LEWIS ACID CATALYZED DIASTEREOSELECTIVE 1,3-DIPOLAR CYCLOADDITION BETWEEN DIAZOOACETOACETATE ENONES AND AZOMETHINE YLIDES

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Abstract – Silver acetate catalyzed 1,3-dipolar cycloaddition reactions of diazoacetoacetate enones and azomethine ylides produce tetrasubstituted pyrrolidines bearing a diazoacetoacetate functional array in excellent yields and diastereoselectivities. The installment of the diazoacetoacetate functional array allows access to diverse heterocyclic scaffolds.

INTRODUCTION
Diazooacetoacetate compounds have been widely utilized in organic synthesis for metal carbene reactions due to their selectivity and stability relative to other classes of diazo compounds.¹ Methodologies to construct highly functionalized diazoacetoacetates have provide advantages in subsequent transformations to produce valuable materials.² We have recently shown that diazoacetoacetate enones (DAAE) 1 are susceptible to a wide range of Lewis acid catalyzed nucleophilic conjugate addition reactions for the construction of complex diazoacetoacetates 2 (Scheme 1, eq. 1).² This strategy has allowed access to different carbo- and heterocycle scaffolds by simply changing the nucleophile for Michael addition prior to metal catalyzed dinitrogen extrusion. We have also envisioned that DAAE 1 could be the building block for dipolar cycloaddition with azomethine ylides to produce pyrrolidines 4 bearing the versatile diazoacetoacetate functionality (Scheme 1, eq. 2). Thus, depending on the substituent $R^2$ installed from the cycloaddition reactions, the subsequent metal catalyzed diazo decomposition would allow access to an array of diverse pyrrolidine-based polyheterocyclic compounds. Herein, we report diastereoselective 1,3-dipolar cycloaddition reactions of DAAE 1 with azomethine ylides³ generated in-situ from imines 3.
to construct highly functionalized pyrrolidines 4, an important structural motif in natural products and pharmaceuticals4 (Scheme 1, eq. 2). In addition, metal catalyzed dinitrogen extrusion reactions of 4 give access to different pyrrolidine frameworks by simply changing the R² substituent of imine 3.

\[
\text{Scheme 1. Reactions of diazoacetoacetate enones}
\]

RESULTS AND DISCUSSION

Our investigation began with the reaction of DAAE 1a and imine 3a in the presence of a variety of Lewis acids (Table 1). Although Zn(OTf)₂,5 Cu(OTf)₂,6 and AgOTf7 have been previously employed as catalysts in 1,3-dipolar cycloaddition reactions between azomethine ylides and electron deficient alkenes, these Lewis acids were not able to catalyze the reaction between 1a and 3a (Table 1, entry 1-3); and 1a did not undergo dinitrogen extrusion. However, use of 10 mol % of Ag(CF₃COO) or Ag(OAc) in DCM gave cycloadduct 4a in moderate yield with complete endo-selectivity (entries 4-5). To improve the yield, a variety of solvents were screened, and diethyl ether gave complete conversion of the starting material to 4a in 96% yield (entries 6-9). Catalyst loading could also be lowered to 2 mol % and essentially provide the same yield (entry 10). The stereochemistry of 4a was obtained by spectral analysis and confirmed by X-ray crystallography of the tosylamide of 4a (Figure 1); note that the substituent on position 2 is cis to the acetoacetate functional array whereas the one on position 3 is trans.
Table 1. Catalyst screening and reaction optimization

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol%)</th>
<th>Solvent</th>
<th>d.r. (endo/exo)</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Zn(OTf)₂ (10)</td>
<td>DCM</td>
<td>-</td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>Cu(OTf)₂ (10)</td>
<td>DCM</td>
<td>-</td>
<td>NR</td>
</tr>
<tr>
<td>3</td>
<td>AgOTf (10)</td>
<td>DCM</td>
<td>-</td>
<td>NR</td>
</tr>
<tr>
<td>4</td>
<td>AgCF₃COO (10)</td>
<td>DCM</td>
<td>&gt;20:1</td>
<td>55</td>
</tr>
<tr>
<td>5</td>
<td>AgOAc (10)</td>
<td>DCM</td>
<td>&gt;20:1</td>
<td>66</td>
</tr>
<tr>
<td>6</td>
<td>AgOAc (10)</td>
<td>THF</td>
<td>&gt;20:1</td>
<td>89</td>
</tr>
<tr>
<td>7</td>
<td>AgOAc (10)</td>
<td>1,4-dioxane</td>
<td>&gt;20:1</td>
<td>88</td>
</tr>
<tr>
<td>8</td>
<td>AgOAc (10)</td>
<td>toluene</td>
<td>&gt;20:1</td>
<td>86</td>
</tr>
<tr>
<td>9</td>
<td>AgOAc (10)</td>
<td>Et₂O</td>
<td>&gt;20:1</td>
<td>96</td>
</tr>
<tr>
<td>10</td>
<td>AgOAc (2)</td>
<td>Et₂O</td>
<td>&gt;20:1</td>
<td>94</td>
</tr>
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</table>

