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Synthesis and kinetic resolution of *N*-Boc-2-arylpiperidines

Edward J. Cochrane, Daniele Leonori, Lorraine A. Hassall and Iain Coldham*

Supplementary Information (SI)

Contents

1. Experimental details

1.1 General

All reagents were obtained from commercial suppliers and were used without further purification unless otherwise specified. Solvents were purified using a Grubbs dry solvent system (model SPS-200-6). Petrol refers to petroleum ether (b.p. 40–60 °C). Reactions were carried out under N_2 using oven-dried and/or flame-dried glassware. Thin layer chromatography was performed on silica plates and visualised by UV irradiation at 254 nm or by staining with an alkaline $KMnO_4$ dip. Column chromatography was performed using silica gel (40–63 micron mesh). Infrared spectra were recorded on Perkin Elmer Spectrum RX Fourier Transform IR System. In situ React-IR infra-red spectroscopic monitoring was performed on a Mettler-Toledo React-IR 4000 spectrometer equipped with a diamond-tipped (DiComp) probe. ^{1}H NMR spectra were either recorded on a Bruker AC400 (400 MHz) or Bruker AC250 (250 MHz) instrument. Chemical shifts are reported in ppm with respect to the residual solvent peaks, with multiplicities given as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Coupling constants, *J*, are quoted to the nearest 0.5 Hz. ^{13}C NMR were recorded on the above instrument at either 100 MHz or 63 MHz. Low and high resolution (accurate mass) mass spectra were recorded on a Walters LCT instrument for Electro–Spray (ES). Chiral stationary phase HPLC was performed on a Gilson instrument and a multiple wavelength, UV/Vis diode array detector; integration was performed at 254 nm.

1.2 Experimental Procedures and Characterisation Data

General Procedure A: Synthesis of (±)-*N*-Boc-2-arylpiperidines 3 from 5-bromovaleronitrile (Scheme 2)

To a 0.1 M solution of 5-bromovaleronitrile (1.0 eq.) in PhMe at 0 ºC was added dropwise the aryllithium (formed *via* bromine–lithium exchange of the relevant aryl bromide with *n*-BuLi unless otherwise stated) (1.2 eq.). After 15 min, the mixture was warmed to room temp. and then aqueous HCl (2 M) was added. The phases were separated and the aqueous phase was extracted with CH_2Cl_2. The aqueous phase was basified to pH 9–10 using aqueous NaOH (2 M) and then was extracted with CH_2Cl_2. The organic phases were combined, dried ($MgSO_4$), filtered and the solvent was evaporated to give the crude imine.

To a solution of the crude imine in MeOH at 0 ºC was added $NaBH_4$ (4.0 eq.) portion-wise. After 30 min, the mixture was warmed to room temp. and then aqueous HCl (2 M) was added. The phases were separated and the aqueous phase was extracted with CH_2Cl_2. The aqueous phase was basified to pH 9–10 using aqueous NaOH (2 M) and then was extracted with CH_2Cl_2. The organic phases were combined, dried ($MgSO_4$), filtered and the solvent was evaporated to give the crude amine.

To a solution of Boc_2O (1.2 eq.) in THF was added a solution of the crude amine in THF at room temp. After 10 min, the mixture was partitioned between 10% aqueous $NaHCO_3$ and Et_2O. The phases were separated and the aqueous phase was extracted with Et_2O. The combined organic phases were washed with brine, dried ($MgSO_4$), filtered and the solvent was evaporated. The crude product was purified by column chromatography on silica gel to give the carbamate **3a**–**g**.

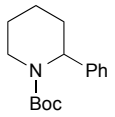
General Procedure B: Kinetic resolution of piperidines 3 (Scheme 4)

n-BuLi (0.7 eq., 2.5 M solution in hexanes) was added to a 0.25 M solution of the *N*-Boc-2-aryl piperidine (1.0 eq.) and (–)-sparteine (0.7 eq.) or (+)-sparteine surrogate (0.7 eq.) in PhMe at –78 ºC. After 3 h, the electrophile (1.5 eq.) was added. The mixture was allowed to warm to room temperature over 16 h then aqueous NH_4Cl (1 mL) was added. Water was added and the mixture was extracted with Et_2O. The organic phases were washed with brine, dried ($MgSO_4$), filtered and the solvent was evaporated. The crude product was purified by column chromatography on silica gel to give the carbamate **3a**–**g**.

General Procedure C: Lithiation–substitution of piperidines 3b–d (Scheme 6)

n-BuLi (1.1 equiv., 2.5 M solution in hexanes) was added dropwise to a stirred solution of the *N*-Boc-2-arylpiperidine **3b**–**d** (1 equiv.) in THF (~4 mL per mmol **3**) at –78 °C. After 5 min, the electrophile (1.5 equiv.) was added dropwise. The mixture was allowed to warm to room temperature over 16 h then aqueous NH_4Cl (1 mL) was added. Water was added and the mixture was extracted with Et_2O. The organic phases were washed with brine, dried ($MgSO_4$), filtered and the solvent was evaporated. The crude product was purified by column chromatography on silica gel to give the carbamate **4b**–**4d**, **5b**–**5c**, **7b**.

_N_-Boc-2-phenylpiperidine 3a



3a

For racemic **3a**:

Using general procedure A, 5-bromovaleronitrile (2.3 mL, 20 mmol), PhLi (24 mL, 24 mmol), $NaBH_4$ (3.1 g, 80 mmol), di-*tert*-butyl dicarbonate (4.3 g, 20 mmol) gave, after purification on silica gel, eluting with petrol–EtOAc (90:10), the piperidine (±)-**3a** (3.1 g, 60%) as an oil which solidified on standing; m.p. 79–81 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.40–7.30 (2H, m), 7.26–7.20 (3H, m), 5.43 (1H, br s), 4.06 (1H, d, *J* 13.5 Hz), 2.72–2.82 (1H, m), 2.32 (1H, dd, *J* 13.5, 2.5 Hz), 1.95–1.83 (1H, m), 1.65–1.36 (4H, m), 1.47 (9H, s); data as reported.[1]

Resolution between the enantiomers of the piperidine **3a** was achieved using a Beckman system fitted with a Phenomenex Lux Cellulose-2 column (250 mm × 460 mm i.d.) as the stationary phase with a mixture of *n*-hexane: ^{i}PrOH (99:1 v/v) as the mobile phase at a flow rate of 1 mL·min^{-1}; ambient temperature, detection by UV absorbance at 254 nm. Injection volume 20 μL of the sample prepared in a 2 g·L^{-1} solution of the eluent. Under these conditions, the components were eluted at 6.8 min (*R*) and 19.4 min (*S*).

For (*R*)-**3a**:

Using general procedure B, piperidine (±)-**3a** (200 mg, 0.77 mmol), *n*-BuLi (0.22 mL, 0.54 mmol, 2.5 M in hexanes), (–)-sparteine (126 mg, 0.54 mmol) and EtOCOCl (0.11 mL, 1.16 mmol) gave, after column chromatograph on silica gel, eluting with petrol–EtOAc (90:10), the piperidine **3a** as an amorphous solid (91 mg, 45%); m.p. 95–97 ºC, lit.[2] for (*R*)-enantiomer: m.p. 78–80 °C, lit.[3] for (*R*)-enantiomer: m.p. 112–114 °C; $[\alpha]_D^{23}$ +84.0 (1.0, $CHCl_3$), lit.[2] for (*R*)-enantiomer: $[\alpha]_D^{23}$ +83.7 (0.98, $CHCl_3$), lit.[3] for (*R*)-enantiomer: $[\alpha]_D^{20}$ +114.8 (1.0, acetone). The enantiomer ratio was determined by chiral stationary phase (CSP) HPLC as described above; er (*R*:*S*) 96:4.

For (*S*)-**3a**:

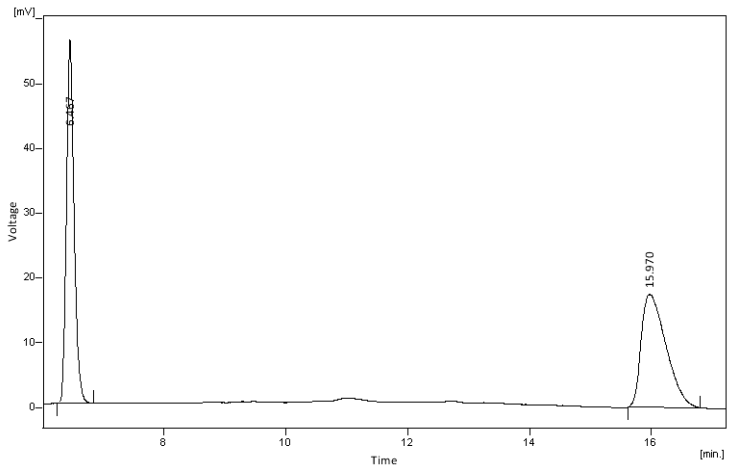
Using general procedure B, piperidine (±)-**3a** (150 mg, 0.57 mmol), *n*-BuLi (0.16 mL, 0.40 mmol, 2.5 M in hexanes), (+)-sparteine surrogate[4] (78 mg, 0.40 mmol) and EtOCOCl (0.08 mL, 0.86 mmol) gave, after column chromatograph on silica gel, eluting with petrol–EtOAc (90:10), the piperidine **3a** as an amorphous solid (64 mg, 43%); m.p. 94–96 ºC, lit.[2] for (*R*)-enantiomer: m.p. 78–80 °C, lit.[5] for (*S*)-enantiomer: m.p. 106–108 °C; $[\alpha]_D^{23}$ –81.0 (1.0, $CHCl_3$), lit.[2] for (*R*)-enantiomer: $[\alpha]_D^{23}$ +83.7 (0.98, $CHCl_3$), lit.[6] for (*S*)-enantiomer: $[\alpha]_D^{21}$ –90.0 (1.0, $CHCl_3$), lit.[7] for (*S*)-enantiomer: $[\alpha]_D^{26}$ –104.6 (1.1, $CHCl_3$). The enantiomer ratio was determined by CSP-HPLC as described above; er (*R*:*S*) 9:91.

Piperidine (*S*)-**3a** was also made from the stannane **6a** (Scheme 5):

n-BuLi (0.06 mL, 0.14 mmol, 2.5 M in hexanes) was added to the stannane **6a** (50 mg, 0.12 mmol) in THF (0.5 mL) at –78 °C. After 30 min, glacial AcOH (0.01 mL) was added and the mixture was allowed to warm to room temperature over 16 h. Aqueous NH_4Cl (1 mL) and water were added and the mixture was extracted with Et_2O. The organic phases were washed with brine, dried ($MgSO_4$), and the solvent was evaporated. Purification by column chromatograph on silica gel, eluting with petrol–EtOAc (90:10), gave the piperidine **3a** (25 mg, 80%) as an amorphous solid; $[\alpha]_D^{23}$ –59.0 (1.0, $CHCl_3$). The enantiomer ratio was determined by CSP-HPLC as described above; er (*R*:*S*) 18:82.

