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Facile synthesis of 1-aminoisoquinolines via the tandem reactions of 2-alkynylbenzaldoximes with isothiocyanates

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ABSTRACT

A new, concise, and efficient route for the synthesis of 1-aminoisoquinolines in good to excellent yields is described; this involves the reaction of 2-alkynylbenzaldoximes and isothiocyanates, which is catalyzed by silver triflate in dichloromethane, at room temperature. This transformation involves tandem 6-*endo* cyclization, [3+2] cycloaddition, and subsequent rearrangement. The simple operational protocol provides a cost-effective, diversity-oriented route to 1-aminoisoquinolines under neutral, mild conditions.

1. Introduction

1-Aminoisoquinolines are important templates for medical applications; they demonstrate diverse pharmacological activities, including anti-malarial, anti-tumor, and anti-cancer activity.[1–14] These compounds are typically synthesized from the corresponding 1-halideisoquinolines, using substitutional reactions, or transition metal-catalyzed cross-coupling reactions.[15–24] The main disadvantage of these approaches is the need for harsh reaction conditions, including high temperatures, strong bases, or expensive metal catalysts. Recently, Wei et al. successfully prepared 1-aminoisoquinolines via the Rh(III)-catalyzed oxidative coupling of *N*-aryl and *N*-alkyl benzamidines with alkynes.[25] Most recently, Wu's group reported the efficient synthesis of 1-aminoisoquinolines via the reaction of 2-alkynylbenzaldoximes with simple amines,[26] isocyanides,[27] or carbodiimides.[28,29] Some drawbacks of these methods are the high costs associated with the use of $[RhCp^*Cl_2]_2$ or PyBroP as reagents, the potential imidazole or indole byproducts, and the lack of availability of carbodiimides. More general, cost-effective, and viable routes are therefore still desirable, in view of the broad range of applications of 1-aminoisoquinolines in biology and chemistry.

2. Results and discussion

Herein, we introduce our recent findings concerning the synthesis of 1-aminoisoquinolines, which was achieved via the tandem electrophilic cyclization—[3+2] cycloaddition—rearrangement reactions of 2-alkynylbenzaldoximes with isothiocyanates.

As part of our drug discovery program, we were interested in constructing a focused library of isoquinolines. The reaction of 2-alkynylbenzaldoxime has proved to be a reliable tool for the formation of highly substituted heterocyclic systems;[30–39] isoquinoline-*N*-oxide can be easily obtained from 2-alkynylbenzaldoxime, via 6-*endo* cyclization catalyzed by Lewis acids, or promoted by electrophiles. We therefore expected that 2-oxo isothiocyanates would be a suitable partner in the reaction of 2-alkynylbenzaldoxime **1**. As illustrated in Scheme 1, in the presence of a silver (I) catalyst, isoquinoline-*N*-oxide compound **A** would react with 2-oxo isothiocyanates, leading to the corresponding fused 1, 2-dihydroisoquinoline compound **B**.

To verify the feasibility of the hypothesis as shown in Scheme 1, our investigations commenced with the model reaction of 2-(phenylethynyl)benzaldehyde oxime **1a** (1.0 equiv) and methyl 2-isothiocyanatoacetate **2a** (1.2 equiv) (Table 1). Since silver triflate has been demonstrated as the most efficient catalyst for the formation of isoquinoline-*N*-oxide via the 6-*endo* cyclization of 2-alkynylbenzaldoxime,[40–44] the reaction was carried out in the presence of 10 mol % of silver triflate in dichloromethane, at room temperature. The product was isolated with a yield of 66% when the

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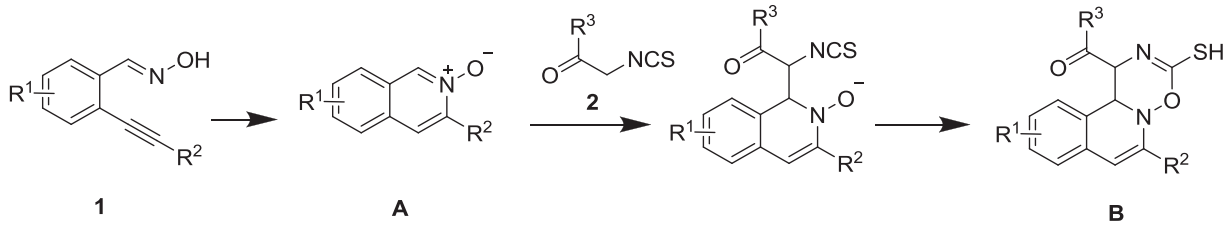
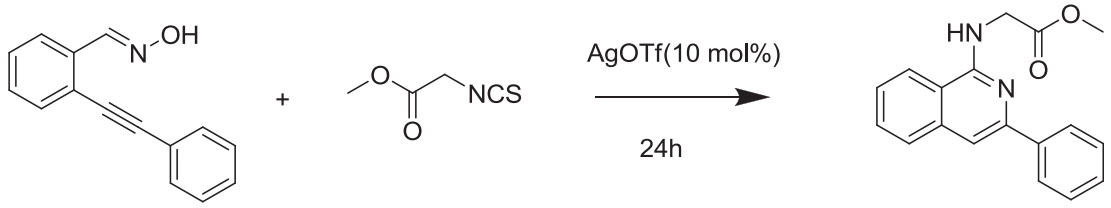


