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Highly functionalised organolithium and organoboron reagents for the preparation of enantiomerically pure α-amino acids

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Abstract—Homochiral, highly functionalised organolithium reagents derived from L-serine have been generated and reacted with electrophiles. The novel enantiomerically pure adducts thus obtained were then converted, through β-amino alcohols, into novel non-proteinogenic α-amino acids. The methodology also made available a novel boronic acid which was then employed as a Suzuki cross-coupling partner, elaborating a new pathway to phenylalanine analogues.

Nucleophilic alanine equivalents have attracted a great deal of attention in recent years.[1–6] These reagents are particularly useful for the preparation of enantiopure proteinogenic and non-proteinogenic α-amino acids,[1] as well as enantiopure α-amino alcohols, and other related 'chiral building blocks' used in natural product synthesis. Prominent examples of these reagents include aspartate-derived anion **1**,[2] related sulfonyl reagent **2**,[3] Wittig reagents **3**[4] and **4**,[5] and the organonickel reagent **5**.[6] Although ground-breaking and potentially valuable, these reagents have not been widely employed in organic synthesis, possibly due to the difficulty of preparation, the additional steps needed to remove the anion-stabilising/activating group or to readjust the oxidation level and, in the case of reagent **5**, its low reactivity.

The organozinc reagent **6** designed and prepared by Jackson and his group,[7] has proved particularly versatile and has been successfully adopted by other researchers for preparation of a number of natural products and medicinally active compounds.[8] This reagent can be employed in a variety of coupling procedures (e.g., to aryl halides and acyl halides[7a]), and its copper derivative also undergoes allylation or conjugate additions.[7b] Unfortunately, due to its low nucleophilicity, reaction with simple aldehydes/ketones is not possible (Fig. 1).

During synthetic efforts towards the synthesis of scyphostatin[9a] and aranorosin,[9b] we required a highly reactive organometallic reagent, i.e. **7**, capable of 1,2-addition to cyclic ketones. In this paper we describe the successful

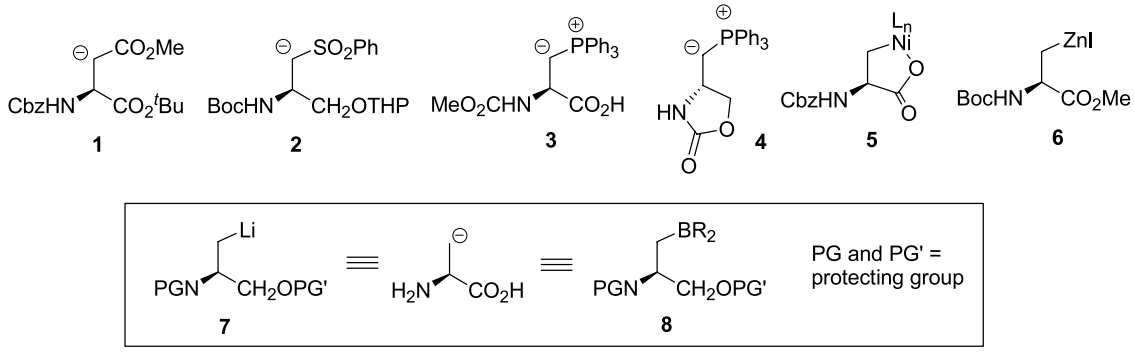

Figure 1. Alanine anion equivalents.

Keywords: Cross-coupling; α-Amino acids; Organolithium; Suzuki; Alanine anions.
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development and application of such highly functionalised organolithium reagents **7**.[10] The novel homochiral adducts are then manipulated into proteinogenic and non-proteinogenic α-amino acids. We also outline the synthesis of a new alkylboron reagent **8**,[11] which is employed in Suzuki cross-coupling reactions. Thus, two new alanine anion equivalents are described.

1. Preparation and application of functionalised organolithium reagents (7)

We first embarked on a program to explore the preparation of organolithium reagents **7** commencing from a readily available proteinogenic α-amino acid (Scheme 1).[12] Standard conditions were employed to convert L-serine via ester **9**[13] into chloro-alcohol **10**. Protection of alcohol **10** was undertaken using a number of different groups, giving the key lithiation precursors **11a–d**.

With precursors **10** and **11a–d** in hand we were able to investigate the generation of organolithium reagents **12a–e** (Scheme 1). Due to the required anion **7** having a β-heteroatom it was obviously crucial to generate a dianionic species in order to impede β-elimination. We therefore employed the *n*-butyllithium/lithium naphthalenide (LiNp) combination pioneered by Yus et al. for β-chloroamide lithiation.[14] This protocol was employed with the unprotected alcohol **10** and with the protected derivatives **11a–d**, the reaction mixture was then quenched with cyclohexanone with the aim of assessing the procedure in terms of the yield of adducts **13a–e** (Table 1).

Table 1. Metallation-trapping of **11a–d** and **10**[a]

Entry	Precursor	Product[b]
i	**11a**, P=TBS	**13a**, P=TBS, 0%
ii	**11b**, P=THP	**13b**, P=THP, 57%
iii	**11c**, P=MOM	**13c**, P=MOM, 82%
iv	**11d**, P=SEM	**13d**, P=SEM, 82%
v[c]	**10**	**13e**, P=H, 0%

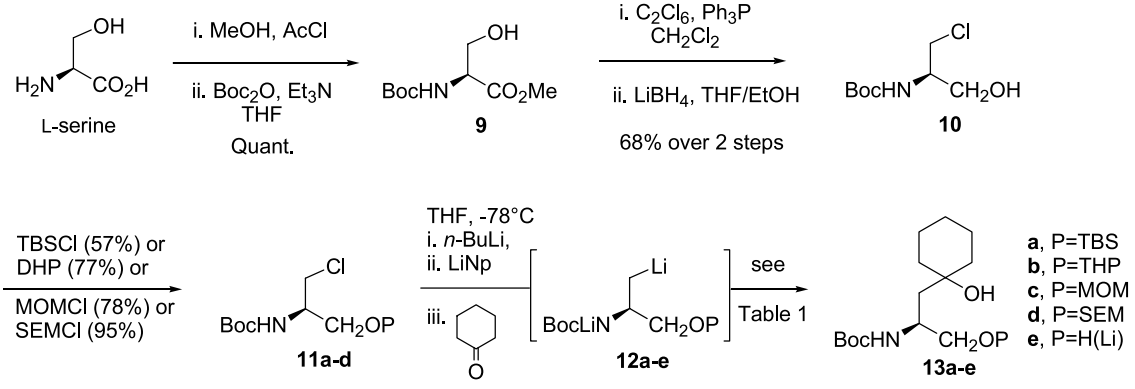
[a] THF, −78 °C: (i) *n*-BuLi (1.1 equiv), (ii) LiNp (2.5–3.0 equiv), (iii) E^+ (1.5–2.5 equiv).
[b] Isolated yields.
[c] 2.1 equiv of *n*-BuLi was employed.

We were encouraged by the promising results with THP, MOM and SEM protecting groups (Table 1, entries ii–iv), indicating the possibility that an additional coordinating site in the protecting group might be advantageous. The unprotected alcohol **10** gave no product, nor did the TBS ether **11a**. The failure of silyl-protected **11a** was presumably due to susceptibility to intramolecular Brook-type rearrangement, although this could not be verified by analysis of the crude product mixture. No further work was carried out with the THP-protected **11b** in view of the diastereomeric nature of the adducts.

As might be anticipated,[15] preliminary deprotection studies showed the SEM ether **13d** could be deprotected more easily than MOM ether **13c**, although many standard methods[15] led to decomposition. *N*-Br-Catecholborane cleanly converted MOM-protected **13c** into alcohol **13e**, but only in a disappointing 58% yield. It should be pointed out that deprotection of the SEM ether employing TBAF (in THF[16] and DMPU[17]) failed at room temperature, and decomposition ensued on heating at elevated temperatures. Fortunately, deprotection of SEM ether **13d** could be performed cleanly using 0.1 M HCl in MeOH[18] over 3 h at room temperature, delivering **13e** (P=H) in an excellent 79% yield. Unfortunately, this reaction time (3 h) led to incomplete conversion, and so starting material was recovered (see Table 2 footnote). Extended reaction times led to substantial cleavage of the Boc group.

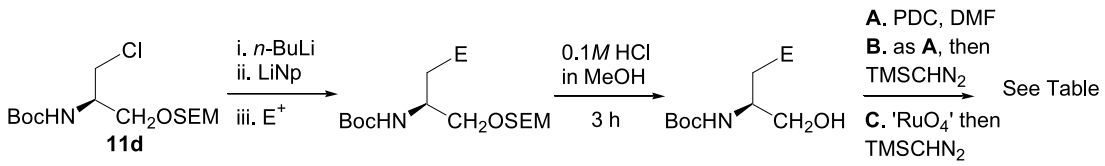
Due to the success of the SEM group in the deprotection studies, it was therefore chosen for further investigation and a range of electrophiles were used to trap the organolithium reagent **12d** (Table 2). Thus, in addition to cyclohexanone (entry i), cyclobutanone, benzaldehyde, Weinreb amides, carbon dioxide, trimethylsilyl chloride, CD_3OD and tributyltin chloride were all successfully employed as electrophilic trapping agents delivering adducts **15**, **18**, **21**, **23**, **25**, **27**, **30** and **33**, respectively, in yields ranging from 51 to 98% (entries ii–viii).

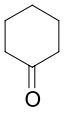
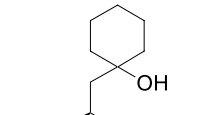
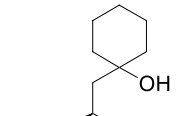
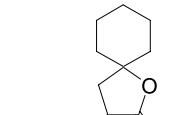
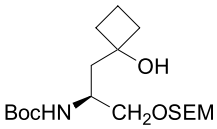
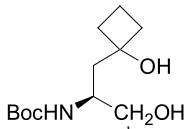
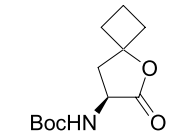
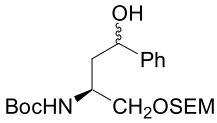
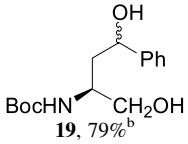
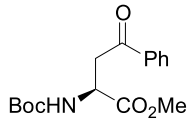
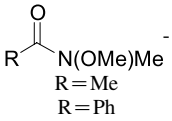
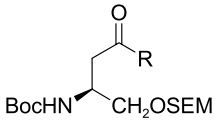
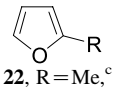
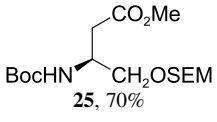
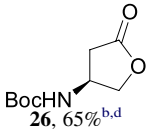
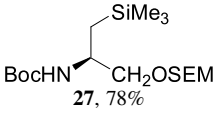
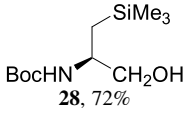
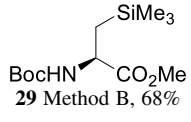
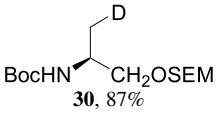
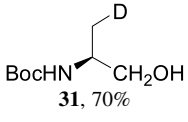
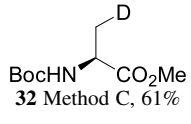
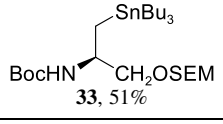
Cleavage of the SEM-protecting groups proceeded smoothly, in most cases, delivering alcohols **13e**, **16**, **19**, **28** and **31** in unoptimised but reasonable yields (entries i–iii, vi–vii). The main exceptions (entry iv) involved methanolysis of ketone adducts **21** and **23** where the only observed products were the furans **22** and **24**, respectively, resulting from a cyclocondensation–aromatisation sequence. In addition (entry v), the alcohol resulting from deprotection of ester **25** underwent partial lactonisation, and a second



Scheme 1. Initial studies.

