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

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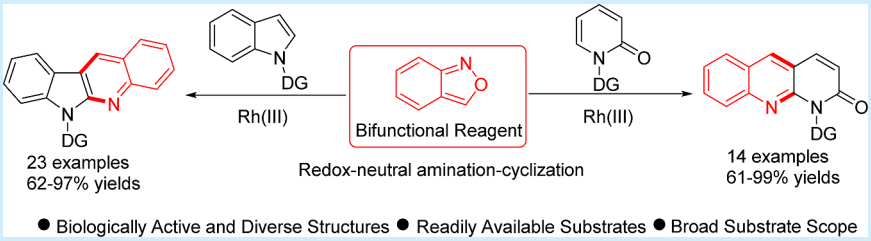
Supporting Information



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

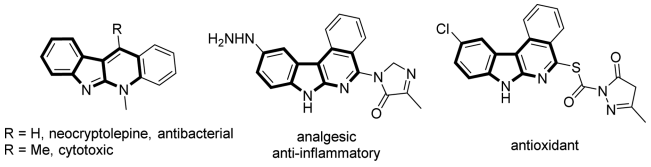
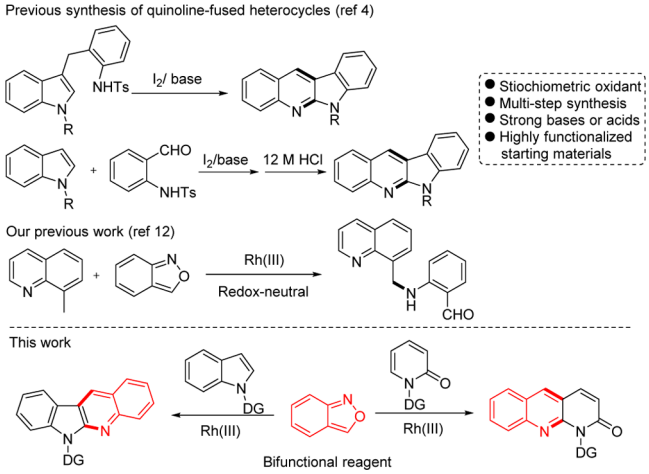


Figure 1. Representative biologically active pyrido[2,3-*b*]indoles.

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 arenes[5] 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) catalysis[7] 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



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, anthranils[9] 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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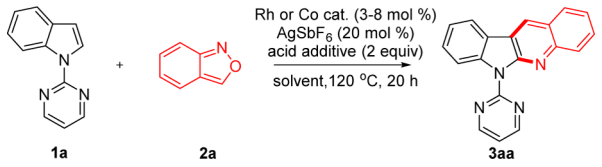
quinoline-fused heterocycles via C−H activation of different classes of arenes.

We commenced our studies by examining the reaction parameters of the coupling of *N*-pyrimidinylindole (**1a**) with anthranil (**2a**) using $[Cp^*RhCl_2]_2/AgSbF_6$ as a catalyst (Table 1). The desired indolo[2,3-*b*]quinoline **3aa** was isolated in 35%

Table 1. Optimization Studies[a]



1a 2a 3aa

entry	cat. (mol %)	additive	solvent	yield[b] (%)
1	$[Cp^*RhCl_2]_2$ (4)	HOPiv	DCE	35
2	$[Cp^*CoI_2CO]$ (8)	HOPiv	DCE	NR
3	$[Cp^*CoCl_2]_2$ (4)	HOPiv	DCE	NR
4	$[Cp^*RhCl_2]_2$ (4)	HOAc	DCE	31
5	$[Cp^*RhCl_2]_2$ (4)	TFA	DCE	trace
6	$[Cp^*RhCl_2]_2$ (4)	HOPiv	TFE	79
7	$[Cp^*RhCl_2]_2$ (4)	HOPiv	MeOH	95
8	$[Cp^*RhCl_2]_2$ (4)	HOPiv	EtOH	83
9	$[Cp^*RhCl_2]_2$ (4)	HOPiv	HFIP	89
10	$[Cp^*RhCl_2]_2$ (3)	HOPiv	MeOH	92
11[c]	$[Cp^*RhCl_2]_2$ (3)	HOPiv	MeOH	74
12	$[Cp^*RhCl_2]_2$ (3)		MeOH	39

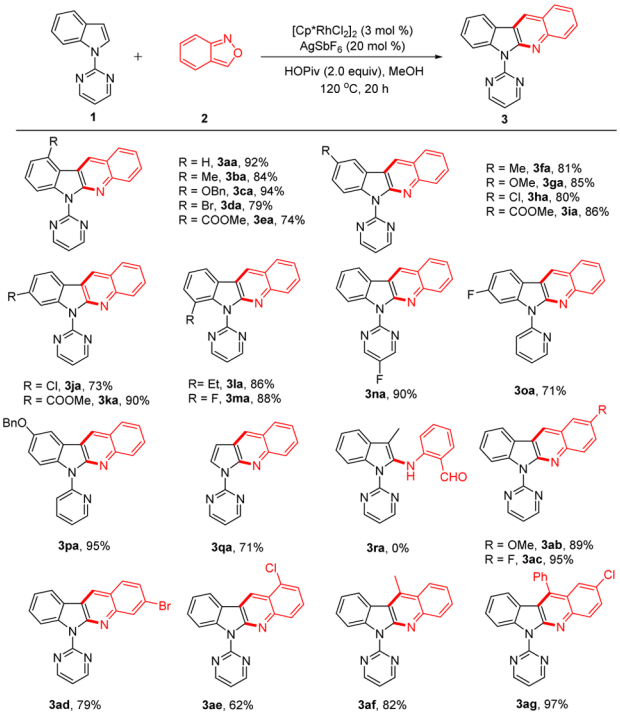
[a]Reaction conditions: **1a** (0.2 mmol), anthranil **2a** (0.4 mmol), catalyst, $AgSbF_6$ (0.04 mmol), and additive (0.4 mmol) in a solvent (3 mL) at 120 °C. [b]Isolated yield. [c]100 °C.