Scheme 1. Proposed synthetic route for the silver triflate-catalyzed reaction of 2-alkynylbenzaldoxime with isothiocyanates.

Table 1
Optimization of reaction conditions



Entry	Base	Solvent	Yield (%)[a]
1	K_2CO_3	CH_2Cl_2	66
2	$NaHCO_3$	CH_2Cl_2	73
3	DBU	CH_2Cl_2	45
4	Et_3N	CH_2Cl_2	65
5	NaOAc	CH_2Cl_2	68
6	K_3PO_4	CH_2Cl_2	55
7	—	CH_2Cl_2	87
8	—	Tetrahydrofuran	59
9	—	Acetonitrile	32
10	—	Ethanol	25
11	—	Toluene	40
12	—	Dioxane	32
13	—	*N*,*N*-Dimethylformamide	15

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

reaction took place in the presence of potassium carbonate (2.0 equiv) (Table 1, entry 1). Unexpectedly, further screening of bases indicated that the reaction worked most efficiently without any base, giving rise to a product yield of 87% (Table 1, entry 7). Next, several organic solvents were tested, including tetrahydrofuran, acetonitrile, and dioxane. These experiments revealed that dichloromethane was the optimal solvent; the use of other solvents resulted in lower yields (Table 1, entries 8–13). However, identification by X-ray diffraction analysis showed that this product had the structure shown here as compound **3a**, rather than the desired structure (**B**) (Fig. 1). These results illustrated the convenient and effective synthesis of 1-aminoisoquinolines, which belong to a very important class of heterocyclic compounds.

With these optimized reaction conditions established [AgOTf (10 mol %), DCM, room temperature], we were interested in determining the substrate scope of our process; the results are shown in Table 2. It was found that, in most cases, this reaction furnished the corresponding isoquinoline compounds **3** with good to excellent yields. Substitutions, including different groups on the aromatic ring or the triple bond of the 2-alkynylbenzaldoximes, were well tolerated. For example, the reaction of benzaldehyde oxime **1b**–**1g** with 2-isothiocyanatoacetate **2a** or **2b** generated the desired product **3b**–**3h** with a yield of 75–90% (Table 2, entries 2–8). Moreover, the reaction of 2-alkynylbenzaldoxime **1b** with benzyl isothiocyanate **2c** also proceeded smoothly, and generated the corresponding product **3i** (Table 2, entry 9). Importantly, the reaction is not restricted to the use of alkyl isothiocyanatoacetates, but can be extended to substituted aromatic isothiocyanatoacetates (Table 2, entry 10). A good chemical yield (81%) was observed in the reaction of aromatic isothiocyanatoacetate **2e**, which bears an electron-withdrawing group (Table 2, entry 11), although a lower yield (67%) was produced by **2f** with a methyl group (Table 2, entry 12). Furthermore, varying the substitutions on the triple bond or in the aromatic ring of the 2-alkynylbenzaldehydes **1** still provided

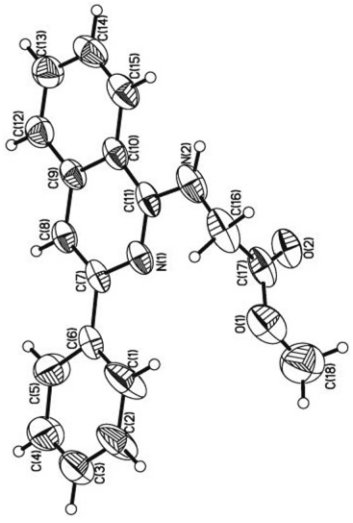
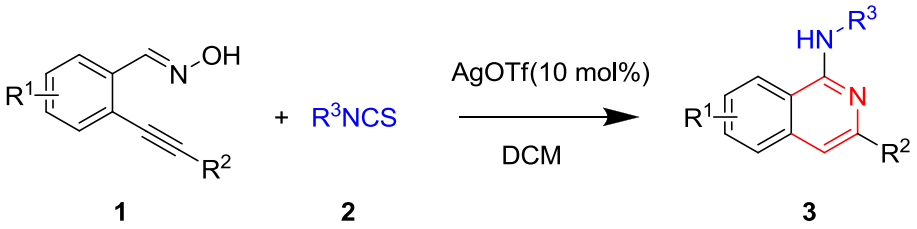


Fig. 1. Single crystal X-ray structure of 1-aminoisoquinoline **3a**.

