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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.5b02376 • Publication Date (Web): 21 Jan 2016

Just Accepted

ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

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

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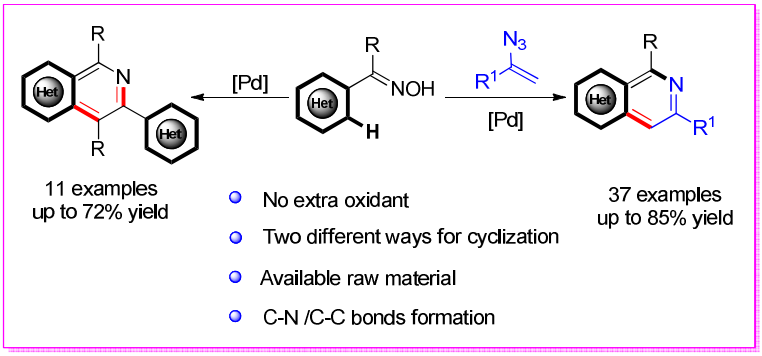


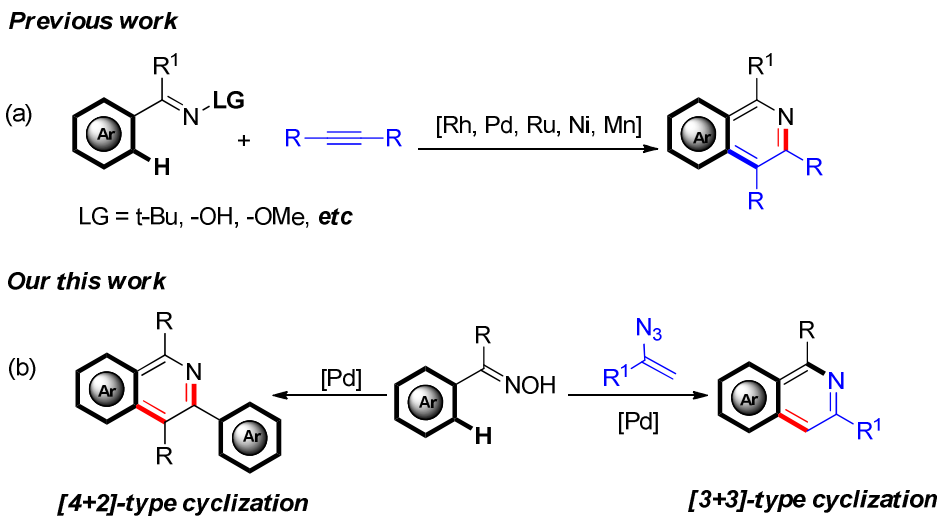
Abstract: An efficient strategy for synthesis of isoquinolines *via* Pd(II)-catalyzed cyclization reaction of oximes with vinyl azides or homocoupling of oximes is reported. Oximes could serve as a directing group and an internal oxidant in the transformation. This reaction features good functional group 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 experiment were conducted for the mechanism research.

INTRODUCTION

Isoquinoline units have served as an important component in biologically active

molecules, natural products and synthetic pharmaceutical agents.[1] They also could be used as chiral ligands for transition metal-catalyzed reactions,[2] and organic light emitting diodes in materials science.[3] Due to the substantial applicability of isoquinolines, the development for their synthesis has received considerable attention. Classical methods for their synthesis involve Bischler-Napieralski,[4a] Pictet-Spengler,[4b] Pomeranz-Fritsh[4c] protocols, *etc.* 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 exhibited mild conditions and good functional group tolerance are highly desirable.[5] Recently, C-H bond activation using transition metal (Rh, Ru, Ni, Pd, Mn) catalysis has become a powerful tool to give the 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 product is 1,3,4-substituted isoquinolines.

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



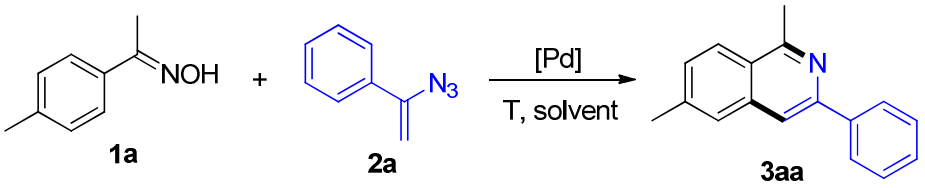
Oximes are fascinating synthetic building blocks which are widely employed in synthetic chemistry [8, 9a] due to their easy preparation, efficient reactivity and harmless byproducts. Moreover, they can also serve as internal oxidants and have been used as substrates for transition metal-catalyzed C–H 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.

