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DOI: 10.1039/C9CC09493H

Journal Name

COMMUNICATION

Palladium-Catalyzed C-H Bond Activation for the Assembly of N-Aryl Carbazoles with Aromatic Amines as Nitrogen Sources

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

DOI: 10.1039/x0xx00000x

www.rsc.org/

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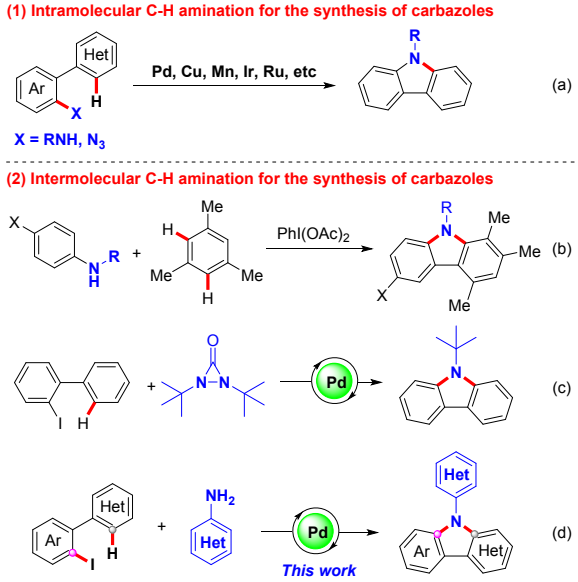
A convenient and efficient palladium-catalyzed C-H bond activation for the assembly of N-aryl carbazole is reported, in which two C-N bonds were formed under one set of conditions. The desired carbazoles were achieved in decent yields with wide substrate scope by utilizing readily available 2-iodo biphenyls and aromatic amines as starting materials.

Carbazoles have emerged as one of the privileged core structural frameworks in diverse array of drugs and natural products,[1] which also have immense applications in interdisciplinary research fields. Due to their wide band gap, high electron density, excellent electrical and optical properties, carbazole derivatives have demonstrably loomed as prevailing molecular entities in OLEDs materials, hole transport materials, electroluminescent materials and photoconductors.[2] Therefore, the development of an expedient method for the synthesis of carbazoles is of remarkable importance in the realm of both pharmaceutical chemistry and materials science.

Given the broad-spectrum bioactivity and characteristic physical property of carbazoles, there has been an extensive interest in the synthesis of carbazoles.[3-8] Transition-metal catalyzed Ulman-type C-N coupling is a classical method for the assembly of N-aryl carbazoles.[3] Since transition-metal catalyzed C-H bond activation is more economical and practical without further pre-functionalization of the raw materials, direct C-H amination of arenes has arguably represented as a promising platform to forge these valuable carbazoles.[4-5] In the past ten years, transition-metal catalyzed intramolecular C-H amination of 2-amino biphenys[4] and 2-azido biphenys[5] have been dominated to access carbazoles (Scheme 1a). With regard to intermolecular C-H amination to afford carbazoles, in 2017, Mal and coworkers developed an intermolecular dehydrogenative annulation of anilides for the construction of carbazoles under mild conditions (Scheme 1b).[6] Recently, Zhang's group described an excellent Pd-catalyzed C-H amination for the synthesis of N-tert-butyl carbazole by employing diaziridinone as nitrogen source and oxidant (Scheme 1c).[7] However, nitrogen sources are limited to diaziridinone. Despite great progress has been made for the assembly of carbazoles, the development of concise route for tailor-made synthesis of N-aryl carbazoles in one-pot under one set conditions is still in demand. Herein, we disclose an expedient Pd-catalyzed C-H bond activation to streamline synthesis of N-aryl carbazoles from easily available 2-iodide biphenys and commercially available aromatic amines (Scheme 1d).



