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Negishi cross-coupling reactions of α-amino acid-derived organozinc reagents and aromatic bromides

Claire L. Oswald, Tomás Carrillo-Márquez, Lorenzo Caggiano*,†, Richard F.W. Jackson*

Department of Chemistry, Dainton Building, The University of Sheffield, Brook Hill, Sheffield S3 7HF, UK

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Abstract

The Negishi cross-coupling reaction of organozinc iodides derived from α-amino acids with aromatic bromides to give substituted phenylalanine derivatives is described, using either $Pd(OAc)_2$ or $Pd_2(dba)_3$ in combination with $P(o\text{-Tol})_3$ as catalyst in DMF at 50 °C. Similar results are obtained using $Pd[P^tBu_3]_2$ as catalyst. The difference in reactivity displayed between aryl iodides and bromides (ArI>ArBr) has been utilised in a short synthesis of an unsymmetrical, orthogonally protected *para*-phenylene bis-alanine derivative.

1. Introduction

The palladium-catalysed Negishi cross-coupling reaction between aromatic halides and α, β and γ-amino acid-derived organozinc iodides has been widely used to synthesise a variety of non-proteinogenic amino acid derivatives.[1] In the course of our investigations, it was found that organozinc reagents derived from α-amino acids possessed enhanced intramolecular co-ordination compared to the β- and γ-amino acid reagents, resulting in increased stability and consequently decreased reactivity (Fig. 1).[1]

Thus cross-coupling reactions of α-amino acid-derived organozinc reagents have generally been performed with a more reactive aromatic iodide as the electrophilic coupling partner, using 2.5 mol % $Pd_2(dba)_3$ and 10 mol % $P(o\text{-Tol})_3$[2] in DMF at 1 M concentration at room temperature, although much lower loadings of Pd are actually required.[3]

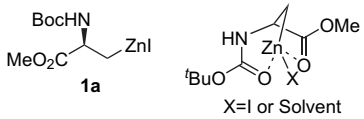
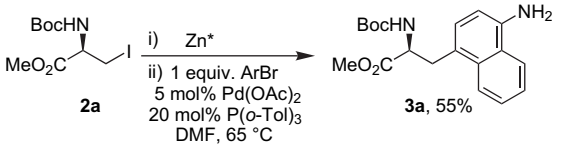


Fig. 1. Intramolecular co-ordination.

Recently the synthesis of a highly potent and selective non-peptidic tyrosine phosphatase inhibitor reported by Szczepankiewicz et al. included a palladium-catalysed cross-coupling reaction between the organozinc iodide **1a**, generated from the serine-derived iodide **2a**, and the aromatic bromide 1-amino-4-bromonaphthalene.[4] This transformation was accomplished using $Pd(OAc)_2$ (5 mol %) and $P(o\text{-Tol})_3$ (20 mol %) at elevated temperature (65 °C, Scheme 1).



Scheme 1. RZnI cross-coupling with 1-amino-4-bromonaphthalene.[4]

The use of aromatic bromides and chlorides as electrophilic coupling partners is attractive due to their lower cost and wider availability. They are less reactive towards oxidative addition than the corresponding aromatic iodides,[5] which is directly related to their bond dissociation energies (D_{298}(Ph–X): Cl=408; Br=346 and I=281 kJ mol^{-1}).[6] The Negishi cross-coupling reaction of organozinc halides and alkyl and aryl

* Corresponding authors. Tel.: +44 114 222 9464; fax: +44 114 222 9303.
E-mail address: r.f.w.jackson@shef.ac.uk (R.F.W. Jackson).
† Present address: Department of Pharmacy and Pharmacology, University of Bath, Bath BA2 7AY, UK.

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electrophiles is very diverse,[7–9] although relatively few examples exist of couplings between functionalised alkylzinc halides and either aromatic bromides or chlorides. Selected examples of functionalised alkylzinc reagents include esters,[10–13] silyl ethers,[14] bicyclic systems[15] and Boc-protected amines.[16,17] Previous reports have shown that the serine-derived alkylzinc reagent **1a** can couple with bromopyridines, although these are activated electrophiles whose reactivity may be further enhanced upon co-ordination with residual metal ions in solution.[18,19] The reaction shown in Scheme 1 is the only example of a palladium-catalysed cross-coupling reaction between an unactivated aromatic bromide and a zinc reagent derived from an α-amino acid.

