IBX-Mediated Oxidation of Unactivated Cyclic Amines: Application in Highly Diastereoselective Oxidative Ugi-type and aza-Friedel-Crafts Reactions

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Table of contents

General information ......................................................... 2
Optimization data .......................................................... 3
Synthetic procedures ....................................................... 5
Substrate synthesis .......................................................... 5
Oxidation of meso-pyrrolidines ........................................... 9
Oxidative Ugi-type three-component reaction ......................... 11
Oxidative aza-Friedel-Crafts reaction .................................. 16
Structural analysis of compound 2f ..................................... 18
Copies of NMRs ............................................................. 21
General information

Starting materials were purchased from Sigma Aldrich, Fisher Scientific and Acros Organics and were used without purification, unless stated otherwise. (3aR,6aS)-Octahydropyrrrole hydrochloride was purchased from AK Scientific and dissolved in CH₂Cl₂, washed with sat. aq. Na₂CO₃, extracted with CH₂Cl₂, dried (Na₂SO₄) and concentrated in vacuo before use. Unless stated otherwise, the solvents were purchased from VWR Chemicals and were used without further treatment. Cyclohexane (cHex) was purified by distillation before use. Celite® 512 medium was purchased from Sigma Aldrich. Column Chromatography was performed on Silica-P Flash Silica Gel (particle size 40-63 μm, pore diameter 60 Å) from Silicycle. Preparative thin layer chromatography was performed on Silica Gel plates F₂₅₄ (20 x 20 cm, 2000 µm, pore diameter 60 Å) from Silicycle. Thin Layer Chromatography (TLC) was performed using TLC plates F₂₅₄ (silica gel 60 on aluminium) from Merck Serono KGaA (Darmstadt) and compounds were visualized by UV detection (254 or 366 nm) and stained with basic aq. KMnO₄ or ninhydrin/ethanol.

¹H, ¹³C, COSY, HSQC, HMBC and NOESY nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 500 (500.23 MHz for ¹H and 125.78 MHz for ¹³C) in CDCl₃ or DMSO-d₆ using the residual solvent as internal standard (CDCl₃: δ = 7.26 for ¹H NMR and δ = 77.16 for ¹³C NMR, DMSO-d₆: δ = 2.50 for ¹H NMR and δ = 39.52 for ¹³C NMR) or Bruker Avance 400 (400.13 MHz for ¹H and 100.62 MHz for ¹³C) using the residual solvent as internal standard (CDCl₃: δ = 7.26 for ¹H NMR and δ = 77.16 for ¹³C NMR, DMSO-d₆: δ = 2.50 for ¹H NMR and δ = 39.52 for ¹³C NMR). Chemical shifts (δ) are given in ppm and coupling constants (J) are quoted in hertz (Hz). Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet), bs (broad singlet) and m (multiplet) or combinations thereof. The COSY-, HMBC- and HSQC-NMR spectra were used for the assignment of the proton signals and the NOESY-NMR spectra were used for the assignment of the relative stereochemistry. The APT-NMR spectra were used for the assignment of the carbons. Names of chemical structures were deduced from generic names and/or important functionalities.

Electrospray Ionization (ESI) high resolution mass spectrometry was carried out using a Bruker micrOTOF-Q instrument in positive ion mode (capillary potential of 4500 V). Infrared (IR) spectra were recorded neat using a FTIR-8400s from Shimadzu. Signal intensities are described as strong (s), medium (m), weak (w) or broad (br). Melting points were determined on a Büchi M-565 and are not corrected.

X-ray single crystal data were collected at 100K on a Bruker X8 Prospector with Cu microsource and focusing optics, and Apex II detector. Data were integrated and corrected for absorption with SAINT V8.34A and SADABS 2012/1, and the structure was solved and refined with SHELX 2014 and shelXle. Hydrogen atoms were detected in the Fourier difference maps, those on C were refined with constraints on bond lengths and angles, those on N were refined freely.
Optimization data

General procedure for optimization of the reaction conditions for the oxidation of meso-pyrrolidine 1a with IBX in Supplementary table S1:

To a solution of pyrrolidine 1a (0.25 mmol, 1.0 eq.) in CH₂Cl₂ (0.2 M) was added IBX (70 mg, 0.25 mmol, 1.0 eq.). The reaction mixture was stirred for 0.5 - 1 h at rt or 60 °C (oil bath, closed vessel). The reaction mixture was cooled to rt, quenched with sat. aq. Na₂S₂O₄ (1 mL), washed with sat. aq. Na₂CO₃/brine (3:1, 10 mL), extracted with CH₂Cl₂ (2 x 10 mL), dried (Na₂SO₄) and concentrated in vacuo. Subsequently, the yield of 2a was determined with ¹H-NMR spectroscopy after dissolving the crude product in CDCl₃ and adding 2,5-dimethylfuran (0.125 mmol, 0.5 eq.) as standard for NMR spectroscopy.

Supplementary table S1: Optimization of reaction conditions for IBX-mediated oxidation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant</th>
<th>Solvent</th>
<th>T [°C]</th>
<th>t</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaIO₃</td>
<td>DMSO</td>
<td>rt</td>
<td>30 min</td>
<td>– (%)</td>
</tr>
<tr>
<td>2</td>
<td>PhI(OAc)₂</td>
<td>DMSO</td>
<td>rt</td>
<td>30 min</td>
<td>38%</td>
</tr>
<tr>
<td>3</td>
<td>PhI(CO₂CF₃)₂</td>
<td>DMSO</td>
<td>rt</td>
<td>30 min</td>
<td>33%</td>
</tr>
<tr>
<td>4</td>
<td>DMP</td>
<td>DMSO</td>
<td>rt</td>
<td>30 min</td>
<td>55%</td>
</tr>
<tr>
<td>5</td>
<td>IBX</td>
<td>DMSO</td>
<td>rt</td>
<td>30 min</td>
<td>90%</td>
</tr>
<tr>
<td>6</td>
<td>IBX</td>
<td>DMF</td>
<td>rt</td>
<td>30 min</td>
<td>92%</td>
</tr>
<tr>
<td>7</td>
<td>IBX</td>
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<td>rt</td>
<td>1 h</td>
<td>19%</td>
</tr>
<tr>
<td>8</td>
<td>IBX</td>
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<td>1 h</td>
<td>78%</td>
</tr>
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<td>9</td>
<td>IBX</td>
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<td>1 h</td>
<td>81%</td>
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<td>10</td>
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<td>1 h</td>
<td>95%</td>
</tr>
<tr>
<td>11</td>
<td>IBX</td>
<td>THF:DMSO (9:1)</td>
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<td>1 h</td>
<td>94%</td>
</tr>
<tr>
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<td>IBX</td>
<td>THF</td>
<td>60</td>
<td>1 h</td>
<td>58%</td>
</tr>
<tr>
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<td>IBX</td>
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<td>1 h</td>
<td>31%</td>
</tr>
<tr>
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<td>60</td>
<td>1 h</td>
<td>47%</td>
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<td>15</td>
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<td>EtOAc</td>
<td>60</td>
<td>1 h</td>
<td>19%</td>
</tr>
<tr>
<td>16</td>
<td>IBX</td>
<td>toluene</td>
<td>60</td>
<td>1 h</td>
<td>10%</td>
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</tbody>
</table>

* used with and without preactivation

**General procedure for optimization of the reaction conditions for the oxidative Ugi-type reaction in Table 3 and Supplementary table S2:**

To a solution of pyrrolidine 1a (0.25 mmol, 1.0 eq.) in CH$_2$Cl$_2$ (0.5 M) were added IBX (70 mg, 0.25 mmol, 1.0 eq.), benzoic acid (0.375 mmol, 1.5 eq.) and tert-butyl isocyanide (0.375 mmol, 1.5 eq.). The reaction mixture was stirred for 24 h at rt or 60 °C (oil bath, closed vessel). The suspension was cooled to rt, quenched with sat. aq. Na$_2$S$_2$O$_4$ (1 mL), washed with sat. aq. Na$_2$CO$_3$/brine (3:1, 10 mL), extracted with CH$_2$Cl$_2$ (2 x 10 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo. Subsequently, the yield of 3a was determined with $^1$H-NMR spectroscopy after dissolving the crude product in CDCl$_3$ and adding 2,5-dimethylfuran (0.125 mmol, 0.5 eq.) as standard for NMR spectroscopy.

**Supplementary table S2: Optimization of reaction conditions for oxidative Ugi-type reaction.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent [0.5 M]</th>
<th>T [°C]</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DMSO [0.2 m]</td>
<td>rt</td>
<td>26%</td>
</tr>
<tr>
<td>2</td>
<td>DMSO</td>
<td>rt</td>
<td>37%</td>
</tr>
<tr>
<td>3</td>
<td>TFE</td>
<td>60</td>
<td>19%</td>
</tr>
<tr>
<td>4</td>
<td>MeOH</td>
<td>60</td>
<td>25%</td>
</tr>
<tr>
<td>5</td>
<td>MeCN</td>
<td>60</td>
<td>50%</td>
</tr>
<tr>
<td>6</td>
<td>CH$_2$Cl$_2$</td>
<td>60</td>
<td>54%</td>
</tr>
</tbody>
</table>
Synthetic procedures

**o-iodoxybenzoic acid** \(^2\) (IBX, S1): To a solution of Oxone\(^\text{®} \) (74.3 g, 242 mmol, 6.0 eq.) in \(\text{H}_2\text{O} \) (0.2 \(\text{M} \)) was added 2-iodobenzoic acid (10.0 g, 40.3 mmol, 1.0 eq.). The reaction mixture was stirred for 3 h at 70 °C and then cooled to rt. The solid was filtered off, washed with cold \(\text{H}_2\text{O} \) (500 mL) and cold acetone (300 mL) and dried in vacuo (60 °C, 18 h). Compound S1 (7.17 g, 25.5 mmol, 63\%) was obtained without the need of purification as an off-white solid. \(^1\text{H} \text{NMR} \) (500 MHz, DMSO-\(d_6 \)): \(\delta\) 8.15 (d, \(J = 8.0 \text{ Hz}, 1\text{H}, \text{C} = \text{Me} \)), 8.06 – 7.97 (m, 2\(\text{H} \)), 7.84 (t, \(J = 7.3 \text{ Hz}, 1\text{H} \)) ppm. \(^{13}\text{C} \text{NMR} \) (126 MHz, DMSO-\(d_6 \)): \(\delta\) 167.6 (C\(\text{a} \)), 146.6 (C\(\text{a} \)), 133.5 (CH), 133.1 (CH), 131.5 (C\(\text{a} \)), 130.1 (CH), 125.1 (CH) ppm. \(\text{IR} \) (neat): \(v_{\text{max}} \) (cm\(^{-1} \)) = 3097 (w), 1636 (m), 1560 (w), 1331 (m), 1294 (s), 1246 (m), 1138 (m), 831 (m), 773 (m), 748 (s), 692 (s), 673 (s), 648 (m), 592 (s), 577 (s).