Scheme 1. Transition-metal-catalyzed C-H bond activation and amination for the synthesis of carbazoles

We commenced our study by using 2-iodobiphenyl (**1a**) and aniline (**2a**) as benchmark substrates. Despondingly, when the reaction was conducted in the presence of 5 mol% $Pd(OAc)_2$ and 10 mol% PPh_3 by employing AgOAc or AgTFA as oxidant, stagnant

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

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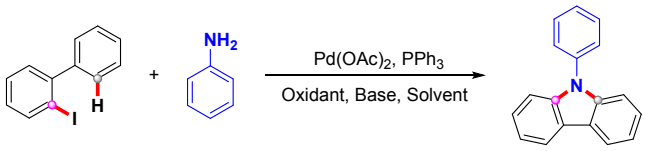
DOI: 10.1039/C9CC09492H

reaction was observed and no targeted product was detected (Table 1, entries 1 and 2). To our delight, N-phenylcarbazole **3a** was obtained in 15% yield when $Cu(TFA)_2$ was used as oxidant (Table 1, entry 3). Replacement of $Cu(TFA)_2$ with $Cu(OAc)_2$ resulted in that the yield of **3a** was significantly increased to 76% (Table 1, entry 4). Subsequently, various inorganic bases were inspected (Table 1, entries 5-8). $NaHCO_3$, K_3PO_4 and KOAc have been shown to reduce the reaction efficiency, whereas Cs_2CO_3 could enhance the reactivity, in which the desired product **3a** was isolated in 90% yield. We also screened a sequence of solvents (Table 1, entry 9-11). Among the solvent tested, N,N-dimethylformamide (DMF) still demonstrated the optimal efficiency. The attempt to lessen the amount of $Cu(OAc)_2$ to 0.5 equiv was failed, in which the yield of **3a** decreased gravely (Table 1, entry 12). When the model reaction was conducted in the absence of PPh_3, relatively low yield of the targeted product **3a** was obtained, which manifested that PPh_3 played an important role in this system (Table 1, entry 13). When the reaction was performed without $Pd(OAc)_2$, no desired product **3a** was obtained (Table 1, entry 14).

Table 1. Screening of the Reaction Conditions



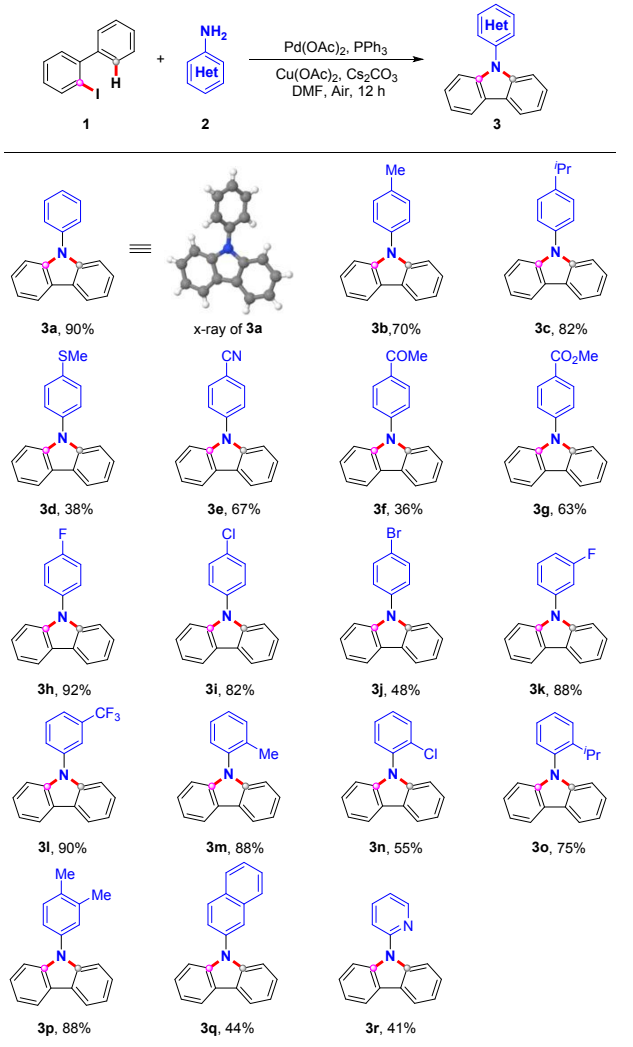
1a **2a** **3a**

Entry[a]	Oxidant	Solvent	Base	Yield[b]
1	AgOAc	DMF	Na_2CO_3	N.R
2	AgTFA	DMF	Na_2CO_3	N.R
3	$Cu(TFA)_2$	DMF	Na_2CO_3	15
4	$Cu(OAc)_2$	DMF	Na_2CO_3	76
5	$Cu(OAc)_2$	DMF	$NaHCO_3$	21
6	$Cu(OAc)_2$	DMF	K_3PO_4	34
7	$Cu(OAc)_2$	DMF	KOAc	47
8	$Cu(OAc)_2$	DMF	Cs_2CO_3	90
9	$Cu(OAc)_2$	CH_3CN	Cs_2CO_3	14
10	$Cu(OAc)_2$	DMSO	Cs_2CO_3	45
11	$Cu(OAc)_2$	1.4-dioxane	Cs_2CO_3	19
12[c]	$Cu(OAc)_2$	DMF	Cs_2CO_3	35
13[d]	$Cu(OAc)_2$	DMF	Cs_2CO_3	37
14[e]	$Cu(OAc)_2$	DMF	Cs_2CO_3	N.R

