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Pd-Catalyzed Intramolecular Aerobic Oxidative C−H Amination of 2-Aryl-3-(arylamino)quinazolinones: Synthesis of Fluorescent Indazolo[3,2-*b*]quinazolinones

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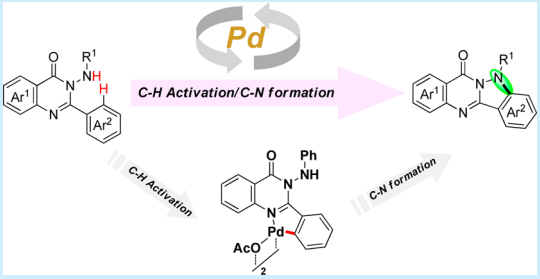
Supporting Information

ABSTRACT: A palladium-catalyzed intramolecular aerobic oxidative C−H amination of 2-aryl-3-(arylamino)quinazolinones has been developed, providing a variety of substituted indazolo[3,2-*b*]quinazolinone derivatives in moderate to excellent yields. Preliminary mechanistic studies suggested that a palladacycle dimer could be the key intermediate, which underwent a cascade "rollover" cyclometalation and C−H amination sequence. Furthermore, the potential utility of these products has been demonstrated as a new class of blue fluorophores for fluorescent materials.

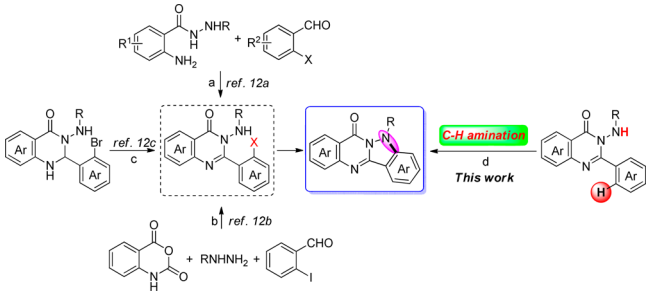


The development of new C−H amination technology has been a research area of intense interest.[1] In contrast to the traditional metal-catalyzed C−N cross-coupling reactions by employing prefunctionalized substrates,[2] the direct C−H amination is a highly appealing synthetic strategy, as it utilizes the abundant C−H bond in nature.[3] The intramolecular C−H amination provides a straightforward approach for the synthesis of *N*-containing heterocycles.[4] The general issue of C−H activation using a directing group-assisted strategy is the tedious installation/removal of these groups from the reaction substrates/products,[5−9] but this might not be a problem if these directing groups are a required functionality in the product for further manipulation.

Nitrogen-containing heterocycles have been widely used as directing groups in metal-catalyzed C−H functionalization reactions,[10] but the use of quinazolinone in selective C−H functionality has been less explored.[11] Also, the resulting indazolo[3,2-*b*]quinazolinone derivatives are important biologically active molecules and potent inhibitors of phosphdiesterase 4 (PDE4).[12b] To the best of our knowledge, the previous examples of synthesis of indazolo[3,2-*b*]quinazolinones have been limited to the use of arylhalides as coupling partners (Scheme 1a-1c).[12] Under this background, the development of new C−H functionalization synthetic strategies for the preparation of indazolo[3,2-*b*]quinazolinones still remains highy desirable.

Our interest in the development of new methods for metal-catalyzed C−H activation[13a] and the synthesis of quinazolinone-based fused poly-*N*-heterocycles[12c,13b] led us to explore this transformation. We herein report a new synthetic procedure for the preparation of indazolo[3,2-*b*]quinazolinones by palladium-catalyzed intramolecular C−H amination of 2-aryl-3-(arylamino)quinazolinones with molecular oxygen as the ideal terminal oxidant[14] under mild conditions (Scheme 1d).

