CHAPTER II

EXPERIMENTAL

The following compounds were purchased from Fluka: 1-acetonaphthone, 2-acetonaphthone, liquid bromine (Br_2), sodium hydroxide, sodium azide, salicylaldehyde, sodium borohydride, 4-methoxy benzaldehyde, di-*t*-butylmalonate, 2-cyclopenten-1-one, 2-cyclohexen-1-one, lithium aluminium hydride 1 M in THF ($LiAlH_4$), tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]praseodym(III) ($Pr(hfc)_3$), and (*R*)-methoxy-2-phenyl-3,3,3-trifluoropropanoic acid ((*R*)-MTPA). (-)-*B*-diisopinocampheylborane ((-)-Ipc_2BCl or (-)-DIPCl™), trimethylsilylcyanide (TMSCN), titanium isopropoxide ($Ti(O\text{-}^iPr)_4$), and 10 % palladium on activated charcoal were purchased from Aldrich. Toluene, methanol, and 2-propanol were purchased from Merck Co.Ltd.. All of the AR grade chemicals were used without any purification, except 2-cyclohexen-1-one which was distilled before use in Michael reaction. Diethyl phosphite was prepared as previously described.[*29*] Tetrahydrofuran (THF) which was purchased from Lab Scan, was distilled by using sodium benzophenone ketyl as a drying agent and indicator. Distilled commercial grade solvents were used for extraction and column chromatography.

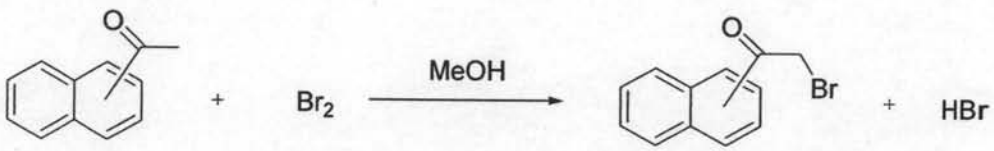
For thin-layer chromatography (TLC), silica gel plates (Merck 60 F_{254}) were used and compounds were visualized by irradiation with UV light (254 nm) and/or by treatment with potassium permanganate, cobalt(II) thiocyanate, or anisaldehyde solution followed by heating. Flash column chromatography was performed on 230-400 mesh silica gel.

Nuclear magnetic resonance (NMR) spectra were recorded on a Varian Mercury 400 spectrometer operating at 400 MHz for ^{1}H-NMR and 100 MHz for ^{13}C NMR at ambient temperature. Chemical shifts are given in parts per million (ppm) relative to tetramethylsilane (TMS). Coupling constants *J* are reported in Hz. HPLC experiments were carried out using Waters Delta 600 pump and Waters 2996 photodiode array detector. Chiral HPLC column (Chiralpak AD-H®) was purchased from Chiral Technologies, Co, Ltd.. GC experiments were operated by Mr. Wuttichai Reainthippayasakul under the supervision of Assistant Professor Dr.Aroonsiri Shitangkoon on a 6890 Agilent gas chromatograph, using flame ionization detector

(FID) equipped with 10 % BSiMe in PS 255 (14.321 m × 0.25 mm × 0.25 μm) as a capillary column. The mass spectra of some new compounds were measured on a Microflex MALDI-TOF mass spectrometer (Bruker daltonic) using recrystallized α-cyano-4-hydroxy cinnamic acid (CCA) as a matrix. TFA (0.1%) in acetonitrile:water(1:2) was used as the diluent for preparation of MALDI-TOF samples.

2.1 Synthesis of the ligands

2.1.1 2-bromo-1-(naphthalen-1-yl)ethanone (42a) and 2-bromo-1-(naphthalene-2-yl)ethanone (42b)



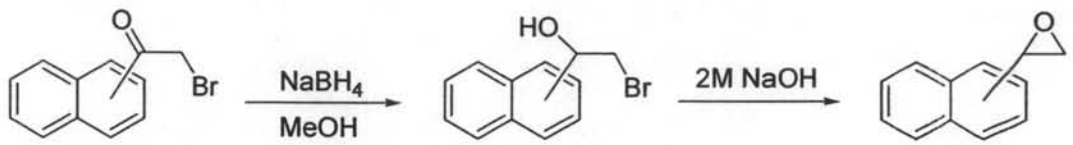
To a 250 mL round-bottomed flask containing a solution of 1- or 2-acetonaphthone (6.8084 g, 40.00 mmol) in 20 mL of MeOH was added dropwise a solution of liquid Br_2 (2.26 mL, 44 mmol) in 20 mL of MeOH. The initially formed clear brown solution decolourized to clear pale-yellow over a 5 min period. The reaction mixture was stirred overnight at 30 °C.

2-bromo-1-(naphthalen-1-yl)ethanone (42a): After 12 h, methanol in the reaction mixture was evaporated, then 10 mL of water and 20 × 3 mL of CH_2Cl_2 were added to extract the desired product. The CH_2Cl_2 layers were combined and dried over anhydrous Na_2SO_4. The solvent was evaporated to give a yellow liquid (9.7845 g, 39.88 mmol, 98 %) of **42a** which was used in the next steps without further purification. ^{1}H-NMR($CDCl_3$, 400 MHz) δ 4.58 [2H, s, C*H*$_2$Br], 7.50-7.59 [2H, m, Ar*H*], 7.64 [1H, t, $^3J_{HH}$ = 8.3 Hz, Ar*H*], 7.90 [1H, d, $^3J_{HH}$ = 8.0 Hz], 7.93 [1H, dd, $^3J_{HH}$ = 7.3 and $^4J_{HH}$ = 0.5 Hz, Ar*H*], 8.07 [1H, d, $^3J_{HH}$ = 8.3 Hz, Ar*H*], 8.63 [1H, d, $^3J_{HH}$ = 8.6 Hz, Ar*H*]; ^{13}C-NMR($CDCl_3$, 100 MHz) δ 34.3 [*C*H$_2$Br], 124.3, 125.7, 126.8, 128.5, 128.6, 128.8, 130.6, 132.1, 134.0, 134.0 [Ar], 194.3 [Ar*C*OCH$_2$]

2-bromo-1-(naphthalen-2-yl)ethanone (42b): After 12 h, some of the product crystallized spontaneously. The reaction mixture was cooled in an ice-bath, then the solid was filtered under vacuum. After washing with cold methanol, white crystals of **42b** were obtained (7.8771 g, 31.62 mmol, 97 %) and were used in the next steps

without any purification. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 4.58 [2H, s, C*H*$_2$Br], 7.56-7.66 [2H, m, Ar*H*], 7.89-7.94 [2H, m, Ar*H*], 7.98-8.05 [2H, m, Ar*H*], 8.52 [1H, s, Ar*H*]; ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 31.2 [*C*H$_2$Br], 124.1 , 127.1, 127.8, 128.8, 129.1, 129.7, 130.9, 131.0, 132.3, 135.8 [Ar], 191.2 [Ar*C*OCH$_2$].

