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An expeditious approach to 1-aminoisoquinolines via an unexpected reaction of 2-alkynylbenzaldoxime, carbodiimide, with bromine

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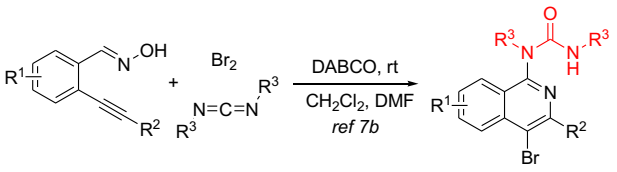
ABSTRACT

A three-component reaction of 2-alkynylbenzaldoxime, carbodiimide, and bromine provides a novel and efficient approach to functionalized 1-aminoisoquinolines. This unexpected reaction proceeds through electrophilic cyclization, [3+2] cycloaddition, rearrangement and hydrolyzation.

1. Introduction

Isoquinolines are ubiquitous features in many nature products and small molecule chemotherapeutics.[1] Among the family of isoquinolines, 1-aminoisoquinolines have attracted less attention although remarkable biological activities have been displayed for this kind of compound. For instance, it was reported that 1-aminoisoquinolines could serve as selective inhibitors of mutant protein kinase and anti-tumor reagents.[2] They are also valuable intermediates in organic synthesis, since they are easily converted into functionalized isoquinolines. So far, several methods have appeared for the formation of 1-aminoisoquinoline derivatives, such as substitutional reaction of 1-haloisoquinolines by amines,[3] or transition metal-catalyzed cross-coupling reactions of 1-haloisoquinolines with amines.[4] However, the methods usually required high temperature, strong base, or expensive metal catalysts. Additionally, toxic compounds, such as $POCl_3$ are inevitable for 1-haloisoquinolines formation,[5] which restricts the generation of a collection of structurally complex and diverse 1-aminoisoquinolines. Recently Londregan and co-workers reported the synthesis of 2-aminopyridines through the phosphonium salt activated reaction of pyridine-*N*-oxide with amine.[6] In this reaction, one example was presented for the generation of 1-aminoisoquinoline under the standard conditions. However, this method required the utilization of large amount of phosphonium salt to promote the reaction with the corresponding *N*-oxides. Thus, development of novel and efficient routes under mild conditions for the preparation of functionalized 1-aminoisoquinolines is highly desirable.

Recently, we reported an efficient pathway for the generation of 1-(isoquinolin-1-yl)ureas[7a] via three-component reaction of 2-alkynylbenzaldoxime, carbodiimide, with electrophile (bromine or iodine monochloride) under mild conditions (Scheme 1).[7b] The reaction proceeded smoothly at room temperature in the presence of DABCO as a base in CH_2Cl_2/DMF. Only a trace amount of product was detected without the addition of base when the reaction was performed in CH_2Cl_2. The desired product could be isolated as well when DMF was used as the co-solvent, along with a new product with a trace amount. In this reaction, we conceived that the presence of a base or Lewis base (such as DMF) served as a scavenging agent of HX (X=Br or Cl). However, what was the new product formed simultaneously? With these considerations in mind, thus we started to explore the possibility of this transformation.



Scheme 1. Three-component reaction of 2-alkynylbenzaldoxime, carbodiimide, and bromine.

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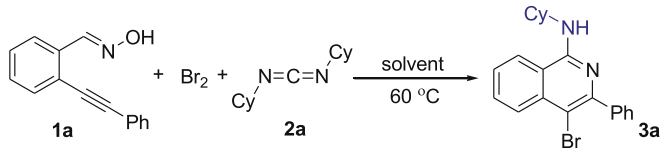
2. Results and discussion

The initial attempt was carried out with the three-component reaction of 2-alkynylbenzaldoxime **1a**, carbodiimide **2a**, and bromine (Table 1). When dichloroethane (DCE) was utilized as the co-solvent in the reaction at room temperature, to our surprise, we did not obtain the desired 1-(isoquinolin-1-yl)urea product. The new compound was generated, whereas in low yield (8%), and the structure was identified as 1-aminoisoquinoline **3a**. The yield increased to 52% when the reaction occurred at 60 °C. With this interesting result in hand, we further screened other solvents. It was found that the reaction worked the most efficiently when 1,4-dioxane was used as the co-solvent, which generated compound **3a** in 86% yield (Table 1, entry 7). Although it is no doubt that 1-aminoisoquinoline **3a** was furnished via hydrolyzation of the corresponding 1-(isoquinolin-1-yl)urea,[8] this reaction provides a novel and expeditious approach to 1-aminoisoquinolines with high efficiency under mild conditions. Additionally, heavy metal salts and harsh reaction conditions are avoided compared with previous reports.[3,4] In the reaction process, we reasoned that HBr generated in situ might play the key role for the hydrolyzation of 1-(isoquinolin-1-yl)urea. Usually, high temperature or oxidant is required for cleavage of ureas.[8,9] It seems that the advantage of the mild conditions presented here is clear, which provides an alternative route for hydrolysis of ureas.

