Asymmetric synthesis of β-haloaryl β-amino acid derivatives

Steven D. Bull, Stephen G. Davies,* Santiago Delgado-Ballester, Peter M. Kelly, Luke J. Kotchie, Massimo Gianotti, Mario Laderas and Andrew D. Smith

The Dyson Perrins Laboratory, University of Oxford, South Parks Road, Oxford, UK OX1 3QY. E-mail: steve.davies@chemistry.ox.ac.uk

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Lithium *N*-benzyl-*N*-α-methyl-4-methoxybenzylamide may be employed as a homochiral ammonia equivalent for the synthesis of homochiral β-haloaryl β-amino acid derivatives *via* a strategy involving its conjugate addition to α,β-unsaturated β-haloaryl acceptors and subsequent oxidative deprotection with ceric ammonium nitrate.

Introduction

β-Haloaryl β-amino acids are an important sub-class of β-amino acids which have been widely employed within medicinal chemistry.[1] Previous synthetic strategies employed for the synthesis of these pharmacologically active compounds include the enzymatic resolution of β-haloaryl β-amino esters using the lipase Amano PS,[2] diastereoselective cycloaddition between β-haloaryl imines and ketenes,[3] and the Lewis acid catalyzed addition of a tributylstannane to a chiral oxazolidine.[4] While these reports represent efficient approaches towards the asymmetric synthesis of specific β-haloaryl β-amino acid targets, they lack generality and are therefore not applicable to the synthesis of libraries of homochiral β-haloaryl β-amino acid derivatives.[5] We have previously shown that a wide range of β-amino acid derivatives can be efficiently prepared *via* the conjugate addition of homochiral lithium amides derived from α-methylbenzylamine to α,β-unsaturated esters and subsequent reductive *N*-deprotection.[6] While these approaches offer versatile routes to β-amino acid derivatives, β-haloaryl β-amino acid derivatives are incompatible with this methodology as the haloaryl functionality within the substrate is labile under either the hydrogenolytic or Birch reduction conditions required for deprotection of the *N*-α-methylbenzyl group. We have previously described the development of a third generation homochiral ammonia equivalent, lithium (*S*)-*N*-benzyl-*N*-α-methyl-4-methoxybenzylamide, for the asymmetric synthesis of homochiral β-amino acids and β-lactams which involves deprotection *via* oxidative debenzylation[7] and now describe herein how this methodology may be employed for the asymmetric synthesis of a wide range of homochiral β-haloaryl β-amino acid derivatives. Part of this work has been previously communicated.[8]

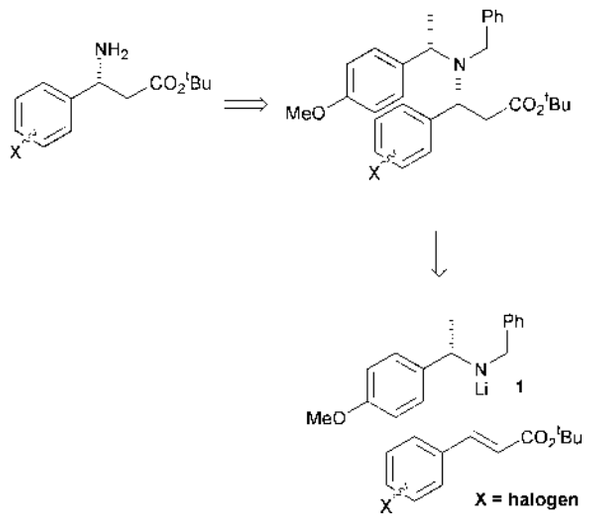
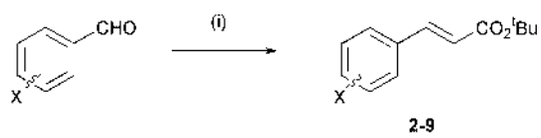


Fig. 1 General strategy for the asymmetric synthesis of β-haloaryl β-amino acid derivatives.



	X	Isolated Yield (%)
2	3-F	92
3	2-I	93
4	3-I	85
5	4-I	94
6	3-Cl	92
7	2-Br	93
8	3-Br	85
9	4-Br	92

Scheme 1 *Reagents and conditions*: (i) *tert*-butyl diethylphosphonoacetate (1.15 equiv.), *n*-BuLi (1.10 equiv.), THF, −78 °C then haloaryl aldehyde, −78 °C to RT.

Results and discussion

Synthesis of *tert*-butyl β-haloaryl α,β-unsaturated esters

Our synthetic strategy for the synthesis of β-haloaryl β-amino esters relied upon the conjugate addition of homochiral lithium *N*-benzyl-α-methyl-4-methoxybenzylamide **1** to suitably functionalised β-haloaryl α,β-unsaturated esters (Fig. 1). The required fluoro-, chloro-, bromo- and iodo-substituted *tert*-butyl (*E*)-β-haloarylprop-2-enoate conjugate acceptors **2**–**9** were readily prepared in >95% crude de[9] *via* Wadsworth–Emmons reaction of the parent benzaldehyde with the lithium anion of *tert*-butyl diethylphosphonoacetate. Purification gave multigram quantities of **2**–**9** in high yields as single diastereoisomers (Scheme 1).

Conjugate addition of *N*-benzyl-α-methyl-4-methoxybenzylamide 1 to α,β-unsaturated esters 2–9

Conjugate addition of (*S*)-**1** to the fluoro- and iodo- substituted α,β-unsaturated esters **2**–**5** and (*R*)-**1** to the bromo- and chloro-substituted α,β-unsaturated esters **6**–**9** afforded the *N*-benzyl-*N*-α-methyl-4-methoxybenzyl protected β-amino esters **10**–**17** with high levels of crude diastereoselectivity (88–94% de). While 3-fluoro (3*R*,α*S*)-**10**, 2-iodo (3*R*,α*S*)-**11** and 2-bromo (3*S*,α*R*)-**15** could be purified by fractional recrystallis-

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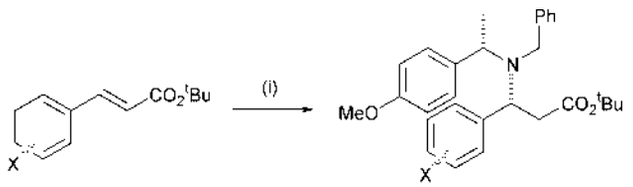
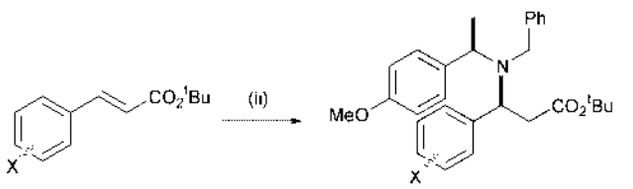
ation (Et_2O–hexane) to 97% de, 98% de and 98% de, respectively, repeated chromatography of the oily β-amino esters **12**–**14** and **16**–**17** did not enhance the diastereoselectivity of the products arising from the crude reaction mixtures. β-Amino esters **12**–**14** and **16**–**17** were therefore carried forward as mixtures of diastereoisomers (Scheme 2).

The absolute configurations of **10**–**17** were assigned by analogy to the model previously developed to explain the stereoselectivity observed during addition of homochiral lithium amides to α,β-unsaturated acceptors,[10] and the known stereoselectivity of lithium amide **1** upon addition to *tert*-butyl cinnamate.[7]



2-5 **10-13**

α,β-Unsaturated Acceptor	Addition Product	Crude d.e.[a]	Isolated Yield (%)	Isolated d.e.[a]
3-F **2**	(3*R*,α*S*)-**10**	92%	77	97%
2-I **3**	(3*R*,α*S*)-**11**	92%	76	98%
3-I **4**	(3*R*,α*S*)-**12**	88%	74	88%
4-I **5**	(3*R*,α*S*)-**13**	94%	79	94%



6-9 **14-17**

α,β-Unsaturated Acceptor	Addition Production	Crude d.e.[a]	Isolated Yield (%)	Isolated d.e.[a]
3-Cl **6**	(3*S*,α*R*)-**14**	88%	78	88%
2-Br **7**	(3*S*,α*R*)-**15**	90%	82	98%
3-Br **8**	(3*S*,α*R*)-**16**	90%	80	90%
4-Br **9**	(3*S*,α*R*)-**17**	92%	86	92%

Scheme 2 *Reagents and conditions*: (i) (*S*)-**1** (1.6 equiv.), THF, −78 °C; (ii) (*R*)-**1** (1.6 equiv.), THF, −78 °C. [a] As shown by ^{1}H NMR spectroscopic analysis.

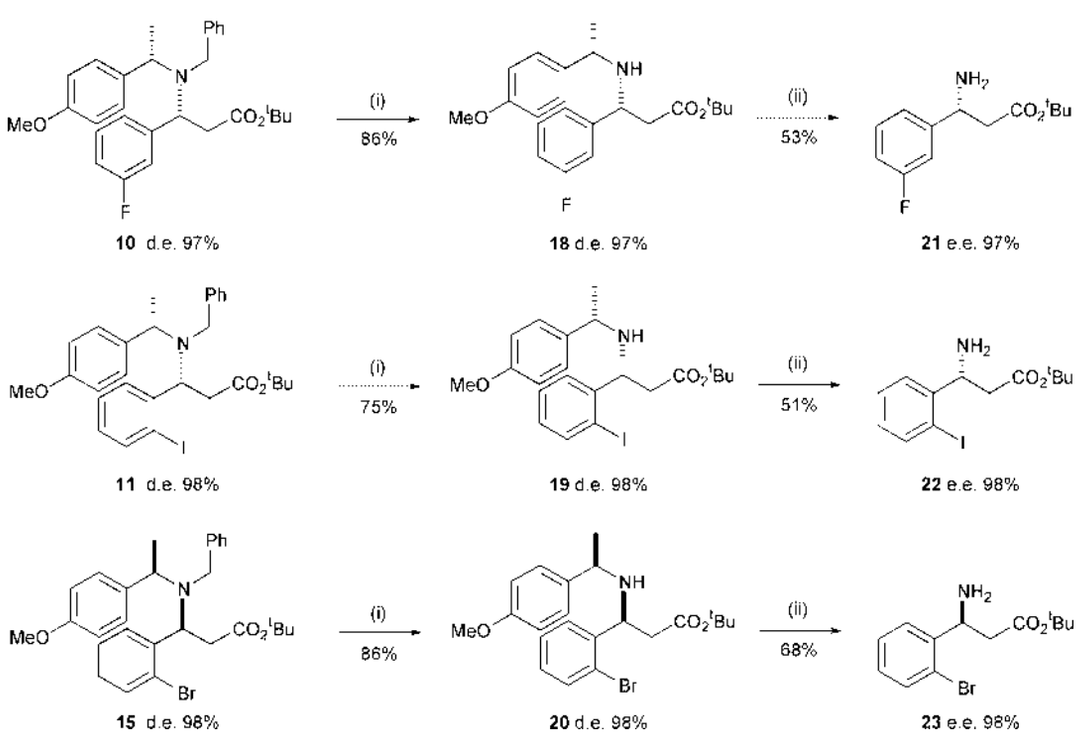
CAN promoted oxidative debenzylations

3-Fluoro (3*R*,α*S*)-**10** (97% de), 2-iodo (3*R*,α*S*)-**11** (98% de), and 2-bromo (3*S*,α*R*)-**15** (98% de), were subjected to mono *N*-benzylic deprotection *via* treatment with CAN (2.1 equiv.), furnishing the *N*-α-methyl-4-methoxybenzyl protected β-amino esters **18**–**20** in 75–86% yield. Further treatment of 3-fluoro (3*R*,α*S*)-**18**, 2-iodo (3*R*,α*S*)-**19** and 2-bromo (3*S*,α*R*)-**20** with CAN (4.0 equiv.) gave the desired *tert*-butyl 3-amino β-haloarylpropanoates **21**–**23** in 51–68% yield. The ee of each β-amino ester **21**–**23** was shown to be 97–98%, *via* derivatisation with Mosher's acid chloride and comparison of the ^{19}F and ^{1}H NMR spectra of the resulting amides with authentic racemic samples (Scheme 3).

Treatment of tertiary β-amino ester **12** (88% de) with CAN (2.1 equiv.) gave *tert*-butyl (3*R*,α*S*)-3-(α-methyl-4-methoxybenzylamino)-3-(iodophenyl)propanoate **24** in 77% yield and 88% de. (3*R*,α*S*)-**24** could not be purified to homogeneity at this stage by chromatography, so further treatment of (3*R*,α*S*)-**24** (88% de) with CAN (4.0 equiv.) gave *tert*-butyl (*R*)-3-amino-3-iodophenylpropanoate **25** in 49% yield and in 88% ee as determined by Mosher's ester analysis (Scheme 4).

