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Supporting Information

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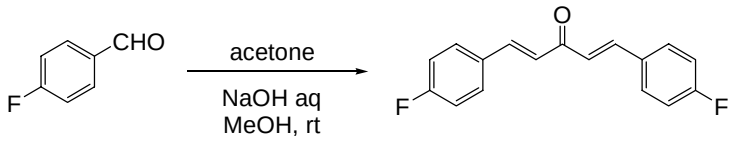
Enantio- and Diastereoselective Catalytic Mannich-Type Reaction of a Glycine Schiff Base Using a Chiral Two-Center Phase-Transfer Catalyst**

Akihiro Okada, Tomoyuki Shibuguchi, Takashi Ohshima,* Hyuma Masu, Kentaro Yamaguchi, Masakatsu Shibasaki*

General: NMR spectra were measured on a JEOL JNM-LA500 spectrometer, operating at 500 MHz for ^{1}H, 126 MHz for ^{13}C, 470 MHz for ^{19}F. For ^{1}H and ^{13}C NMR, chemical shifts are reported in ppm on the δ scale relative to TMS (d = 0 for ^{1}H NMR) or residual solvent as internal reference. For ^{19}F NMR, chemical shifts are reported in ppm on the δ scale with trifluoroacetic acid or phosphoric acid as an external reference, respectively. Infrared (IR) spectra were recorded on a JASCO FT/IR-410 diffraction grating infrared spectrophotometer. ESI mass spectra were measured on Waters-ZQ4000. EI mass spectra were measured on a JEOL JMS-BU20 GCmate. FAB mass spectra were measured on a JEOL JMS-BU20 GCmate or a JEOL JMS-700V. Optical rotations were measured on a JASCO P-1010 polarimeter. Melting points were measured on a Yamato Melting Point Apparatus MP-21. The enantiomeric excess (ee) was determined by HPLC analysis. HPLC was performed on JASCO HPLC systems consisting of the following: pump, PU980; detector; UVIDEC-100-IV, measured at 245 nm; column, DAICEL CHIRALPAK AD-H and DAICEL CHIRALCEL OD-H; mobil phase, hexane–2-propanol. Column chromatography was performed with silica gel Merck 60 (230–400 mesh ASTM). Reactions were carried out in dry solvents under an argon atmosphere, unless otherwise mentioned.

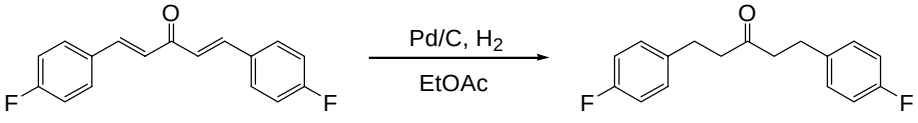
Catalyst preparation

1,5-[Bis(4-fluorofphenyl)]-1,4-pentadien-3-one.



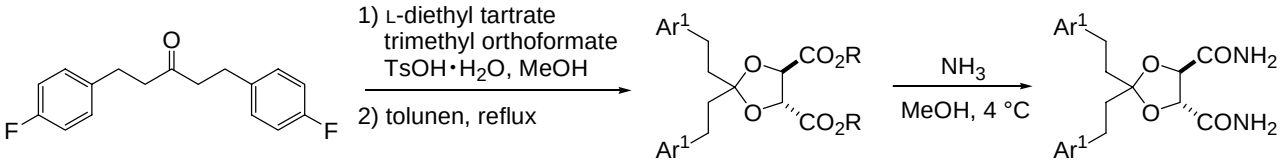
To a solution of NaOH (2.5 g) in H_2O-EtOH (25 mL/25 mL) was added a solution of 4-fluorobenzaldehyde (2.7 mL, 25.0 mmol) in acetone (1.0 mL, 13.0 mmol) at room temperature. The solution color turned to yellow immediately, and gradually changed to yellow suspension. After 1 hour, the yellow solid was isolated via glass filter filtration and washed with water. Drying *in vacuo* gave 1,5-[bis(4-fluorofphenyl)]-1,4-pentadien-3-one (3.78 g, >99%): pale yellow powder; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (d, *J* = 15.9 Hz, 2H), 7.61 (dd, *J* = 8.6 Hz, 8.5 Hz, 4H), 7.11 (dd, *J* = 8.6 Hz, 8.5 Hz, 4H), 6.99 (d, *J* = 15.9 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 188.4, 164.0 (d, *J* = 251 Hz), 142.1, 130.9, 130.3 (d, *J* = 8 Hz), 125.0, 116.1 (d, *J* = 22Hz); ^{19}F NMR (470.4 MHz, $CDCl_3$): — 109.9.

1,5-[Bis(4-fluorofphenyl)]-3-pentanone.



To a solution of 1,5-[bis(4-fluorofphenyl)]-1,4-pentadien-3-one (5.0 g, 18.5 mmol) in EtOAc (150 mL) was added Pd on charcoal (10%, 500 mg) at room temperature. The reaction mixture was stirred at the same temperature under H_2 atmosphere for 2 h. Pd and charcoal were filtered off and the mixture was concentrated. The residue was purified by flash column chromatography (silica gel, hexane/ether 10/1 to 5/1) to give 1,5-[bis(4-fluorofphenyl)]-3-pentanone (3.33 g, 66%): colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.09 (dd, *J* = 7.4 Hz, 5.5 Hz, 4H), 6.94 (dd, *J* = 8.6 Hz, 8.2 Hz, 4H), 2.85 (t, *J* = 7.4 Hz, 4H), 2.67 (t, *J* = 7.4 Hz, 4H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 208.7, 161.4 (d, *J* = 244 Hz), 136.5 (d, *J* = 2.1 Hz), 129.6 (d, *J* = 7.3 Hz), 115.1 (d, *J* = 21 Hz), 44.5, 28.7; ^{19}F NMR (470.4 MHz, $CDCl_3$): －118.1.

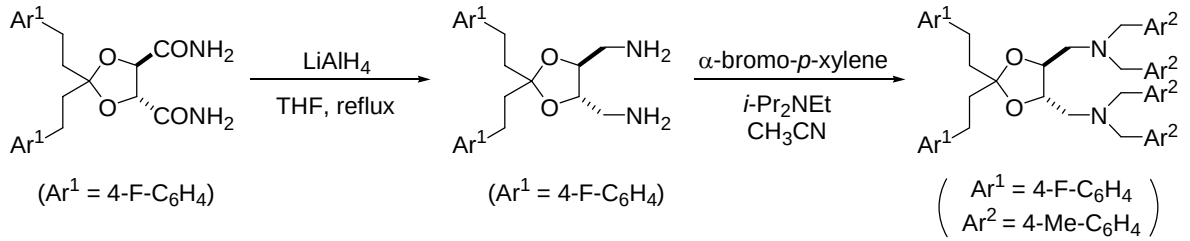
(4*S*,5*S*)-2,2-Bis[(4-fluorophenyl)-2-ethyl]-1,3-dioxolane-4,5-dicarboxamide.



To a solution of 1,5-[bis(4-fluorofphenyl)]-3-pentanone (4.48 g, 16.3 mmol) and methyl orthoformate (2.2 mL, 19.6 mmol) in methanol (15 mL) was added *p*-toluenesulfonic acid monohydrate (171.2 mg, 0.9 mmol) at room temperature. The mixture was gently refluxed while methyl formate formed in the reaction was distilled off. To the cooled reaction mixture, were added diethyl L-tartrate (3.4 mL, 19.6 mmol) and toluene (20 mL). The mixture was allowed to reflux for 72 h. The cooled reaction mixture was basified by the addition of potassium carbonate and stirred at room temperature for 30 min. The mixture was concentrated and the residue was purified by flash column chromatography (silica gel, hexane/ether 10/1 to 5/1) to give a mixture of methyl and ethyl ester (6.17 g), which was used for the next reaction without further purification.

A solution of obtained esters (6.17 g) in methanol (50 mL) was cooled to 4 ºC and then ammonia gas was introduced by bubbling for 30 min. The mixture was concentrated to give crude (4*S*,5*S*)-2,2-bis[(4-fluorophenyl)-2-ethyl]-1,3-dioxolane-4,5-dicarboxamide (5.48 g, ca 83%).

(4*S*,5*S*)-2,2-Bis[(4-fluorophenyl)-2-ethyl]-*N*,*N*,*N'*,*N'*-tetrakis[(4-methylphenyl)methyl]-1,3-dioxolane-4,5-dimethanamine.

