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TfOH-Catalyzed Formal [3 + 2] Cycloaddition of Cyclopropane 1,1-Diesters with Nitriles

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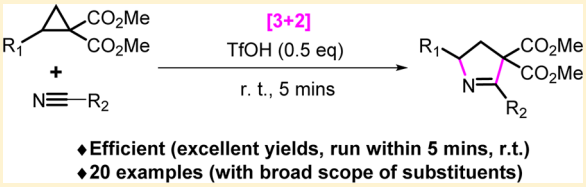
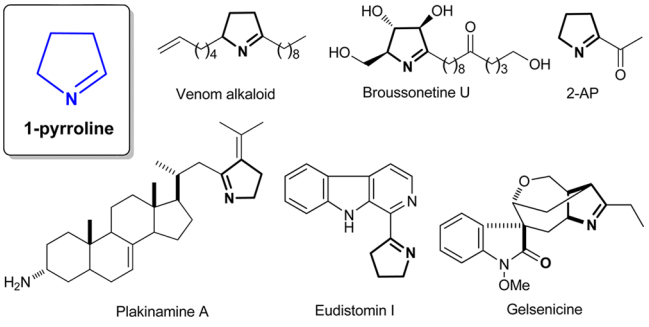
Supporting Information

ABSTRACT: A triflic acid-catalyzed formal [3 + 2] cycloaddition of cyclopropane 1,1-diesters with nitriles was developed. This reaction was expeditious, and the scope of the substituents in both cyclopropanes and nitriles was broad. This supplies an efficient and practical method for the synthesis of 1-pyrrolines.



Because cyclic skeletons broadly exist in biologically active natural and unnatural products, developing highly efficient strategies to construct such skeletons is important for the synthesis of natural products, pharmaceuticals, agrochemicals, and other functional molecules. As a kind of cyclic imines, 1-pyrroline (3,4-dihydro-2*H*-pyrrole) is a core cyclic skeleton existing in natural products and synthetic biological molecules (Scheme 1).[1,2] Additionally, 1-pyrroline is also a key intermediate[3,4] for the synthesis of pyrrole or pyrrolidine-containing alkaloids and related biologically active molecules. Many efforts have been made to develop new synthetic routes for the construction of 1-pyrrolines.[3,5,6]

Scheme 1. Representative Natural Products Containing a 1-Pyrroline Core



Donor–acceptor cyclopropanes have proved to be versatile building blocks in Lewis acid (LA)-promoted formal cycloadditions for the construction of various cyclic skeletons.[7] Although a [3 + 2] cycloaddition of cyclopropanes with nitriles is seemingly a promising method for the efficient construction of 1-pyrroline, only limited examples have been reported (Scheme 2).[8] Pagenkopf et al.[8i] reported a [3 + 2] cycloaddition of cyclopropanol-based donor–acceptor cyclopropanes with nitriles, by which carbohydrate-derived 1-pyrrolines were prepared. Trushkov et al.[8a,c] reported the first [3 + 2] cycloaddition of cyclopropane 1,1-diesters with nitriles under promotion of $SnCl_4$ (2.0 equiv). Subsequently, Srinivasan et al.[8b] reported a similar reaction. In the latter two methods, the scope of the substituents in cyclopropane 1,1-diesters is limited to aryls. We herein report a TfOH-catalyzed [3 + 2] cycloaddition but with a more broad scope of substituents in the constructed 1-pyrrolines.

The reaction of cyclopropane **1a** and nitrile **2a** was performed for our initial investigation. We found that TfOH could efficiently promote the reaction to give the [3 + 2] cycloadduct **3a** and/or γ-lactone **4**. Because the nitriles might be protonated with TfOH, excess **2a** was needed to complete the reaction. Several Bronsted acids were screened (Table 1), and the optimal reaction conditions were selected as 0.5 equiv of TfOH, room temperature, **1a**/**2a** = 1:5, and without solvent (entry 11). Under the optimal conditions, [3 + 2] cycloadduct **3a** was obtained solely within 5 min and in an excellent yield (96%). When the reaction was performed in dichloromethane (DCM), we found that a competing ring-opening cyclization happened to afford γ-lactone **4** (entries 7–10).[9] With the increase of temperature, the ratio of **4** to **3a** increased, and **4** was obtained quantitatively when the reaction was carried out at room temperature. The formation of **4** might be due to the hydrolysis of ester with contaminated water in the reaction system followed by cyclization of the resulting carboxylic acid (entry 13). This provides a mild and efficient method for synthesis of γ-lactones, an important core in natural products.

Under the optimal conditions, the scope of nitriles was investigated, and the result is summarized in Table 2. [3 + 2] cycloadditions of **1a** with various nitriles were successful. The nitrile substrates proved to be structurally diverse. Various alkyl nitriles (**2b–f**), including the tertiary one (**2d**), those with vinyl groups (**2e** and **2f**), and most of the aryl ones (**2g–j**), worked well. α,β-Unsaturated nitrile **2k** also gave an excellent result. The reactions of 2-nitrobenzonitrile and 4-nitrobenzonitrile gave γ-lactones **4** in moderate yields.

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Scheme 2. Reported Examples for Preparation of 1-Pyrrolines by [3 + 2] Cycloadditions of Cyclopropanes with Nitriles

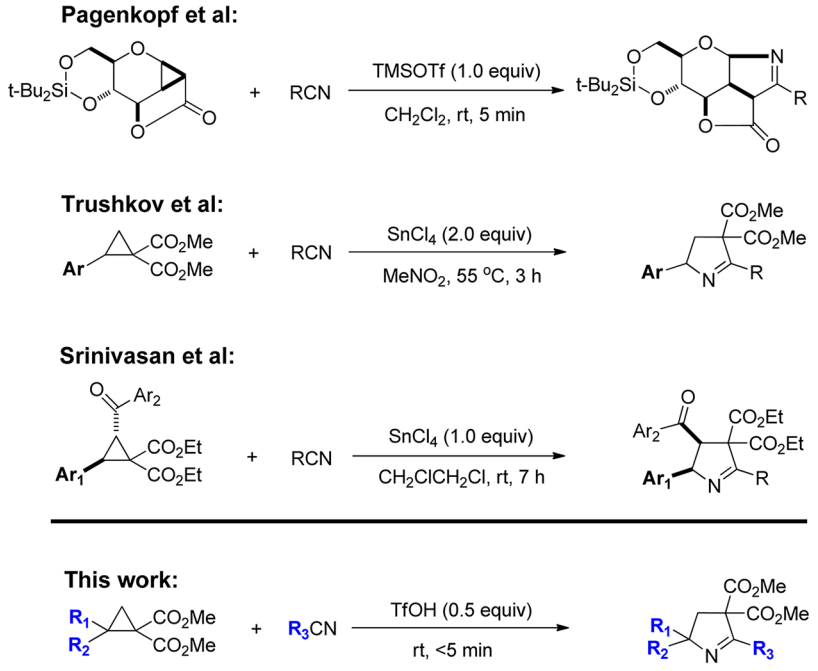
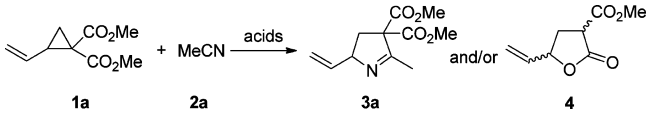


