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PII: S0040-4020(19)30451-X

DOI: https://doi.org/10.1016/j.tet.2019.04.039

Reference: TET 30284

To appear in: *Tetrahedron*

Received Date: 24 January 2019

Revised Date: 22 March 2019

Accepted Date: 16 April 2019

Please cite this article as: Lin W, Hu X-X, Zhuang C-W, Wang Y-Z, Easy access to synthesize isoquinolines from aryl ketoximes and internal alkynes *via* iridium (III)-Catalyzed C—-H/N—-O bond activation, *Tetrahedron* (2019), doi: https://doi.org/10.1016/j.tet.2019.04.039.

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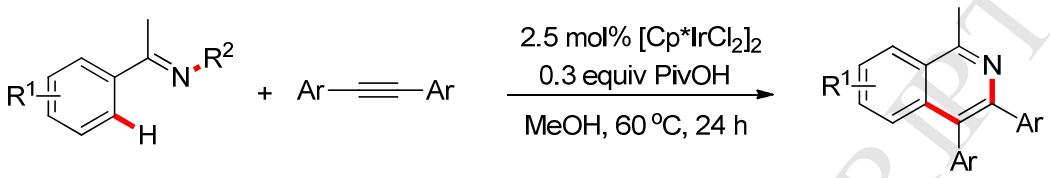

Easy Access to Synthesize Isoquinolines from Aryl Ketoximes and Internal Alkynes *via* Iridium (III)-Catalyzed C-H/N-O Bond Activation

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Abstract: A highly efficient approach to synthesize isoquinoline derivatives through Iridium(III)-catalyzed cyclization of aryl ketoximes and internal alkynes without oxidant is reported. A broad range isoquinolines are obtained in good to excellent yields and various functional groups are well tolerated.

Keywords: isoquinoline, synthesis; cyclization, Iridium(III)-catalysis

1. Introduction

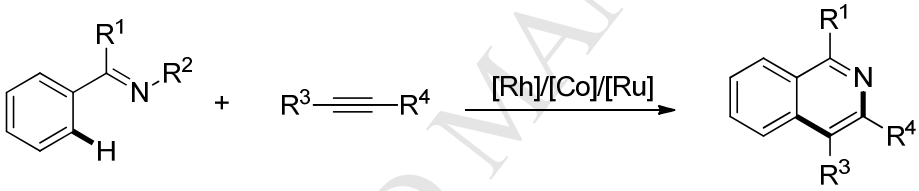
Recently, transition-metal-catalyzed directed C−H functionalization has emerged as a practical approach for organic synthesis, which has been witnessed tremendous progress [1]. Among the most promising activation strategies is to utilize cleverly the proximate effect by coordination of a directing group in given substrate to the metal center of a catalyst, which brings regioselective C-H bond activation and functionalization [2].

As well known, isoquinoline framework is an important *N*-heterocyclic structural motif, which is found in many naturally occurring compounds that exhibit a variety of biological activities [3]. And many substituted isoquinolines are also often used in the synthesis of inhibitors, pharmaceuticals and chiral ligands [4]. In the past decades, various transition-metal (Rh, Ru, Co) catalyzed annulations by C-H/N-O functionalizations have been proved elegant methods for the synthesis of isoquinolines (Scheme 1) [5-7]. For example, Shunsuke Chiba group developed a useful synthetic method for isoquinoline derivatives from readily available starting materials by using $Cu(OAc)_2$ and $[Cp^*RhCl_2]_2$ bimetallic relay catalysts in 2011 [8]. An efficient ruthenium-catalyzed redox-neutral annulations of alkynes different oximes through C-H/N-O functionalization was reported

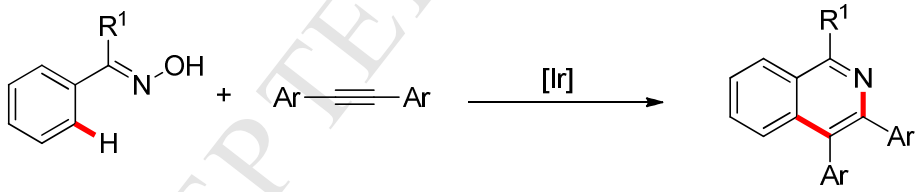
by Lutz Ackermann group [9]. Recently, Shigeki Matsunaga group demonstrated one unique Cp*Co^{III} catalyst that exhibited high site selectivity and reactivity for the synthesis of multisubstituted isoquinolines from unsymmetrical *O*-acyl oximes and terminal as well as internal alkynes by site-selective C-H bond activation [10]. We hypothesized introducing a new catalyst to induce the C-H annulation high efficiently, a wider substrate scope and better functional group tolerance could be observed.

Iridium(III) catalyzed C-H functionalization has achieved significant development, greatly enriching the type of reaction and the substrate scope [11]. To our knowledge, C-H annulation to synthesize isoquinoline from ketoxime substrates using Iridium(III) as catalyst has few reports. Herein, we report the first example of the Ir(III) complex as a highly efficient catalyst in promoting C-H/N-O annulation of ketoxime with internal alkynes to build isoquinoline skeleton without using external oxidant (Scheme 1) [12].

Previous work:



This work:



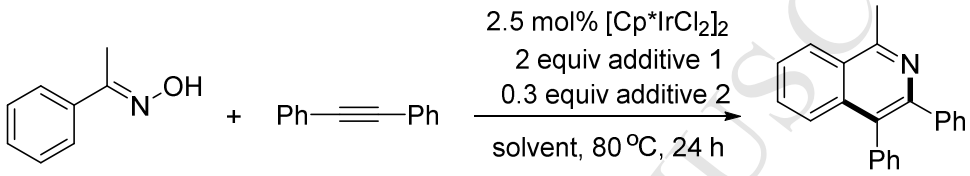
Scheme 1. Transition-metal-catalyzed directed C-H/N-O bond activation

2. Results and Discussion

We began our initial study by treating acetophenone oxime **1a** with diphenylacetylene **2a** in the presence of $[Cp^*IrCl_2]_2$ (2.5 mol%) and $Cu(OAc)_2 \cdot H_2O$ (2 equiv) in DCE at 80 ^oC for 24 h in a sealed vial. Unfortunately, only 15% yield of 1-methyl-3,4-diphenylisoquinoline **3a** was detected by GC at the first run (Table 1, entry1). Screening other solvents, including MeOH, EtOH, TFE and HFIP (Table 1, entries 2-5), led to the identification of MeOH as the optimal solvent (Table 1, entry 2). We subsequently tested other base additives such as LiOAc, NaOAc, KOAc and AgOAc. However, none of them gave better results (Table 1, entries 6-9). Acid additives were also investigated, most

of them displaying positive effect on the product yield (Table 1, entries 10-15). Notably, PivOH was the best additive, which greatly promoting the annulation reaction and gave 82% yield of product **3a** (Table 1, entry 10). Much to our delight, we observed that lowering the temperature to 60 °C further increased the yield of **3a** to 89% (Table 1, entry 16). Notably, additional $Cu(OAc)_2 \cdot H_2O$ in the presence of PivOH had not further promoted the reaction (Table 1, entry 17). Control experiment showed the annulation failed to proceed in the absence of Ir(III) catalyst, indicating the Iridium could not be replaced in this transformation (Table 1, entry 18).

