Practical iridium-catalyzed direct $\alpha$-arylation of N-heteroarenes with (hetero)arylboronic acids by $\text{H}_2\text{O}$-mediated $\text{H}_2$ evolution

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Despite the widespread applications of 2-(hetero)aryl N-heteroarenes in numerous fields of science and technology, universal access to such compounds is hampered due to the lack of a general method for their synthesis. Herein, by a $\text{H}_2\text{O}$-mediated $\text{H}_2$-evolution cross-coupling strategy, we report an iridium(III)-catalyzed facile method to direct $\alpha$-arylation of N-heteroarenes with both aryl and heteroaryl boronic acids, proceeding with broad substrate scope and excellent functional compatibility, oxidant and reductant-free conditions, operational simplicity, easy scalability, and no need for prefunctionalization of N-heteroarenes. This method is applicable for structural modification of biomedical molecules, and offers a practical route for direct access to 2-(hetero)aryl N-heteroarenes, a class of potential cyclometalated C$^\equiv$N ligands and N$^\equiv$N bidentate ligands that are difficult to prepare with the existing $\alpha$-C-H arylation methods, thus filling an important gap in the capabilities of synthetic organic chemistry.
2-(Hetero)aryl N-heteroarenes represent a class of important compounds in numerous fields of science and technology, as they are extensively applied for the development of bioactive molecules, drugs, functional materials, ligands, and chemosensors. For instance, N-Heteroarenes illustrate exhibit diverse interesting bioactivities. Selexipag (uptravi) is a top-selling drug used for the treatment of cardiovascular diseases. Later, the C–H arylation protocols. In recent years, Minisci-type radical coupling has also been nicely employed to arylate the a-C–H bond of N-heteroarenes, but the related transformations generally produce several regioisomers, and consume excess of less environmentally benign oxidants. The substrates containing oxidant-sensitive groups (e.g., −NR2 and −SR) do not allow to afford the desired products. Moreover, all the above-described a-C–H arylation protocols are incompatible with heteroaryl bromides, metallic agents, and carboxylates, thus the preparation of 2-heteroaryl N-heteroarenes including N,N bidentate ligands is restricted. In this context, there is a need for a new catalytic system enabling the direct and efficient introduction of both aryl and heteroaryl groups into the a-site of N-heteroarenes, preferably with readily available and stable feedstocks.

Inspired by our recent discovery of hydrogen-transfer-mediated a-functionalization of 1,8-Naphthyridines with tetrahydroquinolines under iridium catalysis, we were motivated to test a reductive a-arylation of non-activated quinoline A1 with p-tolylboronic acid B1. However, with the same iridium(III) catalyst system, the reaction of A1 and B1 in t-amyl alcohol employing different reductants (such as i-PrOH, NH2BH3, Hantzsch esters, HCO2H, HCO2Na, HCO2Et, CO2Et, CO2F, NO2, acetal, OPh, and NPh2) on the aryl rings of boronic acids were well tolerated, and the retention of these functional groups offers the potential for molecular complexity.

**Results**

**Investigation of reaction conditions.** Initially, we wished to screen an efficient reaction system and the coupling of substrates A1 and B1 was chosen as a model system to evaluate different parameters (Table 1). At first, the reaction in t-amyl alcohol was performed at 110 °C for 24 h by testing different catalyst precursors (Ir(III), Ir(I), Ru(0), and Pd(II)). [Cp*IrCl2]2 exhibited the best performance to afford product C1 in 22% yield (entries 1–4). [Cp*IrCl2]2 was utilized to further evaluate a series of additives (entries 5–8), the results showed that the bases had a detrimental effect on the reaction (entries 5 and 6), whereas amino acids, such as glycine and L-proline, significantly improved the product yields, and the use of 20 mol% L-proline showed to be the best choice (entries 7 and 8). Then, we tested different solvents, we noticed that the reaction performed in dry 1,4-dioxane failed to produce any product C1 (entry 9), whereas the use of aqueous solution significantly increased the product yield to 60% (entry 10), which clearly implies that the presence of H2O plays a decisive role on the product formation. Interestingly, the mixed solution of H2O and 1,4-dioxane (v/v = 10/1) further improved the yield to 72% (entry 11). However, change of volume ratio was unable to further increase the product yield (entry 12). In comparison, H2O in combination with other solvents in a volume ratio of 10:1 showed to be inferior to the mixed solution of H2O and 1,4-dioxane (entries 13–15). Decrease or increase of the reaction temperature also failed to improve the reaction efficiency (entry 16). The blank experiments indicated that only the presence of both [Cp*IrCl2]2 and L-proline can constitute an efficient catalyst system (entries 17 and 18). Finally, the application of other iridium catalysts showed that they were inferior to [Cp*IrCl2]2 (entry 19). Hence, the optimal conditions are shown in entry 11 when the reaction is performed in mixed H2O and 1,4-dioxane solution (v/v = 10/1) at 110 °C for 24 h in the presence of 1 mol% of [Cp*IrCl2]2 and 20 mol% of L-proline.

