Copper-Catalyzed Diamination of Unactivated Alkenes with Hydroxylamines

Kun Shen and Qiu Wang*
Department of Chemistry, Duke University, Durham, North Carolina 27708
Email: qiu.wang@duke.edu

Supporting Information

Content
I. General Procedures S1
II. Materials and Instrumentation S1
III. Supplementary Tables for Condition Optimization S2-3
IV. Substrate Synthesis S3-8
V. General Procedure for Diamination Reaction S8-14
VI. Mechanism Investigation S14-15
VII. Deprotection Conditions for 3aa S15-16
VIII. Synthesis of (±)-FAUC-179 S16-17
IX. References S17
X. NMR Spectra S18-106

I. General Procedures. Glassware and stir bars were dried in an oven at 140 °C for at least 12 h and then cooled in a desiccator cabinet over Drierite prior to use. Optimization and substrate screens were performed in 8-mL microwave vials. Vials were fitted with crimp top septa under a positive pressure of nitrogen that had been passed through a column (5 x 20 cm) of Drierite, unless otherwise noted. All other reactions were performed in round-bottom flasks sealed with rubber septa. Plastic syringes or glass pipets were used to transfer liquid reagents. Reactions were stirred magnetically using Teflon-coated, magnetic stir bars. Analytical thin-layer chromatography (TLC) was performed using aluminum plates pre-coated with 0.25 mm of 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light and/or exposure to KMnO₄ stain. Organic solutions were concentrated under reduced pressure using a rotary evaporator. Flash-column chromatography was performed on silica gel (60 Å, standard grade) or with pre-packed FLASH silica gel columns.

II. Materials and Instrumentation. Nuclear magnetic resonance spectra were recorded at ambient temperature (unless otherwise stated) on 400 MHz or 500 MHz spectrometers. All values for proton chemical shifts are reported in parts per million (δ) and are referenced to the residual protium in CDCl₃ (δ 7.26). All values for carbon chemical shifts are reported in parts per million (δ) and are referenced to the carbon resonances in CDCl₃ (δ 77.0). NMR data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, br = broad), coupling constant (Hz), and integration. Infrared spectroscopic data are reported in wavenumbers (cm⁻¹). High-resolution mass spectra were obtained using a liquid chromatography-electrospray ionization and Time-of-flight mass spectrometer.
III. Supplementary Tables for Condition Optimization

a. Condition optimizations for the diamination of alkene 1a and hydroxylmorpholine 2a

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>base</th>
<th>solvent</th>
<th>temp (°C)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cu(OAc)₂</td>
<td>K₂CO₃</td>
<td>toluene</td>
<td>80</td>
<td>68</td>
</tr>
<tr>
<td>2</td>
<td>Cu(OAc)₂</td>
<td>K₂CO₃</td>
<td>THF</td>
<td>80</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>Cu(OAc)₂</td>
<td>K₂CO₃</td>
<td>DCE</td>
<td>80</td>
<td>48</td>
</tr>
<tr>
<td>4</td>
<td>Cu(OAc)₂</td>
<td>K₂CO₃</td>
<td>CH₃CN</td>
<td>80</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>Cu(OAc)₂</td>
<td>K₂CO₃</td>
<td>MTBE</td>
<td>80</td>
<td>84 (80)³</td>
</tr>
<tr>
<td>6</td>
<td>Cu(OAc)₂</td>
<td>K₂CO₃</td>
<td>DMF</td>
<td>80</td>
<td>trace</td>
</tr>
<tr>
<td>7</td>
<td>Cu(CF₃COO)₂</td>
<td>K₂CO₃</td>
<td>MTBE</td>
<td>80</td>
<td>60</td>
</tr>
<tr>
<td>8</td>
<td>Cu(OTf)₂</td>
<td>K₂CO₃</td>
<td>MTBE</td>
<td>80</td>
<td>46</td>
</tr>
<tr>
<td>9</td>
<td>Cu(acac)₂</td>
<td>K₂CO₃</td>
<td>MTBE</td>
<td>80</td>
<td>24</td>
</tr>
<tr>
<td>10</td>
<td>CuCl₂</td>
<td>K₂CO₃</td>
<td>MTBE</td>
<td>80</td>
<td>39</td>
</tr>
<tr>
<td>11</td>
<td>CuF₂</td>
<td>K₂CO₃</td>
<td>MTBE</td>
<td>80</td>
<td>trace</td>
</tr>
<tr>
<td>12</td>
<td>CuOAc</td>
<td>K₂CO₃</td>
<td>MTBE</td>
<td>80</td>
<td>60</td>
</tr>
<tr>
<td>13</td>
<td>-</td>
<td>K₂CO₃</td>
<td>MTBE</td>
<td>80</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>Cu(OAc)₂</td>
<td>-</td>
<td>MTBE</td>
<td>80</td>
<td>60</td>
</tr>
<tr>
<td>15</td>
<td>Cu(OAc)₂</td>
<td>Na₂CO₃</td>
<td>MTBE</td>
<td>80</td>
<td>58</td>
</tr>
<tr>
<td>16</td>
<td>Cu(OAc)₂</td>
<td>Cs₂CO₃</td>
<td>MTBE</td>
<td>80</td>
<td>0</td>
</tr>
<tr>
<td>17⁴</td>
<td>Cu(OAc)₂</td>
<td>K₂CO₃</td>
<td>MTBE</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>18⁴</td>
<td>Cu(OAc)₂</td>
<td>K₂CO₃</td>
<td>MTBE</td>
<td>60</td>
<td>44</td>
</tr>
<tr>
<td>19</td>
<td>Cu(OAc)₂</td>
<td>K₂CO₃</td>
<td>MTBE</td>
<td>100</td>
<td>74</td>
</tr>
</tbody>
</table>

⁴Reaction Conditions: The reactions were performed in a sealed tube with 1a (0.20 mmol, 1.0 equiv), 2a (0.24 mmol, 1.2 equiv), catalyst (0.02 mmol, 10 mol%), base (0.40 mmol, 2.0 equiv) and solvent (1 mL) for 2 h, unless otherwise noted. 
⁵The yield was determined by ¹H NMR with diboromethane as an internal standard. 
⁶The number in the parathesis was the isolation yield. 
⁷The reaction was run for 4 h.
b. Condition optimization for the diamination reaction of 1a and \textit{N,N}-diethyl-\textit{O}-benzoyl hydroxylamine 2g

<table>
<thead>
<tr>
<th>entry</th>
<th>Cu(OAc)$_2$ (mol%)</th>
<th>2g (equiv)</th>
<th>temp (°C)</th>
<th>yield (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>1.2</td>
<td>80</td>
<td>22</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>1.2</td>
<td>80</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>1.2</td>
<td>80</td>
<td>23</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>1.2</td>
<td>120</td>
<td>36</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>1.2</td>
<td>120</td>
<td>41</td>
</tr>
<tr>
<td>6</td>
<td>40</td>
<td>1.2</td>
<td>120</td>
<td>37</td>
</tr>
<tr>
<td>7</td>
<td>20</td>
<td>2.0</td>
<td>80</td>
<td>31</td>
</tr>
<tr>
<td>8</td>
<td>20</td>
<td>2.0</td>
<td>120</td>
<td>54</td>
</tr>
</tbody>
</table>

$^a$Reaction were performed in a 0.1 mmol scale. $^b$The yield was determined by $^1$H NMR with diboromethane as an internal standard.

IV. Synthesis of Substrates.

\textit{N-Methoxy-2,2-diphenylpent-4-enamide (1a)}.

To a solution of 2,2-diphenylpent-4-enoic acid (5.04 g, 20 mmol) in CH$_2$Cl$_2$ (20 mL) was added dropwise oxalyl chloride (2.2 mL, 26 mmol) followed by a catalytic amount of DMF. The mixture was stirred at room temperature for 1 h, and then was concentrated under reduced pressure to remove the solvent. The resulting residue was added dropwise to a biphasic mixture of MeONH$_2$HCl (2.51 g, 30 mmol) and K$_2$CO$_3$ (5.52 g, 40 mmol) in EtOAc (36 mL) and H$_2$O (18 mL). The reaction was stirred at room temperature for 2 h. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined extracts were washed with brine, dried over Na$_2$SO$_4$, and filtrated. The filtrate was concentrated. Purification by column chromatography (33% EtOAc in hexanes) gave 1a as a white solid (5.0 g, 89% yield); R$_f$ = 0.55 (50% EtOAc in EtOAc in hexanes). $^1$H NMR (400 MHz, CDCl$_3$): δ 8.16 (s, 1H), 7.45 – 7.15 (m, 10H), 5.85 – 5.65 (m, 1H), 4.99 (d, J = 17.6 Hz, 1H), 4.95 (d, J = 11.6 Hz, 1H), 3.66 (s, 3H), 3.20 (d, J = 6.8 Hz, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 171.9, 141.9, 134.5, 128.7, 128.3, 127.1, 118.2, 64.0, 58.9, 43.2; IR (neat): 3272, 1650, 1488, 1442, 906, 733, 699 cm$^{-1}$; HRMS (m/z) Calcd for (C$_{18}$H$_{20}$NO$_2$) ([M+H$^+$]): 282.1489; found: 282.1486.

\textit{N-(Benzyloxy)-2,2-diphenylpent-4-enamide (1b)}.