Table 1. Optimization of the Reaction Conditions[a]



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

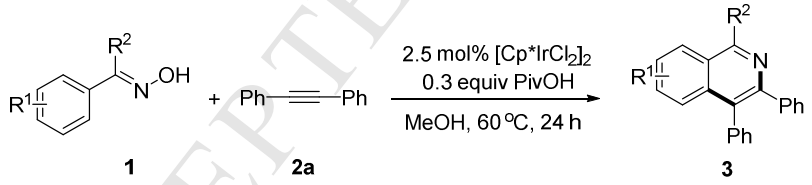
Entry	Solvent	Additive 1	Additive 2	GC-Yield[b]
1	DCE	$Cu(OAc)_2 \cdot H_2O$	-	15%
2	MeOH	$Cu(OAc)_2 \cdot H_2O$	-	33%
3	EtOH	$Cu(OAc)_2 \cdot H_2O$	-	<5%
4	TFE	$Cu(OAc)_2 \cdot H_2O$	-	18%
5	HFIP	$Cu(OAc)_2 \cdot H_2O$	-	<5%
6	MeOH	LiOAc	-	<5%
7	MeOH	NaOAc	-	<5%
8	MeOH	KOAc	-	<5%
9	MeOH	AgOAc	-	12%
10	MeOH	-	PivOH	82%
11	MeOH	-	1-$AdCO_2H$	69%
12	MeOH	-	HOAc	63%
13	MeOH	-	$MesCO_2H$	65%
14	MeOH	-	$AgSbF_6$	41%
15	MeOH	-	$AgNTf_2$	10%
16[c]	MeOH	-	PivOH	89%(86)[d]

17[c]	MeOH	$Cu(OAc)_2{\cdot}H_2O$	PivOH	90%
18[c,e]	MeOH	-	PivOH	0

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), $[Cp^*IrCl_2]_2$ (2.5mol%), additive 1 (0.2 mmol), additive 2 (0.03 mmol), solvent (1 mL), 80 °C, 24 h. [b]GC yield of **3a** determined using tridecane as internal standard. [c]60 °C. [d]Isolated yield. [e]No catalyst.

With the optimized conditions in hand, the scope of aryl ketoximes **1** was examined. As illustrated in Table 2, a broad range of aryl ketoximes **1** were well tolerated and corresponding products were obtained in moderate to excellent yields. A variety of *para*-substituted substrates **1a**-**1o** was readily converted to annulation products with internal alkynes, including electron-donating groups and electron-withdrawing groups. To our delight, even the iodine substitution on the aromatic ring was achieved in 78% yield without any modifying reaction conditions (**3j**). When *ortho*- and *meta*-substituted substrates were applied to the method, good yields were observed, such as **3p**, **3q**, **3r**, **3s** and **3t**. For unsymmetrically substituted oximes (**1s** and **1t,** except **1u**), the Cp^*Ir^{III} catalyst exhibited much site selectivity, both the oximes were converted into the desired products **3s**–**3t** with > 20:1 site selectivity and in 52–87% yield. However, for the substrate **1u**, the less steric functional group results in the poor selectivity at the ortho position, the **1u** could convert into two different products **3u** and **3u'**, along with 50% and 32% yields respectively. It was also worth mentioning that heterocyclic substrate **1w** also proved to be suitable for the C-H annulation, when employing $Cu(OAc)_2{\cdot}H_2O$ as the additive at high temperature. Furthermore, an oxime-containing bicyclic substrate and sterically more demanding substituent furnished the assembly of the tricyclic product **3aa** in low yield.

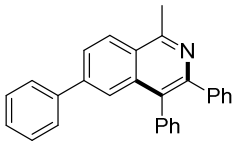
Table 2. Substrate Scope of aryl ketoximes



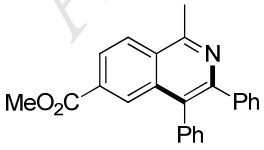
1 **2a** **3**

R^2 = Me

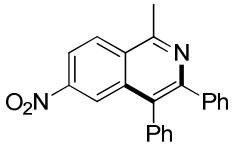
R^1 = 4-Me, **3b**, 93%[b]
R^1 = 4-Et, **3c**, 93%[b]
R^1 = 4-*i*Pr, **3d**, 90%
R^1 = 4-*t*Bu, **3e**, 92%[b]
R^1 = 4-MeO, **3f**, 65%
R^1 = 4-F, **3g**, 96%[c]
R^1 = 4-Cl, **3h**, 84%[b]
R^1 = 4-Br, **3i**, 89%
R^1 = 4-I, **3j**, 78%
R^1 = 4-CF_3, **3k**, 96%[b]



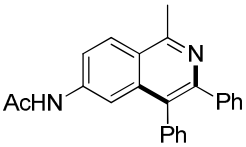
3l, 94%[b]



3m, 93%[b]

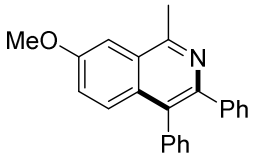


3n, 92%[b,d]

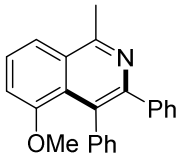


3o, 70%[b]

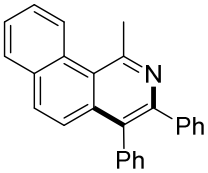
R^1= 2-F, **3p,** 49%[e,f]
R^1= 2-Me, **3q,** 66%
R^1= 2-OMe, **3r,** 83%
R^1= 3-Br, **3s**, 52%
R^1= 3-Me, **3t,** 87%



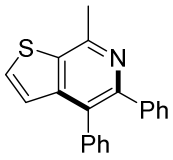
3u, 50%



3u', 32%

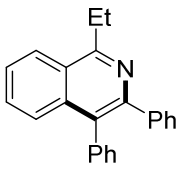


3v, 63%[b]

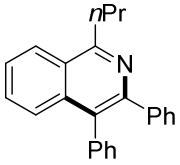


3w, 88%[e,f]

