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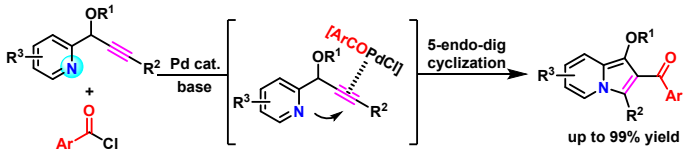
TOC

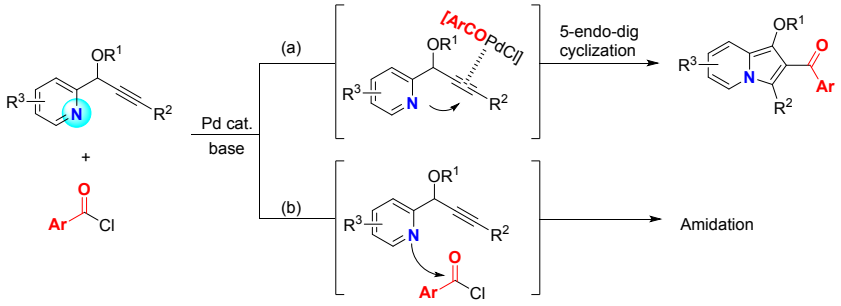


ABSTRACT: An efficient synthesis of indolizine derivatives from propargylic pyridines and aroyl chlorides was developed. The 5-*endo-dig* cyclization was initiated by the in situ formed acylpalladium species from the facile oxidative addition of aroyl chloride to Pd(0) complex. This transformation successfully occurred in the presence of an *N*-nucleophilic moiety and acid chlorides, a good electrophilic partner, affording highly functionalized indolizines in good-to-excellent yields.

INTRODUCTION

Pd-catalyzed cross-coupling reactions play a key role in current organic synthesis.[1,2] Among different electrophiles, acid chlorides are a useful and versatile coupling partner, easily available from inexpensive and numerous available carboxylic acids.[3] Owing to the facile oxidative addition to metal centers, acid chlorides have been used in the reactions with various substrates such as alkenes,[4] alkynes,[5] allenes,[6] and organometallic reagents.[7] Diverse transformations have been achieved because the carbonyl and chloro functionalities in acid chlorides can be involved in the catalytic system. For example, ketones can be obtained by arylacylation,[8] while various types of C−C bonds can be constructed by decarbonylative cross-coupling reactions.[9] Moreover, C-Cl bonds can be formed with or without the loss of CO.[10]

Indolizine is one of the most important skeletons among nitrogen-containing heterocycles and has been found in several natural products and biologically active compounds. Among the strategies to access indolizine structures, propargylic pyridines have attracted much attention, affording diverse indolizine derivatives.[11-13] Pd-catalyzed carbonylative cyclization of propargylic pyridines has been developed to efficiently form indolizines, where acylpalladium species is assumed to be the key intermediate in initiating the cyclization.[13a,13b] Considering the convenient formation of acylpalladium species from acid chlorides and Pd(0) complex, we envisioned that the acylpalladium species would induce 5-*endo-dig* cyclization to form highly functionalized indolizine derivatives (Scheme 1, Path a). Transition-metal-catalyzed coupling reactions using acid chlorides as a good electrophilic partner for substrates with an *N*-nucleophilic moiety in the molecular structure were rarely studied, where the nitrogen atom might easily react with acid chlorides to form the corresponding amides (Scheme 1, Path b). Herein, we report an efficient synthesis of indolizine derivatives by the cyclization of propargylic pyridines with aroyl chlorides triggered by the oxidative addition of aroyl chloride to Pd(0) complex.

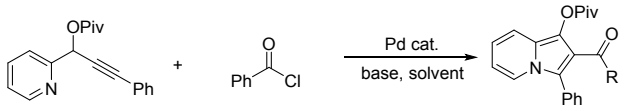


Scheme 1. Possible Reactions of Propargylic Pyridines and Aroyl Chlorides

RESULTS AND DISCUSSION

Initially, the reaction between substrate **1a** and benzoyl chloride (**2a**) was evaluated to optimize the reaction conditions (Table 1). In the presence of 5 mol% $Pd(PPh_3)_4$, indolizine **3aa** was isolated in 76% yield when using toluene as the solvent and Et_3N as the base at 60 °C (entry 1). The yield of **3aa** increased

Table 1. Screening of the Reaction Conditions[a]



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

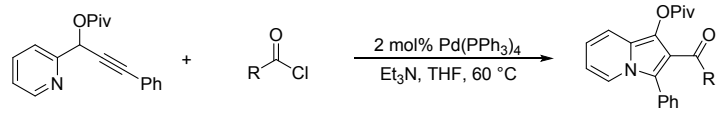
entry	cat. (mol %)	solvent	base	temp (°C)	yield[b] (%)
1	$Pd(PPh_3)_4$/5	Toluene	NEt_3	60	76
2	$Pd(PPh_3)_4$/5	THF	NEt_3	60	89
3	$Pd(PPh_3)_4$/5	MeCN	NEt_3	60	59
4	$Pd(PPh_3)_4$/5	THF	$NaHCO_3$	60	0
5	$Pd(PPh_3)_4$/5	THF	AcONa	60	0
6	$Pd(PPh_3)_4$/5	THF	DABCO	60	82
7	$Pd(PPh_3)_4$/5	THF	DBU	60	0
8	$Pd(PPh_3)_4$/5	THF	pyridine	60	0
9	$Pd(^tBu_3P)_2$/5	THF	NEt_3	60	0
10	$Pd(dppf)Cl_2$/5	THF	NEt_3	60	0
11	$Pd(PPh_3)_2Cl_2$/5	THF	NEt_3	60	70
12[c]	$Pd(OAc)_2$/5	THF	NEt_3	60	53
13	$Pd(PPh_3)_4$/2	THF	NEt_3	60	87
14	$Pd(PPh_3)_4$/2	THF	NEt_3	20	3

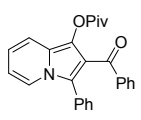
[a] Conditions: 0.25 mmol of **1a**, 0.5 mmol of **2a**, 0.75 mmol of base, 2.5 mL of solvent, 20-24 h. [b] Isolated yield. [c] 10 mol % of PPh_3 as the ligand.