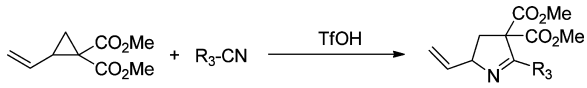
Table 1. Optimization of the Reaction Conditions[a,b,c]



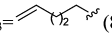
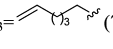
entry[a]	acid (equiv)	T (°C)	solvent	yield[b]	3a/4[c]
1	TfOH (1.0)	25		99	**3a** only
2[c]	TFA (1.0)	25		0	
3	CSA (1.0)	25		0	
4	HCl (1.0)	25		0	
5	H_2SO_4 (1.0)	25		0	
6	PTSA (1.0)	25		0	
7	TfOH (1.0)	−78	DCM	31	**3a** only
8	TfOH (1.0)	−40	DCM	41	4:1
9	TfOH (1.0)	0	DCM	37	1:1
10	TfOH (1.0)	25	DCM	99	**4** only
11	TfOH (0.5)	25		96	**3a** only
12	TfOH (0.2)	25		55	**3a** only
13[d]	TfOH (0.5)	25	DCM	98	**4** only

[a]Reactions were performed by the addition of acid to a mixture of 5.0 mmol of **2a** and 1.0 mmol of **1a** (with or without solvent). [b]Isolated yields. [c]Ratio of **3a**/**4** was determined by ^{1}H NMR. [d]A control experiment was performed in the absence of acetonitrile **2a**.

Table 2. TfOH-Catalyzed [3 + 2] Cycloadditions of Various Nitriles (2b−k) with Cyclopropane 1a[a,b]

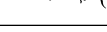


3b: R_3= ^{i}Pr (87%); **3c**: R_3= ^{n}Bu (96%); **3d**: R_3= ^{t}Bu (91%);

3e: R_3=  (82%); **3f**: R_3=  (79%);

3g: R_3= Ph (98%); **3h**: R_3= *p*-Me-Ph (92%);

3i: R_3= *p*-MeO-Ph (84%)[c]; **3j**: R_3= *p*-Cl-Ph (81%)[c];

3k: R_3=  (88%)

[a]Reaction conditions: 1.0 mmol of **1a**, 5.0 mmol of **2**, 0.5 mmol of TfOH, 25 °C, 5 min. [b]Isolated yields. [c]2.0 mmol of **2i** or **2j** was used.

Benzonitrile (**2g**) was then selected to test the scope of the cyclopropane 1,1-diesters (Table 3). [3 + 2] cycloadditions of various cyclopropanes **1** with **2g** were successfully carried out. Nonsubstituted cyclopropane **1l**, which was generally less reactive, also worked well (40 °C, 2 h). Phenyl (**1c**), 2,2-disubstituted (**1d**), and benzyl (**1e**) substrates all worked well. The fused (*cis*-**1f**) and spiro (**1g**) cyclopropanes also gave the desired bicyclic 7-aza-[4.3.0]nonane (**3p**) and 2-aza-spiro[4.5]-decane (**3q**) cycloadducts, respectively, in excellent yields. The relative stereochemistry of **3p** was determined to be trans by 2D NOESY NMR. To our surprise, oxindole derivate monoactivated cyclopropane **1h** also worked well in a nearly quantitative yield. It should be noted that the bicyclic or tricyclic core skeletons in **3p−r** broadly exist in natural products.[10]

When we performed the reaction of fused cyclopropane ketoester **1i** with **2g**, two isomers (**3s** and **3t**) were obtained with a ratio of 1:1 (Scheme 3). The fused 8-aza-[4.3.0]nonane and bridged 7-aza-[4.2.1]nonane compact cores in **3s** and **3t** are important skeletons in natural products.[1f,11] The relative stereochemistry of **3s** was determined to be cis by 2D NOESY NMR.

An enantiopure substrate, (*S*)-**1c**, was synthesized and subjected to subsequent [3 + 2] cycloaddition with **2a** (Scheme 4). Unlike the $SnCl_4$-promoted negative result reported by Trushkov et al.,[8a] the reaction proceeded successfully, and cycloadduct **3m** was obtained in 97% yield and 73% ee. Further treatment of **3m** under the same reaction conditions for 0.5 h did not show any loss of the ee value. The decrease of the ee value probably arose from the partial racemization of

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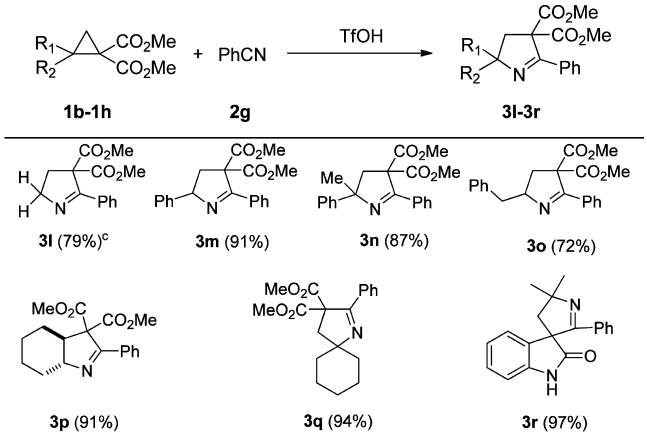
Table 3. TfOH-Catalyzed [3 + 2] Cycloadditions of Various Cyclopropans (1b–h) with 2g[a,b]



[a]Reaction conditions: 1.0 mmol of **1**, 5.0 mmol of **2g**, 0.5 mmol of TfOH, 25 °C, 5 min. [b]Isolated yields. [c]Reacted at 40 °C for 2 h.

cyclopropane **1c** under the stronger acidic conditions.[12] This example was important for the potential application of the method to natural products synthesis and for understanding the mechanism.

