Angewandte Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Supporting Information

69451 Weinheim, Germany

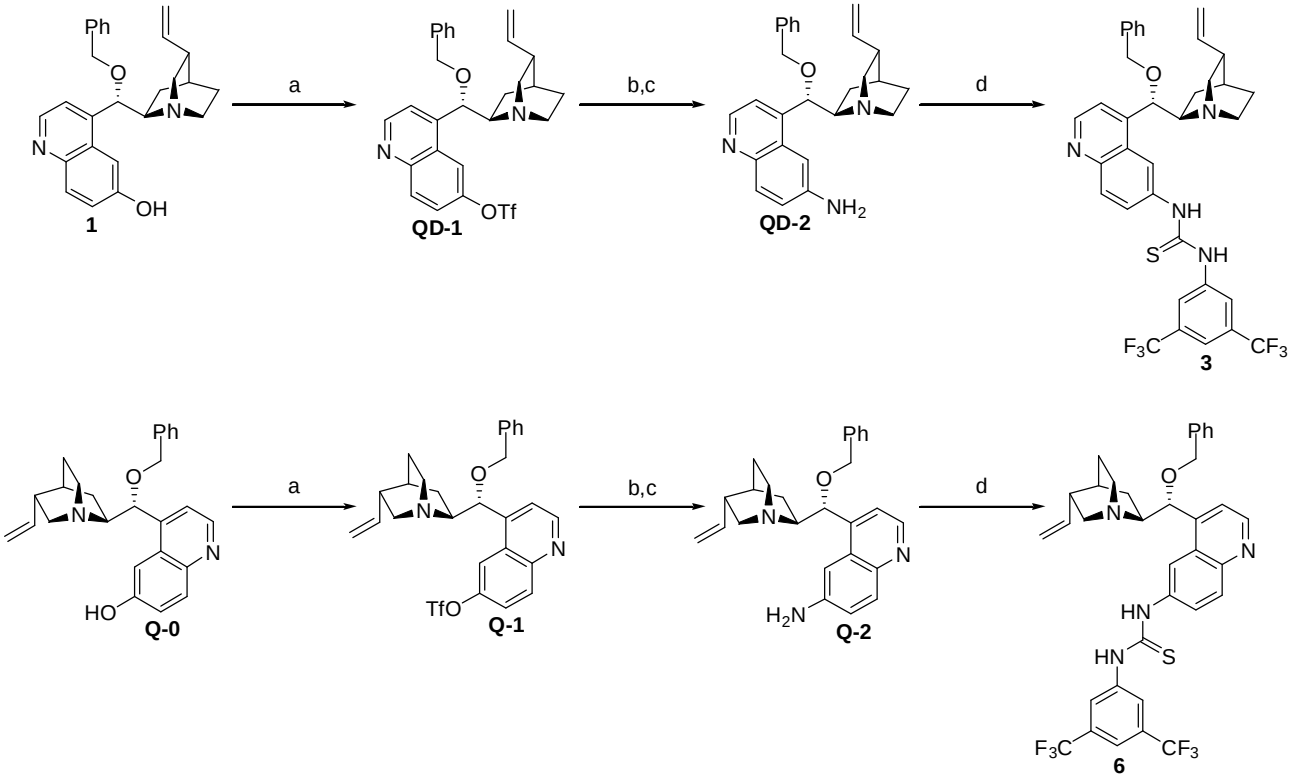
Asymmetric Organocatalytic Nitroaldol Reaction

Tommaso Marcelli, Richard N. S. van der Haas, Jan H. Van Maarseveen and Henk Hiemstra*

General Remarks

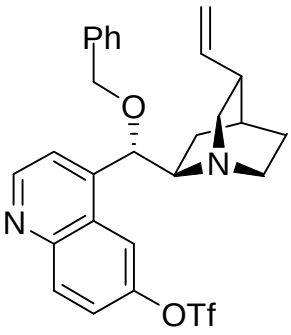
Solvents were obtained from Biosolve, petroleum ether (boiling fraction 40-65 °C) was distilled prior to use. THF was distilled from sodium/benzophenone; CH_2Cl_2 was pre-dried on P_2O_5 and distilled from CaH_2. Column chromatography was performed using Aldrich silica gel (70-230 mesh, 60 Å). Reagents were obtained from Aldrich or Fluka and used without further purification. 9-O-Benzylcupreidine (**1**)[1] and 9-O-benzylcupreine (**Q-0**)[2] were prepared according to Deng *et al.* Aldehyde **4h**[3] was prepared according to Tietze *et al.* 400 MHz ^{1}H-NMR, 100 MHz ^{13}C-NMR and 2D ^{13}C-^{1}H HSQC NMR spectra were obtained using a Bruker Avance 400 spectrometer. ^{1}H-NMR chemical shifts (δ) are given in ppm downfield from tetramethylsilane. ^{13}C-NMR chemical shifts are given using $CDCl_3$ as the internal standard. IR spectra were recorded on a Bruker IFS28 spectroscope. ES-HRMS was performed on a JEOL JMS SX/SX 102A four-sector mass spectrometer coupled to a JEOL MSMP9021D/UPD system program. Optical rotations ($[\alpha]^{25}_D$) were measured on a Perkin-Elmer 241 polarimeter. HPLC was performed using a Meyvis-Gilson equipment (injector model 231 and a 307 pump) and a Daicel Chiralcel OD-H column. A Pharmacia LKB-VWM 2141 detector was used for detection and the chromatograms were recorded with an HP3395 integrator.

Preparation of the catalysts



Conditions: a) $PhNTf_2$, DMAP, DCM; b) $Pd(OAc)_2$, BINAP, Cs_2CO_3, THF, $Ph_2C{=}NH$; c) citric acid, THF, H_2O; d) 3,5-$(CF_3)_2$PhNCS, THF.

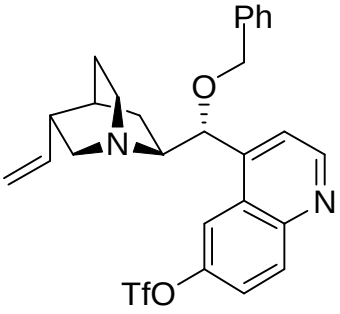
6'-*O*-trifluoromethylsulfonyl-9-*O*-benzylcinchonine (QD-1):



