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Copper(II)-Catalyzed Indolizines Formation Followed by Dehydrogenative Functionalization Cascade to Synthesize 1-Bromoindolizines

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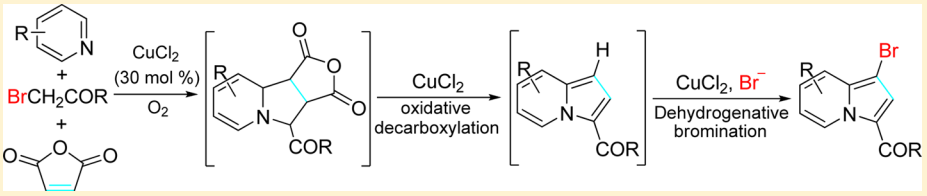
Supporting Information



ABSTRACT: A one-pot, three-component cascade reaction between pyridine, α-acylmethylbromide, and maleic anhydride leading to direct access of 1-bromoindolizines in high yields has been developed. This protocol is accomplished via a reaction sequence of 1,3-dipolar cycloaddition of the pyridinium ylide with maleic anhydride, oxidative decarboxylation of the primary cycloadduct, and dehydrogenative bromination of the resulting 1-unsubstituted indolizine. Copper chloride was used as a catalyst and oxygen as the terminal oxidant. This reaction represents the first example of transition-metal-catalyzed direct dehydrogenative bromination of indolizine at the C-1 position. Moreover, the obtained 1-bromoindolizines can be transformed to other 1-substituted indolizines such as 1-arylindolizines via a simple reaction process.

INTRODUCTION

As a class of important nitrogen-containing heterocycles, indolizine derivatives exhibit a wide array of biological activities,[1] such as cytotoxicity,[2] multidrug resistance (MDR) reversal in cancer cell lines,[3] and topoisomerase I inhibiting ability.[4] The high fluorescence quantum yield of indolizine derivatives in the UV−visible region has made them useful in designing biological markers[5] and electroluminescent materials.[6] Therefore, indolizines with diverse substituents are important synthetic target compounds.[7] As a part of our program on developing an efficient method to different substituted indolizines, we were particularly interested in finding efficient approaches to 1-brominated indolizines because they are important synthetic intermediates and can be transformed to many other 1-substituted indolizines. Existing synthetic protocols to 1-bromoindolizines are limited to electrophilic substitution reactions of indolizines with Br_2 or NBS.[8] However, these protocols generally have shortcomings, such as low regioselectivity, unsatisfactory yield, poor functional group tolerance, and being not eco-friendly. Consequently, new and efficient synthetic protocols to 1-bromoindolizines are highly desired.

On the other hand, direct C−H functionalization of heterocyclic compounds has emerged as one of the most important topics in the field of metal-catalyzed C−H bond activation.[9] As an important heterocyclic compound, direct C−H functionalization of indolizines for the access of various substituted indolizines has attracted much attention.[10] However, existing reports mainly focused on the indolizines dehydrogenative functionalization at the C-3 position adjacent to the nitrogen atom, which is easily activated, such as in halogenation,[10a] arylation,[10b−f] vinylation,[10g,h] or acylation,[10i,j] whereas dehydrogenative functionalization of indolizines at the C-1 position has not so far been achieved. Moreover, current employed methods of indolizine C−H functionalization usually use indolizines as substrates. To date, there is no report on the synthesis of a substituted indolizine by combining indolizine formation and C−H functionalization in one pot.

Herein, we report an effective copper(II)-catalyzed protocol to synthesize 1-bromoindolizines by three-component reactions of pyridine, α-acylmethylbromide, and maleic anhydride. To the best of our knowledge, this is the first report of transition-metal-catalyzed direct dehydrogenative bromination reaction of indolizines at the C-1 position. The obtained 1-bromoindolizines can be used as a synthetic precursor for other C-1 substituted indolizines such as 1-arylindolizines via a simple operation.

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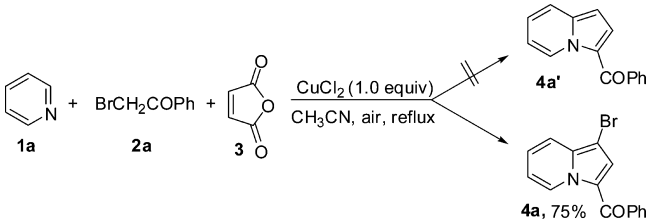
RESULT AND DISCUSSION

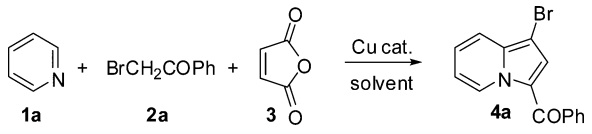
Metal-catalyzed decarboxylation reaction is an important research topic of organic chemistry.[11] Following our interest in copper-catalyzed reactions,[12] we initially planned to design a copper-catalyzed cycloaddition/decarboxylation protocol to synthesize 3-acylindolizine via a three-component reaction of pyridine, α-acylmethylbromide, and maleic anhydride. However, after heating a mixture of pyridine **1a** (3.0 mmol), bromide **2a** (1.0 mmol), and maleic anhydride **3** (1.0 mmol) in acetonitrile for 24 h in the air in the presence of 1.0 equiv of copper(II) chloride, we obtained 1-bromo-3-benzoylindolizine **4a** in 75% yield instead of the preconceived 3-benzoylindolizine **4a′** (Scheme 1). This illustrated that indolizine C-1 direct dehydrogenative functionalization occurred under this reaction condition.

Scheme 1. Synthesis of 1-Bromoindolizines



Encouraged by this promising result, we began to optimize the reaction conditions. The above-mentioned reaction of pyridine **1a**, bromide **2a**, and maleic anhydride **3** was chosen as a model reaction, and the representative results are shown in Table 1. In the presence of 1 equiv of copper(II) chloride, we first examined the reaction using different solvents and found that acetonitrile was the best choice (Table 1, entries 1−5). The kind of copper salts was then investigated by using acetonitrile as solvent, and copper(II) chloride and copper(II) triflate were confirmed to be better than other copper(II) salts (Table 1, entries 5−8). Subsequently, we screened the amount of copper(II) chloride and found that 30 mol % copper(II) chloride was enough in an oxygen atmosphere to ensure the high yield (Table 1, entries 9−11). Finally, we optimized the reaction temperature and found that refluxing in acetonitrile gave the best result (Table 1, entry 12). Therefore, the optimized reaction conditions were found to be refluxing the mixture of pyridine **1a**, bromide **2a**, and maleic anhydride **3** in acetonitrile for 24 h in an oxygen atmosphere, using 30 mol % copper(II) chloride as the catalyst.

Table 1. Optimization of the Reaction Conditions[a]

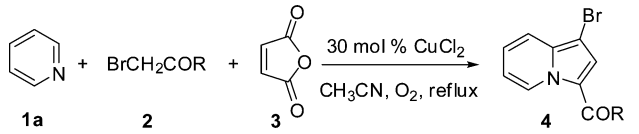


entry	solvent	copper (equiv)	temp (°C)	yield (%)[b]
1	dioxane	$CuCl_2$ (1.0)	80	52
2	$CHCl_3$	$CuCl_2$ (1.0)	reflux	trace
3	DMF	$CuCl_2$ (1.0)	80	22
4	toluene	$CuCl_2$ (1.0)	80	25
5	CH_3CN	$CuCl_2$ (1.0)	reflux	75
6	CH_3CN	$CuBr_2$ (1.0)	reflux	70
7	CH_3CN	$Cu(OAc)_2$ (1.0)	reflux	67
8	CH_3CN	$Cu(OTf)_2$ (1.0)	reflux	75
9	CH_3CN	$CuCl_2$ (0.2)[c]	reflux	48
10	CH_3CN	$CuCl_2$ (0.3)[c]	reflux	75
11	CH_3CN	$CuCl_2$ (0.4)[c]	reflux	75
12	CH_3CN	$CuCl_2$ (0.3)[c]	60	46

[a]Reaction conditions: the mixture of pyridine **1a** (3.0 mmol), bromide **2a** (1.0 mmol), maleic anhydride **3** (1.0 mmol), and copper(II) salt was heated in the solvent for 24 h in the air. [b]Isolated yield. [c]Heated in an oxygen atmosphere.

With the optimized conditions in hand, we then investigated the reactant scope in this reaction. First, different bromides **2** were used to react with pyridine **1a** and maleic anhydride **3**. It was found that various aryl bromoketones **2a**−**2h** having either an electron-donating or an electron-withdrawing substituent on the benzene ring take part in the reaction well, giving the desired products **4a**−**4h** in modest to high yields, although an electron-withdrawing group usually gave higher yields than an electron-donating group (Table 2, entries 1−8). Alkyl

Table 2. Reaction of 1a with 2[a]



entry	2 R	product	yield (%)[b]
1	**2a** R = Ph	**4a**	75
2	**2b** R = 4-ClPh	**4b**	79
3	**2c** R = 4-MeOPh	**4c**	68
4	**2d** R = 4-BrPh	**4d**	77
5	**2e** R = 4-FPh	**4e**	82
6	**2f** R = 4-MePh	**4f**	72
7	**2g** R = 2-ClPh	**4g**	76
8	**2h** R = 3,4-Cl_2Ph	**4h**	80
9	**2i** R = CH_3	**4i**	66
10	**2j** R = O-*t*-Bu	**4j**	69

[a]Reaction conditions: refluxing the mixture of pyridine **1a** (3.0 mmol), bromides **2** (1.0 mmol), maleic anhydride **3** (1.0 mmol), and copper(II) chloride (0.30 mmol) in acetonitrile for 24 h in an O_2 atmosphere. [b]Isolated yield.

bromoketone **2i** can also react with pyridine **1a** and maleic anhydride **3**, leading to product **4i** in modest yield (Table 2, entry 9). Using *tert*-butyl bromoacetate **2j** gave the desired 1-bromoindolizine **4j** in 69% yield (Table 2, entry 10). When methyl bromoester **2k** or ethyl bromoester **2l** was used in this reaction, no desired product was found, presumably due to the labile nature of these ester groups under the reaction conditions.

