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Synthesis of 2-aminoquinolines via palladium-catalyzed intermolecular oxidative cyclization of 2-vinylanilines with isocyanides

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ABSTRACT

An efficient palladium-catalyzed intermolecular oxidative cyclization of 2-vinylanilines with isocyanides to the synthesis of 2-aminoquinolines is achieved. This transformation is applicable to a broad range of 2-vinylanilines and isocyanides.

1. Introduction

Quinoline nucleus is prevalent in a broad range of natural and synthetic compounds which possesses different biological and pharmacological activities.[1] Among them, the significant 2-aminoquinoline derivatives are widely used as potential precursors because they often exhibit many biological and medicinal activities such as antidepressant, antiprotozoal, anthelmintic, and antihypertensive activities.[2] Recently, Cheng and Judd reported that 2-aminoquinoline compound **A** (Fig. 1) is a potent inhibitor of *beta*-site amyloid precursor protein cleaving enzyme 1 (BACE1).[3] Compound **B** was prepared and evaluated by DeVita in melanin-concentrating hormone receptor 1 (MCH1R) binding and functional antagonist assays as a potential target for obesity (Fig. 1).[4] Helical chiral 2-aminopyridinium ion (compound **C**) was found as an obviously more practicable dual hydrogen-bonding catalyst than commonly used (thio)urea-based systems (Fig. 1).[5] Despite the importance of 2-aminoquinoline derivatives, only limited efficient synthetic methods were reported.[6] Therefore, the development of more direct and economical approaches for the efficient synthesis of such compounds is highly desirable.

Isocyanides and CO represent two kinds of versatile C1 synthons which have been extensively applied in organic synthesis chemistry, especially in the synthesis of natural and drug-like products or their intermediates.[7,8] Impressive progress has been made in transition metal-catalyzed carbonylation reactions since the beginning of the 20th century because CO is an inexpensive and easily available C1 source.[8] Though isocyanides as C1 synthons are relatively new, transition-metal-catalyzed isocyanide insertion reaction is an attractive area for the construction of various heterocycles.[9,10] Recently, Alper reported the palladium-catalyzed oxidative cyclocarbonylation of *N*-monosubstituted-2-vinylanilines for the synthesis of 2(1*H*)-quinolines (Scheme 1, Eq. 1).[11] In view of the importance of 2-aminoquinoline compounds and our previous work on the synthesis of 4-aminoquinoline derivatives based on Pd-catalyzed isocyanide insertion (Scheme 1, Eq. 2),[10j,k] we envisioned that Pd-catalyzed intermolecular oxidative cyclization of 2-vinylanilines with isocyanides may offer a new efficient route to 2-aminoquinoline derivatives (Scheme 1, Eq. 3).

2. Results and discussion

Based on our recent work,[10j,k] we began the investigation with 2-vinylaniline **1a** and *tert*-butyl isocyanide **2a** as model substrates in CH_3CN catalyzed by $Pd(OAc)_2$ (10 mol %) in the presence of 1,10-phen (20 mol %), $Cu(OAc)_2$ (2.0 equiv), and Cs_2CO_3 (2.0 equiv). To our disappointment, we failed to observe the desired product

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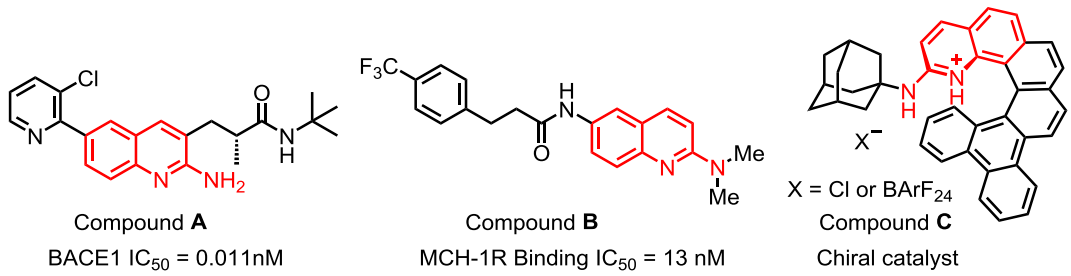
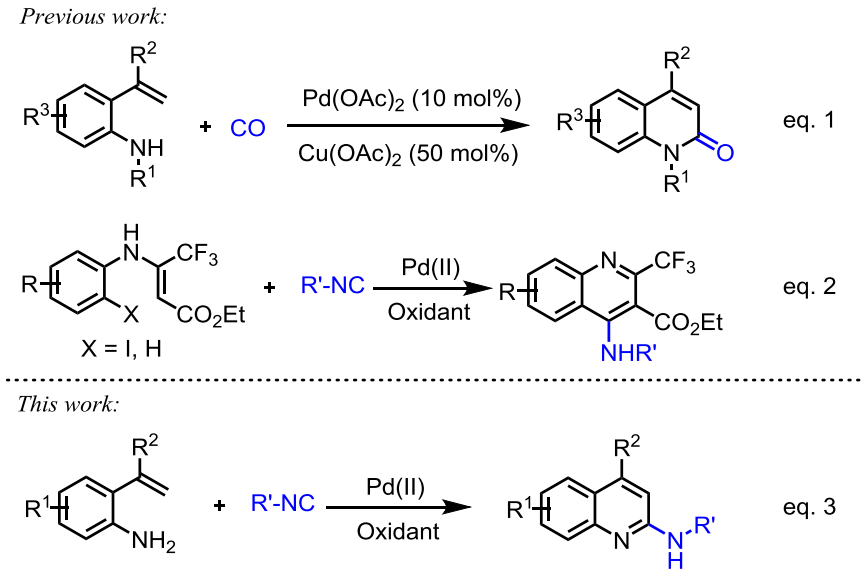