**Substrate scope.** With the optimal reaction conditions in hand, we then examined the generality of the synthetic method. First, quinoline A1 in combination with a wide array of arylboronic acids B (see Supplementary Fig. 1 in Supplementary Information) were examined. As illustrated in Fig. 4, all the reactions proceeded smoothly and the desired products in good to excellent isolated yields (C2–C28). These products have the potential to serve as C=N ligands and generate cyclometalates. Interestingly, a variety of functionalities (i.e., alkyl, −OMe, −SMe, −F, −Cl, −Br, −SiMe3, −COMe, −CO2Et, −CF3, −NO2, acetal, −OPh, and −NPh2) on the aryl rings of boronic acids were well tolerated, and the retention of these functional groups offers the potential for molecular complexity.

**Fig. 1 Selected examples containing useful 2-(hetero)aryl N-heteroarenes.** Structurally related pharmaceuticals, ligands, and photocatalyst.
via further chemical transformations. In general, arylboronic acids bearing electron-donating groups (C4–C6, C8–C9, and C20–C22) afforded the products in higher yields than those of arylboronic acids with strong electron-withdrawing groups (C15–C19), implying that the reaction involves a nucleophilic coupling step. Besides, ortho-substituted arylboronic acids resulted in relatively lower yields (C3, C7, and C10), showing that the steric hindrance has a certain influence on the reaction. In addition to arylboronic acids, heteroaryl boronic acids such as indolyl, pyr-)

Fig. 2 Previous methods for access to 2-aryl N-heteroarenes. a Transition metal-mediated C–H arylation of N-heteroarenes. b Minisci-type radical arylation of N-heteroarenes.

Fig. 3 Observation on direct α-arylation of quinoline. a Hydrogen-transfer-mediated α-functionalization of 1,8-naphthyridines with tetrahydroquinolines under iridium catalysis. b Attempts on iridium-catalyzed α-arylation of quinoline with p-tolyboronic acid. c General iridium-catalyzed direct α-(hetero) arylation of N-heteroarenes.
### Table 1 Optimization of reaction conditionsa.

| Entry | Catalyst | Additive | Solvent | C1 (%)b |
|-------|----------|----------|---------|---------|
| 1     | [Cp*IrCl2]2 | –        | t-AmOH  | 22      |
| 2     | [IrCl(cod)]2 | –        | t-AmOH  | <5      |
| 3     | Ru3(CO)12  | –        | t-AmOH  | 0       |
| 4     | Pd(OAc)2   | –        | t-AmOH  | 0       |
| 5     | [Cp*IrCl2]2 | K3PO4    | t-AmOH  | Trace   |
| 6     | [Cp*IrCl2]2 | Cs2CO3   | t-AmOH  | Trace   |
| 7     | [Cp*IrCl2]2 | Glycine  | t-AmOH  | 35      |
| 8     | [Cp*IrCl2]2 | L-proline| t-AmOH  | (37, 40, 35)c |
| 9     | [Cp*IrCl2]2 | L-proline| dry 1,4-dioxane | - |
| 10    | [Cp*IrCl2]2 | L-proline| H2O     | 60      |
| 11    | [Cp*IrCl2]2 | L-proline| H2O/1,4-dioxane | 72d |
| 12    | [Cp*IrCl2]2 | L-proline| H2O/1,4-dioxane | (66, 70)e |
| 13    | [Cp*IrCl2]2 | L-proline| H2O/DMSO| 35      |
| 14    | [Cp*IrCl2]2 | L-proline| H2O/DMF  | 30      |
| 15    | [Cp*IrCl2]2 | L-proline| H2O/1,4-dioxane | (65, 72)f |
| 16    | [Cp*IrCl2]2 | L-proline| H2O/1,4-dioxane | 0      |
| 17    | [Cp*IrCl2]2 | L-proline| H2O/1,4-dioxane | 48      |
| 18    | [Cp*IrCl2]2 | L-proline| H2O/1,4-dioxane | (<5, <5, 32)g |
| 19    | [Ir complexes] | L-proline| H2O/1,4-dioxane | 77%     |

