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Palladium(II)-Catalyzed Three-Component Tandem Cyclization Reaction for the One-Pot Assembly of 4-Arylquinazolines

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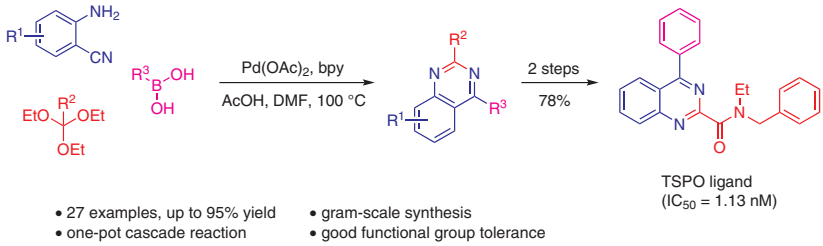

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Abstract A one-pot method for joining three separate components leading to an assortment of 4-arylquinazolines (27 examples) in good to excellent yields is described. The method consists of a palladium(II)-catalyzed cascade reaction involving C(sp)–C(sp^2) coupling followed by intramolecular C–N bond formation. The reaction was readily scaled up to gram quantity and successfully applied to the synthesis of a translocator protein (TSPO) ligand.

Key words 4-arylquinazolines, palladium(II) catalysis, one-pot assembly, tandem cyclization reaction, ligands

The transition-metal-catalyzed transformation of nitriles is emerging as an important strategy for direct C–N bond formation.[1] Quinazoline derivatives, as an essential family of *N*-fused heterocyclic compounds, have drawn much attention due to their potential medicinal properties and broad biological activities such as anti-inflammatory,[2,3] antihypertensive,[4] anticonvulsant, anticancer,[5–8] and antimicrobial activities.[9–12] Among quinazoline derivatives, 4-arylquinazolines are frequently found in bioactive compounds and pharmaceuticals, such as NTRC-808 and translocator protein (TSPO) ligand (Figure 1).[13–16]

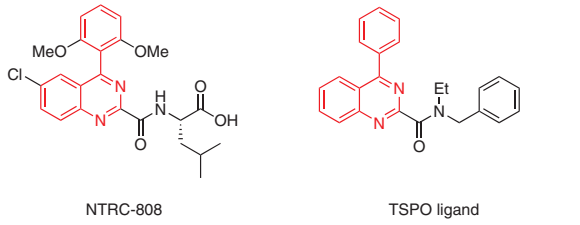

Figure 1 Selected examples of bioactive molecules containing 4-arylquinazolines

Because of the broad biological properties of 4-arylquinazolines, a large number of synthetic strategies for their preparation have been developed. Especially, the strategies using nitriles to attain 4-arylquinazolines have drawn attention. In 2018, Chen and co-workers reported the access to 2-(4-arylquinazolin-2-yl)anilines by a palladium-catalyzed tandem reaction of 2-(quinazolinone-3(4*H*)-yl)benzonitriles with arylboronic acids (Scheme 1a).[17] This preparation of 2-(4-arylquinazolin-2-yl)anilines involves sequential nucleophilic addition and intramolecular cyclization, followed by ring opening. Then, they described a palladium-catalyzed three-component tandem reaction of 2-aminobenzonitriles, aldehydes, and arylboronic acids to obtain quinazolines (Scheme 1b).[18] However, only benzaldehydes were researched for this reaction. In 2019, Liu and co-workers reported the synthesis of 4-arylquinazolines from (*E*)-*N*′-(2-cyanophenyl)-*N*,*N*-dimethylformimidamides and arylboronic acids *via* a palladium-catalyzed tandem cyclization reaction (Scheme 1c).[19]

Although these methods successfully achieved the synthesis of 4-arylquinazolines, it remains necessary to explore a new synthetic method for these compounds which is more convenient and practical. Herein, to achieve the high-value transformation of nitriles, we report a one-pot method for the construction of 4-arylquinazolines from commercially available 2-aminobenzonitriles, triethyl orthocarboxylates, and boronic acids *via* a palladium(II)-catalyzed cascade reaction (Scheme 1).

Initially, the commercially available 2-amino-4-chlorobenzonitrile (**1a**), triethyl orthoformate (**2a**), and phenylboronic acid (**3a**) were chosen as starting materials, and extensive investigations were carried out to establish the optimal reaction conditions. As shown in Table 1, the desired product **4a** was obtained in 11% yield when **1a**, **2a**, and **3a** were treated with $Pd(OAc)_2$ (20 mol%) in DMF (2.0 mL) at 40 °C for 12 hours (entry 1). A study of the effect of

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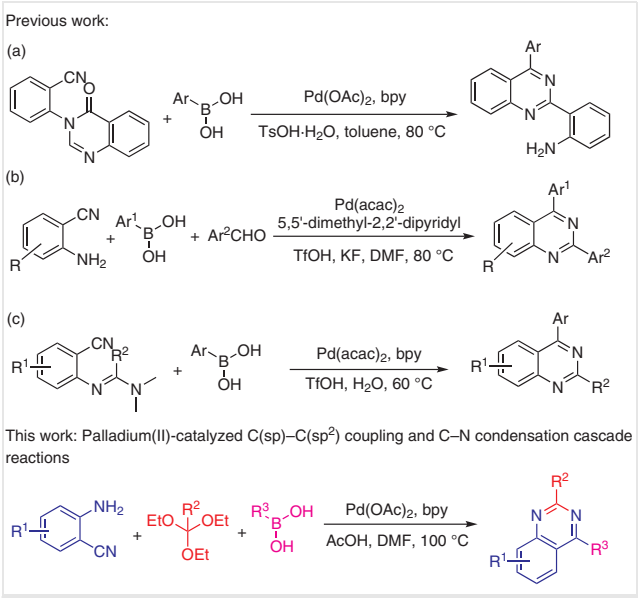
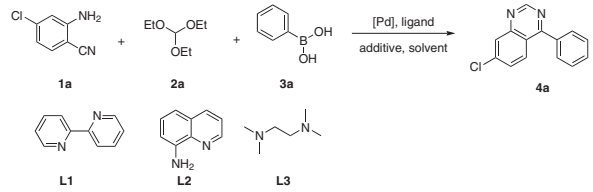


