Practical Iridium-Catalyzed Direct α-arylation of N-heteroarenes with (Hetero)arylboronic Acids by H2O-Mediated H2 Evolution

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Abstract

Despite the widespread applications of 2-(hetero)aryl N-heteroarenes in numerous fields of science and technology, universal access to such compounds is easily hampered due to the lack of a general method for their synthesis. Herein, by a H2O-mediated H2-evolution cross-coupling strategy, we report a new iridium(III)-catalyzed facile method to direct α-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 offers applicability for structural modification of biomedical molecules, but also a practical route for direct access to 2-(hetero)aryl N-heteroarenes, a class of potential cyclometalated C^N ligands and N^N bidentate ligands that are inaccessible or difficult to prepare with the existing α-C-H arylation methods, thus filling an important gap in the capabilities of synthetic organic chemistry.

Introduction

2-(Hetero)aryl N-heteroarenes represent a class of extremely 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.[1-3] For instance, compounds **1**-**3** illustrated in Figure 1 exhibit diverse interesting bioactivities.[4-6] Selexipag (uptravi) **4** as a top-selling drug is used for the treatment of cardiovascular diseases.[7,8] 2-Pyridyl N-heteroarenes **5** possess unique binding capability towards various metals, which make them highly useful bidentate ligands in catalysis and organometallic chemistry.[9-11] In addition, 2-aryl N-heteroarenes also play a key role in photochemistry and functional materials,[12-17] as they can serve as C^N ligands to generate cyclometalated complexes with diverse photophysical properties (example **6**).

Due to the widespread applications, the introduction of (hetero)aryl groups to the *α*-site of N-heteroarenes is of significant importance, as it enables key step to access various desired 2-(hetero)aryl N-heteroarenes. Conventionally, such compounds are synthesized by Pd-catalyzed Suzuki cross-coupling of 2-halogenated N-heteroarenes with aryl boronic acids.[18] However, the halo substrates used are often hard to prepare due to the difficulties in the control of the chemo- and regioselectivity during the halogenation processes. Later, the C-C cross-coupling at C_2-position of quinolines or related N-heterocycles was achieved with ArZnEt and Ni(0) catalyst,[19,20] or with ArMgX by using Fe(III)[21]or Co(II) catalyst[22-23], or preferentially with aryl bromides in the presence of Rh(I) catalyst but at 175-190 ^oC[24-25] (Scheme 1a). Nevertheless, the need for high reaction temperatures or stringent protecting operations toward air and moisture-sensitive organometallic agents limit the practicality of these synthetic protocols. In recent years, Minisci-type radical coupling has also been nicely employed to arylate the *α*-C-H bond of N-heteroarenes (Scheme 1b),[26-31] but the related transformations generally produce several regioisomers, and consume excess of less environmentally benign oxidants ($K_2S_2O_8$ and Selectfluor). The substrates containing oxidant-sensitive groups (e.g., $-NR_2$ and $-SR$) do not allow to afford the desired products.

Moreover, all the above-described *α*-C-H arylation protocols[19-31] 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 high demand for new strategies enabling direct and efficient introduction of both aryl and heteroaryl groups into the *α*-site of N-heteroarenes, preferably with readily available and stable feedstocks.

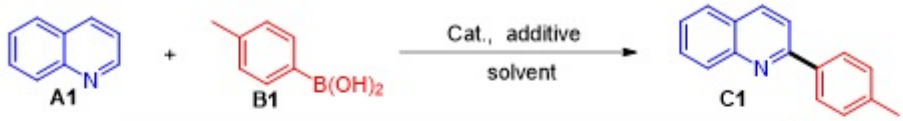
(see Scheme 1 in the Supplementary Files)

Inspired by our recent discovery of hydrogen transfer-mediated *α*-functionalization of 1,8-Naphthyridines with tetrahydroquinolines under iridium catalysis (Scheme 2a),[32] we were motivated to test a reductive *α*-arylation of non-activated quinoline **A1** with *p*-tolyboronic 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,[33-35] NH_3BH_3,[36] Hantzsch esters,[37,38] HCO_2H,[39] and HCO_2Na[40,41]) all failed to afford the desired 2-aryl tetrahydroquinoline **C1'** (Scheme 2b). Interestingly, the absence of reductant resulted in the production of 2-(*p*-tolyl)quinoline **C1** in 22% yield at 110 ^oC. Based on this observation, we wish herein to report, for the first time, an iridium-catalyzed direct *α*-arylation of N-heteroarenes with both aryl and heteroarylboronic acids by a H_2O-mediated hydrogen-evolution cross-coupling strategy (Scheme 1c), which offers a practical platform for direct structural modification of pyridine-containing molecules including drugs and functional materials, and facile preparation of N-bidentate ligands as well.