HPLC traces:

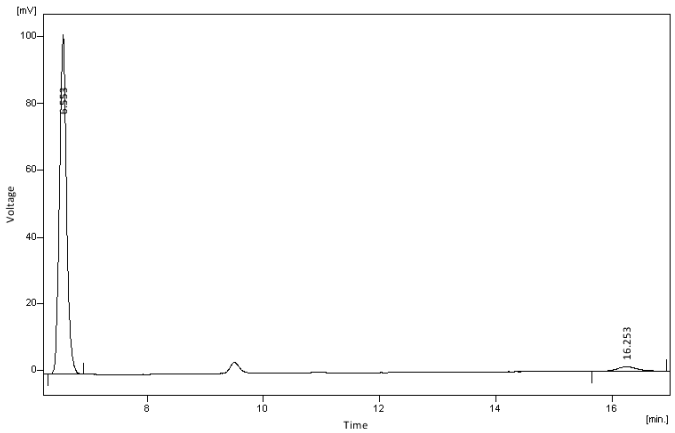
Racemic **3a**



Result Table - Calculation Method: Uncal

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	6.457	491.745	56.134	49.9	76.3	0.14
2	15.970	493.761	17.482	50.1	23.7	0.46
	Total	985.506	73.616	100.0	100.0	

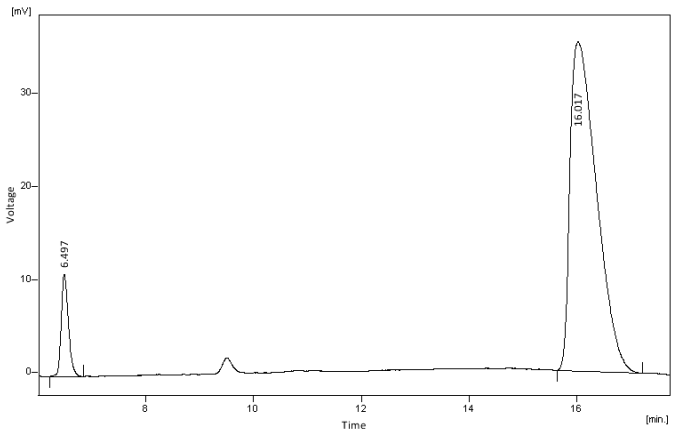
(*R*)-**3a**



Result Table - Calculation Method: Uncal

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	6.553	866.211	101.706	96.3	98.7	0.13
2	16.253	32.455	1.339	3.7	1.3	0.36
	Total	888.666	103.045	100.0	100.0	

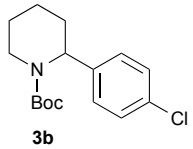
(*S*)-**3a**



Result Table - Calculation Method: Uncal

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	6.497	102.195	10.981	7.8	23.7	0.14
2	16.017	1207.822	35.382	92.2	76.3	0.55
	Total	1310.007	46.363	100.0	100.0	

tert-Butyl-2-(4-chlorophenyl)piperidine-1-carboxylate 3b



3b

For racemic **3b**:

Using general procedure A, 5-bromovaleronitrile (2.3 mL, 20 mmol), 4-bromochlorobenzene (2.8 mL, 24 mmol) and *n*-BuLi (10.4 mL, 26 mmol, 2.5 M in hexanes), $NaBH_4$ (3.1 g, 80 mmol), di-*tert*-butyl dicarbonate (4.3 g, 20 mmol) gave, after purification on silica gel, eluting with petrol–EtOAc (90:10), the carbamate

(±)-**3b** (3.6 g, 61%) as an oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39–7.30 (2H, m), 7.22–7.11 (2H, m), 5.39 (1H, dd, *J* 5.5, 2.5 Hz), 4.06 (1H, dt, *J* 12.0, 2.5 Hz), 2.74 (1H, ddd, *J* 13.5, 12.0, 3.5 Hz), 2.31–2.20 (1H, br m), 1.90 (1H, tdd, *J* 13.5, 5.5, 3.5 Hz), 1.68–1.35 (4H, m), 1.48 (9H, s); data as reported.[8]

Resolution between the enantiomers of the carbamate **3b** was achieved using a Beckman system fitted with a Phenomenex Lux Cellulose-2 column (250 mm × 460 mm i.d.) as the stationary phase with a mixture of *n*-hexane: ^{i}PrOH (97:3 v/v) as the mobile phase at a flow rate of 1 mL·min^{-1}; ambient temperature, detection by UV absorbance at 254 nm. Injection volume 20 μL of the sample prepared in a 2 g·L^{-1} solution of the eluent. Under these conditions, the components were eluted at 5.3 min (*S*) and 5.8 min (*R*).

For (*R*)-**3b**:

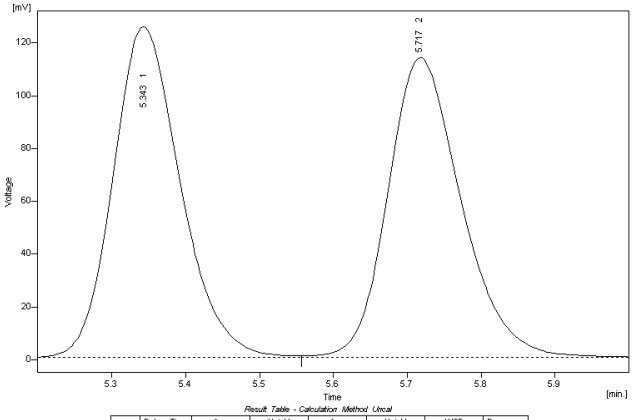
Using general procedure B, carbamate (±)-**3b** (500 mg, 1.69 mmol), *n*-BuLi (0.47 mL, 1.18 mmol, 2.5 M in hexanes), (–)-sparteine (277 mg, 1.18 mmol) and EtOCOCl (0.24 mL, 2.54 mmol) gave, after column chromatography on silica gel, eluting with petrol–EtOAc (90:10), the carbamate **3b** as an oil (205 mg, 41%); $[\alpha]_D^{23}$ +74.0 (1.0, $CHCl_3$). The enantiomer ratio was determined by CSP-HPLC as described above; er (*R*:*S*) 96:4.

For (*S*)-**3b**:

Using general procedure B, carbamate (±)-**3b** (296 mg, 1.00 mmol), *n*-BuLi (0.28 mL, 0.70 mmol, 2.5 M in hexanes), (+)-sparteine surrogate[4] (105 mg, 0.54 mmol) and EtOCOCl (0.11 mL, 1.16 mmol) gave, after column chromatography on silica gel, eluting with petrol–EtOAc (90:10), the carbamate **3b** as an oil (124 mg, 42%); $[\alpha]_D^{23}$ –52.0 (1.0, $CHCl_3$). The enantiomer ratio was determined by CSP-HPLC as described above; er (*R*:*S*) 16:84.

HPLC traces:

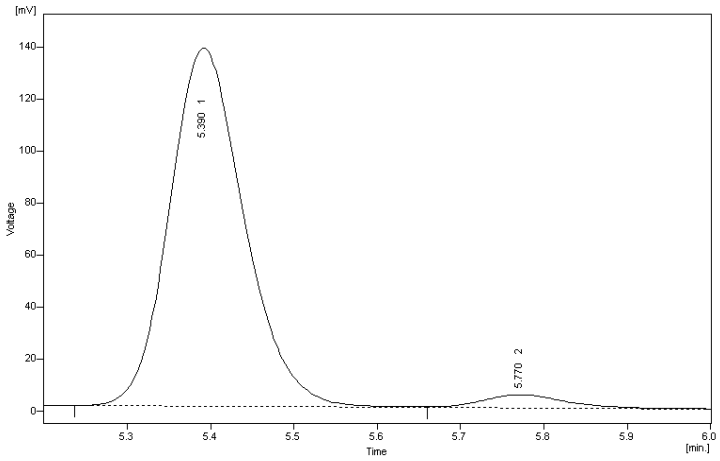
Racemic **3b**



Result Table - Calculation Method: Uncal

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Response Factor
1	5.343	794.847	125.475	50.4	52.5	0.10	0.0
2	5.717	783.676	113.657	49.6	47.5	0.11	0.0
	Total	1578.524	239.132	100.0	100.0		-

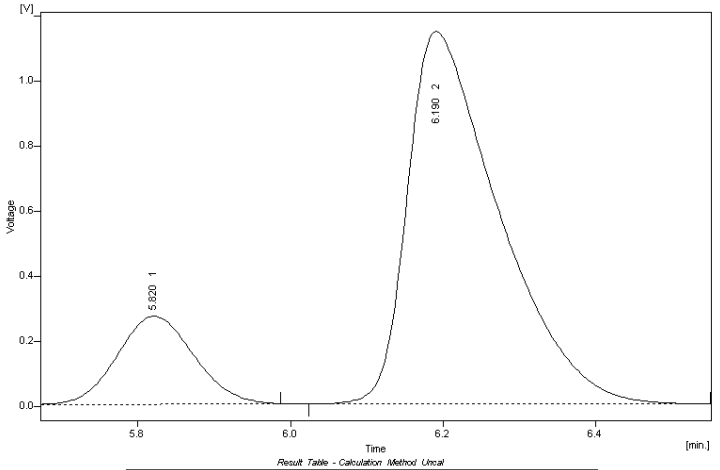
(*R*)-**3b**



Result Table - Calculation Method: Uncal

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Response Factor
1	5.390	857.186	137.523	96.1	96.4	0.10	0.0
2	5.770	34.847	5.065	3.9	3.6	0.11	0.0
	Total	892.032	142.588	100.0	100.0		-

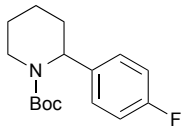
(*S*)-**3b**



Result Table - Calculation Method: Uncal

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Response Factor
1	5.820	1874.136	270.188	16.4	19.1	0.11	0.0
2	6.190	9530.590	1145.556	83.6	80.9	0.13	0.0
	Total	11404.726	1415.743	100.0	100.0		-

***tert*-Butyl-2-(4-fluorophenyl)piperidine-1-carboxylate 3c**



3c

For racemic **3c**:

Using general procedure A, 5-bromovaleronitrile (2.3 mL, 20 mmol), 4-bromofluorobenzene (2.6 mL, 24 mmol) and *n*-BuLi (10.4 mL, 26 mmol, 2.5 M in hexanes), $NaBH_4$ (3.1 g, 80 mmol), di-*tert*-butyl dicarbonate (4.3 g, 20 mmol) gave, after purification on silica gel, eluting with petrol–EtOAc (90:10), the carbamate (±)-**3c** (1.3 g, 24%) as an amorphous solid; m.p. 53–56 ºC; R_f 0.42 [petrol–EtOAc (90:10)]; FT-IR ν_{max} film/cm^{-1} 2945, 2920, 2860, 1680; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (2H, dd, *J* 8.0, 5.5 Hz), 7.07–6.99 (2H, m), 5.39 (1H, br s), 4.04 (1H, br d, *J* 13.5 Hz), 2.73 (1H, ddd, *J* 13.5, 12.0, 4.0 Hz), 2.31–2.21 (1H, m), 1.89 (1H, tdd, *J* 13.5, 5.5, 4.0 Hz), 1.70–1.34 ppm (4H, m), 1.47 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 161.7 (d, *J* 245.5 Hz), 156.6, 136.1, 128.0, 115.2 (d, *J* 21 Hz), 79.7, 52.7, 40.0, 28.4, 28.2, 25.4, 19.3; HRMS (ES) Found: MH^+, 279.1646. $C_{16}H_{22}FNO_2$, requires 279.1635.

Resolution between the enantiomers of the carbamate **3c** was achieved using a Beckman system fitted with a Phenomenex Lux Cellulose-2 column (250 mm × 460 mm i.d.) as the stationary phase with a mixture of *n*-hexane: ^{i}PrOH (99:1 v/v) as the mobile phase at a flow rate of 1 mL·min^{-1}; ambient temperature, detection by UV absorbance at 254 nm. Injection volume 20 μL of the sample prepared in a 2 g·L^{-1} solution of the eluent. Under these conditions, the components were eluted at 6.0 min (*R*) and 10.7 min (*S*).

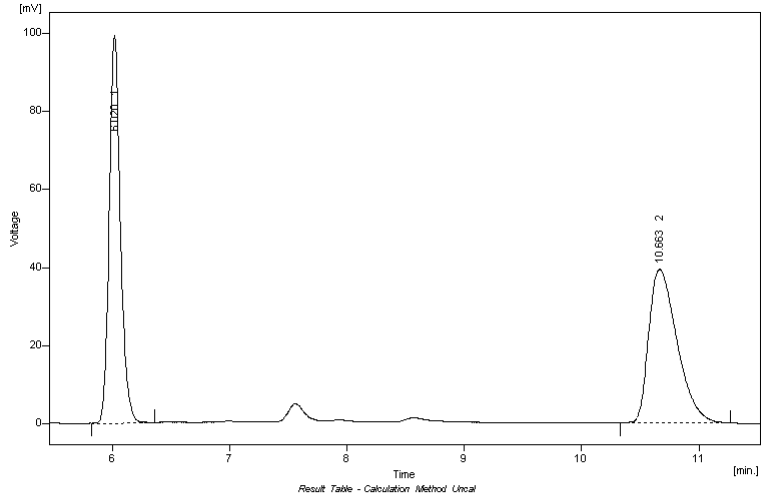
For (*R*)-**3c**:

Using general procedure B, carbamate (±)-**3c** (253 mg, 0.91 mmol), *n*-BuLi (0.26 mL, 0.64 mmol, 2.5 M in hexanes), (–)-sparteine (150 mg, 0.64 mmol) and EtOCOCl (0.10 mL, 1.08 mmol) gave, after column chromatography on silica gel, eluting with petrol–EtOAc (90:10), the carbamate **3c** as an amorphous solid (121 mg, 48%); m.p.

79–81 ºC; $[\alpha]_D^{23}$ +93.0 (1.0, $CHCl_3$). The enantiomer ratio was determined by CSP-HPLC as described above; er (*R*:*S*) 94:6.

