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Methylenecyclopropane Ring Formation/Opening Cascade for the Synthesis of Indolizines

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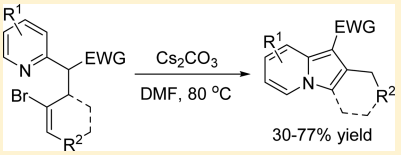
Supporting Information

ABSTRACT: A unique strategy toward the synthesis of polysubstituted indolizines has been developed. When 2-pyridinyl-2-(2′-bromoallyl)-1-carboxylates were treated with Cs_2CO_3, the starting material went through a methylenecyclopropane ring formation/opening cascade, and the corresponding indolizines were obtained in moderate to good yield as a single regioisomer.



N-fused heterocycles are one of the abundantly applicable motifs in organic chemistry, and they are widely applied in medicinal and material chemistry. Countless pharmaceutical intermediates, dyes, and high-performance materials are prepared.[1] Among all the nitrogen-containing heterocycles, indolizines are one important subclass due to their signigficant biological activities. Various enzyme inhibitors and antimicrobial and anticancer agents are developed (Figure 1).[2]

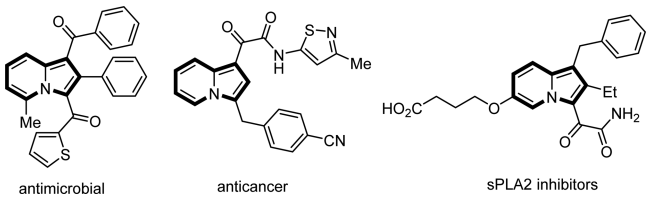
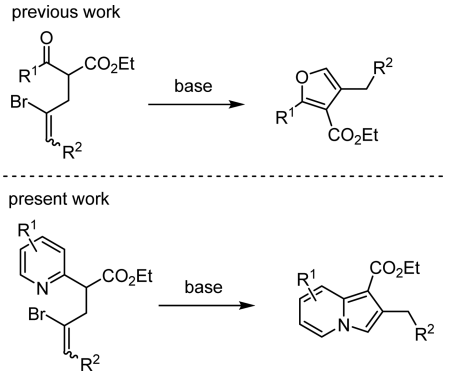


Figure 1. Representative biologically active indolizine derivatives.

Indolizines have received great attention from the synthetic community, and versatile strategies and methods have been developed to access the scaffold and its derivatives.[3] Most of the approaches toward indolizines can be categorized into four types of reactions: cyclocondensations,[4] cycloadditions,[5] cyclization/elimination,[6] and cycloisomerizations.[7] These methods, however, would require either harsh reaction conditions or transition metals and ligands. We believe that there is still unexplored territories in indolizine synthesis, and a novel and environmentally friendly methodology is regarded as a necessity.

Previously, we developed a novel strategy toward the synthesis of furan-3-carboxylates from 3-substituted 2-(2′-bromoallyl)-3-oxo-1-carboxylate (Scheme 1).[8] The reaction went through an allenic intermediate and methylenecyclopropane ring formation/opening sequence. We further envisioned that substrates bearing a pyridinyl functionality, in place of the carbonyl group, could be used to achieve similar transformation

Scheme 1. Previous and Current Work Comparison



to access indolizines by utilizing the nucleophilic character of the nitrogen atom. To the best of our knowledge, this is the first example of preparing polysubstituted indolizines from 2-pyridinyl-2-(2′-bromoallyl)-1-carboxylates.

To optimize the reaction conditions, pyridine derivative **1a** was tested under various conditions (Table 1). Starting with the optimized conditions from our previous research,[8a] the reaction went smoothly and 77% yield of **2a** was obtained in the presence of 2 equiv of Cs_2CO_3 and DMF as solvent (entry 1). The spectroscopic data displayed by **2a** were identical to those reported in the literature.[4c] Extensive base screening showed that Cs_2CO_3 remained the best choice (entries 2−9), and only K_3PO_4 gave comparable yield (entry 3), whereas no reaction occurred in the absence of base (entry 10). Polar aprotic solvents such as DMF and DMSO (entry 11) were preferred in this transformation. No reactions were detected when halogenated solvents (entries 12−14) and toluene (entry 17) were used as solvents. Other polar solvents such as dioxane

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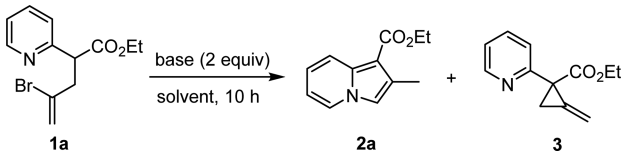
Table 1. Reaction of Ethyl 4-Bromo-2-(pyridin-2-yl)pent-4-enoate under Various Conditions