Although the absolute configuration of (+)-**3m** was not determined, the maintained ee value together with the configuration reversal in the reaction of **1f** to **3p** suggested an S_N2 mechanism in which a Ritter nitrilium intermediate was involved (Scheme 5). Different from the one proposed by Trushkov et al., this mechanism is supposed to be similar to that of the [3 + 2] cycloaddition of cyclopropane 1,1-diesters with aldehydes suggested by Johnson et al.[12]

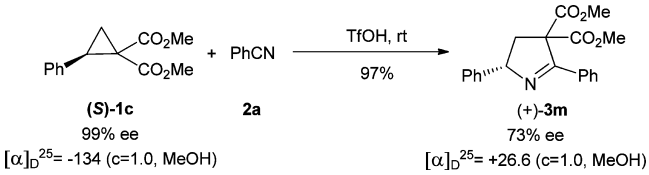
A [4 + 2] cycloaddition of **3k** and ketene **5** was carried out to exhibit the potential application of the method (Scheme 6). The obtained compound **6** contains an indolizidine core, which broadly exists in natural products.

In conclusion, we developed a TfOH-catalyzed formal intermolecular [3 + 2] cycloaddition of cyclopropane 1,1-diesters with nitriles. To the best of our knowledge, this is the first catalytic version of [3 + 2] cycloaddition between donor–acceptor cyclopropanes with nitriles. Features of this method include an expeditious process, mild conditions, and a broad scope of substituents in both of the substrates. This supplies an efficient and practical method for the synthesis of structurally diverse 1-pyrrolines.

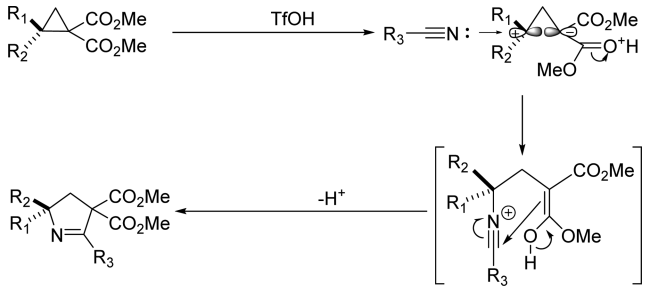
EXPERIMENTAL SECTION

General Information. All reactions were performed open to the air. Nitriles were purchased and used without further purification. Flash column chromatography was performed on neutral aluminum oxide (100–300 mesh) using petroleum ether/ethyl acetate as eluting solvents. Thin-layer chromatography (TLC) was performed on silica gel GF254 plates and visualized by UV light (254 nm) or $KMnO_4$.

Scheme 4. [3 + 2] Cycloaddition of (*S*)-1c with 2a



Scheme 5. Proposed Mechanism



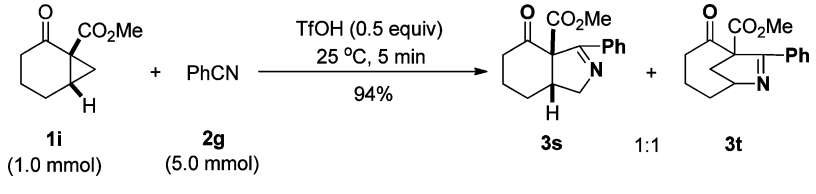
Nuclear magnetic resonance spectra were recorded in deuteriochloroform ($CDCl_3$), unless otherwise indicated, at ambient temperature operating at 400 MHz for ^1H and 100 MHz for ^{13}C. The chemical shifts (δ) were measured in ppm and with the solvents as references (for $CDCl_3$, ^1H: δ = 7.26 ppm and ^{13}C δ = 77.1 ppm). Infrared absorption spectra were recorded as a film on KBr. Melting points were obtained on a apparatus and are uncorrected. High-resolution mass spectra were recorded with MALDI-TOF resource. All HPLC were performed with an AD-H column using *n*-hexane/isopropanol as the mobile phase.

Cyclopropane 1,1-diester **1a**,[13] **1b**,[14] **1g**,[15] and **1i**[16] were known compounds and prepared according to literature procedures. Cyclopropane 1,1-diester **1h** was prepared from dimethyloxosulfonium methylide and 3-(propan-2-ylidene)indolin-2-one[17] according to a reported procedure.[18] Cyclopropane 1,1-diesters **1c**, **1d**, **1e**, and **1f** were prepared from dimethyl 2-diazomalonate and the corresponding alkene, which was catalyzed by $Rh_2(esp)_2$. (*S*)-**1c** was prepared according to Johnson's procedure.[12]

General Procedure for the Cycloaddition Reaction of Cyclopropanes with Nitriles. Cyclopropanes **1** (1 equiv, 1 mmol) and nitrile (5 equiv, 5 mmol) were mixed, and TfOH (0.5 equiv, 45 μL, 0.5 mmol) was added at 0 °C. The reaction mixture was then warmed to 25 °C. The reaction was monitored by TLC. After the cyclopropane 1,1-diester was fully consumed, the reaction mixture was filtered thought a short pad of neutral aluminum oxide and washed with 25 mL of petroleum ether/ethyl acetate (1:1). After removal of the solvent under pressure, the crude product was purified by flash column chromatography to give the corresponding product.

Preparation of 2,2-Dimethylspiro[cyclopropane-1,3′-indolin]-2′-one (1h). In a mixture of oxindole (10 mmol, 1.33 g) and acetone (10 mL) were added ethanol (10 mL) and piperidine (4 mL). The mixture was heated at 35 °C until all of the solid dissolved and stirred at room temperature overnight. When the reaction completed, 60 mL of ethyl acetate was added. The mixture was washed with 1 M $KHSO_4$, water, and saturated aqueous NaCl. After being dried by $MgSO_4$, the solvent was removed under pressure, and the crude 3-

Scheme 3. TfOH-Catalyzed [3 + 2] Cycloaddition of 1i with 2g



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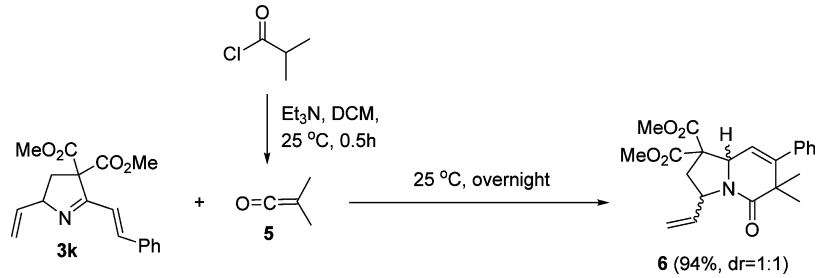
Scheme 6. [4 + 2] Cycloaddition of 3k with Ketene 5