Fig. 1. Representative examples of 2-aminoquinoline-based active molecules and chiral catalyst.



Scheme 1. Pd-catalyzed intermolecular oxidative cyclization.

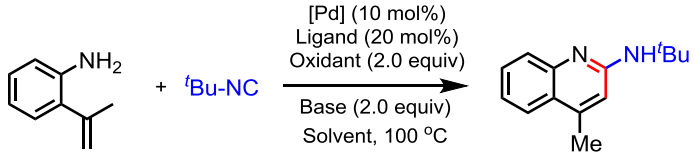
(Table 1, entry 1). However this reaction proceeded smoothly when ethylenediamine was used as ligand, and the product **3a** could be obtained in moderate isolated yield (50%) (Table 1, entry 2). Ligand screening revealed that commercially available bidentate P-ligand (dppe) was the best one, affording 65% yield (Table 1, entries 3–7). Only 45% yield of product **3a** was obtained under ligand-free conditions, which indicated the presence of ligand is critical to the success of the reaction (Table 1, entry 8). Subsequently, screening various bases revealed that the base also played an important role in this transformation, and DBU provided the best yield of 73% (Table 1, entries 9–19). A control reaction showed that no desired product was observed in the absence of base (Table 1, entry 20). Further investigation revealed that $Cu(OAc)_2$ was superior to other oxidants such as $Cu(OAc)_2{\cdot}H_2O$, $CuCl_2$, O_2, and Ag_2CO_3 (Table 1, entries 21–24). Replacing the catalyst $Pd(OAc)_2$ with other Pd(II) and Pd(0) sources failed to increase the reaction activity (Table 1, entries 26–31). Finally, no better results were obtained when the reaction was carried out in other solvents (see SI).

With the optimized conditions in hands, we started to explore the scope of substrates. Electron-donating groups on the aryl ring of 2-vinylaniline are compatible with this reaction (**3b**–**e**), although the 4-methoxy group offers a lower yield (**3e**, 41%). Various electron-withdrawing groups such as fluoro and chloro are well-tolerated in general, providing the desired products (**3f**–**k**) in 63–90% yields. In the cases of bromo-substituted substrates gave the lower yields due to the formation of by-products via Pd-catalyzed isocyanide insertion into C–Br bond. Various 2-(1-arylvinyl)anilines also could proceed well, resulting in the corresponding products (**3n**–**q**) in good yields. For instance, substrate 2-(1-(*p*-tolyl)vinyl)aniline reacted with *tert*-butyl isocyanide **2a** giving the desired product **3o** in 83% yield. Fortunately, the substrate 2-(1-(thiophen-2-yl)vinyl)aniline was also compatible affording the product **3r** in 48% yield (see Table 2).

We further investigated the reaction of several other isocyanides with substrate **1a** under standard conditions. Notably, when other tertiary, secondary, or primary aliphatic isocyanides **2b**–**e** were applied in this process as coupling partners, the reactions proceeded smoothly to afford the desired products **3s**–**v** in moderate yields (48–66%, Table 3, entries 1–4). The results (**3a**, **3s**–**v**) show that the reactivity of tertiary isocyanides (**2a** and **2b**) is a little better than that of secondary and primary isocyanides (**2c**–**e**) (Table 3, entries 2–4). Unfortunately, when aromatic isocyanides (**2f**–**g**) were employed, it was found that only traces of desired products (**3w**–**x**) were observed (Table 3, entries 5 and 6). It is worth noting that when we finished our experiments, we noticed a related but independent work reported by Zeng and co-workers via palladium-catalyzed direct coupling of 2-vinylanilines and isocyanides using expensive Ag_2CO_3 as oxidant.[11] The results of aryl isocyanides also show poor reactivity.

