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Palladium-Catalyzed Three-Component Tandem Process: One-Pot Assembly of Quinazolines

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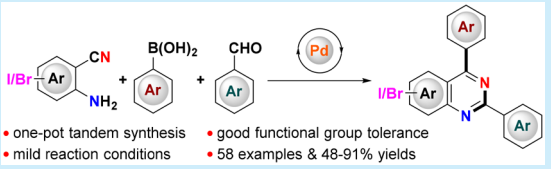
Supporting Information

ABSTRACT: The first example of the palladium-catalyzed, three-component tandem reaction of 2-aminobenzonitriles, aldehydes, and arylboronic acids has been developed, providing a new approach for one-pot assembly of diverse quinazolines in moderate to good yields. A noteworthy feature of this method is the tolerance of bromo and iodo groups, which affords versatility for further synthetic manipulations. Preliminary mechanistic experiments indicate that this tandem process involves two possible mechanistic pathways for the formation of quinazolines via catalytic carbopalladation of the cyano group.

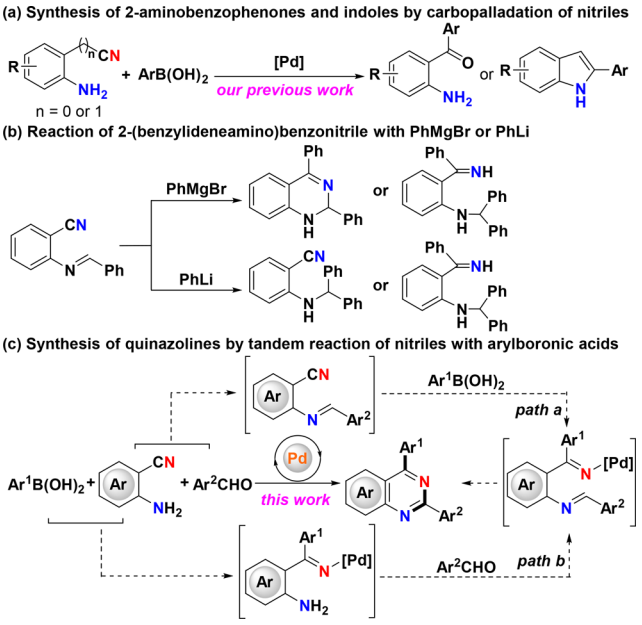


Quinazoline and derivatives represent an important class of fused nitrogen-containing heterocycles because they are prevalent structural motifs in many natural products, pharmaceuticals, ligands, and C−H bond activation partners.[1] Therefore, the design of novel protocols to construct quinazoline skeletons more efficiently has been an active area of research in organic chemistry during the past several decades.[2,3] However, less attention has been paid to the formation of quinazolines from nitriles.[4]

The nitrile is one of the most versatile scaffolds in both synthetic and medicinal chemistry.[5] It is well-known, however, that nitriles have been usually used as solvents or ligands in organometallic reactions, presumably due to the inherently inert nature of the C≡N bond.[6] In a pioneering report in 1999, Larock established carbocycle synthesis via carbopalladation of nitriles.[7] The past decade has witnessed noticeable progress in the development of transition-metal-catalyzed addition of an organoboron reagent to nitriles.[8,9] One of the principal challenges in the field of transition-metal-catalyzed transformation of nitriles that limits the application of functional ketones or *N*-heterocycle synthesis is largely rooted in both selectivity and reactivity. To achieve the high-value transformation of nitriles, we have developed the palladium-catalyzed direct addition of arylboronic acids to free amino-substituted nitriles such as 2-aminobenzonitriles and 2-aminophenylacetonitriles, providing a new protocol for the synthesis of 2-aminobenzophenones and 2-arylindoles, respectively (Scheme 1a).[10] However, the development of an efficient catalytic system that can incorporate the nitrogen atom of a cyano group into *N*-heterocycle products, rather than undergoing hydrolysis of ketamine intermediates, still remains a challenge. Very recently, we have successfully developed a tandem synthesis of isoquinolines and isoquinolones via carbopalladation of nitriles.[11]

As shown in Scheme 1b, the reaction of 2-(benzylideneamino)benzonitrile with PhMgBr was conducted in THF to produce cyclization product 2,4-diphenyl-1,2-dihydroquinazoline and adduct *N*-benzhydryl-2-(imino-