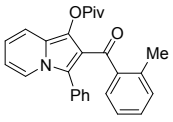
to 89% when THF was used as the solvent (entry 2), while 58% yield of **3aa** was obtained when MeCN was used as the solvent (entry 3). Bases were evaluated using THF as the solvent. No desired product was formed when $NaHCO_3$ or AcONa was used as the base (entries 4 and 5). When DABCO was used as the base, indolizine **3aa** was obtained in 82% yield (entry 6). However, **3aa** was not formed when DBU or pyridine was used as the base (entries 7 and 8). The results showed that the choice of base is important to the transformation. Inorganic bases did not work due to the heterogeneous reactions. When organic bases were used, Et_3N and DABCO could promote the reaction, while pyridine and DBU prevented the cyclization. The stable salt formed from pyridine or DBU with aroyl chloride might prevent the formation of ArCOPd(II)Cl intermediate. Then, different Pd catalysts were evaluated using THF as

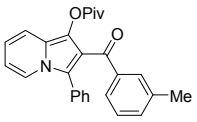
the solvent and NEt_3 as the base (entries 9-12). Indolizine **3aa** was not formed when using a Pd catalyst with strong electron-donor ligand $^tBu_3P$ or bidentate ligand dppf. When Pd(II) catalyst $Pd(PPh_3)_2Cl_2$ was replaced with $Pd(PPh_3)_4$, the yield of **3aa** decreased to 70%. When $Pd(OAc)_2$ was used as the precursor of Pd catalyst and PPh_3 was used as the ligand, **3aa** was obtained in 53% yield. When the content of $Pd(PPh_3)_4$ was reduced to 2 mol%, indolizine **3aa** was obtained in 87% yield, similar to that of 5 mol% $Pd(PPh_3)_4$ (entry 13). The yield decreased significantly when the reaction was carried out at room temperature (entry 14).

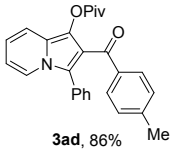
Table 2. Synthesis of Indolizine Derivatives from 1a with Different Aroyl Chlorides[a]

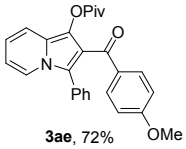


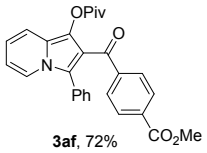

3aa, 87% (83%)[b]

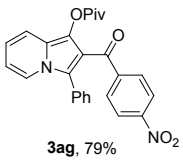

3ab, 54%

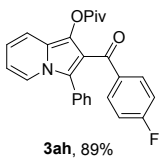

3ac, 95%

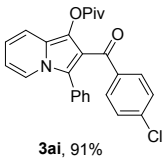

3ad, 86%

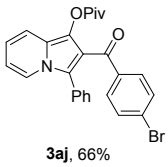

3ae, 72%

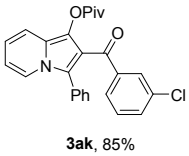

3af, 72%

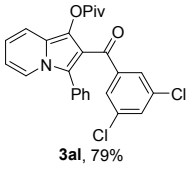

3ag, 79%

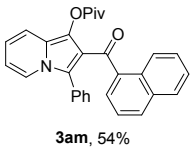

3ah, 89%

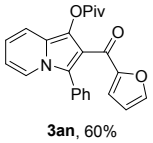

3ai, 91%

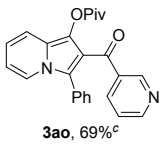

3aj, 66%


3ak, 85%


3al, 79%


3am, 54%


3an, 60%

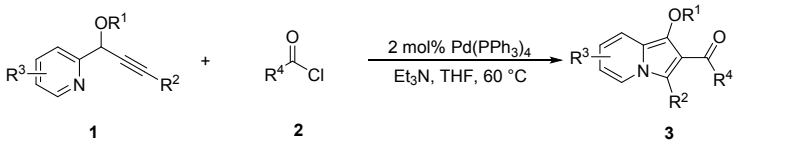

3ao, 69%[c]

[a] Conditions: 0.25 mmol of **1a**, 0.5 mmol of **2**, 2 mol% of $Pd(PPh_3)_4$, 0.75 mmol of Et_3N, 2.5 mL of THF, 20-24 h, isolated yield. [b] yield of 2 mmol scale up reaction. [c] nicotinoyl chloride hydrochloride (0.5 mmol) and Et_3N (1.25 mmol) were used.

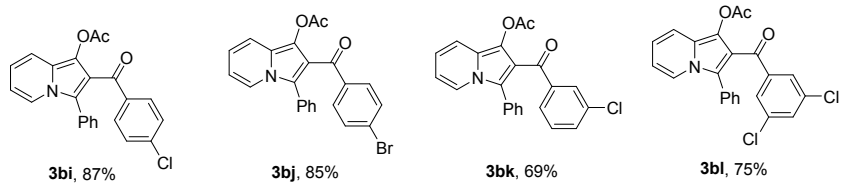
The reactions of **1a** with different aroyl chlorides were evaluated in the presence of 2 mol% $Pd(PPh_3)_4$, THF as the solvent, and Et_3N as the base at 60 °C (Table 2). Aroyl chlorides with electron-donating (Me and OMe, **3ab-3ae**) or electron-withdrawing (CO_2Me, NO_2 and F, **3af-3ah**) substituents successfully

afforded indolizines in high isolated yields. The reaction of *o*-toluoyl chloride afforded the corresponding indolizine **3ab** in 54% yield, indicating that the reaction is affected by steric hindrance. Aroyl chlorides with different halide substituents also smoothly furnished the corresponding indolizines (**3ah**-**3al**). Indolizine **3am** was obtained in moderate yield from 1-naphthoyl chloride because of the steric effect. Besides, heteroaroyl moieties were successfully introduced to the indolizine structures, affording products **3an** and **3ao** in 60% and 69% yields, respectively.

