Unified mild reaction conditions for C2-selective Pd-catalysed tryptophan arylation, including tryptophan-containing peptides

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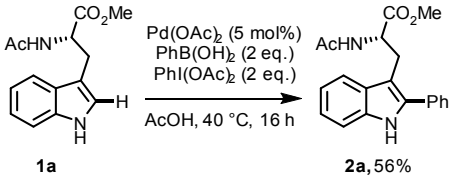
Pd-mediated C–H bond functionalisation protocols have been designed and developed on tryptophan derivatives and tryptophan-containing peptides. The examination of different arylation reactions (three sets of different conditions A–C), all of which are notable for their low temperatures (≤ 40 °C), allowed identification of unified and complementary synthetic approaches toward a series of functionalised tryptophan-containing products. Tryptophan-containing peptides demonstrated to be susceptible to aromatic oxidation were successfully and selectively modified through the application of diaryliodonium salts in good yields.

Introduction

Pd-mediated cross-couplings for the formation of C–C bonds are well established and effective methods for selective functionalisation and modification of simple molecular systems.[1] Metal-mediated direct C–H bond functionalisation has emerged as a viable alternative[2] to classical cross-coupling methodologies as they eliminate, either in part or in full, the need for substrate pre-functionalisation, which potentially presents improved utility in the synthesis of natural products[3] and biomolecules.[4] For example, we have reported the mild[5] and selective direct C–H bond functionalisation of sensitive purine nucleosides, adenosine and 2'-deoxyadenosine.[6] In this paper we have focused on the development of unified synthetic protocols facilitating the mild and efficient arylation of tryptophan derivatives and tryptophan-containing peptides.

Tryptophan is a hydrophobic, indole-containing amino acid which alters the structure of proteins and is a natural fluorescent marker.[7] Extension of the π-system within tryptophans, through conjugation with an aromatic group, significantly improves the intrinsic photophysical properties of the indole motif, which has been evidenced in 2-aryl-,[8] 5-aryl- and 7-aryl-tryptophans.[9c] The 2-aryl-tryptophans can be accessed *via* classical Pd-mediated cross-couplings,[9] or frontier-leading C–H bond functionalisations.[10] Ackermann *et al.* have reported the selective metal-free arylation of engineered indole derivatives on non-natural peptidic scaffolds.[11a] The conditions facilitated selective *C2*-arylation of the synthetic indole, in the presence of a tryptophan.[11b]

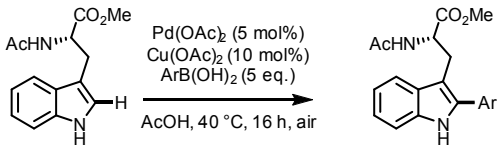


1a **2a**, 56%

Scheme 1. Direct arylation of tryptophan with $PhI(OAc)_2$ using "Conditions A".

Recently, we communicated a convenient method for the *C2*-selective Pd-mediated direct arylation of a tryptophan derivative **1a** and tryptophan-containing peptides.[8] The initial work for our Pd-mediated C–H bond functionalisation processes utilised conditions reported by Sanford *et al.* using $PhB(OH)_2$ and $PhI(OAc)_2$.[12] This allowed access to the desired *C2*-arylation product **2a** in moderate yield ("Conditions A", Scheme 1). The notable advantage of this protocol is the mild temperature and use of readily available reagents to effect the desired transformation.

It was found subsequently that eliminating $PhI(OAc)_2$ and adding $Cu(OAc)_2$ as a co-catalyst for re-oxidation of the Pd^0 (atmospheric air being the terminal oxidant) afforded **2a** in an improved yield of 93%. This methodology was then demonstrated on a series of arylboronic acids under the conditions described in Scheme 2 ("Conditions B").



1a

Ar = C_6H_5, **2a**, 93%
Ar = 4-Me-C_6H_4, **2b**, 88%
Ar = 4-OMeC_6H_4, **2c**, 28%
Ar = 4-F-C_6H_4, **2d**, 77%
Ar = 4-CF_3-C_6H_4, **2e**, 58%

Scheme 2. Direct arylation of **1a** with $Cu(OAc)_2$ as a co-catalyst using "Conditions B".

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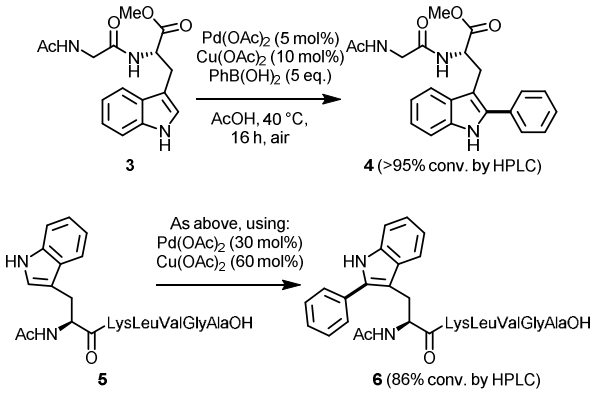
Electronic Supplementary Information (ESI) available: HPLC-ESI-MS data for peptide arylations, UV-Vis spectra for novel compounds and NMR spectra for all compounds. See DOI: 10.1039/x0xx00000x

"Conditions B" were successfully applied to the arylations of two selected tryptophan-containing peptides **3** and **5** (Scheme 3), both of which afforded high conversion to the desired arylation products **4** and **6**, respectively.



Scheme 3. Direct arylation of two selected peptides using "Conditions B".

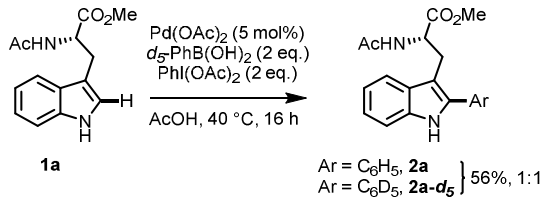
Results and Discussion

With the primary goal of identifying unified synthetic protocols facilitating the mild and efficient arylation of tryptophan derivatives and tryptophan-containing peptides, a focus was placed on understanding the role of the proposed oxidant in the reaction described in Scheme 1, namely $PhI(OAc)_2$.

An analogous experiment was conducted using d_5-$PhB(OH)_2$ (Scheme 4), which allows the delineation of the structure of the arylating reagent formed *in situ*, *i.e*. whether the arylating reagent was derived from $PhB(OH)_2$, $PhI(OAc)_2$ or both.

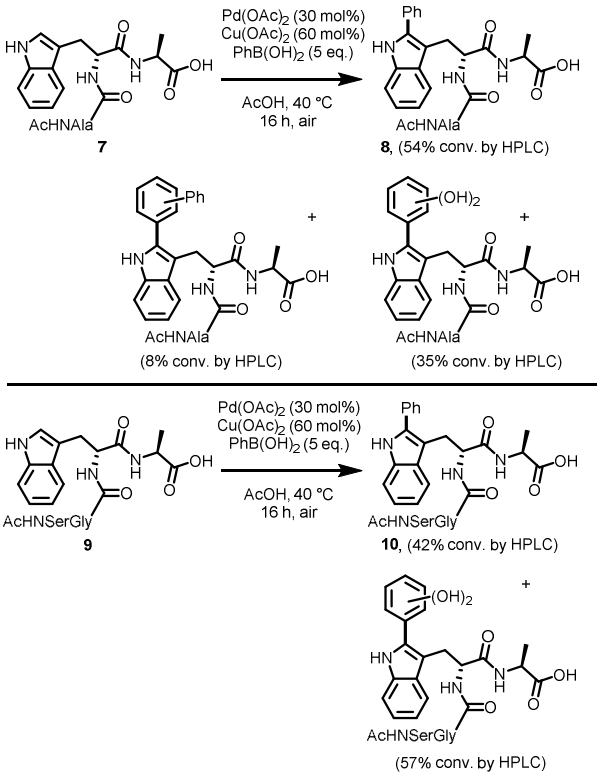
ESI-HRMS (+ve mode) analysis of the product isotopologues from this reaction indicated that an approximately 1:1 mixture of H- and D-labelled products were formed under the reaction conditions. The outcome suggests that $PhI(OAc)_2$ is not simply acting as an oxidant. Indeed, it has been proposed previously that a mixture of an organoboronic acid and $PhI(OAc)_2$ can form an I^{III}-based arylating agent *in situ* under similar reaction conditions. Our observation makes a more convincing case for a role of an *in situ* generated symmetrical Ph_2I^+ species, which adequately accounts for our observation.[13]

The non-selective aryl donation from the diaryliodonium(III) species does present a potential synthetic problem, as it required that the aryl group of the organoboronic acid matched that of the I^{III} reagent, an issue that would become significant for the introduction of substituted aromatic groups. The higher-yielding "Conditions B" appeared an ideal way of circumventing this dilemma *vide infra*.



Scheme 4. Direct arylation of tryptophan with d_5-$PhB(OH)_2$ using "Conditions A". Ratio of isotopologues **2a** and **2a-d$_5$** determined by ESI-HRMS.

In other work on the peptide arylation reactions mediated by Pd and Cu, in the presence of $PhB(OH)_2$ alone, it was found that two specific tryptophan-containing peptides were susceptible to aromatic oxidation, namely Ac-AlaTrpAla-OH **7** and Ac-SerGlyTrpAla-OH **9** (Scheme 5). From the reaction of AlaTrpAla-OH **7**, arylation was noted along with complete loss of starting material; HPLC-MS analysis also revealed the formation of dihydroxylated byproducts as well as diarylated byproducts (selectivity ratio 1:0.6:0.1). The reaction of Ac-SerGlyTrpAla-OH **9** afforded the desired arylation product and similar dihdroxylation byproducts (selectivity ratio 1:1.4). The involvement of Cu^{II} in the oxidation process (*i.e.* oxidative C-H bond activation)[14] appears to be critical, as does the presence of a terminal alanine neighbouring tryptophan. Free C-terminus alanines are known to form stable complexes with Cu^{II},[15] therefore it is proposed that such species are responsible for the observed hydroxylation of the arylated peptide products.



Scheme 5. Direct arylation of two peptides containing a C-terminal alanine residue using "Conditions B".

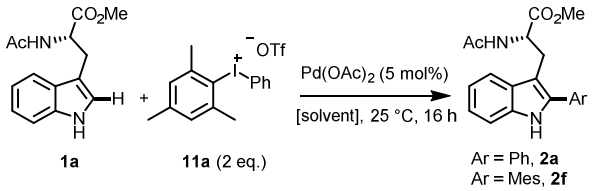
Given these limitations we chose to avoid the use of Cu^{II} as a co-catalyst, thus circumventing the over-oxidation issues. It was hypothesised that utilising a single arylating reagent would be more appealing, also avoiding O_2 as the terminal oxidant required in the Pd/Cu chemistry. Upon recalling our observations regarding the formation of Ph_2I^+ species *in situ*, we examined the reactivity of pre-synthesised highly electrophilic diaryliodine(III) salts, which have garnered a great deal of interest for use in C–H bond functionalisations in recent years.[16] These species can be furnished with a sterically-hindered aryl group which does not transfer in the catalytic process to Pd (and the organic substrate), in tandem with a second aryl group that can incorporate a range of chemical substituents.

