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Synthesis of 2-Arylindoles by Rhodium-Catalyzed/Copper-Mediated Annulative Coupling of *N*-Aryl-2-aminopyridines and Propargyl Alcohols via Selective C−H/C−C Activation

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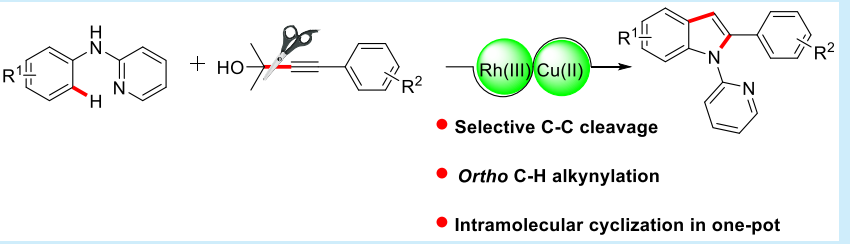
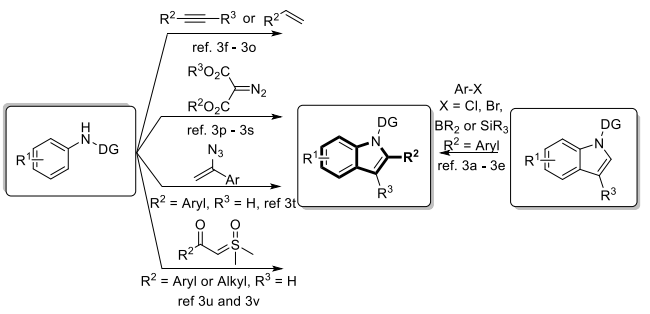
Supporting Information



ABSTRACT: A versatile rhodium-catalyzed/copper-mediated C−H/C−C activation and cascade annulation reaction was described to form 2-arylindole derivatives. Highly selective C−C bond cleavage of γ-substituted *tert*-propargyl alcohols occurred, together with pyridine-directed *ortho* C(sp^2)−H bond activation, affording a series of 2-arylindoles with yields up to 90%. Subsequent derivations were smoothly conducted to access polyfunctionalized 2-arylindoles, illustrating the potential applications of this method.

Indole skeletons are crucial structural motifs existing in abundant natural products and drug molecules.[1] Conventional syntheses of multisubstituted indoles, for example, the Fischer, Bischler, Larock, and Bartoli indole synthetic methods, have emerged as practical and efficient routes up to now.[2] Nonetheless, transition-metal (Co, Ru, Rh, Ir, Pd, etc.)-catalyzed direct C−H activation reactions with auxiliary directing groups have attracted increasing attention in indole skeleton construction with synthetic diversity and general substance availability in recent years (Scheme 1).[3] In particular, 2-arylindoles are well established as important components of various biological active compounds, such as tubulin polymerization inhibitors and strong antiplasmodial activity molecular (isocryptolepine) and antiviral hepatitis C virus (HCV) inhibitors (Figure 1).[4] It is well noted that two

Scheme 1. Transition-Metal-Catalyzed Indole Derivative Synthesis



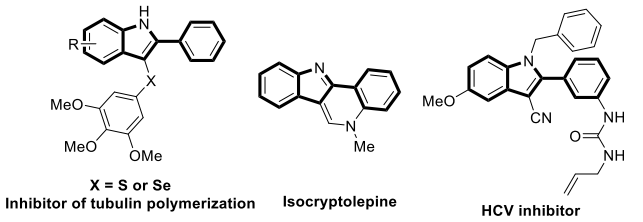


Figure 1. Selected examples of 2-arylindole-containing biologically active molecules.

elegant approaches to 2-arylindoles were reported recently by the Cui[3t] and Huang[3u] groups, respectively. In spite of this progress in 2-arylindole synthesis, the feasibility to derivations and abundance in biological active molecules still render it highly appealing for facile synthesis.

