Tetrahedron: *Asymmetry* 23 (2012) 910–925

Contents lists available at SciVerse ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Asymmetric synthesis of β-fluoroaryl-β-amino acids

Stephen G. Davies *, Ai M. Fletcher, Linlu Lv, Paul M. Roberts, James E. Thomson

Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford OX1 3TA, UK

ARTICLE INFO

Article history:
Received 4 July 2012
Accepted 4 July 2012

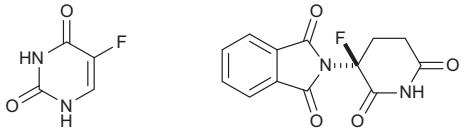
Dedicated to Professor Philip J. Parsons on the occasion of his 60th birthday

ABSTRACT

The conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to a range of β-fluoroaryl-α,β-unsaturated esters gave the corresponding β-amino esters with high diastereoselectivity and in good isolated yields. Sequential treatment of the resultant β-fluoroaryl-β-amino esters under optimised hydrogenolysis conditions, followed by ester hydrolysis with 2.0 M aq HCl, provided access to a range of β-fluoroaryl-β-amino acids in good yield.

1. Introduction

The incorporation of fluorine atom(s) into medicinally important molecules may bring about remarkable changes in their physical, chemical and biological properties.[1] Hence, the synthesis of fluorinated compounds as potential therapeutic agents has been an extremely active area of research in recent years.[2] For example, antineoplastic agent 5-fluorouracil **1**[3] and the non-racemisable α-fluoro substituted analogue of thalidomide, (*S*)-fluorothalidomide **2**,[4] were developed based on the strategy of replacing a hydrogen atom with a fluorine atom (Fig. 1).



5-fluorouracil **1** (*S*)-fluorothalidomide **2**

Figure 1. 5-Fluorouracil **1** and (*S*)-fluorothalidomide **2**.

Fluorinated α-amino acids and peptides have been identified as valuable building blocks for a wide range of medicinal applications.[5] Somewhat surprisingly, the synthesis and application of the corresponding fluorinated β-amino acids have been explored relatively less frequently.[6] α-Fluorinated β-amino acid derivatives **8** and **12–14** have been reported to be competitive inhibitors of α-chymotrypsin due to hydrogen-bonding between the fluorine atom(s) within **8** and **12–14**, and the amide proton within the active site of serine and cysteine proteases. Both reported preparations of these α-fluoro-β-amino acids relied on the homologation of the corresponding naturally occurring parent α-amino acids followed by fluorination. In Ohba's synthesis,[7] phenylalanine Weinreb amide derivative **3** was homologated by reduction with $LiAlH_4$ followed by cyanohydrin formation giving **4** in 70% yield for the 2 step procedure. Sequential hydrolysis and derivatisation to the corresponding methyl ester **5** followed by oxidation with Dess–Martin periodinane gave α-keto-ester **6** in 74% overall yield. Fluorination of **6** was then achieved in modest yield by employing diethylaminosulfur trifluoride (DAST).[8] Subsequent protecting group manipulation gave (*S*)-*N*-acetyl-α,α-bisfluoro-β-phenylalanine methyl ester **8** in 56% yield. Abell et al. reported syntheses of the analogous α-fluoro-β-amino acid derivatives **12–14** in 2010.[9] In their syntheses, **12–14** were prepared by Arndt–Eistert homologation of the corresponding α-amino acid, followed by appropriate N-protection. Treatment of **9–11** with LDA followed by *N*-fluorobenzenesulfonimide (NFSI) gave mixtures of *anti*- and *syn*-α-fluoro-β-amino esters **12–17**. Diastereoisomerically pure samples of *anti*-**13** and *anti*-**14** were obtained after column chromatography in 16 and 6% yield, respectively (Scheme 1).[7,9]

We have recently demonstrated the concise asymmetric synthesis of the fluorinated β-amino acid derivative (−)-(*R*)-sitagliptin (JANUVIA™) **22**,[10] an orally active dipeptidyl peptidase IV (DPP-4) inhibitor for the treatment of type 2 diabetes.[11] In this study, two different asymmetric syntheses of (−)-(*R*)-sitagliptin **22** were accomplished, both in 7 steps from commercially available starting materials, by employing our well-established, highly diastereoselective lithium amide conjugate addition methodology[12,13] as the key step. Two alternative protecting group strategies were evaluated which gave comparable overall yields of (−)-(*R*)-sitagliptin **22** from commercially available starting materials: 43% overall yield employing *N*-benzyl-*N*-α-methylbenzyl protection and 42% overall yield using *N*-benzyl-*N*-α-methyl-*p*-methoxybenzyl protection (Fig. 2).

* Corresponding author.
E-mail address: steve.davies@chem.ox.ac.uk (S.G. Davies).

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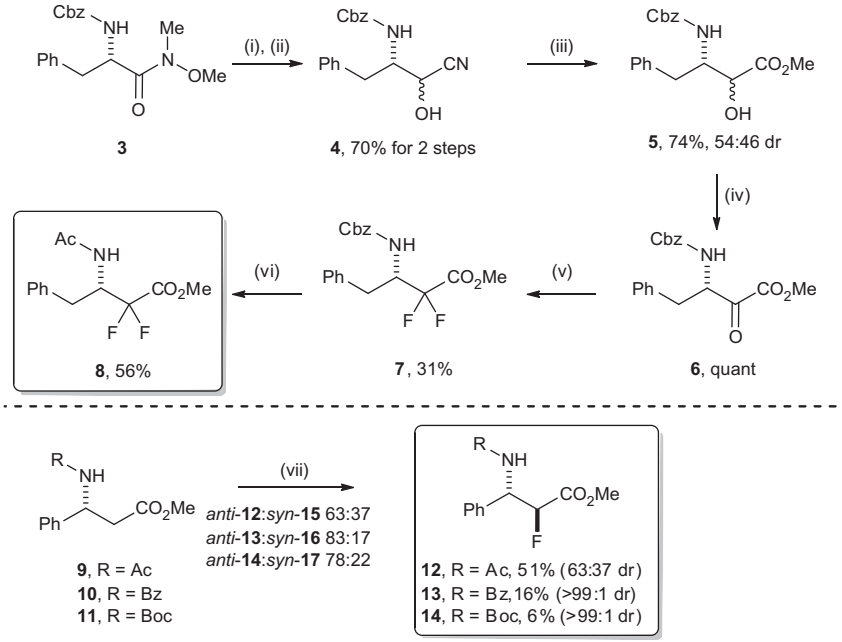
http://dx.doi.org/10.1016/j.tetasy.2012.07.001



Scheme 1. Reagents and conditions: (i) $LiAlH_4$, THF, 0 °C; (ii) KCN, THF/H_2O, rt; (iii) HCl, 1,4-dioxane, MeOH, 5 °C then H_2O; (iv) Dess–Martin periodinane, TFA, CH_2Cl_2, rt; (v) DAST, DME, rt; (vi) NH_4CO_2H, 10% Pd/C, DMF, rt then Ac_2O, pyridine, rt; (vii) LDA, THF, −78 °C, 1 h then NFSI, THF, −78 °C, 2.5 h.

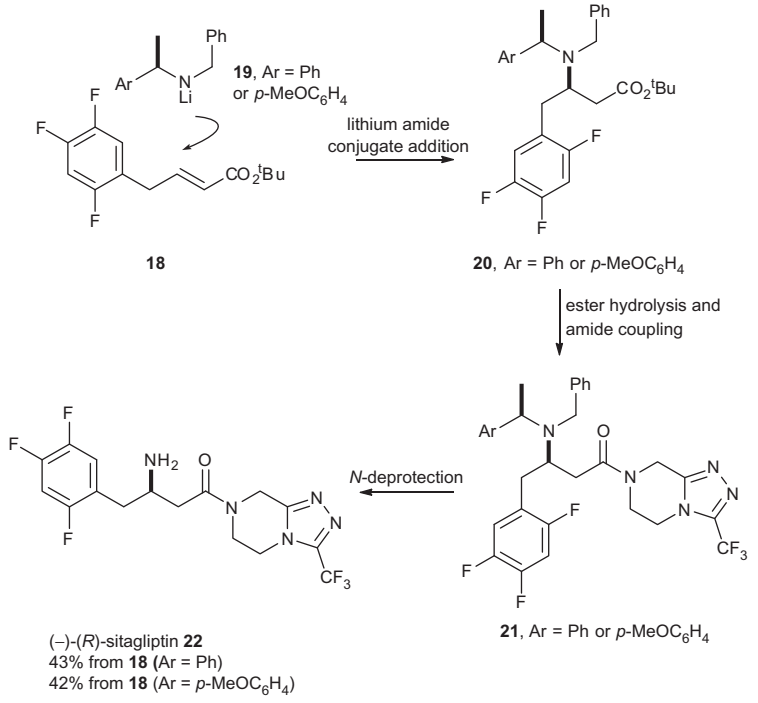


Figure 2. The asymmetric syntheses of (−)-(*R*)-sitagliptin **22** using the conjugate addition of enantiopure lithium amides as the key step.

We have previously employed this conjugate addition methodology as the key step to access several β-haloaryl-β-amino acids and their derivatives.[14] As part of our ongoing research programme in this area we anticipated that the highly diastereoselective conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **24** to a range of β-fluoroaryl-α,β-unsaturated esters **23**, followed by hydrogenolysis and ester hydrolysis, would enable efficient access to a range of β-fluoroaryl-β-amino acids **26** (Fig. 3). Herein we delineate the full details of these investigations.

2. Results and discussion

2.1. Preparation of β-fluoroaryl-α,β-unsaturated esters

The required β-fluoroaryl-α,β-unsaturated esters **43–57** were prepared via a one step procedure from the corresponding fluorobenzaldehydes. For this study, a range of commercially available fluorobenzaldehydes were chosen so as to include all the regioisomers of fluorobenzaldehyde **28–30** and difluorobenzaldehyde **31–36**, one

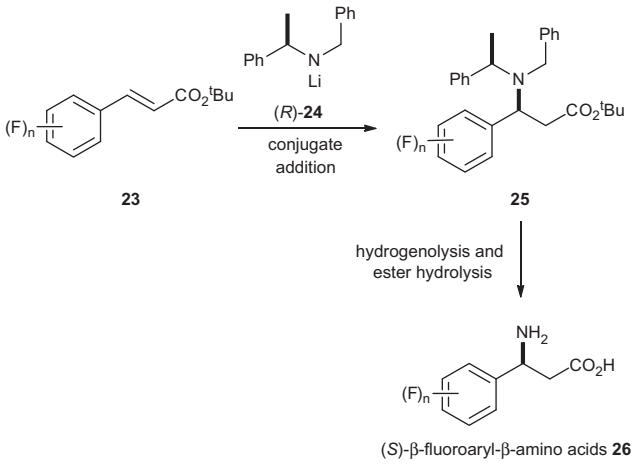
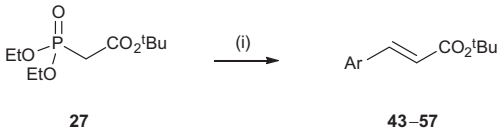


Figure 3. General strategy for the asymmetric synthesis of β-fluoroaryl-β-amino acids.

representative trifluorobenzaldehyde **37**, pentafluorobenzaldehyde **38** and four other representative functionalised fluorobenzladehydes **39–42**. Treatment of **28–42** with *tert*-butyl diethylphosphonoacetate **27** under our highly diastereoselective modified Wadsworth-Emmons reaction protocol (in which MeMgBr is employed as the base)[15] gave (*E*)-β-fluoroaryl-α,β-unsaturated esters **43–57** as single diastereoisomers (>99:1 dr), which were isolated in 79–90% yield after chromatographic purification (Scheme 2).

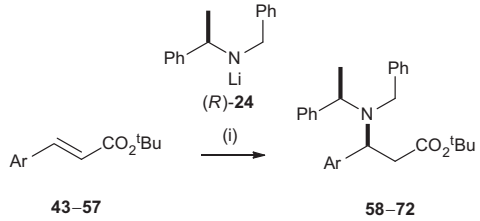


aldehyde	Ar	α,β-unsaturated ester	yield (%)	dr[a] [(*E*):(*Z*)]	$J_{2,3}$ value (Hz)
28	(2-F)C_6H_4	**43**	80	>99:1	16.1
29	(3-F)C_6H_4	**44**	79	>99:1	15.9
30	(4-F)C_6H_4	**45**	88	>99:1	15.9
31	(2,3-F)C_6H_3	**46**	88	>99:1	16.2
32	(2,4-F)C_6H_3	**47**	89	>99:1	16.2
33	(2,5-F)C_6H_3	**48**	87	>99:1	16.2
34	(2,6-F)C_6H_3	**49**	88	>99:1	16.2
35	(3,4-F)C_6H_3	**50**	90	>99:1	16.0
36	(3,5-F)C_6H_3	**51**	89	>99:1	16.0
37	(2,4,5-F)C_6H_2	**52**	88	>99:1	16.1
38	C_6F_5	**53**	84	>99:1	16.4
39	(2-Me-3-F)C_6H_3	**54**	79	>99:1	15.7
40	(2-F-5-OMe)C_6H_3	**55**	80	>99:1	16.2
41	(3-OPh-4-F)C_6H_3	**56**	82	>99:1	15.9
42	(2-F-3-CF_3)C_6H_3	**57**	87	>99:1	16.4

Scheme 2. Reagents and conditions: (i) MeMgBr, THF, rt, 15 min, then ArCHO, reflux, 15 h. [[a]crude and isolated].

2.2. Conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to β-fluoroaryl-α,β-unsaturated esters: preparation of β-fluoroaryl-β-amino esters

Conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **24** to β-fluoroaryl-α,β-unsaturated esters **43–57** proceeded with high diastereoselectivity (⩾91:9 dr in each case), and the corresponding β-fluoroaryl-β-amino esters **58–72** were isolated in good yield (⩾70%) and ⩾91:9 dr after chromatographic purification (Scheme 3). In each case, the configuration at the newly formed C(3)-stereogenic centre within the major diastereoisomer was assigned by reference to the transition state mnemonic previously developed by us to rationalise the diastereoselectivity observed during conjugate addition of either antipode of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **24** to an α,β-unsaturated ester,[16] as well as by analogy to numerous other examples reported in the literature.[13]

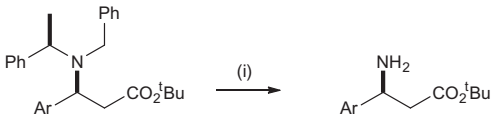


α,β-unsaturated ester	Ar	β-amino ester	yield (%)	dr[a]
43	(2-F)C_6H_4	**58**	89	98:2
44	(3-F)C_6H_4	**59**	83	98:2
45	(4-F)C_6H_4	**60**	88	98:2
46	(2,3-F)C_6H_3	**61**	84	96:4
47	(2,4-F)C_6H_3	**62**	82	>99:1
48	(2,5-F)C_6H_3	**63**	87	96:4
49	(2,6-F)C_6H_3	**64**	86	97:3
50	(3,4-F)C_6H_3	**65**	82	96:4
51	(3,5-F)C_6H_3	**66**	80	98:2
52	(2,4,5-F)C_6H_2	**67**	88	97:3
53	C_6F_5	**68**	72	94:6
54	(2-Me-3-F)C_6H_3	**69**	73	98:2
55	(2-F-5-OMe)C_6H_3	**70**	70	95:5
56	(3-OPh-4-F)C_6H_3	**71**	76	98:2
57	(2-F-3-CF_3)C_6H_3	**72**	80	91:9

Scheme 3. Reagents and conditions: (i) (*R*)-**24**, THF, −78 °C, 2 h. [[a]crude and isolated].