HPLC traces:

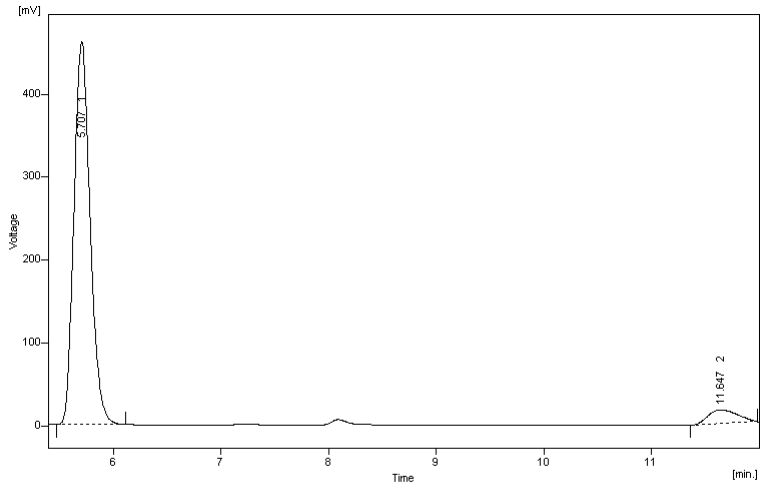
Racemic **3c**



Result Table - Calculation Method Uncal

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Response Factor
1	5.707	665.087	99.270	49.8	71.6	0.10	0.0
2	10.663	669.499	39.361	50.2	28.4	0.26	0.0
	Total	1334.586	138.630	100.0	100.0		-

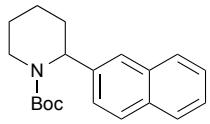
(*R*)-**3c**



Result Table - Calculation Method Uncal

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Response Factor
1	5.707	4822.249	461.918	93.9	96.6	0.17	0.0
2	11.647	311.093	16.309	6.1	3.4	0.34	0.0
	Total	5133.342	478.227	100.0	100.0		-

***tert*-Butyl-2-(2-naphthyl)piperidine-1-carboxylate 3d**



3d

For racemic **3d**:

Using general procedure A [but with addition of 4-dimethylaminopyridine (2.44 g, 20 mmol) in the Boc-protection step], 5-bromovaleronitrile (2.3 mL, 20 mmol), 2-bromonaphthalene (3.1 mL, 24 mmol) and *n*-BuLi (10.4 mL, 26 mmol, 2.5 M in hexanes), $NaBH_4$ (3.1 g, 80 mmol), di-*tert*-butyl dicarbonate (4.3 g, 20 mmol) gave, after purification on silica gel, eluting with petrol–EtOAc (90:10), the carbamate (±)-**3d** (2.0 g, 32%) as an amorphous solid; m.p. 101–103 ºC; R_f 0.41 [petrol–EtOAc (90:10)]; FT-IR ν_{max} film/cm^{-1} 2975, 2940, 2855, 1690; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89–7.77 (3H, m), 7.66 (1H, s), 7.54–7.42 (2H, m), 7.39 (1H, dd, *J* 8.5, 1.5 Hz), 5.59 (1H, br d, *J* 4.5 Hz), 4.13 (1H, d, *J* 13.5 Hz), 2.96–2.77 (1H, m), 2.52–2.38 (1H, m), 2.07–1.91 (1H, m), 1.73–1.44 (4H, m), 1.50 (9H, s). Data in accordance with the literature (no lit. m.p. given).[9]

Resolution between the enantiomers of the carbamate **3d** was achieved using a Beckman system fitted with a Phenomenex Lux Cellulose-2 column (250 mm × 460 mm i.d.) as the stationary phase with a mixture of *n*-hexane: ^{i}PrOH (99:1 v/v) as the mobile phase at a flow rate of 1 mL·min^{-1}; ambient temperature, detection by UV absorbance at 254 nm. Injection volume 20 μL of the sample prepared in a 2 g·L^{-1} solution of the eluent. Under these conditions, the components were eluted at 7.3 min (*R*) and 8.2 min (*S*).

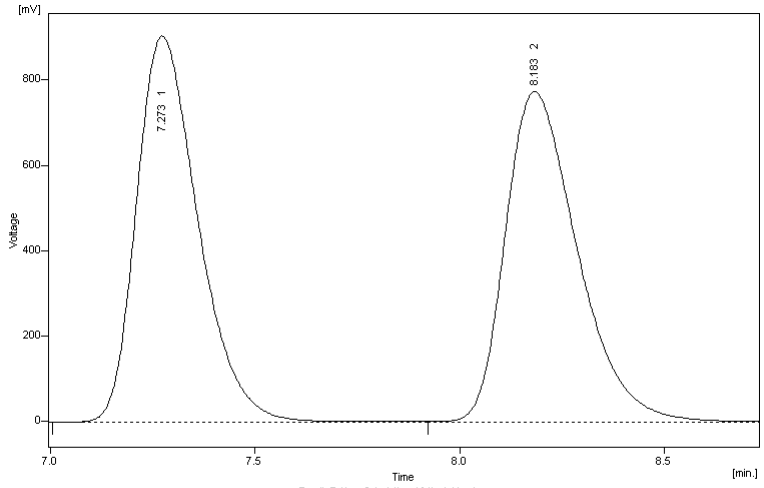
For (*R*)-**3d**:

Using general procedure B, carbamate (±)-**3d** (240 mg, 0.77 mmol), *n*-BuLi (0.22 mL, 0.54 mmol, 2.5 M in hexanes), (–)-sparteine (127 mg, 0.54 mmol) and EtOCOCl (0.11 mL, 1.16 mmol) gave, after column chromatography on silica gel, eluting with petrol–EtOAc (90:10), the carbamate **3d** as an amorphous solid (96 mg, 40%); m.p.

88–91 ºC; $[\alpha]_D^{23}$ +136.0 (1.0, $CHCl_3$). The enantiomer ratio was determined by CSP-HPLC as described above; er (*R*:*S*) 97:3.

HPLC traces:

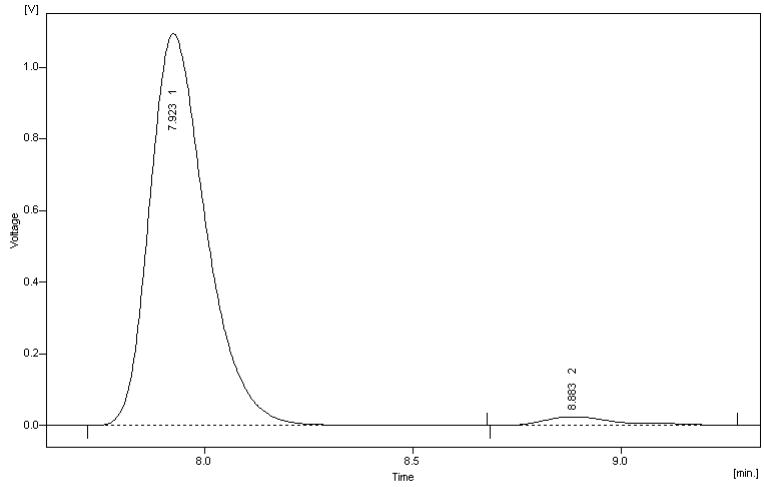
Racemic **3d**



Result Table - Calculation Method Uncal

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Response Factor
1	7.273	9438.717	904.124	50.0	53.9	0.16	0.0
2	8.183	9426.953	772.935	50.0	46.1	0.19	0.0
	Total	18865.671	1677.059	100.0	100.0		-

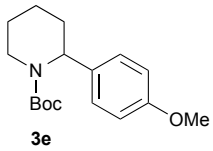
(*R*)-**3d**



Result Table - Calculation Method Uncal

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Response Factor
1	7.923	10254.160	1093.602	97.1	97.8	0.15	0.0
2	8.883	302.296	24.682	2.9	2.2	0.17	0.0
	Total	10556.455	1118.284	100.0	100.0		-

***tert*-Butyl-2-(4-methoxyphenyl)piperidine-1-carboxylate 3e**



3e

For racemic **3e**:

Using general procedure A, 5-bromovaleronitrile (2.3 mL, 20 mmol), 4-bromoanisole (3.0 mL, 24 mmol) and *n*-BuLi (10.4 mL, 26 mmol, 2.5 M in hexanes), $NaBH_4$ (3.1 g, 80 mmol), di-*tert*-butyl dicarbonate (4.3 g, 20 mmol) gave, after purification on silica gel, eluting with petrol–EtOAc (90:10), the carbamate (±)-**3e** (408 mg, 7%) as an amorphous solid; m.p. 76–78 ºC; lit.[1] m.p. 77–78 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18–7.10 (2H, m), 6.92–6.85 (2H, m), 5.38 (1H, d, *J* 4.0 Hz), 4.03 (1H, br d, *J* 13.5 Hz), 3.81 (3H, s), 2.75 (1H, ddd, *J* 13.5, 11.5, 4.0 Hz), 2.32–2.22 (1H, m), 1.95–1.80 (1H, m), 1.62–1.39 (4H, m), 1.47 (9 H, s). Data in accordance with the literature.[1]

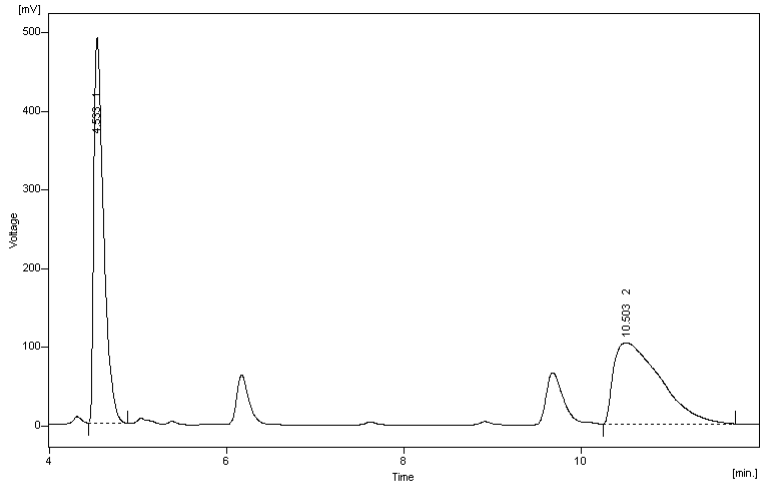
Resolution between the enantiomers of the carbamate **3e** was achieved using a Beckman system fitted with a Phenomenex Lux Cellulose-2 column (250 mm × 460 mm i.d.) as the stationary phase with a mixture of *n*-hexane: ^{i}PrOH (90:10 v/v) as the mobile phase at a flow rate of 0.5 mL·min^{-1}; ambient temperature, detection by UV absorbance at 254 nm. Injection volume 20 μL of the sample prepared in a 2 g·L^{-1} solution of the eluent. Under these conditions, the components were eluted at 4.5 min (*R*) and 10.5 min (*S*).

For (*R*)-**3e**:

Using general procedure B, carbamate (±)-**3e** (150 mg, 0.51 mmol), *n*-BuLi (0.14 mL, 0.36 mmol, 2.5 M in hexanes), (–)-sparteine (84 mg, 0.36 mmol) and EtOCOCl (0.07 mL, 0.76 mmol) gave, after column chromatography on silica gel, eluting with petrol–EtOAc (90:10), the carbamate **3e** as an amorphous solid (99 mg, 49%); m.p. 97–99 ºC; $[\alpha]_D^{23}$ +84.0 (1.0, $CHCl_3$), lit.[10] $[\alpha]_D^{21}$ +55.0 (0.2, $CHCl_3$) for er 82:18 (*R*:*S*);. The enantiomer ratio was determined by CSP-HPLC as described above; er (*R*:*S*) 90:10.

