

Ruthenium-Catalyzed Annulation of *N*-Cbz Hydrazones via C–H/N–N Bond Activation for the Rapid Synthesis of Isoquinolines

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- ✓ Microwave-assisted rapid synthesis
- ✓ Rarely explored directing group
- ✓ No external oxidant
- ✓ No additives
- ✓ PEG as a biodegradable green solvent
- ✓ Wide substrate scope
- ✓ Easy work up process
- ✓ Easily prepared substrates

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Abstract In this work, *N*-Cbz hydrazone has been employed as a rarely explored directing group for the synthesis of isoquinolines by annulation with internal alkynes via C–H/N–N activation using Ru catalyst. Additive as well as external oxidant-free rapid protocol has been established for the synthesis of isoquinolines using microwave strategy. Use of non-volatile and biodegradable PEG as a green solvent with lower catalyst loading makes the proposed protocol environmentally benign. Further, higher functional group tolerance and wide substrate scope has been observed under the stated methodology with higher yields.

Key words C–H/N–N activation, ruthenium, microwave-assisted, isoquinolines, annulation, hydrazones

Currently, the strategy of transition-metal-catalyzed direct C–H activation has become a powerful technique for chemical transformations in the area of synthetic methodology.¹ Because of step and atom efficiency, nobility and influence on ecology, it represents a potent approach above conventional methods of organic synthesis, opening new opportunities in retrosynthetic directions. In the past decade, among transition metals, ruthenium has been emerged as a capable and cost-effective catalyst for the chemical transformations using C–H bond functionalization approach.²

Directing groups, by acting as Lewis base to co-ordinate the transition metals, play vital role in selective C–H bond activation.³ Considering the reaction pathway, in order to recycle metal catalysts in its active form, equivalent or excessive quantity of external oxidants are often required. These external oxidants are responsible for generation of equivalent amount of waste, causing environmental nuisance. Thus, in order to avoid the use of external oxidants, researchers have pioneered a concept called redox-neutral strategy, in which directing group itself acts as an internal

oxidant too.⁴ Further, this strategy has additional advantages like enhanced reactivity as well as selectivity with improved yields and the simultaneous breaking of the directing group.

On the other hand, most of the previous reports for C–H/N–N activation use volatile organic solvents, convicted for serious ecological hazards. Thus, in order to reduce the ecological pressures by conventional organic solvents, replacing it with polyethylene glycols (PEGs) is one of the best solutions.⁵ Owing to the properties like negligible vapor pressure, inexpensiveness, thermal stability, degradable, reusable, relatively inexpensive, and less harmful, PEGs serve as an appropriate media for safe and ecologically gentle chemical conversions. Taking into consideration the importance of PEG as a solvent, our research group has communicated some scientific reports.⁶

The beginning of twenty-first century has witnessed a revolutionary advancement in the area of microwave-assisted organic synthesis.⁷ Due to the capability of expeditious heating and thermal quenching, the methodology has several advantages of improvement into rates, efficiency, and yields of chemical transformations. Uniform and selective heating throughout the material with minimal heat loss, low operating cost, and minimal side reactions makes it a promising and environmentally benign technique. Moreover, many novel organic transformations could be achieved using microwave strategy, which could not succeed by conventional heating.

Isoquinolines have emerged as an important class of heterocyclic scaffolds that is present in various natural as well as pharmaceutical products with broad range of biological activities⁸ (Figure 1). Moreover, isoquinoline moieties are employed for the development of ligands, photosensitizers, alkaloids, OLEDs, and inhibitors.⁹ For instance, tetrahydropalmatine, sanguinarine, and papaverine are the naturally occurring alkaloids containing isoquinoline scaf-

