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ARTICLE TYPE

Palladium catalyzed dual C-H functionalization of indoles with cyclic diaryliodoniums, an approach to ring fused carbazole derivatives

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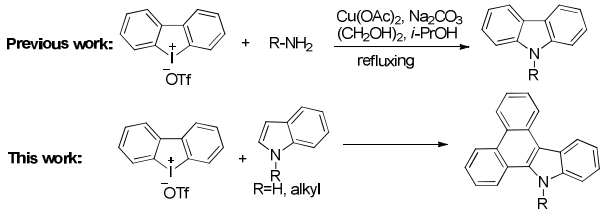
Palladium (Ⅱ)-catalyzed dual C-H functionalization of indoles with cyclic diaryliodoniums was successfully achieved, providing a concise method to synthesize dibenzocarbazoles. In one single operation, two C-C bonds and one ring were formed. The reaction was ligand free and tolerated air and moisture conditions.

Linear diaryliodoniums have been extensively investigated as arylating reagents.[1] In these arylation reactions, the formation of iodoarene Ar-I was usually ignored and the iodoarene was inevitably discarded as a waste (Scheme S1, Supporting Information). Compared to linear iodoniums, cyclic iodoniums are advantageous in terms of atom economy because the iodoarene remains as a part of the arylated product with cyclic iodoniums as arylating reagents. Moreover, the incorporated iodoarene could be employed as another potential arylating reagent, ready for further transformations.[2] However, the synthetic application of cyclic iodoniums is less developed although they have potential to set up cascade reactions atom and step economically.[3] As a part of our ongoing studies, we have conveniently synthesized a variety of cyclic diaryliodoniums employing Olofsson's method.[4] Our recent studies have demonstrated that cyclic iodoniums can be employed to construct carbazoles and methylienefluorenes, either by a dual amination,[5] or a multi-component cascade reaction.[2]

Carbazole derivatives have received dramatic attention for the reason that their structure core is omnipresent in natural products and biologically active compounds.[6-7] Due to their unique properties and potential pharmacological activities,[8] a number of methodologies to construct the carbazole rings have been reported. Traditional methods for synthesis of carbazole from benzene derivatives include Fischer–Borsche synthesis.[9] In addition, carbazoles can be synthesized from indole derivatives via different strategies, such as Diels-Alder reaction,[10] electro-cyclic reaction,[11] and cyclization of ketosulfoxide.[12] In our previous study, we have discovered that a range of diversified carbazoles can be obtained from amines and cyclic diaryliodoniums (Scheme 1).[5]

Recently, condensed heterocycles, particularly carbazole derivatives have been proved to be potential DNA intercalating drugs,[13] or CDK inhibitors.[14] Goggiamani has recently reported the synthesis of dibenzocarbazoles from 2-(2-bromoaryl)-3-arylindoles.[15] In their report, a heavily pre-functionalized indole as a starting material was not easy to obtain. As aforementioned, our previous work indicated that the carbazoles were able to be obtained from cyclic iodoniums with a number of anilines, alkyl amines, and aromatic sulphonamides. Thus it was of our hypothesis that cyclic diaryliodoniums might be exploited as the dual arylating reagents to construct dibenzocarbazoles from indoles via double C-H functionalizations. Herein, we report a concise method to access this special type of carbazoles, catalyzed by $Pd(OAc)_2$ via dual C-H activation/arylation of indoles (Scheme 1).



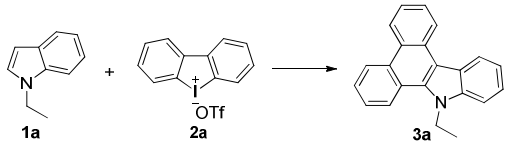
Scheme 1. The strategies to obtain carbazoles from cyclic diaryliodoniums.

Arylation of indole at C2 or C3 position was widely reported, resulting in various novel functionalized indole derivatives [16]. Sanford and co-workers reported that highly regioselective C2 arylation of indoles with linear diaryliodoniums was realized at room temperature.[17] With similar diaryliodoniums, Gaunt's group demonstrated that regioselective C2 or C3 arylation of indoles could be well controlled by varying *N*-positioned protective group, mediated by $Cu(OTf)_2$.[18] It was of our high interest to investigate whether both 2 and 3 arylations of indoles could be realized at same time. Considering cyclic diaryliodoniums could be employed as dual arylating reagents, we hypothesized that a first single arylation of indoles regardless of C2 or C3 position should be easily realized based on the findings of these two groups while the intra-molecular arylation could follow up under a certain conditions.

