JOC The Journal of Organic Chemistry

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Synthesis of Quinolines via Rh(III)-Catalyzed Oxidative Annulation of Pyridines

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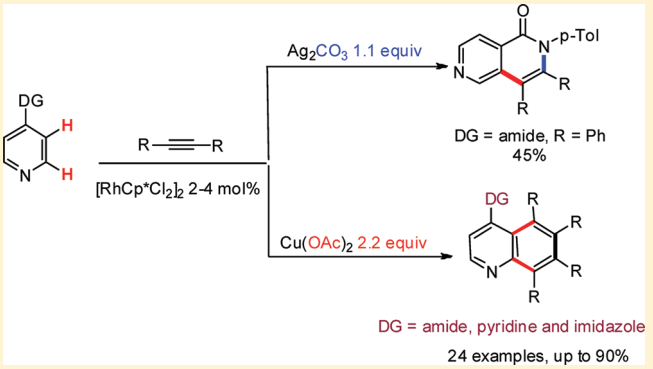
Supporting Information

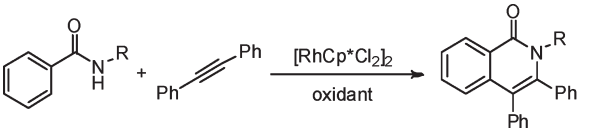
ABSTRACT: Selective synthesis of quinolines has been achieved via oxidative annulation of functionalized pyridines with two alkyne molecules under Rh(III)-catalyzed cascade C−H activation of pyridines using $Cu(OAc)_2$ as an oxidant. The selectivity of this reaction is oxidant-dependent, particularly on the anion of the oxidant.



Quinolines represent an important class of heterocycles as materials, natural products, and biologically active compounds.[1] Various synthetic methods have been developed since late 1800s.[2] Traditional synthetic methods took advantage of the condensation between amines and carbonyl compounds.[2,3] Considering the accessibility of pyridines, transition-metal-mediated synthesis of quinolines and isoquinolines via functionalization of pyridines should be a desirable strategy. In this context, Takahashi and co-workers have reported the stoichiometric coupling of dihalopyridines with zirconacyclopentadienes for the synthesis of quinolines and isoquinolines.[4] Satoh and Miura recently reported synthesis of an isoquinoline starting from a pyridylboronic ester and an alkyne.[5]

Transition-metal-catalyzed direct functionalization of C−H bonds has become an increasingly important tool for the construction of complex organic molecules.[6] Although significance progress has been made, reported examples of direct and selective C−H functionalization of π-deficient heteroarenes such as pyridines are still limited. Simple, direct, and atom-economic access to quinolines via oxidative C−H functionalization of pyridines should be of great advantage. However, C−H bond activation of pyridines can be inhibited by the competitive coordination of the pyridine nitrogen, resulting in lower catalytic efficiency. A number of research groups have made progresses in transition -metal-catalyzed direct functionalization of pyridine rings.[7−15] Catalytic C−H functionalization of unactivated pyridines at the 2-position has been achieved using ruthenium,[7] nickel,[8] silver,[9] and rhodium catalysts.[10] Very recently, Ong[11] and Hiyama and Nakao[12] independently reported direct 4-position C−H functionalization of pyridines, which occurred *via* a nickel η^2-pyridine intermediate. Iridium[13] and palladium[14] catalysts have also successfully enabled the direct C(3)−H functionalization of pyridines. In addition, using an amide directing group, Yu has achieved Pd-catalyzed arylation of pyridines at the 3- and 4-positions.[15] We now report chelation-assisted rhodium(III)-catalyzed oxidative annulation of pyridines with alkynes for the direct synthesis of quinolines, a process that involves 2-fold C−H activation.

Rh(III)-catalyzed[16] coupling between functionalized arenes and alkynes,[17,18] alkenes,[18g,19,20] and imines[21] via a C−H activation pathway has become a powerful tool for the synthesis of isoquinolones,[17a,e,18a,18e] naphthalenes,[5,17d,17e] indoles,[17b,18g] indenols,[18b,d] pyrroles,[17b,18c] isoquinolines,[17f] and pyridones.[18f,h] Recently, we[18e] and others[17e,18a] have reported the oxidative C−C and C−N coupling between benzamides and alkynes for the synthesis of isoquinolones. This was achieved using $[RhCp^*Cl_2]_2$ as a catalyst and $Cu(OAc)_2$ or Ag_2CO_3 as an oxidant (eq 1).

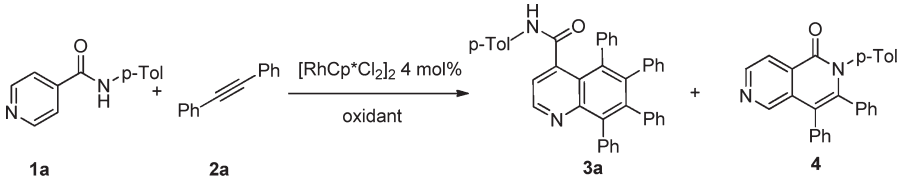


(1)

We initially chose isonicotinamide **1a** as a substrate for the coupling with diphenylacetylene using $[RhCp^*Cl_2]_2$ (4 mol %) as a catalyst and Ag_2CO_3 as an oxidant (CH_3CN, 120 °C). As expected, isoquinolone **4** was obtained (45% yield, entry 1, Table 1).[18e] However, we felt that the pyridine ring is electronically different from its carbocyclic counterpart, which might gave rise to different reaction selectivity. Indeed, we found that 2 equiv of diphenylacetylene was oxidatively incorporated to give

Received: June 20, 2011
Published: August 05, 2011

Table 1. Screening of Oxidants[a]



entry	oxidant	solvent	**3a** (%)[b]	**4** (%)[b]
1	Ag_2CO_3	CH_3CN		45
2	Ag_2CO_3	acetone		41
3	Ag_2O	acetone		29
4	AgOAc	CH_3CN	71	
5	$Cu(OAc)_2$	acetone	89	
6[c]	$Cu(OAc)_2$	acetone	87	
7	$CuCO_3 \cdot Cu(OH)_2$	acetone	42	14

[a] **1a** (0.5 mmol), **2a** (1.1 mmol), oxidant (2.2 equiv for $Cu(OAc)_2$, AgOAc and $CuCO_3 \cdot Cu(OH)_2$ or 1.1 equiv for Ag_2CO_3 and Ag_2O), 4.0 mol % catalyst, solvent (5 mL), sealed tube under nitrogen, 120 °C, 6 h. [b] NMR yield using 1,3,5-trimethoxybenzene as an internal standard. [c] 2 mol % catalyst, isolated yield.

a quinoline (**3a**) in high yield when $Cu(OAc)_2$ was employed as an oxidant (entry 5). This product corresponds to 2-fold C−H activation of the pyridine ring at the 2-and 3-positions. Although transition-metal-catalyzed annulation of carbocyclic arenes is known,[17d,e] no analogous reaction of a pyridine ring has been reported.[5] A series of oxidants has been examined, where significant anion effects of the oxidant were observed. Using Ag_2O and AgOAc as an oxidant, **4** (29%) and **3a** (71%) were obtained as the only product (entries 3 and 4), respectively. It is especially noteworthy that both AgOAc and $Cu(OAc)_2$ afforded the same product in good yield, regardless of the cation of the oxidant. In contrast, a mixture of **3a** and **4** was obtained for $CuCO_3 \cdot Cu(OH)_2$ (entry 7). However, essentially no coupling product was detected using other oxidants such as $CuCl_2$, AgF, and AgOTf. These results suggest that the anion of the oxidant plays a crucial role in controlling the reaction selectivity. Further optimization indicated that by lowering the catalyst loading to 2 mol %, **3a** was still isolated in 87% yield using $Cu(OAc)_2$ as an oxidant (entry 6).