2.3. Hydrogenolysis of β-fluoroaryl-β-amino esters

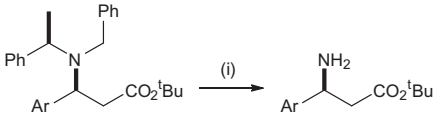
Next, the range of *N*-benzyl-*N*-(α-methylbenzyl)-protected β-fluoroaryl-β-amino esters **58–72** was subjected to hydrogenolytic N-debenzylation conditions [$Pd(OH)_2$/C (50% w/w), H_2 (1 atm), MeOH, rt, 24 h],[17] although competitive defluorination was observed in all cases, consistent with our previous observations concerning dehalogenation of β-haloaryl-β-amino esters under hydrogenolysis conditions.[14] After extensive optimisation of the reaction time for substrates **58–60** and **69–72**, the corresponding primary β-monofluoroaryl-β-amino esters **73–79** were successfully obtained in 91–96% yield (Scheme 4).



tertiary amine	Ar	β-amino ester	time (h)	yield (%)
58	(2-F)C_6H_4	**73**	36	95
59	(3-F)C_6H_4	**74**	9	91
60	(4-F)C_6H_4	**75**	48	93
69	(2-Me-3-F)C_6H_3	**76**	15	96
70	(2-F-5-OMe)C_6H_3	**77**	5	94
71	(3-OPh-4-F)C_6H_3	**78**	4	96
72	(2-F-3-CF_3)C_6H_3	**79**	15	95

Scheme 4. Reagents and conditions: (i) $Pd(OH)_2$/C (50% w/w), H_2 (1 atm), MeOH, rt.

However, the competitive defluorination remained problematic for the remaining substrates **61–68**, which incorporated more than one fluorine substituent around the aromatic ring. Despite attempted optimisation it was apparent that the competitive defluorination occurred during or even before the desired N-debenzylation process, and it was not possible to suppress the defluorination pathway. During the course of these investigations, Liu et al. reported the successful hydrogenolytic N-debenzylation of an analogous substrate.[18] This protocol employed a far lower catalyst loading [$Pd(OH)_2$/C, 6% w/w] under a higher pressure of hydrogen (5 atm). Thus, our range of β-fluoroaryl-β-amino esters **58–68** was next subjected to these conditions for 24 h. Primary β-amino esters **73–75** and **80–86** were then obtained in 90–95% yield, and in each case without defluorinated product(s) being observed. Attempted hydrogenolysis of penta-fluorophenyl substituted **68** under these conditions gave only returned starting material. However, increasing the catalyst loading (to 26% w/w) gave exclusively the corresponding primary β-pentafluoroaryl-β-amino ester **87** in 94% yield (Scheme 5).



58–68 73–75, 80–87

tertiary amine	Ar	β-amino ester	yield (%)
58	(2-F)C_6H_4	**73**	92
59	(3-F)C_6H_4	**74**	93
60	(4-F)C_6H_4	**75**	95
61	(2,3-F)C_6H_3	**80**	94
62	(2,4-F)C_6H_3	**81**	93
63	(2,5-F)C_6H_3	**82**	95
64	(2,6-F)C_6H_3	**83**	93
65	(3,4-F)C_6H_3	**84**	91
66	(3,5-F)C_6H_3	**85**	90
67	(2,4,5-F)C_6H_2	**86**	93
68	C_6F_5	**87**	94[a]

Scheme 5. Reagents and conditions: (i) $Pd(OH)_2$/C (6% w/w), H_2 (5 atm), MeOH, rt, 24 h. [a$Pd(OH)_2$/C (26% w/w)].

2.4. Synthesis of β-fluoroaryl-β-amino acids

Hydrolysis of β-fluoroaryl-β-amino esters **73–87** with 2.0 M aq HCl and subsequent ion-exchange chromatography on Dowex 50WX8-100 resin gave the corresponding β-fluoroaryl-β-amino acids **88–102** in ⩾90% yield. The ^1H and ^{13}C NMR spectroscopic data, melting points and specific rotations of the known β-fluoroaryl-β-amino acids **88–90**, **95**, **98** and **102** showed excellent agreement with those previously reported in the literature (Scheme 6).

3. Conclusion

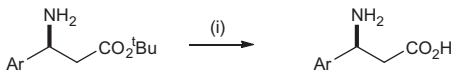
In conclusion, the conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to a range of β-fluoroaryl-α,β-unsaturated esters gave the corresponding β-fluoroaryl-β-amino esters in high diastereoselectivities and good isolated yields. Subsequent efficient global *N*-deprotection was facilitated by hydrogenolysis without the formation of the products arising from defluorination being observed. Finally, hydrolysis of the resultant primary β-fluoroaryl-β-amino esters gave a range of β-fluoroaryl-β-amino acids in excellent yield.

4. Experimental

4.1. General experimental

Reactions involving moisture-sensitive reagents were carried out under a nitrogen atmosphere using standard vacuum line techniques and glassware that was flame-dried and cooled under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.[23] Water was purified by an Elix® UV-10 system. BuLi was purchased from Sigma–Aldrich (as a 1.6 or 2.5 M solution in hexanes) and titrated against diphenylacetic acid before use. Organic layers were dried over $MgSO_4$. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Flash column chromatography was performed either on Kieselgel 60 silica on a glass column, or on a Biotage SP4 automated flash column chromatography platform.

Elemental analyses were recorded by the microanalysis service of London Metropolitan University, U.K. Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected. Optical rotations were recorded on a Perkin–Elmer 241 polarime-



73–87 88–102

β-amino ester	Ar	β-amino acid	yield (%)	mp (°C)	specific rotation	ref.	mp (°C)	specific rotation
73	(2-F)C_6H_4	**88**	96	239–240	$[\alpha]_D^{25}$ –2.7 (*c* 0.3 in H_2O)	19	247[a]	$[\alpha]_D^{22}$ +3.0 (*c* 0.3 in H_2O)[a]
74	(3-F)C_6H_4	**89**	97	220–223	$[\alpha]_D^{25}$ –2.0 (*c* 0.4 in H_2O)	20	226–229	$[\alpha]_D^{25}$ –1.8 (*c* 0.4 in H_2O)
75	(4-F)C_6H_4	**90**	96	220–221	$[\alpha]_D^{25}$ –5.6 (*c* 0.5 in H_2O)	19	220–222	$[\alpha]_D^{22}$ –4.0 (*c* 0.5 in H_2O)
80	(2,3-F)C_6H_3	**91**	96	200–202	$[\alpha]_D^{25}$ –2.5 (*c* 0.5 in H_2O)			
81	(2,4-F)C_6H_3	**92**	92	207–209	$[\alpha]_D^{25}$ –4.9 (*c* 0.5 in H_2O)			
82	(2,5-F)C_6H_3	**93**	93	207–209	$[\alpha]_D^{25}$ –3.2 (*c* 0.5 in H_2O)			
83	(2,6-F)C_6H_3	**94**	95	198–200	$[\alpha]_D^{25}$ –4.8 (*c* 0.5 in H_2O)			
84	(3,4-F)C_6H_3	**95**	90	225–227	$[\alpha]_D^{25}$ –3.9 (*c* 1.0 in H_2O)	14b	226–230	$[\alpha]_D^{23}$ –3.2 (*c* 1.0 in H_2O)
85	(3,5-F)C_6H_3	**96**	90	206–208	$[\alpha]_D^{25}$ –4.5 (*c* 0.5 in H_2O)			
86	(2,4,5-F)C_6H_2	**97**	93	219–221	$[\alpha]_D^{25}$ –7.2 (*c* 0.5 in H_2O)			
87	C_6F_5	**98**	97	188–190	$[\alpha]_D^{25}$ +27.3 (*c* 2.5 in H_2O)	21		$[\alpha]_D^{22}$ +24 (*c* 2.5 in D_2O)
76	(2-Me-3-F)C_6H_3	**99**	95	228–230	$[\alpha]_D^{25}$ –15.6 (*c* 0.5 in H_2O)			
77	(2-F-5-OMe)C_6H_3	**100**	94	189–191	$[\alpha]_D^{25}$ –3.8 (*c* 0.5 in H_2O)			
78	(3-OPh-4-F)C_6H_3	**101**	97	>370	$[\alpha]_D^{25}$ –12.0 (*c* 0.5 in H_2O)			
79	(2-F-3-CF_3)C_6H_3	**102**	95	207–208	$[\alpha]_D^{25}$ –2.2 (*c* 0.5 in H_2O)	22	206	

Scheme 6. Reagents and conditions: (i) HCl (2.0 M, aq), reflux, 6 h, then Dowex 50WX8-100. [alit. data for the antipode].

ter with a water-jacketed 10 cm cell. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g/100 mL. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer using an ATR module (ATR). Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded on Bruker Avance spectrometers in the deuterated solvent stated, at rt. The field was locked by external referencing to the relevant deuteron resonance. Low-resolution mass spectra were recorded on either a VG MassLab 20-250 or a Micromass Platform 1 spectrometer. Accurate mass measurements were run on either a Bruker MicroTOF internally calibrated with polyalanine, or a Micromass GCT instrument fitted with a Scientific Glass Instruments BPX5 column (15 m × 0.25 mm) using amyl acetate as a lock mass.

4.2. General experimental procedures

4.2.1. General procedure 1 for Horner–Wadsworth–Emmons reaction

MeMgBr (1.20 equiv) was added dropwise to a stirred solution of *tert*-butyl diethylphosphonoacetate **27** (1.20 equiv) in anhydrous THF at rt under nitrogen and the resultant mixture was stirred at rt for 15 min. The requisite aldehyde (1.00 equiv) was added dropwise via syringe and the reaction mixture was then heated at reflux for 15 h. Satd aq NH_4Cl was added and the reaction mixture was extracted with EtOAc. The combined organic extracts were washed with brine, then dried and concentrated in vacuo.

4.2.2. General procedure 2 for lithium amide conjugate addition

BuLi (1.55 equiv) was added dropwise to a solution of the requisite amine (1.6 equiv) in THF at −78 °C. The resultant pink solution was stirred at −78 °C for 30 min before the addition of a solution of the requisite α,β-unsaturated ester (1.0 equiv) in THF at −78 °C. The reaction mixture was then stirred at −78 °C for 2 h before the addition of satd aq NH_4Cl. The reaction mixture was then allowed to warm to rt and concentrated in vacuo. The residue was partitioned between H_2O and Et_2O and the aqueous layer was extracted with Et_2O. The combined organic extracts were then washed sequentially with 10% aq citric acid, satd aq $NaHCO_3$ and brine, then dried and concentrated in vacuo.

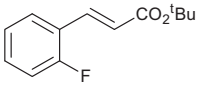
4.2.3. General procedure 3 for hydrogenolytic N-debenzylation

A stirred solution of the requisite amine in MeOH was purged with nitrogen for 15 min. After this time, Pd $(OH)_2$/C was added and the reaction mixture was placed under an atmosphere of H_2 (1 atm or 5 atm). Stirring under H_2 was continued for the stated time, after which, the reaction mixture was filtered by passage through Celite® (eluent MeOH) and concentrated in vacuo.

4.2.4. General procedure 4 for hydrolysis of *tert*-butyl esters

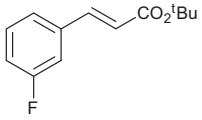
2.0 M aq HCl was added dropwise to a stirred solution of the requisite *tert*-butyl ester at rt and the reaction mixture was heated at reflux for 6 h. After this time, the reaction mixture was concentrated in vacuo. The residue was then purified via ion-exchange chromatography (Dowex50WX8-100, eluent 1.0 M aq NH_4OH).

4.2.5. *tert*-Butyl (*E*)-3-(2′-fluorophenyl)prop-2-enoate 43



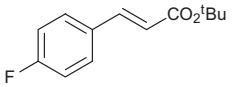
Following *general procedure 1*, **27** (7.57 g, 30.0 mmol), MeMgBr (2.5 M in Et_2O, 12.0 mL, 30.0 mmol) and **28** (3.10 g, 25.0 mmol) in THF (300 mL) gave, after purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 40:1), **43** as a colourless oil (4.44 g, 80%, >99:1 dr);[24] ν_{max} (ATR) 3044 (C–H), 1710 (C=O), 1638 (C=C); δ_H (400 MHz, $CDCl_3$) 1.54 (9H, s, C*Me*$_3$), 6.46 (1H, d, *J* 16.1, C(2)*H*), 7.05–7.16 (2H, m, *Ar*), 7.30–7.35 (1H, m, *Ar*), 7.52 (1H, dt, *J* 7.6, 1.6, *Ar*), 7.72 (1H, d, *J* 16.1, C(3)*H*); δ_C (100 MHz, $CDCl_3$)[25] 28.1 (C*Me*$_3$), 80.7 (*C*Me$_3$), 122.7 (*C*(2)), 116.1, 124.4, 128.8, 131.3 (*C*(3′), *C*(4′), *C*(5′), *C*(6′)), 136.0 (*C*(3)), 161.2 (d, *J* 254, *C*(2′)), 166.1 (*C*(1)); *m/z* (ESI$^+$) 467 ([2M+Na]$^+$, 100%), 245 ([M+Na]$^+$, 82%); HRMS (ESI$^+$) $C_{13}H_{15}FNaO_2^+$ ([M+Na]$^+$) requires 245.0948; found 245.0952.

4.2.6. *tert*-Butyl (*E*)-3-(3′-fluorophenyl)prop-2-enoate 44



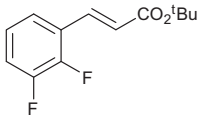
Following *general procedure 1*, **27** (6.05 g, 24.0 mmol), MeMgBr (2.7 M in Et_2O, 8.9 mL, 24.0 mmol) and **29** (2.48 g, 20.0 mmol) in THF (240 mL) gave, after purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 40:1), **44** as a pale yellow oil (3.51 g, 79%, >99:1 dr);[14b] δ_H (400 MHz, $CDCl_3$) 1.54 (9H, s, C*Me*$_3$), 6.37 (1H, d, *J* 15.9, C(2)*H*), 7.03–7.37 (4H, m, *Ar*), 7.54 (1H, d, *J* 15.9, C(3)*H*).

4.2.7. *tert*-Butyl (*E*)-3-(4′-fluorophenyl)prop-2-enoate 45



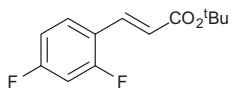
Following *general procedure 1*, **27** (6.05 g, 24.0 mmol), MeMgBr (2.7 M in Et_2O, 8.9 mL, 24.0 mmol) and **30** (2.0 mL, 20.0 mmol) in THF (240 mL) gave, after purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 40:1), **45** as a white, crystalline solid (3.91 g, 88%, >99:1 dr);[26] mp 46–47 °C; {lit.[26] mp 47.5–48.5 °C}; δ_H (400 MHz, $CDCl_3$) 1.54 (9H, s, C*Me*$_3$), 6.30 (1H, d, *J* 15.9, C(2)*H*), 7.05–7.09 (2H, m, C(2′)*H*, C(6′)*H*), 7.48–7.53 (2H, m, C(3′)*H*, C(5′)*H*), 7.55 (1H, d, *J* 15.9, C(3)*H*).

4.2.8. *tert*-Butyl (*E*)-3-(2′,3′-difluorophenyl)prop-2-enoate 46



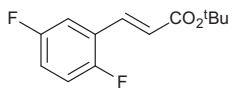
Following *general procedure 1*, **27** (4.26 g, 16.9 mmol), MeMgBr (3.0 M in Et_2O, 5.6 mL, 16.9 mmol) and **31** (2.00 g, 14.1 mmol) in THF (180 mL) gave, after purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 50:1), **46** as a white, crystalline solid (2.98 g, 88%, >99:1 dr); $C_{13}H_{14}F_2O_2$ requires C, 65.0; H, 5.9%; found C, 64.6; H, 5.7%; mp 25–26 °C; ν_{max} (ATR) 2980, 2934 (C–H), 1708 (C=O), 1639 (C=C); δ_H (400 MHz, $CDCl_3$) 1.52 (9H, s, C*Me*$_3$), 6.45 (1H, d, *J* 16.2, C(2)*H*), 7.03–7.26 (3H, m, *Ar*), 7.65 (1H, d, *J* 16.2, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 28.0 (C*Me*$_3$), 80.8 (*C*Me$_3$), 118.2, 123.5, 124.0 (*C*(4′), *C*(5′), *C*(6′)), 124.1 (*C*(2)), 124.9 (*C*(1′)), 134.8 (*C*(3)), 148.7 (dd, *J* 248, 13, *C*F), 151.5 (dd, *J* 254, 13, *C*F), 165.6 (*C*(1)); *m/z* (ESI$^+$) 503 ([2M+Na]$^+$, 74%), 263 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{14}F_2NaO_2^+$ ([M+Na]$^+$) requires 263.0854; found 263.0851.