The synthesis of this compound was accomplished using the procedure described by Corey and Zhang with a slight modification.[4] To a stirred mixture of benzylcupreidine **1** (5.00 g, 12.5 mmol) in dichloromethane (90 mL) was added N-phenyl-bis(trifluoromethanesulfonimide) (4.88 g, 13.7 mmol) and 4-dimethylaminopyridine (135 mg, 1.11 mmol). The mixture was stirred 15 hrs at room temperature after which the solvent was evaporated under reduced pressure. The residue was dissolved in 150 ml of EtOAc and washed three times with saturated sodium carbonate in water and one time with brine, after which it was dried over magnesium sulfate. The solution was concentrated under reduced pressure after which the product was purified by flash chromatography over silica gel (0-5 % MeOH in EtOAc) which gave 6.51 gram (12.2 mmol, 98%) of the pure product as a colorless sticky oil. $[\alpha]^{25}_{D}$ = +77.4 (c 1.00, CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.99 (d, J = 4.4 Hz, 1H), 8.27 (d, J = 9.3 Hz, 1H), 8.22 (b, 1H), 7.64 (dd, J = 9.3, 2.7 Hz, 1H), 7.56 (d, J = 4.4 Hz, 1H), 7.40-7.28 (m, 5H), 5.90 (ddd, J = 17.1, 10.4, 7.3 Hz, 1H), 5.09 (b, 1H), 5.03 (m, J = 10.4, 1.5 Hz, 1H), 5.01 (m, J = 17.1 Hz, 1.5 Hz, 1H), 4.49 (d, J = 11.5 Hz, 1H), 4.36 (d, J = 11.5 Hz, 1H), 3.15

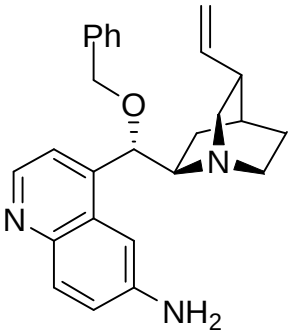
(m, 1H), 3.04 (m, 1H), 2.88 (dd, 13.2, 9.5 Hz, 1H), 2.74 (m, 2H), 2.25 (m, 1H), 1.96 (dd, J = 13.2, 9.5 Hz, 1H), 1.80 (m, 1H), 1.57-1.51 (m, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 151.28, 147.50, 147.03, 140.27, 137.19, 133.19, 128.48, 128.11, 128.07, 128.01, 126.85, 122.76, 120.85, 118.82 (q, J = 320 Hz), 116.23, 114.63, 80.76, 71.63, 60.86, 49.80, 48.99, 39.76, 27.92, 26.37, 23.58 ppm; FTIR ($CHCl_3$): 2944, 2875, 1596, 1509, 1456, 1425, 1249, 1225, 1212, 1141, 930, 846 cm^{-1}; HRMS (ES, M + H$^+$) calculated for [$C_{27}H_{27}F_3N_2O_4S$ + H]$^+$: 533.1722, found 533.1725.

6'-*O*-trifluoromethylsulfonyl-9-*O*-benzyl-cinchonidine (Q-1):



This compound was prepared following the same procedure as described above. Starting from benzylcupreine **Q-0** (1.01 g, 2.51 mmol), N-phenyl-bis(trifluoromethanesulfonimide) (0.999 g, 2.79 mmol) and 4-dimethylaminopyridine (31 mg, 0.25 mmol). The triflate (**Q-1**) was obtained in 1.13 gram (2.13 mmol, 85%) yield as a colorless sticky oil. [α]$^{25}_D$ = -25.6 (c 1.00, CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.98 (d, J = 4.0 Hz, 1H), 8.27 (d, J = 9.6 Hz, 1H), 8.24 (b, 1H,), 7.64 (dd, J = 9.6, 2.6 Hz, 1H), 7.56 (d, J = 4.0 Hz, 1H), 7.40-7.28 (m, 5H), 5.80 (ddd, J = 17.6, 10.4, 7.6 Hz, 1H), 5.08 (b, 1H), 5.02-4.94 (m, 2H), 4.47 (2d, J = 11.6 Hz, 1H), 4.39 (d, J = 11.6 Hz, 1H), 3.20 (m, 2H), 3.01 (dd, J = 10.4, 14.0 Hz, 1H), 2.65 (m, 1H), 2.57 (m, 1H), 2.27 (m, 1H), 1.84 (m, 2H), 1.67 (m, 2H), 1.58-1.50 (m, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 151.13, 147.35, 147.08, 146.91, 141.56, 137.14, 133.04, 128.33, 127.81, 127.65, 126.61, 122.60, 120.64, 118.64 (q, J = 321 Hz), 116.16, 114.24, 81.45, 71.39, 60.77, 56.42, 42.46, 39.65, 27.61, 27.59, 20.29 ppm; FTIR ($CHCl_3$): 3035, 2947, 2869, 1596, 1509, 1455, 1425, 1249, 1225, 1208, 1141, 931, 845 cm^{-1}; HRMS (ES, M + H$^+$) calculated for [$C_{27}H_{27}F_3N_2O_4S$ + H]$^+$: 533.1722, found 532.1715.

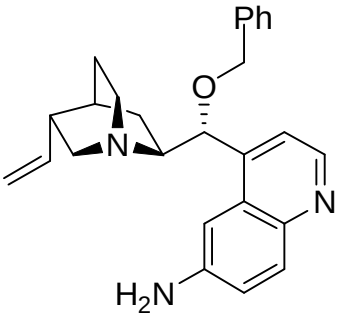
6'-Amino-9-*O*-benzylcinchonine (QD-2):



This compound was prepared from triflate (**QD-1**) following the procedure for the Buchwald amination described by Corey and Zhang[4]: to a warm (66°C) solution of triflate **QD-1** (6.51 g, 12.23 mmol) in 55 mL THF were added palladium acetate (0.163 g, 0.76 mmol), BINAP (0.688 g, 1.1 mmol), cesiumcarbonate (5.612 g, 17.2 mmol) and benzophenone imine (2.13 mL, 12.6 mmol). The mixture was stirred for 24 hrs, after which the product mixture was filtered through a Celite pad using dichloromethane as the eluens. Volatiles were removed *in vacuo* to yield crude imine that was hydrolyzed without further

purification: the residue was dissolved in 20 ml THF and 40 ml of a solution of 10% citric acid in water. The mixture was stirred for another 24 hours. Ethyl acetate (150 mL) and a saturated solution of sodium carbonate in water (100 mL) were then added, the water layer was separated and extracted one more time with 50 mL EtOAc. The combined organic layers were extracted with 1 M HCl (2 times with 100 mL). The combined water layers were washed with dichloromethane (3 times, 75 mL). Ethyl acetate (75 mL) was added and the water layer was neutralized with saturated Na_2CO_3 in water. The organic layer was separated and the water layer was extracted two more times with ethyl acetate (75 mL). The combined organic layers were dried over magnesium sulfate and concentrated in vacuo, yielding pure amine (4.47 gram, 91%) as a yellow foam. $[\alpha]^{25}_D$ = +140.1 (c 1.00, CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.66 (d, J = 4.4 Hz, 1H), 7.97 (d, J = 9.2 Hz, 1H), 7.42 (d, J = 4.4 Hz, 1H), 7.39-7.33 (m, 5H), 7.29-7.16 (m, 2H), 6.01 (ddd, J = 17.6, 10.4, 8.0 Hz, 1H), 5.29 (b, 1H), 5.03 (m, 2H), 4.49 (d, J = 11.5 Hz, 1H), 4.41 (d, J = 11.5 Hz, 1H), 4.07 (b, 2H), 3.36 (m, 1H), 3.05 (m, 1H), 2.94 (dd, J = 13.2, 9.5 Hz, 1H), 2.74 (m, 2H), 2.25 (m, 1H), 1.96 (dd, J = 13.2, 9.5 Hz, 1H), 1.80 (m, 1H), 1.57-1.51 (m, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 146.37, 144.99, 143.63, 143.11, 140.63, 137.86, 131.62, 128.38, 128.03, 127.85, 127.75, 121.11, 118.75, 114.49, 103.07, 80.55, 71.30, 59.60, 50.05, 49.53, 40.14, 28.22, 26.44, 21.01 ppm; FTIR ($CHCl_3$) : 3400, 3069, 2944, 2876, 1631, 1516, 1455, 1358, 1274, 1213, 1116, 1051, 916, 828 cm^{-1}; HRMS (ES, M + H^+) calculated for $[C_{26}H_{30}N_3O]^+$: 400.2389, found 400.2388.

