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Efficient synthesis of isoquinolines in water by a Pd-catalyzed tandem reaction of functionalized alkylnitriles with arylboronic acids†

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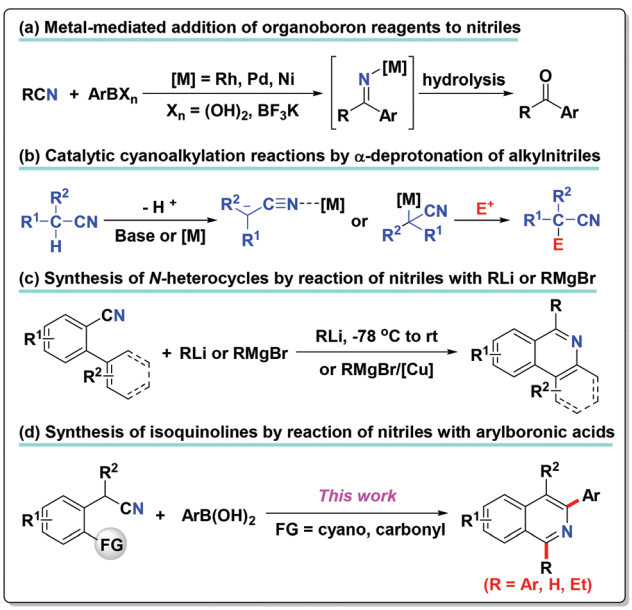
A palladium-catalyzed tandem reaction of 2-(cyanomethyl)benzonitriles or 2-(2-carbonylphenyl)acetonitriles with arylboronic acids in water has been developed for the first time. This reaction features good functional group tolerance and provides a new strategy for the synthesis of diverse isoquinolines under mild conditions. The use of water as the reaction medium makes the synthesis process environmentally benign. Preliminary mechanistic experiments indicate that the major reaction pathway involves carbopalladation of the C(sp^3)–cyano group and subsequent intramolecular cyclization findings that were further supported by density functional theory (DFT) calculations.

Introduction

Isoquinoline derivatives have become increasingly popular in the past few years because they are an important class of N-heterocycles with a wide range of molecules of biological and pharmaceutical relevance,[1] materials science fields[2] and ligands for metal catalysis.[3] A variety of synthetic strategies for the preparation of isoquinoline derivatives have been developed, which involve Bischler–Napieralski,[4] Pictet–Spengler,[5] and Pomeranz–Fritsch[6] protocols, among others.[7] However, less attention has been paid to the formation of isoquinolines from nitriles.

Transition-metal-catalyzed transformations of nitriles offer an attractive route for the creation of novel carbon–carbon and carbon–heteroatom bonds.[8] Larock's group has performed pioneering work in the development of the addition of arylpalladium species to the cyano group.[9] Since then, remarkable advances in this area have been documented by several other groups[10] including our group,[11] but this chemistry exclusively provides aryl ketone products (Scheme 1a). Compared to aromatic nitriles, nucleophilic addition reactions of aliphatic nitriles are limited by poor electrophilic activation that is insufficient to perform the addition. On the other hand, alkylnitriles are used as carbon pronucleophiles in carbon–carbon bond-forming reactions (Scheme 1b) in different modes of alkylnitrile activation, such as α-cyano carbanions or metalated nitriles,[12] making the addition reaction of aliphatic nitriles more difficult to perform than that of aromatic nitriles. Therefore, the development of a practical and general approach to isoquinolines using aliphatic nitriles as substrates remains a challenging area for exploration. Despite the preva-



Scheme 1 Reactions involving the participation of nitriles.

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lence of transformation of the cyano group into various functional groups, only sporadic examples of the tandem reaction for access to N-heterocycles initiated by the nucleophilic addition of an organometallic reagent were reported.[13,14] For example, the synthesis of isoquinolines or phenanthridines by the addition of organolithium reagents[13] and Grignard reagents[14] to the aromatic nitrile carbons, respectively, was reported (Scheme 1c).

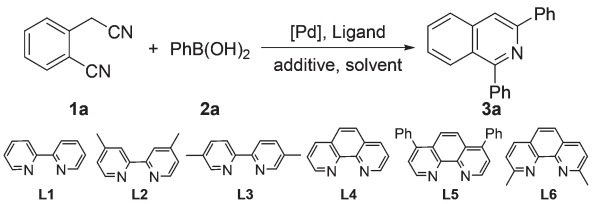
Compared with Grignard reagents and organolithium reagents, organoboron reagents[15] hold great promise due to low toxicity and ease of handling, stability under atmospheric conditions and good functional group tolerance. To our knowledge, there are no studies in the literature that report the synthesis of isoquinolines by the tandem reaction of aliphatic nitriles with organoboron reagents.[16] Additionally, water as the reaction medium has recently attracted considerable attention in organic synthesis due to its environmental acceptability, abundance, safety and low cost, and would thus be highly advantageous alternatives to organic solvents from both economical and ecological standpoints.[17]

As part of the continuing efforts in our laboratory toward the development of novel transition metal-catalyzed coupling reactions with organoboron reagents,[18] and the synthesis of N-heterocycles,[19] we herein report a palladium-catalyzed tandem reaction of functionalized alkylnitriles with arylboronic acids in water to afford symmetrical or unsymmetrical 1,3-diarylisoquinolines and 3-arylisoquinolines (Scheme 1d). Facile access to such ring systems which possess diverse functional groups would be of high value to both synthetic and medicinal chemistry.

Results and discussion

Initially, the readily available 2-(cyanomethyl)benzonitrile (**1a**) and phenylboronic acid (**2a**) were chosen as model substrates and extensive investigations were carried out to define the optimal reaction conditions. As shown in Table 1, no target product was detected with $Pd(acac)_2$/**L1**/trifluoroacetic acid (TFA) using absolute ethanol as a solvent (entry 1). However, a trace amount of the desired 1,3-diphenylisoquinoline (**3a**) was detected by GC-MS when 95% ethanol was used as the solvent (entry 2), indicating that the presence of H_2O improved both the reaction yield and total mass balance (entries 3 and 4). Interestingly, further investigation of the effect of solvent revealed that the yield of the 1,3-diphenylisoquinoline (**3a**) was greatly increased to 77% in water (entries 3–5). The role of the water in the reaction is not clear. Water is known to be a unique ligand in many useful palladium transformations.[20] Control experiments in the absence of additives showed that no desired product was observed (entry 6). The observed dramatic impact of TFA on this reaction prompted us to further test a variety of additives (entries 7–11). Replacement of TFA with other acids, including HCl, acetic acid and trifluoromethanesulfonic acid (TfOH) resulted in little or no desired product **3a** (entries 7–9). We were delighted to find that the yield of **3a** could be improved to 92% yield when the combination of $Pd(acac)_2$, 2,2′-bipyridine, and *p*-toluenesulfonic acid monohydrate ($TsOH{\cdot}H_2O$) was employed in water (entry 10). Reducing $TsOH{\cdot}H_2O$ to 2 equiv. resulted in lower yield. The use of *p*-nitrobenzenesulfonic acid (NsOH) as the additive provided a comparable yield (85%) of **3a** (entry 11). It is well known that organic ligands play crucial roles in transition metal-catalyzed organic reactions. Among bidentate nitrogen ligands (**L1–L6**), 2,2′-bipyridine was found to efficiently promote the reaction and afforded the product in 92% yield (entries 12–16). In contrast, this reaction did not work using steric ligands such as 2,9-dimethyl-1,10-phenanthroline (**L6**) as a ligand (entry 16). Finally, a brief screen of palladium sources showed that commonly used palladium catalysts affected the yields of the reaction to some extent (entries 17–21). $Pd(acac)_2$ exhibited the highest catalytic reactivity with 92% yield (entry 10), but $Pd(PPh_3)_4$ did not work in this reaction (entry 21). No desired product was observed if either $Pd(acac)_2$ or ligand was absent (entries 23 and 24).

