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Palladium-Catalyzed Cascade Reaction of 2-Amino-*N'*-arylbenzohydrazides with Triethyl Orthobenzoates to Construct Indazolo[3,2-*b*]quinazolinones

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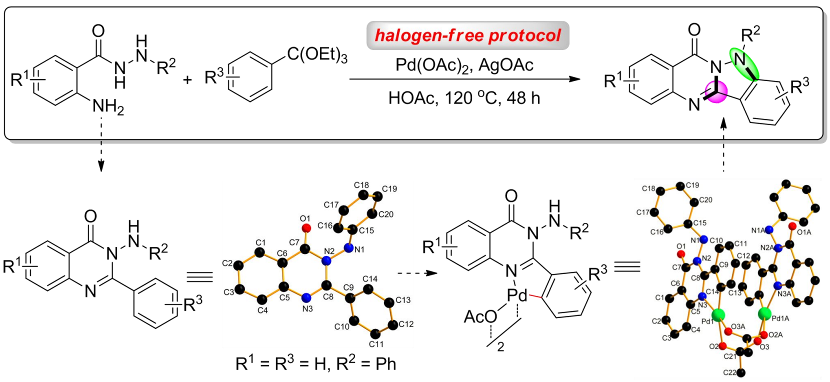
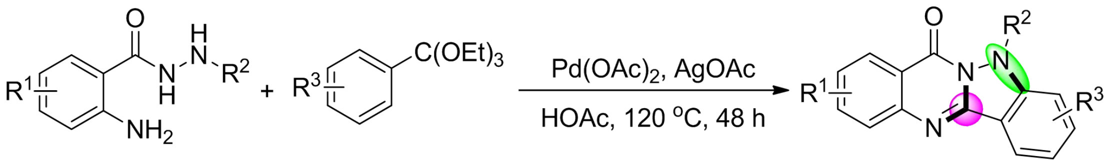


ABSTRACT: A palladium-catalyzed sequential cyclization/C-H activation cascade reaction of 2-amino-*N'*-arylbenzohydrazides with triethyl orthobenzoates has been developed, providing indazolo[3,2-*b*]quinazolinones in good to high yields. Two key intermediates of the reaction, 2-phenyl-3-(phenylamino)quinazolinone and C-H insertion palladacycle, were isolated, and their structures were unambiguously confirmed by X-ray crystallography. This method represents an unprecedented example for a halogen-free protocol to access indazolo[3,2-*b*]quinazolinones. Moreover, this chemistry also provides a useful tool for the discovery of fluorescent materials.

INTRODUCTION

Quinazolinone-based fused poly-*N*-heterocycles have shown to be important class of alkaloids in the past few years because they are widely found in natural products such as luotonin A,[1] cruciferane,[2] circumdatins,[3] rutaecarpine,[4] vasicinone,[5] and tryptanthrin,[6] *etc.* The combined molecules of indazole and quinazolinone frameworks, indazoloquinazolinone derivatives, are important biological molecules and some of them are potent inhibitors of phosphodiesterase 4 (PDE4).[7a] However, the efficient synthetic method has been under-developed. Pal,[7a] Wang,[7b] and our group[7c] have independently reported the methods for the preparation of indazoloquinazolinone derivatives, but the use of halogenated substrates put a limitation on the reported method. For example, halogenated compounds themselves and halide byproducts are generally environmental pollutants. In addition, halogenated compounds are not always easily available and their preparation often involves tedious steps, harsh reaction conditions, and production of waste. As a consequence, the development of new synthetic strategies to access unique quinazolinone-based fused poly-*N*-heterocycles for new leads in drug discovery is still highly desirable. From a synthetic standpoint, developing cascade processes involving transition-metal-catalyzed C-H bond amination represents one of the most versatile and practical approaches for installation nitrogen-containing molecules.[8] Recently, we reported palladium-catalyzed intramolecular aerobic oxidative C−H amination of 2-aryl-3-(arylamino)quinazolinones for the synthesis of indazolo[3,2-*b*]quinazolinones.[9]

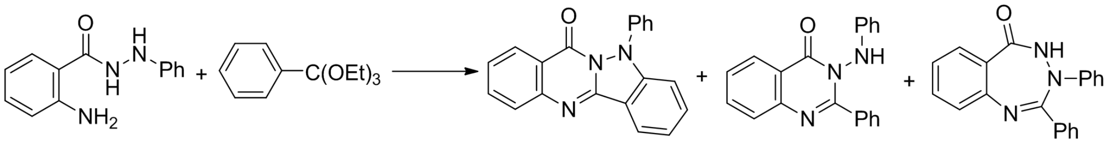
This work stands for part of the ongoing program in our laboratory toward the development of new metal-catalyzed C-H activation[10] for the synthesis of quinazolinone derivatives.[11] Herein, we report a new protocol to construct indazolo[3,2-*b*]quinazolinones (**3**) from 2-amino-*N′*-arylbenzohydrazides (**1**) with triethyl orthobenzoates (**2**) in one-pot formation of triple C-N bonds via palladium-catalyzed sequential cyclization/C-H activation cascade process (Scheme 1).



Scheme 1. Synthesis of indazolo[3,2-*b*]quinazolinones

RESULTS AND DISCUSSION

Our preliminary studies were focused on the reaction between 2-amino-*N′*-phenylbenzohydrazide (**1a**) and triethyl orthobenzoate (**2a**) to obtain 2,3-diphenyl-3*H*-benzo[*e*][1,2,4] triazepin-5(4*H*)-one (**5a**)[12] by condensation /intramolecular cyclization reaction (Scheme 2). Through the screening process, no target product **5a** was detected under a variety of conditions. We were surprised to find that a trace amount of unexpected 5-phenylindazolo[3,2-*b*]quinazolinone (**3a**) and 2-phenyl-3-(phenylamino)quinazolinone (**4a**) were observed by GC/MS (EI) analysis using benzoquinone[13] as an oxidant in the presence of $Pd(OAc)_2$. When oxone was used as the oxidant, compounds **3a** and **4a** were obtained in 17% and 39% isolated yields, respectively. Their structures were unambiguously confirmed by X-ray crystallography (Figure 1).[14] The formation of the unexpected product **3a** may undergo cyclization reaction of **1a** and **2a** followed by intramolecular C-H amination of the key intermediate **4a**.



