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Palladium-Catalyzed Intermolecular Aerobic Oxidative Cyclization of 2-Ethynylanilines with Isocyanides: Regioselective Synthesis of 4-Halo-2-aminoquinolines

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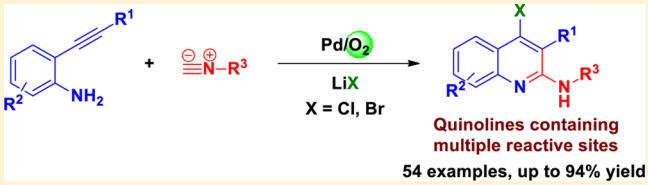
Supporting Information

ABSTRACT: A robust and regioselective palladium-catalyzed intermolecular aerobic oxidative cyclization of 2-ethynylanilines with isocyanides to the synthesis of 4-halo-2-aminoquinolines is reported herein. The procedure constructs various 4-halo-2-aminoquinolines with moderate to excellent yields (47−94%) and broad substrates scope. Furthermore, this process can be easily extended to synthesis of various 6*H*-indolo[2,3-*b*]quinolines via an intramolecular Buchwald−Hartwig cross-coupling reaction in two-step one-pot manner.

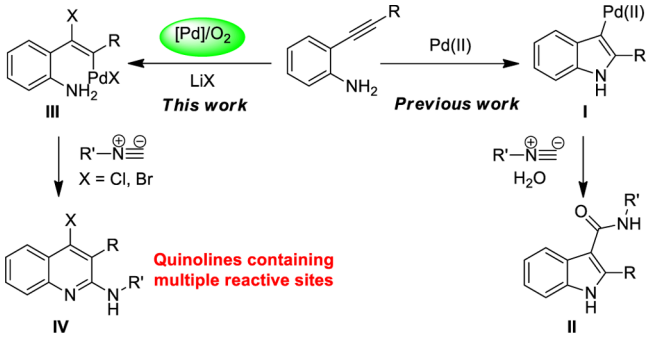


INTRODUCTION

The quinoline nucleus is arguably one of the most important substructures present in many natural products and synthetic drugs with different biological activities.[1] Because of their widespread biological activities, many different strategies for the preparation of quinolines have been developed. Although classical methods are widely recognized for the preparation of quinolines, these syntheses generally involve multiple steps and/or complex substrates.[2] On the other hand, significant efforts have been made with regard to the modification of quinolines.[3] Despite numerous approaches that have been developed, the preparation of quinolines bearing different substituents at specific positions employing readily available starting materials is still an attractive research area[4] since 2-aminoquinolines are often required by medicinal and material chemists.[5] Nevertheless, the efficient synthesis of 2-aminoquinoline architectures from easily available raw materials remains elusive. And only a few examples were developed for the procedure of 2-aminoquinolines.[6] Meanwhile, aromatic halides are an important class of compounds not only widely utilized in drug and natural product synthesis,[7] but also providing good opportunities for further formation of C−C and/or C−heteroatom bonds by transition-metal-catalyzed coupling reactions. Thus, the development of simple and efficient methods for halo-2-aminoquinolines is highly desirable because of their great significance.

Isocyanides have been recognized as powerful C1 synthons in the construction of structurally appealing heteroarenes.[8] Therefore, it is not surprising that special attention has been paid to the insertion of isocyanides into the C−Pd bond in recent years.[9] In addition, palladium-catalyzed aerobic oxidation has drawn wide attention because of its inexpensive and environmentally benign characteristics, particularly when molecular oxygen is used as the sole oxidant.[10] However, only few processes utilizing molecular oxygen have been reported concerning palladium-catalyzed isocyanides insertion.[9g,h] 2-Ethynylanilines are known to be used widely in the synthesis of substituted indoles,[11] so it is straightforward that 3-amidylindoles (**II**) can be prepared via an intramolecular aminopalladation of 2-ethynylanilines to form the indolylpalladium complexes (**I**), followed by insertion of isocyanides (Scheme 1).[9i,j] Considering the importance of quinoline compounds and our previous work on the construction of *N*-heterocycles involving isocyanides,[12] we envisioned that 2-ethynylanilines could undergo a halopalladation process to give the vinylpalladium complexes (**III**), and the subsequent isocyanides insertion would provide access to highly functionalized quinolines (**IV**) in a single step (Scheme 1). As well, 2-ethynylanilines have also been explored for the preparation of substituted quinolines.[13] Herein, for the first time, we present a simple and efficient method to the construction of various of 4-halo-2-aminoquinolines via palladium-catalyzed oxidative inter-

Scheme 1. Aminopalladation vs Halopalladation of 2-Ethynylanilines for the Synthesis of 3-Amidylindoles and 4-Halo-2-aminoquinolines



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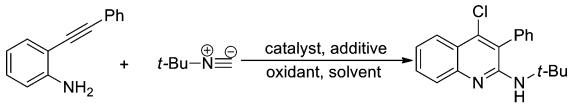
molecular cyclization of 2-ethynylanilines with isocyanides using molecular oxygen as the sole oxidant.

RESULTS AND DISCUSSION

To verify our hypothesis, we began our investigation with 2-(phenylethynyl)aniline (**1a**) and *tert*-butylisocyanide (**2a**) in toluene as model substrates catalyzed by $PdCl_2$ (5 mol %) in the presence of $CuCl_2$ (2.0 equiv). To our delight, *N*-(*tert*-butyl)-4-chloro-3-phenylquinolin-2-amine (**3aa**) could be obtained in 35% yield (Table 1, entry 1). Screening various

Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3aa

entry	catalyst	additive (equiv)	oxidant	solvent	yield (%)[b]
1	$PdCl_2$	–	$CuCl_2$	toluene	35
2	$PdCl_2$	–	$CuCl_2$	DMF	13
3	$PdCl_2$	–	$CuCl_2$	THF	10
4	$PdCl_2$	–	$CuCl_2$	dioxane	trace
5	$PdCl_2$	–	$CuCl_2$	DMSO	80
6	$PdCl_2$	–	1 atm O_2	DMSO	trace
7	$PdCl_2$	LiCl (1)	1 atm O_2	DMSO	63
8	$PdCl_2$	LiCl (2)	1 atm O_2	DMSO	83
9	$PdCl_2$	LiCl (2)	1 atm O_2	DMSO	90 (86)
10	$PdCl_2$	LiCl (2)	1 atm N_2	DMSO	n.d.[d]
11	$PdCl_2$	KI (2)	1 atm O_2	DMSO	n.d.[d]
12	$Pd(PPh_3)_4$	LiCl (2)	1 atm O_2	DMSO	n.d.[d]
13	$Pd(OAc)_2$	LiCl (2)	1 atm O_2	DMSO	trace
14	PdI_2	LiCl (2)	1 atm O_2	DMSO	trace
15[c]	$PdBr_2$	LiBr (2)	1 atm O_2	DMSO	57(52)

[a]Reaction conditions: Unless otherwise noted, all reactions were performed with **1a** (0.5 mmol), **2a** (0.6 mmol), catalyst (5 mol %), additive, and oxidant (2.0 equiv to **1a**) in 2.0 mL of solvent (100 °C for entries 1–8 and 120 °C for entries 9–15) for 12 h. [b]Analyzed by GC–MS using dodecane as the internal standard. Data in parentheses is isolated yield. [c]140 °C for 12 h, and 4-bromo-*N*-(*tert*-butyl)-3-phenylquinolin-2-amine was obtained. [d]n.d = not detected.

solvents revealed that the solvent played an important role in this reaction (entries 1–5). Notably, DMSO was identified as the optimal solvent for the formation of **3aa** (entry 5). Considering our previous work on palladium-catalyzed oxidation reactions with molecular oxygen as the sole oxidant,[10c] $CuCl_2$ was replaced by 1 atm of O_2 in this system; however, only trace amount of **3aa** was observed (entry 6). The yields of **3aa** could be increased sharply when LiCl was added (entries 7–8).[14] Importantly, the reaction conducted at 120 °C for 12 h gave the desired product in 86% isolated yield (entry 9). Further investigation revealed that $PdCl_2$ was superior to any other palladium catal^{y}sts so far tested (entries 11–14). Additionally, 52% yield of 4-bromo-*N*-(*tert*-butyl)-3-phenylquinolin-2-amine was formed when the reaction was performed with $PdBr_2$ (5 mol %) and 2 equiv of LiBr at 140 °C (entry 15).

With efficient reaction conditions in hand (Table 1, entry 9), we next surveyed the substrate scope of the reaction by employing a variety of 2-ethynylanilines (**1**) (Table 2). Substituent at the terminal alkynyl (R^1) of 2-ethynylanilines was first evaluated under the standard conditions. The results demonstrated that the electronic effects on substituted (R^1) 2-ethynylanilines had only a slight influence on the formation of the desired 4-chloro-2-aminoquinolines (Table 2, entries 1–13). As shown in Table 2, aryl substituted (R^1) 2-ethynylanilines with either an electron-donating or electron-withdrawing group on the benzene ring were able to undergo cyclization with *tert*-butylisocyanide (**2a**) to afford an array of 4-chloro-2-aminoquinolines in good to excellent yields (**3aa**–**3ma**). The molecular structure of **3ka** was further characterized by X-ray crystal diffraction measurement.[15] It is noted that the *ortho*-substituted substrates (**1g** and **1j**) showed slightly lower yields than the *para*-substituted ones (Table 2, entries 7–9, 10–11), which was probably caused by the steric effects. Gratifyingly, the standard conditions were compatible with the 2-thienyl group (**1n**), providing the corresponding product in 87% yield (entry 14). While either alkyl (entries 15–18) or propargyl alcohol (entries 19–22) substituted (R^1) 2-ethynylanilines were treated under the same conditions, the corresponding products were obtained in lower yields to some extent. However, silyl- and diphenylmethanol-substituted 2-ethynylanilines failed to give the desired products (entries 17–18 and 22). Furthermore, we found that the addition of TFA to the reaction mixture (after the formation of **3aa** was completed) and subsequent heating at 80 °C for further 5 h gave 4-chloro-3-phenylquinolin-2-amine (**3wa**) in 82% yield (Table 2, entry 23).[6b]