Scheme 1. Design of New Approach to Quinazolines



(phenyl)methyl)aniline in a 3:1 ratio.[12] However, treatment of 2-(benzylideneamino)benzonitrile with PhLi delivered the adducts 2-(benzhydrylamino)benzonitrile or *N*-benzhydryl-2-(imino(phenyl)methyl)aniline.[12]

Compared to Grignard reagents and organolithium reagents, organoboron reagents[13] hold great promise due to their low toxicity, ease of handling, and good functional group tolerance, etc. The development of new transformations in which the inert C≡N bond reacts as a functional group holds great promise for expediting *N*-heterocycle syntheses. On the basis of the two distinct modes of reactivity of 2-aminobenzonitriles with

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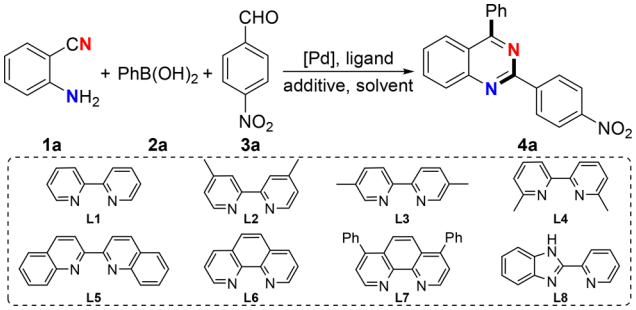
nucleophiles ($Ar^1B(OH)_2$) and electrophiles (Ar^2CHO), we envisioned two possible reaction pathways that could involve carbopalladation of the cyano group to deliver the desired quinazolines (Scheme 1c). As part of our efforts on the development of novel transformations of nitriles[9−11] and quinazoline synthesis,[14] herein we report a Pd-catalyzed tandem reaction of simple and commercially available starting materials (2-aminobenzonitriles, aldehydes, and arylboronic acids), providing a new and complementary method for the synthesis of quinazolines. To our knowledge, this is the first example of a three-component tandem quinazoline synthesis through carbopalladation of the cyano group in one pot.

Our study commenced by examining the reaction of 2-aminobenzonitrile (**1a**), phenylboronic acid (**2a**), and 4-nitrobenzaldehyde (**3a**) for the screening of reaction conditions (Table 1). No target product was detected with HCl as an additive under a variety of conditions. However, when the additive was changed to an organic acid such as CH_3CO_2H, a trace amount of the desired product 2-(4-nitrophenyl)-4-phenylquinazoline (**4a**) was detected by GC−MS along with small amounts of two condensation byproducts, (*E*)-2-((4-nitrobenzylidene)amino)benzonitrile and 2-aminobenzophenone (entry 1). The use of CF_3SO_3H (TfOH) as an additive greatly increased the yield of **4a** to 60% (entry 7). Other additives, including $PhCO_2H$, CF_3CO_2H, *p*-$CH_3C_6H_4SO_3H$ (TsOH), *p*-$NO_2C_6H_4SO_3H$ (PNSA), and D-camphorsulfonic acid (CSA), were less efficient (entries 2−6). Among the Pd(II) catalysts used, $Pd(acac)_2$ exhibited the highest catalytic reactivity, providing 71% yield (entries 7−12). In contrast, this transformation did not work when Pd(0) catalysts such as $Pd(PPh_3)_4$ were used (entry 13). The choice of ligand was also vital to the success of the catalytic reaction. Among the various bidentate ligands tested (**L2**−**L8**) (entries 14−20), 5,5′-dimethyl-2,2′-bipyridine (**L3**) achieved the best result (86% yield, entry 15). In contrast, little to no product **4a** was observed when sterically hindered ligands, such as 6,6′-dimethyl-2,2′-bipyridine (**L4**) and 2,2′-biquinoline (**L5**) (entries 16 and 17), were used. Finally, we studied the solvent effect and found that DMF was superior to THF, EtOH, toluene, and *N*,*N*-dimethylacetamide (DMA) (entries 15 and 21−24). The reaction failed to give **4a** if either palladium catalyst or ligand was absent (entries 25 and 26).