Table 2. Metallation-trapping–methanolysis–oxidation of **11d**[a]

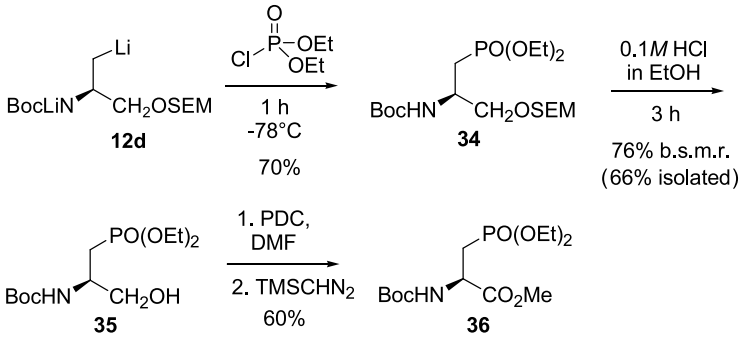


	Electrophile (E^+)	Adduct	Methanolysis product	Oxidation product
i		 **13d**, 82%	 **13e**, 88%[b]	 **14** Method A, 69%
ii		 **15**, 81%	 **16**, 76%[b]	 **17** Method A, 74%
iii	PhCHO	 **18**, 98% (3:2) ratio	 **19**, 79%[b]	 **20** Method B, 47%, Method C, 44%
iv	 R = Me R = Ph	 **21** R = Me, 82%, **23** R = Ph, 80%	 **22**, R = Me,[c] **24**, R = Ph[c]	—
v	CO_2, then $TMSCHN_2$	 **25**, 70%	 **26**, 65%[b,d]	—
vi	Me_3SiCl	 **27**, 78%	 **28**, 72%	 **29** Method B, 68%
vii	CD_3OD	 **30**, 87%	 **31**, 70%	 **32** Method C, 61%
viii	Bu_3SnCl	 **33**, 51%	—	—

[a] Trapping of **12d** using the electrophile indicated; deprotection using 0.1 M HCl in MeOH for 3 h; oxidation/esterification using Method A: PDC, DMF, Method B: (i) PDC, DMF, (ii) $TMSCHN_2$ or Method C: (i) $RuCl_3$ (cat.), $NaIO_4$, $CCl_4/H_2O/CH_3CN$, (ii) $TMSCHN_2$; isolated yields are shown.
[b] Based on recovered starting material (isolated yields were **13e**, 79%; **16**, 65%; **19**, 64%; **26**, 50%).
[c] The desired deprotected product was not observed. Due to the volatility of **22** and **24** isolated yields were not obtained; these were the only products observed by TLC and ^1H NMR spectroscopy.
[d] Lactonisation to give **26** was completed by treatment with CSA in PhH.[19]

treatment of the crude material with CSA in benzene[19a] completed lactonisation to give the known γ-lactone **26**.[19] The standard deprotection method failed to effect clean removal of the SEM from the tributyltin adduct **33** (entry viii).

The Boc-protected β-amino alcohol derivatives obtained by SEM-deprotection were then oxidised to the corresponding Boc-protected α-amino acids which were converted into their methyl esters using trimethylsilyl diazomethane. Thus, fully protected α-amino acids **20**,[20] **29** and **32** were obtained

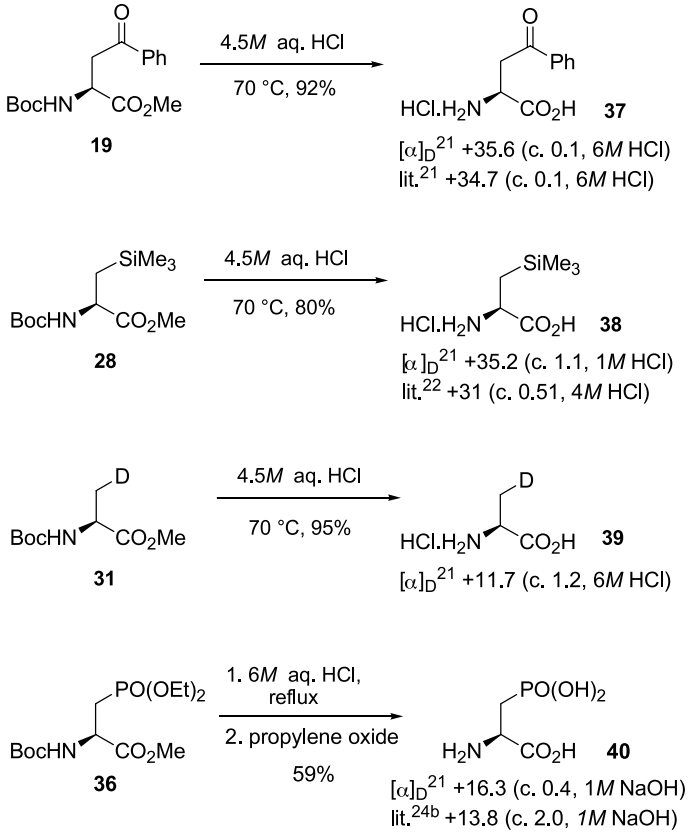


Scheme 2. Preparation of phosphonate α-amino acid **36**.

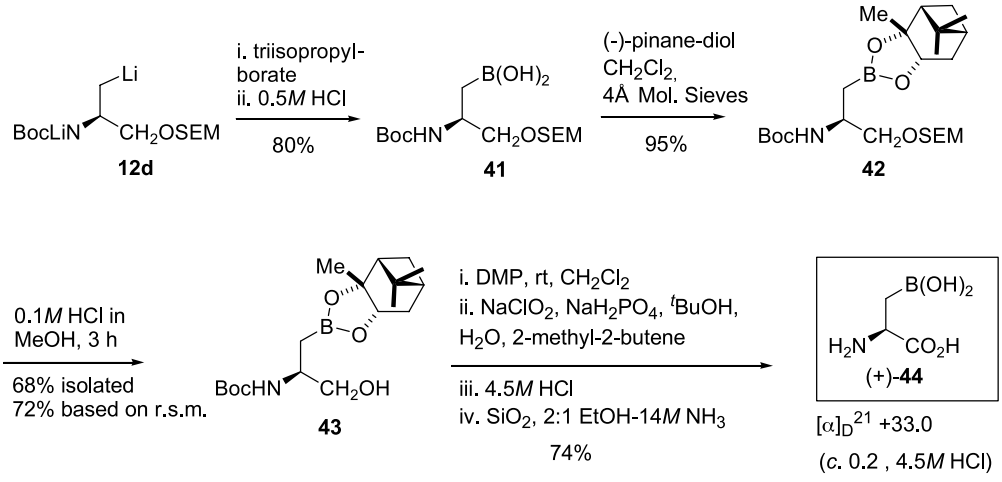
in reasonable yields (entries iii and vi–vii). Oxidation of 1°/3° diols **13e** and **16** under these PDC oxidation conditions gave the spirocyclic lactones **14** and **17**, respectively, by in situ lactonisation (entries i and ii). It should be noted that the problems with methanolysis of the SEM–ketone adducts, such as **21** and **23**, were overcome by double oxidation of the deprotected benzaldehyde adduct **19**, therefore allowing the synthesis of β-keto-α-amino acid **20** (entry iii).[20]

A more demanding electrophile such as diethyl chlorophosphate could also be employed. Reaction of organolithium **12d** with diethyl chlorophosphate delivered a good yield of the phosphonate **34** (Scheme 2), although reduced reaction times were required to minimise side reactions. SEM-deprotection was then carried out efficiently by means of 0.1 M ethanolic HCl, avoiding trans-esterification problems. The subsequent alcohol **35** was converted into the protected α-amino acid **36** in the manner described above.

Hydrolysis of the protected amino acids **19**, **28** and **31** was straightforward (Scheme 3). Thus, treatment of the *N*-Boc amino ester **19** with 4.5 M HCl at 70 °C for 3 h gave the hydrochloride salt **37** in 92% yield. The optical rotation was in good agreement with the published value $\{[\alpha]_D^{21} = +35.6$ (c 0.1, 6 M HCl); lit.[21] +34.7 (c 0.1, 6 M HCl)$\}$. Similarly, trimethylsilylalanine was obtained as its hydrochloride salt **38** from **28** in 80% yield $\{[\alpha]_D^{21} = +35.2$ (c 1.1, 1 M HCl); lit.[22] +31 (c 0.51, 4 M HCl)$\}$. The deutero-alanine HCl salt **39** was obtained in 95% yield from **31** in the same manner $\{[\alpha]_D^{21} = +11.7$ (c 1.2, 6 M HCl)$\}$. This labelled amino acid has been observed in the reaction of alanine with hydroxyl radicals,[23] but has never been isolated and characterised.



Scheme 3. Preparation of (+)-α-amino acids.



Scheme 4. Preparation of aspartic acid mimic (+)-**44**.

Future employment of this deuterated amino acid (+)-**39** could be envisaged in biological studies.

L-2-Amino-3-phosphonopropionic acid **40** has been shown to be an antagonist of the metabotropic glutamate receptor.[24a] This can lead to inhibition of phosphoserine phosphatase, which catalyses the final step in the major pathway of L-serine biosynthesis in the brain. The synthesis of phosphonic acid **40** was achieved through global deprotection of the phosphonate **36** in 6 M HCl under reflux, followed by treatment with propylene oxide (Scheme 3).[24b] The optical rotation value $\{[\alpha]_D^{21} = +16.3$ (*c* 0.4, 1 M NaOH)} of amino acid **40** was in good agreement with that reported by Smith et al. {lit.[24b] +13.8 (*c* 2, 1 M NaOH)}.

We also employed this novel methodology to complete the first asymmetric synthesis of the aspartic acid mimic (+)-**44**, in which the β-carboxylic acid has been substituted by a boronic acid (Scheme 4). This compound has already been synthesised as a racemate,[25,26] and in one case resolution was performed by separation of a dipeptide derivative.[26] It is a member of the increasing number of biomolecules which synthetic chemists have altered by incorporation of boron-containing moieties.[27]

Reaction of the functionalised organolithium reagent **12d** with triisopropylborate followed by treatment with mild acid delivered the boronic acid **41** in 80% yield (Scheme 4). In order to manipulate the boronic acid adduct **41**, protection as the (−)-pinane-diol boronate ester was undertaken. This was followed by methanolysis of the SEM ether **42**, giving the alcohol **43** in reasonable yield. The oxidation of alcohol **43** was found to be sensitive to the reagent used, for example, both PDC/DMF and 'RuO_4' oxidations led to decomposition. Fortunately, sequential Dess–Martin periodinane/sodium chlorite oxidations gave the crude carboxylic acid[28] which was directly deprotected using 4.5 M HCl. The crude hydrogen chloride salt of the amino acid could then be purified on silica gel eluting with 2:1 EtOH–14 M NH_3[29] to deliver the aspartic acid mimic (+)-**44**, $\{[\alpha]_D^{21} = +33.0$ (*c* 0.2, 4.5 M HCl)}.[30] This constitutes the first asymmetric synthesis of the aspartic acid mimic (+)-**44**, increasing its potential in future biological studies.

2. Preparation and application of functionalised organoboron reagents (8)

Recently, we have explored the use of complex alkyl-borane Suzuki cross-coupling partners derived from readily available chiral-pool starting materials. The homoalanine and bis-homoalanine alkyl-organoboranes **45** and **46**,[12] obtained by hydroboration of alkenyl-precursors, were employed in cross-coupling reactions delivering a variety of novel non-proteinogenic α-amino acids (Fig. 2). Attempts to synthesise alanine-organoborane derivatives (**47**, BR_2=9-BBN) had previously been made, but unfortunately hydroboration of the dehydro-amino acid derivatives failed.[31] The synthesis of boronic acid **41** (Scheme 4) raises the possibility of its application as the lower homologue of **45** and **46**. Application of this lower homologue to Suzuki cross-coupling would expand the scope of the methodology. An added benefit is that boronic acid **41** is stable and presumably has a low level of toxicity,[32] compared to the organoboranes **45** and **46**,[12] both of which need to be prepared immediately before use.

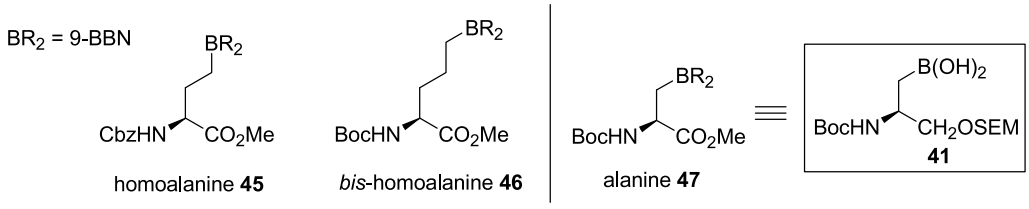


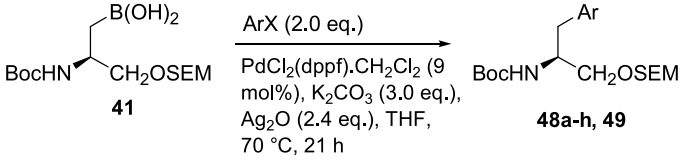
Figure 2. Suzuki cross-coupling substrates.