**Substrate synthesis**

**imid S2a:** To a solution of maleimide (7.28 g, 75.0 mmol, 1.0 eq.) in diethyl ether (0.68 \(\text{L} \)) was added cyclopentadiene (7.0 mL, 80.0 mmol, 1.06 eq.) dropwise. The reaction mixture was stirred for 2 h at rt. The product was filtered off and washed with diethyl ether. Compound S2a (12.0 g, 73.5 mmol, 98\%) was obtained without the need of purification as an off-white solid. \(R_t = 0.30 \) (CH\(_2\)Cl\(_2\):MeOH 100:1 v/v). \(\text{mp:} \) 184.4 – 188.6 °C. \(^1\text{H} \text{NMR} \) (500 MHz, CDCl\(_3 \)): \(\delta\) 8.47 (bs, 1H, NH\(_f \)), 6.17 (d, \(J = 2.0 \text{ Hz}, 2\text{H}, \text{CH} = \text{CH} \)), 3.36 (s, 2H, C(O)CH\(_2\)CH\(_2\)CH\(_2\)), 3.31 – 3.22 (m, 2H, C(O)CH\(_2\)), 1.72 (d, \(J = 8.8 \text{ Hz}, 1\text{H}, \text{CH} \)), 1.51 (d, \(J = 8.8 \text{ Hz}, 1\text{H}, \text{CH} \)) ppm. \(^{13}\text{C} \text{NMR} \) (126 MHz, CDCl\(_3 \)): \(\delta\) 178.5 (C\(\text{a} \)), 134.7 (CH), 52.4 (CH\(_2\)), 47.4 (CH), 45.0 (CH) ppm. \(\text{IR} \) (neat): \(v_{\text{max}} \) (cm\(^{-1} \)) = 3159 (m), 2991 (m), 1753.17 (m), 1697 (s), 1352 (m), 1294 (m), 1186 (s), 1120 (s), 991 (m), 839 (s), 829 (s), 729 (s), 660 (s), 604 (s). \(\text{HRMS} \) (ESI): \(m/z \) calculated for C\(_9\)H\(_{10}\)NO\(_2\) [M+H\(^+\)]: 164.0706, found: 164.0711.

**imid S2b:** To a solution of palladium on carbon 10\% (15 mg, 0.04 mol\%) in CH\(_2\)Cl\(_2\) (0.1 mL) and methanol (27 mL) was added imid S2a (6.56 g, 4.0 mmol). The reaction mixture was stirred for 63 h at rt under H\(_2\) atmosphere (1 atm.). The reaction mixture was filtered over Celite\(^\text{®} \), washed with methanol and concentrated in vacuo. Compound S2b (5.86 g, 36.3 mmol, 90\%) was obtained without the need of purification as an off-white solid. \(R_t = 0.21 \) (CH\(_2\)Cl\(_2\):MeOH 100:1 v/v). \(\text{mp:} \) 175 – 177 °C. \(^1\text{H} \text{NMR} \) (500 MHz, CDCl\(_3 \)): \(\delta\) 9.01 (bs, 1H, NH\(_f \)), 3.10 (s, 2H, C(O)CH\(_2\)), 2.72 (s, 2H, C(O)CH\(_2\)CH\(_2\)) ppm. \(^{13}\text{C} \text{NMR} \) (126 MHz, CDCl\(_3 \)): \(\delta\) 179.6 (C\(\text{a} \)), 50.3 (CH), 42.2 (CH\(_2\)), 39.3 (CH), 24.8 (CH\(_2\)) ppm. \(\text{IR} \) (neat): \(v_{\text{max}} \) (cm\(^{-1} \)) = 3173 (w), 1695 (s), 1350 (m), 1331 (m), 1294 (m), 1186 (s), 1120 (s), 991 (m), 839 (s), 829 (s), 729 (s), 660 (s), 604 (s). 

imid S2c: To a solution of maleimide (1.46 g, 15 mmol, 1.0 eq.) in H₂O (1.07 m) was added furan (1.34 mL, 18 mmol, 1.2 eq.) dropwise. The reaction mixture was stirred for 1 h at 90 °C under microwave irradiation and then cooled to rt. The product was filtered off and washed with H₂O (100 mL) and diethyl ether (20 mL). Compound S2c (1.38 g, 0.84 mmol, 54%) was obtained without the need of purification as an off-white solid. Rf = 0.23 (CH₂Cl₂:MeOH 100:1 v/v). mp: 168.6 - 171.3 °C. ¹H NMR (500 MHz, CDCl₃): δ 8.15 (bs, 1H, NH), 6.52 (s, 2H, CH=CH), 5.32 (s, 2H, OCH), 2.89 (s, 2H, C(O)CH) ppm. ¹³C NMR (126 MHz, CDCl₃): δ 176.1 (C*), 136.7 (CH), 81.1 (CH), 48.9 (CH) ppm. IR (neat): νmax (cm⁻¹) = 3148 (w), 1772 (m), 1701 (s), 1352 (m), 1287 (m), 1204 (m), 1186 (s), 897 (m), 820 (s), 733 (w), 588 (s), 459 (s). HRMS (ESI): m/z calulated for C₈H₇NNaO₂ [M+Na]⁺: 188.0682, found: 188.0689.

imid S2d: To a solution of palladium on carbon 10% (0.10 g, 0.04 mol%) in CH₂Cl₂ (0.1 mL) and methanol (100 mL) was added imid S2c (10.19 g, 62.0 mmol). The reaction mixture was stirred for 48 h at rt under H₂ atmosphere (1 atm.). The reaction mixture was filtered over Celite®, washed with methanol and concentrated in vacuo. Compound S2d (9.9 g, 59.0 mmol, 96%) was obtained without the need of purification as an off-white solid. Rf = 0.21 (CH₂Cl₂:MeOH 100:1 v/v). mp: 184 - 186 °C. ¹H NMR (500 MHz, CDCl₃): δ 8.76 (bs, 1H, NH), 4.94 - 4.86 (m, 2H, OCH), 2.91 (s, 2H, NC(O)CH), 1.90 - 1.83 (m, 2H, CH₂CH₂), 1.62 - 1.54 (m, 2H, CH₂CH₂) ppm. ¹³C NMR (126 MHz, CDCl₃): δ 177.8 (C*), 79.2 (CH), 51.4 (CH), 28.6 (CH) ppm. IR (neat): νmax (cm⁻¹) = 3004 (w), 1672 (s), 1306 (m), 1182 (s), 899 (m), 839 (m), 815 (s), 559 (m), 455 (s).

imid S2f:³ To a solution of Mn(ClO₄)₂·6 H₂O (15 mg, 0.3 mol%) in acetone (100 mL) was added picolic acid (44 mg, 1.8 mol%) and maleimide (1.94 g, 20.0 mmol, 1.0 eq.). The reaction mixture was cooled to 0 °C and an aq. sodiumacetate solution (1.0 mL, 0.6 m) and hydrogen peroxide (2.58 mL, 30.0 mmol, 1.5 eq.) were added. The solution was stirred for 29 h at rt, after which it was quenched with solid sodium thiosulfate. The suspension was filtered, washed with acetone, dried (Na₂SO₄) and concentrated in vacuo. The resulting oil was diluted in acetone (100 mL) and 2,2-dimethoxypropane (9.2 mL, 74.9 mmol, 4.0 eq.) and p-toluensulfonic acid monohydrate (356 mg, 1.9 mmol, 0.1 eq.) were added. The solution was stirred 144 h at rt (until conversion was complete according to TLC). The reaction was quenched with sat. aq. NaHCO₃ (20 mL), extracted with CH₂Cl₂ (3 x 20 mL), dried (Na₂SO₄) and concentrated in vacuo. The crude product was purified by flash chromatography (SiO₂) with an eluent gradient (10:1 → 1:1 v/v CH₃:EtOAc) to obtain compound S2f (740 mg, 4.30 mmol, 22%) as a colourless oil. Rf = 0.31 (CH₃:EtOAc 1:1 v/v). mp: 143.4 - 146.4 °C. ¹H NMR (500 MHz, CDCl₃): δ 8.13 (bs, 1H, NH), 4.88 (s, 2H, CH), 1.51 (s, 3H, CH₃), 1.44 (s, 3H, CH₃) ppm. ¹³C NMR (126 MHz, CDCl₃): δ 172.2 (C*), 116.5 (C*), 76.1 (CH), 26.8

pyrrolidine 1a: To a solution of LiAlH₄ (3.5 g, 92.0 mmol, 1.5 eq.) in THF⁴ (500 mL, anh.) was slowly added imid S2a (10.0 g, 61.0 mmol, 1.0 eq.) under N₂ atmosphere at 0 °C. The reaction mixture was stirred for 18 h at 45 °C, after which the reaction was quenched with H₂O (5 mL) to remove the excess of LiAlH₄. The suspension was filtered over Celite®, washed with THF and concentrated in vacuo to give compound 1a (3.0 g, 22.0 mmol, 36%) as a yellow solid. Rf = 0.09 (CH₂Cl₂:MeOH:NEt₃ 100:1:0.5 v/v). mp: 100.5 – 109.4 °C. ¹H NMR (500 MHz, CDCl₃): δ 6.24 – 6.15 (m, 2H, CH=CH₂), 2.84 – 2.78 (m, 2H, NHCH₂CHCH₂H), 2.76 – 2.64 (m, 3H, NHCH₂CH₂H), 2.57 (d, J = 12.2 Hz, 2H, NHCH₂), 1.78 (bs, 1H, NH), 1.47 – 1.36 (m, 2H, CHCH₂CH₃) ppm. ¹³C NMR (126 MHz, CDCl₃): δ 135.8 (CH), 53.1 (CH₂), 50.1 (CH₂), 48.2 (CH), 46.5 ppm. IR (neat): v max (cm⁻¹) = 3051 (w), 2957 (m), 2930 (s), 1344 (m), 1250 (m), 1092 (m), 895 (m), 870 (m), 800 (s), 743 (s), 689 (m). HRMS (ESI): m/z calculated for C₈H₁₃N [M+H]⁺: 136.1126, found: 136.1126.