Table 1 Optimization of the reaction conditions[a]



Entry	[Pd]	Ligand	Additive	Solvent	Yield[b] (%)
1	$Pd(acac)_2$	**L1**	TFA	Absolute EtOH	0
2	$Pd(acac)_2$	**L1**	TFA	$EtOH/H_2O$	Trace[c]
3	$Pd(acac)_2$	**L1**	TFA	THF/H_2O	Trace[d]
4	$Pd(acac)_2$	**L1**	TFA	$Toluene/H_2O$	23[d]
5	$Pd(acac)_2$	**L1**	TFA	H_2O	77
6	$Pd(acac)_2$	**L1**		H_2O	0
7	$Pd(acac)_2$	**L1**	HCl	H_2O	0
8	$Pd(acac)_2$	**L1**	AcOH	H_2O	9
9	$Pd(acac)_2$	**L1**	TfOH	H_2O	0
10	**$Pd(acac)_2$**	**L1**	**$TsOH{\cdot}H_2O$**	**H_2O**	**92** (53)[e]
11	$Pd(acac)_2$	**L1**	NsOH	H_2O	85
12	$Pd(acac)_2$	**L2**	$TsOH{\cdot}H_2O$	H_2O	61
13	$Pd(acac)_2$	**L3**	$TsOH{\cdot}H_2O$	H_2O	74
14	$Pd(acac)_2$	**L4**	$TsOH{\cdot}H_2O$	H_2O	85
15	$Pd(acac)_2$	**L5**	$TsOH{\cdot}H_2O$	H_2O	69
16	$Pd(acac)_2$	**L6**	$TsOH{\cdot}H_2O$	H_2O	0
17	$Pd(OAc)_2$	**L1**	$TsOH{\cdot}H_2O$	H_2O	77
18	$PdCl_2$	**L1**	$TsOH{\cdot}H_2O$	H_2O	63
19	$Pd(CF_3CO_2)_2$	**L1**	$TsOH{\cdot}H_2O$	H_2O	74
20	$Pd(dba)_2$	**L1**	$TsOH{\cdot}H_2O$	H_2O	65
21	$Pd(PPh_3)_4$	**L1**	$TsOH{\cdot}H_2O$	H_2O	0
22	$Pd(acac)_2$	**L1**	$TsOH{\cdot}H_2O$	H_2O	81[f]
23		**L1**	$TsOH{\cdot}H_2O$	H_2O	0
24	$Pd(acac)_2$		$TsOH{\cdot}H_2O$	H_2O	0

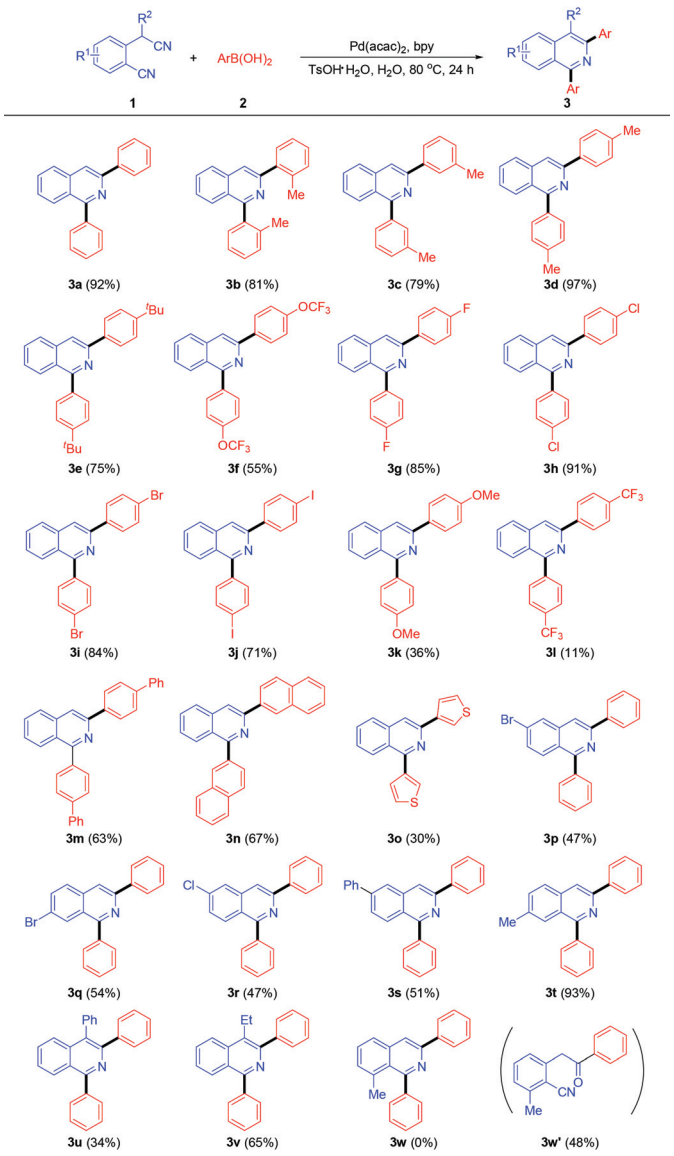
[a] Conditions: **1a** (0.4 mmol), **2a** (1.6 mmol), indicated Pd source (5 mol%), ligand (10 mol%), additive (10 equiv.), solvent (2 mL), 80 °C, 24 h, air. [b] Isolated yield. [c] 95% EtOH/5% H_2O. [d] THF or toluene (1.8 mL)/H_2O (0.2 mL). [e] $TsOH{\cdot}H_2O$ (2 equiv.). [f] $Pd(acac)_2$ (2.5 mol%) and **L1** (5 mol%).

Having the optimized reaction conditions in hand, the substrate scope of the tandem addition cyclization reaction was investigated (Table 2). Initially, the reactivities of *para*-, *meta*-, and *ortho*-tolylboronic acid were evaluated, and the results demonstrated that the steric effects of substituents had some effects on the reaction. For example, the tandem reaction of **1a** with *para*-tolylboronic acid gave 97% yield of **3d**, while the *ortho*- and *meta*-tolylboronic acid afforded the desired products with diminished yields of 81% and 79% (**3b** and **3c**). As shown in Table 2, not only electron-donating groups, such as methyl (**3b–3d**), tertiary butyl (**3e**), and trifluoromethoxy (**3f**), but also electron-withdrawing groups, such as fluoro (**3g**), chloro (**3h**), bromo (**3i**) and iodo (**3j**) on the phenyl ring of the arylboronic acids at the *para* position, were tolerated in this transformation, achieving moderate to good yields, which indicated that the electronic effects of substituents affected the reactivity to some extent. Both strongly electron-donating (*e.g.*, –OMe) and electron-withdrawing (*e.g.*, $-CF_3$) groups were compatible with this reaction, affording the corresponding products **3k** and **3l** in 36% and 11% yields, respectively. Biarylboronic acids, such as 4-phenylphenylboronic acid and 2-naphthylboronic acid also gave the desired products in 63% and 67% yields, respectively (**3m** and **3n**). In transition metal-catalyzed reactions, any nitrogen or sulphur atoms present in heterocyclic substrates will coordinate strongly with metal catalysts. Although this coordination can lead to palladium catalyst poisoning, we found that thiophen-3-ylboronic acid was successfully used as a reaction partner, albeit in lower yield (**3o**).

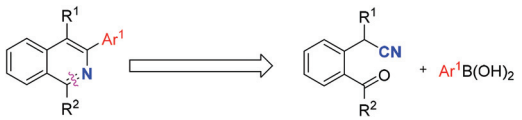
We next turned our attention to the effect of the reactions of various 2-(cyanomethyl)benzonitriles with **2a** under the standard conditions (**3p–3w**). First, the electronic properties of substituents on the phenyl ring moiety of 2-(cyanomethyl) benzonitriles had obvious effects on the reactivity. In general, substrates bearing an electron-donating substituent (*e.g.*, –Me) (**3t**) produced a higher yield than those analogues bearing an electron-withdrawing substituent (*e.g.*, –Br, –Cl, –Ph) (**3p–3s**). For example, treatment of **2a** with 2-(cyanomethyl)-5-methylbenzonitrile afforded **3t** in 93% yield, while the yield of **3q** was decreased to 54% with 5-bromo-2-(cyanomethyl)benzonitrile. Bromo (**3p** and **3q**) and chloro (**3r**) groups on the aryl ring are also amenable to further synthetic elaborations. The α-substituted substrates, such as 2-(1-cyanopropyl)benzonitrile reacted to give **3v** in a respectable yield of 65%, but phenyl substitution in the reaction partner decreased the yield to only 34% (**3u**). Finally, we examined the reaction of 2-(cyanomethyl)-6-methylbenzonitrile with **2a** under the standard conditions. 2-Methyl-6-(2-oxo-2-phenylethyl)benzonitrile (**3w′**) was obtained in 48% yield instead of the desired product 8-methyl-1,3-diphenylisoquinoline (**3w**), suggesting that the steric effects of the *ortho*-substituent had effects on the reaction.