On the other hand, propargyl alcohols have served as flexible building blocks involved in allene and alkyne formation as well as cyclization reactions.[5] Especially, they could act as terminal alkyne precursors via C−C bond activation, which participated in cross coupling reactions with alkynes,[6] alkenes,[7] aryl halides,[8] H-phosphonates,[9] or benzylic carbonates.[10] For example, Wen and co-workers reported Rh/Cu-catalyzed reactions merging C−C cleavage of γ-substitued *tert*-propargyl alcohols and C−H activation with directing group assistance to afford C2-selective alkynylated indoles (R = Me) and pyrido[2,1-*a*]indoles (R = H), respectively, in 2016 (Scheme

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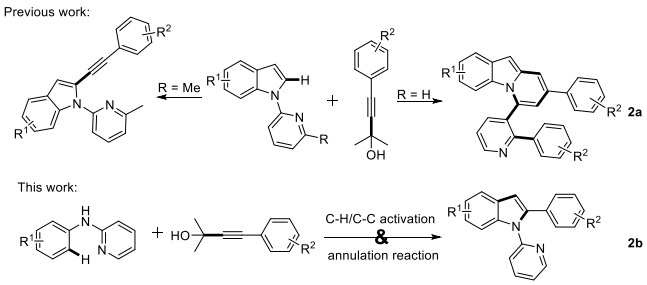
2a).[11] In continuation of our work on C−C activation[12] and synthesis of heterocyclic compounds,[13] herein we disclosed

Scheme 2. Propargyl Alcohols Involved C−H/C−C Activation Reactions

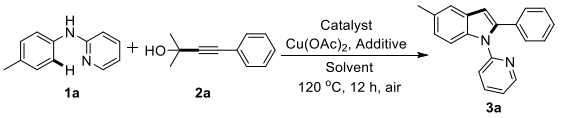


rhodium-catalyzed/copper-mediated aniline derivative *ortho* C−H alkynylation and cascade intramolecular annulation reactions toward 2-arylindole derivatives in one pot (Scheme 2b). This work features the following items: highly selective C−C cleavage of propargyl alcohols, *ortho* C−H alkynylation of aniline derivatives, and one-pot cascade reaction to form 2-arylindoles.

Our investigation commenced with the reaction between *N*-4-methylphenyl-2-animopyridine (**1a**) and 2-methyl-4-phenyl-but-3-yn-2-ol (**2a**) in 1,4-dioxane in the presence of 5 mol % $[Cp^*RhCl_2]_2$ and 2.0 equiv of $Cu(OAc)_2$ at 120 °C for 12 h under air. As shown in Table 1, the desired C−H/C−C activation and annulation product **3a** was obtained in 55% yield. Sequential metal salt screening revealed that Ni(II), Co(II), Ru(II), and Pd(II) were not beneficial to the reaction without formation of **3a** (Table 1, entries 2−5). Solvent effects were then explored, and 1,4-dioxane was shown to be better than others including DCE, toluene, MeCN, DMF, DMSO, and MeOH (Table 1, entries 6−11). We then equipped this reaction under a N_2 or O_2 atmosphere, and a dramatic increased yield (66%) was observed with N_2 while only a trace of **3a** was detected, which would be possibly caused by the instability of **1a** under an O_2 atmosphere (Table 1, entries 12 and 13). Meanwhile, when the temperature was decreased to 100 °C, this reaction was almost suppressed (Table 1, entry 14). We also increased the temperature to 130 °C, but no better yield was achieved (Table 1, entry 15). Meanwhile, acid (HOAc and PivOH) or base (K_2CO_3 and Cs_2CO_3) additives were also studied, affording inferior product yields (Table 1, entries 16−19). To our delight, the reaction was significantly improved to give **3a** in 77% isolated yield with a loading of 3.0 equiv of **2a** and 2.5 equiv of $Cu(OAc)_2$ (Table 1, entry 20). Prolonging the reaction time to 24 h did not facilitate the formation of **3a** (Table 1, entry 21). At last, control experiments indicated the necessity of $[Cp^*RhCl_2]_2$ and $Cu(OAc)_2$, as no **3a** was formed in the absence of either of them (Table 1, entries 22 and 23). Phenylacetylene instead of **2a** was employed in this reaction with only a trace amount of **3a** being obtained (Table 1, entry 24). Therefore, 5 mol % $[Cp^*RhCl_2]_2$, 2.5 equiv of $Cu(OAc)_2$, and 3.0 equiv of **2a** in 1,4-dioxane (1.0 mL) at 120 °C for 12 h under N_2 were selected as the optimal reaction conditions.

