Organic & Biomolecular Chemistry

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2018, **16**, 8596

Pd-Catalyzed tandem reaction of *N*-(2-cyanoaryl) benzamides with arylboronic acids: synthesis of quinazolines†

Jianghe Zhu,‡ Yinlin Shao,‡ Kun Hu, Linjun Qi, Tianxing Cheng and Jiuxi Chen *

Received 28th September 2018,
Accepted 24th October 2018

DOI: 10.1039/c8ob02421a

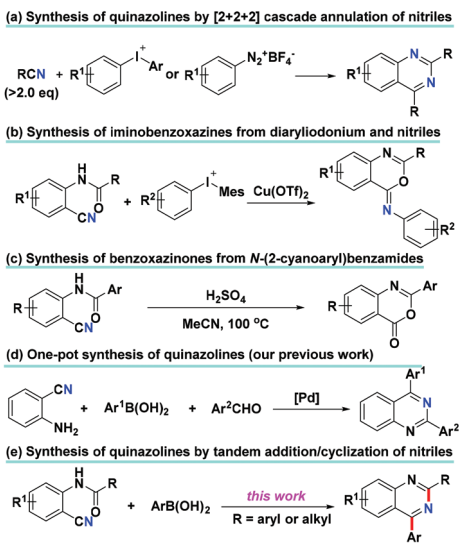
rsc.li/obc

The synthesis of 2,4-disubstituted quinazolines by a palladium-catalyzed reaction of arylboronic acids with *N*-(2-cyanoaryl)benzamides has been developed with moderate to excellent yields. The method shows good functional group tolerance. In particular, halogen and hydroxyl substituents, which are amenable for further synthetic elaborations, are well tolerated. Moreover, the present synthetic route could be readily scaled up to gram quantity without difficulty. The mechanism possibly involves nucleophilic addition to the nitrile function, forming an imine intermediate followed by an intramolecular addition to the amide and dehydration to the quinazoline ring.

Introduction

The transition-metal-catalyzed transformation of nitriles provides a highly attractive approach to generate carbon–carbon and carbon–heteroatom bonds for organic chemistry research and the fine chemical industry.[1] Remarkable progress over the past few decades in the transition-metal-catalyzed addition of organoboron reagents to nitriles[2] has been documented since the pioneering work on the addition of arylpalladium species to the cyano group reported by Larock and co-workers.[3] In recent years, we also developed the palladium-catalyzed addition of organoboron reagents to nitriles for access to alkyl aryl ketones, diketones, 2-aminobenzophenones, benzofurans, and indoles.[4]

Quinazolines occur in natural products,[5] biologically active molecules,[6] and functionalized materials.[7] Because of their great value, numerous methodologies for the synthesis of quinazolines have been reported, which mainly start from *ortho*-functionalized anilines,[8] amidines[9] or *ortho*-functionalized-halide,[10] generally with multiple-step reactions.[11] In 2013, our group developed copper-catalyzed direct access to 2-substituted quinazolines by a copper-catalyzed tandem reaction of (2-aminophenyl)methanols, aldehydes, and ammonium chloride.[12] However, only sporadic examples of the tandem reaction of commercially available nitriles for access to 2,4-disubstituted quinazolines have been reported to date. Chen[13a] and Liu[13b] independently developed one-pot synthesis of quinazolines *via* [2 + 2 + 2] cascade annulation of diaryliodonium salts (or aryldiazonium salts) with two nitriles (Scheme 1a). Novák developed a copper-catalyzed oxidative ring-closing reaction of *N*-(2-cyanoaryl)benzamides with diaryliodonium salts for the synthesis of iminobenzoxazines (Scheme 1b).[14] Recently, Mo and co-workers reported the synthesis of 2-aryl-substituted benzoxazinones by intramolecular condensation in the presence of sulfuric acid (Scheme 1c).[15] However, efficient catalytic transformation of *N*-(2-cyanoaryl)benzamides toward quinazolines has not been realized yet. Only a few groups have developed strategies for the synthesis of quinazolines *via*



Scheme 1 Design of a new approach to quinazolines.

College of Chemistry & Materials Engineering, Wenzhou University, Wenzhou 325035, P. R. China. E-mail: jiuxichen@wzu.edu.cn

†Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra for products. See DOI: 10.1039/c8ob02421a

‡These authors contributed equally.

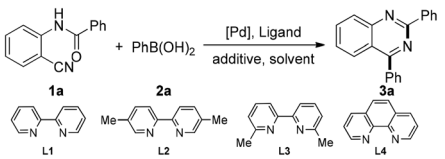
quantitative addition of organometallics with *N*-(2-cyanoaryl) amides,[16] implying that the development of a practical catalytic approach to quinazoline using aryl nitriles and amides as substrates remains a challenging area for exploration.

Very recently, we developed tandem addition/cyclization for access to isoquinolines,[17a,b] isoquinolones,[17b] and quinazolines (Scheme 1d)[17c,d] *via* catalytic carbopalladation of nitriles. Inspired by these results, we envisioned that sequential catalytic carbopalladation of *N*-(2-cyanoaryl)benzamides with arylboronic acids followed by an intramolecular cyclization would result in a tandem procedure for the preparation of structurally diverse quinazolines (Scheme 1e).

Results and discussion

To test this hypothesis, we initiated our investigations by examining the reaction of easily accessible *N*-(2-cyanophenyl) benzamide (**1a**) with phenylboronic acid (**2a**) to identify the optimal conditions (Table 1). We tested the formation of the desired product 2,4-diphenylquinazoline (**3a**) in the presence of different acid additives in THF, with $Pd(acac)_2$ as the catalyst and 2,2′-bipyridine (**L1**) as the ligand. While methanesulfonic acid resulted in only trace amounts of **3a**, acetic acid or benzoic acid led to 27% and 31% yield of the desired product, respectively (entries 1–3). The yield was further improved to 71% and 84% when D-camphorsulfonic acid (CSA) and trifluoroacetic acid (TFA) were used, respectively. However, the reaction failed to deliver the desired product when using hydrochloric acid as an additive (entry 6). An investigation of the effect of Pd(II) catalysts (entries 5, 7–10) revealed that the use of $Pd(OAc)_2$ as a catalyst achieved the best result (95%, entry 10), with only a trace amount of byproduct (biphenyl). In contrast, this transformation did not work using Pd(0), such as $Pd(PPh_3)_4$, as a catalyst (entry 11). Replacement of 2,2′-bipyridine (**L1**) with other ligands, including 5,5′-dimethyl-2,2′-bipyridine (**L2**), 6,6′-dimethyl-2,2′-bipyridine (**L3**) and 1,10-phenanthroline (**L4**), resulted in relatively lower yields (entries 10, 12–14). Other solvents, including toluene, hexane, 1,4-dioxane, DMF and 1,2-dichloroethane, were less efficient (entries 15–19). Decreasing the amount of boronic acid reduced the yield to some extent (entry 20). In addition, the desired product **3a** was isolated in lower yield when the procedure was carried out under a N_2 atmosphere (entry 21). No desired product was observed if either palladium catalyst or ligand was absent (entries 22 and 23). Other reaction parameters including the amount of TFA and reaction temperature were also examined (see Table S1 in the ESI†). The results showed that 2 equivalents of TFA were sufficient. The yield was decreased to some extent when the reaction was performed at a lowered or elevated temperature.

