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

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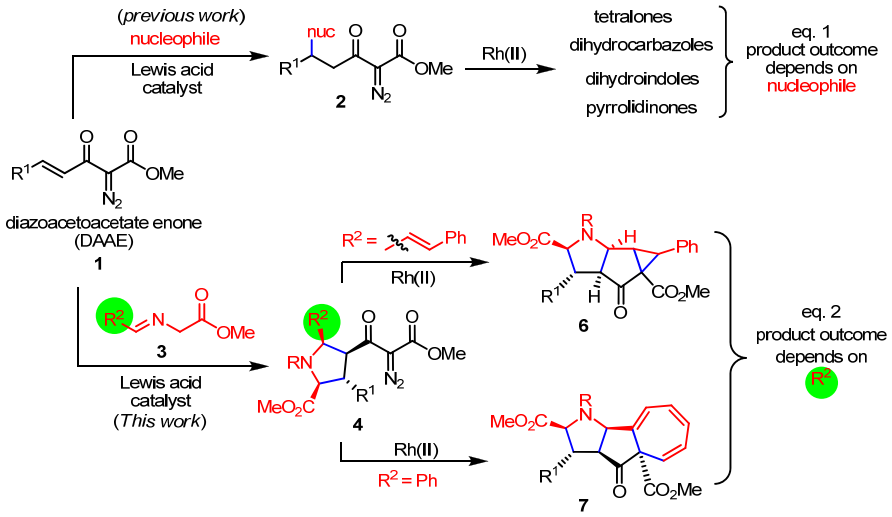
Abstract – Silver acetate catalyzed 1,3-dipolar cycloaddition reactions of diazoacetoacetate enones and azomethine ylides produce tetrasubstituted pyrrolidines bearing a diazoacetoacetate functional array in excellent yields and diastereoselectivities. The installment of the diazoacetoacetate functional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

INTRODUCTION

Diazoacetoacetate 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).[2d] 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 ylides[3] generated *in-situ* from imines **3**

Dedicated with continued friendship to Professor Victor Snieckus on the occasion of his 77th birthday.

to construct highly functionalized pyrrolidines **4**, an important structural motif in natural products and pharmaceuticals[4] (Scheme 1, eq. 2). In addition, metal catalyzed dinitrogen extrusion reactions of **4** give access to different pyrrolidine frameworks by simply changing the R^2 substituent of imine **3**.

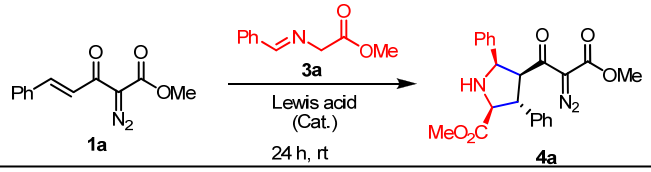


Scheme 1. Reactions of diazoacetoacetate enones

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 AgOTf[7] 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 $Ag(CF_3COO)$ 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[a]



Entry	Catalyst (mol%)	Solvent	d.r. (*endo/exo*)[b]	Yield[c]
1	$Zn(OTf)_2$ (10)	DCM	-	NR
2	$Cu(OTf)_2$ (10)	DCM	-	NR
3	AgOTf (10)	DCM	-	NR
4	$AgCF_3COO$ (10)	DCM	>20:1	55
5	AgOAc (10)	DCM	>20:1	66
6	AgOAc (10)	THF	>20:1	89
7	AgOAc (10)	1,4-dioxane	>20:1	88
8	AgOAc (10)	toluene	>20:1	86
9	AgOAc (10)	Et_2O	>20:1	96
10	AgOAc (2)	Et_2O	>20:1	94

[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 ^{1}H NMR spectrum of the reaction mixture prior to work up. [c] Isolated yield after column chromatography.

