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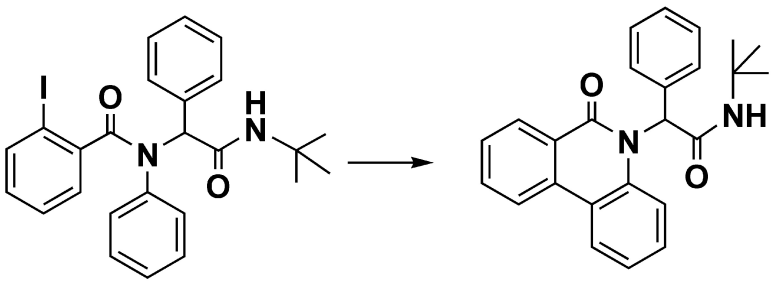

10 **11**

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Synthesis of Functionalized Quinolines via Ugi and Pd-Catalyzed Intramolecular Arylation Reactions

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Two types of quinoline scaffolds were constructed in a combinatorial format via the Ugi four-component reaction (U-4CR) and Pd-catalyzed intramolecular arylation reaction. The scope of this two-step synthetic sequence was examined from commercially available and synthetically accessible starting materials.

Introduction

In chemical genetics, development of synthetic methods to construct libraries based on privileged scaffolds[1] in an efficient manner is of high priority, since such libraries can be specifically utilized to facilitate biological pathway explorations in cells or organisms.[2]

Quinoline and isoquinoline represent privileged moieties in medicinal chemistry[3] and are ubiquitous substructures in material science and pharmaceuticals.[4] For example, ARC-111 (**1**) (Figure 1) has potent TOP1-targeting activity and pronounced antitumor activity.[5] Compound **2** is a selective estrogen receptor modulator with biological activity similar to that of tamoxifen.[6] NSC314622 (**3**) belongs to a class of cytotoxic topoisomerase I inhibitors that offer certain advantages over the camptothecins.[7] Compound **4** is a poly-ADP−ribose polymerase-1 inhibitor with a structural framework of phenanthridin-6-one and has significant protective effects in rat models of stroke and heart ischemia.[8] Compound **5** was found to be an active molecule, which induces S and G2/M arrests of cell cycle, leading to apoptosis.[9]

Because of its biological importance, quinoline has attracted much attention to its syntheses.[10,11] However, despite much effort to its preparation, efficient methods for the synthesis of quinoline remain to be developed. We report herein a novel way to construct quinoline by using the Ugi four-component reaction (U-4CR)[12] and Pd-catalyzed arylation as key synthetic steps.

Results and Discussion

In our previous communication,[13] we reported a concise synthesis of isoquinolines via the U-4CR/Heck reaction, and a variety of unique isoquinolines were made.

Considering the value of the U-4CR as a useful tool to quickly assemble a broad range of structurally diverse α-acylamino amides **A** and **C** (Figure 2), we chose to apply the Ugi products to synthesize quinolines **B** (type I) and **D** (type II) by the metal-catalyzed intramolecular arylation that proceeds via C−H bond activation. If successful, we might find an efficient way to synthesize the tricyclic or tetracyclic quinolines and isoquinolines (see **1**−**5** Figure 1), which could not be synthetically accessible by our previous published U-4CR/Heck reaction.[13]

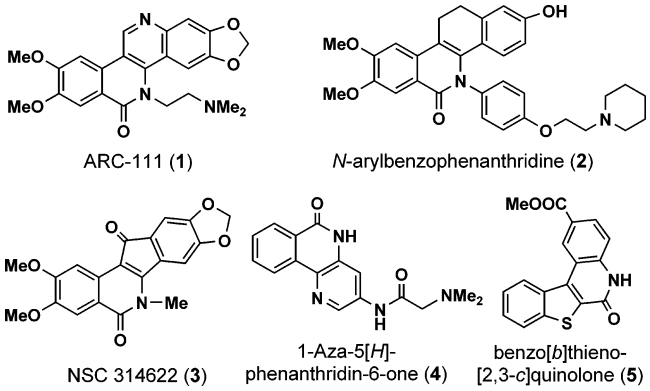

Figure 1. Biologically active compounds.

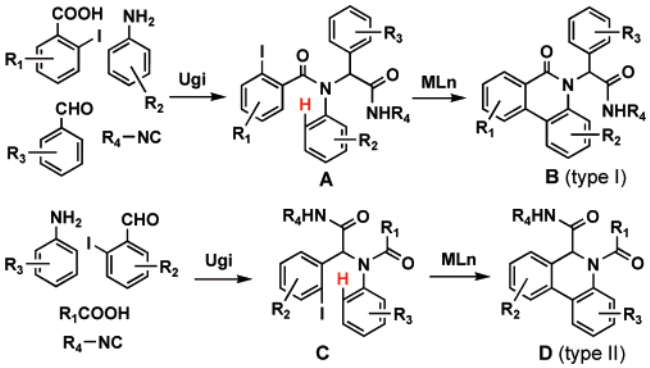

Figure 2. Arylation via the metal-catalyzed C−H activation.

Recently, significant progress has been witnessed in the metal-catalyzed C−H bond activation of aromatics to directly generate the C−C bond of biaryl molecules.[14] For the direct arylation of aromatic compounds, coordination of the substrate with the aryl−metal complex[15] or restriction of the

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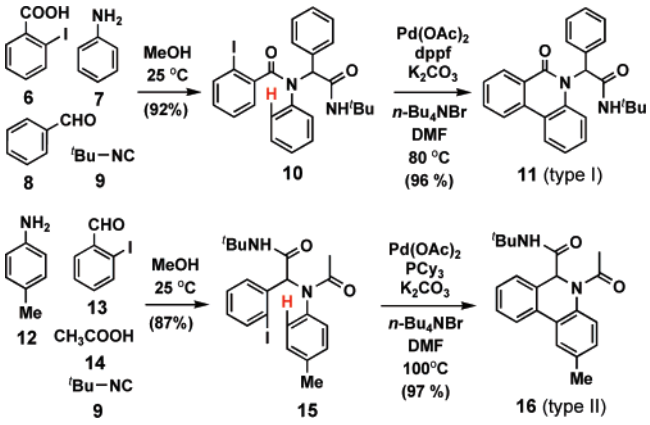
Scheme 1. Two-Step Syntheses of Quinolines **11** and **16**



aryl fragments in certain spatial distance[16] plays a key role in the reaction. Thus, we envisaged that the aryl−metal complex formed by oxidative addition of aryl iodide **A** or **C** might also couple with the other aromatic ring to form quinolines **B** or **D** via C−H activation because of their close spatial distance.

To test the feasibility of the proposed quinoline synthesis, substrates **10** and **15** were made by the U-4CR based on the procedure described in our previous paper.[13] Under the conditions, **10** and **15** were generated in 92% and 87% yields, respectively, from two groups of substrates **6**−**9** and **9**, **12**−**14** (Scheme 1).

We then began to evaluate Pd-catalyzed annulation. After a systematic evaluation of the reaction conditions (see the Supporting Information for details), we found that two types of ligands were proved to be effective for Pd-catalyzed intramolecular arylation reactions.

