SUPPORTING INFORMATION

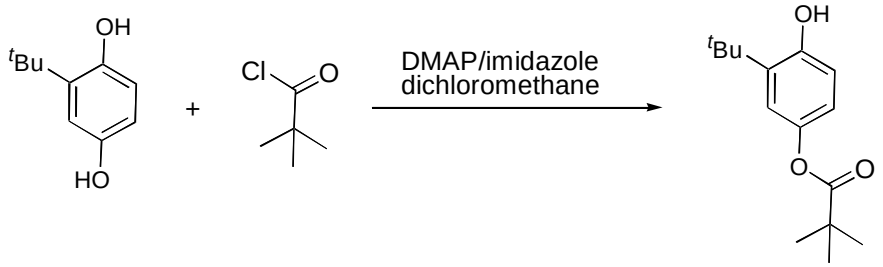
Enantioselective Catalytic Addition of HCN to Ketoimines. Catalytic Synthesis of Quaternary Amino Acids

Petr Vachal and Eric N. Jacobsen*

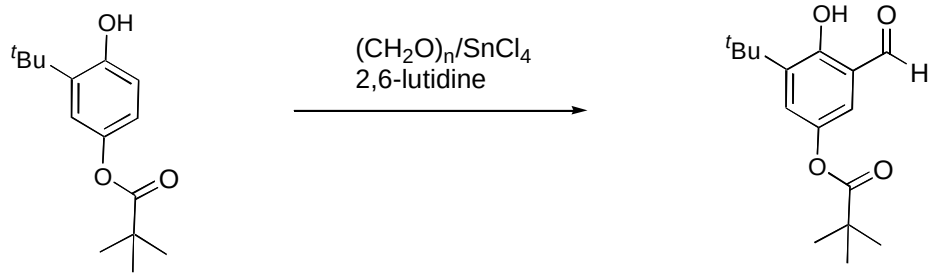
Harvard University, Department of Chemistry and Chemical Biology, Cambridge, MA 02138

General: TMSCN was purchased from Aldrich and distilled before use. (*R*,*R*)-1,2-Diaminocyclohexane was resolved by literature methods.[1] Preparation of **1a** and **1b** was carried out in fritted 20 mL disposable chromatography columns. Resin-bound intermediates and products were isolated in the columns by filtration and rinsed with DMF, THF, dichloromethane, methanol, and toluene (sequence repeated 3 times).[2] D-*tert*-Leucine was prepared in 99% ee according to our previously reported procedure.[2] Imines **2a**[3], **2b**[4], **2e**[5], **2f**[6], **2g**[7], **2h**[8], **2i**[9], **2m**[10] have been reported previously. All other chemicals were purchased from commercial suppliers and used without further purification.

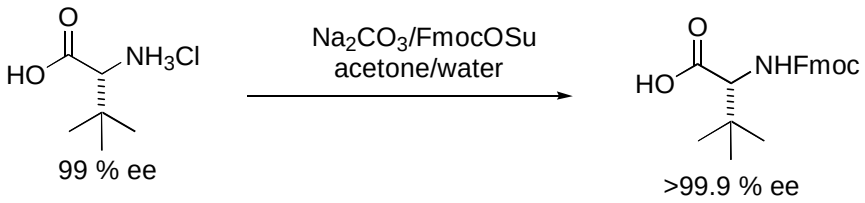
Preparation of Catalyst 1c:[2]



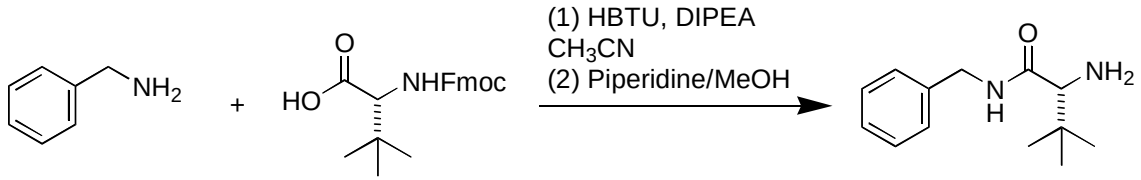
4-Pivoyl-2-*tert*-butylphenol:[11] A 50 ml round bottom flask was charged with 1.00 g (6.02 mmol) of 2-*tert*-butylhydroquinone, 717 mg (10.53 mmol, 1.75 equiv.) of imidazole, 110 mg (0.903 mmol, 0.15 equiv.) of DMAP, and dichloromethane (12 mL). Pivoyl chloride (799 mg, 1.1 equiv.) was added at 0 °C via syringe and the reaction mixture was allowed to stir for 4h, and then was diluted with dichloromethane (100 mL). The mixture was washed with saturated solution of ammonium chloride and dried over sodium sulfate. Solvents were removed *in vacuo* and the residual yellow oil was purified by flash chromatography on silica gel (eluent 10% AcOEt/hexanes) yielding 1.46 g (97% yield) of a white solid, IR (thin layer) 3462, 1728 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 9H), 1.38 (s, 9H), 4.81 (s, 1H), 6.60 (d, J = 8 Hz, 1H), 6.74 (dd, J_1 = 8 Hz, J_2 = 2 Hz, 1H), 6.89 (d, J = 1 Hz); ^{13}C NMR $\{^1H\}$ (400 MHz, $CDCl_3$) δ 177.7, 151.7, 144.4, 137.3, 120.2, 119.5, 117.0, 39.4, 35.0, 29.7, 27.6.



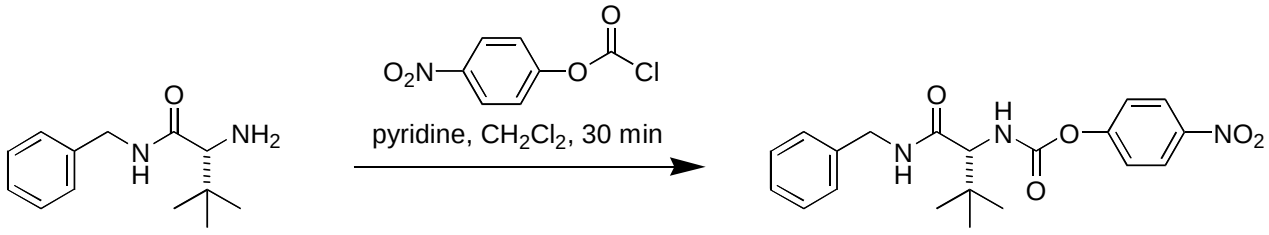
4-Pivoylaldehyde-2-*tert*-butylsalicylaldehyde:[11] A 100 ml round bottom flask was charged with 1.45 g (5.79 mmol) of 4-Pivoyl-2-*tert*-butylphenol, 0.604 g (2.32 mmol, 0.4 equiv.) of $SnCl_4$, 0.993 g (9.26 mmol, 1.equiv.) of 2,6-lutidine, and 15 mL of toluene. The reaction mixture was allowed to stir 45 min at 0 °C, and then for an additional 15 min at room temperatur. Paraformaldehyde (1.06 g, 35.3 mmol, 6.1 equiv.) was added at room temperature and the reaction mixture was then heated to reflux for 48 h. To the reaction mixture, 50 mL of water was added, followed by acidification to pH = 2 with 2N HCl. The organic layer was separated, filtered and dried over sodium sulfate. Solvents were removed *in vacuo* and product was obtained by flash chromatography on silica gel (10% AcOEt/Hexanes) as a yellow solid (1.16 g, 72 % yield). The product can also be recrystallized from methanol. IR (thin layer) 3360, 1750, 1654 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.36 (d, *J* = 2 Hz, 9H), 1.41 (d, *J* = 2 Hz, 9H), 7.14 (m, 2H), 9.82 (s, 1H), 11.69 (s, 1H); ^{13}C NMR {^1H} (400 MHz, $CDCl_3$) δ 196.5, 177.7, 159.0, 143.5, 140.5, 128.0, 123.2, 119.8, 39.5, 35.1, 29.1, 27.2.



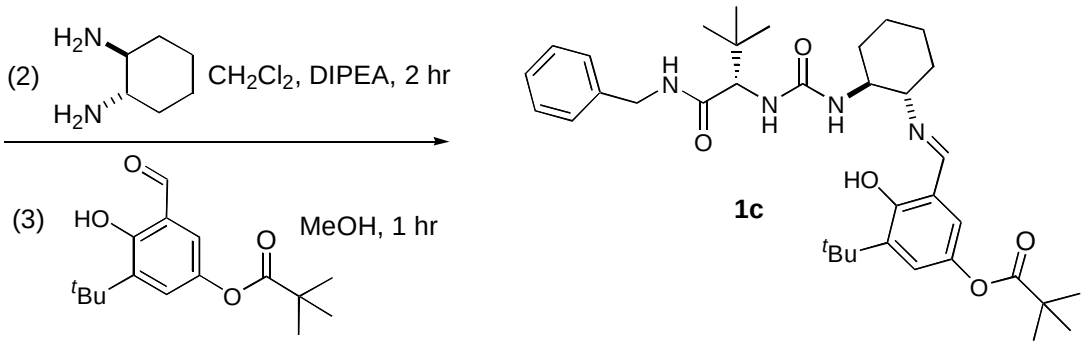
Fmoc-D-*tert*-Leucine: was prepared[12] from D-*tert*-Leucine.[2] Recrystallization of 3.65 g of crude product from 130 mL of 10:1 hexanes/AcOEt yielded 2.85 g (78% overall) of optically pure Fmoc-D-*tert*-Leucine (>99.9% ee by chiral HPLC analysis).



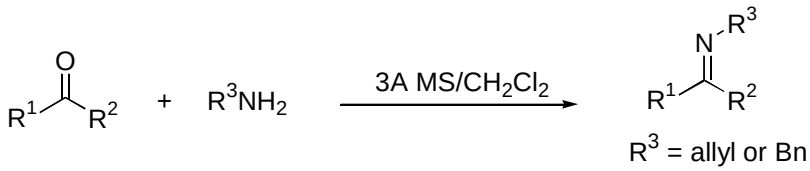
To a solution of 2.10 g of Fmoc-D-*tert*-Leucine (5.94 mmol, >99.9% ee) and 2.07 mL of DIPEA (11.9 mmol, 2.0 equiv) in acetonitrile (50 mL), 2.25 g of HBTU (5.95 mmol, 1.0 equiv) was added. After 1 min, 649 µL of benzyl amine (5.95 mmol, 1.0 equiv) was added and the reaction stirred for 2 h. The mixture was combined with dichloromethane (100 mL) and H_2O (100 mL) and organic layer separated. The organic phase was washed with H_2O (2 X 50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The solid residue was dissolved in 45 mL of 5:4 methanol/diethyl amine, stirred for 25 min and partitioned between 350 mL of $CHCl_3$ and 150 mL H_2O. The organic phase was washed with H_2O (100 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by silica gel chromatography (3% MeOH/CH_2Cl_2) afforded 895 mg of a white solid (68% yield, 2 steps); mp 53-54 °C; IR (KBr) 3303, 1650 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 5H), 7.05 (s, 1H), 4.45 (d, *J* = 0.9 Hz, 1H), 4.43 (d, *J* = 0.9 Hz, 1H), 3.14 (s, 1H), 1.41 (s, 2H), 1.01 (s, 9H); ^{13}C NMR {^1H} (100 MHz, $CDCl_3$) δ 173.4, 138.5, 128.5, 127.8, 127.3, 64.3, 43.0, 34.1, 26.7; HRMS (CI) *m/z* $(MH)^+$ calcd 221.1654, found 221.1658.



PNP-Ester: To a solution of the amine (860 mg, 3.90 mmol), pyridine (631 µL, 2 equiv.), and CH_2Cl_2 (30 mL) was added *p*-nitrophenyl chloroformate (803 mg, 1.02 equiv.). This mixture was allowed to stir for 30 min then the solvent was removed *in-vacuo*. The resulting residue was purified by silica gel chromatography (5%EtOAc/CH_2Cl_2) to yield a 1.411 mg of a white solid in 94% yield: IR (KBr) 3324, 2965, 1731, 1654, 1524, 1489, 1347, 1212 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (m, 2H), 7.27 (m, 3H), 7.17 (m, 4H), 6.59 (s, 1H), 6.24 (d, *J* = 9.4 Hz, 1H), 4.41 (dd, *J* = 6.0, 14.9 Hz, 1H), 4.23 (*J* = 6.0, 14.9 Hz, 1H), 4.08 (d, *J* = 9.4 Hz, 1H), 1.05 (s, 9H); ^{13}C NMR {^1H} (100 MHz, $CDCl_3$) δ 170.0, 155.6, 153.4, 144.7, 137.4, 128.7, 127.6, 127.5, 125.0, 121.8, 63.2, 43.5, 34.9, 26.5; HRMS (CI) *m/z* $(M+Na)^+$ calcd 408.1536, found 408.1538.

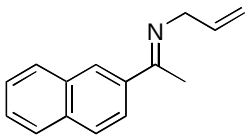


Solution Phase Catalyst (1c): (1) To a solution of the PNP ester (1.38 g, 3.58 mmol) and 30 mL of CH_2Cl_2 was added (*S*,*S*)-1,2-diaminocyclohexane (1.22 g, 3 equiv.) and allow to stir for two minutes, followed by addition of diisopropyl ethylamine (687 µL, 1.1 equiv.). The reaction mixture was allowed to stir for an additional 40 min. The resulting mixture was partitioned between CH_2Cl_2 (150 mL) and 2% aq. Na_2CO_3 (30 mL). The organic layer was washed with twice with 20% aq. Na_2CO_3 (30 mL ea.), dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. The resulting residue (1.30 g) was dissolved in MeOH (25 mL). This solution was treated with aldehyde (996 mg, 1.0 equiv.) and allowed to stir for 40 min. The solvent was removed by reduced pressure and the resulting residue was purified by silica gel chromatography (25% EtOAc/Hexane) to yield **1c** as a yellow solid (1.85 g, 83%, 2 steps). The overall yield for **1c** from Fmoc-D-*tert*-Leucine was 53% (5 steps). IR (KBr) 3309, 2960, 1752, 1684, 1550, 1437, 1270, 1150, 1116 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 14.32 (s, 1H), 8.08 (s, 1H), 7.23 (d, *J* = 2.6 Hz, 1H), 7.12 (m, 2H), 7.08 (m, 2H), 7.02 (d, *J* = 2.6 Hz, 1H), 7.00 (t, *J* = 7.1 Hz, 1H), 6.67 (m, 1H), 5.63 (m, 1H), 4.59 (m, 1H), 4.37 (dd, *J* = 14.8, 6.6 Hz, 1H), 4.29 (d, *J* = 9.1 Hz, 1H), 3.86 (dd, *J* = 14.8, 4.6 Hz, 1H), 3.43 (m, 1H), 3.15 (m, 1H), 1.95 (m, 1H), 1.68- 1.0 (m, 7H), 1.51 (s, 9H), 1.30 (s, 9H), 1.05 (s, 9H); ^{13}C NMR {^1H} (100 MHz, $CDCl_3$) δ 177.4, 172.0, 164.3, 158.1, 157.7, 141.7, 138.5, 130.1, 128.4, 127.4, 127.1, 122.6, 121.2, 118.1, 70.3, 61.5, 54.0, 43.1, 38.9, 34.8, 34.7, 31.5, 29.1, 27.1, 26.7, 24.2, 23.6, 22.6; HRMS (ES) *m/z* (M^+) calcd 621.4016, found 621.3986.