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 ^oC under 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 best to 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 to the transformation. Further examination of the temperature showed that 90 ^oC proved to be the best, affording **3aa** in 91% GC yield (entries 18-20). Additionally, control experiments showed that O_2 and N_2 atmosphere had no significant effects on the reaction (entries 21-22). However, no reaction occurred in the absence of palladium catalyst (entry 23). Furthermore, other Lewis acids could not promote this

transformation (entries 24-26).

Table 1. Optimization of the Reaction Conditions [a]



1a 2a 3aa

Entry	[Pd]	Additive	Solvent	T (^{o}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

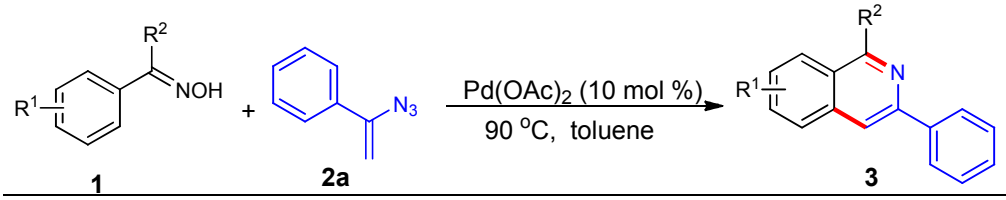
[a] Reaction conditions: unless otherwise noted all reactions were performed with **1a** (0.1 mmol), **2a** (0.12 mmol) catalyst (10 mol %) and additive (0.1 mmol) for 8 h. [b] Yields and conversions analyzed by GC/MS are based on **1a**. [c] Isolated yield. [d] Under N_2 atmosphere. [e] Under O_2

atmosphere.

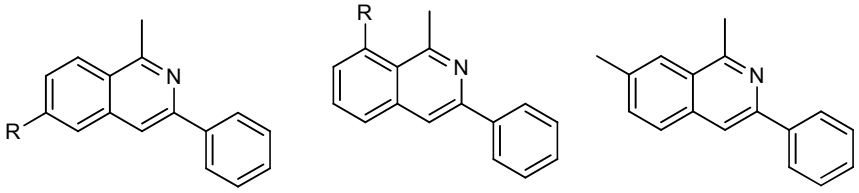
With the optimal conditions in hand, we investigated the substrate scope of this reaction between various aryloximes **1** and (1-azidovinyl)benzene (**2a**) (Table 2). Generally, this reaction proceeded smoothly and gave the desired products **3** in moderate to good yields. Substituted acetophenone oximes with electron-withdrawing groups gave lower yields than those with electron-donating groups. All of the *para*-, *ortho*-, *meta*-substituted alkyl and aryl substituted acetophenone oximes were able to give the corresponding products in good to excellent yields (**3aa-3af, 3an-3aq**). Strong 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 group, such as fluoride, chloride and bromide (**3al-3ao**). The acetophenone oxime with strong 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 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. Such as benzaldehyde, propiophenone, *n*-butyrophenone, *i*-butyrophenone, 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.

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



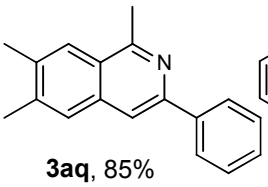
1 **2a** **3**



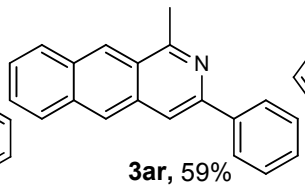
3aa, R = Me, 83%
3ab, R = H, 82%
3ac, R = Et, 81%
3ad, R = n-Bu, 79%
3ae, R = *i*-Bu, 76%
3af, R = Ph, 73%
3ag, R = OBn, 72%
3ah, R = SMe, 68%
3ai, R = N,N-dimethyl, 72%
3aj, R = F, 46%[b]
3ak, R = Cl, 39%[b]
3al, R = Br, 35%[b]
3am, R = NO_2, 29%[b]