Table 1. Optimization of Reaction Conditions[a]



entry	Pd catalyst	ligand	additive	solvent	yield[b] (%)
1	$Pd(OAc)_2$	**L1**	CH_3CO_2H	DMF	trace
2	$Pd(OAc)_2$	**L1**	$PhCO_2H$	DMF	11
3	$Pd(OAc)_2$	**L1**	CF_3CO_2H	DMF	23
4	$Pd(OAc)_2$	**L1**	$TsOH·H_2O$	DMF	51
5	$Pd(OAc)_2$	**L1**	PNSA	DMF	36
6	$Pd(OAc)_2$	**L1**	CSA	DMF	48
7	$Pd(OAc)_2$	**L1**	TfOH	DMF	60
8	$PdCl_2$	**L1**	TfOH	DMF	trace
9	$Pd(PPh_3)_2Cl_2$	**L1**	TfOH	DMF	trace
10	$Pd(CH_3CN)_2Cl_2$	**L1**	TfOH	DMF	trace
11	$Pd(CF_3CO_2)_2$	**L1**	TfOH	DMF	65
12	$Pd(acac)_2$	**L1**	TfOH	DMF	71
13	$Pd(PPh_3)_4$	**L1**	TfOH	DMF	0
14	$Pd(acac)_2$	**L2**	TfOH	DMF	79
15	**$Pd(acac)_2$**	**L3**	**TfOH**	**DMF**	**86**
16	$Pd(acac)_2$	**L4**	TfOH	DMF	trace
17	$Pd(acac)_2$	**L5**	TfOH	DMF	trace
18	$Pd(acac)_2$	**L6**	TfOH	DMF	45
19	$Pd(acac)_2$	**L7**	TfOH	DMF	38
20	$Pd(acac)_2$	**L8**	TfOH	DMF	30
21	$Pd(acac)_2$	**L3**	TfOH	THF	31
22	$Pd(acac)_2$	**L3**	TfOH	EtOH	26
23	$Pd(acac)_2$	**L3**	TfOH	toluene	39
24	$Pd(acac)_2$	**L3**	TfOH	DMA	62
25		**L3**	TfOH	DMF	0
26	$Pd(acac)_2$		TfOH	DMF	0

[a]Conditions: **1a** (0.3 mmol), **2a** (0.75 mmol), **3a** (0.6 mmol), Pd catalyst (5 mol %), ligand (10 mol %), additive (4 equiv), KF (0.6 mmol), solvent (3 mL), 80 °C, 48 h, air. [b]Isolated yield.

With the optimized conditions in hand, we proceeded to examine the substrate scope (Scheme 2). When benzaldehydes bearing a variety of electron-withdrawing groups, such as nitro (**4b**,**c**), trifluoromethyl (**4d**), fluoro (**4e**), chloro (**4f**), and bromo (**4g**), were used, the reactions proceeded smoothly, and moderate to good yields were obtained. The reaction of benzaldehydes bearing electron-donating groups such as methyl (**4h**,**i**) and methoxy (**4j**) afforded the corresponding products in acceptable yields. Notably, treatment of 2-naphthaldehyde with **1a** and **1b** also proceeded smoothly and gave the desired product **4k** in 81% yield. It was noteworthy that steric hindrance did not have an obvious effect on the reaction; for example, the reactivities of *p*-, *m*-, and *o*-tolylboronic acid were evaluated, and the corresponding products **4m**, **4n**, and **4o** were obtained in 74%, 72%, and 67% yields, respectively. A variety of functional groups, including electron-donating groups such as methyl (**4m**−**o**), *tert*-butyl (**4p**), methoxy (**4q**), and [1,3]-dioxolo (**4r**) and electron-withdrawing groups such as fluoro (**4s**), chloro (**4t**), and bromo (**4u**), were well tolerated. Biphenyl-4-ylboronic acid was amenable to the reaction conditions, affording the desired product **4v** in 85% yield. Electron-donating groups such as methyl (**4w**−**x**) and electron-withdrawing groups such as fluoro (**4y**) and chloro (**4z**−**4aa**) were tolerated in the aromatic nitrile, achieving the desired products with moderate to good yields. Electronic effects of substituents affected the reactivity to some extent. Both strongly electron-withdrawing (e.g., $-CF_3$) and electron-donating (e.g., −OMe) groups were compatible with this reaction, affording the corresponding products **4ab** and **4ac** in 73% and 86% yields, respectively. An excellent yield of **4ad** was obtained when the disubstituted substrate 2-amino-4,5-dimethoxybenzonitrile was used.