With the optimized reaction conditions in hand, a series of substituted *N*-aryl-2-aminopyridines were investigated, and the reactions were performed smoothly with yields ranging from 26 to 90%, as depicted in Scheme 3. Steric effects seemed to be vital for the reaction. For example, substrate bearing an *ortho*

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	solvent	yield[b] (%)
1	$[Cp^*RhCl_2]_2$	1,4-dioxane	55
2	$Ni(OAc)_2{\cdot}4H_2O$	1,4-dioxane	0
3	$Co(OAc)_2{\cdot}4H_2O$	1,4-dioxane	0
4	$[RuCl_2(p\text{-cymene})]_2$	1,4-dioxane	0
5	$Pd(OAc)_2$	1,4-dioxane	0
6	$[Cp^*RhCl_2]_2$	DCE	18
7	$[Cp^*RhCl_2]_2$	toluene	27
8	$[Cp^*RhCl_2]_2$	MeCN	50
9	$[Cp^*RhCl_2]_2$	DMF	41
10	$[Cp^*RhCl_2]_2$	DMSO	39
11	$[Cp^*RhCl_2]_2$	MeOH	45
12[c]	$[Cp^*RhCl_2]_2$	1,4-dioxane	66
13[d]	$[Cp^*RhCl_2]_2$	1,4-dioxane	trace
14[c,e]	$[Cp^*RhCl_2]_2$	1,4-dioxane	0
15[c,f]	$[Cp^*RhCl_2]_2$	1,4-dioxane	62
16[c,g]	$[Cp^*RhCl_2]_2$	1,4-dioxane	49
17[c,h]	$[Cp^*RhCl_2]_2$	1,4-dioxane	42
18[c,i]	$[Cp^*RhCl_2]_2$	1,4-dioxane	42
19[c,j]	$[Cp^*RhCl_2]_2$	1,4-dioxane	37
20[c,k]	$[Cp^*RhCl_2]_2$	1,4-dioxane	**81**(77)
21[c,k,l]	$[Cp^*RhCl_2]_2$	1,4-dioxane	75
22[c]		1,4-dioxane	0
23[c,m]	$[Cp^*RhCl_2]_2$	1,4-dioxane	0
24[c,n]	$[Cp^*RhCl_2]_2$	1,4-dioxane	trace

[a]General conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), catalyst (5 mol %), and $Cu(OAc)_2$ (2.0 equiv) in solvent (1.0 mL) were stirred at 120 °C for 12 h in the air. [b]NMR yields using CH_2Br_2 as the internal standard and isolated yields were shown in parentheses. [c]Under N_2 atmosphere. [d]Under O_2 atmosphere. [e]Reaction temperature 100 °C. [f]Reaction temperature 130 °C. [g]HOAc (2.0 equiv). [h]PivOH (2.0 equiv). [i]K_2CO_3 (2.0 equiv). [j]Cs_2CO_3 (2.0 equiv). [k]**2a** (3.0 equiv) and $Cu(OAc)_2$ (2.5 equiv). [l]24 h. [m]Without $Cu(OAc)_2$. [n]Phenylacetylene (3.0 equiv) instead of **2a**.

methyl group gave a yield of 26% (**3p**), while 77% (**3a**) and 67% (**3l**) yields were obtained in the case of *para* and *meta* methyl group substituted substrates. In addition, *para* isopropyl (**3c**), −OMe (**3d**), phenyl (**3e**), and −Ac (**3h**) substituted *N*-aryl-2-aminopyridines as well as *N*-phenyl-2-aminopyridine (**3b**) could be employed well with moderate to good yields. It was worth noting that substrates containing a chloro (**3f** and **3m**) or bromo group (**3g**) could also be applicable in this reaction, which indicated the potential derivative applications. Dimethyl and dichloro substrates also underwent these transformations smoothly (**3n** and **3o**). Meanwhile, the substrates with strong electron-withdrawing groups (−CF_3, −CN, and −F) delivered relatively lower yields of 55% (**3i**), 39% (**3j**), and 31% (**3k**), respectively.

Next, the scope of *tert*-propargyl alcohols was explored as shown in Scheme 4. Substrates with an *ortho* methyl substituent gave the desired product (**3q**, 65%) in a relatively lower yield compared with the *meta* methyl substituted one (**3r**, 76%) and the *para* methyl substituted one (**3s**, 77%) due to the possible steric hindrance. Substrates bearing other *para* substituents (**3t**−**3z**) afforded the corresponding products in moderate to good yields, among which the strong electron-withdrawing moiety (−CN) suppressed this reaction to some