3an, R = Me, 68 %
3ao, R = F, 36%[b]

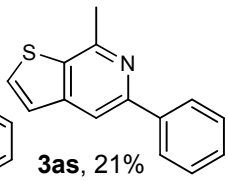
3ap, 78%



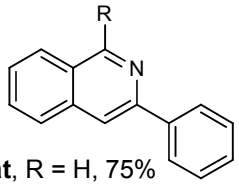
3aq, 85%



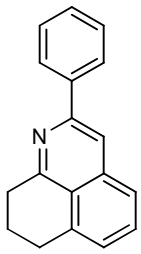
3ar, 59%



3as, 21%



3at, R = H, 75%
3au, R = Et, 83%
3av, R = n-Pr, 85%
3aw, R = i-Pr, 76%,
3ax, R = Bu, 84%
3ay, R = Ph, 75%



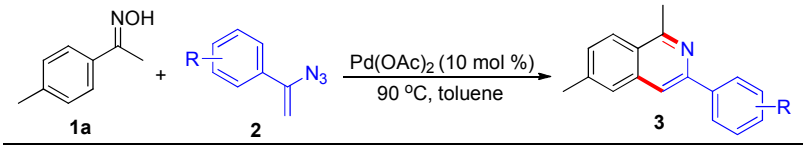
3az, 75%

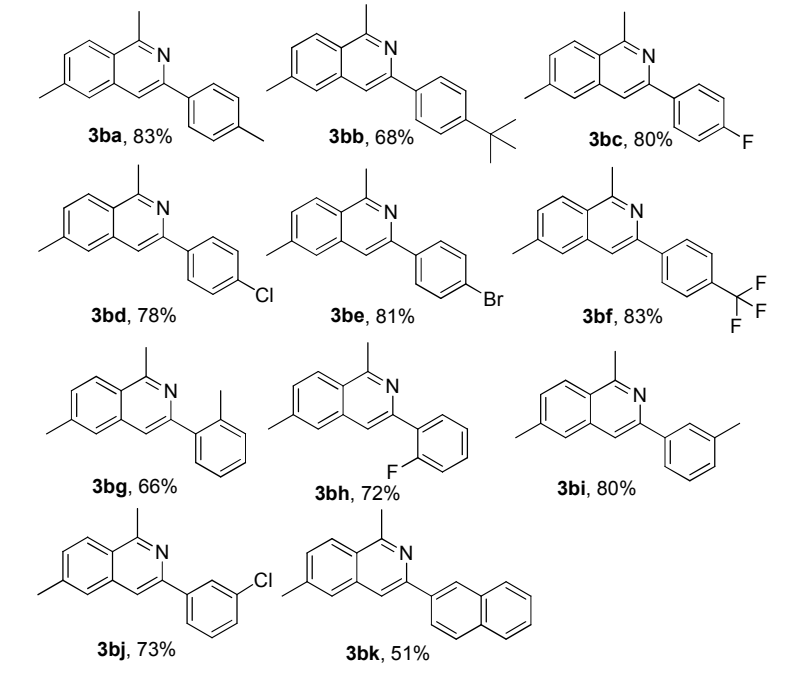
[a] Reactions were performed with **1** (0.3 mmol), **2a** (0.36 mmol), $Pd(OAc)_2$ (10 mol %) in 2 mL toluene at 90 °C for 8 h; Isolated yield was given. [b] 10 mol % $Zn(OTf)_2$ was added.

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.