The development of new methods for the introduction of halogen (e.g., bromo and iodo) substituents into target products is attractive and promising because of their potential for further synthetic elaborations. Next, we turned our attention to the reaction of 2-aminobenzonitriles bearing bromo or iodo groups such as 2-amino-5-bromobenzonitrile (**1b**), 2-amino-3-bromobenzonitrile (**1c**), and 2-amino-5-iodobenzonitrile (**1d**) to afford a diverse range of bromo- or iodo-substituted

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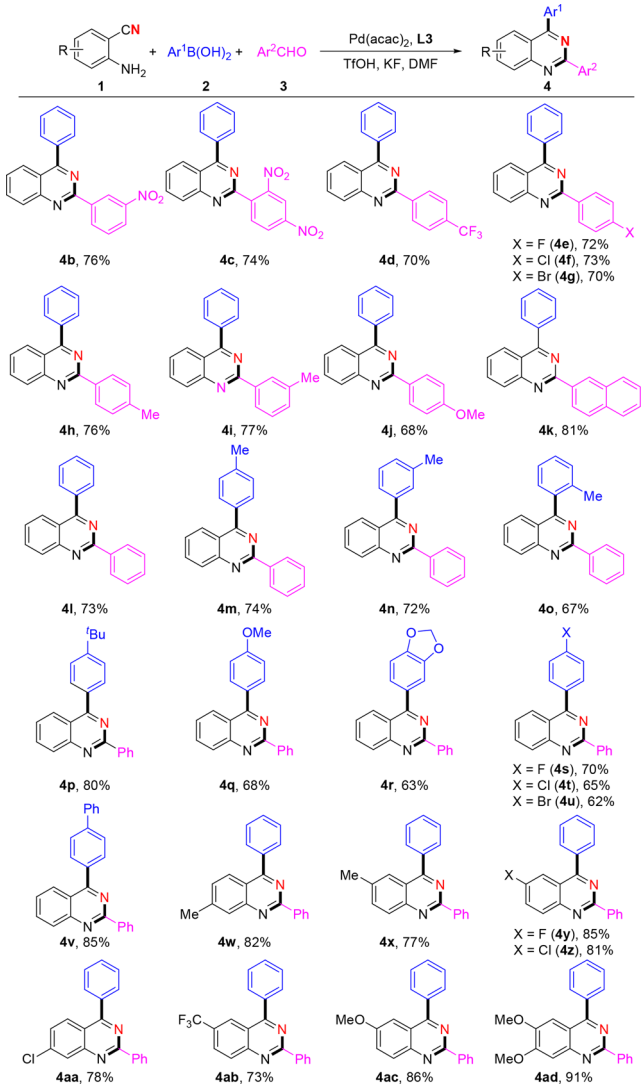
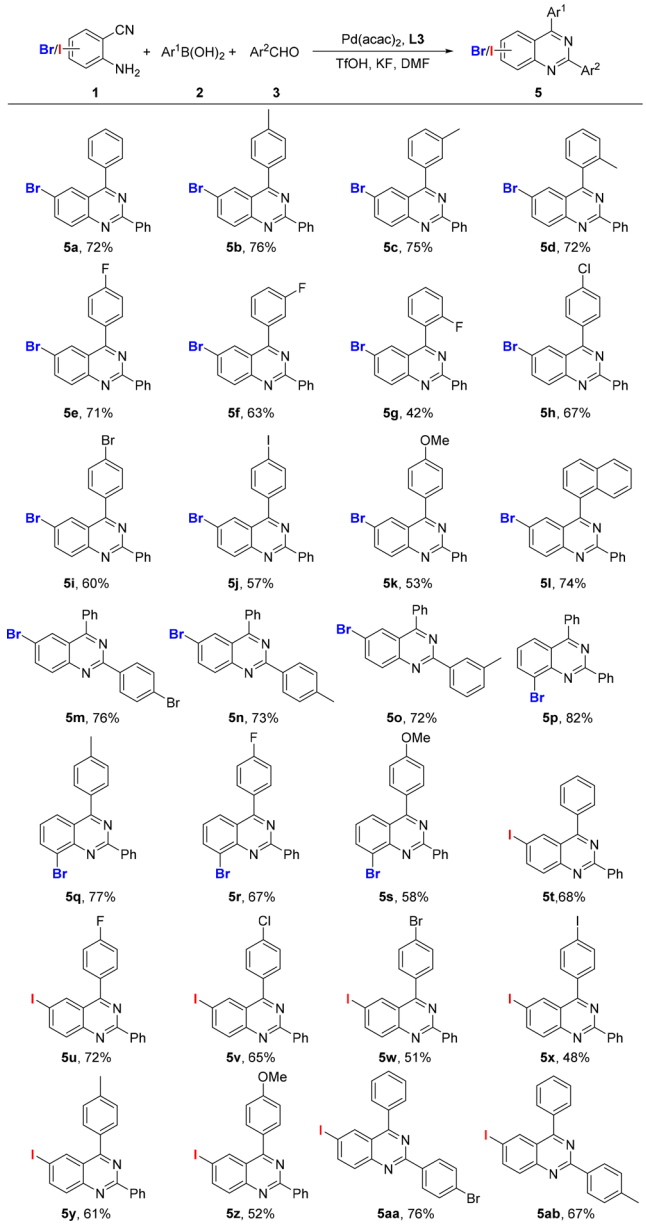
Scheme 2. Synthesis of Quinazoline Derivatives[a]