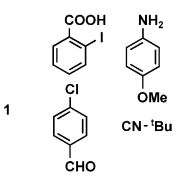
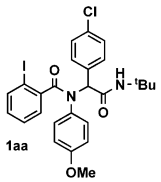
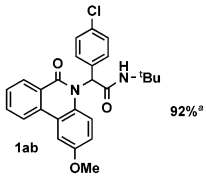
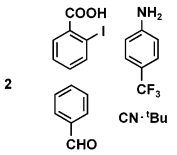
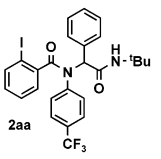
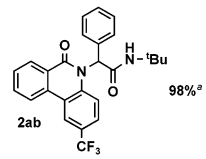
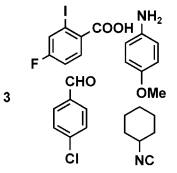
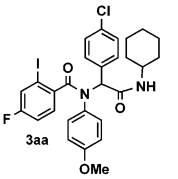
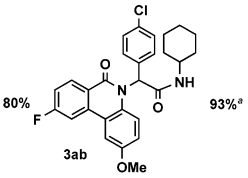
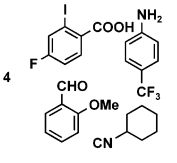
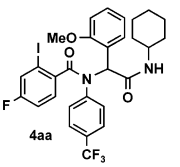
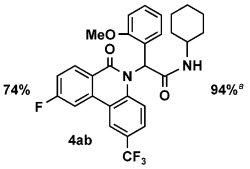
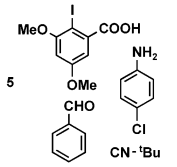
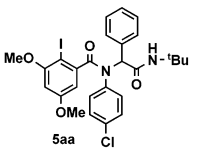
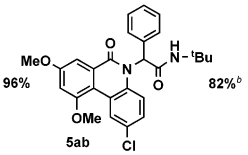
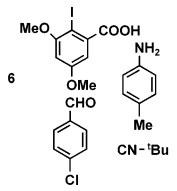
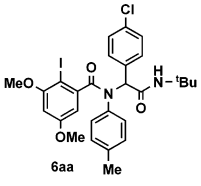
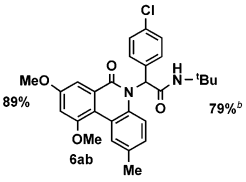
For the substrate **10**, dppf was identified to be the ligand in its Pd-catalyzed arylation, and the desired product **11** was obtained in 96% yield at 80 °C. However, when substrate **15** was used to do the Pd-catalyzed annulation, the electron-rich ligand PCy_3 had to be applied, presumably because of its lack of the electron-withdrawing group (such as the amide in compound **10**), and the reaction was carried out at 100 °C to give the desired product **16** in 97% yield.

The potential of this method was then explored through its application in syntheses of diverse quinolines (type I). Accordingly, we used commercially available isocyanides, aldehydes, anilines, and iodobenzoic acids to make the Ugi products **1aa**−**6aa**, and applied them to Pd-catalyzed arylations to generate the annulated products **1ab**−**6ab** (see Table 1). It is worthwhile to notice that as the electron density of iodobenzoic acid is increased, the oxidative capability of its Ugi product to the metal is decreased. As a result, the electron-rich ligand PCy_3 was eventually utilized to promote its annulation (see entries 5 and 6 in Table 1).

To make type II quinolines, compounds **1ba**−**7ba** were made from different types of substrates for the U-4CR under our optimized conditions, and their arylations were achieved efficiently through Pd-catalyzed C−H activation. The results are listed in Table 2.

Considering the chemical versatility, we then explored the feasibility to synthesize even more complex molecules (such as **5** in Figure 1) by this two-step sequence.

Table 1. Two-Step Syntheses of Quinolines (Type I)

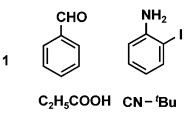
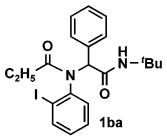
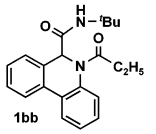
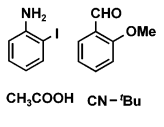
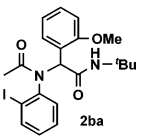
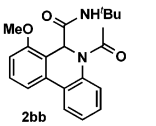
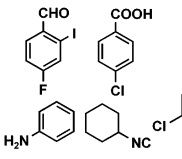
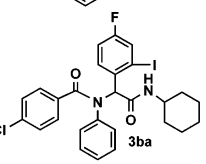
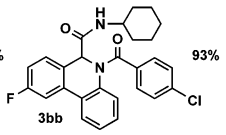
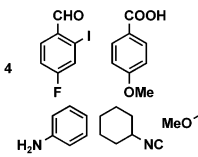
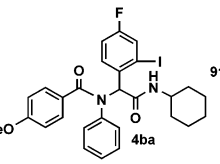
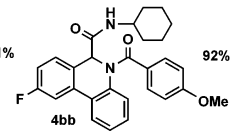
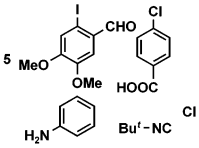
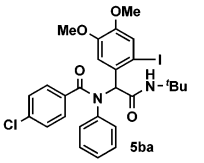
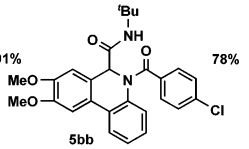
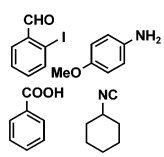
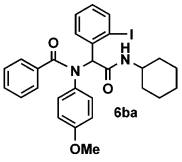
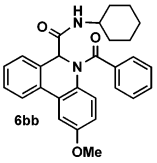
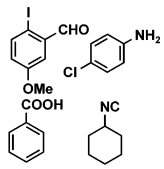
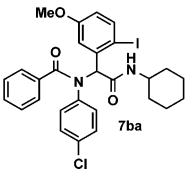
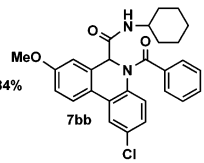
entry	starting material	Ugi product	yield	product	yield
1			90%		92%[a]
2			90%		98%[a]
3			80%		93%[a]
4			74%		94%[a]
5			96%		82%[b]
6			89%		79%[b]

[a] Reagents and conditions for the Pd-catalyzed annulation: substrate (1.0 equiv), $Pd(OAc)_2$ (5 mol %), dppf (6 mol %), *n*-Bu_4NBr (1.0 equiv), and K_2CO_3 (2.0 equiv) were dissolved in DMF (0.1 M) and heated to 80 °C for 1 h. [b] Reagents and conditions for the Pd-catalyzed annulation: substrate (1.0 equiv), $Pd(OAc)_2$ (5 mol %), PCy_3 (12 mol %), *n*-Bu_4NBr (1.0 equiv), and K_2CO_3 (2.0 equiv) were dissolved in DMF (0.1 M) and heated to 80 °C for 1 h.

To this end, we first made the 3-iodo-benzo[*b*]thiophene-2-carboxylic acid **17**,[9] and then carried out its U-4CR with substrates **8**, **9**, and **18**. As a result, the α-acylamino amide **19** was obtained in 92% yield. Thus, under the optimized conditions, we got the desired product **20** in 93% yield by Pd-catalyzed intramolecular arylation from substrate **19**, realizing an efficient way to make a derivative of benzo[*b*]-thiophene[2,3-*c*]quinolone **5** (see Scheme 2).

