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# A Methylenecyclopropane Ring Formation/Opening Cascade for the Synthesis of Indolizines

Congjun Zhu,[a] Peng Zhao,[b] Yan Qiao,[c] Ke Xiao,[a] Chuanjun Song,*[a] and Junbiao Chang*[a,d]

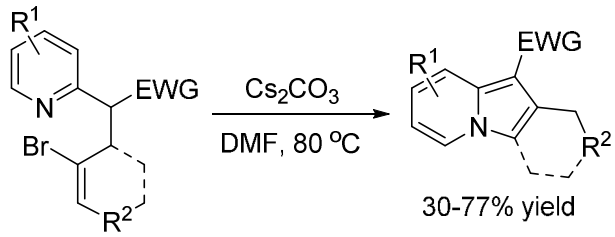
[a] College of Chemistry and Molecular Engineering, Zhengzhou University, Zhengzhou 450001, P. R. of China

[b] Department of Chemistry, University of California, 1102 Natural Sciences II, Irvine, California 92697-2025, United States

[c] Pathophysiology Department, Basic Medical College of Zhengzhou University, 100 Science Avenue, Zhengzhou 450001, P. R. of China

[d] Collaborative Innovation Center of New Drug Research and Safety Evaluation, Henan Province, 100 Science Avenue, 450001, P. R. of China

chjsong@zzu.edu.cn (C.S.); changjunbiao@zzu.edu.cn (J.C.)




Abstract: A unique strategy towards the synthesis of polysubstituted indolizines has been developed. Treating 2-pyridinyl-2-(2′-bromoallyl)-1-carboxylates 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 motif 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 inhibitor, antimicrobial and anticancer agents are developed (Figure 1).[2] Indolizines have

received great attention from synthetic community and versatile strategies and methods have been developed to access the scaffold and its derivatives.[3] Most of the approaches towards indolizines can be categorized into 4 type 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 indolizines synthesis and a novel and environmental-friendly methodology is regarded as a necessity.

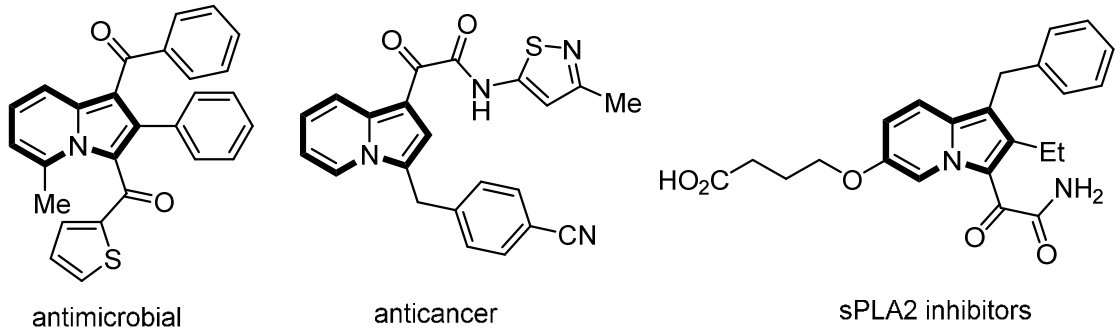
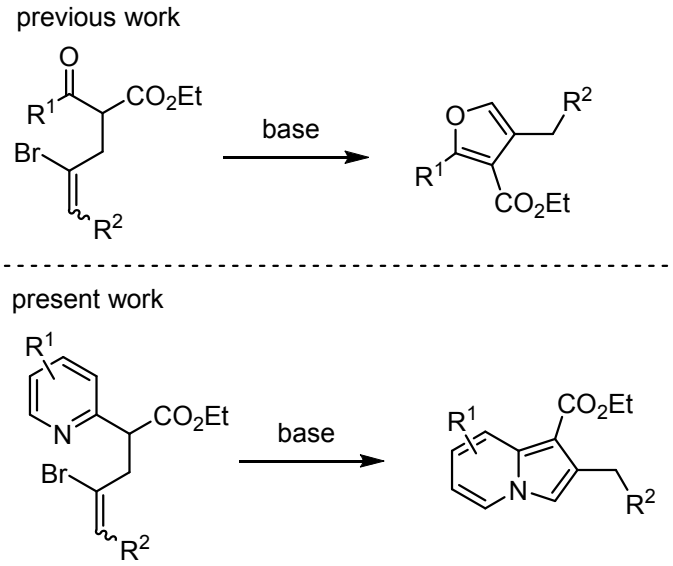



**Figure 1**. Representative biologically active indolizine derivatives.

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 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.