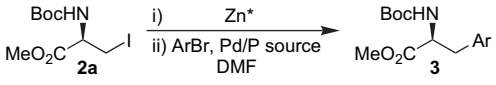
In an effort to extend the Negishi cross-coupling reaction to aromatic bromides and chlorides, alternative reagents and methods have been reported. A tetradentate phosphine ligand with $PdCl[(C_3H_5)]_2$ has been successfully used to couple unfunctionalised alkylzinc bromides with aryl bromides in THF at 70 °C.[20] Cross-coupling with aromatic chlorides requires more forcing conditions and has been reported with simple alkylzinc chlorides by Dai and Fu using $Pd[P^tBu_3]_2$,[21] a complex originally prepared by Otsuka,[22] and Kappe using $Pd_2(dba)_3$ under microwave irradiation.[23]

The example reported by Szczepankiewicz et al. in Scheme 1 uses $Pd(OAc)_2$, which is reduced in situ by PAr_3 to generate the catalytically active Pd(0) species required for cross-coupling.[24,25] Complex mixtures of potentially catalytically active neutral and anionic Pd(0) species are generated,[26–31] including an acetate bridged cyclopalladated dinuclear palladium complex.[32] In addition, halide anions play a major role in catalysis.[31] Use of $Pd_2(dba)_3$ as the Pd-source is further complicated by the fact that the dba ligand is not simply a spectator, but may affect the rate of oxidative addition.[33–35]

We have therefore investigated the Negishi cross-coupling reaction between the organozinc iodide **1a** and aromatic bromides using the reported conditions, $Pd(OAc)_2/P(o\text{-Tol})_3$ (Method A)[4] and our usual system $Pd_2(dba)_3/P(o\text{-Tol})_3$ (Method B).[1] Given the encouraging reports of Dai and Fu, a third palladium source $Pd[P^tBu_3]_2$ (Method C)[21] was also investigated.

2. Results and discussion

The serine-derived iodide **2a** was prepared following literature procedures,[36,37] and treated with zinc activated either with chlorotrimethylsilane (TMSCl),[38,39] or catalytic I_2 following a procedure originally reported for insertion into alkyl bromides.[40] Initial results showed that PhBr could be coupled with the organozinc reagent **1a** with either $Pd(OAc)_2/P(o\text{-Tol})_3$ (Method A) or $Pd_2(dba)_3/P(o\text{-Tol})_3$ (Method B) in modest yields (Scheme 2 and Table 1).



Scheme 2. Zinc insertion and Pd-catalysed cross-coupling.

Table 1
Pd-catalysed cross-coupling of iodide **2a** with PhBr[a]

Entry	Temp (°C)	Method A yield %	Method B yield %
1	25	40	39
2	50	60	58
3	75	51	66

[a] Method A: 5 mol % $Pd(OAc)_2$ and 10 mol % $P(o\text{-Tol})_3$. Method B: 2.5 mol % $Pd_2(dba)_3$ and 10 mol % $P(o\text{-Tol})_3$. Reactions conducted in DMF for 16 h. Yields refer to isolated products after column chromatography.

The yield of the cross-coupling reaction between zinc reagent **1a** and 4-bromoanisole in DMF using $Pd[P^tBu_3]_2$ (5 mol %) as catalyst (Method C) at a range of temperatures gave modest yields (25–31%), essentially independent of temperature.

Based on these initial results, further optimisation of methods A and B was conducted at 50 °C. The effect of Pd:phosphine ratio was also examined in the $Pd(OAc)_2$ and $Pd_2(dba)_3$ systems and the results are shown in Table 2.

A phosphine-free $Pd(OAc)_2$-catalysed Fukuyama cross-coupling reaction was recently reported between an alkylzinc iodide and a thiolactone.[41] In the absence of any phosphine ligand, no reaction occurred in the system described above (entry 1, Table 2). The highest yields obtained with $Pd(OAc)_2$ were achieved with a ratio of 1:2 (Pd:$P(o\text{-Tol})_3$, entry 3). Interestingly, the yield decreased using a molar ratio of 1:4 Pd:P (entry 5), the conditions reported by Szczepankiewicz et al.[4] The $Pd_2(dba)_3$ system appeared largely insensitive to the amount of phosphine, with consistent yields being obtained with various Pd:phosphine ratios (entries 6–8).

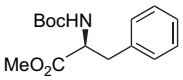
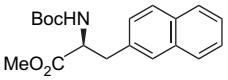
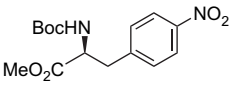
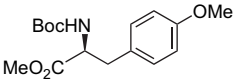
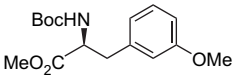
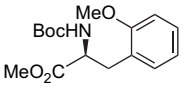
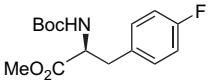
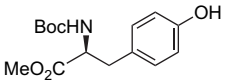
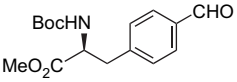
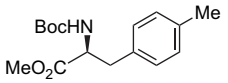
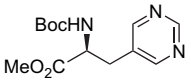
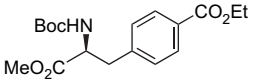
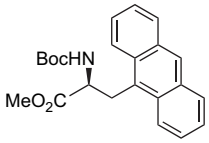
Table 2
Effects of Pd:phosphine ratio[a]

Entry	Method	Pd:$P(o\text{-Tol})_3$ ratio	Yield[b] %
1	A: 5 mol % $Pd(OAc)_2$	1:0	NOR[c]
2		1:1	45
3		1:2	60
4		1:3	53
5		1:4	46
6	B: 2.5 mol % $Pd_2(dba)_3$	1:1	58
7		1:2	58
8		1:4	53

[a] Reactions conducted with organozinc iodide **1a** and 1.3 equiv PhBr at 50 °C in DMF for 16 h.
[b] Yields refer to isolated products after column chromatography.
[c] NOR—no observable reaction.