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



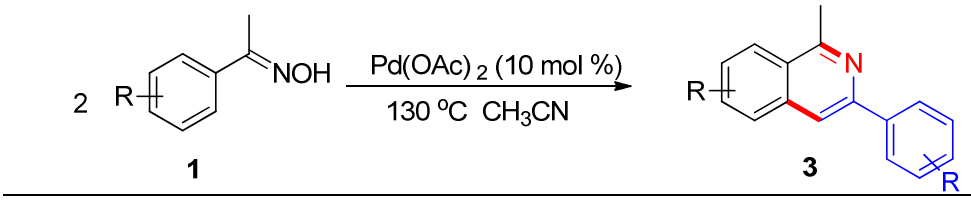


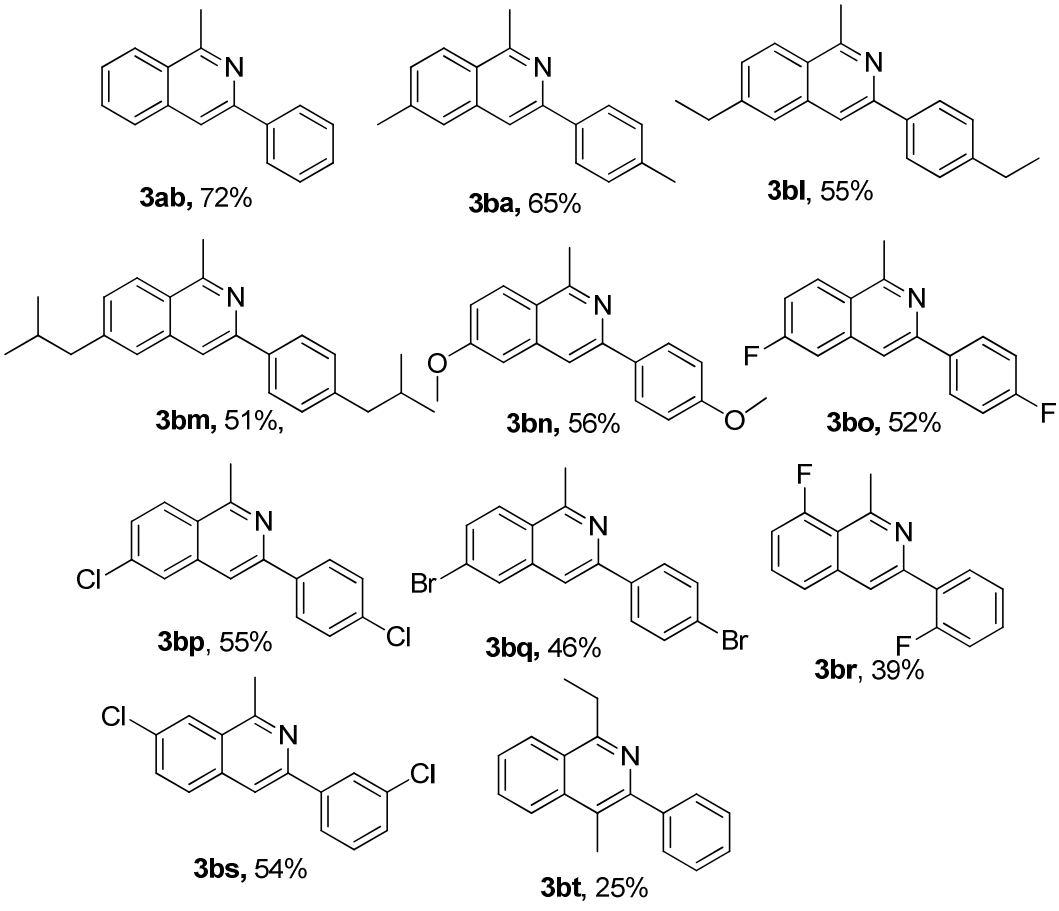
[a] Reactions were performed with **1a** (0.3 mmol), **2** (0.36 mmol), $Pd(OAc)_2$ (10 mol %) in 2 mL

toluene at 90 ^{o}C for 8 h; Isolated yield was given.

We also observed the formation of symmetrical isoquinoline **3** during the process of screening the optimal reaction condition, which might be derived from the oxidative homocoupling of **1.** Interestingly, when increasing the temperature to 130 ^{o}C and prolonging the reaction time 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 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.

