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Synthesis of 3,4-disubstituted cinnolines by the Pd-catalyzed annulation of 2-iodophenyltriazenes with an internal alkyne

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ABSTRACT

A simple and efficient synthesis of cinnolines was achieved by a palladium-catalyzed annulation methodology. 3,4-Disubstituted cinnolines are prepared via palladium-catalyzed annulation of 2-iodophenyltriazenes with an internal alkyne in moderate to good yields. Several internal alkynes are applicable to this reaction and it is compatible with a number of functional groups.

1. Introduction

Cinnolines and their derivatives exhibit a broad range of biological activity, such as: anticancer, fungicidal, bactericidal, and anti-inflammatory properties.[1] Additionally, compounds containing a cinnoline fragment demonstrate a series of interesting physical characteristics, such as luminescent and nonlinear optical properties.[2] Hence, the synthesis of cinnoline has been studied for many years.[3] Most syntheses of cinnolines involve arenediazonium salts,[4] arylhydrazones,[5] arylhydrazines,[6] and nitriles[7] as their starting materials. These procedures often suffer from certain drawbacks, such as multi-step reactions and harsh reaction conditions. Recently, alkynyl-substituted aryltriazene was used as the precursor to prepare cinnoline,[8] however high temperatures or strong acidic conditions were still required. These reported annulation reactions prompted us to investigate a single catalytic reaction to prepare cinnolines and their derivatives. Palladium-catalyzed annulation of alkynes by functionally substituted aryl halides has been demonstrated to be a versatile methodology to construct a wide variety of complicated hetero- and carbocycles.[9] Herein, we would like to report a novel and efficient protocol to synthesize various 3,4-disubstituted cinnolines by the reaction of 2-iodotriazenes with internal alkyne with a palladium catalyst.

2. Results and discussion

The palladium-catalyzed reactions of 2-iodophenyltriazene with diphenylacetylene are summarized in Table 1. 2-Iodophenyltriazene **1a** was treated with diphenylacetylene (3 equiv) and Et_3N (2 equiv) in the presence of 10 mol % $Pd(dba)_2$ in DMF and the reaction mixture was heated at 100 °C for 24 h. As we expected, 3,4-diphenylcinnoline **3a** was obtained in 40% yield (entry 1). Polar solvents gave better yields and DMF was found as the best solvent amongst the four solvents examined (entries 1–4). $PdCl_2/PPh_3$ gave a similar result with 42% yield of **3a** (entry 5). Various phosphine ligands were tested and P(*o*-Tolyl)$_3$ gave higher yield than the others (entries 6–9). Furthermore, different bases, such as Et_3N, $^{i}Pr_2NEt$, $^{n}Bu_3N$, and K_2CO_3 were tested in the reaction, it was revealed that $^{n}Bu_3N$ is superior to the others (entries 10–13). When lower catalyst loadings were tested with 7.5 mol % and 5 mol % $PdCl_2$, cinnoline **3a** was still obtained in 71% and 69% yields, although they required longer reaction times, 15 h and 36 h, respectively (entries 13 and 14). We therefore conclude that the optimal reaction conditions for this annulation reaction is as follows: a mixture of 2-iodophenyltriazene and 3 equiv of alkyne in DMF in the presence of 7.5 mol % of $PdCl_2$, 15 mol % P(*o*-Tolyl)$_3$ and 2 equiv of $^{n}Bu_3N$ are stirred at 90 °C.

We proceeded to examine the scope and generality of this reaction. A series of 4-substituted phenyltriazenes were employed in this reaction (Table 2). We found that the reaction can tolerate a lot of functional groups, such as alkyl, methoxy, cyano, nitro, trifluoromethyl, acetyl, and methoxycarbonyl groups. The triazenes

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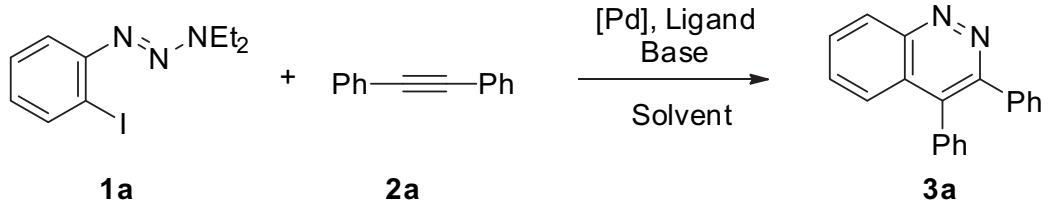
Table 1
Palladium-catalyzed reaction of 2-iodophenyltriazene **1a** with Diphenylacetylene **2a**[a]

