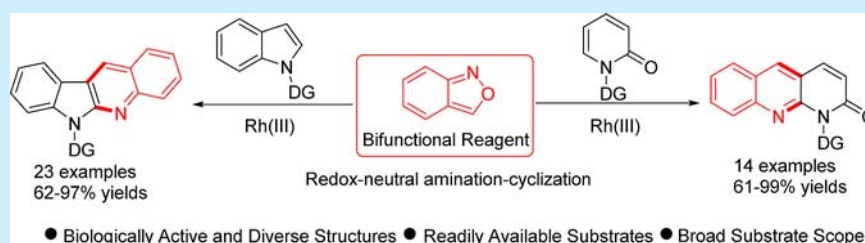


Access to Structurally Diverse Quinoline-Fused Heterocycles via Rhodium(III)-Catalyzed C–C/C–N Coupling of Bifunctional Substrates

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Supporting Information



ABSTRACT: Rhodium(III)-catalyzed C–H activation of heteroarenes and functionalization with bifunctional substrates such as anthranils allows facile construction of quinoline-fused heterocycles under redox-neutral conditions. The couplings feature broad substrate scope and provide step-economical access to two classes of quinoline-fused condensed heterocycles.

Fused heterocycles such as indolo[2,3-*b*]quinoline are extended π -systems widely found in pharmaceuticals and in natural products,¹ and they have explicitly exhibited a broad spectrum of biological activities including antifungal, anti-inflammatory, antibacterial, cytotoxicity, and antimalarial activities,² among others (Figure 1).³ These fascinating



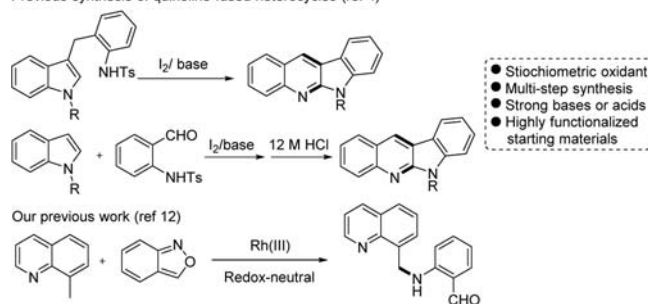
Figure 1. Representative biologically active pyrido[2,3-*b*]indoles.

biological activities have called for considerable efforts in developing more efficient synthetic strategies because most of the existing methods suffer from highly functionalized starting materials, harsh conditions, low atom-economy, and lack of substrate generality (Scheme 1).⁴ Therefore, the development of novel strategies for the construction of these useful scaffolds in a green, efficient, and atom-economic fashion is highly desirable.

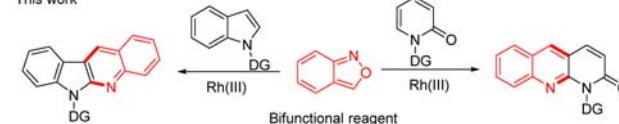
Transition-metal catalysts have exhibited profound potentials in C–H activation of arenes⁵ for the construction of condensed heterocycles. However, metal-catalyzed synthesis of quinoline-fused heterocycles such as indolo[2,3-*b*]quinoline and benzo-[*b*][1,8]naphthyridin-2-one via a C–H activation pathway is unknown. As a continuation of our interest in C–H activation chemistry,⁶ we pondered the employment of Rh(III) catalysis⁷ for this purpose starting from readily available bifunctional substrates. Through the retrosynthetic analyses of this molecular architecture, the key step in the synthesis of such a scaffold boils down to the construction of a pyridine ring via

Scheme 1. Representative Methods for Synthesis of Quinoline-Fused Heterocycles

Previous synthesis of quinoline-fused heterocycles (ref 4)



This work



C–N and C–C formations, which have been well exemplified in Rh(III) catalysis (Scheme 1).⁸ A strategy can thus be envisioned to fulfill this synthetic target by taking advantage of an electrophilic aminating reagent that delivers a proximal electrophilic carbonyl group upon amination. This bifunctionality electronically matches that in an electron-rich arene. For this purpose, anthranils⁹ have been identified as bifunctional aminating reagents via a transannulation strategy. Thus, electrophilic C–H amination occurs first,¹⁰ followed by Friedel–Crafts cyclization–condensation.¹¹ We now report our findings in Rh(III)-catalyzed efficient synthesis of diverse

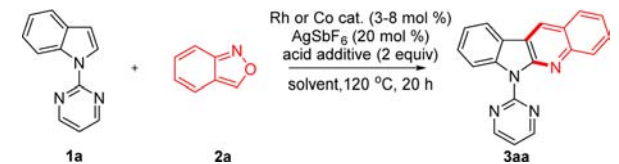
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quinoline-fused heterocycles via C–H activation of different classes of arenes.

