JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

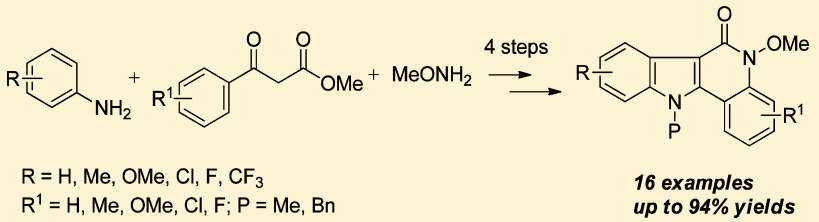
Synthesis of Diversely Substituted Indoloquinolinones via Pd(II)/Cu(II)-Mediated Oxidative C−C Bond Formation and I(III)-Mediated C−N Bond Formation

Xiang Zhang,[†] Daisy Zhang-Negrerie,[†] Jun Deng,[†,‡] Yunfei Du,*[,†,‡] and Kang Zhao*[,†]

[†]Tianjin Key Laboratory for Modern Drug Delivery & High-Efficiency, School of Pharmaceutical Science and Technology, Tianjin University, Tianjin 300072, China

[‡]Collaborative Innovation Center of Chemical Science and Engineering (Tianjin), Tianjin 300072, China

Supporting Information



ABSTRACT: A series of indoloquinolinones bearing different aromatic substitutents were readily synthesized starting from an aryl amine, a methyl 3-oxo-3-phenylpropanoate derivative, and methoxylamine through a series of reactions of coupling/enamination, oxidative annulation, a one-pot sequence of N-alkylation, saponification and methoxyamidation, and final intramolecular oxidative C−N bond formation. The underpinning of the strategy entails $Pd(OAc)_2/Cu(OAc)_2$-mediated oxidative $C(sp^2)-C(sp^2)$ bond formation and I(III)-mediated oxidative $C(sp^2)-N$ bond formation.

INTRODUCTION

Indoloquinolinone derivatives exhibit potent practical value in organic synthesis because of their wide occurrence in numerous bioactive natural products.[1] Indoloquinolinones (Figure 1, **A1** and **A2**), the structures of which belong to compounds that are effective DNA intercalators, show cytotoxic ability against many forms of cancer, such as leukemia and ovarian, breast, colon, and central nervous system cancer.[2] This coplanar tetracyclic structure can also be utilized as useful building blocks for the synthesis of many other potential antineoplastics (Figure 1, **B1**−**B4**) as well as natural products such as isocryptolepine (Figure 1, **C**).[2b,3]

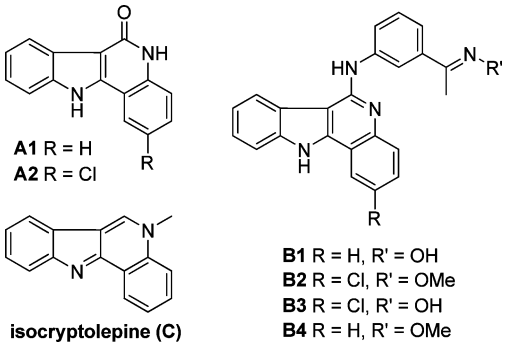


Figure 1. Biologically active indoloquinolinones and their derivatives.

A literature survey indicates that there are a handful of strategies that have been developed for the construction of the indoloquinolinone skeleton. Arguably, the most commonly used approach involves the reaction between a substituted phenylhydrazine derivative and a 4-piperidinone derivative, a method known as the Fisher indole synthesis (Figure 2, path a).[2b] The indoloquinolinone skeleton can also be constructed through an intramolecular displacement reaction involving an aromatic fluorine (Figure 2, path b).[4] The copper-catalyzed cyclic antinucleometalation carboxylation of 2-alkynylanilines followed by treatment with EDCI and detosylation is also an effective approach to access this privileged molecule (Figure 2, path c).[5] The skeleton can also be assembled from an indole-3-carboxylate derivative via intramolecular lactamization (Figure 2, path d).[6] Furthermore, the target spatial arrangement of the nuclei can be formed via a microwave-assisted thermal electrocyclization of a phenyl isocyanate (Figure 2, path e).[3c] The CuI-catalyzed photochemical or thermal reaction of 3-(2-azidobenzylidene)-lactams (Figure 2, path f)[7] and an intermolecular condensation between 2-aminobenzylamine and isatin can also provide the desired indoloquinolinone skeleton (Figure 2, path g).[8] Generally speaking, the mainstream approach of the currently existing strategies remains at the level of modification or functionalization of indole-, indolinone-, or quinolinone-based compounds as starting materials, which naturally limits the substituent pattern in the

Received: October 18, 2013

   dx.doi.org/10.1021/jo4023292 | J. Org. Chem. XXXX, XXX, XXX−XXX

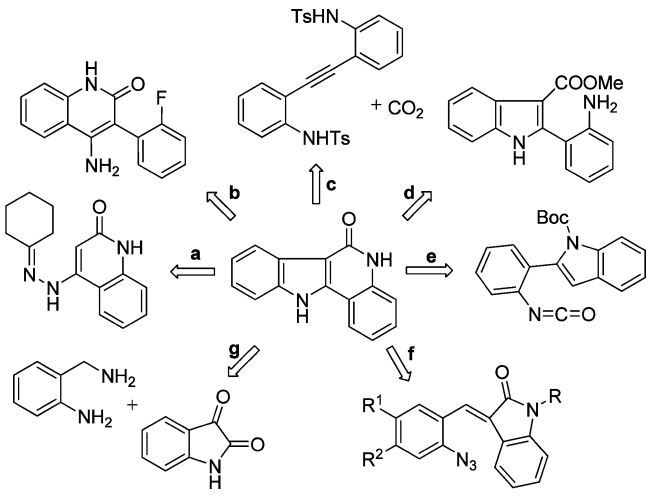


Figure 2. Existing strategies for the construction of the indoloquinolinone skeleton.

phenyl ring(s). In this regard, it is highly desirable to develop new approaches that would allow the construction of indoloquinolinones bearing a versatile category of substituents on either of the two phenyl rings.

Our retrosynthetic analysis for the synthesis of the indoloquinolinone skeleton is illustrated in Figure 3. We

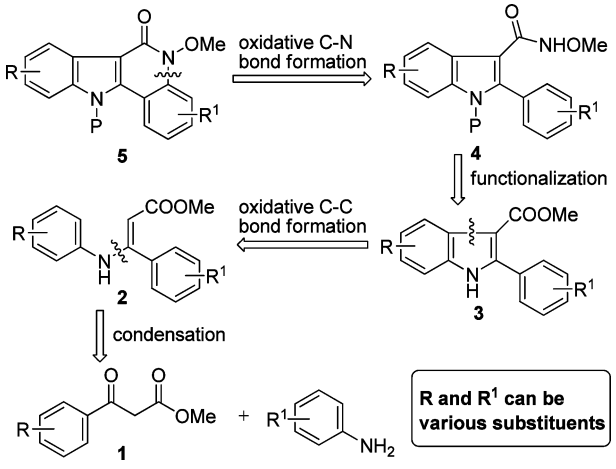


Figure 3. Retrosynthetic analysis.

envisaged that 5-methoxyindoloquinolinone **5** could be accessed from *N*-methoxyamide **4** through intramolecular oxidative C−N bond formation.[9] Intermediate **4** could be prepared from indole-3-carboxylic ester **3** through an N-alkylation−hydrolysis−methoxyamidation sequence.[10] The preparation of intermediate **3** was attempted from *N*-aryl enamine **2** through intramolecular oxidative C−C bond formation mediated by either a transition metal or a hypervalent iodine reagent.[11] Key intermediate **2** could be easily formed from the condensation between *β*-ketoesters **1** and the readily available correspondingly substituted anilines.[12] The method ensures versatile functionalization of the target indoloquinolinone compound, as the various substituents in the phenyl ring of both **1** and anilines are expected to survive the proposed reactions and to show up eventually in the final product.

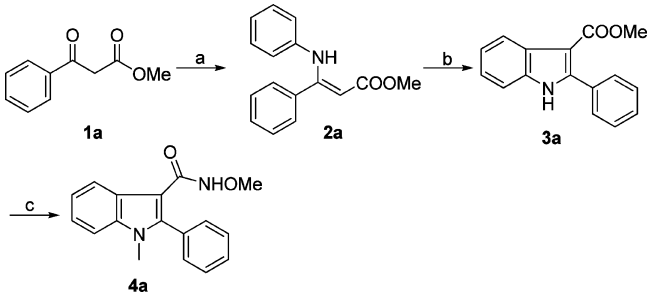
RESULTS AND DISCUSSION

Adopting the synthetic strategy described earlier, the simplest substrate, **4a**, with no substituent in either of the phenyl rings was first prepared. The reaction of 3-oxo-3-phenyl propanoate **1a** with aniline in glacial acetic acid provided *N*-phenyl enamine **2a** in 79% yield. Following Glorius' method by treating **2a** with $Pd(OAc)_2/Cu(OAc)_2$ under basic conditions, an oxidative C−C bond formation occurred in **2a**, leading to corresponding indole product **3a** in moderate yield.[11a,c] Similarly, the other indole-3-carboxylates, **3b−o**, could be readily obtained by this transition-metal-mediated oxidative C−C bond-formation approach (Table 1). Both electron-donating and electron-withdrawing groups on the phenyl ring of the aniline moiety could be well-tolerated in the process, with desired indoles **3b−g** being achieved in moderate to good yields (Table 1, entries 2−7). However, the electronic nature of the R^1 substituents on the phenyl ring significantly influenced the reaction yield (Table 1, entries 8 and 9, 12 and 13). Specifically, when R^1 was an electron-withdrawing group, the reaction gave the desired cyclized product in much lower yields relative to the substrate bearing no substituent (R^1 = H) (Table 1, entries 12 and 13). The method could also be well-applied to the substrates bearing substituents on both aromatic rings, affording the corresponding indole products in moderate to good yields (Table 1, entries 10 and 11, 14 and 15).

We also attempted to accomplish the conversion using the iodobenzene diacetate (PIDA)-mediated oxidative cyclization method developed in our own laboratory, but unfortunately product **3a** was achieved in only 20% yield.[11b]

Next, N-unsubstituted indole **3a** was smoothly transformed into intermediate **4a** over a three-step sequence of methylation, saponification, and methoxyamidation (Scheme 1). Adopting the same strategy, the other *N*-methoxyamides, **4b−p**, could be conveniently achieved in 44−77% yield (see details in the Experimental Section).