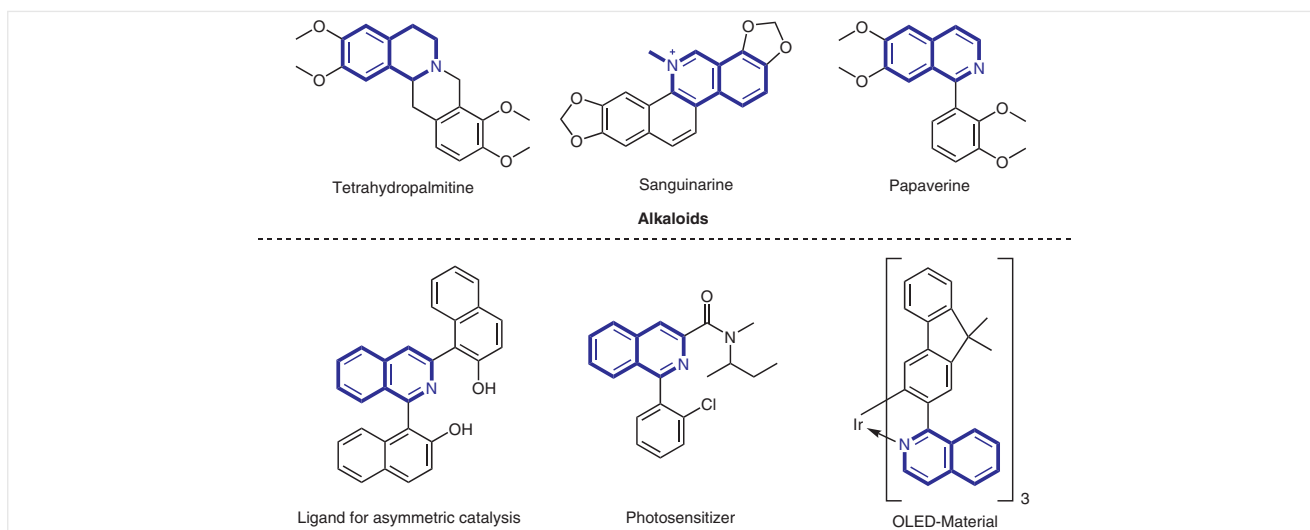


Figure 1 Examples of isoquinoline moieties with pharmaceutical and other importance

folds, which are widely used as analgesic, antibacterial, and vasodilator, respectively.¹⁰

Due to the prosperity of isoquinoline moieties, chemists have developed progressively effective approaches toward their synthesis. In this regard, many researchers reported synthesis of isoquinolines using multistep approaches.¹¹ However, these are suffered with lacunas such as lesser yields, poor regioselectivity, and lengthier reaction times. Overcoming these issues, later, annulation reactions with alkynes by C–H functionalization using different directing groups and catalysts provided an efficient alternate route for their synthesis. Transition metals like Rh¹² and Co¹³ assisted with various directing groups are very well known for the synthesis of isoquinolines by these kinds of transformations, while Ru is rarely utilized for the isoquinoline synthesis by C–H activation reactions.¹⁴ Likewise, *N*-Cbz hydrazone is rarely examined as a directing group for C–H/N–N activation reactions. On the other hand, almost all previous approaches for the synthesis of isoquinolines are reported in volatile organic solvents using conventional heating method for longer reaction time involving use of additives and oxidants, having its own disadvantages. However, recently, the Bolm and Huang research groups reported additive-free C–H functionalization reactions using Ru(II) catalysts.¹⁵

Considering all these facts, there continues to be the need to develop a protocol for the synthesis of isoquinolines which is rapid and free from additives as well as external oxidants using non-volatile greener solvent. In this perspective, continuing our endeavors to develop *N*-heterocycles,^{14b,16} herein, we disclose the ruthenium-catalyzed microwave-assisted synthesis of isoquinolines by C–H/N–N activation using rarely explored acetophenone *N*-Cbz hydrazone as a directing group in PEG-400 as a green solvent (Scheme 1). Furthermore, the proposed strategy works in

very short time without use of any additives and external oxidants.

We initiated our studies by investigating the annulation reactions of acetophenone *N*-Cbz hydrazone with diphenylacetylene in the presence of [Ru(*p*-cymene)Cl₂]₂ and AgSbF₆ in PEG-400 at 100 °C for 10 minutes as model reaction. Monitoring the reaction at different temperatures, we found that there was no satisfactory yield at 100 °C (Table 1, entry 1). While, increasing the temperature to 110 °C, isoquinoline **3aa** was produced in 87% yield (entry 2). Only a slight improvement in the product yield was observed on further increase in temperature (entry 3). Next, screening the reaction at different periods of time, increase in the reaction time from 10 minutes to 12 minutes did not induce