Table 1 Optimization of the reaction conditions[a]

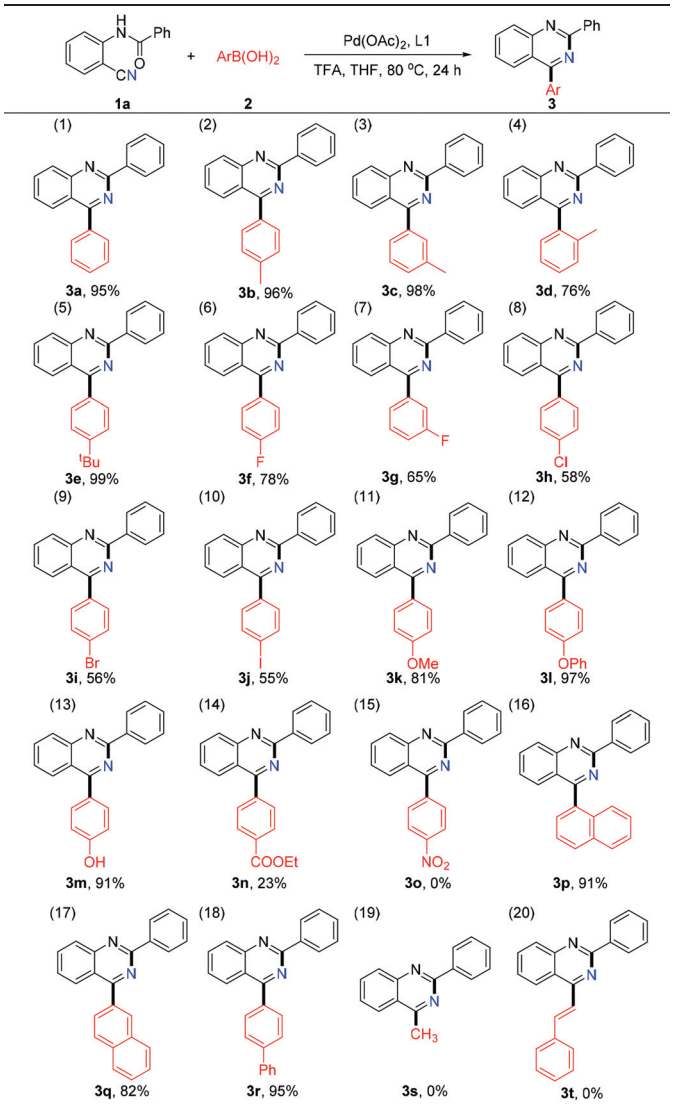


Entry	[Pd]	Ligand	Additive	Solvent	Yield[b] (%)
1	$Pd(acac)_2$	**L1**	CH_3SO_3H	THF	Trace
2	$Pd(acac)_2$	**L1**	CH_3SO_2H	THF	27
3	$Pd(acac)_2$	**L1**	$PhCO_2H$	THF	31
4	$Pd(acac)_2$	**L1**	CSA	THF	71
5	$Pd(acac)_2$	**L1**	TFA	THF	84
6	$Pd(acac)_2$	**L1**	HCl	THF	0
7	$PdCl_2$	**L1**	TFA	THF	11
8	$Pd(CH_3CN)_2Cl_2$	**L1**	TFA	THF	15
9	$Pd(CF_3CO_2)_2$	**L1**	TFA	THF	87
10	**$Pd(OAc)_2$**	**L1**	**TFA**	**THF**	**95**
11	$Pd(PPh_3)_4$	**L1**	TFA	THF	0
12	$Pd(OAc)_2$	**L2**	TFA	THF	92
13	$Pd(OAc)_2$	**L3**	TFA	THF	38
14	$Pd(OAc)_2$	**L4**	TFA	THF	58
15	$Pd(OAc)_2$	**L1**	TFA	Toluene	53
16	$Pd(OAc)_2$	**L1**	TFA	Hexane	41
17	$Pd(OAc)_2$	**L1**	TFA	1,4-Dioxane	25
18	$Pd(OAc)_2$	**L1**	TFA	DMF	76
19	$Pd(OAc)_2$	**L1**	TFA	$ClCH_2CH_2Cl$	59
20[c]	$Pd(OAc)_2$	**L1**	TFA	THF	34(85)[d]
21[e]	$Pd(OAc)_2$	**L1**	TFA	THF	24(63)[f]
22		**L1**	TFA	THF	0
23	$Pd(OAc)_2$		TFA	THF	0

[a] Conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), Pd catalyst (5 mol%), ligand (10 mol%), additive (2 equiv.), solvent (1 mL), 80 °C, 24 h, air. [b] Isolated yield. [c] 1.0 equivalent of **2a** was used. [d] 1.5 equivalents of **2a** were used. [e] 1.0 equivalent of **2a** was used, under N_2. [f] 2.0 equivalent of **2a** were used, under N_2.

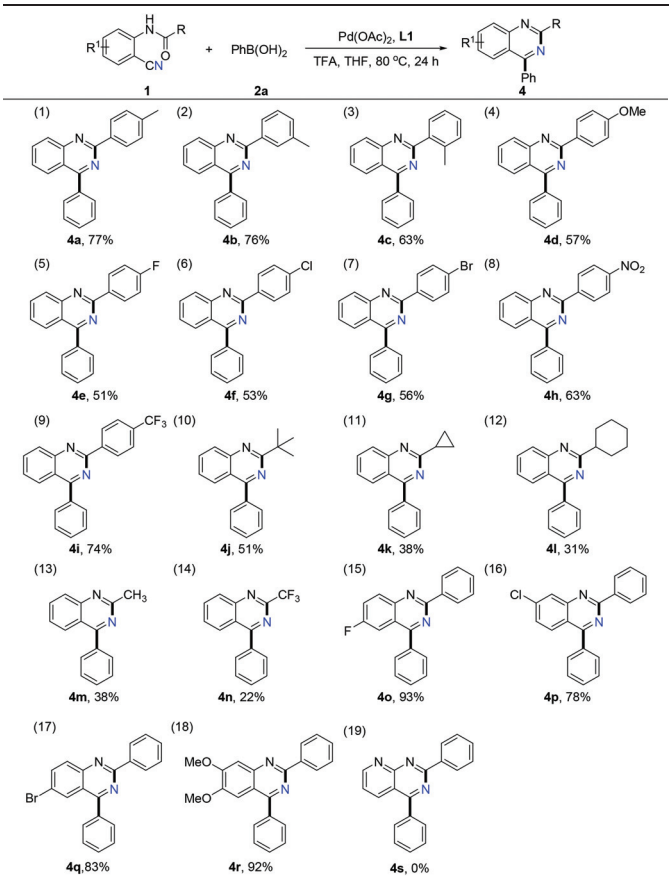
With the optimized conditions in hand, we began to test this reaction of *N*-(2-cyanophenyl)benzamide (**1a**) with various arylboronic acids **2** to examine the scope and generality of this protocol (Table 2). The reaction was found to work well with a variety of arylboronic acids. First, the reactivities of *para*-, *meta*-, and *ortho*-tolylboronic acids were evaluated, and the results demonstrated that the steric effect of the substituent had an obvious impact on the reaction. For example, treatment of **1a** with *para*- and *meta*-tolylboronic acids provided 96% and 98% yields of **3b** and **3c**, respectively (entries 2 and 3), while the *ortho*-tolylboronic acid afforded the desired product **3d** with a diminished yield of 76% (entry 4). Similarly, substrate (4-(*tert*-butyl)phenyl)boronic acid afforded the desired product **3e** in 99% yield (entry 5). 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, the substrates bearing an electron-donating substituent provided a slightly higher yield than those bearing halogenated phenylboronic acids (entries 6–13). For example, moderate yields of the halogen-substituted (*e.g.* –F, –Cl, –Br, –I) products **3f–3j** were obtained, while good to excellent yields of the methoxy-, phenoxy- or hydroxyl-substituted products **3k–3m** were obtained. The method tolerates the entire range of halogen substituents, which makes this method particularly appealing. Boronic acids with strong electron-withdrawing substituents decreased the efficiency obviously (entries 14 and 15). For example, (4-(ethoxycarbonyl)phenyl)boronic acid could afford the desired product only in 23% yield, while (4-nitrophenyl)

Table 2 Reaction of various arylboronic acids with *N*-(2-cyanophenyl) amide[a]



[a] Conditions: **1** (0.2 mmol), **2** (0.4 mmol), $Pd(OAc)_2$ (5 mol%), **L1** (10 mol%), TFA (2 equiv.), THF (1 mL), 80 °C, 24 h, air. Isolated yield.