Table 1
Initial studies for the synthesis of 1-aminoisoquinoline **3a** via three-component reaction of 2-alkynylbenzaldoxime **1a**, carbodiimide **2a**, and bromine

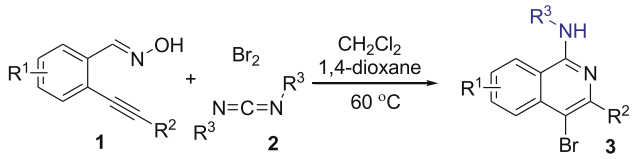


Entry	Solvent	Yield (%)[a]
1	CH_2Cl_2/DMF	Trace
2	CH_2Cl_2/DCE	52
3	CH_2Cl_2/THF	60
4	CH_2Cl_2/MeCN	24
5	CH_2Cl_2/$CHCl_3$	61
6	CH_2Cl_2/1,4-dioxane	86

[a] Isolated yield based on 2-alkynylbenzaldoxime **1a**.

We next applied the optimized reaction conditions (CH_2Cl_2/1,4-dioxane, 60 °C) to a variety of 2-alkynylbenzaldoxime **1** (Table 2). All reactions worked well to generate the desired 1-aminoisoquinolines **3** in good to excellent yields. Not only *N*-((cyclohexylimino)methylene)-cyclohexanamine **2a** but also *N*-((isopropylimino)methylene)-propan-2-amine **2b** was suitable partner in the transformation. For instance, 5-fluoro-substituted 2-alkynylbenzaldoxime **1b** reacted with carbodiimide **2a** leading to the corresponding 1-aminoisoquinolines **3c** in 98% yield (Table 2, entry 3). Compound **3d** was afforded in 80% yield when carbodiimide **2b** was employed in the above reaction (Table 2, entry 4). As mentioned in our previous reports,[7b] the reaction proceeded through intramolecular electrophilic cyclization first to produce the bromo-containing isoquinoline-*N*-oxide intermediate, which then underwent further [3+2] cycloaddition reaction. Thus, 2-alkynylbenzaldoximes with electron-donating group attached on the aromatic ring would diminish the reactivity. As expected, a low yield was observed for the reaction of methoxy-substituted 2-alkynylbenzaldoxime **1f**, carbodiimide **2a**, with bromine (41% yield, Table 2, entry 11). We next examined the reactions of 2-alkynylbenzaldoximes **1** with different groups attached to the C≡C triple bond. No big difference was displayed for the substrates with aryl or alkyl group (such as cyclopropyl group) attached on the position.

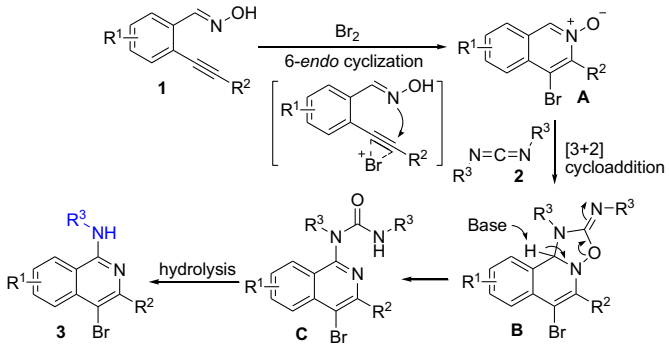
Table 2
Synthesis of 1-aminoisoquinoline **3** via three-component reaction of 2-alkynylbenzaldoxime **1**, carbodiimide **2**, and bromine



Entry	R^1, R^2	R^3	Yield (%)[a]
1	H, Ph (**1a**)	Cy (**2a**)	86 (**3a**)
2	H, Ph (**1a**)	*i*-Pr (**2b**)	63 (**3b**)
3	5-F, Ph (**1b**)	Cy (**2a**)	98 (**3c**)
4	5-F, Ph (**1b**)	*i*-Pr (**2b**)	80 (**3d**)
5	4-F, Ph (**1c**)	Cy (**2a**)	78 (**3e**)
6	4-F, Ph (**1c**)	*i*-Pr (**2b**)	68 (**3f**)
7	5-Cl, Ph (**1d**)	Cy (**2a**)	77 (**3g**)
8	5-Cl, Ph (**1d**)	*i*-Pr (**2b**)	94 (**3h**)
9	5-Me, Ph (**1e**)	Cy (**2a**)	66 (**3i**)
10	5-Me, Ph (**1e**)	*i*-Pr (**2b**)	72 (**3j**)
11	4-OMe, Ph (**1f**)	Cy (**2a**)	41 (**3k**)
12	H, 4-ClC_6H_4 (**1g**)	Cy (**2a**)	82 (**3l**)
13	H, 4-ClC_6H_4 (**1g**)	*i*-Pr (**2b**)	70 (**3m**)
14	H, 4-MeC_6H_4 (**1h**)	Cy (**2a**)	68 (**3n**)
15	H, 4-MeC_6H_4 (**1h**)	*i*-Pr (**2b**)	65 (**3o**)
16	H, 4-$MeOC_6H_4$ (**1i**)	*i*-Pr (**2b**)	52 (**3p**)
17	5-F, 4-MeC_6H_4 (**1j**)	Cy (**2a**)	86 (**3q**)
18	5-F, 4-MeC_6H_4 (**1j**)	*i*-Pr (**2b**)	89 (**3r**)
19	4-F, 4-MeC_6H_4 (**1k**)	Cy (**2a**)	77 (**3s**)
20	4-F, 4-MeC_6H_4 (**1k**)	*i*-Pr (**2b**)	67 (**3t**)
21	5-Cl, cyclopropyl (**1l**)	Cy (**2a**)	94 (**3u**)
22	5-Cl, cyclopropyl (**1l**)	*i*-Pr (**2b**)	99 (**3v**)
23	5-F, cyclopropyl (**1m**)	Cy (**2a**)	86 (**3w**)
24	5-F, cyclopropyl (**1m**)	*i*-Pr (**2b**)	85 (**3x**)
25	4-F, cyclopropyl (**1n**)	Cy (**2a**)	77 (**3y**)
26	4-F, cyclopropyl (**1n**)	*i*-Pr (**2b**)	77 (**3z**)

[a] Isolated yield based on 2-alkynylbenzaldoxime **1**.