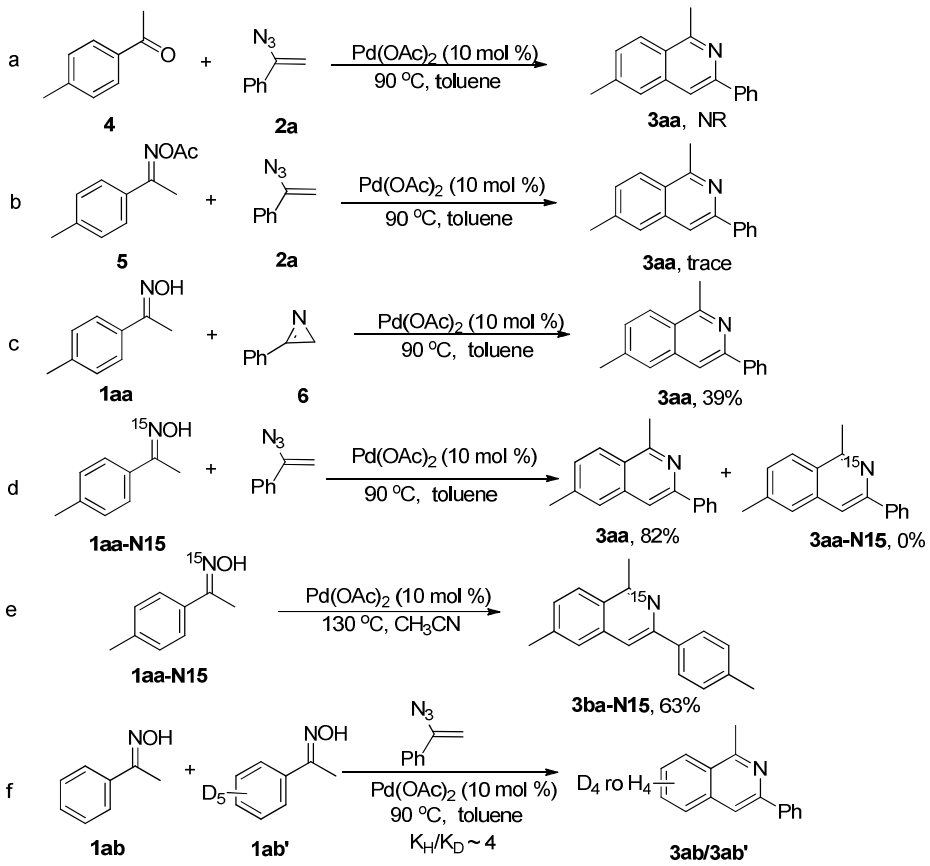
Table 4. Aryloximes Scope of Pd-Catalyzed Homocoupling [a]