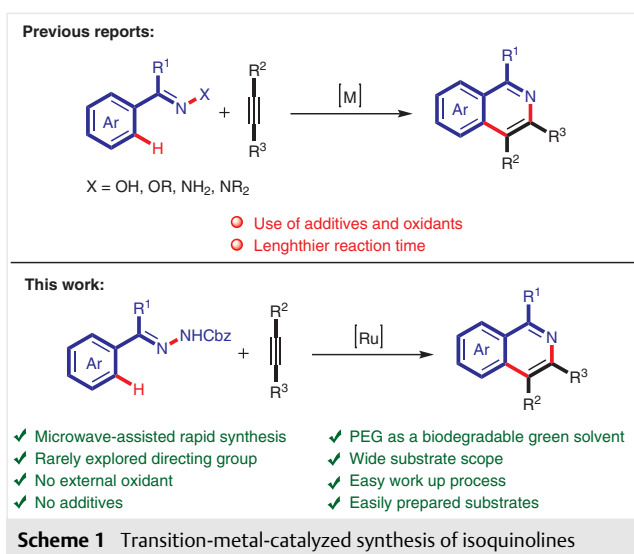
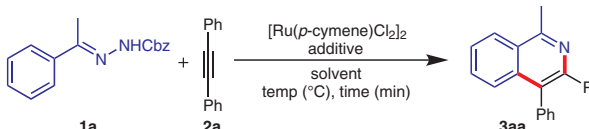


Table 1 Optimization of the Reaction Conditions^a


Entry	Additive	Solvent	Temp (°C)	Time (min)	Yield (%) ^b
1	AgSbF ₆	PEG-400	100	10	62
2	AgSbF ₆	PEG-400	110	10	87
3	AgSbF ₆	PEG-400	120	10	90
4	AgSbF ₆	PEG-400	110	12	88
5	AgSbF ₆	PEG-400	110	8	76
6 ^c	AgSbF ₆	PEG-400	110	10	78
7 ^d	AgSbF ₆	PEG-400	110	10	86
8 ^e	AgSbF ₆	PEG-400	110	10	55
9 ^d	–	PEG-400	110	10	87
10 ^d	–	PEG-200	110	10	58
11 ^d	–	PEG-600	110	10	71
12 ^d	–	ethylene glycol	110	10	28
13 ^{d,f}	–	PEG-400	110	10	34

^a Reaction conditions: *N*-Cbz hydrazone **1a** (0.5 mmol), diphenylacetylene (**2a**; 0.6 mmol), [Ru(*p*-cymene)Cl₂]₂ (5 mol%), additive (10 mol%), solvent (2 mL).

^b GC yield.

^c [Ru(*p*-cymene)Cl₂]₂ used: 7.5 mol%.

^d [Ru(*p*-cymene)Cl₂]₂ used: 2.5 mol%.

^e [Ru(*p*-cymene)Cl₂]₂ used: 1.5 mol%.

^f Under standard conditions without microwave irradiation (conventional oil-bath heating).

any noteworthy progress in the product yield (entry 4), although a consequent decrease in time to 8 minutes reduced the product yield to 76% (entry 5).

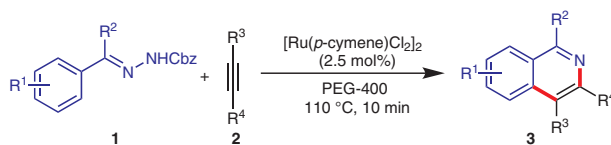
In addition, organized optimization with respect to catalyst loading, within the 1.5–7.5 mol% range (Table 1, entries 6–8), allowed the identification of its optimal quantity (2.5 mol%), which leads to the higher yield and the product was obtained in 86% yield. Considering the environmental threats by the use of antimonate salt, we checked the necessity of AgSbF₆ as an additive for the proposed transformation. Pleasantly, the reaction worked also in the absence of silver salt with the same efficiency (entry 9). The catalytic reaction was also tested with various solvents such as ethylene glycol and with some biodegradable solvents like PEG-200, PEG-400, and PEG-600. PEG-200 and PEG-600 gave product in 58% and 71% yield, respectively (entries 10 and 11). While in the presence of ethylene glycol, the unsatisfactory product yield 28% was obtained (entry 12). Finally,

PEG-400 proved to be a compatible solvent for the stated methodology. The reaction was also attempted without microwave irradiation (conventional oil-bath heating) under standard condition, however, only 34% product yield was obtained (entry 13).