pyrrolidine 1b: To a solution of LiAlH₄ (2.0 g, 54.0 mmol, 1.5 eq.) in THF⁴ (300 mL, anh.) was slowly added imid S2b (5.8 g, 36.0 mmol, 1.0 eq.) under N₂ atmosphere at 0 °C. The reaction mixture was stirred for 18 h at 70 °C, after which the reaction was quenched with H₂O (4 mL) to remove the excess of LiAlH₄. The suspension was filtered over Celite®, washed with THF and concentrated in vacuo to give compound 1b (3.6 g, 26.0 mmol, 72%) as a yellow solid. Rf = 0.66 (CH₂Cl₂:MeOH:NEt₃ 100:1:0.5 v/v). mp: 96.8 – 103.3 °C. ¹H NMR (500 MHz, CDCl₃): δ 2.91 (d, J = 12.0 Hz, 2H, NHCH₂), 2.64 – 2.55 (m, 2H, NHCH₂), 2.41 – 2.35 (m, 2H, NHCH₂CH₂), 2.13 (s, 2H, NHCH₂CHCH₂), 1.88 (bs, 1H, NH), 1.54 – 1.26 (m, 6H, CH₂CHCH₂CH₂) ppm. ¹³C NMR (126 MHz, CDCl₃): δ 135.8 (CH), 53.1 (CH₂), 50.1 (CH₂), 48.2 (CH), 46.5 (CH) ppm. IR (neat): v max (cm⁻¹) = 2937 (s), 2864 (m), 1290 (m), 1250 (m), 1221 (w), 1184 (w), 1111 (m), 1005 (m), 961 (w), 910 (m), 843 (s), 797 (m), 598 (s). HRMS (ESI): m/z calculated for C₉H₁₃N [M+H]⁺: 138.1277, found: 138.1291.

pyrrolidine 1c: To a solution of LiAlH₄ (1.7 g, 45.0 mmol, 1.5 eq.) in THF⁵ (250 mL, anh.) was slowly added imid S2c (5.0 g, 30.0 mmol, 1.0 eq.) under N₂ atmosphere at 0 °C. The reaction mixture was stirred for 18 h at 40 °C, after which the reaction was quenched with H₂O (4 mL) to remove the excess of LiAlH₄. The suspension was filtered over Celite®, washed with THF and concentrated in vacuo to give compound 1c (3.1 g, 20.0 mmol, 65%) as a red oil. Rf = 0.07 (CH₂Cl₂:MeOH:NEt₃ 100:1:0.5 v/v). ¹H NMR (500 MHz, CDCl₃): δ 6.36 (s, 2H, CH=CH₂), 4.70 (s, 2H, OC₃H₃), 2.92 – 2.83 (m, 4H, CH₂), 2.45 (bs, 1H, NH), 2.30 – 2.22 (m, 2H, CH₂CH₂) ppm. ¹³C NMR (126 MHz, CDCl₃): δ 137.1 (CH), 83.9 (CH), 51.6 (CH₂), 46.8 (CH) ppm. IR (neat): v max (cm⁻¹) = 3258 (w), 2991 (w), 2926 (w), 1308 (w), 1067 (w), 949 (m), 891 (s).

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⁴ Distilled under nitrogen from sodium/benzophenone before use
⁵ Distilled under nitrogen from sodium/benzophenone before use

**pyrrolidine 1d:** To a solution of LiAlH₄ (3.4 g, 86.0 mmol, 1.5 eq.) in THF (500 mL, anh.) was slowly added imid S2d (9.6 g, 58.0 mmol, 1.0 eq.) under N₂ atmosphere at 0 °C. The reaction mixture was stirred for 19 h at 45 °C, after which the reaction was quenched with H₂O (5 mL) to remove the excess of LiAlH₄. The suspension was filtered over Celite®, washed with THF and concentrated in vacuo to give compound 1d (6.0 g, 43.0 mmol, 75%) as a yellow oil. Rf = 0.07 (CH₂Cl₂:MeOH:NEt₃ 100:1:0.5 v/v).

**¹H NMR** (400 MHz, CDCl₃): δ 4.30 – 4.23 (m, 2H, OH), 2.92 (dd, J = 11.3 Hz, 6.4 Hz, 2H, NCH₂), 2.69 (dd, J = 11.3, 2.4 Hz, 2H, NCH₂), 2.40 (bs, 1H, NH), 2.24 – 2.20 (m, 2H, NCH₂CH), 1.64 – 1.56 (m, 2H, CH₂CH₂), 1.42 – 1.35 (m, 2H, CH₂CH₂) ppm. **¹³C NMR** (126 MHz, CDCl₃): δ 81.3 (CH), 53.3 (CH₂), 49.9 (CH), 28.9 (CH₂) ppm. IR (neat): vₘₐₓ (cm⁻¹) = 3173 (m), 2945 (s), 2909 (m), 2853 (s), 1221 (m), 1182 (s), 1082 (s), 1024 (s), 1005 (s), 989 (s), 959 (s), 912 (s), 795 (s), 629 (s), 584 (s).

HRMS (ESI): m/z calculated for C₈H₁₂NO [M+H]⁺: 140.1070, found: 140.1069.

**pyrrolidine 1f:** To a solution of LiAlH₄ (230 mg, 6.1 mmol, 1.5 eq.) in THF (35 mL, anh.) was slowly added imid S2f (700 mg, 4.1 mmol, 1.0 eq.) under N₂ atmosphere at 0 °C. The reaction mixture was stirred for 18 h at 55 °C, after which the reaction was quenched with H₂O (2 mL) to remove the excess of LiAlH₄. The suspension was filtered over Celite®, washed with THF and concentrated in vacuo to give compound 1f (444 mg, 3.1 mmol, 51%) as a colourless oil. Rf = 0.16 (CH₂Cl₂:MeOH:NEt₃ 100:1:0.5 v/v).

**¹H NMR** (500 MHz, CDCl₃): δ 4.65 (s, 2H, NHCH₂C), 3.11 (d, J = 14.0 Hz, 2H NHCH₂), 2.51 (d, J = 13.3 Hz, 2H, NHCH₂), 1.75 (bs, 1H, NH), 1.45 (s, 3H, CH₃), 1.31 (s, 3H, CH₃) ppm. **¹³C NMR** (126 MHz, CDCl₃): δ 110.3 (C*), 81.7 (CH), 54.4 (CH₂), 26.1 (CH₃), 23.9 (CH₂) ppm. IR (neat): vₘₐₓ (cm⁻¹) = 2980 (m), 2928 (s), 1373 (m), 1207 (s), 1150 (m), 1080 (m), 1034 (s), 897 (m), 851 (s), 822 (m), 625 (m).

HRMS (ESI): m/z calculated for C₇H₁₂NO₂ [M+H]⁺: 144.1019, found: 144.1025.

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Distilled under nitrogen from sodium/benzophenone before use.
**Oxidation of meso-pyrroldines**

**General procedure 1:**
To a solution of the pyrroldine (0.5 mmol, 1.0 eq.) in CH₂Cl₂ (0.2 mL) was added IBX (140 mg, 0.5 mmol, 1.0 eq.). The reaction mixture was stirred for 1 h at 60 °C (oil bath) in a closed vessel. The reaction was cooled to rt, quenched with sat. aq. Na₂SO₄ (2 mL), washed with sat. aq. Na₂CO₃/brine (3:1, 20 mL), extracted with CH₂Cl₂ (2 x 20 mL), dried (Na₂SO₄) and concentrated in vacuo. If necessary, the crude product was purified by flash chromatography.

**1-pyrroldine 2a:** Pre pared from pyrroldine 1a (69 mg, 0.50 mmol, 1 eq.) according to general procedure 1. Purification was achieved by flash chromatography (SiO₂) with an eluent gradient (1:1 → 1.2 v/v CHCl₃:EtOAc, 100:1 → 50:1 v/v CH₂Cl₂:MeOH), to obtain compound 2a (59 mg, 0.44 mmol, 88%) as a light yellow solid. R<sub>f</sub> = 0.24 (CH₂Cl₂:MeOH 100:1 v/v). IR (neat): v<sub>max</sub> (cm⁻¹) = 169.2 (CH), 60.9 (CH₂), 2.16 (s, 1H, NCH₂), 3.70 (m, 1H, NC=CHCH₂), 3.61 (m, 1H, NC=CHC₂H), 58.3 (CH), 42.6 (CH), 42.1 (CH₂), 40.0 (CH), 38.5 (CH), 26.0 (CH₂), 22.1 (CH₃) ppm. HRMS (ESI): m/z calculated for C₉H₁₀N [M+H]<sup>+</sup>: 136.0964, found: 110.0966.