Further optimisation studies showed that the reaction with $Pd(OAc)_2$ or $Pd_2(dba)_3$ (Method A or B) was complete after 2 h at 50 °C and that the catalyst loading of $Pd[P^tBu_3]_2$ (Method C) could be reduced from 5 mol % to 1.25 mol %, with slightly improved yields. To investigate the substrate scope and limitations of the reaction, a series of experiments with various aryl bromides was conducted using the optimised conditions. Due to the similar results obtained using both $Pd(OAc)_2$ and $Pd_2(dba)_3$, and the lower price of the former, $Pd(OAc)_2$ was chosen as the Pd-source (Method A). A number of reactions were also conducted using $Pd[P^tBu_3]_2$ (Method C), for comparison. The results are shown in Table 3; see also Scheme 2.

Table 3
Pd-catalysed cross-coupling of zinc reagent **1a** with aryl bromides

Entry	ArBr	Product	Structure	Method A[a] yield %	Method C[a] yield %	ArI yield[b] %
1	PhBr	**3b**		60	54	64[c]
2	2-Naphthyl bromide	**3c**		34	46	—
3	4-O_2N–C_6H_4Br	**3d**		47	—	57[c]
4	4-MeO–C_6H_4Br	**3e**		48	36	—
5	3-MeO–C_6H_4Br	**3f**		35	—	—
6	2-MeO–C_6H_4Br	**3g**		13	—	57[c]
7	4-F–C_6H_4Br	**3h**		40	—	58[c]
8	4-HO–C_6H_4Br	**3i**		23	—	59[d]
9	4-OHC–C_6H_4Br	**3j**		43	—	—
10	4-Me–C_6H_4Br	**3k**		44	42	—
11	5-Bromo-pyrimidine	**3l**		20	33	—
12	4-EtO_2C–C_6H_4Br	**3m**		—	36	—
13	9-Bromo-anthracene	**3n**		—	42	—

[a] Method A: 5 mol % $Pd(OAc)_2$, 10 mol % P(*o*-Tol)$_3$, 2 h. Method C: 1.25 mol % Pd[P^{t}Bu$_3$]$_2$, 16 h. Reactions were conducted using ArBr (1.3 equiv) at 50 °C in DMF. Yields refer to isolated products after column chromatography, based on starting serine-derived iodide **2a**.
[b] Yield from the corresponding ArI, using Method B.
[c] See Ref 42.
[d] See Ref 43.

Pd-catalysed cross-coupling with bromobenzene gave modest yields with both methods, comparable to that obtained with PhI (entry 1, Table 3). Similar yields were obtained with the electron poor 4-NO_2 derivative and the electron rich 4-MeO derivative (47% and 48% yield, respectively, Method A, entries 3 and 4). The yield however did diminish with the 3-MeO substituent (35%, entry 5) dropping to 13% yield with the 2-MeO derivative, presumably due to steric crowding, although 57% yield was still achieved using 2-iodoanisole (entry 6). Unprotected phenols are tolerated in the Negishi cross-coupling reaction with phenolic iodides (59%),[43] however, the slower rate of cross-coupling with aryl bromides results in a much reduced yield (entry 8), although aldehydes were shown to be compatible (entry 9). Using either Method A or

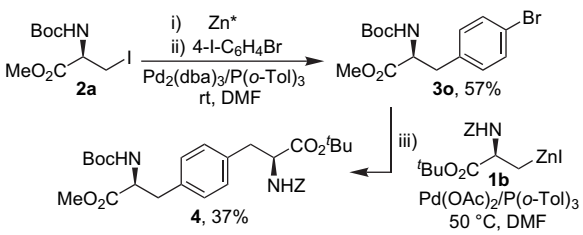
C with 5-bromopyrimidine gave poor yields (20% and 33%, respectively, entry 11), defining the scope of the process. While the enantiomeric purity of the products was not explicitly determined, the lack of any detectable racemisation in all previous work, combined with specific rotations of known compounds in good agreement with the literature, suggests that the compounds are enantiomerically pure.

2.1. Application

The difference in reactivity displayed between aromatic iodides and bromides with α-amino acid-derived organozinc reagents can be used to synthesise orthogonally protected, unsymmetrical and enantiomerically pure phenylene bis-alanine derivatives. Phenylene bis-amino acid derivatives have attracted interest as structural variants of 2,6-diaminopimelic acid[44,45] and related bis-amino acids, which are present in various cyclic peptide antibiotics.[46] A dilactoside derivative based on *m*-phenylene bis-alanine was recently shown to inhibit selectively galectin-1,[47] a member of a family of proteins associated with cancer.[48] Phenylene bis-amino acid derivatives have also been studied as mimics of a helix-turn-helix present in DNA-binding proteins,[49] supramolecular polymers[50] and as asymmetric catalysts.[51]

