed with dichloromethane, the filtrate collected and the solvent removed *in vacuo* to obtain the desired product (**42**) as a yellow oil (1.85 g, 94.7%). ^{1}H NMR ($CDCl_3$, 200 MHz); δ 4.87 (2H, s, C$\underline{H}_2$Ph), 7.27-7.49 (8H, m, Ar), 7.81-7.86 (2H, m, Ar), 8.41 (1H, s, $\underline{H}$C=N); ^{13}C NMR ($CDCl_3$, 50 MHz); δ 65.1 (C$\underline{H}_2$Ph), 127.1, 128.0, 128.4, 128.6, 128.7, 130.8, 136.2, 139.4 (Ar), 162.0 (H$\underline{C}$=N).

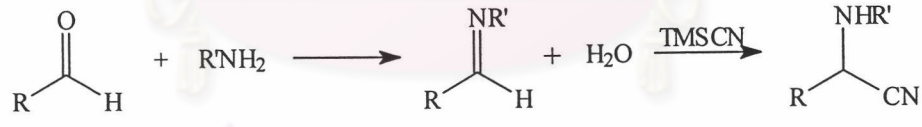
2.3.2 Synthesis of *N*-Benzylidene benzhydrylamine (24a)



24a

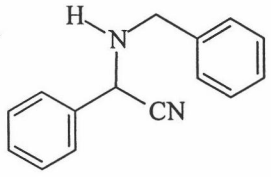
Imine **24a** was synthesized according to the procedure by Krueger *et al.*[31] Benzaldehyde (0.51 mL, 5 mmoL) was added to a solution of *N*-benzhydrylamine (0.86 mL, 5 mmol) in benzene (5 mL) in the presence of anhydrous magnesium sulfate at room temperature and stirred for 8 h. The filtrate was collected and the solvent was removed *in vacuo* to afford the product (**24a**) as a white crystalline solid (1.30 g, 95.7%) (mp 83-85 °C). ^{1}H NMR ($CDCl_3$, 200 MHz); δ 5.64 (1H, s, $\underline{H}CPh_2$), 7.20-7.41 (13H, m, Ar), 7.81-7.91 (2H, m, Ar), 8.46 (1H, s, $\underline{H}C{=}N$); ^{13}C NMR ($CDCl_3$, 50 MHz); δ 78.0 ($\underline{C}HPh_2$), 127.1, 127.7, 128.5, 128.6, 130.8, 136.3, 143.9 (Ar), 160.9 ($H\underline{C}{=}N$).

2.4 General procedure for the preparation of racemic 2-aminonitriles



An equimolar amount of an aldehyde was added to a solution of an amine in a solvent at room temperature to afford the Schiff base. After stirring until starting material disappeared, trimethylsilyl cyanide (1.5-2 eq) was added. The reaction was complete quite rapidly instantly and the desired product was obtained. Using this method, the following compounds were prepared.

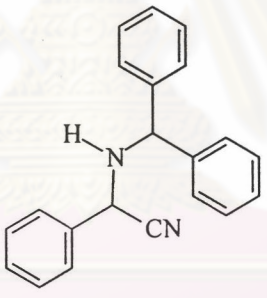
2.4.1 (*R*,*S*)-2-Benzylamino-2-phenylacetonitrile (43)



43

The reaction of benzaldehyde (254 μL, 2.5 mmol), benzylamine (273 μL, 2.5 mmol), and TMSCN (626 μL, 5 mmol) in chloroform resulted in the title compound as a yellow oil in quantitative yield (lit.[41] mp 30-32 °C); ^{1}H NMR ($CDCl_3$, 200 MHz); δ 1.86 (1H, br, NH), 4.01 (2H, AB-q, J = 13.0 Hz, CH_2Ph), 4.75 (1H, s, CH), 7.29-7.57 (10H, m, Ar); ^{13}C NMR ($CDCl_3$, 50 MHz); δ 51.3, 53.5 (CH_2, CH), 118.8 (CN), 127.3, 127.7, 128.4, 128.7, 129.0, 129.1, 134.8, 138.1 (Ar).