Scheme 1 Construction of the 4-arylquinazoline skeleton

temperature showed that 100 °C was the best temperature for this reaction (entries 1–5). Replacement of acetic acid with other additives, including formic acid, trifluoroacetic acid, and $FeCl_3$, resulted in relatively lower yields (entries 6–8). Next, different palladium catalysts were used to explore their catalytic capability; the results revealed that $Pd(OAc)_2$ was the best catalyst for this cascade reaction (entries 4, 9–11). Ligand screening showed that 2,2′-bipyridine (bpy, L1) gave the highest yield of **4a** (entries 4, 12–14). Clearly, DMF stood out as the best choice of solvent for further reactions, with its highest product yield (entries 4, 15–18). A decreased amount of $Pd(OAc)_2$ reduced the reaction yield, while an increase in the catalyst loading did not lead to a significant increase in the yield (entries 19 and 20). Similarly, decreasing the amount of triethyl orthoformate (**2a**) to 3 equivalents or phenylboronic acid (**3a**) to 1.5 equivalents influenced the reaction, with lower yields (entries 21 and 22). Increasing the amount of **2a** to 5 equivalents or **3a** to 2.5 equivalents did not produce a noticeable change in the yield of **4a** (entries 23 and 24). Therefore, the best reaction conditions were obtained when 2-amino-4-chlorobenzonitrile (1 mmol), triethyl orthoformate (4 mmol), and phenylboronic acid (2 mmol) were stirred in DMF (2.0 mL) at 100 °C for 12 hours in the presence of $Pd(OAc)_2$ (20 mol%), bpy (20 mol%), and AcOH (1 equiv) (Table 1, entry 4).

Having optimized the reaction conditions, we evaluated the scope of 2-aminobenzonitriles. As shown in Scheme 2, the corresponding products **4a–4m** were obtained in good to excellent yields (61–91%) regardless of the electronic nature and position of the substituent attached to the phenyl ring of the 2-aminobenzonitriles. When the substituent was at different positions of the phenyl ring, the results

Table 1 Optimization of the Reaction Conditions[a]



Entry	[Pd]	Ligand	Solvent	Temp (°C)	Additive	Yield (%)[b]
1	$Pd(OAc)_2$	L1	DMF	40	AcOH	11
2	$Pd(OAc)_2$	L1	DMF	60	AcOH	48
3	$Pd(OAc)_2$	L1	DMF	80	AcOH	64
4	**$Pd(OAc)_2$**	**L1**	**DMF**	**100**	**AcOH**	**72**
5	$Pd(OAc)_2$	L1	DMF	120	AcOH	65
6	$Pd(OAc)_2$	L1	DMF	100	HCOOH	28
7	$Pd(OAc)_2$	L1	DMF	100	CF_3COOH	36
8	$Pd(OAc)_2$	L1	DMF	100	$FeCl_3$	21
9	$Pd(PPh_3)_2Cl_2$	L1	DMF	100	AcOH	33
10	$Pd(PPh_3)_4$	L1	DMF	100	AcOH	trace
11	–	L1	DMF	100	AcOH	trace
12	$Pd(OAc)_2$	L2	DMF	100	AcOH	31
13	$Pd(OAc)_2$	L3	DMF	100	AcOH	56
14	$Pd(OAc)_2$	–	DMF	100	AcOH	trace
15	$Pd(OAc)_2$	L1	toluene	100	AcOH	13
16	$Pd(OAc)_2$	L1	MeCN	100	AcOH	trace
17	$Pd(OAc)_2$	L1	EtOH	100	AcOH	28
18	$Pd(OAc)_2$	L1	DMSO	100	AcOH	21
19[c]	$Pd(OAc)_2$	L1	DMF	100	AcOH	47
20[d]	$Pd(OAc)_2$	L1	DMF	100	AcOH	73
21[e]	$Pd(OAc)_2$	L1	DMF	100	AcOH	67
22[f]	$Pd(OAc)_2$	L1	DMF	100	AcOH	61
23[g]	$Pd(OAc)_2$	L1	DMF	100	AcOH	73
24[h]	$Pd(OAc)_2$	L1	DMF	100	AcOH	73

[a] Reaction conditions: **1a** (1 mmol), **2a** (4 mmol), **3a** (2 mmol), [Pd] (20 mol%), ligand (20 mol%), additive (1.0 equiv), solvent (2 mL), 12 h.
[b] Isolated yield.
[c] $Pd(OAc)_2$ catalyst (10 mol%) was used.
[d] $Pd(OAc)_2$ catalyst (30 mol%) was used.
[e] **2a** (3 equiv) was used.
[f] **3a** (1.5 equiv) was used.
[g] **2a** (5 equiv) was used.
[h] **3a** (2.5 equiv) was used.

showed that steric effects affected the yield of this transformation to some extent (Scheme 2, 4a–4c, 4d–4f). Then, when 2-aminobenzonitriles bearing an electron-withdrawing group were used, the reaction gave the desired 4-arylquinazolines in higher yields (**4g** vs **4i**, **4j** vs **4k**). Notably, products **4l** and **4m** with a bromo substituent were

