JOC The Journal of Organic Chemistry

pubs.acs.org/joc Article

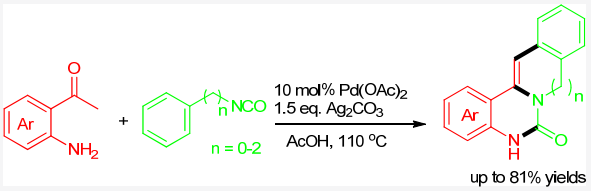
Expeditious Approach to Indoloquinazolinones via Double Annulations of *o*-Aminoacetophenones and Isocyanates

Yuxin Ding,[#] Huihui Yan,[#] Rener Chen, Xuqiong Xiao, Zhiming Wang, Lei Wang, and Yongmin Ma*

Cite This: *J. Org. Chem.* 2021, 86, 1448−1455 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: A novel procedure for a one-pot cascade reaction of *o*-aminoacetophenones and aryl/aliphatic isocyanates catalyzed/oxidized by the [Pd]/[Ag] system was developed. The reaction involves two C−N bond and one C−C bond formations during the double annulation process and the desired indoloquinazolinones and derivatives were afforded up to 81% yields from readily available substrates with a tolerance of a broad variety.



INTRODUCTION

Quinazolinone[1] and indole[2] are two important structural motifs which can be found in many natural products and synthetic pharmaceutical compounds, exhibiting a broad spectrum of biological activities. Indole-fused quinazolinones such as indoloquinazolinone derivatives are shown to possess a variety of promising biological activities, including antibacterial,[3] anticancer,[4] and antifungal activities.[5] One typical example is tryptanthrin (6-oxo indolo[1,2-*b*]quinazolinone), which has been found in many kinds of plants[3a,6] and exhibits intriguing biological properties such as anticancer, antibacterial, antifungal antiprotozoal, antiparasitic, and antitubercular activities.[6b,7] As such, the indole-fused quinazolinones have attracted considerable attention as a pharmacophore.

To date, several synthetic methods have been developed to prepare the indoloquinazolinones. The general procedure for preparation of indoloquinazolinones is performed by a coupling of isatin and isatoic anhydride under basic conditions.[8] Vaidya and Argade reported an aryne insertion reaction to a variety of quinazolinones to achieve a concise total synthesis of phaitanthrins.[9] Wang and co-workers developed a concise method for the preparation of tryptanthrins from indoles and indoline-2,3-diones via copper-catalyzed aerobic oxidation.[10] Takemoto et al. described a palladium(0)-catalyzed cyclization of chloroquinazolinones via C−H functionalization for the synthesis of indoloquinazolinones.[11] Lv and co-workers utilized gem-dibromovinyl systems to build the indoloquinazolinones framework by a copper-catalyzed domino intramolecular cyclization.[12] Alternatively, indoloquinazolinones can also be synthesized based on a rearrangement of 11-oxo-10,11-dihydrodibenzo[*b*,*f*]azepine-5-carbonnitrile under basic conditions[13] or from 2-iodobenzamide and indole derivatives via palladium-catalyzed intramolecular C−H amidation in the presence of a stoichiometric amount of silver salt as oxidant.[14] Recently, Badigenchala and Sekar reported NIS-mediated cross-coupling of C(sp^2)-H and N−H bonds toward an approach of indoloquinazolinones.[15] However, all the above cited protocols are presented on the synthesis of indolo[1,2-*a*]quinazolinones (Figure 1A) or indolo[1,2-*b*]quinazolinones (Figure 1B). There are a very few methods available for the synthesis of indolo[1,2-*c*]quinazolinones (Figure 1C).[16]

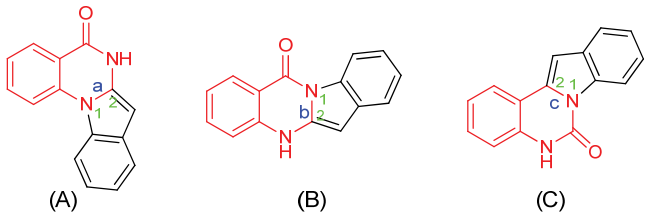


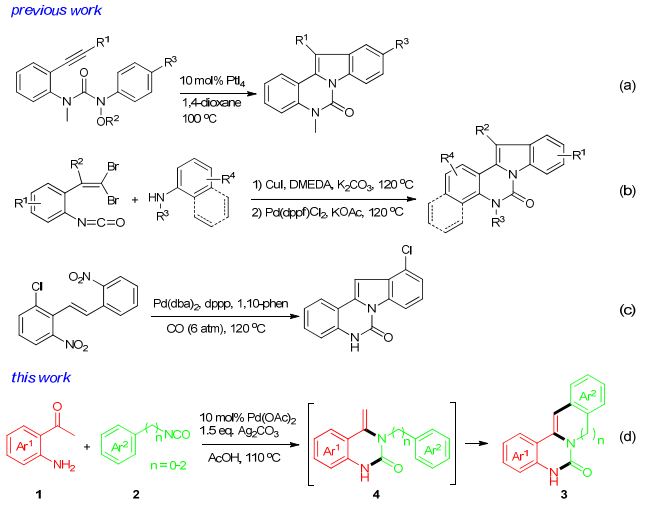
Figure 1. Types of indoloquinazolinones.

Nakamura et al. described a platinum-catalyzed cyclization of ortho-alkynylphenylureas to afford the corresponding tetracyclic indoloquinazolinones (Scheme 1a).[16c] Bao et al. developed a one-pot synthesis of indoloquinazolinones through a nucleophilic addition/Cu-catalyzed N-arylation/Pd-catalyzed C−H activation (Scheme 1b).[16d] The Soderberg group reported a palladium-catalyzed carbon monoxide mediated reductive cyclizations of chloro-substituted 1,2-bis(2-nitrophenyl)alkenes (Scheme 1c).[16e] However, all the reported reactions suffer from one or more drawbacks, such as the use of complex raw materials or multistep preparation of starting materials, expensive catalysts, and harsh reaction conditions. Thus, a great demand exists for a straightforward,

Received: September 6, 2020
Published: December 29, 2020

https://dx.doi.org/10.1021/acs.joc.0c02155
J. Org. Chem. 2021, 86, 1448−1455

Scheme 1. Previous Reported Synthesis of Indolo[1,2-*c*]quinazolinones and Our Work

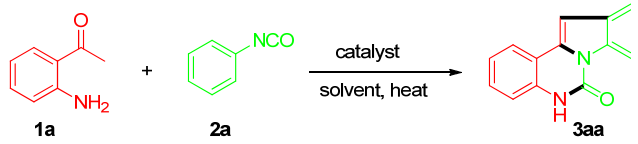


convenient protocol for the synthesis of indolo[1,2-*c*]-quinazolinones. We have previously reported a cyclization of 2-aminoacetophenones with isocyanate to form 4-methylene-quinazolinones (**4**) promoted by sodium hydroxide.[17] Encouraged by several reports of palladium-catalyzed C−H activation and C−C bond formation,[18] we envisioned that the *in situ* resultant compound **4** could perform a palladium-catalyzed intramolecular C−C bond formation to afford indolo[1,2-*c*]quinazolinone in a one-pot fashion. Herein, we wish to report an efficient and atom-economical method for direct cascade reaction of *o*-aminoacetophenones and aryl isocyanates for a one-pot formation of indolo[1,2-*c*]-quinazolinones via intermediate **4** (Scheme 1d).

RESULTS AND DISCUSSION

Initially, we began our study with *o*-aminoacetophenone (**1a**) and phenylisocyanate (**2a**) as a model to investigate the optimal reaction conditions (Table 1). When **1a** and **2a** at 1 equiv in the presence of $Pd(OAc)_2$ (10 mol %) was refluxed in toluene under air atmosphere for 24 h, to our delight, the desired double-annulated product 9-methylindolo[1,2-*c*]-quinazolin-6(5H)-one (**3aa**) was obtained in 21% yield (entry 1). Other catalysts such as Ag_2CO_3, $Cu(OAc)_2$, and $Co(OAc)_2$ were also examined but none was found to be effective for the annulation (entries 2−4). It is well-known that copper and silver salts have been widely used as oxidants in palladium-catalyzed arylation reactions.[18c,e,19] Therefore, we chose $Cu(OAc)_2$, $Cu(OTf)_2$, Ag_2CO_3, and Ag_2O as the additive for the reaction. Among the additives selected (entries 5−8), only Ag_2CO_3 (1 equiv) gave significant improvement of the product yield from 21% to 48%. The reaction was also successively carried out under N_2 atmosphere, indicating that oxygen from air was not involved in the oxidation process (entry 7). The yield of the product was slightly increased by replacing Ag_2CO_3 with AgOAc (entry 8). Although the conversion rate of the starting materials is high in the presence of Ag_2O, a mixture of unidentified compounds was detected (entry 9). A slight improvement was achieved when Ag_2CO_3 (1.5 equiv) was used (entry 10). We then screened the effect of solvent on the reaction. When toluene was replaced by other solvents (entries 11−15), the yield varies and acetic acid was found to be the most effective solvent for the catalytic reaction

Table 1. Optimization of Reaction Conditions[a]



