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A Highly Efficient Copper-Catalyzed Three-Component Synthesis of 4-Aminoquinazolines

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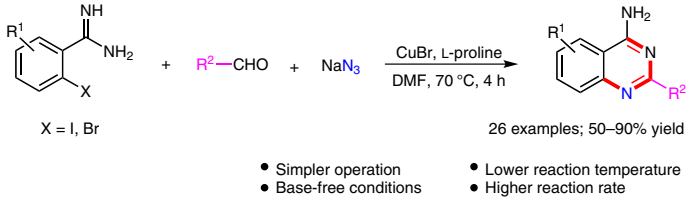

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Abstract A highly efficient copper-catalyzed one-pot protocol is developed for the synthesis of 4-aminoquinazolines from easily available 2-iodo- or 2-bromobenzimidamides, aldehydes, and sodium azide. This one-pot approach proceeds via consecutive copper-catalyzed S_NAr substitution, reduction, cyclization, oxidation and tautomerization. The corresponding target products (26 examples) are obtained in 50–90% yield.

Key words copper, 2-halobenzimidamides, sodium azide, catalysis, 4-aminoquinazolines

4-Aminoquinazoline, one of the most important nitrogen-containing heterocycles, is exemplified as a privileged structure that exists in many pharmaceutical drugs and biologically active molecules.[1,2] For example, gefitinib[1a] and erlotinib[1b] are well-known drugs used to treat non-small cell lung cancer, which act on the epidermal growth factor receptor. Alfuzosin[1c] is an antagonist of the α_1 adrenergic receptor for the treatment of benign prostatic hyperplasia. Prazosin[1d] is a sympatholytic drug utilized to treat high blood pressure, anxiety, and post-traumatic stress disorder, acting as an inverse agonist at α_1 adrenergic receptors (Figure 1). In addition, many 4-aminoquinazoline derivatives are the key synthetic intermediates for the synthesis of biologically active compounds, including opioid receptor like-1 antagonists,[2a] nociception receptor antagonists,[2b] capsaicin receptor antagonists,[2c] C-C chemokine receptor 4 antagonists,[2d] human adenosine A3 receptor antagonists,[2e] receptor tyrosine kinase inhibitors,[2f] aurora A/B kinase inhibitors,[2g] and selective Toll-like receptor 4 ligands.[2h]

In view of their great value, the synthesis of 4-aminoquinazolines has gained much attention in the past decade.[3–8] The main synthetic methods toward this skeleton are summarized in Scheme 1. Among these, a classical approach to these substances converged on the further decoration of the existing quinazoline nucleus,[3,4] including the nucleophilic substitution reaction of amines with 4-halo- or 4-mercaptoquinazolines,[3] the reduction of 4-azidoquinazolines,[4a] and the Suzuki–Miyaura coupling of 2-chloro-4-aminoquinazolines.[4b] However, the commercially unavailable quinazolines used as starting materials, the

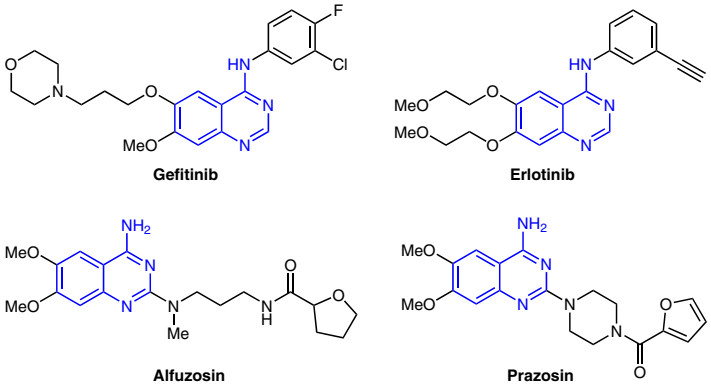
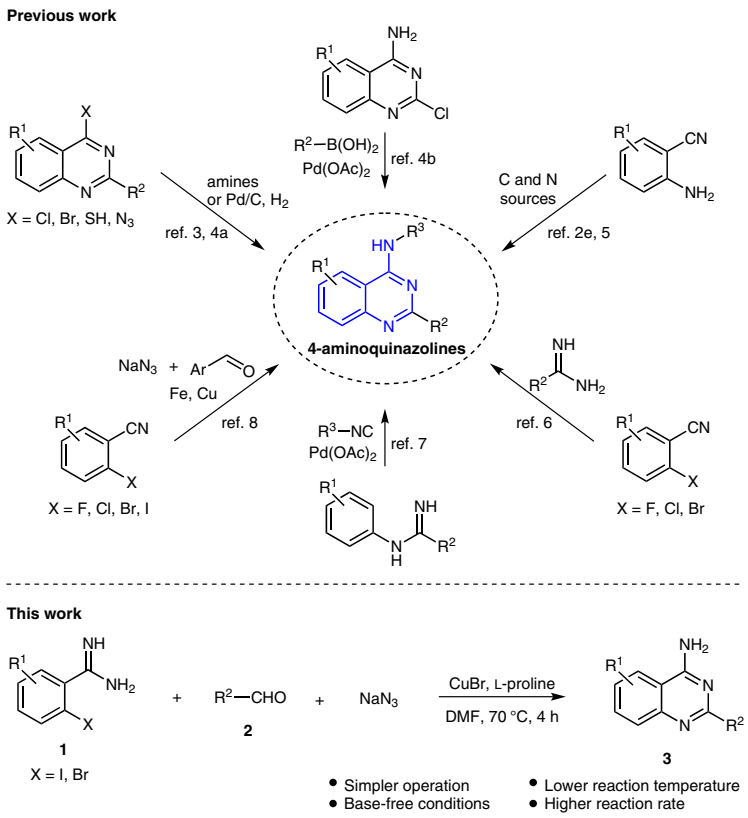


Figure 1 Structures of selected 4-aminoquinazoline derivatives

preparation of which required multistep routes from uncommon 2-aminobenzoic acid derivatives, has restricted applications in synthetic chemistry. Therefore, increasing efforts have been devoted to developing more efficient methods for the generation of 4-aminoquinazolines, which mainly involved the cyclization reactions of anthranilonitrile derivatives with different carbon and nitrogen sources,[2e,5] the cyclization of 2-halobenzonitrile derivatives with various amidines,[6] and the aryl C–H amidination of *N*-arylamidines with isonitriles.[7] Recently, Wu and co-workers developed a novel and efficient Fe/Cu-relay-catalyzed domino protocol for the synthesis of 2-phenyl-4-aminoquinazolines from 2-halobenzonitriles, aromatic aldehydes, and sodium azide.[8] Although these reactions provide efficient access to various substituted 4-aminoquinazolines, their applications are limited due to certain disadvantages, including narrow substrate scope, tedious multistep procedures, high reaction temperatures and complex reaction conditions. Consequently, the development of simple, effective, mild and economic methods for the preparation of 4-aminoquinazolines are still highly desirable.