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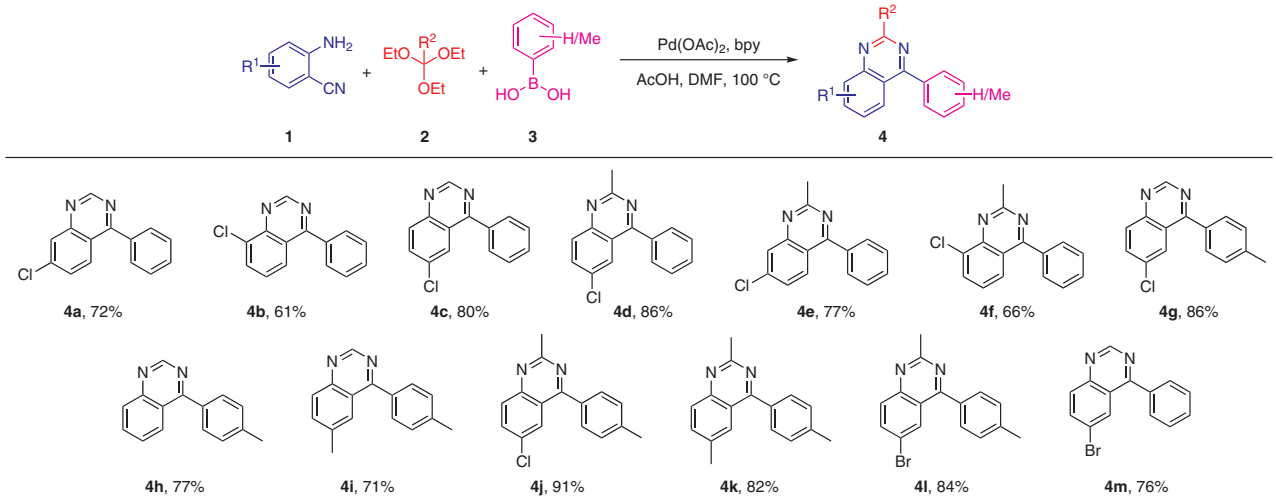
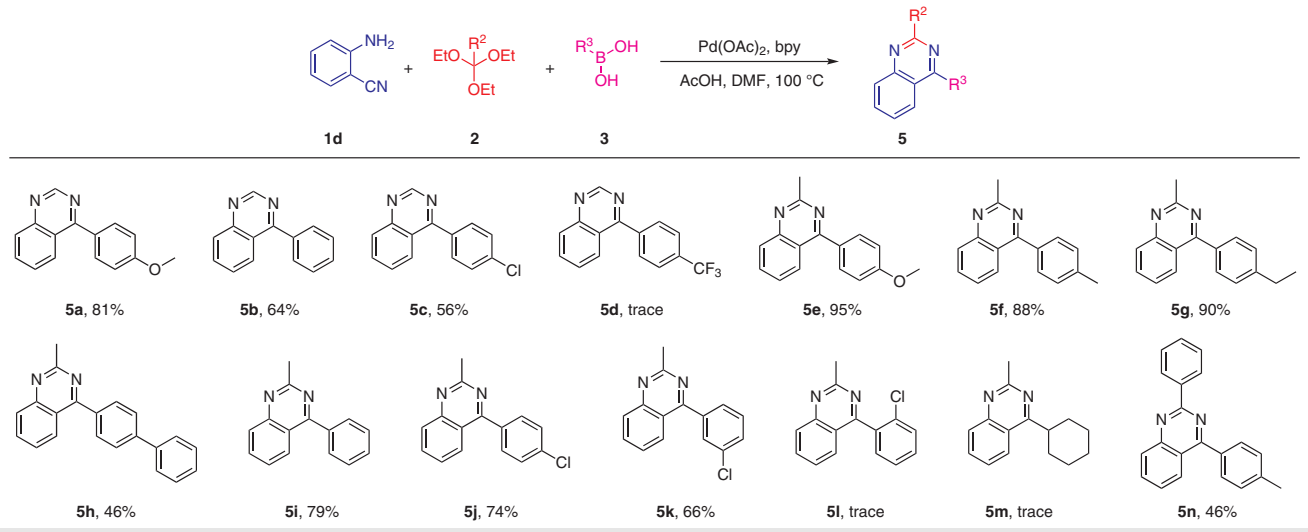


Scheme 2 Reaction scope of 2-aminobenzonitriles. *Reagents and conditions*: **1** (1 mmol), **2** (4 mmol), **3** (2 mmol), $Pd(OAc)_2$ (20 mol%), bpy (20 mol%), AcOH (1.0 equiv), DMF (2 mL), 100 °C, 12 h; isolated yields.

smoothly produced in excellent yields (**4l**, 84%; **4m**, 76%), thus allowing for further transformations to form more complex molecules *via* cross-coupling reactions.

We next turned our attention to the effect of boronic acids on the reaction under the standard conditions. Boronic acids containing an electron-donating substituent were more compatible for this transformation, giving higher yields (Scheme 3; **5a**–**5d**, **5e**–**5g** vs **5j**). However, 4-(trifluoromethyl)phenylboronic acid had no activity under the reaction conditions, possibly due to the strong electron-withdrawing effects of the trifluoromethyl group (**5d**). 4-Biphenylboronic acid gave product **5h** in 46% yield, probably due to the steric effects of the phenyl ring. Then, the reactivities of *p*-, *m*-, and *o*-chlorophenylboronic acid were evaluated, and the results demonstrated that the steric effect of the substituent had an obvious impact on the reaction. For example, treatment of 2-aminobenzonitrile and triethyl orthoacetate with *p*- and *m*-chlorophenylboronic acid provided **5j** in 74% yield and **5k** in 66% yield, respectively, while *o*-chlorophenylboronic acid did not afford the desired product **5l**. Cyclohexylboronic acid did not give the desired product **5m**, probably because it is not easy to undergo the transmetalation reaction with $Pd(OAc)_2$ as catalyst.

As for triethyl orthocarboxylates, the scope of the reaction was also examined under the standard reaction conditions. The results showed that triethyl orthoacetate gave higher yields than triethyl orthoformate (Scheme 3; **5b** vs



Scheme 3 Reaction scope of boronic acids. *Reagents and conditions*: **1d** (1 mmol), **2** (4 mmol), **3** (2 mmol), $Pd(OAc)_2$ (20 mol%), bpy (20 mol%), AcOH (1.0 equiv), DMF (2 mL), 100 °C, 12 h; isolated yields.

