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Rhodium-catalyzed annulative coupling of *N*-aryl-2-aminopyridine and propargylic amine *via* selective C−C and C-H bond activation

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Abstract: A Rh(III)-catalyzed/Cu(II)-mediated cascade reaction between *N*-aryl-2-aminopyridine and propargylic amine has been developed. Selective C(sp^2)-H bond activation and C(sp)-C(sp^3) cleavage occurred during reaction, which was followed by cyclization reaction to provide an unprecedented synthetic route to form 1,2-disubstituted indoles in yields up to 85%.

Arylated indoles are frequently encountered as core structural motifs in bioactive products and pharmaceutical molecules.[1] For example, 2-arylindoles could serve as significant scaffolds as marketed drugs such as cytotoxic inhibitor and liver X receptors.[2] On the other hand, the cleavage of non-strained C-C bond has attracted increasing attentions as it can directly reorganize the molecular skeletons and thereby synthesize new compounds conveniently. Various strategies have been developed to realize C-C single bonds activation in spite of the intrinsic challenges including thermodynamic stability and constrained directionality of σ-orbital.[3] For example, the cleavage of C-C bonds involving β-carbon elimination *via* M-O-C-C intermediate generated from the secondary/tertiary alcohols has been well explored.[4] Among them, the tertiary propargylic alcohols are proved to be good precursors of terminal alkynes with ketone extrusion through β-carbon elimination, which can participate in dozens of cross coupling reactions.[5] For example, Wen group described the reaction between 1-(pyridin-2-yl)-1H-indoles and *tert*-propargyl alcohols by using Rh/Cu catalyst system to offer a novel synthetic route of pyrido[2,1-a]indoles, which involved three C-C bonds cleavage in one pot.[6] In our previous study, a Rh-catalyzed Cu-mediated reaction of 4-methylphenyl-2-animopyridine with γ-substituted *tert*-propargyl alcohols was also investigated, affording 2-arylindoles successfully.[7]

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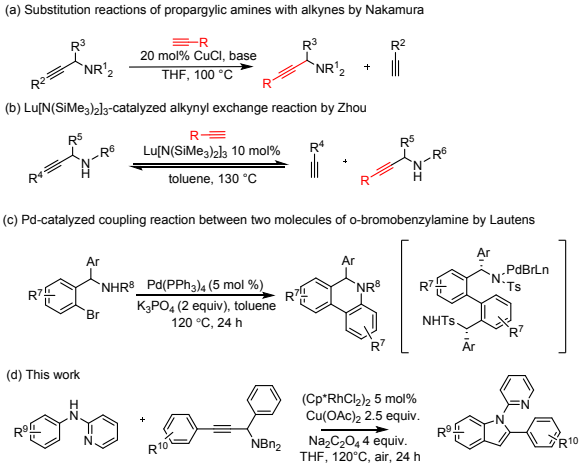
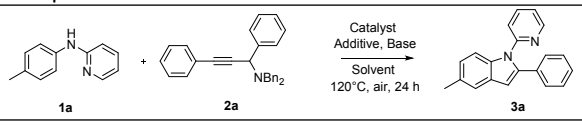


Scheme 1 Transition metal-catalyzed β-carbon elimination of amines.

Compared with the C-C bond activation of alcohol *via* β-carbon elimination, transition metal-catalyzed β-carbon elimination of the amines is rarely reported probably due to the formation of a strong M-N bond.[4] In 2010, Nakamura[8] and co-workers described the first example of the transition metal-catalyzed β-carbon elimination of amines, in which the substitution reactions of propargylic amines with alkynes proceeded in the presence of copper(I) catalyst (Scheme 1a). Zhou et al. reported a similar reaction with $Lu[N(SiMe_3)_2]_3$ as catalyst (Scheme 1b).[9] Lautens and co-workers realized the generation of 5,6-dihydro-phenanthridine skeletons by Pd(0)-catalyzed coupling reaction between two molecules of *N*-sulfonyl substituted racemic *o*-bromobenzylamine (Scheme 1c).[10] Despite these accomplishments, applications of β-carbon elimination of amines are largely underdeveloped. In consideration of that propargylic amines are potentially important building blocks in organic synthesis, developing divergent methodologies to access valuable scaffolds with general substrate availability by C-C bond activation of propargylic amines is in great demand. On the basis of our previous work on C-C activation[11] and synthesis of heterocyclic

compounds,[12] herein we developed an annulative coupling reaction between propargylic amines with arylamines to form 2-arylated indoles (Scheme 1d). This reaction involves the selective cleavage of the carbon-carbon bond of the propargylic amines, functionalization of carbon-hydrogen bond of arylamines and cyclization procedure, which contributes the first example of employing propargylic amines as coupling partners to obtain indole derivatives.