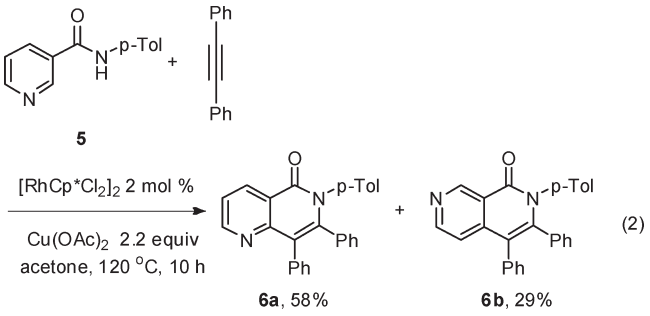
With the optimized reaction conditions in hand, we explored the scope and the limitation of this quinoline synthesis (Scheme 1). Isonicotinamides bearing either an electron-rich or -poor group in the *N*-phenyl ring reacted with diphenylacetylene to give products **3a**−**d** in high yield under the standard conditions. The use of *N*-alkyl groups, including *N*-Me (**3e**), *N*-allyl (**3f**), and *N*-^{t}Bu (**3g**), can also be tolerated, although a lower yield of **3g** was obtained due to steric effects. Simple isonicotinamide **1h** afforded the same type of product, and this is in contrast to our previously reported tetracyclic products obtained when $PhC(O)NH_2$ was used, where formation of two C−C and two C−N bonds was involved.[18e] Since this current reaction involves no formal NH cleavage, oxidative coupling of *N*, *N*-diethylisonicotinamide is expected. However, no desired coupling product was observed under the standard conditions. Moving to a more active $[RhCp^*(CH_3CN)_3]_2[SbF_6]_2$ catalyst, coupling with diphenylacetylene was achieved to afford quinoline **3i** (21%). Further examination of the reaction scope reveals that pyridines bearing electron-withdrawing groups reacted in good yield (**3j**, **3m**), while the introduction of a methoxy group at the 3-position tends to lower the catalytic efficiency (**3k**). Substitutents at the 2-position of pyridine can be well tolerated as in the formation of quinolines **3l** and **3m**, which indicates that the C(3)−H activation occurred at the less sterically hindered position. When quinoline-4-carboxamide was subjected to the conditions, an acridine product (**3n**) was obtained in good yield (73%).

Other internal alkynes are also applicable. Thus alkynes substituted by electron-neutral, -deficient, and -rich aryl groups coupled with **1a** to afford the corresponding quinolines **3o**−**q** in high yield. The present catalytic reaction was successfully extended to heteroaryl and aliphatic alkynes, where **3r** and **3s** were isolated in 82% and 61% yield, respectively. To study the regioselectivity of this reaction, unsymmetrical alkynes such as 1-phenyl-1-pentyne and 2-(pent-1-yn-1-yl)thiophene were employed, and in both cases single regioisomeric products **3t** (68%) and **3u** (79%) were isolated. Pyridines bearing 4-position directing groups other than amides have been successfully applied for quinolone synthesis. The reaction of 2,4′-bipyridine with diphenylacetylene gave 4-(2-pyridinyl)quinoline **3v** in 87% yield. Interestingly, when 4-(1-methylimidazol-2-yl)pyridine was used, both quinoline **3w** and acridine **3x** were isolated, as a result of 2-fold and 4-fold C−H activation, respectively. The isolation of **3x** indicates that the imidazole directing group is more sterically accessible so that further directing effect can be exerted.

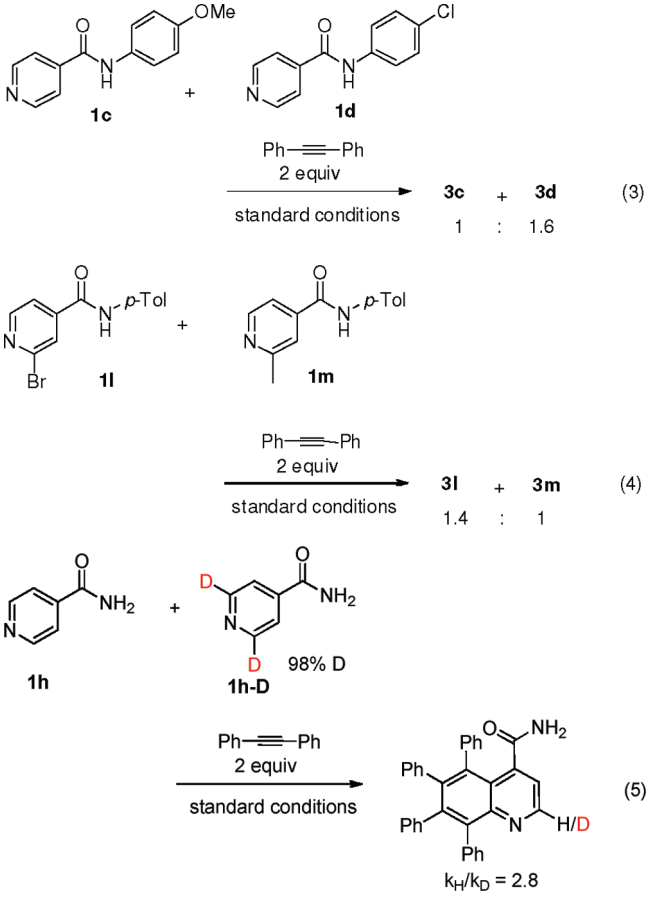
To further define the scope of this reaction, a nicotinamide **5** was used as a substrate with the expectation of an isoquinoline product. However, no such product was generated in the coupling between **5** and diphenylacetylene. Instead, two isomeric naphthyridinones, **6a** (58%) and **6b** (29%), were isolated as a result of different selectivities of C−H activation (eq 2). These results suggest that C(2)−H bond is more reactive than the C(4)−H ones in this reaction system. This is important not only for controlling the regioselectivity of C−H activation but also for shifting the possible activation of the 2′-position C−H bond to N−H bond cleavage and subsequent C−N bond formation.