We commenced our studies by examining the reaction parameters of the coupling of *N*-pyrimidinylindole (**1a**) with anthranil (**2a**) using $[\text{Cp}^*\text{RhCl}_2]_2/\text{AgSbF}_6$ as a catalyst (Table 1). The desired indolo[2,3-*b*]quinoline **3aa** was isolated in 35%

Table 1. Optimization Studies^a



entry	cat. (mol %)	additive	solvent	yield ^b (%)
1	$[\text{Cp}^*\text{RhCl}_2]_2$ (4)	HOPiv	DCE	35
2	$[\text{Cp}^*\text{CoI}_2\text{CO}]$ (8)	HOPiv	DCE	NR
3	$[\text{Cp}^*\text{CoCl}_2]_2$ (4)	HOPiv	DCE	NR
4	$[\text{Cp}^*\text{RhCl}_2]_2$ (4)	HOAc	DCE	31
5	$[\text{Cp}^*\text{RhCl}_2]_2$ (4)	TFA	DCE	trace
6	$[\text{Cp}^*\text{RhCl}_2]_2$ (4)	HOPiv	TFE	79
7	$[\text{Cp}^*\text{RhCl}_2]_2$ (4)	HOPiv	MeOH	95
8	$[\text{Cp}^*\text{RhCl}_2]_2$ (4)	HOPiv	EtOH	83
9	$[\text{Cp}^*\text{RhCl}_2]_2$ (4)	HOPiv	HFIP	89
10	$[\text{Cp}^*\text{RhCl}_2]_2$ (3)	HOPiv	MeOH	92
11 ^c	$[\text{Cp}^*\text{RhCl}_2]_2$ (3)	HOPiv	MeOH	74
12	$[\text{Cp}^*\text{RhCl}_2]_2$ (3)		MeOH	39

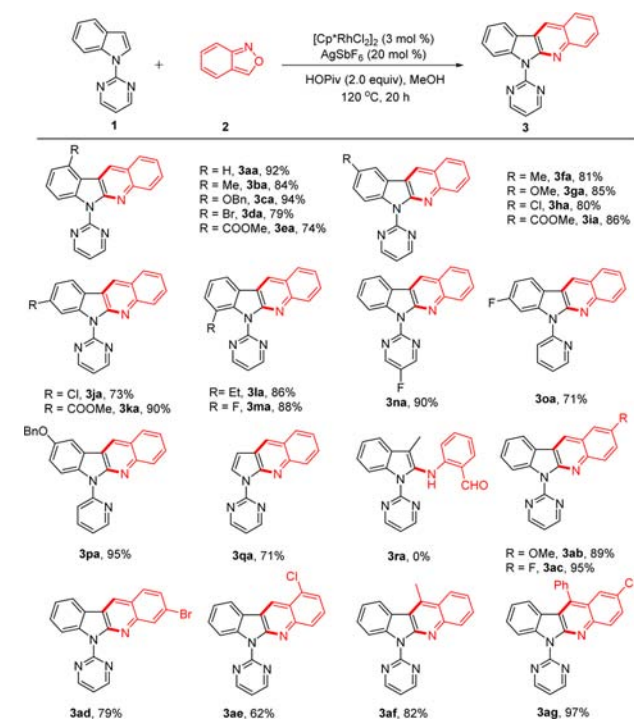
^aReaction conditions: **1a** (0.2 mmol), anthranil **2a** (0.4 mmol), catalyst, AgSbF_6 (0.04 mmol), and additive (0.4 mmol) in a solvent (3 mL) at 120 °C. ^bIsolated yield. ^c100 °C.

yield in DCE (entry 1). Switching the rhodium catalyst to related cobalt(III) ones, however, led to no desired reaction (entries 2 and 3). PivOH proved to be an optimal and necessary additive (entries 4, 5, and 12), which likely facilitated both the C–H activation and the cyclization processes. Further screening revealed that protic solvents tend to favor this reaction. To our delight, the yield of the isolated **3aa** was dramatically improved to 95% when MeOH was chosen as a solvent (entries 6–9). A similar yield was obtained when the catalyst loading was lowered to 3 mol %, while lowering the reaction temperature gave a diminished yield (entries 10 and 11).

