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

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Supplementary Information (SI)

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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 N₂ 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 KMnO₄ 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. ¹H 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. ¹³C 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 °C 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 CH₂Cl₂. The aqueous phase was basified to pH 9–10 using aqueous NaOH (2 M) and then was extracted with CH₂Cl₂. The organic phases were combined, dried (MgSO₄), filtered and the solvent was evaporated to give the crude imine.

To a solution of the crude imine in MeOH at 0 °C was added NaBH₄ (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 CH₂Cl₂. The aqueous phase was basified to pH 9–10 using aqueous NaOH (2 M) and then was extracted with CH₂Cl₂. The organic phases were combined, dried (MgSO₄), filtered and the solvent was evaporated to give the crude amine.

To a solution of Boc₂O (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 NaHCO₃ and Et₂O. The phases were separated and the aqueous phase was extracted with Et₂O. The combined organic phases were washed with brine, dried (MgSO₄), 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 °C. 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$_4$Cl (1 mL) was added. Water was added and the mixture was extracted with Et$_2$O. 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-aryl piperidine 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$_4$Cl (1 mL) was added. Water was added and the mixture was extracted with Et$_2$O. 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**

For racemic 3a:

Using general procedure A, 5-bromovaleronitrile (2.3 mL, 20 mmol), PhLi (24 mL, 24 mmol), NaBH₄ (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; ¹H NMR (400 MHz, CDCl₃) δ = 7.40–7.30 (2H, m), 7.26–7.20 (3H, m), 5.43 (1H, br s), 4.06 (1H, d, J₁₃.₅ Hz), 2.72–2.82 (1H, m), 2.32 (1H, dd, J₁₃.₅, 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:¹PrOH (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 °C, lit.² for (R)-enantiomer: m.p. 78–80 °C, lit.³ for (R)-enantiomer: m.p. 112–114 °C; [α]ᵣ²⁺ = +84.0 (1.0, CHCl₃), lit.² for (R)-enantiomer: [α]ᵣ²⁺ = +83.7 (0.98, CHCl₃), lit.³ for (R)-enantiomer: [α]ᵣ²⁰⁺ = +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 (78 mg, 0.40 mmol) and EtOOCOCl (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 °C, lit.² for (R)-enantiomer: m.p. 78–80 °C, lit.⁵ for (S)-enantiomer: m.p. 106–108 °C; [α]D²³ –81.0 (1.0, CHCl₃), lit.² for (R)-enantiomer: [α]D²³ +83.7 (0.98, CHCl₃), lit.⁶ for (S)-enantiomer: [α]D²¹ –90.0 (1.0, CHCl₃), lit.⁷ for (S)-enantiomer: [α]D²⁶ –104.6 (1.1, CHCl₃). 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 NH₄Cl (1 mL) and water were added and the mixture was extracted with Et₂O. The organic phases were washed with brine, dried (MgSO₄), 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; [α]D²³ –59.0 (1.0, CHCl₃). The enantiomer ratio was determined by CSP-HPLC as described above; er (R:S) 18:82.

HPLC traces:
Racemic 3a
(R)-3a

![Graph](image)

(S)-3a

![Graph](image)

**tert-Butyl-2-(4-chlorophenyl)piperidine-1-carboxylate 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), NaBH₄ (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
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(±)-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: iPrOH (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%); [α]$_D^{23}$ +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%); [α]$_D^{23}$ −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**

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

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


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

![Chemical structure](image)

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), NaBH₄ (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; Rₙ 0.42 [petrol–EtOAc (90:10)]; FT-IR νₘₐₓ film/cm⁻¹ 2945, 2920, 2860, 1680; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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. C₁₆H₂₂FNO₂, 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: ⁹PrOH (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 °C; $[\alpha]_D^{23} +93.0$ (1.0, CHCl$_3$). The enantiomer ratio was determined by CSP-HPLC as described above; er ($R$:S) 94:6.

