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Palladium-Catalyzed C–H Functionalization of Aromatic Oximes: A Strategy for the Synthesis of Isoquinolines

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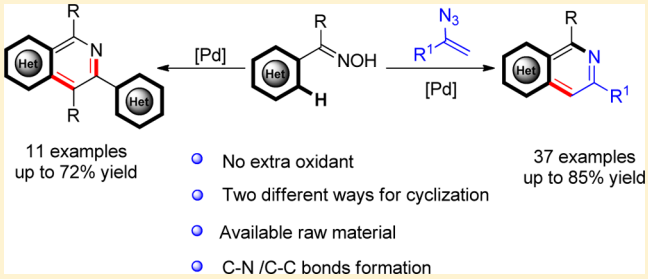
Supporting Information

ABSTRACT: An efficient strategy for synthesis of isoquinolines via Pd(II)-catalyzed cyclization reaction of oximes with vinyl azides or homocoupling of oximes is reported. Oximes could serve as a directing group and an internal oxidant in the transformation. This reaction features good functional group tolerance and provides a useful protocol for the synthesis of different kinds of isoquinolines under mild conditions. Some control experiments and ^{15}N isotope labeling experiments were conducted for the mechanistic research.

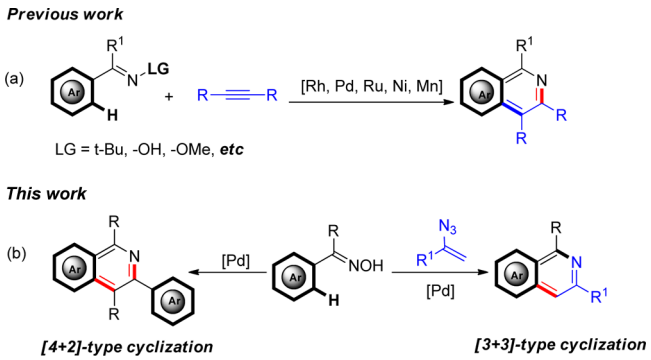


INTRODUCTION

Isoquinoline units have served as an important component in biologically active molecules, natural products, and synthetic pharmaceutical agents.[1] They also can be used as chiral ligands for transition-metal-catalyzed reactions[2] and in organic light emitting diodes in materials science.[3] Due to the substantial applicability of isoquinolines, the development of their synthesis has received considerable attention. Classical methods for their synthesis involve Bischler–Napieralski,[4a] Pictet–Spengler,[4b] and Pomeranz–Fritsh[4c] protocols, among others. However, these processes usually require harsh conditions such as strong acids and high temperature, which are not suitable for the sensitive substrates. Thus, the development of efficient transformations that exhibit mild conditions and good functional group tolerance is highly desirable.[5] Recently, C–H bond activation using transition metal (Rh, Ru, Ni, Pd, Mn) catalysis has become a powerful tool to give isoquinolines with directing groups such as aromatic imines, oximes, azides, etc. (Scheme 1a).[6−8] However, another synthon is alkyne in most cases and the products are 1,3,4-substituted isoquinolines.

Oximes are fascinating synthetic building blocks which are widely employed in synthetic chemistry[8,9a] due to their easy preparation, efficient reactivity, and harmless byproducts. Moreover, they can also serve as internal oxidants and have been used as substrates for transition-metal-catalyzed C–H activation. Inspired by our previous research on palladium-catalyzed transformations[9] and metal-catalyzed coupling reaction of oximes,[10] herein, we present a Pd(II)-catalyzed cyclization of oximes with vinyl azides or Pd(II)-catalyzed homocoupling of oximes for the synthesis of substituted isoquinolines.

Scheme 1. Synthesis of Isoquinolines via Transition-Metal-Catalyzed C–H Functionalization



RESULTS AND DISCUSSION

Initially, we used 1-(*p*-tolyl)ethanone oxime (**1a**) and (1-azidovinyl)benzene (**2a**) as model substrates to screen the reaction conditions (Table 1). To our delight, the desired product **3aa** was detected in 41% GC yield when using $PdCl_2$ as the catalyst in CH_3CN at 80 °C in air (entry 1). Various palladium catalysts were examined (entries 2–6), and **3aa** could be afforded in 66% GC yield when using $Pd(OAc)_2$ instead of $PdCl_2$. Further investigation of the solvents revealed that toluene was the best in the reaction and gave **3aa** in 75% GC yield (entries 7–10). Subsequently, different additives were also tested (entries 11–17), but they did not show apparent positive effects on the transformation. Further examination of the temperature showed that 90 °C proved to be the best, affording **3aa** in 91% GC yield (entries 18–20). Additionally, control experiments showed that O_2 and N_2 atmospheres had no significant effects on the reaction (entries 21 and 22). However, no reaction occurred in the absence of palladium catalyst (entry

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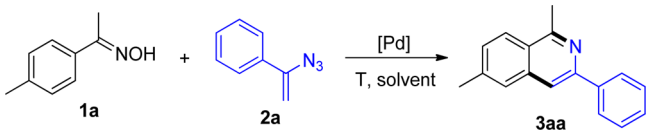
Table 1. Optimization of the Reaction Conditions[a]



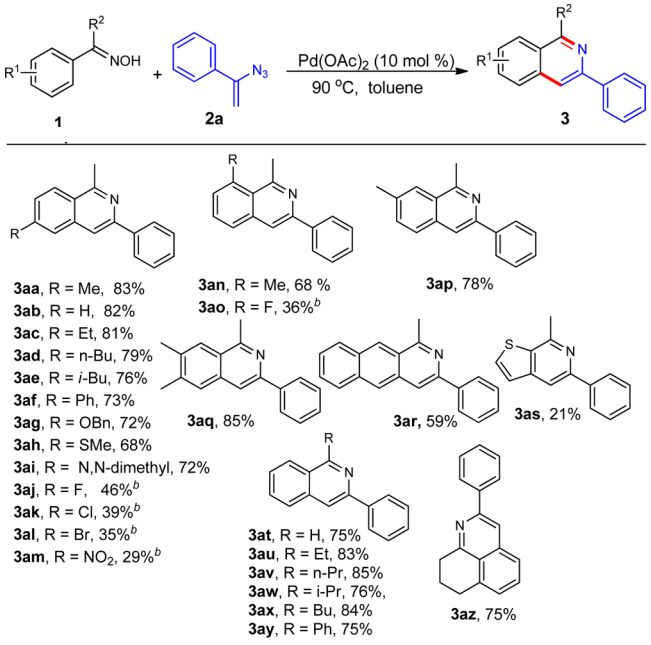
entry	[Pd]	additive	solvent	T (°C)	yield (%)[b]
1	$PdCl_2$		CH_3CN	80	41
2	$Pd(OAc)_2$		CH_3CN	80	66
3	$PdBr_2$		CH_3CN	80	24
4	$Pd(TFA)_2$		CH_3CN	80	45
5	$Pd_2(dba)_3$		CH_3CN	80	trace
6	$Pd(Pph_3)_4$		CH_3CN	80	trace
7	$Pd(OAc)_2$		DMSO	80	41
8	$Pd(OAc)_2$		DMF	80	45
9	$Pd(OAc)_2$		toluene	80	75
10	$Pd(OAc)_2$		1,4-dioxane	80	21
11	$Pd(OAc)_2$	K_3PO_4	toluene	80	NR
12	$Pd(OAc)_2$	K_2CO_3	toluene	80	trace
13	$Pd(OAc)_2$	$NaHSO_3$	toluene	80	46
14	$Pd(OAc)_2$	$BF_3{\cdot}OEt_2$	toluene	80	NR
15	$Pd(OAc)_2$	$CuCl_2$	toluene	80	32
16	$Pd(OAc)_2$	$Ag(OAc)_2$	toluene	80	NR
17	$Pd(OAc)_2$	$Zn(OTf)_2$	toluene	80	74
18	$Pd(OAc)_2$		toluene	70	60
19	**$Pd(OAc)_2$**		**toluene**	**90**	**91 (83)**[c]
20	$Pd(OAc)_2$		toluene	100	65
21[d]	$Pd(OAc)_2$		toluene	90	88
22[e]	$Pd(OAc)_2$		toluene	90	86
23			toluene	90	NR
24	$Zn(OTf)_2$		toluene	90	NR
25	$FeCl_3$		toluene	90	NR
26	$InCl_3$		toluene	90	NR

[a]Reaction conditions unless otherwise noted: all reactions were performed with **1a** (0.1 mmol), **2a** (0.12 mmol), catalyst (10 mol %), and additive (0.1 mmol) for 8 h. [b]Yields and conversions analyzed by GC/MS are based on **1a**. [c]Isolated yield. [d]Under a N_2 atmosphere. [e]Under a O_2 atmosphere.

23). Furthermore, other Lewis acids could not promote this transformation (entries 24−26).