Table 3 Reaction of various *N*-(2-cyanoaryl)amides with phenylboronic acid[a]

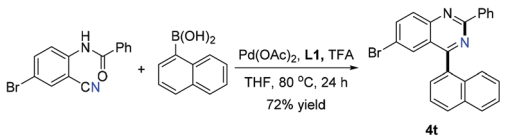


[a] Conditions: **1** (0.2 mmol), **2** (0.4 mmol), $Pd(OAc)_2$ (5 mol%), **L1** (10 mol%), TFA (2 equiv.), THF (1 mL), 80 °C, 24 h, air. Isolated yield.

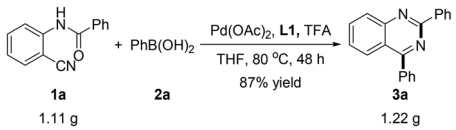
boronic acid was an inefficient substrate. Naphthalen-1-ylboronic acid, naphthalen-2-ylboronic acid, and biphenyl-4-ylboronic acid were also good partners and coupled with **1a** efficiently, affording the corresponding products **3p–3r** in good to excellent yields (entries 16–18). However, the reaction failed to deliver the desired product when methylboronic acid or (*E*)-styrylboronic acid was used as the substrate (entries 19 and 20).

We next turned our attention to the effect of the reactions between other *N*-(2-cyanoaryl)benzamides **1** and phenylboronic acid (**2a**) under standard conditions (Table 3). The influence of substitutions on the amide moiety (R = aryl) was first investigated. The steric effects of the substituents affected the yields of this transformation to some extent. For example, when substrates bearing a *para*-, *meta*-, and *ortho*-methyl group on the phenyl ring were examined, **4a** and **4b** were obtained in 77% and 76% yields, respectively, while **4c** possessing an *ortho*-methyl group was obtained in 63% yield (entries 1–3). Not only electron-donating groups, such as methyl (**4a–4c**) and methoxy (**4d**), but also electron-withdrawing groups, such as fluoro (**4e**), chloro (**4f**), bromo (**4g**), nitro (**4h**) and trifluoromethyl (**4i**) on the phenyl ring at the *para* position, were tolerated in this transformation. In contrast, aliphatic substrates (R = alkyl) made the reactions less effective, which may arise from the decreased reactivity of carbonyl on the amide moiety (entries 10–14). Functional groups (R^1) such as fluoro, bromo, chloro, and methoxy on the 'left' side phenyl ring of the substrates were well tolerated, affording the corresponding products **4o–4r** in good to excellent yields (entries 15–18). Notably, the presence of the halogen substituents in products **4o–4q** is useful for further synthetic manipulations. However, the reaction failed to deliver the desired product when a heterocycle-containing substrate namely *N*-(3-cyanopyridin-2-yl)benzamide was used (entry 19).

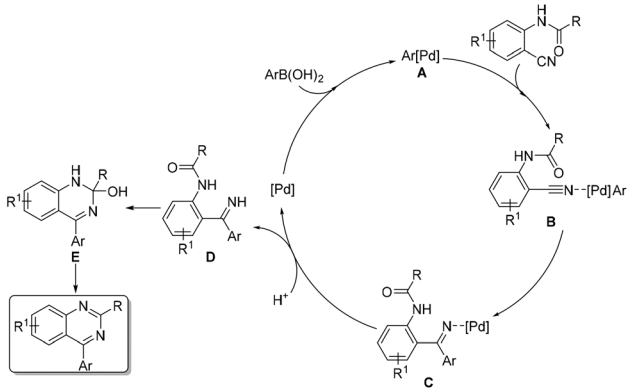
Additionally, the tandem reaction of *N*-(4-bromo-2-cyanophenyl)benzamide bearing a bromo group with naphthalen-1-ylboronic acid was performed to produce the desired product



Scheme 2 Synthesis of product **4t** bearing a bromo group.



Scheme 3 Gram-scale synthesis of **3a**.



Scheme 4 Plausible reaction mechanism for the formation of quinazolines.

6-bromo-4-(naphthalen-1-yl)-2-phenylquinazoline (**4t**) in 72% yield (Scheme 2).

The efficiency of this catalytic system was further demonstrated by running the transformation on a laboratory preparative scale. For example, we performed the model reaction on a gram scale (5 mmol), and **3a** was obtained in 87% isolated yield, albeit with a prolonged reaction time (48 h) (Scheme 3).

A possible reaction mechanism for the formation of quinazolines from *N*-(2-cyanoaryl)benzamides and arylboronic acids as a representative example is shown in Scheme 4. The following key steps are included in the catalytic pathway: (i) transmetallation of the palladium species with arylboronic acids to form the palladium-aryl species **A**, which was followed by (ii) the coordination of *N*-(2-cyanoaryl)benzamides **1** to give intermediate **B**; (iii) carbopalladation of the cyano group to result in the formation of the corresponding ketimine palladium intermediate **C**; and (iv) protonation of intermediate **C** by TFA to afford the *N*-(2-(imino(aryl)methyl)aryl)benzamide (**D**) and regenerate the palladium catalyst. Next, the nucleophilic attack of the resulting imine on the carbonyl group generates the dihydroquinazolin-2-ol (**E**). Finally, dehydration of the dihydroquinazolin-2-ol (**E**) would deliver the corresponding quinazolines as the desired products.

Conclusions

In summary, we have developed a new strategy for the synthesis of quinazolines in moderate to excellent yields by the Pd-catalyzed tandem addition/cyclization of *N*-(2-cyanoaryl) benzamides with arylboronic acids. This protocol provides an alternative synthetic pathway to access 2,4-disubstituted quinazolines. Further efforts to extend this catalytic system to the preparation of other useful heterocyclic compounds are currently underway in our laboratories.

Experimental section

General methods

Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 500 MHz spectrometer (^{1}H NMR at 500 MHz, ^{13}C NMR at 125 MHz), using $CDCl_3$ as the solvent with tetramethylsilane (TMS) as an internal standard at room temperature. Chemical shifts are given in δ relative to TMS, and the coupling constants J are given in hertz. High-resolution mass spectra were recorded on an ESI-Q-TOF mass spectrometer. *N*-(2-Cyanoaryl)benzamides were synthesized from 2-aminobenzonitrile derivatives and the appropriate acyl chloride or anhydride according to modified literature procedures.[14,18] Other commercially obtained reagents were used without further purification. All reactions were conducted under a nitrogen atmosphere using standard Schlenk techniques. Column chromatography was performed using EM silica gel 60 (300–400 mesh).