4.2.9. *tert*-Butyl (*E*)-3-(2′,4′-difluorophenyl)prop-2-enoate 47



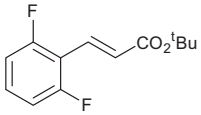
Following *general procedure 1*, **27** (4.26 g, 16.9 mmol), MeMgBr (3.0 M in Et_2O, 5.6 mL, 16.9 mmol) and **32** (2.00 g, 14.1 mmol) in THF (180 mL) gave, after purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 50:1), **47** as a white solid (3.01 g, 89%, >99:1 dr);[27] mp 42–43 °C; {lit.[27] mp 43 °C}; δ_H (400 MHz, $CDCl_3$) 1.52 (9H, s, C*Me*$_3$), 6.39 (1H, d, *J* 16.2, C(2)*H*), 6.80–6.90 (2H, m, *Ar*), 7.46–7.52 (1H, m, *Ar*), 7.63 (1H, d, *J* 16.2, C(3)*H*).

4.2.10. *tert*-Butyl (*E*)-3-(2′,5′-difluorophenyl)prop-2-enoate 48



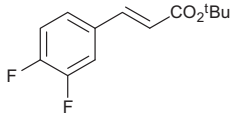
Following *general procedure 1*, **27** (4.26 g, 16.9 mmol), MeMgBr (3.0 M in Et_2O, 5.6 mL, 16.9 mmol) and **33** (2.00 g, 14.1 mmol) in THF (180 mL) gave, after purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 50:1), **48** as a white solid (2.94 g, 87%, >99:1 dr); $C_{13}H_{14}F_2O_2$ requires C, 65.0; H, 5.9%; found C, 64.9; H, 5.8%; mp 52–53 °C; ν_{max} (ATR) 2980, 2934 (C–H), 1708 (C=O), 1640 (C=C); δ_H (400 MHz, $CDCl_3$) 1.54 (9H, s, C*Me*$_3$), 6.43 (1H, d, *J* 16.2, C(2)*H*), 7.01–7.18 (2H, m, *Ar*), 7.20–7.23 (1H, m, *Ar*), 7.65 (1H, d, *J* 16.2, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 28.2 (C*Me*$_3$), 80.8 (*C*Me$_3$), 114.4, 117.2, 117.8 (*C*(3′), *C*(4′), *C*(6′)), 123.9 (*C*(2)), 124.0 (*C*(1′)), 134.8 (*C*(3)), 156.7 (d, *J* 208, *C*F), 159.2 (d, *J* 222, *C*F), 165.6 (*C*(1)); *m*/*z* (ESI$^+$) 503 ([2M+Na]$^+$, 100%), 263 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{14}F_2NaO_2^+$ ([M+Na]$^+$) requires 263.0854; found 263.0853.

4.2.11. *tert*-Butyl (*E*)-3-(2′,6′-difluorophenyl)prop-2-enoate 49



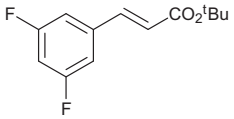
Following *general procedure 1*, **27** (4.26 g, 16.9 mmol), MeMgBr (3.0 M in Et_2O, 5.6 mL, 16.9 mmol) and **34** (2.00 g, 14.1 mmol) in THF (180 mL) gave, after purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 50:1), **49** as a white solid (2.98 g, 88%, >99:1 dr);[15] mp 56–57 °C; {lit.[15] mp 55–56 °C};δ_H (400 MHz, $CDCl_3$) 1.54 (9H, s, C*Me*$_3$), 6.43 (1H, d, *J* 16.2, C(2)*H*), 6.90–6.94 (2H, m, *Ar*), 7.24–7.31 (1H, m, *Ar*), 7.68 (1H, d, *J* 16.2, C(3)*H*).

4.2.12. *tert*-Butyl (*E*)-3-(3′,4′-difluorophenyl)prop-2-enoate 50



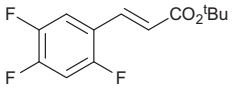
Following *general procedure 1*, **27** (4.26 g, 16.9 mmol), MeMgBr (3.0 M in Et_2O, 5.6 mL, 16.9 mmol) and **35** (2.00 g, 14.1 mmol) in THF (180 mL) gave, after purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 50:1), **50** as a white solid (3.04 g, 90%, >99:1 dr);[14b] mp 60–61 °C; {lit.[14b] mp 61 °C}; δ_H (400 MHz, $CDCl_3$) 1.51 (9H, s, C*Me*$_3$), 6.26 (1H, d, *J* 16.0, C(2)*H*), 7.06–7.34 (3H, m, *Ar*), 7.46 (1H, d, *J* 16.0, C(3)*H*).

4.2.13. *tert*-Butyl (*E*)-3-(3′,5′-difluorophenyl)prop-2-enoate 51



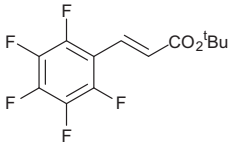
Following *general procedure 1*, **27** (4.26 g, 16.9 mmol), MeMgBr (3.0 M in Et_2O, 5.6 mL, 16.9 mmol) and **36** (2.00 g, 14.1 mmol) in THF (180 mL) gave, after purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 50:1), **51** as a white, crystalline solid (3.01 g, 89%, >99:1 dr); mp 68–69 °C; ν_{max} (ATR) 2980, 2934 (C–H), 1708 (C=O), 1644 (C=C); δ_H (400 MHz, $CDCl_3$) 1.54 (9H, s, C*Me*$_3$), 6.35 (1H, d, *J* 16.0, C(2)*H*), 6.79–6.83 (1H, m, *Ar*), 7.00–7.03 (2H, m, *Ar*), 7.47 (1H, d, *J* 16.0, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 28.2 (C*Me*$_3$), 81.2 (*C*Me$_3$), 105.0, 110.4, 110.6 (*C*(2′), *C*(4′), *C*(6′)), 122.9 (*C*(2)), 138.0 (*C*(1′)), 140.9 (*C*(3)), 161.8, 164.3 (*C*(2′), *C*(5′)), 165.4 (*C*(1)); *m*/*z* (ESI$^+$) 503 ([2M+Na]$^+$, 15%), 263 ([M+Na]$^+$, 50%); HRMS (ESI$^+$) $C_{13}H_{14}F_2NaO_2^+$ ([M+Na]$^+$) requires 263.0854; found 263.0854.

4.2.14. *tert*-Butyl (*E*)-3-(2′,4′,5′-trifluorophenyl)prop-2-enoate 52



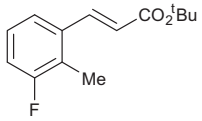
Following *general procedure 1*, **27** (4.26 g, 16.9 mmol), MeMgBr (3.0 M in Et_2O, 5.6 mL, 16.9 mmol) and **37** (2.26 g, 14.1 mmol) in THF (180 mL) gave, after purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 50:1), **52** as a white, crystalline solid (3.20 g, 88%, >99:1 dr); $C_{13}H_{13}F_3O_2$ requires C, 60.5; H, 5.1%; found C, 60.4; H, 5.0%; mp 86–87 °C; ν_{max} (ATR) 2973, 2938 (C–H), 1695 (C=O), 1634 (C=C); δ_H (400 MHz, $CDCl_3$) 1.54 (9H, s, C*Me*$_3$), 6.37 (1H, d, *J* 16.1, C(2)*H*), 6.93–7.00 (1H, m, *Ar*), 7.30–7.37 (1H, m, *Ar*), 7.60 (1H, d, *J* 16.1, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 28.2 (C*Me*$_3$), 81.1 (*C*Me$_3$), 106.1, 115.9 (*C*(3′), *C*(6′)), 119.3 (*C*(1′)), 123.6 (*C*(2)), 133.7 (*C*(3)), 149.6, 152.0, 155.2 (*C*(2′), *C*(4′), *C*(5′)), 165.4 (*C*(1)); *m*/*z* (ESI$^+$) 539 ([2M+Na]$^+$, 62%), 281 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{13}F_3NaO_2^+$ ([M+Na]$^+$) requires 281.0760; found 281.0758.

4.2.15. *tert*-Butyl (*E*)-3-(pentafluorophenyl)prop-2-enoate 53



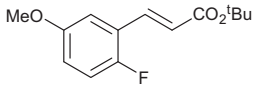
Following *general procedure 1*, **27** (3.03 g, 12.0 mmol), MeMgBr (2.4 M in Et_2O, 5.0 mL, 12.0 mmol) and **38** (1.96 g, 10.0 mmol) in THF (120 mL) gave, after purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 30:1), **53** as a white, crystalline solid (2.47 g, 84%, >99:1 dr);[27] mp 37–38 °C; δ_H (400 MHz, $CDCl_3$) 1.54 (9H, s, C*Me*$_3$), 6.67 (1H, d, *J* 16.4, C(2)*H*), 7.55 (1H, d, *J* 16.4, C(3)*H*).

4.2.16. *tert*-Butyl (*E*)-3-(2′-methyl-3′-fluorophenyl)prop-2-enoate 54



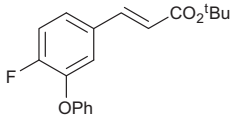
Following *general procedure1*, **27** (6.57 g, 26.4 mmol), MeMgBr (2.6 M in Et_2O, 10.2 mL, 26.4 mmol) and **39** (3.00 g, 21.7 mmol) in THF (300 mL) gave, after purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 40:1), **54** as a colourless oil (4.05 g, 79%, >99:1 dr); ν_{max} (ATR) 3004 (C–H), 1711 (C=O), 1637 (C=C); δ_H (400 MHz, $CDCl_3$) 1.56 (9H, s, C*Me*$_3$), 2.32 (3H, s, C(2′)*Me*), 6.30 (1H, d, *J* 15.7, C(2)*H*), 7.01–7.03 (1H, m, C(4′)*H*), 7.15 (1H, dd, *J* 7.8, 5.8, C(5′)*H*), 7.32 (1H, d, *J* 7.8, C(6′)*H*), 7.84 (1H, d, *J* 15.7, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 10.6 (C(2′)*Me*), 28.1 (C*Me*$_3$), 80.7 (*C*Me$_3$), 116.0 (*C*(4′)), 122.0 (*C*(6′)), 122.6 (*C*(2)), 124.4 (*C*(2′)), 126.8 (*C*(5′)), 135.9 (*C*(1′)), 140.1 (*C*(3)), 161.3 (d, *J* 243, *C*(3′)), 166.0 (*C*(1)); *m/z* (ESI$^+$) 495 ([2M+Na]$^+$, 100%), 259 ([M+Na]$^+$, 69%); HRMS (ESI$^+$) $C_{14}H_{17}FNaO_2^+$ ([M+Na]$^+$) requires 259.1105; found 259.1106.

4.2.17. *tert*-Butyl (*E*)-3-(2′-fluoro-5′-methoxyphenyl)prop-2-enoate 55



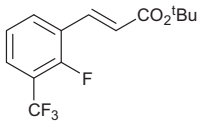
Following *general procedure 1*, **27** (5.45 g, 21.6 mmol), MeMgBr (2.7 M in Et_2O, 8.0 mL, 21.6 mmol) and **40** (2.77 g, 18.0 mmol) in THF (220 mL) gave, after purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 30:1), **55** as a white, crystalline solid (3.63 g, 80%, >99:1 dr); $C_{14}H_{17}FO_3$ requires C, 66.7; H, 6.8%; found C, 66.6; H, 6.8%; mp 34–35 °C; ν_{max} (ATR) 3072 (C–H), 1708 (C=O), 1638 (C=C); δ_H (400 MHz, $CDCl_3$) 1.54 (9H, s C*Me*$_3$), 3.81 (3H, s, O*Me*), 6.44 (1H, d, *J* 16.2, C(2)*H*), 6.85–6.89 (1H, m, C(3′)*H*), 7.01–7.04 (2H, m, C(4′)*H*, C(6′)*H*), 7.69 (1H, d, *J* 16.2, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 28.1 (C*Me*$_3$), 55.8 (O*Me*), 80.7 (*C*Me$_3$), 112.5 (*C*(4′), 116.7, 117.1 (*C*(3′), *C*(6′)), 122.7 (*C*(2)), 122.9 (*C*(1′)), 136.1 (*C*(3)), 155.8 (*C*(5′)), 157.0 (*C*(2′)), 166.0 (*C*(1)); *m/z* (ESI$^+$) 527 ([2M+Na]$^+$, 100%), 275 ([M+Na]$^+$, 89%); HRMS (ESI$^+$) $C_{14}H_{17}FNaO_3^+$ ([M+Na]$^+$) requires 275.1054; found 275.1057.

4.2.18. *tert*-Butyl (*E*)-3-(3′-phenoxy-4′-fluorophenyl)prop-2-enoate 56



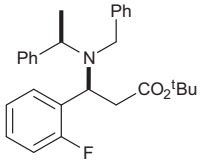
Following *general procedure 1*, **27** (2.39 g, 9.48 mmol), MeMgBr (2.4 M in Et_2O, 4.0 mL, 9.48 mmol) and **41** (1.0 mL, 7.90 mmol) in THF (100 mL) gave, after purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 40:1), **56** as a white, crystalline solid (2.04 g, 82%, >99:1 dr); $C_{19}H_{19}FO_3$ requires C, 72.6; H, 6.1%; found C, 72.75; H, 6.15%; mp 88–90 °C; ν_{max} (ATR) 3063 (C–H), 1707 (C=O), 1639 (C=C); δ_H (400 MHz, $CDCl_3$) 1.52 (9H, s, C*Me*$_3$), 6.21 (1H, d, *J* 15.9, C(2)*H*), 7.01–7.36 (8H, m, *Ar*, *Ph*), 7.46 (1H, d, *J* 15.9, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 28.1 (C*Me*$_3$), 80.7 (*C*Me$_3$), 117.4, 117.6, 120.3, 120.7, 124.5, 129.8 (*C*(2′), *C*(5′), *C*(6′), *o*,*m*,*p*-*Ph*), 123.6 (*C*(2)), 131.8 (*C*(1′)), 141.7 (*C*(3)), 143.0, 153.8, 156.8 (*C*(3′), *C*(4′), *i*-*Ph*), 165.9 (*C*(1)); *m/z* (ESI$^+$) 651 ([2M+Na]$^+$, 100%), 337 ([M+Na]$^+$, 49%); HRMS (ESI$^+$) $C_{19}H_{19}FNaO_3^+$ ([M+Na]$^+$) requires 337.1210; found 337.1209.

4.2.19. *tert*-Butyl (*E*)-3-[2′-fluoro-3′-(trifluoromethyl)phenyl]-prop-2-enoate 57



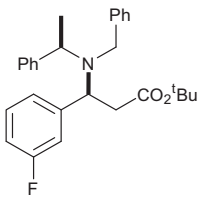
Following *general procedure 1*, **27** (7.88 g, 31.2 mmol), MeMgBr (2.6 M in Et_2O, 12.0 mL, 31.2 mmol) and **42** (5.00 g, 26.0 mmol) in THF (320 mL) gave, after purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 40:1), **57** as a colourless oil (6.56 g, 87%, >99:1 dr); ν_{max} (ATR) 1713 (C=O), 1643 (C=C); δ_H (400 MHz, $CDCl_3$) 1.54 (9H, s, C*Me*$_3$), 6.49 (1H, d, *J* 16.4, C(2)*H*), 7.23–7.27 (1H, m, C(5′)*H*), 7.57–7.60 (1H, m, C(6′)*H*), 7.70–7.73 (1H, m, C(4′)*H*), 7.71 (1H, d, *J* 16.4, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 28.1 (C*Me*$_3$), 81.0 (*C*Me$_3$), 119.4 (m, *C*(3′)), 121.0 (q, *J* 273, *C*F$_3$), 123.7 (*C*(1′)), 124.1 (*C*(5′)), 124.5 (*C*(2)), 128.0 (*C*(6′)), 132.3, 134.1 (*C*(3), *C*(4′)), 157.7 (d, *J* 265, *C*(2′)), 165.4 (*C*(1)); *m/z* (ESI$^+$) 603 ([2M+Na]$^+$, 97%), 313 ([M+Na]$^+$, 61%); HRMS (ESI$^+$) $C_{14}H_{14}F_4NaO_2^+$ ([M+Na]$^+$) requires 313.0822; found 313.0823.