Table 1 Optimization of reaction conditions[a]



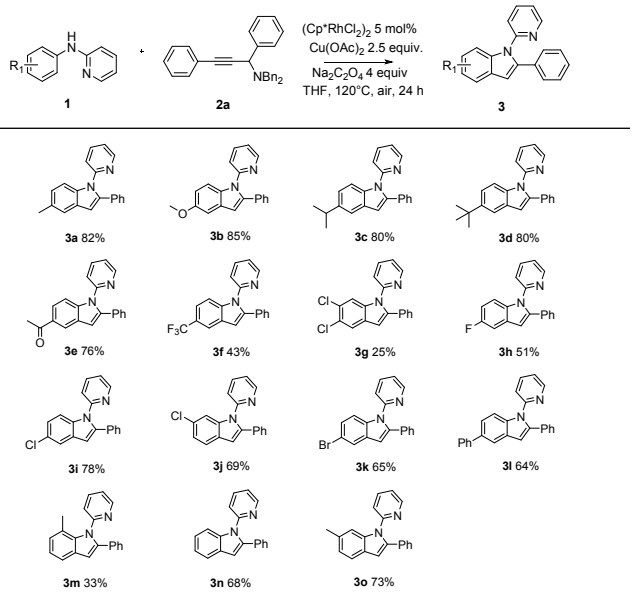
1a 2a 3a

Entry	Catalyst	Additive	Solvent	Base	Yield[b] (%)
1	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$	dioxane	-	48
2	$RhCl_3$	$Cu(OAc)_2$	dioxane	-	0
3	$Pd(OAc)_2$	$Cu(OAc)_2$	dioxane	-	0
4	$Ni(OAc)_2$	$Cu(OAc)_2$	dioxane	-	0
5	$RuCl_3$	$Cu(OAc)_2$	Dioxane	-	0
6	$[Cp^*Co(CO)I_2]$	$Cu(OAc)_2$	Dioxane	-	6
7	$[Cp^*RhCl_2]_2$	$CuBr_2$	dioxane	-	0
8	$[Cp^*RhCl_2]_2$	$Cu(TFA)_2$	dioxane	-	0
9	$[Cp^*RhCl_2]_2$	$Cu(NO_3)_2$	dioxane	-	0
10	$[Cp^*RhCl_2]_2$	$CuF_2{\cdot}H_2O$	dioxane	-	14
11	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$	THF	-	56
12	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$	MeCN	-	38
13	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$	toluene	-	trace
14	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$	DCM	-	18
15	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$	MeOH	-	12
16	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$	THF	Et_3N	52
17	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$	THF	K_2CO_3	60
18	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$	THF	$NaHCO_3$	43
19	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$	THF	$Na_2C_2O_4$	68
20	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$	THF	$K_2C_2O_4$	66
21	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$	THF	Na_2CO_3	54
22	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$	THF	Cs_2CO_3	trace
23[c]	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$	THF	$Na_2C_2O_4$	60
24[d]	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$	THF	$Na_2C_2O_4$	53
25[e]	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$	THF	$Na_2C_2O_4$	70
26[f]	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$	THF	$Na_2C_2O_4$	82
27[g]	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$	THF	$Na_2C_2O_4$	63
28[h]	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$	THF	$Na_2C_2O_4$	77
29[i]	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$	THF	$Na_2C_2O_4$	45
30[f]	-	$Cu(OAc)_2$	THF	$Na_2C_2O_4$	0
31[f]	$[Cp^*RhCl_2]_2$	-	THF	$Na_2C_2O_4$	0

[a]General conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), catalyst (5 mol%), additive (2.5 equiv) and base (4.0 equiv) in solvent (1.0 mL) were stirred at 120 °C for 24 h in the air. [b]Isolated yields. [c]Under N_2 atmosphere. [d]$Na_2C_2O_4$ (3.0 equiv) was used. [e]$Na_2C_2O_4$ (4.0 equiv) was used. [f]**2a** (3.0 equiv) was used. [g]Reaction temperature 100 °C. [h]Reaction temperature 110 °C. [i]Reaction temperature 130 °C.

