Asymmetric Deprotonation using *s*-BuLi or *i*-PrLi and Chiral Diamines in THF: the Diamine Matters

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Supporting Information Available: Full experimental procedures and data, $^{1}H/^{13}C$ NMR spectra of new compounds and full details of the ^{6}Li and ^{13}C NMR spectroscopic study.

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Investigation of the solution structure of *i*-PrLi complexed with (–)-sparteine and the (+)-sparteine surrogate using NMR spectroscopy

General methods for the NMR spectroscopy study

Glassware and syringes were dried at 50 °C in a vacuum oven before being transferred into a glove box (Braun equipped with a gas purification system that removes O_2 and moisture) containing a N_2 atmosphere. Typical moisture and O_2 content was less than 1.5 ppm. All manipulations concerning the addition reactions were carried out using gas-tight syringes. Et_2O-d_{10} and THF-d_8 were distilled under N_2 from sodium and benzophenone and were kept over 4 Å molecular sieves in septum-sealed flasks inside the glove box. (–)-Sparteine and the (+)-sparteine surrogate [(+)-(1*R*,2*S*,9*S*)-11-Methyl-7,11-Diazatricyclo[7.3.1.$0^{2,7}$]tridecane] were distilled from CaH_2.

All NMR spectra were recorded using a Varian Unity 500 spectrometer equipped with three channels using a 5 mm ^{1}H,^{13}C,^{6}Li triple resonance probe head, custom built by the Nalorac Company. The measurement frequencies were 500 MHz (^{1}H), 125 MHz (^{13}C) and 73 MHz (^{6}Li). The ^{13}C NMR spectra were referenced to the solvent Et_2O-d_{10} signal at δ 65.5 (^{13}C, –**C**D_2) and the THF-d_8 signal at δ 67.6 (^{13}C, –**C**D_2). The ^{6}Li NMR spectra were referenced to external 0.3 M [^{6}Li]Cl in MeOH-d_4 (δ = 0.0). A typical 90° ^{6}Li pulse on the instrument is 20 μs.

For the ^{6}Li,^{1}H-HOESY spectrum[1] the following parameters were used: spectral width of 2000 Hz (f_2= ^{6}Li) and 8000 Hz (f_1= ^{1}H); 96 increments and 32 scans per increment in t_1; mixing time= 1.0 s; relaxation delay 6 s; sine-bell weighting in f_1 and f_2 for the phase sensitive spectrum; 23 μs proton 90° decouple pulse.

Preparation of [^{6}Li]-*i*-PrLi

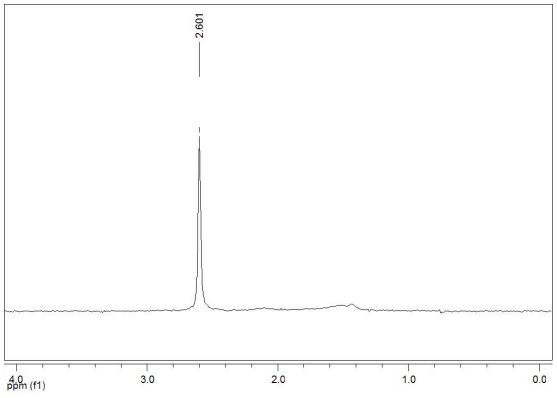
[^{6}Li]-*i*-PrLi was prepared as outlined below according to a published procedure.[2]

A block of ^{6}Li (250 mg, 36.6 mmol, 96% ^{6}Li) was cut into small pieces and placed in a 50 mL two-necked round-bottomed flask at rt under Ar. The ^{6}Li was rinsed with 2-propanol (10 mL) and the solvent was removed using a syringe. Then, hexane (10 mL) was added and the flask was placed in an ultrasonic bath for 5 min. The suspension of LiOH in hexane was removed using a syringe. Then, hexane (10 mL) was added and the flask was placed in an ultrasonic bath for 5 min. The suspension of LiOH in hexane was removed using a syringe. This procedure was repeated until the hexane remained clear and the previously black ^{6}Li pieces showed a metallic sheen. Then, 2-chloropropane (1.10 mL, 12.0 mmol) was added dropwise to a stirred suspension of the ^{6}Li pieces in TBME (7 μL, 0.05%) and pentane (5 mL) at rt under Ar. The resulting suspension was stirred and heated at reflux for 1.5 h. After being allowed to cool to rt, the suspension was centrifuged to remove any solids and the resulting solution was transferred *via* a syringe into a 25 mL round-bottomed flask under Ar. Assuming quantitative conversion of the 2-chloropropane, this produced 12.0 mmol of [^{6}Li]-*i*-PrLi in pentane (5 mL) i.e. a 2.4 M solution of [^{6}Li]-*i*-PrLi in pentane, which was stored at −30 °C under Ar.

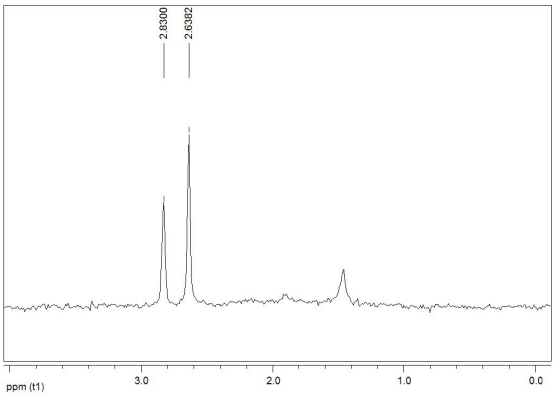
NMR spectra of *i*-PrLi/(–)-sparteine in Et_2O-d_{10}

20 μL of a 2.4 M solution of [^{6}Li]-*i*-PrLi in pentane (0.048 mmol) was added to an NMR tube containing 700 μL of Et_2O-d_{10} (i.e. ~0.07 M solution of [^{6}Li]-*i*-PrLi) through a rubber septum inside the glove box. The NMR tube was then transferred to the NMR instrument and cooled to –80 °C. A ^{6}Li NMR spectrum was recorded (Figure S1a). Then, 5 μL of (–)-sparteine (0.02 mmol, ~0.5 eq.) was added and a ^{6}Li NMR spectrum was recorded (Figure S1b). Then, a further 5 μL of (–)-sparteine (0.02 mmol, ~0.5 eq.) was added and a ^{6}Li NMR spectrum was recorded (Figure S1c). Then, a further 10 μL of (–)-sparteine (0.04 mmol, ~1.0 eq.) was added and a ^{6}Li NMR spectrum was recorded (Figure S1d). Then, a further 20 μL of (–)-sparteine (0.08 mmol, ~2.0 eq.) was added and a ^{6}Li NMR spectrum was recorded (Figure S1e).

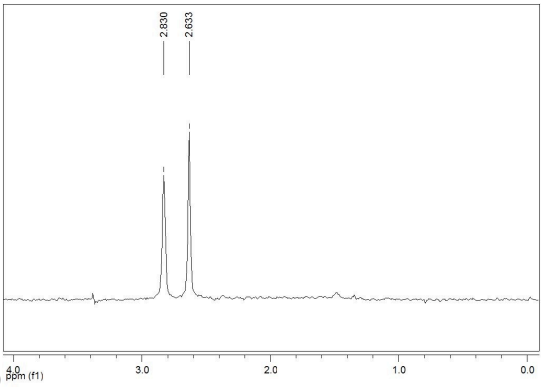
Figure S1. ^{6}Li NMR spectra of [^{6}Li]-*i*-PrLi/(–)-sparteine in Et_2O-d_{10}: (a) No (–)-sparteine; (b) 0.5 eq. (–)-sparteine; (c) 1.0 eq. (–)-sparteine; (d) 2.0 eq. (–)-sparteine; (e) 4.0 eq. (–)-sparteine.



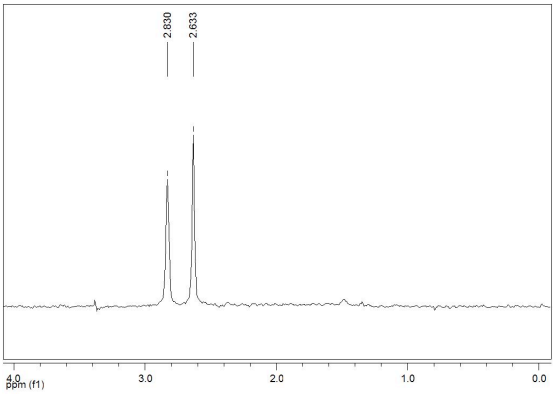
(a) No (–)-sparteine



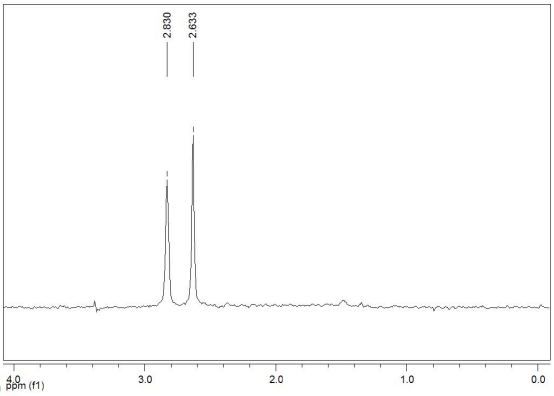
(b) 0.5 eq. (–)-sparteine



(c) 1.0 eq. (–)-sparteine

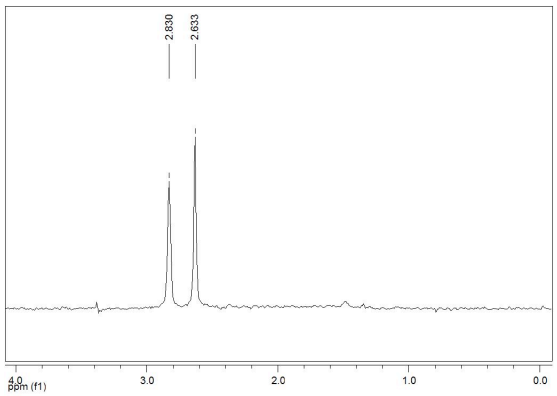


(d) 2.0 eq. (–)-sparteine



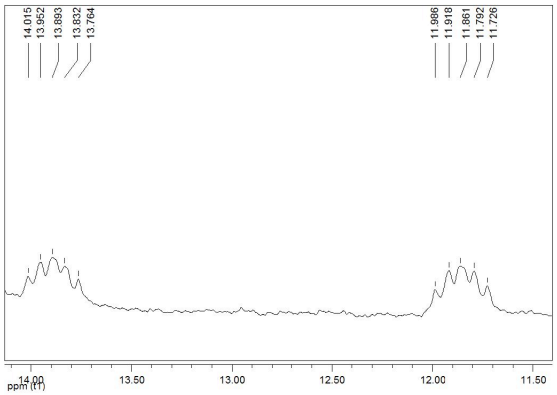
(e) 4.0 eq. (–)-sparteine

Figure S2. ^{6}Li NMR spectra of [^{6}Li]-*i*-PrLi and 2.0 eq. (–)-sparteine in Et_2O-d_{10}.



The ^{6}Li NMR spectrum shows two different lithium environments.

Figure S3. ^{13}C NMR spectra of [^{6}Li]-*i*-PrLi and 2.0 eq. (–)-sparteine in Et_2O-d_{10}.

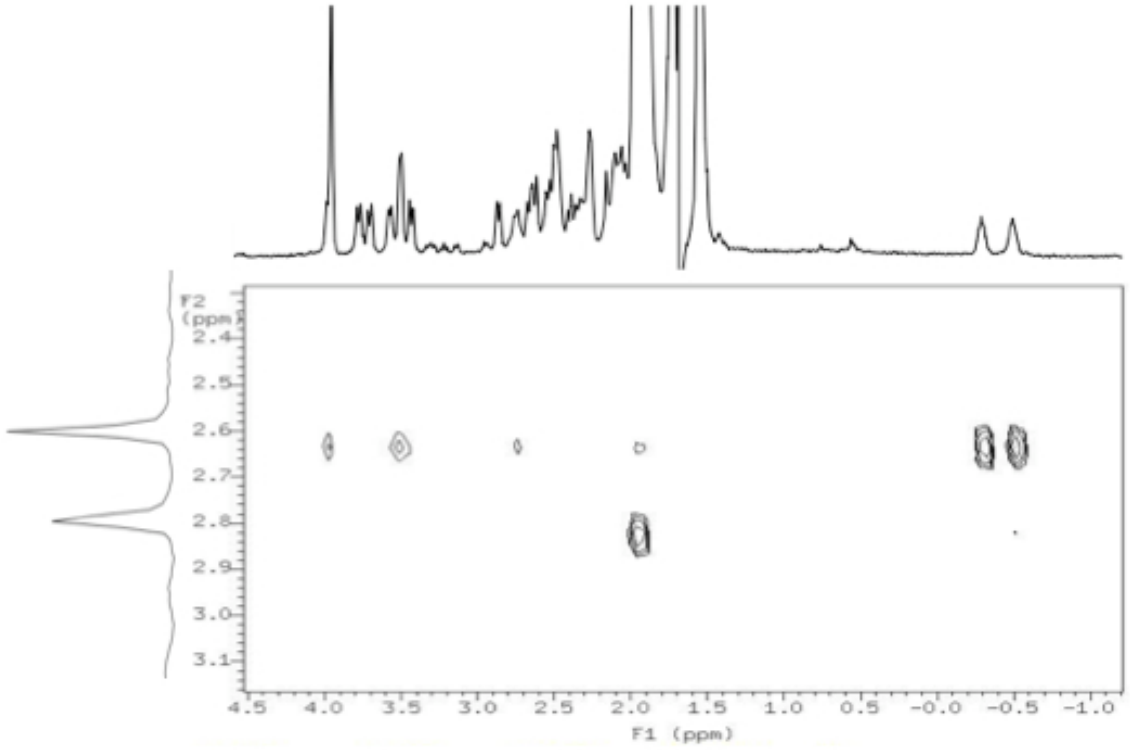


δ 13.89 ppm (^{1}J(^{6}Li,^{13}C) = 8.0 Hz)

δ 11.86 ppm (^{1}J(^{6}Li,^{13}C) = 8.5 Hz)

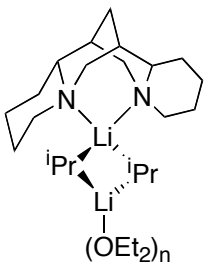
The ^{13}C NMR spectrum shows two different carbon environments for the CH carbons of the *i*-Pr groups. Both are quintets which indicates that each CH couples to two lithium atoms. The magnitudes of the ^{1}J(^{6}Li,^{13}C) coupling constants (8.0 and 8.5 Hz) suggest a dimeric aggregate based on the empirical Bauer-Winchester-Schleyer rule for coupling constants (J(^{6}Li,^{13}C) = (17 ± 2)/n_C where n_C is the number of ^{6}Li cations directly connected to the observed ^{13}C).[3] The ^{13}C NMR spectrum also shows signals due to uncomplexed (–)-sparteine and (–)-sparteine complexed to the *i*-PrLi.

Figure S4. ^{6}Li,^{1}H-HOESY of [^{6}Li]-*i*-PrLi and 2.0 eq. (–)-sparteine in Et_2O-d_{10} at –80 °C.[1]



The signal at δ 2.83 ppm does not show any NOE interactions with the (–)-sparteine resonances but does show a strong NOE interaction with the methyl group of the *i*-PrLi. In contrast, the signal at δ 2.63 ppm shows several NOE interactions with the (–)-sparteine resonances and a strong NOE to the CH protons of the *i*-PrLi.

Taking all of the NMR spectroscopic data together, heterodimer **3** (a 2:1 complex of *i*-PrLi and (–)-sparteine) was characterised for the solution structure of *i*-PrLi and 2.0 eq. (–)-sparteine (excess) in Et_2O at –80 °C. This is in agreement with the structure previously proposed by Beak and co-workers.[4]

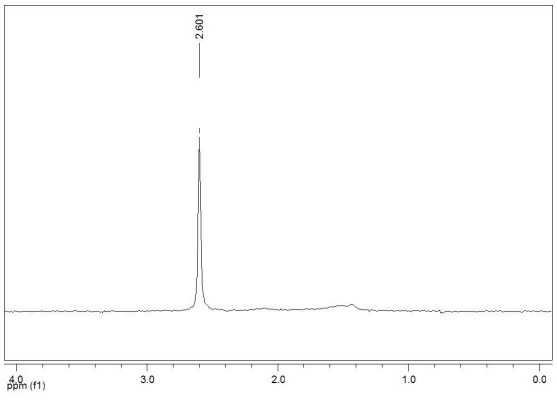


3

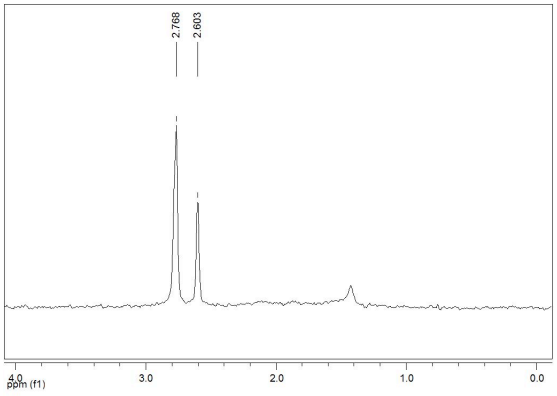
NMR spectra of *i*-PrLi/(+)-sparteine surrogate in Et_2O-d_{10}

20 μL of a 2.4 M solution of [^{6}Li]-*i*-PrLi in pentane (0.048 mmol) was added to an NMR tube containing 700 μL of Et_2O-d_{10} (i.e. ~0.07 M solution of [^{6}Li]-*i*-PrLi) through a rubber septum inside the glove box. The NMR tube was then transferred to the NMR instrument and cooled to –80 °C. A ^{6}Li NMR spectrum was recorded (Figure S5a). Then, 5 μL of (+)-sparteine surrogate (0.025 mmol, ~0.5 eq.) was added and a ^{6}Li NMR spectrum was recorded (Figure S5b). Then, a further 5 μL of (+)-sparteine surrogate (0.025 mmol, ~0.5 eq.) was added and a ^{6}Li NMR spectrum was recorded (Figure S5c). Then, a further 5 μL of (+)-sparteine surrogate (0.025 mmol, ~0.5 eq.) was added and a ^{6}Li NMR spectrum was recorded (Figure S5d). Then, a further 5 μL of (+)-sparteine surrogate (0.025 mmol, ~0.5 eq.) was added and a ^{6}Li NMR spectrum was recorded (Figure S5e).

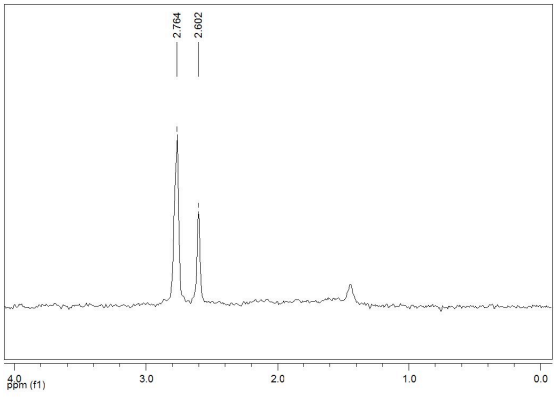
Figure S5. ^{6}Li NMR spectra of [^{6}Li]-*i*-PrLi/(+)-sparteine surrogate in Et_2O-d_{10}: (a) No (+)-sparteine surrogate; (b) 0.5 eq. (+)-sparteine surrogate; (c) 1.0 eq. (+)-sparteine surrogate; (d) 1.5 eq. (+)-sparteine surrogate; (e) 2.0 eq. (+)-sparteine surrogate.