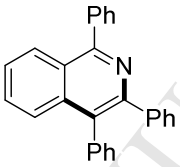
R^1 = H



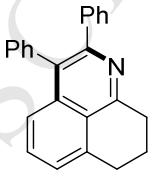
3x, 50%



3y, 85%[e]



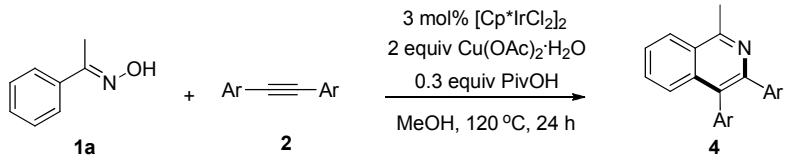
3z, 35%[b,f]



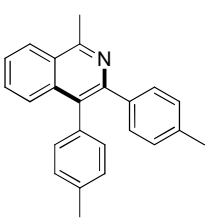
3aa, 36%

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), $[Cp^*IrCl_2]_2$ (2.5 mol%), PivOH (0.06 mmol), MeOH (2 mL), 60 °C, 24 h. Isolated yield. [b]100 °C. [c]80 °C. [d]$[Cp^*IrCl_2]_2$ (5mol%). [e]120 °C. [f]$Cu(OAc)_2 \cdot H_2O$ (0.2 mmol).

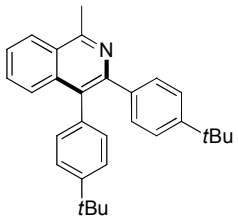
Table 3. Substrate Scope of internal alkynes [a]



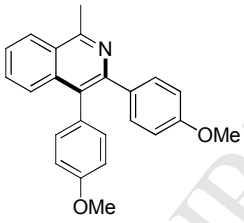
1a + **2** → **4**



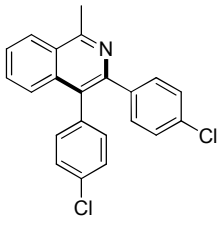
4a, 65%



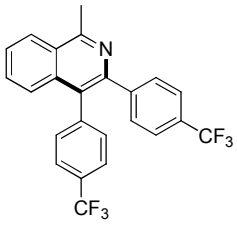
4b, 50%



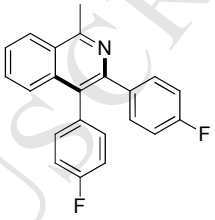
4c, 61%



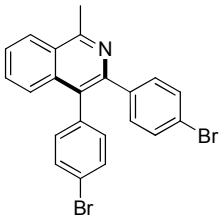
4d, 53%



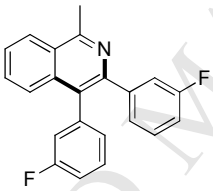
4e, 72%



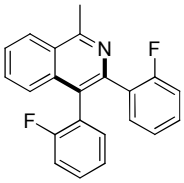
4f, 44%



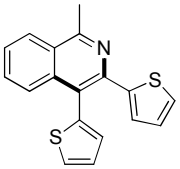
4g, 41%



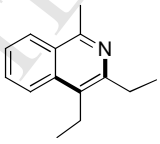
4h, 52%[b]



4i, 78%[b]



4j, 47%[b]



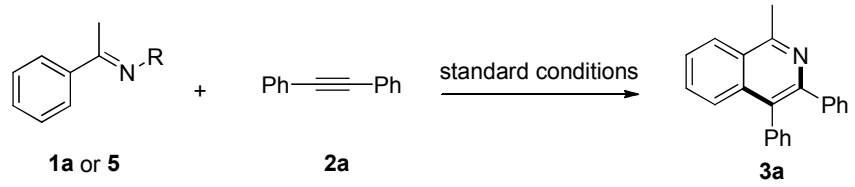
4k, trace

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), $[Cp^*IrCl_2]_2$ (3.0 mol%), $Cu(OAc)_2 \cdot H_2O$ (0.4 mmol), PivOH (0.06 mmol), MeOH (2 mL), 120 °C, 24 h, Isolated yield. [b]TFE (2 mL)

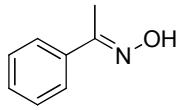
Subsequently, different internal alkynes were tested in this Ir(III)-catalyzed protocol, mainly involving aryl and heteroaryl alkynes (Table 3). 2 Equiv $Cu(OAc)_2 \cdot H_2O$ was found quite necessary to promote the reaction through further modifying the conditions and desired products could be isolated in moderate yields. We speculated that $Cu(OAc)_2 \cdot H_2O$ play an important role in catalyst regeneration through helping oxidization of the Ir(I) to Ir(III). Unfortunately, the alkyl-substituted alkyne was found hardly to react with

acetophenone oxime **1a**, just the starting materials remained (**4k**).

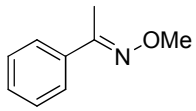
Table 4. Different protecting groups directed C-H annulation [a]



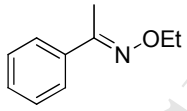
1a or **5** + **2a** → **3a**



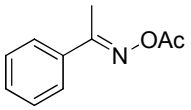
1a, 86%



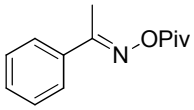
5a, 43%



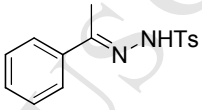
5b, 36%



5c, 15%



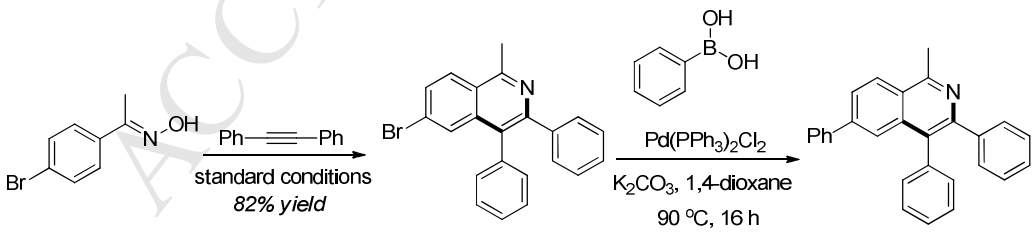
5d, 37%



5e, 15%

[a]Reaction conditions: **1a** or **5** (0.2 mmol), **2a** (0.24 mmol), $[Cp^*IrCl_2]_2$ (2.5mol%), PivOH (0.06 mmol), MeOH (2 mL), 60 °C, 24 h, Isolated yield.

Meanwhile, other protecting groups of acetophenone were also examined in the protocol (Table 4). We were pleased to find that all the annulation could occur with the assistance of these directing groups, and the desired product could be achieved in low to moderate yields. Besides, the gram-scale reaction was successfully obtained with 2 mol% $[Cp^*IrCl_2]_2$, which highlighted the power of this approach. And the corresponding product could be coupled with phenylboronic acid, affording **3l** in 81% yield (Scheme 2).