Scheme 1. Preparation of Intermediate 4a from Methyl 3-Oxo-3-phenylpropanoate 1a[a]

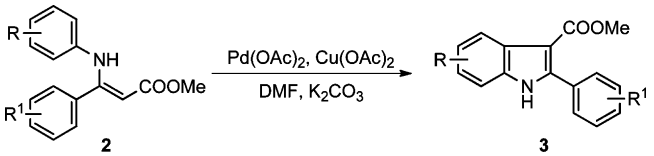


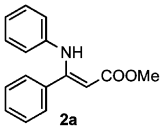
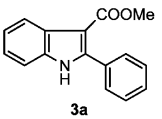
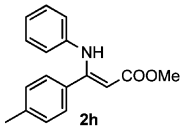
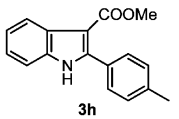
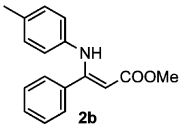
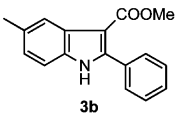
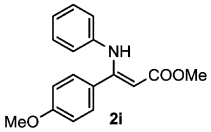
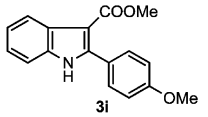
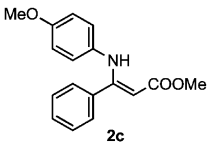
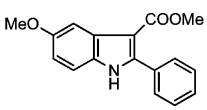
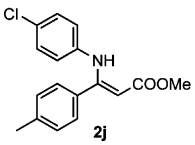
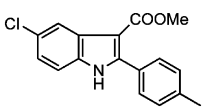
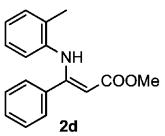
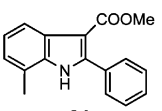
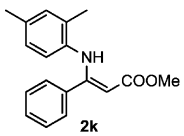
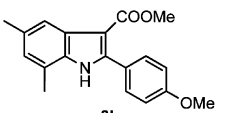
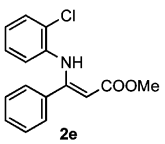
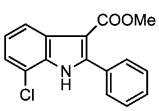
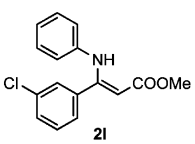
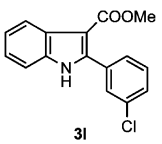
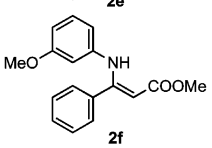
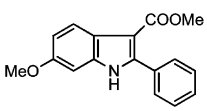
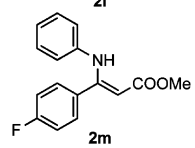
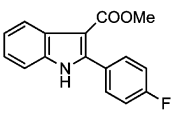
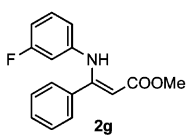
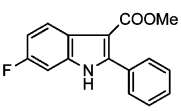
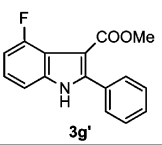
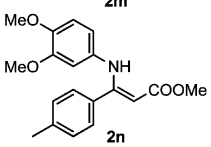
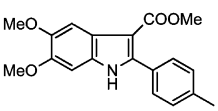
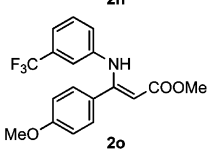
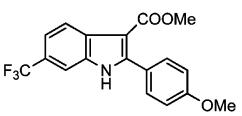
[a]Reagents and conditions: (a) $ArNH_2$, AvOH, 80 °C, 20 h, 79%; (b) $Pd(OAc)_2$, $Cu(OAc)_2$, K_2CO_3, DMF, 80 °C, 15 h, 51%; (c) (1) NaOH, CH_3I, THF, rt, 2 h, (2) 2 N NaOH, EtOH, 80 °C, 9 h, then 4 N HCl, (3) $SOCl_2$, DCM, rt, 2 h, then NH_2OMe, TEA, DCM, −20 to 0 °C, 2 h (77% over three steps).

With *N*-methoxyamide **4a** in hand, we set out to realize the last step in the synthesis of the titled compound, namely, the intramolecular ring-closure reaction to form cyclized product **5a**. First, we found that the application of bis(trifluoroacetoxy)-iodobenzene (PIFA) as oxidant in dichloroethane (DCE) conveniently converted **4a** to **5a** in 76% yield (Table 2, entry 1). Later, we realized that the replacement of PIFA by PIDA further improved the yield to a satisfactory 84% (Table 2, entry

dx.doi.org/10.1021/jo4023292 | J. Org. Chem. XXXX, XXX, XXX−XXX

Table 1. $Pd(OAc)_2/Cu(OAc)_2$-Mediated Oxidative Indolization[a]



entry	enamine **2**	indole **3**	T (°C)	time (h)[b]	yield (%)[c]	entry	enamine **2**	indole **3**	T (°C)	time (h)[b]	yield (%)[c]
1	 **2a**	 **3a**	80	15	51	8	 **2h**	 **3h**	120	12	53
2	 **2b**	 **3b**	80	30	48	9	 **2i**	 **3i**	120	15	46
3	 **2c**	 **3c**	140	8	87	10	 **2j**	 **3j**	90	15	69
4	 **2d**	 **3d**	110	4	74	11	 **2k**	 **3k**	90	10	81
5	 **2e**	 **3e**	80	4	78	12	 **2l**	 **3l**	90	10	42
6	 **2f**	 **3f**	100	12	57	13	 **2m**	 **3m**	100	18	29
7	 **2g**	 **3g**  **3g'**	60	12	56[d]	14	 **2n**	 **3n**	80	18	55
						15	 **2o**	 **3o**	80	15	53

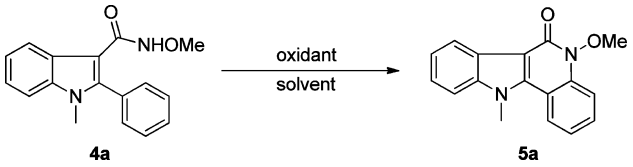
[a]Reaction conditions: *N*-aryl enamine **2** (10 mmol), $Pd(OAc)_2$ (10 mol %), $Cu(OAc)_2$ (30 mmol), and K_2CO_3 (30 mmol) were stirred in DMF (125 mL) under an atmosphere of argon. [b]The reaction was not stopped until the total consumption of *N*-aryl enamine **2**. [c]Isolated yields. [d]Yield of two separable regioisomers (**3g**/**3g′** = 56:44).

2). Solvent-screening studies including THF, MeCN, TFE, DMF, and TFA revealed that none of them were superior to DCE (Table 2, entries 3−7). Parallel experiments indicated that reactions run at a lower concentration of **4a** (0.02 M) resulted in a slightly improved yield (86%), whereas a higher concentration (0.08 M) resulted in a decreased yield of the product (Table 2, entries 8 and 9). Other hypervalent iodine reagents (i.e., PhIO and $PhICl_2$) were also tested. Results showed that reactions using PhIO afforded the desired product in only 17% yield, whereas $PhICl_2$ was not effective for the reaction (Table 2, entries 10 and 11).

Under the optimal conditions, a series of enamides **4**, prepared via the approach described in Scheme 1, was converted to the corresponding cyclized products in satisfactory to high yields (Table 3). The electronic nature of the R group on the phenyl ring of the indole moiety, electron-donating or electron-withdrawing, exhibited no effect on the efficacy of the reaction, with the desired indoloquinolinones **5b−g** achieved in similar good to excellent yields (Table 3, entries 2−7). However and as expected, the electronic nature of the R^1 substituents on the phenyl ring to which the N-atom cyclizes did influence the reaction yield to a certain degree. Specifically,

dx.doi.org/10.1021/jo4023292 | J. Org. Chem. XXXX, XXX, XXX−XXX

Table 2. Optimization of Reaction Conditions[a]



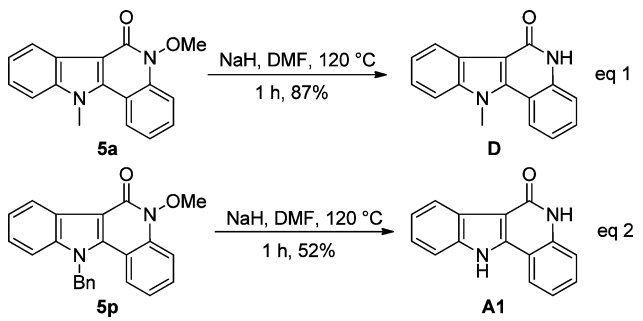
entry	oxidant (equiv)	solvent	c (mol/L)	T (°C)	time (h)[b]	yield (%)[c]
1	PIFA (1.2)	DCE	0.05	rt	0.08	76
2	PIDA (1.2)	DCE	0.05	rt	0.5	84
3	PIDA (1.2)	THF	0.05	rt	0.5	68
4	PIDA (1.2)	MeCN	0.05	rt	0.17	51
5	PIDA (1.2)	TFE	0.05	rt	0.08	65
6	PIDA (1.2)	DMF	0.05	rt	0.5	82
7	PIDA (1.2)	TFA	0.05	rt	0.08	78
8[d]	PIDA (1.2)	DCE	0.02	rt	1	86
9[e]	PIDA (1.2)	DCE	0.08	rt	0.08	80
10	PhIO (1.2)	DCE	0.05	rt	12	17
11	$PhICl_2$ (1.2)	DCE	0.05	rt	16	ND

[a]Reaction conditions: **4a** (0.2 mmol) and oxidant (0.24 mmol) in solvent (4 mL) unless otherwise stated. [b]The reaction was not stopped until the total consumption of substrate **4a**. [c]Isolated yields. [d]DCE (10 mL) was used. [e]DCE (2.5 mL) was used.

when R^1 was an electron-donating group, the reaction gave the desired cyclized product in slightly higher yields relative to that with no substituent (Table 3, entries 8−11); the opposite was true when R^1 was an electron-withdrawing group (Table 3, entries 12−13). It is worth noting that PIDA was not effective for the conversion of substrate **4n** or **4o**. Desired products **5n** and **5o** were obtained in 75 and 82% yields, respectively, when PIFA was used as the oxidant instead (Table 3, entries 14−15). Entry 16 shows that the method is also applicable to substrates where a benzyl substituent is attached to the N-atom of the indole moiety. This result adds another dimension to the versatility of the indoloquinolinones that can be obtained through this method (Table 3, entry 16).

Finally, it is worth mentioning that the *N*-methoxy moiety in the final product can be conveniently removed by known procedures to afford the NH-free indoloquinolinone product.[13] For example, compound **5a**, upon treatment with NaH in DMF at 120 °C for 1 h, can be converted to product **D** in 87% yield (Scheme 2, eq 1). Moreover, N-benzylated **5p** can be converted to bioactive product **A1** in moderate yield under the same reaction conditions, with both the *N*-methoxy and the *N*-benzyl moieties being effectively removed (Scheme 2, eq 2).

Scheme 2. Deprotection of 5-Methoxy Indoloquinolinone 5a and 5p



CONCLUSIONS

We have disclosed an alternative approach to construct the synthetically and biologically important indoloquinolinone compounds from readily available 3-oxo-3-phenylpropanoate derivatives and substituted anilines that involves Pd/Cu-catalyzed C−C bond formation and I(III)-mediated oxidative C−N bond formation. By starting from simple starting materials and constructing the skeleton in four steps, the strategy allows for the various substituents in the starting materials to be carried through, which neatly provides convenient access to a variety of biologically active indolequinolinone derivatives containing different substituents on the two phenyl rings.

EXPERIMENTAL SECTION

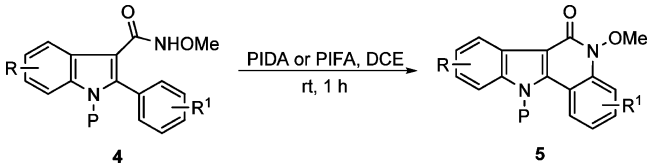
General Information. ^1H and ^{13}C NMR spectra were recorded on a 600 MHz (150 MHz for ^{13}C NMR) spectrometer at 25 °C. Chemical-shift values are given in ppm and referenced to the internal standard, TMS (tetramethylsilane). The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet; dd, doublet of doublets, and br s, broad singlet. The coupling constants (J) are reported in Hertz (Hz). High-resolution mass spectrometry (HRMS) was obtained on a Q-TOF microspectrometer. Melting points were determined with a National micromelting point apparatus without corrections. DCM, DCE, CH_3CN, toluene, DMF, and THF were dried by CaH_2 before use. Flash column chromatography was performed over silica gel 200−300 mesh, and the eluent was a mixture of DCM and MeOH.