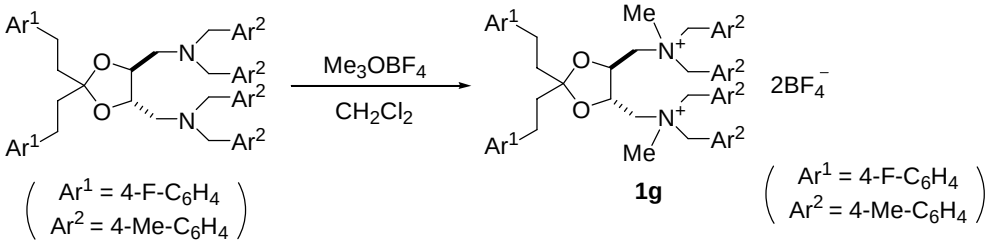


To a solution of (4*S*,5*S*)-2,2-bis[(4-fluorophenyl)-2-ethyl]-1,3-dioxolane-4,5-dicarboxamide (2.83 g)

in anhydrous THF (100 mL) was carefully added lithium aluminum hydride (930.1 mg, 24.5 mmol) at –78 ºC. The mixture was allowed to warm to room temperature then gently refluxed for 2 h. The reaction mixture was cooled to –78 ºC, quenched by addition of water (0.93 mL), followed by 4N aqueous NaOH (0.93 mL) and water (3.0 mL). The suspension was stirred at room temperature for 1 h. The solid was filtered off and washed with THF then combined filtrates were concentrated to afford the crude diamine (2.75 g) as pale brown oil.

To a solution of obtained diamine (2.75 g) in CH_3CN–CH_2Cl_2 (70 mL/30 mL) were added *i*-Pr_2NEt (12.2 mL, 70 mmol) and α-bromo-*p*-xylene (5.18 g, 28.0 mmol) at room temperature. The mixture was stirred for 30 h, then quenched by the addition of water. After concentration of the mixture, water layer was extracted with EtOAc (3 times). The combined organic layers were washed with water and brine, dried over magnesium sulfate and concentrated. The residue was purified by flash column chromatography (silica gel, hexane/ether 50/1 to 20/1) to give (4*S*,5*S*)-2,2-bis[(4-fluorophenyl)-2-ethyl]-*N*,*N*,*N'*,*N'*-tetrakis[(4-methylphenyl)methyl]-1,3-dioxolane-4,5-dimethanamine (3.35 g, 50% from ketone): pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20 (d, *J* = 7.9 Hz, 8H), 7.08 (d, *J* = 7.7 Hz, 8H), 6.99 (dd, *J* = 8.6 Hz, 5.5 Hz, 4H), 6.92 (dd, *J* = 8.9 Hz, 8.6 Hz, 4H), 3.78 (brs, 2H), 3.60 (d, *J* = 13.8 Hz, 4H), 3.53 (d, *J* = 13.7 Hz, 4H), 2.58–2.52 (m, 8H), 2.30 (s, 12H), 1.84 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 161.4 (d, *J* = 245 Hz), 137.8, 136.3, 136.2, 129.6 (d, *J* = 7 Hz), 128.8, 114.9 (d, *J* = 22Hz), 110.9, 79.1, 58.4, 55.2, 40.4, 29.3, 21.1; ^{19}F NMR (470.4 MHz, $CDCl_3$): −118.9; IR (neat, cm^{-1}): 2922, 1601, 1510, 1221, 1056, 806; MS (ESI) m/z 793 $[M+H]^+$; HRMS (FAB) Calcd for $C_{53}H_{59}F_2N_2O_5$ (793.4545) $[M+1]^+$. Found: 793.4548; $[\alpha]^{19}{}_D$ +7.1 (*c* 1.26, $CHCl_3$).

(4*S*,5*S*)-2,2-Bis[(4-fluorophenyl)-2-ethyl]-*N*,*N'*-dimethyl-*N*,*N*,*N'*,*N'*-tetrakis[(4-methylphenyl)methyl]-1,3-dioxolane-4,5-dimethan-aminium ditetrafluoroborate (TaDiAS 1g).

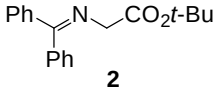


To a solution of (4*S*,5*S*)-2,2-bis[(4-fluorophenyl)-2-ethyl]-*N*,*N*,*N'*,*N'*-tetrakis [(4-methylphenyl)methyl]-1,3-dioxolane-4,5-dimethanamine (3.3461 g, 4.2 mmol) in CH_2Cl_2 (50 mL) was added trimethyloxonium tetrafluoroborate (1.80 g, 12.2 mmol) at room temperature. The mixture was stirred for 24 hours, and concentrated. The residue was purified by flash column chromatography (silica gel, hexane/acetone 3/1 to 1/1) to give (4*S*,5*S*)-2,2-bis[(4-fluorophenyl)-2-ethyl]-*N*,*N'*-dimethyl-*N*,*N*,*N'*,*N'*-tetrakis-[(4-methylphenyl)methyl]-1,3-dioxolane-4,5-dimethan-aminium ditetrafluoroborate (**1g**) (2.17 g, 52%) : colorless amorphous; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (d, *J* = 8.0 Hz, 4H), 7.30 (d, *J* = 7.9 Hz, 4H), 7.25 (d, *J* = 8.0 Hz, 4H), 7.22 (d, *J* = 7.9 Hz, 4H), 7.15 (dd,

J = 8.6 Hz, 5.5 Hz, 4H), 6.94 (dd, J = 8.6 Hz, 8.5 Hz, 4H), 4.68 (m, 2H), 4.62 (d, J = 12.9 Hz, 2H), 4.58 (d, J = 12.8 Hz, 2H), 4.32 (d, J = 12.8 Hz, 2H), 4.16 (d, J = 12.9 Hz, 2H), 3.76–3.84 (m, 4H), 2.74 (s, 6H), 2.59 (m, 4H), 2.37 (s, 6H), 2.36 (s, 6H); ^{13}C NMR (126MHz, $CDCl_3$): δ 161.8 (d, J = 245 Hz), 141.4, 136.7(d, J = 3 Hz), 133.2, 133.1, 130.2, 129.8 (d, J = 7 Hz), 123.2, 123.1, 115.8, 115.2 (d, J = 22Hz), 72.9, 67.4, 66.8, 62.6, 45.7, 38.5, 29.3, 21.3; ^{19}F NMR (470.4 MHz, $CDCl_3$): −118.1, −149.4; IR (KBr, cm^{-1}): 3451, 2972, 2925, 1509, 1223, 1057, 803; Anal. Calcd for $C_{55}H_{64}B_2F_{10}N_2O_2$: C 66.28, H 6.47, N 2.81. Found: C 66.37, H 6.70, N 2.63; $[\alpha]^{22}{}_D$ –23.8 (*c* 1.02, $CHCl_3$).

Substrate preparation

N-(Diphenylmethylene)glycine *tert*-butyl ester (2)



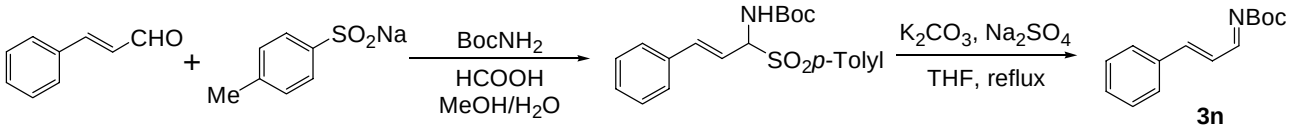
2

2 was prepared according to the reported procedure.[1)]

Boc–imine (3e-n)

All Boc–imines except *trans*-cinnamaldehyde *N*-(*tert*-butoxycarbonyl)imine (**3n**) were prepared according to the reported procedure.[2)]

trans-Cinnamaldehyde *N*-(*tert*-Butoxycarbonyl)imine (3n).



3n

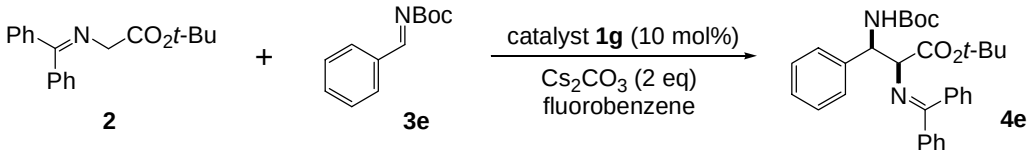
To a solution of sodium *p*-toluenesulfinate (7.2 g, 40.4 mmol) in THF–H_2O (50 mL/6 mL) were added HCO_2H (6 mL) at room temperature. The suspension became clear solution after several minutes. To this solution were added *tert*-butylcarbamate[3)] (2.4 g, 20.5 mmol) and *trans*-cinnamaldehyde (2.5 mL, 19.8 mmol) then reaction mixture was warmed to 40 ºC. The reaction mixture gradually became suspension. After 6 days, the suspension was filtrated by glass filter and the obtained white solid was washed with water and ether. The white solid was dissolved in CH_2Cl_2 and through a short pad silica gel column (CH_2Cl_2/EtOAc 10/1). Resulting white solid 1,3-bis(4-methylphenylsulfonyl) -*N*-(*tert*-butoxycarbonyl)-3-phehylpropylamine (2.8 g) was dried under reduced pressure and used for the next reaction without further purification.