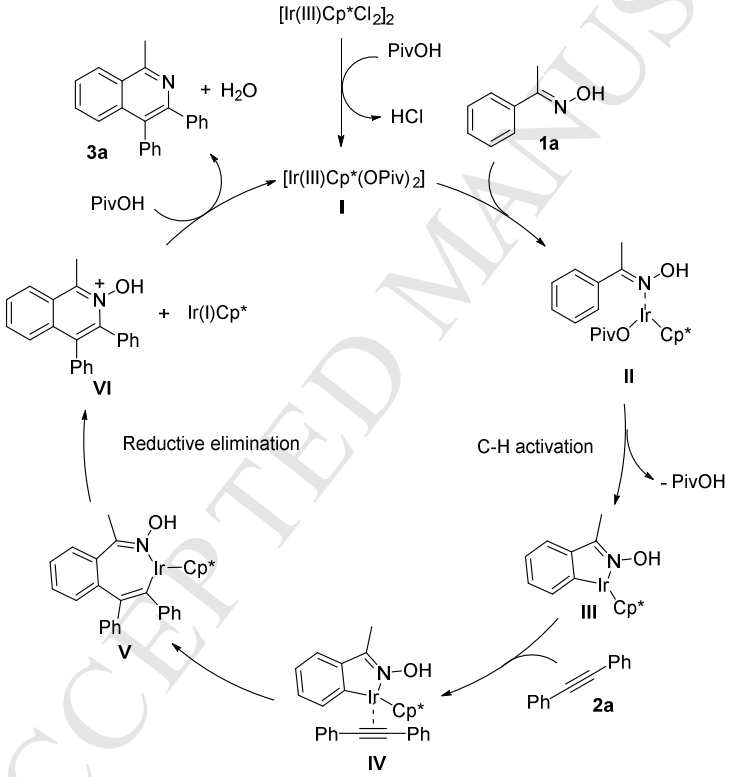


1i, 4.70 mmol, 1 g → **3i**, 1.44 g → **3l**, 81% yield

Scheme 2. Scaling up and coupling with phenylboronic acid

Based on previous mechanistic study and the recent reports, a plausible mechanism for the Ir(III)-catalyzed C-H annulation of ketoxime is proposed in Scheme 3 [13]. The catalytic cycle is likely initiated by the dissociation of the $[Cp^*IrCl_2]_2$ dimer and the

exchange of pivaloyl with the coordinated chloro ligand to form a pivaloyl-ligated species. Then, coordination of the nitrogen atom to the Ir(III) center, followed by arene ortho C-H cleavage lead to the generation of five-membered Iridiumcycle **III**. The coordination of the alkyne π-bond to Iridiumcycle **III**, followed by insertion of the alkyne, forms the C-C bond and produces key intermediate **V**. The subsequent intramolecular annulation and reductive elimination provides the *N*-hydroxyisoquinoline cation **VI**, which could serve as an oxidant for the regeneration of Ir(III) catalyst for the next cycle and affords the isoquinoline as the final product.



Scheme 3. Proposed catalytic cycle

3. Conclusion

In summary, we have reported a novel and highly efficient iridium-catalyzed C-H/N-O Bond of aryl ketoximes with internal alkynes for the synthesis of isoquinolines without external oxidant. A broad range of aryl ketoximes substituted by various groups could be well tolerated in this new method, giving the corresponding products in moderate to excellent yields.

4. Experimental Section

4.1. General

Unless otherwise noted, all reagents were purchased from commercial suppliers and used without further purification. HRMS analysis was carried out using TOF-MS instrument with ESI source. ^{1}H NMR and ^{13}C NMR were determined on Varian Invoa-400 MHz spectrometer in $CDCl_3$ solution. *J* values are in Hz. Chemical shifts are expressed in ppm downfield from internal standard TMS. Multiplicities are recorded as s = singlet, d = doublet, t = triplet, dd = doublet of doublets, m = multiplet.

4.2. Characterization data of 3 are represented as follows.

A mixture of compounds **1** or **5** (0.2 mmol), diphenylacetylene **2a** (0.24 mmol, 1.2 equiv), $[Cp^*IrCl_2]_2$ (2.5 mol%), PivOH (0.06 mmol, 0.3 equiv) and MeOH (2 mL) in a 15 mL glass vial [sealed with poly(tetrafluoroethylene) (PTFE) cap] was heated at 60 °C with vigorous stirring for 24 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through Celite. The filtrate was concentrated in vacuo and purified by column chromatography on silica gel to give the corresponding product **3**.

*4.2.1. 1-Methyl-3,4-diphenylisoquinoline (**3a**)*: Brown solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21-8.19 (m, 1H), 7.67-7.57 (m, 3H), 7.38-7.17 (m, 10H), 3.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 149.0, 140.6, 137.1, 135.5, 131.0, 129.8, 129.5, 128.7, 127.7, 127.2, 126.7, 126.5, 126.1, 125.8, 125.7, 125.1, 22.3; HRMS : m/z calcd for $C_{22}H_{17}NNa$ $[M+Na]^+$: 318.1259; Found: 318.1274.

*4.2.2. 1,6-Dimethyl-3,4-diphenylisoquinoline (**3b**)*: White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.8 Hz, 1H), 7.41 (d, *J* = 7.6 Hz, 2H), 7.35-7.33 (m, 5H), 7.23-7.16 (m, 5H), 3.04 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 149.1, 140.7, 139.7, 137.3, 135.8, 131.0, 129.8, 128.3, 128.2, 127.7, 127.1, 126.6, 126.4, 125.0, 124.6, 124.1, 22.2, 21.7; HRMS : m/z calcd for $C_{23}H_{20}N$ $[M+H]^+$: 310.1596; Found: 310.1591.

*4.2.3. 6-Ethyl-1-methyl-3,4-diphenylisoquinoline (**3c**):* White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.4 Hz, 1H), 7.48-7.43 (m, 2H), 7.36-7.34 (m, 5H), 7.24-7.17 (m, 5H), 3.05 (s, 3H), 2.76-2.70 (m, 2H), 1.23 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 149.6, 146.4, 141.2, 137.8, 136.3, 131.5, 130.3, 128.9, 128.2, 127.6, 127.0, 126.8, 125.6, 124.8, 124.0, 29.4, 22.7, 15.4; HRMS : m/z calcd for $C_{24}H_{22}N$ $[M+H]^+$: 324.1752; Found: 324.1757.