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (1.2 equiv, 0.24 mmol), 5 mol% $Pd(OAc)_2$, 10 mol% PPh_3, 1.0 equiv oxidant, 1.0 equiv base, 2 mL solvent, 120 °C, Air, 12 h. [b] The isolated yield of **3a**. [c] 0.5 equiv of $Cu(OAc)_2$ was used. [d] Without PPh_3. [e] without $Pd(OAc)_2$.

With optimized conditions in hand, the substrate scope for this Pd-catalyzed C-H bond activation was evaluated (Scheme 2). Overall, all the tested aromatic amines were proved to be suitable nitrogen sources, enabling the production of the corresponding carbazoles in decent yields. The structure of **3a** was unambiguously confirmed by X-ray crystallographic analysis. Anilines bearing electron-donating and electron-withdrawing groups were good candidates in this transformation, delivering the products **3b**-**3g** 36%-82% yields. It is noteworthy that halogen-substituted anilines were well-tolerated under the identified conditions as well, leading to the formation of halogen-substituted N-aryl carbazole derivatives (**3i**-**3k**) in 48%-92%, which could undergo further transformations. In addition to *para*-position substituted anilines, meta-position and *ortho*-position substituted anilines also demonstrated good reactivity, furnishing the exected products **3k**-**3o** in good yields. The treatment of di-substituted aniline **2p** in this reaction was also successful, in which the targeted carbazole **3p** was isolated in 88% yield. To our delight, 2-naphthylamine and 2-aminopyridine could also be engaged in this Pd-catalyzed C-H bond activation and the expected **3q** and **3r** were achieved in moderate yields.

Scheme 2. Substrate Scope with Respect to Aromatic amines



Reaction conditions: **1** (0.2 mmol), **2** (1.2 equiv, 0.24 mmol), 5 mol% $Pd(OAc)_2$, 10 mol% PPh_3, 1.0 equiv $Cu(OAc)_2$, 1.0 equiv Cs_2CO_3, 2 mL DMF, 120 °C, Air, 12 h.

Subsequently, we turned our attention toward the scope of 2-iodobiphenyl (Scheme 3). Firstly, we investigated the compatibility of various functional groups by using unsubstituted aniline as coupling reagent. 2-Iodobiphenyls having either the electron-withdrawing or the electron-donating groups could work smoothly in this reaction, affording the desired carbazoles **4a**-**4f** in 63%-90% yields. To our delight and surprise, 2'-iodo-[1,1'-biphenyl]-4-carbaldehyde was also amenable to Pd-catalyzed C-H bond activation, giving rise to the formation of **4g** in 88%, in which the formyl group was intact. We also investigated a range of functional

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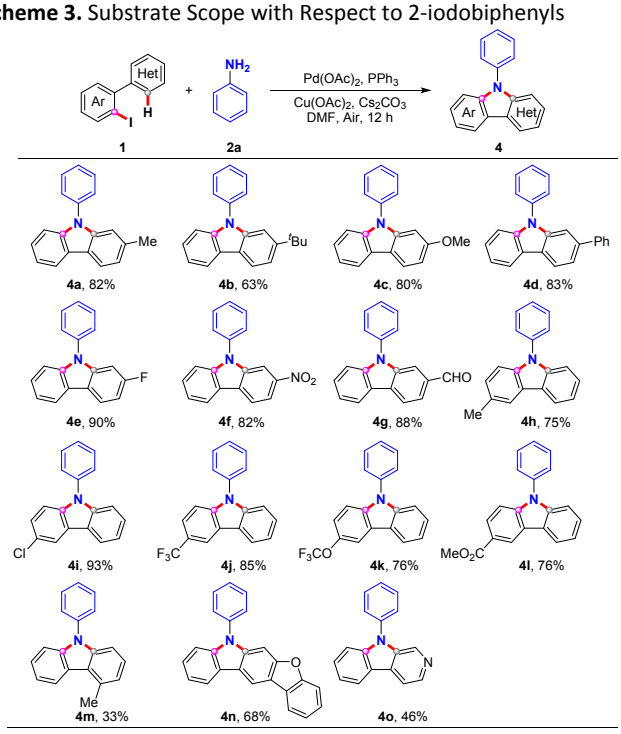
groups on the aromatic ring of iodobenzene. The functional groups, Such as methyl, fluorine, chlorine, trifluoromethyl, trifluoromethoxy and ester groups were-well compatible in this transformation, providing the corresponding N-aryl carbazoles **4h**-**4n** in moderate to excellent yields. The fused 3-iodo-2-phenyldibenzo[b,d]furan and heterocyclic 4-(2-iodophenyl)pyridine were proved to be suitable substrates in this reaction, rendering the desired products **4o** and **4p** in 68% and 46% yields, respectively.

