Supporting Information

Late-Stage C–H Acylation of Tyrosine-Containing Oligopeptides with Alcohols

İñaki Urruzuno,[a] Paula Andrade-Sampedro,[a,b] and Arkaitz Correa[a]*

[a] University of the Basque Country (UPV/EHU), Department of Organic Chemistry I, Joxe Mari Korta R&D Center, Avda. Tolosa 72, 20018 Donostia-San Sebastián (Spain).
E-mail: arkaitz.correa@ehu.eus

[b] Donostia International Physics Center (DIPC), Paseo Manuel de Lardizabal 4, 20018 Donostia-San Sebastián (Spain)

1.-General Considerations S2
2.-Optimization Details S3
3.-Preparation of the Starting Materials S6
4.-Pd-Catalyzed C(sp²)-H Acylation of Tyr-Containing Compounds S13
5.-Control Experiments and Mechanism Proposal S30
6.-¹H NMR and ¹³C NMR Spectra S32
1.-General Considerations

Reagents. Commercially available materials were used without further purification. Palladium acetate and T-Hydro (tert-butyl hydroperoxide solution, 70 wt % in water) were purchased from Sigma-Aldrich. Ethanol absolute was purchased from VWR. All the alcohols were commercially available and were used without further purification.

Analytical Methods. $^1$H NMR and $^{13}$C NMR spectra as well as IR, HRMS and melting points (where applicable) are included for all new compounds. $^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker 300, 400 or 500 MHz at 20 °C, unless otherwise indicated. All $^1$H NMR spectra are reported in parts per million (ppm) downfield of TMS and were measured relative to the signals for CHCl$_3$ (7.26 ppm), unless otherwise indicated. All $^{13}$C NMR spectra were reported in ppm relative to residual CHCl$_3$ (77 ppm), unless otherwise indicated, and were obtained with $^1$H decoupling. Coupling constants, $J$, are reported in Hertz. Melting points were measured using open glass capillaries in a Büchi SMP-20 apparatus. High resolution mass spectra (HRMS) were performed by SGIker and were acquired on a LC/Q-TOF mass spectrometer equipped with an electrospray source ESI Agilent Jet Stream. Infrared spectra were recorded on a Bruker Alpha P. Flash chromatography was performed with EM Science silica gel 60 (230-400 mesh). The yields reported in the manuscript correspond to isolated yields and represent an average of at least two independent runs.
2.-Optimization Details

General Procedure:

A reaction tube containing a stirring bar was charged with Boc-Tyr(OPy)-Leu-OMe$^1$ (1a) (0.15 mmol, 73 mg), oxidant (0.90 mmol) (if solid) and metal source (10 mol %). The reaction tube was then evacuated and back-filled with dry argon (this sequence was repeated up to three times). Then, EtOH (3.75 mmol, 220 μL), oxidant (if liquid), and the corresponding solvent (1.0 mL) were added by syringe under argon atmosphere. The reaction tube was next warmed up to the corresponding temperature in a heating block and stirred for 16 hours. The mixture was allowed to cool to room temperature, diluted with EtOAc and washed with a saturated aqueous solution of NaHCO$_3$. The aqueous layer was extracted with EtOAc, and the combined organic layers were dried over MgSO$_4$ and concentrated under reduced pressure. The resulting crude was purified by flash chromatography (hexanes/EtOAc, 1/1). The purity of the corresponding product 2aa was verified by $^1$H NMR.

$^1$ San Segundo, M.; Correa, A. *Chem. Sci.* **2020**, *11*, 11531.
Table S1. Screening of Acylation with EtOH<sup>a</sup>

| Entry | Variation from the standard conditions | 2aa (%)<sup>b</sup> |
|-------|----------------------------------------|---------------------|
| 1     | none                                   | 60                  |
| 2     | DTBP as oxidant                        | 0                   |
| 3     | TBPB as oxidant                        | 0                   |
| 4     | DCP as oxidant                         | 0                   |
| 5     | PIDA as oxidant                        | degradation         |
| 6     | K$_2$S$_2$O$_8$ as oxidant             | degradation         |
| 7     | 1,4-dioxane as solvent                 | 15                  |
| 8     | toluene/water (9:1)                    | 21                  |
| 9     | DMF as solvent                         | 0                   |
| 10    | DCE as solvent                         | degradation         |
| 11    | EtOH as solvent                        | degradation         |
| 12    | tBuPh as solvent                       | 48                  |
| 13    | o-xylene as solvent                    | 48                  |
| 14    | PhCF$_3$ as solvent                    | 45                  |
| 15    | PdCl$_2$ as catalyst                   | 27                  |
| 16    | Pd(OPiv)$_2$ as catalyst               | 44                  |
| 17    | Pd(PPh)$_3$ as catalyst                | 41                  |
| 18    | PdCl$_2$(MeCN)$_2$ as catalyst          | 46                  |
| 19    | Pd(dba)$_2$ as catalyst                | 42                  |
| 20    | Pd(OTFA)$_2$ as catalyst               | 35                  |
| 21    | under air                              | 53                  |
| 22    | T = 130 ºC                             | 54                  |
| 23    | T-Hydro (5.0 equiv)                    | 60                  |
| 24    | T-Hydro (4.0 equiv)                    | 25                  |
| 25    | EtOH (10 equiv)                        | 40                  |
| 26    | Pd(OAc)$_2$ (5 mol%)                   | 32                  |

<sup>a</sup>Reaction conditions: 1a (0.15 mmol), EtOH (3.75 mmol), TBHPaq (0.90 mmol), toluene (1.0 mL), Ar, 16h at 120 ºC. <sup>b</sup>Yield of isolated product after column chromatography.
Table S2. Screening with 4-(trifluoromethyl)benzyl alcohol$^a$

![Chemical structure of compounds 1a and 2ae]

| Entry | Variation from the standard conditions | Yield (%)$^b$ |
|-------|---------------------------------------|--------------|
| 1     | none                                  | 40 (20)$^c$  |
| 2     | DCE as solvent                        | 48$^c$       |
| 3     | PhCl as solvent                       | 43$^c$       |
| 4     | Pd(OTFA)$_2$ as catalyst              | degradation  |
| 5     | T-Hydro (4.0 equiv)                   | 63           |
| 6     | H$_2$O as solvent                     | 30$^c$       |

$^a$Reaction conditions: 1a (0.15 mmol), alcohol (0.45 mmol), Pd(OAc)$_2$ (10 mol%), T-Hydro (6.0 equiv), toluene (1.0 mL), Ar, 16h at 120 °C. $^b$Yield of isolated product after column chromatography. $^c$Yield of isolated difunctionalized product after column chromatography.

Table S3. Influence of the DG$^a$

![Chemical structure of Tyr compounds]

| Tyre compounds | Reaction conditions: 1 (0.15 mmol), EtOH (3.75 mmol), T-Hydro (6.0 equiv), toluene (1.0 mL), Ar, 16h at 120 °C. |
|----------------|---------------------------------------------------------------------------------------------------------------|
3. Preparation of the Starting Materials

*a* Prepared following literature procedures. *b* Synthesis reported herein.
General Procedure for the O-Arylation of Tyr-Containing Peptides

A reaction tube containing a stirring bar was charged with the corresponding tyrosine derivative (1.0 equiv), CuCl (20 mol %), K$_3$PO$_4$ (2.0 equiv) and 2-picolinic acid (40 mol %). The reaction tube was then evacuated and back-filled with dry Ar (this sequence was repeated up to three times). Then DMSO (2.5 mL/mmol) and 2-iodopyridine (2.0 equiv) were added under argon atmosphere. The reaction tube was next warmed up to 100 °C and stirred for 16 h. After cooling down to room temperature, brine was added to the above solution, washed with a saturated aqueous solution of NaHCO$_3$, and extracted with EtOAc. The organic layers were combined and evaporated under vacuum. The resulting crude was then purified by column chromatography to afford the corresponding product.

Methyl (S)-2-(1,3-dioxoisindolin-2-yl)-3-(4-(pyridin-2-yl)oxy phenyl)propanoate (1b). Following the general procedure, using NPhth-Tyr-OMe$^3$ (12.31 mmol, 4.00 g) provided 4.30 g (87% yield) of 1b as a white solid. Mp 89–90 °C. Column chromatography (Hex/EtOAc 1:1). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.14 (ddd, $J$ = 5.0, 2.0, 0.8 Hz, 1H), 7.79 (dd, $J$ = 5.4, 3.1 Hz, 2H), 7.69 (dd, $J$ = 5.5, 3.1 Hz, 2H), 7.62 (ddd, $J$ = 8.3, 7.2, 2.0 Hz, 1H), 7.23 – 7.13 (m, 2H), 7.04 – 6.89 (m, 3H), 6.84 – 6.70 (m, 1H), 5.17 (dd, $J$ = 10.8, 5.7 Hz, 1H), 3.78 (s, 3H), 3.73 – 3.44 (m, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 169.4, 167.6, 163.7, 153.0, 147.8, 139.5, 134.3, 133.0, 131.7, 130.2, 123.6, 121.3, 118.6, 111.5, 53.2, 53.0, 34.2. IR (cm$^{-1}$): 1753, 1707, 1388, 716. HRMS (ESI) m/z: (M$^+$) calcd for (C$_{23}$H$_{18}$N$_2$O$_5$): 402.1216, found 402.1214.

$^2$ Chu, J.-H.; Chen, S.-T.; Chiang, M.-F.; Wu, M.-J. Organometallics 2015, 34, 953.
$^3$ Sather, A. C.; Lee, H. G.; De La Rosa, V. Y.; Yang, Y.; Müller, P.; Buchwald, S. L. J. Am. Chem. Soc. 2015, 137, 13433.
Methyl \( O\)-acetyl-\( N\)-\((\text{tert}-\text{butyloxycarbonyl})\)amino\)-3-\((4\text{-}(\text{pyridin}-2\text{-yloxy})\)phenyl\)propanoyl-\( L\)-serinate (\( 1i \)). To a solution of Boc-Tyr(OPy)-Ser-OMe\(^1\) (2.0 mmol, 919 mg) and triethylamine (6.0 mmol, 0.83 mL) in dichloromethane (10 mL), acetic anhydride (4.0 mmol, 0.39 mL) was added at 0 °C and the resulting solution was stirred at room temperature for 5 h. The organic phase was washed with a solution of NaOH 1M and brine, consecutively. The solvent was removed under reduced pressure and the product was purified by flash chromatography (EtOAc/hexanes, 6:4) to provide 519 mg (52% yield) of \( 1i \) as a white solid. Mp 91-92 °C.