(propan-2-ylidene)indolin-2-one was obtained as a yellow solid that was used in the next step without further purification. In a mixture of NaH (2.6 mmol, 0.104 g, 1.3 equiv) and trimethylsulfoxonium iodide (2.2 mmol, 0.486 g, 1.1 equiv) in DMSO (3 mL) was added a solution of 3-(propan-2-ylidene)indolin-2-one (2 mmol, 0.346 g, 1 equiv) in DMSO (3 mL) under Ar. The mixture was stirred at room temperature overnight. After the reaction completed, the mixture was quenched with 3 mL of saturated aqueous NH_4Cl. Ethyl acetate (20 mL) was added, and the organic layer was separated and dried by $MgSO_4$. After removal of the solvent under pressure, the crude product was purified by flash column chromatography on silica gel (200−300 mesh, petroleum ether/ethyl acetate, 1:1). Yield: 172 mg, 92%, yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.89 (s, 1H), 7.10 (dt, J = 7.6, 4.5 Hz, 1H), 6.89 (t, J = 5.8 Hz, 3H), 1.78 (d, J = 4.6 Hz, 1H), 1.48 (d, J = 2.6 Hz, 4H), 1.33 (s, 3H).

Dimethyl 2-Methyl-5-vinyl-4,5-dihydro-3*H*-pyrrole-3,3-dicarboxylate (3a). **3a** was prepared according to the general procedure. Purification by column chromatography on neutral aluminum oxide (100−300 mesh, petroleum ether/ethyl acetate, 10:1). Yield: 216 mg, 96%, light yellow oil. ^{1}H (400 MHz, $CDCl_3$) δ 5.85 (ddd, J = 17.2, 10.3, 6.7 Hz, 1H), 5.24−5.09 (m, 2H), 4.57−4.44 (m, 1H), 3.77 (d, J = 1.9 Hz, 6H), 2.83 (dd, J = 13.3, 7.3 Hz, 1H), 2.26 (dd, J = 13.4, 7.1 Hz, 1H), 2.19 (d, J = 2.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 168.5, 168.1, 138.3, 116.1, 72.6, 71.7, 53.2, 39.8, 18.3. IR (film, cm^{-1}): 2956, 2926, 1733, 1650, 1435, 1274, 1215, 1200, 1110, 1076, 924. HRMS (MALDI-TOF) m/z: $[M + H]^+$ calcd for $C_{11}H_{16}NO_4$, 226.1079; found, 226.1077.

Dimethyl 2-Isopropyl-5-vinyl-4,5-dihydro-3*H*-pyrrole-3,3-dicarboxylate (3b). **3b** was prepared according to the general procedure. Purification by column chromatography on neutral aluminum oxide (100−300 mesh, petroleum ether/ethyl acetate, 20:1). Yield: 220 mg, 87%, colorless oil. ^{1}H (400 MHz, $CDCl_3$) δ 5.86 (ddd, J = 17.1, 10.3, 6.7 Hz, 1H), 5.20 (d, J = 17.2 Hz 1H), 5.11 (dt, J = 10.3 Hz, 1H), 4.61−4.54 (m, 1H), 3.77 (d, J = 1.3 Hz, 6H), 2.91−2.82 (m, 1H), 2.79 (dd, J = 13.4, 7.5 Hz, 1H), 2.28 (dd, J = 13.4, 6.7 Hz, 1H), 1.18 (dd, J = 9.0, 6.8 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.8, 169.6, 169.2, 138.7, 115.9, 72.7, 71.9, 53.2, 53.1, 39.6, 30.8, 22.2, 22.0. IR (film, cm^{-1}): 2972, 2965, 2873, 1734, 1647, 1630, 1435, 1270, 1198, 914, 746. HRMS (MALDI-TOF) m/z: $[M + H]^+$ calcd for $C_{13}H_{19}NO_4$, 254.1392; found, 254.1394.

Dimethyl 2-Butyl-5-vinyl-4,5-dihydro-3*H*-pyrrole-3,3-dicarboxylate (3c). **3c** was prepared according to the general procedure. Purification by column chromatography on neutral aluminum oxide (100−300 mesh, petroleum ether/ethyl acetate, 20:1). Yield: 257 mg, 96%, colorless oil. ^{1}H (400 MHz, $CDCl_3$) δ 5.86 (ddd, J = 17.1, 10.3, 6.7 Hz, 1H), 5.16 (dd, J = 38.4, 13.7 Hz, 2H), 4.57−4.52 (m, 1H), 3.76 (d, J = 2.0 Hz, 6H), 2.80 (dd, J = 13.3, 7.3 Hz, 1H), 2.49−2.42 (m, 2H), 2.27 (dd, J = 13.3, 6.9 Hz, 1H), 1.71−1.60 (m, 2H), 1.35 (m,2H), 0.90 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4, 169.5, 168.9, 138.6, 115.9, 72.7, 71.9, 53.2, 53.1, 39.7, 31.4, 28.8, 22.6, 14.0. IR (film, cm^{-1}): 2957, 2873, 1735, 1648, 1435, 1271, 1200, 1172, 1116, 1066, 992, 924. HRMS (MALDI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{22}NO_4$, 268.1549; found, 268.1549.

Dimethyl 2-(*tert*-Butyl)-5-vinyl-4,5-dihydro-3*H*-pyrrole-3,3-dicarboxylate (3d). **3d** was prepared according to the general procedure. Purification by column chromatography on neutral aluminum oxide (100−300 mesh, petroleum ether/ethyl acetate, 20:1). Yield: 243 mg, 91%, colorless oil. ^{1}H (400 MHz, $CDCl_3$) δ 5.86 (ddd, J = 17.0, 10.3, 6.5 Hz, 1H), 5.13 (ddd, J = 13.2, 10.3, 1.2 Hz, 2H), 4.51 (q, J = 7.0 Hz, 1H), 3.75 (d, J = 5.7 Hz, 6H), 2.77 (dd, J = 13.0, 7.1 Hz, 1H), 2.37 (dd, J = 13.0, 7.0 Hz, 1H), 1.24 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.8, 170.2, 169.7, 138.4, 115.9, 71.8, 70.4, 52.9, 52.8, 43.6, 38.0, 29.9. IR (film, cm^{-1}): 2080, 2956, 2912, 1732, 1616, 1435, 1264, 1197, 1107, 1069, 1008, 924. HRMS (MALDI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{22}NO_4$, 268.1549; found, 268.1548.

