Organic & Biomolecular Chemistry

Accepted Manuscript

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View Article Online
DOI: 10.1039/C7OB00389G

Journal Name

ARTICLE

Ru(II)-Catalyzed Annulation of Benzamidines and Alkynes by C-H/N-H Activation: A Facile Synthesis of 1-Aminoisoquinolines

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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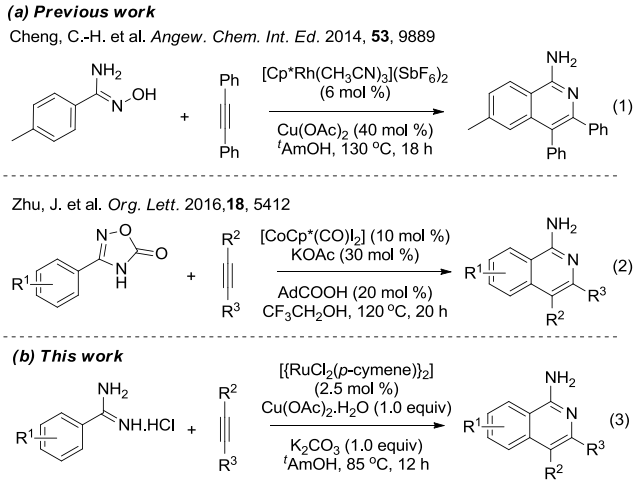
An inexpensive Ru(II) complex catalyzes the oxidative annulation reaction of disubstituted alkynes with benzamidines to provide highly valuable 1-aminoisoquinolines in high yields. The reaction also features excellent regioselectivity with some unsymmetrical alkynes.

Introduction

1-Aminoisoquinolines are very important compounds due to the wide range of biological activities exhibited by them. For example, they are the inhibitors of thrombin, factor Xa, rho kinase-I and they display antitumor and antimalarial activities.[1] Because of the high biological profile, there is a continued strong demand for efficient and selective synthesis of 1-aminoisoquinolines for highthroughput drug screening. The most common methods to prepare 1-aminoisoquinoline derivatives are through nucleophilic aromatic substitution reactions of an existing 1-haloisoquinoline with amino compounds.[1]

In the last two decades, the transition-metal-catalyzed organic reactions via C-H activation have evolved as a powerful tool to construct functional molecules.[2] The C-H activation and functionalization reactions could be used effectively for the synthesis of isoquinolines substituted with a secondary amino group at 1-position, which needs to be removed to obtain the more biologically important primary amine counterparts.[3] The first use of C-H bond activation and annulation reaction to synthesize *N*-unsubstituted 1-aminoisoquinoline was reported by Cheng and co-workers using *N'*-hydroxy-4-methylbenzimidamide and diphenyl acetylene as the starting materials and $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$ as the catalyst to afford 6-methyl-3,4-diphenylisoquinolin-1-amine (eqn 1, Scheme 1).[4] However, they reported the synthesis of only one derivative of 1-aminoisoquinoline and the high cost of the used rhodium(III) catalyst are the main limitations of this approach. Very recently, Zhu and co-workers developed a Co(III)-catalyzed C-H activation and annulation reaction of oxadiazolones and disubstituted alkynes for the synthesis of 1-aminoisoquinolines (eqn 2, Scheme 1).[5] In continuation of our work on transition-metal-catalyzed C-C/C-H activation and functionalization reactions,[6] herein, we report a C–H activation and annulation reaction of readily available benzamidines with disubstituted alkynes catalyzed by inexpensive and readily available ruthenium catalyst $[RuCl_2(p\text{-cymene})]_2$, for the synthesis of a wide range of 1-aminoisoquinolines (eqn 3, Scheme 1). Notably, the annulation reaction of benzamidine with some alkynes were highly regioselective in this Ru(II)-catalyzed reaction.



Scheme 1. Synthetic routes for *N*-unsubstituted 1-aminoisoquinolines

Results and discussion

Initially, we studied the Ru(II)-catalyzed oxidative annulation reaction of benzamidine hydrochloride (**1a**) with diphenyl acetylene (**2a**) in the presence of different oxidants using ^{t}AmOH as the solvent for the synthesis of 1-aminoisoquinoline **3aa**[7] (entries 1-6, Table 1). Among the oxidants screened for this annulations reaction, $Cu(OAc)_2$ provided the highest yield of **3aa** (entry 4). In the absence of oxidant, the reaction did not work (entry 7). Further screening of solvents and additives could not provide better yield of **3aa** (entries 8-13).

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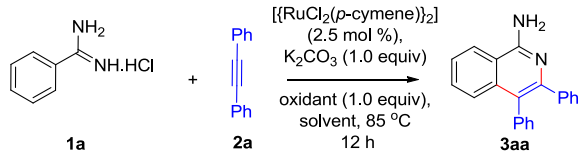
Electronic Supplementary Information (ESI) available: Experimental procedures, characterization data, spectra of synthesized compounds. See DOI: 10.1039/x0xx00000x

Table 1. Optimization study for 1-aminoisoquinoline synthesis[a]



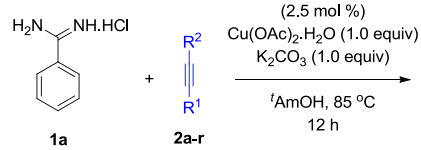
1a 2a 3aa

entry	oxidant	additive	solvent	yield (%)[b]
1	NaOAc	-	^{t}AmOH	63
2	KOAc	-	^{t}AmOH	78
3	AgOAc	-	^{t}AmOH	76
4	$Cu(OAc)_2.H_2O$	-	^{t}AmOH	90
5	CsOAc	-	^{t}AmOH	80
6	$CuBr_2$	-	^{t}AmOH	23
7	-	-	^{t}AmOH	0
8[c]	$Cu(OAc)_2.H_2O$	-	MeOH	65
9	$Cu(OAc)_2.H_2O$	-	H_2O	46
10	$Cu(OAc)_2.H_2O$	-	MeCN	53
11	$Cu(OAc)_2.H_2O$	-	PhMe	27
12	$Cu(OAc)_2.H_2O$	$AgSbF_6$	^{t}AmOH	64
13	$Cu(OAc)_2.H_2O$	KPF_6	^{t}AmOH	57