[a]Conditions: **1** (0.3 mmol), **2** (0.75 mmol), **3** (0.6 mmol), $Pd(acac)_2$ (5 mol %), **L3** (10 mol %), TfOH (4 equiv), KF (2 equiv), DMF (3 mL), 80 °C, 48 h, air. Isolated yield.

Scheme 3. Synthesis of Bromo- or Iodo-Substituted Quinazolines[a]



[a]Conditions: **1** (0.3 mmol), **2** (0.75 mmol), **3** (0.6 mmol), $Pd(acac)_2$ (5 mol %), **L3** (10 mol %), TfOH (4 equiv), KF (2 equiv), DMF (3 mL), 80 °C, 48 h, air. Isolated yield.

quinazolines (Scheme 3). In this series, the steric effects of substituents affected the yields of the reaction to some extent. For example, the reaction with *p*-, *m*-, and *o*-tolylboronic acid efficiently afforded **5b**, **5c**, and **5d** in 76%, 75%, and 72% yields, respectively. However, the reaction with *p*-, *m*-, and *o*-fluorophenylboronic acid was examined, and 71% of **5e** and 63% of **5f** were obtained, while the yield of **5g** was decreased to 42%. Both electron-deficient halogens (e.g., −Cl, −Br, −I) and electron-rich (e.g., −OMe) substituents were tolerated (**5h**−**k**), although slightly lower yields were observed. It is worth noting that the desired product 6-bromo-4-(naphthalen-1-yl)-2-phenylquinazoline (**5l**) was isolated in 74% yield when 1-naphthylboronic acid was used. The structure of **5l** was characterized by X-ray crystallography. The products **5m**, **5n**, and **5o** were obtained in 76%, 73%, and 72% yields, respectively.

Treatment of 2-amino-3-bromobenzonitrile (**1c**) with phenylboronic acid and benzaldehyde also proceeded smoothly and gave the desired product **5p** in 82% yield. The electronic properties of the substituents on the phenyl ring of the arylboronic acids affected the yields of the reaction to some extent. In general, arylboronic acids bearing an electron-donating substituent (e.g., −Me) (**5q**) produced a slightly higher yield of product than that of an analogue bearing an electron-withdrawing substituent (e.g., −F) (**5r**). However, an arylboronic acid with a strongly electron-donating group (e.g., −OMe) decreased the yield of **5s** to 58%. Finally, the reaction of 2-amino-5-iodobenzonitrile (**1d**) was further investigated. The desired product **5t** was isolated in 68% yield. Arylboronic acids with electron-deficient halogens (e.g., −F, −Cl, −Br, − I) and electron-rich (e.g., −OMe) substituents were compatible with this reaction, allowing the introduction of a wide range of functional groups into iodo-substituted quinazolines (**5u**−**z**). The results showed that an electron-withdrawing substituent

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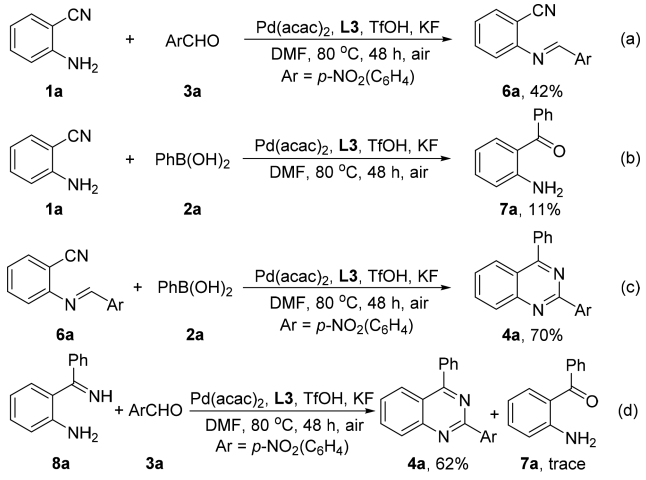
(e.g., −Br) was beneficial for this transformation, and the corresponding product **5aa** was obtained in 76% isolated yield. In contrast, the electron-rich substituents (e.g., −Me) made the reactions less effective, which may arise from the increased electron density on the phenyl ring. When 4-methylbenzaldehyde was used as the substrate, for example, the desired product **5ab** was isolated in 67% yield.