General Procedure for the Preparation of *N*-Aryl Enamines 2.[11b] A mixture of β-ketone ester (20.0 mmol), substituted aniline (30 mmol), and glacial acetic acid (30 mmol) was stirred at 80 °C under a nitrogen atmosphere until TLC indicated the total consumption of the β-ketone ester. Then, the resulting mixture was purified by column chromatography using a mixture of petroleum ether (PE) and EtOAc as eluent to afford *N*-aryl enamines **2** as a single *Z* configuration.

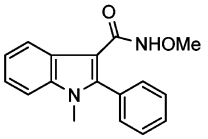
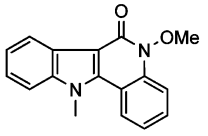
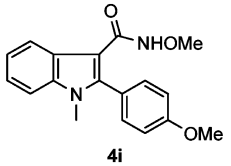
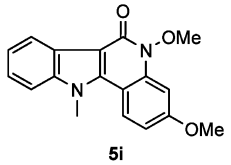
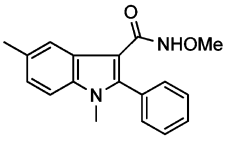
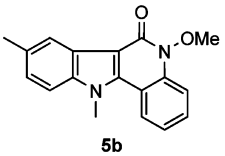
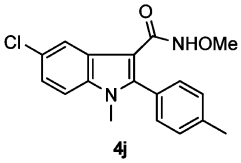
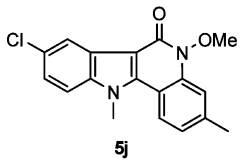
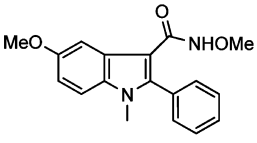
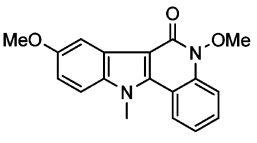
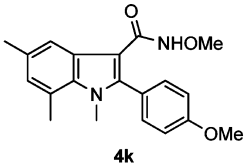
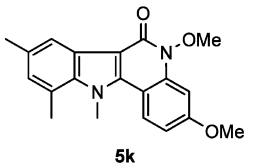
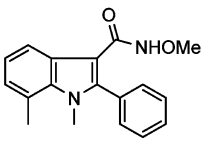
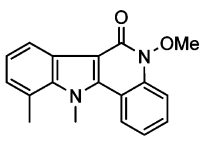
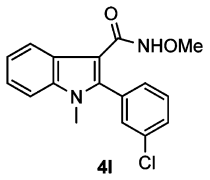
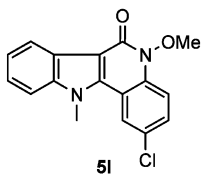
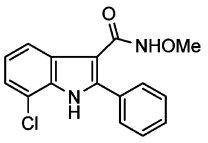
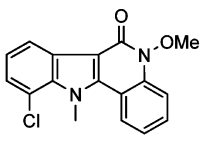
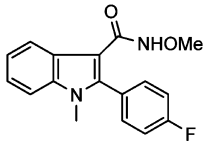
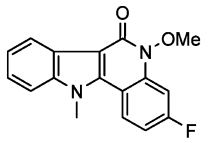
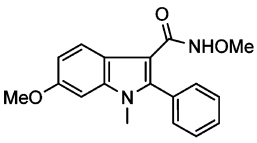
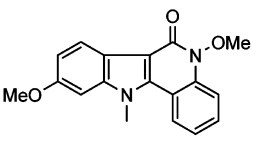
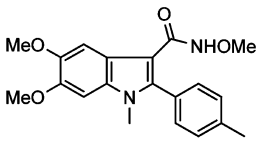
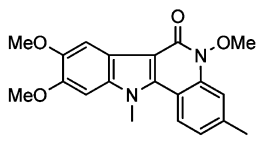
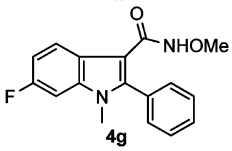
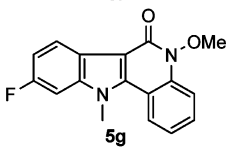
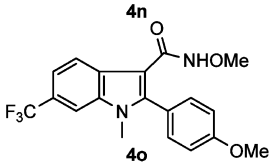
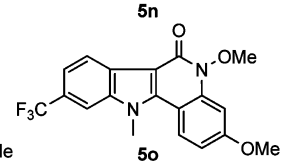
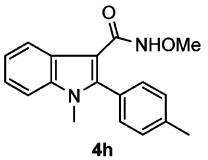
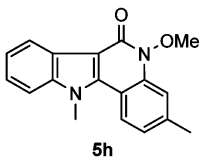
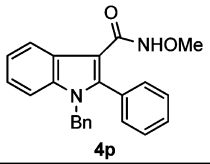
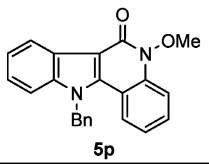
Following this general procedure, known *N*-aryl enamines **2a**,[14,15] **2b**,[11b] **2c**,[12b,15] **2d**,[15] **2f**,[12b] **2g**,[12a] **2h**,[16] **2i**,[11c] and **2m**[16] were prepared in 79, 87, 86, 40, 80, 58, 66, 57, and 81% yields, respectively. The properties and ^1H NMR data of **2a−d**, **2f−i**, and **2m** were consistent with those in the literature. Novel *N*-aryl enamines **2e**, **2j−l**, **2n**, and **2o** thus obtained were characterized as follows:

dx.doi.org/10.1021/jo4023292 | J. Org. Chem. XXXX, XXX, XXX−XXX

Table 3. I(III)-Mediated Synthesis of Indoloquinolinones[a]



4 5

entry	substrate 4	product 5	yield (%)[b]	entry	substrate 4	product 5	yield (%)[b]
1	 4a	 5a	86	9	 4i	 5i	94
2	 4b	 5b	85	10	 4j	 5j	93
3	 4c	 5c	86	11	 4k	 5k	86
4	 4d	 5d	88	12	 4l	 5l	83[c]
5	 4e	 5e	84	13	 4m	 5m	79
6	 4f	 5f	91	14[d]	 4n	 5n	75
7	 4g	 5g	81	15[d]	 4o	 5o	82
8	 4h	 5h	91	16	 4p	 5p	85

[a]Optimal reaction conditions: **4** (0.2 mmol, 1 equiv), PIDA (0.24 mmol, 1.2 equiv), DCE (10 mL), room temperature. [b]Isolated yields. [c]Yield of two inseparable regioisomers (**5l**/**5l′** = 10:1). [d]The reaction was carried out using 1.1 equiv of PIFA in DCM at room temperature.

*(Z)-Methyl 3-((2-Chlorophenyl)amino)-3-phenylacrylate (**2e**).* Following the general procedure for 40 h, **2e** was isolated as a light yellow solid. Yield: 1.26 g, 22%, mp 52−58 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.34 (br s, 1H), 7.35−7.27 (m, 6H), 6.82−6.78 (m, 2H), 6.29 (d, J = 7.9 Hz, 1H), 5.12 (s, 1H), 3.76 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.1, 158.0, 137.5, 135.7, 129.7, 129.6, 128.6, 128.0, 126.4, 125.8, 123.5, 123.4, 93.0, 50.9. HRMS (ESI) m/z calcd for $C_{16}H_{14}ClNNaO_2^+$ [M + Na$^+$], 310.0605; found, 310.0592.

dx.doi.org/10.1021/jo4023292 | J. Org. Chem. XXXX, XXX, XXX−XXX

*(Z)-Methyl 3-((4-Chlorophenyl)amino)-3-(p-tolyl)acrylate (**2j**).* Following the general procedure for 18 h, **2j** was isolated as a white solid. Yield: 3.31 g, 55%, mp 91−92 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.23 (br s, 1H), 7.21 (d, J = 7.8 Hz, 2H), 7.10 (d, J = 7.8 Hz, 2H), 7.04 (d, J = 9.0 Hz, 2H), 6.59 (d, J = 9.0 Hz, 2H), 6.02 (s, 1H), 3.74 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.5, 158.9, 139.9, 139.2, 132.6, 129.3, 128.7, 128.2, 128.1, 123.3, 90.1, 50.7, 21.4. HRMS (ESI) m/z calcd for $C_{17}H_{16}ClNNaO_2^+$ [M + Na$^+$], 324.0762; found, 324.0759.

*(Z)-Methyl 3-((2,4-Dimethylphenyl)amino)-3-(4-methoxyphenyl)-acrylate (**2k**).* Following the general procedure for 18 h, **2k** was isolated as a white solid. Yield: 2.80 g, 45%, mp 93−95 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.04 (br s, 1H), 7.20 (d, J = 8.4 Hz, 2H), 6.93 (s, 1H), 6.75 (d, J = 8.4 Hz, 2H), 6.62 (d, J = 8.4 Hz, 1H), 6.29 (d, J = 8.4 Hz, 1H), 4.96 (s, 1H), 3.76 (s, 3H), 3.73 (s, 3H), 2.35 (s, 3H), 2.19 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.8, 160.4, 160.2, 136.6, 133.2, 131.1, 130.4, 129.6, 128.4, 126.5, 124.3, 113.7, 88.7, 55.2, 50.6, 20.7, 18.1. HRMS (ESI) m/z calcd for $C_{19}H_{21}NNaO_3^+$ [M + Na$^+$], 334.1414; found, 334.1403.

*(Z)-Methyl 3-(3-Chlorophenyl)-3-(phenylamino)acrylate (**2l**).* Following the general procedure for 8 h, **2l** was isolated as a light yellow oil. Yield: 4.65 g, 81%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.22 (br s, 1H), 7.38 (s, 1H), 7.31 (d, J = 6.8 Hz, 1H), 7.22−7.16 (m, 2H), 7.11 (t, J = 7.5 Hz, 2H), 6.94 (t, J = 7.2 Hz, 1H), 6.67 (d, J = 7.8 Hz, 2H), 4.99 (s, 1H), 3.74 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.3, 157.6, 139.9, 137.8, 134.5, 129.7, 129.6, 128.8, 128.2, 126.5, 123.4, 122.4, 91.3, 50.9. HRMS (ESI) m/z calcd for $C_{16}H_{14}ClNNaO_2^+$ [M + Na$^+$], 310.0605; found, 310.0598.

*(Z)-Methyl 3-((3,4-Dimethoxyphenyl)amino)-3-(p-tolyl)acrylate (**2n**).* Following the general procedure for 18 h, **2n** was isolated as a light yellow solid. Yield: 4.25 g, 65%, mp 84−85 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.23 (br s, 1H), 7.21 (d, J = 8.1 Hz, 2H), 7.07 (d, J = 8.0 Hz, 2H), 6.60 (d, J = 8.6 Hz, 1H), 6.29 (dd, J = 8.6, 2.5 Hz, 1H), 6.20 (d, J = 2.5 Hz, 1H), 4.94 (s, 1H), 3.77 (s, 3H), 3.73 (s, 3H), 3.55 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.6, 159.9, 148.6, 145.2, 139.4, 133.9, 133.2, 129.0, 128.2, 114.6, 111.1, 107.5, 88.9, 55.9, 55.5, 50.6, 21.3. HRMS (ESI) m/z calcd for $C_{19}H_{21}NNaO_4^+$ [M + Na$^+$], 350.1363; found, 350.1358.