To assess the generality of this one-pot synthetic reaction, particularly with regard to the generation of structurally diverse analogues of compound **5**, we selected four additional groups of substrates to do the U-4CRs, and the generated Ugi products underwent Pd-catalyzed annulation to afford the desired biaryl products **1cb**−**4cb** in good to excellent yields (see entries 1−4 in Table 3).

Table 2. Two-Step Syntheses of Quinolines (Type II)[a]

entry	starting material	Ugi product	yield	product	yield
1		 1ba	78%	 1bb	82%
2		 2ba	84%	 2bb	92%
3		 3ba	90%	 3bb	93%
4		 4ba	91%	 4bb	92%
5		 5ba	91%	 5bb	78%
6		 6ba	89%	 6bb	95%
7		 7ba	84%	 7bb	91%

[a] Reagents and conditions for the Pd-catalyzed annulation: substrate (1.0 equiv), $Pd(OAc)_2$ (5 mol %), PCy_3(12 mol %), *n*-Bu_4NBr (1.0 equiv), and K_2CO_3 (2.0 equiv) were dissolved in DMF (0.1 M) and heated to 100 °C for 1 h.

In conclusion, we have developed a highly efficient approach to synthesize structurally diverse quinoline-based polycyclic compounds via a sequence of U-4CR/Pd-catalyzed intramolecular arylation. This two-step synthetic approach allows us to make a variety of quinoline-based heterocycles easily. We anticipate that this method may have interesting implications on the construction of structurally diverse heterocyclic molecules and will find an application in the field of combinatorial chemistry, diversity-oriented synthesis, and drug discovery.

Experimental Section

General Procedure for the Ugi Reaction. To a solution of arylamine (1.0 mmol) in MeOH (1.0 mL) was added aldehyde (1.0 mmol), and the reaction mixture was stirred at room temperature for 10 min. After addition of acid (1.0 mmol) to the reaction mixture, the reaction mixture was stirred for 5 min followed by addition of isocyanide (1.0 mmol), and the reaction mixture was stirred overnight. The solvent was removed under vacuum, and the residue was purified by flash chromatography ($EtOAc/CH_2Cl_2$/petroleum ether) to give the corresponding Ugi product.

Scheme 2. Synthesis of Compound **20**

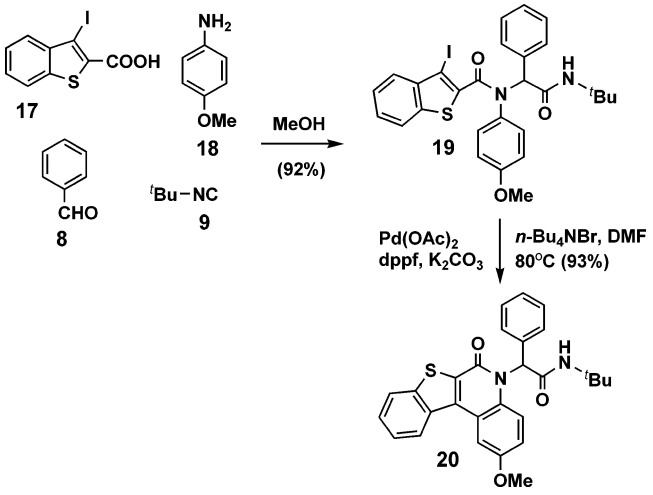
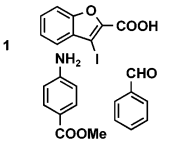
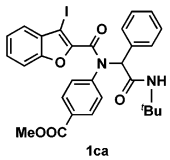
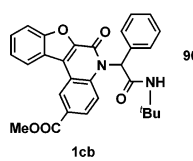
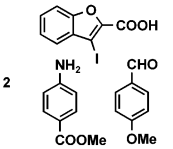
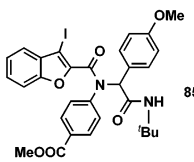
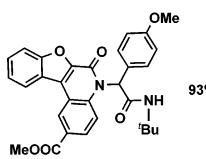
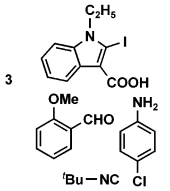
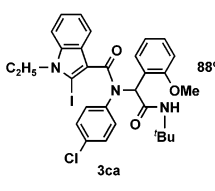
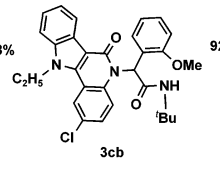
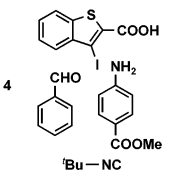
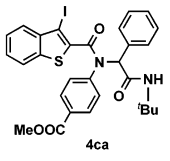
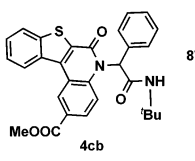


Table 3. Two-Step Syntheses of Polycyclic Heterocycles[a]

entry	starting material	Ugi product	yield	product	yield
1		 1ca	98%	 1cb	90%
2		 2ca	85%	 2cb	93%
3		 3ca	88%	 3cb	92%
4		 4ca	97%	 4cb	87%

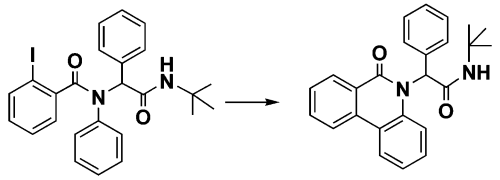
[a] Reagents and conditions for the Pd-catalyzed annulation: substrate (1.0 equiv), $Pd(OAc)_2$ (5 mol %), dppf (6 mol %), *n*-Bu_4NBr (1.0 equiv), and K_2CO_3 (2.0 equiv) were dissolved in DMF (0.1 M) and heated to 80 °C for 1 h.

General Procedure for the Systematic Evaluation of Pd-Catalyzed Arylation with Compound 10 as the Tested Substrate (Table 4). To a solution of the palladium catalyst, ligand, and the Ugi product (0.5 mmol) in DMF (5 mL) were added tetrabutylammonium bromide (161 mg, 1.0 mmol) and K_2CO_3 (138 mg, 2.0 mmol) under nitrogen in a dry Schlenk

Table 4. Conditions Screening for C−H Activation Reactions

entry	Pd-catalyst	loading (%)	ligand	base	additive	temp (°C)	time (h)	yield (%)
1	$Pd(OAc)_2$	10	dppf	K_2CO_3	*n*-$Bu_4N^+Br^-$	80	1	95
2	$Pd(OAc)_2$	10	dppp	K_2CO_3	*n*-$Bu_4N^+Br^-$	80	1	97
3	$Pd(OAc)_2$	10	PPh3	K_2CO_3	*n*-$Bu_4N^+Br^-$	80	1	97
4	$Pd(dppf)_2Cl_2$	10		K_2CO_3	*n*-$Bu_4N^+Br^-$	80	5	68
5	$Pd(PPh_3)_2Cl_2$	10		K_2CO_3	*n*-$Bu_4N^+Br^-$	80	5	78
6	$Pd(PPh_3)_4$	10		K_2CO_3	*n*-$Bu_4N^+Br^-$	80	24	91
7	$Pd_2(dba)_3$	5	PPh_3	K_2CO_3	*n*-$Bu_4N^+Br^-$	80	7	83
8	$Pd(OAc)_2$	10		K_2CO_3	*n*-$Bu_4N^+Br^-$	80	7	82
9	$Pd(OAc)_2$	10	PPh_3	K_2CO_3	*n*-$Bu_4N^+Br^-$	80	1	97
10	$Pd(OAc)_2$	10	PPh_3	K_2CO_3		80	1	96
11	$Pd(OAc)_2$	3	PPh_3	K_2CO_3	*n*-$Bu_4N^+Br^-$	80	22	58
12	$Pd(OAc)_2$	5	PPh_3	K_2CO_3	*n*-$Bu_4N^+Br^-$	80	3	92
13	$Pd(OAc)_2$	10	PPh_3	Et_3N	*n*-$Bu_4N^+Br^-$	80	3	17
14	$Pd(OAc)_2$	5	dppp	K_2CO_3	*n*-$Bu_4N^+Br^-$	80	2.5	95
15	$Pd(OAc)_2$	5	dppf	K_2CO_3	*n*-$Bu_4N^+Br^-$	80	1	96
16	$Pd(OAc)_2$	5	dppf	Et_3N	*n*-$Bu_4N^+Br^-$	80	1.5	NR
17	$Pd(OAc)_2$	5	dppf	K_2CO_3	*n*-$Bu_4N^+Br^-$	80	1	91