1a 2a 3aa

entry	solvent	catalyst	additive (equiv)	*T* (°C)	yield (%)
1	$PhCH_3$	$Pd(OAc)_2$	-	110	21
2	$PhCH_3$	Ag_2CO_3	-	110	0
3	$PhCH_3$	$Cu(OAc)_2$	-	110	trace
4	$PhCH_3$	$Co(OAc)_2$	-	110	0
5	$PhCH_3$	$Pd(OAc)_2$	$Cu(OAc)_2$ (1)	110	30
6	$PhCH_3$	$Pd(OAc)_2$	$Cu(OTf)_2$ (1)	110	20
7	$PhCH_3$	$Pd(OAc)_2$	Ag_2CO_3 (1)	110	48, 46[b]
8	$PhCH_3$	$Pd(OAc)_2$	AgOAc (2)	110	52
9	$PhCH_3$	$Pd(OAc)_2$	Ag_2O (1)	110	0[c]
10	$PhCH_3$	$Pd(OAc)_2$	Ag_2CO_3 (1.5)	110	52
11	PhCl	$Pd(OAc)_2$	Ag_2CO_3 (1.5)	110	23
12	DMF	$Pd(OAc)_2$	Ag_2CO_3 (1.5)	110	13
13	DMSO	$Pd(OAc)_2$	Ag_2CO_3 (1.5)	110	trace
14	**AcOH**	**$Pd(OAc)_2$**	**Ag_2CO_3(1.5)**	**110**	**80**
15	CF_3CO_2H	$Pd(OAc)_2$	Ag_2CO_3 (1.5)	75	0
16	AcOH	$Pd(OAc)_2$	Ag_2CO_3 (1.5)	80	0
17	AcOH	$Pd(OAc)_2$	Ag_2CO_3 (1.5)	100	trace
18	AcOH	$Pd(OAc)_2$	Ag_2CO_3(1.5)	120	78

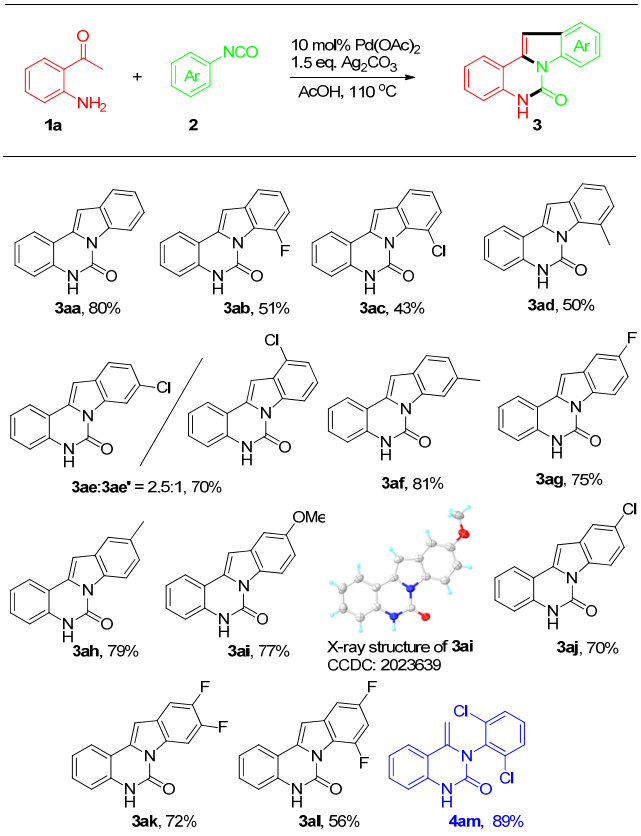
[a]Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), catalyst (10 mol %), solvent (3 mL), and an additive at the indicated amount in a sealed tube at 110 °C for 24 h. [b]Reaction under N_2 atmosphere; [c]The starting materials were consumed, and unidentified mixtures were detected.

(entry 14). The effect of temperature on the reaction was also examined. The desired product **3aa** was obtained at 80% yield at 110 °C (entry 14). Surprisingly, decreasing the temperature slightly leads to a dramatic drop of the yield (entries 16 and 17 vs 14). On the other hand, no marked improvement of the yield was achieved when the temperature was increased from 110 to 120 °C (entry 18 vs 14). Therefore, the optimal reaction conditions were established as depicted in entry 14.

Under the optimal reaction conditions, the generality of the synthetic protocol for various aryl isocyanates **2** was investigated (Table 2). A series of *ortho*-, *meta*-, and *para*-substituted aryl isocyanates containing an electron-donating group (−Me, −OMe) or an electron-withdrawing group (−F, −Cl) were investigated and the corresponding indolo[1,2-*c*]quinazolinones were achieved in moderate to good yields (**3aa**−**3aj**). In order to confirm the structures, **3ai** (CCDC2023639) was analyzed by X-ray crystallography (see the Supporting Information). Both electron-donating group (EDG) and electron-withdrawing group (EWG) on the aryl ring were tolerated in the reaction conditions. However, the yields of the products bearing with an EDG were markedly higher than those bearing an EWG (**3ad** vs **3ab**−**3ac**, **3af** vs **3ae**, **3ah** vs **3ag**). On the other hand, the stereochemistry significantly influenced the yield. For instance, *para*- and *meta*-methyl substituted isocyanates gave the desired products at 79% and 81% yield, respectively, whereas *ortho*-methyl isocyanate only provided the corresponding indoloquinazolinone at 50% yield (**3ad**, **3af**, and **3ah**). Same results were achieved for chloro- and fluoro-substituted analogues (**3ae** vs **3ac** and **3ag** vs **3ab**). It is worthy to mention that when *ortho*-chloro isocyanate (**2c**) was investigated for the annulation

https://dx.doi.org/10.1021/acs.joc.0c02155
J. Org. Chem. 2021, 86, 1448−1455

Table 2. Substrate Scope Based on Aryl Isocyanates[a]

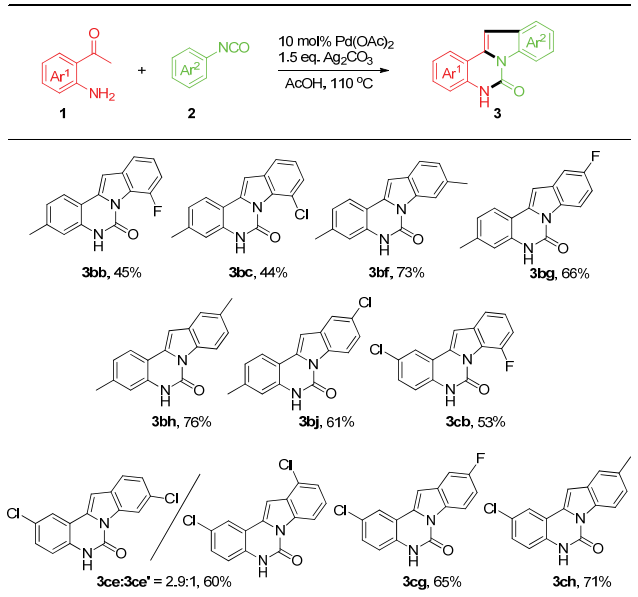


[a]Reaction conditions: **1a** (1 mmol), **2** (1 mmol), $Pd(OAc)_2$ (10 mol %), Ag_2CO_3 (1.5 mmol), and AcOH (3 mL) in a sealed tube at 110 °C for 24 h.

reaction, the C−Cl bond were found to be inactive in the Pd(II)/Ag(I) catalytic system as the corresponding indoloquinazolinones resulted from the cross-coupling between the C−H bond from **1** and the C−Cl bond from isocyanates **2** were not detected. On the other hand, two regioisomeric indoloquinazolinones were afforded when *meta*-chloro isocyanate (**2e**) was employed. Most likely because of the steric factor, less crowded indoloquinazolinones predominated, which the annulation mainly occurred at the *para*-position of the isocyano group. In addition, disubstituted isocyanates were also investigated and the corresponding indoloquinazolinones were furnished in moderate yields (**3ak** and **3al**). Furthermore, when 2,6-dichloro isocyanate (**2m**) was attempted for the reaction where both *ortho*-positions of the isocyano group were blocked with a chloro group, the desired indoloquinazolinone failed to be afforded. Instead, quinazolinone (**4am**) was obtained in a high yield. This result also demonstrated that the C−Cl bond is inactive in this Pd(II)/Ag(I) catalytic system. In addition, several aryl isothiocyanates were examined to react with **1a** under the standard conditions but all failed.

To further explore the universality of the double annulation reaction, another two substituted 2-aminoacetophenones (**1b** and **1c**) were also investigated. One contains a methyl group and the other is a chloro-substituted analogue. In a similar fashion to the aforesaid reaction, both electronic nature and steric nature of the substituted isocyanates had considerable influence on the reaction efficiency. For example, *ortho*-substituted isocyanates gave lower yields by comparison to their *meta*- and *para*-substituted analogues (**3bb** vs **3bg**, **3bc** vs **3bj**, **3cb** vs **3cg**) and the isocyanates attached with an EDG offered higher yields than those with an EWG (**3bh** vs **3bg** and **3bj**, **3ch** vs **3cg**). Again, when *meta*-chloro isocyanate (**2e**) was employed, two regioisomeric indoloquinazolinones were formed and the less crowded analogue predominated (Table 3). In addition, when 2-aminoacetophenones containing a

Table 3. Substrate Scope with Respect to Both 2′-Aminoacetophenones and Aryl Isocyanates[a]



[a]Reaction conditions: **1** (1 mmol), **2** (1 mmol), $Pd(OAc)_2$ (10 mol %), Ag_2CO_3 (1.5 mmol), and AcOH (3 mL) in a sealed tube at 110 °C for 24 h.

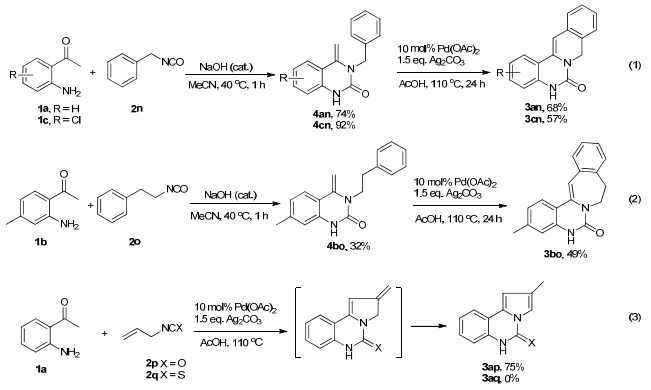
strong electron-withdrawing group such as 5-NO_2 or a strong electron-donating group such as 3,4-dimethoxy on the aromatic ring were investigated under the standard conditions, the expected product was not afforded.