*(Z)-Methyl 3-(4-Methoxyphenyl)-3-((3-(trifluoromethyl)phenyl)-amino)acrylate (**2o**).* Following the general procedure for 18 h, **2o** was isolated as a colorless oil. Yield: 3.23 g, 46%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.32 (br s, 1H), 7.27 (d, J = 8.7 Hz, 2H), 7.21−7.05 (m, 2H), 6.93 (s, 1H), 6.83 (d, J = 8.7 Hz, 2H), 6.77 (d, J = 7.8 Hz, 1H), 5.06 (s, 1H), 3.79 (s, 3H), 3.74 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.4, 161.0, 158.1, 141.3, 131.1 (q, J = 32.4 Hz), 129.6, 129.1, 127.3, 124.7, 123.7 (q, J = 272.4 Hz), 119.1 (q, J = 3.6 Hz), 118.4 (q, J = 3.4 Hz), 114.1, 91.8, 55.3, 50.8. HRMS (ESI) m/z calcd for $C_{18}H_{16}{}^{19}F_3NNaO_3^+$ [M + Na$^+$], 374.0974; found, 374.0963.

General Procedure for the Preparation of Indole-3-carboxylates 3.[11a,c] *N*-Aryl enamine **2** (10 mmol) was stirred in DMF (125 mL) together with $Pd(OAc)_2$ (10 mol %), $Cu(OAc)_2$ (30 mmol), and K_2CO_3 (30 mmol) at 60−140 °C under an atmosphere of argon. After completion of the reaction (as indicated by TLC), the reaction mixture was cooled to room temperature, diluted with EtOAc (150 mL), and filtered through a short pad of silica, which was then washed with EtOAc (600 mL). Removal of the solvent in vacuo and purification of the residue by column chromatography using a mixture of PE and EtOAc as eluent provided indole-3-carboxylate **3** as a white to light yellow solid.

Following this general procedure, known indole-3-carboxylates **3a**,[17,18] **3b**,[11b] **3h**,[6] and **3i**[11c,19] were prepared in 51, 48, 53, and 46% yields, respectively. The properties and ^{1}H NMR data of **3a−b** and **3h−i** were consistent with those in the literature. Novel indole-3-carboxylates **3c−g** and **3j−o** thus obtained were characterized as follows:

*Methyl 5-Methoxy-2-phenyl-1H-indole-3-carboxylate (**3c**).* Following the general procedure at 140 °C for 8 h, **3c** was isolated as a yellow solid. Yield: 2.44 g, 87%, mp 104−106 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.42 (br s, 1H), 7.72 (d, J = 2.4 Hz, 1H), 7.63 (dd, J = 7.6, 2.4 Hz, 2H), 7.50−7.41 (m, 3H), 7.27 (d, J = 8.8 Hz, 1H), 6.92 (d, J = 8.8 Hz, 1H), 3.91 (s, 3H), 3.81 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.0, 155.8, 144.9, 132.2, 130.3, 129.5, 129.1, 128.5, 128.1, 113.5, 111.9, 104.1, 103.7, 55.8, 50.8. HRMS (ESI) m/z calcd for $C_{17}H_{16}NO_3^+$ [M + H$^+$], 282.1125; found, 282.1123.

*Methyl 7-Methyl-2-phenyl-1H-indole-3-carboxylate (**3d**).* Following the general procedure at 110 °C for 4 h, **3d** was isolated as a white solid. Yield: 1.96 g, 74%, mp 152−153 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.55 (br s, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.62 (dd, J = 8.0, 1.9 Hz, 2H), 7.41−7.38 (m, 3H), 7.18 (t, J = 7.5 Hz, 1H), 7.05 (d, J = 7.5 Hz, 1H), 3.78 (s, 3H), 2.47 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.1, 144.6, 134.9, 132.2, 129.6, 129.1, 128.1, 127.2, 123.9, 122.3, 120.5, 119.8, 104.9, 50.9, 16.6. HRMS (ESI) m/z calcd for $C_{17}H_{16}NO_2^+$ [M + H$^+$], 266.1176; found, 266.1165.

*Methyl 7-Chloro-2-phenyl-1H-indole-3-carboxylate (**3e**).* Following the general procedure at 80 °C for 4 h, **3e** was isolated as a white solid. Yield: 2.24 g, 78%, mp 164−166 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.78 (br s, 1H), 8.08 (d, J = 7.8 Hz, 1H), 7.62 (m, 2H), 7.40 (br s, 3H), 7.24 (d, J = 7.5 Hz, 1H), 7.18 (t, J = 7.6 Hz, 1H), 3.80 (s, 3H).^{13}C NMR (150 MHz, $CDCl_3$) δ 165.4, 145.1, 132.5, 131.4, 129.6, 129.5, 129.0, 128.2, 122.8, 122.6, 120.8, 116.5, 105.5, 51.1. HRMS (ESI) m/z calcd for $C_{16}H_{13}ClNO_2^+$ [M + H$^+$], 286.0629; found, 286.0614.

*Methyl 6-Methoxy-2-phenyl-1H-indole-3-carboxylate (**3f**).* Following the general procedure at 100 °C for 12 h, **3f** was isolated as a light yellow solid. Yield: 1.60 g, 57%, mp 147−149 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.88 (br s, 1H), 8.02 (d, J = 9.0 Hz, 1H), 7.52−7.29 (5H), 6.79 (d, J = 9.0 Hz, 1H), 6.71 (s, 1H), 3.74 (s, 3H), 3.71 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.2, 157.0, 143.8, 136.1, 132.0, 129.4, 128.9, 128.1, 122.8, 121.8, 111.9, 104.0, 94.6, 55.6, 50.9. HRMS (ESI) m/z calcd for $C_{17}H_{16}NO_3^+$ [M + H$^+$], 282.1125; found, 282.1117.

*Methyl 6-Fluoro-2-phenyl-1H-indole-3-carboxylate (**3g**) and Methyl 4-Fluoro-2-phenyl-1H-indole-3-carboxylate (**3g′**).* Following the general procedure at 60 °C for 12 h, **3g** and **3g′** were isolated as two regioisomers. Yield: 1.51 g, 56% (**3g**/**3g′** = 56:44). **3g**: white solid, mp 202−205 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.24 (br s, 1H), 8.04 (dd, J = 9.0, 5,4 Hz, 1H), 7.70 (d, J = 6.6 Hz, 2H), 7.52−7.48 (m, 3H), 7.22 (dd, J = 9.0, 1.8 Hz, 1H), 7.08 (ddd, J = 9.6, 9.0, 1.8 Hz, 1H), 3.74 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 164.6, 159.1 (d, J = 235.6 Hz), 145.2 (d, J = 2.7 Hz), 135.5 (d, J = 2.7 Hz), 131.5, 129.8, 129.0, 127.9, 123.8, 122.5 (d, J = 9.8 Hz), 109.8 (d, J = 23.6 Hz), 102.7, 97.8 (d, J = 25.4 Hz), 50.5. HRMS (ESI) m/z calcd for $C_{16}H_{13}{}^{19}FNO_2^+$ [M + H$^+$], 270.0925; found, 270.0922. **3g′**: light yellow solid, mp 162−164 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.83 (br s, 1H), 7.53 (dd, J = 6.1, 2.7 Hz, 2H), 7.44−7.33 (m, 3H), 7.16−7.12 (m, 2H), 6.90 (dd, J = 11.2, 7.6 Hz, 1H), 3.76 (s, 3H).^{13}C NMR (150 MHz, $CDCl_3$) δ 165.6, 156.1 (d, J = 251.8 Hz), 143.3, 139.43, 137.8 (d, J = 10.1 Hz), 131.5, 129.2, 129.1, 128.3, 123.9 (d, J = 8.2 Hz), 115.6 (d, J = 19.1 Hz), 107.8 (d, J = 21.4 Hz), 104.0 (d, J = 2.4 Hz), 51.47. HRMS (ESI) m/z calcd for $C_{16}H_{13}{}^{19}FNO_2^+$ [M + H$^+$], 270.0925; found, 270.0916.

*Methyl 5-Chloro-2-(p-tolyl)-1H-indole-3-carboxylate (**3j**).* Following the general procedure at 90 °C for 15 h, **3j** was isolated as a yellow solid. Yield: 2.06 g, 69%, mp 194−196 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.76 (br s, 1H), 8.12 (s, 1H), 7.44 (d, J = 7.8 Hz, 2H), 7.21−7.15 (m, 2H), 7.13 (d, J = 7.8 Hz, 2H), 3.80 (s, 3H), 2.32 (s, 3H).^{13}C NMR (150 MHz, $CDCl_3$) δ 165.6, 146.2, 139.7, 133.5, 129.2, 128.9, 128.7, 128.4, 127.8, 123.4, 121.6, 112.1, 103.8, 51.0, 21.3. HRMS (ESI) m/z calcd for $C_{17}H_{15}ClNO_2^+$ [M + H$^+$], 300.0786; found, 300.0785.

*Methyl 2-(4-Methoxyphenyl)-5,7-dimethyl-1H-indole-3-carboxylate (**3k**).* Following the general procedure at 90 °C for 10 h, **3k** was isolated as a light yellow solid. Yield: 2.50 g, 81%, mp 148−149 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.42 (br s, 1H), 7.80 (s, 1H), 7.55 (d, J = 8.7 Hz, 2H), 6.97−6.82 (m, 3H), 3.82 (s, 3H), 3.78 (s, 3H), 2.46 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.2, 160.3, 144.6, 133.0, 131.7, 130.9, 127.5, 125.4, 124.5, 119.8, 119.3, 113.6, 104.0, 55.3, 50.8, 21.7, 16.5. HRMS (ESI) m/z calcd for $C_{19}H_{20}NO_3^+$ [M + H$^+$], 310.1438; found, 310.1434.

dx.doi.org/10.1021/jo4023292 | J. Org. Chem. XXXX, XXX, XXX−XXX

*Methyl 2-(3-Chlorophenyl)-1H-indole-3-carboxylate (**3l**).* Following the general procedure at 90 °C for 10 h, **3l** was isolated as a white solid. Yield: 1.21 g, 42%, mp 157−158 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.79 (br s, 1H), 8.18 (d, J = 6.7 Hz, 1H), 7.58 (s, 1H), 7.48 (d, J = 7.1 Hz, 1H), 7.32 (d, J = 7.0 Hz, 2H), 7.29−7.24 (m, 3H), 3.83 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.8, 142.8, 135.2, 134.0, 133.6, 129.4, 129.4, 129.2, 127.9, 127.3, 123.6, 122.3, 122.2, 111.3, 104.9, 51.1. HRMS (ESI) m/z calcd for $C_{16}H_{13}ClNO_2^+$ [M + H$^+$], 286.0629; found, 286.0627.

*Methyl 2-(4-Fluorophenyl)-1H-indole-3-carboxylate (**3m**).* Following the general procedure at 100 °C for 18 h, **3m** was isolated as a white solid. Yield: 0.78 g, 29%, mp 158−159 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.80 (br s, 1H), 8.16 (d, J = 7.2 Hz, 1H), 7.59−7.50 (m, 2H), 7.31 (d, J = 7.4 Hz, 1H), 7.28−7.24 (m, 2H), 7.03 (t, J = 8.5 Hz, 2H), 3.80 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.1, 163.2 (d, J = 249.7 Hz), 143.7, 135.2, 131.5 (d, J = 8.4 Hz), 127.9, 127.4, 123.4, 122.3, 122.1, 115.2 (d, J = 21.8 Hz), 111.2, 104.4, 51.0. HRMS (ESI) m/z calcd for $C_{16}H_{13}{}^{19}FNO_2^+$ [M + H$^+$], 270.0925; found, 270.0921.