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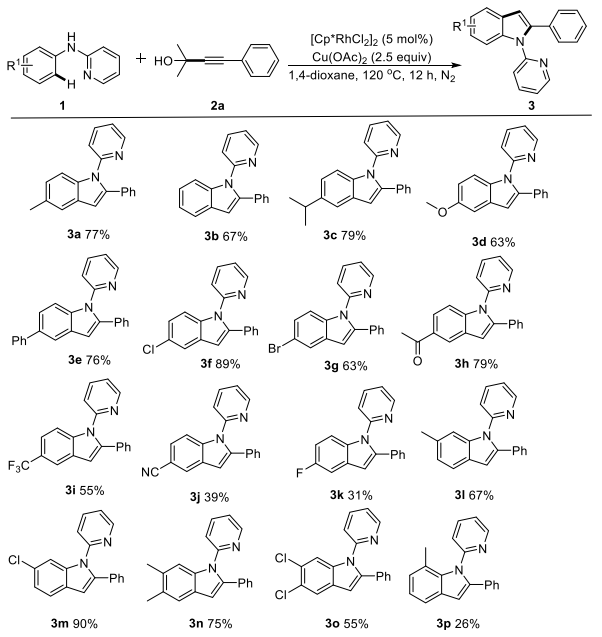
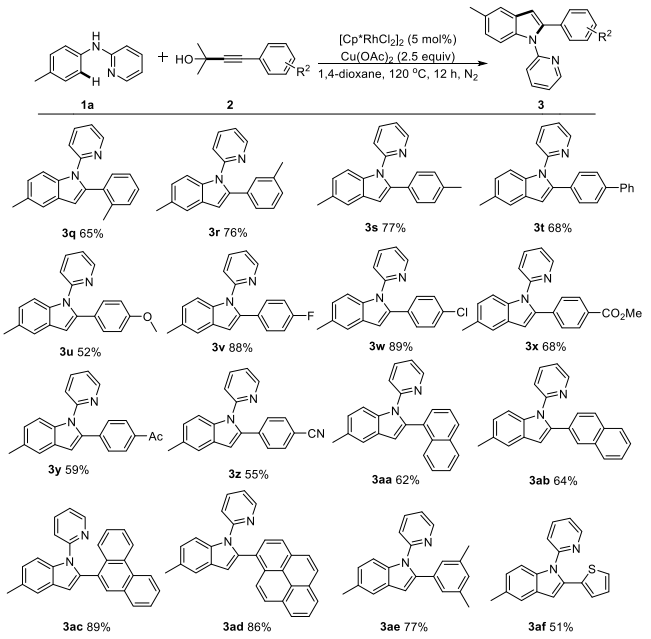
Scheme 3. Scope of *N*-Aryl-2-aminopyridines[a,b]



[a]**1** (0.2 mmol), **2a** (3.0 equiv), $[Cp^*RhCl_2]_2$ (5 mol %), and $Cu(OAc)_2$ (2.5 equiv) were stirred in 1,4-dioxane (1.0 mL) at 120 °C for 12 h in N_2. [b]Isolated yields.

extent (**3z**). 1-Naphthalenyl (**3aa**), 2-naphthalenyl (**3ab**), 9-phenanthrenyl (**3ac**), and 1-pyrenyl (**3ad**) were successfully involved in this reaction approach to more conjugated 2-substituted indole derivatives. The dimethyl substituent was also tolerated, giving the product **3ae** in 77% yield. Thiophene-containing propargyl alcohol smoothly participated in this reaction as well with a reasonable 51% yield of **3af**.

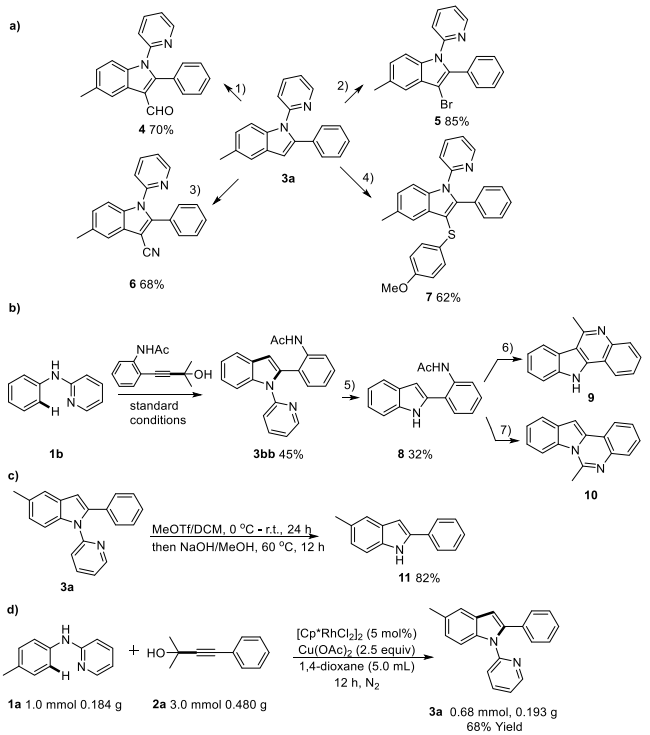
Scheme 4. Scope of *tert*-Propargyl Alcohols[a,b]