Dimethyl 2-(Pent-4-en-1-yl)-5-vinyl-4,5-dihydro-3*H*-pyrrole-3,3-dicarboxylate (3e). **3e** was prepared according to the general procedure. Purification by column chromatography on neutral aluminum oxide (100−300 mesh, petroleum ether/ethyl acetate, 20:1). Yield: 229 mg, 82%, colorless oil. ^{1}H (400 MHz, $CDCl_3$) δ 5.92−5.72 (m, 2H), 5.17 (dd, J = 38.3, 13.8 Hz, 2H), 5.05−4.91 (m, 2H), 4.56 (d, J = 6.8 Hz, 1H), 3.76 (d, J = 2.1 Hz, 6H), 2.81 (dd, J = 13.4, 7.4 Hz, 1H), 2.54−2.44 (m, 2H), 2.28 (dd, J = 13.4, 6.9 Hz, 1H), 2.11 (q, J = 7.1 Hz, 2H), 1.84−1.73 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3, 168.8, 138.5, 138.4, 116.0, 115.0, 72.6, 71.9, 53.2, 53.1, 39.7, 33.4, 31.0, 25.8. IR (film, cm^{-1}): 2959, 2923, 2854, 1735, 1687, 1460, 1437, 1260, 1103, 1081, 1016, 797. HRMS (MALDI-TOF) m/z: $[M + H]^+$ calcd for $C_{15}H_{22}NO_4$, 280.1549; found, 280.1549.

Dimethyl 2-(Hex-5-en-1-yl)-5-vinyl-4,5-dihydro-3*H*-pyrrole-3,3-dicarboxylate (3f). **3f** was prepared according to the general procedure. Purification by column chromatography on neutral aluminum oxide (100−300 mesh, petroleum ether/ethyl acetate, 20:1). Yield: 231 mg, 79%, colorless oil. ^{1}H (400 MHz, $CDCl_3$) δ 5.87−5.81 (m, 2H), 5.25−5.11 (m, 2H), 5.04−4.89 (m, 2H), 4.56 (q, J = 7.2 Hz, 1H), 3.77 (d, J = 2.0 Hz, 6H), 2.82 (dd, J = 13.4, 7.4 Hz, 1H), 2.48 (ddd, J = 9.1, 6.9, 2.2 Hz, 2H), 2.28 (dd, J = 13.3, 6.9 Hz, 1H), 2.07 (q, J = 7.1 Hz, 2H), 1.76−1.66 (m, 2H), 1.48−1.41 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4, 168.9, 138.9, 138.5, 116.0, 114.5, 72.7, 71.9, 53.2, 53.2, 39.8, 33.7, 31.5, 28.8, 26.1. IR (film, cm^{-1}): 3076, 3009, 2953, 2932, 2855, 1733, 1640, 1434, 1268, 1199, 1171, 1101, 1070, 992, 918. HRMS (MALDI-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{24}NO_4$, 294.1705; found, 294.1703.

Dimethyl 2-Phenyl-5-vinyl-4,5-dihydro-3*H*-pyrrole-3,3-dicarboxylate (3g). **3g** was prepared according to the general procedure. Purification by column chromatography on neutral aluminum oxide (100−300 mesh, petroleum ether/ethyl acetate, 20:1). Yield: 281 mg, 98%, colorless oil. ^{1}H (400 MHz, $CDCl_3$) δ 7.93−7.82 (m, 2H), 7.45−7.31 (m, 3H), 5.99 (ddd, J = 17.0, 10.3, 6.5 Hz, 1H), 5.31 (d, J = 17.2 Hz, 1H), 5.20 (d, J = 10.3 Hz, 1H), 4.78 (q, J = 6.9 Hz, 1H), 3.72 (d, J = 19.1 Hz, 6H), 3.05 (dd, J = 13.0, 7.0 Hz, 1H), 2.49 (dd, J = 13.0, 7.3 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 169.3, 167.6, 138.1, 133.0, 130.7, 128.8, 128.2, 116.4, 72.6, 70.3, 53.3, 53.2, 42.9. IR (film, cm^{-1}): 3607, 3006, 2954, 2845, 1729, 1643, 1608, 1573, 1495, 1446, 1258, 1198, 1070, 1022, 993, 923, 796, 760, 692. HRMS (MALDI-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{18}NO_4$, 288.1236; found, 228.1237.

Dimethyl 2-(*p*-Tolyl)-5-vinyl-4,5-dihydro-3*H*-pyrrole-3,3-dicarboxylate (3h). **3h** was prepared according to the general procedure. Purification by column chromatography on neutral aluminum oxide (100−300 mesh, petroleum ether/ethyl acetate, 20:1). Yield: 277 mg, 92%, colorless oil. ^{1}H (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.2 Hz, 2H), 7.16 (d, J = 8.1 Hz, 2H), 5.99 (ddd, J = 17.0, 10.3,

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6.5 Hz, 1H), 5.30 (d, J = 17.2 Hz, 1H), 5.18 (d, J = 10.3 Hz, 1H), 4.76 (q, J = 6.9 Hz, 1H), 3.74 (s, 3H), 3.70 (s, 3H), 3.03 (dd, J = 12.9, 7.0 Hz, 1H), 2.47 (dd, J = 12.9, 7.2 Hz, 1H), 2.36 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 169.3, 167.4, 141.0, 138.3, 130.2, 129.0, 128.8, 116.3, 72.5, 70.2, 53.3, 53.1, 42.9, 21.5. IR (film, cm^{-1}): 3083, 3007, 2953, 1733, 1608, 1565, 1513, 1434, 1292, 1266, 1199, 1068, 991, 924, 826. HRMS (MALDI-TOF) m/z: [M + H]$^+$ calcd for $C_{17}H_{20}NO_4$, 302.1390; found, 302.1390.