a The catalyst was added to a solution containing 1a (69 mg, 0.30 mmol) and 3a (58 mg, 0.33 mmol) in 2.0 mL of solvent and stirred at room temperature for 24 h. b Determined by the ¹H NMR spectrum of the reaction mixture prior to work up. c Isolated yield after column chromatography.

Figure 1. ORTEP view of the tosylamide of 4a showing product stereochemistry. Ellipsoids are shown at 30% probability (CCDC 947991).

The ability to install various substituent classes into a molecule is one of the key elements of the overall DAAE strategy because the product outcome from diazo decomposition is solely dependent on the substituent that is installed cis to the diazoacetoacetate. The generality of the cycloaddition between various DAAEs 1 (variation of R¹) and azomethine ylides 3 (variation of R²) was evaluated under the optimized conditions determined from Table 1, and these results are reported in Table 2. The reactions provided excellent yields and diastereoselectivities with aryl groups for R¹ having both electron-donating
and electron-withdrawing substituents (Table 2, entries 1-4). Variation of R² was also general allowing for aryl, fural, styryl, and alkyl substitutions (entries 5-10). Each reaction exhibits a >20:1 diastereoselectivity except when R² is cyclohexyl (d.r. = 10:1). The products of these reactions are designed to allow subsequent metal carbene-induced intramolecular reactions such as aromatic substitution and cyclopropanation.¹a

Table 2. Reaction scope

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>R¹</th>
<th>R²</th>
<th>d.r. (endo:exo)</th>
<th>Yield (%)</th>
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<tr>
<td>1</td>
<td>4a</td>
<td>C₆H₅</td>
<td>C₆H₅</td>
<td>&gt;20:1</td>
<td>94</td>
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<tr>
<td>2</td>
<td>4b</td>
<td>2-ClC₆H₄</td>
<td>C₆H₅</td>
<td>&gt;20:1</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>4c</td>
<td>4-FC₆H₄</td>
<td>C₆H₅</td>
<td>&gt;20:1</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>4d</td>
<td>4-OMeC₆H₄</td>
<td>C₆H₅</td>
<td>&gt;20:1</td>
<td>86</td>
</tr>
<tr>
<td>5</td>
<td>4e</td>
<td>C₆H₅</td>
<td>2-fural</td>
<td>&gt;20:1</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>4f</td>
<td>C₆H₅</td>
<td>styryl</td>
<td>&gt;20:1</td>
<td>79</td>
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<tr>
<td>7</td>
<td>4g</td>
<td>C₆H₅</td>
<td>cyclohexyl</td>
<td>10:1</td>
<td>82</td>
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<tr>
<td>8</td>
<td>4h</td>
<td>C₆H₅</td>
<td>4-OMeC₆H₄</td>
<td>&gt;20:1</td>
<td>93</td>
</tr>
<tr>
<td>9</td>
<td>4i</td>
<td>C₆H₅</td>
<td>4-CF₃C₆H₄</td>
<td>&gt;20:1</td>
<td>91</td>
</tr>
<tr>
<td>10</td>
<td>4j</td>
<td>C₆H₅</td>
<td>4-ClC₆H₄</td>
<td>&gt;20:1</td>
<td>90</td>
</tr>
</tbody>
</table>

¹a AgOAc (2 mol %) was added to a solution containing 1 (0.30 mmol) and 3 (0.33 mmol) in 2.0 mL of diethyl ether and stirred at room temperature for 24 h. b Determined by ¹H NMR of the reaction mixture prior to work up. c Isolated yield after column chromatography.

Representative substrates were treated with rhodium acetate, a common catalyst for reactions of diazoacetoacetates,¹a to evaluate 4 for metal carbene reactions. However, treatment of 4a in dichloromethane at reflux with Rh₂(OAc)₄ for 24 hours did not produce the expected aromatic cycloaddition product,¹a but instead left starting material unreacted, presumably due to sequestration of the Rh-catalyst by an irreversible Lewis acid-base interaction of the basic pyrrolidine nitrogen. When the temperature was increased to 100 °C in toluene, decomposition of 4a gave a complex mixture of products. Sensing that N-H insertion might be one of the competing reactions, the secondary amine was converted to a tertiary amine by the action of iodomethane (Scheme 2). N-Methylpyrrolidines 5a and 5b were produced in 81% and 75% yields, respectively.