4.2.20. *tert*-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-3-(2′-fluorophenyl)propanoate 58



Following *general procedure 2*, BuLi (2.6 M in hexanes, 4.0 mL, 10.5 mmol) and (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (1.95 g, 14.4 mmol) in THF (50 mL) at −78 °C, and **43** (2.28 g, 10.8 mmol, >99:1 dr) in THF (50 mL) at −78 °C gave **58** in 98:2 dr. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 30:1) gave **58** as a colourless oil (4.16 g, 89%, 98:2 dr); $[\alpha]_D^{25}$ +7.6 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2977 (C–H), 1728 (C=O); δ_H (400 MHz, $CDCl_3$) 1.22 (9H, s, C*Me*$_3$), 1.28 (3H, d, *J* 6.8, C(α)*Me*), 2.49 (2H, d, *J* 7.9, C(2)H_2), 3.74 (2H, app q, J_{AB} 14.9, NCH_2Ph), 4.06 (1H, q, *J* 6.8, C(α)*H*), 4.75 (1H, app t, *J* 7.9, C(3)*H*), 7.06–7.47 (14H, m, *Ar*, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.6 (C(α)*Me*), 27.7 (C*Me*$_3$), 39.3 (*C*(2)), 50.8 (NCH_2Ph), 53.8 (*C*(α)), 56.7 (*C*(3)), 80.2 (*C*Me$_3$), 115.5, 115.8, 123.8, 126.5, 126.8, 127.9, 128.0, 128.1, 128.8, 129.6 (*C*(3′), *C*(4′), *C*(5′), *C*(6′), *o*,*m*,*p*-*Ph*), 128.5 (*C*(1′)), 141.5, 143.9 (*i*-*Ph*), 161.4 (d, *J* 246.1, *C*(2′)), 171.2 (*C*(1)); *m/z* (ESI$^+$) 456 ([M+Na]$^+$, 91%), 434 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{33}FNO_2^+$ ([M+H]$^+$) requires 434.2490; found 434.2490.

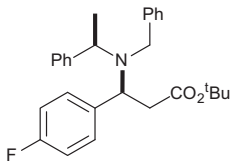
4.2.21. *tert*-Butyl (3*S*, α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-3-(3′-fluorophenyl)propanoate 59



Following *general procedure 2*, BuLi (2.3 M in hexanes, 9.1 mL, 20.9 mmol) and (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (4.56 g,

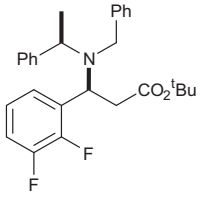
21.6 mmol) in THF (75 mL) at −78 °C, and **44** (3.00 g, 13.5 mmol, >99:1 dr) in THF (65 mL) at −78 °C gave **59** in 98:2 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 25:1) gave **59** as a colourless oil (4.85 g, 83%, 98:2 dr);[28] $[\alpha]_D^{25}$ +3.4 (*c* 1.0 in $CHCl_3$); {lit.[28] for enantiomer $[\alpha]_D^{21}$ −7.6 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.27 (9H, s, C*Me*$_3$), 1.31 (3H, d, *J* 7.0, C(α)*Me*), 2.45–2.54 (2H, m, C(2)H_2), 3.69 (2H, app s, NCH_2Ph), 4.00 (1H, q, *J* 7.0, C(α)*H*), 4.43 (1H, dd, *J* 9.6, 5.6, C(3)*H*), 6.93–7.45 (14H, m, *Ar*, *Ph*).

4.2.22. *tert*-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-3-(4′-fluorophenyl)propanoate 60



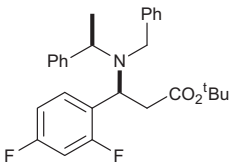
Following *general procedure 2*, BuLi (2.3 M in hexanes, 6.1 mL, 14.0 mmol) and (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (3.04 g, 14.4 mmol) in THF (50 mL) at −78 °C, and **45** (2.00 g, 9.00 mmol, >99:1 dr) in THF (45 mL) at −78 °C gave **60** in 98:2 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 30:1) gave **60** as a colourless oil (3.43 g, 88%, 98:2 dr); $[\alpha]_D^{25}$ +4.7 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2976 (C–H), 1725 (C=O); δ_H (400 MHz, $CDCl_3$) 1.25 (9H, s, C*Me*$_3$), 1.29 (3H, d, *J* 7.0, C(α)*Me*), 2.45–2.56 (2H, m, C(2)H_2), 3.68 (2H, s, NCH_2Ph), 3.98 (1H, q, *J* 7.0, C(α)*H*), 4.40 (1H, dd, *J* 10.4, 4.8, C(3)*H*), 7.18–7.43 (14H, m, *Ar*, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.7 (C(α)*Me*), 27.8 (C*Me*$_3$), 38.2 (*C*(2)), 50.8 (NCH_2Ph), 57.3 (*C*(α)), 59.0 (*C*(3)), 80.3 (*C*Me$_3$), 114.8, 115.0, 126.6, 126.9, 127.8, 127.9, 128.2, 129.8 (*C*(2′), *C*(3′), *C*(5′), *C*(6′), *o*,*m*,*p*-*Ph*), 137.7 (*C*(1′)), 141.6, 143.9 (*i*-*Ph*), 161.2 (d, *J* 244, *C*(4′)), 171.0 (*C*(1)); *m*/*z* (ESI$^+$) 456 ([M+Na]$^+$, 97%), 434 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{33}FNO_2^+$ ([M+H]$^+$) requires 434.2490; found 434.2479.

4.2.23. *tert*-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-3-(2′,3′-difluorophenyl)propanoate 61



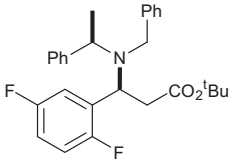
Following *general procedure 2*, BuLi (2.5 M in hexanes, 7.8 mL, 19.4 mmol) and (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (4.23 g, 20.0 mmol) in THF (50 mL) at −78 °C, and **46** (3.00 g, 12.5 mmol, >99:1 dr) in THF (50 mL) at −78 °C gave **61** in 96:4 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 25:1) gave **61** as a colourless oil (4.74 g, 84%, 96:4 dr); $C_{28}H_{31}F_2NO_2$ requires C, 74.5; H, 6.9; N, 3.1%; found C, 74.4; H, 6.9; N, 3.0%; $[\alpha]_D^{25}$ +16.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2977 (C–H), 1724 (C=O); δ_H (400 MHz, $CDCl_3$) 1.24 (9H, s, C*Me*$_3$), 1.32 (3H, d, *J* 6.8, C(α)*Me*), 2.61–2.64 (2H, m, C(2)H_2), 3.75 (2H, app q, J_{AB} 14.9, NCH_2Ph), 4.05 (1H, q, *J* 6.8, C(α)*H*), 4.76–4.80 (1H, m, C(3)*H*), 7.06–7.47 (13H, m, *Ar*, *Ph*); δ_C (400 MHz, $CDCl_3$) 15.0 (C(α)*Me*), 27.7 (C*Me*$_3$), 38.9 (*C*(2)), 50.7 (NCH_2Ph), 53.4 (*C*(3)), 57.0 (*C*(α)), 80.4 (*C*Me$_3$), 115.9, 116.1, 123.6, 124.0, 126.7, 126.9, 127.9, 128.1, 128.2 (*C*(4′), *C*(5′), *C*(6′), *o*,*m*,*p*-*Ph*), 131.3 (*C*(1′)), 141.2, 143.5 (*i*-*Ph*), 148.8 (d, *J* 260, *C*F), 150.9 (d, *J* 253, *C*F), 170.3 (*C*(1)); *m*/*z* (ESI$^+$) 474 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{31}F_2NNaO_2^+$ ([M+Na]$^+$) requires 474.2215; found 474.2207.

4.2.24. *tert*-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-3-(2′,4′-difluorophenyl)propanoate 62



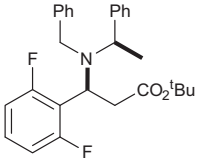
Following *general procedure 2*, BuLi (2.5 M in hexanes, 7.8 mL, 19.4 mmol) and (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (4.23 g, 20.0 mmol) in THF (50 mL) at −78 °C, and **47** (3.00 g, 12.5 mmol, >99:1 dr) in THF (50 mL) at −78 °C gave **62** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 25:1) gave **62** as a colourless oil (4.62 g, 82%, >99:1 dr); $C_{28}H_{31}F_2NO_2$ requires C, 74.5; H, 6.9; N, 3.1%; found C, 74.4; H, 6.7; N, 2.9%; $[\alpha]_D^{25}$ +18.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2978 (C–H), 1722 (C=O); δ_H (400 MHz, $CDCl_3$) 1.27 (9H, s, C*Me*$_3$), 1.35 (3H, d, *J* 6.8, C(α)*Me*), 2.64–2.66 (2H, m, C(2)H_2), 3.77 (2H, app q, J_{AB} 14.7, NCH_2Ph), 4.08 (1H, q, *J* 6.8, C(α)*H*), 4.75–4.79 (1H, m, C(3)*H*), 6.85–6.90 (2H, m, *Ar*), 7.10–7.49 (11H, m, *Ar*, *Ph*); δ_C (400 MHz, $CDCl_3$) 15.0 (C(α)*Me*), 27.7 (C*Me*$_3$), 38.9 (*C*(2)), 50.7 (NCH_2Ph), 53.4 (*C*(3)), 57.0 (*C*(α)), 80.4 (*C*Me$_3$), 104.0, 110.9, 111.0, 126.6, 126.9, 127.9, 128.1, 128.2, 130.3 (*C*(3′), *C*(5′), *C*(6′), *o*,*m*,*p*-*Ph*), 124.7 (*C*(1′)), 141.3, 143.6 (*i*-*Ph*), 160.4 (d, *J* 243, *C*F), 163.0 (d, *J* 238, *C*F), 170.3 (*C*(1)); *m*/*z* (ESI$^+$) 474 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{31}F_2NNaO_2^+$ ([M+Na]$^+$) requires 474.2215; found 474.2213.

4.2.25. *tert*-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-3-(2′,5′-difluorophenyl)propanoate 63



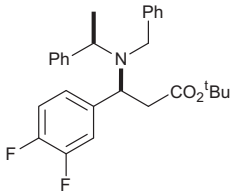
Following *general procedure 2*, BuLi (2.5 M in hexanes, 7.8 mL, 19.4 mmol) and (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (4.23 g, 20.0 mmol) in THF (50 mL) at −78 °C, and **48** (3.00 g, 12.5 mmol, >99:1 dr) in THF (50 mL) at −78 °C gave **63** in 96:4 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 25:1) gave **63** as a white solid (4.90 g, 87%, 96:4 dr); $C_{28}H_{31}F_2NO_2$ requires C, 74.5; H, 6.9; N, 3.1%; found C, 74.3; H, 7.0; N, 2.9%; mp 59–60 °C; $[\alpha]_D^{25}$ +17.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2977 (C–H), 1725 (C=O); δ_H (400 MHz, $CDCl_3$) 1.25 (9H, s, C*Me*$_3$), 1.32 (3H, d, *J* 6.8, C(α)*Me*), 2.57–2.60 (2H, m, C(2)H_2), 3.74 (2H, app q, J_{AB} 14.7, NCH_2Ph), 4.04 (1H, q, *J* 6.8, C(α)*H*), 4.72–4.76 (1H, m, C(3)*H*), 6.92–7.46 (13H, m, *Ar*, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.9 (C(α)*Me*), 27.7 (C*Me*$_3$), 38.9 (*C*(2)), 50.8 (NCH_2Ph), 53.6 (*C*(3)), 57.0 (*C*(α)), 80.5 (*C*Me$_3$), 115.1, 115.8, 116.6, 126.7, 126.9, 127.9, 128.0, 128.1, 128.2 (*C*(3′), *C*(4′), *C*(6′), *o*,*m*,*p*-*Ph*), 130.6 (*C*(1′)), 141.1, 143.6 (*i*-*Ph*), 156.7 (d, *J* 256, *C*F), 159.1 (d, *J* 249, *C*F), 170.2 (*C*(1)); *m*/*z* (ESI$^+$) 474 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{31}F_2NNaO_2^+$ ([M+Na]$^+$) requires 474.2215; found 474.2212.

4.2.26. *tert*-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-3-(2′,6′-difluorophenyl)propanoate 64



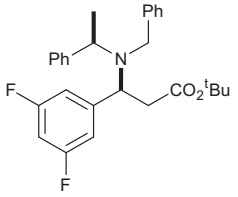
Following *general procedure 2*, BuLi (2.5 M in hexanes, 7.8 mL, 19.4 mmol) and (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (4.23 g, 20.0 mmol) in THF (50 mL) at −78 °C, and **49** (3.00 g, 12.5 mmol, >99:1 dr) in THF (50 mL) at −78 °C gave **64** in 97:3 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 25:1) gave **64** as a white solid (4.85 g, 86%, 97:3 dr); mp 52–53 °C; $[\alpha]_D^{25}$ +16.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2977 (C–H), 1726 (C=O); δ_H (400 MHz, $CDCl_3$) 1.25 (9H, s, C*Me*$_3$), 1.31 (3H, d, *J* 6.8, C(α)*Me*), 2.74 (1H, dd, *J* 14.9, 5.8, C(2)H_A), 2.94–3.01 (1H, m, C(2)H_B), 3.79 (2H, app q, J_{AB} 14.9, NCH_2Ph), 4.23 (1H, q, *J* 6.8, C(α)*H*), 4.83–4.87 (1H, m, C(3)*H*), 6.90–9.99 (2H, m, *Ar*), 7.12–7.51 (11H, m, *Ar*, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.7 (C(α)*Me*), 27.7 (C*Me*$_3$), 39.3 (*C*(2)), 51.0 (NCH_2Ph), 51.7 (*C*(3)), 56.4 (*C*(α)), 80.2 (*C*Me$_3$), 111.6, 111.9, 126.5, 126.7, 127.9, 128.0, 128.1, 129.1 (*C*(3′), *C*(4′), *C*(5′), *o*,*m*,*p*-*Ph*), 117.4 (*C*(1′)), 141.3, 143.8 (*i*-*Ph*), 161.5 (d, *J* 246, *C*(2′), *C*(6′)), 170.5 (*C*(1)); *m*/*z* (ESI$^+$) 474 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{31}F_2NNaO_2^+$ ([M+Na]$^+$) requires 474.2215; found 474.2210.

4.2.27. *tert*-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-3-(3′,4′-difluorophenyl)propanoate 65



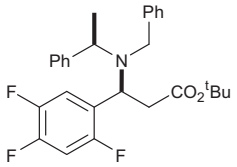
Following *general procedure 2*, BuLi (2.5 M in hexanes, 7.8 mL, 19.4 mmol) and (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (4.23 g, 20.0 mmol) in THF (50 mL) at −78 °C, and **50** (3.00 g, 12.5 mmol, >99:1 dr) in THF (50 mL) at −78 °C gave **65** in 96:4 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 35:1) gave **65** as a colourless oil (4.62 g, 82%, 96:4 dr); $[\alpha]_D^{25}$ +19.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2977 (C–H), 1722 (C=O); δ_H (400 MHz, $CDCl_3$) 1.32 (9H, s, C*Me*$_3$), 1.35 (3H, d, *J* 6.8, C(α)*Me*), 2.45–2.57 (2H, m, C(2)H_2), 3.71 (2H, app q, J_{AB} 14.9, NCH_2Ph), 4.0 (1H, q, *J* 6.8, C(α)*H*), 4.42–4.45 (1H, m, C(3)*H*), 7.11–7.45 (13H, m, *Ar*, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.4 (C(α)*Me*), 27.9 (C*Me*$_3$), 37.5 (*C*(2)), 50.9 (NCH_2Ph), 57.6 (*C*(α)), 58.4 (*C*(3)), 80.6 (*C*Me$_3$), 116.7, 117.1, 123.9, 126.8, 127.1, 127.8, 127.9, 128.3, 128.4 (*C*(2′), *C*(5′), *C*(6′), *o*,*m*,*p*-*Ph*), 139.5 (*C*(1′)), 141.1, 143.6 (*i*-*Ph*), 148.6 (d, *J* 233, *C*F), 150.9 (d, *J* 249, *C*F), 170.8 (*C*(1)); *m*/*z* (ESI$^+$) 474 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{31}F_2NNaO_2^+$ ([M+Na]$^+$) requires 474.2215; found 474.2209.