Encouraged by these initial results, the substrate versatility of 2-ethynylanilines was next examined using different substituents (R^2) on the anilines (Table 3, **4a**–**4j**). The electron-donating 4-methyl- (**4a**) and 5-methoxy-substituted (**4b**) 2-ethynylanilines were both reacted with **2a** under the optimal conditions to provide **5aa** and **5ba** in 85 and 92% yields, respectively. However, the 2-ethynylanilines (**4c**–**4j**) with electron-withdrawing groups (R^2) reacted sluggishly with **2a** and a higher reaction temperature was needed. Especially, when 2,6-dichloro- (**4f**), -CN (**4i**) and -COOMe (**4j**) substituted 2-ethynylanilines were applied to this transformation, no desired products were formed even with extended reaction time at 140 °C. Pleasingly, heterocyclic substituted 2-ethynylaniline **4k** efficiently annulated with **2a** and afforded **5ka** in 83% yield. Unfortunately, 3-(phenylethynyl)pyridin-2-amine (**4l**) failed to afford the desired product **5la**. We suspected that the coordination of the two adjacent nitrogens of **4l** with Pd catalyst might be too strong to catalyze this reaction.[12d,e] Moreover, various isocyanides were also applied to probe the scope and limitations of this approach (Table 3, **2b**–**2i**). Fortunately, almost all the isocyanides were found compatible with this transformation, affording the corresponding 4-chloro-2-aminoquinolines in good to excellent yields (Table 3, **5mb**–**5mi**). Notably, ethyl isocyanoacetate (**2d**) was also compatible for these reaction conditions and gave **5md** in 86% yield. In addition, bromo-substituted 2-ethynylaniline (**4n**) was also reacted with various isocyanides (**2d**–**2i**) effectively at 140 °C and afforded the corresponding products (**5nd**–**5ni**) in good to excellent yields. However, when we extended our method to the synthesis of 4-bromo-2-aminoquinolines under the similar conditions (Table 1, entry 15), only moderate yields of corresponding products (**6aa**–**6ea**) could be obtained (Scheme 2).[16]

It is well-known that the tetracyclic indolo[3,2-*b*]quinoline ring system exhibits numerous biological activities and found in many important natural products.[17] Procedures for the synthesis of these scaffolds from readily available starting materials remained scarcely described in the literature; hence, the development of simple and general methods for their preparation still remains a great challenge.[18] Having successfully

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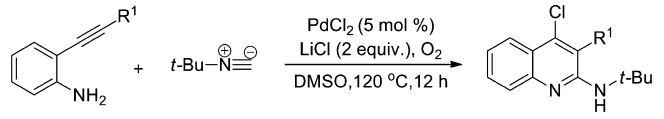
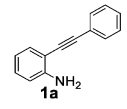
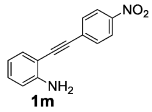
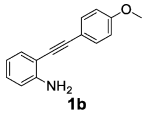
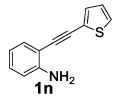
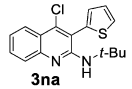
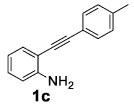
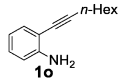
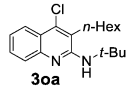
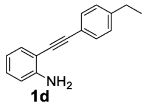
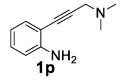
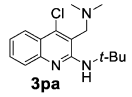
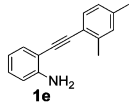
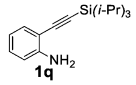
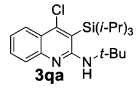
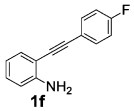
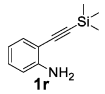
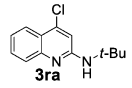
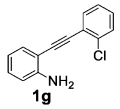
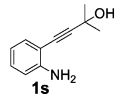
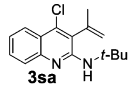
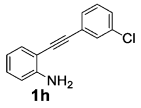
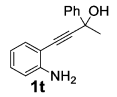
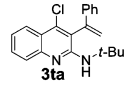
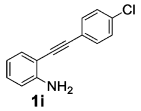
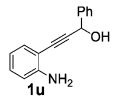
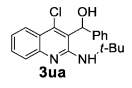
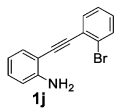
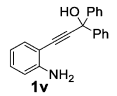
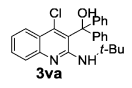
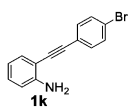
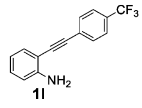
Table 2. Scope of 2-Ethynylanilines (R^1) for the Synthesis of 4-Chloro-2-aminoquinolines[a]



1 2a 3

entry	aniline (R^1)	product	yield (%)[b]	entry	aniline (R^1)	product	yield (%)[b]
1	 1a	3aa	86	13	 1m	3ma	85
2	 1b	3ba	91	14	 1n	 3na	87
3	 1c	3ca	87	15	 1o	 3oa	78
4	 1d	3da	85	16	 1p	 3pa	82
5	 1e	3ea	82	17	 1q	 3qa	n.r
6[c]	 1f	3fa	83	18	 1r	 3ra	trace
7[c]	 1g	3ga	81	19	 1s	 3sa	87
8	 1h	3ha	85	20	 1t	 3ta	81
9	 1i	3ia	92	21	 1u	 3ua	82
10[c]	 1j	3ja	84	22	 1v	 3va	n.d
11	 1k	3ka	94	23[d]	1a	 3wa	82
12	 1l	3la	88				

[a]Reaction conditions: Unless otherwise noted, **1** (0.5 mmol), **2a** (0.6 mmol), $PdCl_2$ (5 mol %), LiCl (1.0 mmol), and O_2 (1 atm) in 2.0 mL of DMSO at 120 °C for 12 h. [b]Isolated yield. [c]140 °C for 12 h. [d]TFA (5 equiv) was added for further 5 h at 80 °C. n.r. = no reaction. n.d. = not detected.

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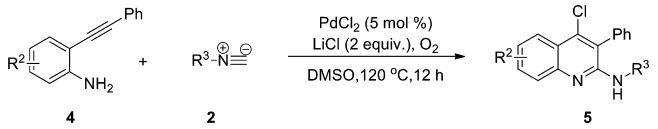
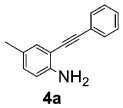
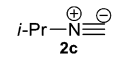
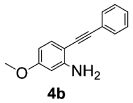
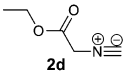
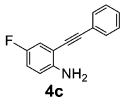
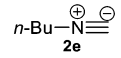
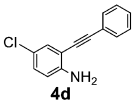
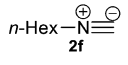
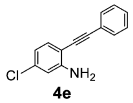
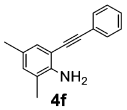
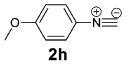
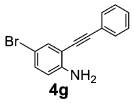
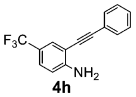
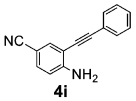
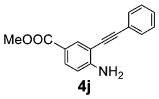
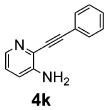
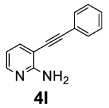
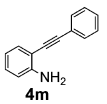
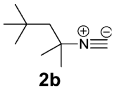
Table 3. Versatility of 2-Ethynylanilines (R^2) and Isocyanides for the Synthesis of 4-Chloro-2-aminoquinolines[a]



4 2 5

entry	aniline (**4**)	isocyanide	yield (%) [b]	entry	aniline (**4**)	isocyanide	yield (%) [b]
1	 **4a**	**2a**	**5aa**, 85	14	**4m**	 **2c**	**5mc**, 88
2	 **4b**	**2a**	**5ba**, 92	15	**4m**	 **2d**	**5md**, 86
3 [c]	 **4c**	**2a**	**5ca**, 80	16	**4m**	 **2e**	**5me**, 94
4 [c]	 **4d**	**2a**	**5da**, 88	17	**4m**	 **2f**	**5mf**, 84
5 [c]	 **4e**	**2a**	**5ea**, 84	18	**4m**	 **2g**	**5mg**, 91
6 [c]	 **4f**	**2a**	**5fa**, n.r	19	**4m**	 **2h**	**5mh**, 83
7 [c]	 **4g**	**2a**	**5ga**, 82	20	**4m**	 **2i**	**5mi**, 87
8 [c]	 **4h**	**2a**	**5ha**, 79	21 [c]	 **4n**	**2d**	**5nd**, 81
9 [c]	 **4i**	**2a**	**5ia**, n.r	22 [c]	**4n**	**2e**	**5ne**, 92
10 [c]	 **4j**	**2a**	**5ja**, trace	23 [c]	**4n**	**2f**	**5nf**, 83
11 [c]	 **4k**	**2a**	**5ka**, 83	24 [c]	**4n**	**2g**	**5ng**, 87
12 [c]	 **4l**	**2a**	**5la**, n.r	25 [c]	**4n**	**2h**	**5nh**, 80
13 [c]	 **4m**	 **2b**	**5mb**, 79	26 [c]	**4n**	**2i**	**5ni**, 85

[a]Reaction conditions: Unless otherwise noted, **4** (0.5 mmol), **2** (0.6 mmol), $PdCl_2$ (5 mol %), LiCl (1.0 mmol), and O_2 (1 atm) in 2.0 mL of DMSO at 120 °C for 12 h. [b]Isolated yield. [c]140 °C for 12 h. n.r. = no reaction.

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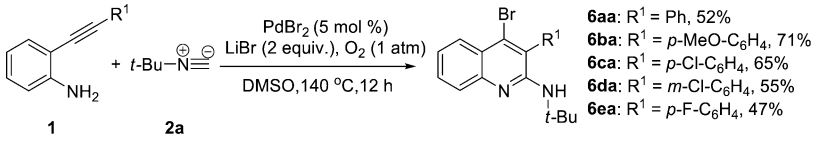
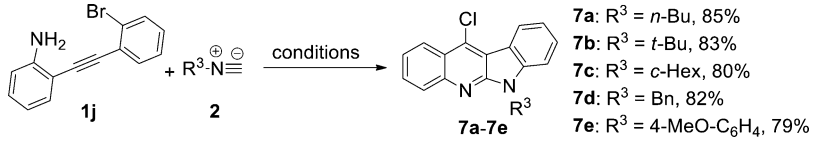
Scheme 2. Synthesis of 4-Bromo-2-aminoquinolines

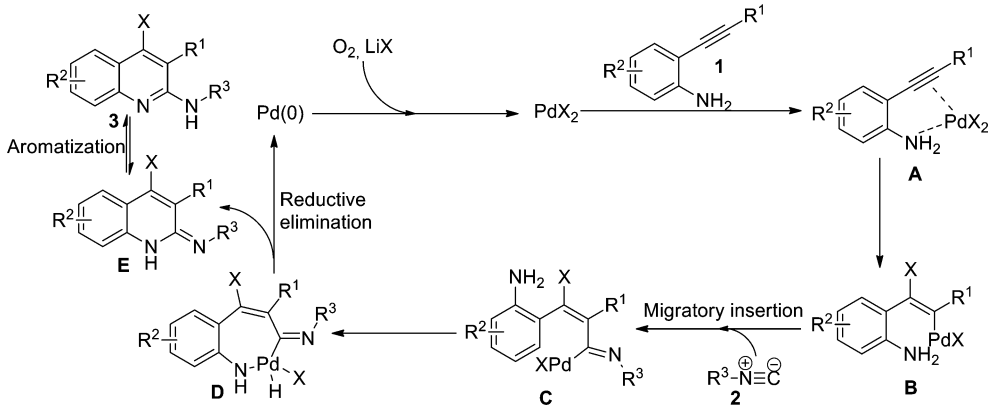


Scheme 3. Two-Step One-Pot Synthesis of 11-Chloro-6*H*-indolo[2,3-*b*]quinolines[a]



[a]Reaction conditions: step (1) **1j** (0.5 mmol), **2** (0.6 mmol), $PdCl_2$ (5 mol %), LiCl (2 equiv) in 2 mL of DMSO at 140 °C for 12 h under 1 atm O_2; step (2) $Pd_2(dba)_3$ (5 mol %), P(*o*-tol)$_3$ (10 mol %), and *t*-BuONa (2 equiv) in 2.0 mL of toluene at 85 °C for 12 h.