tube, and the reaction mixture was stirred at 80 °C for 1 or 24 h. The reaction mixture was first cooled to room temperature and added to water (30 mL) and CH_2Cl_2 (10 mL). The organic layers were separated, and the water phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with brine (3 × 10 mL) and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography (EtOAc/CH_2Cl_2/PE = 1/1/7) to give the corresponding annulated product **11**.



10 **11**

***N-tert*-Butyl-2-(6-oxo-6*H*-phenanthridin-5-yl)-2-phenylacetamide (11).** To a solution of $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), dppf (16.6 mg, 0.03 mmol), and **10** (256 mg, 0.5 mmol) in DMF (5 mL) were added tetrabutylammonium bromide (160.6 mg, 1.0 mmol) and K_2CO_3 (138 mg, 2.0 mmol) under nitrogen in a dried Schlenk tube, and the reaction mixture was stirred at 80 °C for 1 h. The reaction mixture was first cooled to room temperature and added to water (30 mL) and CH_2Cl_2 (10 mL). The organic layers were separated, and the water phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with brine (3 × 10 mL) and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography (eluting solvent: EtOAc/CH_2Cl_2/PE = 1/1/6) to give the corresponding annulated product **11** (185 mg) in 96% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29 (s, 9H), 6.11 (s, 1H), 6.91 (br, 1H), 7.22−7.39 (m, 7H), 7.45 (dd, J = 8.4 Hz, J = 1.2 Hz, 1H), 7.54−7.59 (m, 1H), 7.73−7.79 (m, 1H), 8.24−8.29 (m, 2H), 8.54 (dd, J = 8.1 Hz, J = 1.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.4, 51.5, 61.7, 117.6, 119.7, 121.7, 122.9, 123.1, 125.1, 127.5, 127.6, 127.9, 128.4, 129.0, 132.9, 133.9, 134.4, 136.8, 162.3, 167.4. HRMS (EI): calcd for $C_{25}H_{24}N_2O_2$ (M^+), 384.1838; found, 384.1837.

***N-tert*-Butyl-2-(4-chlorophenyl)-2-(2-methoxy-6-oxo-6*H*-phenanthridin-5-yl)-acetamide (1ab).** To a solution of $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), dppf (16.6 mg, 0.03 mmol), and **1aa** (228 mg, 0.5 mmol) in DMF (5 mL) were added tetrabutylammonium bromide (160.6 mg, 1.0 mmol) and K_2CO_3 (138 mg, 2.0 mmol) under nitrogen in a dried Schlenk tube, and the reaction mixture was stirred at 80 °C for 1 h. The reaction mixture was first cooled to room temperature and added to water (30 mL) and CH_2Cl_2 (10 mL). The organic layers were separated, and the water phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with brine (3 × 10 mL) and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography (eluting solvent: EtOAc/CH_2Cl_2/PE = 1/1/6) to give the corresponding annulated product **1ab** (207 mg) in 92% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27 (s, 9H), 3.86 (s, 3H), 6.19 (s, 1H), 6.93 (dd, J = 9.0 Hz, 2.7 Hz, 1H), 7.06 (br, 1H), 7.23−7.30 (m, 4H), 7.36 (d, J = 9.3 Hz, 1H), 7.57−7.63 (m, 1H), 7.74 (d, J = 1.8 Hz, 1H), 7.77−7.83 (m, 1H), 8.26 (d, J = 8.1 Hz, 1H), 8.53 (dd, J = 8.1 Hz, J = 1.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.4, 51.6, 55.4, 60.0, 107.2, 115.8, 119.2, 120.8, 121.8, 125.1, 128.2, 128.4, 129.1, 129.2, 130.2, 132.9, 133.0, 133.2, 133.6, 155.3, 161.9, 167.2. HRMS (EI): calcd for $C_{26}H_{25}N_2ClO_3$ (M^+), 448.1554; found, 448.1554.

***N-tert*-Butyl-2-(6-oxo-2-trifluoromethyl-6*H*-phenanthridin-5-yl)-2-phenylacetamide (2ab).** To a solution of $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), dppf (16.6 mg, 0.03 mmol), and **2aa** (290.2 mg, 0.5 mmol) in DMF (5 mL) were added tetrabutylammonium bromide (161 mg, 1.0 mmol) and K_2CO_3 (138 mg, 2.0 mmol) under nitrogen in a dried Schlenk tube, and the reaction mixture was stirred at 80 °C for 1 h. The reaction mixture was first cooled to room temperature and added to water (30 mL) and CH_2Cl_2 (10 mL). The organic layers were separated, and the water phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with brine (3 × 10 mL) and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography (eluting solvent: EtOAc/CH_2Cl_2/PE = 1/1/9) to give the corresponding annulated product **2ab** (228 mg) in 98% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33 (s, 9H), 6.01 (s, 1H), 6.91 (s, 1H), 7.26−7.37 (m, 5H), 7.51−7.59 (m, 2H), 7.65−7.70 (m, 1H), 7.84−7.90 (m, 1H), 8.33 (d, J = 8.1 Hz, 1H), 8.51 (s, 1H), 8.57 (dd, J = 7.8 Hz, J = 1.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.5, 51.9, 61.9, 118.5, 119.9, 120.6, 120.6, 121.9, 122.2, 124.7, 125.2, 125.3, 125.35, 125.38, 125.8, 127.6, 128.0, 128.8, 128.9, 129.3, 133.1, 133.5, 134.2, 139.1, 162.4, 167.0. HRMS (EI): calcd for $C_{26}H_{23}N_2O_2F_3$ (M^+), 452.1712; found, 452.1713.