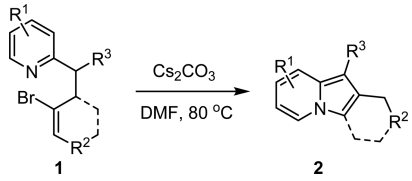
entry	base	solvent	temp (°C)	yield of **2a**[a] (%)	yield of **3**[a] (%)
1	Cs_2CO_3	DMF	80	77	
2	NaH	DMF	80	13	
3	K_3PO_4	DMF	80	72	
4	CaOAc	DMF	80	20	
5[b]	$NaHCO_3$	DMF	80		
6	K_2CO_3	DMF	80	4	
7[b]	DIPEA	DMF	80		
8[b]	DBU	DMF	80		
9[b]	NMM	DMF	80		
10[b]		DMF	80		
11	Cs_2CO_3	DMSO	80	71	
12[b]	Cs_2CO_3	DCM	80		
13[b]	Cs_2CO_3	DCE	80		
14[b]	Cs_2CO_3	$CHCl_3$	80		
15[b]	Cs_2CO_3	dioxane	80		
16	Cs_2CO_3	MeCN	80	trace	
17[b]	Cs_2CO_3	toluene	80		
18	Cs_2CO_3	NMP	80	47	
19	Cs_2CO_3[c]	DMF	80	42	
20	Cs_2CO_3[d]	DMF	80	59	
21	Cs_2CO_3[e]	DMF	80	65	
22	Cs_2CO_3	DMF	60	25	50
23	Cs_2CO_3	DMF	70	20	45
24	Cs_2CO_3	DMF	90	75	
25	Cs_2CO_3	DMF	100	72	

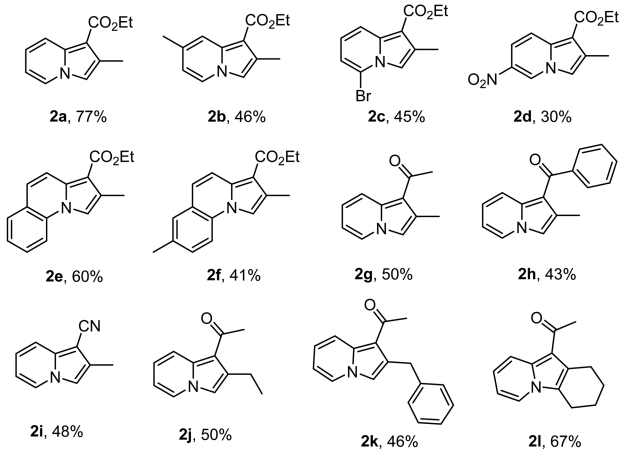
[a]Isolated yield. [b]No reaction. [c]1.0 equiv. [d]1.5 equiv. [e]2.5 equiv.

(entry 15), MeCN (entry 16), and NMP (entry 18) did not lead to any acceptable yield, probably because these are not ideal for solvating the cesium cation. The amount of base required for this reaction was also examined (entries 1 and 19–21), and 2 equiv of Cs_2CO_3 was found to give the highest yield. It was interesting to realize that the methylenecyclopropane intermediate **3** could be isolated when the reaction was run at lower temperature: 50 and 45% yields of intermediate **3** were isolated at 60 and 70 °C, respectively (entries 22 and 23). The isolated intermediate **3** is not stable while neat, and it will transform into indolizine **2a** spontaneously at room temperature overnight. Heating **3** could accelerate the conversion rate to **2a**. Isolation of the methylenecyclopropane intermediate **3** supports our hypothesis of the reaction mechanism. Although elevated temperature favored the formation of **2a**, no improvement was observed at a temperature higher than 80 °C (entries 24 and 25 vs 1).

The substrate scope was further explored, and the results were collected in Table 2. Reactions of substrates with either an electron-donating or electron-withdrawing group substituted pyridine ring proceeded smoothly to afford the desired product in moderate yield (**2b–d**). When pyridines were replaced by more π-electron-delocalized quinolines, no reactivity decrease was observed (**2e**, **2f**). This transformation was also compatible with various electron-withdrawing groups other than esters on the benzylic position: methylketone, benzophenone, and