We further carried out competition reactions to explore this reaction mechanism. A mixture of **1c**, **1d**, and diphenylacetylene in 1:1:2 molar ratio was subjected to the standard conditions, and this coupling reaction is favored for isonicotinamides with electron-poor *N*-aryl groups (eq 3). This observation agrees with

dx.doi.org/10.1021/jo201266u |*J. Org. Chem.* 2011, 76, 7583–7589



N-ligation of the substrate in the catalytic cycle,[18a] although the O-atom can also offer chelation-assistance as in the case of **1i**.[18b,19a] A competition reaction between **1l** and **1m** also led to the conclusion that electron-poor pyridine rings in isonicotinamides react with alkynes in slight preference (eq 4).[18a,e,20a] Considering the important role of C(2)−H activation in controlling the reaction selectivity, an intermolecular competition reaction between **1h** and **1h-D** was conducted (eq 5). A kinetic isotope effect of 2.8 was obtained,[22] which indicates that cleavage of C(2)−H bond in amide **1h** is involved in the rate-determining step.



On the basis of these results and previous reports,[18a] a plausible catalytic cycle is proposed to account for this present reaction (Scheme 2). The catalytic cycle starts from RhCp*-$(OAc)_2$, which is derived from the ligand exchange between the rhodium dimer and the acetate oxidant. Nitrogen coordination of isonicotinamide and subsequent *ortho* C−H activation generates a five-membered rhodacyclic intermediate **8** with the liberation of an acetic acid molecule. Regioselective insertion of the alkyne into the Rh−C bond of **8** affords a seven-membered intermediate **10**. When AgOAc or $Cu(OAc)_2$ is used, protonolysis of the Rh−N bond of **10** by acetic acid is proposed to give a vinyl intermediate **11**, which subsequently undergoes a second *ortho* C−H activation to yield intermediate **12**. A second regioselective insertion of alkyne[23] and subsequent reductive elimination generate the quinoline product **3** and a Rh(I) species, and the latter is oxidized by Cu(II) to complete the catalytic cycle. When Ag_2CO_3 or Ag_2O is employed as an oxidant, water is released after initial cyclometalation. In this case, the Rh−N bond in intermediate **10** is less susceptible to protonolysis due to the poor acidity of water, and consequently 2,6-naphthyridinone product **4** is generated from C−N reductive elimination of **10**. In this catalytic cycle, the role of oxidant probably is 3-fold. It forms a rhodium-bound active catalyst to facilitate C−H activation likely via a concerted metalation-deprotonation (CMD) mechanism.[18a] It releases a HOAc or H_2O byproduct so that the reaction selectivity can be tuned. It also reoxidizes the Rh(I) specie to Rh(III).

In conclusion, we have developed a Rh(III)-catalyzed synthesis of quinolines and acridines starting from isonicotinamides and alkynes using $Cu(OAc)_2$ as an oxidant. The selectivity of the coupling reaction is oxidant-dependent. This coupling reaction gives the first examples of chelation-assisted 2-fold C−H functionalization of pyridine rings at the 2- and 3-positions. Pyridines with various directing groups are applicable, allowing access to diversified products. Additionally, the catalytic reaction is highly regioselective for unsymmetrically substituted alkynes. We observed significant anion effect of the oxidant in the efficiency and selectivity of this coupling reaction.

EXPERIMENTAL SECTION

General Procedure for Rh(III)-Catalyzed Quinoline (3) Synthesis. Isonicotinamide **1a** (106 mg, 0.5 mmol), diphenylacetylene **2a** (196 mg, 1.1 mmol, 2.2 equiv), $Cu(OAc)_2$ (200 mg, 1.1 mmol, 2.2 equiv), and $[RhCp^*Cl_2]_2$ (6.2 mg, 0.01 mmol, 2 mol %) were charged into a 25 mL pressure tube, and acetone (5 mL) was added. After being purged with nitrogen, the mixture was stirred at 120 °C for 6 h. The mixture was then diluted with CH_2Cl_2 (20 mL) and washed with saturated sodium bicarbonate solution. The organic phase was separated, dried with sodium sulfate, and filtered through Celite. All volatiles were removed under reduced pressure. The purification was performed by flash column chromatography on silica gel using EtOAc in petroleum ether.

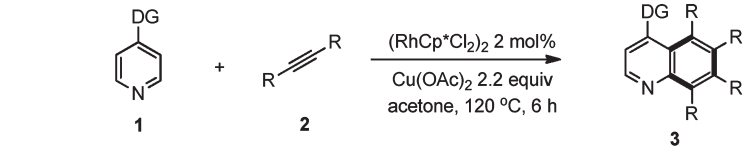
Compound 3a. White solid, 87%. ^{1}H NMR (400 MH_Z, DMSO-d_6): δ 10.05 (s, 1H, NH), 8.93 (d, J = 4.0 Hz, 1H), 7.53 (d, J = 4.0 Hz, 1H), 7.10−7.21 (m, 10H), 6.64−6.99 (m, 14H), 2.25 (s, 3H). ^{13}C NMR (100 MH_Z, DMSO-d_6): 165.9, 149.9, 146.9, 144.7, 142.7, 141.6, 140.07, 140.03, 139.98, 139.5 (two overlapping signals), 138.2, 138.1, 136.6, 132.3, 131.7 (two overlapping signals), 131.1 (two overlapping signals), 128.7, 127.2, 126.9, 126.7, 126.6, 126.3, 126.0, 125.8, 122.6, 121.6, 119.8, 20.9. HRMS (ESI): calcd for $[C_{41}H_{30}N_2O + H]^+$ 567.2431, found 567.2437.