2-(4-Chloro-phenyl)-*N*-cyclohexyl-2-(9-fluoro-2-methoxy-6-oxo-6*H*-phenanthridin-5-yl)-acetamide (3ab). To a solution of $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), dppf (16.6 mg, 0.03 mmol), and **3aa** (310 mg, 0.5 mmol) in DMF (5 mL) were added tetrabutylammonium bromide (161 mg, 1.0 mmol) and K_2CO_3 (138 mg, 2.0 mmol) under nitrogen in a dried Schlenk tube, and the reaction mixture was stirred at 80 °C for 1 h. The reaction mixture was first cooled to room

temperature and added to water (30 mL) and CH_2Cl_2 (10 mL). The organic layers were separated, and the water phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with brine (3 × 10 mL) and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography (eluting solvent: EtOAc/CH_2Cl_2/PE = 1/1/8) to give the corresponding annulated product **3ab** (229 mg) in 93% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92−1.95 (m, 10H), 3.78−3.85 (m, 1H), 3.86 (s, 3H), 6.20 (d, J = 8.1 Hz, 1H), 6.93 (dd, J = 10.5 Hz, J = 2.4 Hz, 1H), 7.00 (br, 1H), 7.25−7.36 (m, 6H), 7.58 (d, J = 2.7 Hz, 1H), 7.85 (dd, J = 9.3 Hz, J = 2.7 Hz, 1H), 8.53 (dd, J = 9.0 Hz, J = 3.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.5, 24.6, 25.2, 32.4, 32.5, 48.6, 55.5, 59.8, 107.2, 107.7, 108.0, 116.2, 116.5, 116.7, 119.1, 119.9, 120.0, 121.6, 121.7, 128.6, 129.1, 130.7, 132.3, 132.5, 132.8, 133.4, 136.2, 136.3, 155.3, 161.2, 164.1, 166.9, 167.4. HRMS (EI): calcd for $C_{28}H_{26}N_2ClFO_3$ (M^+), 492.1616; found, 492.1617.

***N*-Cyclohexyl-2-(9-fluoro-6-oxo-2-triflouromethyl-6*H*-phenanthridin-5-yl)-2-(2-methoxyphenyl)-acetamide (4ab).** To a solution of $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), dppf (16.6 mg, 0.03 mmol), and **4aa** (327 mg, 0.5 mmol) in DMF (5 mL) were added tetrabutylammonium bromide (161 mg, 1.0 mmol) and K_2CO_3 (138 mg, 2.0 mmol) under nitrogen in a dried Schlenk tube, and the reaction mixture was stirred at 80 °C for 1 h. The reaction mixture was first cooled to room temperature and added to water (30 mL) and CH_2Cl_2 (10 mL). The organic layers were separated, and the water phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with brine (3 × 10 mL) and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography (eluting solvent: EtOAc/CH_2Cl_2/PE = 1/1/8) to give the corresponding annulated product **4ab** (247 mg) in 94% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.08−1.86 (m, 10H), 3.86−3.89 (m, 1H), 3.91 (s, 3H), 5.69 (d, J = 8.4 Hz, 1H), 6.63 (s, 1H), 6.92−7.28 (m, 2H), 7.30−7.47 (m, 4H), 7.64 (dd, J = 9.0 Hz, J = 1.5 Hz, 1H), 7.92 (dd, J = 10.2 Hz, J = 2.4 Hz, 1H), 8.37 (s, 1H), 8.59 (dd, J = 9.0 Hz, J = 6.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.58, 24.61, 25.5, 32.65, 32.71, 48.4, 55.7, 58.9, 107.7, 108.0, 110.9, 116.7, 116.9, 117.2, 119.18, 119.22, 120.88, 120.94, 121.5, 122.2, 122.4, 122.5, 122.6, 124.7, 125.1, 125.8, 126.4, 126.5, 128.9, 130.4, 132.4, 132.6, 135.6, 135.8, 140.7, 157.0, 161.6, 164.2, 166.3, 167.6. HRMS (EI): calcd for $C_{29}H_{26}N_2O_3F_4$ (M^+), 526.1880; found, 526.1874.

***N*-*tert*-Butyl-2-(2-chloro-8,10-dimethoxy-6-oxo-6*H*-phenanthridin-5-yl)-2-phenylacetamide (5ab).** To a solution of $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), PCy_3 (16.8 mg, 0.06 mmol), and **5aa** (310 mg, 0.5 mmol) in DMF (5 mL) were added tetrabutylammonium bromide (161 mg, 1.0 mmol) and K_2CO_3 (138 mg, 2.0 mmol) under nitrogen in a dried Schlenk tube, and the reaction mixture was stirred at 80 °C for 1 h. The reaction mixture was first cooled to room temperature and added to water (30 mL) and CH_2Cl_2 (10 mL). The organic layers were separated, and the water phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with brine (3 × 10 mL) and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography (eluting solvent: EtOAc/CH_2Cl_2/PE = 1/1/9) to give the corresponding annulated product **5ab** (196 mg) in 82% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31 (s, 9H), 3.92 (s, 3H), 4.05 (s, 3H), 6.20 (s, 1H), 6.82 (br, 1H), 6.90 (d, J = 2.4 Hz, 1H), 7.21 (dd, J = 9.0 Hz, J = 2.4 Hz, 1H), 7.27−7.33 (m, 5H), 7.40 (d, J = 9.0 Hz, 1H), 7.66 (d, J = 2.4 Hz, 1H), 9.18 (d, J = 2.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.4, 51.6, 55.6, 56.0, 62.5, 101.9, 104.9, 116.8, 118.2, 121.1, 126.9, 127.2, 127.5, 127.7, 128.2, 128.5, 128.6, 133.8, 134.2, 158.7, 159.9, 161.8, 167.3. HRMS (EI): calcd for $C_{30}H_{24}NO_5$ (M^+), 478.1655; found, 478.1653.

***N*-*tert*-Butyl-2-(2-chlorophenyl)-2-(8,10-dimethoxy-2-methyl-6-oxo-6*H*-phenanthridin-5-yl)-acetamide (6ab).** To a solution of $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), PCy_3 (16.8 mg, 0.06 mmol), and **6aa** (310 mg, 0.5 mmol) in DMF (5 mL) were added tetrabutylammonium bromide (161 mg, 1.0 mmol) and K_2CO_3 (138 mg, 2.0 mmol) under nitrogen in a dried Schlenk tube, and the reaction mixture was stirred at 80 °C for 1 h. The reaction mixture was first cooled to room temperature and added to water (30 mL) and CH_2Cl_2 (10 mL). The organic layers were separated, and the water phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with brine (3 × 10 mL) and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography (eluting solvent: EtOAc/CH_2Cl_2/PE = 1/1/10) to give the corresponding annulated product **6ab** (194 mg) in 79% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28 (s, 9H), 2.43 (s, 3H), 3.96 (s, 3H), 4.09 (s, 3H), 6.22 (s, 1H), 6.90 (br, 1H), 6.95 (d, J = 2.4 Hz, 1H), 7.12 (dd, J = 8.4 Hz, J = 1.8 Hz, 1H), 7.25−7.30 (m, 5H), 7.69 (d, J = 2.4 Hz, 1H), 8.99 (d, J = 1.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.3, 28.5, 51.7, 55.7, 56.0, 61.3, 101.8, 105.1, 116.8, 118.0, 119.8, 127.9, 128.2, 128.4, 129.1, 132.4, 132.7, 133.0, 133.2, 158.8, 159.5, 162.0, 167.4. HRMS (EI): calcd for $C_{28}H_{29}N_2O_4{}^{35}Cl$ (M^+), 492.1816; found, 492.1818.