*Methyl 5,6-Dimethoxy-2-(p-tolyl)-1H-indole-3-carboxylate (**3n**).* Following the general procedure at 80 °C for 18 h, **3n** was isolated as a white solid. Yield: 1.79 g, 55%, mp 148−151 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.77 (br s, 1H), 7.56 (d, J = 8.0 Hz, 2H), 7.55 (s, 1H), 7.28 (d, J = 8.0 Hz, 2H), 6.96 (s, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.72 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 165.1, 147.1, 145.9, 142.6, 137.9, 129.9, 129.5, 129.3, 128.4, 120.4, 103.4, 102.3, 94.9, 55.8, 55.6, 50.3, 20.9. HRMS (ESI) m/z calcd for $C_{19}H_{20}NO_4^+$ [M + H$^+$], 326.1387; found, 326.1382.

*Methyl 2-(4-Methoxyphenyl)-6-(trifluoromethyl)-1H-indole-3-carboxylate (**3o**).* Following the general procedure at 80 °C for 15 h, **3o** was isolated as a light yellow solid. Yield: 1.32 g, 53%, mp 191−192 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.48 (br s, 1H), 8.21 (d, J = 8.4 Hz, 1H), 7.73 (s, 1H), 7.70 (d, J = 8.7 Hz, 2H), 7.50 (d, J = 8.5 Hz, 1H), 7.10 (d, J = 8.6 Hz, 2H), 3.86 (s, 3H), 3.77 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 164.5, 160.2, 147.3, 134.3, 131.3, 130.0, 125.9 (q, J = 271.4 Hz), 123.1, 122.7 (q, J = 31.4 Hz), 121.9, 117.5 (q, J = 2.5 Hz), 113.4, 108.8 (q, J = 2.7 Hz), 102.4, 55.2, 50.7. HRMS (ESI) m/z calcd for $C_{18}H_{15}{}^{19}F_3NO_3^+$ [M + H$^+$], 350.0999; found, 350.0995.

Preparation of Indole-3-carboxamides 4.[10−12] To a solution of indole **3** (2.5 mmol) in THF (25 mL) was added NaOH (25 mmol) followed by the addition of iodomethane (5.0 mmol) (for substrate **4m**, benzyl bromide (2.5 mmol) was used instead). The solution was stirred for at room temperature for 2 h. After the completion of the reaction, the reaction mixture was evaporated in vacuum. Then, water (20 mL) and ethanol (20 mL) were added to the mixture, and the mixture was heated at 80 °C for 15 h. After the mixture was cooled and acidified with HCl(aq) (4 N), the precipitate was collected, washed with water, and dried in the air overnight to afford carboxylic acid.

Method A. To a solution of the carboxylic acid intermediate (1 mmol) in DCM (10 mL) was added thionyl chloride (2 mmol) dropwise at room temperature. After stirring at room temperature for 1 h, the dark mixture was added dropwise to a solution of methoxamine (4 mmol) in DCM (10 mL) at −20 to 0 °C. The reaction mixture was stirred at room temperature for 2 h, diluted with water (50 mL), extracted with DCM (50 mL × 3), and washed with brine (30 mL × 1). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to afford the crude amide. Purification by column chromatography using a mixture of PE and EtOAc as eluent gave substrate **4** as a white to yellow solid.

Method B. To a solution of the carboxylic acid intermediate (1 mmol) in DCM (10 mL) were added 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDCI, 1.1 mmol) and *N*-hydroxybenzotriazole (HOBT, 1.1 mmol). The mixture was stirred at room temperature for 1 h. Methoxamine (4 mmol) was then added. The reaction mixture was diluted with water (50 mL), extracted with DCM (50 mL × 3), and washed with brine (30 mL × 1). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to afford the crude amide. Purification by column chromatography using a mixture of PE and EtOAc as eluent gave substrate **4** as a solid.

*N-Methoxy-1-methyl-2-phenyl-1H-indole-3-carboxamide (**4a**).* Following general procedure A, **4a** was isolated as a white solid. Yield: 215.6 mg, 77%, mp 131−134 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.29 (d, J = 7.8 Hz, 1H), 7.73 (br s, 1H), 7.61−7.52 (m, 3H), 7.46 (dd, J = 6.3, 2.7 Hz, 2H), 7.35 (d, J = 7.9 Hz, 1H), 7.33 (t, J = 7.4 Hz, 1H), 7.29 (t, J = 7.1 Hz, 1H), 3.66 (s, 3H), 3.54 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.6, 141.4, 136.9, 130.8, 130.4, 130.0, 129.3, 126.8, 123.2, 122.0, 121.7, 109.7, 106.3, 64.4, 30.9. HRMS (ESI) m/z calcd for $C_{17}H_{16}N_2NaO_2^+$ [M + Na$^+$], 303.1104; found, 303.1102.

*N-Methoxy-1,5-dimethyl-2-phenyl-1H-indole-3-carboxamide (**4b**).* Following general procedure A, **4b** was isolated as a white solid. Yield: 129.4 mg, 44%, mp 171−174 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.71 (br s, 1H), 7.60−7.52 (m, 3H), 7.48−7.42 (m, 2H), 7.23 (d, J = 8.3 Hz, 1H), 7.14 (d, J = 8.3 Hz, 1H), 3.66 (s, 3H), 3.50 (s, 3H), 2.50 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.8, 141.3, 135.4, 131.5, 130.9, 130.4, 129.9, 129.2, 127.0, 124.7, 121.3, 109.3, 105.8, 64.4, 30.9, 21.6. HRMS (ESI) m/z calcd for $C_{18}H_{18}N_2NaO_2^+$ [M + Na$^+$], 317.1260; found, 317.1257.

*N,5-Dimethoxy-1-methyl-2-phenyl-1H-indole-3-carboxamide (**4c**).* Following general procedure A, **4c** was isolated as a light yellow solid. Yield: 142.6 mg, 46%, mp 145−148 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75 (d, J = 2.5 Hz, 1H), 7.60 (br s, 1H), 7.51−7.46 (m, 3H), 7.37−7.35 (m, 2H), 7.13 (d, J = 8.9 Hz, 1H), 6.87 (dd, J = 8.8, 2.5 Hz, 1H), 3.81 (s, 3H), 3.56 (s, 3H), 3.41 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.9, 155.9, 141.3, 132.0, 130.9, 130.4, 130.1, 129.3, 127.7, 113.9, 110.5, 105.8, 102.9, 64.3, 55.8, 30.9. HRMS (ESI) m/z calcd for $C_{18}H_{18}N_2NaO_3^+$ [M + Na$^+$], 333.1210; found, 333.1202.

*N-Methoxy-1,7-dimethyl-2-phenyl-1H-indole-3-carboxamide (**4d**).* Following general procedure A, **4d** was isolated as a white solid. Yield: 144.1 mg, 49%, mp 169−172 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.12 (d, J = 8.0 Hz, 1H), 7.68 (br s, 1H), 7.55−7.54 (m, 3H), 7.45−7.39 (m, 2H), 7.11 (t, J = 7.6 Hz, 1H), 7.00 (d, J = 7.1 Hz, 1H), 3.73 (s, 3H), 3.60 (s, 3H), 2.76 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.6, 142.1, 136.0, 131.1, 130.6, 130.0, 129.3, 127.7, 126.2, 121.9, 121.3, 119.6, 106.6, 64.3, 34.3, 20.3. HRMS (ESI) m/z calcd for $C_{18}H_{18}N_2NaO_2^+$ [M + Na$^+$], 317.1260; found, 317.1254.

*7-Chloro-N-methoxy-1-methyl-2-phenyl-1H-indole-3-carboxamide (**4e**).* Following general procedure A, **4e** was isolated as a white solid. Yield: 211.1 mg, 67%, mp 147−148 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.15 (d, J = 8.0 Hz, 1H), 7.79 (br s, 1H), 7.61−7.53 (m, 3H), 7.43−7.42 (m, 2H), 7.22 (d, J = 7.8 Hz, 1H), 7.11 (t, J = 7.8 Hz, 1H), 3.83 (s, 3H), 3.59 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.9, 142.9, 132.5, 130.5, 130.4, 130.2, 129.8, 129.4, 125.0, 122.3, 120.4, 117.0, 107.0, 64.2, 34.3. HRMS (ESI) m/z calcd for $C_{17}H_{15}ClN_2NaO_2^+$ [M + Na$^+$], 337.0714; found, 337.0710.

*4,N-Dimethoxy-1-methyl-2-phenyl-1H-indole-3-carboxamide (**4f**).* Following general procedure A, **4f** was isolated as a white solid. Yield: 226.3 mg, 73%, mp 159−161 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.12 (d, J = 8.8 Hz, 1H), 7.80 (br s, 1H), 7.61−7.48 (m, 3H), 7.43−7.42 (m, 2H), 6.90 (dd, J = 8.8, 2.2 Hz, 1H), 6.75 (d, J = 2.2 Hz, 1H), 3.86 (s, 3H), 3.62 (s, 3H), 3.45 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.7, 157.1, 140.3, 137.8, 130.9, 130.5, 129.9, 129.2, 122.4, 121.0, 111.5, 100.0, 93.2, 64.3, 55.7, 30.9. HRMS (ESI) m/z calcd for $C_{18}H_{18}N_2NaO_3^+$ [M + Na$^+$], 333.1210; found, 333.1203.

*6-Fluoro-N-methoxy-1-methyl-2-phenyl-1H-indole-3-carboxamide (**4g**).* Following general procedure A, **4g** was isolated as a light yellow solid. Yield: 172.8 mg, 58%, mp 166−168 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.24 (dd, J = 8.7, 5.5 Hz, 1H), 7.71 (br s, 1H), 7.65−7.52 (m, 3H), 7.51−7.38 (m, 2H), 7.07−6.99 (m, 2H), 3.64 (s, 3H), 3.49 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.2, 160.4 (d, J = 240.3 Hz), 159.6, 141.5 (d, J = 3.3 Hz), 137.1 (d, J = 12.1 Hz), 130.5, 130.4, 130.2, 129.4, 123.0 (d, J = 9.7 Hz), 123.0, 110.6 (d, J = 23.8 Hz), 96.1 (d, J = 26.4 Hz), 64.4, 31.0. HRMS (ESI) m/z calcd for $C_{17}H_{15}{}^{19}FN_2NaO_2^+$ [M + Na$^+$], 321.1010; found, 321.1006.

*N-Methoxy-1-methyl-2-(p-tolyl)-1H-indole-3-carboxamide (**4h**).* Following general procedure A, **4h** was isolated as a light yellow solid. Yield: 194.0 mg, 66%, mp 170−172 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.29 (d, J = 7.7 Hz, 1H), 7.83 (br s, 1H), 7.35 (d, J = 7.7 Hz,

dx.doi.org/10.1021/jo4023292 | J. Org. Chem. XXXX, XXX, XXX−XXX

2H), 7.33−7.21 (m, 5H), 3.65 (s, 3H), 3.48 (s, 3H), 2.46 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.8, 141.5, 140.2, 136.9, 130.3, 130.0, 127.6, 126.9, 123.0, 121.9, 121.7, 109.6, 106.1, 64.4, 30.8, 21.5. HRMS (ESI) m/z calcd for $C_{18}H_{18}N_2NaO_2^+$ [M + Na^+], 317.1260; found, 317.1258.