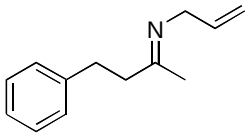


General procedure for the preparation of *N*-allyl substituted imines: A flame dried 250 mL round bottom flask was charged with activated 3Å molecular sieves (30g) and 50 mL CH_2Cl_2 (freshly distilled from CaH_2). To this mixture, substrate (40 mmol) was added followed by syringe addition of allyl amine (1.5 equiv., 60mmol) at room temperature. Reaction progress was followed by ^{1}H NMR (15-48 h). The sieves were removed by filtration and washed with CH_2Cl_2 (10 mL). The filtrate was collected and volatiles were removed *in vacuo*. The imines thus prepared were used in the Strecker reactions without any additional purification.

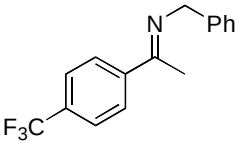
General procedure for benzyl substituted imines: A flame dried 250 mL round bottom flask was charged with activated 3Å molecular sieves (30g) and 50 mL CH_2Cl_2 (freshly distilled from CaH_2). To this mixture, substrate (40 mmol) was added followed by syringe addition of benzyl amine (generally 1 equiv., 40mmol; in case of **2m**, volatile ketone was used in excess of 10%) room temperature. Reaction conversion was followed by ^{1}H NMR (15-60 h). The sieves were removed by filtration and washed with CH_2Cl_2 (10 mL). The filtrate was collected and solvent was removed *in vacuo*. Further purification was accomplished by vacuum distillation or recrystallization.



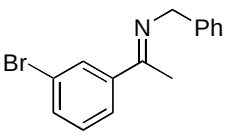
2c: Product was obtained as a white solid in 70% yield after recrystallization from hexanes; IR (thin film) 1627 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 3H), 4.28 (m, 2H), 5.26 (dm, *J* = 8 Hz, 1H), 5.37 (dm, *J* = 10 Hz, 1H), 6.26 (m, 1H), 7.53 (m, 2H), 7.87 (m, 2H), 7.93 (m, 1H), 8.15 (dm, *J* = 10 Hz, 1H), 8.23 (m, 1H); ^{13}C NMR {^{1}H} (400 MHz, $CDCl_3$) δ 166.1, 138.5, 136.3, 134.2, 133.2, 129.0, 128.1, 127.8, 126.9, 126.8, 126.4, 124.5, 115.5, 55.1, 15.9; HRMS (CI) *m/z* $(MH)^+$ calcd 210.1283, found 210.1292.



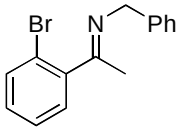
2d: Product was obtained as a clear oil in 97% yield; IR (thin film) 1662 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.81 (s, 3H), 2.59 (t, *J* = 3 Hz, 2H), 2.92 (t, *J* = 3 Hz, 2H), 3.96 (m, 2H), 5.13 (m, 2H), 6.02 (m, 1H), 7.18-7.32 (m, 5H); ^{13}C NMR {^{1}H} (500 MHz, $CDCl_3$) δ 170.3, 142.0, 136.7, 136.3, 128.6, 128.6, 126.1, 115.2, 44.4, 32.9, 18.0; HRMS (EI) *m/z* (M^+) calcd 187.1361, found 187.1367.



2j: Product was obtained as a clear oil in 78% yield after vacuum distillation. (125 °C/0.05Torr); IR (thin film) 1637 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.41 (s, 3H), 4.87 (s, 2H), 7.44 (m, 1H), 7.54 (m, 2H), 7.63 (m, 2H), 7.78 (d, *J* = 8 Hz, 2H), 8.11 (d, *J* = 8 Hz, 2H); ^{13}C NMR {^{1}H} (500 MHz, $CDCl_3$) δ 164.9, 144.5, 140.7, 131.7, 131.5, 128.9, 128.1, 127.5, 127.1, 125.5 (q, *J* = 16 Hz), 56.2, 15.9; HRMS (EI) *m/z* (M^+) calcd 277.1078, found 277.1073.

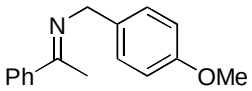


2k: Product was obtained as a clear oil in 71% yield after vacuum distillation (175 °C/0.6Torr), IR (thin film) 1634 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.35 (s, 3H), 4.80 (s, 2H), 7.29-7.53 (m, 6H), 7.59 (d, *J* = 8 Hz, 1H), 7.85 (d, *J* = 8 Hz, 1H), 8.14 (s, 1H); ^{13}C NMR {^{1}H} (500 MHz, $CDCl_3$) δ 164.8, 143.3, 140.6, 132.9, 130.2, 130.1, 128.8, 128.1, 127.1, 125.7, 123.0, 56.1, 16.1; HRMS (EI) *m/z* (M^+) calcd 287.0309, found 287.0295.

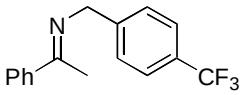


2l: Product was obtained as a clear oil in 41% yield after vacuum distillation (150 °C/0.6Torr); IR (thin film) 1652 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.37 (s, 0.8H), 2.44 (s, 2.2H), 4.28 (d, *J* =

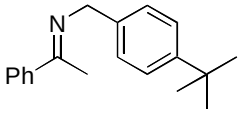
15 Hz, 0.75H), 4.44 (d, J = 15 Hz, 0.75H), 4.77 (s, 0.5H), 7.21-7.68 (m, 9H); ^{13}C NMR {^{1}H} (500 MHz, $CDCl_3$) δ 169.5, 168.1, 144.9, 141.0, 140.2, 140.1, 133.2, 133.2, 130.1, 129.9, 129.6, 128.8, 128.7, 128.4, 128.3, 128.1, 127.9, 127.6, 127.1, 120.5, 119.6, 57.8, 56.2, 28.4, 20.2; HRMS (EI) *m/z* (M^+) calcd 287.0309, found 287.0302.



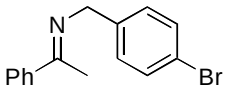
2n: Product was obtained as a white solid in 79% yield after recrystallization from hexanes; IR (thin film) 1633 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.37 (s, 3H), 3.85 (s, 3H), 4.74 (s, 2H), 6.96 (d, J = 8 Hz, 2H), 7.41 (d, J = 8 Hz, 2H), 7.45 (m, 3H), 7.92 (m, 2H); ^{13}C NMR {^{1}H} (500 MHz, $CDCl_3$) δ 166.1, 158.7, 141.4, 133.0, 129.9, 129.1, 128.5, 127.1, 114.1, 55.6, 55.4, 16.1; HRMS (EI) *m/z* (M^+) calcd 239.1310, found 239.1312.



2o: Product was obtained as a white solid in 77% yield after recrystallization from pentane; IR (thin film) 1633 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.39 (s, 3H), 4.81 (s, 2H), 7.48 (m 3H), 7.67 (dd, J_1 = 8 Hz, J_2 = 20 Hz 4H), 7.97 (m, 2H); ^{13}C NMR {^{1}H} (500 MHz, $CDCl_3$) δ 166.9, 145.2, 145.2, 141.0, 130.2, 129.2, 128.6, 128.3, 127.0, 125.6 (q, J = 15 Hz), 55.4, 16.2; HRMS (EI) *m/z* (M^+) calcd 277.1078, found 277.1067.



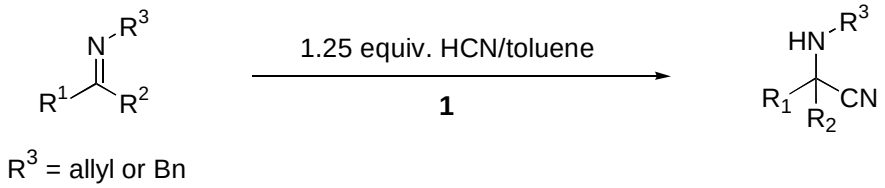
2p: Product was obtained as a clear oil in 98% yield; IR (thin film) 1635 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.52 (s, 9H), 2.45 (s, 3H), 4.88 (s, 2H), 7.55 (m, 7H), 8.05 (m, 2H); ^{13}C NMR {^{1}H} (500 MHz, $CDCl_3$) δ 166.0, 149.7, 141.5, 138.0, 130.0, 128.6, 127.8, 127.2, 125.7, 55.8, 34.9, 31.9, 16.1; HRMS (EI) *m/z* (M^+) calcd 265.1830, found 265.1824.

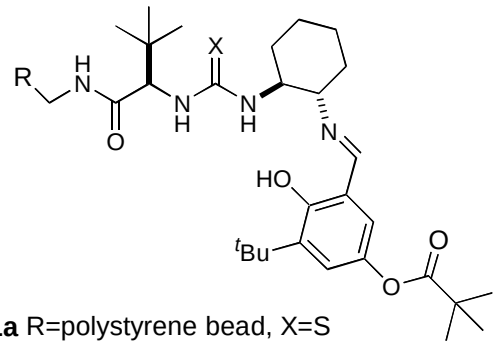


2q: Product was obtained as a white solid in 77% yield after recrystallization from pentane; IR (thin film) 1633 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.37 (s, 3H), 4.71 (s, 2H), 7.41 (d, J = 8 Hz, 2H), 7.48 (m, 3H), 7.56 (d, J = 8 Hz , 2H), 7.95 (m, 2H); ^{13}C NMR {^{1}H} (500 MHz, $CDCl_3$) δ 166.6, 141.1, 140.1, 131.7, 130.1, 129.8, 128.6, 127.1, 120.6, 55.3, 16.3; HRMS (EI) *m/z* (M^+) calcd 287.0309, found 287.0295.

General procedure for preparation of racemic Strecker adducts: A 10 mL round-bottom flask equipped with a stir bar was charged with a solution of substrate (1 mmol) in dichloromethane (2 mL). A solution of HCN (1.5 equiv., generated prior to the reaction from TMSCN and methanol; see General Procedure for Asymmetric Strecker) in dichloromethane (1 mL) was added by syringe addition at 5 °C. The reaction was allowed to stir at 5 °C for 10h. Solvents were removed *in-vacuo*. Racemic samples were used for chiral HPLC or GC analyses without further purification.

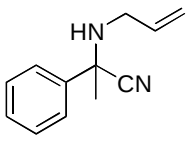
Derivatization of Allyl Protected Strecker Adducts (for the purpose of chiral GC Analysis): To a 10 mL round bottom flask, 10 mg of **3** was dissolved in 2 mL of dichloromethane and an excess trifluoroacetic anhydride was added in one portion. Solvents were removed *in vacuo* and residual oil was dissolved in dichloromethane (3 mL). The crude product was used for chiral GC or HPLC analyses without further purification.



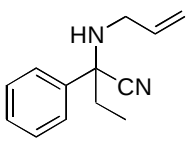


1a R=polystyrene bead, X=S
1b R=polystyrene bead, X=O
1c R=Ph, X=O

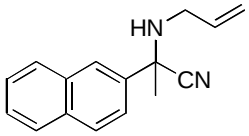
General procedure for asymmetric Strecker reaction: A 10 mL round-bottom flask equipped with a stir bar was charged with 3.7 mg catalyst **1c** (0.006 mmol, 0.02 equiv.), 2 mL of toluene and substrate (0.3 mmol) were combined. The reaction was cooled to –75 ºC by means of a constant temperature bath. In a separate 2 mL flask equipped with a stir bar, 1 mL of toluene and 50 µL of TMSCN (1.25 equiv.) were combined. This solution was cooled to 5 ºC and 15 µL (1.25 equiv.) of methanol was added. The solution was allowed to stir for 2 h at 5 °C, cooled to -78 °C and then added to the reaction flask by syringe addition. The reaction conversion was monitored by either ^{1}H NMR or HPLC analyses and upon the conversion >99%, the solvents were removed *in-vacuo*. The residual mixture of catalyst **1c** and Strecker adduct **3** was separated either by recrystallization from hexanes or by short column flash chromatography on silica gel or neutral alumina (eluent 20% AcOEt in hexanes) to afford **3**.



3a: Product was obtained in 97% yield and 85% ee by Chiral GC analysis (as trifluoroacet amide, γ-TA, 100 °C isothermal, t_r(minor) = 93 min, t_r(major) = 100 min); IR (thin film) 3327, 2224 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.75 (s, 3H), 1.80 (s, 1H), 3.06 (m, 1H), 3.39 (m, 1H), 5.11 (m, 1H), 5.26 (m, 1H), 5.91 (m, 1H), 7.33-7.42 (m, 3H), 7.64 (m, 2H); ^{13}C NMR {^{1}H} (500 MHz, $CDCl_3$) δ 140.1, 135.7, 129.2, 128.9, 125.8, 121.6, 116.7, 60.4, 48.1, 31.5; HRMS (CI) *m/z* $(MH)^+$ calcd 187.1235, found 187.1234.

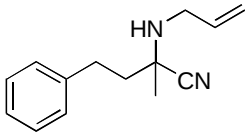


3b: Product was obtained in 96% yield as a clear oil and 69% ee by Chiral HPLC analysis (S,S-Whelco, 0.2% IPA/Hexanes, 1 mL/min, t_r(minor) = 40 min, t_r(major) = 45 min); IR (thin film) 3326, 2223 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.92 (t, J = 8 Hz, 3H), 1.75 (s, 1H), 1.96 (m, 1H), 2.04 (m, 1H), 3.01 (dm, J = 9 Hz, 1H), 3.36 (m, 1H), 5.11 (dd, J_1 = 11 Hz, J_2 = 6 Hz, 1H), 5.26 (dm, J = 9 Hz, 1H), 5.91 (m, 1H), 7.33-7.42 (m, 3H), 7.61 (m, 2H); ^{13}C NMR {^{1}H} (500 MHz, $CDCl_3$) δ 138.4, 135.8, 129.0, 128.8, 126.5, 120.9, 116.7, 65.9, 47.9, 36.9, 9.1.