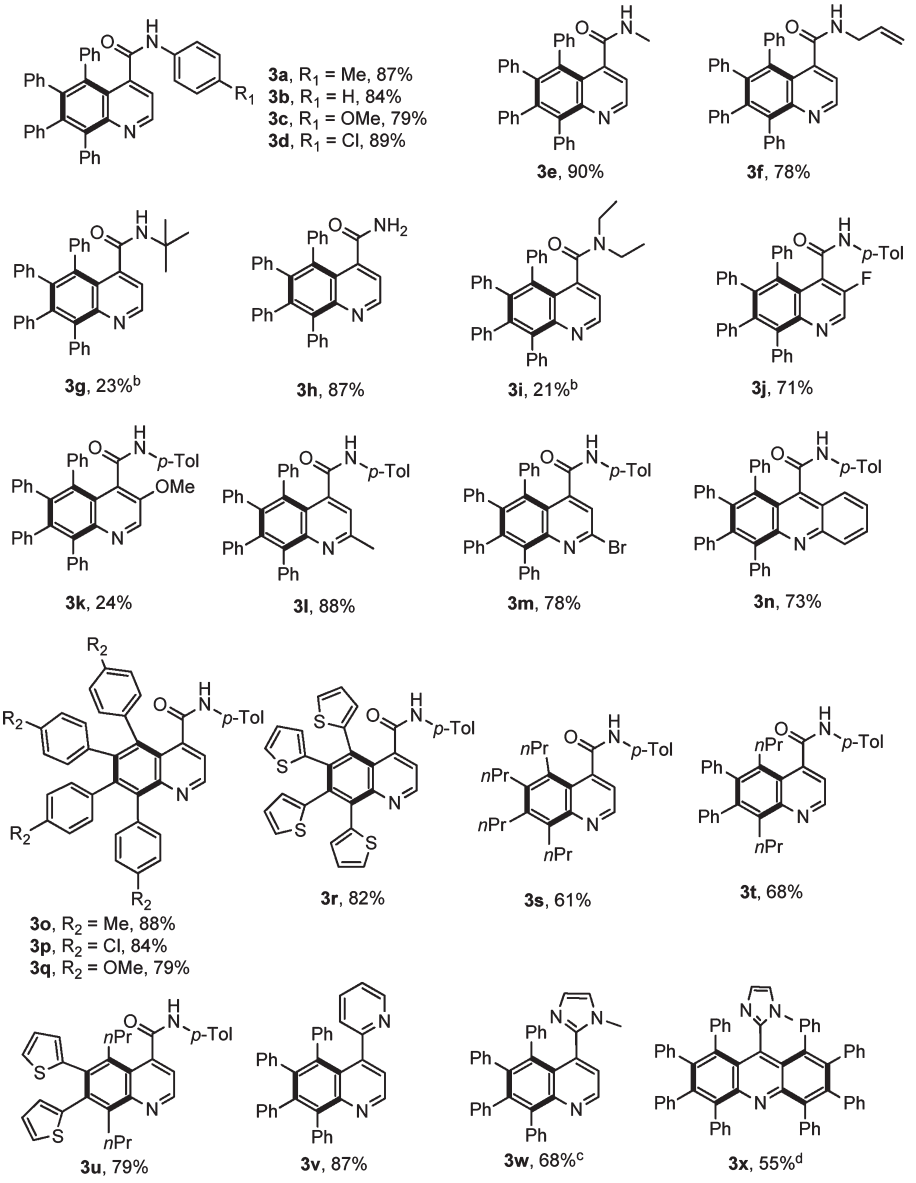
Compound 3b. White solid, 84%. ^{1}H NMR (500 MH_Z, DMSO-d_6): δ 10.12 (s, 1H, NH), 8.90 (d, J = 4.0 Hz, 1H), 7.50 (d, J = 4.0 Hz, 1H), 7.12−7.21 (m, 9H), 7.04 (d, J = 6.0 Hz, 2H), 6.64−7.01 (m, 14H). ^{13}C NMR (125 MH_Z, DMSO-d_6): 165.7, 149.4, 146.4, 144.1, 142.3, 141.2, 139.6, 139.5 (two overlapping signals), 139.0, 138.6, 137.7, 137.6, 131.2 (two overlapping signals), 130.6 (two overlapping signals), 130.5, 127.8, 126.7, 126.4, 126.2, 126.1, 125.8, 125.5, 125.3, 123.0, 122.0, 121.1, 119.3. HRMS (ESI): calcd for $[C_{40}H_{28}N_2O + H]^+$ 553.2274, found 553.2269.

Compound 3c. White solid, 79%. ^{1}H NMR (400 MH_Z, DMSO-d_6): δ 9.97 (s, 1H, NH), 8.91 (d, J = 4.0 Hz, 1H), 7.50 (d, J = 4.0 Hz, 1H), 7.08−7.18 (m, 7H), 7.03 (d, J = 6.0 Hz, 2H), 6.62−6.87 (m, 15H), 3.68 (s, 3H). ^{13}C NMR (100 MH_Z, DMSO-d_6): 165.2, 155.0, 149.4, 146.4,

dx.doi.org/10.1021/jo201266u |J. Org. Chem. 2011, 76, 7583–7589

Scheme 1. Scope of Rh(III)-Catalyzed Quinoline Synthesis[a]





[a] Conditions: **1** (0.5 mmol), **2** (1.1 mmol), $[RhCp^*Cl_2]_2$ (0.01 mmol, 2 mol %), $Cu(OAc)_2$ (1.1 mmol), acetone (5 mL), sealed tube under nitrogen, 120 °C, 6 h, isolated yield. [b] $[RhCp^*(CH_3CN)_3](SbF_6)_2$ (5 mol %) was used as catalyst, *o*-xylene (5 mL), 140 °C, 12 h. [c] 1 mmol (2 0 equiv) of diphenylacetylene was used, acetone (5 mL), 80 °C, 12 h. [d] 2.5 mmol (5.0 equiv) of diphenylacetylene was used, acetone (5 mL), 120 °C, 12 h.

144.3, 142.2, 141.2, 139.6, 139.55, 139.52, 139.0, 137.8, 137.6, 131.9, 131.2 (two overlapping signals), 130.7 (two overlapping signals), 130.5, 126.7, 126.4, 126.2, 126.1, 125.8, 125.5, 125.3, 122.1, 121.1, 120.7, 113.0, 55.0. HRMS (ESI): calcd for $[C_{41}H_{30}N_2O_2 + H]^+$ 583.2380, found 583.2378.

Compound 3d. White solid, 89%. ^{1}H NMR (500 MH_Z, DMSO-d_6): δ 10.21 (s, 1H, NH), 8.90 (d, J = 4.0 Hz, 1H), 7.52 (d, J = 4.0 Hz, 1H), 7.11−7.25 (m, 10H), 7.04 (d, J = 7.5 Hz, 2H), 6.59−6.90 (m, 12H). ^{13}C NMR (125 MH_Z, DMSO-d_6): 165.8, 149.4, 146.4, 143.8, 142.3, 141.3, 139.6, 139.5, 139.4, 138.9, 137.3, 137.6, 137.5, 131.9, 131.2 (two overlapping signals), 130.6 (two overlapping signals), 127.7, 126.7, 126.6, 126.4, 126.3, 126.2, 125.8, 125.6, 125.3, 121.9, 121.1, 120.7. HRMS (ESI): calcd for $[C_{40}H_{27}ClN_2O + H]^+$ 587.1885, found 587.1893.