*N-Methoxy-1-methyl-2-(4-methoxyphenyl)-1H-indole-3-carboxamide (**4i**).* Following general procedure A, **4i** was isolated as a light yellow solid. Yield: 161.2, 52%, mp 169−172 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.30 (d, J = 7.4 Hz, 1H), 7.81 (br s, 1H), 7.37 (d, J = 8.7 Hz, 2H), 7.35−7.24 (m, 3H), 7.08 (d, J = 8.7 Hz, 2H), 3.90 (s, 3H), 3.68 (s, 3H), 3.51 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.8, 160.9, 141.4, 136.9, 131.8, 126.9, 123.0, 122.5, 121.9, 121.7, 114.8, 109.6, 106.2, 64.4, 55.5, 30.8. HRMS (ESI) m/z calcd for $C_{18}H_{18}N_2NaO_3^+$ [M + Na^+], 333.1210; found, 333.1204.

*5-Chloro-N-methoxy-1-methyl-2-(p-tolyl)-1H-indole-3-carboxamide (**4j**).* Following general procedure A, **4j** was isolated as a white solid. Yield: 246.0 mg, 75%, mp 169−170 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.76 (br s, 1H), 7.38 (d, J = 7.9 Hz, 2H), 7.33 (d, J = 7.9 Hz, 2H), 7.24−7.17 (m, 2H), 3.65 (s, 3H), 3.49 (s, 3H), 2.48 (s, 3H).^{13}C NMR (150 MHz, $CDCl_3$) δ 164.2, 142.4, 140.6, 135.3, 130.2, 130.2, 128.0, 127.7, 127.2, 123.4, 121.3, 110.6, 105.8, 64.4, 31.0, 21.5. HRMS (ESI) m/z calcd for $C_{18}H_{17}ClN_2NaO_2^+$ [M + Na^+], 351.0871; found, 351.0869.

*N-Methoxy-2-(4-methoxyphenyl)-1,5,7-trimethyl-1H-indole-3-carboxamide (**4k**).* Following the general procedure, **4k** was isolated as a light yellow solid. Yield: 260.3 mg, 77%, mp 199−200 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.69 (br s, 1H), 7.33 (d, J = 8.5 Hz, 2H), 7.06 (d, J = 8.5 Hz, 2H), 6.84 (s, 1H), 3.89 (s, 3H), 3.70 (s, 3H), 3.65 (s, 3H), 2.72 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.0, 160.7, 142.0, 134.4, 131.9, 131.3, 128.1, 127.8, 122.9, 120.8, 119.2, 114.8, 106.0, 64.4, 55.4, 34.1, 21.2, 20.1. HRMS (ESI) m/z calcd for $C_{20}H_{22}N_2NaO_3^+$ [M + Na^+], 361.1523; found, 361.1514.

*2-(3-Chlorophenyl)-N-methoxy-1-methyl-1H-indole-3-carboxamide (**4l**).* Following the general procedure, **4l** was isolated as a light yellow solid. Yield: 175.8 mg, 56%, mp 98−99 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.15 (br s, 1H), 8.06 (d, J = 7.9 Hz, 1H), 7.47 (t, J = 8.1 Hz, 1H), 7.44 (t, J = 7.7 Hz, 1H), 7.40 (s, 1H), 7.34−7.27 (m, 3H), 7.22 (t, J = 7.2 Hz, 1H), 3.64 (s, 3H), 3.49 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.4, 140.1, 136.9, 134.8, 132.4, 130.5, 130.3, 129.8, 128.8, 126.2, 123.3, 122.0, 121.2, 109.9, 106.6, 64.3, 31.0. HRMS (ESI) m/z calcd for $C_{17}H_{15}ClN_2NaO_2^+$ [M + Na^+], 337.0714; found, 337.0708.

*2-(4-Fluorophenyl)-N-Methoxy-1-methyl-1H-indole-3-carboxamide (**4m**).* Following the general procedure, **4m** was isolated as a light yellow solid. Yield: 226.5 mg, 76%, mp 157−158 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.18 (d, J = 7.8 Hz, 1H), 7.83 (br s, 1H), 7.49−7.41 (m, 2H), 7.36−7.23 (m, 5H), 3.69 (s, 3H), 3.53 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.65, 163.5 (d, J = 250.9 Hz), 140.7, 136.9, 132.5 (d, J = 8.4 Hz), 126.6, 126.3, 126.6 (d, J = 3.6 Hz), 123.3, 122.1, 121.4, 116.4 (d, J = 21.7 Hz), 116.3, 109.8, 106.4, 64.5, 30.9. HRMS (ESI) m/z calcd for $C_{17}H_{15}{}^{19}FN_2NaO_2^+$ [M + Na^+], 321.1010; found, 321.1008.

*N,5,6-Trimethoxy-1-methyl-2-(p-tolyl)-1H-indole-3-carboxamide (**4n**).* Following the general procedure, **4n** was isolated as a white solid. Yield: 240.7 mg, 68%, mp 188−200 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.74 (br s, 1H), 7.37 (d, J = 7.2 Hz, 2H), 7.32 (d, J = 7.2 Hz, 2H), 6.77 (s, 1H), 3.98 (s, 3H), 3.95 (s, 3H), 3.66 (s, 3H), 3.47 (s, 3H), 2.47 (s, 3H).^{13}C NMR (150 MHz, $CDCl_3$) δ 165.1, 147.6, 146.5, 140.1, 139.4, 131.2, 130.4, 130.1, 127.9, 120.1, 105.6, 103.1, 92.7, 64.4, 56.2, 30.9, 21.5 (one carbon signal missing because of peak overlap). HRMS (ESI) m/z calcd for $C_{20}H_{22}N_2NaO_4^+$ [M + Na^+], 377.1472; found, 377.1469.

*N-Methoxy-2-(4-methoxyphenyl)-1-methyl-6-(trifluoromethyl)-1H-indole-3-carboxamide (**4o**).* Following general procedure A, **4o** was isolated as a white solid. Yield: 245.7 mg, 65%, mp 163−164 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.75 (br s, 1H), 8.00 (s, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.46 (d, J = 8.6 Hz, 2H), 7.11 (d, J = 8.6 Hz, 2H), 3.85 (s, 3H), 3.70 (s, 3H), 3.59 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.4, 159.9, 144.2, 135.3, 131.9, 128.1, 125.2 (t, J = 271.6 Hz), 122.5 (d, J = 30.9 Hz), 121.6, 120.5, 116.9 (d, J = 3.1 Hz), 113.8, 108.3 (q, J = 3.7 Hz), 107.34, 62.9, 55.2, 31.1. HRMS (ESI) m/z calcd for $C_{19}H_{17}{}^{19}F_3N_2NaO_3^+$ [M + Na^+], 401.1083; found, 401.1082.

*1-Benzyl-N-methoxy-2-phenyl-1H-indole-3-carboxamide (**4p**).* Following general procedure A, **4p** was isolated as a white solid. Yield: 249.2 mg, 70%, mp 154−155 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.33 (d, J = 7.9 Hz, 1H), 7.75 (br s, 1H), 7.51− 7.50 (m, 1H), 7.48−7.44 (m, 2H), 7.39−7.35 (m, 2H), 7.31−7.25 (m, 1H), 7.24−7.18 (m, 5H), 6.86 (dd, J = 7.0, 2.5 Hz, 2H), 5.15 (s, 2H), 3.65 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.5, 141.4, 136.9, 136.6, 130.4, 130.1, 129.2, 128.8, 127.5, 127.1, 126.0, 123.5, 122.2, 121.9, 110.5, 107.1, 64.4, 47.6. HRMS (ESI) m/z calcd for $C_{23}H_{20}N_2NaO_2^+$ [M + Na^+], 379.1417; found, 379.1412.

General Procedure for the Conversion of Indole-3-carboxamides 4 to Indoloquinolinone 5.[20] To a solution of indole-3-carboxamide **4** (0.2 mmol) in DCE (10 mL) was added PIDA (0.24 mmol) gradually at room temperature for 1 h. Then, the mixture was treated with saturated $NaHCO_3$ (40 mL) and extracted with CH_2Cl_2 (20 mL × 3). The combined organic phases were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to remove the solvent. The given residue was purified by flash chromatography using a mixture of DCM and MeOH as eluent to provide desired indoloquinolinone **5**.

*5-Methoxy-11-methyl-5H-indolo[3,2-c]quinolin-6(11H)-one (**5a**).* Following the general procedure, **5a** was isolated as a yellow solid. Yield: 48 mg, 86%, mp 208−210 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.54 (d, J = 7.8 Hz, 1H), 8.34 (d, J = 8.1 Hz, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.61 (t, J = 7.8 Hz, 1H), 7.46−7.41 (m, 2H), 7.36−7.34 (m, 2H), 4.25 (s, 3H), 4.17 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.7, 139.7, 138.2, 136.7, 129.2, 124.7, 124.3, 122.9, 122.2, 122.1, 121.9, 113.2, 113.0, 109.0, 108.0, 63.0, 33.5. HRMS (ESI) m/z calcd for $C_{17}H_{15}N_2O_2^+$ [M + H^+], 279.1128; found, 279.1125.

*5-Methoxy-8,11-dimethyl-5H-indolo[3,2-c]quinolin-6(11H)-one (**5b**).* Following the general procedure, **5b** was isolated as a yellow solid. Yield: 50 mg, 85%, mp 245−246 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.30 (s, 1H), 8.28 (d, J = 8.2 Hz, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.57 (t, J = 7.8 Hz, 1H), 7.32 (t, J = 7.8 Hz, 1H), 7.28 (d, J = 8.4 Hz, 1H), 7.20 (d, J = 8.4 Hz, 1H), 4.17 (s, 3H), 4.16 (s, 3H), 2.50 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.8, 138.1, 138.0, 136.7, 131.5, 129.0, 126.2, 124.4, 122.8, 122.1, 121.7, 113.2, 113.2, 108.6, 107.5, 63.0, 33.5, 21.4. HRMS (ESI) m/z calcd for $C_{18}H_{17}N_2O_2^+$ [M + H^+], 293.1285; found, 293.1277.

*5,8-Dimethoxy-11-methyl-5H-indolo[3,2-c]quinolin-6(11H)-one (**5c**).* Following the general procedure, **5c** was isolated as a yellow solid. Yield: 53 mg, 86%, mp 203−204 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.23 (d, J = 8.2 Hz, 1H), 7.94 (d, J = 2.4 Hz, 1H), 7.72 (d, J = 8.6 Hz, 1H), 7.59−7.53 (m, 1H), 7.33−7.28 (m, 1H), 7.26 (d, J = 8.2 Hz, 1H), 7.00 (dd, J = 8.6, 2.4 Hz, 1H), 4.15 (s, 3H), 4.13 (s, 3H), 3.92 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.9, 155.6, 138.1, 136.6, 134.5, 129.0, 124.8, 122.7, 122.1, 115.2, 113.2, 109.9, 107.5, 102.9, 63.0, 55.8, 33.5 (one carbon signal missing because of peak overlap). HRMS (ESI) m/z calcd for $C_{18}H_{17}N_2O_3^+$ [M + H^+], 309.1234; found, 309.1232.

*5-Methoxy-10,11-dimethyl-5H-indolo[3,2-c]quinolin-6(11H)-one (**5d**).* Following the general procedure, **5d** was isolated as a yellow solid. Yield: 51 mg, 88%, mp 234−237 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.37 (d, J = 7.7 Hz, 1H), 8.13 (d, J = 8.1 Hz, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.53 (t, J = 7.7 Hz, 1H), 7.29−7.26 (m, 1H), 7.14 (t, J = 7.3 Hz, 1H), 7.03 (d, J = 7.3 Hz, 1H), 4.27 (s, 3H), 4.13 (s, 3H), 2.73 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.6, 139.5, 139.4, 136.7, 129.0, 128.2, 125.2, 123.3, 122.1, 122.0, 120.8, 120.1, 113.1, 112.8, 108.3, 63.0, 36.8, 20.7. HRMS (ESI) m/z calcd for $C_{18}H_{17}N_2O_2^+$ [M + H^+], 293.1285; found, 293.1279.