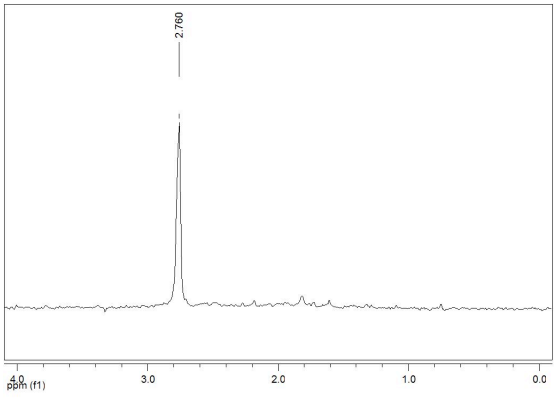
(a) No (+)-sparteine surrogate



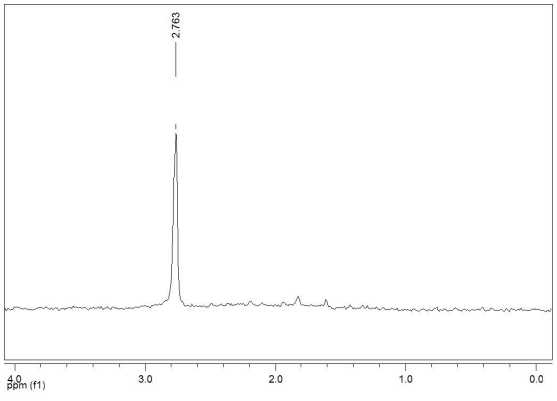
(b) 0.5 eq. (+)-sparteine surrogate



(c) 1.0 eq. (+)-sparteine surrogate

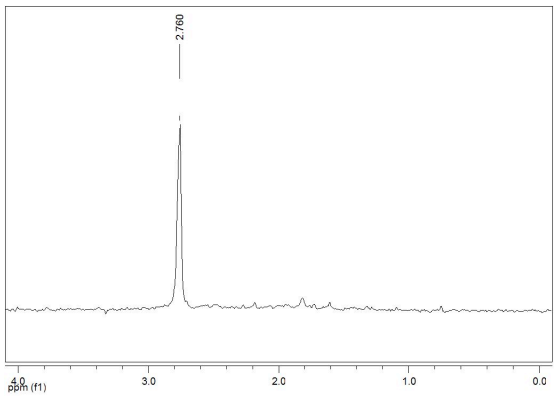


(d) 1.5 eq. (+)-sparteine surrogate



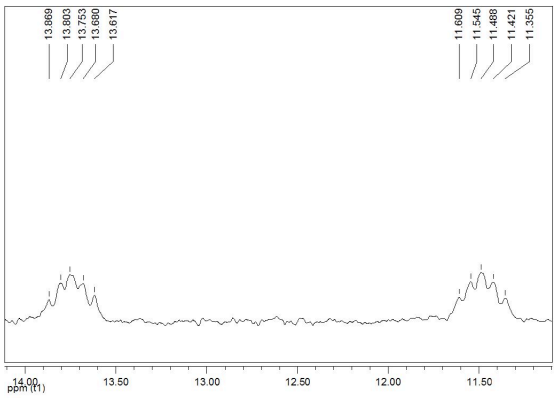
(e) 2.0 eq. (+)-sparteine surrogate

Figure S6. ^{6}Li NMR spectra of [^{6}Li]-*i*-PrLi and 1.5 eq. (+)-sparteine surrogate in Et_2O-d_{10}.



The ^{6}Li NMR spectrum shows one lithium environment.

Figure S7. ^{13}C NMR spectra of [^{6}Li]-*i*-PrLi and 1.5 eq. (+)-sparteine surrogate in Et_2O-d_{10}.

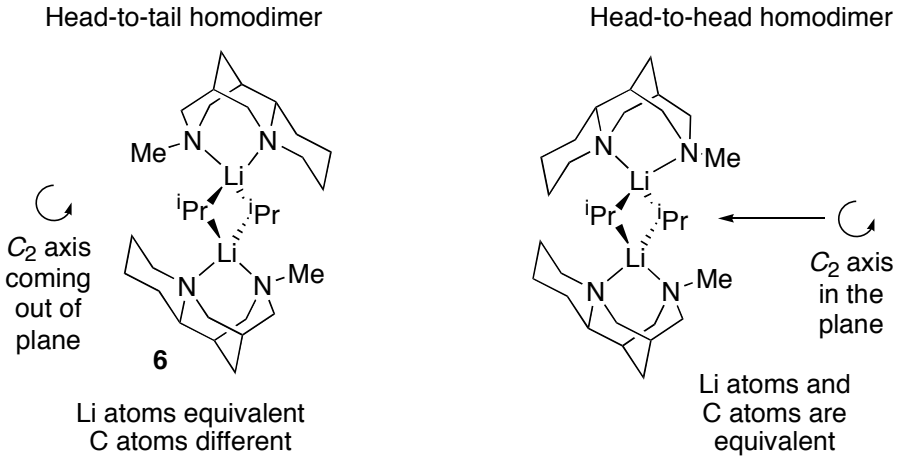


δ 13.75 ppm (^{1}J(^{6}Li,^{13}C) = 8.0 Hz)

δ 11.49 ppm (^{1}J(^{6}Li,^{13}C) = 8.0 Hz)

The ^{13}C NMR spectrum shows two different carbon environments for the CH carbons of the *i*-Pr groups. Both are quintets which indicates that each CH couples to two lithium atoms. The magnitudes of the ^{1}J(^{6}Li,^{13}C) coupling constants (8.0 Hz) suggest a dimeric aggregate based on the empirical Bauer-Winchester-Schleyer rule for coupling constants (J(^{6}Li,^{13}C) = (17 ± 2)/n_C where n_C is the number of ^{6}Li cations directly connected to the observed ^{13}C).[3] The ^{13}C NMR spectrum also shows signals due to uncomplexed (+)-sparteine surrogate and (+)-sparteine surrogate complexed to the *i*-PrLi.

Taking all of the NMR spectroscopic data together, a homodimer was characterised for the solution structure of *i*-PrLi and 1.5 eq. (+)-sparteine surrogate in Et_2O at –80 °C. However, there are two possible homodimers: a head-to-tail homodimer (**6**) and a head-to-head homodimer as shown below.

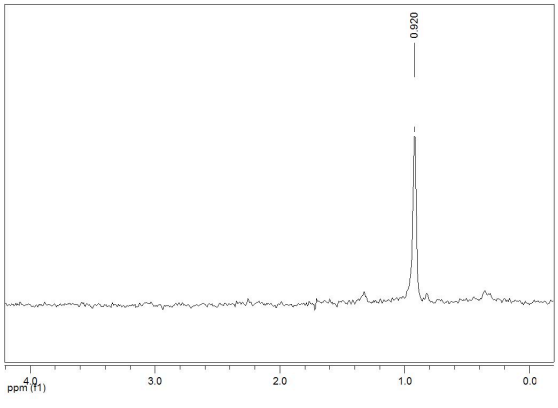


The head-to-tail homodimer **6** has equivalent lithium atoms and inequivalent carbon atoms due to the C_2 axis coming out of the plane. This is consistent with the ^{6}Li and ^{13}C NMR spectra. The head-to-head homodimer has equivalent lithium and carbon atoms due to the location of the C_2 axis as indicated above. Hence, head-to-tail homodimer was characterised for the solution structure of *i*-PrLi and 1.5 eq. (+)-sparteine surrogate in Et_2O at –80 °C.

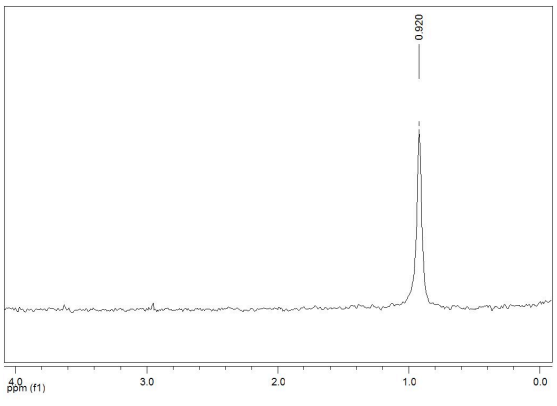
NMR spectra of *i*-PrLi/(–)-sparteine in THF-d_8

20 μL of a 2.4 M solution of [^{6}Li]-*i*-PrLi in pentane (0.048 mmol) was added to an NMR tube containing 700 μL of THF-d_8 (i.e. ~0.07 M solution of [^{6}Li]-*i*-PrLi) through a rubber septum inside the glove box. The NMR tube was then transferred to the NMR instrument and cooled to –80 °C. A ^{6}Li NMR spectrum was recorded (Figure S8a). Then, 5 μL of (–)-sparteine (0.02 mmol, ~0.5 eq.) was added and a ^{6}Li NMR spectrum was recorded (Figure S8b). Then, a further 5 μL of (–)-sparteine (0.02 mmol, ~0.5 eq.) was added and a ^{6}Li NMR spectrum was recorded (Figure S8c). Then, a further 20 μL of (–)-sparteine (0.08 mmol, ~2.0 eq.) was added and a ^{6}Li NMR spectrum was recorded (Figure S8d). Then, a further 30 μL of (–)-sparteine (0.12 mmol, ~3.0 eq.) was added and a ^{6}Li NMR spectrum was recorded (Figure S8e).

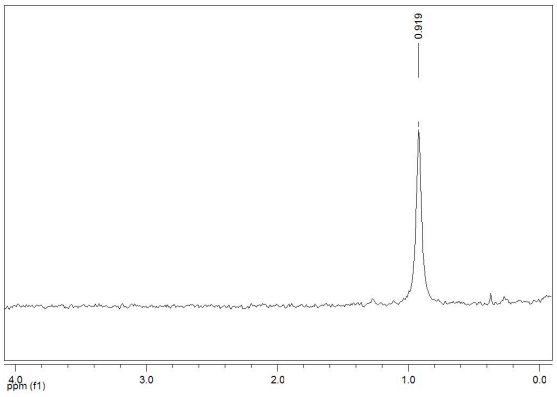
Figure S8. ^{6}Li NMR spectra of [^{6}Li]-*i*-PrLi/(–)-sparteine in THF-d_8: (a) No (–)-sparteine; (b) 0.5 eq. (–)-sparteine; (c) 1.0 eq. (–)-sparteine; (d) 3.0 eq. (–)-sparteine; (e) 6.0 eq. (–)-sparteine.



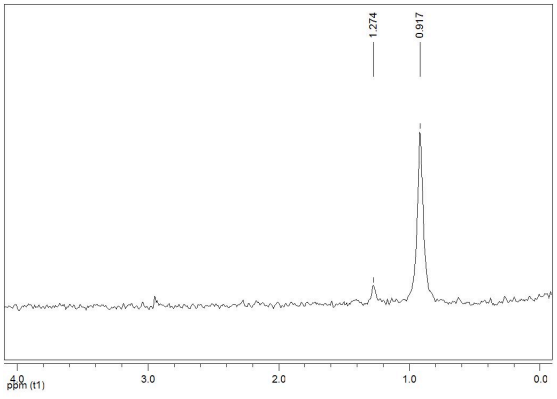
(a) No (–)-sparteine



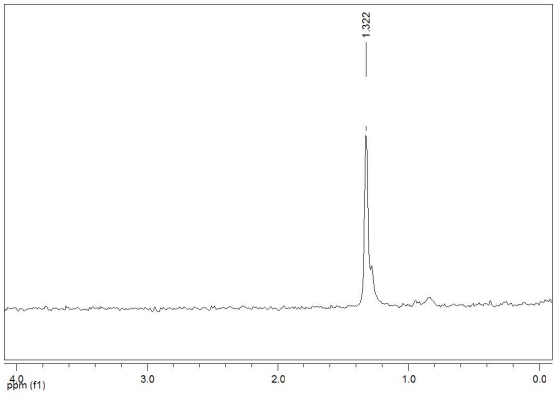
(b) 0.5 eq. (–)-sparteine



(c) 1.0 eq. (–)-sparteine

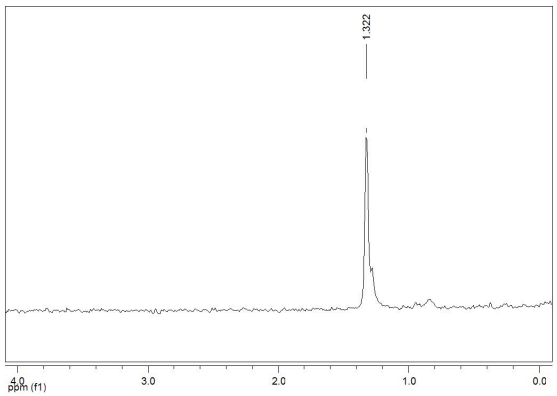


(d) 3.0 eq. (–)-sparteine



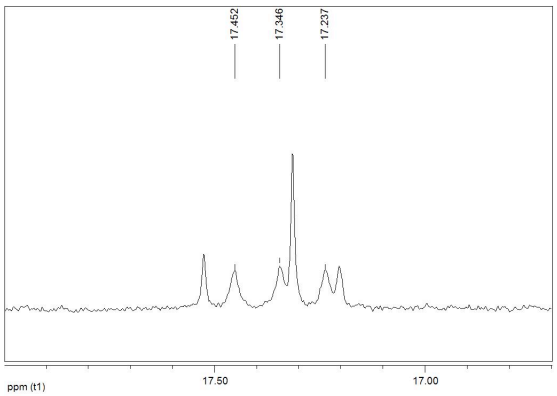
(e) 6.0 eq. (–)-sparteine

Figure S9. ^{6}Li NMR spectra of [^{6}Li]-*i*-PrLi and 6.0 eq. (–)-sparteine in THF-d_8.



The ^{6}Li NMR spectrum shows one lithium environment. The shoulder on the signal is most likely due to a shimming artefact.

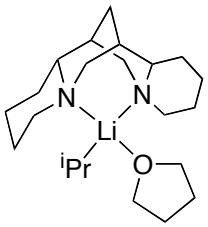
Figure S10. ^{13}C NMR spectra of [^{6}Li]-*i*-PrLi and 6.0 eq. (–)-sparteine in THF-d_8.



δ 17.35 ppm 1:1:1 triplet (^{1}J(^{6}Li,^{13}C) = 13.5 Hz) plus other signals (provisionally assigned to (–)-sparteine)

The ^{13}C NMR spectrum shows one carbon environment for the CH carbon of the *i*-Pr group. It is a 1:1:1 triplet which indicates that the CH couples to one lithium atom. The magnitude of the ^{1}J(^{6}Li,^{13}C) coupling constant (13.5 Hz) is slightly lower than expected for a monomeric aggregate based on the empirical Bauer-Winchester-Schleyer rule for coupling constants (J(^{6}Li,^{13}C) = (17 ± 2)/n_C where n_C is the number of ^{6}Li cations directly connected to the observed ^{13}C).[3] The ^{13}C NMR spectrum also shows signals due to uncomplexed (–)-sparteine and (–)-sparteine complexed to the *i*-PrLi.

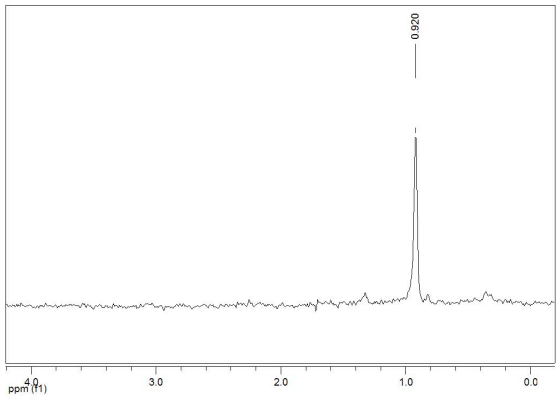
Taking all of the NMR spectroscopic data together, a monomer was characterised for the solution structure of *i*-PrLi and 6.0 eq. (–)-sparteine in THF at –80 °C.



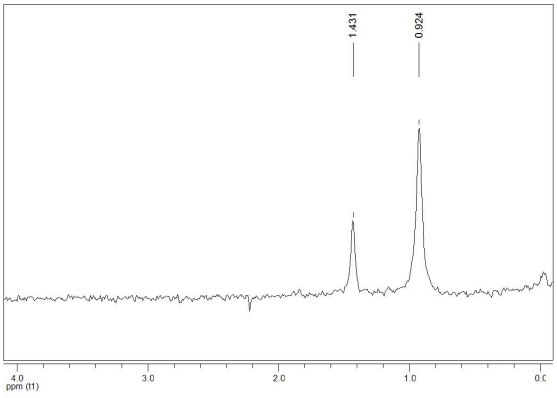
NMR spectra of *i*-PrLi/(+)-sparteine surrogate in THF-d_8

20 μL of a 2.4 M solution of [^{6}Li]-*i*-PrLi in pentane (0.048 mmol) was added to an NMR tube containing 700 μL of THF-d_8 (i.e. ~0.07 M solution of [^{6}Li]-*i*-PrLi) through a rubber septum inside the glove box. The NMR tube was then transferred to the NMR instrument and cooled to –80 °C. A ^{6}Li NMR spectrum was recorded (Figure S11a). Then, 5 μL of (+)-sparteine surrogate (0.025 mmol, ~0.5 eq.) was added and a ^{6}Li NMR spectrum was recorded (Figure S11b). Then, a further 5 μL of (+)-sparteine surrogate (0.025 mmol, ~0.5 eq.) was added and a ^{6}Li NMR spectrum was recorded (Figure S11c). Then, a further 5 μL of (+)-sparteine surrogate (0.025 mmol, ~0.5 eq.) was added and a ^{6}Li NMR spectrum was recorded (Figure S11d).

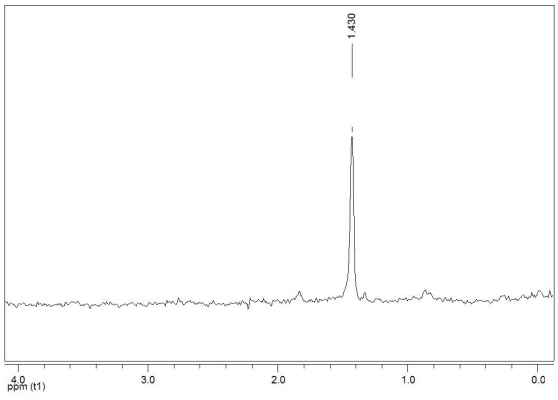
Figure S11. ^{6}Li NMR spectra of [^{6}Li]-*i*-PrLi/(+)-sparteine surrogate in THF-d_8: (a) No (+)-sparteine surrogate; (b) 0.5 eq. (+)-sparteine surrogate; (c) 1.0 eq. (+)-sparteine surrogate; (d) 1.5 eq. (+)-sparteine surrogate.



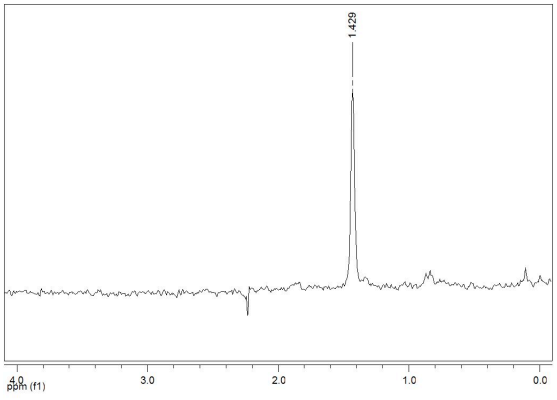
(a) No (+)-sparteine surrogate



(b) 0.5 eq. (+)-sparteine surrogate

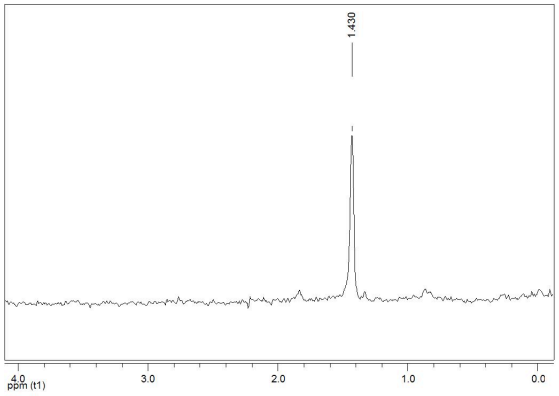


(c) 1.0 eq. (+)-sparteine surrogate



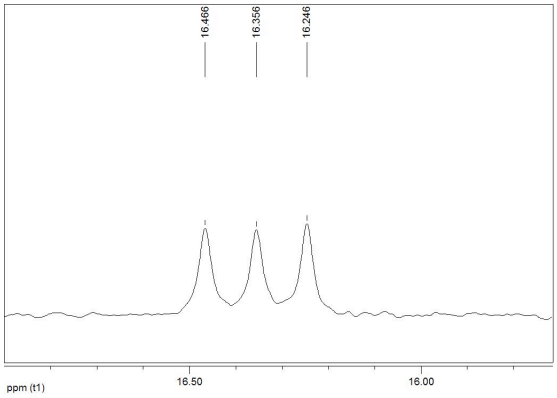
(d) 1.5 eq. (+)-sparteine surrogate

Figure S12. ^{6}Li NMR spectra of [^{6}Li]-*i*-PrLi and 1.0 eq. (+)-sparteine surrogate in THF-d_8.



The ^{6}Li NMR spectrum shows one lithium environment.