Scheme 2. Methylation of pyrrolidines
The Rh$_2$(OAc)$_4$ catalyzed diazo decomposition of 5b (R$^2$ = styryl) gave the fused-azatricyclic cyclopropane 6 in 66% yield as a single diastereomer (Scheme 3). N-Methylpyrrolidines 5a (R$^2$ = phenyl) underwent a Buchner reaction$^8$ catalyzed by Rh$_2$(OAc)$_4$ to afford the azatricyclic cycloheptatriene 7 in excellent yield (Scheme 3). Compound 7 was isomerized with TFA to the corresponding tetralone 8, then aromatization of intermediate 8 with 10% Pd/C provided the benzoindole 9 in 73% yield (Scheme 3). Surprisingly, aromatization of 8 occurred with deoxygenation, but such transformations have been previously observed.$^{10b}$ These results show that the fate of the diazo decomposition product of 5 depends solely on the R$^2$ substituent of the azomethine imines 3.

Scheme 3. Further elaboration of the pyrrolidines 4

In conclusion, we have developed a diastereoselective 1,3-dipolar cycloaddition of DAAEs 1 with azomethine ylides for the production of tetrasubstituted pyrrolidines bearing the versatile diazoacetoacetate functionality. Furthermore, we have demonstrated that the outcome of the subsequent metal catalyzed dinitrogen extrusion is controlled by installing the desired reactive functional group via the readily available $\alpha$-imino esters. The R$^2$-substituent includes aryl, furyl, styryl, and an alkyl substituent which allow the construction of functionalized heterocycles by pairing the reactivity of these substituents to the impending metal carbene transformations. The advantage of this strategy is the ability to generate variety of different structural frameworks based on one general reaction with DAAE building blocks.

EXPERIMENTAL

General. Dichloromethane (DCM) was distilled over calcium hydride prior to use. Thin layer chromatography (TLC) was carried out using EM Science silica gel 60 F254 plates. Metal triflate salts were purchased from Aldrich and used as received. $^1$H NMR and $^{13}$C NMR spectra were recorded in
CDCl3 on a Bruker Advance 400 MHz spectrometer. Chemical shifts are reported in ppm with the residual CHCl3 or the TMS signal as the reference, and coupling constants (J) are given in Hertz. IR spectra were recorded (neat) on a Thermo Nicolet IR200 spectrometer. Melting points were obtained on a Electro-Thermo Mel-Temp DLX 104. High-resolution mass spectra (HRMS) were performed on a JEOL AccuTOF-ESI mass spectrometer using CsI as the standard.

**Starting Materials.** Diazaacetocetate enones (DAAEs) 1a-1d2a and α-imino esters 3a-3f11a and 3g11b were prepared according to the literature procedures.

**General Procedure for the Synthesis of Pyrrolidines 4a-4j.** Silver acetate (1.0 mg, 2.0 mol%) was added to a solution containing 1 (0.30 mmol) and 3 (0.33 mmol) in 2.0 mL of Et2O. The reaction solution was stirred for 24 h at room temperature, concentrated, and the residue was purified by flash chromatography (SiO2) with hexanes and EtOAc as the eluents to provide pyrrolidines 4. Diazoo carbon was not detected in the 13C NMR unless stated otherwise.

**Methyl 4-(2-Diazo-3-methoxy-3-oxopropanoyl)-3,5-diphenylpyrrolidine-2-carboxylate (4a).** The reaction between DAAE 1a and α-imino ester 3a gave 4a as a single isomer in 94% yield; Colorless liquid; TLC Rf = 0.3 (2:1 hexanes/EtOAc); 1H NMR (400 MHz, CDCl3) δ 7.36 – 7.20 (comp, 10H), 4.99 (d, J = 9.2 Hz, 1H), 4.65 (dd, J = 9.2, 8.0 Hz, 1H), 4.14 – 4.01 (comp, 2H), 3.71 – 3.68 (comp, 6H), 2.79 (br, 1H); 13C NMR (100 MHz, CDCl3) δ 190.5, 172.9, 161.2, 140.2, 138.9, 128.6, 128.0, 127.8, 127.7, 127.4, 127.0, 67.5, 65.6, 61.3, 52.1, 51.9, 51.9; IR (neat) 2137, 1714, 1648 cm−1; HRMS (ESI) m/z calculated for C22H21N3O5 [M+H]+ 408.1559, found: 408.1556.