Having established optimization conditions, the scope of the annulation reaction of substituted acetophenone *N*-Cbz hydrazones **1a–q** with diphenylacetylenes **2a–d** was explored as shown in Table 2. The annulation proceeded smoothly for a wide range of substrates in good to excellent yields. Acetophenone *N*-Cbz hydrazone without any substitution led to the formation of desired isoquinoline product **3aa** in an isolated yield of 87% (Table 2, entry 1). *N*-Cbz Hydrazones with electron-donating groups (i.e., methyl and methoxy) at *para*-position led to a considerable increase in yields of products **3ba** and **3ca** to 90% and 92% yield, respectively (entries 2 and 3).

Notably, the presence of electron-withdrawing groups (e.g., bromo, chloro, fluoro, and nitro) at *para*-position of hydrazones provided the corresponding products **3da**, **3ea**, **3fa**, and **3ga** in 82%, 84%, 79% and 80% yield, respectively (Table 2, entries 4–7). Next, the reactions of *meta*-substituted acetophenone *N*-Cbz hydrazones were investigated. It was noted that hydrazones containing Me, Cl, and NO₂ at *meta*-position preferentially annulated with alkynes at the less hindered position to form the corresponding products **3ha**, **3ja**, and **3ka** particularly in 85%, 78% and 74% yield, respectively, while *N*-Cbz hydrazone with OMe at the *meta*-position generated two regioselective products **3ia** and **3ia'** in 48% and 34% yield, respectively (entries 8–11). Furthermore, the disubstituted acetophenone *N*-Cbz hydrazone, gave the respective product **3la** with exclusive regioselectivity in 82% isolated yield (entry 12). In the next set of experiments, *N*-Cbz hydrazones derived from various ketones such as propiophenone, cyclopropyl phenyl ketone, and benzophenone were explored as substrates, which led to the formation of corresponding isoquinoline products **3ma**, **3na**, and **3oa**, respectively in very good yields (entries 13–15). Fused *N*-Cbz hydrazone derived from 1-acetylnaphthalene could also be converted into the desired product **3pa** in 81% yield (entry 16). In addition, *N*-Cbz hydrazone of heterocyclic ketone also could be smoothly converted into the corresponding product **3qa** in 79% yield (entry 17).

Further, the scope of the symmetrical and unsymmetrical substituted internal alkynes for the stated methodology was investigated. Hex-3-yne, 1-phenylbut-1-yne, and 1-phenylprop-1-yne reacted hassle-free with acetophenone *N*-Cbz hydrazone to generate corresponding products **3ab**, **3ac**, and **3ad** in 76%, 82% and 80% yield, respectively (Table 2, entries 18–20).

Table 2 Ruthenium-Catalyzed Annulation of *N*-Cbz Hydrazones with Alkynes^a

Entry	1	2	Product 3	Yield (%) ^b
1				87
2				90
3				92
4				82
5				84
6				79
7				80
8				85

Table 2 (continued)

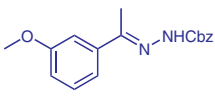
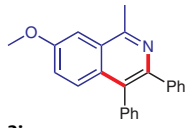
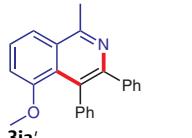
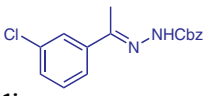
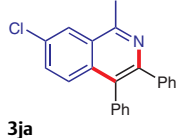
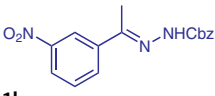
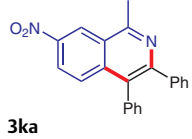
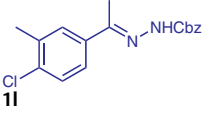
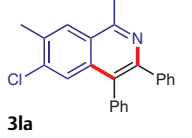
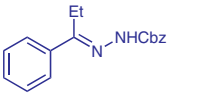
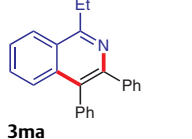
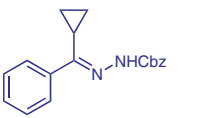
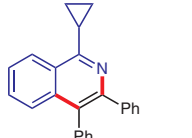
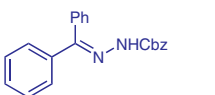
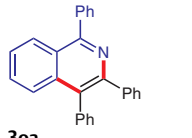
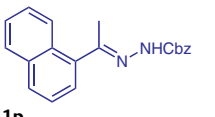
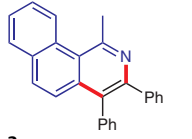
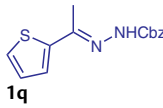
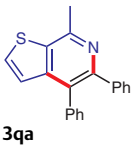
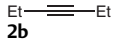
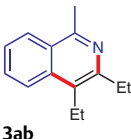
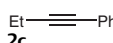
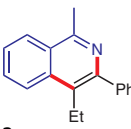
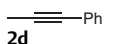
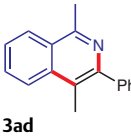
Entry	1	2	Product 3	Yield (%) ^b
9	 1i	2a	 3ia	48
			 3ia'	34
10	 1j	2a	 3ja	78
11	 1k	2a	 3ka	74
12	 1l	2a	 3la	82
13	 1m	2a	 3ma	89
14	 1n	2a	 3na	88
15	 1o	2a	 3oa	93
16	 1p	2a	 3pa	81