*10-Chloro-5-methoxy-11-methyl-5H-indolo[3,2-c]quinolin-6-(11H)-one (**5e**).* Following the general procedure, **5e** was isolated as a yellow solid. Yield: 52 mg, 84%, mp 237−240 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.49 (d, J = 7.8 Hz, 1H), 8.29 (d, J = 8.3 Hz, 1H), 7.79 (d, J = 8.3 Hz, 1H), 7.63 (t, J = 7.8 Hz, 1H), 7.36 (t, J = 7.8 Hz, 2H), 7.24 (t, J = 7.8 Hz, 1H), 4.58 (s, 3H), 4.16 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.3, 140.4, 137.1, 135.7, 129.7, 127.8, 126.9,

dx.doi.org/10.1021/jo4023292 | J. Org. Chem. XXXX, XXX, XXX−XXX

123.6, 122.9, 122.3, 121.0, 116.6, 113.4, 112.6, 108.4, 63.1, 36.8. HRMS (ESI) m/z calcd for $C_{17}H_{14}ClN_2O_2^+$ [M + H$^+$], 313.0738; found, 313.0735.

*5,9-Dimethoxy-11-methyl-5H-indolo[3,2-c]quinolin-6(11H)-one (**5f**).* Following the general procedure, **5f** was isolated as a yellow solid. Yield: 56 mg, 91%, mp 213−215 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.33 (d, J = 8.6 Hz, 1H), 8.21 (d, J = 8.1 Hz, 1H), 7.70 (d, J = 8.1 Hz, 1H), 7.53(t, J = 7.8 Hz, 1H), 7.29 (t, J = 7.8 Hz, 1H), 6.91 (dd, J = 8.6, 2.1 Hz, 1H), 6.76 (d, J = 2.1 Hz, 1H), 4.14 (s, 3H), 4.09 (s, 3H), 3.87 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.3, 155.6, 140.8, 137.5, 136.1, 128.6, 122.7, 122.4, 122.1, 118.1, 113.1, 111.0, 108.0, 99.9, 93.0, 63.0, 55.6, 33.5. HRMS (ESI) m/z calcd for $C_{18}H_{17}N_2O_3^+$ [M + H$^+$], 309.1234; found, 309.1228.

*9-Fluoro-5-methoxy-11-methyl-5H-indolo[3,2-c]quinolin-6(11H)-one (**5g**).* Following the general procedure, **5g** was isolated as a yellow solid. Yield: 48 mg, 81%, mp 198−200 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.38 (dd, J = 8.5, 5.6 Hz, 1H), 8.24 (d, J = 8.2 Hz, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.57 (t, J = 7.8 Hz, 1H), 7.32 (t, J = 7.7 Hz, 1H), 7.05−7.00 (m, 2H), 4.14 (s, 3H), 4.13 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.3 (d, J = 243.8 Hz), 155.4, 140.1 (d, J = 11.6 Hz), 136.4, 135.6, 129.2, 123.0 (d, J = 9.3 Hz), 122.6, 122.3, 120.5, 113.2, 112.8, 110.4 (d, J = 23.9 Hz), 107.8 (d, J = 3.6 Hz), 96.0 (d, J = 27.7 Hz), 63.1, 33.7. HRMS (ESI) m/z calcd for $C_{17}H_{14}{}^{19}FN_2O_2^+$ [M + H$^+$], 297.1034; found, 297.1027.

*5-Methoxy-3,11-dimethyl-5H-indolo[3,2-c]quinolin-6(11H)-one (**5h**).* Following the general procedure, **5h** was isolated as a yellow solid. Yield: 53 mg, 91%, mp 184−185 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.41 (d, J = 7.7 Hz, 1H), 7.98 (d, J = 8.3 Hz, 1H), 7.39 (s, 1H), 7.31−7.26 (m, 1H), 7.26−7.20 (m, 2H), 7.01 (dd, J = 8.3, 0.9 Hz, 1H), 4.11 (s, 3H), 3.99 (s, 3H), 2.43 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.7, 139.8, 139.4, 138.3, 136.6, 124.3, 124.2, 123.4, 122.6, 121.7, 121.6, 112.9, 110.4, 108.8, 107.0, 62.9, 33.2, 21.9. HRMS (ESI) m/z calcd for $C_{18}H_{17}N_2O_2^+$ [M + H$^+$], 293.1285; found, 293.1282.

*3,5-Dimethoxy-11-methyl-5H-indolo[3,2-c]quinolin-6(11H)-one (**5i**).* Following the general procedure, **5i** was isolated as a yellow solid. Yield: 58 mg, 94%, mp 231−232 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.44 (d, J = 7.7 Hz, 1H), 8.14 (d, J = 9.0 Hz, 1H), 7.37−7.32 (m, 2H), 7.32−7.28 (m, 1H), 7.15 (d, J = 2.5 Hz, 1H), 6.87 (dd, J = 9.0, 2.5 Hz, 1H), 4.14 (s, 3H), 4.10 (s, 3H), 3.92 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.7, 155.9, 155.6, 138.1, 136.6, 134.5, 129.0, 124.8, 122.7, 122.1, 115.2, 113.2, 109.9, 107.5, 102.9, 63.0, 55.8, 33.5. HRMS (ESI) m/z calcd for $C_{18}H_{17}N_2O_3^+$ [M + H$^+$], 309.1234; found, 309.1230.

*8-Chloro-5-methoxy-3,11-dimethyl-5H-indolo[3,2-c]quinolin-6(11H)-one (**5j**).* Following the general procedure, **5j** was isolated as a yellow solid. Yield: 61 mg, 93%, mp > 250 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.32 (s, 1H), 8.05 (d, J = 8.2 Hz, 1H), 7.43 (s, 1H), 7.19 (m, 2H), 7.11 (d, J = 8.2 Hz, 1H), 4.11 (s, 3H), 4.09 (s, 3H), 2.51 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.4, 140.4, 139.0, 137.7, 136.7, 127.4, 125.0, 124.5, 123.7, 122.7, 121.0, 113.1, 110.2, 109.9, 106.3, 63.0, 33.5, 22.0. HRMS (ESI) m/z calcd for $C_{18}H_{16}ClN_2O_2^+$ [M + H$^+$], 327.0895; found, 327.0891.

*3,5-Dimethoxy-8,10,11-trimethyl-5H-indolo[3,2-c]quinolin-6(11H)-one (**5k**).* Following the general procedure, **5k** was isolated as a yellow solid. Yield: 58 mg, 86%, mp 226−227 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.16 (s, 1H), 8.08 (d, J = 9.0 Hz, 1H), 7.20 (s, 1H), 6.90 (s, 1H), 6.89 (d, J = 9.0 Hz, 1H), 4.29 (s, 3H), 4.15 (s, 3H), 3.95 (s, 3H), 2.74 (s, 3H), 2.45 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.4, 155.9, 139.9, 138.5, 137.4, 131.4, 129.3, 125.5, 124.7, 120.2, 119.3, 109.9, 106.6, 105.9, 96.8, 62.8, 55.6, 36.6, 21.1, 20.6. HRMS (ESI) m/z calcd for $C_{20}H_{21}N_2O_3^+$ [M + H$^+$], 337.1547; found, 337.1546.

*2-Chloro-5-methoxy-11-methyl-5H-indolo[3,2-c]quinolin-6(11H)-one (**5l**) and 4-Chloro-5-methoxy-11-methyl-5H-indolo[3,2-c]-quinolin-6(11H)-one (**5l′**).* Following the general procedure, an inseparable mixture of **5l** and **5l′** was obtained as a yellow solid. Yield: 52 mg, 83% (**5l**/**5l′** = 10:1), mp 199−200 °C. **5l**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.53 (d, J = 7.8 Hz, 1H), 8.28 (s, 1H), 7.74 (d, J = 8.9 Hz, 1H), 7.56 (d, J = 8.9 Hz, 1H), 7.49−7.45 (m, 2H), 7.37 (t, J = 6.8 Hz, 1H), 4.26 (s, 3H), 4.17 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.3, 139.6, 136.7, 135.1, 129.2, 127.7, 125.1, 123.9, 122.3, 122.2, 122.1, 114.6, 113.9, 109.1, 108.6, 63.2, 33.4. HRMS (ESI) m/z calcd for $C_{17}H_{14}ClN_2O_2^+$ [M + H$^+$], 313.0738; found, 313.0732.

*3-Fluoro-5-methoxy-11-methyl-5H-indolo[3,2-c]quinolin-6(11H)-one (**5m**).* Following the general procedure, **5m** was isolated as a yellow solid. Yield: 47 mg, 79%, mp 224−225 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.43 (d, J = 7.8 Hz, 1H), 8.23 (dd, J = 8.7, 5.7 Hz, 1H), 7.41−7.38 (m, 1H), 7.38−7.34 (m, 2H), 7.30 (t, J = 6.9 Hz, 1H), 7.05 (dd, J = 11.5, 5.2 Hz, 1H), 4.15 (s, 3H), 4.14 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.2 (d, J = 254.8 Hz), 155.7, 139.4, 138.4 (d, J = 10.9 Hz), 137.8, 124.9 (d, J = 9.9 Hz), 124.7, 124.0, 122.1, 121.8, 110.2 (d, J = 23.3 Hz), 109.5 (d, J = 2.4 Hz), 109.0, 106.9, 100.2 (d, J = 27.8 Hz), 63.2, 33.4. HRMS (ESI) m/z calcd for $C_{17}H_{14}{}^{19}FN_2O_2^+$ [M + H$^+$], 297.1034; found, 297.1029.

*5,8,9-Trimethoxy-3,11-dimethyl-5H-indolo[3,2-c]quinolin-6-(11H)-one (**5n**).* Following the general procedure except that 1.1 equiv of PIFA and DCM were employed instead of PIDA and DCE, **5n** was isolated as a gray solid. Yield: 53 mg, 75%, mp 191−192 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.93 (d, J = 8.2 Hz, 1H), 7.82 (s, 1H), 7.40 (s, 1H), 7.03 (d, J = 8.2 Hz, 1H), 6.64 (s, 1H), 4.12 (s, 3H), 3.98 (s, 3H), 3.93 (s, 3H), 3.91 (s, 3H), 2.48 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.9, 148.4, 146.1, 138.8, 136.7, 135.7, 133.8, 123.4, 122.0, 116.7, 112.9, 110.8, 106.6, 102.5, 92.1, 63.0, 56.2, 56.0, 33.3, 21.9. HRMS (ESI) m/z calcd for $C_{20}H_{21}N_2O_4^+$ [M + H$^+$], 353.1496; found, 353.1494.

*3,5-Dimethoxy-11-methyl-9-(trifluoromethyl)-5H-indolo[3,2-c]-quinolin-6(11H)-one (**5o**).* Following the general procedure except that 1.1 equiv of PIFA and DCM were employed instead of PIDA and DCE, **5o** was isolated as a gray solid. Yield: 62 mg, 82%, mp > 250 °C. ^{1}H NMR (600 MHz, DMSO) δ 8.51 (d, J = 8.9 Hz, 1H), 8.39 (d, J = 7.9 Hz, 1H), 8.22 (s, 1H), 7.59 (d, J = 7.9 Hz, 1H), 7.20 (s, 1H), 7.05 (d, J = 8.6 Hz, 1H), 4.34 (s, 3H), 4.07 (s, 3H), 3.95 (s, 3H). Unfortunately, the poor solubility of **5o** prevented ^{13}C NMR characterization. HRMS (ESI) m/z calcd for $C_{19}H_{16}{}^{19}F_3N_2O_3^+$ [M + H$^+$], 377.1108; found, 377.1103.