Follow the same procedure with 1a. Purification by column chromatography (33% EtOAc in hexanes) gave 1b as a yellow solid (91% yield); R$_f$ = 0.42 (20% EtOAc in hexanes). $^1$H NMR (400 MHz, CDCl$_3$): δ 8.12 (s, 1H), 7.45 – 7.15 (m, 10H), 5.85 – 5.65 (m, 1H), 4.99 (d, J = 17.6 Hz, 1H), 4.95 (d, J = 11.6 Hz, 1H), 3.66 (s, 3H), 3.20 (d, J = 6.8 Hz, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 171.9, 141.9, 134.5, 128.7, 128.3, 127.1, 118.2, 64.0, 58.9, 43.2; IR (neat): 3272, 1650, 1488, 1442, 906, 733, 699 cm$^{-1}$; HRMS (m/z) Calcd for (C$_{18}$H$_{20}$NO$_2$) ([M+H$^+$]): 282.1489; found: 282.1486.
1H), 7.38–7.18 (m, 15H), 5.85–5.65 (m, 1H), 4.99 (d, J = 11.6 Hz, 1H), 4.97–4.92 (m, 1H), 4.85 (s, 2H), 3.22 (d, J = 6.8 Hz, 2H); 13C NMR (100 MHz, CDCl3): δ 171.3, 141.8, 134.8, 134.4, 129.1, 128.6, 128.4, 128.3, 128.1, 118.0, 77.7, 58.9, 43.0; IR (neat): 3261, 3063, 3033, 1646, 1491, 1464, 1441, 917, 745, 691 cm⁻¹; HRMS (m/z) Calcd for (C24H24NO2) ([M+H⁺]): 358.1802; found: 358.1802.

N-Benzyl-2,2-diphenylpent-4-enamide (1d).

Follow the same procedure with 1a. Purification by column chromatography (15% EtOAc in hexanes) gave 1d as a yellow solid (88% yield); Rf = 0.54 (20% EtOAc in hexanes); 1H NMR (400 MHz, CDCl3): δ 7.34–7.28 (m, 8H), 7.28–7.20 (m, 5H), 7.10–7.03 (m, 2H), 5.86 (s, br, 1H), 5.81–5.69 (m, 1H), 5.02–4.89 (m, 2H), 4.44 (d, J = 5.6 Hz, 2H), 3.25 (d, J = 6.8 Hz, 2H); 13C NMR (100 MHz, CDCl3): δ 173.9, 142.8, 138.1, 135.1, 129.0, 128.5, 128.2, 127.3, 127.2, 126.9, 117.8, 60.6, 43.7, 43.3; IR (neat): 3332, 3060, 3026, 1643, 1524, 1247, 733, 694 cm⁻¹; HRMS (m/z) Calcd for (C24H24NO) ([M+H⁺]): 342.1852; found: 342.1853.

N-Methoxy-2,2-dimethylpent-4-enamide (1f).

Follow the same procedure with 1a. Purification by column chromatography (25% EtOAc in hexanes) gave 1f as a yellow oil (55% yield); Rf = 0.31 (50% EtOAc in hexanes); 1H NMR (400 MHz, CDCl3): δ 9.72 (s, 1H), 5.71–5.55 (m, 1H), 4.98–4.88 (m, 2H), 3.60 (s, 3H), 2.17 (d, J = 7.6 Hz, 2H), 1.06 (s, 3H); 13C NMR (100 MHz, CDCl3): δ 174.8, 133.7, 117.8, 63.4, 44.6, 40.8, 24.3; IR (neat): 3212, 2970, 2934, 1640, 1498, 1473, 1473, 1048, 908, 575 cm⁻¹; HRMS (m/z) Calcd for (C8H16NO2) ([M+H⁺]): 158.1176; found: 158.1176.

1-Allyl-N-methoxycyclohexane-1-carboxamide (1g).

Follow the same procedure with 1a. Purification by column chromatography (25% EtOAc in hexanes) gave 1g as a yellow oil (54% yield); Rf = 0.48 (50% EtOAc in hexanes); 1H NMR (400 MHz, CDCl3): δ 9.61 (s, 1H), 5.70–5.56 (m, 1H), 4.92 (d, J = 16.0 Hz, 1H), 4.90 (d, J = 11.2 Hz, 1H), 3.61 (s, 3H), 2.14 (d, J = 7.2 Hz, 2H), 1.93–1.79 (m, 2H), 1.51–1.09 (m, 8H); 13C NMR (100 MHz, CDCl3): δ 173.3, 133.3, 117.6, 63.5, 45.1, 43.9, 33.1, 25.5, 22.4; IR (neat): 3142, 2925, 1636, 1520, 1435, 1047, 901, 619 cm⁻¹; HRMS (m/z) Calcd for (C11H20NO2) ([M+H⁺]): 198.1489; found: 198.1488.

2-Allyl-N-methoxy-1,3-dithiane-2-carboxamide (1h).

Follow the same procedure with 1a. Purification by column chromatography (50% EtOAc in hexanes) gave 1h as a white solid (47% yield); Rf = 0.17 (50% EtOAc in hexanes); 1H NMR (400 MHz, CDCl3): δ 9.73 (s, 1H), 5.86–5.72 (m, 1H), 5.22–5.12 (m, 2H), 3.78 (s, 3H), 2.96 (dd, J = 12.4, 2.8 Hz, 1H), 2.92 (dd, J = 12.4, 2.8 Hz, 1H), 2.72 (dd, J = 4.4, 3.2 Hz, 1H), 2.69 (dd, J = 4.4, 3.2 Hz, 1H), 2.66 (dt, J = 11.8, 0.8 Hz, 2H), 2.14–2.03 (m, 1H), 1.92–1.77 (m, 1H); 13C NMR (100 MHz, CDCl3): δ 166.5, 129.9, 119.6, 63.7, 56.0, 44.2,
27.9, 23.7; IR (neat): 3273, 2932, 2905, 1661, 1481, 1415, 1045, 992, 926, 730, 661, 534 cm⁻¹; HRMS (m/z) Calcd for (C₉H₈NO₂S₂) ([M+H⁺]): 234.0617; found: 234.0617.

**N-Methoxy-2,2,4-trimethylpent-4-enamide (1k).**

Follow the same procedure with 1a. Purification by column chromatography (33% EtOAc in hexanes) gave 1k as a yellow oil (67% yield); Rᵢ = 0.31 (50% EtOAc in hexanes); ¹H NMR (400 MHz, CDCl₃): δ 8.59 (s, 1H), 4.82–4.79 (m, 1H), 4.68–4.64 (m, 1H), 3.71 (s, 3H), 2.27 (s, 2H), 1.67 (s, 3H), 1.15 (s, 6H); ¹³C NMR (100 MHz, CDCl₃): δ 175.4, 142.3, 114.6, 64.0, 48.3, 41.1, 25.4, 23.8; IR (neat): 3212, 2967, 2934, 1642, 1497, 1472, 1052, 890, 585, 539 cm⁻¹; HRMS (m/z) Calcd for (C₁₅H₂₃NO₂) ([M+H⁺]): 234.1019; found: 234.1019.

**2-Allyl-N-methoxybenzamide (II).**

Follow the same procedure with 1a. Allylbenzoic acid was synthesized according to literature procedure¹. Purification by column chromatography (33% EtOAc in hexanes) gave II as a white solid (45% yield); Rᵢ = 0.38 (50% EtOAc in hexanes); ¹H NMR (400 MHz, CDCl₃): δ 9.53 (s, 1H), 7.37 (t, J = 7.6 Hz, 1H), 7.30 (d, J = 7.6 Hz, 1H), 7.23 (d, J = 7.6 Hz, 1H), 7.18 (t, J = 7.6 Hz, 1H), 6.00–5.87 (m, 1H), 5.10–4.95 (m, 2H), 3.77 (s, 3H), 3.49 (d, J = 6.4 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 167.4, 138.4, 137.0, 132.5, 130.4, 130.2, 127.5, 126.0, 116.0, 64.0, 37.0; IR (neat): 3123, 2935, 2820, 1633, 1529, 1316, 1039, 902, 746 cm⁻¹; HRMS (m/z) Calcd for (C₁₅H₂₃NO₂) ([M+H⁺]): 234.1019; found: 234.1019.

**N-Methoxy-3,3-dimethylpent-4-enamide (1i).**

To a solution of 3,3-dimethylpent-4-enioic acid (1.28 g, 10 mmol) in CH₂Cl₂ (10 mL), was added sequentially triethylamine (2.2 mL, 16 mmol), EDCI (3.44 g, 18 mmol) and MeONH₂·HCl (1.33 g, 16 mmol). The resulting mixture was stirred at room temperature overnight and then was filtered through a pale of Celite. The filtrate was concentrated. Purification by column chromatography (33% EtOAc in hexanes) gave 1i as a colorless oil (68% yield); Rᵢ = 0.28 (50% EtOAc in hexanes); ¹H NMR (400 MHz, CDCl₃): δ 9.21 (s, br, 1H), 5.85 (dd, J = 17.6, 10.8 Hz, 1H), 4.95 (d, J = 17.6 Hz, 1H), 4.93 (d, J = 10.0 Hz, 1H), 3.68 (s, 3H), 2.07 (s, 2H), 1.10 (s, 6H); ¹³C NMR (100 MHz, CDCl₃): δ 168.9, 146.9, 111.2, 64.0, 45.3, 36.2, 26.8; IR (neat): 3170, 2962, 1649, 1515, 1463, 1438, 1364, 1068, 910, 724, 675, 590 cm⁻¹; HRMS (m/z) Calcd for (C₁₁H₁₉NO₂) ([M+H⁺]): 158.1176; found: 158.1176.