HPLC traces:

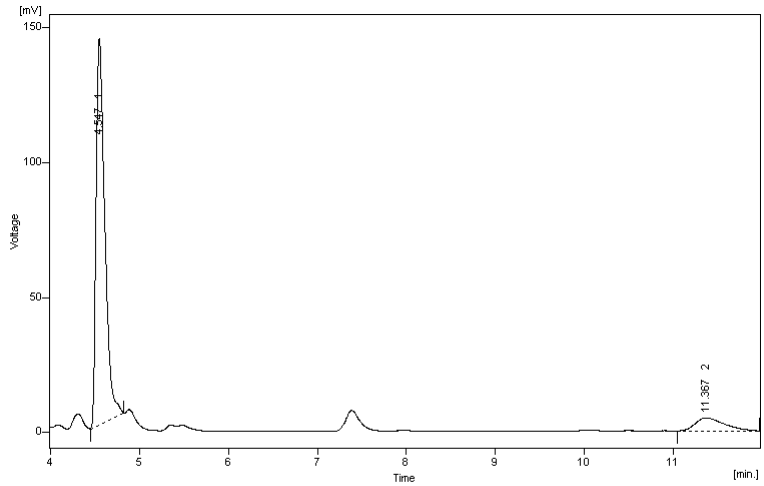
Racemic **3e**



Result Table - Calculation Method Uncal

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Response Factor
1	4.633	3767.035	489.889	50.1	82.6	0.12	0.0
2	10.503	3754.842	103.130	49.9	17.4	0.60	0.0
	Total	7521.877	593.020	100.0	100.0		-

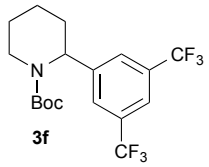
(*R*)-**3e**



Result Table - Calculation Method Uncal

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Response Factor
1	4.547	977.995	143.389	90.1	96.8	0.11	0.0
2	11.367	107.476	4.760	9.9	3.2	0.36	0.0
	Total	1085.470	148.149	100.0	100.0		-

***tert*-Butyl-2-(3,5-*bis*-trifluoromethylphenyl)piperidine-1-carboxylate 3f**



For racemic **3f**:

Using general procedure A, 5-bromovaleronitrile (2.3 mL, 20 mmol), 3,5-*bis*--trifluoromethylbromobenzene (4.1 mL, 24 mmol) and *n*-BuLi (10.4 mL, 26 mmol, 2.5 M in hexanes), $NaBH_4$ (3.1 g, 80 mmol), di-*tert*-butyl dicarbonate (4.3 g, 20 mmol) gave, after purification on silica gel, eluting with petrol–EtOAc (90:10), the carbamate (±)-**3f** (2.1 g, 27%) as an oil; R_f 0.48 [petrol–EtOAc (90:10)]; FT-IR ν_{max} film/cm^{-1} 2940, 2865, 1690; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.77 (1H, s), 7.65 (2H, s), 5.46 (1H, br s), 4.10 (1H, br d, *J* 13.5 Hz), 2.72 (1H, ddd, *J* 13.5, 12.0, 4.0 Hz), 2.35–2.25 (1H, m), 2.06–1.93 (1H, m), 1.74–1.65 (1H, m), 1.59–1.50 (2H, m), 1.47 (9H, s), 1.40–1.28 (1H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.4, 143.9, 131.9 (q, *J* 33 Hz), 126.8, 123.4 (q, *J* 273 Hz), 120.7, 80.4, 53.1, 40.4, 28.3, 28.0, 25.0, 19.2; HRMS (ES) Found: MH^+, 397.1483. $C_{18}H_{21}F_6NO_2$, requires 397.1476.

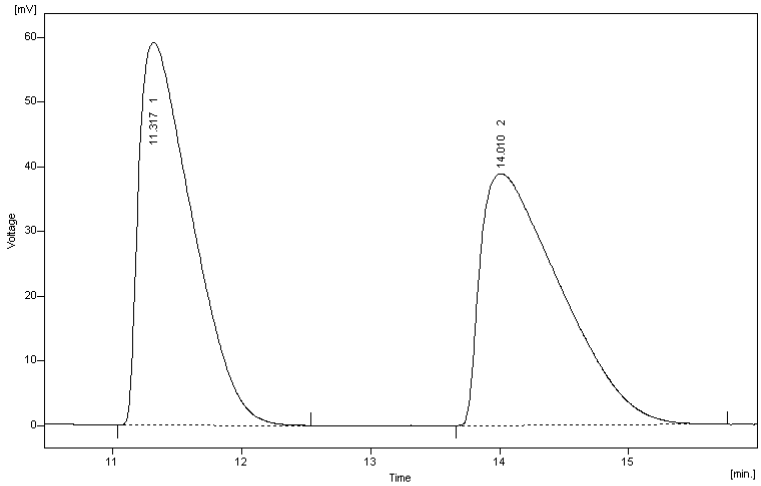
Resolution between the enantiomers of the carbamate **3f** was achieved using a Beckman system fitted with a Phenomenex Lux Cellulose-2 column (250 mm × 460 mm i.d.) as the stationary phase with a mixture of *n*-hexane: ^{i}PrOH (99.9:0.1 v/v) as the mobile phase at a flow rate of 1 mL·min^{-1}; ambient temperature, detection by UV absorbance at 254 nm. Injection volume 20 μL of the sample prepared in a 2 g·L^{-1} solution of the eluent. Under these conditions, the components were eluted at 11.3 min (*R*) and 14.0 min (*S*).

For (*R*)-**3f**:

Using general procedure B, carbamate (±)-**3f** (347 mg, 0.87 mmol), *n*-BuLi (0.24 mL, 0.61 mmol, 2.5 M in hexanes), (–)-sparteine (143 mg, 0.61 mmol) and EtOCOCl (0.14 mL, 1.3 mmol) gave, after column chromatography on silica gel, eluting with petrol–EtOAc (90:10), the carbamate **3f** as an oil (137 mg, 39%); $[\alpha]_D^{23}$ +36.0 (1.0, $CHCl_3$). The er was determined by CSP-HPLC as described above; er (*R*:*S*) 75:25.

HPLC traces:

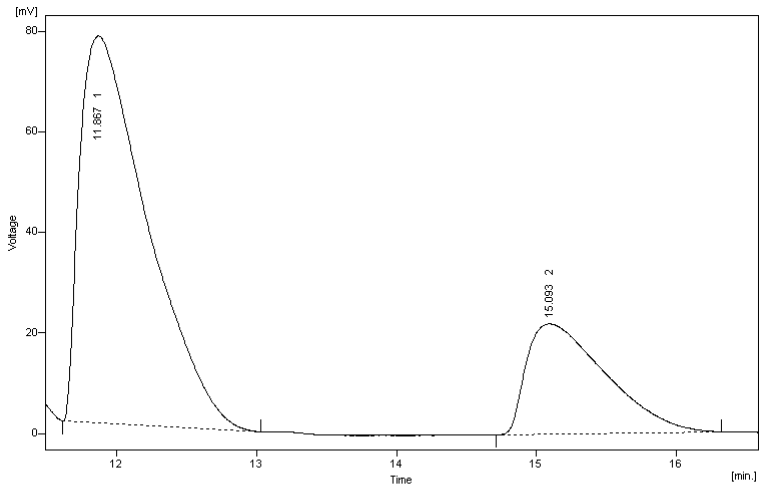
Racemic **3f**



Result Table - Calculation Method Uncal

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Response Factor
1	11.317	1694.665	59.167	50.2	60.3	0.46	0.0
2	14.010	1679.673	38.916	49.8	39.7	0.70	0.0
	Total	3374.338	98.083	100.0	100.0		-

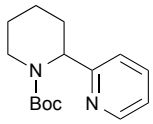
(*R*)-**3f**



Result Table - Calculation Method Uncal

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Response Factor
1	11.867	2593.377	76.979	75.2	77.9	0.52	0.0
2	15.093	856.667	21.865	24.8	22.1	0.63	0.0
	Total	3450.044	98.845	100.0	100.0		-

***tert*-Butyl-2-(2-pyridinyl)piperidine-1-carboxylate 3g**



3g

For racemic **3g**:

Using general procedure A, 5-bromovaleronitrile (2.3 mL, 20 mmol), 2-bromopyridine (2.3 mL, 24 mmol) and *n*-BuLi (10.4 mL, 26 mmol, 2.5 M in hexanes), $NaBH_4$ (3.1 g, 80 mmol), di-*tert*-butyl dicarbonate (4.3 g, 20 mmol) gave, after purification on silica gel, eluting with petrol–EtOAc (90:10), the carbamate (±)-**3g** (3.0 g, 57%) as an amorphous solid; m.p. 56–59 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64–8.55 (1H, m), 7.69–7.62 (1H, m), 7.19–7.11 (2H, m), 5.46–5.36 (1H, m), 4.16–4.05 (1H, m), 2.86 (1H, td, *J* 13.0, 3.5 Hz), 2.71–2.60 (1H, m), 1.83 (1H, tdd, *J* 13.5, 5.5, 3.5 Hz), 1.65–1.48 (3H, m), 1.45 (9H, s), 1.37–1.24 (1H, m). Data in accordance with the literature, except that the literature quotes an oil.[8,11]

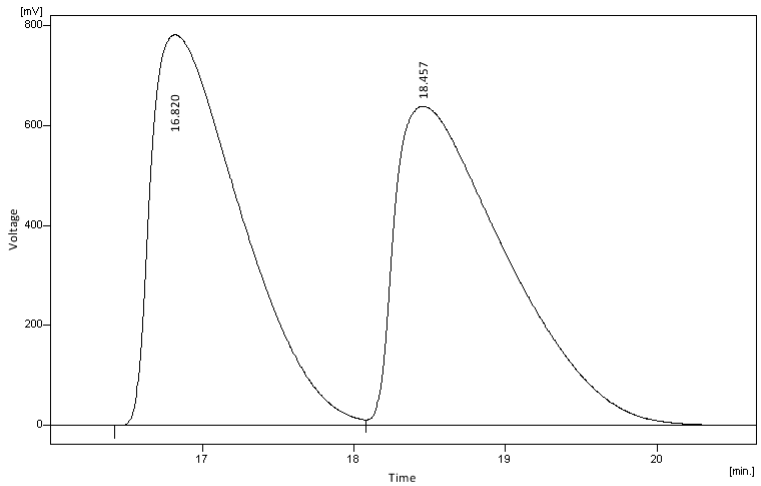
Resolution between the enantiomers of the carbamate **3g** was achieved using a Beckman system fitted with a Phenomenex Lux Cellulose-2 column (250 mm × 460 mm i.d.) as the stationary phase with a mixture of *n*-hexane: ^{i}PrOH (99:1 v/v) as the mobile phase at a flow rate of 0.5 mL·min^{-1}; ambient temperature, detection by UV absorbance at 254 nm. Injection volume 20 μL of the sample prepared in a 2 g·L^{-1} solution of the eluent. Under these conditions, the components were eluted at 7.5 min (*R*) and 8.9 min (*S*).

For (*R*)-**3g**:

Using general procedure B, carbamate (±)-**3g** (202 mg, 0.77 mmol), *n*-BuLi (0.22 mL, 0.54 mmol, 2.5 M in hexanes), (–)-sparteine (127 mg, 0.54 mmol) and EtOCOCl (0.11 mL, 1.16 mmol) gave, after column chromatography on silica gel, eluting with petrol–EtOAc (90:10), the carbamate **3g** as an amorphous solid (78 mg, 39%); m.p. 50–53 ºC; $[\alpha]_D^{23}$ +51.0 (1.0, $CHCl_3$), lit.[12] $[\alpha]_D^{21}$ +93.1 (1.0, $CHCl_3$) for er 93:7 (*R*:*S*);. The enantiomer ratio was determined by CSP-HPLC as described above; er (*R*:*S*) 80:20.

HPLC traces:

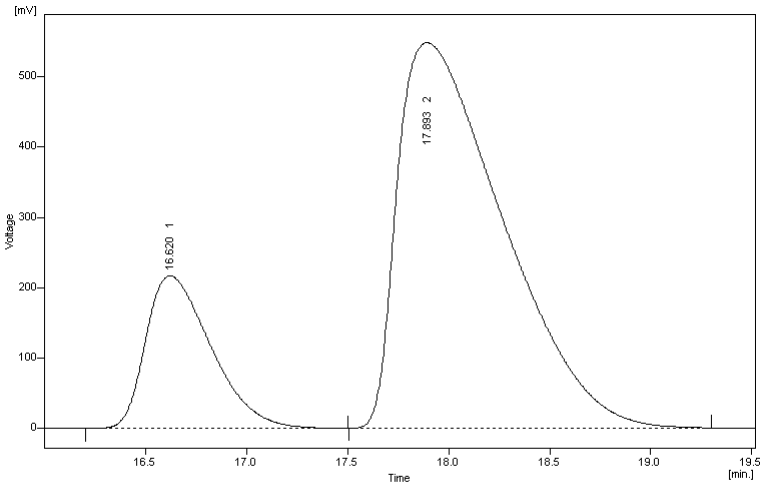
Racemic **3g**



Result Table - Calculation Method Uncal

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	16.820	32173.040	780.852	49.8	55.0	0.66
2	18.457	32464.487	637.637	50.2	45.0	0.80
	Total	64637.527	1418.488	100.0	100.0	

(*R*)-**3g**

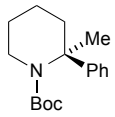


Result Table - Calculation Method Uncal

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Response Factor
1	16.620	4881.829	217.129	19.7	28.4	0.35	0.0
2	17.893	19838.875	547.530	80.3	71.6	0.58	0.0
	Total	24720.704	764.659	100.0	100.0		-

