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Note

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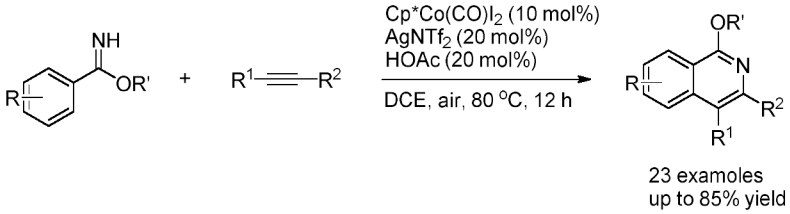
Synthesis of isoquinolines from benzimidates and alkynes via cobalt(III)-catalyzed C-H functionalization/cyclization

Shasha Gong,† Wanlin Xi,† Zhenhua Ding,* Haiying Sun*

Jiangsu Key Laboratory of Drug Design and Optimization, Department of Medicinal Chemistry, China Pharmaceutical University, Nanjing 210009, China

Supporting Information



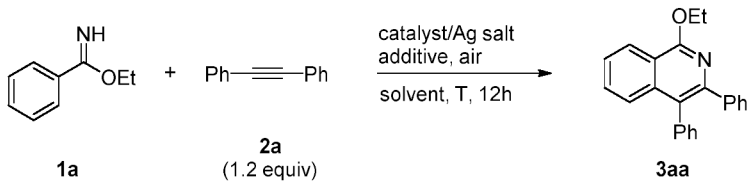
Abstract: C-H alkenylation/annulation of benzimidates with alkynes has been realized by Cp*Co(III) catalyst under air. A series substituted isoquinolines were obtained with moderate to good yields under mild reaction conditions.

Isoquinoline represents ubiquitous structural motif that occurs in a broad range of biologically active compounds and pharmaceuticals.[1] Consequently, the development of efficient preparative methods for isoquinoline derivatives has attracted considerable attention from synthetic chemists. In the past several decades, transition-metal-catalyzed C-H activation has emerged as a powerful method for the construction of heterocycles.[2] The formation of isoquinoline compounds through direct C-H functionalization has also been developed.[3] Most of these transformations were achieved by expensive second-row transition metals, especially rhodium[4], ruthenium[5] and palladium[6] complexes. In this context, the exploitation of naturally abundant first-row transition metal catalysts has received special attention.[7] Recently, high-valent cobalt complexes have been reported as efficient catalysts for direct C-H functionalization.[8] Particularly, the formation of biologically and pharmaceutically active heterocycles through cobalt(III)-catalyzed C-H activation has received considerable attention.[9]

Various of N-containing directing groups have been used in Co(III)-catalyzed C-H activation. Aryl imidates as one type of the easily achieved compounds has also been investigated in C-H functionalization and exhibited good reactivity.[10] Our interest in cobalt(III)-catalyzed C-H activation and isoquinolines construction motivated us to explore the reaction of ethyl benzimidate **1a** and diphenylacetylene **2a** catalyzed by cobalt(III) catalyst. We began our investigation with an evaluation of a range of cobalt source, silver(I) salt, additive, solvent, and temperature (**Table 1**). The cobalt(III) complex $Cp^*Co(CO)I_2$ (10 mol%) combined with silver(I) salt (10 mol%) and KOAc (20 mol%) in dichloromethane (DCE) promoted the reaction (entry 1-4). The silver (I) salt is essential for this transformation (entry 5) and $AgNTf_2$ gave the optimal results (entry 4). The reaction yields decreased to 10% without KOAc (entry 6). Replacement of KOAc with K_2CO_3 led catalytic inhibition, while HOAc showed the slight improvement of the reaction and afforded the product in 81% yield (entry 8). Lower down the

reaction temperature to 50 °C or room temperature, the product was obtained in 44% and 25% yields, respectively. The other solvents did not improve the reaction yields. As for the other cobalt sources, $CoBr_2$ and $Co(OAc)_2$ were entirely ineffective under the reaction conditions.

Table 1. Optimize Reaction Conditions [a]



