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Rhodium(III)-Catalyzed One-Pot Access to Isoquinolines and Heterocycle-Fused Pyridines in Aqueous Medium through C–H Cleavage

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An efficient Rh^{III}-catalyzed *ortho*-C–H bond activation for the synthesis of substituted isoquinolines and heterocycle-fused pyridines in aqueous medium has been developed. This method involves the in situ generation of ketimines from ketones and ammonium acetate and subsequent oxidative C–H bond activation/annulation of ketimines with alkynes to form the C–C/C–N bonds spontaneously. Various aryl ketones and internal alkynes were smoothly transformed into the desired heterocycles in moderate to excellent yields. The reaction exploits molecular oxygen as the sole oxidant by producing water as the only byproduct. Moreover, easily available NH_4OAc was utilized as the nitrogen source, which makes this protocol practical and environmentally friendly.

Introduction

The efficient synthesis of heterocycles, especially nitrogen-containing heterocyclic compounds,[1] has been a significant goal of synthetic organic chemists. In particular, isoquinoline and pyridine structural motifs are ubiquitous in natural products and pharmaceuticals,[2] and isoquinoline derivatives have been employed as chiral ligands in transition-metal-catalyzed asymmetric syntheses.[3] Thus, the efficient preparation of these heterocyclic scaffolds has attracted extensive attention. Traditionally, several famous name reactions (e.g., Bischler–Napieralski, Pomeranz–Fritsch, and Pictet–Spengler reactions) have been widely employed for the synthesis of isoquinoline derivatives by condensation.[4] Although these reactions provide a facile approach to give isoquinolines, they suffer from harsh reaction conditions and an additional dehydrogenation step in some cases. In recent years, transition-metal-catalyzed cross-coupling reactions of aryl halides with alkynes have appeared as an alternative and efficient method for the synthesis of isoquinoline ring systems.[5] However, the preactivation of the substrate (i.e., halogenation and/or *ortho*-functionalization) is required for these transformations.

Currently, the strategy of direct C–H bond functionalization[6] has prompted much attention in the synthesis of heterocycles because of its high atom- and step-economic nature. In 2009, Fagnou and co-workers demonstrated an elegant Rh^{III}-catalyzed oxidative isoquinoline synthesis from *N*-*tert*-butyl-benzaldimines and alkynes.[7a] In their reaction, a stoichiometric amount of $Cu(OAc)_2$ was used as an external oxidant to regenerate the Rh^{III} species. Later, Miura and Satoh[7b] developed a method for synthesis of isoquinoline derivatives by using the Rh^{III}-catalyzed oxidative cyclization of benzophenone, N–H imines, and alkynes. New approaches for the preparation of isoquinolines and functionalized pyridines have been reported by Chiba,[8] Cheng,[9a] and Dong,[10] respectively, by employing the external-oxidant-free strategy, in which the N–X (X = O, N, S) bond of the directing groups performed as internal oxidants. Hua and co-workers described an efficient three-component cascade reaction of aryl ketones, hydroxylamine, and alkynes to synthesize isoquinolines and heterocycle-fused pyridines.[7e] Despite these significant advances, limitations remain in this area. For examples, stoichiometric amounts of metal oxidants are generally required to maintain the catalytic cycles. The installation of N–X bonds as internal oxidants usually requires additional steps or complex starting materials. Herein, we report the efficient and practical access to isoquinolines and heterocycle-fused pyridines by employing Rh^{III} catalysis. A broad scope of aryl ketones and alkynes participated in the reaction to afford the corresponding heterocycles. Importantly, molecular oxygen[11–13] was exploited as the sole oxidant in the reaction, and water was produced as the only coproduct.

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Furthermore, easily available NH_4OAc was utilized as the nitrogen source, which makes this method quite practical and inexpensive. It is interesting that the reaction efficiently proceeds in aqueous medium to give the desired products in moderate to excellent yields.

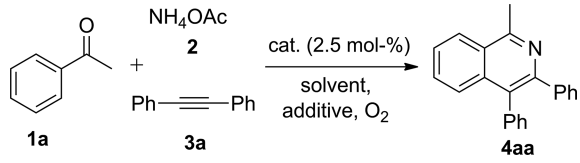
Results and Discussion

Reactions for organic synthesis that are performed in aqueous conditions have attracted tremendous attention and are becoming some of the most exciting research areas.[14] However, transition-metal-catalyzed C–H bond transformations that take place in an aqueous medium are underdeveloped.[15–18] We initiated our study by using acetophenone (**1a**), ammonium acetate (**2**), and 1,2-diphenylethyne (**3a**) in the presence of 2.5 mol-% $[Cp^*RhCl_2]_2$ (Cp^* = pentamethylcyclopentadienyl) in DMF (*N*,*N*-dimethylformamide) at 100 °C with O_2 as the sole oxidant. To our delight, a trace amount of the desired product **4aa** was observed after 48 h by GC–MS analysis (see Table 1, Entry 1). The efficiency of the reaction improved to give **4aa** in 13 and 37% yield, respectively, when KOAc and AcOH were used as additives (see Table 1, Entries 2 and 3). However, the yield of the desired heterocyclic product **4aa** increased significantly to 65% when the reaction was conducted in water with 1.0 mmol of AcOH as the additive (see Table 1, Entry 4). The investigation of other acidic additives identified pivalic acid (PivOH) to be optimal, as it gave the corresponding product in 82% yield (see Table 1, Entry 10). Further experiments showed that $[Cp^*RhCl_2]_2$ was the first choice for the catalyst precursor, and other metal salts such as $RhCl(PPh_3)_3$, $RhCl_3{\cdot}3H_2O$, and $[(p\text{-cymene})RuCl_2]_2$ were not effective (see Table 1, Entries 11–13). No reaction was observed in the absence of the rhodium catalyst (see Table 1, Entry 14), and we determined that 100 °C was the optimal temperature to perform the transformation. Temperatures above or below 100 °C did not lead to a better outcome (see Table 1, Entries 15 and 16). When the catalytic system was employed under N_2, no reaction was observed (see Table 1, Entry 17). This result indicates that O_2 is crucial for the success of the annulation reaction. Thus, the optimum reaction conditions, which were used for all subsequent transformations, involved 2.5 mol-% of $[Cp^*RhCl_2]_2$, 1.0 mmol of PivOH, 1.2 mmol of NH_4OAc, 0.20 mmol of the alkyne, and 0.4 mmol of the ketone in 1.0 mL of H_2O. The reaction mixture was stirred at 100 °C for 48 h under O_2.