With the optimal conditions in hand, we investigated the substrate scope of this reaction between various aryloximes **1** and (1-azidovinyl)benzene (**2a**) (Table 2). Generally, this reaction proceeded smoothly and gave the desired products **3** in moderate to good yields. Substituted acetophenone oximes with electron-withdrawing groups gave yields lower than those with electron-donating groups. All of the para-, ortho-, and meta-substituted alkyl- and aryl-substituted acetophenone oximes were able to give the corresponding products in good to excellent yields (**3aa**−**3af**, **3an**−**3aq**). Strongly electron donating functional groups such as benzyloxy-, methylthio-, and amino-substituted substrates underwent the reaction smoothly and resulted in the desired isoquinolines in good yields (**3ag**−**3ak**). The transformation was also compatible with halide groups, such as fluoride, chloride, and bromide (**3al**−**3ao**). The acetophenone oxime with a strongly electron withdrawing group could also transfer to the corresponding product, though the yield was relatively low (**3am**). When 1-acetylnaphthalene oxime was used as the substrate, **3ar** could be isolated in 59% yield. The heteroarene oxime was compatible in this transformation (**3as**) with a low yield. The main reason was that the heteroarene oxime **3as** was readily hydrolyzed and transformed

Table 2. Aryloxime Scope of Pd-Catalyzed Cyclization with Vinyl Azides[a]



[a]Reactions were performed with **1** (0.3 mmol), **2a** (0.36 mmol), $Pd(OAc)_2$ (10 mol %) in 2 mL toluene at 90 °C for 8 h; Isolated yield was given. [b]10 mol % $Zn(OTf)_2$ was added.

into the corresponding ketone under the optimized reaction conditions. Moreover, the strategy was available for the construction of different 3-substituted and 1,3-disubstituted isoquinolines in good yields. Benzaldehyde, propiophenone, *n*-butyrophenone, isobutyrophenone, valerophenone, and benzophenone oximes could be converted to the corresponding isoquinolines in good yields (**3at**−**3ay**). Similarly, 1-tetralone oxime proceeded smoothly to give the polycyclic product **3az** in good yield.

We next explored the scope of this reaction with respect to the substituted aryl vinyl azides (Table 3). The results indicated that this reaction was facile with both electron-withdrawing and electron-donating groups of (1-azidovinyl)benzenes and delivered the desired products in moderate to excellent yields. The halide (Cl, Br, F)-substituted vinyl azides were well tolerated, affording the corresponding products in good yields which could be further applied in traditional cross-coupling reactions (**3bc**−**3be**). Electronic effects associated with electron-donating and -withdrawing substituents at the para, ortho, or meta position on the arene ring of the vinyl azide did not affect the efficiency of the process (**3bg**−**3bj**). In addition, the naphthalene vinyl azide was also compatible in this transformation, affording the desired product **3bk** in moderate yield.

We also observed the formation of symmetrical isoquinoline **3** during the process of screening the optimal reaction conditions, which might be derived from the oxidative homocoupling of **1.** Interestingly, when the temperature was increased to 130 °C and the reaction time prolonged to 24 h, the desired self-coupling product of oxime **3ab** could be obtained in 72% yield. Subsequently, we explored the generality of the protocol with a series of oximes under the optimized conditions. As shown in Table 4, the desired products were synthesized in moderate to good yields. Various functional

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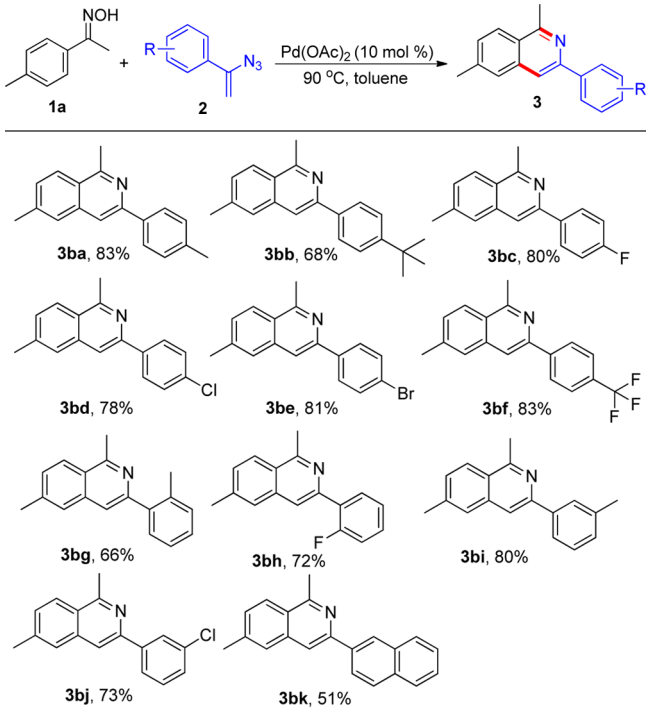
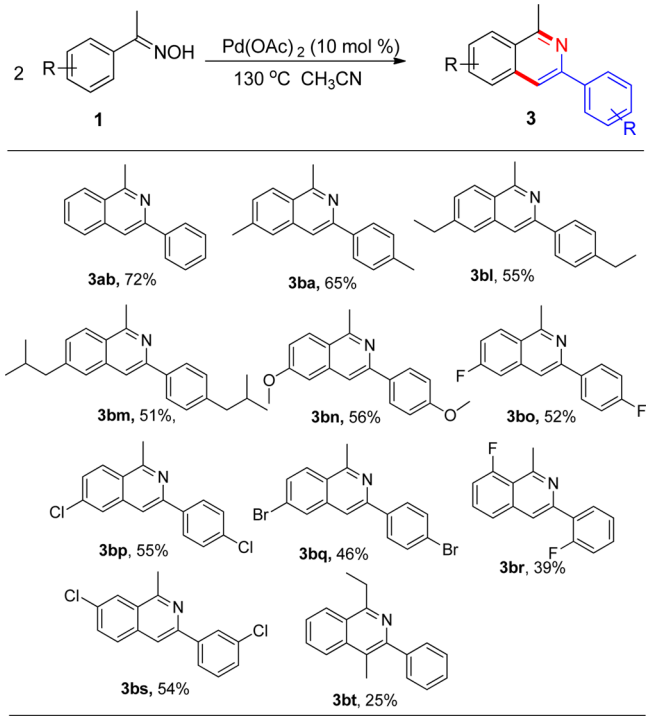
Table 3. Vinyl Azide Scope of Pd-Catalyzed Cyclization with Oximes[a]



[a]Reactions were performed with **1a** (0.3 mmol), **2** (0.36 mmol), and $Pd(OAc)_2$ (10 mol %) in 2 mL of toluene at 90 °C for 8 h. Isolated yields are given.

Table 4. Aryloxime Scope of Pd-Catalyzed Homocoupling[a]



[a]Reactions were performed with **1** (0.6 mmol) and $Pd(OAc)_2$ (10 mol %) in the solvent (2 mL) at 130 °C for 24 h. Isolated yields are given.

groups, including methyl, ethyl, methoxyl, chloro, fluoro, and bromine groups, were compatible in this reaction system (**3ba**, **3bl**–**3br**). However, other aryl ketone oximes such as propiophenone oxime gave the desired product with a lower yield (**3bt**). These results suggest that the steric properties of the substituents of oximes should have a significant influence on the reaction efficiency.

To get more insight into this transformation, a series of control experiments were conducted (Scheme 2). Under the standard conditions, the reaction of ketone **4** with **2a** did not give the target product **3aa** and similar results were observed when using the oxime ester **5** instead of **1a** (Scheme 2a,b). We used aryl-2*H*-azirine, which has been considered to be a possible intermediate generated from aryl vinyl azides in relevant reports[6d,11] to react with **1a** under the standard conditions, and **3aa** could be obtained in 39% GC yield (Scheme 2c). Furthermore, when the labeled ^{15}N oxime was added to the standard conditions, the lack of formation of ^{15}N-labeled product revealed that the nitrogen of this product was derived from vinyl azide **2a** (Scheme 2d). Subsequently, the self-coupling product **3ab**-^{15}N was successfully obtained under the standard conditions (Scheme 2e). An intermolecular competition between **1ab** and **1ab′** demonstrated a kinetic isotope effect (k_H/k_D = 4; Scheme 2f), which suggests that Pd(II)-catalyzed C–H activation of **1ab** is probably involved in the rate-determining step.

On the basis of the results above and the literature,[9a,11] a tentative mechanism for the Pd(II)-catalyzed C–H functionalization of oxime is proposed in Scheme 3. First, an oxime directing *o*-C–H bond cleavage by Pd(II) occurred to form the key palladacycle intermediate **A**. The thermal decomposition of vinyl azide **2** occurred to afford 2*H*-azirine **6**, which underwent migratory insertion into palladacycle **A** to give intermediate **B**. Then, the reductive elimination of **B** provided intermediate **C** and released the Pd species, which further underwent oxidative addition across the N–O bond to provide the imido-Pd(II) species **D**. Intramolecular condensation of **D** regenerated the Pd(II) catalyst and afforded **E**, which concomitantly released a hydroxylamine to form product **3**.

In summary, we have reported an efficient and convenient Pd(II)-catalyzed cross-coupling of oximes with vinyl azides and homocoupling of oximes for the synthesis of 3-substituted and 1,3-disubstituted isoquinolines. No stoichiometric external oxidants were needed by using oxime as the internal directing group. The use of simple starting materials, no need for additives, no toxic byproducts, and the operational simplicity make this practical and atom-economical method particularly attractive.