Scheme 2. Reaction of 1a with 2a

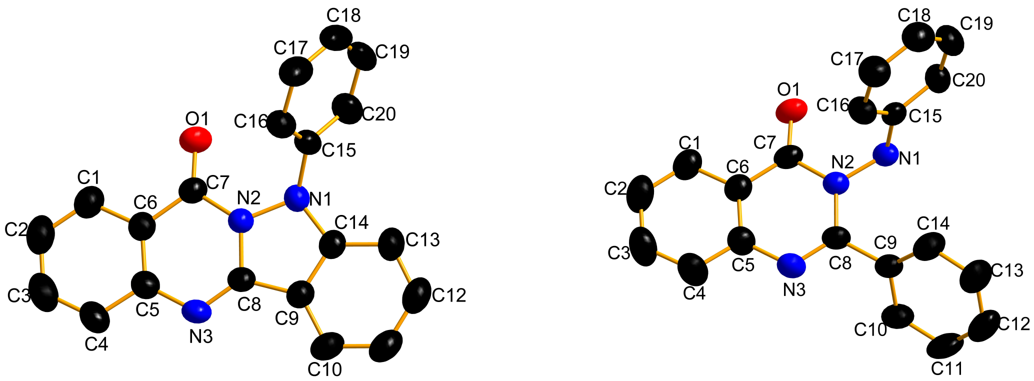
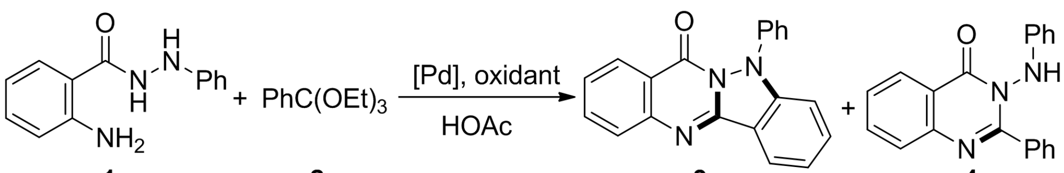


Figure 1. X-ray crystal structure of compound 3a and 4a. Thermal ellipsoids are drawn at 50% probability, and H atoms have been omitted for clarity.

This finding inspired us to explore the more challenging cascade reactions for the synthesis of **3a**. We next investigated the model reaction using silver salts as the oxidant. Silver salts such as Ag_2O, Ag_2SO_4 and Ag(TFA) could promote the reaction, leading to **3a** in 53%, 45% and 79% yields, respectively (Table 1, entries 2-4). Other oxidants exhibited lower efficiencies (see entries 1–13 of Table S1 in the Supporting Information). We were delighted to find that the yield of **3a** was improved to 88% yield when the combination of $Pd(OAc)_2$ and AgOAc was employed in HOAc (Table 1, entry 5). Replacement of $Pd(OAc)_2$ with other Pd sources resulted in lower yields (see Table 1, entries 6-8, and entries 14-19 of Table S1 in the Supporting Information). In addition, adjusting other reaction parameters, including solvents, temperatures, and molar ratios, failed to increase the yields of **3a** (see entries 20-29 of Table S1 in the Supporting Information). Catalytic activity was also observed under O_2 or N_2 atmosphere, albeit in slightly low yields of 79% and 81%, respectively (Table 1, entries 9-10). In the absence of the palladium catalyst or silver salt, no or only a trace amount of the desired **3a** was detected (Table 1, entries 11-12).

Table 1. Screening of Reaction Conditions[a]



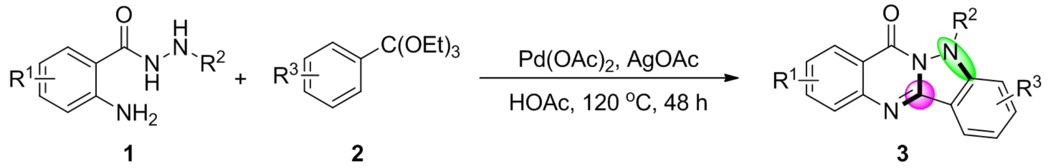
Entry	[Pd]	Oxidant	Yield (%)[b]	
			3a	**4a**
1	$Pd(OAc)_2$	oxone	17	39
2	$Pd(OAc)_2$	Ag_2O	53	21
3	$Pd(OAc)_2$	Ag_2SO_4	45	34
4	$Pd(OAc)_2$	Ag(TFA)	79	trace
5	**$Pd(OAc)_2$**	**AgOAc**	**88**	**0**
6	$PdCl_2$	AgOAc	52	32
7	$Pd(acac)_2$	AgOAc	72	trace
8	$Pd(TFA)_2$	AgOAc	76	trace
9	$Pd(OAc)_2$	AgOAc	79[c]	0
10	$Pd(OAc)_2$	AgOAc	81[d]	0
11	$Pd(OAc)_2$		trace	72
12		AgOAc	0	83

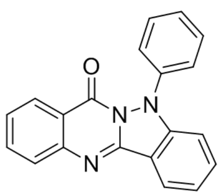
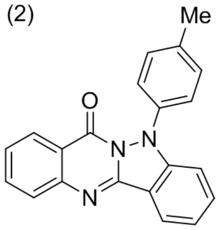
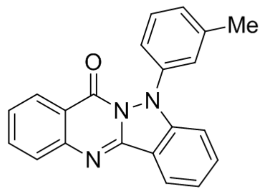
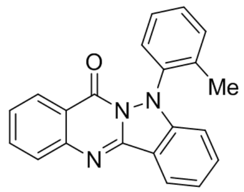
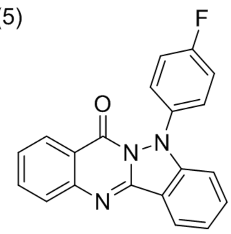
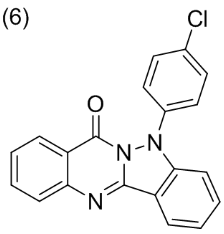
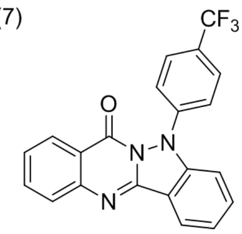
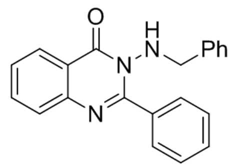
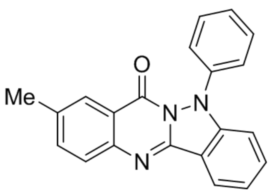
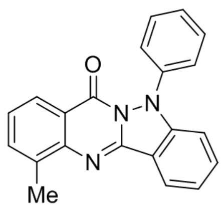
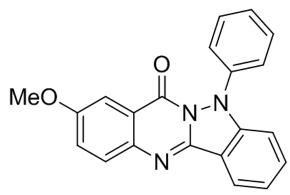
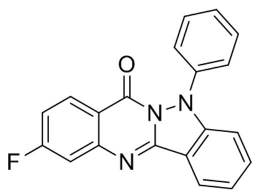
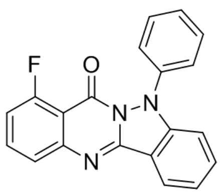
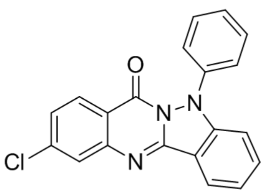
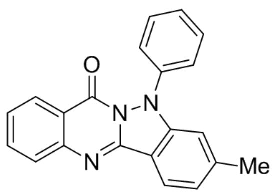
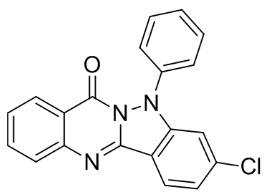
[a] Unless otherwise noted, all reactions were carried out as follows: **1a** (0.2 mmol), **2a** (0.8 mmol), Pd source (10 mol%), oxidant (4 equiv) and AcOH (6 mL), air, 120 °C, 48 h. [b] Isolated yield. [c] Under O_2 atmosphere. [d] Under N_2 atmosphere.