Based on the previous studies,[12] a plausible mechanism for this intermolecular oxidative cyclization is proposed in Scheme 2. Firstly, the addition of nitrogen atom of the aniline to Pd(II) species leads to the formation of a Pd–N bond. Secondly, the coordination and insertion of isocyanide **2a** result in the palladium intermediate **III**. Thirdly, alkene insertion into the Pd–C bond of Pd(II) species **III** could give an alkyl palladium intermediate **IV**. Then, β-hydride elimination of **IV** could generate the products **3a′**, **3a″**, and Pd(0) species. Finally, 2-aminoquinoline **3a** is formed from **3a′** via [1,3]-H-

Table 1
Optimization of reaction conditions[a]



1a **2a** **3a**

Entry	[Pd]	Ligand	Oxidant	Base	Solvent	Yield (%)
1	$Pd(OAc)_2$	1,10-phen	$Cu(OAc)_2$	Cs_2CO_3	CH_3CN	NR
2	$Pd(OAc)_2$	Ethylenediamine	$Cu(OAc)_2$	Cs_2CO_3	CH_3CN	50
3	$Pd(OAc)_2$	DMEDA	$Cu(OAc)_2$	Cs_2CO_3	CH_3CN	46
4	$Pd(OAc)_2$	TMEDA	$Cu(OAc)_2$	Cs_2CO_3	CH_3CN	—
5	$Pd(OAc)_2$	PPh_3	$Cu(OAc)_2$	Cs_2CO_3	CH_3CN	20
6	$Pd(OAc)_2$	dppp	$Cu(OAc)_2$	Cs_2CO_3	CH_3CN	35
7	$Pd(OAc)_2$	dppe	$Cu(OAc)_2$	Cs_2CO_3	CH_3CN	65
8	$Pd(OAc)_2$	—	$Cu(OAc)_2$	Cs_2CO_3	CH_3CN	45
9	$Pd(OAc)_2$	dppe	$Cu(OAc)_2$	K_2CO_3	CH_3CN	30
10	$Pd(OAc)_2$	dppe	$Cu(OAc)_2$	Na_2CO_3	CH_3CN	35
11	**$Pd(OAc)_2$**	**dppe**	**$Cu(OAc)_2$**	**DBU**	**CH_3CN**	**73**
12	$Pd(OAc)_2$	dppe	$Cu(OAc)_2$	DABCO	CH_3CN	61
13	$Pd(OAc)_2$	dppe	$Cu(OAc)_2$	^{t}BuONa	CH_3CN	20
14	$Pd(OAc)_2$	dppe	$Cu(OAc)_2$	Pyridine	CH_3CN	45
15	$Pd(OAc)_2$	dppe	$Cu(OAc)_2$	Et_3N	CH_3CN	40
16	$Pd(OAc)_2$	dppe	$Cu(OAc)_2$	CsOAc	CH_3CN	49
17	$Pd(OAc)_2$	dppe	$Cu(OAc)_2$	CsF	CH_3CN	56
18	$Pd(OAc)_2$	dppe	$Cu(OAc)_2$	$NaHCO_3$	CH_3CN	47
19	$Pd(OAc)_2$	dppe	$Cu(OAc)_2$	NaOAc	CH_3CN	Trace
20	$Pd(OAc)_2$	dppe	$Cu(OAc)_2$	—	CH_3CN	Trace
21	$Pd(OAc)_2$	dppe	$Cu(OAc)_2 \cdot H_2O$	DBU	CH_3CN	65
22	$Pd(OAc)_2$	dppe	$CuCl_2$	DBU	CH_3CN	Trace
23	$Pd(OAc)_2$	dppe	O_2	DBU	CH_3CN	25
24	$Pd(OAc)_2$	dppe	Ag_2CO_3	DBU	CH_3CN	15
25	$Pd(OAc)_2$	dppe	—	DBU	CH_3CN	NR
26	$PdCl_2$	dppe	$Cu(OAc)_2$	DBU	CH_3CN	62
27	$Pd(PhCN)_2Cl_2$	dppe	$Cu(OAc)_2$	DBU	CH_3CN	40
28	$Pd(PPh_3)_2Cl_2$	dppe	$Cu(OAc)_2$	DBU	CH_3CN	38
29	$Pd(TFA)_2$	dppe	$Cu(OAc)_2$	DBU	CH_3CN	50
30	$Pd(PPh_3)_4$	dppe	$Cu(OAc)_2$	DBU	CH_3CN	35
31	$Pd_2(dba)_3$	dppe	$Cu(OAc)_2$	DBU	CH_3CN	36

[a] Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), **2a** (0.4 mmol, 2.0 equiv), [Pd] catalyst: 10 mol %, ligand: 20 mol %, oxidant: 2.0 equiv, base: 2.0 equiv, solvent: 2 mL, 100 °C. NR: no reaction.

shift and aromatization. Pd(II) is regenerated by $Cu(OAc)_2$ to finish the catalytic cycle.

3. Conclusion

In conclusion, we have developed an efficient palladium-catalyzed intermolecular oxidative cyclization of 2-vinylanilines with isocyanides to the synthesis of 2-aminoquinolines in moderate to good yields. The presence of oxidant and base are very crucial for this reaction. Various aliphatic isocyanides (including tertiary, secondary, and primary isocyanides) are compatible in the process.