Scheme 4. Proposed Mechanism



established the general method for the synthesis of various 4-halo-2-aminoquinolins, we envisioned that 3-(2-bromophenyl)-4-chloro-2- aminoquinolins (Table 3, **5nd**−**5ni**) could easily undergo an intramolecular Buchwald−Hartwig[19] cross-coupling reaction to afford various indolo[3,2-*b*]quinolines. As expected, we found that 11-chloro-6*H*-indolo[2,3-*b*]quinolines (**7a**−**7e**) could be conveniently prepared in good yields through a one-pot two-step process (Scheme 3).

On the basis of our previous work on isocyanides and the influence of the chloride ion concentration in Table 1, we proposed a plausible mechanism in Scheme 4. Coordination of PdX_2 with the carbon−carbon triple bond affords intermediate **A**, followed by *trans*-halopalladation[14] to give intermediate **B**. Subsequently, the migratory insertion of isocyanides **2** into the σ-vinylpalladium intermediate would result in the formation of intermediate **C**. Then, the seven-membered azapalladacyclic intermediate **D** is formed by the intramolecular annulations of intermediate **C**. Finally, reductive elimination affords **E**, HX, and Pd(0) species. The Pd(0) species is oxidized to the active PdX_2 species by O_2. And the unstable product **E** would easily aromatize to give the final product **3**.

CONCLUSION

In summary, we have developed a novel and efficient strategy for the construction of 4-halo-2-aminoquinolines involving Pd-catalyzed aerobic oxidative annulations of commercially available isocyanides with readily accessible 2-ethynylanilines. The reaction exhibits a broad substrate scope and gives various 4-halo-2-aminoquinolines in good to excellent yields. Importantly, this process can be extended to the synthesis of various 6*H*-indolo[2,3-*b*]quinolines via an intramolecular Buchwald−Hartwig cross-coupling reaction in a two-step one-pot manner.

EXPERIMENTAL SECTION

General Information. Melting points were measured by a melting point instrument and were uncorrected. ^1H and ^{13}C NMR spectra were recorded by using a 400 MHz NMR spectrometer. The chemical shifts are referenced to signals at 7.24 and 77.0 ppm, respectively, and chloroform is used as a solvent with TMS as the internal standard. IR spectra were obtained either as potassium bromide pellets or as liquid films between two potassium bromide pellets with an infrared spectrometer. GC−MS was obtained using electron ionization. The data of HRMS was carried out on a high-resolution mass spectrometer (LCMS-IT-TOF). TLC was performed by using commercially available 100−400 mesh silica gel plates (GF254). Unless otherwise noted, all purchased chemicals were used without further purification. All the 2-ethynylanilines were known compounds and readily prepared from the reactions of the corresponding 2-iodobenzenamines with terminal alkynes directly by reported procedures.[20]

Typical Experimental Procedure for Synthesis of 4-Halo-2-aminoquinolines. To the mixture of 2-ethynylanilines (**1**, 0.5 mmol), PdX_2 (5 mol %) and LiX (2.0 equiv) in DMSO were added successively in a test tube. After stirring for 5 min at room temperature, isocyanide (**2**, 0.6 mmol) was added, and then the mixture was stirred at 120−140 °C for 12 h under 1 atm of O_2. Upon completion, the reaction mixture was extracted with ethyl acetate (3 × 10 mL), and the organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was separated by flash column chromatography (the eluents phases were V_{hexane}/V_{EtOAc} = 100:1, and the stationary phases were 300−400 mesh silica gel) to give the pure products **3** (X = Cl) and **5** (X = Br).

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*N-(tert-Butyl)-4-chloro-3-phenylquinolin-2-amine (**3aa**).* Light yellow oil (133 mg, 86%): IR (KBr) 3432, 2962, 1605, 1517, 1415, 1223, 758, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 8.4 Hz, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.60−7.47 (m, 4H), 7.35−7.27 (m, 3H), 4.31 (br. s, 1H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 147.8, 139.6, 135.2, 129.8, 129.8, 129.3, 128.5, 126.8, 124.4, 124.2, 122.4, 121.1, 51.9, 29.0; HRMS (ESI) m/z calcd for $C_{19}H_{20}ClN_2^+$, 311.1310, found 311.1306.

*N-(tert-Butyl)-4-chloro-3-(4-methoxyphenyl)quinolin-2-amine (**3ba**).* White solid (155 mg, 91%): mp 132−134 °C; IR (KBr) 3429, 2960, 1598, 1515, 1415, 1245, 757; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 8.4 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.53−7.50 (m, 1H), 7.20 (d, J = 7.2 Hz, 3H), 7.02 (d, J = 7.2 Hz, 2H), 4.34 (br. s, 1H), 3.84 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 154.8, 147.7, 139.9, 131.1, 129.7, 127.1, 126.7, 124.4, 124.0, 122.3, 121.2, 114.8, 55.2, 51.8, 29.0; HRMS (ESI) m/z calcd for $C_{20}H_{22}ClN_2O^+$, 341.1415, found 341.1424.

*N-(tert-Butyl)-4-chloro-3-(p-tolyl)quinolin-2-amine (**3ca**).* White solid (141 mg, 87%): mp 116−118 °C; IR (KBr) 3431, 2962, 1602, 1517, 1415, 1222, 811, 756; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.4 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.55−7.51 (m, 1H), 7.32 (d, J = 7.6 Hz, 2H), 7.26−7.22 (m, 1H),7.18 (d, J = 7.2 Hz, 2H), 4.34 (br. s, 1H), 2.43 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 147.8, 139.7, 138.4, 132.4, 132.2, 130.1, 129.7, 126.8, 124.5, 124.4, 122.4, 121.3, 51.9, 29.1, 21.5; HRMS (ESI) m/z calcd for $C_{20}H_{22}ClN_2^+$, 325.1466, found 325.1459.

*N-(tert-Butyl)-4-chloro-3-(4-ethylphenyl)quinolin-2-amine (**3da**).* White solid (144 mg, 85%): mp 122−124 °C; IR (KBr) 3430, 2964, 2360, 1763, 1600, 1517, 1415, 1239, 1053, 756; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.51 (t, J = 7.6 Hz, 1H), 7.32 (d, J = 7.6 Hz, 2H), 7.22−7.18 (m, 3H), 4.32 (br. s, 1H), 2.71 (q, J_1 = J_2 = 7.6 Hz, 2H), 1.41 (s, 9H), 1.28 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 147.7, 144.5, 139.6, 132.3, 129.7, 129.7, 128.8, 126.8, 124.4, 124.3, 122.3, 121.2, 51.9, 29.0, 28.7, 15.2; HRMS (ESI) m/z calcd for $C_{21}H_{24}ClN_2^+$, 339.1623, found 339.1619.

*N-(tert-Butyl)-4-chloro-3-(2,4-dimethylphenyl)quinolin-2-amine (**3ea**).* Light gray solid (139 mg, 82%): mp 105−107 °C; IR (KBr) 3422, 2961, 1602, 1516, 1415, 1222, 756; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 8.4 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.58 (t, J = 7.6 Hz, 1H), 7.29 (m, J = 7.6 Hz, 1H), 7.21 (s, 1H), 7.17 (d, J = 7.6 Hz, 1H), 7.06 (d, J = 7.6 Hz, 1H), 4.22 (br. s, 1H), 2.43 (s, 3H), 2.10 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 147.9, 139.8, 138.7, 136.8, 131.6, 131.3, 129.7, 129.6, 127.6, 126.8, 124.3, 123.8, 122.2, 121.2, 51.7, 29.0, 21.3, 19.1; HRMS (ESI) m/z calcd for $C_{21}H_{24}ClN_2^+$, 339.1623, found 339.1628.

*N-(tert-Butyl)-4-chloro-3-(4-fluorophenyl)quinolin-2-amine (**3fa**).* White solid (136 mg, 83%): mp 115−117 °C; IR (KBr) 3435, 2962, 2361, 1597, 1514, 1414, 1229, 757; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.58−7.54 (m, 1H), 7.30−7.20 (m, 5H), 4.20 (br. s, 1H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7 (J = 246.9 Hz), 154.4, 147.8, 140.0, 131.8 (J = 8.1 Hz), 131.0 (J = 3.3 Hz), 130.0, 126.8, 124.4, 123.2, 122.5, 121.1, 116.6 (J = 21.5 Hz), 52.0, 29.0; HRMS (ESI) m/z calcd for $C_{19}H_{19}ClFN_2^+$, 329.1215, found 329.1213.

*N-(tert-Butyl)-4-chloro-3-(2-chlorophenyl)quinolin-2-amine (**3ga**).* Yellow oil (139 mg, 81%): IR (KBr) 3433, 2961, 1764, 1608, 1516, 1413, 1240, 1054, 756; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 7.6 Hz, 1H), 7.61−7.58 (m, 2H), 7.44−7.43 (m, 2H), 7.31−7.27 (m, 2H), 4.05 (br. s, 1H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 148.0, 140.5, 134.3, 133.9, 131.8, 130.3, 130.3, 130.1, 127.8, 126.9, 124.4, 122.5, 121.9, 120.9, 52.0, 29.0; HRMS (ESI) m/z calcd for $C_{19}H_{19}Cl_2N_2^+$, 345.0920, found 345.0917.