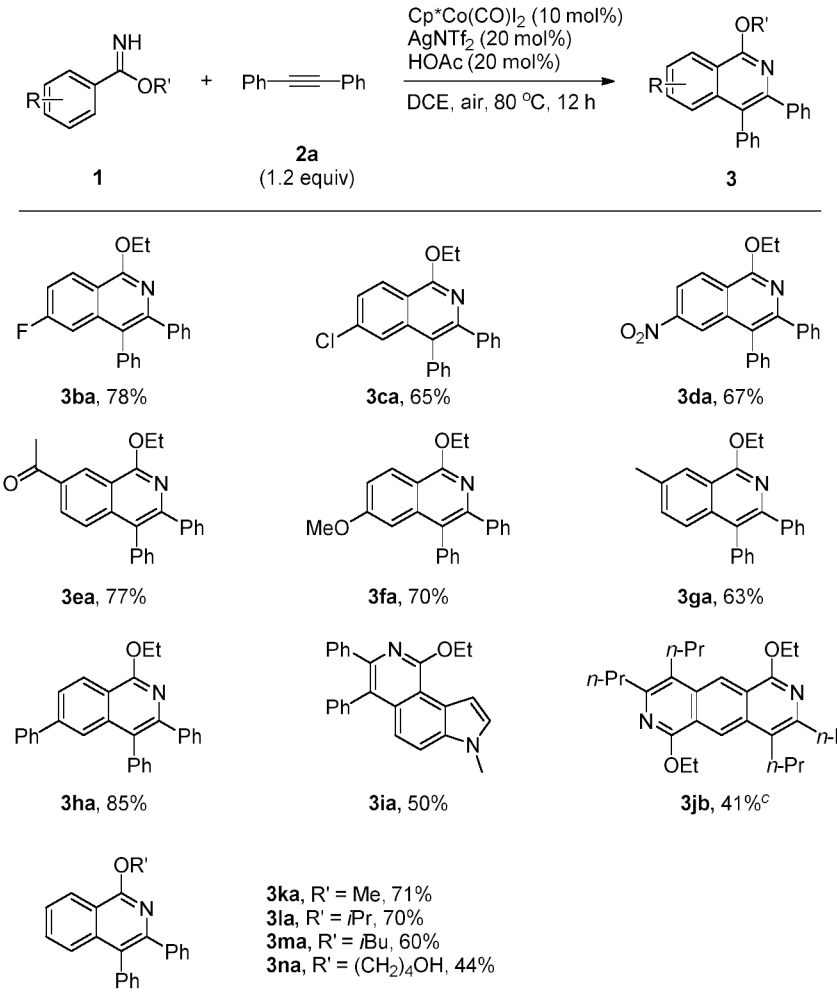
1a **2a** (1.2 equiv) **3aa**

Entry	Catalyst	Ag(I) salt	Additive	solvent	T (°C)	Yield (%) [b]
1	Cp*Co(CO)I_2	$AgBF_4$	KOAc	DCE	80	22
2	Cp*Co(CO)I_2	$AgSbF_6$	KOAc	DCE	80	67
3	Cp*Co(CO)I_2	$AgPF_6$	KOAc	DCE	80	47
4	Cp*Co(CO)I_2	$AgNTf_2$	KOAc	DCE	80	75
5	Cp*Co(CO)I_2	-	KOAc	DCE	80	0
6	Cp*Co(CO)I_2	$AgNTf_2$	-	DCE	80	10
7	Cp*Co(CO)I_2	$AgNTf_2$	K_2CO_3	DCE	80	21
8	Cp*Co(CO)I_2	$AgNTf_2$	HOAc	DCE	80	81
9	Cp*Co(CO)I_2	$AgNTf_2$	HOAc	DCE	50	44
10	Cp*Co(CO)I_2	$AgNTf_2$	HOAc	DCE	25	25
11	Cp*Co(CO)I_2	$AgNTf_2$	HOAc	dioxane	80	53
12	Cp*Co(CO)I_2	$AgNTf_2$	HOAc	THF	80	51
13	Cp*Co(CO)I_2	$AgNTf_2$	HOAc	acetonitrile	80	27
14	$Co(OAc)_2$	$AgNTf_2$	HOAc	DCE	80	0
15	$CoBr_2$	$AgNTf_2$	HOAc	DCE	80	0

[a] General reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), cobalt catalyst (10 mol%), Ag(I) salt (20 mol%), additive (20 mol%), solvent (1 mL), 12 h. [b] Isolated yields.

With the optimized reaction condition in hand, we next examined the substrate scope of substituted benzimidates **1** (**Scheme 1**). Benzimidates bearing halogen substituents including fluoro, chloro could be tolerated under the present conditions and the corresponding products were obtained in 78% (**3ba**) and 65% (**3ca**), respectively. Both electron-withdrawing and electro-donating substituents such as nitro (**3da**), acetyl (**3ea**), methoxyl (**3fa**) and methyl groups (**3ga**) were tolerated well in this reaction. A 4-phenyl-substituted benzimidate also underwent the reaction with good reactivity (**3ha**). The reaction also proceeded when employing indole-4-carbimidate as substrates and afforded a fused indole ring in 50% yield (**3ia**). The terephthalimidate also participated the reaction and gave a fluorescent compound with moderate yields (**3ja**). It was found that the reaction of other alkyl benzimidates even with some steric hindrance were also viable under present reaction conditions and afforded the products in good yields (**3ka**, **3la**, **3ma**). The substrate 4-hydroxybutyl benzimidate underwent the reaction and gave the product in moderate yield with the hydroxyl group untouched (**3na**).