**Methyl 3-(2-Chlorophenyl)-4-(2-diazo-3-methoxy-3-oxopropanoyl)-5-phenylpyrrolidine-2-carboxylate (4b).** The reaction between DAAE 1b and α-imino ester 3a gave 4b as a single isomer in 91% yield: Yellow solid, mp 93–95 °C; TLC Rf = 0.3 (2:1 hexanes/EtOAc); 1H NMR (400 MHz, CDCl3) δ 7.46 (dd, J = 7.8, 1.5 Hz, 1H), 7.38 (dd, J = 7.9, 1.3 Hz, 1H), 7.34 – 7.24 (comp, 6H), 7.24-7.16 (m, 1H), 4.96 (d, J = 8.7 Hz, 1H), 4.72 (dd, J = 8.7, 7.0 Hz, 1H), 4.63 – 4.56 (m, 1H), 4.09 (d, J = 8.4 Hz, 1H), 3.74 (s, 3H), 3.67 (s, 3H), 3.02 (br, 1H); 13C NMR (100 MHz, CDCl3) δ 190.5, 172.9, 161.2, 138.2, 138.0, 134.4, 130.0, 128.5, 128.2, 128.1, 128.0, 127.4, 127.3, 66.5, 66.0, 60.1, 52.4, 51.9, 49.0; IR (neat) 2142, 1735, 1718, 1637 cm−1; HRMS (ESI) m/z calculated for C22H21ClN3O5 [M+H]+ 442.1170, found: 442.1174.

**Methyl 4-(2-Diazo-3-methoxy-3-oxopropanoyl)-3-(4-fluorophenyl)-5-phenylpyrrolidine-2-carboxylate (4c).** The reaction between DAAE 1c and α-imino ester 3a gave 4c as a single isomer in 92% yield: Colorless liquid; TLC Rf = 0.3 (2:1 hexanes/EtOAc); 1H NMR (400 MHz, CDCl3) δ 7.35 – 7.21 (comp, 7H), 4.99 (d, J = 9.3 Hz, 1H), 4.62 – 4.55 (m, 1H), 4.10 (t, J = 9.0 Hz, 1H), 4.00 (d, J = 9.5 Hz, 1H), 3.71 (s, 3H), 3.70 (s, 3H), 2.86 (br, 1H); 13C NMR (100 MHz, CDCl3) δ 190.2, 172.8, 161.8 (d, J = 245.4 Hz), 161.2, 139.0, 135.8 (d, J = 3.2 Hz), 129.3 (d, J = 8.0 Hz), 128.1, 127.9, 127.5, 115.5 (d, J = 21.3 Hz), 67.4, 65.3, 61.4, 52.1, 52.0, 50.9; IR (neat) 2138, 1717, 1648 cm−1; HRMS (ESI)
**Methyl 4-(2-Diazo-3-methoxy-3-oxopropanoyl)-3-(4-methoxyphenyl)-5-phenylpyrrolidine-2-carboxylate (4d).** The reaction between DAAE 1d and α-imino ester 3a gave 4d as a single isomer in 86% yield: Light green liquid; TLC Rf = 0.25 (2:1 hexanes/EtOAc); 1H NMR (400 MHz, CDCl3) δ 7.32 – 7.27 (comp, 4H), 7.27 – 7.21 (comp, 3H), 6.88 – 6.83 (comp, 2H), 4.97 (d, J = 9.3 Hz, 1H), 4.60 (dd, J = 8.2 Hz, 1H), 4.09 – 3.97 (comp, 2H), 3.78 (s, 3H), 3.71 (s, 3H), 3.71 (s, 3H), 2.87 (br, 1H); 13C NMR (100 MHz, CDCl3) δ 190.5, 173.1, 161.3, 158.6, 139.2, 132.2, 128.8, 128.1, 127.9, 127.5, 114.1, 67.6, 65.5, 61.5, 55.2, 52.6, 52.0, 51.3; IR (neat) 2141, 1715, 1648 cm -1; HRMS (ESI) m/z calculated for C22H21FN3O5 [M+H]+ 426.1465, found: 426.1466.