Table 2. Substrate Scope

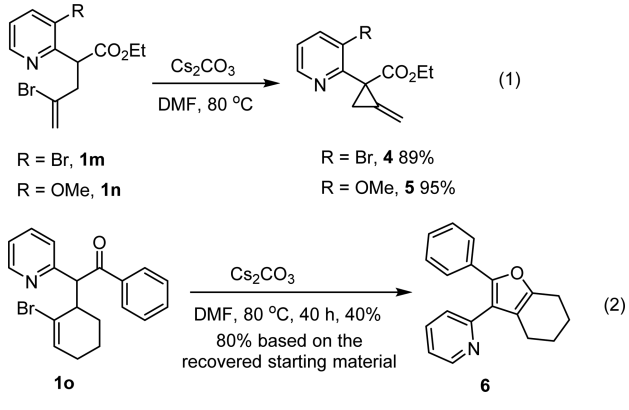




cyanide derivatives delivered the corresponding cycloadduct eventlessly (**2g–i**). In regards to acceptor scope, the sterically disfavored 5-methyl (**2j**) and 5-phenyl (**2k**) substituted alkenes, as well as strained cyclic alkene (**2l**), could all participate in the reaction successfully. It should be noted that only 1,2-disubstituted indolizines were isolated, and no other isomers (i.e., 1,3-disubstituted derivatives or the corresponding furan derivatives resulting from nucleophilic attack of the methylenecyclopropane ring with the carbonyl oxygen atom) were observed. Increasing the bulkiness around the alkenes (**2j–l**) did not alter the regiochemical outcome, which indicated that the indolizine formation is highly regioselective.

The limits of the substrates scope were revealed as we were testing the edge of this methodology. First, for substrates with a 3-substituted pyridine ring, no indolizines but the methylenecyclopropanes **4** and **5** were isolated (Scheme 2, eq 1). The electrostatic nature of the pyridine ring would not be the reason why no nucleophilic ring opening proceeds. Both electron-rich and electron-poor pyridines have been demonstrated to deliver the indolizine products (**2b–d**). It is possible that the substitutions on the pyridine ring distort the conformation of

Scheme 2. Substrate Limitations



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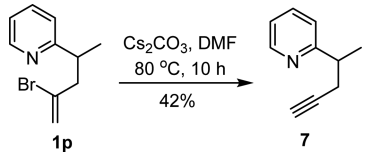
the methylenecyclopropane intermediate and make the lone pair on the nitrogen stay away from the Bürgi−Dunitz angle of the cyclopropane ring. Calculations were conducted on the transition state of the nucleophilic ring opening step, and the high-energy profiles obtained supported our rationale. Second, reaction of the highly sterically hindered substrate **1o** proceeded slowly and cleanly to provide fused furan **6** instead of the desired indolizine (Scheme 2, eq 2). The flanking phenyl group may block the nucleophilic pyridine, thus facilitating O-attack over N-attack.

Finally, we tested the possibility of indolizine formation of compound **1p** (Scheme 3). However, only alkyne **7** was

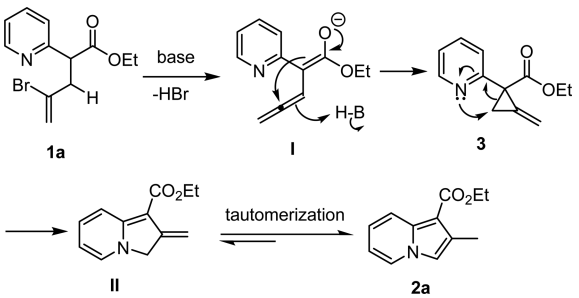
Scheme 3. Control Experiment for Determining the Reaction Mechanism



isolated. This result implied that an electron-withdrawing group at the benzylic position of the pyridine ring (thus facilitating methylenecyclopropane ring formation) is essential to the reaction. More importantly, this evidence indicated that direct addition/elimination sequence from nitrogen to vinyl bromide is not the preferred pathway.

Based on the results above and our previous research outcome, a plausible mechanism involving cyclopropane ring formation and nucleophilic cyclopropane ring opening was proposed in Scheme 4. Enolization and elimination of HBr in

Scheme 4. Proposed Mechanism



the presence of base afforded intermediate **I**, and subsequent intramolecular enolate attack provided methylenecyclopropane **3**. Pyridine nucleophilic addition opened the cyclopropane ring from the less sterically hindered side to give **II**, which underwent tautomerization to produce indolizine **2a**.

In summary, we have developed a novel Cs_2CO_3-mediated protocol toward the synthesis of indolizines. The reaction mechanism was believed to proceed via a methylenecyclopropane ring formation/opening sequence. This approach is environmentally friendly with a broad spectrum of substrate scope.

EXPERIMENTAL SECTION

Solvents were dried according to standard procedures[9] where needed. Melting points were determined on a hot-stage apparatus and were uncorrected. Infrared spectra were obtained using an FT-IR spectrometer. ^1H and ^{13}C NMR spectra were obtained on a 400 MHz spectrometer. Mass spectra were recorded on a Q-TOF micro spectrometer. Flash column chromatography was performed over 200−300 mesh silica gel.