Table 2 (continued)

Entry	1	2	Product 3	Yield (%) ^b
17		2a		79
18	1a			76
19	1a			82
20	1a			80

^a Reaction conditions: ketazine **1** (0.5 mmol), alkyne **2** (0.6 mmol), [Ru(*p*-cymene)Cl₂]₂ (2.5 mol%), PEG-400 (2 mL), 110 °C (microwave heating), 10 min.

^b Isolated yield.

In conclusion, we have developed a microwave-assisted rapid protocol for the synthesis of isoquinolines by annulation reaction with internal alkynes via C–H/N–N activation. *N*-Cbz Hydrazones were employed as directing group for redox-neutral Ru-catalyzed transformation. Additionally, the stated methodology works efficiently in the absence of any additives as well as external oxidants. This protocol is applicable to a wide range of *N*-Cbz hydrazones possessing electron-donating and electron-withdrawing groups as well as internal alkynes for the synthesis of isoquinolines, producing corresponding products in good to excellent yields. Use of non-volatile and biodegradable solvent is the additional advantage of the present system.

All chemicals and solvents were purchased with high purities and used without further purification. PEGs were dried prior to use by the literature methods. Microwave-assisted annulation reactions were carried out in 'Discover' (CEMSP 1245) CEM Corporation USA) microwave reactor. The progress of the reaction was monitored by GC with a flame ionization detector (FID) using a capillary column (30 m × 0.25 mm × 0.25 μm) and TLC (using silica gel 60 F-254 plates). The products were visualized with a 254 nm UV lamp. GC-MS [Rtx-17, 30 m × 25 mm ID, film thickness (df = 0.25 μm) (column flow 2 mL min⁻¹, 80 to 240 °C at 10 °C min⁻¹ rise] was used for the mass analysis of the products. Products were purified by column chromatography on 100–200 mesh silica gel. The ¹H NMR spectra were recorded on an Agilent Technologies 400 MHz spectrometer using TMS as an internal standard. The ¹³C NMR spectra were recorded on 100 MHz and chemical

shifts were reported in parts per million (δ) relative to TMS as an internal standard. Coupling constant (*J*) values were reported in hertz (Hz). Standard abbreviations were used for describing the splitting patterns of proton in ¹H NMR spectroscopic analysis. The products were confirmed by GCMS, ¹H, and ¹³C NMR spectroscopy analysis.

Ruthenium-Catalyzed Isoquinoline Synthesis; 1-Methyl-3,4-diphenylisoquinoline (**3aa**);^{13d} Typical Procedure

A microwave vessel was charged with *N*-Cbz hydrazone **1a** (134 mg, 0.5 mmol), diphenylacetylene (**2a**; 107 mg, 0.6 mmol), [Ru(*p*-cymene)Cl₂]₂ (8 mg, 2.5 mol%), and PEG-400 (2 mL). The closed reaction vessel was irradiated at 110 °C using microwave irradiation of 50 W power for 10 min. At the end of the reaction, the reaction mixture was cooled, and diluted with Et₂O. The upper layer of Et₂O containing the product mixture was separated, the solvent evaporated, and the residue was purified through a silica gel column using PE and EtOAc as eluents to give pure **3aa**; yield: 134 mg (87%); pale yellow solid; mp 154–156 °C.

¹H NMR (400 MHz, CDCl₃): δ = 8.21–8.19 (m, 1 H), 7.65 (d, *J* = 3.1 Hz, 1 H), 7.60–7.57 (m, 2 H), 7.37–7.32 (m, 5 H), 7.24–7.17 (m, 5 H), 3.08 (s, 3 H).