The possible mechanism was described in Scheme 2. As previous report,[7b] 4-bromoisoquinoline-*N*-oxide **A** would be formed from the reaction of 2-alkynylbenzaldoxime **1** with bromine via 6-*endo* cyclization. Then, 4-bromoisoquinoline-*N*-oxide **A** reacted with carbodiimide **2** via [3+2] cycloaddition giving rise to the key intermediate **B**, which underwent an intramolecular rearrangement to afford 4-bromo-1-(isoquinolin-1-yl)urea **C**. The subsequent hydrolyzation of 4-bromo-1-(isoquinolin-1-yl)urea **C** furnished the 1-aminoisoquinoline **3**.



Scheme 2. Possible mechanism for 1-aminoisoquinoline **3** generation.

3. Conclusions

In conclusion, we have described a novel and efficient route for the synthesis of 1-amino-4-bromoisoquinolines via three-

component reaction of 2-alkynylbenzaldoxime, carbodiimide, and bromine. This method provides an excellent complement for the 1-aminoisoquinoline generation. Moreover, the preparation of diverse 1-aminoisoquinolines could be expected since further decorations through palladium-catalyzed cross-coupling reactions are known. The advantages of this method, which include high efficiency, good substrate generality, mild reaction conditions, and experimental ease will prompt us for the further library construction.

4. Experimental section

4.1. General procedure for the synthesis of 1-aminoisoquinoline 3 via a three-component reaction of 2-alkynylbenzaldoxime 1, carbodiimide 2, and bromine

2-Alkynylbenzaldoxime **1** (0.2 mmol) was added to a solution of bromine (0.20 mmol) in CH_2Cl_2 (0.5 mL). After stirred at room temperature for 10 min, carbodiimide **2** (0.5 mmol) was added followed by 1,4-dioxane (2.0 mL). The mixture was stirred at 60 °C. After completion of the reaction as indicated by TLC (overnight), the reaction was quenched with aqueous NH_4Cl (10 mL, 1.0 M), extracted with EtOAc (2×10 mL), dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by purification on silica gel provided the product **3**.

*4.1.1. 4-Bromo-N-cyclohexyl-3-phenylisoquinolin-1-amine (**3a**).* Yellow solid; melting point: 93.4–93.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20–1.32 (m, 3H), 1.38–1.48 (m, 2H), 1.62–1.68 (m, 1H), 1.74–1.78 (m, 2H), 2.15 (dd, J=2.9, 11.7 Hz, 2H), 4.15–4.24 (m, 1H), 5.13 (d, J=6.9 Hz, 1H), 7.37–7.49 (m, 4H), 7.65–7.73 (m, 2H), 7.78–7.89 (m, 2H), 8.22 (d, J=8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9, 25.9, 33.2, 49.4, 104.6, 118.5, 121.2, 126.1, 127.5, 127.6, 127.8, 130.1, 130.6, 136.6, 141.7, 150.1, 152.8; HRMS (ESI) calcd for $C_{21}H_{21}BrN_2$: 381.0966 (M+H$^+$), found: 381.0961.

*4.1.2. 4-Bromo-N-isopropyl-3-phenylisoquinolin-1-amine (**3b**).* White solid; melting point: 71.9–72.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (d, J=6.2 Hz, 6H), 4.48–4.51 (m, 1H), 5.07 (d, J=6.6 Hz, 1H), 7.37–7.52 (m, 4H), 7.67–7.73 (m, 2H), 7.78 (d, J=8.4 Hz, 2H), 8.23 (d, J=8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.9, 42.7, 104.8, 118.4, 121.3, 126.2, 127.5, 127.6, 127.8, 130.1, 130.6, 136.6, 141.7, 150.2, 152.8; HRMS (ESI) calcd for $C_{18}H_{17}BrN_2$: 341.0653 (M+H$^+$), found: 341.0666.

*4.1.3. 4-Bromo-N-cyclohexyl-7-fluoro-3-phenylisoquinolin-1-amine (**3c**).* Yellow solid; melting point: 118.0–118.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22–1.32 (m, 3H), 1.37–1.46 (m, 2H), 1.62–1.66 (m, 1H), 1.73–1.77 (m, 2H), 2.14 (d, J=3.3, 12.4 Hz, 2H), 4.13–4.21 (m, 1H), 4.92 (d, J=7.3 Hz, 1H), 7.33–7.46 (m,5H), 7.77 (d, J=6.9 Hz, 2H), 8.22 (dd, J=5.8, 9.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9, 25.9, 33.1, 49.6, 104.2, 105.8 (d, $^2J_{CF}$=21.4 Hz), 119.0 (d, $^3J_{CF}$=6.9 Hz), 120.0 (d, $^2J_{CF}$=23.7 Hz), 127.5, 127.9, 130.1, 130.5 (d, $^3J_{CF}$=8.4 Hz), 133.5, 141.3, 149.5 (d, $^4J_{CF}$=2.3 Hz), 152.2 (d, $^4J_{CF}$=3.8 Hz), 160.7 (d, $^1J_{CF}$=247.3 Hz); HRMS (ESI) calcd for $C_{21}H_{20}BrFN_2$: 399.0872 (M+H$^+$), found: 399.0854.