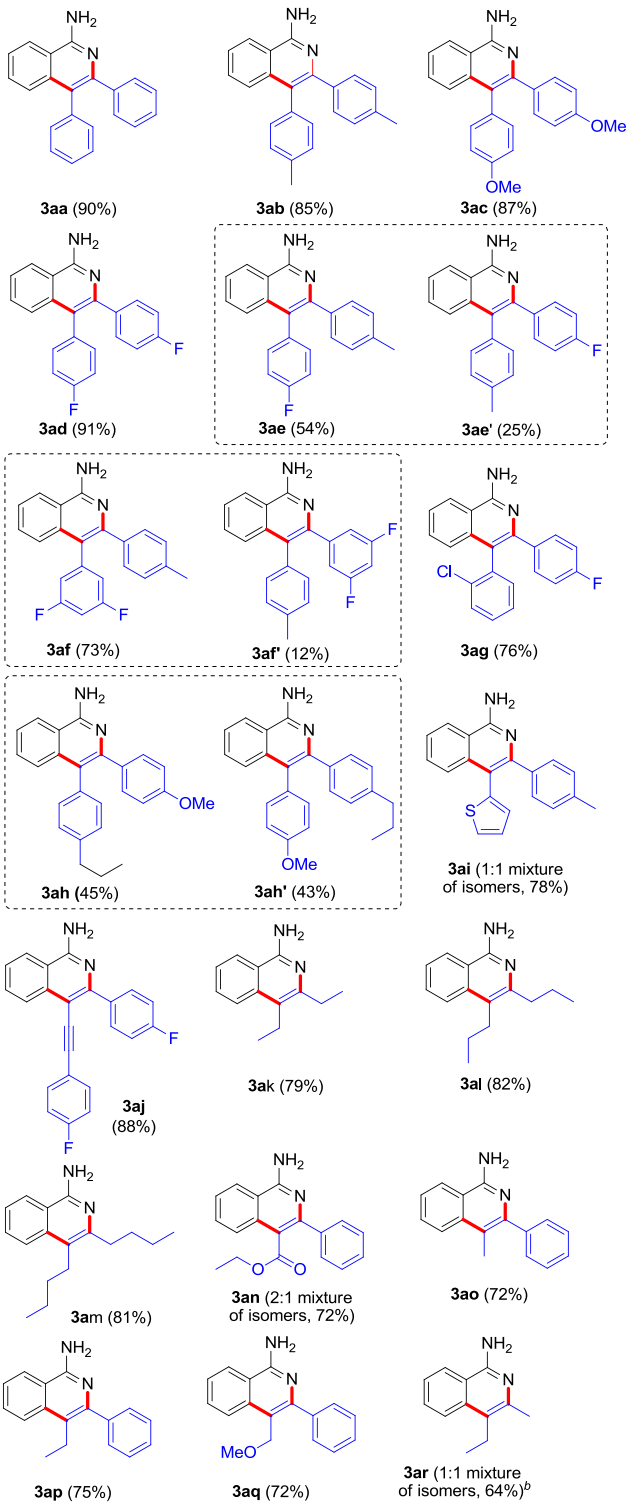
[a]*Reaction conditions*: **1a** (0.5 mmol), **2a** (0.5 mmol), catalyst (2.5 mol %), K_2CO_3 (0.5 mmol), oxidant (0.5 mmol), solvent (6 mL), 85 °C, 12 h; unless otherwise mentioned. [b]Isolated yields. [c]Temperature 64 °C.

The scope of the oxidative annulation reaction of benzamidine (**1a**) was then tested with representative disubstituted alkynes **2a**-**r** (Table 2). All the tested diaryl-substituted symmetrical alkynes, substituted with electron-donating and electron-withdrawing groups (**2b**-**d**) were found to be good substrates to afford 1-aminoisoquinolines **3aa**-**ad** in good yields. Similarly, the diaryl-substituted unsymmetrical alkynes substituted with electron-donating and electron-withdrawing groups on the phenyl rings (**2e**-**f,2h**) provided a mixture of isomers with **1a**, which were easily separated by silica gel column chromatography to afford **3ae**, **3ae'** (~2:1), **3af**, **3af'** (~6:1) and **3ah**, **3ah'** (~1:1). In contrast, the annulation reaction of **1a** with unsymmetrical alkyne **2g** was highly regioselective to provide only one isomer **3ag**. The alkyne substituted with an aryl and heteroaryl rings **2i**, was well tolerated to afford a 1:1 mixture of 1-aminoisoquinolines **3ai**. Dialkyne **2j** also turned out to be a very good substrate for this annulation reaction and it provided alkyne substituted aminoisoquinoline **3aj** in high yield, which could be used for further functional group transformations. Dialkyl-substituted symmetrical alkynes **2k**-**m** were also found to be good substrates for this reaction to provide compounds **3ak**-**am**. The alkyne ethyl 3-phenylpropiolate (**2n**) afforded a mixture of the product **3an** (2:1). The reactions of aryl alkyl substituted alkynes **2o**-**q** with **1a** were highly regioselective to afford **3ao**-**aq**. The regioselectivity of the products were determined by their ^{1}H, ^{13}C, HMQC, HMBC and NOE spectra studies. The annulated products obtained with unsymmetrical alkynes were similar to the reported transition-metal-catalyzed annulation reactions, where the electon rich group occupy the position

Table 2. Scope with substituted alkynes (**2a**-**r**)[a]



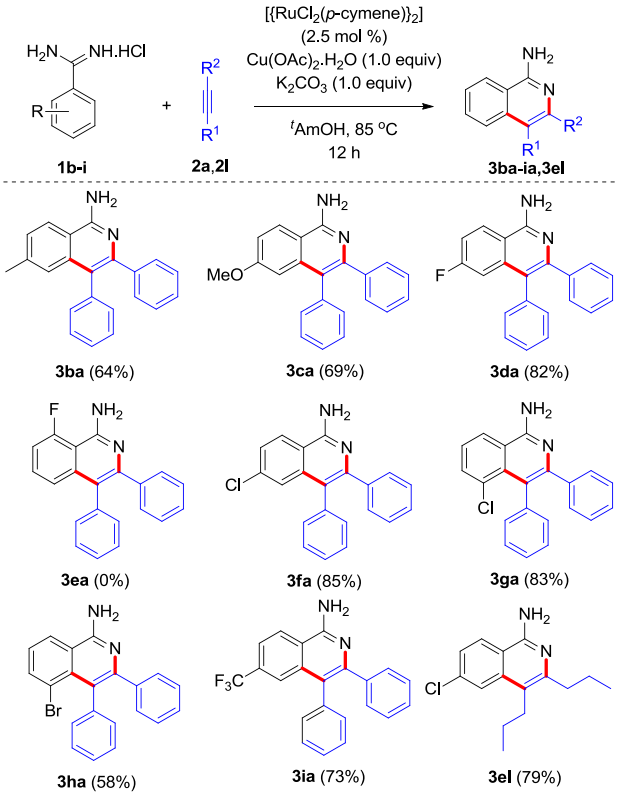
1a 2a-r 3aa-ar,3ae'-ag'



[a]*Reaction conditions*: **1a** (0.5 mmol), **2** (0.5 mmol), K_2CO_3 (0.5 mmol), catalyst (2.5 mol %), $Cu(OAc)_2.H_2O$ (0.5 mmol), ^{t}AmOH (6.0 mL), 85 °C, 12 h; unless otherwise mentioned. [b]Temperature 50 °C.