Furthermore, benzyl isocyanate (**2n**) and phenethyl isocyanate (**2o**) were also examined for this double annulation reaction. However, when the reaction was performed directly from **1** and **2**, low yields (<20%) of the desired products were given. We then prepared the intermediates **4** using aqueous NaOH as the catalyst as reported previously,[17] and **4** was carried out under standard conditions. Moderate yields of the desired 6- and 7-membered rings were afforded (Scheme 2, eqs 1 and 2). Interestingly, when allyl isocyanate (**2p**) was attempted to react with **1a** under one-pot reaction conditions, the double-annulated product was successively afforded and it was easily converted to the more stable isomer (**3ap**) (Scheme 2, eq 3). Again, the corresponding product was not afforded when **2p** was replaced by allyl isothiocyanate (**2q**).

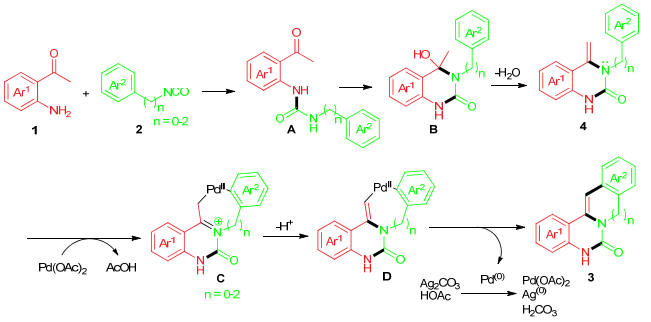
Based on the above results and those of previous studies,[18] a plausible mechanism is proposed (Scheme 3). The coupling of *o*-aminoacetophenone **1** and isocyanate **2** forms intermediate **A**. The N-3 of urea **A** carried out a nucleophilic attack on the carbonyl group and was followed by removal of one water to afford intermediate **4**. The reaction of the intermediate **4** with $Pd(OAc)_2$ performs an insertion of Pd between the methylene group (affected by the lone pair of N atom next to the olefin) and the *ortho*-position of the aryl ring originally from the

https://dx.doi.org/10.1021/acs.joc.0c02155
J. Org. Chem. 2021, 86, 1448−1455

Scheme 2. Synthesis of Indoloquinazolinones (3) Based on Aliphatic Isocyanates



Scheme 3. Possible Reaction Mechanism



isocyanates, resulting in the palladacycle species **C**, respectively. The C−C bond forming reductive elimination of the intermediate **C** produces the final annulation compound **3** and $Pd^{(0)}$, which can regenerate $Pd(OAc)_2$ by the oxidation with Ag_2CO_3.

CONCLUSION

In summary, we have successfully developed an efficient Pd-catalyzed one-pot cascade synthesis of indoloquinazolineones from *o*-aminoacetophenones and aryl/aliphatic isocyanates. The dual C−N bond and one C−C bond formations with the generality and high selectivity utilizing readily available substrates are the notable advantageous features of the present method and make this protocol very attractive.

EXPERIMENTAL SECTION

General Methods. All reagents and solvents were used from commercial sources unless otherwise stated. All raw materials are obtained from commercial sources. All experiments were conducted in the air. All the reactions were monitored by thin-layer chromatography (TLC) and visualized with ultraviolet light. TLC was performed on precoated silica gel plates (Qingdao Haiyang Chemical Co., Ltd., China). Column chromatography was performed on silica gel (240−400 mesh) with petroleum ether and ethyl acetate as eluent. ^1H and ^{13}C NMR (400 and 101 MHz) spectra were recorded on a Bruker Avance 400 MHz with tetramethylsilane as the internal standard. Melting points were determined using an X-4 digital micro melting point apparatus and are uncorrected. High-resolution mass spectra (HRMS) were performed on a Waters SYNAPT G2-Si mass spectrometer with quadrupole time-of-flight tandem mass spectrometry analysis. The single crystal X-ray diffraction studies were carried out on a Bruker Smart APEX-II CCD diffractometer equipped with graphite monochromated Mo Kα radiation (λ = 0.71073 Å) using the ω-2θ scan mode.

General Procedure for the Synthesis of ***3*** *(****3aa*** *as an Example).* 2-Aminoacetophenone (**1a**, 135 mg, 1 mmol), phenyl isocyanate (**2a**, 119 mg, 1 mmol), palladium acetate (22.4 mg, 0.1 mmol), silver carbonate (414 mg, 1.5 mmol), and acetic acid (3 mL) in a sealed tube was heated at 110 °C in an oil bath for 24 h. The reaction was monitored by TLC. Once the reaction was completed, the reaction mixture was treated with H_2O (15.0 mL) and EtOAc (8.0 mL). The organic and aqueous layers were then separated, and the aqueous layer was extracted with EtOAc (3 × 8 mL). The combined organic extracts were dried (Na_2SO_4), then the solvent was removed under reduced pressure, and the remaining residue was purified by column chromatography (petroleum ether/EtOAc = 2:1). Compound **3aa** (187 mg, 80% yield) was obtained as a white solid.

General Procedure for the Synthesis of ***4*** *(****4an*** *as an Example).* 2-Aminoacetophenone (**1a**, 135 mg, 1 mmol) and benzyl isocyanate (**2a**, 133 mg, 1 mmol) in acetonitrile (3 mL) in a reaction vessel was heated at 40 °C in an oil bath. NaOH solution (1 N, 10%) was added, and the reaction was monitored by TLC. Once the reaction was completed (1 h), the reaction mixture was cooled to room temperature and treated with H_2O (5 mL). The precipitate was filtered and washed with a mixture of acetonitrile/water. The crude product was recrystallized from acetone/EtOH to afford a white solid (185 mg, 74%).

*Indolo[1,2-c]quinazolin-6(5H)-one (****3aa****).*[20] Petroleum ether/ethyl acetate = 2:1; pale brown powder (yield: 187 mg, 80%); ^1H NMR (400 MHz, DMSO-d_6) δ 11.35 (s, 1H), 8.58−8.54 (m, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.78−7.74 (m, 1H), 7.44 (t, J = 8.4 Hz, 1H), 7.38−7.34 (m, 3H), 7.29−7.23 (m, 2H). $^{13}C\{H\}$ NMR (101 MHz, DMSO-d_6) δ 147.6, 134.7, 134.6, 133.8, 130.1, 129.9, 124.2, 123.9, 123.4, 120.7, 116.0, 115.8, 114.1, 98.7. ESI-MS: m/z $[M + H]^+$ 235.

*8-Fluoroindolo[1,2-c]quinazolin-6(5H)-one (****3ab****).* Petroleum ether/ethyl acetate = 2:1; magenta powder (yield: 129 mg, 51%); ^1H NMR (400 MHz, DMSO-d_6) δ 11.35 (s, 1H), 8.11 (dd, J = 7.9, 2.9 Hz, 1H), 7.58 (dd, J = 7.8, 2.3 Hz, 1H), 7.54−7.42 (m, 2H), 7.42−7.33 (m, 1H), 7.27 (dd, J = 9.5, 5.0 Hz, 2H), 7.18 (dd, J = 12.7, 7.8 Hz, 1H). $^{13}C\{H\}$ NMR (101 MHz, DMSO-d_6) δ 149.8 (d, $^1J_{C-F}$ = 254 Hz), 145.8, 136.6, 135.2, 134.4 (d, $^3J_{C-F}$ = 4.2 Hz), 130.3, 125.1 (d, $^3J_{C-F}$ = 7.0 Hz), 124.4, 123.3, 120.3 (d, $^2J_{C-F}$ = 11.3 Hz), 116.9 (d, $^4J_{C-F}$ = 3.9 Hz), 115.6, 113.7, 111.1 (d, $^2J_{C-F}$ = 22.2 Hz), 100.1. HRMS (ESI) m/z: calcd for $C_{15}H_{10}FN_2O$ $[M + H]^+$: 253.0772, found 253.0764.

*8-Chloroindolo[1,2-c]quinazolin-6(5H)-one (****3ac****).* Petroleum ether/ethyl acetate = 2:1; white powder (yield: 115 mg, 43%); ^1H NMR (400 MHz, DMSO-d_6) δ 11.22 (s, 1H), 8.06 (d, J = 7.9 Hz, 1H), 7.71 (d, J = 7.6 Hz, 1H), 7.49−7.39 (m, 3H), 7.35 (t, J = 7.7 Hz, 1H), 7.29−7.19 (m, 2H). $^{13}C\{H\}$ NMR (101 MHz, DMSO-d_6) δ 146.4, 137.1, 135.2, 134.4, 130.8, 130.4, 126.5, 125.5, 124.5, 123.3, 120.7, 119.8, 115.5, 114.1, 100.4. HRMS (ESI) m/z: calcd for $C_{15}H_{10}ClN_2O$ $[M + H]^+$: 269.0476, found 269.0487.

*8-Methylindolo[1,2-c]quinazolin-6(5H)-one (****3ad****).* Petroleum ether/ethyl acetate = 2:1; white powder (yield: 124 mg, 50%); ^1H NMR (400 MHz, DMSO-d_6) δ 11.15 (s, 1H), 8.08 (d, J = 7.8 Hz, 1H), 7.58 (d, J = 7.7 Hz, 1H), 7.49−7.38 (m, 2H), 7.32−7.21 (m, 3H), 7.18 (d, J = 7.3 Hz, 1H), 2.86 (s, 3H). $^{13}C\{H\}$ NMR (101 MHz, DMSO-d_6) δ 147.5, 135.7, 134.9, 133.6, 131.9, 129.9, 127.5, 126.4, 124.5, 124.1, 123.2, 118.6, 115.3, 114.5, 100.4, 24.6. HRMS (ESI) m/z: calcd for $C_{16}H_{13}N_2O$ $[M + H]^+$: 249.1022, found 249.1019.