4.2.28. *tert*-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-3-(3′,5′-difluorophenyl)propanoate 66



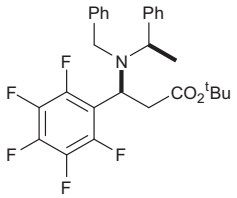
Following *general procedure 2*, BuLi (2.5 M in hexanes, 7.8 mL, 19.4 mmol) and (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (4.23 g, 20.0 mmol) in THF (50 mL) at −78 °C, and **51** (3.00 g, 12.5 mmol, >99:1 dr) in THF (50 mL) at −78 °C gave **66** in 98:2 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 30:1) gave **66** as a colourless oil (4.51 g, 80%, 98:2 dr); $[\alpha]_D^{25}$ +22.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2978 (C–H), 1722 (C=O); δ_H (400 MHz, $CDCl_3$) 1.34 (9H, s, C*Me*$_3$), 1.36 (3H, d, *J* 6.8, C(α)*Me*), 2.48–2.51 (2H, m, C(2)H_2), 3.71 (2H, app q, J_{AB} 14.7, NCH_2Ph), 4.00 (1H, q, *J* 6.8, C(α)*H*), 4.44–4.48 (1H, m, C(3)*H*), 6.75–6.79 (1H, m, *Ar*), 6.95–7.11 (2H, m, *Ar*), 7.15–7.45 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.5 (C(α)*Me*), 27.9 (C*Me*$_3$), 37.3 (*C*(2)), 51.1 (NCH_2Ph), 57.6 (*C*(α)), 58.5 (*C*(3)), 80.7 (*C*Me$_3$), 102.4, 110.8, 126.9, 127.2, 127.7, 128.0, 128.3, 128.4 (*C*(2′), *C*(4′), *C*(6′), *o*,*m*,*p*-*Ph*), 140.9, 143.3 (*i*-*Ph*), 146.9 (*C*(1′)), 163.1 (d, *J* 259, *C*(3′), *C*(5′)), 170.7 (*C*(1)); *m*/*z* (ESI$^+$) 474 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{31}F_2NNaO_2^+$ ([M+Na]$^+$) requires 474.2215; found 474.2216.

4.2.29. *tert*-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-3-(2′,4′,5′-trifluorophenyl)propanoate 67



Following *general procedure 2*, BuLi (2.5 M in hexanes, 13.9 mL, 34.8 mmol) and (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (7.35 g, 34.8 mmol) in THF (100 mL) at −78 °C, and **52** (3.00 g, 11.6 mmol, >99:1 dr) in THF (50 mL) at −78 °C gave **67** in 97:3 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 30:1) gave **67** as a colourless oil (4.79 g, 88%, 97:3 dr); $[\alpha]_D^{25}$ +22.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2977 (C–H), 1727 (C=O); δ_H (400 MHz, $CDCl_3$) 1.25 (9H, s, C*Me*$_3$), 1.32 (3H, d, *J* 6.8, C(α)*Me*), 2.48–2.59 (2H, m, C(2)H_2), 3.70 (2H, app q, J_{AB} 14.9, NCH_2Ph), 4.00 (1H, q, *J* 6.8, C(α)*H*), 4.66–4.70 (1H, m, C(3)*H*), 6.90–7.05 (1H, m, *Ar*), 7.15–7.42 (11H, m, *Ar*, *Ph*); δ_C (400 MHz, $CDCl_3$) 15.2 (C(α)*Me*), 27.8 (C*Me*$_3$), 38.6 (*C*(2)), 50.7 (NCH_2Ph), 53.2 (*C*(α)), 57.2 (*C*(3)), 80.6 (*C*Me$_3$), 105.4, 106.0, 117.2, 126.8, 127.1, 127.9, 128.2, 128.3 (*C*(3′), *C*(6′), *o*,*m*,*p*-*Ph*), 125.6 (*C*(1′)), 141.0, 143.2 (*i*-*Ph*), 146.6 (d, *J* 253, *C*F), 150.2 (d, *J* 247, *C*F), 156.2 (d, *J* 223, *C*F), 170.0 (*C*(1)); *m*/*z* (ESI$^+$) 492 ([M+Na]$^+$, 100%), 470 ([M+H]$^+$, 43%); HRMS (ESI$^+$) $C_{28}H_{30}F_3NNaO_2^+$ ([M+Na]$^+$) requires 492.2121; found 492.2113.

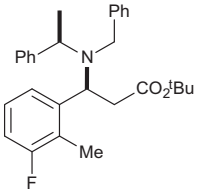
4.2.30. *tert*-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-3-(pentafluorophenyl)propanoate 68



Following *general procedure 2*, BuLi (2.3 M in hexanes, 6.9 mL, 15.8 mmol) and (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (3.45 g, 16.3 mmol) in THF (80 mL) at −78 °C, and **53** (3.00 g, 10.2 mmol, >99:1 dr) in THF (50 mL) at −78 °C gave **68** in 94:6 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 55:1) gave **68** as a pale yellow oil (3.71 g, 72%, 94:6 dr); $[\alpha]_D^{25}$ +35.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2979 (C–H), 1730 (C=O); δ_H (400 MHz, $CDCl_3$) 1.29 (9H, s, C*Me*$_3$), 1.31 (3H, d, *J* 6.8, C(α)*Me*), 2.70 (1H, dd, *J* 15.4, 5.6, C(2)H_A), 2.95 (1H, dd, *J* 15.4, 10.4, C(2)H_B), 3.68–3.86 (2H, m, NCH_2Ph), 4.14 (1H, q, *J* 6.8, C(α)*H*), 4.79 (1H, dd, *J* 10.4, 5.6, C(3)*H*), 7.12–7.44 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$)[29] 14.8 (C(α)*Me*), 27.8 (C*Me*$_3$), 38.2 (*C*(2)), 50.9

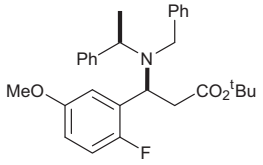
(NCH$_2$Ph), 51.7 (*C*(α)), 56.9 (*C*(3)), 80.8 (*C*Me$_3$), 126.8, 127.1, 127.7, 127.8, 128.1, 128.2 (*o*,*m*,*p*-*Ph*), 136.4 (*C*(1′)), 140.3, 142.9 (*i*-*Ph*), 170.0 (*C*(1)); *m*/*z* (ESI$^+$) 528 ([M+Na]$^+$, 98%), 506 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{29}F_5NO_2^+$ ([M+H]$^+$) requires 506.2113; found 506.2107.

4.2.31. *tert*-Butyl (3*S*,*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-3-(2′-methyl-3′-fluorophenyl)propanoate 69



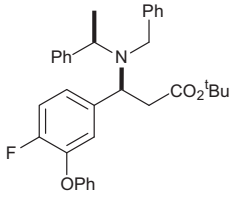
Following *general procedure 2*, BuLi (2.5 M in hexanes, 7.9 mL, 19.7 mmol) and (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (4.29 g, 20.3 mmol) in THF (75 mL) at −78 °C, and **54** (3.00 g, 12.7 mmol, >99:1 dr) in THF (60 mL) at −78 °C gave **69** in 98:2 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et$_2$O, 20:1) gave **69** as a white, crystalline solid (4.14 g, 73%, 98:2 dr); $C_{29}H_{34}FNO_2$ requires C, 77.8; H, 7.7; N, 3.1%; found C, 78.0; H, 7.7; N, 3.1%; mp 69–72 °C; $[\alpha]_D^{25}$ +51.7 (*c* 1.0 in CHCl$_3$); ν_{max} (ATR) 2976 (C–H), 1723 (C=O); δ_H (400 MHz, CDCl$_3$) 1.13 (9H, s, C*Me*$_3$), 1.35 (3H, d, *J* 6.8, C(α)*Me*), 2.26 (3H, s, C(2′)*Me*), 2.32–2.38 (1H, m, C(2)*H*$_A$), 2.66–2.70 (1H, m, C(2)*H*$_B$), 3.72–3.82 (2H, m, NC*H*$_2$Ph), 3.96 (1H, q, *J* 6.8, C(α)*H*), 4.58 (1H, dd, *J* 10.9, 5.0, C(3)*H*), 6.90–7.41 (13H, m, *Ph, Ar*); δ_C (100 MHz, CDCl$_3$) 10.5 (C(2′)*Me*), 14.2 (C(α)*Me*), 27.6 (C*Me*$_3$), 40.0 (*C*(2)), 51.0 (NCH$_2$Ph), 57.2 (*C*(α)), 58.5 (*C*(3)), 80.2 (*C*Me$_3$), 113.4, 113.7, 123.8, 126.3, 126.4, 127.6, 127.9, 128.0, 128.1 (*C*(4′), *C*(5′), *C*(6′), *o*,*m*,*p*-*Ph*), 124.7, 142.6 (*C*(1′)), *C*(2′)), 142.3, 143.9 (*i*-*Ph*), 162.9 (*C*(3′)), 170.9 (*C*(1)); *m*/*z* (ESI$^+$) 470 ([M+Na]$^+$, 92%), 448 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{35}FNO_2^+$ ([M+H]$^+$) requires 448.2646; found 448.2645.

4.2.32. *tert*-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-3-(2′-fluoro-5′-methoxyphenyl)propanoate 70



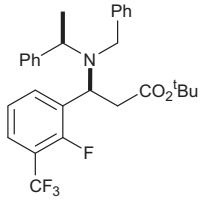
Following *general procedure 2*, BuLi (2.6 M in hexanes, 5.9 mL, 15.4 mmol) and (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (3.35 g, 15.9 mmol) in THF (50 mL) at −78 °C, and **55** (2.50 g, 9.92 mmol, >99:1 dr) in THF (50 mL) at −78 °C gave **70** in 95:5 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et$_2$O, 15:1) gave **70** as a pale yellow, crystalline solid (3.22 g, 70%, 95:5 dr); $C_{29}H_{34}FNO_3$ requires C, 75.1; H, 7.4; N, 3.0%; found C, 75.3; H, 7.4; N, 2.9%; mp 61–63 °C; $[\alpha]_D^{25}$ +11.4 (*c* 1.0 in CHCl$_3$); ν_{max} (ATR) 2976 (C–H), 1727 (C=O); δ_H (400 MHz, CDCl$_3$) 1.23 (9H, s, C*Me*$_3$), 1.29 (3H, d, *J* 6.8, C(α)*Me*), 2.58–2.61 (2H, m, C(2)*H*$_2$), 3.67–3.77 (2H, m, NC*H*$_2$Ph), 3.78 (3H, s, O*Me*), 4.06 (1H, q, *J* 6.8, C(α)*H*), 4.68 (1H, dd, *J* 9.4, 6.3, C(3)*H*), 6.74–7.45 (13H, m, *Ph, Ar*); δ_C (100 MHz, CDCl$_3$) 14.6 (C(α)*Me*), 27.7 (C*Me*$_3$), 39.4 (*C*(2)), 50.8 (NCH$_2$Ph), 54.1 (*C*(3)), 55.7 (O*Me*), 56.8 (*C*(α)), 80.2 (*C*Me$_3$), 113.4, 113.5, 114.8, 115.9, 116.2, 126.5, 126.8, 127.9, 128.0 (*C*(3′), *C*(4′), *C*(6′), *o*,*m*,*p*-*Ph*), 129.2 (*C*(1′)), 141.5, 143.9 (*i*-*Ph*), 155.4 (*C*(5′)), 155.7 (d, *J* 238, *C*(2′)), 171.2 (*C*(1)); *m*/*z* (ESI$^+$) 486 ([M+Na]$^+$, 95%), 464 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{35}FNO_3^+$ ([M+H]$^+$) requires 464.2595; found 464.2596.

4.2.33. *tert*-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-3-(3′-phenoxy-4′-fluoro-phenyl)propanoate 71



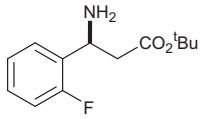
Following *general procedure 2*, BuLi (2.5 M in hexanes, 5.9 mL, 14.8 mmol) and (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (3.23 g, 15.3 mmol) in THF (50 mL) at −78 °C, and **56** (3.00 g, 9.55 mmol, >99:1 dr) in THF (50 mL) at −78 °C gave **71** in 98:2 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et$_2$O, 20:1) gave **71** as a colourless oil (3.81 g, 76%, 98:2 dr); $C_{34}H_{36}FNO_3$ requires C, 77.7; H, 6.9; N, 2.7%; found C, 77.7; H, 6.8; N, 2.6%; $[\alpha]_D^{25}$ +5.0 (*c* 1.0 in CHCl$_3$); ν_{max} (ATR) 2976 (C–H), 1725 (C=O); δ_H (400 MHz, CDCl$_3$) 1.25 (9H, s, C*Me*$_3$), 1.29 (3H, d, *J* 6.8, C(α)*Me*), 2.39–2.52 (2H, m, C(2)*H*$_2$), 3.59–3.67 (2H, app s, NC*H*$_2$Ph), 3.93 (1H, q, *J* 6.8, C(α)*H*), 4.68 (1H, dd, *J* 10.1, 4.6, C(3)*H*), 6.99–7.38 (18H, m, *Ar*, *Ph*); δ_C (100 MHz, CDCl$_3$) 17.3 (C(α)*Me*), 27.8 (C*Me*$_3$), 37.4 (*C*(2)), 50.8 (NCH$_2$Ph), 57.6 (*C*(α)), 58.6 (*C*(3)), 80.4 (*C*Me$_3$), 116.2, 116.4, 117.6, 121.6, 123.2, 123.9, 126.6, 127.0, 127.7, 127.8, 128.2, 129.7 (*C*(2′), *C*(5′), *C*(6′), *o*,*m*,*p*-*Ph*), 123.8 (*C*(1′)), 139.1, 141.3, (*i*-*Ph*), 143.0 153.8, 157.3 (*i*-*Ph*, *C*(3′), *C*(4′)), 170.9 (*C*(1)); *m*/*z* (ESI$^+$) 548 ([M+Na]$^+$, 52%), 526 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{34}H_{37}FNO_3^+$ ([M+H]$^+$) requires 526.2752; found 526.2750.