*4.1.4. 4-Bromo-7-fluoro-N-isopropyl-3-phenylisoquinolin-1-amine (**3d**).* Yellow solid; melting point: 146.7–147.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (d, J=6.6 Hz, 6H), 4.45–4.49 (m, 1H), 4.87 (d, J=6.9 Hz, 1H), 7.34–7.46 (m, 5H), 7.77 (d, J=8.8 Hz, 2H), 8.24 (dd, J=5.5, 9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8, 42.9, 104.3, 105.9 (d, $^2J_{CF}$=21.4 Hz), 119.0 (d, $^3J_{CF}$=6.9 Hz), 120.1 (d, $^2J_{CF}$=23.7 Hz), 127.6, 127.9, 130.0, 130.5 (d, $^3J_{CF}$=8.4 Hz), 133.5, 141.4, 149.6 (d, $^4J_{CF}$=3.1 Hz), 152.3 (d, $^4J_{CF}$=3.8 Hz), 160.8 (d, $^1J_{CF}$=247.3 Hz); HRMS (ESI) calcd for $C_{18}H_{16}BrFN_2$: 359.0559 (M+H$^+$), found: 359.0562.

*4.1.5. 4-Bromo-N-cyclohexyl-6-fluoro-3-phenylisoquinolin-1-amine (**3e**).* White solid; melting point: 93.7–94.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21–1.32 (m, 3H), 1.38–1.46 (m, 2H), 1.62–1.66 (m, 1H), 1.72–1.77 (m, 2H), 2.14 (dd, J=3.3, 12.1 Hz, 2H), 4.14–4.20 (m, 1H), 5.08 (d, J=7.3 Hz, 1H), 7.19 (dt, J=2.6, 8.4 Hz, 1H), 7.36–7.47 (m, 3H), 7.10 (dd, J=5.1, 9.1 Hz, 1H), 7.77 (d, J=6.9 Hz, 2H), 7.96 (dd, J=2.2, 10.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9, 25.8, 33.2, 49.5, 103.6 (d, $^4J_{CF}$=4.6 Hz), 112.1 (d, $^2J_{CF}$=23.7 Hz), 115.2, 115.4 (d, $^2J_{CF}$=24.4 Hz), 124.3 (d, $^3J_{CF}$=9.9 Hz), 127.5, 128.0, 130.0, 139.0 (d, $^3J_{CF}$=9.9 Hz), 141.4, 151.4, 152.6, 163.9 (d, $^1J_{CF}$=248.8 Hz); HRMS (ESI) calcd for $C_{21}H_{20}BrFN_2$: 399.0872 (M+H$^+$), found: 399.0869.

*4.1.6. 4-Bromo-6-fluoro-N-isopropyl-3-phenylisoquinolin-1-amine (**3f**).* Yellow solid; melting point: 84.1–84.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (d, J=6.5 Hz, 6H), 4.47–4.51 (m, 1H), 5.02 (d, J=6.9 Hz, 1H), 7.20 (dt, J=2.6, 8.4 Hz, 1H), 7.38–7.47 (m, 3H), 7.73 (dd, J=5.5, 9.2 Hz, 1H), 7.77 (d, J=7.7 Hz, 2H), 7.88 (dd, J=2.6, 10.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8, 42.8, 103.8 (d, $^4J_{CF}$=4.6 Hz), 112.1 (d, $^2J_{CF}$=23.7 Hz), 115.2, 115.5 (d, $^2J_{CF}$=24.4 Hz), 124.4 (d, $^3J_{CF}$=9.9 Hz), 127.5, 128.0, 129.9, 138.9 (d, $^3J_{CF}$=9.9 Hz), 141.4, 151.5, 152.7, 163.9 (d, $^1J_{CF}$=248.8 Hz); HRMS (ESI) calcd for $C_{18}H_{16}BrFN_2$: 359.0559 (M+H$^+$), found: 359.0550.

*4.1.7. 4-Bromo-7-chloro-N-cyclohexyl-3-phenylisoquinolin-1-amine (**3g**).* Yellow solid; melting point: 53.6–54.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21–1.31 (m, 3H), 1.37–1.46 (m, 2H), 1.62–1.67 (m, 1H), 1.72–1.78 (m, 2H), 2.13 (dd, J=3.3, 12.4 Hz, 2H), 4.12–4.20 (m, 1H), 5.01 (d, J=7.3 Hz, 1H), 7.35–7.46 (m, 4H), 7.57 (dd, J=1.8, 9.2 Hz, 1H), 7.67 (d, J=1.8 Hz, 1H), 7.77 (d, J=6.6 Hz, 1H), 8.14 (d, J=8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9, 25.8, 30.1, 49.6, 104.0, 119.0, 120.7, 126.5, 127.5, 128.0, 129.5, 130.0, 131.1, 135.1, 141.2, 150.5, 151.8; HRMS (ESI) calcd for $C_{21}H_{20}BrClN_2$: 415.0577 (M+H$^+$), found: 415.0580.