2.1.2 Racemic 2-(naphthalen-1-yl)oxirane (43a) and 2-(naphthalen-2-yl)oxirane (43b)



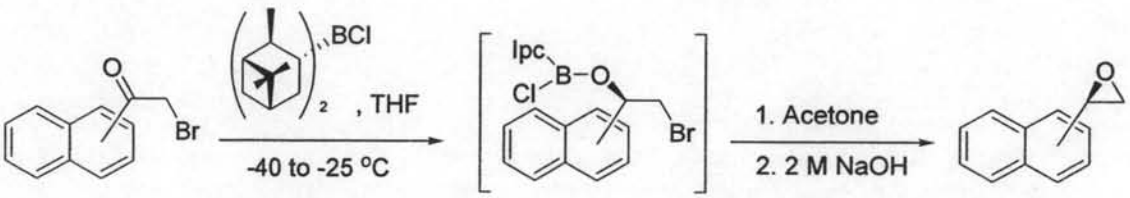
A 250 mL round-bottomed flask was charged with **42a** or **42b** (3.0390 g, 12.20 mmol) which was dissolved in 15 mL of MeOH. The flask was immersed in an ice bath and the solution was stirred on the ice bath for about 15 min. $NaBH_4$ (0.56 g, 15 mmol) was then added and the solution was stirred at ambient temperature (ca. 30 °C). After 12 h, the reaction mixture was cooled again in the ice-bath, then 2 M NaOH (30 mL) was added and the solution was stirred at room temperature for 1.5 h. The reaction was extracted with dichloromethane (20 mL × 3). The dichloromethane layers were collected, dried over anhydrous Na_2SO_4, followed by evaporation.

2-(naphthalen-1-yl)oxirane (43a): The crude product was obtained as a brown liquid. After purification by flash column chromatography using 100 % hexanes as mobile phase, a colourless liquid of **43a** (0.6437 g, 3.782 mmol, 31 %) was obtained. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.83 [1H, dd ABX system, $^2J_{AB}$ = 5.8 Hz and $^3J_{AX}$ = 2.6 Hz , C(O)H_AH_B], 3.32 [1H, dd ABX system, $^2J_{AB}$ = 6.1 Hz and $^3J_{AX}$ = 4.1 Hz , C(O)H_AH_B], 4.51 [1H, apt, ArC*H*(O)], 7.46-7.61 [4H, m, Ar*H*], 7.83 [1H, d, $^3J_{HH}$ = 7.6 Hz, Ar*H*], 7.92 [1H, d, $^3J_{HH}$ = 7.6 Hz, Ar*H*], 8.17 [1H, d, $^3J_{HH}$ = 8.1 Hz, Ar*H*]; ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 50.2 [ArCH(O)*C*H$_2$], 50.8 [Ar*C*H(O)CH$_2$], 122.3, 123.0, 125.6, 126.0, 126.4, 128.3, 128.8, 131.6, 133.4, 133.8 [Ar].

2-(naphthalene-2-yl)oxirane (43b): The crude product was obtained as a pale-yellow solid. After stirring the solid vigorously in hexanes, the suspension was kepted in the freezer at 0 °C and then filtered under vacuum. A white crystalline solid of **43b** 1.3430 g (7.90 mmol, 65 %) was obtained. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.91 [1H, dd ABX system, $^2J_{AB}$ = 5.4 Hz and $^3J_{AX}$ = 2.6 Hz, C(O)H_AH_B], 3.23 [1H, dd ABX system, $^2J_{AB}$ = 5.4 Hz and $^3J_{AX}$ = 4.1 Hz, C(O)H_AH_B], 4.04 [1H, dd ABX system, $^3J_{AX}$

= 3.9 Hz and $^3J_{BX}$ = 2.6 Hz, ArC*H*(O)], 7.33 [1H, dd $^3J_{HH}$ = 8.5 Hz and $^4J_{HH}$ = 1.6 Hz, Ar*H*], 7.45-7.52 [2H, m, Ar*H*], 7.80-7.84 [4H, m, Ar*H*]; ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 51.3 [ArCH(O)*C*H_2], 52.6 [(Ar*C*H(O)CH$_2$], 122.6, 125.2, 126.1, 126.4, 127.8, 128.4, 133.2, 133.3, 135.1 [Ar].

2.1.3 (*R*)-2-(naphthalen-1-yl)oxirane (44a) and (*R*)-2-(naphthalen-2-yl)oxirane (44b)



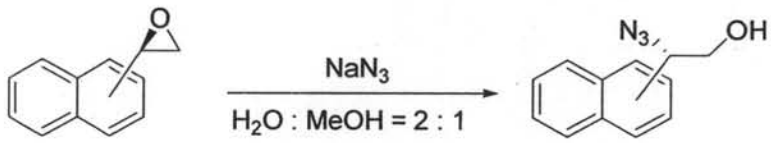
An oven-dried 250 mL round-bottomed flask, equipped with a magnetic bar and capped with a rubber septum, was charged with (-)-Ipc$_2$BCl (12.0 g, 37.4 mmol) under a nitrogen atmosphere. THF (15 mL) was added *via* a syringe to dissolve the solid. After the solid had been completely dissolved, the reaction flask was cooled in dry ice(-40 °C) for 1 h. Then a solution of **42a** or **42b** (4.6600 g, 18.71 mmol) in 5 mL of THF was slowly added to the solution. The nitrogen balloon was then removed. The septum was sealed with parafilm. The reaction flask was placed in a freezer at -25 °C for 72 h. After the reduction was complete (NMR), acetone (5.5 mL, 75 mmol) was added to the reaction mixture at -25 °C. The solution was stirred at ambient temperature for an additional 4 h. THF was removed by evaporation to give a brown liquid. The crude product was dissolved again in 15 mL of diethyl ether, cooled to 0 °C in an ice bath, followed by addition of 2 M NaOH (38 mL, 76 mmol). The two-phase solution was stirred vigorously while the temperature was raised from 0 °C to room temperature over a period of 5 h. After that, brine was added, the diethyl ether layer was separated, and the aqueous layer was extracted by diethyl ether (10 mL × 3). All fractions of diethyl ether extracts were combined, dried over anhydrous Na_2SO_4, and the solvent was evaporated to give crude (*R*)-**44a** or (*R*)-**44b**.