Anhydrous potassium carbonate (9.2 g, 66.2 mmol) and anhydrous sodium sulfate (5.5 g) were flame-dried under vacuum. Once cool, 1,3-bis(4-methylphenylsulfonyl)-*N*-(*tert*-butoxycarbonyl)-3-phehylpropylamine (3.0 g, 5.5 mmol) was added, followed by THF (80 mL). The reaction mixture (white suspension) was heated at 70 ºC for 40 hours, then cooled to room temperature. The white

precipitate was filtered off and obtained yellow solution was concentrated. The residue was purified by Kugelrohr distillation apparatus to give *trans*-cinnamaldehyde *N*-(*tert*-butoxycarbonyl)imine (**3n**) (606.3 mg, 48%): pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.70 (d, *J* = 9.2 Hz, 1H), 7.54 (br d, *J* = 3.7 Hz, 2H), 7.42-7.38 (m, 3H), 7.36 (d, *J* = 15.9 Hz, 1H), 6.99 (dd, *J* = 9.2 Hz, 15.9 Hz, 1H), 1.57 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 171.6, 162.3, 150.5, 134.7, 130.8, 129.0, 128.1, 126.8, 81.9, 27.9; IR (neat, cm^{-1}): 2978, 2925, 1714, 1632, 1253, 1146, 967,; MS (EI) m/z 231 $[M]^+$; HRMS (EI) Calcd for $C_{14}H_{17}NO_2$ (231.1259) $[M]^+$. Found: 231.1253.

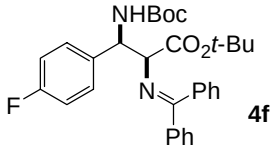
General procedure for the catalytic asymmetric Mannich–type reaction.

***tert*-Butyl (2*S*,3*R*)-3-(*tert*-Butoxycarbonylamino)-2-[(diphenylmethylene)amino]-3-phenylpropaonate (4e).**



To a solution of benzaldehyde *N*-(*tert*-butoxycarbonyl)imine (**3e**) (10.7 mg, 52.3 μmol), *N*-(diphenylmethylene)glycine *tert*-butyl ester (**2**) (14.8 mg, 50.1 μmol) and (4*S*,5*S*)-2,2-bis[(4-fluorophenyl)-2-ethyl]-*N*,*N*'-dimethyl-*N*,*N*,*N*',*N*'-tetrakis[(4-methylphenyl)methyl] -1,3-dioxolane-4,5-dimethan-aminium ditetrafluoroborate (**1g**) (5.0 mg, 5.0 μmol) in fluorobenzene (0.5 mL) was added Cs_2CO_3 (32.6 mg, 100.1 μmol) at –30 ºC. After 19 hours, the reaction was quenched by the addition of water. The water layer was extracted with EtOAc 3 times. The combined organic layer was dried over magnesium sulfate and concentrated. The residue was purified by flash column chromatography (silica gel, hexane/ether 10/1) to give *tert*-butyl (2*S*,3*R*)-3-(*tert*-butoxycarbonylamino)-2-[(diphenylmethylene)amino]-3-phenylpropaonate (**4e**) (24.5 mg, 98%): Colorless amorphous; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60 (d, *J* = 7.3 Hz, 2H), 7.47-7.20 (m, 11H), 6.55 (br d, *J* = 6.1 Hz, 2H), 6.41 (br d, *J* = 8.8 Hz, 1H), 5.48 (br d, *J* = 8.6 Hz, 1H), 4.18 (br s, 1H), 1.52 (s, 9H), 1.51 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 172.1, 169.1, 155.2, 140.7, 138.9, 136.1, 130.4, 128.8, 128.4, 128.2, 128.1, 128.0, 127.2, 126.9, 126.6, 70.0, 56.7, 28.4, 27.9; IR (KBr, cm^{-1}): 3436, 2978, 2925, 1718, 1490, 1153, 697; Anal. Calcd for $C_{31}H_{36}N_2O_4$: C 74.37, H 7.25, N 5.60. Found: C 74.35, H 7.13, N 5.40; $[\alpha]^{22}_{D}$ –62.3 (*c* 1.08, $CHCl_3$), (70% ee); HPLC (DAICEL CHIRALPAK AD-H, hexane/2-propanol 98/2, 1.0 mL/min) t_R: 11.8 min (minor), 13.0 (*trans*), 16.3 (*trans*), and 21.1 min (major).

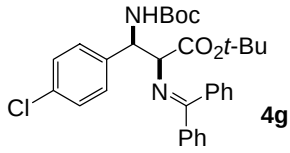
***tert*-Butyl-3-(*tert*-Butoxycarbonylamino)-2-[(diphenylmethylene)amino]-3-(4-fluorophenyl)prop aonate (4f)**



4f

Colorless amorphous; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56 (d, *J* = 7.4 Hz, 2H), 7.43-7.28 (m, 6H), 7.14 (dd, *J* = 7.9 Hz, 5.5 Hz, 2H), 6.92 (dd, *J* = 8.6 Hz, 8.9 Hz, 2H), 6.57 (br d, *J* = 6.4 Hz, 2H), 6.34 (br d, *J* = 9.2 Hz, 1H), 5.38 (br d, *J* = 8.5 Hz, 1H), 4.10 (br s, 1H), 1.47 (s, 9H), 1.45 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 172.3, 168.9, 161.8 (d, *J* = 246 Hz, 1C), 155.1, 138.7, 136.6, 136.0, 130.6, 128.8, 128.6, 128.3, 128.2 (d, *J* = 8 Hz, 1C), 128.0, 127.1, 114.9 (d, *J* = 21 Hz, 1C), 82.0, 79.4, 70.1, 56.1, 28.4, 27.9; ^{19}F NMR (470.4 MHz, $CDCl_3$): δ -117.0; IR (KBr, cm^{-1}): 3437, 2979, 1718, 1450, 1155, 696; Anal. Calcd for $C_{31}H_{35}FN_2O_4$: C 71.79, H 6.80, N 5.40. Found: C 71.52, H 6.90, N 5.25; $[\alpha]^{23}_{D}$ –63.0º (*c* 1.05, $CHCl_3$), (72% ee); HPLC (DAICEL CHIRALPAK AD-H, hexane/2-propanol 98/2, 1.0 mL/min) t_R: 12.3 min (minor), 13.9 min (*trans*), 16.8 min (*trans*), and 25.6 min (major).

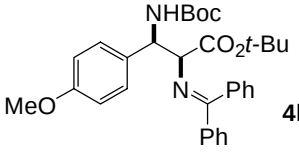
tert-Butyl-3-(_tert_-Butoxycarbonylamino)-2-[(diphenylmethylene)amino]-3-(4-chlorophenyl)propaonate (4g)



4g

Colorless amorphous; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55 (d, *J* = 7.3 Hz, 2H), 7.44-7.27 (m, 6H), 7.20 (d, *J* = 8.6 Hz, 2H), 7.11 (d, *J* = 8.2 Hz, 2H), 6.58 (br d, *J* = 6.7 Hz, 2H), 6.34 (br d, *J* = 8.6 Hz, 1H), 5.37 (br d, *J* = 8.6 Hz, 1H), 4.11 (br s, 1H), 1.47 (s, 9H), 1.45 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 172.4, 168.8, 155.1, 139.4, 138.7, 136.0, 132.7, 130.6, 128.8, 128.6, 128.3, 128.25, 128.0, 128.0, 127.1, 82.1, 79.5, 69.9, 56.3, 28.4, 27.9; IR (KBr, cm^{-1}): 3434, 2978, 2927, 1718, 1490, 1161, 1088, 697; Anal. Calcd for $C_{31}H_{35}ClN_2O_4$: C 69.59, H 6.59, N 5.24. Found: C 69.33, H 6.62, N 5.15; $[\alpha]^{23}_{D}$ –37.8 (*c* 0.83, $CHCl_3$), (58% ee); HPLC (DAICEL CHIRALPAK AD-H, hexane/2-propanol 98/2, 1.0 mL/min) t_R: 12.2 min (minor), 15.9 min (*trans*), 19.1 min (*trans*), and 30.8 min (major).

tert-Butyl (2_S_,3_R_)-3-(_tert_-Butoxycarbonylamino)-2-[(diphenylmethylene)amino]--3-(4-methoxyphenyl)propaonate (4h)