EXPERIMENTAL SECTION

General Information. Melting points were measured with a melting point instrument and were uncorrected. ^1H and ^{13}C NMR spectra were recorded using a 400 MHz NMR spectrometer. The chemical shifts are referenced to signals at 7.26 and 77.0 ppm, respectively, and chloroform was used as the solvent with TMS as the internal standard. GC-MS was obtained using electron ionization. HRMS was obtained with a LCMS-IT-TOF mass spectrometer. TLC was performed by using commercially prepared 100–400 mesh silica gel plates, and visualization was effected at 254 nm. IR spectra were obtained either as potassium bromide pellets or as liquid films between two potassium bromide pellets with an infrared Fourier spectrometer. High-resolution mass spectra (ESI) were obtained with a LCMS-IT-TOF mass spectrometer.

General Procedure for Oximes. To a solution of aromatic ketones or aromatic aldehydes (2 mmol) in a mixture of C_2H_5OH and H_2O (v/v 1/1) were added hydroxylamine hydrochloride (2.2 mmol)

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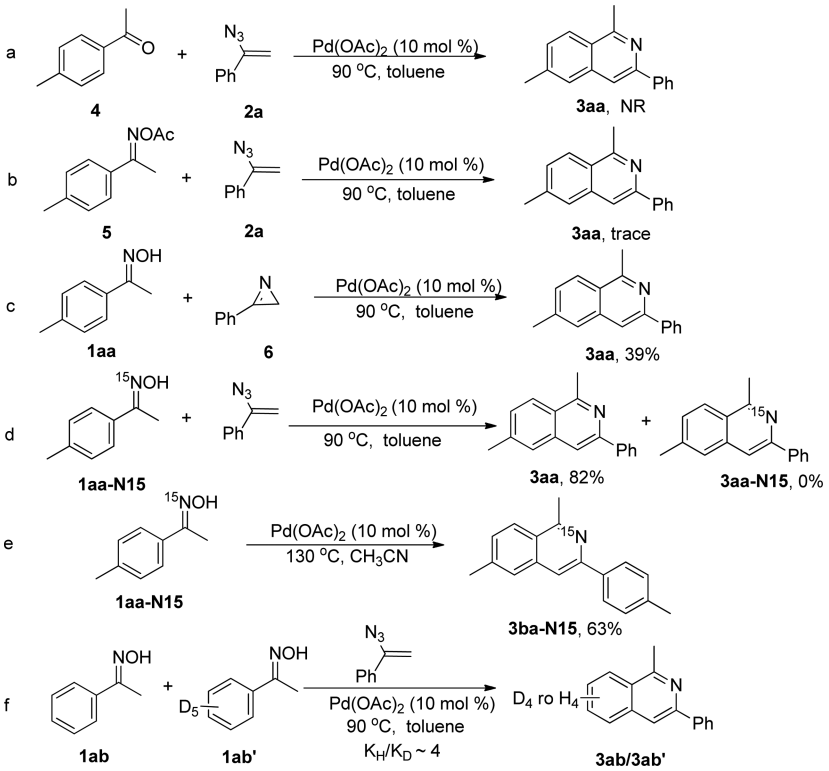
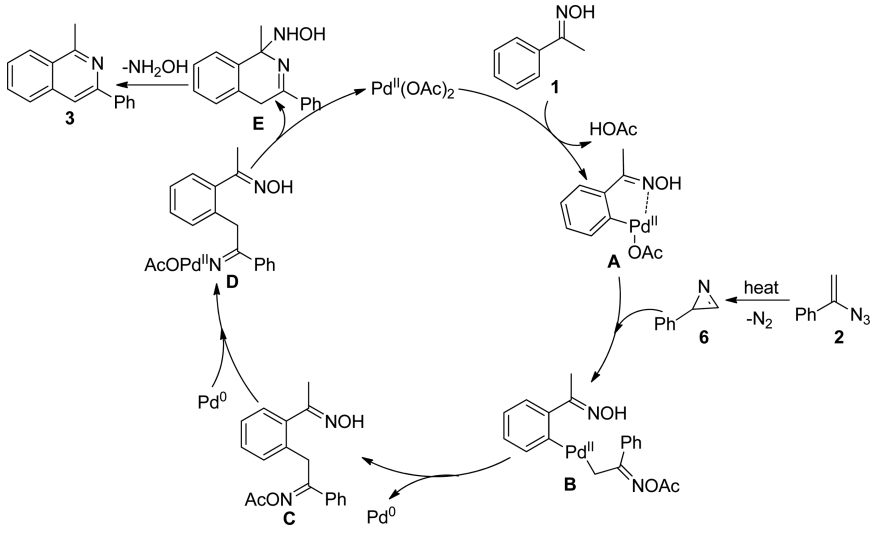
Scheme 2. Mechanistic Studies



Scheme 3. Proposed Mechanism



and NaOAc (3 mmol) in one portion, and the reaction mixture was stirred at 100 °C (when the substrates were aromatic ketones) or at room temperature (when the substrates were aromatic aldehydes) for 6−8 h. Upon completion of the reaction as indicated by TLC, the reaction mixture was diluted with water, extracted with ethyl acetate, and dried over anhydrous Na_2SO_4. The solvent was removed and concentrated under reduced pressure to give oximes.

General Procedure for Azidovinylbenzene. The procedure for dibromination of substituted styrene was slightly modified from Sudalai's method.[12b] To a solution of substituted styrene (5 mmol) and LiBr (12 mmol) in acetic acid (8 mL) was added $NaIO_4$ (2.6 mmol) portionwise during 15 min. After the reaction mixture was stirred at room temperature for 5 h, it was then diluted with water and the product was extracted with CH_2Cl_2. The organic layers were washed with saturated aqueous $NaHCO_3$, $Na_2S_2O_3$, and brine. They were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give the dibromide. To a solution of the dibromide in dry DMF (20 mL) was added NaN_3 (15 mmol). The mixture was stirred for 24 h at room temperature and then diluted with water and extracted with diethyl ether. The combined organic layers were washed with water (3 × 10 mL) and dried with anhydrous Na_2SO_4. After removal of the solvent, the crude residue was purified by column chromatography using silica gel with hexanes as the eluent to give vinyl azides **2**. Their general information and analytical data could be obtained from the literature.[11,12]

General Procedure for 3-Phenyl-2*H*-azirine 6..[11a,13] A solution of (1-azidovinyl)benzene (**2a**; 2 mmol) and diazabicyclo[2.2.2]octane (0.2 mmol) in dry toluene (6 mL) was stirred at 110 °C for 50 min. Upon completion of the reaction as indicated by TLC, the solvent was removed and concentrated under reduced pressure to give the crude

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raffinate. The crude raffinate was purified by column chromatography using silica gel with petroleum ether/EtOAc as eluent (10/1) to afford azirine **6** as a light yellow oil (198.5 mg, 85% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 7.4 Hz, 2H), 7.63−7.52 (m, 3H), 1.79 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 132.9, 129.6, 129.1, 125.5, 19.7.

General Procedure for the Synthesis of Isoquinolines 3aa−3bk. Oximes **1** (0.3 mmol), azidovinylbenzene **2** (0.36 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), and 2 mL of dry toluene were placed in a 10 mL screw-capped tube. The reaction vessel was closed with the cap, and the reaction mixture was stirred at 90 °C (oil bath) for 8 h. The crude product was cooled to room temperature and concentrated under vacuum to give a residue, which was purified by flash column chromatography to afford the isoquinoline products.

General Procedure for the Synthesis of Symmetrical Isoquinolines. Oxime (0.6 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), and 2 mL of dry acetonitrile were placed in a sealed tube under N_2. The reaction mixture was heated to 130 °C (oil bath) for 24 h. The crude product was cooled to room temperature and concentrated under vacuum to give a residue, which was purified by flash column chromatography to afford the isoquinoline products.

*1,6-Dimethyl-3-phenylisoquinoline (**3aa**).* This compound was obtained as a yellow oil (58 mg, 83% yield): R_f = 0.5 (petroleum ether/EtOAc 20/1); IR (KBr) 3448, 2922, 1670, 1571, 1409, 1019, 822, 748 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 7.6 Hz, 2H), 7.99 (d, J = 8.5 Hz, 1H), 7.83 (s, 1H), 7.59 (s, 1H), 7.52 (t, J = 7.5 Hz, 2H), 7.42 (t, J = 7.2 Hz, 1H), 7.37 (d, J = 8.5 Hz, 1H), 3.02 (s, 3H), 2.54 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 150.1, 137.1, 129.0, 128.7, 128.2, 127.0, 126.6, 125.5, 125.0, 114.8, 22.6, 21.8 ppm; HRMS (ESI) m/z calcd for $C_{17}H_{16}N$ $[M + H]^+$ 234.1277, found 234.1281.

*1-Methyl-3-phenylisoquinoline (**3ab**).*[8b] This compound was obtained as a yellow oil (54 mg, 82% yield): R_f = 0.5 (petroleum ether/EtOAc 20/1); IR (KBr) 2922, 2855, 1670, 1630, 1409, 1268, 822, 748 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (t, J = 8.6 Hz, 3H), 7.92 (s, 1H), 7.85 (d, J = 8.1 Hz, 1H), 7.67 (d, J = 14.9 Hz, 1H), 7.57 (d, J = 15.2 Hz, 1H), 7.51 (d, J = 14.9 Hz, 2H), 7.41 (d, J = 14.5 Hz, 1H), 3.05 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 150.0, 139.8, 136.9, 136.8, 130.1, 128.7, 128.3, 127.7, 127.0, 126.8, 126.6, 125.7, 115.3, 22.6 ppm; MS (EI) m/z 63, 108, 141, 176, 219.