5-Acetyl-2-methyl-5,6-dihydrophenanthridine-6-carboxylic Acid *tert*-Butylamide (16). To a solution of $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), PCy_3 (16.8 mg, 0.06 mmol), and **15** (232 mg, 0.5 mmol) in DMF (5 mL) were added tetrabutylammonium bromide (161 mg, 1.0 mmol) and K_2CO_3 (138 mg, 2.0 mmol) under nitrogen in a dried Schlenk tube, and the reaction mixture was stirred at 100 °C for 1 h. The reaction mixture was first cooled to room temperature and added to water (30 mL) and CH_2Cl_2 (10 mL). The organic layers were separated, and the water phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with brine (3 × 10 mL) and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography (eluting solvent: EtOAc/CH_2Cl_2/PE = 1/1/7) to give the corresponding annulated product **16** (163 mg) in 97% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.13 (s, 9H), 2.26 (s, 3H), 2.42 (s, 3H), 5.80 (br, 1H), 6.34 (s, 1H), 7.14 (br, 2H), 7.33−7.46 (m, 3H), 7.62 (s, 1H), 7.81 (d, J = 7.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.2, 22.3, 28.6, 51.2, 57.8, 123.1, 123.3, 124.7, 125.3, 128.0, 128.5, 128.6, 130.6, 132.7, 133.6,

136.3, 167.6, 170.4. HRMS (EI): calcd for $C_{21}H_{24}N_2O_2$ (M^+), 336.1838; found, 336.1841.

5-Propionyl-5,6-dihydrophenanthridine-6-carboxylic Acid *tert*-Butylamide (1bb). To a solution of $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), PCy_3 (16.8 mg, 0.06 mmol), and **1ba** (232 mg, 0.5 mmol) in DMF (5 mL) were added tetrabutylammonium bromide (161 mg, 1.0 mmol) and K_2CO_3 (138 mg, 2.0 mmol) under nitrogen in a dried Schlenk tube, and the reaction mixture was stirred at 100 °C for 1 h. The reaction mixture was first cooled to room temperature and added to water (30 mL) and CH_2Cl_2 (10 mL). The organic layers were separated, and the water phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with brine (3 × 10 mL) and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography (eluting solvent: EtOAc/CH_2Cl_2/PE = 1/1/8) to give the corresponding annulated product **1bb** (141 mg) in 82% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.11−1.15 (m, 12H), 2.40−2.48 (m, 1H), 2.65−2.78 (m, 1H), 5.80 (s, 1H), 6.34 (br, 1H), 7.28−7.46 (m, 6H), 7.81 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.6, 27.3, 28.3, 51.1, 58.0, 123.3, 124.7, 125.0, 126.5, 127.8, 128.0, 128.4, 128.6, 128.8, 130.5, 133.7, 134.9, 167.5, 174.1. HRMS (EI): calcd for $C_{21}H_{24}N_2O_2$ (M^+), 336.1838; found, 336.1834.

5-Acetyl-7-methoxy-5,6-dihydrophenanthridine-6-carboxylic Acid *tert*-Butylamide (2bb). To a solution of $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), PCy_3 (16.8 mg, 0.06 mmol), and **2ba** (240 mg, 0.5 mmol) in DMF (5 mL) were added tetrabutylammonium bromide (161 mg, 1.0 mmol) and K_2CO_3 (138 mg, 2.0 mmol) under nitrogen in a dried Schlenk tube, and the reaction mixture was stirred at 100 °C for 1 h. The reaction mixture was first cooled to room temperature and added to water (30 mL) and CH_2Cl_2 (10 mL). The organic layers were separated, and the water phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with brine (3 × 10 mL) and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography (eluting solvent: EtOAc/CH_2Cl_2/PE = 1/1/8) to give the corresponding annulated product **2bb** (162 mg) in 92% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.16 (s, 9H), 2.28 (s, 3H), 3.95 (s, 3H), 6.22 (br, 1H), 6.78 (s, 1H), 6.93 (dd, J = 7.8 Hz, J = 1.2 Hz, 1H), 7.25−7.46 (m, 5H), 7.76 (dd, J = 7.2 Hz, J = 1.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.5, 28.6, 50.9, 52.0, 55.8, 110.0, 116.0, 123.1, 124.7, 125.1, 125.9, 128.1, 129.1, 132.1, 136.4, 155.2, 167.6, 170.2. HRMS (EI): calcd for $C_{21}H_{24}N_2O_3$ (M^+), 352.1787; found, 352.1799.

5-(4-Chlorobenzoyl)-9-fluoro-5,6-dihydrophenanthridine-6-carboxylic Acid Cyclohexylamide (3bb). To a solution of $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), PCy_3 (16.8 mg, 0.06 mmol), and **3ba** (295 mg, 0.5 mmol) in DMF (5 mL) were added tetrabutylammonium bromide (161 mg, 1.0 mmol) and K_2CO_3 (138 mg, 2.0 mmol) under nitrogen in a dried Schlenk tube, and the reaction mixture was stirred at 100 °C for 1 h. The reaction mixture was first cooled to room temperature and added to water (30 mL) and CH_2Cl_2 (10 mL). The organic layers were separated, and the water phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with brine (3 × 10 mL) and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography (eluting solvent: EtOAc/CH_2Cl_2/PE = 1/1/8) to give the corresponding annulated product **3bb** (214 mg) in 93% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92−1.78 (m, 10H), 3.59−3.62 (m, 1H), 6.14 (br, 2H), 6.65 (d, J = 7.8 Hz, 1H), 7.03−7.41 (m, 8H), 7.57 (dd, J = 9.9 Hz, J = 2.4 Hz, 1H), 7.74 (d, J = 7.8 Hz, J = 1.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.3, 24.4, 25.3, 32.5, 32.7, 48.1, 58.8, 110.3, 110.6, 115.1, 115.4, 124.7, 125.7, 126.2, 126.78, 126.81, 128.4, 128.6, 129.8, 129.87, 129.94, 130.3, 131.0, 132.2, 132.7, 132.8, 135.6, 137.5, 161.5, 164.8, 167.1, 168.9. HRMS (EI): calcd for $C_{27}H_{24}N_2O_2FCl$ (M^+), 462.1510; found, 462.1511.

9-Fluoro-5-(4-methoxybenzoyl)-5,6-dihydrophenanthridine-6-carboxylic Acid Cyclohexylamide (4bb). To a solution of $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), PCy_3 (16.8 mg, 0.06 mmol), and **4ba** (293 mg, 0.5 mmol) in DMF (5 mL) were added tetrabutylammonium bromide (161 mg, 1.0 mmol) and K_2CO_3 (138 mg, 2.0 mmol) under nitrogen in a dried Schlenk tube, and the reaction mixture was stirred at 100 °C for 1 h. The reaction mixture was first cooled to room temperature and added to water (30 mL) and CH_2Cl_2 (10 mL). The organic layers were separated, and the water phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with brine (3 × 10 mL) and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography (eluting solvent: EtOAc/CH_2Cl_2/PE = 1/1/10) to give the corresponding annulated product **4bb** (211 mg) in 92% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.79−1.83 (m, 10H), 3.59−3.79 (m, 1H), 3.80 (s, 3H), 6.14 (s, 1H), 6.37−6.40 (m, 1H), 6.66 (dd, J = 7.8 Hz, J = 0.9 Hz, 1H), 6.78 (d, J = 9.3 Hz, 2H), 6.99−7.21 (m, 3H), 7.35−7.43 (m, 3H), 7.56 (dd, J = 9.3 Hz, J = 2.4 Hz, 1H), 7.73 (dd, J = 7.8 Hz, J = 1.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.3, 24.4, 25.4, 29.7, 32.6, 32.7, 48.0, 55.3, 59.0, 110.1, 110.4, 113.5, 114.9, 115.2, 124.7, 125.6, 125.70, 125.72, 126.76, 126.78, 128.2, 128.86, 128.89, 129.86, 129.94, 131.9, 132.9, 133.0, 136.3, 161.9, 162.1, 164.3, 167.6, 169.9. HRMS (FAB): calcd for $C_{28}H_{28}N_2O_3F$ ([M + H]$^+$), 459.2080; found, 459.2078.