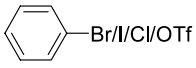
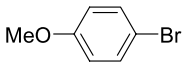
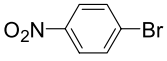
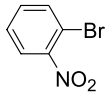
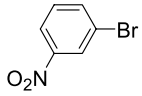
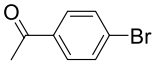
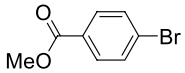
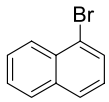
Traditionally, Suzuki cross-coupling reactions with alkyl boronic acids were thought to be non-viable, due to their low nucleophilicity and tendency for β-hydride elimination after transmetallation.[32] Over recent years this has been proved to be wrong with pioneering work by Falck,[33] Molander[34] and Fu,[35] who have shown that, by judicious choice of catalyst and conditions, clean Suzuki cross-coupling of alkyl-boronic acids is possible.

We first wished to discover if our highly functionalised boronic acid **41** was applicable to Suzuki cross-coupling with aryl halides, and whether we could then transform the adducts into phenylalanine analogues. Through optimisation[11] we were able to devise conditions delivering good yields of the coupled products **48a–h** and **49** (Table 3). Employment of modified Falck[33] conditions ($Pd^{II}Cl_2(dppf).CH_2Cl_2/K_2CO_3/Ag_2O$/THF) gave a clean conversion into the coupled products **48a–h**, **49** at 70 °C over 21 h. It should be pointed out that the maximum yield of coupled products from boronic acid **41** is 82%, due to 18% of the starting alkyl boronic acid being lost during reduction of the Pd^{II} precatalyst to Pd^0. A variety of aryl halides were found to react smoothly in the coupling procedure, from electron-rich *p*-bromoanisole (entry ii) to the electron-deficient *o*, *m* and *p*-nitrobromobenzenes (entries iii–v). Unsurprisingly iodobenzene also reacted well, but chlorobenzene failed to react. Rather unexpectedly, phenyl trifluoromethanesulfonate (PhOTf) failed, despite these conditions previously being employed effectively with triflates.[33] The presence of carbonyl groups in the aryl halide was found to be tolerated (entries vi and vii). A doubly coupled product **49** was isolated in a modest 35% yield by reaction of the boronic acid with 0.5 equiv of 1,4-diiodobenzene (entry ix).

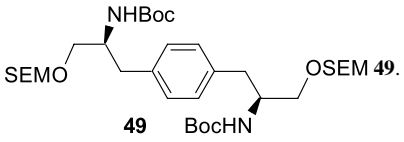
The bromobenzene and *p*-bromonitrobenzene systems were

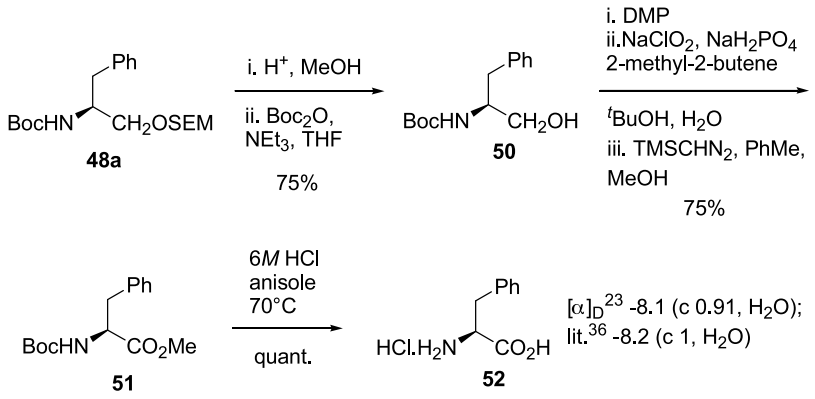
Table 3. Suzuki cross-coupling of alkyl boronic acid **35** with aryl halides[a]



Entry	ArX	Yield (%)[b]	Product
i		72/73/0/0	**48a**
ii		65	**48b**
iii		65	**48c**
iv		70	**48d**
v		67	**48e**
vi		68	**48f**
vii		52	**48g**
viii		73	**48h**
ix		35[c]	**49**

[a] All performed on 0.10–0.13 mmol scale at ca. 0.1 mol L^{-1} concentration.
[b] Yields are based on boronic acid **41**.
[c] 0.5 equiv of dihalide used; doubly coupled product **49** formed:





Scheme 5. Preparation of (−)-phenylalanine hydrochloride **52**.

demonstrated to be amenable to a modest scale-up (ca. 0.5 mmol), giving a reasonable 63% yield of **48a** and a better 71% yield of **48c**, respectively. No problems are foreseen in further scale-ups.

To demonstrate the synthetic utility of these adducts and to prove that no racemisation occurred during the coupling process we transformed the phenyl adduct **48a** into (−)-phenylalanine **52** (Scheme 5). A two-step deprotection procedure was used, whereby both SEM and Boc groups were removed to deliver the β-amino alcohol, which was reprotected with Boc, giving **50**. A two-step Dess–Martin periodinane/sodium chlorite oxidation was then employed to deliver the amino acid, which was again protected as a methyl ester, producing the fully protected phenylalanine **51**. This was then globally deprotected as before with 6 M HCl, this time including anisole as a cation trap. The optical rotation of the so-obtained HCl salt, **52**, matched the known data {$[\alpha]_D^{23} = -8.1$ (*c* 0.91, H_2O); [lit.[36] $[\alpha]_D^{23} = -8.2$ (*c* 1, H_2O)]}.

In summary, we have prepared a number of highly functionalised organolithium reagents from L-serine using the Yus procedure in the key lithiation step and established that they can be employed as alaninol/alanine anion equivalents. The optimum SEM-protected reagent **11d** has been used to prepare a range of novel adducts which were hydrolysed to give alaninol derivatives and then oxidised to give known and novel non-proteinogenic amino acids as their protected derivatives. A selection of these compounds was converted into the amino acid hydrochloride salts. We were also able to undertake the first asymmetric synthesis of the aspartic acid mimic (+)-**44**. In addition, the alkyl boronic acid **41** was employed as a β-alanine anion equivalent in Suzuki cross-coupling reactions with aryl halides. One of the cross-coupled adducts was then manipulated into (−)-phenylalanine hydrochloride **52**.

3. Experimental

3.1. General experimental

NMR spectra were recorded on a Jeol EX-270 or Jeol EX-400 instrument (specified below); chemical shifts are quoted in parts per million (ppm) calibrated to residual non-deuterated solvent. An external sample of $BF_3 \cdot OEt_2$ was used to calibrate ^{11}B NMR spectra. Infrared spectra were recorded on a ThermoNicolet IR100 spectrometer with NaCl plates. Optical rotation values were measured on a JASCO DIP-370 digital polarimeter using a sodium lamp. Low-resolution electron impact (EI) mass spectra were recorded on a Kratos MS 25 spectrometer. Chemical ionisation (CI) and high-resolution mass spectra were recorded on a Micromass Autospec spectrometer. Melting points were recorded on Gallenkamp apparatus and are uncorrected. Thin layer chromatography was performed on aluminium plates coated with Merck silica gel 60 F_{254}. Flash column chromatography was carried out using Fluka flash silica gel 60 and the eluent is specified. Where necessary, ether and THF were distilled from sodium benzophenone ketyl immediately before use and CH_2Cl_2 distilled from calcium hydride. Except where specified, all reagents were purchased from commercial sources and used without further purification.

3.2. Synthesis of (*R*)-[2-chloro-1-(2-trimethylsilanyl-ethoxymethoxymethyl)-ethyl]-carbamic acid *tert*-butyl ester (11d)

3.2.1. 2-(*R*)-*tert*-Butoxycarbonylamino-3-chloro-propionic acid methyl ester. A solution of triphenylphosphine (19.2 g, 73.2 mmol) and hexachloroethane (17.3 g, 73.2 mmol) in dichloromethane (50 mL) was added in one portion to a solution of *N*-Boc-serine methyl ester **9**[12] (14.6 g, 66.5 mmol) in dichloromethane (250 mL) under an atmosphere of argon. The reaction was stirred at room temperature for 2 h, then quenched with a saturated solution of sodium hydrogen carbonate (50 mL). The organic phase was separated and washed with brine (100 mL), dried ($MgSO_4$), evaporated then triturated with Et_2O (300 mL). After filtration and evaporation the subsequent residue was purified on silica gel, eluting with petrol(40–60)–EtOAc 5:1, delivering 2-*tert*-butoxycarbonylamino-3-chloro-propionic acid methyl ester (13.2 g, 84%) as a white solid, mp 62–64 °C; R_f 0.31 (4:1, petrol(40–60)–Et_2O); ν_{max}(film)/cm^{-1} 3362 (NH), 2982 (CH), 1721 (CO); $[\alpha]_D^{21} = +37.8$ (*c* 1.5, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 5.37 (1H, brd, J= 7.5 Hz), 4.65 (1H, m), 3.90 (1H, dd, J=3 Hz, 11.5), 3.78 (1H, dd, J=3.5, 11.5 Hz), 3.73 (3H, s), 1.40 (9H, s); δ_C (100 MHz; $CDCl_3$) 169.6, 154.9, 80.5, 54.4, 52.9, 45.5,

28.2. (Found: MNH_4^+, 255.1110. $C_8H_{16}NO_4^{35}Cl$ requires MNH_4, 255.1112 (0.8 ppm)).

3.2.2. (2-(*R*)-Chloro-1-hydroxymethyl-ethyl)-carbamic acid *tert*-butyl ester 10. Lithium borohydride (1.18 g, 54.1 mmol) was added in portions to a stirred solution of the above ester (12.9 g, 54.1 mmol) in ethanol–THF 9:1 (700 mL) at 0 °C under an atmosphere of argon. The reaction was stirred for 18 h at room temperature then quenched with a saturated solution of ammonium chloride (10 mL). The organics were then evaporated and the residue partitioned between water (300 mL) and Et_2O (300 mL). After separation, the aqueous was further extracted with Et_2O (300 mL). The combined organics were dried ($MgSO_4$) and evaporated to give a gummy residue which was purified on silica gel, eluting with petrol(40–60)–Et_2O 2:1, giving the alcohol **10** (8.1 g, 81%) as a gum; R_f 0.42 (1:2, petrol(40–60)–Et_2O); ν_{max}(film)/cm^{-1} 3353 (OH), 2978 (CH), 1689 (CO); $[\alpha]_D^{21} = -4.6$ (*c* 0.7, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 4.94 (1H, br s), 3.86 (1H, br s), 3.8–3.55 (4H, m), 1.42 (9H, s); δ_C (100 MHz; $CDCl_3$) 155.6, 80.2, 62.0, 52.5, 44.2, 28.3. (Found: MH^+, 210.0889. $C_8H_{16}NO_3^{35}Cl$ requires MH, 210.0897 (4.0 ppm)).

3.2.3. [2-(*R*)-Chloro-1-(2-trimethylsilanyl-ethoxymethoxymethyl)-ethyl]-carbamic acid *tert*-butyl ester 11d. SEMCl (1.27 mL, 7.2 mmol) was added dropwise to a stirred solution of alcohol **10** (1.58 g, 7.57 mmol) and Hunig's base (1.44 mL, 8.29 mmol) in dichloromethane (20 mL) at 0 °C under an atmosphere of argon. The reaction was allowed to warm to room temperature and stirred for 18 h. The reaction was evaporated and partitioned between Et_2O (50 mL) and water (30 mL). After separation, further extraction with Et_2O (2×40 mL), the combined organics were dried ($MgSO_4$) and evaporated. The subsequent crude residue was purified on silica gel, eluting with petrol(40–60)–Et_2O 4:1, giving the ether **11d** (2.31 g, 95%) as a colourless oil; R_f 0.30 (4:1, petrol(40–60)–Et_2O); ν_{max}(film)/cm^{-1} 3346 (NH), 2955, 2932, 2893 (CH), 1719 (CO); $[\alpha]_D^{21} = +12.4$ (*c* 0.4, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 5.03 (1H, br d, *J*=8.0 Hz), 4.67 (2H, s), 4.01 (1H, br s), 3.80 (1H, dd, *J*=4, 10 Hz), 3.71 (1H, dd, *J*=4, 11 Hz), 3.6–3.5 (4H, m), 1.44 (9H, s), 0.95 (2H, t, *J*=9 Hz), 0.02 (9H, s); δ_C (100 MHz; $CDCl_3$) 155.4, 95.4, 80.2, 66.4, 65.8, 51.1, 44.3, 28.7, 18.4, −1.1. (Found: MH^+, 340.1711. $C_{14}H_{30}NO_4^{35}ClSi$ requires MH, 340.1711 (0.0 ppm)).