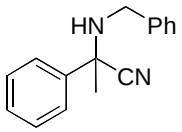


3c: Product was obtained in 97% yield as a clear oil and 89% ee by Chiral HPLC analysis (Chiralcel OD, 1% IPA/Hexanes, 1 mL/min, t_r(minor) = 10.7 min, t_r(major) = 11.4 min); IR (thin film) 3328, 2223 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.81 (s, 1H), 1.88 (s, 3H), 3.10 (d, J = 8 Hz, 1H), 3.46 (m, 1H), 5.17 (d, J = 8 Hz, 1H), 5.32 (d, J = 13 Hz, 1H), 5.96 (m, 1H), 7.56 (m, 2H), 7.74 (m, 1H), 7.90 (m, 3H), 8.19 (s, 1H); ^{13}C NMR {^{1}H} (500

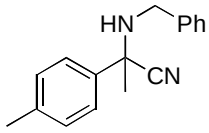
MHz, $CDCl_3$) δ 137.3, 135.6, 133.6, 133.3, 129.3, 128.5, 127.9, 127.0, 126.9, 126.4, 123.0, 121.7, 116.9, 60.7, 48.2, 31.3; HRMS (EI) *m/z* (M^+) calcd 236.1313, found 236.1309.



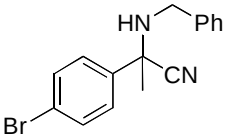
3d: Product was obtained in 98% yield as a clear oil and 41% ee by Chiral GC analysis (γ-TA, 90 °C isothermal, t_r(minor) = 378 min, t_r(major) = 399 min); IR (thin film) 3320, 2219 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.42 (t, *J* = 8 Hz, 1H), 1.51 (s, 3H), 1.99 (m, 2H), 2.82 (m, 2H), 3.41 (t, *J* = 6 Hz, 2H), 5.17 (dd, J_1 = 6 Hz, J_2 = 1 Hz, 1H), 5.29 (dm, *J* = 8 Hz, 1H), 5.93 (m, 1H), 7.24 (m, 3H), 7.33 (m, 2H); ^{13}C NMR {^1H} (400 MHz, $CDCl_3$) δ 140.7, 135.7, 128.8, 128.6, 126.5, 122.2, 117.0, 55.7, 47.8, 42.1, 30.8, 25.3; HRMS (CI) *m/z* $(MH)^+$ calcd 215.1548, found 215.1537.



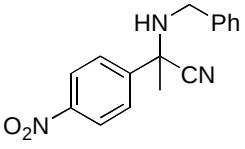
3e: Product[13] was obtained in 97% as a clear oil and 90% ee by Chiral HPLC analysis (Chiralcel OD, 3% IPA/Hexanes, 1 mL/min, t_r(minor) = 9.8 min, t_r(major) = 12.4 min).



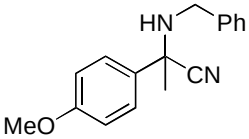
3f: Product was obtained in 98% yield as a clear oil and 91% ee by Chiral HPLC analysis (Chiralcel OD, 3% IPA/Hexanes, 1 mL/min, t_r(major) = 8.4 min, t_r(minor) = 9.9 min); IR (thin film) 3321, 2223 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.83 (s, 3H), 1.98 (s, 1H), 2.47 (s, 3H), 3.65 (d, *J* = 12 Hz, 1H), 3.97 (d, *J* = 12 Hz, 1H), 7.32 (d, *J* = 8 Hz, 2H), 7.63-7.44 (m, 5H), 7.69 (d, *J* = 8 Hz, 2H); ^{13}C NMR {^1H} (400 MHz, $CDCl_3$) δ 139.4, 138.6, 137.2, 129.9, 128.8, 128.6, 127.6, 125.8, 121.7, 60.7, 49.9, 31.7, 21.6; HRMS (EI) *m/z* (M^+) calcd 250.1470, found 250.1466.



3g: Crude product was obtained as a solid (quantitative as a mixture with catalyst) in 93% ee. Recrystallization from hexanes afforded product in 76% overall yield as white needles and >99.9% ee by Chiral HPLC analysis (Catalyst **1c** remained dissolved in the mother liquid). (Chiralcel OD, 3% IPA/Hexanes, 1 mL/min, t_r(major) = 15.9 min, t_r(minor) = 19.5 min); IR (thin film) 3323, 2224 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.80 (s, 3H), 2.02 (d, *J* = 5 Hz, 1H), 3.58 (m, 1H), 3.93 (d, *J* = 10 Hz, 1H), 7.26-7.42 (m, 5H), 7.59 (d, *J* = 6 Hz, 2H), 7.65 (d, *J* = 6 Hz, 2H); ^{13}C NMR {^1H} (400 MHz, $CDCl_3$) δ 139.4, 139.1, 132.4, 128.9, 128.6, 127.8, 127.8, 123.0, 121.2, 60.4, 49.8, 31.5, mp = 79.9-80.1 °C (hexanes); $[\alpha]_D^{23}$ = -58.6° (c = 1.0, CH_2Cl_2); HRMS (EI) *m/z* (M^+) calcd 314.0418, found 314.0414.

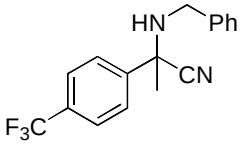


3h: Crude product was obtained as a solid (quantitative as a mixture with catalyst) in 93% ee. Recrystallization from hexanes afforded product in 79% overall yield as white needles and >99.9% ee by Chiral HPLC analysis (Catalyst **1c** remained dissolved in the mother liquid). (Chiralcel OD, 10% Ethanol/Hexanes, 1 mL/min, t_r(major) = 17.9 min, t_r(minor) = 27.3 min); IR (thin film) 3328, 2227 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.83 (s, 3H), 2.07 (s, 1H), 3.51 (d, *J* = 12 Hz, 1H), 3.93 (d, *J* = 12 Hz, 1H), 7.28-7.51 (m, 5H), 7.92 (d, *J* = 8 Hz, 2H), 8.27 (d, *J* = 8 Hz, 2H); ^{13}C NMR {^1H} (400 MHz, $CDCl_3$) δ 148.2, 147.1, 138.4, 128.8, 128.4, 127.8, 127.0, 124.4, 120.5, 60.6, 50.0, 31.6, mp = 141.2-141.4 °C (hexanes); $[\alpha]_D^{23}$ = -81.5° (c = 1.0, CH_2Cl_2); HRMS (CI) *m/z* $(MH)^+$ calcd 282.1243, found 282.1253.

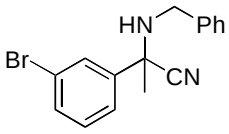


3i: Product was obtained in 98% yield as a clear oil and 88% ee by Chiral HPLC analysis (Chiralcel OD, 3% IPA/Hexanes, 1 mL/min, t_r(major) = 11.9 min, t_r(minor) = 14.8 min); IR (thin film) 3321, 2221 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.79 (s, 3H), 1.92 (s, 1H), 3.59 (d, *J* = 12 Hz, 1H), 3.84 (s, 3H) 3.89 (d, *J* = 12 Hz, 1H), 6.97 (d, *J* = 9 Hz, 2H), 7.29-7.38 (m, 5H), 7.65 (d, *J* = 9 Hz, 2H); ^{13}C NMR {^1H} (400 MHz, $CDCl_3$) δ 159.9, 139.3,

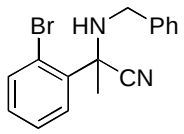
132.0, 128.7, 128.5, 127.6, 127.0, 121.8, 114.4, 60.3, 55.7, 49.8, 31.7; HRMS (EI) *m/z* (M^+) calcd 266.1419, found 266.1411.



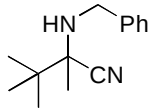
3j: Crude product was obtained as a solid (quantitative as a mixture with catalyst) in 95% ee. Recrystallization from hexanes afforded product in 75% overall yield as white needles and >99.9% ee by Chiral HPLC analysis (Catalyst **1c** remained dissolved in the mother liquid). (Chiralcel OD, 10% IPA/Hexanes, 1 mL/min, t_r(major) = 11.6 min, t_r(minor) = 23.1 min); IR (thin film) 3323, 2225 cm^{-1}, ^1H NMR (400 MHz, $CDCl_3$) δ 1.83 (s, 3H), 2.02 (s, 1H), 3.55 (d, *J* = 13 Hz, 1H), 3.95 (d, *J* = 12 Hz, 1H), 7.12-7.22 (m, 5H), 7.73 (d, *J* = 8 Hz, 2H), 7.89 (d, *J* = 8 Hz, 2H); ^{13}C NMR {^1H} (400 MHz, $CDCl_3$) δ 144.0, 138.7, 131.3, 131.0, 128.8, 128.5, 127.8, 126.4, 126.2 (q, *J* = 17 Hz), 120.9, 60.7, 50.0, 31.6, mp = 111.2-111.3 °C (hexanes); $[\alpha]_D^{23}$ = -55.6° (c = 1.0, CH_2Cl_2); HRMS (EI) *m/z* (M^+) calcd 304.1187, found 304.1178.



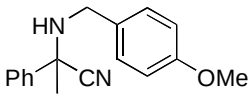
3k: Product was obtained in 97% yield as a clear oil and 91% ee by Chiral HPLC analysis (Chiralcel OD, 7% IPA/Hexanes, 1 mL/min, t_r(major) = 8.8 min, t_r(minor) = 11.9 min); IR (thin film) 3322, 2224 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.78 (s, 3H), 1.85 (s, 1H), 3.58 (m, 1H), 3.90 (d, *J* = 12 Hz, 1H), 7.28-7.39 (m, 6H), 7.51 (dm, *J* = 8 Hz, 1H), 7.68 (dm, *J* = 8 Hz, 1H), 7.92 (s, 1H); ^{13}C NMR {^1H} (400 MHz, $CDCl_3$) δ 142.5, 138.9, 132.1, 130.8, 128.9, 128.8, 128.5, 127.7, 124.6, 123.3, 120.9, 60.4, 49.9, 31.6.



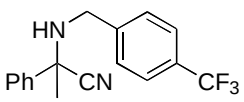
3l: Product was obtained in 45% yield as a clear oil and 42% ee by Chiral HPLC analysis (Chiralcel OD, 1% IPA/Hexanes, 1 mL/min, t_r(major) = 29.3 min, t_r(minor) = 33.3 min); IR (thin film) 3323, 2220 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.99 (s, 3H), 2.22 (m, 1H), 3.65 (dd, J_1 = 12 Hz, J_2 = 8 Hz, 1H), 3.95 (dd, J_1 = 12 Hz, J_2 = 4 Hz, 1H), 7.23-7.47 (m, 7H), 7.68 (dd, J_1 = 8 Hz, J_2 = 2 Hz, 1H), 7.92 (dd, J_1 = 8 Hz, J_2 = 2 Hz, 1H); ^{13}C NMR {^1H} (400 MHz, $CDCl_3$) δ 139.0, 136.5, 135.9, 130.4, 129.0, 128.8, 128.7, 128.3, 127.7, 121.2, 120.6, 61.1, 49.9, 27.7.



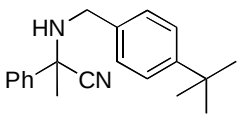
3m: Product was obtained in 98% yield as a clear oil and 70% ee by Chiral HPLC analysis (Chiralcel OD, 0.5% IPA/Hexanes, 1 mL/min, t_r(major) = 8.3 min, t_r(minor) = 10.7 min); IR (thin film) 3346, 2216 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.14 (s, 9H), 1.44 (s, 3H), 1.60 (s, 1H), 3.93 (s, 2H), 7.28-7.42 (m, 5H); ^{13}C NMR {^1H} (400 MHz, $CDCl_3$) δ 139.9, 128.7, 128.4, 127.5, 122.3, 63.8, 49.8, 37.6, 25.5, 19.8.



3n: Product was obtained in 97% yield as a clear oil and 93% ee by Chiral HPLC analysis (Chiralcel OD, 10% IPA/Hexanes, 1 mL/min, t_r(minor) = 6.4 min, t_r(major) = 8.4 min); IR (thin film) 3320, 2223 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.78 (s, 3H), 1.93 (s, 1H), 3.51 (d, *J* = 8 Hz, 1H), 3.78 (s, 3H) 3.84 (d, *J* = 8 Hz, 1H), 6.88 (d, *J* = 8 Hz, 2H), 7.28-7.44 (m, 5H), 7.73 (d, *J* = 8 Hz, 2H); ^{13}C NMR {^1H} (400 MHz, $CDCl_3$) δ 159.0, 140.1, 131.3, 129.7, 129.1, 128.8, 125.8, 121.6, 114.1, 60.8, 55.6, 49.3, 31.7; HRMS (EI) *m/z* (M^+) calcd 266.1419, found 266.1417.

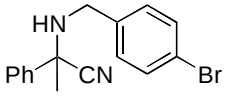


3o: Product was obtained in 95% yield as a clear oil and 92% ee by Chiral HPLC analysis (Chiralcel OD, 3% IPA/Hexanes, 1 mL/min, t_r(minor) = 9.5 min, t_r(major) = 16.0 min); IR (thin film) 3322, 2224 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.82 (s, 3H), 1.98 (d, *J* = 5 Hz, 1H), 3.63 (m, 1H), 3.98 (d, *J* = 13 Hz, 1H), 7.37-7.58 (m, 5H), 7.59 (d, *J* = 8 Hz, 2H), 7.71 (d, *J* = 8 Hz, 2H); ^{13}C NMR {^1H} (400 MHz, $CDCl_3$) δ 143.2, 139.6, 129.9, 129.6, 129.2, 129.0, 128.6, 125.7, 126.6 (q, 13 Hz), 121.3, 60.8, 49.3, 31.6; HRMS (EI) *m/z* (M^+) calcd 304.1187, found 304.1199.