Selected examples of previous syntheses include those using phase transfer catalysis,[52–54] diastereoselective[45,50,55–57] and non-selective[58] alkylation, and catalytic asymmetric hydrogenation,[59–61,49] which was applied to the synthesis of unsymmetrical phenylene bis-α-amino acids. An unsymmetrical orthogonally protected biphenyl derivative has been reported using a Pd-catalysed Suzuki–Miyaura cross-coupling reaction, although the product was found to be racemic.[54]

Using the previously reported standard cross-coupling reaction conditions for aromatic iodides,[1,62] reaction of the organozinc reagent **2a** with 1-bromo-4-iodobenzene, in the presence of 2.5 mol % $Pd_2(dba)_3$ and 10 mol % P(*o*-Tol)$_3$ at room temperature, selectively gave the 4-bromo-phenylalanine derivative **3o** in 57% yield after column chromatography (Scheme 3). Treatment of the aromatic bromide **3o** with the differentially protected serine-derived organozinc reagent **1b**,[63] in the presence of 5 mol % $Pd(OAc)_2$ and 10 mol % P(*o*-Tol)$_3$ at 50 °C for 2 h (Method A), gave the orthogonally protected, unsymmetrical *para*-phenylene bis-alanine derivative **4** in 37% isolated yield.



Scheme 3. Sequential Pd-catalysed cross-coupling. (i) Zn, cat. I_2, DMF. (ii) 4-I–C_6H_4Br, 2.5 mol % $Pd_2(dba)_3$, 10 mol % P(*o*-Tol)$_3$, rt, 16 h. (iii) **1b**, 5 mol % $Pd(OAc)_2$, 10 mol % P(*o*-Tol)$_3$, 50 °C, 2 h, DMF (Method A).

3. Conclusions

From the initial reported example, the palladium-catalysed Negishi cross-coupling reaction of α-amino acid-derived organozinc reagents has been extended to include a range of aromatic bromide electrophiles. The reaction proceeds with various palladium sources at 50 °C, although it is more susceptible to the presence of acidic protons and to steric crowding than coupling with the corresponding aromatic iodide.

The synthesis of the bis-alanine derivative **4** serves to demonstrate the application of this methodology to the synthesis of unsymmetrical, orthogonally protected and enantiomerically pure phenylene bis-alanine derivatives. In addition, this flexible approach could be used to incorporate a variety of α, β and/or γ-amino acids with various substituted aromatic cores.

4. Experimental

4.1. General experimental

All moisture/air sensitive reactions were conducted under a positive pressure of nitrogen in flame dried glassware. All reagents used were purchased from commercial sources without further purification or prepared and purified according to literature procedure. Dry DMF was distilled from calcium hydride and stored over 4 Å molecular sieves. Petroleum ether refers to the fraction with a boiling point between 40–60 °C. Thin layer chromatography (TLC) was performed on precoated plates (Merck aluminium sheets silica 60 F_{254}, Art. no. 5554). Flash column chromatography was performed on silica gel 60 (Merck 9385).

For known compounds, data is only included when literature values are either unavailable or, in the case of NMR data, recorded at lower field strength. Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker AMX2-400 or a Bruker DRX-500 NMR spectrometer at room temperature. Chemical shifts were measured relative to residual solvent and are expressed in parts per million (δ). Coupling constants (J) are given in hertz and are quoted to the nearest 0.5 Hz. High-resolution mass spectra were recorded using a MicroMass LCT operating in electrospray (ES) mode or a MicroMass Prospec operating in electro impact (EI) mode. Chemical analyses were performed using a Perkin–Elmer 2400 CHN elemental analyser. Optical rotations were measured on a Perkin–Elmer 241 automatic polarimeter at λ 589 nm (Na, D-line) with a path length of 1 dm at the stated temperature and concentrations. The concentration is given in g/100 mL and the optical rotations are quoted in 10^{-1} deg cm^2 g^{-1}. Infrared spectra were recorded on a Perkin–Elmer Paragon 100 FTIR spectrophotometer (ν_{max} in cm^{-1}) with KBr disks.

4.1.1. General procedure for Negishi cross-coupling reactions catalysed by $Pd(OAc)_2$ or $Pd_2(dba)_3$ (Method A or B)

A catalytic amount of iodine (typically 5–10 mg) was added to a rapidly stirred suspension of zinc dust (392 mg, 6 mmol) in

DMF (1.0 mL) in a 25 mL one-necked round-bottomed flask fitted with a 3-way tap with a magnetic stirrer bar. *N*-(*tert*-Butoxycarbonyl)-L-iodoalanine methyl ester **2a** (329 mg, 1 mmol) was then added in one portion to the rapidly stirred suspension of now activated zinc in DMF and a slight exotherm was observed. The reaction mixture was stirred for a further 5 min, until the temperature had returned to room temperature. Stirring was stopped and the zinc dust allowed to settle. The solution was removed from the activated zinc via syringe and added to a separate side-arm round bottom flask, containing the electrophile (1.3 mmol), P(*o*-Tol)$_3$ (30 mg, 0.1 mmol, 10 mol %) and either Pd(OAc)$_2$ (11 mg, 0.05 mmol, 5 mol %, Method A) or Pd$_2$(dba)$_3$ (23 mg, 0.025 mmol, 2.5 mol %, Method B), and rapidly stirred for 2 h at 50 °C under a nitrogen atmosphere. The crude reaction mixture was placed directly on a silica gel column and purified by gradient column chromatography with petroleum ether–EtOAc.