3.3. General lithiation procedure

n-BuLi (0.21 mL, 0.42 mmol, 1.98 M solution in hexanes, 1.1 equiv) was added dropwise to a stirred solution of chloride **11d** (128 mg, 0.38 mmol, 1.0 equiv) in THF (5 mL, ~12 mL/mmol) at −78 °C under an atmosphere of argon. Stirring was continued for 15 min, followed by the dropwise addition of LiNp[14] (2.2 mL, 1.1 mmol, 0.5 M solution in THF, 2.5–3.0 equiv) over 5 min. The dark solution was stirred at −78 °C for 2 h. Subsequently electrophile (1.1 mmol, 1.5–3.0 equiv) was added dropwise to the solution causing decolourisation. The reaction mixture was kept cold (ca. −78 to −40 °C) overnight then quenched with a saturated solution of ammonium chloride (~1 mL) and allowed to warm to room temperature. The reaction was diluted with ether (20 mL) and saturated ammonium chloride (20 mL). The layers were separated and the aqueous layer was extracted with ether (2×10 mL). The combined organics were dried ($MgSO_4$), filtered and evaporated to give a crude product which was purified by flash column chromatography on silica gel, eluting with diethyl ether–petrol ether (40–60) to give the product.

3.3.1. [2-(1-Hydroxy-cyclohexyl)-1-(*S*)-(2-trimethylsilanyl-ethoxymethoxymethyl)-ethyl]-carbamic acid *tert*-butyl ester 13d. 149 mg, 82%. Colourless oil; R_f 0.10 (2:1, petrol(40–60)–Et_2O); ν_{max}(film)/cm^{-1} 3448 (OH), 2932, 2867 (CH), 1691 (CO); $[\alpha]_D^{21} = -5.0$ (*c* 0.6, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 5.13 (1H, br s), 4.65 (2H, s), 3.95 (1H, br s), 3.6–3.5 (4H, m), 2.98 (1H, br s), 1.65–1.2 (21H, m), 0.94 (2H, t, *J*=8.5 Hz), 0.01 (9H, s); δ_C (100 MHz; $CDCl_3$) 156.3, 95.3, 79.8, 71.9, 70.4, 65.5, 46.8, 44.6, 38.5, 37.9, 29.5, 26.0, 22.4, 22.3, 18.2, −1.3. (Found: MH^+, 404.2831. $C_{20}H_{41}NO_5Si$ requires MH, 404.2832 (0.4 ppm)).

3.3.2. [2-(1-Hydroxy-cyclobutyl)-1-(*S*)-(2-trimethylsilanyl-ethoxymethoxymethyl)-ethyl]-carbamic acid *tert*-butyl ester 15. 204 mg, 81%. Colourless oil; R_f 0.18 (1:1, petrol(40–60)–Et_2O); ν_{max}(film)/cm^{-1} 3397 (OH), 2977, 2953, 2934 (CH), 1686 (CO); $[\alpha]_D^{21} = -1.6$ (*c* 0.2, $CHCl_3$); δ_H (270 MHz; $CDCl_3$) 5.19 (1H, br d, *J*=8 Hz), 4.68 (2H, s), 4.41 (1H, br s), 3.97 (1H, br m), 3.7–3.6 (4H, m), 2.2–1.8 (6H, m), 1.7–1.5 (2H, m), 1.44 (9H, s), 0.96 (2H, t, *J*=8.5 Hz), 0.03 (9H, s); δ_C (100 MHz; $CDCl_3$) 156.3, 95.3, 80.1, 73.3, 71.6, 65.4, 47.3, 42.5, 35.9, 35.6, 28.4, 18.1, 13.0, −1.5. (Found: MH^+, 376.2521. $C_{18}H_{37}NO_5Si$ requires MH, 376.2519 (−0.4 ppm)).

3.3.3. [3-(*RS*)-Hydroxy-3-phenyl-1-(*S*)-(2-trimethylsilanyl-ethoxymethoxymethyl)-propyl]-carbamic acid *tert*-butyl ester 18. 162 mg, 98%. Crude ratio 3:2.

Diastereomer 1. Colourless oil; R_f 0.25 (1:1, petrol(40–60)–Et_2O); ν_{max}(film)/cm^{-1} 3422 (OH), 2954, 2894 (CH), 1689 (CO); $[\alpha]_D^{21} = -0.3$ (*c* 0.6, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 7.5–7.2 (5H, m), 5.29 (1H, br d, *J*=8 Hz), 4.8–4.6 (3H, m), 4.46 (1H, d, *J*=3.5 Hz), 4.10 (1H, br s), 3.7–3.5 (4H, m), 1.93 (1H, m), 1.75 (1H, m), 1.48 (9H, s), 0.93 (2H, t, *J*=8.5 Hz), 0.00 (9H, s); δ_C (100 MHz; $CDCl_3$) 156.3, 144.1, 128.2, 127.0, 125.5, 95.2, 80.1, 70.8, 69.9, 65.4, 47.5, 43.3, 28.3, 18.0, −1.5. (Found: MH^+, 412.2519. $C_{21}H_{37}NO_5Si$ requires MH, 412.2519 (0.0 ppm)).

Diastereomer 2. Colourless oil; R_f 0.12 (1:1, petrol(40–60)–Et_2O); ν_{max}(film)/cm^{-1} 3373 (OH), 2953, 2893 (CH), 1696 (CO); $[\alpha]_D^{21} = +17.0$ (*c* 0.3, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 7.4–7.2 (5H, m), 5.10 (1H, br d), 4.78 (1H, t, *J*=6.5 Hz), 4.65 (2H, s), 3.89 (1H, br s), 3.7–3.5 (4H, m), 3.26 (1H, br s), 1.97 (2H, t, *J*=6.5 Hz) 1.43 (9H, s), 0.93 (2H, t, *J*=8.5 Hz), 0.00 (9H, s); δ_C (100 MHz; $CDCl_3$) 155.8, 144.6, 128.4, 127.4, 125.7, 95.1, 79.5, 72.0, 70.2, 65.4, 48.6, 42.0, 28.4, 18.0, −1.5.

3.3.4. [3-Oxo-1-(*S*)-(2-trimethylsilanyl-ethoxymethoxymethyl)-butyl]-carbamic acid *tert*-butyl ester 21. 170 mg, 82%. Colourless oil; R_f 0.09 (2:1, petrol(40–60)–Et_2O); ν_{max}(film)/cm^{-1} 3348 (NH), 2954 (CH), 1715 (CO); $[\alpha]_D^{21} = -2.3$ (*c* 1.2, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 5.15 (1H, br d, *J*=7 Hz), 4.63 (2H, s), 4.11 (1H, br m), 3.7–3.5

(4H, m), 2.8–2.65 (2H, m), 2.15 (3H, s), 1.42 (9H, s), 0.93 (2H, t, $J=8.5$ Hz), 0.02 (9H, s); δ_C (100 MHz; $CDCl_3$) 207.5, 155.4, 95.3, 79.6, 69.2, 65.5, 47.1, 44.9, 30.5, 28.5, 18.2, −1.3. (Found: MH^+, 348.2201. $C_{16}H_{33}NO_5Si$ requires MH, 348.2206 (1.4 ppm)).

3.3.5. [3-Oxo-3-phenyl-1-(*S*)-(2-trimethylsilanyl-ethoxymethoxymethyl)-propyl]-carbamic acid *tert*-butyl ester 23. 214 mg, 80%. Colourless oil; R_f 0.39 (1:1, petrol(40–60)–Et_2O); ν_{max}(film)/cm^{-1} 3356 (NH), 2954 (CH), 1715, 1688 (2×CO); $[\alpha]_D^{21}=+6.6$ (*c* 1.0, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 7.96 (2H, d, $J=7.5$ Hz), 7.56 (1H, t, $J=7.5$ Hz), 7.45 (2H, t, $J=7.5$ Hz), 5.32 (1H, br d, $J=7.5$ Hz), 4.63 (2H, s), 4.28 (1H, br m), 3.75 (1H, dd, $J=4$, 9.5 Hz), 3.64 (1H, dd, $J=5$, 9.5 Hz), 3.54 (2H, t, $J=8.5$ Hz), 3.36 (1H, br m), 3.23 (1H, dd, $J=7$, 16.5 Hz), 1.42 (9H, s) 0.89 (2H, t, $J=8.5$ Hz), −0.03 (9H, s); δ_C (100 MHz; $CDCl_3$) 199.0, 155.6, 137.2, 133.6, 129.0, 128.4, 95.5, 79.7, 69.3, 65.7, 47.7, 39.9, 28.7, 18.4, −1.1. (Found: MH^+, 410.2362. $C_{21}H_{35}NO_5Si$ requires MH, 410.2363 (0.3 ppm)).

3.3.6. 3-(*S*)-*tert*-Butoxycarbonylamino-4-(2-trimethylsilanyl-ethoxymethoxy)-butyric acid methyl ester 25. An excess of $TMSCHN_2$ (~1.2 equiv, 2 M in ether) was added to the crude carboxylic acid in MeOH–PhMe at 0 °C. The reaction was then evaporated delivering the crude ester, which was purified on silica gel.
102 mg, 70%. Colourless oil; R_f 0.16 (2:1, petrol(40–60)–Et_2O); ν_{max}(film)/cm^{-1} 3356 (NH), 2954 (CH), 1741, 1718 (2×CO); $[\alpha]_D^{21}=-2.2$ (*c* 0.9, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 5.19 (1H, br d, $J=8$ Hz), 4.65 (2H, s), 4.13 (1H, br s), 3.67 (3H, s), 3.65–3.5 (4H, m), 2.7–2.5 (2H, m), 1.43 (9H, s), 0.93 (2H, t, $J=8.5$ Hz), 0.02 (9H, s); δ_C (100 MHz; $CDCl_3$) 172.0, 155.3, 95.3, 79.6, 69.1, 65.5, 51.8, 47.4, 36.2, 28.5, 18.2, −1.3. (Found: MH^+, 364.2154. $C_{16}H_{33}NO_6Si$ requires MH, 364.2155 (0.4 ppm)).

3.3.7. [2-Trimethylsilanyl-1-(*R*)-(2-trimethylsilanyl-ethoxymethoxymethyl)-ethyl]-carbamic acid *tert*-butyl ester 27. 158 mg, 78%. Colourless oil; R_f 0.11 (6:1, petrol(40–60)–Et_2O); ν_{max}(film)/cm^{-1} 3360 (NH), 2954, 2897 (CH), 1716 (CO); $[\alpha]_D^{21}=-11.6$ (*c* 1.0, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 4.7–4.65 (3H, m), 3.88 (1H, br s), 3.61 (2H, m), 3.55–3.4 (2H, m), 1.43 (9H, s), 0.94 (2H, m), 0.85 (2H, d, $J=7$ Hz), 0.04 (9H, s), 0.02 (9H, s); δ_C (100 MHz; $CDCl_3$) 155.0, 95.1, 79.0, 72.5, 65.2, 47.7, 28.5, 20.6, 18.1, −1.0, −1.4. (Found: MH^+, 378.2497. $C_{17}H_{39}NO_4Si_2$ requires MH, 378.2496 (−0.4 ppm)).

3.3.8. [1-(*S*)-Deuteromethyl-2-(2-trimethylsilanyl-ethoxymethoxy)-ethyl]-carbamic acid *tert*-butyl ester 30. 101 mg, 87%. Colourless oil; R_f 0.40 (2:1, petrol(40–60)–Et_2O); ν_{max}(film)/cm^{-1} 3351 (NH), 2954 (CH), 1715 (CO); $[\alpha]_D^{21}=-13.6$ (*c* 1.0, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 4.78 (1H, br s), 4.65 (2H, s), 3.91 (1H, br s), 3.60 (2H, t, $J=8.5$ Hz), 3.48 (2H, m), 1.42 (9H, s), 1.15 (2H, m), 0.93 (2H, t, $J=8.5$ Hz), 0.00 (9H, s); δ_C (100 MHz; $CDCl_3$) 155.5, 92.2, 79.2, 71.4, 65.3, 46.3, 28.5, 18.2, 17.8 (t, $J=19.8$ Hz, CH_2D), −1.3. (Found: MH^+, 307.2162. $C_{14}H_{31}NDO_4Si$ requires MH, 307.2163 (0.5 ppm)).

3.3.9. [2-Tributylstannanyl-1-(*R*)-(2-trimethylsilanyl-ethoxymethoxymethyl)-ethyl]-carbamic acid *tert*-butyl ester 33. 174 mg, 51%. Colourless oil; R_f 0.31 (9:1, petrol(40–60)–Et_2O); ν_{max}(film)/cm^{-1} 3350 (NH), 2954, 2914 (CH), 1716 (CO); $[\alpha]_D^{21}=-8.6$ (*c* 0.9, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 4.66–4.62 (3H, m), 3.92 (1H, bs), 3.63–3.59 (2H, m), 3.49–3.41 (2H, m), 1.60–1.25 (22H, m), 0.96–0.83 (19H, m), 0.02 (9H, s); δ_C (100 MHz; $CDCl_3$) 155.1, 95.2, 79.1, 72.8, 65.3, 49.6, 29.3, 28.6, 27.5, 18.2, 13.8, 13.4, 9.4, −1.3. (Found: MH^+, 592.3141. $C_{26}H_{57}NO_4Si^{116}Sn$ requires MH, 592.3153 (1.9 ppm)).