(*R*)-2-(naphthalen-1-yl)oxirane (44a): The crude product, which was a brown liquid, was purified by flash-column chromatography (SiO_2, 1 % Et_3N in hexanes) to give pure (*R*)-**44a** (1.3739 g, 8.072 mmol, 43 %) as a colourless liquid. ^{1}H-NMR experiment by an addition of tris[3-(heptafluoropropylhydroxymethylene)-*d*-

camphorato]praseodymium(III) ($Pr(hfc)_3$) as a chiral-shift reagent indicated that the product was more than 99 % enantiomerically pure. $[\alpha]_D^{27}$ (c=1.01, $CHCl_3$) = -81.3 (lit. $[\alpha]_D^{22}$ (c=1.2, $CHCl_3$) = -63.51 for 65 %*ee*)[*45*].

(*R*)-2-(naphthalen-2-yl)oxirane (44b): The crude product was originally obtained as a clear brown liquid which turned to a pale-yellow crystalline solid after standing overnight at the room temperature. Hexanes (15 mL) was added to the solid followed by trituration using a spatula. The suspension was kept in the freezer, filtered under vacuum and then washed by extremely cold hexanes (10 mL). After being air-dried, (*R*)-**44b** (2.0037 g, 11.77 mmol, 67 %) was obtained as a white solid. ^{1}H-NMR experiment by an addition of Tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]praseodymium(III) ($Pr(hfc)_3$) as a chiral-shift reagent indicated that %*ee* of (*R*)-**44b** was higher than 99 %. $[\alpha]_D^{27}$ (c=1.01, $CHCl_3$) = -10.27 (lit. $[\alpha]_D^{22}$ (c=1.1, $CHCl_3$) = -11.4) [*46*].

2.1.4 (*S*)-2-azido-2-(naphthalen-1-yl)ethanol (45a) and (*S*)-2-azido-2-(naphthalen-2-yl)ethanol (45b)



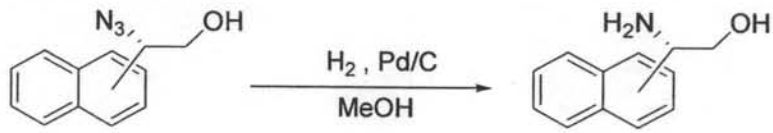
Five equivalents of sodium azide, relative to (*R*)-**44a** or (*R*)-**44b**, were weighed in a 100 mL round-bottomed flask and dissolved with water to give a clear solution. A solution of (*R*)-**44a** or (*R*)-**44b** in MeOH was added into the flask. The reaction mixture was stirred at room temperature for 72 h. Then, brine and dichloromethane were added to extract the desired product. The aqueous layer was extracted again by dichloromethane and diethyl ether twice for each solvent. The organic phases were combined and dried over anhydrous sodium sulphate, followed by evaporation. The crude (*S*)-**45a** or (*S*)-**45b**, was firstly obtained as a light brown liquis which usually solidified upon standing overnight. If the crude product of (*S*)-**45a** or (*S*)-**45b** did not solidify, flash-column chromatography using 30% EtOAc in hexanes was used for purification. A small amount of hexanes was added to the solid followed by trituration using a spatula. The suspension was frozen, vacuum-filtered,

and the solid then washed by a small amount of an extremely cold hexane. After air-dried, (*S*)-**45a** or (*S*)-**45b** was obtained.

(*S*)-2-azido-2-(naphthalen-1-yl)ethanol (45a) was obtained from a reaction of 1.3739 g (8.0715 mmol) of (*R*)-**44a** , 2.63 g (40.4 mmol) of sodium azide, 8 mL of H_2O, and 4 mL of MeOH as a white solid (1.1048 g, 5.1810 mmol, 65 %). Enantiomeric excess was determined by chiral HPLC (Chiralpak AD-H, i-PrOH/hexanes = 20/80, flow rate = 0.5 ml/min, λ = 254 nm, t_{minor} = 16.0 min, t_{major} = 18.3 min) to be > 99 %*ee*; $[\alpha]_D^{26}$ (c=1.00, $CHCl_3$) = +94.2; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.88 [1H, dd ABX system, $^2J_{AB}$ = 11.7 Hz and $^3J_{AX}$ = 8.4 Hz, C(OH)H_AH_B], 3.96 [1H, dd ABX system, $^2J_{BA}$ = 11.7 Hz and $^3J_{BX}$ = 4.1 Hz, C(OH)H_AH_B], 5.49 [1H, dd ABX system, $^3J_{XA}$ = 8.3 Hz and $^3J_{XB}$ = 4.1 Hz, CH_X(N_3)], 7.49-7.62 [4H, m, Ar*H*], 7.86 [1H, d $^3J_{HH}$ = 8.2 Hz, Ar*H*], 7.91 [1H, d $^3J_{HH}$ = 7.8 Hz, Ar*H*], 8.09 [1H, d $^3J_{HH}$ = 8.3 Hz]; ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 134.0, 131.9, 130.8, 129.2, 129.2, 126.8, 126.0, 125.4, 125.0, 122.6 [Ar], 66.0 [Ar*C*H(N_3)], 64.9 [*C*H_2OH]; Anal Calcd for $C_{12}H_{11}N_3O$: C, 67.59; H, 5.20; N, 19.71 Found: C, 67.61; H, 5.23; N, 19.76.

(*S*)-2-azido-2-(naphthalen-2-yl)ethanol (45b) was obtained from a reaction of 2.0037 g (11.772 mmol) of (*R*)-**3b** , 3.83 g (58.8 mmol) of sodium azide, 10 mL of H_2O, and 5 mL of MeOH as a white solid (1.6254 g, 7.6224 mmol, 65 %). Enantiomeric excess was determined by chiral HPLC (Chiralpak AD-H, i-PrOH/hexane = 20/80, flow rate = 0.5 ml/min, λ = 254 nm, t_{minor} = 14.8 min, t_{major} = 17.2 min) to be > 99 %*ee*; $[\alpha]_D^{26}$ (c=0.50, $CHCl_3$) = +217.3 (lit. $[\alpha]_D^{18}$ (c = 0.48, $CHCl_3$) = +229)[*57*]; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.83 [2H, apd, CH_2(OH)], 4.84 [1H, apt, C*H*(N_3)], 7.43 [1H, dd $^3J_{HH}$ = 8.4 Hz and $^4J_{HH}$ = 1.6 Hz], 7.52-7.54 [2H, m, Ar*H*], 7.82 [1H, d, $^4J_{HH}$ = 0.6 Hz, Ar*H*], 7.85-7.90 [3H, m, Ar*H*]; ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 133.6, 133.3, 133.1, 128.9, 128.0, 127.7, 126.6, 126.6, 126.5, 124.4 [Ar], 68.0 [Ar*C*H(N_3)], 66.4 [*C*H_2OH].