[a]**1a** (0.2 mmol), **2** (3.0 equiv), $[Cp^*RhCl_2]_2$ (5 mol %), and $Cu(OAc)_2$ (2.5 equiv) were stirred in 1,4-dioxane (1.0 mL) at 120 °C for 12 h in N_2. [b]Isolated yields.

To further demonstrate the utility of this C−H/C−C activation and cascade annulation reaction, ongoing derivations toward the synthesis of versatile 1,2,3-trisubstitued indoles were implemented. As shown in Scheme 5, 2-phenyl-5-methyl

Scheme 5. Product Transformations[a] **and a Scale-Up Experiment**[b]



[a]Reaction conditions: (1) $POCl_3$, DMF, 50 °C, 5 h, air; (2) NBS, $CHCl_3$, rt, 5 h, air; (3) CuI, $PhCH_2CN$, DMF, 130 °C, 40 h, air; (4) $(4\text{-}MeOC_6H_4S)_2$, KIO_3, glycerol, 100 °C, 6 h, air; (5) MeOTf, DCM, 0 °C to rt, 12 h, air followed by $Pd(OH)_2/C$, NH_4HCO_3, MeOH, 60 °C, 24 h, air; (6) Tf_2O, Ph_3PO, DCM, rt, 15 min, air; (7) $POCl_3$, xylene, 120 °C, 15 min, air. [b]Reaction conditions: **1a** (1.0 mmol, 0.184 g), **2a** (3.0 mmol, 0.480 g), $[Cp^*RhCl_2]_2$ (0.05 mmol, 0.031 g), and $Cu(OAc)_2$ (2.5 mmol, 0.5 g) were stirred in 1,4-dioxane (5.0 mL) at 120 °C for 12 h in N_2.

N-pyridine indoles bearing 3-CHO, 3-Br, 3-CN, and 3-SAr functional groups that could be successfully achieved with moderate to good yields incorporated **3a** with DMF, NBS, benzyl cyanide, and aryl disulfide, respectively (Scheme 5a).[14] Meanwhile, *tert*-propargyl alcohol containing an *ortho* NHAc group was applicable in this reaction and gave product **3bb** in a 45% yield. **3bb** underwent cleavage of the 2-pyridyl directing group, affording *N*-[2-(1*H*-indol-2-yl)phenyl]acetamide (**8**).[15] Compound **8** has been reported to undergo intramolecular cyclizations, smoothly leading to 6-methyl-11*H*-indolo[3,2-*c*]quinoline (**9**) and 6-methylindolo[1,2-*c*]quinazoline (**10**), respectively (Scheme 5b).[16] Also, the pyridyl directing group of more general products such as **3a** could be removed according to the literature (Scheme 5c).[17] By the way, a scale-up experiment of **1a** (1.0 mmol) was conducted to give the desired product **3a** in 68% yield (Scheme 5d). These strategies came up with novel and feasible synthesis routes to functionalized indole skeletons, which existed abundantly in biological active compounds, as mentioned in Figure 1.