3.3.10. [2-(*R*)-(*tert*-Butoxycarbonylamino-3-(2-trimethylsilanyl-ethoxymethoxy)-propyl]-phosphonic acid diethyl ester 34. 136 mg, 70%. Colourless oil; R_f 0.32 (2:1, EtOAc–petrol(40–60)); ν_{max}(film)/cm^{-1} 3298 (NH), 2978, 2955, 2931 (CH), 1714 (CO), 1249 (P=O), 1174 (PO); $[\alpha]_D^{21}=-8.8$ (*c* 1.2, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 5.23 (1H, br d, $J=6.0$ Hz), 4.64 (2H, s), 4.10–4.05 (5H, m), 3.69 (1H, dd, $J=4.0$, 10.0 Hz), 3.67–3.54 (3H, m), 2.08 (2H, dd, $J=6.0$, 18.0 Hz), 1.40 (9H, s), 1.29 (6H, t, $J=7.0$ Hz), 0.95 (2H, t, $J=8.5$ Hz) 0.02 (9H, s); δ_C (100 MHz; $CDCl_3$) 155.1, 95.3, 79.5, 69.7 (d, $^3J_{C,P}=7.5$ Hz), 65.5, 61.9 (d, $^2J_{C,P}=7.0$ Hz), 61.8 (d, $^2J_{C,P}=6.0$ Hz), 46.4, 27.8 (d, $^1J_{C,P}=131.0$ Hz), 18.1, 16.5 (d, $^3J_{C,P}=6.0$ Hz) −1.3. (Found: MH^+, 442.2386. $C_{19}H_{40}NO_7SiP$ requires MH, 442.2390 (0.9 ppm)).

3.4. General SEM deprotection procedure

0.1 M HCl[18] in methanol (2 mL, ~6 mL/mmol) was added to a SEM-ether (0.28 mmol). The subsequent reaction mixture was stirred at room temperature for 3 h. Excess triethylamine (~0.1 mL) was then added and the volatiles were removed under reduced pressure to deliver a crude mixture, this was then purified by flash column chromatography on silica gel, eluting with diethyl ether to give the product.

3.4.1. [2-(1-Hydroxy-cyclohexyl)-1-(*S*)-hydroxymethyl-ethyl]-carbamic acid *tert*-butyl ester 13e. 62 mg, 79%, 9% s.m. recovered, 88% b.s.m.r. Colourless oil; R_f 0.20 (Et_2O); ν_{max}(film)/cm^{-1} 3348 (OH), 2933, 2861 (CH), 1689 (CO); $[\alpha]_D^{21}=-5.8$ (*c* 0.8, $CHCl_3$); δ_H (270 MHz; $CDCl_3$) 5.31 (1H, br s), 3.83 (1H, br m), 3.66 (1H, dd, $J=5$, 11 Hz), 3.58 (1H, dd, $J=4$, 11 Hz), 1.7–1.35 (21H, m); δ_C (67.5 MHz; $CDCl_3$) 156.2, 79.8, 71.1, 66.4, 49.2, 43.1, 38.0, 37.8, 28.4, 25.6, 22.2, 22.1. (Found: MH^+, 274.2016. $C_{14}H_{27}NO_4$ requires MH, 274.2018 (0.8 ppm)).

3.4.2. [2-(1-Hydroxy-cyclobutyl)-1-(*S*)-hydroxymethyl-ethyl]-carbamic acid *tert*-butyl ester 16. 86 mg, 65%, 11% s.m. recovered, 76% b.s.m.r. Colourless oil; R_f 0.20 (Et_2O); ν_{max}(film)/cm^{-1} 3339 (OH), 2980, 2935 (CH), 1682 (CO); $[\alpha]_D^{21}=-0.5$ (*c* 0.4, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 5.22 (1H, br s), 4.27 (1H, br s), 3.81 (1H, br m), 3.51 (2H, br m), 3.45 (1H, br s), 2.15–2.05 (2H, m), 1.89 (1H, dd, $J=9$, 14 Hz), 1.85–1.7 (2H, m), 1.58 (1H, m), 1.42 (9H, s); δ_C (100 MHz; $CDCl_3$) 156.8, 80.0, 73.9, 65.7, 49.4, 41.2, 36.2, 35.8, 28.4, 12.7. (Found: MH^+, 246.1703. $C_{12}H_{23}NO_4$ requires MH, 246.1705 (0.9 ppm)).

3.4.3. (3-(*RS*)-Hydroxy-1-(*S*)-hydroxymethyl-3-phenyl-propyl)-carbamic acid *tert*-butyl ester 19. 87 mg, 64%, 15% s.m. recovered, 79% b.s.m.r.

Diastereomer 1. Colourless oil; R_f 0.29 (Et_2O); ν_{max}(film)/cm^{-1} 3382 (NH, OH), 2978, 2932 (CH), 1683 (CO); $[\alpha]_D^{21} = -7.5$ (*c* 2.0, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 7.4–7.2 (5H, m), 5.18 (1H, br d, $J=7.5$ Hz), 4.73 (1H, br d, $J=8.5$ Hz), 4.11 (1H, br s), 3.95 (1H, br m), 3.72 (1H, br d, $J=8.5$ Hz), 3.63 (1H, dd, $J=4$, 10.5 Hz), 2.60 (1H, br s), 1.82 (2H, m), 1.46 (9H, s); δ_C (100 MHz; $CDCl_3$) 157.3, 144.1, 128.4, 127.3, 125.5, 80.2, 70.4, 65.4, 49.7, 42.3, 28.3. (Found: MH^+, 282.1711. $C_{15}H_{24}NO_4$ requires MH, 282.1705 (−1.8 ppm)).

Diastereomer 2. Colourless oil; R_f 0.17 (Et_2O); ν_{max}(film)/cm^{-1} 3358 (NH, OH), 2976, 2931 (CH), 1686 (CO); $[\alpha]_D^{21} = +33.8$ (*c* 0.8, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 7.35–7.25 (5H, m), 5.25 (1H, br s), 4.84 (1H, br d, $J=7$ Hz), 3.78 (1H, br s), 3.67 (2H, br s), 3.30 (1H, br s), 2.03 (1H, ddd, $J=4.6$, 15 Hz), 1.92 (1H, ddd, $J=6.5$, 9, 15 Hz), 1.45 (9H, s); δ_C (100 MHz; $CDCl_3$) 156.5, 144.4, 128.8, 127.9, 125.8, 79.9, 71.9, 65.9, 51.0, 41.3, 28.5. (Found: MH^+, 282.1700. $C_{15}H_{24}NO_4$ requires MH, 282.1705 (2.0 ppm)).

3.4.4. (*S*)-(5-Oxo-tetrahydro-furan-3-yl)-carbamic acid *tert*-butyl ester 26. Crude mixture was treated with CSA (~10 mol%) in benzene at 80 °C overnight. Evaporation and purification on silica gel, eluting with Et_2O–petrol(40–60) 1:2, gave the product (27 mg, 50%, 15% s.m. recovered, 65% b.s.m.r.). Colourless blades, mp 109–110 °C (Et_2O), (lit.[19b] 113–114 °C); ν_{max}(film)/cm^{-1} 3317 (NH), 1767, 1687 (CO); $[\alpha]_D^{21} = -64.2$ (*c* 0.5, $CHCl_3$); ^1H NMR was identical to that reported in the literature.[19b]

3.4.5. (1-(*R*)-Hydroxymethyl-2-trimethylsilanyl-ethyl)-carbamic acid *tert*-butyl ester 28. 71 mg, 72%. Colourless oil; R_f 0.48 (Et_2O); ν_{max}(film)/cm^{-1} 3256 (OH), 2954 (CH), 1695 (CO); $[\alpha]_D^{21} = -14.6$ (*c* 0.8, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 4.51 (1H, br s), 3.79 (1H, br s), 3.63 (1H, br d, $J=9$ Hz), 3.44 (1H, dd, $J=6.5$, 10.5 Hz), 2.47 (1H, br s), 1.44 (9H, s), 0.74 (2H, m), 0.05 (9H, s); δ_C (100 MHz; $CDCl_3$) 156.6, 80.0, 69.1, 50.6, 28.8, 20.1, −0.72. (Found: MH^+, 248.1679. $C_{11}H_{25}NO_3Si$ requires MH, 248.1682 (1.2 ppm)).

3.4.6. (2-Hydroxy-1-(*S*)-deuteromethyl-ethyl)-carbamic acid *tert*-butyl ester 31. 34 mg, 70%. Colourless oil; R_f 0.42 (Et_2O); ν_{max}(film)/cm^{-1} 3361 (OH), 2978, 2936 (CH), 1690 (CO); $[\alpha]_D^{21} = -12.6$ (*c* 1.1, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 4.71 (1H, br s), 3.68 (1H, br s), 3.55 (1H, m), 3.43 (1H, dd, $J=6.0$, 10.5 Hz), 3.00 (1H, br s), 1.38 (9H, s), 1.07 (2H, m); δ_C (100 MHz; $CDCl_3$) 156.6, 79.8, 67.4, 48.6, 28.5, 17.2 (t, $J=19$ Hz, CH_2D). (Found: MH^+, 177.1353. $C_8H_{17}NDO_3$ requires MH, 177.1350 (2.2 ppm)).

3.4.7. (2-(*R*)-*tert*-Butoxycarbonylamino-3-hydroxy-propyl)-phosphonic acid diethyl ester 35. 0.1 M HCl in ethanol was employed in this deprotection using the general procedure described above. (54 mg, 66%, 10% s.m. recovered, 76% b.s.m.r.). Colourless oil; R_f 0.30 (9:1, EtOAc–MeOH); ν_{max}(film)/cm^{-1} 3358 (OH, NH), 2978, 2933 (CH), 1713 (CO), 1249 (P=O), 1172 (PO); $[\alpha]_D^{21} = +14.9$ (*c* 0.7, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 5.23 (1H, br d, $J=8.0$ Hz), 4.11–4.07 (4H, m), 3.94–3.89 (1H, m), 3.78 (1H, dd, $J=4.0$, 11.5 Hz), 3.66 (1H, dd, $J=4.0$, 11.5 Hz), 2.21–2.01 (2H, m), 1.41 (9H, s), 1.31 (6H, t, $J=7.0$ Hz); δ_C (100 MHz; $CDCl_3$) 155.7, 79.7, 64.8 (d, $^3J_{C,P}=6.0$ Hz), 62.1 (d, $^2J_{C,P}=5.0$ Hz), 62.1 (d, $^2J_{C,P}=5.0$ Hz), 48.3, 28.5, 27.8 (d, $^1J_{C,P}=133.5$ Hz), 16.5 (d, $^3J_{C,P}=6.0$ Hz). (Found: MH^+, 312.1576. $C_{12}H_{26}NO_6P$ requires MH, 312.1576 (0.0 ppm)).

3.5. General oxidation procedures

3.5.1. Method A. PDC (1.1 mmol, 6 equiv) was added to a stirred solution of the diol (0.18 mmol, 1 equiv) in anhydrous dimethylformamide (1.5 mL, ~8 mL/mmol). The reaction mixture was stirred for 6 h, then water (5 mL) was added and the mixture was extracted with dichloromethane (2×15 mL). The combined extracts were then washed with water (2×20 mL) and brine (20 mL), then dried ($MgSO_4$) and evaporated under reduced pressure. The crude residue was purified on silica gel, eluting with petrol(40–60)–Et_2O 1:1, delivering the product.

3.5.1.1. (*S*)-(2-Oxo-1-oxa-spiro[4.5]dec-4-yl)-carbamic acid *tert*-butyl ester 14. Method A (34 mg, 69%) white foam; R_f 0.20 (1:1, petrol(40–60)–Et_2O); ν_{max}(film)/cm^{-1} 3365 (NH), 2937, 2863 (CH), 1778, 1697 (2×CO); $[\alpha]_D^{21} = +17.7$ (*c* 1.1, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 5.05 (1H, br s), 4.51 (1H, br s), 2.73 (1H, br t, $J=10$ Hz), 1.8–1.4 (20H, m); δ_C (100 MHz; $CDCl_3$) 175.0, 155.8, 84.9, 80.8, 51.0, 41.4, 38.6, 36.1, 28.6, 25.2, 22.9, 22.8. (Found: MNH_4^+, 287.1977. $C_{14}H_{23}NO_4$ requires MNH_4, 287.1971 (−2.1 ppm)).