**Methyl 4-(2-Diazo-3-methoxy-3-oxopropanoyl)-3-(4-methoxyphenyl)-5-phenylpyrrolidine-2-carboxylate (4e).** The reaction between DAAE 1a and α-imino ester 3b gave 4e as a single isomer in 90% yield: Yellow liquid; TLC Rf = 0.2 (2:1 hexanes/EtOAc); 1H NMR (400 MHz, CDCl3) δ 7.34 – 7.29 (comp, 5H), 7.25 – 7.20 (m, 1H), 6.33 – 6.28 (comp, 2H), 5.06 (d, J = 8.7 Hz, 1H), 4.59 – 4.52 (m, 1H), 4.09 (t, J = 9.4 Hz, 1H), 3.99 (d, J = 9.4 Hz, 1H), 3.78 (s, 3H), 3.68 (s, 3H), 3.01 (br, 1H); 13C NMR (100 MHz, CDCl3) δ 188.9, 173.1, 161.4, 152.6, 142.2, 139.8, 128.6, 127.8, 127.1, 110.3, 107.9, 67.0, 60.4, 58.8, 52.2, 52.1, 50.7; IR (neat) 2139, 1717, 1650 cm -1; HRMS (ESI) m/z calculated for C20H20N3O6 [M+H]+ 398.1352, found: 398.1355.

**Methyl 4-(2-Diazo-3-methoxy-3-oxopropanoyl)-3-phenyl-5-((E)-styryl)pyrrolidine-2-carboxylate (4f).** The reaction between DAAE 1a and α-imino ester 3c gave 4f as a single isomer in 79% yield: Yellow liquid; TLC Rf = 0.2 (2:1 hexanes/EtOAc); 1H NMR (400 MHz, CDCl3) δ 7.35 – 7.21 (comp, 10H), 6.55 (d, J = 15.6 Hz, 1H), 6.11 (dd, J = 15.6, 8.3 Hz, 1H), 4.59 – 4.49 (comp, 2H), 4.05 – 3.99 (m, 1H), 3.86 (d, J = 7.3 Hz, 1H), 3.71 (s, 3H), 3.71 (s, 3H), 3.54 (dd, J = 7.2, 4.3 Hz, 1H), 3.32 (dd, J = 8.9, 6.7 Hz, 1H), 2.78 (br, 1H), 2.07 (d, J = 12.9 Hz, 1H), 1.84 – 1.48 (m, 5H), 1.33 – 1.02 (m, 5H); 13C NMR (100 MHz, CDCl3) δ 190.1, 173.4, 161.3, 140.1, 136.4, 132.8, 128.7, 128.5, 127.8, 127.8, 127.1, 126.8, 126.6, 67.4, 63.5, 60.4, 52.2, 52.1, 51.7; IR (neat) 2140, 1718, 1647 cm -1; HRMS (ESI) m/z calculated for C24H24N3O5 [M+H]+ 434.1716, found: 434.1718.

**Methyl 5-Cyclohexyl-4-(2-diazo-3-methoxy-3-oxopropanoyl)-3-phenylpyrrolidine-2-carboxylate (4g).** The reaction between DAAE 1a and α-imino ester 3d gave 4g as a mixture of inseparable diastereomers (10:1) in 82% yield: White solid, mp 100–102 °C; TLC Rf = 0.3 (2:1 hexanes/EtOAc); 1H NMR (400 MHz, CDCl3) δ 7.36 – 7.29 (comp, 2H), 7.28 – 7.21 (comp, 3H), 4.50 (dd, J = 6.5, 4.4 Hz, 1H), 3.86 (d, J = 7.3 Hz, 1H), 3.71 (s, 3H), 3.71 (s, 3H), 3.54 (dd, J = 7.2, 4.3 Hz, 1H), 3.32 (dd, J = 8.9, 6.7 Hz, 1H), 2.78 (br, 1H), 2.07 (d, J = 12.9 Hz, 1H), 1.84 – 1.48 (m, 5H), 1.33 – 1.02 (m, 5H); 13C NMR (100 MHz, CDCl3) δ 193.9, 172.7, 161.1, 141.9, 128.6, 127.2, 126.9, 70.7, 68.9, 56.3, 56.0, 52.2, 52.1, 53.8, 31.6, 31.1, 26.2, 26.0, 25.7; IR (neat) 2144, 1727, 1700, 1650 cm -1; HRMS (ESI) m/z calculated for C22H28N3O5 [M+H]+ 414.2029, found: 414.2025.
Methyl 4-(2-Diazo-3-methoxy-3-oxopropanoyl)-5-(4-methoxyphenyl)-3-phenylpyrrolidine-2-carboxylate (4h). The reaction between DAAE 1a and α-imino ester 3e gave 4h as a single isomer in 93% yield: Colorless liquid; TLC R_f = 0.1 (2:1 hexanes/EtOAc); 1H NMR (400 MHz, CDCl_3) δ 7.36 – 7.28 (comp, 4H), 7.23 (d, J = 8.8 Hz, 3H), 6.82 (d, J = 8.8 Hz, 2H), 4.96 (d, J = 9.3 Hz, 1H), 4.60 (dd, J = 9.1, 8.4 Hz, 1H), 4.13 – 4.05 (m, 1H), 4.02 (d, J = 9.3 Hz, 1H), 3.78 (s, 3H), 3.71 (s, 3H), 3.69 (s, 3H), 2.80 (br, 1H); 13C NMR (100 MHz, CDCl_3) δ 190.6, 173.0, 161.2, 159.0, 140.3, 131.1, 128.7, 128.6, 127.8, 127.0, 113.4, 67.4, 65.1, 61.4, 55.2, 52.1, 51.9; IR (neat) 2138, 1717, 1649 cm^{-1}; HRMS (ESI) m/z calculated for C_{23}H_{24}N_3O_6 [M+H]^+ 438.1665, found: 438.1669.