*4.2.4. 6-Isopropyl-1-methyl-3,4-diphenylisoquinoline (**3d**):* Brown solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.4 Hz, 1H), 7.58-7.52 (m, 2H), 7.42-7.38 (m, 5H), 7.31-7.23 (m, 5H), 3.11 (s, 3H), 3.06-3.02 (m, 1H), 1.31 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 156.9, 150.4, 149.1, 140.8, 137.3, 135.8, 131.0, 129.8, 128.6, 127.7, 127.1, 126.6, 126.3, 125.4, 125.2, 124.5, 122.3, 34.1, 23.2, 22.2; HRMS : m/z calcd for $C_{25}H_{24}N$ $[M+H]^+$: 338.1909; Found: 338.1922.

*4.2.5. 6-(Tert-butyl)-1-methyl-3,4-diphenylisoquinoline (**3e**)*: White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 8.8 Hz, 1H), 7.69-7.62 (m, 2H), 7.36-7.30 (m, 5H), 7.24-7.15 (m, 5H), 3.04 (s, 3H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 152.5, 149.1, 140.8, 137.3, 135.5, 131.0, 129.8, 128.9, 127.6, 127.1, 126.6, 126.3, 124.9, 124.8, 124.0, 120.8, 34.8, 30.5, 22.1; HRMS : m/z calcd for $C_{26}H_{26}N$ $[M+H]^+$: 352.2065; Found: 352.2055.

*4.2.6. 6-Methoxy-1-methyl-3,4-diphenylisoquinoline (**3f**)*: White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 9.2 Hz, 1H), 7.36-7.32 (m, 5H), 7.24-7.17 (m, 6H), 6.92-6.91 (m, 1H), 3.73 (s, 3H), 3.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 156.5, 149.6, 140.6, 137.6, 137.4, 130.8, 129.8, 128.2, 127.8, 127.1, 127.0, 126.6, 126.4, 121.4, 118.3, 104.0, 54.8, 22.1; HRMS : m/z calcd for $C_{23}H_{20}NO$ $[M+H]^+$: 326.1545; Found: 326.1560.

*4.2.7. 6-Fluoro-1-methyl-3,4-diphenylisoquinoline (**3g**)*: White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24-8.20 (m, 1H), 7.39-7.32 (m, 6H), 7.27 (dd, J_1 = 6.8 Hz, J_2 = 2.4 Hz, 1H), 7.22-7.19 (m, 5H), 3.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 161.5, 157.1, 150.0, 140.2, 137.7, 137.6, 136.7, 130.7, 129.8, 128.5, 128.4, 128.2, 128.1, 128.0, 127.0, 126.9, 126.7, 123.0, 116.3, 116.1, 109.5, 109.3, 22.4; HRMS : m/z calcd for $C_{22}H_{17}FN$ $[M+H]^+$: 314.1345; Found: 314.1357.

*4.2.8. 6-Chloro-4-(cyclohexa-1,5-dien-1-yl)-1-methyl-3-phenylisoquinoline (**3h**)*: White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 8.8 Hz, 1H), 7.63-7.62 (m, 1H), 7.53 (dd, J_1 = 8.8 Hz, J_1 = 2.0 Hz, 1H), 7.37-7.34 (m, 5H), 7.22-7.18 (m, 5H), 3.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 150.2, 140.2, 136.7, 136.4, 135.9, 130.8, 129.7, 128.0, 127.9, 127.2, 127.0, 126.9, 126.7, 124.7, 123.9, 22.3; HRMS : m/z calcd for $C_{22}H_{17}ClN$ $[M+H]^+$: 330.1050; Found: 330.1048.

*4.2.9. 6-Bromo-1-methyl-3,4-diphenylisoquinoline (**3i**)*: White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 8.8 Hz, 1H), 7.81-7.80 (m, 1H), 7.67 (dd, J_1 = 8.8 Hz, J_2 = 2.0 Hz, 1H), 7.37-7.34 (m, 5H), 7.22-7.18 (m, 5H), 3.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 150.1, 140.1, 136.9, 136.3, 130.8, 129.7, 129.5, 128.0, 127.8, 127.2, 127.0, 126.8, 126.7, 124.6, 124.1, 22.2; HRMS : m/z calcd for $C_{22}H_{17}BrN$ $[M+H]^+$: 374.0544; Found: 374.0542.

*4.2.10. 6-Iodo-1-methyl-3,4-diphenylisoquinoline (**3j**)*: Green solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04-8.03 (m, 1H), 7.92-7.84 (m, 2H), 7.38-7.32 (m, 5H), 7.21-7.18 (m, 5H), 3.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 150.4, 140.6, 137.5, 136.8, 135.3, 135.1, 131.3, 130.2, 128.4, 128.0, 127.6, 127.4, 127.2, 127.0, 124.8, 97.7, 22.6; HRMS : m/z calcd for $C_{22}H_{17}IN$ $[M+H]^+$: 422.0406; Found: 422.0398.

*4.2.11. 1-Methyl-3,4-diphenyl-6-(trifluoromethyl)isoquinoline (**3k**)*: White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, J = 8.8 Hz, 1H), 7.98 (s, 1H), 7.77 (d, J = 8.8 Hz, 1H), 7.39-7.37 (m, 5H), 7.24-7.20 (m, 5H), 3.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 150.4, 140.0, 136.0, 135.0, 131.2, 130.9, 130.8, 129.8, 129.2, 128.0, 127.3, 127.2, 126.9, 126.5, 126.4, 124.7, 123.5, 123.4, 122.0, 121.8, 121.7, 22.4; HRMS : m/z calcd for $C_{23}H_{17}F_3N$ $[M+H]^+$: 364.1313; Found: 364.1327.

*4.2.12. 1-Methyl-3,4,6-triphenylisoquinoline (**3l**)*: White solid; ^{1}H NMR (400 MHz, $CDCl_3$)

δ 8.34-8.32 (m, 1H), 7.92-7.90 (m, 2H), 7.64-7.62 (m, 2H), 7.51-7.38 (m, 8H), 7.34-7.25 (m, 5H), 3.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 149.5, 142.0, 140.6, 140.0, 137.0, 135.9, 131.0, 129.8, 128.9, 128.4, 127.8, 127.5, 127.2, 127.1, 126.7, 126.5, 125.7, 124.7, 123.6, 22.3; HRMS : m/z calcd for $C_{28}H_{22}N$ $[M+H]^+$: 372.1752; Found: 372.1745.