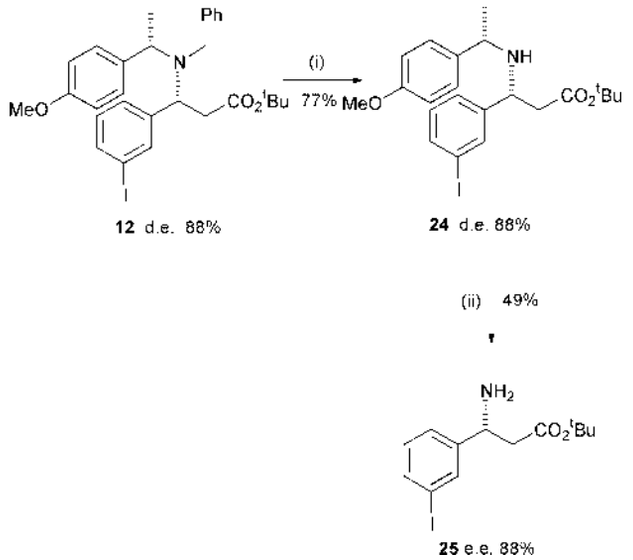
An alternative deprotection strategy was next devised to enable the corresponding (*R*)-methyl ester **27** to be obtained in high enantiomeric excess. Thus, treatment of (3*R*,α*S*)-**24** (88% de) with methanolic HCl afforded the methyl ester hydrochloride salt of (3*R*,α*S*)-**26** which was recrystallised [ethyl acetate–hexane (6 : 1)]. Conversion of (3*R*,α*S*)-**26**·HCl to its free amine using saturated aqueous $NaHCO_3$ solution gave (3*R*,α*S*)-**26** in 75% overall yield and 97% de as shown by ^{1}H NMR spectroscopic analysis. Deprotection of **26** *via* treatment with CAN afforded (*S*)-**27** in 48% yield. The ee of (*S*)-**27** was shown to be 97% by Mosher's amide derivatisation and comparison of the ^{19}F NMR spectrum with an authentic racemic standard (Scheme 5).

This protocol was therefore adopted for the deprotection of those β-amino esters **13**–**14**, **16**–**17** which could not be purified to homogeneity after the conjugate addition of lithium amide **1** to the appropriate α,β-unsaturated acceptor. Thus, CAN

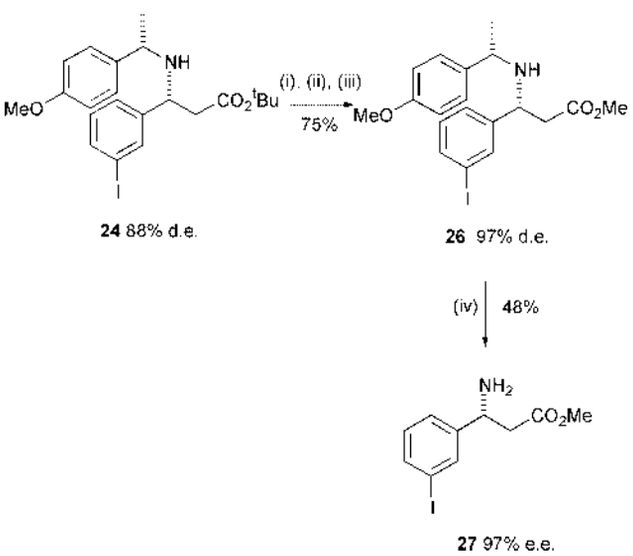


Scheme 3 *Reagents and conditions*: (i) CAN (2.1 equiv.), MeCN–H_2O (5 : 1), RT; (ii) CAN (4.0 equiv.), MeCN–H_2O (5 : 1), RT.

mono-debenzylation of **13**–**14**, **16**–**17** gave mono-deprotected secondary β-amino *tert*-butyl esters **28**–**31** in good yields, which were subsequently treated with methanolic HCl, recrystallised and treated with saturated aqueous bicarbonate to give the mono-deprotected secondary β-amino methyl esters **32**–**35** in 94–96% de. Deprotection of **32**–**35** *via* treatment with CAN afforded **36**–**39** in 51–61% yield. The ee's of β-amino esters **36**–**39** were shown to be 94–96% by conversion to the Mosher's amide and comparison of the ^{19}F NMR spectrum of each with an authentic racemic standard (Scheme 6).

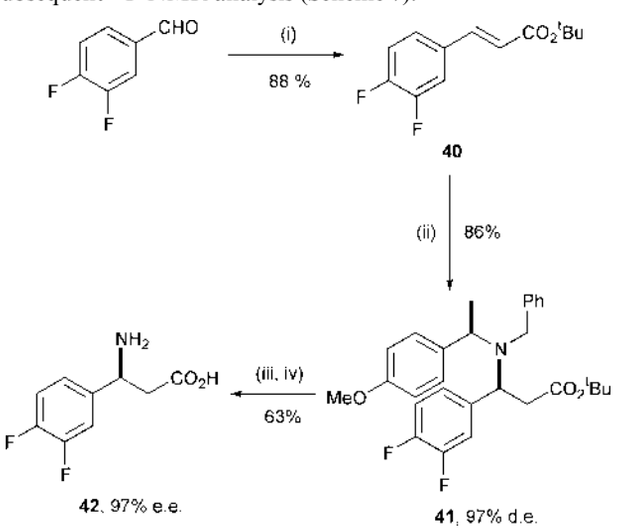


Scheme 4 *Reagents and conditions*: (i) CAN (2.1 equiv.), MeCN–H_2O (5 : 1), RT; (ii) CAN (4.0 equiv.), MeCN–H_2O (5 : 1), RT.

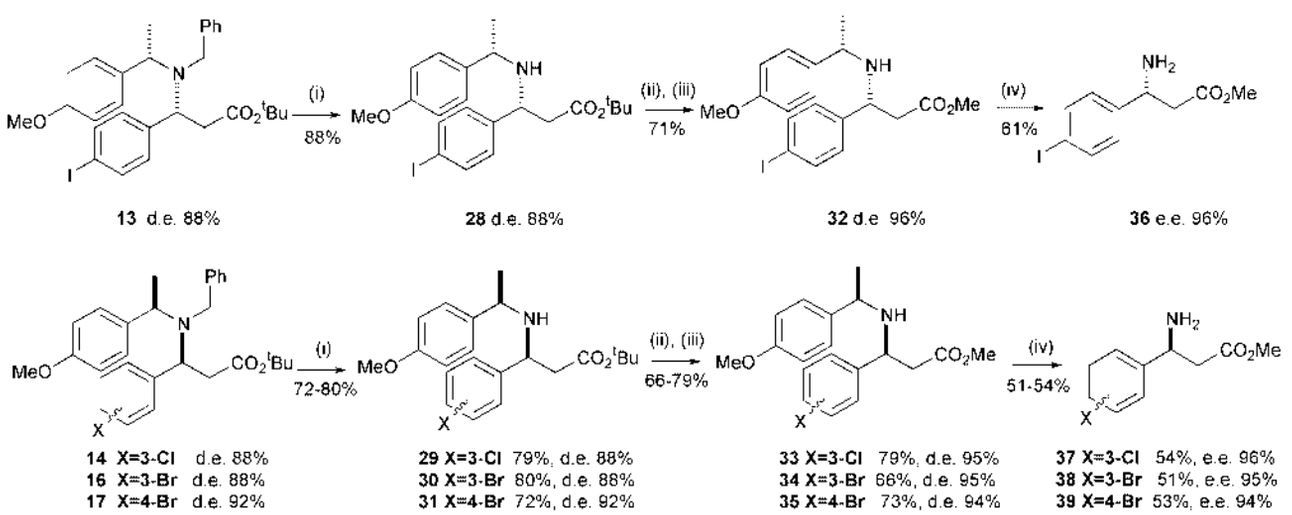


Scheme 5 *Reagents and conditions*: (i) HCl, MeOH; (ii) recrystallisation [ethyl acetate–hexane (6 : 1)]; (iii) $NaHCO_3$ (aq); (iv) CAN (4.0 equiv.), MeCN–H_2O (5 : 1), RT.

Having demonstrated the wide applicability of this stepwise oxidative *N*-deprotection protocol for the preparation of β-monohaloaryl β-amino acid derivatives, extension to the preparation of β-3,4-difluorophenyl-3-aminopropanoic acid **42**, an integral part of a variety of biologically active pseudopeptides shown to exhibit potent pharmacological activity,[1] was undertaken. Thus, *tert*-butyl 3-(3,4-difluorophenyl)prop-2-enoate **40** was prepared by Wittig reaction with 3,4-difluorobenzaldehyde, giving **40** as a single diastereoisomer after recrystallisation in 88% yield. Conjugate addition of lithium amide (*R*)-**1** gave *tert*-butyl (3*S*,α*R*)-3-(3,4-difluorophenyl)-3-(*N*-benzyl-α-methyl-4-methoxybenzylamino)propanoate **41** with a crude de of 90%. Recrystallisation allowed purification of (3*S*,α*R*)-**41** to 97% de in 86% yield. To demonstrate the versatility of this oxidative deprotection methodology, *N*-debenzylation of both *N*-protecting groups by treatment of (3*S*,α*R*)-**41** with CAN (6 equiv.) and subsequent treatment with aqueous acid gave (*S*)-3-(3,4-difluorophenyl)-3-aminopropanoic acid **42** in 63% yield. The ee of **42** was shown to be 97% by conversion to the methyl ester, derivatisation with homochiral and racemic Mosher's acid chloride and subsequent ^{19}F NMR analysis (Scheme 7).



Scheme 7 *Reagents and conditions*: (i) *tert*-butyl diethylphosphonoacetate, *n*-BuLi, THF, −78 °C; (ii) (*R*)-**1** (1.6 equiv.), THF, −78 °C; (iii) CAN (6.0 equiv.), MeCN–H_2O then HCl (aq); (iv) Dowex 50W–X8.



Scheme 6 *Reagents and conditions*: (i) CAN (2.1 equiv.), MeCN–H_2O (5 : 1), RT; (ii) HCl, MeOH; (iii) recrystallisation [ethyl acetate–hexane (6 : 1)]; then $NaHCO_3$ (aq); (iv) CAN (4.0 equiv.), MeCN–H_2O (5 : 1), RT.

Conclusions

In summary, the full potential of lithium *N*-benzyl-*N*-α-methyl-4-methoxybenzylamide **1** as a homochiral ammonia equivalent for the asymmetric synthesis of a range of β-haloaryl β-amino acid derivatives has been demonstrated. The two-step deprotection protocol allows the direct isolation of β-amino esters ready for further synthetic elaboration of the amine functionality (*e.g.* for β-peptide synthesis). Although only one example is given, the one-step deprotection protocol is general and gives the parent β-amino acids directly. Work is currently underway directed towards transferring this versatile methodology to polymer support for the asymmetric synthesis of libraries of homochiral β-amino acids.

Experimental

General experimental

All reactions involving organometallic or other moisture-sensitive reagents were performed under an atmosphere of nitrogen *via* standard vacuum line techniques. All glassware was flame-dried and allowed to cool under vacuum. THF was distilled under an atmosphere of dry nitrogen from sodium benzophenone ketyl. Water was distilled. All other solvents were used as supplied (analytical or HPLC grade), without prior purification. All organometallic reagents were used as supplied. All other reagents were used as supplied, without prior purification. Reactions were dried with $MgSO_4$. Thin layer chromatography (TLC) was performed on aluminium sheets coated with 60 F_{254} silica gel. Sheets were visualised using iodine, UV light or 1% aqueous $KMnO_4$ solution. Flash chromatography was performed on Kieselgel 60 silica gel. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker DPX 400 (^{1}H: 400 MHz and ^{13}C: 100.6 MHz) spectrometer or a Bruker AC 200 (^{1}H: 200 MHz and ^{13}C: 50.3 MHz) spectrometer in the deuteriated solvent stated. All chemical shifts (δ) are quoted in ppm and coupling constants (J) in Hz. Coupling constants are quoted twice, each being recorded as observed in the spectrum without averaging. Residual signals from the solvents were used as an internal reference. ^{13}C multiplicities were assigned using a DEPT sequence. Infrared spectra were recorded on a Perkin-Elmer 1750 IR Fourier Transform spectrophotometer using either thin films on NaCl plates (film) or KBr discs (KBr) as stated. Only the characteristic peaks are quoted. Low resolution mass spectra (*m*/*z*) were recorded on VG MassLab 20–250 or Micromass Platform 1 spectrometers and high resolution mass spectra (HRMS) on a Micromass Autospec 500 OAT spectrometer. Techniques used were chemical ionisation (CI, NH_3), or atmospheric pressure chemical ionisation (APCI) using partial purification by HPLC with methanol–acetonitrile–water (40 : 40 : 20) as the eluent. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a path length of 1 dm and are given in units of 10^{-1} deg cm^2 g^{-1}. Concentrations are quoted in g/100 ml. Melting points were recorded on a Leica VMTG Galen III apparatus and are uncorrected. Elemental analyses were performed by the microanalysis service of the Inorganic Chemistry Laboratory, Oxford.

General procedure 1

n-Butyllithium (1.05 equiv.) was added dropwise to a stirred solution of *tert*-butyl diethylphosphonoacetate (1.1 equiv.) in anhydrous THF at −78 °C under N_2 and the solution left to stir for thirty minutes. The phosphonate solution was transferred *via* cannula to the aldehyde (1.0 equiv.) in anhydrous THF at −78 °C under Ar and the resulting solution warmed to RT over two hours. The reaction was quenched with saturated aqueous ammonium chloride (5 ml), partitioned between EtOAc and H_2O, dried and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel.

General procedure 2

n-Butyllithium (1.55 equiv.) was added dropwise to a stirred solution of amine (1.6 equiv.) in anhydrous THF at −78 °C under N_2 and stirred for thirty minutes before addition of the β-haloaryl-α,β-unsaturated acceptor in anhydrous THF *via* cannula at −78 °C and stirred for a further two hours. The reaction was quenched with saturated aqueous ammonium chloride (5 ml) and partitioned between brine and 1 : 1 Et_2O–DCM. The organic layer was washed successively with 10% citric acid solution, saturated aqueous sodium bicarbonate solution and brine, dried and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel.

General procedure 3

CAN (2.1 equiv.) was added to a solution of the amine (1.0 equiv.) in 5 : 1 MeCN–H_2O and the solution stirred for two hours at room temperature. The reaction was quenched by addition of saturated aqueous sodium bicarbonate solution and partitioned between brine and Et_2O, dried and concentrated *in vacuo*. The crude product was purified by column chromatography.