**1-pyrroldine 2b:** Prepared from pyrroldine 1b (73 mg, 0.50 mmol, 1 eq.) according to general procedure 1. Purification was achieved by flash chromatography (SiO₂) with an eluent gradient (1:1 v/v CHCl₃:EtOAc, 100:1 v/v CH₂Cl₂:MeOH), to obtain compound 2b (65 mg, 0.48 mmol, 97%) as a light yellow solid. R<sub>f</sub> = 0.24 (CH₂Cl₂:MeOH 100:1 v/v). IR (neat): v<sub>max</sub> (cm⁻¹) = 164.1 (CH), 109.2 (CH₂), 72.5 (CH), 72.5 (CH₂), 67.0 (CH), 3.72 (m, 1H, N=CHCH₂), 3.62 (m, 1H, NC=CHC₂H), 2.50 (s, 1H, N=CHCH₂CH₂), 2.16 (s, 1H, N=CHCCH₂CH₂), 1.52 (d, J = 9.4 Hz, 1H, CH₂CH₂), 1.31 (d, J = 6.3 Hz, 2H, CH₂CH₂), 1.19 (d, J = 7.4 Hz, 2H, CH₂CH₂) ppm. HRMS (ESI): m/z calculated for C₉H₁₀N [M+H]<sup>+</sup>: 136.1121, found: 136.1125.

**1-pyrroldine 2c:** Prepared from pyrroldine 1c (79 mg, 0.50 mmol, 1 eq.) according to general procedure 1. Purification was achieved by flash chromatography (SiO₂) with an eluent gradient (1:1 v/v CHCl₃:EtOAc, 100:1 → 10:1 v/v CH₂Cl₂:MeOH), to obtain compound 2c (66 mg [3% CHCl₃], 0.47 mmol, 95%) as a reddish brown solid. R<sub>f</sub> = 0.18 (CH₂Cl₂:MeOH 100:1 v/v). IR (neat): v<sub>max</sub> (cm⁻¹) = 109.2 (CH₂), 106.0 (CH), 7.36 (m, 1H, N=CHCH₂), 5.94 (m, 2H, C=CH₂), 2.57 – 2.44 (m, 1H, NCH₂CH₂) ppm. HRMS (ESI): m/z calculated for C₉H₁₀N [M+H]<sup>+</sup>: 164.1 (CH), 159.1 (CH)
137.5 (CH), 136.2 (CH), 84.2 (CH), 79.7 (CH), 63.6 (CH₂), 59.7 (CH), 42.3 (CH) ppm. IR (neat): vₘₚₒₓ (cm⁻¹) = 2978 (m), 1458 (w), 1342 (m), 1229 (m), 1190 (m), 1157 (s), 1032 (s), 997 (m), 949 (s), 897 (s), 866 (m), 810 (s), 723 (s), 692 (s), 681 (s), 625 (s). HRMS (ESI): m/z calculated for C₉H₁₂NO [M+H⁺]: 136.0757, found: 136.0758.

1-pyrrole 2d: Prepared from pyrrolidine 1d (72 mg, 0.50 mmol, 1 eq.) according to general procedure 1. Purification was achieved by flash chromatography (SiO₂) with an eluent gradient (1:1 cHex:EtOAc, 100:1 → 20:1 v/v) to obtain compound 2d (60 mg [17% CH₂Cl₂], 0.36 mmol, 71%) as a light yellow solid. Rᵣ = 0.18 (CH₂Cl₂:MeOH 100:1 v/v). mp: 150.6 – 157.2 °C.

¹H NMR (500 MHz, CDCl₃): δ 7.35 (d, J = 3.3 Hz, 1H, N=CH), 4.51 (d, J = 4.7 Hz, 1H, NCH₂CH₂O), 4.34 (d, J = 4.7 Hz, 1H, N=CHCH₂), 4.10 – 4.00 (m, 1H, NCH₂), 3.74 – 3.65 (m, 1H, NCH₂), 3.03 (dd, J = 7.8 Hz, J = 2.9 Hz, 1H, N=CHCH₂), 2.42 – 2.34 (m, 1H, NCH₂CH₂), 1.79 – 1.64 (m, 2H, CH₂CH₂), 1.58 – 1.43 (m, 2H, CH₂CH₂) ppm. ¹³C NMR (126 MHz, CDCl₃): δ 165.1 (CH), 82.6 (CH), 77.4 (CH), 67.9 (CH₂), 61.1 (CH), 44.1 (CH), 29.3 (CH₂), 28.7 (CH₂) ppm. IR (neat): vₘₚₒₓ (cm⁻¹) = 2949 (m), 1655 (w), 1393 (m), 1315 (m), 1225 (s), 1215 (s), 1175 (s), 1047 (m), 972 (s), 924 (s), 805 (s), 623 (s). HRMS (ESI): m/z calculated for C₉H₁₂NO [M+H⁺]: 138.0913, found: 138.0916.

1-pyrrole 2e: Prepared from pyrrolidine 1e (56 mg, 0.50 mmol, 1 eq.) according to general procedure 1. Compound 2e (38 mg, 0.35 mmol, 70%) was obtained without the need of purification as a light yellow solid. Rᵣ = 0.38 (CH₂Cl₂:MeOH 100:1 v/v). mp: 99.8 – 111.7 °C. ¹H NMR (500 MHz, CDCl₃): δ 7.32 – 7.28 (m, 1H, NHCH), 4.11 – 3.98 (m, 1H, NHCH₂), 3.57 – 3.46 (m, 1H, NHCH₂), 3.27 (t, J = 8.9 Hz, 1H, NHCHCH₂), 2.72 – 2.57 (m, 1H, NHCH₂CH₂), 1.73 – 1.19 (m, 6H, CH₂CH₂CH₂) ppm. ¹³C NMR (126 MHz, CDCl₃): δ 169.6 (CH), 70.3 (CH₂), 55.2 (CH), 38.7 (CH), 34.8 (CH₂), 29.4 (CH₂), 25.0 (CH₂) ppm. IR (neat): vₘₚₒₓ (cm⁻¹) = 2931 (s), 2901 (m), 1466 (m), 1306 (m), 1204 (s), 1182 (s), 1157 (m), 1134 (s), 1070 (m), 932 (s). HRMS (ESI): m/z calculated for C₉H₁₂N [M+H⁺]: 110.0964, found: 110.0973.

α-hydroxypyrrolidine 2f: To a solution of pyrrolidine 1f (0.25 mmol, 1.0 eq.) in CH₂Cl₂ (0.2 mL) was added IBX (70 mg, 0.25 mmol, 1.0 eq.). The reaction mixture was stirred for 1 h at 60 °C in an oil bath. The reaction was cooled to rt, quenched with sat. aq. Na₂SO₄ (1 mL), washed with sat. aq. Na₂CO₃/brine (3:1, 10 mL), extracted with CH₂Cl₂ (2 x 10 mL), dried (Na₂SO₄) and concentrated in vacuo. Compound 2f was obtained in 48% yield, as determined with ¹H-NMR spectroscopy after dissolving the crude product in CDCl₃ and adding 2.5-dimethylfuran (0.125 mmol, 0.5 eq.) as standard for NMR spectroscopy. ¹H NMR (500 MHz, CDCl₃) δ 4.72 – 4.66 (m, 1H, NHCH₂CH₂), 4.37 (dd, J = 7.1, 3.9 Hz, 1H, NHCHOCCH₂), 3.33 (dd, J = 9.9, 6.1 Hz, 1H, NHCH₂), 3.26 (t, J = 4.1 Hz, 1H, NHCH₂) ppm. ¹³C NMR (126 MHz, CDCl₃) δ 113.6 (C*), 85.4 (CH), 80.8 (CH), 77.4 (CH), 52.5 (CH₂), 27.0 (CH₃), 25.2 (CH₂).

Signals of the trimerized product are visible in the NMR spectrum. Full characterization was not possible due to instability of compound 2f towards aqueous workup and silica gel chromatography. Proposed structure was determined with 2D-NMR spectroscopy.

S10
Oxidative Ugi-type three-component reaction

General procedure 2:

To a solution of the pyrrolidine (0.5 mmol, 1.0 eq.) in CH₂Cl₂ (0.5 mL) were added IBX (140 mg, 0.5 mmol, 1.0 eq.), the carboxylic acid (0.75 mmol, 1.5 eq.) and the isocyanide (0.75 mmol, 1.5 eq.). The reaction mixture was stirred for 48 h at 60 °C (oil bath) in a closed vessel. The suspension was cooled to rt, quenched with sat. aq. Na₂S₂O₄ (2 mL), washed with sat. aq. Na₂CO₃-brine (3:1, 20 mL), extracted with CH₂Cl₂ (2 x 20 mL), dried (Na₂SO₄) and concentrated in vacuo. If necessary, the crude product was purified by flash chromatography or preparative thin layer chromatography. Note: Rotamers were observed in all NMR spectra.⁹

