Practical iridium-catalyzed direct α-arylation of N-heteroarenes with (hetero)arylboronic acids by H$_2$O-mediated H$_2$ evolution

Liang Cao[1], He Zhao[1], Rongqing Guan[1], Huanfeng Jiang ●[1], Pierre. H. Dixneuf[2] & Min Zhang ●[1✉]

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 H$_2$O-mediated H$_2$-evolution cross-coupling strategy, we report an 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 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^N ligands and N^N bidentate ligands that are difficult to prepare with the existing α-C-H arylation methods, thus filling an important gap in the capabilities of synthetic organic chemistry.

[1] Key Lab of Functional Molecular Engineering of Guangdong Province, School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou, China. [2] University of Rennes, ISCR, Rennes, France. ✉email: minzhang@scut.edu.cn

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[1–3]. For instance, N-Heteroarenes 1-3 illustrated exhibit diverse interesting bioactivities (Fig. 1)[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 (Fig. 1 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 arylboronic 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 C2-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 °C[24,25] (Fig. 2a). 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 (Fig. 2b)[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 strategies enabling the direct and efficient introduction of both aryl and heteroaryl groups into the α-site of N-heteroarenes, preferably with readily available and stable feedstocks [32,33].

Inspired by our recent discovery of hydrogen-transfer-mediated α-functionalization of 1,8-Naphthyridines with
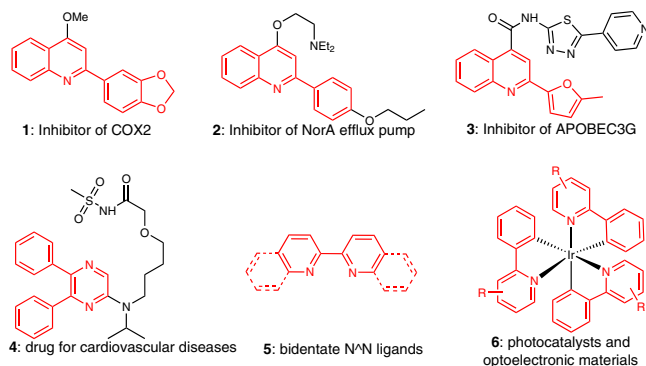
tetrahydroquinolines under iridium catalysis (Fig. 3a)[34], we were motivated to test a reductive α-arylation of non-activated quinoline A1 with p-tolyboronic acid B1. However, with the same iridium(III) catalyst system, the reaction of A1 and B1 in t-amyl alcohol employing different reductants (such as i-PrOH[35–37], NH$_3$BH$_3$[38], Hantzsch esters[39,40], HCO$_2$H[41], and HCO$_2$Na[42,43]) all failed to afford the desired 2-aryl tetrahydroquinoline C1′ (Fig. 3b). Interestingly, the absence of reductant resulted in the production of 2-(p-tolyl)quinoline C1 in 22% yield at 110 °C.

Here, we wish to report a practical iridium-catalyzed direct α-arylation of N-heteroarenes with both aryl and heteroarylboronic acids by a H$_2$O-mediated hydrogen-evolution cross-coupling strategy (Fig. 3c), which offers a practical platform for direct structural modification of pyridine-containing molecules including drugs and functional materials, and facile preparation of N-heteroarene bidentate ligands as well.

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*IrCl$_2$]$_2$ exhibited the best performance to afford product C1 in 22% yield (entries 1–4). So, [Cp*IrCl$_2$]$_2$ 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 H$_2$O plays a decisive role on the product formation. Interestingly, the mixed solution of H$_2$O and 1,4-dioxane (v/v = 10/1) further improved the yield to 72% (entry 11). However, change of volume ratios was unable to further increase the product yield (entry 12). In comparison, H$_2$O in combination with other solvents in a volume ratio of 10: 1 showed to be inferior to the mixed solution of H$_2$O 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*IrCl$_2$]$_2$ and L-proline can constitute an efficient catalyst system (entries 17 and18). Finally, the application of other iridium catalysts showed that they were inferior to [Cp*IrCl$_2$]$_2$ (entry 19). Hence, the optimal conditions are as shown in entry 11 when the reaction is performed in mixed H$_2$O and 1,4-dioxane solution (v/v = 10/1) at 110 °C for 24 h in the presence of 1 mol% of [Cp*IrCl$_2$]$_2$ 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 (SI) for structural information) were examined. As illustrated in Fig. 4, 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$_2$Et, –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