Reaction of two equivalents of the [MesPhI]OTf salt **11a** (readily synthesised in a high-yielding one-pot procedure)[17] with **1a** is shown under the conditions described in Table 1. Pleasingly, in acetic acid this gave the desired arylation product **2a** in a yield of 65% (Entry 1), indicating that a Cu^{II} co-catalyst is not necessary for the reaction. Variation of the solvent showed that MeCN, acetone or DMF were not viable (Entries 2–4). Increasing yields, in a range of alcohols, were recorded, in the order MeOH < EtOH < ^{i}PrOH (Entries 5–7). The best solvent however, was found to be EtOAc, which showed full conversion to **2a** (Entry 8, "Conditions C").

In addition to the desired phenylated product **2a**, a small amount of the mesitylated product **2f** was also isolated, formed by donation of the sterically hindered mesityl group, giving a product ratio of **2a**:**2f** of 28:1. In an attempt to prevent this non-selective arylation, the optimised conditions found in the solvent screen (Table 1, Entry 8) were used with another sterically-hindered 2,4,6-tri-*iso*propylphenyl group on the iodonium salt (**11b**). This however did not have the desired effect, as it appeared to lower the reactivity of the system and reduce product selectivity, with the ratio of **2a** to tri-*iso*propylphenyl side product **2g** being 5:1 (Table 1, Entry 9).

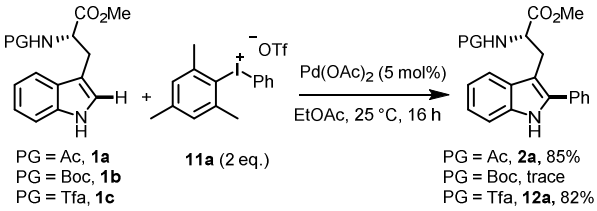
Application of "Conditions C" to small tryptophan-containing peptides was next examined to assess the methodology against more structurally complex systems. A protection/deprotection strategy was chosen to prepare small tryptophan-containing dipeptides, but the *N*-Ac protecting group previously used for compound **1a** proved synthetically challenging when utilised in these dipeptides. A switch to an *N*-Boc protecting group was therefore explored. During these efforts it was discovered that when the optimised arylation conditions shown in Table 1, Entry 8 ("Conditions C") were applied to *N*-Boc, *O*-Me protected tryptophan **1b**, only a trace of the desired arylation product was observed. Unreacted starting material **1a** was recovered along with the expected side products from the diaryliodonium salts used (*i.e.* iodobenzene/ iodomesitylene) A switch to the *N*-Tfa protecting group circumvented this problem and when "Conditions C" were applied to the *N*-Tfa, *O*-Me protected tryptophan **1c** the desired arylation product **12a** was obtained in 82% isolated yield (with 17% of the undesired mesityl product **12b**) (Scheme 6).

Table 1. Solvent screening in the direct arylation of **1a** using [MesPhI]OTf.[a]



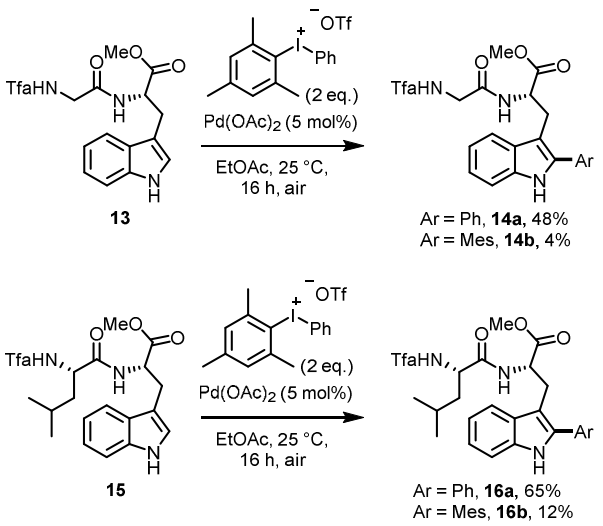
Entry	Solvent	2a, %[b] (yield, %)[c]	2f, %[b] (yield, %)[c]
1	AcOH (at 40 °C)	70 (65)	0
2	MeCN	0	0
3	Acetone	0	0
4	DMF	0	0
5	MeOH	12	0
6	EtOH	15	0
7	^{i}PrOH	47	3
8	EtOAc[d]	91 (85)	9 (3)
9	EtOAc[e,f]	50	10

[a] All reactions conducted with **1a** (0.192 mmol), **11a** (0.384 mmol), $Pd(OAc)_2$ (5 mol%) and solvent (5 mL) at 25 °C, unless otherwise stated. [b] Conversion determined by ^{1}H NMR spectroscopic analysis. [c] Following flash column chromatography. [d] Referred to throughout as "Conditions C". [e] Using iodonium triflate salt **11b** (0.384 mmol), containing a 2,4,6-tri-*iso*propylphenyl group, instead of **11a**. [f] 50% **2a**, 10% **2g** rather than **2f**, 40% starting material (**1a**).



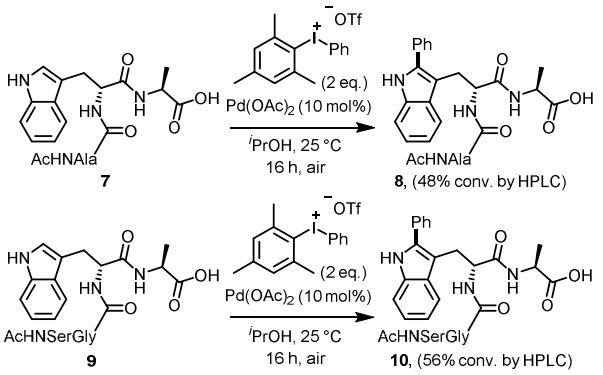
Scheme 6. Effect of *N*-protecting group on the direct arylation of tryptophans using "Conditions C".

"Conditions C" were demonstrated on the dipeptides Tfa-GlyTrp-OMe **13** and Tfa-LeuTrp-OMe **15** (Scheme 7), affording the desired arylation products **14a** and **16a** in moderate to good yields, thus highlighting the utility of this protocol when applied to small tryptophan-containing peptides.



Scheme 7. Direct arylation of two selected peptides using a diaryliodonium salt ("Conditions C").

"Conditions C" were also applied to peptides **7** and **9**, which had proved problematic with the Cu-containing "Conditions B" (Scheme 5), affording the desired arylation products **8** and **10** (Scheme 8); for these polar molecules, *iso*propanol was used in place of ethyl acetate as the reaction solvent. None of the mesityl byproduct was detected in these reactions, possibly because of greater steric encumbrance from the peptides as compared to a single tryptophan residue. Importantly "Conditions C" provide complete selectivity for the desired arylation products, addressing the drawbacks of "Conditions B" highlighted *vida infra*, pleasingly this is also achieved at significantly lower catalyst loadings.



Scheme 8. Direct arylation of peptides susceptible to dihydroxylation using a diaryliodonium salt.

Conclusion

The global aim of this study was to develop synthetic protocols that facilitate the mild and efficient arylation of tryptophan derivatives and tryptophan-containing peptides. This has been broadly achieved, with the different reaction conditions (A–C) being particularly attractive and highly complementary.

Our previous work demonstrated the use of both an aryl boronic acid/iodobenzene diacetate system ("Conditions A") as well as conditions utilising Cu(II) as a co-catalyst ("Conditions B").[8] These conditions allowed several *C2*-aryl tryptophan analogues to be accessed in high yields. The use of a Cu^{II} salt was shown to be incompatible with certain peptidic motifs; in the examples tested a free C-terminal alanine neighbouring tryptophan proved problematic, leading to aromatic oxidation (major competing side reactions) and also diarylation (minor competing side reaction), demonstrating poor product selectivity (1:0.6:0.1 and 1:1.4).

Our methodology was therefore extended to the use of pre-synthesised asymmetric diaryliodonium salts ("Conditions C"), the arylation conditions for which have been developed and optimised to proceed effectively at 25 °C in ethyl acetate under air (which is not necessary as an oxidant, but allows reactions to be run conveniently without the need for inert conditions). Other advantages of "Conditions C" include the avoidance of strong oxidants and metal co-catalysts (*e.g.* Cu^{II}. These conditions have been successfully applied to small tryptophan-containing peptides and the desired arylation products obtained with complete selectively and in synthetically useful yields, without the undesirable aromatic oxidation previously observed.

Our current work is involved with extending these methodologies to more complex systems, as well as examining the underlying mechanisms involved with the arylation of **1a** and derivatives under the different reaction conditions described within this paper.

Experimental

General Experimental Details. Commercially available reagents were purchased from Sigma Aldrich, Fluorochem, Fisher Scientific, Alfa Aesar or Acros Organics and used as received unless otherwise noted. Room temperature (rt) refers to reactions where no thermostatic control was applied and was recorded as 16–22 °C. Petrol refers to the fraction of petroleum ether boiling in the range of 40–60 °C. Dry THF was first obtained from a Pure Solv MD-7 solvent machine and stored under nitrogen, then dried further and any hydroperoxide species removed by refluxing over sodium for 3 days and distilling under argon. Dry methanol was obtained by drying over activated 3 Å molecular sieves and storing under nitrogen. Triethylamine (Et_3N) and di*iso*propylethylamine (DIPEA) were distilled from potassium hydroxide and stored under nitrogen. Air sensitive procedures were performed using standard Schlenk techniques and carried out in oven- or flame-dried glassware. Nitrogen gas was oxygen free and dried immediately prior to use by passing through a column of potassium hydroxide pellets and silica. Thin layer chromatography (TLC) analysis was performed using Merck 5554 aluminium backed silica plates and visualised using UV light (λ_{max} = 254 nm). All flash column chromatography was performed using Merck silica gel 60 (particle size 40 – 63 μm) and a solvent system as stated in the text. Retardation factors are quoted to two decimal places. Optical rotations were