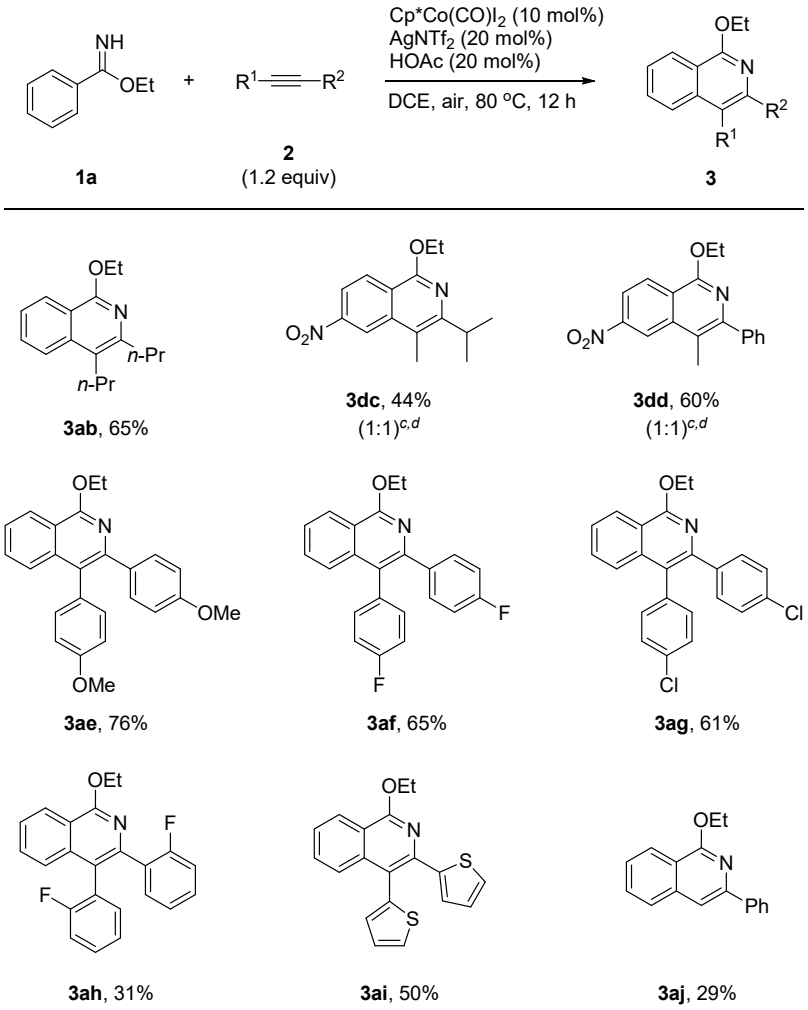
Scheme 1. Substrate Scope of Benzimidates [a,b]



[a] Reaction performed in 0.2 mmol scale. [b] Isolated yields. [c] 4-Octyne was used instead of diphenylacetylene.

We then investigated the scope of alkynes **2** (**Scheme 2**). Symmetrical aliphatic alkyne 4-octyene participated smoothly in the reaction and afforded the annulation product **3ab** in 65% yield. The reaction of benzimidate with unsymmetrical aliphatic alkyne **2c** provided the products **3dc** and **3dc'** in 44% yields with 1:1 ratio. 1-Phenyl-1-propyne underwent the reaction and the products **3dd** and **3dd'** were obtained in 60% yields without regioselectivity. The structure of **3dd'** was determined by the NOE spectrum. Diarylalkyne also gave the desired products in moderate to good yields. Methoxyl, Fluoro, chloro-substituents in *para* position of the benzene ring tolerated in this transformation and afforded the products **3ae**, **3af** and **3ag** in moderate to good yields. The reaction became sluggish when arylalkyne bore a substituent at *orth* position because of the steric hindrance (**3ah**). The reaction of heteroarylalkyne also proceeded and gave the product in moderate yield (**3ai**). The terminal alkyne participated in the reaction but with low reactivity under the present reaction conditions (**3aj**).

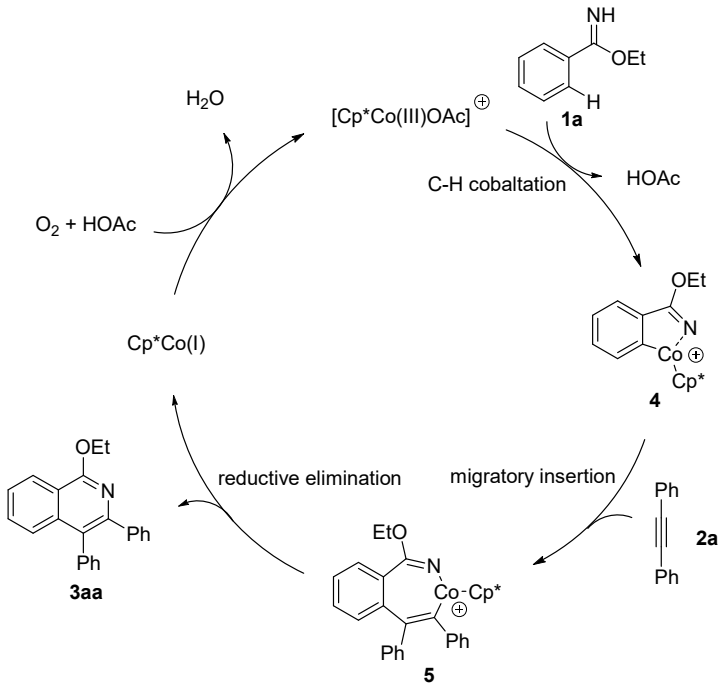
Scheme 2. Substrate Scope of Alkynes [a,b]



[a] Reaction performed in 0.2 mmol scale. [b] Isolated yields. [c] ethyl 4-notrobenzimidate was used instead of ethyl benzimidate. [d] one of the isomer was shown.

According to the reported work,[9d, 11] we proposed the reaction mechanism of this transformation (**Scheme 3**). First, acetate-assisted C-H cobaltation to generate a five-membered metalacycle **4**. A subsequent migratory insertion of alkyne to afford the seven-membered ring intermediate **5**. The reductive elimination of **5** to generate the desired isoquinoline product along with a Co(I) species. The catalytic cycle is completed by the regeneration of Co(III) species by oxidation of Co(I) with O_2 in the air.

Scheme 3. Plausible Catalytic Cycle



In summary, we have developed a cobalt(III)-catalyzed C-H functionalization of benzimidates with alkynes under air. Various benzimidates and alkynes could be applied in this reaction, and the corresponding isoquinoline products were obtained in moderate to good yields.