2.4.2 (*R*,*S*)-2-Benzhydrylamino-2-phenylacetonitrile (25a)

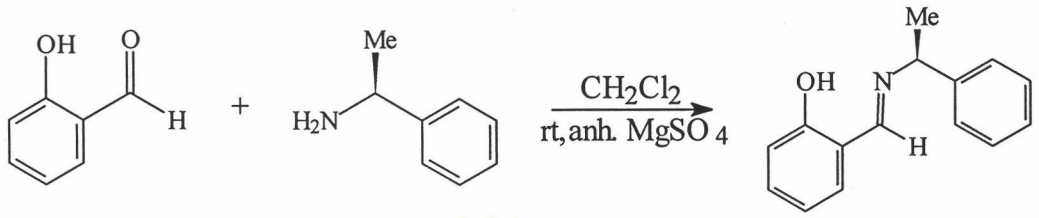


25a

The reaction of benzaldehyde (0.51 mL, 5 mmol), aminodiphenylmethane (0.86 mL, 5 mmol), and TMSCN (1.25 mL, 10 mmol) in toluene yielded a light yellow oil. Hexanes/ethyl acetate was added with stirring to afford yellow precipitates that could be further purified by silica gel chromatography (1% ethyl acetate-hexanes) to give a white solid (mp 85-86 °C). ^{1}H NMR ($CDCl_3$, 200 MHz); δ 2.14 (1H, d, J = 12.0 Hz, NH), 4.59 (1H, d, J = 12.0 Hz, HC-CN), 5.24 (1H, s, $HCPh_2$), 7.20-7.59 (15H, several m, Ar); ^{13}C NMR ($CDCl_3$, 50 MHz); δ 52.4, 65.6 (CH), 118.8 (CN), 127.1, 127.2, 127.5, 127.7, 127.9, 128.8, 129.0, 134.9, 141.1, 142.7 (Ar).

2.5 Synthesis of catalysts

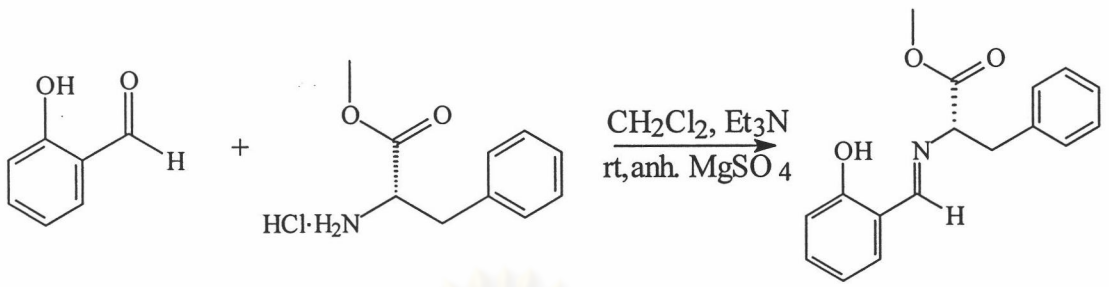
2.5.1 Synthesis of (*S*)-*N*-Salicylidene-1-phenylethylamine (48)



48

To a 25 mL round bottom flask equipped with a magnetic bar was added a solution of (*S*)-α-methylbenzylamine (1.27 mL, 10 mmol) in dichloromethane (10 mL). Salicylaldehyde (1.05 mL, 10 mmol) was added to the solution followed by an addition of anhydrous magnesium sulfate. The mixture was stirred at room temperature until the reaction was complete. After filtration, the solvent was removed by distillation at reduced pressure to give a yellow crystalline product (**48**) in quantitative yield (mp 62-63 °C). ^{1}H NMR ($CDCl_3$, 200 MHz); δ 1.64 (3H, d, J = 6.7 Hz, CH-C<u>H</u>$_3$), 4.55 (1H, q, J = 6.7 Hz, C<u>H</u>-CH$_3$), 6.84-7.00 (2H, m, Ar), 7.22-7.40 (7H, m, Ar), 8.41 (1H, s, <u>H</u>C=N); ^{13}C NMR ($CDCl_3$, 50 MHz); δ 25.0 (CH-<u>C</u>H$_3$), 68.6 (<u>C</u>H-CH$_3$), 117.0, 118.7, 118.9, 126.4, 127.3, 128.7, 131.4, 132.3, 143.9 (Ar), 161.1 (<u>C</u>-OH), 163.5 (H<u>C</u>=N); IR (KBr)/cm^{-1}; ν 3603-3300, 3058, 2980, 2879, 1633, 1575, 1498, 1459, 1382, 1280, 1087.