Compound 3e. White solid, 90%. ^{1}H NMR (500 MH_Z, $CDCl_3$): δ 8.89 (d, J = 4.5 Hz, 1H), 7.31 (d, J = 4.0 Hz, 1H), 7.15−7.21 (m, 5H), 7.11 (5H), 6.82−6.86 (m, 7H), 6.77−6.79 (m, 2H), 6.69−6.71 (m, 2H), 2.32 (d, J = 5 Hz, 3H). ^{13}C NMR (125 MH_Z, $CDCl_3$): 169.2, 149.4, 147.4, 143.8, 143.0, 141.9, 140.3, 139.8, 139.7, 138.9, 138.8, 137.3, 132.2,

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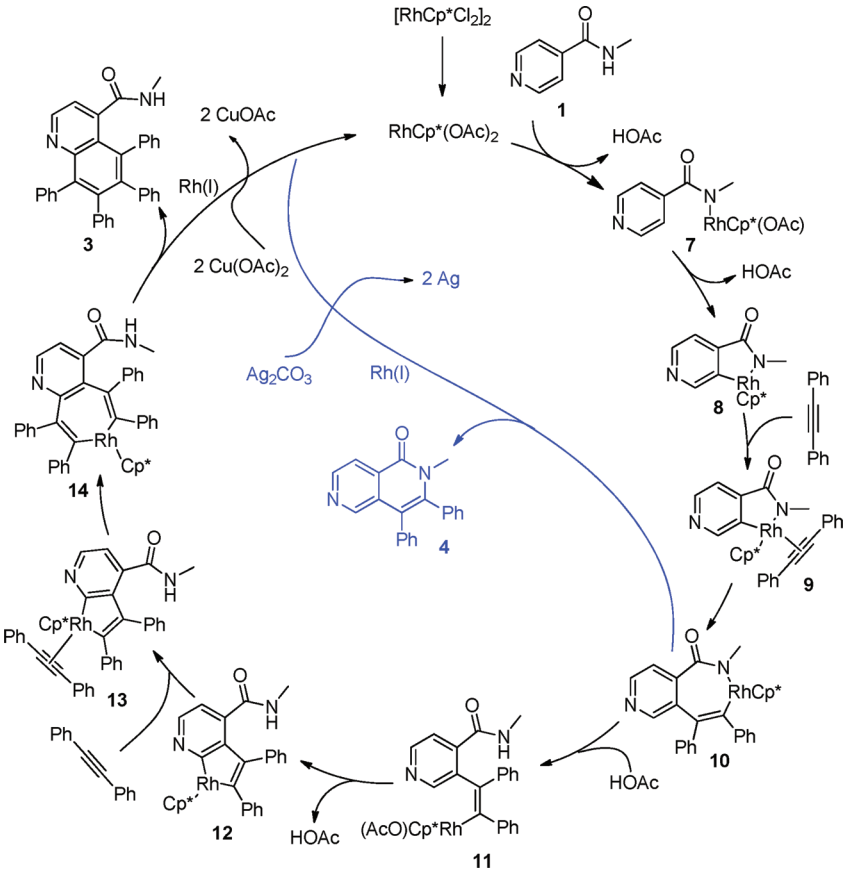
Scheme 2. A Plausible Mechanism of Rh(III)-Catalyzed Quinoline Synthesis



131.4, 131.0, 130.9, 127.1, 126.9, 126.8, 126.7, 126.6, 126.4, 125.6, 125.5, 122.8, 120.7, 26.2. HRMS (ESI): calcd for $[C_{35}H_{26}N_2O + H]^+$ 491.2118, found 491.2123.

Compound 3f. White solid, 78%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.83 (d, J = 4.5 Hz, 1H), 8.22 (t, J = 5.5 Hz, 1H, NH), 7.34 (d, J = 4.0 Hz, 1H), 7.03−7.18 (m, 10H), 6.76−6.85 (m, 10H), 5.61−5.66 (m, 1H), 5.08 (dq, J = 17.0, 1.5 Hz, 1H), 5.00 (dq, J = 10.0, 1.5 Hz, 1H), 3.09 (br, 2H). ^{13}C NMR (125 MHz, DMSO-d_6): 167.2, 149.3, 146.3, 144.5, 142.1, 141.0, 139.62, 139.55, 139.49, 139.0, 137.9, 137.6, 134.7, 131.1, 130.7, 130.5, 126.7, 126.4, 126.24, 126.20, 126.0 (two overlapping signals), 125.7, 125.5, 125.3, 122.2, 121.0, 115.3, 41.0. HRMS (ESI): calcd for $[C_{37}H_{28}N_2O + H]^+$ 517.2274, found 517.2270.

Compound 3g. Reaction conditions: **1g** (89 mg, 0.5 mmol), diphenylacetylene **2a** (196 mg, 1.1 mmol, 2.2 equiv), $Cu(OAc)_2$ (200 mg, 1.1 mmol, 2.2 equiv), $[RhCp^*(CH_3CN)_3](SbF_6)_2$ (20.8 mg, 0.025 mmol, 5 mol %), and *o*-xylene (5 mL) in a sealed pressure tube, 140 °C, 12 h. White solid, 23%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.88 (d, J = 4.0 Hz, 1H), 7.31 (d, J = 4.0 Hz, 1H), 7.05−7.21 (m, 11H), 6.80−6.85 (m, 6H), 6.75−6.77 (m, 2H), 6.64−6.65 (m, 2H), 1.04 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): 167.7, 149.4, 147.6, 145.1, 142.9, 141.9, 140.0, 139.9, 139.8, 139.4, 139.0, 137.6, 132.3, 131.4, 131.0, 130.9, 127.07, 127.03, 126.97, 126.6, 126.5, 126.3, 125.5, 125.3, 122.7, 121.2, 51.7, 28.6. HRMS (ESI): calcd for $[C_{38}H_{32}N_2O + H]^+$ 533.2587, found 533.2581.

Compound 3h. White solid, 87%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.81 (d, J = 4.5 Hz, 1H), 7.49 (br, 1H, NH), 7.34 (d, J = 4.5 Hz, 1H), 7.12−7.16 (m, 4H), 7.04−7.10 (m, 4H), 6.99 (d, J = 7.5 Hz, 2H), 6.76−6.86 (m, 10H), 6.73 (br, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 169.4, 149.3, 146.4, 145.1, 142.1, 140.9, 139.7, 139.6, 139.4, 139.1, 138.1, 137.7, 132.3, 131.2, 130.7, 130.5, 126.7, 126.5, 126.4, 126.3, 126.1, 125.7, 125.5, 125.3, 122.4, 120.8. HRMS (ESI): calcd for $[C_{34}H_{24}N_2O + H]^+$ 477.1961, found 477.1956.