Sodium azide (NaN_3), as a convenient and inexpensive nitrogen source, has been widely applied in various chemical transformations, such as 1,3-dipolar cycloadditions[9] and Cu-catalyzed S_NAr reactions.[10] Encouraged by the results of recent studies on copper-catalyzed multicomponent syntheses of nitrogen-containing benzoheterocycles utilizing NaN_3 as the nitrogen source,[8,11] herein we present a similar protocol for the synthesis of 4-aminoquinazolines from readily available 2-iodo- or 2-bromobenzimidamides, aldehydes and NaN_3 (Scheme 1). Compared with the reported methods,[3–8] this approach is more suitable for synthesizing multifarious 4-aminoquinazoline derivatives from readily available substrates under mild conditions. Moreover, our approach shows good tolerance of various alkyl aldehydes and aromatic aldehydes, featuring simpler operations, a lower reaction temperature and a higher reaction rate, being superior to the previously reported methodologies.[6,8]

Based on previous work,[11c,12] we attempted to develop an efficient synthetic protocol to construct 2-substituted quinazolin-4-amines via copper-catalyzed consecutive reactions. Our investigation was carried out using 2-iodobenzimidamide (**1a**), benzaldehyde (**2a**) and NaN_3 as model substrates under different reaction conditions (Table 1). In the presence of CuI (10 mol%) and L-proline (**L-1**) (20 mol%), the reaction took place in *N*,*N*-dimethylformamide (DMF) at 70 °C to give the desired product **3a** in 57% yield (Table 1, entry 1). Next, a series of copper catalysts was screened for this reaction under the same reaction conditions (Table 1, entries 2–8). When CuBr was used as the catalyst, the yield

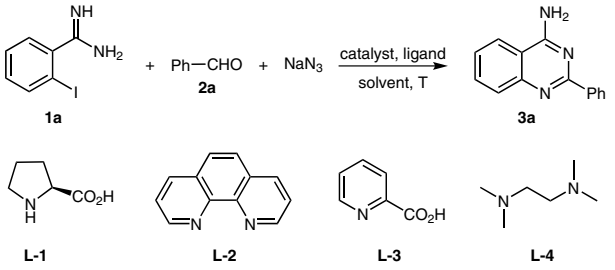


Scheme 1 Synthetic routes to 4-aminoquinazoline derivatives

was further improved to 81% (Table 1, entry 2). We then examined three other ligands including 1,10-phenanthroline (**L-2**), picolinic acid (**L-3**) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (**L-4**), however, the reaction yields decreased significantly (Table 1, compare entries 2 and 9–11). Further investigations indicated that both CuBr and L-proline were necessary for this transformation (Table 1, entries 12 and 13). Moreover, replacing NaN_3 with other nitrogen sources such as ammonium acetate, ammonium hydroxide and ammonium chloride, gave unsatisfactory results (Table 1, entries 14–16). Subsequently, the effect of different solvents was investigated, and DMF proved to be the optimum solvent (Table 1, compare entries 2 and 17–21). It should be noted that when H_2O was used as the solvent, the desired product **3a** was obtained in a moderate 40% yield (Table 1, entry 19), which suggests a potential application in green chemistry. Increasing or decreasing the reaction temperature did not lead to any further improvement in the yield, and a temperature of 70 °C gave the best result (Table 1, compare entries 2, 22 and 23). In addition, an increase in the amount of NaN_3 (0.2 mmol) did not result in a higher yield of the desired product (Table 1, compare entries 2 and 24). Finally, the optimized reaction conditions were determined as: **1a** (0.4 mmol), **2a** (1.2 equiv), NaN_3 (2.0 equiv) as the nitrogen source, CuBr (0.1 equiv) as the catalyst, L-proline (0.2 equiv) as the ligand and DMF (3 mL) as the solvent at 70 °C under an air atmosphere.

With optimized conditions in hand, we explored the substrate scope of this copper-catalyzed, three-component reaction, and the results are summarized in Scheme 2. We first examined 2-bromobenzimidamide, 2-chlorobenzimidamide and 2-fluorobenzimidamide as substrates in reactions with benzaldehyde (**2a**) and NaN_3 under the standard reaction conditions. 2-Bromobenzimidamide (**1b**) underwent this transformation smoothly, and gave the desired product **3a** in a slightly lower yield. Unfortunately, other *ortho*-halogenated benzimidamides such as 2-chlorobenzimidamides and 2-fluorobenzimidamides all had no reactivity under the optimized conditions, despite increasing the reaction temperature. The reactivity order is as follow: aryl iodides > aryl bromides > aryl chlorides (fluorides). We then further investigated the scope of this reaction using different aldehydes. First, a variety of aromatic aldehydes bearing different substituents reacted with 2-iodobenzimidamide (**1a**) to give the corresponding products **3a–j** in moderate to good yields (50–90%). The electronic effects of the substituents on the aromatic ring, including electron-neutral (H, **3a**), electron-withdrawing (3-O_2N, **3b**; 4-Cl, **3c**; 3,5-Cl_2, **3g**; 5-Br, **3h**) and electron-donating (2-OH, **3d**; 2-Me, **3e**; 5-*t*-Bu, **3i**; 3-MeO; **3j**) groups, did not lead to any significant differences in reactivity. Much to our satisfaction, the reactions with aromatic aldehydes containing 2-phenolic hydroxy groups proceeded smoothly to afford the corresponding products **3d** and **3g–j** in 70–90% yield, which provided the possibility for further functionalization. However, when using 2,6-dimethylbenzaldehyde as the coupling partner under the optimized conditions, the corresponding product **3f** was obtained in a low yield (50%), which indicated that the reaction was sensitive to the large steric hindrance due to the substituents on the aromatic