On the other hand, the retrosynthesis of isoquinolines revealed that it could be performed with 2-(2-carbonylphenyl) acetonitriles and arylboronic acids *via* carbopalladation of the cyano group and subsequent intramolecular cyclization (Scheme 2). Thus, we investigated the palladium-catalyzed tandem reaction of 2-(2-carbonylphenyl)acetonitriles with arylboronic acids to test the feasibility of preparing a variety of unsymmetrical 1,3-diarylisoquinolines or 3-arylisoquinolines (Table 3).

Table 2 Synthesis of 1,3-diaryl isoquinolines *via* Pd-catalyzed tandem reaction of 2-(cyanomethyl)benzonitriles with arylboronic acids[a]

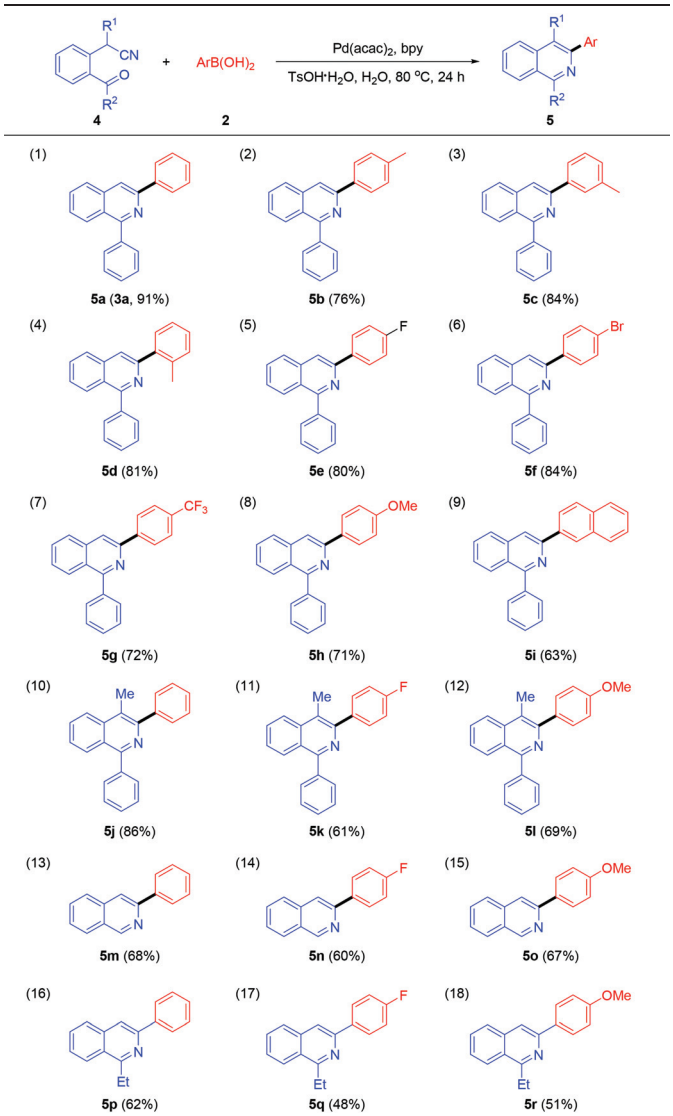


[a] Conditions: **1** (0.4 mmol), **2** (1.6 mmol), $Pd(acac)_2$ (5 mol%), bpy (10 mol%), $TsOH{\cdot}H_2O$ (10 equiv.), H_2O (2 mL), 80 °C, 24 h, air. Isolated yield.



Scheme 2 Retrosynthesis of isoquinolines.

Table 3 Synthesis of unsymmetrical 1,3-disubstituted isoquinolines *via* Pd-catalyzed tandem reaction of 2-(2-carbonylphenyl)acetonitriles with arylboronic acids[a]

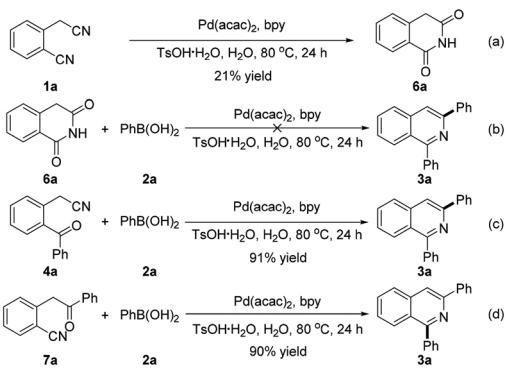


[a] Conditions: **4** (0.4 mmol), **2** (1.2 mmol), $Pd(acac)_2$ (5 mol%), bpy (10 mol%), $TsOH{\cdot}H_2O$ (10 equiv.), H_2O (2 mL), 80 °C, 24 h, air. Isolated yield.

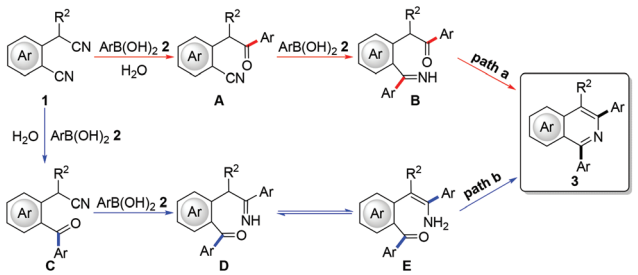
Delightfully, treatment of 2-(2-benzoylphenyl)acetonitrile (**4a**) with **2a** under the standard conditions afforded the desired product **5a** in 91% yield (entry 1). We were pleased to find that *para*-, *meta*-, and even sterically hindered *ortho*-substituted boronic acids (**5b–5d**, 76–84% yield) can all be effectively coupled (entries 2–4). The protocol is tolerant of a broad range of arylboronic acids bearing both electron-donating substituent (*e.g.*, –Me, –OMe, entries 2–4 and 8) and electron-withdrawing substituent (*e.g.*, –F, –Br, $–CF_3$, entries 5–7). For example, (4-(trifluoromethyl)phenyl)boronic acid and (4-methoxyphenyl)boronic acid gave the corresponding products **5g** and **5h** in 72% and 71% yields, respectively (entries 7 and 8), suggesting that the electronic effects of the substituents had no obvious impact on the reactivity. Moderate yield of **5i** was observed when 2-naphthylboronic acid was used as a substrate (entry 9). The α-substituted substrates, such as 2-(2-benzoylphenyl)propanenitrile was amenable to the reaction conditions, affording the desired products **5j–5l** in 86%, 61% and 69% yields, respectively (entries 10–12). The substrate 2-(2-formylphenyl)acetonitrile bearing a formyl group reacted with arylboronic acids to give monosubstituted isoquinolines (**5m–5o**) in moderate yields (entries 13–15). Finally, the scope of the tandem reaction for the synthesis of 1-alkyl-3-arylisoquinolines was also examined. Treatment of 2-(2-propionylphenyl)acetonitrile with arylboronic acids proceeded to give the desired products **5p–5r** in 48–62% yields (entries 16–18).

To elucidate the reaction mechanism of the formation of isoquinolines, some control experiments were performed under the standard conditions as shown in Scheme 3. We found that isoquinoline-1,3(2*H*,4*H*)-dione (**6a**) was obtained in 21% yield when phenylboronic acid (**2a**) was absent (Scheme 3a). However, the reaction failed to deliver the desired product **3a** when **6a** was treated with **2a** (Scheme 3b). Treatment of 2-(2-benzoylphenyl)acetonitrile (**4a**) with **2a** provided the desired product **3a** in 91% yield (Scheme 3c). Additionally, we found that **3a** was also obtained in excellent yield when the reaction of 2-(2-oxo-2-phenylethyl)benzonitrile (**7a**) with **2a** was performed (Scheme 3d). These results indicated that **4a** or **7a** was proposed as a possible intermediate for the transformation.

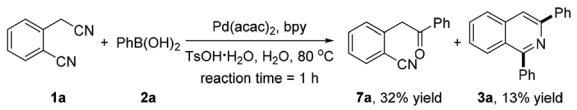
On the basis of the above experimental results and relevant reports in the literature, we proposed two possible reaction pathways for the formation of isoquinolines (Scheme 4). In path a, intermediate **A** is formed from the addition and hydrolysis reactions between the $C(sp^3)$–cyano group and arylboronic acids **2**. The $C(sp^2)$-cyano group of the intermediate **A** can then react with arylboronic acids **2** to give an imine intermediate **B**, which after intramolecular cyclization generates isoquinolines **3** as the desired products. In path b, the first step may involve the addition and hydrolysis reactions of the $C(sp^2)$–cyano group with arylboronic acids **2** leading to intermediate **C**. Next, further addition reaction between the $C(sp^3)$–CN of intermediate **C** with arylboronic acids **2** generates an imine intermediate **D**. Imine–enamine tautomerism of intermediate **D** affords



Scheme 3 Control experiments.