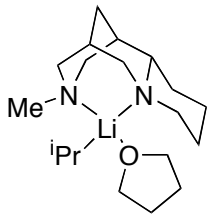
Figure S13. ^{13}C NMR spectra of [^{6}Li]-*i*-PrLi and 1.0 eq. (+)-sparteine surrogate in THF-d_8.



δ 16.36 ppm 1:1:1 triplet (^{1}J(^{6}Li,^{13}C) = 14.0 Hz)

The ^{13}C NMR spectrum shows one carbon environment for the CH carbon of the *i*-Pr group. It is a 1:1:1 triplet which indicates that the CH couples to one lithium atom. The magnitude of the ^{1}J(^{6}Li,^{13}C) coupling constant (14.0 Hz) is slightly lower than expected for a monomeric aggregate based on the empirical Bauer-Winchester-Schleyer rule for coupling constants (J(^{6}Li,^{13}C) = (17 ± 2)/n_C where n_C is the number of ^{6}Li cations directly connected to the observed ^{13}C).[3]

Taking all of the NMR spectroscopic data together, monomer **7** was characterised for the solution structure of *i*-PrLi and 1.0 eq. (+)-sparteine surrogate in THF at –80 °C.



7

Investigation of asymmetric deprotonation reactions using *i*-PrLi and *s*-BuLi with chiral diamines in different solvents

General

Water is distilled water. Et_2O, THF, TBME (*tert*-butylmethyl ether) and 2-methyl-THF were freshly distilled from benzophenone ketyl. All diamines, *N*-Boc pyrrolidine **8** and *O*-alkyl carbamate **12** used in lithiation reactions were distilled from CaH_2 before use. *s*-BuLi was titrated against *N*-benzylbenzamide before use.[5] Petrol refers to the fraction of petroleum ether with a boiling point range of 40-60 °C. All non-aqueous reactions were carried out under O_2 free N_2 or Ar atmosphere using oven-dried and/or flame-dried glassware. Flash column chromatography was carried out using Fluka Silica gel 60 (0.035-0.070 mm particle size). Thin layer chromatography was performed on Merck F_{254} alumina backed silica plates. For Kügelrohr distillation, the temperatures quoted are the oven temperatures.

Proton (400 MHz) and carbon (100.6 MHz) NMR spectra were recorded on a Jeol ECX 400 instrument using an internal deuterium lock. All samples were recorded in $CDCl_3$. Chemical shifts are quoted in parts per million and referenced relative to $CHCl_3$ (7.27 ppm for ^{1}H NMR and 77.0 for ^{13}C NMR spectroscopy). Coupling constants (*J*) are quoted in Hertz. Carbon NMR spectra were recorded with broadband proton decoupling and assigned using DEPT experiments and HSQC experiments.

Optical rotations were recorded at 20 °C on a Jasco DIP-370 polarimeter (using the sodium D line; 259 nm) and $[\alpha]_D$ values are given in units of 10^{-1} deg cm^3 g^{-1}. Chiral stationary phase HPLC was performed on an Agilent 1200 series chromatograph using a Chiralcel OD column.

The (+)-sparteine surrogate[6] and Alexakis' diamine (*R*,*R*)-**11**[7] were prepared using the published procedures.

General Procedures

General procedure A: asymmetric deprotonation-trapping of *N*-Boc pyrrolidine 8

s-BuLi (1.3 M solution in hexanes, 1.3 eq.) or *i*-PrLi (0.56-0.7 M solution in pentane, 1.3 eq.) was added dropwise to a stirred solution of (–)-sparteine or the (+)-sparteine surrogate (1.3 eq.) in Et_2O, THF, TBME or 2-methyl-THF (5 mL) at –78 °C under Ar. After stirring at –78 °C for 15 min, a solution of *N*-Boc pyrrolidine **8** (304 mg, 1.78 mmol, 1.0 eq.) in Et_2O, THF, TBME or 2-methyl-THF (1 mL) was added dropwise. The resulting pale yellow solution was stirred at –78 °C for 3 h. Then, a solution of benzaldehyde (378 mg, 3.56 mmol, 2.0 eq.) in Et_2O, THF, TBME or 2-methyl-THF (1 mL) was added dropwise and the resulting solution was allowed to warm to rt and stirred at rt for 16 h. 1 M $HCl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product.

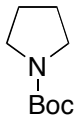
General procedure B: asymmetric deprotonation-trapping of *O*-alkyl carbamate 12

s-BuLi (1.3 M solution in hexanes, 1.2 eq.) was added dropwise to a stirred solution of (–)-sparteine or the (+)-sparteine surrogate (1.2 eq.) in Et_2O or THF (3 mL) at –78 °C under Ar. After stirring at –78 °C for 15 min, a solution of *O*-alkyl carbamate **12** (300 mg, 1.14 mmol, 1.0 eq.) in Et_2O or THF (2 mL) was added dropwise. The resulting pale yellow solution was stirred at –78 °C for 5 h. Then, methyl chloroformate (221 mg, 2.30 mmol, 2.0 eq.) was added dropwise and the resulting solution was allowed to warm to rt and stirred at rt for 16 h. 1 M $HCl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (4 x 10 mL) and the combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product.

General procedure C: asymmetric deprotonation-trapping of phosphine borane 14

s-BuLi (1.3 M solution in hexanes) (1.1. eq.) was added dropwise to a stirred solution of (–)-sparteine or the (+)-sparteine surrogate (1.2 eq.) in Et_2O or THF (2 mL) at –78 °C under Ar. After stirring at –78 °C for 15 min, a solution of phosphine borane **14** (0.76 mmol, 1.0 eq.) in Et_2O or THF (7 mL) was added dropwise. The resulting pale yellow solution was stirred at –78 °C for 3 h. Then, a solution of benzophenone (152 mg, 0.83 mmol, 1.1 eq.) in Et_2O or THF (2 mL) was added dropwise and the resulting solution was allowed to warm to rt and stirred at rt for 16 h. 1 M $HCl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with EtOAc (5 x 10 mL) and the combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product.

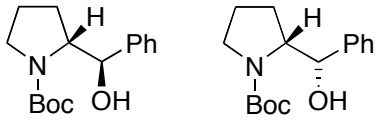
***N*-Boc Pyrrolidine 8**



8

Pyrrolidine (8.60 g, 10.0 mL, 120.92 mmol) was added dropwise to a stirred solution of di-*tert*-butyl dicarbonate (21.65 g, 99.2 mmol) in CH_2Cl_2 (340 mL) at 0 ºC under Ar. The resulting colourless solution was allowed to warm to rt and stirred for 3 h. Then, the solvent was evaporated under reduced pressure to give the crude product. Purification by Kügelrohr distillation gave *N*-Boc pyrrolidine **8** (16.58 g, 98%) as a colourless oil, bp 90-100 ºC/0.6 mmHg (lit.,[8] bp 70-75 ºC/0.5 mmHg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.26 (br s, 2H, NCH_2), 3.21 (br s, 2H, NCH_2), 1.72 (br s, 4H, CH_2), 1.35 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) mixture of rotamers δ 154.7 (C=O, Boc), 78.8 (CMe_3), 45.9 (CH_2N), 45.6 (CH_2N), 28.5 (CMe_3), 25.7 (CH_2), 24.9 (CH_2). Spectroscopic data consistent with those reported in the literature.[8]

(1*R*,2*R*)- and (1*S*,2*R*)-2-(Hydroxyphenylmethyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester *syn*-9 and *anti*-9



syn-**9** *anti*-**10**

Table 1, entry 1:

Using general procedure A, *i*-PrLi (4.06 mL of a 0.70 M solution in pentane, 2.28 mmol) and (−)-sparteine (533 mg, 2.28 mmol) in Et_2O (5 mL), *N*-Boc pyrrolidine **8** (300 mg, 1.75 mmol) in Et_2O (1 mL) and benzaldehyde (371 mg, 3.50 mmol) in Et_2O (1 mL) gave the crude product as a pale yellow oil which contained an approximately 75:25 mixture of alcohols (1*R*,2*R*)-**9** and (1*S*,2*R*)-**10** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as

eluent gave alcohol (1*R*,2*R*)-**9** (310 mg, 64%, 97:3 er by CSP-HPLC) as a colourless oil, $[\alpha]^{20}_{D}$ −1.8 (*c* 1.0 in $CHCl_3$) (lit.,[9] $[\alpha]_D$ −1.9 (*c* 1.0 in $CHCl_3$) for (1*R*,2*R*)-**9** of 95:5 er); R_F (98:2 CH_2Cl_2-acetone) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.18 (m, 5H, Ph), 5.81 (br s, 1H, OH), 4.45 (br d, *J* = 8.0 Hz, 1H, CHO), 4.02 (td, *J* = 8.0, 3.5 Hz, 1H, NCH), 3.44-3.36 (m, 1H, NCH), 3.35-3.25 (m, 1H, NCH), 1.77-1.59 (m, 2H, 2 x CH), 1.58-1.38 (m, 2H, 2 x CH), 1.45 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 158.2 (C=O), 142.5 (*ipso*-Ph), 128.3 (Ph), 127.7 (Ph), 127.2 (Ph), 80.7 (*C*Me_3), 79.2 (CHO), 64.1 (NCH), 47.6 (NCH_2), 28.4 (CH_2), 28.2 (C*Me*$_3$), 23.7 (CH_2); HPLC: chiralcel OD (98:2 hexane-^{i}PrOH, 0.5 mLmin^{-1}) (1*R*,2*R*)-**9** 22.2 min, (1*S*,2*S*)-**9** 27.6 min and alcohol (1*S*,2*R*)-**10** (107 mg, 22%, 95:5 er by CSP-HPLC) as a white solid, mp 53-55 °C (lit.,[9] 52-53 °C); $[\alpha]^{20}_{D}$ +100.7 (*c* 1.0 in $CHCl_3$) (lit.,[9] $[\alpha]_D$ +95.3 (*c* 1.0 in $CHCl_3$) for (1*S*,2*R*)-**10** of 97:3 er); R_F(98:2 CH_2Cl_2-acetone) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) (75:25 mixture of rotamers) δ 7.38-7.25 (m, 5H, Ph), 5.50 (br s, 0.75H, OH), 5.18 (br s, 0.25H, OH), 4.87 (br s, 0.75H, CHO), 4.32 (br s, 0.75H, NCH), 4.02 (br s, 0.25H, CHO), 3.58 (br s, 0.25H, NCH), 3.30 (m, 1H, NCH), 2.82 (br s, 0.75H, NCH), 2.32 (br s, 0.25H, NCH), 2.03-1.86 (m, 1H, CH_2), 1.85-1.72 (m, 1H, CH_2), 1.63 (s, 2.25H, CMe_3), 1.62-1.46 (m, 1H, CH_2), 1.52 (s, 6.75H, CMe_3), 1.21-1.13 (m, 1H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) mixture of rotamers δ 157.1 (C=O), 153.4 (C=O), 141.6 (*ipso*-Ph), 139.8 (*ipso*-Ph), 128.6 (Ph), 128.3 (Ph), 127.8 (Ph), 127.5 (Ph), 127.4 (Ph), 127.2 (Ph), 80.9 (*C*Me_3), 80.3 (*C*Me_3), 78.9 (CHO), 63.2 (NCH), 48.0 (NCH_2), 47.7 (NCH_2), 28.2 (C*Me*$_3$), 27.1 (CH_2), 26.9 (CH_2), 23.2 (CH_2), 22.8 (CH_2); HPLC: chiralcel OD (98:2 hexane-*i*-PrOH, 0.5 mLmin^{-1}) (1*S*,2*R*)-**10** 19.7 min, (1*R*,2*S*)-**10** 22.0 min. Spectroscopic data consistent with those reported in the literature.[9]

Table 1, entry 2:

Using general procedure A, *s*-BuLi (1.78 mL of a 1.30 M solution in cyclohexanes, 2.31 mmol) and (−)-sparteine (541 mg, 2.31 mmol) in Et_2O (5 mL), *N*-Boc pyrrolidine **8** (304 mg, 1.78 mmol) in Et_2O (1 mL) and benzaldehyde (378 mg, 3.56 mmol) in Et_2O (1 mL) gave the crude product as a pale yellow oil which contained an approximately 75:25 mixture of alcohols (1*R*,2*R*)-**9** and (1*S*,2*R*)-**10** by ^{1}H NMR

spectroscopy. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave (1*R*,2*R*)-**9** (298 mg, 63%, 97:3 er by CSP-HPLC) as a colourless oil, $[\alpha]^{20}_D$ −1.0 (*c* 1.0 in $CHCl_3$); HPLC: chiralcel OD (98:2 hexane-*i*-PrOH, 0.5 mLmin^{-1}) (1*R*,2*R*)-**9** 21.5 min, (1*S*,2*S*)-**9** 27.0 min and alcohol (1*S*,2*R*)-**10** (109 mg, 23%, 97:3 er by CSP-HPLC) as a white solid, mp 53-55 °C (lit.,[9] 52-53 °C); $[\alpha]^{20}_D$ +92.5 (*c* 0.6 in $CHCl_3$); HPLC: chiralcel OD (98:2 hexane-*i*-PrOH, 0.5 mLmin^{-1}) (1*S*,2*R*)-**10** 19.3 min, (1*R*,2*S*)-**10** 22.7 min.

Table 1, entry 3:

Using general procedure A, *s*-BuLi (1.75 mL of a 1.30 M solution in cyclohexanes, 2.34 mmol) and (−)-sparteine (548 mg, 2.34 mmol) in TBME (5 mL), *N*-Boc pyrrolidine **8** (309 mg, 1.80 mmol) in TBME (1 mL) and benzaldehyde (382 mg, 3.60 mmol) in TBME (1 mL) gave the crude product as a pale yellow oil which contained an approximately 75:25 mixture of alcohols (1*R*,2*R*)-**9** and (1*S*,2*R*)-**9** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave alcohol (1*R*,2*R*)-**9** (255 mg, 51%, 97:3 er by CSP-HPLC) as a colourless oil, $[\alpha]^{20}_D$ −1.3 (*c* 1.0 in $CHCl_3$); HPLC: chiralcel OD (98:2 hexane-*i*-PrOH, 0.5 mLmin^{-1}) (1*R*,2*R*)-**9** 22.2 min, (1*S*,2*S*)-**9** 27.6 min and alcohol (1*S*,2*R*)-**10** (121 mg, 24%, 98:2 er by CSP-HPLC) as a white solid, $[\alpha]^{20}_D$ +93.3 (*c* 0.6 in $CHCl_3$); HPLC: chiralcel OD (98:2 hexane-*i*-PrOH, 0.5 mLmin^{-1}) (1*S*,2*R*)-**10** 19.7 min, (1*R*,2*S*)-**10** 22.9 min.

Table 1, entry 4:

Using general procedure A, *i*-PrLi (4.06 mL of a 0.70 M solution in pentane, 2.28 mmol) and (−)-sparteine (533 mg, 2.28 mmol) in THF (5 mL), *N*-Boc pyrrolidine **8** (300 mg, 1.75 mmol) in THF (1 mL) and benzaldehyde (371 mg, 3.50 mmol) in THF (1 mL) gave the crude product as a pale yellow oil which contained an approximately 75:25 mixture of alcohols (1*R*,2*R*)-**9** and (1*S*,2*R*)-**9** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave alcohol (1*R*,2*R*)-**9** (317 mg, 65%, 63:37 er by CSP-HPLC) as a colourless oil, $[\alpha]^{20}_D$ −0.3 (*c*

0.75 in $CHCl_3$); HPLC: chiralcel OD (98:2 hexane-*i*-PrOH, 0.5 $mLmin^{-1}$) (1*R*,2*R*)-**9** 22.6 min, (1*S*,2*S*)-**9** 27.8 min and alcohol (1*S*,2*R*)-**10** (106 mg, 22%, 60:40 er by CSP-HPLC) as a white solid, $[\alpha]^{20}_D$ +31.2 (*c* 1.0 in $CHCl_3$); HPLC: chiralcel OD (98:2 hexane-*i*-PrOH, 0.5 $mLmin^{-1}$) (1*S*,2*R*)-**10** 19.3 min, (1*R*,2*S*)-**10** 21.5 min.

Table 1, entry 5:

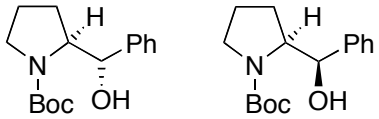
Using general procedure A, *s*-BuLi (1.75 mL of a 1.30 M solution in cyclohexanes, 2.28 mmol) and (−)-sparteine (539 mg, 2.30 mmol) in THF (5 mL), *N*-Boc pyrrolidine **8** (300 mg, 1.75 mmol) in THF (1 mL) and benzaldehyde (376 mg, 3.54 mmol) in THF (1 mL) gave the crude product as a pale yellow oil which contained an approximately 75:25 mixture of alcohols (1*R*,2*R*)-**9** and (1*S*,2*R*)-**10** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave alcohol (1*R*,2*R*)-**9** (232 mg, 50%, 51:49 er by CSP-HPLC) as a colourless oil, HPLC: chiralcel OD (98:2 hexane-*i*-PrOH, 0.5 $mLmin^{-1}$) (1*R*,2*R*)-**9** 23.7 min, (1*S*,2*S*)-**9** 28.5 min and alcohol (1*S*,2*R*)-**10** (66 mg, 14%, 51:49 er by CSP-HPLC) as a white solid, HPLC: chiralcel OD (98:2 hexane-*i*-PrOH, 0.5 $mLmin^{-1}$) (1*S*,2*R*)-**10** 19.5 min, (1*R*,2*S*)-**10** 22.8 min.

Table 1, entry 6:

Using general procedure A, *s*-BuLi (1.83 mL of a 1.30 M solution in cyclohexanes, 2.38 mmol) and (−)-sparteine (558 mg, 2.38 mmol) in 2-methyl-THF (5 mL), *N*-Boc pyrrolidine **8** (314 mg, 1.83 mmol) in 2-methyl-THF (1 mL) and benzaldehyde (388 mg, 3.66 mmol) in 2-methyl-THF (1 mL) gave the crude product as a pale yellow oil which contained an approximately 75:25 mixture of alcohols (1*R*,2*R*)-**9** and (1*S*,2*R*)-**10** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave alcohol (1*R*,2*R*)-**9** (256 mg, 50%, 59:41 er by CSP-HPLC) as a colourless oil, $[\alpha]^{20}_D$ −0.4 (*c* 0.9 in $CHCl_3$); HPLC: chiralcel OD (98:2 hexane-*i*-PrOH, 0.5 $mLmin^{-1}$) (1*R*,2*R*)-**9** 23.0 min, (1*S*,2*S*)-**9** 28.4 min and alcohol (1*S*,2*R*)-**10** (109 mg, 29%, 55:45 er by CSP-HPLC)

as a white solid, $[\alpha]^{20}_{D}$ +28.8 (*c* 1.0 in $CHCl_3$); HPLC: chiralcel OD (98:2 hexane-*i*-PrOH, 0.5 mLmin^{-1}) (1*S*,2*R*)-**10** 19.7 min, (1*R*,2*S*)-**10** 22.1 min.

(1*S*,2*S*)- and (1*R*,2*S*)-2-(Hydroxyphenylmethyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester *syn*-9 and *anti*-10



syn-**9** *anti*-**10**

Table 2, entry 1:

Using general procedure A, *i*-PrLi (4.13 mL of a 0.56 M solution in pentane, 2.31 mmol) and the (+)-sparteine surrogate (442 mg, 2.27 mmol) in Et_2O (5 mL), *N*-Boc pyrrolidine **8** (305 mg, 1.78 mmol) in Et_2O (1 mL) and benzaldehyde (378 mg, 3.56 mmol) in Et_2O (1 mL) gave the crude product as a pale yellow oil which contained an approximately 75:25 mixture of alcohols (1*S*,2*S*)-**9** and (1*R*,2*S*)-**10** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave alcohol (1*S*,2*S*)-**9** (331 mg, 68%, 98:2 er by CSP-HPLC) as a colourless oil, $[\alpha]^{20}_{D}$ +2.7 (*c* 1.0 in $CHCl_3$); HPLC: chiralcel OD (98:2 hexane-*i*-PrOH, 0.5 mLmin^{-1}) (1*R*,2*R*)-**9** 23.3 min, (1*S*,2*S*)-**9** 28.1 min and alcohol (1*R*,2*S*)-**10** (107 mg, 23%, 95:5 er by CSP-HPLC) as a white solid, $[\alpha]^{20}_{D}$ −102.1 (*c* 1.0 in $CHCl_3$); HPLC: chiralcel OD (98:2 hexane-*i*-PrOH, 0.5 mLmin^{-1}) (1*S*,2*R*)-**10** 19.4 min, (1*R*,2*S*)-**10** 21.4 min.