Scheme 1. Strategies for the Synthesis of Indazolo[3,2-*b*]quinazolinones



We began our investigation by examining the conversion of 2-phenyl-3-(phenylamino)quinazolinone (**1a**) into 5-phenylindazolo[3,2-*b*]quinazolinone (**2a**) (Table 1). After an initial screen, we found that the use of 5 mol % $Pd(OAc)_2$ in DMF at 120 °C under an oxygen atmosphere afforded **2a** in 23% yield (see Table 1, entry 1, and entries 1−11 of Table S1 in the Supporting Information (SI)). The yield of **2a** was increased to 35% with 4 Å molecular sieves[15] as an additive. Encouraged by this promising result, we further screened other reaction parameters in order to obtain more satisfactory results. Among the different bases evaluated, sodium bicarbonate was the optimal base as the yield was increased to 89% with the combination of palladium acetate (Table 1, entry 4). Other bases (see Table 1, entries 1−3, and entries 12−17 of Table S1 in the SI) and Other palladium catalysts (see Table 1, entries 5−9, and entries 19−23 of Table S1 in the SI) exhibited lower efficiencies. In the absence of the palladium catalyst, no or only a trace amount of the desired **2a** was detected (Table 1, entry

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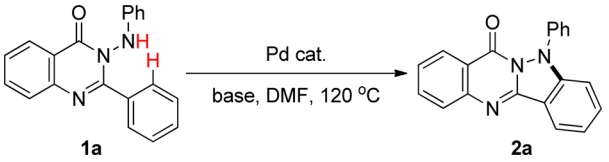
Table 1. Optimization of Reaction Conditions[a]



1a 2a

entry	Pd catalyst	base	gas atm	yield (%)[b]
1	$Pd(OAc)_2$	Cs_2CO_3	O_2	23 (35)[c]
2	$Pd(OAc)_2$	^tBuOK	O_2	11
3	$Pd(OAc)_2$	NaOAc	O_2	73
4	**$Pd(OAc)_2$**	**$NaHCO_3$**	**O_2**	**89**
5	$PdCl_2$	$NaHCO_3$	O_2	46
6	$Pd(PPh_3)_4$	$NaHCO_3$	O_2	17
7	$Pd(acac)_2$	$NaHCO_3$	O_2	58
8	$PdCl_2(PPh_3)_2$	$NaHCO_3$	O_2	38
9	Na_2PdCl_4	$NaHCO_3$	O_2	59
10		$NaHCO_3$	O_2	trace
11	$Pd(OAc)_2$	$NaHCO_3$	air	45
12	$Pd(OAc)_2$	$NaHCO_3$	N_2	trace
13	$Pd(OAc)_2$	$NaHCO_3$	N_2	0 (46)[d]

[a]Reaction conditions: **1a** (0.2 mmol), Pd catalyst (5 mol %), base (1.0 equiv), and solvent (5 mL), 120 °C, 48 h. [b]Isolated yield. [c]With MS 4 Å (60 mg). [d]46% yield of 2-phenylquinazolin-4(3*H*)-one was obtained with 1.5 equiv of $Cu(OAc)_2$ as an oxidant.

10). Catalytic activity was also found under an air atmosphere, though the formation of **2a** was slower (Table 1, entry 11). In contrast, this reaction did not work under a N_2 atmosphere (Table 1, entry 12). It is worth noting that **1a** was dissociated into 2-phenylquinazolin-4(3*H*)-one in 46% yield via N−N bond cleavage without any cyclized product in the presence of $Cu(OAc)_2$ under a N_2 atmosphere (Table 1, entry 13). Other oxidants such as AgOAc, $K_2S_2O_8$, benzoquinone (BQ), and $PhI(OAc)_2$ were also less effective (see entries 24−27 of Table S1 in the SI).