**3-Ethyl-N-methoxy-2,2-diphenylpent-4-enamide (1j).**

To a solution of 2,2-diphenylacetic acid (2.12 g, 10 mmol) in CH₂Cl₂ (10 mL) was added dropwise oxalyl chloride (0.93 mL, 11 mmol) followed by a catalytic amount of DMF. The mixture was stirred at room...
temperature for 1 h, and then was added dropwise pyridine (1.76 mL, 22 mmol) and (E)-pent-2-en-1-ol (1.22 mL, 12 mmol). The resulting mixture was stirred at room temperature overnight and then was quenched by the addition of a saturated aqueous solution of Na₂CO₃. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried over Na₂SO₄, and filtrated. The filtrate was concentrated, providing the crude ester product which was directly used for the next step. To the solution of the crude ester product in THF (10 mL), was added dropwise at –78 °C the freshly prepared LDA solution (20 mmol, 2 equiv) in THF (15 mL). The reaction mixture was allowed to stir at –78 °C for 1 h and then was added TMSCl (2.7 mL, 21 mmol). The reaction mixture was slowly warmed to room temperature and then stirred at 60 °C overnight. After cooling down to room temperature, the reaction was quenched with an aqueous solution of HCl (2 M). The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined extracts were washed with brine, dried over Na₂SO₄, and filtrated. The filtrate was concentrated. Purification by column chromatography (10% EtOAc in hexanes) gave 3-ethyl-2,2-diphenylpent-4-enic acid as a white solid (1.67 g, 60% yield); Rₛ = 0.44 (20% EtOAc in hexanes); ¹H NMR (400 MHz, CDCl₃): δ 7.40–7.16 (m, 10H); 5.34–5.06 (m, 3H), 3.41 (t, J = 8.8 Hz, 1H), 1.71–1.54 (m, 1H), 0.89 (t, J = 7.2 Hz, 3H), 0.64–0.46 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 179.6, 137.6, 130.9 (2C), 130.1 (2C), 127.6 (2C), 127.03 (2C), 127.00 (2C), 126.8 (2C), 119.0, 64.9, 48.8, 23.5, 12.0; IR (neat): 3246, 2962, 1654, 1494, 1441, 909, 717, 696 cm⁻¹; HRMS (m/z) Calcd for (C₁₉H₂₀O₂) ([M+H⁺]: 281.1536; found: 281.1536.

To a solution of 3-ethyl-2,2-diphenylpent-4-enic acid (1.04 g, 3.7 mmol) in CH₂Cl₂ (5 mL) was added dropwise oxaly chloride (0.42 mL, 4.9 mmol) followed by a catalytic amount of DMF. The mixture was stirred at room temperature for 1 h, and then was concentrated under reduced pressure. The residue was added dropwise to a biphasic mixture of MeONH₂·HCl (464 mg, 5.6 mmol) and K₂CO₃ (1.02 g, 7.4 mmol) in EtOAc (20 mL) and H₂O (10 mL). The reaction mixture was stirred at room temperature for 2 h. Then the organic layer was separated and the aqueous layer was extracted with EtOAc. The combined extracts were washed with brine, dried over Na₂SO₄, and filtrated. The filtrate was concentrated. Purification by column chromatography (33% EtOAc in hexanes) gave 1j as a yellow oil (520 mg, 46% yield); Rₛ = 0.59 (50% EtOAc in hexanes); ¹H NMR (400 MHz, CDCl₃): δ 8.37 (s, 1H), 7.33 (t, J = 7.2 Hz, 4H), 7.30–7.18 (m, 6H), 5.48–5.36 (m, 1H), 5.13–5.03 (m, 2H), 3.49 (s, 3H), 3.38 (t, J = 9.6 Hz, 1H), 1.75–1.62 (m, 1H), 0.89 (t, J = 7.2 Hz, 3H), 0.79–0.65 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 171.2, 140.6, 140.2, 137.6, 130.0, 129.5, 127.7, 127.6, 126.9, 126.8, 118.3, 63.5, 63.4, 50.0, 23.6, 12.0; IR (neat): 3246, 2962, 1654, 1494, 1441, 909, 717, 696 cm⁻¹; HRMS (m/z) Calcd for (C₂₀H₂₄N₂O₂) ([M+H⁺]: 310.1802; found: 310.1802.

2,2-Diphenyl-N-tosylpent-4-enamide (1c).

To a solution of 2,2-diphenylpent-4-enic acid (1.26 g, 5 mmol) in THF (20 mL) was added p-tosyl isocyanate (985 mg, 5 mmol), followed by the dropwise addition of triethyl amine (0.7 mL, 5 mmol) with release of gas. The mixture was stirred at room temperature for 3 h, and then was concentrated. Purification by column chromatography (20% EtOAc in hexanes) gave 1c as a white solid (1.17 g, 59% yield); Rₛ = 0.46 (20% EtOAc in hexanes); ¹H NMR (400 MHz, CDCl₃): δ 7.89 (s, 1H), 7.72 (d, J = 8.4 Hz, 2H), 7.34–7.22 (m, 8H), 7.17–7.08 (m, 4H), 5.58–5.43 (m, 1H), 4.90–4.79 (m, 2H), 3.04 (d, J = 6.8 Hz, 2H), 2.43 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 171.3, 144.9, 140.1, 134.9, 133.3, 129.3, 128.7, 128.6, 127.6, 119.0, 61.4, 42.6, 21.6; IR (neat): 3273, 3067, 3026, 1718, 1698, 1398, 1341, 1305, 698, 659, 550 cm⁻¹; HRMS (m/z) Calcd for (C₂₅H₂₄N₂O₂S) ([M+H⁺]: 406.1471; found: 406.1471.

1-Allyl-1-benzyl-3-methoxyurea (1m).
To a solution of triphosgene (7.8 g, 26 mmol) in anhydrous CH₂Cl₂ (50 mL) at −20 °C, was added dropwise pyridine (5.2 mL, 52 mmol), followed by a solution of N-benzylprop-2-en-1-amine (2.94 g, 20 mmol) in CH₂Cl₂ (10 mL). The reaction mixture was stirred at room temperature for 12 h and then was quenched with a saturated aqueous solution of NH₄Cl. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂. The combined extracts were washed with brine, dried over Na₂SO₄, and filtered. The filtrate was concentrated, providing the crude carbamoyl chloride product that was directly used for the next step. The crude carbamoyl chloride product was added dropwise to a biphasic mixture of MeONH₂·HCl (2.5 g, 30 mmol) and K₂CO₃ (5.52 g, 40 mmol) in EtOAc (30 mL) and H₂O (15 mL). The reaction mixture was stirred at 60 °C overnight and then the organic layer was separated. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, and filtered. The filtrate was concentrated. Purification by column chromatography (50% EtOAc in hexanes) gave 1m as a yellow solid (2.97 g, 68% yield); R_f = 0.33 (50% EtOAc in hexanes); ¹H NMR (400 MHz, CDCl₃): δ 7.51 (s, 1H), 7.31–7.15 (m, 5H), 5.74–5.62 (m, 1H), 5.17–5.07 (m, 2H), 4.11 (s, 2H), 3.74 (d, J = 5.6 Hz, 2H), 3.64 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 159.4, 136.9, 132.8, 128.5, 127.4 (2C), 117.2, 64.0, 49.6, 48.6; IR (neat): 3247, 2992, 2962, 2929, 2890, 1650, 1497, 1479, 1250, 943, 693 cm⁻¹; HRMS (m/z) Calcd for (C₁₂H₁₇N₂O₂) [(M+H)⁺]: 221.1285; found: 221.1285.

(S)-1-Benzyl-3-methoxy-1-(4-methylpent-1-en-3-yl) (1n).

To a solution of triphosgene (1.55 g, 5.2 mmol) in anhydrous CH₂Cl₂ (10 mL) at −20 °C, was added dropwise pyridine (1 mL, 10 mmol) followed by a solution of (S)-N-benzyl-4-methylpent-1-en-3-amine (756 mg, 4 mmol) in CH₂Cl₂ (2 mL). The reaction mixture was stirred at room temperature for 9 h, and then was quenched with a saturated aqueous solution of NH₄Cl. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂. The combined extracts were washed with brine, dried over Na₂SO₄, and filtered. The filtrate was concentrated, providing the crude carbamoyl chloride product that was directly used for the next step. The crude carbamoyl chloride product was added dropwise to a biphasic mixture of MeONH₂·HCl (501 mg, 6 mmol) and K₂CO₃ (1.1 g, 8 mmol) in EtOAc (20 mL) and H₂O (10 mL). The reaction mixture was stirred at 60 °C for 14 h and then the organic layer was separated. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, and filtered. The filtrate was concentrated. Purification by column chromatography (20% EtOAc in hexanes) gave 1n as a white solid (438 mg, 42% yield); [α]²⁰D = +9.0 (c = 1.0, CHCl₃); R_f = 0.52 (50% EtOAc in hexanes); ¹H NMR (400 MHz, CDCl₃): δ 7.35–7.20 (m, 5H), 6.96 (s, 1H), 5.75 (dd, J = 17.2, 10.0, 8.4 Hz, 1H), 5.22 (dd, J = 17.2, 0.8 Hz, 1H), 5.17 (dt, J = 10.0, 0.8 Hz, 1H), 4.36 (d, J = 16.8 Hz, 1H), 4.27 (d, J = 16.8 Hz, 1H), 4.22 (t, J = 9.6 Hz, 1H), 3.56 (s, 3H), 2.04–1.90 (m, 1H), 0.92 (d, J = 6.8 Hz, 3H), 0.89 (d, J = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 159.5, 137.1, 135.7, 128.9, 127.7, 126.7, 118.9, 65.8, 64.0, 47.4, 29.8, 20.1, 19.5; IR (neat): 3205, 2958, 2873, 1728, 1637, 1475, 927, 717, 578 cm⁻¹; HRMS (m/z) Calcd for (C₁₃H₂₃N₂O₂) [(M+H)⁺]: 263.1754; found: 263.1754.