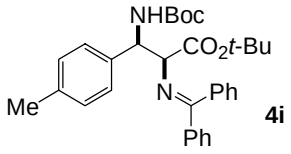


4h

Colorless amorphous; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57 (d, *J* = 7.4 Hz, 2H), 7.40-7.27 (m, 6H), 7.08 (d, *J* = 8.5 Hz, 2H), 6.76 (d, *J* = 8.6 Hz, 2H), 6.56 (br s, 2H), 6.31 (br d, *J* = 8.9 Hz, 1H), 5.36 (br d, *J* = 8.9 Hz, 1H), 4.10 (br s, 1H), 3.76 (s, 3H), 1.46 (s, 9H), 1.44 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 172.0, 169.1, 158.5, 155.1, 138.9, 136.1, 133.0, 130.4, 128.8, 128.4, 128.2, 128.0, 127.7, 127.2, 113.5, 81.8, 79.2, 70.2, 56.2, 55.2, 28.4, 27.9; IR (KBr, cm^{-1}): 3436, 2977, 2925, 1718, 1636, 1490, 1149, 781; Anal. Calcd for $C_{32}H_{38}N_2O_5$: C 72.43, H 7.22, N 5.28. Found: C 72.28, H 7.34, N

5.17; $[\alpha]^{22}_{D}$ –66.3 (*c* 1.02, $CHCl_3$), (83% ee); HPLC (DAICEL CHIRALPAK AD-H, hexane/2-propanol 95/5, 1.0 mL/min) t_R: 9.1 min (minor), 11.5 min (*trans*), 12.2 min (*trans*), and 26.0 min (major).

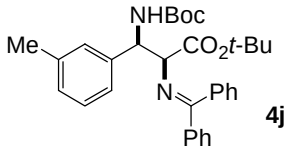
tert-Butyl-3-(_tert_-Butoxycarbonylamino)-2-[(diphenylmethylene)amino]-3-(4-methylphenyl)propaonate (4i)



4i

Colorless amorphous; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56 (d, *J* = 7.1 Hz, 2H), 7.38-7.24 (m, 6H), 7.05-7.02 (m, 4H), 6.53 (br d, *J* = 7.0 Hz, 2H), 6.32 (br d, *J* = 9.2 Hz, 1H), 5.38 (br d, *J* = 9.2 Hz, 1H), 4.11 (br s, 1H), 2.28 (s, 3H), 1.46 (s, 9H), 1.44 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 171.9, 169.2, 155.1, 139.0, 137.7, 136.4, 136.1, 130.4, 128.8, 128.8, 128.4, 128.2, 127.9, 127.2, 126.5, 81.8, 79.1, 70.2, 56.5, 28.4, 27.9, 21.0; IR (KBr, cm^{-1}): 3433, 2979, 1718, 1491, 1162, 696; Anal. Calcd for $C_{32}H_{38}N_2O_4$: C 74.68, H 7.44, N 5.44. Found: C 74.48, H 7.50, N 5.54; $[\alpha]^{23}_{D}$ –64.3 (*c* 1.04, $CHCl_3$), (80% ee); HPLC (DAICEL CHIRALPAK AD-H, hexane/2-propanol 98/2, 1.0 mL/min) t_R: 12.0 min (minor), 13.3 min (*trans*), 14.6 min (*trans*), and 22.5 min (major).

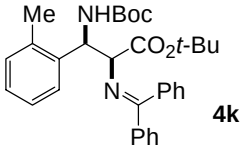
tert-Butyl-3-(_tert_-Butoxycarbonylamino)-2-[(diphenylmethylene)amino]-3-(3-methylphenyl)propaonate (4j)



4j

Colorless amorphous; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55 (d, *J* = 7.0 Hz, 2H), 7.39-7.24 (m, 5H), 7.11 (t, *J* = 7.3 Hz, 1H), 6.97 (br t, *J* = 8.0 Hz, 2H), 6.92 (s, 1H), 6.49 (br s, 2H), 6.33 (br d, *J* = 8.9 Hz, 1H), 5.38 (br d, *J* = 8.9 Hz, 1H), 4.12 (br s, 1H), 2.24 (s, 3H), 1.48 (s, 9H), 1.46 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 172.0, 169.2, 155.2, 140.6, 139.0, 137.6, 136.1, 130.4, 128.8, 128.4, 128.1, 128.0, 127.9, 127.6, 127.5, 127.2, 123.6, 81.8, 79.2, 70.2, 56.7, 28.4, 28.0, 21.3; IR (KBr, cm^{-1}): 3440, 2977, 2925, 1718, 1628, 1490, 1161, 778, 696; Anal. Calcd for $C_{32}H_{38}N_2O_4$: C 74.68, H 7.44, N 5.44. Found: C 74.62, H 7.72, N 5.20; $[\alpha]^{23}_{D}$ –71.7 (*c* 0.76, $CHCl_3$), (70% ee); HPLC (DAICEL CHIRALPAK AD-H, hexane/2-propanol 98/2, 1.0 mL/min) t_R: 9.9 min (*trans*), 10.3 min (minor), 13.6 min (*trans*), and 17.8 min (major).

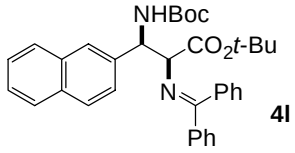
tert-Butyl-3-(_tert_-Butoxycarbonylamino)-2-[(diphenylmethylene)amino]-3-(2-methylphenyl)propaonate (4k)



4k

Colorless amorphous; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.59 (d, *J* = 7.3 Hz, 2H), 7.42-7.02 (m, 10H), 6.42 (br d, *J* = 8.8 Hz, 1H), 6.31 (br s, 1H), 5.64 (br d, *J* = 8.3 Hz, 1H), 4.02 (br s, 1H), 2.08 (s, 3H), 1.48 (s, 9H), 1.44 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 172.2 (CO_2*t*-Bu), 169.3 (CONH), 155.1 (Ar), 138.8 (Ar), 138.6(Ar), 136.0 (Ar), 134.7 (Ar), 130.5 (Ar), 130.2 (Ar), 128.8 (Ar), 128.3 (Ar), 128.1 (Ar), 128.0 (Ar), 127.0 (Ar), 126.9 (Ar), 126.4 (Ar), 125.6 (Ar), 81.8 ($C(CH_3)_3$;CO_2*t*-Bu), 79.2 (*C*$(CH_3)_3$;Boc), 67.6, 53.7, 28.4, 27.9, 18.4 (Me); IR (KBr, cm^{-1}): 3429, 2974, 1718, 1628, 1490, 1149, 750, 699; Anal. Calcd for $C_{32}H_{38}N_2O_4$: C 74.68, H 7.44, N 5.44. Found: C 74.66, H 7.45, N 5.40; $[\alpha]^{21}_{D}$ –83.1 (*c* 0.74, $CHCl_3$), (68% ee); HPLC (DAICEL CHIRALPAK AD-H, hexane/2-propanol 98/2, 1.0 mL/min) t_R: 5.8 min (minor), 8.4 min (*trans*), 9.8 min (*trans*), and 15.5 min (major).

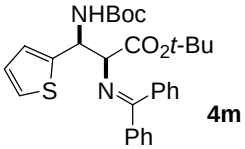
tert-Butyl-3-(_tert_-Butoxycarbonylamino)-2-[(diphenylmethylene)amino]-3-(2-naphthyl)propaonate (4l)



4l

Colorless amorphous; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77-7.69 (m, 4H), 7.63 (s, 1H), 7.53 (d, *J* = 7.3 Hz, 2H), 7.43-7.27 (m, 6H), 7.14 (br t, *J* = 7.6 Hz, 2H), 6.46 (br d J = 8.9 Hz, 1H), 6.42 (br s, 2H), 5.58 (br d, *J* = 7.4 Hz, 1H), 4.26 (br s, 1H), 1.49 (s, 9H), 1.47 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 172.2, 169.1, 155.2, 138.8, 138.2, 136.0, 133.2, 132.5, 130.5, 130.2, 128.7, 128.4, 128.1, 128.0, 127.9, 127.8, 127.7, 127.5, 127.1, 125.9, 125.5, 125.4, 124.8, 82.0, 79.4, 70.0, 56.8, 28.4, 27.9; IR (KBr, cm^{-1}): 3429, 2975, 1744, 1716, 1487, 1149, 694; Anal. Calcd for $C_{35}H_{38}N_2O_4$: C 76.34, H 6.96, N 5.09. Found: C 76.08, H 6.95, N 5.00; $[\alpha]^{24}_{D}$ –40.8 (*c* 0.78, $CHCl_3$), (60% ee); HPLC (DAICEL CHIRALPAK AD-H, hexane/2-propanol 98/2, 1.0 mL/min) t_R: 18.0 min (minor), 19.6 min (*trans*), 21.7 min (*trans*), and 26.9 min (minor).