recorded using a JASCO DIP-370 digital polarimeter at 20 °C (using the sodium D line, 259 nm) using a path length of 100 mm and at a concentration indicated in the text. The appropriate solvent was used as a background with ten readings taken for each sample and the average $[\alpha]_D$ values in units of 10^{-1} deg cm^3 g^{-1} are quoted to one decimal place. Melting points were recorded using a Stuart digital SMP3 machine and are quoted to the nearest whole number. Where applicable, decomposition (dec) is noted. NMR spectra were recorded on either a Jeol ECS400 or Jeol ECX400 spectrometer and processed using MestReNova. Spectra were typically recorded at 298K, unless otherwise specified. Chemical shifts are reported in parts per million (ppm). Coupling constants are reported in Hz and quoted to ±0.5 Hz. Multiplicities are described as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin), sextet, (sext), heptet (hept), multiplet (m), apparent (app) and broad (br). ^{1}H NMR spectra were typically recorded at 400 MHz. Chemical shifts are internally referenced to residual undeuterated solvent and given to two decimal places. ^{13}C NMR spectra were recorded at 101 MHz. Chemical shifts are internally referenced to residual undeuterated solvent and given to one decimal place. ^{11}B NMR spectra were recorded at 128 MHz and obtained with ^{1}H decoupling. Chemical shifts are externally referenced to $BF_3{\bullet}OEt_2$ and given to one decimal place. ^{19}F NMR spectra were recorded at 376 MHz and obtained with ^{1}H decoupling. Chemical shifts are externally referenced to $CFCl_3$ and given to one decimal place. ^{31}P NMR spectra were recorded at 162 MHz and obtained with ^{1}H decoupling. Chemical shifts are externally referenced to H_3PO_4 and given to one decimal place. Mass spectrometry was performed using a Bruker Daltronics micrOTOF spectrometer using electrospray ionization (ESI). Mass to charge ratios (*m/z*) are reported in Daltons with percentage abundance in parentheses along with the corresponding fragment ion, where known. Where complex isotope patterns were observed, the most abundant ion is reported. High resolution mass spectra are reported with <5 ppm error. IR spectrometry was performed using a Bruker Alpha FT-IR spectrometer and signals are reported in wavenumbers (cm^{-1}) to the nearest whole number. UV-visible spectroscopy was performed using a Jasco V-560 spectrometer. A baseline in the appropriate solvent was obtained prior to recording spectra. Elemental (CHN) analysis was carried out using an Exeter Analytical CE-440 Elemental Analyser. All values are given as percentages to two decimal places. "Conditions A" and "Conditions B" are also reported in our preliminary communication on this work.[8]

General Procedure 1: direct arylation using arylboronic acids ("Conditions B").[8] To a microwave tube was added substrate (1 eq.), the desired boronic acid (2 eq.), $Cu(OAc)_2$ (10 mol%), $Pd(OAc)_2$ (5 mol%) and AcOH. The reaction mixture was stirred at 40 °C for 16 h. The resulting brown reaction mixture was filtered through Celite then washed with sat. aq. $NaHCO_3$. The organic layer was collected and dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give the crude residue. The residue was dry-loaded onto silica gel and purified by flash column chromatography to give the title compound.

General Procedure 2: preparation of diaryl iodonium salts.[17] Bis(acetyloxy)phenyl-λ^3-iodane (1 eq.) and the desired aryl substrate (1.1 eq.) were added to a round-bottomed flask and dissolved in CH_2Cl_2. The mixture was cooled to 0 °C then trifluoromethanesulfonic acid (1.1 eq.) was added dropwise with stirring. After complete addition the reaction was stirred for 2 h over which time it was allowed to warm to rt. After 2 h the solvent was removed under reduced pressure to give an orange-white residue to which Et_2O was added to precipitate a white solid. This was filtered through a glass sinter and washed on the filter with more Et_2O until the filtrate ran clear of coloured components. The solid was then dried *in vacuo* at 100 °C to give the title compound.

General Procedure 3: direct arylation using diaryl iodonium salts ("Conditions C"). To a microwave tube was added substrate (1 eq.), the desired diaryl iodonium salt (2 eq.), $Pd(OAc)_2$ (5 mol%) and EtOAc. The reaction mixture was stirred at 25 °C for 16 h. The resulting black reaction mixture was filtered through Celite then washed with sat. aq. $NaHCO_3$. The organic layer was collected and dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give the crude residue. This was dry-loaded onto silica gel and purified by flash column chromatography to give the title compound.

Methyl (2*S*)-2-amino-3-(1*H*-indol-3-yl)propanoate hydrochloride.[18] To a Schlenk tube under N_2 was added dry MeOH (50 mL). Thionyl chloride (4.3 mL, 7.02 g, 59 mmol, 2.4 eq.) was added dropwise at −15 °C. L-Tryptophan 20 (5 g, 24.5 mmol, 1 eq.) was then added in three portions, resulting in a white suspension. The reaction mixture was warmed to ambient temperature and stirred for 24 h. During this time a clear orange solution was formed. Water (5 mL) was added to the reaction mixture and the solvent removed under reduced pressure to give product as an off-white solid (6.18 g, 99%). Mp 205–206 °C dec (lit.[19] 214 °C dec); ^{1}H NMR (400 MHz, CD_3OD, δ): 10.61 (br s, 1H), 7.54 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.40 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.22 (s, 1H), 7.14 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 7.07 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 4.33 (dd, *J* = 7.5, 5.5 Hz, 1H), 3.79 (s, 3H), 3.46 (dd, *J* = 15.0, 5.5 Hz, 1H), 3.37 (dd, *J* = 15.0, 7.5 Hz, 1H); ^{13}C NMR (101 MHz, CD_3OD, δ): 170.8, 138.3, 128.2, 125.6, 122.9, 120.3, 118.8, 112.7, 107.4, 54.6, 53.6, 27.5; ESI-MS *m/z* (ion, %): 219 ($[M-Cl]^+$, 100); ESI-HRMS *m/z*: 219.1130 $[M-Cl]^+$ (calc. for $C_{12}H_{15}N_2O_2$ 219.1128); IR (solid state ATR, cm^{-1}): 3259, 2856, 1747, 1501, 1436, 1351, 1210, 1108, 730; anal. calc. for $C_{12}H_{15}ClN_2O_2$: C 56.58, H 5.94, N 11.00 found: C 56.44, H 5.85, N 10.87.

Methyl (2*S*)-2-acetamido-3-(1*H*-indol-3-yl)propanoate, 1a.[18] To a three-necked round-bottomed flask fitted with a reflux condenser and purged with N_2 was added methyl (2*S*)-2-amino-3-(1*H*-indol-3-yl)propanoate hydrochloride (3 g, 13.7 mmol, 1 eq.), dry THF (150 mL) and dry triethylamine (2 mL). The mixture was stirred to give a white suspension before being cooled to 0 °C, then acetic anhydride (1.4 mL, 1.5 g, 15.1 mmol, 1.1 eq.) was added in one portion. The reaction was then stirred for 2 h at 80 °C to give a white suspension. This

was added to deionised water (150 mL) and extracted into EtOAc (3 × 150 mL). The organic layers were combined and washed sequentially with 1 M aq. HCl (100 mL), sat. aq. $NaHCO_3$ (100 mL) and brine (100 mL). The organic layer was collected and dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give a colourless oil. Trituration with Et_2O resulted in the product as an off-white solid (2.93 g, 82%). [α]D = +41.5 (*c* 0.10, $CHCl_3$); Mp 154–155 °C (lit.[19] 155–156 °C); ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.27 (s, 1H), 7.53 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.39–7.33 (m, 1H), 7.19 (ddd, 8.0, 7.0, 1.0 Hz, 1H), 7.12 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.97 (d, *J* = 2.5 Hz, 1H), 6.03 (d, *J* = 8.0 Hz, 1H), 4.96 (dt, *J* = 8.0, 5.0 Hz, 1H), 3.70 (s, 3H), 3.35 (dd, *J* = 15.0, 5.0 Hz, 1H), 3.29 (dd, *J* = 15.0, 5.0 Hz, 1H), 1.95 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$, δ): 172.6, 169.4, 136.1, 127.1, 123.7, 120.1, 118.4, 118.0, 111.5, 109.6, 53.2, 51.8, 27.1, 22.3; ESI-MS *m/z* (ion, %): 261 ($[M+H]^+$, 5), 283 ($[M+Na]^+$, 100); ESI-HRMS *m/z*: 283.1053 $[M+Na]^+$ (calc. for $C_{14}H_{16}N_2O_3Na$ 283.1053); IR (solid state, ATR, cm^{-1}): 3405, 3315, 1732, 1661, 1520, 1434, 1220, 1123, 746, 665, 613, 519, 427; anal. calc. for $C_{14}H_{16}N_2O_3$: C 64.60, H 6.20, N 10.76 found C 64.34, H 6.23, N 10.47.

Methyl (2S)-2-{[(*tert*-butoxy)carbonyl]amino}-3-(1H-indol-3-yl)propanoate, 1b.[20] To a round-bottomed flask containing a solution of methyl (2*S*)-2-amino-3-(1*H*-indol-3-yl)propanoate hydrochloride (100 mg, 0.39 mmol, 1 eq.) and K_2CO_3 (54 mg, 0.39, 1 eq.) in deionised water (1 mL) was added a solution of di-*tert*-butyl dicarbonate (85 mg, 0.39 mmol, 1 eq.) in acetone (1 mL) at 0 °C with stirring. The solution was stirred for 2 h during which time it was allowed to warm to rt. After 2 h the acetone was removed under reduced pressure and deionised water added. This was extracted into EtOAc three times, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give the product as an off-white solid (117 mg, 94%).[α]D = +43.1 (*c* 0.10, $CHCl_3$); Mp 146–148 °C (lit.[21] 145–146 °C) ; ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.20 (br s, 1H), 7.58–7.53 (m, 1H), 7.35 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.19 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 7.12 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.99 (s, 1H), 5.09 (d, *J* = 8.0 Hz, 1H), 4.71–4.59 (m, 1H), 3.68 (s, 3H), 3.29 (dd, *J* = 5.5, 3.0 Hz, 2H), 1.43 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$, δ): 172.9, 155.4, 136.3, 127.6, 123.0, 122.1, 119.5, 118.6, 111.4, 109.8, 80.0, 54.3, 52.3, 28.4, 28.0; ESI-MS *m/z* (ion, %): 319 ($[M+H]^+$, 14), 341 ($[M+Na]^+$, 100); ESI-HRMS *m/z*: 341.1465 $[M+Na]^+$ (calc. for $C_{17}H_{22}N_2NaO_4$ 341.1472).