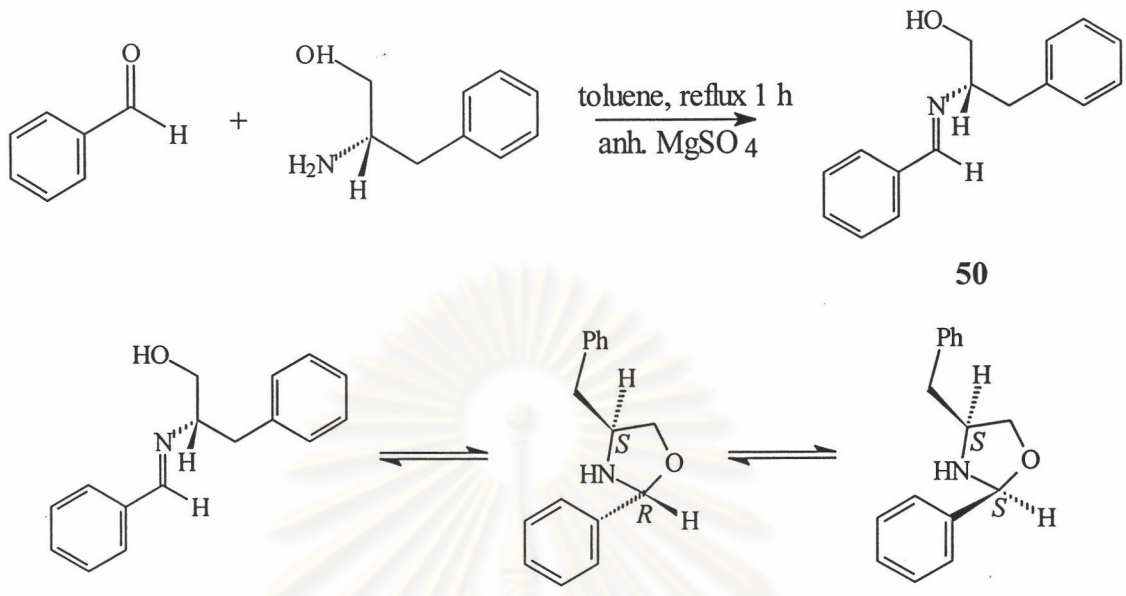
2.5.2 Synthesis of 2-[Salicylidene-amino]-3-phenylpropionic acid methyl ester (49)



49

Salicylaldehyde (1.05 mL, 10 mmol) was added to the suspension of L-phenylalanine methyl ester hydrochloride (2.16 g, 10 mmol), anhydrous magnesium sulfate in dichloromethane (10 mL) followed by triethylamine (1.39 mL, 10 mmol) while stirring at room temperature. Stirring was continued until the starting material disappeared and the mixture was then filtered. The filtrate was washed with water and dried with sodium sulfate. The solvent was evaporated *in vacuo* to give a viscous yellow oil (1.89 g, 66.7%). ^{1}H NMR ($CDCl_3$, 200 MHz); δ 3.26 (2H, ABX system, J_{AB} = 13.6, J_{AX} = 4.7, J_{BX} = 9.0 Hz, CH-C$\underline{H}_2$Ph), 3.74 (3H, s, OC$\underline{H}_3$), 4.16 (1H, ABX system, J_{AX} = 4.7, C$\underline{H}$-CH_2Ph), 6.82-6.98 (2H, m, Ar), 7.06-7.31 (7H, m, Ar), 7.96 (1H, s, $\underline{H}$C=N); ^{13}C NMR ($CDCl_3$, 50 MHz); δ 40.0 (CH-$\underline{C}H_2$), 52.5 (O$\underline{C}H_3$), 73.1 ($\underline{C}$H-CH_2), 117.1, 118.4, 118.7, 126.9, 128.6, 129.6, 131.8, 132.8, 136.7 (Ar), 160.9 ($\underline{C}$-OH), 167.0 (H$\underline{C}$=N), 171.3 ($\underline{C}$OOCH$_3$).