5-(4-Chlorobenzoyl)-8,9-dimethoxy-5,6-dihydrophenanthridine-6-carboxylic Acid *tert*-Butylamide (5bb). To a solution of $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), PCy_3 (16.8 mg, 0.06 mmol), and **5ba** (303 mg, 0.5 mmol) in DMF (5 mL) were added tetrabutylammonium bromide (161 mg, 1.0 mmol) and K_2CO_3 (138 mg, 2.0 mmol) under nitrogen in a dried Schlenk tube, and the reaction mixture was stirred at 100 °C for 1 h. The reaction mixture was first cooled to room temperature and added to water (30 mL) and CH_2Cl_2 (10 mL). The organic layers were separated, and the water phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with brine (3 × 10 mL) and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography (eluting solvent: EtOAc/CH_2Cl_2/PE = 1/1/8) to give the corresponding annulated product **5bb** (186 mg) in 78% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.16 (s, 9H), 3.97 (s,

3H), 4.02 (s, 3H), 6.07 (s, 1H), 6.12 (s, 1H), 6.60 (d, J = 7.8 Hz, 1H), 6.90 (s, 1H), 6.93−6.98 (m, 1H), 7.17−7.38 (m, 6H), 7.73 (d, J = 7.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.5, 51.3, 56.0, 56.1, 59.5, 106.5, 111.0, 123.3, 123.9, 125.7, 125.8, 126.1, 126.8, 127.9, 128.5, 131.0, 132.4, 134.9, 137.3, 149.4, 149.5, 167.6, 168.8. HRMS (FAB): calcd for $C_{27}H_{28}N_2O_4Cl$ ([M + H]$^+$), 479.1727; found, 479.1732.

5-Benzoyl-2-methoxy-5,6-dihydrophenanthridine-6-carboxylic Acid Cyclohexylamide (6bb). To a solution of $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), PCy_3 (16.8 mg, 0.06 mmol), and **6ba** (284 mg, 0.5 mmol) in DMF (5 mL) were added tetrabutylammonium bromide (161 mg, 1.0 mmol) and K_2CO_3 (138 mg, 2.0 mmol) under nitrogen in a dried Schlenk tube, and the reaction mixture was stirred at 100 °C for 1 h. The reaction mixture was first cooled to room temperature and added to water (30 mL) and CH_2Cl_2 (10 mL). The organic layers were separated, and the water phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with brine (3 × 10 mL) and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography (eluting solvent: EtOAc/CH_2Cl_2/PE = 1/1/9) to give the corresponding annulated product **6bb** (208 mg) in 95% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93−1.75 (m, 10H), 3.60−3.65 (m, 1H), 3.81 (s, 3H), 6.19−6.21 (m, 2H), 6.53−6.54 (m, 2H), 7.25−7.52 (m, 9H), 7.86 (d, J = 7.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.3, 24.4, 25.4, 32.6, 32.7, 48.0, 55.4, 59.4, 109.2, 113.6, 123.5, 126.8, 128.2, 128.4, 128.8, 128.9, 129.0, 129.5, 130.2, 130.9, 131.0, 133.0, 134.2, 157.4, 167.6, 169.8. HRMS (EI): calcd for $C_{28}H_{28}N_2O_3$ (M^+), 440.2100; found, 440.2102.

5-Benzoyl-2-chloro-8-methoxy-5,6-dihydrophenanthridine-6-carboxylic Acid Cyclohexyl Amide (7bb). To a solution of $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), PCy_3 (16.8 mg, 0.06 mmol), and **7ba** (301 mg, 0.5 mmol) in DMF (5 mL) were added tetrabutylammonium bromide (161 mg, 1.0 mmol) and K_2CO_3 (138 mg, 2.0 mmol) under nitrogen in a dried Schlenk tube, and the reaction mixture was stirred at 100 °C for 1 h. The reaction mixture was first cooled to room temperature and added to water (30 mL) and CH_2Cl_2 (10 mL). The organic layers were separated, and the water phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with brine (3 × 10 mL) and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography (eluting solvent: EtOAc/CH_2Cl_2/PE = 1/1/7) to give the corresponding annulated product **7bb** (219 mg) in 91% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.86−1.64 (m, 10H), 3.59−3.65 (m, 1H), 3.87 (s, 3H), 6.16 (s, 1H), 6.23 (d, J = 7.5 Hz, 1H), 6.55 (d, J = 8.4 Hz, 1H), 6.86 (dd, J = 8.4 Hz, J = 2.4 Hz, 1H), 6.93 (d, J = 2.4 Hz, 1H), 7.04 (dd, J = 8.7 Hz, J = 2.4 Hz, 1H), 7.27−7.45 (m, 5H), 7.69 (d, J = 2.4 Hz, 1H), 7.76 (d, J = 8.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.36, 24.42, 25.4, 32.6, 32.8, 48.2, 55.5, 59.5, 113.1, 115.3, 122.7, 123.8, 125.0, 126.5, 126.8, 128.3, 129.2, 129.5, 131.4, 133.6, 133.7, 134.4, 160.2, 167.1, 170.1. HRMS (EI): 474 (M^+): calcd for $C_{28}H_{27}N_2O_3Cl$ (M^+), 474.1710; found, 474.1700.

***N-tert*-Butyl-2-(2-methoxy-6-oxo-6*H*-7-thia-5-aza-benzo[*c*]fluoren-5-yl)-2-phenyl Acetamide (20).** To a solution of $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), dppf (16.6 mg, 0.03 mmol), and **19** (299 mg, 0.5 mmol) in DMF (5 mL) were added tetrabutylammonium bromide (161 mg, 1.0 mmol) and K_2CO_3 (138 mg, 2.0 mmol) under nitrogen in a dried Schlenk tube, and the reaction mixture was stirred at 80 °C for 1 h. The reaction mixture was first cooled to room temperature and added to water (30 mL) and CH_2Cl_2 (10 mL). The organic layers were separated, and the water phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with brine (3 × 10 mL) and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography (eluting solvent: EtOAc/CH_2Cl_2/PE = 1/1/9) to give the corresponding annulated product **20** (218 mg) in 93% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32 (s, 9H), 3.90 (s, 3H), 6.24 (s, 1H), 6.98 (dd, J = 9.3, J = 2.7 Hz, 1H), 7.12 (br, 1H), 7.23−7.37 (m, 5H), 7.50−7.62 (m, 3H), 7.95−7.98 (m, 1H), 8.09 (d, J = 2.7 Hz, 1H), 8.59−8.63 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.4, 51.7, 55.5, 60.9, 107.8, 114.9, 119.7, 120.8, 123.7, 125.2, 125.4, 127.1, 127.6, 127.7, 128.4, 131.6, 132.5, 134.4, 135.5, 135.7, 142.7, 155.0, 158.7, 167.1. HRMS (EI): calcd for $C_{28}H_{26}N_2O_3S$ (M^+), 470.1664; found, 470.1666.