Various 4-substituted pyridines were then investigated by reacting with bromides **2** and maleic anhydride **3** under the optimal conditions, and the results are shown in Table 3. It was found that substituted pyridines **1b**−**1f** were appropriate substrates in this reaction. Pyridines with an electron-withdrawing group (carbonyls in ketone or ester) could react with bromoketones or bromoesters well, yielding the desired products **5a**−**5m** in 71−95% yield (Table 3, entries 1−13). Meanwhile, pyridines with an electron-donating group (aryl or alkyl) could also react with bromoketones or bromoester, giving the target products **5n**−**5r** in good yields (Table 3, entries 14−18).

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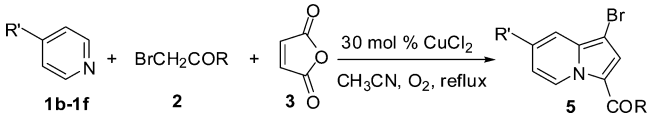
Table 3. Reaction of Substituted Pyridines 1b−1f with 2[a]

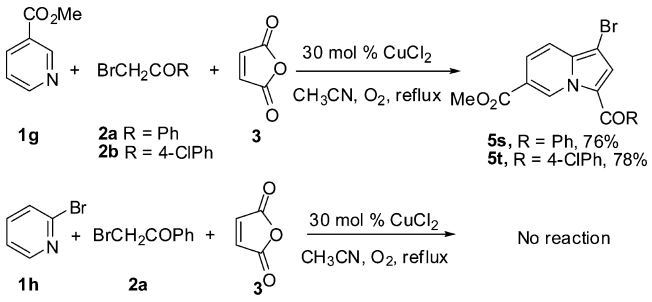


entry	1 R′	2 R	product	yield (%)[b]
1	**1b** R′ = CO_2Me	**2a** R = Ph	**5a**	90
2	**1b** R′ = CO_2Me	**2b** R = 4-ClPh	**5b**	93
3	**1b** R′ = CO_2Me	**2c** R = 4-MeOPh	**5c**	89
4	**1b** R′ = CO_2Me	**2k** R = OMe	**5d**	85
5	**1b** R′ = CO_2Me	**2l** R = OEt	**5e**	83
6	**1c** R′ = CO_2Et	**2b** R = 4-ClPh	**5f**	95
7	**1c** R′ = CO_2Et	**2c** R = 4-MeOPh	**5g**	90
8	**1c** R′ = CO_2Et	**2k** R = OMe	**5h**	86
9	**1c** R′ = CO_2Et	**2l** R = OEt	**5i**	83
10	**1c** R′ = CO_2Et	**2j** R = $OC(CH_3)_3$	**5j**	87
11	**1d** R′ = COMe	**2a** R = Ph	**5k**	78
12	**1d** R′ = COMe	**2b** R = 4-ClPh	**5l**	83
13	**1d** R′ = COMe	**2l** R = OEt	**5m**	71
14	**1e** R′ = Ph	**2a** R = Ph	**5n**	82
15	**1e** R′ = Ph	**2b** R = 4-ClPh	**5o**	85
16	**1e** R′ = Ph	**2m** R = OCH_2Ph	**5p**	77
17	**1f** R′ = *t*-Bu	**2a** R = Ph	**5q**	73
18	**1f** R′ = *t*-Bu	**2e** R = 4-FPh	**5r**	79

[a]Reaction conditions: refluxing the mixture of pyridine (**1b−1f**, respectively, 3.0 mmol), bromide **2** (1.0 mmol), maleic anhydride **3** (1.0 mmol), and copper(II) chloride (0.30 mmol) in acetonitrile for 24 h in an O_2 atmosphere. [b]Isolated yield.

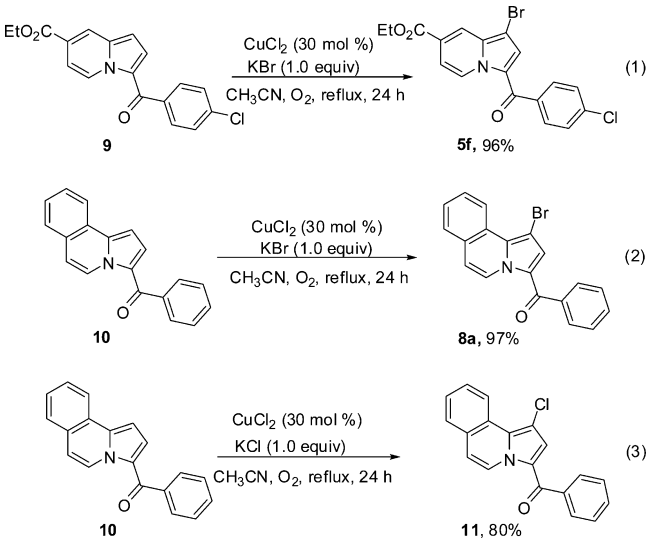
We also used 3-substituted pyridine to carry out this reaction. After refluxing methyl nicotinate **1g** (3.0 mmol) with bromide **2a** or **2b** (1.0 mmol), maleic anhydride **3** (1.0 mmol), and copper(II) chloride (0.30 mmol) in acetonitrile for 24 h in an O_2 atmosphere, we obtained product **5s** or **5t** with high regioselectivity. When 2-bromopyridine **1h** was used as substrate under the same conditions, unfortunately, no desired product was obtained, probably due to steric hindrance (Scheme 2).

Scheme 2. Reaction of 3-Substituted or 2-Substituted Pyridine



In order to expand the substrate scope further, we used quinoline **6a** or isoquinoline **6b** in this reaction for the synthesis of annulated indolizines, as shown in Table 4. To our delight, quinoline **6a** could react with bromoketones or bromoesters **2**, and maleic anhydride **3** under the optimal conditions to generate the desire products **7a−7h** in 68−91% yields. The structure of **7a** was unambiguously established by X-ray crystallography (see the Supporting Information). Similarly, isoquinoline **6b** could also react with various bromides and maleic anhydride, leading to products **8a−8c** in good to excellent yields.

In order to shed light on the details of the reaction mechanism, we performed the control experiments as shown in Scheme 3 and eqs 1−3. After heating a mixture of ethyl



isonicotinate **1c** (3.0 mmol), bromoketone **2b** (1.0 mmol), and maleic anhydride **3** (1.0 mmol) in acetonitrile in an O_2 atmosphere using copper(II) chloride (0.30 mmol) as the catalyst for 4 h, 3-benzoylindolizine **9** was formed in 30% yield, together with only a trace amount of 1-bromo-3-benzoylindolizine **5f**. By prolonging the refluxing time, the yield of **5f** increased gradually and that of **9** increased initially and then decreased. After the reaction time was prolonged to 24 h, product **9** disappeared completely and **5f** was found as the sole product (Scheme 3). This showed typical kinetic characteristics of a consecutive reaction with the C1-unsubstituted **9** as a primary product, which then underwent C-1 dehydrogenative bromination to give **5f**.

In addition, when the independently prepared compound **9** or **10**[13] was subjected to heating with potassium bromide (1.0 equiv), and copper(II) chloride (0.3 equiv) in acetonitrile in an O_2 atmosphere for 24 h, **5f** or **8a** was obtained in excellent yield, respectively (eqs 1 and 2). Besides, when refluxing **10** (1.0 mmol) with potassium chloride (1.0 mmol), and copper(II) chloride (0.30 mmol) in acetonitrile in an O_2 atmosphere for 24 h, chlorinated indolizine **11** could also be obtained in 80% yield (eq 3). These results confirmed the above conclusion further.