General Procedure for the Preparation of 2a−l, 4, 5, 6, and 7. A sealed tube was charged with **1a−1p** (1.0 mmol), Cs_2CO_3 (2.0 mmol), and DMF (10 mL). The reaction system was recharged with nitrogen three times. The reaction mixture was allowed to stir at 80 °C until completion of reaction according to TLC. The cooled mixture was diluted with water (2 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with brine (3 × 10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuum. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc) to afford the products.

*Ethyl 2-Methylindolizine-1-carboxylate (**2a**).*[4c] The title compound was prepared according to the general procedure by stirring a mixture of ethyl 4-bromo-2-(pyridin-2-yl)pent-4-enoate **1a** (56.6 mg, 0.2 mmol), Cs_2CO_3 (133.0 mg, 0.4 mmol), and DMF (2.0 mL) at 80 °C for 10 h. The crude product was purified by silica gel column chromatography (10% EtOAc in petroleum ether) to afford **2a** (31.5 mg, 77% yield) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (1H, d, J = 9.0 Hz), 7.87 (1H, d, J = 6.8 Hz), 7.04 (1H, s), 6.97 (1H, ddd, J = 9.0, 6.7, 1.0 Hz), 6.62 (1H, td, J = 6.8, 1.1 Hz), 4.36 (2H, q, J = 7.1 Hz), 2.48 (3H, d, J = 0.8 Hz), 1.41 (3H, t, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 136.5, 128.4, 125.2, 121.8, 119.6, 113.3, 111.9, 102.5, 59.1, 14.6, 12.9; IR (neat) ν_{max}/cm^{-1} 1680, 1506, 1427, 1259, 1214, 1080, 1028; HRMS (ESI-TOF) (m/z) [M + Na]$^+$ calcd for $C_{12}H_{13}NNaO_2$ 226.0839, found 226.0848.

*Ethyl 2,7-Dimethylindolizine-1-carboxylate (**2b**).*[4c] The title compound was prepared according to the general procedure by stirring a mixture of ethyl 4-bromo-2-(4-methylpyridin-2-yl)pent-4-enoate **1b** (59.4 mg, 0.2 mmol), Cs_2CO_3 (133.0 mg, 0.4 mmol), and DMF (2.0 mL) at 80 °C for 10 h. The crude product was purified by silica gel column chromatography (7% EtOAc in petroleum ether) to afford **2b** (20.0 mg, 46% yield) as a pale yellow solid: mp 54−56 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (1H, s), 7.76 (1H, d, J = 6.9 Hz), 6.95 (1H, s), 6.46 (1H, dd, J = 6.9, 1.5 Hz), 4.36 (2H, q, J = 7.2 Hz), 2.45 (3H, d, J = 0.6 Hz), 2.34 (3H, s), 1.41 (3H, t, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 137.2, 132.7, 128.1, 124.7, 118.1, 114.5, 112.5, 101.1, 59.0, 21.4, 14.7, 13.0; IR (neat) ν_{max}/cm^{-1} 1660, 1513, 1416, 1266, 1235, 1081, 1038; HRMS (ESI-TOF) (m/z) [M + H]$^+$ calcd for $C_{13}H_{16}NO_2$ 218.1176, found 218.1172.

*Ethyl 5-Bromo-2-methylindolizine-1-carboxylate (**2c**).* The title compound was prepared according to the general procedure by stirring a mixture of ethyl 4-bromo-2-(6-bromopyridin-2-yl)pent-4-enoate **1c** (73.0 mg, 0.2 mmol), Cs_2CO_3 (133.0 mg, 0.4 mmol), and DMF (2.0 mL) at 80 °C for 10 h. The crude product was purified by silica gel column chromatography (2% EtOAc in petroleum ether) to afford **2c** (25.3 mg, 45% yield) as a white solid: mp 51−53 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (1H, d, J = 8.8 Hz), 7.37 (1H, s), 6.92 (1H, d, J = 7.0 Hz), 6.85 (1H, t, J = 7.5 Hz), 4.38 (2H, q, J = 7.1 Hz), 2.52 (3H, s), 1.43 (3H, t, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 138.0, 128.7, 121.7, 118.4, 115.9, 114.8, 114.2, 104.7, 59.4, 14.6, 13.1; IR (neat) ν_{max}/cm^{-1} 1680, 1482, 1433, 1274, 1249, 1202, 1085; HRMS (ESI-TOF) (m/z) [M + H]$^+$ calcd for $C_{12}H_{13}BrNO_2$ 282.0124, found 282.0128.