4.2.34. *tert*-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-3-[2′-fluoro-3′-(trifluoromethyl)phenyl]propanoate 72



Following *general procedure 2*, BuLi (2.0 M in hexanes, 8.0 mL, 16.0 mmol) and (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (3.50 g, 16.5 mmol) in THF (60 mL) at −78 °C, and **57** (3.00 g, 10.3 mmol, >99:1 dr) in THF (50 mL) at −78 °C gave **72** in 91:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et$_2$O, 20:1) gave **72** as a colourless oil (4.14 g, 80%, 91:9 dr); $[\alpha]_D^{25}$ +5.2 (*c* 1.0 in CHCl$_3$); ν_{max} (ATR) 2978 (C–H), 1726 (C=O); δ_H (400 MHz, CDCl$_3$) 1.20 (9H, s, C*Me*$_3$), 1.32 (3H, d, *J* 6.8, C(α)*Me*), 2.61 (2H, app d, *J* 7.8, C(2)*H*$_2$), 3.67 (1H, d, *J* 14.9, NC*H*$_A$H$_B$Ph), 3.77 (1H, d, J_{AB} 14.9, NCH$_A$*H*$_B$Ph), 4.01 (1H, q, *J* 6.8, C(α)*H*), 4.78–4.82 (1H, m, C(3)*H*), 7.18–7.63 (13H, m, *Ar*, *Ph*); δ_C (100 MHz, CDCl$_3$) 14.9 (C(α)*Me*), 27.6 (C*Me*$_3$), 38.9 (*C*(2)), 50.8 (NCH$_2$Ph), 53.4 (*C*(3)), 57.2 (*C*(α)), 80.6 (*C*Me$_3$), 118.9 (*C*F$_3$), 123.6, 126.0, 126.7, 127.0, 127.8, 127.9, 128.1, 128.2, 133.4 (*C*(4′), *C*(5′), *C*(6′), *o*,*m*,*p*-*Ph*), 126.3 (*C*(3′)), 130.6 (*C*(1′)), 141.1, 143.3 (*i*-*Ph*), 157.0 (*C*(2′)), 170.1 (*C*(1)); *m*/*z* (ESI$^+$) 524 ([M+Na]$^+$, 94%), 502 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{32}F_4NO_2^+$ ([M+H]$^+$) requires 502.2364; found 502.2364.

4.2.35. *tert*-Butyl (*S*)-3-amino-3-(2′-fluorophenyl)propanoate 73

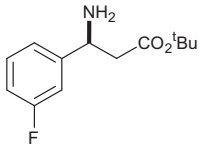


Method A: Following *general procedure 3*, **58** (433 mg, 1.00 mmol, 98:2 dr), Pd(OH)$_2$/C (50% w/w, 217 mg) and H$_2$

(1 atm) in MeOH (9 mL) after 36 h gave **73** as a pale yellow oil (227 mg, 95%); $[\alpha]_D^{25}$ −9.3 (*c* 0.5 in $CHCl_3$); ν_{max} (ATR) 3384 (N–H), 1726 (C=O); δ_H (500 MHz, $CDCl_3$) 1.40 (9H, s, C*Me*$_3$), 1.99 (2H, br s, N*H*$_2$), 2.60–2.69 (2H, m, C(2)*H*$_2$), 4.60–4.63 (1H, m, C(3)*H*), 7.00–7.04 (1H, m, *Ar*), 7.10–7.13 (1H, m, *Ar*), 7.21–7.25 (1H, m, *Ar*), 7.41–7.43 (1H, m, *Ar*); δ_C (125 MHz, $CDCl_3$) 28.0 (C*Me*$_3$), 43.6 (*C*(2)), 47.0 (*C*(3)), 80.7 (*C*Me$_3$), 115.5, 124.2, 127.6, 128.7 (*C*(3′), *C*(4′), *C*(5′), *C*(6′)), 131.3 (*C*(1′)), 160.3 (d, *J* 244, *C*(2′)), 171.0 (*C*(1)); *m/z* (ESI$^+$) 262 ([M+Na]$^+$, 90%), 240 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{19}FNO_2^+$ ([M+H]$^+$) requires 240.1394; found 240.1394.

Method B: Following *general procedure 3*, **58** (433 mg, 1.00 mmol, 98:2 dr), $Pd(OH)_2/C$ (6% w/w, 26 mg) and H_2 (5 atm) in MeOH (9 mL) after 24 h gave **73** as a pale yellow oil (220 mg, 92%).

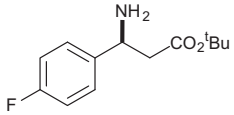
4.2.36. *tert*-Butyl (*S*)-3-amino-3-(3′-fluorophenyl)propanoate 74



Method A: Following *general procedure 3*, **59** (433 mg, 1.00 mmol, 98:2 dr), $Pd(OH)_2/C$ (50% w/w, 217 mg) and H_2 (1 atm) in MeOH (9 mL) after 9 h gave **74** as a pale yellow oil (217 mg, 91%);[14b] $[\alpha]_D^{25}$ −14.0 (*c* 1.0 in $CHCl_3$); {lit.[14b] for enantiomer $[\alpha]_D^{20}$ +11.6 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.41 (9H, s, C*Me*$_3$), 1.93 (2H, br s, N*H*$_2$), 2.56 (2H, d, *J* 6.8, C(2)*H*$_2$), 4.35–4.39 (1H, m, C(3)*H*), 6.91–7.37 (4H, m, *Ar*).

Method B: Following *general procedure 3*, **59** (433 mg, 1.00 mmol, 98:2 dr), $Pd(OH)_2/C$ (6% w/w, 26 mg) and H_2 (5 atm) in MeOH (9 mL) after 24 h gave **74** as a pale yellow oil (222 mg, 93%).

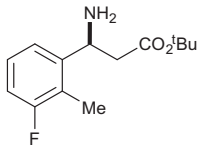
4.2.37. *tert*-Butyl (*S*)-3-amino-3-(4′-fluorophenyl)propanoate 75



Method A: Following *general procedure 3*, **60** (433 mg, 1.00 mmol), $Pd(OH)_2/C$ (50% w/w, 217 mg) and H_2 (1 atm) in MeOH (9 mL) after 48 h gave **75** as a pale yellow oil (222 mg, 93%);[30] $[\alpha]_D^{25}$ −7.9 (*c* 0.5 in $CHCl_3$); ν_{max} (ATR) 3382 (N–H), 1725 (C=O); δ_H (400 MHz, $CDCl_3$) 1.42 (9H, s, C*Me*$_3$), 1.87 (2H, br s, N*H*$_2$), 2.56–2.58 (2H, m, C(2)*H*$_2$), 4.36–4.39 (1H, m, C(3)*H*), 7.00–7.04 (2H, m, *Ar*), 7.32–7.36 (2H, m, *Ar*); δ_C (125 MHz, $CDCl_3$) 28.0 (C*Me*$_3$), 44.8 (*C*(2)), 52.0 (*C*(3)), 80.9 (*C*Me$_3$), 115.3 (*C*(2′), *C*(6′)), 128.0 (*C*(3′), *C*(5′)), 139.5 (*C*(1′)), 162.0 (d, *J* 244, *C*(4′)), 170.9 (*C*(1)); *m/z* (ESI$^+$) 262 ([M+Na]$^+$, 61%), 240 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{19}FNO_2^+$ ([M+H]$^+$) requires 240.1394; found 240.1395.

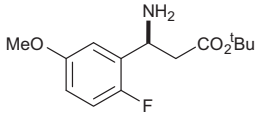
Method B: Following *general procedure 3*, **60** (433 mg, 1.00 mmol, 98:2 dr), $Pd(OH)_2/C$ (6% w/w, 26 mg) and H_2 (5 atm) in MeOH (9 mL) after 24 h gave **75** as a pale yellow oil (227 mg, 95%).

4.2.38. *tert*-Butyl (*S*)-3-amino-3-(2′-methyl-3′-fluorophenyl)-propanoate 76



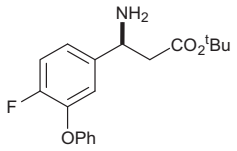
Following *general procedure 3*, **69** (447 mg, 1.00 mmol, 98:2 dr), $Pd(OH)_2/C$ (50% w/w, 224 mg) and H_2 (1 atm) in MeOH (9 mL) after 15 h gave **76** as a pale yellow oil (243 mg, 96%); $[\alpha]_D^{25}$ −14.4 (*c* 0.5 in $CHCl_3$); ν_{max} (ATR) 3383 (N–H), 1725 (C=O); δ_H (400 MHz, $CDCl_3$) 1.43 (9H, s, C*Me*$_3$), 1.75 (2H, br s, N*H*$_2$), 2.28 (3H, s, C(2′)*Me*), 2.52–2.54 (2H, m, C(2)*H*$_2$), 4.59–4.63 (1H, m, C(3)*H*), 6.89–6.94 (1H, m, *Ar*), 7.15 (1H, dd, *J* 7.8, 5.8, *Ar*), 7.24 (1H, d, *J* 7.8, *Ar*); δ_C (100 MHz, $CDCl_3$) 9.9 (C(2′)*Me*), 28.0 (C*Me*$_3$), 44.2 (*C*(2)), 48.2 (*C*(3)), 80.9 (*C*Me$_3$), 113.5, 120.7, 127.0 (*C*(4′), *C*(5′), *C*(6′)), 122.0 (*C*(1′)), 145.0 (*C*(2′)), 161.0 (d, *J* 242, *C*(3′)), 171.3 (*C*(1)); *m/z* (ESI$^+$) 276 ([M+Na]$^+$, 46%), 254 ([M+H]$^+$, 87%); HRMS (ESI$^+$) $C_{14}H_{21}FNO_2^+$ ([M+H]$^+$) requires 254.1551; found 254.1551.

4.2.39. *tert*-Butyl (*S*)-3-amino-3-(2′-fluoro-5′-methoxyphenyl)-propanoate 77



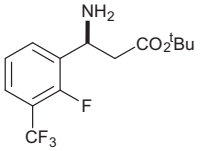
Following *general procedure 3*, **70** (463 mg, 1.00 mmol, 95:5 dr), $Pd(OH)_2/C$ (50% w/w, 232 mg) and H_2 (1 atm) in MeOH (9 mL) after 5 h gave **77** as a pale yellow oil (253 mg, 94%); $[\alpha]_D^{25}$ −5.7 (*c* 0.5 in $CHCl_3$); ν_{max} (ATR) 3384 (N–H), 1725 (C=O); δ_H (400 MHz, $CDCl_3$) 1.41 (9H, s, C*Me*$_3$), 2.14 (2H, br s, N*H*$_2$), 2.57–2.68 (2H, m, C(2)*H*$_2$), 3.78 (3H, s, O*Me*), 4.61 (1H, dd, *J* 8.6, 5.1, C(3)*H*), 6.70–6.85 (1H, m, *Ar*), 6.86–6.97 (2H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 28.0 (C*Me*$_3$), 43.5 (*C*(2)), 47.1 (*C*(3)), 55.7 (O*Me*), 80.9 (*C*Me$_3$), 112.5, 113.4, 116.0 (*C*(3′), *C*(4′), *C*(6′)), 132.0 (*C*(1′)), 153.4 (d, *J* 236, *C*(2′)), 155.8 (*C*(5′)), 171.0 (*C*(1)); *m/z* (ESI$^+$) 292 ([M+Na]$^+$, 19%), 270 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{21}FNO_3^+$ ([M+H]$^+$) requires 270.1500; found 270.1500.

4.2.40. *tert*-Butyl (*S*)-3-amino-3-(3′-phenoxy-4′-fluorophenyl)-propanoate 78



Following *general procedure 3*, **71** (525 mg, 1.00 mmol, 98:2 dr), $Pd(OH)_2/C$ (50% w/w, 263 mg) and H_2 (1 atm) in MeOH (11 mL) after 4 h gave **78** as a white powder (318 mg, 96%); mp 42–44 °C; $[\alpha]_D^{25}$ −18.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3425 (N–H), 1721 (C=O); δ_H (400 MHz, $CDCl_3$) 1.41 (9H, s, C*Me*$_3$), 2.53 (2H, br s, N*H*$_2$), 2.52 (2H, d, *J* 6.8, C(2)*H*$_2$), 4.32 (1H, app t, *J* 6.8, C(3)*H*), 6.95–6.99 (2H, m, *Ar*), 7.01–7.36 (6H, m, *Ar*, *Ph*); δ_C (100 MHz, $CDCl_3$) 28.1 (C*Me*$_3$), 45.3 (*C*(2)), 52.1 (*C*(3)), 80.9 (*C*Me$_3$), 117.0, 117.2, 119.8, 122.5, 123.1, 129.7 (*C*(2′), *C*(5′), *C*(6′), *o*,*m*,*p*-*Ph*), 141.7, 143.5, 157.3 (*C*(1′), (*C*(3′), *i*-*Ph*), 153.4 (d, *J* 246, *C*(4′)), 171.0 (*C*(1)); *m/z* (ESI$^+$) 354 ([M+Na]$^+$, 29%), 332 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{23}FNO_3^+$ ([M+H]$^+$) requires 332.1656; found 332.1644.

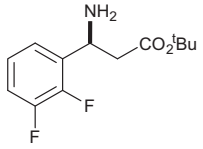
4.2.41. *tert*-Butyl (*S*)-3-amino-3-[2′-fluoro-3′-(trifluoromethyl)-phenyl]propanoate 79



Following *general procedure 3*, **72** (501 mg, 1.00 mmol, 91:1 dr), $Pd(OH)_2/C$ (50% w/w, 251 mg) and H_2 (1 atm) in MeOH (10 mL)

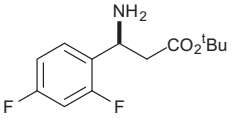
after 15 h gave **79** as a pale yellow oil (292 mg, 95%); $[\alpha]_D^{25}$ −8.1 (*c* 0.5 in $CHCl_3$); υ_{max} (ATR) 3385 (N–H), 1725 (C=O); δ_H (400 MHz, $CDCl_3$) 1.41 (9H, s, CMe_3), 1.80 (2H, br s, NH_2), 2.59–2.70 (2H, m, C(2)H_2), 4.27 (1H, dd, *J* 8.3, 5.3, C(3)*H*), 7.22–7.26 (1H, m, C(5′)*H*), 7.50–7.53 (1H, m, C(6′)*H*), 7.68–7.71 (1H, m, C(4′)*H*); δ_C (125 MHz, $CDCl_3$) 28.0 (CMe_3), 43.4 (*C*(2)), 46.4 (*C*(3)), 81.1 (*C*Me$_3$), 118.4 (m, *C*(3′)), 121.5 (q, *J* 271, *C*F$_3$), 124.1 (*C*(5′)), 125.9 (*C*(6′)), 131.8 (*C*(4′)), 133.1 (*C*(1′)), 157.0 (d, *J* 246, *C*(2′)), 170.5 (*C*(1)); *m/z* (ESI$^+$) 330 ([M+Na]$^+$, 12%), 308 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{18}F_4NO_2^+$ ([M+H]$^+$) requires 308.1268; found 308.1267.

4.2.42. *tert*-Butyl (*S*)-3-amino-3-(2′,3′-difluorophenyl)propanoate 80



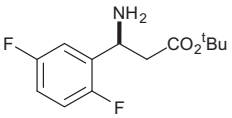
Following *general procedure 3*, **61** (451 mg, 1.00 mmol, 96:4 dr), Pd(OH)$_2$/C (6% w/w, 27 mg) and H_2 (5 atm) in MeOH (8 mL) after 24 h gave **80** as a pale yellow oil (242 mg, 94%); $[\alpha]_D^{25}$ −22.0 (*c* 1.0 in $CHCl_3$); υ_{max} (ATR) 3312 (N–H), 1724 (C=O); δ_H (500 MHz, $CDCl_3$) 1.32 (9H, s, CMe_3), 1.82 (2H, br s, NH_2), 2.53–2.56 (2H, m, C(2)H_2), 4.55–4.66 (1H, m, C(3)*H*), 6.94–7.11 (3H, m, *Ar*); δ_C (125 MHz, $CDCl_3$) 27.8 (CMe_3), 43.5 (*C*(2)), 46.7 (*C*(3)), 81.0 (*C*Me$_3$), 115.7, 122.2, 124.0 (*C*(4′), *C*(5′), *C*(6′)), 134.0 (*C*(1′)), 148.2 (d, *J* 246, *C*F), 150.5 (d, *J* 242, *C*F), 170.6 (*C*(1)); *m/z* (ESI$^+$) 280 ([M+Na]$^+$, 92%), 258 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{18}F_2NO_2^+$ ([M+H]$^+$) requires 258.1300; found 258.1300.