***tert*-Butyl 2-Methyl-2-phenylpiperidine-1-carboxylate 4a**

(Scheme 3)



4a

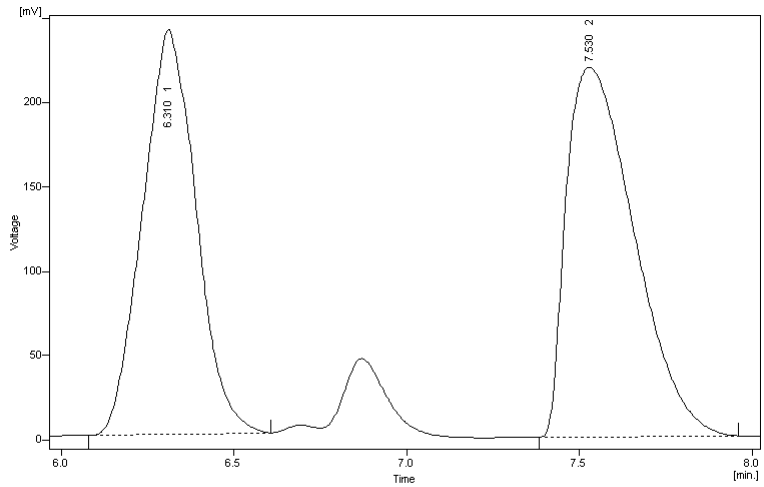
N-Boc-2-phenylpiperidine (200 mg, 0.77 mmol) in PhMe (0.5 mL) was added to a 0.25 M solution of (–)-sparteine (99 mg, 0.42 mmol) and *n*-BuLi (0.17 mL, 0.42 mmol, 2.5 M solution in hexanes) in PhMe at –78 ºC (pre-mixed for 5 min). After 5 min, MeI (0.07 mL, 1.16 mmol) was added. The mixture was allowed to warm to room temperature over 16 h then aqueous NH_4Cl (1 mL) was added. Water was added and the mixture was extracted with Et_2O. The organic phases were washed with brine, dried ($MgSO_4$), filtered and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), gave the carbamate **4a** (63 mg, 30%) as an oil; R_f 0.50 [petrol–EtOAc (9:1)]; $[\alpha]_D^{23}$ –4.0 (1.0, $CHCl_3$), lit.[6] for (*S*)-enantiomer: $[\alpha]_D^{21}$ –8.6 (0.58, $CHCl_3$) for er 97:3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.22 (4H, m, 4 × CH), 7.18–7.11 (1H, m, CH), 3.72 (1H, ddd, *J* 13.5, 7.0, 5.0 Hz, NCH) 3.52 (1H, ddd, *J* 13.5, 8.5, 5.0 Hz, NCH), 1.85–1.73 (2H, m, 2 × CH), 1.72 (3H, s, CH_3), 1.71–1.62 (2H, m, 2 × CH), 1.60–1.50 (2H, m, 2 × CH) 1.09 (9H, s, *t*-Bu); data in accordance with the literature. The er (*S*:*R*) 79:21 was determined by CSP-HPLC:

Resolution between enantiomers of the carbamate **4a** was achieved using a Beckman system fitted with a Chiralcel OD column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane: ^{i}PrOH (99:1 v/v) as the mobile phase at a flow rate of 1 mL·min^{-1}; ambient temperature, detection by UV absorbance at 254 nm. Injection volume of 20 μm of sample prepared in a 2 g·L^{-1} solution of the eluent. Under these conditions the components were eluted at 5.9 min (*R*) and 7.1 min (*S*).

Recovered **3a**: 52%, er 84:16 by CSP-HPLC.

HPLC traces:

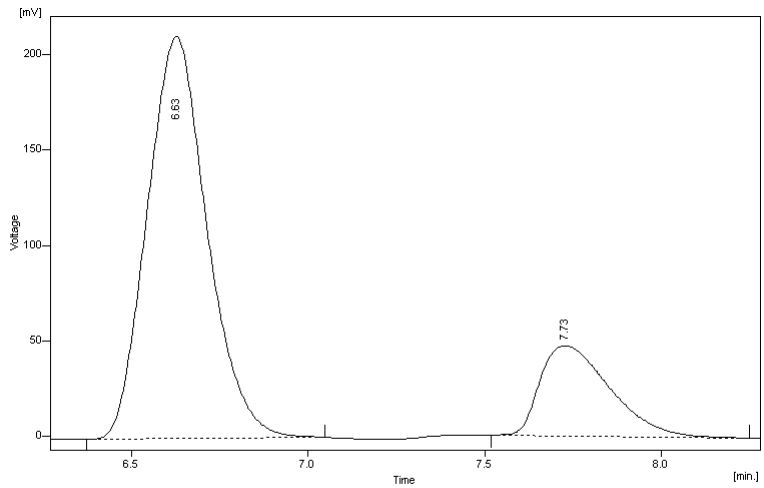
Racemic **4a**



Result Table - Calculation Method Uncal

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Response Factor
1	6.310	2584.228	240.405	49.8	53.4	0.17	0.0
2	7.530	2603.384	210.139	50.2	46.6	0.22	0.0
	Total	5187.613	450.544	100.0	100.0		-

(*S*)-**4a**

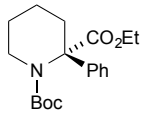


Result Table - Calculation Method Uncal

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	6.627	2481.333	210.555	79.3	81.7	0.19
2	7.727	646.457	47.256	20.7	18.3	0.22
	Total	3127.790	257.811	100.0	100.0	

1-*tert*-Butyl-2-ethyl-2-phenylpiperidine-1,2-dicarboxylate 5a

(Table 1, entry 5)



5a

Using general procedure B, carbamate (±)-**3a** (200 mg, 0.77 mmol), *n*-BuLi (0.17 mL, 0.42 mmol, 2.5 M in hexanes), (–)-sparteine (99 mg, 0.42 mmol) and EtOCOCl (0.11

mL, 1.16 mmol) gave, after column chromatography on silica gel, eluting with petrol–EtOAc (90:10), the carbamate **5a** as an oil (108 mg, 42%); R_f 0.50 [petrol–EtOAc (9:1)]; $[\alpha]_D^{23}$ –27.0 (1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.40–7.30 (4H, m, 4 × CH), 7.27–7.22 (1H, m, CH), 4.29–4.09 (2H, m, OCH_2), 3.90–3.76 (1H, m, NCH), 3.35 (1H, br s, NCH), 2.37–2.19 (2H, m, 2 × CH), 1.74–1.51 (4H, m, 4 × CH), 1.35 (9H, s, *t*-Bu), 1.26 (3H, t, *J* 7.0 Hz, CH_3); data in accordance with the literature (but no specific rotation reported).[13] The er (*S*:*R*) 92:8 was determined by CSP-HPLC:

Resolution between enantiomers of the carbamate **5a** was achieved using a Beckman system fitted with a Chiralcel OD column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane: ^{i}PrOH (99:1 v/v) as the mobile phase at a flow rate of 1 mL·min^{-1}; ambient temperature, detection by UV absorbance at 254 nm. Injection volume of 20 μm of sample prepared in a 2 g·L^{-1} solution of the eluent. Under these conditions the components were eluted at 7.8 min (*R*) and 8.7 min (*S*).

Recovered **3a**: 50%, er 75:25 by CSP-HPLC.

Yields and er values for recovered **3a** for other entries in Table 1:

entry 1: 56%, er 89:11

entry 2: 64%, er 70:30

entry 3: 64%, er 77:23

entry 4: 58%, er 73:27

Carbamate **5a** was also prepared as shown in Scheme 3:

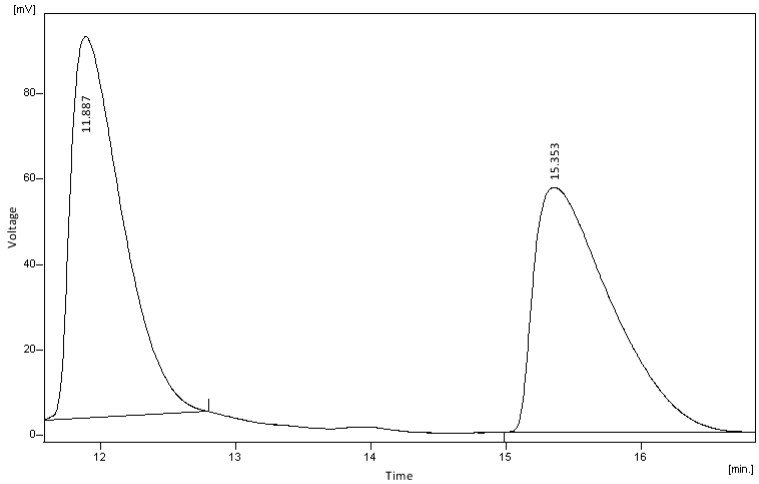
N-Boc-2-phenylpiperidine (200 mg, 0.77 mmol) in PhMe (0.5 mL) was added to a 0.25 M solution of (–)-sparteine (99 mg, 0.42 mmol) and *n*-BuLi (0.17 mL, 0.42 mmol, 2.5 M solution in hexanes) in PhMe at –78 ºC (pre-mixed for 5 min). After 5 min, EtOCOCl (0.11 mL, 1.16 mmol) was added. The mixture was allowed to warm to room temperature over 16 h then aqueous NH_4Cl (1 mL) was added. Water was added and the mixture was extracted with Et_2O. The organic phases were washed with

brine, dried ($MgSO_4$), filtered and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (90:10), gave the carbamate **5a** (127 mg, 50%) as an oil; $[\alpha]_D^{23}$ –26.0 (1.0, $CHCl_3$); data as above. The er (*S*:*R*) 89:11 was determined by CSP-HPLC as described above.

Recovered **3a**: 49%, er 85:15 by CSP-HPLC.

HPLC traces:

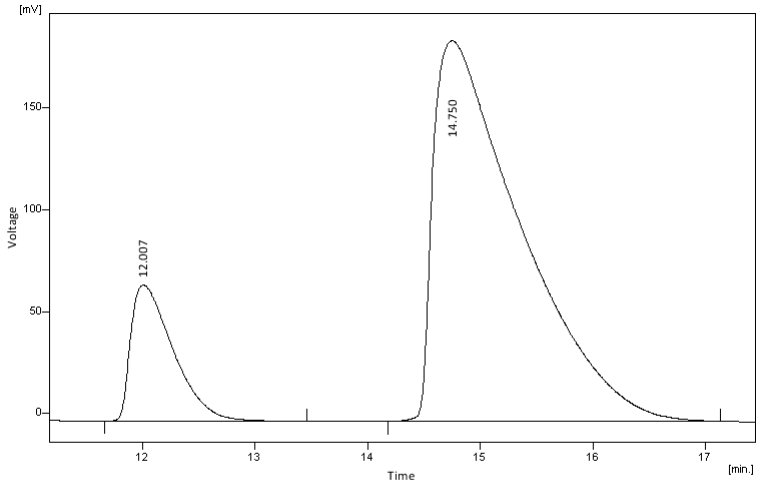
Racemic **5a**



Result Table - Calculation Method: Uncal

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	11.887	2353.736	89.228	51.0	60.9	0.42
2	15.353	2263.277	57.199	49.0	39.1	0.62
	Total	4617.013	146.427	100.0	100.0	

(*R*)-**5a**

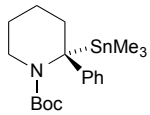


Result Table - Calculation Method: Uncal

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	12.007	1741.274	66.692	14.8	26.3	0.41
2	14.750	10056.521	186.473	85.2	73.7	0.83
	Total	11797.795	253.164	100.0	100.0	

***tert*-Butyl-2-phenyl-2-(trimethylstannyl)piperidine-1-carboxylate 6a**

(Scheme 5)



6a

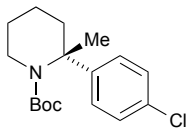
Using general procedure B, piperidine (±)-**3a** (200 mg, 0.77 mmol), *n*-BuLi (0.22 mL, 0.54 mmol, 2.5 M in hexanes), (–)-sparteine (126 mg, 0.54 mmol) and $SnMe_3Cl$ (153 mg, 0.77 mmol) gave, after purification by column chromatograph on silica gel, eluting with petrol–EtOAc (93:7), the piperidine **6a** as a gum (154 mg, 47%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34–7.27 (2H, m) 7.09–7.02 (1H, m) 6.95 (2H, dd, *J* 8.5, 1.0 Hz) 4.02–3.91 (1H, m), 2.82–2.69 (1H, m), 2.62 (1H, dd, *J* 14.5, 1.5 Hz) 2.01–1.82 (1H, m), 1.58–1.44 (4H, m), 1.51 (9H, s), –0.13 (9H, s); data in accordance with the literature.[6]

Recovered **3a**: 42%, er 94:6 by CSP-HPLC.