Table 3. Synthesis of Indolizine Derivatives from Propargylic Pyridines with Aroyl Chlorides[a]



1 **2** **3**

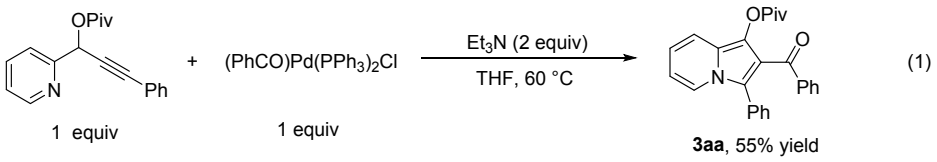


[a] Conditions: 0.25 mmol of **1**, 0.5 mmol of **2**, 2 mol% of $Pd(PPh_3)_4$, 0.75 mmol of Et_3N, 2.5 mL of THF, 20-24 h, isolated yield. [b] 30 h. [c] R^1 = H, 0.75 mmol of **2a**, 1.0 mmol of Et_3N.

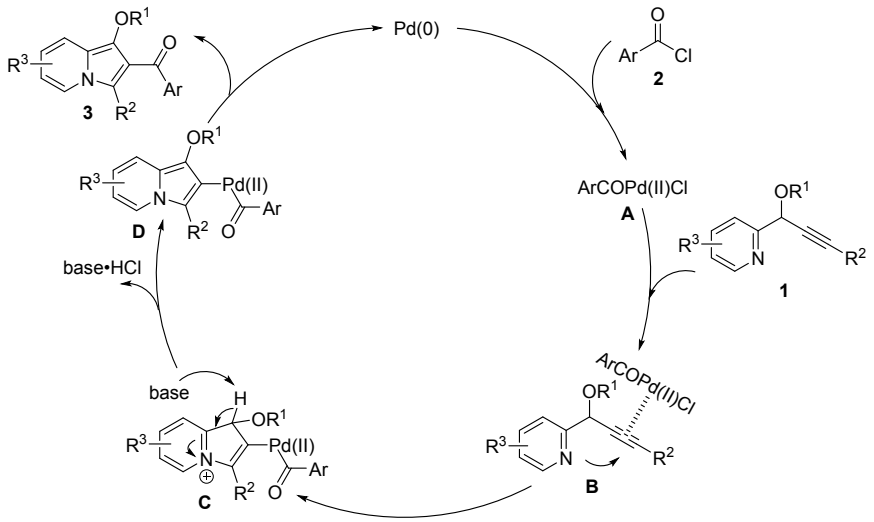
The reaction conditions were then applied to diverse propargylic pyridines and aroyl chlorides (Table 3). When the pivaloyl group of substrate was replaced with an acetyl group, the corresponding indolizine products were isolated in good yields (**3bi-3bl**). The reactions of benzoate and cinnamate afforded the

indolizine products in good-to-excellent yields. Indolizine **3ea** was obtained in 54% yield from the corresponding furan-2-carboxylate. The reaction of substrate with a TBS group gave **3fa** in 51% yield with a longer reaction time. The indolizine was obtained in 67-89% yields when the substituent on the alkynyl moiety was changed to butyl group, but a trace amount of product was observed for *tert*-butyl (**3ha**) due to steric hindrance. The presence of a chlorine or methyl substituent on the pyridine ring resulted in indolizine **3ia** and **3ja** in 53% and 99% yields, respectively. When the propargylic alcohol **1k** reacted with benzoyl chloride, the corresponding ester **1c** was quickly formed as the major product (92% yield) using one equivalent of benzoyl chloride. The indolizine product **3ka** was obtained in 83% yield using excessive benzoyl chloride.

To elucidate the mechanism, $(PhCO)Pd(PPh_3)_2Cl$ was prepared from $Pd(PPh_3)_4$ and benzoyl chloride.[14] Then, $(PhCO)Pd(PPh_3)_2Cl$ was used in the reaction with propargylic pyridine **1a** in the presence of Et_3N, affording indolizine **3aa** in 55% isolated yield (Equation 1). The results indicate that ArCOPdX formed from Pd(0) complex and aroyl chloride might be the key intermediate to induce the 5-*endo-dig* cyclization. On the basis of the above results, a possible mechanism is proposed in Scheme 2. First, the oxidative addition of aroyl chlorides with Pd(0) complex forms ArCOPd(II)Cl intermediate. Subsequent coordination of ArCOPd(II)Cl to the triple bond initiates 5-*endo-dig* cyclization. The indolizine **3** is released after reductive elimination.



(1)



Scheme 2. Proposed Mechanism for the Cyclization

In conclusion, an efficient synthesis of indolizine derivatives was developed by Pd-catalyzed cyclization of propargylic pyridines with aroyl chlorides. The cyclization was triggered by the in situ formed ArCOPdX species obtained from the facile oxidative addition of aroyl chloride to Pd(0) complex. This method provides a convenient route to synthesize indolizines as an alternative of carbonylation/cyclization.

EXPERIMENTAL SECTION

General Considerations. Unless otherwise noted, all the chemicals were purchased from commercial suppliers and were used as received. Solvents were dried and distilled by standard procedures prior to use. All reactions were performed under an inert atmosphere of nitrogen unless otherwise stated. All ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were recorded on JEOL 400 and JEOL 600 spectrometers. The NMR chemical shift values refer to $CDCl_3$ (δ (^{1}H), 7.26 ppm; δ (^{13}C), 77.16 ppm). Mass spectra were obtained on a micrOTOF-Q II mass spectrometer.

General Procedures for the Preparation of Propargylic Pyridines 1: To a solution of alkyne (6.5 mmol, 1.3 equiv) in THF (10 mL) was added ethylmagnesium bromide (2 mL, 3 M in Et_2O, 6 mmol, 1.2 equiv) dropwise at 0 °C under N_2 atmosphere. The reaction mixture was stirred at 0 °C for 30 min and

then cooled to -78 °C. A solution of pyridine-2-carboxaldehyde (5 mmol, 1 equiv) in THF (4 mL) was added dropwise. The reaction mixture was stirred at -78 °C for 1 h and allowed to warm to room temperature, quenched with saturated NH_4Cl solution (10 mL). The aqueous phase was extracted by ethyl acetate (10 mL) three times. The combined organic solution was washed with brine and dried over anhydrous Na_2SO_4, filtered and concentrated to give the crude propargyl alcohol. The crude propargyl alcohol was dissolved in DCM (20 mL). DMAP (0.5 mmol, 0.1 equiv) and Et_3N (12.5 mmol, 2.5 equiv) was added. Then acyl chloride (7.5 mmol, 1.5 equiv) was added dropwise to the solution at 0 °C. The reaction was stirred at 0 °C until the alcohol disappeared, quenched with saturated NH_4Cl solution (20 mL). The aqueous phase was extracted by DCM (15 mL) three times. The combined organic solution was washed with brine and dried over anhydrous Na_2SO_4, filtered and concentrated. The resultant residue was purified by column chromatography to give the product. New substrates **1c-e**, **1i** were prepared by this known method. Substrates **1a-b**, **1f-h** and **1j** are known compounds and were synthesized following the literature procedure.[13a-c] Products **3ag-h**, **3aj-o**, **3bi-l, 3cd**, **3ck**, **3da**, **3ea**, **3fa**, **3gd**, **3gi**, **3gk, 3ia**, **3ja** and **3ka** are new compounds, **3aa-f** and **3ai** are known compounds[13b] and were confirmed by ^1H NMR and ^{13}C NMR.