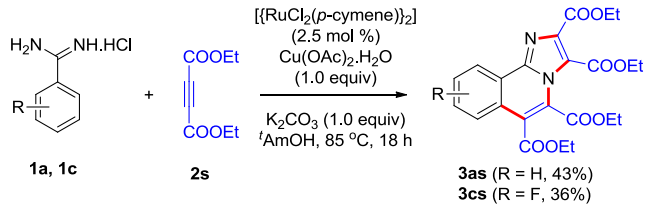
closer to the heteroatom of the heterocycle.[7] The unsymmetrical low boiling alkyne 2-pentyne (**2r**) was also found to be a good annulating partner with **1a** to afford a 1:1 mixture of **3ar**. Similarly, the annulation reaction of some representative benzamidines (**1b-i**) were also tested (Table 3). The electron releasing group containing benzamidines **1b-c**

Table 3. Scope with substituted benzamidines **1b-i**[a]



[a]*Reaction conditions:* **1** (0.5 mmol), **2** (0.5 mmol), K_2CO_3 (0.5 mmol), catalyst (2.5 mol %), $Cu(OAc)_2.H_2O$ (0.5 mmol), ^{t}AmOH (6.0 mL), 85 °C, 12 h; unless otherwise mentioned.

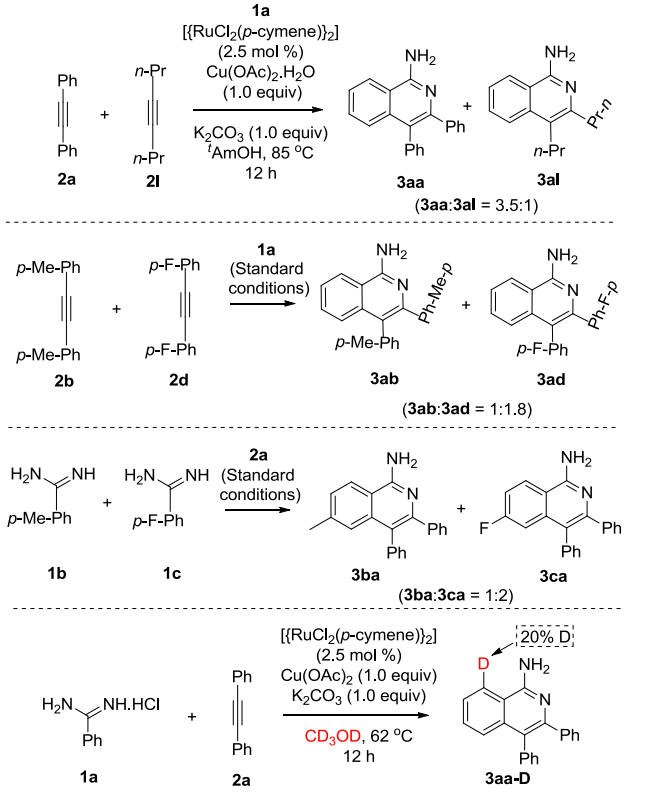
Table 4. Synthesis of imidazo[2,1-*a*]isoquinoline[a]



[a]*Reaction conditions*: **1** (0.5 mmol), **2s** (0.5 mmol), K_2CO_3 (0.5 mmol), catalyst (2.5 mol %), $Cu(OAc)_2.H_2O$ (1.0 mmol), ^{t}AmOH (6.0 mL), 85 °C, 18 h.

afforded moderate yield of the corresponding products **3ba-ca**. However, the electron withdrawing group containing benzamidines **1d**,**1f-i** provided good yields of 1-aminoisoquinolines **3da**,**3fa-ia**,**3el,** irrespective of the position of the substituent present on the aromatic ring. Notably, the reactions of **1g-h** and **2a** were highly regioselective to afford **3ga-ha**. Surprisingly, the *ortho*-substituted benzamidine **1e** could not afford the desired product **3ea** under the optimized condition. Then, the annulation reaction of benzamidines **1a** and **1c** was studied with diester containing alkyne **2s**. Interestingly, these reactions afforded imidazo[2,1-*a*]isoquinolines **3as** and **3cs** as the only products, though with low yields (Table 4). Imidazo[2,1-*a*]isoquinoline is the key motif of wide range of natural and biologically important molecules.[8]

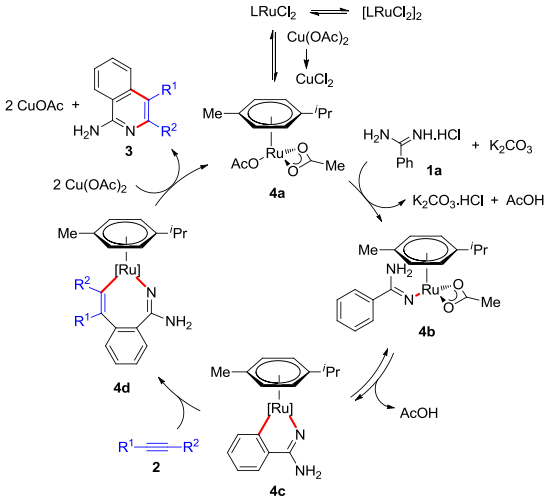
The intermolecular competition experiments performed with differently substituted alkynes revealed the preferential conversion of aryl substituted alkynes and electron poor alkyne to their corresponding isoquinoline derivatives **3aa** and **3ad** (Scheme 2). In contrast, the competition experiment performed with benzimidines substituted with electron-donating and electron-withdrawing substituents indicated electron-withdrawing substituent on the phenyl ring to be favourable (**3ca**, Scheme 2). The isocoumarin **3aa-D** obtained by the reaction of **1a** and **2a** in CD_3OD under standard conditions, resulted in a significant D/H exchange in the eight aromatic proton of the isoquinoline ring (Scheme 2), indicating a reversible C-H bond ruthenation step.



Scheme 2. Intermolecular competition and isotopically labelled reactions

On the basis of our studies and previous studies on ruthenium metal catalyzed C-H activation and functionalization reactions,[9] a mechanism is proposed for the formation of **3**, which is shown in Scheme 3. The active Ru(II) species **4a** first reacts with benzamidine **1a** irreversibly to form the Ru-benzamidine complex **4b**. In the competition experiment between **1b**, **1c** and **2a** (Scheme 2), preferential formation of **3ca** supports the formation of **4b**, as the formation of the intermediate **4b** would be easier for more acidic benzamidine **1c**. This intermediate **4b** on reversible cycloruthenation affords the complex **4c**. Migratory insertion of alkyne **2** with **4c**, followed by reductive elimination in the

presence of $Cu(OAc)_2$ provides compound **3** and regenerates the active Ru(II) catalyst.



Scheme 3. Proposed mechanism

Conclusions

In summary, we have developed one new method for the synthesis of highly valuable 1-amino isocoumarins using Ru(II)-catalyzed C-H/N-H activation and functionalization reaction of benzamidines and disubstituted alkynes. Owing to the importance of the products, simplicity in the experimental procedure, high regioselectivity and high yield, this oxidative coupling reaction would be of synthetic utility.