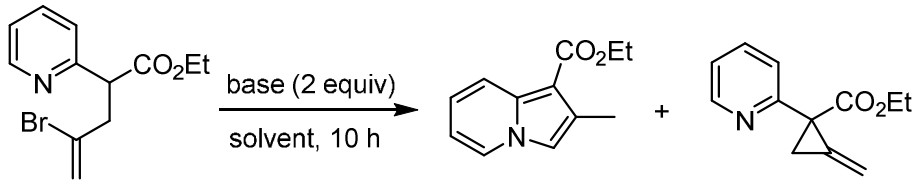



**Scheme 1**. Previous and current work comparison.

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 equivalents 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), while no reaction occurred in the absence of base (entry 10) Polar aprotic solvents 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 like dioxane (entry 15), MeCN (entry 16) and NMP (entry 18) didn't lead to any acceptable yield probably because these are not ideal at solvate the cesium cation. The amount of base required for this reaction was also examined (entries 1, 19-21) and 2 equivalents 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% yield of intermediate **3** were isolated at 60 $^oC$ and 70 $^oC$, respectively (entries 22, 23). The isolated intermediate **3** is not stable while neat and it will transform into indolizine **2a** spontaneously at room temperature for 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, 25 vs 1).

**Table 1**. Reaction of ethyl 4-bromo-2-(pyridin-2-yl)pent-4-enoate under various conditions.




**1a** **2a** **3**

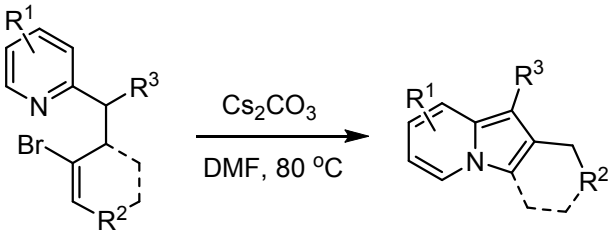
| Entry | Base | Solvent | Temp. (°C) | **2a** Yield (%)[a] | **3** Yield (%)[a] |
|---|---|---|---|---|---|
| 1 | $Cs_2CO_3$ | DMF | 80 | 77 | - |
| 2 | NaH | DMF | 80 | 13 | - |
| 3 | $K_3PO_4$ | DMF | 80 | 72 | - |
| 4 | CaOAc | DMF | 80 | 20 | - |
| 5[b] | $NaHCO_3$ | DMF | 80 | - | - |
| 6 | $K_2CO_3$ | 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.

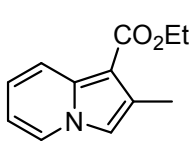
The substrate scope was further explored and the results were collected in table 2. Reactions of substrates with either an electron-donating or electron-withdrawing group substituted pyridine ring proceeded smoothly to afford the desired product in moderate yield (**2b-d**). When pyridines were replaced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

the benzylic position: methylketone, benzophenone and cyanide derivatives delivered the corresponding cycloadduct eventlessly (**2g-i**). In regards to acceptors scope, the sterically disfavored 5-methyl (**2j**) and 5-phenyl (**2k**) substituted alkenes, as well as strained cyclic alkene (**2l**), could all participate 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**-**2l**) didn't alter the regiochemical outcome, which indicated that the indolizine formation is highly regioselective.

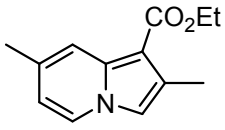
**Table 2**. Substrate scope.



