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Tandem Rh(III)-Catalyzed C−H Amination/Annulation Reactions: Synthesis of Indoloquinoline Derivatives in Water

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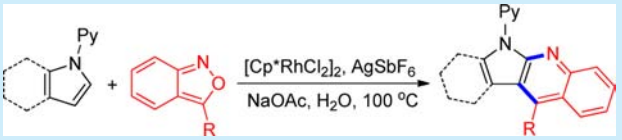
Supporting Information

ABSTRACT: An efficient Rh(III)-catalyzed synthetic method for indoloquinoline derivatives from readily available indoles and isoxazoles was developed. This annulation procedure undergoes tandem C−H activation, cyclization, and condensation steps. In this domino cyclization reaction, water is an efficient solvent. A catalytically competent five-membered rhodacycle has been isolated and characterized, thus revealing a key intermediate in the catalytic cycle.



Discovering pharmaceutical candidates is a resource-intensive enterprise that frequently needs the parallel synthesis of a great deal of molecules. C−N bonds are widely present in pharmaceutical agents and natural products. Therefore, developing selective, rapid, and efficient methods for transforming these bonds into new chemical entities has the potential to promote pharmaceutical development.[1] Over the past decade, transition-metal-catalyzed direct C−H activation to build C−N bonds has attracted much attention in organic synthesis.[2] In this regard, the Buchwald−Hartwig reaction has been used as a general method for the amination of organo-(pseudo)halides.[3] Although this strategy is greatly promising as it alleviates the need for prefunctionalization, it frequently suffers from the generation of stoichiometric amounts of byproducts from external oxidants,[4] halide salts, or bases.[5] Employing organic azides as a readily available and convenient N atom source would determine these limitations because those reactions do not need oxidant or bases and release environmentally benign N_2 as the byproduct.[6] Recently, several research groups reported Rh-, Ru-, and Ir-catalyzed direct C−H amination protocols using organic azides as the amino source.[7−12] Meanwhile, other elegant amination reagents were also developed to give synthetically valuable products.[13]

In the past decade, Rh(III) complexes have been widely employed as catalysts in the activation of alkynes, alkenes, and allenes coupling with amides, amines, oximes, and anilines to obtain isoquinolone,[14] pyridone,[14d,15] isoquinoline,[16] pyridine,[16f,17] indole,[16f,18] and pyrrole derivatives.[18c,19] Furthermore, Rh(III)-catalyzed C−H bond activation based on carbene migratory insertion has been reported as a attractive method toward C−H functionalization.[20] Yu first reported an elegant example of Rh(III)-catalyzed carbene migratory insertion into arene C−H bonds employing diazo compounds.[21a] Rh(III)-catalyzed cyclization use diazo compounds as coupling/cyclization partners have continued to be developed by other groups.[21]

Indoloquinolines are privileged scaffolds for the design and discovery of drugs, and many of them exhibit potent biological activity as antibacterial, antifungal, antimalarial, anticancer, antiplatelet, aggregation, analgesic, and antihypertensive agents.[22] Some approaches to these polyheteroaromatic ring systems have been developed;[23] however, these synthetic methods are frequently restricted due to substrate generality, and they involve two or more steps with exhaustive purification.

Although the synthesis of heterocycles via a Rh(III) complex has made significant progress, it is necessary to explore coupling partners because of the structural diversity of heterocycles. Herein, we report an efficient Rh(III)-catalyzed approach to multisubstituted indoloquinolines via cascade reactions of 1-(pyridin-2-yl)-1*H*-indole with under mild conditions. During the review of our manuscript, the Li group also reported anthranil as a bifunctional aminating reagent for C−H bonds.[13f]

As shown in Table 1, reaction of 1-(pyridin-2-yl)-1*H*-indole (**1a**) with benzo[*c*]isoxazole (**2a**) leading to 6-(pyridin-2-yl)-6*H*-indolo[2,3-*b*]quinoline (**3aa**) was applied as the model to optimize reaction conditions. The initial experiments were performed with **1a** with **2a** in the presence of $[Cp^*RhCl_2]_2$ (5 mol %) and $AgSbF_6$ (20 mol %) as the catalyst system at 100 °C under Ar atmosphere in THF (2 mL) for 12 h, as shown in Table 1. Delightedly, under these conditions, the desired product **3aa** was obtained in 37% yield. The structure of **3aa** was confirmed by ^1H and ^{13}C NMR spectroscopy and high-resolution mass spectrometry (HRMS). Motivated by this result, first, the effect of additives was investigated (Table 1, compare entries 2−8), and NaOAc gave the best result as the yield of **3aa** increased to 85% (Table 1, entry 3). On the basis of a survey of different solvents,