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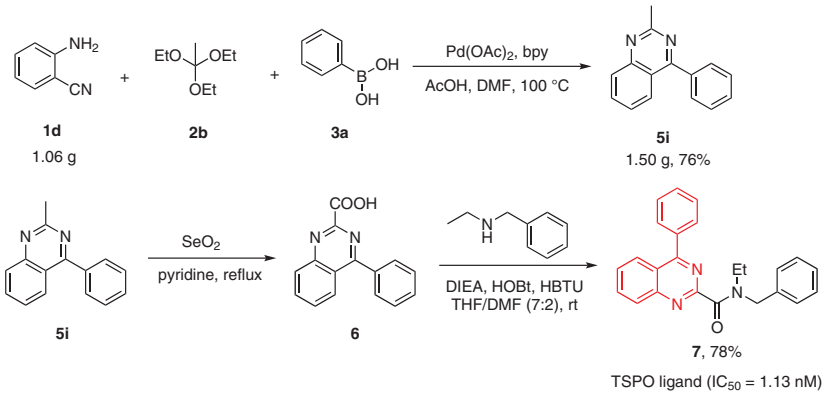


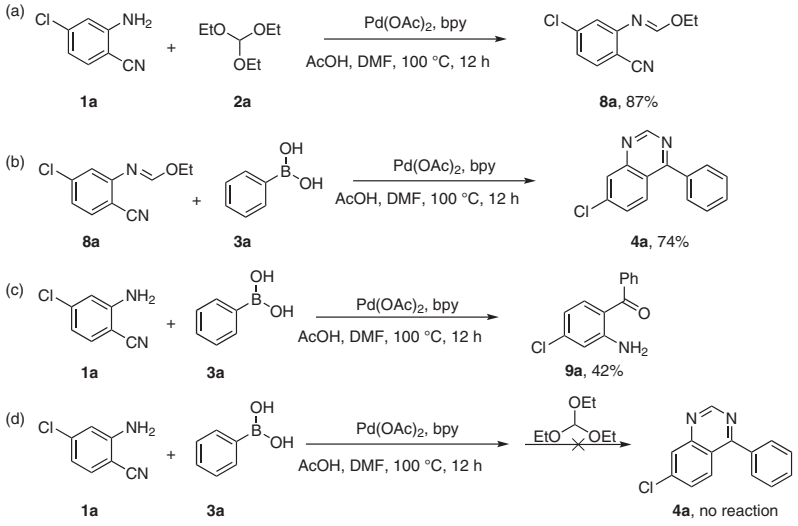
Scheme 4 Gram-scale synthesis of **5i** and its further derivatization

5i, **5c** vs **5j**), possibly because intermediate **8** is more stable (see Scheme 6). Additionally, triethyl orthobenzoate afforded product **5n** in 46% yield, which demonstrated that the steric effect of the substituent (R^2) had an impact on the reaction (**5f** vs **5n**).

To further demonstrate the practicality of this method, we next scaled up the reaction. The reaction with 2-aminobenzonitrile was performed on a gram scale (1.06 g, 9 mmol), and product **5i** was obtained in 76% yield (Scheme 4). Then, product **5i** was applied to the synthesis of bioactive compound **7**, which is a highly potent and selective TSPO ligand,[11] in a two-step method with high efficiency. Similarly, our 4-arylquinazoline products could also be used to synthesize other TSPO ligands.

To gain insight into the reaction mechanism, four control experiments were performed (Scheme 5). First, the reaction of **1a** with **2a** produced intermediate **8a** in 87% yield. The desired product **4a** could be synthesized successfully in considerable yield (74%) from the reaction of **8a** with **3a**. Then, (2-amino-4-chlorophenyl)(phenyl)methanone (**9a**) was gained in 42% yield from the reaction of **1a** with **3a** in the absence of **2a**. However, conducting the reaction of **1a** and **3a** for 12 hours, then adding **2a** to the reaction mixture, did not afford product **4a**, indicating that **8a** is the possible intermediate for this transformation.

On the basis of the preliminary results and previous reports,[17,20–22] a plausible mechanism for this transformation is illustrated in Scheme 6. The reaction of **1** with **2** will produce intermediate **8**, which participates in the catalytic cycle. Initially, the transmetalation reaction of the Pd(II) catalyst with arylboronic acid provides intermediate **B**, which is followed by coordination of the N atom of the cyano group to give intermediate **C**. Carbopalladation of the cyano group generates the corresponding ketimine–Pd(II) complex **D**. Then, intermediate **D** exchanges with AcOH to produce ketimine derivative **E** and to regenerate the Pd(II) catalyst. Finally, cyclization of ketimine derivative **E** affords the corresponding 4-arylquinazoline **F**.



Scheme 5 Control experiments

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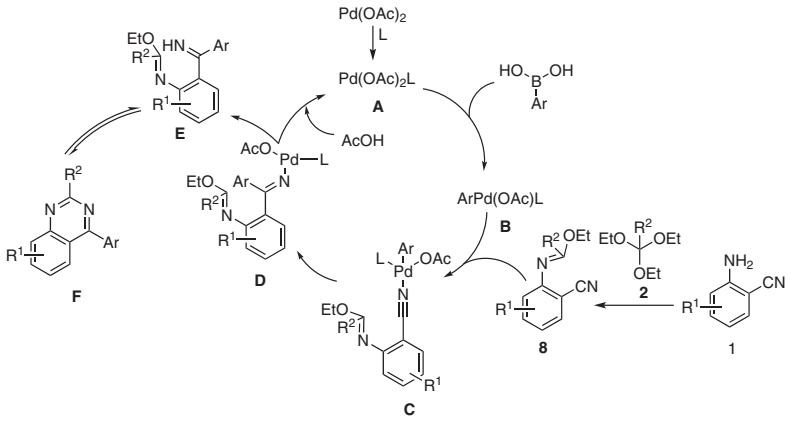

Scheme 6 Plausible mechanism for the transformation

In conclusion, a straightforward one-pot assembly of 4-arylquinazolines has been successfully developed. It involves a palladium(II)-catalyzed cascade reaction from commercially available 2-aminobenzonitriles, triethyl orthocarboxylates, and boronic acids in good to excellent yields (up to 95% yield). This reaction features good functional group tolerance and can be scaled up to gram quantity. Moreover, this synthetic protocol is able to act as an efficient strategy to synthesize biologically active 4-arylquinazoline derivatives.

All solvents were purified according to standard methods prior to use. Melting points were recorded on a Büchi B-540 melting point apparatus. NMR spectra were recorded at 500 MHz (^{1}H NMR) and 125 MHz (^{13}C NMR). For ^{1}H NMR, TMS served as internal standard (δ = 0) and data are reported as follows: chemical shift, multiplicity (standard abbreviations), coupling constant(s) in hertz, and integration. For ^{13}C NMR, TMS (δ = 0) was used as internal standard and spectra were obtained with complete proton decoupling. HRMS data were obtained using an Agilent Technologies 6224 TOF LC/MS system. The starting materials were commercially available.