(E)-2,2-dimethylpent-4-enioic-5-d acid.

To a suspension of Cp₂ZrHCl (2.55 g, 9.9 mmol) in THF (16 mL) at room temperature under nitrogen, was added dropwise a solution of methyl 2,2-dimethylpent-4-ynoate in THF (2 mL). The reaction was stirred for 2 h and was added D₂O (1 mL). After 24 h, the mixture was concentrated under reduced pressure. To the resulting crude, were added NaOH (1.5 g, 37.5 mmol), MeOH (10 mL) and H₂O (5 mL) and the resulting reaction mixture was stirred at 60 °C for 5 h. After cooling down to room temperature, the reaction mixture was concentrated and then diluted with H₂O (15 mL). The aqueous mixture was washed with EtOAc. The aqueous layer was acidified with a concentrated aqueous solution of HCl and extracted with EtOAc. The
organic extracts were washed with brine, dried over Na₂SO₄, and filtrated. The filtrate was concentrated. The crude residue was purified by column chromatography (2% ethyl acetate in hexanes) to give the (E)-2,2-dimethylpent-4-enio-5-ß-acid as a yellow oil (550 mg, 48%). Rₜ= 0.58 (20% EtOAc in hexanes); ¹H NMR (400 MHz, CDCl₃): δ 11.2 (br, 1H), 5.74 (dt, J = 17.2, 7.2 Hz, 1H), 5.03 (dt, J = 17.2, 1.2 Hz, 1H), 2.27 (dd, J = 17.2, 1.2 Hz, 2H), 1.17 (s, 6H); ¹³C NMR (100 MHz, CDCl₃): δ 184.5, 133.7, 117.9 (t, J = 25 Hz), 44.3, 42.1, 24.5; IR (neat): 3212, 2967, 2934, 1645, 1498, 1473, 1048, 982, 940, 873, 830, 552 cm⁻¹; HRMS (m/z) Calcd for (C₁₈H₁₀DNO₃) [(M+H)⁺]: 282.0829; found: 282.0829.

(E)-N-Methoxy-2,2-dimethylpent-4-enio-5-ß-amide (d-1f).

To a solution of (E)-2,2-dimethylpent-4-enio-5-ß-acid (387 mg, 3 mmol) in CH₂Cl₂ (5 mL), was added dropwise oxalyl chloride (0.33 mL, 3.9 mmol) followed by a catalytic amount of DMF. The mixture was stirred at room temperature for 1 h and then was added dropwise to a biphasic mixture of MeONH₂·HCl (376 mg, 4.5 mmol) and K₂CO₃ (828 mg, 6 mmol) in EtOAc (10 mL) and H₂O (5 mL). The reaction mixture was stirred at room temperature for 2 h. Then the organic layer was separated and the aqueous layer was extracted with EtOAc. The combined extracts were washed with brine, dried over Na₂SO₄, and filtrated. The filtrate was concentrated. Purification by column chromatography (25% EtOAc in hexanes) gave 3f as a yellow oil (215 mg, 46% yield); Rₜ= 0.31 (50% EtOAc in hexanes); ¹H NMR (400 MHz, CDCl₃): δ 9.30 (s, 1H), 5.66 (dt, J = 17.2, 7.6 Hz, 1H), 4.98 (dd, J = 17.2, 1.2 Hz, 1H), 3.64 (s, 3H), 2.20 (dd, J = 7.6, 1.2 Hz, 2H), 1.09 (s, 6H); ¹³C NMR (100 MHz, CDCl₃): δ 174.9, 133.7, 117.9 (t, J = 25 Hz), 63.8, 44.7, 41.0, 24.4; IR (neat): 3212, 2967, 2934, 1645, 1498, 1473, 1048, 982, 903, 592 cm⁻¹; HRMS (m/z) Calcd for (C₁₈H₁₀DNO₃) [(M+H)⁺]: 159.1238; found: 159.1238.

V. General Procedure for Diamination Reaction.

To a reaction tube charged with N-methoxylamide 1 (0.3 mmol, 1.0 equiv) and hydroxylamine 2 (0.36 mmol, 1.2 equiv), was added Cu(OAc)₂ (0.6 mmol, 2.0 mol%), K₂CO₃ (0.6 mmol, 2.0 equiv) and MTBE (1.5 mL). The reaction tube was capped and the resulting mixture was stirred at 80 °C for 2 h. After cooling down to room temperature, the reaction mixture was diluted with EtOAc (5 mL) and washed with a saturated aqueous solution of Na₂CO₃ (5 mL). The aqueous layers were extracted with EtOAc (10 mL × 2). The combined organic layers were dried over Na₂SO₄, and filtered. The filtrate was concentrated in vacuo. The resulting crude mixture was subject to flash column chromatography to provide the diaminated product 3.

1-Methoxy-5-(morpholinomethyl)-3,3-diphenylpyrrolidin-2-one (3aa). Purification by column chromatography (50% EtOAc in hexanes then 50% EtOAc in hexanes containing 2% TEA) gave 3aa as a yellow oil (87.9 mg, 80% yield); Rₜ= 0.25 (33% EtOAc in hexanes containing 2% TEA); ¹H NMR (400 MHz, CDCl₃): δ 7.40–7.16 (m, 10H), 3.92–3.82 (m, 1H), 3.81 (s, 3H), 3.72–3.61 (m, 4H), 2.95 (dd, J = 12.8, 6.4 Hz, 1H), 2.75 (dd, J = 12.8, 4.0 Hz, 1H), 2.52 (dd, J = 12.8, 8.4 Hz, 1H), 2.50–2.40 (m, 5H); ¹³C NMR (100 MHz, CDCl₃): δ 171.9, 143.7, 141.7, 128.4, 128.2, 128.6, 127.63, 127.62, 127.1, 126.8, 66.8, 62.7, 60.7, 54.3, 50.7, 46.9, 45.8, 44.3, 42.1.
54.2, 53.0, 38.2; IR (neat): 2930, 2860, 2820, 1708, 1445, 1278, 1252, 1115, 697 cm⁻¹; HRMS (m/z) Caled for (C₂₂H₂₇N₂O₅) ([M+H⁺]: 367.2016; found: 367.2016.

1-(Benzyloxy)-5-(morpholinomethyl)-3,3-diphenylpyrrolidin-2-one (3ba). The reaction was runned in a 0.2 mmol scale. Purification by column chromatography (50% EtOAc in hexanes then 50% EtOAc in hexanes containing 2% TEA) gave 3ba as a yellow oil (65.4 mg, 74% yield; R_f = 0.32 (33% EtOAc in hexanes containing 2% TEA); ¹H NMR (400 MHz, CDCl₃): δ 7.40–7.18 (m, 15H), 5.04 (d, J = 10.4 Hz, 1H), 4.95 (d, J = 10.4 Hz, 1H), 3.70–3.57 (m, 4H), 3.57–3.48 (m, 1H), 2.90 (dd, J = 13.2, 6.4 Hz, 1H), 2.62 (dd, J = 12.8, 4.0 Hz, 1H), 2.43 (dd, J = 12.8, 8.0 Hz, 1H), 2.41–2.33 (m, 4H), 2.31 (dd, J = 12.8, 7.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 171.6, 144.1, 141.6, 135.0, 129.7, 128.8, 128.44, 128.42, 128.2, 127.7, 127.1, 126.7, 76.8, 66.8, 60.4, 54.3, 54.1, 53.8, 38.1; IR (neat): 2918, 2850, 1701, 1493, 1445, 1114, 751, 695 cm⁻¹; HRMS (m/z) Caled for (C₂₈H₃₁N₂O₃) ([M+H⁺]: 443.2329; found: 443.2329.

1-Methoxy-5-(4′-tert-butyloxycarbonylpiperazinomethyl)-3,3-diphenylpyrrolidin-2-one (3ab). Purification by column chromatography (50% EtOAc in hexanes then 50% EtOAc in hexanes containing 2% TEA) gave 3ab as a yellow oil (114.4 mg, 82% yield; R_f = 0.31 (33% EtOAc in hexanes containing 2% TEA); ¹H NMR (400 MHz, CDCl₃): δ 7.40–7.15 (m, 10H), 3.90–3.83 (m, 1H), 3.80 (s, 3H), 3.50–3.26 (m, 4H), 2.95 (dd, J = 13.2, 6.4 Hz, 1H), 2.75 (dd, J = 12.8, 4.0 Hz, 1H), 2.50 (dd, J = 13.2, 8.0 Hz, 1H), 2.45 (dd, J = 12.8, 7.2 Hz, 1H), 2.48–2.34 (m, 4H), 1.43 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 171.9, 154.6, 143.7, 141.6, 128.5, 128.3, 127.6, 127.1, 126.8, 79.7, 62.6, 60.3, 54.2, 53.7 (2C), 53.1, 38.2, 28.3; IR (neat): 2975, 2934, 1695, 1421, 1246, 1171, 1006, 699 cm⁻¹; HRMS (m/z) Caled for (C₂₇H₃₆N₃O₄) ([M+H⁺]: 466.2700; found: 466.2698.

