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Direct Access to Nitrogen Bi-heteroarenes via Iridium-Catalyzed Hydrogen-Evolution Cross-Coupling Reaction

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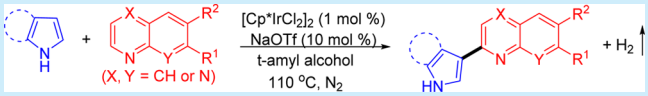
Supporting Information

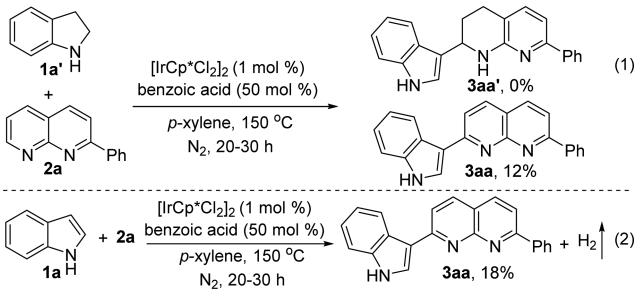
ABSTRACT: Through cooperative actions of iridium catalyst and NaOTf additive we report a new direct access to nitrogen bi-heteroarenes via hydrogen-evolution cross-coupling of the β-site of indoles/pyrrole with the α-site of *N*-heteroarenes. The reaction proceeds in an atom- and redox-economic fashion together with the merits of an easily available catalyst system, broad substrate scope, excellent functional tolerance, and no need for external oxidants, offering a practical way to create π-conjugated systems.



Bi-heteroaryl motifs are widely distributed in numerous natural products, dyes, liquid crystals, and functional materials.[1] Consequently, the selective construction of such compounds is of significant importance. In general, the bi-heteroaryl synthesis is realized by transition-metal-catalyzed cross-coupling of organometallic reagents with heteroaryl halides or pseudohalides.[2] Nevertheless, these transformations require preinstallations to generate reactive functionalities (such as halogens, −OTs, $-SiR_3$, $-BR_2$, $-SnR_3$, −ZnR, −MgR) and eliminate less useful inorganic salts, and their applications to large-scale production are easily restricted. In recent years, the direct C−H (hetero)arylation of (hetero)-arenes with halo substrates has emerged as an attractive tool since less prefunctionalization steps are needed.[3−5] Moreover, by consumption of stoichiometric amount of oxidants, the oxidative coupling of two heteroaryl C−H units has also been nicely demonstrated,[6] which offers more effective routes to access the related products. More recently, the hydrogen-evolution cross-coupling without a need for external oxidants has appeared as a highly desirable tool in creation of functionalized products[7] because such a synthesis proceeds in an atom- and redox-economic manner. Despite these significant achievements, the utilization of such a strategy to construct nitrogen biheteroarenes is rarely explored.[8]

As part of our continuous research interest in creation of N-heterocycles by transfer hydrogenative coupling strategy,[9] we have recently reported a C(sp^3)−H bond alkylation by using tetrahydro-N-heteroarenes as both the coupling partners and the hydrogen donors.[9g] We were therefore motivated to test the transfer hydrogenative coupling of indoline (**1a′**) with 2-phenyl-1,8-naphthyridine (**2a**). However, the reaction did not produce the expected product **3aa′**, and a dehydrogenative coupling compound **3aa** was detected as a sole product in 12% yield (Scheme 1, eq 1). Considering that the preparation of indoline starting materials requires a pre-preparation step via catalytic hydrogenation of indole derivatives, we subsequently tested the direct coupling of indole **1a** with **2a** under the same conditions. Interestingly, it resulted in product **3aa** in an even higher yield (eq 2, 18%) by release of H_2 gas (determined by GC). To the best of our knowledge, although a series of methods have been elegantly explored to functionalize different sites of the indole[10−12] and pyrrole[13] skeletons, the direct heteroarylation of indoles without directing groups assistance, prefunctionalization, or consumption of external oxidants still remains an unresolved goal to date. Upon a thorough investigation for the above new observation, we report here a new direct access to nitrogen biheteroarenes via iridium-catalyzed hydrogen-evolution cross-coupling of the β-site of indoles/pyrrole with the α-site of *N*-heteroarenes.