EXPERIMENTAL SECTION

General Experimental Methods. Unless otherwise noted, all chemicals were purchased from commercial suppliers and used without further purification. All reactions were performed by standard Schlenk techniques in oven-dried reaction vessels under air. Flash column chromatography was carried out using commercially available 300-400 mesh under pressure unless otherwise indicated. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AV-300 (300 MHz) NMR spectrometer. ^{1}H and ^{13}C NMR spectra are reported in parts per million (ppm) downfield from an internal standard, tetramethylsilane (0 ppm) and $CHCl_3$ (77.0 ppm), respectively. HRMS data were recorded on an ESI-Q-TQF mass spectrometer. Anhydrous 1,2-dichloroethane (DCE) was distilled and stored over molecular sieves. $Cp^*Co(CO)I_2$ was prepared by following the procedure as described in the literature.[12] benzimidate derivatives **1** were prepared by following the same procedure as described in the literature.[13]

General Procedure for the cobalt(III)-catalyzed Annulations. To a dried screw capped vial were added benzimidate **1** (0.2 mmol, 1.0 equiv), alkyne **2** (0.24 mmol, 1.2 equiv), $Cp^*Co(CO)I_2$ (9.5 mg, 10 mol %), $AgNTf_2$ (15.5 mg, 20 mol %), HOAc (2.4 mg, 20 mol %) and 1,2-dichloroethane (1.0 mL). The reaction mixture was stirred at 80 °C for 12 h. After cooling to ambient temperature, to the resulting mixture was added water (2 mL) and extracted with EtOAc (5 mL × 3), the combined organic layer was dried over Na_2SO_4, after filtration, solvents were removed under reduced pressure and the residue was purified by column chromatography on silica gel (PE/EtOAc = 100/1) to give the desired product.

1-Ethoxy-3,4-diphenylisoquinoline (3aa)

52.7 mg, 81% yield; pale yellow solid; m.p. 126-127 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.37-8.33 (m, 1H), 7.55-7.53 (m, 3H), 7.42-7.31 (m, 5H), 7.24-7.21 (m, 2H), 7.18-7.16 (m, 2H), 4.68 (q, *J*

= 7.08 Hz, 2H), 1.54 (t, *J* = 7.08 Hz, 3H); ^{13}C NMR (75 MHz, CDCl3): δ 158.8, 146.4, 140.5, 137.9, 137.6, 131.2, 129.8, 129.7, 127.8, 126.9, 126.5, 126.4, 125.5, 124.9, 124.1, 123.5, 118.0, 61.4, 14.2; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{20}NO$ 326.1545, found 326.1544.

1-Ethoxy-6-fluoro-3,4-diphenylisoquinoline (3ba)

Purified by column chromatography on silica gel (PE/EtOAc = 200/1) to give the desired product. 53.6 mg, 78% yield; yellow solid; m.p. 156-157 °C; ^{1}H NMR (300MHz, $CDCl_3$): δ 8.39-8.34 (m, 1H), 7.42-7.34 (m, 5H), 7.27-7.17 (m, 7H), 4.68 (q, *J* = 7.05, 2H), 1.54 (t, *J* = 7.08, 3H); ^{13}C NMR (75 MHz, CDCl3): δ 165.0, 161.7, 158.6 , 147.8, 140.1, 139.9, 137.1, 131.0, 129.8, 128.6, 127.5, 126.9, 126.7,126.6，115.4, 115.1, 109.1, 108.8, 61.6, 14.2; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{19}FNO$ 344.1451, found 344.1447.

1-Ethoxy-6-chloro-3,4-diphenylisoquinoline (3ca)

Purified by column chromatography on silica gel (PE/EtOAc = 300/1) to give the desired product. 46.8 mg, 65% yield; white solid; m.p. 171-172 °C; ^{1}H NMR (300MHz, $CDCl_3$): δ 8.31 (d, *J* = 8.67 Hz, 1H), 7.54-7.54 (m, 1H), 7.49-7.46 (m, 1H), 7.43-7.38(m, 5H), 7.25-7.19 (m, 5H), 4.71(q, *J* = 7.05 Hz, 2H), 1.56 (t, *J* = 7.02 Hz, 3H); ^{13}C NMR (75 MHz, CDCl3): δ 158.7, 147.9, 140.1, 139.1, 136.9, 136.4, 131.1, 129.8, 128.0, 126.9, 126.8, 126.7, 126.3, 125.3, 123.9, 123.4, 116.2, 61.6, 14.2; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{19}ClNO$ 360.1155, found 360.1154.

1-Ethoxy-6-nitro-3,4-diphenylisoquinoline (3da)

Purified by column chromatography on silica gel (PE/EtOAc = 200/1) to give the desired product. 49.6 mg, 67% yield; yellow solid; m.p. 151-152 °C; ^{1}H NMR (300MHz, $CDCl_3$): δ 8.48-8.43 (m, 2H), 8.23-8.19 (m, 1H), 7.39-7.36 (m, 5H), 7.21-7.17 (m, 5H), 4.69 (q, *J* = 7.08 Hz, 2H), 1.54 (t, *J* = 7.08 Hz, 3H); ^{13}C NMR (75 MHz, CDCl3): δ 159.0, 149.4, 148.9, 139.9, 138.3, 136.4, 131.5, 130.3, 129.4, 128.8, 127.8, 127.6, 126.3, 125.4, 121.6, 120.1, 119.5, 62.7, 14.6; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{19}N_2O_3$ 371.1396, found 371.1395.