prolyl peptide 3a: Prepared from pyrrolidine 1a (69 mg, 0.50 mmol, 1.0 eq.), benzoic acid (92 μL, 0.75 mmol, 1.5 eq.) and t-butyl isocyanide (87 μL, 0.75 mmol, 1.5 eq.) according to general procedure 2. Purification was achieved by flash chromatography (SiO₂) with an eluent gradient (4:1 → 2:1 v/v cHex:EtOAc), to obtain compound 3a (99 mg, 0.29 mmol, 59%) as an off-white solid. Rₛ = 0.48 (cHex:EtOAc 1:1 v/v). mp: 191.0 – 193.7 °C (decomposition).¹¹H NMR (500 MHz, CDCl₃): δ 7.45 – 7.32 (m, 5H, Ph), 6.64 (s, 1H, NH₃), 6.20 (dd, J = 5.7 Hz, J = 3.0 Hz, 1H, NCH₂CHCH₂CH=CH), 5.91 (dd, J = 5.7 Hz, J = 3.0 Hz, 1H, C(O)CHCH₃CH=CH), 4.43 (s, 1H, C(O)CH₃), 3.55 (dd, J = 11.7 Hz, J = 8.6 Hz, 1H, NCH₂CH), 3.45 – 3.38 (m, 1H, C(O)CH₃), 3.08 – 2.98 (m, 2H, NCH₂CHCH₂CH=CH), 2.93 – 2.84 (m, 1H, NCH₂CHCH₂CH=CH), 2.82 – 2.74 (m, 1H, NCH₂CH), 1.49 – 1.36 (m, 2H, CH₂CH₃), 1.32 (s, 9H, C(CH₃)₃) ppm.¹³C NMR (126 MHz, CDCl₃): δ 170.3 (C*), 169.7 (C*), 136.7 (C*), 134.9 (CH), 134.4 (CH), 130.1 (CH), 128.5 (CH), 126.6 (CH), 63.0 (CH), 52.1 (CH₂), 51.7 (CH₂), 47.1 (CH), 46.6 (CH), 45.6 (CH), 45.0 (CH), 28.8 (CH₂) ppm. IR (neat): νmax (cm⁻¹) = 3300 (w), 2935 (w), 1670 (m), 1599 (s), 1566 (s), 1535 (s), 1410 (s), 1389 (m), 1317 (m), 1223 (m), 1205 (m), 716 (s), 621 (m). HRMS (ESI): m/z calculated for C₂₁H₂₀N₂O₅ [M+H]⁺: 339.2067, found: 339.2056.

prolyl peptide 3b: Prepared from pyrrolidine 1a (69 mg, 0.50 mmol, 1.0 eq.), 4-nitrobenzoic acid (125 mg, 0.75 mmol, 1.5 eq.) and t-butyl isocyanide (87 μL, 0.75 mmol, 1.5 eq.) according to general procedure 2. Purification was achieved by flash chromatography (SiO₂) with an eluent gradient (4:1 → 2:1 v/v cHex:EtOAc), to obtain compound 3b (114 mg [12% CH₂Cl₂], 0.26 mmol, 52%) as an off-white solid. Rₛ = 0.40 (cHex:EtOAc 1:1 v/v). mp: >150 °C decomposition.¹¹H NMR (500 MHz, CDCl₃): δ 8.27 (d, J = 8.3 Hz, 2H, C(NO₂)CH₂), 7.59 – 7.51 (m, 2H, C(NO₂)CH₃), 6.40 (s, 1H, NH₃), 6.22 (dd, J = 5.7 Hz, J = 3.0 Hz, 1H, CH=CH₂), 5.93 (dd, J = 5.8 Hz, J = 3.0 Hz, 1H, CH=CH₂), 4.37 (d, J = 2.0 Hz, 1H, NCH₃), 3.60 (dd, J = 11.7 Hz, J = 8.9 Hz, 1H, NCH₂CH), 3.43 – 3.31 (m, 1H, NCH₂CH), 3.04 (s, 1H, CH₃), 2.97 – 2.89 (m, 2H, CH₂), 2.81 (s, 1H, CH₂), 1.51 (d, J = 8.6 Hz, 1H, CH₂CH₂CH₂), 1.42 (d, J = 8.6 Hz, 1H, CH₂CH₂CH₂), 1.34 (s, 9H, C(CH₃)₃) ppm.¹³C NMR (126 MHz, CDCl₃): δ 169.9 (C*), 167.4 (C*), 148.7 (C*), 142.6 (C*), 135.1 (CH), 134.5 (CH), 127.8 (CH), 124.0 (CH), 63.5 (CH), 52.2 (CH₂), 51.8 (CH₂), 51.4 (C*), 47.0 (CH), 46.7 (CH), 45.7 (CH), 28.9 (CH₂) ppm. IR (neat): νmax (cm⁻¹) =

⁹ Two sets of resonances were observed in all ¹H and ¹³C spectra, corresponding to different rotamers. Incomplete coalescence was observed at 100 °C, as depicted on S38.
prolyl peptide 3c: Prepared from pyrrolidine 1a (69 mg, 0.50 mmol, 1.0 eq.), 2-[(4-methoxyphenyl)acetic acid (126 mg, 0.75 mmol, 1.5 eq.) and t-butyl isocyanide (87 μL, 0.75 mmol, 1.5 eq.) according to general procedure 2. Purification was achieved by flash chromatography (SiO2) with an eluent gradient (10:1 → 1:1 v/v chex:EtOAc), to obtain compound 3c (103 mg, 0.28 mmol, 56%) as an off-white solid. Rf = 0.34 (chex:EtOAc 1:1 v/v). mp: 133.7 – 140.9 °C (decomposition). 1H NMR (500 MHz, CDCl3): δ 7.12 (d, J = 9.0 Hz, 2H, C(OMe)CHCH₃), 6.84 (d, J = 8.0 Hz, 2H, C(OMe)CH₂), 6.10 – 6.03 (m, 1H, CH=CH₂), 5.74 – 5.63 (m, 1H, CH=CH₂), 4.14 (s, 1H, NCH), 3.78 (s, 3H, H₂CO), 3.52 – 3.45 (m, 2H, C₂H₅), 3.36 – 3.22 (m, 2H, NCH₂, CH₂), 3.24 – 3.15 (m, 1H, NCH₂), 2.94 (s, 1H, CH), 2.91 – 2.87 (m, 1H, CH), 2.83 (s, 1H, CH), 1.66 (s, 1H, NH), 1.39 – 1.34 (m, 1H, CH₂CH₂CH₂), 1.31 – 1.25 (m, 10H, C(CH₃)₂, CH₂CH₂CH₂) ppm. 13C NMR (126 MHz, CDCl₃): δ 170.5 (C*), 170.0 (C*), 158.7 (C*), 135.2 (CH), 134.5 (CH), 129.9 (CH), 126.3 (C*), 114.2 (CH), 63.2 (CH₂), 51.7 (CH₂), 51.1 (C*), 50.0 (CH₂), 47.1 (CH), 46.6 (CH), 45.8 (CH), 45.2 (CH), 41.8 (CH₂), 28.8 (CH₃) ppm. IR (neat): νmax (cm⁻¹) = 3283 (w), 2934 (w), 1647 (s), 1626 (s), 1516 (m), 1389 (w), 1290 (w), 1277 (w), 1250 (s), 1219 (m), 1024 (m), 856 (w), 820 (m), 735 (m). HRMS (ESI): m/z calculated for C₂₁H₂₁N₂O₃ [M+H]⁺: 384.1918, found: 384.1908.

prolyl peptide 3d: Prepared from pyrrolidine 1b (73 mg, 0.50 mmol, 1.0 eq.), benzoic acid (92 mg, 0.75 mmol, 1.5 eq.) and 1,3-dimethylbenzene isocyanate (98 mg, 0.75 mmol, 1.5 eq.) according to general procedure 2. Purification was achieved by flash chromatography (SiO2) with an eluent gradient (100:1 → 5:1 v/v chex:EtOAc), to obtain compound 3d (118 mg, 0.30 mmol, 61%) as an off-white solid. Rf = 0.64 (chex:EtOAc 1:1 v/v). mp: 77.7 – 91.8 °C. 1H NMR (500 MHz, CDCl₃): δ 8.09 (bs, 1H, NH), 7.59 – 7.37 (m, 5H, Ph), 7.12 – 7.01 (m, 3H, C(CH₃)CH₂CHCH₃), 5.22 (s, 1H, NCH), 3.62 (dd, J = 11.9 Hz, J = 8.4 Hz, 1H, NCH₃), 3.49 (d, J = 12.0 Hz, 1H, NCH₃), 3.30 – 3.17 (m, 1H, NCHCH₂), 2.78 – 2.66 (m, 1H, NCH₂CH₂), 2.42 (s, 1H, NCHCH₂CH₂CH₂), 2.33 – 2.14 (m, 7H, CH₃, CH₃, NCH₂CH₂CH₂), 1.72 – 1.19 (m, 6H, CH₂CH₂CH₂CH₂) ppm. 13C NMR (126 MHz, CDCl₃): δ 169.57 (C*), 169.58 (C*), 136.1 (C*), 135.2 (C*), 133.9 (C*), 130.5 (CH), 128.6 (CH), 128.3 (CH), 127.3 (CH), 126.8 (CH), 60.6 (CH), 50.3 (CH₂), 44.4 (CH), 44.3 (CH), 42.0 (CH₂), 41.5 (CH), 41.0 (CH), 23.3 (CH₂), 22.9 (CH₂), 18.6 (CH₃) ppm. IR (neat): νmax (cm⁻¹) = 3263 (br), 2953 (w), 1684 (s), 1609 (s), 1516 (s), 1447 (s), 1420 (s), 1398 (s), 1375 (s), 1296 (w), 1175 (m), 881 (m), 766 (s), 721 (s), 698 (s). HRMS (ESI): m/z calculated for C₂₅H₂₅N₂O₂ [M+H]⁺: 389.2224, found: 389.2221.