Scheme 4 Plausible reaction pathways.

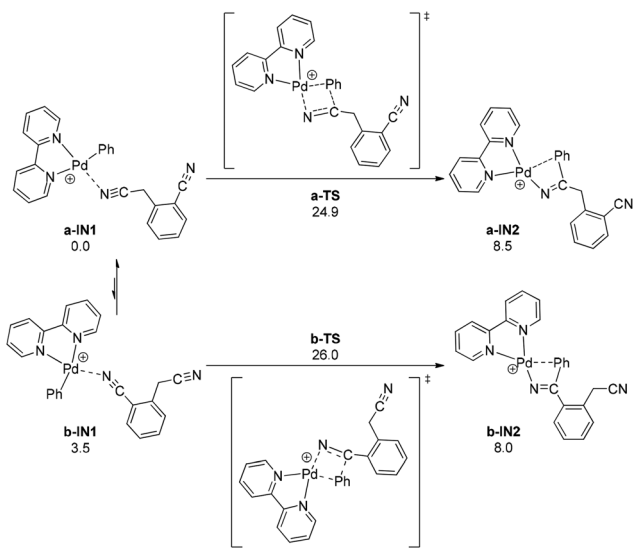


Scheme 5 Control experiment.

intermediate **E**, which undergoes an intramolecular cyclization to deliver isoquinolines **3** as the desired products.

A further experiment was performed to gain insight into the reactivity of the C(sp^3)–cyano group (path a) and the C(sp^2)–cyano group (path b) in this transformation. When the reaction time was shortened to one hour, we were delighted to find that the ketone intermediate **7a** was isolated in 32% yield, accompanied by 13% yield of **3a** (Scheme 5). The results suggested that the reactivity of the C(sp^3)–cyano group is more favourable than the C(sp^2)–cyano group in these palladium-catalyzed nucleophilic addition reactions.

Preliminary DFT calculations at the M06/6-311+G(d,p)/SDD//B3LYP/6-31G(d)/LANL2DZ level of theory were carried to shed some light on the above mechanism (Scheme 6). According to preceding experimental and theoretical studies,[21]



Scheme 6 Preliminary DFT results (relative free energies are in kcal mol^{-1}).

cationic intermediates **a-IN1** and **b-IN1** could be involved in the current transformation, and calculations show that the former one is about 3.5 kcal mol^{-1} lower in energy. From these two intermediates, the arylation of different cyano groups may occur *via* **a-TS** and **b-TS** with activation barriers of 24.9 and 26.0 kcal mol^{-1}, respectively, generating arylation intermediates **a-IN2** and **b-IN2**. Thus, arylation at the C(sp^3)–cyano moiety is 1.1 kcal mol^{-1} more kinetically favorable, being in qualitative agreement with the control experiments (Scheme 5). The higher energy of **b-TS** could be attributed to the steric effects between the two phenyl groups.

Conclusions

In summary, we have developed an alternative synthetic pathway to access diverse isoquinolines in moderate to excellent yields *via* palladium-catalyzed tandem addition/cyclization of functionalized nitriles with arylboronic acids. Control experiments clearly indicate that the major reaction pathway involves carbopalladation of the C(sp^3)–cyano group and subsequent intramolecular cyclization findings that were further supported by density functional theory (DFT) studies. Further studies to extend this catalytic system to the preparation of other useful heterocyclic compounds are currently underway in our laboratories.

Experimental section

General methods

All reagents were commercially available and used without further purification unless otherwise noted. Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 500 MHz spectrometer using DMSO-d_6 or $CDCl_3$ as the solvent with tetramethylsilane (TMS) as an internal standard at room temperature. Chemical shifts are given in δ relative to TMS, and the coupling constants J are given in hertz. High-resolution mass spectrometry (HRMS) was performed with a TOF MS instrument with an EI or ESI source. 2-(2-Carbonylphenyl)acetonitriles were synthesized according to the method described in the literature.[22] Other commercially obtained reagents were used without further purification. Column chromatography was performed using EM silica gel 60 (300–400 mesh). All DFT studies were carried out by running Gaussian 09.[23] The geometric structures were fully optimized by the B3LYP/6-31G(d)/LANL2DZ method and frequency calculations were done with the same method. The solvation effects of water were included by single point calculations with M06/6-311+G(d,p)/SDD, and all energies given are relative solvation free energies.

General procedure for the synthesis of isoquinolines *via* Pd-catalyzed tandem reaction of 2-(cyanomethyl)benzonitriles with arylboronic acids

2-(Cyanomethyl)benzonitriles **1** (0.4 mmol), arylboronic acid **2** (1.6 mmol), $Pd(acac)_2$ (5 mol%), bpy (10 mol%), TsOH·H_2O

(10 equiv.), and H_2O (2 mL) were successively added into a Schlenk reaction tube in air. The reaction mixture was stirred for 10 minutes at room temperature for proper mixing of the reactants, and then heated at 80 °C with vigorous stirring for 24 hours. After reaching the reaction equilibrium, the mixture was poured into ethyl acetate, which was washed with saturated $NaHCO_3$ (2 × 10 mL) and then brine (10 mL). After the aqueous layer was extracted with ethyl acetate, the combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified by flash column chromatography (hexane/ethyl acetate) to afford the desired products **3a–3w′**.

1,3-Diphenylisoquinoline (3a). Pale-yellow solid (103.5 mg, 92%), mp 78–79 °C (lit.[24] 73–74.5 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25–8.23 (m, 2H), 8.15–8.14 (m, 1H), 8.09 (s, 1H), 7.95–7.93 (m, 1H), 7.84–7.83 (m, 2H), 7.70–7.67 (m, 1H), 7.59–7.50 (m, 6H), 7.44–7.40 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.5, 150.3, 140.1, 139.8, 138.0, 130.4, 130.2, 128.8, 128.7, 128.6, 128.4, 127.7, 127.6, 127.2, 127.0, 126.0, 115.8.

1,3-Di-*o*-tolylisoquinoline (3b). Pale-yellow liquid (99.9 mg, 81%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92–7.91 (m, 1H), 7.76 (s, 1H), 7.72–7.67 (m, 2H), 7.54–7.47 (m, 2H), 7.40–7.28 (m, 7H), 2.44 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.0, 153.1, 140.9, 139.2, 137.0, 136.6, 136.4, 130.8, 130.4, 130.2, 129.9, 128.5, 128.1, 127.7, 127.2, 127.1, 126.2, 126.0, 119.6, 115.9, 20.7, 20.1. IR (KBr): 3056, 2923, 2857, 2356, 1615, 1565, 1494, 1446, 1382, 1334, 896, 761, 692, 528 cm^{-1}. HRMS (EI, 70 eV) calcd for $C_{23}H_{19}N$ [M^+]: 309.1517, found 309.1517.

1,3-Di-*m*-tolylisoquinoline (3c). Pale-yellow liquid (98.1 mg, 79%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12–7.92 (m, 5H), 7.70–7.57(m, 3H), 7.52–7.32 (m, 4H), 7.23–7.21 (m, 1H), 2.49 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.7, 150.5, 140.0, 139.8, 138.3, 138.1, 137.9, 130.9, 130.0, 129.4, 129.3, 128.7, 128.2, 128.0, 127.7, 127.5, 127.4, 126.8, 126.0, 124.4, 115.8, 21.7, 21.6. IR (KBr): 3054, 2921, 2857, 1614, 1563, 1492, 1446, 1384, 1334, 887, 798, 773, 696, 528 cm^{-1}. HRMS (ESI) calcd for $C_{23}H_{20}N^+$ [M + H]$^+$: 310.1590, found 310.1600.

1,3-Di-*p*-tolylisoquinoline (3d). Pale-yellow liquid (120.1 mg, 97%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15–8.11 (m, 3H), 8.03 (s, 1H), 7.92–7.90 (m, 1H), 7.72–7.65 (m, 3H), 7.50–7.47 (m, 1H), 7.38–7.36 (m, 2H), 7.31–7.29 (m, 2H), 2.48 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.4, 150.3, 138.6, 138.5, 138.0, 137.2, 137.0, 130.3, 130.0, 129.5, 129.1, 127.8, 127.5, 127.1, 126.7, 125.8, 115.1, 21.5, 21.4.