\(^{1}\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 8.18 (s, 1H), 7.68 (t, \( J = 7.7 \) Hz, 1H), 7.24 (d, \( J = 10.7 \) Hz, 2H), 7.07 (d, \( J = 8.3 \) Hz, 2H), 7.04 - 6.94 (m, 1H), 6.89 (d, \( J = 8.3 \) Hz, 1H), 6.72 (d, \( J = 7.3 \) Hz, 1H), 5.08 - 5.01 (m, 1H), 4.83 - 4.77 (m, 1H), 4.49 - 4.15 (m, 3H), 3.75 (s, 3H), 3.09 (dd, \( J = 6.6, 3.9 \) Hz, 2H), 2.02 (s, 3H), 1.43 (s, 9H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 171.2, 170.5, 169.4, 163.6, 153.2, 147.7, 139.4, 132.6, 130.6, 130.5, 121.4, 118.5, 111.6, 80.4, 63.7, 55.6, 52.8, 51.8, 37.5, 28.3, 20.6. IR (cm\(^{-1}\)): 3292, 1645, 1505, 1427, 1242, 1152. HRMS (ESI) m/z: (M\(^+\)) calcd for \( \text{C}_{25}\text{H}_{31}\text{N}_{3}\text{O}_{8} \): 501.2111, found 501.2118.

tert-Butyl \( \text{(S)}\)-3-\([(\text{benzyloxy})\text{carbonyl}]\text{amino}\)-4-\([(\text{S})\text{-}\text{methoxy}-1\text{-}\text{oxo}-3-(4-(\text{pyridin}-2\text{-yloxy})\text{phenyl})\text{propan-2-yl}][\text{amino}]\)-4\text{-oxobutanoate} (\( 1j \)). A solution of Boc-Tyr(OPy)-OMe\(^1\) (2.0 mmol, 745 mg) in dichloromethane was treated with trifluoroacetic acid (20 mmol, 1.5 mL) and stirred for 5 h. After evaporation of the solvent, the resulting crude was diluted with EtOAc and washed with a saturated aqueous solution of NaHCO\(_3\). After evaporation of the solvent, the so-obtained crude (without further purification) was dissolved in dichloromethane (10 mL) at 0 °C. EDC·HCl (2.4 mmol, 460 mg), HOBt (2.4 mmol, 323 mg), Cbz-Asp(O'Bu)-OH (2.4 mmol, 647 mg) and triethylamine (3.0 mmol, 0.45 mL) were subsequently added and stirred at room temperature overnight. The resulting solution was washed with water and extracted with dichloromethane. The
solvent was removed under reduced pressure and the corresponding product was purified by flash chromatography (Hexane:EtOAc, 6:4) to provide 890 mg (77% yield) of 1j as a colorless oil. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.19 – 8.05 (m, 1H), 7.63 (t, $J$ = 7.7 Hz, 1H), 7.32 – 7.23 (m, 4H), 7.15 – 7.08 (m, 3H), 6.99 (d, $J$ = 8.3 Hz, 2H), 6.96 – 6.91 (m, 1H), 6.84 (d, $J$ = 8.3 Hz, 1H), 6.09 (d, $J$ = 8.2 Hz, 1H), 5.18 – 4.97 (m, 2H), 4.85 – 4.77 (m, 1H), 4.57 – 4.52 (s, 1H), 3.67 (s, 3H), 3.13 – 3.05 (m, 1H), 2.85 – 2.71 (m, 1H), 2.67 – 2.53 (m, 1H), 1.38 (s, 9H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 171.3, 170.7, 170.2, 163.5, 155.9, 153.0, 147.4, 139.3, 135.9, 131.9, 130.4, 128.3, 128.0, 127.9, 121.1, 118.3, 111.3, 81.5, 67.0, 53.2, 52.2, 50.9, 37.0, 27.8. IR (cm$^{-1}$): 3289, 2956, 1647, 1241, 1163. HRMS (ESI) m/z: (M$^+$) calcd for (C$_{31}$H$_{35}$N$_3$O$_8$): 577.2424, found 577.2427.

Methyl [(S)-2-((S)-3-(4-(benzyloxy)phenyl)-2-((tert-butoxycarbonyl)amino)propanamido-3-(4-pyridin-2-ylxyloxy)phenyl)propanoyl]-L-leucinate (1m). A solution of Boc-Tyr(OPy)-Leu-OMe (2.06 mmol, 1.00 g) in dichloromethane was treated with trifluoroacetic acid (20.6 mmol, 1.54 mL) and stirred for 5 h. After evaporation of the solvent, the resulting crude was diluted with EtOAc and washed with a saturated aqueous solution of NaHCO$_3$. After evaporation of the solvent, the so-obtained crude (without further purification) was dissolved in dichloromethane (10 mL at 0 °C. EDC·HCl (2.25 mmol, 431mg), HOBt (2.25 mmol, 304 mg), Boc-Tyr(OBn)-OH (2.25 mmol, 837 mg) and triethylamine (2.25 mmol, 0.30 mL) were subsequently added and stirred at room temperature overnight. The resulting solution was washed with water and extracted with dichloromethane. The solvent was removed under reduced pressure and the corresponding product was purified by flash chromatography (Hexane:EtOAc, 1:1) to provide 810 mg (54% yield) of 1m as a white solid. Mp 176-177 °C. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.12 (ddd, $J$ = 5.0, 2.0, 0.9 Hz, 1H), 7.65 (ddd, $J$ = 8.2, 7.1, 2.0 Hz, 1H), 7.47 – 7.27 (m, 4H), 7.20 – 6.81 (m, 11H), 6.63 (d, $J$ = 8.0 Hz, 1H), 6.49 – 6.37 (m, 1H), 5.02 (s, 2H), 4.98 – 4.84 (m, 1H), 4.67 (q, $J$ = 7.0 Hz, 1H), 4.56 – 4.58 (m, 1H), 4.38 – 4.17 (m, 1H), 3.70 (s, 3H), 3.04 (dtt, $J$ = 34.4, 14.2, 6.5 Hz, 4H), 1.65 – 1.42 (m, 3H), 1.36 (s, 9H), 0.97 – 0.78 (m, 6H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 172.8, 171.4, 170.3, 163.8, 158.0, 153.2, 147.7, 139.6, 137.0, 132.7, 130.8, 130.6, 130.4, 128.7, 128.6, 128.6, 127.5, 121.6,
Methyl [(S)-2-((S)-2-((tert-butoxycarbonyl)amino)-5-((2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yl)sulfonyl)guanidino)pentanamido)-3-(4-(pyridin-2-yl oxy)phenyl)propanoyl]-L-leucinate (1p). A solution of H-Tyr(OPy)-Leu-OMe (2.02 mmol, 777 mg) was dissolved in dichloromethane (10 mL) at 0 °C. EDC·HCl (2.22 mmol, 425 mg), HOBt (2.22 mmol, 300 mg), Boc-Arg(Pbf)-OH (2.22 mmol, 1.16 g) and triethylamine (2.22 mmol, 0.30 mL) were subsequently added and stirred at room temperature overnight. The resulting solution was washed with water and extracted with dichloromethane. The solvent was removed under reduced pressure and the corresponding product was purified by flash chromatography (EtOAc) to provide 890 mg (47% yield) of 1p as a white solid. Mp 122-123 °C. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.25 – 7.99 (m, 1H), 7.73 – 7.45 (m, 2H), 7.20 – 7.07 (m, 3H), 7.04 – 6.90 (m, 3H), 6.81 (dd, $J$ = 8.4, 0.9 Hz, 1H), 6.40 (s, 2H), 6.25 (s, 1H), 5.65 (d, $J$ = 7.4 Hz, 1H), 4.68 (q, $J$ = 7.4 Hz, 1H), 4.46 (q, $J$ = 7.2 Hz, 1H), 4.19 (d, $J$ = 6.6 Hz, 1H), 3.62 (s, 3H), 3.08 (dd, $J$ = 17.1, 11.1, 6.3 Hz, 4H), 2.89 (s, 2H), 2.56 (s, 3H), 2.49 (s, 3H), 2.05 (s, 3H), 1.86 – 1.46 (m, 7H), 1.41 (s, 6H), 1.43 (s, 9H), 0.94 – 0.66 (m, 6H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 172.9, 172.6, 171.2, 163.7, 158.7, 156.6, 155.9, 153.0, 147.6, 139.6, 138.3, 133.1, 132.9, 132.2, 130.7, 124.6, 121.1, 118.6, 117.5, 111.5, 86.4, 79.9, 54.8, 54.0, 52.2, 51.0, 43.2, 40.8, 40.3, 37.0, 29.7, 28.6, 28.3, 25.5, 24.6, 22.8, 21.8, 21.5, 19.4, 18.0, 12.5. IR (cm$^{-1}$): 3318, 1742, 1650, 1547, 1506, 1244. HRMS (ESI) m/z: (M$^+$) calcd for (C$_{45}$H$_{63}$N$_7$O$_{10}$S): 893.4357, found 893.4357.
Methyl ((S)-2-(2-((tert-butoxycarbonyl)amino)acetamido)-3-(4-(pyridin-2-ylxy)phenyl)propanoyl)-L-leucinate (1q). A solution of Boc-Tyr(OPy)-Leu-OMe (2.0 mmol, 971 mg) in dichloromethane was treated with trifluoroacetic acid (20 mmol, 1.5 mL) and stirred for 5 h. After evaporation of the solvent, the resulting crude was diluted with EtOAc and washed with a saturated aqueous solution of NaHCO₃. After evaporation of the solvent, the so-obtained crude (without further purification) was dissolved in dichloromethane (10 mL) at 0 ºC. EDC·HCl (2.4 mmol, 460 mg), HOBt (2.4 mmol, 323 mg), Boc-Gly-OMe (2.4 mmol, 420 mg) and triethylamine (3.0 mmol, 0.45 mL) were subsequently added and stirred at room temperature overnight. The resulting solution was washed with water and extracted with dichloromethane. The solvent was removed under reduced pressure and the corresponding product was purified by flash chromatography (Hexane:EtOAc, 1:1) to provide 663 mg (61% yield) of 1q as a white solid. Mp 75-76 ºC. ¹H NMR (400 MHz, CDCl₃) δ 8.13 (dd, J = 5.0, 1.4 Hz, 1H), 7.63 (t, J = 6.8 Hz, 1H), 7.19 (d, J = 8.4 Hz, 2H), 7.10 (s, 1H), 6.99 (d, J = 8.4 Hz, 2H), 6.97 – 6.93 (m, 2H), 6.84 (d, J = 8.3 Hz, 1H), 5.56 (s, 1H), 4.77 (q, J = 6.9 Hz, 1H), 4.56 – 4.43 (m, 1H), 3.78 – 3.70 (m, 2H), 3.66 (s, 3H), 3.05 (d, J = 6.6 Hz, 2H), 1.64 – 1.45 (m, 3H), 1.39 (s, 9H), 0.85 (d, J = 5.7 Hz, 6H). ¹³C NMR (101 MHz, CDCl₃) δ 172.7, 170.5, 169.6, 163.6, 156.0, 153.0, 147.5, 139.4, 132.6, 130.6, 121.1, 118.4, 111.4, 80.0, 54.0, 52.2, 50.9, 44.1, 41.0, 37.4, 28.2, 24.6, 22.6, 21.8. IR (cm⁻¹): 3292, 1645, 1242, 1152, 1505, 1427. HRMS (ESI) m/z: (M⁺) calcd for (C₂₈H₃₈N₄O₇): 542.2740, found 542.2750.