Table 2
Silver triflate-catalyzed reaction of 2-alkynylbenzaldoxime **1** with isothiocyanates **2**



1 **2** **3**

Entry	R^1, R^2	R^3	Product	Yield (%)[a]
1	H, C_6H_5(**1a**)	CH_3OCOCH_2(**2a**)	**3a**	87
2	4-F, C_6H_5(**1b**)	CH_3OCOCH_2(**2a**)	**3b**	81
3	4,5-$(OMe)_2$, C_6H_5(**1c**)	CH_3OCOCH_2(**2a**)	**3c**	89
4	H, cyclopropyl(**1d**)	CH_3OCOCH_2(**2a**)	**3d**	78
5	H, *n*-Bu(**1e**)	CH_3OCOCH_2(**2a**)	**3e**	82
6	4-F, *n*-Bu(**1f**)	CH_3OCOCH_2(**2a**)	**3f**	75
7	H, *n*-Bu(**1e**)	$CH_3CH_2OCOCH_2$(**2b**)	**3g**	85
8	4-F,H(**1g**)	$CH_3CH_2OCOCH_2$(**2b**)	**3h**	90
9	4-F, C_6H_5(**1b**)	$C_6H_4CH_2$ (**2c**)	**3i**	74
10	H, C_6H_5(**1a**)	C_6H_5(**2d**)	**3j**	78
11	H, C_6H_5(**1a**)	4-Cl-3-$CF_3C_6H_3$(**2e**)	**3k**	81
12	H, C_6H_5(**1a**)	3-$CH_3C_6H_4$(**2f**)	**3l**	67
13	4-F, C_6H_5(**1b**)	C_6H_5(**2d**)	**3m**	77
14	4,5-$(OMe)_2$, C_6H_5(**1c**)	4-Cl-3-$CF_3C_6H_3$(**2e**)	**3n**	92
15	4-F, *n*-Bu(**1f**)	C_6H_5(**2d**)	**3o**	85
16	4-F, *n*-Bu(**1f**)	4-Cl-3-$CF_3C_6H_3$(**2e**)	**3p**	87
17	4-F, cyclopropyl(**1h**)	C_6H_5(**2d**)	**3q**	78
18	H, *n*-Bu(**1e**)	C_6H_5(**2d**)	**3r**	75
19	4-F,H(**1g**)	C_6H_5(**2d**)	**3s**	62
20	4-F,$SiMe_3$(**1i**)	C_6H_5(**2d**)	**3t**	Complicated
21	5-NO_2, cyclopropyl(**1j**)	C_6H_5(**2d**)	**3u**	Trace
22	5-NO_2, C_6H_5 (**1k**)	C_6H_5(**2d**)	**3v**	-[b]

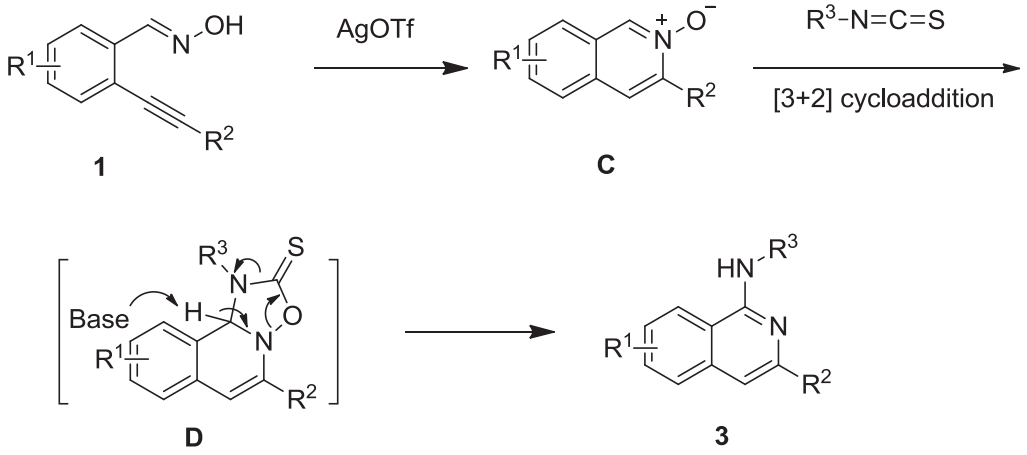
[a] Isolated yield based on 2-alkynylbenzaldoxime **1a**.
[b] No desired product.