1,3-Bis(4-(*tert*-butyl)phenyl)isoquinoline (3e). Pale-yellow solid (118.1 mg, 75%), mp 125–127 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20–8.14 (m, 3H), 8.03 (s, 1H), 7.93–7.91 (m, 1H), 7.78–7.76 (m, 2H), 7.68–7.65 (m, 1H), 7.59–7.57 (m, 2H), 7.53–7.48 (m, 3H), 1.43 (s, 9H), 1.38 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.4, 151.7, 151.6, 150.4, 138.0, 137.2, 137.1, 130.1, 130.0, 127.9, 127.5, 127.0, 126.7, 125.8, 125.7, 125.4, 115.2, 34.9, 34.8, 31.6, 31.5. IR (KBr): 3430, 2956, 2364, 1614, 1375, 1261, 1110, 840, 755, 684, 563 cm^{-1}. HRMS (EI, 70 eV) calcd for $C_{29}H_{31}N$ [M^+]: 393.2457, found 393.2460.

1,3-Bis(4-(trifluoromethoxy)phenyl)isoquinoline (3f). Pale-yellow solid (98.1 mg, 55%), mp 108–109 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23–8.22 (m, 2H), 8.10–8.06 (m, 2H), 7.96–7.94 (m, 1H), 7.85–7.83 (m, 2H), 7.73–7.71 (m, 1H), 7.58–7.55 (m, 1H), 7.43–7.41 (m, 2H), 7.36–7.34 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 149.8, 149.0, 138.5, 138.2, 138.0, 131.8, 130.6, 128.6, 127.8, 127.6, 127.3, 123.8, 123.7, 121.8, 121.7, 121.3, 120.9, 119.7, 119.6, 117.7, 117.6, 116.2. IR (KBr): 3442, 3070, 2356, 1614, 1567, 1508, 1294, 1211, 1157, 848, 682, 532 cm^{-1}. HRMS (EI, 70 eV) calcd for $C_{23}H_{13}F_6NO_2$ [M^+]: 449.0850, found 449.0854.

1,3-Bis(4-fluorophenyl)isoquinoline (3g). Pale-yellow solid (107.6 mg, 85%), mp 115–116 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20–8.17 (m, 2H), 8.09–8.08 (m, 1H), 8.02 (s, 1H), 7.94–7.92 (m, 1H), 7.80–7.78 (m, 2H), 7.72–7.68 (m, 1H), 7.55–7.52 (m, 1H), 7.27–7.24 (m, 5H), 7.20–7.16 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.5, 164.3, 162.5, 162.4, 159.5, 149.3, 138.0, 136.0, 135.9, 135.8, 135.7, 132.1, 132.0, 130.4, 128.9, 128.8, 127.6, 127.4, 127.3, 125.8, 115.8, 115.6, 115.5, 115.4. IR (KBr): 3438, 3062, 2360, 1606, 1509, 1226, 831, 746, 526 cm^{-1}. HRMS (EI, 70 eV) calcd for $C_{21}H_{13}F_2N$ [M^+]: 317.1016, found 317.1013.

1,3-Bis(4-chlorophenyl)isoquinoline (3h). Pale-yellow solid (126.9 mg, 91%), mp 150–151 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15–8.13 (m, 2H), 8.08–8.06 (m, 2H), 7.95–7.93 (m, 1H), 7.76–7.69 (m, 3H), 7.56–7.53 (m, 3H), 7.48–7.45 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 149.1, 138.3, 138.0, 137.9, 135.1, 134.8, 131.6, 130.5, 129.0, 128.7, 128.4, 127.7, 127.5, 127.3, 125.9, 115.9. IR (KBr): 3438, 3060, 2358, 1556, 1490, 1378, 1334, 1091, 827, 748, 520 cm^{-1}. HRMS (EI, 70 eV) calcd for $C_{21}H_{13}Cl_2N$ [M^+]: 349.0425, found 349.0423.

1,3-Bis(4-bromophenyl)isoquinoline (3i). Pale-yellow solid (146.7 mg, 84%), mp 167–168 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09–8.07 (m, 4H), 7.95–7.93 (m, 1H), 7.72–7.67 (m, 5H), 7.63–7.61 (m, 2H), 7.56–7.53 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 149.2, 138.7, 138.4, 138.0, 132.0, 131.9, 131.7, 130.5, 128.7, 127.7, 127.6, 127.3, 125.9, 123.3, 123.1, 116.0. IR (KBr): 3448, 3068, 3052, 2360, 2341, 1556, 1486, 1380, 1334, 1008, 825, 746, 520 cm^{-1}. HRMS (EI, 70 eV) calcd for $C_{21}H_{13}Br_2N$ [M^+]: 436.9415, found 436.9417.

1,3-Bis(4-iodophenyl)isoquinoline (3j). Pale-yellow solid (150.6 mg, 71%), mp 173–174 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08–8.07 (m, 2H), 7.95–7.90 (m, 5H), 7.83–7.81 (m, 2H), 7.72–7.69 (m, 1H), 7.55–7.53, (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5, 149.2, 139.3, 139.0, 138.0, 137.9, 137.7, 132.1, 130.5, 128.9, 127.8, 127.6, 127.3, 125.8, 116.0, 95.2, 94.9. IR (KBr): 3426, 3056, 2364, 1556, 1484, 1384, 1332, 1002, 746, 522 cm^{-1}. HRMS (EI, 70 eV) calcd for $C_{21}H_{13}I_2N$ [M^+]: 532.9137, found 532.9134.

1,3-Bis(4-methoxyphenyl)isoquinoline (3k). Pale-yellow solid (48.8 mg, 36%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20–8.15 (m, 3H), 7.96 (s, 1H), 7.88 (d, J = 8.5 Hz, 1H), 7.79 (d, J = 8.5 Hz, 2H), 7.64 (t, J = 7.5 Hz, 1H), 7.47 (t, J = 7.5 Hz, 1H), 7.10 (d, J = 8.0 Hz, 2H), 7.03 (d, J = 8.5 Hz, 2H), 3.92 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.2, 160.1, 159.8, 149.9, 138.1, 132.6, 132.4, 131.6, 129.9, 128.3, 127.6, 127.3, 126.4, 125.5, 114.2, 114.1, 113.8, 55.43, 55.38.

1,3-Bis(4-(trifluoromethyl)phenyl)isoquinoline (3l). Pale-yellow solid (19.1 mg, 11%), mp 105–106 °C. ^{1}H NMR

(500 MHz, $CDCl_3$) δ 8.32–8.31 (m, 2H), 8.17 (s, 1H), 8.08–8.06 (m, 1H), 8.01–7.99 (m, 1H), 7.94–7.90 (m, 2H), 7.85–7.83 (m, 2H), 7.80–7.74 (m, 3H), 7.61–7.58 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 148.7, 143.1, 142.6, 137.1, 131.0, 130.6, 130.54 (q, J = 44 Hz), 130.5, 127.8, 127.3, 127.0, 126.9 (q, J = 244 Hz), 125.7 (q, J = 4 Hz), 125.4 (q, J = 4 Hz), 125.3, 123.2, 123.1, 117.3. IR (KBr): 3442, 3064, 2356, 1617, 1565, 1326, 1168, 1106, 840, 682 cm^{-1}. HRMS (EI, 70 eV) calcd for $C_{23}H_{13}F_6N$ [M$^+$]: 417.0952, found 417.0951.

1,3-Di([1,1′-biphenyl]-4-yl)isoquinoline (3m). Pale-yellow solid (108.7 mg, 63%), mp 161–162 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35–8.33 (m, 2H), 8.24–8.22 (m, 1H), 8.14 (s, 1H), 7.97–7.93 (m, 3H), 7.82–7.81 (m, 2H), 7.77–7.69 (m, 7H), 7.57–7.47 (m, 5H), 7.43–7.37 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.2, 150.0, 141.7, 141.4, 141.0, 140.9, 140.0, 138.7, 128.1, 130.8, 130.3, 129.0, 128.9, 127.7, 127.6, 127.5, 127.4, 127.3 127.2, 127.1 127.0, 126.0, 115.7. IR (KBr): 3424, 3031, 1556, 1482, 1380, 1332, 840, 761, 690, 514 cm^{-1}. HRMS (EI, 70 eV) calcd for $C_{33}H_{23}N$ [M$^+$]: 433.1830, found 433.1823.