General procedure for the synthesis of *N*-(2-cyanophenyl) benzamides

To a Schlenk tube were added *N*-(2-cyanoaryl) benzamides **1** (0.2 mmol), arylboronic acids **2** (0.4 mmol), $Pd(OAc)_2$ (5 mol%), **L1** (10 mol%), TFA (2 equiv.) and THF (1 mL) under air. The reaction mixture was stirred vigorously at 80 °C for 24 h under air. The mixture was poured into ethyl acetate, which was washed with saturated $NaHCO_3$ (2 × 10 mL) and then brine (1 × 10 mL). After the aqueous layer was extracted with ethyl acetate, the combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified by flash column chromatography with petroleum ether/ethyl acetate (30 : 1 to 10 : 1) to afford the desired products.

2,4-Diphenylquinazoline (3a). Yellow solid (53.6 mg, 95%), mp 116–117 °C (lit.[8e] 117–119 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.71 (d, J = 8.0 Hz, 2H), 8.20 (d, J = 8.0 Hz, 1H), 8.14 (d, J = 8.0 Hz, 1H), 7.92–7.88 (m, 3H), 7.64–7.59 (m, 3H), 7.58–7.48 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 160.2, 151.9, 138.2, 137.7, 133.6, 130.5, 130.2, 129.9, 129.1, 128.7, 128.5, 127.0, 121.7.

2-Phenyl-4-(*p*-tolyl)quinazolines (3b). Yellow solid (56.9 mg, 96%), mp 125–127 °C (lit.[8e] 128–130 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.71 (d, J = 7.0 Hz, 2H) 8.17 (t, J = 9.0 Hz, 2H), 7.88 (m, 1H), 7.81 (d, J = 8.0 Hz, 2H), 7.58–7.48 (m, 4H), 7.41 (d, J =

7.5 Hz, 2H), 2.51 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 160.2, 151.9, 140.2, 138.2, 134.9, 133.5, 130.5, 130.2, 129.3, 129.1, 128.7, 128.5, 127.1, 126.9, 121.7, 21.5.

2-Phenyl-4-(*m*-tolyl)quinazolines (3c). Yellow solid (58.1 mg, 98%), mp 81–83 °C (lit.[19] 84 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.71 (d, J = 7.0 Hz, 2H), 8.18 (d, J = 7.5 Hz, 1H), 8.13 (d, J = 7.5 Hz, 1H), 7.89 (t, J = 7.5 Hz, 1H), 7.71 (s, 1H), 7.66 (d, J = 7.5 Hz, 1H), 7.58–7.46 (m, 5H), 7.41 (d, J = 7.5 Hz, 1H), 2.52 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 160.3, 151.9, 138.4, 138.3, 137.7, 133.5, 130.7, 130.7, 130.5, 129.1, 128.8, 128.5, 128.4, 127.4, 127.1, 126.9, 121.8, 21.5.

2-Phenyl-4-(*o*-tolyl)quinazolines (3d). Yellow solid (45.1 mg, 76%), mp 140–141 °C (lit.[19] 143–145 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (d, J = 7.0 Hz, 2H), 8.21 (d, J = 8.0 Hz, 1H), 7.90 (t, J = 7.5 Hz, 1H), 7.70 (d, J = 8.5 Hz, 1H), 7.55–7.49 (m, 4H), 7.46 (t, J = 7.5 Hz, 1H), 7.41 (d, J = 7.5 Hz, 2H), 7.38 (d, J = 8.5 Hz, 1H), 2.24 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 160.3, 151.3, 138.1, 136.9, 136.5, 133.8, 130.8, 130.6, 129.7, 129.3, 128.9, 128.8, 128.6, 127.1, 127.1, 125.6, 122.7, 20.0.

4-(4-(*tert*-Butyl)phenyl)-2-phenylquinazoline (3e). Oil (67.0 mg, 99%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.74 (d, J = 7.0 Hz, 2H), 8.18 (m, 2H), 7.90–7.85 (m, 3H), 7.64 (d, J = 8.0 Hz, 2H), 7.58–7.50 (m, 4H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 160.3, 153.3, 125.0, 138.3, 134.9, 133.4, 130.5, 130.1, 129.1, 128.7, 128.5, 127.2, 126.9, 125.6, 121.8, 34.9, 31.4. HRMS (ESI) calcd for $C_{24}H_{23}N_2$ $[M + H]^+$: 333.1856, found: 333.1857.

4-(4-Fluorophenyl)-2-phenylquinazoline (3f). Yellow solid (46.8 mg, 78%), mp 132–134 °C (lit.[9b] 134–136 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (d, J = 7.5 Hz, 2H), 8.19 (d, J = 8.5 Hz, 2H), 8.11 (d, J = 8.5 Hz, 1H), 7.95–7.88 (m, 3H), 7.60–7.49 (m, 4H), 7.30 (t, J = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.2, 165.0, 163.0, 160.2, 152.0, 138.1, 133.8, 133.8, 133.7, 133.2, 133.2, 130.6, 129.3, 128.7, 128.6, 127.2, 126.7, 121.6, 115.8, 115.6.

4-(3-Fluorophenyl)-2-phenylquinazoline (3g). Yellow solid (39.0 mg, 65%), mp 104–105 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (d, J = 7.0 Hz, 2H), 8.19 (d, J = 8.5 Hz, 1H), 8.11 (d, J = 8.5 Hz, 1H), 7.91 (t, J = 7.5 Hz, 1H), 7.67 (d, J = 7.5 Hz, 1H), 7.63 (t, J = 9.5 Hz, 1H), 7.60–7.50 (m, 5H), 7.30 (t, J = 8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 163.8, 161.8, 160.2, 151.9, 139.8, 139.7, 137.8, 133.8, 130.7, 130.2, 130.1, 129.2, 128.7, 128.6, 127.3, 126.6, 126.0, 125.9, 121.5, 117.3, 117.1, 117.0, 116.9. HRMS (ESI) calcd for $C_{20}H_{14}FN_2Na$ $[M + Na]^+$: 323.0961, found: 323.0964.

4-(4-Chlorophenyl)-2-phenylquinazoline (3h). Yellow solid (36.7 mg, 58%), mp 136–137 °C (lit.[20] 146–147 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (d, J = 7.0 Hz, 2H), 8.24 (d, J = 8.0 Hz, 1H), 8.09 (d, J = 8.0 Hz, 1H), 7.92 (t, J = 7.5 Hz, 1H), 7.85 (d, J = 8.0 Hz, 2H), 7.58 (t, J = 7.5 Hz, 3H), 7.56–7.50 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.2, 160.2, 152.0, 137.9, 136.4, 136.1, 133.8, 131.5, 130.7, 129.3, 128.9, 128.7, 128.6, 127.3, 126.6, 121.5.

4-(4-Bromophenyl)-2-phenylquinazoline (3i). Yellow solid (40.4 mg, 56%), mp 146–148 °C (lit.[8e] 154–156 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (d, J = 7.0 Hz, 2H), 8.17 (d, J = 9.0 Hz, 1H), 8.07 (d, J = 8.5 Hz, 1H), 7.90 (t, J = 7.5 Hz, 1H), 7.80 (d, J = 8.0 Hz, 2H), 7.54 (d, J = 8.0 Hz, 2H), 7.59–7.50 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 159.2, 150.9, 136.9, 135.5, 132.8, 130.8, 130.7, 129.7, 128.2, 127.7, 127.6, 126.2, 125.5, 123.7, 120.4.

4-(4-Iodophenyl)-2-phenylquinazoline (3j). Yellow solid (44.9 mg, 55%), mp 139–140 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (d, J = 7.5 Hz, 2H), 8.23 (d, J = 8.0 Hz, 1H), 8.08 (d, J = 8.0 Hz, 1H), 7.96 (d, J = 8.0 Hz, 2H), 7.92 (t, J = 7.5 Hz, 1H), 7.63 (d, J = 8.0 Hz, 2H), 7.58 (t, J = 8.0 Hz, 1H), 7.55–7.50 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 159.2, 150.9, 136.8, 136.8, 136.1, 132.8, 130.8, 129.7, 128.2, 127.7, 127.6, 126.3, 125.5, 120.4, 95.6. HRMS (ESI) calcd for $C_{20}H_{14}IN_2$ $[M + H]^+$: 409.0196, found: 409.0223.