1-Ethoxy-7-acetyl-3,4-diphenylisoquinoline (3ea)

Purified by column chromatography on silica gel (PE/EtOAc = 300/1) to give the desired product. 56.6 mg, 77% yield; white solid; m.p. 95-96 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.24 (d, *J* = 9.03 Hz, 1H), 7.39-7.28 (m, 5H), 7.23-7.09 (m, 6H), 6.83 (d, *J* = 2.37 Hz, 1H), 4.65 (q, *J* = 7.08 Hz, 2H), 3.68 (s, 3H), 1.51 (t, *J* = 7.08 Hz, 3H); ^{13}C NMR (75 MHz, CDCl3): δ 160.6, 158.8, 147.3, 140.7, 140.0, 137.9, 131.1, 129.9, 127.9, 126.9, 126.4, 125.4, 123.7, 116.9, 113.0, 104.4, 61.3,54.9, 14.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{25}H_{22}NO_2$ 368.1651, found 368.1648.

1-Ethoxy-6-methoxy-3,4-diphenylisoquinoline (3fa)

Purified by column chromatography on silica gel (PE/EtOAc = 300/1) to give the desired product. 49.8 mg, 70% yield; pale yellow solid; m.p. 97-98 °C; ^{1}H NMR (300MHz, $CDCl_3$): δ 8.27-8.24 (d, *J* = 9.03 Hz, 1H), 7.40-7.30 (m, 5H), 7.24-7.21 (m, 2H), 7.18-7.10 (m, 4H), 6.84-6.83 (d, 1H), 4.66 (q, *J* = 7.08 Hz, 2H), 3.71 (s, 3H), 1.52 (t, *J* = 7.08 Hz, 3H); ^{13}C NMR (75 MHz, CDCl3): δ 160.6, 158.7, 147.3, 140.6, 139.9, 137.8, 131.1, 129.8, 127.9, 127.6, 126.9, 126.43, 126.36, 125.4, 123.7, 116.9, 112.9, 104.3, 61.2, 54.6, 14.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{22}NO_2$ 356.1651, found 356.1650.

1-Ethoxy-7-methyl-3,4-diphenylisoquinoline (3ga)

Purified by column chromatography on silica gel (PE/EtOAc = 300/1) to give the desired product. 42.8 mg, 63% yield; pale yellow solid; m.p. 119-120 °C; ^{1}H NMR (300MHz, $CDCl_3$): δ 8.13 (s, 1H), 7.46-7.31 (m, 7H), 7.19-7.15 (m, 5H), 4.54 (q, *J* = 7.05 Hz, 2H), 2.53 (s, 3H), 1.55 (t, *J* = 7.05 Hz, 3H); ^{13}C NMR (75 MHz, CDCl3): δ 158.4, 145.5, 140.5, 137.8, 136.6 (, 135.5, 131.8, 131.2, 129.8, 129.5, 127.8, 126.9, 126.4, 126.3, 124.9, 124.1, 122.5, 118.1, 61.4, 21.1,14.3; HRMS (ESI-

TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{22}NO$ 340.1701, found 340.1698.

1-Ethoxy-3,4,6-triphenylisoquinoline (3ha)

Purified by column chromatography on silica gel (PE/EtOAc = 300/1) to give the desired product. 68.3 mg, 85% yield; white solid; m.p. 180-181 °C; ^{1}H NMR (300MHz, $CDCl_3$): δ 8.41 (d, J = 8.34 Hz, 1H), 7.78-7.74 (m, 2H), 7.55-7.53 (m, 2H), 7.43-7.38 (m, 4H), 7.36-7.31 (m, 4H), 7.27-7.24 (m, 2H), 7.18-7.16 (m, 3H), 4.71 (q, J = 7.08 Hz, 2H), 1.56 (t, J = 7.05 Hz, 3H); ^{13}C NMR (75 MHz, CDCl3): δ 159.3, 147.5, 142.9, 140.9, 140.8, 138.8, 131.7, 130.4, 128.9, 128.4, 127.8, 127.6, 127.4, 127.0, 126.9, 125.7, 124.8, 124.6, 123.4, 117.5, 62.0, 14.8; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{29}H_{24}NO$ 402.1858, found 402.1853.

1-Ethoxy-7-methyl-3,4-diphenyl-7H-pyrrolo [2,3-h]isoquinoline (3ia)

Purified by column chromatography on silica gel (PE/EtOAc = 150/1) to give the desired product. 37.8 mg, 50% yield; brown solid; m.p. 158-159 °C; ^{1}H NMR (300MHz, $CDCl_3$): δ 7.55-7.52 (m, 1H), 7.47-7.41 (m, 3H), 7.35-7.33 (m, 4H), 7.27-7.15 (m, 6H), 4.79 (q, J = 7.05 Hz, 2H), 3.88 (s, 3H), 1.65 (t, J = 7.05 Hz, 3H); ^{13}C NMR (75 MHz, CDCl3): δ 159.7, 144.9, 141.5, 139.3, 134.6, 134.0, 131.9, 130.4, 128.2, 128.0, 127.3, 126.7, 126.5, 125.4, 121.6, 119.5, 114.3, 112.2, 105.1, 61.8, 33.2, 14.9; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{23}N_2O$ 379.1810, found 379.1822.