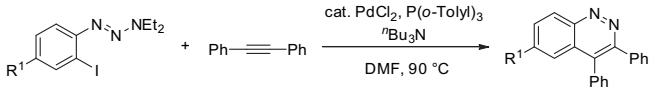


1a **2a** **3a**

Entry	Catalyst	Solvent	Base	Ligand	Temp (°C)	Time (h)	Yield (%)
1	$Pd(dba)_2$	DMF	Et_3N	None	100	24	40
2	$Pd(dba)_2$	CH_3CN	Et_3N	None	Reflux	24	30
3	$Pd(dba)_2$	Toluene	Et_3N	None	100	24	7
4	$Pd(dba)_2$	1,4-Dioxane	Et_3N	None	100	24	8
5	$PdCl_2$	DMF	Et_3N	PPh_3	90	24	42
6	$PdCl_2$	DMF	Et_3N	P(*o*-Tolyl)$_3$	90	12	62
7	$PdCl_2$	DMF	Et_3N	dppe	90	24	Trace
8	$PdCl_2$	DMF	Et_3N	dppf	90	24	45
9	$PdCl_2$	DMF	Et_3N	P(2-Furyl)$_3$	90	24	30
10	$PdCl_2$	DMF	$^iPr_2NEt$	P(*o*-Tolyl)$_3$	90	24	65
11	$PdCl_2$	DMF	$^nBu_3N$	P(*o*-Tolyl)$_3$	90	12	67
12	$PdCl_2$	DMF	K_2CO_3	P(*o*-Tolyl)$_3$	100	12	65
13	$PdCl_2$	DMF	$^nBu_3N$	P(*o*-Tolyl)$_3$	90	15	71[b]
14	$PdCl_2$	DMF	$^nBu_3N$	P(*o*-Tolyl)$_3$	90	24	69[c]

[a] Compound **1a** (0.25 mmol), **2a** (0.75 mmol), [Pd] (10 mol %), ligand (20 mol %), base (0.5 mmol), and solvent (5 mL) were heated under N_2.
[b] $PdCl_2$ (7.5 mol %) and 15 mol % P(*o*-Tolyl)$_3$ were employed.
[c] $PdCl_2$ (5 mol %) and 10 mol % P(*o*-Tolyl)$_3$ were employed.

Table 2
Palladium-Catalyzed Reaction of 2-Iodophenyltriazene **1** with diphenylacetylene **2a**[a]



1a-i **2a** **3a-i**

Entry	R^1	Time (h)		Yield (%)
1	H (**1a**)	15	**3a**	71
2	Me (**1b**)	15	**3b**	73
3	^{t}Bu (**1c**)	12	**3c**	84
4	OMe (**1d**)	15	**3d**	50[b]
5	CN (**1e**)	24	**3e**	42
6	NO_2 (**1f**)	36	**3f**	46[c]
7	CF_3 (**1g**)	24	**3g**	52
8	COMe (**1h**)	18	**3h**	64
9	COOMe (**1i**)	24	**3i**	60

[a] Conditions: **1** (0.25 mmol), **2a** (0.75 mmol), $PdCl_2$ (7.5 mol %), P(*o*-Tolyl)$_3$ (15 mol %), and $^nBu_3N$ (0.5 mmol) in 5 mL DMF under N_2 atm, 90 °C.
[b] K_2CO_3 (2 equiv) was used as base and stirred at 100 °C for 24 h.
[c] $^nBu_3N$ (5 equiv) was employed.

gave the corresponding annulation products in moderate to good yields. Amongst these substrates triazenes bearing alkyl substitutions lead to higher yields (entries 2 and 3).

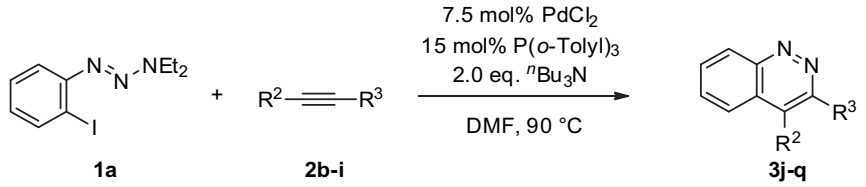
Next, we examined the applicability of internal alkynes for this reaction (Table 3). Symmetrical alkynes were tested first to check the functional group tolerance. When 4,4′-substituted diphenylacetylenes **2b**–**e** were used in the reaction with 3,3-diethyl-(2-iodophenyl)triazene (**1a**), the corresponding 3,4-disubstituted cinnolines **3j**–**m** were obtained in good yields (entries 1–4). Thus, carbonyl and chloro groups on the phenyl ring of the internal alkyne were found to be tolerated. When we used unsymmetrical alkynes, such as ethyl phenylpropiolate (**2g**), 1-phenylpropyne (**2h**), and 1-phenylhexyne (**2i**), two regioisomers of cinnolines were obtained in moderate yields in 56:44, 59:41, and 33:67 ratios, respectively (entries 6–8). Although the consumption of the iodophenyltriazene **1a** was faster in the reaction with electron deficient alkyne such as ethyl phenylpropiolate, the reaction gave cinnoline and unidentified byproducts. (3,3-Diethoxyprop-1-ynyl) benzene (**2f**) gave a mixture of regioselective products, 3-phenylcinnolines having an acetal or aldehyde moiety. Coordination of the ethoxy group of the alkyne may facilitate the regioselective addition of organopalladium intermediate although we are not sure because the yield of the regioselective product is not high enough to discuss the regioselectivity.