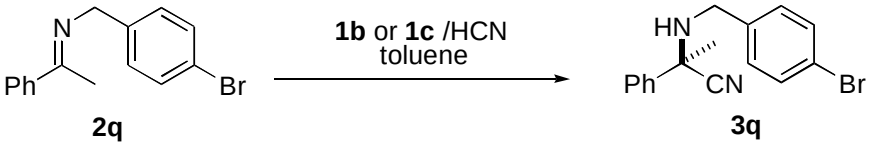
3p: Product was obtained in 95% yield as a clear oil and 89% ee by Chiral HPLC analysis (Chiralcel OD, 3% IPA/Hexanes, 1 mL/min, t_r(minor) = 5.7 min, t_r(major) = 9.2 min); IR (thin film) 3321, 2224 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 9H), 1.85 (s, 3H), 1.96

(s, 1H), 3.62 (d, J = 12 Hz, 1H), 3.94 (d, J = 12 Hz, 1H), 7.37-7.51 (m, 7H), 7.80 (d, J = 8 Hz, 2H); ^{13}C NMR {^{1}H} (400 MHz, $CDCl_3$) δ 150.5, 140.1, 136.3, 129.2, 128.9, 128.3, 125.8, 125.7, 121.6, 60.9, 49.6, 35.0, 31.9, 31.8; HRMS (EI) *m/z* (M^+) calcd 292.1939, found 292.1935.



3q: For optimized yields and ee's, see: Synthesis of Optically Pure α-Methyl Phenylglycine. Crude product was obtained as a solid (quantitative as a mixture with catalyst) in 92% ee. Recrystallization from hexanes afforded product in 75% overall yield as white needles and >99.9% ee by Chiral HPLC analysis (Catalyst **1c** remained dissolved in the mother liquid). (Chiralcel OD, 3% IPA/Hexanes, 1 mL/min, t_r(minor) = 10.0 min, t_r(major) = 14.7 min); IR (thin film) 3323, 2223 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.80 (s, 3H), 1.86 (m, 1H), 3.51 (m, 1H), 3.84 (d, J = 8 Hz, 1H), 7.23 (d, J = 8 Hz, 2H), 7.35-7.46 (m, 5H), 7.68 (d, J = 8 Hz, 2H); ^{13}C NMR {^{1}H} (400 MHz, $CDCl_3$) δ 139.6, 138.1, 131.7, 130.1, 129.2, 128.9, 125.7, 121.4, 94.7, 60.8, 49.2, 31.7, mp = 79.9-80.0 °C (hexanes); $[\alpha]_D^{23}$ = -81.8° (c = 1.0, CH_2Cl_2); HRMS (CI) *m/z* $(MH)^+$ calcd 315.0497, found 315.0508.

Synthesis of optically pure α-methyl phenylglycine (6):

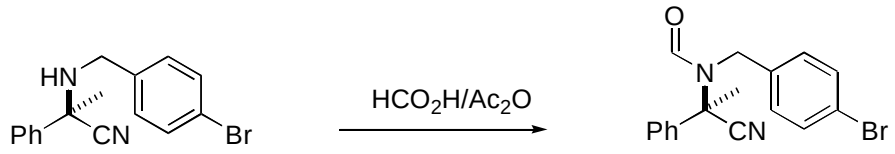


2q **3q**

>99.9% ee

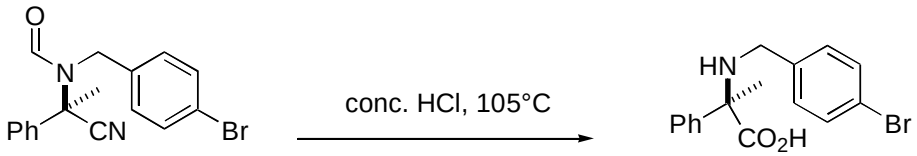
(A) **3q** using solid supported catalyst **1b** at -40 °C: To a 25 mL round bottom flask, 1.00 g (3.47 mmol) of **2q** and 0.580 g (0.55 mmol/g, 0.10 equiv.) of **1c** were combined with 6 mL of freshly distilled toluene. The mixture was allow to stir 5 min at room temperature, cooled to -40 °C and a solution of HCN, which was generated from 0.176 mL (1.25 equiv.) of anhydrous methanol and 0.578 mL (1.25 equiv.) of freshly distilled TMSCN as described previously, and than cooled to –78 °C, was added (0.3 M solution). The reaction mixture was allowed to stir gently (stirring speed approximately 2 s^{-1}) at –40 °C for 6 h, after which it was warmed to ambient temperature and stirred *in vacuo* for 2h to remove excess HCN. Catalyst was filtered off and washed with toluene (2 X 10 mL) and recycled in identical reactions. The solvent was removed *in vacuo* at 25 °C to yield 1.09 g (quantitative yield) of a white solid, 90% ee by chiral HPLC analysis. Recrystallization from hexanes (10.0 mL) afforded 841 mg (77% overall yield), of white needles and >99.9% ee by chiral HPLC analysis.(For spectroscopic and physical data see General Section).

(B) **3q** using solution phase catalyst **1c** at 5 °C (For reaction at -78 °C see general procedure for asymmetric Strecker): To a 10 mL round bottom flask, 400 mg (1.39 mmol) of **2q** and 17 mg (0.027 mmol, 0.02 equiv.) of **1c** were combined with 1.2 mL of freshly distilled toluene. The mixture was cooled to 5 °C and a solution of HCN, which was generated from 70 μL (1.25 equiv.) of anhydrous methanol and 231 μL (1.25 equiv.) of freshly distilled trimethylsilyl cyanide as described previously, and than cooled to –78 °C, was added (0.5 M solution). The reaction mixture was allowed to stir at 5 °C for 8 minutes. The solvents were removed *in vacuo* to yield 451 mg of a solid, 87% ee by chiral HPLC. Washing the solids with pentane (1 mL) removed the catalyst **1c** and afforded 415 mg of white solid, which was recrystallized from hexanes (4.2 mL) yielding 315 mg (72% overall yield) of white needles in >99.9% ee by chiral HPLC analysis. By concentration of the pentane wash followed by flash chromatography on silica gel (eluent 30% AcOEt/hexanes), catalyst **1c** was recovered in 97% yield and recycled in identical reactions.



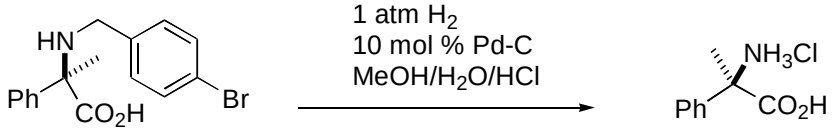
3q **4q**

(**4q**): Mixed acetic formic anhydride, prepared[14] from 12.5 mL (13.5 g, 0.132 mol) of acetic anhydride and 5.0 mL (6.10 g, 0.133 mol) formic acid by heating at 60 °C, was cooled to 0 °C and added to 1.60 g (5.07 mmol, >99.9% ee) of **3q**. The reaction mixture was allowed to stir for 10 min and poured into cold water (150 mL) and extracted with dichloromethane (300 mL). The organic layer was washed with 10% aqueous solution of sodium bicarbonate (300 mL) and dried over Na_2SO_4. The solvents were removed *in-vacuo* yielding 1.71 g (98% yield) of **4q** as a clear oil; IR (thin film) 2240, 1676 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.02 (s, 3H), 4.57 (dd, J_1 = 28 Hz, J_2 = 16 Hz, 2H), 7.07 (d, J = 8 Hz, 2H), 7.19 (m, 2H), 7.27 (m, 1H), 7.40 (m, 4H), 8.65 (s, 1H); ^{13}C NMR {^1H} (400 MHz, $CDCl_3$) δ 162.5, 138.0, 137.2, 136.0, 131.8, 130.0, 129.8, 129.8, 129.2, 128.4, 126.0, 125.5, 121.7, 119.3, 61.0, 46.3, 28.9, HRMS (ES) *m/z* $(MH)^+$ calcd 343.0446, found 343.0462.



4q **5q**

(**5q**) To a 250 mL round bottom flask, 1.70g of (4.95 mmol) of **4q** was dissolved in 100 mL of conc. HCl. The reaction mixture was then heated to 105 °C 3 h. Solvents were removed under reduced pressure to yield a white solid. To remove ammonium chloride (byproduct of the hydrolysis of CN group), the solids were washed with water (3 x 15 mL) to afford 1.75 g of **5q** (95% yield) as its hydrochloric salt (It was also possible to extract **5q** from pH = 6.8 with $CHCl_3$/IPA=3/1 in 95% yield). IR (KBr) 1613 cm^{-1}; ^1H NMR (500 MHz, d_6-DMSO) δ 1.65 (s, 3H), 3.60 (dd, , J_1 = 30 Hz, J_2 = 12 Hz, 2H), 7.35 (m, 5H), 7.53 (m, 4H); ^{13}C NMR {^1H} (400 MHz, d_6-DMSO for **5q**.HCl) δ 171.9, 135.2, 133.6, 132.0, 131.9, 130.1, 129.5, 128.2, 122.9, 67.8, 47.1, 20.6; HRMS (ES) *m/z* $(MH)^+$ calcd 334.0442, found 334.0439.



5q **6**

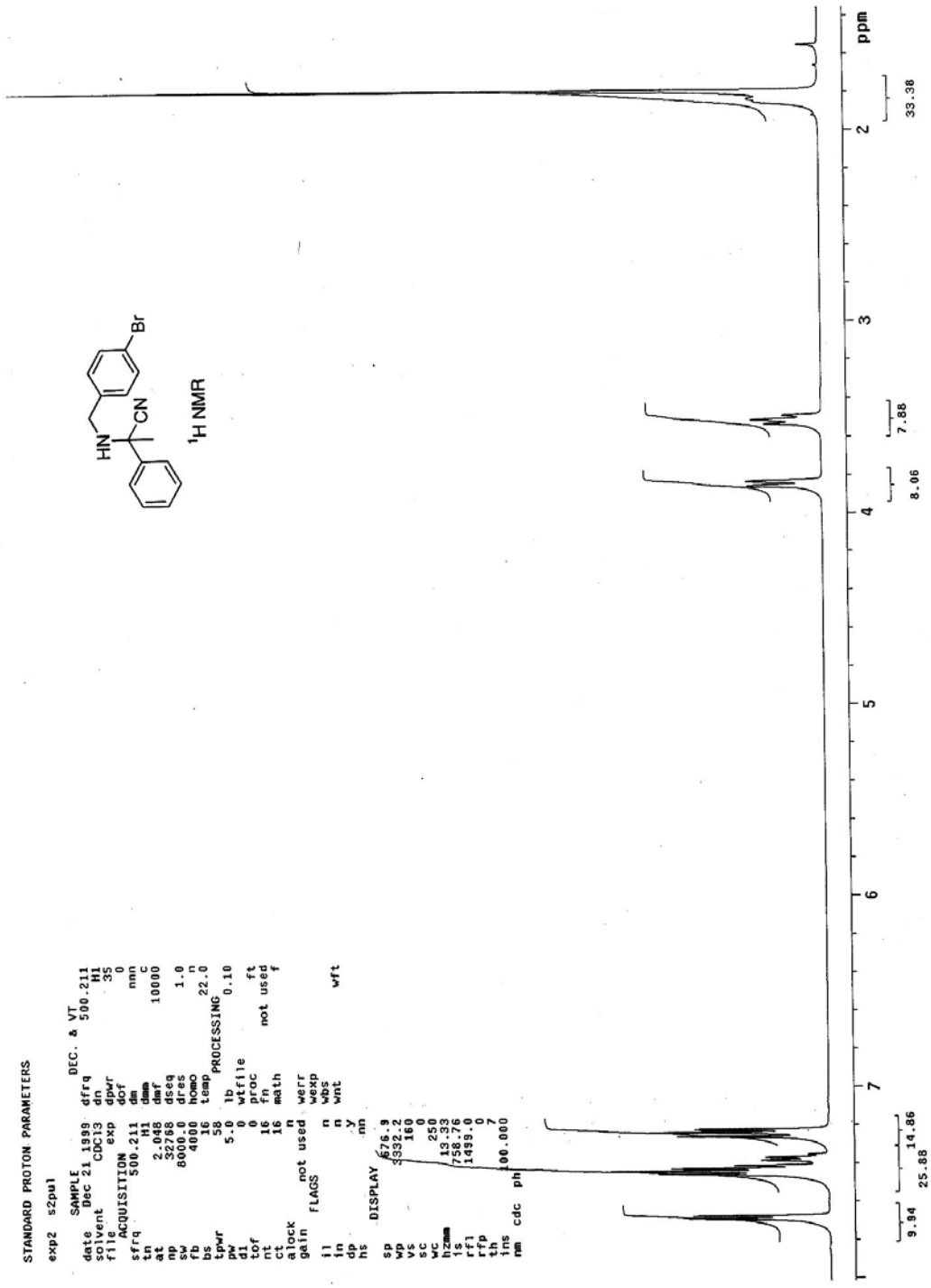
>99.9% ee

(**6**) To a 100 mL three-neck round bottom flask 1.11 g (3.00 mmol) of **5q** was dissolved in a mixture of methanol (30 mL), water (30 mL) and conc. HCl (10 mL) and under inert atmosphere of nitrogen 320 mg (1.24 mmol, 0.10 equiv.) of 10% (w/w) palladium on activated carbon was added. The reaction mixture was allowed to hydrogenate under atmospheric pressure of hydrogen 10 h. The catalyst was removed by filtration through Celite® and the solvents were removed *in vacuo*. The yellow solid residue was washed with AcOEt (3 x 10 mL) to yield 0.605 g (3.00 mmol, quantitative yield) of **6** as a white solid, >99.9% ee by chiral GC analysis (as the N-trifluoroaceto-α-methyl phenylglycine methyl ester, γ-TA, isothermal 120 °C, t_r(major) = 7.7 min, t_r(major) = 8.1 min); $[\alpha]_D^{23}$ = -85.5° (c = 1.0, 1N HCl).[15]

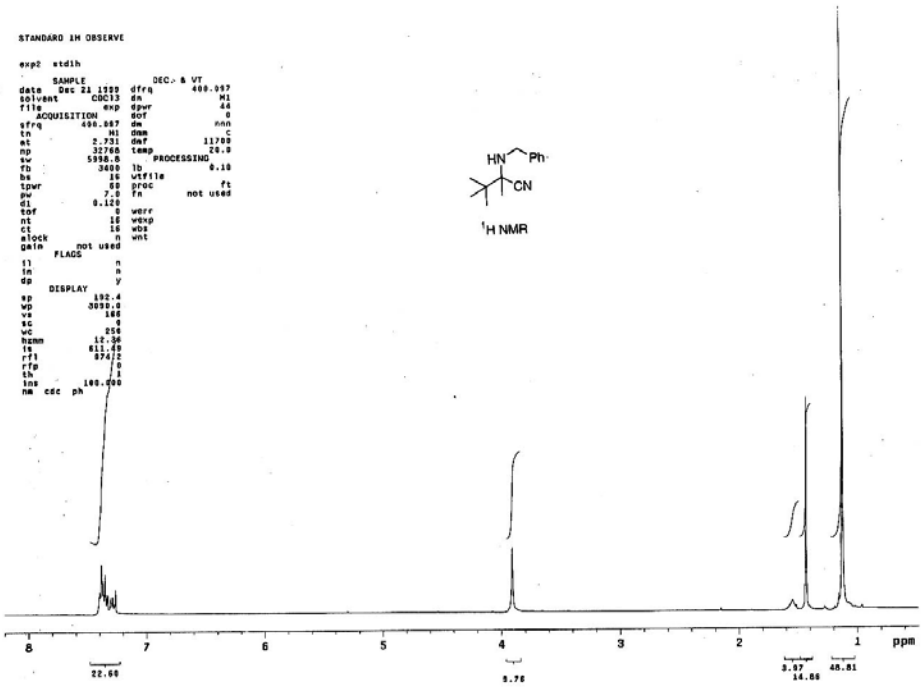
Derivatization of α-methyl phenylglycine for Chiral GC Analysis: A 10 mL round bottom flask was charged with 10 mg of **6** and 2 mL of dichloromethane. To this suspension, 1 mL of trifluoroacetic anhydride was added followed by heating the reaction mixture to reflux for 2 minutes. Solvents were removed *in vacuo* and residual solids were dissolved in methanol (3 mL). An excess of $TMSCHN_2$ was added at room temperature and the reaction mixture was allowed to stir for 5 minutes. The reaction mixture was used for Chiral GC analysis without further purification.