2.1.5 (*S*)-2-amino-2-(naphthalen-1-yl)ethanol (46a) and (*S*)-2-amino-2-(naphthalen-2-yl)ethanol (46b)

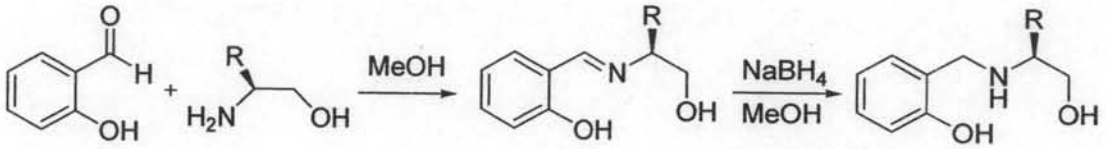


A 100 mL round-bottomed flask equipped with a magnetic bar was placed with **45a** or **45b** and 5 % w/w, relative to **45a** or **45b**, of 10 % Pd/C. MeOH was then added. Using a 3-way stopcock, the reaction flask was charged with hydrogen gas from a balloon and the suspension stirred for 12 h at room temperature under hydrogen atmosphere. At the end of the reaction, hydrogen was displaced by air. The Pd/C was removed by filtration over a piece of pleated filter paper. After rinsing with MeOH, the filtrate was collected and evaporated. The solid of **46a** or **46b** was obtained and used in the next step without any purification.

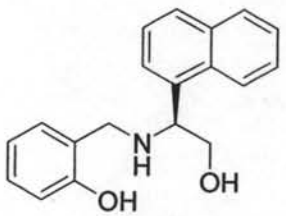
(*S*)-2-amino-2-(naphthalen-1-yl)ethanol (46a) was obtained from a reaction of (*S*)-**45a** 1.0939 g (5.1299 mmol), 0.0547 g of 10 % Pd/C and 10 mL of MeOH as a yellow solid (0.9114 g, 4.868 mmol, 95 %). $[\alpha]_D^{27}$ (c=1.02, MeOH) = +69.7; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.64 [2H, s, NH_2], 3.70 [1H, dd ABX system, $^2J_{AB}$ = 10.5 Hz and $^3J_{AX}$ = 8.5 Hz, C(OH)H_AH$_B$], 3.94 [1H, dd ABX system, $^2J_{BA}$ = 11.0 Hz and $^3J_{AX}$ = 3.5 Hz, C(OH)H$_A$$H_B$], 4.95 [1H, dd ABX system, $^3J_{XA}$ = 8.0 Hz and $^3J_{XB}$ = 3.5 Hz, CH(NH$_2$)], 7.43-7.53 [3H, m, ArH], 7.59 [1H, d, $^3J_{HH}$ = 7.2 Hz, ArH], 7.75 [1H, d, $^3J_{HH}$ = 8.2 Hz, ArH], 7.85 [1H, d, $^3J_{HH}$ = 7.4 Hz, ArH], 8.07 [1H, d, $^3J_{HH}$ = 8.1 Hz, ArH]; ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 52.7 [CH$_2$OH], 67.2 [ArCH(NH$_2$)], 122.6, 122.8, 125.5, 125.7, 126.3, 127.9, 129.0, 130.8, 133.8, 137.9 [Ar].

(*S*)-2-amino-2-(naphthalen-2-yl)ethanol (46b) was obtained from a reaction of (*S*)-**45b** 1.6138 g (7.5680 mmol), 0.0814 g of Pd/C, and 10 mL of MeOH as a white solid (1.3744 g, 7.3403 mmol, 97 %). $[\alpha]_D^{27}$ (c=1.01, MeOH) = +20.2; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.64 [1H, apt, C(OH)H_AH$_B$], 3.80 [1H, dd ABX system, $^2J_{BA}$ = 10.8 Hz and $^3J_{BX}$ = 4.0 Hz, C(OH)H$_A$$H_B$], 4.18 [1H, dd ABX system, $^3J_{XA}$ = 7.6 Hz and $^3J_{XB}$ = 4.1 Hz, CH(NH$_2$)], 7.40 [1H, d, $^3J_{HH}$ = 8.2 Hz, ArH], 7.46 [2H, apt, ArH], 7.75 [1H, s, ArH], 7.79-7.81 [3H, m, ArH]; ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 57.4 [CH$_2$OH], 67.7 [ArCH(NH$_2$)], 124.7, 125.1, 125.8, 126.2, 127.6, 127.8, 128.3, 132.8, 133.3, 139.8 [Ar].

2.1.6 *(S)*-2-((1-hydroxy-2-alkylethylamino)methyl)phenol or *(S)*-2-((2-hydroxy-1-arylethylamino)methyl)phenol

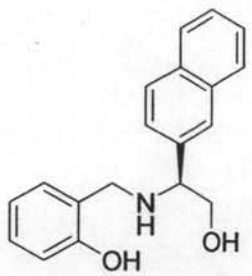


Salicylaldehyde (1.1 equivalents) was added to a solution of the amino alcohol in methanol. The colour of the solution immediately changed from colourless to clear bright yellow indicating the formation of the Schiff's base (precipitation was observed in some cases). The reaction mixture was stirred at room temperature for 12 h. The reaction flask was then cooled to 0 °C in an ice bath for 30 min, followed by a slow addition of 2 equivalents of sodium borohydride. Bubbles of hydrogen gas were evolved accompanied by a colour change from yellow back to colourless. The reaction was stirred at ambient temperature for 4-6 h. Water was added to the reaction mixture, followed by extraction with brine and dichloromethane. All of the organic layers were combined, dried over anhydrous Na_2SO_4 and the solvent was evaporated. Alternatively, if addition of water caused precipitation, the reaction mixture was cooled and the precipitate collected by filtration under vacuum. Crystallization or column chromatography might be required for purification of the crude ligands.

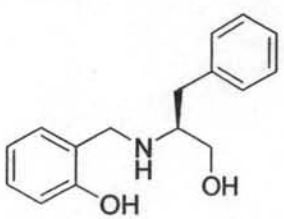


(*S*)-2-((2-hydroxy-1-(naphthalen-1-yl)ethylamino)methyl)phenol (47a): Starting from (*S*)-**46a** (0.9114 g, 4.868 mmol), salicylaldehyde (0.6538 g, 5.354 mmol), $NaBH_4$ (0.37 g, 9.7 mmol) and 50 mL of MeOH, a pale-yellow solid was obtained after extraction by CH_2Cl_2 and evaporation. Crystallization from toluene gave pure (*S*)-**47a** (0.8140 g, 2.775 mmol, 57%) as a white solid. $[\alpha]_D^{23}$ (c = 1.00 ,MeOH) = +11.6; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.76 [1H, d AB system, $^2J_{AB}$ = 13.7 Hz, ArCH_AH$_B$NH], 3.82 [1H, dd ABX system, $^2J_{AB}$ = 10.9 Hz and $^3J_{AX}$ = 7.9 Hz, CH_AH$_B$(OH)], 3.94 [1H, dd ABX system, $^2J_{BA}$ = 10.9 Hz and $^3J_{BX}$ = 3.1 Hz, CH$_A$$H_B$(OH)], 4.00 [1H, d AB system, $^2J_{AB}$ = 13.7 Hz, ArCH$_A$$H_B$NH], 4.80 [1H, br,