*4.1.8. 4-Bromo-7-chloro-N-isopropyl-3-phenylisoquinolin-1-amine (**3h**).* Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (d, J=6.2 Hz, 6H), 4.46–4.50 (m, 1H), 4.97 (d, J=6.9 Hz, 1H), 7.37–7.47 (m, 3H), 7.60 (dd, J=1.8, 9.2 Hz, 1H), 7.70 (d, J=1.8 Hz, 1H), 7.77 (d, J=8.4 Hz, 2H), 8.16 (d, J=9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8, 42.9, 104.2, 119.0, 120.7, 127.5, 128.0, 129.5, 130.0, 131.1, 131.9, 135.1, 141.3, 150.5, 151.9; HRMS (ESI) calcd for $C_{18}H_{16}BrClN_2$: 375.0264 (M+H$^+$), found: 375.0260.

*4.1.9. 4-Bromo-N-cyclohexyl-7-methyl-3-phenylisoquinolin-1-amine (**3i**).* Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25–1.32 (m, 3H), 1.38–1.46 (m, 2H), 1.63–1.68 (m, 1H), 1.74–1.79 (m, 2H), 2.16 (dd, J=3.3, 12.1 Hz, 2H), 2.53 (s, 3H), 4.16–4.22 (m, 1H), 5.07 (d, J=6.9 Hz, 1H), 7.36–7.40 (m, 1H), 7.42–7.51 (m, 4H), 7.79 (d, J=8.4 Hz, 2H), 8.11 (d, J=8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 24.9, 25.9, 33.2, 49.4, 104.7, 118.5, 120.6, 127.4, 127.5, 127.7, 130.1, 132.4, 134.7, 136.2, 141.7, 146.9, 152.4; HRMS (ESI) calcd for $C_{22}H_{23}BrN_2$: 395.1123 (M+H$^+$), found: 395.1112.

*4.1.10. 4-Bromo-N-isopropyl-7-methyl-3-phenylisoquinolin-1-amine (**3j**).* Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (d, J=6.6 Hz, 6H), 2.53 (s, 3H), 4.47–4.51 (m, 1H), 5.01 (d, J=6.6 Hz, 1H), 7.35–7.39 (m, 1H), 7.42–7.46 (m, 2H), 7.49–7.53 (m, 2H), 7.78 (d, J=8.4 Hz, 2H), 8.11 (d, J=8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 22.9, 42.7, 104.8, 118.5, 120.6, 127.4, 127.5, 127.7, 130.1, 132.4, 134.6, 136.2, 141.7, 149.1, 152.4; HRMS (ESI) calcd for $C_{19}H_{19}BrN_2$: 355.0810 (M+H$^+$), found: 355.0810.

*4.1.11. 4-Bromo-N-cyclohexyl-6-methoxy-3-phenylisoquinolin-1-amine (**3k**).* White solid; melting point: 211.4–212.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23–1.31 (m, 3H), 1.38–1.47 (m, 2H), 1.63–1.67 (m, 1H), 1.73–1.78 (m, 2H), 2.14 (dd, J=2.9, 12.1 Hz, 2H), 3.97 (s, 3H), 4.14–4.22 (m, 1H), 5.01 (d, J=7.3 Hz, 1H), 7.09 (dd, J=2.6, 9.2 Hz, 1H), 7.37–7.47 (m, 3H), 7.55 (d, J=2.6 Hz, 1H), 7.64 (d, J=9.2 Hz, 1H), 7.77 (d, J=6.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9, 25.9, 33.3, 49.4,

55.5, 104.3, 106.8, 113.1, 117.6, 123.3, 127.5, 127.8, 130.1, 138.7, 141.5, 150.9, 152.7, 161.4; HRMS (ESI) calcd for $C_{22}H_{23}BrN_2O$: 411.1072 ($M+H^+$), found: 411.1069.

*4.1.12. 4-Bromo-3-(4-chlorophenyl)-N-cyclohexylisoquinolin-1-amine (**3l**).* Yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 1.22–1.32 (m, 3H), 1.34–1.48 (m, 2H), 1.62–1.68 (m, 1H), 1.73–1.78 (m, 2H), 2.13 (dd, J=2.9, 12.1 Hz, 2H), 4.12–4.20 (m, 1H), 7.41 (d, J=8.4 Hz, 2H), 7.47 (dt, J=1.1, 7.5 Hz, 1H), 7.66–7.75 (m, 4H), 8.21 (d, J=8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9, 25.9, 33.1, 49.5, 104.6, 118.5, 121.3, 126.4, 127.6, 127.7, 130.7, 131.5, 133.7, 136.5, 140.1, 148.8, 152.8; HRMS (ESI) calcd for $C_{21}H_{20}BrClN_2$: 415.0577 ($M+H^+$), found: 415.0581.

*4.1.13. 4-Bromo-3-(4-chlorophenyl)-N-isopropylisoquinolin-1-amine (**3m**).* Yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 1.31 (d, J=6.6 Hz, 6H), 4.44–4.49 (m, 1H), 5.10 (d, J=6.2 Hz, 1H), 7.41 (d, J=8.4 Hz, 2H), 7.50 (dt, J=1.1, 7.5 Hz, 1H), 7.67–7.75 (m, 4H), 8.22 (d, J=8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8, 42.8, 104.7, 118.5, 121.3, 126.4, 127.6, 127.7, 130.7, 131.5, 133.7, 136.5, 140.1, 148.9, 152.9; HRMS (ESI) calcd for $C_{18}H_{16}BrClN_2$: 375.0264 ($M+H^+$), found: 375.0268.