3.5.1.2. (*S*)-(6-Oxo-5-oxa-spiro[3.4]oct-7-yl)-carbamic acid *tert*-butyl ester 17. Method A (63 mg, 74%) amorphous solid; ν_{max}(film)/cm^{-1} 3321 (NH), 2976, 2945 (CH), 1761, 1712 (2×CO); $[\alpha]_D^{21} = +1.2$ (*c* 1.1, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 5.06 (1H, br s), 4.41 (1H, br m), 2.95 (1H, br m), 2.63 (1H, q, $J=10$ Hz), 2.36 (1H, q, $J=10$ Hz), 2.25–1.95 (3H, m), 1.88 (1H, m), 1.67 (1H, m), 1.45 (9H, s); δ_C (100 MHz; $CDCl_3$) 174.8, 155.8, 83.2, 80.9, 50.9, 41.5, 34.6, 28.7, 28.3, 12.7. (Found: MH^+, 242.1398. $C_{12}H_{19}NO_4$ requires MH, 242.1392 (−2.3 ppm)).

3.5.2. Method B. PDC (1.2 mmol, 6 equiv) was added to a stirred solution of alcohol (0.29 mmol, 1 equiv) in anhydrous dimethylformamide (3 mL, ~8 mL/mmol). The reaction mixture was stirred for 18 h, then quenched with water (5 mL) and extracted with EtOAc (2×20 mL). The combined extracts were then washed with water (2×20 mL) and brine (20 mL), then dried ($MgSO_4$) and evaporated under reduced pressure to deliver the crude carboxylic acid. This was then dissolved in MeOH–toluene (3 mL, 1:1) and treated with $TMSCHN_2$ (0.29 mL, 0.58 mmol, 2.0 M solution in hexanes) at 0 °C. The reaction was stirred for 1 h then all volatiles were removed under reduced pressure to deliver a crude mixture, which was then purified by flash column chromatography on silica gel, eluting with Et_2O–petrol(40–60) 1:2 to give the product.

3.5.2.1. 2-(*S*)-*tert*-Butoxycarbonylamino-4-oxo-4-phenyl-butyric acid methyl ester 20. Method B (36 mg, 47%) colourless oil; R_f 0.25 (1:1, petrol(40–60)–Et_2O); ν_{max}(film)/cm^{-1} 3383 (NH), 2979, 2932 (CH), 1748, 1714 (2×CO); $[\alpha]_D^{21} = +59.9$ (*c* 1.1, DCM); ^1H NMR spectrum identical to literature.[20] *m/z* 308 (10, M^+), 252 (40, M−*t*Bu), 208 (100, M−Boc).

3.5.2.2. 2-(*R*)-*tert*-Butoxycarbonylamino-3-trimethylsilanyl-propionic acid methyl ester 29. Method B (54 mg, 68%) colourless waxy solid, mp 40–42 °C; R_f 0.34 (2:1, petrol(40–60)–Et_2O); ν_{max}(film)/cm^{-1} 3373 (NH), 2977, 2955 (CH), 1745, 1715 (2×CO); $[\alpha]_D^{21}=+10.8$ (*c* 1.2, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 4.84 (1H, br s), 4.28 (1H, br m), 3.67 (3H, s), 1.37 (9H, s), 1.05 (1H, dd, *J*=6, 9.5 Hz), 0.88 (1H, dd, *J*=9.5, 14.5 Hz), 0.00 (9H, s); δ_C (100 MHz; $CDCl_3$) 174.3, 154.9, 79.8, 52.1, 50.6, 28.4, 21.4, −1.3. (Found: MH$^+$, 276.1633. $C_{12}H_{25}NO_4Si$ requires MH, 276.1631 (−0.6 ppm)).

3.5.2.3. 2-(*R*)-*tert*-Butoxycarbonylamino-3-(diethoxyphosphoryl)-propionic acid methyl ester 36. Method B (61 mg, 60%) colourless oil, R_f 0.50 (9:1, EtOAc–MeOH); ν_{max}(film)/cm^{-1} 3371 (NH), 2982, 2929 (CH), 1751 (CO), 1716 (CO), 1249 (P=O), 1166 (PO); $[\alpha]_D^{21}=+12.8$ (*c* 1.0, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 5.68 (1H, br d, *J*=7.5 Hz), 4.58–4.46 (1H, m), 4.10–4.03 (4H, m), 3.73 (3H, s), 2.34–2.27 (2H, m), 1.41 (9H, s), 1.29 (6H, t, *J*=7.0 Hz); δ_C (100 MHz; $CDCl_3$) 171.5 (d, $^3J_{C,P}$=8.0 Hz), 155.3, 80.2, 62.1 (d, $^2J_{C,P}$=4.0 Hz), 62.1 (d, $^2J_{C,P}$=3.0 Hz), 52.7, 49.2 (d, $^2J_{C,P}$=5.0 Hz), 28.4, 28.0 (d, $^1J_{C,P}$=141.5 Hz), 16.5 (d, $^3J_{C,P}$=2.0 Hz), 16.4 (d, $^3J_{C,P}$=2.0 Hz). (Found: MH$^+$, 340.1523. $C_{13}H_{26}NO_7P$ requires MH, 340.1525 (0.6 ppm)).

3.5.3. Method C.

3.5.3.1. (*S*)-*N*-Boc-deuteroalanine methyl ester 32. Ruthenium chloride (4 mg, 21 μmol, 5 mol%) was added to a stirred suspension of alcohol **31** (75 mg, 0.43 mmol) and sodium periodate (273 mg, 1.28 mmol) in CH_3CN–H_2O–CCl_4 (3 mL, 2:3:2) at room temperature. The reaction mixture went dark after 30 min. Stirring was continued for 12 h in total then the reaction was diluted with a saturated solution of ammonium chloride (10 mL) and EtOAc (10 mL). After separation the aqueous was extracted again with EtOAc (2×10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to deliver the crude carboxylic acid. This was then dissolved in MeOH–toluene (2 mL, 1:1) and treated with $TMSCHN_2$ (0.42 mL, 0.85 mmol, 2.0 M solution in hexanes) at 0 °C. The reaction was stirred for 1 h then all volatiles were removed under reduced pressure to deliver a crude mixture, which was then purified by flash column chromatography on silica gel, eluting with Et_2O–petrol(40–60) 1:2 to give the protected amino acid **32** (53 mg, 61%) as a colourless oil; R_f 0.20 (2:1, petrol(40–60)–Et_2O); ν_{max}(film)/cm^{-1} 3382 (NH), 2980 (CH), 1748, 1716 (2×CO); $[\alpha]_D^{21}=-43.5$ (*c* 1.4, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 5.03 (1H, br s), 4.31 (1H, br m), 3.74 (3H, s), 1.44 (9H, s), 1.36 (2H, br d, *J*=7.5 Hz); δ_C (100 MHz; $CDCl_3$) 174.0, 155.2, 80.0, 52.3, 49.2, 28.5, 18.6 (t, *J*=20 Hz, *C*H_2D). (Found: MH$^+$, 205.1296. $C_9H_{17}NDO_4$ requires MH, 205.1299 (1.3 ppm)).

3.6. General amino acid deprotection procedure

The protected amino acid (~50 mg, 0.25 mmol) was heated at 70 °C with 4.5 M HCl (~2 mL) for 3 h. After cooling, the aqueous phase was diluted with water (10 mL) and washed with diethyl ether (10 mL). The aqueous phase was then evaporated under reduced pressure delivering a solid which was triturated with diethyl ether. After decanting and drying, the product was obtained.

3.6.1. 2-(*S*)-Amino-4-oxo-4-phenyl-butyric acid hydrochloride 37. 24 mg, 92%. White powder, mp ~200 °C decomposed (lit.[21] mp 207–209 °C decomposed); $[\alpha]_D^{21}=+35.6$ (*c* 0.104, 6 M HCl), lit.[21] $[\alpha]_D=+34.7$ (*c* 0.098, 6 M HCl); ^{1}H NMR spectrum identical to literature.[21]

3.6.2. (*R*)-Trimethylsilanylalanine hydrochloride 38. 31 mg, 80%. White solid, mp ~180 °C decomposed; $[\alpha]_D^{22}=+35.2$ (*c* 1.1, 1 M HCl), lit.[23] $[\alpha]_D=+31$ (*c* 0.51, 4 M HCl); δ_H (400 MHz; D_2O) 4.01 (1H, dd, *J*=5.5, 10.5 Hz), 1.22 (1H, dd, *J*=10.5, 14.5 Hz), 1.16 (1H, dd, *J*=5.5, 14.5 Hz), 0.08 (9H, s); δ_C (100 MHz; D_2O) 17.3, 51.7, 19.3, −2.3; *m/z* (ESI) 176 (100%, M$^+$), 162 (35%, M−Cl).

3.6.3. (*S*)-Deuteroalanine hydrochloride 39. 31 mg, 95%. Off-white wax; $[\alpha]_D^{21}=+11.7$ (*c* 1.2, 6 M HCl); δ_H (400 MHz, D_2O) 4.09 (1H, t, *J*=7.5 Hz), 1.50 (2H, d, *J*=7.5 Hz); δ_C (100 MHz; D_2O) 172.8, 48.7, 15.0 (t, *J*=20 Hz, *C*H_2D). (Found: M−Cl$^+$, 91.0620. $C_3H_7NClO_2D$ requires M−Cl, 91.0618 (1.9 ppm)).

3.6.4. 2-(*S*)-Amino-3-phosphono-propionic acid 40. The protected amino acid **36** (61 mg, 0.18 mmol) was heated with 6 M HCl (~3 mL) under reflux for 21 h. After cooling, the aqueous phase was diluted with water (5 mL) and washed with ethyl acetate (2×5 mL). The aqueous phase was then evaporated under reduced pressure delivering an off-white solid which was triturated with diethyl ether. After decanting and drying, the salt was obtained as an off-white solid. Propylene oxide (~1 mL) was added dropwise to a suspension of the salt in EtOH (~1 mL) at 0 °C and the resulting mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure delivering a white solid. Recrystallisation from 50% EtOH/H_2O followed by trituration with EtOH gave the phosphate **40** (18 mg, 59%) as a white solid, mp ~225 °C decomposed, lit.[24b] 224–226 °C decomposed; $[\alpha]_D^{21}=+16.3$ (*c* 0.4, 1 M NaOH), lit.[24b] $[\alpha]_D^{24}=+13.8$ (*c* 2, 1 M NaOH); δ_H (400 MHz; D_2O) 4.17–4.12 (1H, m), 2.36–2.26 (1H, m), 2.14–2.04 (1H, m); δ_C (100 MHz; D_2O) 172.1 (d, $^3J_{C,P}$=13.0 Hz), 49.9 (d, $^2J_{C,P}$=4.5 Hz), 28.2 (d, $^1J_{C,P}$=131.0 Hz); *m/z* ESI (−ve) 168 ([M−H$^+$]$^-$, 100%).

3.7. Synthesis of aspartic acid mimic 44

3.7.1. [2-Borono-1-(*S*)-(2-trimethylsilanyl-ethoxymethoxymethyl)-ethyl]-carbamic acid *tert*-butyl ester 41. *n*-BuLi (0.48 mL, 0.95 mmol, 1.97 M solution in hexanes) was added dropwise to a stirred solution of chloride **11d** (291 mg, 0.89 mmol) in THF (5 mL) at −78 °C under an atmosphere of argon. Stirring was continued for 15 min, followed by the dropwise addition of LiNp (5.7 mL, 2.83 mmol, 0.5 M solution in THF) over 5 min. The dark solution was stirred at −78 °C for 2 h. Subsequently triisopropylborate (0.5 mL, 2.15 mmol) was added dropwise to the solution. The reaction mixture was kept cold (ca. −78 to −40 °C) overnight then quenched with a saturated solution of ammonium chloride (1 mL), then allowed to warm to room temperature. To the mixture was then added an aqueous solution of 0.5 M HCl (5 mL, saturated with NaCl), and stirring was continued for 30 min. The solution was then extracted with petrol(40–60) (3× 20 mL). The combined organics were then extracted with

2 M NaOH (3×15 mL). These extracts were combined and acidified (~pH 1–2) with 4.5 M HCl, then extracted again with Et_2O (3×30 mL). The final combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the boronic acid **41** (238 mg, 80%) as a light yellow oil. δ_H (400 MHz; acetone-d^6) 6.95–6.8 (1H, br), 6.55–6.45 (1H, br), 5.88 (1H, br s), 4.63 (2H, s), 3.88 (1H, br m), 3.63 (2H, m), 3.53 (1H, dd, J=5.5, 9.5 Hz), 3.47 (1H, dd, J=5.5, 9.5 Hz), 1.5–1.35 (9H, several singlets), 1.07 (1H, dd, J=6, 16 Hz), 1.00 (2H, m), 0.05–0.00 (9H, several singlets). Due to the many possible solution structures of the boronic acid, the compound was better characterised as the boronate ester **42**.