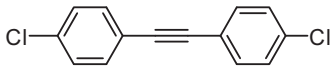
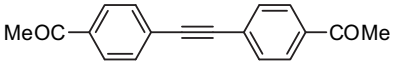
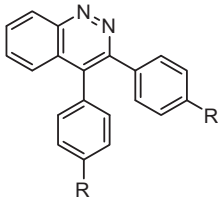
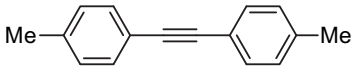
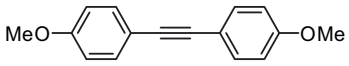
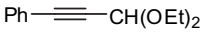
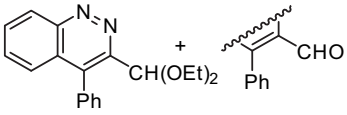
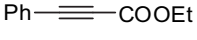
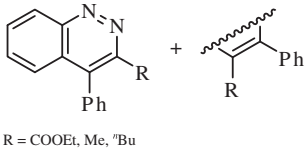
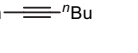
Plausible mechanisms for the annulation reaction of **1** with internal alkyne **2** are illustrated in Scheme 1. Oxidative addition of the 2-iodoaryltriazene to the in situ generated palladium(0) species leads to arylpalladium intermediate **A**, which is followed by the formation of vinylpalladium iodide complex **B** via addition to the alkyne. One pathway is intermediate **B** undergoes a 6-*endo* addition[10] of the vinylpalladium intermediate to the nitrogen–nitrogen double bond to form an aminopalladium intermediate **F**[11] or a 6π electron cyclization[8c–e] occurs to give another aminopalladium intermediate **E**. And then β-amino elimination from **E** or **F** forms the desired cinnoline as well as a diethylaminopalladium species, which undergoes a β-hydride elimination and subsequent elimination of HI by base to regenerate the Pd(0) catalyst. An alternative pathway is that coordination of the pendent triazene to vinylic palladium to form a seven-membered palladacyle **C**, which subsequently generates a diethyliminoimmonium salt **D** as well as Pd(0) via reductive elimination.[12] As previously suggested by Haley the diethyliminommounium salt **D** would afford cinnoline **3** in presence of base.[8d]

3. Conclusion

In summary, we have demonstrated a simple and efficient strategy for the synthesis of potentially important 3,4-disubstituted cinnoline derivatives by palladium-catalyzed annulation of *o*-iodophenyltriazene and internal alkyne. A wide range of functionalized *o*-iodophenyltriazene as well as symmetric and asymmetric internal alkyne can be utilized.

Table 3
Synthesis of 3,4-disubstituted cinnoline of **1a** with **2**[a]



Entry	Alkyne	Time (h)	Product	Yield %
1		18	**3j**	75
2		18	 R = Cl, COMe, Me, OMe **3k**	82
3		18	**3l**	73
4		15	**3m**	78
5		15	 **3n**+**3n′** (92:8)	50
6		15	**3o**+**3o′** (56:44)	35
7		15	 R = COOEt, Me, ^{n}Bu **3p**+**3p′** (59:41)	81[b]
8		15	**3q**+**3q′** (33:67)	80

[a] Conditions: **1a** (0.25 mmol), **2** (0.75 mmol), $PdCl_2$ (7.5 mol %), P(*o*-Tolyl)$_3$ (15 mol %), and ^{n}Bu$_3$N (0.5 mmol) in 5 mL DMF under N_2, 90 °C.
[b] The two regioisomers were obtained as an inseparable mixture and their regiostructures were not assigned.