Compound 3i. Reaction conditions: **1g** (89 mg, 0.5 mmol), diphenylacetylene (196 mg, 1.1 mmol, 2.2 equiv), $Cu(OAc)_2$ (200 mg, 1.1 mmol, 2.2 equiv), $[RhCp^*(CH_3CN)_3](SbF_6)_2$ (20.8 mg, 0.025 mmol, 5 mol %), and *o*-xylene (5 mL) in a sealed pressure tube, 140 °C, 12 h. White solid, 21%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.88 (d, J = 4.0 Hz, 1H), 7.30 (d, J = 7.5 Hz, 1H), 7.03−7.23 (m, 8H), 6.99−7.01 (m, 2H), 6.74−6.85 (m, 9H), 6.63−6.66 (m, 1H), 3.27−3.34 (m, 1H), 2.96−3.03 (m, 1 h), 2.68−2.75 (m, 1H), 2.48−2.55 (m, 1H), 1.07 (t, J = 7.0 Hz, 3H), 0.91 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 168.6, 149.1, 147.3, 144.0, 142.9, 142.0, 140.4, 139.9, 139.8, 139.0, 138.0, 137.6, 133.5, 131.1, 131.0, 130.8, 130.72, 130.68, 127.09, 127.05, 126.7, 126.5, 126.4, 126.32, 126.29, 125.7, 125.5, 125.3, 122.7, 119.7, 45.3, 40.1, 14.1, 13.7. HRMS (ESI): calcd for $[C_{38}H_{32}N_2O + H]^+$ 533.2587, found 533.2591.

Compound 3j. White solid, 71%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.85 (s, 1H), 7.14−7.25 (m, 6H), 6.95−7.04 (m, 7H), 6.68−6.86 (m, 12H), 2.28 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 160.3, 153.1 (d, J_{F-C} = 257 Hz), 144.2, 143.4, 142.4, 140.8, 140.6, 140.4, 139.5 (d, J_{F-C} = 9.5 Hz), 138.5, 137.6 (d, J_{F-C} = 4.7 Hz), 137.5, 134.5, 134.2, 133.1, 131.1, 130.9 (two overlapping signals), 129.7, 129.0, 127.4 (d, J_{F-C} = 15 Hz), 127.17, 127.14, 126.7 (two overlapping signals), 126.5, 125.7 (d, J_{F-C} = 15.8 Hz), 123.3, 121.2, 119.7, 20.8. HRMS (ESI): calcd for $[C_{41}H_{29}FN_2O + H]^+$ 585.2337, found 585.2334.

Compound 3k. White solid, 24%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.90 (s, 1H), 7.15−7.23 (m, 6H), 6.95−6.99 (m, 7H), 6.70−6.86 (m, 12H), 3.99 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 163.0, 149.4, 142.9, 142.8, 140.9, 140.0, 139.9 (two overlapping signals), 139.1,

dx.doi.org/10.1021/jo201266u |*J. Org. Chem.* 2011, 76, 7583–7589

139.0, 137.9, 136.9, 135.0, 133.6, 131.4 (two overlapping signals), 131.1, 130.8, 128.9, 128.8, 127.1, 126.8 (two overlapping signals), 126.6, 126.4, 126.3, 125.5, 125.4, 123.5, 119.5, 58.0, 20.9. HRMS (ESI): calcd for $[C_{42}H_{32}N_2O_2 + H]^+$ 597.2537, found 597.2544.

Compound 3l. White solid, 88%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.97 (s, 1H, NH), 7.39 (s, 1H), 7.01−7.16 (m, 9H), 6.93 (d, J = 8.5 Hz, 2H), 6.61−6.85 (m, 13H), 2.52 (s, 3H), 2.20 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): 165.5, 157.5, 145.9, 144.4, 142.1, 140.1, 139.8, 139.7, 139.0, 138.9, 137.9, 137.4, 136.2, 131.7, 131.4 (two overlapping signals), 130.7, 130.6, 128.2, 126.5, 126.4, 126.2, 126.1, 126.0, 125.7, 125.4, 125.2, 121.7, 120.6, 119.3, 24.7, 20.4. HRMS (ESI): calcd for $[C_{42}H_{32}N_2O + H]^+$ 581.2587, found 581.2583.

Compound 3m. White solid, 78%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 (s, 1H), 7.14−7.22 (m, 5H), 7.05 (d, J = 7.0 Hz, 2H), 6.99 (d, J = 8.4 Hz, 2H), 6.93−6.95 (m, 3H), 6.81−6.90 (m, 9H), 6.76−6.78 (m, 2H), 6.68−6.70 (m, 2H), 2.28 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): 163.7, 148.6, 148.0, 146.2, 143.6, 141.8, 139.2, 139.1, 138.7, 138.0, 137.9, 137.2, 135.9, 132.1, 131.17, 131.09, 130.6, 130.4, 128.3, 126.8, 126.5, 126.34, 126.30, 126.2, 126.0, 125.7, 125.4, 121.8, 121.4, 119.4, 20.4. HRMS (ESI): calcd for $[C_{41}H_{29}BrN_2O + H]^+$ 645.1536, found 645.1541.

Compound 3n. White solid, 73%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.23 (s, 1H, NH), 7.85−7.89 (m, 2H), 7.77 (t, J = 7.4 Hz, 1H), 7.57 (t, J = 7.4 Hz, 1H), 7.16−7.24 (m, 8H), 7.11 (d, J = 7.3 Hz, 1H), 6.71−7.01 (m, 13H), 6.68 (t, J = 7.2 Hz, 1H), 6.57 (d, J = 7.4 Hz, 1H), 2.23 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): 164.2, 147.2, 147.0, 142.8, 142.4, 141.3, 139.7, 139.6, 139.0, 138.9, 137.5, 137.2, 136.1, 132.5, 132.0, 131.9, 131.53 (two overlapping signals), 131.49, 130.6 (two overlapping signals), 130.4, 130.2, 129.4, 128.4 (two overlapping signals), 127.0, 126.7 (two overlapping signals), 126.5, 126.4, 126.22, 126.17, 126.14 (two overlapping signals), 126.0, 125.57, 125.54, 125.46, 125.3, 123.0, 119.8, 119.2 (two overlapping signals), 20.4. HRMS (ESI): calcd for $[C_{45}H_{32}N_2O + H]^+$ 617.2587, found 617.2591.

Compound 3o. White solid, 88%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.89 (d, J = 4.2 Hz, 1H), 7.33 (d, J = 4.2 Hz, 1H), 7.06 (d, J = 8.1 Hz, 2H), 7.03−6.94 (m, 7H), 6.91 (d, J = 7.5 Hz, 2H), 6.71−6.60 (m, 8H), 6.57 (d, J = 8.0 Hz, 2H), 2.28 (s, 3H), 2.27 (s, 3H), 2.10 (s, 3H), 2.08 (s, 3H), 1.92 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 166.3, 149.1, 147.7, 143.7, 143.4, 142.1, 140.1, 137.3, 137.0, 136.8, 136.4, 136.0, 135.8, 135.5, 135.0, 134.7, 134.6, 133.6, 131.7, 131.3, 130.83, 130.76, 128.9, 127.9, 127.8, 127.3, 127.2, 122.9, 120.4, 119.4, 21.3, 21.05, 21.01, 20.86, 20.8. HRMS (ESI): calcd for $[C_{45}H_{38}N_2O + H]^+$ 623.3057, found 623.3060.