Table 1 Investigation of the Conditions for the Copper-Catalyzed Synthesis of 2-Phenylquinazolin-4-amine (**3a**) Using 2-Iodobenzimidamide (**1a**), Benzaldehyde (**2a**) and NaN_3 as the Substrates[a]



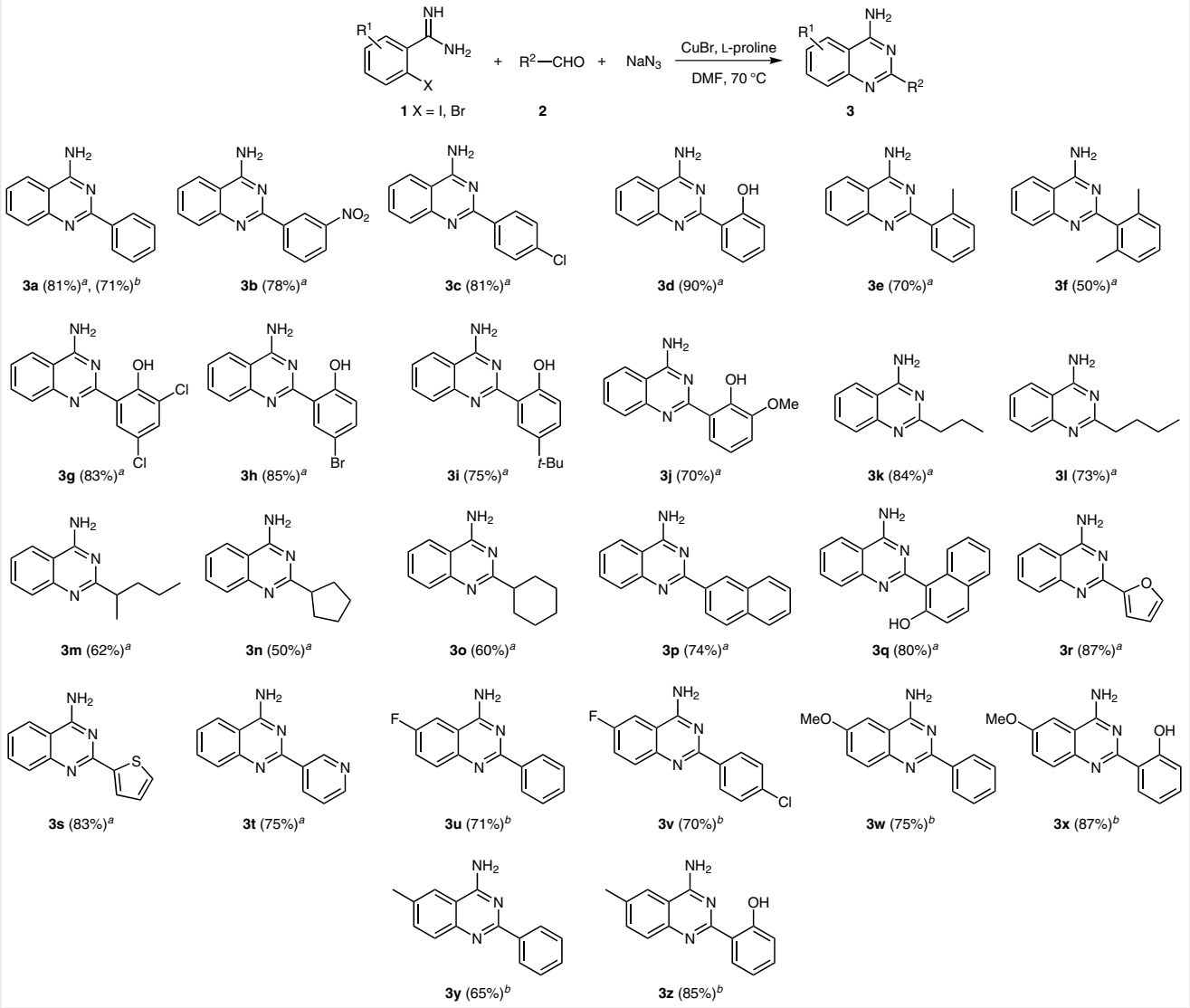
Entry	Cat.	Ligand	Solvent	Temp (°C)	Yield (%)[b]
1	CuI	**L-1**	DMF	70	57
2	CuBr	**L-1**	DMF	70	81
3	CuCl	**L-1**	DMF	70	35
4	Cu_2O	**L-1**	DMF	70	trace
5	CuO	**L-1**	DMF	70	N.R.
6	$CuBr_2$	**L-1**	DMF	70	trace
7	$CuCl_2$	**L-1**	DMF	70	N.R.
8	$Cu(OAc)_2$	**L-1**	DMF	70	N.R.
9	CuBr	**L-2**	DMF	70	30
10	CuBr	**L-3**	DMF	70	25
11	CuBr	**L-4**	DMF	70	23
12	CuBr	–	DMF	70	20
13	–	**L-1**	DMF	70	trace
14[c]	CuBr	**L-1**	DMF	70	45
15[d]	CuBr	**L-1**	DMF	70	17
16[e]	CuBr	**L-1**	DMF	70	N.R.
17	CuBr	**L-1**	DMSO	70	66
18	CuBr	**L-1**	THF	70	52
19	CuBr	**L-1**	H_2O	70	40
20	CuBr	**L-1**	DCE	70	trace
21	CuBr	**L-1**	toluene	70	trace
22	CuBr	**L-1**	DMF	55	57
23	CuBr	**L-1**	DMF	85	75
24[f]	CuBr	**L-1**	DMF	70	78

[a] Reaction conditions: **1a** (0.4 mmol), **2a** (0.48 mmol), NaN_3 (0.8 mmol), catalyst (0.04 mmol), ligand (0.08 mmol), solvent (3 mL), under air, 4 h.
[b] Yield of isolated product. N.R. = no reaction.
[c] Ammonium acetate was used as the nitrogen source.
[d] Ammonium hydroxide was used as the nitrogen source.
[e] Ammonium chloride was used as the nitrogen source.
[f] NaN_3 (0.2 mmol) was used.