*Mixture of 9- and 11-Chloroindolo[1,2-c]quinazolin-6(5H)-one (****3ae*** *and* ***3ae'****) (2.5:1).* Petroleum ether/ethyl acetate = 5:1; magenta powder (yield: 188 mg, 70%); ^1H NMR (400 MHz, DMSO-d_6) δ 11.54 and 11.50 (s, 1H), 8.62 (s, 0.72H), 8.53 (d, J = 8.4 Hz, 0.28H), 8.23 (d, J = 7.6 Hz, 0.28H), 8.10 (d, J = 7.7 Hz, 0.72H), 7.77 (d, J = 8.5 Hz, 0.72H), 7.51−7.24 (m, 5.28H). $^{13}C\{H\}$ NMR (101 MHz, DMSO-d_6) δ 147.4, 147.3, 135.7, 135.5, 134.9, 134.7, 134.5, 134.0, 132.0, 130.5, 130.2, 128.9, 127.7, 127.7, 124.6, 124.5, 124.3, 124.2, 124.2, 123.6, 123.5, 122.0, 115.9, 115.9, 115.5, 114.9, 113.9, 113.7, 98.5, 96.4. HRMS (ESI) m/z: calcd for $C_{15}H_{10}ClN_2O$ $[M + H]^+$: 269.0472, found 269.0489.

*9-Methylindolo[1,2-c]quinazolin-6(5H)-one (****3af****).* Petroleum ether/ethyl acetate = 4:1; white powder (yield: 201 mg, 81%); ^1H

https://dx.doi.org/10.1021/acs.joc.0c02155
J. Org. Chem. 2021, 86, 1448−1455

NMR (400 MHz, DMSO-d_6) δ 11.36 (s, 1H), 8.41 (s, 1H), 8.08 (d, J = 8.0 Hz, 1H), 7.64 (d, J = 8.1 Hz, 1H), 7.41 (td, J = 8.0, 1.6 Hz, 1H), 7.32 (s, 1H), 7.28−7.19 (m, 3H), 2.61 (s, 3H). ^{13}C{H} NMR (101 MHz, DMSO-d_6) δ 147.7, 134.6, 134.2, 134.0, 132.9, 129.6, 127.9, 125.5, 124.0, 123.4, 120.3, 115.9, 115.8, 114.3, 98.6, 22.1. HRMS (ESI) m/z: calcd for $C_{16}H_{13}N_2O$ [M + H]$^+$: 249.1022, found 249.1028.

10-Fluoroindolo[1,2-c]quinazolin-6(5H)-one (**3ag**). Petroleum ether/ethyl acetate = 4:1; magenta powder (yield: 189 mg, 75%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.60 (d, J = 2.6 Hz, 1H), 7.96 (d, J = 7.9 Hz, 1H), 7.72 (t, J = 7.7 Hz, 1H), 7.46−7.38 (m, 2H), 7.38−7.30 (m, 2H), 7.29−7.21 (m, 2H). ^{13}C{H} NMR (101 MHz, DMSO-d_6) δ 162.8, 162.1 (d, $^1J_{C-F}$ = 243 Hz), 150.7, 140.3, 138.9, 135.7, 132.4 (d, $^4J_{C-F}$ = 3.2 Hz), 131.7 (d, $^3J_{C-F}$ = 8.8 Hz), 128.1, 125.2, 123.0, 116.1 (d, $^2J_{C-F}$ = 22.6 Hz), 115.7, 114.8, 112.7 (d, $^2J_{C-F}$ = 21.1 Hz). HRMS (ESI) m/z: calcd for $C_{15}H_{10}FN_2O$ [M + H]$^+$: 253.0772, found 253.0767.

10-Methylindolo[1,2-c]quinazolin-6(5H)-one (**3ah**). Petroleum ether/ethyl acetate = 4:1; white powder (yield: 196 mg, 79%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.39 (s, 1H), 8.44 (d, J = 8.4 Hz, 1H), 8.10 (d, J = 7.8 Hz, 1H), 7.54 (s, 1H), 7.44 (t, J = 7.6 Hz, 1H), 7.32−7.23 (m, 3H), 7.20 (d, J = 8.5, 1.7 Hz, 1H), 2.48 (s, 3H). ^{13}C{H} NMR (101 MHz, DMSO-d_6) δ 147.5, 134.8, 134.6, 132.9, 132.1, 130.4, 129.8, 124.9, 124.1, 123.4, 120.3, 115.8, 115.6, 114.1, 98.4, 21.7. HRMS (ESI) m/z: calcd for $C_{16}H_{13}N_2O$ [M + H]$^+$: 249.1022, found 249.1030.

10-Methoxyindolo[1,2-c]quinazolin-6(5H)-one (**3ai**). Petroleum ether/ethyl acetate = 4:1; white solid (yield: 203 mg, 77%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.34 (s, 1H), 8.41 (d, J = 9.2 Hz, 1H), 8.07 (d, J = 7.6 Hz, 1H), 7.43 (td, J = 7.6, 1.2 Hz, 1H), 7.22−7.29 (m, 4H), 6.97 (dd, J = 8.8, 2.8 Hz, 1H), 3.83 (s, 3H). ^{13}C{H} NMR (101 MHz, DMSO-d_6) δ 156.5, 147.4, 135.0, 134.6, 131.1, 129.8, 128.5, 124.0, 123.4, 116.6, 115.8, 113.9, 112.8, 102.6, 98.5, 55.8. HRMS (ESI) m/z: calcd for $C_{16}H_{13}N_2O_2$ [M + H]$^+$: 265.0972, found 265.0958.

10-Chloroindolo[1,2-c]quinazolin-6(5H)-one (**3aj**). Petroleum ether/ethyl acetate = 4:1; white solid (yield: 188 mg, 70%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.49 (s, 1H), 8.53 (d, J = 8.8 Hz, 1H), 8.10 (d, J = 7.8 Hz, 1H), 7.81 (d, J = 1.6 Hz, 1H), 7.46 (t, J = 8.0 Hz, 1H), 7.36 (dd, J = 8.8, 2.0 Hz, 1H), 7.34 (s, 1H), 7.27 (t, J = 8.8 Hz, 2H). ^{13}C{H} NMR (101 MHz, DMSO-d_6) δ 147.3, 136.0, 134.8, 132.2, 131.5, 130.4, 128.4, 124.3, 123.6, 123.3, 119.9, 117.3, 115.9, 113.7, 98.0. HRMS (ESI) m/z: calc. for $C_{15}H_{10}ClN_2O$ [M + H]$^+$: 269.0476, found 269.0486.

9,10-Difluoroindolo[1,2-c]quinazolin-6(5H)-one (**3ak**). Petroleum ether/ethyl acetate = 4:1; white powder (yield: 194 mg, 72%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.43 (s, 1H), 8.10 (d, J = 8.0 Hz, 1H), 7.48 (t, J = 7.2 Hz, 1H), 7.46 (s, 1H), 7.41 (dd, J = 7.6, 2.4 Hz, 1H), 7.27 (d, J = 8.0 Hz, 1H), 7.25 (t, J = 7.6 Hz, 1H), 7.17 (ddd, J = 12.1, 9.7, 2.4 Hz, 1H). ^{13}C{H} NMR (101 MHz, DMSO-d_6) δ 159.0 (dd, $^1J_{C-F}$ = 239.7, $^2J_{C-F}$ = 10.3 Hz), 149.5 (dd, $^1J_{C-F}$ = 257.0 Hz, $^2J_{C-F}$ = 14.2 Hz), 145.5, 138.2, 135.2, 134.3 (dd, $^3J_{C-F}$ = 12.2 Hz, $^4J_{C-F}$ = 5.5 Hz), 130.7, 124.6, 123.4, 117.3 (d, $^3J_{C-F}$ = 11.0 Hz), 115.6, 113.3, 102.0 (dd, $^2J_{C-F}$ = 23.5 Hz, $^3J_{C-F}$ = 4.2 Hz), 100.4, (d, $^2J_{C-F}$ = 27.3 Hz), 100.0. HRMS (ESI) m/z: calcd for $C_{15}H_9F_2N_2O$ [M + H]$^+$: 271.0677, found 271.0683.

8,10-Difluoroindolo[1,2-c]quinazolin-6(5H)-one (**3al**). Petroleum ether/ethyl acetate = 4:1; magenta powder (yield: 151 mg, 56%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.42 (s, 1H), 8.10 (d, J = 7.6 Hz, 1H), 7.47 (t, J = 7.2 Hz, 1H), 7.45 (s, 1H), 7.40 (dd, J = 8.0, 2.4 Hz, 1H), 7.26 (d, J = 8.0 Hz, 1H), 7.25 (t, J = 7.2 Hz, 1H), 7.17 (ddd, J = 12, 9.6, 2.4 Hz, 1H). ^{13}C{H} NMR (101 MHz, DMSO-d_6) δ 159.0 (dd, $^1J_{C-F}$ = 239 Hz, $^3J_{C-F}$ = 10.1 Hz), 149.5 (dd, $^1J_{C-F}$ = 256 Hz, $^3J_{C-F}$ = 13.9 Hz), 145.5, 138.2, 135.2, 134.3 (dd, $^2J_{C-F}$ = 11.9 Hz, $^4J_{C-F}$ = 5.3 Hz), 130.7, 124.5, 123.4, 117.3 (d, $^3J_{C-F}$ = 10.9 Hz), 115.6, 113.2, 102.0 (dd, $^2J_{C-F}$ = 22.9 Hz, $^4J_{C-F}$ = 4.5 Hz), 100.3 (dd, $^2J_{C-F}$ = 29.3, 26.7 Hz), 100.1. HRMS (ESI) m/z: calcd for $C_{15}H_9F_2N_2O$ [M + H]$^+$: 271.0677, found 271.0692.