Having the optimial reaction conditions, we further expanded the substrate scope containing different functional groups (Table 2). First, the variation of the R^2 group of 2-amino-*N′*-arylbenzohydrazides **1** was investigated by testing the reaction between various 2-amino-*N′*-arylbenzohydrazides and triethyl orthobenzoate (**2a**) under the standard conditions. The results showed that both electron-donating and electron-withdrawing substituents were well-tolerated and provided the corresponding products in moderate to good yields. For example, substrates bearing methyl group afforded the cyclized products **3b** and **3c** in 87% and 82% yield, respectively (Table 2, entries 2 and 3). To our satisfaction, it was found that *ortho*-methyl group is also well-tolerated, affording the desired product **3d** in 69% yield (Table 2, entry 4). It is noteworthy that only trace yield of **3d** was detected in our previous protocol.[9] The electron-withdrawing fluoro, chloro, and trifluoromethyl groups allowed formation of the cyclized products **3e**, **3f** and **3g** in 83−91% yields (Table 2, entries 5-7). However, 3-(benzylamino)-2-phenylquinazolinone (**3h'**) was isolated in 16% yield and confirmed by NMR when 2-amino-*N*'-benzylbenzohydrazide was used as substrate (Table 2, entry 8).

We next examined the substitution effect on the aromatic ring of 2-amino-*N′*-arylbenzohydrazides **1**. Substrates bearing a *para*-, and *ortho*-methyl substituent with respect to the amino group were evaluated, affording **3i** (83% yield) and **3j** (64% yield) respectively (Table 2, entries 9 and 10). The lower yield of **3i** may arise from the steric hindrance. The electronic property of the substituents is not critical for this transformation. In general, the substrates bearing an electron-

Table 2. Palladium-catalyzed synthesis of indazolo[3,2-*b*]quinazolinones[a]



(1)  **3a** (88%)	(2)  **3b** (87%)	(3)  **3c** (82%)	(4)  **3d** (69%)
(5)  **3e** (83%)	(6)  **3f** (91%)	(7)  **3g** (90%)	(8)  **3h'** (16%)
(9)  **3i** (83%)	(10)  **3j** (64%)	(11)  **3k** (89%)	(12)  **3l** (82%)
(13)  **3m** (78%)	(14)  **3n** (75%)	(15)  **3o** (85%)	(16)  **3p** (76%)

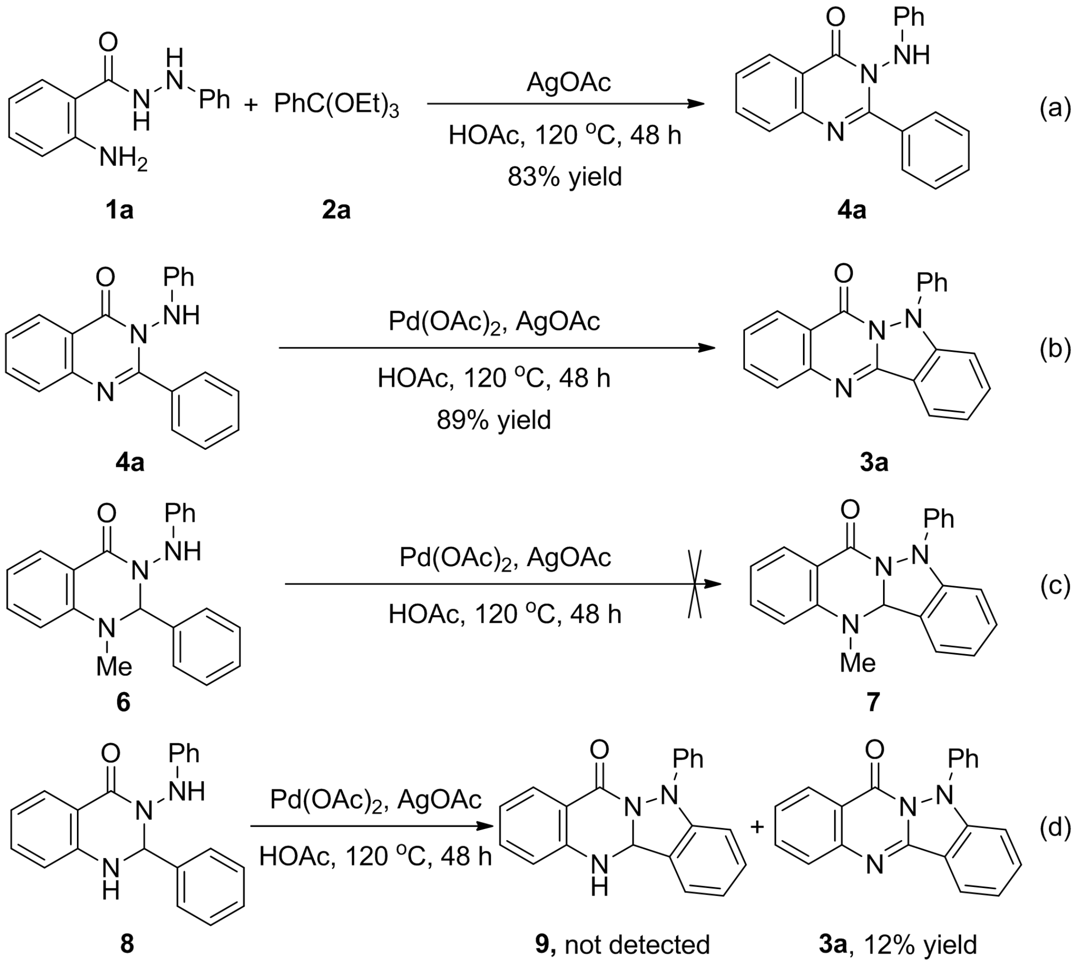
[a] Unless otherwise noted, all reactions were carried out as follows: **1** (0.2 mmol), **2** (0.8 mmol), $Pd(OAc)_2$ (10 mol%), AgOAc (4 equiv) and AcOH (6 mL), air, 120 °C, 48 h. [b] Isolated yield are provided in parentheses.

donating substituent (e.g., –OMe) provided a slightly higher yield than those bearing an electron-withdrawing substituent (e.g., –F or –Cl) (Table 2, entries 11-14). Finally we tested the reaction scope of triethyl orthobenzoates. The results showed that electron-donating groups had more favorable effects than electron-withdrawing groups. For example, treatment of 2-amino-*N′*-phenyl benzohydrazide (**1a**) with *p*-methyl triethyl orthobenzoate afforded **3o** in 85% yield, while the yield of **3p** was decreased to 76% with *p*-chloro triethyl orthobenzoate (Table 2, entries 15 and 16).

It is noteworthy that the ability to incorporate the whole range of halogen substituents makes this method particularly appealing, since the successful synthesis of halogen-substituted products, such as **3e**, **3f**, **3l**, **3m**, **3n**, and **3p** (Table 2, entries 5, 6, 12-14 and 16) enabled further access to more complex compounds in combination with cross-coupling transformations.

To elucidate the mechanism of the formation of indazolo[3,2-*b*]quinazolinones, some control experiments were performed under the standard conditions as shown in Scheme 3. It was found that 2-phenyl-3-(phenylamino)quinazolinone (**4a**) was obtained in 83% yield when the reaction of 2-amino-*N′*-phenylbenzohydrazide (**1a**) and triethyl orthobenzoate (**2a**) was performed in the absence of palladium catalyst (Scheme 3a). The desired product **3a** was isolated in 89% yield when **4a** was used (Scheme 3b). However, the product **7** could not be detected when *N*-methyl-2-phenyl-3-(phenylamino)-2,3-dihydroquinazolin-4(1*H*)-one (**6**) was used as substrate under the standard conditions, almost 90% of **6** was recovered (Scheme

3c). The reaction of 2-phenyl-3-(phenylamino)-2,3-dihydroquinazolin-4(1*H*)-one (**8**) failed to deliver 5-phenyl-12,12a-dihydroindazolo[3,2-*b*]quinazolin-7(5*H*)-one (**9**) along with product **3a** in 12% yield (Scheme 3d). These results above revealed that 2-phenyl-3-(phenylamino)quinazolinone (**4a**) is the key intermediate for the transformation.