Methyl 4-(2-Diazo-3-methoxy-3-oxopropanoyl)-3-phenyl-5-(4-(trifluoromethyl)phenyl)pyrrolidine-2-carboxylate (4i). The reaction between DAAE 1a and α-imino ester 3f gave 4i as a single isomer in 91% yield: Colorless liquid; TLC R_f = 0.25 (2:1 hexanes/EtOAc); 1H NMR (400 MHz, CDCl_3) δ 7.55 (d, J = 8.3 Hz, 2H), 7.47 (d, J = 8.3 Hz, 2H), 7.36 – 7.31 (comp, 4H), 7.28 – 7.21 (m, 1H), 5.07 (d, J = 9.0 Hz, 1H), 4.68 (dd, J = 9.0, 7.9 Hz, 1H), 4.15 – 4.06 (comp, 2H), 3.73 (s, 3H), 3.70 (s, 3H), 2.90 (br, 1H); 13C NMR (100 MHz, CDCl_3) δ 189.9, 172.8, 161.2, 143.7, 139.8, 129.9 (q, J = 32.4 Hz), 128.7, 128.0, 127.7, 127.1, 124.9 (q, J = 3.7 Hz), 67.3, 64.6, 60.8, 52.1, 52.0, 51.4; IR (neat) 2141, 1716, 1650 cm^{-1}; HRMS (ESI) m/z calculated for C_{23}H_{21}F_3N_3O_5 [M+H]^+ 476.1433, found: 476.1430.

Methyl 5-(4-Chlorophenyl)-4-(2-diazo-3-methoxy-3-oxopropanoyl)-3-phenylpyrrolidine-2-carboxylate (4j). The reaction between DAAE 1a and α-imino ester 3g gave 4j as a single isomer in 90% yield: Colorless liquid; TLC R_f = 0.25 (2:1 hexanes/EtOAc); 1H NMR (400 MHz, CDCl_3) δ 7.32 (d, J = 4.3 Hz, 4H), 7.29 – 7.20 (comp, 5H), 4.99 (d, J = 9.1 Hz, 1H), 4.62 (dd, J = 9.1, 8.1 Hz, 1H), 4.13 – 4.02 (comp, 2H), 3.73 (s, 3H), 3.70 (s, 3H), 2.84 (br, 1H); 13C NMR (100 MHz, CDCl_3) δ 190.1, 172.9, 161.2, 139.9, 137.9, 133.5, 129.0, 128.7, 128.2, 127.8, 127.1, 67.3, 64.6, 60.8, 52.1, 52.0, 51.6; IR (neat) 2139, 1717, 1650 cm^{-1}; HRMS (ESI) m/z calculated for C_{23}H_{21}ClN_3O_5 [M+H]^+ 442.1170, found: 442.1173.

General Procedure for the Synthesis of N-Methylpyrrolidines 5a and 5b. A solution of 4 (0.50 mmol) DMF (2 mL) was added K_2CO_3 (207 mg, 1.5 mmol), followed by MeI (62 µL, 1.0 mmol) at room temperature. The mixture was stirred for 4 h and then Et_2O (25 mL) was added. The mixture was washed with H_2O (25 mL), and the aqueous phase was extracted with Et_2O 20 (mL). The organic phases were combined, dried, and filtered. The solution was concentrated, and the residue was purified by flash chromatography (SiO_2) with hexanes and EtOAc as the eluent to provide pyrrolidines 5.