On the basis of these experimental results, a possible reaction mechanism was suggested as shown in Scheme 4. Initially, pyridinium ylide I generated in situ by pyridine and bromide underwent 1,3-dipolar cycloaddition with maleic anhydride, leading to tetrahydroindolizine II. Hydrolysis of II in the presence of excess pyridine and adventitious water leading to III and subsequent oxidative decarboxylation and aromatization of III furnished 3-benzoylindolizine **4a′**. The 3-acylindolizine **4a′** then reacted with $CuCl_2$ via a single electron transfer (SET) process, giving the radical cation IV, which is nucleophilically trapped by the bromide ion, giving radical intermediate V,[14] which, upon further electron transfer with $CuCl_2$, followed by deprotonation of the carbocation V, gave the 1-bromo-3-benzoylindolizine **4a**. The $CuCl_2$ can be regenerated via oxidation of the cuprous chloride by oxygen.[15]

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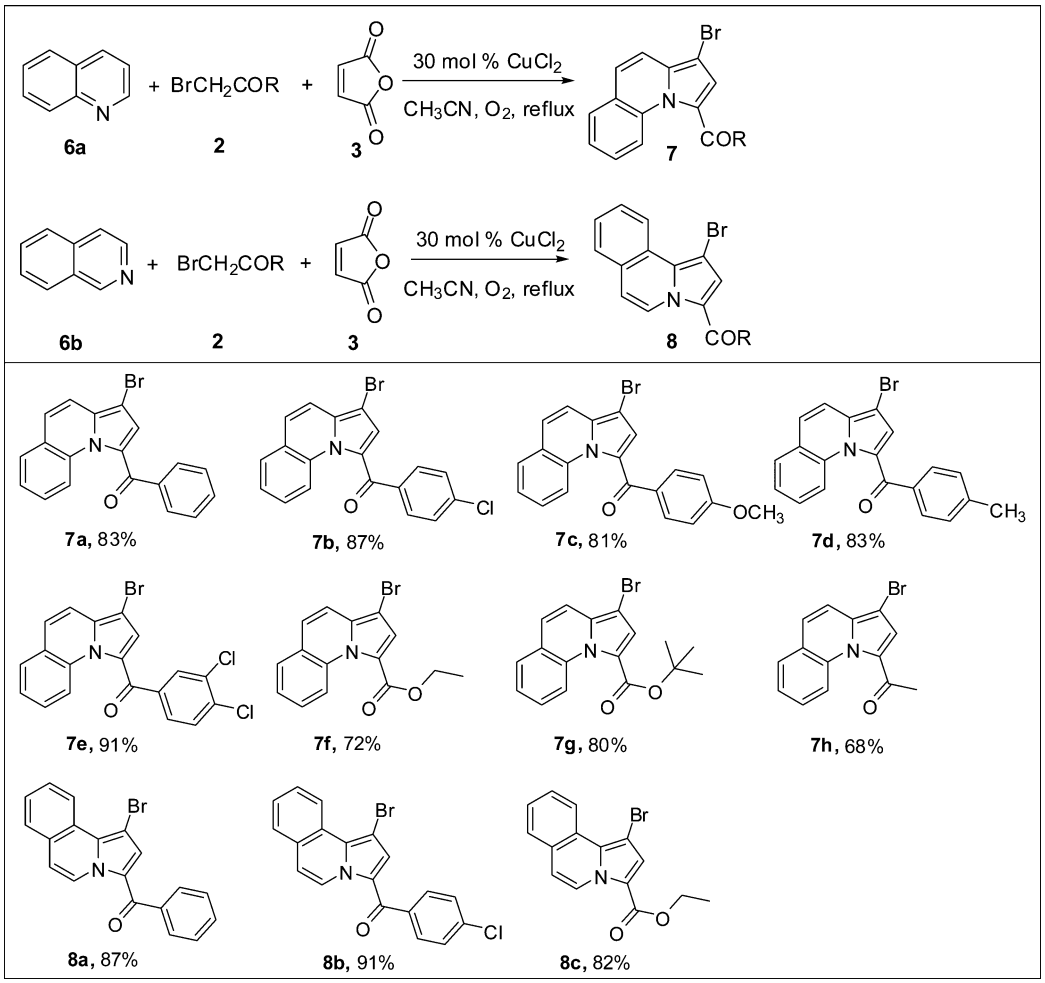
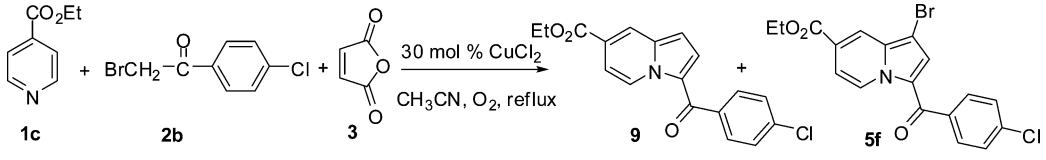
Table 4. Reaction of 6a or 6b with 2 and 3[a]



[a]Reaction conditions: refluxing the mixture of quinoline **6a** or isoquinoline **6b** (3.0 mmol), bromides **2** (1.0 mmol), maleic anhydride **3** (1.0 mmol), and hydrated copper(II) chloride (0.30 mmol) in acetonitrile for 24 h in an O_2 atmosphere.

Scheme 3. Control Experiment



time	yield
4 h	**9**, 30%, **5f**, trace
8 h	**9**, 52%, **5f**, 26%
12 h	**9**, 37%, **5f**, 48%
24 h	**9**, 0%, **5f**, 95%

To test the proposed SET mechanism further, we used $Mn(OAc)_3$ (2.0 equiv) as oxidant to react with compound **9** (1.0 equiv) and potassium bromide (2.0 equiv) by refluxing in acetonitrile for 24 h, and the C-1 brominated indolizine **5f** was formed in 46% yield at a 50% conversion of **9** (Scheme 5a). When pyridine (2.0 equiv) was added to this reaction mixture, the conversion of **9** raised to 100% in 24 h under otherwise the same conditions, with 95% yield of **5f** (Scheme 5b). Similarly, reaction of **9** (1.0 equiv) with potassium bromide (2.0 equiv) in the presence of $FeCl_3$ (2.0 equiv) and pyridine (2.0 equiv) in refluxing acetonitrile for 24 h led to a complete conversion of **9** to give product **5f** in 93% yield (Scheme 5c). These results strongly support the SET mechanism we suggested above.[16,17]

We have also carried out a DFT/UB3LYP calculation of the charge density distribution in the 3-acetylindolizine cation radical at the 6-31+G (d,p) level,[18] and the result (see the Supporting Information) clearly indicated that either with or without the summing up of the charge density at the hydrogen atom to the attached carbon atom, C1 is the most positively charged carbon atom in the cation radical and, therefore, the site of nucleophilic attack by Br^-. This result provided additional support to the suggested SET mechanism and also rationalized the regioselectivity in the bromination reaction.

In order to demonstrate the utility of these 1-bromoindolizine products, we synthesized 1-phenylindolizines from 1-bromoindolizines under the Suzuki–Miyaura conditions

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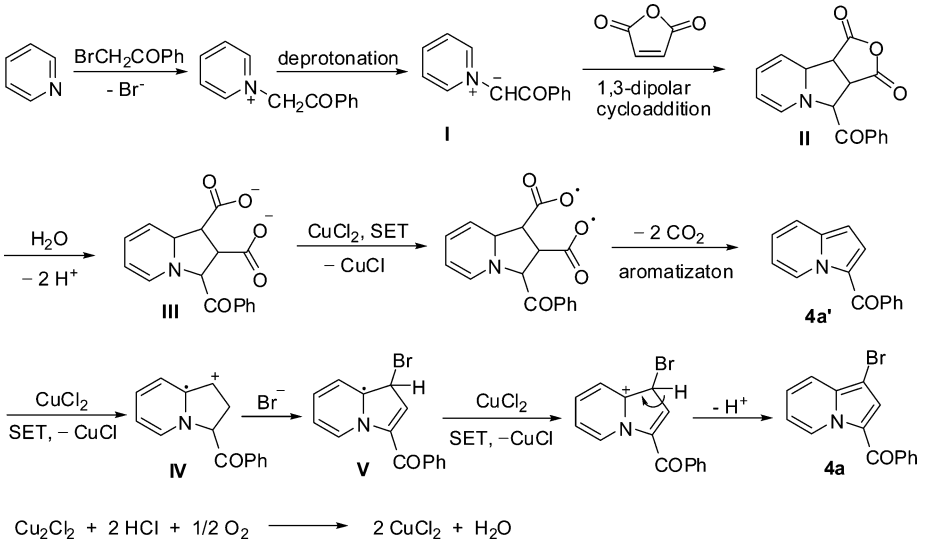
Scheme 4. Plausible Reaction Mechanism



(Scheme 6). As we expected, in the presence of 2 mol % $PdCl_2(PPh_3)_2$, 1-bromoindolizine **5a** took part in the coupling reaction with phenylboronic acid smoothly, affording 1-phenylindolizine **12** in 91% yield. Similarly, **5g** can also be transformed to **13** in 90% yield under the same condition.

CONCLUSIONS

In summary, 1-bromoindolizines have been synthesized by a copper(II)-catalyzed cycloaddition/decarboxylative aromatization/dehydrogenative functionalization cascade via multicomponent reactions of pyridine, α-acylmethylbromide, and maleic anhydride. This strategy provides a general and high-yielding synthesis of 1-bromoindolizines via easily accessible starting materials by a simple one-pot procedure. This is the first report of a transition-metal-catalyzed indolizine C-1 dehydrogenative bromination reaction. Moreover, the synthesized 1-bromoindolizines may serve as precursors for other 1-functionalized indolizines as exemplified by the synthesis of 1-arylindolizines efficiently via the Suzuki−Miyaura reactions.

EXPERIMENTAL SECTION

General. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively using $CDCl_3$ as solvent. HRMS data were recorded on a mass spectrometer with electrospray ionization and TOF mass analyzer.

General Procedure for the Synthesis of 4. A mixture of pyridine **1a** (3.0 mmol), bromides **2** (1.0 mmol), maleic anhydride **3** (1.0 mmol), and hydrated copper chloride (0.30 mmol) in acetonitrile (15 mL) was refluxed for 24 h with magnetic stirring in an O_2 atmosphere. The reaction course was monitored by TLC. After the reaction was completed, the solvent was removed under reduced pressure, and the residue was separated by flash chromatography on a silica gel column with ethyl acetate/petroleum ether (1:20) as eluent to give the products **4**.