1,6-Diethoxy-3,4,8,9-tetrapropylpyrido[3,4-g]isoquinoline (3jb)

Purified by column chromatography on silica gel (PE/EtOAc = 500/1) to give the desired product. 35.8 mg, 41% yield; bright yellow-green solid; m.p. 101-102 °C; ^{1}H NMR (300MHz, $CDCl_3$): δ 8.77 (s, 2H), 4.62 (q, J = 7.05 Hz, 4H), 3.02 (t, J = 7.92 Hz, 4H), 2.80(t, J = 7.44 Hz, 4H), 1.89-1.79 (m, 4H), 1.75-1.65 (m,4H), 1.53 (t, J = 7.05 Hz, 6H), 1.10 (t, J = 7.38 Hz, 6H), 1.02 (t, J = 7.38 Hz, 6H); ^{13}C-NMR (75 MHz, CDCl3): δ 158.2, 147.3, 133.7, 120.8, 120.3, 118.9, 61.6, 36.7, 29.5, 24.0, 22.8, 14.7, 14.5, 14.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{28}H_{41}N_2O_2$ 437.3168, found 437.3165.

1-Methoxy-3,4-diphenylisoquinoline (3ka)

Purified by column chromatography on silica gel (PE/EtOAc = 500/1) to give the desired product. 44.2mg, 71% yield; white solid; m.p. 166-167 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.33-8.30 (m, 1H), 7.55-7.46 (m, 3H), 7.44-7.40 (m, 2H), 7.37-7.29 (m, 3H), 7.23-7.14 (m, 5H), 4.21 (s, 3H); ^{13}C NMR (75 MHz, CDCl3): δ 141.9, 138.4, 138.0, 131.7, 130.4, 128.4, 127.5, 127.1, 127.0, 126.2, 125.5, 124.9, 124.0, 118.5, 53.7; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{18}NO$ 312.1388, found 312.1395.

1-Isopropoxy-3,4-diphenylisoquinoline (3la)

Purified by column chromatography on silica gel (PE/EtOAc = 500/1) to give the desired product. 47.6mg, 70% yield; pale yellow solid; m.p. 108-109 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.36-8.33 (m, 1H), 7.55-7.46 (m, 3H), 7.42-7.30 (m, 5H), 7.24-7.21 (m, 2H), 7.19-7.15 (m, 3H), 5.73 (m, J = 6.18 Hz, 1H), 1.51 (d, J = 6.18 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.1, 138.6, 138.2, 131.8, 130.5, 128.4, 127.5, 127.0, 127.0, 126.1, 125.5, 124.4, 124.2, 118.9, 68.4, 22.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{22}NO$ 340.1701, found 340.1712.

1-Isobutoxy-3,4-diphenylisoquinoline (3ma)

Purified by column chromatography on silica gel (PE/EtOAc = 500/1) to give the desired product. 42.4mg, 60% yield; pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.36-8.33 (m, 1H), 7.55-7.48 (m, 3H), 7.41-7.37 (m, 2H), 7.34-7.29 (m, 3H), 7.22-7.13 (m, 5H), 4.39 (d, J = 3.29 Hz, 2H), 2.26 (m, J = 6.66 Hz, 1H), 1.12 (d, J = 3.36 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.5, 147.0, 140.9, 138.4, 138.1, 131.7, 130.4, 130.3, 128.3, 127.4, 127.0, 125.4, 124.6, 124.0, 118.5, 72.4, 28.3, 19.6; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{25}H_{24}NO$ 354.1858, found 354.1868.

4-((3,4-Diphenylisoquinolin-1-yl)oxy)butan-1-ol (3na)

Purified by column chromatography on silica gel

(PE/EtOAc = 500/1) to give the desired product. 32.5 mg, 44% yield; yellow solid; m.p. 88-89 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.25-8.22 (m, 1H), 7.47-7.39 (m, 3H), 7.33-7.29 (m, 2H), 7.28-7.21 (m, 3H), 7.15-7.07 (m, 5H), 4.58 (t, J = 5.80 Hz, 2H); 3.59 (t, J = 6.20 Hz, 2H); 1.99 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2, 146.9, 140.8, 138.5, 138.0, 130.4, 130.3, 128.4, 127.5, 127.0, 126.2, 125.5, 124.6, 123.9, 118.4, 65.3, 44.9, 29.8, 26.6.

1-Ethoxy-3, 4-dipropylisoquinoline (3ab)

Purified by column chromatography on silica gel (PE/EtOAc = 500/1) to give the desired product. 33.5 mg, 65% yield; yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.25 (d, J = 8.10 Hz, 1H), 7.84 (d, J = 8.49 Hz, 1H), 7.65-7.60 (m, 1H), 7.46-7.40 (m, 1H), 4.55 (q, J = 7.05 Hz, 2H), 2.92-2.87 (m, 2H), 2.82-2.77 (m, 2H), 1.87-1.75 (m, 2H), 1.69-1.58 (m, 2H), 1.48 (t, J = 7.08 Hz, 3H), 1.11-1.04 (t, J = 7.32, 3H), 1.04-0.98 (t, J = 7.41, 3H); ^{13}C-NMR (75 MHz, CDCl3): δ 157.5, 148.9, 137.1, 129.3, 124.2, 123.9, 122.3, 120.5, 117.8, 60.8, 36.2, 28.9, 23.5, 22.3, 14.2, 14.0, 13.8; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{24}NO$ 258.1858, found 258.1856.