NHCH_X(Ar)H_AH_B], 5.61 [1H, br, N*H*], 6.71 [1H, t, $^3J_{HH}$ = 7.3 Hz, Ar*H*], 6.79 [1H, d, $^3J_{HH}$ = 7.2 Hz, Ar*H*], 6.88 [1H, d, $^3J_{HH}$ = 8.0 Hz, Ar*H*], 7.15 [1H, t, $^3J_{HH}$ = 7.3 Hz, Ar*H*], 7.49-7.53 [3H, m, Ar*H*], 7.60 [1H, d, $^3J_{HH}$ = 7.0 Hz, Ar*H*], 7.82 [1H, d, $^3J_{HH}$ = 8.1 Hz, Ar*H*], 7.89 [1H, apt, Ar*H*], 8.00 [1H, d, $^3J_{HH}$ = 7.7 Hz, Ar*H*]; ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 50.0, 65.6, 116.3, 119.3, 122.3, 122.4, 123.9, 123.9, 125.5, 125.8, 126.5, 128.5, 128.8, 129.0, 129.1, 131.6, 133.7, 134.0, 157.5; *m/z* (MALDI-TOF) = 293.03; Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found : C, 77.05; H, 6.91; N, 4.80.

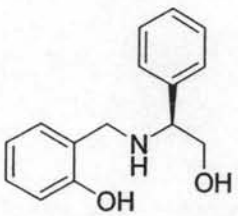


(*S*)-2-((2-hydroxy-1-(naphthalen-2-yl)ethylamino)methyl)phenol (47b): Starting from (*S*)-**46b** (1.3744 g, 7.3403 mmol), salicylaldehyde (0.9860 g, 8.0743 mmol), $NaBH_4$ (0.57 g, 15 mmol), and 50 ml of MeOH, a pale-yellow precipitate was obtained after addition of water. Crystallization from EtOAc/heptane gave (*S*)-**47b** (1.5073 g, 5.1382 mmol, 70%) as a white solid. $[\alpha]_D^{23}$ (c = 1.00, MeOH) = +50.5; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.74 [1H, d AB system, $^2J_{AB}$ = 13.7 Hz, ArC$H_A$$H_B$NH], 3.90-3.92 [2H, m], 3.99–4.04 [2H, m], 4.58 [1H, br, N*H*], 6.75 [1H, t, $^3J_{HH}$ = 7.3 Hz, Ar*H*], 6.87 [2H, apt, Ar*H*], 7.16 [1H, t, $^3J_{HH}$ = 7.5 Hz, Ar*H*], 7.45 [1H, d, $^3J_{HH}$ = 7.5 Hz, Ar*H*], 7.50-7.52 [2H, m, Ar*H*], 7.77 [1H, s, Ar*H*], 7.84-7.89 [3H, m, Ar*H*]; ^{13}C-NMR (DMSO-d_6 , 100 MHz) δ 48.0 [*C*H_2OH], 64.3 [NH*C*H(Ar)], 66.4 [Ar*C*H_2NH], 115.6, 119.0, 125.6, 126.0, 126.2, 126.4, 126.8, 127.9, 128.0, 128.2, 128.2, 129.2, 132.9, 133.4, 139.4, 157.0[Ar]; *m/z* (MALDI-TOF) = 293.77 ; Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found : C, 77.74; H, 6.60; N, 4.74.

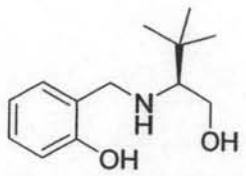


(*S*)-2-((1-hydroxy-3-phenylpropan-2-ylamino)methyl)phenol (26): Starting from (*S*)-phenylalaninol (1.5124 g, 10.002 mmol), salicylaldehyde (1.3436 g, 11.002 mmol), $NaBH_4$ (0.76 g, 20 mmol), and 25 ml of MeOH, a white precipitate of (*S*)-**26**

formed after addition of water (1.9814 g, 7.6998 mmol, 77 %). No purification was required. $[\alpha]_D^{23}$ (c= 1.00, MeOH) = -13.9 (lit. $[\alpha]_D^{23}$ (c = 1.0, $CHCl_3$) = -23.2) [*56*]; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.81 [1H, dd ABX system, $^2J_{AB}$ = 13.6 Hz and $^3J_{AX}$ = 7.5 Hz, ArCH_AH$_B$CH$_X$], 2.89 [1H, dd ABX system, $^2J_{BA}$ = 13.7 Hz and $^3J_{BX}$ = 6.3 Hz, ArCH$_A$$H_BCH_X$], 2.98 [1H,s br, NHC*H*(Bz)], 3.53 [1H, dd ABX system, $^2J_{AB}$ = 11.0 Hz and $^3J_{AX}$ = 4.7 Hz, CH$_X$CH_AH$_B$OH], 3.73 [1H, dd ABX system, $^2J_{BA}$ = 11.0 Hz and $^3J_{BX}$ = 3.6 Hz, CH$_X$CH$_A$$H_B$OH], 4.00 [2H, s, ArC$H_2$NH], 6.78 [1H, t, $^3J_{HH}$ = 7.3 Hz, Ar*H*], 6.83 [1H, d, $^3J_{HH}$ = 8.0 Hz, Ar*H*], 6.97 [1H, d, $^3J_{HH}$ = 7.2 Hz, Ar*H*], 7.15-7.33 [6H, m, Ar*H*]; ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 37.3 [Ar*C*H$_2$CH], 50.3 [Ar*C*H$_2$NH], 59.7 [NH*C*H(Bz)CH$_2$], 62.5 [*C*H$_2$OH], 116.5, 119.2, 122.9, 126.6, 128.2, 128.7, 128.8, 129.2, 138.1, 158.0 [Ar].