On the basis of the optimization studies, we then evaluated the scope and generality of this transformation by using 1,2-diphenylethyne (**3a**) and a variety of aryl ketones **1** as shown in Table 2. Several aryl ketones were suitable substrates to give the desired products in moderate to good yields. The electronic properties of the substituents on the aryl ring of the ketone influenced the efficiency of the reaction. In general, aryl ketones that contained an electron-donating substituent (e.g., $-CH_3$, $-OCH_3$) produced a higher yield of product than their analogues that contained an electron-withdrawing substituent (e.g., $-CF_3$; see Table 2, Entries 1–4). A fluoro, chloro, or bromo group on the aromatic ring of the ketone was tolerated and afforded halogen-containing products **4ea**–**4ga** in good yields, which could undergo further cross-coupling reactions to facilitate expedient syntheses of complex isoquinolines (see Table 2, Entries 5–7). To our surprise, 1-(4-aminophenyl)ethanone was well tolerated and afforded product **4ha** in moderate yield (see Table 2, Entry 8). The steric effects of substituents on the aryl ring of the ketones had an obvious impact on the outcome of the reaction, as 1-(*o*-tolyl)ethanone generated the corresponding product **4ia** in low yield (see Table 2, Entry 9). This method also allowed for the construction of a heterocycle-fused pyridine structure. 1-(1*H*-Indol-3-yl)-ethanone, the N–H bond of which needs protection in some transition-metal-catalyzed C–H bond activations,[19] participated in the reaction easily to furnish the desired product **4ja** in good yield (see Table 2, Entry 10). The cyclization reaction also proceeded smoothly for 1-(thiophen-3-yl)-ethanone and 1-(thiophen-2-yl)ethanone to afford the corresponding heterocycles **4ka** and **4la** in moderate to good yields (see Table 2, Entries 11 and 12).

Benzophenone was examined in the reaction, and 1,3,4-triphenylisoquinoline was generated smoothly in a good yield of 75% (see Table 2, Entry 13). (2-Aminophenyl)-(phenyl)methanone was also well tolerated, and the corre-

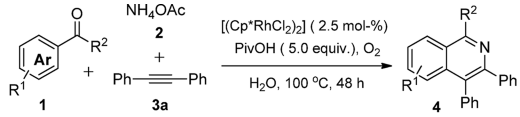
Table 1. Optimization of the reaction conditions.[a]

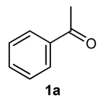
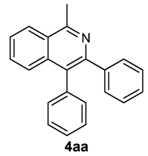
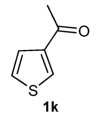
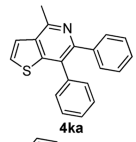
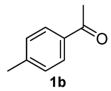
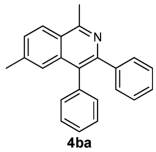
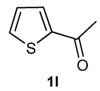
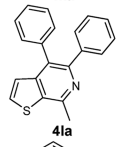
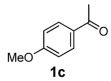
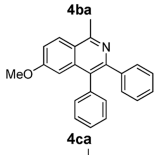
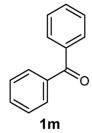
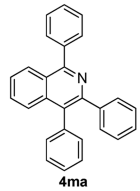
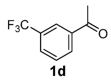
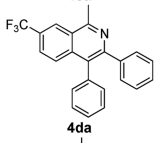
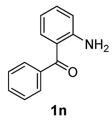
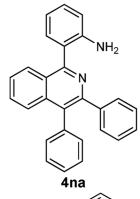
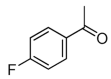
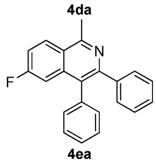
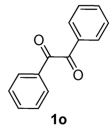
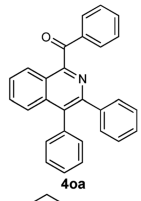
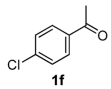
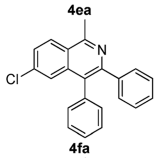
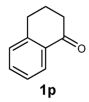
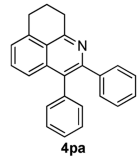
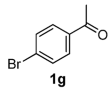
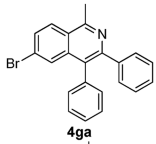
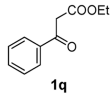
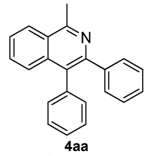
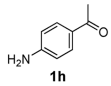
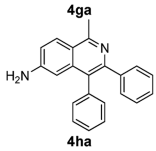
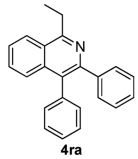
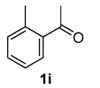
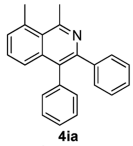
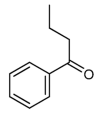
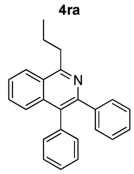
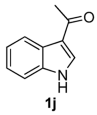
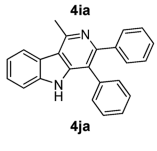


Entry	Catalyst	Additive	Solvent	*T* [°C]	Yield [%][b]
1	$[Cp^*RhCl_2]_2$	–	DMF	100	trace
2	$[Cp^*RhCl_2]_2$	KOAc	DMF	100	13[c]
3	$[Cp^*RhCl_2]_2$	AcOH	DMF	100	37
4	$[Cp^*RhCl_2]_2$	AcOH	H_2O	100	65
5	$[Cp^*RhCl_2]_2$	TFA[d]	H_2O	100	n.d.[d]
6	$[Cp^*RhCl_2]_2$	TfOH[d]	H_2O	100	<5
7	$[Cp^*RhCl_2]_2$	MsOH[d]	H_2O	100	trace
8	$[Cp^*RhCl_2]_2$	TsOH	H_2O	100	n.r.[d]
9	$[Cp^*RhCl_2]_2$	$PhCO_2H$	H_2O	100	n.d.
10	$[Cp^*RhCl_2]_2$	PivOH	H_2O	100	82
11	$RhCl(PPh_3)_3$	PivOH	H_2O	100	n.r.
12	$RhCl_3{\cdot}3H_2O$	PivOH	H_2O	100	n.r.
13	$[(p\text{-cymene})RuCl_2]_2$	PivOH	H_2O	100	34
14	–	PivOH	H_2O	100	n.r.
15	$[Cp^*RhCl_2]_2$	PivOH	H_2O	120	85
16	$[Cp^*RhCl_2]_2$	PivOH	H_2O	80	79[e]
17	$[Cp^*RhCl_2]_2$	PivOH	H_2O	100	n.r.[f]