With the optimial reaction conditions in hand, the scope of this C−H amination was examined (Figure 1). The influence of substitutions on the *N*-aryl ring moiety of the 2-aryl-3-(arylamino)quinazolinone was first investigated. The steric effects of substituents had an obvious impact on the efficiency of this transformation. For example, when substrates bearing a *para*-, *meta*-, and *ortho*-methyl group were examined, **2b** and **2c** were obtained in 92% and 90% yield respectively, while little-to-no target product **2d** possessing an *ortho*-methyl group was detected. The electronic properties of the substituents on the *N*-aryl ring moiety affected the yields to some extent. In general, the *N*-aryl ring moiety bearing an electron-donating substituent (e.g., −Me) (compounds **2b**−**2c**) generally produced a higher yield than those analogues bearing an electron-withdrawing substituent (e.g., −F, −Cl, and $-CF_3$) (compounds **2e**−**2g**). No observation of the desired products **2h** and **2i** from 3-(benzylamino)-2-phenylquinazolinone (**1h**) and *N*-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)benzamide (**1i**) could indicate that the electronic properties of the *N*-substituted moiety (R^1) are necessary for this process.

Next, we turned our attention to the effect of the various electron-donating and -withdrawing groups on aromatic Ar^2 of substrates (compounds **2j**−**2q**). The results showed that electron-donating goups had more favorable effects than electron-withdrawing goups. Similarly, the intramolecular C−H amination takes place at the less hindered C−H bond position (compounds **2j**−**2l**). Interestingly, when 3-(phenyl-

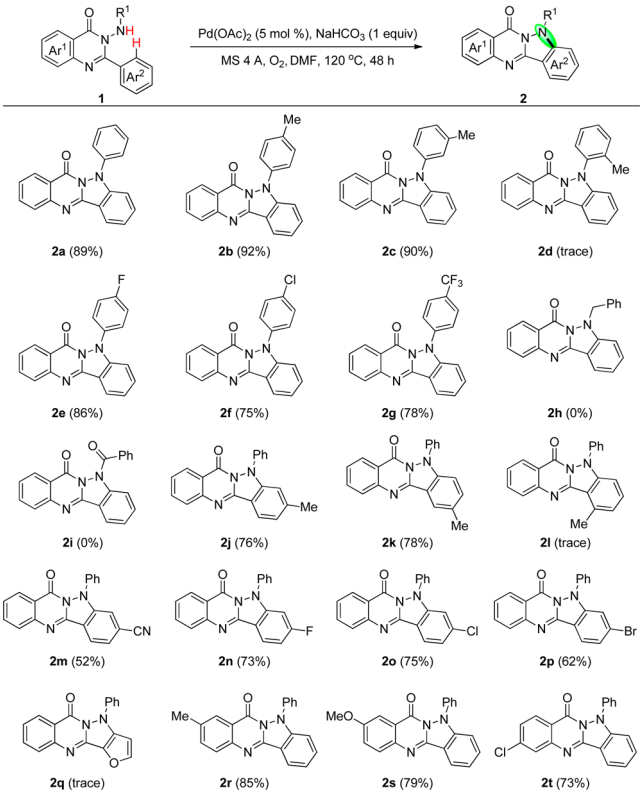


Figure 1. Synthesis of indazolo[3,2-*b*]quinazolinones. Reaction conditions: **1** (0.2 mmol), $Pd(OAc)_2$ (5 mol %), $NaHCO_3$ (1.0 equiv), MS 4 Å (60 mg), and DMF (5 mL), O_2, 120 °C, 48 h. Isolated yields are provided in parentheses.

