A Convenient Synthesis of 1,4-Disubstituted Isoquinolines by Reactions of α-Substituted 2-Lithio-β-methoxystyrenes with Nitriles

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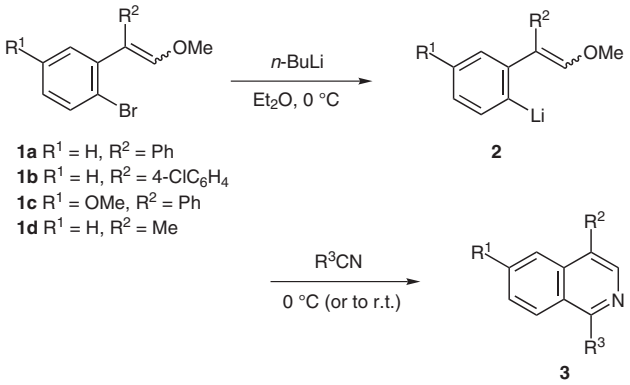
Abstract: It has been found that halogen–lithium exchange between α-substituted 2-bromo-β-methoxystyrene derivatives and *n*-butyllithium generates α-substituted 2-lithio-β-methoxystyrene derivatives, which successfully react with a range of nitriles to afford the corresponding 1,4-disubstituted isoquinolines in reasonable yields.

Key words: benzyl anion, isoquinoline, nitrile, organolithium, styrene

After our recent finding that the reaction of 2-(2-methoxyethenyl)benzonitrile derivatives with organolithiums affords isoquinoline derivatives,[1] we wished to extend this study and investigate the possibility of reacting α-substituted 2-lithio-β-methoxystyrene derivatives **2** with nitriles, for the preparation of isoquinoline derivatives such as **3**. This would constitute an improvement of the previous method, since the precursors of these lithium compounds, α-substituted 2-bromo-β-methoxystyrene derivatives **1**, are simpler to prepare than the 2-(2-methoxyethenyl)benzonitrile derivatives, and a wider range of nitriles are available, compared to organolithiums. We now report a new synthesis of isoquinolines, which enabled us to prepare a range of 1,4-disubstituted derivatives. Since compounds based on the isoquinoline skeleton have received considerable attention because of their biological utilities,[2] a number of approaches for the construction of this system have recently been developed.[3]



Scheme 1 For R^3, see Table 1

α-Substituted 2-bromo-β-methoxystyrene derivatives **1**[4] were obtained as mixtures of stereoisomers, in good yields, by the reaction of readily available *o*-bromophenyl ketones[5,6] with (methoxymethylene)triphenylphosphoran. The reactions used for the preparation of 1,4-disubstituted isoquinolines **3** were carried out as shown in Scheme 1. Thus, bromine–lithium exchange of **1** through treatment with *n*-butyllithium in diethyl ether at 0 °C generated α-substituted 2-lithio-β-methoxystyrene derivatives **2**. Almost quantitative generation of 2-lithio-β-methoxy-α-phenylstyrene from 2-bromo-β-methoxy-α-phenylstyrene (**1a**) was confirmed by the observation that β-methoxy-α-phenylstyrene[7] was formed in high yields (>95%) after quenching with aqueous ammonium chloride. Subsequently, these lithium products were allowed to react with nitriles at the same temperature to give, after the usual aqueous workup followed by purification by preparative TLC on silica gel, the desired isoquinoline derivatives **3** in the yields summarized in Table 1. It can be seen that the reactions of **1a** and α-(4-chlorophenyl)-2-bromo-β-methoxystyrene (**1b**) with aromatic nitriles provide satisfactory yields of the corresponding isoquinoline derivatives (Entries 1–6, 11 and 12). Nitriles bearing an α-hydrogen proved to give similar results (Entries 9 and 10).

In order to investigate the scope of the present method, reactions using pyridine-2-carbonitrile, cinnamonitrile, and propanenitrile were carried out. In all cases, the desired products were obtained albeit in somewhat lower yields (Entries 7, 8 and 13, respectively). Subsequently, we examined halogenated nitriles; however, the reaction of 2-lithio-β-methoxy-α-phenylstyrene (**2a**) with trichloroacetonitrile, under the same conditions, gave a rather complex mixture of products, from which only trace amounts of the desired product could be isolated. Similarly, the reactions with 4-bromobutanenitrile and 2-bromomethylbenzonitrile both failed to produce the corresponding isoquinoline derivatives.