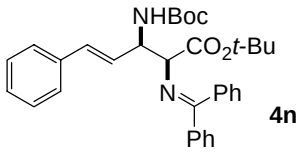
tert-Butyl-3-(_tert_-Butoxycarbonylamino)-2-[(diphenylmethylene)amino]-3-(2-thiophenyl)propaonate (4m)



4m

Colorless amorphous; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (d, *J* = 8.3 Hz, 2H), 7.41-7.32 (m, 6H), 7.12 (d, *J* = 4.9 Hz, 1H), 6.89-6.87 (m, 4H), 6.27 (br d, *J* = 9.2 Hz, 1H), 5.68 (br d, *J* = 9.2 Hz, 1H), 4.20 (br s, 1H), 1.45 (s, 18H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 172.9, 168.6, 154.9, 144.8, 138.9, 136.2, 130.6, 129.0, 128.6, 128.3, 128.0, 127.2, 126.4, 124.5, 124.4, 82.0, 79.4, 69.9, 53.0, 28.3, 27.8; IR (KBr, cm^{-1}): 3437, 2977, 2925, 1718, 1490, 1156, 845, 692; Anal. Calcd for $C_{29}H_{34}N_2O_4S$: C 68.75, H 6.76, N 5.53. Found: C 68.56, H 7.04, N 5.28; $[\alpha]^{21}_{D}$ –93.1 (*c* 1.05, $CHCl_3$), (80% ee); HPLC (DAICEL CHIRALPAK AD-H, hexane/2-propanol 98/2, 1.0 mL/min) t_R: 11.1 min (minor), 13.1 min (*trans*), and 24.9 min (major).

***tert*-Butyl-3-(*tert*-Butoxycarbonylamino)-2-[(diphenylmethylene)amino]-5-phenyl-4-pentenoate (4n)**

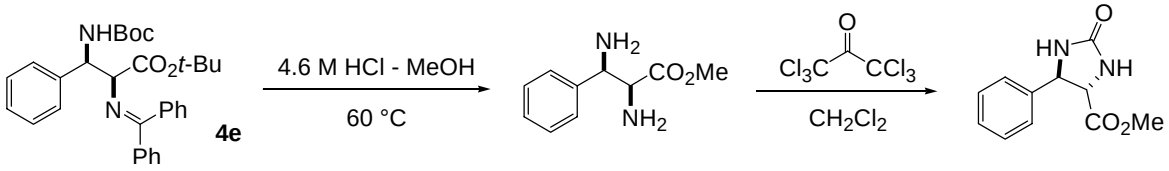


4n

Colorless amorphous; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64 (d, *J* = 7.9 Hz, 2H), 7.40-7.08 (m, 11H), 7.07 (d, *J* = 5.5 Hz, 2H), 6.51 (d, *J* = 15.9 Hz, 1H), 5.98 (dd, *J* = 15.9 Hz, 6.4 Hz, 1H), 5.91 (br d, *J* = 6.4 Hz, 1H), 4.97 (br s, 1H), 4.12 (br s, 1H), 1.46 (s, 9H), 1.45 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 172.3, 169.1, 155.1, 139.1, 136.8, 136.4, 130.7, 130.6, 128.9, 128.7, 128.5, 128.46, 128.46, 128.0, 127.5, 127.4, 126.4, 81.8, 79.2, 68.8, 55.1, 28.4, 27.9; IR (KBr, cm^{-1}): 3436, 2978, 2931, 1718, 1628, 1490, 1154, 695; Anal. Calcd for $C_{33}H_{38}N_2O_4$: C 75.26, H 7.27, N 5.32. Found: C 75.16, H 7.32, N 5.10; $[\alpha]^{22}_{D}$ +7.7 (*c* 0.79, $CHCl_3$), (66% ee); HPLC (DAICEL CHIRALCEL OD-H, hexane/2-propanol 99/1, 0.5 mL/min) t_R: 13.5 min (minor), 15.8 min (major), and 17.2 min (*trans*).

Determination of relative and absolute configulation of 4a

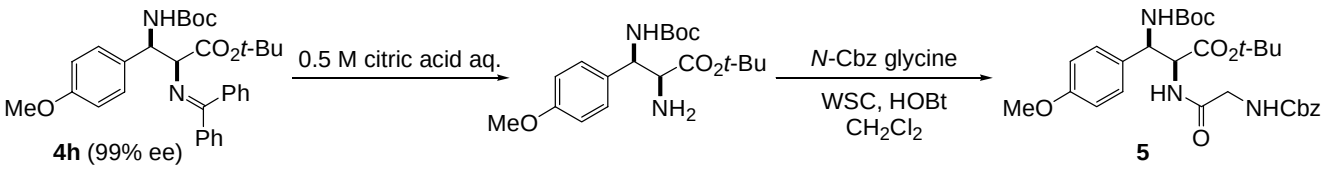
Conversion to (4*S*,5*R*)-4-(Methoxycarbonyl)-5-phenyl-2-imidazolidinone.



tert-Butyl-(2*S*,3*R*)-3-(*tert*-Butoxycarbonylamino)-2-[(diphenylmethylene)amino]-3-phenylpropaonate (**4e**) (23.3 mg, 46.5 μmol) was dissolved in 4.6 M HCl–methanol solution and heated to 60 ºC. After 12 h, the mixture was concentrated and added excess Et_3N and toluene then re-evaporated. To the residue (yellow solid) was added a solution of triphosgene (9.3 mg, 31.3 μmol) in CH_2Cl_2 (1.2 mL) at 4 ºC. After 2 h, the mixture was evaporated. The residue was purified by preparative TLC (EtOAc) to give (4*S*,5*R*)-4-(Methoxycarbonyl)-5-phenyl-2-imidazolidinone (4.0 mg, 39%): white solid, mp: 206.0 ºC (dec.); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31-7.23 (m, 5H), 4.79 (d, *J* = 4.5 Hz, 1H), 4.01 (d, *J* = 4.5 Hz, 1H), 3.72 (s, 3H); $[\alpha]^{23}_{D}$ +53.0 (*c* 0.40, MeOH). Relative and absolute configuration was determined by comparison with ^{1}H NMR spectrum and optical rotation of the literature[4]. (lit[4]. $[\alpha]^{20}_{D}$ –101.7 (*c* 1.0, MeOH)).

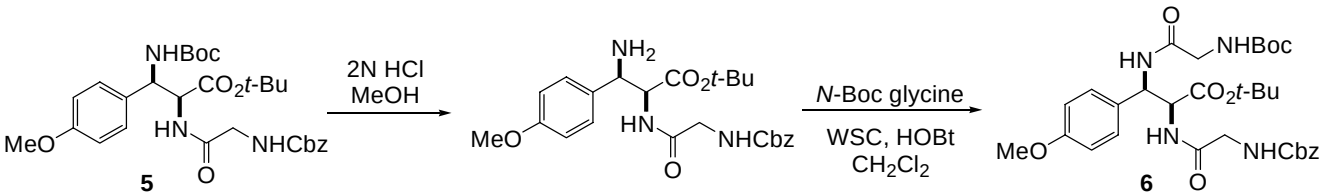
Tripeptide Synthesis

Synthesis of 5



To a solution of *tert*-Butyl (2*R*,3*S*)-3-(*tert*-butoxycarbonylamino)-2-[(diphenylmethylene)amino]--3-(4-methoxyphenyl)propionate **4h** (609 mg, 1.15 mmol) in THF (20 mL) was added 0.5 M citric acid (15 mL) at room temperature and stirred for 1 h. The mixture was extracted with Et_2O (5 mL × 3), and aqueous phase was basified by saturated aqueous $NaHCO_3$. Then it was extracted with EtOAc (5 mL × 3), washed with brine (15 mL), and dried over anhydrous Na_2SO_4 and concentrated. This crude mixture was dissolved in CH_2Cl_2 (30 mL), and Cbz-glycine (460 mg, 2.2 mmol) and HOBt (186 mg, 1.38 mmol) were added at 4 ℃. WSC·HCl (265 mg, 1.38 mmol) was added to this solution at 4 ℃. After stirring for 12 h at same temperature, 1N HCl (15 mL) was added. The solution was extracted with Et_2O (5 mL × 3), washed with H_2O (5 mL), brine (10 mL), and dried over Na_2SO_4. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 5/1) to give **5** (576 mg, 1.03 mmol, 90%). Colorless amorphous; ^{1}H NMR ($CDCl_3$): δ 7.36-7.31 (m, 5H), 7.20 (d, *J* = 8.3 Hz, 2H), 7.05 (br-s, 1H), 6.85 (d, *J* = 8.5 Hz, 2H), 5.40 (br-s, 1H), 5.25 (br-s, 1H), 5.14 (s, 2H), 4.90 (m, 1H), 3.91 (br-s, 2H), 3.78 (s, 3H), 1.39 (s, 9H), 1.24 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 169.5, 168.6, 158.9, 156.4, 155.4, 136.0, 130.0, 128.2, 127.7, 113.6, 82.3, 79.4, 66.7, 57.8, 55.7, 54.9, 43.9, 28.0, 27.4; IR (KBr, cm^{-1}): 3376, 2979, 2936, 1718, 1685, 1515, 1249, 1159; Anal. Calcd for $C_{29}H_{39}N_3O_8$: C 62.46, H 7.05, N 7.54. Found: C 62.23, H 7.28, N 7.35. $[\alpha]^{26}_D$ −16.9 (*c* 1.00, $CHCl_3$), (99% ee).