Table 2, entry 2:

Using general procedure A, *s*-BuLi (1.61 mL of a 1.30 M solution in cyclohexanes, 2.09 mmol) and the (+)-sparteine surrogate (406 mg, 2.09 mmol) in Et_2O (5 mL), *N*-Boc pyrrolidine **8** (298 mg, 1.61 mmol) in Et_2O (1 mL) and benzaldehyde (334 mg, 3.15 mmol) in Et_2O (1 mL) gave the crude product as a pale yellow oil which contained an approximately 75:25 mixture of alcohols (1*S*,2*S*)-**9** and (1*R*,2*S*)-**10** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave alcohol (1*S*,2*S*)-**9** (248 mg, 58%, 95:5 er by CSP-HPLC) as a colourless oil,

$[\alpha]^{20}_{D}$ +1.7 (*c* 1.0 in $CHCl_3$); HPLC: chiralcel OD (98:2 hexane-*i*-PrOH, 0.5 mLmin^{-1}) (1*R*,2*R*)-**9** 24.6 min, (1*S*,2*S*)-**9** 29.7 min and alcohol (1*R*,2*S*)-**10** (98 mg, 23%, 94:6 er by CSP-HPLC) as a white solid, $[\alpha]^{20}_{D}$ −93.1 (*c* 1.1 in $CHCl_3$); HPLC: chiralcel OD (98:2 hexane-*i*-PrOH, 0.5 mLmin^{-1}) (1*S*,2*R*)-**10** 20.2 min, (1*R*,2*S*)-**10** 21.8 min.

Table 2, entry 3:

Using general procedure A, *s*-BuLi (1.75 mL of a 1.30 M solution in cyclohexanes, 2.28 mmol) and the (+)-sparteine surrogate (452 mg, 2.33 mmol) in TBME (5 mL), *N*-Boc pyrrolidine **8** (306 mg, 1.79 mmol) in TBME (1 mL) and benzaldehyde (371 mg, 3.58 mmol) in TBME (1 mL) gave the crude product as a pale yellow oil which contained an approximately 75:25 mixture of alcohols (1*S*,2*S*)-**9** and (1*R*,2*S*)-**10** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave alcohol (1*S*,2*S*)-**9** (272 mg, 56%, 94:6 er by CSP-HPLC) as a colourless oil, $[\alpha]^{20}_{D}$ +2.3 (*c* 1.2 in $CHCl_3$); HPLC: chiralcel OD (98:2 hexane-*i*-PrOH, 0.5 mLmin^{-1}) (1*R*,2*R*)-**9** 22.8 min, (1*S*,2*S*)-**9** 27.7 min and alcohol (1*R*,2*S*)-**10** (151 mg, 31%, 93:7 er by CSP-HPLC) as a white solid, $[\alpha]^{20}_{D}$ −101.6 (*c* 1.1 in $CHCl_3$); HPLC: chiralcel OD (98:2 hexane-*i*-PrOH, 0.5 mLmin^{-1}) (1*S*,2*R*)-**10** 19.8 min, (1*R*,2*S*)-**10** 22.1 min.

Table 2, entry 4:

Using general procedure A, *i*-PrLi (4.13 mL of a 0.56 M solution in pentane, 2.31 mmol) and the (+)-sparteine surrogate (442 mg, 2.28 mmol) in THF (5 mL), *N*-Boc pyrrolidine **8** (299 mg, 1.75 mmol) in THF (1 mL) and benzaldehyde (371 mg, 3.50 mmol) in THF (1 mL) gave the crude product as a pale yellow oil which contained an approximately 75:25 mixture of alcohols (1*S*,2*S*)-**9** and (1*R*,2*S*)-**10** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave alcohol (1*S*,2*S*)-**9** (320 mg, 66%, 97:3 er by CSP-HPLC) as a colourless oil, $[\alpha]^{20}_{D}$ +2.3 (*c* 1.0 in $CHCl_3$); HPLC: chiralcel OD (98:2 hexane-*i*-PrOH, 0.5 mLmin^{-1}) (1*R*,2*R*)-**9** 23.3 min, (1*S*,2*S*)-**9** 27.7 min and alcohol (1*S*,2*R*)-**10** (106 mg, 21%, 97:3 er by CSP-HPLC) as a white solid, $[\alpha]^{20}_{D}$ −105.1

(*c* 1.0 in $CHCl_3$); HPLC: chiralcel OD (98:2 hexane-*i*-PrOH, 0.5 $mLmin^{-1}$) (1*S*,2*R*)-**10** 19.6 min, (1*R*,2*S*)-**10** 21.5 min.

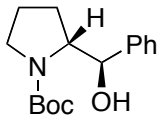
Table 2, entry 5:

Using general procedure A, *s*-BuLi (1.65 mL of a 1.30 M solution in cyclohexanes, 2.15 mmol) and the (+)-sparteine surrogate (418 mg, 2.15 mmol) in THF (5 mL), *N*-Boc pyrrolidine **8** (307 mg, 1.65 mmol) in THF (1 mL) and benzaldehyde (355 mg, 3.30 mmol) in THF (1 mL) gave the crude product as a pale yellow oil which contained an approximately 75:25 mixture of alcohols (1*S*,2*S*)-**9** and (1*R*,2*S*)-**10** by ^1H NMR spectroscopy. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave alcohol (1*S*,2*S*)-**9** (195 mg, 45%, 95:5 er by CSP-HPLC) as a colourless oil, $[\alpha]^{20}_D$ +2.4 (*c* 1.0 in $CHCl_3$); HPLC: chiralcel OD (98:2 hexane-*i*-PrOH, 0.5 $mLmin^{-1}$) (1*R*,2*R*)-**9** 24.1 min, (1*S*,2*S*)-**9** 28.9 min and alcohol (1*R*,2*S*)-**10** (86 mg, 20%, 95:5 er by CSP-HPLC) as a white solid, $[\alpha]^{20}_D$ −104.5 (*c* 1.0 in $CHCl_3$); HPLC: chiralcel OD (98:2 hexane-*i*-PrOH, 0.5 $mLmin^{-1}$) (1*S*,2*R*)-**10** 20.4 min, (*R*,*S*)-**10** 21.9 min.

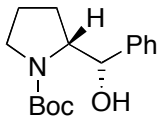
Table 2, entry 6:

Using general procedure A, *s*-BuLi (1.85 mL of a 1.30 M solution in cyclohexanes, 2.41 mmol) and the (+)-sparteine surrogate (467 mg, 2.41 mmol) in 2-methyl-THF (5 mL), *N*-Boc pyrrolidine **8** (316 mg, 1.85 mmol) in 2-methyl-THF (1 mL) and benzaldehyde (392 mg, 3.70 mmol) in 2-methyl-THF (1 mL) gave the crude product as a pale yellow oil which contained an approximately 75:25 mixture of alcohols (1*S*,2*S*)-**9** and (1*R*,2*S*)-**10** by ^1H NMR spectroscopy. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave alcohol (1*S*,2*S*)-**9** (272 mg, 53%, 93:7 er by CSP-HPLC) as a colourless oil, $[\alpha]^{20}_D$ +1.1 (*c* 0.75 in $CHCl_3$); HPLC: chiralcel OD (98:2 hexane-*i*-PrOH, 0.5 $mLmin^{-1}$) (1*R*,2*R*)-**9** 23.2 min, (1*S*,2*S*)-**9** 28.1 min and alcohol (1*R*,2*S*)-**10** (113 mg, 22%, 93:7 er by CSP-HPLC) as a white solid, $[\alpha]^{20}_D$ −78.7 (*c* 0.6 in $CHCl_3$); HPLC: chiralcel OD (98:2 hexane-*i*-PrOH, 0.5 $mLmin^{-1}$) (1*S*,2*R*)-**10** 19.7 min, (1*R*,2*S*)-**10** 22.0 min.

(1*R*,2*R*)- and (1*S*,2*R*)-2-(Hydroxyphenylmethyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester *syn*-9 and *anti*-9



syn-**9**

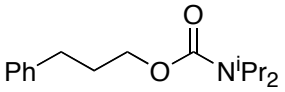


anti-**10**

Scheme 2:

Using general procedure A, *s*-BuLi (1.90 mL of a 1.30 M solution in cyclohexanes, 2.44 mmol) and diamine (1*R*,2*R*)-**11** (607 mg, 2.46 mmol) in THF (5 mL), *N*-Boc pyrrolidine **8** (322 mg, 1.88 mmol) in THF (1 mL) and benzaldehyde (399 mg, 3.76 mmol) in THF (1 mL) gave the crude product as a pale yellow oil which contained an approximately 75:25 mixture of alcohols (1*R*,2*R*)-**9** and (1*S*,2*R*)-**10** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave alcohol (1*R*,2*R*)-**9** (302 mg, 59%, 50:50 er by CSP-HPLC) as a colourless oil, HPLC: chiralcel OD (98:2 hexane-*i*-PrOH, 0.5 mLmin^{-1}) (1*R*,2*R*)-**9** 21.7 min, (1*S*,2*S*)-**9** 27.0 min and alcohol (1*S*,2*R*)-**10** (122 mg, 24%, 53:47 er by CSP-HPLC) as a white solid, HPLC: chiralcel OD (98:2 hexane-*i*-PrOH, 0.5 mLmin^{-1}) (1*S*,2*R*)-**10** 19.7 min, (1*R*,2*S*)-**10** 22.0 min.

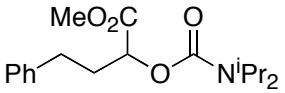
3-Phenylpropyl *N,N*-diisopropylcarbamate 12



12

A solution of diisopropylcarbamoyl chloride (500 mg, 3.06 mmol, 1.05 eq.) in Et_2O (5 mL) was added dropwise over 10 min to a stirred solution of NaH (80 mg of 60% wt dispersion in mineral oil, 3.35 mmol, pre-washed with Et_2O (3 x 10 mL)) and 3-phenyl-1-propanol (396 mg, 2.91 mmol, 1.0 eq.) in Et_2O (5 mL) at rt under Ar. The resulting mixture was stirred at rt for 16 h. Then, 1 M $HCl_{(aq)}$ (10 mL) was added and the resulting mixture was stirred vigorously for 5 min. The two layers were separated and the aqueous layer was extracted with Et_2O (4 x 10 mL). The combined organic extracts were dried (2:1 Na_2SO_4-$NaHCO_3$) and evaporated under reduced pressure to give the crude product as a yellow oil. Purification by flash column chromatography on silica with petrol-Et_2O (5:1) as eluent gave *O*-alkyl carbamate **12** (581 mg, 76%) as a colourless oil; R_F(5:1 petrol-Et_2O) 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.28 (m, 2H, Ph), 7.22-7.18 (m, 3H, Ph), 4.21-3.63 (br m, 2H, 2 x NCH), 4.13 (t, J = 6.5 Hz, 2H, OCH_2), 2.73 (t, J = 8.0 Hz, 2H, CH_2Ph), 2.03-1.95 (m, 2H, CH_2), 1.23 (d, J = 7.0 Hz, 12H, 2 x NCHMe_2); ^{13}C NMR (100.6 MHz, $CDCl_3$), 155.8 (C=O), 141.6 (*ipso*-Ph), 128.40 (Ph), 128.38 (Ph), 125.9 (Ph), 64.0 (OCH_2), 45.8 (NCH), 32.6 (CH_2), 30.9 (Me), 21.1 (CH_2). Spectroscopic data consistent with those reported in the literature.[10]

***rac*-2-Diisopropylcarbamoyl-4-phenylbutyric acid *rac*-13**

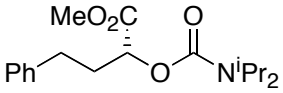


rac-**13**

s-BuLi (1.38 mL of a 1.30 M solution in cyclohexanes, 1.54 mmol, 1.3 eq.) was added dropwise to a stirred solution of *O*-alkyl carbamate **12** (311 mg, 1.14 mmol, 1.0 eq.) in THF (5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 ˚C for 5 h. Then, methyl chloroformate (221 mg, 2.34 mmol, 2.0 eq.) was added dropwise and the resulting solution was allowed to warm to rt and stirred at rt for 16 h. 1 M $HCl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was

extracted with Et_2O (3 x 10 mL) and the combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product as a yellow oil. Purification by flash column chromatography on silica with 4:1-2:1 petrol-Et_2O as eluent gave ester *rac*-**13** (271 mg, 74%) as a colourless oil, R_F(4:1 petrol-Et_2O) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.28 (m, 2H, Ph), 7.23-7.19 (m, 3H, Ph), 5.08 (t, J = 6.5 Hz, 1H, CHO), 4.11 (br s, 1H, NCH), 3.81 (br s, 1H, NCH), 3.73 (s, 3H, CO_2Me), 2.79-2.75 (m, 2H, CH_2), 2.21-2.15 (m, 2H, CH_2), 1.31-1.24 (m, 12H, 2 x NCHMe_2); ^{13}C NMR (100.6 MHz, $CDCl_3$), 172.0 (C=O, CO_2Me), 155.2 (C=O, NCO_2), 141.3 (*ipso*-Ph), 128.7 (Ph), 128.6 (Ph), 126.4 (Ph), 71.9 (CHO), 51.8 (CO_2Me), 46.5 (N*C*HMe_2), 46.4 (N*C*HMe_2), 32.9 (CH_2), 31.4 (CH_2), 21.4 (NCHMe_2), 21.0 (N*C*HMe_2). Spectroscopic data consistent with those reported in the literature.[11]

(*R*)-2-Diisopropylcarbamoyl-4-phenyl-butyric (*R*)-13



(R)-**13**

Table 3, entry 1:

Using general procedure B, *s*-BuLi (1.05 mL of a 1.30 M solution in cyclohexanes, 1.37 mmol) and (−)-sparteine (321 mg, 1.37 mmol) in Et_2O (3 mL), *O*-alkyl carbamate **12** (300 mg, 1.14 mmol) in Et_2O (2 mL) and methyl chloroformate (221 mg, 2.30 mmol) gave the crude product as a pale yellow oil. Purification by flash column chromatography on silica with 4:1-2:1 petrol-Et_2O as eluent gave ester (*R*)-**13** (308 mg, 84%, 97:3 er by CSP-HPLC) as a colourless oil, $[\alpha]^{20}_D$ −17.3 (*c* 1.0 in CH_2Cl_2) (lit.,[11] $[\alpha]^{20}_D$ −17.3 (*c* 1.2 in CH_2Cl_2)); HPLC: chiralcel OD (95:5 hexane-*i*-PrOH, 0.5 mLmin^{-1}) (*S*)-**13** 10.0 min, (*R*)-**13** 11.3 min.

Table 3, entry 2:

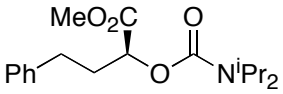
Using general procedure B, *s*-BuLi (1.11 mL of a 1.30 M solution in cyclohexanes, 1.39 mmol) and (−)-sparteine (338 mg, 1.42 mmol) in THF (3 mL), *O*-alkyl carbamate **12** (315 mg, 1.15 mmol) in THF (2 mL) and methyl chloroformate (233 mg, 2.40 mmol) gave the crude product as a pale yellow oil.

Purification by flash column chromatography on silica with 4:1-2:1 petrol-Et_2O as eluent gave ester (*R*)-**13** (262 mg, 68%, 61:39 er by CSP-HPLC) as a colourless oil, $[\alpha]^{20}_D$ −2.5 (*c* 0.75 in CH_2Cl_2); HPLC: chiralcel OD (95:5 hexane-*i*-PrOH, 0.5 mLmin^{-1}) (*S*)-**13** 10.3 min, (*R*)-**13** 11.8 min.

Table 3, entry 3:

Using general procedure B, *s*-BuLi (1.06 mL of a 1.30 M solution in cyclohexanes, 1.38 mmol) and (−)-sparteine (1.078 g, 4.61 mmol, 3.3 eq. relative to *s*-BuLi) in THF (3 mL), *O*-alkyl carbamate **12** (303 mg, 1.15 mmol) in THF (2 mL) and methyl chloroformate (228 mg, 2.41 mmol) gave the crude product as a pale yellow oil. Purification by flash column chromatography on silica with 4:1-2:1 petrol-Et_2O as eluent gave ester (*R*)-**13** (87 mg, 24%, 61:39 er by CSP-HPLC) as a colourless oil, $[\alpha]^{20}_D$ −2.8 (*c* 0.75 in CH_2Cl_2); HPLC: chiralcel OD (95:5 hexane-*i*-PrOH, 0.5 mLmin^{-1}) (*S*)-**13** 9.8 min, (*R*)-**13** 11.1 min.

(*S*)-2-Diisopropylcarbamoyl-4-phenylbutyric (*S*)-13



(S)-**13**

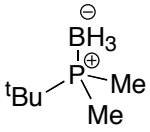
Table 3, entry 4:

Using general procedure B, *s*-BuLi (0.81 mL of a 1.30 M solution in cyclohexanes, 1.06 mmol) and the (+)-sparteine surrogate (207 mg, 0.88 mmol) in Et_2O (3 mL), *O*-alkyl carbamate **12** (366 mg, 1.14 mmol) in Et_2O (2 mL) and methyl chloroformate (172 mg, 2.12 mmol) gave the crude product as a pale yellow oil. Purification by flash column chromatography on silica with 4:1-2:1 petrol-Et_2O as eluent gave ester (*S*)-**13** (190 mg, 67%, 93:7 er by CSP-HPLC) as a colourless oil, $[\alpha]^{20}_D$ +16.3 (*c* 0.8 in CH_2Cl_2); HPLC: chiralcel OD (95:5 hexane-*i*-PrOH, 0.5 mLmin^{-1}) (*S*)-**13** 9.9 min, (*R*)-**13** 11.3 min.

Table 3, entry 5:

Using general procedure B, *s*-BuLi (0.98 mL of a 1.30 M solution in cyclohexanes, 1.28 mmol) and the (+)-sparteine surrogate (249 mg, 1.28 mmol) in THF (3 mL), *O*-alkyl carbamate **12** (281 mg, 1.37 mmol) in THF (2 mL) and methyl chloroformate (208 mg, 2.14 mmol) gave the crude product as a pale yellow oil. Purification by flash column chromatography on silica with 4:1-2:1 petrol-Et_2O as eluent gave ester (*S*)-**13** (248 mg, 72%, 93:7 er by CSP-HPLC) as a colourless oil, $[\alpha]^{20}_D$ +16.0 (*c* 1.0 in CH_2Cl_2); HPLC: chiralcel OD (95:5 hexane-*i*-PrOH, 0.5 $mLmin^{-1}$) (*S*)-**13** 9.9 min, (*R*)-**13** 11.3 min.

