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View Article Online
DOI: 10.1039/C9CC08297B

COMMUNICATION

Ir(III)-Catalyzed Direct C–H Functionalization of *N*-phenylacetamide with *α*-Diazo Quinones: A Novel Strategy to 2-hydroxy-2′-amino-1,2′-biaryl Scaffolds

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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α-Diazo quinones are applied to a Ir(III)-catalyzed direct C–H functionalization assisted by *N*-phenylacetamide for the construction of highly functionalized 2-hydroxy-2′-amino-1,1′-biaryl scaffolds (HABAs) in good to excellent yields. This strategy features operationally simple, atom- and step-economic and high efficiency.

2-Amino/hydroxy-2′-hydroxy/amino-1,1′-biaryl motif, which is one of the most important scaffolds, are broadly distributed in chiral catalysts chiral phosphonium barfate, BINAM, BINOL, and NOBIN, biologically active molecules and natural products, such as *R*-Streptonigrin and TMC-95A (Fig 1).[1]

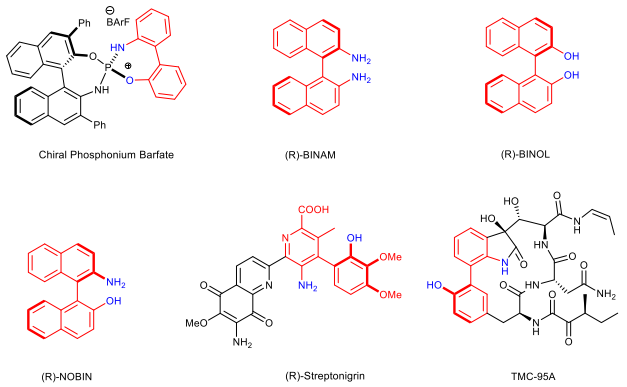

Fig. 1 Representative examples of important biaryl compounds.

As essential skeletons existed in both medicinal chemistry and organometallics, a myriad of synthetic strategies had been developed and disclosed. However, among these seminal works most of the newly constructed products were either *o*-benzidine[2] or *o*-biphenol,[3] and it was rarely disclosed for the formation of 2-hydroxy-2′-amino-1,1′-biaryls derivatives. In addition, comparing with the traditional synthetic methods of these binary scaffolds that were achieved *via* classical coupling reactions,[4] in which harsh reaction conditions and pre-functionalization of the C-H bond were typically required, our strategy could achieve the transformation through direct C-H bond functionalization under mild reaction conditions. Recently, a strategy of [3,3]-sigmatropic rearrangement have been applied for the synthesis of highly functionalized 2-hydroxy-2′-amino-1,1′-biaryl scaffolds (Scheme 1a and 1b). In 2013, Kürti and co-workers utilized 2-halonitroarenesand aryl Grignard reagent to afford the construction of halogenated 2-amino-2′-hydroxy-1,1′-biaryls (Scheme 1a).[5a] However, such limitations were included in this strategy: (a) substrates were limited to *o*-nitro group installed halogenobenzene which also resulted in a confined product list; (b) the whole process should be carried out under anaerobic and anhydrous conditions which confined its potential synthetic utility. To date, Gao *et al.* disclosed the synthesis of 2-hydroxy-2′-amino-1,1′-biaryl scaffolds starting from *N*-arylhydroxylamines and electron-deficient fluoroaromatics (Scheme 1b).[5b] However, this methodology still exhibited drawbacks including a narrow substrate scope since only nitro or strong electron-withdrawing group incorporated fluorobenzene at its *para*-position could be tolerated and proceeded smoothly. Additionally, in 2014, Zhao *et al.* discovered a hypervalent-iodine-mediated oxidative coupling reaction of 2-substituted *N*-phenylbenzamides in which the dibenzodihydro-1,3-diazepin-2-ones could be achieved through a metal-free rearrangement and be further transformed into diaryl compounds. [5c] Therefore, it is in high need to develop a strategy that can be carried out under mild reaction conditions with a broad generality. In recent years, many reviews have summarized the progress of Rh and Ir-catalyzed C-H