ring. Better than the existing method,[8] our approach showed good tolerance toward alkyl aldehydes, and provided the corresponding products **3k–o** in 50–84% yield. Meanwhile, the optimized conditions were also found to be suitable for 2-naphthaldehyde and 2-hydroxy-1-naphthaldehyde to give the desired products **3p**,**q** in 74–80% yield. Furthermore, 2-furanaldehyde, 2-thienaldehyde, and 3-pyridinaldehyde were successfully applied to construct 2-heteroaryl-4-aminoquinazolines **3r–t** in good yields under the optimized conditions. It was noticed that compound **3t** was a precursor for the synthesis of novel human adenosine A3 receptor antagonists.[2e]

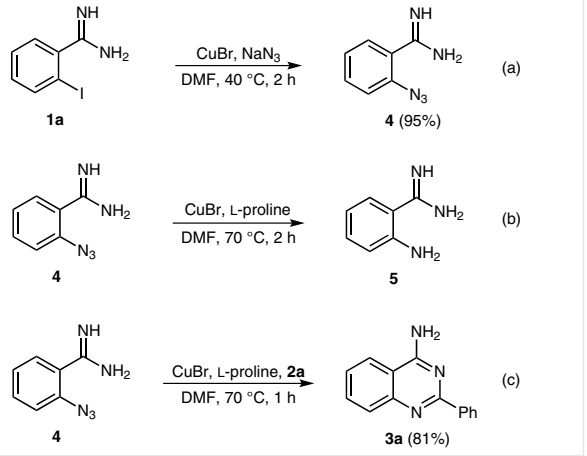
Next, we turned our attention to expand the scope of the *ortho*-halogenated benzimidamides with benzaldehydes as the reaction partners under the optimized conditions. Generally, the reactions proceeded well with these substrates to deliver the 2,6-disubstituted 4-aminoquinazolines **3u–z** in moderate to good yields. The results demonstrated that the electronic features of the additional substituent on the *ortho*-halogenated benzimidamide had limited influence on this copper-catalyzed consecutive reaction. Therefore, this approach showed high functional group tolerance and proved to be a quite general method for the preparation of multifarious 4-aminoquinazoline derivatives under mild conditions.

In order to explore the reaction mechanism for the synthesis of 4-aminoquinazoline derivatives, some control experiments were performed. First, 2-iodobenzimidamide



Scheme 2 Scope of 2-halobenzimidamides and aldehydes. *Reagents and conditions*: 2-halobenzimidamide (0.4 mmol), aldehyde (0.48 mmol), NaN_3 (0.8 mmol), CuBr (0.04 mmol), L-proline (0.08 mmol), DMF (3 mL), 70 °C, under air, 1–4 h. [a] Product was obtained from 2-iodobenzimidamide. [b] Product was obtained from 2-bromobenzimidamide.

(**1a**) was treated with NaN_3 (2 equiv) in DMF in the presence of CuBr at 40 °C for two hours, giving 2-azidobenzimidamide (**4**) (*m*/*z* = 184.1, $[M + Na]^+$) in 95% yield (Scheme 3, a). Next, when **4** was heated at 70 °C for two hours in DMF in the presence of CuBr and L-proline (Scheme 3, b), we fortunately observed the mass ion for 2-aminobenzimidamide (**5**) (*m*/*z* = 133.1, $[M - 2H]^{2-}$). Furthermore, the reaction of **4** with benzaldehyde (**2a**) proceeded smoothly in DMF at 70 °C using CuBr as the catalyst and L-proline as the ligand to afford the target product **3a** in 81% yield (Scheme 3, c). In this process, the MS spectrum after about 0.5 hours reaction time showed the mass ion for Schiff base **V**, or possibly the cyclized intermediate **VI** (*m*/*z* = 246.1, $[M + Na]^+$) (see Scheme 4; R^2 = Ph).



Scheme 3 Control experiments

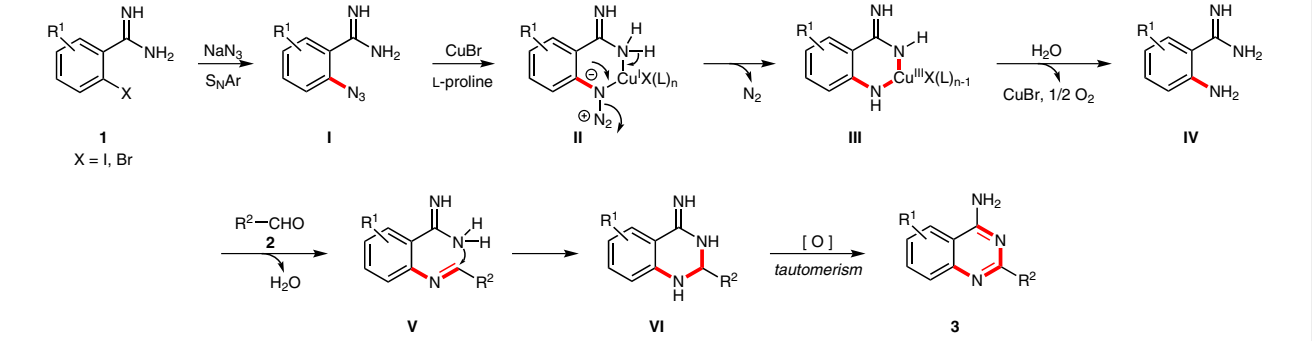
Based on the above observations and the reported literature,[8,11c,13] a possible mechanism for the copper-catalyzed one-pot synthesis of 4-aminoquinazoline derivatives is proposed in Scheme 4. First, the copper-catalyzed S_NAr product, 2-azidobenzimidamide **I**, is prepared from 2-halobenzimidamide **1** and NaN_3. Then, with the aid of L-proline and trace H_2O in DMF, the copper-mediated denitrogenation of **I** affords 2-aminobenzimidamide **IV** via the Cu(I) complex **II** and the Cu(III) complex **III**,[13] meanwhile releasing nitrogen. Next, **IV** could easily condense with aldehyde **2**, leading to the formation of Schiff base **V**. Subsequently, intramolecular nucleophilic attack of the amidine nitrogen on the imine carbon in **V** gives intermediate **VI**. Finally, **VI** undergoes oxidative dehydrogenation and amine–imine tautomerization to produce the target product **3**.