2-Bromo-β,4-dimethoxy-α-phenylstyrene (**1c**) and 2-bromo-β-methoxy-α-methylstyrene (**1d**) could also be used in the present isoquinoline synthesis, but the product yields were somewhat lower than those using **1a** and **1b**. This decrease in yield is probably due to the lower stability of the benzyl anion intermediates **5**, arising from attack of the nitrogen anion of **4** on the α-carbon atom of the methoxyvinyl moiety (Scheme 2).[8] In the case of **1d**, it was necessary to raise the reaction temperature to room

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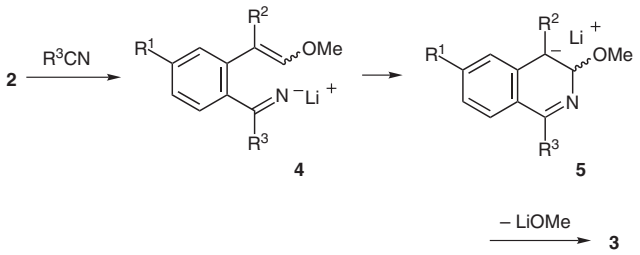
Table 1 Preparation of 1,4-Disubstituted Isoquinolines **3**

Entry	**1**	R^3 of R^3CN	**3** (Yield/%)[a]
1	**1a**	Ph	**3a** (73)
2	**1a**	*o*-Tol	**3b** (64)
3	**1a**	2-FC_6H_4	**3c** (68)
4	**1a**	4-ClC_6H_4	**3d** (68)
5	**1a**	4-$CF_3C_6H_4$	**3e** (66)
6	**1a**	Naphthalen-1-yl	**3f** (52)
7	**1a**	Pyridin-2-yl	**3g** (38)
8	**1a**	(*E*)-PhCH=CH	**3h** (38)
9	**1a**	*i*-Pr	**3i** (62)
10	**1a**	Cy	**3j** (62)
11	**1b**	Ph	**3k** (71)
12	**1b**	Phenanthren-9-yl	**3l** (51)
13	**1b**	Et	**3m** (40)
14	**1c**	Ph	**3n** (43)
15	**1c**	4-ClC_6H_4	**3o** (45)
16	**1c**	4-$CF_3C_6H_4$	**3p** (44)
17	**1c**	*t*-Bu	**3q** (43)
18	**1d**	Ph	**3r** (36)[b]

[a] Isolated yields.
[b] Reaction was allowed to come to room temperature after addition of PhCN.

temperature in order to allow the reaction to reach completion.

In the present work, we have demonstrated an efficient synthetic method that allows access to 1,4-disubstituted isoquinolines. The operational simplicity, together with the ready availability of the starting materials, makes this new procedure attractive. Work on investigating the possibility of preparing related heterocycles, using reactions of 2-lithio-β-methoxystyrene derivatives with other electrophiles, are currently in progress in our laboratory.



Scheme 2

Melting points were determined on a Laboratory Devices MEL-TEMP II melting-point apparatus and are uncorrected. The IR spectra were recorded on a Shimadzu FTIR-8300 spectrometer. The ^1H NMR spectra were determined using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 500 MHz in $CDCl_3$. Low-resolution mass spectra were recorded on a JEOL AUTOMASS 20 spectrometer (Center for Joint Research and Development, this University). Thin-layer chromatography (TLC) was carried out on Merck Kieselgel 60 PF_{254}. All solvents used were dried over appropriate drying agents and distilled under argon prior to use.

(2-Bromophenyl)phenylmethanone[5], 2-bromophenyl(4-chlorophenyl)methanol,[6] (2-bromo-5-methoxyphenyl)phenylmethanone,[6] and 1-bromo-2-(2-methoxy-1-methylethenyl)benzene (**1d**)[4] were prepared by literature methods. All other chemical used in this study were commercially available.

2-Bromophenyl(4-chlorophenyl)methanone

This compound was prepared by the oxidation of 2-bromophenyl(4-chlorophenyl)methanol[6] with PCC at r.t. in DCE.