Experimental

General information

Melting points were measured with a Buchi B-540 melting point apparatus and are uncorrected. IR spectra were recorded on Elmer FT-IR-2000 spectrometer on a thin film using chloroform. NMR spectra were recorded on Bruker Avance III 500 MHz FTNMR spectrometer using tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on Trace DSQ GCMS instrument. All the commercially available regents were used as received. All experiments were monitored by thin layer chromatography (TLC). TLC was performed on pre-coated silica gel plates (Merck). Column chromatography was performed on silica gel (100-200 mesh, Merck). The benzamidine hydrochlorides were synthesized using known procedure.[10]

General procedure for the synthesis of 1-aminoisoquinolines: A solution of benzamidine hydrochloride (0.5 mmol), alkyne (0.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), $Cu(OAc)_2.H_2O$ (0.5 mmol) and K_2CO_3 (0.5 mmol) in ^{t}AmOH (6.0 mL) was stirred at 85 ^{o}C for 12 hours. The solvent was removed under vacuo and the crude reaction mixture was poured into water and extracted with ethylacetate (25 mL x 3). The ethylacetate layer was then washed with brine. Finally, it was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuo. The crude product obtained was purified by silica gel (100-200 mesh) column chromatography using EtOAc/Hexane (7:3) as the eluant to afford 1-aminoisoquinolines.

General procedure for the synthesis of imidazo[2,1-*a*]isoquinolines: A solution of benzamidine hydrochloride (0.5 mmol), diethyl acetylenedicarboxylate (0.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), $Cu(OAc)_2.H_2O$ (0.5 mmol) and K_2CO_3 (0.5 mmol) in ^{t}AmOH (6.0 mL) was stirred at 85 ^{o}C for 18 hours. The solvent was removed under vacuo and the crude reaction mixture was poured into water and extracted with ethylacetate (25 mL x 3). The ethylacetate layer was then washed with brine. Finally, it was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuo. The crude product obtained was purified by silica gel (100-200 mesh) column chromatography using EtOAc/Hexane (1:4) as the eluant to afford imidazo[2,1-*a*]isoquinoline.

3,4-Diphenylisoquinolin-1-amine (3aa). Yield 90% (133 mg). M.p.: 188 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.1 Hz, 1H), 7.59–7.46 (m, 3H), 7.34–7.26 (m, 5H), 7.21–7.14 (m, 5H), 5.39 (bs, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.2, 148.7, 141.0, 137.9, 137.5, 131.8, 130.1, 130.0, 128.04, 127.4, 126.8, 126.6, 126.1, 125.7, 122.7, 122.4, 116.4. IR ($CHCl_3$, cm^{-1}): 3294, 2933, 1632, 1505, 1342, 701. MS (EI, m/z): 296. Anal. calcd. for $C_{21}H_{16}N_2$: C, 85.11; H, 5.44; N, 9.45; Found: C, 85.03; H, 5.49; N, 9.37.

3,4-di-*p*-Tolylisoquinolin-1-amine (3ab). Yield 85% (137 mg). M.p.: 110 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.8 Hz, 1H), 7.49–7.31 (m, 3H), 7.14 (d, *J* = 6.2 Hz, 2H), 7.04 (d, *J* = 7.8 Hz, 2H), 6.98 (d, *J* = 7.9 Hz, 2H), 6.89 (d, *J* = 7.1 Hz, 2H), 5.48 (bs, 2H), 2.27 (s, 3H), 2.17 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 148.1, 137.7, 136.4, 136.1, 134.9, 131.6, 130.9, 130.1, 129.9, 129.6, 129.0, 128.8, 128.3, 128.2, 126.1, 125.6, 122.6, 21.2, 21.1. IR ($CHCl_3$, cm^{-1}): 3364, 2924, 1614, 1515, 1439, 1220, 771. MS (EI, m/z): 324. Anal. calcd. for $C_{23}H_{20}N_2$: C, 85.15; H, 6.21; N, 8.63; Found: C, 85.48; H, 6.44; N, 8.52.

3,4-bis(4-Methoxyphenyl)isoquinolin-1-amine (3ac). Yield 87% (155 mg). M.p.: 205 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.2 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.28 (d, *J* = 8.7 Hz, 2H), 7.11 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 6.73 (d, *J* = 8.7 Hz, 2H), 5.36 (bs, 2H), 3.82 (s, 3H), 3.75 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.3, 158.2, 154.9, 148.3, 137.9, 133.6, 132.7, 131.2, 130.2, 129.9, 126.1, 125.4, 122.4, 121.9, 116.3, 113.6, 112.9, 55.1, 55.0. IR ($CHCl_3$, cm^{-1}): 3307, 2925, 1606, 1515, 1248, 771. MS (EI, m/z): 356. Anal. calcd. for $C_{23}H_{20}N_2O_2$: C, 77.51; H, 5.66; N, 7.86; Found: C, 77.38; H, 5.79; N, 7.70.

3,4-bis(4-Fluorophenyl)isoquinolin-1-amine (3ad). Yield 91% (151 mg). M.p.: 190 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.3 Hz, 1H), 7.60–7.46 (m, 3H), 7.32–7.22 (m, 2H), 7.17–7.10 (m, 2H), 7.03 (t, *J* = 8.5 Hz, 2H), 6.87 (t, *J* = 8.5 Hz, 2H). 5.74 (bs, 2H) ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.6 (d, *J* = 245 Hz), 155.3, 147.9, 137.4, 133.2 (d, *J* = 7.5 Hz), 131.6 (d, *J* = 7.5 Hz), 130.3, 125.9, 125.8, 122.5, 116.4, 115.2 (d, *J* = 21.3 Hz), 114.5 (d, *J* = 21.3 Hz). IR ($CHCl_3$, cm^{-1}): 3300, 2926, 1635, 1509, 1209, 1157, 834, 768. MS (EI, m/z): 332. Anal. calcd. for $C_{21}H_{14}F_2N_2$: C, 75.89; H, 4.25; N, 8.43; Found: C, 75.75; H, 4.39; N, 8.27.

4-(4-Fluorophenyl)-3-(*p*-tolyl)isoquinolin-1-amine (3ae). Yield 54% (88 mg) M.p.: 162 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.2 Hz, 1H), 7.56–7.46 (m, 3H), 7.23–7.12 (m, 4H),

7.07–6.97 (m, 4H), 5.31(bs, 2H) 2.28 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.7 (d, *J* = 243.8 Hz), 155.1, 149.0, 137.9, 137.5, 136.5, 133.2 (d, *J* = 7.5 Hz), 130.1, 129.8, 128.3, 125.8, 125.6, 122.4, 121.4, 116.3, 115.1 (d, *J* = 21.3 Hz), 21.1. IR ($CHCl_3$, cm^{-1}): 3343, 3924, 1621, 1507, 1221, 765. MS (EI, m/z): 328. Anal. calcd. for $C_{22}H_{17}FN_2$: C, 80.47; H, 5.22; N, 8.53; Found: C, 80.65; H, 5.41; N, 8.68.