In conclusion, we have developed an efficient and practical copper-catalyzed one-pot method for the synthesis of 4-aminoquinazoline derivatives under mild reaction conditions, starting from readily available 2-iodo- or 2-bromobenzimidamides, aldehydes and NaN_3. The reactions proceed via a consecutive process involving a copper-catalyzed S_NAr substitution, reduction, cyclization, oxidation and tautomerization. It is hoped that the method will provide a novel synthetic strategy for bioactive molecules containing a 4-aminoquinazoline nucleus, and investigations on the further utilization of this protocol to construct more complex nitrogen-containing heterocycles are underway in our laboratory.

All commercial materials and solvents were used directly without further purification. Reactions were monitored by TLC on silica gel 60 F254 plates (Qingdao Ocean Chemical Company, China). Column chromatography was carried out on silica gel (200–300 mesh, Qingdao Ocean Chemical Company, China). Melting points were determined on an RY-1 melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were measured on Bruker AV-300 or AV-500 spectrometers with tetramethylsilane (TMS) as the internal standard. Low- and high-resolution mass spectra (LRMS and HRMS) were recorded in electron impact mode on Agilent 1100 LC/DAD/MSD or Q-Tof Micro MS/MS spectrometers.

2-Halobenzimidamides (1); General Procedure

To a solution of 2-halobenzonitrile (4.0 mmol) in THF (1 mL) was added dropwise $LiN(SiMe_3)_2$ (4 mL, 1 M in anhydrous THF, 4.4 mmol) at r.t. The reaction mixture was stirred overnight at the same temperature until the disappearance of the reactants (monitored by TLC), and then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc) to give the desired products **1**.



Scheme 4 Possible mechanism for the copper-catalyzed one-pot synthesis of 4-aminoquinazoline derivatives

2-Iodobenzimidamide (1a)[14]

Yield: 0.93 g (95%); red oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 7.9 Hz, 1 H), 7.35 (d, *J* = 4.3 Hz, 2 H), 7.02–7.08 (m, 1 H), 5.45 (br s, 3 H).

MS (ESI): *m*/*z* = 247.0 $[M + H]^+$.

2-Bromobenzimidamide (1b)[15]

Yield: 0.76 g (95%); yellow oil.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.84 (d, *J* = 7.8 Hz, 1 H), 7.37–7.41 (m, 1 H), 7.28 (dd, *J* = 7.6, 1.6 Hz, 1 H), 7.06–7.12 (m, 1 H), 6.36 (br s, 3 H).

MS (ESI): *m*/*z* = 199.0 $[M + H]^+$.

2-Bromo-5-fluorobenzimidamide (1c)

Yield: 0.81 g (93%); yellow oil.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.92 (d, *J* = 8.9 Hz, 1 H), 7.70 (d, *J* = 6.9 Hz, 2 H), 6.90 (br s, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 165.4, 161.6, 132.3, 132.2, 120.8, 115.7, 115.7.

MS (ESI): *m*/*z* = 217.0 $[M + H]^+$.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_7H_7N_2FBr$: 216.9777; found: 216.9782.

2-Bromo-5-methoxybenzimidamide (1d)

Yield: 0.90 g (98%); white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.52 (d, *J* = 8.8 Hz, 1 H), 7.02 (d, *J* = 2.9 Hz, 1 H), 6.87 (dd, *J* = 8.8, 3.0 Hz, 1 H), 5.05 (br s, 3 H), 3.85 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.2, 158.5, 136.8, 133.9, 117.1, 113.9, 109.0, 55.2.

MS (ESI): *m*/*z* = 229.0 $[M + H]^+$.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_8H_{10}N_2OBr$: 228.9976; found: 228.9974.

2-Bromo-5-methylbenzimidamide (1e)

Yield: 0.77 g (90%); red oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42 (d, *J* = 8.1 Hz, 1 H), 7.24 (d, *J* = 12.7 Hz, 1 H), 7.06 (d, *J* = 7.9 Hz, 1 H), 6.63 (br s, 3 H), 2.28 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.5, 137.5, 132.7, 132.01, 131.5, 129.3, 115.5, 20.2.

MS (ESI): *m*/*z* = 213.0 $[M + H]^+$.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_8H_{10}N_2Br$: 213.0027; found: 213.0023.

Quinazolin-4-amines (3); General Procedure

To a solution of 2-iodo- or 2-bromobenzimidamide (**1**) (0.4 mmol) in DMF (3 mL) was added an aldehyde (0.48 mmol), NaN_3 (52 mg, 0.8 mmol), CuBr (5.7 mg, 0.04 mmol), and L-proline (9.2 mg, 0.08 mmol). The reaction mixture was stirred at 70 °C under air. After the disappearance of the reactants (monitored by TLC), H_2O (30 mL) was added and the mixture was then extracted with EtOAc (3 × 10 mL). The combined extracts were washed with sat. NaCl solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (PE–EtOAc, 10:1 to 5:1) to give the desired product **3**.

2-Phenylquinazolin-4-amine (3a)[8]

Yield: 71 mg (81%); yellow solid; mp 144–145 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.44 (dd, *J* = 6.5, 3.0 Hz, 2 H), 8.22 (d, *J* = 8.1 Hz, 1 H), 7.79 (br s, 2 H), 7.74 (t, *J* = 5.7 Hz, 2 H), 7.40–7.53 (m, 4 H).

MS (ESI): *m*/*z* = 222.1 $[M + H]^+$.

2-(3-Nitrophenyl)quinazolin-4-amine (3b)[8]

Yield: 82 mg (78%); yellow solid; mp 237–239 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.22 (s, 1 H), 8.85 (d, *J* = 7.9 Hz, 1 H), 8.33 (d, *J* = 7.4 Hz, 1 H), 8.26 (d, *J* = 8.2 Hz, 1 H), 8.02 (br s, 2 H), 7.77–7.81 (m, 3 H), 7.48–7.51 (m, 1 H).