Yield: 89%; yellow oil; R_f = 0.42 (EtOAc–hexane, 1:5).

IR (neat): 1668 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.3–7.5 (5 H, m), 7.65 (1 H, dd, *J* = 7.3, 1.3 Hz), 7.75 (2 H, d, *J* = 8.9 Hz).

Anal. Calcd for $C_{13}H_8BrClO$: C, 52.83; H, 2.73. Found: C, 52.71; H, 3.01.

Bromo-2-(2-methoxy-1-phenylethenyl)benzene (1a)

To a stirred suspension of (methoxymethyl)triphenylphosphonium chloride (6.9 g, 20 mmol) in THF (40 mL) at 0 °C was added *n*-BuLi (1.6 M in hexane, 20 mmol) dropwise. After 15 min, a solution of (2-bromophenyl)phenylmethanone (2.1 g, 8.1 mmol) in THF (7 mL) was added and stirring was continued for an additional 30 min. The mixture was treated with H_2O (50 mL) and the organic materials were extracted with Et_2O (2 × 20 mL). The combined extracts were washed with brine (20 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was purified by column chromatography on silica gel (EtOAc–hexane, 1:20) to give **1a** as a mixture of stereoisomers (*E*:*Z* = ca. 7:3). Yield: 1.8 g (75%); pale-yellow oil.

An analytical specimen of each isomer was obtained by fractional column chromatography.

E-Isomer

Pale-yellow oil; R_f = 0.45 (Et_2O–hexane, 1:20).

IR (neat): 1636 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 3.81 (3 H, s), 6.25 (1 H, s), 7.14–7.19 (2 H, m), 7.26–7.34 (4 H, m), 7.37 (2 H, dd, *J* = 7.8, 0.9 Hz), 7.59 (1 H, d, *J* = 8.2 Hz).

Anal. Calcd for $C_{15}H_{13}BrO$: C, 62.30; H, 4.53. Found: C, 62.14; H, 4.60.

Z-Isomer

White solid; mp 80–82 °C (hexane–Et_2O).

IR (KBr): 1645 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 3.74 (3 H, s), 6.67 (1 H, s), 7.12 (2 H, d, *J* = 7.8 Hz), 7.17 (2 H, dd, *J* = 7.8, 7.3 Hz), 7.23–7.26 (3 H, m), 7.33 (1 H, t, *J* = 7.3 Hz), 7.64 (1 H, d, *J* = 7.8 Hz).

Anal. Calcd for $C_{15}H_{13}BrO$: C, 62.30; H, 4.53. Found: C, 61.94; H, 4.54.

1-Bromo-2-[2-methoxy-1-(4-chlorophenyl)ethenyl]benzene (1b)

This compound was prepared from 2-bromophenyl(4-chlorophenyl)methanone,[6] in a manner similar to that described for the preparation of **1a**, as a mixture of stereoisomers (*E*:*Z* = ~7:3). Yield: 74%; colorless oil.

An analytical specimen of each isomer was obtained by fractional column chromatography.

E-Isomer

Colorless oil; R_f = 0.41 (CH_2Cl_2–hexane, 1:4).

IR (neat): 1634 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 3.82 (3 H, s), 6.26 (1 H, s), 7.19 (1 H, ddd, *J* = 9.2, 6.3, 2.4 Hz), 7.22 (2 H, d, *J* = 8.7 Hz), 7.29–7.34 (4 H, m), 7.59 (1 H, dd, *J* = 7.8, 1.4 Hz).

Anal. Calcd for $C_{15}H_{12}BrClO$: C, 55.67; H, 3.74. Found: C, 55.65; H, 3.81.

Z-Isomer

White solid; mp 74–78 °C (hexane–Et_2O).

IR (KBr): 1638 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 3.75 (3 H, s), 6.66 (1 H, s), 7.03 (2 H, d, *J* = 8.7 Hz), 7.16–7.24 (4 H, m), 7.34 (1 H, ddd, *J* = 7.8, 7.3, 1.4 Hz), 7.64 (1 H, dd, *J* = 7.8, 1.4 Hz).

Anal. Calcd for $C_{15}H_{12}BrClO$: C, 55.67; H, 3.74. Found: C, 55.44; H, 3.84.