*3-Phenyl-1-(pyridin-2-yl)prop-2-yn-1-yl benzoate (**1c**)*: Purified by flash chromatography on silica gel with hexanes/EtOAc (v/v = 5:1), 1.2 g, 76% yield, brown solid, m.p. 96-97 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, J = 4.5 Hz, 1H), 8.09 (d, J = 7.9 Hz, 2H), 7.75-7.68 (m, 2H), 7.54-7.21 (m, 9H), 6.94 (s, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 165.4, 156.4, 149.8, 137.3, 133.4, 132.2, 130.1, 129.7, 129.0, 128.5, 128.3, 123.7, 122.1, 121.9, 87.7, 85.0, 67.8. HRMS (ESI) *m/z* calcd for $C_{21}H_{15}NO_2$ $(M + Na)^+$ 336.0995, found 336.0996.

*3-Phenyl-1-(pyridin-2-yl)prop-2-yn-1-yl cinnamate (**1d**)*: Purified by flash chromatography on silica

gel with hexanes/EtOAc (v/v = 5:1), 1.1 g, 62% yield, pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 4.8 Hz, 1H), 7.76-7.69 (m, 2H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.47-7.42 (m, 4H), 7.33-7.31 (m, 3H), 7.26-7.19 (m, 4H), 6.82 (s, 1H), 6.49 (d, *J* = 16 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 165.6, 156.3, 149.8, 146.2, 137.3, 134.4, 132.1, 130.6, 129.0, 128.9, 128.3, 128.3, 123.7, 122.1, 122.0, 117.4, 87.6, 85.0, 67.3. HRMS (ESI) *m/z* calcd for $C_{23}H_{17}NO_2$ $(M + Na)^+$ 362.1151, found 362.1151.

*3-Phenyl-1-(pyridin-2-yl)prop-2-yn-1-yl furan-2-carboxylate (**1e**)*: Purified by flash chromatography on silica gel with hexanes/EtOAc (v/v = 5:1), 0.9 g, 60% yield, brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (ddd, *J* = 4.8, 1.6, 0.9 Hz, 1H), 7.80-7.72 (m, 2H), 7.60 (dd, *J* = 1.7, 0.8 Hz, 1H), 7.50-7.47 (m, 2H), 7.235-7.27 (m, 5H), 6.96 (s, 1H), 6.51 (dd, *J* = 3.5, 1.7 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 157.4, 155.9, 149.8, 146.9, 144.1, 137.3, 132.2, 129.0, 128.4, 123.8, 122.0, 119.2, 112.1, 88.0, 84.6, 67.6. HRMS (ESI) *m/z* calcd for $C_{19}H_{13}NO_3$ $(M + Na)^+$ 326.0788, found 326.0795.

*1-(4-Chloropyridin-2-yl)-3-phenylprop-2-yn-1-yl pivalate (**1i**)*: Purified by flash chromatography on silica gel with hexanes/EtOAc (v/v = 5:1),1.3 g, 79% yield, white solid, m.p. 58-59 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, *J* = 5.3 Hz, 1H), 7.54 (d, *J* = 1.8 Hz, 1H), 7.39 (dd, *J* = 7.4, 1.6 Hz, 2H), 7.25-7.19 (m, 4H), 6.61 (s, 1H), 1.21 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 176.9, 158.3, 150.6, 145.2, 132.2, 129.1, 128.4, 123.9, 122.0, 121.9, 87.6, 84.5, 66.5, 39.0, 27.2. HRMS (ESI) *m/z* calcd for $C_{19}H_{18}ClNO_2$ $(M + Na)^+$ 350.0918, found 350.0953.

General Procedure for the Synthesis of Indolizine Derivatives by Pd-Catalyzed Cyclization of Propargylic Pyridines with Aroyl Chlorides: To a 25 mL Schlenk tube were added **1a** (73 mg, 0.25 mmol), $Pd(PPh_3)_4$ (5.8 mg, 2 mol%) under nitrogen. Then benzoyl chloride **2a** (70 mg, 0.5 mmol), THF (2.5 mL) and Et_3N (104 μL, 0.75 mmol) were added sequentially to the reaction. The Schlenk tube was placed in an oil bath and heated to 60 °C. After stirring at 60 °C for 20 h, the reaction mixture was cooled

to room temperature and concentrated under vacuum. The residue was purified by flash chromatography on silica gel with hexanes/EtOAc (v/v = 5:1) as eluent to afford the product **3aa** (86 mg, 87% yield).

Procedure for the 2.0 mmol Scale up Reaction: To a 50 mL Schlenk flask were added **1a** (587 mg, 2.0 mmol), $Pd(PPh_3)_4$ (46.4 mg, 2 mol%) under nitrogen. Then benzoyl chloride **2a** (560 mg, 4.0 mmol), THF (20 mL) and Et_3N (830 μL, 6.0 mmol) were added sequentially to the reaction. The flask was placed in an oil bath and heated to 60 °C. After stirring at 60 °C for 30 h, the reaction mixture was cooled to room temperature and concentrated under vacuum. The residue was purified by flash chromatography on silica gel with hexanes/EtOAc (v/v = 5:1) as eluent to afford the product **3aa** (660 mg, 83% yield).