satisfactory yields (Table 2, entries 13–19). When the trimethylsilyl group was attached on the triple bond, the reaction was complicated (Table 2, entry 20). Either no or only a trace amount of desired product was detected when the R^1 group was changed to 5-NO_2 group (Table 2, entries 21–22). Compared with the methods described in the literature, this method has two main, significant advantages; (1) it is low-cost, with simple experimental procedures, and good substrate generality, and (2) it uses neutral, mild conditions. A wide variety of functions can be readily accommodated, and diverse structures can be easily introduced.

A possible mechanism for the domino reaction to quinolines is suggested in Scheme 2. In the first step of the reaction, 2-alkynylbenzaldoxime **1** would be cyclized to isoquinoline *N*-oxides **C** in the presence of silver triflate.[31,33] Subsequently, isoquinoline *N*-oxides would react with isothiocyanate **2** via [3+2] cycloaddition, leading to the key intermediate **D**.[44,45] After base-promoted intramolecular rearrangement, the corresponding 1-aminoisoquinolines would be generated.[28,39,43]

3. Conclusion

To conclude, we have successfully developed a new approach for the preparation of 1-aminoisoquinolines via the treatment of 2-alkynylbenzaldoximes with isothiocyanates, in the presence of



1 **C** **D** **3**

Scheme 2. Proposed synthetic route for the reaction of 2-alkynylbenzaldoxime **1** with isothiocyanates **2**.

AgOTf, under very mild conditions. We believe that this method provides an excellent complement to the suite of 1-aminoisoquinoline synthesis methods. The advantages of this method lie not only in its neutral reaction conditions and high yields, but also in its economical use of reagents in simple procedures.

4. Experimental section

4.1. General conditions

Solvents and reagents were obtained from commercial sources, and were used without purification. Column chromatography was carried out on silica gel (200–300 mesh). Melting points were obtained on a Yanaco-241 apparatus, and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 300 MHz or 500 MHz spectrometer, using TMS as an internal standard. The chemical proton shifts were reported in parts per million (ppm) downfield from tetramethylsilane. Coupling constants are reported in Hertz (Hz). HRMS (ESI) data were determined using a Waters Q-Tof mirco™ HPLC/MS instrument.

4.2. General procedure for synthesis of 3a–3s

2-Alkynylbenzaldoxime **1** (0.30 mmol), isothiocyanates **2** (0.36 mmol) were added to a solution of AgOTf (0.03 mmol) in DCM (2.0 mL), then stirred for 24 h at room temperature. The mixture was purified using silica gel column chromatography (EtOAc/hexane) to obtain the desired product **3**.

4.3. Characterization

*4.3.1. Methyl 2-(3-phenylisoquinolin-1-ylamino)acetate (**3a**).* White solid; mp 158–159 °C. H NMR (500 MHz, $CDCl_3$) δ 8.14(d, J=7.5 Hz, 2H), 7.91 (s, 1H), 7.77 (d, J=8.1 Hz, 1H), 7.62 (t, J=7.4 Hz, 1H), 7.46–7.51 (m, 4H), 7.27(s, 1H), 5.86(s, 1H), 4.53(d, J=4.9 Hz, 2H), 3.84(s, 3H), 1.54(s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.18, 153.75, 137.91, 129.99, 128.44, 128,19, 127.54, 126.53, 125.92, 121.71, 117.41, 107.73, 52.16, 43.88; HRMS (ESI) calcd for $C_{18}H_{17}N_2O_2$: 293.1285($M+H^+$), found: 293.1277.