*Ethyl 2-Methyl-6-nitroindolizine-1-carboxylate (**2d**).*[4c] The title compound was prepared according to the general procedure by stirring a mixture of ethyl 4-bromo-2-(5-nitropyridin-2-yl)pent-4-enoate **1d** (65.6 mg, 0.2 mmol), Cs_2CO_3 (133.0 mg, 0.4 mmol), and DMF (2.0 mL) at 80 °C for 15 h. The crude product was purified by silica gel column chromatography (7% EtOAc in petroleum ether) to afford **2d** (15.0 mg, 30% yield) as a yellow solid: mp 118−121 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.03 (1H, dd, J = 1.2, 0.6 Hz), 8.20 (1H, d, J = 9.9 Hz), 7.71 (1H, dd, J = 10.0, 2.0 Hz), 7.28 (1H, s), 4.40 (2H, q, J = 7.1 Hz), 2.52 (3H, d, J = 0.9 Hz), 1.43 (3H, t, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 136.9, 136.0, 132.4, 125.5, 119.3, 115.7, 115.1, 106.3, 59.9, 14.5, 13.1; IR (neat) ν_{max}/cm^{-1} 1681, 1634, 1543, 1500, 1321, 1281, 1190, 1072; HRMS (ESI-TOF) (m/z) [M + H]$^+$ calcd for $C_{12}H_{13}N_2O_4$ 249.0870, found 249.0875.

*Ethyl 2-Methylpyrrolo[1,2-a]quinoline-3-carboxylate (**2e**).*[4c] The title compound was prepared according to the general procedure by

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stirring a mixture of ethyl 4-bromo-2-(quinolin-2-yl)pent-4-enoate **1e** (66.6 mg, 0.2 mmol), Cs_2CO_3 (133.0 mg, 0.4 mmol), and DMF (2.0 mL) at 80 °C for 6 h. The crude product was purified by silica gel column chromatography (10% EtOAc in petroleum ether) to afford **2e** (30.4 mg, 60% yield) as a white solid: mp 120−122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (1H, d, J = 9.5 Hz), 7.84 (1H, d, J = 8.4 Hz), 7.69 (1H, d, J = 7.5 Hz), 7.57 (1H, S), 7.54 (1H, t, J = 8.3 Hz), 7.37 (1H, t, J = 7.3 Hz), 7.28 (1H, d, J = 9.5 Hz), 4.40 (2H, q, J = 7.1 Hz), 2.52 (3H, s), 1.43 (3H, t, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 134.6, 132.2, 128.7, 128.5, 126.7, 124.1, 123.7, 122.9, 118.7, 114.5, 111.8, 106.2, 59.4, 14.6, 13.1; IR (neat) ν_{max}/cm^{-1} 1669, 1549, 1448, 1263, 1213, 1074; HRMS (ESI-TOF) (m/z) [M + H]$^+$ calcd for $C_{16}H_{16}NO_2$ 254.1176, found 254.1183.

*Ethyl 2,7-Dimethylpyrrolo[1,2-a]quinoline-3-carboxylate (**2f**).* The title compound was prepared according to the general procedure by stirring a mixture of ethyl 4-bromo-2-(6-methylquinolin-2-yl)pent-4-enoate **1f** (69.4 mg, 0.2 mmol), Cs_2CO_3 (133.0 mg, 0.4 mmol), and DMF (2.0 mL) at 80 °C for 10 h. The crude product was purified by silica gel column chromatography (10% EtOAc in petroleum ether) to afford **2f** (22.0 mg, 41% yield) as a white solid: mp 118−120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (1H, d, J = 9.4 Hz), 7.78 (1H, d, J = 8.5 Hz), 7.59 (1H, s), 7.52 (1H, s), 7.40 (1H, dd, J = 8.5, 1.5 Hz), 7.28 (1H, s), 4.42 (2H, q, J = 7.1 Hz), 2.54 (3H, d, J = 0.7 Hz), 2.50 (3H, s), 1.46 (3H, t, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 134.5, 133.7, 130.4, 129.8, 128.4, 126.6, 123.7, 122.8, 118.6, 114.3, 111.7, 105.9, 59.3, 21.0, 14.6, 13.1; IR (neat) ν_{max}/cm^{-1} 1669, 1549, 1433, 1272, 1197, 1079; HRMS (ESI-TOF) (m/z) [M + H]$^+$ calcd for $C_{17}H_{18}NO_2$ 268.1332, found 268.1332.