6'-Amino-9-*O*-benzylcinchonidine (Q-2):



Following the same protocol the amine has been prepared from triflate **Q-1** (1.08, 2.04 mmol), $Pd(OAc)_2$ (24 mg, 0.11 mmol), BINAP (110 mg, 0.18 mmol), Cs_2CO_3 (2.69 mmol), and benzophenone imine (0.40 mL, 2.38 mmol) The pure product was obtained in 0.63 gram (1.58 mmol, 78%) yield as a yellow foam. $[\alpha]^{25}_D$ = -73.6 (c 0.95, CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.67 (d, J = 4.4 Hz, 1H), 7.97 (d, J = 9.6 Hz, 1H), 7.44 (d, J = 4.4 Hz, 1H), 7.39-7.32 (m, 5H), 7.19-7.15 (m, 2H), 5.75 (ddd, J = 17.6, 10.4, 8.0 Hz, 1H), 5.25 (b, 1H), 4.97 (d, J = 17.6 Hz, 1H), 4.93 (d, J = 10.4 Hz, 1H), 4.48 (d, J = 11.6 Hz, 1H), 4.41 (d, J = 11.6 Hz, 1H), 4.07 (b, 2H, NH_2), 3.49 (m, 1H, H-?), 3.19-3.10 (m, 2H), 2.73-2.65 (m, 2H), 2.30 (m, 1H), 1.93 (m, 1H), 1.83-1.75 (m, 2H), 1.53 (m, 2H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 146.23, 144.90, 143.44, 142.90, 141.44, 137.77, 131.48, 128.30, 128.23, 127.62, 127.58, 127.48, 120.96, 118.27, 114.30, 102.78, 80.21, 71.00, 59.82, 56.84, 43.19, 39.74, 27.79, 27.31, 20.90 ppm; FTIR ($CHCl_3$): 3400, 3068, 2944, 2876, 1631, 1516, 1454, 1358, 1274, 1213, 1116,

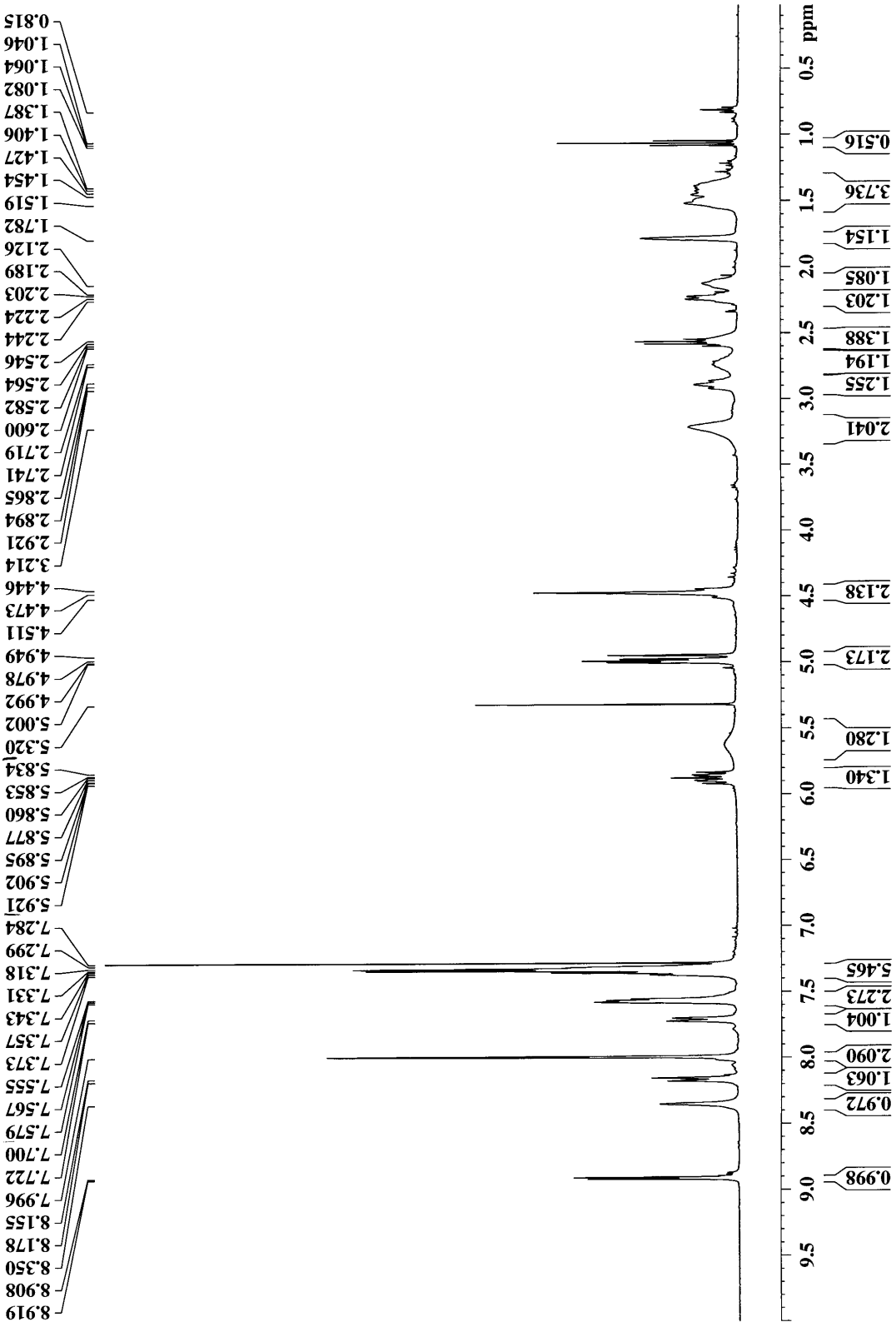
1051, 918, 856, 826 cm^{-1}; HRMS (ES, M + H^+) calculated for $[C_{26}H_{29}N_3O]^+$: 400.2389, found 400.2388.