*N-(tert-Butyl)-4-chloro-3-(3-chlorophenyl)quinolin-2-amine (**3ha**).* White solid (146 mg, 85%): mp 109−111 °C; IR (KBr) 3436, 2962, 1763, 1606, 1517, 1241, 1052, 756; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.56 (t, J = 7.6 Hz, 1H), 7.48−7.42 (m, 2H), 7.32 (s, 1H), 7.28−7.18 (m, 2H), 4.17 (br. s, 1H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 147.8, 139.9, 137.0, 135.2, 130.7, 130.1, 130.1, 128.8, 128.1, 126.9, 124.5, 122.8, 122.6, 121.0, 52.1, 29.0; HRMS (ESI) m/z calcd for $C_{19}H_{19}Cl_2N_2^+$, 345.0920, found 345.0911.

*N-(tert-Butyl)-4-chloro-3-(4-chlorophenyl)quinolin-2-amine (**3ia**).* Light yellow solid (158 mg, 92%): mp 122−124 °C; IR (KBr) 3850, 3435, 2922, 2355, 1744, 1605, 1515, 1239, 1050, 758; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8.0 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.54−7.50 (m, 1H), 7.47 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.4 Hz, 3H), 4.14 (br. s, 1H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 147.8, 140.0, 134.7, 133.6, 131.4, 130.0, 129.7, 126.9, 124.4, 123.0, 122.6, 121.0, 52.1, 29.0; HRMS (ESI) m/z calcd for $C_{19}H_{19}Cl_2N_2^+$, 345.0920, found 345.0914.

*3-(2-Bromophenyl)-N-(tert-butyl)-4-chloroquinolin-2-amine (**3ja**).* White solid (163 mg, 84%): mp 138−140 °C IR (KBr) 3438, 2960, 2918, 1763, 1609, 1517, 1414, 1242, 1048, 761; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.0 Hz, 1H), 7.76 (d, J = 8.0 Hz, 2H), 7.59−7.55 (m, 1H), 7.50−7.46 (m, 1H), 7.36−7.32 (m, 1H), 7.29−7.25 (m, 2H), 4.00 (br. s, 1H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 148.0, 140.3, 136.1, 133.5, 131.9, 130.4, 130.1, 128.4, 126.9, 124.4, 124.3, 123.5, 122.5, 120.9, 52.0, 29.0; HRMS (ESI) m/z calcd for $C_{19}H_{19}BrClN_2^+$, 389.0415, found 389.0403.

*3-(4-Bromophenyl)-N-(tert-butyl)-4-chloroquinolin-2-amine (**3ka**).* White solid (182 mg, 94%): mp 141−143 °C IR (KBr) 3435, 2962, 2920, 1758, 1606, 1516, 1414, 1241, 1052, 758; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 8.4 Hz, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.55 (d, J = 8.0 Hz, 2H), 7.45 (t, J = 7.6 Hz, 1H), 7.15 (t, J = 7.6 Hz, 1H), 7.08 (d, J = 8.0 Hz, 2H), 4.08 (br. s, 1H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 147.8, 139.9, 134.1, 132.6, 131.7, 130.0, 126.9, 124.4, 122.9, 122.9, 122.6, 121.0, 52.1, 29.0; HRMS (ESI) m/z calcd for $C_{19}H_{19}BrClN_2^+$, 389.0415, found 389.0413.

*N-(tert-Butyl)-4-chloro-3-(4-(trifluoromethyl)phenyl)quinolin-2-amine (**3la**).* Brown solid (166 mg, 88%): mp 104−106 °C IR (KBr) 3439, 2965, 2361, 1764, 1322, 1242, 1065, 757; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.0 Hz, 1H), 7.80 (d, J = 8.0 Hz, 2H), 7.74 (d, J = 8.4 Hz, 1H), 7.58 (t, J = 7.6 Hz, 1H), 7.46 (d, J = 8.0 Hz, 2H), 7.28 (t, J = 7.4 Hz, 1H), 4.08 (br. s, 1H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 148.0, 140.0, 139.1, 130.8 (q, J = 32.5 Hz), 130.6, 130.2, 127.0, 126.4 (q, J = 3.6 Hz), 124.5, 124.0 (q, J = 270.6 Hz), 122.8, 122.7, 121.0, 52.2, 29.1; HRMS (ESI) m/z calcd for $C_{20}H_{19}ClF_3N_2^+$, 379.1183, found 379.1175.

*N-(tert-Butyl)-4-chloro-3-(4-nitrophenyl)quinolin-2-amine (**3ma**).* Yellow solid (151 mg, 85%): mp 142−144 °C IR (KBr) 3436, 2965, 2362, 1605, 1518, 1346, 1238, 758; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, J = 8.8 Hz, 2H), 8.00 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.61−7.57 (m, 1H), 7.52 (d, J = 8.4 Hz, 2H), 7.29 (t, J = 7.2 Hz, 1H), 4.00 (br. s, 1H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 148.0, 147.9, 142.2, 140.0, 131.4, 130.5, 127.0, 124.6, 124.4, 122.9, 121.9, 120.7, 52.3, 29.0; HRMS (ESI) m/z calcd for $C_{19}H_{19}ClN_3O_2^+$, 356.1160, found 356.1153.

*N-(tert-Butyl)-4-chloro-3-(thiophen-2-yl)quinolin-2-amine (**3na**).* Yellow oil (137 mg, 87%): IR (KBr) 3425, 2990, 2362, 1764, 1243, 1055, 756; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.55−7.50 (m, 2H), 7.22−7.15 (m, 2H), 7.05 (d, J = 3.6 Hz, 1H), 4.61 (br. s, 1H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 148.2, 142.2, 135.2, 130.3, 129.0, 127.8, 127.7, 126.9, 124.7, 122.5, 121.0, 117.1, 52.0, 29.0; HRMS (ESI) m/z calcd for $C_{17}H_{18}ClN_2S^+$, 317.0874, found 317.0867.

*N-(tert-Butyl)-4-chloro-3-hexylquinolin-2-amine (**3oa**).* Yellow oil (124 mg, 78%): IR (KBr) 3468, 2957, 2925, 1599, 1517, 1412, 1222, 755; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8.4 Hz, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.49−7.46 (m, 1H), 7.21 (d, J = 6.8 Hz, 1H), 4.57 (br. s, 1H), 2.74 (t, J = 8.0 Hz, 2H), 1.61−1.49 (m, 11H), 1.45−1.33 (m, 6H), 0.89 (t, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 146.7, 139.6, 128.9, 126.7, 124.1, 122.3, 122.3, 121.5, 51.9, 31.6, 29.4, 29.2, 28.6, 27.2, 22.6, 14.0; HRMS (ESI) m/z calcd for $C_{19}H_{28}ClN_2^+$, 319.1936, found 319.1932.

*N-(tert-Butyl)-4-chloro-3-dimethylaminomethyl-quinolin-2-amine (**3pa**).* Yellow solid (119 mg, 82%): mp 106−108 °C; IR (KBr) 3433, 2924, 2858, 1745, 1602, 1365, 1047, 757; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.0 Hz, 1H), 7.71 (br. s, 1H), 7.65 (d, J = 8.4 Hz, 2H), 7.51−7.47 (m, 1H), 7.22−7.19 (m, 1H), 3.73 (s, 2H), 2.26

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(s, 6H), 1.52 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 147.7, 140.2, 129.3, 126.6, 124.5, 121.8, 120.9, 118.1, 58.1, 51.1, 44.2, 29.1; HRMS (ESI) m/z calcd for $C_{16}H_{23}ClN_3^+$, 292.1575, found 292.1585.

*N-(tert-Butyl)-4-chloro-3-(prop-1-en-2-yl)quinolin-2-amine (**3sa**).* Yellow solid (119 mg, 87%): mp 87−89 °C; IR (KBr) 3426, 2962, 1745, 1598, 1517, 1417, 1232, 756; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.4 Hz, 1H), 7.67 (d, J = 7.2 Hz, 1H), 7.52−7.48 (m, 1H), 7.23−7.20 (m, 1H), 5.49 (s, 1H), 5.07 (s, 1H), 4.96 (br. s, 1H), 2.04 (s, 3H), 1.51 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 147.3, 140.6, 137.7, 129.5, 126.7, 125.7, 124.0, 122.3, 121.0, 118.9, 51.7, 29.1, 21.8; HRMS (ESI) m/z calcd for $C_{16}H_{20}ClN_2^+$, 275.1310, found 275.1302.

*N-(tert-Butyl)-4-chloro-3-(1-phenylvinyl)quinolin-2-amine (**3ta**).* Yellow oil (136 mg, 81%): IR (KBr) 3430, 2960, 2357, 1743, 1595, 1518, 1221, 758; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.59−7.55 (m, 1H), 7.38−7.26 (m, 6H), 6.16 (s, 1H), 5.45 (s, 1H), 4.83 (br. s, 1H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 147.8, 142.7, 139.8, 137.5, 129.8, 128.7, 128.5, 126.8, 125.9, 124.4, 124.0, 122.4, 121.0, 118.7, 51.9, 28.9; HRMS (ESI) m/z calcd for $C_{21}H_{22}ClN_2^+$, 337.1466, found 337.1471.

*(2-(tert-Butylamino)-4-chloroquinolin-3-yl)(phenyl)methanol (**3ua**).* Red oil (139 mg, 82%): IR (KBr) 3740, 3057, 2359, 1742, 1452, 1243, 830, 767, 691; ^{1}H NMR (400 MHz, DMSO-d) δ 8.00 (d, J = 8.0 Hz, 1H), 7.58−7.53 (m, 2H), 7.36−7.24 (m, 6H), 7.05 (d, J = 3.6 Hz, 1H), 6.70 (br. s, 1H), 6.63 (d, J = 3.2 Hz, 1H), 1.29 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d) δ 154.2, 146.9, 141.2, 138.1, 129.9, 128.0, 127.1, 126.0, 125.0, 124.2, 123.4, 122.4, 119.9, 69.6, 50.9, 28.6; HRMS (ESI) m/z calcd for $C_{20}H_{20}ClN_2O^-$, 339.1270, found 339.1289.

*4-Chloro-3-phenylquinolin-2-amine (**3wa**).* Brown solid (104 mg, 82%): mp 120−122 °C; IR (KBr) 3478, 3397, 2979, 2362, 1610, 1429, 1245, 1048, 756; ^{1}H NMR (400 MHz, acetone-d) δ 7.65−7.57 (m, 4H), 7.53−7.49 (m, 1H), 7.44−7.42 (m, 2H), 7.37−7.33 (m, 1H), 5.60 (br. s, 2H); ^{13}C NMR (100 MHz, acetone-d) δ 157.4, 149.0, 140.9, 136.1, 131.0, 130.6, 130.1, 129.4, 127.1, 125.1, 124.4, 123.7, 122.5; HRMS (ESI) m/z calcd for $C_{15}H_{12}ClN_2^+$, 255.0684, found 255.0678.