Fig. 1 Selected examples containing useful 2-(hetero)aryl N-heteroarenes. Structurally related pharmaceuticals, ligands, and photocatalyst.
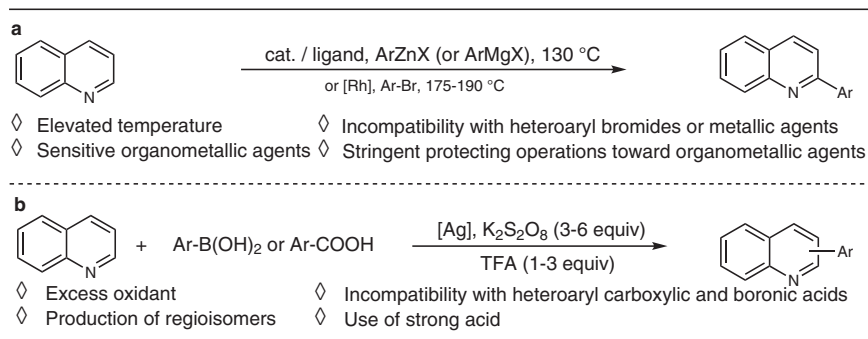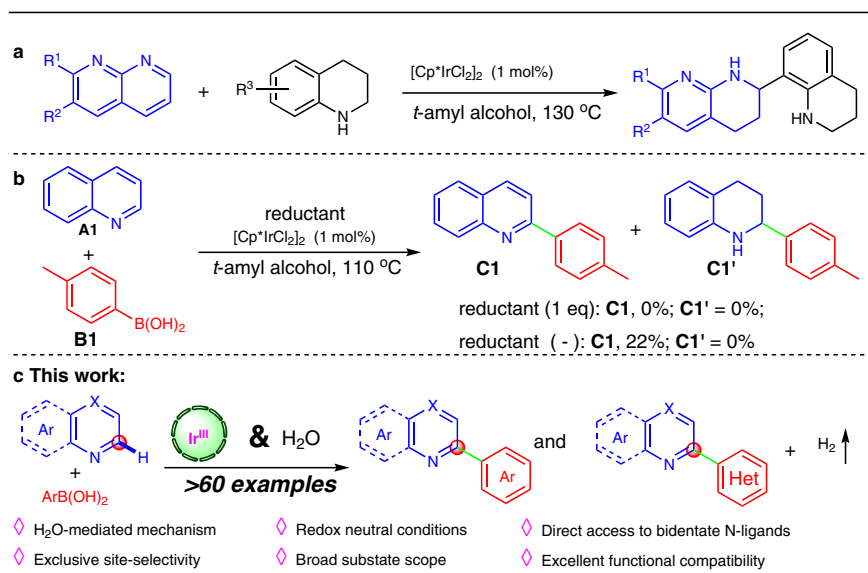
Fig. 2 Previous methods for access to 2-aryl N-heteroarenes. a Transition metal-mediated C-H arylation of N-heteroarenes. **b** Minisci-type radical arylation of N-heteroarenes.
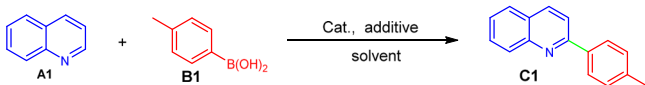

Fig. 3 Observation on direct α-arylation of quinoline. a Hydrogen-transfer-mediated α-functionalization of 1,8-naphthyridines with tetrahydroquinolines under iridium catalysis. **b** Attempts on iridium-catalyzed α-arylation of quinoline with *p*-tolyboronic acid. **c** General iridium-catalyzed direct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

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, 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**).

Then, we screened the reaction with a variety of N-heteroarenes (**A2**-**A22**, see Supplementary Fig. 1 for their structures) employing *p*-tolyboronic acid **B1**. First, a variety of quinolines with different substitution patterns (**A2**–**A18**) were tested. As illustrated in Fig. 5, 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, –CO₂Me, –NO₂) were also well tolerated, and N-heteroarenes containing electro-withdrawing groups gave relatively higher yields (**C34**-**C37**, **C44** and **C45**) than those of electron-rich ones (**C33** and **C43**), which is rationalized as the

electron-deficient quinolines are beneficial to nucleophilic coupling with arylboronic 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. Interestingly, by introducing 20 mol% of CF₃COOH as the activating agent, the α-arylation of pyridine derivatives was also successful, albeit the product yields were somewhat low (**C56**-**C58**). As shown in Figs. 4, 5, the demonstrated examples indicate that the synthetic protocol showed broad substrate scope and excellent functional group compatibility, regardless of oxidant and acid-sensitive ones (**C9** and **C23**).

The preparation of N-bidentate ligands with the existing C–H arylation protocols still remains an unresolved goal due to the difficulties in the preparation of 2-heteroaryl organometallic

3

Table 1 Optimization of reaction conditions[a].