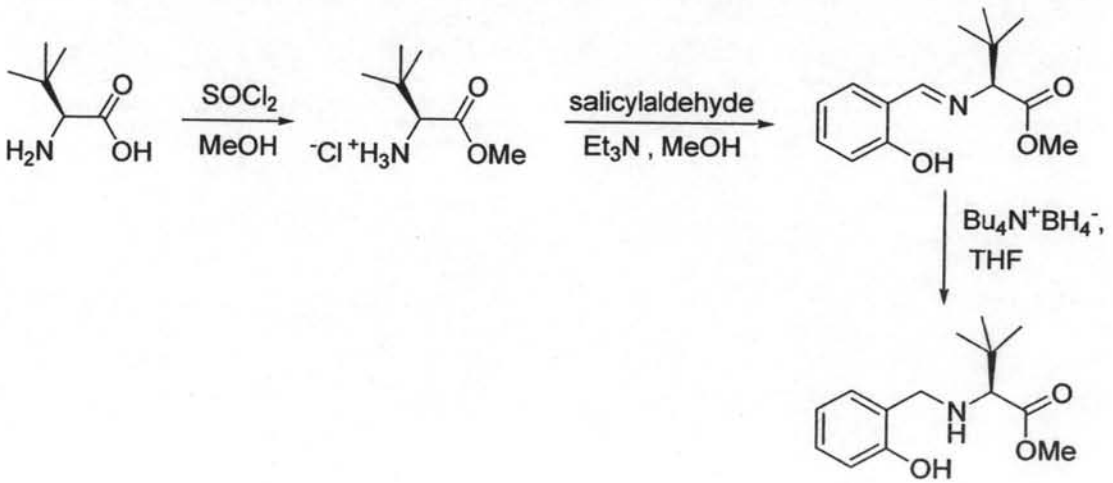


(*S*)-2-((2-hydroxy-1-phenylethylamino)methyl)phenol (47c): Starting from (*S*)-phenylglycinol (1.3718 g, 10.000 mmol), salicylaldehyde (1.3439 g, 11.004 mmol), $NaBH_4$ (0.76 g, 20 mmol), and 25 mL of MeOH, a white precipitate of (*S*)-**47c** was formed after addition of water (2.1912 g, 9.0062 mmol, 90%). No purification was required. $[\alpha]_D^{23}$ (c = 1.00, MeOH) = +82.3 (lit. $[\alpha]_D^{23}$ (c = 1.0, $CHCl_3$) = +64.0) [*56*]; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.71 [1H, d AB system, $^2J_{AB}$ = 13.7 Hz, ArCH_AH$_B$NH], 3.77-3.85 [3H, m, NHC*H*(Ar)CH_2OH], 3.96 [1H, d AB system, $^2J_{BA}$ = 13.7 Hz, ArCH$_A$$H_B$], 4.73 [1H, br, N*H*], 6.75 [1H, t, $^3J_{HH}$ = 7.4 Hz, Ar*H*], 6.84 [1H, d, $^3J_{HH}$ = 8.00 Hz, Ar*H*], 6.89 [1H, d, $^3J_{HH}$ = 7.1 Hz, Ar*H*], 7.15 [1H, t, $^3J_{HH}$ = 7.1 Hz, Ar*H*], 7.31-7.35 [3H, m, Ar*H*], 7.37-7.41 [2H, m, Ar*H*]; ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 50.1 [Ar*C*H$_2$NH], 63.8 [NH*C*H(Ar)CH$_2$], 66.4 [*C*H$_2$OH], 116.4, 119.3, 122.5, 127.5, 128.2, 128.5, 128.9, 129.0, 138.4, 157.7 [Ar].



(*S*)-2-((1-hydroxy-3,3-dimethylbutan-2-ylamino)methyl)phenol (25): Started from (*S*)-*tert*-leucinol (1.1775 g, 10.048 mmol), salicylaldehyde (1.3500 g, 11.055 mmol), $NaBH_4$ (0.76 g, 20 mmol), and 25 mL of MeOH, a pale-brown liquid was obtained after extraction with CH_2Cl_2 followed by evaporation. Flash-column chromatography (SiO_2, 20 % EtOAc in hexanes) gave (*S*)-**25** (1.8090 g, 8.1008 mmol, 81 %) as a white solid. $[\alpha]_D^{23}$ (c = 2.00, MeOH) = -1.8 (lit. $[\alpha]_D^{23}$ (c = 1.0, $CHCl_3$) = +5.3) [*56*]; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.00 [9H, s, C*H*$_3$], 2.41 [1H, dd ABX system, $^3J_{XA}$ = 5.9 Hz and $^3J_{XB}$ = 3.7 Hz, C*H*(C_4H_9)], 3.72 [1H, dd ABX system, $^2J_{AB}$ = 11.4 Hz and $^3J_{AX}$ = 6.0 Hz, CH_AH$_B$OH], 3.96 [1H, dd ABX system, $^2J_{BA}$ = 11.4 Hz and $^3J_{BX}$ = 3.7 Hz], 4.01 [1H, d AB system, $^2J_{AB}$ = 13.5 Hz, ArCH_AH$_B$NH], 4.18 [1H, d AB system, $^2J_{AB}$ = 13.5 Hz, ArCH$_A$*H*$_B$], 4.80 [1H, br, N*H*], 6.78 [1H, td, $^3J_{HH}$ = 7.4 Hz and $^4J_{HH}$ = 0.9 Hz, Ar*H*], 6.87 [1H, d, $^3J_{HH}$ = 8.0 Hz, Ar*H*], 7.02 [1H, d, $^3J_{HH}$ = 7.2 Hz, Ar*H*], 7.20 [1H, td, $^3J_{HH}$ = 8.8 Hz and $^4J_{HH}$ = 1.4 Hz, Ar*H*]; ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 27.4 [*C*H$_3$], 34.1 [*C*(CH$_3$)$_3$], 53.0 [*C*H(C_4H_9)CH$_2$OH], 61.2 [*C*H$_2$OH], 67.7 [ArCH$_2$NH], 116.3, 119.2, 123.5, 128.4, 128.8, 158.0 [Ar].

2.1.7 (*S*)-methyl 2-(2-hydroxybenzylamino)-3,3-dimethylbutanoate (48).[*25*]



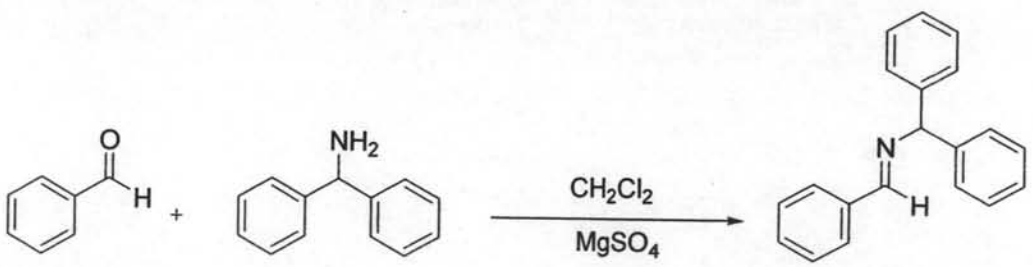
(*S*)-*tert*-Leucine (0.6559 g, 5.000 mmol) was placed in a 100 mL round-bottomed flask and dissolved by 5 mL of methanol. Thionyl chloride ($SOCl_2$, 0.39 mL, 5.4 mmol) was added dropwise. The reaction mixture was allowed to stir at room