*4.3.2. Methyl 2-(6-fluoro-3-phenylisoquinolin-1-ylamino)acetate (**3b**).* White solid; mp 178–179 °C. ^{1}H *NMR* (300 MHz, $CDCl_3$) δ 8.10 (d, J=8.4 Hz, 2H), 7.85–7.82 (m, 1H), 7.44–7.50 (m, 2H), 7.32–7.41 (m, 2H), 7.26–7.39 (m, 1H), 7.09–7.15(m, 1H), 6.02(s, 1H), 4.48(d, J=5.1 Hz, 2H), 3.83(s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.21, 163.35 (d, $^1J_{CF}$=248.6 Hz), 153.69, 139.83 (d, $^3J_{CF}$=10.1 Hz), 129.92, 128.51, 127.67, 126.63, 124.72, 115.47 (d, $^2J_{CF}$=24.6 Hz), 114.34(d, $^2J_{CF}$=20.5 Hz), 107.34(d, $^2J_{CF}$=3.5 Hz), 52.25, 43.86; HRMS (ESI) calcd for $C_{18}H_{16}FN_2O_2$: 311.1190 ($M+H^+$), found: 311.1181.

*4.3.3. Methyl 2-((6,7-dimethoxy-3-phenylisoquinolin-1-yl)amino) acetate (**3c**).* White solid; mp 176–177 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.11(d, J=7.8 Hz, 2H), 7.46 (t, J=7.2 Hz, 2H), 7.33–7.37 (m, 2H), 7.04 (s, 1H), 6.94(s, 1H), 6.32(s, 1H), 4.45(s, 2H), 3.99(s, 3H), 3.84(s, 3H), 3.73(s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.39, 152.72, 152.13, 149.01, 139.71, 133.89, 128.36, 127.79, 126.20, 112.12, 107.27, 106.06, 101.25, 55.79, 52.09, 44.08; HRMS (ESI) calcd for $C_{20}H_{21}N_2O_4$:353.1496 ($M+H^+$), found: 353.1483.

*4.3.4. Methyl 2-(3-cyclopropylisoquinolin-1-ylamino)acetate (**3d**).* White solid; mp 187–188 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75(d, J=8.4 Hz, 1H), 7.48–7.58 (m, 2H), 7.30–7.36 (m, 1H), 6.88 (s, 1H),5.74(s, 1H), 4.29(d, J=4.8 Hz, 2H), 3.79(s, 3H), 1.98(s, 1H), 1.01–1.06 (m, 2H), 0.82–0.88(m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.09, 153.77, 137.71, 129.65, 126.16, 124.53, 121.47, 116.45, 107.95, 51.99, 43.66, 16.61; HRMS (ESI) calcd for $C_{15}H_{17}N_2O_2$:257.1285 ($M+H^+$), found: 257.1287.

*4.3.5. Methyl 2-(3-butylisoquinolin-1-ylamino)acetate (**3e**).* White solid; mp 102–104 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79(d, J=8.4 Hz, 1H), 7.46–7.65 (m, 3H), 7.34–7.39(m, 1H), 6.79 (s, 1H), 5.80(s, 1H), 4.40(d, J=5.1 Hz, 2H), 3.78(s, 3H), 2.68–2.73(m, 2H), 1.68–1.83 (m, 2H), 1.32–1.46(m, 2H), 0.91–1.01(m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.20, 153.59, 151.90, 137.81, 129.60, 126.59, 124.97, 121.52, 117.94, 109.06, 52.03, 43.71, 37.53, 31.32, 22.38, 14.01; HRMS (ESI) calcd for $C_{16}H_{21}N_2O_2$:273.1598 ($M+H^+$), found: 273.1588.

*4.3.6. Methyl 2-(3-butyl-6-fluoroisoquinolin-1-ylamino)acetate (**3f**).* White solid; mp 106–107 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78–7.82(m, 1H), 7.16–7.20(m, 1H), 7.06–7.12(m, 1H), 6.73 (s, 1H), 5.82(s, 1H), 4.38(d, J=5.1 Hz, 2H), 3.80(d, J=9.0 Hz, 3H), 2.66–2.71(t, J=7.5 Hz, 2H), 1.67–1.82 (m, 2H), 1.31–1.45(m, 2H), 0.92–0.98(m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.1, 163.18(d, $^1J_{CF}$=248.2 Hz), 153.52, 151.54, 139.71(d, $^3J_{CF}$=10.1 Hz), 130.52(d, $^3J_{CF}$=9.9 Hz), 124.45(d, $^4J_{CF}$=9.6 Hz), 114.58(d, $^2J_{CF}$=24.8 Hz), 110.08(d, $^2J_{CF}$=20.3 Hz), 108.85(d, $^4J_{CF}$=4.1 Hz), 52.12, 43.66, 37.50, 31.23, 22.38, 13.99; HRMS (ESI) calcd for $C_{16}H_{20}FN_2O_2$:291.1503 ($M+H^+$), found: 291.1496.