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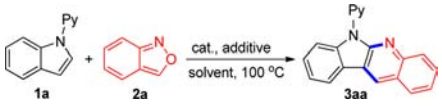
Table 1. Optimization of the Reaction Conditions for the Synthesis of 3aa[a]



entry	catalyst system	solvent	additive	yield[b] (%)
1	$[Cp^*RhCl_2]_2$/ $AgSbF_6$	THF		37
2	$[Cp^*RhCl_2]_2$/ $AgSbF_6$	THF	HOAc	47
3	**$[Cp^*RhCl_2]_2$/ $AgSbF_6$**	**THF**	**NaOAc**	**85**
4	$[Cp^*RhCl_2]_2$/ $AgSbF_6$	THF	KOAc	82
5	$[Cp^*RhCl_2]_2$/ $AgSbF_6$	THF	CsOAc	63
6	$[Cp^*RhCl_2]_2$/ $AgSbF_6$	THF	AgOAc	78
7	$[Cp^*RhCl_2]_2$/ $AgSbF_6$	THF	$Zn(OAc)_2$	51
8	$[Cp^*RhCl_2]_2$/ $AgSbF_6$	THF	$Cu(OAc)_2$	trace
9	$[Cp^*RhCl_2]_2$/ $AgSbF_6$	dioxane	NaOAc	58
10	$[Cp^*RhCl_2]_2$/ $AgSbF_6$	DCE	NaOAc	69
11	$[Cp^*RhCl_2]_2$/ $AgSbF_6$	DCM	NaOAc	51
12	$[Cp^*RhCl_2]_2$/ $AgSbF_6$	MeCN	NaOAc	54
13	$[Cp^*RhCl_2]_2$/ $AgSbF_6$	toluene	NaOAc	trace
14	$[Cp^*RhCl_2]_2$/ $AgSbF_6$	MeOH	NaOAc	62
15	**$[Cp^*RhCl_2]_2$/ $AgSbF_6$**	**H_2O**	**NaOAc**	**81**
16	$AgSbF_6$	H_2O	NaOAc	0
17	$[Cp^*RhCl_2]_2$	H_2O	NaOAc	0
18	$[Cp^*Rh(MeCN)_3][(SbF_6)_2]$	H_2O	NaOAc	29
19[c]	$[Cp^*RhCl_2]_2$/ $AgSbF_6$	H_2O	NaOAc	52
20	$[(p\text{-cymene})RuCl_2]_2/AgSbF_6$	H_2O	NaOAc	trace
21	$[Cp^*IrCl_2]_2$/ $AgNTf_2$	H_2O	NaOAc	trace

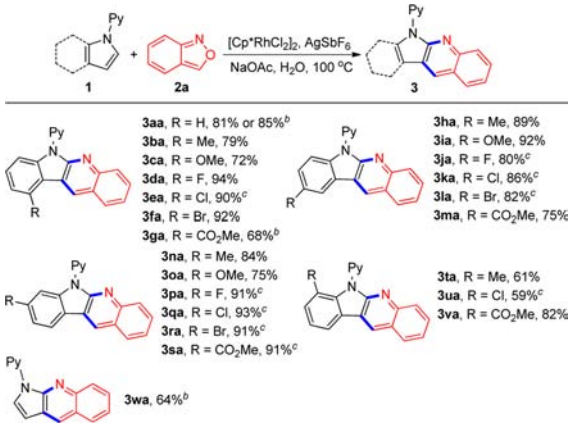
[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), $[Cp^*RhCl_2]_2$ (5 mol %), $AgSbF_6$ (20 mol %), additive (0.08 mmol), solvent (2 mL), 100 °C, 12 h, under Ar atmosphere. [b]Isolated yield. [c]2-Pyrimidyl was used instead of pyridyl.

THF gave the best result (Table 1, entries 3 and 9−15). To our surprise, the use of H_2O as solvent delivered **3aa** in 81% yield. Considering the cost and environmental factor, we decided to employ water as the best solvent. A control experiment showed that both $[Cp^*RhCl_2]_2$ and $AgSbF_6$ were essential for this transformation as their omission led to no formation of **3aa** (Table 1, entries 16 and 17). When $[Cp^*Rh(MeCN)_3][(SbF_6)_2]$ was employed instead of $[Cp^*RhCl_2]_2/AgSbF_6$, the yield of **3aa** declined to 29% (Table 1, entry 18). When 2-pyrimidyl was used instead of pyridyl as the directing group, **3aa** was obtained in 52% yield (entry 19). The transformation did not occur by using $[(p\text{-cymene})RuCl_2]_2/AgSbF_6$ or $[Cp^*IrCl_2]_2/AgNTf_2$ as the catalyst system (Table 1, entries 20 and 21).