The following compounds are listed in the order as given in Scheme 6:

***(R)-tert*-Butyl-2-methyl-2-(4-chlorophenyl)piperidine-1-carboxylate 4b**

(Scheme 6)



4b

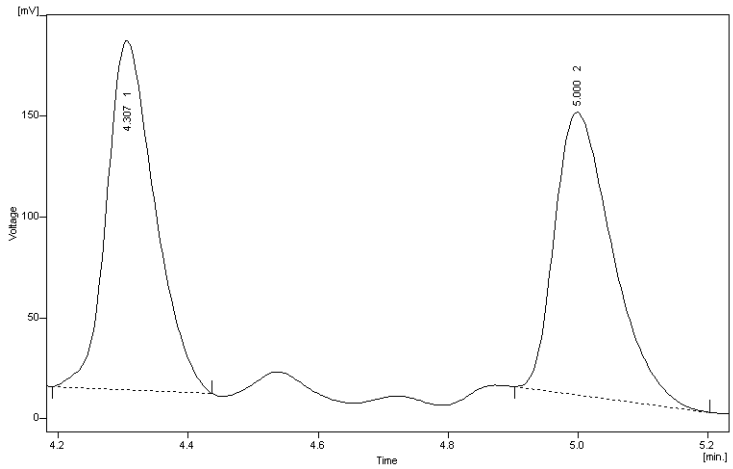
Using the General Procedure C, (*R*)-*N*-Boc-2-(4-chlorophenyl)piperidine **3b** (35 mg, 0.12 mmol), *n*-BuLi (0.06 mL, 0.14 mmol, 2.5 M in hexanes) and iodomethane (0.01 mL, 0.18 mmol) gave, after column chromatograph on silica gel, eluting with petrol–EtOAc (90:10), the carbamate **4b** as an oil (28 mg, 88%); R_f 0.50 [petrol–EtOAc (90:10)]; FT-IR ν_{max} film/cm^{-1} 2975, 2935, 2865, 1680; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.27–7.21 (4H, m), 3.76 (1H, ddd, *J* 13.5, 6.5, 5.0 Hz), 3.47 (1H, ddd, *J* 13.5, 9.0, 4.5 Hz), 1.86–1.49 (6H, m), 1.72 (3H, s), 1.15 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.8, 148.8, 131.1, 127.9, 126.0, 79.6, 59.6, 41.2 (2 × CH_2), 28.1,

23.6, 23.1, 18.0; HRMS (ES) Found: MH^+, 310.1584, $C_{17}H_{24}NO_2{}^{35}Cl$, requires 310.1574; $[\alpha]_D^{23}$ 20.0 (0.5, $CHCl_3$); er (*R*:*S*) 96:4 determined using CSP-HPLC:

Resolution between enantiomers of the carbamate **4b** was achieved using a Beckman system fitted with a Phenomenex Lux Cellulose-1 (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:^{i}PrOH (97:3 v/v) as the mobile phase at a flow rate of 1 $mL{\cdot}min^{-1}$; ambient temperature, detection by UV absorbance at 254 nm. Injection volume of 20 µm of sample prepared in a 2 $g{\cdot}L^{-1}$ solution of the eluent. Under these conditions the components were eluted at 4.3 min (*R*) and 5.0 min (*S*).

HPLC traces:

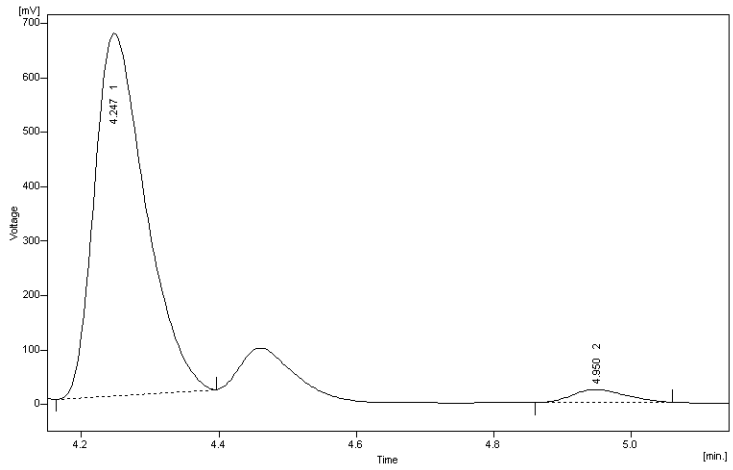
Racemic **4b**



Result Table - Calculation Method Uncal

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Response Factor
1	4.307	894.867	173.250	50.8	55.3	0.08	0.0
2	5.000	867.246	140.133	49.2	44.7	0.10	0.0
	Total	1762.112	313.383	100.0	100.0		-

(*R*)-**4b**

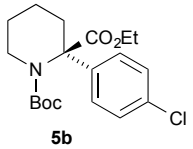


Result Table - Calculation Method Uncal

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Response Factor
1	4.247	3428.290	666.752	96.4	96.6	0.08	0.0
2	4.950	126.254	23.583	3.6	3.4	0.09	0.0
	Total	3554.545	690.335	100.0	100.0		-

(*R*)-1-*tert*-Butyl-2-ethyl-2-(4-chlorophenyl)piperidine-1,2-dicarboxylate 5b

(Scheme 6)



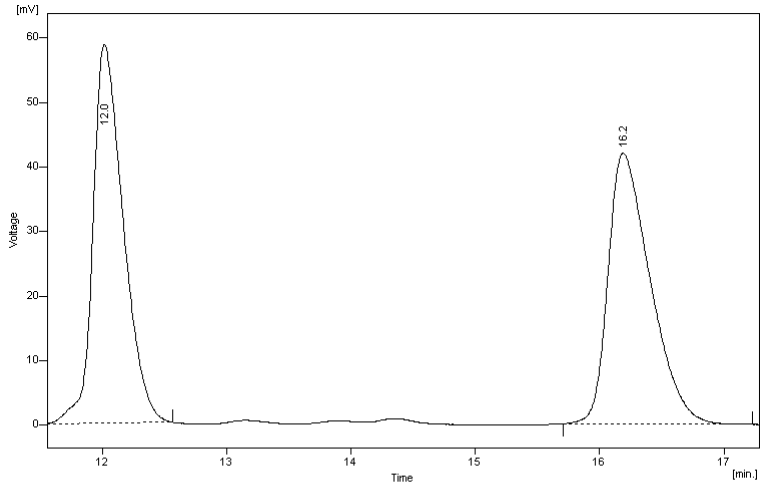
5b

Using the General Procedure C, (*R*)-*N*-Boc-2-(4-chlorophenyl)piperidine **3b** (34 mg, 0.12 mmol), *n*-BuLi (0.06 mL, 0.14 mmol, 2.5 M in hexanes) and EtOCOCl (0.02 mL, 0.18 mmol) gave, after column chromatograph on silica gel, eluting with petrol–EtOAc (90:10), the carbamate **5b** as an oil (28 mg, 72%); R_f 0.30 [petrol–EtOAc (90:10)]; FT-IR ν_{max} film/cm^{-1} 2975, 2940, 2865, 1740, 1695; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.31 (4H, br s), 4.27–4.10 (2H, m), 3.89–3.72 (1H, m), 3.47–3.21 (1H, m), 2.21 (2H, m), 1.76–1.50 (4H, m), 1.35 (9H, br s), 1.26 (3H, t, *J* 7.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$, one C not detected) δ = 172.4, 156.0, 132.7, 128.9, 127.9, 80.7, 67.1, 61.2, 42.3, 28.4, 23.4, 18.5 (2 × CH_2), 14.0; HRMS (ES) Found: MH^+, 368.1620, $C_{19}H_{26}{}^{35}ClNO_4$, requires 368.1629; $[\alpha]_D^{23}$ +33.0 (1.0, $CHCl_3$); er (*R*:*S*) 96:4 determined using CSP-HPLC:

Resolution between enantiomers of the carbamate **5b** was achieved using a Beckman system fitted with a Chiralpak IC column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:^{i}PrOH (99:1 v/v) as the mobile phase at a flow rate of 1 mL·min^{-1}; ambient temperature, detection by UV absorbance at 254 nm. Injection volume of 20 μm of sample prepared in a 2 g·L^{-1} solution of the eluent. Under these conditions the components were eluted at 13.1 min (*R*) and 19.6 min (*S*).

HPLC traces:

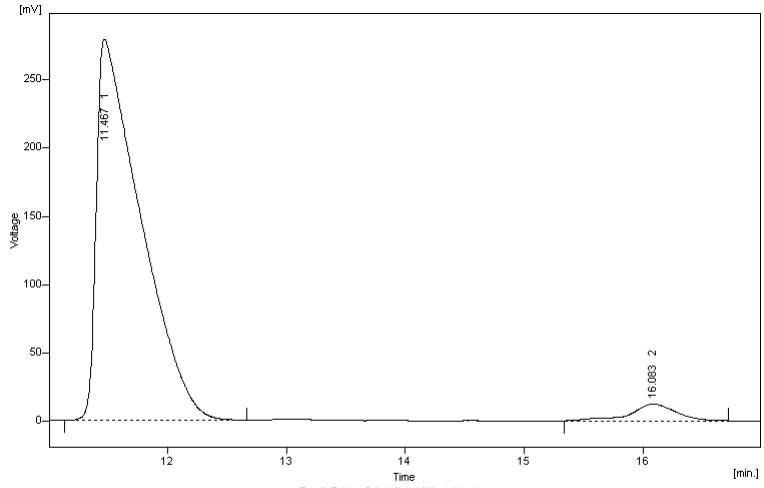
Racemic **5b**



Result Table - Calculation Method Uncal

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	12.017	993.749	58.687	50.1	58.3	0.26
2	16.190	988.284	41.906	49.9	41.7	0.37
	Total	1982.033	100.593	100.0	100.0	

(*R*)-**5b**

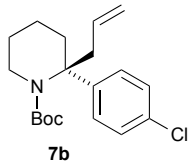


Result Table - Calculation Method Uncal

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Response Factor
1	11.467	7241.308	279.314	95.8	95.8	0.41	0.0
2	16.083	321.264	12.095	4.2	4.2	0.37	0.0
	Total	7562.572	291.408	100.0	100.0		-

(*R*)-*tert*-Butyl-2-allyl-2-(4-chlorophenyl)piperidine-1-carboxylate 7b

(Scheme 6)



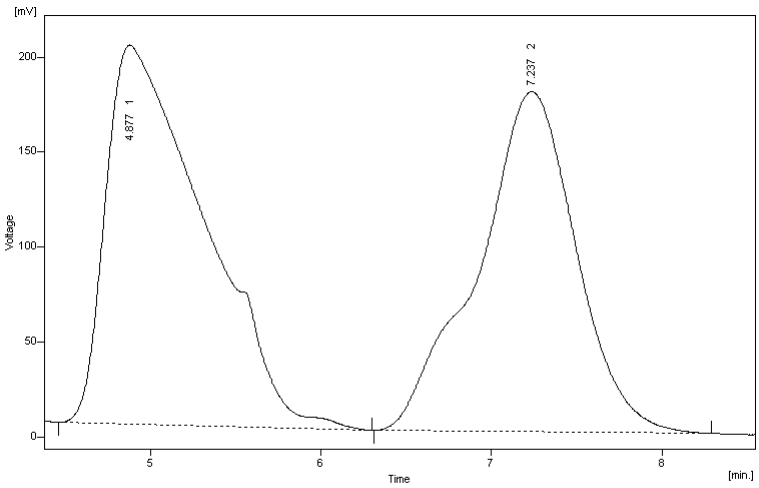
7b

Using the General Procedure C, (*R*)-*N*-Boc-2-(4-chlorophenyl)piperidine **3b** (38 mg, 0.13 mmol), *n*-BuLi (0.06 mL, 0.15 mmol, 2.5 M in hexanes) and allyl bromide (0.02 mL, 0.20 mmol) gave, after column chromatograph on silica gel, eluting with petrol–EtOAc (90:10), the carbamate **7b** as an oil (26 mg, 67%); R_f 0.55 [petrol–EtOAc (90:10)]; FT-IR ν_{max} film/cm^{-1} 2935, 2865, 1680; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.29–7.25 (2H, m), 7.24–7.18 (2H, m), 5.87 (1H, dddd, *J* 17.0, 10.0, 8.0, 6.5 Hz), 5.23–5.11 (2H, m), 3.92 (1H, dt, *J* 13.5, 5.0 Hz) 3.36–3.18 (2H, m), 2.66 (1H, dd, *J* 13.5, 8.0 Hz), 2.27–2.14 (1H, m), 1.82–1.72 (2H, m), 1.71–1.64 (2H, m), 1.23 (9H, s), 1.36–1.19 (1H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.4, 146.2, 133.8, 131.4, 127.8, 126.7, 118.8, 79.7, 62.2, 44.6, 40.9, 35.7, 28.2, 21.6, 15.8; HRMS (ES) Found: MH^+, 336.1724, $C_{19}H_{26}NO_2{}^{35}Cl$, requires 336.1730; $[\alpha]_D^{23}$ +15.8 (1.5, $CHCl_3$); er (*R*:*S*) 92:8 determined using CSP-HPLC:

Resolution between enantiomers of the carbamate **7b** was achieved using a Beckman system fitted with a Chiralcel OJ column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:^{i}PrOH (99:1 v/v) as the mobile phase at a flow rate of 1 mL·min^{-1}; ambient temperature, detection by UV absorbance at 254 nm. Injection volume of 20 μm of sample prepared in a 2 g·L^{-1} solution of the eluent. Under these conditions the components were eluted at 4.9 min (*R*) and 7.2 min (*S*).