MS (ESI): *m*/*z* = 267.1 $[M + H]^+$.

2-(4-Chlorophenyl)quinazolin-4-amine (3c)[6d]

Yield: 82 mg (81%); white solid; mp 151–153 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.44 (d, *J* = 8.5 Hz, 2 H), 8.23 (d, *J* = 8.1 Hz, 1 H), 7.88 (br s, 2 H), 7.69–7.79 (m, 2 H), 7.54 (d, *J* = 8.5 Hz, 2 H), 7.47 (t, *J* = 6.3 Hz, 1 H).

MS (ESI): *m*/*z* = 256.1 $[M + H]^+$.

2-(2-Hydroxyphenyl)quinazolin-4-amine (3d)

Yield: 86 mg (90%); yellow solid; mp 205–207 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 14.58 (br s, 1 H), 8.40–8.43 (m, 1 H), 8.26 (d, *J* = 8.1 Hz, 1 H), 8.21 (br s, 2 H), 7.77–7.87 (m, 1 H), 7.73 (d, *J* = 8.2 Hz, 1 H), 7.50 (t, *J* = 7.5 Hz, 1 H), 7.31–7.36 (m, 1 H), 6.87–6.92 (m, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 161.4, 160.9, 160.7, 147.5, 133.8, 132.2, 128.9, 126.1, 125.6, 123.8, 119.0, 118.0, 117.3, 112.8.

MS (ESI): *m*/*z* = 238.1 $[M + H]^+$.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{12}N_3O$: 238.0980; found: 238.0986.

2-(2-Methylphenyl)quinazolin-4-amine (3e)[8]

Yield: 66 mg (70%); brown solid; mp 174–175 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 8.2 Hz, 1 H), 7.59–7.87 (m, 3 H), 7.48 (t, *J* = 7.4 Hz, 1 H), 7.29 (d, *J* = 11.5 Hz, 3 H), 6.07 (br s, 2 H), 2.52 (s, 3 H).

MS (ESI): *m*/*z* = 236.1 $[M + H]^+$.

2-(2,6-Dimethylphenyl)quinazolin-4-amine (3f)

Yield: 50 mg (50%); brown solid; mp 201–203 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 8.3 Hz, 1 H), 7.75–7.83 (m, 2 H), 7.52 (t, *J* = 7.5 Hz, 1 H), 7.14–7.24 (m, 1 H), 7.10 (d, *J* = 7.4 Hz, 2 H), 6.04 (br s, 2 H), 2.17 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.5, 161.0, 150.1, 139.2, 134.8, 132.8, 131.2, 128.2, 127.5, 127.1, 125.5, 121.0, 112.0, 19.2.

MS (ESI): *m*/*z* = 250.1 $[M + H]^+$.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{16}N_3$: 250.1344; found: 250.1349.

2-(3,5-Dichloro-2-hydroxyphenyl)quinazolin-4-amine (3g)

Yield: 101 mg (83%); yellow solid; mp 158–160 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 16.01 (s, 1 H), 8.44 (br s, 2 H), 8.35 (d, *J* = 2.6 Hz, 1 H), 8.29 (d, *J* = 8.2 Hz, 1 H), 7.76–7.90 (m, 2 H), 7.63 (d, *J* = 2.6 Hz, 1 H), 7.56 (t, *J* = 7.5 Hz, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 162.1, 159.5, 156.4, 147.1, 134.7, 131.7, 127.1, 126.9, 126.4, 124.4, 122.6, 121.6, 121.3, 113.5.

MS (ESI): *m*/*z* = 304.0 $[M - H]^-$.

HRMS: *m*/*z* [M – H]$^-$ calcd for $C_{14}H_8N_3OCl_2$: 304.0044; found: 304.0041.

2-(5-Bromo-2-hydroxyphenyl)quinazolin-4-amine (3h)

Yield: 106 mg (85%); white solid; mp 260–261 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 14.72 (s, 1 H), 8.54 (d, *J* = 2.6 Hz, 1 H), 8.22–8.43 (m, 3 H), 7.72–7.88 (m, 2 H), 7.43–7.58 (m, 2 H), 6.89 (d, *J* = 8.7 Hz, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 161.5, 159.9, 159.6, 147.2, 134.5, 134.0, 130.8, 126.1, 126.0, 123.8, 120.8, 119.7, 113.0, 109.2.

MS (ESI): *m*/*z* = 314.0 [M – H]$^-$.

HRMS: *m*/*z* [M – H]$^-$ calcd for $C_{14}H_9N_3OBr$: 313.9929; found: 313.9924.

2-[5-(*tert*-Butyl)-2-hydroxyphenyl]quinazolin-4-amine (3i)

Yield: 88 mg (75%); yellow solid; mp 151–152 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.52 (d, *J* = 2.3 Hz, 1 H), 7.74–7.81 (m, 3 H), 7.43–7.45 (m, 2 H), 6.98 (d, *J* = 8.6 Hz, 1 H), 5.84 (s, 2 H), 1.38 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.1, 160.9, 159.1, 148.1, 141.0, 133.8, 130.1, 127.2, 125.9, 125.5, 121.7, 117.2, 34.2, 31.6.

MS (ESI): *m*/*z* = 292.1 [M – H]$^-$.

HRMS: *m*/*z* [M – H]$^-$ calcd for $C_{18}H_{18}N_3O$: 292.1450; found: 292.1453.

2-(3-Methoxy-2-hydroxyphenyl)quinazolin-4-amine (3j)

Yield: 75 mg (70%); yellow solid; mp 212–214 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 8.1 Hz, 1 H), 7.74–7.83 (m, 3 H), 7.45–7.50 (m, 1 H), 7.00 (d, *J* = 7.7 Hz, 1 H), 6.87 (t, *J* = 8.0 Hz, 1 H), 5.77 (br s, 2 H), 3.95 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.5, 160.3, 151.3, 148.4, 147.3, 133.4, 126.6, 125.5, 121.2, 120.4, 118.7, 116.9, 113.7, 112.0, 55.7.

MS (ESI): *m*/*z* = 290.1 [M + Na]$^+$.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{13}N_3O_2Na$: 290.0905; found: 290.0898.