4. Experimental

4.1. General

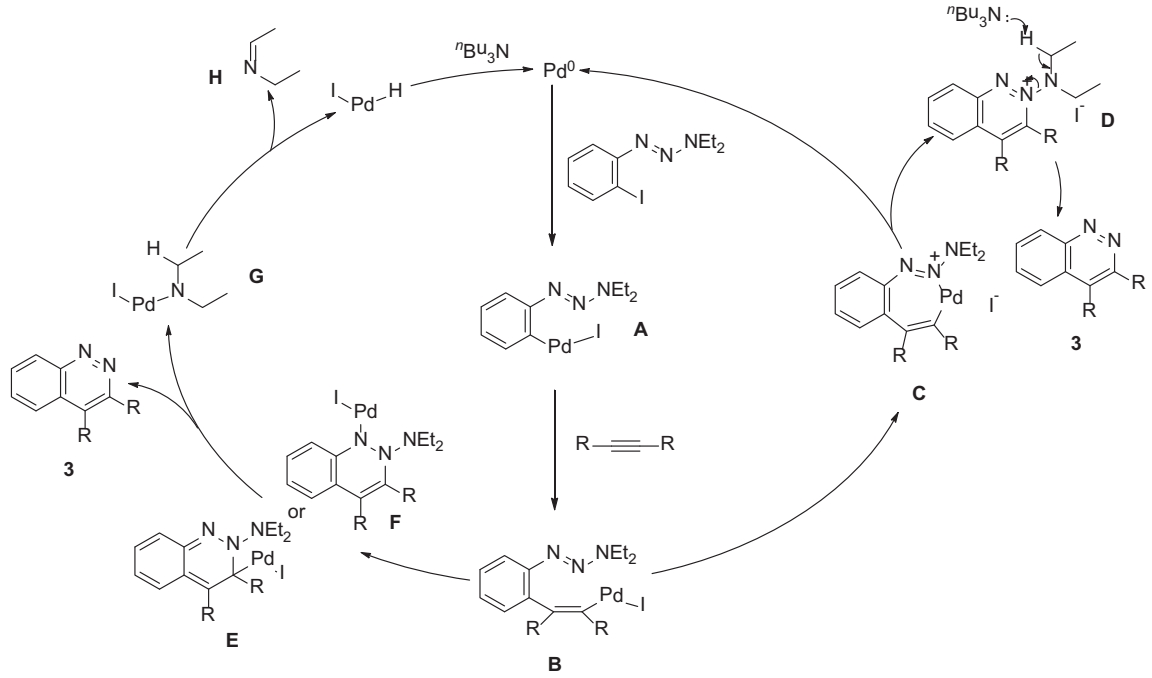
^{1}H NMR spectra were recorded at Bruker 400 MHz in $CDCl_3$ [using $(CH_3)_4Si$ (for ^{1}H, δ=0.00) as internal standard]. ^{13}C NMR spectra were recorded at Bruker 100 MHz in $CDCl_3$ [using $CDCl_3$ (for ^{13}C, δ=77.00) as internal standard]. IR spectra were recorded on a Shimazu IR Prestige-21 FT-IR Spectrometer. High-resolution mass spectra were obtained with a Finnigan MAT 95 XP mass spectrometer (Thermo Electron Corporation). Melting points were uncorrected and were recorded on a Buchi B-54 melting point apparatus.

Compounds **1a**–**i** were prepared according to known procedures.[8e]

*4.1.1. 1-[4-(3,3-Diethyltriaz-1-en-1-yl)-3-iodophenyl]ethan-1-one (**1i**).* Yellow oil; IR (neat) 2974, 2934, 2872, 1674, 1581, 1542 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.35 (dt, *J*=19.6, 7.0 Hz, 6H), 3.84 (q, *J*=7.0 Hz, 4H), 7.40 (d, 1H, *J*=8.4 Hz), 7.87 (dd, *J*=8.4, 1.6 Hz, 1H), 8.42 (d, *J*=1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=10.9, 14.4, 26.5, 42.7, 49.7, 96.2, 116.8, 128.9, 134.8, 139.8, 153.9, 196.1. ESI-HRMS calcd for $C_{12}H_{17}N_3OI$ 346.0416, found 346.0416.

4.2. General procedure for annulation of 2-iodoaryltriazene with internal alkyne

A solution of compound **1** (0.25 mmol), alkyne (0.75 mmol), $PdCl_2$ (3.3 mg, 0.02 mmol), P(*o*-Tolyl)$_3$ (11.4 mg, 0.04 mmol), and



Scheme 1. Possible reaction mechanisms.

^{n}Bu$_3$N (119 μL, 0.50 mmol) in DMF (5 mL) was stirred at 90 °C until **1** was consumed as monitored by TLC. The reaction mixture was allowed to cool to room temperature. The solvent was evaporated and the residue was purified by column chromatography on silica gel (hexane/ethyl acetate/dichloromethane 10–5:1:1) to afford corresponding cinnoline.

*4.2.1. 3,4-Diphenylcinnoline (**3a**)*[13]. R_f=0.29 (ethyl acetate/hexane 1:3); yield: 71% (50.1 mg, 0.18 mmol); pale yellow solid; mp 150–151 °C (ethyl acetate); IR (neat) 3105, 3061, 2980, 2930, 2245, 1636 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.24–7.28 (m, 5H), 7.40–7.42 (m, 3H), 7.47–7.49 (m, 2H), 7.64–7.68 (m, 1H), 7.72–7.75 (m, 1H), 7.80–7.84 (m, 1H), 8.61–8.64 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=125.3, 125.5, 127.87, 127.9, 128.3, 128.5, 129.8, 129.9, 130.4, 130.5, 131.2, 132.9, 134.1, 137.6, 149.4, 153.0. ESI-HRMS: found: *m*/*z* 283.1236. Calcd for $C_{20}H_{15}N_2$: $(M+H)^+$ 283.1235.

*4.2.2. 6-Methyl-3,4-diphenylcinnoline (**3b**).* R_f=0.27 (ethyl acetate/hexane 1:3); yield: 73% (54.0 mg, 0.18 mmol); pale yellow solid; mp 211–212 °C (ethyl acetate); IR (neat) 3055, 2982, 2951, 2305, 1622 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ=2.47 (s, 3H), 7.22–7.26 (m, 5H), 7.39–7.41 (m, 3H), 7.45–7.47 (m, 3H), 7.63 (dd, *J*=8.4, 1.2 Hz, 1H), 8.49 (d, *J*=8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=22.2, 123.5, 125.6, 127.8, 128.2, 128.5, 129.6, 130.4, 130.5, 132.3, 134.3, 137.8, 141.9, 148.4, 153.0. ESI-HRMS: found: *m*/*z* 297.1398. Calcd for $C_{21}H_{17}N_2$: $(M+H)^+$ 297.1392.