3.7.2. [2-(−)-Pinaneboronate-1-(*S*)-(2-trimethylsilanylethoxymethoxymethyl)-ethyl]-carbamic acid *tert*-butyl ester 42. (−)-Pinane diol (47 mg, 0.28 mmol) was added to a stirred solution of **41** (88 mg, 0.25 mmol) and powdered 4 Å molecular sieves (~100 mg) in dry dichloromethane (3 mL) under an atmosphere of argon. The reaction mixture was stirred for 18 h then filtered and evaporated. The subsequent residue was purified on silica gel, eluting with petrol(40–60)–Et_2O 3:1, delivering boronate ester **42** (113 mg, 95%) as a colourless oil; R_f 0.26 (3:1, petrol(40–60)–Et_2O); ν_{max}(film)/cm^{-1} 2926 (CH), 1718 (CO); $[\alpha]_D^{21}=-200$ (c 0.1, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 5.06 (1H, br d, J=7 Hz), 4.65 (2H, s), 4.25 (1H, dd, J=2, 9 Hz), 4.01 (1H, br s), 3.60 (2H, t, J=8.5 Hz), 3.53 (2H, d, J=4.5 Hz), 2.32 (1H, m), 2.20 (1H, m), 2.03 (1H, t, J=5 Hz), 1.9–1.8 (2H, m), 1.43 (9H, s), 1.37 (3H, s), 1.28 (3H, s), 1.2–1.05 (2H, m), 0.93 (2H, t, J=8.5 Hz), 0.9–0.8 (4H, m), 0.02 (9H, s); δ_C (100 MHz; $CDCl_3$) 155.4, 95.1, 85.8, 77.8, 71.5, 65.3, 51.4, 39.6, 38.3, 36.2, 35.6, 29.2, 28.7, 28.6, 27.2, 26.6, 24.2, 22.8, 18.2, −1.3. (Found: MH^+, 484.3271. $C_{24}H_{46}NBO_6Si$ requires MH, 484.3266 (−1.1 ppm)).

3.7.3. (2-(−)-Pinaneboronate-1-(*S*)-hydroxymethylethyl)-carbamic acid *tert*-butyl ester 43. 0.1 M HCl in methanol (2 mL, ~6 mL/mmol) was added to SEM-ether **42** (99 mg, 0.21 mmol). The subsequent reaction mixture was stirred at room temperature for 3 h. Excess triethylamine (~0.1 mL) was then added and the volatiles were removed under reduced pressure to deliver a crude mixture, which was then purified by flash column chromatography on silica gel, eluting with petrol(40–60)–Et_2O 1:2 to give starting material (4 mg, 4%) and the alcohol **43** (49 mg, 68%) as a colourless oil; R_f 0.51 (Et_2O); ν_{max}(film)/cm^{-1} 3420 (OH), 2975, 2929, 2872 (CH), 1694 (CO); $[\alpha]_D^{21}=-148$ (c 0.9, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 5.01 (1H, br s), 4.24 (1H, d, J=2, 9 Hz), 3.89 (1H, br s), 3.60 (1H, br d, J=10.5 Hz), 3.51 (1H, m), 2.31 (1H, m), 2.19 (1H, m), 2.02 (1H, m), 1.95–1.75 (2H, m), 1.41 (9H, s), 1.35 (3H, s), 1.26 (3H, s), 1.25 (1H, m), 1.15–1.0 (2H, m), 0.81 (3H, s). (Found: MH^+, 354.2452. $C_{18}H_{32}NBO_5$ requires MH, 354.2452 (−0.2 ppm)).

3.7.4. 2-(*S*)-Amino-3-boronopropionic acid 44. Dess–Martin periodinane (78 mg, 0.18 mmol) was added to a stirred solution of **43** (54 mg, 0.15 mmol) in dichloromethane (2 mL) under an atmosphere of argon. After 2 h, 1 M sodium sulfite (5 mL) was added and the mixture was extracted with Et_2O (2×10 mL). The combined organic extracts were washed with 1 M sodium hydrogen carbonate (10 mL), dried (Na_2SO_4) and evaporated. The crude mixture was then dissolved in *t*-butanol (3 mL) and treated with a solution of 2-methyl-2-butene (1.5 mL, 3.1 mmol, 2 M in THF). A solution of NaH_2PO_4 (167 mg, 1.07 mmol) and $NaClO_2$ (125 mg, 1.38 mmol) in water (2 mL) was added and the reaction was stirred for 1 h. The *t*-butanol was evaporated in vacuo and the residue was partitioned between 0.5 M HCl (5 mL) and EtOAc (10 mL). After separation and further extraction (EtOAc 2×5 mL), the combined extracts were dried ($MgSO_4$) and evaporated. The subsequent residue was heated at 70 °C with 4.5 M HCl (3 mL) for 3 h. After cooling the aqueous solution was washed with dichloromethane (2×2 mL). The aqueous solution was then evaporated in vacuo. The crude residue was purified on silica gel, eluting with 2:1 EtOH–14 M NH_3, delivering the 2-amino-3-boronopropionic acid **44** (15 mg, 74%) as a white solid. After trituration with acetone the product was obtained as a white powder, mp >290 °C decomposed. δ_H (400 MHz; D_2O) 3.94 (1H, br t, J=9.5 Hz), 1.08 (1H, br dd, J=9.5, 13 Hz), 0.79 (1H, br dd, J=10.5, 12 Hz); δ_C (100 MHz; D_2O) 178.0, 53.4, 20.4 (br); δ_B[11] (160 MHz; D_2O) 16.38; m/z ESI (-ve) 160 ($[M-H^+]^-$, 75%), 343 ($(2[M-H^+]+Na^+)^-$, 100%). HCl salt[30] $[\alpha]_D^{21}=+33.0$ (c 0.2, 4.5 M HCl); δ_H (400 MHz, D_2O) 4.15 (1H, dd, J=7, 10 Hz), 1.35 (1H, dd, J=7, 15 Hz), 1.19 (1H, dd, J=10, 15 Hz); δ_C (125 MHz; D_2O) 175.3, 52.4, 18.6 (br); δ_B[11] (160 MHz; D_2O) 24.85.

3.8. General procedure for Suzuki coupling of boronic acid 41

The boronic acid **41** (ca. 0.12 mmol), K_2CO_3 (3.0 equiv), $PdCl_2$(dppf).CH_2Cl_2 (0.09 equiv) and Ag_2O (2.4 equiv) were placed under Ar. Tetrahydrofuran (1.0 mL) and the aryl halide (2 equiv) were added and the resulting mixture was refluxed for 21 h. The reaction mixture was filtered through a 0.5 cm pad of Celite™ and eluted with diethyl ether (40 mL). The filtrate was concentrated to afford an oil. Subjection of this material to flash chromatography on silica gel and concentration of the appropriate fractions provided the coupled product.

3.8.1. [1-(*S*)-2-Phenyl-1-(2-trimethylsilanylethoxymethoxymethyl)ethyl]carbamic acid *tert*-butyl ester (48a). 72%. Colourless oil; R_f 0.25 (4:1, petrol(40–60)–Et_2O); ν_{max}/cm^{-1} (thin film) 3352, 2953, 1714, 1497; $[\alpha]_D^{20}=-14.4$ (c 1.1, $CHCl_3$); δ_H (270 MHz, $CDCl_3$) 7.31–7.18 (complex m, 5H), 4.95 (1H, broad d, J=7 Hz), 4.67 (2H, m), 3.94 (1H, br m), 3.63 (2H, m), 3.49 (1H, dd, J=10, 4 Hz) 3.45 (1H, dd, J=10, 4 Hz), 2.91 (1H, br dd, J=13.5, 5 Hz), 2.82 (1H, dd, J=13.5, 8 Hz), 1.41 (9H, s), 0.94 (2H, m), 0.03 (9H, s); δ_C (100 MHz, $CDCl_3$) 155.5, 138.3, 129.5, 128.5, 126.5, 95.4, 79.4, 68.6, 65.5, 51.8, 38.1, 28.5, 18.2, −1.3. (Found (CI^+) MH^+, 382.2413. $C_{20}H_{36}NO_4Si$ requires MH^+, 382.2414 (0.0 ppm)).

3.8.2. [1-(*S*)-2-(4-Methoxyphenyl)-1-(2-trimethylsilanylethoxymethoxymethyl)ethyl]carbamic acid *tert*-butyl ester (48b). 65%. Pale yellow oil; R_f 0.18 (3:1, petrol(40–60)–Et_2O); ν_{max}/cm^{-1} (thin film) 3359, 2953, 1714, 1613, 1513, 1248, 1173; $[\alpha]_D^{20}=-13.1$ (c 0.9, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) δ 7.13 (2H, d, J=8 Hz), 6.82 (2H, d, J=8 Hz), 4.92 (1H, br d, J=8.0 Hz), 4.68 (2H, m), 3.89

(1H, br m), 3.78 (3H, s), 3.63 (2H, m), 3.46 (2H, m), 2.86 (1H, dd, $J=13$, 5 Hz), 2.75 (1H, dd, $J=13$, 8 Hz), 1.42 (9H, s), 0.95 (2H, m), 0.03 (9H, s); δ_C (100 MHz, $CDCl_3$) 158.3, 155.5, 130.5, 130.3, 114.0, 95.4, 79.3, 68.6, 65.5, 55.4, 51.9, 37.1, 28.5, 18.2, −1.3. (Found (CI^+): 412.2520. $C_{21}H_{38}NO_5Si$ requires (MH^+): 412.2519 (0.1 ppm)).

3.8.3. [1-(*S*)-2-(4-Nitrophenyl)-1-(2-trimethylsilanylethoxymethoxymethyl)ethyl]carbamic acid *tert*-butyl ester (48c). 65%. Colourless oil; R_f 0.30 (2:1, petrol(40–60)–Et_2O); ν_{max}/cm^{-1} (thin film) 3412, 2953, 2894, 1714, 1604, 1522, 1346; $[\alpha]_D^{20}=-34.2$ (c 1.4, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) δ 8.14 (2H, d, $J=8.5$ Hz), 7.39 (2H, d, $J=8.5$ Hz), 5.04 (1H, br d, $J=8$ Hz), 4.67 (2H, m), 3.97 (1H, br m), 3.63 (2H, m), 3.50 (2H, d, $J=4$ Hz), 3.02–2.92 (2H, complex m), 1.38 (9H, s), 0.94 (2H, m), 0.02 (9H, s); δ_C (100 MHz, $CDCl_3$) 155.4, 146.8, 146.4, 130.3, 123.7, 95.5, 79.7, 68.9, 65.7, 51.5, 38.2, 28.4, 18.2, −1.3. (Found (CI^+): 427.2266. $C_{20}H_{35}N_2O_6Si$ requires (MH^+): 427.2264 (0.5 ppm)).

3.8.4. [1-(*S*)-2-(2-Nitrophenyl)-1-(2-trimethylsilanylethoxymethoxymethyl)ethyl]carbamic acid *tert*-butyl ester (48d). 70%. Pale yellow oil; R_f 0.17 (2:1, petrol(40–60)–Et_2O); ν_{max}/cm^{-1} (thin film) 3351, 2954, 2892, 1713, 1610, 1528, 1453; $[\alpha]_D^{20}=-22.9$ (c 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) δ 7.91 (1H, d, $J=8$ Hz), 7.52 (1H, dd, $J=8$ Hz, 7.5), 7.42–7.34 (2H, complex m), 5.03 (1H, br d, $J=9$ Hz), 4.68 (2H, m), 4.14 (1H, br m), 3.66–3.58 (4H, complex m), 3.22 (1H, dd, $J=13.5$, 5 Hz), 3.09 (1H, dd, $J=13.5$, 9.5 Hz), 1.30 (9H, s), 0.95 (2H, m), 0.03 (9H, s); δ_C (100 MHz, $CDCl_3$) 155.3, 150.1, 133.8, 132.9, 127.6, 124.9, 95.4, 79.3, 70.1, 65.6, 51.3, 35.4, 28.4, 18.2, −1.3 (one C obscured). (Found (CI^+): 427.2264. $C_{20}H_{35}N_2O_6Si$ requires (MH^+): 427.2264 (0.0 ppm)).

3.8.5. [1-(*S*)-2-(3-Nitrophenyl)-1-(2-trimethylsilanylethoxymethoxymethyl)ethyl]carbamic acid *tert*-butyl ester (48e). 67%. Colourless oil; R_f 0.21 (2:1, petrol(40–60)–Et_2O); ν_{max}/cm^{-1} (thin film) 3346, 2954, 2930, 2894, 1714, 1531, 1504, 1453; $[\alpha]_D^{20}=-19.8$ (c 1.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) δ 8.09–8.07 (2H, complex m), 7.59 (1H, d, $J=7.3$ Hz), 7.46 (1H, m), 5.04 (1H, broad d, $J=8.2$ Hz), 4.68 (2H, m), 3.97 (1H, br m), 3.64 (2H, m), 3.51 (2H, m), 2.97 (2H, m), 1.37 (9H, s), 0.95 (2H, m), 0.02 (9H, s); δ_C(100 MHz, $CDCl_3$) 155.4, 148.4, 140.3, 135.8, 129.4, 124.4, 121.7, 95.5, 79.7, 68.9, 65.7, 51.6, 38.0, 28.4, 18.2, −1.3. (Found (CI^+): 427.2268. $C_{20}H_{35}N_2O_6Si$ requires (MH^+): 427.2264 (0.9 ppm)).