1,3-Di(naphthalen-2-yl)isoquinoline (3n). Pale-yellow solid (102.2 mg, 67%), mp 105–106 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.78 (s, 1H), 8.39–8.37 (m, 1H), 8.32 (s,1H), 8.26 (s, 1H), 8.22–8.20 (m, 1H), 8.08–8.07 (m, 1H), 8.03–7.98 (m, 6H), 7.90–7.88 (m, 1H), 7.74–7.71 (m, 1H), 7.61–7.50 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.6, 150.2, 138.1, 137.4, 137.0, 133.9, 133.7, 133.6, 133.3, 130.3, 129.8, 128.9, 128.7, 128.5, 128.2, 128.1, 127.9, 127.8, 127.7, 127.2, 126.7, 126.5, 126.4, 126.3, 126.2, 125.0, 116.2. IR (KBr): 3436, 3046, 1560, 809, 740, 470 cm^{-1}. HRMS (EI, 70 eV) calcd for $C_{29}H_{19}N$ [M$^+$]: 381.1517, found 381.1519.

1,3-Di(thiophen-3-yl)isoquinoline (3o). Brown liquid (35.0 mg, 30%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31–8.29 (m, 1H), 8.10–8.09 (m, 1H), 7.89–7.87 (m, 2H), 7.80–7.79 (m, 2H), 7.68–7.65 (m, 2H), 7.54–7.49 (m, 2H), 7.43–7.42 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.7, 146.7, 142.5, 141.2, 138.0, 130.3, 129.8, 127.5, 127.3, 127.0, 126.5, 126.3, 126.2, 126.0, 125.6, 123.6, 115.1. IR (KBr): 3048, 2921, 2358, 1949, 1567, 1490, 1442, 1380, 1336, 1155, 1085, 1029, 983, 894, 769, 696, 522, 445 cm^{-1}. HRMS (EI, 70 eV) calcd for $C_{17}H_{11}NS_2$ [M$^+$]: 293.0333, found 293.0335.

6-Bromo-1,3-diphenylisoquinoline (3p). Pale-yellow solid (67.7 mg, 47%), mp 118–120 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20–8.19 (m, 2H), 8.09–8.08 (m, 1H), 7.99–7.96 (m, 2H), 7.79–7.70 (m, 2H), 7.58–7.49 (m, 6H), 7.44–7.41 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.6, 151.4, 139.5, 139.2, 139.1, 130.4, 130.3, 129.6, 129.5, 129.0, 128.9, 128.8, 128.5, 127.2, 125.0, 124.2, 114.6. IR (KBr): 3419, 3039, 2921, 1602, 1550, 1446, 1384, 885, 765, 686, 565, 464 cm^{-1}. HRMS (ESI) calcd for $C_{21}H_{15}BrN^+$ [M + H]$^+$: 360.0383, found 360.0398.

7-Bromo-1,3-diphenylisoquinoline (3q). Pale-yellow solid (78.4 mg, 54%), mp 136–137 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28–8.27 (m, 1H), 8.21–8.19 (m, 2H), 8.03 (s, 1H), 7.81–7.78 (m, 4H), 7.60–7.49 (m, 5H), 7.44–7.41 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.6, 150.7, 139.3, 139.2, 136.4, 133.7, 130.2, 129.8, 129.2, 129.0, 128.9, 128.8, 128.6, 127.2, 127.8, 120.7, 115.4. IR (KBr): 3424, 3046, 2919, 1550, 1375, 867, 759, 688, 524 cm^{-1}. HRMS (EI, 70 eV) calcd for $C_{21}H_{14}BrN$ [M$^+$]: 359.0310, found 359.0311.

6-Chloro-1,3-diphenylisoquinoline (3r). Pale-yellow solid (59.4 mg, 47%), mp 118–119 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22–8.20 (m, 2H), 8.07–8.05 (m, 1H), 7.97 (s, 1H), 7.91–7.90 (m, 1H), 7.80–7.78 (m, 2H), 7.59–7.49 (m, 5H), 7.44–7.41 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.6, 151.5, 139.6, 139.3, 138.9, 136.5, 130.3, 129.5, 129.0, 128.9, 128.8, 128.5, 127.9, 127.3, 126.2, 124.1, 114.8. IR (KBr): 3432, 3046, 2356, 1604, 1552, 1386, 1078, 968, 892, 757, 678, 563, 468 cm^{-1}. HRMS (EI, 70 eV) calcd for $C_{21}H_{14}ClN$ [M$^+$]: 315.0815, found 315.0816.

1,3,6-Triphenylisoquinoline (3s). Pale-yellow solid (72.9 mg, 51%), mp 107–109 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26–8.24 (m, 2H), 8.21–8.20 (m, 1H), 8.13–8.12 (m, 2H), 7.87–7.85 (2H), 7.78–7.75 (m, 3H), 7.60–7.50 (m, 7H), 7.46–7.41 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.4, 150.8, 142.8, 140.3, 140.0, 139.8, 138.4, 130.4, 129.2, 128.9, 128.8, 128.7, 128.5, 128.3, 128.2, 127.7, 127.2, 126.8, 125.3, 125.0, 116.0. IR (KBr): 3438, 3039, 1616, 1554, 1444, 1388, 1346, 757, 694, 491 cm^{-1}. HRMS (EI, 70 eV) calcd for $C_{27}H_{19}N$ [M$^+$]: 357.1517, found 357.1519.

7-Methyl-1,3-diphenylisoquinoline (3t). Pale-yellow solid (109.9 mg, 93%), mp 76–77 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24–8.22 (m, 2H), 8.04–8.00 (m, 2H), 7.83–7.82 (m, 2H), 7.70 (s, 1H), 7.58–7.50 (m, 5H), 7.43–7.40 (m, 1H), 7.35–7.33 (m, 1H), 2.56 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.2, 150.4, 140.4, 140.2, 139.9, 138.3, 130.3, 129.3, 128.8, 128.6, 128.5, 128.4, 127.5, 127.2, 126.5, 124.4, 115.4, 22.0. IR (KBr): 3423, 3041, 1619, 1562, 1490, 1446, 1380, 763, 686, 578, 466 cm^{-1}. HRMS (EI, 70 eV) calcd for $C_{22}H_{17}N$ [M$^+$]: 295.1361, found 295.1366.

1,3,4-Triphenylisoquinoline (3u). Pale-yellow solid (48.8 mg, 34%), mp 121–122 °C (lit.[25] 130–132 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21–8.19 (m, 1H), 7.84–7.83 (m, 2H), 7.75–7.73 (m, 1H), 7.60–7.50 (m, 5H), 7.45–7.35 (m, 5H), 7.32–7.31 (m, 2H), 7.21–7.16 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.0, 149.8, 141.1, 140.0, 137.7, 137.2, 131.5, 130.6, 130.4, 130.1, 129.9, 128.7, 128.5, 128.4, 127.7, 127.6, 127.4, 127.1, 126.7, 126.2, 125.6.

4-Ethyl-1,3-diphenylisoquinoline (3v). Pale-yellow solid (79.9 mg, 65%), mp 121–123 °C (lit.[26] not reported). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17–8.13 (m, 2H), 7.77–7.71 (m, 3H), 7.60–7.59 (m, 2H), 7.55–7.44 (m, 6H), 7.41–7.38 (m, 1H), 3.11 (dd, J = 7.5, 15.0 Hz, 2H), 1.36 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.4, 151.3, 142.0, 140.1, 136.2, 130.3, 130.0, 129.6, 129.5, 128.5, 128.4, 128.3, 128.2, 127.6, 126.4, 126.1, 124.1, 22.0, 15.8.

2-Methyl-6-(2-oxo-2-phenylethyl)benzonitrile (3w′). Pale-yellow solid (45.2 mg, 48%), mp 115–117 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06–8.04 (m, 2H), 7.06 (t, J = 7.5 Hz, 1H), 7.50 (t, J = 7.5 Hz, 2H), 7.44 (t, J = 7.5 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 7.18 (d, J = 7.5 Hz, 1H), 4.54 (s, 2H), 2.57 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.5, 142.6, 138.8, 136.4, 133.6, 132.3, 128.8, 128.78, 128.4, 128.1, 117.1, 114.2, 44.0, 20.9. IR (KBr): 2225, 1689, 1597, 1449, 1332, 1221, 992, 758, 690 cm^{-1}.