4.1.2. General procedure for Negishi cross-coupling reactions catalysed by Pd[^{t}Bu$_3$]$_2$ (Method C)

Chlorotrimethylsilane (6 μL) was added to a stirred suspension of zinc dust (294 mg, 4.5 mmol) in DMF (0.5 mL) in a 25 mL one-necked round-bottomed flask fitted with a 3-way tap. After 30 min the solvent was removed by syringe and the zinc washed with 0.5 mL of DMF. The solvent was removed again via syringe and the activated zinc dried under vacuum. A solution of *N*-(*tert*-butoxycarbonyl)-L-iodoalanine methyl ester **2a** (247 mg, 0.75 mmol) in DMF (0.75 mL) was added to the activated zinc and stirred. After 10–15 min, TLC [petroleum ether–EtOAc (1:1)] showed complete zinc insertion. The electrophile (1 mmol) followed by Pd[P^{t}Bu$_3$]$_2$ (5 mg, 0.01 mmol, 1.25 mol %) was added and the mixture stirred for 16 h at 50 °C under nitrogen. The resulting mixture was diluted with Et$_2$O (50 mL) and washed with saturated ammonium chloride solution (20 mL), brine (20 mL) and dried over anhydrous MgSO$_4$. The solvent was removed under reduced pressure and the residue purified by column chromatography with dichloromethane–EtOAc.

*4.1.2.1. Methyl 2-(S)-((tert-butoxycarbonyl)amino)-3-phenylpropanoate (**3b**).* Using Method A, with 0.75 mmol of iodide **2a**, compound **3b** (129 mg, 60%) was isolated as a light yellow oil. Method C gave **3b** (112 mg, 54% yield). $[\alpha]_D^{22}$ +41.8 (*c* 0.55, CH_2Cl_2), lit. value[42] $[\alpha]_D^{20}$ +46.9 (*c* 3.43, CH_2Cl_2); *m/z* (ES$^+$) found MH$^+$ 280.1548. $C_{15}H_{22}NO_4$ requires 280.1549. Spectroscopic data consistent with that previously reported.[42]

*4.1.2.2. Methyl 2-(S)-((tert-butoxycarbonyl)amino)-3-(2-naphthyl)propanoate (**3c**).* Using Method A, with 0.75 mmol of iodide **2a**, compound **3c** (85.5 mg, 34%) was isolated as a colourless solid. Method C gave compound **3c** (113 mg, 46% yield). Mp 84–86 °C, lit. value[64] 85–86 °C; $[\alpha]_D^{21}$ +58.3 (*c* 0.99, CH_2Cl_2), lit. value[64] $[\alpha]_D^{32}$ +59.9 (*c* 2.62, $CHCl_3$). Anal. found C, 69.17; H, 7.12; N, 4.07. $C_{19}H_{23}NO_4$ requires C, 69.28; H, 7.04; N, 4.25%; *m/z* (ES$^+$) found MH$^+$ 330.1702. $C_{19}H_{24}NO_4$ requires 330.1705. Spectroscopic data consistent with that previously reported.[64]

*4.1.2.3. Methyl 2-(S)-((tert-butoxycarbonyl)amino)-3-(4′-nitrophenyl)propanoate (**3d**).* By Method A, compound **3d** was isolated as a yellow/orange oil, and recrystallised from Et$_2$O–heptane to yield a pale yellow solid (153 mg, 47%), mp 100–101 °C, lit. value[42] 95–97 °C; *m/z* (EI$^+$) found M$^+$ 324.13123. $C_{15}H_{20}N_2O_6$ requires 324.13214. Spectroscopic data consistent with that previously reported.[42]

*4.1.2.4. Methyl 2-(S)-((tert-butoxycarbonyl)amino)-3-(4′-methoxyphenyl)propanoate (**3e**).* By Method A (148 mg, 48%) and Method C (83 mg, 36% yield), compound **3e** was isolated as a colourless oil. $[\alpha]_D^{20}$ +50.0 (*c* 1.8, $CHCl_3$), lit.[65] value $[\alpha]_D^{20}$ +59.2 (*c* 1.8, $CHCl_3$); δ_H (500 MHz; $CDCl_3$) 1.34 (9H, s, $CO_2{}^tBu$), 2.92 (1H, dd, *J* 14.0 and 5.5 Hz, C*H*$_A$H$_B$CHNH), 2.98 (1H, dd, *J* 14.0 and 6.0 Hz, CH$_A$*H*$_B$CHNH), 3.64 (3H, s, CO_2Me), 3.71 (3H, s, ArO*Me*) 4.44–4.48 (1H, m, CH_2CHNH), 4.89 (1H, br d, *J* 8.0 Hz, CH_2CHNH), 6.72 (2H, d, *J* 8.0 Hz, Ar) and 6.96 (2H, d, *J* 8.0 Hz, Ar); δ_C (125 MHz; $CDCl_3$) 27.3, 32.2, 51.2, 53.5, 54.2, 78.9, 113.0, 126.9, 129.3, 154.1, 157.7 and 171.4; *m/z* (ES$^+$) found MH$^+$ 310.1655. $C_{16}H_{24}NO_5$ requires 310.1654. Spectroscopic data consistent with the 200 MHz ^{1}H NMR previously reported.[65]