Under the optimum reaction conditions above (Table 1, entries 3 and 15), we investigated the substrate scope for synthesis of indoloquinoline derivatives (**3**). Benzo[*c*]isoxazole (**2a**) was kept as a representative reaction partner (Scheme 1). A wide range of substituted indole derivatives were transformed smoothly to the corresponding indoloquinoline derivatives in good to excellent yields. Functional groups, regardless of the substitution positions and electronic nature, including methyl (**3ba**, **3ha**, **3na**, **3ta**), methoxyl (**3ca**, **3ia**, **3oa**), fluoro (**3da**, **3ja**, **3pa**), chloro (**3ea**, **3ka**, **3qa**, **3ua**), bromo (**3fa**, **3la**, **3ra**), and ester groups (**3ga**, **3ma**, **3sa**, **3va**), were well tolerated. It is worth noting that this cyclization was also extended to pyrroloquinoline (**3wa**) synthesis by using 2-(1*H*-pyrrol-1-yl)pyridine and **2a** as starting materials, and this conversion gave only one regioisomer of **3wa** in 64% yield.

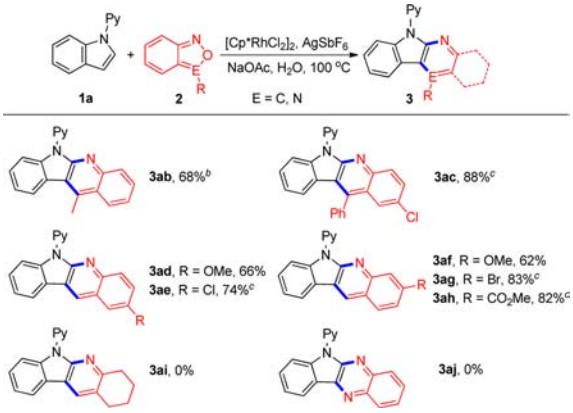
Further, we investigated the scope of isoxazole derivatives with 1-(pyridin-2-yl)-1*H*-indole (**1a**) as the reaction partner (Scheme 2). Isoxazole derivatives containing substituents such as methyl (**3ab**), methoxyl (**3ad**, **3af**), chloro (**3ae**), bromo (**3ag**), phenyl

Scheme 1. Rh(III)-Catalyzed C−H Amination/Annulation of Substituted Indole Derivatives 1 with 2a[a]



[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol), $[Cp^*RhCl_2]_2$ (5 mol %), $AgSbF_6$ (20 mol %), NaOAc (0.08 mmol), H_2O (2 mL), 100 °C, 12 h, under Ar atmosphere, isolated yields are shown. [b]Using THF as solvent. [c]Reaction temperature is 120 °C.

Scheme 2. Rh(III)-Catalyzed C−H Amination/Annulation of 1a with Isoxazole Derivatives 2[a]



[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol), $[Cp^*RhCl_2]_2$ (5 mol %), $AgSbF_6$ (20 mol %), NaOAc (0.08 mmol), H_2O (2 mL), 100 °C, 12 h, under Ar atmosphere, isolated yields are shown. [b]Using THF as solvent. [c]Reaction temperature is 120 °C.

(**3ac**), and ester groups (**3ah**) accessed the desired products **3ab**−**3ah** in 62−88% yields. Notably, the reaction efficiency was dependent on the electronic effect. For isoxazole derivatives, the electron-withdrawing ester group exhibited higher reactivity than those with electron-donating groups (Scheme 2, compare **3ah**, **3ab**, **3ad**, and **3af**). To our regret, when 4,5,6,7-tetrahydrobenzo-[*c*]isoxazole (**2i**) and benzo[*c*][1,2,5]oxadiazole (**2j**) were employed as the reaction partners, no corresponding product was obtained.

In order to further confirm the structure of the product **3aa**, the pyridyl group of **3aa** was removed, and the 6*H*-indolo[2,3-*b*]quinoline **4** was obtained in 92% yield (Scheme 3, eq 1).[24] The ^1H and ^{13}C NMR spectra and HRMS of **4** were consistent with literature.[23h] A gram-scale reaction was conducted to evaluate the reaction efficacy on a preparative scale. The reaction of 1-(pyridin-2-yl)-1*H*-indole (**1a**) with benzo[*c*]isoxazole (**2a**)

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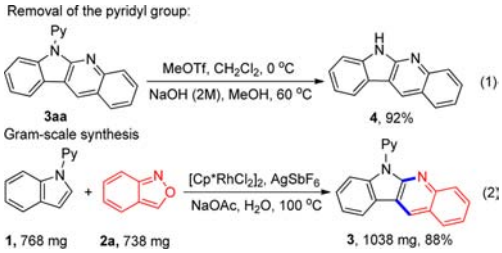
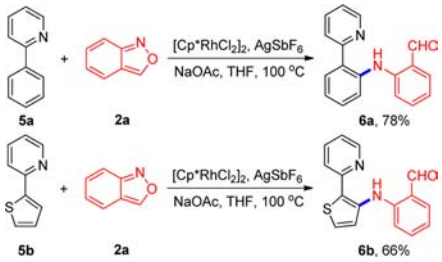
Scheme 3. Removal of the Pyridyl Group and Gram-Scale Synthesis



under the standard conditions provided the target product in 88% yield (Scheme 3, eq 2). Therefore, the present method is very effective for the synthesis of 6-(pyridin-2-yl)-6*H*-indolo[2,3-*b*]quinoline (**3aa**).