4. Experimental

4.1. General

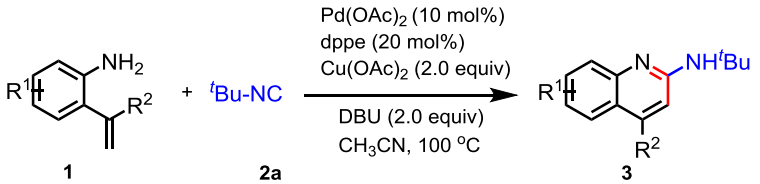
General procedure for the palladium-catalyzed intermolecular oxidative cyclization of 2-vinylanilines with isocyanides to the synthesis of 2-aminoquinolines: A mixture of 2-vinylaniline **1** (0.2 mmol) and isocyanide **2** (0.4 mmol, 2.0 equiv), $Pd(OAc)_2$ (10 mol %), dppe (20 mol %), $Cu(OAc)_2$ (0.4 mmol, 2.0 equiv), DBU (0.4 mmol, 2.0 equiv), and CH_3CN (2 mL) were added into a sealed tube. The mixture was stirred at 100 °C or about 24 h (monitored by TLC). After being cooling to room temperature, evaporation of the solvent under reduced pressure followed purification by silica gel chromatography using petroleum ether/ethyl acetate (20:1 to 10:1) as eluent to provide the desired products **3**.

*4.1.1. N-(tert-Butyl)-4-methylquinolin-2-amine (**3a**).* Isolated (R_f=0.4, EtOAc–petroleum ether=1:10) as a yellow oil (73% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J=8.0 Hz, 1H), 7.66 (d, J=8.4 Hz, 1H), 7.49 (t, J=7.6 Hz, 1H), 7.20 (t, J=7.4 Hz, 1H), 6.46 (s, 1H), 4.58 (s, 1H), 2.53 (s, 3H), 1.53 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 147.9, 144.1, 129.0, 126.8, 123.5, 123.3, 121.6, 113.0, 51.3, 29.6, 18.8. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{19}N_2$; 215.1548; found: 215.1536.

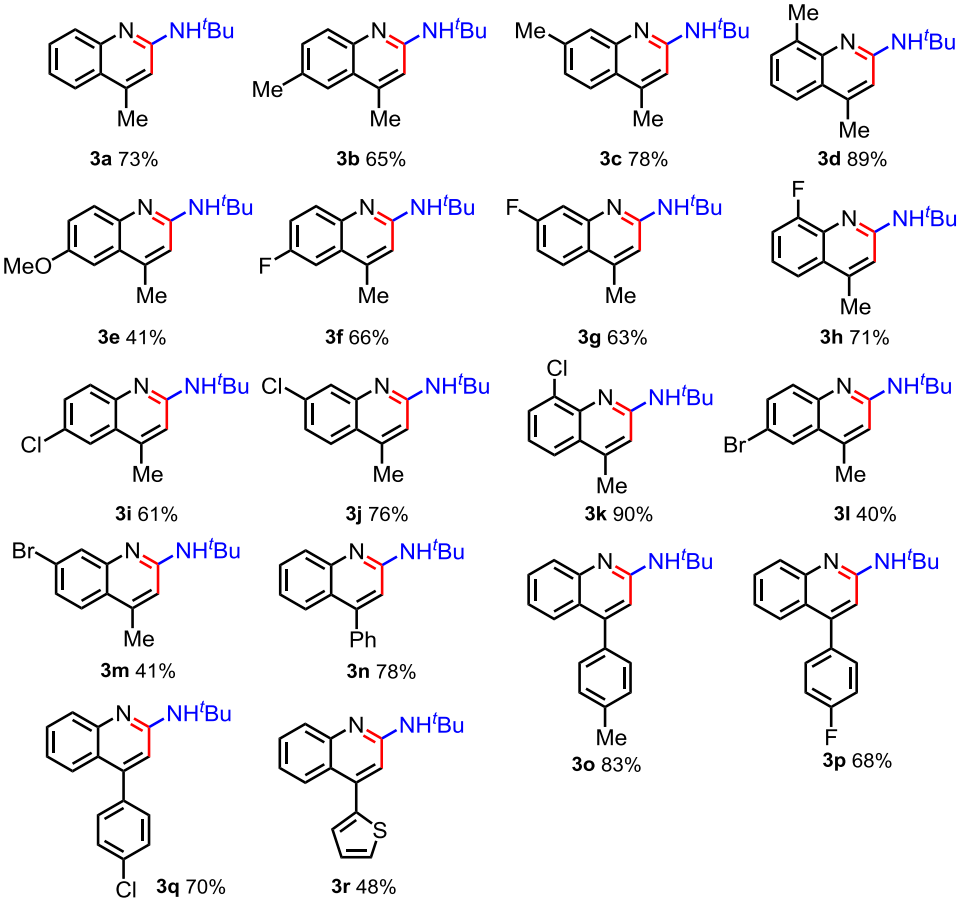
*4.1.2. N-(tert-Butyl)-4,6-dimethylquinolin-2-amine (**3b**).* Isolated (R_f=0.5, EtOAc–petroleum ether=1:10) as a yellow solid (78% yield), mp: 105–107 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J=8.4 Hz, 1H), 7.49 (s, 1H), 7.32 (d, J=6.0 Hz, 1H), 6.43 (s, 1H), 4.48 (s, 1H), 2.50 (s, 3H), 2.45 (s, 3H), 1.51 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 146.3, 143.5, 130.9, 130.8, 126.8, 123.2, 122.7, 112.9, 51.2, 29.7, 21.4, 18.8. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{15}H_{21}N_2$; 229.1705; found: 229.1704.