General procedure 4

CAN (4.0 equiv.) was added to a solution of the amine (1.0 equiv.) in 5 : 1 MeCN–H_2O and the solution stirred overnight at room temperature. The reaction was quenched by addition of saturated aqueous sodium bicarbonate solution and partitioned between brine and Et_2O, dried and concentrated *in vacuo*. The crude product was purified by column chromatography.

General procedure 5

Hydrogen chloride gas was bubbled through MeOH at RT for ten minutes before addition of the amine in MeOH. After two hours the reaction was concentrated *in vacuo* and the resultant solid recrystallised. After recrystallisation, the white solid was partitioned between Et_2O and saturated aqueous sodium bicarbonate solution, dried and concentrated *in vacuo*.

Preparation of *tert*-butyl (*E*)-3-(3-fluorophenyl)prop-2-enoate 2

Following general procedure 1, *tert*-butyl diethylphosphonoacetate (2.73 g, 10.83 mmol), *n*-BuLi (2.5 M, 4.2 ml, 10.3 mmol) in THF (10 ml) and 3-fluorobenzaldehyde (1.22 g, 9.85 mmol) in THF (10 ml) gave, after purification by column chromatography on silica gel (hexane–Et_2O 40 : 1), **2** (2.01 g, 92%) as a colourless oil; ν_{max} (film) 2980 (CH), 1712 (C=O); δ_H (400 MHz, $CDCl_3$) 1.56 [9H, s, OC(*Me*)$_3$], 6.38 [1H, d, *J* 16.0, C(2)*H*], 7.07 [1H, m, Ph(5)*H* C_6H_4F], 7.18–7.38 [3H, m, Ph(2)*H*, Ph(4)*H* and Ph(6)*H* C_6H_4F], 7.52 [1H, d, *J* 16.0, C(3)*H*]; δ_C (100 MHz, $CDCl_3$) 28.6, 81.2, 114.6, 117.2, 122.1, 124.3, 130.8, 137.4, 142.5, 163.3, 166.5; *m*/*z* (CI$^+$) 223 (MH$^+$, 50%), 166 (MH$^+$ − C_4H_8 100%); HRMS (CI$^+$) $C_{13}H_{16}FO_2$ requires 223.1134, found 223.1133.

Preparation of *tert*-butyl (*E*)-3-(2-iodophenyl)prop-2-enoate 3

Following general procedure 1, *tert*-butyl diethylphosphonoacetate (5.0 g, 19.8 mmol), *n*-BuLi (1.6 M, 11.85 ml, 19.0 mmol) in THF (20 ml) and 2-iodobenzaldehye (4.0 g, 17.2 mmol) in THF (10 ml) gave, after purification by column chromatography on silica gel (hexane–Et_2O 40 : 1), **3** (5.39 g, 93%) as a yellow oil; ν_{max} (film) 2977 (CH), 1708 (C=O), 1637 (C=C); δ_H (400 MHz, $CDCl_3$) 1.55 [9H, s, OC(*Me*)$_3$], 6.25 [1H, d, *J* 15.7, C(2)*H*], 7.04 [1H, t, *J* 7.6, Ph(4)*H* C_6H_4I], 7.34 [1H, t, *J* 7.6, Ph(5)*H* C_6H_4I], 7.56 [1H, d, *J* 7.6, Ph(6)*H* C_6H_4I], 7.83 [1H, d, *J* 15.7, C(3)*H*], 7.90 [1H, d, *J* 7.6, Ph(3)*H* C_6H_4I]; δ_C (100 MHz, $CDCl_3$) 28.6, 81.2, 101.7, 123.4, 127.7, 128.9, 130.7, 135.9, 140.4, 147.1, 166.0; *m*/*z* (CI$^+$) 331 (MH$^+$, 10%),

348 (MNH_4^+, 30%); HRMS (CI^+) $C_{13}H_{16}IO_2$ requires 331.0195, found 331.0194.

Preparation of *tert*-butyl (*E*)-3-(3-iodophenyl)prop-2-enoate 4

Following general procedure 1, *tert*-butyl diethylphosphonoacetate (4.1 g, 16.3 mmol), *n*-BuLi (2.5 M, 6.2 ml, 15.5 mmol) in THF (15 ml) and 3-iodobenzaldehye (3.43 g, 14.8 mmol) in THF (15 ml) gave, after purification by column chromatography on silica gel (hexane–Et_2O 40 : 1), **4** (4.15 g, 85%) as a yellow oil; ν_{max} (film) 1707 (C=O), 1638 (C=C); δ_H (400 MHz, $CDCl_3$) 1.54 [9H, s, $OC(Me)_3$], 6.36 [1H, d, *J* 16.0, C(2)*H*], 7.12 [1H, t, *J* 7.8, Ph(5)*H* C_6H_4I], 7.47 [1H, d, *J* 16.0, C(3)*H*], 7.48 [1H, d, *J* 8.0, Ph(6)*H* C_6H_4I], 7.69 [1H, d, *J* 8.3, Ph(4)*H* C_6H_4I], 7.87 [1H, s, Ph(2)*H* C_6H_4I]; δ_C (100 MHz, $CDCl_3$) 28.6, 81.2, 95.1, 122.0, 127.6, 130.9, 137.0, 137.3, 139.1, 142.1, 166.2; *m*/*z* (CI^+) 331 (MH^+, 40%), 348 (MNH_4^+, 35%); HRMS (CI^+) $C_{13}H_{16}IO_2$ requires 331.0195, found 331.0197.

Preparation of *tert*-butyl (*E*)-3-(4-iodophenyl)prop-2-enoate[11] 5

Following general procedure 1, *tert*-butyl diethylphosphonoacetate (3.9 g, 15.5 mmol), *n*-BuLi (2.5 M, 9.25 ml, 14.8 mmol) in THF (20 ml) and 4-iodobenzaldehye (3.1 g, 13.5 mmol) in THF (20 ml) gave, after purification by column chromatography on silica gel (hexane–Et_2O 40 : 1) and recrystallisation (hexane–Et_2O), **5** (4.2 g, 94%) as white needles; mp 65–66 °C (hexane–Et_2O); δ_H (400 MHz, $CDCl_3$) 1.54 [9H, s, $OC(Me)_3$], 6.38 [1H, d, *J* 16.0, C(2)*H*], 7.24 [2H, m, Ph(2)*H* and Ph(6)*H* C_6H_4I], 7.51 [1H, d, *J* 16.0, C(3)*H*], 7.72 [2H, d, *J* 8.5, Ph(3)*H* and Ph(5)*H* C_6H_4I].

Preparation of *tert*-butyl (*E*)-3-(3-chlorophenyl)prop-2-enoate 6

Following general procedure 1, *tert*-butyl diethylphosphonoacetate (5.9 g, 23.5 mmol), *n*-BuLi (2.5 M, 9.0 ml, 22.5 mmol) in THF (15 ml) and 3-chlorobenzaldehyde (3.0 g, 21.4 mmol) in THF (15 ml) gave, after purification by column chromatography on silica gel (hexane–Et_2O 40 : 1), **6** (4.69 g, 92%) as a colourless oil; ν_{max} (film) 2979 (CH), 1712 (C=O); δ_H (400 MHz, $CDCl_3$) 1.54 [9H, s, $OC(Me)_3$], 6.38 [1H, d, *J* 16.0, C(2)*H*], 7.18 [1H, m, Ph(4)*H* C_6H_4Cl], 7.25–7.39 [2H, m, Ph(5)*H* and Ph(6)*H* C_6H_4Cl], 7.50 [1H, s, Ph(2)*H* C_6H_4Cl], 7.52 [1H, d, *J* 16.0, C(3)*H*]; δ_C (100 MHz, $CDCl_3$) 28.0, 80.8, 121.8, 126.3, 127.8, 130.0, 130.2, 135.0, 136.7, 142.1, 166.1; *m*/*z* (CI^+) 239 (MH^+, 65%), 182 ($MH^+ - C_4H_8$, 100%); HRMS (CI^+) $C_{13}H_{16}ClO_2$ requires 239.0839, found 239.0838.

Preparation of *tert*-butyl (*E*)-3-(2-bromophenyl)prop-2-enoate 7

Following general procedure 1, *tert*-butyl diethylphosphonoacetate (5.8 g, 23.1 mmol), *n*-BuLi (2.5 M, 9.25 ml, 21.1 mmol) in THF (20 ml) and 2-bromobenzaldehyde (3.3 g, 17.8 mmol) in THF (20 ml) gave, after purification by column chromatography on silica gel (hexane–Et_2O 40 : 1), **7** (4.7 g, 93%) as a colourless oil; ν_{max} (film) 1710 (C=O), 1635 (C=C); δ_H (400 MHz, $CDCl_3$) 1.54 [9H, s, $CO_2C(Me)_3$], 6.32 [1H, d, *J* 15.9, C(2)*H*], 7.19 [1H, m, Ph(4)*H* C_6H_4Br], 7.30 [1H, m, Ph(5)*H* C_6H_4Br], 7.58 [2H, m, Ph(3)*H* and Ph(6)*H* C_6H_4Br], 7.96 [1H, d, *J* 15.9, C(3)*H*]; δ_C (100 MHz, $CDCl_3$) 28.1, 80.7, 122.9, 125.2, 127.6, 130.9, 133.3, 134.6, 141.9, 165.7; *m*/*z* (CI^+) 283 (MH^+, 10%); HRMS (CI^+) $C_{13}H_{16}BrO_2$ requires 283.0334, found 283.0336.

Preparation of *tert*-butyl (*E*)-3-(3-bromophenyl)prop-2-enoate 8

Following general procedure 2, *tert*-butyl diethylphosphonoacetate (1.5 g, 5.94 mmol), *n*-BuLi (2.5 M, 2.27 ml, 5.67 mmol) in THF (10 ml) and 3-bromobenzaldehyde (1.0 g, 5.40 mmol) in THF (10 ml) gave, after purification by column chromatography on silica gel (hexane–Et_2O 40 : 1), **8** (1.3 g, 85%) as a colourless oil; ν_{max} (film) 1709 (C=O), 1639 (C=C); δ_H (400 MHz, $CDCl_3$) 1.54 [9H, s, $OC(Me)_3$], 6.36 [1H, d, *J* 16.0, C(2)*H*], 7.24 [1H, t, *J* 7.9, Ph(5)*H* C_6H_4Br], 7.42 [1H, m, Ph(6)*H* C_6H_4Br], 7.48 [1H, m, Ph(4)*H* C_6H_4Br], 7.50 [1H, d, *J* 16.0, C(3)*H*], 7.65 [1H, s, Ph(2)*H* C_6H_4Br]; δ_C (100 MHz, $CDCl_3$) 28.1, 80.8, 121.7, 122.9, 126.5, 130.3, 130.6, 132.7, 136.7, 141.7, 165.8; *m*/*z* (CI^+) 283 (MH^+, 30%); HRMS (CI^+) $C_{13}H_{16}BrO_2$ requires 283.0334, found 283.0329.

Preparation of *tert*-butyl (*E*)-3-(4-bromophenyl)prop-2-enoate 9

Following general procedure 1, *tert*-butyl diethylphosphonoacetate (2.7 g, 10.9 mmol), *n*-BuLi (2.5 M, 4.2 ml, 10.3 mmol) in THF (10 ml) and 4-bromobenzaldehyde (1.2 g, 9.9 mmol) in THF (10 ml) gave, after purification by column chromatography on silica gel (hexane–Et_2O 40 : 1), **9** (2.0 g, 92%) as white needles; mp 66 °C (hexane–Et_2O); found C, 55.3%, H, 5.1%; $C_{13}H_{15}BrO_2$ requires C, 55.15%, H, 5.3%; ν_{max} (KBr) 1707 (C=O), 1637 (C=C); δ_H (400 MHz, $CDCl_3$) 1.53 [9H, s, $CO_2C(Me)_3$], 6.35 [1H, d, *J* 16.0, C(2)*H*], 7.35–7.53 [5H, m, *Ph* and C(3)*H*)]; δ_C (50 MHz, $CDCl_3$) 28.1, 80.7, 120.9, 124.1, 129.3, 132.0, 133.5, 142.1, 166.0; *m*/*z* (NH_3) 284.2 (MH^+, 25%), 228.2 ($MH^+ - C_4H_8$, 100%).

Preparation of *tert*-butyl (3*R*,α*S*)-3-(3-fluorophenyl)-3-(*N*-benzyl-*N*-α-methyl-4-methoxybenzylamino)propanoate 10

Following general procedure 2, *n*-BuLi (2.5 M, 2.8 ml, 7.0 mmol), (*S*)-α-methyl-4-methoxybenzylamine (1.74 g, 7.2 mmol) in THF (10 ml) and (*E*)-**2** (1.0 g, 4.5 mmol) in THF (10 ml) gave, after purification by column chromatography on silica gel (hexane–Et_2O 10 : 1) and recrystallisation (hexane–Et_2O), **10** (1.60 g, 77%) as a white solid; found: C, 75.2; H, 7.3; N 3.0%; $C_{29}H_{34}FNO_3$ requires C, 75.1; H, 7.4; N, 3.0%; mp 87–88 °C (hexane–Et_2O); $[a]_D^{20}$ −25.0 (*c* 1.0, $CHCl_3$); ν_{max} (KBr disc) 2971 (CH), 1735 (C=O), 1509 (OMe), 1246 (Ph–OMe); δ_H (400 MHz, $CDCl_3$) 1.27 [9H, s, $OC(Me)_3$], 1.28 [3H, d, *J* 6.9, C(α)*Me*], 2.46 [1H, dd, $J_{2A,2B}$ 14.8, $J_{2A,3}$ 9.9, C(2) H_A], 2.52 [1H, dd, $J_{2B,2A}$ 14.8, $J_{2B,3}$ 5.0, C(2)H_B], 3.66 (2H, s, NCH_2Ph), 3.81 (3H, s, O*Me*), 3.93 [1H, q, *J* 6.9, C(α)*H*], 4.42 [1H, dd, $J_{3,2A}$ 9.9, $J_{3,2B}$ 5.0, C(3)*H*], 6.88 [2H, m, Ph(3)*H* and Ph(5)*H* C_6H_4OMe], 6.95 [1H, m, Ph(2)*H* C_6H_4F], 7.16–7.35 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.8, 27.8, 38.0, 50.7, 55.2, 56.5, 58.9, 80.9, 113.5, 113.9, 115.1, 123.7, 126.6, 127.9, 128.2, 128.8, 129.5, 135.7, 141.4, 145.0, 158.5, 162.8, 171.0; *m*/*z* ($APCI^+$) 464 (MH^+, 20%).