1-Ethoxy-3-isopropyl-4-methyl-6-nitroisoquinoline (3dc)

Purified by column chromatography on silica gel (PE/EtOAc = 100/1) to give the desired product. 12.6 mg, 23% yield; yellow solid; m.p. 58-59 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.02 (d, J = 1.71 Hz, 1H), 8.40 (d, J = 9.03 Hz, 1H), 8.14 (dd, J_1 = 2.01 Hz, J_2 = 9.06 Hz, 1H), 4.56 (q, J_1 = 7.08 Hz, J_2 = 14.16 Hz, 2H), 3.76-3.66 (m, 1H), 2.64 (s, 3H), 1.51 (t, J = 7.04 Hz, 9H); ^{13}C NMR (75 MHz, CDCl3): δ 157.5, 148.2, 148.0, 136.4, 127.8, 119.9, 117.7, 62,1, 29.7, 29.4, 28.3, 23.6, 21.9, 18.3, 14.6; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{19}N_2O_3$ 275.1396, found 275.1392.

1-Ethoxy-4-isopropyl-3-methyl-6-nitroisoquinoline (3dc')

Purified by column chromatography on silica gel (PE/EtOAc = 100/1) to give the desired product. 11.6 mg, 21% yield; yellow solid; m.p. 75-76 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.76 (d, J = 1.92 Hz, 1H), 8.34 (d, J = 9.00 Hz, 1H), 8.15 (dd, J_1 = 2.13 Hz, J_2 = 9.00 Hz, 1H), 4.60 (q, J_1 = 7.05 Hz, J_2 = 14.10 Hz, 2H), 3.48-3.39 (m, 1H), 2.55 (s, 3H), 1.50 (t, J = 7.05 Hz, 3H), 1.30 (d, J = 6.69 Hz, 6H); ^{13}C NMR (75 MHz, CDCl3): δ 157.9, 156.7, 148.5, 137.9, 131.1, 126.4, 124.8, 121.8, 119.4, 118.1, 115.9, 61.9, 31.4, 29.7, 21.9, 14.6, 12.7; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{19}N_2O_3$ 275.1396, found 275.1393.

1-Ethoxy-4-methyl-6-nitro-3-phenylisoquinoline (3dd)

Purified by column chromatography on silica gel (PE/EtOAc = 50/1) to give the desired product. 17.9 mg, 29% yield; yellow solid; m.p. 103-104 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.41 (d, J = 8.82 Hz, 1H), 8.19-8.14 (m, 2H), 7.55-7.45 (m, 4H), 7.28-7.26 (m, 2H), 4.64 (q, J_1 = 7.08 Hz, J_2 = 14.16 Hz, 2H), 2.36 (s, 3H), 1.54 (t, J = 7.08 Hz, 3H); ^{13}C NMR (75 MHz, CDCl3): δ 158.8, 149.1, 148.8, 137.8, 136.8, 130.5, 128.9, 127.9, 126.2, 125.5, 120.9, 119.9, 118.5, 63.5, 23.0, 14.6; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{17}N_2O_3$ 309.1239, found 309.1238.

1-Ethoxy-3-methyl-6-nitro-4-phenylisoquinoline (3dd')

Purified by column chromatography on silica gel (PE/EtOAc = 50/1) to give the desired product. 19.1 mg, 31% yield; yellow solid; m.p. 131-132 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.84 (d, J = 1.86 Hz, 1H), 8.45 (d, J = 9.00 Hz, 1H), 8.26 (q, J_1 = 2.13 Hz, J_2 = 9.00 Hz, 1H), 7.63-7.60 (m, 2H), 7.51-7.39 (m, 3H), 4.61 (q, J_1 = 7.08 Hz, J_2 = 14.16 Hz, 2H), 2.62 (s, 3H), 1.50 (t, J = 7.07 Hz, 3H); ^{13}C NMR (75 MHz, CDCl3): δ 158.8, 146.4, 140.5, 137.9, 137.6, 131.2, 129.8, 129.7, 127.8, 126.9, 126.5, 126.4, 125.5, 124.9, 124.1, 123.5, 118.0, 61.4, 15.3, 14.6; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{17}N_2O_3$ 309.1239, found 309.1237.

1-Ethoxy-3,4-Bis(4-methoxylphenyl)isoquinoline (3ae)

Purified by column chromatography on silica gel (PE/EtOAc = 300/1) to give the desired product.

58.6 mg, 76% yield; off-white solid; m.p. 128-129 °C; ^{1}H NMR (300MHz, $CDCl_3$): δ 8.31-8.28 (d, 1H), 7.52-7.42 (m, 3H), 7.38-7.35 (m, 2H), 7.13-7.10 (m, 2H), 6.90-6.88 (m, 2H), 6.72-6.69 (m, 2H), 4.67 (q, J = 7.08 Hz, 2H), 3.82 (s, 3H), 3.73 (s,3H), 1.51 (t, J = 7.05 Hz, 3H); ^{13}C NMR (75 MHz, CDCl3): δ 159.1, 158.6, 158.5, 146.5, 138.9, 133.6, 132.69, 131.6, 130.5, 130.1, 125.8, 125.3, 123.9, 123.5, 118.3, 113.9, 112.9, 61.9, 55.3, 55.2, 14.8; HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{25}H_{24}NO_3$ 386.1756, found 386.1753.