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

Scheme 2. Mechanistic Studies

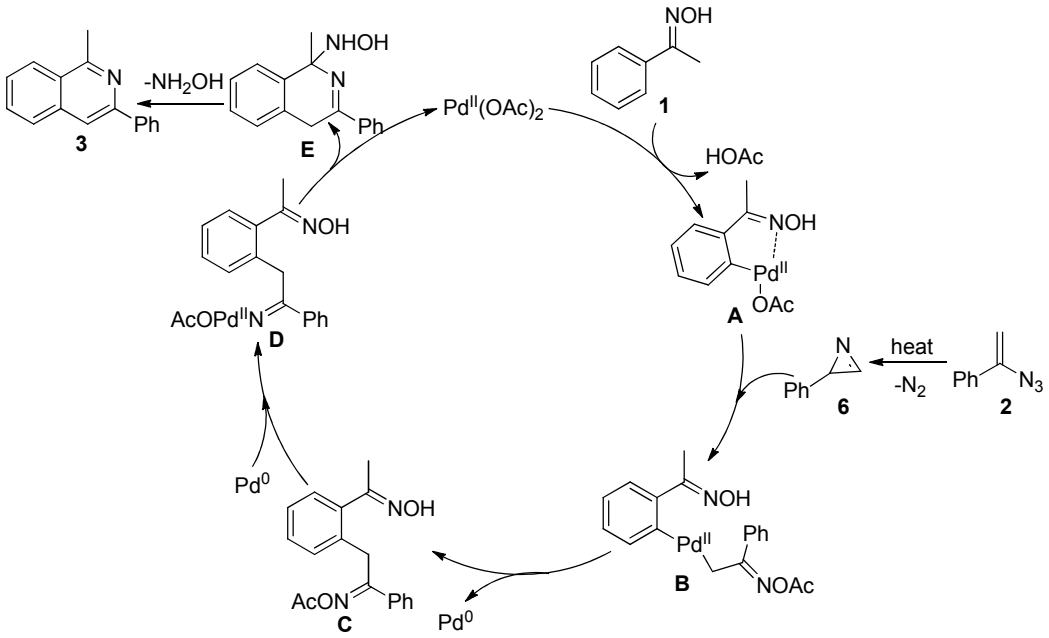


To get more insight into this transformation, a series of control experiments were conducted (Scheme 2). Under the standard conditions, the reaction of ketone **4** with **2a** did not give the target product **3aa** and similar results were observed when using the oxime ester **5** instead of **1a** (Scheme 2a, 4b). 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 into the standard conditions, no formation of ^{15}N-labeling 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. Firstly, an oxime directing *ortho*-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*-azirines **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**.

Scheme 3. Proposed Mechanism



In summary, we report 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 of additives, no toxic byproducts, as well as 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. ^{1}H 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 is solvent with TMS as the internal standard. IR spectra were obtained either as potassium bromide pellets or as liquid films between two potassium bromide pellets with a spectrometer. 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 the mixture of C_2H_5OH/H_2O (v/v = 1:1) was added hydroxylamine hydrochloride (2.2 mmol), NaOAc (3 mmol) in one portion, and the

reaction mixture was stirred at 100 ^{o}C (when the substrates are aromatic ketones) or at room temperature (when the substrates are 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 azidovinyl benzene: 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 minutes. After the reaction mixture was stirred at room temperature for 5 h, then diluted with water, the product was extracted with CH_2Cl_2. The organic layers were washed with saturated aq. $NaHCO_3$, $Na_2S_2O_3$, and brine. It was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give dibromide. To a solution of dibromide in dry DMF (20 mL) was added NaN_3 (15 mmol). The mixture was stirred for 24 h at room temperature, 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 get vinyl azides **2**. Their general information and analytical data could be obtained from literatures.[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]octan (0.2 mmol) in dry toluene (6 mL) was stirred at 110 ^{o}C for 50 minutes. Upon completion of the reaction

as indicated by TLC, the solvent was removed and concentrated under reduced pressure to give crude raffinate. The crude raffinate was purified by column chromatography using silica gel with eluent (petroleum ether: EtOAc = 10: 1) to afford azirines **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), azidovinyl benzene **2** (0.36 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), and 2 mL of dry toluene were added in a 10 mL screw-capped tube. The reaction vessel was closed with the cap and the reaction mixture was stirred at 90 ^{o}C (oil bath) for 8 h. The crude product was cooled to room temperature and concentrated in 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 added to a sealed tube under N_2. The reaction mixture was heated to 130 ℃ (oil bath) for 24 h. The crude product was cooled to room temperature and concentrated in vacuum to give a residue, which was purified by flash column chromatography to afford the isoquinoline products.

1,6-Dimethyl-3-phenylisoquinoline (3aa): 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] **:** 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): 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): 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}; ^1H 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): 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}, ^1H 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): as a yellow solid (65 mg, 73% yield); mp 130-132 ^oC; R_f = 0.5 (petroleum ether : EtOAc = 20 : 1); IR (KBr): 3450, 2922, 2375, 1661, 1567, 1397, 754, 691 cm^{-1}; ^1H 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): as a yellow solid (70 mg, 72% yield); mp 100-101 ^{o}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): as a yellow solid (54 mg, 68% yield); mp 93-94 ^{o}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):** as a light yellow solid (57 mg, 72% yield); mp 149-150 ^{o}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): 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}; ^1H 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): 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}; ^1H 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): 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}; ^1H 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.

1-Methyl-6-nitro-3-phenylisoquinoline (3am): as a yellow solid (23 mg, 29% yield); mp 121-123 ^oC; 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): 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): 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**): 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): as a white solid (63 mg, 85% yield); mp 98-99 ^oC; 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): as a yellow solid (48 mg, 59% yield); mp 108-110 ^oC; 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): 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, *2*H), 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 $C_{14}H_{12}N$ S$[M+H]^+$, 226.0685; found 226.0686.