Initially, *N*-(*p*-tolyl)pyridin-2-amine (**1a**) and *N*,*N*-dibenzyl-1,3-diphenylprop-2-yn-1-amine (**2a**) were chosen as model substrates for the optimization of reaction conditions. As shown in Table 1, when $[Cp^*RhCl_2]_2$ (5 mol%) was used as catalyst in the presence of $Cu(OAc)_2$ (2 equiv) in 1,4-dioxane at 120 °C for 24 h, the desired prodcut **3a** could be obtained in 48% yield (Table 1, entry 1). Screening other metal catalysts including $RhCl_3$, $Pd(OAc)_2$, $Ni(OAc)_2$, $RuCl_3$, $[Cp^*Co(CO)I_2]$ or other copper salts such as $CuBr_2$, $Cu(TFA)_2$, $Cu(NO_3)_2$ and $CuF_2{\cdot}H_2O$ resulted in inferior results (Table 1, entries 2-10). Then, the solvent effects were studied, and THF exhibited to be better than others including MeCN, toluene, DCM, and MeOH in yield of 56% (Table 1, entries 11-15). Furthermore, it was reported that addition of base would be beneficial to the C-C bond cleavage.[8] Therefore, a series of bases were screened, and $Na_2C_2O_4$ was found to be better than others including $NaHCO_3$, $K_2C_2O_4$ and Na_2CO_3, affording the desired product **3a** in 68% yield (Table 1, entries 16-22). Moreover, inert atmosphere seemed to be unnecessary for the reaction (Table 1, entry 23). At last, after screening the amount of base and **2a**, as well as reaction temperature (Table 1, entries 24-29), the best yield 82% was obtained. The control experiments further proved the necessity of the Rh/Cu catalyst system, and no product was obtained in the absence either of them (Table 1, entries 30-31). These experiments concluded the optimized reaction condition consists of **1a** (0.2 mmol), **2a** (3 equiv), $[Cp^*RhCl_2]_2$ (5 mol%), $Cu(OAc)_2$ (2.5 equiv.) and $Na_2C_2O_4$ (4.0 equiv) in THF (1.0 mL) at 120 °C for 24 h in the air.

Scheme 2 Substrate scope of *N*-aryl-2-aminopyridines[a,b]



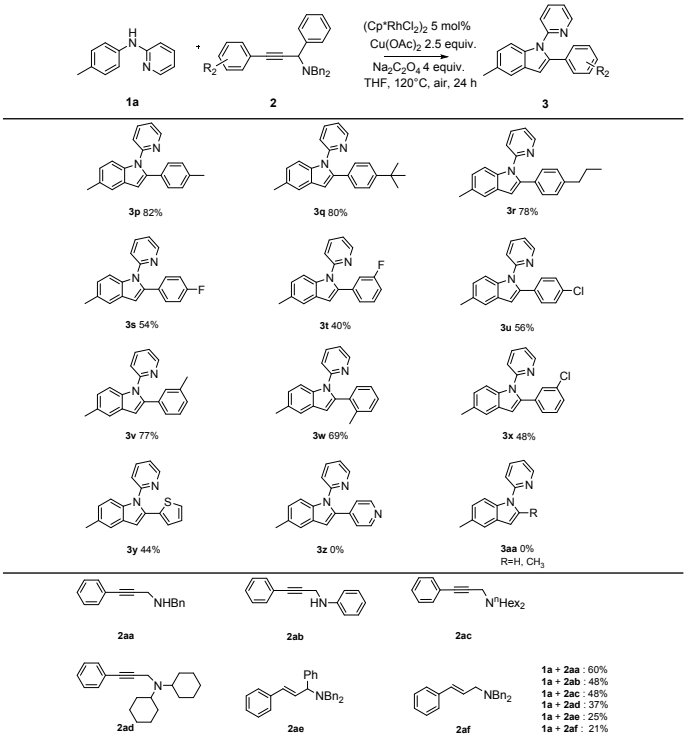
[a]Reaction conditions: **1** (0.2 mmol), **2a** (3.0 equiv), $[Cp^*RhCl_2]_2$ (5 mol%), $Cu(OAc)_2$ (2.5 equiv) and $Na_2C_2O_4$ (4.0 equiv) in THF (1.0 mL) were stirred at 120 °C for 24 h in the air. [b]Isolated yields.