Scheme 1. Unexpected New Observation



Our initial studies focused on developing a more efficient catalytic system for the cross-coupling of indole **1a** with 2-phenyl-1,8-naphthyridine **2a** as a model system. At the start of the work, the effect of four iridium precatalysts, representative additives,[14] solvents, and different temperatures was evaluated (see Table S2). An optimal yield (88%) of **3aa** was obtained by using **1a** (0.2 mmol), **2a** (0.3 mmol), $[Cp^*IrCl_2]_2$ (1 mol %), NaOTf (10 mol %), and *tert*-amyl alcohol (1.0 mL) at 110 °C for 16 h under N_2 protection (standard conditions).

With the optimal conditions in hand, we next examined the generality and the limitations of the synthetic protocol. First,

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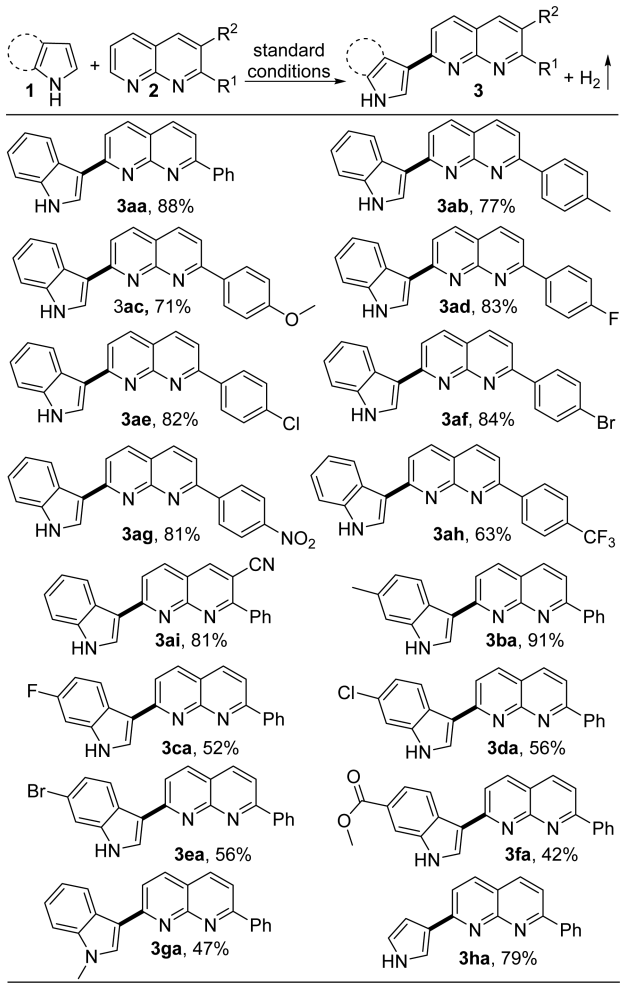
the reactions of indole **1a** with a series of 1,8-naphthyridines **2** (**2a**–**i**, for their structures, see Scheme S1) were tested. As shown in Scheme 2, all of the reactions proceeded smoothly

Scheme 2. Both Variations of Two Coupling Partners[a]

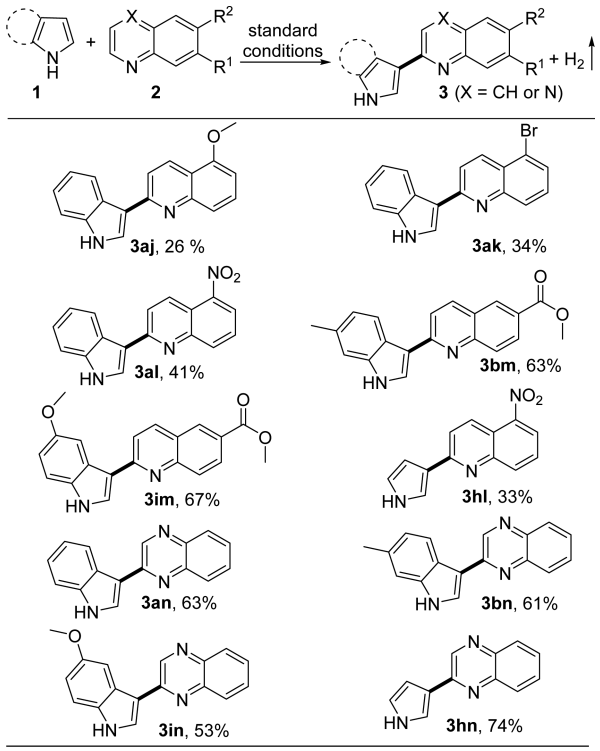


[a]Standard conditions: the reaction in *tert*-amyl alcohol (1.0 mL) was performed with **1** (0.2 mmol), **2** (0.3 mmol), $[Cp^*IrCl_2]_2$ (1 mol %), and NaOTf (10 mol %) at 110 °C for 16 h under N_2 protection.