Scheme 3. Control Experiments

On the other hand, although we could not observe the formation of six-membered palladacycle complex[15] (Figure 2, mode **I**), we were able to obtain the key intermediate five-membered palladacycle complex **10** (Figure 2, mode **II**) and its structure was confirmed by X-ray crystallography,[9] by the treatment of 2-

phenyl-3-(phenylamino)quinazolinone (**4a**) with a stoichiometric equivalent of $Pd(OAc)_2$ in dichloromethane (Scheme 4a). It was found palladacycle complex **10** can be smoothly converted to **3a** in the presence of AgOAc in AcOH at 120 °C (Scheme 4b). This implies that the cascade reaction of 2-amino-*N'*-arylbenzohydrazides with triethyl orthobenzoates could proceed via palladacycle complex **10**.

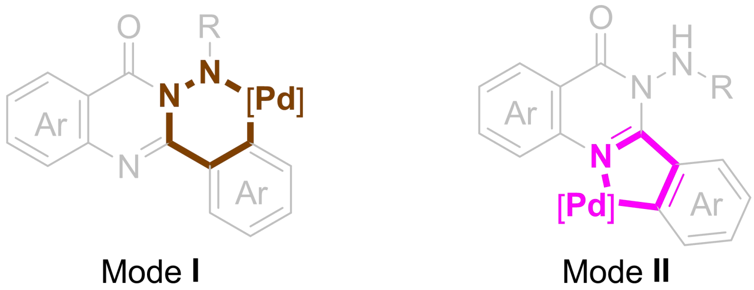
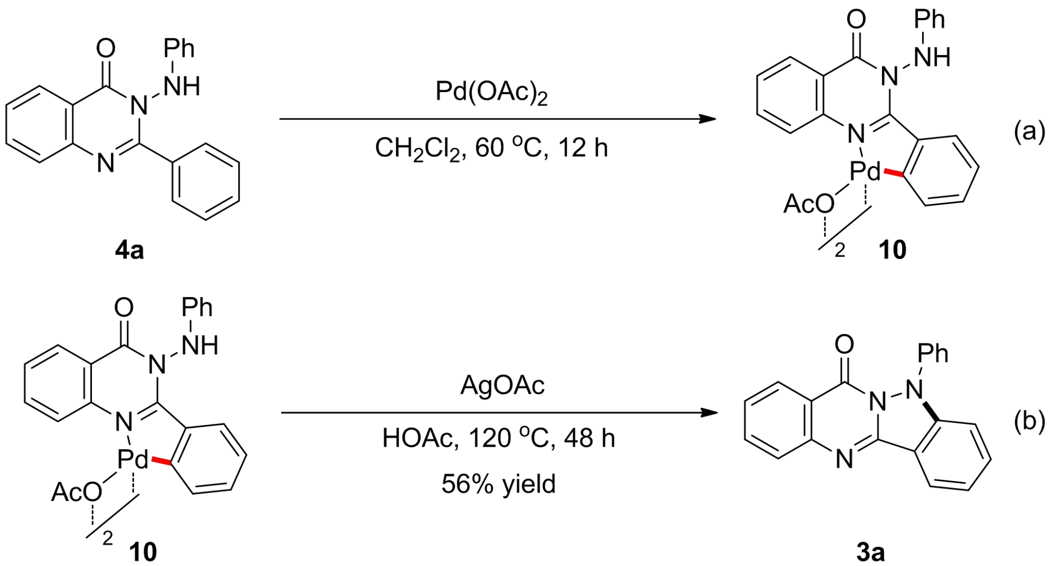
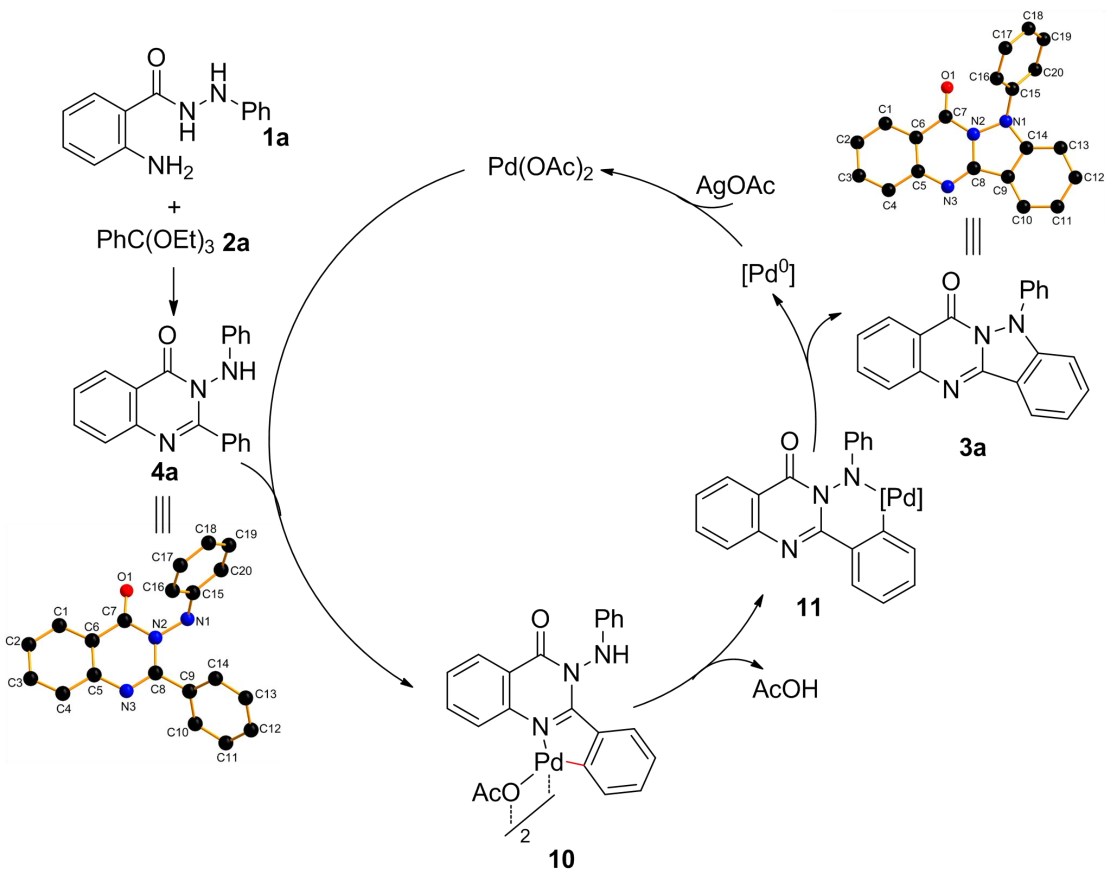


Figure 2. Coordination Mode



Scheme 4. Control Experiments

On the basis of these results and relevant reports in the literature,[16] a possible mechanism for this cascade reaction was proposed in Scheme 5. The first step may involve the formation of 2-phenyl-3-(phenylamino)quinazolinone (**4a**) by condensation/cyclization reaction of 2-amino-*N*'-phenyl benzohydrazide (**1a**) with triethyl orthobenzoate (**2a**). Next, C−H activation of **4a** generates five-membered complex **10**, which undergoes "rollover" cyclometalation[17] in the presence of AgOAc and AcOH with the increasing of temperature to afford six-membered palladacycle complex **11** by intramolecular ligand exchange with H-N(Ph)quinazolinone. Finally, the reductive elimination of complex **11** along with the C-N bond formation affords the desired product **3a** and Pd(0). AgOAc as an oxidant reoxidizes Pd(0) to Pd(II) to close the catalytic cycle. However, the mechanism of the reaction through a Pd(II)/Pd(IV) pathway cannot be ruled out.[18] A detailed mechanism need to be addressed with further studies.