Next, the substrate scope of *N*-aryl-2-aminopyridines was investigated. As shown in Scheme 2, various functional groups substituted on the phenyl ring were well tolerated, leading to the corresponding products in moderate to good yields. Electron-donating substituents seemed to be more beneficial to the reaction. For example, *para* methyl or methoxyl substituted substrates give products above 80% yields (**3a**, **3b**), while only 43% yields was obtained in the case of trifluoromethyl substituted substrate (**3f**). For the steric effect, *o*-methyl substituted substrate was converted to be the corresponding product **3m** in only 33% yield, indicating an apparent steric

hindrance in this transformation. Moreover, when bromo-substituted arylamine was employed as substrate, the corresponding product **3k** could be obtained in 65% yield, suggesting the possibility to derive more complex molecules.

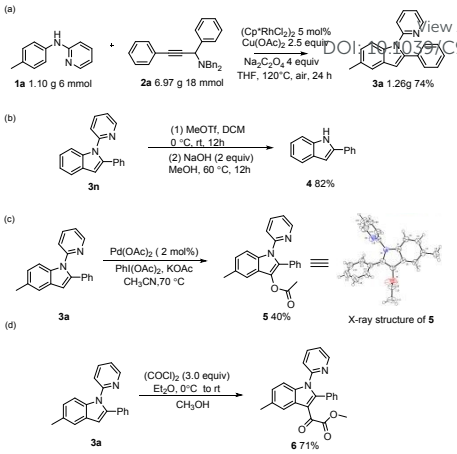
Furthermore, a variety of substituted propargylic amines were also screened. As shown in Scheme 3, the substituents on the phenyl ring of propargylic amines markedly affected the reaction outcome. Electron-donating substituents were found again to be favorable for the reaction (**3q**, **3r**, **3s**, **3u**). Steric effects seemed to have some influence on the results. For example, propargylic amines substituted with *p*-methyl group gave **3p** in 82% yield, whereas *meta* or *ortho*-substituted substrates resulted in 77% and 69% yields, respectively (**3v**, **3w**). Propargylic amine bearing thienyl group (**3y**) was also smoothly converted to the corresponding product, however, alkyl alkyne and terminal alkyne substrates (**3aa**) resulted in no desired products. The catalytic system could also be applied for the secondary amine substrates, *N*-alkyl substituted substrates and allylic amine substrates, albeit with lower yields (**2aa**-**2af**).

Scheme 3 Substrate scope of propargylic amines[a,b]

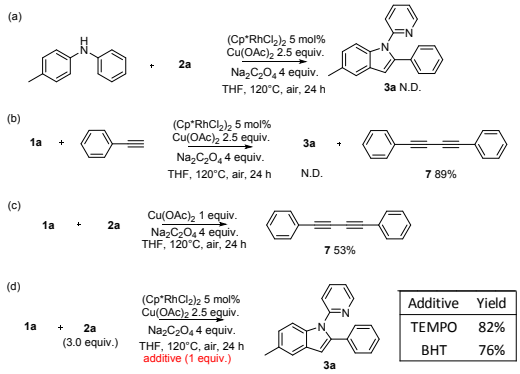


[a]Reaction conditions: **1a** (0.2 mmol), **2** (3.0 equiv), $[Cp^*RhCl_2]_2$ (5 mol%), $Cu(OAc)_2$ (2.5 equiv) and $Na_2C_2O_4$ (4.0 equiv) in THF (1.0 mL) were stirred at 120 °C for 24 h in the air. [b]Isolated yields.