5-(*tert*-Butylcarbamoyl-phenyl-methyl)-6-oxo-5,6-hydidro-7-oxa-5-aza-benzo[*c*]fluorine-2-carboxylic Acid Methyl Ester (1cb). To a solution of $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), dppf (16.6 mg, 0.03 mmol), and **1ca** (305 mg, 0.5 mmol) in DMF (5 mL) were added tetrabutylammonium bromide (161 mg, 1.0 mmol) and K_2CO_3 (138 mg, 2.0 mmol) under nitrogen in a dried Schlenk tube, and the reaction mixture was stirred at 80 °C for 1 h. The reaction mixture was first cooled to room temperature and added to water (30 mL) and CH_2Cl_2 (10 mL). The organic layers were separated, and the water phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with brine (3 × 10 mL) and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography (eluting solvent: EtOAc/CH_2Cl_2/PE = 1/1/7) to give the corresponding annulated product **1cb** (217 mg) in 90% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (s, 9H), 3.99 (s, 3H), 6.04 (s, 1H), 7.09 (br, 1H), 7.27−7.36 (m, 5H), 7.54−7.77 (m, 4H), 8.02 (dd, J = 9.0, J = 1.8 Hz, 1H), 8.38 (d, J = 7.5 Hz, 1H), 9.00 (d, J = 1.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.4, 52.0, 52.3, 60.8, 112.9, 117.2, 118.3, 122.6, 122.9, 124.4, 124.5, 124.7, 126.3, 127.8, 127.9, 128.6, 128.7, 128.9, 133.9, 139.8, 142.7, 154.9, 156.6, 166.0, 166.7. HRMS (EI): calcd for $C_{29}H_{26}N_2O_5$ (M^+), 482.1842; found, 482.1837.

5-(*tert*-Butylcarbamoyl-4-methoxyphenylmethyl)-6-oxo-5,6-hydidro-7-oxa-5-aza-benzo[*c*]-fluorine-2-carboxyl-ic Acid Methyl Ester (2cb). To a solution of $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), dppf (16.6 mg, 0.03 mmol), and **2ca** (320.2 mg, 0.5 mmol) in DMF (5 mL) were added tetrabutylammonium bromide (161 mg, 1.0 mmol) and K_2CO_3 (138 mg, 2.0 mmol) under nitrogen in a dried Schlenk tube, and the reaction mixture was stirred at 80 °C for 1 h. The reaction mixture was first cooled to room temperature and added to water (30 mL) and CH_2Cl_2 (10 mL). The organic layers were

separated, and the water phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with brine (3 × 10 mL) and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography (eluting solvent: EtOAc/CH_2Cl_2/PE = 1/1/7) to give the corresponding annulated product **2cb** (238 mg) in 93% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35 (s, 9H), 3.78 (s, 3H), 3.98 (s, 3H), 6.13 (s, 1H), 6.85−6.90 (m, 2H) 6.97 (br, 1H), 7.28−7.35 (m, 2H), 7.50−7.55 (m, 1H), 7.60−7.71 (m, 3H), 8.02 (dd, J = 9.0 Hz, J = 2.1 Hz, 1H), 8.31 (d, J = 7.8 Hz, 1H), 8.93 (d, J = 2.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.5, 52.0, 52.3, 55.2, 61.0, 113.1, 114.2, 117.4, 118.0, 122.8, 123.0, 124.5, 124.7, 125.9, 126.4, 128.8, 129.0, 129.3, 139.9, 143.0, 155.0, 156.8, 159.2, 166.1, 166.9. HRMS (EI): calcd for $C_{30}H_{28}N_2O_6$ (M^+), 512.1947; found, 512.1948.

***N-tert*-Butyl-2-(2-chlroro-11-ethyl-6-oxo-6*H*,11-indolo-[3,2-*c*]quinolin-5-yl)-2-(2-methoxyphenyl)-acetamide (3cb).** To a solution of $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), dppf (16.6 mg, 0.03 mmol), and **3ca** (322 mg, 0.5 mmol) in DMF (5 mL) were added tetrabutylammonium bromide (161 mg, 1.0 mmol) and K_2CO_3 (138 mg, 2.0 mmol) under nitrogen in a dried Schlenk tube, and the reaction mixture was stirred at 80 °C for 1 h. The reaction mixture was first cooled to room temperature and added to water (30 mL) and CH_2Cl_2 (10 mL). The organic layers were separated, and the water phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with brine (3 × 10 mL) and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography (eluting solvent: EtOAc/CH_2Cl_2/PE = 1/1/10) to give the corresponding annulated product **3cb** (237 mg) in 92% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32 (s, 9H), 1.68 (t, J = 7.2 Hz, 3H), 3.87 (s, 3H), 4.73 (q, J = 7.2 Hz, 2H), 5.80 (s, 1H), 6.84−6.89 (m, 1H), 6.96 (d, J = 7.8 Hz, 1H), 7.03 (br, 1H), 7.26−7.55 (m, 6H), 7.62 (d, J = 9.3 Hz, 1H), 8.13 (d, J = 2.1 Hz, 1H), 8.57 (dd, J = 7.8 Hz, J = 1.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.8, 28.5, 40.3, 51.4, 55.6, 58.1, 108.3, 108.9, 110.8, 115.7, 119.1, 120.9, 122.0, 122.0, 122.3, 123.3, 124.2, 124.9, 127.4, 128.1, 128.5, 129.5, 137.3, 137.8, 139.1, 157.2, 160.0, 167.3. HRMS (EI): calcd for $C_{30}H_{30}N_3O_3$-Cl (M^+), 515.1976; found, 515.1980.

***N-tert*-Butylcarbamoylphenylmethyl-6-oxo-5,6-dihydro-7-thia-5-aza-benzo[*c*]fluorine-2-carboxylic Acid Methyl Ester (4cb).** To a solution of $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), dppf (16.6 mg, 0.03 mmol), and **4ca** (323 mg, 0.5 mmol) in DMF (5 mL) were added tetrabutylammonium bromide (161 mg, 1.0 mmol) and K_2CO_3 (138 mg, 2.0 mmol) under nitrogen in a dried Schlenk tube, and the reaction mixture was stirred at 80 °C for 1 h. The reaction mixture was first cooled to room temperature and added to water (30 mL) and CH_2Cl_2 (10 mL). The organic layers were separated, and the water phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with brine (3 × 10 mL) and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography (eluting solvent: EtOAc/CH_2Cl_2/PE = 1/1/8) to give the corresponding annulated product **4cb** (217 mg) in 87% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (s, 9H), 3.98 (s, 3H), 6.10 (s, 1H), 7.08 (s, 1H), 7.27−7.39 (m, 5H), 7.59−7.71 (m, 3H), 7.98−8.03 (m, 2H), 8.76 (dd, J = 7.2 Hz, J = 1.8 Hz, 1H), 9.37 (d, J = 1.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.5, 52.0, 52.4, 61.5, 118.4, 119.6, 123.8, 124.5, 125.7, 125.8, 125.9, 127.6, 127.7, 128.0, 128.7, 128.8, 132.4, 134.1, 135.3, 136.0, 140.6, 142.9, 159.3, 166.3, 166.7. HRMS (EI): calcd for $C_{29}H_{26}N_2O_4S$ (M^+), 498.1613; found, 498.1616.

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Supporting Information Available. Experimental procedure and NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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