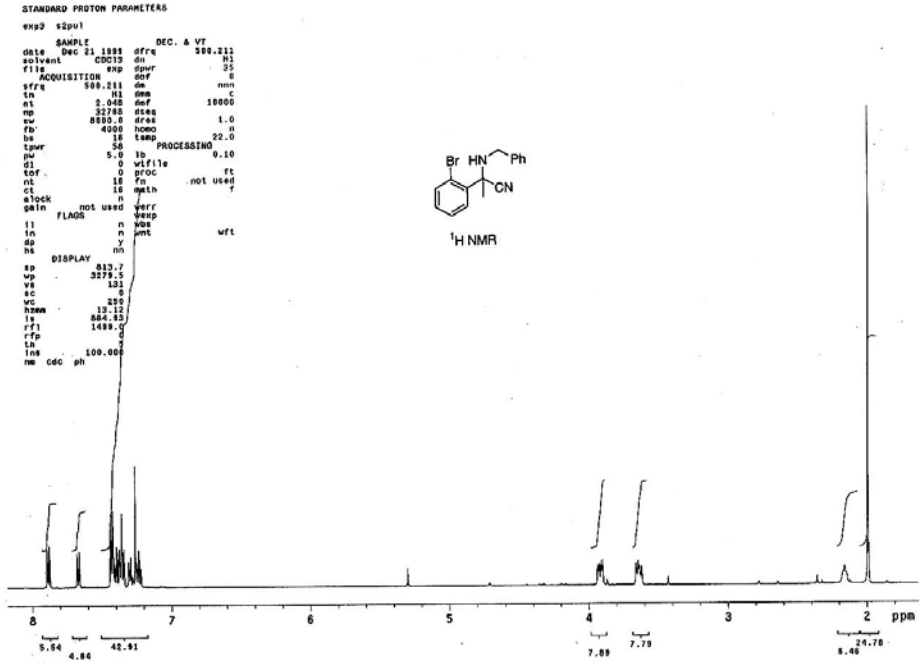
Notes and References

(1) Larrow, J. F.; Jacobsen, E. N.; Gao, Y.; Hong, Y.; Nie, X.; Zepp, C. M. *J. Org. Chem.* **1994**, *59*, 1939.
(2) Sigman, M. S.; Vachal, P; Jacobsen, E. N., submitted for publication.
(3) Wolf, G.; Wuerthwein, E. U. *Chem. Ber*. **1991**, *124*, 655.
(4) Okamoto, H.; Kato, S.; Ogasawara, M.; Konnai, M.; Takematsu, T. *Agric. Biol. Chem.* **1991**, *55*, 2733.
(5) Armesto, D.; Esteban, S.; Horspool, W. M.; Martin, J.-A. F.; Martinez-Alcazar, P.; Perez-Ossorio, R.; *J. Chem. Soc. Perkin Trans. 1* **1989**, 751.
(6) Couture, A.; Grandclaudon, P. *Synthesis* **1986**, *7*, 576.
(7) Rai, M.; Kumar, S.; Krishan, K.; Singh, A. *J. Indian Chem. Soc.* **1981**, *58*, 1111.
(8) Ikegami; Y. *Chem. Pharm. Bull.* **1966**, *14*, 1389.
(9) Couture, A.; Grandclaudon, P.; Hooijer, S. O. *J. Org. Chem.* **1991**, *56*, 4977.
(10) Armesto, D.; Horspool, W. M.; Martin, J. A. F.; Perez-Ossorio, R. *Tetrahedron Lett.* **1985**, *26* 5217.
(11) Ready, J. M.; Jacobsen, E. N. Unpublished results.
(12) Sasaki, Y.; Ambo, A.; Midorikawa, K.; Suzuki, K. *Chem. Pharm. Bull.* **1993**, *41*, 1391.
(13) Ojima, I.; Inaba, S.; Nakatsugawa, K.; Nagai, Y. *Chem. Lett.* **1975**, 331.
(14) Edwards, R. *J. Amer. Chem. Soc.* **1942**, *64*, 1583.
(15) (a) Terashima, S.; Yamada, S. I. *Chem. Pharm. Bull.* **1968**, *15*, 1953. (b) Obrecht, D.; Bohdal, U.; Broger, C.; Bur, D.; Lehmann, C.; Ruffieux, R.; Schoenholzer, P.; Spiegler, C.; Mueller, K. *Helv.Chim.Acta* **1995**, *78*, 563. . For a contrary, and presumaby incorrect assignment, see: (c) Kruizinga, W. H.; Bolster, J.; Kellogg, R. M.; Kamphuis, J.; Boesten, W. H. J. et al. *J. Org. Chem.* **1988**, *53*, 1826.

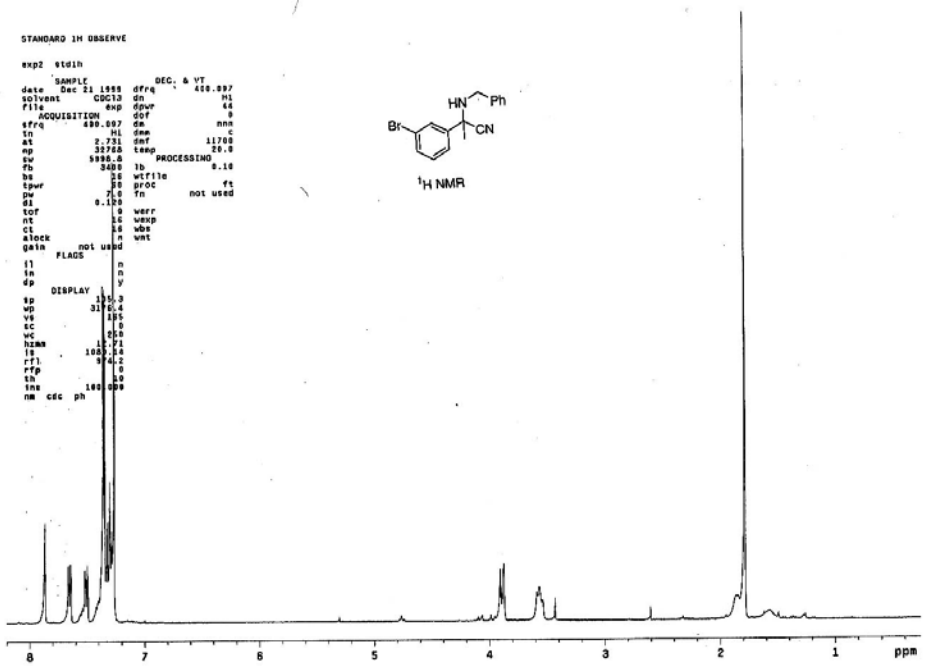

STANDARD PROTON PARAMETERS
exp2 s2pul
SAMPLE
date Dec 21 1999
solvent CDCl3
file exp
ACQUISITION
sfrq 500.211
tn H1
at 2.048
np 32768
sw 8000.0
fb 4000
bs 16
tpwr 58
pw 5.0
d1 0
tof 0
nt 16
ct 16
alock n
gain not used
FLAGS
il n
in n
dp y
hs nn
DISPLAY
sp 676.3
wp 3332.2
vs 160
sc 0
wc 250
hzmm 13.33
is 758.76
rfl 1499.0
rfp 0
th 7
ins 100.000
nm cdc ph
DEC. & VT
dfrq 500.211
dn H1
dpwr 35
dof 0
dm nnn
dmm c
dmf 10000
dseq
dres 1.0
homo n
temp 22.0
PROCESSING
lb 0.10
wtfile
proc ft
fn not used
math f
werr
wexp
wbs
wnt wft
Br
HN
CN
^{1}H NMR
ppm
9.94
25.88
14.86
8.06
7.88
33.38

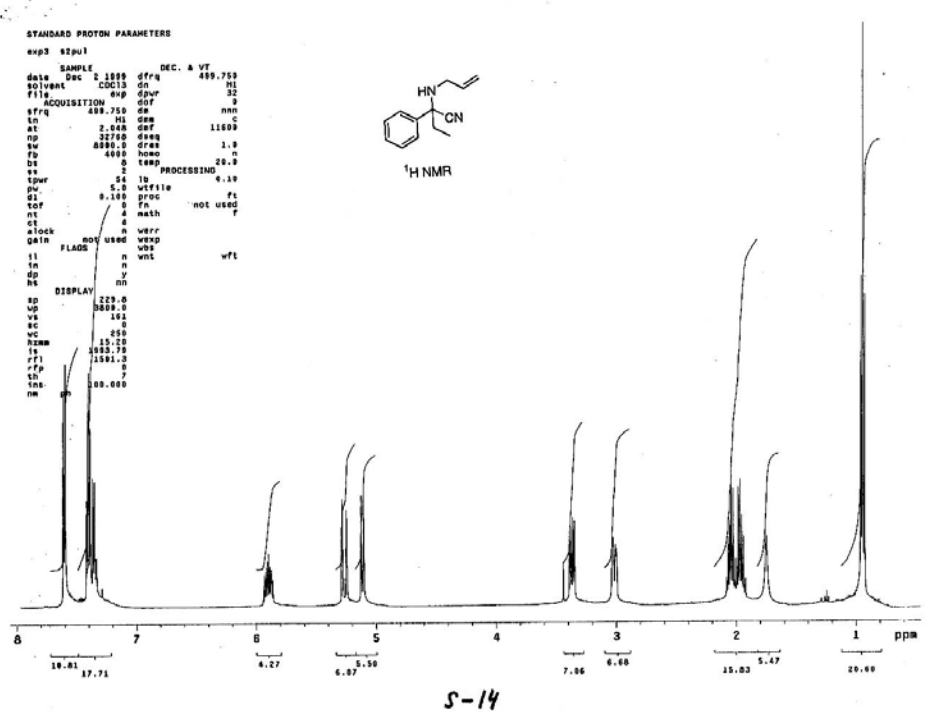
S-12


HN
Ph
CN
^{1}H NMR
8
7
6
5
4
3
2
1
ppm
22.68
9.78
3.07
14.88
48.81

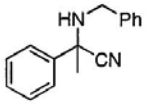

Br
HN
Ph
CN
^{1}H NMR
8
7
6
5
4
3
2
ppm
5.54
4.84
42.91
7.89
7.79
24.78
5.46

S-13

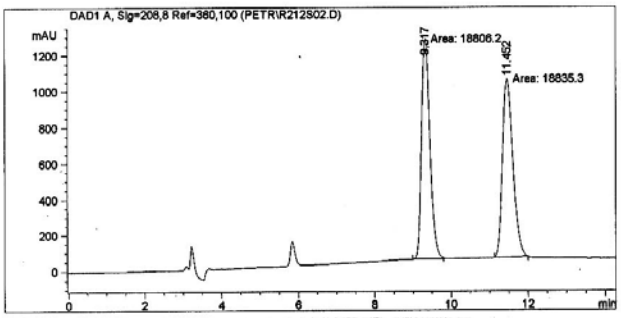

STANDARD 1H OBSERVE
exp2 stdih
SAMPLE
date Dec 21 1998
solvent CDCl3
file exp
ACQUISITION
sfrq 400.097
tn H1
at 2.731
np 32768
sw 5996.8
fb 3400
bs 16
tpwr 50
pw 7.0
d1 0.120
tof 0
nt 16
ct 16
alock n
gain not used
FLAGS
il n
in n
dp y
DISPLAY
sp 1185.3
wp 3176.4
vs 195
sc 0
wc 250
hzmm 12.71
is 1083.54
rfl 5941.2
rfp 0
th 10
ins 100.000
nm cdc ph
DEC. & VT
dfrq 400.097
dn H1
dpwr 44
dof 0
dm nnn
dmm c
dmf 11700
temp 28.0
PROCESSING
lb 0.10
wtfile
proc ft
fn not used
werr
wexp
wbs
wnt
HN
Ph
Br
CN
1H NMR
8
7
6
5
4
3
2
1
ppm

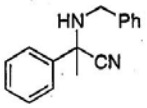

STANDARD PROTON PARAMETERS
exp3 s2pul
SAMPLE
date Dec 2 1999
solvent CDCl3
file exp
ACQUISITION
sfrq 499.750
tn H1
at 2.048
np 32768
sw 8000.0
fb 4000
bs 8
tpwr 54
pw 5.8
d1 0.100
tof 0
nt 4
ct 4
alock n
gain not used
FLAGS
il n
in n
dp y
hs nn
DISPLAY
sp 229.6
wp 3808.8
vs 191
sc 0
wc 250
hzmm 15.28
is 1083.79
rfl 1591.3
rfp 0
th 7
ins 100.000
nm ph
DEC. & VT
dfrq 499.753
dn H1
dpwr 32
dof 0
dm nnn
dmm c
dmf 11609
dseq
dres 1.9
homo n
temp 28.8
PROCESSING
lb 0.10
wtfile
proc ft
fn not used
math f
werr
wexp
wbs
wnt wft
HN
CN
1H NMR
8
7
6
5
4
3
2
1
ppm
10.81
17.71
4.27
6.07
5.50
7.06
6.68
15.83
5.47
20.69