Preparation of *tert*-butyl (3*R*,α*S*)-3-(2-iodophenyl)-3-(*N*-benzyl-*N*-α-methyl-4-methoxybenzylamino)propanoate 11

Following general procedure 2, *n*-BuLi (2.5 M, 1.88 ml, 4.7 mmol), (*S*)-α-methyl-4-methoxybenzylamine (1.17 g, 4.9 mmol) in THF (10 ml) and (*E*)-**3** (1.0 g, 3.0 mmol) in THF (10 ml) gave, after purification by column chromatography on silica gel (hexane–Et_2O 15 : 1) and recrystallisation (hexane–Et_2O), **11** (1.32 g, 76%) as white crystals; mp 98–99 °C (hexane–Et_2O); found: C, 61.1; H, 6.05; N, 2.5%; $C_{29}H_{34}INO_3$ requires C, 60.95; H, 6.0; N, 2.45%; $[a]_D^{22}$ −34.5 (*c* 1.0, $CHCl_3$); ν_{max} (film) 3020 (CH), 1716 (C=O), 1512 (OMe), 1216 (Ph–OMe); δ_H (400 MHz, $CDCl_3$) 1.19 [9H, s, $OC(Me)_3$], 1.49 [3H, d, *J* 6.8, C(α)*Me*], 2.18 [1H, dd, $J_{2A,2B}$ 14.0, $J_{2A,3}$ 9.6, C(2)H_A], 2.60 [1H, dd, $J_{2B,2A}$ 14.0, $J_{2B,3}$ 5.8, C(2)H_B], 3.75 (2H, ABq, NCH_2Ph), 3.76 (3H, s, O*Me*), 3.88 [1H, q, *J* 6.8, C(α)*H*], 4.74 [1H, dd, $J_{3,2A}$ 9.6, $J_{3,2B}$ 5.8, C(3)*H*], 6.81 [2H, m, Ph(3)*H* and Ph(5)*H* C_6H_4OMe], 6.95 [1H, m, Ph(6)*H* C_6H_4I], 7.21 (5H, m, *Ph*), 7.27 [2H, m, Ph(2)*H* and Ph(6)*H* C_6H_4OMe], 7.40 [1H, m, Ph(5)*H* C_6H_4I], 7.64 [1H, m, Ph(4)*H* C_6H_4I], 7.81 [1H, m, Ph(3)*H* C_6H_4I]; δ_C (100 MHz, $CDCl_3$) 13.2, 28.3, 43.4, 50.8, 55.7, 56.6, 66.7, 80.8, 102.2, 113.7, 126.8, 128.0, 128.6, 128.8, 129.5, 130.3, 136.3, 140.1, 143.3, 145.9, 158.8, 170.7; *m*/*z* ($APCI^+$) 572 (MH^+, 15%), 135 ($C_9H_{11}O^+$, 95%).

Preparation of *tert*-butyl (3*R*,α*S*)-3-(3-iodophenyl)-3-(*N*-benzyl-*N*-α-methyl-4-methoxybenzylamino)propanoate 12

Following general procedure 2, *n*-BuLi (2.5 M, 3.9 ml, 9.7

mmol), (*S*)-α-methyl-4-methoxybenzylamine (2.26 g, 9.4 mmol) in THF (20 ml) at −78 °C and (*E*)-**4** (2.0 g, 6.06 mmol) in THF (20 ml) gave, after purification by column chromatography on silica gel (hexane–Et_2O 15 : 1), **12** (2.56 g, 74%) as a pale green oil; $[\alpha]_D^{20}$ −18.0 (*c* 1.0, $CHCl_3$); ν_{max} (film) 1725 (C=O), 1511 (OMe), 1247 (Ph–OMe); δ_H (400 MHz, $CDCl_3$) 1.29 [9H, s, OC(*Me*)$_3$], 1.30 [3H, d, *J* 6.9, C(α)*Me*], 2.42 [1H, dd, $J_{2A,2B}$ 14.7, $J_{2A,3}$ 10.0, C(2)H_A], 2.48 [1H, dd, $J_{2B,2A}$ 14.7, $J_{2B,3}$ 5.1, C(2)H_B], 3.64 (2H, s, NCH_2Ph), 3.81 (3H, s, O*Me*), 3.93 [1H, q, *J* 6.9, C(α)*H*], 4.36 [1H, dd, $J_{3,2A}$ 10.0, $J_{3,2B}$ 5.1, C(3)*H*], 6.88 [2H, m, Ph(3)*H* and Ph(5)*H* C_6H_4OMe], 7.08 [1H, m, Ph(5)*H* C_6H_4I], 7.20–7.28 (4H, m, *Ph*), 7.30 [2H, m, Ph(2)*H* and Ph(6)*H* C_6H_4OMe], 7.41 [1H, m, Ph(6)*H* C_6H_4I], 7.58 [1H, m, Ph(4)*H* C_6H_4I], 7.75 [1H, m, Ph(2)*H* C_6H_4I]; δ_C (100 MHz, $CDCl_3$) 16.9, 27.8, 34.6, 50.7 55.2, 56.6, 58.9, 80.5, 94.1, 113.5, 126.6, 127.5, 127.9, 128.1, 128.8, 129.9, 135.6, 136.0, 137.2, 141.4, 144.8, 158.5, 170.8; *m*/*z* (APCI$^+$) 572 (MH$^+$, 5%), 135 ($C_9H_{11}O^+$, 100%); HRMS (CI$^+$) $C_{29}H_{35}INO_3$ requires 572.1662, found 572.1658.

Preparation of *tert*-butyl (3*R*,α*S*)-3-(4-iodophenyl)-3-(*N*-benzyl-*N*-α-methyl-4-methoxybenzylamino)propanoate 13

Following general procedure 2, *n*-BuLi (2.5 M, 2.2 ml, 5.4 mmol), (*S*)-α-methyl-4-methoxybenzylamine (1.27 g, 5.25 mmol) in THF (15 ml) and (*E*)-**5** (1.12 g, 3.4 mmol) in THF (15 ml) gave, after purification by column chromatography on silica gel (hexane–Et_2O 15 : 1), **13** (1.53 g, 79%) as a white foam; $[\alpha]_D^{20}$ −6.9 (*c* 1.0, $CHCl_3$); ν_{max} (film) 2975 (CH), 1726 (C=O), 1511 (OMe), 1248 (Ph–OMe); δ_H (400 MHz, $CDCl_3$) 1.25 [9H, s, OC(*Me*)$_3$], 1.26 [3H, d, *J* 6.4, C(α)*Me*], 2.42 [1H, dd, $J_{2A,2B}$ 14.8, $J_{2A,3}$ 10.1, C(2)H_A], 2.48 [1H, dd, $J_{2B,2A}$ 14.8, $J_{2B,3}$ 4.9, C(2)H_B], 3.62 (2H, ABq, NCH_2Ph), 3.80 (3H, s, O*Me*), 3.89 [1H, q, *J* 6.4, C(α)*H*], 4.35 [1H, dd, $J_{3,2A}$ 10.1, $J_{3,2B}$ 4.9, C(3)*H*], 6.86 [2H, m, Ph(3)*H* and Ph(5)*H* C_6H_4OMe], 7.16 [2H, m, Ph(2)*H* and Ph(6)*H* C_6H_4I], 7.25 (5H, m, *Ph*), 7.29 [2H, m, Ph(2)*H* and Ph(6)*H* C_6H_4OMe], 7.65 [2H, m, Ph(3)*H* and Ph(5)*H* C_6H_4I]; δ_C (100 MHz, $CDCl_3$) 16.9, 27.8, 37.9, 50.7, 55.2, 56.6, 58.9, 80.5, 92.6, 113.7, 126.8, 128.1, 128.4, 129.0, 130.5, 136.0, 137.4, 141.7, 142.3, 158.8, 171.3; *m*/*z* (CI$^+$) 572 (MH$^+$, 30%); HRMS (CI$^+$) $C_{29}H_{35}INO_3$ requires 572.1662, found 572.1660.

Preparation of *tert*-butyl (3*S*,α*R*)-3-(3-chlorophenyl)-3-(*N*-benzyl-*N*-α-methyl-4-methoxybenzylamino)propanoate 14

Following general procedure 2, *n*-BuLi (2.5 M, 2.6 ml, 6.5 mmol), (*R*)-α-methyl-4-methoxybenzylamine (1.61 g, 6.7 mmol) in THF (15 ml) and (*E*)-**6** (1.12 g, 3.4 mmol) in THF (15 ml) gave, after purification by column chromatography on silica gel (hexane–Et_2O 15 : 1), **14** (1.26 g, 78%) as a pale green oil; $[\alpha]_D^{20}$ −19.2 (*c* 1.0, $CHCl_3$); ν_{max} (film) 2976 (C–H), 1726 (C=O), 1512 (OMe), 1249 (Ph–OMe); δ_H (400 MHz, $CDCl_3$) 1.27 [9H, s, OC(*Me*)$_3$], 1.28 [3H, d, *J* 6.9, C(α)*Me*], 2.45 [1H, dd, $J_{2A,2B}$ 14.7, $J_{2A,3}$ 9.9, C(2)H_A], 2.50 [1H, dd, $J_{2B,2A}$ 14.7, $J_{2B,3}$ 5.1, C(2)H_B], 3.65 (2H, ABq, NCH_2Ph), 3.81 (3H, s, O*Me*), 3.93 [1H, q, *J* 6.9, C(α)*H*], 4.40 [1H, dd, $J_{3,2A}$ 9.9, $J_{3,2B}$ 5.1, C(3)*H*], 6.89 [2H, m, Ph(3)*H* and Ph(5)*H* C_6H_4OMe], 7.19–7.33 (10H, m, Ar*H*), 7.41 [1H, s, Ph(2)*H* C_6H_4Cl]; δ_C (100 MHz, $CDCl_3$) 16.8, 27.8, 38.0, 50.7, 55.2, 56.6, 59.0, 80.5, 113.4, 126.4, 126.6, 127.2, 127.9, 128.2, 128.3, 128.8, 129.4, 133.9, 135.63, 141.4, 144.4, 158.5, 170.9; *m*/*z* (APCI$^+$) 480 (MH$^+$, 10%); HRMS (CI$^+$) $C_{29}H_{35}ClNO_3$ requires 480.2306, found 480.2307.

Preparation of *tert*-butyl (3*S*,α*R*)-3-(2-bromophenyl)-3-(*N*-benzyl-*N*-α-methyl-4-methoxybenzylamino)propanoate 15

Following representative procedure 2, *n*-BuLi (2.5 M, 5.5 ml, 13.7 mmol), (*R*)-α-methyl-4-methoxybenzylamine (3.4 g, 14.1 mmol) in THF (20 ml) and (*E*)-**7** (2.5 g, 8.8 mmol) in THF (30 ml) gave, after successive purification by column chromatography on silica gel (hexane–Et_2O 5 : 1) and recrystallisation, **15** as a white solid (3.77 g, 82%); found C, 66.2; H, 7.0, N, 2.6%; $C_{29}H_{34}BrNO_3$ requires C, 66.4; H, 6.5; N, 2.7%; $[\alpha]_D^{23}$ +59.4 (*c* 1.03, $CHCl_3$); ν_{max} (film) 1729 (C=O), 1510 (OMe), 1249 (Ph–OMe); δ_H (400 MHz, $CDCl_3$) 1.17 [9H, s, $CO_2C(Me)_3$], 1.43 [3H, d, *J* 6.8, C(α)*Me*)], 2.28 [1H, dd, $J_{2A,2B}$ 13.9, $J_{2A,3}$ 10.3, C(2)H_A], 2.63 [1H, dd, $J_{2B,2A}$ 13.9, $J_{2B,3}$ 5.4, C(2)H_B], 3.76 (2H, ABq, *J* 15.4, NCH_2Ph), 3.78 (3H, s, O*Me*), 3.91 [1H, q, *J* 6.8, C(α)*H*], 4.91 [1H, dd, $J_{3,2A}$ 10.3, $J_{3,2B}$ 5.4, C(3)*H*], 6.82 [2H, m, Ph(3)*H* and Ph(5)*H* C_6H_4OMe], 7.11 [1H, m, Ph(4)*H* C_6H_4Br], 7.14–7.27 (5H, m, *Ph*), 7.29 [2H, m, Ph(2)*H* and Ph(6)*H* C_6H_4OMe], 7.36 [1H, m, Ph(3)*H* C_6H_4Br], 7.53 [1H, m, Ph(5)*H* C_6H_4Br], 7.65 [1H, m, Ph(6)*H* C_6H_4Br]; δ_C (100 MHz, $CDCl_3$) 12.9, 27.6, 42.2, 50.4, 55.2, 56.2, 61.0, 80.3, 113.2, 125.3, 126.3, 127.5, 128.0, 128.7, 129.0, 130.0, 132.9, 135.8, 141.9, 142.6, 158.3, 170.2; *m*/*z* (APCI$^+$) 524 (MH$^+$, 20%).