4-(4-Methoxyphenyl)-2-phenylquinazoline (3k). Yellow solid (50.6 mg, 81%), mp 120–121 °C (lit.[8g] 118–119 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.71 (d, J = 7.0 Hz, 2H), 8.16 (t, J = 9.5 Hz, 2H), 7.90 (d, J = 8.5 Hz, 2H), 7.86 (d, J = 8.0 Hz, 1H), 7.55–7.50 (m, 4H), 7.12 (d, J = 8.5 Hz, 2H), 3.93 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 161.3, 160.1, 152.0, 138.3, 133.4, 131.9, 130.5, 130.2, 129.1, 128.7, 128.5, 127.1, 126.9, 121.7, 114.1, 55.5.

4-(4-Phenoxyphenyl)-2-phenylquinazoline (3l). Yellow solid (72.6 mg, 97%), mp 106–108 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (d, J = 7.0 Hz, 2H), 8.17 (d, J = 8.0 Hz, 2H), 7.92–7.86 (m, 3H), 7.58–7.48 (m, 4H), 7.41 (t, J = 8.0 Hz, 2H), 7.19 (t, J = 8.0 Hz, 3H), 7.15 (d, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 159.2, 158.4, 155.3, 151.0, 137.2, 132.5, 131.3, 131.0, 129.5, 129.0, 128.2, 127.7, 127.5, 126.0, 125.9, 123.1, 120.6, 118.7, 117.2. HRMS (ESI) calcd for $C_{26}H_{19}N_2O$ $[M + H]^+$: 375.1492, found: 375.1497.

4-(2-Phenylquinazolin-4-yl)phenol (3m). Yellow solid (54.8 mg, 91%), 193–194 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (d, J = 7.0 Hz, 2H), 8.17 (m, 2H), 7.88–7.84 (m, 3H), 7.56–7.52 (m, 4H), 7.04 (d, J = 8.0 Hz, 2H), 5.66 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 160.2, 157.5, 133.5, 132.1, 130.5, 130.3, 129.2, 129.1, 128.7, 128.5, 127.2, 127.1, 126.96, 121.6, 115.6. HRMS (ESI) calcd for $C_{20}H_{15}N_2O$ $[M + H]^+$: 299.1179, found: 299.1190.

Ethyl-4-(2-phenylquinazolin-4-yl)benzoate (3n). Yellow solid (16.7 mg, 23%), mp 141–142 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (d, J = 7.0 Hz, 2H), 8.28 (d, J = 8.0 Hz, 2H), 8.22 (d, J = 6.0 Hz, 1H), 8.06 (d, J = 8.0 Hz, 1H), 8.00–7.87 (m, 3H), 7.61–7.47 (m, 4H), 4.46 (q, J = 7.1 Hz, 2H), 1.46 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 166.2, 160.3, 151.9, 141.8, 137.9, 133.9, 131.8, 130.8, 130.2, 129.7, 129.3, 128.7, 127.4, 126.6, 121.6, 61.3, 14.4.

4-(Naphthalen-1-yl)-2-phenylquinazoline (3p). Yellow solid (60.5 mg, 91%), mp 178–180 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (d, J = 5.5 Hz, 2H), 8.23 (d, J = 8.0 Hz, 1H), 8.07 (m, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.90 (t, J = 7.0 Hz, 1H), 7.69–7.62 (m, 4H), 7.56–7.48 (m, 4H), 7.45–7.37 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.1, 160.4, 151.4, 138.1, 134.9, 133.9, 133.8, 131.7, 130.6, 129.8, 129.0, 128.9, 128.6, 128.4, 128.0, 127.3, 127.1, 126.7, 126.3, 125.8, 125.1, 123.4. HRMS (ESI) calcd for $C_{24}H_{17}N_2$ $[M + H]^+$: 333.1386, found: 333.1385.

4-(Naphthalen-2-yl)-2-phenylquinazoline (3q). Yellow solid (54.5 mg, 82%), mp 161–162 °C (lit.[8g] 164–166 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.75 (d, J = 7.0 Hz, 2H), 8.37 (s, 1H), 8.20 (t, J = 11.0 Hz, 2H), 8.08 (d, J = 8.0 Hz, 1H), 8.05–7.95 (m, 3H), 7.91 (m, J = 7.0 Hz, 1H), 7.65–7.60 (m, 2H), 7.59–7.49 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 160.3, 152.0, 138.2, 135.1, 134.0, 133.6, 133.0, 130.6, 130.3, 129.2, 128.7, 128.6, 128.4, 127.8, 127.3, 127.3, 127.1, 127.1, 126.7, 121.9.

4-([1,1′-Biphenyl]-4-yl)-2-phenylquinazoline (3r). Yellow solid (68.1 mg, 95%), mp 217–218 °C (lit.[17c] 217–218 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.73 (d, J = 7.5 Hz, 2H), 8.21 (d, J = 8.0 Hz, 2H), 8.00 (d, J = 7.5 Hz, 2H), 7.91 (t, J = 7.5 Hz, 1H), 7.84 (d, J = 7.5 Hz, 2H), 7.72 (d, J = 7.5 Hz, 2H), 7.60–7.50 (m, 6H), 7.43 (t, J = 7.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 159.2, 150.9, 141.9, 139.4, 137.1, 135.6, 132.6, 129.7, 129.6, 128.2, 127.9, 127.7, 127.5, 126.8, 126.3, 12.63, 126.0, 126.0, 120.7. HRMS (ESI) calcd for $C_{26}H_{19}N_2^+$ $[M + H]^+$: 359.1543, found: 359.1543.

4-Phenyl-2-(*p*-tolyl)quinazolines (4a). Yellow solid (45.6 mg, 77%), mp 162–165 °C (lit.[8e] 166–168 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (d, J = 8.0 Hz, 2H), 8.20 (s, 1H), 8.12 (d, J = 8.0 Hz, 1H), 7.90–7.87 (m, 3H), 7.61–7.59 (m, 3H), 7.54 (t, J = 8.0 Hz, 1H),7.34 (t, J = 7.5 Hz, 2H), 2.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 160.3, 151.8, 140.8, 137.8, 135.4, 133.5, 130.2, 129.5, 129.3, 129.0, 128.7, 128.5, 127.0, 126.8, 121.6, 21.5.

4-Phenyl-2-(*m*-tolyl)quinazolines (4b). Yellow solid (45.0 mg, 76%), mp 112–114 °C (lit.[8e] 115–117 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (d, J = 8.5 Hz, 2H), 8.17 (d, J = 8.5 Hz, 1H), 8.13 (d, J = 8.5 Hz, 1H), 7.90–7.87 (m, 3H), 7.63–7.58 (m, 3H), 7.55 (t, J = 8.5 Hz, 1H), 7.43 (t, J = 7.5 Hz, 1H), 7.32 (d, J = 7.5 Hz, 1H), 2.50 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 160.4, 152.0, 138.1, 137.7, 133.5, 131.4, 130.2, 129.9, 129.2, 129.1, 128.6, 128.5, 127.0, 126.9, 126.0, 121.7, 22.6.