Methyl (2*S*)-3-(1*H*-indol-3-yl)-2-(trifluoroacetamido)propanoate, 1c.[22] To a round-bottomed flask containing methyl (2*S*)-2-amino-3-(1*H*-indol-3-yl)propanoate hydrochloride (1.27 g, 5 mmol, 1 eq.) was added Et_3N (0.75 mL, 0.54 g, 5 mmol, 1 eq.) and MeOH (2.5 mL) and the resulting suspension stirred for 5 min. After 5 min ethyl trifluoroacetate (0.85 mL, 1.01 g, 6.35 mmol, 1.27 eq.) was added and the mixture stirred at rt for 16 h, during which time a clear solution formed. After 16 h the solvent was removed under reduced pressure and the resulting residue acidified with 2M HCl, before being extracted into EtOAc three times. The organic layers were combined then washed with brine, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give the product as an off-white solid (1.35 g, 90%). R_f 0.16 (3:1 petrol/EtOAc *v/v*); [α]D = +50.7 (*c* 0.10, $CHCl_3$); Mp 108–109 °C (lit.[23] 107–109 °C); ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.30 – 8.18 (br s, 1H), 7.54–7.47 (m, 1H), 7.36 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.22 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 7.15 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.96 (d, *J* = 2.5 Hz, 1H), 6.95 (s, 1H), 4.94 (dt, *J* = 8.0, 5.0 Hz, 1H), 3.73 (s, 3H), 3.42 (dd, *J* = 5.0, 1.0 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$, δ): 170.8, 156.9 (q, $^2J_{CF}$ = 37.5), 136.2, 127.4, 123.1, 122.6, 120.0, 118.3, 116.3 (q, $^1J_{CF}$ = 287.0), 111.6, 108.8, 53.5, 53.0, 27.2; ^{19}F NMR (376 MHz, $CDCl_3$, δ): −75.8; ESI-MS *m/z* (ion, %): 315 ($[M+H]^+$, 50), 332 ($[M+NH_4]^+$, 40), 337 ($[M+Na]^+$, 100), 353 ($[M+K]^+$, 10); ESI-HRMS *m/z*: 315.0950 $[M+H]^+$ (calc. for $C_{14}H_{14}F_3N_2O_3$ 315.0951).

Methyl (2*S*)-2-acetamido-3-(2-phenyl-1*H*-indol-3-yl)propanoate, 2a. Method A ("Conditions A"): To a microwave tube was added phenylboronic acid (47 mg, 0.384 mmol, 2 eq.), bis(acetyloxy)phenyl-λ^3-iodane (123 mg, 0.384 mmol, 2 eq.), $Pd(OAc)_2$ (2 mg, 9.6 µmol, 5 mol%) and AcOH (5 mL). The reaction mixture was stirred at 40 °C for 10 min. To the resulting orange-brown solution was added methyl (2*S*)-2-acetamido-3-(1*H*-indol-3-yl)propanoate (50 mg, 0.192 mmol, 1 eq.) **1a**. The reaction was stirred at 40°C for 16 h. The resulting black reaction mixture was filtered through Celite, and the solvent removed under reduced pressure to give a brown solid. This was dissolved in EtOAc (10 mL) then washed with sat. aq. $NaHCO_3$. The organic layer was collected and dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give a brown solid. This was dry-loaded onto silica gel and purified by flash column chromatography (40% petrol/EtOAc, *v/v*) to give product as an off-white solid (36 mg, 56%). **Method B:** Synthesised using General Procedure 1 from methyl (2*S*)-2-acetamido-3-(1*H*-indol-3-yl)propanoate **1a** (50 mg, 0.192 mmol, 1 eq.), phenylboronic acid (47 mg, 0.384 mmol, 2 eq.), $Cu(OAc)_2$ (3.5 mg, 19.2 µmol, 10 mol%) and $Pd(OAc)_2$ (2 mg, 9.6 µmol, 5 mol%) in AcOH (5 mL). Flash column chromatography (40% petrol/EtOAc, *v/v*) gave the product as an off-white solid (60 mg, 93%). **Method C:** Synthesised using General Procedure 3 from methyl (2*S*)-2-acetamido-3-(1*H*-indol-3-yl)propanoate **1a** (50 mg, 0.192 mmol, 1 eq.), phenyl (2,4,6-trimethylphenyl)iodonium trifluoromethanesulfonate **11a** (181 mg, 0.384 mmol, 2 eq.) and $Pd(OAc)_2$ (2 mg, 9.6 µmol, 5 mol%) in EtOAc (5 mL). Flash column chromatography (40% petrol/EtOAc, *v/v*) gave the product as an off-white solid (55 mg, 85%). R_f 0.27 (40% petrol/EtOAc *v/v*); [α]D = +47.3 (*c* 0.10, $CHCl_3$); Mp 83–84 °C (lit.[24] 85–86 °C); ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.20 (s, 1H), 7.60–7.54 (m, 3H), 7.51–7.45 (m, 2H), 7.42–7.34 (m, 2H), 7.21 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 7.14 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 5.79 (d, *J* = 8.0 Hz, 1H), 4.84 (dt, *J* = 8.0, 5.5 Hz, 1H), 3.55 (dd, *J* = 5.5, 1.0 Hz, 2H), 3.29 (s, 3H), 1.66 (s, 3H); ^{13}C NMR (101 MHz, ($CDCl_3$, δ): 172.3, 169.9, 136.1, 135.9, 133.3, 129.4, 129.1, 128.4, 128.0, 122.5, 120.0, 118.8, 111.2, 106.5, 52.9, 52.1, 26.6, 22.9; ESI-MS *m/z* (ion, %): 337 ($[M+H]^+$, 40), 359 ($[M+Na]^+$, 100); ESI-HRMS *m/z*: 337.1546 $[M+H]^+$ (calc. for

$C_{20}H_{20}N_2O_3$ 337.1547); IR (solid state ATR, cm^{-1}): 3272, 1735, 1651, 1519, 1436, 1373, 1215, 739, 696, 496.

Methyl (2*S*)-2-acetamido-3-[2-(4-methylphenyl)-1*H*-indol-3-yl]propanoate, 2b. Synthesised using General Procedure 1 from methyl (2*S*)-2-acetamido-3-(1*H*-indol-3-yl)propanoate **1a** (50 mg, 0.192 mmol, 1 eq.), 4-methylphenylboronic acid (52 mg, 0384 mmol, 2 eq.), $Cu(OAc)_2$ (3.5 mg, 19.2 µmol, 10 mol%) and $Pd(OAc)_2$ (2 mg, 9.6 µmol, 5 mol%) in AcOH (5 mL). Flash column chromatography (1:1 petrol/EtOAc, *v/v*) gave the product as an off-white solid (59 mg, 88%). R_f 0.32 (1:1 EtOAc/petrol); [α]D = +51.9 (*c* 0.11, $CHCl_3$); Mp 97–99 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.09 (s, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.48–7.44 (m, 2H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.19 (ddd, J= 8.0, 7.0, 1.0 Hz, 1H), 7.13 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 5.77 (d, *J* = 8.0 Hz, 1H), 4.82 (dt, *J* = 8.0, 5.5 Hz, 1H), 3.53 (d, *J* = 5.5 Hz, 1H), 3.52 (d, *J* = 5.5 Hz, 1H), 3.33 (s, 3H), 2.41 (s, 3H), 1.66 (s, 3H); ^{13}C NMR (126 MHz, CDCl3, δ): 172.3, 169.8, 138.0, 136.2, 135.7, 130.3, 128.2, 122.4, 120.0, 118.8, 111.1, 106.4, 60.5, 53.0, 52.1, 26.7, 22.9, 21.3, 14.3; ESI-MS *m/z* (ion, %): 391 ($[M+H]^+$), 100); ESI-HRMS *m/z*: 350.1628 $[M+H]^+$ (calc. for $C_{21}H_{22}N_2O_3$ 350.1630); IR (solid state ATR, cm^{-1}) 3331, 2951, 1731, 1657, 1506, 1372, 1305, 1215, 1010, 822, 742; UV-Vis (DMSO, nm) λ_{max} 310 (ε = 8893 mol dm^{-3} cm^{-1}).

Methyl (2*S*)-2-acetamido-3-[2-(4-methoxyphenyl)-1*H*-indol-3-yl]propanoate, 2c. Synthesised using General Procedure 1 from methyl (2*S*)-2-acetamido-3-(1*H*-indol-3-yl)propanoate **1a** (50 mg, 0.192 mmol, 1 eq.), 4-methoxyphenylboronic acid (58 mg, 0384 mmol, 2 eq.), $Cu(OAc)_2$ (3.5 mg, 19.2 µmol, 10 mol%) and $Pd(OAc)_2$ (2 mg, 9.6 µmol, 5 mol%) in AcOH (5 mL). Flash column chromatography (1:1 petrol/EtOAc, *v/v*) gave the product as a brown solid (20 mg, 28%). R_f 0.15 (1:1 EtOAc/petrol *v/v*); [α]D = +34.9 (*c* 0.10, $CHCl_3$); Mp 202–205 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.56 (br s, 1H), 7.57–7.51 (m, 1H), 7.46–7.39 (m, 2H), 7.34–7.28 (m, 1H), 7.17 (dd, *J* = 7.0, 1.5 Hz, 1H), 7.12 (dd, *J* = 7.0, 1.5 Hz, 1H), 6.95 – 6.90 (m, 2H), 5.85 (d, *J* = 8.0 Hz, 1H), 4.81 (dt, *J* = 8.0, 5.5 Hz, 1H), 3.81 (s, 3H), 3.48 (d, *J* = 5.5 Hz, 2H), 3.34 (s, 3H), 1.66 (s, 3H); ^{13}C NMR (101 MHz, ($CDCl_3$, δ): 172.4, 169.8, 159.5, 136.1, 135.7, 129.6, 129.5, 125.6, 122.2, 119.9, 118.6, 114.6, 111.1, 105.9, 55.5, 53.0, 52.2, 26.7, 23.0; ESI-MS *m/z* (ion, %): 367 ($[M+H]^+$, 50), 389 ($[M+Na]^+$, 100); ESI-HRMS *m/z*: 389.1458 $[M+Na]^+$ (calc. for $C_{21}H_{22}N_2NaO_4$ 389.1472).

Methyl (2*S*)-2-acetamido-3-[2-(4-fluorophenyl)-1*H*-indol-3-yl]propanoate, 2d. Synthesised using General Procedure 1 from methyl (2S)-2-acetamido-3-(1*H*-indol-3-yl)propanoate **1a** (50 mg, 0.192 mmol, 1 eq.), 4-fluorophenylboronic acid (54 mg, 0384 mmol, 2 eq.), $Cu(OAc)_2$ (3.5 mg, 19.2 µmol, 10 mol%) and $Pd(OAc)_2$ (2 mg, 9.6 µmol, 5 mol%) in AcOH (5 mL). Flash column chromatography (1:1 petrol/EtOAc, *v/v*) gave the product as a brown solid (52 mg, 77%). R_f 0.23 (1:1 EtOAc/petrol *v/v*); [α]D = +54.4 (*c* 0.10, $CHCl_3$); Mp 213–216 °C dec; ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.18 (br s, 1H), 7.56 (ddt, *J* = 8.0, 1.5, 1.0 Hz, 1H), 7.54–7.48 (m, 2H), 7.34 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.20 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 7.17–7.12 (m, 3H), 5.84 (d, *J* = 8.0 Hz, 1H), 4.83 (dt, *J* = 8.0, 5.5 Hz, 1H), 3.56–3.40 (m, 2H), 3.33 (s, 3H), 1.70 (s, 3H); ^{13}C NMR (101 MHz, ($CDCl_3$, δ): 172.3, 169.7, 162.9 (d, $^1J_{CF}$ = 249.0 Hz), 135.8, 135.1, 130.3 (d, $^3J_{CF}$ = 8.0 Hz), 129.5, 129.4 (d, $^4J_{CF}$ = 3.5 Hz), 122.8, 120.3, 119.0, 116.3 (d, $^2J_{CF}$ = 21.5 Hz), 111.1, 107.0, 52.9, 52.2, 26.8, 23.1; ^{19}F NMR (376 MHz, $CDCl_3$, δ): −112.8–−112.9 (m); ESI-MS *m/z* (ion, %): 355 ($[M+H]^+$, 60), 377 ($[M+Na]^+$, 100); ESI-HRMS *m/z*: 355.1442 $[M+H]^+$ (calc. for $C_{20}H_{20}FN_2O_3$ 355.1452).