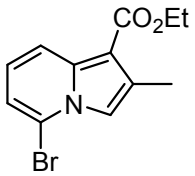

**1** **2**



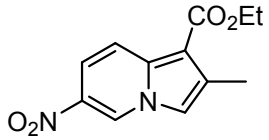

**2a**, 77%



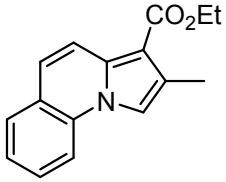

**2b**, 46%



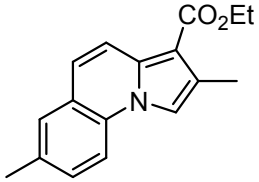

**2c**, 45%



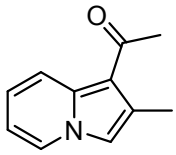

**2d**, 30%



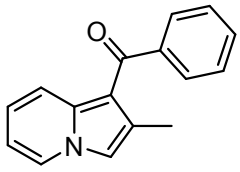

**2e**, 60%



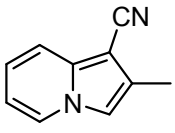

**2f**, 41%



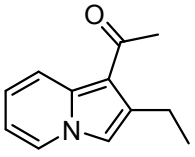

**2g**, 50%



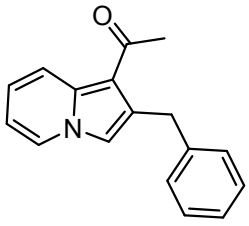

**2h**, 43%



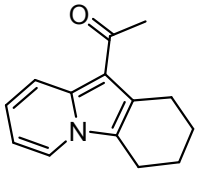

**2i**, 48%




**2j**, 50%

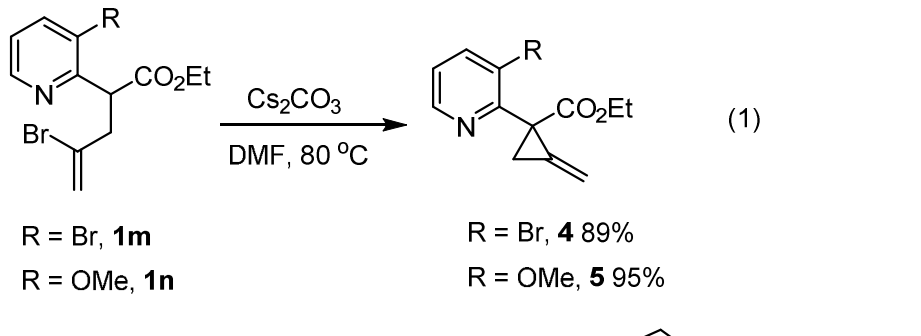


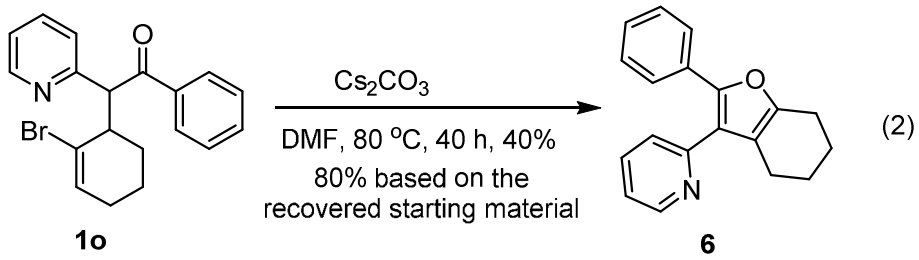

**2k**, 46%




**2l**, 67%

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 wouldn't 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**-**2d**). It is possible that the substitutions on the pyridine ring distort the conformation of the methylenecyclopropane intermediate and makes the lone pair on 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 while 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 facilitate O-attack over *N*-attack.