Preparation of *tert*-butyl (3*S*,α*R*)-3-(3-bromophenyl)-3-(*N*-benzyl-*N*-α-methyl-4-methoxybenzylamino)propanoate 16

Following general procedure 2, *n*-BuLi (2.5 M, 5.64 ml, 14.1 mmol), (*R*)-α-methyl-4-methoxybenzylamine (3.37 g, 14.1 mmol) in THF (20 ml) and (*E*)-**8** (2.5 g, 8.8 mmol) in THF (30 ml) gave, after purification by column chromatography on silica gel (hexane–Et_2O 5 : 1), **16** (3.7 g, 80%) as a colourless oil; $[\alpha]_D^{20}$ +18.6 (*c* 1.03, $CHCl_3$); ν_{max} (film) 1724 (s, C=O); δ_H (400 MHz, $CDCl_3$) 1.28 [9H, s, OC(*Me*)$_3$], 1.29 [3H, d, *J* 6.8, C(α)*Me*], 2.44 [1H, dd, $J_{2A,2B}$ 14.7, $J_{2A,3}$ 9.9, C(2)H_A], 2.50 [1H, dd, $J_{2B,2A}$ 14.7, $J_{2B,3}$ 5.6, C(2)H_B], 3.65 (2H, m, NCH_2PH), 3.81 (3H, s, O*Me*), 3.93 [1H, q, *J*6.8, C(α)*H*], 4.39 [1H, dd, $J_{3,2A}$ 9.8, $J_{3,2B}$ 5.0, C(3)*H*], 6.88 [2H, m, Ph(3)*H* and Ph(5)*H* C_6H_4OMe], 7.20–7.29 [6H, m, *Ph* and Ph(5)*H* C_6H_4Br], 7.32 [2H, m, Ph(2)*H* and Ph(6)*H* C_6H_4OMe], 7.38 [2H, m, Ph(4)*H* and Ph(6)*H* C_6H_4Br], 7.56 [Ph(2)*H* C_6H_4Br]; δ_C (100 MHz, $CDCl_3$) 16.9, 27.8, 38.0, 50.7, 55.2, 56.6, 59.0, 80.4, 113.5, 122.2, 126.6, 126.9, 127.9, 128.2, 128.8, 130.1, 129.6, 130.1, 131.2, 135.6, 141.4, 144.7, 158.5, 170.9; *m*/*z* (APCI$^+$) 524 (MH$^+$, 5%); HRMS (CI$^+$) $C_{29}H_{35}BrNO_3$ requires 524.1800, found 524.1795.

Preparation of *tert*-butyl (3*S*,α*R*)-3-(4-bromophenyl)-3-(*N*-benzyl-*N*-α-methyl-4-methoxybenzylamino)propanoate 17

Following general procedure 2, *n*-BuLi (1.6 M, 3.5 ml, 5.47 mmol, 1.55 equiv.), (*R*)-α-methyl-4-methoxybenzylamine (1.38 g, 5.7 mmol, 1.6 equiv.) and in THF (20 ml) and (*E*)-**9** (1.0 g, 3.53 mmol, 1.0 equiv.) in THF (10 ml) gave, after purification by column chromatography on silica gel (hexane–Et_2O 6 : 1) **17** (1.60 g, 86%) as a colourless oil; $[\alpha]_D^{24}$ +10.4 (*c* 1.0, $CHCl_3$); ν_{max} (film) 2976, 2933 (C–H), 1725 (C=O), 1511 (OMe), 1248 (Ph–OMe), 1153 (C–O); δ_H (400 MHz, $CDCl_3$) 1.26 [9H, s, $CO_2C(Me)_3$], 1.27 [3H, d, *J* 7.4, C(α)*Me*], 2.45 [1H, dd, $J_{2A,2B}$ 14.8, $J_{2A,3}$ 10.1, C(2)H_A], 2.53 [1H, dd, $J_{2B,2A}$ 14.8, $J_{2B,3}$ 4.8, C(2)H_B], 3.64 (2H, ABq, NCH_2), 3.81 (3H, s, O*Me*), 3.92 [1H, q, *J* 7.4, C(α)*H*], 4.38 [1H, dd, $J_{3,2A}$ 10.1, $J_{3,2B}$ 4.8, C(3)*H*], 6.87 [2H, d, *J* 8.6, Ph(3)*H* and Ph(5)*H* C_6H_4OMe], 7.17–7.33 (9H, m, *Ph*), 7.46 [2H, d, *J* 8.4, Ph(3)*H* and Ph(5)*H* C_6H_4Br]; δ_C (100 MHz, $CDCl_3$) 16.9, 27.8, 37.9, 50.7, 55.2, 56.6, 58.7, 80.4, 113.5, 120.8, 126.6, 127.9, 128.1, 128.8, 129.9, 131.1, 135.7, 141.2, 141.4, 158.5, 170.9; *m*/*z* (APCI$^+$) 524.0 (MH$^+$, 10%), 134.8 ($C_9H_{11}O^+$, 100%); HRMS (CI$^+$) $C_{29}H_{35}BrNO_3$ requires 524.1800; found 524.1798.

Preparation of *tert*-butyl (3*R*,α*S*)-3-(3-fluorophenyl)-3-(*N*-α-methyl-4-methoxybenzylamino)propanoate 18

Following general procedure 3, CAN (2.49 g, 4.53 mmol) and **10** (1.0 g, 2.16 mmol) in 5 : 1 MeCN–H_2O (12 ml) gave, after work up and purification by column chromatography on silica gel (hexane–Et_2O 4 : 1–1% NEt_3), **18** (706 mg, 86%) as a yellow oil; $[\alpha]_D^{20}$ −20.3 (*c* 1.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 3329 (NH), 1724 (C=O); δ_H (400 MHz, $CDCl_3$) 1.36 [3H, d, *J* 6.5, C(α)*Me*], 1.40

[9H, s, OC(*Me*)$_3$], 2.56 [1H, dd, $J_{2A,2B}$ 14.9, $J_{2A,3}$ 6.6, C(2)H_A], 2.64 [1H, dd, $J_{2B,2A}$ 14.9, $J_{2B,3}$ 6.6, C(2)H_B], 3.66 [1H, q, *J* 6.5, C(α)*H*], 3.79 (3H, s, O*Me*), 4.15 [1H, t, *J* 6.6, C(3)*H*], 6.83 [2H, m, Ph(3)*H* and Ph(5)*H* C_6H_4OMe], 6.92 [1H, m, Ph(2)*H* C_6H_4F], 7.04 [2H, m, Ph(4)*H* and Ph(6)*H* C_6H_4F], 7.18 [2H, m, Ph(2)*H* and Ph(6)*H* C_6H_4OMe], 7.24 [1H, m, Ph(5)*H* C_6H_4F]; δ_C (100 MHz, $CDCl_3$) 22.4, 28.0, 43.5, 54.1, 55.2, 56.7, 80.6, 113.7, 113.9, 114.1, 122.7, 127.6, 129.8, 137.8, 145.7, 158.5, 162.9, 170.7; *m*/*z* (APCI$^+$) 374 (MH^+, 55%), 135 ($C_9H_{11}O^+$, 100%); HRMS (CI$^+$) $C_{22}H_{29}FNO_3$ requires 374.2132, found 374.2138.

Preparation of *tert*-butyl (3*R*,α*S*)-3-(2-iodophenyl)-3-(*N*-α-methyl-4-methoxybenzylamino)propanoate 19

Following general procedure 3, CAN (7.05 g, 12.8 mmol) and **11** (3.5 g, 6.12 mmol) in 5 : 1 MeCN–H_2O (90 ml) gave, after work up and purification by column chromatography on silica gel (hexane–Et_2O 8 : 1–1% NEt_3), **19** (632 mg, 75%) as a pale green oil; ν_{max} (film) 3326 (NH), 1722 (C=O), 1512 (OMe), 1247 (Ph–OMe); $[\alpha]_D^{19}$ −33.8 (*c* 1.0, $CHCl_3$); δ_H 400 MHz, $CDCl_3$) 1.36 [3H, d, *J* 6.5, C(α)*Me*], 1.45 [9H, s, OC(*Me*)$_3$], 2.38 [1H, dd, $J_{2A,2B}$ 14.9, $J_{2A,3}$ 9.3, C(2)H_A], 2.59 [1H, dd, $J_{2B,2A}$ 14.9, $J_{2B,3}$ 6.4, C(2)H_B], 3.54 [1H, q, *J* 6.5, C(α)*H*], 3.79 (3H, s, O*Me*), 4.54 [1H, dd, $J_{3,2A}$ 9.3, $J_{3,2B}$ 6.4, C(3)*H*], 6.81 [2H, m, Ph(3)*H* and Ph(5)*H* C_6H_4OMe], 6.95 [1H, m, Ph(6)*H* C_6H_4I], 7.19 [2H, m, Ph(2)*H* and Ph(6)*H* C_6H_4OMe], 7.31 [1H, m, Ph(4)*H* C_6H_4I], 7.37 [1H, m, Ph(5)*H* C_6H_4I], 7.80 [1H, m, Ph(3)*H* C_6H_4I]; δ_C (100 MHz, $CDCl_3$) 22.1, 28.1, 43.0, 53.9, 55.2, 60.9, 80.7, 99.9, 113.6, 127.6, 127.8, 128.4, 128.9, 138.1, 139.6, 144.3, 158.4, 170.6; *m*/*z* (CI$^+$) 482 (MH^+, 100%), 135 ($C_9H_{11}O^+$, 75%); HRMS (CI$^+$) $C_{22}H_{29}INO_3$ requires 482.1192, found 482.1193.

Preparation of *tert*-butyl (3*S*,α*R*)-3-(2-bromophenyl)-3-(*N*-α-methyl-4-methoxybenzylamino)propanoate 20

Following general procedure 3, CAN (6.59 g, 12.0 mmol) and **15** (3.0 g, 5.73 mmol) in 5 : 1 MeCN–H_2O (60 ml) gave, after work up and purification by column chromatography on silica gel (hexane–EtOAc 9 : 1–1% NEt_3), **19** (2.14 g, 86%) as a colourless oil; ν_{max} (film) 2979, 2929 (C–H), 1721 (C=O), 1513 (OMe), 1266 (Ph–OMe); $[\alpha]_D^{23}$ +28.7 (*c* 1.03, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.35 [3H, d, *J* 6.5, C(α)*Me*], 1.43 [9H, s, OC(*Me*)$_3$], 1.95 (1H, br s, N*H*), 2.47 [1H, dd, $J_{2A,2B}$ 14.8, $J_{2A,3}$ 8.8, C(2)H_A], 2.63 [1H, dd, $J_{2B,2A}$ 14.8, $J_{2B,3}$ 5.0, C(2)H_B], 3.56 [1H, q, *J* 6.5, C(α)*H*], 3.78 (3H, s, O*Me*), 4.69 [1H, dd, $J_{3,2A}$ 8.8, $J_{3,2B}$ 5.0, C(3)*H*], 6.82 [2H, m, Ph(3)*H* and Ph(5)*H* C_6H_4OMe], 7.09 [1H, td, *J* 7.8, *J* 1.7, Ph(4)*H* C_6H_4Br], 7.19 [2H, d, Ph(2)*H* and Ph(6)*H* C_6H_4OMe], 7.28 [1H, td, *J* 8.0, *J* 1.2, Ph(5)*H* C_6H_4Br], 7.40 [1H, dd, *J* 7.8, *J* 1.6, Ph(3)*H* C_6H_4Br], 7.52 [1H, dd, *J* 8.0, *J* 1.2, Ph(6)*H* C_6H_4Br]; δ_C (100 MHz, $CDCl_3$) 22.2, 28.0, 42.7, 54.0, 55.2, 56.0, 80.6, 113.6, 123.7, 127.5, 127.6, 128.4, 128.5, 132.9, 138.1, 141.5, 158.4, 170.7; *m*/*z* (APCI$^+$) 434 (MH^+, 35%); HRMS (CI$^+$) $C_{22}H_{29}BrNO_3$ requires 434.1331, found 434.1335.

Preparation of *tert*-butyl (*R*)-3-(3-fluorophenyl)-3-amino-propanoate 21

Following general procedure 4, CAN (2.19 g, 4.0 mmol) and **18** (373 mg, 1.0 mmol) in 5 : 1 MeCN–H_2O (12 ml) gave, after work up and purification by column chromatography on silica gel (hexane–Et_2O 1 : 1), 21 (126 mg, 53%) as a yellow oil; $[\alpha]_D^{20}$ +11.6 (*c* 1.0, $CHCl_3$); ν_{max} (film) 3382 (NH), 1725 (C=O); δ_H (400 MHz, $CDCl_3$) 1.43 [9H, s, OC(*Me*)$_3$], 1.82 (2H, br s, NH_2), 2.57 [2H, m, C(2)H_2], 4.38 [1H, m, C(3)*H*], 6.95 [1H, m, Ph(5)*H* C_6H_4F], 7.10 [1H, m, Ph(2)*H* C_6H_4F], 7.14 [1H, m, Ph(6)*H* C_6H_4F], 7.29 [1H, m, Ph(4)*H* C_6H_4F]; δ_C (100 MHz, $CDCl_3$) 28.0, 45.0, 52.3, 80.9, 113.3, 114.1, 121.9, 130.0, 147.2, 162.9, 171.0; *m*/*z* (APCI$^+$) 240 (MH^+, 5%), 184 ($MH^+ - C_4H_8$, 100%); HRMS (CI$^+$) $C_{13}H_{19}FNO_2$ requires 240.1400, found 240.1402.