and furnished the desired products in moderate to high isolated yields (**3aa**–**ai**) with liberation of molecular H_2 (see Figure S1). The substituents on the aryl ring of reactant **2** slightly influenced the reaction to some extent. Specifically, the electron-deficient substituents (see **3ad**–**ag**) were able to afford the corresponding products in relatively higher yields than those of electron-rich substituents (see **3ab**–**ac**), which might be because the electron-withdrawing groups could enhance the electrophilicity of the naphthyridyl skeleton, thus favoring the coupling process. However, the $-CF_3$-substituted 1,8-naphthyridine **2h** only gave a 63% yield, which is due to the relatively easy occurrence of transfer hydrogenation of **2h** into the 1,2,3,4-tetrahydro-1,8-naphthyridine derivative. Next, we focused on the variation of indoles. Gratifyingly, a series of indoles underwent efficient hydrogen-evolution cross-coupling reactions, and the electron-rich indole (**1b**) delivered the corresponding product (**3ba**) in much higher yield than electron-deficient indoles (see **3ca**–**fa**), presumably because the electron-donating methyl group could enhance the nucleophilicity of the indole skeleton, which is also beneficial for the coupling step. Moreover, the N-substituted indole **1g** and pyrrole **1h** also effectively coupled with 1,8-naphthyridine **2a** to give the desired product **3ga** and **3ha** in acceptable yields. It is worth mentioning that a series of functional groups (such as −Me, −OMe, −F, −Cl, −Br, $-CO_2Me$, $-NO_2$, $-CF_3$) on both the indolyl and naphthyridyl skeletons are well tolerated, and the retention of these functional groups would offer potential for further chemical transformations.

Subsequently, we turned our attention to the α,β-coupling of indoles/pyrrole with different N-heteroaromatics. As depicted in Scheme 3, quinolines, the more challenging substrates, were

Scheme 3. Variation of *N*-Heteroaroarenes



also amenable to the catalytic transformation, affording the desired product in reasonable to good isolated yields (**3aj**–**al**,**im**,**bm**,**hl**). Similar to the phenomenon described in Scheme 2, the reactions of electron-rich indoles (**1b**,**i**) with electron-poor quinoline (**2m**) could give satisfactory yields (**3bm**,**im**). Interestingly, quinoxaline (**2n**) has two possible reactive α-sites, which preferentially underwent mono-cross-coupling even in the presence of excess indoles/pyrrole, giving the desired products in good yields (**3an**,**bn**,**in**,**hn**). The exclusive selectivity is attributed to the steric hindrance after the first α-coupling of **2n**, and such a speculation was further supported by the reaction of 2-phenylquinoxaline with indole, which was unable to afford the α,β-coupling product.

Further, we were interested in exploring the synthetic utility of the developed chemistry. Under the standard conditions, compound **3jo**, a potent inhibitor of PDE4B (phosphodiesterase type 4B), could be prepared in a single step with 41% yield (Scheme 4, eq 3). In comparison with the existed synthetic protocol,[15] such a synthesis does not need installation of reactants, demonstrating the potential of the new method in concise synthesis of other related compounds that lead to the discovery of new bioactive candidates.

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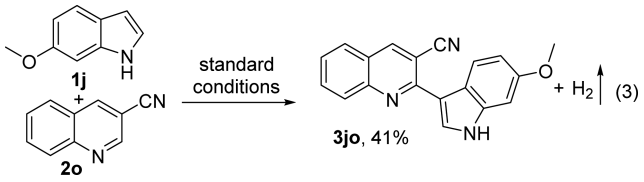
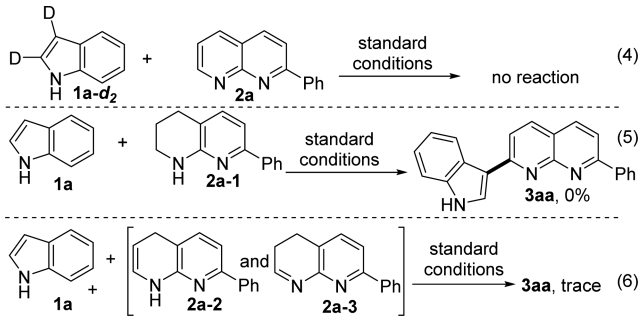
Scheme 4. Synthetic Utility