1-Methoxy-3,3-diphenyl-5-(piperidinomethyl)pyrrolidin-2-one (3ac). Purification by column chromatography (50% EtOAc in hexanes then 50% EtOAc in hexanes containing 2% TEA) gave 3ac as a yellow oil (83.0 mg, 76% yield; R_f = 0.31 (33% EtOAc in hexanes containing 2% TEA); ¹H NMR (400 MHz, CDCl₃): δ 7.42–7.16 (m, 10H), 3.90–3.81 (m, 1H), 2.97 (dd, J = 13.2, 6.4 Hz, 1H), 2.75 (dd, J = 12.8, 4.4 Hz, 1H), 2.49 (dd, J = 13.2, 8.0 Hz, 1H), 2.49–2.29 (m, 5H), 1.63–1.47 (m, 4H), 1.40 (q, J = 5.6 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 172.0, 143.9, 141.8, 128.4, 128.2, 127.7, 127.6, 126.7, 62.7, 61.4, 55.5, 54.3, 53.5, 38.6, 24.1; IR (neat): 2935, 2778, 1707, 1444, 1025, 695 cm⁻¹; HRMS (m/z) Caled for (C₂₃H₂₉N₂O₂) ([M+H⁺]: 365.2224; found: 365.2222.
1-Methoxy-5-(3'-methylpiperidinomethyl)-3,3-diphenylpyrrolidin-2-one (3ad). Purification by column chromatography (50% EtOAc in hexanes then 50% EtOAc in hexanes containing 2% TEA) gave 3ad as a yellow oil (79.9 mg, 71% yield, inseparable diastereoisomer, $dr = 1:1$); $R_f = 0.34$ (33% EtOAc in hexanes containing 2% TEA); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.39–7.22 (m, 10H), 3.93–3.83 (m, 1H), 3.82 (s, 3H), 2.97 (dd, $J = 12.8$, 6.0 Hz, 1H), 2.82–2.67 (m, 3H), 2.56–2.44 (m, 1H), 2.37 (dd, $J = 12.8$, 7.6 Hz, 1H), 2.03–1.87 (m, 1H), 1.73–1.45 (m, 5H), 0.92–0.78 (m, 1H), 0.85 (d, $J = 6.4$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 172.0, 171.9, 143.91, 143.89, 141.9, 141.8, 128.4, 128.2, 127.73, 127.69, 127.03, 127.02, 126.7, 63.2, 62.77, 62.75, 62.7, 61.2, 55.2, 54.6, 54.26, 54.24, 53.5, 38.62, 38.59, 32.69, 32.67, 31.08, 31.06, 25.48, 25.44, 19.60, 19.58; IR (neat): 2927, 1711, 1494, 1446, 1043, 1027, 761, 698 cm$^{-1}$; HRMS (m/z) Calcd for (C$_{29}$H$_{31}$N$_2$O$_2$)$^+$: [M+H$^+$]: 379.2380; found: 379.2381.

1-Methoxy-5-(4'-ethoxycarbonylpiperidinomethyl)-3,3-diphenylpyrrolidin-2-one (3ae). Purification by column chromatography (50% EtOAc in hexanes then 50% EtOAc in hexanes containing 2% TEA) gave 3ae as a yellow oil (102.7 mg, 81% yield); $R_f = 0.26$ (33% EtOAc in hexanes containing 2% TEA); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.40–7.15 (m, 10H), 4.10 (q, $J = 7.2$ Hz, 2H), 3.88–3.80 (m, 1H), 3.79 (s, 3H), 2.95 (dd, $J = 13.2$, 6.4 Hz, 1H), 2.85–2.73 (m, 2H), 2.72 (dd, $J = 12.4$, 4.0 Hz, 1H), 2.48 (dd, $J = 13.2$, 8.0 Hz, 1H), 2.39 (dd, $J = 12.4$, 7.6 Hz, 1H), 2.24 (tt, $J = 11.2$, 4.0 Hz, 1H), 2.16–2.04 (m, 2H), 1.90–1.80 (m, 2H), 1.78–1.63 (m, 2H), 1.23 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 175.0, 172.0, 143.8, 141.8, 128.5, 128.2, 127.68, 127.65, 127.0, 126.7, 62.7, 60.6, 60.3, 54.2, 54.1, 53.5, 53.4, 40.8, 38.3, 28.28, 28.22, 14.2; IR (neat): 2929, 1708, 1445, 1260, 1179, 1043, 1026, 760, 698 cm$^{-1}$; HRMS (m/z) Calcd for (C$_{28}$H$_{33}$N$_2$O$_4$)$^+$: 437.2435; found: 437.2435.

5-(4-(Azepanomethyl)-1-methoxy-3,3-diphenylpyrrolidin-2-one (3af). Purification by column chromatography (50% EtOAc in hexanes then 50% EtOAc in hexanes containing 2% TEA) gave 3af as a yellow oil (49.9 mg, 44% yield); $R_f = 0.30$ (33% EtOAc in hexanes containing 2% TEA); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.38–7.32 (m, 4H), 7.32–7.25 (m, 4H), 7.25–7.18 (m, 2H), 3.88–3.78 (m, 1H), 3.80 (s, 3H), 3.05–2.95 (m, 2H), 2.73–2.64 (m, 4H), 2.58–2.47 (m, 2H), 1.72–1.48 (m, 8H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 171.9, 143.9, 141.7, 128.4, 128.2, 127.7, 127.6, 127.0, 126.7, 62.6, 59.8, 56.2, 54.2, 54.1, 38.3, 28.0, 27.0; IR (neat): 2925, 2852, 1708, 1445, 1042, 1026, 761, 698 cm$^{-1}$; HRMS (m/z) Calcd for (C$_{24}$H$_{31}$N$_2$O$_2$)$^+$: 379.2380; found: 379.2381.

5-((Diethylamino)methyl)-1-methoxy-3,3-diphenylpyrrolidin-2-one (3ag). Purification by column chromatography (50% EtOAc in hexanes then 50% EtOAc in hexanes containing 2% TEA) gave 3ag as a yellow oil (48.9 mg, 47% yield); $R_f = 0.33$ (33% EtOAc in hexanes containing 2% TEA); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.39–7.17 (m, 10H), 3.84–3.74 (m, 1H), 3.81 (s, 3H), 3.03 (dd, $J = 13.2$, 6.4 Hz, 1H), 2.87 (dd, $J = 13.2$, 3.6 Hz, 1H), 2.61–2.39 (m, 6H), 0.97 (t, $J = 7.2$ Hz, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 171.7, 144.0, 141.5, 128.3, 128.1, 127.6, 127.5, 126.9, 126.5, 62.4, 55.5, 54.12, 54.07, 47.8, 38.5, 11.7; IR
5-((Diallylamino)methyl)-1-methoxy-3,3-diphenylpyrrolidin-2-one (3ah). Purification by column chromatography (50% EtOAc in hexanes then 50% EtOAc in hexanes containing 2% TEA) gave 3ah as a yellow oil (45.4 mg, 40% yield); Rf = 0.40 (33% EtOAc in hexanes containing 2% TEA); 1H NMR (400 MHz, CDCl3): δ 7.38–7.18 (m, 10H), 5.85–5.70 (m, 2H), 5.18–5.07 (m, 4H), 3.88–3.80 (m, 1H), 3.78 (s, 3H), 3.16–3.03 (m, 4H), 2.99 (dd, J = 13.2, 6.4 Hz, 1H), 2.86 (dd, J = 12.8, 4.0 Hz, 1H), 2.50 (dd, J = 13.2, 8.4 Hz, 1H), 2.44 (dd, J = 13.2, 8.0 Hz, 1H); 13C NMR (100 MHz, CDCl3): δ 171.9, 144.0, 141.6, 135.3, 128.4, 128.3, 127.74, 127.67, 126.7, 117.8, 62.5, 58.0, 55.6, 54.2, 53.9, 38.4; IR (neat): 2931, 2813, 1710, 1446, 1261, 1042, 1027, 920, 761, 698 cm⁻¹; HRMS (m/z) Calcd for (C22H29N2O2) ([M+H]+): 353.2224; found: 353.2223.

5-((Benzyl(methyl)amino)methyl)-1-methoxy-3,3-diphenylpyrrolidin-2-one (3ai). Purification by column chromatography (50% EtOAc in hexanes then 50% EtOAc in hexanes containing 2% TEA) gave 3ai as a colorless oil (64.2 mg, 54% yield); Rf = 0.33 (33% EtOAc in hexanes containing 2% TEA); 1H NMR (400 MHz, CDCl3): δ 7.36–7.20 (m, 15H), 3.90–3.82 (m, 1H), 3.81 (d, J = 12.8 Hz, 1H), 2.99 (dd, J = 13.2, 6.4 Hz, 1H), 2.87 (dd, J = 12.4, 4.0 Hz, 1H), 2.52 (dd, J = 12.4, 8.4 Hz, 1H), 2.48 (dd, J = 13.2, 8.0 Hz, 1H), 2.27 (s, 3H); 13C NMR (100 MHz, CDCl3): δ 172.0, 143.8, 141.8, 138.7, 128.9, 128.5, 128.3, 128.2, 127.7, 127.6, 127.2, 127.0, 126.7, 62.5, 58.0, 55.6, 54.2, 53.9, 38.4; IR (neat): 2921, 2848, 1705, 1448, 1024, 698 cm⁻¹; HRMS (m/z) Calcd for (C26H29N2O2) ([M+H]+): 401.2224; found: 401.2222.