5,8-Dihydro-6H-isoquinolino[2,3-c]quinazolin-6-one (**3an**). Petroleum ether/ethyl acetate = 5:1; white powder (yield: 169 mg, 68%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.63 (s, 1H), 8.18 (d, J = 8.0 Hz, 1H), 7.66−7.60 (m, 1H), 7.60−7.55 (m, 2H), 7.39−7.31 (m, 3H), 7.29−7.24 (m, 2H), 7.16−7.11 (m, 1H), 5.33 (s, 2H). ^{13}C{H} NMR (101 MHz, DMSO-d_6) δ 162.4, 150.7, 139.9, 137.8, 135.6, 128.9, 128.8, 128.1, 127.9, 127.5, 127.2, 126.5, 123.1, 115.7, 114.2, 43.6. HRMS (ESI) m/z: calcd for $C_{16}H_{13}N_2O$ [M + H]$^+$: 249.1022, found 249.1036.

2-Methylpyrrolo[1,2-c]quinazolin-5(6H)-one (**3ap**). Petroleum ether/ethyl acetate = 5:1; white powder (yield: 149 mg, 75%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.39 (s, 1H), 7.85 (d, J = 7.9 Hz, 1H), 7.37 (s, 1H), 7.31−7.28 (m, 1H), 7.25−7.15 (m, 2H), 6.85 (s, 1H), 2.20 (s, 3H). ^{13}C{H} NMR (101 MHz, DMSO-d_6) δ 145.68, 133.02, 129.57, 127.86, 124.46, 123.40, 122.48, 115.88, 114.50, 113.62, 106.59, 12.53. HRMS (ESI) m/z: calcd for $C_{12}H_{11}N_2O$ [M + H]$^+$: 199.0866, found 199.0873.

8-Fluoro-3-methylindolo[1,2-c]quinazolin-6(5H)-one (**3bb**). Petroleum ether/ethyl acetate = 4:1; magenta powder (yield: 120 mg, 45%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.29 (s, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.39 (s, 1H), 7.36−7.31 (m, 1H), 7.13 (dd, J = 8.0, 12.4 Hz, 1H), 7.06 (d, J = 8.0 Hz, 1H), 7.05 (s, 1H), 2.37 (s, 3H). ^{13}C{H} NMR (101 MHz, DMSO-d_6) δ 149.8 (d, $^1J_{C-F}$ = 254 Hz), 145.9, 140.3, 136.7, 135.2, 134.5 (d, $^3J_{C-F}$ = 4.2 Hz), 125.1 (d, $^3J_{C-F}$ = 7.5 Hz), 124.5, 124.3, 120.2 (d, $^2J_{C-F}$ = 10.9 Hz), 116.7 (d, $^4J_{C-F}$ = 3.0 Hz), 115.5, 111.2, 110.9 (d, $^2J_{C-F}$ = 22.5 Hz), 99.3, 21.7. HRMS (ESI) m/z: calcd for $C_{16}H_{12}FN_2O$ [M + H]$^+$: 267.0928, found 267.0927.

8-Chloro-3-methylindolo[1,2-c]quinazolin-6(5H)-one (**3bc**). Petroleum ether/ethyl acetate = 4:1; white powder (yield: 124 mg, 44%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.16 (s, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.68 (dd, J = 7.6, 1.3 Hz, 1H), 7.42−7.29 (m, 4H), 7.08−7.04 (m, 1H), 7.02 (s, 1H), 2.37 (s, 3H). ^{13}C{H} NMR (101 MHz, DMSO-d_6) δ 146.6, 140.5, 137.3, 135.3, 134.5, 130.7, 126.3, 125.4, 124.5, 124.4, 120.7, 119.6, 115.4, 111.6, 99.7, 21.7. HRMS (ESI) m/z: calcd for $C_{16}H_{12}ClN_2O$ [M + H]$^+$: 283.0633, found 283.0617.

3,9-Dimethylindolo[1,2-c]quinazolin-6(5H)-one (**3bf**). Petroleum ether/ethyl acetate = 4:1; white powder (yield: 191 mg, 73%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.28 (s, 1H), 8.38 (s, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.22 (s, 1H), 7.18 (d, J = 8.0 Hz, 1H), 7.05 (d, J = 8.0 Hz, 1H), 7.04 (s, 1H), 2.49 (s, 3H), 2.36 (s, 3H). ^{13}C{H} NMR (101 MHz, DMSO-d_6) δ 147.8, 139.5, 134.6, 134.1, 134.1, 132.6, 128.0, 125.4, 124.5, 123.9, 120.2, 115.9, 115.7, 111.8, 97.8, 22.1, 21.7. HRMS (ESI) m/z: calcd for $C_{17}H_{15}N_2O$ [M + H]$^+$: 263.1179, found 263.1193.

10-Fluoro-3-methylindolo[1,2-c]quinazolin-6(5H)-one (**3bg**). Petroleum ether/ethyl acetate = 4:1; magenta powder (yield: 176 mg, 66%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.39 (s, 1H), 8.52 (dd, J = 9.0, 4.9 Hz, 1H), 7.98 (d, J = 7.9 Hz, 1H), 7.50 (dd, J = 9.5, 2.6 Hz, 1H), 7.26 (s, 1H), 7.20−7.11 (m, 1H), 7.11−7.03 (m, 2H), 2.37 (s, 3H). ^{13}C{H} NMR (101 MHz, DMSO-d_6) δ 159.5 (d, $^1J_{C-F}$ = 231 Hz), 147.4, 140.3, 136.4, 134.9, 131.3 (d, $^3J_{C-F}$ = 10.6 Hz), 130.3, 124.7, 124.3, 117.1 (d, $^3J_{C-F}$ = 9.6 Hz), 115.8, 111.2, 110.9 (d, $^2J_{C-F}$ = 25.1 Hz), 105.6 (d, $^2J_{C-F}$ = 23.5 Hz), 97.7 (d, $^4J_{C-F}$ = 4.3 Hz), 21.7. HRMS (ESI) m/z: calcd for $C_{16}H_{12}FN_2O$ [M + H]$^+$: 267.0928, found 267.0934.

3,10-Dimethylindolo[1,2-c]quinazolin-6(5H)-one (**3bh**). Petroleum ether/ethyl acetate = 4:1; white powder (yield: 199 mg, 76%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.27 (s, 1H), 8.40 (d, J = 8.4 Hz, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.49 (s, 1H), 7.18 (s, 1H), 7.15 (d, J = 8.4 Hz, 1H), 7.06 (d, J = 8.4 Hz, 2H), 7.05 (s, 1H), 2.45 (s, 3H), 2.37 (s, 3H). ^{13}C{H} NMR (101 MHz, DMSO-d_6) δ 147.6, 139.7, 134.7, 132.8, 132.0, 130.5, 124.6, 124.5, 124.0, 120.2, 115.7, 115.5, 111.7, 106.6, 97.6, 21.7, 21.7. HRMS (ESI) m/z: calcd for $C_{17}H_{15}N_2O$ [M + H]$^+$: 263.1179, found 263.1178.

10-Chloro-3-methylindolo[1,2-c]quinazolin-6(5H)-one (**3bj**). Petroleum ether/ethyl acetate = 4:1; white powder (yield: 172 mg, 61%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.45 (s, 1H), 8.52 (d, J = 8.8 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 2.1 Hz, 1H), 7.34

https://dx.doi.org/10.1021/acs.joc.0c02155
J. Org. Chem. 2021, 86, 1448−1455

(dd, J = 8.8, 2.2 Hz, 1H), 7.27 (s, 1H), 7.09 (d, J = 8.0 Hz, 1H), 7.07 (s, 1H), 2.38 (s, 3H). $^{13}C\{H\}$ NMR (101 MHz, DMSO-d_6) δ 147.4, 140.4, 136.3, 135.0, 132.2, 131.7, 128.3, 124.8, 124.3, 123.0, 121.1, 119.7, 117.2, 115.9, 97.3, 21.7. HRMS (ESI) m/z: calcd for $C_{16}H_{12}ClN_2O$ $[M + H]^+$: 283.0633, found 283.0631.

*3-Methyl-8,9-dihydrobenzo[4,5]azepino[1,2-c]quinazolin-6(5H)-one (**3bo**).* Petroleum ether/ethyl acetate = 5:1; white powder (yield: 135 mg, 49%); ^1H NMR (400 MHz, DMSO-d_6) δ 11.39 (s, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.34−7.27 (m, 2H), 7.27−7.18 (m, 3H), 7.03 (dd, J = 8.1, 1.6 Hz, 1H), 6.98−6.93 (m, 1H), 4.09 (t, J = 7.92 Hz, 2H), 2.87 (t, J = 7.76 Hz, 2H), 2.37 (s, 3H). $^{13}C\{H\}$ NMR (101 MHz, DMSO-d_6) δ 162.1, 150.6, 146.1, 139.9, 139.1, 132.7, 129.1, 128.9, 128.8, 127.8, 126.8, 124.3, 115.9, 115.3, 111.9, 41.6, 33.8, 21.9. HRMS (ESI) m/z: calcd for $C_{18}H_{17}N_2O$ $[M + H]^+$: 277.1335, found 277.1332.