*4.2.13. 1-Methyl-3,4-diphenylisoquinoline-6-carboxylate (**3m**):* White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41-8.40 (m, 1H), 8.25 (d, J = 8.8 Hz, 1H), 8.17 (dd, J_1 = 8.8 Hz, J_2 = 1.6 Hz, 1H), 7.38-7.34 (m, 5H), 7.24-7.19 (m, 5H), 3.91 (s, 3H), 3.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 157.3, 150.0, 140.2, 136.3, 135.0, 130.9, 130.7, 129.8, 129.6, 128.5, 127.9, 127.2, 127.0, 126.7, 125.6, 125.5, 52.0, 22.4; HRMS : m/z calcd for $C_{24}H_{20}NO_2$ $[M+H]^+$: 354.1494; Found: 354.1486

*4.2.14. 1-Methyl-6-nitro-3,4-diphenylisoquinoline (**3n**)*: Brown solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60-8.59 (m, 1H), 8.37-8.31 (m, 2H), 7.41-7.37 (m, 5H), 7.24-7.22 (m, 5H), 3.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 151.1, 147.8, 139.5, 135.5, 135.4, 130.7, 130.0, 129.7, 128.3, 127.6, 127.3, 127.2, 127.1, 122.2, 119.4, 22.5; HRMS : m/z calcd for $C_{22}H_{17}N_2O_2$ $[M+H]^+$: 341.1290; Found: 341.1283.

*4.2.15. N-(1-Methyl-3,4-diphenylisoquinolin-6-yl)acetamide (**3o**)*: White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 9.2 Hz, 1H), 8.03 (d, J = 9.2 Hz, 1H), 7.64 (s, 1H), 7.52 (s, 1H), 7.34-7.28 (m, 5H), 7.21-7.16 (m, 5H), 3.02 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 157.3, 140.8, 139.6, 137.5, 137.0, 131.3, 130.2, 128.8, 128.3, 127.6, 127.2, 127.0, 123.4, 120.3, 113.8, 24.6, 22.5; HRMS : m/z calcd for $C_{24}H_{21}N_2O$ $[M+H]^+$: 353.1654; Found: 353.1642.

*4.2.16. 8-Fluoro-1-methyl-3,4-diphenylisoquinoline (**3p**)*: White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51-7.46 (m, 1H), 7.43-7.41 (m, 1H), 7.37-7.34 (m, 5H), 7.22-7.18 (m, 6H), 3.19 (d, J = 7.6 Hz, 3H); HRMS : m/z calcd for $C_{22}H_{17}FN$ $[M+H]^+$: 314.1345; Found: 314.1355.

*4.2.17. 1,8-Dimethyl-3,4-diphenylisoquinoline (**3q**)*: White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.49 (m, 1H), 7.40-7.33 (m, 7H), 7.23-7.17 (m, 5H), 3.25 (s, 3H), 3.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 148.1, 140.4, 137.8, 137.6, 135.5, 131.0, 129.7, 129.6, 129.0, 128.7, 127.7, 127.1, 126.7, 126.6, 126.5, 124.6, 29.5, 25.5; HRMS : m/z calcd for $C_{23}H_{20}N$ $[M+H]^+$: 310.1596; Found: 310.1588.

*4.2.18. 8-Methoxy-1-methyl-3,4-diphenylisoquinoline (**3r**)*: White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (t, J = 8.4 Hz, 1H), 7.40-7.28 (m, 5H), 7.24-7.17 (m, 6H), 6.93 (d, J = 7.6 Hz, 1H), 4.05 (s, 3H), 3.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 157.5, 149.5, 141.0, 138.9, 138.2, 131.4, 130.2, 130.0, 128.4, 128.2, 127.5, 127.0, 126.9, 119.1, 118.4, 105.9, 55.6, 29.3; HRMS : m/z calcd for $C_{23}H_{20}NO$ $[M+H]^+$: 326.1545; Found: 326.1555.

*4.2.19. 7-Bromo-1-methyl-3,4-diphenylisoquinoline (**3s**)*: White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35-8.34 (m, 1H), 7.64 (dd, J_1 = 9.2 Hz, J_2 = 2.0 Hz, 1H), 7.54 (d, J = 8.8 Hz, 1H), 7.37-7.34 (m, 5H), 7.21-7.18 (m, 5H), 3.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 149.4, 140.1, 136.5, 134.2, 132.8, 130.8, 129.7, 128.6, 127.9, 127.8, 127.4, 127.2, 126.9, 126.8, 126.7, 120.0, 22.2; HRMS : m/z calcd for $C_{22}H_{17}BrN$ $[M+H]^+$: 374.0544; Found: 374.0528.

*4.2.20. 1,7-Dimethyl-3,4-diphenylisoquinoline (**3t**)*: White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.44-7.41 (m, 1H), 7.37-7.33 (m 5H), 7.23-7.17 (m, 5H), 3.05 (s, 3H), 2.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 148.6, 141.1, 137.8, 136.4, 134.2, 132.1, 131.4, 130.3, 129.1, 128.2, 127.6, 127.1, 126.8, 126.4,

126.1, 124.5, 22.8, 21.9; HRMS : m/z calcd for $C_{23}H_{20}N$ $[M+H]^+$: 310.1596; Found: 310.1601.

*4.2.21. 7-Methoxy-1-methyl-3,4-diphenylisoquinoline (**3u**)*: White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 8.4 Hz, 1H), 7.53 (t, J = 8.0 Hz, 1H), 7.24-7.10 (m, 10H), 6.96 (d, J = 7.6 Hz, 1H), 3.41 (s, 3H), 3.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 156.9, 151.1, 141.6, 141.4, 130.4, 130.2, 127.9, 127.8, 127.5, 127.3, 127.1, 126.5, 125.6, 118.1, 110.1, 55.6, 23.4; HRMS : m/z calcd for $C_{23}H_{20}NO$ $[M+H]^+$: 326.1545; Found: 326.1556.

*4.2.21.1. 5-Methoxy-1-methyl-3,4-diphenylisoquinoline (**3u'**)*: White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 9.2 Hz, 1H), 7.40-7.32 (m, 6H), 7.24-7.17 (m, 6H), 3.99 (s, 3H), 3.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 156.0, 147.7, 141.0, 137.7, 131.4, 130.2, 128.2, 128.0, 127.6, 127.3, 127.1, 126.7, 122.3, 103.5, 55.5, 22.9; HRMS : m/z calcd for $C_{23}H_{20}NO$ $[M+H]^+$: 326.1545; Found: 326.1553.

*4.2.22. 1-Methyl-3,4-diphenylbenzo[h]isoquinoline (**3v**)*: White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (d, J = 8.4 Hz, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.76-7.69 (m, 2H), 7.65-7.61 (m, 1H), 7.53 (d, J = 8.8 Hz, 1H), 7.42-7.31 (m, 5H), 7.24-7.16 (m, 5H), 3.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 150.5, 140.2, 137.6, 136.8, 132.5, 131.2, 130.7, 129.8, 129.2, 128.3, 127.8, 127.2, 126.8, 126.7, 126.4, 126.2, 123.8, 123.5, 30.1; HRMS : m/z calcd for $C_{26}H_{20}N$ $[M+H]^+$: 346.1596; Found: 346.1585.