Methyl [(S)-2-((tert-butoxycarbonyl)amino)-3-(4-(pyridin-2-ylxy)phenyl)propanoyl]glycyl-L-phenylalanyl-L-leucinate (1r). The title compound was synthesized through iterative hydrolysis employing LiOH and posterior coupling with the corresponding amino acid methyl ester (Gly, Phe, and Leu, in this order), starting from Boc-Tyr(OPy)-OMe (5.0 mmol, 1.9 g). Purification by flash chromatography (EtOAc) provided 746 mg (22% yield) of 1r as a brown solid. Mp 84-85 ºC. ¹H NMR (300 MHz, CDCl₃) δ 8.14 (d, J = 4.9 Hz, 1H), 7.64 (t, J = 6.8 Hz, 1H), 7.27 – 7.13 (m, 9H), 7.04 – 6.97 (m, 2H), 6.95 (d, J = 5.2 Hz, 2H), 6.84 (d, J = 8.3 Hz, 1H), 5.41 (d, J = 6.5 Hz, 1H), 4.80 (q, J = 7.1 Hz, 1H), 4.54 (q, J = 6.8, 5.3 Hz, 1H), 4.49 – 4.38 (m, 1H), 3.96 – 3.79
(m, 2H), 3.67 (s, 3H), 3.16 – 3.06 (m, 2H), 3.06 – 2.98 (m, 1H), 3.00 – 2.85 (m, 1H), 1.65 – 1.46 (m, 3H), 1.37 (s, 9H), 0.86 (d, J = 5.7 Hz, 6H).  $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 173.0, 172.1, 170.7, 168.6, 163.6, 155.6, 153.0, 147.6, 139.4, 136.4, 133.0, 130.5, 129.3, 128.4, 126.8, 121.1, 118.4, 111.4, 80.0, 55.6, 54.4, 52.2, 50.8, 43.0, 41.0, 38.2, 37.9, 28.3, 24.7, 22.7, 21.8. IR (cm$^{-1}$): 3290, 1639, 1506, 1428, 1244, 1162. HRMS (ESI) m/z: (M$^+$) calcd for (C$_{37}$H$_{47}$N$_5$O$_8$): 689.3425, found 689.3425.
4.-Pd-Catalyzed C(sp²)-H Acylation of Tyr-Containing Compounds

**General Procedure A (Acetylation):** A reaction tube containing a stirring bar was charged with the corresponding peptide (0.15 mmol) and Pd(OAc)_2 (10 mol %). The reaction tube was then evacuated and back-filled with dry argon (this sequence was repeated up to three times). Then, a commercially available solution of tert-butyl hydroperoxide (70 wt % in water) (0.90 mmol), EtOH (3.75 mmol) and toluene (1 mL) were added by syringe under argon atmosphere. The reaction tube was next warmed up to the corresponding temperature in a heating block and stirred for 16 hours. The mixture was then allowed to warm to room temperature, diluted with EtOAc and washed with aq. NaHCO₃ (20 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL), dried over MgSO₄ and evaporated under vacuum. The resulting crude was then purified by column chromatography to afford the corresponding product.

**General Procedure B:** A reaction tube containing a stirring bar was charged with the corresponding peptide (0.15 mmol) and Pd(OAc)_2 (10 mol %). The reaction tube was then evacuated and back-filled with dry argon (this sequence was repeated up to three times). Then, a commercially available solution of tert-butyl hydroperoxide (70 wt % in water) (0.90 mmol), the corresponding alcohol (0.75 mmol) and toluene (1 mL) were added by syringe under argon atmosphere. The reaction tube was next warmed up to the corresponding temperature in a heating block and stirred for 16 hours. The mixture was then allowed to warm to room temperature, diluted with EtOAc and washed with aq. NaHCO₃ (20 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL), dried over MgSO₄ and evaporated under vacuum. The resulting crude was then purified by column chromatography to afford the corresponding product.

**General Procedure C:** A reaction tube containing a stirring bar was charged with the corresponding peptide (0.15 mmol) and Pd(OAc)_2 (10 mol %). The reaction tube was then evacuated and back-filled with dry argon (this sequence was repeated up to three times). Then, a commercially available solution of tert-butyl hydroperoxide (70 wt % in water) (0.90 mmol), the corresponding alcohol (0.75 mmol) and toluene (1 mL) were added by syringe under argon atmosphere. The reaction tube was next warmed up to the corresponding temperature in a heating block and stirred for 16 hours. The mixture was then allowed to warm to room temperature, diluted with EtOAc and washed with aq. NaHCO₃ (20 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL), dried over MgSO₄ and evaporated under vacuum. The resulting crude was then purified by column chromatography to afford the corresponding product.
times). Then, a commercially available solution of tert-butyl hydroperoxide (70 wt % in water) (0.60 mmol), the corresponding benzyl alcohol (0.45 mmol) and toluene (1 mL) were added by syringe under argon atmosphere. The reaction tube was next warmed up to the corresponding temperature in a heating block and stirred for 16 hours. The mixture was then allowed to warm to room temperature, diluted with EtOAc and washed with aq. NaHCO₃ (20 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL), dried over MgSO₄ and evaporated under vacuum. The resulting crude was then purified by column chromatography to afford the corresponding product.

Methyl [(S)-3-(3-acetyl-4-(pyridin-2-yloxy)phenyl)-2-((tert-butoxycarbonyl)amino)propanoyl]-L-leucinate (2aa). Following the general procedure A, using 1a (0.15 mmol, 73 mg) and EtOH (3.75 mmol, 0.22 mL) provided 47 mg (60% yield) of 2aa as a colorless oil. Column chromatography (Hex/EtOAc 1:1). $^1$H NMR (400 MHz, CDCl₃) δ 8.12 (dd, $J_1 = 5.1$, $J_2 = 1.9$ Hz, 1H), 7.76 – 7.62 (m, 2H), 7.38 (dd, $J_1 = 8.4$, $J_2 = 2.4$ Hz, 1H), 7.06 – 6.88 (m, 3H), 6.88 – 6.70 (m, 1H), 5.33 (d, $J_1 = 8.4$ Hz, 1H), 4.60 – 4.54 (m, 1H), 4.43 – 4.41 (m, 1H), 3.69 (s, 3H), 3.15 (dd, $J_1 = 14.1$, $J_2 = 6.2$ Hz, 1H), 3.02 (dd, $J_1 = 13.9$, $J_2 = 7.4$ Hz, 1H), 2.48 (s, 3H), 1.61 – 1.57 (m, 3H), 1.39 (s, 9H), 0.88 (dd, $J_1 = 6.0$, $J_2 = 3.8$ Hz, 6H). $^{13}$C NMR (101 MHz, CDCl₃) δ 198.3, 173.0, 171.0, 163.0, 155.4, 151.8, 147.7, 139.8, 134.5, 133.6, 131.5, 131.1, 123.0, 118.9, 111.6, 80.1, 55.3, 52.3, 50.7, 41.3, 37.3, 30.8, 28.2, 24.7, 22.8, 21.8. IR (cm⁻¹): 3305, 1743, 1665, 1657, 1427, 1160, 776. HRMS (ESI) m/z: (M⁺) calcd for (C₂₈H₃₇N₃O₇): 527.2632, found 527.2638. This reaction was also performed in a higher scale: the use of 1a (2.06 mmol, 1.00 g), EtOH (20 equiv, 2.40 mL) and TBHP (5.0 equiv, 1.58 mL) in toluene (14 mL) provided 670 mg (62% yield) of 2aa as a colorless oil.
Methyl [(S)-2-((tert-butoxycarbonyl)amino)-3-(3-butyryl-4-(pyridin-2-yloxy)phenyl)propanoyl]-L-leucinate (2ab). Following the general procedure B, using 1a (0.15 mmol, 73 mg) and n-BuOH (0.75 mmol, 69 μL) provided 61.5 mg (74% yield) of 2ab as a colorless oil. Column chromatography (Hex/EtOAc 1:1). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.15 – 8.07 (m, 1H), 7.78 – 7.66 (m, 1H), 7.58 (d, $J = 2.3$ Hz, 1H), 7.37 (dd, $J = 8.3$, 2.3 Hz, 1H), 7.24 (d, $J = 13.7$ Hz, 1H), 7.08 – 6.91 (m, 3H), 6.40 (dd, $J = 27.0$, 8.3 Hz, 1H), 5.15 – 4.91 (m, 1H), 4.58 (td, $J = 8.4$, 4.8 Hz, 1H), 4.44 – 4.21 (m, 1H), 3.70 (s, 3H), 3.23 – 2.99 (m, 2H), 2.83 (t, $J = 7.3$ Hz, 2H), 1.68 – 1.46 (m, 5H), 1.42 (s, 9H), 0.90 (dd, $J = 6.2$, 3.9 Hz, 6H), 0.83 (t, $J = 7.4$ Hz, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 201.4, 172.9, 171.0, 163.1, 155.4, 151.1, 147.6, 139.7, 133.8, 133.6, 133.0, 132.1, 130.7, 122.9, 121.1, 118.8, 111.6, 80.1, 55.3, 52.2, 50.7, 44.5, 41.2, 37.3, 28.2, 24.6, 22.7, 21.8, 17.4, 13.6. IR (cm$^{-1}$): 3308, 1743, 1657, 1465, 1264, 729. HRMS (ESI) m/z: (M$^+$) calc for (C$_{28}$H$_{37}$N$_3$O$_7$): 527.2632, found 527.2638. This reaction was also performed in a higher scale: the use of 1a (2.06 mmol, 1.00 g), n-BuOH (5.0 equiv, 0.95 mL) and TBHP (5.0 equiv, 1.58 mL) in toluene (14 mL) provided 843 mg (74% yield) of 2ab as a colorless oil.