*2-(4-Nitrobenzoyl)-3-phenylindolizin-1-yl pivalate (**3ag**)*: Purified by flash chromatography on silica gel with hexanes/EtOAc (v/v = 10:1), 87.7 mg, 79% yield, brown solid, m.p. 158-159 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.8 Hz, 2H), 7.89 (d, *J* = 7.3 Hz, 1H), 7.78 (d, *J* = 8.7 Hz, 2H), 7.30-7.22 (m, 6H), 6.73 (dd, *J* = 9.1, 6.4 Hz, 1H), 6.52-6.49 (m, 1H), 1.25 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 190.2, 176.9, 149.5, 143.8, 130.8, 130.5, 129.3, 128.9, 128.8, 126.2, 124.0, 123.1, 122.1, 118.7, 117.5, 117.1, 113.1, 39.1, 27.1. HRMS (ESI) *m/z* calcd for $C_{26}H_{22}N_2O_5$ $(M + Na)^+$ 465.1421, found 465.1419.

*2-(4-Fluorobenzoyl)-3-phenylindolizin-1-yl pivalate (**3ah**)*: Purified by flash chromatography on silica gel with hexanes/EtOAc (v/v = 10:1), 92 mg, 89% yield, brown solid, m.p. 121-122 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.0 Hz, 1H), 7.70-7.67 (m, 2H), 7.29-7.19 (m, 4H), 7.13 (d, *J* = 8.8 Hz, 1H), 6.86 (t, *J* = 8.4 Hz, 2H), 6.64 (dd, *J* = 8.5, 6.8 Hz, 1H), 6.41 (t, *J* = 6.7 Hz, 1H), 1.11 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.3, 176.8, 166.6, 164.1, 135.2, 135.2, 132.5, 132.4, 130.7, 129.7, 128.9, 128.5, 125.8, 123.5, 122.7, 122.1, 118.3, 117.1, 115.2, 115.0, 112.6, 39.1, 27.1. HRMS (ESI) *m/z* calcd for $C_{26}H_{22}FNO_3$ $(M + Na)^+$ 438.1476, found 438.1470.

*2-(4-Bromobenzoyl)-3-phenylindolizin-1-yl pivalate (**3aj**)*: Purified by flash chromatography on silica gel with hexanes/EtOAc (v/v = 10:1), 79 mg, 66% yield, pale yellow solid, m.p. 106-107 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.2 Hz, 1H), 7.52 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.3 Hz, 2H), 7.28-7.18 (m, 7H), 7.12 (d, *J* = 9.1 Hz, 1H), 6.64 (dd, *J* = 9.1, 6.3 Hz, 1H), 6.41 (t, *J* = 6.7 Hz, 1H), 1.11 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 190.7, 176.7, 137.6, 131.4, 131.3, 130.7, 129.6, 128.9, 128.6, 127.4, 125.9, 123.6, 122.7, 122.1, 118.3, 118.0, 117.1, 112.7, 39.1, 27.1. HRMS (ESI) *m/z* Calcd. for $C_{26}H_{22}BrNO_3$ $(M + Na)^+$ 498.0675, found: 498.0681.

*2-(3-Chlorobenzoyl)-3-phenylindolizin-1-yl pivalate (**3ak**)*: Purified by flash chromatography on silica gel with hexanes/EtOAc (v/v = 10:1), 92.6 mg, 85% yield, pale yellow solid, m.p. 136-137 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.3 Hz, 1H), 7.59 (t, *J* = 1.5 Hz, 1H), 7.52 (d, *J* = 7.7 Hz, 1H), 7.28-7.08 (m, 8H), 6.62 (dd, *J* = 8.9, 6.4 Hz, 1H), 6.41-6.37 (m, 1H), 1.12 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 190.3, 176.7, 140.4, 134.2, 132.1, 130.7, 130.0, 129.6, 129.4, 128.8, 128.6, 127.7, 125.9, 123.9, 122.8, 122.1, 118.3, 117.8, 117.1, 112.7, 39.1, 27.1. HRMS (ESI) *m/z* calcd for $C_{26}H_{22}ClNO_3$ $(M + Na)^+$ 454.1180, found 454.1182.

*2-(3,5-Dichlorobenzoyl)-3-phenylindolizin-1-yl pivalate (**3al**)*: Purified by flash chromatography on silica gel with hexanes/EtOAc (v/v = 10:1), 92 mg, 79% yield, pale yellow solid, m.p. 131-132 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.3 Hz, 1H), 7.55 (d, *J* = 2 Hz, 2H), 7.36-7.27 (m, 6H), 7.25 (d, *J* = 9.2 Hz, 1H), 6.74 (ddd, *J* = 9.2, 6.4, 0.6 Hz, 1H), 6.53-6.50 (m, 1H), 1.29 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 189.0, 176.9, 141.1, 134.8, 131.7, 130.7, 129.4, 128.9, 128.8, 128.2, 126.1, 124.1, 122.9, 122.1, 118.6, 117.2, 117.1, 113.0, 39.2, 27.1. HRMS (ESI) *m/z* calcd for $C_{26}H_{21}Cl_2NO_3$ $(M + Na)^+$ 488.0791, found 488.0788.

*2-(1-Naphthoyl)-3-phenylindolizin-1-yl pivalate (**3am**)*: Purified by flash chromatography on silica gel

with hexanes/EtOAc (v/v = 10:1), 60 mg, 54% yield, pale yellow solid, m.p. 70-71 °C.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 7.9 Hz, 1H), 7.78-7.72 (m, 3H), 7.61 (d, *J* = 6.4 Hz, 1H), 7.51-7.42 (m, 2H), 7.26-7.09 (m, 7H), 6.69 (m, 1H), 6.45 (t, *J* = 7.0 Hz, 1H), 1.12 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 193.3, 177.0, 137.6, 133.6, 131.6, 130.9, 130.5, 129.5, 129.2, 128.3, 128.2, 128.0, 127.3, 126.4, 126.1, 125.9, 125.0, 124.3, 122.8, 122.2, 119.9, 118.1, 117.1, 112.7, 39.1, 27.0. HRMS (ESI) *m/z* calcd for $C_{30}H_{25}NO_3$ $(M + Na)^+$ 470.1727, found 470.1733.