*4.1.2.5. Methyl 2-(S)-((tert-butoxycarbonyl)amino)-3-(3′-methoxyphenyl)propanoate (**3f**).* By Method A, compound **3f** was isolated as a pale orange oil (108 mg, 35%). $[\alpha]_D^{22}$ +24.7 (*c* 1.9, $CHCl_3$); ν_{max}/cm^{-1} (KBr disk) 3368, 1746, 1715, 1608 and 1586; δ_C (125 MHz; $CDCl_3$) 28.3, 38.3, 52.2, 54.3, 55.2, 79.9, 112.5, 115.0, 121.6, 129.6, 137.5, 155.1, 159.7 and 172.2; *m/z* (ES$^+$) found MH$^+$ 310.1647. $C_{16}H_{24}NO_5$ requires 310.1654. Spectroscopic data consistent with that previously reported.[66]

*4.1.2.6. Methyl 2-(S)-((tert-butoxycarbonyl)amino)-3-(2′-methoxyphenyl)propanoate (**3g**).* By Method A, compound **3g** was isolated as a pale orange oil (40 mg, 13%). $[\alpha]_D^{22}$ +12.9 (*c* 0.68, CH_2Cl_2), lit.[42] value $[\alpha]_D^{20}$ +14.9 (*c* 0.68, CH_2Cl_2); *m/z* (EI$^+$) found M$^+$ 309.15719. $C_{16}H_{23}NO_5$ requires 309.15762. Spectroscopic data consistent with that previously reported.[42]

*4.1.2.7. Methyl 2-(S)-((tert-butoxycarbonyl)amino)-3-(4′-fluorophenyl)propanoate (**3h**).* By Method A, compound **3h** was isolated as a pale yellow oil (119 mg, 40%). $[\alpha]_D^{21}$ +44.1 (*c* 0.72, CH_2Cl_2), lit.[42] value $[\alpha]_D^{20}$ +30.5 (*c* 0.1, CH_2Cl_2); *m/z* (ES$^+$) found MH$^+$ 298.1464. $C_{15}H_{21}NO_4F$ requires 298.1455. Spectroscopic data consistent with that previously reported.[42]

*4.1.2.8. Methyl 2-(S)-((tert-butoxycarbonyl)amino)-3-(4′-hydroxyphenyl)propanoate (**3i**).* By Method A, compound **3i** was isolated as a pale yellow oil (67 mg, 23%). $[\alpha]_D^{21}$ +53.1 (*c* 1.0, $CHCl_3$), lit.[67] value $[\alpha]_D^{20}$ +48.2 (*c* 1.0, $CHCl_3$); *m/z* (ES$^+$) found MH$^+$ 296.1490. $C_{15}H_{22}NO_5$ requires 296.1498. Spectroscopic data consistent with that previously reported.[68]

*4.1.2.9. Methyl 2-(S)-((tert-butoxycarbonyl)amino)-3-(4′-formyl-phenyl)propanoate (**3j**).* By Method A, compound **3j**

was isolated as an orange oil (132 mg, 43%). $[\alpha]_D^{23}$ +43.4 (*c* 0.87, $CHCl_3$), lit.[69] value $[\alpha]_D^{20}$ +64.0 (*c* 2.0, $CHCl_3$); *m/z* (ES^+) found MNa^+ 330.1310. $C_{16}H_{21}NO_5Na$ requires 330.1317. Spectroscopic data consistent with that previously reported.[69]

*4.1.2.10. Methyl 2-(S)-((tert-butoxycarbonyl)amino)-3-p-tolyl-propanoate (**3k**).* By Method A (130 mg, 44%) and Method C (92 mg, 42% yield), compound **3k** was isolated as an orange oil. $[\alpha]_D^{21}$ +46.0 (*c* 0.93, $CHCl_3$), lit.[70] value $[\alpha]_D^{24}$ +52.1 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} (KBr disk) 3370, 1747, 1716 and 1515; δ_H (500 MHz; $CDCl_3$) 1.35 (9H, s, $CO_2{}^tBu$), 2.24 (3H, s, Ar*Me*) 2.94 (1H, dd, *J* 14.0 and 6.0 Hz, CH_AH_BCHNH), 3.00 (1H, dd, *J* 14.0 and 5.5 Hz, CH_AH_BCHNH), 3.64 (3H, s, CO_2Me), 4.45–4.50 (1H, m, CH_2CHNH), 4.89 (1H, br d, *J* 8.0 Hz, CH_2CHNH), 6.93 (2H, d, *J* 8.0 Hz, Ar) and 7.02 (2H, d, *J* 8.0 Hz, Ar); δ_C (125 MHz; $CDCl_3$) 21.1, 28.3, 37.9, 52.2, 54.5, 79.9, 129.2, 129.3, 132.8, 136.6, 155.1 and 172.4; *m/z* (EI^+) 293 (M^+, 3%), 177 (24), 176 (100), 106 (24) and 105 (67). Found M^+ 293.16278. $C_{16}H_{23}NO_4$ requires 293.16271. Spectroscopic data consistent with the 250 MHz previously reported.[70]