(see Scheme 2 in the Supplementary Files)

Initially, we wished to screen an efficient reaction system. The coupling of substrates **A1** and **B1** was chosen as a model reaction to evaluate different parameters (Table 1). At first, the reaction was performed in *t*-amyl alcohol at 110 °C for 24 h, the use of Ir(I), Ru(0), and Pd(II) catalysts resulted in either low yield or no product formation (entries 1-3). So, $[Cp^*IrCl_2]_2$ was used as a preferred catalyst to evaluate a series of additives (entries 4-7), the results showed that the bases had a detrimental effect on the reaction (entries 4 and 5), 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 6-7). Then, we tested different solvents, we noticed that the reaction performed in dry 1,4-dioxane failed to produce any product **C1** (entry 8), whereas the addition of H_2O significantly increased the product yield to 60% (entry 9), which clearly implies that the presence of H_2O plays a decisive role on the product formation. Interestingly, the mixed solution of H_2O and 1,4-dioxane (v/v = 10/1) further improved the yield to 72% (entry 10). However, change of volume ratios was unable to further increase the product yield (entry 11). In comparison, H_2O in combination with other solvents in a volume ratio of 10 : 1 showed to be inferior to the mixed solution of H_2O and 1,4-dioxane (entries 12-14). Decrease or increase of the reaction temperature also failed to improve the reaction efficiency (entry 15). Hence, the optimal conditions are as shown in entry 10 of Table 1 when the reaction is performed in mixed H_2O and 1,4-dioxane solution (v/v =10/1) at 110 °C for 24 h by using 1 mol % of $[Cp^*IrCl_2]_2$ and 20 mol% of *L*-proline.

Table 1. Optimization of reaction conditions[a]



Entry	Catalyst	Additive	Solvent	C1 (%)[b]
1	$[IrCl(cod)]_2$	-	*t*-AmOH	<5
2	$Ru_3(CO)_{12}$	-	*t*-AmOH	0
3	$Pd(OAc)_2$	-	*t*-AmOH	0
4	$[Cp^*IrCl_2]_2$	K_3PO_4	*t*-AmOH	trace
5	$[Cp^*IrCl_2]_2$	Cs_2CO_3	*t*-AmOH	trace
6	$[Cp^*IrCl_2]_2$	Glycine	*t*-AmOH	35
7	$[Cp^*IrCl_2]_2$	*L*-Proline	*t*-AmOH	(40, 37, 35)[c]
8	$[Cp^*IrCl_2]_2$	*L*-Proline	dry 1,4-dioxane	-
9	$[Cp^*IrCl_2]_2$	*L*-Proline	H_2O	60
10	$[Cp^*IrCl_2]_2$	*L*-Proline	H_2O/1,4-dioxan	72[d]
11	$[Cp^*IrCl_2]_2$	*L*-Proline	H_2O/1,4-dioxan	(66, 70)[e]
12	$[Cp^*IrCl_2]_2$	*L*-Proline	H_2O/*t*-AmOH	40
13	$[Cp^*IrCl_2]_2$	*L*-Proline	H_2O/DMSO	35
14	$[Cp^*IrCl_2]_2$	*L*-Proline	H_2O/DMF	30
15	$[Cp^*IrCl_2]_2$	*L*-Proline	H_2O/1,4-dioxan	(65, 72)[f]

[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 ºC for 24 h under N_2. [b] Isolated yield. [c] Yields are with respect to use of 10 mol%, 20 mol% and 40 mol% *L*-Proline, respectively. [d] Mixed H_2O and 1,4-dioxane solution in a volume ratio of 10 : 1. [e] Yields are with respect to use mixed H_2O 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 ºC and 120 ºC, respectively.

With the optimal reaction conditions in hand, we then examined the generality of the newly developed synthetic method. First, quinoline **A1** in combination with a wide array of arylboronic acids **B** (see Scheme **S1** in Supplementary Information (SI) for structural information) were examined. As illustrated in Scheme 3, all the reactions proceeded smoothly and furnished 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.[16,17] Interestingly, a variety of functionalities (i.e., alkyl, –OMe, –SMe, –F, –Cl, –Br, –$SiMe_3$, –COMe, –CO_2Et, –CF_3, –NO_2, acetal, –OPh, and–NPh_2) on the aryl rings of boronic acids were well tolerated, and the retention of these functional groups offers the potential for molecular complexity 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 aryl boronic acids, heteroaryl boronic acids such as indolyl, pyridyl, furanyl, and thiophenyl ones (**B24**–**B28**) were also

amenable to the transformation, affording the desired 2-heteroaryl N-heteroarenes in moderate yields (**C24**–**C28**).

(see Scheme 3 in the Supplementary Files)