Dimethyl 2-(4-Methoxyphenyl)-5-vinyl-4,5-dihydro-3*H*-pyrrole-3,3-dicarboxylate (3i). **3i** was prepared according to the general procedure except 2 equiv of **2i** was used instead. Purification by column chromatography on neutral aluminum oxide (100−300 mesh, petroleum ether/ethyl acetate, 10:1). Yield: 266 mg, 84%, colorless oil. ^{1}H (400 MHz, $CDCl_3$) δ 7.86 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 5.98 (ddd, J = 17.0, 10.3, 6.7 Hz, 1H), 5.31 (d, J = 17.2 Hz, 1H), 5.19 (d, J = 10.2 Hz, 1H), 4.75 (dd, J = 13.6, 6.7 Hz, 1H), 3.84 (s, 3H), 3.73 (d, J = 15.0 Hz, 6H), 3.04 (dd, J = 12.9, 7.0 Hz, 1H), 2.47 (dd, J = 12.9, 7.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 169.4, 166.8, 161.6, 138.4, 130.6, 125.5, 116.2, 113.6, 72.4, 70.2, 55.4, 53.3, 53.2, 43.0. IR (film, cm^{-1}): 1731, 1607, 1514, 1258, 913, 745. HRMS (MALDI-TOF) m/z: [M + H]$^+$ calcd for $C_{17}H_{20}NO_5$, 318.1341; found, 318.1339.

Dimethyl 2-(4-Chlorophenyl)-5-vinyl-4,5-dihydro-3*H*-pyrrole-3,3-dicarboxylate (3j). **3j** was prepared according to the general procedure exept 2 equiv of **2j** was used instead. Purification by column chromatography on neutral aluminum oxide (100−300 mesh, petroleum ether/ethyl acetate, 10:1). Yield: 260 mg, 81%, colorless oil. ^{1}H (400 MHz, $CDCl_3$) δ 7.83 (d, J = 8.7 Hz, 2H), 7.34 (d, J = 8.7 Hz, 2H), 5.98 (ddd, J = 17.0, 10.3, 6.5 Hz, 1H), 5.31 (dt, J = 17.3, 1.4 Hz, 1H), 5.21 (dt, J = 10.4, 1.3 Hz, 1H), 4.77 (q, J = 6.9 Hz, 1H), 3.76 (s, 3H), 3.72 (s, 3H), 3.09−3.01 (m, 1H), 2.48 (dd, J = 13.0, 7.3 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 168.9, 137.5, 130.5, 128.7, 116.9, 72.3, 70.2, 53.5, 53.4, 42.6. IR (film, cm^{-1}): 3009, 2961, 1716, 1645, 1611, 1251, 1077, 933, 775. HRMS (MALDI-TOF) m/z: [M]$^+$ calcd for $C_{16}H_{16}ClNO_4$, 321.0768; found, 321.0774.

Dimethyl (*E*)-2-Styryl-5-vinyl-4,5-dihydro-3*H*-pyrrole-3,3-dicarboxylate (3k). **3k** was prepared according to the general procedure. Purification by column chromatography on neutral aluminum oxide (100−300 mesh, petroleum ether/ethyl acetate, 20:1). Yield: 275 mg, 88%, light brown oil. ^{1}H (400 MHz, $CDCl_3$) δ 7.51 (m, 3H), 7.41−7.31 (m, 3H), 6.93 (d, J = 16.3 Hz, 1H), 5.94 (ddd, J = 17.1, 10.3, 6.8 Hz, 1H), 5.37−5.26 (m, 1H), 5.19 (d, J = 10.3 Hz, 1H), 4.72 (d, J = 7.1 Hz, 1H), 3.80 (d, J = 1.4 Hz, 6H), 2.98 (dd, J = 13.3, 7.3 Hz, 1H), 2.36 (dd, J = 13.3, 7.1 Hz, 1H).). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5, 168.7, 138.3, 135.9, 129.4, 128.9, 127.8, 120.4, 116.6, 72.8, 70.6, 53.5, 53.4, 40.5. IR (film, cm^{-1}): 3028, 3005, 2954, 2925, 1733, 1634, 1586, 1510, 1494, 1449, 1434, 1260, 1200, 1099, 1071, 1019, 992, 924, 799, 749, 699. HRMS (MALDI-TOF) m/z: [M + H]$^+$ calcd for $C_{18}H_{20}NO_4$, 314.1392; found, 314.1388.

Dimethyl 2-Phenyl-4,5-dihydro-3*H*-pyrrole-3,3-dicarboxylate (3l). **3l** was prepared according to the general procedure at 40 °C instead of 25 °C. Purification by column chromatography on neutral aluminum oxide (100−300 mesh, petroleum ether/ethyl acetate, 20:1). Yield: 206 mg, 79%, colorless oil. The NMR data coincided with the literature.[19] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94−7.79 (m, 2H), 7.46−7.32 (m, 3H), 4.12 (t, J = 6.7 Hz, 2H), 3.73 (s, 6H), 2.77 (t, J = 6.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 167.6, 133.0, 130.4, 128.5, 128.2, 69.8, 59.3, 53.1, 37.2.

Dimethyl 2,5-Diphenyl-4,5-dihydro-3*H*-pyrrole-3,3-dicarboxylate (3m). **3m** was prepared according to the general procedure. Purification by column chromatography on neutral aluminum oxide (100−300 mesh, petroleum ether/ethyl acetate, 20:1). Yield: 306 mg, 91%, white solid, mp 134−136 °C. ^{1}H (400 MHz, $CDCl_3$) δ 7.91−7.85 (m, 2H), 7.35−7.23 (m, 7H), 7.21−7.16 (m, 1H), 5.25 (dd, J = 8.5, 6.9 Hz, 1H), 3.69 (s, 3H), 3.55 (s, 3H), 3.26 (dd, J = 13.0, 6.9 Hz, 1H), 2.48 (dd, J = 13.0, 8.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 168.9, 167.8, 142.3, 132.9, 130.7, 128.8, 128.6, 128.2, 127.4, 126.7, 73.5, 70.7, 53.3, 53.1, 45.9. IR (film, cm^{-1}): 3060, 3028, 2953, 1732, 1607, 1573, 1519, 1494, 1447, 1434, 1292, 1268, 1172, 1070, 1027, 967, 919, 796, 757, 695. HRMS (MALDI-TOF) m/z: [M + H]$^+$ calcd for $C_{20}H_{20}NO_4$, 338.1392; found, 338.1390. For (+)-**3m**, α_D^{25} +26.6 (c 1.0, MeOH).