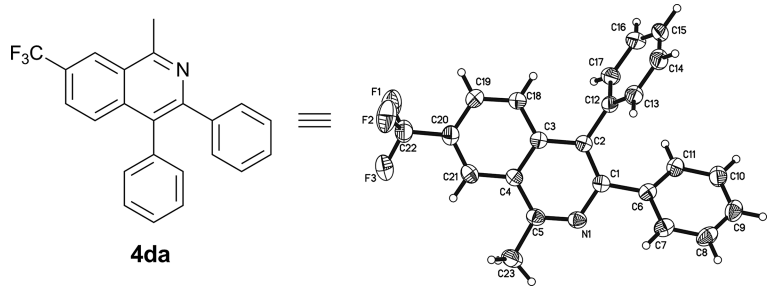
[a] Reagents and conditions: **1a** (2.0 equiv.), **2** (6.0 equiv.), **3a** (0.2 mmol), catalyst (2.5 mol-%), and acid additive (5.0 equiv.) under O_2 (1 atm) at 100 °C for 48 h. [b] Isolated yields based on **3a**. [c] KOAc (0.4 mmol) was used. [d] TFA = trifluoroacetic acid, n.d.: not determined, TfOH = triflic acid, MsOH = methanesulfonic acid, n.r.: no reaction. [e] Reaction time prolonged to 72 h. [f] Reaction performed under N_2.

Table 2. Reaction of different ketones.[a]



Entry	Substrate **1**	Product **4**	Yield (%)[b]	Entry	Substrate **1**	Product **4**	Yield (%)[b]
1	 **1a**	 **4aa**	82	11	 **1k**	 **4ka**	84
2	 **1b**	 **4ba**	92	12	 **1l**	 **4la**	55 [c]
3	 **1c**	 **4ca**	89	13	 **1m**	 **4ma**	75
4	 **1d**	 **4da**	48	14	 **1n**	 **4na**	44
5	 **1e**	 **4ea**	95	15	 **1o**	 **4oa**	41
6	 **1f**	 **4fa**	80	16	 **1p**	 **4pa**	62 [d]
7	 **1g**	 **4ga**	96	17	 **1q**	 **4aa**	60 [e]
8	 **1h**	 **4ha**	50	18	 **1r**	 **4ra**	67
9	 **1i**	 **4ia**	39	19	 **1s**	 **4sa**	83
10	 **1j**	 **4ja**	92				

[a] Reaction conditions: **1** (2.0 equiv.), **2** (6.0 equiv.), **3a** (0.2 mmol), [(Cp*RhCl$_2$)$_2$] (2.5 mol-%), and PivOH (5.0 equiv) under 1 atm of O$_2$, 100 °C, 48 h. [b] Isolated yields based on **3a**. [c] Cu(OAc)$_2$·H$_2$O was added. [d] Ketone was 1-tetralone. [e] Only decarboxylic result was observed.

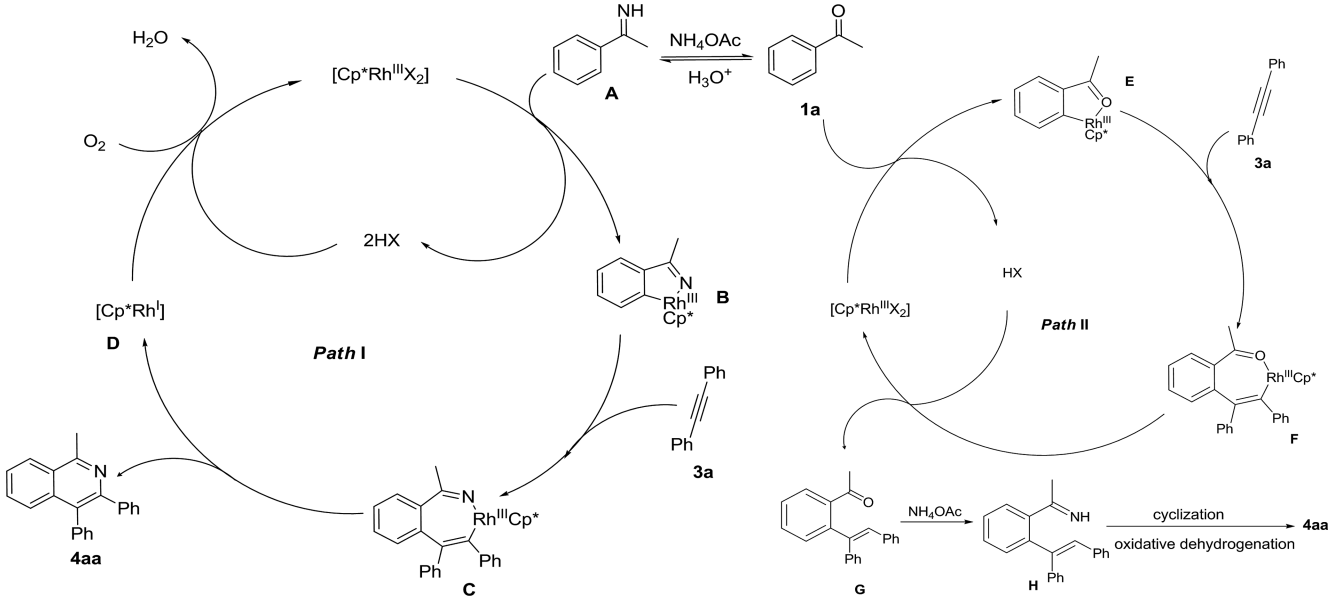


Scheme 1. X-ray crystal structure of **4da**.

sponding product **4na** was produced in moderate yield (see Table 2, Entry 14). Fortunately, benzil was compatible in this transformation and afforded **4oa** in 41% yield (see Table 2, Entry 15). 1-Tetralone was successfully employed for the preparation of 2,3-diphenyl-8,9-dihydro-7*H*-benzo[*de*]quinoline (**4pa**) in a yield of 62% (see Table 2, Entry 16). Interestingly, only the result of a decarboxylation was observed when ethyl 3-oxo-3-phenylpropanoate participated in the reaction (see Table 2, Entry 17). In addition, the reaction of **3a** with propiophenone (**1r**) and 1-phenylbutan-1-one (**1s**) resulted in the formation of the corresponding desired products **4ra** and **4sa** in 67 and 83% yield, respectively (see Table 2, Entries 18 and 19). 1-[3-(Trifluoromethyl)phenyl]ethanone easily participated in this reaction, which proceeded regioselectively, as the reaction predominantly occurred at the less congested position (see Table 2, Entry 4). The structure of the final product **4da** was further confirmed by X-ray crystal structure analysis (see Scheme 1).[20]