*4.2.23. 7-Methyl-4,5-diphenylthieno[2,3-c]pyridine (**3w**)*: Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 5.6 Hz, 1H), 7.37-7.30 (m, 5H), 7.25-7.19 (m, 6H), 2.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 151.0, 145.7, 140.5, 138.3, 134.2, 130.9, 130.6, 130.3, 128.3, 127.7, 127.2, 127.1, 124.3, 23.7; HRMS : m/z calcd for $C_{20}H_{16}NS$ $[M+H]^+$: 302.1003; Found: 302.1016.

*4.2.24. 1-Ethyl-3,4-diphenylisoquinoline (**3x**)*: White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23-8.20 (m, 1H), 7.64-7.62 (m, 1H), 7.56-7.53 (m, 2H), 7.37-7.29 (m, 5H), 7.22-7.14 (m, 5H), 3.44-3.39 (m, 2H), 1.51 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 148.8, 140.7, 137.3 135.9, 130.9, 129.9, 129.2, 128.5, 127.7, 127.1, 126.6, 126.4, 126.0, 125.9, 124.8, 124.7, 28.3, 13.5; HRMS : m/z calcd for $C_{23}H_{20}N$ $[M+H]^+$: 310.1596; Found: 310.1586.

*4.2.25. 3,4-Diphenyl-1-propylisoquinoline (**3y**)*: White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34-8.32 (m, 1H), 7.76-7.74 (m, 1H), 7.68-7.65 (m, 2H), 7.48-7.41 (m, 5H), 7.34-7.25 (m, 5H), 3.50-3.46 (m, 2H), 2.13-2.07 (m, 2H), 1.23 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 148.8, 140.7, 137.3, 135.9, 130.9, 129.9, 129.2, 128.5, 127.7, 127.1, 126.6, 126.4, 125.9, 125.1, 124.8, 37.2, 22.7, 14.1; HRMS : m/z calcd for $C_{24}H_{22}N$ $[M+H]^+$: 324.1752; Found: 324.1759.

*4.2.26. 1,3,4-Triphenylisoquinoline (**3z**)*: White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 6.4 Hz, 1H), 7.90-7.88 (m, 2H), 7.79 (d, J = 6.4 Hz, 1H), 7.63-7.60 (m, 3H), 7.56-7.51 (m, 4H), 7.45-7.36 (m, 6H), 7.25-7.22 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 149.7, 141.0, 139.9, 137.7, 137.1, 131.5, 130.6, 130.4, 130.1, 129.9, 128.7, 128.5, 128.4, 127.7, 127.6, 127.4, 127.1, 126.7, 126.1, 125.5; HRMS : m/z calcd for $C_{27}H_{20}N$ $[M+H]^+$: 358.1596; Found: 358.1611.

*4.2.27. 2,3-Diphenyl-8,9-dihydro-7H-benzo[de]quinolone (**3aa**)*: Brown solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.48 (m, 2H), 7.37-7.32 (m, 6H), 7.25-7.17 (m, 5H), 3.39 (t, J = 6.4 Hz, 2H), 3.20 (t, J = 6.4 Hz, 2H), 2.30-2.25 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

158.8, 149.0, 140.7, 138.1, 137.4, 135.8, 130.9, 129.8, 129.5, 128.6, 127.7, 127.2, 127.1, 126.6, 126.4, 124.3, 123.4, 123.1, 34.3, 30.3, 23.0; HRMS : m/z calcd for $C_{24}H_{20}N$ $[M+H]^+$: 322.1596; Found: 322.1582.

4.3. Characterization data of 4 are represented as follows.

A mixture of acetophenone oxime **1a** (0.2 mmol), diphenylacetylene **2** (0.24 mmol, 1.2 equiv), $[Cp^*IrCl_2]_2$ (3 mol%), PivOH (0.06 mmol, 0.3 equiv), $Cu(OAc)_2 \cdot H_2O$ (0.4 mmol, 2 equiv) and MeOH (2 mL) in a 15 mL glass vial [sealed with poly(tetrafluoroethylene) (PTFE) cap] was heated at 120 °C with vigorous stirring for 24 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through Celite. The filtrate was concentrated in vacuo and purified by column chromatography on silica gel to give the corresponding product **4**.

*4.3.1. 1-Methyl-3,4-di-p-tolylisoquinoline (**4a**)*: White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21-8.19 (m, 1H), 7.69-7.67 (m, 1H), 7.60-7.58 (m, 2H), 7.32-7.28 (m, 2H), 7.20-7.13 (m, 4H), 7.04 (d, J = 8.0 Hz, 2H), 3.09 (s, 3H), 2.42 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 149.4, 138.3, 136.6, 136.5, 136.3, 134.7, 131.2, 130.2, 129.7, 129.0, 128.9, 128.4, 126.3, 126.1, 125.5, 22.7, 21.3, 21.2; HRMS : m/z calcd for $C_{24}H_{22}N$ $[M+H]^+$: 324.1752; Found: 324.1762.

*4.3.2. 3,4-Bis(4-(tert-butyl)phenyl)-1-methylisoquinoline (**4b**)*: White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26-8.24 (m, 1H), 7.80-7.76 (m, 1H), 7.65-7.63 (m, 2H), 7.43 (d, J = 8.0 Hz, 2H), 7.35 (t, J = 8.4 Hz, 3H), 7.24-7.21 (m, 3H), 3.14 (s, 3H), 1.42 (s, 9H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 149.5, 149.1, 148.9, 137.5, 135.8, 134.1, 130.5, 129.4, 129.3, 128.6, 125.9, 125.8, 125.6, 125.0, 124.5, 124.0, 34.1, 33.9, 30.9, 30.8, 22.2; HRMS : m/z calcd for $C_{30}H_{34}N$ $[M+H]^+$: 408.2691; Found: 408.2693.

*4.3.3. 3,4-Bis(4-methoxyphenyl)-1-methylisoquinoline (**4c**)*: White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18-8.16 (m, 1H), 7.68-7.66 (m, 1H), 7.58-7.56 (m, 2H), 7.33 (d, J = 8.8 Hz, 2H), 7.14 (d, J = 8.4 Hz, 2H), 6.91 (d, J = 8.4 Hz, 2H), 6.75 (d, J = 8.8 Hz, 2H), 3.85 (s, 3H), 3.77 (s, 3H), 3.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 158.5, 157.4, 149.1, 136.4, 132.4, 131.5, 130.0, 126.2, 126.1, 125.5, 113.8, 113.2, 55.3, 55.2, 22.7; HRMS : m/z calcd for $C_{24}H_{22}NO_2$ $[M+H]^+$: 356.1651; Found: 356.1646.