Conversion 5 to tripeptide 6.

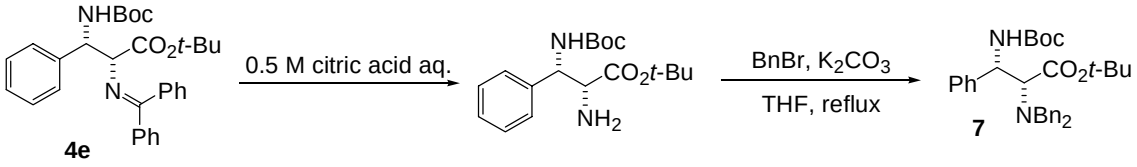


The solution of **5** (492 mg, 0.88 mmol) in 2N HCl-MeOH (20 ml) was stirred at room temperature for 10 h. Then the mixture was quenched by aqueous $NaHCO_3$ (30 mL), extracted with EtOAc (20 mL × 2), and dried over Na_2SO_4. The extracts was concentrated and dissolved in dry CH_2Cl_2 (20 mL). To this solution, Boc-glycine (170 mg, 0.97 mmol), and HOBt (143 mg, 1.06 mmol) was added at 4 ℃. WSC·HCl (265 mg, 1.38 mmol) was added to this solution at 4 ℃ and stirred for 2 h at same temperature. Then, aqueous 1N HCl (20 mL) was added to the mixture. The solution was extracted with EtOAc (20 mL × 2), washed with 1N HCl (10 mL), water (10 mL × 2), brine (15 mL), and dried over Na_2SO_4. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 1/3) to give **6** (497 mg, 0.81 mmol, 92%). Colorless amorphous; ^{1}H NMR ($CDCl_3$): δ 7.36-7.31 (m, 5H), 7.26 (d, *J* = 8.6 Hz, 2H), 7.05 (br-s, 1H), 6.98 (br-s, 1H), 6.85 (d, *J* = 8.6 Hz, 2H), 5.76 (br-s, 1H), 5.38 (br-s, 1H), 5.21-5.10 (m, 3H), 4.84 (m, 1H), 3.89-3.86 (m, 2H), 3.78 (s, 3H), 3.68-3.64 (m, 2H), 1.40 (s, 9H), 1.20 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 168.6, 159.6, 157.1, 156.5, 136.4, 129.7, 129.1, 128.6, 128.3, 114.1, 82.7, 80.2, 67.2, 57.9, 55.4, 44.5,

44.3, 28.4, 27.7; IR (KBr, cm^{-1}): 3311, 2979, 2936, 1672, 1515, 1368, 1251, 1158; MS (ESI) *m/z* 637 $[M+23]^+$; HRMS (FAB) Calcd for $C_{31}H_{43}N_4O_9$ (615.3025) $[M+1]^+$. Found: 615.3024; $[\alpha]^{25}_D$ −41.0 (*c* 1.05, $CHCl_3$), (99% ee).

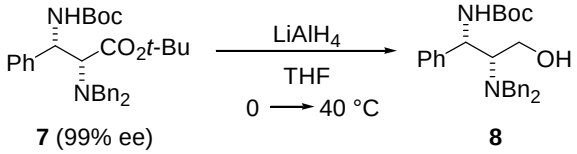
Transformation of 4e to 8 the key intermediate of CP-99,994

***tert*-Butyl (2*R*,3*S*)-3-(*tert*-butoxycarbonylamino)-2-(dibenzylamino)-3-phenylpropaonate (7).**



To a solution of *tert*-Butyl (2*R*,3*S*)-3-(*tert*-butoxycarbonylamino)-2-[(diphenylmethylene)amino]-3-phenylpropionate **4e** (1.52g, 3.04 mmol) in THF (20 mL) was added 0.5 M citric acid (20 mL) at room temperature and stirred for 2 h. The mixture was extracted with Et_2O (5 mL × 3), and aqueous phase was basified by saturated aqueous $NaHCO_3$. Then it was extracted with EtOAc (5 mL × 3), washed with brine (15 mL), and dried over anhydrous Na_2SO_4 and concentrated. This crude mixture was dissolved in CH_3CN (10 mL), and *i*-Pr_2NEt (2.67 mL, 15 mmol) was added. To this solution benzyl bromide (1.57g, 9.1 mmol) was added and stirred at 60 ℃ for 7 h. After cooling to room temperature, H_2O (5 mL) was added and the mixture was extracted with Et_2O (5 mL × 3) , washed with brine (10 mL) and dried over Na_2SO_4. The crude mixture was concentrated and purified by flash column chromatography (silica gel, hexane/EtOAc = 7/1). The obtained compound was recrystallized from hexane/EtOAc to give optically pure **7** (648mg, 1.26 mmol, 42%). white solid; mp: 135 °C; ^{1}H NMR ($CDCl_3$): δ 7.37-7.31 (m, 8H), 7.30-7.27 (m, 2H), 7.21-7.18 (m, 3H), 7.17-7.20 (m, 2H), 5.27 (m, 1H), 4.06 (d, *J* = 13.8 Hz, 2H), 3.40 (d, *J* =13.8 Hz, 2H), 3.28 (d, *J* = 11.5 Hz, 1H), 1.43 (br-s, 9H), 1.29 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 168.0, 155.4, 138.8, 129.2, 128.6, 128.5, 128.3, 128.1, 127.7, 127.3, 81.7, 79.4, 69.7, 66.2, 54.3, 28.4, 28.1; IR (KBr, cm^{-1}): 3418, 2979, 1717, 1507, 1153, 697; MS (ESI) *m/z* 517 $[M+1]^+$; HRMS (FAB) Calcd for $C_{32}H_{41}N_2O_4$ (517.3061) $[M+1]^+$. Found: 517.3063; $[\alpha]^{24}_D$ +47.1 (*c* 0.99, $CHCl_3$), (>99% ee); HPLC (DACEL CHIRALPAK OD-H, hexane/2-propanol 95/5, 0.5 mL/min). t_R: 8.1 min (major), 9.0 min (minor).

(2*R*,3*S*)-3-(*tert*-Butoxycarbonylamino)-2-(dibenzylamino)-3-phenylpropanol (8).



To a solution of $LiAlH_4$ (28.5 mg, 0.75 mmol) in THF (3.0 mL), the solution of *tert*-Butyl (2*R*,3*S*)-3-(*tert*-butoxycarbonylamino)-2-(dibenzylamino)-3-phenylpropaonate **7** (258.2 mg, 0.5 mmol) in THF (2.0 mL) at 4 ℃ was slowly added. The mixture was stirred at 40 °C for 4 h. After

cooling to 4 ℃, the mixture was treated with water (0.3 mL), 4 N sodium hydroxide solution (0.3 mL), and water (0.93 mL). The mixture was stirred at room temperature until the gray color turned to white. After filtration, the extract was evaporated. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 10/1) and gave **8** (204 mg, 0.46 mmol, 91%). Colorless amorphous; ^{1}H NMR ($CDCl_3$): δ 7.38-7.29 (m, 10H), 7.28-7.22 (m, 3H), 7.10 (d, *J* = 6.9 Hz, 2H), 5.43-5.42 (m, 1H), 4.71-4.70 (m, 1H), 3.95 (d, *J* = 13.2 Hz, 2H), 3.76 (d, *J* =13.8 Hz, 2H), 3.51-3.48 (m, 2H) 2.94-2.88 (m, 1H), 1.26 (br-s, 9H); ^{13}C NMR ($CDCl_3$): δ 155.4, 139.3, 129.1, 128.5, 128.4, 127.5, 127.4, 127.2, 127.0, 126.9, 79.4, 62.7, 59.2, 54.3, 28.4; IR (KBr, cm^{-1}): 3398, 2977, 1701, 1495, 1366, 1168, 751, 700; MS (ESI) *m/z* 447 $[M+1]^+$; HRMS (FAB) Calcd for $C_{28}H_{35}N_2O_3$ (447.2642) $[M+1]^+$. Found: 447.2643; $[\alpha]^{23}_D$ −9.3 (*c* 0.83, $CHCl_3$), (>99% ee).