*6-Ethyl-1-methyl-3-phenylisoquinoline (**3ac**).* This compound was obtained as a yellow oil (60 mg, 81% yield): R_f = 0.55 (petroleum ether/EtOAc 20/1); IR (KBr) 3383, 3064, 2966, 2863, 1626, 1570, 895, 833 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 6.2 Hz, 2H), 8.04 (d, J = 8.5 Hz, 1H), 7.88 (s, 1H), 7.64 (s, 1H), 7.54 (d, J = 5.9 Hz, 2H), 7.43 (d, J = 7.6 Hz, 2H), 3.04 (s, 3H), 2.85 (q, J = 7.5 Hz, 2H), 1.38 (t, J = 7.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 150.1, 146.4, 140.1, 137.2, 128.8, 128.3, 128.0, 127.0, 125.6, 125.3, 123.9, 115.1, 29.1, 22.7,15.2 ppm; HRMS (ESI) m/z calcd for $C_{18}H_{18}N$ $[M + H]^+$ 248.1434, found 248.1435.

*6-Butyl-1-methyl-3-phenylisoquinoline (**3ad**).* This compound was obtained as a yellow oil (65 mg, 79% yield): R_f = 0.55 (petroleum ether/EtOAc 20/1); IR (KBr) 3064, 2959, 2923, 2860, 1626, 1571, 1450, 1399, 763, 690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 8.0 Hz, 2H), 8.03 (d, J = 8.5 Hz, 1H), 7.88 (s, 1H), 7.62 (s, 1H), 7.53 (t, J = 7.4 Hz, 2H), 7.42 (t, J = 7.9 Hz, 2H), 3.03 (s, 3H), 2.81 (t, J = 7.7 Hz, 2H), 1.79−1.66 (m, 2H), 1.41−1.47 (m, 2H), 1.00 (t, J = 7.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 150.1, 145.1, 140.1, 137.1, 128.7, 128.4, 128.2, 127.0, 126.0, 125.6, 125.3, 115.0, 35.9, 33.3, 22.7, 22.5, 14.0 ppm; HRMS (ESI) m/z calcd for $C_{20}H_{22}N$ $[M + H]^+$ 276.1747, found 276.1750.

*6-Isobutyl-1-methyl-3-phenylisoquinoline (**3ae**).* This compound was obtained as a yellow oil (63 mg, 76% yield): R_f = 0.5 (petroleum ether/EtOAc 20/1); IR (KBr) 3034, 2927, 2860, 1679, 1571, 1269, 897, 760 cm^{-1}, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 7.7 Hz, 2H), 8.03 (d, J = 8.5 Hz, 1H), 7.88 (s, 1H), 7.60 (s, 1H), 7.52 (t, J = 7.5 Hz, 2H), 7.43−7.37 (m, 2H), 3.04 (s, 3H), 2.68 (d, J = 7.1 Hz, 2H), 2.06−2.00 (m, 1H), 0.99 (d, J = 6.5 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 150.1, 144.0, 140.1, 137.0, 128.9, 128.7, 128.2, 127.0, 126.9, 125.4, 125.3, 115.1, 45.6, 30.1, 22.6, 22.5 ppm; HRMS (ESI) m/z calcd for $C_{20}H_{22}N$ $[M + H]^+$ 276.1747, found 276.1751.

*1-Methyl-3,6-diphenylisoquinoline (**3af**).* This compound was obtained as a yellow solid (65 mg, 73% yield): mp 130−132 °C; R_f = 0.5 (petroleum ether/EtOAc 20/1); IR (KBr) 3450, 2922, 2375, 1661, 1567, 1397, 754, 691 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20−8.15 (m, 3H), 8.02 (s, 1H), 7.96 (s, 1H), 7.80 (d, J = 8.6 Hz, 1H), 7.74 (d, J = 7.4 Hz, 2H), 7.53 (t, J = 6.4 Hz, 4H), 7.48−7.41 (m, 2H), 3.06 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 150.5, 142.6, 140.2, 139.9, 137.2, 129.0, 128.8, 128.4, 128.1, 127.5, 127.1, 126.5, 126.3, 125.7, 125.3, 22.7 ppm; HRMS (ESI) m/z calcd for $C_{22}H_{18}N$ $[M + H]^+$ 296.1434, found 296.1438.

*6-(Benzyloxy)-1-methyl-3-phenylisoquinoline (**3ag**).* This compound was obtained as a yellow solid (70 mg, 72% yield): mp 100−101 °C; R_f = 0.4 (petroleum ether/EtOAc 20/1); IR (KBr) 3452, 2959, 1674, 1571, 1408, 762, 690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 7.6 Hz, 2H), 8.02 (d, J = 9.1 Hz, 1H), 7.79 (s, 1H), 7.49−7.46 (m, 4H), 7.43−7.35 (m, 4H), 7.24 (s, 1H), 7.18 (s, 1H), 5.20 (s, 2H), 2.98 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 158.0, 150.6, 139.9, 138.8, 128.7, 128.7, 128.3, 128.3, 127.6, 127.1, 122.4, 119.8, 114.9, 106.6, 70.2, 22.5 ppm; HRMS (ESI) m/z calcd for $C_{23}H_{20}NO$ $[M + H]^+$ 326.1539, found 326.1544.

*Methyl-6-(methylthio)-3-phenylisoquinoline (**3ah**).* This compound was obtained as a yellow solid (54 mg, 68% yield): mp 93−94 °C; R_f = 0.35 (petroleum ether/EtOAc 20/1); IR (KBr) 3062, 2919, 1676, 1611, 1566, 1394, 764, 692 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 7.3 Hz, 2H), 7.93 (d, J = 8.8 Hz, 1H), 7.77 (s, 1H), 7.52−7.46 (m, 3H), 7.42−7.36 (m, 2H), 2.97 (s, 3H), 2.58 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 150.7, 142.0, 139.8, 137.4, 128.7, 128.4, 127.0, 125.8, 125.7, 124.2, 121.3, 114.2, 22.5, 15.0 ppm; HRMS (ESI) m/z calcd for $C_{17}H_{16}NS$ $[M + H]^+$ 266.0998, found 266.1000.

*N,N,1-Trimethyl-3-phenylisoquinolin-6-amine (**3ai**).* This compound was obtained as a light yellow solid (57 mg, 72% yield): mp 149−150 °C; R_f = 0.2 (petroleum ether/EtOAc 20/1); IR (KBr) 3058, 2920, 2854, 1618, 1408, 811, 693 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 7.7 Hz, 2H), 7.96 (d, J = 9.2 Hz, 1H), 7.71 (s, 1H), 7.47 (t, J = 7.4 Hz, 2H), 7.37 (t, J = 7.2 Hz, 1H), 7.13 (d, J = 9.2 Hz, 1H), 6.81 (s, 1H), 3.11 (s, 6H), 2.95 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 151.1, 150.1, 140.3, 138.9, 128.6, 128.0, 127.0, 126.9, 119.7, 115.9, 114.4, 104.5, 40.3, 22.1 ppm; HRMS (ESI) m/z calcd for $C_{18}H_{19}N_2$ $[M + H]^+$ 263.1543, found 263.1547.

*6-Fluoro-1-methyl-3-phenylisoquinoline (**3aj**).* This compound was obtained as a yellow oil (33 mg, 46% yield): R_f = 0.45 (petroleum ether/EtOAc 20/1); IR (KBr) 2922, 1570, 1631, 1429, 1223, 845, 747 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (t, J = 8.6 Hz, 3H), 7.86 (s, 1H), 7.52−7.41 (m, 4H), 7.31 (t, J = 8.8 Hz, 1H), 3.02 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2 (d, J = 250.0 Hz),, 158.5, 151.1, 139.4, 138.5 (d, J = 10.0 Hz), 128.8, 128.6, 127.1, 123.8, 117.1, 116.8, 114.9 (d, J = 5.0 Hz), 110.7 (d, J = 21.0 Hz), 22.8 ppm; HRMS (ESI) m/z calcd for $C_{16}H_{13}FN$ $[M + H]^+$ 238.1027, found 238.1031.

*6-Chloro-1-methyl-3-phenylisoquinoline (**3ak**).* This compound was obtained as a yellow oil (27 mg, 39% yield): R_f = 0.6 (petroleum ether/EtOAc 20/1); IR (KBr) 3064, 2921, 2853, 1612, 1566, 1084, 758, 690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 7.3 Hz, 2H), 8.04 (d, J = 8.9 Hz, 1H), 7.80 (s, 2H), 7.54−7.48 (m, 3H), 7.43−7.37 (m, 1H), 3.01 (s, 2H) ppm;^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 151.2, 139.4, 137.7, 136.2, 128.8, 128.7, 127.6, 127.4, 127.1, 126.3, 124.8, 114.3, 22.7 ppm; HRMS (ESI) m/z calcd for $C_{16}H_{13}ClN$ $[M + H]^+$ 254.0731, found 254.0734.