Scheme 5. Plausible Mechanism for the Formation of Indazolo[3,2-*b*]quinazolinones through Pd-catalyzed C-H Activation

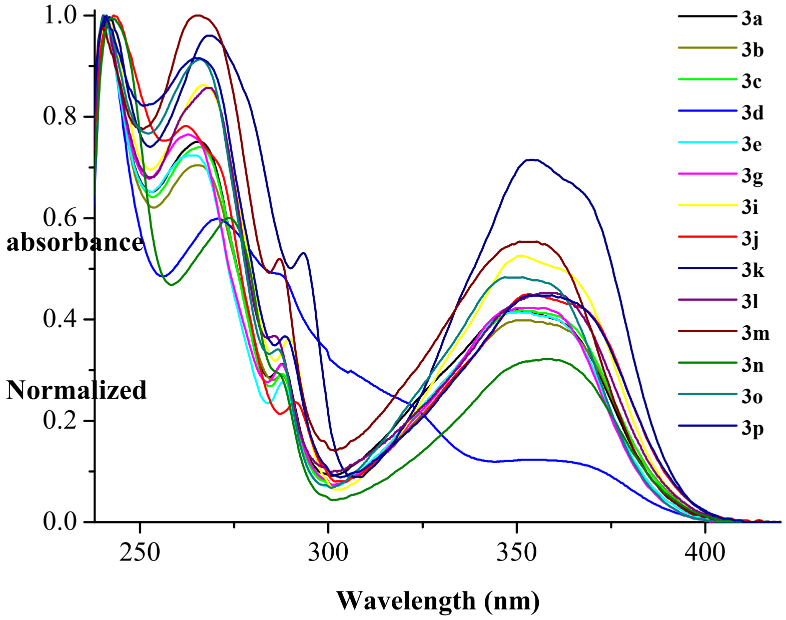


Figure 3. UV-vis Absorption Spectra of Indazolo[3,2-*b*]quinazolinones 3 in $CHCl_3$ (1×10^{-5} mol/L).

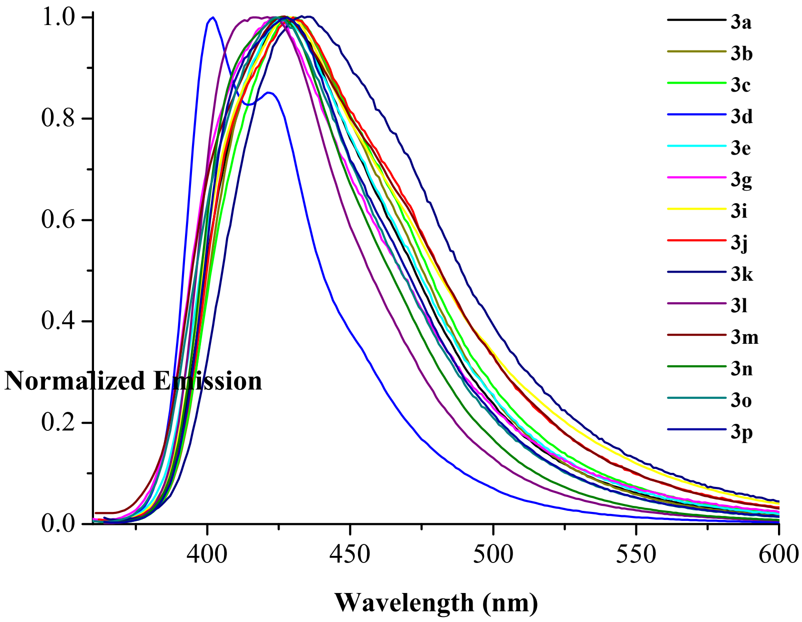


Figure 4. Fluorescence Spectra of Indazolo[3,2-*b*]quinazolinones 3 in $CHCl_3$ (1×10^{-5} mol/L). EX Slit: 5.0 nm; EM Slit: 5.0 nm; Voltage: 700 V.

Considering that nitrogen-containing heterocycles often showed excellent photophysical properties and were widely used in the field of organic fluorescent materials,[19] the UV-vis absorption and fluorescence spectra of indazolo[3,2-*b*]quinazolinones were measured in $CHCl_3$ (Figure 3, Figure 4 and Table 3).

Table 3. Photophysical Properties of Indazolo[3,2-*b*]quinazolinones in $CHCl_3$

Compd	λ_{abs} (nm)	λ_{em} (λ_{ex}, nm)	Stokes shift (nm)	Φ_{PL}
3a	241, 266, 288, 348	427 (360)	79	0.07
3b	241, 266, 288, 350	429 (352)	79	0.10
3c	241, 266, 288, 351	430 (357)	79	0.08
3d	241, 271, 354	402, 422 (356)	68	0.20
3e	241, 264, 288, 350	426 (350)	76	0.07
3g	241, 263, 287, 350	424 (349)	74	0.03
3i	241, 267, 290, 351	429 (352)	78	0.05
3j	243, 262, 291, 354	430 (352)	76	0.06
3k	242, 269, 293, 353	434 (354)	81	0.02
3l	240, 268, 358	424 (354)	66	0.27
3m	240, 265, 287, 353	426 (351)	73	0.02
3n	243, 274, 357	426 (353)	69	0.09
3o	240, 267, 287, 348	424 (350)	76	0.04
3p	241, 265, 289, 354	428 (354)	74	0.11

Indazolo[3,2-*b*]quinazolinones showed well-resolved absorption peaks between 241 nm and 357 nm, and emited blue fluorescence light in the range of 403–430 nm. It was found that indazolo[3,2-*b*]quinazolinones with electron-donating (e.g., –Me and –OMe) and electron-withdrawing groups (e.g., –F, –Cl and –CF_3)

exhibited slight influence. The novel dyes showed outstanding Stokes shifts between 68 nm and 81 nm, which is an attractive property for the detection of emission wavelength by avoiding the interference from the excitation wavelength.[20] In addition, the fluorescence efficiency (Φ_F) of indazolo[3,2-*b*]quinazolinones was determined to be in the range of 0.02–0.2, using quinine sulfate solution (Φ_F = 0.55 in 0.5 mol/L H_2SO_4) as the fluorescence reference.[21] Thus, the potential utility of indazolo[3,2-*b*]quinazolinones has been demonstrated as a new class of blue fluorophores in the field of organic fluorescent materials.