*2-Chloro-8-fluoroindolo[1,2-c]quinazolin-6(5H)-one (**3cb**).* Petroleum ether/ethyl acetate = 4:1; magenta powder (yield: 152 mg, 53%); ^1H NMR (400 MHz, DMSO-d_6) δ 11.44 (s, 1H), 8.23 (d, J = 2.4 Hz, 1H), 7.61 (d, J = 1.7 Hz, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.47 (dd, J = 8.7, 2.3 Hz, 1H), 7.40−7.33 (m, 1H), 7.24 (d, J = 8.7 Hz, 1H), 7.18 (dd, J = 12.0, 7.2 Hz, 1H). $^{13}C\{H\}$ NMR (101 MHz, DMSO-d_6) δ 149.8 (d, $^1J_{C-F}$ = 254.2 Hz), 145.5, 135.3, 134.2 (d, $^3J_{C-F}$ = 4.2 Hz), 134.0, 130.0, 127.3, 125.3 (d, $^3J_{C-F}$ = 6.9 Hz), 123.7, 120.5 (d, $^2J_{C-F}$ = 11.2 Hz), 117.4, 117.2, 115.3, 111.5 (d, $^2J_{C-F}$ = 22.5 Hz), 101.4. HRMS (ESI) m/z: calcd for $C_{15}H_9ClFN_2O$ $[M + H]^+$: 287.0382, found 287.0379.

*Mixture of 2,9- and 2,11-Dichloroindolo[1,2-c]quinazolin-6(5H)-one (**3ce** and **3ce′**) (2.9:1).* Petroleum ether/ethyl acetate = 5:1; white powder (yield: 181 mg, 60%); ^1H NMR (400 MHz, DMSO-d_6) δ 11.58 and 11.54 (s, 1H), 8.50 and 8.47 (s, 1H), 8.33 and 8.17 (d, J = 2.0 Hz, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.5−7.35 (m, 3H), 7.25 and 7.23 (d, J = 8.7 Hz, 1H). $^{13}C\{H\}$ NMR (101 MHz, DMSO-d_6) δ 147.0, 147.0, 134.5, 134.3, 134.2, 134.0, 133.7, 133.5, 132.0, 130.1, 129.8, 128.6, 128.6, 128.1, 127.6, 127.6, 124.8, 124.7, 124.3, 123.9, 123.5, 123.5, 122.2, 117.1, 117.7, 115.5, 115.3, 114.8, 99.7, 97.8. HRMS (ESI) m/z: calcd for $C_{15}H_9Cl_2N_2O$ $[M + H]^+$: 303.0086, found 303.0075.

*2-Chloro-10-fluoroindolo[1,2-c]quinazolin-6(5H)-one (**3cg**).* Petroleum ether/ethyl acetate = 4:1; magenta powder (yield: 187 mg, 65%): ^1H NMR (400 MHz, DMSO-d_6) δ 11.51 (s, 1H), 8.48 (dd, J = 9.1, 4.9 Hz, 1H), 8.21 (d, J = 2.3 Hz, 1H), 7.50 (dd, J = 9.5, 2.7 Hz, 1H), 7.47−7.40 (m, 2H), 7.27 (d, J = 8.7 Hz, 1H), 7.22 (dt, J = 9.2, 2.4 Hz, 1H). $^{13}C\{H\}$ NMR (101 MHz, DMSO-d_6) δ 159.5 (d, $^1J_{C-F}$ = 236 Hz), 147.0, 134.9, 133.7, 130.9 (d, $^3J_{C-F}$ = 10.6 Hz), 130.4, 129.9, 127.5, 123.6, 117.7, 117.2 (d, $^3J_{C-F}$ = 9.5 Hz), 115.3, 111.7 (d, $^2J_{C-F}$ = 25.6 Hz), 105.9 (d, $^2J_{C-F}$ = 23.8 Hz), 99.7 (d, $^4J_{C-F}$ = 4.4 Hz). HRMS (ESI) m/z: calcd for $C_{15}H_9ClFN_2O$ $[M + H]^+$: 287.0382, found 287.0398.

*2-Chloro-10-methylindolo[1,2-c]quinazolin-6(5H)-one (**3ch**).* Petroleum ether/ethyl acetate = 4:1; white powder (yield: 200 mg, 71%); ^1H NMR (400 MHz, DMSO-d_6) δ 11.45 (s, 1H), 8.41 (d, J = 8.4 Hz, 1H), 8.23 (s, 1H), 7.54 (s, 1H), 7.45 (dd, J = 8.8, 2.4 Hz, 1H),7.43 (s, 1H), 7.25 (d, J = 8.8 Hz, 1H), 7.21 (d, J = 8.4 Hz, 1H), 2.46 (s, 3H). $^{13}C\{H\}$ NMR (101 MHz, DMSO-d_6) δ 147.2, 133.5, 133.1, 132.2, 130.2, 129.5, 127.4, 125.4, 123.4, 120.6, 117.6, 115.8, 115.6, 108.0, 99.8, 21.6. HRMS (ESI) m/z: calcd for $C_{16}H_{12}ClN_2O$ $[M + H]^+$: 283.0633, found 283.0627.

*2-Chloro-5,8-dihydro-6H-isoquinolino[2,3-c]quinazolin-6-one (**3cn**).* Petroleum ether/ethyl acetate = 5:1; white powder (yield: 161 mg, 57%); ^1H NMR (400 MHz, DMSO-d_6) δ 11.70 (s, 1H), 7.88 (d, J = 2.5 Hz, 1H), 7.73 (dd, J = 8.7, 2.5 Hz, 1H), 7.33−7.30 (m, 4H), 7.25−7.21 (m, 2H), 5.08 (s, 2H). $^{13}C\{H\}$ NMR (101 MHz, DMSO-d_6) δ 161.5, 150.4, 138.8, 137.6, 135.5, 130.5, 128.9, 128.8, 128.0, 127.6, 127.3, 127.0, 126.8, 118.0, 115.6, 43.8. HRMS (ESI) m/z: calcd for $C_{16}H_{12}ClN_2O$ $[M + H]^+$: 283.0633, found 283.0636.

*3-(2,6-Dichlorophenyl)-4-methylene-3,4-dihydroquinazolin-2(1H)-one (**4am**).* White powder (yield: 271 mg, 89%); ^1H NMR (400 MHz, DMSO-d_6) δ 7.73 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 8.0 Hz, 2H), 7.53 (t, J = 8.0 Hz, 1H), 7.36 (t, J = 8.0 Hz, 1H), 7.04 (t, J = 8.0 Hz, 1H), 6.99 (d, J = 8.0 Hz, 1H), 4.83 (d, J = 2.4 Hz, 1H), 3.38 (d, J = 8.0 Hz, 1H). $^{13}C\{H\}$ NMR (101 MHz, DMSO-d_6) δ 148.4, 140.2, 136.0, 135.0, 133.8, 131.4, 131.2, 129.8, 124.8, 123.0, 115.9, 115.6, 84.7. HRMS (ESI) m/z: calcd for $C_{15}H_{11}Cl_2N_2O$ $[M + H]^+$: 305.0243, found 305.0237.

*3-Benzyl-4-methylene-3,4-dihydroquinazolin-2(1H)-one (**4an**).*[17] White powder (yield: 185 mg, 74%); ^1H NMR (400 MHz, DMSO-d_6) δ 10.28 (s, 1H), 7.62 (d, J = 8.1 Hz, 1H), 7.36−7.19 (m, 6H), 7.00−6.92 (m, 2H), 5.01 (s, 2H), 4.82 (d, J = 2.4 Hz, 1H), 4.12 (d, J = 2.5 Hz, 1H). $^{13}C\{H\}$ NMR (101 MHz, DMSO-d_6) δ 150.6, 140.2, 137.5, 136.1, 130.7, 128.9, 127.2, 126.8, 124.4, 122.6, 116.5, 115.1, 85.7, 46.3. ESI-MS: m/z $[M + H]^+$: 251.

*7-Methyl-4-methylene-3-phenethyl-3,4-dihydroquinazolin-2(1H)-one (**4bo**).* White powder (yield: 89 mg, 32%); ^1H NMR (400 MHz, DMSO-d_6) δ 10.15 (s, 1H), 7.57 (d, J = 8.2 Hz, 1H), 7.34−7.26 (m, 4H), 7.25−7.19 (m, 1H), 6.80 (dd, J = 8.3, 1.7 Hz, 1H), 6.69 (t, J = 1.3 Hz, 1H), 4.88 (d, J = 2.4 Hz, 1H), 4.36 (d, J = 2.5 Hz, 1H), 3.93 (t, J = 8.12 Hz, 2H), 2.88 (t, J = 7.84 Hz, 2H), 2.25 (s, 3H). $^{13}C\{H\}$ NMR (101 MHz, DMSO-d_6) δ 150.0, 140.3, 140.2, 139.3, 136.0, 129.1, 128.9, 126.7, 124.5, 123.6, 115.0, 114.0, 83.3, 44.2, 31.8, 21.3. HRMS (ESI) m/z: calcd for $C_{18}H_{18}N_2O$ $[M + H]^+$: 279.1492, found 279.1523.

*3-Benzyl-6-chloro-4-methylene-3,4-dihydroquinazolin-2(1H)-one (**4cn**).*[17] White powder (yield: 261 mg, 92%); ^1H NMR (400 MHz, DMSO-d_6) δ 10.44 (s, 1H), 7.71 (d, J = 2.2 Hz, 1H), 7.33 (dd, J = 8.8, 6.8 Hz, 3H), 7.27−7.21 (m, 3H), 6.95 (d, J = 8.6 Hz, 1H), 4.99 (s, 2H), 4.93 (d, J = 2.8 Hz, 1H), 4.17 (d, J = 2.8 Hz, 1H). $^{13}C\{H\}$ NMR (101 MHz, DMSO-d_6) δ 150.3, 139.1, 137.3, 135.1, 130.5, 129.0, 127.3, 126.8, 126.6, 123.9, 118.2, 117.0, 87.4, 46.3. ESI-MS: m/z $[M + H]^+$: 285.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02155.