**HPLC traces:**

**Racemic 3c**

![HPLC trace of racemic 3c]

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

![HPLC trace of ($R$)-3c]
**tert-Butyl-2-(2-naphthyl)piperidine-1-carboxylate 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), NaBH₄ (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 °C; R₇ 0.41 [petrol–EtOAc (90:10)]; FT-IR νₘₐₓ film/cm⁻¹ 2975, 2940, 2855, 1690; ¹H NMR (400 MHz, CDCl₃) 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).

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: iPrOH (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 °C; $[\alpha]_D^{23}$ +136.0 (1.0, CHCl₃). The enantiomer ratio was determined by CSP-HPLC as described above; er ($R:S$) 97:3.

HPLC traces:

Racemic 3d

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

![Chemical Structure](image)

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), NaBH₄ (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 °C; lit.¹ m.p. 77–78 °C; ¹H NMR (400 MHz, CDCl₃) 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: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 °C; [α]D²³ +84.0 (1.0, CHCl₃), lit.¹⁰ [α]D²¹ +55.0 (0.2, CHCl₃) 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**

![HPLC trace for racemic 3e]

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

![HPLC trace for ($R$)-3e]

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

![Chemical structure of 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), NaBH₄ (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; Rₚ 0.48 [petrol–EtOAc (90:10)]; FT-IR νmax film/cm⁻¹ 2940, 2865, 1690; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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. C₁₈H₂₁F₆NO₂, 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 x 460 mm i.d.) as the stationary phase with a mixture of n-hexane: iPrOH (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%); [α]D²³ +36.0 (1.0, CHCl₃). The er was determined by CSP-HPLC as described above; er (R:S) 75:25.
HPLC traces:

Racemic $3f$

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<th>Area (%)</th>
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$(R)$-$3f$

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tert-Butyl-2-(2-pyridinyl)piperidine-1-carboxylate 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), NaBH₄ (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 °C; ¹H NMR (400 MHz, CDCl₃) 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: ᵃPrOH (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 °C; [α]D²³ +51.0 (1.0, CHCl₃), lit.¹² [α]D²¹ +93.1 (1.0, CHCl₃) 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

(\(R\))-3g
**tert-Butyl 2-Methyl-2-phenylpiperidine-1-carboxylate 4a**

(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 °C (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 NH₄Cl (1 mL) was added. Water was added and the mixture was extracted with Et₂O. The organic phases were washed with brine, dried (MgSO₄), 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; Rₜ 0.50 [petrol–EtOAc (9:1)]; [α]D²₃ −4.0 (1.0, CHCl₃), lit.⁶ for (S)-enantiomer: [α]D²¹ −8.6 (0.58, CHCl₃) for er 97:3; ¹H NMR (400 MHz, CDCl₃) 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, CH₃), 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: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 µL 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

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(S)-4a

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

(Table 1, entry 5)

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)]; [α]$_D^{23}$ = −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). 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:$^1$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 °C (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$_4$Cl (1 mL) was added. Water was added and the mixture was extracted with Et$_2$O. The organic phases were washed with
brine, dried (MgSO₄), 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; [α]D²³ –26.0 (1.0, CHCl₃); 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

(R)-5a
**tert-Butyl-2-phenyl-2-(trimethylstannyl)piperidine-1-carboxylate 6a**

(Scheme 5)

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 SnMe₃Cl (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, CDCl₃) 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)

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⁺ 0.50 [petrol–EtOAc (90:10)]; FT-IR ν max film/cm⁻¹ 2975, 2935, 2865, 1680; ^1^H NMR (400 MHz, CDCl₃) 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); ^1^C NMR (101 MHz, CDCl₃) δ = 155.8, 148.8, 131.1, 127.9, 126.0, 79.6, 59.6, 41.2 (2 × CH₂), 28.1,
23.6, 23.1, 18.0; HRMS (ES) Found: MH$^+$, 310.1584, C$_{17}$H$_{24}$NO$_2$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: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 of 20 µm of sample prepared in a 2 g L$^{-1}$ solution of the eluent. Under these conditions the components were eluted at 4.3 min (R) and 5.0 min (S).