*4.3.4. 3,4-Bis(4-chlorophenyl)-1-methylisoquinoline (**4d**)*: White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22-8.20 (m, 1H), 7.64-7.61 (m, 3H), 7.36 (d, J =8.4 Hz, 2H), 7.29 (d, J =8.4 Hz, 2H), 7.20 (d, J =8.4 Hz, 2H), 7.16 (d, J =8.8 Hz, 2H), 3.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 148.2, 139.2, 135.7, 133.5, 133.3, 132.7, 131.6, 130.3, 128.8, 128.0, 126.9, 126.3, 125.9, 125.7, 22.8; HRMS : m/z calcd for $C_{22}H_{16}Cl_2N$ $[M+H]^+$: 364.0660; Found: 364.0651.

*4.3.5. 1-Methyl-3,4-bis(4-(trifluoromethyl)phenyl)isoquinoline (**4e**)*: White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21-8.19 (m, 1H), 7.62-7.59 (m, 3H), 7.53-7.50 (m, 1H), 7.45-7.40 (m, 4H), 7.32 (d, J = 8.0 Hz, 2H), 7.21 (s, 1H), 3.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 147.8, 141.0, 135.5, 131.7, 130.7, 130.6, 127.4, 126.4, 125.8, 125.5, 125.4, 124.9, 124.8, 22.7; HRMS : m/z calcd for $C_{24}H_{16}F_6N$ $[M+H]^+$: 432.1187; Found: 432.1182.

*4.3.6. 3,4-Bis(4-fluorophenyl)-1-methylisoquinoline (**4f**)*: White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24-8.22 (m, 1H), 7.64-7.63 (m, 3H), 7.36-7.32 (m, 2H), 7.21-7.18 (m, 2H), 7.09 (t, *J* = 8.8 Hz, 2H), 6.93 (t, *J* = 8.8 Hz, 2H), 3.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 160.8, 158.1, 136.0, 132.9, 132.8, 132.0, 131.9, 126.8, 125.9, 125.7, 115.6, 115.3, 114.8, 114.6, 22.6; HRMS : m/z calcd for $C_{22}H_{16}F_2N$ $[M+H]^+$: 332.1251; Found: 332.1253.

*4.3.7. 3,4- Bis(4-bromophenyl)-1-methylisoquinoline (**4g**)*: White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22-8.20 (m, 1H), 7.64-7.61 (m, 3H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 3.07 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 147.6, 147.5, 135.7, 135.3, 132.6, 132.5, 131.5, 131.3, 130.5, 130.0, 126.6, 125.4, 125.3, 121.2, 22.2; HRMS : m/z calcd for $C_{22}H_{16}Br_2N$ $[M+H]^+$: 451.9649; Found: 451.9629.

*4.3.8. 3,4- Bis(3-fluorophenyl)-1-methylisoquinoline (**4h**)*: White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23-8.21 (m, 1H), 7.64-7.63 (m, 3H), 7.37-7.32 (m, 1H), 7.19-7.01 (m, 5H), 6.98-6.88 (m, 2H), 3.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1, 161.0, 158.0, 147.6, 142.4, 139.1, 135.2, 129.9, 129.5, 128.7, 127.7, 126.7, 126.6, 125.8, 125.5, 125.2, 117.9, 117.7, 116.8, 116.5, 114.1, 113.9, 113.6, 22.3; HRMS : m/z calcd for $C_{22}H_{16}F_2N$ $[M+H]^+$: 332.1251; Found: 332.1262.

*4.3.9. 3,4-Bis(2-fluorophenyl)-1-methylisoquinoline (**4i**)*: White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25-8.23 (m, 1H), 7.66-7.63 (m, 2H), 7.57-7.56 (m, 1H), 7.38-7.34 (m, 1H), 7.31-7.28 (m, 1H), 7.23-7.15 (m, 2H), 7.08-7.03 (m, 3H), 6.93-6.88 (m, 1H), 3.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 160.9, 159.1, 158.7, 158.4, 146.2, 135.4, 132.7, 131.6, 130.4, 129.8, 129.6, 127.2, 126.5, 125.8, 125.7, 125.4, 123.8, 123.6, 115.5, 115.2, 22.7; HRMS : m/z calcd for $C_{22}H_{16}F_2N$ $[M+H]^+$: 332.1251; Found: 332.1265.

*4.3.10. 1-Methyl-3,4-di(thiophen-2-yl)isoquinoline (**4j**)*: Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* =8.0 Hz, 1H), 7.56-7.50 (m, 4H), 7.24-7.23 (m, 1H), 7.21-7.18 (m, 2H), 7.03-7.02 (m, 1H), 6.86-6.84 (m, 1H), 3.01(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 137.9, 129.5, 128.2, 127.9, 127.7, 127.6, 127.0, 126.1, 125.8, 125.7, 29.7; HRMS : m/z calcd for $C_{18}H_{14}S_2N$ $[M+H]^+$: 308.0568; Found: 308.0577.

4.4. Scaling Up and and coupling with phenylboronic acid

A mixture of acetophenone oxime **1i** (1001.0 mg, 4.70 mmol), diphenylacetylene **2a** (1004.4 mg, 5.64 mmol, 1.2 equiv), $[Cp^*IrCl_2]_2$ (2 mol%), PivOH (144.0 mg, 1.41 mmol, 0.3 equiv) and MeOH (25 mL) in a 100 mL glass vial [sealed with poly(tetrafluoroethylene) (PTFE) cap] was heated at 60 °C with vigorous stirring for 24 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through Celite. The filtrate was concentrated in vacuo and purified by column chromatography on silica gel to give the desired product **3i** in 1.44 g, 82% yield.

A mixture of product **3i** (0.2 mmol), phenylboronic acid (0.22 mmol, 1.1 equiv), $Pd(PPh_3)_2Cl_2$ (10 mol%), K_2CO_3 (0.2 mmol, 1 equiv) and 1,4-dioxane (2 mL) in a 15 mL glass vial [sealed with poly(tetrafluoroethylene) (PTFE) cap] was heated at 90 °C with

vigorous stirring for 16 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through Celite. The filtrate was concentrated in vacuo and purified by column chromatography on silica gel to give the desired product **3l** in 60.1 mg, 81% yield.

Acknowledgements

We acknowledge the financial support from the Foundation of the Natural Science Foundation of China (No. 21502074), Qing Lan Project of Jiangsu Province and Postgraduate Research & Practice Innovation Program of Jiangsu Province (SJCX18-0985)

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