*(1-Bromoindolizin-3-yl)phenylmethanone (**4a**).* Yellow solid, yield 224 mg (75%); mp 80−82 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (t, J = 6.8 Hz, 1H), 7.28−7.32 (m, 1H), 7.38 (s, 1H), 7.48−7.56 (m, 3H), 7.62 (d, J = 8.8 Hz, 1H), 7.78 (dt, J = 7.6, 0.4 Hz, 2H), 9.86 (dd, J = 72, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.1, 140.2, 136.8, 131.2, 128.9, 128.7, 128.3, 127.1, 125.2, 122.1, 117.2, 114.6, 89.6; IR (KBr) 1629, 1574, 1469, 1355, 1232, 1137, 1014 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{15}H_{11}BrNO$: 300.0024; found: 300.0033.

*(1-Bromoindolizin-3-yl)(4-chlorophenyl)methanone (**4b**).* Yellow solid, yield 262 mg (79%); mp 151−152 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (td, J = 6.8, 1.2 Hz, 1H), 7.30−7.32 (m, 1H), 7.34 (s, 1H), 7.48 (dt, J = 8.8, 1.6 Hz, 2H), 7.62 (dt, J = 8.8, 1.2 Hz, 1H), 7.73 (dt, J = 8.8, 2.0 Hz, 2H), 9.92 (dd, J = 7.2, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.6, 138.5, 137.4, 137.0, 130.2, 128.7, 128.6, 126.9, 125.5, 121.8, 117.3, 114.8, 89.9; IR (KBr) 1614, 1561, 1509, 1470, 1358, 1230, 1144, 1014 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{15}H_{10}BrClNO$: 333.9634; found: 333.9640.

*(1-Bromoindolizin-3-yl)(4-methoxyphenyl)methanone (**4c**).* Yellow solid, yield 223 mg (68%); mp 149−150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 (s, 3H), 6.96 (td, J = 7.2, 1.2 Hz, 1H), 7.00 (dt, J = 6.8, 2.0 Hz, 2H), 7.26 (td, J = 8.8, 1.2 Hz, 1H), 7.39 (s, 1H), 7.59 (d, J = 8.8 Hz, 1H), 7.80 (dt, J = 8.8, 2.0 Hz, 2H), 9.89 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.2, 162.3, 136.5, 132.6, 131.1, 128.6, 126.6, 124.8, 122.2, 117.2, 114.3, 113.6, 89.2, 55.5; IR (KBr) 1628, 1562, 1508, 1471, 1351, 1261, 1177, 1028 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{16}H_{13}BrNO_2$: 330.0130; found: 330.0133.

*(1-Bromoindolizin-3-yl)(4-bromophenyl)methanone (**4d**).* Yellow solid, yield 289 mg (77%); mp 163−165 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (t, J = 7.2 Hz, 1H), 7.32−7.34 (m, 2H), 7.61−7.68 (m, 5H), 9.92 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.7, 139.0, 137.1, 131.6, 130.4, 130.3, 128.8, 127.0, 125.9, 125.6, 125.5, 121.9, 117.3, 114.8, 89.9; IR (KBr) 1613, 1560, 1508, 1439, 1394, 1227, 1178 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{15}H_{10}Br_2NO$: 377.9129; found: 377.9133.

*(1-Bromoindolizin-3-yl)(4-fluorophenyl)methanone (**4e**).* Yellow solid, yield 261 mg (82%); mp 130−131 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (td, J = 7.2, 1.2 Hz, 1H), 7.18 (tt, J = 8.4, 2.0 Hz, 2H), 7.29−7.33 (m, 1H), 7.35 (s, 1H), 7.62 (d, J = 9.2 Hz, 1H), 7.79−7.83 (m, 2H), 9.92 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.6, 164.5 (d, $^1J_{C-F}$ = 250 Hz), 136.9, 136.4, 136.3, 131.2 (d, $^3J_{C-F}$ = 8.9 Hz), 128.7, 126.9, 125.4, 121.9, 117.3, 115.4 (d, $^2J_{C-F}$ = 21.7 Hz), 114.7, 89.7; IR (KBr) 1616, 1585, 1543, 1504, 1468, 1347, 1234, 1156, 1015 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{15}H_{10}BrFNO$: 317.9930; found: 317.9923.

*(1-Bromoindolizin-3-yl)(4-methylphenyl)methanone (**4f**).* Yellow solid, yield 226 mg (72%); mp 145−147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45 (s, 3H), 6.97 (td, J = 7.2, 1.2 Hz, 1H), 7.27−7.31 (m, 3H), 7.38 (s, 1H), 7.60 (d, J = 8.8 Hz, 1H), 7.70 (d, J = 8.0 Hz, 2H), 9.93 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.1, 141.7, 137.5, 136.7, 129.2, 129.1, 129.0, 128.7, 127.0, 125.0, 122.3, 117.2, 114.5, 89.4, 21.6; IR (KBr) 1618, 1566, 1511, 1467, 1351, 1234, 1186, 1012 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{16}H_{13}BrNO$: 314.0181; found: 314.0172.

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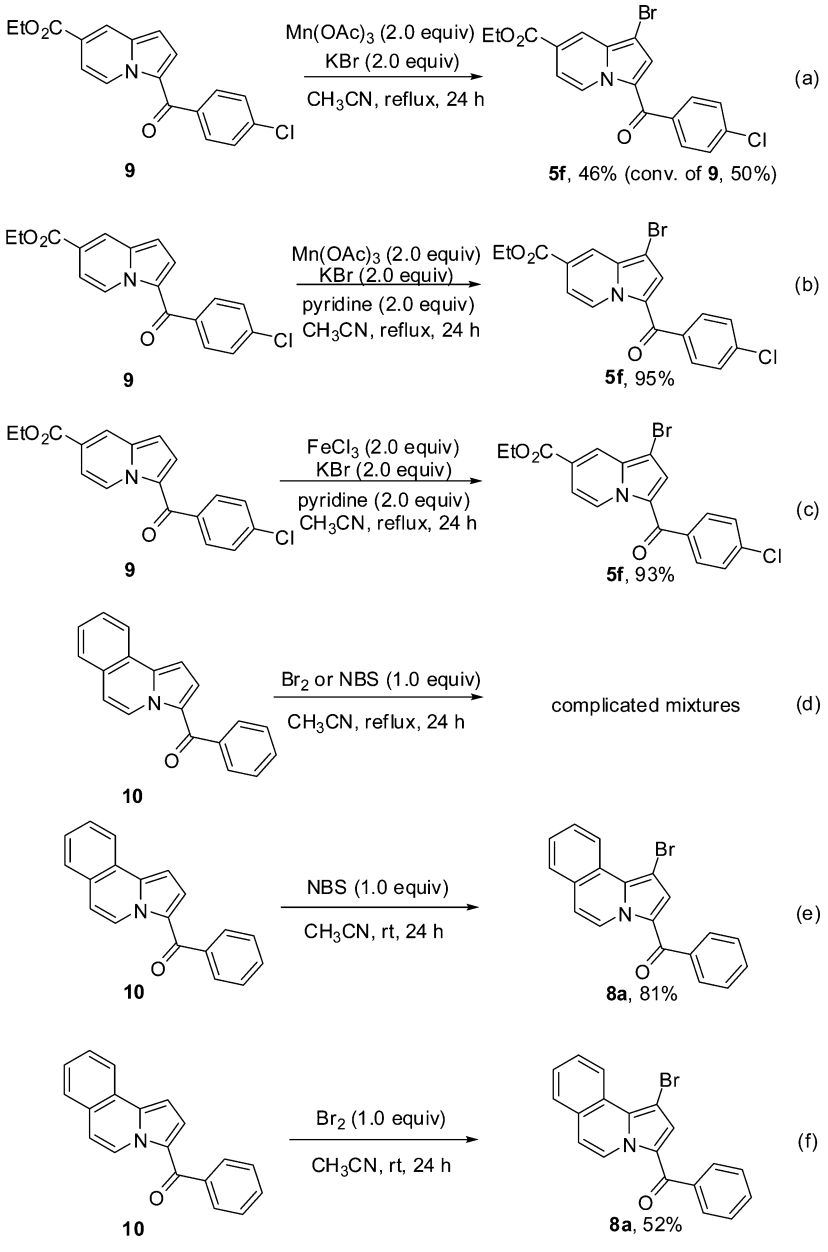
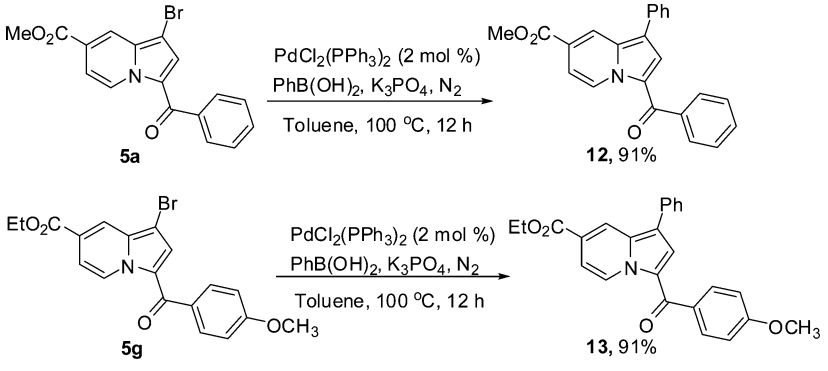
Scheme 5. Mechanism Confirmation



Scheme 6. Synthesis of 1-Phenylindolizines



*(1-Bromoindolizin-3-yl)(2-chlorophenyl)methanone (**4g**).* Yellow solid, yield 253 mg (76%); mp 162−164 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (s, 1H), 7.06 (td, J = 7.2, 1.2 Hz, 1H), 7.33−7.38 (m, 2H), 7.40−7.45 (m, 2H), 7.47−7.49 (m, 1H), 7.62 (d, J = 8.8 Hz, 1H), 10.02 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.8, 139.3, 137.5, 131.4, 130.7, 130.1, 129.1, 129.0, 127.4, 126.5, 126.0,

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122.3, 117.4, 115.1, 90.3; IR (KBr) 1612, 1541, 1508, 1468, 1351, 1228, 1134, 1014 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{15}H_{10}BrClNO$: 333.9634; found: 333.9646.