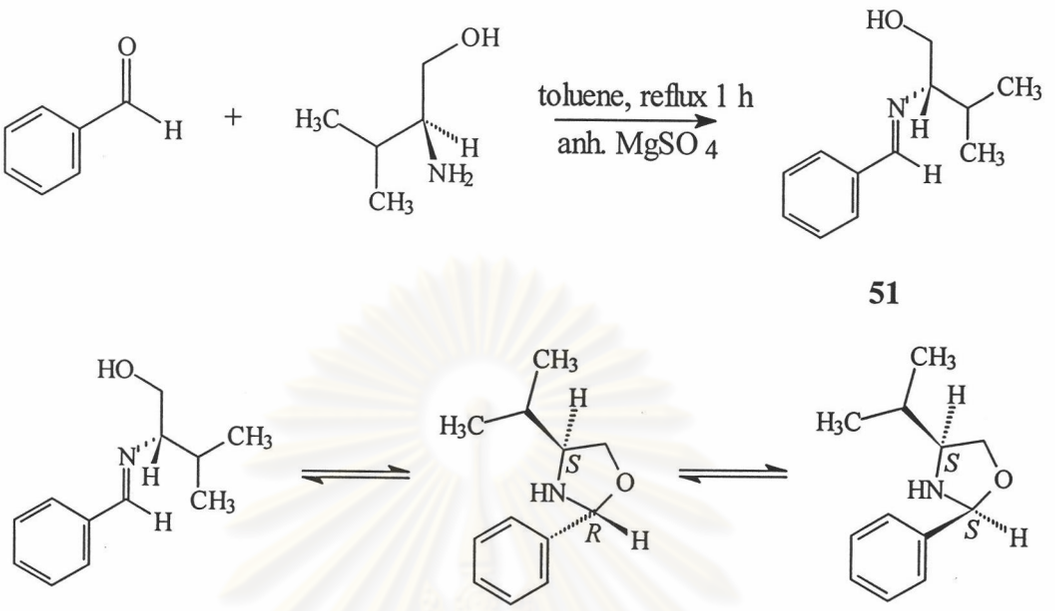
2.5.3 Synthesis of (*E*)-(2*S*)-(−)-2-Benzylidenamino-3-phenyl-1-propanol (50)



50

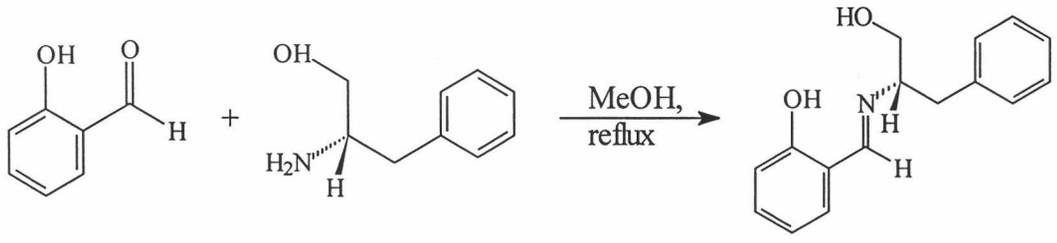
Ligand **50** was prepared according to the method by Aitken *et al.*[42] with a slight modification. Benzaldehyde (102 μL, 1 mmol) was added into a stirred mixture of (*S*)-2-amino-3-phenyl-1-propanol (L-phenylalaninol) (0.15 g, 1 mmol) and anhydrous magnesium sulfate in toluene (2 mL). The mixture was heated under reflux for 1 h and then filtered. The solvent was evaporated under reduced pressure. Evaporation yielded the product which was recrystallized from hexanes to give colorless needles (0.21 g, 85.7%) (mp 71-72 °C). ^{1}H NMR ($CDCl_3$, 200 MHz); δ 2.63 (1H, br, -OH), 2.90 (2H, m, CH_2Ph), 3.55 (1H, m, CH), 3.85 (2H, m, CH_2OH), 5.45 (s, oxazolidine)[43], 5.60 (s, oxazolidine), 7.12-7.26 (5H, m, Ar), 7.34-7.45 (3H, m, Ar), 7.56-7.60 (2H, m, Ar), 7.90 (1H, s, HC=N); ^{13}C NMR ($CDCl_3$, 50 MHz); δ 39.0 (CH_2), 65.9 (CH_2), 74.3 (CH–N=), 92.0 (oxazolidine), 93.5 (oxazolidine), 126.2, 128.3, 128.5, 129.7, 130.8, 135.7, 138.6 (Ar), 162.6 (HC=N); IR (KBr)/cm^{-1}; ν 3468-3115, 3056, 3027, 2916, 2863, 1644, 1499, 1451, 1412, 1156, 1054.