*11-Benzyl-5-methoxy-5H-indolo[3,2-c]quinolin-6(11H)-one (**5p**).* Following the general procedure, **5p** was isolated as a yellow solid. Yield: 60 mg, 85%, mp > 250 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.62−8.52 (m, 1H), 7.86 (d, J = 8.2 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.46 (t, J = 7.8 Hz, 1H), 7.31−7.30 (m, 3H), 7.26 (t, J = 7.3 Hz, 2H), 7.22 (t, J = 7.3 Hz, 1H), 7.11−7.06 (m, 3H), 5.76 (s, 2H), 4.14 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.7, 140.0, 138.1, 136.7, 136.0, 129.3, 129.2, 127.9, 125.7, 125.1, 124.4, 123.0, 122.4, 122.4, 122.1, 113.1, 112.3, 109.3, 108.5, 63.1, 49.2. HRMS (ESI) m/z calcd for $C_{23}H_{19}N_2O_2^+$ [M + H$^+$], 355.1441; found, 355.1439.

General Procedure for the Preparation of Bioactive Indoloquinolinones A1 and D.[13] To a solution of **5a** or **5p** (0.5 mmol) in DMF was added NaH (60% in mineral oil, 5 mmol) gradually. The reaction mixture was heated at 120 °C for 1 h. After cooling to room temperature, the reaction mixture was diluted with water (50 mL), extracted with EtOAc (50 mL × 3), and washed with brine (30 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to remove the solvent. The residue was purified by flash chromatography using a mixture of PE and EtOAc as eluent.

Following this general procedure, indoloquinolinones **A1**[21] and **D**[7] were prepared in 87 and 52% yields, respectively. The properties and ^{1}H NMR data of **A1** and **D** were in consistent with those in the literature.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: duyunfeier@tju.edu.cn (Y.D.).
*E-mail: kangzhao@tju.edu.cn (K.Z.).

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Y.D. acknowledges the National Natural Science Foundation of China (21072148), the Foundation (B) for Peiyang Scholar−Young Core Faculty of Tianjin University (2013XR-0144), and the Innovation Foundation of Tianjin University (2013XJ-0005) for financial support.

■ REFERENCES

(1) (a) Tominaga, M.; Tone, H.; Nakagawa, K.; Takada, K.; Hoshino, Y.; Watanabe, K. *Chem. Pharm. Bull.* **1981**, *29*, 2166. (b) Tzeng, C. C.; Lee, K. H.; Wang, T. C.; Han, C. H.; Chen, Y. L. *Pharm. Res.* **2000**, *17*, 715. (c) Segraves, N. L.; Crews, P. *J. Nat. Prod.* **2005**, *68*, 1484. (d) Wang, F. F.; Xu, M. J.; Lin, W. H.; Li, Q. S.; Sattler, I. *Molecules* **2010**, *15*, 2782.

(2) (a) Xiao, Z. L.; Waters, N. C.; Woodard, C. L.; Li, Z. Y.; Li, P. K. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2875. (b) Chen, Y. L.; Chung, C. H.; Chen, I. L.; Chen, P. H.; Jeng, H. Y. *Bioorg. Med. Chem.* **2002**, *10*, 2705.

(3) (a) Fang, K. C.; Chen, Y. L.; Sheu, J. Y.; Wang, T. C.; Tzeng, C. C. *J. Med. Chem.* **2000**, *43*, 3809. (b) Chen, Y. L.; Fang, K. C.; Sheu, J. Y.; Hsu, S. L.; Tzeng, C. C. *J. Med. Chem.* **2001**, *44*, 2374. (c) Hayashi, K.; Choshi, T.; Chikaraishi, K.; Oda, A.; Yoshinaga, R.; Hatae, N.; Ishikura, M.; Hibino, S. *Tetrahedron* **2012**, *68*, 4274.

(4) Walser, A.; Silverman, G.; Flynn, T.; Fryer, R. I. *J. Heterocycl. Chem.* **1975**, *12*, 351.

(5) Li, S. H.; Ma, S. M. *Adv. Synth. Catal.* **2012**, *354*, 2387.

(6) Zhou, L.; Doyle, M. P. *J. Org. Chem.* **2009**, *74*, 9222.

(7) Shi, Z. J.; Ren, Y. W.; Li, B.; Lu, S. C.; Zhang, W. *Chem. Commun.* **2010**, *46*, 3973.

(8) (a) Bergman, J.; Engqvist, R.; Stalhandsk, C.; Wallberg, H. *Tetrahedron* **2003**, *59*, 1033. (b) Primik, M. F.; Göschl, S.; Jakupec, M. A.; Roller, A.; Keppler, B. K.; Arion, V. B. *Inorg. Chem.* **2010**, *49*, 11084.

(9) (a) Herrero, M. T.; Tellitu, I.; Dominguez, E.; Hernandez, S.; Moreno, I.; SanMartin, R. *Tetrahedron* **2002**, *58*, 8581. (b) Herrero, M. T.; Tellitu, I.; Dominguez, E.; Moreno, I.; SanMartin, R. *Tetrahedron Lett.* **2002**, *43*, 8273. (c) Herrero, M. T.; Tellitu, I.; Hernandez, S.; Dominguez, E.; Moreno, I.; SanMartin, R. *ARKIVOC* **2002**, *V*, 31. (d) Serna, S.; Tellitu, I.; Dominguez, E.; Moreno, I.; SanMartin, R. *Tetrahedron Lett.* **2003**, *44*, 3483. (e) Serna, S.; Tellitu, I.; Dominguez, E.; Moreno, I.; SanMartin, R. *Tetrahedron* **2004**, *60*, 6533. (f) Correa, A.; Tellitu, I.; Dominguez, E.; Moreno, I.; SanMartin, R. *J. Org. Chem.* **2005**, *70*, 2256. (g) Churruca, F.; SanMartin, R.; Tellitu, I.; Dominguez, E. *Eur. J. Org. Chem.* **2005**, 2481. (h) Churruca, F.; SanMartin, R.; Carril, M.; Urtiaga, M. K.; Solans, X.; Tellitu, I.; Dominguez, E. *J. Org. Chem.* **2005**, *70*, 3178. (i) Serna, S.; Tellitu, I.; Dominguez, E.; Moreno, I.; SanMartin, R. *Org. Lett.* **2005**, *7*, 3073. (j) Correa, A.; Tellitu, I.; Dominguez, E.; SanMartin, R. *J. Org. Chem.* **2006**, *71*, 8316. (k) Correa, A.; Tellitu, I.; Dominguez, E.; SanMartin, R. *J. Org. Chem.* **2006**, *71*, 3501. (l) Correa, A.; Tellitu, I.; Dominguez, E.; SanMartin, R. *Tetrahedron* **2006**, *62*, 11100. (m) Tellitu, I.; Urrejola, A.; Serna, S.; Moreno, I.; Herrero, M. T.; Dominguez, E.; SanMartin, R.; Correa, A. *Eur. J. Org. Chem.* **2007**, 437. (n) Tellitu, I.; Serna, S.; Herrero, M. T.; Moreno, I.; Dominguez, E.; SanMartin, R. *J. Org. Chem.* **2007**, *72*, 1526. (o) Wang, G. W.; Yuan, T. T.; Li, D. D. *Angew. Chem., Int. Ed.* **2011**, *50*, 1380. (p) Gui, Q. W.; Yang, Z. Y.; Chen, X.; Liu, J. D.; Tan, Z.; Guo, R. Q.; Yu, W. *Synlett* **2013**, *24*, 1016.

(10) (a) Bogatskii, A. V.; Kondrat'eva, R. V.; Galatina, A. I.; Novikova, N. S. *J. Org. Chem. USSR* **1986**, *22*, 1286. (b) Kong, A. D.; Han, X. L.; Lu, X. Y. *Org. Lett.* **2006**, *8*, 1339. (c) Suzuki, T.; Imai, K.; Nakagawa, H.; Miyata, N. *ChemMedChem* **2006**, *1*, 1059. (d) Mitsuru, M.; Azusa, F.; Tetsuya, S.; Koji, H.; Masahiro, M. *Chem.—Eur. J.* **2009**, *15*, 3674. (e) Chen, Y.; Cho, C. H.; Shi, F.; Larock, R. C. *J. Org. Chem.* **2009**, *74*, 6802. (f) Johansson, H.; Jorgensen, T. B.; Gloriam, D. E.; Braeuner-Osborne, H.; Pedersen, D. S. *RSC Adv.* **2013**, *3*, 945.

(11) (a) Würtz, S.; Rakshit, S.; Neumann, J. J.; Dröge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2008**, *47*, 7230. (b) Yu, W. Q.; Du, Y. F.; Zhao, K. *Org. Lett.* **2009**, *11*, 2417. (c) Neumann, J. J.; Rakshit, S.; Dröge, T.; Würtz, S.; Glorius, F. *Chem.—Eur. J.* **2011**, *17*, 7298.

(12) (a) Rao, V. V. R.; Wentrup, C. *J. Chem. Soc., Perkin Trans. 1* **2002**, *10*, 1232. (b) Zheng, H. J.; Chen, W. B.; Deng, J. G.; Lin, W. Q.; Yuan, W. C.; Zhang, X. M.; Wu, Z. J. *Chem.—Eur. J.* **2008**, *14*, 9864. (c) Zhao, M.; Wang, F.; Li, X. M. *Org. Lett.* **2012**, *14*, 1412.

(13) Zhong, H. B.; Yang, D.; Wang, S. Q.; Huang, J. H. *Chem. Commun.* **2012**, *48*, 3236.

(14) Fustero, S.; Torre, M. G.; Jofré, V.; Carlon, R. P.; Navarro, A.; Fuentes, A. S.; Carrió, J. S. *J. Org. Chem.* **1998**, *63*, 8825.

(15) Zhang, X.; Yang, B.; Li, G. Z.; Shu, X.; Mungra, D. C.; Zhu, J. *Synlett* **2012**, *23*, 622.

(16) Dai, Q.; Yang, W. R.; Zhang, X. M. *Org. Lett.* **2005**, *7*, 5343.

(17) Gabriele, B.; Veltri, L.; Mancuso, R.; Salerno, G.; Costa, M. *Eur. J. Org. Chem.* **2012**, *13*, 2549.

(18) Yang, J. F.; Liu, S. J.; Zheng, J. F.; Zhou, J. R. *Eur. J. Org. Chem.* **2012**, *31*, 6248.

(19) Irvine, R. W.; Summers, J. C.; Taylor, W. C. *Aust. J. Chem.* **1983**, *36*, 1419.

(20) Miyasaka, M.; Fukushima, A.; Satoh, T.; Hirano, K.; Miura, M. *Chem.—Eur. J.* **2009**, *15*, 3674.

(21) (a) Li, H. B.; Yang, H.; Petersen, J. L.; Wang, K. K. *J. Org. Chem.* **2004**, *69*, 4500. (b) Imai, K.; Inokuchi, T.; Pang, C. Q.; Wang, M. Q.; Wang, N.; Yonezawa, M.; Zhang, Y.; Nokami, J. *Bull. Chem. Soc. Jpn.* **2013**, *86*, 864.