***N*-[3,5-bis(trifluoromethyl)phenyl]-*N'*-(9-*O*-benzylcinchon-6'-yl) thiourea (3)**: To a solution of amine **QD-2** (3.01 gram, 7.51 mmol) in THF (80 mL) was added 3,5-bis-trifluoromethylphenyl isothiocyanate (1.50 mL, 8.21 mmol) and the mixture was stirred for 2 hours at room temperature. The THF was removed under reduced pressure and the crude product was purified over silica gel using EtOAC / MeOH /Et_3N (94.5 : 5 : 0.5) as the eluens. This yielded 4.06 grams (81 %) of an off-white foam. $[\alpha]^{25}_D$ = +81.1 (c 0.99, CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.91 (d, J = 4.4 Hz, 1H), 8.35 (bs, 1H), 8.17 (d, J = 9.2 Hz, 1H), 8.00 (s, 2H), 7.71 (bd, J = J = 9.2 Hz, 1H), 7.57 (m, 2H), 7.38-7.29 (m, 5H), 5.88 (ddd, J = 17.2, 10.4, 7.6 Hz, 1H), 5.63 (b, 1H), 4.99 (d, J = 10.4 Hz, 1H), 4.97 (d, J = 17.2 Hz, 1H), 4.47 (m, 2H), 3.21 (b, 2H), 2.89 (m, 1H), 2.73 (m, 1H), 2.56 (m, 1H), 2.21 (m, 2H), 2.13 (m, 1H), 1.78 (m, 1H), 1.60-1.35 (m, 3H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ 179.90, 150.43, 146.89, 145.99, 140.19, 139.41, 137.20, 135.45, 132.18, 131.61 (q J = 33.4 Hz), 128.58, 128.50, 128.03, 126.79, 126.69, 123.98, 123.25 (q, J = 275 Hz), 118.64, 115.21, 114.54, 119.32, 71.58, 60.95, 49.91, 49.16, 39.45, 27.69, 25.89, 21.86 ppm;[5] FTIR ($CHCl_3$): 3088, 2955, 2874, 1552, 1508, 1471, 1384, 1324, 1279, 1213, 1181, 1140, 887 cm^{-1}; HRMS (ES, M + H^+) calculated for $[C_{35}H_{33}F_6N_4OS]^+$: 671.2279, found 671.2280.

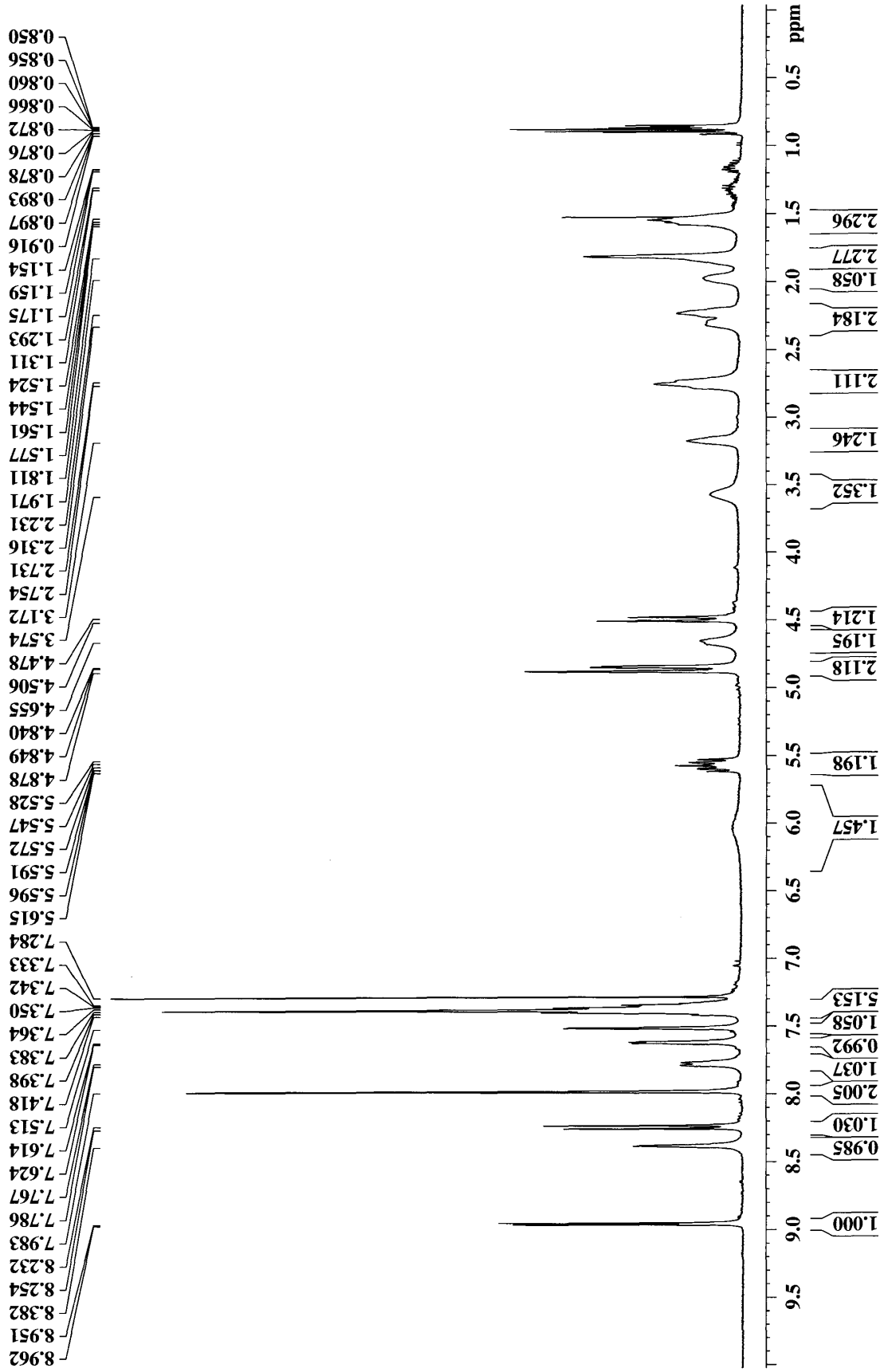
***N*-[3,5-bis(trifluoromethyl)phenyl]-*N'*-(9-*O*-benzylcinchonid-6'-yl) thiourea (6)**: The same procedure was applied starting from **Q-2** (0.61 g, 1.53 mmol), 3,5-bis-trifluoromethylphenyl isothiocyanate (0.41 mL, 2.25 mmol) and THF (30 mL). After the reaction THF was removed under reduced pressure, the crude product was redissolved in dichloromethane (10 mL) and precipitated by addition of 50 mL of petroleum ether (boiling range 40-65°C). Yield: 0.59 gram (0.87 mmol, 57%). $[\alpha]^{25}_D$ = -146.9 (c 1.00, CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.97 (d, J = 4.4 Hz, 1H), 8.38 (bs, 1H), 8.26 (d, J = 8.8 Hz, 1H), 7.97 (s, 2H), 7.73 (bd, J = 8.8 Hz, 1H), 7.61 (m, 1H), 7.54 (bs, 1 H), 7.41-7.30 (m, 5H), 5.95 (b, 1H), 5.60 (m, 1H), 4.87 (m, 2H), 4.64 (b, 1H), 4.48 (d, J = 11.2 Hz, 1H), 3.53 (b, 1H), 3.19 (b, 1H), 2.76 (m, 2H), 2.31 (b, 1H), 2.23 (b, 1H),

1.93 (b, 1H), 1.81 (b, 2H), 1.68-1.50 (m, 2H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ 180.18, 151.83, 150.990, 147.31, 140.65, 139.65, 137.41, 135.06, 132.65, 131.42 (q, J = 33.5 Hz), 128.37, 128.37, 127.75, 127.45, 126.78, 126.72, 124.08, 124.03, 122.97 (q, J = 274 Hz), 118.55 (2 carbons), 114.80, 71.18, 61.50, 56.73, 42.90, 39.32, 27.38, 26.80 ppm; FTIR ($CHCl_3$) : 3084, 2948, 2874, 1549, 1508, 1471, 1384, 1324, 1279, 1213, 1181, 1140, 887 cm^{-1}; HRMS (ES, M + H^+) calculated for $[C_{35}H_{33}F_6N_4OS]^+$: 671.2279, found 671.2280.