Preparation of *tert*-butyl (*R*)-3-(2-iodophenyl)-3-amino-propanoate 22

Following general procedure 4, CAN (4.56 g, 8.31 mmol) and **19** (1.0 g, 2.08 mmol) in 5 : 1 MeCN–H_2O (24 ml) gave, after work up and purification by column chromatography on silica gel (hexane–Et_2O 8 : 1–1% NEt_3), **22** (368 mg, 51%) as a pale green oil; $[\alpha]_D^{22}$ +36.9 (*c* 0.95, $CHCl_3$); ν_{max} (film) 3379 (NH), 1725 (C=O); δ_H (400 MHz, $CDCl_3$) 1.44 [9H, s, OC(*Me*)$_3$], 2.47 [1H, dd, $J_{2A,2B}$ 15.9, $J_{2A,3}$ 9.5, C(2)H_A], 2.67 [1H, dd, $J_{2B,2A}$ 15.9, $J_{2B,3}$ 4.0, C(2)H_B], 4.38 [1H, dd, $J_{3,2A}$ 9.5, $J_{3,2B}$ 4.0, C(3)*H*], 6.95 [1H, m, Ph(4)*H* C_6H_4I], 7.35 [1H, m, Ph(5)*H* C_6H_4I], 7.50 [1H, m, Ph(6)*H* C_6H_4I], 7.82 [1H, m, Ph(2)*H* C_6H_4I]; δ_C (100 MHz, $CDCl_3$) 28.1, 43.4, 56.2, 80.9, 99.3, 127.0, 128.6, 129.0, 139.6, 146.1, 171.0; *m*/*z* (APCI$^+$) 348 (MH^+, 30%), 292 ($MH^+ - C_4H_8$, 100%); HRMS (CI$^+$) $C_{13}H_{19}INO_2$ requires 348.0461, found 348.0466.

Preparation of *tert*-butyl (*S*)-3-(2-bromophenyl)-3-amino-propanoate 23

Following general procedure 4, CAN (2.71 g, 4.94 mmol) and **20** (536 mg, 1.24 mmol) in 5 : 1 MeCN–H_2O (24 ml) gave, after work up and purification by column chromatography on silica gel (hexane–Et_2O 1 : 1), **23** (254 mg, 68%) as a yellow oil; $[\alpha]_D^{20}$ −45.0 (*c* 1.02, $CHCl_3$); ν_{max} (film) 3381 (NH), 2978 (C–H), 1724 (C=O), 1150 (C–O); δ_H (400 MHz, $CDCl_3$) 1.43 [9H, s, OC(*Me*)$_3$], 1.82, (2H, br s, NH_2), 2.49 [1H, dd, $J_{2A,2B}$ 15.8, $J_{2A,3}$ 9.3, C(2)H_A], 2.68 [1H, dd, $J_{2B,2A}$ 15.8, $J_{2B,3}$ 4.0, C(2)H_B], 4.75 [1H, dd, $J_{3,2A}$ 9.3, $J_{2,2B}$ 4.0, C(3)*H*], 7.08–7.13 and 7.29–7.33 [2 × 1H, m, Ph(4)*H* and Ph(5)*H* C_6H_4Br], 7.52–7.54 [2H, m, Ph(3)*H* and Ph(6)*H* C_6H_4Br]; δ_C (100 MHz, $CDCl_3$) 28.0, 43.2, 51.4, 80.8, 123.0, 127.4, 127.7, 128.6, 132.9, 143.3, 171.0; *m*/*z* (APCI$^+$) 302.0 (MH^+, 15%), 246.0 ($MH^+ - C_4H_8$, 100%); HRMS (CI$^+$) $C_{13}H_{19}BrNO_2$ requires 300.0599, found 300.0609.

Preparation of *tert*-butyl (3*R*,α*S*)-3-(3-iodophenyl)-3-(*N*-α-methyl-4-methoxybenzylamino)propanoate 24

Following general procedure 3, CAN (2.01 g, 3.7 mmol) and **12** (2.0 g, 3.5 mmol) in 5 : 1 MeCN–H_2O (24 ml) gave, after work up and purification by column chromatography on silica gel (hexane–Et_2O 8 : 1–1% NEt_3), **24** (1.30 g, 77%) as a pale green oil; $[\alpha]_D^{19}$ −18.0 (*c* 1.0, $CHCl_3$); ν_{max} (film) 3328 (NH), 1724 (C=O); δ_H (400 MHz, $CDCl_3$) 1.34 [3H, d, *J* 6.5, C(α)*Me*], 1.38 [9H, s, OC(*Me*)$_3$], 2.51 [1H, dd, $J_{2A,2B}$ 14.8, $J_{2A,3}$ 6.4, C(2)H_A], 2.60 [1H, dd, $J_{2B,2A}$ 14.8, $J_{2B,3}$ 6.4, C(2)H_B], 3.63 [1H, q, *J* 6.5, C(α)*H*], 3.79 (3H, s, O*Me*), 4.05 [1H, t, *J* 6.4, C(3)*H*], 6.81 [2H, d, *J* 8.7, Ph(3)*H* and Ph(5)*H* C_6H_4OMe], 7.02 [1H, t, *J* 7.8, Ph(5)*H* C_6H_4I], 7.15 [2H, m, Ph(2)*H* and Ph(6)*H* C_6H_4OMe], 7.23 [1H, m, Ph(6)*H* C_6H_4I], 7.55 [1H, m, Ph(4)*H* C_6H_4I], 7.60 [1H, m, Ph(2)*H* C_6H_4I]; δ_C (100 MHz, $CDCl_3$) 22.5, 28.0, 43.6, 54.3, 55.2, 56.8, 80.7, 94.4, 113.7, 126.6, 127.6, 130.1, 136.1, 136.3, 137.7, 145.5, 158.5, 170.6; *m*/*z* (APCI$^+$) 482 (MH^+, 10%), 135 ($C_9H_{11}O^+$, 100%); HRMS (CI$^+$) $C_{22}H_{29}INO_3$ requires 482.1192, found 482.1197.

Preparation of *tert*-butyl (*R*)-3-(3-iodophenyl)-3-amino-propanoate 25

Following general procedure 4, CAN (3.10 g, 5.65 mmol) and **24** (680 mg, 1.41 mmol) in 5 : 1 MeCN–H_2O (18 ml) gave, after work up and purification by column chromatography on silica gel (hexane–Et_2O 1 : 2), **25** (240 mg, 49%) as a yellow oil; $[\alpha]_D^{22}$ +11.2 (*c* 0.99, $CHCl_3$); ν_{max} (film) 3380 (NH), 1732 (C=O); δ_H (400 MHz, $CDCl_3$) 1.41 [9H, s, OC(*Me*)$_3$], 1.79 (2H, br s, NH_2), 2.55 [2H, d, *J* 6.8, C(2)H_2], 4.31 [1H, t, *J* 6.8, C(3)*H*], 7.06 [1H, t, *J* 7.8, Ph(5)*H* C_6H_4I], 7.32 [1H, d, *J* 7.8, Ph(6)*H* C_6H_4I], 7.58 [1H, m, Ph(4)*H* C_6H_4I], 7.72 [1H, m, Ph(2)*H* C_6H_4I]; δ_C (100 MHz, $CDCl_3$) 28.0, 45.1, 52.2, 81.0, 94.5, 125.6, 130.3, 135.3, 136.3, 147.1, 170.9; *m*/*z* (APCI$^+$) 348 (MH^+, 5%), 292 (MH^+ −

C_4H_8, 100%); HRMS (CI^+) $C_{13}H_{19}INO_2$ requires 348.0461, found 348.0473.

Preparation of methyl (3*R*,α*S*)-3-(3-iodophenyl)-3-(*N*-α-methyl-4-methoxybenzylamino)propanoate 26

Following general procedure 5, **24** (1.5 g, 3.12 mmol) was added to a saturated solution of HCl in MeOH (20 ml). Concentration *in vacuo*, recrystallisation (EtOAc–hexane) and treatment with saturated aqueous $NaHCO_3$ gave **26** (1.03 g, 75%) as a colourless oil; mp (HCl salt) 168–169 °C (EtOAc–hexane); found: C, 48.0; H, 4.8; N, 3.0%; $C_{19}H_{23}ICINO_3$ requires C, 48.0; H, 4.9; N, 2.9%; $[\alpha]_D^{19}$ −17.1 (*c* 1.0, $CHCl_3$); ν_{max} (film) 3326 (NH), 1734 (C=O), 1513 (OMe), 1246 (Ph–OMe); δ_H (400 MHz, $CDCl_3$) 1.35 [3H, d, *J* 6.5, C(α)*Me*], 2.61 [1H, dd, $J_{2A,2B}$ 15.4, $J_{2A,3}$ 6.0, C(2)H_A], 2.70 [1H, dd, $J_{2B,2A}$ 15.4, $J_{2B,3}$ 7.8, C(2)H_B], 3.61 [1H, q, *J* 6.5, C(α)*H*], 3.64, 3.80 (2 × 3H, s, CO_2Me and O*Me*), 4.10 [1H, dd, $J_{3,2A}$ 6.0, $J_{3,2B}$ 7.8, C(3)*H*], 6.81 [2H, m, Ph(3)*H* and Ph(5)*H* C_6H_4OMe], 7.03 [1H, m, Ph(5)*H* C_6H_4I], 7.14 [2H, m, Ph(2)*H* and Ph(6)*H* C_6H_4OMe], 7.23 [1H, d, *J* 7.7, Ph(6)*H* C_6H_4I], 7.58 [1H, m, Ph(4)*H* C_6H_4I], 7.60 [1H, m, Ph(2)*H* C_6H_4I]; δ_C (100 MHz, $CDCl_3$) 22.4, 42.2, 51.7, 54.3, 55.2, 56.4, 94.5, 115.0, 126.2, 127.6, 130.2, 136.1, 136.3, 137.6, 145.3, 158.5, 171.8; *m*/*z* ($APCI^+$) 440 (MH^+, 5%), 135 ($C_9H_{11}O^+$, 100%); HRMS (CI^+) $C_{19}H_{23}INO_3$ requires 440.0723, found 440.0716.

Preparation of methyl (*R*)-3-(3-iodophenyl)-3-aminopropanoate 27

Following general procedure 4, CAN (1.90 g, 3.46 mmol) and **26** (380 mg, 0.85 mmol) in 5 : 1 MeCN–H_2O (12 ml) gave, after work up and purification by column chromatography on silica gel (hexane–Et_2O 1 : 2–1% NEt_3), gave **27** (125 mg, 48%) as a yellow oil; $[\alpha]_D^{20}$ +12.8 (*c* 1.0, $CHCl_3$); ν_{max} (film) 3377 (NH), 2949 (CH), 1732 (C=O); δ_H (400 MHz, toluene-d_8) 2.20 [1H, dd, $J_{2A,2B}$ 16.1, $J_{2A,3}$ 4.8, C(2)H_A], 2.25 [1H, dd, $J_{2B,2A}$ 16.1, $J_{2B,3}$ 8.8, C(2)H_B], 3.31 (3H, s, CO_2Me), 4.01 [1H, dd, $J_{3,2B}$ 8.8, $J_{3,2A}$ 4.8, C(3)*H*], 6.65 [1H, m, Ph(5)*H* C_6H_4I], 6.99 [1H, m, Ph(6)*H* C_6H_4I], 7.36 [1H, m, Ph(4)*H* C_6H_4I], 7.60 [1H, m, Ph(2)*H* C_6H_4I]; δ_C (100 MHz, toluene-d_8) 44.2, 51.4, 52.6, 95.2, 126.2, 130.7, 136.2, 136.9, 148.4, 172.1; *m*/*z* ($APCI^+$) 306 (MH^+, 50%); HRMS (CI^+) $C_{10}H_{13}INO_2$ requires 305.9991, found 305.9984.

Preparation of *tert*-butyl (3*R*,α*S*)-3-(4-iodophenyl)-3-(*N*-α-methyl-4-methoxybenzylamino)propanoate 28

Following general procedure 3, CAN (11.6 g, 21.1 mmol) and **13** (5.75 g, 10.1 mmol) in 5 : 1 MeCN–H_2O (90 ml) gave, after work up and purification by column chromatography on silica gel (hexane–Et_2O 8 : 1–1% NEt_3), **28** (4.26 g, 88%) as a yellow oil; $[\alpha]_D^{19}$ −23.9 (*c* 1.0, $CHCl_3$); ν_{max} (film) 3326 (NH), 1723 (C=O) 1512 (OMe), 1246 (Ph–OMe); δ_H (400 MHz, $CDCl_3$) 1.32 [3H, d, *J* 6.5, C(α)*Me*], 1.38 [9H, s, OC(*Me*)$_3$], 2.51 [1H, dd, $J_{2A,2B}$ 14.9, $J_{2A,3}$ 6.1, C(2)H_A], 2.59 [1H, dd, $J_{2B,2A}$ 14.9, $J_{2B,3}$ 7.8, C(2)H_B], 3.59 [1H, q, *J* 6.5, C(α)*H*], 3.79 (3H, s, O*Me*), 4.08 [1H, dd, $J_{3,2A}$ 6.1, $J_{3,2B}$ 7.8, C(3)*H*], 6.81 [2H, m, Ph(3)*H* and Ph(5)*H* C_6H_4OMe], 7.03 [2H, m, Ph(2)*H* and Ph(6)*H* C_6H_4I], 7.14 [2H, m, Ph(2)*H* and Ph(6)*H* C_6H_4OMe], 7.61 [2H, m, Ph(3)*H* and Ph(5)*H* C_6H_4I]; δ_C (100 MHz, $CDCl_3$) 22.3, 28.0, 43.6, 54.1, 55.3, 56.7, 80.7, 92.4, 113.7, 127.5, 129.2, 137.4, 137.9, 142.8, 158.5, 170.7; *m*/*z* ($APCI^+$) 482 (MH^+, 5%), 135 ($C_9H_{11}O^+$, 100%); HRMS (CI^+) $C_{22}H_{29}INO_3$ requires 482.1192, found 482.1201.