4-Arylquinazolines 4 and 5; General Procedure

A mixture of 2-aminobenzonitrile **1** (1.0 mmol, 1.0 equiv), triethyl orthocarboxylate **2** (4.0 mmol, 4.0 equiv), boronic acid **3** (2.0 mmol, 2.0 equiv), AcOH (1.0 mmol, 1.0 equiv), bpy (0.2 mmol, 0.2 equiv), and $Pd(OAc)_2$ (0.2 mmol, 0.2 equiv) was stirred in DMF (2.0 mL) at 100 °C for 12 h. After reaction completion, the mixture was filtered through diatomite. Water (10 mL) was added to the filtrate. The aqueous phase was extracted with EtOAc (3 × 10 mL). The organic layer was washed with brine, dried over Na_2SO_4, concentrated in vacuo, and purified by flash column chromatography (PE/EtOAc, 20:1) to yield **4** or **5**.

7-Chloro-4-phenylquinazoline (4a)

Yield: 173.3 mg (72%); pale yellow solid; mp 134–135 °C (Lit.[23] 134–136 °C).

IR (KBr): 3390, 3301, 3044, 2946, 1711, 1543, 1069, 820, 723 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.36 (s, 1 H), 8.11 (d, *J* = 2.0 Hz, 1 H), 8.08 (d, *J* = 9.0 Hz, 1 H), 7.78–7.72 (m, 2 H), 7.60–7.52 (m, 4 H).

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{10}ClN_2$ [M + H]$^+$: 241.0527; found: 241.0521.

8-Chloro-4-phenylquinazoline (4b)

Yield: 146.8 mg (61%); pale yellow solid; mp 96–97 °C (Lit.[23] 95–97 °C).

IR (KBr): 3389, 3346, 3034, 2875, 1745, 1568, 1034, 855, 776 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.49 (s, 1 H), 8.07 (dd, *J* = 8.5, 1.5 Hz, 1 H), 8.02 (dd, *J* = 7.5, 1.5 Hz, 1 H), 7.80–7.72 (m, 2 H), 7.62–7.56 (m, 3 H), 7.53 (dd, *J* = 8.5, 7.5 Hz, 1 H).

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{10}ClN_2$ [M + H]$^+$: 241.0527; found: 241.0534.

6-Chloro-4-phenylquinazoline (4c)

Yield: 192.6 mg (80%); pale yellow solid; mp 135–137 °C.

IR (KBr): 3366, 3335, 3065, 2965, 1776, 1534, 1034, 834, 723 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.38 (s, 1 H), 8.11 (d, *J* = 2.5 Hz, 1 H), 8.07 (d, *J* = 9.0 Hz, 1 H), 7.85 (dd, *J* = 9.0, 2.5 Hz, 1 H), 7.78–7.74 (m, 2 H), 7.63–7.58 (m, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.75, 154.14, 149.80, 140.26, 137.90, 135.95, 134.61, 130.00, 129.46, 128.66, 125.85, 123.30.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{10}ClN_2$ [M + H]$^+$: 241.0527; found: 241.0533.

6-Chloro-2-methyl-4-phenylquinazoline (4d)

Yield: 218.5 mg (86%); white solid; mp 105–106 °C (Lit.[25] 105–107 °C).

IR (KBr): 3323, 3286, 3024, 2928, 1726, 1524, 1068, 857, 702 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.01 (s, 1 H), 7.95 (d, *J* = 9.0 Hz, 1 H), 7.79 (d, *J* = 9.0 Hz, 1 H), 7.76–7.69 (m, 2 H), 7.61–7.55 (m, 3 H), 2.93 (s, 3 H).

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{12}ClN_2$ [M + H]$^+$: 255.0684; found: 255.0687.

7-Chloro-2-methyl-4-phenylquinazoline (4e)

Yield: 196.1 mg (77%); pale yellow solid; mp 104–105 °C.

IR (KBr): 3299, 3278, 3023, 2943, 1756, 1523, 1074, 867, 723 cm^{-1}.

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^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.02–7.96 (m, 2 H), 7.76–7.68 (m, 2 H), 7.60–7.52 (m, 3 H), 7.46 (dd, *J* = 8.5, 2.0 Hz, 1 H), 2.93 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.61, 165.15, 152.20, 139.99, 136.98, 130.26, 129.91, 128.87, 128.61, 127.93, 127.37, 119.56, 26.77.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{12}ClN_2$ [M + H]$^+$: 255.0684; found: 255.0687.

8-Chloro-2-methyl-4-phenylquinazoline (4f)

Yield: 168.1 mg (66%); pale yellow solid; mp 83–84 °C.

IR (KBr): 3323, 3304, 3024, 2945, 1767, 1578, 1035, 831, 703 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.95 (t, *J* = 8.5 Hz, 2 H), 7.75–7.69 (m, 2 H), 7.59–7.52 (m, 3 H), 7.42 (t, *J* = 8.0 Hz, 1 H), 3.01 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.15, 164.88, 148.19, 137.05, 133.51, 132.65, 130.19, 129.99, 128.77, 126.42, 126.20, 122.40, 27.06.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{12}ClN_2$ [M + H]$^+$: 255.0684; found: 255.0693.

6-Chloro-4-(*p*-tolyl)quinazoline (4g)

Yield: 219.1 mg (86%); white solid; mp 162–163 °C (Lit.[24] 163–164 °C).

IR (KBr): 3334, 3299, 3034, 2956, 1745, 1535, 1046, 846, 756 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.35 (s, 1 H), 8.13 (d, *J* = 2.5 Hz, 1 H), 8.05 (d, *J* = 9.0 Hz, 1 H), 7.84 (dd, *J* = 9.0, 2.5 Hz, 1 H), 7.68 (d, *J* = 8.0 Hz, 2 H), 7.41 (d, *J* = 7.5 Hz, 2 H), 2.49 (s, 3 H).

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{12}ClN_2$ [M + H]$^+$: 255.0684; found: 255.0685.

4-(*p*-Tolyl)quinazoline (4h)

Yield: 169.6 mg (77%); pale yellow solid; mp 42–43 °C (Lit.[19] 41–42 °C).