3-(4-fluorophenyl)-4-(*p*-tolyl)isoquinolin-1-amine (3ae'). Yield 25% (41 mg). M.p.: 171 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 8.3 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.51–7.46 (m, 1H), 7.31 (dd, *J* = 8.1 Hz, 5.7 Hz, 2H), 7.14 (d, *J* = 7.8 Hz, 2H), 7.06 (d, *J* = 7.8 Hz, 2H), 6.87 (t, *J* = 8.6 Hz, 2H), 5.28 (bs, 2H), 2.38 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.7 (d, *J* = 245 Hz), 154.9, 147.6, 137.6, 136.3, 134.6, 131.6 (d, *J* = 8.0 Hz), 131.5, 130.1, 128.9, 128.5, 126.2, 125.7, 122.3, 116.4, 114.2 (d, *J* = 21.0 Hz), 21.2. IR ($CHCl_3$, cm^{-1}): 3312, 3935, 1607, 1533, 1234, 771. MS (EI, m/z): 328. Anal. calcd. for $C_{22}H_{17}FN_2$: C, 80.47; H, 5.22; N, 8.53; Found: C, 80.19; H, 5.20; N, 8.63.

3-(3,5-Difluorophenyl)-4-(*p*-tolyl)isoquinolin-1-amine (3af). Yield 73% (126 mg). M.p.: 210 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.0 Hz, 1H), 7.60–7.49 (m, 3H), 7.17 (d, *J* = 7.8 Hz, 2H), 7.07 (d, *J* = 8.1 Hz, 2H), 6.91–6.84 (m, 2H), 6.58–6.62 (m, 1H), 5.29 (bs, 2H) 2.39 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.2 (d, *J* = 245.0 Hz), 162.1 (d, *J* = 246.3 Hz), 154.9, 144.5, 137.5, 136.8, 133.9, 131.26, 130.2, 129.1, 126.4, 126.2, 123.2, 122.3, 113.0 (d, *J* = 26.3 Hz), 112.9 (d, *J* = 25.8 Hz), 102.3 (d, *J* = 25.0 Hz), 102.1 (d, *J* = 25.0 Hz), 21.2. IR ($CHCl_3$, cm^{-1}): 3294, 2988, 1639, 1512, 1469, 1217, 1184, 755. MS (EI, m/z): 346. Anal. calcd. For $C_{22}H_{16}F_2N_2$: C, 76.29; H, 4.66; N, 8.09; Found: C, 76.10; H, 4.83; N, 8.24.

3-(3,5-Difluorophenyl)-3-(*p*-tolyl)isoquinolin-1-amine 3af'. Yield 12% (21 mg). M.p.: 225 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 11.3 Hz, 8.4 Hz, 1H), 7.64–7.50 (m, 3H), 7.24–7.01 (m, 4H), 6.86–6.72 (m, 3H), 5.40 (S, 2H), 2.30 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.7 (d, *J* = 247.5 Hz), 162.6 (d, *J* = 247.5 Hz), 155.4, 148.9, 139.0, 137.3, 137.0, 136.8, 132.5, 130.8, 129.5, 128.4, 127.1, 126.2, 125.9, 125.4, 122.5 (d, *J* = 10.0 Hz), 114.8 (d, *J* = 19.0 Hz), 114.7 (d, *J* = 18.8 Hz), 102.4 (d, *J* = 25.0 Hz), 102.2 (d, *J* = 25.0 Hz), 21.2. IR ($CHCl_3$, cm^{-1}): 3324, 2961, 1622, 1236, 767. MS (EI, m/z): 346. Anal. calcd. for $C_{22}H_{16}F_2N_2$: C, 76.29; H, 4.66; N, 8.09; Found: C, 76.01; H, 4.57; N, 7.87.

3-(2-Chlorophenyl)-4-(4-fluorophenyl)isoquinolin-1-amine (3ag). Yield 76% (132 mg). M.p.: 256 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.3 Hz, 1H), 7.59–7.54 (m, 1H), 7.53–7.49 (m, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.34 (dd, *J* = 8.3 Hz, 5.9 Hz, 2H), 7.31–7.26 (m, 2H), 7.22–7.17 (m, 1H), 7.12 (dd, *J* = 7.5 Hz, 1.2 Hz, 1H), 6.88 (t, *J* = 8.8 Hz, 2H), 5.37 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.9 (d, *J* = 245 Hz), 155.5, 148.3, 136.8, 136.8, 135.5, 133.4, 131.0, 130.8 (d, *J* = 7.5 Hz), 129.37, 128.8, 126.7, 125.9, 125.7, 122.5, 120.1, 116.3, 114.4 (d, *J* = 21.3 Hz). IR ($CHCl_3$, cm^{-1}): 3296, 2991, 1637, 1509, 1441, 1345, 1217, 1155, 839, 766. MS (EI, m/z): 348. Anal. calcd. for $C_{21}H_{14}ClFN_2$: C, 72.31; H, 4.05; N, 8.03; Found: C, 72.19; H, 4.21; N, 7.81.

3-(4-Methoxyphenyl)-4-(4-propylphenyl)isoquinolin-1-amine (3ah). Yield 45% (83 mg) M.p.: 163 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.0 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.53 (d, *J* = 8.3 Hz, 1H), 7.50–7.46 (m, 1H), 7.27 (d, *J* = 8.3 Hz, 2H), 7.14 (d, *J* = 7.7 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 6.71 (d, *J* = 8.4 Hz, 2H), 5.50 (bs, 2H), 3.75 (s, 3H), 2.65–2.58 (m, 2H), 1.70–1.63 (m, 2H), 0.98–0.91 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.4, 154.8, 141.0, 137.7, 135.0, 131.5, 131.2, 130.2, 128.3, 126.2, 125.6, 122.5, 112.9, 55.1, 37.6, 24.3, 13.6. IR ($CHCl_3$, cm^{-1}): 3378, 3138, 2959, 1618, 1567, 1426, 1343, 763. MS (EI, m/z): 368. Anal. calcd. for $C_{25}H_{24}N_2O$: C, 81.49; H, 6.57; N, 7.60; Found: C, 81.31; H, 6.71; N, 7.49.

4-(4-Methoxyphenyl)-3-(4-propylphenyl)isoquinolin-1-amine (3ah'). Yield 43% (79 mg). M.p.: 190 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.1 Hz, 1H), 7.59 (d, *J* = 8.3 Hz, 1H), 7.53 (dd, *J* = 7.6, 6.7 Hz, 1H), 7.47 (dd, *J* = 10.9 Hz, 4.0 Hz, 1H), 7.26–7.21 (m, 2H), 7.10 (d, *J* = 8.3 Hz, 2H), 6.99 (d, *J* = 7.9 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 5.42 (s, 2H), 3.82 (s, 3H), 2.54–2.48 (m, 2H), 1.61–1.54 (m, 2H), 0.91–0.86 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.2, 154.8, 148.4, 141.1, 138.1, 137.8, 132.7, 130.1, 129.8, 127.7, 126.1, 125.5, 122.4, 122.1, 116.4, 113.5, 55.1, 37.6, 24.3, 13.7. IR ($CHCl_3$, cm^{-1}): 3338, 2983, 1656, 1569, 1255, 763. MS (EI, m/z): 368. Anal. calcd. for $C_{25}H_{24}N_2O$: C, 81.49; H, 6.57; N, 7.60; Found: C, 81.37; H, 6.75; N, 7.43.