2.5.4 Synthesis of (*E*)-(2*S*)-(−)-*N*-(2-Hydroxy-1-isopropylethyl) benzylideneamine (51)



Ligand **51** was obtained from a procedure by Aitken *et al.*[42] and Takahashi *et al.*[44] with a minor modification. A mixture of (*S*)-2-amino-3-methyl-1-butanol (L-valinol) (0.11 g, 1.1 mmol) and anhydrous magnesium sulfate in toluene (2 mL) was added with benzaldehyde (113 μL, 1.1 mmol). The mixture was heated under reflux for 1 h. Magnesium sulfate was removed by filtration and the filtrate washed with toluene. The filtrate was concentrated under reduced pressure and the residue was allowed to stand at room temperature to give crystals of **51**. Recrystallization from *n*-pentane gave colorless prisms (0.18 g, 86.3%) (mp 58-59 °C). ^{1}H NMR ($CDCl_3$, 200 MHz); δ 0.85 (3H, d, J = 6.7 Hz, CH-C$\underline{H}_3$), 0.93 (3H, d, J = 6.7 Hz, CH-C$\underline{H}_3$) 1.03 (oxazolidine), 1.62 (m, oxazolidine), 1.93 (1H, octet, J = 6.8 Hz, C$\underline{H}$-$(CH_3)_2$), 2.27 (br), 2.89-3.20 (1H, m, $\underline{H}$CN=), 3.42-3.50 (m, oxazolidine), 3.71-3.89 (2$\underline{H}$, m, C$\underline{H}_2$OH), 3.96-4.05 (m, oxazolidine), 5.42 (s, oxazolidine),[43] 5.45 (s, oxazolidine), 7.28-7.50 (m, Ar), 7.65-7.69 (m, Ar), 8.19 (1H, s, $\underline{H}$C=N); ^{13}C NMR ($CDCl_3$, 50 MHz); δ 19.6 (CH-$\underline{C}H_3$), 19.8 (CH-$\underline{C}H_3$), 20.0, 20.6, 30.2 ($\underline{C}$H), 32.1, 32.3, 64.7, 64.9 ($\underline{C}H_2$OH), 66.7, 70.0, 70.5, 79.6 ($\underline{C}$H), 92.6 (oxazolidine), 93.8 (oxazolidine), 126.9, 127.0, 129.0, 129.2, 129.3, 129.4, 131.5, 136.8 (Ar), 163.1 (H$\underline{C}$=N); IR (KBr)/cm^{-1}; ν 3506-3110, 3061, 2974, 2926, 2868, 1639, 1581, 1470, 1354, 1223, 1054, 1030.

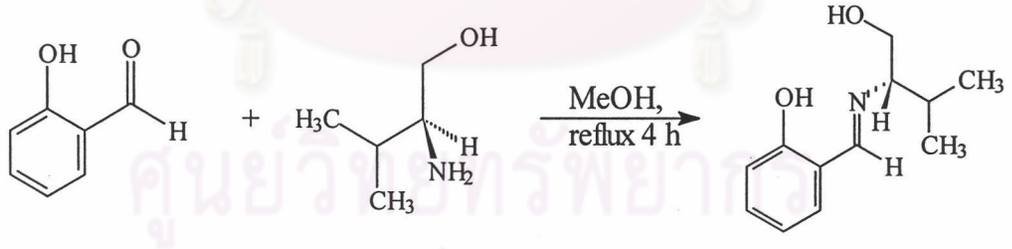
2.5.5 Synthesis of (*S*)-2-(*N*-Salicylideneamino)-3-phenyl-1-propanol (52)



52

A mixture of methanol (1 mL), L-phenylalaninol (0.032 g, 0.21 mmol), and salicylaldehyde (22 μL, 0.21 mmol) was refluxed until the starting materials was totally consumed. After solvent removal, **52** was obtained as a viscous yellow oil in quantitative yield and slowly crystallized on standing (mp 53-55 °C). ^{1}H NMR ($CDCl_3$, 200 MHz); δ 2.90 (2H, ABX system, J_{AB} = 13.6, J_{AX} = 4.8, J_{BX} = 8.3 Hz, C$\underline{H}_2$Ph), 3.48 (1H, AB$\underline{X}$, m, C$\underline{H}$), 3.75 (2H, m, C$\underline{H}_2$OH), 6.80-6.95 (2H, m, Ar), 7.05-7.28 (7H, m, Ar), 8.02 (1H, s, $\underline{H}$C=N); ^{13}C NMR ($CDCl_3$, 50 MHz); δ 39.0 ($\underline{C}H_2$Ph), 65.7 ($\underline{C}H_2$OH), 73.1 ($\underline{C}$HCH$_2$Ph), 117.0, 118.5, 118.7, 126.5, 128.5, 129.5, 131.6, 132.5, 137.9 (Ar), 161.3 ($\underline{C}$-OH), 165.9 (H$\underline{C}$=N); IR (KBr)/cm^{-1}; ν 3588-3134, 3023, 2911, 2848, 1630, 1586, 1497, 1456, 1281, 1151, 1049.