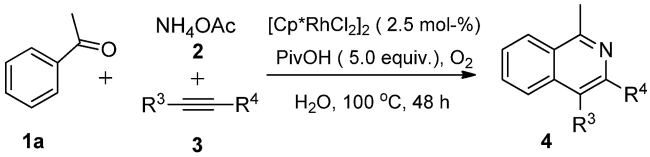
We next examined the reactivity of other alkynes. As shown in Table 3, the reaction of acetophenone (**1a**) with various substituted alkynes **3** furnished the annulation products **4** in moderate to good yields. The experimental results revealed that the weak electron-withdrawing-substituted alkynes had better reactivity than the electron-donating-substituted ones. For instance, methyl- and methoxy-substituted alkynes gave the corresponding cyclization products in 73 and 69% yield, respectively (see Table 3, Entries 1 and 2), whereas the chloro-substituted alkyne afforded the corresponding product in 81% yield (see Table 3, Entry 3). On the other hand, the presence of the strong electron-withdrawing fluoro substituent significantly decreased the yield to 30% (see Table 3, Entry 4). The product was isolated in 79% yield when the aliphatic alkyne oct-4-yne was employed (see Table 3, Entry 5). Significantly, unsymmetrical alkyne but-1-yn-1-ylbenzene yielded the product in a moderate yield with high regioselectivity (see Table 3, Entry 6). An explanation for this occurrence is that in the seven-membered rhodacycle, the phenyl group of the alkyne is close to the Rh atom but far away from the C atom.[21]

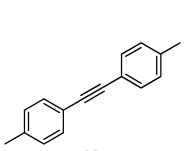
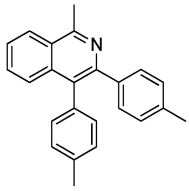
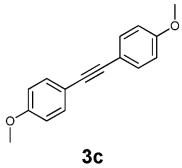
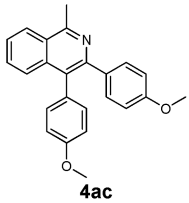
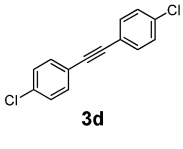
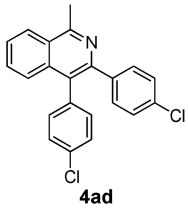
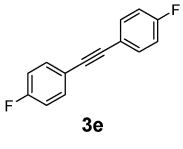
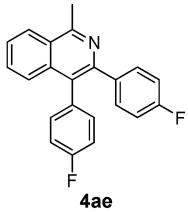
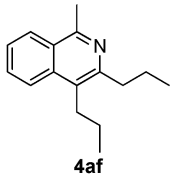
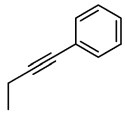
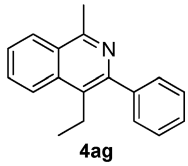
On the basis of previous studies[22] and our experimental results, we propose that this Rh^{III}-catalyzed C–H bond activation proceeds through one of two possible pathways as shown in Scheme 2. In path I, ketimine **A** is formed in situ from acetophenone (**1a**) and NH_4OAc in an aqueous medium and coordinates to the Rh^{III} catalyst to generate the



Scheme 2. Two possible mechanisms of Rh^{III}-catalyzed C–H bond activation/annulation of aryl ketones.

Table 3. Reaction of different alkynes.[a]



Entry	Substrate **3**	Product **4**	Yield (%)[b]
1	 **3b**	 **4ab**	73
2	 **3c**	 **4ac**	69
3	 **3d**	 **4ad**	81
4	 **3e**	 **4ae**	30
5	 **3f**	 **4af**	79
6	 **3g**	 **4ag**	56

[a] Reaction conditions: **1** (2.0 equiv.), **2** (6.0 equiv.), **3** (0.2 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol-%), and PivOH (5.0 equiv.) under 1 atm of O_2, 100 °C, 48 h. [b] Isolated yields based on **3**.

five-membered rhodacycle **B** by releasing HX. The insertion of alkyne **3a** into intermediate **B** gives seven-membered rhodacycle complex **C**, which undergoes a reductive elimination to yield the desired product **4aa** and Rh^I species **D**. The subsequent oxidation of Rh^I species by molecular oxygen under acidic conditions regenerates the Rh^{III} catalyst (see Scheme 2, Path I). Another reasonable pathway involves a ketone-directed C–H bond activation to give metallacycle **E**. The alkyne insertion into metallacycle **E** affords seven-membered rhodacycle **F**, which generates compound **G** after protonation. Ketimine **H** is formed spontaneously under the reaction conditions and proceeds in the intramolecular cyclization. The subsequent aromatization gives the desired isoquinoline derivative **4aa** (see Scheme 2, Path II). To explore the mechanism, the reactions of ketone **1m** and diphenylmethanimine **K** were performed under our standard conditions, but in the absence of NH_4OAc. The olefination product **J** was not observed [see Scheme 3, Equation (1)], which implies that a ketone-directed olefination might not occur in this transformation. In contrast, the desired product **4ma** was isolated from the reaction of diphenylmethanimine **K** with 1,2-diphenylethyne [see Scheme 3, Equation (2)]. This result shows that the reaction might occur through path I. In addition, the oxidant is not needed according to the catalytic cycle of path II. However, we found the reaction did not occur under nitrogen (see Table 1, Entry 17). This result also supports path I, as oxygen is required as an oxidant to regenerate the Rh^{III} catalyst from Rh^I in this path.