4-(Thiophen-2-yl)-3-(*p*-tolyl)isoquinolin-1-amine and 3-(thiophen-2-yl)-4-(p-tolyl)isoquinolin-1-amine (3ai, 1:1). Yield 78% (123 mg). M.p.: 184 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94–7.80 (m, 1H), 7.64–7.44 (m, 3H), 7.35–7.28 (m, 1H), 7.20–7.12 (m, 2H), 7.09–6.98 (m, 2.5H), 6.92–6.82 (m, 1H), 6.92–6.81 (m, 0.5H), 5.3 (bs, 1H), 5.30 (bs, 1H), 2.37 (s, 1.5H), 2.28 (s, 1.5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.7, 155.1, 154.9, 149.0, 137.5, 136.5, 136.3, 133.3, 133.2, 131.7, 131.6, 131.5, 130.1, 130.0, 129.8, 128.9, 128.3, 126.2, 125.8, 125.7, 125.6, 122.4, 122.3, 121.4, 115.2, 115.0, 114.4, 114.2, 21.2, 21.1. IR ($CHCl_3$, cm^{-1}): 3376, 3025, 1611, 1515, 1498, 1426, 1218, 768. MS (EI, m/z): 316. Anal. calcd. for $C_{20}H_{16}N_2S$: C, 75.92; H, 5.10; N, 8.85; Found: C, 75.95; H, 5.26; N, 8.71.

3-(4-Fluorophenyl)-4-{(4-fluorophenyl)ethynyl}isoquinolin-1-amine (3aj). Yield 88% (157 mg). M.p.: 221 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (d, *J* = 8.3 Hz, 1H), 8.05 (dd, *J* = 8.4, 5.4 Hz, 2H), 7.83 (d, *J* = 8.3 Hz, 1H), 7.77 (t, *J* = 7.6 Hz, 1H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.45–7.41 (m, 2H), 7.17 (t, *J* = 8.5 Hz, 2H), 7.05 (t, *J* = 8.8 Hz, 2H), 5.46 (bs, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.8 (d, *J* = 246.3 Hz), 162.2 (d, *J* = 247.5 Hz), 154.9, 152.8, 137.8, 136.2, 132.7 (d, *J* = 7.5 Hz), 131.5 (d, *J* = 8.8 Hz), 131.0, 126.5, 126.2, 122.5, 119.8, 118.1, 115.8, 115.6 (d, *J* = 21.3 Hz), 114.6 (d, *J* = 21.3 Hz), 103.6, 95.3, 86.1. IR ($CHCl_3$, cm^{-1}): 3356, 3031, 1617, 1523, 1488, 1433, 1203, 771. MS (EI, m/z): 356. Anal. calcd. for $C_{23}H_{14}F_2N_2$: C, 77.52; H, 3.96; N, 7.86; Found: C, 77.39; H, 3.87; N, 7.68.

3,4-Diethylisoquinolin-1-amine (3ak). Yield 79% (79 mg). M.p.: 83 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.5 Hz, 1H), 7.79 (d, *J* = 8.3 Hz, 1H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 5.35 (s, 2H), 2.91 (q, *J* = 7.5 Hz, 2H), 2.79 (q, *J* = 7.6 Hz, 2H), 1.29 (t, *J* = 7.5 Hz, 3H), 1.22 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.2, 151.2, 136.6, 129.8, 124.5, 123.3, 123.1, 120.0, 116.7, 28.0, 20.2, 15.3, 14.6. IR ($CHCl_3$, cm^{-1}): 3372, 2955, 1615, 1563, 1426, 1343, 764. MS (EI, m/z): 200. Anal. calcd. for $C_{13}H_{16}N_2$: C, 77.96; H, 8.05; N, 13.99; Found: C, 77.85; H, 8.26; N, 13.80.

DOI: 10.1039/C7OB00389G

3,4-Dipropylisoquinolin-1-amine (3al). Yield 82% (93 mg). M.p.: 45 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.5 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.61 (t, *J* = 7.5 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 1H), 5.15 (bs, 2H), 2.90–2.83 (m, 2H), 2.78–2.71 (m, 2H), 1.78–1.71 (m, 2H), 1.66–1.59 (m, 2H), 1.09–0.99 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.9, 150.3, 136.9, 129.7, 124.5, 123.6, 123.0, 119.3, 116.6, 37.0, 29.4, 24.1, 23.5, 14.4, 14.3. IR ($CHCl_3$, cm^{-1}): 3376, 2957, 1617, 1566, 1425, 1278, 763. MS (EI, m/z): 228. Anal. calcd. for $C_{15}H_{20}N_2$: C, 78.90; H, 8.83; N, 12.27; Found: C, 78.97; H, 8.94; N, 12.06.

3,4-Dibutylisoquinolin-1-amine (3am). Yield 81% (103 mg). M.p.: 37 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90–7.81 (m, 2H), 7.63 (m, *J* = 7.5 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 1H), 5.77 (bs, 2H), 2.90–2.83 (m, 2H), 2.81–2.73 (m, 2H), 1.73–1.65 (m, 2H), 1.60–1.55 (m, 2H), 1.53–1.43 (m, 4H), 1.01–0.94 (m, 6H). ^{13}C NMR (125 MHz, CDCl3) δ 154.0, 149.1, 136.9, 130.2, 124.7, 123.6, 123.3, 119.0, 116.7, 34.2, 33.0, 32.4, 26.9, 23.1, 22.9, 14.0, 13.9. IR ($CHCl_3$, cm^{-1}): 3356, 2969, 1631, 1547, 1251, 766. MS (EI, m/z): 256. Anal. calcd. for $C_{17}H_{24}N_2$: C, 79.64; H, 9.44; N, 10.93; Found: C, 79.44; H, 9.69; N, 10.69.

Ethyl 1-amino-3-phenylisoquinoline-4-carboxylate and ethyl 1-amino-4-phenylisoquinoline-3-carboxylate (2:1, 3an). Yield 72% (105 mg). M.p.: 155 °C ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.5 Hz, 0.33H) 8.08 (d, *J* = 8.5 Hz, 0.67H), 7.87–7.58 (m, 4H), 7.56–7.35 (m, 3.67H), 7.33–7.29 (m, 0.33H) 5.87 (bs, 0.67H), 5.69 (bs, 1.3H), 4.30–3.98 (m, 2H), 1.06–0.76 (m, 3H). ^{13}C NMR (125 MHz, CDCl3) δ 169.2, 167.6, 156.7, 156.5, 151.6, 151.0, 141.0, 139.8, 135.1, 132.7, 131.3, 131.2, 130.2, 129.2, 128.9, 128.1, 128.0, 126.6, 126.3, 126.2, 125.5, 124.8, 122.5, 122.4, 116.0, 115.5, 114.8, 61.0, 60.7, 13.5, 13.3. IR ($CHCl_3$, cm^{-1}): 3271, 2931, 1685, 1601, 1506, 1471, 1277, 1171, 1023, 823. MS (EI, m/z): 292. Anal. calcd. For $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58; Found: C, 74.01; H, 5.59; N, 9.39.