Methyl (2S)-2-acetamido-3-{2-[4-(trifluoromethyl)phenyl]-1H-indol-3-yl}propanoate, 2e. Synthesised using General Procedure 1 from methyl (2S)-2-acetamido-3-(1*H*-indol-3-yl)propanoate **1a** (50 mg, 0.192 mmol, 1 eq.), 4-(trifluoromethyl)phenylboronic acid (36 mg, 0.384 mmol, 2 eq.), $Cu(OAc)_2$ (3.5 mg, 19.2 µmol, 10 mol%) and $Pd(OAc)_2$ (2 mg, 9.6 µmol, 5 mol%) in AcOH (5 mL). Flash column chromatography (1:1 petrol/EtOAc, *v/v*) gave the product as a brown solid (45 mg, 58%). R_f 0.34 (1:1 EtOAc/petrol); [α]D = +62.0 (*c* 0.13, $CHCl_3$); Mp 202–206 °C; ^{1}H NMR (400 MHz, CDCl3, δ): 8.41 (s, 1H), 7.72–7.63 (m, 4H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.22 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.15 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 5.87 (d, *J* = 8.0 Hz, 1H), 4.84 (dt, *J* = 8.0, 5.2 Hz, 1H), 3.59 – 3.48 (m, 2H), 3.29 (s, 3H), 1.67 (s, 3H); ^{13}C NMR (101 MHz, CDCl3, δ): 172.2, 169.9, 136.9, 136.1, 134.3, 129.9 (q, $^2J_{CF}$ = 32.0 Hz), 129.5, 128.5, 126.1 (q, $^3J_{CF}$ = 4.0 Hz), 124.1 (q, $^1J_{CF}$ = 247.0 Hz), 123.3, 120.4, 119.2, 111.4, 108.2, 53.0, 52.2, 27.0, 23.0; ESI-MS *m/z* (ion, %): 405 ($[M+H]^+$, 30), 427 ($[M+Na]^+$, 100); ESI-HRMS *m/z*: 405.1410 $[M+H]^+$ (calc. for $C_{21}H_{20}F_3N_2O_3$ 405.1421); IR (solid state ATR, cm^{-1}) 3288, 2925, 2860, 1730, 1651, 1505, 1438, 1285, 1245, 1215, 1027, 835, 743; UV-Vis (DMSO, nm) λ_{max} 318 (ε = 10297 mol dm^{-3} cm^{-1}).

Methyl (2*S*)-2-acetamido-3-[2-(2,4,6-trimethylphenyl)-1*H*-indol-3-yl]propanoate, 2f. Synthesised using General Procedure 3 from methyl (2S)-2-acetamido-3-(1*H*-indol-3-yl)propanoate **1a** (50 mg, 0.192 mmol, 1 eq.), phenyl (2,4,6-trimethylphenyl)iodonium trifluoromethanesulfonate **11a** (181 mg, 0.384 mmol, 2 eq.) and $Pd(OAc)_2$ (2 mg, 9.6 µmol, 5 mol%) in EtOAc (5 mL). Flash column chromatography (40% petrol/EtOAc, *v/v*) gave the product as an off-white solid (2 mg, 3%). R_f 0.31 (1:1 EtOAc/petrol *v/v*); [α]D = +35.2 (*c* 0.10, $CHCl_3$); Mp 158–159 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.89 (br s, 1H), 7.61 (ddt, *J* = 7.5, 1.5, 1.0 Hz, 1H), 7.37–7.33 (m, 1H), 7.20 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.16 (d, *J* = 7.5 Hz, 1H), 6.99 (ddt, *J* = 4.0, 1.5, 1.0 Hz, 2H), 5.64 (d, *J* = 7.5 Hz, 1H), 4.72 (ddd, *J* = 7.5, 7.0, 5.0 Hz, 1H), 3.47 (s, 3H), 3.17 (dd, *J* = 15.0, 5.0 Hz, 1H), 3.02 (dd, *J* = 15.0, 7.0 Hz, 1H), 2.35 (s, 3H), 2.11 (d, *J* = 1.0 Hz, 6H), 1.75 (s, 3H); ^{13}C NMR (101 MHz, ($CDCl_3$, δ): 172.5, 169.9, 138.9, 138.3, 138.2, 135.9, 134.7, 128.8, 128.7, 128.7, 128.6, 122.1, 119.9, 118.8, 110.9, 108.0, 100.1, 53.1, 52.3, 27.2, 23.1, 21.3, 20.4, 20.3; ESI-MS *m/z* (ion, %): 379 ($[M+H]^+$, 40), 401 ($[M+Na]^+$, 100); ESI-HRMS *m/z*: 379.2015 $[M+H]^+$ (calc. for $C_{23}H_{27}N_2O_3$ 379.2016); IR (solid state, ATR, cm^{-1}): 3402, 3289, 2953, 2919, 2852, 1741, 1646, 1515, 1458, 1435, 1373, 1304, 1293, 1260, 1239, 1218, 1129, 1031, 1012, 987, 854, 798, 744, 591, 505, 445; UV-Vis (DMSO, nm): λ_{max} 288 (ε = 15092 mol dm^{-3} cm^{-1}).

2-Acetamidoacetic acid. To a round-bottomed flask was added glycine (5 g, 66.6 mmol, 1 eq.) and water (150 mL). To this, acetic anhydride (18.9 mL, 20.4 g, 200 mmol, 3 eq.) was added dropwise and the reaction mixture was stirred at rt for 1 h. The mixture was then cooled to 4 °C for 16 h, and the resulting precipitate collected by filtration through a sintered funnel to give product as a white solid (4.46 g, 57%). Mp 207–208 °C (lit.[25] 206–208 °C dec); ^{1}H NMR (400 MHz, $(CD_0)_2SO$) δ 12.51 (s, 1H), 8.18 (s, 1H), 3.71 (d, *J* = 6.0 Hz, 2H), 1.84 (s, 3H); ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 171.5, 169.6, 40.6, 22.3; ESI-MS *m/z* (ion, %): 118 ($[M+H]^+$, 40), 140 ($[M+Na]^+$, 100); ESI-HRMS *m/z*: 118.0501 $[M+H]^+$ (calc. for $C_4H_8NO_3$ 118.0499); IR (solid state ATR, cm^{-1}) 3350, 1944, 1897, 1717, 1580, 1547, 1439, 1379, 1351, 1276, 1227, 1137, 993, 902. 682.

Methyl (2*S*)-2-(2-acetamidoacetamido)-3-(1*H*-indol-3-yl)propanoate, 3. To a Schlenk tube was added methyl (2*S*)-2-amino-3-(1*H*-indol-3-yl)propanoate hydrochloride (190 mg, 0.872 mmol, 1 eq.), 2-Acetamidoacetic acid (102 mg, 0.872 mmol, 1 eq.) and *N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC•HCl) (167 mg, 0.872 mmol, 1 eq.). The reaction mixture was placed under vacuum and refilled with N_2, and this process repeated twice. Dry CH_2Cl_2 (5 mL) was added, and the mixture stirred for 16 h at ambient temperature. The solvent was removed under reduced pressure. The resulting residue was dissolved in EtOAc (15 mL) and washed with 1 M aq. HCl (20 mL), sat. aq. $NaHCO_3$ (40 mL) and brine (40 mL). The organic layer was collected and dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give product as a white solid (96 mg, 35%). [α]D = +36.5 (*c* 0.10, $CHCl_3$); Mp 98–102 °C (lit.[26] 178 °C); ^{1}H NMR (400 MHz, CD_3OD) δ 7.48 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.31 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.10–7.04 (m, 3H), 7.00 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 4.73 (dd, *J* = 7.0, 6.0 Hz, 1H), 3.83 (d, *J* = 16.5, 1H), 3.78 (d, *J* = 16.5 Hz, 1H), 3.64 (s, 3H), 3.27 (ddd, *J* = 14.5, 7.0, 0.5 Hz, 1H), 3.19 (ddd, *J* = 14.5, 7.0, 0.5 Hz, 1H), 1.92 (s, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 173.9, 173.7, 171.4, 138.0, 128.7, 124.6, 122.5, 119.9, 119.1, 112.3, 110.3, 54.8, 52.7, 49.0, 43.4, 28.4; ESI-MS *m/z* (ion, %): 318 ($[M+H]^+$, 20), 340 ($[M+Na]^+$, 100); ESI-HRMS *m/z*: 318.1433 $[M+H]^+$ (calc. for $C_{16}H_{20}N_3O_4$ 318.1448); IR (solid state ATR, cm^{-1}) 3286, 2947, 1737, 1655, 1610, 1508, 1460, 1439, 1372, 1285, 1248, 1215, 1177, 1030.

Methyl (2*S*)-2-(2-acetamidoacetamido)-3-(2-phenyl-1*H*-indol-3-yl)propanoate, 4. Synthesised using General Procedure 1 from methyl (2*S*)-2-(2-acetamidoacetamido)-3-(1*H*-indol-3-yl)propanoate **3** (10 mg, 0.032 mmol, 1 eq.), phenylboronic acid (20 mg, 0.16 mmol, 5 eq.), $Cu(OAc)_2$ (0.6 mg, 3.2 µmol, 10 mol%) and $Pd(OAc)_2$ (0.36 mg, 1.6 µmol, 5 mol%) in AcOH (0.5 mL). Flash column chromatography (2% MeOH/EtOAc, *v/v*) gave the product as an off-white solid (42 mg, 68%). R_f 0.24 (2% MeOH/EtOAc, *v/v*); [α]D = +32.1 (*c* 0.10, $CHCl_3$); Mp 199 °C dec; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.61–7.50 (m, 3H), 7.50–7.41 (m, 2H), 7.39–7.33 (m, 2H), 7.19 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 7.15 (s, ddd, *J* = 8.0, 7.0, 1.5, 1H), 6.18 (br d, *J* = 8.0 Hz, 1H), 5.95 (br t, *J* = 5.0 Hz, 1H), 4.80 (dt, *J* = 8.0, 5.5 Hz, 1H), 3.66 – 3.38 (m, 4H), 3.34 (s, 3H), 1.87 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8, 170.3, 168.3, 136.2, 135.9, 133.2, 129.4, 129.3, 128.4, 128.2, 122.8, 120.2, 118.8, 111.3, 106.5, 77.4, 53.1, 52.3, 42.7, 26.6, 23.0; ESI-MS *m/z* (ion, %): 394 ($[M+H]^+$, 10), 416 ($[M+Na]^+$, 100); ESI-HRMS *m/z*: 394.1763 $[M+H]^+$ (calc. for $C_{22}H_{24}N_3O_4$ 394.1761).