IR (KBr): 3322, 3298, 3034, 2945, 1756, 1578, 1039, 833, 721 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.36 (s, 1 H), 8.16 (dd, *J* = 8.5, 1.5 Hz, 1 H), 8.10 (d, *J* = 8.5 Hz, 1 H), 7.91 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1 H), 7.70 (d, *J* = 8.0 Hz, 2 H), 7.60 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1 H), 7.38 (d, *J* = 8.0 Hz, 2 H), 2.48 (s, 3 H).

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{13}N_2$ [M + H]$^+$: 221.1073; found: 221.1068.

6-Methyl-4-(*p*-tolyl)quinazoline (4i)

Yield: 166.4 mg (71%); yellow solid; mp 96–97 °C.

IR (KBr): 3345, 3235, 3055, 2967, 1745, 1587, 1023, 845, 767 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.30 (s, 1 H), 8.00 (d, *J* = 8.5 Hz, 1 H), 7.90 (s, 1 H), 7.73 (dd, *J* = 9.0, 2.0 Hz, 1 H), 7.68 (d, *J* = 8.0 Hz, 2 H), 7.39 (d, *J* = 7.5 Hz, 2 H), 2.51 (s, 3 H), 2.48 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.75, 154.14, 149.80, 140.26, 137.90, 135.95, 134.61, 130.00, 129.46, 128.66, 125.85, 123.30, 22.04, 21.60.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{15}N_2$ [M + H]$^+$: 235.1230; found: 235.1232.

6-Chloro-2-methyl-4-(*p*-tolyl)quinazoline (4j)

Yield: 244.6 mg (91%); pale yellow solid; mp 125–126 °C.

IR (KBr): 3306, 3300, 3045, 2945, 1745, 1565, 1034, 832, 726 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 2.0 Hz, 1 H), 7.94 (d, *J* = 9.0 Hz, 1 H), 7.78 (dd, *J* = 9.0, 2.0 Hz, 1 H), 7.64 (d, *J* = 8.0 Hz, 2 H), 7.39 (d, *J* = 7.5 Hz, 2 H), 2.92 (s, 3 H), 2.48 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.89, 164.28, 150.03, 140.58, 134.54, 133.97, 132.31, 129.99, 129.87, 129.62, 125.96, 121.70, 26.69, 21.58.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{14}ClN_2$ [M + H]$^+$: 269.0840; found: 269.0845.

2,6-Dimethyl-4-(*p*-tolyl)quinazoline (4k)

Yield: 203.6 mg (82%); pale yellow solid; mp 104–105 °C.

IR (KBr): 3336, 3327, 3046, 2928, 1780, 1503, 1035, 867, 789 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 8.5 Hz, 1 H), 7.81 (s, 1 H), 7.68 (dd, *J* = 9.0, 2.0 Hz, 1 H), 7.64 (d, *J* = 8.5 Hz, 2 H), 7.37 (d, *J* = 8.0 Hz, 2 H), 2.91 (s, 3 H), 2.47 (s, 3 H), 2.47 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.96, 163.10, 150.09, 139.98, 136.71, 135.85, 134.74, 129.89, 129.40, 127.89, 125.79, 121.10, 26.63, 21.88, 21.56.

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{17}N_2$ [M + H]$^+$: 249.1386; found: 249.1393.

6-Bromo-2-methyl-4-(*p*-tolyl)quinazoline (4l)

Yield: 263.1 mg (84%); pale yellow solid; mp 116–117 °C.

IR (KBr): 3379, 3334, 3056, 2937, 1739, 1555, 1096, 857, 710 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.21 (d, *J* = 2.0 Hz, 1 H), 7.94–7.85 (m, 2 H), 7.64 (d, *J* = 8.0 Hz, 2 H), 7.39 (d, *J* = 7.5 Hz, 2 H), 2.92 (s, 3 H), 2.48 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.86, 164.41, 150.27, 140.66, 137.16, 133.98, 130.11, 129.92, 129.69, 129.33, 122.27, 120.35, 26.77, 21.62.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{14}BrN_2$ [M + H]$^+$: 313.0335; found: 313.0338.

6-Bromo-4-phenylquinazoline (4m)

Yield: 215.8 mg (76%); pale yellow solid; mp 88–89 °C (Lit.[19] 89–90 °C).

IR (KBr): 3334, 3307, 3045, 2966, 1736, 1564, 1078, 835, 778 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.39 (s, 1 H), 8.27 (dd, *J* = 2.0, 1.0 Hz, 1 H), 8.02–7.95 (m, 2 H), 7.80–7.73 (m, 2 H), 7.64–7.57 (m, 3 H).

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{10}BrN_2$ [M + H]$^+$: 285.0022; found: 285.0029.

4-(4-Methoxyphenyl)quinazoline (5a)

Yield: 191.4 mg (81%); white solid; mp 82–83 °C (Lit.[19] 83–84 °C).

IR (KBr): 3369, 3305, 3064, 2936, 1757, 1584, 858, 722 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.33 (s, 1 H), 8.17 (d, *J* = 8.5 Hz, 1 H), 8.09 (d, *J* = 8.5 Hz, 1 H), 7.89 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1 H), 7.78 (d, *J* = 9.0 Hz, 2 H), 7.60 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1 H), 7.09 (d, *J* = 8.5 Hz, 2 H), 3.91 (s, 3 H).

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{13}N_2O$ [M + H]$^+$: 237.1022; found: 237.1024.

4-Phenylquinazoline (5b)

Yield: 132.0 mg (64%); pale yellow solid; mp 96–97 °C (Lit.[26] 95–97 °C).

IR (KBr): 3301, 3035, 2968, 1677, 1589, 1057, 857, 798 cm^{-1}.

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^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.38 (s, 1 H), 8.12 (t, *J* = 8.5 Hz, 2 H), 7.91 (t, *J* = 6.5 Hz, 1 H), 7.81–7.74 (m, 2 H), 7.63–7.55 (m, 4 H).

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{11}N_2$ [M + H]$^+$: 207.0917; found: 207.0923.

4-(4-Chlorophenyl)quinazoline (5c)

Yield: 134.8 mg (56%); pale yellow solid; mp 117–119 °C (Lit.[26] 116–118 °C).