To gain insight into the reaction information, several control experiments were performed. First, replacing indole (**1a**) of the model reaction with 2,3-dideuterated indole (**1a-d_2**) under the standard conditions failed to result in any coupling product (Scheme 5, eq 4), which implies that the reaction initiates with

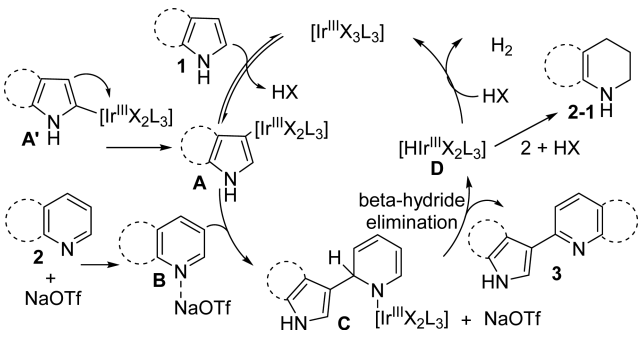
Scheme 5. Control Experiments



an iridiumation at position or 3 of the indolyl skeleton.[10] Moreover, because a small portion of 1,2,3.4-tetrahydroquinoline (**2a-1**) was detected in the model reaction, the reaction of **2a-1** with indole (**1a**) was therefore performed under the standard conditions, which did not generate any desired product **3aa** (eq 5). Similarly, the reaction of **2a-1** or dihydro-1,8-naphthyridines (the mixture of enamine **2a-2** and imine **2a-3**) with indole (**1a**) still failed to give product **3aa** (eqs 5 and 6), indicating that **2a-1**, **2a-2**, and **2a-3** are not the reaction intermediates, and the coupling should occur directly between indole **1a** and 1,8-naphthyridine **2a**. Further, the reaction of α-deuterated 1,8-naphthyridine (**2a-*dn***, 90% α-deuterium) with **1a** gave a similar yield (SI, see the α-D-labeling experiment, 38%) as the reaction of **2a** with **1a** (entry 16 of Table S2, 41%), showing that the reaction does not initiate with the α-metalation via oxidative addition of Ir to the α-C−H of **2a**.

On the basis of the above observations, a plausible reaction pathway is proposed in Scheme 6. Initially, indole/pyrrole **1** with the catalyst $[Ir^{III}X_3L_3]$ undergoes revisible β-metalation to form complex **A** by elimination of HX. Alternatively, the

Scheme 6. Plausible Catalytic Cycle



metalation at position-2 followed by a nucleophilic attack of the enamine unit to the Ir center also gives **A** by β-proton abstraction of the indole. Meanwhile, the *N*-heteroarene **2** is activated by the coordination of NaOTf to the N atom of **2** to afford species **B**. Then, the insertion of a carbon−iridium bond of **A** into the imino unit of **B** followed by β-hydride elimination of **C** (not a rate-determining step, see the kinetic isotope effect experiment in SI: KIE = 1.128) would produce the product **3** and complex **D** $[HIrIIIX_2L_3]$. Finally, the interaction of HX with $[HIrIIIX_2L_3]$ would regenerate the catalyst and release the H_2 gas. Noteworthy, the reactive metal hydride species **D** is able to transfer the hydrogen to the N-heteroarene **2** under the assistance of HX, which rationalizes the formation of tetrahydro N-heteroarene **2-1**.

In conclusion, by cooperative actions of iridium and NaOTf, we have developed a new method for direct assemble of nitrogen biheteroarenes via hydrogen-evolution cross-coupling of the β-site of indoles/pyrrole with the α-site of N-heteroarenes. The reaction proceeds in an atom- and redox-economic fashion together with the advantages of an easily available catalyst system, broad substrate scope, excellent functional tolerance, and no need for external oxidants, offering a practical way to create extended π-conjugated systems.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01349.

Detailed experimental procedures; spectroscopic and analytical data (PDF)

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Notes

The authors declare no competing financial interest.

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