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]



[a]Reaction conditions: indole (0.2 mmol), anthranil (0.4 mmol), $[Cp^*RhCl_2]_2$ (3 mol %), $AgSbF_6$ (20 mol %), and HOPiv (0.4 mmol) in MeOH (3 mL) at 120 °C. [b]Isolated 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 pyrimidyl 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 antiplasmodial activity.[1a]

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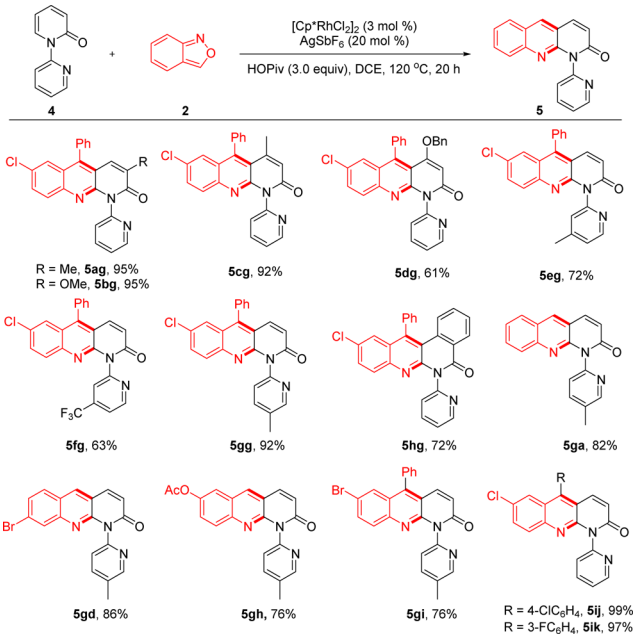
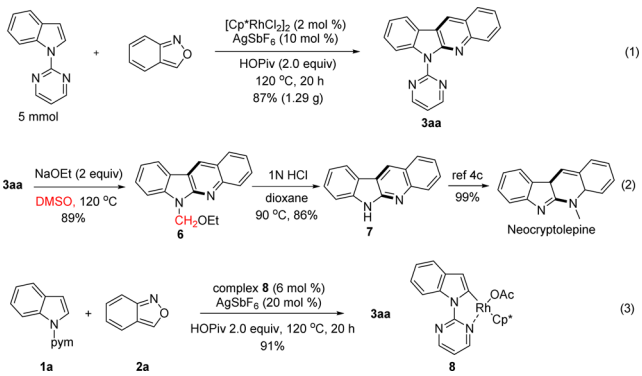
Scheme 3. Amination−Annulation of 2-Pyridones[a,b]



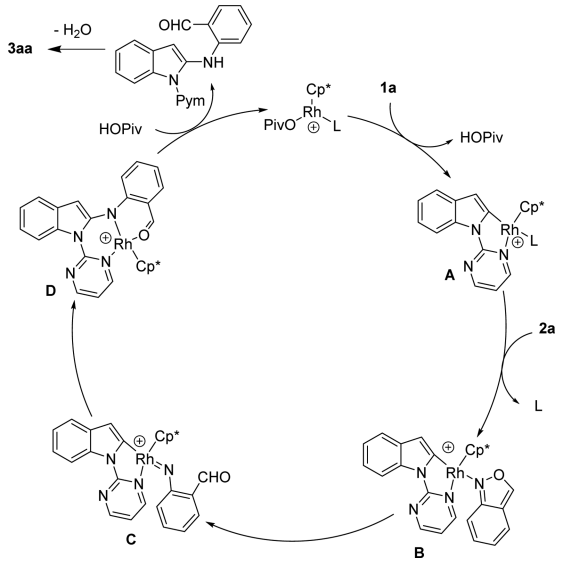
[a]Reaction conditions: 2-pyridone (0.2 mmol), anthranil (0.4 mmol), $[Cp^*RhCl_2]_2$ (3 mol %), $AgSbF_6$ (20 mol %), and HOPiv (0.6 mmol) in DCE (3 mL) at 120 °C for 20 h. [b]Isolated yield after column chromatography.



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 $[RhCp^*(OPiv)L]^+$ 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-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.

Scheme 4. Proposed Mechanism



■ 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, ^{13}C, and ^{19}F NMR spectra of the products (PDF)

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Author Contributions

†S.Y. and Y.L. contributed equally.

Notes

The authors declare no competing financial interest.

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