1-Bromo-4-methoxy-2-(2-methoxy-1-phenylethenyl)benzene (1c)

This compound was prepared from (2-bromo-5-methoxyphenyl)phenylmethanone,[6] in a manner similar to that described for the preparation of **1a**, as a mixture of stereoisomers (*E*:*Z* = ~1:1). Yield: 63%; colorless oil.

IR (neat): 1637 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 3.75, 3.77, 3.80, and 3.82 (combined 6 H, 4 × s), 6.26 (0.5 H, s), 6.66 (0.5 H, s), 6.73–6.76 (1 H, m), 6.79 (0.5 H, d, *J* = 3.2 Hz), 6.88 (0.5 H, d, *J* = 3.2 Hz), 7.12–7.29 (4 H, m), 7.39 (1 H, dd, *J* = 8.2, 1.4 Hz), 7.46 (0.5 H, d, *J* = 8.7 Hz), 7.52 (0.5 H, d, *J* = 8.7 Hz).

Anal. Calcd for $C_{16}H_{15}BrO_2$: C, 60.21; H, 4.74. Found: C, 59.98; H, 4.84.

1,4-Diphenylisoquinoline (3a);[9] Typical Procedure

To a stirred solution of **1a** (0.25 g, 0.85 mmol) in Et_2O (4 mL) at 0 °C was added *n*-BuLi (1.6M in hexane, 0.85 mmol) dropwise. After 1 h, PhCN (97 mg, 0.94 mmol) was added and the mixture was stirred at the same temperature for an additional 30 min. H_2O (10 mL) was added and the organic materials were extracted with Et_2O (2 × 15 mL). The combined extracts were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was purified by preparative TLC on silica gel (Et_2O–hexane, 1:3). Yield: 0.18 g (73%); white solid; mp 139–140 °C (hexane–Et_2O) (Lit.[9] 141 °C).

IR (KBr): 1614 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.45–7.65 (9 H, m), 7.66 (1 H, t, *J* = 8.2 Hz), 7.74 (2 H, dd, *J* = 8.2, 1.3 Hz), 7.98 (1 H, d, *J* = 7.9 Hz), 8.18 (1 H, dd, *J* = 8.2, 1.3 Hz), 8.57 (1 H, s).

MS (EI): *m*/*z* (%) = 281 (96) [M^+], 280 (100).

1-(2-Methylphenyl)-4-phenylisoquinoline (3b)

Pale-yellow oil; R_f = 0.17 (hexane–THF, 3:1).

IR (neat): 1614 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 2.14 (3 H, s), 7.31–7.43 (4 H, m), 7.46–7.52 (2 H, m), 7.54–7.61 (4 H, m), 7.65 (1 H, ddd, *J* = 8.2, 6.9, 1.4 Hz), 7.73 (1 H, d, *J* = 8.2 Hz), 7.98 (1 H, d, *J* = 8.7 Hz), 8.57 (1 H, s).

MS (EI): *m*/*z* (%) = 294 (100) [M^+].

Anal. Calcd for $C_{22}H_{17}N$: C, 89.46; H, 5.80; N, 4.74. Found: C, 89.39; H, 5.86; N, 4.68.

1-(2-Fluorophenyl)-4-phenylisoquinoline (3c)

White solid; mp 116–118 °C (hexane–Et_2O).

IR (KBr): 1616 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.27 (1 H, ddd, *J* = 8.7, 7.3, 0.9 Hz), 7.36 (1 H, ddd, *J* = 7.8, 7.3, 0.9 Hz), 7.50–7.59 (7 H, m), 7.62 (1 H, td, *J* = 7.3, 1.8 Hz), 7.67 (1 H, ddd, *J* = 8.2, 6.9, 1.4 Hz), 7.89 (1 H, dd, *J* = 8.2, 2.7 Hz), 7.98 (1 H, d, *J* = 8.2 Hz), 8.60 (1 H, s).

MS (EI): *m*/*z* (%) = 299 (100) [M^+].

Anal. Calcd for $C_{21}H_{14}FN$: C, 84.26; H, 4.71; N, 4.68. Found: C, 84.24; H, 4.69; N, 4.53.

1-(4-Chlorophenyl)-4-phenylisoquinoline (3d)

Colorless needles; mp 155–157 °C (hexane–Et_2O).