S-14



HPLC Conditions: Chiralcel OD, 3 % Ethanol/Hexanes, 1ml/min

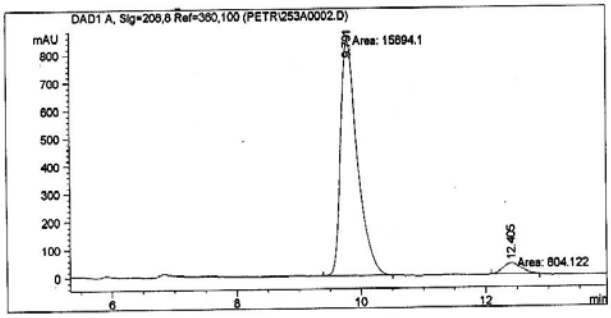


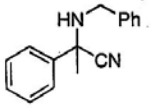


Racemic sample

Signal 1: DAD1 A, Sig=208,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.317	MM	0.2561	1.88062e4	1223.92017	49.9613
2	11.452	MM	0.3157	1.88353e4	994.48846	50.0387



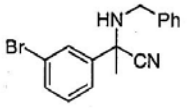


Reaction product

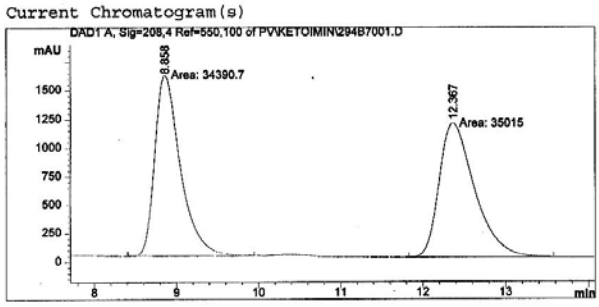
Signal 1: DAD1 A, Sig=208,8 Ref=360,100

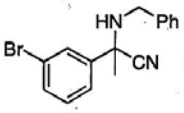
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.791	MM	0.3139	1.58941e4	843.81409	95.1844
2	12.405	MM	0.3429	804.12195	39.08368	4.8156

S-15



HPLC Conditions: Chiralcel OD, 7 % Ethanol/Hexanes, 1ml/min

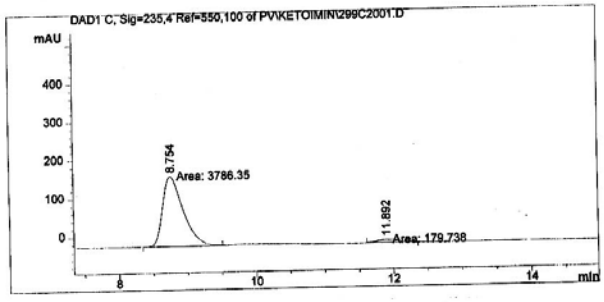


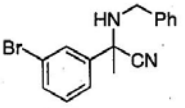


Racemic sample

Signal 1: DAD1 A, Sig=208,4 Ref=550,100

Peak #	RT [min]	Type	Width [min]	Area [mAU*sec]	Height [mAU]	Area %
1	8.858	MM	0.362	34390.74609	1585.13782	49.5503
2	12.367	MM	0.496	35015.00000	1175.73279	50.4497



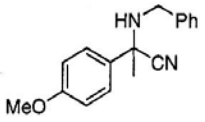


Reaction product

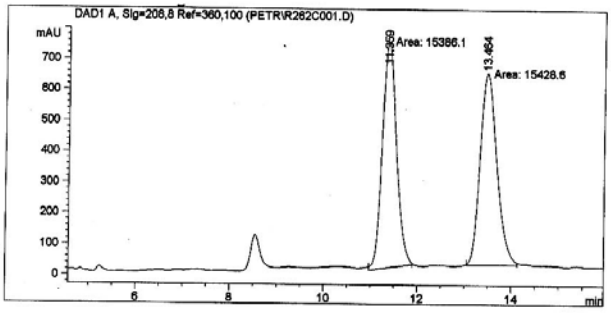
Signal 1: DAD1 C, Sig=235,4 Ref=550,100

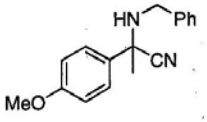
Peak #	RT [min]	Type	Width [min]	Area [mAU*sec]	Height [mAU]	Area %
1	8.754	MM	0.348	3786.35327	181.58493	95.4681
2	11.892	MM	0.380	179.73781	7.87396	4.5319

S-16



HPLC Conditions: Chiralcel OD, 3 % Ethanol/Hexanes, 1ml/min

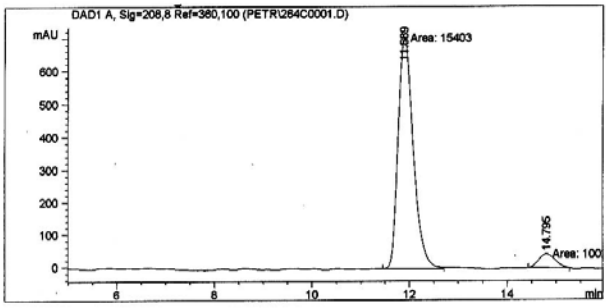


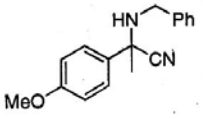


Racemic sample

Signal 1: DAD1 A, Sig=208,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.359	MM	0.3489	1.53861e4	734.94000	49.9310
2	13.464	MM	0.4133	1.54286e4	622.10181	50.0690



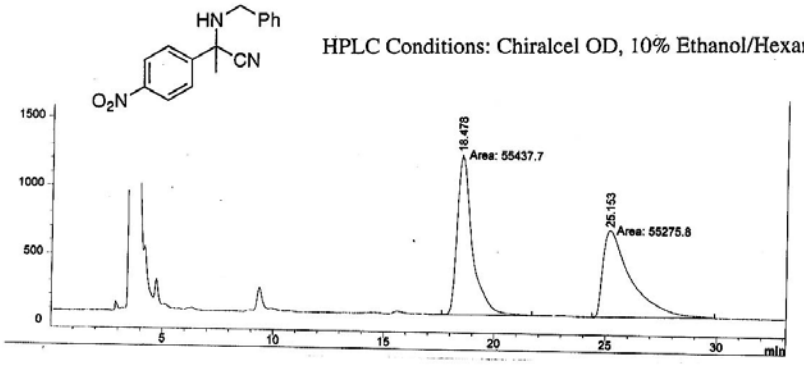


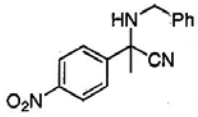
Reaction product

Signal 1: DAD1 A, Sig=208,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.889	MM	0.3639	1.54030e4	705.38873	93.8888
2	14.795	MM	0.3975	1002.58539	42.03888	6.1112

S-17

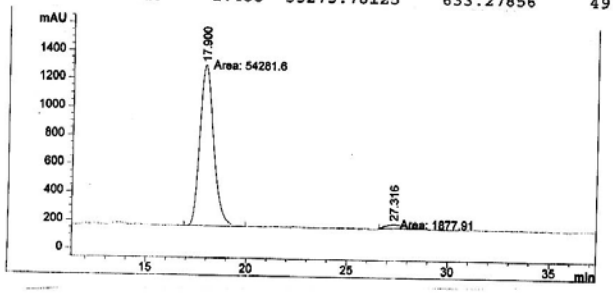


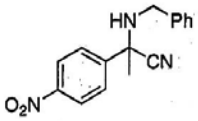


Racemic sample

Signal 1: DAD1 A, Sig=208,4 Ref=550,100

Peak #	RT [min]	Type	Width [min]	Area [mAU*sec]	Height [mAU]	Area %
1	18.478	MM	0.788	55437.65625	1172.46936	50.0731
2	25.153	MM	1.455	55275.78125	633.27856	49.9269

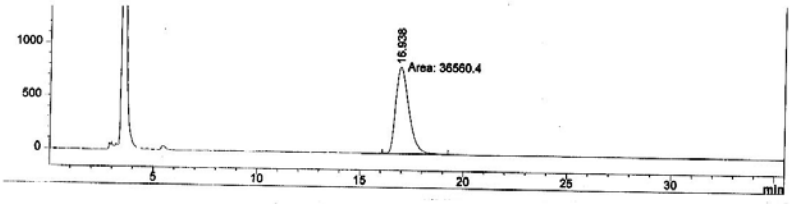


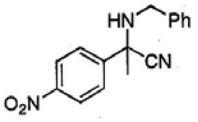


Reaction product

Signal 1: DAD1 A, Sig=208,4 Ref=550,100

Peak #	RT [min]	Type	Width [min]	Area [mAU*sec]	Height [mAU]	Area %
1	17.900	MM	0.798	54281.62891	1133.15967	96.6561
2	27.316	MM	1.063	1877.91174	29.43464	3.3439



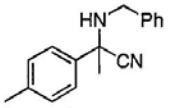


After recrystalization

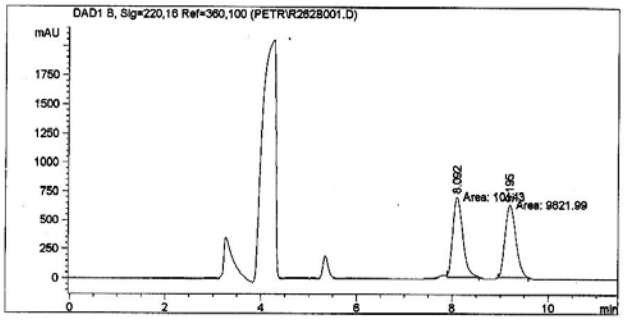
Signal 1: DAD1 B, Sig=220,4 Ref=550,100

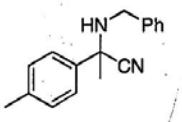
Peak #	RT [min]	Type	Width [min]	Area [mAU*sec]	Height [mAU]	Area %
1	16.938	MM	0.743	36560.40234	820.61029	100.0000

S-18



HPLC Conditions: Chiralcel OD, 3 % Ethanol/Hexanes, 1ml/min

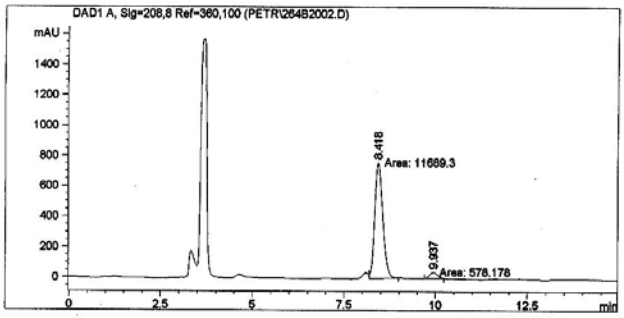


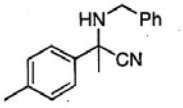


Racemic sample

Signal 1: DAD1 B, Sig=220,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.092	MM	0.2424	1.01430e4	697.49188	50.8040
2	9.195	MM	0.2600	9821.98828	629.63715	49.1960



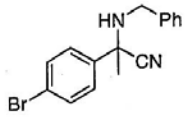


Reaction product

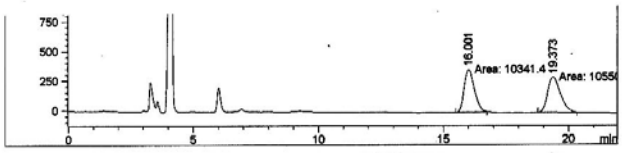
Signal 1: DAD1 A, Sig=208,8 Ref=360,100

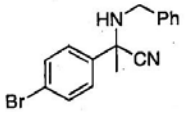
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.418	FM	0.2552	1.16893e4	763.43768	95.2869
2	9.937	MM	0.2466	578.17792	39.08101	4.7131

S-19



HPLC Conditions: Chiralcel OD, 3% IPA/Hexanes, 1ml/min

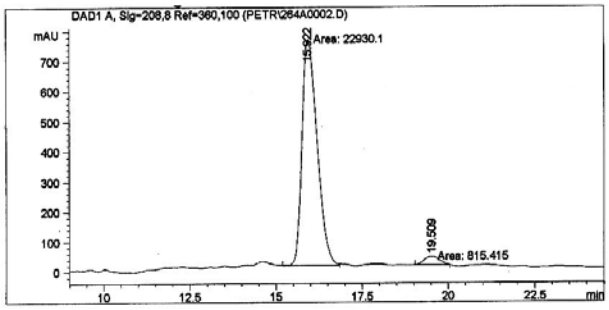


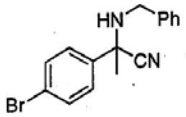


Racemic sample

Signal 1: DAD1 A, Sig=208,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.001	MM	0.4760	1.03414e4	362.06897	49.5000
2	19.373	MM	0.5877	1.05503e4	299.17987	50.5000

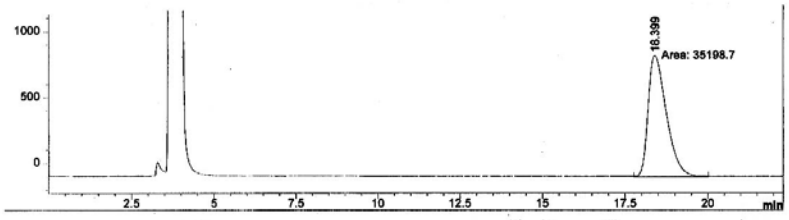


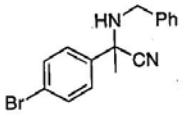


Reaction product

Signal 1: DAD1 A, Sig=208,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.922	MM	0.5083	2.29301e4	751.81525	96.5660
2	19.509	MM	0.5019	815.41516	27.07678	3.4340



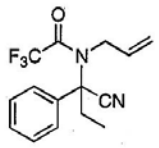


After recrystalization

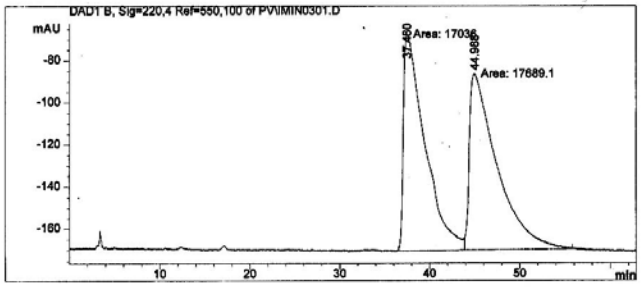
Signal 1: DAD1 A, Sig=208,4 Ref=550,100

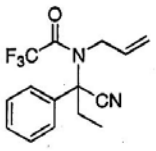
Peak #	RT [min]	Type	Width [min]	Area [mAU*sec]	Height [mAU]	Area %
1	18.399	MM	0.637	35198.66016	920.82947	100.0000