Cp* 1,2,3,4,5-pentamethylcyclopentadiene, cod 1,5-cyclooctadiene, DMSO dimethyl sulfoxide, DMF N,N-dimethylformamide.

a Unless otherwise stated, the reaction in t-amyl alcohol (1.5 mL) was performed with A1 (0.3 mmol), B1 (0.36 mmol), catalyst (1 mol%), additive (20 mol%) at 110 °C for 24 h under N2.
b Isolated yield.
c Yields are with respect to use of 10 mol%, 20 mol%, and 40 mol% L-proline, respectively.
d Mixed H2O and 1,4-dioxane solution in a volume ratio of 10:1.
e Yields are with respect to used mixed H2O and 1,4-dioxane solution in volume ratios of 9:1 and 11:1, respectively.
f Yields are with respect to the temperatures at 100 °C and 120 °C, respectively.
g Yields are with respect to use of catalyst [IrCl(cod)]2, [Ir(OMe)(1,5-cod)]2, IrCl3·3H2O, respectively.

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**Fig. 4 Synthesis of 2-aryl quinolines by variation of arylboronic acids.** Reactions were conducted on a 0.3 mmol scale under the standard conditions. The isolated yields are reported.
Herein, we successfully addressed such an issue by utilizing our synthetic method. As shown in Fig. 6, representative pyridin-2-yl and quinolin-8-yl boronic acids (B29 and B30) were employed to react with quinoline A1 and quinoxaline A19, respectively. All the reactions smoothly afforded the desired cross-coupling products in moderate yields. Interestingly, these obtained N^N bidentate ligands (C59–C63) and the commercially available 2,2'-bipyridine as well as 1,10-phenanthroline all did not undergo further α-arylation even in the presence of excess arylboronic acids, presumably because they can coordinate to the Ir(III) catalyst, and hamper the participation of Ir(III) in activation of reagents and in situ formation 2-heteroaryl radicals.\(^{19-31}\)
cross-coupling of N-heterocycles in as the intermediates is not likely, as it was the case for reductive the reaction involving tetrahydroquinoline and dihydroquinoline.

Mechanistic investigations. To gain mechanistic insights into the α-C–H arylation reaction, several control experiments were carried out (Fig. 7). First, the model reaction does not occur at all in the absence of Ir(III) catalyst (Table 1, entry 17), and both 1,2,3,4-tetrahydroquinoline (A1-a) and dihydroquinolines (A1-b and A1-c) were unable to couple with p-tolyboronic acid (B1) to yield product C1 (Fig. 7a) under the standard conditions, showing that the reaction involving tetrahydroquinoline and dihydroquinoline as the intermediates is not likely, as it was the case for reductive cross-coupling of N-heterocycles in t-amyl alcohols34, and the catalyst plays a crucial role in initiating the reaction. Upon a concurrent competition experiment of p-tolyboronic acid B1 with quinoline A1 and its α-deuterated counterpart A1-d (Supplementary Fig. 2), 1H-NMR analysis showed a kinetic isotope effect (KIE) value of 1.4 (Supplementary Fig. 3), indicating that the cleavage of α-C–H bond of quinoline A1 is not the rate-determining step in the reaction (Fig. 7b). Noteworthy, after completion of the reaction, B(OH)3 and H2 by-products44-46 were detected by means of 11B-NMR and GC, respectively (Figs. 7c and 7d, see Supplementary Figs. 4 and 5, Supplementary Table 1). To further understand the role of L-proline in the reaction, we prepared complex Cp’Ir(L-Pro)Cl from [Cp*IrCl2][L-Pro]. The transmetalation19,20 between p-tolyboronic acid B1 and [IrIII] forms aryl-Ir complex Int-1 with the elimination of XB(OH)2. The metathesis of XB(OH)2 and H2O produces HX and B(OH)3 (detected by 1B-NMR, Supplementary Fig. 4). Then, quinoline A1 undergoes carbon-Ir bond insertion of complex Int-1 into its imino motif (Int-2), and the subsequent β-hydride elimination from Int-2 gives rise to the desired product C1 along with the generation of metal hydride species [H-IrIII](L-Pro)Cl. (L-Pro)Cl is the reaction catalyst, and L-proline serves as a ligand to form the iridium catalyst.