3-Phenylisoquinoline (3at): 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): 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 (100MHz, $CDCl_3$) 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): 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}; ^{1}H 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): 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}, ^{1}H 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): 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}**,** ^{1}H 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] **:** 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}; ^{1}H 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-7*H*-benzo[*de*]quinoline (3az): 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}; ^{1}H 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] **:** as a yellow oil (62 mg, 83% yield); R_f = 0.55 (petroleum 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): 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) : as a white solid (60 mg, 80% yield); mp 73-74 ^oC; 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) : as a yellow solid (62 mg, 75%); mp 55-57 ^{o}C; R_f = 0.55 (petroleum ether : EtOAc = 20 : 1);IR (KBr): 3064, 2918, 1628, 1569, 1493, 1093, 830, 721 cm^{-1}; ^{1}H 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): as a white solid (76 mg, 81%); mp 103-105 ^{o}C; R_f = 0.5 (petroleum ether : EtOAc = 20 : 1); IR (KBr): 3065, 2918, 1627, 1568, 1491, 894, 828 cm^{-1}; ^{1}H 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): as a yellow solid (75 mg, 83%); mp 144-145 ^{o}C; R_f = 0.55 (petroleum ether : EtOAc = 20 : 1); IR (KBr): 3068, 2923, 1624, 1571, 1324, 1118, 844, 683 cm^{-1}; ^{1}H 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): as a yellow solid (49 mg, 66% yield); mp 90-91 ^oC; 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): as a yellow solid (54mg, 72%); mp 55-57 ^oC; 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): as a yellow solid (60 mg, 80%); mp 65-67 ^oC; 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): as a yellow solid (58mg, 73%); mp 86-88 ^{o}C; R_f = 0.55 (petroleum ether : EtOAc = 20 : 1); IR (KBr): 3067, 2956, 2854, 1587, 1485, 1385, 873, 756 cm^{-1}; ^{1}H 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): as a blue solid (43 mg, 51%); mp 63-65 ^{o}C; R_f = 0.5 (petroleum ether:EtOAc = 20:1); IR (KBr):2920, 2850, 1665, 1576, 1408, 811, 750, cm^{-1}; ^{1}H 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): 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};^{1}H 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): 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}; ^{1}H 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] **:** as a yellow solid (47 mg, 56%); mp 109-110 ^oC; R_f = 0.4 (petroleum ether : EtOAc = 20 : 1); IR (KBr): 3064, 2970, 1621, 1570, 1406, 1241, 878, 690 cm^{-1}; ^{1}H 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, 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]: as a blue solid (38 mg, 51%); mp 107-108 ^{o}C; R_f = 0.55 (petroleum ether : EtOAc = 20 : 1); IR (KBr): 2922, 1631, 1570, 1429, 1223, 845, 809 cm^{-1}, ^{1}H 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]**:** as a white solid (48mg, 55%); mp 107-109^{o}C; R_f = 0.6 (petroleum ether : EtOAc = 20 : 1); IR (KBr: 2920, 2851, 1605, 1562, 1484, 1405, 820, 754 cm^{-1}; ^{1}H 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]: as a blue solid (55 mg, 49%); mp 125-126 ^{o}C; R_f = 0.5 (petroleum ether : EtOAc = 20 : 1); IR (KBr): 2920, 2851, 1605, 1562, 1405, 820, 754 cm^{-1}; ^{1}H 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): as a blue solid (55mg, 49%); mp 45-46 ^{o}C; R_f = 0.6 (petroleum ether : EtOAc = 20 : 1); IR (KBr): 2968, 1624, 1572, 1411, 1019, 836, 765 cm^{-1}; ^{1}H 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) : as a white solid (46 mg, 54%); mp 107-109^{o}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): 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}; ^{1}H 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): (48 mg, 65%) R_f = 0.5 (petroleum ether : EtOAc = 20 : 1); ^{1}H 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: Under air atmosphere, **1ab** (0.3 mmol), **1ab'** (0.3 mmol), **2a** (0.3 mmol), $Pd(OAc)_2$ (10 mol %) in 2 mL toluene at 90 ^{o}C were allowed to react for 1.5 h. The crude product was cooled to room temperature and concentrated in 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 ^{1}H NMR analysis (see the Supporting Information for details). Compounds **3ab**/**3ab'**, ^{1}H 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.

Acknowledgements

We are grateful to the National Natural Science Foundation of China (21172076 and 21420102003) and the Fundamental Research Funds for the Central Universities (2015ZY001).

Supporting Information

Spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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