*4.1.14. 4-Bromo-N-cyclohexyl-3-p-tolylisoquinolin-1-amine (**3n**).* Yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 1.22–1.31 (m, 3H), 1.37–1.48 (m, 2H), 1.62–1.66 (m, 1H), 1.72–1.77 (m, 2H), 2.15 (dd, J=3.3, 12.1, 2H), 2.42 (s, 3H), 4.16–4.22 (m, 1H), 5.12 (d, J=6.9 Hz, 1H), 7.26 (d, J=8.4 Hz, 2H), 7.46 (t, J=7.7 Hz, 1H), 7.65–7.71 (m, 4H), 8.21 (d, J=8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 24.9, 25.9, 33.2, 49.4, 104.5, 118.4, 121.2, 126.0, 127.5, 128.2, 130.0, 130.5, 136.7, 137.6, 138.8, 150.1, 152.7; HRMS (ESI) calcd for $C_{22}H_{23}BrN_2$: 395.1123 ($M+H^+$), found: 395.1131.

*4.1.15. 4-Bromo-N-isopropyl-3-p-tolylisoquinolin-1-amine (**3o**).* White solid; melting point: 89.2–89.6 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 1.31 (d, J=6.6 Hz, 6H), 2.42 (s, 3H), 4.48–4.52 (m, 1H), 5.06 (d, J=6.6 Hz, 1H), 7.26 (d, J=8.1 Hz, 2H), 7.47 (dt, J=1.1, 4.7 Hz, 1H), 7.65–7.71 (m, 4H), 8.22 (d, J=8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 22.9, 42.7, 104.7, 118.4, 121.2, 126.1, 127.6, 128.3, 130.0, 130.5, 136.6, 137.6, 138.9, 150.2, 152.8; HRMS (ESI) calcd for $C_{19}H_{19}BrN_2$: 355.0810 ($M+H^+$), found: 355.0798.

*4.1.16. 4-Bromo-N-isopropyl-3-(4-methoxyphenyl)isoquinolin-1-amine (**3p**).* White solid; melting point: 101.7–102.2 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (d, J=6.6 Hz, 6H), 3.87 (s, 3H), 4.50–4.54 (m, 1H), 5.06 (d, J=6.6 Hz, 1H), 6.98 (d, J=8.8 Hz, 2H), 7.47 (dt, J=1.1, 7.5 Hz, 1H), 7.66–7.72 (m, 2H), 7.78 (d, J=8.8 Hz, 2H), 8.22 (d, J=8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.9, 42.7, 55.2, 104.5, 112.9, 118.3, 121.3, 126.0, 127.5, 130.5, 131.5, 134.2, 136.7, 149.7, 152.7, 159.3; HRMS (ESI) calcd for $C_{19}H_{19}BrN_2O$: 371.0759 ($M+H^+$), found: 371.0758.

*4.1.17. 4-Bromo-N-cyclohexyl-7-fluoro-3-p-tolylisoquinolin-1-amine (**3q**).* Yellow solid; melting point: 61.2–62.2 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 1.22–1.31 (m, 3H), 1.36–1.47 (m, 2H), 1.62–1.67 (m, 1H), 1.72–1.77 (m, 2H), 2.14 (dd, J=3.3, 12.1 Hz, 2H), 2.42 (s, 3H), 4.12–4.20 (m, 1H), 4.90 (d, J=6.9 Hz, 1H), 7.26 (d, J=8.1 Hz, 2H), 7.34 (dd, J=2.2, 9.5 Hz, 1H), 7.41 (dt, J=2.2, 8.6 Hz, 1H), 7.68 (d, J=8.1 Hz, 2H), 8.22 (dd, J=5.5, 9.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 24.9, 25.9, 33.1, 49.6, 104.0, 105.8 (d, $^2J_{CF}$=21.4 Hz), 118.9 (d, $^3J_{CF}$=6.9 Hz), 120.0 (d, $^2J_{CF}$=23.7 Hz), 128.3, 130.0, 130.4 (d, $^3J_{CF}$=8.4 Hz), 133.6, 137.7, 138.5, 149.5, 152.2 (d, $^4J_{CF}$=4.6 Hz), 160.7 (d, $^1J_{CF}$=247.3 Hz); HRMS (ESI) calcd for $C_{22}H_{22}BrFN_2$: 413.1029 ($M+H^+$), found: 413.1035.

*4.1.18. 4-Bromo-7-fluoro-N-isopropyl-3-p-tolylisoquinolin-1-amine (**3r**).* White solid; melting point: 76.5–77.2 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 1.30 (d, J=6.2 Hz, 6H), 2.41 (s, 3H), 4.45–4.49 (m, 1H), 4.85 (d, J=6.9 Hz, 1H), 7.26 (d, J=8.1 Hz, 2H), 7.34 (dd, J=2.2, 9.6 Hz, 1H), 7.42 (dt, J=2.6, 8.6 Hz, 1H), 7.67 (d, J=8.0 Hz, 2H), 8.23 (dd, J=5.5, 9.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 22.8, 42.8, 104.2, 105.8 (d, $^2J_{CF}$=21.4 Hz), 118.9 (d, $^3J_{CF}$=6.9 Hz), 120.0 (d, $^2J_{CF}$=23.6 Hz), 128.3, 129.9, 130.4 (d, $^3J_{CF}$=8.4 Hz), 133.5, 137.7, 138.5, 149.6 (d, $^4J_{CF}$=2.3 Hz), 152.2 (d, $^4J_{CF}$=3.8 Hz), 160.7 (d, $^1J_{CF}$=247.3 Hz); HRMS (ESI) calcd for $C_{19}H_{18}BrFN_2$: 373.0716 ($M+H^+$), found: 373.0706.