*N-(tert-Butyl)-4-chloro-6-methyl-3-phenylquinolin-2-amine (**5aa**).* Yellow oil (138 mg, 85%): IR (KBr) 3433, 2962, 1600, 1515, 1417, 1323, 1221, 823, 701; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.56−7.52 (m, 2H), 7.49−7.45 (m, 1H), 7.42−7.40 (m, 1H), 7.34−7.31 (m, 2H), 4.21 (br. s, 1H), 2.50 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 146.1, 139.1, 135.4, 131.9, 131.7, 129.9, 129.3, 128.5, 126.7, 124.1, 123.5, 121.0, 51.8, 29.1, 21.4; HRMS (ESI) m/z calcd for $C_{20}H_{22}ClN_2^+$, 325.1466, found 325.1464.

*N-(tert-Butyl)-4-chloro-7-methoxy-3-phenylquinolin-2-amine (**5ba**).* Light yellow solid (156 mg, 92%): mp 130−132 °C; IR (KBr) 3740, 2961, 2359, 1764, 1609, 1516, 1242, 1037, 701; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 9.2 Hz, 1H), 7.53−7.42 (m, 3H), 7.30 (d, J = 7.2 Hz, 2H), 7.10 (s, 1H), 6.91 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 4.26 (br. s, 1H), 3.94 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 155.0, 149.4, 139.4, 135.3, 130.1, 129.3, 128.4, 125.7, 121.8, 115.8, 114.2, 106.1, 55.4, 51.9, 29.1; HRMS (ESI) m/z calcd for $C_{20}H_{22}ClN_2O^+$, 341.1415, found 341.1408.

*N-(tert-Butyl)-4-chloro-6-fluoro-3-phenylquinolin-2-amine (**5ca**).* White solid (131 mg, 80%): mp 104−106 °C; IR (KBr) 3433, 2961, 2355, 1601, 1516, 1416, 1236, 701; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73−7.66 (m, 2H), 7.56−7.53 (m, 2H), 7.49−7.46 (m, 1H), 7.34−7.30 (m, 3H), 4.27 (br. s, 1H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3 (d, J = 239.9 Hz), 154.0, 144.6, 138.9, 134.9, 129.7, 129.4, 128.8, 128.7, 125.0, 121.5 (d, J = 9.6 Hz), 119.1 (d, J = 24.7 Hz), 108.6 (d, J = 24.4 Hz), 51.9, 29.0; HRMS (ESI) m/z calcd for $C_{19}H_{19}ClFN_2^+$, 329.1215, found 329.1214.

*N-(tert-Butyl)-4,6-dichloro-3-phenylquinolin-2-amine (**5da**).* White solid (151 mg, 88%): mp 106−108 °C; IR (KBr) 3431, 2960, 1764, 1598, 1514, 1415, 1239, 704; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 2.4 Hz, 1H), 7.65 (d, J = 9.2 Hz, 1H), 7.55−7.51 (m, 2H), 7.48−7.45 (m, 2H), 7.30−7.28 (m, 2H), 4.31 (br. s, 1H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 146.2, 138.6, 134.8, 130.4, 129.7, 129.4, 128.8, 128.3, 127.7, 125.0, 123.5, 121.9, 52.0, 28.9; HRMS (ESI) m/z calcd for $C_{19}H_{19}Cl_2N_2^+$, 345.0920, found 345.0913.

*N-(tert-Butyl)-4,7-dichloro-3-phenylquinolin-2-amine (**5ea**).* Light yellow solid (144 mg, 84%): mp 82−84 °C; IR (KBr) 2991, 1764, 1604, 1516, 1378, 1243, 1055; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 8.8 Hz, 1H), 7.73 (s, 1H), 7.55−7.44 (m, 3H), 7.29 (d, J = 7.6 Hz, 2H), 7.19 (d, J = 8.8 Hz, 1H), 4.34 (br. s, 1H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 148.3, 139.4, 135.7, 134.8, 129.8, 129.4, 128.7, 125.8, 125.7, 124.4, 123.0, 119.7, 52.1, 28.9; HRMS (ESI) m/z calcd for $C_{19}H_{19}Cl_2N_2^+$, 345.0920, found 345.0915.

*6-Bromo-N-(tert-butyl)-4-chloro-3-phenylquinolin-2-amine (**5ga**).* Light yellow solid (159 mg, 82%): mp 119.4−121 °C; IR (KBr) 2986, 2360, 1743, 1514, 1373, 1241, 1047; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.62−7.45 (m, 5H), 7.28 (d, J = 6.8 Hz, 2H), 4.32 (br. s, 1H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 146.5, 138.5, 134.7, 133.0, 129.7, 129.4, 128.8, 128.5, 126.7, 125.0, 122.5, 115.4, 52.1, 28.9; HRMS (ESI) m/z calcd for $C_{19}H_{19}BrClN_2^+$, 389.0415, found 389.0403.

*N-(tert-Butyl)-4-chloro-3-phenyl-6-(trifluoromethyl)quinolin-2-amine (**5ha**).* Light yellow solid (149 mg, 79%): mp 103−105 °C; IR (KBr) 3739, 3431, 2925, 2356, 1519, 1299, 1242, 1123, 837, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.72−7.70 (m, 1H), 7.56−7.46 (m, 3H), 7.29 (d, J = 6.8 Hz, 2H), 4.46 (br. s, 1H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 149.3, 140.0, 134.4, 129.6, 129.5, 128.9, 127.5, 125.7 (q, J = 9.3 Hz), 125.4, 124.6 (q, J = 270 Hz), 124.1(q, J = 32.5 Hz), 122.6 (q, J = 4.3 Hz), 120.4, 52.3, 28.9; HRMS (ESI) m/z calcd for $C_{20}H_{19}ClF_3N_2^+$, 379.1183, found 379.1194.

*N-(tert-Butyl)-4-chloro-3-phenyl-1,5-naphthyridin-2-amine (**5ka**).* Yellow solid (129 mg, 83%): mp 134−136 °C; IR (KBr) 3430, 2962, 2924, 2362, 1593, 1517, 1411, 1217, 701; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (dd, J_1 = 1.2 Hz, J_2 = 4.0 Hz,1H), 7.99 (dd, J_1 = 1.2 Hz, J_2 = 8.4 Hz, 1H), 7.55−7.44 (m, 4H), 7.32−7.30 (m, 2H), 4.41 (br. s, 1H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 149.3, 140.0, 134.4, 129.6, 129.5, 128.9, 127.5, 125.7 (q, J = 9.3 Hz), 125.4, 124.6 (q, J = 270 Hz), 124.1(q, J = 32.5 Hz), 122.6 (q, J = 4.3 Hz), 120.4, 52.3, 28.9; HRMS (ESI) m/z calcd for $C_{18}H_{19}ClN_3^+$, 312.1262, found 312.1252.

*4-Chloro-3-phenyl-N-(2,4,4-trimethylpentan-2-yl)quinolin-2-amine (**5mb**).* White solid (145 mg, 79%): mp 102−104 °C; IR (KBr) 3439, 2954, 2360, 1607, 1517, 1417, 1224, 757; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 7.2 Hz, 1H), 7.58−7.51 (m, 3H), 7.48−7.44 (m, 1H), 7.29−7.25 (m, 3H), 4.35 (br. s, 1H), 1.84 (s, 2H), 1.50 (s, 6H), 0.83 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 147.8, 139.6, 135.2, 129.9, 129.8, 129.4, 128.6, 126.8, 124.4, 124.4, 122.3, 121.0, 55.8, 52.1, 31.6, 314, 29.2; HRMS (ESI) m/z calcd for $C_{23}H_{28}ClN_2^+$, 367.1936, found 367.1925.

*4-Chloro-N-isopropyl-3-phenylquinolin-2-amine (**5mc**).* Red oil (130 mg, 88%): IR (KBr) 3431, 2967, 1604, 1512, 1412, 1166, 758, 703; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.58−7.44 (m, 4H), 7.32−7.22 (m, 3H), 4.47−4.37 (m, 1H), 4.16 (d, J = 6.8 Hz, 1H), 1.15 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 148.1, 140.1, 134.8, 130.0, 129.9, 129.4, 128.6, 126.5, 124.5, 123.6, 122.5, 121.4, 42.6, 22.8; HRMS (ESI) m/z calcd for $C_{18}H_{18}ClN_2^+$, 297.1153, found 297.1164.

*Ethyl 2-((4-chloro-3-phenylquinolin-2-yl)amino)acetate (**5md**).* Dark green oil (146 mg, 86%): IR (KBr) 3424, 2927, 2357, 1742, 1515, 1410, 1200, 759; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 8.0 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.60−7.46 (m, 4H), 7.40−7.30 (m, 3H), 4.97 (br. s, 1H), 4.27 (d, J = 5.6 Hz, 2H), 4.17 (q, J_1 = J_2 = 7.0 Hz, 2H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 154.1, 147.4, 140.5, 134.3, 130.1, 129.9, 129.4, 128.8, 126.7, 124.5, 123.6, 123.1, 121.9, 61.1, 43.5, 14.1; HRMS (ESI) m/z calcd for $C_{19}H_{18}ClN_2O_2^+$, 341.1051, found 341.1044.

*N-Butyl-4-chloro-3-phenylquinolin-2-amine (**5me**).* Yellow solid (146 mg, 94%): mp 50−52 °C; IR (KBr) 3441, 2926, 2356, 1742, 1606, 1517, 1243, 758; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.60−7.46 (m, 4H), 7.35−7.27 (m, 3H), 4.35 (br. s, 1H), 3.52 (q, J = 6.8 Hz, 2H), 1.56−1.48 (m, 2H), 1.37−1.28 (m, 2H), 0.92 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz,

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$CDCl_3$) δ 154.9, 148.0, 140.0, 134.8, 130.0, 129.8, 129.4, 128.6, 126.5, 124.5, 123.6, 122.5, 121.5, 41.2, 31.5, 20.1, 13.8; HRMS (ESI) m/z calcd for $C_{19}H_{20}ClN_2^+$, 311.1310, found 311.1315.

4-Chloro-N-cyclohexyl-3-phenylquinolin-2-amine (**5mf**). Yellow oil (141 mg, 84%): IR (KBr) 3430, 2928, 2359, 1606, 1512, 1412, 1341, 757, 702; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.58−7.46 (m, 4H), 7.34−7.32 (m, 2H), 7.28−7.25 (m, 1H), 4.25 (br.s, 1H), 4.20−4.10 (m, 1H), 2.04−1.98 (m, 2H), 1.64−1.58 (m, 3H), 1.48−1.37 (m, 2H), 1.19−1.02 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 148.1, 140.0, 134.8, 130.0, 129.8, 129.4, 128.6, 126.4, 124.8, 123.7, 122.4, 121.4, 49.2, 32.9, 25.8, 24.7; HRMS (ESI) m/z calcd for $C_{21}H_{22}ClN_2^+$, 337.1466, found 337.1460.