At the outset of our studies, the two reported systems, namely Sanford's Pd(II)/ligand/AcOH and Guant's $Cu(OTf)_2$/base/1,2-dichloroethane, were tried with *N*-ethyl indole **1a** and diphenyleneiodonium **2a** (Entry 1-2, Table 1). Surprisingly, both systems did not initiate the desired reactions at room temperature. The copper system tended to only generate a side-product, 2-iodobiphenyl while the temperature was increased to 80℃ (data not shown). To our delight, the Pd system provided 9H-

dibenzocarbazole **3a** at high temperature (Entry 3). Further study indicated that the addition of a ligand was not necessary (Entry 4). Furthermore, this transformation showed no sensitive to air and moisture (Entry 5). 1, 2-dichloroethane was found to replace acetic acid without affecting the reaction yield, wherein the reaction workup was easier (Entry 6). The yield was slightly improved to 56% while the temperature was further increased to 100 ℃ (Entry 7). In addition, four other common solvents were also screened for the reaction with 1, 2-dichloroethane still remaing the best (Entry 8-11). Three other palladium species were also investigated but gave lower yield (Entry 12-14). Further studies confirmed that the addition of sodium carbonate favoured the reaction after a base screening (Entry 15-18). It is noteworthy that no reaction happened in the absence of palladium species.

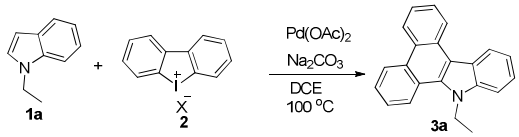
Table 1. Optimization of the reaction conditions [a]



Entry	Catalyst	Solvent	*T* [ºC]	Base	Yield [%]
1	$Cu(OTf)_2$	DCE	RT	Dtbpy	ND
2[b]	$Pd(OAc)_2$	AcOH	RT	—	ND
3[b]	$Pd(OAc)_2$	AcOH	80	—	48
4	$Pd(OAc)_2$	AcOH	80	—	50
5[c]	$Pd(OAc)_2$	AcOH	80	—	47
6	$Pd(OAc)_2$	DCE	80	—	52
7	$Pd(OAc)_2$	DCE	100	—	56
8	$Pd(OAc)_2$	TFE	100	—	47
9	$Pd(OAc)_2$	DMF	100	—	10
10	$Pd(OAc)_2$	DMSO	100	—	ND
11	$Pd(OAc)_2$	Toluene	100	—	ND
12	$PdCl_2$	DCE	100	—	21
13	$Pd(PPh_3)_2Cl_2$	DCE	100	—	13
14	$Pd(PPh_3)_4$	DCE	100	—	12
15	$Pd(OAc)_2$	DCE	100	Na_2CO_3	66
16	$Pd(OAc)_2$	DCE	100	$NaHCO_3$	49
17	$Pd(OAc)_2$	DCE	100	K_3PO_4	ND
18	$Pd(OAc)_2$	DCE	100	Et_3N	ND

[a] Reaction conditions: **1a** (1.0 equiv), **2a** (1.5 equiv), and catalyst (10 mol %), with or without base (2.0 equiv), under air, 17 h. [b] 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene (10 mol %) added. [c] Under argon. Notes: Dtbpy, 2, 6-*di*-tert-butylpyridine; DCE, 1,2-dichloroethane; TFE, 2,2,2-trifluoroethanol; ND, not detected.

Table 2. Effect of the anions of iodoniums [a]



Entry	X	Yield [%]
1	OTf	66
2	OTs	49
3	Cl	ND
4	OTFA	26

[a] Reaction conditions: **1a** (1 equiv), **2** (1.5equiv), $Pd(OAc)_2$ (10 mol%), Na_2CO_3 (2 equiv), 1,2-dichloroethane, 100 ℃, 17h.

Subsequently, the effect exerted by the anions of iodoniums 2 was also investigated (Table 2). The results showed that satisfied results were obtained while trifluoromethanesulfonate (OTf) or p-toluenesulfonate (OTs) was used as an anion (Entry 1-2). Diphenyleneiodonium trifluoroacetate (OTFA) gave low yield, and the chloride salt failed the reaction.