*(1-Bromoindolizin-3-yl)(3,4-dichlorophenyl)methanone (**4h**).* Yellow solid, yield 294 mg (80%); mp 195−196 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.03 (td, J = 7.2, 1.6 Hz, 1H), 7.32−7.36 (m, 2H), 7.56−7.65 (m, 3H), 7.87 (d, J = 2.0 Hz, 1H), 9.91 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.9, 139.9, 137.4, 135.6, 132.9, 130.7, 130.4, 128.8, 128.0, 126.9, 125.9, 121.6, 117.4, 115.1, 90.3; IR (KBr) 1608, 1551, 1473, 1355, 1240, 1227, 1146, 1019 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{15}H_9BrCl_2NO$: 367.9245; found: 367.9245.

*1-(1-Bromoindolizin-3-yl)ethanone (**4i**).* White solid, yield 156 mg (66%); mp 82−83 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 2.53 (s, 3H), 6.91 (td, J = 7.2, 1.2 Hz, 1H), 7.20−7.24 (m, 1H), 7.51 (s, 1H), 7.55 (d, J = 9.2 Hz, 1H), 9.83 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.2, 136.1, 128.5, 124.6, 124.4, 122.4, 117.1, 114.4, 88.9, 27.2; IR (KBr) 1623, 1514, 1473, 1352, 1244, 1218, 1026 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{10}H_9BrNO$: 237.9868; found: 237.9863.

*tert-Butyl 1-Bromoindolizine-3-carboxylate (**4j**).* Yellow liquid, yield 203 mg (69%); ^1H NMR (400 MHz, $CDCl_3$) δ 1.60 (s, 9H), 6.80 (td, J = 7.2, 1.6 Hz, 1H), 7.04−7.08 (m, 1H), 7.45 (s, 1H), 7.49 (dt, J = 7.6, 1.2 Hz, 1H), 9.39 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 135.0, 127.3, 122.6, 122.1, 117.3, 115.2, 113.1, 87.7, 80.9, 28.6; IR (KBr) 1682, 1515, 1472, 1370, 1305, 1228, 1166, 1026 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{13}H_{15}BrNO_2$: 296.0286; found: 296.0293.

General Procedure for the Synthesis of 5. A mixture of substituted pyridines **1b−1g** (3.0 mmol), bromides **2** (1.0 mmol), maleic anhydride **3** (1.0 mmol), and hydrated copper chloride (0.30 mmol) in acetonitrile (15 mL) was refluxed for 24 h with magnetic stirring in an O_2 atmosphere. The reaction course was monitored by TLC. After the reaction was completed, the solvent was removed under reduced pressure, and the residue was separated by flash chromatography on a silica gel column with ethyl acetate/petroleum ether (1:20) as eluent to give the products **5**.

*Methyl 3-Benzoyl-1-bromoindolizine-7-carboxylate (**5a**).* Yellow solid, yield 320 mg (90%); mp 167−168 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 4.00 (s, 3H), 744 (s, 1H), 7.52 (t, J = 7.6 Hz, 3H), 7.60 (t, J = 7.2 Hz, 1H), 7.80 (dd, J = 8.0, 1.2 Hz, 2H), 8.34 (s, 1H), 9.08 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.8, 165.2, 139.5, 135.3, 131.7, 128.9, 128.4, 128.0, 127.4, 125.7, 123.6, 120.1, 113.3, 93.2, 52.7; IR (KBr) 1730, 1624, 1574, 1524, 1458, 1346, 1292, 1227, 1128 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{13}BrNO_3$: 358.0079; found: 358.0083.

*Methyl 1-Bromo-3-(4-chlorobenzoyl)indolizine-7-carboxylate (**5b**).* Yellow solid, yield 363 mg (93%); mp 200−202 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 4.00 (s, 3H), 7.40 (s, 1H), 7.49−7.53 (m, 3H), 7.75 (dt, J = 8.4, 1.6 Hz, 2H), 8.33 (d, J = 0.4 Hz, 1H), 9.84 (dd, J = 7.6, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 138.0, 137.9, 135.6, 130.3, 128.8, 128.0, 127.2, 126.0, 120.1, 113.5, 93.4, 52.7; IR (KBr) 1724, 1622, 1588, 1455, 1337, 1228, 1136, 1091 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{12}BrClNO_3$: 391.9689; found: 391.9695.

*Methyl 1-Bromo-3-(4-methoxybenzoyl)indolizine-7-carboxylate (**5c**).* Yellow solid, yield 346 mg (89%); mp 184−186 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 3.91 (s, 3H), 3.99 (s, 3H), 7.01 (d, J = 8.8 Hz, 2H), 7.44 (s, 1H), 7.47 (dd, J = 7.6, 2.0 Hz, 1H), 7.82 (d, J = 8.8 Hz, 2H), 8.32 (dd, J = 1.6, 0.8 Hz, 1H), 9.80 (dd, J = 7.2, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.8, 165.3, 162.7, 135.0, 132.0, 131.3, 129.0, 126.8, 125.3, 123.7, 120.2, 113.8, 113.0, 93.0, 55.5, 52.6; IR (KBr) 1721, 1622, 1573, 1509, 1457, 1427, 1339, 1286, 1247, 1173, 1032 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{15}BrNO_4$: 388.0184; found: 388.0184.

*Dimethyl 1-Bromoindolizine-3,7-dicarboxylate (**5d**).* White solid, yield 265 mg (85%); mp 133−135 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 3.95 (s, 3H), 3.99 (s, 3H), 7.39 (dd, J = 7.6, 2.0 Hz, 1H), 7.58 (s, 1H), 8.28 (d, J = 0.8 Hz, 1H), 9.40 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 160.8, 134.1, 126.7, 123.6, 123.4, 120.4, 112.3, 92.5, 52.5, 51.6; IR (KBr) 1721, 1699, 1522, 1459, 1363, 1286, 1256, 1045 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{12}H_{11}BrNO_4$: 311.9871; found: 311.9880.

*3-Ethyl 7-Methyl 1-bromoindolizine-3,7-dicarboxylate (**5e**).* White solid, yield 270 mg (83%); mp 137−138 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.41 (t, J = 7.2 Hz, 3H), 3.97 (s, 3H), 4.39 (q, J = 7.6 Hz, 2H), 7.37 (dd, J = 7.6, 2.0 Hz, 1H), 7.58 (s, 1H), 8.26 (dd, J = 2.0, 1.2 Hz, 1H), 9.38 (dd, J = 7.6, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 160.4, 134.0, 126.7, 123.5, 123.3, 120.4, 116.2, 112.2, 92.4, 60.6, 52.5, 14.5; IR (KBr) 1723, 1695, 1526, 1505, 1429, 1376, 1299, 1118, 1090 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{13}H_{13}BrNO_4$: 326.0028; found: 326.0035.

*Ethyl 1-Bromo-3-(4-chlorobenzoyl)indolizine-7-carboxylate (**5f**).* Yellow solid, yield 384 mg (95%); mp 175−176 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.46 (t, J = 7.2 Hz, 3H), 4.45 (q, J = 7.2 Hz, 2H), 7.40 (s, 1H), 7.50 (dt, J = 8.8, 2.0 Hz, 2H), 7.52 (dd, J = 7.6, 2.4 Hz, 1H), 7.75 (dt, J = 8.8, 2.0 Hz, 2H), 8.33 (dd, J = 2.0, 0.8 Hz, 1H), 9.85 (dd, J = 7.2, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.3, 164.7, 138.0, 137.9, 135.7, 130.3, 128.8, 128.0, 127.2, 126.4, 123.2, 120.0, 113.5, 93.4, 61.8, 14.3; IR (KBr) 1716, 1616, 1567, 1458, 1351, 1280, 1140, 1087, 1014 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{14}BrClNO_3$: 405.9846; found: 405.9854.

*Ethyl 1-Bromo-3-(4-methoxybenzoyl)indolizine-7-carboxylate (**5g**).* Yellow solid, yield 362 mg (90%); mp 138−139 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.45 (t, J = 7.2 Hz, 3H), 3.91 (s, 3H), 4.46 (q, J = 7.2 Hz, 2H), 7.01 (d, J = 8.8 Hz, 2H), 7.44 (s, 1H), 7.47 (dd, J = 7.6, 2.0 Hz, 1H), 7.83 (dt, J = 8.8, 2.0 Hz, 2H), 8.31 (dd, J = 2.0, 0.8 Hz, 1H), 9.80 (dd, J = 7.6, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.7, 164.8, 162.7, 135.0, 132.0, 131.2, 127.8, 126.8, 125.7, 123.7, 120.0, 113.7, 113.0, 92.9, 61.7, 55.5, 14.4; IR (KBr) 1723, 1618, 1571, 1509, 1454, 1354, 1281, 1173, 1096, 1026 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{19}H_{17}BrNO_4$: 402.0341; found: 402.0349.