4.2.43. *tert*-Butyl (*S*)-3-amino-3-(2′,4′-difluorophenyl)propanoate 81



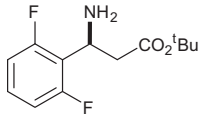
Following *general procedure 3*, **62** (451 mg, 1.00 mmol, >99:1 dr), Pd(OH)$_2$/C (6% w/w, 27 mg) and H_2 (5 atm) in MeOH (8 mL) after 24 h gave **81** as a pale yellow oil (239 mg, 93%); $[\alpha]_D^{25}$ −13.0 (*c* 0.5 in $CHCl_3$); υ_{max} (ATR) 3312 (N–H), 1724 (C=O); δ_H (500 MHz, $CDCl_3$) 1.42 (9H, s, CMe_3), 1.76 (2H, br s, NH_2), 2.60–2.62 (2H, m, C(2)H_2), 4.59 (1H, app t, *J* 6.1, C(3)*H*), 6.76–6.80 (1H, m, *Ar*), 6.84–6.87 (1H, m, *Ar*), 7.38–7.43 (1H, m, *Ar*); δ_C (125 MHz, $CDCl_3$) 28.0 (CMe_3), 43.6 (*C*(2)), 46.6 (*C*(3)), 80.9 (*C*Me$_3$), 103.8, 111.4, 128.7 (*C*(3′), *C*(5′), *C*(6′)), 127.5 (*C*(1′)), 160.1 (d, *J* 229, *C*F), 162.1 (d, *J* 234, *C*F), 170.8 (*C*(1)); *m/z* (ESI$^+$) 280 ([M+Na]$^+$, 53%), 258 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{18}F_2NO_2^+$ ([M+H]$^+$) requires 258.1300; found 258.1298.

4.2.44. *tert*-Butyl (*S*)-3-amino-3-(2′,5′-difluorophenyl)propanoate 82



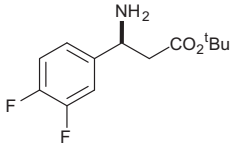
Following *general procedure 3*, **63** (451 mg, 1.00 mmol, 96:4 dr), Pd(OH)$_2$/C (6% w/w, 27 mg) and H_2 (5 atm) in MeOH (8 mL) after 24 h gave **82** as a pale yellow oil (244 mg, 95%); $[\alpha]_D^{25}$ −13.6 (*c* 0.5 in $CHCl_3$); υ_{max} (ATR) 3309 (N–H), 1725 (C=O); δ_H (400 MHz, $CDCl_3$) 1.41 (9H, s, CMe_3), 2.34 (2H, br s, NH_2), 2.58–2.63 (2H, m, C(2)H_2), 4.58–4.61 (1H, m, C(3)*H*), 6.86–6.92 (1H, m, *Ar*), 6.95−7.00 (1H, m, *Ar*), 7.14–7.19 (1H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 28.0 (CMe_3), 43.4 (*C*(2)), 46.6 (*C*(3)), 81.0 (*C*Me$_3$), 114.3, 114.8, 116.5 (*C*(3′), *C*(4′), *C*(6′)), 128.3 (*C*(1′)), 157.4, 159.8 (*C*(2′), *C*(5′)), 170.7 (*C*(1)); *m/z* (ESI$^+$) 280 ([M+Na]$^+$, 51%), 258 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{18}F_2NO_2^+$ ([M+H]$^+$) requires 258.1300; found 258.1301.

4.2.45. *tert*-Butyl (*S*)-3-amino-3-(2′,6′-difluorophenyl)propanoate 83



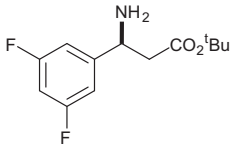
Following *general procedure 3*, **64** (451 mg, 1.00 mmol, 97:3 dr), Pd(OH)$_2$/C (6% w/w, 27 mg) and H_2 (5 atm) in MeOH (8 mL) after 24 h gave **83** as a pale yellow oil (239 mg, 93%); $[\alpha]_D^{25}$ −14.2 (*c* 0.5 in $CHCl_3$); υ_{max} (ATR) 3308 (N–H), 1722 (C=O); δ_H (400 MHz, $CDCl_3$) 1.36 (9H, s, CMe_3), 2.16 (2H, br s, NH_2), 2.68 (1H, dd, *J* 15.4, 6.3, C(2)H_A), 2.80–2.86 (1H, m, C(2)H_B), 4.68–4.72 (1H, m, C(3)*H*), 6.82–6.86 (2H, m, *Ar*), 7.14–7.18 (1H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 28.0 (CMe_3), 43.3 (*C*(2)), 44.0 (*C*(3)), 80.8 (*C*Me$_3$), 111.7 (*C*(3′), *C*(5′)), 119.9 (*C*(4′)), 128.7 (*C*(1′)), 160.2 (d, *J* 249, *C*(2′), *C*(6′)), 170.5 (*C*(1)); *m/z* (ESI$^+$) 280 ([M+Na]$^+$, 100%), 258 ([M+H]$^+$, 73%); HRMS (ESI$^+$) $C_{13}H_{18}F_2NO_2^+$ ([M+H]$^+$) requires 258.1300; found 258.1302.

4.2.46. *tert*-Butyl (*S*)-3-amino-3-(3′,4′-difluorophenyl)propanoate 84



Following *general procedure 3*, **65** (451 mg, 1.00 mmol, 96:4 dr), Pd(OH)$_2$/C (6% w/w, 27 mg) and H_2 (5 atm) in MeOH (8 mL) after 24 h gave **84** as a white solid (234 mg, 91%);[31] mp 31–33 °C; $[\alpha]_D^{25}$ −21.5 (*c* 1.0 in $CHCl_3$); υ_{max} (ATR) 3310 (N–H), 1717 (C=O); δ_H (400 MHz, $CDCl_3$) 1.35 (9H, s, CMe_3), 1.70 (2H, br s, NH_2), 2.44–2.46 (2H, m, C(2)H_2), 4.26–4.28 (1H, m, C(3)*H*), 6.97–7.19 (3H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 27.9 (CMe_3), 45.1 (*C*(2)), 51.8 (*C*(3)), 80.8 (*C*Me$_3$), 115.2, 116.8, 122.2 (*C*(2′), *C*(5′), *C*(6′)), 141.9 (*C*(1′)), 148.6 (d, *J* 235, *C*F), 150.9 (d, *J* 239, *C*F), 170.7 (*C*(1)); *m/z* (ESI$^+$) 280 ([M+Na]$^+$, 63%), 258 ([M+H]$^+$, 65%); HRMS (ESI$^+$) $C_{13}H_{18}F_2NO_2^+$ ([M+H]$^+$) requires 258.1300; found 258.1300.

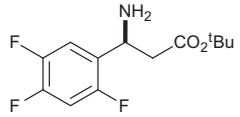
4.2.47. *tert*-Butyl (*S*)-3-amino-3-(3′,5′-difluorophenyl)propanoate 85



Following *general procedure 3*, **66** (451 mg, 1.00 mmol, 98:2 dr), Pd(OH)$_2$/C (6% w/w, 27 mg) and H_2 (5 atm) in MeOH (8 mL) after 24 h gave **85** as a pale yellow oil (231 mg, 90%); $[\alpha]_D^{25}$ −12.6 (*c* 0.5

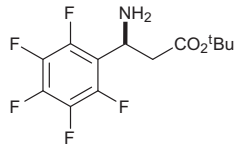
in $CHCl_3$); υ_{max} (ATR) 3314 (N–H), 1724 (C=O); δ_H (500 MHz, $CDCl_3$) 1.42 (9H, s, CMe_3), 1.73 (2H, br s, NH_2), 2.51–2.53 (2H, m, C(2)H_2), 4.33–4.35 (1H, m, C(3)*H*), 6.65–6.69 (1H, m, *Ar*), 6.89–6.91 (2H, m, *Ar*); δ_C (125 MHz, $CDCl_3$) 28.0 (CMe_3), 45.0 (*C*(2)), 52.2 (*C*(3)), 81.2 (*C*Me$_3$), 102.5 (*C*(4′)), 109.2 (*C*(2′), *C*(6′)), 148.9 (*C*(1′)), 162.4 (d, *J* 260, *C*(3′), *C*(5′)), 170.7 (*C*(1)); *m/z* (ESI$^+$) 280 ([M+Na]$^+$, 41%), 258 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{18}F_2NO_2^+$ ([M+H]$^+$) requires 258.1300; found 258.1295.

4.2.48. *tert*-Butyl (*S*)-3-amino-3-(2′,4′,5′-trifluorophenyl)propanoate 86



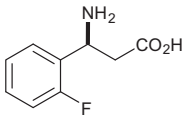
Following *general procedure 3*, **67** (469 mg, 1.00 mmol, 97:3 dr), $Pd(OH)_2/C$ (6% w/w, 28 mg) and H_2 (5 atm) in MeOH (9 mL) after 24 h gave **86** as a pale yellow solid (256 mg, 93%); mp 60–62 °C; $[\alpha]_D^{25}$ −19.9 (*c* 0.5 in $CHCl_3$); υ_{max} (ATR) 3358 (N–H), 1729 (C=O); δ_H (500 MHz, $CDCl_3$) 1.43 (9H, s, CMe_3), 1.75 (2H, br s, NH_2), 2.54 (1H, dd, *J* 15.9, 8.6, C(2)H_A), 2.62 (1H, dd, *J* 15.9, 4.8, C(2)H_B), 4.59 (1H, dd, *J* 8.6, 4.8, C(3)*H*), 6.87–6.92 (1H, m, *Ar*), 7.30–7.35 (1H, m, *Ar*); δ_C (125 MHz, $CDCl_3$) 27.9 (CMe_3), 43.5 (*C*(2)), 46.0 (*C*(3)), 81.1 (*C*Me$_3$), 105.5, 115.8 (*C*(3′), *C*(6′)), 128.1 (*C*(1′)), 146.8 (d, *J* 244, *C*F), 148.8 (d, *J* 259, *C*F), 154.8 (d, *J* 272, *C*F), 170.7 (*C*(1)); *m/z* (ESI$^+$) 298 ([M+Na]$^+$, 100%), 276 ([M+H]$^+$, 36%); HRMS (ESI$^+$) $C_{13}H_{16}F_3NNaO_2^+$ ([M+Na]$^+$) requires 298.1025; found 298.1020.

4.2.49. *tert*-Butyl (*S*)-3-amino-3-(pentafluorophenyl)propanoate 87



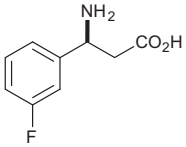
Following *general procedure 3*, **68** (505 mg, 1.00 mmol, 94:6 dr), $Pd(OH)_2/C$ (26% w/w, 131 mg) and H_2 (5 atm) in MeOH (9 mL) after 24 h gave **87** as a pale yellow oil (292 mg, 94%); $[\alpha]_D^{25}$ −26.2 (*c* 1.0 in $CHCl_3$); υ_{max} (ATR) 3356 (N–H), 1726 (C=O); δ_H (400 MHz, $CDCl_3$) 1.41 (9H, s, CMe_3), 2.18 (2H, br s, NH_2), 2.70 (1H, dd, *J* 15.7, 6.6, C(2)H_A), 2.82–2.88 (1H, m, C(2)H_B), 4.69–4.73 (1H, m, C(3)*H*); δ_C (100 MHz, $CDCl_3$)[29] 28.0 (CMe_3), 42.9 (*C*(2)), 44.3 (*C*(3)), 81.4 (*C*Me$_3$), 169.8 (*C*(1)); *m/z* (ESI$^+$) 334 ([M+Na]$^+$, 71%), 312 ([M+H]$^+$, 37%); HRMS (ESI$^+$) $C_{13}H_{15}F_5NO_2^+$ ([M+H]$^+$) requires 312.1017; found 312.1012.

4.2.50. (*S*)-3-Amino-3-(2′-fluorophenyl)propanoic acid 88



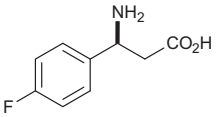
Following *general procedure 4*, 2.0 M aq HCl (15 mL) and **73** (184 mg, 0.77 mmol) followed by purification *via* ion exchange chromatography (Dowex 50 WX8-100, eluent 1.0 M aq NH_4OH) gave **88** as a white powder (135 mg, 96%);[19] mp 239–240 °C; {lit.[19] for enantiomer mp 247 °C};$[\alpha]_D^{25}$ −2.7 (*c* 0.3 in H_2O); {lit.[19] for enantiomer $[\alpha]_D^{22}$ +3.0 (*c* 0.3 in H_2O)}; δ_H (400 MHz, D_2O) 2.77 (1H, dd, *J* 16.2, 6.8, C(2)H_A), 2.87 (1H, dd, *J* 16.2, 8.1, C(2)H_B), 4.80–4.84 (1H, m, C(3)*H*), 7.11–7.22 (2H, m, *Ar*), 7.35–7.42 (2H, m, *Ar*).

4.2.51. (*S*)-3-Amino-3-(3′-fluorophenyl)propanoic acid 89



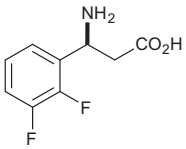
Following *general procedure 4*, 2.0 M aq HCl (15 mL) and **74** (184 mg, 0.77 mmol) followed by purification *via* ion exchange chromatography (Dowex 50WX8-100, eluent 1.0 M aq NH_4OH) gave **89** as a white powder (137 mg, 97%);[20] mp 220–223 °C; {lit.[20] mp 226–229 °C};$[\alpha]_D^{25}$ −2.0 (*c* 0.4 in H_2O); {lit.[20] $[\alpha]_D^{25}$ −1.8 (*c* 0.4 in H_2O)}; δ_H (400 MHz, D_2O) 2.72 (1H, dd, *J* 16.2, 6.8, C(2)H_A), 2.80 (1H, dd, *J* 16.2, 7.8, C(2)H_B), 4.55–4.58 (1H, m, C(3)*H*), 7.06–7.42 (4H, m, *Ar*).

4.2.52. (*S*)-3-Amino-3-(4′-fluorophenyl)propanoic acid 90



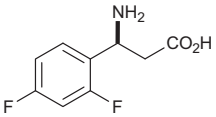
Following *general procedure 4*, 2.0 M aq HCl (15 mL) and **75** (184 mg, 0.77 mmol) refluxing 6 h followed by purification *via* ion exchange chromatography (Dowex 50 WX8-100, eluent 1.0 M aq NH_4OH) gave **90** as a white powder (135 mg, 96%);[19] mp 220–221 °C; {lit.[19] mp 220–222 °C}; $[\alpha]_D^{25}$ −5.6 (*c* 0.5 in H_2O); {lit.[19] $[\alpha]_D^{22}$ −4.0 (*c* 0.5 in H_2O)}; δ_H (400 MHz, AcOH-d_4) 3.15–3.20 (1H, m, C(2)H_A), 3.48–3.55 (1H, m, C(2)H_B), 4.94 (1H, br s, C(3)*H*), 7.16–7.20 (2H, m, C(2′)*H*, C(6′)*H*), 7.66–7.67 (2H, m, C(3′)*H*, C(5′)*H*).

4.2.53. (*S*)-3-Amino-3-(2′,3′-difluorophenyl)propanoic acid 91



Following *general procedure 4*, 2.0 M aq HCl (15 mL) and **80** (198 mg, 0.77 mmol) followed by purification *via* ion exchange chromatography (Dowex 50WX8-100, eluent 1.0 M aq NH_4OH) gave **91** as a pale yellow powder (149 mg, 96%); mp 200–202 °C; $[\alpha]_D^{25}$ −2.5 (*c* 0.5 in H_2O); υ_{max} (ATR) 3429 (O–H, N–H), 1623 (C=O); δ_H (500 MHz, AcOH-d_4) 3.20 (1H, dd, *J* 17.7, 6.3, C(2)H_A), 3.51 (1H, dd, *J* 17.7, 7.6, C(2)H_B), 4.95–4.97 (1H, m, C(3)*H*), 7.31–7.63 (3H, m, *Ar*); δ_C (125 MHz, AcOH-d_4) 36.8 (*C*(2)), 45.7 (*C*(3)), 118.2, 123.7, 125.1, (*C*(4′), *C*(5′), *C*(6′)), 132.5 (*C*(1′)), 148.5 (d, *J* 236, *C*F), 150.3 (d, *J* 239, *C*F), 174.1 (*C*(1)); *m/z* (ESI$^+$) 224 ([M+Na]$^+$, 100%), 202 ([M+H]$^+$, 13%); HRMS (ESI$^+$) $C_9H_9F_2NNaO_2^+$ ([M+Na]$^+$) requires 224.0494; found 224.0497.