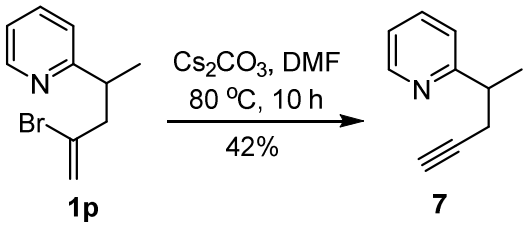



**Scheme 2**. Substrate limitations.

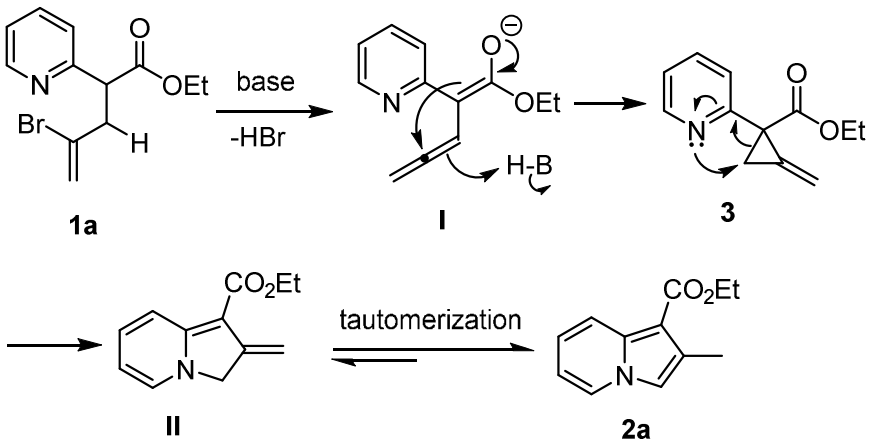
Finally, we tested the possibility of indolizine formation of compound **1p** (Scheme 3). However, only alkyne **7** was isolated. This result implied that an electron-withdrawing group at the benzylic position of the pyridine ring (thus facilitating methylenecyclopropane ring formation) is essential to

the reaction. More importantly, this evidence indicated that direct addition/elimination sequence from nitrogen to vinyl bromide is not the preferred pathway.




**Scheme 3**. Control experiment for determining reaction mechanism.

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 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**.




**Scheme 4**. Proposed mechanism.

In summary, we have developed a novel $Cs_2CO_3$-mediated protocol towards the synthesis of indolizines. The reaction mechanism was believed to proceed via a methylenecyclopropane ring

formation/opening sequence. This approach is environmental-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. $^{1}H$ 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 silica gel 200–300 mesh.

**General procedure for the preparation of 2a-l, 4, 5, 6, 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 for three times. The reaction mixture was allowed to stir at 80 $^{o}$C until completion of reaction according to TLC. The cooled mixture was diluted with water (2 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with brine (3 x 10 mL), and then 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 $^{o}$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; $^{1}H$ NMR (400 MHz, $CDCl_3$): $\delta$ 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, $CDCl_3$): $\delta$ 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): $\nu_{max}$/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 $^oC$ 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 $^oC$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 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, $CDCl_3$): $\delta$ 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): $\nu_{max}/cm^{-1}$ 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 $^oC$ 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 soild; mp 51-53 $^oC$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 8.17 (1H, d, 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, $CDCl_3$): $\delta$ 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): $\nu_{max}/cm^{-1}$ 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-carboxylat (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℃ 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 soild; mp 118-121 $^oC$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 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, $J$ = 7.1Hz), 2.52 (3H, d, $J$ = 0.9 Hz), 1.43 (3H, t, $J$ = 7.1 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 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): $\nu_{max}/cm^{-1}$ 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 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 $^oC$ 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 $^oC$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 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, $CDCl_3$): $\delta$ 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): $\nu_{max}/cm^{-1}$ 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 $^oC$ 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 $^oC$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 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, $CDCl_3$): $\delta$ 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): $\nu_{max}/cm^{-1}$ 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 $^oC$ 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 $^oC$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 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, $CDCl_3$): $\delta$ 193.3, 136.7, 127.0, 125.1, 123.4, 120.2, 114.1, 113.1, 112.7, 30.8, 14.2; IR (neat): $\nu_{max}$/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, $CDCl_3$): $\delta$ 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, $CDCl_3$): $\delta$ 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): $\nu_{max}$/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, $CDCl_3$): $\delta$ 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, $CDCl_3$): $\delta$ 137.7, 128.5, 125.8, 122.0, 117.2, 116.7, 112.4, 112.3, 82.8, 11.1; IR (neat): $\nu_{max}$/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, $CDCl_3$): $\delta$ 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, $CDCl_3$): $\delta$ 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): $\nu_{max}$/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 $^o$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, $CDCl_3$): $\delta$ 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), 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, $CDCl_3$): $\delta$ 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): $\nu_{max}$/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 $^o$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 $^o$C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 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, $CDCl_3$): $\delta$ 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): $\nu_{max}$/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, $CDCl_3$): $\delta$ 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, $CDCl_3$): $\delta$ 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): $\nu_{max}$/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, 0.2mmol), $Cs_2CO_3$ (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, $CDCl_3$): $\delta$ 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, $CDCl_3$): $\delta$ 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; IR (neat): $\nu_{max}$/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, $CDCl_3$): $\delta$ 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, $CDCl_3$): $\delta$ 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): $\nu_{max}$/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, $CDCl_3$): $\delta$ 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): $\nu_{max}$/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.

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Supporting Information. $^1$H and $^{13}$C NMR spectra of compounds **2a-l**, **3-7**.

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