^{1}H-NMR Spectrum of **3** (400 MhZ, $CDCl_3$)



^{1}H-NMR Spectrum of **6** (400 MhZ, $CDCl_3$)



Preparation of the racemates

Racemic nitroalcohols were prepared according to Simoni *et al.*:[6] 0,1 mmol aldehyde was dissolved in 1.0 mL $MeNO_2$ and the resulting solution was cooled to 0 °C. One drop of tetramethylguanidine was added and stirring was continued for 15-60 minutes. Three drops from the reaction mixture were passed through a short pad of silica gel (pasteur pipette) and eluted with EtOAc. Volatiles were removed in vacuo and the residue was dissolved in 2 mL of heptane/isopropanol 90:10, filtered and analyzed by HPLC.

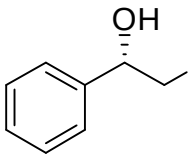
Stereochemical Assignments

The absolute configurations for compound **5a**, **5b**, **5d**, **5e** and **5f** were assigned by comparison of their optical rotation with literature values. The absolute configurations for compounds **5c**, **5g**, and **5h** were assigned by analogy.

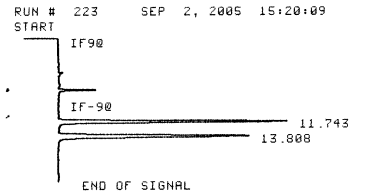
General procedure for the enantioselective nitroaldol reaction

A screw cap vial was loaded with catalyst **3** (67 mg, 0.1 mmol), THF (1 mL) and the aldehyde (1.0 mmol). The resulting solution was cooled to –20 °C (freezer), then $MeNO_2$ (536 µL, 10.0 mmol) was added. The solution was kept at –20 °C for the indicated time, then absorbed on a chromatography column packed with silica gel and eluted with the indicated PE/EtOAc mixture. All enantiomeric excesses were determined using a Chiralcel OD-H column, unless otherwise stated.

(*S*)-2-Nitro-1-phenyl-ethanol (5a):

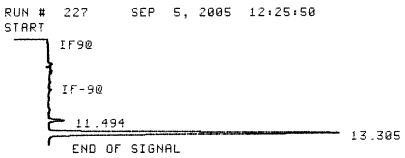


48 hours; PE/EtOAc 9:1; 90% yield. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.28-7.42 (m, 5H, Ar**H**), 5.43 (dd, *J* = 9.5, 3.1 Hz, 1H, C**H**OH), 4.62 (dd, *J* = 13.1, 9.5 Hz, 1H, C**H**$_2$CHOH), 4.50 (dd, *J* = 13.1, 3.1 Hz, 1H, C**H**$_2$CHOH), 3.08 (bs, 1H, CHO**H**). HPLC: *n*-heptane/isopropanol 85:15, 0.8 mL/min, 215 nm; major enantiomer t_R=11.49 min, minor enantiomer t_R=13.39 min; 92% ee. $[\alpha]^{25}_D$ = +40.8 (c 1.02, CH_2Cl_2), lit:[7] $[\alpha]^{25}_D$ = -39.0, **(*R*)-5a** (c 1.00, CH_2Cl_2, 92% *ee*).




```
Closing signal file M:SIGNAL   .BNA

RUN#   223          SEP  2, 2005  15:20:09

SIGNAL FILE: M:SIGNAL.BNA
AREA%
      RT      AREA TYPE  WIDTH      AREA%
  11.743  69813632   PB   .327   49.62768
  13.808  70861120   PU   .400   50.37232
```

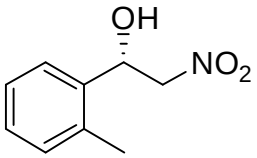
Racemic



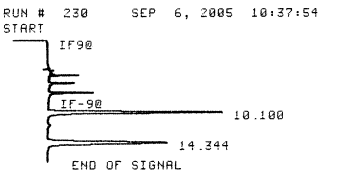

```
Closing signal file M:SIGNAL   .BNA

RUN#   227          SEP  5, 2005  12:25:50

SIGNAL FILE: M:SIGNAL.BNA
AREA%
      RT      AREA TYPE  WIDTH      AREA%
  11.494   2271886   BP   .301    4.23916
  13.305  51320896   PB   .378   95.76083
```

(S)-isomer

(*S*)-2-Nitro-1-*o*-tolyl-ethanol (5b):



96 hours; PE/EtOAc 9:1; 97% yield. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.51 (m, 1H, Ar**H**), 7.27-7.30 (m, 2H, Ar**H**), 7.20-7.22 (m, 1H, Ar**H**), 5.67 (dd, *J* = 9.6, 2.7 Hz, 1H, C**H**OH), 4.54 (dd, *J* = 13.3, 9.6 Hz, 1H, C**H**$_2$CHOH), 4.44 (dd, *J* = 13.3, 2.7 Hz, 1H, C**H**$_2$CHOH), 3.02 (bs, 1H, CHO**H**), 2.40 (s, 3H, C**H**$_3$). HPLC: *n*-heptane/isopropanol 85:15, 0.8 mL/min, 215 nm; minor enantiomer t_R=9.81 min, major enantiomer t_R=13.49 min; 91% ee. $[\alpha]^{25}_D$ = +44.7 (c 1.71, CH_2Cl_2), lit:[8] $[\alpha]^{21}_D$ = -50.1, **(*R*)-5b** (c 1.01, CH_2Cl_2, 93% *ee*).