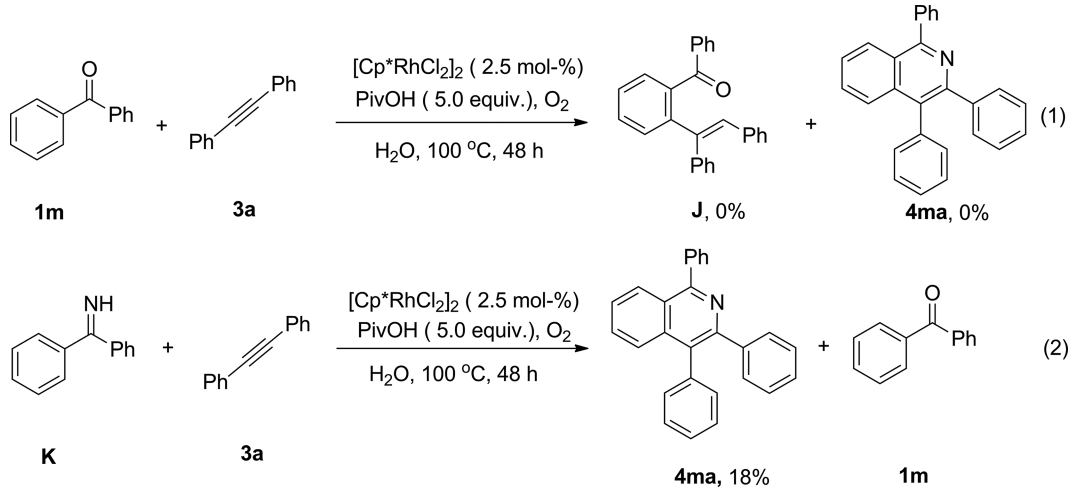
Conclusions

In summary, we have successfully developed an efficient rhodium-catalyzed C–H bond activation/annulation of aryl ketones with alkynes for the synthesis of isoquinolines and heterocycle-fused pyridines in aqueous medium. This method, which tolerates a wide range of functional groups, follows a reliable procedure for the rapid conversion of readily available aryl ketones into a variety of valuable heterocycles in moderate to good yields. More importantly, this reaction employs oxygen at ambient pressure as the terminal oxidant, which obviates the need for stoichiometric amounts of metal oxidants. The employment of readily available NH_4OAc as a nitrogen source makes the reaction highly valuable in terms of economics and safety. Further attempts to expand this catalytic system to other useful transformations in an aqueous medium are currently underway.

Experimental Section

General Methods: All materials and solvents were purchased from common commercial sources and used without additional purification. The ^1H NMR spectroscopic data were recorded at 400 or 500 MHz, and the ^{13}C NMR spectroscopic data were recorded at 100 or 125 MHz. TMS was used as the internal standard. The patterns of the signals are described as singlet (s), doublet (d), triplet (t), and multiplet (m). The mass spectrometry data were collected by using MS-ESI and HRMS-EI instruments.

General Procedure for Products 4aa–4pa, 4ra, 4sa, and 4ab–4ag: A flask with a magnetic stir bar was charged with the aryl ketone (0.4 mmol), the alkyne (0.2 mmol), $[Cp^*RhCl_2]_2$ (3.1 mg, 0.005 mmol), PivOH (102 mg, 1.0 mmol), and H_2O (1.0 mL). The mixture was stirred at 100 °C in an oil bath for 48 h under O_2 (1 atm). Upon completion of the reaction, the mixture was cooled



Scheme 3. Control experiments to explore mechanism.

and made neutral to slightly alkaline by the addition of a saturated K_2CO_3 solution (5 mL). The resulting mixture was stirred for 30 min. H_2O (10 mL) and EtOAc (20 mL) were then added successively to the cooled reaction mixture. The organic phase was separated, and the aqueous phase was further extracted with EtOAc (2× 10 mL). The combined organic layers were dried with anhydrous Na_2SO_4. The solvent was evaporated to give a residue, which was purified by flash chromatography on a silica gel column [petroleum ether (PE)/EtOAc] to give the desired product **4**.

Characterization Data of the Products

1-Methyl-3,4-diphenylisoquinoline (4aa).[7g] Flash chromatography on a silica gel column (petroleum ether/ethyl acetate, 20:1) afforded a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22–8.20 (m, 1 H), 7.68–7.65 (m, 1 H), 7.62–7.59 (m, 2 H), 7.38–7.32 (m, 5 H), 7.24–7.17 (m, 5 H), 3.10 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.8, 149.4, 141.0, 137.6, 136.0, 131.5, 130.3, 130.0, 129.3, 128.2, 127.2, 127.0, 126.6, 126.3, 126.2, 125.6, 22.8 ppm. MS: *m*/*z* (%) = 296 (81), 295 (100) $[M]^+$, 294 (100), 252 (54), 77 (10).

1,6-Dimethyl-3,4-diphenylisoquinoline (4ba):[7g] Flash chromatography on a silica gel column (petroleum ether/ethyl acetate, 20:1) afforded a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 8.4 Hz, 1 H), 7.40–7.30 (m, 7 H), 7.21–7.15 (m, 5 H), 3.02 (s, 3 H), 2.40 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.4, 149.6, 141.2, 140.3, 137.8, 136.3, 131.5, 130.3, 128.8, 128.7, 128.2, 127.6, 127.1, 126.9, 125.5, 125.2, 124.6, 22.7, 22.2 ppm. MS: *m*/*z* (%) = 309 (61) $[M]^+$, 308 (100), 252 (15), 77 (5).

6-Methoxy-1-methyl-3,4-diphenylisoquinoline (4ca):[7g] Flash chromatography on a silica gel column (petroleum ether/ethyl acetate, 10:1) afforded a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 9.2 Hz, 1 H), 7.35–7.27 (m, 5 H), 7.22–7.15 (m, 6 H), 6.90 (s, 1 H), 3.68 (s, 3 H), 3.00 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.6, 157.0, 150.2, 141.2, 138.1, 137.9, 131.4, 130.3, 128.6, 128.3, 127.6, 127.5, 127.1, 126.9, 121.9, 118.7, 104.5, 55.2, 22.7 ppm. MS: *m*/*z* (%) = 325 (65) $[M]^+$, 324 (100), 281 (39), 280 (12), 125 (6).

1-Methyl-3,4-diphenyl-7-(trifluoromethyl)isoquinoline (4da): Flash chromatography on a silica gel column (petroleum ether/ethyl acetate, 20:1) afforded a white solid; m.p. 130–131 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.48 (s, 1 H), 7.80–7.23 (m, 2 H), 7.38–7.34 (m, 5 H), 7.22–7.19 (m, 5 H), 3.12 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.7, 151.5, 140.4, 137.6, 136.8, 131.3, 130.3, 129.1, 128.6, 128.5, 128.4, 128.1, 127.9, 127.8, 127.6, 127.6, 127.4, 125.5, 125.5, 125.5, 125.1, 123.5, 123.4, 123.4, 123.3, 123.0, 22.7 ppm. IR: $\tilde{\nu}$ = 2926, 2855, 1703, 1630, 1432, 1305, 1168, 1126, 968, 699 cm^{-1}. MS: *m*/*z* (%) = 364 (17), 363 (83) $[M]^+$, 362 (100), 294 (2), 69 (8). HRMS (EI-TOF): calcd. for $C_{23}H_{16}F_3N$ $[M]^+$ 363.1235; found 363.1233.

6-Fluoro-1-methyl-3,4-diphenylisoquinoline (4ea):[7g] Flash chromatography on a silica gel column (petroleum ether/ethyl acetate, 20:1) afforded a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (dd, *J* = 9.2 Hz, *J* = 5.6 Hz, 1 H), 7.37–7.31 (m, 6 H), 7.29–7.23 (m, 1 H), 7.20–7.16 (m, 5 H), 3.05 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.2 ($J_{C,F}$ = 249.7 Hz), 157.6, 150.5, 140.7, 138.1 ($J_{C,F}$ = 9.3 Hz), 137.2, 131.2, 130.3, 128.7 ($J_{C,F}$ = 8.2 Hz), 128.5, 127.7, 127.4, 127.2, 123.5, 116.7 ($J_{C,F}$ = 25.7 Hz), 109.9 ($J_{C,F}$ = 22.4 Hz), 124.6, 22.8 ppm. MS: *m*/*z* (%) = 314 (20), 313 (93) $[M]^+$, 312 (100), 270 (19), 155 (12), 77 (4).