temperature in a closed system for 6 hours. Triethylamine (0.77 mL, 5.5 mmol) and salicylaldehyde (0.6794 g, 5.563 mmol) were then added, respectively. After stirring for 12 h, methanol was evaporated and 10 mL of diethyl ether was added. The precipitated triethylamine hydrochloride was removed by vacuum filtration. The bright-yellow filtrate was collected and evaporated. The resulting solid was dissolved in dried THF. Tetrabutylammonium borohydride (Bu_4NBH_4, 1.44 g, 5.60 mmol) was slowly added to the solution. After stirring at room temperature for 4 hours, the solution was evaporated. The crude product was purified by flash-column chromatography (SiO_2, 5% EtOAc in hexanes) to give (*S*)-**48** (0.1916 g, 15 %) as a colourless liquid. $[\alpha]_D^{27}$ (c= 1.00, MeOH) = -4.4; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.02 [9H, s, C*H*$_3$], 3.10 [1H, s, C*H*(C_4H_9)], 3.75 [3H, s, OC*H*$_3$], 3.79 [1H, d AB system, $^2J_{AB}$ = 13.8 Hz, ArCH_AH$_B$], 4.01 [1H, d AB system, $^2J_{AB}$ = 13.5 Hz, ArCH$_A$*H*$_B$], 6.80 [1H, t, $^3J_{HH}$ = 7.7 Hz, Ar*H*], 6.97 [2H, m, Ar*H*], 7.20 [1H, t, $^3J_{HH}$ = 7.8 Hz]; ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 26.8 [C(*C*H$_3$)$_3$], 33.8 [*C*(CH$_3$)$_3$], 51.5 [Ar*C*H$_2$NH], 51.6 [O*C*H$_3$], 69.5 [NH*C*(C_4H_9)], 116.4, 119.3, 122.2, 128.6, 129.1, 157.7 [Ar], 173.8 [*C*OOMe].

2.2 Evaluation of catalytic activities of (47a) and (47b) as potential novel ligands in catalytic asymmetric addition reactions.

2.2.1 Asymmetric Strecker reaction

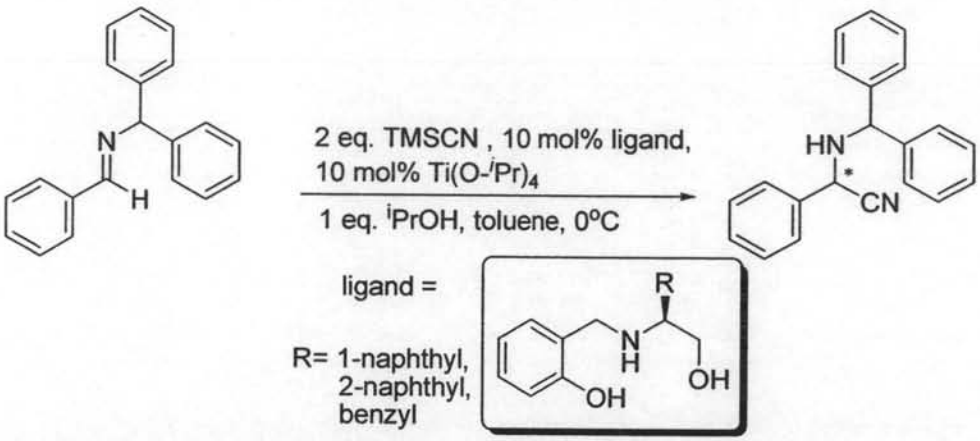
2.2.1.1 Synthesis of (*E*)-*N*-benzylidenediphenylmethanamine (49).



A 250 mL round-bottomed flask was placed with α-aminodiphenylmethane (1.8326 g, 10.000 mmol) dissolved in 50 mL of dichloromethane. Anhydrous magnesium sulphate (100 mg) was added followed by benzaldehyde (1.0610 g, 9.9981 mmol). The resulting solution was stirred at the room temperature for 12 h. The solvent was evaporated to afford a white solid as crude product. Crystallization from hexanes yielded **49** as a white crystal (1.2355 g, 4.5530 mmol, 46 %). ^{1}H-NMR

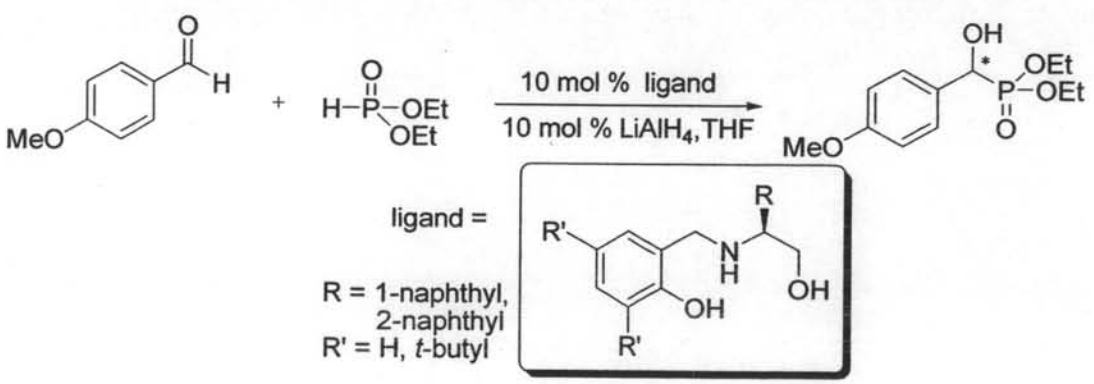
($CDCl_3$, 400 MHz) δ 5.63 [1H, s, C*H*Ar_2], 7.26 [2H, m, Ar*H*], 7.34 [4H, apt, Ar*H*], 7.43 [7H, m, Ar*H*], 7.87 [2H, m, Ar*H*], 8.45 [1H, s, ArC*H*=N].