Methyl [(S)-2-((tert-butoxycarbonyl)amino)-3-(3-methylpentanoyl)-4-(pyridin-2-yloxy)phenyl)propanoyl]-L-leucinate (2ac). Following the general procedure B, using 1a (0.15 mmol, 73 mg) and 4-methylpentan-1-ol (0.75 mmol, 93 μL) provided 64.4 mg (74% yield) of 2ac as a white solid. Mp 91-92 ºC. Column chromatography (Hex/EtOAc 1:1). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.13 (ddd, $J = 5.0$, 2.0, 0.8 Hz, 1H), 7.71 (ddd, $J = 8.2$, 7.2, 2.0 Hz, 1H), 7.58 (d, $J = 2.3$ Hz, 1H), 7.37 (dd, $J = 8.4$, 2.3 Hz, 1H), 7.07 – 6.97
(m, 2H), 6.94 (dt, J = 8.3, 0.9 Hz, 1H), 6.46 (d, J = 8.2 Hz, 1H), 5.09 (d, J = 8.3 Hz, 1H),
4.58 (td, J = 8.5, 4.9 Hz, 1H), 4.37 (d, J = 8.3 Hz, 1H), 3.70 (s, 3H), 3.23 – 2.94 (m, 2H),
2.94 – 2.69 (m, 2H), 1.64 – 1.44 (m, 6H), 1.41 (s, 9H), 0.90 (dd, J = 6.1, 3.6 Hz, 6H),
0.81 – 0.70 (m, 6H).\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 201.9, 173.0, 170.9, 163.2, 155.5,
151.3, 147.8, 139.8, 133.9, 133.6, 132.4, 130.9, 123.2, 119.0, 111.8, 80.5, 55.5, 52.4,
50.9, 41.6, 41.0, 37.3, 32.9, 28.3, 27.8, 24.8, 22.9, 22.4, 22.0. IR (cm\(^{-1}\))): 3322, 1747, 1691,
1655, 1524, 1169, 778. HRMS (ESI) m/z: (M\(^+\)) calcd for (C\(_{32}\)H\(_{45}\)N\(_3\)O\(_7\)): 583.3258, found
583.3265.

Methyl \([(S)-2-((tern-butoxycarbonyl)amino)-3-(3-palmitoyl-4-(pyridin-2-yloxy)
phenyl)propanoyl]-L-leucinate (2ad). Following the general procedure B, using 1a
(0.15 mmol, 73 mg) and palmityl alcohol (0.75 mmol, 181 mg) provided 76.6 mg (71% yield) of 2ad as a yellowish oil. Column chromatography (Hex/EtOAc 7:3). \(^1\)H NMR
(400 MHz, CDCl\(_3\)) \(\delta\) 8.14 (dd, J = 4.9, 2.0 Hz, 1H), 7.75 – 7.66 (m, 1H), 7.59 (d, J = 2.3 Hz,
1H), 7.37 (dd, J = 8.3, 2.3 Hz, 1H), 7.09 – 6.98 (m, 2H), 6.95 (d, J = 8.2 Hz, 1H),
6.37 (d, J = 8.2 Hz, 1H), 5.03 (d, J = 8.1 Hz, 1H), 4.61 – 4.56 (m, 1H), 4.37 – 4.35 (m,
1H), 3.71 (s, 3H), 3.21 – 2.95 (m, 2H), 2.84 (t, J = 7.4 Hz, 2H), 1.65 – 1.50 (m, 5H), 1.42
(s, 9H), 1.22 (d, J = 25.3 Hz, 24H), 0.95 – 0.81 (m, 9H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\)
201.7, 173.0, 170.9, 163.2, 155.5, 151.3, 147.7, 139.8, 133.9, 133.6, 132.4, 130.9, 123.2,
118.9, 111.8, 80.5, 55.5, 52.4, 50.9, 42.9, 41.6, 37.3, 32.0, 29.8, 29.8, 29.7, 29.6, 29.5,
29.5, 29.3, 28.3, 24.8, 24.2, 22.9, 22.8, 21.9, 14.2. IR (cm\(^{-1}\)): 3305, 1744, 1680, 1656,
1428, 1241, 1165, 775. HRMS (ESI) m/z: (M\(^+\)) calcd for (C\(_{42}\)H\(_{65}\)N\(_3\)O\(_7\)): 723.4823, found
723.4826.
Methyl \[\text{((S)-2-((tert-butoxycarbonyl)amino)-3-(4-(pyridin-2-yloxy)-3-(4-(trifluoromethyl)benzoyl)phenyl)propanoyl)-L-leucinate}\ (2ae).\] Following the general procedure C, using 1a (0.15 mmol, 73 mg), 4-(trifluoromethyl)benzyl alcohol (0.55 mmol, 82 µL) provided 62.3 mg (63% yield) of 2ae as a white solid. Column chromatography (Hex/EtOAc 1:1). The spectroscopic data correspond to those previously reported in the literature.\(^1\)\(^\text{1H NMR}\ (400 MHz, CDCl}_3\) \(\delta\) 7.96 (dd, \(J = 5.0, 1.9\) Hz, 1H), 7.81 (d, \(J = 8.1\) Hz, 2H), 7.56 (d, \(J = 8.2\) Hz, 2H), 7.53 – 7.47 (m, 1H), 7.46 (dd, \(J = 8.3, 2.3\) Hz, 1H), 7.42 (d, \(J = 2.2\) Hz, 1H), 7.19 (d, \(J = 8.3\) Hz, 1H), 6.88 (dd, \(J = 7.2, 5.0\) Hz, 1H), 6.54 (d, \(J = 8.3\) Hz, 1H), 6.43 (d, \(J = 8.3\) Hz, 1H), 5.12 (d, \(J = 8.2\) Hz, 1H), 4.64 – 4.51 (m, 1H), 4.38 (d, \(J = 7.9\) Hz, 1H), 3.67 (s, 3H), 3.25 – 2.99 (m, 2H), 1.67 – 1.49 (m, 4H), 1.41 (s, 9H), 0.90 (dd, \(J = 6.1, 3.2\) Hz, 6H).\(^\text{13C NMR}\ (101 MHz, CDCl}_3\) \(\delta\) 194.2, 173.0, 170.7, 162.7, 150.8, 146.9, 140.6, 139.7, 134.0, 133.9 (q, \(J_{\text{C-F}} = 32.5\) Hz), 133.6, 131.5, 131.3, 130.0, 125.1 (q, \(J_{\text{C-F}} = 4.0\) Hz), 123.3, 123.0 (q, \(J_{\text{C-F}} = 272.6\) Hz), 118.8, 111.5, 80.6, 55.6, 52.5, 50.9, 41.6, 37.4, 28.4, 24.8, 22.9, 21.9.

Methyl \[\text{((S)-3-(3-benzoyl-4-(pyridin-2-yloxy)phenyl)-2-((tert-butoxycarbonyl)amino)propanoyl)-L-leucinate}\ (2af).\] Following the general procedure C, using 1a (0.15 mmol, 73 mg) and benzyl alcohol (0.54 mmol, 47 µL) provided 52 mg (59% yield) of 2af as a white solid. Mp 61-62 ºC. Column chromatography (Hex/EtOAc 1:1).\(^\text{1H NMR}\ (400 MHz, CDCl}_3\) \(\delta\) 7.99 – 7.96 (m, 1H), 7.75 – 7.71 (m, 2H), 7.53 – 7.47 (m, 1H), 7.51 – 7.43 (m, 1H), 7.42 (dd, \(J = 8.3, 2.2\) Hz, 1H), 7.38 (s, 1H), 7.33 (t, \(J = 7.7\) Hz, 2H), 7.19
(d, J = 8.3 Hz, 1H), 6.86 (ddd, J = 7.1, 5.0, 0.9 Hz, 1H), 6.59 (d, J = 8.3 Hz, 1H), 6.44 (d, J = 8.3 Hz, 1H), 5.09 (d, J = 8.2 Hz, 1H), 4.58 (td, J = 8.6, 5.0 Hz, 1H), 4.43 – 4.29 (m, 1H), 3.67 (s, 3H), 3.17 (dd, J = 14.1, 6.5 Hz, 1H), 3.08 (dd, J = 14.3, 6.9 Hz, 1H), 1.64 – 1.55 (m, 2H), 1.54 – 1.48 (m, 1H), 1.41 (s, 9H), 0.91 (d, J = 3.6 Hz, 3H), 0.89 (d, J = 4.4 Hz, 3H). 13C NMR (101 MHz, CDCl3) δ 195.0, 172.9, 170.7, 162.9, 155.4, 150.5, 146.9, 140.0, 137.3, 133.1, 132.8, 132.2, 131.0, 129.8, 128.0, 122.9, 118.5, 111.4, 80.4, 55.4, 52.3, 50.7, 41.5, 37.1, 28.2, 24.7, 22.8, 21.8. IR (cm−1): 3304, 2956, 1657, 1428, 1242, 1158. HRMS (ESI) m/z: (M+) calcd for (C33H39N3O7): 589.2788, found 589.2799.

**Methyl ((S)-3-[3-acetyl-4-(pyridin-2-yloxy)phenyl]-2-(1,3-dioxoisindolin-2-yl)propanoate (2b).** Following the general procedure A, using NPhth-Tyr(OPy)-OMe (1b) (0.15 mmol, 60 mg) in PhCl as solvent provided 39 mg (58% yield) of 2b as a white solid. Mp 108-109 °C. Column chromatography (Hex/EtOAc 1:1). 1H NMR (400 MHz, CDCl3) δ 8.09 (dd, J = 5.1, 2.0 Hz, 1H), 7.79 (dd, J = 5.5, 3.1 Hz, 2H), 7.75 – 7.60 (m, 4H), 7.33 (dd, J = 8.4, 2.4 Hz, 1H), 7.01 – 6.93 (m, 2H), 6.92 – 6.82 (m, 1H), 5.15 (dd, J = 10.9, 5.4 Hz, 1H), 3.76 (s, 3H), 3.68 – 3.47 (m, 2H), 2.40 (s, 3H). 13C NMR (101 MHz, CDCl3) δ 198.1, 169.2, 167.5, 163.0, 151.8, 147.8, 139.8, 143.3, 133.8, 133.6, 131.7, 131.6, 130.6, 123.7, 123.2, 119.0, 111.7, 53.1, 53.0, 34.1, 30.7. IR (cm−1): 1777, 1744, 1709, 1672, 1387, 1268, 859. HRMS (ESI) m/z: (M+) calcd for (C25H20N2O6): 444.1321, found 444.1323.