prolyl peptide 3e: Prepared from pyrrolidine 1b (73 mg, 0.50 mmol, 1.0 eq.), acetic acid (43 μL, 0.75 mmol, 1.5 eq.) and 1,3-dimethylbenzene isocyanide (98 mg, 0.75 mmol, 1.5 eq.) according to general procedure 2. Purification was achieved by preparative thin layer chromatography (SiO2, chex:EtOAc 1:1 v/v), to obtain compound 3e (70 mg, 0.22 mmol, 43%) as an off-white solid. Two-step procedure: To a solution of pyrrolidine 1b (72 mg, 0.5 mmol, 1.0 eq.) in CH₂Cl₂ (0.2 mL) were added IBX (140 mg, 0.5 mmol,
1.0 eq.). The reaction mixture was stirred for 1 h at 60 °C (oil bath) in a closed vessel. The suspension was cooled to rt and acetic acid (43 µL, 0.75 mmol, 1.5 eq.) and 1,3-dimethylbenzene isocyanide (98 mg, 0.75 mmol, 1 eq.) were added, after which stirring proceeded for 23 h at 60 °C (oil bath) in a closed vessel. The suspension was cooled to rt, quenched with sat. aq. Na₂SO₄ (2 mL), washed with sat. aq. Na₂CO₃ brine (3:1, 20 mL), extracted with CH₂Cl₂ (2 x 20 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification was achieved by preparative thin layer chromatography (SiO₂, CH₆:EtOAc 1:1 v/v), to obtain compound 3e (88 mg, 0.27 mmol, 54%) as an off-white solid. Rᵣ = 0.73 (CH₆:EtOAc 1:1 v/v). m.p: 171.6 – 179.5 °C. ¹H NMR (500 MHz, CDCl₃): δ 8.18 (bs, 1H, NHδ), 7.16 – 7.00 (m, 3H, Ar), 4.89 (s, 1H, NCH₂), 3.62 (d, J = 11.5 Hz, 1H, NCH₂), 3.47 (dd, J = 11.7 Hz, J = 8.3 Hz, 1H, NCH₂), 3.18 (dd, J = 10.9 Hz, 1H, NCHCH₂), 2.81 – 2.68 (m, 1H, NCH₂CH₂), 2.44 – 2.34 (m, 1H, NCHCHCH₂), 2.34 – 2.30 (m, 1H, NCH₂CHCH₂), 2.18 (d, J = 5.1 Hz, 6H, CH₃), 1.60 – 1.58 (m, 1H, CHCH₂CH), 1.54 – 1.49 (m, 1H, CHCH₂CH), 1.45 – 1.39 (m, 2H, CH₂CH₂), 1.35 – 1.27 (m, 2H, CH₂CH₂) ppm. ¹³C NMR (126 MHz, CDCl₃): δ 169.8 (C*), 169.6 (C*), 135.2 (C*), 134.0 (C*), 128.2 (CH), 127.1 (CH), 77.4 (CH), 60.2 (CH), 48.4 (CH₂), 44.6 (CH), 43.8 (CH), 42.0 (CH₂), 41.5 (CH), 40.9 (CH), 23.3 (CH₂), 22.9 (CH₂), 22.6 (CH₂), 18.5 (CH₃) ppm. IR (neat): v max (cm⁻¹) = 3309 (w), 1647 (s), 1506 (m), 1471 (m), 1406 (s), 1375 (m), 1192 (m), 1034 (w), 847 (w), 773 (m), 640 (m). HRMS (ESI): m/z calculated for C₂₀H₂₉N₂NaO₂ [M+Na⁺]: 349.1886, found: 349.1879.

**prolyl peptide 3f:** Prepared from pyrrolidine 1e (56 mg, 0.50 mmol, 1.0 eq.), benzoic acid (92 mg, 0.75 mmol, 1.5 eq.) and cyclohexyl isocyanide (95 µL, 0.75 mmol, 1.5 eq.) according to general procedure 2. Purification was achieved by flash chromatography (SiO₂) with an eluent gradient (100:1 → 8:1 v/v CH₆:EtOAc), to obtain compound 3f (96 mg, 0.27 mmol, 54%) as a yellow oil. Rᵣ = 0.45 (CH₆:EtOAc 1:1 v/v). ¹H NMR (500 MHz, CDCl₃): δ 7.52 – 7.32 (m, 5H, Ph), 6.73 (d, J = 8.3 Hz, 1H NHδ), 4.65 – 4.54 (m, 1H, CHC(O)), 3.85 – 3.67 (m, 2H, NCH₂, NCHCH₂), 3.29 (d, J = 11.3 Hz, 1H, NCH₂), 3.24 – 3.13 (m, 1H, NCH₂CH₂), 2.75 – 2.68 (m, 1H, C(O)NHCH₂), 2.02 – 1.51 (m, 10H, CH₂)¹⁰, 1.42 – 1.03 (m, 6H, CH₃)¹⁰ ppm. ¹³C NMR (126 MHz, CDCl₃): δ 170.6 (C*), 170.1 (C*), 136.3 (C*), 130.3 (CH), 128.6 (CH), 127.0 (CH), 66.6 (CH), 56.0 (CH₂), 48.3 (CH), 44.3 (CH), 43.4 (CH), 33.1 (CH₂), 32.8 (CH₂), 26.3 (CH₂), 25.6 (CH₂), 24.7 (CH₃) ppm. IR (neat): v max (cm⁻¹) = 3302 (br), 2928 (s), 1616 (s), 1541 (s), 1522 (m), 1418 (s), 1225 (w), 891 (w), 725 (m), 698 (s). HRMS (ESI): m/z calculated for C₂₀H₂₉N₂NaO₂ [M+Na⁺]: 341.2224, found: 341.2207.

**prolyl peptide 3g:** Prepared from pyrrolidine 1e (56 mg, 0.50 mmol, 1.0 eq.), benzoic acid (92 mg, 0.75 mmol, 1.5 eq.) and benzyl isocyanide (86 µL, 0.75 mmol, 1.5 eq.) according to general procedure 2. Purification was achieved by flash chromatography (SiO₂) with an eluent gradient (100:1 → 2:1 v/v CH₆:EtOAc and by preparative thin layer chromatography (SiO₂, CH₆:EtOAc 1:1 v/v), to obtain compound 3g (72 mg, 0.21 mmol, 41%) as a yellow oil.

¹⁰ Signals are overlapped with the signals of the rotamers.
PROTOCOL:

Ri = 0.35 (cHex:EtOAc 1:1 v/v).

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.46 – 7.09 (m, 10H, Ph)$^{11}$, 4.63 (s, 1H, CH(OC)), 4.47 – 4.31 (m, 2H, NHCH$_2$)$^{10}$, 3.67 (dd, $J = 11.3$ Hz, $J = 7.4$ Hz, 1H, NCH$_2$), 3.26 (dd, $J = 11.2$ Hz, $J = 2.8$ Hz, 1H, NCH$_2$), 3.22 – 3.12 (m, 1H, NCHCH$_2$), 2.78 – 2.58 (m, 1H, NCH$_2$CH$_2$), 1.97 – 1.16 (m, 6H, CH$_2$CH$_2$CH$_2$)$^{10}$ ppm. $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 171.1 (C$^*$), 170.7 (C$^*$), 138.5 (C$^*$), 136.1 (C$^*$), 128.5 (CH), 128.4 (CH), 127.6 (CH), 127.4 (CH), 127.2 (CH), 127.1 (CH), 66.5 (CH), 56.0 (CH$_2$), 44.6 (CH), 43.6 (CH$_2$), 43.5 (CH), 33.1 (CH$_2$), 32.7 (CH$_2$), 31.1 (CH$_2$), 26.3 (CH$_2$), 25.7 (CH$_2$) ppm. IR (neat): $v_{\max}$ (cm$^{-1}$) = 3290 (br), 2945 (w), 1616 (s), 1541 (m), 1497 (m), 1447 (m), 1418 (s), 1361 (w), 1228 (m), 721 (m), 696 (s), 677 (m), 663 (m). HRMS (ESI): m/z calculated for C$_{23}$H$_{26}$N$_2$O$_6$ [M+H]$^+$: 349.1911, found: 349.1895.

Prolyl peptide 3h: Prepared from pyrrolidine 1f (72 mg, 0.50 mmol, 1.0 eq.), cinnamic acid (109 mg, 0.75 mmol, 1.5 eq.) and 1-(isocyanomethyl)-3,5-dimethoxybenzyl (117 µL, 0.75 mmol, 1.5 eq.) according to general procedure 2. Purification was achieved by flash chromatography (SiO$_2$) with an eluent gradient (20:1 → 12 v/v cHex:EtOAc) and by preparative thin layer chromatography (SiO$_2$, cHex:EtOAc 1:1 v/v), to obtain compound 3h (110 mg [3% CH$_2$Cl$_2$], 0.23 mmol, 45%) as a yellow solid. Ri = 0.34 (cHex:EtOAc 1:1 v/v). mp: 52.1 – 61.5°C. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.71 (d, $J = 15.4$ Hz, 1H, C(O)CH$_2$CH$_2$), 7.53 (dd, $J = 6.5$ Hz, $J = 3.0$ Hz, 2H, Ph), 7.43 – 7.35 (m, 3H, Ph), 7.12 (d, $J = 8.0$ Hz, 1H, CH$_2$C$^*_2$CH$_2$), 6.72 (d, $J = 15.5$ Hz, 1H, C(O)CH$_2$CH$_2$), 6.43 – 6.37 (m, 2H, CH$_2$C$^*_2$CH$_2$CH$_2$(OMe)CH$_2$), 5.13 (d, $J = 5.7$ Hz, 1H, NCH$_2$), 4.95 – 4.89 (m, 2H, CHO), 4.41 – 4.33 (m, 1H, NHCH$_2$), 4.31 – 4.23 (m, 1H, NHCH$_2$), 4.00 (d, $J = 11.9$ Hz, 1H, NCH$_2$), 3.81 (s, 3H, OCH$_3$), 3.77 (s, 3H, OCH$_3$), 3.72 – 3.66 (m, 1H, NCH$_2$), 1.75 (bs, 1H, NH$_2$), 1.41 (s, 3H, C$^*_2$CH$_2$), 1.32 (s, 3H, C$^*_2$CH$_2$) ppm. $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 168.7 (C$^*$), 165.8 (C$^*$), 160.6 (C$^*$), 158.6 (C$^*$), 143.7 (CH), 134.9 (C$^*$), 130.2 (CH), 129.0 (CH), 128.1 (CH), 118.6 (C$^*$), 117.2 (CH), 112.0 (C$^*$), 103.9 (CH), 98.6 (CH), 80.6 (CH), 79.8 (CH), 65.7 (CH), 55.5 (CH$_3$), 53.2 (CH$_2$), 39.1 (CH$_2$), 26.9 (CH$_3$), 24.9 (CH$_3$) ppm. IR (neat): $v_{\max}$ (cm$^{-1}$) = 3294 (br), 2935 (w), 1647 (s), 1610 (m), 1578 (w), 1508 (s), 1418 (s), 1373 (m), 1261 (m), 1205 (s), 1155 (s), (m), 1034 (m), 974 (m), 764 (m), 702 (m), 565 (w). HRMS (ESI): m/z calculated for C$_{26}$H$_{32}$N$_2$O$_6$ [M+H]$^+$: 467.2177, found: 467.2167.