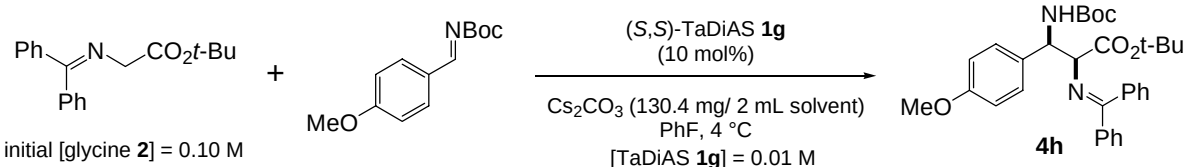
Initial kinetic Studies

General Procedure for kinetic study of Mannich type reaction:

Glycine Schiff base **2** was added to a stirred solution of (*S*,*S*)-TaDiAS **1g** in fluorobenzene at room temperature. After stirring for 5 min at the same temperature, imine **3h** was added and the reaction mixture was cooled to 4 ℃. After stirring for 20 min at same temperature, Cs_2CO_3 was added and stirred vigorously.

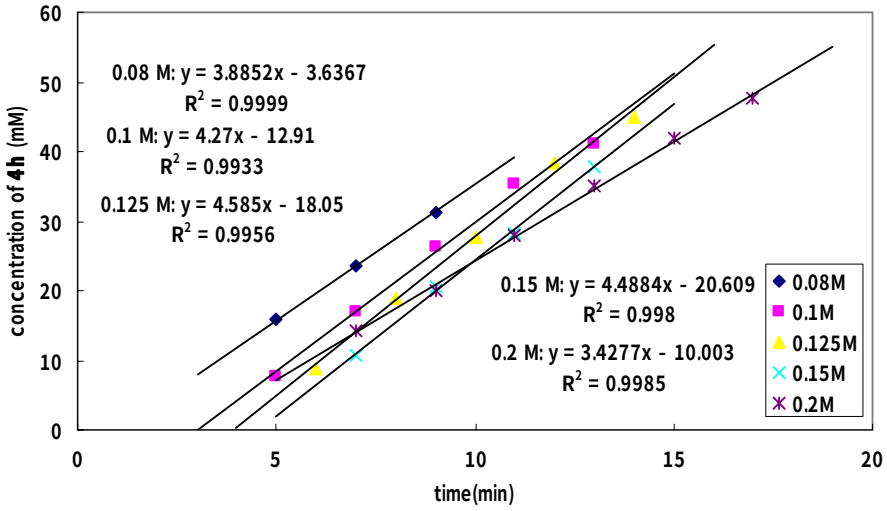
Samples were taken at recorded times according to the following procedure: 0.05 mL of the reaction mixture was taken with a syringe filled with 0.2 mL of water and was immediately poured onto water. The resulting mixture was extracted with ethyl acetate. After evaporating solvents, the crude residue was analyzed by ^{1}H NMR to determine yield.

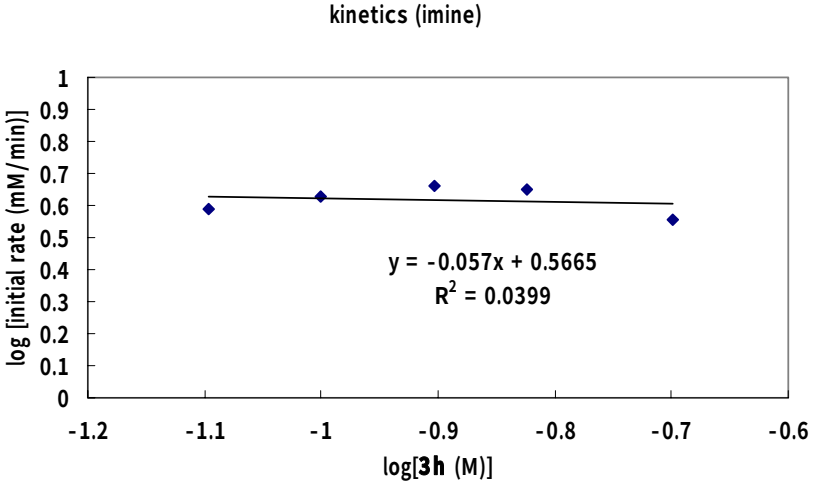
<Initial rate kinetics of imine 3h>



initial [glycine **2**] = 0.10 M

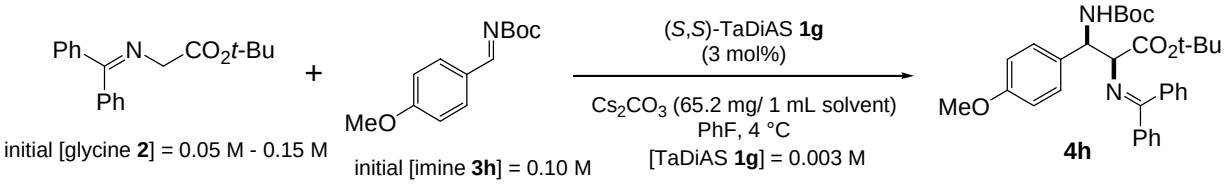
initial [imine **3h**] = 0.08 M - 0.20 M





The dependency on imine (**3h**) concentration is **0 order**.

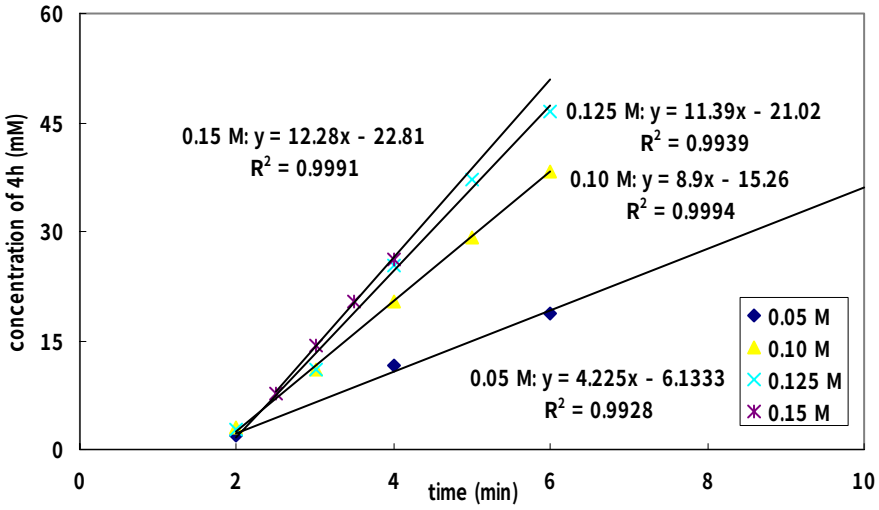
<Initial rate kinetics of glycine Schiff base 2>



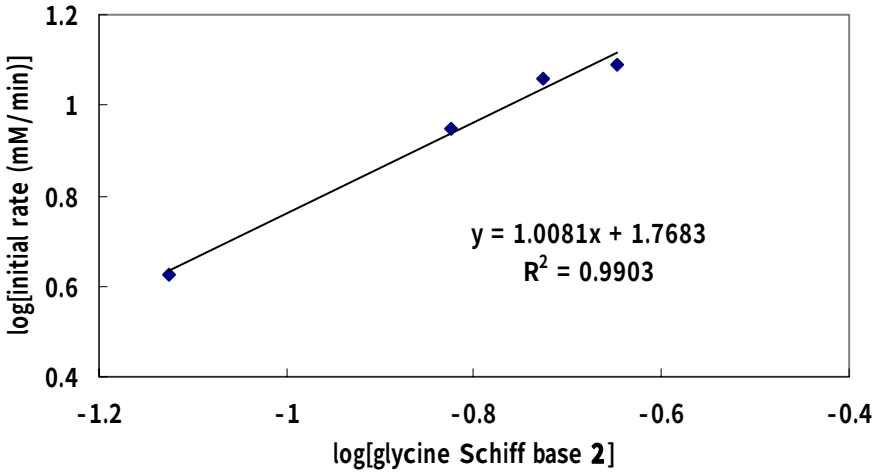
initial [glycine **2**] = 0.05 M - 0.15 M