HRMS (ESI) calcd for $C_{16}H_{14}NO^+$ $[M + H]^+$: 236.1070, found 236.1088.

General procedure for the synthesis of isoquinolines *via* Pd-catalyzed tandem reaction of 2-(2-carbonylphenyl) acetonitriles with arylboronic acids

2-(2-Carbonylphenyl)acetonitriles **4** (0.4 mmol), arylboronic acid **2** (1.2 mmol), $Pd(acac)_2$ (5 mol%), bpy (10 mol%), $TsOH{\cdot}H_2O$ (10 equiv.), and H_2O (2 mL) were successively added into a Schlenk reaction tube in air. The reaction mixture was stirred for 10 minutes at room temperature for proper mixing of the reactants, and then heated at 80 °C with vigorous stirring for 24 hours. After reaching the reaction equilibrium, the mixture was poured into ethyl acetate, which was washed with saturated $NaHCO_3$ (2 × 10 mL) and then brine (10 mL). After the aqueous layer was extracted with ethyl acetate, the combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified by flash column chromatography (hexane/ethyl acetate) to afford the desired products **5a–5r**.

1,3-Diphenylisoquinoline (5a). Pale-yellow solid (102.3 mg, 91%), mp 78–79 °C (lit.[24] 73–74.5 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25–8.23 (m, 2H), 8.15–8.14 (m, 1H), 8.09 (s, 1H), 7.95–7.93 (m, 1H), 7.84–7.83 (m, 2H), 7.70–7.67 (m, 1H), 7.59–7.50 (m, 6H), 7.44–7.40 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.5, 150.3, 140.1, 139.8, 138.0, 130.4, 130.2, 128.8, 128.7, 128.6, 128.4, 127.7, 127.6, 127.2, 127.0, 126.0, 115.8.

1-Phenyl-3-(*p*-tolyl)isoquinoline (5b). Pale-yellow solid (89.8 mg, 76%), δ mp 112–113 °C (lit.[27] oil). ^{1}H NMR (500 MHz, $CDCl_3$) 8.13–8.11 (m, 3H), 8.05 (s, 1H), 7.93–7.91 (m, 1H), 7.83–7.81 (m, 2H), 7.69–7.65 (m, 1H), 7.58–7.48 (m, 4H), 7.32–7.30 (m, 2H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.4, 150.4, 140.1, 138.5, 138.0, 137.0, 130.4, 130.1, 129.6, 128.7, 128.4, 127.7, 127.5, 127.1, 126.8, 125.8, 115.3, 21.4.

1-Phenyl-3-(*m*-tolyl)naphthalene (5c). Pale-yellow solid (99.3 mg, 84%), mp 94–95 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14–8.12 (m, 1H), 8.07–8.06 (m, 2H), 8.01–7.99 (m, 1H), 7.94–7.93 (m, 1H), 7.83–7.82 (m, 2H), 7.70–7.67 (m, 1H), 7.59–7.49 (m, 4H), 7.41–7.38 (m, 1H), 7.24–7.22 (m, 1H), 2.47 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.4, 150.5, 140.0, 139.7, 138.4, 137.9, 130.4, 130.1, 129.4, 128.7, 128.6, 128.4, 127.9, 127.7, 127.5, 126.9, 125.9, 124.3, 115.9, 21.8. IR (KBr): 3433, 3042, 2914, 2355, 1560, 1487, 1440, 1377, 1326, 1138, 1027, 972, 915, 855, 753, 692 cm^{-1}. HRMS (EI, 70 eV) calcd for $C_{22}H_{17}N$ $[M^+]$: 295.1361, found 295.1358.

1-Phenyl-3-(*o*-tolyl)isoquinoline (5d). Pale-yellow solid (95.7 mg, 81%), mp 98–99 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17–8.15 (m, 1H), 7.93–7.91 (m, 1H), 7.78–7.70 (m, 4H), 7.58–7.48 (m, 5H), 7.31 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.0, 153.1, 140.7, 139.8, 137.5, 136.4, 130.8, 130.2, 130.1, 128.5, 128.3, 128.1, 127.6, 127.3, 127.0, 125.9, 125.3, 119.5, 20.7. IR (KBr): 3437, 3046, 2923, 2355, 1965, 1615, 1558, 1488, 1443, 1378, 1335, 1139, 1033, 972, 859, 760, 698, 521, 456 cm^{-1}. HRMS (EI, 70 eV) calcd for $C_{22}H_{17}N$ $[M^+]$: 295.1361, found 295.1362.

3-(4-Fluorophenyl)-1-phenylisoquinoline (5e). White solid (95.6 mg, 80%), mp 103–104 °C (lit.[28] oil). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22–8.19 (m, 2H), 8.13 (d, J = 8.5 Hz, 1H), 8.02 (m, 1H), 7.92 (d, J = 8.5 Hz, 1H), 7.81 (d, J = 7.5 Hz, 2H), 7.68 (t, J = 8.0 Hz, 1H), 7.59–7.50 (m, 4H), 7.18 (t, J = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.3, 163.3, 160.5, 149.2, 139.8, 137.9, 135.79, 135.77, 130.2, 130.1, 128.9, 128.8, 128.7, 128.3, 127.6, 127.4, 127.0, 125.7, 115.6, 115.5, 115.3.

3-(4-Bromophenyl)-1-phenylisoquinoline (5f). Pale-yellow solid (120.1 mg, 84%), mp 122–124 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14–8.09 (m, 3H), 8.04 (s, 1H), 7.92–7.91 (m,1H), 7.81–7.79 (m, 2H), 7.70–7.67 (m, 1H), 7.62–7.51 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.7, 149.0, 139.8, 138.6, 137.9, 131.9, 130.3, 130.2, 128.8, 128.7, 128.4, 127.7, 127.6, 127.3, 126.0, 123.0, 115.7. IR (KBr): 3431, 3049, 2924, 2857, 1728, 1609, 1554, 1485, 1376, 1331, 1170, 1071, 1003, 817, 754, 687, 521 cm^{-1}. HRMS (EI, 70 eV) calcd for $C_{21}H_{14}BrN$ $[M^+]$: 359.0310, found 359.0313.

1-Phenyl-3-(4-(trifluoromethyl)phenyl)isoquinoline (5g). Pale-yellow solid (100.6 mg, 72%), mp 86–88 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34–8.33 (m, 2H), 8.17–8.12 (m, 2H), 7.96–7.95 (m, 1H), 7.82–7.81 (m, 2H), 7.76–7.70 (m, 3H), 7.60–7.53 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.7, 148.5, 143.0, 138.7 (q, J = 244 Hz), 130.4, 130.3 (q, J = 31 Hz), 130.2, 128.8, 128.4, 127.7, 127.6, 127.58, 127.3, 126.2, 125.6 (q, J = 4 Hz), 125.5, 123.4, 116.5. IR (KBr): 1616, 1560, 1491, 1441, 1418, 1391, 1318, 1167, 1115, 1068, 1013, 975, 881, 859, 841, 821, 801, 776, 755, 740, 728, 703, 682 cm^{-1}. HRMS (ESI) calcd for $C_{22}H_{15}F_3N^+$ $[M + H]^+$: 350.1151, found 350.1168.

3-(4-Methoxyphenyl)-1-phenylisoquinoline (5h). Pale-yellow solid (88.4 mg, 71%), mp 112–113 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19–8.17 (m, 2H), 8.12–8.10 (m, 1H), 8.00 (s, 1H), 7.90–7.89 (m, 1H), 7.82–7.81 (m, 2H), 7.67–7.64 (m, 1H), 7.58–7.46 (m, 4H), 7.04–7.02 (m, 2H), 3.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.3, 160.2, 150.1, 140.1, 138.1, 132.4, 130.3, 130.1, 128.6, 128.4, 128.3, 127.6, 127.4, 126.6, 125.6, 114.7, 114.2, 55.5. IR (KBr): 3436, 3050, 2925, 2354, 1607, 1563, 1509, 1440, 1387, 1338, 1244, 1167, 1023, 828, 760, 689, 536 cm^{-1}. HRMS (EI, 70 eV) calcd for $C_{22}H_{17}NO$ $[M^+]$: 311.1310, found 311.1316.