Preparation of *tert*-butyl (3*S*,α*R*)-3-(3-chlorophenyl)-3-(*N*-α-methyl-4-methoxybenzylamino)propanoate 29

Following general procedure 3, CAN (2.45 g, 4.56 mmol) and **14** (1.04 g, 2.17 mmol) in 5 : 1 MeCN–H_2O (12 ml) gave, after work up and purification by column chromatography on silica gel (hexane–Et_2O 8 : 1–1% NEt_3), **29** (664 mg, 79%) as a clear oil; $[\alpha]_D^{20}$ +20.0 (*c* 1.0, $CHCl_3$); ν_{max} (film) 3329 (NH), 1728 (C=O); δ_H (400 MHz, $CDCl_3$) 1.35 [3H, d, *J* 6.5, C(α)*Me*], 1.39 [9H, s, OC(*Me*)$_3$], 2.54 [1H, dd, $J_{2A,2B}$ 14.8, $J_{2A,3}$ 6.4, C(2)H_A], 2.62 [1H, dd, $J_{2B,2A}$ 14.8, $J_{2B,3}$ 7.6, C(2)H_B], 3.64 [1H, q, *J* 6.5, C(α)*H*], 3.79 (3H, s, O*Me*), 4.11 [1H, dd, $J_{3,2A}$ 7.6, $J_{3,2B}$ 6.4, C(3)*H*], 6.82 [2H, m, Ph(3)*H* and Ph(5)*H* C_6H_4OMe], 7.16–7.21 [5H, m, Ph(4)*H*, Ph(5)*H*, Ph(6)*H* C_6H_4Cl and Ph(2)*H*, Ph(6)*H* C_6H_4OMe], 7.24 [1H, s, Ph(2)*H* C_6H_4Cl]; δ_C (100 MHz, $CDCl_3$) 22.5, 28.0, 43.5, 53.4, 55.2, 56.8, 80.7, 113.7, 125.2, 127.0, 127.2, 127.7, 129.6, 134.1, 137.8, 145.2, 158.5, 170.7; *m*/*z* ($APCI^+$) 390 (MH^+, 15%), 135 ($C_9H_{11}O^+$, 100%); HRMS (CI^+) $C_{22}H_{29}ClNO_3$ requires 390.1836, found 390.1836.

Preparation of *tert*-butyl (3*S*,α*R*)-3-(3-bromophenyl)-3-(*N*-α-methyl-4-methoxybenzylamino)propanoate 30

Following general procedure 3, CAN (1.96 g, 3.6 mmol) and **16** (937 mg, 1.8 mmol) in 5 : 1 MeCN–H_2O (24 ml) gave, after work up and purification by column chromatography on silica gel (hexane–Et_2O 8 : 1–1% NEt_3), **30** (621 mg, 80%) as a clear oil; $[\alpha]_D^{20}$ +21.5 (*c* 0.96, $CHCl_3$); ν_{max} (film) 3328 (NH), 1724 (C=O); δ_H (400 MHz, $CDCl_3$) 1.34 [3H, d, *J* 6.5, C(α)*Me*], 1.39 [9H, s, OC(*Me*)$_3$], 1.84 (1H, br s, N*H*), 2.53 [1H, dd, $J_{2A,2B}$ 14.8, $J_{2A,3}$ 6.1, C(2)H_A], 2.61 [1H, dd, $J_{2B,2A}$ 14.8, $J_{2B,3}$ 7.7, C(2)H_B], 3.63 [1H, q, *J* 6.5, C(α)*H*], 3.79 (3H, s, O*Me*), 4.09 [1H, dd, $J_{3,2A}$ 6.1, $J_{3,2B}$ 7.7, C(3)*H*], 6.82 [2H, m, Ph(3)*H* and Ph(5)*H* C_6H_4OMe], 7.16 [2H, m, Ph(2)*H* and Ph(6)*H* C_6H_4OMe], 7.17–7.21 [2H, m, Ph(5)*H* and Ph(6)*H* C_6H_4Br], 7.35 [1H, m, Ph(4)*H* C_6H_4Br], 7.42 [1H, m, Ph(2)*H* C_6H_4Br]; δ_C (100 MHz, $CDCl_3$) 22.5, 28.0, 43.6, 54.3, 55.2, 56.8, 80.7, 113.7, 122.4, 125.6, 127.6, 129.9, 130.2, 130.3, 137.8, 145.5, 158.5, 170.6; HRMS (CI^+) $C_{22}H_{29}BrNO_3$ requires 434.1331, found 434.1330.

Preparation of *tert*-butyl (3*S*,α*R*)-3-(4-bromophenyl)-3-(*N*-α-methyl-4-methoxybenzylamino)propanoate 31

Following representative procedure 3, CAN (2.20 g, 4.0 mmol) and **17** (1.0 g, 1.9 mmol) in MeCN–H_2O 5 : 1 (9 ml) gave, after work-up and column chromatography on silica gel (hexane–Et_2O 5 : 1), **31** (595 mg, 72%) as a colourless oil; $[\alpha]_D^{24}$ + 32.8 (*c* 1.0, $CHCl_3$); ν_{max} (film) 2974, 2930 (C–H), 1725 (C=O), 1512 (OMe), 1246 (Ph–OMe), 1152 (C–O); δ_H (400 MHz, $CDCl_3$) 1.33 [3H, d, *J* 6.4, C(α)*Me*], 1.38 [9H, s, $CO_2C(Me)_3$], 2.50–2.61 [2H, m, C(2)H_2], 3.59 [1H, q, *J* 6.8, C(α)*H*], 3.79 (3H, s, O*Me*), 4.09 [1H, app t, *J* 6.9, C(3)*H*], 6.81 [2H, m, Ph(3)*H* and Ph(5)*H* C_6H_4OMe], 7.13–7.17 (4H, m, C_6H_4Br), 7.41 [2H, d, *J* 8.5, Ph(2)*H* and Ph(6)*H* C_6H_4OMe]; δ_C (50 MHz, $CDCl_3$) 22.4, 28.0, 43.6, 54.1, 55.3, 56.6, 80.7, 113.7, 120.8, 127.5, 128.8, 131.4, 137.8, 142.0, 158.4, 170.7; *m*/*z* ($APCI^+$) 434.1 (MH^+, 10%), 134.9 ($C_9H_{11}O^+$, 100%); HRMS (CI^+) $C_{22}H_{29}BrNO_3$ requires 434.1331, found 434.1334.

Preparation of methyl (3*R*,α*S*)-3-(4-iodophenyl)-3-(*N*-α-methyl-4-methoxybenzylamino)propanoate 32

Following general procedure 5, **28** (3.0 g, 6.24 mmol) was added to a saturated solution of HCl in MeOH (20 ml). Concentration *in vacuo*, recrystallisation (EtOAc–hexane) and treatment with saturated aqueous $NaHCO_3$ gave **32** (2.12 g, 71%) as a colourless oil; mp (HCl salt) 181–182 °C (EtOAc–hexane); $[\alpha]_D^{22}$ −21.6 (*c* 1.2, $CHCl_3$); ν_{max} (film) 3326 (NH), 1737 (C=O), 1511 (OMe), 1246 (Ph–OMe); δ_H (400 MHz, $CDCl_3$) 1.32 [3H, d, *J* 6.5, C(α)*Me*], 2.61 [1H, dd, $J_{2A,2B}$ 15.4, $J_{2A,3}$ 6.3, C(2)H_A], 2.71 [1H, dd, $J_{2B,2A}$ 15.4, $J_{2B,3}$ 7.3, C(2)H_B], 3.59 [1H, q, *J* 6.5, C(α)*H*], 3.63, 3.79 (2 × 3H, s, CO_2Me and O*Me*), 4.13 [1H, dd, $J_{3,2B}$ 7.3, $J_{3,2A}$ 6.3, C(3)*H*], 6.81 [2H, m, Ph(3)*H* and Ph(5)*H* C_6H_4OMe], 7.03 [2H, m, Ph(2)*H* and Ph(6)*H* C_6H_4I], 7.14 [2H, m, Ph(2)*H* and Ph(6)*H* C_6H_4OMe], 7.62 [2H, m, Ph(3)*H* and Ph(5)*H* C_6H_4I]; δ_C (100 MHz, $CDCl_3$) 22.3, 42.1, 51.6, 54.1, 55.3, 56.3, 92.6, 113.6, 127.0, 129.0, 137.5, 137.7, 142.5, 158.5, 171.9; *m*/*z* ($APCI^+$) 440 (MH^+, 5%), 135 ($C_9H_{11}O^+$, 100%); HRMS (CI^+) $C_{19}H_{23}INO_3$ requires 440.0723, found 440.0721.

Preparation of methyl (3*S*,α*R*)-3-(3-chlorophenyl)-3-(*N*-α-methyl-4-methoxybenzylamino)propanoate 33

Following general procedure 5, **29** (1.89 g, 4.87 mmol) was added to a saturated solution of HCl in MeOH (20 ml). Concentration *in vacuo*, recrystallisation (EtOAc–hexane) and treatment with saturated aqueous $NaHCO_3$ gave **33** (1.48 g, 79%) as a colourless oil; mp (HCl salt) 169–170 °C (EtOAc–hexane); $[\alpha]_D^{20}$ +17.2 (*c* 1.0, $CHCl_3$); found C, 59.4; H, 6.0; N, 3.8%; $C_{19}H_{23}Cl_2NO_3$ requires C, 59.4; H, 6.0; N, 3.6%; ν_{max} (film) 3329 (NH), 1737 (C=O); δ_H (400 MHz, $CDCl_3$) 1.34 [3H, d, *J* 6.5, C(α)*Me*], 1.86 (1H, br s, N*H*), 2.63 [1H, dd, $J_{2A,2B}$ 15.4, $J_{2A,3}$ 6.1, C(2)H_A], 2.73 [1H, dd, $J_{2B,2A}$ 15.4, $J_{2B,3}$ 7.8, C(2)H_B], 3.63 [1H, q, *J* 6.5, C(α)*H*], 3.64, 3.79 (2 × 3H, s, CO_2Me and O*Me*), 4.16 [1H, dd, $J_{2A,3}$ 6.1, $J_{2B,3}$ 7.8, C(3)*H*], 6.83 [2H, m, Ph(3)*H*, Ph(5)*H* C_6H_4OMe], 7.16 [2H, m, Ph(2)*H*, Ph(6)*H* C_6H_4OMe], 7.16 [1H, m, Ph(6)*H* C_6H_4Cl], 7.19–7.23 [3H, m, Ph(2)*H*, Ph(4)*H*, Ph(5)*H* C_6H_4Cl]; δ_C (100 MHz, $CDCl_3$) 22.4, 42.1, 51.6, 54.2, 55.7, 56.5, 113.7, 125.1, 127.2, 127.4, 127.6, 129.8, 134.3, 137.6, 145.0, 158.5, 171.9; *m*/*z* ($APCI^+$) 348 (MH^+, 10%).

Preparation of methyl (3*S*,α*R*)-3-(3-bromophenyl)-3-(*N*-α-methyl-4-methoxybenzylamino)propanoate 34

Following general procedure 5, **30** (750 mg, 173 mmol) was added to a saturated solution of HCl in MeOH (20 ml). Concentration *in vacuo*, recrystallisation (EtOAc–hexane) and treatment with saturated aqueous $NaHCO_3$ gave **34** (487 mg, 66%) as a colourless oil; $[\alpha]_D^{20}$ +13.5 (*c* 1.0, $CHCl_3$); ν_{max} (film) 3326 (NH), 1736 (C=O), 1512 (OMe), 1246 (Ph–OMe); δ_H (400 MHz, $CDCl_3$) 1.38 [3H, d, *J* 6.5, C(α)*Me*], 1.84 (1H, br s, N*H*), 2.63 [1H, dd, $J_{2A,2B}$ 15.4, $J_{2A,3}$ 6.1, C(2)H_A], 2.72 [1H, dd, $J_{2B,2A}$ 15.4, $J_{2B,3}$ 7.7, C(2)H_B], 3.62 [1H, q, *J* 6.5, C(α)*H*], 3.64, 3.79 (2 × 3H, s, CO_2Me and O*Me*), 4.14 [1H, dd, $J_{3,2B}$ 7.7, $J_{3,2A}$ 6.1, C(3)*H*], 6.81 [2H, m, Ph(3)*H* and Ph(5)*H* C_6H_4OMe], 7.14–7.21 [4H, m, Ph(2)*H* and Ph(6)*H* C_6H_4OMe, Ph(5)*H* and Ph(6)*H* C_6H_4Br], 7.37 [1H, m, Ph(2)*H* C_6H_4Br], 7.41 [1H, m, Ph(4)*H* C_6H_4Br]; δ_C (100 MHz, $CDCl_3$) 22.4, 42.1, 51.6, 54.3, 55.2, 56.5, 113.7, 122.6, 125.6, 127.6, 130.1, 130.1, 130.4, 137.6, 145.3, 158.5, 171.8; *m*/*z* (CI^+) 392 (MH^+, 15%), 135 ($C_9H_{11}O^+$, 100%); HRMS (CI^+) $C_{19}H_{23}BrNO$ requires 392.0861, found 392.0858.