6-Chloro-1-methyl-3,4-diphenylisoquinoline (4fa):[7g] Flash chromatography on a silica gel column (petroleum ether/ethyl acetate, 5:1) afforded a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 8.4 Hz, 1 H), 7.62 (d, *J* = 2.0 Hz, 1 H), 7.63 (dd, *J* = 9.1 Hz, *J* = 2.0 Hz, 1 H), 7.35–7.34 (m, 5 H), 7.20–7.17 (m, 5 H), 3.04 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.7, 150.7, 140.6, 137.2, 136.9, 136.4, 131.3, 130.3, 128.5, 128.5, 127.7, 127.5, 127.4, 127.2, 125.2, 124.4, 22.8 ppm. MS: *m*/*z* (%) = 331 (25), 330 (58), 329 (62) $[M]^+$, 328 (100), 295 (12), 294 (25), 77 (6).

6-Bromo-1-methyl-3,4-diphenylisoquinoline (4ga):[7g] Flash chromatography on a silica gel column (petroleum ether/ethyl acetate, 20:1) afforded a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 8.8 Hz, 1 H), 7.80 (d, *J* = 2.0 Hz, 1 H), 7.63 (dd, *J* = 8.8 Hz, *J* = 2.0 Hz, 1 H), 7.35–7.33 (m, 5 H), 7.20–7.17 (m, 5 H), 3.03 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.8, 150.7, 140.7, 137.5, 136.9, 131.3, 130.3, 130.1, 128.5, 128.5, 128.4, 127.7, 127.5, 127.4, 127.3, 125.1, 124.6, 22.8 ppm. MS: *m*/*z* (%) = 375 (53), 374 (100), 373 (52) $[M]^+$, 372 (89), 294 (18), 292 (25), 77 (5).

1-Methyl-3,4-diphenylisoquinolin-6-amine (4ha): Flash chromatography on a silica gel column (petroleum ether/ethyl acetate, 20:1) afforded a white solid; m.p. 189–191 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 8.8 Hz, 1 H), 7.32–7.23 (m, 5 H), 7.19–7.11 (m, 5 H), 6.92 (dd, *J* = 8.0 Hz, *J* = 2.0 Hz, 1 H), 6.64 (d, *J* = 2.0 Hz, 1 H), 4.12 (s, 2 H), 2.94 (s, 3 H) ppm. ^{13}C NMR (100 MHz,

$CDCl_3$): δ = 156.9, 149.6, 148.0, 141.1, 138.2, 138.1, 131.5, 130.2, 128.2, 127.7, 127.5, 127.5, 126.9, 126.8, 120.7, 118.0, 106.1, 22.3 ppm. IR: $\tilde{\nu}$ = 3346, 2966, 2922, 1613, 1535, 1502, 1414, 1270, 1048, 969, 699 cm^{-1}. MS: *m*/*z* (%) = 310 (62) $[M]^+$, 309 (100), 267 (6), 113 (2), 77 (5). HRMS (EI-TOF): calcd. for $C_{22}H_{18}N_2$ $[M]^+$ 310.1470; found 310.1474.

1,8-Dimethyl-3,4-diphenylisoquinoline (4ia):[7g] Flash chromatography on a silica gel column (petroleum ether/ethyl acetate, 20:1) afforded a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.48 (m, 1 H), 7.40–7.30 (m, 7 H), 7.21–7.15 (m, 5 H), 3.24 (s, 3 H), 3.00 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.6, 148.5, 140.8, 138.3, 138.1, 136.0, 131.5, 130.2, 130.1, 129.5, 129.2, 128.2, 127.6, 127.2, 127.1, 127.0, 125.1, 29.9, 26.0 ppm. MS: *m*/*z* (%) = 309 (63) $[M]^+$, 308 (100), 294 (7), 252 (14), 77 (5).

1-Methyl-3,4-diphenyl-5*H*-pyrido[4,3-*b*]indole (4ja):[7e] Flash chromatography on a silica gel column (petroleum ether/ethyl acetate, 5:1) afforded a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.46 (s, 1 H), 8.17 (d, *J* = 8.0 Hz, 1 H), 7.47–7.24 (m, 10 H), 7.19–7.17 (m, 3 H), 3.13 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.9, 151.4, 144.0, 139.9, 139.6, 135.9, 130.5, 130.3, 129.1, 127.6, 127.3, 126.3, 122.7, 122.5, 121.0, 117.1, 117.0, 111.0, 23.3 ppm. MS: *m*/*z* (%) = 335 (22), 334 (90) $[M]^+$, 333 (100), 318 (8), 291 (9), 77 (3).

4-Methyl-6,7-diphenylthieno[3,2-*c*]pyridine (4ka): Flash chromatography on a silica gel column (petroleum ether/ethyl acetate, 20:1) afforded a white solid; m.p. 147–149 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.50 (d, *J* = 5.6 Hz, 1 H), 7.44 (d, *J* = 5.6 Hz, 1 H), 7.44–7.43 (m, 2 H), 7.39–7.38 (m, 5 H), 7.19 (s, 3 H), 2.93 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.6, 150.0, 149.6, 140.2, 138.6, 133.8, 130.4, 129.8, 128.7, 127.79, 127.76, 127.7, 127.6, 127.3, 122.6, 22.9 ppm. IR: $\tilde{\nu}$ = 2921, 2853, 1669, 1548, 1416, 1079, 1048, 968, 898, 699 cm^{-1}. MS: *m*/*z* (%) = 302 (17), 301 (60) $[M]^+$, 300 (100), 285 (4), 77 (7). HRMS (EI-TOF): calcd. for $C_{20}H_{15}NS$ $[M]^+$ 301.0925; found 301.0924.

7-Methyl-4,5-diphenylthieno[2,3-*c*]pyridine (4la):[7e] Flash chromatography on a silica gel column (petroleum ether/ethyl acetate, 20:1) afforded a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.60 (d, *J* = 5.2 Hz, 1 H), 7.36–7.34 (m, 2 H), 7.31–7.28 (m, 3 H), 7.25–7.19 (m, 6 H), 2.90 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.4, 151.0, 145.7, 140.5, 138.3, 134.3, 131.0, 130.6, 130.3, 128.3, 127.7, 127.2, 127.1, 124.3, 23.7 ppm. MS: *m*/*z* (%) = 302 (12), 301 (50) $[M]^+$, 300 (100), 258 (11), 149 (10), 77 (12).