¹³C NMR (101 MHz, CDCl₃): δ = 157.70, 149.29, 140.80, 137.49, 136.02, 131.37, 130.25, 129.97, 129.24, 128.17, 127.58, 127.03, 126.94, 126.54, 126.23, 126.13, 125.52, 22.62.

GCMS (EI 70 eV): *m/z* = 295 (M⁺), 294, 278, 253, 145.

6-Methoxy-1-methyl-3,4-diphenylisoquinoline (**3ca**)^{13d}

Yield: 150 mg (92%); pale yellow solid; mp 179–181 °C.

¹H NMR (400 MHz, CDCl₃): δ = 8.10 (d, *J* = 9.1 Hz, 1 H), 7.35–7.29 (m, 5 H), 7.24–7.14 (m, 6 H), 6.91 (d, *J* = 2.2 Hz, 1 H), 3.71 (s, 3 H), 3.02 (s, 3 H).

^{13}C NMR (101 MHz, CDCl_3): δ = 160.61, 156.95, 149.97, 140.97, 138.10, 137.78, 131.25, 130.20, 128.63, 128.24, 127.53, 127.46, 127.08, 126.88, 121.84, 118.71, 104.50, 55.18, 22.51.

GCMS (EI 70 eV): m/z = 325 (M^+), 324, 281, 154, 146.

6-Bromo-1-methyl-3,4-diphenylisoquinoline (3da)^{13d}

Yield: 153 mg (82%); slightly yellow solid; mp 192–194 °C.

^1H NMR (400 MHz, CDCl_3): δ = 8.04 (d, J = 8.8 Hz, 1 H), 7.80 (d, J = 1.8 Hz, 1 H), 7.66–7.64 (m, 1 H), 7.34 (m, 5 H), 7.24–7.17 (m, 5 H), 3.04 (s, 3 H).

^{13}C NMR (101 MHz, CDCl_3): δ = 157.76, 150.53, 140.50, 137.40, 136.77, 131.26, 130.18, 130.03, 128.41, 128.33, 128.30, 127.63, 127.45, 127.29, 127.19, 125.10, 124.57, 22.61.

GCMS (EI 70 eV): m/z = 375 (M^+ , 2%), 373 (M^+), 374, 372, 293, 292, 252, 147, 139, 125.

1,7-Dimethyl-3,4-diphenylisoquinoline (3ha)^{13d}

Yield: 131 mg (85%); slightly yellow solid; mp 131–133 °C.

^1H NMR (400 MHz, CDCl_3): δ = 7.96 (s, 1 H), 7.56 (d, J = 8.6 Hz, 1 H), 7.43–7.32 (m, 6 H), 7.24–7.17 (m, 5 H), 3.05 (s, 3 H), 2.57 (s, 3 H).

^{13}C NMR (101 MHz, CDCl_3): δ = 156.98, 148.55, 140.97, 137.71, 136.40, 134.19, 132.08, 131.36, 130.25, 129.09, 128.13, 127.55, 127.03, 126.80, 126.32, 126.10, 124.49, 22.66, 21.86.

GCMS (EI 70 eV): m/z = 309 (M^+), 308, 293, 252, 146, 139.

7-Methoxy-1-methyl-3,4-diphenylisoquinoline (3ia)^{13d}

Yield: 78 mg (48%); slightly yellow solid; mp 142–144 °C.

^1H NMR (400 MHz, CDCl_3): δ = 7.57 (d, J = 9.2 Hz, 1 H), 7.38–7.31 (m, 6 H), 7.25–7.14 (m, 6 H), 3.98 (s, 3 H), 3.04 (s, 3 H).

^{13}C NMR (101 MHz, CDCl_3): δ = 157.90, 155.95, 147.46, 140.60, 137.5, 131.39, 131.31, 130.22, 129.26, 128.14, 128.01, 127.54, 127.31, 127.09, 126.77, 122.37, 103.52, 55.48, 22.68.

GCMS (EI 70 eV): m/z = 325 (M^+), 324, 308, 293, 154, 146.

5-Methoxy-1-methyl-3,4-diphenylisoquinoline (3ia')^{12a}

Yield: 55 mg (34%); white solid; mp 145–147 °C.

^1H NMR (400 MHz, CDCl_3): δ = 7.79 (d, J = 8.4 Hz, 1 H), 7.52 (t, J = 7.8 Hz, 1 H), 7.23–7.21 (m, 2 H), 7.16–7.08 (m, 8 H), 6.95 (d, J = 7.7 Hz, 1 H), 3.39 (s, 3 H), 3.04 (s, 3 H).