Compound 3p. White solid, 84%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.94 (d, J = 4.2 Hz, 1H), 7.43 (d, J = 4.1 Hz, 1H), 7.22 (d, J = 8.4 Hz, 2H), 7.03−7.12 (m, 5H), 6.84−7.01 (m, 10H), 6.69 (d, J = 8.5 Hz, 2H), 6.61 (d, J = 8.0 Hz, 2H), 2.30 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 165.6, 150.0, 147.3, 143.6, 141.8, 140.6, 139.8, 137.6, 137.4, 136.9, 136.6, 136.4, 134.5, 134.4, 133.6, 132.9, 132.64, 132.59, 132.4, 132.3, 132.02, 131.95, 129.4, 127.8, 127.5 (two overlapping signals), 127.4, 122.9, 120.9, 119.4, 20.9. HRMS (ESI): calcd for $[C_{41}H_{26}Cl_4N_2O + H]^+$ 703.0872, found 703.0870.

Compound 3q. White solid, 79%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.88 (d, J = 3.0 Hz, 1H), 7.32−7.36 (m, 3H), 6.98−7.22 (m, 9H), 6.58−6.88 (m, 10H), 3.79 (br, 6H), 3.72 (s, 3H), 3.58 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 166.1, 159.6, 159.2, 158.3, 158.1, 149.5, 147.7, 143.8, 143.1, 140.3, 139.7, 135.0, 133.9, 132.7, 132.6, 132.5 (two overlapping signals), 131.9, 131.5, 130.5, 129.0, 125.5, 123.0, 120.6, 119.4, 115.3, 113.7, 113.1, 112.9, 112.7, 55.2 (two overlapping signals), 55.0 (two overlapping signals), 20.8. HRMS (ESI): calcd for $[C_{45}H_{38}N_2O_5 + H]^+$ 687.2853, found 687.2850.

Compound 3r. Yellow solid, 82%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.02 (d, J = 4.2 Hz, 1H), 7.51 (d, J = 4.1 Hz, 1H), 7.39 (dd, J = 5.1, 1.1 Hz, 1H), 7.15 (d, J = 8.4 Hz, 2H), 7.12 (dd, J = 5.1, 1.0 Hz, 1H), 7.09 (dd, J = 5.1, 1.1 Hz, 1H), 7.03−7.05 (m, 3H), 6.97−6.98 (m, 2H), 6.91−6.94 (m, 2H), 6.71 (dd, J = 5.0, 3.6 Hz, 1H), 6.65−6.69 (m, 2H), 6.61 (dd, J = 3.5, 1.0 Hz, 1H), 6.56 (dd, J = 3.5, 1.0 Hz, 1H), 2.30 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 165.5, 150.3, 147.9, 147.6, 143.9, 140.2, 139.8, 138.4, 138.2, 137.2, 136.0, 134.9, 134.1, 133.6, 132.8, 132.6, 132.0, 129.9, 129.6, 129.3, 129.1, 128.1, 127.0, 126.5, 126.2, 125.8, 125.7, 124.6, 121.9, 119.5, 20.8. HRMS (ESI): calcd for $[C_{33}H_{22}N_2OS_4 + H]^+$ 591.0688, found 591.0684.

Compound 3s. White solid, 61%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.76 (d, J = 4.1 Hz, 1H), 7.49−7.51 (m, 3H), 7.20 (d, J = 4.1 Hz, 1H), 7.16 (d, J = 8.2 Hz, 2H), 3.19−3.30 (m, 2H), 2.95−2.98 (m, 2H), 2.77−2.81 (m, 2H), 2.71−2.74 (m, 2H), 2.34 (s, 3H), 1.48−1.67 (m, 8H), 1.06−1.13 (m, 9H), 0.84 (t, J = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 168.8, 147.3, 146.7, 141.9, 141.5, 140.3, 137.9, 135.4, 134.4, 133.9, 129.7, 121.3, 119.6, 119.3, 32.8, 32.4, 32.3, 30.5, 25.8, 25.0, 24.8, 24.6, 20.8, 15.03, 15.0, 14.9, 14.5. HRMS (ESI): calcd for $[C_{29}H_{38}N_2O + H]^+$ 431.3057, found 431.3061.

Compound 3t. White solid, 68%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.91 (d, J = 4.2 Hz, 1H), 7.75 (br, 1H), 7.50 (d, J = 8.4 Hz, 2H), 8.91 (d, J = 4.2 Hz, 1H), 7.00−7.17 (m, 8H), 6.92−6.99 (m, 4H), 2.97−3.04 (m, 2H), 2.75−2.83 (m, 2H), 2.33 (s, 3H), 1.54−1.63 (m, 2H), 1.33 (br, 2H), 0.81 (t, J = 7.3 Hz, 3H), 0.50 (t, J = 7.2 Hz, 3H). 13C NMR (125 MHz, $CDCl_3$): 168.3, 147.86, 147.84, 143.3, 142.7, 142.4, 140.8, 140.6, 138.2, 135.2, 134.7, 134.5, 130.1 (two overlapping signals), 129.9, 129.7, 127.1, 126.10, 126.06, 121.9, 120.0, 119.7, 33.5, 31.9, 25.7, 24.6, 20.9, 14.7, 14.2. HRMS (ESI): calcd for $[C_{35}H_{34}N_2O + H]^+$ 499.2744, found 499.2746.

Compound 3u. White solid, 79%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.00 (d, J = 4.1 Hz, 1H), 7.51 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 4.1 Hz, 1H), 7.44 (br, 1H), 7.21 (dd, J = 5.1, 1.1 Hz, 1H), 7.15−7.19 (m, 3H), 6.87 (dd, J = 5.1, 3.5 Hz, 1H), 6.83 (dd, J = 5.1, 3.5 Hz, 1H), 6.71 (dd, J = 3.4, 1.1 Hz, 1H), 6.69 (dd, J = 3.4, 1.0 Hz, 1H), 3.04−3.18 (m, 2H), 2.79−2.98 (m, 2H), 2.34 (s, 3H), 1.61−1.73 (m, 2H), 1.46 (br, 2H), 0.91 (t, J = 7.3 Hz, 3H), 0.64 (t, J = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): 167.8, 148.6, 148.0, 142.8, 141.3, 140.9, 140.6, 137.9, 136.6, 135.5, 135.1, 134.7, 129.8, 128.6, 128.2, 126.0 (two overlapping signals), 125.5, 125.4, 122.3, 120.6, 119.7, 33.9, 32.4, 26.6, 25.2, 20.9, 14.8, 14.3. HRMS (ESI): calcd for $[C_{31}H_{30}N_2OS_2 + H]^+$ 511.1872, found 511.1876.