*4.2.3. 6-tert-Butyl-3,4-diphenylcinnoline (**3c**).* R_f=0.37 (ethyl acetate/hexane 1:3); yield: 84% (71.2 mg, 0.21 mmol); pale yellow solid; mp 147–148 °C; IR (neat) 3051, 2966, 2909, 2870, 1620, 1554 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.32 (s, 9H), 7.25–7.27 (m, 5H), 7.40–7.41 (m, 3H), 7.46–7.48 (m, 2H), 7.65 (d, *J*=2.0 Hz, 1H), 7.92 (dd, *J*=8.8, 2.0 Hz, 1H), 8.55 (d, *J*=8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=30.7, 35.5, 119.6, 125.3, 127.7, 127.8, 128.2, 128.4, 129.1, 129.4, 130.4, 130.5, 133.0, 134.3, 137.9, 148.4, 153.1, 154.4. ESI-HRMS: found: *m*/*z* 339.1861. Calcd for $C_{24}H_{23}N_2$: $(M+H)^+$ 339.1869.

*4.2.4. 6-Methoxy-3,4-diphenylcinnoline (**3d**).* R_f=0.22 (ethyl acetate/hexane 1:3); yield: 50% (39.1 mg, 0.13 mmol); pale brown solid; mp 161–162 °C (ethyl acetate); IR (neat) 3084, 3055, 2980, 2964, 2253, 1620 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ=3.77 (s, 3H), 6.87 (d, *J*=2.8 Hz, 1H), 7.23–7.26 (m, 5H), 7.39–7.46 (m, 5H), 8.48 (d, *J*=9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=55.6, 101.3, 123.6, 127.6, 127.8, 128.2, 128.6, 130.2, 130.5, 131.7, 131.9, 134.6, 137.8, 146.8, 153.0, 161.2. ESI-HRMS: found: *m*/*z* 313.1347. Calcd for $C_{21}H_{17}N_2O$: $(M+H)^+$ 313.1341.

*4.2.5. 3,4-Diphenylcinnoline-6-carbonitrile (**3e**).* R_f=0.30 (ethyl acetate/hexane 1:3); yield: 42% (32.3 mg, 01.0 mmol); yellow solid; mp 171–172 °C (ethyl acetate); IR (neat) 3103, 3055, 2984, 2253, 2231, 1645, 1616 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.24–7.26 (m, 2H), 7.31–7.32 (m, 3H), 7.48–7.49 (m, 5H), 7.95 (dd, *J*=8.8, 1.6 Hz, 1H), 8.16 (d, *J*=1.6 Hz, 1H), 8.75 (d, *J*=8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=114.9, 117.8, 125.0, 128.1, 128.6, 129.0, 129.2, 130.0, 130.2, 130.5, 131.6, 132.7, 132.8, 136.7, 148.4, 154.5. ESI-HRMS: found: *m*/*z* 308.1198. Calcd for $C_{21}H_{14}N_3$: $(M+H)^+$ 308.1188.

*4.2.6. 6-Nitro-3,4-diphenylcinnoline (**3f**).* R_f=0.36 (ethyl acetate/hexane 1:3); yield: 46% (37.6 mg, 0.12 mmol); yellow solid; mp 192–193 °C (ethyl acetate); IR (neat) 3090, 3049, 2986, 2305, 1624 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.27–7.33 (m, 5H), 7.48–7.50 (m, 5H), 8.53–8.56 (m, 1H), 8.69 (d, *J*=2.0 Hz, 1H), 8.81 (d, *J*=9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=123.0, 123.2, 125.0, 128.1, 128.6, 129.1, 129.3, 130.3, 130.5, 132.4, 132.6, 134.2, 136.5, 148.4, 149.1, 154.5; ESI-HRMS: found: *m*/*z* 328.1092. Calcd for $C_{20}H_{14}N_3O_2$: $(M+H)^+$ 328.1086.

*4.2.7. 3,4-Diphenyl-6-(trifluoromethyl)cinnoline (**3g**).* R_f=0.52 (ethyl acetate/hexane 1:3); yield: 52% (45.4 mg, 0.13 mmol); yellow solid; mp 164–165 °C (ethyl acetate); IR (neat) 3084, 3053, 2984, 2253, 1634 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.26–7.31

(m, 5H), 7.45–7.49 (m, 5H), 7.97–8.00 (m, 1H), 8.07 (s, 1H), 8.77 (d, J=8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=122.0, 123.3 (q, J=272.0 Hz), 123.7 (q, J=5.0 Hz), 124.8, 125.5 (q, J=3.0 Hz), 128.0, 128.4, 128.89, 128.94, 130.3, 130.5, 131.6, 132.5 (q, J=22.0 Hz), 133.1, 133.6, 137.0, 149.2, 154.2. ESI-HRMS: found: m/z 351.1119. Calcd for $C_{21}H_{14}F_3N_2$: $(M+H)^+$ 351.1109.