*2-(Furan-2-carbonyl)-3-phenylindolizin-1-yl pivalate (**3an**)*: Purified by flash chromatography on silica gel with hexanes/EtOAc (v/v = 10:1), 58 mg, 60% yield, pale yellow solid, m.p. 151-152 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.2 Hz, 1H), 7.44-7.36 (m, 5H), 7.31 (t, *J* = 7.2 Hz, 1H), 7.20 (d, *J* = 9.1 Hz, 1H), 6.91 (d, *J* = 3.3 Hz, 1H), 6.70 (dd, *J* = 8.7, 6.5 Hz, 1H), 6.47 (t, *J* = 6.7 Hz, 1H), 6.33 (d, *J* = 1.8 Hz, 1H), 1.24 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 178.3, 176.8, 153.0, 146.5, 130.5, 129.9, 128.9, 128.4, 125.7, 123.0, 122.8, 122.1, 119.8, 118.2, 117.9, 117.1, 112.5, 112.1, 39.2, 27.3. HRMS (ESI) *m/z* calcd for $C_{24}H_{21}NO_4$ $(M + Na)^+$ 410.1363, found 410.1357.

*2-Nicotinoyl-3-phenylindolizin-1-yl pivalate (**3ao**)*: Purified by flash chromatography on silica gel with hexanes/EtOAc (v/v = 5:1), 68.7 mg, 69% yield, yellow solid, m.p. 157-158 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.78 (s, 1H), 8.47 (s, 1H), 7.86 (d, *J* = 7.8 Hz, 1H), 7.81 (d, *J* = 7.2 Hz, 1H), 7.27-7.22 (m, 4H), 7.18 (t, *J* = 6.5 Hz, 1H), 7.15 (d, *J* = 9.1 Hz, 1H), 7.08 (dd, *J* = 7.6, 4.9 Hz, 1H), 6.64 (dd, *J* = 9.1, 6.5 Hz, 1H), 6.41 (t, *J* = 6.8 Hz, 1H), 1.14 (s, 9H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 190.1, 176.8, 152.4, 150.9, 136.8, 134.3, 130.9, 129.4, 128.9, 128.7, 126.1, 124.0, 122.9, 122.1, 118.5, 117.7, 117.1, 112.9, 39.1, 27.1. HRMS (ESI) *m/z* calcd for $C_{25}H_{22}N_2O_3$ $(M + Na)^+$ 421.1523, found 421.1519.

*2-(4-Chlorobenzoyl)-3-phenylindolizin-1-yl acetate (**3bi**)*: Purified by flash chromatography on silica gel with hexanes/EtOAc (v/v = 10:1), 85 mg, 87% yield, yellow solid, m.p. 160-161 °C. ^{1}H NMR (400

MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.0 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 2H), 7.33-7.26 9 (m, 6H), 7.20 (d, *J* = 8.0 Hz, 2H), 6.73 (t, *J* = 7.7 Hz, 1H), 6.50 (t, *J* = 6.7 Hz, 1H), 2.14 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 190.8, 169.7, 138.6, 137.0, 131.2, 130.7, 129.6, 128.9, 128.6, 128.2, 126.0, 123.7, 123.1, 122.2, 118.5, 117.8, 117.2, 112.8, 20.5. HRMS (ESI) *m/z* calcd for $C_{23}H_{16}ClNO_3$ $(M + Na)^+$ 412.0711, found 412.0707.

*2-(4-Bromobenzoyl)-3-phenylindolizin-1-yl acetate (**3bj**)*: Purified by flash chromatography on silica gel with hexanes/EtOAc (v/v = 10:1), 92 mg, 85% yield, pale yellow solid, m.p. 129-130 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.3 Hz, 1H), 7.54 (d, *J* = 8.6 Hz, 2H), 7.37 (d, *J* = 8.6 Hz, 2H), 7.33-7.28 (m, 6H), 6.73 (ddd, *J* = 9.2, 6.4, 0.8 Hz, 1H), 6.50 (m, 1H), 2.14 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 191.0, 169.7, 137.4, 131.3, 131.2, 130.7, 129.5, 128.9, 128.6, 127.3, 126.0, 123.7, 123.1, 122.1, 118.5, 117.7, 117.1, 112.8, 20.5. HRMS (ESI) *m/z* calcd for $C_{23}H_{16}BrNO_3$ $(M + Na)^+$ 456.0206, found 456.0206.

*2-(3-chlorobenzoyl)-3-phenylindolizin-1-yl acetate (**3bk**)*: Purified by flash chromatography on silica gel with hexanes/EtOAc (v/v = 10:1), 67 mg, 69% yield, pale yellow solid, m.p. 110-111 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.3 Hz, 1H), 7.55 (s, 1H), 7.49 (d, *J* = 7.7 Hz, 1H), 7.27-7.18 (m, 7H), 7.09 (t, *J* = 7.8 Hz, 1H), 6.67 (dd, *J* =9.1, 6.5 Hz, 1H), 6.43 (t, *J* = 7.1 Hz, 1H), 2.10 (s, 3H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 190.6, 169.7, 140.2, 134.1, 132.0, 130.7, 129.9, 129.6, 129.3, 128.9, 128.7, 127.7, 126.2, 124.0, 123.2, 122.2, 118.6, 117.5, 117.2, 112.9, 20.5. HRMS (ESI) *m/z* Calcd. for $C_{23}H_{16}ClNO_3$ $(M + Na)^+$ 412.0711, found: 412.0711.

*2-(3,5-Dichlorobenzoyl)-3-phenylindolizin-1-yl acetate (**3bl**)*: Purified by flash chromatography on silica gel with hexanes/EtOAc (v/v = 10:1), 79.3 mg, 75% yield, orange solid, m.p. 130-131 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.3 Hz, 1H), 7.47 (d, *J* = 1.8 Hz, 2H), 7.34-7.24 (m, 7H), 6.74 (dd, *J* = 9.1, 6.4 Hz, 1H), 6.50 (m, 1H), 2.24 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 189.3, 169.8, 140.9,

134.7, 131.6, 130.7, 129.4, 128.9, 128.0, 126.3, 124.2, 123.3, 122.2, 118.8, 117.2, 116.9, 113.1, 20.6. HRMS (ESI) *m/z* calcd for $C_{23}H_{15}Cl_2NO_3$ $(M + Na)^+$ 446.0321, found 446.0323.