3-(Naphthalen-2-yl)-1-phenylisoquinoline (5i). Pale-yellow solid (83.5 mg, 63%), mp 119–120 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.36–8.34 (m, 1H), 8.23–8.14 (m, 2H), 7.98–7.86 (m, 6H), 7.72–7.69 (m, 1H), 7.60–7.51 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.7, 150.2, 140.1, 138.1, 137.0, 133.9, 133.7, 130.4, 130.3, 128.9, 128.8, 128.5, 127.8, 127.7, 127.6, 127.1, 126.5, 126.4, 126.3, 126.1, 125.0, 116.1. IR (KBr): 3055, 2924, 2854, 2356, 1950, 1685, 1616, 1563, 1498, 1443, 1380, 1186, 1142, 973, 901, 855, 816, 751, 701, 627, 528, 478 cm^{-1}. HRMS (EI, 70 eV) calcd for $C_{25}H_{17}N$ $[M^+]$: 331.1361, found 331.1358.

4-Methyl-1,3-diphenylisoquinoline (5j). Yellow solid (101.6 mg, 86%), mp 123–124 °C (lit.[25] 77–78 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, J = 8.5 Hz, 2H), 7.78–7.72 (m, 3H), 7.65 (d, J = 7.5 Hz, 2H), 7.56–7.45 (m, 6H), 7.40–7.37 (m, 1H), 2.71 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.3, 151.1, 141.6,

140.0, 137.1, 130.2, 130.1, 129.9, 128.3, 128.2, 128.1, 128.0, 127.5, 126.3, 125.4, 123.9, 123.1, 15.7.

3-(4-Fluorophenyl)-4-methyl-1-phenylisoquinoline (5k). Pale-yellow solid (76.5 mg, 61%), mp 149–150 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (t, J = 7.5 Hz, 2H), 7.77 (t, J = 7.5 Hz, 1H), 7.73 (d, J = 7.5 Hz, 2H), 7.65–7.62 (m, 2H), 7.57–7.46 (m, 4H), 7.17 (t, J = 9.0 Hz, 2H), 2.70 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.4, 161.5, 158.4, 150.1, 139.8, 137.6, 137.57, 137.1, 131.9, 131.8, 130.2, 130.0, 128.4, 128.3, 128.1, 126.4, 125.5, 123.9, 123.1, 115.0, 114.9, 15.7. IR (KBr): 3060, 1673, 1656, 1597, 1550, 1508, 1438, 1381, 1335, 1219, 1152, 1000, 945, 839, 743, 700, 662 cm^{-1}. HRMS (ESI) calcd for $C_{22}H_{17}FN^+$ $[M + H]^+$: 314.1340, found 314.1343.

3-(4-Methoxyphenyl)-4-methyl-1-phenylisoquinoline (5l). Pale-yellow solid (89.8 mg, 69%), mp 148–149 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (t, J = 7.0 Hz, 2H), 7.74 (d, J = 7.0 Hz, 3H), 7.62 (d, J = 8.0 Hz, 2H), 7.51–7.45 (m, 4H), 7.02 (d, J = 8.0 Hz, 2H), 3.86 (s, 3H), 2.70 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 158.1, 150.8, 140.0, 137.2, 134.1, 131.4, 130.2, 129.8, 128.3, 128.2, 128.1, 126.1, 125.3, 123.9, 122.8, 113.5, 55.4, 15.8. IR (KBr): 2822, 1895, 1610, 1557, 1512, 1441, 1391, 1338, 1288, 1246, 1172, 1109, 1040, 997, 949, 836, 793, 770, 740, 702, 668. HRMS (ESI) calcd for $C_{23}H_{20}NO^+$ $[M + H]^+$: 326.1539, found 326.1539.

3-Phenylisoquinoline (5m). Pale-yellow solid (55.8 mg, 68%), mp 98–99 °C (lit.[29] 103.4–104.4 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.35 (s, 1H), 8.14 (d, J = 7.5 Hz, 2H), 8.07 (s, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.87 (d, J = 8.5 Hz, 1H), 7.70 (t, J = 7.5 Hz, 1H), 7.59 (t, J = 7.5 Hz, 1H), 7.52 (t, J = 7.5 Hz, 2H), 7.43 (t, J = 7.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.4, 151.4, 139.6, 136.7, 130.5, 128.8, 128.5, 127.8, 127.6, 127.1, 127.0, 126.9, 116.5.

3-(4-Fluorophenyl)isoquinoline (5n). Pale-yellow solid (53.6 mg, 60%), mp 131–132 °C (lit.[30] 124–125 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.32 (s, 1H), 8.12–8.09 (m, 2H), 8.02–7.99 (m, 2H), 7.87 (d, J = 8.0 Hz, 1H), 7.71 (t, J = 8.0 Hz, 1H), 7.59 (t, J = 8.0 Hz, 1H), 7.19 (t, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.3, 162.3, 152.4, 150.3, 136.7, 135.7, 130.7, 128.8, 128.7, 127.7, 127.6, 127.2, 126.9, 116.2, 115.8, 115.6.

3-(4-Methoxyphenyl)isoquinoline (5o). Pale-yellow solid (63.1 mg, 67%), mp 99–100 °C (lit.[31] 102–103 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.37 (s, 1H), 8.33 (s, 1H), 8.18 (d, J = 8.5 Hz, 2H), 8.11 (d, J = 8.5 Hz, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.77 (t, J = 7.0 Hz, 1H), 7.64 (t, J = 7.0 Hz, 1H), 7.08 (d, J = 8.0 Hz, 2H), 3.83 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.8, 152.1, 149.8, 136.3, 131.4, 130.7, 127.8, 127.5, 127.0, 126.9, 126.8, 114.6, 114.2.

1-Ethyl-3-phenylisoquinoline (5p).[28] Oil (57.9 mg, 62%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20–8.17 (m, 3H), 7.93 (s, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.66 (t, J = 7.0 Hz, 1H), 7.57 (t, J = 8.0 Hz, 1H), 7.52 (t, J = 7.5 Hz, 2H), 7.42 (t, J = 7.5 Hz, 1H), 3.43 (q, J = 7.5 Hz, 2H), 1.54 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.8, 149.8, 139.9, 137.1, 129.8, 128.7, 128.3, 127.8, 127.0, 126.7, 125.9, 125.2, 115.0, 28.5, 13.4.

1-Ethyl-3-(4-fluorophenyl)isoquinoline (5q).[28] Oil (48.3 mg, 48%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18–8.15 (m, 3H), 7.87–7.84 (m, 2H), 7.66 (t, J = 7.5 Hz, 1H), 7.58–7.55 (m, 1H) 7.18 (t, J = 9.0 Hz, 2H), 3.40 (q, J = 7.5 Hz, 2H), 1.52 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.2, 162.9, 162.2, 148.8, 137.1, 136.1, 129.9, 128.7, 128.6, 127.8, 126.7, 125.8, 125.2, 115.6, 115.4, 114.6, 28.4, 13.3.

1-Ethyl-3-(4-methoxyphenyl)isoquinoline (5r).[28] Oil (53.7 mg, 51%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, J = 8.5 Hz, 3H), 7.85–7.82 (m, 2H), 7.63 (t, J = 7.0 Hz, 1H), 7.53 (t, J = 7.0 Hz, 1H), 7.04 (d, J = 9.0 Hz, 2H), 3.88 (s, 3H), 3.40 (q, J = 7.5 Hz, 2H), 1.53 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.6, 160.0, 149.5, 137.2, 132.6, 129.7, 128.2, 127.7, 126.3, 125.5, 125.2, 114.1, 113.8, 55.4, 28.4, 13.3.

Isoquinoline-1,3(2*H*,4*H*)-dione (6a). White solid, mp 240–241 °C (lit.[32] 241–242 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.30 (s, 1H), 8.01 (d, J = 8.0 Hz, 1H), 7.64 (t, J = 7.5 Hz, 1H), 7.45 (t, J = 8.0 Hz, 1H), 7.38 (d, J = 7.5 Hz, 1H), 4.03 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.9, 165.3, 136.6, 133.4, 127.8, 127.4, 127.1, 125.0, 35.9.

2-(2-Oxo-2-phenylethyl)benzonitrile (7a). White solid, mp 112–113 °C (lit.[33] 109–111 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07–8.05 (m, 2H), 7.71–7.69 (d, J = 8.0 Hz, 1H), 7.62–7.56 (m, 2H), 7.53–7.50 (m, 2H), 7.41–7.38 (m, 2H), 4.56 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.4, 138.6, 136.3, 133.7, 132.8, 131.0, 128.8, 128.4, 127.6, 117.9, 113.7, 100.0, 43.6.

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