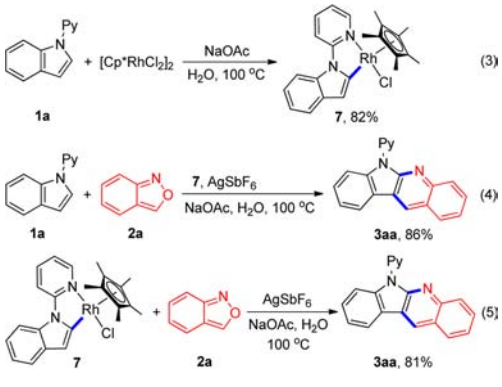
We also explored the reactivity of other heterocyclic rings, such as 2-phenylpyridine (**5a**) or 2-(thiophene-2-yl)pyridine (**5b**), but we could only obtain the open-chain products (Scheme 4, **6a**, **6b**).

Scheme 4. Treatment of 2-Phenylpyridine (5a) or 2-(Thiophene-2-yl)pyridine (5b) with 2a under the Standard Conditions



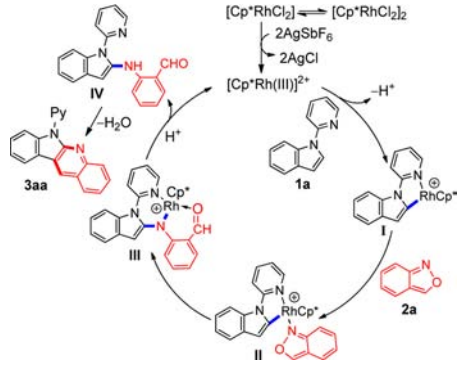
To probe the reaction mechanism of the present reaction, 1-phenyl-1*H*-indole was subjected to the reaction instead of **1a**, and no product was detected. It suggested that the pyridyl group as a directing group is crucial for this transformation. A rhodacyclic complex **7** was isolated by the reaction of **1a** with $[Cp^*RhCl_2]_2$ (Scheme 5, eq 3). Its structure was characterized by ^1H and ^{13}C NMR spectra and HRMS (see the Supporting Information). In the ^1H NMR spectrum of **7**, the signal of the C-2 proton disappeared, suggesting the formation of a Rh−C bond. When complex **7** was used as the catalyst instead of $[Cp^*RhCl_2]_2$ under the standard conditions, the desired product **3aa** was obtained in 86% yield (Scheme 5, eq 4). Furthermore, the stoichiometric reaction of complex **7** with **2a** gave **3aa** in 81% yield (Scheme 5, eq 5). These results supported that the reaction may undergo a cyclometalation step and complex **7** probably was an active species in this reaction.

Scheme 5. Mechanistic Studies: Synthesis and Reactions of Complex 7



Based on the above experimental results and literature reports,[21h,25] a plausible mechanism was proposed (Scheme 6).

Scheme 6. Plausible Catalytic Cycle



First, substituted indole (**1a**) reacts with Cp*Rh(III) through directed C−H cleavage to form intermediate **I**. The coordination of benzo[*c*]isoxazole (**2a**) to **I** delivers intermediate **II**. Subsequently, the migration insertion of the coordinated **2a** into the Rh−C bond leads to intermediate **III**. Protonation of **III** leads to the intermediate **IV** and releases the Rh(III) species for the next catalytic cycle. Then intermediate **IV** undergoes intramolecular cyclization by elimination of water to give the final product **3aa**. According this mechanism, **6a** and **6b** cannot be transformed to the annulation products, probably due to the lower electron densities of benzene and thiophene then that of indole, which led to lower activities in electrophilic cyclization and condensation.

In summary, we have developed an efficient Rh(III)-catalyzed synthetic method for indoloquinoline derivatives from readily available indoles and isoxazole derivatives. This annulation procedure undergoes tandem C−H activation, cyclization, and condensation steps. In this domino cyclization reaction, water is an efficient solvent. As such, this environmentally friendly approach to indoloquinoline derivatives will attract much attention in academic and industrial research.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01234.

Full experimental procedures, optimization of reaction conditions, characterization and ^1H, ^{13}C, and ^{19}FNMR spectra of products (PDF)

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Notes

The authors declare no competing financial interest.

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