IR (KBr): 3409, 3345, 3005, 2960, 1706, 1500, 1057, 857, 713 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.37 (s, 1 H), 8.12 (d, *J* = 8.5 Hz, 1 H), 8.08 (d, *J* = 8.5 Hz, 1 H), 7.93 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1 H), 7.74 (d, *J* = 8.0 Hz, 2 H), 7.63 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1 H), 7.56 (d, *J* = 8.5 Hz, 2 H).

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{10}ClN_2$ [M + H]$^+$: 241.0527; found: 241.0537.

4-(4-Methoxyphenyl)-2-methylquinazoline (5e)

Yield: 237.8 mg (95%); yellow solid; mp 47–48 °C (Lit.[19] 48–49 °C).

IR (KBr): 3466, 3336, 3046, 2888, 1768, 1536, 1089, 858, 725 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 8.5 Hz, 1 H), 7.99 (d, *J* = 8.5 Hz, 1 H), 7.84 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1 H), 7.74 (d, *J* = 8.5 Hz, 2 H), 7.51 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1 H), 7.08 (d, *J* = 9.0 Hz, 2 H), 3.90 (s, 3 H), 2.93 (s, 3 H).

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{15}N_2O$ [M + H]$^+$: 251.1179; found: 251.1184.

2-Methyl-4-(*p*-tolyl)quinazoline (5f)

Yield: 206.2 mg (88%); white solid; mp 94–95 °C (Lit.[19] 93–94 °C).

IR (KBr): 3406, 3357, 3078, 2964, 1736, 1568, 1047, 857, 709 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 8.5 Hz, 1 H), 8.00 (d, *J* = 8.5 Hz, 1 H), 7.89–7.81 (m, 1 H), 7.66 (d, *J* = 6.5 Hz, 2 H), 7.55–7.49 (m, 1 H), 7.37 (d, *J* = 7.5 Hz, 2 H), 2.94 (s, 3 H), 2.47 (s, 3 H).

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{15}N_2$ [M + H]$^+$: 235.1230; found: 235.1239.

2-Methyl-4-(4-ethylphenyl)quinazoline (5g)

Yield: 223.5 mg (90%); colorless oil.

IR (KBr): 3356, 3308, 3111, 2946, 1756, 1567, 1068, 865, 727 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 8.5 Hz, 1 H), 7.86 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1 H), 7.61 (d, *J* = 8.0 Hz, 1 H), 7.46 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 2 H), 7.41 (d, *J* = 6.5 Hz, 1 H), 7.33 (td, *J* = 7.5, 1.5 Hz, 1 H), 7.27 (dd, *J* = 7.5, 1.5 Hz, 1 H), 2.95 (s, 3 H), 1.73 (s, 2 H), 1.02 (t, *J* = 7.5 Hz, 3 H).

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{17}N_2$ [M + H]$^+$: 249.1386; found: 249.1378.

4-(1,1′-Biphenyl-4-yl)-2-methylquinazoline (5h)

Yield: 139.3 mg (46%); white solid; mp 156–157 °C (Lit.[19] 155–156 °C).

IR (KBr): 3357, 3346, 3035, 2467, 1746, 1556, 1024, 867, 778 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.14 (d, *J* = 8.5 Hz, 1 H), 8.03 (d, *J* = 8.5 Hz, 1 H), 7.93–7.82 (m, 3 H), 7.83–7.76 (m, 2 H), 7.70–7.65 (m, 2 H), 7.56 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1 H), 7.52–7.46 (m, 2 H), 7.45–7.37 (m, 1 H), 2.97 (s, 3 H).

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{17}N_2$ [M + H]$^+$: 297.1386; found: 297.1381.

2-Methyl-4-phenylquinazoline (5i)

Yield: 170.4 mg (79%); yellow solid; mp 48–49 °C (Lit.[19] 47–48 °C).

IR (KBr): 3378, 3356, 3078, 2945, 1789, 1530, 1035, 864, 773 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 8.5 Hz, 1 H), 8.02–7.99 (m, 1 H), 7.86 (t, *J* = 8.5 Hz, 1 H), 7.77–7.71 (m, 2 H), 7.58–7.54 (m, 3 H), 7.51 (t, *J* = 7.0 Hz, 1 H), 2.95 (s, 3 H).

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{13}N_2$ [M + H]$^+$: 221.1073; found: 221.1077.

4-(4-Chlorophenyl)-2-methylquinazoline (5j)

Yield: 188.5 mg (74%); white solid; mp 127–128 °C (Lit.[19] 128–129 °C).

IR (KBr): 3387, 3324, 3078, 2685, 1774, 1504, 1025, 876, 711 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.01 (t, *J* = 9.5 Hz, 2 H), 7.88 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1 H), 7.74–7.68 (m, 2 H), 7.58–7.52 (m, 3 H), 2.94 (s, 3 H).

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{12}ClN_2$ [M + H]$^+$: 255.0684; found: 255.0691.

4-(3-Chlorophenyl)-2-methylquinazoline (5k)

Yield: 168.1 mg (66%); pale yellow solid; mp 84–85 °C.

IR (KBr): 3396, 3324, 3066, 2846, 1766, 1589, 1038, 868, 710 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 8.5 Hz, 1 H), 8.00 (d, *J* = 8.0 Hz, 1 H), 7.88 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1 H), 7.75 (t, *J* = 1.5 Hz, 1 H), 7.62 (dt, *J* = 7.5, 1.5 Hz, 1 H), 7.58–7.52 (m, 2 H), 7.52–7.47 (m, 1 H), 2.95 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.15, 163.96, 151.60, 139.09, 134.90, 134.03, 130.08, 130.01, 129.95, 128.43, 128.15, 127.19, 126.67, 120.93, 26.71.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{12}ClN_2$ [M + H]$^+$: 255.0684; found: 255.0680.

2-Phenyl-4-(*p*-tolyl)quinazoline (5n)

Yield: 136.3 mg (46%); yellow solid; mp 125–126 °C (Lit.[18] 126–127 °C).

IR (KBr): 3357, 3300, 3057, 2967, 1734, 1512, 866, 744 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.73–8.66 (m, 2 H), 8.18–8.13 (m, 2 H), 7.88 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1 H), 7.81 (d, *J* = 8.0 Hz, 2 H), 7.58–7.48 (m, 4 H), 7.41 (d, *J* = 7.5 Hz, 2 H), 2.50 (s, 3 H).