Entry	Catalyst	Additive	Solvent	C1 (%)[b]
1	[Cp*IrCl$_2$]$_2$	–	t-AmOH	22
2	[IrCl(cod)]$_2$	–	t-AmOH	<5
3	Ru$_3$(CO)$_{12}$	–	t-AmOH	0
4	Pd(OAc)$_2$	–	t-AmOH	0
5	[Cp*IrCl$_2$]$_2$	K$_3$PO$_4$	t-AmOH	Trace
6	[Cp*IrCl$_2$]$_2$	Cs$_2$CO$_3$	t-AmOH	Trace
7	[Cp*IrCl$_2$]$_2$	Glycine	t-AmOH	35
8	[Cp*IrCl$_2$]$_2$	L-proline	t-AmOH	(37, 40, 35)[c]
9	[Cp*IrCl$_2$]$_2$	L-proline	dry 1,4-dioxane	–
10	[Cp*IrCl$_2$]$_2$	L-proline	H$_2$O	60
11	[Cp*IrCl$_2$]$_2$	L-proline	H$_2$O/1,4-dioxane	72[d]
12	[Cp*IrCl$_2$]$_2$	L-proline	H$_2$O/1,4-dioxane	(66, 70)[e]
13	[Cp*IrCl$_2$]$_2$	L-proline	H$_2$O/t-AmOH	40
14	[Cp*IrCl$_2$]$_2$	L-proline	H$_2$O/DMSO	35
15	[Cp*IrCl$_2$]$_2$	L-proline	H$_2$O/DMF	30
16	[Cp*IrCl$_2$]$_2$	L-proline	H$_2$O/1,4-dioxane	(65, 72) [f]
17	–	L-proline	H$_2$O/1,4-dioxane	0
18	[Cp*IrCl$_2$]$_2$	–	H$_2$O/1,4-dioxane	48
19	Ir complexes	L-Proline	H$_2$O/1,4-dioxane	(<5, <5, 32) [g]