With the establishment of optimal reaction conditions, we next investigated the scope and generality of this coupling system (Scheme 2). It was found that *N*-pyrimidinylindoles bearing both electron-donating and -withdrawing substituents at different positions all coupled smoothly with simple anthranil (**2a**), and the corresponding products were isolated in 73–92% yields. In addition to a pyrimidinyl DG, a pyridyl group also offered comparable directing effects (**3oa** and **3pa**). Notably, this protocol was applicable to the synthesis of a pyrrolo[2,3-*b*]pyridine (**3qa**) in good yield starting from a pyrrole. The scope of anthranil was next examined, and introduction of electron-donating and -withdrawing groups into different positions of the anthranil ring was fully tolerated (**3ab**–**3ag**, 62–97%). In contrast, subjection of 3-methyl-1-(pyrimidin-2-yl)-1*H*-indole to the standard conditions gave no amination product (**3ra**), indicating that annulation and aromatization offered important driving forces for the reaction.

It has been demonstrated that nucleophilicity of the site vicinal to the C–H bond that undergoes activation plays a

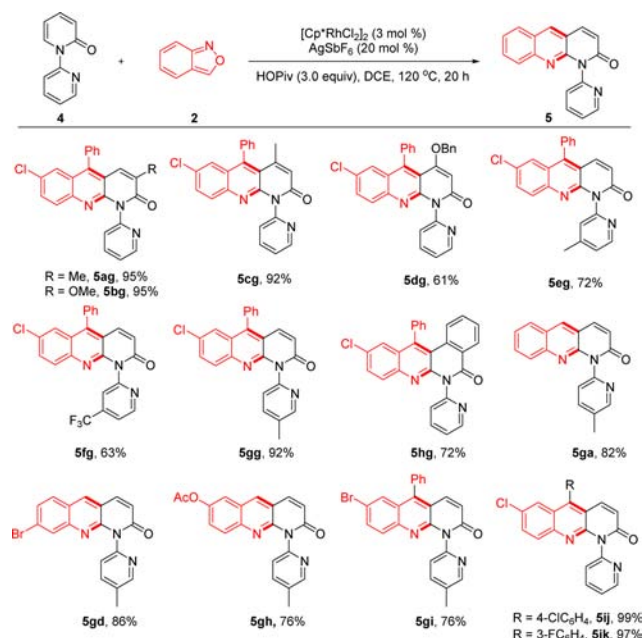
Scheme 2. Amination–Annulation of Indoles^{a,b}



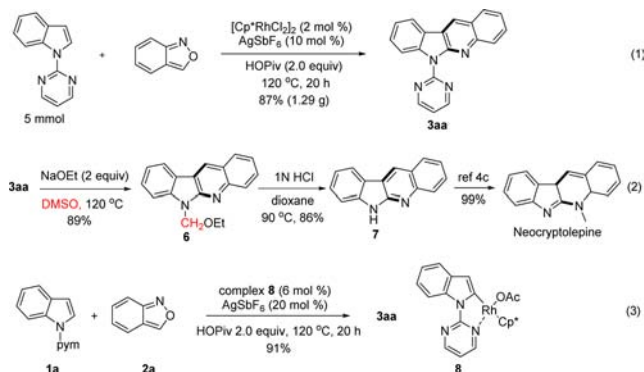
^aReaction conditions: indole (0.2 mmol), anthranil (0.4 mmol), $[\text{Cp}^*\text{RhCl}_2]_2$ (3 mol %), AgSbF_6 (20 mol %), and HOPiv (0.4 mmol) in MeOH (3 mL) at 120 °C. ^bIsolated yield.

crucial role in ensuring annulation between arenes and an electrophilic coupling partner.¹¹ For example, electron-poor arenes such as 2-phenylpyridine only underwent amination with anthranil with no further cyclization.¹² We reasoned that *N*-pyridyl-2-pyridone is sufficiently nucleophilic at the 5-position.¹³ Meanwhile, the vicinal C(6)–H should readily undergo activation when catalyzed by Rh(III).¹⁴ Thus, this may lead to the synthesis of benzo[*b*][1,8]naphthyridin-2-ones, another class of useful condensed heterocycles (Scheme 3).¹⁵ Indeed, reaction of *N*-pyridyl-2-pyridone and an anthranil under modified conditions afforded a benzo[*b*][1,8]-naphthyridin-2-one in high yield (**5ag**). Electron-donating groups at different positions of the 2-pyridone ring are compatible, and the reaction also tolerated steric perturbation at the 4 position (**5cg** and **5dg**). In addition, the arene substrate has been extended to an isoquinolone, affording an even larger π -conjugation system (**5hg**). Next, the scope of the anthranil was investigated. The reaction proceeded smoothly with high efficiency and good functional group tolerance (**5ga**–**ik**, 76–99%).