2.5.6 Synthesis of (*S*)-2-(*N*-Salicylideneamino)-3-methyl-1-butanol (53)

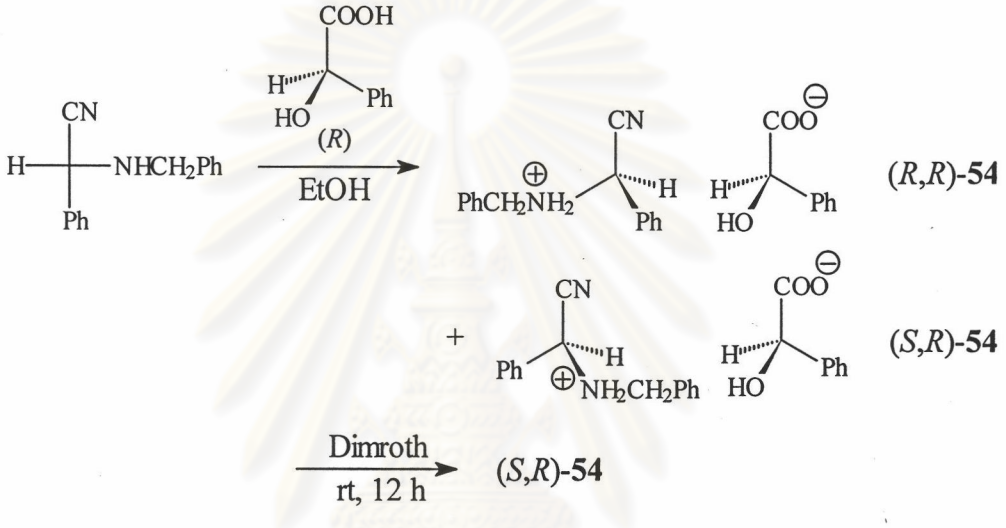


53

Ligand **53** was synthesized according to the method by Nobuki *et al.*[45] A mixture of methanol (2 mL), L-valinol (0.21 g, 2.05 mmol), and salicylaldehyde (215 μL, 2.05 mmol) was refluxed for 4 h. The solvent was removed, and the yellow solid obtained was recrystallized from hexanes-benzene (10:1) to give **53** as yellow needles (0.379 g, 88.9%) (mp 88-89 °C). ^{1}H NMR ($CDCl_3$, 200 MHz); δ 0.91 (6H, d, J = 6.7 Hz, (C$\underline{H}_3$)$_2$), 1.92 (1H, sept, J = 6.7 Hz, C$\underline{H}$(CH$_3$)$_2$), 3.00 (1H, m, $\underline{H}$CN=), 3.72 (2H,

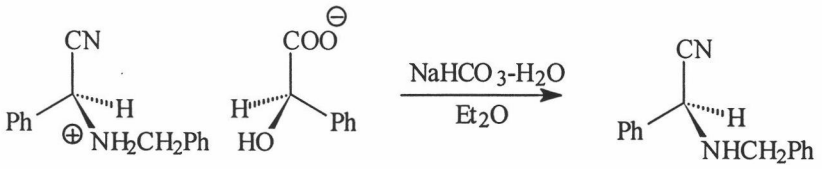
m, C<u>H</u>$_2$OH), 6.81-6.93 (2H, m, Ar), 7.22-7.33 (2H, m, Ar), 8.29 (1H, s, <u>H</u>C=N); ^{13}C NMR ($CDCl_3$, 50 MHz); δ 18.5 and 19.8 (2×<u>C</u>H$_3$), 30.0 (<u>C</u>H(CH$_3$)$_2$), 64.4 (<u>C</u>H$_2$OH), 77.4 (<u>C</u>HCH$_2$), 117.1, 118.5, 118.6, 131.5, 132.4 (Ar), 161.5 (<u>C</u>-OH), 165.8 (H<u>C</u>=N); IR (KBr)/cm^{-1}; ν 3468-3158, 3023, 2965, 2931, 2877, 2844, 1635, 1581, 1499, 1465, 1281, 1156,1030.

2.6 Asymmetric transformation of the second kind of (*R*)-mandelate 54 of racemic aminonitriles 43



(*R*)-Mandelate **54** was prepared according to a procedure by Jochims *et al.*[46] A solution of racemic **43** (2.5 mmol) in ethanol (0.5 mL) was added to a cold (0 °C) solution of (*R*)-mandelic acid (0.38 g, 2.5 mmol) in ethanol (0.5 mL). After stirring for a few minutes a clear solution was obtained, from which the mandelate soon started to crystallize. The mixture was kept (with stirring as long as possible) at room temperature for 12 h. The precipitate was collected by filtration and the residue was washed with cold ethanol followed by diethyl ether, and dried to afford the optically active mandelate salt as white crystalline powders.