Arylated product of Ac-TrpLysLeuValGlyAla-OH 5, 6. To a microwave tube was added peptide **5** (10 mg, 0.014 mmol, 1 eq.), phenylboronic acid (8.5 mg, 0.07 mmol, 5 eq.), $Cu(OAc)_2$ (1.5 mg, 0.0084 mmol, 60 mol%), $Pd(OAc)_2$ (0.9 mg, 0.0042 mmol, 30 mol%) and AcOH (1 mL). The reaction mixture was stirred at 40 °C for 16 h. The solvent was removed under reduced pressure to give a brown residue, which was analysed by HPLC-ESI-MS. ESI-MS *m/z* (ion, %): 791 (M^+, 86).

Arylated product of Ac-AlaTrpAla-OH 7, 8. Method A: To a microwave tube was added peptide **7** (10 mg, 0.026 mmol, 1 eq.), phenylboronic acid (16 mg, 0.13 mmol, 5 eq.), $Cu(OAc)_2$ (2.8 mg, 0.0156 mmol, 60 mol%), $Pd(OAc)_2$ (1.8 mg, 0.0078 mmol, 30 mol%) and AcOH (1 mL). The reaction mixture was stirred at 40 °C for 16 h. The solvent was removed under reduced pressure to give a brown residue, which was analysed by HPLC-ESI-MS. **Method B:** To a microwave tube was added peptide **7** (10 mg, 0.026 mmol, 1 eq.), phenyl(2,4,6-trimethylphenyl)iodonium trifluoromethanesulfonate, **11a** (25 mg, 0.052 mmol, 2 eq.), $Pd(OAc)_2$ (0.6 mg, 0.0026 mmol, 10 mol%) and ^{i}PrOH (1 mL). The reaction mixture was stirred at 25 °C for 16 h. The resulting brown reaction mixture was filtered through Celite with MeOH (5 mL) and the solvent removed under reduced pressure to give a brown residue, which was analysed by HPLC-ESI-MS. ESI-MS *m/z* (ion, %): 465 ($[M+H]^+$, 100).

Arylated product of Ac-SerGlyTrpAla-OH 9, 10. Method A: To a microwave tube was added peptide **9** (10 mg, 0.022 mmol, 1 eq.), phenylboronic acid (13 mg, 0.11 mmol, 5 eq.), $Cu(OAc)_2$ (2.4 mg, 0.0132 mmol, 60 mol%), $Pd(OAc)_2$ (1.5 mg, 0.0066 mmol, 30 mol%) and AcOH (1 mL). The reaction mixture was stirred at 40 °C for 16 h. The solvent was removed under reduced pressure to give a brown residue, which was analysed by HPLC-ESI-MS. **Method B:** To a microwave tube was added peptide **9** (10 mg, 0.022 mmol, 1 eq.), phenyl(2,4,6-trimethylphenyl)iodonium trifluoromethanesulfonate, **11a** (21 mg, 0.044 mmol, 2 eq.), $Pd(OAc)_2$ (0.5 mg, 0.0022 mmol, 10 mol%) and ^{i}PrOH (1 mL). The reaction mixture was stirred at 25 °C for 16 h. The resulting brown reaction mixture was filtered through Celite with MeOH (5 mL) and the solvent removed under reduced pressure to give a brown residue, which was analysed by HPLC-ESI-MS. ESI-MS *m/z* (ion, %): 538 ($[M+H]^+$, 100).

Phenyl(2,4,6-trimethylphenyl)iodonium trifluoromethanesulfonate, 11a. Synthesised using General Procedure 2 from bis(acetyloxy)phenyl-λ^3-iodane (3.22 g, 10 mmol, 1 eq.), 1,3,5-trimethylbenzene (1.54 mL, 1.32 g, 11

mmol, 1.1 eq.) and trifluoromethanesulfonic acid (0.96 mL, 1.65 g, 11 mmol, 1.1 eq.) in CH_2Cl_2 (20 mL) to give the product as a white solid (4.49 g, 95%). Mp 149–150 °C (lit.[27] 147–148 °C); ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.69 (d, *J* = 7.5 Hz, 2H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.09 (s, 2H), 2.61 (s, 6H), 2.34 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$, δ): 144.5, 142.6, 133.1, 132.4, 131.9, 130.5, 120.5, 111.8, 27.2, 21.2; ^{19}F NMR (376 MHz, $CDCl_3$, δ): −78.2 (s, 3F); ESI-MS *m/z* (ion, %): 323 ([M−OTf]$^+$, 100); ESI-HRMS *m/z*: 323.0303 [M−OTf]$^+$ (calc. for $C_{15}H_{16}I$ 323.0291); IR (solid state, ATR, cm^{-1}): 3060, 2919, 1445, 1247, 1222, 1158, 1025, 985, 945, 857, 741, 683, 632, 574, 515, 454; anal. calc. for $C_{16}H_{16}F_3IO_3S$: C 40.69, H 3.41 found: C 40.43, H 3.24.

Phenyl(2,4,6-tri*iso*propylphenyl)iodonium trifluoromethanesulfonate, 11b. Synthesised using General Procedure 2 from bis(acetyloxy)phenyl-λ^3-iodane (805 mg, 2.5 mmol,1 eq.), 1,3,5-tri*iso*propylbenzene (665 µl, 562 mg, 2.75 mmol, 1.1 eq.) and trifluoromethanesulfonic acid (241 µL, 413 mg, 2.75 mmol, 1.1 eq.) in CH_2Cl_2 (5 mL) to give the product as a white solid (1.19 g, 86%). Mp 177–179 °C (lit.[17] 169–179 °C); ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.70–7.65 (m, 2H), 7.58–7.52 (m, 1H), 7.47–7.40 (m, 2H), 7.19 (s, 2H), 3.25 (quin, *J* = 6.5 Hz, 2H), 2.96 (hept, *J* = 7.0 Hz, 1H), 1.26 (dd, *J* = 15.0, 7.0 Hz, 18H); ^{13}C NMR (101 MHz, $CDCl_3$, δ): 193.8, 155.9, 152.6, 132.7, 132.1, 125.5, 120.4, 113.0, 100.1, 39.7, 34.4, 24.4, 23.8; ESI-MS *m/z* (ion, %): 407 ([M−OTf]$^+$, 100); ESI-HRMS *m/z*: 407.1247 [M−OTf]$^+$ (calc. for $C_{21}H_{28}I$ 407.1230); anal. calc. for $C_{22}H_{28}F_3IO_3S$: C 47.49, H 5.07 found: C 47.26, H 4.93.

Methyl (2*S*)-3-(2-phenyl-1*H*-indol-3-yl)-2-(trifluoroacetamido)propanoate, 12a. Synthesised using General Procedure 3 from methyl (2*S*)-3-(1*H*-indol-3-yl)-2-(trifluoroacetamido)propanoate **1c** (58 mg, 0.192 mmol, 1 eq.), phenyl (2,4,6-trimethylphenyl)iodonium trifluoromethanesulfonate **11a** (181 mg, 0.384 mmol, 2 eq.) and $Pd(OAc)_2$ (2 mg, 9.6 µmol, 5 mol%) in EtOAc (5 mL). Flash column chromatography (3:1 petrol/EtOAc, *v/v*) gave the product as an off-white solid (59 mg, 82%). R_f 0.32 (3:1 petrol/EtOAc, *v/v*); [α]D = +42.4 (*c* 0.10, $CHCl_3$); Mp 155–156 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.15 (br s, 1H), 7.58–7.52 (m, 3H), 7.50 (dd, *J* = 8.0, 7.0 Hz, 2H), 7.44–7.36 (m, 2H), 7.23 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 7.19–7.14 (m, 1H), 6.64 (d, *J* = 8.0 Hz, 1H), 4.83 (dt, *J* = 8.0, 5.5 Hz, 1H), 3.61 (dd, *J* = 5.5, 1.0 Hz, 2H), 3.35 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$, δ): 170.7, 156.7 (q, *J* = 37.5), 136.5, 135.8, 132.6, 129.3, 129.1, 128.5, 128.4, 122.9, 120.4, 118.7, 114.9 (q, *J* = 288.0 Hz), 111.2, 105.6, 53.4, 52.6, 26.5; ^{19}F NMR (376 MHz, $CDCl_3$, δ): −75.9; ESI-MS *m/z* (ion, %): 391 ([M+H]$^+$, 10), 408 ([M+NH_4]$^+$, 35), 413 ([M+Na]$^+$, 100), 429 ([M+K]$^+$, 10); ESI-HRMS *m/z*: 413.1074 [M+Na]$^+$ (calc. for $C_{20}H_{17}F_3N_2NaO_3$ 413.1083).