*4.1.19. 4-Bromo-N-cyclohexyl-6-fluoro-3-p-tolylisoquinolin-1-amine (**3s**).* Yellow solid; melting point: 54.7–55.3 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 1.21–1.29 (m, 3H), 1.36–1.47 (m, 2H), 1.62–1.66 (m, 1H), 1.72–1.77 (m, 2H), 2.13 (dd, J=3.3, 12.1 Hz, 2H), 2.42 (s, 3H), 4.14–4.22 (m, 1H), 5.06 (d, J=6.9 Hz, 1H), 7.17 (dt, J=2.6, 8.4 Hz, 1H), 7.26 (d, J=8.0 Hz, 2H), 7.67–7.72 (m, 3H), 7.85 (dd, J=2.6, 11.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 24.9, 25.8, 33.2, 49.5, 103.5 (d, $^4J_{CF}$=3.8 Hz), 112.0 (d, $^2J_{CF}$=23.6 Hz), 115.1, 115.3 (d, $^2J_{CF}$=24.4 Hz), 124.3 (d, $^3J_{CF}$=9.9 Hz), 128.3, 129.9, 137.9, 138.5, 139.0 (d, $^3J_{CF}$=9.9 Hz), 151.4, 152.6, 163.8 (d, $^1J_{CF}$=248.8 Hz); HRMS (ESI) calcd for $C_{22}H_{22}BrFN_2$: 413.1029 ($M+H^+$), found: 413.1032.

*4.1.20. 4-Bromo-6-fluoro-N-isopropyl-3-p-tolylisoquinolin-1-amine (**3t**).* White solid; melting point: 118.5–119.0 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 1.30 (d, J=6.2 Hz, 6H), 2.42 (s, 3H), 4.47–4.51 (m, 1H), 5.00 (d, J=6.9 Hz, 1H), 7.19 (dt, J=2.6, 8.4 Hz, 1H), 7.26 (d, J=8.4 Hz, 2H), 7.68 (d, J=8.1 Hz, 2H), 7.71 (dd, J=5.1, 8.8 Hz, 1H), 7.86 (dd, J=2.6, 11.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 22.8, 42.8, 103.7, 112.1 (d, $^2J_{CF}$=23.7 Hz), 115.1, 115.3 (d, $^2J_{CF}$=24.4 Hz), 124.3 (d, $^3J_{CF}$=9.9 Hz), 128.3, 129.9, 137.9, 138.6, 139.0 (d, $^3J_{CF}$=9.9 Hz), 151.5, 152.6, 163.9 (d, $^1J_{CF}$=248.8 Hz); HRMS (ESI) calcd for $C_{19}H_{18}BrFN_2$: 373.0716 ($M+H^+$), found: 373.0721.

*4.1.21. 4-Bromo-7-chloro-N-cyclohexyl-3-cyclopropylisoquinolin-1-amine (**3u**).* Yellow solid; melting point: 74.7–75.3 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 0.90–0.95 (m, 2H), 1.09–1.12 (m, 2H), 1.19–1.28 (m, 3H), 1.38–1.49 (m, 2H), 1.65–1.69 (m, 1H), 1.75–1.79 (m, 2H), 2.08 (dd, J=2.9, 12.1 Hz, 2H), 2.56–2.64 (m, 1H), 3.92–4.00 (m, 1H), 4.89 (d, J=6.9 Hz, 1H), 7.50 (dd, J=1.8, 8.8 Hz, 1H), 7.57 (d, J=2.2 Hz, 1H), 7.97 (d, J=9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.0, 16.0, 25.0, 25.9, 33.0, 50.0, 104.5, 118.4, 120.6, 128.2, 130.5, 130.8, 134.6, 151.8, 152.3; HRMS (ESI) calcd for $C_{18}H_{20}BrClN_2$: 379.0577 ($M+H^+$), found: 379.0585.

*4.1.22. 4-Bromo-7-chloro-3-cyclopropyl-N-isopropylisoquinolin-1-amine (**3v**).* Yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 0.92–0.96 (m, 2H), 1.10–1.14 (m, 2H), 1.28 (d, J=6.1 Hz, 6H), 2.59–2.64 (m, 1H), 4.27–4.30 (m, 1H), 4.84 (d, J=6.6 Hz, 1H), 7.51 (dd, J=1.8, 8.8 Hz, 1H), 7.58 (d, J=1.8 Hz, 1H), 7.98 (d, J=9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.1, 16.0, 22.7, 42.9, 104.7, 118.4, 120.6, 128.2, 130.5, 130.8, 134.6, 151.9, 152.3; HRMS (ESI) calcd for $C_{15}H_{16}BrClN_2$: 339.0264 ($M+H^+$), found: 339.0265.