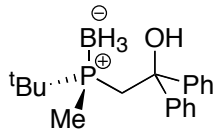
***tert*-Butyldimethylphosphine borane 14**



14

A solution of MeMgBr (5.50 mL of a 3 M solution in Et_2O, 16.50 mmol, 2.6 eq.) in THF (6 mL) was added dropwise over 1 h to a stirred solution of *t*-butyldichlorophosphine (1.00 g, 6.29 mmol, 1 eq.) in THF (10 mL) at –10 °C under Ar. The resulting mixture was stirred at rt for 5 h. Then, BH_3·DMS (3.80 mL of a 2 M solution in THF, 7.60 mmol, 1.2 eq.) was added dropwise over 20 min. The solution was stirred at rt for 1 h and poured onto a mixture of ice (15 g) and concentrated $HCl_{(aq)}$ (1.50 mL). The mixture was extracted with EtOAc (4 x 10 mL) and the combined organic extracts were dried ($NaSO_4$) and evaporated under reduced pressure to give the crude product as a white solid. Purification by recrystallisation from hexane (10 mL) gave phosphine borane **14** (510 mg, 60%) as a white solid, mp 164-166 ˚C (lit.,[12] 160-163 ˚C); R_F(4:1 petrol-Et_2O) 0.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (d, *J* = 10.0 Hz, 6H, PMe), 1.16 (d, *J* = 14.0 Hz, 9H, CMe_3), 0.45 (qd, *J* = 95.0, 13.0 Hz, 3H, BH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 26.3 (d, *J* = 35.0 Hz, P*C*Me_3), 24.4 (d, *J* = 3.0 Hz, PC*Me*$_3$), 6.8 (d, *J* = 36.0 Hz, PMe). Spectroscopic data consistent with those reported in the literature.[12]

(*S*)-*P*-(2,2-Diphenyl-2-hydroxyethyl)-*P*-methyl-*tert*-butylphosphine borane (*S*)-15



(*S*)-**15**

Table 4, entry 1:

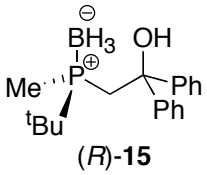
Using general procedure C, *s*-BuLi (0.69 mL of a 1.30 M solution in cyclohexanes, 0.97 mmol) and (−)-sparteine (226 mg, 0.96 mmol) in Et_2O (2 mL), phosphine borane **14** (109 mg, 0.81 mmol) in Et_2O (7 mL) and benzophenone (162 mg, 0.89 mmol) in Et_2O (2 mL) gave the crude product as a white solid. Purification by flash column chromatography on silica with 95:5 petrol-EtOAc as eluent gave alcohol (*S*)-**15** (223 mg, 88%, 95:5 er by CSP-HPLC) as a white solid, mp 113-115 °C (lit.,[13] 116.5-117.5 °C); $[\alpha]^{20}_D$ +22.0 (*c* 1.0 in $CHCl_3$) (lit.,[13] $[\alpha]_D$ –14.9 (*c* 0.47 in $CHCl_3$) for (*R*)-**15** of 96:4 er); R_F(95:5 petrol-EtOAc) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.47 (m, 4H, Ph), δ 7.36-7.30 (m, 4H, Ph), δ 7.25-7.21 (m, 2H, Ph), 4.59 (s, 1H, OH), 2.89 (t, *J* = 14.5 Hz, 1H, PCH_AH_B), 2.68 (dd, *J* = 14.5, 7.0 Hz, 1H, PCH_AH_B), 1.18 (d, *J* = 13.5 Hz, 9H, CMe_3), 0.74 (d, *J* = 10.0 Hz, 3H, PMe), 0.56-0.19 (m, 3H, BH_3); ^{13}C NMR (100MHz, $CDCl_3$) δ: 148.1 (d, *J*= 8.5 Hz, *ipso*-Ph), 145.6 (d, *J* = 2.5 Hz, *ipso*-Ph), 128.5 (Ph), 128.4 (Ph), 127.4 (Ph), 126.3 (Ph), 125.5 (Ph), 77.0 (d, *J* = 1.0 Hz, COH), 34.0 (d, *J* = 28.0 Hz, PCH_2), 27.7 (d, *J* = 36.0 Hz , P*C*Me_3), 24.4 (d, *J* = 2.0 Hz, PC*Me*$_3$), 6.1 (d, *J* = 35.0 Hz, PMe); HPLC: chiralcel OD (95:5 hexane-*i*-PrOH, 0.5 mLmin^{-1}) (*R*)-**15** 10.9 min, (*S*)-**15** 13.1 min. Spectroscopic data consistent with that reported in the literature.[14]

Table 4, entry 2:

Using general procedure C, *s*-BuLi (0.63 mL of a 1.30 M solution in cyclohexanes, 0.89 mmol) and (−)-sparteine (205 mg, 0.87 mmol) in THF (2 mL), phosphine borane **14** (100 mg, 0.74 mmol) in THF (7 mL) and benzophenone (148 mg, 0.81 mmol) in THF (2mL) gave the crude product as a white solid. Purification by flash column chromatography on silica with 95:5 petrol-EtOAc as eluent gave alcohol

(*S*)-**15** (70 mg, 30%, 50:50 er by CSP-HPLC) as a white solid, HPLC: chiralcel OD (95:5 hexane-*i*-PrOH, 0.5 mLmin^{-1}) (*R*)-**15** 11.1 min, (*S*)-**15** 13.5 min.

(*R*)-*P*-(2,2-Diphenyl-2-hydroxyethyl)-*P*-methyl-*tert*-butylphosphine borane (*R*)-15



(*R*)-**15**

Table 4, entry 3:

Using general procedure C, *s*-BuLi (0.64 mL of a 1.30 M solution in cyclohexanes, 0.84 mmol) and the (+)-sparteine surrogate (177 mg, 0.91 mmol) in Et_2O (2 mL), phosphine borane **14** (103 mg, 0.76 mmol) in Et_2O (7 mL) and benzophenone (152 mg, 0.83 mmol) in Et_2O (2 mL) gave the crude product as a white solid. Purification by flash column chromatography on silica with 95:5 petrol-EtOAc as eluent gave alcohol (*R*)-**15** (279 mg, 89%, 95:5 er by CSP-HPLC) as a white solid, $[\alpha]^{20}_D$ −22.0 (*c* 1.0 in $CHCl_3$); HPLC: chiralcel OD (95:5 hexane-*i*-PrOH, 0.5 mLmin^{-1}) (*R*)-**15** 10.8 min, (*S*)-**15** 13.1 min.

Table 4, entry 4:

Using general procedure C, *s*-BuLi (0.68 mL of a 1.30 M solution in cyclohexanes, 0.81 mmol) and the (+)-sparteine surrogate (173 mg, 0.89 mmol) in THF (2 mL), phosphine borane **14** (100 mg, 0.74 mmol) in THF (7 mL) and benzophenone (148 mg, 0.81 mmol) in THF (2 mL) gave the crude product as a white solid. Purification by flash column chromatography on silica with 95:5 petrol-EtOAc as eluent gave alcohol (*R*)-**15** (103 mg, 44%, 88:12 er by CSP-HPLC) as a white solid, $[\alpha]_D$ −16.2 (*c* 1.0 in $CHCl_3$); HPLC: chiralcel OD (95:5 hexane-*i*-PrOH, 0.5 mLmin^{-1}) (*R*)-**15** 11.9 min, (*S*)-**15** 13.1 min.

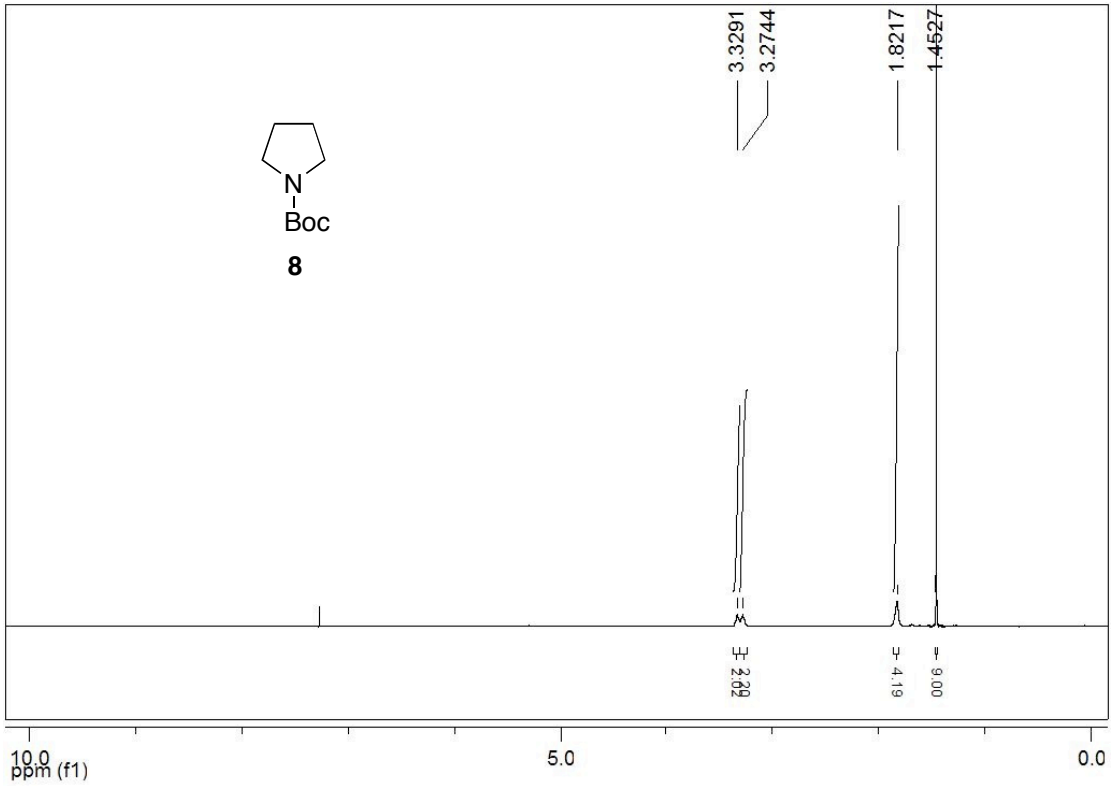
Table 4, entry 5:

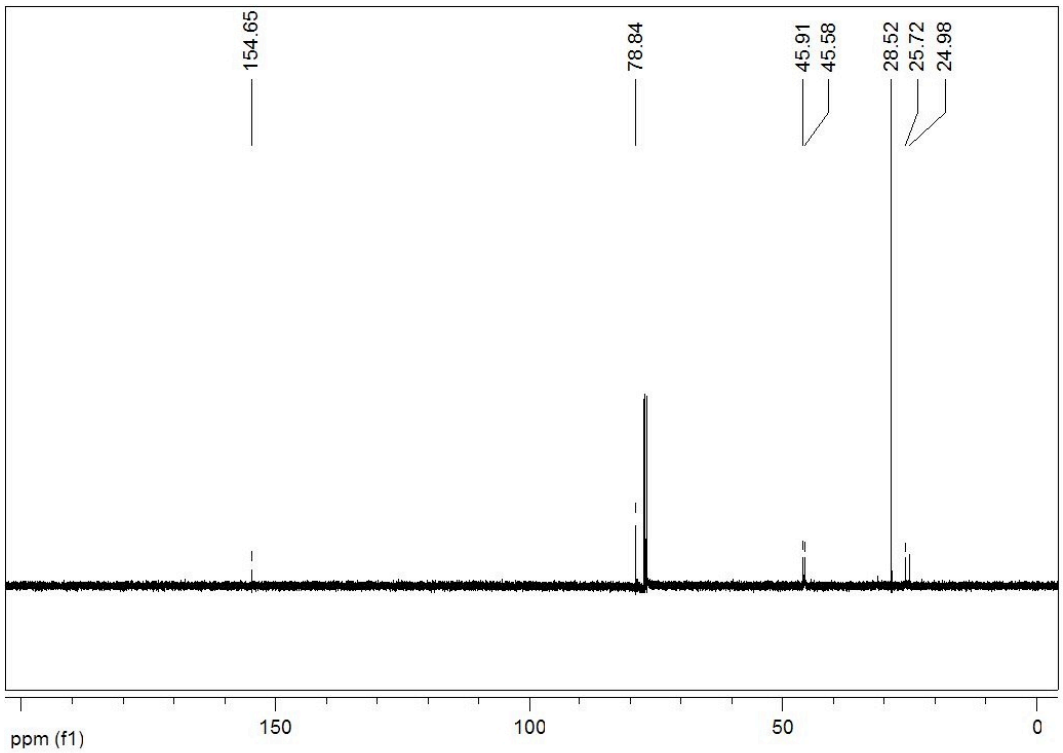
Using general procedure C, *s*-BuLi (1.02 mL of a 1.30 M solution in cyclohexanes, 1.33 mmol) and the (+)-sparteine surrogate (260 mg, 1.34 mmol) in THF (2 mL), phosphine borane **14** (139 mg, 1.02

mmol) in THF (2 mL) and benzophenone (205 mg, 1.12 mmol) in THF (1 mL) gave the crude product as a white solid. Purification by flash column chromatography on silica with 95:5 petrol-EtOAc as eluent gave alcohol (*R*)-**15** (250 mg, 78%, 91:9 er by CSP-HPLC) as a white solid, $[\alpha]_D$ −18.6 (*c* 1.15 in $CHCl_3$); HPLC: chiralcel OD (95:5 hexane-*i*-PrOH, 0.5 $mLmin^{-1}$) (*R*)-**15** 11.0 min, (*S*)-**15** 13.2 min.

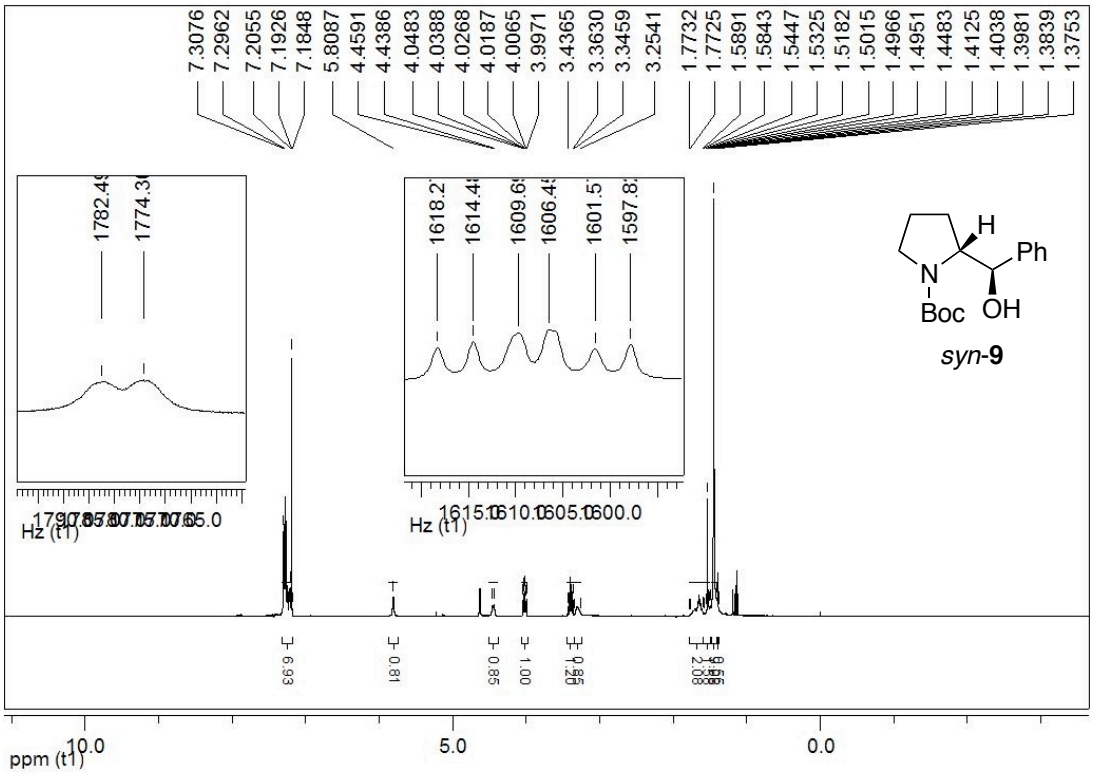
$^{1}H/^{13}C$ NMR spectra and CSP-HPLC/ data:

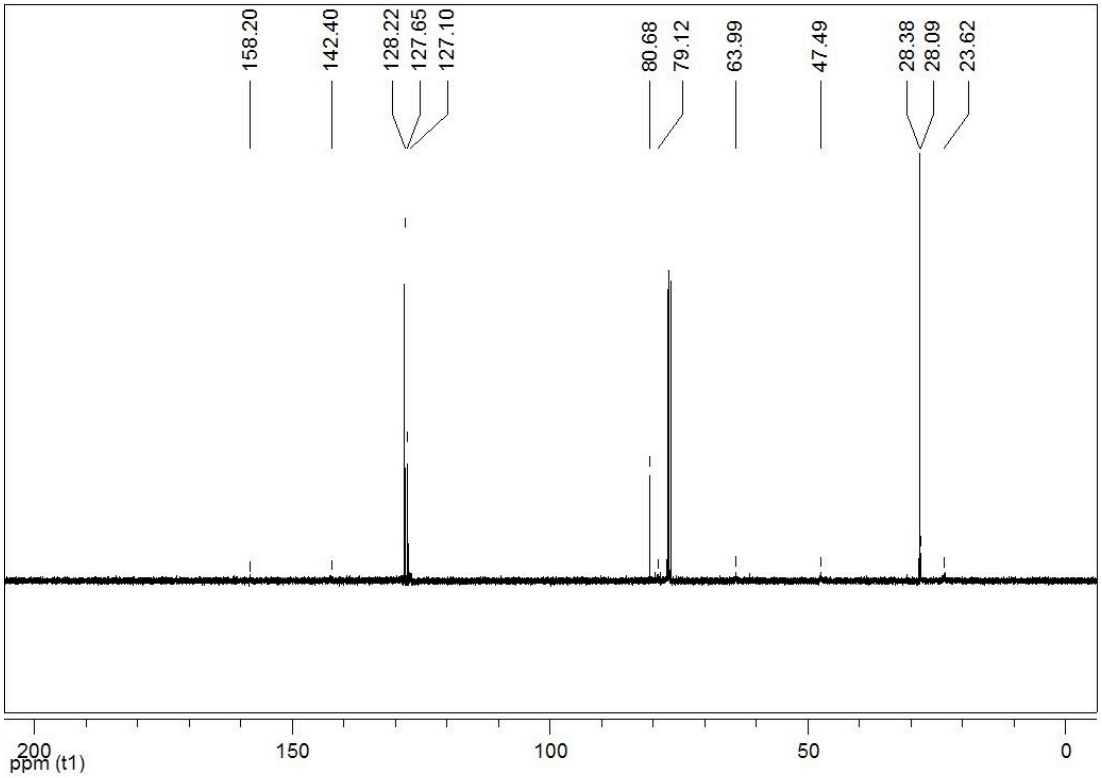
400 MHz ^{1}H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; $CDCl_3$



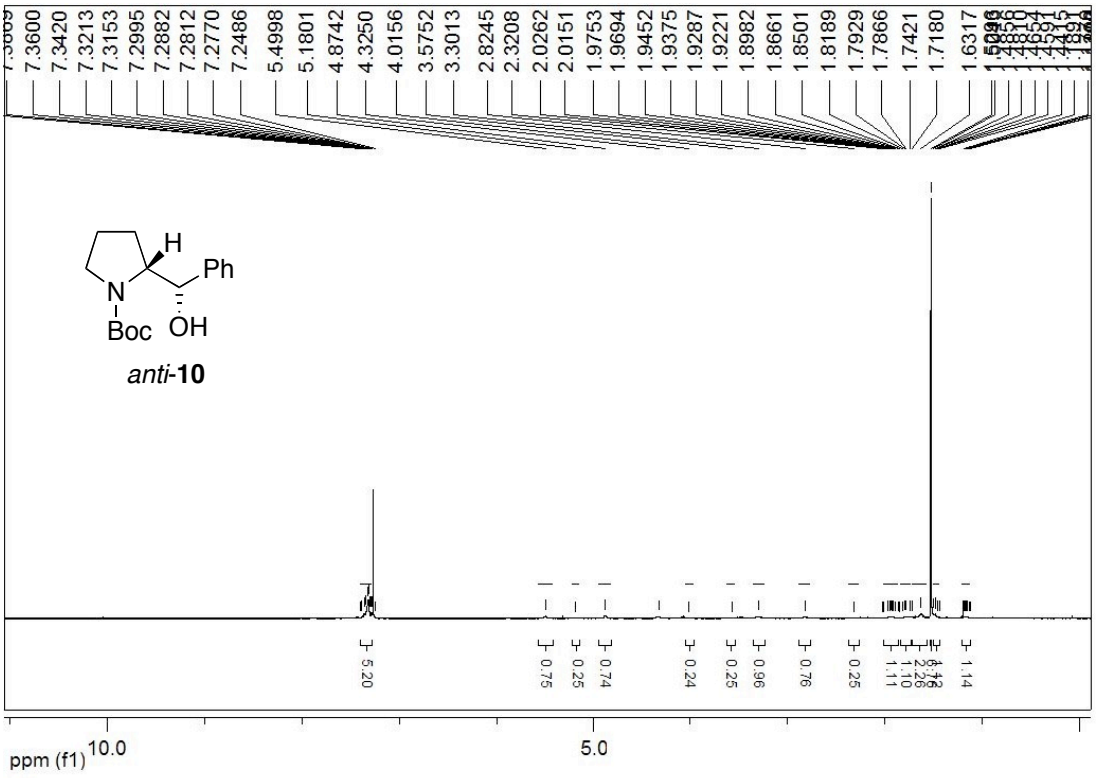


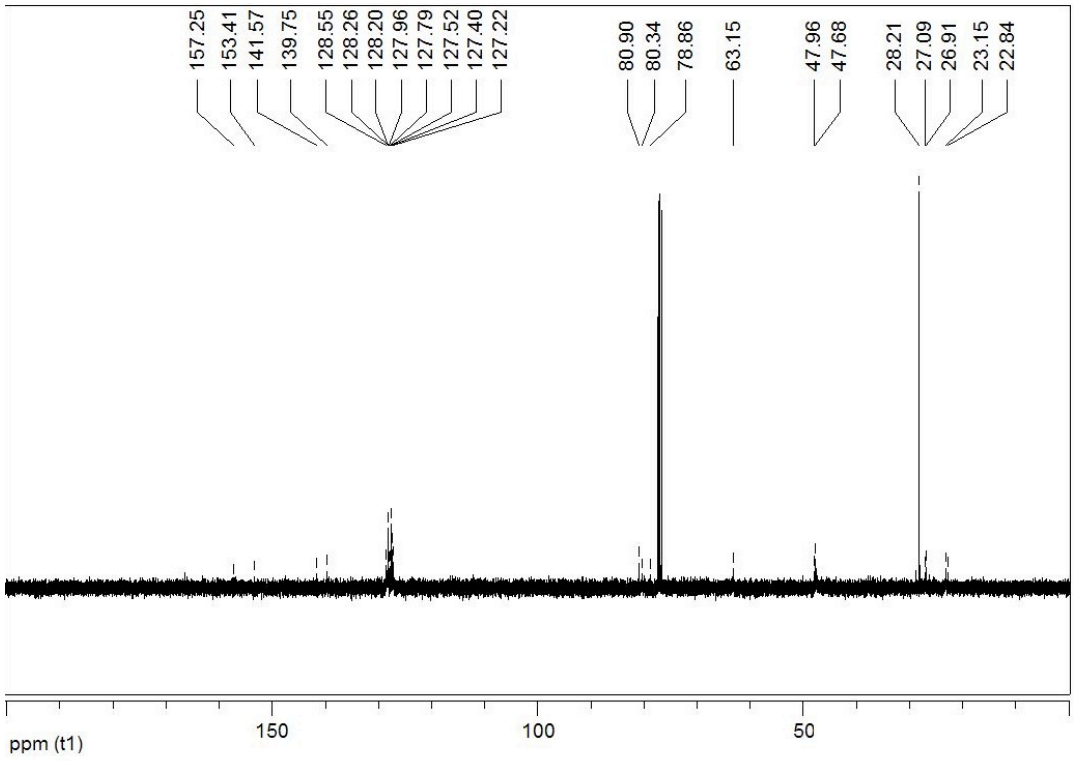
400 MHz ^{1}H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; $CDCl_3$