*1-(2-Methylindolizin-1-yl)ethanone (**2g**).*[10] The title compound was prepared according to the general procedure by stirring a mixture of 5-bromo-3-(pyridin-2-yl)hex-5-en-2-one **1g** (51.0 mg, 0.2 mmol), Cs_2CO_3 (133.0 mg, 0.4 mmol), and DMF (2.0 mL) at 80 °C for 10 h. The crude product was purified by silica gel column chromatography (7% EtOAc in petroleum ether) to afford **2g** (17.5 mg, 50% yield) as a light yellow needle-like solid: mp 69−72 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (1H, d, J = 9.1 Hz), 7.90 (1H, d, J = 6.8 Hz), 7.09−7.04 (2H, m), 6.70 (1H, td, J = 6.8, 1.1 Hz), 2.55 (3H,s), 2.50 (3H, d, J = 0.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.3, 136.7, 127.0, 125.1, 123.4, 120.2, 114.1, 113.1, 112.7, 30.8, 14.2; IR (neat) ν_{max}/cm^{-1} 1633, 1604, 1489, 1406, 1228, 1140, 1020; HRMS (ESI-TOF) (m/z) [M + H]$^+$ calcd for $C_{11}H_{12}NO$ 174.0913, found 174.0912.

*(2-Methylindolizin-1-yl)(phenyl)methanone (**2h**).*[11] The title compound was prepared according to the general procedure by stirring a mixture of 4-bromo-1-phenyl-2-(pyridin-2-yl)pent-4-en-1-one **1h** (63 mg, 0.2 mmol), Cs_2CO_3 (133.0 mg, 0.4 mmol), and DMF (2.0 mL) at 80 °C for 10 h. The crude product was purified by silica gel column chromatography (5% EtOAc in petroleum ether) to afford **2h** (20.0 mg, 43% yield) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (1H, d, J = 6.8 Hz), 7.67 (2H, t, J = 6.9, 1.5 Hz), 7.51 (1H, ttt, J = 8.4, 7.4, 1.2 Hz), 7.47−7.41 (3H, m), 7.10 (1H, s), 6.88 (1H, ddd, J = 7.7, 6.7, 0.9 Hz), 6.64 (1H, td, J = 6.8, 1.0 Hz), 2.24 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.1, 142.1, 137.0, 130.8, 128.5, 128.3, 128.2, 125.3, 122.4, 119.4, 114.3, 112.7, 12.9; IR (neat) ν_{max}/cm^{-1} 1605, 1493, 1415, 1299, 1239, 1137; HRMS (ESI-TOF) (m/z) [M + H]$^+$ calcd for $C_{16}H_{14}NO$ 236.1070, found 236.1079.

*2-Methylindolizine-1-carbonitrile (**2i**).*[12] The title compound was prepared according to the general procedure by stirring a mixture of 4-bromo-2-(pyridin-2-yl)pent-4-enenitrile **1i** (47.2 mg, 0.2 mmol), Cs_2CO_3 (133.0 mg, 0.4 mmol), and DMF (2.0 mL) at 80 °C for 10 h. The crude product was purified by silica gel column chromatography (10% EtOAc in petroleum ether) to afford **2i** (15.0 mg, 48% yield) as a white needle-like solid: mp 99−101 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (1H, d, J = 6.9 Hz), 7.51 (1H, d, J = 9.0 Hz), 7.05 (1H, s), 7.98 (1H, ddd, J = 8.8, 6.7, 0.8 Hz), 6.67 (1H, td, J = 6.8, 0.9 Hz), 2.38 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7, 128.5, 125.8, 122.0, 117.2, 116.7, 112.4, 112.3, 82.8, 11.1; IR (neat) ν_{max}/cm^{-1} 2201, 1635, 1519, 1298, 1249, 1137; HRMS (ESI-TOF) (m/z) [M + H]$^+$ calcd for $C_{10}H_9N_2$ 157.0760, found 157.0761.

*1-(2-Ethylindolizin-1-yl)ethanone (**2j**).* The title compound was prepared according to the general procedure by stirring a mixture of 5-bromo-3-(pyridin-2-yl)hept-5-en-2-one **1j** (53.4 mg, 0.2 mmol), Cs_2CO_3 (133.0 mg, 0.4 mmol), and DMF (2.0 mL) at 80 °C for 20 h. The crude product was purified by silica gel column chromatography (17% EtOAc in petroleum ether) to afford **2j** (19.0 mg, 50% yield) as a pale yellow needle-like solid: mp 87−89 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (1H, d, J = 9.1 Hz), 7.93 (1H, d, J = 6.8 Hz), 7.08−7.04 (2H, m), 6.69 (1H, td, J = 6.8, 1.1 Hz), 2.96 (2H, qd, J = 7.4, 0.6 Hz), 2.56 (3H, s), 1.32 (3H, t, J = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.2, 136. 8, 134.1, 125.5, 123.3, 120.1, 112.8, 112.6, 112.6, 31.0, 21.3, 14.2; IR (neat) ν_{max}/cm^{-1} 1881, 1760, 1680, 1540, 1375, 1270, 1108; HRMS (ESI-TOF) (m/z) [M + H]$^+$ calcd for $C_{12}H_{14}NO$ 188.1070, found 188.1070.