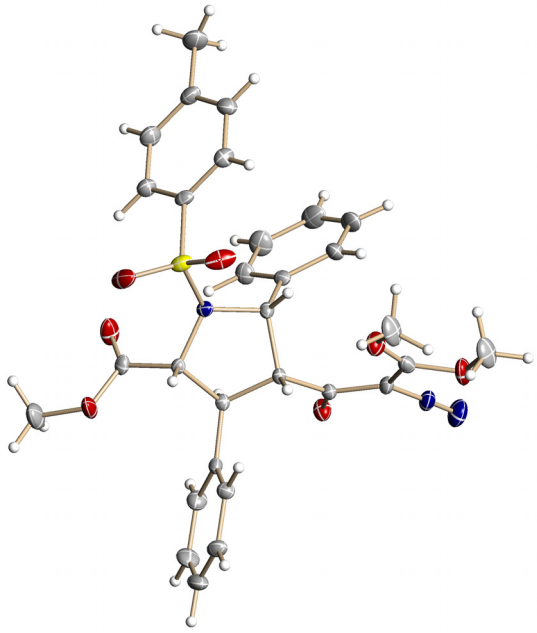
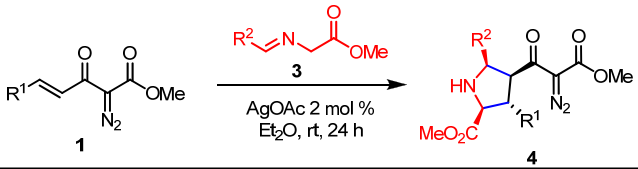


Figure 1. ORTEP view of the tosylamide of **4a** showing product stereochemistry. Ellipsoids are shown at 30% probability (CCDC 947991).

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 R^1) and azomethine ylides **3** (variation of R^2) 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 R^1 having both electron-donating

and electron-withdrawing substituents (Table 2, entries 1-4). Variation of R^2 was also general allowing for aryl, fural, styryl, and alkyl substitutions (entries 5-10). Each reaction exhibits a >20:1 diastereoselectivity except when R^2 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]

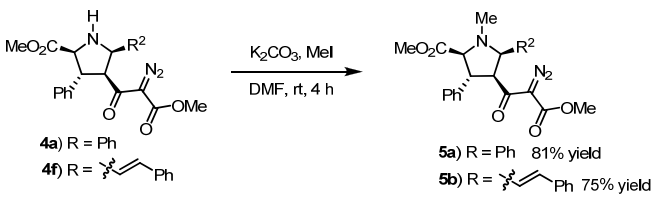
Table 2. Reaction scope[a]



Entry	Product	R^1	R^2	d.r. (*endo:exo*)[b]	Yield (%)[c]
1	**4a**	C_6H_5	C_6H_5	>20:1	94
2	**4b**	2-ClC_6H_4	C_6H_5	>20:1	91
3	**4c**	4-FC_6H_4	C_6H_5	>20:1	92
4	**4d**	4-$OMeC_6H_4$	C_6H_5	>20:1	86
5	**4e**	C_6H_5	2-fural	>20:1	90
6	**4f**	C_6H_5	styryl	>20:1	79
7	**4g**	C_6H_5	cyclohexyl	10:1	82
8	**4h**	C_6H_5	4-$OMeC_6H_4$	>20:1	93
9	**4i**	C_6H_5	4-$CF_3C_6H_4$	>20:1	91
10	**4j**	C_6H_5	4-ClC_6H_4	>20:1	90

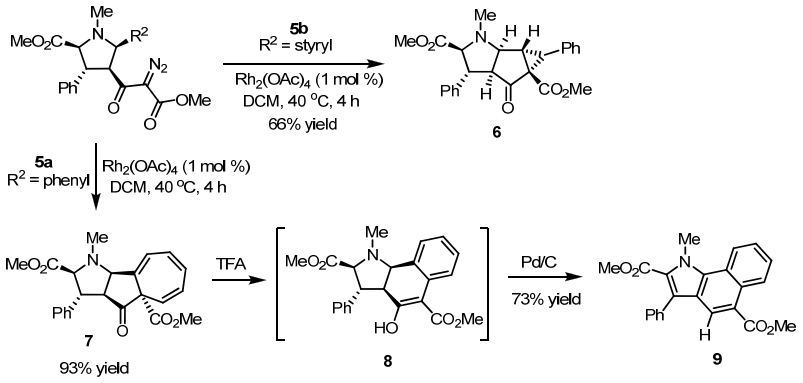
[a] AgOAc (2 mol %) was added to a solution containing **1** (0.30 mmol) and **3** (0.33 mmol) in 2.0 mL of diethyl ether and stirred at room temperature for 24 h. [b] Determined by ^{1}H NMR of the reaction mixture prior to work up. [c] Isolated yield after column chromatography.