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{17}N_2$ [M + H]$^+$: 297.1386; found: 297.1381.

Synthesis of TSPO Ligand 7

4-Phenylquinazoline-2-carboxylic Acid (6)

A mixture of **5i** (5 mmol), selenium dioxide (5 mmol), and pyridine (5 mL) was refluxed for 2 h. Reaction progress was monitored by TLC. After reaction completion, the mixture was concentrated under reduced pressure, then water (10 mL) was added, which was followed by acidification with 1 N HCl. The mixture was filtered to afford product **6**.

Yield: 1.1 g (91%); pale pink solid; mp 97–98 °C (Lit.[16b] 98 °C).

IR (KBr): 3511, 3356, 3035, 2888, 2135, 1464, 1068, 811, 703 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.25–8.06 (m, 3 H), 7.89–7.77 (m, 3 H), 7.65 (s, 3 H), 3.36 (s, 1 H).

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{11}N_2O_2$ [M + H]$^+$: 251.0815; found: 251.0811.

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***N*-Benzyl-*N*-ethyl-4-phenylquinazoline-2-carboxamide (7)**

A solution of acid **6** (268 mg, 1.07 mmol), HOBt (328 mg, 2.14 mmol), HBTU (812 mg, 2.14 mmol), and DIEA (0.76 mL, 4.28 mmol) in anhydrous THF/DMF (7:2, 9 mL) was added to a solution of *N*-benzylethanamine (144 mg, 1.07 mmol) in anhydrous THF (3 mL) under an N_2 atmosphere. The reaction mixture was stirred at room temperature overnight and then concentrated in vacuo. The residue was dissolved in EtOAc (100 mL), and the mixture was washed with sat. aq $NaHCO_3$ solution (3 × 30 mL) and brine. The organic solution was dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by flash column chromatography (PE/EtOAc, 10:1) afforded compound **7**.

Yield: 307 mg (78%, based on **6**); white solid; mp 69–70 °C (Lit.[16b] 68–71 °C).

IR (KBr): 3478, 3356, 3025, 2977, 1630, 1036, 827, 711 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.19–8.05 (m, 3 H), 7.85–7.77 (m, 2 H), 7.73–7.68 (m, 1 H), 7.67–7.57 (m, 3 H), 7.44–7.37 (m, 3 H), 7.33–7.23 (m, 2 H), 4.76, 4.44 (2 s, 2 H), 3.42, 3.14 (2 q, *J* = 7.0 Hz, 2 H), 1.12, 1.07 (2 t, *J* = 7.0 Hz, 3 H).

HRMS (ESI): *m*/*z* calcd for $C_{24}H_{22}N_3O$ $[M + H]^+$: 368.1757; found: 368.1764.

Control Experiments (Scheme 5)

(a) 2-Aminobenzonitrile **1a** (1.0 mmol), triethyl orthoformate (**2a**; 4.0 mmol), AcOH (1.0 mmol), bpy (0.2 mmol), and $Pd(OAc)_2$ (0.2 mmol) were stirred in DMF (2.0 mL) at 100 °C for 12 h. After reaction completion, the mixture was filtered through diatomite. Water (10 mL) was added to the filtrate. The aqueous phase was extracted with EtOAc (3 × 10 mL). The organic layer was washed with brine, dried over Na_2SO_4, concentrated in vacuo, and purified by flash column chromatography (PE/EtOAc, 10:1) to afford ethyl *N*-(5-chloro-2-cyanophenyl)formimidate (**8a**).

Yield: 181.5 mg (87%); pale pink solid; mp 72–73 °C (Lit.[27] 71–73 °C).

IR (KBr): 3401, 3344, 3325, 3022, 2925, 1777, 1554, 1064, 878 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.75 (s, 1 H), 7.53 (d, *J* = 8.5 Hz, 1 H), 7.16 (dd, *J* = 8.5, 2.0 Hz, 1 H), 7.00 (d, *J* = 2.0 Hz, 1 H), 4.41 (q, *J* = 7.0 Hz, 2 H), 1.41 (t, *J* = 7.0 Hz, 3 H).

HRMS (ESI): *m*/*z* calcd for $C_{10}H_{10}ClN_2O$ $[M + H]^+$: 209.0476; found: 209.0471.

(b) Ethyl *N*-(5-chloro-2-cyanophenyl)formimidate (**8a**; 1.0 mmol), phenylboronic acid (**3a**; 2.0 mmol), AcOH (1.0 mmol), bpy (0.2 mmol), and $Pd(OAc)_2$ (0.2 mmol) were stirred in DMF (2.0 mL) at 100 °C for 12 h. After reaction completion, the mixture was filtered through diatomite. Water (10 mL) was added to the filtrate. The aqueous phase was extracted with EtOAc (3 × 10 mL). The organic layer was washed with brine, dried over Na_2SO_4, concentrated in vacuo, and purified by flash column chromatography (PE/EtOAc, 20:1) to afford **4a**; yield: 154 mg (74%).

(c) 2-Aminobenzonitrile **1a** (1.0 mmol), phenylboronic acid (**3a**; 2.0 mmol), AcOH (1.0 mmol), bpy (0.2 mmol), and $Pd(OAc)_2$ (0.2 mmol) were stirred in DMF (2.0 mL) at 100 °C for 12 h. After reaction completion, the mixture was filtered through diatomite. Water (10 mL) was added to the filtrate. The aqueous phase was extracted with EtOAc (3 × 10 mL). The organic layer was washed with brine, dried over Na_2SO_4, concentrated in vacuo, and purified by flash column chromatography (PE/EtOAc, 10:1) to afford **9a**; yield: 97 mg (42%).

HRMS (ESI): *m*/*z* calcd for $C_{13}H_{11}ClNO$ $[M + H]^+$: 232.0524; found: 232.0519.

(d) 2-Aminobenzonitrile **1a** (1.0 mmol), phenylboronic acid (**3a**; 2.0 mmol), AcOH (1.0 mmol), bpy (0.2 mmol), and $Pd(OAc)_2$ (0.2 mmol) were stirred in DMF (2.0 mL) at 100 °C for 12 h. Then, triethyl orthoformate (**2a**; 4.0 mmol) was added to the solution for further reaction.

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Supporting Information

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