*6-Bromo-1-methyl-3-phenylisoquinoline (**3al**).* This compound was obtained as a yellow oil (31 mg, 35% yield): R_f = 0.6 (petroleum ether/EtOAc 20/1); IR (KBr) 3033, 2923, 2854, 1609, 1564, 1272, 969, 756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 7.3 Hz, 2H), 8.01 (s, 1H), 7.97 (d, J = 8.6 Hz, 1H), 7.80 (s, 1H), 7.63 (d, J = 8.8 Hz, 1H), 7.50 (t, J = 7.0 Hz, 2H), 7.42 (m, 1H), 3.01 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 151.1, 139.4, 138.1, 130.2, 129.7, 128.8, 128.7, 127.4, 127.1, 125.0, 124.8, 114.1, 22.6 ppm; HRMS (ESI) m/z calcd for $C_{16}H_{13}BrN$ $[M + H]^+$ 298.0226, found 298.0229.

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*1-Methyl-6-nitro-3-phenylisoquinoline (**3am**).* This compound was obtained as a yellow solid (23 mg, 29% yield): mp 121−123 °C; R_f = 0.4 (petroleum ether/EtOAc 20/1); IR (KBr) 2989, 2921,2851, 1765, 1262, 823, 753, 691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 8.29 (s, 2H), 8.16 (d, J = 7.3 Hz, 2H), 8.07 (s, 1H), 7.53 (t, J = 7.0 Hz, 2H), 7.47−7.43 (m, 1H), 3.10 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 152.1, 148.3, 138.6, 136.3, 129.2, 128.9, 128.1, 127.8, 127.1, 123.8, 120.0, 116.0, 22.9 ppm; HRMS (ESI) m/z calcd for $C_{16}H_{13}N_2O_2$ $[M + H]^+$ 265.0972, found 265.0974.

*1,8-Dimethyl-3-phenylisoquinoline (**3an**).* This compound was obtained as a yellow oil (47 mg, 68% yield): R_f = 0.45 (petroleum ether/EtOAc 20/1); IR (KBr) 3058, 2924, 1609, 1566, 1432, 1266, 773, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 7.4 Hz, 2H), 7.88 (s, 1H), 7.69 (d, J = 8.1 Hz, 1H), 7.50 (m, 3H), 7.41 (t, J = 7.1 Hz, 1H), 7.34 (d, J = 6.9 Hz, 1H), 3.23 (s, 3H), 2.96 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 148.8, 139.4, 139.0, 136.2, 130.3, 129.4, 128.7, 128.3, 127.5, 126.9, 126.7, 116.1, 29.7, 25.7 ppm; HRMS (ESI) m/z calcd for $C_{17}H_{16}N$ $[M + H]^+$ 234.1277, found 234.1281.

*8-Fluoro-1-methyl-3-phenylisoquinoline (**3ao**).* This compound was obtained as a yellow oil (26 mg, 36% yield): R_f = 0.7 (petroleum ether/EtOAc 20/1); IR (KBr) 2968, 1672, 1624, 1411, 1019, 836, 769 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 7.5 Hz, 2H), 7.89 (s, 1H), 7.63 (d, J = 8.1 Hz, 1H), 7.59−7.56 (m, 1H), 7.50 (t, J = 7.5 Hz, 2H), 7.42 (t, J = 7.2 Hz, 1H), 7.21−7.16 (m, 1H), 3.17 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2 (d, J = 255 Hz), 156.7(d, J = 6.2 Hz), 150.5, 139.5(d, J = 3.5 Hz), 139.1, 130.3 (d, J = 9.1 Hz), 128.8, 128.7, 127.0, 123.6(d, J = 6.4 Hz), 117.3, 114.3(d, J = 2.6 Hz), 112.1(d, J = 23.2 Hz), 27.2, 27.1 ppm; HRMS (ESI) m/z calcd for $C_{16}H_{13}FN$ $[M + H]^+$ 238.1027, found 238.1030.

*1,7-Dimethyl-3-phenylisoquinoline (**3ap**).* This compound was obtained as a yellow oil (55 mg, 78% yield): R_f = 0.5 (petroleum ether/EtOAc 20/1); IR (KBr) 3075, 2919, 2857, 1593, 1502, 919, 804, 692 cm^{-1}, ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 7.6 Hz, 2H), 7.88 (s, 2H), 7.74 (d, J = 8.3 Hz, 1H), 7.51 (m, 3H), 7.42 (t, J = 7.3 Hz, 1H), 3.03 (s, 3H), 2.57 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 149.2, 140.0, 136.7, 135.0, 132.2, 128.7, 128.2, 127.5, 126.9, 124.6, 123.9, 115.1, 22.7, 22.1 ppm; HRMS (ESI) m/z calcd for $C_{17}H_{16}N$ $[M + H]^+$ 234.1277, found 234.1281.

*1,6,7-Trimethyl-3-phenylisoquinoline (**3aq**).* This compound was obtained as a white solid (63 mg, 85% yield): mp 98−99 °C; R_f = 0.45 (petroleum ether/EtOAc 20/1); IR (KBr) 3058, 2918, 1568, 1404, 1025, 889, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 7.2 Hz, 2H), 7.81 (d, J = 5.9 Hz, 2H), 7.58−7.48 (m, 3H), 7.43 (t, J = 7.3 Hz,1H), 3.01 (s, 3H), 2.45(s, 3H), 2.43 (s,3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 149.2, 140.2, 136.6, 135.7, 128.7, 128.1, 127.1, 126.9, 125.6, 125.1, 114.5, 22.6, 20.6, 20.4 ppm; HRMS (ESI) m/z calcd for $C_{18}H_{18}N$ $[M + H]^+$ 248.1434, found 248.1439.

*1-Methyl-3-phenylbenzo[g]isoquinoline (**3ar**).* This compound was obtained as a yellow solid (48 mg, 59% yield): mp 108−110 °C; R_f = 0.5 (petroleum ether/EtOAc 20/1); IR (KBr) 3053, 2919, 1612, 1569, 1437, 888, 743,694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, J = 7.3 Hz, 1H), 8.32 (d, J = 7.9 Hz, 1H), 8.21 (d, J = 7.4 Hz, 2H), 8.09−7.96 (m, 3H), 7.57−7.50 (m, 4H), 7.43 (t, J = 6.9 Hz, 1H), 3.16 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 147.7, 139.8, 134.2, 133.1, 132.1, 129.2, 128.8, 128.3, 127.8, 127.4, 126.9, 125.9, 125.9, 125.5, 125.1, 114.5, 23.2 ppm; HRMS (ESI) m/z calcd for $C_{20}H_{16}N$ $[M + H]^+$ 270.1277, found 270.1281.

*7-Methyl-5-phenylthieno[2,3-c]pyridine (**3as**).* This compound was obtained as a yellow oil (17 mg, 25% yield): R_f = 0.5 (petroleum ether/EtOAc 20/1); IR (KBr) 3035, 2956, 2853, 1724, 1635, 1389, 764, 693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 7.6 Hz, 2H), 7.96 (s, 1H), 7.67 (d, J = 5.2 Hz, 1H), 7.48 (t, J = 7.4 Hz, 2H), 7.42−7.37 (m, 2H), 2.89 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 151.9, 146.0, 140.0, 134.2, 131.3, 128.7, 128.3, 127.1, 124.1, 112.5, 23.7 ppm; HRMS (ESI) m/z calcd for $C_{14}H_{12}NS$ $[M + H]^+$ 226.0685, found 226.0686.

*3-Phenylisoquinoline (**3at**).* This compound was obtained as a yellow oil (50 mg, 75% yield): R_f = 0.4 (petroleum ether/EtOAc 20/1); IR (KBr) 3429, 3054, 1660, 1576, 1451, 753, 686 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.35 (s, 1H), 8.14 (d, J = 7.6 Hz, 2H), 8.07 (s, 1H), 7.98 (d, J = 8.1 Hz, 1H), 7.86 (d, J = 8.2 Hz, 1H), 7.69 (t, J = 7.5 Hz, 1H), 7.58 (t, J = 7.5 Hz, 1H), 7.52 (t, J = 7.4 Hz, 2H), 7.43 (t, J = 7.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.4, 151.3, 139.6, 136.7, 130.5, 128.8, 128.5, 127.8, 127.6, 127.1, 127.0, 126.9, 116.6, 70.5 ppm; HRMS (ESI) m/z calcd for $C_{15}H_{12}N$ $[M + H]^+$ 206.0964, found 206.0967.

*1-Ethyl-3-phenylisoquinoline (**3au**).* This compound was obtained as a yellow oil (58 mg, 83% yield): R_f = 0.7 (petroleum ether/EtOAc 20/1);IR (KBr) 3432, 2925, 1570, 1452, 1409, 769, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 3H), 7.93 (s, 1H), 7.86 (s, 1H), 7.66 (t, J = 7.5 Hz, 1H), 7.57 (s, 1H), 7.51 (s, 2H), 7.41 (s, 1H), 3.43 (d, J = 7.5 Hz, 2H), 1.54 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 149.8, 144.9, 139.9, 137.1, 129.9, 128.7, 128.3, 127.8, 127.0, 126.7, 125.9, 125.2, 115.0, 28.4, 13.4 ppm; HRMS (ESI) m/z calcd for $C_{17}H_{16}N$ $[M + H]^+$ 234.1277, found 234.1281.