To demonstrate the synthetic utility of the catalytic reactions, gram-scale synthesis of **3aa** has been realized in high yield under a reduced catalyst loading (eq 1). Surprisingly, attempts to remove the pyrimidinyl DG by treatment of **3aa** with NaOEt in DMSO afforded an ethoxymethyl-protected indole (**6**) instead of the expected NH indole (eq 2). Formation of **6** was proposed to occur via Pummerer rearrangement, where DMSO participated in the rearrangement to provide the methylene unit in **6** (see the Supporting Information for the mechanism of this transformation). This unexpected compound was then hydrolyzed in aqueous HCl to give the NH indole **7** in excellent yield, which can be readily transferred to neocryptolepine,^{4c,f} an alkaloid with pronounced antiparasmodial activity.^{1a}

Scheme 3. Amination–Annulation of 2-Pyridones^{a,b}

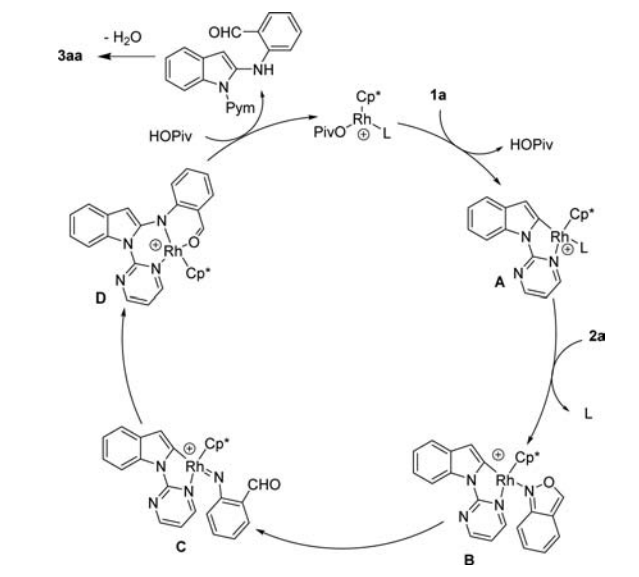
^aReaction conditions: 2-pyridone (0.2 mmol), anthranil (0.4 mmol), $[\text{Cp}^*\text{RhCl}_2]_2$ (3 mol %), AgSbF_6 (20 mol %), and HOPIv (0.6 mmol) in DCE (3 mL) at 120 °C for 20 h. ^bIsolated yield after column chromatography.



Rhodacyclic complexes **8** were then used as a catalyst for the C–H activation of an indole, and the corresponding annulated product **3aa** was isolated in excellent yield (eq 3), indicating relevancy of C–H activation in the coupling. On the basis of previous work,^{11,12} a plausible pathway is proposed starting from an active $[\text{RhCp}^*(\text{OPiv})\text{L}]^+$ species (L = a weakly coordinating species, Scheme 4). Cyclometalation of *N*-pyrimidinylindole affords a rhodacycle **A**, to which anthranil coordinates to give intermediate **B**, which undergoes elimination of a formyl group with concomitant formation of a nitrido species **C**.¹² The Rh–aryl bond then migratorily inserts into the nitrene to give a tripodal intermediate **D**,¹² which undergoes protonolysis to lead to an aminated intermediate **E**. Friedel–Crafts cyclization eventually delivers the annulated product **3aa**, and this annulation process is favored in a protic solvent.

In summary, we have developed a general strategy to construct quinoline-fused heterocycles, which likely have biological activities. Two classes of condensed heteroarenes were synthesized in high efficiency via Rh(III)-catalyzed C–H activation of arenes such as *N*-substituted indoles and 2-

Scheme 4. Proposed Mechanism



pyridones. These couplings feature the employment of bifunctional arenes and a bifunctional aminating reagent under redox-neutral conditions. These efficient and concise protocols to access such important scaffolds may find applications in the synthesis of complex biologically active products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01032.

Experimental procedures, characterization data, derivatization reactions, mechanistic studies, and ¹H, ¹³C, and ¹⁹F NMR spectra of the products (PDF)

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Notes

The authors declare no competing financial interest.

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