**Methyl [(S)-3-(3-acetyl-4-(pyridin-2-yloxy)phenyl)-2-((tert-butoxycarbonyl)amino)propanoyl]-L-valinate (2c).** Following the general procedure A, using Boc-Tyr(OPy)Val-OMe1 (1c) (0.15 mmol, 71 mg) and EtOH (3.75 mmol, 0.22 mL) provided 40 mg (52% yield) of 2c as a yellowish oil. Column chromatography (Hex/EtOAc 1:1). 1H NMR (400 MHz, CDCl3) δ 8.13 (dd, J = 5.1, 2.0 Hz, 1H), 7.76 – 7.61 (m, 2H), 7.38
(dd, J = 8.4, 2.3 Hz, 1H), 7.08 – 6.97 (m, 2H), 6.94 (d, J = 8.3 Hz, 1H), 6.62 (d, J = 8.8 Hz, 1H), 5.18 (d, J = 8.2 Hz, 1H), 4.48 (dd, J = 8.7, 5.0 Hz, 1H), 4.44 – 4.30 (m, 1H), 3.69 (s, 3H), 3.15 (dd, J = 14.0, 6.4 Hz, 1H), 3.04 (dd, J = 14.1, 7.3 Hz, 1H), 2.48 (s, 3H), 2.13 (ddd, J = 13.8, 6.9, 5.1 Hz, 2H), 1.40 (s, 9H), 0.86 (dd, J = 10.3, 6.9 Hz, 6H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 198.4, 172.0, 171.0, 163.1, 155.5, 151.9, 147.8, 139.9, 134.4, 133.6, 131.7, 131.1, 123.2, 119.0, 111.8, 80.4, 57.3, 55.6, 52.2, 37.2, 31.3, 30.9, 28.3, 18.9, 17.8. IR (cm$^{-1}$): 3306, 1740, 1679, 1655, 1427, 1239, 775. HRMS (ESI) m/z: (M$^+$) calcd for (C$_{27}$H$_{35}$N$_3$O$_7$): 513.2475, found 513.2478.

Methyl [(S)-3-(3-acetyl-4-(pyridin-2-yloxy)phenyl)-2-((tert-butoxycarbonyl)amino)propanoyl]-L-phenylalaninate (2da). Following the general procedure A, using Boc-Tyr(OPy)-Phe-OMe$^1$ (1d) (0.15 mmol, 78 mg) and EtOH (3.75 mmol, 0.22 mL) provided 40.3 mg (48% yield) of 2da as a colorless oil. Column chromatography (Hex/EtOAc 1:1).

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.16 (dd, J = 5.1, 1.9 Hz, 1H), 7.75 (ddd, J = 8.3, 7.2, 2.0 Hz, 1H), 7.67 (d, J = 2.3 Hz, 1H), 7.46 – 7.35 (m, 1H), 7.32 – 7.19 (m, 3H), 7.12 – 7.02 (m, 4H), 6.99 (d, J = 8.3 Hz, 1H), 6.40 (d, J = 8.2 Hz, 1H), 5.02 (s, 1H), 4.93 – 4.78 (m, 1H), 4.38 – 4.36 (m, 1H), 3.72 (s, 3H), 3.17 – 3.03 (m, 4H), 2.53 (s, 3H), 1.44 (s, 9H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 198.4, 171.5, 170.6, 163.1, 155.3, 152.0, 147.8, 139.9, 135.7, 134.4, 133.5, 131.8, 131.1, 129.3, 128.8, 127.3, 123.3, 119.1, 111.8, 80.4, 55.5, 53.4, 53.2, 52.5, 58.0, 37.6, 30.9, 28.3. IR (cm$^{-1}$): 3318, 1742, 1685, 1655, 1427, 1264, 1210, 699. HRMS (ESI) m/z: (M$^+$) calcd for (C$_{31}$H$_{35}$N$_3$O$_7$): 561.2475, found 561.2479.

Methyl [(S)-2-((tert-butoxycarbonyl)amino)-3-(3-(4-methylpentanoyl)-4-(pyridin-2-yloxy)phenyl)propanoyl]-L-phenylalaninate (2db). Following the general procedure
B, using Boc-Tyr(OPy)-Phe-OMe\(^1\) (1d) (0.15 mmol, 78 mg) and 4-methylpentan-1-ol (0.75 mmol, 93 \(\mu\)L) in PhCl as solvent provided 39 mg (42% yield) of 2db as a colorless oil. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.15 (d, \(J = 3.0\) Hz, 1H), 7.73 (ddd, \(J = 8.2, 7.3, 2.0\) Hz, 1H), 7.58 (d, \(J = 2.2\) Hz, 1H), 7.36 (ddd, \(J = 8.3, 2.3\) Hz, 1H), 7.31 – 7.22 (m, 3H), 7.12 – 6.90 (m, 5H), 6.40 (d, \(J = 7.7\) Hz, 1H), 5.00 (s, 1H), 4.83 (q, \(J = 6.7\) Hz, 1H), 4.35 (m, 1H), 3.71 (s, 3H), 3.26 – 3.03 (m, 4H), 2.89 – 2.71 (m, 2H), 1.61 – 1.35 (m, 12H), 0.81 (d, \(J = 6.4\) Hz, 6H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 202.4, 172.0, 171.1, 163.8, 151.9, 148.3, 140.3, 136.3, 134.3, 134.1, 133.1, 131.4, 129.9, 129.2, 127.8, 123.8, 119.5, 112.3, 80.4, 56.1, 53.9, 53.0, 41.5, 38.5, 38.1, 33.5, 28.9, 28.4, 22.9. IR (cm\(^{-1}\)): 3327, 2955, 1677, 1428, 1264, 1167, 970, 730. IR (cm\(^{-1}\)): 3318, 1742, 1685, 1655, 1427, 1264, 1210, 699. HRMS (ESI) m/z: (M\(^+\)) calcd for (C\(_{35}\)H\(_{43}\)N\(_3\)O\(_7\)): 617.3101, found 617.3105.

**Methyl (S)-3-[3-acetyl-4-(pyridin-2-yloxy)phenyl]-2-[[S]-6-(((benzyloxy)carbonyl)amino)-2-(((tert-butoxycarbonyl)amino)hexanamido)propanoate (2e).** Following the general procedure A, using Boc-Lys(Cbz)-Tyr(OPy)-OMe\(^1\) (1e) (0.15 mmol, 95 mg) in PhCl as solvent provided 42.4 mg (41% yield) of 2e as a colorless oil. Column chromatography (Hex/EtOAc 3:7). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.18 (d, \(J = 4.9\) Hz, 1H), 7.83 – 7.71 (m, 1H), 7.59 (d, \(J = 2.3\) Hz, 1H), 7.46 – 7.25 (m, 6H), 7.11 – 6.94 (m, 3H), 6.80 (d, \(J = 7.9\) Hz, 1H), 5.37 (d, \(J = 7.9\) Hz, 1H), 5.17 – 5.13 (m, 1H), 5.09 (s, 2H), 4.89 (q, \(J = 6.3\) Hz, 1H), 4.12 – 4.10 (m, 1H), 3.74 (s, 3H), 3.35 – 3.01 (m, 4H), 2.52 (s, 3H), 1.87 – 1.80 (m, 2H), 1.72 – 1.47 (m, 4H), 1.42 (s, 9H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 198.6, 172.0, 171.6, 163.0, 156.7, 155.9, 152.3, 147.8, 140.1, 136.7, 134.4, 132.7, 131.4, 131.2, 128.6, 128.2, 128.1, 123.1, 119.2, 112.0, 80.1, 66.7, 54.4, 53.0, 52.6, 40.4, 37.1, 31.6, 31.0, 29.4, 28.3, 22.5. IR (cm\(^{-1}\)): 3320, 1742, 1673, 1465, 1239, 1163. HRMS (ESI) m/z: (M\(^+\)) calcd for (C\(_{36}\)H\(_{44}\)N\(_4\)O\(_9\)): 676.3108, found 676.3109.
Methyl (S)-3-(3-acetyl-4-(pyridin-2-xyloxy)phenyl)-2-((S)-2-((tert-butoxycarbonyl) amino)propanamido)propanoate (2f). Following the general procedure A, using Boc-Ala-Tyr(OPy)-OMe\(^1\) (1f) (0.15 mmol, 66 mg) and EtOH (3.75 mmol, 0.22 mL) provided 54 mg (74% yield) of 2f as a colorless oil. Column chromatography (Hex/EtOAc 1:1). 1H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.24 – 8.11 (m, 1H), 7.83 – 7.70 (m, 1H), 7.58 (d, \(J = 2.3\) Hz, 1H), 7.35 – 7.26 (m, 1H), 7.06 (t, \(J = 6.8\) Hz, 2H), 7.01 (d, \(J = 8.3\) Hz, 1H), 6.81 (d, \(J = 7.8\) Hz, 1H), 5.27 (s, 1H), 4.89 (dt, \(J = 7.7, 5.7\) Hz, 1H), 4.19 – 4.16 (m, 1H), 3.77 (s, 3H), 3.28 (dd, \(J = 13.9, 5.6\) Hz, 1H), 3.11 (dd, \(J = 13.9, 5.9\) Hz, 1H), 2.53 (s, 3H), 1.43 (s, 9H), 1.36 (d, \(J = 7.1\) Hz, 3H). 13C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 198.7, 172.6, 171.5, 163.0, 155.7, 152.3, 147.8, 147.7, 140.0, 134.5, 132.8, 131.2, 123.1, 119.2, 112.0, 80.2, 53.0, 52.7, 50.2, 37.1, 31.1, 28.4, 18.0. IR (cm\(^{-1}\)): 3306, 1742, 1668, 1427, 1239, 1163, 777. HRMS (ESI) m/z: (M\(^{+}\) calecd) for (C\(_{25}\)H\(_{31}\)N\(_{3}\)O\(_{7}\)): 485.2162, found 485.2166.

**tert-Butyl (S)-2-[(S)-3-(3-acetyl-4-(pyridin-2-xyloxy)phenyl)-1-methoxy-1-oxopropan-2-yl]carbamoyl]pyrrolidine-1-carboxylate (2g).** Following the general procedure A, using 1g (0.15 mmol, 79 mg) and EtOH (3.75 mmol, 0.22 mL) provided 38 mg (50% yield) of 2g as a yellow oil. Column chromatography (Hex/EtOAc 1:1). 1H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.17 – 8.09 (m, 1H), 7.71 (t, \(J = 7.7\) Hz, 1H), 7.58 (dd, \(J = 7.7, 2.1\) Hz, 1H), 7.34 – 7.25 (m, 1H), 7.05 – 6.97 (m, 2H), 6.94 (d, \(J = 8.2\) Hz, 1H), 4.97 – 4.73 (m, 1H), 4.32 – 4.12 (m, 1H), 3.72 (s, 3H), 3.47 – 3.28 (m, 2H), 3.13 (dt, \(J = 36.1, 14.1, 6.1\) Hz, 2H), 2.49 (s, 3H), 2.30 – 1.73 (m, 4H), 1.41 (s, 9H). 13C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 198.0, 171.5, 171.4, 162.9, 152.1, 147.7, 147.7, 139.7, 134.1, 132.8, 131.5, 130.8, 123.0, 118.9, 111.6, 80.4, 60.0, 53.1, 52.4, 46.9, 37.3, 30.8, 29.6, 28.3, 24.4. IR (cm\(^{-1}\)): 3305, 2976, 1744, 1678, 1428, 1238, 1191. HRMS (ESI) m/z: (M\(^{+}\) calecd) for (C\(_{27}\)H\(_{33}\)N\(_{3}\)O\(_{7}\)): 511.2319, found 511.2325.
Methyl (S)-[3-(3-acetyl-4-(pyridin-2-yloxy)phenyl)-2-((tert-butoxycarbonyl)amino)propanoyl]glycinate (2h). Following the general procedure A, using 1h (0.15 mmol, 79 mg) and EtOH (3.75 mmol, 0.22 mL) provided 37 mg (53% yield) of 2h as a white solid. Mp 57-58 °C. Column chromatography (Hex/EtOAc 1:1). 1H NMR (400 MHz, CDCl3) δ 8.15 (dd, J = 5.0, 1.9 Hz, 1H), 7.72 (ddd, J = 8.8, 7.4, 2.0 Hz, 1H), 7.67 (d, J = 2.3 Hz, 1H), 7.40 (dd, J = 8.4, 2.3 Hz, 1H), 7.05 (d, J = 8.4 Hz, 1H), 7.02 (dd, J = 7.3, 5.1 Hz, 1H), 6.97 (d, J = 8.3 Hz, 1H), 6.61 (s, 1H), 5.08 (s, 1H), 4.48 – 4.37 (m, 1H), 4.06 (dd, J = 18.3, 5.4 Hz, 1H), 3.98 (dd, J = 18.3, 5.2 Hz, 1H), 3.74 (s, 3H), 3.18 (dd, J = 14.0, 6.3 Hz, 1H), 3.07 (dd, J = 14.0, 7.2 Hz, 1H), 2.51 (s, 3H), 1.41 (s, 9H). 13C NMR (101 MHz, CDCl3) δ 198.3, 171.2, 169.9, 163.0, 155.4, 151.9, 147.7, 139.8, 134.3, 133.4, 131.7, 131.0, 123.2, 119.0, 111.7, 80.5, 55.4, 52.4, 41.2, 37.5, 30.8, 28.2. IR (cm⁻¹): 3238, 1741, 1656, 1427, 1240, 1155. HRMS (ESI) m/z: (M⁺) calcd for (C24H29N3O7): 471.2006, found 471.2004.