*1-(2-Phenylindolizin-1-yl)ethanone (**2k**).* The title compound was prepared according to the general procedure by stirring a mixture of 5-bromo-6-phenyl-3-(pyridin-2-yl)hex-5-en-2-one **1k** (65.8 mg, 0.2 mmol), Cs_2CO_3 (133.0 mg, 0.4 mmol), and DMF (2.0 mL) at 80 °C for 16 h. The crude product was purified by silica gel column chromatography (10% EtOAc in petroleum ether) to afford **2k** (23.0 mg, 46% yield) as a brown oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (1H, d, J = 9.0 Hz), 7.66 (1H, d, J = 7.0 Hz), 7.25−7.22 (2H, m), 7.19−7.16 (1H, m), 7.10 (2H, d, J = 7.0 Hz), 7.04 (1H, ddd, J = 8.9, 6.7, 0.9 Hz), 6.89 (1H, s), 6.65 (1H, td, J = 6.9, 1.2 Hz), 4.14 (2H, s), 2.43 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8, 135.7, 134.7, 127.8, 127.3, 125.9, 122. 5, 122.2, 121.9, 119.8, 115.3, 112.3, 111.6, 31.4, 26.9; IR (neat) ν_{max}/cm^{-1} 1830, 1750, 1685, 1500,1450, 1275, 1150; HRMS (ESI-TOF) (m/z) [M + H]$^+$ calcd for $C_{17}H_{16}NO$ 250.1226, found 250.1230.

*1-(1,2,3,4-Tetrahydropyrido[1,2-a]indol-10-yl)ethanone (**2l**).*[13] The title compound was prepared according to the general procedure by stirring a mixture of 1-(2-bromocyclohex-2-en-1-yl)-1-(pyridin-2-yl)propan-2-one **1l** (58.6 mg, 0.2 mmol), Cs_2CO_3 (133.0 mg, 0.4 mmol), and DMF (2.0 mL) at 80 °C for 16 h. The crude product was purified by silica gel column chromatography (5% EtOAc in petroleum ether) to afford **2l** (28.6 mg, 67% yield) as a yellow needle-like solid: mp 153−156 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (1H, d, J = 9.0 Hz), 7.71 (1H, d, J = 6.8 Hz), 7.07 (1H, ddd, J = 8.9, 6.7, 0.9 Hz), 6.76 (1H, td, J = 6.8, 1.2 Hz), 2.98 (2H, t, J = 6.1 Hz), 2.67 (2H, t, J = 6.1 Hz), 2.51 (3H, s), 1.98−1.93 (2H, m), 1.91−1.85 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.0, 135.6, 125.6, 122.7, 121.9, 121.7, 120.1, 112.6, 111.6, 30.8, 25.0, 23.6, 22.2, 21.3. IR (neat) ν_{max}/cm^{-1} 1800, 1575, 1430, 1350, 1200, 1120, 1075; HRMS (ESI-TOF) (m/z) [M + H]$^+$ calcd for $C_{14}H_{16}NO$ 214.1226, found 214.1230.

*Ethyl 1-(3-Bromopyridin-2-yl)-2-methylenecyclopropanecarboxylate (**4**).* The title compound was prepared according to the general procedure by stirring a mixture of ethyl 4-bromo-2-(3-bromopyridin-2-yl)pent-4-enoate **1m** (72.6 mg, 0.2 mmol), Cs_2CO_3 (133.0 mg, 0.4 mmol), and DMF (2.0 mL) at 80 °C for 15 h. The crude product was purified by silica gel column chromatography (7% EtOAc in petroleum ether) to afford **4** (50.0 mg, 89% yield) as a pale yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (1H, dd, J = 4.7, 1.4 Hz), 7.87 (1H, dd, J = 8.0, 1.5 Hz), 7.10 (1H, dd, J = 8.0, 4.7 Hz), 5.98 (1H, t, J = 2.9 Hz), 5.57 (1H, t, J = 2.3 Hz), 4.21−4.10 (2H, m), 2.41 (1H, dt, J = 9.5, 2.6 Hz), 2.23 (1H, dt, J = 9.5, 2.6 Hz), 1.18 (3H, t, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 154.9, 147.3, 140.3, 133.7, 124.0, 123.7, 104.9, 61.4, 35.1, 18.8, 14.1; IR (neat) ν_{max}/cm^{-1} 1719, 1571, 1443, 1246, 1087, 1017; HRMS (ESI-TOF) (m/z) [M + H]$^+$ calcd for $C_{12}H_{13}BrNO_2$ 282.0124, found 282.0129.