^1H NMR, ^{13}C NMR, and X-ray crystallographic data (PDF)

Accession Codes

CCDC 2023639 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Yongmin Ma − *Institute of Advanced Studies and School of Pharmaceutical and Chemical Engineering, Taizhou University, Taizhou 318000, P R China; School of Pharmaceutical Science, Zhejiang Chinese Medical University, Hangzhou 310053, P R China;* orcid.org/0000-0002-9521-767X; Email: yongmin.ma@tzc.edu.cn

Authors

Yuxin Ding − *Institute of Advanced Studies and School of Pharmaceutical and Chemical Engineering, Taizhou University, Taizhou 318000, P R China; School of Pharmaceutical Science, Zhejiang Chinese Medical University, Hangzhou 310053, P R China*

Huihui Yan − *School of Pharmaceutical Science, Zhejiang Chinese Medical University, Hangzhou 310053, P R China*

Rener Chen − *Institute of Advanced Studies and School of Pharmaceutical and Chemical Engineering, Taizhou University, Taizhou 318000, P R China*

Xuqiong Xiao − *Key Laboratory of Organosilicon Chemistry and Material Technology of Ministry of Education, Hangzhou Normal University, Hangzhou 311121, P R China;* orcid.org/0000-0001-8424-9898

Zhiming Wang − *Institute of Advanced Studies and School of Pharmaceutical and Chemical Engineering, Taizhou University, Taizhou 318000, P R China;* orcid.org/0000-0002-6583-3826

Lei Wang − *Institute of Advanced Studies and School of Pharmaceutical and Chemical Engineering, Taizhou University, Taizhou 318000, P R China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.0c02155

Author Contributions

#Y.D. and H.Y. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the Leading Innovative and Entrepreneur Team Introduction Program of Zhejiang (Grant No. 2019R01005) is gratefully acknowledged.

■ REFERENCES

(1) (a) Gatadi, S.; Nanduri, S. New potential drug leads against MDR-MTB: A short review. *Bioorg. Chem.* **2020**, *95*, 103534. (b) Zhao, Y.; Liu, F.; He, G.; Li, K.; Zhu, C.; Yu, W.; Zhang, C.; Xie, M.; Lin, J.; Zhang, J.; Jin, Y. Discovery of arylamide-5-anilinoquinazoline-8-nitro derivatives as VEGFR-2 kinase inhibitors: Synthesis, in vitro biological evaluation and molecular docking. *Bioorg. Med. Chem. Lett.* **2019**, *29*, 126711. (c) Gatadi, S.; Lakshmi, T. V.; Nanduri, S. 4(3H)-Quinazolinone derivatives: Promising antibacterial drug leads. *Eur. J. Med. Chem.* **2019**, *170*, 157−172. (d) Qiu, J.; Chen, W.; Zhang, Y.; Zhou, Q.; Chen, J.; Yang, L.; Gao, J.; Gu, X.; Tang, D. Assessment of quinazolinone derivatives as novel non-nucleoside hepatitis B virus inhibitors. *Eur. J. Med. Chem.* **2019**, *176*, 41−49. (e) Khan, I.; Ibrar, A.; Abbas, N.; Saeed, A. Recent advances in the structural library of functionalized quinazoline and quinazolinone scaffolds: Synthetic approaches and multifarious applications. *Eur. J. Med. Chem.* **2014**, *76*, 193−244. (f) Khan, I.; Ibrar, A.; Ahmed, W.; Saeed, A. Synthetic approaches, functionalization and therapeutic potential of quinazoline and quinazolinone skeletons: The advances continue. *Eur. J. Med. Chem.* **2015**, *90*, 124−169.

(2) (a) Noble, C.; Cannaert, A.; Linnet, K.; Stove, C. P. Application of an activity-based receptor bioassay to investigate the in vitro activity of selected indole- and indazole-3-carboxamide-based synthetic cannabinoids at CB1 and CB2 receptors. *Drug Test. Anal.* **2019**, *11*, 501−511. (b) Singh, T. P.; Singh, O. M. Recent Progress in Biological Activities of Indole and Indole Alkaloids. *Mini-Rev. Med. Chem.* **2017**, *18*, 9−25. (c) Ishikura, M.; Abe, T.; Choshi, T.; Hibino, S. Simple indole alkaloids and those with a nonrearranged monoterpenoid unit. *Nat. Prod. Rep.* **2015**, *32*, 1389−1471. (d) Sravanthi, T. V.; Manju, S. L. Indoles - A promising scaffold for drug development. *Eur. J. Pharm. Sci.* **2016**, *91*, 1−10. (e) Inman, M.; Moody, C. J. Indole synthesis - something old, something new. *Chem. Sci.* **2013**, *4*, 29−41. (f) Ishikura, M.; Abe, T.; Choshi, T.; Hibino, S. Simple indole alkaloids and those with a non-rearranged monoterpenoid unit. *Nat. Prod. Rep.* **2013**, *30*, 694−752.

(3) (a) Jahng, Y. Progress in the studies on tryptanthrin, an alkaloid of history. *Arch. Pharmacal Res.* **2013**, *36*, 517−535. (b) Rudolph, I.; Ramm, M.; Moellmann, U.; Imming, P. Synthesis and determination of antimycobacterial activity of tryptanthrine, vasicine, vasicinone and derivatives thereof. *Planta Med.* **2012**, *78*, PK5.

(4) (a) Gali, R.; Banothu, J.; Porika, M.; Velpula, R.; Hnamte, S.; Bavantula, R.; Abbagani, S.; Busi, S. Indolylmethylene benzo h thiazolo 2,3-b quinazolinones: Synthesis, characterization and evaluation of anticancer and antimicrobial activities. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 4239−4242. (b) Long, S.; Resende, D. I. S. P.; Kijjoa, A.; Silva, A. M. S.; Pina, A.; Fernandez-Marcelo, T.; Vasconcelos, M. H.; Sousa, E.; Pinto, M. M. M. Antitumor Activity of Quinazolinone Alkaloids Inspired by Marine Natural Products. *Mar. Drugs* **2018**, *16*, 261. (c) Sonawane, V.; Mohd Siddique, M. U.; Jadav, S. S.; Sinha, B. N.; Jayaprakash, V.; Chaudhuri, B. Cink4T, a quinazolinone-based dual inhibitor of Cdk4 and tubulin polymerization, identified via ligand-based virtual screening, for efficient anticancer therapy. *Eur. J. Med. Chem.* **2019**, *165*, 115−132.

(5) (a) Ashok, P.; Chander, S.; Chow, L. M. C.; Wong, I. L. K.; Singh, R. P.; Jha, P. N.; Sankaranarayanan, M. Synthesis and in-vitro anti-leishmanial activity of (4-arylpiperazin-1-yl) (1-(thiophen-2-yl)-9H-pyrido 3,4-b indol-3-yl) methanone derivatives. *Bioorg. Chem.* **2017**, *70*, 100−106. (b) Chripkova, M.; Zigo, F.; Mojzis, J. Antiproliferative Effect of Indole Phytoalexins. *Molecules* **2016**, *21*, 1626. (c) Kornsakulkarn, J.; Saepua, S.; Srijomthong, K.; Rachtawee, P.; Thongpanchang, C. Quinazolinone alkaloids from actinomycete Streptomyces sp BCC 21795. *Phytochem. Lett.* **2015**, *12*, 6−8.

(6) (a) Garcellano, R. C.; Moinuddin, S. G. A.; Young, R. P.; et al. Isolation of Tryptanthrin and Reassessment of Evidence for Its Isobaric Isostere Wrightiadione in Plants of the Wrightia Genus. *J. Nat. Prod.* **2019**, *82*, 440−448. (b) Kaur, R.; Manjal, S. K.; Rawal, R. K.; Kumar, K. Recent synthetic and medicinal perspectives of tryptanthrin. *Bioorg. Med. Chem.* **2017**, *25*, 4533−4552.

(7) (a) Shankar, G. M.; Antony, J.; Anto, R. J. Quercetin and Tryptanthrin: Two Broad Spectrum Anticancer Agents for Future Chemotherapeutic Interventions. *Enzymes* **2015**, *37*, 43−72. (b) Yang, C.; He, B.; Zheng, Q.; Wang, D.; Qin, M.; Zhang, H.; Dai, W.; Zhang, Q.; Meng, X.; Wang, X. Nano-encapsulated tryptanthrin derivative for combined anticancer therapy via inhibiting indoleamine 2,3-dioxygenase and inducing immunogenic cell death. *Nanomedicine* **2019**, *14*, 2423−2440. (c) Duca, G.; Pogrebnoi, S.; Boldescu, V.; Aksakal, F.; Uncu, A.; Valica, V.; Uncu, L.; Negres, S.; Nicolescu, F.; Macaev, F. Tryptanthrin Analogues as Inhibitors of Enoyl-acyl Carrier Protein Reductase: Activity against Mycobacterium tuberculosis, Toxicity, Modeling of Enzyme Binding. *Curr. Top. Med. Chem.* **2019**, *19*, 609−619. (d) Kamal, A.; Reddy, B. V. S.; Sridevi, B.; Ravikumar, A.; Venkateswarlu, A.; Sravanthi, G.; Sridevi, J. P.; Yogeeswari, P.; Sriram, D. Synthesis and biological evaluation of phaitanthrin congeners as anti-mycobacterial agents. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 3867−3872. (e) McClay, K.; Mehboob, S.; Yu, J.; Santarsiero, B. D.; Deng, J.; Cook, J. L.; Jeong, H.; Johnson, M. E.; Steffan, R. J. Indole trimers with antibacterial activity against Gram-positive organisms produced using combinatorial biocatalysis. *AMB Express* **2015**, *5*, 38. (f) Gaitanis, G.; Magiatis, P.; Mexia, N.; Melliou, E.; Efstratiou, M. A.; Bassukas, I. D.; Velegraki, A. Antifungal activity of selected Malassezia indolic compounds detected in culture. *Mycoses* **2019**, *62*, 597−603. (g) Guda, R.; Narsimha, S.; Babu, R.; Muthadi, S.; Lingabathula, H.; Palabindela, R.; Yellu, N. R.; Kumar, G.; Kasula, M. Novel substituted hydrazono indolo 2,1-b quinazoline-6,12-dione analogues as cytostatic agents: Synthesis, crystal structure, biological evaluation and molecular docking studies. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 5517−5523. (h) Hwang, J.-M.; Oh, T.; Kaneko, T.; Upton, A. M.; Franzblau, S. G.; Ma, Z.; Cho, S.-N.; Kim, P. Design, Synthesis, and Structure-Activity Relationship Studies of Tryptanthrins As Antitubercular Agents. *J. Nat. Prod.* **2013**, *76*, 354−367.