Dimethyl 5-Methyl-2,5-diphenyl-4,5-dihydro-3*H*-pyrrole-3,3-dicarboxylate (3n). **3n** was prepared according to the general procedure. Purification by column chromatography on neutral aluminum oxide (100−300 mesh, petroleum ether/ethyl acetate, 20:1). Yield: 305 mg, 87%, white solid, mp 153−155 °C. ^{1}H (400 MHz, $CDCl_3$) δ 7.97−7.91 (m, 2H), 7.45−7.36 (m, 5H), 7.31 (t, J = 7.6 Hz, 2H), 7.27−7.18 (m, 1H), 3.76 (s, 3H), 3.45 (s, 3H), 3.04 (d, J = 5.7 Hz, 2H), 1.66 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3, 169.6, 165.7, 147.3, 133.3, 130.6, 129.0, 128.4, 128.3, 126.8, 125.5, 71.1, 53.3, 53.0, 50.5, 29.9. IR (film, cm^{-1}): 2961, 2920, 2851, 1736, 1609, 1518, 1440, 1260, 1093, 1022, 800, 739, 695. HRMS (MALDI-TOF) m/z: [M + H]$^+$ calcd for $C_{21}H_{22}NO_4$, 352.1549; found, 352.1551.

Dimethyl 5-Benzyl-2-phenyl-4,5-dihydro-3*H*-pyrrole-3,3-dicarboxylate (3o). **3o** was prepared according to the general procedure. Purification by column chromatography on neutral aluminum oxide (100−300 mesh, petroleum ether/ethyl acetate, 20:1). Yield: 252 mg, 72%, yellow oil. ^{1}H (400 MHz, $CDCl_3$) δ 7.82 (d, J = 7.0 Hz, 2H), 7.41−7.15 (m, 8H), 4.45 (dt, J = 14.3, 7.0 Hz, 1H), 3.65 (d, J = 9.6 Hz, 6H), 3.31 (dd, J = 13.6, 5.7 Hz, 1H), 2.76 (ddd, J = 22.2, 13.4, 7.7 Hz, 2H), 2.35 (dd, J = 13.2, 7.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.13, 169.24, 166.54, 138.68, 133.05, 132.53, 130.42, 129.36, 128.99, 128.70, 128.47, 128.13, 126.42, 72.25, 70.21, 53.09, 53.06, 42.06, 41.84. IR (film, cm^{-1}): 2958, 2918, 1850, 1735, 1639, 1263, 1090, 1021, 801, 765, 697. HRMS (MALDI-TOF) m/z: [M + H]$^+$ calcd for $C_{21}H_{22}NO_4$, 352.1549; found, 352.1549.

Dimethyl 2-Phenyl-3a,4,5,6,7,7a-hexahydro-3*H*-indole-3,3-dicarboxylate (3p). **3p** was prepared according to the general procedure. Purification by column chromatography on neutral aluminum oxide (100−300 mesh, petroleum ether/ethyl acetate, 20:1). Yield: 287 mg, 91%, colorless oil. ^{1}H (400 MHz, $CDCl_3$) δ 7.76−7.68 (m, 2H), 7.45−7.32 (m, 3H), 3.80 (s, 3H), 3.64 (s, 3H), 3.44 (td, J = 11.3, 3.6 Hz, 1H), 2.61−2.46 (m, 2H), 2.06−1.98 (m, 1H), 1.93 (d, J = 12.5 Hz, 1H), 1.89−1.82 (m, 1H), 1.60−1.31 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6, 169.4, 167.3, 134.0, 130.3, 128.2, 128.0, 73.4, 72.1, 56.9, 53.0, 52.7, 31.9, 26.5, 26.1, 25.6. IR (film, cm^{-1}): 3032, 2930, 2857, 1732, 1597, 1568, 1521, 1441, 1365, 1254, 1214, 1099, 1063, 1025, 915, 799, 774, 689. HRMS (MALDI-TOF) m/z: [M + H]$^+$ calcd for $C_{18}H_{22}NO_4$, 315.1471; found, 315.1470.

Dimethyl 2-Phenyl-1-azaspiro[4.5]dec-1-ene-3,3-dicarboxylate (3q). **3q** was prepared according to the general procedure. Purification by column chromatography on neutral aluminum oxide (100−300 mesh, petroleum ether/ethyl acetate, 20:1). Yield: 309 mg, 94%, colorless oil. ^{1}H (400 MHz, $CDCl_3$) δ 7.83 (d, J = 6.9 Hz, 2H), 7.42−7.30 (m, 3H), 3.72 (s, 6H), 2.63 (s, 2H), 1.81 (dd, J = 16.5, 9.9 Hz, 5H), 1.55−1.36 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 163.4, 133.5, 130.3, 128.9, 128.2, 75.6, 70.6, 53.2, 46.3, 37.9, 37.9, 25.6, 23.4. IR (film, cm^{-1}): 2875, 1740, 1611, 1587, 1544, 1227, 1136, 1044, 915, 689. HRMS (MALDI-TOF) m/z: [M]$^+$ calcd for $C_{19}H_{23}NO_4$, 329.1627; found, 329.1633.

5′,5′-Dimethyl-2′-phenyl-4′,5′-dihydrospiro[indoline-3,3′-pyrrol]-2-one (3r). **3r** was prepared according to the general procedure. Purification by column chromatography on neutral aluminum oxide (100−300 mesh, petroleum ether/ethyl acetate, 10:1). Yield: 281 mg, 97%, white solid, mp 187−189 °C. ^{1}H (400 MHz, $CDCl_3$) δ 8.98−8.62 (br, s, 1H), 7.41 (d, J = 7.6 Hz, 2H), 7.29−7.19 (m, 2H), 7.19−7.08 (m, 3H), 7.01 (t, J = 7.6 Hz, 1H), 6.92 (d, J = 7.8 Hz, 1H), 2.67 (d, J = 13.4 Hz, 1H), 2.24 (d, J = 13.4 Hz, 1H), 1.63 (d, J = 11.7 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.5, 140.5, 132.9, 130.6, 128.9, 128.5, 127.9, 123.9, 123.5, 110.5, 73.4, 67.5, 51.6, 31.2, 30.8. IR (film, cm^{-1}): 2957, 2925, 2859, 1734, 1706, 1443, 1384, 1332, 1261, 1211, 1136, 1094, 1022, 913, 802, 759. HRMS (MALDI-TOF) m/z: [M + H]$^+$ calcd for $C_{19}H_{19}N_2O$, 291.1497 found 291.1493.