*4.1.2.11. Methyl 2-(S)-((tert-butoxycarbonyl)amino)-3-(pyrimidin-5-yl)propanoate (**3l**).* By Method A (56 mg, 20%) and Method C (69 mg, 33% yield), compound **3l** was isolated as a yellow oil. R_f [EtOAc] 0.34; $[\alpha]_D^{21}$ +32.7 (*c* 1.26, $CHCl_3$); ν_{max}/cm^{-1} (KBr disk) 3248, 1745, 1712, 1563 and 1523; δ_H (500 MHz; $CDCl_3$) 1.35 (9H, s, $CO_2{}^tBu$), 2.96 (1H, dd, *J* 14.0 and 5.0 Hz, CH_AH_BCHNH), 3.15 (1H, dd, *J* 14.0 and 7.0 Hz, CH_AH_BCHNH), 3.69 (3H, s, CO_2Me), 4.53–4.58 (1H, m, CH_2CHNH), 5.12 (1H, br d, *J* 8.0 Hz, CH_2CHNH), 8.48 (2H, s, Ar) and 9.05 (1H, s, Ar); δ_C (125 MHz; $CDCl_3$) 27.2, 32.2, 51.7, 52.8, 79.5, 128.9, 153.9, 156.5, 156.6 and 170.2; *m/z* (EI^+) 281 (M^+, 4%), 94 (27), 85 (78), 83 (100) and 57 (39). Found M^+ 281.13703, $C_{13}H_{19}N_3O_4$ requires 281.13756.

*4.1.2.12. Methyl 2-(S)-((tert-butoxycarbonyl)amino)-3-(4′-ethoxycarbonylphenyl)propanoate (**3m**).* By Method C, compound **3m** was isolated as a pale yellow oil (95 mg, 36% yield). $[\alpha]_D^{22}$ +51.3 (*c* 1.00, CH_2Cl_2); ν_{max} (liquid film)/cm^{-1} 3347, 2986, 1737, 1714, 1687 and 1609; δ_H (400 MHz, $CDCl_3$) 1.37 (3H, t, *J* 7.0 Hz, CH_2CH_3), 1.40 (9H, s, $CO_2{}^tBu$), 3.08 (1H, dd, *J* 13.5 and 5.5 Hz, CH_AH_BCHNH), 3.18 (H, dd, *J* 13.5 and 5.5 Hz, CH_AH_BCHNH), 3.70 (3H, s, CO_2Me), 4.35 (2H, q, *J* 7.0 Hz, CH_2CH_3), 4.58–4.62 (1H, m, CH_AH_BCHNH), 5.00 (1H, d, *J* 7.5 Hz, CH_AH_BCHNH), 7.19 (2H, d, *J* 8.0 Hz, Ar) and 7.96 (2H, d, *J* 8.0 Hz, Ar); δ_C (100 MHz, $CDCl_3$) 14.3, 28.2, 38.3, 52.3, 54.2, 60.9, 80.0, 129.3, 129.7, 130.2, 141.3, 157.8, 166.4 and 171.9; *m/z* (EI) 352 (MH^+, 100%), 296 (60) and 137 (86). Anal. found C, 61.31; H, 7.04; N, 3.73%. $C_{18}H_{25}NO_6$ requires C, 61.52; H, 7.17; N, 3.99%.

*4.1.2.13. Methyl 2-(S)-((tert-butoxycarbonyl)amino)-3-(anthracen-9-yl)propanoate (**3n**).* By Method C, compound **3n** was isolated as a yellow solid (119 mg, 42% yield). Mp 159.8–160.0 °C; $[\alpha]_D^{22}$ +21.4 (*c* 2.24, CH_2Cl_2); ν_{max} (KBr)/cm^{-1} 3369, 2930, 1736, 1686, 1524, 1255 and 1164; δ_H (500 MHz, $CDCl_3$) 1.38 (9H, s, $CO_2{}^tBu$), 3.30 (3H, s, CO_2Me), 4.00–4.06 (1H, m, CH_AH_BCHNH), 4.15 (1H, dd, *J* 14.0 and 7.0 Hz, CH_AH_BCHNH), 4.75–4.80 (1H, m, CH_AH_BCHNH), 5.31 (1H, d, *J* 7.5 Hz, CH_AH_BCHNH), 7.47 (2H, t, *J* 7.5 Hz, Ar), 7.54 (2H, dt, *J* 8.5 and 1.0 Hz, Ar), 8.00 (2H, d, *J* 8.5 Hz, Ar), 8.31 (2H, d, *J* 8.5 Hz, Ar) and 8.38 (1H, s, Ar); δ_C (100 MHz, $CDCl_3$) 28.2, 31.1, 52.1, 54.5, 79.8, 123.9, 124.8, 126.1, 127.0, 128.3, 129.2, 130.5, 131.3, 154.8 and 172.6. *m/z* (EI) 380 (MH^+, 8%), 324 (37), 280 (100), 263 (14) and 249 (4). Found MH^+ 380.1867, $C_{23}H_{26}NO_4$ requires 380.1862.