*4.2.8. 1-(3,4-Diphenylcinnolin-6-yl)ethan-1-one (**3h**).* R_f=0.19 (ethyl acetate/hexane 1:3); yield: 64% (51.8 mg, 0.16 mmol); yellow solid; mp 170–171 °C (ethyl acetate); IR (neat) 3053, 2984, 2304, 2252, 1687 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ=2.60 (s, 3H), 7.27–7.31 (m, 5H), 7.44–7.49 (m, 5H), 8.32–8.34 (m, 2H), 8.69 (d, J=9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=26.7, 125.0, 127.5, 127.8, 128.0, 128.2, 128.79, 128.85, 130.4, 130.5, 130.6, 133.4, 134.0, 137.1, 138.3, 149.7, 154.0, 197.0. ESI-HRMS: found: m/z 325.1335. Calcd for $C_{22}H_{17}N_2O$: $(M+H)^+$ 325.1341.

*4.2.9. Methyl 3,4-diphenylcinnoline-6-carboxylate (**3i**).* R_f=0.30 (ethyl acetate/hexane 1:3); yield: 60% (51.0 mg, 0.15 mmol); yellow solid; mp 199–200 °C (ethyl acetate); IR (neat) 3053, 2986, 2955, 2305, 1724 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ=3.94 (s, 3H), 7.26–7.30 (m, 5H), 7.44–7.49 (m, 5H), 8.37–8.40 (m, 1H), 8.49–8.50 (m, 1H), 8.66–8.69 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=52.7, 124.8, 128.0, 128.2, 128.8, 129.2, 130.4, 130.5, 132.1, 133.4, 133.9, 137.2, 149.7, 153.9, 165.8. ESI-HRMS: found: m/z 341.1294. Calcd for $C_{22}H_{17}N_2O_2$: $(M+H)^+$ 341.1290.

*4.2.10. 3,4-Bis(4-chlorophenyl)cinnoline (**3j**).* R_f=0.31 (ethyl acetate/hexane 1:3); yield: 75% (65.6 mg, 0.19 mmol); pale yellow solid; mp 164–165 °C (ethyl acetate); IR (neat) 3053, 2984, 2305, 1645, 1636, 1597 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.20 (d, J=8.4 Hz, 2H), 7.28 (d, J=8.4 Hz, 2H), 7.40 (d, J=8.4 Hz, 2H), 7.43 (d, J=8.4 Hz, 2H), 7.70 (m, 2H), 7.84 (m, 1H), 8.61 (d, J=8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=124.8, 125.1, 128.3, 129.1, 130.0, 130.2, 131.61, 131.65, 131.7, 131.8, 132.3, 134.4, 134.8, 135.8, 149.3, 151.7. ESI-HRMS: found: m/z 351.0453. Calcd for $C_{20}H_{13}Cl_2N_2$: $(M+H)^+$ 351.0456.

*4.2.11. 1-{4-[3-(4-Acetylphenyl)cinnolin-4-yl]phenyl}ethan-1-one (**3k**).* R_f=0.22 (ethyl acetate/hexane 1:1); yield: 82% (75.0 mg, 0.20 mmol); pale yellow solid; mp 182–183 °C (ethyl acetate); IR (neat) 3053, 3003, 2984, 1684, 1606 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ=2.60 (s, 3H), 2.66 (s, 3H), 7.40 (d, J=8.4 Hz, 2H), 7.58 (d, J=8.4 Hz, 2H), 7.68 (d, J=8.4 Hz, 1H), 7.75 (dd, J=8.4, 6.8 Hz, 1H), 7.88–7.93 (m, 3H), 8.03 (d, J=8.4 Hz, 2H), 8.68 (d, J=8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=26.6, 124.8, 124.9, 128.0, 130.2, 130.6, 130.71, 130.74, 131.9, 132.3, 136.4, 137.0, 138.7, 141.9, 149.4, 151.6, 197.3, 197.7. ESI-HRMS: found: m/z 367.1448. Calcd for $C_{24}H_{19}N_2O_2$: $(M+H)^+$ 367.1447.

*4.2.12. 3,4-Bis(4-methylphenyl)cinnoline (**3l**).* R_f=0.38 (ethyl acetate/hexane 1:3); yield: 73% (56.6 mg, 0.18 mmol); pale yellow solid; mp 136–137 °C (ethyl acetate); IR (neat) 3049, 3030, 2982, 2922, 2243, 1612 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ=2.32 (s, 3H), 2.40 (s, 3H), 7.08 (d, J=8.0 Hz, 2H), 7.13 (d, J=8.0 Hz, 2H), 7.21 (d, J=8.0 Hz, 2H), 7.39 (d, J=8.0 Hz, 2H), 7.60–7.7.64 (m, 1H), 7.71–7.74 (m, 1H), 7.75–7.79 (m, 1H), 8.57–8.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=21.2, 21.3, 125.4, 125.7, 128.6, 129.2, 129.6, 129.8, 130.2, 130.4, 130.9, 131.2, 132.7, 134.8, 137.6, 138.0, 149.2, 153.0. ESI-HRMS: found: m/z 311.1542. Calcd for $C_{22}H_{19}N_2$: $(M+H)^+$ 311.1548.