HPLC traces:

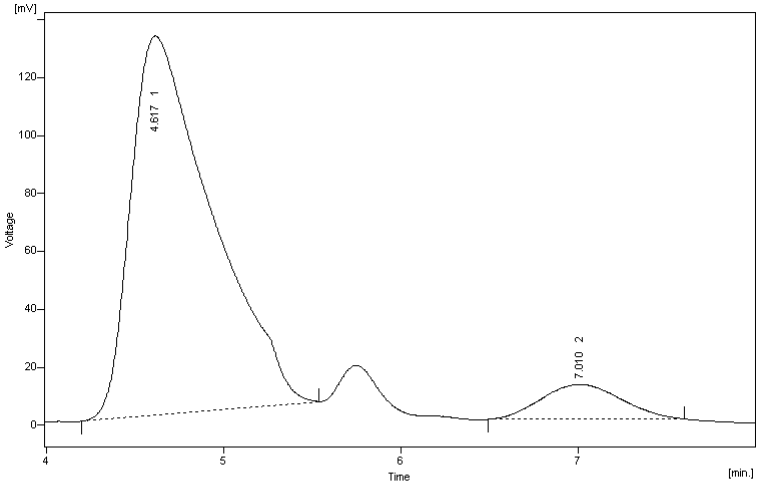
Racemic **7b**



Result Table - Calculation Method: Uncal

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Response Factor
1	4.877	8015.881	199.722	52.8	52.7	0.64	0.0
2	7.237	7158.748	179.105	47.2	47.3	0.57	0.0
	Total	15174.628	378.827	100.0	100.0		-

(*R*)-**7b**

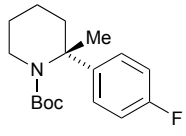


Result Table - Calculation Method: Uncal

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Response Factor
1	4.617	4147.745	130.839	91.7	91.6	0.50	0.0
2	7.010	376.729	11.926	8.3	8.4	0.51	0.0
	Total	4524.474	142.766	100.0	100.0		-

(*R*)-1-*tert*-Butyl-2-methyl-2-(4-fluorophenyl)piperidine-1-carboxylate 4c

(Scheme 6)



4c

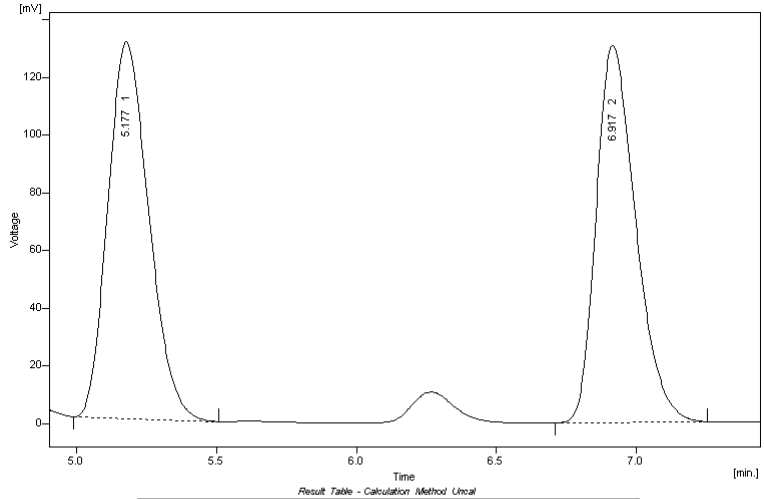
Using the General Procedure C, (*R*)-*N*-Boc-2-(4-fluorophenyl)piperidine **3c** (39 mg, 0.14 mmol), *n*-BuLi (0.07 mL, 0.17 mmol, 2.5 M in hexanes) and iodomethane (0.02

mL, 0.21 mmol) gave, after column chromatograph on silica gel, eluting with petrol–EtOAc (90:10), the carbamate **4c** as an oil (30 mg, 73%); R_f 0.45 [petrol–EtOAc (90:10)]; FT-IR ν_{max} film/cm^{-1} 2975, 2940, 2865, 1685; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.30–7.21 (2H, m), 7.01–6.93 (2H, m), 3.76 (1H, ddd, *J* 13.5, 7.0, 5.0 Hz), 3.50 (1H, ddd, *J* 13.5, 8.5, 4.5 Hz), 1.84–1.62 (4H, m), 1.73 (3H, s), 1.62–1.51 (2H, m), 1.14 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 160.0 (d, *J* 244 Hz), 155.9, 126.0, 114.5 (d, *J* 21 Hz), 79.5, 59.6, 41.2, 41.1, 28.1, 23.9, 23.1, 17.9; HRMS (ES) Found: MH^+, 294.1861, $C_{17}H_{24}NO_2F$, requires 294.1869; $[\alpha]_D^{23}$ +1.6 (1.3, $CHCl_3$); er (*R*:*S*) 91:9 determined using CSP-HPLC:

Resolution between enantiomers of the carbamate **4c** was achieved using a Beckman system fitted with a Phenomenex Lux Cellulose-1 (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:^{i}PrOH (99:1 v/v) as the mobile phase at a flow rate of 1 mL·min^{-1}; ambient temperature, detection by UV absorbance at 254 nm. Injection volume of 20 μm of sample prepared in a 2 g·L^{-1} solution of the eluent. Under these conditions the components were eluted at 6.3 min (*R*) and 10.5 min (*S*).

HPLC traces:

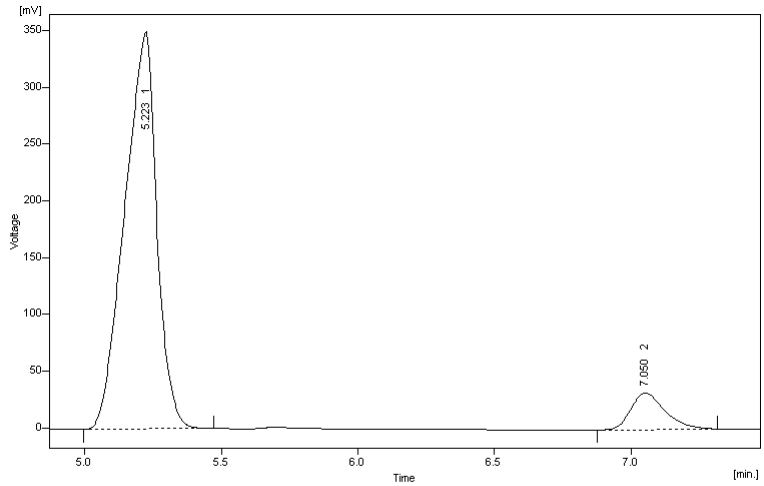
Racemic **4c**



Result Table - Calculation Method: Uncal

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Response Factor
1	5.177	1331.959	130.702	50.9	50.0	0.16	0.0
2	6.917	1283.419	130.512	49.1	50.0	0.16	0.0
	Total	2615.378	261.214	100.0	100.0		-

(*R*)-**4c**

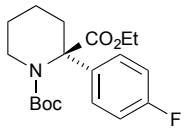


Result Table - Calculation Method: Uncal

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Response Factor
1	5.223	2859.385	350.257	91.1	91.5	0.13	0.0
2	7.050	278.894	32.380	8.9	8.5	0.13	0.0
	Total	3138.279	382.637	100.0	100.0		-

(*R*)-1-*tert*-Butyl-2-ethyl-(4-fluorophenyl)piperidine-1,2-dicarboxylate 5c

(Scheme 6)



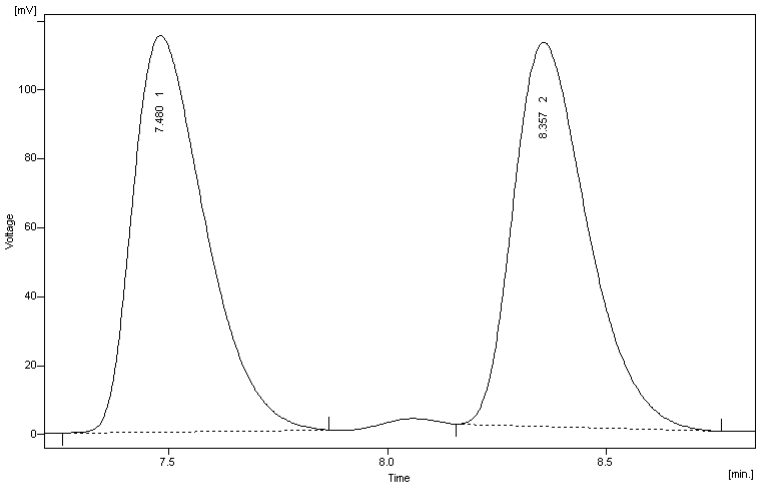
5c

Using the General Procedure C, (*R*)-*N*-Boc-2-(4-fluorophenyl)piperidine **3c** (39 mg, 0.14 mmol), *n*-BuLi (0.07 mL, 0.17 mmol, 2.5 M in hexanes) and EtOCOCl (0.02 mL, 0.21 mmol) gave, after column chromatograph on silica gel, eluting with petrol–EtOAc (90:10), the carbamate **5c** as an oil (32 mg, 84%); R_f 0.30 [petrol–EtOAc (90:10)]; FT-IR ν_{max} film/cm^{-1} 2975, 2940, 2870, 1740, 1695; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.37–7.29 (2H, m), 7.07–6.98 (2H, m), 4.27–4.08 (2H, m), 3.95–3.76 (1H, m), 3.28 (1H, m), 2.35–2.19 (2H, m), 1.78–1.50 (4H, m), 1.35 (9H, s), 1.25 (3H, t, *J* 7.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$, one C not detected) δ = 172.6, 161.5 (d, *J* 244.5 Hz), 156.1, 129.3, 114.6 (d, *J* 21.5 Hz), 80.7, 67.0, 61.2, 42.2, 28.1, 23.4, 18.5 (2 × CH_2), 14.1; HRMS (ES) Found: MH^+, 352.1928, $C_{19}H_{26}FNO_4$, requires 352.1924; $[\alpha]_D^{23}$ +22.0 (1.0, $CHCl_3$); er (*R*:*S*) 93:7 determined using CSP-HPLC:

Resolution between enantiomers of the carbamate **5c** was achieved using a Beckman system fitted with a Phenomenex Lux Cellulose-1 (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:^{i}PrOH (99:1 v/v) as the mobile phase at a flow rate of 1 mL·min^{-1}; ambient temperature, detection by UV absorbance at 254 nm. Injection volume of 20 µm of sample prepared in a 2 g·L^{-1} solution of the eluent. Under these conditions the components were eluted at 6.3 min (*R*) and 10.5 min (*S*).