Then, we screened the reaction with a variety of N-heteroarenes (**A2**-**A22**, see Scheme S1 for their structures) employing *p*-tolyboronic acid **B1**. At first, a variety of quinolines with different substitution patterns (**A2**–**A18**) were tested. As illustrated in Scheme 4, all the substrates underwent smooth cross-coupling to generate the desired products in moderate to excellent yields upon isolation (**C29**–**C45**). A series of functional groups on quinolyl skeleton (i.e., –Me, –OMe, –F, –Cl, –Br, –I, $-CO_2Me$, $-NO_2$) were also well tolerated, and N-heteroarenes containing electro-withdrawing groups gave relatively higher yields (**C34**-**C37** and **C44**-**C45**) than those of electron-rich ones (**C33** and **C43**), which is rationalized as the electron-deficient quinolines are beneficial to nucleophilic coupling with aryl boronic acids. Except for quinoline derivatives, other types of N-heteroarenes such as quinoxaline, quinazoline,1,5-naphthyridine, 1,8-naphthyridine, imidazo[1,2-*a*]pyrazine, 7,8-benzoquinoline, phenanthridine, and thieno[3,2-*b*]pyridine (**A19**-**A26**) were also compatible coupling partners to react with *p*-tolyboronic acid **B1**, delivering the desired cross-coupling products in reasonable yields (**C46**–**C53**). Noteworthy, reactants **A19**-**A22** have two reactive *α*-sites, but the reaction only generated *mono*-arylated products even in the presence of excess boronic acids, showing that the reaction merits unique chemoselectivity. In addition, the more challenging pyrimidine and pyrazine can also give the corresponding products **C54** and **C55** by prolonging the reaction time. As shown in Scheme 3 and 4, the demonstrated examples indicate that the newly developed synthetic protocol has broad substrate scope and excellent functional group compatibility, regardless of oxidant and acid-sensitive ones (**C9** and **C23**).

(see Scheme 4 in the Supplementary Files)

The preparation of N-bidentate ligands with the existing C–H arylation protocols still remains an unresolved goal due to the difficulties in preparation of 2-heteroaryl organometallic reagents and *in situ* formation 2-heteroaryl radicals.[19-31] Herein, we successfully addressed such an issue by utilizing our newly developed synthetic method. As shown in Scheme 5, 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 (**C56**–**C60**) 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 these bis-nitrogen heteroarenes. Thus, the present work offers a practical platform for direct and selective preparation of valuable N-bidentate ligands.[9-11]

(see Scheme 5 in the Supplementary Files)

To gain mechanistic insights into the newly developed *α*-C-H arylation reaction, several control experiments were carried out (Scheme 6). First, the model reaction does not occur at all in the absence of

Ir(III) catalyst, 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** (eq. 1), 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 alcohols,[32] 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**, ^{1}H-NMR analysis showed a KIE value of 1.4, indicating that the cleavage of *α*-C-H bond of quinoline **A1** is not the rate-determining step in the reaction (eq. 2). Noteworthy, after completion of the reaction, $B(OH)_3$ and H_2 by-products[42-44] were detected by means of ^{11}B-NMR and GC, respectively (eqs. 3-4, see Figure S3 and Figure S4. in SI).

(see Scheme 6 in the Supplementary Files)

Although the mechanistic details have not been fully elucidated, a plausible reaction pathway for the model reaction is depicted in Scheme 7 based on the above-described findings. Initially, the *L*-proline serves as a ligand[45-47] of Ir metal to form the complex [$Ir^{III}X_3Ln$]. The transmetalation[19,20] between *p*-tolyboronic acid **B1** and [$Ir^{III}X_3L_n$] forms aryl-Ir complex **Int-1** by elimination of $XB(OH)_2$. Meanwhile, the metathesis of $XB(OH)_2$ and H_2O produces HX and $B(OH)_3$ (detected by ^{11}B-NMR, Figure S3 in SI). 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 generation of metal hydride species [$HIr^{III}X_2L_n$] (**Int-3**). Finally, the interaction of [$HIr^{III}X_2L_n$] with HX would regenerate the Iridium catalyst and liberate H_2 gas (detected by gas chromatography, Figure S4 in SI). In the whole catalytic cycle, H_2O-mediated H_2 evolution plays a crucial role in facilitating the transmetalation process and regenerating the catalyst. The profitable role of the proline is not explained yet, but it is likely coordinated through its carboxylate to Ir(III) as a X ligand as in copper(I) catalyst. [42-44]

(see Scheme 7 in the Supplementary Files)

Finally, we were interested in demonstrating the synthetic utility of the developed chemistry. As shown in Scheme 8, gram-scale synthesis of 2-arylquinoline **C1** (1.42 g) was achieved by scaling up substrates **A1** and **B1** to 10 mmol and 12 mmol, respectively (Scheme 8a), and the reaction still afforded a desirable isolated yield (65%). Meanwhile, the transfer hydrogenation of compound **C1** produced a synthetically useful tetrahydroquinoline[48] **C1'** in excellent yield (Scheme 8b). Brominated compound **C37** underwent smooth Suzuki cross-coupling to afforded arylated product **C37'** in 75% yield (Scheme 8c). Moreover, the reaction is also applicable for structural functionalization of biomedical molecule such as hydroquinidine, delivering the desired *p*-tolyl-hydroquinidine hybrid in 40% yields (Scheme 8d).

(see Scheme 8 in the Supplementary Files)

Conclusions

In conclusion, by a H_2O-mediated H_2-evolution cross-coupling strategy, we have developed an iridium-catalysed direct *α*-arylation of non-activated N-heteroarenes with both aryl and heteroaryl boronic acids. This new 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, and 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 functionalization of other unsaturated hydrocarbons and further design of new reactions.

Declarations

Competing financial interests:

The authors declare no competing financial interests.

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Data availability

Materials and methods, experimental procedures, and NMR spectra are available in the Supplementary Information or from the corresponding author upon reasonable request.

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