HPLC traces:

Racemic 4b

(R)-4b

HPLC traces:

Racemic 4b

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

(Scheme 6)

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%); Rf 0.30 [petrol–EtOAc (90:10)]; FT-IR ν max film/cm⁻¹ 2975, 2940, 2865, 1740, 1695; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃, 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 × CH₂), 14.0; HRMS (ES) Found: MH⁺, 368.1620, C₁₉H₂₆₃₅ClNO₄, requires 368.1629; [α]D₂₃ +33.0 (1.0, CHCl₃); 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: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**

![HPLC trace for racemic 5b]

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

![HPLC trace for ($R$)-5b]

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

(Scheme 6)

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*<sub>f</sub> 0.55 [petrol–EtOAc (90:10)]; FT-IR ν<sub>max</sub> film/cm<sup>–1</sup> 2935, 2865, 1680; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 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); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) 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<sup>+</sup>, 336.1724, C<sub>19</sub>H<sub>26</sub>NO<sub>2</sub>Cl, requires 336.1730; [α]<sub>D</sub><sup>23</sup> +15.8 (1.5, CHCl<sub>3</sub>); 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:iPrOH (99:1 v/v) as the mobile phase at a flow rate of 1 mL min<sup>–1</sup>; ambient temperature, detection by UV absorbance at 254 nm. Injection volume of 20 µm of sample prepared in a 2 g L<sup>–1</sup> 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

(R)-7b

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

(Scheme 6)

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%); Rf 0.45 [petrol–EtOAc (90:10)]; FT-IR νmax film/cm−1 2975, 2940, 2865, 1685; 1H NMR (400 MHz, CDCl3) 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); 13C NMR (101 MHz, CDCl3) 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, C17H24NO2F, requires 294.1869; [α]D23 +1.6 (1.3, CHCl3); 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: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
(R)-1-tert-Butyl-2-ethyl-(4-fluorophenyl)piperidine-1,2-dicarboxylate 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 chromatogaph on silica gel, eluting with petrol–EtOAc (90:10), the carbamate 5c as an oil (32 mg, 84%); Rf 0.30 [petrol–EtOAc (90:10)]; FT-IR νmax film/cm⁻¹ 2975, 2940, 2870, 1740, 1695; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃, 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 × CH₂), 14.1; HRMS (ES) Found: MH⁺, 352.1928, C₁₉H₂₆FNO₄, requires 352.1924; [α]D²³ +22.0 (1.0, CHCl₃); 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:iPrOH (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 µL 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**

![HPLC trace for racemic 5c](image1)

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

![HPLC trace for $R$-5c](image2)
(R)-tert-Butyl-2-(2-naphthyl)piperidine-1-carboxylate 4d

(Scheme 6)

(N)

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%); Rf 0.45 [petrol–EtOAc (90:10)]; FT-IR νmax film/cm−1 2945, 2870, 1675; 1H NMR (400 MHz, CDCl3) 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); 13C NMR (101 MHz, CDCl3) 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, C21H27NO2, requires 326.2120; [α]D 23 +3.0 (1.0, CHCl3); 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: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**

![HPLC trace for racemic 4d]

<table>
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<tr>
<th>Retention time [min]</th>
<th>Area [%]</th>
<th>Height [arb. units]</th>
<th>Area [%]</th>
<th>Height [arb. units]</th>
<th>Result [%]</th>
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<td>0.402</td>
<td>6098.793</td>
<td>1708.35</td>
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<td>10.1</td>
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</tr>
<tr>
<td>Total</td>
<td>0.444</td>
<td>6192.753</td>
<td>12340.1</td>
<td>91.2</td>
<td>0.34</td>
<td></td>
</tr>
</tbody>
</table>

**\((R)\) 4d**

![HPLC trace for (R) 4d]

<table>
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<tr>
<th>Retention time [min]</th>
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<th>Height [arb. units]</th>
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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 ν_C=O. After addition of n-BuLi, a new peak at 1640 cm⁻¹ was observed which was assigned to ν_C=O in the lithiated intermediate.

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