(8) Mason, J. J.; Janosik, T.; Bergman, J. A New Approach to Methoxyisatins Leading to the Total Synthesis of Ophiuroidine and Other Hydroxytryptanthrins. *Synthesis* **2009**, *2009*, 3642−3648.

(9) Vaidya, S. D.; Argade, N. P. Aryne Insertion Reactions Leading to Bioactive Fused Quinazolinones: Diastereoselective Total Synthesis of Cruciferane. *Org. Lett.* **2013**, *15*, 4006−4009.

(10) Wang, C.; Zhang, L.; Ren, A.; Lu, P.; Wang, Y. Cu-Catalyzed Synthesis of Tryptanthrin Derivatives from Substituted Indoles. *Org. Lett.* **2013**, *15*, 2982−2985.

(11) Tsukano, C.; Okuno, M.; Nishiguchi, H.; Takemoto, Y. Palladium(0)-Catalyzed Carbon-Hydrogen Bond Functionalization

for the Synthesis of Indoloquinazolinones. *Adv. Synth. Catal.* **2014**, *356*, 1533−1538.
(12) Xia, Z.; Wang, K.; Zheng, J.; Ma, Z.; Jiang, Z.; Wang, X.; Lv, X. Copper-catalyzed domino intramolecular cyclization: a facile and efficient approach to polycyclic indole derivatives. *Org. Biomol. Chem.* **2012**, *10*, 1602−1611.
(13) Vangrevelinghe, E.; Zimmermann, K.; Schoepfer, J.; Portmann, R.; Fabbro, D.; Furet, P. Discovery of a potent and selective protein kinase CK2 inhibitor by high-throughput docking. *J. Med. Chem.* **2003**, *46*, 2656−2662.
(14) Kotipalli, T.; Kavala, V.; Janreddy, D.; Kuo, C.-W.; Kuo, T.-S.; Huang, H.-N.; He, C.-H.; Yao, C.-F. Syntheses of indolo 1,2-a quinazolinone derivatives via palladium catalyzed intramolecular C-H amidation. *RSC Adv.* **2014**, *4*, 2274−2283.
(15) Badigenchala, S.; Sekar, G. NIS Mediated Cross-Coupling of C(sp(2))-H and N-H Bonds: A Transition-Metal-Free Approach toward Indolo 1,2-a quinazolinones. *J. Org. Chem.* **2017**, *82*, 7657−7665.
(16) (a) Guo, S.; Wang, F.; Tao, L.; Zhang, X.; Fan, X. Solvent-Dependent Copper-Catalyzed Indolyl C3-Oxygenation and N1-Cyclization Reaction: Selective Synthesis of 3H-Indol-3-ones and Indolo[1,2-c]quinazolines. *J. Org. Chem.* **2018**, *83*, 3889−3896. (b) Zheng, J.; Zhang, Y.; Cui, S. Rh(III)-Catalyzed Selective Coupling of N-Methoxy-1H-indole-1-carboxamides and Aryl Boronic Acids. *Org. Lett.* **2014**, *16*, 3560−3563. (c) Nakamura, I.; Sato, Y.; Terada, M. Platinum-Catalyzed Dehydroalkoxylation-Cyclization Cascade via N-O Bond Cleavage. *J. Am. Chem. Soc.* **2009**, *131*, 4198−4199. (d) Wang, Z.-J.; Yang, J.-G.; Yang, F.; Bao, W. One-Pot Synthesis of Pyrimido 1,6-a indol-1(2H)-one Derivatives by a Nucleophilic Addition/Cu-Catalyzed N-Arylation/Pd-Catalyzed C-H Activation Sequential Process. *Org. Lett.* **2010**, *12*, 3034−3037. (e) Ansari, N. H.; Dacko, C. A.; Akhmedov, N. G.; Soderberg, B. C. G. Double Palladium Catalyzed Reductive Cyclizations. Synthesis of 2,2 '-, 2,3 '-, and 3,3 '-Bi-1H-indoles, Indolo 3,2-b indoles, and Indolo 2,3-b indoles. *J. Org. Chem.* **2016**, *81*, 9337−9349. (f) Hou, Z.-W.; Mao, Z.-Y.; Zhao, H.-B.; Melcamu, Y. Y.; Lu, X.; Song, J.; Xu, H.-C. Electrochemical C-H/N-H Functionalization for the Synthesis of Highly Functionalized (Aza)indoles. *Angew. Chem., Int. Ed.* **2016**, *55*, 9168−9172. (g) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Ghirga, F.; Goggiamani, A.; Iazzetti, A.; Marinelli, F. Palladium-Catalyzed Cascade Approach to 12-(Aryl)indolo[1,2-c]quinazolin-6(5H)-ones. *Synthesis* **2018**, *50*, 1133−1140.
(17) Yan, H.; Xiao, X.-Q.; Hider, R. C.; Ma, Y. A Simple Metal-Free Cyclization for the Synthesis of 4-Methylene-3-Substituted Quinazolinone and Quinazolinthione Derivatives: Experiment and Theory. *Front. Chem.* **2019**, *7*, 584.
(18) (a) Wei, Y.; Deb, I.; Yoshikai, N. Palladium-Catalyzed Aerobic Oxidative Cyclization of N-Aryl Imines: Indole Synthesis from Anilines and Ketones. *J. Am. Chem. Soc.* **2012**, *134*, 9098−9101. (b) Würtz, S.; Rakshit, S.; Neumann, J. J.; Dröge, T.; Glorius, F. Palladium-Catalyzed Oxidative Cyclization of N-Aryl Enamines: From Anilines to Indoles. *Angew. Chem., Int. Ed.* **2008**, *47*, 7230−7233. (c) He, G.; Chen, G. A Practical Strategy for the Structural Diversification of Aliphatic Scaffolds through the Palladium-Catalyzed Picolinamide-Directed Remote Functionalization of Unactivated C(sp(3))-H Bonds. *Angew. Chem., Int. Ed.* **2011**, *50*, 5192−5196. (d) Wang, G.-W.; Yuan, T.-T.; Li, D.-D. One-Pot Formation of C-C and C-N Bonds through Palladium-Catalyzed Dual C-H Activation: Synthesis of Phenanthridinones. *Angew. Chem., Int. Ed.* **2011**, *50*, 1380−1383. (e) Wan, J.-C.; Huang, J.-M.; Jhan, Y.-H.; Hsieh, J.-C. Novel Syntheses of Fluorenones via Nitrile-Directed Palladium-Catalyzed C-H and Dual C-H Bond Activation. *Org. Lett.* **2013**, *15*, 2742−2745. (f) Luo, Y.-C.; Yang, C.; Qiu, S.-Q.; Liang, Q.-J.; Xu, Y.-H.; Loh, T.-P. Palladium(II)-Catalyzed Stereospecific Alkenyl C-H Bond Alkylation of Allylamines with Alkyl Iodides. *ACS Catal.* **2019**, *9*, 4271−4276.
(19) (a) Chen, X.; Li, W.-J.; Li, S.; Tang, J.; Du, X.; Zheng, X.-L.; Yuan, M.-L.; Fu, H.-Y.; Li, R.-X.; Chen, H. Palladium-Catalyzed Direct Arylation of Alkylpyridine via Activated N-Methylpyridinium Salts. *J. Org. Chem.* **2020**, *85*, 622−632. (b) Feng, Z.; Min, Q.-Q.; Xiao, Y.-L.; Zhang, B.; Zhang, X. Palladium-Catalyzed Difluoroalkylation of Aryl Boronic Acids: A New Method for the Synthesis of Aryldifluoromethylated Phosphonates and Carboxylic Acid Derivatives. *Angew. Chem., Int. Ed.* **2014**, *53*, 1669−1673. (c) Hari Balakrishnan, M.; Mannathan, S. Palladium/Copper-Catalyzed Denitrogenative Alkylidenation and ortho-Alkynylation Reaction of 1,2,3-Benzotriazin-4(3H)-ones. *Org. Lett.* **2020**, *22*, 542−546. (d) Bhaskararao, B.; Singh, S.; Anand, M.; Verma, P.; Prakash, P.; Athira, C.; Malakar, S.; Schaefer, H. F.; Sunoj, R. B. Is silver a mere terminal oxidant in palladium catalyzed C-H bond activation reactions? *Chem. Sci.* **2020**, *11*, 208−216. (e) Mai, S.; Li, W.; Li, X.; Zhao, Y.; Song, Q. Palladium-catalyzed Suzuki-Miyaura coupling of thioureas or thioamides. *Nat. Commun.* **2019**, *10*, 5709. (f) Yoo, K.; Jwa, D. G.; Lee, H. E.; Kim, H. J.; Kim, C.; Kim, M. Recent Organic Transformations with Silver Carbonate as a Key External Base and Oxidant. *Catalysts* **2019**, *9*, 1032.
(20) Ponpandian, T.; Muthusubramanian, S. Copper catalysed domino decarboxylative cross coupling-cyclisation reactions: synthesis of 2-arylindoles. *Tetrahedron Lett.* **2012**, *53*, 4248−4252.

https://dx.doi.org/10.1021/acs.joc.0c02155
J. Org. Chem. 2021, 86, 1448−1455