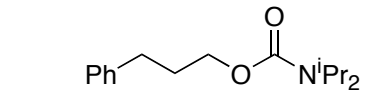


400 MHz ^{1}H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; $CDCl_3$

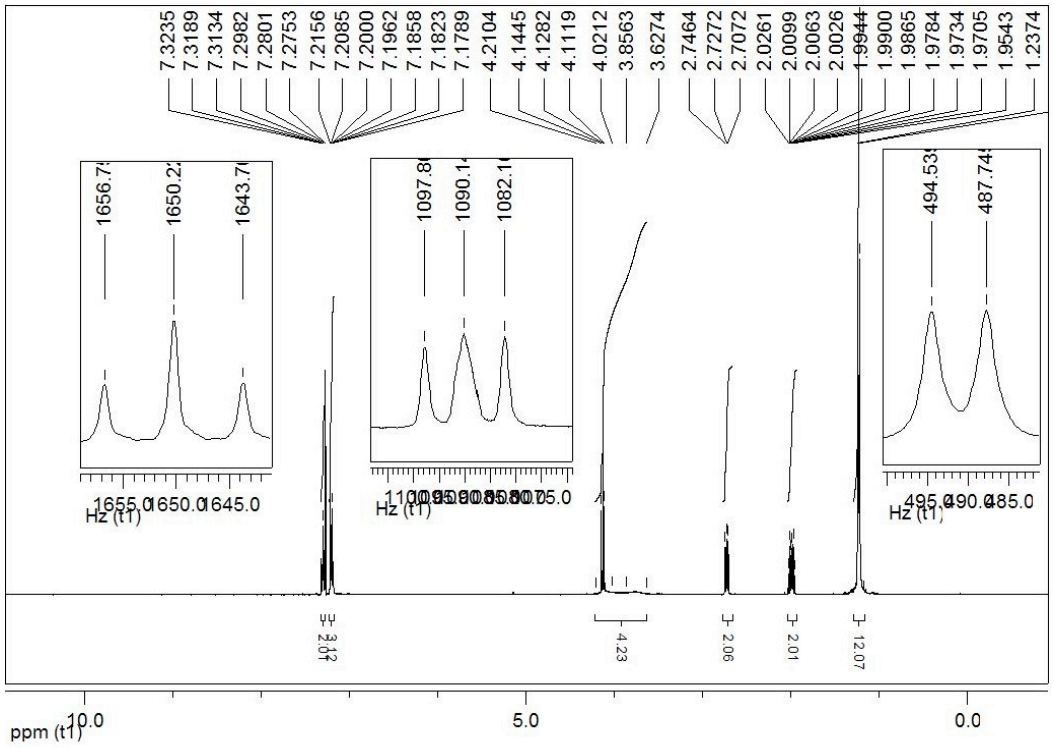


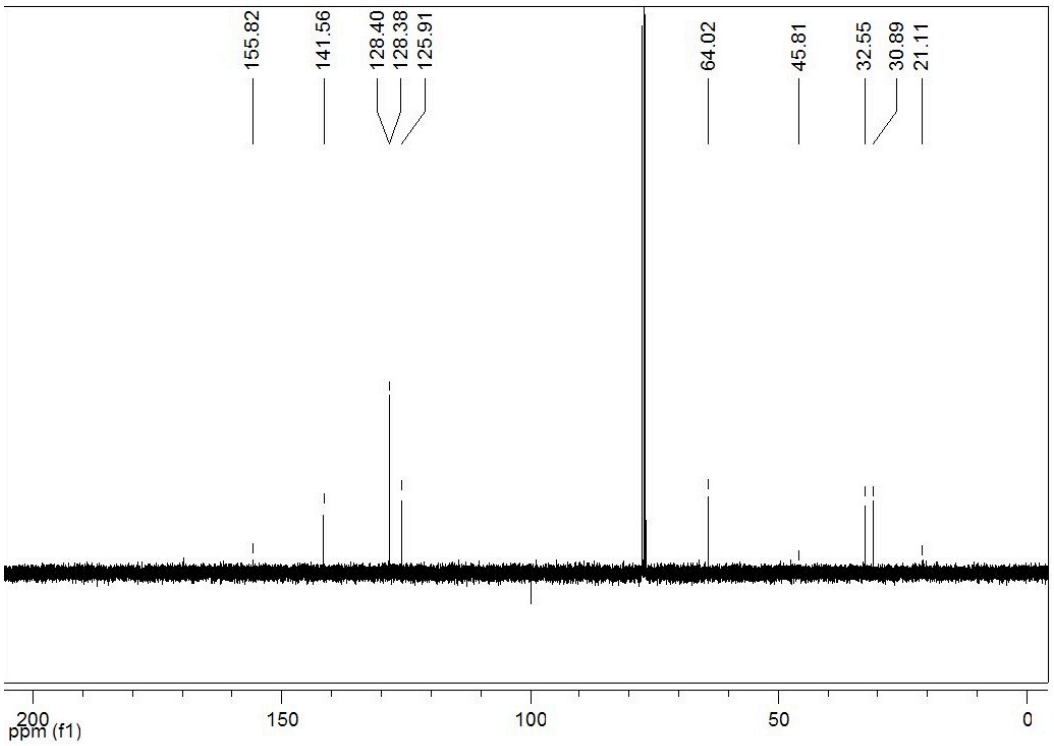


400 MHz ^{1}H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; $CDCl_3$

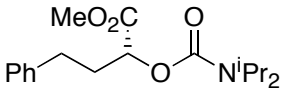


12

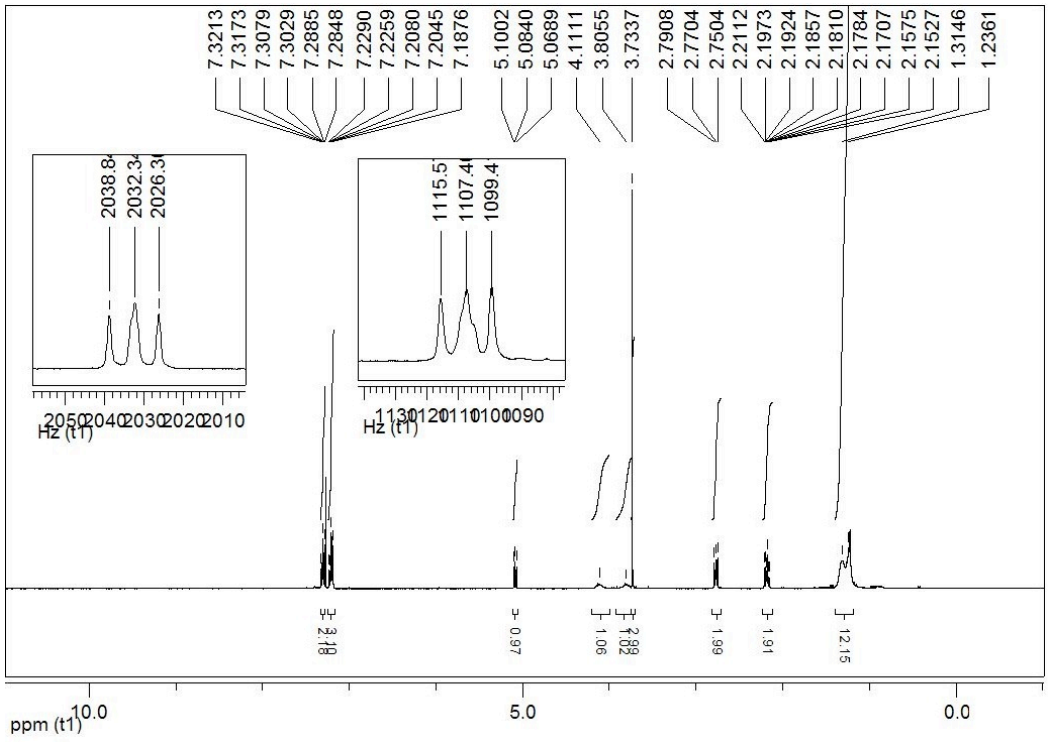


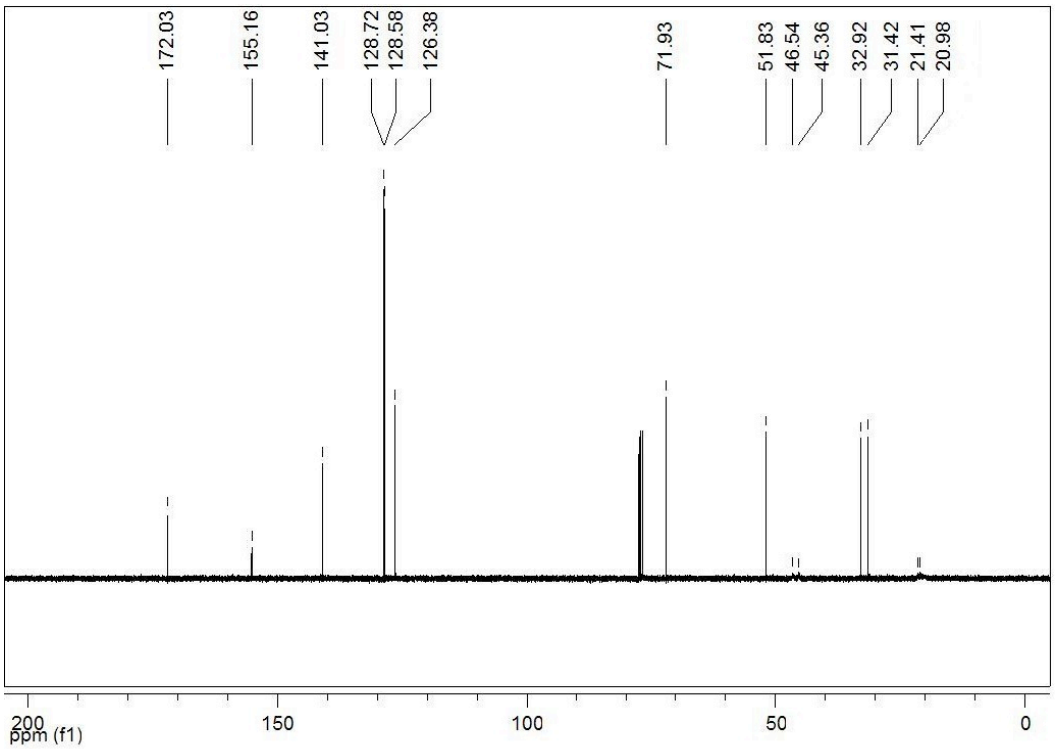


400 MHz ^{1}H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; $CDCl_3$

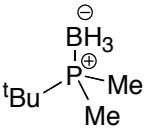


(R)-**13**





400 MHz ^{1}H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; $CDCl_3$



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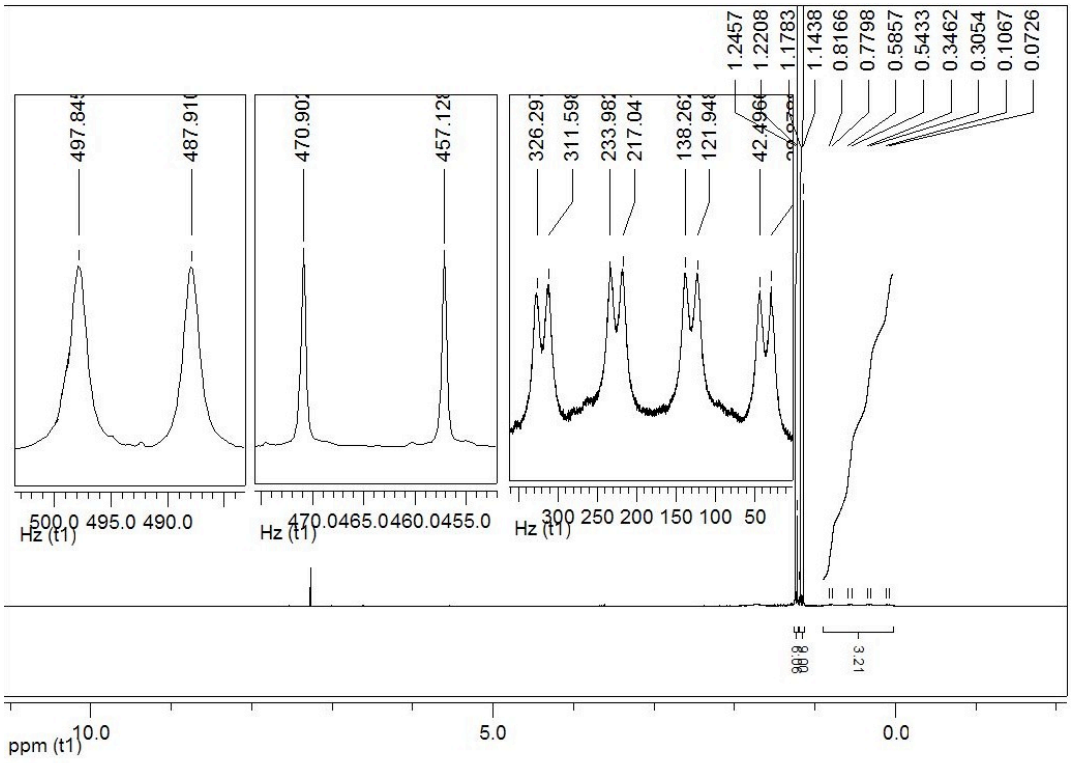
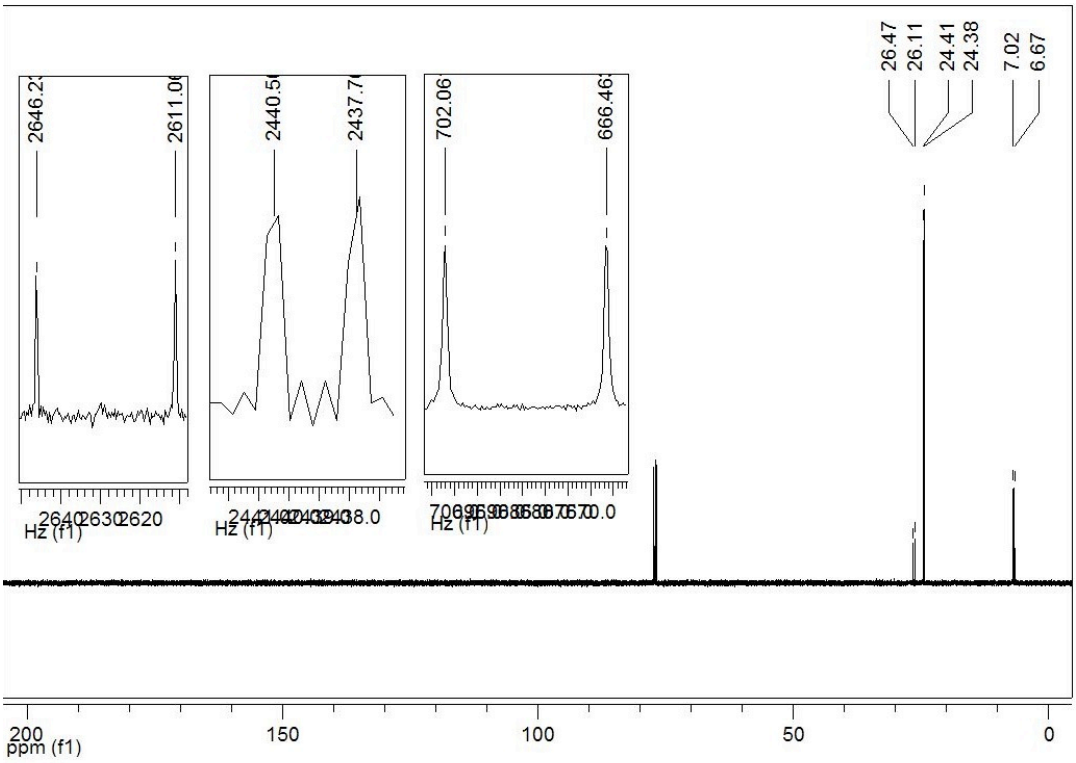
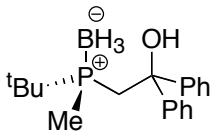
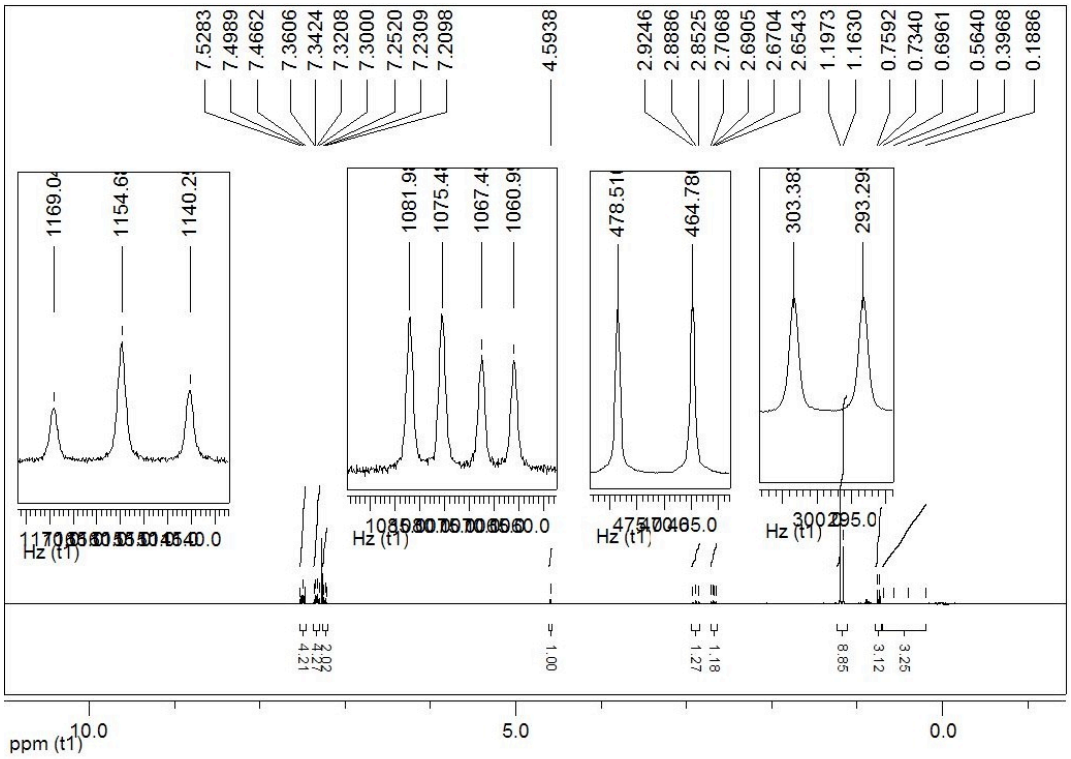