IR (KBr): 1616 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.47–7.59 (8 H, m), 7.67 (1 H, ddd, *J* = 8.2, 6.9, 1.4 Hz), 7.70 (2 H, d, *J* = 8.2 Hz), 7.98 (1 H, d, *J* = 8.7 Hz), 8.12 (1 H, d, *J* = 8.2 Hz), 8.56 (1 H, s).

MS (EI): *m*/*z* (%) = 315 (86) [M^+], 314 (100).

Anal. Calcd for $C_{21}H_{14}ClN$: C, 79.87; H, 4.47; N, 4.44. Found: C, 79.56; H, 4.53; N, 4.40.

4-Phenyl-1-(4-trifluoromethylphenyl)isoquinoline (3e)

White solid; mp 115–118 °C (hexane–Et_2O).

IR (KBr): 1616 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.49–7.61 (6 H, m), 7.69 (1 H, ddd, *J* = 8.2, 6.9, 1.4 Hz), 7.83 (2 H, d, *J* = 7.8 Hz), 7.87 (2 H, d, *J* = 7.8 Hz), 8.00 (1 H, d, *J* = 8.7 Hz), 8.09 (1 H, d, *J* = 8.2 Hz), 8.59 (1 H, s).

MS (EI): *m*/*z* (%) = 349 (100) [M^+].

Anal. Calcd for $C_{22}H_{14}F_3N$: C, 75.64; H, 4.04; N, 4.01. Found: C, 75.38; H, 4.09; N, 3.98.

1-(Naphthalen-1-yl)-4-phenylisoquinoline (3f)

Colorless viscous oil; R_f = 0.12 (EtOAc–hexane, 1:2).

IR (neat): 1614 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.36 (1 H, ddd, *J* = 7.8, 7.3, 1.4 Hz), 7.42 (1 H, ddd, *J* = 8.2, 6.9, 1.4 Hz), 7.48–7.54 (3 H, m), 7.58 (2 H, dd, *J* = 7.8, 7.3 Hz), 7.62–7.67 (5 H, m), 7.69 (1 H, d, *J* = 8.2 Hz), 7.97 (1 H, dd, *J* = 7.8, 1.4 Hz), 8.01–8.03 (2 H, m), 8.66 (1 H, s).

MS (EI): *m*/*z* (%) = 331 (76) [M^+], 330 (100).

Anal. Calcd for $C_{25}H_{17}N$: C, 90.60; H, 5.17; N, 4.23. Found: C, 90.58; H, 5.26; N, 4.16.

4-Phenyl-1-(pyridin-2-yl)isoquinoline (3g)

Yellow viscous oil; R_f = 0.23 (hexane–Et_2O, 1:2).

IR (neat): 1625 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.43 (1 H, ddd, *J* = 7.8, 7.3, 1.4 Hz), 7.49–7.57 (5 H, m), 7.61 (1 H, ddd, *J* = 8.2, 6.9, 1.4 Hz), 7.67 (1 H, ddd, 8.2, 6.9, 1.4 Hz), 7.94 (1 H, td, *J* = 7.3, 1.8 Hz), 7.97 (1 H, d, *J* = 8.7 Hz), 8.03 (1 H, dd, *J* = 6.9, 0.9 Hz), 8.59 (1 H, s), 8.64 (1 H, dd, *J* = 9.1, 0.9 Hz), 8.81–8.84 (1 H, m).

MS (EI): *m*/*z* (%) = 282 (100) [M$^+$].

Anal. Calcd for $C_{20}H_{14}N_2$: C, 85.08; H, 5.00; N, 9.92. Found: C, 84.94; H, 5.13; N, 9.85.

4-Phenyl-1-[(*E*)-2-phenylvinyl]isoquinoline (3h)
Pale-yellow oil; R_f = 0.31 (hexane–CH_2Cl_2, 1:1).

IR (neat): 1628, 1615, 1601 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35 (1 H, t, *J* = 7.3 Hz), 7.44 (2 H, dd, *J* = 7.6, 7.3 Hz), 7.46–7.51 (1 H, m), 7.52–7.57 (5 H, m), 7.64–7.68 (2 H, m), 7.73 (1 H, d, *J* = 7.6 Hz), 7.94–7.97 (1 H, m), 8.02 (1 H, d, *J* = 15.6 Hz), 8.07 (1 H, d, *J* = 15.6 Hz), 8.44–8.47 (1 H, m), 8.53 (1 H, s).