1-Methoxy-3,3-dimethyl-5-(morpholinomethyl)pyrrolidin-2-one (3fa). Purification by column chromatography (50% EtOAc in hexanes then 50% EtOAc in hexanes containing 2% TEA) gave 3fa as a yellow oil (65.1 mg, 90% yield); Rf = 0.29 (50% EtOAc in hexanes containing 2% TEA); 1H NMR (400 MHz, CDCl3): δ 3.80–3.70 (m, 1H), 3.74 (s, 3H), 3.66–3.61 (m, 4H), 2.66 (dd, J = 12.8, 4.4 Hz, 1H), 2.50–2.42 (m, 4H), 2.37 (dd, J = 12.8, 7.2 Hz, 1H), 1.98 (dd, J = 12.8, 7.2 Hz, 1H), 1.62 (dd, J = 12.8, 7.6 Hz, 1H), 1.16 (s, 3H), 1.07 (s, 3H); 13C NMR (100 MHz, CDCl3): δ 176.2, 66.8, 62.4, 61.4, 54.4, 52.7, 37.8, 37.3, 25.7, 25.1; IR (neat): 2962, 2848, 2808, 1699, 1448, 1024, 698 cm⁻¹; HRMS (m/z) Calcd for (C12H23N2O3) ([M+H]+): 243.1704; found: 243.1704.
2-Methoxy-3-(morpholinomethyl)-2-azaspiro[4.5]decan-1-one (3ga). Purification by column chromatography (50% EtOAc in hexanes then 50% EtOAc in hexanes containing 2% TEA) gave 3ga as a yellow oil (69 mg, 81% yield); Rf = 0.28 (50% EtOAc in hexanes containing 2% TEA); 1H NMR (400 MHz, CDCl3): δ 3.75–3.68 (m, 1H), 3.72 (s, 3H), 3.63 (t, J = 4.8 Hz, 4H), 2.65 (dd, J = 12.8, 4.0 Hz, 1H), 2.45 (t, J = 4.8 Hz, 4H), 2.35 (dd, J = 12.8, 7.2 Hz, 1H), 2.11 (dd, J = 13.2, 7.6 Hz, 1H), 1.75–1.45 (m, 6H), 1.40–1.16 (m, 5H); 13C NMR (100 MHz, CDCl3): δ 176.0, 66.8, 62.5, 61.6, 54.4, 53.0, 41.4, 34.2, 33.5, 32.0, 25.1, 21.54, 21.50; IR (neat): 2924, 2851, 2798, 2755, 1701, 1442, 1364, 1278, 1114, 866 cm⁻¹; HRMS (m/z) Calcd for (C13H22N3O3) [(M+H)⁺]: 283.16; found: 283.2014.

![Chemical structure of 3ga](image)

2-Methoxy-3-(morpholinomethyl)-6,10-dithia-2-azaspiro[4.5]decan-1-one (3ha). Purification by column chromatography (50% EtOAc in hexanes then 50% EtOAc in hexanes containing 2% TEA) gave 3ha as a yellow oil (48.6 mg, 51% yield); Rf = 0.29 (50% EtOAc in hexanes containing 2% TEA); 1H NMR (400 MHz, CDCl3): δ 3.72 (t, J = 13.2 Hz, 1H), 3.65–3.55 (m, 1H), 3.53 (s, 3H), 3.44 (t, J = 13.2 Hz, 1H), 3.39 (t, J = 4.8 Hz, 4H), 2.46 (dd, J = 12.8, 4.4 Hz, 1H), 2.32–2.24 (m, 1H), 2.28 (dd, J = 14.0, 3.6 Hz, 1H), 2.19 (t, J = 4.8 Hz, 4H), 2.22–2.14 (m, 1H), 1.95 (dd, J = 14.0, 6.8 Hz, 1H), 1.97–1.88 (m, 1H), 1.71 (dd, J = 14.0, 7.2 Hz, 1H), 1.67–1.52 (m, 1H); 13C NMR (100 MHz, CDCl3): δ 169.8, 66.8, 62.4, 60.5, 54.3, 52.5, 43.1, 37.7, 27.4, 27.0, 24.3; IR (neat): 2922, 2851, 2813, 1706, 1423, 1278, 1114, 866 cm⁻¹; HRMS (m/z) Calcd for (C13H22N3O3S2) [(M+H)⁺]: 319.1145; found: 319.1145.

![Chemical structure of 3ha](image)

1-Methoxy-4,4-dimethyl-5-(morpholinomethyl)pyrrolidin-2-one (3ia). Purification by column chromatography (50% EtOAc in hexanes then 50% EtOAc in hexanes containing 2% TEA) gave 3ia as a yellow oil (26.2 mg, 36% yield); Rf = 0.26 (50% EtOAc in hexanes containing 2% TEA); 1H NMR (400 MHz, CDCl3): δ 3.77 (s, 3H), 3.65 (t, J = 4.4 Hz, 4H), 3.43 (t, J = 5.6 Hz, 1H), 2.55 (d, J = 5.6 Hz, 2H), 2.52–2.41 (m, 4H), 2.27 (d, J = 16.4 Hz, 1H), 2.05 (d, J = 16.4 Hz, 1H), 1.20 (s, 3H), 1.10 (s, 3H); 13C NMR (125 MHz, CDCl3): δ 163.4, 60.0, 56.7, 55.4, 49.2, 47.3, 36.5, 26.8, 22.0, 16.0; IR (neat): 2957, 2851, 1702, 1453, 1292, 1114, 1061, 865 cm⁻¹; HRMS (m/z) Calcd for (C12H23N2O3) [(M+H)⁺]: 243.1703; found: 243.1703.

![Chemical structure of 3ia](image)

(trans)-4-Ethyl-1-methoxy-5-(morpholinomethyl)-3,3-diphenylpyrrolidin-2-one (3ja). Purification by column chromatography (50% EtOAc in hexanes then 50% EtOAc in hexanes containing 2% TEA) gave 3ja as a yellow oil (66.3 mg, 56% yield, dr > 20:1); Rf = 0.28 (33% EtOAc in hexanes containing 2% TEA); 1H NMR (400 MHz, CDCl3): δ 7.64 (d, J = 7.6 Hz, 2H), 7.34 (t, J = 7.6 Hz, 2H), 7.28 (d, J = 7.6 Hz, 1H), 7.25–7.15 (m, 3H), 6.94 (d, J = 7.6 Hz, 2H), 3.93 (s, 3H), 3.69–3.53 (m, 5H), 3.10 (dt, J = 8.8, 5.6 Hz, 1H), 2.57 (dd, J = 4.8, 2.0 Hz, 2H), 2.53–2.38 (m, 4H), 1.20–1.00 (m, 2H), 0.88 (t, J = 7.6 Hz, 3H); 13C NMR (100 MHz, CDCl3): δ 172.1, 141.7, 141.5, 128.9, 128.4, 128.0, 127.9, 127.1, 126.7, 66.9, 62.6, 59.4, 58.7, 58.1, 54.3, 43.7, 24.2, 12.7; IR (neat): 2960, 2933, 2850, 2809, 1707, 1494, 1444, 1116, 700 cm⁻¹; HRMS (m/z) Calcd for (C20H13N3O3) [(M+H)⁺]: 395.2329; found: 395.2328.

S12
The relative stereochemistry of 3ja was determined by NOESY.

1-Methoxy-3,3,5-trimethyl-5-(morpholinomethyl)pyrrolidin-2-one (3ka). Purification by column chromatography (50% EtOAc in hexanes then 50% EtOAc in hexanes containing 2% TEA) gave 3ka as a yellow oil (48.4 mg, 62% yield); Rf = 0.35 (50% EtOAc in hexanes containing 2% TEA); 1H NMR (400 MHz, CDCl3): δ 3.80 (s, 3H), 3.65–3.50 (m, 4H), 2.65–2.54 (m, 2H), 2.52 (d, J = 13.6 Hz, 1H), 2.41–2.29 (m, 2H), 2.03 (d, J = 6.0 Hz, 1H), 2.00 (d, J = 6.0 Hz, 1H), 1.56 (d, J = 13.6 Hz, 1H), 1.27 (s, 3H), 1.23 (s, 3H), 1.18 (s, 3H); 13C NMR (100 MHz, CDCl3): δ 174.9, 67.0, 63.8 (2C), 61.1, 55.2, 43.0, 36.4, 29.4, 26.0, 25.0; IR (neat): 2964, 2853, 2805, 1697, 1454, 1381, 1356, 1315, 1115, 1009, 864 cm⁻¹; HRMS (m/z) Calcd for (C13H25N2O3) ([M+H]+): 257.1860; found: 257.1860.

2-Methoxy-3-(morpholinomethyl)-3,4-dihydroisoquinolin-1(2H)-one (3la). Purification by column chromatography (50% EtOAc in hexanes then 50% EtOAc in hexanes containing 2% TEA) gave 3la as a yellow oil (53 mg, 65% yield); Rf = 0.23 (50% EtOAc in hexanes containing 2% TEA); 1H NMR (400 MHz, CDCl3): δ 8.04 (d, J = 7.6 Hz, 1H), 7.38 (t, J = 7.6 Hz, 1H), 7.28 (t, J = 7.6 Hz, 1H), 7.13 (d, J = 7.6 Hz, 1H), 4.00–3.92 (m, 1H), 3.85 (s, 3H), 3.61–3.51 (m, 2H), 3.51–3.42 (m, 2H), 3.36 (dd, J = 16.0, 6.0 Hz, 1H), 3.16 (dd, J = 16.0, 2.4 Hz, 1H), 2.55 (dd, J = 13.2, 3.6 Hz, 1H), 2.47–2.35 (m, 3H), 2.35–2.25 (m, 2H); 13C NMR (100 MHz, CDCl3): δ 162.9, 135.5, 132.1, 128.6, 127.68, 127.66, 126.9, 66.8, 62.6, 57.9, 56.6, 54.1, 32.2; IR (neat): 2933, 2852, 2808, 1663, 1458, 1266, 1114, 1004, 866, 730, 689 cm⁻¹; HRMS (m/z) Calcd for (C15H21N2O3) ([M+H]+): 277.1547; found: 277.1547.