Prolyl peptide 3i (major) and prolyl peptide 3i' (minor): Prepared from pyrrolidine 1c (40 mg [87% pure], 0.25 mmol, 1.0 eq.), benzoic acid (46 mg, 0.38 mmol, 1.5 eq.) and tert-butyl isocyanide (44 µL, 0.38 mmol, 1.5 eq.) according to general procedure 2. Purification was achieved by preparative thin layer chromatography (SiO$_2$, cHex:EtOAc 1:3, v/v), to obtain the compound 3i (32 mg, 0.09 mmol, 38%) as an off-white solid and the diastereoisomer 3i' (16 mg, 0.05 mmol, 19%) as an off-white solid in a 2:1 diastereoisomeric ratio. 3i: Rf = 0.14 (cHex:EtOAc 1:1 v/v). mp: 176.8 – 185.3°C. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.49 – 7.38 (m, 5H, Ph), 6.93 (s, 1H, NH$_2$), 6.42 (dd, $J = 6.1$ Hz, $J = 1.9$ Hz, 1H, NCH$_2$CHCH=CH), 6.35 (dd, $J = 1.5$ Hz, $J = 1.5$ Hz, 1H, NH$_2$).

$^{11}$ Signals are overlapped with the signals of the rotamers and CHCl$_3$.

S14
NCH₂CHCH₃CH=CH₂, 4.95 – 4.84 (m, 2H), NCH₂CHCHO, NCH₂), 4.65 (s, 1H, NCHCHCHO), 3.73 (dd, J = 11.9 Hz, J = 8.3 Hz, 1H, NCH₂), 3.52 (dd, J = 12.0 Hz, J = 1.9 Hz, 1H, NCH₂), 2.98 (d, J = 7.1 Hz, 1H, NCHCH₂), 2.42 (t, J = 7.8 Hz, 1H, NCH₂CH₃), 1.35 (s, 9H, C(CH₃)₃) ppm. \(^{13}C\) NMR (126 MHz, CDCl₃): δ 170.1 (C*), 169.8 (C*), 137.1 (CH), 136.6 (CH), 136.2 (CH), 130.3 (CH), 128.6 (CH), 127.0 (C*), 84.0 (CH), 83.7 (CH), 64.1 (CH), 52.9 (CH₂), 51.4 (C*), 44.7 (CH), 44.3 (CH), 28.8 (CH₂) ppm. IR (neat): ν\(_{max}\) (cm\(^{-1}\)) = 3292 (w), 2966 (w), 1767 (s), 1601 (s), 1570 (s), 1558 (m), 1477 (s), 1456 (s), 1394 (s), 1366 (s), 1283 (m), 1171 (w), 885 (w), 750 (s), 594 (w), 32.7 (CH(C*), 128.3 (CH), 125.5 (CH), 118.4 (CH), 118.0 (CH), 112.2 (CH), 75.0 (CH), 45.0 (C*), 41.4 (CH), 32.7 (CH₂), 29.8 (C*), 22.9 (CH₃), 22.6 (CH₃), 22.4 (CH₂) ppm. IR (neat): ν\(_{max}\) (cm\(^{-1}\)) = 3285 (br), 2966 (w), 1653 (s), 1558 (m), 1477 (s), 1456 (s), 1394 (s), 1366 (s), 1283 (m), 1171 (w), 885 (w), 750 (s), 594 (w). HRMS (ESI): m/z calculated for \(\text{C}_{20}\text{H}_{25}\text{N}_{2}\text{O}_{3}\) [M+H]\(^{+}\): 341.1860, found: 341.1849. 3f: \(R_t = 0.10\) (cHex:EtOAc 1:1 v/v). mp: 184.0 – 190.0 °C (decomposition). \(^{1}H\) NMR (500 MHz, DMSO-d₆): δ 7.59 – 7.19 (m, 5H, Ph), 6.50 – 6.31 (m, 2H, H-C=CH₂), 4.86 (s, 1H, CHO), 4.78 – 4.59 (m, 2H, NCH₂CH₃), 3.53 (t, J = 9.7 Hz, 1H), 3.40 – 3.30 (m, 1H, NCH₂), 2.68 – 2.56 (m, 1H, NHCH₂CH₃), 2.54 – 2.40 (m, 1H, NCHCH₂), 1.30 (s, 9H, C(CH₃)₃) ppm. \(^{13}C\) NMR (126 MHz, DMSO-d₆): δ 168.4 (C*), 168.0 (C*), 137.2 (CH), 137.1 (C*), 136.7 (CH), 130.3 (CH), 128.7 (CH), 79.4 (CH, CH), 60.5 (CH), 53.0 (CH₂), 50.7 (C*), 47.2 (CH), 45.4 (CH), 29.1 (CH₃) ppm. IR (neat): ν\(_{max}\) (cm\(^{-1}\)) = 2974 (w), 1670 (s), 1624 (s), 1418 (s), 1313 (w), 1223 (m), 1142 (m), 986 (m), 951 (m), 906 (m), 822 (w), 661 (w). HRMS (ESI): m/z calculated for \(\text{C}_{20}\text{H}_{25}\text{N}_{2}\text{O}_{3}\) [M+H]\(^{+}\): 341.1860, found: 341.1850.

<Diagram>

prolyl peptide 3j: To a solution of 3,3-dimethylindoline (37 mg, 0.25 mmol, 1.0 eq.) in DMSO (0.5 mL) were added IBX (70 mg, 0.25 mmol, 1.0 eq.), furoic acid (43 mg, 0.38 mmol, 1.5 eq.) and i-propyl isocyanide (35 μL, 0.38 mmol, 1.5 eq.). The reaction mixture was stirred for 48 h at rt. The suspension was quenched with sat. aq. Na₂SO₃ (2 mL), washed with sat. aq. Na₂CO₃/brine (3:1, 20 mL), extracted with CH₂Cl₂ (2 x 20 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification was achieved by flash chromatography (SiO₂) with an eluent gradient (100:1 → 5:1 v/v cHex:EtOAc) and by preparative thin layer chromatography (SiO₂, cHex:EtOAc 1:1, v/v), to obtain compound 3j (32 mg [13% CH₂Cl₂], 0.09 mmol, 35%) as a yellow solid. \(R_t = 0.32\) (cHex:EtOAc 1:1 v/v). mp: 63.2 – 73.8 °C. \(^{1}H\) NMR (500 MHz, CDCl₃): δ 8.17 (d, J = 8.2 Hz, 1H, NCH), 7.59 – 7.55 (m, 1H, OCHCH₂), 7.31 – 7.27 (m, 2H, OCHCH₂, NC=CH₂), 7.20 – 7.13 (m, 2H, NC=C=CH₂), 6.54 (dd, J = 3.5 Hz, J = 1.8 Hz, 1H, OCH₂), 5.43 – 5.35 (m, 1H, NH), 4.95 (s, 1H, NCH₂), 4.07 – 3.93 (m, 1H, NHCH₂), 1.43 (s, 3H, C*CH₃), 1.40 (s, 3H, C*CH₃), 0.94 (dd, J = 13.5 Hz, J = 6.5 Hz, 6H, CH(CH₃)₃) ppm. \(^{13}C\) NMR (126 MHz, CDCl₃): δ 168.6 (C*), 158.1 (C*), 147.5 (C*), 147.5 (CH), 141.1 (C*), 139.9 (C*), 128.3 (CH), 125.5 (CH), 125.5 (CH), 118.4 (CH), 118.0 (CH), 112.2 (CH), 75.0 (CH), 45.0 (C*), 41.4 (CH), 32.7 (CH₂), 29.8 (C*), 22.9 (CH₃), 22.6 (CH₃), 22.4 (CH₂) ppm. IR (neat): ν\(_{max}\) (cm\(^{-1}\)) = 3285 (br), 2966 (w), 1653 (s), 1558 (m), 1477 (s), 1456 (s), 1394 (s), 1366 (s), 1283 (m), 1171 (w), 885 (w), 750 (s), 594 (w). HRMS (ESI): m/z calculated for \(\text{C}_{19}\text{H}_{32}\text{N}_{2}\text{O}_{3}\) [M+H]\(^{+}\): 327.1707, found: 327.1707.

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12 Signal overlaps with H₂O peak. The H₂O was an impurity in the solvent MeOD-d₆.
13 Signal overlaps with residual solvent peak of MeOD-d₆.
14 Signals are overlapped with the signals of the rotamers.
**Oxidative aza-Friedel-Crafts reaction**

General procedure 3:
To a solution of the pyrrolidine (0.25 mmol, 1.0 eq.) in CH$_2$Cl$_2$ (0.25 mL) were added IBX (70 mg, 0.25 mmol, 1.0 eq.). The reaction mixture was stirred for 1 h at 60 °C (oil bath) in a closed vessel. The suspension was cooled to rt and trifluoroacetic acid (38 µL, 0.5 mmol, 2.0 eq.) and the pyrrole or indole (0.5 mmol, 2.0 eq.) were added. The reaction mixture was stirred for 1 h at 60 °C (oil bath) in a closed vessel. The suspension was cooled to rt, quenched with sat. aq. Na$_2$S$_2$O$_4$ (2 mL), washed with sat. aq. Na$_2$CO$_3$/brine (3:1, 20 mL), extracted with CH$_2$Cl$_2$ (2 x 20 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo. If necessary, the crude product was purified by flash chromatography.