2.2.1.2 A representative procedure for Strecker reaction



An oven-dried NMR tube was charged with the ligand (0.02 mmol) which was dissolved in 400 μL of toluene. Titanium isopropoxide (5.86 μL, 0.02 mmol) was added into the tube. The stopper was placed and the solution was shaken vigorously over a period of 15 min, during which the colour of solution changed from colourless to bright yellow (if the ligand was insoluble, sonication might be necessary). The imine **49** (0.0543 g, 0.200 mmol) was added as a solid. The tube was shaken until all of the solid was completely dissolved, The tube was sealed with parafilm and cooled in an ice-salt bath for 30 min with occasional shakings. Trimethylsilyl cyanide (TMSCN, 50.3 μL, 0.400 mmol) was added, followed by 2-propanol (15.3 μL, 0.200 mmol). The stopper was resealed with parafilm, the reaction mixture was cooled in an ice-salt bath over 12 h with occassional shaking. Percent enantiomeric excess was determined from the crude sample by ^{1}H-NMR experiment, using (+)-camphorsulfonic acid as a chiral solvating agent.[*28*]

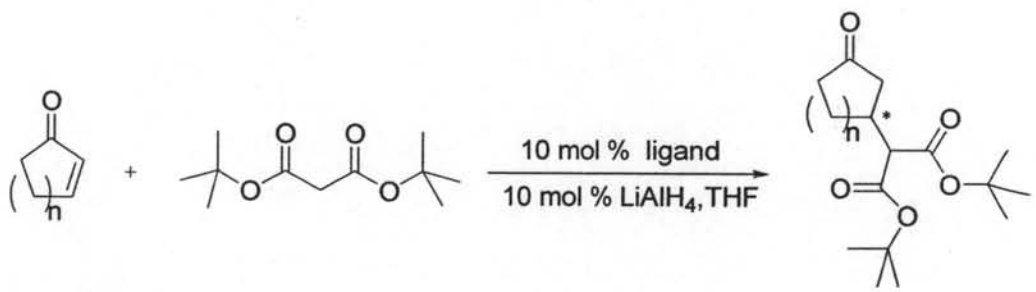
2.2.2 A representative procedure for asymmetric Pudovik reaction[*29*]



The ligand (0.05 mmol) was weighed into an oven-dried 25 mL round-bottom flask, then dissolved with 1 mL of dried THF under a nitrogen atmosphere. A $LiAlH_4$ solution (1 M solution in hexanes (50 μL, 0.05 mmol)) was added. After stirring for 1 h, an anisaldehyde (0.0680 g, 0.5 mmol) solution in THF was injected. The reaction mixture was allowed to stir at room temperature for 5 days. The crude reaction mixture was purified by flash-column chromatography (SiO_2, 60-80 % EtOAc / hexane) and the desired product was afforded as a white solid. The enantioselectivity of the product was determined by chiral GC experiment.

Diethyl 1-hydroxy-(4-methoxyphenyl)methylphosphonate (50): ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.21 [3H, t, $^3J_{HH}$ = 7.1 Hz, CH_2CH_3], 1.26 [3H, $^3J_{HH}$ = 7.1 Hz, CH_2CH_3], 3.79 [3H, s, OCH_3], 3.92-4.08 [4H, m, OCH_2CH_3], 4.94 [1H, d, $^2J_{HP}$ = 10.0 Hz, ArCH(OH)], 6.88 [2H, d, $^3J_{HH}$ = 8.5 Hz, ArH], 7.39 [2H, dd, $^3J_{HH}$ = 8.5 Hz and $^4J_{HH}$ = 1.7 Hz, ArH]; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 16.3, 16.4, 16.4 [CH_2CH_3], 55.2 [OCH_3], 63.0, 63.1, 63.2, 63.3 [OCH_2CH_3], 70.0, 71.1 [ArCH(OH)P], 113.7, 113.7 [CH_3OCCH], 128.4, 128.5 [CHCCH(OH)], 128.5, 128.5 [CCH(OH)], 159.5 [CH_3OC].

2.2.3 The representative procedure for enantioselective Michael reaction between di-*t*-butylmalonate and a cyclic enone[27]



The ligand (0.05 mmol) was weighed into an oven-dried 25 mL round-bottom flask, then dissolved with 1 mL of dried THF under a nitrogen atmosphere. A $LiAlH_4$ solution (1 M solution in hexane (50 μL, 0.05 mmol) was added. After 1 h of stirring, the period of complex formation, a di-*tert*-butylmalonate (112 μL , 0.5 mmol) solution in THF was added. The reaction mixture was allowed to stir at room temperature for 5 h. Then, the crude reaction mixture was purified by flash-column chromatography (SiO_2, 5 % EtOAc / hexanes) and afford the desired product. The enantioselectivity of the product was determined by chiral GC experiment.

di-*tert*-butyl 2-(3-oxocyclopentyl)malonate (51a): Starting from 2-cyclopenten-1-one (41 μL, 0.500 mmol), product **51a** was obtained as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.43 [18H, s, CH_3], 1.60 [1H, m, $CH_2CH_aH_bCO$], 1.94 [1H, m, $CH_cH_dCH_2CO$], 2.21 [3H, m], 2,42 [1H, dd ABX system $^2J_{AB}$ = 18.4 Hz and $^3J_{AX}$ = 8 Hz, CH_AH_BCO], 2.72 [1H, m, C*H*CH($CO_2{}^t$Bu)$_2$], 3.07 [1H, d $^3J_{HH}$ = 8 Hz, C*H*($CO_2{}^t$Bu)$_2$]; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 27.5 [CH_2CHCH_2], 27.9 [CH_3], 27.9 [CH_3], 36.2 [C(O)CH_2CH_2], 38.2 [C(O)CH_2CH_2], 43.0 [C(O)CH_2CH], 58.6 [C(O)CHC(O)], 81.9 [O$C(CH_3)_3$], 81.9 [O$C(CH_3)_3$], 167.5 [CH_2C(O)O], 167.5 [CH_2C(O)O], 217.8 [CH_2C(O)CH_2].

di-*tert*-butyl 2-(3-oxocyclohexyl)malonate (51b): Starting from 2-cyclohexen-1-one (48 µL, 0.500 mmol), product **51b** was obtained as a colourless liquid or solid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.49 [18H, s, C(CH_3)$_3$], 1.53 [1H, m, $CH_cH_dCH_aH_bCO$], 1.68 [1H, m, $CH_cH_dCH_2CO$], 2.01 [1H, m, $CH_2CH_aH_bCO$], 2.10 [2H, m, $CH_cH_dCH_2CH$], 2.28, [2H, m, $CHCH_2CO$], 2.43 [1H, m, C*H*CH($CO_2{}^t$Bu)$_2$], 3.10 [1H, d, $^2J_{HH}$ = 7.6 Hz, C*H*($CO_2{}^t$Bu)$_2$]; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 24.6 [$CH_2CH_2CH_2$], 27.9 [CH_3], 27.9 [CH_3], 28.8 [CH_2CHCH_2], 37.8 [CH_2CH_2CH], 41.1 [C(O)CH_2CH_2], 45.2 [C(O)CH_2CH], 58.8 [C(O)CHC(O)], 81.9 [O$C(CH_3)_3$], 81.9 [O$C(CH_3)_3$], 167.2 [CH_2C(O)O], 167.2 [CH_2C(O)O] , 210.1 [CH_2C(O)CH_2].