1-Ethoxy-3,4-Bis(4-fluorophenyl)isoquinoline (3af)

Purified by column chromatography on silica gel (PE/EtOAc = 500/1) to give the desired product. 47.0 mg, 65% yield; white solid; m.p. 140-141 °C; ^{1}H NMR (300MHz, $CDCl_3$): δ 8.36-8.34 (d, 1H), 7.58-7.48 (m, 3H), 7.38-7.33 (m, 2H), 7.19-7.14 (m, 2H), 7.08-7.03 (m, 2H), 6.90-6.85 (t, 2H), 4.68 (q, J = 7.05 Hz, 2H), 1.54 (t, J = 7.05 Hz, 3H); ^{13}C NMR (75 MHz, CDCl3): δ 163.7, 163.6, 160.4, 160.3, 159.5, 146.2, 138.4, 136.8, 136.8, 133.8, 133.8, 133.3, 133.2, 132.1, 131.9, 131.7, 130.6, 130.5, 130.4, 128.5, 127.6, 127.1, 126.3, 126.2, 125.4, 125.1, 124.2, 124.2, 123.4, 118.5, 115.7, 115.5, 115.4, 115.3, 114.6, 114.2, 62.1, 14.7; HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{23}H_{18}F_2NO$ 362.1356, found 362.1353.

1-Ethoxy-3,4-Bis(4-chlorophenyl) isoquinoline (3ag)

Purified by column chromatography on silica gel (PE/EtOAc = 500/1) to give the desired product. 48.1 mg, 61% yield; white solid; m.p. 135-136 °C; ^{1}H NMR (300MHz, $CDCl_3$): δ 8.36-8.33 (d, 1H), 7.59-7.46 (m, 3H), 7.36-7.29 (m, 4H), 7.18-7.13 (m, 4H), 4.66 (q, J = 7.05 Hz, 2H), 1.52 (t, J = 7.05 Hz, 3H); ^{13}C NMR (75 MHz, CDCl3): δ 159.9, 145.9, 139.1, 138.1, 136.3, 133.3, 133.2, 132.9, 131.6, 130.7, 128.8, 127.9, 127.8, 126.5, 125.1, 124.2, 123.4, 118.6, 62.1, 14.7; HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{23}H_{18}Cl_2NO$ 394.0765, found 394.0761.

1-Ethoxy-3,4-bis(2-fluorophenyl)isoquinoline (3ah)

Purified by column chromatography on silica gel (PE/EtOAc = 500/1) to give the desired product. 22.4 mg, 31% yield; white solid; m.p. 84-85 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.39-8.36 (m, 1H), 8.62-7.53 (m, 2H), 7.44-7.42 (m, 1H), 7.35-7.01 (m, 7H), 6.92-6.86 (m, 1H), 4.63 (q, J_1 = 6.99 Hz, J_2 = 12.15 Hz, 2H), 1.51 (t, J = 7.08 Hz, 3H); ^{13}C NMR (75 MHz, CDCl3): δ 158.8, 146.4, 140.5, 137.9, 137.6, 131.2, 129.8, 129.7, 127.8, 126.9, 126.5, 126.4, 125.5, 124.9, 124.1, 123.5, 118.0, 61.4, 14.2; HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{23}H_{18}F_2NO$ 362.1356, found 362.1351.

1-Ethoxy-3,4-di(thiophen-2-yl)isoquinoline (3ai)

Purified by column chromatography on silica gel (PE/EtOAc = 500/1) to give the desired product. 33.7 mg, 50% yield; white solid; m.p. 140-141°C; ^{1}H NMR (300MHz, $CDCl_3$): δ 8.23-8.20 (m, 1H), 7.54-7.49 (m, 2H), 7.45-7.40 (m, 2H), 7.23-7.20 (m, 2H), 7.03-7.02 (d, 1H), 6.67-6.83 (t, 1H), 6.67-6.66 (d, 1H), 4.68 (q, J = 7.08 Hz, 2H), 1.53 (t, J = 7.05 Hz, 3H); ^{13}C NMR (75 MHz, CDCl3): δ 159.4, 145.4, 142.4, 140.00, 138.4, 130.8, 129.2, 127.9, 127.7, 127.5, 127.09, 126.1, 125,3, 123.9, 118.3, 113.9, 62.5, 14.6; HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{19}H_{16}NOS_2$ 338.0673, found 338.0670.

1-Ethoxy-3-phenylisoquinoline (3aj)

Purified by column chromatography on silica gel (PE/EtOAc = 300/1) to give the desired product. 14.5 mg, 29% yield; pale yellow solid; m.p. 41-42 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.26 (d, J = 8.19, 1H), 8.17-8.14 (m, 2H), 7.76 (d, J = 8.13 Hz, 1H), 7.66-7.59 (m, 2H), 7.51-7.45 (m, 3H), 7.39-7.35 (m, 1H), 4.72 (q, J = 7.08 Hz, 2H), 1.55 (t, J = 7.08 Hz, 3H); ^{13}C-NMR (75 MHz, CDCl3): δ 160.1, 147.9, 139.6, 138.8, 130.4, 128.6, 126.6, 126.3, 124.2, 119.0, 110.1, 61.9, 14.7; HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{17}H_{16}NO$ 250.1232, found 250.1229.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:
^{1}H NMR and ^{13}C NMR spectra (PDF)

AUTHOR INFORMATION

Corresponding Author
*E-mail: *zhding@cpu.edu.cn;
*haiyings1969@163.com
Author Contributions
† S. Gong. and † W. Xi. contributed equally.

Notes
The authors declare no competing financial interest.

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