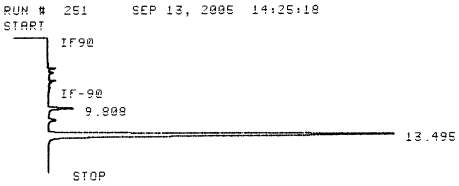
RUN # 230 SEP 6, 2005 10:37:54

Closing signal file M:SIGNAL .BNA

RUN# 230 SEP 6, 2005 10:37:54

SIGNAL FILE: M:SIGNAL.BNA
AREA%

RT	AREA	TYPE	WIDTH	AREA%
10.100	11750496	BB	.292	50.39746
14.344	11565152	BB	.420	49.60254



RUN # 251 SEP 13, 2005 14:25:18

Closing signal file M:SIGNAL .BNA

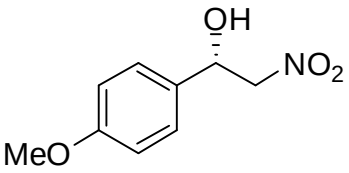
RUN# 251 SEP 13, 2005 14:25:18

SIGNAL FILE: M:SIGNAL.BNA
AREA%

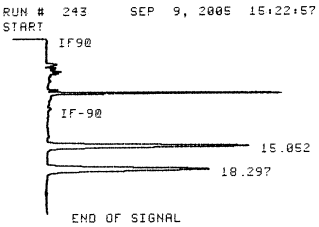
RT	AREA	TYPE	WIDTH	AREA%
9.909	6167427	PB	.269	4.27396
13.495	139135120	PB	.434	95.72605

Racemic ***(S)-isomer***

(*S*)-1-(4-Methoxy-phenyl)-2-nitro-ethanol (5c):



168 hours; PE/EtOAc 9:1; 94% yield. ^{1}H-NMR (400 MHz, $CDCl_3$):[9] δ 7.34 (d, *J* = 8.8 Hz, 2H, Ar**H**), 6.94 (d, *J* = 8.8 Hz, 2H, Ar**H**), 5.41-5.44 (m, 1H, C**H**OH), 4.62 (dd, *J* = 13.1, 9.6 Hz, 1H, C**H**$_2$CHOH), 4.49 (dd, *J* = 13.1, 3.0 Hz, 1H, C**H**$_2$CHOH), 3.84 (s, 3H, C**H**$_3$O), ~2.3-3.0 (bs, 1H, CHO**H**). HPLC: *n*-heptane/isopropanol 85:15, 0.8 mL/min, 215 nm; minor enantiomer t_R=15.05 min, major enantiomer t_R=18.30 min; 89% ee. $[\alpha]^{25}_D$ = +61.4 (c 1.04, CH_2Cl_2).



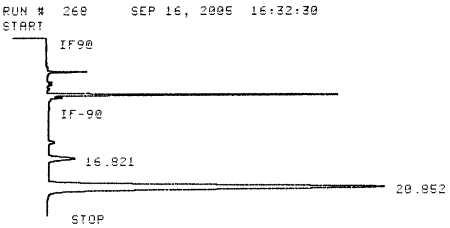
RUN # 243 SEP 9, 2005 15:22:57

Closing signal file M:SIGNAL .BNA

RUN# 243 SEP 9, 2005 15:22:57

SIGNAL FILE: M:SIGNAL.BNA
AREA%

RT	AREA	TYPE	WIDTH	AREA%
15.052	21354480	BB	.456	50.10989
18.297	21260816	BP	.565	49.89011



RUN # 268 SEP 16, 2005 16:32:30

Closing signal file M:SIGNAL .BNA

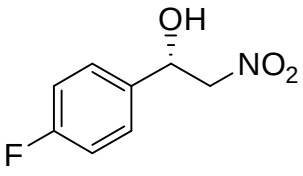
RUN# 268 SEP 16, 2005 16:32:30

SIGNAL FILE: M:SIGNAL.BNA
AREA%

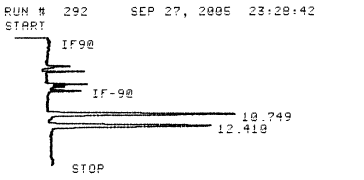
RT	AREA	TYPE	WIDTH	AREA%
16.821	6616996	BB	.527	5.70396
20.952	109390520	BB	.705	94.29613

Racemic ***(S)-isomer***

(*S*)-1-(4-Fluoro-phenyl)-2-nitro-ethanol (5d):



24 hours; PE/EtOAc 9:1; 99% yield. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.39-7.43 (m, 2H, Ar**H**), 7.09-7.15 (m, 2H, Ar**H**), 5.49 (dd, *J* = 9.6, 3.1 Hz, 1H, C**H**OH), 4.62 (dd, *J* = 13.3, 9.6 Hz, 1H, C**H**$_2$CHOH), 4.51 (dd, *J* = 13.3, 3.1 Hz, 1H, C**H**$_2$CHOH), 2.91 (bs, 1H, CHO**H**). HPLC: *n*-heptane/isopropanol 85:15, 0.8 mL/min, 215 nm; minor enantiomer t_R=10.75 min, major enantiomer t_R=12.41 min; 85% ee. $[\alpha]^{25}_D$ = +35.4 (c 1.38, CH_2Cl_2), lit:[10] $[\alpha]^{25}_D$ = -44.8, **(R)-5x** (c 1.05, CH_2Cl_2, 92% *ee*).



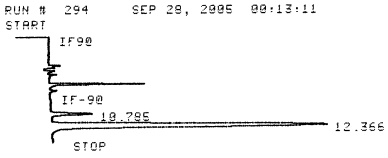
Closing signal file M:SIGNAL .BNA

RUN# 292 SEP 27, 2005 23:20:42

SIGNAL FILE: M:SIGNAL.BNA
AREA%

RT	AREA	TYPE	WIDTH	AREA%
10.749	14215384	BB	.320	49.57786
12.410	14457472	BB	.384	50.42214

Racemic



Closing signal file M:SIGNAL .BNA

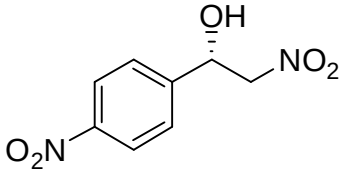
RUN# 294 SEP 28, 2005 00:13:11

SIGNAL FILE: M:SIGNAL.BNA
AREA%

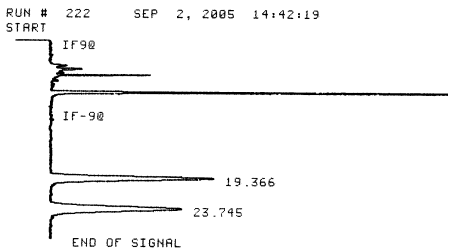
RT	AREA	TYPE	WIDTH	AREA%
10.795	5979659	BB	.313	7.71734
12.366	70307969	BB	.551	92.28266

(S)-isomer

(*S*)-2-Nitro-1-(4-nitro-phenyl)-ethanol (5e):



4 hours; PE/EtOAc 85:15; 91% yield. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.28 (d, *J* = 8.8 Hz, 2H, Ar**H**), 7.65 (d, *J* = 8.8 Hz, 2H, Ar**H**), 5.61-5.64 (m, 1H, C**H**OH), 4.56-4.66 (m, 2H, C**H**$_2$CHOH), 3.23 (bs, 1H, CHO**H**). HPLC: *n*-heptane/isopropanol 85:15, 0.8 mL/min, 215 nm; minor enantiomer t_R=19.37 min, major enantiomer t_R=23.74 min; 86% ee. $[\alpha]^{25}_D$ = +29.4 (c 1.02, CH_2Cl_2), lit:[8] $[\alpha]^{21}_D$ = -31.6, **(*R*)-5b** (c 1.05, CH_2Cl_2, 78% *ee*).