4-Phenyl-2-(*o*-tolyl)quinazolines (4c). Yellow solid (37.3 mg, 63%), mp 73–75 °C (lit.[8e] 72–74 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (t, J = 8.0 Hz, 2H), 7.98 (d, J = 7.5 Hz, 1H), 7.92 (t, J = 8.0 Hz, 1H), 7.87 (d, J = 7.5 Hz, 2H), 7.63–7.55 (m, 4H), 7.39–7.31 (m, 3H), 2.67 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1, 163.4, 151.6, 138.7, 137.5, 137.5, 133.6, 131.3, 130.8, 130.2, 129.9, 129.3, 129.0, 128.6, 127.3, 127.0, 126.0, 121.0, 21.3.

2-(4-Methoxyphenyl)-4-phenylquinazoline (4d). Yellow solid (23.1 mg, 36%), mp 159–160 °C (lit.[9b] 160–161 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (d, J = 8.5 Hz, 2H), 8.14 (d, J = 8.0 Hz, 1H), 8.10 (d, J = 8.5 Hz, 1H), 7.89–7.85 (m, 3H), 7.60 (t, J = 9.0 Hz, 3H), 7.51 (t, J = 8.0 Hz, 1H), 7.04 (d, J = 9.0 Hz, 2H), 3.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 161.9, 160.0, 151.9, 147.2, 137.8, 133.6, 130.4, 130.2, 129.9, 128.8, 128.5, 127.0, 126.6, 121.4, 113.96, 55.4.

2-(4-Fluorophenyl)-4-phenylquinazoline (4e). Yellow solid (30.6 mg, 51%), mp 144–145 °C (lit.[8f] 153–155 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.71 (t, J = 8.0 Hz, 2H), 8.17–8.10 (m, 2H), 7.92–7.85 (m, 3H), 7.60 (s, 3H), 7.55 (t, J = 7.5 Hz, 1H), 7.20 (t, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 165.7, 163.7, 159.3, 151.9, 137.6, 134.3, 133.7, 130.9, 130.8, 130.2, 130.0, 129.0, 128.6, 127.1, 121.6, 115.5, 115.4.

2-(4-Chlorophenyl)-4-phenylquinazoline (4f). Yellow solid (33.6 mg, 53%), mp 180–181 °C (lit.[9b] 175–176 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (d, J = 8.0 Hz, 2H), 8.23 (d, J = 7.5 Hz, 1H), 8.14 (t, J = 9.0 Hz, 1H), 7.94–7.87 (m, 3H), 7.62–7.57 (m, 4H), 7.50 (d, J = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 159.3, 152.0, 137.6, 136.8, 136.7, 133.7, 130.2, 130.1, 130.0, 129.2, 128.7, 128.6, 127.2, 127.1, 121.8.

2-(4-Bromophenyl)-4-phenylquinazoline (4g). Yellow solid (40.5 mg, 56%), mp 185–186 °C (lit.[8g] 192–194 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (d, J = 8.5 Hz, 2H), 8.16 (d, J = 8.0 Hz, 1H), 8.14 (d, J = 8.5 Hz, 1H), 7.93–7.85 (m, 3H), 7.65 (d, J = 8.5 Hz, 2H), 7.60 (t, J = 8.0 Hz, 3H), 7.57 (t, J = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 159.3, 151.8, 137.5, 137.1, 133.8, 131.7, 130.3, 130.2, 130.1, 129.1, 128.6, 127.3, 127.1, 125.4, 121.8.

2-(4-Nitrophenyl)-4-phenylquinazoline (4h). Yellow solid (43.9 mg, 63%), mp 207–209 °C (lit.[9b] 198–199 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.89 (d, J = 9.0 Hz, 2H), 8.36 (d, J = 8.5 Hz, 2H), 8.22 (d, J = 8.5 Hz, 1H), 8.18 (d, J = 8.5 Hz, 1H), 7.96 (t, J = 7.5 Hz, 1H), 7.92–7.86 (m, 2H), 7.67–7.60 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9, 158.0, 151.7, 149.3, 144.0, 137.2, 134.1, 130.3, 130.2, 129.6, 129.3, 128.7, 128.1, 127.2, 123.7, 122.0.

4-Phenyl-2-(4-(trifluoromethyl)phenyl)quinazolines (4i). Yellow solid (51.9 mg, 74%), mp 115–116 °C (lit.[9b] 123–126 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.83 (d, J = 8.0 Hz, 2H), 8.21 (d, J = 8.0 Hz, 1H), 8.17 (d, J = 8.5 Hz, 1H), 7.93 (t, J = 8.5 Hz, 1H), 7.90–7.88 (m, 2H), 7.78 (d, J = 8.0 Hz, 2H), 7.62–7.59 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 158.8, 151.7, 141.4, 137.4, 133.9, 132.3, 132.0, 130.2 (d, J = 3.75 Hz), 129.2, 129.0, 128.6, 127.7, 127.1, 125.5 (q, J = 7.5 Hz), 123.2, 122.0, 100.0

2-(*tert*-Butyl)-4-phenylquinazoline (4j). Yellow solid (27.0 mg, 51%), mp 68–71 °C (lit.[8e] 70–72 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (t, J = 8.0 Hz, 2H), 7.84 (m, 3H), 7.56 (m, 3H), 7.51 (t, J = 7.5 Hz, 1H), 1.57 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 167.4, 151.4, 138.0, 132.9, 130.2, 129.6, 128.9, 128.3, 126.7, 126.4, 120.9, 39.7, 29.7. HRMS (ESI) calcd for $C_{18}H_{19}N_2$ $[M + H]^+$: 263.1543, found: 263.1545.

2-Cyclopropyl-4-phenylquinazoline (4k). Yellow oil (18.6 mg, 38%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, J = 7.5 Hz, 1H), 7.98 (d, J = 7.5 Hz, 1H), 7.84–7.73 (m, 3H), 7.56 (m, 3H), 7.46 (d, J = 6.0 Hz, 1H), 2.46 (s, 1H), 1.33 (m, 2H), 1.13 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.2, 167.6, 151.4, 137.6, 133.5, 130.0, 129.8, 128.5, 127.5, 127.0, 126.1, 121.3, 18.6, 10.6. HRMS (ESI) calcd for $C_{17}H_{15}N_2$ $[M + H]^+$: 247.1230, found: 247.1228.

2-Cyclohexyl-4-phenylquinazoline (4l). Yellow oil (17.6 mg, 31%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (m, 2H), 7.85 (t, J = 7.5 Hz, 1H), 7.78 (m, 2H), 7.56 (m, 3H), 7.51 (t, J = 7.5 Hz, 1H), 3.21 (t, J = 11.5 Hz, 1H), 2.13 (m, 2H), 1.92–1.74 (m, 5H), 1.53–1.43 (m, 2H), 1.41–1.32 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 168.4, 151.4, 137.7, 133.3, 130.0, 129.8, 128.5, 128.4, 126.9, 126.6, 121.4, 47.8, 32.0, 26.3, 26.1. HRMS (ESI) calcd for $C_{20}H_{21}N_2$ $[M + H]^+$: 289.1699, found: 289.1702.

2-Methyl-4-phenylquinazoline (4m). Yellow solid (16.7 mg, 38%), mp 47–48 °C (lit.[16a] 48–49 °C). ^{1}H NMR (500 MHz,

$CDCl_3$) δ 8.00 (t, J = 9.0 Hz, 2H), 7.83 (t, J = 8.0 Hz, 1H), 7.74–7.70 (m, 2H), 7.56–7.42 (m, 4H), 2.93 (s, 3H); ^{13}C NMR (125 MHz, CDCl3) δ 168.6, 163.8, 151.4, 137.3, 133.7, 129.9, 128.6, 128.1, 127.0, 126.7, 121.1, 26.6.