*4.2.13. 3,4-Bis(4-methoxyphenyl)cinnoline (**3m**).* R_f=0.12 (ethyl acetate/hexane 1:3); yield: 78% (66.8 mg, 0.20 mmol); pale yellow solid; mp 137–138 °C (ethyl acetate); IR (neat) 3051, 3005, 2960, 2936, 2837, 2250, 1609 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ=3.79 (d, J=1.2 Hz, 3H), 3.85 (d, J=0.8 Hz, 3H), 6.82 (d, J=8.4 Hz, 2H), 6.96 (d, J=8.4 Hz, 2H), 7.17 (d, J=8.4 Hz, 2H), 7.44 (d, J=8.4 Hz, 2H), 7.61–7.65 (m, 1H), 7.75–7.79 (m, 2H), 8.56–8.58 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=55.1, 55.2, 113.4, 114.1, 125.3, 125.9, 126.3, 129.5, 129.8, 130.2, 130.9, 131.6, 131.8, 132.1, 149.2, 152.8, 159.3, 159.5. ESI-HRMS: found: m/z 343.1454. Calcd for $C_{22}H_{19}N_2O_2$: $(M+H)^+$ 343.1447.

*4.2.14. 4-(Diethoxymethyl)-3-phenylcinnoline (**3n**).* R_f=0.35 (ethyl acetate/hexane 1:3); yield: 46% (35.4 mg, 0.11 mmol); pale brown oil. The regiostructure of **3n** was confirmed by NOESY analysis, which shows no correlation between the hydrogen next to ethoxy groups and the hydrogen on 5-cabon of cinnoline; IR (neat) 3061, 2957, 2930, 2870, 1738, 1657 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.15 (t, J=7.2 Hz, 6H), 3.36 (m, 2H), 3.68 (m, 2H), 5.60 (s, 1H), 7.52–7.58 (m, 3H), 7.69–7.71 (m, 2H), 7.77 (dd, J=8.4, 8.4 Hz, 1H), 7.83 (dd, J=8.4, 8.4 Hz, 1H), 8.58 (d, J=8.4 Hz, 1H), 8.81 (d, J=8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=15.2, 64.0, 102.3, 123.5, 126.8, 128.0, 128.4, 128.8, 129.9, 130.0, 130.2, 130.7, 137.2, 150.6, 153.5. ESI-HRMS: found: m/z 309.1599. Calcd for $C_{19}H_{21}N_2O_2$: $(M+H)^+$ 309.1603.

*4.2.15. 4-Phenylcinnoline-3-carbaldehyde (**3n′**).* R_f=0.25 (ethyl acetate/hexane 1:3); yield: 5% (3.2 mg, 0.01 mmol); pale yellow solid. The regiostructure of **3n′** was confirmed by NOESY analysis, which shows no correlation between the hydrogen on the formyl group and the hydrogen on 5-cabon of cinnoline; mp 245–246 °C; IR (neat) 3163, 3001, 2943, 2291, 2253, 1634 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6, using residual DMSO as the internal standard; δ=2.50) δ=7.23–7.31 (m, 2H), 7.51 (d, J=7.6 Hz, 1H), 7.56–7.63 (m, 3H), 7.77–7.79 (m, 2H), 8.21 (d, J=7.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, using DMSO-d_6 as the internal standard; δ=39.5) δ=112.0, 113.5, 121.0, 122.4, 123.7, 125.8, 129.0, 129.77, 129.84, 129.9, 135.9, 149.1, 185.5. ESI-HRMS: found: m/z 257.0700. Calcd for $C_{15}H_{10}NaN_2O$: $(M+Na)^+$ 257.0691.

*4.2.16. Ethyl 4-phenylcinnoline-3-carboxylate (**3o**).* R_f=0.28 (ethyl acetate/hexane 1:3); yield: 19% (13.2 mg, 0.05 mmol); pale yellow viscous oil. The regiostructure of **3o** was assumed according to the assignment of the regiostructure of **3o′**; IR (neat) 3055, 2984, 2936, 1722, 1626 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.11 (t, J=7.2 Hz, 3H), 4.27 (q, J=7.2 Hz, 2H), 7.38–7.40 (m, 2H), 7.52–7.55 (m, 3H), 7.75 (d, J=3.6 Hz, 1H), 7.91–7.95 (m, 1H), 8.68 (d, J=8.4 Hz, 1H), 8.65 (dd, J=8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=13.8, 62.0, 125.1, 125.8, 128.5, 129.0, 129.2, 130.2, 131.5, 131.8, 133.1, 135.6, 145.9, 150.5, 165.9. ESI-HRMS: found: m/z 279.1129. Calcd for $C_{17}H_{15}N_2O_2$: $(M+H)^+$ 279.1134.