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 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$_2$O and 1,4-dioxance solution in a volume ratio of 10:1
[e] Yields are with respect to used mixed H$_2$O 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)]$_2$, IrCl$_3$·3H$_2$O, respectively
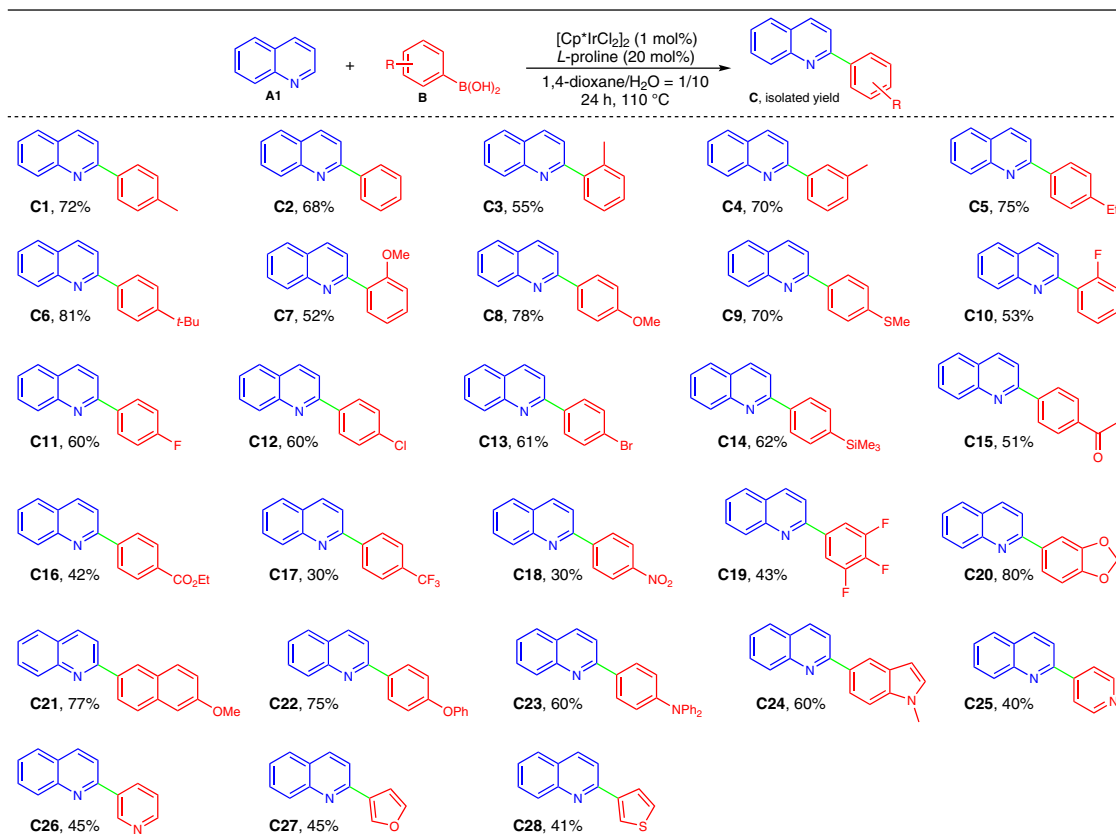
Fig. 4 Synthesis of 2-aryl quinolines by variation of arylboronic acids. Reactions were conducted on a 0.3 mmol scale under the standard conditions. The isolated yields are reported.
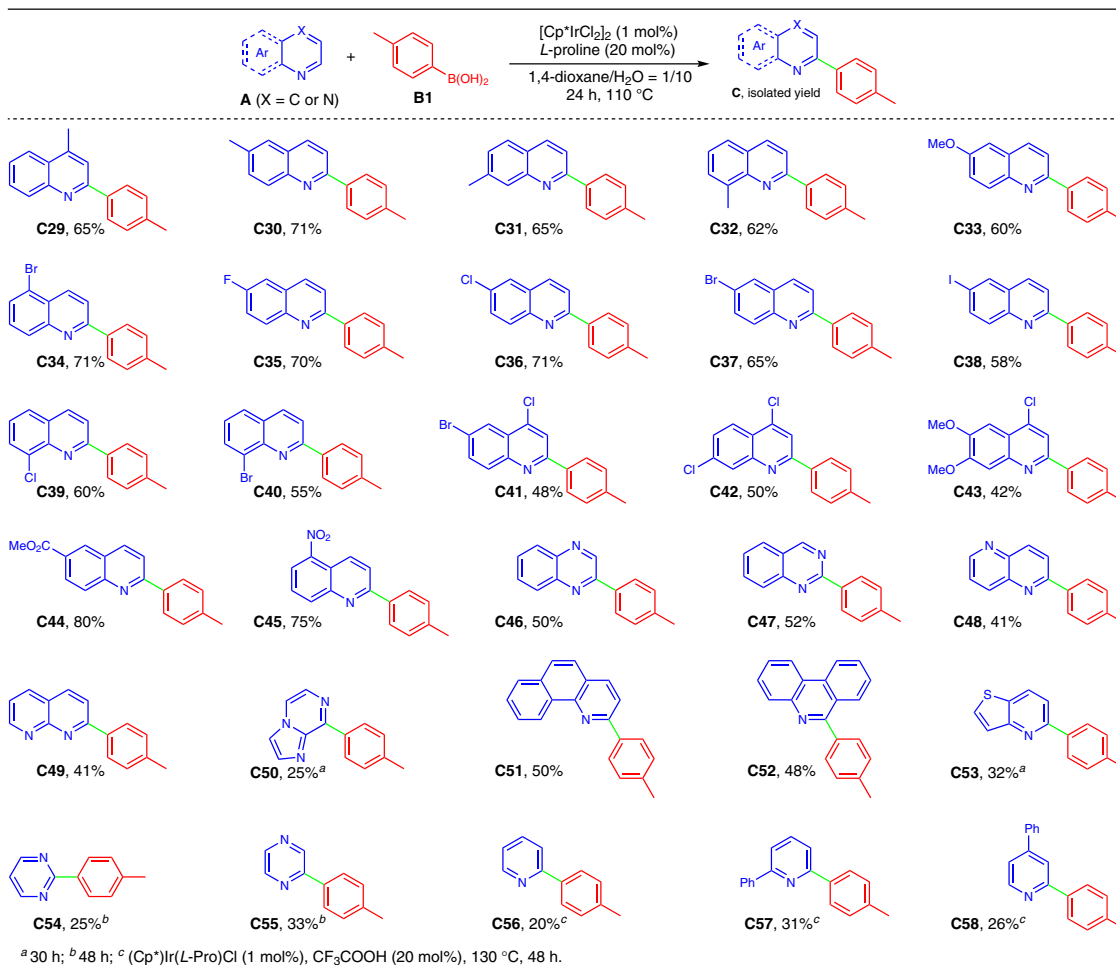
Fig. 5 Synthesis of 2-*p*-tolyl products by variation of N-heteroarenes. Reactions were conducted on a 0.3 mmol scale under the standard conditions. The isolated yields are reported.
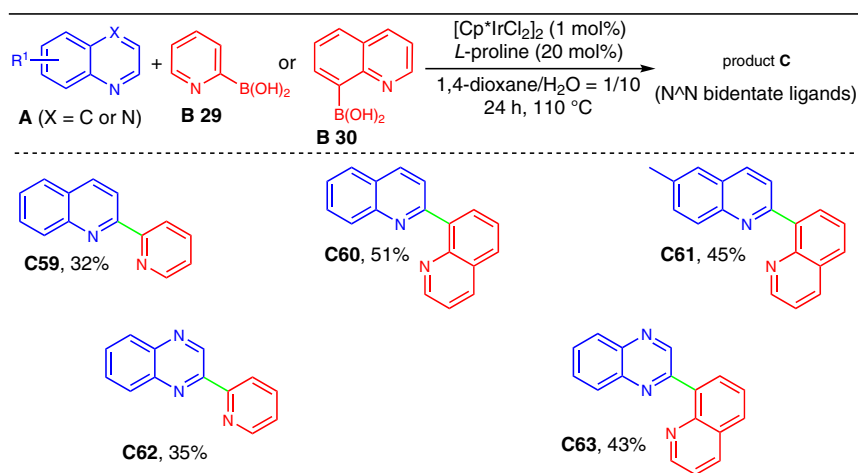
Fig. 6 Direct access to different N-bidentate ligands by α-heteroarylation of N-heteroarenes. Reactions were conducted on a 0.3 mmol scale under the standard conditions. The isolated yields are reported.