*4.3.7. Ethyl 2-(3-butylisoquinolin-1-ylamino)acetate (**3g**).* White solid; mp 60–62 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79(d, J=8.4 Hz, 1H), 7.59(d, J=7.8 Hz, 1H),7.46–7.54(m, 1H), 7.34–7.39(m, 1H), 6.79 (s, 1H), 5.77(s, 1H), 4.37(d, J=5.1 Hz, 2H), 4.22–4.29(m, 2H), 2.70(t, J=7.5 Hz, 2H), 1.69–1.80 (m, 2H), 1.37–1.44(m, 2H), 1.28–1.34(m, 3H), 0.96–0.98(m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) : δ 171.77, 153.65, 137.81, 129.51, 126.57, 124.91, 121.49, 108.96, 61.06, 43.86, 37.64, 31.34, 22.42, 14.17; HRMS (ESI) calcd for $C_{17}H_{23}N_2O_2$:287.1754 ($M+H^+$), found: 287.1743.

*4.3.8. Ethyl 2-((6-fluoroisoquinolin-1-yl)amino)acetate (**3h**).* White solid; mp 99–101 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96(d, J=8.7 Hz, 1H), δ 7.86–7.89(m, 1H), 7.29(dd, J_1=2.5 Hz, J_1=9.5 Hz, 1H), 7.20–7.24(m, 1H), 6.92 (d, J=6.0 Hz, 1H), 5.83(s, 1H), 4.36(d, J=5.0 Hz, 2H), 4.28(q, J=7.0 Hz, 2H), 1.32(t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.58, 163.56(d, $^1J_{CF}$=249.6 Hz), 154.31, 141.86, 139.22 (d, $^3J_{CF}$=9.9 Hz), 125.02(d, $^3J_{CF}$=9.8 Hz), 116.13(d, $^2J_{CF}$=24.6 Hz), 115.35, 111.76(d, $^4J_{CF}$=4.0 Hz), 111.08(d, $^2J_{CF}$=20.5 Hz), 61.75, 44.08, 14.45; HRMS (ESI) calcd for $C_{13}H_{14}FN_2O_2$:249.1034 ($M + H^+$), found: 249.1029.

*4.3.9. N-Benzyl-N-(6-fluoro-3-phenylisoquinolin-1-yl)amine (**3i**).* Brown oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09–8.13(m, 2H), 7.67–7.72(m, 1H),7.41–7.50(m, 4H), 7.23–7.38(m, 6H), 7.08–7.26(m, 1H), 5.44(s, 1H), 4.94(d, J=5.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.21(d, $^1J_{CF}$=248.4 Hz), 154.24, 150.25, 139.99(d, $^3J_{CF}$=10.1 Hz), 139.79, 139.72, 128.66, 128.41, 128.11, 127.32, 127.08, 126.76, 124.17(d, $^3J_{CF}$=9.0 Hz), 115.08(d, $^2J_{CF}$=24.8 Hz), 114.20, 111.13(d, $^2J_{CF}$=20.3 Hz), 106.66(d, $^4J_{CF}$=4.2 Hz), 45.95; HRMS (ESI) calcd for $C_{22}H_{18}FN_2$:329.1449 ($M+H^+$), found: 329.1440.

*4.3.10. N,3-Diphenylisoquinolin-1-amine (**3j**).* White solid; mp 89–91 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.15–8.18(m,2H), 7.91–7.96(m, 1H),7.82–7.88(m, 3H), 7.64–7.72(m, 2H), 7.37–7.56(m, 7H), 7.08–7.13(m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.41, 151.68, 140.54, 138.50, 130.92, 130.20, 128.87, 128.65, 128.41, 128.06, 126.80, 126.38, 122.57, 121.60, 120.13, 117.97, 109.33; HRMS (ESI) calcd for $C_{21}H_{17}N_2$: 297.1386 ($M+H^+$), found: 297.1396.

*4.3.11. N-(4-Chloro-3-(trifluoromethyl)phenyl)-3-phenylisoquinolin-1-amine (**3k**).* White solid; mp 208–210 °C. ^{1}H NMR (300 MHz,

$CDCl_3$): δ 8.56(d, *J*=2.7 Hz, 1H), 8.10–8.13 (m, 2H), 7.90(d, *J*=8.7 Hz, 1H), 7.79–7.84(m, 2H), 7.64–7.70(m, 2H), 7.37–7.58(m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.71, 148.53, 139.35, 139.12, 139.43, 130.43, 128.74, 128.64, 128.24, 126.41 (q, $^1J_{CF}$=260.5 Hz), 126.74, 126.68, 123.31, 120.99, 118.93, 118.85, 118.78, 118.70, 117.65, 110.19; HRMS (ESI) calcd for $C_{22}H_{15}ClF_3N_2$:399.0870 ($M+H^+$), found: 399.0866.