Methyl (2*S*)-3-(2-phenyl-1*H*-indol-3-yl)-2-(trifluoroacetamido)propanoate, 12b. Synthesised using General Procedure 3 from methyl (2*S*)-3-(1*H*-indol-3-yl)-2-(trifluoroacetamido)propanoate **1c** (58 mg, 0.192 mmol, 1 eq.), phenyl (2,4,6-trimethylphenyl)iodonium trifluoromethanesulfonate **11a** (181 mg, 0.384 mmol, 2 eq.) and $Pd(OAc)_2$ (2 mg, 9.6 µmol, 5 mol%) in EtOAc (5 mL). Flash column chromatography (3:1 petrol/EtOAc, *v/v*) gave the product as an off-white solid (14 mg, 17%). R_f 0.42 (3:1 petrol/EtOAc *v/v*); [α]D = +34.4 (*c* 0.10, $CHCl_3$); Mp 58–60 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.00 (br s, 1H), 7.59 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.39–7.34 (m, 1H), 7.22 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 7.17 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.99 (d, *J* = 2.5 Hz, 2H), 6.58 (d, *J* = 7.5 Hz, 1H), 4.76 (td, *J* = 7.0, 5.5 Hz, 1H), 3.50 (s, 3H), 3.26 (dd, *J* = 15.0, 5.5 Hz, 1H), 3.13 (dd, *J* = 15.0, 7.0 Hz, 1H), 2.36 (s, 3H), 2.10 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$, δ): 170.8, 157.0 (q, $^2J_{CF}$ = 38.0 Hz), 139.0, 138.1, 135.9, 135.2, 128.7, 128.3, 128.0, 122.2, 120.0, 118.4 (q, $^1J_{CF}$ = 288.0 Hz), 111.1, 106.7, 53.5, 52.7, 27.0, 21.2, 20.1; ^{19}F NMR (376 MHz, $CDCl_3$, δ): −75.7; ESI-MS *m/z* (ion, %): 433 ([M+H]$^+$, 5), 450 ([M+NH_4]$^+$, 40), 455 ([M+Na]$^+$, 100), 471 ([M+K]$^+$, 5); ESI-HRMS *m/z*: 455.1547 [M+Na]$^+$ (calc. for $C_{23}H_{23}F_3N_2NaO_3$ 455.1553); IR (solid state, ATR, cm^{-1}): 3391, 2955, 2919, 2851, 1712, 1614, 1543, 1458, 1439, 1378, 1344, 1292, 1206, 1163, 1011, 909, 853, 731, 510; UV-Vis (DMSO, nm): λ_{max} 288 (ε = 9725 mol dm^{-3} cm^{-1}).

2-(Trifluoroacetamido)acetic acid.[22] To a round-bottomed flask containing glycine (826 mg, 11 mmol, 1 eq.) was added Et_3N (1.5 mL, 1.11 g, 11 mmol, 1 eq.) and MeOH (5.5 mL) and the resulting suspension stirred for 5 min. After 5 min ethyl trifluoroacetate (1.7 mL, 1.99 g, 14 mmol, 1.27 eq.) was added and the mixture stirred at rt for 16 h, during which time a clear solution formed. After 16 h the solvent was removed under reduced pressure and the resulting residue acidified with 2M HCl, before being extracted into EtOAc three times. The organic layers were combined then washed with brine, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give the product as a white solid (1.68 g, 89%). Mp 119–121 °C (lit.[28] 118–119 °C dec); ^{1}H NMR (400 MHz, CD_3OD, δ): 4.00 (s, 2H); ^{13}C NMR (101 MHz, CD_3OD, δ): 171.5, 159.4 (q, $^2J_{CF}$ = 37.5 Hz), 117.4 (q, $^1J_{CF}$ = 286.0 Hz), 41.7; ^{19}F NMR (376 MHz, CD_3OD, δ): −77.3; ESI-MS *m/z* (ion, %): 194 ([M+Na]$^+$, 100); ESI-HRMS *m/z*: 194.0033 [M+Na]$^+$ (calc. for $C_4H_4F_3NNaO_3$ 194.0035).

Methyl (2*S*)-3-(1*H*-indol-3-yl)-2-[2-(trifluoroacetamido) acetamido]propanoate, 13. 2-(trifluoroacetamido)acetic acid (100 mg, 0.58 mmol, 1 eq.), methyl (2*S*)-2-amino-3-(1*H*-indol-3-yl)propanoate (163 mg, 0.64 mmol, 1.1 eq.) and *O*-(Benzotriazol-1-yl)-*N,N,N′,N*′-tetramethyluronium tetrafluoroborate (TBTU) (225 mg, 0.70 mmol, 1.2 eq.) were added to a round-bottomed flask which was fitted with a septum and flushed with argon from a balloon for 20 min. After 20 min dry, distilled DIPEA (0.4 mL, 300 mg, 2.32 mmol, 4 eq.) and dry CH_3CN (5.8 mL) were added *via* syringe to give a clear solution and the reaction was stirred at rt for 2 h. After 2 h CH_2Cl_2 was added, then the reaction mixture was washed with sat. aq. NH_4Cl and extracted three times with CH_2Cl_2. The organic layers were combined, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give a crude residue. This was dry-loaded onto silica gel and purified by

flash column chromatography (3:1 EtOAc/petrol, *v/v*) to give the product as an off-white solid (201 mg, 93%). R_f 0.52 (3:1 EtOAc/petrol *v/v*); [α]D = +40.7 (*c* 0.10, $CHCl_3$); Mp 53–55 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.28–8.18 (br s, 1H), 7.50–7.44 (m, 1H), 7.38 (t, *J* = 5.0 Hz, 1H), 7.30 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.18 (ddd, *J* = 8.0, 7.0, 1.2 Hz, 1H), 7.11 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.94 (d, *J* = 2.5 Hz, 1H), 6.57 (d, *J* = 8.0 Hz, 1H), 4.93 (dt, *J* = 8.0, 5.5 Hz, 1H), 3.85 3.74 (m, 2H), 3.73 (s, 3H), 3.37–3.24 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$, δ): 172.3, 166.8, 157.3 (q, $^2J_{CF}$ = 38.0 Hz), 136.2, 127.4, 123.2, 122.5, 120.0, 118.3, 116.6 (q, $^1J_{CF}$ = 287.0 Hz), 111.6, 109.4, 53.2, 52.8, 42.5, 27.5; ^{19}F NMR (376 MHz, $CDCl_3$, δ): −75.6; ESI-MS *m/z* (ion, %): 372 ($[M+H]^+$, 10), 394 ($[M+Na]^+$, 100); ESI-HRMS *m/z*: 394.0988 $[M+Na]^+$ (calc. for $C_{16}H_{16}F_3N_3NaO_4$ 394.0985); IR (solid state, ATR, cm^{-1}): 3391, 3341, 1729, 1704, 1654, 1560, 1532, 1445, 1351, 1215, 1184, 1150, 1005, 968, 742, 608, 536, 428; UV-Vis (DMSO, nm): λ_{max} 284 (ε = 10138 mol dm^{-3} cm^{-1}).

Methyl (2*S*)-3-(2-phenyl-1*H*-indol-3-yl)-2-[2-(trifluoroacetamido)acetamido]propanoate, 14a. Synthesised using General Procedure 3 from methyl (2*S*)-3-(1*H*-indol-3-yl)-2-[2-(trifluoroacetamido)acetamido]propanoate **9** (71 mg, 0.192 mmol, 1 eq.), phenyl (2,4,6-trimethylphenyl)iodonium trifluoromethanesulfonate **11a** (181 mg, 0.384 mmol, 2 eq.) and $Pd(OAc)_2$ (2 mg, 9.6 μmol, 5 mol%) in EtOAc (5 mL). Flash column chromatography (40% EtOAc/petrol, *v/v*) gave the product as an off-white solid (41 mg, 48%). R_f 0.28 (40% EtOAc/petrol, *v/v*); [α]D = +51.0 (*c* 0.10, $CHCl_3$); Mp 82–84 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.22 (br s, 1H), 7.55–7.49 (m, 3H), 7.46 (dd, *J* = 8.0, 7.0 Hz, 2H), 7.40–7.33 (m, 2H), 7.22 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 7.12 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.93 (br s, 1H), 6.00 (d, *J* = 7.5 Hz, 1H), 4.83 (dt, *J* = 7.5, 5.0, 1H), 3.70–3.60 (m, 2H), 3.42 (s, 3H), 3.30–3.20 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$, δ): 171.6, 166.1, 156.7 (q, $^2J_{CF}$ = 37.5 Hz), 141.9, 136.3, 135.8, 133.2, 129.4, 129.2, 128.3, 128.3, 128.1, 122.9, 120.3, 118.7, 114.9 (q, $^1J_{CF}$ = 287.0 Hz), 111.2, 106.2, 53.3, 52.6, 42.0, 26.3; ^{19}F NMR (376 MHz, $CDCl_3$, δ): −75.7; ESI-MS *m/z* (ion, %): 470 ($[M+Na]^+$, 100); ESI-HRMS *m/z*: 470.1292 $[M+Na]^+$ (calc. for $C_{22}H_{20}F_3N_3NaO_4$ 470.1298); IR (solid state, ATR, cm^{-1}): 3340, 3061, 2954, 2930, 1722, 1666, 1528, 1441, 1351, 1211, 1153, 1074, 1004, 908, 730, 698, 515; UV-Vis (DMSO, nm): λ_{max} 308 (ε = 20684 mol dm^{-3} cm^{-1}).

Methyl (2*S*)-2-[2-(trifluoroacetamido)acetamido]-3-[2-(2,4,6-trimethylphenyl)-1*H*-indol-3-yl]propanoate, 14b. Synthesised using General Procedure 3 from methyl (2*S*)-3-(1*H*-indol-3-yl)-2-[2-(trifluoroacetamido)acetamido]propanoate **13** (71 mg, 0.192 mmol, 1 eq.), phenyl (2,4,6-trimethylphenyl)iodonium trifluoromethanesulfonate **11a** (181 mg, 0.384 mmol, 2 eq.) and $Pd(OAc)_2$ (2 mg, 9.6 μmol, 5 mol%) in EtOAc (5 mL). Flash column chromatography (40% EtOAc/petrol, *v/v*) gave the product as an off-white solid (4 mg, 4%). R_f 0.38 (40% EtOAc/petrol, *v/v*); [α]D = +33.3 (*c* 0.10, $CHCl_3$); Mp 90–92 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.87 (br s, 1H), 7.56 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.36 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.22 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 7.16 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 7.05–7.00 (m, 2H), 6.89 (d, *J* = 1.0 Hz, 1H), 5.74 (d, *J* = 7.5 Hz, 1H), 4.76 (dt, *J* = 7.5, 5.5 Hz, 1H), 3.74 (dd, *J* = 17.0, 4.5 Hz, 1H), 3.57 (dd, *J* = 17.0, 4.5 Hz, 1H), 3.50 (s, 3H), 3.18 (d, *J* = 5.5 Hz, 2H), 2.36 (s, 3H), 2.14 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$, δ): 171.7, 166.2, 156.0 (q, $^2J_{CF}$ = 37.5 Hz), 139.3, 138.2, 138.1, 135.8, 134.7, 128.9, 128.8, 128.6, 128.6, 122.3, 120.0, 118.4, 115.7 (q, $^1J_{CF}$ = 287.0 Hz), 111.1, 107.4, 53.5, 52.5, 42.1, 27.0, 21.2, 20.3, 20.2; ^{19}F NMR (376 MHz, $CDCl_3$, δ): −75.7; ESI-MS *m/z* (ion, %): 512 ($[M+Na]^+$, 100); ESI-HRMS *m/z*: 512.1773 $[M+Na]^+$ (calc. for $C_{25}H_{26}F_3N_3NaO_4$ 512.1768); IR (solid state, ATR, cm^{-1}): 3339, 2959, 2919, 2850, 1718, 1670, 1523, 1458, 1437, 1260, 1157, 1006, 853, 800, 744, 517; UV-Vis (DMSO, nm): λ_{max} 288 (ε = 12188 mol dm^{-3} cm^{-1}).