Methyl O-acetyl-N-[(S)-3-(3-acetyl-4-(pyridin-2-yloxy)phenyl)-2-[(tert-butoxycarbonyl)amino]propanoyl]-L-serinate (2i). Following the general procedure A, using 1i (0.15 mmol, 75 mg) and EtOH (3.75 mmol, 0.22 mL) provided 42 mg (51% yield) of 2i as a white solid. Mp 148-149 °C. Column chromatography (Hex/EtOAc 1:1). 1H NMR (300 MHz, CDCl3) δ 8.17 – 8.10 (m, 1H), 7.75 – 7.67 (m, 1H), 7.66 (t, J = 2.3 Hz, 1H), 7.37 (d, J = 8.3 Hz, 1H), 7.06 – 7.00 (m, 2H), 6.99 – 6.91 (m, 2H), 6.87 (d, J = 7.8 Hz, 0H), 5.15 (s, 1H), 4.79 (dt, J = 7.4, 3.5 Hz, 1H), 4.47 – 4.37 (m, 2H), 4.27 (ddd, J = 28.7, 11.4, 3.5 Hz, 1H), 3.73 (s, 3H), 3.15 (dd, J = 14.6, 7.4 Hz, 1H), 3.05 (dd, J = 13.9, 7.1 Hz, 1H), 2.49 (s, 3H), 2.00 (s, 3H), 1.40 (s, 9H). 13C NMR (75 MHz, CDCl3) δ 198.2, 171.0, 170.5, 169.4, 163.0, 155.2, 151.9, 147.7, 139.7, 134.2, 133.2, 131.6, 130.9, 123.1, 118.9, 111.7, 80.4, 63.6, 55.3, 52.8, 51.6, 37.4, 30.7, 28.2, 20.5. IR (cm⁻¹): 3262, 1746, 1650, 1217. HRMS (ESI) m/z: (M⁺) calcd for (C27H33N3O9): 543.2217, found 543.2209.
** tert-Butyl (S)-4-[(S)-3-(3-acetyl-4-(pyridin-2-yl)oxy)phenyl]-1-methoxy-1-oxopropan-2-yl]amino]-3-[(benzyloxy)carbonyl]amino]-4-oxobutanoate (2j).**

Following the general procedure A, using 1j (0.15 mmol, 87 mg) and EtOH (3.75 mmol, 0.22 mL) provided 49 mg (53% yield) of 2j as a white solid. Mp 49-50 °C. Column chromatography (Hex/EtOAc 1:1). $^1$H NMR (300 MHz, CDCl$_3$) δ 8.14 (dd, $J = 5.3$, 1.6 Hz, 1H), 7.72 (dd, $J = 8.3$, 3.7, 2.0 Hz, 1H), 7.61 (dd, $J = 12.0$, 2.2 Hz, 1H), 7.37 – 7.26 (m, 5H), 7.01 (dd, $J = 8.2$, 2.7 Hz, 3H), 6.95 (d, $J = 8.0$ Hz, 1H), 5.99 (dd, $J = 40.5$, 8.0 Hz, 1H), 5.18 – 5.03 (m, 2H), 4.83 (dd, $J = 13.4$, 6.0 Hz, 1H), 4.62 – 4.45 (m, 1H), 3.73 (s, 3H), 3.18 (dd, $J = 13.7$, 5.4 Hz, 1H), 3.06 (dd, $J = 13.9$, 6.1 Hz, 1H), 2.86 (dd, $J = 17.1$, 4.5 Hz, 1H), 2.68 – 2.55 (m, 1H), 2.50 (s, 3H), 1.41 (s, 9H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 198.2, 171.1, 170.8, 170.3, 163.0, 156.2, 152.1, 147.8, 139.7, 136.1, 134.3, 132.6, 131.6, 131.0, 128.5, 128.2, 128.0, 123.1, 118.9, 111.7, 81.8, 67.2, 53.2, 52.5, 51.0, 37.2, 37.0, 30.8, 28.0. IR (cm$^{-1}$): 3324, 1726, 1677, 1239, 1153. HRMS (ESI) m/z: (M$^+$) calcd for (C$_{33}$H$_{37}$N$_3$O$_9$): 619.2530, found 619.2523.

** Dimethyl [(S)-3-(3-acetyl-4-(pyridin-2-yl)oxy)phenyl]-2-[(tert-butoxycarbonyl) amino]propanoyl]-L-glutamate (2ka).** Following the general procedure A, using 1k (0.15 mmol, 77 mg) and EtOH (3.75 mmol, 0.22 mL) provided 43 mg (52% yield) of 2ka as a white solid. Mp 45-46 °C. Column chromatography (Hex/EtOAc 1:1). $^1$H NMR (400 MHz, CDCl$_3$) δ 8.14 (td, $J = 5.0$, 1.9 Hz, 1H), 7.72 (td, $J = 7.8$, 2.0 Hz, 1H), 7.66 (dd, $J = 4.4$, 2.3 Hz, 1H), 7.39 (d, $J = 8.4$ Hz, 1H), 7.06 (dd, $J = 8.4$, 2.2 Hz, 1H), 7.02 (dd, $J = 7.2$, 5.1 Hz, 1H), 6.97 (d, $J = 8.3$ Hz, 1H), 6.85 – 6.60 (m, 1H), 5.04 (s, 1H), 4.58 (dd, $J = 7.4$ Hz, 1H), 4.47 – 4.30 (m, 1H), 3.72 (s, 3H), 3.64 (s, 3H), 3.15 (dt, $J = 13.5$, 6.6 Hz, 1H), 3.06 (dt, $J = 13.4$, 6.3 Hz, 1H), 2.51 (s, 3H), 2.41 – 2.25 (m, 2H), 2.25 – 2.07 (m,


\[1H), 2.02 – 1.88 (m, 1H), 1.42 (s, 9H). ^{13}C\text{ NMR (101 MHz, CDCl}_3\delta 198.3, 173.1, 171.7, 170.9, 163.0, 155.3, 151.9, 147.7, 139.8, 134.3, 133.3, 131.7, 131.0, 123.3, 118.9, 111.7, 80.4, 55.5, 52.6, 51.8, 51.6, 37.3, 30.8, 29.8, 28.2, 27.2. IR (cm\(^{-1}\)): 3270, 1736, 1684, 1649, 1243, 1158. HRMS (ESI) m/z: (M\(^+\)) calcd for (C\(_{28}\)H\(_{35}\)N\(_3\)O\(_9\)): 557.2323, found 557.2376.

Dimethyl [(S)-2-((tert-butoxycarbonyl)amino)-3-(3-(4-methylpentanoyl)-4-(pyridin-2-yloxy)phenyl)propanoyl]-L-glutamate (2kb). Following the general procedure B, using 1k (0.15 mmol, 77 mg) and 4-methylpentan-1-ol (0.75 mmol, 93 µL) provided 38 mg (52% yield) of 2kb as a yellow oil. Column chromatography (Hex/EtOAc 1:1). ^1H NMR (400 MHz, CDCl\(_3\)) \(\delta 8.16 – 8.09 (m, 1H), 7.72 (t, J = 7.7 Hz, 1H), 7.61 – 7.54 (m, 1H), 7.37 (d, J = 8.1 Hz, 1H), 7.06 (d, J = 8.3 Hz, 1H), 7.04 – 6.98 (m, 1H), 6.95 (d, J = 8.2 Hz, 1H), 6.86 – 6.65 (m, 1H), 5.03 (s, 1H), 4.66 – 4.51 (m, 1H), 4.44 – 4.31 (m, 1H), 3.72 (s, 3H), 3.64 (s, 3H), 3.21 – 3.11 (m, 1H), 3.11 – 3.00 (m, 4H), 2.87 – 2.79 (m, 2H), 2.39 – 2.26 (m, 2H), 2.24 – 2.11 (m, 1H), 2.00 – 1.89 (m, 1H), 1.49 – 1.35 (m, 12H), 0.79 (d, J = 6.1 Hz, 6H). ^{13}C NMR (101 MHz, CDCl\(_3\)) \(\delta 201.7, 173.1, 171.8, 171.0, 163.1, 155.3, 151.2, 147.6, 139.7, 133.7, 133.3, 132.4, 130.7, 123.3, 118.8, 111.6, 80.4, 55.5, 52.6, 51.8, 51.7, 40.8, 37.3, 32.8, 29.8, 28.2, 27.7, 27.2, 27.0, 22.3. IR (cm\(^{-1}\)): 3323, 2955, 1739, 1675, 1428, 1242, 1167. HRMS (ESI) m/z: (M\(^+\)) calcd for (C\(_{32}\)H\(_{43}\)N\(_3\)O\(_9\)): 613.2999, found 613.3011.