reagents and in situ formation 2-heteroaryl radicals[19–31]. 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
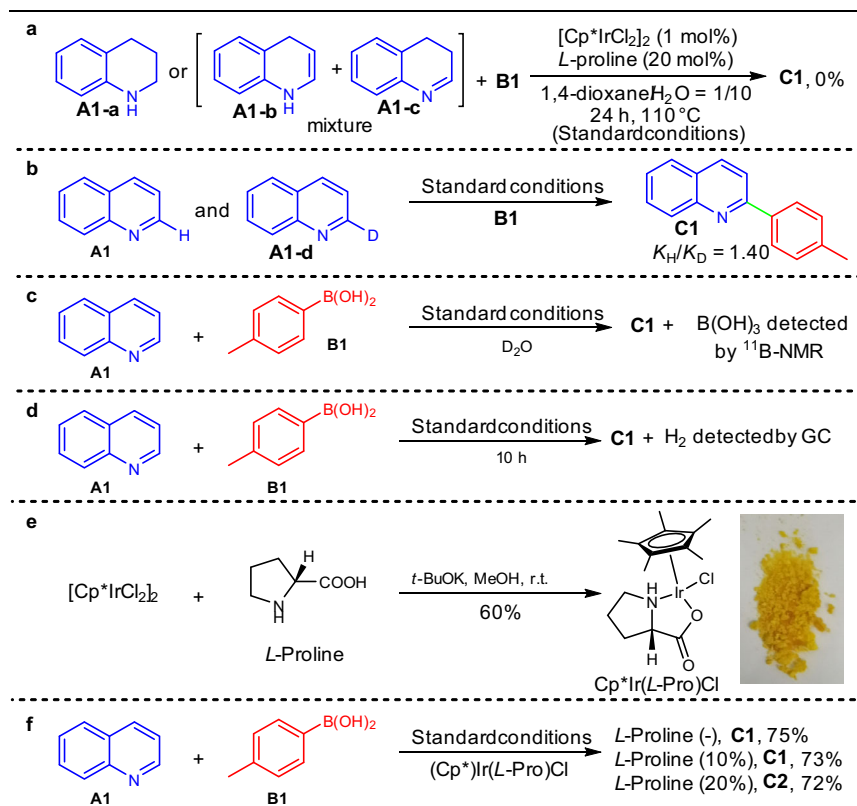
Fig. 7 Control experiments. a Verification experiment for intermediate analysis. **b** Kinetic isotope effect experiment. **c** Detection of B(OH)$_3$. **d** Detection of H$_2$. **e** Synthesis of the active catalyst Cp*Ir(L-Pro)Cl. **f** Verification experiments for the active catalyst Cp*Ir(L-Pro)Cl.

these bis-nitrogen heteroarenes. Thus, the present work offers a practical platform for the direct and selective preparation of valuable N-bidentate ligands [9–11].

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 alcohols[34], 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), ^{1}H-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 H$_2$ by-products[44–46] were detected by means of ^{11}B-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*IrCl$_2$]$_2$ and L-proline (Fig. 7e). The application of Cp*Ir(L-Pro)Cl in the model reaction resulted in product **C1** in 75% yield, whereas the combination of this complex with additional L-proline failed to improve the product yields (Fig. 7f). In comparison, the use of [Cp*IrCl$_2$]$_2$ catalyst without L-proline only gave a 48% product yield (Table 1, entry 18). These experiments indicate that Cp*Ir
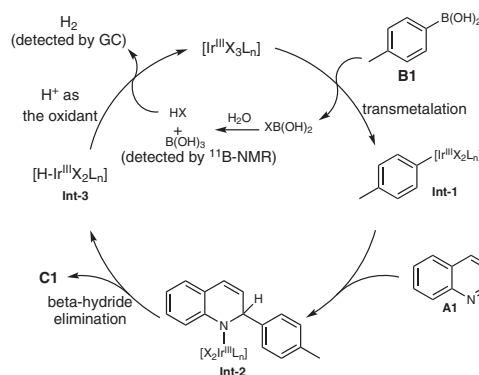
Fig. 8 Plausible reaction mechanism. Iridium-catalyzed H$_2$O-mediated H$_2$ evolution α-arylation of quinoline with p-tolyboronic acid.

(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 ligand[47–49] of Ir(III) metal species (Fig. 7e) to form the complex [Ir^{III}X$_3$L$_n$]. The transmetalation[19,20] between p-tolyboronic acid **B1** and [Ir^{III}X$_3$L$_n$] forms aryl-Ir complex **Int-1** with the elimination of XB(OH)$_2$. The metathesis of XB(OH)$_2$ and H$_2$O produces HX and B(OH)$_3$ (detected by ^{11}B-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-Ir^{III}X$_2$L$_n$] (**Int-**
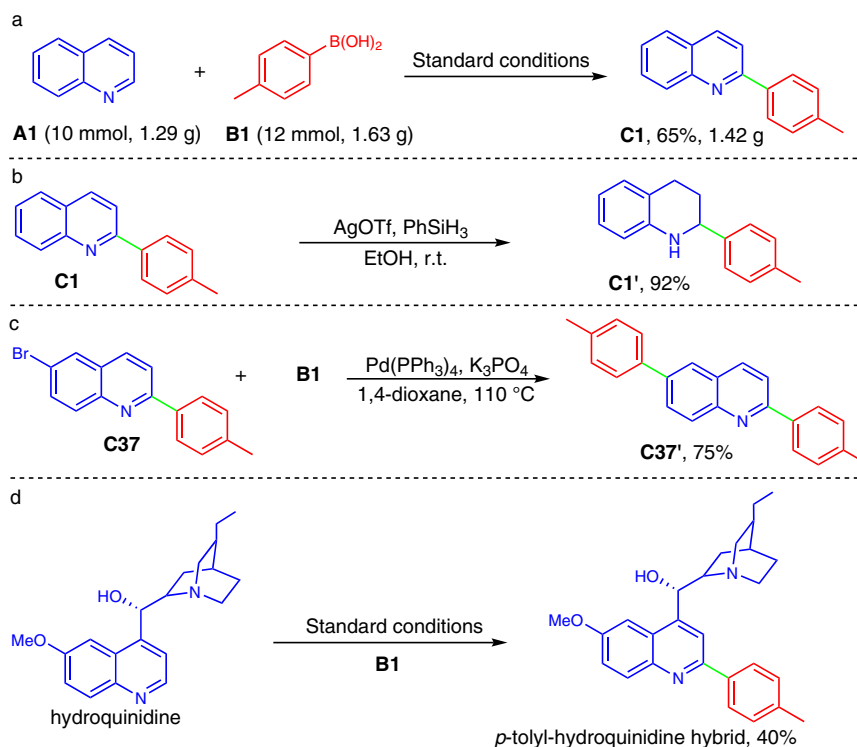
Fig. 9 Synthetic utility of the developed chemistry. a Gram-scale synthesis. **b** Reduction. **c** Cross-coupling. **d** Structural modification of biomedical molecule.