*4.1.2.14. Methyl 2-(S)-((tert-butoxycarbonyl)amino)-3-(4′-bromophenyl)propanoate (**3o**).* By Method B using zinc dust (432 mg, 6.6 mmol), *N*-(*tert*-butoxycarbonyl)-L-iodoalanine methyl ester (362 mg, 1.1 mmol), 4-iodobromobenzene (283 mg, 1 mmol), $Pd_2(dba)_3$ (23 mg, 2.5 mol %) and P(*o*-Tol)$_3$ (30 mg, 10 mol %) in DMF (1.0 mL) for 16 h at room temperature gave, after purification by column chromatography, compound **3o** as a yellow oil (204 mg, 57%). R_f [petroleum ether–EtOAc (8:2)] 0.33; $[\alpha]_D^{21}$ +29.6 (*c* 1.35, $CHCl_3$); ν_{max}/cm^{-1} (KBr disk) 3372, 1746 and 1715; δ_H (500 MHz; $CDCl_3$) 1.35 (9H, s, $CO_2{}^tBu$), 2.92 (1H, dd, *J* 14.0 and 6.5 Hz, CH_AH_BCHNH), 3.02 (1H, dd, *J* 14.0 and 5.5 Hz, CH_AH_BCHNH), 3.64 (3H, s, CO_2Me), 4.47–4.51 (1H, m, CH_2CHNH), 4.91 (1H, br d, *J* 8.0 Hz, CH_2CHNH), 6.93 (2H, d, *J* 8.0 Hz, Ar) and 7.34 (2H, d, *J* 8.0 Hz, Ar); *m/z* (ES^+) 380 (MNa^+, 5%), 358 (MH^+, 8), 304 (32), 302 (35), 260 (90) and 258 (100). Found MH^+ 358.0660, $C_{15}H_{21}NO_4Br$ requires 358.0654. Spectroscopic data consistent with the ^1H NMR previously reported.[71]

*4.1.2.15. 1-{(2S)-2-[(Benzyloxycarbonyl)amino]-2-[(tert-butoxycarbonyl)]ethyl}-4-{(2S)-2-[(tert-butoxycarbonyl)amino]-2-(methoxycarbonyl)ethyl}-benzene (**4**).* By Method A using zinc dust (176 mg, 2.7 mmol), *N*-(benzyloxycarbonyl)-L-iodoalanine *tert*-butyl ester[63] (162 mg, 0.40 mmol), aryl bromide **3o** (134 mg, 0.375 mmol), $Pd(OAc)_2$ (4.2 mg, 0.0187 mmol), P(*o*-Tol)$_3$ (11 mg, 0.0361 mmol) in DMF (1.0 mL) for 2 h at 50 °C gave, after purification by column chromatography, compound **4** as a yellow/orange oil (78 mg, 37%). R_f [petroleum ether–EtOAc (8:2)] 0.17; $[\alpha]_D^{21}$ +53 (*c* 1.4, CH_2Cl_2); ν_{max}/cm^{-1} (KBr disk) 3347, 1716 and 1505; δ_H (500 MHz; $CDCl_3$) 1.31 (9H, s, $CO_2{}^tBu$), 1.34 (9H, s, $CO_2{}^tBu$), 2.92–3.02 (4H, m, 2×CH_2CHNH), 3.61 (3H, s, CO_2Me), 4.41–4.98 (2H, m, 2×CH_2CHNH), 4.88 (1H, br d, *J* 8.0 Hz, $NHCO_2$), 5.02 (2H, s, $NHCO_2CH_2Ph$), 5.17 (1H, d, *J* 7.5 Hz, $NHCO_2$) 6.95 (2H, d, *J* 7.5 Hz, Ar), 7.00 (2H, d, *J* 7.5 Hz, Ar) and 7.22–7.29 (5H, m, CH_2Ph); δ_C (125 MHz; $CDCl_3$) 28.0, 28.3, 37.9, 38.1, 52.2, 54.4, 55.2, 68.9, 79.9, 82.3, 128.1, 128.2, 128.5, 129.3, 129.7, 134.7, 134.9, 133.7, 155.1, 155.6, 170.5 and 172.3; *m/z* (ES^+) 557 (MH^+, 22%), 304 (50) and 302 (54). Found MH^+ 557.2868, $C_{30}H_{41}N_2O_8$ requires 557.2863.

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