*Ethyl 1-(3-Methoxypyridin-2-yl)-2-methylenecyclopropanecarboxylate (**5**).* The title compound was prepared according to the general procedure by stirring a mixture of ethyl 4-bromo-2-(3-methoxypyridin-2-yl)pent-4-enoate **1n** (62.6 mg, 0.2 mmol), Cs_2CO_3 (133.0 mg, 0.4 mmol), and DMF (2.0 mL) at 80 °C for 48 h. The crude product was purified by silica gel column chromatography (17% EtOAc in petroleum ether) to afford **5** (44.3 mg, 95% yield) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (1H, dd, J = 4.5, 1.6 Hz), 7.19 (1H, dd, J = 8.2, 4.5 Hz), 7.15 (1H, dd, J = 8.2, 4.5 Hz), 5.75 (1H, t, J = 2.8 Hz), 5.53 (1H, t, J = 2.2 Hz), 4.18−4.05 (2H, m), 3.86 (3H, s), 2.35 (1H, dt, J = 9.4, 2.5 Hz), 2.18 (1H, dt, J = 9.4, 2.5 Hz), 1.15 (3H, t, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 154.4, 145.3, 139.3, 132.9, 122.4, 116.3, 103.2, 59.9, 54.42, 30.5, 16. 9, 13.1;

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IR (neat) ν_{max}/cm^{-1} 1720, 1560, 1465, 1258, 1090, 1024; HRMS (ESI-TOF) (m/z) $[M + H]^+$ calcd for $C_{13}H_{16}NO_3$ 234.1125, found 234.1141.

*2-(2-Phenyl-4,5,6,7-tetrahydrobenzofuran-3-yl)pyridine (**6**).*[14] The title compound was prepared according to the general procedure by stirring a mixture of 2-(2-bromocyclohex-2-en-1-yl)-1-phenyl-2-(pyridin-2-yl)ethanone **1o** (71.0 mg, 0.2 mmol), Cs_2CO_3 (133.0 mg, 0.4 mmol), and DMF (2.0 mL) at 80 °C for 40 h. The crude product was purified by silica gel column chromatography (10% EtOAc in petroleum ether) to afford **6** (44.0 mg, 40% yield) together with 35.5 mg of **1o** recovered.

Compound **6**: colorless solid; mp 113−115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (1H, dq, J = 4.9, 0.9 Hz), 7.63 (1H, td, J = 7.7, 1.9 Hz), 7.49−7.47 (2H, m), 7.33 (1H, d, J = 7.8 Hz), 7.30−7.27 (2H, m), 7.24−7.19 (2H, m), 2.72 (2H, tt, J = 6.2, 1.6 Hz), 2.52 (2H, tt, J = 6.2, 1.6 Hz), 1.95−1.89 (2H, m), 1.82−1.76 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 150.7, 149.8, 148.4, 136.1, 131.3, 128.3, 127.2, 126.2, 124.5, 122.0, 121.5, 119.4, 23.3, 23.0, 22.9, 21.6; IR (neat) ν_{max}/cm^{-1} 1850, 1720, 1557, 1500, 1430, 1280, 1095, 1035; HRMS (ESI-TOF) (m/z) $[M + H]^+$ calcd for $C_{19}H_{18}NO$ 276.1383, found 276.1385.

*2-(Pent-4-yn-2-yl)pyridine (**7**).* The title compound was prepared according to the general procedure by stirring a mixture of 2-(4-bromopent-4-en-2-yl)pyridine **1p** (45 mg, 0.2 mmol), Cs_2CO_3 (133.0 mg, 0.4 mmol), and DMF (2.0 mL) at 80 °C for 25 h. The crude product was purified by silica gel column chromatography (5% EtOAc in petroleum ether) to afford **7** (12.5 mg, 42% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (1H, d, J = 4.7 Hz), 7.60 (1H, td, J = 7.7, 1.7 Hz), 7.18 (1H, d, J = 7.8 Hz), 7.11 (1H, dd, J = 7.3, 5.4 Hz), 3.16−3.07 (1H, m), 2.62 (1H, ddd, J = 16.7, 6.6, 2.6 Hz), 2.51 (1H, ddd, J = 16.7, 6.6, 2.6 Hz), 1.92 (1H, t, J = 5.2 Hz), 1.39 (3H, d, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 149.3, 136.3, 121.8, 121.6, 83.0, 69.4, 40.9, 25.8, 19.7; IR (neat) ν_{max}/cm^{-1} 2120, 1520, 1470, 1402, 1150, 1018; HRMS (ESI-TOF) (m/z) $[M + H]^+$ calcd for $C_{10}H_{12}N$ 146.0964, found 146.0978.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b01073.

^{1}H and ^{13}C NMR spectra of compounds **2a−l** and **3−7** (PDF)

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Notes

The authors declare no competing financial interest.

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