2-Propylquinazolin-4-amine (3k)[6a]

Yield: 63 mg (84%); yellow solid; mp 148–150 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.82–7.91 (m, 2 H), 7.74–7.79 (m, 1 H), 7.46 (t, *J* = 7.6 Hz, 1 H), 6.04 (br s, 2 H), 2.86 (t, *J* = 6.3 Hz, 2 H), 1.90 (dt, *J* = 15.2, 7.4 Hz, 2 H), 1.03 (t, *J* = 7.4 Hz, 3 H).

MS (ESI): *m*/*z* = 188.1 [M + H]$^+$.

2-Butylquinazolin-4-amine (3l)

Yield: 59 mg (73%); brown solid; mp 200–202 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.15 (d, *J* = 7.9 Hz, 1 H), 7.62–7.70 (m, 4 H), 7.37 (t, *J* = 7.5 Hz, 1 H), 2.65 (t, *J* = 7.3 Hz, 2 H), 1.67–1.76 (m, 2 H), 1.31 (dt, *J* = 14.4, 7.3 Hz, 2 H), 0.88 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 166.8, 161.8, 150.1, 132.4, 126.8, 124.3, 123.3, 38.7, 30.1, 22.0, 13.8.

MS (ESI): *m*/*z* = 202.1 [M + H]$^+$.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{16}N_3$: 202.1344; found: 202.1349.

2-(Pentan-2-yl)quinazolin-4-amine (3m)

Yield: 53 mg (62%); white solid; mp 162–164 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.14 (d, *J* = 6.6 Hz, 1 H), 7.66 (d, *J* = 6.7 Hz, 1 H), 7.51–7.59 (m, 3 H), 7.38 (d, *J* = 6.3 Hz, 1 H), 2.71–2.78 (m, 1 H), 1.77 (s, 1 H), 1.46 (s, 1 H), 1.19–1.21 (m, 5 H), 0.82 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 170.3, 161.9, 150.2, 132.3, 127.0, 124.3, 123.3, 112.9, 42.2, 37.9, 20.3, 19.8, 14.0.

MS (ESI): *m*/*z* = 216.2 [M + H]$^+$.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{18}N_3$: 216.1501; found: 216.1505.

2-Cyclopentylquinazolin-4-amine (3n)

Yield: 43 mg (50%); yellow solid; mp 189–191 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.14 (d, *J* = 7.9 Hz, 1 H), 7.63–7.71 (m, 1 H), 7.57–7.59 (m, 3 H), 7.34–7.39 (m, 1 H), 3.07–3.12 (m, 1 H), 1.90–1.93 (m, 4 H), 1.72–1.74 (m, 2 H), 1.58–1.65 (m, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 169.7, 161.9, 150.1, 132.4, 127.0, 124.3, 123.3, 112.9, 48.2, 31.9, 25.6.

MS (ESI): *m*/*z* = 214.1 [M + H]$^+$.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{16}N_3$: 214.1344; found: 214.1350.

2-Cyclohexylquinazolin-4-amine (3o)[16]

Yield: 55 mg (60%); white solid; mp 230–232 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 8.6 Hz, 1 H), 7.76–7.67 (m, 2 H), 7.42 (t, *J* = 7.6 Hz, 1 H), 5.70 (br s, 2 H), 2.79 (dd, *J* = 16.0, 7.6 Hz, 1 H), 1.99–2.04 (m, 2 H), 1.82–1.86 (m, 2 H), 1.62–1.74 (m, 4 H), 1.37–1.51 (m, 2 H).

MS (ESI): *m*/*z* = 228.1 [M + H]$^+$.

2-(Naphthalen-2-yl)quinazolin-4-amine (3p)[8]

Yield: 80 mg (74%); white solid; mp 150–151 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.00 (s, 1 H), 8.60 (d, *J* = 8.6 Hz, 1 H), 8.26 (d, *J* = 8.3 Hz, 1 H), 8.04–8.07 (m, 1 H), 7.99–8.02 (m, 1 H), 7.95–7.96 (m, 1 H), 7.86 (s, 2 H), 7.79 (dd, *J* = 8.3, 5.7 Hz, 2 H), 7.54–7.58 (m, 2 H), 7.45–7.50 (m, 1 H).

MS (ESI): *m*/*z* = 272.1 [M + H]$^+$.

2-(2-Hydroxynaphthalen-1-yl)quinazolin-4-amine (3q)

Yield: 92 mg (80%); yellow solid; mp 204–205 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 15.33 (s, 1 H), 9.62 (d, *J* = 8.7 Hz, 1 H), 8.29–8.33 (m, 3 H), 7.77–7.90 (m, 4 H), 7.47–7.57 (m, 2 H), 7.33 (t, *J* = 7.3 Hz, 1 H), 7.18 (d, *J* = 8.9 Hz, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 162.1, 160.9, 160.3, 147.6, 133.8, 132.7, 128.3, 126.7, 126.3, 126.0, 125.6, 123.7, 122.4, 120.0, 112.2, 111.3.

MS (ESI): *m*/*z* = 286.1 [M – H]$^-$.

HRMS: *m*/*z* [M – H]$^-$ calcd for $C_{18}H_{12}N_3O$: 286.0980; found: 286.0988.

2-(Furan-2-yl)quinazolin-4-amine (3r)[8]

Yield: 73 mg (87%); black solid; mp 220–223 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.19 (d, *J* = 8.1 Hz, 1 H), 7.91 (br s, 2 H), 7.84 (s, 1 H), 7.67–7.78 (m, 2 H), 7.44 (t, *J* = 7.4 Hz, 1 H), 7.19 (d, *J* = 3.2 Hz, 1 H), 6.64–6.65 (m, 1 H).

MS (ESI): *m*/*z* = 212.1 [M + H]$^+$.

2-(Thiophen-2-yl)quinazolin-4-amine (3s)[8]

Yield: 75 mg (83%); brown solid; mp 178–181 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.19 (d, *J* = 8.1 Hz, 1 H), 7.90 (s, 1 H), 7.89 (br s, 2 H), 7.78–7.70 (m, 1 H), 7.66 (d, *J* = 6.8 Hz, 2 H), 7.42 (t, *J* = 7.5 Hz, 1 H), 7.21–7.12 (m, 1 H).