*7-Ethyl 3-Methyl 1-Bromoindolizine-3,7-dicarboxylate (**5h**).* Yellow solid, yield 279 mg (86%); mp 137−138 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.44 (t, J = 7.2 Hz, 3H), 3.93 (s, 3H), 4.43 (q, J = 7.2 Hz, 2H), 7.39 (dd, J = 7.6, 2.0 Hz, 1H), 7.57 (s, 1H), 8.26 (dd, J = 2.0, 1.2 Hz, 1H), 9.38 (dd, J = 7.6, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 160.8, 134.2, 126.7, 124.0, 123.4, 120.3, 115.8, 112.4, 92.4, 61.6, 51.6, 14.4; IR (KBr) 1723, 1696, 1568, 1524, 1463, 1367, 1281, 1089 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{13}H_{13}BrNO_4$: 326.0028; found: 326.0036.

*Diethyl 1-Bromoindolizine-3,7-dicarboxylate (**5i**).* White solid, yield 280 mg (83%); mp 114−116 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.39−1.46 (m, 6H), 4.36−4.45 (m, 4H), 7.38 (dd, J = 7.6, 1.6 Hz, 1H), 7.58 (s, 1H), 8.25 (s, 1H), 9.38 (dd, J = 7.6, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 160.4, 134.1, 126.7, 123.9, 123.3, 120.3, 116.1, 112.3, 92.3, 61.5, 60.5, 14.5, 14.4; IR (KBr) 1710, 1690, 1521, 1456, 1377, 1336, 1214, 1088 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{14}H_{15}BrNO_4$: 340.0184; found: 340.0176.

*7-Ethyl 3-tert-Butyl 1-Bromoindolizine-3,7-dicarboxylate (**5j**).* Yellow solid, yield 318 mg (87%); mp 119−121 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.44 (t, J = 7.2 Hz, 3H), 1.61 (s, 9H), 4.43 (q, J = 7.2 Hz, 2H), 7.35 (dd, J = 7.2, 2.0 Hz, 1H), 7.50 (s, 1H), 8.24 (dd, J = 1.6, 0.8 Hz, 1H), 9.38 (dd, J = 7.2, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 160.0, 133.7, 126.7, 123.5, 123.3, 120.3, 117.3, 112.0, 92.1, 81.6, 61.5, 28.5, 14.4; IR (KBr) 1714, 1693, 1525, 1459, 1365, 1300, 1235, 1166, 1090 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{16}H_{19}BrNO_4$: 368.0497; found: 368.0492.

*1-(3-Benzoyl-1-bromoindolizin-7-yl)ethanone (**5k**).* Yellow solid, yield 265 mg (78%); mp 168−169 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 2.71 (s, 3H), 7.44 (s, 1H), 7.49−7.54 (m, 3H), 7.58−7.72 (m, 1H), 7.80−7.82 (m, 2H), 8.18 (s, 1H), 9.86 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.2, 184.8, 139.4, 135.0, 132.1, 131.7, 128.9, 128.4, 128.1, 127.3, 123.7, 119.0, 111.8, 93.8, 26.2; IR (KBr) 1689, 1627, 1560, 1517, 1490, 1456, 1336, 1229, 1145, 1077 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{13}BrNO_2$: 342.0130; found: 342.0134.

*1-(1-Bromo-3-(4-chlorobenzoyl)indolizin-7-yl)ethanone (**5l**).* Yellow solid, yield 312 mg (83%); mp 190−192 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 2.71 (s, 3H), 7.40 (s, 1H), 7.50 (d, J = 8.4 Hz, 3H), 7.75 (d,

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J = 8.8 Hz, 2H), 8.17 (s, 1H), 9.82 (dd, J = 7.2, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.2, 183.4, 138.1, 137.8, 135.4, 132.4, 130.4, 128.8, 128.2, 127.1, 123.5, 119.1, 112.1, 94.0, 26.2; IR (KBr) 1684, 1613, 1561, 1522, 1452, 1360, 1286, 1229, 1127, 1088 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{17}H_{12}BrClNO_2$: 375.9740; found: 375.9750.

*Ethyl 7-Acetyl-1-bromoindolizine-3-carboxylate (**5m**).* Yellow solid, yield 218 mg (71%); mp 107−109 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (t, J = 7.2 Hz, 3H), 2.67 (s, 3H), 4.39 (q, J = 7.2 Hz, 2H), 7.38 (dd, J = 7.2, 1.6 Hz, 1H), 7.59 (s, 1H), 8.10 (dd, J = 1.6, 0.8 Hz, 1H), 9.38 (dd, J = 7.6, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.4, 160.4, 133.7, 130.2, 126.9, 123.4, 119.6, 116.5, 110.8, 93.2, 60.6, 26.1, 14.4; IR (KBr) 1696, 1682, 1519, 1459, 1371, 1335, 1220, 1048 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{13}H_{13}BrNO_3$: 310.0079; found: 310.0086.

*(1-Bromo-7-phenylindolizin-3-yl)phenylmethanone (**5n**).* Yellow solid, yield 306 mg (82%); mp 151−153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, J = 7.6 Hz, 1H), 7.40 (s, 1H), 7.45−7.58 (m, 6H), 7.75 (dd, J = 7.6, 1.2 Hz, 2H), 7.80−7.82 (m, 3H), 10.0 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.9, 140.1, 138.0, 137.2, 131.2, 129.2, 129.1, 128.9, 128.8, 128.7, 128.3, 128.2, 127.6, 126.8, 126.7, 122.0, 114.1, 113.9, 90.3; IR (KBr) 1628, 1596, 1542, 1509, 1458, 1339, 1230 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{21}H_{15}BrNO$: 376.0337; found: 376.0330.

*(1-Bromo-7-phenylindolizin-3-yl)(4-chlorophenyl)methanone (**5o**).* Yellow solid, yield 348 mg (85%); mp 210−212 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (s, 1H), 7.30 (d, J = 7.2 Hz, 1H), 7.44−7.54 (m, 5H), 7.73−7.76 (m, 4H), 7.79−7.80 (m, 1H), 9.95 (dd, J = 7.2, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.4, 138.5, 138.3, 137.9, 137.5, 137.4, 130.2, 129.2, 128.9, 128.8, 128.6, 127.4, 126.8, 121.7, 114.3, 114.0, 90.5; IR (KBr) 1628, 1560, 1459, 1340, 1233, 1094 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{21}H_{14}$-BrClNO: 409.9947; found: 409.9944.

*Benzyl 1-Bromo-7-phenylindolizine-3-carboxylate (**5p**).* Yellow solid, yield 311 mg (77%); mp 100−102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.37 (s, 2H), 7.15 (dd, J = 7.6, 2.0 Hz, 1H), 7.34−7.43 (m, 4H), 7.45−7.51 (m, 4H), 7.59 (s, 1H), 7.69−7.72 (m, 3H), 9.46 (dd, J = 7.6, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 138.3, 136.4, 136.0, 135.7, 129.1, 128.6, 128.4, 128.2, 128.0, 127.5, 126.7, 123.5, 114.2, 113.2, 88.9, 65.8; IR (KBr) 1688, 1558, 1542, 1458, 1390, 1349, 1233, 1050 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{22}H_{17}BrNO_2$: 406.0443; found: 406.0450.

*(1-Bromo-7-tert-butylindolizin-3-yl)phenylmethanone (**5q**).* Yellow solid, yield 258 mg (73%); mp 139−141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 9H), 7.06 (dd, J = 7.6, 2.0 Hz, 1H), 7.34 (s, 1H), 7.47−7.54 (m, 4H), 7.77 (dd, J = 8.4, 1.6 Hz, 2H), 9.87 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.7, 149.8, 140.4, 137.2, 131.0, 128.9, 128.4, 128.3, 127.4, 121.6, 114.0, 111.8, 89.3, 35.1, 30.5; IR (KBr) 1614, 1572, 1541, 1507, 1456, 1334, 1231 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{19}H_{19}BrNO$: 356.0650; found: 356.0653.

*(1-Bromo-7-tert-butylindolizin-3-yl)(4-fluorophenyl)methanone (**5r**).* Yellow liquid, yield 295 mg (79%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 9H), 7.07 (dd, J = 7.2, 2.0 Hz, 1H), 7.17 (t, J = 8.4 Hz, 2H), 7.31 (s, 1H), 7.47 (dd, J = 2.0, 0.4 Hz, 1H), 7.78−7.82 (m, 2H), 9.83 (dd, J = 7.6, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.1, 164.4 (d, $^1J_{C-F}$ = 250 Hz), 149.9, 137.2, 136.5, 131.1 (d, $^3J_{C-F}$ = 8.8 Hz), 128.4, 127.1, 121.4, 115.4 (d, $^2J_{C-F}$ = 21.6 Hz), 114.1, 111.8, 89.4, 35.1, 30.4; IR (KBr) 1613, 1585, 1504, 1456, 1337, 1235, 1204, 1153 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{19}H_{18}BrFNO$: 374.0556; found: 374.0549.

*Methyl 3-Benzoyl-1-bromoindolizine-6-carboxylate (**5s**).* Yellow solid, yield 271 mg (76%); mp 154−156 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.98 (s, 3H), 7.47 (s, 1H), 7.50−7.53 (m, 2H), 7.57−7.62 (m, 2H), 7.79−7.81 (m, 3H), 10.58 (t, J = 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.4, 165.4, 139.5, 136.8, 132.5, 131.6, 129.0, 128.9, 128.4, 126.2, 124.3, 123.1, 118.3, 116.7, 115.9, 90.5, 52.5; IR (KBr) 1717, 1606, 1574, 1554, 1471, 1440, 1359, 1242, 1216 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{17}H_{13}BrNO_3$: 358.0079; found: 358.0087.