*4.1.3. N-(tert-Butyl)-4,7-dimethylquinolin-2-amine (**3c**).* Isolated (R_f=0.3, EtOAc–petroleum ether=1:10) as a yellow oil (65% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J=8.4 Hz, 1H), 7.47 (s, 1H), 7.02 (d, J=8.4 Hz, 1H), 6.37 (s, 1H), 4.54 (s, 1H), 2.48 (s, 3H), 2.45 (s,

Table 2
Palladium-catalyzed insertion reactions of *tert*-butyl isocyanides **2a** with substituted 2-vinylanilines **1**



1 **2a** **3**



3H), 1.51 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 148.2, 143.9, 139.0, 126.4, 123.5, 123.2, 121.2, 112.2, 51.3, 29.6, 21.6, 18.7. HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{15}H_{21}N_2$; 229.1705; found: 229.1701.

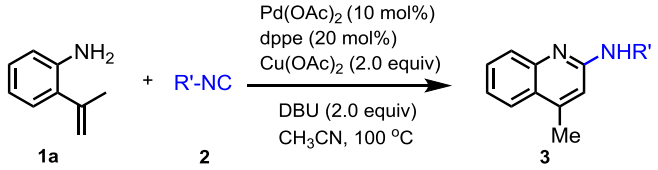
*4.1.4. N-(tert-Butyl)-4,8-dimethylquinolin-2-amine (**3d**).* Isolated (R_f=0.7, EtOAc–petroleum ether=1:20) as a yellow solid (89% yield), mp: 132–135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J*=8.0 Hz, 1H), 7.37 (d, *J*=7.2 Hz, 1H), 7.08 (t, *J*=8.0 Hz, 1H), 6.33 (s, 1H), 4.37 (s, 1H), 2.66 (s, 3H), 2.48 (s, 3H), 1.55 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 146.9, 144.1, 134.8, 129.2, 122.9, 121.3, 121.0, 113.1, 51.4, 29.1, 18.9, 18.8. HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{15}H_{21}N_2$; 229.1705; found: 229.1707.

*4.1.5. N-(tert-Butyl)-6-methoxy-4-methylquinolin-2-amine (**3e**).* Isolated (R_f=0.4, EtOAc–petroleum ether=1:10) as a yellow oil (41% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J*=8.8 Hz, 1H), 7.19 (d, *J*=9.2 Hz, 1H), 7.06 (s, 1H), 6.49 (s, 1H), 3.88 (s, 3H), 2.50 (s, 3H), 1.51 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 154.8, 143.9, 142.2, 123.3, 120.0, 117.2, 113.0, 113.7, 55.6, 51.3, 2.7, 19.0. HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{15}H_{21}N_2O$; 245.1654; found: 245.1640.

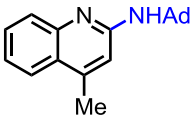
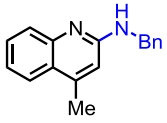
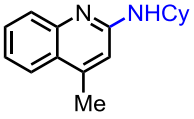
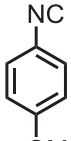
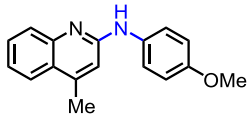
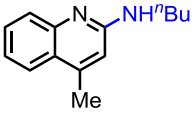
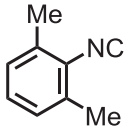
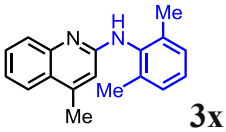
*4.1.6. N-(tert-Butyl)-6-fluoro-4-methylquinolin-2-amine (**3f**).* Isolated (R_f=0.5, EtOAc–petroleum ether=1:20) as a yellow solid (66% yield), mp: 108–110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (dd, *J*=9.2, 5.6 Hz, 1H), 7.33 (dd, *J*=10.0, 2.8 Hz, 1H), 7.26–7.22 (m, 1H), 6.44 (s, 1H), 4.47 (s, 1H), 2.46 (s, 3H), 1.51 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9 (d, $^1J_{C-F}$=238.6 Hz), 155.9, 144.9, 143.3, 128.8 (d, $^3J_{C-F}$=8.4 Hz), 123.5 (d, $^3J_{C-F}$=8.6 Hz), 117.9 (d, $^2J_{C-F}$=24.4 Hz), 113.9, 107.4 (d, $^2J_{C-F}$=22.0 Hz), 51.4, 29.5, 18.7. HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{14}H_{18}N_2F$; 233.1454; found: 233.1452.