*2-(4-Methylbenzoyl)-3-phenylindolizin-1-yl benzoate (**3cd**)*: Purified by flash chromatography on silica gel with hexanes/CH_2Cl_2 (v/v = 5:1), 83 mg, 77% yield, brown solid, m.p. 130-131 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00-7.94 (m, 3H), 7.65 (d, *J* = 8.1 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.45-7.27 (m, 8H), 6.99 (d, *J* = 8.0 Hz, 2H), 6.73 (dd, *J* = 8.6, 6.4 Hz, 1H), 6.53- 6.49 (m, 1H), 2.20 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 191.7, 165.0, 143.0, 136.2, 133.5, 130.7, 130.2, 129.9, 129.8, 129.1, 128.8, 128.7, 128.4, 128.4, 125.9, 123.5, 123.1, 122.2, 118.5, 118.3, 117.6, 21.6. HRMS (ESI) *m/z* calcd for $C_{29}H_{21}NO_3$ $(M + H)^+$ 432.1594, found 432.1584.

*2-(3-Chlorobenzoyl)-3-phenylindolizin-1-yl benzoate (**3ck**)*: Purified by flash chromatography on silica gel with hexanes/CH_2Cl_2 (v/v = 5:1), 105 mg, 93% yield, brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05-8.03 (m, 2H), 7.95 (d, *J* = 7.3 Hz, 1H), 7.67 (t, *J* = 1.7 Hz, 1H), 7.61-7.56 (m, 2H), 7.45-7.27 (m, 8H), 7.20-7.17 (m, 1H), 7.09 (t, *J* = 7.8 Hz, 1H), 6.75 (ddd, *J* = 9.1, 6.4, 0.6 Hz, 1H), 6.55-6.51 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 190.5, 165.1, 140.4, 134.1, 133.7, 131.9, 130.8, 130.3, 129.9, 129.6, 129.3, 129.0, 128.9, 128.7, 128.5, 127.6, 126.1, 124.1, 123.3, 122.2, 118.6, 117.7, 117.6, 112.9. HRMS (ESI) *m/z* calcd for $C_{28}H_{18}ClNO_3$ $(M + Na)^+$ 474.0867, found 474.0863.

*2-Benzoyl-3-phenylindolizin-1-yl cinnamate (**3da**)*: Purified by flash chromatography on silica gel with hexanes/CH_2Cl_2 (v/v = 5:1), 107.5 mg, 97% yield, brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dt, *J* = 7.3, 1.0 Hz, 1H), 7.74-7.72 (m, 2H), 7.64 (d, *J* = 16 Hz, 1H), 7.49-7.46 (m, 2H), 7.41-7.37 (m, 5H), 7.34-7.26 (m, 5H), 7.25-7.20 (m, 2H), 6.73 (ddd, *J* = 9.2, 6.4, 0.9 Hz, 1H), 6.52-6.48 (m, 1H), 6.44 (d, *J* = 16 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 192.1, 165.4, 146.7, 138.7, 134.3, 132.3, 130.8, 130.7, 129.8, 129.8, 129.0, 128.8, 128.5, 128.4, 128.0, 126.0, 123.8, 123.1, 122.2, 118.3, 118.3, 117.5,

116.6, 112.6. HRMS (ESI) *m/z* calcd for $C_{30}H_{21}NO_3$ $(M + Na)^+$ 466.1414, found 466.1436.

*2-Benzoyl-3-phenylindolizin-1-yl furan-2-carboxylate (**3ea**)*: Purified by flash chromatography on silica gel with hexanes/CH_2Cl_2 (v/v = 3:1), 53 mg, 54% yield, brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.3 Hz, 1H), 7.63-7.61 (m, 2H), 7.48 (d, *J* = 0.7 Hz, 1H), 7.31-7.15 (m, 7H), 7.09 (d, *J* = 7.3 Hz, 2H), 7.03 (d, *J* = 3.4 Hz, 1H), 6.64 (dd, *J* = 8.9, 6.3 Hz, 1H), 6.43-6.39 (m, 1H), 6.38 (dd, *J* = 3.5, 1.7 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 191.9, 156.8, 147.2, 143.5, 138.7, 132.1, 130.7, 129.7, 129.6, 128.8, 128.5, 127.9, 125.2, 123.8, 123.2, 122.1, 119.6, 118.2, 117.4, 112.7, 112.1. HRMS (ESI) *m/z* calcd for $C_{26}H_{17}NO_4$ $(M + Na)^+$ 430.1050, found 430.1049.

*(1-((tert-Butyldimethylsilyl)oxy)-3-phenylindolizin-2-yl)(phenyl)methanone (**3fa**)*: Purified by flash chromatography on silica gel with hexanes/EtOAc (v/v = 10:1), 54.5 mg, 51% yield, brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89-7.86 (m, 3H), 7.47-7.27 (m, 9H), 6.53 (ddd, *J* = 9.1, 6.3, 0.8 Hz, 1H), 6.39-6.35 (m, 1H), 0.79 (s, 9H), -0.06 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 192.9, 138.8, 132.6, 131.3, 130.7, 130.5, 130.4, 128.8, 128.1, 128.0, 122.1, 121.7, 121.6, 118.3, 118.2, 115.4, 112.2, 25.6, 18.0, -4.6. HRMS (ESI) *m/z* calcd for $C_{27}H_{29}NO_2Si$ $(M + K)^+$ 466.1605, found 466.1613.

*3-Butyl-2-(4-methylbenzoyl)indolizin-1-yl pivalate (**3gd**)*: Purified by flash chromatography on silica gel with hexanes/EtOAc (v/v = 10:1), 65.6 mg, 67% yield, brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72-7.69 (m, 3H), 7.22 (d, *J* = 7.9 Hz, 2H), 7.08 (dt, *J* = 9.1, 1.3 Hz, 1H), 6.61 (ddd, *J* = 9.1, 6.4, 0.9 Hz, 1H), 6.54-6.50 (m, 1H), 3.03 (t, *J* = 7.6 Hz, 2H), 2.39 (s, 3H), 1.65-1.57 (m, 2H), 1.39-1.30 (m, 2H), 0.97 (s, 9H), 0.87 (t, *J* = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 192.2, 176.5, 143.1, 137.3, 130.0, 129.0, 125.1, 124.4, 121.7, 121.4, 117.5, 117.4, 116.7, 112.1, 39.0, 30.2, 26.9, 24.1, 22.7, 21.7, 14.0. HRMS (ESI) *m/z* calcd for $C_{25}H_{29}NO_3$ $(M + Na)^+$ 414.2040, found 414.2040.