2.7 Preparation of optically active aminonitriles 43 from their mandelate 54



(*S*,*R*)-**54** (*S*)-**43**

Optically active aminonitriles **43** was prepared according to procedure by Jochims *et al.*[46] A suspension of the diastereochemically pure mandalate **54** (0.20 mmol) and $NaHCO_3$ (0.22 mmol) in H_2O (0.4 mL) and Et_2O (0.4 mL) was shaken vigorously until a clear solution was obtained. The organic layer was separated, washed with H_2O and dried over Na_2SO_4. Evaporation of the solvent afforded the optically active aminonitrile, (*S*)-2-benzylamino-2-phenylacetonitrile, with spectra undiscernible from those of the racemic aminonitrile (±)-**43**.

2.7.1 (*S*)-2-Benzylamino-2-phenylacetonitrile (*S*)-43

From the (*S*,*R*)-mandelate (*S*,*R*)-**54** (0.075 g, 0.20 mmol). (*S*)-**43** was obtained as a colorless oil (0.031 g, 70.3 %); lit.[33] mp 49-51 °C (decomp.)

2.8 General methods for optical purity determination of α-aminonitriles

2.8.1 Attempted stereochemical analysis of α-aminonitriles using (1*R*)-(−)-menthyl chloroformate as a derivatizing agent.[47] α-Aminonitriles (1 eq) and pyridine (1.1 eq) were added to the standard solution of (1*R*)-(−)-menthyl chloroformate in toluene (1.1 eq), and the reaction mixture was allowed to stand at room temperature for 30 min. After washing with water and drying with sodium sulfate, an aliquot of the solution (~0.5 μL) was diluted on directly injected into the gas chromatograph equipped with a 30 m × 0.25 μm DB™ −1 (100% dimethylpolysiloxane) capillary column using suitable temperature program and optimum GC conditions. Relative amounts of what was believed to be the pair of diastereomers were determined by relative peak area integration.

2.8.2 Attempted analysis of α-aminonitriles using a chiral HPLC column. α-Aminonitriles were dissolved in appropriate solvent composition (100% hexanes to 9:1 hexane/2-propanol) and filtered through a membrane filter (Millex®-HV). An aliquot of the solution was injected into the Daicel Chiralcel OD® column (250 mm × 1.4 mm id cellulose tris(3,5-dimethylphenylcarbamate) on a 10 μm silica gel substrate). Elution with the mobile phase 97:3 to 9:1 (hexane/2-propanol) resulted in no separation.

2.8.3 Analysis of α-aminonitriles using ^{1}H NMR spectroscopy. The enantiomeric purities of the optically active aminonitriles **25a** and **43** were determined by ^{1}H NMR spectroscopy at 200 MHz from solutions in $CDCl_3$ after addition of chiral solvating agents such as (1*S*)-(+)-camphor-10-sulfonic acid, *R*-(–)-α-acetoxy phenylacetic acid, *R*-(–)-1,1′-binaphthalene-2,2′-diyl hydrogenphosphate (PNP), *S*-(–)-α-methoxy-α-trifluoromethylphenylacetic acid (Mosher's acid), and *R*-(+)-1,1′-bi (2-naphthol). The spectra were recorded at intervals of each 0.5 eq added.

2.9 General procedure for asymmetric Strecker reaction (TMSCN): methods A and B. To a oven-dried 10 mL round bottom flask equipped with a stir bar was added a solution of 10 mol% chiral ligand (0.02 mmol) in 0.25 mL toluene, and a solution of 10 mol% of metal salts in 0.50 mL ethanol ($Mn(OAc)_2{\cdot}4H_2O$, $Cu(OAc)_2{\cdot}H_2O$, $ZnCl_2$, $AlCl_3$, $Yb(OTf)_3$, $Sc(OTf)_3$, and $Zn(OAc)_2{\cdot}2H_2O$). The reaction mixture was stirred for 12 h and solvent removed *in vacuo*. The residue so obtained was dissolved or suspended in dried toluene (0.3 mL). The mixture was stirred continuously while a solution of **42** (0.2 mmol) in 0.4 mL of dried toluene was added *via* syringe followed by TMSCN (50 μL, 2 eq). The solution was allowed to stir for 15 h at room temperature (method A) or –5–0 °C for not more than 10 h (method B). The solution was evaporated and passed through a short plug of neutral aluminium oxide in a pasteur pipette to obtain the desired **43** which was analyzed for conversion and enantioselectivity by ^{1}H–NMR spectroscopy (*vide infra*). In the case of labile nitriles, 2 eq of the chiral solvating agent was added to the crude product directly to prevent further racemization on prolonged study.