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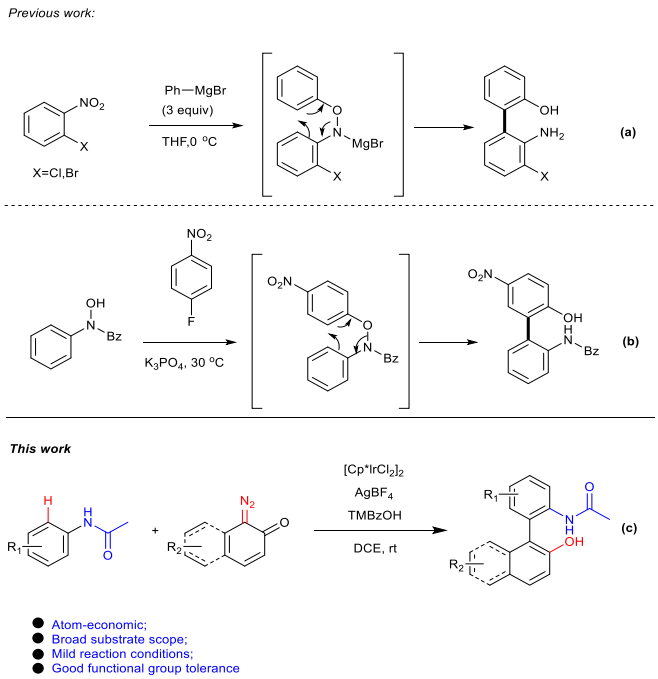
Electronic Supplementary Information (ESI) available: Data for new compounds and experimental procedures. See DOI: 10.1039/x0xx00000x

functionalization,[6] however, the emergence and latest development of direct C-H bond activation provided another approach for the construction of 2-hydroxy-2′-amino-1,1′-biaryls.

α-Diazo quinone was an efficient carbene precursor, which had been broadly utilized in the transition-metal-catalyzed reactions and considering this carbene precursor could be further converted and protonated to afford thephenol motif,[7] herein, we successfully developed a strategy between *N*-phenylacetamide and *α*-diazo quinone approaching for the synthesis of 2-amino-2′-hydroxy-1,1′-biaryl scaffold via Ir(III)-catalyzed direct C-H bond activation assisted by a removable directing group (DG) under mild conditions. This strategy was proved to be step-economic with broad generality. (Scheme 1c).



Scheme 1. Approach for the synthesis of 2-hydroxy-2′-amino-1,1′-biaryl scaffolds.

Before we triggered our studies, a comprehensive literatures review revealed that Yu *et al.*, reported the first example of arene coupled with diazo compounds through a Rh(III)-catalyzed direct C-H bond activation.[8] and this method has been applied to the construction of heterocyclic compounds.[9] Afterwards, a Co(II)-catalyzed coupling reaction between diazoacetates and pyridine was achieved with good regioselectivity.[9i] In addition, the *α*-diazo quinones were involved in the synthesis of 2-hydroxy-1,1′-biaryls *via* transition metal catalyzed reactions including Rh, Ir, and Fe which were disclosed by Wang,[7a] Yang,[7b] Che, [7c], Cramer [7d], and Lee [7e], respectively. In 2019, Peng gave a comprehensive review of these reactions. [7f] Under the basis of these reported works, our studies were initiated by examining the coupling of *N*-phenylacetamide (**1a**) and quinone diazide (**2a**) catalyzed by various transition-metals. After careful investigation of the reaction conditions, we found that treating *N*-phenylacetamide (**1a**; 0.3 mmol) with quinone diazide (**2a**; 0.3 mmol) in the presence of $[Cp^*IrCl_2]_2$ (3.0 mol %), TMBzOH (20 mol %) and $AgBF_4$ (12 mol %) in 2mL DCE at rt under Ar for 12h afforded compound **3aa** in 87% isolated yield (see Table S1 in ESI for details)