1-Benzyl-3-methoxy-4-(morpholinomethyl)imidazolidin-2-one (3ma). Purification by column chromatography (50% EtOAc in hexanes then 50% EtOAc in hexanes containing 2% TEA) gave 3ma as a yellow oil (36.8 mg, 41% yield); Rf = 0.24 (50% EtOAc in hexanes containing 2% TEA); 1H NMR (400 MHz, CDCl3): δ 7.35–7.15 (m, 5H), 4.40 (d, J = 14.8 Hz, 1H), 4.25 (d, J = 14.8 Hz, 1H), 3.82 (s, 3H), 3.70–3.52 (m, 1H), 3.60 (t, J = 4.0 Hz, 4H), 3.22 (t, J = 8.4 Hz, 1H), 2.86 (t, J = 9.2 Hz, 1H), 2.70 (dd, J = 12.4, 4.8 Hz, 1H), 2.44 (dd, J = 12.4, 8.0 Hz, 1H), 2.46–2.32 (m, 4H); 13C NMR (100 MHz, CDCl3): δ 162.5, 135.8, 128.6, 128.1, 127.6, 66.7, 64.4, 60.5, 56.6, 54.1, 47.7, 45.5; IR (neat): 2934, 2852, 2811, 1723, 1436, 1239, 1114, 1034, 699 cm⁻¹; HRMS (m/z) Calcd for (C16H28N2O3) ([M+H]+): 306.1812; found: 306.1812.
(45,5S)-1-Benzyl-5-isopropyl-3-methoxy-4-(morpholinomethyl)imidazolidin-2-one (3na). Purification by column chromatography (50% EtOAc in hexanes then 50% EtOAc in hexanes containing 2% TEA) gave 3na as a yellow oil (47 mg, 46% yield); [α] D = −18.3 (c = 0.6, CHCl3); Rf = 0.31 (33% EtOAc in hexanes containing 2% TEA); 1H NMR (400 MHz, CDCl3): δ 7.35–7.18 (m, 5H), 4.90 (d, J = 14.8 Hz, 1H), 3.86 (d, J = 14.8 Hz, 1H), 3.85 (s, 3H), 3.56 (t, J = 4.4 Hz, 4H), 3.41 (q, J = 5.6 Hz, 1H), 3.13 (dd, J = 5.6, 3.6 Hz, 1H), 2.47 (dd, J = 13.2, 5.6 Hz, 1H), 2.44–2.29 (m, 4H), 2.25 (dd, J = 13.2, 5.6 Hz, 1H), 2.06–1.94 (m, 1H), 0.83 (d, J = 3.6 Hz, 3H), 0.81 (d, J = 3.6 Hz, 3H); 13C NMR (125 MHz, CDCl3): δ 161.7, 136.3, 128.6, 128.1, 127.6, 66.8, 64.0, 60.2, 59.1, 55.5, 54.2, 50.1, 27.4, 18.1, 15.8; IR (neat): 2958, 2852, 2808, 1717, 1424, 1115, 700 cm⁻¹; HRMS (m/z) Calcd for (C19H30N3O3) ([M+H]+): 348.2282; found: 348.2283.

The relative stereochemistry of 3pa was determined by NOESY.

VI. Mechanism Investigation.

To a reaction tube charged with (E)-N-methoxy-2,2-dimethylpent-4-en-5-d-amide d-1f (31.6 mg, 0.2 mmol) and hydroxylamine 2a (49.7 mg, 0.24 mmol), was added Cu(OAc)2 (3.6 mg, 0.02 mmol), K2CO3 (55.2 mg, 0.4 mmol), and MTBE (1 mL). The reaction tube was capped and the resulting mixture was stirred at 80 °C for 2 h. After cooling down to room temperature, the reaction mixture was diluted with EtOAc (5 mL) and washed with a saturated aqueous solution of Na2CO3 (5 mL). The aqueous layer was separated and extracted with EtOAc (10 mL × 2). The combined organic layers were dried over Na2SO4, and filtered. The filtrate was concentrated in vacuo. Purification by column chromatography (50% EtOAc in hexanes then 50% EtOAc in hexanes containing 2% TEA) gave 1-methoxy-3,3-dimethyl-5-(morpholinomethyl)-d-pyrrolidin-2-one d-3fa as a yellow oil (32.1 mg, 66% yield, inseparable diastereoisomer, dr = 1:1); Rf = 0.29 (50% EtOAc in hexanes containing 2% TEA); 1H NMR (400 MHz, CDCl3): δ 3.79–3.72 (m, 1H), 3.75 (s, 3H), 3.68–3.62 (m, 4H), 2.67 (d, J = 4.4 Hz, 0.5H), 2.53–2.40 (m, 4H), 2.36 (d, J = 6.8 Hz, 0.5H), 1.99 (dd, J = 12.8, 7.6 Hz, 1H), 1.62 (dd, J = 12.8, 7.6 Hz, 1H), 1.17 (s, 3H), 1.08 (s, 3H); 13C NMR (100 MHz, CDCl3): δ 176.2, 66.9, 62.5, 61.0 (t, J = 20 Hz), 54.4, 52.7, 37.8, 37.3, 25.7, 25.1; IR (neat): 2958, 2848, 2809, 1699, 1453, 1270, 1112, 1013, 859 cm⁻¹; HRMS (m/z) Calcd for (C12H26N2O3) ([M+H]+): 244.1766; found: 244.1765.
To a reaction tube charged with N-methoxy-2,2-diphenylpent-4-enamide (56.2 mg, 0.2 mmol) and hydroxylamine (49.7 mg, 0.24 mmol), was added Cu(OAc)$_2$ (3.6 mg, 0.02 mmol), K$_2$CO$_3$ (55.2 mg, 0.4 mmol), TEMPO (55.2 mg, 0.4 mmol) and MTBE (1 mL). The reaction tube was capped and the resulting mixture was stirred at 80 °C for 24 h. After cooling down to room temperature, the reaction mixture was diluted with EtOAc (5 mL), washed with a saturated aqueous solution of Na$_2$S$_2$O$_3$ (5 mL) and a saturated aqueous solution of Na$_2$CO$_3$ (5 mL). The aqueous layers were extracted with EtOAc (10 mL × 2). The combined organic layers were dried over Na$_2$SO$_4$, and filtered. The filtrate was concentrated in vacuo.

Purification by column chromatography (5% EtOAc in hexanes) gave 1-methoxy-3,3-diphenyl-5-(((2,2,6,6-tetramethylpiperidin-1-yl)oxy)-methyl)pyrrolidin-2-one 4 as a colorless oil (31.4 mg, 36% yield); R$_f$ = 0.25 (12.5% EtOAc in hexanes); $^1$H NMR (400 MHz, CDCl$_3$): δ 7.42–7.20 (m, 10H), 4.04–3.93 (m, 2H), 3.93–3.82 (m, 1H), 3.85 (s, 3H), 2.93 (dd, $J$ = 12.8, 6.4 Hz, 1H), 2.64 (dd, $J$ = 13.2, 8.8 Hz, 1H), 1.52–1.40 (m, 4H), 1.37–1.27 (m, 2H), 1.17 (s, 3H), 1.16 (s, 3H), 1.11 (s, 3H), 1.08 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 171.7, 143.8, 141.4, 128.4, 128.0, 127.7, 127.6, 126.8, 76.0, 62.4, 60.0, 54.3, 53.6, 39.7, 36.3, 20.1, 16.9; IR (neat): 2971, 2928, 1712, 1446, 1373, 1359, 1045, 697 cm$^{-1}$; HRMS (m/z) Calcd for (C$_{31}$H$_{37}$N$_2$O$_3$) ([M+H]$^+$): 437.2799; found: 437.2797.

Follow the dianimation reaction procedure. The reaction was runned in a 0.2 mmol scale. Purification by column chromatography (20% EtOAc in hexanes) gave 5-((butyl(pent-4'-en-1'-yl)amino)methyl)-1-methoxy-3,3-diphenylpyrrolidin-2-one 3ak as a colorless oil (37.8 mg, 45% yield); R$_f$ = 0.50 (33% EtOAc in hexanes containing 2% TEA); $^1$H NMR (400 MHz, CDCl$_3$): δ 7.42–7.19 (m, 10H), 5.85–5.71 (m, 1H), 5.04–4.91 (m, 2H), 3.87–3.78 (m, 1H), 3.82 (s, 3H), 3.06 (dd, $J$ = 13.2, 6.4 Hz, 1H), 2.88 (dd, $J$ = 13.2, 3.6 Hz, 1H), 2.60–2.34 (m, 6H), 2.10–1.98 (m, 2H), 1.58–1.42 (m, 2H), 1.42–1.20 (m, 4H), 0.89 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 172.0, 144.1, 141.5, 138.4, 128.5, 128.3, 127.3, 127.2, 126.8, 76.0, 62.4, 60.0, 54.3, 53.6, 39.7, 36.3, 20.1, 16.9; IR (neat): 2971, 2928, 1712, 1446, 1373, 1359, 1045, 697 cm$^{-1}$; HRMS (m/z) Calcd for (C$_{32}$H$_{39}$N$_2$O$_3$) ([M+H]$^+$): 421.2850; found: 421.2847.