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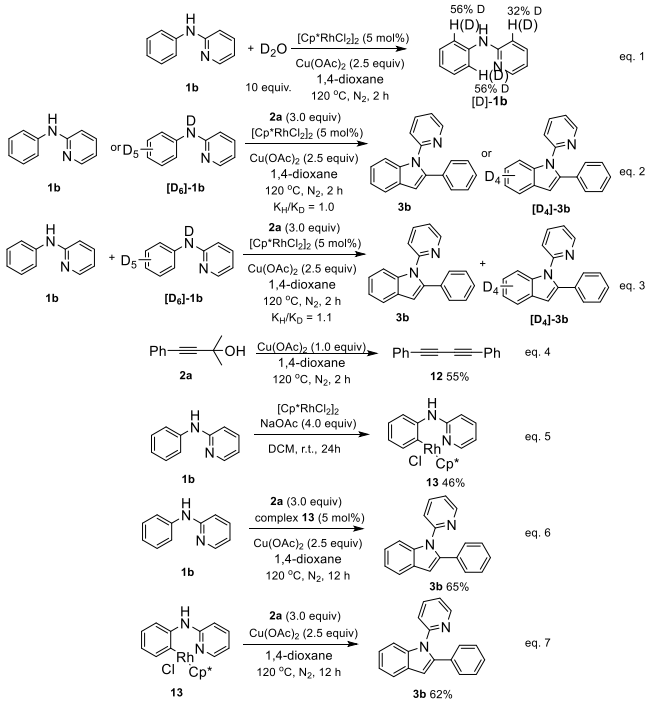
To gain some insight into the possible reaction pathways, a series of experiments were carried out, as shown in Scheme 6.

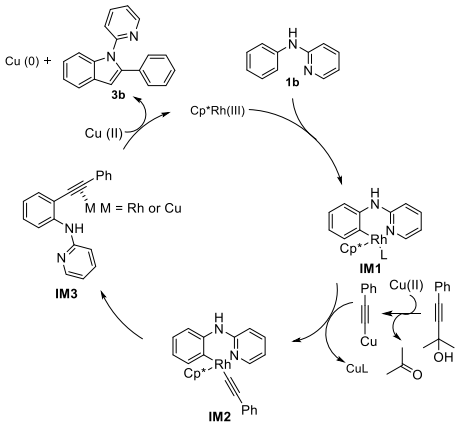
Scheme 6. Studies of the Reaction Pathway



First, the H/D exchange experiment of **1b** with D_2O (10 equiv) led to 56% *ortho* deuterated [D]-**1b**, indicating the *ortho* C−H cleavage might be reversible during the reaction (Scheme 6, eq 1). Parallel and intermolecular competitive reactions were also performed, and the kinetic isotope effect values (k_H/k_D) were determined to be 1.0 and 1.1, respectively (Scheme 6, eqs 2 and 3). These results implied the *ortho* C−H activation process might not be involved in the rate-determining step. In addition, **2a** was reacted only in the presence of $Cu(OAc)_2$ in 1,4-dioxane, and the corresponding Glaser coupling product **12** was obtained in 55% yield, which showcased the pathway of $Cu(OAc)_2$-mediated C−C bond cleavage of **2a** (Scheme 6, eq 4). Then, *N*-phenyl-2-aminopyridine-Rh(III) complex **13** was synthesized according to the literature (Scheme 6, eq 5).[18] The catalytic and stoichiometric reactions by using complex **13** were performed, affording the desired product in 65 and 62% yields, which implied complex **13** would be involved in the catalytic reactions (Scheme 6, eqs 6 and 7).

On the basis of the above experimental results and related literature,[11a,19] a proposed reaction pathway is illustrated below (Scheme 7). At first, the rhodium complex **IM1** was formed via proton abstraction and *ortho* C(sp^2)−H metalation. C−C bond cleavage of **2a** occurred in situ with the assistance of $Cu(OAc)_2$, delivering alkynylcopper species. Alkynylrhodium **IM2** was then obtained via transmetalation. At last, **IM2** went through reductive elimination followed by sequential Lewis acid (rhodium or copper salts) promoted cyclization via nucleophilic attack of the amino group to the activated alkynyl moiety to afford the desired product **3b**. Meanwhile, the oxidation of Rh(I) to the reactive Rh(III) species by Cu(II) completed the catalytic cycle.

Scheme 7. Plausible Mechanistic Pathway



In summary, we have developed a one-pot rhodium-catalyzed/copper-mediated C−H/C−C activation and annulation reaction to assemble 2-arylindoles. This synthetic methodology features broad substrate scope, highly selective C−C bond cleavage of *tert*-propargyl alcohols, and pyridine-directed *ortho* C(sp^2)−H bond activation. Expedient derivations to 1,2,3-trisubstitued indoles, 6-methyl-11*H*-indolo[3,2-*c*]quinoline, and 6-methylindolo[1,2-*c*]quinazoline verified the practicability of this reaction. Further attempts to access more heterocycles on the basis of auxiliary C−H activation and propargyl alcohols are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02767.

Experimental details and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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