initial [imine **3h**] = 0.10 M

[TaDiAS **1g**] = 0.003 M

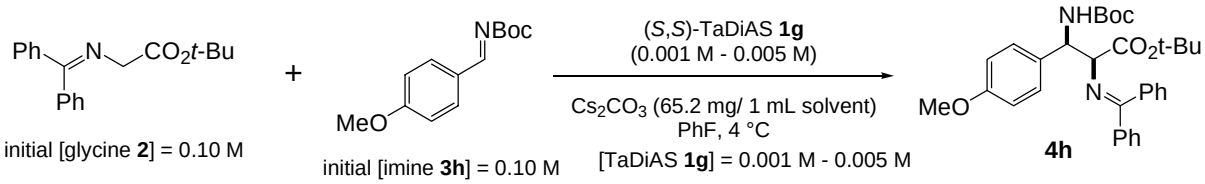


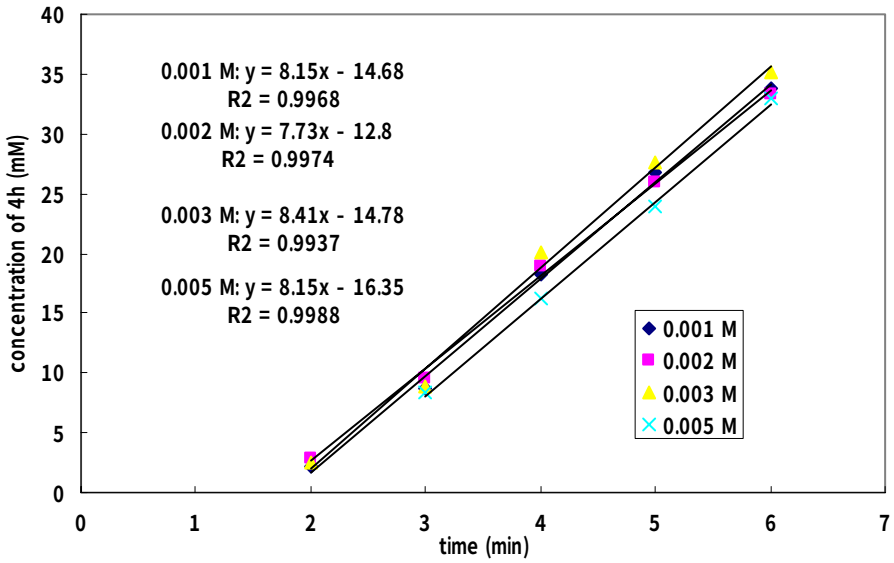
initial rate kinetics (glycine)

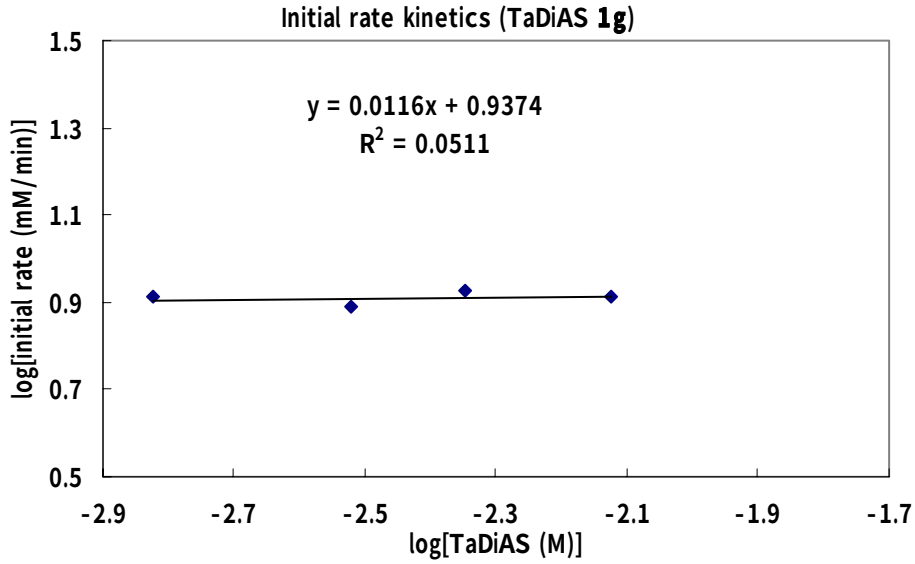


The dependency on glycine Schiff base **2** is **first-order**.

<Initial rate kinetics of (*S*,*S*)-TaDiAS 1g>

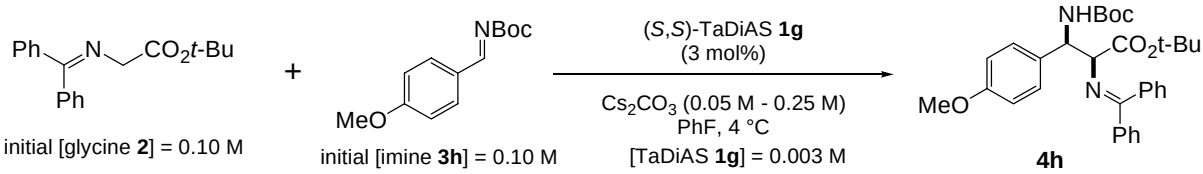






The dependency on TaDiAS **1g** concentration is **0 order**.

<Initial rate kinetics of Cs_2CO_3>



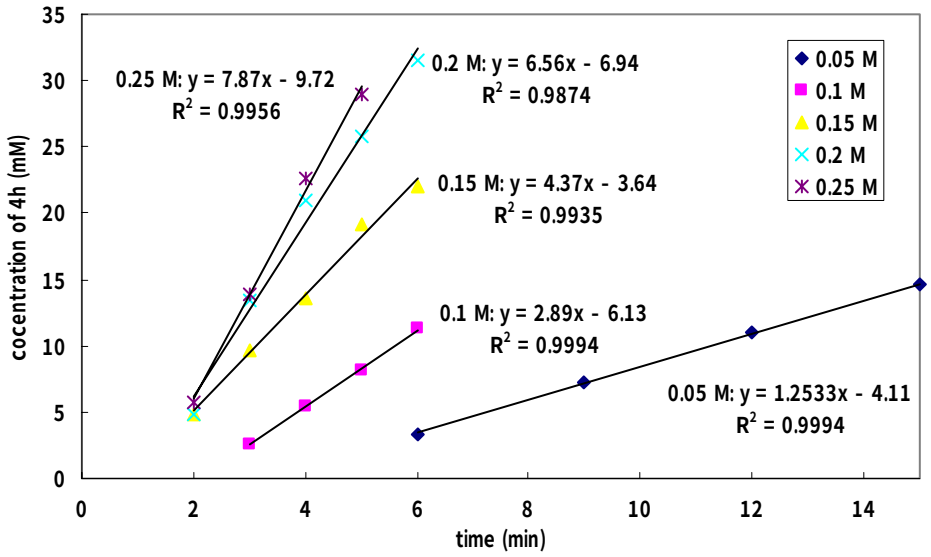
initial [glycine **2**] = 0.10 M

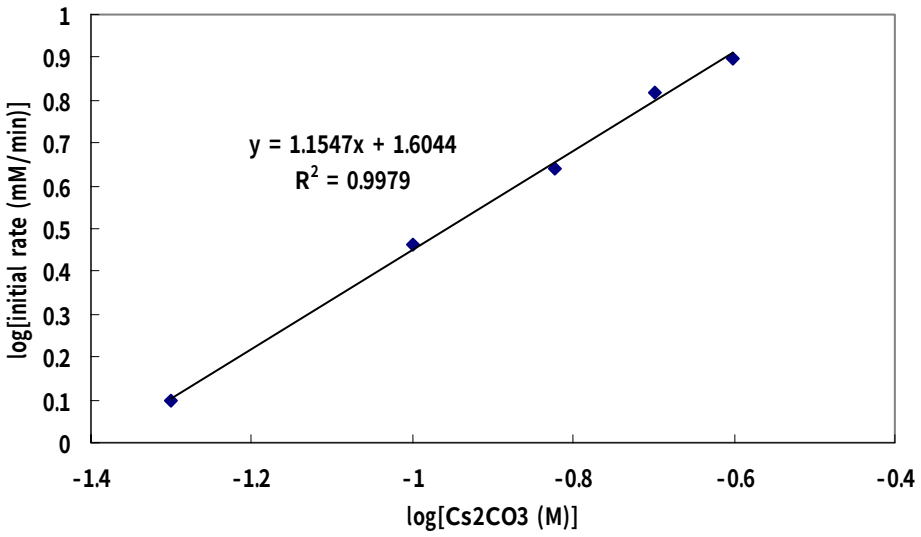
initial [imine **3h**] = 0.10 M

[TaDiAS **1g**] = 0.003 M

4h

Cs_2CO_3: 16.3 mg - 81.5 mg/ 1 mL solvent





The dependency on Cs_2CO_3 concentration is **1.2 order**.

Reference

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3) Y. Tuzuki, K. Chiba, K. Mizuno, K. Tomita, K. Suzuki, *Tetrahedron Asymmetry* **2001**, *12*, 2989.
4) S. –H. Lee, J. Yoon, S. –H. Chung, Y. –S. Lee, *Tetrahedron*, **2001**, *57*, 2139.