**pyrrolidyl pyrrolidine 4a:** Prepared from pyrrolidine 1a (33 mg, 0.25 mmol, 1.0 eq.) and pyrrole (35 µL, 0.50 mmol, 2.0 eq.) according to general procedure 3. Purification was achieved by flash chromatography (SiO$_2$) with an eluent gradient (100:0 → 20:1 v/v CH$_2$Cl$_2$:MeOH), to obtain compound 4a (24 mg, 0.12 mmol, 48%) as a grey solid. $R_f$ = 0.32 (CH$_2$Cl$_2$:MeOH 20:1 v/v). mp: > 86.3 °C decomposition. $^1$H NMR (500 MHz, CDCl$_3$): δ 9.04 (bs, 1H, C*NH), 6.72 – 6.64 (m, 1H, C*NHCH), 6.32 – 6.21 (m, 2H, H=C=CH), 6.20 – 6.14 (m, 1H, C*NHCHCH), 6.05 – 5.95 (m, 1H, C*NHCHCHCH), 3.82 (d, J = 4.5 Hz, 1H, C*CHNH), 3.06 (dt, J = 9.0 Hz, J = 4.4 Hz, 1H, NHCHCH), 3.00 – 2.95 (m, 1H, CH$_2$CH$_2$H), 2.93 – 2.78 (m, 3H, CH$_2$CHCH, NHCH$_2$CH$_2$H), 2.50 (dd, J = 11.8 Hz, J = 4.6 Hz, 1H, NHCH$_2$), 2.29 – 2.06 (bs, 1H, CH$_2$NH), 1.60 (dt, J = 8.2 Hz, J = 1.8 Hz, 1H, CH$_2$CH$_2$H), 1.52 (dt, J = 8.2 Hz, J = 1.5 Hz, 1H, CH$_2$CH$_2$H) ppm. $^{13}$C NMR (126 MHz, CDCl$_3$): δ 155.5 (C*), 136.5 (CH), 116.7 (CH), 108.5 (CH), 104.4 (CH), 58.7 (CH), 54.7 (CH), 53.6 (CH$_2$), 49.0 (CH$_2$), 48.7 (CH), 46.0 (CH), 45.8 (CH) ppm. IR (neat): $\nu_{max}$ (cm$^{-1}$) = 3072 (w), 2934 (m), 2862 (m), 1448 (w), 1414 (w), 1028 (w), 918 (m), 879 (m), 833 (m), 725 (s), 563 (w). HRMS (ESI): m/z calculated for C$_{13}$H$_7$N$_2$ [M+H]$^+$: 201.1386, found: 201.1394.

**pyrrolidyl 5-methoxy-1H-indole 4b:** Prepared from pyrrolidine 1b (38 mg, 0.26 mmol, 1.0 eq.) and 5-methoxy-1H-indole (77 µL, 0.52 mmol, 2.0 eq.) according to general procedure 3. Purification was achieved by flash chromatography (SiO$_2$) with an eluent gradient (100:0 → 20:1 v/v CH$_2$Cl$_2$:MeOH), to obtain compound 4b (44 mg, 0.16 mmol, 60%) as a dark yellow oil. $R_f$ = 0.66 (CH$_2$Cl$_2$:MeOH 50:1 v/v). $^1$H NMR (500 MHz, CDCl$_3$): δ 7.94 (bs, 1H, C*NH), 7.23 (d, J = 8.7 Hz, 1H, NH*C=H), 7.09 (s, 1H, C*CH=CH=CH=O), 6.98 (s, 1H, C*NHCH*C*), 6.85 (d, J = 9.0 Hz, 1H, C(Ome)CH$_2$), 4.45 (s, 1H, CH$_2$NHCH), 3.86 (s, 3H, OCH$_3$), 3.03 – 2.91 (m, 2H, NHCH$_2$), 2.78 – 2.54 (m, 2H, NHCH$_2$CH, NHCH), 2.46 – 2.36 (m, 1H, NHCH$_2$CH=CHCH=$CH_2$), 2.01 – 2.19 (m, 1H, NHCH$_2$CHCH$_2$H), 1.80 (t, J = 9.4 Hz, 1H, CH$_2$), 1.71 – 1.36 (m, 5H, CH$_2$CH$_2$CH$_2$H) ppm. $^{13}$C NMR (126 MHz, CDCl$_3$): δ 154.0 (C*), 131.9 (C*), 126.8 (C*), 121.4 (CH), 119.9 (C*), 112.3 (CH), 112.0 (CH), 101.0 (CH), 56.1 (CH), 55.0 (CH$_2$), 52.0 (CH), 46.4 (CH$_2$), 45.9 (CH), 43.4 (CH$_2$), 40.9 (CH), 40.8 (CH), 23.6 (CH$_2$), 23.1 (CH$_2$) ppm. IR (neat): $\nu_{max}$ (cm$^{-1}$) = 2941 (w), 1481 (m), 1437 (m), 1290 (w).

$^{15}$ Very weak signal assigned with HMBC.
pyrrolyl pyrrolidine 4c: Prepared from pyrrolidine 1f (36 mg, 0.25 mmol, 1.0 eq.) and pyrrole (35 µL, 0.50 mmol, 2.0 eq.) according to general procedure 3. Purification was achieved by flash chromatography (SiO$_2$) with an eluent gradient (100:0 → 20:1 v/v CH$_2$Cl$_2$:MeOH), to obtain compound 4c (27 mg, 0.13 mmol, 52%, $dr > 13$:1) as a brown solid. $R_f = 0.92$ (CH$_2$Cl$_2$:MeOH 50:1 v/v). mp: 112.0 – 124.2 °C. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.80 (bs, 1H, NHC), 6.77 – 6.65 (m, $J = 3.1$ Hz, $J = 1.7$ Hz, 1H, C*NHCH$_2$H), 6.16 (q, $J = 2.9$ Hz, 1H, C*NHCH$_2$H), 6.05 – 6.00 (m, 1H, C*NHCHCH$_2$H), 4.95 (d, $J = 5.4$ Hz, 1H, NHCH$_2$H), 4.67 (dd, $J = 5.4$ Hz, $J = 3.7$ Hz, 1H, NHCH$_2$H), 4.34 (s, 1H, NHCH$_2$C*), 3.03 (d, $J = 13.6$, 1H, NHCH$_2$), 2.63 (dd, $J = 13.6$, 3.9 Hz, 1H, NHCH$_2$), 2.47 (bs, 1H, CH$_2$NH$_2$), 1.50 (s, 3H, C*CH$_3$), 1.36 (s, 3H, C*CH$_3$) ppm. $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 129.3 (C*), 116.7 (CH), 110.6 (C*), 108.8 (CH), 105.1 (CH), 86.0 (CH), 82.3 (CH), 62.5 (CH$_2$), 26.1 (CH$_3$), 23.9 (CH$_3$) ppm. IR (neat): $v_{max}$ (cm$^{-1}$) = 3265 (w), 1381 (w), 1367 (w), 1204 (m), 1090 (m), 1051 (m), 1028 (m), 924 (m), 795 (m), 733 (m), 640 (m), 606 (m). HRMS (ESI): m/z calculated for C$_{18}$H$_{22}$N$_2$O [M+H]$: 283.1805$, found: 283.1801.

pyrrolyl pyrrolidine 4d: Prepared from pyrrolidine 1e (29 mg, 0.25 mmol, 1.0 eq.) and indole (60 mg, 0.50 mmol, 2.0 eq.) according to general procedure 3. Purification was achieved by flash chromatography (SiO$_2$) with an eluent gradient (100:0 → 20:1 v/v CH$_2$Cl$_2$:MeOH), to obtain compound 4d (43 mg, 0.19 mmol, 75%) as a brown solid. $R_f = 0.10$ (CH$_2$Cl$_2$:MeOH 20:1 v/v). mp: > 69.8 °C decomposition.$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.22 (bs, 1H, NHC*), 7.74 (d, $J = 7.9$ Hz, 1H, NH*C*CH$_3$), 7.35 (d, $J = 8.0$ Hz, 1H, NH*C*CH$_3$), 7.23 – 7.06 (m, 3H, C*NHC*CHCH$_2$H), 3.92 (d, $J = 7.1$ Hz, 1H, NHCH$_2$H), 3.40 (dd, $J = 10.7$, 8.0 Hz, 1H, NHCH$_2$H), 2.89 – 2.73 (m, 2H, NHCH$_2$CHCH$_2$), 2.55 (dd, $J = 10.7$, 7.1 Hz, 1H, NHCH$_2$H), 2.40 (bs, 1H, NHCH$_2$), 1.74 – 1.43 (m, 6H, CH$_2$NH$_2$CH$_2$) ppm. $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 136.7 (C*), 126.6 (C*), 122.2 (CH), 122.0 (CH), 119.6 (CH), 119.6 (CH), 117.1 (C*), 111.5 (CH), 63.1 (CH), 53.7 (CH$_2$), 50.8 (CH), 44.3 (CH), 32.1 (CH$_2$), 31.4 (CH$_2$), 25.5 (CH$_2$) ppm. IR (neat): $v_{max}$ (cm$^{-1}$) = 2930 (w), 2860 (w), 1456 (w), 1448 (w), 1339 (w), 735 (s), 608 (m), 426 (m). HRMS (ESI): m/z calculated for C$_{18}$H$_{22}$N$_2$O [M+H]$: 227.1542$, found: 227.1542.
Structural analysis of compound 2f

Relative stereochemistry at the hemiaminal stereocenter undetermined

\(^{16}\) Relative stereochemistry at the hemiaminal stereocenter undetermined
Copies of NMRs
S2c
Figure S1. High temperature NMR spectra of 3b in DMSO-$d_6$ showing incomplete coalescence of the rotameric signals.