Methyl 4-(2-Diazo-3-methoxy-3-oxopropanoyl)-1-methyl-3,5-diphenylpyrrolidine-2-carboxylate (5a). White solid; TLC R_f = 0.3 (4:1 hexanes/EtOAc); 1H NMR (400 MHz, CDCl_3) δ 7.38 – 7.18 (comp, 10H), 4.60 – 4.51 (m, 1H), 4.43 (t, J = 9.9 Hz, 1H), 4.19 (d, J = 10.5 Hz, 1H), 3.71 (s, 3H), 3.68 (s, 3H), 3.46 (d, J = 10.2 Hz, 1H), 2.25 (s, 3H); 13C NMR (100 MHz, CDCl_3) δ 189.5, 172.2, 161.4, 139.5, 138.9, 128.8, 128.6, 128.1, 127.8, 127.8, 127.1, 74.5, 72.3, 58.8, 51.9, 51.9, 48.6, 39.1; IR (neat) 2141, 1748,
1711, 1656 cm\(^{-1}\); HRMS (ESI) \(m/z\) calculated for C\(_{23}H_{24}N_3O_5\) [M+H]\(^+\) 422.1716, found: 422.1715.

Methyl 4-(2-Diazo-3-methoxy-3-oxopropanoyl)-1-methyl-3-phenyl-5-((E)-styryl)pyrrolidine-2-carboxylate (5b). Yellow solid; TLC \(R_f\) = 0.3 (4:1 hexanes/EtOAc); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.36 – 7.31 (comp, 3H), 7.31 – 7.27 (comp, 6H), 7.25 – 7.19 (comp, 2H), 6.52 (d, \(J = 15.7\) Hz, 1H), 6.06 (dd, \(J = 15.7, 9.2\) Hz, 1H), 4.48 (t, \(J = 9.9\) Hz, 1H), 4.32 (t, \(J = 9.9\) Hz, 1H), 3.75 – 3.69 (m, 1H), 3.67 (s, 3H), 3.66 (s, 3H), 3.38 (d, \(J = 10.2\) Hz, 1H), 2.37 (s, 2H); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 189.5, 172.0, 161.4, 139.2, 136.3, 133.6, 128.6, 128.53, 128.0, 127.7, 127.3, 127.1, 126.4, 74.7, 70.4, 57.5, 52.0, 51.8, 48.9, 39.0; IR (neat) 2138, 1718, 1650 cm\(^{-1}\); HRMS (ESI) \(m/z\) calculated for C\(_{25}H_{26}N_3O_5\) [M+H]\(^+\) 448.1872, found: 448.1870.

Dimethyl 1-Methyl-4-oxo-3,5-diphenyloctahydro-1\(H\)-cyclopropa[4,5]cyclopenta[1,2-b]pyrrole-2,4a-dicarboxylate (6). \(\text{Rh}_2(\text{OAc})_4\) (1.3 mg, 0.003 mmol) was added to a solution containing 5b (134 mg, 0.30 mmol) in DCM (2.0 mL). The reaction was refluxed for 4 h, concentrated, and the residue was purified by flash chromatography (SiO\(_2\)) with hexanes and EtOAc as the eluent to provide 6 (83 mg, 66% yield).

Light green solid: mp 171–172 °C; TLC \(R_f\) = 0.25 (2:1 hexanes/EtOAc); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.36 – 7.19 (comp, 10H), 3.69 (dd, \(J = 8.8, 4.7\) Hz, 1H), 3.66 (s, 3H), 3.50 (d, \(J = 6.5\) Hz, 1H), 3.45 (s, 3H), 3.38 (d, \(J = 5.8\) Hz, 1H), 3.36 (d, \(J = 8.8\) Hz, 1H), 2.90 (d, \(J = 5.8\) Hz, 1H), 2.84 (dd, \(J = 6.5, 4.7\) Hz, 1H), 2.60 (s, 3H); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 204.1, 171.4, 164.8, 141.5, 132.7, 128.7, 128.6, 128.3, 127.9, 127.6, 127.0, 76.3, 67.2, 56.3, 52.1, 52.0, 50.0, 46.0, 39.0, 38.8, 34.9; IR (neat) 1728, 1710 cm\(^{-1}\); HRMS (ESI) \(m/z\) calculated for C\(_{25}H_{26}NO_5\) [M+H]\(^+\) 420.1811, found: 420.1814.

Dimethyl 1-Methyl-4-oxo-3-phenyl-2,3,3a,4,4a,9b-hexahydro-1\(H\)-azuleno[1,2-b]pyrrole-2,4a-dicarboxylate (7). \(\text{Rh}_2(\text{OAc})_4\) (1.3 mg, 0.003 mmol) was added to a solution containing 5a (126 mg, 0.30 mmol) in DCM (2.0 mL). The reaction was refluxed for 4 h, concentrated, and the residue was purified by flash chromatography (SiO\(_2\)) with hexanes and EtOAc as the eluent to provide 6 (109 mg, 93% yield).