4-Phenyl-2-(trifluoromethyl)quinazoline (4n). Yellow solid (11.6 mg, 22%), mp 87–88 °C (lit.[16a] 92 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (t, J = 9.0 Hz, 2H), 8.03 (t, J = 7.0 Hz, 1H), 7.87–7.80 (m, 2H), 7.76 (t, J = 8.0 Hz, 1H), 7.61 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 152.5, 152.24 (s), 150.9, 136.2, 134.7, 130.7, 130.3, 129.6, 128.8, 127.3, 123.3, 121.2, 119.0.

6-Fluoro-2,4-diphenylquinazoline (4o). Yellow solid (55.9 mg, 93%), mp 173–174 °C (lit.[9b] 172–173 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (d, J = 8.0 Hz, 2H), 8.21 (m, 1H), 7.88 (m, 2H), 7.78–7.73 (m, 1H), 7.70–7.65 (m, 1H), 7.64–7.59 (m, 3H), 7.56–7.48 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 161.4, 159.9, 159.4, 149.0, 137.8, 137.3, 131.7 (d, J = 8.5 Hz), 130.7, 130.2, 130.0, 128.7, 128.6 (d, J = 5.0 Hz), 124.0 (d, J = 25.5 Hz), 122.2 (d, J = 8.875 Hz), 110.5 (d, J = 23.0 Hz).

7-Chloro-2,4-diphenylquinazoline (4p). Yellow solid (49.4 mg, 78%), mp 151–152 °C. (lit[17c] 151–152 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (d, J = 7.5 Hz, 2H), 8.18 (s, 1H), 8.06 (d, J = 9.0 Hz, 1H), 7.86 (d, J = 2.5 Hz, 2H), 7.61 (d, J = 2.0 Hz, 3H), 7.53 (d, J = 6.0 Hz, 3H), 7.49 (d, J = 9.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 161.2, 152.6, 139.8, 137.7, 137.3, 130.9, 130.2, 130.1, 128.9, 128.7, 128.6, 128.5, 128.1, 128.0, 120.1. HRMS (ESI) calcd for $C_{20}H_{14}ClN_2$ $[M + H]^+$: 317.0840, found: 317.0841.

6-Bromo-2,4-diphenylquinazoline (4q). Yellow solid (60.0 mg, 83%), mp 204–205 °C (lit.[9b] 204–205 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (d, J = 8.0 Hz, 2H), 8.27 (s, 1H), 8.00 (d, J = 9.0 Hz, 1H), 7.95 (d, J = 9.0 Hz, 1H), 7.87 (t, J = 9.0 Hz, 2H), 7.63 (m, 3H), 8.53 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 160.5, 150.6, 137.7, 137.1, 130.9, 130.9, 130.3, 130.1, 129.1, 128.8, 128.6, 127.7, 120.7.

6,7-Dimethoxy-2,4-diphenylquinazoline (4r). Yellow solid (63.0 mg, 92%), mp 176–178 °C (lit.[8e] 178–180 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 (d, J = 7.5 Hz, 2H), 7.89 (d, J = 6.5 Hz, 2H), 7.62–7.55 (m, 3H), 7.53–7.45 (m, 4H), 7.34 (s, 1H), 4.10 (s, 3H), 3.91 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 159.3, 155.7, 150.0, 149.8, 138.4, 138.2, 130.1, 129.8, 129.7, 128.6, 128.5, 128.3, 117.1, 107.4, 104.2, 56.4, 56.1.

6-Bromo-4-(naphthalen-1-yl)-2-phenylquinazoline (4t). Yellow solid (59.2 mg, 52%), mp 189–190 °C (lit.[17c] 189–190 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (d, J = 3.5 Hz, 2H), 8.09 (d, J = 8.0 Hz, 2H), 8.01 (d, J = 8.0 Hz, 1H), 7.95 (d, J = 9.0 Hz, 1H), 7.82 (s, 1H), 7.69–7.65 (m, 3H), 7.56 (t, J = 8.0 Hz, 1H), 7.52 (s, 3H), 7.44 (t, J = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.2, 160.7, 150.4, 137.8, 137.4, 134.2, 133.9, 131.6, 130.9, 130.8, 130.1, 129.3, 128.9, 128.7, 128.5, 128.1, 127.0, 126.5, 125.6, 125.1, 124.4, 120.7.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

We thank the National Natural Science Foundation of China (No. 21572162), the Natural Science Foundation of Zhejiang Province (No. LY16B020012 and LQ18B020006), the Science and Technology Project of Zhejiang Province (No. 2016C31022) and the Xinmiao Talent Planning Foundation of Zhejiang Province (No. 2017R426052) for financial support.

References

1 For selected reviews, see: (*a*) F. F. Fleming and Q. Wang, *Chem. Rev.*, 2003, **103**, 2035; (*b*) V. Y. Kukushkin and A. J. L. Pombeiro, *Chem. Rev.*, 2002, **102**, 1771.

2 (*a*) B. W. Zhao and X. Y. Lu, *Org. Lett.*, 2006, **8**, 5987; (*b*) Y. C. Wong, K. Parthasarathy and C. H. Cheng, *Org. Lett.*, 2010, **12**, 1736; (*c*) S. Demir, M. Yiğit and I. Özdemir, *J. Organomet. Chem.*, 2013, **732**, 21; (*d*) M. Yousuf, T. Das and S. Adhikari, *New J. Chem.*, 2015, **39**, 8763; (*e*) J. Sävmarker, J. Rydfjord, J. Gising, L. R. Odell and M. Larhed, *Org. Lett.*, 2012, **14**, 2394.

3 (*a*) R. C. Larock, Q. Tian and A. A. Pletnv, *J. Am. Chem. Soc.*, 1999, **121**, 3238; (*b*) C. Zhou and R. C. Larock, *J. Am. Chem. Soc.*, 2004, **126**, 2302; (*c*) C. Zhou and R. C. Larock, *J. Org. Chem.*, 2006, **71**, 3551.

4 (*a*) X. Wang, M. Liu, L. Xu, Q. Wang, J. Chen, J. Ding and H. Wu, *J. Org. Chem.*, 2013, **78**, 5273; (*b*) J. Chen, T. L. Chen and W. Su, *Org. Biomol. Chem.*, 2014, **12**, 8204; (*c*) S. Yu, L. Qi, K. Hu, J. Gong, T. Cheng, Q. Wang, J. Chen and H. Wu, *J. Org. Chem.*, 2017, **82**, 3631.

5 For reviews, see: (*a*) J. P. Michael, *Nat. Prod. Rep.*, 2008, **25**, 166; (*b*) A. Witt and J. Bergman, *Curr. Org. Chem.*, 2003, **7**, 659; (*c*) Y. Bansal and O. Silakari, *Bioorg. Med. Chem.*, 2012, **20**, 6208 and references therein.

6 For selected examples, see: (*a*) M. K. Krapf, J. Gallus and M. Wiese, *Eur. J. Med. Chem.*, 2017, **139**, 587; (*b*) S. V. Eswararao, V. Venkataramireddy, M. Srinivasareddy and P. Kumar, *Asian J. Chem.*, 2017, **29**, 1434; (*c*) I. Khan, A. Ibrar, W. Ahmed and A. Saeed, *Eur. J. Med. Chem.*, 2015, **90**, 124; (*d*) A. Machara, V. Lux, M. Kozisek, K. G. Saskova, O. Stepnek, M. Kotora, K. Parkan, M. Pavova, B. Glass, P. Sehr, J. Lewis, B. Müller, H. G. Kräusslich and J. Konvalinka, *J. Med. Chem.*, 2016, **59**, 545.