N-Benzyl-4-chloro-3-phenylquinolin-2-amine (**5 mg**). Light yellow solid (157 mg, 91%): mp 108−110 °C; IR (KBr) 3438, 2925, 2360, 1743, 1604, 1514, 1243, 757; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 8.0 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.59−7.55 (m, 1H), 7.52−7.48 (m, 2H), 7.44−7.41 (m, 1H), 7.34−7.18 (m, 8H), 4.76 (br. s, 1H), 4.75 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 147.8, 140.4, 139.5, 134.5, 130.1, 129.8, 129.4, 128.7, 128.4, 127.4, 127.0, 126.6, 124.5, 123.6, 122.8, 121.8, 45.3; HRMS (ESI) m/z calcd for $C_{22}H_{18}ClN_2^+$, 345.1153, found 345.1158.

4-Chloro-N-(4-methoxyphenyl)-3-phenylquinolin-2-amine (**5mh**). Yellow oil (149 mg, 83%): IR (KBr) 3419, 2355, 1739, 1600, 1510, 1415, 1239, 759; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 8.4 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.62−7.51 (m, 6H), 7.42−7.34 (m, 3H), 6.87 (d, J = 8.8 Hz, 2H), 6.24 (br. s, 1H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 152.0, 147.2, 140.7, 134.3, 133.1, 130.2, 130.0, 129.6, 129.0, 127.1, 124.4, 124.1, 123.6, 122.2, 121.5, 114.0, 55.5; HRMS (ESI) m/z calcd for $C_{22}H_{18}ClN_2O^+$, 361.1102, found 361.1098.

4-Chloro-N-(2,6-dimethylphenyl)-3-phenylquinolin-2-amine (**5mi**). Red brown solid (156 mg, 87%): mp 156−159 °C; IR (KBr) 3401, 2921, 2358, 1740, 1607, 1501, 1230, 760; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 8.4 Hz, 1H), 7.69−7.61 (m, 3H), 7.57−7.50 (m, 4H), 7.36−7.32 (m, 1H), 7.17−7.05 (m, 3H), 5.72 (br. s, 1H), 2.21 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 147.8, 140.6, 136.4, 135.7, 134.9, 130.0, 129.8, 129.6, 128.9, 128.0, 127.1, 126.3, 124.4, 123.6, 123.1, 122.0, 18.8; HRMS (ESI) m/z calcd for $C_{23}H_{20}ClN_2^+$, 359.1310, found 359.1305.

Ethyl 2-((3-(2-bromophenyl)-4-chloroquinolin-2-yl)amino)-acetate (**5nd**). White solid (169 mg, 81%): mp 132−134 °C; mp 134−136 °C; IR (KBr) 2970, 2361, 1731, 1665, 1475, 1369, 1135, 701; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 8.0 Hz, 1H), 7.79−7.75 (m, 2H), 7.62−7.58 (m, 1H), 7.51−7.47 (m, 1H), 7.38−7.31 (m, 3H), 4.74 (br. s, 1H), 4.38 (dd, J_1 = 5.6 Hz, J_2 = 18.4 Hz, 1H), 4.24−4.10 (m, 3H), 1.24 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 153.4, 147.7, 141.3, 135.2, 133.5, 131.6, 130.6, 130.4, 128.4, 126.8, 124.5, 124.5, 123.2, 122.9, 121.7, 61.1, 43.5, 14.1; HRMS (ESI) m/z calcd for $C_{19}H_{17}BrClN_2O_2^+$, 419.0156, found 419.0159.

3-(2-Bromophenyl)-N-butyl-4-chloroquinolin-2-amine (**5ne**). Yellow solid (178 mg, 92%): mp 70−72 °C; IR (KBr) 3445, 2927, 2353, 1747, 1603, 1519, 1240, 751; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 8.4 Hz, 2H), 7.61−7.57 (m, 1H), 7.50−7.46 (m, 1H), 7.34−7.27 (m, 3H), 4.12 (br. s, 1H), 3.60−3.44 (m, 2H), 1.57−1.50 (m, 2H), 1.38−1.31 (m, 2H), 0.91 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 148.3, 140.8, 135.7, 133.5, 131.7, 130.4, 130.3, 128.4, 126.6, 124.5, 124.5, 122.9, 122.5, 121.2, 41.2, 31.5, 20.1, 13.8; HRMS (ESI) m/z calcd for $C_{19}H_{19}BrClN_2^+$, 389.0415, found 389.0421.

3-(2-Bromophenyl)-4-chloro-N-cyclohexylquinolin-2-amine (**5nf**). Yellow oil (172 mg, 83%): IR (KBr) 3433, 2924, 2362, 1609, 1507, 1410, 1339, 759, 701; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 8.0 Hz, 1H), 7.78−7.74 (m, 2H), 7.60−7.46 (m, 2H), 7.37−7.25 (m, 3H), 4.21−4.09 (m, 1H), 4.00 (br. s, 1H), 2.07−1.96 (m, 2H), 1.61−1.01 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 148.3, 140.8, 135.8, 133.6, 131.8, 130.4, 130.2, 128.4, 126.6, 124.5, 124.4, 123.0, 122.4, 121.2, 49.2, 33.1, 25.8, 24.8; HRMS (ESI) m/z calcd for $C_{21}H_{21}BrClN_2^+$, 415.0571, found 415.0575.

N-Benzyl-3-(2-bromophenyl)-4-chloroquinolin-2-amine (**5 ng**). Yellow solid (184 mg, 87%): mp 128−130 °C; IR (KBr) 3436, 2928, 2361, 1739, 1601, 1511, 1246, 751; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 8.0 Hz, 1H), 7.77−7.72 (m, 2H), 7.60−7.56 (m, 1H), 7.44 (t, J = 7.6 Hz, 1H), 7.31−7.18 (m, 8H), 4.84 (dd, J_1 = 6.0 Hz, J_2 = 15.2 Hz, 1H), 4.71 (dd, J = 6.0 Hz, J_2 = 15.2 Hz, 1H), 4.48 (br.s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 148.1, 141.2, 139.5, 135.5, 133.6, 131.7, 130.5, 130.4, 128.4, 128.4, 127.5, 127.0, 126.8, 124.5, 124.5, 122.9, 122.8, 121.5, 45.3; HRMS (ESI) m/z calcd for $C_{22}H_{17}BrClN_2^+$, 423.0258, found 423.0263.

3-(2-Bromophenyl)-4-chloro-N-(4-methoxyphenyl)quinolin-2-amine (**5nh**). White solid (175 mg, 80%): mp 132−134 °C; mp 134−136 °C; IR (KBr) 2970, 2361, 1731, 1665, 1475, 1369, 1135, 701; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 8.0 Hz, 1H), 7.71−7.64 (m, 2H), 7.50−7.34 (m, 4H), 7.23−7.19 (m, 3H), 6.72 (d, J = 9.2 Hz, 2H), 5.83 (br. s, 1H), 3.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 151.5, 147.5, 141.3, 135.2, 133.17, 132.9, 131.9, 130.7, 130.4, 128.5, 127.1, 124.5, 124.4, 123.6, 123.2, 122.1, 121.9, 113.9, 55.4; HRMS (ESI) m/z calcd for $C_{22}H_{17}BrClN_2O^+$, 439.0207, found 439.0213.

3-(2-Bromophenyl)-4-chloro-N-(2,6-dimethylphenyl)quinolin-2-amine (**5ni**). White solid (185 mg, 85%): mp 219−221 °C; IR (KBr) 3396, 2924, 2360, 1608, 1503, 1223, 754; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 8.4 Hz, 1H), 7.60−7.56 (m, 2H), 7.48−7.34 (m, 3H), 7.13 (s, 3H), 5.52 (br. s, 1H), 2.25 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 148.0, 141.4, 136.0, 135.9, 135.8, 133.7, 131.3, 130.7, 130.3, 128.6, 128.0, 127.2, 126.4, 124.7, 124.4, 123.2, 122.9, 121.7, 18.8; HRMS (ESI) m/z calcd for $C_{23}H_{19}BrClN_2^+$, 437.0415, found 437.0404.

4-Bromo-N-(tert-butyl)-3-phenylquinolin-2-amine (**6aa**). Light yellow oil (92 mg, 52%): IR (KBr) 3431, 2961, 1594, 1515, 1411, 1219, 756; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, J_1 = 1.2 Hz, J_1 = 8.4 Hz, 1H), 7.72 (d, J = 6.4 Hz, 1H), 7.57−7.51 (m, 3H), 7.48−7.46 (m, 1H), 7.29−7.26 (m, 3H), 4.22 (br. s, 1H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 147.7, 137.3, 133.5, 129.8, 129.7, 129.4, 128.6, 127.3, 127.1, 126.8, 122.6, 122.5, 52.0, 29.0; HRMS (ESI) m/z calcd for $C_{19}H_{20}BrN_2^+$, 355.0804, found 355.0797.

4-Bromo-N-(tert-butyl)-3-(4-methoxyphenyl)quinolin-2-amine (**6ba**). Yellow solid (136 mg, 71%): mp 91−93 °C; IR (KBr) 3428, 2961, 1593, 1514, 1109, 616; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, J_1 = 1.2 Hz, J_1 = 8.4 Hz, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.53−7.48 (m, 1H), 7.24−7.16 (m, 3H), 7.02 (d, J = 8.8 Hz, 2H), 4.30 (br. s, 1H), 3.84 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 154.7, 147.7, 133.9, 131.0, 129.7, 129.3, 127.3, 126.8, 126.7, 122.6, 122.5, 114.7,55.2, 51.9, 29.0; HRMS (ESI) m/z calcd for $C_{20}H_{22}BrN_2O^+$, 385.0910, found 385.0906.

4-Bromo-N-(tert-butyl)-3-(4-chlorophenyl)quinolin-2-amine (**6ca**). Light yellow solid (126 mg, 65%): mp 109−111 °C; IR (KBr) 3435, 2962, 1586, 1514, 1411, 1218, 755; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (dd, J_1 = 1.0 Hz, J_1 = 8.8 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.57−7.50 (m, 3H), 7.28−7.22 (m, 3H), 4.15 (br. s, 1H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 147.8, 135.7, 134.7, 133.8, 131.3, 130.0,129.7, 127.3, 126.8, 125.8, 122.8, 122.4, 52.1, 29.0; HRMS (ESI) m/z calcd for $C_{19}H_{19}BrClN_2^+$, 389.0415, found 389.0409.