*Methyl 1-Bromo-3-(4-chlorobenzoyl)indolizine-6-carboxylate (**5t**).* Yellow solid, yield 304 mg (78%); mp 168−170 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.99 (s, 3H), 7.44 (s, 1H), 7.50 (d, J = 8.8 Hz, 2H), 7.64 (td, J = 9.2, 0.8 Hz, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.82 (dd, J = 9.2, 1.2 Hz, 1H), 10.55 (t, J = 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.0, 165.3, 138.1, 137.9, 137.1, 132.5, 130.3, 128.8, 126.0, 124.6, 122.9, 118.6, 116.9, 116.0, 90.8, 52.6; IR (KBr) 1735, 1616, 1589, 1541, 1471, 1357, 1304, 1215, 1118, 1014 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{17}H_{12}BrClNO_3$: 391.9689; found: 391.9678.

General Procedure for the Synthesis of 7. A mixture of quinoline **6a** (3.0 mmol), bromides **2** (1.0 mmol), maleic anhydride **3** (1.0 mmol), and hydrated copper chloride (0.30 mmol) in acetonitrile (15 mL) was refluxed for 24 h with magnetic stirring in an O_2 atmosphere. The reaction course was monitored by TLC. After the reaction was completed, the solvent was removed under reduced pressure, and the residue was separated by flash chromatography on a silica gel column with ethyl acetate/petroleum ether (1:20) as eluent to give the products **7**.

*(3-Bromopyrrolo[1,2-a]quinolin-1-yl)phenylmethanone (**7a**).* Yellow solid, yield 291 mg (83%); mp 151−152 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (s, 1H), 7.43−7.47 (m, 1H), 7.48−7.56 (m, 5H), 7.64 (tt, J = 7.2, 1.6 Hz, 1H), 7.75 (dd, J = 7.6, 1.6 Hz, 1H), 8.05 (dt, J = 7.2, 1.6 Hz, 2H), 8.12 (d, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.2, 139.0, 136.8, 133.7, 132.9, 130.4, 129.3, 129.2, 128.7, 128.2, 126.9, 125.5, 125.3, 120.1, 116.2, 91.9; IR (KBr) 1631, 1575, 1483, 1453, 1351, 1323, 1269, 1203, 1060 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{19}H_{13}BrNO$: 350.0181; found: 350.0190.

*(3-Bromopyrrolo[1,2-a]quinolin-1-yl)(4-chlorophenyl)methanone (**7b**).* Yellow solid, yield 332 mg (87%); mp 142−144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (s, 1H), 7.44−7.57 (m, 6H), 7.76 (dd, J = 7.6, 1.2 Hz, 1H), 8.00 (d, J = 8.8 Hz, 2H), 8.08 (d, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.5, 139.0, 137.1, 136.8, 133.4, 131.4, 129.0, 128.7, 128.5, 127.4, 126.9, 125.4, 125.0, 119.8, 115.9, 91.8; IR (KBr) 1633, 1560, 1480, 1452, 1348, 1268, 1201, 1175, 1091 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{19}H_{12}BrClNO$: 383.9791; found: 383.9797.

*(3-Bromopyrrolo[1,2-a]quinolin-1-yl)(4-methoxyphenyl)methanone (**7c**).* Yellow solid, yield 306 mg (81%); mp 161−163 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.93 (s, 3H), 7.02 (dt, J = 8.8, 2.0 Hz, 2H), 7.20 (s, 1H), 7.42−7.51 (m, 4H), 7.74 (dd, J = 8.0, 1.6 Hz, 1H), 8.03 (d, J = 8.8 Hz, 1H), 8.06 (dt, J = 8.8, 2.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.4, 163.5, 135.8, 133.4, 132.4, 131.2, 128.9, 128.3, 127.8, 126.0, 125.1, 119.7, 116.0, 113.7, 91.3, 55.6; IR (KBr) 1629, 1509, 1450, 1350, 1262, 1174, 1114, 1022 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{20}H_{15}BrNO_2$: 380.0286; found: 380.0284.

*(3-Bromopyrrolo[1,2-a]quinolin-1-yl)(4-methylphenyl)methanone (**7d**).* Yellow solid, yield 302 mg (83%); mp 108−110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.48 (s, 3H), 7.21 (s, 1H), 7.33 (d, J = 8.0 Hz, 2H), 7.40−7.53 (m, 4H), 7.74 (dd, J = 7.6, 1.6 Hz, 1H), 7.96 (d, J = 8.0 Hz, 2H), 8.07 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.0, 143.6, 136.2, 136.1, 133.5, 130.3, 129.2, 128.9, 128.5, 128.4, 128.0, 126.4, 125.2, 125.1, 119.8, 116.0, 91.5, 21.8; IR (KBr) 1628, 1556, 1541, 1452, 1352, 1269, 1176, 1061 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{20}H_{15}BrNO$: 364.0337; found: 364.0335.

*(3-Bromopyrrolo[1,2-a]quinolin-1-yl)(3,4-dichlorophenyl)methanone (**7e**).* Yellow solid, yield 378 mg (91%); mp 145−146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (s, 1H), 7.47−7 58 (m, 4H), 7.62 (d, J = 8.4 Hz, 1H), 7.78 (dd, J = 7.6, 1.2 Hz, 1H), 7.87 (dd, J = 8.0, 2.0 Hz, 1H), 8.07 (d, J = 8.4 Hz, 1H), 8.14 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.0, 138.6, 137.2, 137.1, 133.4, 133.0, 131.8, 130.5, 129.2, 129.1, 129.0, 128.6, 127.3, 127.0, 125.5, 125.1, 119.8, 115.9, 92.0; IR (KBr) 1628, 1556, 1507, 1451, 1349, 1324, 1269, 1200, 1031 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{19}H_{11}$-$BrCl_2NO$: 417.9401; found: 417.9409.

*Ethyl 3-Bromopyrrolo[1,2-a]quinoline-1-carboxylate (**7f**).* White solid, yield 228 mg (72%); mp 93−95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (t, J = 7.2 Hz, 3H), 4.32 (q, J = 7.2 Hz, 2H), 7.37−7.45 (m, 3H), 7.50−7.58 (m, 2H), 7.72 (dd, J = 8.0, 1.6 Hz, 1H), 8.48 (d, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 135.3, 133.8,

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128.7, 128.0, 125.8, 125.1, 124.7, 123.2, 119.8, 116.2, 115.3, 91.4, 61.0, 14.5; IR (KBr) 1706, 1557, 1485, 1456, 1328, 1260, 1223, 1184, 1094 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{15}H_{13}BrNO_2$: 318.0130; found: 318.0137.

*tert-Butyl 3-Bromopyrrolo[1,2-a]quinoline-1-carboxylate (**7g**).* White solid, yield 275 mg (80%); mp 112−114 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.65 (s, 9H), 7.32−7.36 (m, 1H), 7.39−7.44 (m, 2H), 7.48 (s, 1H), 7.54−7.58 (m, 1H), 7.70 (dd, J = 7.6, 1.2 Hz, 1H), 8.40 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 134.8, 133.7, 128.6, 127.8, 125.4, 125.1, 125.0, 124.7, 119.8, 116.2, 91.0, 81.6, 28.4; IR (KBr) 1692, 1557, 1457, 1366, 1353, 1270, 1149, 1091 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{17}BrNO_2$: 346.0443; found: 346.0441.

*1-(3-Bromopyrrolo[1,2-a]quinolin-1-yl)ethanone (**7h**).* White solid, yield 196 mg (68%); mp 134−135 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 2.67 (s, 3H), 7.41−7.50 (m, 3H), 7.53−7.56 (m, 1H), 7.58 (s, 1H), 7.71 (dd, J = 8.0, 1.6 Hz, 1H), 8.32 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.0, 136.7, 133.9, 128.9, 128.6, 128.1, 127.1, 126.8, 125.3, 120.5, 115.9, 91.6, 28.4; IR (KBr) 1648, 1553, 1486, 1451, 1375, 1350, 1189, 1057 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{14}H_{11}BrNO$: 288.0024; found: 288.0031.

General Procedure for the Synthesis of 8. A mixture of isoquinoline **6b** (3.0 mmol), bromides **2** (1.0 mmol), maleic anhydride **3** (1.0 mmol), and hydrated copper chloride (0.30 mmol) in acetonitrile (15 mL) was refluxed for 24 h with magnetic stirring in an O_2 atmosphere. The reaction course was monitored by TLC. After the reaction was completed, the solvent was removed under reduced pressure, and the residue was separated by flash chromatography on a silica gel column with ethyl acetate/petroleum ether (1:20) as eluent to give the products **8**.

*(1-Bromopyrrolo[2,1-a]isoquinolin-3-yl)phenylmethanone (**8a**).* Yellow solid, yield 303 mg (87%); mp 168−169 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, J = 7.6 Hz, 1H), 7.32 (s, 1H), 7.49−7.53 (m, 2H), 7.56−7.65 (m, 3H), 7.73 (dd, J = 7.6, 1.2 Hz, 1H), 7.81−7.84 (m, 2H), 9.28 (dd, J = 8.0, 1.2 Hz, 1H), 9.60 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.1, 140.0, 131.6, 129.5, 129.1, 128.4, 128.3, 127.5, 126.9, 125.2, 124.8, 123.8, 114.3, 91.1; IR (KBr) 1617, 1572, 1520, 1481, 1449, 1409, 1360, 1229, 1140 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{19}H_{13}BrNO$: 350.0181; found: 350.0183.