*4.2.17. Ethyl 3-phenylcinnoline-4-carboxylate (**3o′**).* R_f=0.32 (ethyl acetate/hexane 1:3); yield: 16% (11.2 mg, 0.04 mmol); pale yellow solid. The structure of **3o′** was confirmed by comparing the spectral data of the authentic compound, which was synthesized according to the reference;[14] ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.10 (t, J=7.2 Hz, 3H), 4.32 (q, J=7.2 Hz, 2H), 7.51–7.56 (m, 3H), 7.82–7.92 (m, 4H), 8.03 (d, J=8.0 Hz, 1H), 8.65 (d, J=8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=13.7, 62.4, 122.3, 124.0, 124.6, 128.6, 129.27, 129.29, 130.4, 132.5, 137.2, 149.3, 151.1, 166.6.

*4.2.18. 3-Methyl-4-phenylcinnoline (**3p**) and 4-methyl-3-phenylcinnoline (**3p′**).* R_f=0.18 (ethyl acetate/hexane 1:3); an inseparable 59:41 mixture of two isomers **3p** and **3p′** were obtained in 81% yield (44.6 mg, 20.2 mmol) as a pale yellow solid. Their regiostructures were not assigned. IR (neat) 3051, 2980, 2930, 2304, 1616 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) for minor isomer: δ=2.76 (s, 3H), 7.30–7.32 (m, 2H), 7.47–7.62 (m, 5H), 7.73–7.77 (m, 1H), 8.53 (d, J=8.4 Hz, 1H). ^{1}H NMR (400 MHz, $CDCl_3$) for major isomer: δ=2.71 (s, 3H), 7.47–7.62 (m, 3H), 7.67–7.70 (m, 2H), 7.78–7.86 (m, 2H), 8.07–8.09 (m, 1H), 8.56–8.58 (m, 1H). ^{13}C NMR (100 MHz,

$CDCl_3$) for mixture: δ=14.6, 20.9, 123.3, 124.7, 125.4, 126.4, 128.3, 128.46, 128.52, 128.8, 129.1, 129.2, 129.6, 129.7, 130.2, 130.4, 130.8, 130.9, 133.5, 134.3, 138.0, 148.5, 149.3, 151.5, 155.3. ESI-HRMS: found: *m*/*z* 221.1081. Calcd for $C_{15}H_{13}N_2$: $(M+H)^+$ 221.1079.

*4.2.19. 3-Butyl-4-phenylcinnoline (**3q**).* R_f=0.24 (ethyl acetate/hexane 1:3); yield: 27% (17.7 mg, 0.07 mmol); pale yellow viscous oil. The regiostructure of **3q** was confirmed by NOESY analysis, which showed no correlation between butyl hydrogen and the hydrogen on 5-carbon of the cinnoline ring. IR (neat) 3061, 2959, 2930, 2870, 1634, 1614 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ=0.82 (t, *J*=7.4 Hz, 3H), 1.24–1.32 (m, 2H), 1.70–1.76 (m, 2H), 3.00–3.04 (m, 2H), 7.29–7.31 (m, 2H), 7.44 (d, *J*=8.4 Hz, 1H), 7.51–7.60 (m, 4H), 7.72–7.76 (m, 1H), 8.54 (d, *J*=8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=13.8, 22.5, 32.5, 33.4, 125.0, 125.7, 128.4, 128.6, 129.1, 129.4, 129.8, 130.7, 133.2, 134.3, 149.0, 155.3. ESI-HRMS: found: *m*/*z* 263.1541. Calcd for $C_{18}H_{19}N_2$: $(M+H)^+$ 263.1548.

*4.2.20. 4-Butyl-3-phenylcinnoline (**3q**′).* R_f=0.33 (ethyl acetate/hexane 1:3); yield: 53% (34.8 mg, 0.13 mmol); pale yellow solid. The regiostructure of **3q**′ was confirmed by NOESY analysis, which showed a correlation between butyl hydrogen and the hydrogen on 5-carbon of the cinnoline ring. Mp 68–69 °C (ethyl acetate); IR (neat) 3061, 2959, 2930, 2870, 1638, 1614 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ=0.85 (t, *J*=7.4 Hz, 3H), 1.32–1.38 (m, 2H), 1.60–1.66 (m, 2H), 3.05–3.09 (m, 2H), 7.49–7.56 (m, 3H), 7.60–7.63 (m, 2H), 7.77–7.84 (m, 2H), 8.09 (dd, *J*=7.8, 1.8 Hz, 1H), 8.58 (dd, *J*=7.8, 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=13.6, 22.9, 27.5, 33.0, 123.4, 125.7, 128.3, 129.6, 129.8, 130.7, 130.8, 133.2, 138.4, 149.2, 155.5. ESI-HRMS: found: *m*/*z* 263.1539. Calcd for $C_{18}H_{19}N_2$: $(M+H)^+$ 263.1548.

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Supplementary data

Supplementary data associated with this article include ^1H and ^{13}C NMR of **1i** and **3a**–**q**. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.04.079. These data include MOL files and InChIKeys of the most important compounds described in this article.

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