S-20



HPLC Conditions: S,S-Whelko, 0.2% IPA/ Hexanes

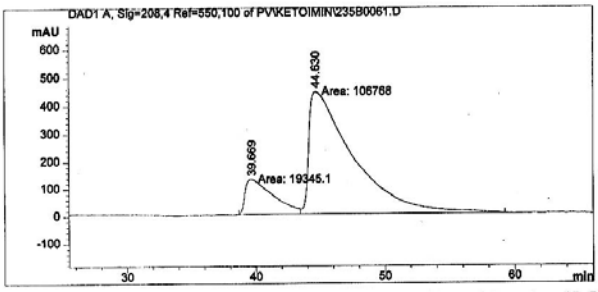


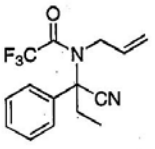


Racemic sample

Signal 1: DAD1 B, Sig=220,4 Ref=550,100

Peak #	RT [min]	Type	Width [min]	Area [mAU*sec]	Height [mAU]	Area %
1	37.480	MF	2.754	17035.96484	103.08439	49.0595
2	44.988	FM	3.513	17689.14453	83.92152	50.9405



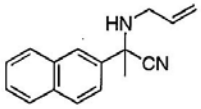


Reaction product

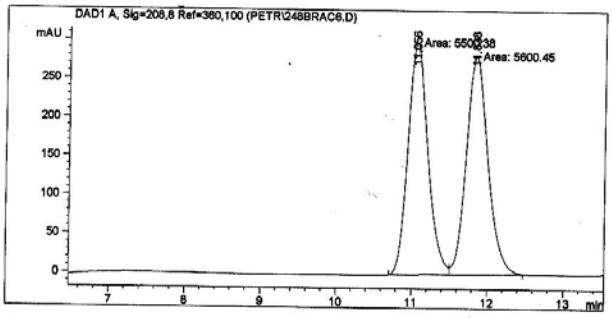
Signal 1: DAD1 A, Sig=208,4 Ref=550,100

Peak #	RT [min]	Type	Width [min]	Area [mAU*sec]	Height [mAU]	Area %
1	39.669	MF	2.493	19345.06055	129.30890	15.3395
2	44.630	FM	3.999	106767.60938	444.94583	84.6605

S-21

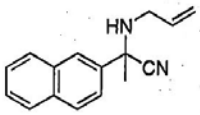


HPLC Conditions: Chiralcel OD, 1% IPA/Hexanes, 1ml/min

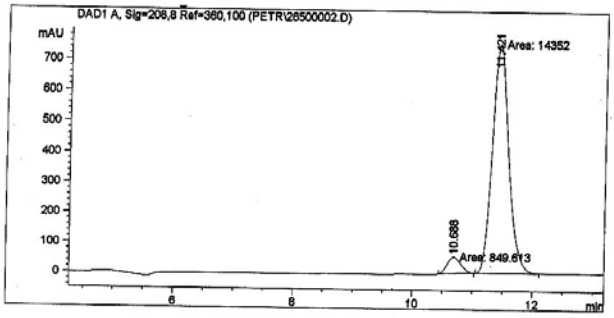


Signal 1: DAD1 A, Sig=208,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.056	MF	0.3059	5500.37646	299.66580	49.5492
2	11.838	FM	0.3311	5600.45264	281.95383	50.4508

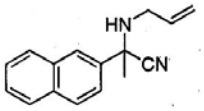


Racemic sample



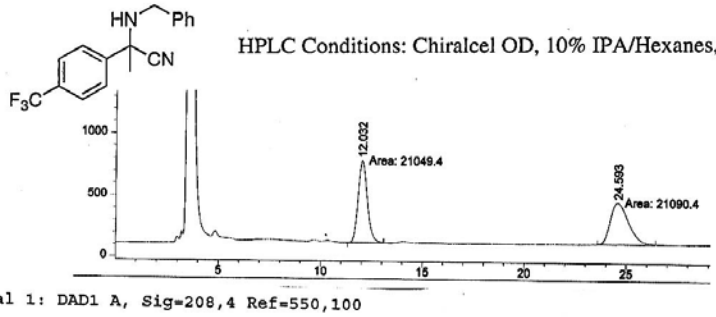
Signal 1: DAD1 A, Sig=208,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.688	MM	0.2637	849.61340	53.69230	5.5890
2	11.421	MM	0.3180	1.43520e4	752.10950	94.4110



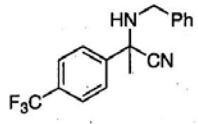
Reaction product

S - 22

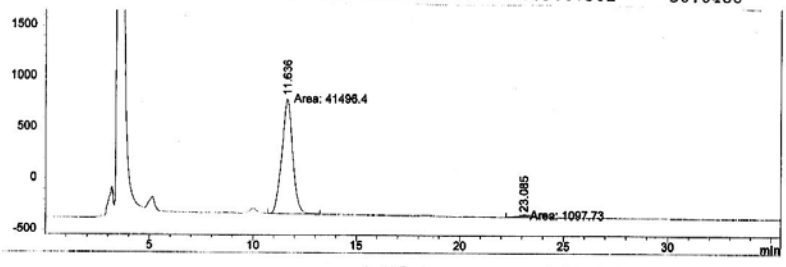


Signal 1: DAD1 A, Sig=208,4 Ref=550,100

Peak #	RT [min]	Type	Width [min]	Area [mAU*sec]	Height [mAU]	Area %
1	12.032	MM	0.526	21049.42383	666.69751	49.9514
2	24.593	MM	1.035	21090.42383	339.67361	50.0486

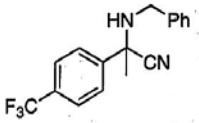


Racemic sample

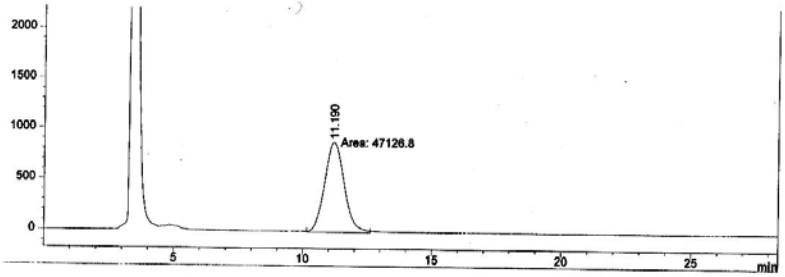


Signal 1: DAD1 A, Sig=208,4 Ref=550,100

Peak #	RT [min]	Type	Width [min]	Area [mAU*sec]	Height [mAU]	Area %
1	11.636	MM	0.611	41496.35547	1131.11426	97.4228
2	23.085	MM	0.949	1097.73413	19.27080	2.5772

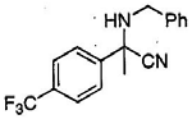


Reaction product



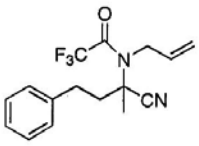
Signal 1: DAD1 B, Sig=220,4 Ref=550,100

Peak #	RT [min]	Type	Width [min]	Area [mAU*sec]	Height [mAU]	Area %
1	11.190	MM	0.887	47126.79688	885.65009	100.0000

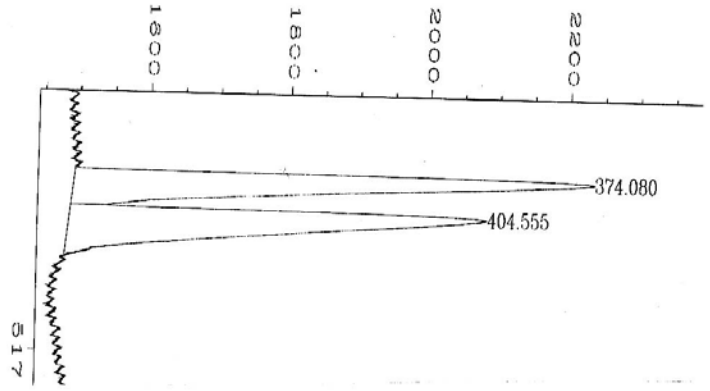


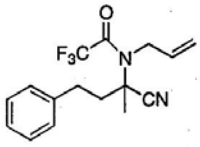
After recrystalization

S-23



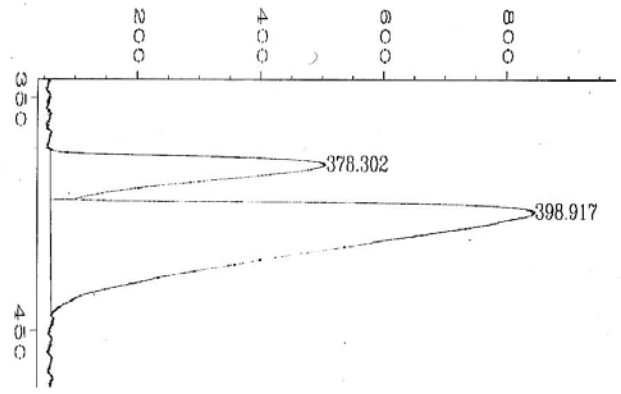
GC Conditions: γ-TA, 90 °C isothermal

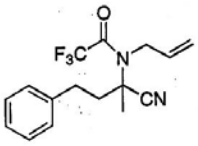




Racemic sample

Pk#	Ret Time	Area	Height	Type	Width	Area %
1	374.080	702232	743	MF	15.754	49.6430
2	404.555	712332	597	FM	19.882	50.3570

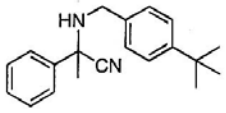




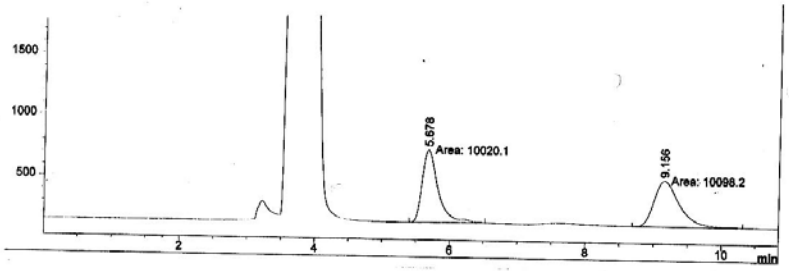
Reaction product

Pk#	Ret Time	Area	Height	Type	Width	Area %
1	378.302	309286	446	BV	8.936	22.0532
2	398.917	1093167	787	PB	16.997	77.9468

S-24

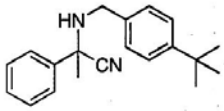


HPLC Conditions: Chiralcel OD, 3 % IPA/Hexanes, 1ml/min

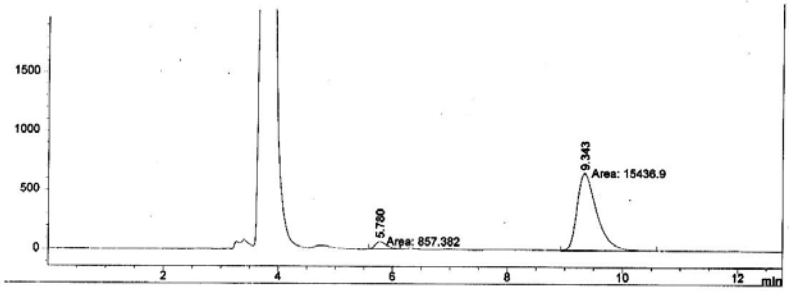


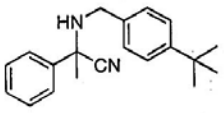
Signal 1: DAD1 A, Sig=208,4 Ref=550,100

Peak #	RT [min]	Type	Width [min]	Area [mAU*sec]	Height [mAU]	Area %
1	5.678	MM	0.277	10020.05078	602.83990	49.8058
2	9.156	MM	0.438	10098.17090	384.15112	50.1942



Racemic sample



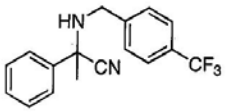


Reaction product

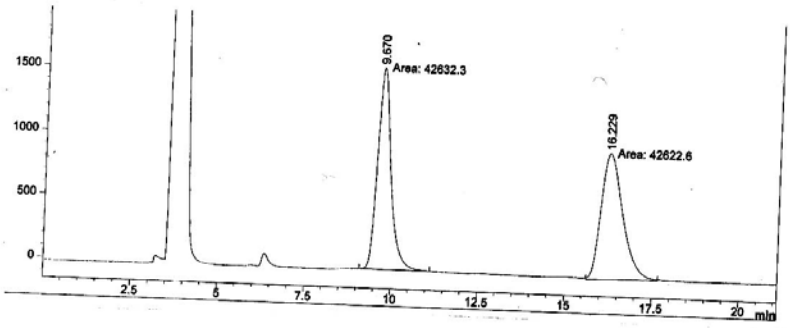
Signal 1: DAD1 A, Sig=208,4 Ref=550,100

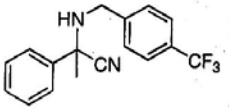
Peak #	RT [min]	Type	Width [min]	Area [mAU*sec]	Height [mAU]	Area %
1	5.780	MM	0.225	857.38171	63.40765	5.2619
2	9.343	MM	0.396	15436.87305	649.15814	94.7381

S-25



HPLC Conditions: Chiralcel OD, 3 % IPA/Hexanes, 1ml/min

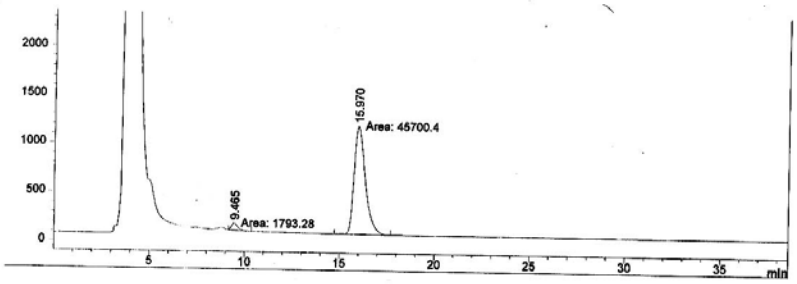


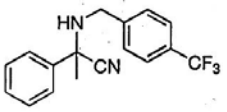


Racemic sample

Signal 1: DAD1 A, Sig=208,4 Ref=550,100

Peak #	RT [min]	Type	Width [min]	Area [mAU*sec]	Height [mAU]	Area %
1	9.670	MM	0.451	42632.33984	1574.14978	50.0057
2	16.229	MM	0.719	42622.58984	987.90540	49.9943
Totals :				85254.92969	2562.05518	