amino)-2-(*m*-tolyl)quinazolinone (**1k**) was subjected to this procedure, the *para* position intramolecular C−H amination product **2k** was obtained in 78% yield with high regioselectivity. It is noteworthy that no cyclization product was detected using *ortho*-substituted on aromatic Ar^2 3-(phenylamino)-2-(*o*-tolyl)-quinazolinone (**1l**) as a substrate under the standard conditions. Substrate 2-(4-cyanophenyl)-3-(phenylamino)-quinazolinone (**1m**) bearing a strong electron-withdrawing cyano group delivered the desired product **2m** in moderate yield. The ability to incorporate the whole tolerance of a range of halogen substituents makes this method particularly appealing. Substrates with *para*-halogenated aromatic Ar^2 were used under standard conditions, leading to the corresponding halogen-substituted products **2n**, **2o**, and **2p**, which may enable further access to more complex compounds in various transformations. However, we found that 5-phenylindazolo[3,2-*b*]quinazolinone (**2a**) was obtained in 62% yield involving C−Br bond cleavage/C−N bond formation when an *ortho* halogenated aromatic Ar^2 of substrates such as 2-(2-bromophenyl)-3-(phenylamino)quinazolinone (**1u**) was used (Scheme 2, eq 1). When a heterocycle-substituted substrate, such as 2-(furan-2-yl)-3-(phenylamino)-quinazolinone (**1q**), was used, the product **2q** could not be detected and almost 90% of **1q** was recovered. Finally, several substituents (e.g., −Me and −OMe, and −Cl) on aromatic Ar^1 of substrates were also examined. The results showed that electron-rich functionalities were beneficial for this transformation and the corresponding products **2r** and **2s** were obtained in 85% and 79% yield, respectively. In contrast, electron-withdrawing substituents made the reactions less

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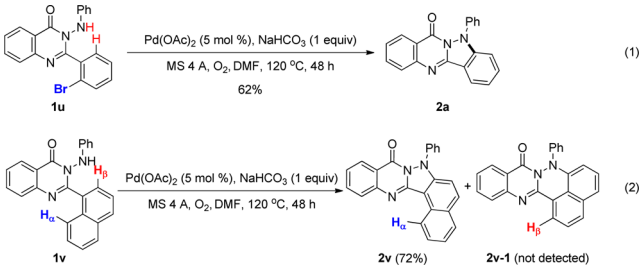
Scheme 2. Pd-Catalyzed Intramolecular Amination of 1u



effective, which may arise from the decreased electron density on the phenyl ring. When 7-chloro-2-phenyl-3-(phenylamino)-quinazolinone (**1t**) was used as the substrate, for example, the desired product **2t** was isolated in 73% yield.

It is worth mentioning that 2-(naphthalen-1-yl)-3-(phenylamino)quinazolinone (**1v**) was proven to be a suitable substrate, affording excellent regioselective β-position intramolecular C−H amination product **2v** in 72% yield instead of α-position amination product **2v-1** (Scheme 2, eq 2).

To gain a better understanding of the catalytic mechanism, we tried to isolate and identify the carbopalladation intermediate. Gratifyingly, the C−H insertion palladacycle dimer complex **3** was prepared by the reaction of **1a** with a stoichiometric amount of $Pd(OAc)_2$ in CH_2Cl_2 at 60 °C. The X-ray crystallography results show that complex **3** adopts a head-to-tail U-shaped geometry (Figure 2). The structure of

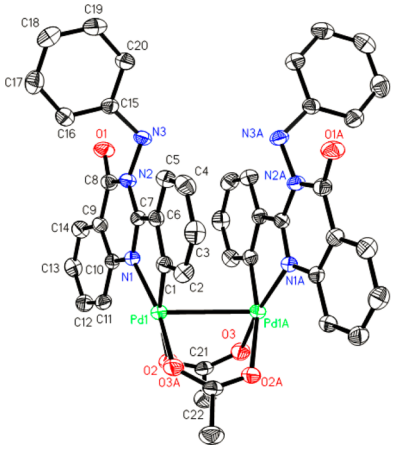
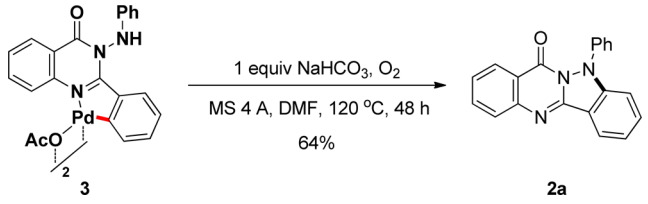


Figure 2. Proposed intermediate and X-ray structure of **3**.