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 $Rh_2(OAc)_4$ 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 ºC 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**,[9] then aromatization of intermediate **8** with 10% Pd/C provided the benzoindole **9** in 73% yield (Scheme 3).[10] 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 α-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

$CDCl_3$ on a Bruker Advance 400 MHz spectrometer. Chemical shifts are reported in ppm with the residual $CHCl_3$ 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. Diazoaectoacetate enones (DAAEs) **1a-1d**[2a] and α-imino esters **3a-3f**,[11a] and **3g**[11b] 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 Et_2O. The reaction solution was stirred for 24 h at room temperature, concentrated, and the residue was purified by flash chromatography (SiO_2) with hexanes and EtOAc as the eluents to provide pyrrolidines **4**. Diazo carbon was not detected in the ^{13}C 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 R_f = 0.3 (2:1 hexanes/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{22}H_{21}N_3O_5$ $[M+H]^+$ 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 R_f = 0.3 (2:1 hexanes/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.9, 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 $C_{22}H_{21}ClN_3O_5$ $[M+H]^+$ 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 R_f = 0.3 (2:1 hexanes/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.21 (comp, 7H), 7.04 – 6.96 (comp, 2H), 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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)

m/z calculated for $C_{22}H_{21}FN_3O_5$ $[M+H]^+$ 426.1465, found: 426.1466.

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 R_f = 0.25 (2:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) 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* = 9.3, 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{23}H_{24}N_3O_6$ $[M+H]^+$ 438.1665, found: 438.1667.

Methyl 4-(2-Diazo-3-methoxy-3-oxopropanoyl)-5-(furan-2-yl)-3-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 R_f = 0.2 (2:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{20}H_{20}N_3O_6$ $[M+H]^+$ 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 R_f = 0.2 (2:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) 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), 3.97 (d, *J* = 9.1 Hz, 1H), 3.75 (s, 3H), 3.68 (s, 3H), 2.73 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{24}H_{24}N_3O_5$ $[M+H]^+$ 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 R_f = 0.3 (2:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.29 (comp, 2H), 7.28 – 7.16 (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); ^{13}C NMR (100 MHz, $CDCl_3$) 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, 38.7, 31.6, 31.1, 26.2, 26.0, 25.7; IR (neat) 2144, 1727, 1700, 1650 cm^{-1}; HRMS (ESI) *m/z* calculated for $C_{22}H_{28}N_3O_5$ $[M+H]^+$ 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); ^{1}H 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); ^{13}C 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); ^{1}H 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); ^{13}C 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-carbxylate (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); ^{1}H 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); ^{13}C 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, 61.0, 52.2, 52.0, 51.6; IR (neat) 2139, 1717, 1650 cm^{-1}; HRMS (ESI) *m/z* calculated for $C_{22}H_{21}ClN_3O_5$ $[M+H]^+$ 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); ^{1}H 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); ^{13}C 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.

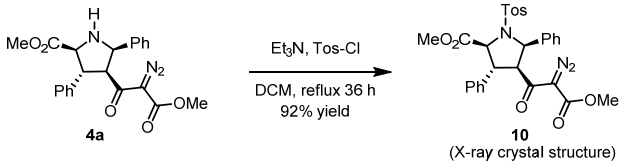
Methyl 4-(2-Diazo-3-methoxy-3-oxopropanoyl)-1-methyl-3-phenyl-5-((*E*)-styryl)pyrrolidine-2-carboxylate (5b). Yellow solid; TLC R_f = 0.3 (4:1 hexanes/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.31 (comp, 3H), 7.31 – 7.27 (comp, 6H), 7.25 – 7.19 (comp, 2H), 6.52 (d, *J* = 15.7 Hz, 1H), 6.06 (dd, *J* = 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, $CDCl_3$) δ 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). $Rh_2(OAc)_4$ (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); ^1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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). $Rh_2(OAc)_4$ (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, $CDCl_3$) δ 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, $CDCl_3$) δ 209.1, 171.6, 167.2, 142.2, 135.0, 129.3, 129.1, 128.8, 128.3, 127.5, 127.0, 125.3, 123.5, 76.2, 71.1, 61.9, 60.1, 52.5, 51.9, 49.4, 36.8; 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[g]indole-2,5-dicarboxylate (9). Triflouroacetic 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); ^1H NMR (400

MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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, $CDCl_3$) δ 185.7, 171.6, 161.1, 143.8, 138.0, 136.0, 134.4, 129.3, 128.7, 128.1, 127.8, 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 $C_{29}H_{27}N_3O_7S$ $[M+H]^+$ 562.1648, found: 562.1649.

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