Methyl [(S)-3-(3-acetyl-4-(pyridin-2-yloxy)phenyl)-2-((tert-butoxycarbonyl)amino)propanoyl]-L-isoleucyl-L-leucinate (2l). Following the general procedure A, using Boc-
Tyr(OPy)-Ile-Leu-OMe\textsuperscript{1} (1I) (0.15 mmol, 90 mg) in PhCl as solvent provided 39 mg (37% yield) of 2l as white solid. Mp 131-132 °C. Column chromatography (Hex/EtOAc 1:1). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 8.12 (d, \( J = 5.0 \) Hz, 1H), 7.80 – 7.61 (m, 5H), 5.41 (d, \( J = 8.0 \) Hz, 1H), 4.57 – 4.52 (m, 1H), 4.53 – 4.27 (m, 2H), 3.70 (s, 3H), 3.23 – 2.94 (m, 2H), 2.48 (s, 3H), 2.08 – 1.78 (m, 1H), 1.67 – 1.50 (m, 5H), 1.36 (s, 9H), 1.34 – 1.06 (m, 1H), 0.90 – 0.84 (m, 11H). \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) \( \delta \) 198.4, 173.1, 171.3, 171.0, 163.1, 155.7, 152.0, 147.8, 139.9, 134.4, 133.7, 131.5, 131.2, 123.1, 119.0, 111.8, 80.3, 57.9, 55.6, 52.3, 50.9, 41.1, 37.4, 37.1, 30.9, 28.3, 24.9, 22.9, 22.0, 15.3, 11.4. IR (cm\textsuperscript{-1}): 3286, 1746, 1685, 1641, 1465, 1158. HRMS (ESI) m/z: (M\textsuperscript{+}) calcd for (C\textsubscript{34}H\textsubscript{48}N\textsubscript{4}O\textsubscript{8}): 640.3472, found 640.3479.

Methyl ((S)-3-(3-acetyl-4-(pyridin-2-yloxy)phenyl)-2-[(S)-3-(4-(benzyloxy)phenyl)-2-((tert-butoxycarbonyl)amino)propanamido]propanoyl]-L-leucinate (2m).

Following the general procedure A, using Boc-Tyr(Obn)-Tyr(OPy)-Leu-OMe (1m) (0.15 mmol, 111 mg) and EtOH (3.75 mmol, 0.22 mL) in PhCl as solvent provided 48 mg (41% yield) of 2m as a white solid. Mp 130-131 °C. Column chromatography (Hex/EtOAc 6:4). \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \( \delta \) 8.09 (ddd, \( J = 5.0, 2.0, 0.8 \) Hz, 1H), 7.70 (ddd, \( J = 8.3, 7.2, 2.0 \) Hz, 1H), 7.53 (d, \( J = 2.3 \) Hz, 1H), 7.44 – 7.28 (m, 6H), 7.16 – 7.07 (m, 3H), 7.05 – 6.84 (m, 6H), 6.70 (d, \( J = 8.2 \) Hz, 1H), 6.51 (d, \( J = 8.0 \) Hz, 1H), 5.09 (d, \( J = 7.2 \) Hz, 1H), 5.02 (s, 2H), 4.73 – 4.67 (m, 1H), 4.56 – 4.48 (m, 1H), 4.33 – 4.26 (m, 1H), 3.70 (s, 3H), 3.18 – 2.99 (m, 3H), 2.88 (dd, \( J = 14.5, 7.8 \) Hz, 1H), 2.49 (s, 3H), 2.06 – 2.02 (m, 2H), 1.72 – 1.43 (m, 4H), 1.34 (s, 9H), 0.88 (d, \( J = 5.8 \) Hz, 6H). \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \( \delta \) 198.5, 172.8, 171.5, 171.0, 163.1, 158.0, 155.7, 152.0, 147.8, 139.9, 137.1, 134.6, 133.3, 131.8, 131.1, 130.4, 128.8, 128.7, 128.0, 127.5, 123.3, 119.1, 115.3, 115.2, 111.8, 80.5, 70.1, 56.3, 53.8, 52.4, 51.1, 41.3, 37.1, 30.9, 28.3, 24.8, 22.9, 22.0. IR (cm\textsuperscript{-1}): 3291, 1742, 1685, 1642, 1549, 1238. HRMS (ESI) m/z: (M\textsuperscript{+}) calcd for (C\textsubscript{44}H\textsubscript{52}N\textsubscript{4}O\textsubscript{9}): 780.3734, found 780.3747.
Methyl [(S)-3-(3-acetyl-4-(pyridin-2-yloxy)phenyl)-2-((tert-butoxycarbonyl)amino)propanoyl]-L-prolyl-L-phenylalanyl-L-phenylalaninate (2n). Following the general procedure A, using Boc-Tyr(OPy)-Pro-Phe-OMe\(^1\) (1n) (0.15 mmol, 114 mg) provided 65 mg of 2n (54% yield) as a white solid. Column chromatography (EtOAc). Mp 59-60 °C. \(^1\)H NMR (500 MHz, DMSO-\(d_6\) at 80 °C) \(\delta\) 8.10 (dd, \(J = 5.0, 2.0\) Hz, 1H), 7.96 (d, \(J = 7.6\) Hz, 1H), 7.91 – 7.69 (m, 1H), 7.68 – 7.53 (m, 2H), 7.46 (d, \(J = 8.3\) Hz, 1H), 7.31 – 7.14 (m, 8H), 7.10 (dd, \(J = 7.2, 4.9\) Hz, 1H), 7.02 (t, \(J = 8.7\) Hz, 1H), 4.63 – 4.26 (m, 4H), 3.58 (s, 3H), 2.96 – 2.74 (m, 1H), 2.41 (s, 2H), 2.03 – 1.65 (m, 3H), 1.32 (s, 9H). \(^{13}\)C NMR (126 MHz, DMSO-\(d_6\) at 80 °C) 197.3, 170.9, 170.5, 170.2, 169.9, 162.4, 150.3, 146.9, 139.6, 137.2, 136.6, 134.0, 133.7, 131.3, 129.8, 128.6, 128.5, 127.7, 127.5, 127.4, 126.0, 125.7, 122.2, 118.6, 111.0, 77.9, 59.4, 54.2, 53.2, 51.2, 46.3, 36.9, 36.6, 35.8, 29.6, 27.7. IR (cm\(^{-1}\)): 3294, 1741, 1637, 1427, 1239, 1047, 699. HRMS (ESI) m/z: (M\(^+\)) calcd for (C\(_{45}\)H\(_{51}\)N\(_{5}\)O\(_{9}\)): 805.3687, found 805.3696.

Methyl [(S)-3-(3-acetyl-4-(pyridin-2-yloxy)phenyl)-2-((S)-1-(N\(^2\),N\(^6\)-bis(tert-butoxycarbonyl)-L-lysyl-L-isoleucyl)pyrrolidine-2-carboxamido)propanoyl]-L-isoleucyl-L-leucinate (2o). Following the general procedure A, using Boc-Lys(Boc)-Ile-Pro-Tyr(OPy)-Ile-Leu-OMe\(^1\) (1o) (0.15 mmol, 155 mg) provided 87.3 mg of 2o (54% yield) as a white solid. Column chromatography (EtOAc). Mp 73-74 °C. \(^1\)H NMR (500MHz,
DMSO-\textit{d}_6 \ \delta \ 8.12 (dd, J = 5.0, 1.9 Hz, 1H), 7.95 (d, J = 7.6 Hz, 2H), 7.92 – 7.80 (m, 1H), 7.79 – 7.36 (m, 7H), 7.25 (d, J = 8.2 Hz, 1H), 7.11 (dd, J = 7.2, 4.8 Hz, 1H), 7.07 – 6.90 (m, 3H), 6.52 (s, 1H), 6.30 (s, 1H), 4.61 (td, J = 8.0, 5.2 Hz, 2H), 4.51 – 4.30 (m, 5H), 4.26 (dd, J = 8.8, 6.9 Hz, 2H), 3.91 (q, J = 7.6 Hz, 2H), 3.70 (s, 1H), 3.61 (s, 5H), 3.53 (s, 2H), 3.12 (dd, J = 14.4, 5.2 Hz, 2H), 3.00 – 2.79 (m, 5H), 2.43 (s, 3H), 1.98 (s, 2H), 1.90 – 1.70 (m, 8H), 1.69 – 1.45 (m, 12H), 1.38 (d, J = 1.7 Hz, 36H), 1.27 (tq, J = 15.8, 9.4, 6.3 Hz, 5H), 1.20 – 1.02 (m, 4H), 0.85 (ddt, J = 17.5, 14.4, 7.2 Hz, 33H).

\begin{align*}
13^C \text{ NMR (126 MHz, DMSO-\textit{d}_6 at 80 ºC)} & \delta 197.2, 172.0, 171.4, 170.8, 170.3, 169.9, 169.8, 169.7, 162.4, 155.1, 154.7, 152.3, 150.3, 147.0, 146.9, 139.6, 139.4, 133.9, 133.4, 131.2, 129.8, 129.7, 122.0, 119.8, 118.6, 118.4, 111.0, 77.8, 77.0, 59.1, 56.4, 54.4, 54.0, 53.2, 51.0, 50.0, 46.6, 36.7, 36.1, 31.1, 29.6, 28.8, 27.9, 27.7, 23.9, 23.8, 23.6, 22.3, 22.1, 21.0, 14.7, 10.5. \text{ IR (cm}^{-1}) \rightarrow 3285, 1746, 1682, 1643, 1465, 1243, 1165. \text{ HRMS (ESI) m/z: (M}^+\text{) calcd for (C}_{56}H_{86}N_8O_{13}) : 1078.6314, \text{ found 1078.6312.}
\end{align*}