3). Finally, the interaction of the hydride in $[H\text{-}Ir^{III}X_2L_n]$ with HX (as an oxidant) would regenerate the iridium(III) catalyst and liberate H_2 gas (detected by gas chromatography, Supplementary Fig. 5). 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 likely coordinated through its carboxylate to Ir(III) as a X ligand as in copper(I) catalyst [44-47] and as a L ligand via its R^2NH group (Fig. 7e).

Application. Finally, we were interested in demonstrating the synthetic utility of the developed chemistry. As shown in Fig. 9, 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 (Fig. 9a), and the reaction still afforded a desirable isolated yield (65%). Meanwhile, the transfer hydrogenation of compound **C1** produced a synthetically useful tetrahydroquinoline[50] **C1'** in excellent yield (Fig. 9b). Brominated compound **C37** underwent smooth Suzuki cross-coupling to afford arylated product **C37'** in 75% yield (Fig. 9c). 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 (Fig. 9d).

Discussion
In conclusion, by a H_2O-mediated H_2-evolution cross-coupling strategy, we have developed an iridium(III)-catalyzed direct α-arylation of non-activated N-heteroarenes with both 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 N_2 atmosphere, $[Cp^*IrCl_2]_2$ (1 mol%), *L*-proline (20 mol%), N-heteroarenes **A** (0.3 mmol), arylboronic acids **B** (0.36 mmol) and $H_2O/1,4$-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 Na_2SO_4. 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.

References
1. Joule, J. A., & Mills, K. *Heterocyclic Chemistry* 5th edn (Wiley-Blackwell, 2010).
2. Taylor, R. D., MacCoss, M. & Lawson, A. D. G. Rings in drugs. *J. Med. Chem.* **57**, 5845–5859 (2014).
3. Bunz, U. H. F. & Freudenberg, J. N-heteroacenes and N-heteroarenes as N-nanocarbon segments. *Acc. Chem. Res.* **52**, 1575–1587 (2019).

4. Vitaku, E., Smith, D. T. & Njardarson, J. T. Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among U.S. FDA approved pharmaceuticals. *J. Med. Chem.* **57**, 10257–10274 (2014).

5. Rodrigues, T., Reker, D., Kunze, J., Schneider, P. & Schneider, G. Revealing the macromolecular targets of fragment-like natural products. *Angew. Chem. Int. Ed.* **54**, 10516–10520 (2015).

6. Sabatini, S. et al. Evolution from a natural flavones nucleus to obtain 2-(4-propoxyphenyl)quinoline derivatives as potent inhibitors of the S. aureus NorA efflux pump. *J. Med. Chem.* **54**, 5722–5736 (2011).

7. Duggan, S. T., Keam, S. J. & Burness, C. B. Selexipag: a review in pulmonary arterial hypertension. *Am. J. Cardiovasc. Drugs* **17**, 73–80 (2017).

8. Skoro-Sajer, N. & Lang, I. M. Selexipag for the treatment of pulmonary arterial hypertension. *Expert Opin. Pharmacother.* **15**, 429–436 (2014).

9. Bruns, D. L., Musaev, D. G. & Stahl, S. S. Can donor ligands make Pd(OAc)$_2$ a stronger oxidant? access to elusive palladium(II) reduction potentials and effects of ancillary ligands via palladium(II)/hydroquinone redox equilibria. *J. Am. Chem. Soc.* **142**, 19678–19688 (2020).

10. Wei, C. Y., He, Y., Shi, X. D. & Song, Z. G. Terpyridine-metal complexes: applications in catalysis and supramolecular chemistry. *Coord. Chem. Rev.* **385**, 1–19 (2019).

11. McPherson, J. N., Das, B. & Colbran, S. B. Tridentate pyridine-pyrrolide chelate ligands: An under-appreciated ligand set with an immensely promising coordination chemistry. *Coord. Chem. Rev.* **375**, 285–332 (2018).