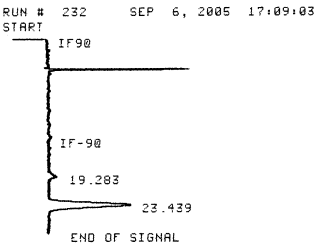
Closing signal file M:SIGNAL .BNA

RUN# 222 SEP 2, 2005 14:42:19

SIGNAL FILE: M:SIGNAL.BNA
AREA%

RT	AREA	TYPE	WIDTH	AREA%
19.366	24631760	BP	.655	49.66670
23.745	24962352	PV	.823	50.33328

Racemic



Closing signal file M:SIGNAL .BNA

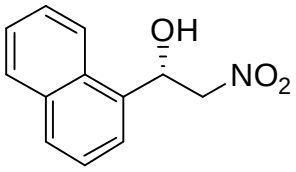
RUN# 232 SEP 6, 2005 17:09:03

SIGNAL FILE: M:SIGNAL.BNA
AREA%

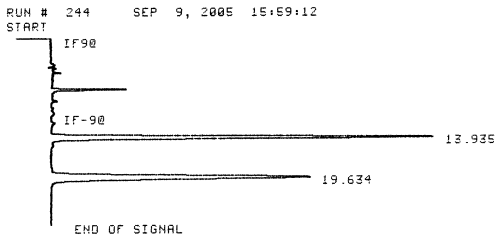
RT	AREA	TYPE	WIDTH	AREA%
19.283	575144	PV	.574	7.05672
23.439	7575152	PV	.793	92.94326

(S)-isomer

(*S*)-1-Naphtalen-1-yl-2-nitro-ethanol (5f):



48 hours; PE/EtOAc 85:15; 99% yield. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.03 (d, *J* = 8.8 Hz, 1H, Ar**H**), 7.89 (d, *J* = 8.8 Hz, 1H, Ar**H**), 7.83 (d, *J* = 8.3 Hz, 1H, Ar**H**), 7.74 (d, *J* = 7.2 Hz, 1H, Ar**H**), 7.47-7.59 (m, 3H, Ar**H**), 6.19-6.22 (m, 1H, C**H**OH), 4.62 (m, 2H, C**H**$_2$CHOH), ~3.2-3.7 (bs, CHO**H**, 1H). HPLC: *n*-heptane/isopropanol 85:15, 0.8 mL/min, 215 nm; minor enantiomer t_R=14.49 min, minor enantiomer t_R=19.74 min; 92% ee. $[\alpha]^{25}_D$ = +17.2 (c 1.02, CH_2Cl_2), lit:[10] $[\alpha]^{25}_D$ = +17.7, **(S)-5d** (c 2.41, CH_2Cl_2, 93% *ee*).



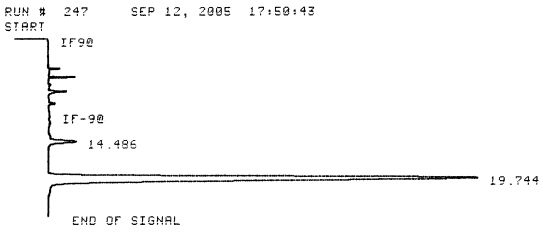
Closing signal file M:SIGNAL .BNA

RUN# 244 SEP 9, 2005 15:59:12

SIGNAL FILE: M:SIGNAL.BNA
AREA%

RT	AREA	TYPE	WIDTH	AREA%
13.935	38055392	PB	.427	49.92472
19.634	38170176	BB	.631	50.07528

Racemic



Closing signal file M:SIGNAL .BNA

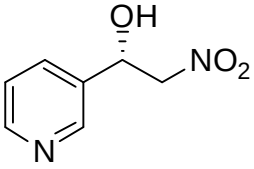
RUN# 247 SEP 12, 2005 17:50:43

SIGNAL FILE: M:SIGNAL.BNA
AREA%

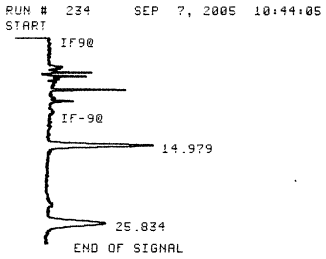
RT	AREA	TYPE	WIDTH	AREA%
14.496	11447688	VP	.448	3.98506
19.744	275817120	BB	.688	96.01494

(S)-isomer

(*S*)-2-Nitro-1-pyridin-3-yl-ethanol (5g):



24 hours; PE/EtOAc 1:1; 91% yield. ^{1}H-NMR (400 MHz, $CDCl_3$):[11] δ 8.55 (s, 1H, Ar**H**), 8.49 (d, *J* = 4.5 Hz, 1H, Ar**H**), 7.83 (m, 1H, Ar**H**), 7.37 (dd, *J* = 7.9, 4.9 Hz, 1H, Ar**H**), 5.54 (dd, *J* = 9.5, 3.1 Hz, 1H, C**H**OH), 4.64 (dd, *J* = 13.1, 9.5 Hz, 1H, C**H**$_2$CHOH), 4.55 (dd, *J* = 13.1, 3.3 Hz, 1H, C**H**$_2$CHOH), ~4.2-5.1 (bs, 1H, CHO**H**). HPLC: *n*-heptane/isopropanol 75:25, 0.7 mL/min, 215 nm; minor enantiomer t_R=15.36 min, major enantiomer t_R=27.71 min; 86% ee. $[\alpha]^{25}_D$ = +37.6 (c 1.04, CH_2Cl_2).



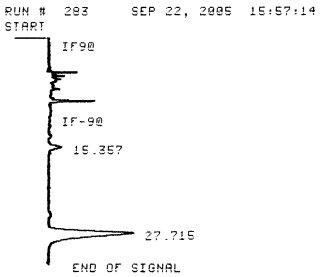
Closing signal file M:SIGNAL .BNA

RUN# 234 SEP 7, 2005 10:44:05

SIGNAL FILE: M:SIGNAL.BNA
AREA%

RT	AREA	TYPE	WIDTH	AREA%
14.979	6144400	BP	.510	49.48662
25.834	6271885	PP	.929	50.51336

Racemic



Closing signal file M:SIGNAL .BNA

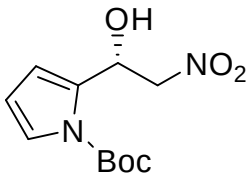
RUN# 283 SEP 22, 2005 15:57:14

SIGNAL FILE: M:SIGNAL.BNA
AREA%

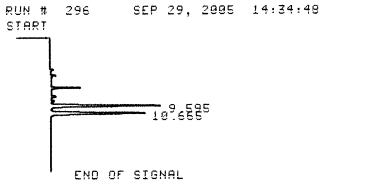
RT	AREA	TYPE	WIDTH	AREA%
15.357	694379	BV	.463	6.59303
27.715	9837639	BV	1.000	93.40698

(S)-isomer

***(S)*-2-(1-Hydroxy-2-nitro-ethyl)-pyrrole-1-carboxylic acid *tert*-butyl ester (5h)**: 24 hours; PE/EtOAc 9:1; 95% yield.