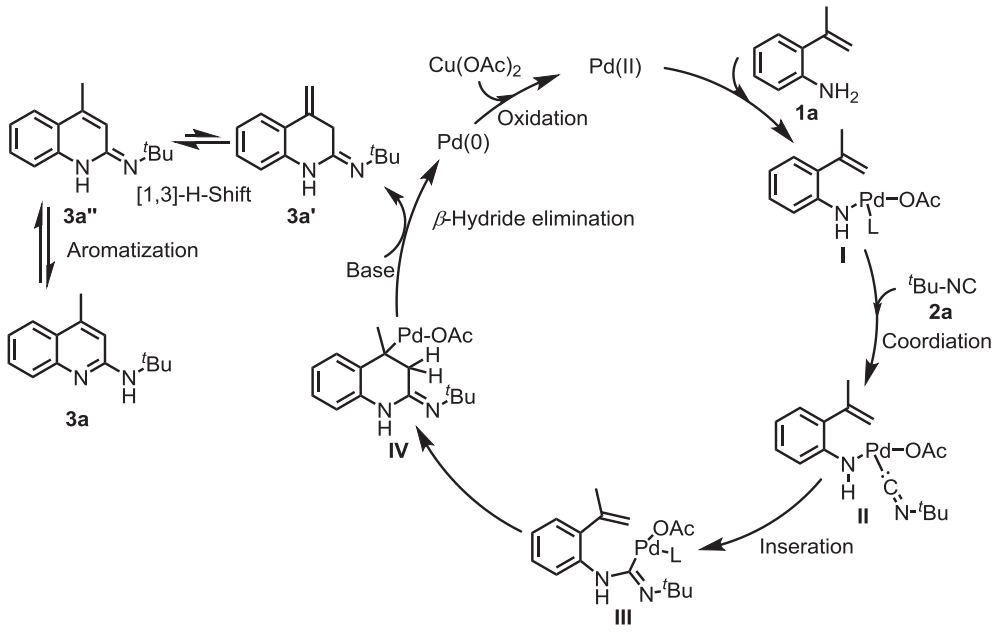
*4.1.7. N-(tert-Butyl)-7-fluoro-4-methylquinolin-2-amine (**3g**).* Isolated (R_f=0.6, EtOAc–petroleum ether=1:20) as a yellow oil (63% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (dd, *J*=8.9, 6.4 Hz, 1H), 7.28 (dd, *J*=11.2, 2.4 Hz, 1H), 6.95–6.91 (m, 1H), 6.35 (s, 1H), 4.57 (s, 1H), 2.47 (s, 3H), 1.51 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4 (d, *J*=244.6 Hz), 157.1, 149.6 (d, *J*=12.9 Hz), 143.8, 125.2 (d, *J*=10.3 Hz),

Table 3
Palladium-catalyzed insertion reactions of various isocyanides **2b**–**g** with 2-(prop-1-en-2-yl)aniline **1a**



1a 2 3

Entry	2	3	Yield (%)	Entry	2	3	Yield (%)
1	AdNC **2b**	 **3s**	66	4	BnNC **2e**	 **3v**	50
2	CyNC **2c**	 **3t**	61	5	 **2f**	 **3w**	Trace
3	^{n}BuNC **2d**	 **3u**	48	6	 **2g**	 **3x**	Trace



Scheme 2. Proposed catalytic cycle.

120.2, 112.3, 111.0, 110.7 (d, J=24.3 Hz), 51.5, 29.5, 18.8. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{18}N_2F$; 233.1454; found: 233.1450.

*4.1.8. N-(tert-Butyl)-8-fluoro-4-methylquinolin-2-amine (**3h**).* Isolated (R_f=0.6, EtOAc–petroleum ether=1:20) as a yellow oil (71% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J=8.0 Hz, 1H), 7.22–7.17 (m, 1H), 7.09–7.04 (m, 1H), 6.48 (s, 1H), 4.73 (s, 1H), 2.50 (s, 3H), 1.52 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0 (d, $^1J_{C-F}$=249.2 Hz), 156.2, 144.0, 138.1 (d, $^3J_{C-F}$=10.6 Hz), 125.3, 120.5 (d, $^3J_{C-F}$=7.9 Hz), 119.0, 113.6, 113.4 (d, $^2J_{C-F}$=19.1 Hz), 51.4, 29.4, 19.1. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{18}N_2F$; 233.1454; found: 233.1445.

*4.1.9. N-(tert-Butyl)-6-chloro-4-methylquinolin-2-amine (**3i**).* Isolated (R_f=0.4, EtOAc–petroleum ether=1:20) as a yellow solid (61% yield), mp: 102–104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J=2.4 Hz, 1H), 7.58 (d, J=8.8 Hz, 1H), 7.41 (dd, J=8.8, 2.4 Hz, 1H), 6.41 (s, 1H), 4.54 (s, 1H), 2.46 (s, 3H), 1.51 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 146.6, 143.1, 129.4, 128.5, 126.7, 124.1, 122.6, 113.9, 51.5, 29.5, 18.6. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{18}N_2Cl$; 249.1159; found: 249.1158.