Although the mechanistic details have not been fully elucidated, a plausible reaction pathway for the model reaction is depicted in Fig. 8 based on the above-described findings. Initially, the L-proline serves as a ligand47–49 of Ir(III) metal species (Fig. 7e) to form the complex [IrIII][L-Pro]. The transmetalation19,20 between p-tolyboronic acid B1 and [IrIII] forms aryl-Ir complex Int-1 with the elimination of XB(OH)2. The metathesis of XB(OH)2 and H2O produces HX and B(OH)3 (detected by 1B-NMR, Supplementary Fig. 4). Then, quinoline A1 undergoes carbon-Ir bond insertion of complex Int-1 into its imino motif (Int-2), and the subsequent β-hydride elimination from Int-2 gives rise to the desired product C1 along with the generation of metal hydride species [H-IrIII] (Int-
In conclusion, by a H₂O-mediated H₂-evolution cross-coupling strategy, we have developed an iridium(III)-catalyzed direct α-arylation of non-activated N-heteroarenes with aryl and heteroaryl boronic acids. This chemical avenue to 2-(hetero)aryl N-heteroarenes proceeds with broad substrate scope and excellent functional compatibility under redox neutral conditions, is operationally simple, scalable, and applicable for structural modification of biomedical molecules, enables direct access to useful bidentate N-ligands that are inaccessible or difficult to prepare with the existing α-C–H arylation protocols, and does not need for prefunctionalization of N-heteroarenes, which fills an important gap in the capabilities of synthetic organic chemistry. This catalytic reaction is anticipated to be applied in numerous fields of science and technology due to the promising potentials of 2-(hetero)aryl N-heteroarenes. Moreover, the strategy employed should be useful in the functionalization of other unsaturated hydrocarbons and further design of other reactions.

**Methods**

**Typical procedure I for the synthesis of α-arylation of N-heteroarenes.** Under N₂ atmosphere, [Cp*IrCl₂]₂ (1 mol%), L-proline (20 mol%), N-heteroarenes A (0.3 mmol), arylboronic acids B (0.36 mmol) and H₂O/1,4-dioxane (10/1, 1.5 mL) were introduced in a Schlenk tube (50 mL), successively. Then, the Schlenk tube was closed and the resulting mixture was stirred at 110 °C (oil bath temperature) for 24 h. After cooling down to room temperature, quenched with water, extracted with ethyl acetate (3 × 5 mL), and dried over anhydrous Na₂SO₄. The reaction mixture was concentrated by removing the solvent under vacuum, and the residue was purified by preparative TLC on silica, eluting with petroleum ether (60–90 °C) and ethyl acetate to give the desired product C.

**Data availability**

The authors declare that all relevant data supporting the findings of this study are available within the paper and its supplementary information files.

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Author contributions
M.Z. and L.C. conceived the idea, analyzed the data, M.Z. wrote the manuscript and directed the project. H.Z. carried out the hydrogen test experiment. R.-Q.G. synthesized the part of raw material. H.F.-J. and P.H.D. revised the manuscript and discussed the mechanistic details. All the authors have read the manuscript and agree with its content.

Competing interests
The authors declare no competing interests.
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