**VII. Deprotection Conditions for 3aa.**

To a solution of 3aa (73.2 mg, 0.2 mmol) in CH$_3$CN-H$_2$O (3.2 mL, 15:1) at room temperature was added Mo(CO)$_6$ (63.4 mg, 0.24 mmol). The resulting mixture was heated and refluxed for 2 h. The solvent was removed under reduced pressure. Purification by column chromatography (50% EtOAc in hexanes containing 2% TEA) gave 5-(morpholinomethyl)-3,3-diphenylpyrrolidin-2-one 3aa', as a white solid (66.8 mg, 99% yield); R$_f$ = 0.14 (50% EtOAc in hexanes containing 2% TEA); $^1$H NMR (400 MHz, CDCl$_3$): δ 7.6 (dd, $J$ = 7.6 Hz, 2H), 7.38–7.17 (m, 8H), 6.90 (s, br, 1H), 3.80–3.70 (m, 1H), 3.70–3.57 (m, 4H), 2.94 (dd, $J$ = 13.2, 6.0 Hz, 1H), 2.58–2.48 (m, 2H), 2.46 (dd, $J$ = 12.8, 4.0 Hz, 1H), 2.42–2.30 (m, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 177.1, 143.9, 141.6, 128.4, 128.0, 127.9, 127.6, 127.0, 126.5, 66.8, 64.0, 57.7, 53.8, 47.6, 41.7; IR (neat): 2921, 2864, 2802, 1696, 1558, 1443, 1301, 1109, 909, 725, 696 cm$^{-1}$; HRMS (m/z) Calcd for (C$_{27}$H$_{27}$N$_2$O) ([M+H]$^+$): 337.1911; found: 337.1912.

To a 25 mL round-bottomed flask was added LiAlH$_4$ (38 mg, 1 mmol) followed by THF (5 mL) and the solution of 3aa' (66.8 mg, 0.2 mmol) in THF (5 mL) at room temperature. The resulting mixture was heated...
and refluxed overnight. The reaction was quenched with the addition of an aqueous solution of NaOH (0.2 M, 5 mL). The mixture was filtered through a pale of Celite. The solvent was removed under reduced pressure. Purification by column chromatography (5% MeOH in CH₂Cl₂) gave 5-(morpholinomethyl)-3,3-diphenylpyrrolidine 3aa as a colorless oil (56.8 mg, 88% yield); R₂ = 0.13 (5% MeOH in CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ 7.35–7.19 (m, 8H), 7.19–7.11 (m, 2H), 3.76–3.60 (m, 5H), 3.55–3.45 (m, 1H), 3.45 (d, J = 11.2 Hz, 1H), 2.80–2.70 (m, 2H), 2.54–2.28 (m, 6H), 2.05 (dd, J = 12.8, 8.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 147.2, 146.5, 128.4 (2C), 128.3 (2C), 127.0 (2C), 126.8 (2C), 126.1 (2C), 66.9, 65.0, 57.0, 56.1, 54.2, 54.0, 43.4; IR (neat): 2936, 2819, 1732, 1599, 1496, 1437, 1233, 1035, 759, 699 cm⁻¹; HRMS (m/z) Calcd for (C₁₇H₂₈N₂O) ([M+H⁺]): 323.2123; found: 323.2125.

VIII. Synthesis of (±)-FAUC-179

Follow the diamination procedure. Purification by column chromatography (50% EtOAc in hexanes then 50% EtOAc in hexanes containing 2% TEA) gave tert-butyl 4-((1'-benzyl-3'-methoxy-2'-oximidazolidin-4'-yl)methyl)piperazine-1-carboxylate 5 as a yellow oil (51.6 mg, 43% yield); R₂ = 0.45 (5% MeOH in CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ 7.34–7.18 (m, 5H), 4.40 (d, J = 14.8 Hz, 1H), 4.27 (d, J = 14.8 Hz, 1H), 3.82 (s, 3H), 3.65–3.55 (m, 1H), 3.40–3.25 (m, 4H), 3.22 (t, J = 8.4 Hz, 1H), 2.86 (t, J = 9.2 Hz, 1H), 2.71 (dd, J = 13.2, 4.8 Hz, 1H), 2.46 (dd, J = 13.2, 8.4 Hz, 1H), 2.40–2.25 (m, 4H), 1.41 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 162.5, 154.6, 135.9, 128.7, 128.1, 127.7, 79.6, 64.5, 60.1, 56.8, 53.5, 47.7, 45.5, 28.3; IR (neat): 2973, 2958, 2835, 2807, 1734, 1445, 1374, 1245, 1115, 909, 726, 698 cm⁻¹; HRMS (m/z) Calcd for (C₁₉H₂₃N₃O₄) ([M+H⁺]): 405.2496; found: 405.2496.

To a round-bottomed flask was charged with 5 (80.8 mg, 0.2 mmol) followed by the addition of HCl (2 M in EtOH, 10 mL). The resulting mixture was stirred at room temperature for 1 h and then was added an aqueous solution of NaOH (2 M, 10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic solvent was dried over Na₂SO₄ and filtered off. The solvent was removed under reduced pressure and the residue was used for the next step. To the crude mixture, were added PhBr (47.1 mg, 0.3 mmol), NaO'Bu (28.8 mg, 0.3 mmol), Pd(OAc)₂ (0.9 mg, 0.004 mmol), JohnPhos (2.4 mg, 0.008 mmol) and toluene (2 mL). The resulting mixture was stirred at 110 °C for 10 h under nitrogen atmosphere. Then the reaction mixture was cooled down to room temperature and filtered through a pale of Celite. The filtrate was concentrated under reduced pressure. Purification by column chromatography (50% EtOAc in hexanes then 100% EtOAc) gave 1-benzyl-3-methoxy-4-(4'-phenylpiperazin-1'-yl)methylimidazolidin-2-one 6 as a yellow oil (66.7 mg, 88% yield); R₂ = 0.43 (5% MeOH in CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ 7.36–7.21 (m, 7H), 6.89 (d, J = 8.8 Hz, 2H), 6.84 (t, J = 7.6 Hz, 1H), 4.44 (d, J = 14.8 Hz, 1H), 4.30 (d, J = 14.8 Hz, 1H), 3.86 (s, 3H), 3.72–3.65 (m, 1H), 3.28 (t, J = 8.6 Hz, 1H), 3.19–3.06 (m, 4H), 2.91 (t, J = 9.2 Hz, 1H), 2.79 (dd, J = 12.4, 14.8 Hz, 1H), 2.67–2.49 (m, 5H); ¹³C NMR (100 MHz, CDCl₃): δ 162.6, 151.1, 136.0, 129.1, 128.7, 128.2, 127.7, 116.0, 64.5, 60.2, 57.0, 53.8, 49.0, 47.8, 45.7; IR (neat): 2936, 2819, 1732, 1599, 1496, 1437, 1323, 1035, 759, 699 cm⁻¹; HRMS (m/z) Calcd for (C₂₉H₂₉N₂O₂) ([M+H⁺]): 381.2285; found: 381.2287.

S16
Spectroscopic data was identical to that reported previously. \( \delta = 7.89 (d, J = 8.4 \text{ Hz}, 2H), 7.80 (t, J = 7.6 \text{ Hz}, 1H), 7.66 (t, J = 8.0 \text{ Hz}, 2H), 7.24 (t, J = 8.0 \text{ Hz}, 2H), 6.98 (d, J = 8.4 \text{ Hz}, 2H), 6.85 (t, J = 7.2 \text{ Hz}, 1H), 4.77-4.65 (m, 1H), 4.21 (t, J = 11.6 \text{ Hz}, 1H), 3.90 (dd, J = 11.6, 7.6 \text{ Hz}, 1H), 3.28-3.18 (m, 4H), 2.94-2.67 (m, 6H). \) HRMS (m/z) Calcd for \((\text{C}_{21}\text{H}_{20}\text{N}_{4})\) ([M+H]+): 325.2387; found: 325.2386.

To a 25 mL round-bottomed flask was added 20% Pd(OH)$_2$/C (50 mg), diamine 7 (26 mg, 0.08 mmol) and MeOH (5 mL) under nitrogen. An atmosphere of hydrogen was introduced by briefly evacuating the flask, then flushing with pure hydrogen (1 atm, hydrogen balloon). The mixture was stirred at room temperature overnight under H$_2$ atmosphere. The hydrogen atmosphere was then removed under vacuum, and the flask was refilled with nitrogen. The mixture was filtered through a pale of Celite and the filtrate was concentrated under reduced pressure. To the crude mixture, was added MeOH (5 mL) and methylbenzimidate hydrochloride (20 mg, 0.12 mmol) at room temperature. The resulting mixture was heated and refluxed for 1 h. Then MeOH was removed under reduced pressure. To the residue, was added EtOAc (10 mL) and a saturated aqueous solution of Na$_2$CO$_3$ (10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (10 mL). The combined organic solvent was removed under reduced pressure. Purification by column chromatography (100% EtOAc containing 5% TEA) gave \((\pm)-\text{FAUC}-179\) as a white solid (13 mg, 51% yield). \(^1\)H NMR (400 MHz, CD$_2$OD): \( \delta = 7.89 (d, J = 7.6 \text{ Hz}, 2H), 7.80 (t, J = 7.6 \text{ Hz}, 1H), 7.66 (t, J = 8.0 \text{ Hz}, 2H), 7.24 (t, J = 8.0 \text{ Hz}, 2H), 6.98 (d, J = 8.4 \text{ Hz}, 2H), 6.85 (t, J = 7.2 \text{ Hz}, 1H), 4.77-4.65 (m, 1H), 4.21 (t, J = 11.6 \text{ Hz}, 1H), 3.90 (dd, J = 11.6, 7.6 \text{ Hz}, 1H), 3.28-3.18 (m, 4H), 2.94-2.67 (m, 6H). \) Spectroscopic data was identical to that reported previously.\(^5\)

**IX. References.**

X. NMR Spectra.