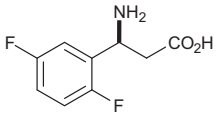
4.2.54. (*S*)-3-Amino-3-(2′,4′-difluorophenyl)propanoic acid 92



Following *general procedure 4*, 2.0 M aq HCl (15 mL) and **81** (198 mg, 0.77 mmol) followed by purification *via* ion exchange chromatography (Dowex 50WX8-100, eluent 1.0 M aq NH_4OH) gave **92** as a pale yellow powder (142 mg, 92%); mp 207–209 °C; $[\alpha]_D^{25}$ −4.9 (*c* 0.5 in H_2O); υ_{max} (ATR) 3121 (O–H, N–H), 1658 (C=O); δ_H (400 MHz, AcOH-d_4) 3.10 (1H, dd, *J* 17.5, 5.6, C(2)H_A),

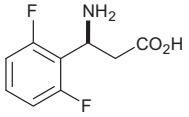
3.40 (1H, dd, *J* 17.5, 6.6, C(2)H_B), 5.25–5.28 (1H, m, C(3)*H*), 7.07–7.12 (2H, m, *Ar*), 7.48–7.55 (1H, m, *Ar*); δ_C (400 MHz, AcOH-d_4) 37.3 (*C*(2)), 46.1 (*C*(3)), 104.5, 112.3, 130.9 (*C*(3′), *C*(5′), *C*(6′)), 119.4 (*C*(1′)), 161.0, (d, *J* 259, *C*F), 163.9 (d, *J* 246, *C*F), 174.8 (*C*(1)); *m/z* (ESI$^+$) 224 ([M+Na]$^+$, 100%), 202 ([M+H]$^+$, 26%); HRMS (ESI$^+$) $C_9H_9F_2NNaO_2^+$ ([M+Na]$^+$) requires 224.0494; found 224.0489.

4.2.55. (*S*)-3-Amino-3-(2′,5′-difluorophenyl)propanoic acid 93



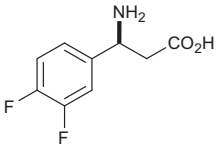
Following *general procedure 4*, 2.0 M aq HCl (15 mL) and **82** (198 mg, 0.77 mmol) refluxing 6 h followed by purification *via* ion exchange chromatography (Dowex 50WX8-100, eluent 1.0 M aq NH_4OH) gave **93** as a beige powder (144 mg, 93%); mp 207–209 °C; $[\alpha]_D^{25}$ −3.2 (*c* 0.5 in H_2O); υ_{max} (ATR) 3043 (O–H, N–H), 1620 (C=O); δ_H (400 MHz, AcOH-d_4) 3.10 (1H, dd, *J* 17.5, 5.8, C(2)H_A), 3.40 (1H, dd, *J* 17.5, 9.1,C(2)H_B), 5.24–5.29 (1H, m, C(3)*H*), 7.06–7.10 (2H, m, *Ar*), 7.47–7.54 (1H, m, *Ar*); δ_C (100 MHz, AcOH-d_4) 37.3 (*C*(2)), 46.5 (*C*(3)), 115.9, 117.7, 118.1 (*C*(3′), *C*(4′), *C*(6′)), 124.7 (*C*(1′)), 156.7 (*C*F), 159.2 (*C*F), 174.9 (*C*(1)); *m/z* (ESI$^+$) 224 ([M+Na]$^+$, 100%), 202 ([M+H]$^+$, 75%); HRMS (ESI$^+$) $C_9H_9F_2NNaO_2^+$ ([M+Na]$^+$) requires 224.0494; found 224.0493.

4.2.56. (*S*)-3-Amino-3-(2′,6′-difluorophenyl)propanoic acid 94



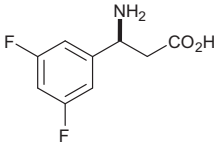
Following *general procedure 4*, 2.0 M aq HCl (15 mL) and **83** (198 mg, 0.77 mmol) followed by purification *via* ion exchange chromatography (Dowex 50WX8-100, eluent 1.0 M aq NH_4OH) gave **94** as a pale yellow powder (147 mg, 95%); mp 198–200 °C; $[\alpha]_D^{25}$ −4.8 (*c* 0.5 in H_2O); υ_{max} (ATR) 2866 (O–H, N–H), 1625 (C=O); δ_H (400 MHz, AcOH-d_4) 3.10 (1H, dd, *J* 17.7, 5.8, C(2)H_A), 3.40 (1H, dd, *J* 17.4, 8.8, C(2)H_B), 5.24–5.28 (1H, m, C(3)*H*), 7.06–7.10 (2H, m, *Ar*), 7.46–7.53 (1H, m, *Ar*); δ_C (100 MHz, AcOH-d_4) 36.8 (*C*(2)), 43.4 (*C*(3)), 111.9 (*C*(1′)), 112.4, 132.4 (*C*(3′), *C*(4′), *C*(5′)), 166.0 (d, *J* 238, *C*(2′), *C*(6′)), 174.8 (*C*(1)); *m/z* (ESI$^+$) 224 ([M+Na]$^+$, 100%), 202 ([M+H]$^+$, 74%); HRMS (ESI$^+$) $C_9H_9F_2NNaO_2^+$ ([M+Na]$^+$) requires 224.0494; found 224.0498.

4.2.57. (*S*)-3-Amino-3-(3′,4′-difluorophenyl)propanoic acid 95



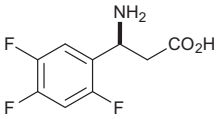
Following *general procedure 4*, 2.0 M aq HCl (15 mL) and **84** (198 mg, 0.77 mmol) followed by purification *via* ion exchange chromatography (Dowex 50WX8-100, eluent 1.0 M aq NH_4OH) gave **95** as a pale yellow powder (139 mg, 90%);[14b] mp 225–227 °C; {lit.[14b] mp 226–230 °C}; $[\alpha]_D^{25}$ −3.9 (*c* 1.0 in H_2O); {lit.[14b] $[\alpha]_D^{25}$ −3.2 (*c* 1.0 in H_2O)}; δ_H (400 MHz, AcOH-d_4) 3.19 (1H, dd, *J* 17.6, 6.1, C(2)H_A), 3.51 (1H, dd, *J* 17.6, 7.3, C(2)H_B), 4.94–4.98 (1H, m, C(3)*H*), 7.30–7.36 (1H, m, *Ar*), 7.49–7.50 (1H, m, *Ar*), 7.58–7.63 (1H, m, *Ar*).

4.2.58. (*S*)-3-Amino-3-(3′,5′-difluorophenyl)propanoic acid 96



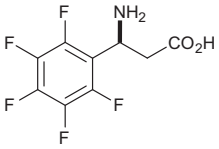
Following *general procedure 4*, 2.0 M aq HCl (15 mL) and **85** (184 mg, 0.77 mmol) followed by purification *via* ion exchange chromatography (Dowex 50WX8-100, eluent 1.0 M aq NH_4OH) gave **96** as a pale yellow powder (139 mg, 90%);[32] mp 206–208 °C; $[\alpha]_D^{25}$ −4.5 (*c* 0.5 in H_2O); δ_H (400 MHz, AcOH-d_4) 3.07 (1H, dd, *J* 17.4, 5.1, C(2)H_A), 3.28 (1H, dd, *J* 17.4, 9.1, C(2)H_B), 4.89–4.92 (1H, m, C(3)*H*), 6.97–7.01 (1H, m, *Ar*), 7.21–7.22 (2H, m, *Ar*).

4.2.59. (*S*)-3-Amino-3-(2′,4′,5′-trifluorophenyl)propanoic acid 97



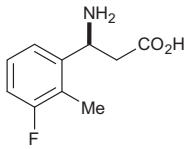
Following *general procedure 4*, 2.0 M HCl (15 mL) and **86** (212 mg, 0.77 mmol) followed by purification *via* ion exchange chromatography (Dowex 50WX8-100, eluent 1.0 M aq NH_4OH) gave **97** as a pale yellow powder (157 mg, 93%); mp 219–221 °C; $[\alpha]_D^{25}$ −7.2 (*c* 0.5 in H_2O); υ_{max} (ATR) 3444 br (O–H, N–H), 1628 (C=O); δ_H (400 MHz, AcOH-d_4) 3.22 (1H, dd, *J* 17.6, 6.5, C(2)H_A), 3.53 (1H, dd, *J* 17.6, 7.3, C(2)H_B), 5.18 (1H, app t, *J* 6.8, C(3)*H*), 7.17–7.24 (1H, m, *Ar*), 7.77–7.84 (1H, m, *Ar*); δ_C (500 MHz, AcOH-d_4) 37.4 (*C*(2)), 46.3 (*C*(3)), 107.1, 118.9 (*C*(3′), *C*(6′)), 120.3 (*C*(1′)), 147.8, 151.7, 156.9 (*C*(2′), *C*(4′), *C*(5′)), 174.6 (*C*(1)); *m/z* (ESI$^+$) 242 ([M+Na]$^+$, 100%), 220 ([M+H]$^+$, 51%); HRMS (ESI$^+$) $C_9H_8F_3NNaO_2^+$ ([M+Na]$^+$) requires 242.0399; found 242.0404.

4.2.60. (*S*)-3-Amino-3-(pentafluorophenyl)propanoic acid 98



Following *general procedure 4*, 2.0 M aq HCl (15 mL) and **87** (239 mg, 0.77 mmol) followed by purification *via* ion exchange chromatography (Dowex 50WX8-100, eluent 1.0 M aq NH_4OH) gave **98** as a pale yellow powder (190 mg, 97%);[21] mp 188–190 °C; $[\alpha]_D^{25}$ +27.3 (*c* 2.5 in H_2O); {lit.[21] $[\alpha]_D^{20}$ +24 (*c* 2.5 in D_2O)}; δ_H (400 MHz, AcOH-d_4) 3.28–3.36 (1H, m, C(2)H_A), 3.55–3.63 (1H, m, C(2)H_B), 5.35–5.48 (1H, m, C(3)*H*).

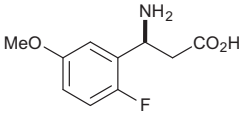
4.2.61. (*S*)-3-Amino-3-(2′-methyl-3′-fluorophenyl)propanoic acid 99



Following *general procedure 4*, 2.0 M aq HCl (19 mL) and **76** (253 mg, 1.00 mmol) followed by purification *via* ion exchange

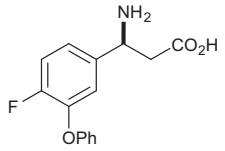
chromatography (Dowex 50 WX8-100, eluent 1.0 M aq NH_4OH) gave **99** as a pale yellow powder (187 mg, 95%); mp 228–230 °C; $[\alpha]_D^{25}$ −15.6 (*c* 0.5 in H_2O); ν_{max} (ATR) 3418 (O–H, N–H), 1647 (C=O); δ_H (400 MHz, AcOH-d_4) 2.35 (3H, s, C(2′)*Me*), 2.87–3.00 (1H, m, C(2)H_A), 3.08–3.39 (1H, m, C(2)H_B), 5.17–5.68 (1H, m, C(3)*H*), 6.97–7.48 (3H, m, *Ar*); δ_C (100 MHz, AcOH-d_4)[33] 9.5 (C(2′)*Me*), 38.2 (*C*(2)), 48.0 (*C*(3)), 115.9, 122.2, 128.2 (*C*(4′), *C*(5′), *C*(6′)), 124.3, 136.9 (*C*(1′), *C*(2′)), 162.0 (d, *J* 226, *C*(3′)); *m/z* (ESI^+) 220 ($[M+Na]^+$, 92%), 198 ($[M+H]^+$, 83%); HRMS (ESI^+) $C_{10}H_{13}FNO_2^+$ ($[M+H]^+$) requires 198.0925; found 198.0925.

4.2.62. (*S*)-3-Amino-3-(2′-fluoro-5′-methoxyphenyl)propanoic acid 100



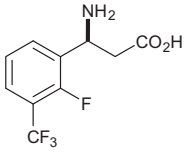
Following *general procedure 4*, 2.0 M aq HCl (20 mL) and **77** (276 mg, 1.03 mmol) followed by purification *via* ion exchange chromatography (Dowex 50 WX8-100, eluent 1.0 M aq NH_4OH) gave **100** as a pale yellow powder (206 mg, 94%); mp 189–191 °C; $[\alpha]_D^{25}$ −3.8 (*c* 0.3 in H_2O); ν_{max} (ATR) 3425 (O–H, N–H), 1641 (C=O); δ_H (400 MHz, D_2O) 2.85 (1H, dd, *J* 16.7, 6.8, C(2)H_A), 2.96 (1H, dd, *J* 16.7, 7.8, C(2)H_B), 3.73 (3H, s, O*Me*), 4.80–4.84 (1H, m, C(3)*H*), 6.93–7.l2 (3H, m, *Ar*); δ_C (125 MHz, D_2O) 38.0 (*C*(2)), 46.7 (*C*(3)), 56.0 (O*Me*), 113.4, 116.4, 117.0 (*C*(3′), *C*(4′), *C*(6′)), 123.0 (*C*(1′)), 154.6 (d, *J* 256, *C*(2′)), 155.3 (*C*(5′)), 175.1 (*C*(1)); *m/z* (ESI^+) 236 ($[M+Na]^+$, 87%), 214 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{10}H_{13}FNO_3^+$ ($[M+H]^+$) requires 214.0874; found 214.0875.

4.2.63. (*S*)-3-Amino-3-(3′-phenoxy-4′-fluorophenyl)propanoic acid 101



Following *general procedure 4*, 2.0 M aq HCl (19 mL) and **78** (331 mg, 1.00 mmol) followed by purification *via* ion exchange chromatography (Dowex 50 WX8-100, eluent 1.0 M aq NH_4OH) gave **101** as a white powder (267 mg, 97%); mp >370 °C; $[\alpha]_D^{25}$ −12.0 (*c* 0.5 in H_2O); ν_{max} (ATR) 3418 (O–H, N–H), 1642 (C=O); δ_H (400 MHz, AcOH-d_4) 3.09 (1H, dd, *J* 17.4, 5.6, C(2)H_A), 3.34 (1H, dd, *J* 17.4, 8.3, C(2)H_B), 4.85–4.89 (1H, m, C(3)*H*), 7.00–7.38 (8H, m, *Ar*); δ_C (100 MHz, AcOH-d_4) 37.8 (*C*(2)), 51.8 (*C*(3)), 117.5, 117.9, 121.9, 123.8, 124.8, 130.2 (*C*(2′), *C*(5′), *C*(6′), *o*,*m*,*p*-*Ph*), 132.9, 143.0, 157.4 (*C*(1′), (*C*(3′), *i*-*Ph*), 154.6 (d, *J* 266, *C*(4′)), 174.9 (*C*(1)); *m/z* (ESI^+) 298 ($[M+Na]^+$, 79%), 276 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{15}H_{15}FNO_3^+$ ($[M+H]^+$) requires 276.1030; found 276.1032.

4.2.64. (*S*)-3-Amino-3-[2′-fluoro-3′-(trifluoromethyl)phenyl]-propanoic acid 102



Following *general procedure 4*, 2.0 M aq HCl (19 mL) and **79** (307 mg, 1.00 mmol) followed by purification *via* ion exchange chromatography (Dowex 50 WX8-100, eluent 1.0 M aq NH_4OH) gave **102** as a white solid (239 mg, 95%);[22] mp 207–208 °C; {lit.[22] mp 206 °C}; $[\alpha]_D^{25}$ −2.2 (*c* 0.5 in H_2O); δ_H (400 MHz, AcOH-d_4) 3.29 (1H, dd, *J* 17.6, 6.0, C(2)H_A), 3.61 (1H, dd, *J* 17.6, 7.2, C(2)H_B), 5.29–5.32 (1H, m, C(3)*H*), 7.48 (1H, app t, *J* 7.2, *Ar*), 7.78 (1H, app t, *J* 7.0, *Ar*), 8.17 (1H, br s, *Ar*).

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