^{13}C NMR (101 MHz, CDCl_3): δ = 157.04, 156.86, 150.91, 141.38, 141.34, 130.35, 130.21, 127.91, 127.48, 127.45, 127.26, 127.16, 126.48, 125.61, 118.04, 110.18, 55.53, 23.24.

GCMS (EI 70 eV): m/z = 325 (M^+), 324, 281, 162, 139.

1-Cyclopropyl-3,4-diphenylisoquinoline (3na)^{12c}

Yield: 141 mg (88%); white solid; mp 149–151 °C.

^1H NMR (400 MHz, CDCl_3): δ = 8.50–8.48 (m, 1 H), 7.65–63 (m, 1 H), 7.59–7.56 (m, 2 H), 7.36–7.33 (m, 5 H), 7.27–7.21 (m, 2 H), 7.16 (d, J = 2.8 Hz, 3 H), 2.83–2.81 (m, 1 H), 1.40–1.25 (m, 2 H), 1.16–1.13 (m, 2 H).

^{13}C NMR (101 MHz, CDCl_3): δ = 160.55, 148.50, 141.42, 138.33, 136.21, 131.40, 130.42, 129.73, 128.30, 128.23, 127.32, 127.07, 126.87, 126.40, 126.26, 126.24, 124.90, 13.60, 9.39.

GCMS (EI 70 eV): m/z = 321 (M^+), 320, 243, 152, 146.

1-Methyl-3,4-diphenylbenzo[*h*]isoquinoline (3pa)^{13d}

Yield: 140 mg (81%); slightly yellow solid; mp 142–144 °C.

^1H NMR (400 MHz, CDCl_3): δ = 8.90 (d, J = 8.3 Hz, 1 H), 7.91 (d, J = 7.4 Hz, 1 H), 7.79–7.71 (m, 2 H), 7.65 (t, J = 7.1 Hz, 1 H), 7.55 (d, J = 9.1 Hz, 1 H), 7.42 (d, J = 5.9 Hz, 2 H), 7.35 (d, J = 6.5 Hz, 3 H), 7.25–7.19 (m, 5 H), 3.44 (s, 3 H).

^{13}C NMR (101 MHz, CDCl_3): δ = 155.39, 150.80, 140.43, 137.95, 137.27, 132.96, 131.64, 131.22, 130.21, 129.73, 128.74, 128.26, 127.64, 127.58, 127.27, 127.19, 126.88, 126.64, 124.19, 123.95, 30.43.

GCMS (EI 70 eV): m/z = 345 (M^+), 344, 343, 342, 307, 265, 154, 146.

7-Methyl-4,5-diphenylthieno[2,3-*c*]pyridine (3qa)^{13d}

Yield: 113 mg (79%); white solid; mp 145–147 °C.

^1H NMR (400 MHz, CDCl_3): δ = 7.61 (d, J = 5.4 Hz, 1 H), 7.35–7.29 (m, 5 H), 7.24–7.18 (m, 6 H), 2.91 (s, 3 H).

^{13}C NMR (101 MHz, CDCl_3): δ = 151.33, 150.78, 145.76, 140.14, 138.16, 134.24, 131.08, 130.51, 130.30, 128.27, 128.23, 127.69, 127.15, 127.10, 124.25, 23.52.

GCMS (EI 70 eV): m/z = 301 (M^+), 300, 258, 150, 149.

4-Ethyl-1-methyl-3-phenylisoquinoline (3ac)^{13d}

Yield: 101 mg (82%); white solid; mp 121–123 °C.

^1H NMR (400 MHz, CDCl_3): δ = 8.17 (d, J = 8.0 Hz, 1 H), 8.07 (d, J = 8.4 Hz, 1 H), 7.73 (t, J = 7.6 Hz, 1 H), 7.59 (t, J = 7.6 Hz, 1 H), 7.51–7.37 (m, 5 H), 3.01–2.97 (m, 5 H), 1.25 (t, J = 7.4 Hz, 3 H).

^{13}C NMR (101 MHz, CDCl_3): δ = 155.82, 150.56, 141.66, 135.16, 129.89, 129.19, 128.62, 128.14, 127.41, 126.68, 126.38, 126.20, 124.13, 22.38, 21.64, 15.66.

GCMS (EI 70 eV): m/z = 247 (M^+), 246, 232, 231, 230, 115.

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Supporting Information

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