Compound 3v. White solid, 87%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.95 (d, J = 4.2 Hz, 1H), 8.28 (d, J = 4.4 Hz, 1H), 7.31 (d, J = 4.2 Hz, 1H), 7.16−7.26 (m, 6H), 6.95 (d, J = 7.8 Hz, 1H), 6.67−6.86 (m, 16H). ^{13}C NMR (125 MHz, $CDCl_3$): 159.4, 149.1, 148.5, 147.86, 147.80, 142.5, 141.5, 140.3, 140.17, 140.13, 140.03, 139.4, 137.8, 135.1, 131.5, 131.2, 131.0, 127.1, 126.6, 126.5, 126.4 (two overlapping signals), 126.2, 125.7, 125.5, 125.2, 124.9, 124.8, 124.2, 121.0. HRMS (ESI): calcd for $[C_{38}H_{26}N_2 + H]^+$ 511.2169, found 511.2176.

Compound 3w. Reaction conditions: 4-(1-methyl-1*H*-imidazol-2-yl)pyridine (79.5 mg, 0.5 mmol), diphenylacetylene (178 mg, 1.0 mmol, 2.0 equiv), $Cu(OAc)_2$ (181 mg, 1.0 mmol, 2.0 equiv), $[RhCp^*Cl_2]_2$ (6.2 mg, 2.0 mol %), and acetone (5 mL) in a pressure tube, 80 °C, 12 h. White solid, 68%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.93 (d, J = 4.2 Hz, 1H), 7.29 (d, J = 4.2 Hz, 1H), 7.12−7.27 (m, 5H), 6.94 (d, J = 7.7 Hz, 1H), 6.72−6.90 (m, 12H), 6.70 (d, J = 1.2 Hz, 1H), 6.69−6.61 (m, 2H), 6.27 (d, J = 1.2 Hz, 1H), 3.24 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 148.8, 147.6, 146.0, 142.8, 142.1, 140.2, 139.9, 139.8, 139.1, 138.4, 137.7, 137.4, 132.5, 131.5, 131.3, 131.1, 130.9, 130.9, 129.0, 128.7, 127.1, 127.0, 126.9, 126.6 (two overlapping signals), 126.4, 126.2, 126.2 (two overlapping signals), 125.9, 125.7, 125.5 (two overlapping signals), 125.5, 125.2, 124.8, 33.5. HRMS (ESI): calcd for $[C_{37}H_{27}N_3 + H]^+$ 514.2278, found 514.2282.

Compound 3x. Reaction conditions: 4-(1-methyl-1*H*-imidazol-2-yl)pyridine (79.5 mg, 0.5 mmol), diphenylacetylene (445 mg, 2.5 mmol, 5.0 equiv), $Cu(OAc)_2$ (455 mg, 2.5 mmol, 2.5 equiv), $[RhCp^*Cl_2]_2$ (6.2 mg, 2.0 mol %), and acetone (5 mL) in a pressure tube, 120 °C, 12 h.

White solid, 55%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.03 (d, J = 7.0 Hz, 4H), 6.90−6.98 (m, 6H), 6.78−6.83 (m, 8H), 6.72−6.77 (m, 10H), 6.68−6.70 (m, 4H), 6.56−6.64 (m, 8H), 6.19 (d, J = 1.1 Hz, 1H), 5.39 (d, J = 1.0 Hz, 1H), 2.98 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 146.6, 143.4, 142.5, 142.3, 140.2, 140.1, 138.9, 138.5, 138.1, 137.2, 133.7, 132.4, 131.6, 131.1, 131.0, 130.8, 129.6, 128.6, 126.6, 126.5 (two overlapping signals), 126.3, 126.0, 125.5, 125.48, 125.47, 125.3, 125.2, 125.1, 124.9, 120.5, 33.8. HRMS (ESI): calcd for $[C_{65}H_{45}N_3 + H]^+$ 868.3686, found 868.3682.

Synthesis of Compound 4. Compound **4** was synthesized in 45% yield by following a literature report.[18e] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61−8.74 (m, 2H), 8.29 (d, J = 5.1 Hz, 1H), 7.18−7.27 (m, 3H), 7.14 (d, J = 6.6 Hz, 2H), 7.03 (d, J = 8.2 Hz, 2H), 6.97 (d, J = 8.3 Hz, 2H), 6.90−6.94 (m, 5H), 2.23 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 161.6, 149.3, 146.4, 143.0, 137.7, 136.2, 134.6, 134.1, 131.7, 131.4, 130.9, 130.3, 129.4, 128.8, 128.2, 127.5, 127.3, 127.2, 120.0, 116.9, 21.0. HRMS (ESI): calcd for $[C_{27}H_{20}N_2O + H]^+$ 389.1648, found 389.1644.

Compounds **6a** and **6b** were synthesized by following the same procedure for the quinolines. Compound **6a**: orange solid, yield 58%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.94 (dd, J = 4.5, 1.9 Hz, 1H), 8.79 (dd, J = 8.0, 1.9 Hz, 1H), 7.42 (dd, J = 8.0, 4.5 Hz, 1H), 7.17−7.20 (m, 2H), 7.12−7.15 (m, 3H), 7.02 (d, J = 8.2 Hz, 2H), 6.97 (d, J = 8.3 Hz, 2H), 6.89−6.94 (m, 5H), 2.24 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): 162.9, 154.7, 153.3, 145.3, 137.6, 136.5, 136.3, 135.5, 134.5, 131.8, 130.8, 129.4, 129.0, 127.5, 127.4, 127.1, 126.7, 121.6, 121.3, 120.6, 21.0. HRMS (ESI): calcd for $[C_{27}H_{20}N_2O + H]^+$ 389.1648, found 389.1645. Compound **6b**: orange solid, yield 29%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.71 (s, 1H), 8.67 (d, J = 5.6 Hz, 1H), 7.17 −7.24 (m, 3H), 7.06 −7.11 (m, 3H), 7.03 (d, J = 8.1 Hz, 2H), 6.92−6.97 (m, 5H), 6.87−6.91(m, 2H), 2.24 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.2, 151.8, 151.4, 146.2, 143.0, 137.8, 136.0, 134.9, 134.2, 131.4, 130.5, 129.4, 129.0, 128.2, 127.7, 127.3 (two overlapping signals), 120.3, 118.2, 117.2, 21.1. HRMS (ESI): calcd for $[C_{27}H_{20}N_2O + H]^+$ 389.1648, found 389.1644.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures for KIE studies and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

We thank the Dalian Institute of Chemical Physics, CAS, for generous financial support. This work was also supported by the NSFC (No. 21072188).

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(22) In a control experiment, **1h**, **2a**, $[RhCp^*Cl_2]_2$, and $Cu(OAc)_2$ were allowed to react in acetone-d_6 (120 °C, 12 h). ^{1}H NMR analysis indicated essentially no (<5%) H/D exchange in the 2-position of the pyridine ring in **3h** (see the Supporting Information). In contrast, significant H/D exchange was observed at the 3-position of the product, suggesting that the KIE at the 3-position cannot be accurately measured using competitive studies.

(23) Alkyne migratory insertion of **13** may occur with a different selectivity to give an isomer of **14**.