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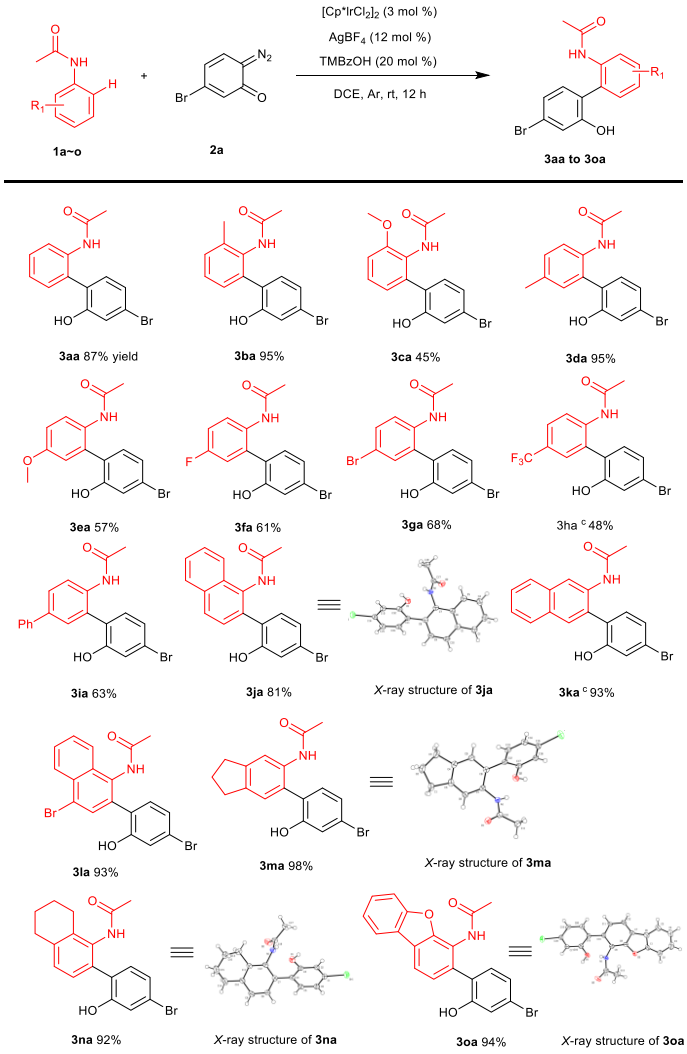
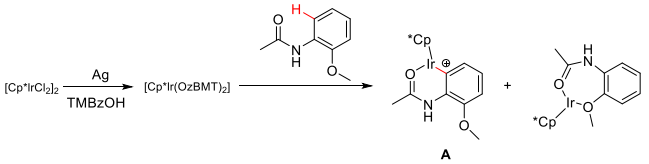
Table 1. Scope of *N*-phenylacetamides [a, b]



[a] General reaction conditions: **1a**-**1o** (0.3 mmol), **2a** (0.45 mmol), $[Cp^*IrCl_2]_2$ (3 mol %), TMBzOH (20 mol %), $AgBF_4$ (12 mol %), Ar, rt, 12 h, DCE (2 mL). [b] Isolated yields. [c] 24 h.