CONCLUSIONS

In summary, we have developed a new strategy for synthesis indazolo[3,2-*b*]quinazolinone derivatives in moderate to excellent yields from the palladium-catalyzed cascade reaction of 2-amino-*N′*-arylbenzohydrazides with triethyl orthobenzoates. X-ray structure of the C−H insertion intermediate has provided valuable insight into the coordination mode of quinazolinones and the possible origin of their power in directing C−H activation. Further efforts to explore the detailed mechanism and extend the applications of the transformation are currently underway in our laboratories. Additionally, the resulting indazolo[3,2-*b*]quinazolinones represent a new class of nitrogen-containing heterocyclic fluorophores with large Stokes shifts and moderate fluorescence efficiency.

EXPERIMENTAL SECTION

General Information. Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were measured on a 500 MHz spectrometer, using DMSO-d_6 or $CDCl_3$ as the solvent with tetramethylsilane (TMS) as an internal standard at room temperature. Chemical shifts are given n δ relative to TMS, and the coupling constants J are given in hertz. High-resolution mass spectra (HRMS) were recorded on a TOF MS instrument with an EI or ESI source. 2-Amino-*N'*-arylbenzohydrazides were synthesized according to the method described in the literature.[22] Other commercially obtained reagents were used without further purification. All reactions under nitrogen atmosphere were conducted using standard Schlenk techniques. Column chromatography was performed using EM silica gel 60 (300−400 mesh).

General Procedure for the Preparation of 2-Amino-*N'*-arylbenzohydrazides. To a 50 mL round bottom flask a suspension of isatoic anhydrides (10 mmol) in THF (20 mL) was treated by slow addition of 1.2 equiv. of hydrazines (12 mmol). The reaction mixture was refluxed for overnight. The mixture was cooled to room temperature and concentrated in vacuo. 2-Amino-N'-arylbenzohydrazides **1** was obtained as white solid after crystallized from ethanol.

General Procedure for the Palladium-Catalyzed Synthesis of Indazolo[3,2-*b*]quinazolinones. In a 25 mL sealed tube, 2-amino-*N'*-arylbenzohydrazides **1** (0.2 mmol), $Pd(OAc)_2$ (0.02 mmol, 10 mol %), AgOAc (0.8 mmol), were dissolved in HOAc (6 mL) under air, then triethyl orthobenzoates **2** (0.8 mmol) was added to the reaction mixture. The reaction mixture was then tightly capped and stirred for 10 minutes at room temperature for proper mixing of the reactants, and then heated at

120 °C with vigorous stirring for 48 hours. The reaction mixture was then cooled to room temperature, diluted with dichloromethane and filtered through a small pad of Celite. The filtrate was washed with saturated $NaHCO_3$ and then brine. After the aqueous layer was extracted with ethyl acetate, the combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under a vacuum. The residue was purified by a silica gel packed flash chromatography column (hexane/ethyl acetate) to afford the desired products **3**.

Preparation of Compounds 6 and 8. To a solution of an isatoic anhydride (2 mmol) in MeCN (3 mL) was added a phenylhydrazine (2 mmol) and the reaction mixture was stirred under reflux (progress of the reaction was monitored by TLC). After the reaction was finished, benzaldehyde (2 mmol) and TsOH (15 mol%) were added, and the reaction mixture was stirred at 80 ^{o}C with vigorous stirring overnight. The reaction mixture was cooled to room temperature and concentrated in vacuo. The resulting residue was purified by a silica gel packed flash chromatography column (hexane/ethyl acetate) to afford compounds **6** and **8** in 63% and 72% yield, respectively.

Intramolecular Amination of Palladium Complex 10. In a 25 mL sealed tube, complex **10** (47.8 mg, 0.05 mmol, 1.0 equiv.), AgOAc (33.4 mg, 0.2 mmol 4.0 equiv.). The reaction mixture was then tightly capped and stirred for 10 minutes at room temperature for proper mixing of the reactants, and then heated at 120 ^{o}C with vigorous stirring for 48 hours. The reaction mixture was then cooled to room temperature, diluted with dichloromethane and filtered through a small pad of Celite.

The filtrate was concentrated in vacuo and purified by a silica gel packed flash chromatography column (hexane/ethyl acetate). The product **3a** was obtained as a white solid amorphous solid (17.4 mg, 56% yield).

*2-Amino-N'-m-tolylbenzohydrazide (**1c**)*: White solid (1.52 g, 63% yield), mp 183-184 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$). δ 7.72 (s, 1H), 7.50-7.48 (m, 1H), 7.29-7.26 (m, 2H), 7.15-7.12 (m, 1H), 6.76-6.69 (m, 4H), 6.21-6.20 (m, 1H), 5.54 (s, 2H), 2.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.3, 149.4, 148.4, 139.3, 133.4, 129.3, 127.1, 122.5, 117.6, 116.8, 114.5, 113.3, 110.9, 21.7. HRMS (EI, 70 eV) calcd for $C_{14}H_{15}N_3O$ [M^+]: 241.1215, found 241.1215.

*2-Amino-N'-(4-fluorophenyl)benzohydrazide (**1e**)*: White solid (1.47 g, 60% yield), mp 141-143 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$). δ 7.81 (s, 1H), 7.48-7.46 (m, 1H), 7.29-7.27 (m, 1H), 6.97-6.92 (m, 2H), 6.91-6.88 (m, 2H), 6.72-6.68 (m, 2H), 6.27 (s, 1H), 5.53 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 159.1, 157.2, 149.4, 144.5, 133.5, 127.1, 117.7, 116.9, 116.0, 115.9, 115.2, 115.1, 113.0. HRMS (EI, 70 eV) calcd for $C_{13}H_{12}FN_3O$ [M^+]: 245.0964, found 245.0961.

*2-Amino-N'-(4-(trifluoromethyl)phenyl)benzohydrazide (**1g**)*: White solid (1.59 g, 54% yield), mp 198-198 ^{o}C. ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 10.19 (s, 1H), 8.44 (s, 1H), 7.68-7.66 (m, 1H), 7.48 (d, J = 8.5 Hz, 2H), 7.22-7.18 (m, 1H), 6.88 (d, J = 8.5 Hz, 2H), 6.75-6.73 (m, 1H), 6.58-6.54 (m, 1H), 6.40 (s, 2H); ^{13}C NMR (125 MHz, DMSO-*d*$_6$) δ 168.8, 152.9, 150.0, 132.4, 128.0, 126.2, 126.1, 124.0, 118.5, 118.3, 118.0, 117.8, 116.5, 114.7, 112.3, 11.5. HRMS (EI, 70 eV) calcd for $C_{14}H_{12}F_3N_3O$ [M^+]: 295.0932, found 295.0935.

*2-Amino-3-methyl-N′-phenylbenzohydrazide (**1j**)*: White solid (1.20 g, 50% yield), mp 171-173 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.07 (d, J = 3.0 Hz, 1H), 7.79 (d, J = 3.0 Hz, 1H), 7.54 (d, J = 7.5 Hz, 1H), 7.16-7.12 (m, 3H), 6.78-6.77 (m, 2H), 6.72-6.69 (m, 1H), 6.52 (t, J = 7.5 Hz, 1H), 6.16 (s, 2H), 2.09 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.3, 149.8, 147.7, 132.9, 128.7, 125.8, 123.1, 118.5, 114.6, 112.9, 112.2, 17.6. HRMS (EI, 70 eV) calcd for $C_{14}H_{15}N_3O$ [M$^+$]: 241.1215, found 241.1215.