12. Skubi, K. L., Blum, T. R. & Yoon, T. P. Dual catalysis strategies in photochemical synthesis. *Chem. Rev.* **116**, 10035–10074 (2016).

13. Yang, W., Fu, H., Song, Q. J., Zhang, M. & Ding, Y. Q. Amidate iridium(III) bis(2-pyridyl)phenyl complexes: application examples of amidate ancillary ligands in iridium(III)-cyclometalated complexes. *Organometallics* **30**, 77–83 (2011).

14. Li, T.-Y. et al. Rational design of phosphorescent iridium(III) complexes for emission color tunability and their applications in OLEDs. *Coord. Chem. Rev.* **374**, 55–92 (2018).

15. Caporale, C. & Massi, M. Cyclometalated iridium(III) complexes for life science. *Coord. Chem. Rev.* **363**, 71–91 (2018).

16. Lepeltier, M., Le Bozec, H., Guerchais, V., Lee, T. K. M. & Lo, K. K. W. Tris-cyclometalated iridium(III) styryl complexes and their saturated analogues: direct functionalization of Ir(4-Me-ppy)$_3$ and hydrogen transfer process. *Organometallics* **24**, 6069–6072 (2005).

17. Beydoun, K., Zaarour, M., Williams, J. A. G., Doucet, H. & Guerchais, V. Palladium-catalysed direct arylation of a tris-cyclometallated Ir(III) complex bearing 2,2'-thienylpyridine ligands: a powerful tool for the tuning of luminescence properties. *Chem. Commun.* **48**, 1260–1262 (2012).

18. Beletskaya, I. P., Alonso, F. & Tyurin, V. The Suzuki-Miyaura reaction after the Nobel prize. *Coord. Chem. Rev.* **385**, 137–173 (2019).

19. Tobisu, M., Hyodo, I. & Chatani, N. Nickel-catalyzed reaction of arylzinc reagents with N-aromatic heterocycles: a straightforward approach to C-H bond arylation of electron-deficient heteroaromatic compounds. *J. Am. Chem. Soc.* **131**, 12070–12071 (2009).

20. Hyodo, I., Tobisu, M. & Chatani, N. Catalytic arylation of a C-H bond in pyridine and related six-membered N-heteroarenes using organozinc reagents. *Chem. Asian J.* **7**, 1357–1365 (2012).

21. Liu, K. M., Liao, L. Y. & Duan, X. F. Iron catalyzed oxidative assembly of N-heteroaryl and aryl metal reagents using oxygen as an oxidant. *Chem. Commun.* **51**, 1124–1127 (2015).

22. Liao, L. Y., Liu, K. M. & Duan, X. F. Unified protocol for cobalt-catalyzed oxidative assembly of two aryl metal reagents using oxygen as an oxidant. *J. Org. Chem.* **80**, 9856–9867 (2015).

23. Zhuo, F. F. et al. TMEDA-assisted effective direct ortho arylation of electron-deficient N-heteroarenes with aromatic Grignard reagents. *J. Org. Chem.* **78**, 3243–3249 (2013).

24. Berman, A. M., Lewis, J. C., Bergman, R. G. & Ellman, J. A. Rh(I)-catalyzed direct arylation of pyridines and quinolines. *J. Am. Chem. Soc.* **130**, 14926–14927 (2008).

25. Berman, A. M., Bergman, R. G. & Ellman, J. A. Rh(I)-catalyzed direct arylation of azines. *J. Org. Chem.* **75**, 7863–7868 (2010).

26. Proctor, R. S. J. & Phipps, R. J. Recent advances in Minisci-type reactions. *Angew. Chem. Int. Ed.* **58**, 13666–13699 (2019).

27. Seiple, I. B. et al. Direct C–H arylation of electron-deficient heterocycles with arylboronic acids. *J. Am. Chem. Soc.* **132**, 13194–13196 (2010).

28. Wang, J., Wang, S., Wang, G., Zhang, J. & Yu, X. Q. Iron-mediated direct arylation with arylboronic acids through an aryl radical transfer pathway. *Chem. Commun.* **48**, 11769–11771 (2012).

29. Singh, P. P., Aithagani, S. K., Yadav, M., Singh, V. P. & Vishwakarma, R. A. Iron-catalyzed cross-coupling of electron-deficient heterocycles and quinone with organoboron species via innate C–H functionalization: application in total synthesis of pyrazine alkaloid botryllazine A. *J. Org. Chem.* **78**, 2639–2648 (2013).

30. Yuan, J.-W., Yang, L.-R., Mao, P. & Qu, L.-B. AgNO$_3$-catalyzed direct C–H arylation of quinolines by oxidative decarboxylation of aromatic carboxylic acids. *Org. Chem. Front.* **4**, 545–554 (2017).

31. Galloway, J. D., Mai, D. N. & Baxter, R. D. Silver-catalyzed Minisci reactions using selectfluor as a mild oxidant. *Org. Lett.* **19**, 5772–5775 (2017).

32. Yang, S. D. et al. Palladium-catalyzed direct arylation of (hetero)arenes with aryl boronic acids. *Angew. Chem. Int. Ed.* **47**, 1473–1476 (2008).