*(1-Bromopyrrolo[2,1-a]isoquinolin-3-yl)(4-chlorophenyl)methanone (**8b**).* Yellow solid, yield 347 mg (91%); mp 211−213 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, J = 7.6 Hz, 1H), 7.29 (s, 1H), 7.49 (d, J = 8.4 Hz, 2H), 7.59−7.66 (m, 2H), 7.73−7.78 (m, 3H), 9.28 (d, J = 7.6 Hz, 1H), 9.55 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.6, 138.3, 137.9, 131.3, 130.5, 129.5, 128.6, 128.5, 128.2, 127.6, 126.9, 125.1, 124.7, 123.8, 123.2, 114.5, 91.3; IR (KBr) 1615, 1542, 1481, 1448, 1362, 1228, 1140, 1084 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{19}H_{12}BrClNO$: 383.9791; found: 383.9793.

*Ethyl 1-Bromopyrrolo[2,1-a]isoquinoline-3-carboxylate (**8c**).* White solid, yield 261 mg (82%); mp 99−101 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.42 (t, J = 7.2 Hz, 3H), 4.38 (q, J = 7.2 Hz, 2H), 7.02 (d, J = 7.6 Hz, 1H), 7.52−7.62 (m, 3H), 7.67 (dd, J = 8.0, 1.6 Hz, 1H), 9.21−9.23 (m, 1H), 9.26 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 129.5, 128.4, 127.6, 127.4, 126.8, 125.1, 124.3, 123.6, 123.3, 115.8, 113.5, 90.2, 60.3, 14.5; IR (KBr) 1688, 1525, 1488, 1411, 1369, 1289, 1223, 1077 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{15}H_{13}BrNO_2$: 318.0130; found: 318.0136.

Procedure for the Synthesis of 9. A mixture of ethyl isonicotinate **1c** (3.0 mmol), bromide **2b** (1.0 mmol), and maleic anhydride **3** (1.0 mmol), in DMF (15 mL) was heated at 90 °C for 12 h with magnetic stirring in the presence of TPCD (1.0 g). The reaction course was monitored by TLC. After the reaction was completed, the solvent was removed under reduced pressure, and the residue was separated by flash chromatography on a silica gel column with ethyl acetate/petroleum ether (1:20) as eluent to give the products **9**.

*Ethyl 3-(4-Chlorobenzoyl)indolizine-7-carboxylate (**9**).* Yellow solid, yield 246 mg (75%); mp 152−154 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.37 (t, J = 7.2 Hz, 3H), 4.36 (q, J = 7.2 Hz, 2H), 6.69 (d, J = 7.6 Hz, 1H), 7.29 (d, J = 4.8 Hz, 1H), 7.40 (d, J = 8.0 Hz, 3H), 7.79 (d, J = 8.4 Hz, 2H), 8.25 (s, 1H), 9.79 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.8, 165.1, 138.6, 138.1, 137.6, 130.4, 128.6, 127.9, 126.7, 125.5, 123.7, 121.5, 112.8, 106.0, 61.6, 14.4; IR (KBr) 1714, 1619, 1568, 1509, 1463, 1334, 1283, 1231, 1088 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{15}ClNO_3$: 328.0740; found: 328.0746.

Procedure for the Synthesis of 10. A mixture of isoquinoline **6b** (3.0 mmol), bromide **2a** (1.0 mmol), and maleic anhydride **3** (1.0 mmol), in DMF (15 mL) was heated at 90 °C for 12 h with magnetic stirring in the presence of TPCD (1.0 g). The reaction course was monitored by TLC. After the reaction was completed, the solvent was removed under reduced pressure, and the residue was separated by flash chromatography on a silica gel column with ethyl acetate/petroleum ether (1:20) as eluent to give the products **10**.

*Phenyl(pyrrolo[2,1-a]isoquinolin-3-yl)methanone (**10**).* Yellow solid, yield 212 mg (78%); mp 145−146 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, J = 4.4 Hz, 1H), 7.13 (d, J = 7.6 Hz, 1H), 7.32 (d, J = 4.4 H, 1H), 7.48−7.58 (m, 5H), 7.23 (d, J = 7.2 Hz, 1H), 7.85 (dt, J = 6.8, 1.2 Hz, 2H), 8.18 (d, J = 8.0 Hz, 1H), 9.61 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.4, 140.6, 136.9, 131.1, 129.1, 128.9, 128.1, 128.0, 127.7, 126.9, 125.9, 125.8, 124.6, 123.6, 113.4, 101.9; IR (KBr) 1610, 1573, 1529, 1468, 1452, 1356, 1233, 1053 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{19}H_{14}NO$: 272.1075; found: 272.1076.

Procedure for the Synthesis of 11. A mixture of compound **10** (0.5 mmol), potassium chloride (0.5 mmol), and hydrated copper chloride (0.15 mmol) in acetonitrile (10 mL) was refluxed for 24 h with magnetic stirring in an O_2 atmosphere. The reaction course was monitored by TLC. After the reaction was completed, the solvent was removed under reduced pressure, and the residue was separated by flash chromatography on a silica gel column with ethyl acetate/petroleum ether (1:20) as eluent to give the products **11**.

*(1-Chloropyrrolo[2,1-a]isoquinolin-3-yl)phenylmethanone (**11**).* Yellow solid, yield 122 mg (80%); mp 175−177 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, J = 7.6 Hz, 1H), 7.24 (s, 1H), 7.50−7.53 (m, 2H), 7.57−7.64 (m, 3H), 7.74 (dd, J = 7.2, 2.0 Hz, 1H), 7.83 (dt, J = 7.2, 1.6 Hz, 2H), 9.10 (dd, J = 8.0, 1.6 Hz, 1H), 9.59 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.2, 140.0, 131.6, 130.1, 129.4, 129.1, 128.3, 128.2, 127.7, 126.8, 125.2, 124.7, 124.0, 122.2, 114.2, 107.3; IR (KBr) 1615, 1561, 1521, 1482, 1410, 1360, 1229, 1084 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{19}H_{13}ClNO$: 306.0686; found: 306.0681.

Procedure for the Synthesis of 12. 1-Bromoindolizine **5a** (0.2 mmol), phenyl boronic acid (0.3 mmol), $PdCl_2(PPh_3)_2$ (0.004 mmol), and K_3PO_4 (0.4 mmol) were added to a Schlenk flask. Then, toluene (2.0 mL) was added through a syringe and the mixture was stirred at 100 °C under an argon atmosphere for 12 h. After the reaction was complete, the mixture was cooled to room temperature and concentrated under reduced pressure, and the residue was subjected to flash column chromatography with ethyl acetate/petroleum ether (1:30) as eluent to give the desired product **12**.

*Methyl 3-Benzoyl-1-phenylindolizine-7-carboxylate (**12**).* Yellow solid, yield 64.7 mg (91%); mp 170−172 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 3.97 (s, 3H), 7.36 (td, J = 7.6, 1.2 Hz, 1H), 7.46−7.59 (m, 9H), 7.85 (dd, J = 8.4, 1.6 Hz, 2H), 8.57 (s, 1H), 9.94 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.4, 165.6, 140.2, 134.7, 133.9, 131.4, 129.0, 128.3, 128.2, 128.1, 127.2, 125.5, 125.4, 123.6, 121.1, 120.7, 112.9, 52.5; IR (KBr) 1719, 1614, 1574, 1508, 1459, 1359, 1280, 1247, 1137 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{23}H_{18}NO_3$: 356.1287; found: 356.1295.

Procedure for the Synthesis of 13. 1-Bromoindolizine **5g** (0.2 mmol), phenyl boronic acid (0.3 mmol), $PdCl_2(PPh_3)_2$ (0.004 mmol), and K_3PO_4 (0.4 mmol) were added to a Schlenk flask. Then, toluene (2.0 mL) was added through a syringe and the mixture was stirred at 100 °C under an argon atmosphere for 12 h. After the reaction was complete, the mixture was cooled to room temperature and concentrated under reduced pressure, and the residue was subjected to flash column chromatography with ethyl acetate/petroleum ether (1:30) as eluent to give the desired product **13**.

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Ethyl 3-(4-Methoxybenzoyl)-1-phenylindolizine-7-carboxylate (13). Yellow solid, yield 72.2 mg (90%); mp 142−144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (t, J = 7.2 Hz, 3H), 3.90 (s, 3H), 4.42 (q, J = 7.2 Hz, 2H), 7.00 (dt, J = 8.8, 2.0 Hz, 2H), 7.36 (t, J = 7.2 Hz, 1H), 7.46−7.52 (m, 4H), 7.58−7.60 (m, 2H), 7.87−7.90 (m, 2H), 8.56−8.57 (m, 1H), 9.86 (dd, J = 7.2, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.4, 165.2, 162.5, 134.4, 134.1, 132.7, 131.3, 129.1, 128.2, 127.9, 127.1, 125.4, 125.0, 123.8, 120.8, 120.7, 113.7, 112.7, 61.5, 55.5. 14.4; IR (KBr) 1717, 1616, 1540, 1508, 1459, 1357, 1257, 1171, 1021 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{25}H_{22}NO_4$: 400.1549; found: 400.1546.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H NMR and ^{13}C NMR spectra for all products, crystal data (CIF) for **7a**, and DFT calculations of the 3-acetylindolizine cation radical. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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with NBS at room temperature in MeCN gave the desired 1-brominated product **8a** in 81% yield, and similar reaction of **10** with Br_2 at room temperature also afforded **8a** in 52% yield (Scheme 5(d)–(f)). However, our $CuCl_2$-catalyzed cascade reaction is a more convenient one-pot approach with better functional group tolerance and is highly atom-economic by using the bromide ion released from the pyridinium salt as a bromine source without needing any additional brominating reagent such as NBS and bromine.

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