Methyl 4-Oxo-3-phenyl-1,4,5,6,7,7a-hexahydro-3a*H*-isoindole-3a-carboxylate (3s). **3s** was prepared according to the general procedure. Purification by column chromatography on neutral aluminum oxide (100−300 mesh, petroleum ether/ethyl acetate,

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10:1). Yield: 127 mg, 47%, white solid, bp 144−146 °C. ^{1}H (400 MHz, $CDCl_3$) δ 7.78−7.73 (m, 2H), 7.40−7.32 (m, 3H), 4.04 (dd, J = 16.1, 6.7 Hz, 1H), 3.77−3.68 (m, 4H), 3.41−3.34 (m, 1H), 2.72−2.62 (m, 1H), 2.30 (dt, J = 14.1, 5.9 Hz, 1H), 2.05−1.91 (m, 3H), 1.69 (ddt, J = 10.7, 7.8, 4.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.9, 170.1, 130.6, 128.5, 128.4, 75.5, 63.0, 53.1, 50.2, 41.0, 25.3, 23.8. IR (film, cm^{-1}): 2946, 2859, 1714, 1607, 1572, 1440, 1308, 1247, 1188, 1103, 1055, 1026, 913, 792, 740, 693. HRMS (MALDI-TOF) m/z: $[M]^+$ calcd for $C_{16}H_{17}NO_3$, 271.1208; found, 271.1208.

Methyl 2-Oxo-8-phenyl-7-azabicyclo[4.2.1]non-7-ene-1-carboxylate (3t). **3t** was prepared according to the general procedure. Purification by column chromatography on neutral aluminum oxide (100−300 mesh, petroleum ether/ethyl acetate, 10:1). Yield: 128 mg, 47%, colorless oil. ^{1}H (400 MHz, $CDCl_3$) δ 7.98−7.90 (m, 2H), 7.44−7.32 (m, 3H), 5.01−4.94 (m, 1H), 3.67 (s, 3H), 2.80 (ddd, J = 15.7, 13.3, 2.5 Hz, 1H), 2.69 (d, J = 13.4 Hz, 1H), 2.61 (ddt, J = 15.4, 6.6, 1.3 Hz, 1H), 2.57−2.49 (m, 1H), 2.32 (dq, J = 14.2, 3.9 Hz, 1H), 1.90 (dddd, J = 14.1, 12.7, 4.1, 2.6 Hz, 1H), 1.73 (ddd, J = 13.8, 6.7, 3.5 Hz, 1H), 1.34−1.21 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.9, 170.7, 166.8, 132.8, 130.7, 128.8, 128.2, 74.5, 69.7, 52.6, 44.3, 41.5, 33.3, 20.1. IR (film, cm^{-1}): 2947, 2861, 1738, 1607, 1573, 1442, 1309, 1252, 1101, 1055, 1029, 791, 695. HRMS (MALDI-TOF) m/z: $[M]^+$ calcd for $C_{16}H_{17}NO_3$, 271.1208; found, 271.1210.

Methyl 2-Oxo-5-vinyltetrahydrofuran-3-carboxylate (4). Dimethyl 2-vinylcyclopropane-1,1-diester **1a** (1 equiv, 184 mg, 1 mmol) was dissolved in 5 mL of DCM, and TfOH (0.5 equiv, 45 μL, 0.5 mmol) was then added. The reaction mixture was stirred at 25 °C for 10 min. The solvent was evaporated, and the crude product was purified by flash column chromatography on silica gel (200−300 mesh, petroleum ether/ethyl acetate, 20:1) to obtain γ-lactone **4** as a pair of unseparable diastereoisomers (1:1, 167 mg, 98%). The NMR data coincided with the literature.[20] ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 (dddd, J = 22.9, 16.8, 10.5, 6.3 Hz, 1H), 5.40 (ddt, J = 17.1, 7.8, 1.1 Hz, 1H), 5.30 (tt, J = 10.5, 1.0 Hz, 1H), 5.11 (qd, J = 6.6, 5.9, 1.3 Hz, 1/2H), 4.93−4.83 (m, 1H), 3.80 (d, J = 1.5 Hz, 3H), 3.71−3.57 (m, 1H), 2.79 (ddd, J = 13.2, 7.2, 5.9 Hz, 1/2H), 2.63 (ddd, J = 13.0, 9.1, 6.3 Hz, 1/2H), 2.47 (ddd, J = 13.0, 11.0, 9.4 Hz, 1/2H), 2.24 (ddd, J = 13.1, 9.2, 6.6 Hz, 1/2H).

Dimethyl 6,6-Dimethyl-5-oxo-7-phenyl-3-vinyl-2,3,6,8a-tetrahydroindolizine-1,1(5*H*)-dicarboxylate (6). Isobutyryl chloride (58 μL, 0.55 mmol, 1.1 equiv) was dissolved in DCM (3 mL), and Et_3N (84 μL, 0.6 mmol, 1.2 equiv) was added to the solution at ambient temperature. The mixture was stirred for 0.5 h. Then, a solution of **3k** (0.157 g, 0.5 mmol, 1 equiv) in DCM (2 mL) was added to the mixture. The reaction mixture was stirred overnight, and the solvent was removed under pressure. The crude product was purified by flash column chromatography on silica gel (200−300 mesh, petroleum ether/ethyl acetate, 20:1) to obtain compound **6** as a pair of unseparable diastereoisomers (178 mg, 94%), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.24 (m, 3H), 7.23−7.18 (m, 1H), 7.13−7.08 (m, 1H), 5.78 (tdd, J = 16.6, 10.4, 6.3 Hz, 1H), 5.40 (t, J = 4.9 Hz, 1H), 5.27−5.14 (m, 2H), 4.83−4.74 (m, 1H), 3.78 (d, J = 2.5 Hz, 3H), 3.76 (s, 3H), 2.92 (ddd, J = 13.7, 8.5, 2.4 Hz, 1H), 2.56 (ddd, J = 13.6, 6.1, 3.6 Hz, 1H), 1.28 (d, 3H), 0.94 (d, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5, 173.5, 169.6, 169.3, 168.8, 140.0, 139.8, 136.4, 136.3, 136.2, 136.1, 129.3, 129.2, 128.4, 128.3, 127.2, 116.5, 116.3, 106.0, 105.7, 77.5, 61.6, 58.2, 57.8, 53.6, 53.6, 53.5, 53.4, 51.3, 51.1, 42.7, 42.6, 37.4, 37.3, 25.7, 25.6, 21.0, 20.5. IR (film, cm^{-1}): 2956, 2930, 2859, 1739, 1672, 1443, 1387, 1260, 1029, 1097, 1022, 801, 701. HRMS (MALDI-TOF) m/z: $[M]^+$ calcd for $C_{22}H_{25}NO_5$, 383.1733; found, 383.1735.

■ ASSOCIATED CONTENT

Supporting Information

Spectra (^{1}H and ^{13}C) of all new compounds, 2D NOESY spectra for **3p** and **3s**, and HPLC method for **1c** and **3m**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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