4-Methyl-3-phenylisoquinolin-1-amine (3ao). Yield 72% (84 mg). M.p.: 159 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.3 Hz, 1H), 7.71 (t, *J* = 8.3 Hz, 1H), 7.54–7.49 (m, 3H), 7.46–7.42 (m, 2H), 7.37 (t, *J* = 7.4 Hz, 1H), 5.38 (bs, 2H), 2.45 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.9, 148.8, 141.1, 137.6, 130.3, 129.5, 127.9, 127.3, 125.5, 124.2, 123.0, 117.0, 115.0, 14.8. IR ($CHCl_3$, cm^{-1}): 3353, 2947, 1611, 1532, 1243, 733. MS (EI, m/z): 234. Anal. calcd. for $C_{16}H_{14}N_2$: C, 82.02; H, 6.02; N, 11.96; Found: C, 81.32; H, 6.23; N, 11.88.

3-Ethyl-4-phenylisoquinolin-1-amine (3ap). Yield 75% (93 mg). M.p.: 113 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.5 Hz, 1H), 7.89 (d, *J* = 8.2 Hz, 1H), 7.72 (t, *J* = 7.5 Hz, 1H), 7.47-750 (m, 5H), 7.39 (d, *J* = 6.9 Hz, 1H), 5.34 (s, 2H), 2.86 (q, *J* = 7.5 Hz, 2H), 1.22 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7, 149.1, 136.6, 130.2, 128.8, 128.0, 127.3, 125.5, 124.2, 123.2, 21.2, 15.6. IR ($CHCl_3$, cm^{-1}): 3233, 2961, 1656, 1233, 731. MS (EI, m/z): 248. Anal. calcd. for $C_{17}H_{16}N_2$: C, 82.22; H, 6.49; N, 11.28; Found: C, 82.16; H, 6.64; N, 11.06.

4-(Methoxymethyl)-3-phenylisoquinolin-1-amine (3aq). Yield 72% (95 mg). M.p.: 112 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.4 Hz, 1H), 7.80–7.62 (m, 4H), 7.50–7.39 (m, 4H), 5.42 (s, 2H), 4.60 (s, 2H), 3.42 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5, 152.0, 140.5, 137.6, 130.6, 129.4, 127.9, 127.7, 125.7, 124.50, 122.6, 116.8, 115.2, 69.0, 57.9. IR ($CHCl_3$, cm^{-1}): 3251, 2962, 1606, 1570, 1272, 771. MS (EI, m/z): 264. Anal. calcd. for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60; Found: C, 77.26; H, 6.17; N, 10.32.

3-Ethyl-4-methylisoquinolin-1-amine and 4-ethyl-3-methylisoquinolin-1-amine (3ar, 1:1). Yield 64% (59 mg). M.p.: 90 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 8.5 Hz, 3.4 Hz, 1H), 7.80 (d, *J* = 8.3 Hz, 1H), 7.64 (t, *J* = 8.3 Hz, 1H), 7.45–7.40 (m, 1H), 5.20 (bs, 2H), 2.91 (q, *J* = 7.5 Hz, 1H), 2.83 (q, *J* = 7.5 Hz, 1H), 2.51 (s, 1.5H), 2.45 (s, 1.5H), 1.28–1.19 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.9, 153.6, 151.3, 145.5, 137.5, 136.4, 130.0, 129.9, 124.6, 124.5, 123.5, 123.2, 123.1, 122.9, 121.0, 116.5, 116.4, 113.8, 28.7, 21.3, 20.6, 14.3, 14.0, 12.9. IR ($CHCl_3$, cm^{-1}): 3244, 2965, 1647, 1249, 741 MS (EI, m/z): 186. Anal. calcd. for $C_{12}H_{14}N_2$: C, 77.38; H, 7.58; N, 15.04; Found: C, 77.23; H, 7.69; N, 15.01.

6-Methyl-3,4-diphenylisoquinolin-1-amine (3ba). Yield 64% (99 mg). M.p.: 182 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.3 Hz, 1H), 7.37–7.29 (m, 7H), 7.20–7.14 (m, 5H), 5.80 (s, 2H), 2.41 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 144.5, 139.9, 137.7, 137.5, 136.2, 131.8, 129.9, 128.0, 127.9, 127.4, 126.9, 126.7, 125.3, 122.5, 114.6, 22.0. IR ($CHCl_3$, cm^{-1}): 3257, 2924, 1623, 1591, 1280, 696. MS (EI, m/z): 310. Anal. calcd. for $C_{22}H_{18}N_2$: C, 85.13; H, 5.85; N, 9.03; Found: C, 85.07; H, 5.92; N, 9.31.

6-Methoxy-3,4-diphenylisoquinolin-1-amine (3ca). Yield 69% (112 mg). M.p.: 201 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 9.0 Hz, 1H), 7.33–7.26 (m, 5H), 7.24–7.13 (m, 5H), 7.12 (dd, *J* = 9.0 Hz, 2.5 Hz, 1H), 6.87 (d, *J* = 2.5 Hz, 1H), 5.24 (s, 2H), 3.71 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.7, 154.8, 149.4, 141.0, 139.5, 138.1, 131.7, 129.9, 128.1, 127.4, 126.7, 126.6, 124.3, 122.5, 117.2, 111.5, 105.1, 55.1. IR ($CHCl_3$, cm^{-1}): 3262, 2925, 1627, 1596, 1279. MS (EI, m/z): 326. Anal. calcd. for $C_{22}H_{18}N_2O$: C, 80.96; H, 5.56; N, 8.58; Found: C, 80.78; H, 5.71; N, 8. 80.

6-Fluoro-3,4-diphenylisoquinolin-1-amine (3da). Yield 82% (129 mg). M.p.: 191 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 9.1 Hz, 1H), 7.34–7.26 (m, 5H), 7.23–7.14 (m, 7H), 5.96 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.4 (d, *J* = 251.3 Hz), 155.2, 145.6, 140.1 (d, *J* = 10.0 Hz), 137.2, 136.1, 131.5, 129.9, 128.4, 127.8, 127.6, 127.3, 126.8 (d, *J* = 8.8 Hz), 121.8, 116.0 (d, *J* = 25.0 Hz), 113.8, 110.6 (d, *J* = 22.5 Hz). IR ($CHCl_3$, cm^{-1}): 3286, 2979, 1631, 1447, 1235, 753. MS (EI, m/z): 314. Anal. calcd. for $C_{21}H_{15}FN_2$: C, 80.24; H, 4.81; N, 8.91; Found: C, 80.07; H, 4.97; N, 8.78.