*3-Butyl-2-(4-methylbenzoyl)indolizin-1-yl pivalate (**3gi**)*: Purified by flash chromatography on silica gel with hexanes/EtOAc (v/v = 10:1), 77 mg, 75% yield, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76-7.71 (m, 3H), 7.40 (d, J = 8.5 Hz, 2H), 7.08 (dt, *J* = 9.1, 1.2 Hz, 1H), 6.63 (ddd, *J* = 9.1, 6.4, 0.7 Hz, 1H), 6.57-6.53 (m, 1H), 3.03 (t, *J* = 7.6 Hz, 2H), 1.66-1.58 (m, 2H), 1.40-1.31 (m, 2H), 1.00 (s, 9H), 0.89 (t, *J* = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 191.1, 176.5, 138.7, 138.2, 131.2, 128.6, 125.5, 124.3, 121.6, 121.5, 117.3, 116.9, 116.8, 112.3, 39.0, 30.1, 26.8, 24.1, 22.7, 13.9. HRMS (ESI) *m/z* calcd for $C_{24}H_{26}ClNO_3$ $(M + Na)^+$ 434.1493, found 434.1493.

*3-Butyl-2-(3-chlorobenzoyl)indolizin-1-yl pivalate (**3gk**)*: Purified by flash chromatography on silica gel with hexanes/EtOAc (v/v = 10:1), 92 mg, 89% yield, pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (t, *J* = 1.7 Hz, 1H), 7.73-7.68 (m, 2H), 7.49 (ddd, *J* = 8.0, 2.1, 1.1 Hz, 1H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.10 (dt, *J* = 9.0, 1.0 Hz, 1H), 6.54 (ddd, *J* = 9.0, 6.4, 0.8 Hz, 1H), 6.57-6.53 (m, 1H), 3.04 (t, *J* = 7.7 Hz, 2H), 1.67-1.59 (m, 2H), 1.42-1.33 (m, 2H), 1.01 (s, 9H), 0.90 (t, *J* = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 190.8, 176.4, 141.5, 134.5, 132.2, 129.9, 129.7, 127.7, 125.8, 124.4, 121.6, 121.5, 117.4, 116.9, 116.6, 112.4, 39.0, 30.1, 26.9, 24.1, 22.7, 13.9. HRMS (ESI) *m/z* calcd for $C_{24}H_{26}ClNO_3$ $(M + Na)^+$ 434.1493, found 434.1495.

*2-Benzoyl-7-chloro-3-phenylindolizin-1-yl pivalate (**3ia**)*: Purified by flash chromatography on silica gel with hexanes/CH_2Cl_2 (v/v = 5:1), 57 mg, 53% yield, brown oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.6 Hz, 1H) 7.65 (d, *J* = 7.4 Hz, 2H), 7.34-7.18 (m, 8H), 7.08 (d, *J* = 1.3, 1H), 6.36 (dd, *J* = 7.6, 2.0 Hz, 1H), 1.04 (s, 9H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 191.4, 176.6, 138.6, 132.6, 130.6, 129.9, 129.3, 128.9, 128.8, 128.2, 125.6, 124.3, 124.2, 123.2, 122.3, 119.4, 115.5, 114.0, 39.1, 27.0. HRMS (ESI) *m/z* calcd for $C_{26}H_{22}ClNO_3$ $(M + Na)^+$ 454.1180, found 454.1172

*2-Benzoyl-5-methyl-3-phenylindolizin-1-yl pivalate (**3ja**)*: Purified by flash chromatography on silica

gel with hexanes/CH_2Cl_2 (v/v = 5:1), 102 mg, 99% yield, brown solid, m.p. 134-135 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66-7.64 (m, 2H), 7.33-7.33 (m, 3 H), 7.26-7.20 (m, 3H), 7.18-7.14 (m, 2H) 7.03 (d, *J* = 8.8 Hz, 1H), 6.57 (dd, *J* = 9.0, 6.6 Hz, 1H), 6.18 (d, *J* = 6.6 Hz, 1H), 1.92 (s, 3H), 0.97 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 191.7, 176.5, 139.2, 135.0, 132.9, 132.7, 132.4, 129.8, 128.5, 128.1, 126.8, 125.0, 124.4, 124.1, 120.4, 117.9, 115.0, 113.9, 39.0, 26.9, 22.8. HRMS (ESI) *m/z* calcd for $C_{27}H_{25}NO_3$ $(M + Na)^+$ 434.1727, found 434.1731.

*2-Benzoyl-3-phenylindolizin-1-yl benzoate (**3ka**)*: Purified by flash chromatography on silica gel with hexanes/CH_2Cl_2 (v/v = 5:1), 87 mg, 83% yield, yellow solid, m.p. 145-146 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90-7.87 (m, 3H), 7.65 (d, *J* = 7.2 Hz, 2H), 7.46 (t, *J* = 7.4 Hz, 1H), 7.34-7.23 (m, 7H), 7.21-7.16 (m, 2H), 7.09 (t, *J* = 7.7 Hz, 2H), 6.64 (dd, *J* = 8.8, 6.4 Hz, 1H), 6.44-6.41 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 192.0, 165.1, 138.8, 133.5, 132.2, 130.7, 130.2, 129.7, 129.7, 129.0, 128.8, 128.5, 128.4, 128.0, 126.0, 123.8, 123.1, 122.2, 118.4, 118.3, 117.6, 112.6. HRMS (ESI) *m/z* calcd for $C_{28}H_{19}NO_3$ $(M + Na)^+$ 440.1257, found 440.1258.

Procedure for the quantitative reaction of $(PhCO)Pd(PPh_3)_2Cl$ with propargylic pyridine 1a: To a 25 mL Schlenk tube were added **1a** (29 mg, 0.1 mmol) and $(PhCO)Pd(PPh_3)_2Cl$ (77 mg, 0.1 mmol) under nitrogen atmosphere. Then THF (1.0 mL) and Et_3N (30 μL, 0.2 mmol) were added by syringe to the reaction. The Schlenk tube was placed in an oil bath and heated to 60 °C. After stirring at 60 °C for 20 h, the reaction mixture was cooled to room temperature and concentrated under vacuum. The residue was purified by flash chromatography on silica gel with hexanes/EtOAc (v/v = 5:1) as eluent to afford the product **3aa** (22 mg, 55% yield).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: .

Spectra of new compounds, including ^{1}H and ^{13}C NMR.

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Notes

The authors declare no competing financial interest.

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