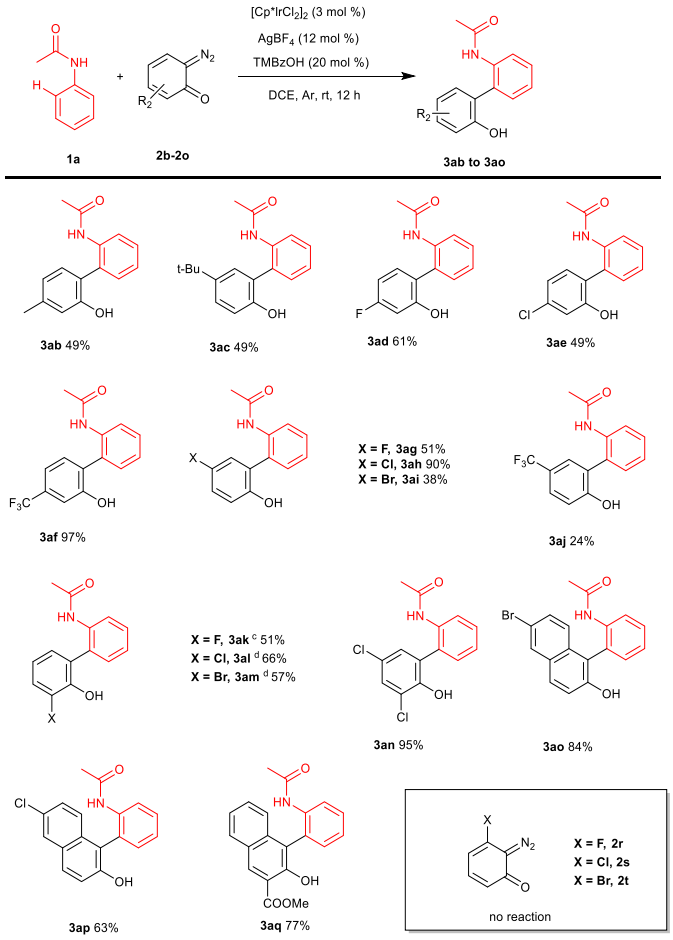
With the optimal reaction conditions in hand, we embarked on the substrate scope investigation. The scope of *N*-phenylacetamides **1a-1n** was first examined (Table 1). It was demonstrated that a variety of *N*-phenylacetamides **1a**-**1n** with substituents installed at the *ortho*- or *para*-position could process smoothly under standard reaction conditions to afford the desired 2-amino-2′-hydroxy -1,1′-biaryls derivatives in moderate to excellent yields (45%-95%). The *N*-phenylacetamides bearing electron-donating substituent was more favourable in obtaining the desired product than substrates bearing electron-withdrawing substituent group. For example, under standard reaction conditions, compound **3da** could be isolated in 95% yield but **3ha** was obtained in only 48% yield even if the reaction time was extended to 24h. Surprisingly,

a diminished yield of the desired product (**3ca**, 45% yield) was observed when an *ortho*-methoxy installed substrate was involved. This was probably caused by the weak coordination effect of methoxy to the Ir(III) complex and this route was presented as below: [14]



Fused acetanilides **1j**-**1n** could also react with **2a** to generate the biaryl products in good to excellent yields (81%-98%) with high chemo- and regioselectivity. In addition, oxygen containing fused heterocyclic product **3oa** could also be obtained with an excellent yield (94%). And the structure of **3ja**, **3ma**, **3na** and **3oa** was unambiguously confirmed by the single crystal X-ray diffraction (see ESI).[15]

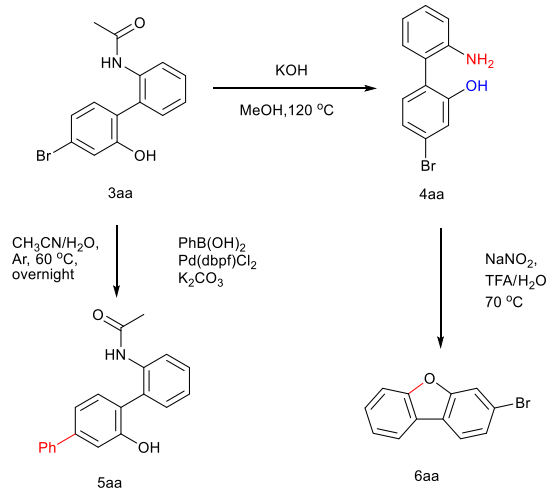
Table 2. Scope of *α*-Diazo Compounds [a, b]



[a] General reaction conditions: **1a** (0.3 mmol), **2b**-**2o** (0.45 mmol), $[Cp^*IrCl_2]_2$ (3 mol %), TMBzOH (20 mol %), $AgBF_4$ (12 mol %), Ar, rt, 12 h, DCE (2 mL). [b] Isolated yields. [c] 24 h. [d] 36 h.

Next, the scope of *α*-diazo quinones was evaluated as depicted in Table 2. *α*-Diazo quinone bearing various substituents including the -Me, -*tert*-Bu, -F, -Cl, -Br and $-CF_3$ groups at different positions was demonstrated to react smoothly with substrate **1a** by obtaining the target products **3ab-3aj** in moderate to high yields (24%-97%). When a substituent group was incorporated on the *ortho*-position of carbonyl, the target products **3ak-3am**could be obtained in moderate yields (51%-66%) by extending the reaction time. Disubstituents incorporated or fused ring containing diazo derivatives could also tolerated to this reaction by obtaining the target molecules (**3an-3ao**) in moderate to excellent yields (63%-95%). However, introduction of substituents on at the *ortho*-position hampered the reactivity(**2r-2t**) due to the steric hindrance.