6-Chloro-3,4-diphenylisoquinolin-1-amine (3fa). Yield 85% (140 mg). M.p.: 240 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.8 Hz, 1H), 7.46 (s, 1H), 7.34 (d, *J* = 8.8 Hz, 1H), 7.27–7.19 (m, 5H), 7.09 (dd, *J* = 4.6 Hz, 3.1 Hz, 5H), 5.28 (bs, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 150.2, 140.6, 138.7, 137.2, 136.5, 131.7, 129.9, 128.3, 127.5, 127.0, 126.9, 126.4, 125.1, 124.2, 122.0, 114.6. IR ($CHCl_3$, cm^{-1}): 3246, 2999, 1602, 1417, 1232, 753. MS (EI, m/z): 330. Anal. calcd. for $C_{21}H_{15}ClN_2$: C, 76.24; H, 4.57; N, 8.47; Found: C, 76.38; H, 4.75; N, 8.38.

5-Chloro-3,4-diphenylisoquinolin-1-amine (3ga). Yield 83% (137 mg). M.p.: 183 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.3 Hz, 1H), 7.66 (d, *J* = 7.5 Hz, 1H), 7.42 (t, *J* = 8.0 Hz, 1H), 7.20–7.07 (m, 10H), 5.66 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ

155.1, 152.2, 141.2, 139.1, 133.9, 133.7, 132.2, 131.9, 129.6, 127.2, 126.9, 126.6, 126.4, 125.8, 122.0, 121.5, 118.5. IR ($CHCl_3$, cm^{-1}): 3285, 2966, 1637, 1451, 1241, 771. MS (EI, m/z): 330. Anal. calcd. for $C_{21}H_{15}ClN_2$: C, 76.24; H, 4.57; N, 8.47; Found: C, 76.21; H, 4.81; N, 8.69.

5-Bromo-3,4-diphenylisoquinolin-1-amine (3ha). Yield 58% (108 mg). M.p.: 189 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 7.5 Hz, 1.0 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.20-7.07 (m, 10H), 5.28 (bs, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.1, 141.4, 138.4, 138.2, 134.6, 132.9, 129.3, 127.2, 127.0, 126.6, 126.5, 126.1, 122.6, 122.3, 120.3, 118.5. IR ($CHCl_3$, cm^{-1}): 3248, 2995, 1600, 1231. MS (EI, m/z): 374. Anal. calcd. for $C_{21}H_{15}BrN_2$: C, 67.21; H, 4.03; N, 7.47; Found: C, 67.20; H, 4.17; N, 7.18.

3,4-Diphenyl-6-(trifluoromethyl)isoquinolin-1-amine (3ia). Yield 73% (133 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.7 Hz, 1H), 7.66–7.58 (m, 2H), 7.36–7.29 (m, 7H), 7.22–7.16 (m, 3H), 5.16 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.1, 153.9, 149.5, 140.1, 139.7, 139.2, 138.2, 137.1, 136.8, 135.7, 131.8, 131.7, 131.4, 131.2, 130.4, 129.8, 128.2 (q, *J* = 31.3 Hz), 127.6 (q, *J* = 31.6 Hz), 123.8, 123.4 (q, *J* = 271.3 Hz), 116.8. IR ($CHCl_3$, cm^{-1}): 3397, 2915, 1643, 1501, 1207, 1163, 761. MS (EI, m/z): 364. Anal. calcd. for $C_{22}H_{15}F_3N_2$: C, 72.52; H, 4.15; N, 7.69; Found: C, 72.39; H, 4.31; N, 7.57.

6-Chloro-3,4-dipropylisoquinolin-1-amine (3el). Yield 79% (103 mg). M.p.: 91 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 2.1 Hz, 1H), 7.71 (d, *J* = 8.8 Hz, 1H), 7.35 (dd, *J* = 8.8 Hz, 2.1 Hz, 1H), 5.00 (s, 2H), 2.83–2.78 (m, 2H), 2.75–2.70 (m, 2H), 1.76–1.70 (m, 2H), 1.64–1.57 (m, 2H), 1.07 (t, *J* = 7.3 Hz, 3H), 1.02 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.6, 152.1, 138.0, 136.0, 125.1, 124.7, 122.8, 118.8, 114.8, 37.1, 29.3, 24.0, 23.3, 14.4, 14.3. IR ($CHCl_3$, cm^{-1}): 3311, 2997, 1646, 1256, 1058, 779. MS (EI, m/z): 262. Anal. calcd. for $C_{15}H_{19}ClN_2$: C, 68.56; H, 7.29; N, 10.66; Found: C, 68.47; H, 7.08; N, 10.41.

Tetraethylimidazo[2,1-*a*]isoquinoline-2,3,5,6-tetracarboxylate (3as). Yield 43% (98 mg). Gum. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.86 (d, *J* = 7.9 Hz, 1H), 7.87 (d, *J* = 8.2 Hz, 1H), 7.83–7.78 (m, 1H), 7.78–7.73 (m, 1H), 4.54–4.47 (m, 4H), 4.45–4.38 (m, 4H), 1.48–1.39 (m, 12H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.1, 162.3, 161.2, 160.5, 143.7, 137.5, 130.6, 130.5, 125.9, 125.5, 124.9, 123.8, 123.6, 62.9, 62.6, 62.2, 61.8, 14.2, 13.9, 13.8, 13.7. IR ($CHCl_3$, cm^{-1}): 3270, 2930, 1686, 1603, 1508, 1470, 1282, 1179, 1033, 817. MS (EI, m/z): 456. Anal. calcd. for $C_{23}H_{24}N_2O_8$: C, 60.52; H, 5.30; N, 6.14; Found: C, 60.70; H, 5.43; N, 6.09.

Tetraethyl 8-fluoroimidazo[2,1-*a*]isoquinoline-2,3,5,6-tetracarboxylate (3cs). Yield 36% (85 mg). Gum. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.88 (dd, *J* = 9.0 Hz, 5.4 Hz, 1H), 7.59 (dd, *J* = 9.7 Hz, 2.5 Hz, 1H), 7.53 (td, *J* = 8.5 Hz, 2.5 Hz, 1H), 4.53–4.47 (m, 4H), 4.44–4.39 (m, 4H), 1.47–1.40 (m, 12H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.7, 164.6, 162.2, 161.4 (d, *J* = 245.2 Hz), 160.4, 143.2 (d, *J* = 8.8 Hz), 133.7, 127.8 (d, *J* = 8.8 Hz), 127.3, 122.4, 119.5 (d, *J* = 23.8 Hz), 111.2 (d, *J* = 23.8 Hz), 63.1, 62.8, 62.3, 61.86, 14.2, 13.9, 13.9, 13.7. IR ($CHCl_3$, cm^{-1}): 3265, 2926, 1679, 1603, 1501, 1473, 1275, 1169, 1031, 801. MS (EI, m/z): 474. Anal. calcd. for $C_{23}H_{23}FN_2O_8$: C, 58.23; H, 4.89; N, 5.90; Found: C, 58.12; H, 4.97; N, 5.79.

Acknowledgements

View Article Online
DOI: 10.1039/C7OB00389G

Authors thank SERB, New Delhi, for financially supporting us with GPP-0303 (YSS/2014/001018) project. P. P. Kaishap thanks UGC for the fellowship. We are grateful to the Director, CSIR-NEIST for his keen interests.

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