*4.1.23. 4-Bromo-N-cyclohexyl-3-cyclopropyl-7-fluoroisoquinolin-1-amine (**3w**).* Yellow solid; melting point: 102.5–102.9 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 0.90–0.94 (m, 2H), 1.08–1.12 (m, 2H), 1.20–1.30 (m, 3H), 1.39–1.49 (m, 2H), 1.65–1.69 (m, 1H), 1.75–1.79 (m, 2H), 2.09 (dd, J=3.3, 12.4 Hz, 2H), 2.57–2.64 (m, 1H), 3.93–4.00 (m, 1H), 4.79 (d, J=5.8 Hz, 1H), 7.24 (dd, J=2.6, 9.5 Hz, 1H), 7.35 (dt, J=2.2, 8.6 Hz, 1H), 8.05 (dd, J=5.5, 9.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.8, 15.8, 25.0, 25.9, 33.1, 50.0, 104.6, 105.7 (d, $^2J_{CF}$=21.0 Hz), 118.2, 119.7 (d, $^2J_{CF}$=23.8 Hz), 129.1 (d, $^3J_{CF}$=7.6 Hz), 133.1, 151.1 (d, $^4J_{CF}$=1.9 Hz), 152.2 (d, $^4J_{CF}$=4.8 Hz), 160.0 (d, $^1J_{CF}$=245.0 Hz); HRMS (ESI) calcd for $C_{18}H_{20}BrFN_2$: 363.0872 ($M+H^+$), found: 363.0879.

*4.1.24. 4-Bromo-3-cyclopropyl-7-fluoro-N-isopropylisoquinolin-1-amine (**3x**).* Yellow solid; melting point: 82.2–82.9 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 0.91–0.95 (m, 2H), 1.10–1.14 (m, 2H), 1.28 (d, J=6.2 Hz, 6H), 2.58–2.65 (m, 1H), 4.28–4.31 (m, 1H), 4.73 (d, J=6.2 Hz, 1H), 7.24 (dd, J=2.6, 9.5 Hz, 1H), 7.35 (dt, J=2.6, 8.6 Hz, 1H), 8.06 (dd, J=5.5, 9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.9,

15.9, 22.8, 42.9, 104.8, 105.7 (d, $^2J_{CF}$=21.4 Hz), 118.3 (d, $^3J_{CF}$=6.9 Hz), 119.8 (d, $^2J_{CF}$=24.4 Hz), 129.1 (d, $^3J_{CF}$=8.4 Hz), 133.1, 151.1 (d, $^4J_{CF}$=2.3 Hz), 152.3 (d, $^4J_{CF}$=4.6 Hz), 160.0 (d, $^1J_{CF}$=245.0 Hz); HRMS (ESI) calcd for $C_{15}H_{16}BrFN_2$: 323.0559 ($M+H^+$), found: 323.0544.

*4.1.25. 4-Bromo-N-cyclohexyl-3-cyclopropyl-6-fluoroisoquinolin-1-amine (**3y**).* Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91–0.95 (m, 2H), 1.10–1.14 (m, 2H), 1.18–1.30 (m, 3H), 1.39–1.49 (m, 2H), 1.65–1.70 (m, 1H), 1.75–1.80 (m, 2H), 2.09 (dd, *J*=2.9, 12.1 Hz, 2H), 2.57–2.62 (m, 1H), 3.94–4.02 (m, 1H), 4.95 (d, *J*=6.6 Hz, 1H), 7.06 (dt, *J*=2.6, 8.6 Hz, 1H), 7.60 (dd, *J*=5.5, 9.2 Hz, 1H), 7.68 (dd, *J*=2.6, 11.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.1, 16.2, 25.0, 25.9, 33.1, 50.0, 104.2 (d, $^4J_{CF}$=3.8 Hz), 110.8 (d, $^2J_{CF}$=23.7 Hz), 114.1 (d, $^2J_{CF}$=24.4 Hz), 114.7, 124.2 (d, $^3J_{CF}$=9.2 Hz), 138.4 (d, $^3J_{CF}$=9.9 Hz), 152.6, 153.3, 163.8 (d, $^1J_{CF}$=248.8 Hz); HRMS (ESI) calcd for $C_{18}H_{20}BrFN_2$: 363.0872 ($M+H^+$), found: 363.0879.

*4.1.26. 4-Bromo-3-cyclopropyl-6-fluoro-N-isopropylisoquinolin-1-amine (**3z**).* White solid; melting point: 130.8–131.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92–0.97 (m, 2H), 1.12–1.16 (m, 2H), 1.28 (d, *J*=6.6 Hz, 6H), 2.58–2.63 (m, 1H), 4.28–4.32 (m, 1H), 4.88 (d, *J*=6.2 Hz, 1H), 7.07 (dt, *J*=2.6, 8.6 Hz, 1H), 7.61 (dd, *J*=5.5, 9.2 Hz, 1H), 7.69 (dd, *J*=2.6, 11.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.2, 16.2, 22.8, 42.8, 104.3 (d, $^4J_{CF}$=4.6 Hz), 110.8 (d, $^2J_{CF}$=23.6 Hz), 114.1 (d, $^2J_{CF}$=24.4 Hz), 114.7, 124.2 (d, $^3J_{CF}$=9.2 Hz), 138.4 (d, $^3J_{CF}$=9.9 Hz), 152.7, 153.4, 163.8 (d, $^1J_{CF}$=248.8 Hz); HRMS (ESI) calcd for $C_{15}H_{16}BrFN_2$: 323.0559 ($M+H^+$), found: 323.0547.

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.04.063. This data include MOL file and InChiKey of the most important compound described in this article.

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