*3-Phenyl-1-propylisoquinoline (**3av**).* This compound was obtained as a yellow oil (63 mg, 85% yield): R_f = 0.65 (petroleum ether/EtOAc 20/1); IR (KBr) 3061, 2962, 2867, 1569,1450, 878, 768, 691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.25−8.13 (m, 3H), 7.93 (s, 1H), 7.86 (d, J = 8.1 Hz, 1H), 7.65 (t, J = 7.5 Hz, 1H), 7.60−7.48 (m, 3H), 7.44 (d, J = 6.9 Hz, 1H), 3.38 (t, J = 7.5 Hz, 2H), 2.12−1.98 (m, 2H), 1.22−1.10 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 149.8, 140.0, 137.1, 129.8, 128.7, 128.3, 127.8, 127.0, 126.7, 126.2, 125.4, 115.0, 37.3, 22.7, 14.4 ppm; HRMS (ESI) m/z calcd for $C_{18}H_{18}N$ $[M + H]^+$ 248.1434, found 248.1438.

*1-Isopropyl-3-phenylisoquinoline (**3aw**).* This compound was obtained as a yellow oil (56 mg, 76% yield): R_f = 0.7 (petroleum ether/EtOAc 20/1); IR (KBr) 3063, 2970, 2865, 1622, 1569, 759, 693 cm^{-1}, ^1H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, J = 7.1 Hz, 2H), 8.24 (d, J = 8.4 Hz, 1H), 7.96 (s, 1H), 7.88 (d, J = 8.1 Hz, 1H), 7.66 (t, J = 7.3 Hz, 1H), 7.59−7.52 (m, 3H), 7.44 (d, J = 7.7 Hz, 1H), 4.04−3.98 (m, 1H), 1.56 (d, J = 6.1 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 149.3, 140.0, 137.4, 129.6, 128.7, 128.3, 128.1, 126.9, 126.6, 125.4, 124.8, 114.5, 31.3, 22.4 ppm. HRMS (ESI) m/z calcd for $C_{18}H_{18}N$ $[M + H]^+$ 248.1434, found 248.1438.

*1-Butyl-3-phenylisoquinoline (**3ax**).* This compound was obtained as a yellow oil (66 mg, 84% yield): R_f = 0.5 (petroleum ether/EtOAc 20/1); IR (KBr) 3443, 3061, 2959, 1621, 1568, 768, 691 cm^{-1}, ^1H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J = 7.4 Hz, 2H), 8.19 (d, J = 8.4 Hz, 1H), 7.94 (s, 1H), 7.86 (d, J = 8.1 Hz, 1H), 7.65 (t, J = 7.5 Hz, 1H), 7.56 (t, J = 9.1 Hz, 3H), 7.45 (t, J = 7.2 Hz, 1H), 3.42 (t,J = 9.1 Hz, 2H), 2.08−1.95 (m, 2H), 1.63−1.58 (m, 2H), 1.08 (t, J = 7.3 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 149.8, 140.1, 137.2, 129.8, 128.8, 128.3, 127.9, 127.1, 126.7, 126.1, 125.4, 115.0, 35.2, 31.6, 23.0, 14.2 ppm; HRMS (ESI) m/z calcd for $C_{19}H_{20}N$ $[M + H]^+$ 262.1590, found 262.1592.

*1,3-Diphenylisoquinoline (**3ay**).*[8b] This compound was obtained as a yellow oil (63 mg, 75% yield): R_f = 0.5 (petroleum ether/EtOAc 20/1); IR (KBr) 3033, 2930, 1675, 1594, 1486, 881, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 7.6 Hz, 2H), 8.15 (d, J = 8.4 Hz, 1H), 8.09 (s, 1H), 7.94 (d, J = 8.1 Hz, 1H), 7.86 (t, J = 11.2 Hz, 2H), 7.69 (t, J = 7.3 Hz, 1H), 7.60−7.50 (m, 6H), 7.43 (t, J = 7.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 149.1, 138.8, 138.5, 136.8, 129.2, 129.0, 127.7, 127.6, 127.4, 127.2, 126.5, 126.4, 126.0, 125.9, 124.7, 114.7 ppm; MS (EI) m/z 77, 139, 176, 202, 252, 281.

*2-Phenyl-8,9-dihydro-7H-benzo[de]quinoline (**3az**).* This compound was obtained as a blue oil (63 mg, 75% yield): R_f = 0.5 (petroleum ether/EtOAc 20/1); IR (KBr) 3054, 2935, 1616, 1577, 1265, 871, 778, 693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 7.3 Hz, 2H), 7.89 (s, 1H), 7.67 (d, J = 8.2 Hz, 1H), 7.58 (d, J = 7.5 Hz, 1H), 7.51 (t, J = 7.7 Hz, 2H), 7.44−7.39 (m, 1H), 7.31 (d, J = 6.8 Hz, 1H), 3.38 (t, J = 6.1 Hz, 2H), 3.14 (t, J = 5.9 Hz, 2H), 2.29−2.19 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 150.0, 139.8, 138.8, 137.0, 130.3, 128.8, 128.4, 127.2, 124.9, 124.8, 123.9, 115.2, 34.5, 30.5, 23.4 ppm; HRMS (ESI) m/z calcd for $C_{18}H_{16}N$ $[M + H]^+$ 246.1277, found 246.1280.

*1,6-Dimethyl-3-(p-tolyl)isoquinoline (**3ba**).*[8b] This compound was obtained as a yellow oil (62 mg, 83% yield): R_f = 0.55 (petroleum

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ether/EtOAc 20/1); IR (KBr) 3439, 2918, 1673, 1571, 893, 822 cm^{-1}; H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 8.0 Hz, 2H), 8.00 (d, J = 8.5 Hz, 1H), 7.80 (s, 1H), 7.60 (s, 1H), 7.37 (d, J = 8.5 Hz, 1H), 7.31 (d, J = 7.8 Hz, 2H), 3.02 (s, 3H), 2.54 (s, 3H), 2.43 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 150.0, 140.3, 138.1, 137.2, 137.0, 129.4, 128.9, 126.9, 126.5, 125.5, 124.9, 114.5, 22.5, 21.9, 21.3 ppm; MS (EI) m/z 77, 115, 189, 202, 232, 247.

*3-(4-(tert-Butyl)phenyl)-1,6-dimethylisoquinoline (**3bb**).* This compound was obtained as a yellow oil (59 mg, 75%); R_f = 0.6 (petroleum ether/EtOAc 20/1); IR (KBr) 2962, 2863, 1627, 1569, 1267, 894, 836 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 8.3 Hz, 2H), 8.00 (d, J = 8.5 Hz, 1H), 7.81 (s, 1H), 7.61 (s, 1H), 7.54 (d, J = 8.3 Hz, 2H), 7.37 (d, J = 8.4 Hz, 1H), 3.01 (s, 3H), 2.54 (s, 3H), 1.40 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 151.3, 150.3, 140.1, 137.3, 137.2, 128.8, 126.8, 126.5, 125.7, 125.5, 124.9, 114.5, 34.7, 31.4, 22.6, 21.9 ppm; HRMS (ESI) m/z calcd for $C_{21}H_{24}N$ $[M + H]^+$ 290.1903, found 290.1904.

*3-(4-Fluorophenyl)-1,6-dimethylisoquinoline (**3bc**).* This compound was obtained as a white solid (60 mg, 80% yield): mp 73−74 °C; R_f = 0.5 (petroleum ether/EtOAc 20/1); IR (KBr) 3070, 2919, 1627, 1573, 1211, 813, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.15−8.06 (m, 2H), 8.00 (d, J = 8.5 Hz, 1H), 7.77 (s, 1H), 7.60 (s, 1H), 7.39 (d, J = 8.5 Hz, 1H), 7.17 (t, J = 8.4 Hz, 2H), 2.99 (s, 3H), 2.54 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, (d, J = 248.0 Hz), 158.3, 149.1, 140.4, 137.2, 136.1, 129.1, 128.7 (d, J = 8.1 Hz), 126.5, 125.5, 124.9, 115.5(d, J = 21.3 Hz), 114.5, 22.5, 21.9 ppm; HRMS (ESI) m/z calcd for $C_{17}H_{15}FN$ $[M + H]^+$ 252.1183, found 252.1186.

*3-(4-Chlorophenyl)-1,6-dimethylisoquinoline (**3bd**).* This compound was obtained as a yellow solid (62 mg, 75%); mp 55−57 °C; R_f = 0.55 (petroleum ether/EtOAc 20/1);IR (KBr) 3064, 2918, 1628, 1569, 1493, 1093, 830, 721 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 8.4 Hz, 2H), 7.96 (d, J = 8.5 Hz, 1H), 7.75 (s, 1H), 7.55 (s, 1H), 7.44 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.5 Hz, 1H), 2.98 (s, 3H), 2.53 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 148.7, 140.4, 138.4, 137.0, 134.2, 128.8, 128.2, 126.6, 125.5, 125.1, 114.7, 22.6, 21.9 ppm; HRMS (ESI) m/z calcd for $C_{17}H_{15}ClN$ $[M + H]^+$ 268.0888, found 268.0889.