MS (EI): *m*/*z* (%) = 307 (61) [M$^+$], 306 (100).

Anal. Calcd for $C_{23}H_{17}N$: C, 89.87; H, 5.57; N, 4.56. Found: C, 89.81; H, 5.58; N, 4.54.

1-(1-Methylethyl)-4-phenylisoquinoline (3i)
Pale-yellow oil; R_f = 0.29 (hexane–Et_2O, 10:1).

IR (neat): 1615 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.50 (6 H, d, *J* = 6.9 Hz), 4.03 (1 H, sept, *J* = 6.9 Hz), 7.44–7.54 (5 H, m), 7.59–7.65 (2 H, m), 7.89–7.93 (1 H, m), 8.29–8.32 (1 H, m), 8.44 (1 H, s).

MS (EI): *m*/*z* (%) = 247 (99) [M$^+$], 220 (100).

Anal. Calcd for $C_{18}H_{17}N$: C, 87.41; H, 6.93; N, 5.66. Found: C, 87.28; H, 7.00; N, 5.52.

1-Cyclohexyl-4-phenylisoquinoline (3j)
Colorless oil; R_f = 0.54 (hexane–CH_2Cl_2, 1:2).

IR (neat): 1616 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.37–1.46 (1 H, m), 1.52–1.61 (2 H, m), 1.82–2.05 (7 H, m), 3.59–3.65 (1 H, m), 7.43–7.53 (5 H, m), 7.58–7.63 (2 H, m), 7.89–7.92 (1 H, m), 8.28–8.31 (1 H, m), 8.43 (1 H, s).

MS (EI): *m*/*z* (%) = 287 (39) [M$^+$], 286 (43), 232 (100).

Anal. Calcd for $C_{21}H_{21}N$: C, 87.76; H, 7.36; N, 4.87. Found: C, 87.71; H, 7.49; N, 4.69.

4-(4-Chlorophenyl)-1-phenylisoquinoline (3k)
White solid; mp 105–107 °C (hexane–Et_2O).

IR (KBr): 1612 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.49–7.57 (8 H, m), 7.68 (1 H, ddd, *J* = 8.7, 6.9, 1.4 Hz), 7.73 (2 H, dd, *J* = 8.2, 1.4 Hz), 7.92 (1 H, d, *J* = 8.7 Hz), 8.18 (1 H, d, *J* = 8.2 Hz), 8.54 (1 H, s).

MS (EI): *m*/*z* (%) = 315 (76) [M$^+$], 314 (100).

Anal. Calcd for $C_{21}H_{14}ClN$: C, 79.87; H, 4.47; N, 4.44. Found: C, 79.67; H, 4.45; N, 4.39.

4-(4-Chlorophenyl)-1-(phenanthren-9-yl)isoquinoline (3l)
White solid; mp 188–190 °C (hexane–Et_2O).

IR (KBr): 1614 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.41–7.48 (2 H, m), 7.50 (1 H, d, *J* = 7.8 Hz), 7.57 (2 H, d, *J* = 9.2 Hz), 7.59 (2 H, d, *J* = 9.2 Hz), 7.64–7.70 (3 H, m), 7.75 (1 H, t, *J* = 7.3 Hz), 7.78 (1 H, d, *J* = 8.2 Hz), 7.91 (1 H, s), 7.94 (1 H, d, *J* = 7.8 Hz), 7.98 (1 H, d, *J* = 8.2 Hz), 8.66 (1 H, s), 8.80 (1 H, d, *J* = 8.2 Hz), 8.83 (1 H, d, *J* = 8.2 Hz).

MS (EI): *m*/*z* (%) = 415 (68) [M$^+$], 414 (100).

Anal. Calcd for $C_{29}H_{18}ClN$: C, 83.75; H, 4.36; N, 3.37. Found: C, 83.72; H, 4.45; N, 3.27.

4-(4-Chlorophenyl)-1-ethylisoquinoline (3m)
Pale-yellow solid; mp 70–73 °C (hexane–Et_2O).