*2-Amino-5-methoxy-N′-phenylbenzohydrazide (**1k**)*: White solid (1.72 g, 67% yield), mp 208-209 °C. ^{1}H NMR (500 MHz, DMSO-d_6). δ 10.10 (s, 1H), 7.78 (s, 1H), 7.24 (d, J = 3.0 Hz, 1H), 7.17-7.14 (m, 2H), 6.90-6.88 (m, 1H), 6.80-6.78 (m, 2H), 6.73-6.68 (m, 2H), 6.18 (s, 2H), 3.72 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.5, 149.8, 149.3, 144.2, 128.7, 120.2, 118.5, 117.8, 112.8, 112.3, 111.4, 55.6. HRMS (EI, 70 eV) calcd for $C_{14}H_{15}N_3O_2$ [M$^+$]: 257.1164, found 257.1165.

*2-Amino-4-fluoro-N′-phenylbenzohydrazide (**1l**)*: White solid (1.49 g, 61% yield), mp 175-176 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.50-7.47 (m, 1H), 7.28-7.24 (m, 2H), 6.94-6.91 (m, 3H), 6.42-6.36 (m, 2H), 6.24 (d, J = 3.0 Hz, 1H), 5.72 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.1, 157.7, 156.9, 148.3, 135.3, 129.4, 129.3, 121.6, 113.8, 104.6, 104.4, 103.4, 103.2, 100.1. HRMS (EI, 70 eV) calcd for $C_{13}H_{12}FN_3O$ [M$^+$]: 245.0964, found 245.0967.

*N-methyl-2-phenyl-3-(phenylamino)-2,3-dihydroquinazolin-4(1H)-one (**6**)*: White solid (0.41 g, 63% yield), mp 172-173 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.35 (s, 1H), 7.77-7.75 (m, 1H), 7.34-7.33 (m, 1H), 7.44-7.31 (m, 3H), 7.29-7.27 (m, 2H), 7.21-7.18 (m, 2H), 6.86-6.82 (m, 3H), 6.80-6.77 (m, 1H), 6.70 (d, J = 8.5Hz, 1H), 5.88 (s, 1H), 2.93 (s, 3H); ^{13}C NMR (125Mz, DMSO-d_6) δ 161.7, 147.6, 146.7, 137.4, 134.2, 128.9, 128.7, 128.5, 127.7, 126.4, 119.3, 117.7, 115.5, 112.4, 112.2, 79.7, 35.1. HRMS (EI, 70 eV) calcd for $C_{21}H_{19}N_3O$ [M^+]: 329.1528, found 329.1531.

*5-Phenylindazolo[3,2-b]quinazolin-7(5H)-one (**3a**).*[7c] White solid (54.7 mg, 88% yield), mp 230-231 ºC (lit. 227-228 ºC); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34-8.32 (m, 1H), 8.29 (d, *J* = 8.0 Hz, 1H), 7.91 (d, *J* = 8.5 Hz, 1H), 7.83-7.80 (m, 1H), 7.63-7.60 (m, 1H), 7.50-7.35 (m, 7H), 7.21 (d, *J*=8.5Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5, 149.2, 148.8, 148.3, 141.9, 134.1, 133.5, 129.6, 128.7, 127.1, 126.8, 125.5, 124.7, 124.4, 123.4, 119.9, 118.9, 112.5.

*5-p-Tolylindazolo[3,2-b]quinazolin-7(5H)-one (**3b**).*[7c] White solid (56.6 mg, 87% yield), mp 184-185 ºC (lit. 184-185 ºC); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34-8.32 (m, 1H), 8.28 (d, *J* = 7.5 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.83-7.79 (m, 1H), 7.63-7.59 (m, 1H), 7.47-7.39 (m, 2H), 7.28-7.24 (m, 4H), 7.18 (d, *J* = 8.0 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5, 149.4, 148.7, 148.3, 139.3, 138.8, 134.1, 135.5, 130.3, 127.0, 126.8, 125.4, 124.7, 124.3, 123.3, 119.9, 118.8, 112.5, 21.4.

*5-m-Tolylindazolo[3,2-b]quinazolin-7(5H)-one (**3c**).*[7c] White solid (53.3 mg, 82% yield), mp 221-223 ºC (lit. 241-242 ºC); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35-8.33 (m, 1H), 8.29 (d, *J* = 8.0 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.84-7.80 (m, 1H), 7.64-7.60 (m, 1H), 7.48-7.34 (m, 3H), 7.22-7.16 (m, 3H), 7.14(s, 1H), 2.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5, 149.3, 148.8, 148.4, 141.9, 139.8, 134.1, 133.5, 129.6, 129.4, 127.1, 126.8, 125.5, 125.0, 124.4, 123.3, 121.7, 119.9, 118.9, 112.6, 21.6.

5-o-Tolylindazolo[3,2-b]quinazolin-7(5H)-one (***3d***).[7c] White solid (44.8 mg, 69% yield), mp 219-221 ºC (lit. 221-223 ºC). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32-8.29 (m, 2H), 7.91 (d, *J* = 8.5 Hz, 1H), 7.82-7.79 (m, 1H), 7.63-7.60 (m, 1H), 7.45-7.34 (m, 4H), 7.22-7.19 (m, 1H). 6.96-6.93 (m, 2H), 2.47 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.4, 148.8, 148.6, 148.0, 140.1, 136.7, 134.0, 133.6, 131.5, 129.5, 127.3, 127.1, 126.7, 125.5, 125.3, 123.8, 123.4, 119.8, 118.6, 111.9, 18.2.

5-(4-Fluorophenyl)indazolo[3,2-b]quinazolin-7(5H)-one (***3e***).[7c] Light green solid (54.6 mg, 83% yield), mp 197-198 ºC (lit. 197-198 ºC); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.25 (d, *J* = 7.5 Hz, 1H), 8.17 (d, *J* = 8.0 Hz, 1H), 7.92-7.88 (m, 2H), 7.77-7.74 (m, 1H), 7.57-7.49 (m, 4H), 7.33-7.30 (m, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.2, 160.2, 155.3, 148.4, 148.2, 147.6, 137.9, 134.0, 133.8, 126.9, 126.6, 126.5, 125.9, 125.3, 124.6, 122.9, 119.4, 118.3, 116.1, 115.9, 112.3.

5-(4-Chlorophenyl)indazolo[3,2-b]quinazolin-7(5H)-one (***3f***).[7b] Light yellow solid (62.6 mg, 91% yield), mp 240-242 ºC (lit. 236-237 ºC); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32-8.30 (m, 1H), 8.28 (d, *J* = 7.5 Hz, 1H), 7.90 (d, *J* = 8.5 Hz, 1H), 7.84-7.80 (m, 1H), 7.64-7.61 (m, 1H), 7.49-7.41 (m, 4H), 7.32-7.30 (m, 2H), 7.17 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5, 148.9, 148.7, 148.1, 140.5, 134.5, 134.2, 133.6, 129.9, 127.2, 126.8, 126.2, 125.7, 124.7, 123.5, 119.8, 119.0, 112.4.