*3-(4-Bromophenyl)-1,6-dimethylisoquinoline (**3be**).* This compound was obtained as a white solid (76 mg, 81%); mp 103−105 °C; R_f = 0.5 (petroleum ether/EtOAc 20/1); IR (KBr) 3065, 2918, 1627, 1568, 1491, 894, 828 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80−7.95 (m, 3H), 7.74 (s, 1H), 7.59 (d, J = 8.4 Hz, 2H), 7.54 (s, 1H), 7.37 (d, J = 8.5 Hz, 1H), 2.97 (s, 3H), 2.52 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 148.7, 140.4, 138.8, 137.0, 131.8, 129.3, 128.5, 126.6, 125.5, 125.1, 122.5, 114.7, 22.6, 21.9 ppm; HRMS (ESI) m/z calcd for $C_{17}H_{15}BrN$ $[M + H]^+$ 312.0382, found 312.0385.

*1,6-Dimethyl-3-(4-(trifluoromethyl)phenyl)isoquinoline (**3bf**).* This compound was obtained as a yellow solid (75 mg, 83%); mp 144−145 °C; R_f = 0.55 (petroleum ether/EtOAc 20/1); IR (KBr) 3068, 2923, 1624, 1571, 1324, 1118, 844, 683 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J = 8.0 Hz, 2H), 7.96 (d, J = 8.5 Hz, 1H), 7.79 (s, 1H), 7.72 (d, J = 8.0 Hz, 2H), 7.56 (s, 1H), 7.39 (d, J = 8.5 Hz, 1H), 2.98 (s, 3H), 2.53 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 148.2, 143.3, 140.6, 136.8, 130.0 (q, J = 32.1 Hz), 129.5, 127.1, 126.7, 125.5 (q, J = 3.7 Hz), 125.5, 125.3, 124.5 (q, J = 270.0 Hz), 115.6, 22.5, 21.8 ppm; HRMS (ESI) m/z calcd for $C_{18}H_{15}F_3N$ $[M + H]^+$ 302.1151, found 302.1153.

*1,6-Dimethyl-3-(o-tolyl)isoquinoline (**3bg**).* This compound was obtained as a yellow solid (49 mg, 66% yield): mp 90−91 °C; R_f = 0.5 (petroleum ether/EtOAc 20/1); IR (KBr) 3062, 2922, 2858, 1627, 1589, 1494, 970, 813 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 8.1 Hz, 1H), 7.60 (s, 1H), 7.49 (d, J = 9.7 Hz, 2H), 7.43 (d, J = 8.2 Hz, 1H), 7.30 (s, 3H), 3.00 (s, 3H), 2.56 (s, 3H), 2.56 (s, 3H), 2.41 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 152.6, 140.9, 140.3, 136.7, 136.2, 130.7, 130.0, 129.1, 127.9, 126.4, 125.9, 125.5, 124.5, 118.4, 22.4, 21.9, 20.5 ppm; HRMS (ESI) m/z calcd for $C_{18}H_{18}N$ $[M + H]^+$ 248.1434, found 248.1439.

*3-(2-Fluorophenyl)-1,6-dimethylisoquinoline (**3bh**).* This compound was obtained as a yellow solid (54 mg, 72%); mp 55−57 °C; R_f = 0.7 (petroleum ether/EtOAc 20/1); IR (KBr) 2919, 1747, 1627, 1573, 1211, 898, 813, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.18 (t, J = 7.7 Hz, 1H), 8.00 (d, J = 8.5 Hz, 1H), 7.95 (s, 1H), 7.61 (s, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.37−7.27 (m, 2H), 7.23−7.15 (m, 1H), 3.01 (s, 3H), 2.54 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6 (d, J = 244.0 Hz), 158.2, 145.2, 140.4, 136.7, 131.3, 131.3, 129.6 (d, J = 8.4 Hz), 129.5, 126.8, 125.4, 125.0, 124.5 (d, J = 3.50 Hz), 119.4 (d, J = 9.8 Hz), 116.1 (d, J = 23.1 Hz), 22.5, 21.9 ppm; HRMS (ESI) m/z calcd for $C_{17}H_{15}FN$ $[M + H]^+$ 252.1183, found 252.1186.

*1,6-Dimethyl-3-(m-tolyl)isoquinoline (**3bi**).* This compound was obtained as a yellow solid (60 mg, 80%); mp 65−67 °C; R_f = 0.5 (petroleum ether/EtOAc 20/1); IR (KBr) 3063, 2917, 1627, 1573, 1398, 888,783 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 8.3 Hz, 2H), 7.78 (d, J = 7.4 Hz, 1H), 7.68 (s, 1H), 7.45 (s, 1H), 7.28−7.21 m, 2H), 7.09 (d, J = 7.3 Hz, 1H), 2.88 (s, 3H), 2.39 (s, 3H), 2.35 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 150.3, 140.2, 140.0, 138.3, 137.1, 129.1, 129.0, 128.6, 127.8, 126.6, 125.5, 125.0, 124.1, 114.9, 22.6, 21.9, 21.7 ppm; HRMS (ESI) m/z calcd for $C_{18}H_{18}N$ $[M + H]^+$ 248.1434, found 248.1437.

*3-(3-Chlorophenyl)-1,6-dimethylisoquinoline (**3bj**).* This compound was obtained as a yellow solid (58 mg, 73%); mp 86−88 °C; R_f = 0.55 (petroleum ether/EtOAc 20/1); IR (KBr) 3067, 2956, 2854, 1587, 1485, 1385, 873, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.96 (t, J = 8.0 Hz, 2H), 7.74 (s, 1H), 7.54 (s, 1H), 7.41−7.36 (m,3H), 2.97 (s, 3H), 2.52 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 148.4, 141.8, 140.4, 136.9, 134.8, 129.9, 129.4, 128.2, 127.1, 126.6, 125.5, 125.2, 124.9, 115.1, 22.5, 21.9 ppm; HRMS (ESI) m/z calcd for $C_{17}H_{15}ClN$ $[M + H]^+$ 268.0888, found 268.0888.

*1,6-Dimethyl-3-(naphthalen-2-yl)isoquinoline (**3bk**).* This compound was obtained as a blue solid (43 mg, 51%); mp 63−65 °C; R_f = 0.5 (petroleum ether:EtOAc = 20:1); IR (KBr)2920, 2850, 1665, 1576, 1408, 811, 750, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.25 (d, J = 8.6 Hz, 1H), 8.04 (d, J = 8.4 Hz, 1H), 8.01−7.94 (m, 3H), 7.88 (d, J = 7.9 Hz, 1H), 7.66 (s, 1H), 7.53−7.47 (m, 2H), 7.42 (d, J = 8.3 Hz, 1H), 3.06 (s, 3H), 2.57 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 149.8, 140.4, 137.2, 137.2, 133.7, 133.4, 129.1, 128.7, 128.3, 127.7, 126.6, 126.2, 126.1, 125.6, 125.1, 124.8, 115.3, 22.6, 21.9. ppm; HRMS (ESI) m/z calcd for $C_{21}H_{18}N$ $[M + H]^+$ 284.1434, found 284.1430.

*6-Ethyl-3-(4-ethylphenyl)-1-methylisoquinoline (**3bl**).* This compound was obtained as a yellow oil (45 mg, 55%); R_f = 0.55 (petroleum ether/EtOAc 20/1); IR (KBr) 3034, 2966, 2863, 1627, 1570, 895, 833 cm^{-1};^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (t, J = 7.7 Hz, 3H), 7.84 (s, 1H), 7.62 (s, 1H), 7.41 (d, J = 8.5 Hz, 1H), 7.33 (d, J = 7.9 Hz, 2H), 3.01 (s, 3H), 2.85 (q, J = 7.5 Hz, 2H), 2.72 (q, J = 7.5 Hz, 2H), 1.35 (t, J = 7.6 Hz, 3H), 1.30 (d, J = 7.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 150.2, 146.4, 144.5, 137.5, 137.3, 128.3, 127.8, 127.0, 125.6, 125.2, 125.1, 114.7, 29.1, 28.7, 22.6, 15.7, 15.2 ppm; HRMS (ESI) m/z calcd for $C_{20}H_{22}N$ $[M + H]^+$ 276.1747, found 276.1748.

*6-Isobutyl-3-(4-isobutylphenyl)-1-methylisoquinoline (**3bm**).* This compound was obtained as a yellow oil (50 mg, 51%); R_f = 0.55 (petroleum ether/EtOAc 20/1); IR (KBr) 3034, 2927, 2860, 1677, 1593, 1258, 758, 691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 7.3 Hz, 3H), 7.98 (d, J = 8.6 Hz, 1H), 7.81 (s, 1H), 7.54 (s, 1H), 7.33 (d, J = 8.5 Hz, 1H), 7.25 (d, J = 7.7 Hz, 2H), 2.98 (s, 3H), 2.63 (d, J = 7.1 Hz, 2H), 2.53 (d, J = 7.0 Hz, 2H), 2.02−1.87 (m, 2H), 0.93 (t, J = 6.2 Hz, 12H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 150.2, 143.9, 141.9, 137.6, 137.1, 129.5, 128.6, 126.8, 126.8, 125.4, 125.1, 114.7, 45.6, 45.3, 30.3, 30.1, 22.6, 22.5, 22.4 ppm; HRMS (ESI) m/z calcd for $C_{24}H_{30}N$ $[M + H]^+$ 332.2373, found 332.2372.