(2*R*)-4-Methyl-2-(trifluoroacetamido)pentanoic acid.[22] To a round-bottomed flask containing L-Leucine (1 g, 7.6 mmol, 1 eq.) was added Et_3N (1.06 mL, 769 mg, 7.6 mmol, 1 eq.) and MeOH (7.6 mL) and the resulting suspension stirred for 5 min. After 5 min ethyl trifluoroacetate (1.13 mL, 1.35 g, 9.5 mmol, 1.25 eq.) was added and the mixture stirred at rt for 16 h, during which time a clear solution formed. After 16 h the solvent was removed under reduced pressure and the resulting residue acidified with 2M HCl, before being extracted into EtOAc three times. The organic layers were combined then washed with brine, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give the product as a white solid (1.67 g, 97%). [α]D = +31.6 (*c* 0.10, $CHCl_3$); Mp 75–77 °C (lit.[29] 76–77 °C dec); ^{1}H NMR (400 MHz, CD_3OD, δ): 4.48 (dd, *J* = 10.0, 5.0 Hz, 1H), 1.81–1.60 (m, 3H), 0.97 (d, *J* = 6.0 Hz, 3H), 0.94 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (101 MHz, CD_3OD, δ): 174.4, 158.9 (q, $^2J_{CF}$ = 38.0 Hz), 117.5 (q, $^1J_{CF}$ = 287.0 Hz), 52.4, 40.7, 26.1, 23.3, 21.5; ^{19}F NMR (376 MHz, CD_3OD, δ): −77.0; ESI-MS *m/z* (ion, %): 250 ($[M+Na]^+$, 100); ESI-HRMS *m/z*: 250.0665 $[M+Na]^+$ (calc. for $C_8H_{12}F_3NNaO_3$ 250.0661).

Methyl (2*S*)-3-(1*H*-indol-3-yl)-2-[(2*R*)-4-methyl-2-trifluoroacetamido)pentanamido] propanoate, 15. (2*R*)-4-methyl-2-(trifluoroacetamido)pentanoic acid (500 mg, 2.2 mmol, 1 eq.), methyl (2*S*)-2-amino-3-(1*H*-indol-3-yl)propanoate (616 mg, 2.42 mmol, 1.1 eq.) and 3-(Diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3-*H*)-one (DEPBT) (790 mg, 2.64 mmol, 1.2 eq.) were added to a round-bottomed flask which was fitted with a septum and flushed with argon from a balloon for 20 min. After 20 min dry, distilled DIPEA (1.5 mL, 1.14 g, 8.8 mmol, 4 eq.) and dry CH_2Cl_2 (22 mL) were added *via* syringe to give a yellow solution and the reaction was stirred at rt for 2 h. After 2 h the reaction mixture was washed with sat. aq. NH_4Cl and extracted three times with CH_2Cl_2. The organic layers were combined, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give a crude yellow residue. This was dry-loaded onto silica gel and purified by flash column chromatography (1:1 EtOAc/petrol, *v/v*) to give the product as an off-white solid (568 mg, 60%). R_f 0.48 (1:1 EtOAc/pxetrol *v/v*); [α]D = +33.9 (*c* 0.10, $CHCl_3$); Mp 129–131 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.19 (br s, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.36–7.33 (m, 1H), 7.23–7.08 (m, 2H), 6.98 (d, *J* = 2.0 Hz, 1H), 6.45 (d, *J* = 8.0 Hz, 1H), 4.97–4.84 (m, 1H), 4.51–4.36 (m, 1H), 3.70 (s, 3H), 3.38–

3.25 (m, 2H), 1.68 (s, 1H), 1.62–1.41 (m, 3H), 1.29–1.18 (m, 3H), 0.89–0.75 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$, δ): 172.0, 170.4, 157.1 (q, $^2J_{CF}$ = 37.5 Hz), 136.2, 127.5, 123.3, 122.5, 120.0, 118.4, 116.6 (q, $^1J_{CF}$ = 288.0 Hz), 111.5, 109.3, 53.2, 52.7, 52.2, 41.5, 27.6, 24.7, 22.7, 22.1; ^{19}F NMR (376 MHz, $CDCl_3$, δ): −75.6; ESI-MS *m/z* (ion, %): 428 ($[M+H]^+$, 75), 450 ($[M+Na]^+$, 100); ESI-HRMS *m/z*: 450.1612 $[M+Na]^+$ (calc. for $C_{20}H_{24}F_3N_3NaO_4$ 450.1611); IR (solid state, ATR, cm^{-1}): 3277, 3084, 2959, 2933, 2873, 1714, 1652, 1551, 1439, 1341, 1209, 1184, 1156, 1094, 1010, 988, 742, 719, 652, 632, 521; UV-Vis (DMSO, nm): λ_{max} 282 (ε = 5734 mol dm^{-3} cm^{-1}).

Methyl (2*S*)-2-[(2*R*)-4-methyl-2-(trifluoroacetamido)pentanamido]-3-(2-phenyl-1*H*-indol-3-yl)propanoate, 16a. Synthesised using General Procedure 3 from methyl (2*S*)-3-(1*H*-indol-3-yl)-2-[(2*R*)-4-methyl-2-(trifluoroacetamido)pentanamido]propanoate **15** (82 mg, 0.192 mmol, 1 eq.), phenyl (2,4,6-trimethylphenyl)iodonium trifluoromethanesulfonate **11a** (181 mg, 0.384 mmol, 2 eq.) and $Pd(OAc)_2$ (2 mg, 9.6 µmol, 5 mol%) in EtOAc (5 mL). Flash column chromatography (3:1 petrol/EtOAc, *v/v*) gave the product as a yellow solid (63 mg, 65%). R_f 0.19 (3:1 petrol/EtOAc, *v/v*); [α]D = +43.8 (*c* 0.10, $CHCl_3$); Mp 83–85 °C dec; ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.18 (br s, 1H), 7.57–7.53 (m, 3H), 7.49 (ddt, *J* = 8.0, 6.5, 1.0 Hz, 2H), 7.42–7.35 (m, 2H), 7.25–7.19 (m, 1H), 7.15 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.91–6.84 (m, 1H), 5.93–5.83 (m, 1H), 4.79 (dq, *J* = 7.5, 5.5, 5.0 Hz, 1H), 3.96 (td, *J* = 8.0, 5.0 Hz, 1H), 3.65–3.48 (m, 2H), 3.38 (s, 3H), 1.54–1.34 (m, 3H), 0.82–0.75 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$, δ): 171.7, 170.1, 156.6 (q, $^2J_{CF}$ = 37.5 Hz), 136.2, 135.8, 132.9, 129.3, 129.2, 129.1, 128.4, 128.3, 128.2, 122.8, 120.2, 118.6 (q, $^1J_{CF}$ = 287.5 Hz), 111.2, 106.2, 53.3, 52.3, 51.8, 42.0, 26.6, 24.6, 22.7, 22.1; ^{19}F NMR (376 MHz, $CDCl_3$, δ): −72.4; ESI-MS *m/z* (ion, %): 504 ($[M+H]^+$, 5), 521 ($[M+NH_4]^+$, 15), 526 ($[M+Na]^+$, 100), 542 ($[M+K]^+$, 5); ESI-HRMS *m/z*: 526.1925 $[M+Na]^+$ (calc. for $C_{26}H_{28}F_3N_3NaO_4$ 526.1924); IR (solid state, ATR, cm^{-1}): 3337, 3061, 2958, 2930, 2873, 1715, 1658, 1530, 1448, 1209, 1155, 742, 698; UV-Vis (DMSO, nm): λ_{max} 308 (ε = 20467 mol dm^{-3} cm^{-1}).

Methyl (2*S*)-2-[(2*R*)-4-methyl-2-(trifluoroacetamido)pentanamido]-3-[2-(2,4,6-trimethylphenyl)-1*H*-indol-3-yl]propanoate, 16b. Synthesised using General Procedure 3 from methyl (2*S*)-3-(1*H*-indol-3-yl)-2-[(2*R*)-4-methyl-2-(trifluoroacetamido)pentanamido]propanoate **15** (82 mg, 0.192 mmol, 1 eq.), phenyl (2,4,6-trimethylphenyl)iodonium trifluoromethanesulfonate **11a** (181 mg, 0.384 mmol, 2 eq.) and $Pd(OAc)_2$ (2 mg, 9.6 µmol, 5 mol%) in EtOAc (5 mL). Flash column chromatography (3:1 petrol/EtOAc, *v/v*) gave the product as a yellow solid (13 mg, 12%). R_f 0.29 (3:1 petrol/EtOAc, *v/v*); [α]D = +31.1 (*c* 0.10, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.87 (br s, 1H), 7.61–7.56 (m, 1H), 7.39–7.34 (m, 1H), 7.22 (td, *J* = 8.0, 7.5, 1.0 Hz, 1H), 7.17 (td, *J* = 7.5, 1.0 Hz, 1H), 7.03 (d, *J* = 3.5 Hz, 2H), 6.91–6.85 (m, 1H), 5.67 (d, *J* = 7.0 Hz, 1H), 4.69 (td, *J* = 7.5, 4.5 Hz, 1H), 4.19–4.08 (m, 1H), 3.54 (s, 3H), 3.23 (dd, *J* = 15.0, 5.0 Hz, 1H), 3.01 (dd, *J* = 15.0, 7.5 Hz, 1H), 2.35 (s, 3H), 2.12 (s, 3H), 2.08 (s, 3H), 1.54 – 1.41 (m, 3H), 0.96 – 0.64 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$, δ): 171.8, 170.3, 156.7 (q, $^2J_{CF}$ = 37.5 Hz), 139.4, 138.3, 137.9, 135.8, 134.7, 129.00, 128.9, 128.4, 128.0, 122.4, 120.1, 118.4, 116.5 (q, $^1J_{CF}$ = 288.0 Hz), 111.1, 107.6, 53.5, 52.5, 51.8, 42.6, 29.6, 27.1, 24.6, 22.8, 22.3, 21.2, 20.3; ^{19}F NMR (376 MHz, $CDCl_3$, δ): −75.8; ESI-MS *m/z* (ion, %): 546 ($[M+H]^+$, 2), 563 ($[M+NH_4]^+$, 15), 568 ($[M+Na]^+$, 100), 584 ($[M+K]^+$, 2); ESI-HRMS *m/z*: 568.2384 $[M+Na]^+$ (calc. for $C_{29}H_{34}F_3N_3NaO_4$ 568.2394); IR (solid state, ATR, cm^{-1}): 3391, 3341, 2957, 2927, 1710, 1661, 1529, 1458, 1439, 1353, 1210, 1155, 1008, 909, 853, 731; UV-Vis (DMSO, nm): λ_{max} 290 (ε = 8712 mol dm^{-3} cm^{-1}).

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