HPLC traces:

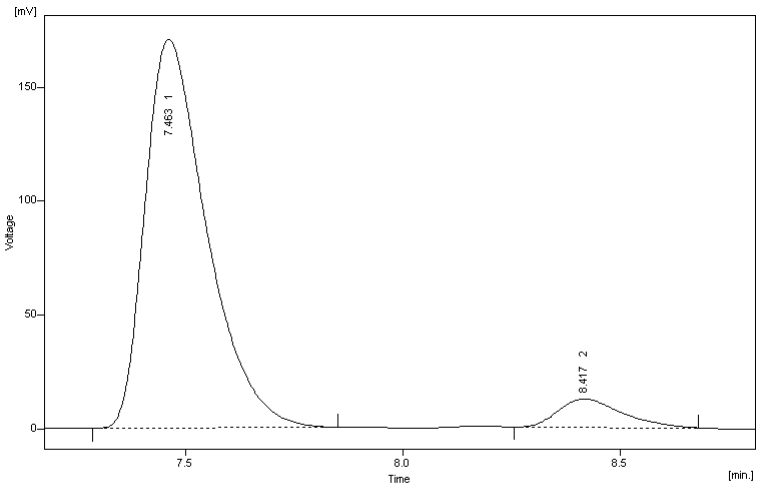
Racemic **5c**



Result Table - Calculation Method Uncal

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Response Factor
1	7.480	1321.482	115.037	50.1	50.8	0.18	0.0
2	8.357	1315.397	111.508	49.9	49.2	0.19	0.0
	Total	2636.880	226.545	100.0	100.0		-

(*R*)-**5c**

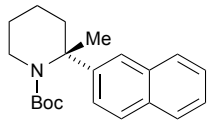


Result Table - Calculation Method Uncal

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Response Factor
1	7.463	1682.523	170.639	93.0	93.2	0.15	0.0
2	8.417	126.836	12.468	7.0	6.8	0.16	0.0
	Total	1809.359	183.107	100.0	100.0		-

(*R*)-*tert*-Butyl-2-(2-naphthyl)piperidine-1-carboxylate 4d

(Scheme 6)



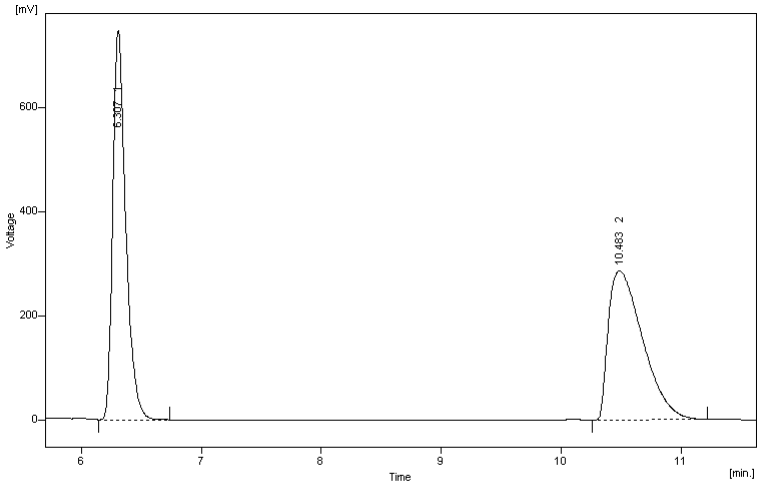
4d

Using the General Procedure C, (*R*)-*N*-Boc-2-(2-naphthyl)piperidine **3d** (39 mg, 0.13 mmol), *n*-BuLi (0.06 mL, 0.15 mmol, 2.5 M in hexanes) and iodomethane (0.01 mL, 0.20 mmol) gave, after column chromatograph on silica gel, eluting with petrol–EtOAc (90:10), the carbamate **4d** as an oil (32 mg, 76%); R_f 0.45 [petrol–EtOAc (90:10)]; FT-IR ν_{max} film/cm^{-1} 2945, 2870, 1675; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.86–7.73 (3H, m), 7.68 (1H, d, *J* 1.5 Hz), 7.52 (1H, dd, *J* 9.0, 1.5 Hz), 7.49–7.39 (2H, m), 3.85 (1H, ddd, *J* 13.5, 6.5, 5.0 Hz), 3.55 (1H, ddd, *J* 13.5, 9.0, 4.5 Hz), 1.98–1.67 (4H, m), 1.66–1.56 (2H, m), 1.86 (3H, s), 1.03 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.1, 147.7, 133.3, 131.8, 127.8, 127.5, 127.4, 125.7, 125.1, 124.0, 122.2, 79.4, 60.1, 41.4, 41.1, 28.0, 23.8, 23.4, 18.4; HRMS (ES) Found: MH^+, 326.2108, $C_{21}H_{27}NO_2$, requires 326.2120; $[\alpha]_D^{23}$ +3.0 (1.0, $CHCl_3$); er (*R*:*S*) 95:5 determined using chiral stationary phase HPLC:

Resolution between enantiomers of the carbamate **4d** was achieved using a Beckman system fitted with a Phenomenex Lux Cellulose-1 (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:^{i}PrOH (99:1 v/v) as the mobile phase at a flow rate of 1 mL·min^{-1}; ambient temperature, detection by UV absorbance at 254 nm. Injection volume of 20 μm of sample prepared in a 2 g·L^{-1} solution of the eluent. Under these conditions the components were eluted at 5.2 min (*R*) and 6.9 min (*S*).

HPLC traces:

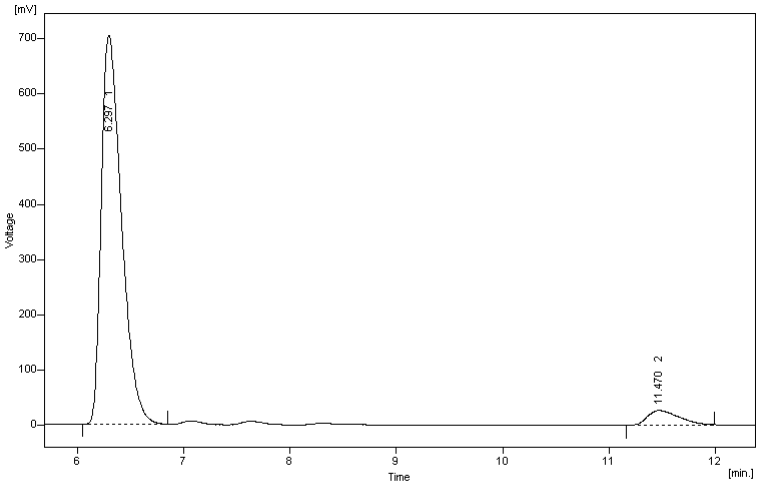
Racemic **4d**



Result Table - Calculation Method Uncal

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Response Factor
1	6.307	5620.184	745.775	49.7	72.3	0.11	0.0
2	10.483	5695.184	286.020	50.3	27.7	0.32	0.0
	Total	11315.367	1031.795	100.0	100.0		-

(*R*)-**4d**



Result Table - Calculation Method Uncal

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Response Factor
1	6.297	9322.802	704.591	94.5	96.4	0.21	0.0
2	11.470	541.996	26.334	5.5	3.6	0.33	0.0
	Total	9864.798	730.926	100.0	100.0		-

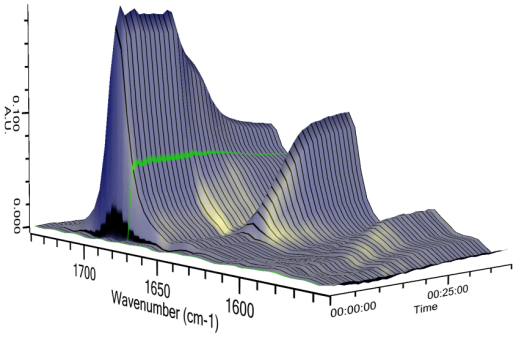
2. In situ IR spectra

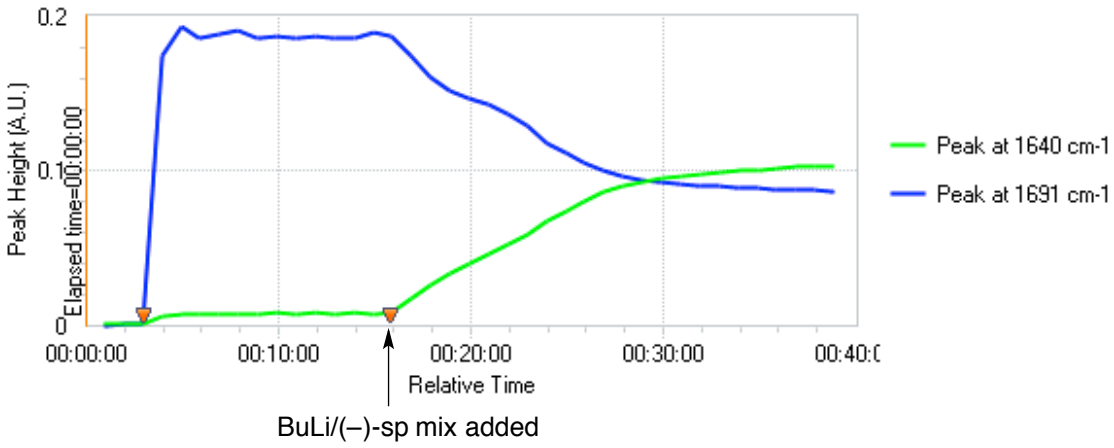
Two modes of addition were studied:

(a) Using pre-mixed n-BuLi/(–)-sparteine

Toluene (12 mL) was added to a flask equipped with a stirrer bar and ReactIR probe at rt under Ar. After cooling to –78 °C, a solution of *N*-Boc-2-phenylpiperidine **3a** (522 mg, 2 mmol) in THF (1 mL) was added dropwise. After 16 min, a pre-mixed solution of *n*-BuLi (0.44 mL, 1.1 mmol) and (–)-sparteine (257 mg, 1.1 mmol) in PhMe (1 mL) was added dropwise. The solution was stirred and was monitored by IR spectroscopy. A peak at 1691 cm^{-1} was observed for **3a** which was assigned to $\nu_{C=O}$. After addition of *n*-BuLi/(–)-sparteine, a new peak at 1640 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate.

The following plot is shown with time in hours:minutes:seconds (total reaction time ~40 min).

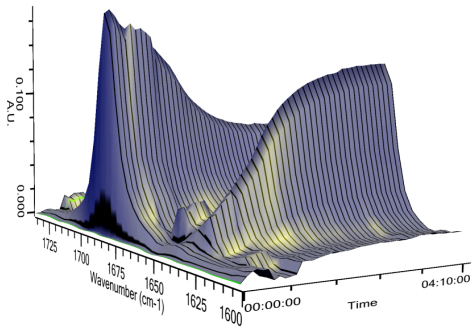


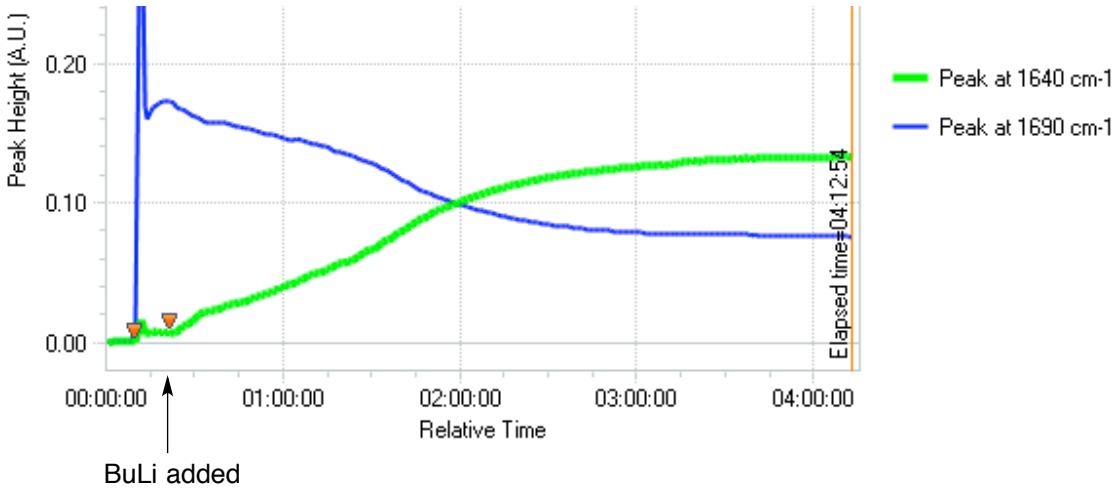


(b) Using addition of n-BuLi to the substrate/(–)-sparteine

Toluene (12 mL) was added to a flask equipped with a stirrer bar and ReactIR probe at rt under Ar. After cooling to –78 °C, a solution of *N*-Boc-2-phenylpiperidine **3a** (522 mg, 2 mmol) and (–)-sparteine (323 mg, 1.4 mmol) in THF (1 mL) was added dropwise. After ~20 min, *n*-BuLi (0.56 mL, 1.4 mmol) was added dropwise. The solution was stirred and was monitored by IR spectroscopy. A peak at 1691 cm^{-1} was observed for **3a** which was assigned to $\nu_{C=O}$. After addition of *n*-BuLi, a new peak at 1640 cm^{-1} was observed which was assigned to $\nu_{C=O}$ in the lithiated intermediate.

The following plot is shown with time in hours:minutes:seconds (total reaction time ~4 h).





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