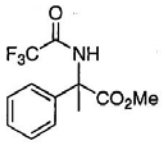


Reaction product

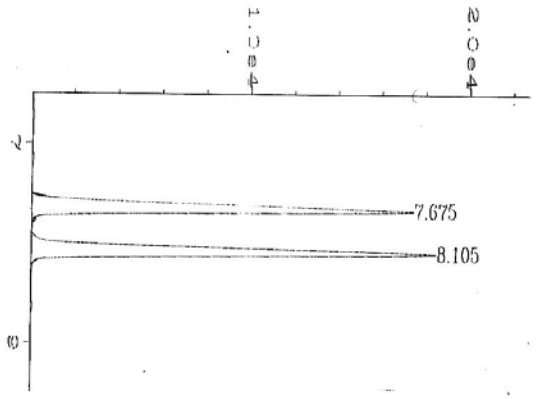
Signal 1: DAD1 A, Sig=208,4 Ref=550,100

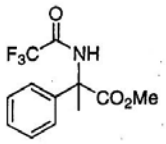
Peak #	RT [min]	Type	Width [min]	Area [mAU*sec]	Height [mAU]	Area %
1	9.465	FM	0.388	1793.27783	77.06589	3.7758
2	15.970	MM	0.687	45700.35938	1107.90027	96.2242

S-26



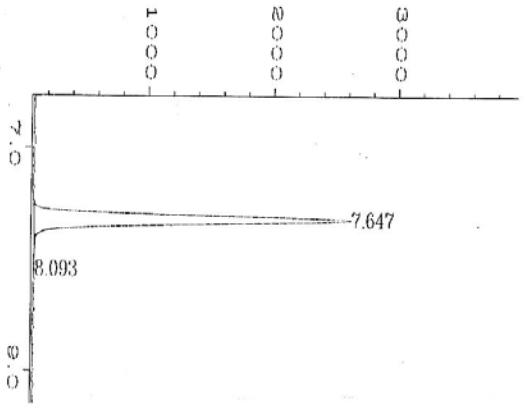
GC Conditions: γ-TA, 120 °C isothermal

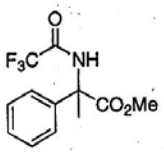




Racemic sample

Pk#	Ret Time	Area	Height	Type	Width	Area %
1	7.675	96132	17423	MM	0.092	50.0210
2	8.105	96051	18509	MM	0.086	49.9790

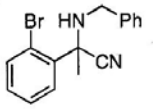




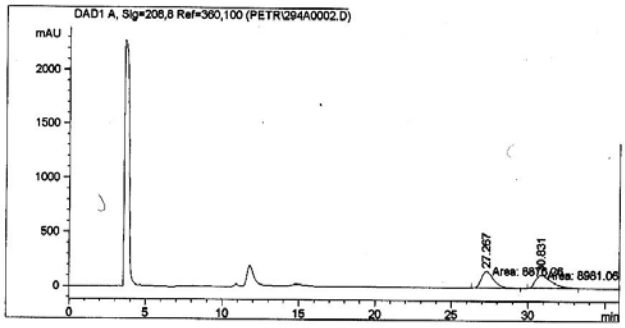
Reaction product

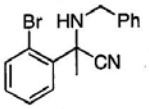
Pk#	Ret Time	Area	Height	Type	Width	Area %
1	7.647	13910	2535	MM	0.091	99.9898
2	8.093	1	3	MM	0.007	0.0102

S-27



HPLC Conditions: Chiralcel OD, 1 %IPA/Hexanes, 1ml/min

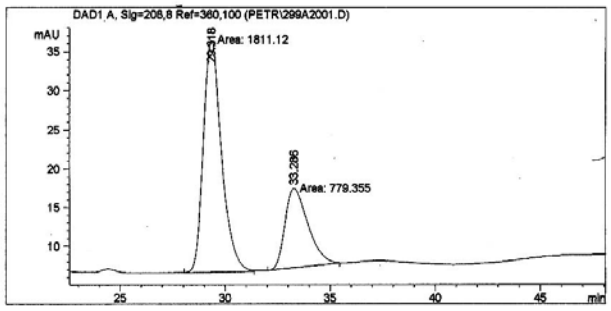


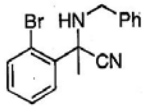


Racemic sample

Signal 1: DAD1 A, Sig=208,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.267	MM	0.9569	8876.26172	154.60080	49.7066
2	30.831	MM	1.2405	8981.05664	120.66767	50.2934



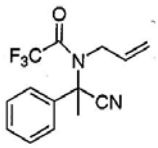


Reaction product

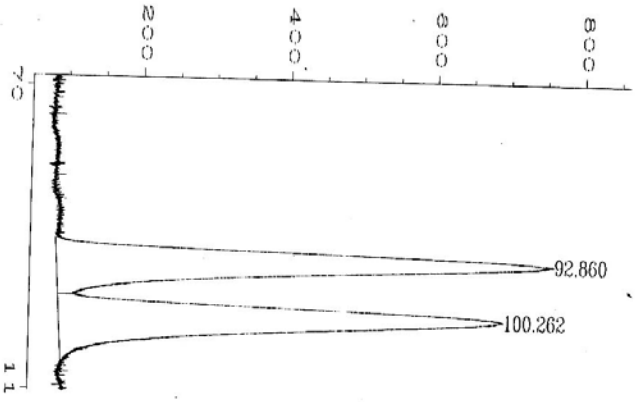
Signal 1: DAD1 A, Sig=208,8 Ref=360,100

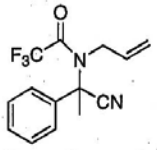
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.318	MM	1.0105	1811.12122	29.87291	69.9146
2	33.286	MM	1.2681	779.35455	10.24324	30.0854

S-28



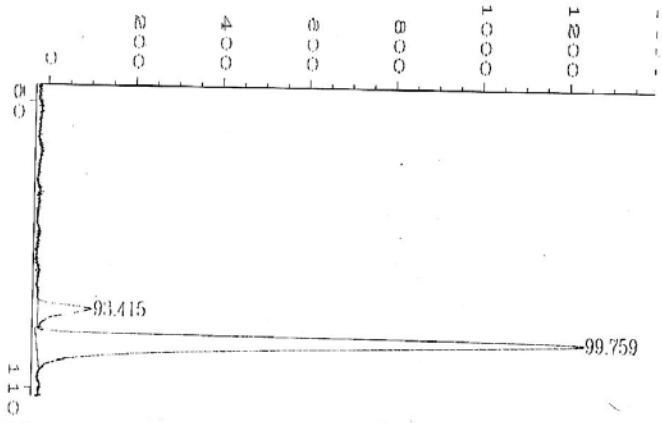
GC Conditions: γ-TA, 100 °C isothermal

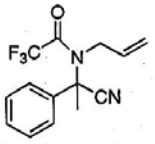




Racemic sample

Pk#	Ret Time	Area	Height	Type	Width	Area %
1	92.860	124685	676	MF	3.074	50.2749
2	100.262	123322	605	FM	3.396	49.7251

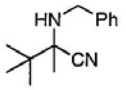




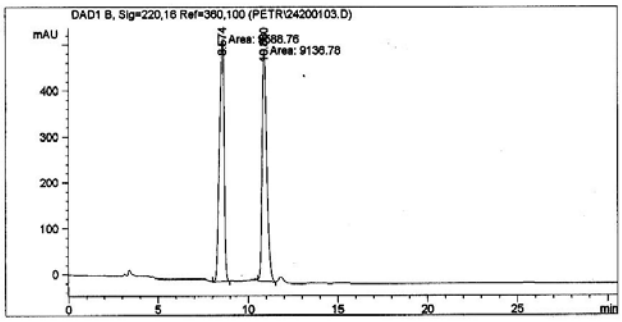
Reaction product

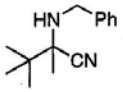
Pk#	Ret Time	Area	Height	Type	Width	Area %
1	93.415	16318	126	MM	2.150	7.2363
2	99.759	209178	1263	MM	2.761	92.7637

S-29



HPLC Conditions: Chiralcel OD, 0.5% Ethanol/Hexanes, 1ml/min

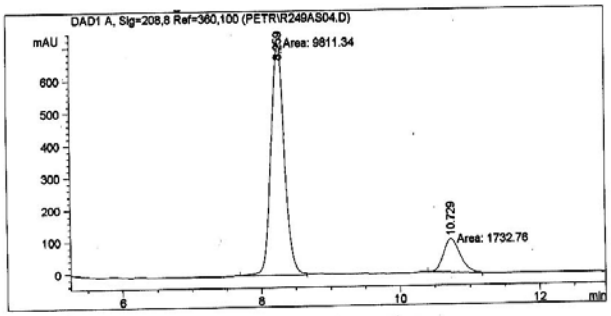


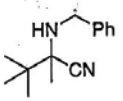


Racemic sample

Signal 1: DAD1 B, Sig=220,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.574	MM	0.3027	9588.75781	528.00061	51.2069
2	10.880	MM	0.3027	9136.77832	503.11914	48.7931



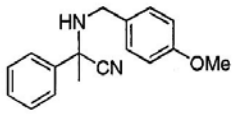


Reaction product

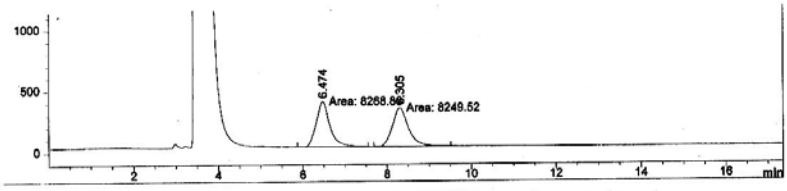
Signal 1: DAD1 A, Sig=208,8 Ref=360,100

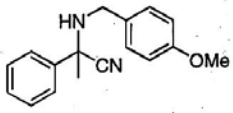
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.259	MM	0.2276	9811.34375	718.46277	84.9901
2	10.729	MM	0.2783	1732.75830	103.76395	15.0099

S-30



HPLC Conditions: Chiralcel OD, 10 % IPA/Hexanes, 1ml/min

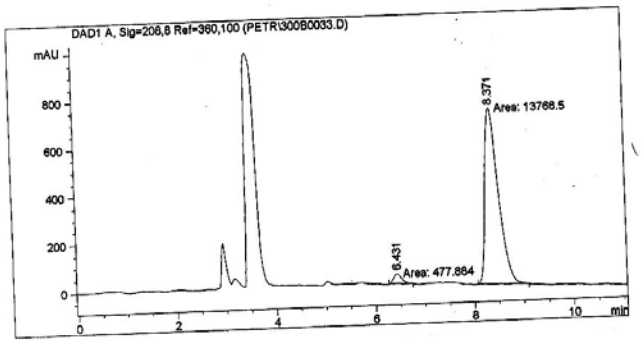


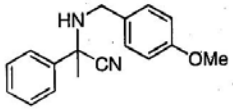


Racemic sample

Signal 1: DAD1 A, Sig=208,4 Ref=550,100

Peak #	RT [min]	Type	Width [min]	Area [mAU*sec]	Height [mAU]	Area %
1	6.474	MM	0.374	8268.86230	368.49973	50.0585
2	8.305	MM	0.438	8249.52246	313.55090	49.9415



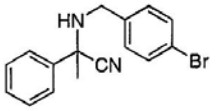


Reaction product

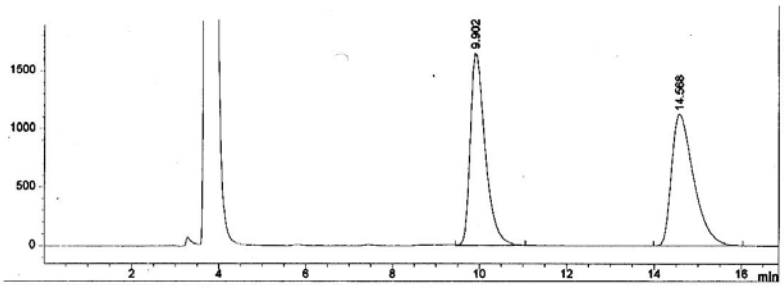
Signal 1: DAD1 A, Sig=208,8 Ref=360,100

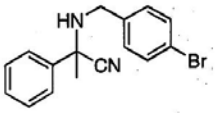
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.431	MM	0.1928	477.88406	41.30902	3.3549
2	8.371	MM	0.3108	1.37665e4	738.21576	96.6451

S-31



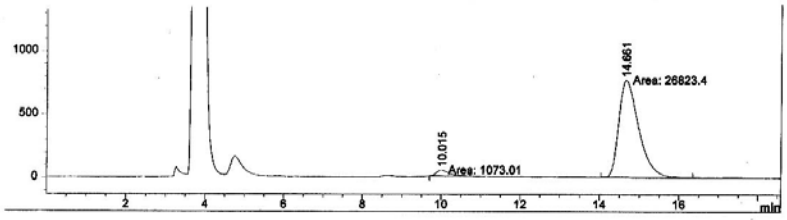
HPLC Conditions: Chiralcel OD, 3% IPA/Hexanes, 1ml/min

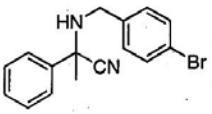




Racemic sample

Peak #	RT [min]	Type	Width [min]	Area [mAU*sec]	Height [mAU]	Area %
1	9.902	FF	0.283	39436.66797	1658.96814	49.7920
2	14.568	FV	0.418	39766.21484	1130.23425	50.2080

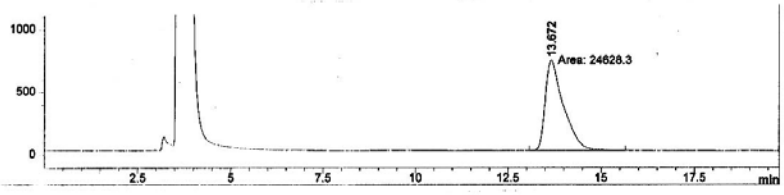


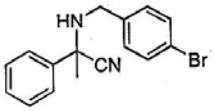


Reaction product

Signal 1: DAD1 A, Sig=208,4 Ref=550,100

Peak #	RT [min]	Type	Width [min]	Area [mAU*sec]	Height [mAU]	Area %
1	10.015	MM	0.383	1073.01379	46.74596	3.8464
2	14.661	MM	0.581	26823.44922	770.06842	96.1536





After recrystalization

Signal 1: DAD1 A, Sig=208,4 Ref=550,100

Peak #	RT [min]	Type	Width [min]	Area [mAU*sec]	Height [mAU]	Area %
1	13.672	MM	0.567	24628.34961	723.34851	100.0000

S-32