1,3,4-Triphenylisoquinoline (4ma):[7g] Flash chromatography on a silica gel column (petroleum ether/ethyl acetate, 20:1) afforded a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.18 (d, *J* = 8.4 Hz, 1 H), 7.82 (d, *J* = 7.2 Hz, 2 H), 7.72 (d, *J* = 8.4 Hz, 1 H), 7.59–7.47 (m, 5 H), 7.44–7.41 (m, 2 H), 7.39–7.34 (m, 3 H), 7.30–7.28 (m, 2 H), 7.19–7.15 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.9, 149.7, 141.0, 139.9, 137.6, 137.0, 131.4, 130.5, 130.3, 130.0, 129.8, 128.6, 128.4, 127.6, 127.5, 127.4, 127.1, 126.7, 126.1, 125.5 ppm. MS: *m*/*z* (%) = 358 (25), 357 (88) $[M]^+$, 356 (100), 277 (21), 182 (19), 77 (31).

2-(3,4-Diphenylisoquinolin-1-yl)aniline (4na): Flash chromatography on a silica gel column (petroleum ether/ethyl acetate, 20:1) afforded a white solid; m.p. 196–198 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.12 (d, *J* = 8.2 Hz, 1 H), 7.71 (d, *J* = 8.2 Hz, 2 H), 7.59–7.55 (m, 1 H), 7.51–7.47 (m, 1 H), 7.41–7.34 (m, 6 H), 7.30–7.22 (m, 3 H), 7.19–7.13 (m, 2 H), 6.91–6.86 (m, 2 H), 4.39 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.8, 149.4, 145.8, 140.8, 137.5, 137.4, 132.0, 131.4, 130.4, 130.3, 129.9, 129.7, 128.4, 127.8, 127.6, 127.4, 127.1, 126.7, 126.0, 124.0, 117.9, 117.1 ppm. IR: $\tilde{\nu}$ = 3372, 2923, 2853, 1615, 1543, 1498, 1451, 1253, 1080, 964, 701 cm^{-1}. MS: *m*/*z* (%) = 372 (42) $[M]^+$, 371 (100), 292 (12), 277 (5), 77 (13). HRMS (EI-TOF): calcd. for $C_{27}H_{20}N_2$ $[M]^+$ 372.1626; found 372.1624.

(3,4-Diphenylisoquinolin-1-yl)(phenyl)methanone (4oa): Flash chromatography on a silica gel column (petroleum ether/ethyl acetate, 10:1) afforded a white solid; m.p. 129–130 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.24–8.22 (m, 1 H), 8.11–8.09 (m, 2 H), 7.74 (d, *J* = 8.0 Hz, 1 H), 7.63–7.54 (m, 3 H), 7.50–7.46 (m, 2 H), 7.42–7.34 (m, 5 H), 7.30–7.28 (m, 2 H), 7.16–7.13 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.8, 155.8, 148.9, 140.1, 137.0, 136.9, 136.7, 133.7, 132.5, 131.2, 131.0, 130.7, 130.4, 128.5, 128.5, 127.9, 127.7, 127.7, 127.4, 126.3, 126.0, 125.1 ppm. IR: $\tilde{\nu}$ = 2925, 2853, 1710, 1619, 1329, 1125, 1168, 968, 890, 699 cm^{-1}. MS: *m*/*z* (%) = 385 (12), 384 (12) $[M]^+$, 299 (27), 298 (100), 105 (99), 77 (67). HRMS (EI-TOF): calcd. for $C_{28}H_{19}NO$ $[M]^+$ 385.1467; found 385.1468.

2,3-Diphenyl-8,9-dihydro-7*H*-benzo[*de*]quinoline (4pa):[8] Flash chromatography on a silica gel column (petroleum ether/ethyl acetate, 20:1) afforded a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.45 (m, 2 H), 7.36–7.27 (m, 6 H), 7.24–7.13 (m, 5 H), 3.38 (t, *J* = 6.2 Hz, 2 H), 3.18 (t, *J* = 6.0 Hz, 2 H), 2.30–2.23 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3, 149.5, 141.1, 138.6, 137.9, 136.3, 131.4, 130.3, 130.0, 129.1, 128.2, 127.6, 127.1, 126.9, 124.8, 123.9, 123.6, 34.8, 30.8, 23.5 ppm. MS: *m*/*z* (%) = 321 (52) $[M]^+$, 320 (100), 304 (7), 77 (2).

1-Ethyl-3,4-diphenylisoquinoline (4ra):[7g] Flash chromatography on a silica gel column (petroleum ether/ethyl acetate, 20:1) afforded a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.23–8.21 (m, 1 H), 7.66–7.65 (m, 1 H), 7.56–7.55 (m, 2 H), 7.38–7.32 (m, 5 H), 7.23–7.16 (m, 5 H), 3.43 (q, *J* = 7.2 Hz, 2 H), 1.53 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.3, 149.3, 141.2, 137.8, 136.4, 131.5, 130.4, 129.8, 129.0, 128.3, 127.6, 127.2, 126.9, 126.5, 126.5, 125.4, 125.2, 28.8, 14.0 ppm. MS: *m*/*z* (%) = 309 (62) $[M]^+$, 308 (100), 293 (10), 280 (10), 77 (14).

3,4-Diphenyl-1-propylisoquinoline (4sa):[7g] Flash chromatography on a silica gel column (petroleum ether/ethyl acetate, 20:1) afforded a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.25–8.23 (m, 1 H), 7.67–7.65 (m, 1 H), 7.58–7.55 (m, 2 H), 7.38–7.32 (m, 5 H), 7.23–7.17 (m, 5 H), 3.39 (t, *J* = 7.6 Hz, 2 H), 2.06–1.96 (m, 2 H), 1.14 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.3, 149.3, 141.3, 137.8, 136.4, 131.4, 130.4, 129.7, 129.0, 128.2, 127.9, 127.6, 127.1, 126.9, 126.4, 125.6, 125.3, 37.7, 23.2, 14.5 ppm. MS: *m*/*z* (%) = 324 (52), 323 (100) $[M]^+$, 295 (10), 308 (44), 280 (20), 77 (8).