MS (ESI): *m*/*z* = 228.0 $[M + H]^+$.

2-(Pyridin-3-yl)quinazolin-4-amine (3t)[8]

Yield: 67 mg (75%); brown solid; mp 216–218 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.55 (s, 1 H), 8.66–8.70 (m, 2 H), 8.25 (d, *J* = 8.0 Hz, 1 H), 7.92 (br s, 2 H), 7.77–7.82 (m, 2 H), 7.47–7.54 (m, 2 H).

MS (ESI): *m*/*z* = 223.1 $[M + H]^+$.

6-Fluoro-2-phenylquinazolin-4-amine (3u)[8]

Yield: 68 mg (71%); yellow solid; mp 133–134 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.46–8.48 (m, 2 H), 8.35–8.38 (m, 1 H), 7.91 (br s, 2 H), 7.48–7.53 (m, 4 H), 7.38–7.42 (m, 1 H).

MS (ESI): *m*/*z* = 240.1 $[M + H]^+$.

6-Fluoro-2-(4-chlorophenyl)quinazolin-4-amine (3v)

Yield: 76 mg (70%); yellow solid; mp 172–174 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.42 (d, *J* = 8.5 Hz, 2 H), 8.32 (dd, *J* = 8.9, 6.2 Hz, 1 H), 7.93 (s, 2 H), 7.54 (d, *J* = 8.5 Hz, 2 H), 7.45 (d, *J* = 10.4 Hz, 1 H), 7.30–7.41 (m, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 162.1, 158.7, 150.2, 137.4, 134.7, 133.0, 131.1, 129.5, 128.7, 128.2, 127.6, 125.3, 123.6, 113.2.

MS (ESI): *m*/*z* = 272.0 $[M - H]^-$.

HRMS: *m*/*z* $[M - H]^-$ calcd for $C_{14}H_8N_3ClF$: 272.0391; found: 272.0386.

6-Methoxy-2-phenylquinazolin-4-amine (3w)[3b]

Yield: 75 mg (75%); yellow solid; mp 146–148 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.52 (d, *J* = 6.9 Hz, 2 H), 7.95 (d, *J* = 9.1 Hz, 1 H), 7.48–7.54 (m, 4 H), 7.03 (d, *J* = 2.5 Hz, 1 H), 5.52 (br s, 2 H), 3.99 (s, 3 H).

MS (ESI): *m*/*z* = 252.1 $[M + H]^+$.

6-Methoxy-2-(2-hydroxyphenyl)quinazolin-4-amine (3x)

Yield: 93 mg (87%); yellow solid; mp 214–216 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 14.52 (s, 1 H), 8.40 (d, *J* = 7.9 Hz, 1 H), 8.07 (s, 2 H), 7.68–7.72 (m, 2 H), 7.44 (dd, *J* = 9.0, 1.5 Hz, 1 H), 7.31 (t, *J* = 7.6 Hz, 1 H), 6.86–6.90 (m, 2 H), 3.88 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 160.7, 160.4, 159.0, 157.0, 142.6, 131.7, 128.5, 127.7, 124.6, 119.2, 118.0, 117.1, 113.3, 103.5, 55.8.

MS (ESI): *m*/*z* = 268.1 $[M + H]^+$.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{14}N_3O_2$: 268.1086; found: 268.1090.

6-Methyl-2-phenylquinazolin-4-amine (3y)[6a]

Yield: 61 mg (65%); yellow solid; mp 156–158 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.45 (d, *J* = 7.7 Hz, 2 H), 8.11 (d, *J* = 7.4 Hz, 1 H), 7.87 (d, *J* = 8.6 Hz, 1 H), 7.58–7.63 (m, 1 H), 7.47–7.53 (m, 5 H), 2.54 (s, 3 H).

MS (ESI): *m*/*z* = 236.1 $[M + H]^+$.

2-Hydroxy-6-methylphenylquinazolin-4-amine (3z)

Yield: 76 mg (85%); yellow solid; mp 225–226 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 14.63 (s, 1 H), 8.41 (dd, *J* = 8.2, 1.6 Hz, 1 H), 8.08 (s, 3 H), 7.63 (s, 2 H), 7.25–7.37 (m, 1 H), 6.81–6.95 (m, 2 H), 2.45 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 161.0, 160.6, 160.2, 145.7, 135.3, 135.2, 132.0, 128.7, 125.9, 122.9, 119.1, 118.0, 117.2, 112.7, 21.0.

MS (ESI): *m*/*z* = 252.1 $[M + H]^+$.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{14}N_3O$: 252.1137; found: 252.1143.

Control Experiments

To a solution of 2-iodobenzimidamide (**1a**) (0.4 mmol) in DMF (3 mL) were added NaN_3 (52 mg, 0.8 mmol) and CuBr (5.7 mg, 0.04 mmol). The reaction mixture was stirred at 40 °C under air for 2 h. H_2O (30 mL) was added to the mixture followed by extraction with EtOAc (3 × 10 mL). The combined extracts were washed with sat. NaCl solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (PE–EtOAc, 5:1) to give azide **4** (*m*/*z* = 184.1, $[M + Na]^+$) as a black solid (61 mg, 95%).

To a solution of **4** (61 mg, 0.38 mmol) in DMF (3 mL) were added CuBr (5.4 mg, 0.038 mmol) and L-proline (8.7 mg, 0.076 mmol). The reaction mixture was stirred at 70 °C under air for 2 h to give 2-aminobenzimidamide **5** (*m*/*z* = 133.1, $[M - 2H]^{2-}$).

To a solution of **4** (61 mg, 0.38 mmol) in DMF (3 mL) were added benzaldehyde (**2a**) (49 mg, 0.46 mmol), CuBr (5.4 mg, 0.038 mmol) and L-proline (8.7 mg, 0.076 mmol). The reaction mixture was stirred at 70 °C under air. After the disappearance of the reactants (monitored by TLC), H_2O (30 mL) was added and the mixture was extracted with EtOAc (3 × 10 mL). The combined extracts were washed with sat. NaCl solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (PE–EtOAc, 10:1) to give **3a** as a yellow solid (68 mg, 81%).

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588727.

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