*6-Methoxy-3-(4-methoxyphenyl)-1-methylisoquinoline (**3bn**).*[8b] This compound was obtained as a yellow solid (47 mg, 56%); mp 109−110 °C; R_f = 0.4 (petroleum ether/EtOAc 20/1); IR (KBr) 3064, 2970, 1621, 1570, 1406, 1241, 878, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 8.6 Hz, 2H), 7.99 (d, J = 9.1 Hz, 1H), 7.75 (s, 1H), 7.15 (d, J = 9.2 Hz, 1H), 7.08 (s, 1H), 7.02 (d, J = 8.5 Hz, 2H), 3.95 (s, 3H), 3.87 (s, 3H), 2.97 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 160.0, 157.8, 150.4, 139.0, 132.6, 128.2, 127.5, 122.0,

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119.1, 114.1, 113.8, 105.1, 55.4, 55.4, 22.5 ppm; MS (EI) m/z 73,135, 193, 236, 264, 279.

*6-Fluoro-3-(4-fluorophenyl)-1-methylisoquinoline (**3bo**).*[8b] This compound was obtained as a blue solid (38 mg, 51%); mp 107−108 °C; R_f = 0.55 (petroleum ether/EtOAc 20/1); IR (KBr) 2922, 1631, 1570, 1429, 1223, 845, 809 cm^{-1}, ^1H NMR (400 MHz, $CDCl_3$) δ 8.19−8.09 (m, 3H), 7.82 (s, 1H), 7.45 (d, J = 9.2 Hz, 1H), 7.34 (t, J = 8.6 Hz, 1H), 7.20 (t, J = 8.3 Hz, 2H), 3.04 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4 (d, J = 247.0 Hz), 163.2 (d, J = 251.0 Hz), 162.1, 162.0, 158.6, 150.0, 138.5 (d, J = 10.2 Hz), 135.5, 128.8(d, J = 8.0 Hz), 128.7, 123.7, 117.0 (d, J = 25.0 Hz), 115.6 (d, J = 21.4 Hz), 114.5 (d, J = 4.7 Hz), 110.7 (d, J = 20.5 Hz), 22.7 ppm; MS (EI) m/z 94, 133, 158, 196, 255.

*6-Chloro-3-(4-chlorophenyl)-1-methylisoquinoline (**3bp**).*[8b] This compound was obtained as a white solid (48 mg, 55%); mp 107−109 °C; R_f = 0.6 (petroleum ether/EtOAc 20/1); IR (KBr: 2920, 2851, 1605, 1562, 1484, 1405, 820, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (t, J = 8.3 Hz, 1H), 7.79 (d, J = 13.6 Hz, 1H), 7.48 (m, 1H), 2.99 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 149.9, 137.8, 137.6, 136.4, 134.7, 128.9, 128.3, 127.9, 127.4, 126.3, 124.9, 114.1, 22.6 ppm; MS (EI) m/z 73, 126, 189, 140, 251, 287.

*6-Bromo-3-(4-bromophenyl)-1-methylisoquinoline (**3bq**).*[8b] This compound was obtained as a blue solid (55 mg, 49%); mp 125−126 °C; R_f = 0.5 (petroleum ether/EtOAc 20/1); IR (KBr) 2920, 2851, 1605, 1562, 1405, 820, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.03−7.95 (m, 4H), 7.77 (s, 1H), 7.63 (t, J = 9.6 Hz, 3H), 2.99 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 149.8, 138.2, 137.9, 131.9, 130.5, 129.7, 128.6, 127.4, 125.1, 125.0, 123.1, 113.9, 22.6 ppm; MS (EI) m/z 94, 107, 149, 189, 217, 296, 376.

*8-Fluoro-3-(2-fluorophenyl)-1-methylisoquinoline (**3br**).* This compound was obtained as a blue solid (55 mg, 49%); mp 45−46 °C; R_f = 0.6 (petroleum ether/EtOAc 20/1); IR (KBr) 2968, 1624, 1572, 1411, 1019, 836, 765 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (t, J = 7.3 Hz, 1H), 8.03 (s, 1H), 7.61 (m, 2H), 7.37 (m, 1H), 7.30 (t, J = 7.4 Hz, 1H), 7.24−7.16 (m, 2H), 3.16 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7 (d, J = 248.2 Hz), 160.1 (d, J = 254.9 Hz), 156.6 (d, J = 6.0 Hz),145.7, 139.1 (d, J = 3.2 Hz), 131.3 (d, J = 3.7 Hz) 130.4 (d, J = 8.3 Hz), 130.0 (d, J = 8.6 Hz), 124.5 (d, J = 3.4 Hz), 123.9 (d, J = 4.5 Hz), 118.9, 116.2 (d, J = 23.0 Hz), 112.4 (d, J = 23.1 Hz), 27.1, 27.0 ppm; HRMS (ESI) m/z calcd for $C_{16}H_{12}NF_2$ $[M + H]^+$ 256.0932, found 256.0934.

*7-Chloro-3-(3-chlorophenyl)-1-methylisoquinoline (**3bs**).* This compound was obtained as a white solid (46 mg, 54%); mp 107−109 °C; R_f = 0.55 (petroleum ether/EtOAc 20/1); IR (KBr) 3064, 2922, 1612, 1565, 1411, 1088, 824, 752 cm^{-1}; H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 7.6 Hz, 2H), 7.96 (s, 1H), 7.67 (d, J = 5.2 Hz, 1H), 7.48 (t, J = 7.4 Hz, 2H), 7.42−7.37 (m, 2H), 2.89 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 148.7, 141.1, 134.9, 134.9, 132.7, 131.2, 130.0, 129.3, 128.5, 127.3, 127.1, 124.9, 124.8, 115.1, 22.5 ppm; HRMS (ESI) m/z calcd for $C_{16}H_{12}Cl_2N$ $[M + H]^+$ 288.0341, found 288.0341.

*1-Ethyl-4-methyl-3-phenylisoquinoline (**3bt**).* This compound was obtained as a yellow oil (18.6 mg, 25%); R_f = 0.5 (petroleum ether/EtOAc 20/1); IR (KBr) 2964, 2869, 1625, 1498, 895, 832, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 8.3 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.75 (t, J = 7.4 Hz, 1H), 7.61 (m, 3H), 7.48 (t, J = 7.4 Hz, 2H), 7.40 (t, J = 7.3 Hz, 1H), 3.38 (q, J = 7.5 Hz, 2H), 2.61 (s, 3H), 1.46 (t, J = 7.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 150.5, 141.5, 136.7, 130.0, 129.9, 128.1, 127.5, 126.3, 125.8, 125.3, 124.4, 122.2, 28.6, 15.5, 14.3 ppm; HRMS (ESI) m/z calcd for $C_{18}H_{18}N$ $[M + H]^+$ 248.1434, found 248.1438.

*1,6-Dimethyl-3-(p-tolyl)isoquinoline (**3ba**-^{15}N).* Yield: 48 mg (65%): R_f = 0.5 (petroleum ether/EtOAc 20/1); ^1H NMR (400 MHz, $CDCl_3$) δ 8.04−7.99 (m, 3H), 7.80 (s, 1H), 7.59 (s, 1H), 7.37 (d, J = 8.5 Hz, 1H), 7.31 (d, J = 7.6 Hz, 2H), 3.02 (s, 3H), 2.54 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 150.0, 140.3, 138.2, 137.2, 137.0, 129.4, 128.9, 126.9, 126.5, 125.5, 124.9, 114.5, 22.5, 21.9, 21.3; HRMS (ESI) m/z calcd for $C_{18}H_{18}{}^{15}N$ $[M + H]^+$ 249.1404, found 249.1416.

Intermolecular Kinetic Isotope Effect Experiment. In an air atmosphere, **1ab** (0.3 mmol), **1ab′** (0.3 mmol), **2a** (0.3 mmol), and $Pd(OAc)_2$ (10 mol %) in 2 mL of toluene at 90 °C were allowed to react for 1.5 h. The crude product was cooled to room temperature and concentrated under vacuum. Then the resulting residue was purified by column chromatography on silica gel with petroleum ether/EtOAc (20/1) as eluent to afford a mixture of **3ab** and **3ab′** in 35% yield (23.0 mg). The KIE value (K_H/K_D = 4) was determined on the basis of ^1H NMR analysis (see the Supporting Information for details). Data for compounds **3ab**/**3ab′**: ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 8.13 (d, J = 5.8 Hz, 1.8H), 7.92 (s, 1H), 7.86 (d, J = 8.2 Hz, 0.8H), 7.67 (t, J = 7.5 Hz, 0.8H), 7.57 (t, J = 7.6 Hz, 0.8H), 7.51 (t, J = 7.4 Hz, 2H), 7.41 (t, J = 7.1 Hz, 1H), 3.05 (s, 3H) ppm. HRMS (ESI) m/z calcd for $C_{16}H_{14}N$ $[M + H]^+$ 220.1121, found 220.1128; HRMS (ESI) m/z calcd for $C_{16}H_{10}D_4N$ $[M + H]^+$ 224.1372, found 224.1374.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02376.

Spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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