1-Methyl-3,4-di-*p*-tolylisoquinoline (4ab):[7g] Flash chromatography on a silica gel column (petroleum ether/ethyl acetate, 20:1) afforded a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.16 (dd, *J* = 6.4 Hz, *J* = 3.2 Hz, 1 H), 7.66–7.64 (m, 1 H), 7.57–7.53 (m, 2 H), 7.28 (d, *J* = 8.0 Hz, 2 H), 7.17–7.10 (m, 4 H), 7.00 (d, *J* = 7.6 Hz, 2 H), 3.05 (s, 3 H), 2.38 (s, 3 H), 2.27 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.4, 149.4, 138.2, 136.6, 136.5, 136.3, 134.7, 131.2, 130.2, 129.8, 129.0, 128.9, 128.4, 126.3, 126.1, 125.5, 114.0, 22.7, 21.3, 21.2 ppm. MS: *m*/*z* (%) = 324 (22), 323 (91) $[M]^+$, 322 (100), 308 (5), 91 (3).

3,4-Bis(4-methoxyphenyl)-1-methylisoquinoline (4ac):[7g] Flash chromatography on a silica gel column (petroleum ether/ethyl acetate, 5:1) afforded a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.18–8.15 (m, 1 H), 7.68–7.66 (m, 1 H), 7.59–7.52 (m, 2 H), 7.34–7.31 (m, 2 H), 7.15–7.12 (m, 2 H), 6.92–6.89 (m, 2 H), 6.77–6.73 (m, 2 H), 3.84 (s, 3 H), 3.76 (s, 3 H), 3.06 (s, 3 H) ppm. ^{13}C NMR

(100 MHz, $CDCl_3$): δ = 158.7, 158.6, 157.6, 149.1, 136.5, 133.6, 132.4, 131.5, 129.9, 129.8, 128.4, 126.3, 126.2, 126.0, 125.5, 113.8, 113.2, 55.3, 55.2, 22.7 ppm. MS: *m*/*z* (%) = 356 (15), 355 (68) $[M]^+$, 354 (100), 268 (13).

3,4-Bis(4-chlorophenyl)-1-methylisoquinoline (4ad):[7g] Flash chromatography on a silica gel column (petroleum ether/ethyl acetate, 20:1) afforded a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.20–8.17 (m, 1 H), 7.62–7.58 (m, 3 H), 7.36–7.28 (m, 4 H), 7.20–7.13 (m, 4 H), 3.05 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.4, 148.2, 139.2, 135.8, 135.7, 133.3, 133.3, 132.7, 131.6, 130.4, 128.8, 128.1, 128.0, 127.0, 126.3, 125.9, 125.7, 22.7 ppm. MS: *m*/*z* (%) = 365 (45), 364 (85), 363 (62) $[M]^+$, 362 (100), 327 (16), 291 (12), 277 (8), 111 (26).

3,4-Bis(4-fluorophenyl)-1-methylisoquinoline (4ae):[7g] Flash chromatography on a silica gel column (petroleum ether/ethyl acetate, 20:1) afforded a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.21–8.19 (m, 1 H), 7.62–7.59 (m, 3 H), 7.34–7.30 (m, 2 H), 7.19–7.16 (m, 2 H), 7.08–7.04 (m, 2 H), 6.93–6.88 (m, 2 H), 3.06 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.1 ($J_{C,F}$ = 245.0 Hz), 162.0 ($J_{C,F}$ = 246.0 Hz), 158.1, 148.6, 136.9 ($J_{C,F}$ = 4.1 Hz), 136.0, 133.3 ($J_{C,F}$ = 3.9 Hz), 132.9 ($J_{C,F}$ = 8.1 Hz), 132.0 ($J_{C,F}$ = 8.2 Hz), 130.2, 128.2, 126.8, 126.2, 125.9, 125.7, 115.5 ($J_{C,F}$ = 20.4 Hz), 114.7 ($J_{C,F}$ = 20.0 Hz), 22.7 ppm. MS: *m*/*z* (%) = 332 (29), 331 (100) $[M]^+$, 330 (100), 288 (35), 97 (7).

1-Methyl-3,4-dipropylisoquinoline (4af):[7g] Flash chromatography on a silica gel column (petroleum ether/ethyl acetate, 20:1) afforded a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.09–8.07 (m, 1 H), 7.96 (d, J = 8.8 Hz, 1 H), 7.67–7.63 (m, 1 H), 7.51–7.47 (m, 1 H), 2.99–2.90 (m, 7 H), 1.82–1.73 (m, 2 H), 1.71–1.62 (m, 2 H), 1.09 (t, J = 7.2 Hz, 3 H), 1.04 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.7, 151.3, 135.5, 129.7, 126.6, 126.2, 126.1, 125.4, 123.6, 37.0, 27.3, 24.2, 23.9, 21.7, 14.6, 14.4 ppm. MS: *m*/*z* (%) = 227 (40) $[M]^+$, 226 (38), 213 (18), 212 (100), 199 (31), 198 (80), 184 (39), 43 (11).

4-Ethyl-1-methyl-3-phenylisoquinoline (4ag):[7g] Flash chromatography on a silica gel column (petroleum ether/ethyl acetate, 20:1) afforded a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.16 (d, J = 8.4 Hz, 1 H), 8.07 (d, J = 8.4 Hz, 1 H), 7.73 (t, J = 7.6 Hz, 1 H), 7.59 (t, J = 8.0 Hz, 1 H), 7.52–7.44 (m, 4 H), 7.41–7.37 (m, 1 H), 3.03–2.97 (m, 5 H), 1.26 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.9, 150.7, 141.9, 135.2, 129.9, 129.2, 128.6, 128.2, 127.4, 126.7, 126.4, 126.2, 124.2, 22.6, 21.7, 15.8 ppm. MS: *m*/*z* (%) = 248 (11), 247 (56) $[M]^+$, 246 (100), 232 (17), 231 (18), 115 (14), 77 (15).

Supporting Information (see footnote on the first page of this article): Copies of the ^1H and ^{13}C NMR spectra for the isolated products and X-ray structure of **4da**.

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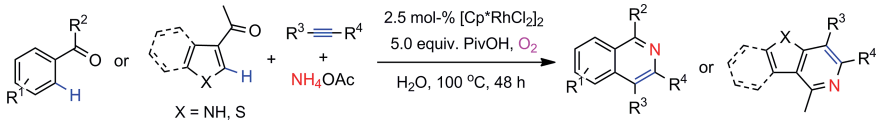
Nitrogen Heterocycles



An efficient Rh^{III}-catalyzed *ortho*-C–H bond activation for the synthesis of substituted isoquinolines and heterocycle-fused pyridines in aqueous medium has been developed. This method involves the in situ generation of ketimines from ketones and ammonium acetate and subsequent oxidative C–H bond activation/annulation of the ketimines with alkynes to form the C–C/C–N bonds spontaneously.

Keywords: Synthetic methods / C–H activation / Nitrogen heterocycles / Annulation / Rhodium / Ketones / Alkynes