*4.3.12. N-(3-Methylphenyl)-N-(3-phenylisoquinolin-1-yl)amine (**3l**).* Brown oil. ^1H NMR (300 MHz, $CDCl_3$): δ 8.12–8.18(m,1H), 8.01–8.07(m, 1H),7.83–7.94(m, 1H), 7.69–7.91(m, 1H), 7.46–7.67 (m, 3H), 7.26–7.44(m, 3H), 6.91–6.93(d, *J*=8.1 Hz, 1H), 2.42(s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.41, 151.68, 140.38, 138.68, 138.47, 130.56, 130.17, 129.24, 128.80, 128.74, 127.09, 127.04, 126.76, 123.43, 121.60, 120.87, 117.94, 116.58, 109.12, 21.48; HRMS (ESI) calcd for $C_{22}H_{19}N_2$: 311.1543 ($M+H^+$), found: 311.1544.

*4.3.13. 6-Fluoro-N,3-diphenylisoquinolin-1-amine (**3m**).* White solid; mp 162–163 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 8.10–8.11(m, 2H), 7.87–7.90(m, 1H), 7.77–7.78(m, 2H), 7.52 (s, 1H), 7.44–7.47(m, 2H), 7.36–7.40(m, 4H), 7.19–7.22(m, 1H), 7.12(s, 1H), 7.06–7.10(m,1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.29(d, $^1J_{CF}$=250.0 Hz), 151.59, 140.32(d, $^3J_{CF}$=11.2 Hz), 139.30, 128.89, 128.63, 128.61, 126.83, 124.39(d, $^3J_{CF}$=10.0 Hz), 122.67, 120.13,115.89(d, $^2J_{CF}$=25.0 Hz), 114.89, 111.40(d, $^2J_{CF}$=20.0 Hz), 108.85(d, $^4J_{CF}$=3.7 Hz); HRMS (ESI) calcd for $C_{21}H_{16}FN_2$:315.1292 ($M+H^+$), found: 315.1303.

*4.3.14. N-(4-Chloro-3-(trifluoromethyl)phenyl)-6,7-dimethoxy-3-phenylisoquinolin-1-amine (**3n**).* White solid; mp 225–227 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 8.36(d, *J*=2.4 Hz, 2H), 8.04–8.07(m, 2H), 7.72(dd, J_1=8.7 Hz, J_2=2.4 Hz, 2H), 7.55 (s, 1H), 7.34–7.49(m, 4H), 7.05(s, 1H), 6.98(s, 1H), 6.93(s, 1H), 4.01(s, 1H), 3.99(s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.61, 149.75, 149.36, 147.26, 139.67, 139.24, 134.84, 128.60, 128.42, 126.26 (q, $^1J_{CF}$=256.2 Hz), 126.25, 122.97, 118.49, 118.42, 118.34, 118.27, 112.49, 109.69, 106.51, 100.35, 56.09, 55.93; HRMS (ESI) calcd for $C_{24}H_{19}ClF_3N_2O_2$:459.1082 ($M+H^+$), found: 459.1093.

*4.3.15. 3-Butyl-6-fluoro-N-phenylisoquinolin-1-amine (**3o**).* Brown oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.84–7.89(m, 1H), 7.70(d, *J*=7.8 Hz, 2H), 7.28–7.32(m, 2H), 7.28(d, *J*=2.7 Hz, 1H), 7.14–7.21(m, 2H), 7.05(t, *J*=7.5 Hz, 1H), 6.91(s, 1H), 2.78(t, *J*=7.5 Hz, 2H), 1.75–1.85(m, 2H), 1.35–1.48(m, 2H), 0.88–0.99(m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.22(d, $^1J_{CF}$=250 Hz), 151.49, 140.73, 140.21, 130.87, 128.86 (d, $^3J_{CF}$=10.0 Hz), 124.74, 122.47, 119.73, 115.16 (d, $^2J_{CF}$=25.0 Hz), 114.24, 110.62, 110.48(d, $^2J_{CF}$=20.0 Hz), 37.37, 31.32, 22.39, 14.00; HRMS (ESI) calcd for $C_{19}H_{20}FN_2$:295.1605 ($M+H^+$), found: 295.1614.