4-Bromo-N-(tert-butyl)-3-(3-chlorophenyl)quinolin-2-amine (**6da**). Light yellow solid (107 mg, 55%): mp 100−102 °C; IR (KBr) 3435, 2979, 2362, 1764, 1243, 1054, 755; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (dd, J_1 = 1.2 Hz, J_1 = 8.4 Hz, 1H), 7.69 (d, J = 7.6 Hz, 1H), 7.53−7.49 (m, 1H), 7.45−7.39 (m, 2H), 7.27−7.20 (m, 2H), 7.13−7.11 (m, 1H), 4.09 (br. s, 1H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 139.0, 135.1, 133.8, 130.7, 130.1, 130.0, 128.9, 128.0, 127.3, 126.8, 125.6, 122.9, 122.3, 108.8, 52.2, 29.0; HRMS (ESI) m/z calcd for $C_{19}H_{19}BrClN_2^+$, 389.0415, found 389.0411.

4-Bromo-N-(tert-butyl)-3-(4-fluorophenyl)quinolin-2-amine (**6ea**). White solid (87 mg, 47%): mp 92−94 °C; IR (KBr) 3434, 2980, 2362, 1764, 1379, 1242, 1057, 755; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (dd, J_1 = 1.2 Hz, J_1 = 8.4 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.53−7.49 (m, 1H), 7.24−7.16 (m, 5H), 4.12 (br. s, 1H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7 (d, J = 247.0 Hz), 154.3,

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147.8, 133.9, 133.2 (d, J = 3.5 Hz), 131.7 (d, J = 8.1 Hz), 129.9, 127.3, 126.8, 126.0, 122.7, 122.4, 116.5 (d, J = 21.5 Hz), 52.0, 29.0; HRMS (ESI) m/z calcd for $C_{19}H_{19}BrFN_2^+$, 373.0710, found 373.0706.

Typical Experimental Procedure for Synthesis of 11-Chloro-6*H*-indolo[2,3-*b*]quinolines. To the mixture of 2-((2-bromophenyl)ethynyl)aniline (**1j**, 0.5 mmol), $PdCl_2$ (5 mol %) and LiCl (2.0 equiv) in DMSO were added successively in a test tube. After stirring for 5 min at room temperature, isocyanide (**2**, 0.6 mmol) was added, and then the mixture was stirred at 140 °C for 12 h under 1 atm of O_2. Upon completion, the reaction mixture was extracted with ethyl acetate (3 × 10 mL), and the organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Then $Pd_2(dba)_3$ (5 mol %), P(*o*-tol)$_3$ (10 mol %) and toluene (2.0 mL) were added to the residue and heated at 85 °C for further 12 h. Upon completion, the reaction mixture was extracted with ethyl acetate (3 × 10 mL), and the organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was separated by flash column chromatography (the eluents phases were pure hexane, and the stationary phases were 300−400 mesh silica gel) to give the pure products **7**.

*6-Butyl-11-chloro-6H-indolo[2,3-b]quinoline (**7a**).* White solid (131 mg, 85%): mp 132−134 °C; IR (KBr) 2970, 2361, 1731, 1665, 1475, 1369, 1135, 701; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, J = 7.6 Hz, 1H), 8.23 (d, J = 8.0 Hz, 1H), 7.98 (d, J = 8.4 Hz, 1H), 7.58 (t, J = 7.2 Hz, 1H), 7.44−7.34 (m, 2H), 7.23 (d, J = 8.0 Hz, 1H), 7.18−7.14 (m, 1H), 4.33 (t, J = 7.6 Hz, 2H), 1.81−1.73 (m, 2H), 1.34−1.25 (m, 2H), 0.84 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 146.9, 142.1, 135.3, 129.1, 128.3, 127.8, 124.2, 123.9, 123.4, 122.2, 120.0, 119.8, 115.3, 108.7, 41.2, 30.5, 20.3, 13.8; HRMS (ESI) m/z calcd for $C_{19}H_{18}ClN_2^+$, 309.1153, found 309.1149.

*6-(tert-Butyl)-11-chloro-6H-indolo[2,3-b]quinoline (**7b**).* Yellow solid (128 mg, 83%): mp 99−101 °C; IR (KBr) 2991, 2362, 1765, 1391, 1243, 1054, 748; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (d, J = 7.6 Hz, 1H), 8.40 (d, J = 8.0 Hz, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.73−7.70 (m, 1H), 7.54−7.49 (m, 2H), 7.30 (t, J = 7.6 Hz, 1H), 2.14 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 146.0, 142.8, 134.5, 128.9, 128.4, 127.8, 124.3, 123.7, 123.6, 121.8, 121.1, 119.5, 115.7, 113.2, 60.3, 30.6; HRMS (ESI) m/z calcd for $C_{19}H_{18}ClN_2^+$, 309.1153, found 309.1161.

*11-Chloro-6-cyclohexyl-6H-indolo[2,3-b]quinoline (**7c**).* Light yellow solid (134 mg, 80%): mp 203−205 °C; IR (KBr) 3847, 3737, 2924, 2357, 1553, 1463, 1249, 742; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, J = 8.0 Hz, 1H), 8.41 (d, J = 8.4 Hz, 1H), 8.12 (d, J = 8.4 Hz, 1H), 7.75−7.71 (m, 1H), 7.64 (d, J = 8.4 Hz, 1H), 7.59−7.50 (m, 2H), 7.33−7.29 (m, 1H), 5.14 (br. s, 1H), 2.63−2.54 (m, 2H), 1.98−1.37 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 146.7, 141.6, 135.3, 129.2, 128.0, 128.0, 124.4, 123.9, 123.6, 122.1, 120.3, 119.7, 115.5, 110.7, 53.7, 30.1, 26.3, 25.7; HRMS (ESI) m/z calcd for $C_{22}H_{20}ClN_2^+$, 335.1285, found 335.1310.

*6-Benzyl-11-chloro-6H-indolo[2,3-b]quinoline (**7d**).* Light yellow solid (140 mg, 82%): mp 178−180 °C; IR (KBr) 3745, 2362, 1743, 1555, 1465, 1403, 1244, 744, 692; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, J = 8.0 Hz, 1H), 8.33 (d, J = 8.4 Hz, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.67−7.63 (m, 1H), 7.47−7.38 (m, 2H), 7.22−7.11 (m, 7H), 5.63 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 147.0, 142.0, 137.0, 135.6, 129.3, 128.6, 128.5, 128.0, 127.4, 127.2, 124.2, 124.0, 123.7, 122.5, 120.5, 120.0, 115.5, 109.4, 45.0; HRMS (ESI) m/z calcd for $C_{22}H_{16}ClN_2^+$, 343.0997, found 343.0981.

*11-Chloro-6-(4-methoxyphenyl)-6H-indolo[2,3-b]quinoline (**7e**).* Yellow solid (141 mg, 79%): mp 227−229 °C; IR (KBr) 3849, 3734, 2355, 2324, 1745, 1515, 1244, 611; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, J = 8.0 Hz, 1H), 8.43 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.71−7.67 (m, 1H), 7.59−7.51 (m, 4H), 7.39−7.36 (m, 2H), 7.14 (d, J = 8.8 Hz, 2H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 152.6, 147.00, 143.1, 135.8, 130.9, 129.3, 129.0, 128.6, 128.4, 124.2, 124.0, 123.9, 122.8, 121.0, 120.0, 115.7, 115.0, 109.9, 55.6; HRMS (ESI) m/z calcd for $C_{22}H_{16}ClN_2O^+$, 359.0946, found 359.0941.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra for all products and the crystallographic data of **3ka** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Andries, K.; Verhasselt, P.; Guillemont, J.; Göhlmann, H. W. H.; Neefs, J.; Winkler, H.; Gestel, J. V.; Timmerman, P.; Zhu, M.; Lee, E.; Williams, P.; de Chaffoy, D.; Huitric, E.; Hoffner, S.; Cambau, E.; Truffot-Pernot, C.; Lounis, N.; Jarlier, V. *Science* **2005**, *307*, 223. (b) Bax, B. D.; Chan, P. F.; Eggleston, D. S.; Fosberry, A.; Gentry, D. R.; Gorrec, F.; Giordano, I.; Hann, M. M.; Hennessy, A.; Hibbs, M.; Huang, J.; Jones, E.; Jones, J.; Brown, K. K.; Lewis, C. J.; May, E. W.; Saunders, M. R.; Singh, O.; Spitzfaden, C. E.; Shen, C.; Suhillings, A.; Theobald, A. J.; Wohlkonig, A.; Pearson, N. D.; Gwynn, M. N. *Nature* **2010**, *466*, 935.

(2) For classical methods on quinoline synthesis, see: (a) Marco-Contelles, J.; Pérez-Mayoral, E.; Samadi, A.; Carreiras, M.; do, C.; Soriano, E. *Chem. Rev.* **2009**, *109*, 2652. (b) Cheng, C.; Yan, S. *Org. React.* **1982**, *28*, 37. (c) Wu, Y.; Liu, L.; Li, H.; Wang, D.; Chen, Y. *J. Org. Chem.* **2006**, *71*, 6592. (d) Akbari, J.; Heydari, A.; Kalhor, H. R.; Kohan, S. A. *J. Comb. Chem.* **2010**, *12*, 137. (e) Manske, R. H. F.; Kukla, M. *Org. React.* **1953**, *7*, 59. (f) Reitsema, R. H. *Chem. Rev.* **1948**, *43*, 43. (g) Bergstrom, F. W. *Chem. Rev.* **1944**, *35*, 77.

(3) For selected recent examples, see: (a) Xia, X.; Zhang, L.; Song, X.; Liu, X.; Liang, Y. *Org. Lett.* **2012**, *14*, 2480. (b) Ali, S.; Zhu, H.; Xia, X.; Ji, K.; Yang, Y.; Song, X.; Liang, Y. *Org. Lett.* **2011**, *13*, 2598. (c) Gao, G.; Niu, Y.; Yan, Z.; Wang, H.; Wang, G.; Shaukat, A.; Liang, Y. *J. Org. Chem.* **2010**, *75*, 1305. (d) Matsubara, Y.; Hirakawa, S.; Yamaguchi, Y.; Yoshida, Z. *Angew. Chem., Int. Ed.* **2011**, *50*, 7670. (e) Cao, K.; Zhang, F.; Tu, Y.; Zhuo, X.; Fan, C. *Chem.—Eur. J.* **2009**, *15*, 6332.