2.10 General procedure for asymmetric Strecker reaction (TMSCN + MeOH): method C. A oven-dried 10 mL round bottom flask equipped with a mechanical stirrer was charged with a chiral ligand (0.02 mmol, 0.1 eq), 0.25 mL toluene, and a metal salt (0.1 eq) in 0.5 mL ethanol. The mixture was stirred at ambient temperature for 12 h, and the solvent was removed *in vacuo*. The residue was dissolved in toluene and was combined with **42** (0.2 mmol) by syringe addition. The mixture was stirred for 10 min and then cooled to –5–0 °C. In another oven-dried 5 mL pear-shaped flask equipped with stir bar, toluene (100 μL) and TMSCN (50 μL, 0.4 mmol) were added successively. This solution was cooled in an ice bath and methanol (16 μL, 0.4 mmol) was added. The solution was allowed to stir for 1 h and then transferred to the first reaction flask by syringe addition. After 6 hours, the reaction mixture was evaporated to dryness. The crude product was passed through a plug of neutral aluminium oxide as described above to afford the desired **43** which were analyzed for conversion and enantioselectivity by ^{1}H–NMR spectroscopy (*vide infra*). In the case of labile nitriles, 2 eq of the chiral solvating agent was added to the crude product directly to prevent further racemization on prolonged study.

2.11 General procedure for Ti-catalyzed addition of TMSCN: A chiral ligand (0.02 mmol) and $Ti(O^iPr)_4$ or $TiCl_4$ (0.02 mmol) were placed in a oven-dried 10 mL round bottom flask. The mixture was dissolved in dried toluene (0.3 mL) and stirred for 10 min at room temperature. Subsequently, **42** (0.2 mmol) in 0.4 mL of dried toluene was added by syringe addition. TMSCN (50 μL, 2 eq) was added to the stirred solution and the mixture was stirred for 15 h at room temperature (or no longer than 10 h at –5–0 °C). The solvent was then removed by distillation at reduced pressure to give a crude product which was passed through a plug of neutral aluminium oxide to yield **43**. Percent conversion and enantioselectivity was analyzed by ^{1}H NMR analysis. In the case of labile nitriles, 2 eq of the chiral solvating agent was added to the crude product directly to prevent further racemization on prolonged study.

2.12 General procedure for Ti-catalyzed addition of TMSCN + MeOH: A chiral ligand (0.02 mmol) and $Ti(O^iPr)_4$ or $TiCl_4$ (0.02 mmol) were placed in a oven-dried 10 mL round bottom flask. The mixture was dissolved in dry toluene (0.3 mL) and stirred for 10 min at room temperature. Substrate **42** (0.2 mmol) in 0.3 mL toluene

was added by syringe addition and then cooled to –5–0 °C. In a oven-dried 5 mL pear flask equipped with a stir bar, 100 μL of toluene and 50 μL of TMSCN (0.4 mmol) were added. This solution was cooled in an ice bath and methanol (16 μL, 0.4 mmol) was added. The solution was allowed to stir for 1 h and then added to the reaction flask by syringe addition. After 6 h, the reaction was allowed to evaporate and the resulting residue was purified by passing through a plug of aluminium oxide and then analyzed by ^{1}H-NMR experiments. In the case of labile nitriles, 2 eq of the chiral solvating agent was added to the crude product directly to prevent further racemization on prolonged study.

2.13 General procedure for catalyzed addition of TMSCN; slow addition: method D.[31] A chiral ligand (10 mol%) and Ti(O^iPr)$_4$ (10 mol%) were dissolved in dried toluene (0.3 mL) and stirred for 10 min at room temperature (or 10 mol% of chiral ligand and metal salt dissolved with EtOH/toluene 0.5/0.25, evaporated before use). Subsequently, the solution of imine **42** (0.2 mmol) in toluene was added *via* syringe. The reaction vessel was cooled to –5–0 °C, and TMSCN (50 μL, 0.4 mmol) was added to the stirred solution. Methanol (16 μL, 0.4 mmol) in toluene (1 mL) was added *via* a syringe over a 10-hour period. The reaction progress was followed by TLC. Solvent was removed by distillation at reduced pressure. The crude product was passed through a plug of aluminium oxide and analyzed for conversion and enantioselectivity by ^{1}H NMR spectroscopy. In the case of labile nitriles, 2 eq of the chiral solvating agent was added to the crude product directly to prevent further racemization on prolonged study.