*4.3.16. 3-Butyl-N-(4-chloro-3-(trifluoromethyl) phenyl)-6-fluoroisoquinolin-1-amine (**3p**).* White solid; mp 122–123 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 8.34(d, *J*=2.7 Hz, 1H), 7.87–7.91(m, 1H), 7.72–7.76(m, 1H), 7.45(d, *J*=8.7 Hz, 1H), 7.30–7.34(m, 1H), 7.20–7.26(m,2H), 6.99(s, 1H), 2.80(t, *J*=7.5 Hz, 2H), 1.76–1.86(m, 2H), 1.39–1.47(m, 2H),0.96–1.01(m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.45 (d, $^1J_{CF}$=250.6 Hz), 154.21, 150.69, 140.35 (d, $^3J_{CF}$=10.1 Hz), 139.32, 126.36 (q, $^1J_{CF}$=265.8 Hz), 124.66, 124.37, 123.41, 118.97, 118.89, 118.82, 115.78 (d, $^2J_{CF}$=25.0 Hz), 113.98, 111.62 (d, $^4J_{CF}$=4.4 Hz), 110.79 (d, $^2J_{CF}$=20.4 Hz), 37.16, 31.27, 22.41, 13.90; HRMS (ESI) calcd for $C_{20}H_{18}ClF_4N_2$:397.1089 ($M+H^+$), found: 397.1101.

*4.3.17. 3-Cyclopropyl-6-fluoro-N-phenylisoquinolin-1-amine (**3q**).* White solid; mp 140–142 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.79–7.84(m, 1H), δ 7.63–7.66(m, 1H), 7.31–7.37(m, 2H), 7.21–7.24(m, 2H), 7.09–7.16(m, 1H), 7.02–7.07(m, 2H), 6.96(s, 1H), 1.98–2.07(m, 1H), 1.10–1.25(m, 2H),0.93–0.97(m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.32(d, $^1J_{CF}$=229.2 Hz), 155.27, 151.75, 140.46, 140.16 (d, $^3J_{CF}$=10.2 Hz), 128.82, 124.54(d, $^3J_{CF}$=9.6 Hz), 122.54, 119.90, 114.74(d, $^2J_{CF}$=24.9 Hz), 113.96, 110.09(d, $^2J_{CF}$=20.4 Hz), 109.18(d, $^4J_{CF}$=4.2 Hz), 16.93, 8.88; HRMS (ESI) calcd for $C_{18}H_{16}FN_2$:279.1292($M+H^+$), found: 279.1302.

*4.3.18. 3-Butyl-N-phenylisoquinolin-1-amine (**3r**).* Yellow solid; mp 83–85 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.85(d, *J*=6.0 Hz, 1H), δ 7.76(dd, J_1=8.7 Hz, J_2=0.9 Hz, 2H), 7.67(d, *J*=7.8 Hz, 1H), 7.55–7.60(m, 1H), 7.41–7.47(m, 1H), 7.32–7.37(m, 3H), 7.00–7.06(m, 1H), 6.97(s, 1H), 2.81(t, *J*=7.2 Hz, 1H), 1.77–1.87(m, 2H), 1.36–1.49(m, 2H), 0.93–0.99(m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 153.63, 151.43, 140.95, 138.32, 129.79, 128.85, 127.06, 125.45, 122.11, 121.54, 119.47, 117.26,110.85, 37.45, 31.45, 22.42, 14.04; HRMS (ESI) calcd for $C_{19}H_{21}N_2$:277.1699 ($M+H^+$), found: 277.1708.

*4.3.19. 6-Fluoro-N-phenylisoquinolin-1-amine (**3s**).* White solid; mp 87–89 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 8.06(d, *J*=5.0 Hz, 1H), δ 7.94–7.98(m, 1H), 7.61(d, *J*=8.0 Hz, 2H), 7.26–7.33(m, 3H), 7.04–7.10 (m, 3H), 6.57(s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.50(d, $^1J_{CF}$=250.1 Hz), 153.85, 141.90, 140.48, 139.78 (d, $^3J_{CF}$=10.3 Hz), 129.06, 125.20(d, $^3J_{CF}$=9.8 Hz), 123.46, 120.92, 116.54(d, $^2J_{CF}$=24.9 Hz), 116.14, 113.42, 111.30(d, $^2J_{CF}$=20.1 Hz); HRMS (ESI) calcd for $C_{15}H_{12}FN_2$:239.0979 ($M+H^+$), found: 239.0975.

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Supplementary data

CCDC 860174 (**3a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Copies of ^1H NMR, ^{13}C NMR spectra of all compounds are provided. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.06.030. These data include MOL files and InChiKeys of the most important compounds described in this article.

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