To illustrate the practical utility of this method, a scale-up experiment (6.0 mmol) was performed by using **1a** and **2a** as substrates, affording the desired product **3a** in 74% yield under the standard conditions (Scheme 4a). Also, the directing group could be easily removed from **3n** in good yields by treatment with MeOTf and subsequent NaOH to form free NH indole (Scheme 4b).[13] Meanwhile, 2-phenyl-3-acetoxyl-5-methyl *N*-pyridine indole **5**, which was reported as precursor for potential 5-HT_6 receptor ligands, could also be achieved by the



Scheme 4 Transformations of product.



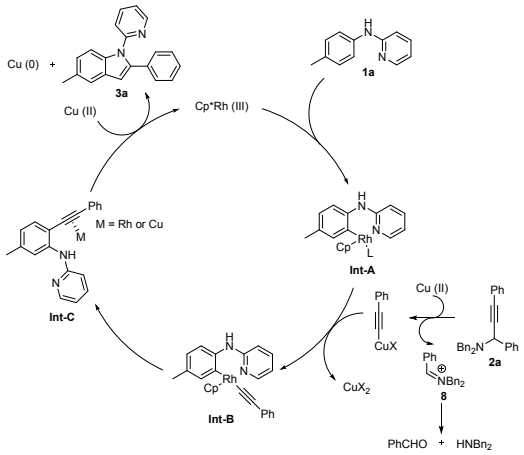
Scheme 5 Studies of the reaction pathway.

reaction of **3a** with $PhI(OAc)_2$.[14] Its structure was confirmed by X-ray crystallographic analysis (Scheme 4c). Furthermore, the reaction between **3a** and oxalyl chloride afforded methyl 2-(5-methyl-2-phenyl-1-(pyridin-2-yl)-1H-indol-3-yl)-2-oxoacetate (**6**) in 71% yield, which was reported as the key building block of the monoindole alkaloid from the marine sponge *Spongosorites* (Scheme 4d).[15]

To get a better understanding of the possible reaction pathway, a series of control experiments were then carried out. Firstly, no product was found when 4-methyl-*N*-phenylaniline was used instead of **1a** under the standard reaction conditions, suggesting the necessity of pyridine directing group (Scheme 5a). Next, only Glaser coupling product **7** was obtained when propargylic amine **2a** was replaced by phenylacetylene, suggesting the necessity of using **2** as substrates (Scheme 5b). Meanwhile, **7** was also obtained in 53% yield when $Cu(OAc)_2$ was used as sole catalyst (Scheme 5c), which further confirmed the reaction would involve the pathway of $Cu(OAc)_2$-mediated C-C bond cleavage of **2a**. At last, addition of 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) or 2,6-di-*tert*-butyl-4-methylphenol (BHT) as radical scavengers would result in 82% and 76% yields for **3a**, which could exclude the radical pathway during reaction (Scheme 5d).

Based on these observations and literature precedents,[7,8,10,16] a plausible catalytic cycle was proposed. As shown in Scheme 6, a pyridine-directed rhodacycle (**Int-A**) was firstly formed from substrate **1a** with $[Cp^*RhCl_2]_2$ *via* C(sp^2)-H

activation. Meanwhile, copper-catalyzed C(sp)-C(sp^3) bond cleavage assisted by the nitrogen lone-pair electrons happened, affording alkynylcopper species while releasing an iminium molecule **8**, which was not stable and decomposed to be benzaldehyde and dibenzylamine (Detected by GC-MS) in this work.[10] Then, **Int-A** underwent transmetalation with alkynylcopper species to generate **Int-B**, which went through reductive elimination to afford **Int-C**. A final nucleophilic attack of the amino group to the activated alkynyl moiety promoted by Lewis acid and thereby intramolecular cyclization produces the desired product **3a**. The oxidation of Rh(I) to Rh(III) by Cu(II) closed the catalytic cycle.



Scheme 6 Proposed catalytic cycle.

Conclusions

In conclusion, a novel cross-coupling reaction between propargylic amine and arylamine has been developed in the presence of rhodium/copper catalyst system. The selective cleavage of the carbon-carbon bond of the propargylic amine and the carbon-hydrogen bond of arylamine occurred during the reaction, which was followed by an intramolecular cyclization procedure, affording a wide variety of substrates 2-arylindoles with good functional group tolerance. Further investigations are currently underway in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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