Methyl [(S)-3-(3-acetyl-4-(pyridin-2-yloxy)phenyl)-2-((S)-2-((tert-butoxycarbonyl)amino)-5-(2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yl)sulfonyl)guanidino]pentanamido)propanoyl]-L-leucinate (2p). Following the general procedure A, in PhCl as solvent using Boc-Arg(Pbf)-Tyr(OPy)-Leu-OMe (1p) (0.15 mmol, 134 mg) provided 56 mg of 2p (40% yield) as a colorless oil. Column chromatography (EtOAc). $^1$H NMR (300MHz, CDCl$_3$) $\delta$ 8.10 (dd, J = 5.0, 1.9 Hz, 1H), 7.80 – 7.59 (m, 2H), 7.52 – 7.32 (m, 2H), 7.09 – 6.86 (m, 4H), 6.32 (s, 2H), 5.55 (d, J = 7.8 Hz, 1H), 4.77 – 4.69 (m, 1H), 4.57 – 4.37 (m, 1H), 4.19 – 4.15 (m, 1H), 3.66 (s, 3H), 3.34 – 2.98 (m, 5H), 2.94 (s, 2H), 2.57 (s, 3H), 2.49 (d, J = 9.6 Hz, 5H), 2.41 (s, 1H), 2.24 (s, 2H), 2.07 (s, 3H), 1.71 – 1.48 (m, 7H), 1.44 (s, 6H), 1.37 (s, 9H), 0.85 (d, J = 3.8 Hz, 6H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 199.3, 173.1, 172.7, 171.0, 163.1, 158.8, 156.8, 156.6, 156.0, 151.7, 147.7, 140.0, 138.5, 134.7, 134.2, 134.1, 133.8, 133.0, 132.4, 131.6, 131.2, 131.0, 130.8, 124.7, 123.2, 121.2, 119.1, 117.6, 111.9, 86.5, 80.1, 54.6, 54.2, 52.4, 51.1, 43.4,
Methyl [(S)-2-((tert-butoxycarbonyl)amino)acetamido]-3-[3-(4-methylpentanoyl) -4-(pyridin-2-yloxy)phenyl]propanoyl]-L-leucinate (2q). Following the general procedure B, using 1q (0.15 mmol, 79 mg) and 4-methylpentan-1-ol (0.75 mmol, 93 µL) provided 38 mg (50% yield) of 2q as a yellow oil. Column chromatography (Hex/EtOAc 2:3). 1H NMR (400 MHz, CDCl$_3$) δ 8.13 (d, $J = 5.0$ Hz, 1H), 7.72 (t, $J = 7.1$ Hz, 1H), 7.55 (d, $J = 2.0$ Hz, 1H), 7.37 (d, $J = 8.1$ Hz, 1H), 7.02 (dd, $J = 12.4, 7.4$ Hz, 2H), 6.96 (d, $J = 8.2$ Hz, 1H), 6.76 (s, 1H), 6.52 (s, 1H), 5.35 (s, 1H), 4.80 – 4.63 (m, 1H), 4.59 – 4.46 (m, 1H), 3.86 – 3.72 (m, 2H), 3.71 (s, 3H), 3.20 – 3.07 (m, 2H), 2.88 – 2.79 (m, 2H), 1.65 – 1.50 (m, 3H), 1.48 – 1.38 (m, 12H), 0.89 (d, $J = 5.5$ Hz, 6H), 0.78 (d, $J = 5.8$ Hz, 6H). 13C NMR (101 MHz, CDCl$_3$) δ 201.7, 173.1, 171.8, 171.0, 163.1, 155.3, 151.2, 147.6, 139.7, 133.7, 133.3, 132.4, 130.7, 123.3, 118.8, 111.6, 80.4, 55.5, 52.6, 51.8, 51.7, 40.8, 37.3, 32.8, 29.8, 28.2, 27.7, 27.2, 27.0, 22.3. IR (cm$^{-1}$): 3289, 2956, 1647, 1241, 1164. HRMS (ESI) m/z: (M$^+$) calcd for (C$_{34}$H$_{48}$N$_4$O$_8$): 640.3472, found 640.3476.

Methyl [(S)-2-((tert-butoxycarbonyl)amino)-3-(4-(pyridin-2-yloxy)-3-(4-(trifluoromethyl)benzoyl)phenyl)propanoylglycyl-L-phenylalanyl-L-leucinate (2r). Following the general procedure C, using 1r (0.15 mmol, 103 mg) and (4-(trifluoromethyl)phenyl)methanol (0.45 mmol, 63 µL) provided 63 mg (50% yield) of 2r.
as a white solid. Mp 95-96 °C. Column chromatography (EtOAc). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.93 (d, $J = 5.0$ Hz, 1H), 7.77 (d, $J = 8.1$ Hz, 2H), 7.52 (d, $J = 8.2$ Hz, 2H), 7.48 – 7.39 (m, 3H), 7.30 – 7.12 (m, 7H), 7.02 (d, $J = 8.0$ Hz, 1H), 6.86 (dd, $J = 6.9$, 5.2 Hz, 1H), 6.80 (d, $J = 8.0$ Hz, 1H), 6.46 (d, $J = 8.3$ Hz, 1H), 5.54 (d, $J = 7.3$ Hz, 1H), 4.76 (dd, $J = 6.9$ Hz, 1H), 4.60 – 4.42 (m, 2H), 3.98 (dd, $J = 16.6$, 5.6 Hz, 1H), 3.80 (dd, $J = 16.6$, 5.1 Hz, 1H), 3.67 (s, 3H), 3.19 (dd, $J = 13.9$, 5.6 Hz, 1H), 3.13 – 2.93 (m, 3H), 1.61 – 1.42 (m, 3H), 1.36 (s, 9H), 0.85 (d, $J = 5.2$ Hz, 6H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 194.2, 173.0, 171.9, 170.6, 168.6, 162.5, 155.6, 150.5, 146.7, 140.5, 139.4, 136.3, 134.0, 133.8, 133.7 (q, $J_{C\cdot F} = 32.5$ Hz), 131.2, 131.1, 129.7, 129.3, 128.5, 126.9, 124.9 (q, $J_{C\cdot F} = 3.8$ Hz), 123.5 (q, $J_{C\cdot F} = 270.0$ Hz), 123.0, 118.6, 111.2, 80.2, 55.4, 54.4, 52.2, 50.8, 43.0, 41.1, 38.2, 37.7, 28.2, 24.7, 22.6, 21.8. IR (cm$^{-1}$): 3294, 1641, 1242, 1165. HRMS (ESI) m/z: (M$^+$) calcd for (C$_{45}$H$_{30}$F$_3$N$_5$O$_9$): 861.3561, found 861.3572.
5. Control Experiments and Mechanism Proposal

\[
\begin{align*}
1a + \text{EtOH} & \xrightarrow{\text{Pd(OAc)}_2 (10 \text{ mol } \%) } \text{T-Hydro (6.0 equiv)} \\
& \xrightarrow{\text{TEMPO (2.0 equiv)}} \text{toluene (0.15 M)} \\
& 120 \degree \text{C, Ar, 16h} \\
& \text{starting material recovered}
\end{align*}
\]

Table S4. Control Experiments with MeCHO

| entry | MeCHO | T-Hydro | Solvent & T | 2aa:2aa' (%) |
|-------|-------|---------|-------------|--------------|
| 1     | 4     | 4       | water at 90 \degree \text{C} | traces       |
| 2     | 4     | 4       | PhMe at 90 \degree \text{C} | 22:61        |
| 3     | 25    | 6       | PhMe at 120 \degree \text{C} | 0:62         |

*Reaction conditions: 1a (0.15 mmol), MeCHO (x mmol), T-Hydro (y mmol), toluene (1.0 mL) under Ar for 16h. * Yield of isolated product after column chromatography.

Methyl [(S)-2-((\text{\text{tert}-butoxycarbonyl})amino)-3-(3,5-diacetyl-4-(pyridin-2-ylxyloxy)phenyl)propanoyl]-L-leucinate (2aa'). Following the general procedure A, using 1a (0.15 mmol, 73 mg) and MeCHO (3.75 mmol, 0.21 mL) provided 53 mg (62% yield) of 2aa’ as a white solid. Mp 90-91 \degree \text{C}. Column chromatography (Hex/EtOAc 1:1). $^1\text{H}$ NMR (400 MHz, CDCl$_3$) $\delta$ 8.01 (dd, $J = 5.1, 1.9$ Hz, 1H), 7.88 – 7.62 (m, 3H), 7.09 – 6.91 (m, 2H), 6.71 (d, $J = 7.8$ Hz, 1H), 5.33 (d, $J = 8.3$ Hz, 1H), 4.61 – 4.45 (m, 1H), 4.48 – 4.43 (m, 1H), 3.70 (s, 3H), 3.23 (dd, $J = 14.1, 6.3$ Hz, 1H), 3.07 (dd, $J = 14.0, 7.0$ Hz, 1H), 2.44 (s, 6H), 1.72 – 1.50 (m, 3H), 1.41 (s, 9H), 0.90 (dd, $J = 6.0, 3.8$ Hz, 6H). $^{13}\text{C}$ NMR (101 MHz, CDCl$_3$) $\delta$ 198.5, 173.0, 170.7, 162.8, 155.4, 148.5, 147.3, 140.1, 134.3, 134.2, 134.0, 118.9, 111.3, 80.3, 55.1, 52.4, 50.8, 41.3, 37.3, 30.4, 28.3, 24.7, 22.8, 21.8. IR (cm$^{-1}$…

S30
The accepted mechanism for simple phenyl systems starts with the coordination of the OPy group with the Pd catalyst and further *ortho*-palladation delivers 6-membered palladacycle \( \text{I} \). The latter, which is often proposed to exist as a dimeric species, could undergo dissociation and further addition of the *in situ* formed acyl radical species from consecutive oxidation events from EtOH, thereby resulting in the formation of a transient Pd(III) species. Although *in-depth* studies are arguably required, intermediate \( \text{II} \) would likely evolve into the corresponding Pd(IV) intermediate (\( \text{III} \)) in the oxidizing reaction conditions. Eventually, reductive elimination would deliver the acetylated peptide and the active Pd(II) catalyst.
6. - $^1$H NMR and $^{13}$C NMR Spectra

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (300 MHz, CDCl$_3$)

$^{13}$C NMR (75 MHz, CDCl$_3$)
$^1$H NMR (300 MHz, CDCl$_3$)

$^{13}$C NMR (75 MHz, CDCl$_3$)
$^1$H NMR (300 MHz, CDCl$_3$)

$^{13}$C NMR (75 MHz, CDCl$_3$)
$^1$H NMR (300 MHz, CDCl$_3$)

$^{13}$C NMR (75 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (300 MHz, CDCl$_3$)

$^{13}$C NMR (75 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

\[
\text{PyO} \quad \text{Boc} \quad \text{H}_2\text{NCO}_2\text{Me}
\]

(2aa)

13C NMR (101 MHz, CDCl$_3$)

\[
\text{PyO} \quad \text{Boc} \quad \text{H}_2\text{NCO}_2\text{Me}
\]

(2aa)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (75 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

(2ae)

$^{13}$C NMR (101 MHz, CDCl$_3$)

(2ae)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^{1}$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^{1}H$ NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (300 MHz, CDCl$_3$)

(2db)

$^{13}$C NMR (75 MHz, CDCl$_3$)

(2db)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (300 MHz, CDCl$_3$)

$^{13}$C NMR (75 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (300 MHz, CDCl$_3$)

$^{13}$C NMR (75 MHz, CDCl$_3$)
$^1$H NMR (300 MHz, CDCl₃)

$^{13}$C NMR (75 MHz, CDCl₃)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

13C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (300 MHz, CDCl$_3$)

$^{13}$C NMR (75 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, DMSO-$d_6$ at 80 ºC)

$^{13}$C NMR (126 MHz, DMSO-$d_6$ at 80 ºC)
$^1$H NMR (500 MHz, DMSO-$d_6$ at 80 °C)

$^{13}$C NMR (126 MHz, DMSO-$d_6$ at 80 °C)
$^1$H NMR (300 MHz, CDCl$_3$)

13C NMR (75 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (300 MHz, CDCl$_3$)

$^{13}$C NMR (75 MHz, CDCl$_3$)