Preparation of methyl (3*S*,α*R*)-3-(4-bromophenyl)-3-(*N*-α-methyl-4-methoxybenzylamino)propanoate 35

Following general procedure 5, **31** (2.2 g, 5.08 mmol) was added to a saturated solution of HCl in MeOH (75 ml). Concentration *in vacuo*, recrystallisation (EtOAc–hexane) and treatment with saturated aqueous $NaHCO_3$ gave **35** (1.45 g, 73%) as a colourless oil; $[\alpha]_D^{20}$ +14.9 (*c* 0.9, $CHCl_3$); ν_{max} (film) 2959 (C–H), 1736 (C=O), 1512 (OMe), 1245 (Ph–OMe); δ_H (400 MHz, $CDCl_3$) 1.32 [3H, d, *J* 6.5, C(α)*Me*], 1.44 (1H, br s, N*H*), 2.61 [1H, dd, $J_{2A,2B}$ 15.4, $J_{2A,3}$ 6.4, C(2)H_A], 2.71 [1H, dd, $J_{2B,2A}$ 15.4, $J_{2B,3}$ 7.5, C(2)H_B], 3.62 [1H, q, *J* 6.5, C(α)*H*], 3.63, 3.79 (2 × 3H, s, CO_2Me and O*Me*), 4.14 [1H, app t, *J* 6.9, C(3)*H*], 6.80–6.84 [2H, m, Ph(3)*H* and Ph(5)*H* C_6H_4OMe], 7.12–7.17 [4H, m, Ph(2)*H* and Ph(6)*H* C_6H_4OMe, Ph(2)*H* and Ph(6)*H* C_6H_4Br], 7.41–7.44 [2H, m, Ph(3)*H* and Ph(5)*H* C_6H_4Br]; δ_C (100 MHz, $CDCl_3$) 22.3, 42.0, 51.6, 54.2, 55.3, 56.2, 113.7, 121.0, 127.6, 128.8, 129.0, 131.6, 131.7, 137.6, 141.7, 150.0, 158.5, 171.8; *m*/*z* (CI^+) 392.1 (MH^+, 10%), 135.1 ($C_9H_{11}O^+$, 100%); HRMS (ESI) $C_{19}H_{23}BrNO_3$ requires 392.0861, found 392.0861.

Preparation of methyl (*R*)-3-(4-iodophenyl)-3-aminopropanoate 36

Following general procedure 4, CAN (1.0 g, 1.84 mmol) and **32** (200 mg, 0.46 mmol) in 5 : 1 MeCN–H_2O (6 ml) gave, after work up and purification by column chromatography on silica gel (hexane–Et_2O 1 : 2), **36** (85 mg, 61%) as a yellow oil; $[\alpha]_D^{20}$ +11.5 (*c* 1.06, $CHCl_3$); ν_{max} (film) 3375 (NH), 2950 (CH), 1732 (C=O); δ_H (400 MHz, $CDCl_3$) 2.64 [2H, m, C(2)H_2], 3.68 (3H, s, CO_2Me), 4.39 [1H, br s, C(3)*H*], 7.12 [2H, m, Ph(2)*H* and Ph(6) C_6H_4I], 7.66 [2H, m, Ph(3)*H* and Ph(5) C_6H_4I]; δ_C (100 MHz, $CDCl_3$) 43.6, 51.7, 52.1, 92.7, 128.3, 137.7, 137.8, 172.1; *m*/*z* ($APCI^+$) 306 (MH^+, 25%); HRMS (CI^+) $C_{10}H_{13}INO_2$ requires 305.9991, found 305.9999.

Preparation of methyl (*S*)-3-(3-chlorophenyl)-3-amino-propanoate 37

Following general procedure 4, CAN (2.58 g, 4.70 mmol) and **33** (408 mg, 1.18 mmol) in 5 : 1 MeCN–H_2O (12 ml) gave, after work up and purification by column chromatography on silica gel (hexane–Et_2O 1 : 2), **37** (135 mg, 54%) as a yellow oil; $[\alpha]_D^{20}$ −11.5 (*c* 1.0, $CHCl_3$); ν_{max} (film) 3376 (NH), 1732 (C=O); δ_H (400 MHz, $CDCl_3$) 1.88 (2H, br s, NH_2), 2.17 [2H, m, C(2)H_2], 3.69 (3H, s, CO_2Me), 4.40 [1H, m, C(3)*H*], 7.21 [1H, t, *J* 7.8, Ph(5)*H* C_6H_4Cl], 7.29 [1H, d, *J* 7.8, Ph(6)*H* C_6H_4Cl], 7.39 [1H, d, *J* 7.8, Ph(4)*H* C_6H_4Cl], 7.53 [1H, s, Ph(2)*H* C_6H_4Cl]; δ_C (100 MHz, $CDCl_3$) 43.7, 51.7, 52.1, 124.9, 129.4, 130.2, 130.6, 134.9, 146.9, 172.1; *m*/*z* ($APCI^+$) 214 (MH^+, 35%); HRMS (CI^+) $C_{10}H_{13}ClNO_2$ requires 214.0635; found 214.0628.

Preparation of methyl (*S*)-3-(3-bromophenyl)-3-amino-propanoate 38

Following general procedure 4, CAN (1.90 g, 3.46 mmol) and **34** (338 mg, 0.86 mmol) in 5 : 1 MeCN–H_2O (12 ml) gave, after work up and purification by column chromatography on silica gel (hexane–Et_2O 1 : 2), **38** (114 mg, 51%) as a yellow oil; $[\alpha]_D^{20}$ −10.7 (*c* 1.0, $CHCl_3$); ν_{max} (film) 3375 (NH), 1732 (C=O); δ_H (400 MHz, $CDCl_3$) 1.89 (2H, br s, NH_2), 2.64 [2H, m, C(2)H_2], 3.69 (3H, s, O*Me*), 4.40 [1H, m, C(3)*H*], 7.22–7.29 [3H, m, Ph(4)*H*, Ph(5)*H*, and Ph(6)*H* C_6H_4Br], 7.37 [1H, s, Ph(2)*H* C_6H_4Br]; δ_C (100 MHz, $CDCl_3$) 43.7, 51.7, 52.2, 124.4, 125.4, 126.5, 127.6, 129.9, 146.6, 174.3; *m*/*z* ($APCI^+$) 258 (MH^+, 20%); HRMS (CI^+) $C_{10}H_{13}BrNO_2$ requires 258.0130, found 258.0131.

Preparation of methyl (*S*)-3-(4-bromophenyl)-3-amino-propanoate 39

Following general procedure 4, CAN (2.79 g, 5.08 mmol) and **35** (500 mg, 1.27 mmol) in 5 : 1 MeCN–H_2O (18 ml) gave, after work up and purification by column chromatography on silica gel (hexane–Et_2O 1 : 1), **39** (172 mg, 52%) as a yellow oil; $[\alpha]_D^{20}$ −12.8 (*c* 0.9, $CHCl_3$); ν_{max} (film) 3373 (NH), 2946 (C–H), 1734 (C=O); δ_H (400 MHz, $CDCl_3$) 1.79 (2H, br s, NH_2), 2.62 [2H, m, C(2)H_2], 3.69 (3H, s, O*Me*), 4.40 [1H, app t, *J* 6.8, C(3)*H*], 7.23–7.26 [2H, m, Ph(2)*H* and Ph(6)*H* C_6H_4Br], 7.44–7.47 [2H, m, Ph(3)*H* and Ph(5)*H* C_6H_4Br]; δ_C (100 MHz, $CDCl_3$) 43.7, 51.7, 52.0, 121.1, 128.0, 131.7, 143.5, 172.2; *m*/*z* ($APCI^+$) 260 (MH^+, 10%); HRMS (ESI) $C_{10}H_{13}BrNO_2$ requires 258.0130, found 258.0134.

Preparation of *tert*-butyl (*E*)-3-(3,4-difluorophenyl)prop-2-enoate 40

(*tert*-Butoxycarbonylmethylene)triphenylphosphorane (5.79 g, 15.4 mmol, 1.1 equiv.) was added to a stirred solution of 3,4-difluorobenzaldehyde (1.98 g, 14.0 mmol, 1.0 equiv.) in DCM (20 ml) under nitrogen at RT and stirred for sixteen hours before being diluted with DCM (30 ml) and concentrated *in vacuo*. Purification of the residue by column chromatography on silica gel (hexane–Et_2O 30 : 1) yielded a partially separable mixture of stereoisomers. The *E* isomer was purified to homogeneity by recrystallisation (hexane–Et_2O) to give **40** as white needles (3.5 g, 88%); mp 61 °C (hexane–Et_2O); found: C, 64.9; H, 5.6%; $C_{13}H_{14}F_2O_2$ requires C, 65.0; H, 5.9%; ν_{max} (KBr) 2979, 2927 (C–H), 1701 (C=O), 1640 (C=C), 1150 (C–O); δ_H (400 MHz, $CDCl_3$) 1.51 [9H, s, $CO_2C(Me)_3$], 6.26 (1H, d, *J* 16.0, C=C*H*$CO_2{}^tBu$), 7.06–7.34 (3H, m, *Ph*), 7.46 (1H, d,

J 16.0, HC=C*H*$CO_2{}^t$Bu); δ_C (50 MHz, $CDCl_3$) 28.1, 80.8, 116.0, 117.6, 121.3, 124.5, 131.8, 141.1, 148.7, 154.3, 165.7; *m*/*z* (CI, NH_3) 284.2 (MH^+, 25%), 228.2 ($MH^+ - C_4H_8$, 100%).

Preparation of *tert*-butyl (3*S*,α*R*)-3-(3,4-difluorophenyl)-3-(*N*-benzyl-*N*-α-methyl-4-methoxybenzylamino)propanoate 41

Following representative procedure **2**, *n*-BuLi (8.64 ml, 2.5 M, 21.6 mmol), (*R*)-**1** (5.37 g, 22.3 mmol) in THF (15 ml) and (*E*)-**40** (3.36 g, 14.0 mmol) gave, after purification by column chromatography on silica gel (hexane–Et_2O 15 : 1) and recrystallisation (Et_2O–hexane), **41** as white crystals (5.8 g, 86%); $[\alpha]_D^{26}$ +13.9 (*c* 1.0, $CHCl_3$); found: C, 72.2; H, 6.9; N, 2.9%; $C_{29}H_{33}F_2NO_3$ requires C, 72.3; H, 6.9; N, 2.9%; mp 84–86 °C; ν_{max} (film) 2973, 2933 (C–H), 1735 (C=O), 1512 (OMe bend), 1243 (Ph–O), 1151 (C–O); δ_H (400 MHz, $CDCl_3$) 1.25 [9H, s, OC(*Me*)$_3$], 1.29 [3H, d, *J* 6.8, C(α)*Me*], 2.46 [2H, m, C(2)H_2], 3.65 (2H, app s, NCH_2Ph), 3.82 (3H, s, O*Me*), 3.92 [1H, q, *J* 6.8, C(α)*H*], 4.39 [1H, dd, $J_{3,2A}$ 10.4, $J_{3,2B}$ 4.3, C(3)*H*], 6.88 (2H, m, *Ph*), 7.07–7.31 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 17.4, 27.8, 37.6, 50.7, 55.2, 56.8, 58.3, 80.5, 113.6, 116.8, 117.1, 123.9, 126.7, 127.9, 128.2, 128.7, 135.6, 139.6, 141.2, 148.7, 150.7, 158.6, 170.8; *m*/*z* (NH_3) 482.1 (MH^+, 10%), 348.1 ($MH^+ - C_9H_{11}O$, 100%).

Preparation of (*S*)-3-(3,4-difluorophenyl)-3-aminopropionic acid 42

CAN (15.0 g, 27.42 mmol) was added portionwise to a stirred solution of **41** (2.20 g, 4.57 mmol) in MeCN–H_2O (150 ml, 5 : 1) at RT. After 16 h sat. aq. $NaHCO_3$ (100 ml) was added. The reaction mixture was partitioned between Et_2O (3 × 50 ml) and H_2O (100 ml) and the solvent removed *in vacuo*. 1 M HCl (15 ml) was added to the crude reaction mixture and the resultant solution was stirred at RT for 16 hours before concentration *in vacuo*. Purification *via* ion exchange chromatography gave **42** (575 mg, 63%) as a white solid; mp 226–230 °C; $[\alpha]_D^{23}$ −3.2 (*c* 1.0, H_2O); ν_{max} (KBr disc) 2955 (C–H), 1617 (C=O); δ_H (500 MHz, D_2O), 2.78 [1H, dd, $J_{2A,2B}$ 16.2, $J_{2A,3}$ 6.7, C(2)H_A], 2.87 [1H, dd, $J_{2B,2A}$ 16.2, $J_{2B,3}$ 7.9, C(2)H_B], 4.63 [1H, app t, *J* 7.3, C(3)*H*], 7.22–7.39 (3H, m, *Ph*); δ_C (125 MHz, D_2O) 40.6, 52.2, 116.7, 118.5, 124.2, 133.4, 150.4, 150.7, 177.2; *m*/*z* (APCI$^+$) 202.1 (MH^+, 80%), 185.0 ($MH^+ - NH_3$, 100%); HRMS (ESI) $C_9H_8NO_2F_2$ requires 200.0523, found 200.0531.

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