(4) Selected recent examples: (a) Ji, X.; Huang, H.; Li, Y.; Chen, H.; Jiang, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 7292. (b) Wang, Y.; Chen, C.; Peng, J.; Li, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 5323. (c) Zhang, X.; Song, X.; Li, H.; Zhang, S.; Chen, X.; Yu, X.; Wang, W. *Angew. Chem., Int. Ed.* **2012**, *51*, 7282. (d) Kulkarni, A.; Török, B. *Green Chem.* **2010**, *12*, 875.

(5) (a) Cheng, Y.; Judd, T. C.; Bartberger, M. D.; Brown, J.; Chen, K.; Fremeau, R. T.; Hickman, D., Jr.; Hitchcock, S. A.; Jordan, B.; Li, V.; Lopez, P.; Louie, S. W.; Luo, Y.; Michelsen, K.; Nixey, T.; Powers, T. S.; Rattan, C.; Sickmier, E. A.; Jean, D. J. S.; Wahl, R. C., Jr.; Wen, P. H.; Wood, S. *J. Med. Chem.* **2011**, *54*, 5836. (b) Takenaka, N.; Chen, J.; Captain, B.; Sarangthem, R. S.; Chandrakumar, A. *J. Am. Chem. Soc.* **2010**, *132*, 4536. (c) He, C.; Hao, J.; Xu, H.; Mo, Y.; Liu, H.; Han, J.; Lei, A. *Chem. Commun.* **2012**, *48*, 11073. (d) Inglis, S. R.; Jones, R. K.; Booker, G. W.; Pyke, S. M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 387.

(6) (a) Tomioka, T.; Takahashi, Y.; Maejima, T. *Org. Biomol. Chem.* **2012**, *10*, 5113. (b) Yin, J.; Xiang, B.; Huffman, M. A.; Raab, C. E.; Davies, I. W. *J. Org. Chem.* **2007**, *72*, 4554.
(7) (a) Payne, J. T.; Andorfer, M. C.; Lewis, J. C. *Angew. Chem., Int. Ed.* **2013**, *52*, 5271. (b) Sun, X.; Shan, G.; Sun, Y.; Rao, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 4440. (c) Wan, X.; Ma, Z.; Li, B.; Zhang, K.; Cao, S.; Zhang, S.; Shi, Z. *J. Am. Chem. Soc.* **2006**, *128*, 7416. (d) Andrews, S.; Burgess, S. J.; Skaalrud, D.; Kelly, J. X.; Peyton, D. H. *J. Med. Chem.* **2010**, *53*, 916.
(8) For selected reviews, see: (a) Gulevich, A. V.; Zhdanko, A. G.; Orru, R. V. A.; Nenajdenko, V. G. *Chem. Rev.* **2010**, *110*, 5235. (b) Lygin, A. V.; de Meijere, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 9094. (c) Dömling, A. *Chem. Rev.* **2006**, *106*, 17. (d) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168. (e) Nair, V.; Rajesh, C.; Vinod, A. U.; Bindu, S.; Sreekanth, A. R.; Mathen, J. S.; Balagopal, L. *Acc. Chem. Res.* **2003**, *36*, 899.
(9) For recent examples on palladium-catalyzed processes to synthesis of *N*-containing heterocycles involving isocyanide insertion, see: (a) Bochatay, V. N.; Boissarie, P. J.; Murphy, J. A.; Suckling, C. J.; Lang, S. *J. Org. Chem.* **2013**, *78*, 1471. (b) Wang, Y.; Zhu, Q. *Adv. Synth. Catal.* **2012**, *354*, 1902. (c) Nanjo, T.; Tsukano, C.; Takemoto, Y. *Org. Lett.* **2012**, *14*, 4270. (d) Tobisu, M.; Imoto, S.; Ito, S.; Chatani, N. *J. Org. Chem.* **2010**, *75*, 4835. (e) Miura, T.; Nishida, Y.; Morimoto, M.; Yamauchi, M.; Murakami, M. *Org. Lett.* **2011**, *13*, 1429. (f) Curran, D. P.; Du, W. *Org. Lett.* **2002**, *4*, 3215. (g) Vlaar, T.; Cioc, R. C.; Mampuys, P.; Maes, B. U. W.; Orru, R. V. A.; Ruijter, E. *Angew. Chem., Int. Ed.* **2012**, *51*, 13058. (h) Wang, Y.; Wang, H.; Peng, J.; Zhu, Q. *Org. Lett.* **2011**, *13*, 4604. (i) Hu, Z.; Liang, D.; Zhao, J.; Huang, J.; Zhu, Q. *Chem. Commun.* **2012**, *48*, 7371. (j) Qiu, G.; Chen, C.; Yao, L.; Wu, J. *Adv. Synth. Catal.* **2013**, *355*, 1579.
(10) For selected reviews, see: (a) Stahl, S. S. *Science* **2005**, *309*, 1824. (b) Liu, G.; Yin, G.; Wu, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 4733. (c) Wu, W.; Jiang, H. *Acc. Chem. Res.* **2012**, *45*, 1736.
(11) (a) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875. (b) Shiri, M. *Chem. Rev.* **2012**, *112*, 3508. (c) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2011**, *111*, PR215. (d) Xu, C.; Murugan, V. K.; Pullarkat, S. A. *Org. Biomol. Chem.* **2012**, *10*, 3875. (e) Gabriele, B.; Veltri, L.; Mancuso, R.; Salerno, G.; Costa, M. *Eur. J. Org. Chem.* **2012**, *2012*, 2549. (f) Guo, Y.; Tang, R.; Li, J.; Zhong, P.; Zhang, X. *Adv. Synth. Catal.* **2009**, *351*, 2615. (g) Kondo, Y.; Shiga, F.; Murata, N.; Sakamoto, T.; Yamanaka, H. *Tetrahedron* **1994**, *50*, 11803. (h) Han, X.; Lu, X. *Org. Lett.* **2010**, *12*, 3336.
(12) (a) Jiang, H.; Liu, B.; Li, Y.; Wang, A.; Huang, H. *Org. Lett.* **2011**, *13*, 1028. (b) Liu, B.; Li, Y.; Jiang, H.; Yin, M.; Huang, H. *Adv. Synth. Catal.* **2012**, *354*, 2288. (c) Li, Y.; Zhao, J.; Chen, H.; Liu, B.; Jiang, H. *Chem. Commun.* **2012**, *48*, 3545. (d) Liu, B.; Li, Y.; Yin, M.; Wu, W.; Jiang, H. *Chem. Commun.* **2012**, *48*, 11446. (e) Liu, B.; Yin, M.; Gao, H.; Wu, W.; Jiang, H. *J. Org. Chem.* **2013**, *78*, 3009.
(13) (a) Pan, X.; Luo, Y.; Wu, J. *Chem. Commun.* **2011**, *47*, 8967. (b) Pan, X.; Luo, Y.; Wu, J. *Org. Biomol. Chem.* **2012**, *10*, 1969. (c) Abbiati, G.; Arcadi, A.; Canevari, V.; Capezzuto, L.; Rossi, E. *J. Org. Chem.* **2005**, *70*, 6454. (d) Arcadi, A.; Aschi, M.; Marinelli, F.; Verdecchia, M. *Tetrahedron* **2008**, *64*, 5354. (e) Toriia, S.; Okumotoa, H.; Xua, L. H.; Sadakanea, M.; Shostakovskyb, M. V.; Ponomaryovb, A. B.; Kalininb, V. N. *Tetrahedron* **1993**, *49*, 6773. (f) Schmittel, M.; Steffen, J.-P.; Rodríguez, D.; Engelen, B.; Neumann, E.; Cinar, M. E. *J. Org. Chem.* **2008**, *73*, 3005. (g) Alajarín, M.; Bonillo, B.; Vidal, Á.; Bautista, D. *J. Org. Chem.* **2008**, *73*, 291. (h) Du, W.; Curran, D. P. *Org. Lett.* **2003**, *5*, 1765. (i) Jonckers, T. H. M.; van Miert, S.; Cimanga, K.; Bailly, C.; Colson, P.; De Pauw-Gillet, M.-C.; van den Heuvel, H.; Claeys, M.; Lemière, F.; Esmans, E. L.; Rozenski, J.; Quirijnen, L.; Maes, L.; Dommisse, R.; Lemière, G. L. F.; Vlietinck, A.; Pieters, L. *J. Med. Chem.* **2002**, *45*, 3497.
(14) The influence of chloride ion content on halopalladation, see: (a) Ma, S.; Lu, X. *J. Org. Chem.* **1991**, *56*, 5120. (b) Wang, Z.; Lu, X. *Tetrahedron Lett.* **1997**, *38*, 5213.
(15) The crystallographic data of **3ka** was deposited at the Cambridge Crystallographic Data Centre and the allocated the deposition number is 936575. For more details, see the Supporting Information.
(16) The major byproducts detected by GC−MS were 3-bromo-2-phenyl-1*H*-indole, 2-phenyl-1*H*-indole.
(17) (a) Mei, Z.; Wang, L.; Lu, W.; Pang, C.; Maeda, T.; Peng, W.; Kaiser, M.; Sayed, I. E.; Inokuchi, T. *J. Med. Chem.* **2013**, *56*, 1431. (b) Sidoryk, K.; Świtalska, M.; Wietrzyk, J.; Jaromin, A.; Piętka-Ottlik, M.; Cmoch, P.; Zagrodzka, J.; Szczepek, W.; Klaczmarek, Ł.; Peczyńska-Czoch, W. *J. Med. Chem.* **2012**, *55*, 5077.
(18) (a) Ali, S.; Li, Y.; Anwar, S.; Yang, F.; Chen, Z.; Liang, Y.-M. *J. Org. Chem.* **2012**, *77*, 424. (b) Hostyn, S.; Baelen, G. V.; Lemière, G. L. F.; Maes, B. U. W. *Adv. Synth. Catal.* **2008**, *350*, 2653. (c) Sundaram, G. S. M.; Venkatesh, C.; Kumar, U. K. S.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2004**, *69*, 5760. (d) Parvatkar, P. T.; Parameswaran, P. S.; Tilve, S. G. *J. Org. Chem.* **2009**, *74*, 8369. (e) Gupta, S.; Kumar, B.; Kundu, B. *J. Org. Chem.* **2011**, *76*, 10154.
(19) (a) Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 15914. (b) Shen, Q.; Hartwig, J. F. *Org. Lett.* **2008**, *10*, 4109.
(20) (a) Rodriguez, A. L.; Koradin, C.; Dohle, W.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 2488. (b) Tang, S.; Yu, Q.; Peng, P.; Li, J.; Zhong, P.; Tang, R. *Org. Lett.* **2007**, *9*, 3413. (c) Shen, Z.; Lu, X. *Adv. Synth. Catal.* **2009**, *351*, 3107.