1H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.36 – 7.29 (comp, 2H), 7.28-7.22 (comp, 3H), 6.55 – 6.47 (comp, 2H), 6.47 – 6.38 (m, 1H), 6.29 (dd, \(J = 9.9, 6.3\) Hz, 1H), 5.36 (d, \(J = 9.9\) Hz, 1H), 3.83 (dd, \(J = 7.1, 2.2\) Hz, 1H), 3.79 (d, \(J = 4.9\) Hz, 1H), 3.67 (s, 3H), 3.63 (s, 3H), 3.36 (d, \(J = 7.1\) Hz, 1H), 2.89 (dd, \(J = 4.8, 2.3\) Hz, 1H), 2.50 (s, 3H); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 209.1, 171.4, 164.8, 141.5, 132.7, 128.7, 128.6, 128.3, 127.9, 127.6, 127.0, 76.3, 67.2, 56.3, 52.1, 52.0, 50.0, 46.0, 39.0, 38.8, 34.9; IR (neat) 2953, 1734 cm\(^{-1}\); HRMS (ESI) \(m/z\) calculated for C\(_{23}H_{24}NO_5\) [M+H]\(^+\) 394.1654, found: 394.1651.

Dimethyl 1-Methyl-3-phenyl-1\(H\)-benzo[gl]indole-2,5-dicarboxylate (9). Trifluoroacetic acid (7.6 µL, 0.10 mmol) was added to a solution of 6 (39 mg, 0.10 mmol) in DCM (1 mL) at room temperature. The reaction was stirred for 10 min and concentrated. The residue was dissolved in toluene (2 mL), then added Pd/C (10 %) (200 mg) and refluxed for 16 h. The reaction was filtered through a short celite plug, concentrate, and the residue was purified by flash chromatography (SiO\(_2\)) with hexanes and EtOAc as the eluent to provide 9 (27 mg, 73% yield). Green solid; TLC \(R_f\) = 0.3 (4:1 hexanes/EtOAc); \(^1\)H NMR (400
MHz, CDCl$_3$) $\delta$ 8.18 (s, 1H), 8.00 (dd, $J = 8.8, 0.9$ Hz, 1H), 7.90 – 7.85 (m, 1H), 7.54 – 7.46 (comp, 5H), 7.46 – 7.41 (m, 1H), 7.38 – 7.32 (m, 1H), 4.15 (s, 3H), 4.01 (s, 3H), 3.74 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 169.5, 162.7, 135.3, 133.6, 130.2, 130.0, 129.2, 128.9, 128.8, 128.3, 128.1, 127.3, 126.6, 123.7, 123.3, 122.9, 111.3, 52.5, 51.8, 33.9; IR (neat) 2949, 1705 cm$^{-1}$; HRMS (ESI) m/z calculated for C$_{23}$H$_{20}$NO$_4$ [M+H]$^+$ 374.1392, found: 374.1395.

**Scheme 4.** X-Ray crystal for structural proof

**Methyl 4-(2-Diazo-3-methoxy-3-oxopropanoyl)-3,5-diphenyl-1-tosylpyrrolidine-2-carboxylate (10).**

Triethylamine (0.140 mL, 1.0 mmol), tosyl chloride (143 mg, 0.75 mmol) were added to a solution containing 4a (203 mg, 0.5 mmol) in DCM (2 mL), and refluxed for 36 h. The product was purified by flash chromatography (SiO$_2$) with hexanes and EtOAc as the eluent to provide 10 (258 mg, 92% yield).

Colorless solid; TLC $R_f = 0.25$ (3:1 hexanes/EtOAc); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.73-7.64 (comp, 2H), 7.43 – 7.38 (comp, 2H), 7.26 – 7.24 (m, 1H), 7.24 – 7.17 (comp, 9H), 7.12 (comp, 2H), 5.70 (d, $J = 9.2$ Hz, 1H), 4.40 – 4.33 (m, 2H), 4.32 – 4.24 (m, 1H), 3.87 (s, 3H), 3.70 (s, 3H), 2.39 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 185.7, 171.6, 161.1, 143.8, 138.0, 136.0, 134.4, 129.3, 128.7, 128.1, 127.8, 127.7, 127.4, 67.1, 64.1, 58.7, 52.4, 52.3, 48.7, 21.5; IR (neat) 2141, 1746, 1726, 1650 cm$^{-1}$; HRMS (ESI) m/z calculated for C$_{29}$H$_{27}$N$_3$O$_7$S [M+H]$^+$ 562.1648, found: 562.1649.

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