To gain insight into the reaction mechanism, further experiments were performed, as shown in Scheme 4. (*E*)-2-((4-Nitrobenzylidene)amino)benzonitrile (**6a**) was obtained in 42% yield when phenyboronic acid was absent (Scheme 4a). Treatment of **1a** with **2a** in the absence of aldehyde afforded (2-aminophenyl)(phenyl)methanone (**7a**) in 11% yield (Scheme 4b). The desired product **4a** was obtained in 70% yield when the reaction of **6a** with **2a** was performed (Scheme 4c). The reaction of 2-(imino(phenyl)methyl)aniline (**8a**) with **3a** also proceeded to give the desired product **4a** in 62% yield, accompanied by a trace amount of **7a** from the hydrolysis of **8a** (Scheme 4d). These results implicate **6a** or **8a** as possible intermediates for this transformation.

Scheme 4. Control Experiments



On the basis of the above experimental results and relevant reports in the literature, two possible mechanistic pathways for the formation of quinazolines are proposed in Scheme 5. In path a, the imine intermediate **A** is formed from the condensation reaction of 2-aminobenzonitriles and aldehydes, followed by the coordination of the arylpalladium species from transmetalation of the palladium catalyst with arylboronic acid to generate intermediate **B**. Next, carbopalladation of the cyano group would result in the formation of a palladium ketimine intermediate **C**. In path b, the first step may involve transmetalation between the palladium catalyst and arylboronic acid to give the arylpalladium species, which was followed by the coordination of the cyano group, leading to the intermediate **E**. Next, the intramolecular carbopalladation of the cyano group generates imine palladium complex **F**, which would be followed by the condensation in the presence of aldehydes to give intermediate **C**. The intermediate **C** undergoes an intramolecular cyclization to palladium complex **D**. Finally, *β*-hydride elimination of the intermediate **D** would afford the desired quinazolines and regenerate the palladium catalyst.

In summary, we have developed an efficient strategy for the one-pot synthesis of quinazolines by a Pd-catalyzed three-component tandem reaction of commercially available 2-aminobenzonitriles, aldehydes, and arylboronic acids. This system shows remarkable chemoselectivity and broad substrate scope. Further studies on the scope, mechanism, and synthetic application of this chemistry are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

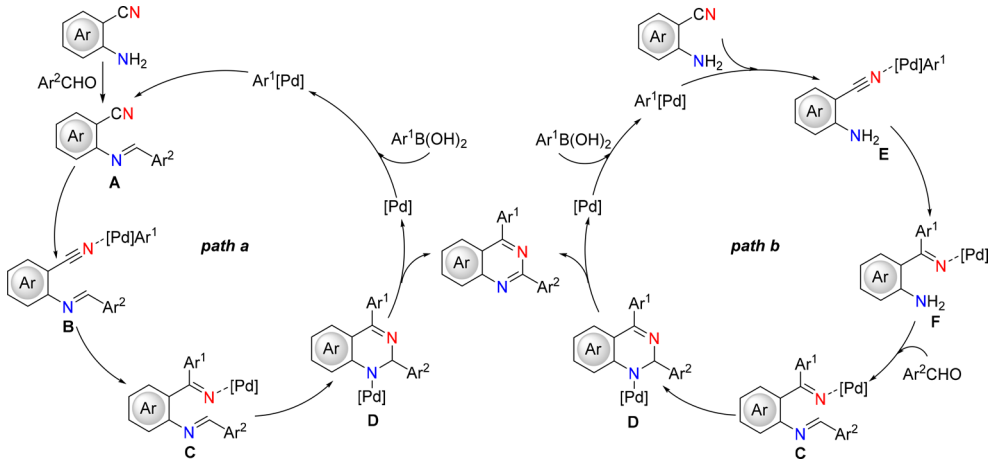
The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01070.

Experimental procedures, characterization data, NMR spectra, and X-ray data for product **5l** (PDF)

Accession Codes

CCDC 1818103 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.

Scheme 5. Two Possible Mechanistic Pathways for the Formation of Quinazolines



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Notes

The authors declare no competing financial interest.

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