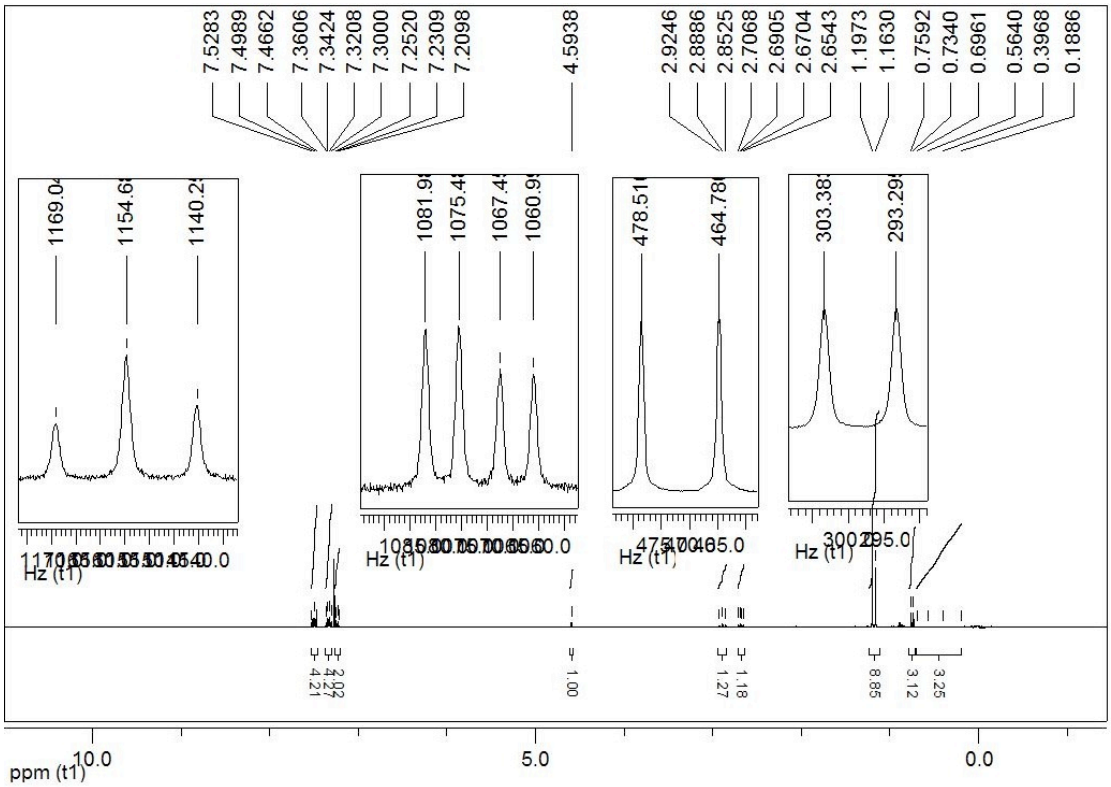


400 MHz ^{1}H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; $CDCl_3$

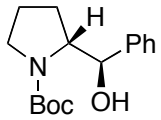


(*S*)-**15**





CSP-HPLC for hydroxy pyrrolidine (1*R*,2*R*)-**9** (97:3 er, Table 1, entry 1)



syn-**9**

Data File C:\CHEM32\1\DATA\GCS_4_354_1.D
Sample Name: GCS_4_354_1.D

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                      (modified after loading)
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    Last changed    : 09/02/2010 09:30:22 PM by Giorgio
    Sample Info     : GCS 4 354 1 (N-Boc pyrrolidine, i-PrLi/(-)-sparteine in
                       Et20, trapping with benzaldehyde
                      OD column, hexane:IPA  98:2, 0.5 mL/min, 10 bar
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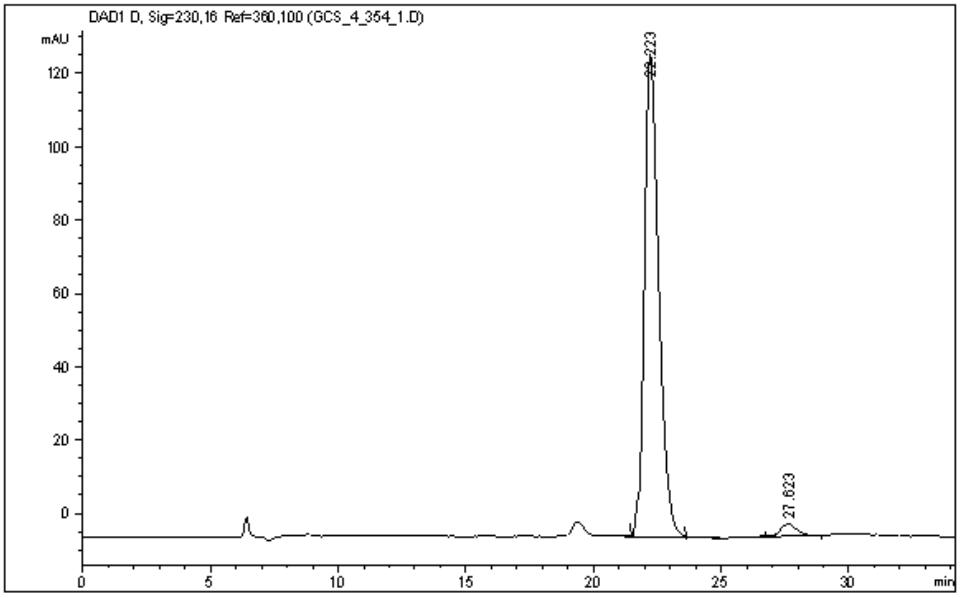


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    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 D, Sig=230,16 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
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       1  22.223 VV    0.5984 5120.18799  131.45538  97.2077
       2  27.623 BB    0.6752  147.07628    3.38279   2.7923

    Totals :                  5267.26427  134.83817
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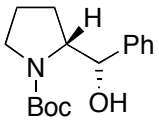
CSP-HPLC for hydroxy pyrrolidine (1*S*,2*R*)-**10** (95:5 er, Table 1, entry 1)



anti-**10**

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Data File C:\CHEM32\1\DATA\GCS_4_354_2.D
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                      (modified after loading)
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    Last changed    : 09/02/2010 10:09:41 PM by Giorgio
    Sample Info     : GCS 4 354 2 (N-Boc pyrrolidine, i-PrLi/(-)-sparteine in
                       Et2O, trapping with benzaldehyde
                      OD column, hexane:IPA  98:2, 0.5 mL/min, 10 bar
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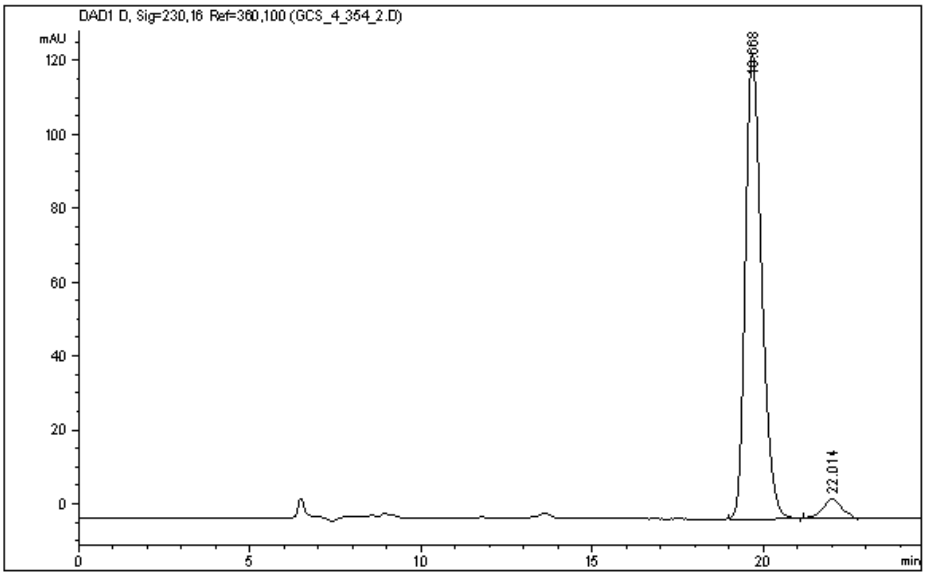


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    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 D, Sig=230,16 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
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    ----|-------|----|------|----------|----------|--------|
       1  19.668 BB    0.5115 4181.31641  125.88693  95.1808
       2  22.014 BV    0.5851  211.70790    5.35690   4.8192
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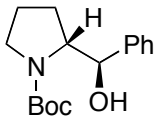
CSP-HPLC for hydroxy pyrrolidine (1*R*,2*R*)-**9** (63:37 er, Table 1, entry 4)



syn-**9**

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Sample Name: GCS_4_355_1

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    Last changed    : 07/02/2010 04:54:05 PM by Graeme
                      (modified after loading)
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    Last changed    : 07/08/2010 10:15:04 PM
                      (modified after loading)
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                      bar
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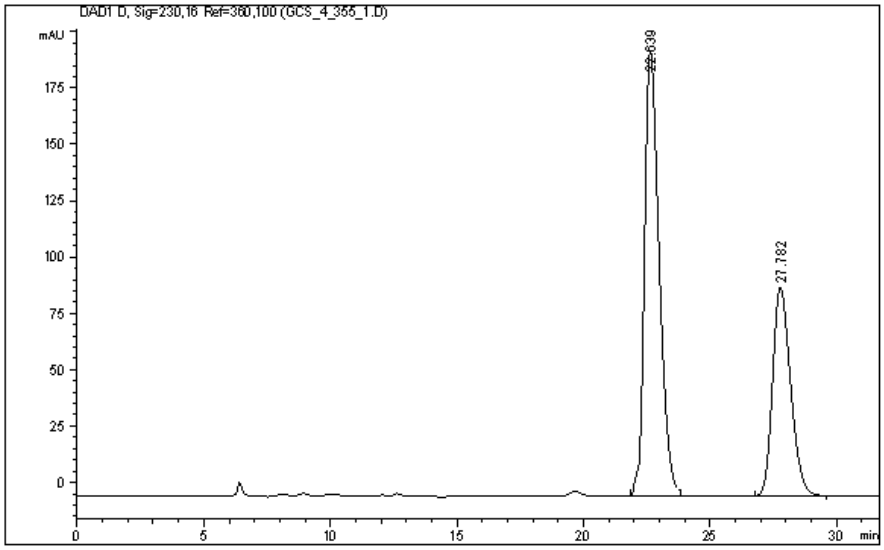


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    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 D, Sig=230,16 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
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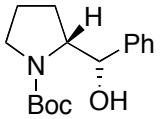
    ----|-------|----|-------|----------|----------|--------|
       1  22.639 VV    0.6119 7922.60010  197.54913  63.2253
       2  27.782 BB    0.7645 4608.14990   92.61582  36.7747

    Totals :                  1.25308e4   290.16496

    ========================================================================

Instrument 1 07/08/2010 10:18:06 PM                                Page 1 of 1
```

CSP-HPLC for hydroxy pyrrolidine (1*S*,2*R*)-**10** (60:40 er, Table 1, entry 4)



anti-**10**

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Data File C:\CHEM32\1\DATA\GCS_4_355_2.D
Sample Name: GCS_4_355_2

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    Acq. Instrument : Instrument 1                  Location : Vial 1
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    Acq. Method     : C:\CHEM32\1\METHODS\GRAEME\DUMMY.M
    Last changed    : 07/02/2010 06:08:32 PM by Giorgio
                      (modified after loading)
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    Last changed    : 07/02/2010 06:43:41 PM by Giorgio
    Sample Info     : GCS_4_355_2 OD column, 98:2 hexane:IPA, 0.5 mL/min, 10
                      bar
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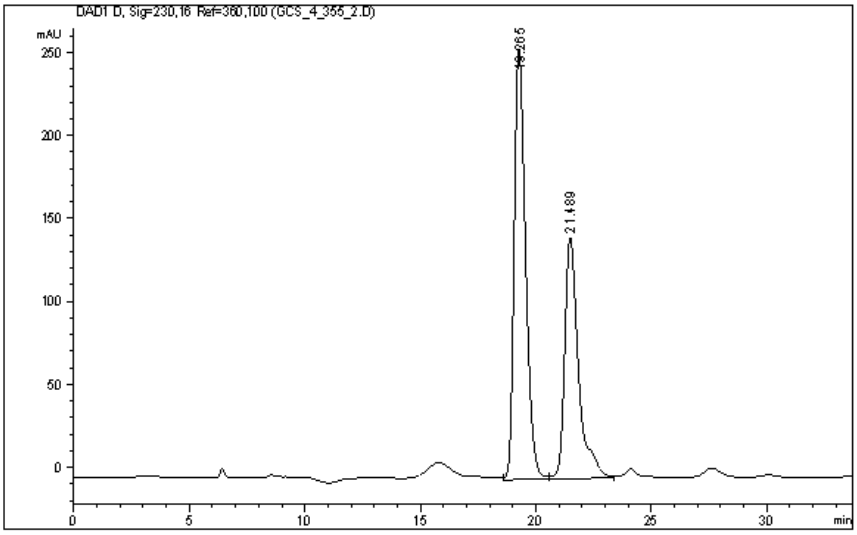


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    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 D, Sig=230,16 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
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    ----|-------|----|-------|----------|----------|--------|
       1  19.265 BV    0.5279 8893.78027  259.49634  59.5621
       2  21.489 VV    0.6243 6038.16064  145.46910  40.4379

    Totals :                  1.49319e4   404.96544

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                              *** End of Report ***

Instrument 1 07/08/2010 10:22:29 PM                          Page 1 of 1
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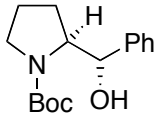
CSP-HPLC for hydroxy pyrrolidine (1*S*,2*S*)-**9** (98:2 er, Table 2, entry 1)



syn-**9**

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Data File C:\CHEM32\1\DATA\GCS_4_362_1.D
Sample Name: GCS_4_362_1.D

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    Last changed    : 09/02/2010 06:49:06 PM by Giorgio
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    Last changed    : 06/08/2010 03:57:15 PM
    Sample Info     : GCS 4 362 1 (N-Boc pyrrolidine, i-PrLi/(+)-sp surrogate
                       in Et20, trapping with benzaldehyde
                      OD column, hexane:IPA  98:2, 0.5 mL/min, 10 bar
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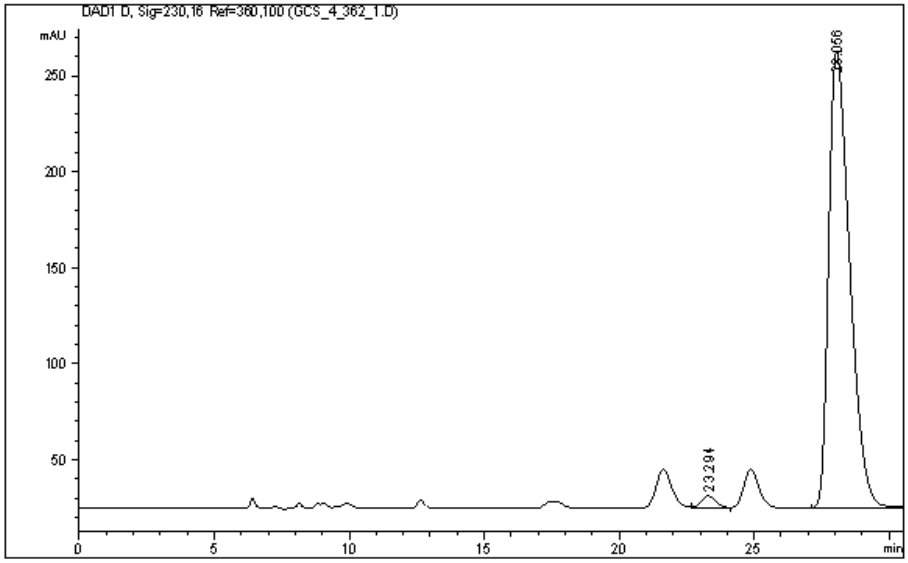


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    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 D, Sig=230,16 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  23.294 VV    0.5690  241.05862    6.37705   1.8377
       2  28.056 BBA   0.8403 1.28763e4   237.58618  98.1623

    Totals :                  1.31174e4   243.96323

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Instrument 1 07/08/2010 10:25:46 PM                          Page 1 of 1
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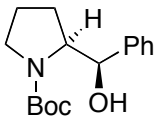
CSP-HPLC for hydroxy pyrrolidine (1*R*,2*S*)-**10** (95:5 er, Table 2, entry 1)



anti-**10**

Data File C:\CHEM32\1\DATA\GCS_4_362_2.D
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    Last changed    : 09/02/2010 08:53:34 PM by Giorgio
    Sample Info     : GCS 4 362 2 (N-Boc pyrrolidine, i-PrLi/(+)-sp surrogate
                       in Et20, trapping with benzaldehyde
                      OD column, hexane:IPA  98:2, 0.5 mL/min, 10 bar
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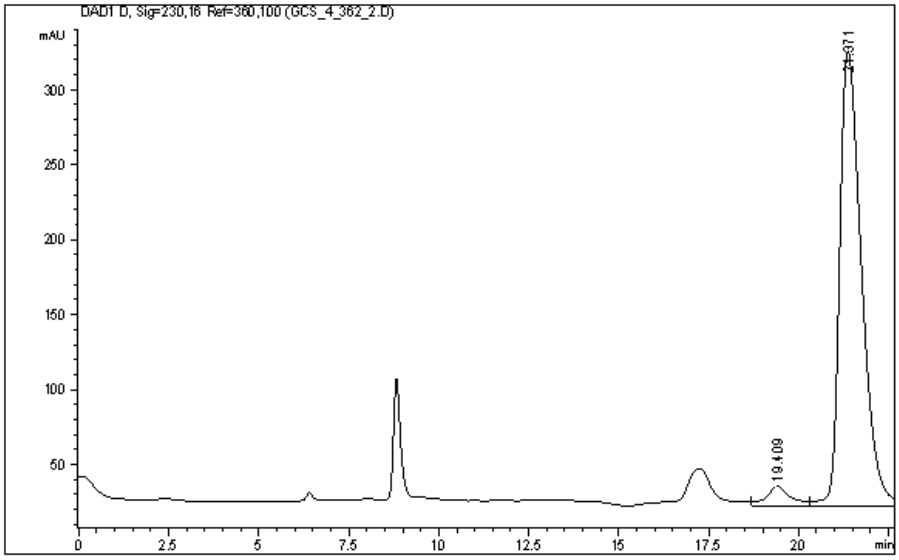


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    ======================================================================

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    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 D, Sig=230,16 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  19.409 BV    0.6603  610.57922   12.99093   4.5665
       2  21.371 VBA   0.6469 1.2760le4   303.26263  95.4335

    Totals :                  1.33707e4   316.25356

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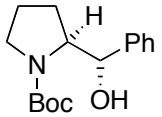
Instrument 1 07/08/2010 10:26:58 PM Page 1 of 1

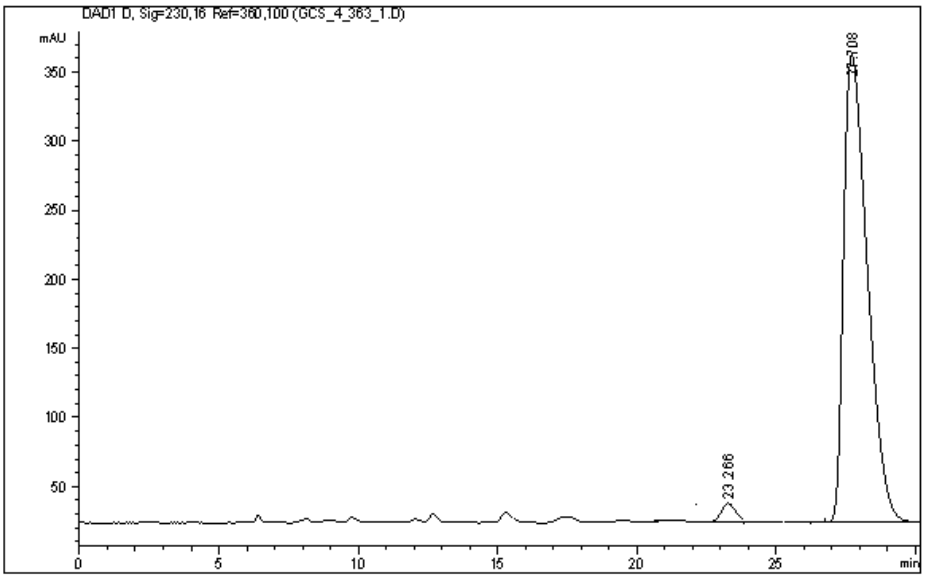
CSP-HPLC for hydroxy pyrrolidine (1*S*,2*S*)-**9** (97:3 er, Table 2, entry 4)



syn-**9**

Data File C:\CHEM32\1\DATA\GCS_4_363_1.D
Sample Name: GCS_4_363_1.D