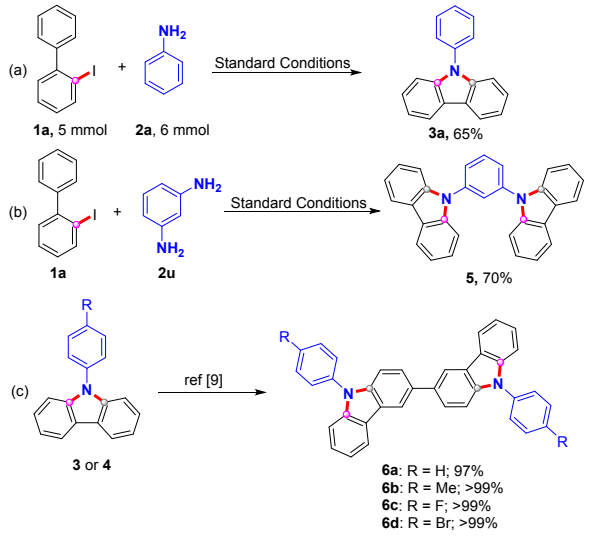
Scheme 3. Substrate Scope with Respect to 2-iodobiphenyls



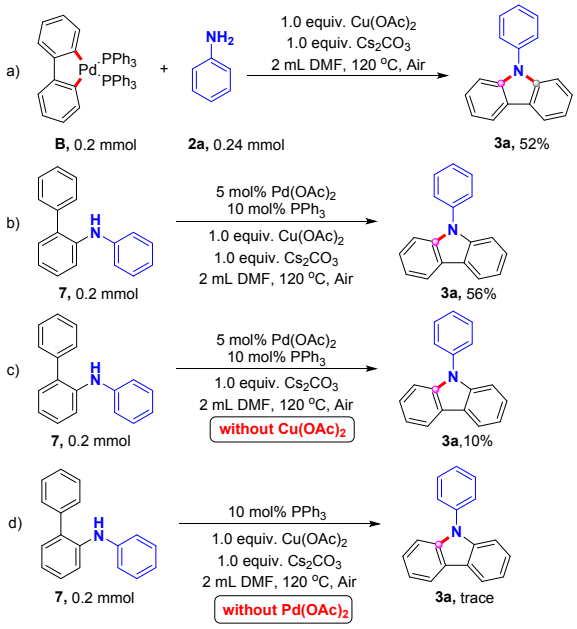
Reaction conditions: **1** (0.2 mmol), **2a** (1.2 equiv, 0.24 mmol), 5 mol% $Pd(OAc)_2$, 10 mol% PPh_3, 1.0 equiv $Cu(OAc)_2$, 1.0 equiv Cs_2CO_3, 2 mL DMF, 120 °C, Air, 12 h.