*4.1.10. N-(tert-Butyl)-7-chloro-4-methylquinolin-2-amine (**3j**).* Isolated (R_f=0.6, EtOAc–petroleum ether=1:20) as a yellow oil (76% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.61 (d, J=8.8 Hz, 1H), 7.12 (d, J=8.8 Hz, 1H), 6.36 (s, 1H), 4.55 (s, 1H), 2.47 (s, 3H), 1.51 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 148.9, 143.7, 134.6, 126.0, 124.7, 122.0, 121.8, 113.3, 51.5, 29.4, 18.6. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{18}N_2Cl$; 249.1159; found: 249.1164.

*4.1.11. N-(tert-Butyl)-8-chloro-4-methylquinolin-2-amine (**3k**).* Isolated (R_f=0.6, EtOAc–petroleum ether=1:20) as a yellow solid (90% yield), mp: 103–105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62–7.60 (m, 2H), 7.06 (t, J=7.8 Hz, 1H), 6.40 (s, 1H), 4.61 (s, 1H), 2.48 (s, 3H), 1.57 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 144.5, 144.2, 131.1, 129.1, 124.5, 122.3, 121.0, 113.8, 51.7, 29.0, 18.9. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{18}N_2Cl$; 249.1159; found: 249.1156.

*4.1.12. 6-Bromo-N-(tert-butyl)-4-methylquinolin-2-amine (**3l**).* Isolated (R_f=0.6, EtOAc–petroleum ether=1:30) as a yellow solid (40% yield), mp: 165–168 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.57–7.50 (m, 2H), 6.42 (s, 1H), 4.55 (s, 1H), 2.47 (s, 3H), 1.51 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 146.9, 143.1, 132.0, 128.8, 125.8, 124.7, 114.5, 113.8, 51.5, 29.5, 18.6. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{18}N_2Br$; 293.0653; found: 293.0660.

*4.1.13. 7-Bromo-N-(tert-butyl)-4-methylquinolin-2-amine (**3m**).* Isolated (R_f=0.6, EtOAc–petroleum ether=1:20) as a yellow oil (41% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.55 (d, J=8.4 Hz, 1H), 7.26 (d, J=8.4 Hz, 1H), 6.38 (s, 1H), 4.55 (s, 1H), 2.47 (s, 3H), 1.52 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 149.2, 143.8, 129.3, 124.8, 124.6, 122.9, 122.0, 113.5, 51.6, 29.4, 18.6. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{18}N_2Br$; 293.0653; found: 293.0658.

*4.1.14. N-(tert-Butyl)-4-phenylquinolin-2-amine (**3n**).* Isolated (R_f=0.7, EtOAc–petroleum ether=1:10) as a yellow oil (78% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J=8.0 Hz, 1H), 7.59 (d, J=8.4 Hz, 1H), 7.54–7.41 (m, 6H), 7.11 (t, J=7.6 Hz, 1H), 6.52 (s, 1H), 4.65 (s, 1H), 1.55 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 148.9, 148.6, 138.7, 129.3, 129.2, 128.4, 128.0, 126.9, 125.6, 121.9, 121.8, 112.9, 51.5, 29.5. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{19}H_{21}N_2$; 277.1705; found: 277.1702.

*4.1.15. N-(tert-Butyl)-4-(p-tolyl)quinolin-2-amine (**3o**).* Isolated (R_f=0.4, EtOAc–petroleum ether=1:20) as a yellow oil (83% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J=8.4 Hz, 1H), 7.61 (d, J=7.2 Hz, 1H), 7.49 (t, J=7.6 Hz, 1H), 7.34 (d, J=8.0 Hz, 2H), 7.27 (d, J=7.8 Hz, 2H), 7.10 (t, J=8.0 Hz, 1H), 6.51 (s, 1H), 4.65 (s, 1H), 2.43 (s, 3H), 1.54 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 148.9, 148.7, 137.9, 135.8, 129.2, 129.1, 126.9, 125.6, 122.1, 121.7, 112.8, 100.0, 51.5, 29.6, 21.3. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{20}H_{23}N_2$; 291.861; found: 291.1870.

*4.1.16. N-(tert-Butyl)-4-(4-fluorophenyl)quinolin-2-amine (**3p**).* Isolated (R_f=0.7, EtOAc–petroleum ether=1:20) as a yellow oil (68% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J=8.0 Hz, 1H), 7.54–7.48 (m, 2H), 7.42–7.39 (m, 2H), 7.19–7.07 (m, 3H), 6.48 (s, 1H), 4.65 (s, 1H), 1.55 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7 (d, J_{C-F}=247.2 Hz), 156.0, 148.7, 147.8, 134.7, 131.0 (d, J_{C-F}=8.0 Hz), 129.3, 127.1, 125.3, 121.9, 121.9, 115.5 (d, J_{C-F}=21.0 Hz), 113.1, 51.5, 29.5. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{19}H_{20}N_2F$; 295.1611; found: 295.1618.