```
    ================================================================
    Acq. Operator   : Giorgio
    Acq. Instrument : Instrument 1                  Location : Vial 1
    Injection Date  : 09/02/2010 04:29:48 PM
    Acq. Method     : C:\CHEM32\1\METHODS\GRAEME\DUMMY.M
    Last changed    : 09/02/2010 03:50:23 PM by Graeme
                      (modified after loading)
    Analysis Method : C:\CHEM32\1\DATA\GCS 4 363 1.D\DA.M (DUMMY.M)
    Last changed    : 09/02/2010 04:59:47 PM by Giorgio
    Sample Info     : GCS 4 363 1 (N-Boc pyrrolidine, i-PrLi/(+)-sp surrogate
                       in THF, trapping with benzaldehyde)
                      OD column, hexane:IPA  98:2, 0.5 mL/min, 9 bar
```




```
    ================================================================
                            Area Percent Report
    ================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 D, Sig=230,16 Ref=360,100

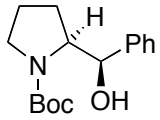
    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  23.266 VV    0.5821  526.16022   14.01259   2.5511
       2  27.708 BBA   0.9242 2.00986e4   338.74274  97.4489

    Totals :                  2.06248e4   352.75533


    ================================================================
```

Instrument 1 07/08/2010 09:57:03 PM Page 1 of 1

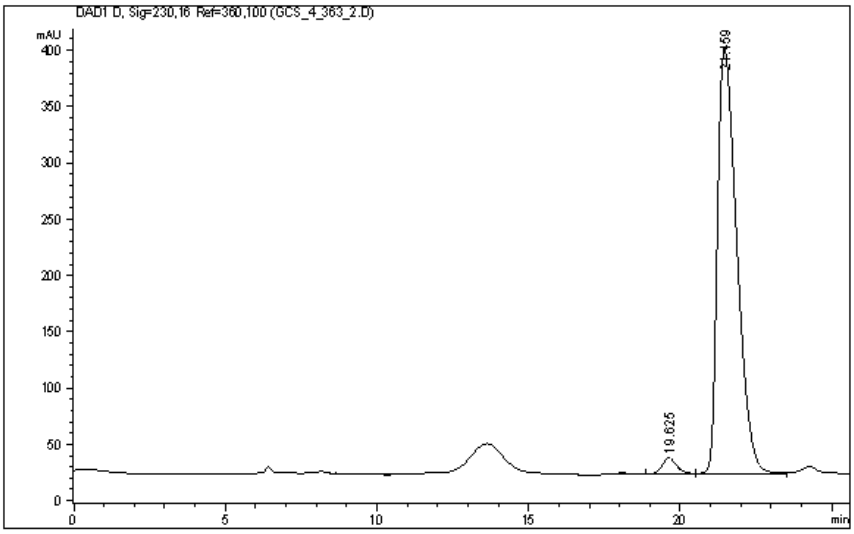
CSP-HPLC for hydroxy pyrrolidine (1*R*,2*S*)-**10** (97:3 er, Table 2, entry 4)



anti-**10**

```
Data File C:\CHEM32\1\DATA\GCS_4_363_2.D
Sample Name: GCS_4_363_2.D

    ================================================================
    Acq. Operator   : Giorgio
    Acq. Instrument : Instrument 1                  Location : Vial 1
    Injection Date  : 09/02/2010 05:05:59 PM
    Acq. Method     : C:\CHEM32\1\METHODS\GRAEME\DUMMY.M
    Last changed    : 09/02/2010 04:59:48 PM by Giorgio
                      (modified after loading)
    Analysis Method : C:\CHEM32\1\DATA\GCS 4 363 2.D\DA.M (DUMMY.M)
    Last changed    : 09/02/2010 05:31:23 PM by Giorgio
    Sample Info     : GCS 4 363 2 (N-Boc pyrrolidine, i-PrLi/(+)-sp surrogate
                       in THF, trapping with benzaldehyde)
                      OD column, hexane:IPA  98:2, 0.5 mL/min, 9 bar
```




```
    ================================================================
                           Area Percent Report
    ================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs

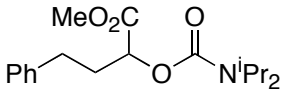

    Signal 1: DAD1 D, Sig=230,16 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  19.625 BV    0.4925  453.21350   14.04364   2.6315
       2  21.459 VV    0.6918 1.67694e4   376.39514  97.3685

    Totals :                  1.72226e4   390.43878

    ================================================================
```

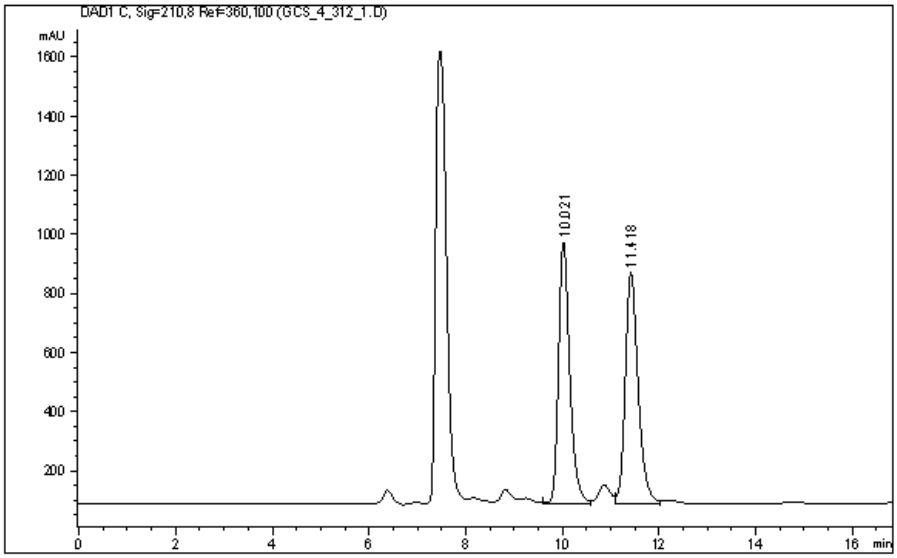
CSP-HPLC for methyl ester *rac*-**13** (50:50 er)



rac-**13**

```
Data File C:\CHEM32\1\DATA\GCS_4_312_1.D
Sample Name: GCS_4_312_1

    ========================================================================
    Acq. Operator   : Giorgio
    Acq. Instrument : Instrument 1                    Location : Vial 1
    Injection Date  : 09/10/2009 11:52:47 AM
    Acq. Method     : C:\CHEM32\1\METHODS\JGR\DUMMY.M
    Last changed    : 07/10/2009 06:41:47 PM by Giorgio
    Analysis Method : C:\CHEM32\1\DATA\GCS 4 312 1.D\DA.M (DUMMY.M)
    Last changed    : 09/10/2009 12:09:54 PM by Giorgio
    Sample Info     : GCS 4 312 1, (0 alkyl carbamate, racemic lithiation/tra
                      pping in THF)
                      OD column 95:5 Hexane -IPA 0.5 mL/min
```




```
    ========================================================================
                               Area Percent Report
    ========================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 C, Sig=210,8 Ref=360,100

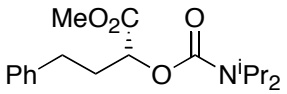
    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  10.021 VV    0.2471 1.43925e4   887.89490  49.8141
       2  11.418 VV    0.2804 1.44999e4   781.76660  50.1859

    Totals :                  2.88925e4  1669.66150

    ========================================================================
                               *** End of Report ***

Instrument 1 13/08/2010 12:36:20 PM                          Page 1 of 1
```

CSP-HPLC for methyl ester (*R*)-**13** (61:39 er, Table 3, entry 2)

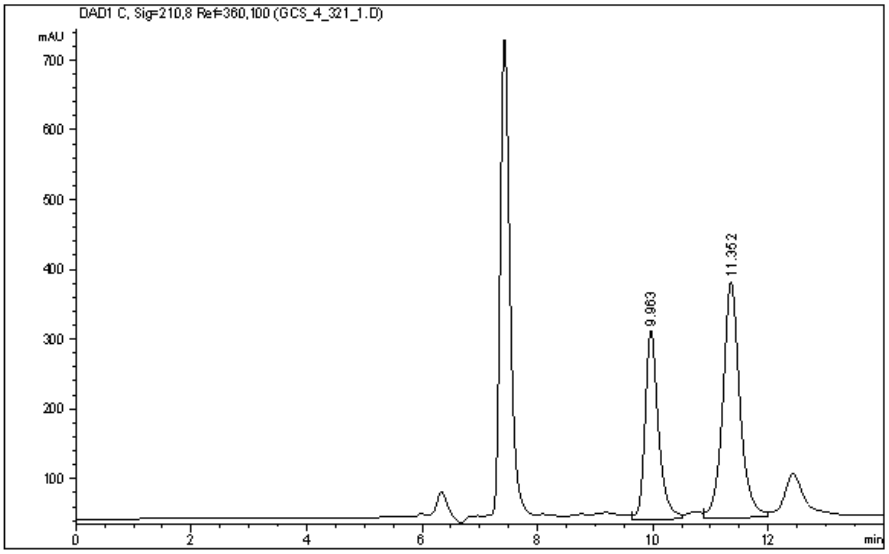


(R)-**13**

Data File C:\CHEM32\1\DATA\GCS_4_321_1.D
Sample Name: GCS_4_321_1

```
    ======================================================================
    Acq. Operator   : Giorgio
    Acq. Instrument : Instrument 1                  Location : Vial 1
    Injection Date  : 20/10/2009 11:24:24 AM
    Acq. Method     : C:\CHEM32\1\METHODS\GRAEME\DUMMY.M
    Last changed    : 20/10/2009 10:54:12 AM by Johannes
                      (modified after loading)
    Analysis Method : C:\CHEM32\1\DATA\GCS 4_321_1.D\DA.M (DUMMY.M)
    Last changed    : 22/10/2009 04:15:21 PM
                      (modified after loading)
    Method Info     : t-butyldimethylphosphine sulfide trapped with pivaldehyde diastereomer
                      2

    Sample Info     : GCS 4 321 1, (o-alkyl carbamate, s-BuLi/(-)-sp in THF,
                      trapping with methyl chloroformate)
                      OD column 95:5 Hexane -IPA 0.5 mL/min
```



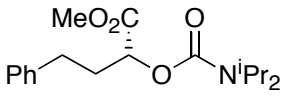

```
    ======================================================================
                              Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 C, Sig=210,8 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1   9.963 VV    0.2421 4360.53174  270.44171  38.5792
       2  11.352 VV    0.3034 6942.28223  338.37476  61.4208
```

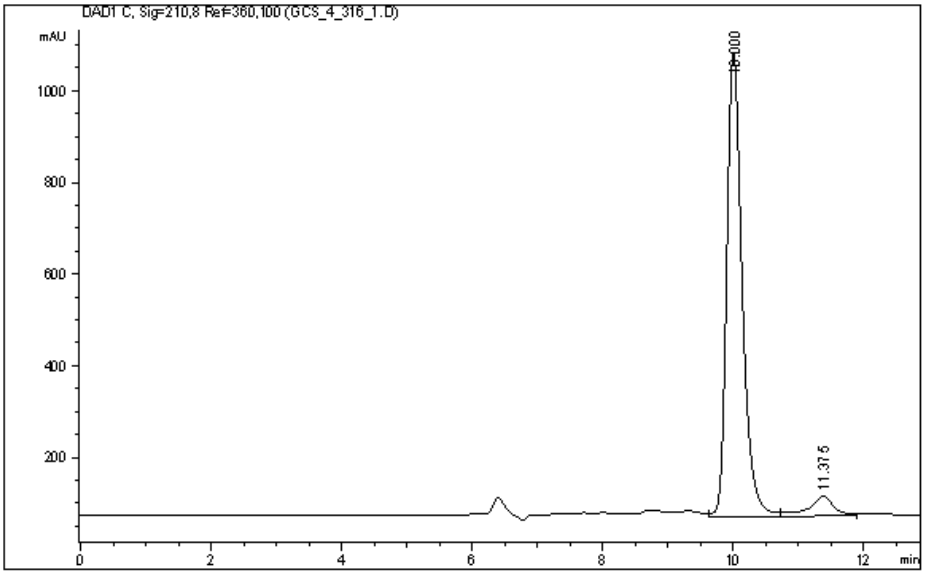
CSP-HPLC for methyl ester (*R*)-**13** (93:7 er, Table 3, entry 5)



(R)-**13**

```
Data File C:\CHEM32\1\DATA\GCS_4_316_1.D
Sample Name: GCS_4_316_1

    ======================================================================
    Acq. Operator   : Giorgio
    Acq. Instrument : Instrument 1                  Location : Vial 1
    Injection Date  : 13/10/2009 12:13:18 AM
    Acq. Method     : C:\CHEM32\1\METHODS\JGR\DUMMY.M
    Last changed    : 13/10/2009 12:07:33 AM by Giorgio
                      (modified after loading)
    Analysis Method : C:\CHEM32\1\DATA\GCS 4 316 1.D\DA.M (DUMMY.M)
    Last changed    : 13/10/2009 12:26:13 AM by Giorgio
    Sample Info     : GCS 4 316 1 (O-alkyl carbamate, s-BuLi/(+)-sp surrogate
                       in THF, trapping with methyl chloroformate)
                      OD column 95:5 Hexane -IPA 0.5 mL/min
```




```
    ======================================================================
                           Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 C, Sig=210,8 Ref=360,100

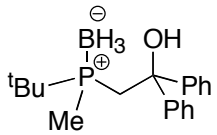
    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  10.000 VV    0.2506 1.67252e4  1013.21417  93.2751
       2  11.375 VV    0.3732 1205.84863   44.63292   6.7249

    Totals :                  1.79310e4  1057.84710

    ======================================================================

Instrument 1 16/10/2009 05:41:32 AM                          Page 1 of 1
```

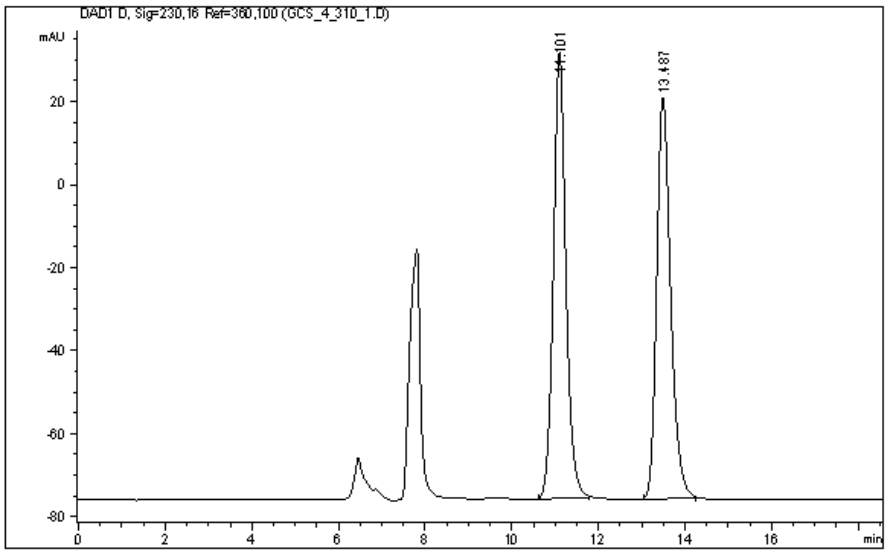
CSP-HPLC for hydroxy phosphine borane *rac*-**15** (50:50 er, Table 4, entry 2)



rac-**15**

```
Data File C:\CHEM32\1\DATA\GCS_4_310_1.D
Sample Name: GCS_4_310_1

    ======================================================================
    Acq. Operator   : Giorgio
    Acq. Instrument : Instrument 1                  Location : Vial 1
    Injection Date  : 07/10/2009 05:02:53 PM
    Acq. Method     : C:\CHEM32\1\METHODS\JGR\DUMMY.M
    Last changed    : 07/10/2009 04:59:11 PM by Giorgio
                      (modified after loading)
    Analysis Method : C:\CHEM32\1\DATA\GCS 4 310 1.D\DA.M (DUMMY.M)
    Last changed    : 07/10/2009 05:21:20 PM by Giorgio
    Sample Info     : GCS 4 310 1, (phospine borane, s-BuLi/(-)-sparteine in
                      THF trapping with benzophenone)
                      OD column 95:5 Hexane -IPA 0.5 mL/min
```




```
    ======================================================================
                              Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 D, Sig=230,16 Ref=360,100

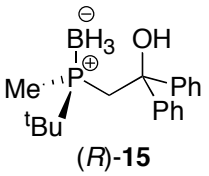
    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  11.101 BB    0.2979 2154.12622  107.46767  49.8565
       2  13.487 BB    0.3414 2166.52515   96.70338  50.1435

    Totals :                  4320.65137  204.17105

    ======================================================================

Instrument 1 22/10/2009 05:21:31 PM                          Page 1 of 1
```

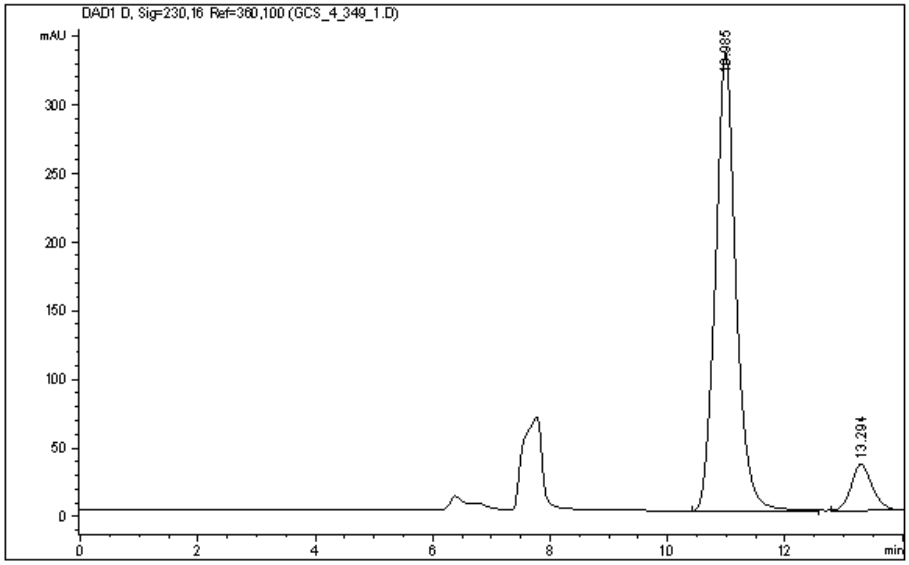
CSP-HPLC for hydroxy phosphine borane (*R*)-**15** (91:9 er, Table 4, entry 5)



(*R*)-**15**

```
Data File C:\CHEM32\1\DATA\GCS_4_349_1.D
Sample Name: GCS_4_349_1

    ========================================================================
    Acq. Operator   : Giorgio
    Acq. Instrument : Instrument 1                    Location : Vial 1
    Injection Date  : 13/01/2010 11:04:48 AM
    Acq. Method     : C:\CHEM32\1\METHODS\SOS-METHOD A.M
    Last changed    : 13/01/2010 10:00:17 AM by ZM
                      (modified after loading)
    Analysis Method : C:\CHEM32\1\DATA\GCS 4_349_1.D\DA.M (SOS-METHOD A.M)
    Last changed    : 06/08/2010 03:30:02 PM
                      (modified after loading)
    Sample Info     : GCS 4 349 1 (phosphine borane, s-BuLi/(+)-sp surrogate
                      in THF
                      OD column 95:5 Hex:IPA, 0.5 ml/min 11 bar
```




```
    ========================================================================
                              Area Percent Report
    ========================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 D, Sig=230,16 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  10.985 BB    0.3563 8147.12695  334.35358  90.6407
       2  13.294 BBA   0.3744  841.24713   33.79466   9.3593

    Totals :                  8988.37408  368.14824

Instrument 1 06/08/2010 03:34:52 PM                          Page 1 of 2
```

References for supporting information:

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