IR (KBr): 1616 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.49 (3 H, t, *J* = 7.3 Hz), 3.48 (2 H, q, *J* = 7.3 Hz), 7.43 (2 H, d, *J* = 8.7 Hz), 7.49 (2 H, d, *J* = 8.7 Hz), 7.60–7.67 (2 H. m). 7.85 (1 H, dd, *J* = 7.8, 1.8 Hz), 8.25 (1 H, dd, *J* = 7.8, 1.8 Hz), 8.36 (1 H, s).

MS (EI): *m*/*z* (%) = 267 (58) [M$^+$], 266 (100).

Anal. Calcd for $C_{17}H_{14}ClN$: C, 76.26; H, 5.27; N, 5.23. Found: C, 76.02; H, 5.28; N, 5.16.

6-Methoxy-1,4-diphenylisoquinoline (3n)[10]
White solid; mp 107–108 °C (hexane–Et_2O).

IR (KBr): 1618 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.82 (3 H, s), 7.17 (1 H, dd, *J* = 9.2, 2.6 Hz), 7.23 (1 H, d, *J* = 2.6 Hz), 7.45–7.6 (8 H, m), 7.71 (2 H, d, *J* = 8.3, 2.0 Hz), 8.07 (1 H, d, *J* = 9.2 Hz), 8.45 (1 H, s).

MS (EI): *m*/*z* (%) = 311 (87) [M$^+$], 310 (100).

1-(4-Chlorophenyl)-6-methoxy-4-phenylisoquinoline (3o)
White solid; mp 117–120 °C (hexane–Et_2O).

IR (KBr): 1618 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.82 (3 H, s), 7.18 (1 H, dd, *J* = 9.2, 2.2 Hz), 7.24 (1 H, d, *J* = 2.2 Hz), 7.47–7.58 (7 H, m), 7.67 (2 H, d, *J* = 8.2 Hz), 8.01 (1 H, d, *J* = 9.2 Hz), 8.47 (1 H, s).

MS (EI): *m*/*z* (%) = 345 (100) [M$^+$].

Anal. Calcd for $C_{22}H_{16}ClNO$: C, 76.41; H, 4.66; N, 4.05. Found: C, 76.45; H, 4.95; N, 3.95.

6-Methoxy-4-phenyl-1-(4-trifluoromethylphenyl)isoquinoline (3p)
White solid; mp 142–145 °C (hexane–Et_2O).

IR (KBr): 1620 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.82 (3 H, s), 7.20 (1 H, dd, *J* = 9.2, 2.7 Hz), 7.25 (1 H, d, *J* = 2.7 Hz), 7.48–7.53 (1 H, m), 7.55–7.59 (4 H, m), 7.81 (2 H, d, *J* = 8.2 Hz), 7.84 (2 H, d, *J* = 8.2 Hz), 7.98 (1 H, d, *J* = 9.2 Hz), 8.49 (1 H, s).

MS (EI): *m*/*z* (%) = 379 (100) [M$^+$].

Anal. Calcd for $C_{23}H_{16}F_3NO$: C, 72.82; H, 4.25; N, 3.69. Found: C, 72.80; H, 4.40; N, 3.68.

1-(1,1-Dimethylethyl)-6-methoxy-4-phenylisoquinoline (3q)
Pale-yellow oil; R_f = 0.28 (hexane–$CHCl_3$, 1:1).

IR (KBr): 1620 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.69 (9 H, s), 3.78 (3 H, s), 7.18–7.20 (2 H, m), 7.43–7.53 (5 H, m), 8.31 (1 H, s), 8.53 (1 H, dd, *J* = 7.8, 2.3 Hz).

MS (EI): *m*/*z* (%) = 291 (32) [M$^+$], 290 (40), 249 (100).

Anal. Calcd for $C_{20}H_{21}NO$: C, 82.44; H, 7.26; N, 4.81. Found: C, 82.43; H, 7.30; N, 4.79.

4-Methyl-1-phenylisoquinoline (3r)[11]
After addition of PhCN, the reaction temperature was raised to room temperature.

White solid; mp 71–74 °C (hexane–Et_2O) (lit.[11] 75–76 °C). Spectral data (IR and ^{1}H NMR) were identical to those reported previously.[11]

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