3.8.6. [1-(*S*)-2-(4-Acetylphenyl)-1-(2-trimethylsilanylethoxymethoxymethyl)ethyl]carbamic acid *tert*-butyl ester (48f). 68%. Colourless oil; R_f 0.21 (2:3, petrol(40–60)–Et_2O); ν_{max}/cm^{-1} (thin film) 3352, 2954, 1712, 1681, 1607, 1517; $[\alpha]_D^{20}=-19.7$ (c 1.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) δ 7.88 (2H, d, $J=8$ Hz), 7.32 (2H, d, $J=8$ Hz), 5.00 (1H, br d, $J=8$ Hz), 4.68 (1H, d, $J=10.5$ Hz), 4.65 (1H, d, $J=10.5$ Hz), 3.96 (1H, br s), 3.63 (2H, m), 3.47 (2H, d, $J=3.5$ Hz), 2.98 (1H, dd, $J=13$, 6.5 Hz), 2.90 (1H, dd, $J=13$, 8 Hz), 2.58 (3H, s), 1.40 (9H s), 0.94 (2H, m), 0.03 (9H, s); δ_C(100 MHz, $CDCl_3$) 198.0, 155.4, 144.2, 135.6, 129.7, 128.6, 95.4, 79.5, 68.7, 65.6, 51.6, 38.2, 28.4, 26.7, 18.2, −1.3. (Found (CI^+): 424.2536. $C_{22}H_{38}NO_5Si$ requires (MH^+): 424.2519 (3.9 ppm)).

3.8.7. [1-(*S*)-2-(4-Carbomethoxyphenyl)-1-(2-trimethylsilanylethoxymethoxymethyl)ethyl]carbamic acid *tert*-butyl ester (48g). 52%. Colourless oil; R_f 0.26 (2:1, petrol(40–60)–Et_2O); ν_{max}/cm^{-1} (thin film) 3365, 2953, 1723, 1612, 1504, 1280; $[\alpha]_D^{20}=-16.5$ (c 1.4, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) δ 7.95 (2H, d, $J=8$ Hz), 7.29 (2H, d, $J=8$ Hz), 4.99 (1H, br d, $J=8$ Hz), 4.67 (1H, d, $J=10.5$ Hz), 4.65 (1H, d, $J=10.5$ Hz), 3.96 (1H, br m), 3.90 (3H, s), 3.62 (2H, m), 3.46 (2H, d, $J=3.5$ Hz), 2.96 (1H, dd, $J=13$, 6.5 Hz), 2.89 (1H, dd, $J=13$, 8 Hz), 1.40 (9H, s), 0.94 (2H, m), 0.02 (9H, s); δ_C (68.5 MHz, $CDCl_3$) 167.2, 155.4, 143.9, 129.8, 129.6, 128.5, 95.5, 79.5, 68.7, 65.6, 52.1, 51.6, 38.1, 28.5, 18.2, −1.3. (Found (CI^+): 440.2468. $C_{22}H_{38}NO_6Si$ requires (MH^+): 440.2468 (0.0 ppm)).

3.8.8. [1-(*S*)-2-(Naphthalen-1-yl)-1-(2-trimethylsilanylethoxymethoxymethyl)ethyl]carbamic acid *tert*-butyl ester (48h). 73%. Colourless oil; R_f 0.25 (4:1, petrol(40–60)–Et_2O); ν_{max}/cm^{-1} (thin film) 3451, 3351, 2953, 2893, 1713, 1495; $[\alpha]_D^{20}=-34.1$ (c 1.7, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) δ 8.39–8.09 (1H, br m), 7.85 (1H, d, $J=8$ Hz), 7.74 (1H, d, $J=8.5$ Hz), 7.57 (1H, m), 7.48 (1H, m), 7.41–7.35 (2H, complex m), 5.17 (1H, br d, $J=7.5$ Hz), 4.72–4.65 (2H, complex m), 4.13 (1H, br m), 3.73–3.62 (2H, complex m), 3.54–3.18 (4H, complex m), 1.50–1.23 (9H, m), 0.96 (2H, m), 0.04 (9H, s); δ_C (100 MHz, $CDCl_3$) 155.4, 134.6, 134.0, 132.5, 128.7, 127.8, 127.4, 126.4, 125.7, 125.5, 124.3, 95.6, 79.3, 68.6, 65.7, 51.1, 35.3, 28.5, 18.2, −1.3. (Found (CI^+): 432.2575. $C_{24}H_{38}NO_4Si$ requires (MH^+): 432.2570 (1.0 ppm)).

3.8.9. 1,4-Bis-[2-(*S*)-2′-(*S*)-2-(*tert*-butoxycarbonylamino)-3-(2-trimethylsilanylethoxymethoxy)propyl]-benzene (49). 35%. Colourless oil; R_f 0.09 (2:1, petrol(40–60)–Et_2O); ν_{max}/cm^{-1} (thin film) 3350, 2952, 2894, 1713, 1514, 1503; $[\alpha]_D^{20}=-16.4$ (c 0.7, $CHCl_3$); δ_H (270 MHz, $CDCl_3$) δ 7.13 (4H, s), 4.94 (2H, br d, $J=8$ Hz), 4.66 (4H, m), 3.90 (2H, br m), 3.63 (4H, m), 3.46 (4H, d, $J=3.5$ Hz), 2.86 (2H, partially obscured dd, $J=13.5$, 6.5 Hz), 2.78 (2H, dd, $J=13.5$, 8 Hz), 1.41 (18H, s), 0.94 (4H, m), 0.03 (18H, s); δ_C (100 MHz, $CDCl_3$) 155.5, 136.3, 129.6, 95.4, 79.3, 68.6, 65.5, 51.7, 37.6, 28.5, 18.2, −1.2. (Found (CI^+): 707.4103. $C_{34}H_{64}N_2O_8Si_2Na$ requires ($M+Na^+$): 707.4099 (0.6 ppm)).

3.9. Synthesis of phenylalanine hydrochloride 52

3.9.1. Deprotection of 48a.

3.9.1.1. [1-(*S*)-2-Phenyl-1-(hydroxymethyl)ethyl]carbamic acid *tert*-butyl ester (50). The SEM-protected phenylalaninol **48a** (54 mg, 0.14 mmol) was treated with a 0.1 M solution of HCl in MeOH (1.4 mL). After 8 h stirring under N_2 at room temperature, the reaction mixture was concentrated under reduced pressure to a white solid. To this residue was added THF (0.70 mL), triethylamine (0.060 mL, 0.43 mmol) and di-*tert*-butyldicarbonate (43 mg, 0.20 mmol) and the resulting mixture was stirred under N_2 at room temperature for 16 h. Water (10 mL) was added and the aqueous layer was extracted with EtOAc (3× 10 mL). The combined organic phases were washed with

brine (10 mL), then dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a yellow oil. Subjection of this material to flash chromatography (2:1, Et_2O–petroleum(40–60) elution) provided the title compound as a white solid (27 mg, 75%), mp 94–95 °C (lit.[37] mp 94.5–95.5 °C); R_f 0.25 (1:2, petrol(40–60)–Et_2O); ν_{max}/cm^{-1} (thin film) 3352, 2961, 2937, 1683, 1526; $[\alpha]_D^{20}=-22.0$ (*c* 1.0, $CHCl_3$), lit.[38] $[\alpha]_D^{20}=-24.0$ (*c* 1, $CHCl_3$)]; δ_H (270 MHz, $CDCl_3$) δ 7.34–7.19 (5H, complex m), 4.71 (1H, br s), 3.87 (1H, br m), 3.66 (1H, m), 3.55 (1H, m), 2.84 (2H, d, $J=7.5$ Hz), 2.23 (1H, br s), 1.41 (9H, s); δ_C (68.5 MHz, $CDCl_3$) 156.2, 138.0, 129.4, 128.6, 126.6, 79.8, 64.0, 53.8, 37.5, 28.4. (Found (CI^+): 252.1603. $C_{14}H_{22}NO_3$ requires (MH^+): 252.1600 (1.3 ppm)).

3.9.2. Oxidation of 50.

3.9.2.1. Methyl 2-(*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-phenylpropanoate (51). A solution of phenyl alaninol **50** (36 mg, 0.14 mmol) in dichloromethane (1.5 mL) under N_2 at room temperature was treated with Dess–Martin periodinane (67 mg, 0.16 mmol). After 1.5 h the cloudy suspension was treated sequentially with saturated aqueous $NaHCO_3$ solution (3 mL), 1 M aqueous NaS_2O_3 solution (10 mL) and Et_2O (10 mL). The biphasic mixture was stirred for 15 min, then partitioned. The aqueous layer was re-extracted with Et_2O (2×10 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a white solid. This residue was dissolved in *t*-BuOH (3.0 mL), and a 2 M solution of 2-methyl-2-butene in THF (1.40 mL, 2.80 mmol) was added. A solution of sodium chlorite (117 mg, 1.29 mmol) and sodium dihydrogen orthophosphate (165 mg, 1.06 mmol) in water (1.40 mL) was cautiously added dropwise. After 1.5 h, the reaction mixture was concentrated and saturated aqueous $NaHCO_3$ solution (10 mL) was added. The aqueous layer was washed with EtOAc (10 mL) and then acidified to pH 1 with 10% HCl solution. The resulting acidic aqueous phase was extracted with EtOAc (3×10 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a colourless oil. This crude carboxylic acid was dissolved in toluene (0.7 mL) and MeOH (0.7 mL) and cooled to 0 °C under an atmosphere of N_2, before being treated with a 2 M ethereal solution of (trimethylsilyl)diazomethane (0.14 mL, 0.28 mmol). The reaction mixture was maintained at 0 °C for 40 min, and then was concentrated to afford a colourless oil. This oil was subjected to flash chromatography (1:3, Et_2O–petrol(40–60) elution) to provide the title compound as a colourless oil (30 mg, 75%); R_f 0.22 (1:2, petrol(40–60)–Et_2O); ν_{max}/cm^{-1} (thin film) 3365, 3030, 2978, 1746, 1714, 1502, 1454; $[\alpha]_D^{20}=+43.6$ (*c* 2.9, CH_2Cl_2) lit.[39] $[\alpha]_D^{20}=+46.9$ (*c* 3.43, CH_2Cl_2); δ_H (270 MHz, $CDCl_3$) δ 7.35–7.23 (3H, complex m), 7.14 (2H, d, $J=6.5$ Hz), 4.99 (1H, br d, $J=7.5$ Hz), 4.61 (1H, dt, $J=7.5$, 6 Hz), 3.73 (3H, s), 3.14 (1H, dd, $J=13.5$, 6 Hz), 3.06 (1H, dd, $J=13.5$, 6 Hz), 1.43 (9H, s); δ_C(100 MHz, $CDCl_3$) 172.5, 155.2, 136.1, 129.4, 128.7, 127.1, 80.0, 54.5, 52.3, 38.5, 28.4.

3.9.3. Deprotection of 51.

3.9.3.1. (*S*)-Phenylalanine hydrochloride (52). The ester **51** (31 mg, 0.11 mmol), anisole (0.020 mL, 0.18 mmol) and a 6 M aqueous HCl solution (2.0 mL) were mixed and heated at 70 °C for 5 h. The resulting mixture was then cooled to room temperature and treated with water (15 mL). The aqueous phase was washed with EtOAc (2×15 mL) and the separated aqueous layer was concentrated under reduced pressure to a white solid (22 mg, 100%), mp (dec.) 215–216 °C [lit.[36] mp 241–243 °C]. ν_{max}/cm^{-1} (thin film) 3385, 2947, 2616, 1731, 1605, 1485; $[\alpha]_D^{20}=-8.1$ (*c* 0.91, H_2O) [lit.[36] $[\alpha]_D^{20}=-8.2$ (*c* 1, H_2O)]; δ_H (400 MHz, $CDCl_3$) δ 7.42–7.32 (3H, complex m), 7.30 (2H, d, $J=7.5$ Hz), 4.25 (1H, dd, $J=7.5$, 5.5 Hz), 3.32 (1H, dd, $J=14.5$, 5.5 Hz), 3.18 (1H, dd, $J=14.5$, 7.5 Hz); δ_C(100 MHz, $CDCl_3$) 171.8, 134.3, 129.5, 129.3, 128.0, 55.4, 35.8.

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