33. Bering, L. & Antonchick, A. P. Regioselective metal-free cross-coupling of quinoline N-oxides with boronic acids. *Org. Lett.* **17**, 3134–3137 (2015).

34. Chen, X. W., Zhao, H., Chen, C. L., Jiang, H. F. & Zhang, M. Hydrogen-transfer-mediated α-functionalization of 1,8-naphthyridines by a strategy overcoming the over-hydrogenation barrier. *Angew. Chem. Int. Ed.* **56**, 14232–14236 (2017).

35. Elangovan, S. et al. Efficient and selective N-alkylation of amines with alcohols catalysed by manganese pincer complexes. *Nat. Commun.* **7**, 12641 (2016).

36. Wang, D. W., Zhao, K. Y., Xu, C. Y., Miao, H. Y. & Ding, Y. Q. Synthesis, structures of benzoxazolyl iridium(III) complexes, and applications on C–C and C–N bond formation reactions under solvent-free conditions: catalytic activity enhanced by noncoordinating anion without silver effect. *ACS Catal.* **4**, 3910–3918 (2014).

37. Deibl, N. & Kempe, R. General and mild cobalt-catalyzed C-alkylation of unactivated amides and esters with alcohols. *J. Am. Chem. Soc.* **138**, 10786–10789 (2016).

38. Ding, F. W. et al. B(C$_6$F$_5$)$_3$-promoted hydrogenations of N-heterocycles with ammonia borane. *Chem. Commun.* **53**, 9262–9264 (2017).

39. Shugrue, C. R. & Miller, S. J. Phosphothreonine as a catalytic residue in peptide-mediated asymmetric transfer hydrogenations of 8-aminoquinolines. *Angew. Chem. Int. Ed.* **54**, 11173–11176 (2015).

40. Rueping, M., Antonchick, A. R. & Theissmann, T. A highly enantioselective Brønsted acid catalyzed cascade reaction: organocatalytic transfer hydrogenation of quinolines and their application in the synthesis of alkaloids. *Angew. Chem. Int. Ed.* **45**, 3683–3686 (2006).

41. Sundararaju, B., Achard, M., Sharma, G. V. M. & Bruneau, C. sp^3 C–H bond activation with ruthenium(II) catalysts and C(3)-alkylation of cyclic amines. *J. Am. Chem. Soc.* **133**, 10340–10343 (2011).

42. Chen, Z. W. et al. Formal direct cross-coupling of phenols with amines. *Angew. Chem. Int. Ed.* **54**, 14487–14491 (2015).

43. Chen, Z. W., Zeng, H. Y., Gong, H., Wang, H. N. & Li, C. J. Palladium-catalyzed reductive coupling of phenols with anilines and amines: efficient conversion of phenolic lignin model monomers and analogues to cyclohexylamines. *Chem. Sci.* **6**, 4174–4178 (2015).

44. Wang, H. M., Gao, X. L., Lv, Z. C., Abdelilah, T. & Lei, A. W. Recent advances in oxidative R^1-H/R^2-H cross-coupling with hydrogen evolution via photo-/electrochemistry. *Chem. Rev.* **119**, 6769–6787 (2019).

45. Liu, K. et al. Electrooxidative para-selective C-H/N-H cross-coupling with hydrogen evolution to synthesize triarylamine derivatives. *Nat. Commun.* **10**, 639 (2019).

46. Chen, B., Wu, L.-Z. & Tung, C.-H. Photocatalytic activation of less reactive bonds and their functionalization via hydrogen-evolution cross-couplings. *Acc. Chem. Res.* **51**, 2512–2523 (2018).

47. Ma, D. W., Geng, Q., Zhang, H. & Jiang, Y. W. Assembly of substituted phenothiazines by a sequentially controlled CuI/*L*-proline-catalyzed cascade C-S and C-N bond formation. *Angew. Chem. Int. Ed.* **49**, 1291–1294 (2010).

48. Diao, X. Q., Wang, Y. J., Jiang, Y. W. & Ma, D. W. Assembly of substituted 1*H*-benzimidazoles and 1,3-dihydrobenzimidazol-2-ones via CuI/*L*-proline catalyzed coupling of aqueous ammonia with 2-iodoacetanilides and 2-iodophenylcarbamates. *J. Org. Chem.* **74**, 7974–7977 (2009).

49. Zhu, W. & Ma, D. W. Synthesis of aryl sulfones via *L*-proline-promoted CuI-catalyzed coupling reaction of aryl halides with sulfinic acid salts. *J. Org. Chem.* **70**, 2696–2700 (2005).

50. Muthukrishnan, I., Sridharan, V. & Menendez, J. C. Progress in the chemistry of tetrahydroquinolines. *Chem. Rev.* **119**, 5057–5191 (2019).

Acknowledgements

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 part of the 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.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41467-021-24468-z.

Correspondence and requests for materials should be addressed to M.Z.

Peer review information *Nature Communications* thanks Christopher Kozak and the other anonymous reviewer(s) for their contribution to the peer review of this work. Peer reviewer reports are available.

Reprints and permission information is available at http://www.nature.com/reprints

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.