*4.1.17. N-(tert-Butyl)-4-(4-chlorophenyl)quinolin-2-amine (**3q**).* Isolated (R_f=0.5, EtOAc–petroleum ether=1:20) as a yellow oil (70% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J=8.0 Hz, 1H), 7.53 (d, J=8.4 Hz, 1H), 7.49 (d, J=7.6 Hz, 1H), 7.42–7.39 (m, 2H), 7.18–7.11 (m, 3H), 6.47 (s, 1H), 4.64 (s, 1H), 1.55 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 161.5, 156.0, 148.7, 147.8, 134.7, 131.0, 130.9, 129.3, 127.1, 125.3, 121.9, 115.5, 115.3, 113.1, 51.5, 29.5. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{19}H_{20}N_2Cl$; 311.1315; found: 311.1318.

*4.1.18. N-(tert-Butyl)-4-(thiophen-2-yl)quinolin-2-amine (**3r**).* Isolated (R_f=0.6, EtOAc–petroleum ether=1:20) as a yellow oil (48% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J=8.4 Hz, 1H), 7.73 (d, J=8.4 Hz, 1H), 7.52 (t, J=8.4 Hz, 1H), 7.44 (d, J=5.2 Hz, 1H), 7.30 (d, J=3.2 Hz, 1H), 7.20–7.17 (m, 2H), 6.65 (s, 1H), 4.66 (s, 1H), 1.55 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 148.8, 141.1, 139.5, 129.4, 127.8, 127.5, 127.1, 126.2, 125.2, 122.1, 121.6, 113.5, 51.6, 29.5. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{17}H_{19}N_2S$; 283.1269; found: 283.1277.

*4.1.19. N-(((3R,5R,7R)-Adamantan-1-yl)methyl)-4-methylquinolin-2-amine (**3s**).* Isolated (R_f=0.4, EtOAc–petroleum ether=1:10) as a yellow solid (66% yield), mp: 139–142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J=8.4 Hz, 1H), 7.64 (d, J=8.4 Hz, 1H), 7.48 (t, J=7.8 Hz, 1H), 7.19 (t, J=7.8 Hz, 1H), 6.49 (s, 1H), 4.55 (s, 1H), 2.52 (s, 3H), 2.33–2.05 (m, 9H), 1.80–1.66 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 148.0, 144.1, 129.0, 126.8, 123.4, 123.3, 121.5, 113.2, 51.9, 42.5, 36.7, 29.8, 18.8. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{20}H_{25}N_2$; 293.2018; found: 293.2021.

*4.1.20. N-Cyclohexyl-4-methylquinolin-2-amine (**3t**).* Isolated (R_f=0.2, EtOAc–petroleum ether=1:10) as a yellow oil (61% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J=8.0 Hz, 1H), 7.64 (d, J=8.8 Hz, 1H), 7.49 (t, J=8.0 Hz, 1H), 7.19 (t, J=7.8 Hz, 1H), 6.47 (s, 1H), 4.62 (s, 1H), 3.85–3.79 (m, 1H), 2.55 (s, 3H), 2.11–2.07 (m, 2H), 1.79–1.74 (m, 2H), 1.70–1.62 (m, 1H), 1.50–1.39 (m, 2H), 1.32–1.16 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 148.3, 144.9, 129.2, 126.4, 123.7, 123.5, 121.5, 111.1, 49.8, 33.6, 25.8, 25.0, 18.9. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{16}H_{21}N_2$; 241.1705; found: 241.1697.

*4.1.21. N-Butyl-4-methylquinolin-2-amine (**3u**).* Isolated (R_f=0.6, EtOAc–petroleum ether=1:3) as a yellow oil (48% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J=8.4 Hz, 1H), 7.67 (d, J=8.4 Hz, 1H), 7.52 (t, J=7.6 Hz, 1H), 7.22 (t, J=7.8 Hz, 1H), 6.50 (s, 1H), 4.83 (s, 1H), 3.48–3.43 (m, 2H), 2.57 (s, 3H), 1.70–1.58 (m, 2H), 1.49–1.43 (m, 2H), 0.97 (t, J=7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9147.8, 145.2, 129.4, 126.3, 123.7, 123.6, 121.7, 110.9, 41.6, 31.9, 20.2, 18.9,

13.9. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{19}N_2$; 215.1548; found: 215.1554.

*4.1.22. N-Benzyl-4-methylquinolin-2-amine (**3v**).* Isolated (R_f=0.4, EtOAc–petroleum ether=1:5) as a yellow oil (50% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J=8.0 Hz, 1H), 7.71 (d, J=8.4 Hz, 1H), 7.54 (t, J=7.6 Hz, 1H), 7.41 (d, J=7.4 Hz, 2H), 7.34 (t, J=7.2 Hz, 2H), 7.28 (d, J=7.2 Hz, 1H), 7.24 (d, J=7.2 Hz, 1H), 6.50 (s, 1H), 5.08 (s, 1H), 4.72 (d, J=5.2 Hz, 2H), 2.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 145.3, 139.5, 129.4, 128.6, 127.7, 127.3, 123.9, 123.6, 122.0, 111.3, 45.8, 18.8. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{17}H_{17}N_2$; 249.1392; found: 249.1396.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2015.12.060.

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