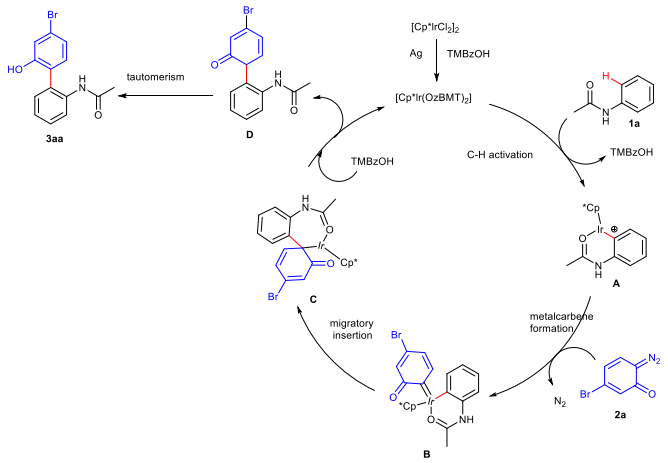
To further investigate the synthetic utility of this strategy, gram-scale reaction was carried out and the aiming product **3aa** could be isolated in 83% yield.The directing group could also be conveniently removed by treating the product with KOH to afford the compound **4aa** in 77% yield (Scheme 2). [2c, 1a] Furthermore, compound **3aa** was further explored as shown in Scheme 2. Aminohydroxyterphenyl **5aa** can be obtained in high yield (98% yield) *via* a simple Suzuki cross-coupling of **3aa** with benzboronic acid (Scheme 2).[10] Removal of the directing group in **4aa** have afforded the dibenzofuran **6aa** in a good yield (Scheme 2, 77% yield).[5a] It was worth mentioning that the dibenzofuran scaffold was served as privileged in numerous natural products and drug candidates. [13a, 13b]



Scheme 2 Removal of the directing groups and synthetic applications of biaryl products.

Finally, to gain insight into the mechanism of the reaction, kinetic isotope effect (KIE) was examined using a 1:1 mixture of **1a** and $[D_5]$-**1a** with **2a** under standard reaction conditions and the KIE value of 1.39 indicated that the *ortho*-C-H bond cleavage of **1a** might not be involved in the rate limiting step. (see ESI).[10] According to the previous reports,[7a,8,9a] a plausible pathway is proposed (Scheme 3). Cp*Ir(III) complex is first activated by ligand exchange with TMBzOH, and the active Cp*Ir(III) catalyst was subsequently inserted into the *ortho* C-H bond of substrate **1a** *via* under the assistance of acetamide to form a six-membered iridacyclic intermediate **A**.[7b,12] Next, **A** reacts with *α*-diazo quinone **2a** to form a metal carbene species **B** with the release of N_2. The subsequent migratory insertion lead to intermediate **C**. Upon protonation with TMBzOH. Intermediate

D was produced and the catalyst is regenerated. The aromatization of intermediate **D** gives the target compound **3aa**.



Scheme 3 Plausible reaction mechanism.

In summary, we have developed a facile strategy to build up the biaryl scaffold through Ir(III)-catalyzed direct C–H bond activation with a cascade intermolecular coupling. This strategy can be proceeded under room temperature and features broad generality and good atomic economy. Most importantly, this strategy is the first to synthesize 2-amino-2′-hydroxy-1,1′-biaryls by Ir(III)-catalyzed direct C-H bond functionalization.

We are grateful to the National Natural Science Foundation of China (Nos. 21632008, 21672231, 21877118, and 81620108027) and the Strategic Priority Research Program of the Chinese Academy of Sciences (XDA12040107 and XDA12040201) for financial support.

Conflicts of interest

There are no conflicts to declare.

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15 The supplementary crystallographic data for **3ja** (CCDC 1974735), **3ma** (CDCC 1974732), **3na** (CDCC 1974734), **3oa** (CDCC 1974733) can be obtained free of charge from the Cambridge Crystallographic Data Center.

View Article Online DOI: 10.1039/C9CC08297B