7 For selected examples, see: (*a*) Y. L. Zhang, M. R. Sheets, E. K. Raja, K. N. Boblak and D. A. Klumpp, *J. Am. Chem. Soc.*, 2011, **133**, 8467; (*b*) D. Zhao, Q. Shen, Y. R. Zhou and J. X. Li, *Org. Biomol. Chem.*, 2013, **11**, 5908; (*c*) S. Achelle, J. Rodriguez-Lopez and G. F. Robin-le, *J. Org. Chem.*, 2014, **79**, 7564; (*d*) J. N. Wilson, W. Liu, A. S. Brown and R. Landgraf, *Org. Biomol. Chem.*, 2015, **13**, 5006; (*e*) D. Liu, Z. Zhang, H. Zhang and Y. Wang, *Chem. Commun.*, 2013, **49**, 10001.

8 (*a*) C. U. Maheswari, G. S. Kumar, M. Venkateshwar, R. A. Kumar, M. L. Kantam and K. R. Reddy, *Adv. Synth. Catal.*, 2010, **352**, 341; (*b*) B. Han, X. L. Yang, C. Wang,

Y. W. Bai, T. C. Pan, X. Chen and W. Yu, *J. Org. Chem.*, 2012, **77**, 1136; (*c*) Y. Yan, Y. Zhang, C. Feng, Z. Zha and Z. Wang, *Angew. Chem., Int. Ed.*, 2012, **51**, 8077; (*d*) J. Zhang, C. Yu, S. Wang, C. Wan and Z. Wang, *Chem. Commun.*, 2010, **46**, 5244; (*e*) J. Zhang, D. Zhu, C. Yu, C. Wan and Z. Wang, *Org. Lett.*, 2010, **12**, 2841; (*f*) B. Han, C. Wang, R. F. Han, W. Yu, X.-Y. Duan, R. Fang and X.-L. Yang, *Chem. Commun.*, 2011, **47**, 7818; (*g*) Y. Yan, M. Shi, B. Niu, X. Meng, C. Zhu, G. Liu, T. Chen and Y. Liu, *RSC Adv.*, 2016, **6**, 36192.

9 (*a*) V. Kumar, C. Mohan, M. Gupta and M. P. Mahajan, *Tetrahedron*, 2005, **61**, 3533; (*b*) J.-P. Lin, F.-H. Zhang and Y.-Q. Long, *Org. Lett.*, 2014, **16**, 2822; (*c*) Z.-C. Shen, P. Yang and Y. J. Tang, *J. Org. Chem.*, 2016, **81**, 309; (*d*) Y. Wang, H. Wang, J. Peng and Q. Zhu, *Org. Lett.*, 2011, **13**, 4604; (*e*) L. Xu, H. Li, Z. Liao, K. Lou, H. Xie, H. Li and W. Wang, *Org. Lett.*, 2015, **17**, 3434; (*f*) M. A. McGowan, C. Z. McAvoy and S. L. Buchwald, *Org. Lett.*, 2012, **14**, 3800; (*g*) Y. Ohta, Y. Tokimizu, S. Oishi, N. Fujii and H. Ohno, *Org. Lett.*, 2010, **12**, 3963; (*h*) Y. Lv, Y. Li, T. Xiong, W. Pu, H. Zhang, K. Sun, Q. Liu and Q. Zhang, *Chem. Commun.*, 2013, **49**, 6439.

10 (*a*) X. Fan, B. Li, S. Guo, Y. Wang and X. Zhang, *Chem. – Asian J.*, 2014, **9**, 739; (*b*) C. Wang, S. Li, H. Liu, Y. Jiang and H. Fu, *J. Org. Chem.*, 2010, **75**, 7936; (*c*) C. Huang, Y. Fu, H. Fu, Y. Jiang and Y. Zhao, *Chem. Commun.*, 2008, 6333; (*d*) V. L. Truong and M. Morrow, *Tetrahedron Lett.*, 2010, **51**, 758; (*e*) J. Ju, R. Hua and J. Su, *Tetrahedron*, 2012, **68**, 9364; (*f*) C. Xu, F.-C. Jia, Z.-W. Zhou, S.-J. Zheng, H. Li and A.-X. Wu, *J. Org. Chem.*, 2016, **81**, 3000.

11 For reviews on the quinazoline synthesis, see: (*a*) D. J. Connolly, D. Cusack, T. P. O'Sullivan and P. J. Guiry, *Tetrahedron*, 2005, **61**, 10153; (*b*) I. M. Abdou and S. S. Al-Neyadi, *Heterocycl. Commun.*, 2015, **21**, 115; (*c*) I. Khan, A. Ibrar, N. Abbas and A. Saeed, *Eur. J. Med. Chem.*, 2014, **76**, 193.

12 Z. Chen, J. Chen, M. Liu, J. Ding, W. Gao, X. Huang and H. Wu, *J. Org. Chem.*, 2013, **78**, 11342.

13 (*a*) X. Su, C. Chen, Y. Wang, J. Chen, Z. Lou and M. Li, *Chem. Commun.*, 2013, **49**, 6752; (*b*) M. Ramanathan and S. T. Liu, *J. Org. Chem.*, 2017, **82**, 8290; (*c*) X. Pang, C. Chen, X. Su, M. Li and L. Wen, *Org. Lett.*, 2014, **16**, 6228; (*d*) X. Pang, C. Chen, M. Li and C. Xi, *Beilstein J. Org. Chem.*, 2015, **11**, 2365; (*e*) C. K. Cao, J. Sheng and C. Chen, *Synthesis*, 2017, **49**, 5081.

14 K. Aradia and Z. Novák, *Adv. Synth. Catal.*, 2015, **357**, 371.

15 W. Chen, S. Wu, X. Mo, L. Wei, C. Liang and D. Mo, *Org. Lett.*, 2018, **20**, 3527.

16 (*a*) J. Bergmann, A. Brynolf, B. Elman and E. Vuorimen, *Tetrahedron*, 1986, **42**, 3697; (*b*) S. H. Kim, S. H. Kim, T. H. Kim and J. N. Kim, *Tetrahedron Lett.*, 2010, **51**, 2774.

17 (*a*) K. Hu, L. Qi, S. Yu, T. Cheng, X. Wang, Z. Li, Y. Xia, J. Chen and H. Wu, *Green Chem.*, 2017, **19**, 1740; (*b*) L. Qi, K. Hu, S. Yu, J. Zhu, T. Cheng, X. Wang, J. Chen and H. Wu, *Org. Lett.*, 2017, **19**, 218; (*c*) K. Hu, Q. Zhen, J. Gong, T. Cheng, L. Qi, Y. Shao and J. Chen, *Org. Lett.*, 2018, **20**, 3083; (*d*) Y. Zhang, Y. Shao, J. Gong, K. Hu, T. Cheng and J. Chen, *Adv. Synth. Catal.*, 2018, **360**, 3260.

18 (*a*) D. R. Stuart, M. Bertrand-Laperle, K. M. N. Burgess and K. Fagnou, *J. Am. Chem. Soc.*, 2008, **130**, 16474; (*b*) U. Ladzita, A. Y. Koposov, K. Y. Lo, J. Willging, V. N. Nemykin and V. V. Zhdankin, *Angew. Chem., Int. Ed.*, 2005, **44**, 7127.

19 B. Shrestha, S. Thapa, S. K. Gurung, R. A. S. Pike and R. Giri, *J. Org. Chem.*, 2016, **81**, 787.

20 L. Tang, P. Wang, Y. Fan, X. Yang, C. Wan and Z. Zha, *ChemCatChem*, 2016, **8**, 3565.