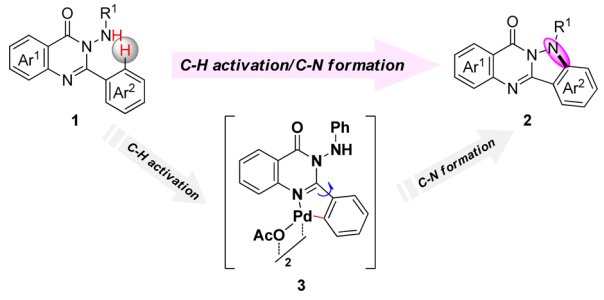
complex **3** confirmed the hypothesis that the sp^2-nitrogen atom in the quinazolinone ring instead of the sp^3-nitrogen atom in the arylamino group is involved in directing C−H activation, which is consistent with the better coordination ability of the sp^2-nitrogen atom with palladium. This implied that the direct C−H amination could proceed through complex **3**. Furthermore, we found complex **3** can be smoothly converted to **2a** in the presence of $NaHCO_3$ in DMF at 120 °C under an oxygen atmosphere (Scheme 3).

On the basis of these above experimental results, a possible reaction pathway for the formation of indazolo[3,2-*b*]-quinazolinones was proposed (Scheme 4). The first step may involve the C−H bond activation of 2-aryl-3-(arylamino)-quinazolinones (**1**), leading to the key C−H insertion intermediate **3**. Then, a "rollover" cyclometalation[16,17] of intermediate **3** and subsequent intramolecular C−N bond

Scheme 3. Intramolecular Amination of 1u or 1v



Scheme 4. Plausible Reaction Pathway



formation afforded the indazolo[3,2-*b*]quinazolinones (**2**). However, a detailed mechanism of the formation of the indazolo[3,2-*b*]quinazolinones remain unclear at the current stage.

Because a number of nitrogen-containing heterocycles were fluorescent and could be developed as good fluorophores,[18] herein, we investigated the photophysical properties of the resulting indazolo[3,2-*b*]quinazolinone derivatives. Their UV−vis absorption and fluorescence spectra were recorded and the corresponding data are collected in $CHCl_3$ (see Figure S1, Figure S2, and Table S2 in the Supporting Information). Most of these derivatives display four obvious absorption peaks in the region from 241 to 377 nm and emit the blue fluorescence in the range of 424−453 nm in $CHCl_3$. It can be conclued that the introduction of different electron-donating and -withdrawing groups to the Ar^1 or Ar^2 of the indazolo[3,2-*b*]quinazolinone skeleton has a slight influence on their photophysical properties. These compounds show large Stokes shifts over 68 nm, which is beneficial for the detection of the emission wavelength by avoiding the interference from the excitation wavelength.[19] Additionally, the fluorescence efficiency (Φ_F) of these compounds is in the range of 0.034−0.56, using quinine sulfate solution (Φ_F = 0.55 in 0.5 mol/L H_2SO_4) as the fluorescence reference.[20] Notably, among these compounds, the compound **2m** exhibited the largest absorption wavelength (377 nm) and emssion wavelength (453 nm), and the highest Φ_F value (0.56), which should be attributed to the introduction of a strong electron-withdrawing cyano group.[21] These results indicate that indazolo[3,2-*b*]quinazolinones have great potential as a new class of small-molecule fluorophores.

In summary, we have developed an original approach for the synthesis of indazolo[3,2-*b*]quinazolinone derivatives by Pd-catalyzed C−H bond activation/intramolecular amination of 2-aryl-3-(arylamino)quinazolinones. In addition, the catalytic reaction with O_2 as the terminal oxidant generates water as the only byproduct and provides a "greener" approach to indazolo[3,2-*b*]quinazolinones. More detailed mechanistic studies and the investigation of new applications of quinazolinone as a directing group are now being undertaken in our laboratory.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, analytical data, NMR spectra, and X-ray data of complex **3**. 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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