We also studied the scalability of this Pd-catalyzed C-H bond activation for the assembly of carbazoles. When the reaction is scaled up to 5 mmol, the yield of **3a** was readily obtained in 65% yield (Scheme 4a). Carbazoles have comprehensive applications in material chemistry. The utility of this protocol is showcased by its application to synthesize host molecules **mCP**.[2j] When metaphenylene diamine was subjected to this reaction, compound **5** was achieved in 70% yield via two folds C-H activation (Scheme 4b). The structure of **5** was definitely confirmed by X-ray crystallographic analysis. In addition, based on previous work, 9,9'-diphenyl-9H,9'H-3,3'-bicarbazoles could be readily gained in qualitative yields via oxidative dehydrogenative coupling (Scheme 4c).[9]

Scheme 4. Larger Synthesis and Synthetic Applications



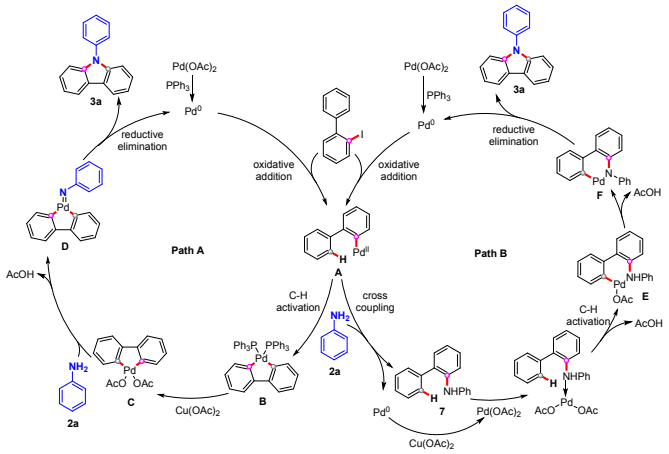
In order to further explore the mechanism of the reaction, we conducted several control experiments. When stoichiometric palladacycle **B**[10] was subjected to this reaction, the desired N-phenyl carbazole **3a** could be obtained in 52% yield (Scheme 5a), which indicated that the palladacycle **B** might be the intermediate. However, at this point, we couldn't absolutely eliminate the pathway to construct carbazole via C-N coupling followed by intramolecular C-H amination. To test this pathway, we prepared N-phenyl-[1,1'-biphenyl]-2-amine **7**.[11] When N-phenyl-[1,1'-biphenyl]-2-amine **7** was employed as starting material, the desired **3a** was also isolated in 56% yield (Scheme 5b). Control experiments manifested that oxidant and palladium acetate were all obligatory for transformation of compound **7** to carbazole **3a** (Scheme 5c and 5d).



Scheme 5. Mechanism studies

Based on the above control experiments and previous reports, we propose two possible mechanisms for this Pd-catalyzed C-H bond activation. As for the pathway of palladacycle (Path A in Scheme 6), firstly, oxidative addition of 2-iodobiphenyl with Pd(0) forms Pd(II) species **A**, which undergoes intramolecular C-H activation to afford palladacycle **B**. Immediately, **B** was oxidized to palladacycle **C** by $Cu(OAc)_2$. Then, the anilines coordinate with the palladacycle **C**, releasing two molecules of acetic acid to give the intermediate **D**. Finally, reductive elimination of intermediate **D** leads to the formation of the targeted product **3** and regenerates

the Pd(0) species to continue the next catalytic cycle. As for the pathway of C-N coupling followed by intramolecular C-H amination (Path B in Scheme 6), compound **7** was formed via cross-coupling reaction between **A** and aniline**.** Then, pre-association of the amino moiety of **7** to $Pd(OAc)_2$ facilitates the *ortho*-palladation process. resulting in the formation of the C-H activation intermidate **E** via releasing one molecule of acetic acid. Subsequently, with the assistance of base, species **F** is produced via loss of another molecule of acetic acid. Finally, reductive elimination of species **F** delivers the carbazole **3** and regenerates Pd(0) species to continue the next catalytic cycle.



Scheme 6. Proposed Reaction Mechanism

In summary, we have demonstrated a convenient and efficient Pd-catalyzed C–H activation for the synthesis of N-aryl carbazoles with easily accessed starting materials. The desired carbazoles were achieved in good yields with a wide range of substrate scope. The current protocol could also be applied to forge host molecules **mCP**. To this end, we propose two possible mechanisms for this Pd-catalyzed C–H activation/dual C–N bond formation. Further investigations of the reaction mechanism synthetic applications of this methods are still underway in our laboratory.

This research was financially supported the National Natural Science Foundation (21772046) and the Natural Science Foundation of Fujian Province (2016J01064) are gratefully acknowledged. We also thank Instrumental Analysis Center of Huaqiao University for analysis support. X. L. thanks for Subsidized Project for Cultivating Postgraduates' Innovative Ability in Scientific Research of Huaqiao University.

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