^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.24 (dd, *J* = 3.4, 1.8 Hz, 1H, Ar**H**), 6.27 (m, 1H, Ar**H**), 6.16 (t, *J* = 3.4 Hz, 1H, Ar**H**), 5.72-5.74 (m, 1H, C**H**OH), 4.85 (dd, *J* = 12.4, 8.9 Hz, 1H, C**H**$_2$CHOH), 4.77 (dd, *J* = 12.4, 4.5 Hz, 1H, C**H**$_2$CHOH), 4.24 (bd, *J* = 6.2, 1H, CHO**H**), 1.64 (s, 9H, (C**H**$_3$)$_3$C). HPLC: *n*-heptane/isopropanol 90:10, 0.7 mL/min, 254 nm; minor enantiomer t_R=9.61 min, major enantiomer t_R=10.63 min; 91% ee. $[\alpha]^{25}_D$ = +5.1 (c 1.09, CH_2Cl_2), lit:[10] $[\alpha]^{25}_D$ = +5.9, **(S)-5d** (c 1.26, CH_2Cl_2, 92% *ee*).



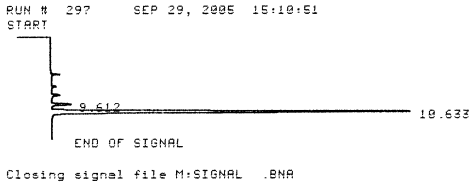
Closing signal file M:SIGNAL .BNA

RUN# 296 SEP 29, 2005 14:34:48

SIGNAL FILE: M:SIGNAL.BNA
AREA%

RT	AREA	TYPE	WIDTH	AREA%
9.595	6523927	BB	.259	50.04239
10.665	6512778	BB	.297	49.95762

Racemic



Closing signal file M:SIGNAL .BNA

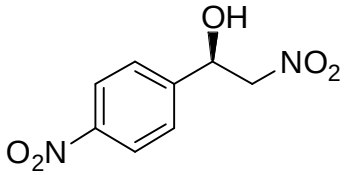
RUN# 297 SEP 29, 2005 15:10:51

SIGNAL FILE: M:SIGNAL.BNA
AREA%

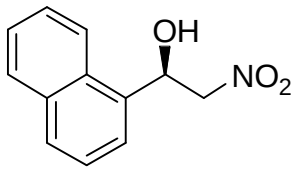
RT	AREA	TYPE	WIDTH	AREA%
9.612	4642797	BB	.249	4.40428
10.633	100772000	BB	.302	95.59574

***(S)*-isomer**

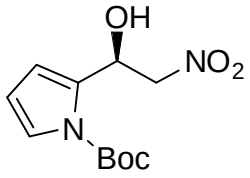
Employment of catalyst **6** using exactly the same procedure afforded nitroalcohols with the opposite absolute configuration:



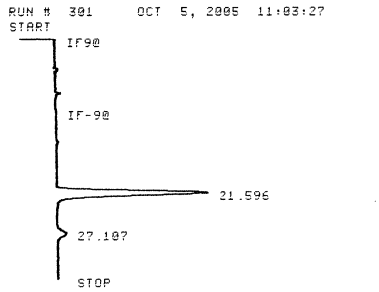
ent-**5e**: 87% yield, 93% *ee*; $[\alpha]^{25}_D$ = -32.2 (c 1.01, CH_2Cl_2).



ent-**5f**: 97% yield, 92% *ee*; $[\alpha]^{25}_D$ = -22.8 (c 1.14, CH_2Cl_2).



ent-**5h**: 97% yield, 87% *ee*; $[\alpha]^{25}_D$ = -5.0 (c 1.00, CH_2Cl_2).

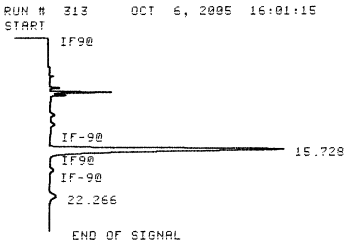


Closing signal file M:SIGNAL .BNA

RUN# 301 OCT 5, 2005 11:03:27

SIGNAL FILE: M:SIGNAL.BNA
AREA%

RT	AREA	TYPE	WIDTH	AREA%
21.596	114919240	PV	.826	96.53853
27.107	4116926	BV	.521	3.46146

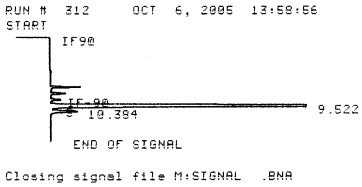


Closing signal file M:SIGNAL .BNA

RUN# 313 OCT 6, 2005 16:01:15

SIGNAL FILE: M:SIGNAL.BNA
AREA%

RT	AREA	TYPE	WIDTH	AREA%
15.729	625982561	BH	.575	96.10832
22.266	2534384	PB	.770	3.89171



Closing signal file M:SIGNAL .BNA

RUN# 312 OCT 6, 2005 13:59:56

SIGNAL FILE: M:SIGNAL.BNA
AREA%

RT	AREA	TYPE	WIDTH	AREA%
9.522	1075015201	SBB	.396	93.55046
10.384	129267041	BB	.267	6.44954

References

[1] H. Li, Y. Wang, L. Tang, L. Deng, *J. Am. Chem. Soc.* **2004**, 9906-9907.
[2] X. Liu, H. Li, L. Deng, *Org. Lett.* **2005**, 167-170.
[3] L. F. Tietze, G. Kettschau, K. Heitmann, *Synthesis* **1996**, 851-857.
[4] E. J. Corey, J. Zhang, *Org. Lett.* **2001**, *20*, 3211-3214.
[5] C-9 could not be detected.
[6] D. Simoni, F. P. Invidiata, S. Manfredini, R. Ferroni, I. Lampronti, M. Roberti, G. P. Pollini, *Tetrahedron Lett.* **1997**, *38*, 2749-2752.
[7] C. Palomo, M. Oiarbide, A. Laso, *Angew. Chem. Int. Ed.* **2005**, *44*, 3881-3884; *Angew. Chem.* **2005**, *117*, 3949-3952.
[8] D. A. Evans, D. Seidel, M. Rueping, H. W. Lam, J. T. Shawn, C. V. Downey, *J. Am. Chem. Soc.* **2003**, *125*, 12692-12693.
[9] P. B. Kisanga, J. G. Verkade, *J. Org. Chem.* **1999**, *64*, 4298-4303.
[10] B. M. Trost, V. S. C. Yeh, *Angew. Chem. Int. Ed.* **2002**, *41*, 861-863; *Angew. Chem.* **2002**, *11*, 889-891.
[11] G. J. T. Kuster, R. H. J. Steeghs, H. W. Scheeren, *Eur. J. Org. Chem.* **2001**, 553-560.