5-(4-(Trifluoromethyl)phenyl)indazolo[3,2-b]quinazolin-7(5H)-one (***3g***).[7c] White solid (68.2 mg, 90% yield), mp 214-215 ºC (lit. 210-212 ºC); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.27 (d, *J* = 8.0 Hz, 1H), 8.19 (d, *J* = 8.0 Hz, 1H), 7.94-7.90 (m, 2H), 7.86 (d, *J* = 8.5 Hz, 2H), 7.79-7.74 (m, 3H), 7.57-7.52 (m, 2H), 7.49 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 155.3, 148.2, 147.7, 147.4, 144.9, 134.2, 133.9, 128.3, 128.0, 127.7, 127.5, 126.9, 126.4, 126.3, 126.0, 125.5, 125.1, 125.0, 124.3, 123.1, 122.8, 119.4, 118.6, 112.2.

*9-Methyl-5-phenylindazolo[3,2-b]quinazolin-7(5H)-one (**3i**).*[7c] White solid (54.0 mg, 83% yield), mp 241-242 °C (lit. 236-238 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.0 Hz, 1H), 8.11 (s, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.65-7.58 (m, 2H), 7.49-7.46 (m, 2H), 7.42-7.38 (m, 2H), 7.36-7.34 (m, 2H), 7.21 (d, *J* = 8.5 Hz, 1H), 2.50 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.4, 149.2, 147.7, 146.8, 142.1, 135.8, 135.7, 133.3, 129.6, 128.5, 126.9, 126.1, 124.5, 124.4, 123.2, 119.7, 119.1, 112.5, 21.5.

*11-Methyl-5-phenylindazolo[3,2-b]quinazolin-7(5H)-one (**3j**).* White solid (41.6 mg, 64% yield), mp 175.7-177.3 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (d, *J* =7.5 Hz, 1H), 8.19-8.18 (m, 1H), 7.66 (d, *J* =8.0 Hz, 1H), 7.62-7.58 (m, 1H), 7.48-7.45 (m, 2H), 7.42-7.39 (m, 3H), 7.36-7.33 (m, 2H), 7.21 (d, *J* = 8.5 Hz, 1H), 2.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.8, 149.2, 147.5, 147.2, 142.1, 135.7, 134.5, 133.2, 129.6, 128.5, 125.1, 124.6, 124.5, 124.3, 123.4, 119.9, 119.5, 112.4, 18.0. IR(KBr): 3059, 2915, 2849, 1671, 1622, 1463, 1264, 1023 cm^{-1}. HRMS (ESI) calcd for $C_{21}H_{16}N_3O$ [M + H]$^+$: 326.1288, found 326.1294.

*9-Methoxy-5-phenylindazolo[3,2-b]quinazolin-7(5H)-one (**3k**).*[9] Light green solid (61.0 mg, 89% yield), mp 222-224 °C (lit. 214-215 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 9.0 Hz, 1H), 7.67 (d, *J* = 3.0 Hz, 1H), 7.60-7.57 (m, 1H), 7.49-7.46 (m, 2H), 7.43-7.35 (m, 5H), 7.19 (d, *J* = 8.0 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 157.6, 156.1, 148.9, 146.5, 143.4, 142.1, 133.0, 129.6, 128.7, 128.6, 125.0, 124.7, 124.4, 123.0, 120.6, 119.1, 112.4, 105.6, 55.9.

10-Fluoro-5-phenylindazolo[3,2-b]quinazolin-7(5H)-one ***(3l)***.[7c] White solid (54.0 mg, 82% yield), mp 214-215 °C (lit. 214-215 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33-8.30 (m, 1H), 8.26 (d, J = 8.0 Hz, 1H), 7.65-7.62 (m, 1H), 7.53-7.35 (m, 7H), 7.21-7.15 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 165.5, 155.9, 151.0, 150.9, 149.3, 149.2, 141.7, 133.8, 129.7, 129.5, 129.4, 128.8, 124.7, 124.6, 123.5, 118.5, 116.6, 114.6, 114.5, 112.5, 112.1, 111.9.

8-Fluoro-5-phenylindazolo[3,2-b]quinazolin-7(5H)-one ***(3m)***. White solid (51.3 mg, 78% yield), mp 179-180 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, J = 7.5 Hz, 1H), 7.95-7.89 (m, 2H), 7.64-7.61 (m, 1H), 7.56-7.52 (m, 1H), 7.50-7.47 (m, 2H). 7.44-7.41 (m, 2H), 7.36-7.34 (m, 2H), 7.20 (d, J = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.1, 159.1, 155.7, 149.1, 147.8, 145.5, 141.8, 133.6, 130.6, 129.7, 129.3, 128.8, 126.2, 124.8, 124.6, 123.3, 123.1, 122.9, 118.8, 118.0, 112.5, 114.4, 111.2. IR (KBr):3064, 2921, 2853, 1674, 1624, 1483, 1269, 1035 cm^{-1}. HRMS (ESI) calcd for $C_{20}H_{12}FN_3O$ $[M + H]^+$: 330.1037, found 330.1041.

10-Chloro-5-phenylindazolo[3,2-b]quinazolin-7(5H)-one ***(3n)***.[7b] Light yellow solid (51.6 mg, 75% yield), mp 204-205 °C (lit. 208-209 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, J = 8.0 Hz, 1H), 8.23 (d, J =8.5 Hz, 1H), 7.89 (d, J = 1.5 Hz, 1H), 7.65-7.62 (m, 1H), 7.50-7.35 (m, 7H), 7.20 (d, J = 8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.9, 149.6, 149.2, 141.5, 140.3, 133.9, 129.7, 128.9, 128.6, 128.2, 126.5, 126.1, 124.8, 124.6, 123.5, 118.5, 118.2, 112.4.

3-Methyl-5-phenylindazolo[3,2-b]quinazolin-7(5H)-one (**3o**).[7c] White solid (55.2 mg, 85% yield), mp 254-255 °C (lit. 248-250 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32-8.31 (m, 1H), 8.16 (d, J = 8.5 Hz, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.82-7.79 (m, 1H), 7.50-7.40 (m, 4H), 7.36-7.35 (m 2H), 7.23 (d, J = 8.0 Hz, 1H), 6.98 (s, 1H), 2.46 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5, 149.6, 148.8, 148.4, 145.0, 142.0, 134.1, 129.6, 128.6, 126.9, 126.8, 126.2, 125.3, 124.6, 123.0, 119.7, 116.4, 112.4, 22.6.

3-Chloro-5-phenylindazolo[3,2-b]quinazolin-7(5H)-one (**3p**).[7c] White solid (52.3 mg, 76% yield), mp 212-213 °C (lit. 255-256 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34-8.30 (m, 2H), 7.92 (d, J = 8.0 Hz, 1H), 7.85-7.82 (m, 1H), 7.66-7.63 (m, 1H), 7.50-7.43 (m, 4H), 7.32-7.31 (m, 2H), 7.19-7.17(m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.3, 149.6, 148.6, 147.4, 141.2, 139.9, 134.3, 129.8, 129.1, 127.1, 126.8, 125.7, 125.3, 124.7, 124.4, 119.8, 117.4, 112.6.

ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra of all products and X-ray data of compounds **3a** and **4a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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