With the optimal reaction conditions in hand, a range of *N*-ethyl indoles with other different positioned substituents was firstly exploited for the transformation of diphenyleneiodonium **1a** to dibenzocarbazole (**3a-3h**, Figure 1). All the indoles with a 4 or 5 or 6 positioned substituent underwent smoothly dual arylations, of which one was intramolcular cyclization, leading to the expected dibenzocarbazoles. The indoles with electron-donating substituents afforded the carbazole derivatives in modest yields (**3a-3c**). Electron-withdrawing groups also delivered the condensed products, albeit with lower yield or requiring higher temperature (**3d-3h**). In our study, a variety of useful substituents including chloro, fluro, ether and ester groups was well tolerated (**3c-3h**), providing opportunities for further functionalization.

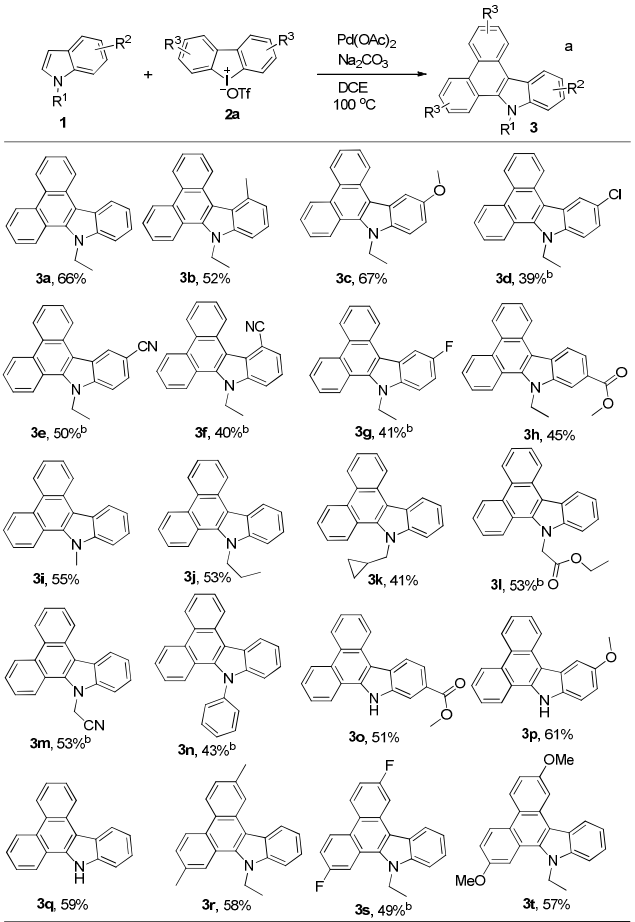


Figure 1. Scope of indoles and iodoniums. [a] Reaction conditions: **1** (1equiv), **2a** (1.5equiv), $Pd(OAc)_2$ (10mol%), Na_2CO_3 (2equiv), 1,2-dichloroethane, 100 ℃, 17h. [b] 130 ℃.

We next investigated the scope of *N*-substituted functional groups on indoles in this type of reaction (**3i-3n**). To our delight, a number of *N*-substituted alkyl groups including cyclopropane, ester, nitrile and phenyl were well compatible under the reaction conditions. In our cases, when a phenyl group replaced an alky group as the *N*-substituent of the indoles, the yield was slightly

decreased even at higher temperature (**3n**). The indoles with *N*-substituted electron-deficient groups were needed to increase the reaction temperature to 130 ℃ (**3l, 3m**). It is worth to mention that *N*-acetylindole did not provide an expected product (data not shown) although the compound was reported to be arylated with linear iodoniums.[16] To our more satisfaction, free indole without *N*-positioned protection could be employed directly and provided the corresponding dibenzocarbazoles efficiently, without affecting the yields (**3o-3q**).

The scope of diaryliodoniums was finally investigated for this transformation. To avoid the problem associated with the regioselectivity of the reaction with cyclic unsymmetrical iodonium salts, encountered in our previous study,[2] three symmetrical diaryliodonium salts **2** with fluoro, methyl, and methoxy substituted were designed and prepared. The expected dibenzocarbazoles (**3r-3t**) were successfully obtained at modest yields, demonstrating the reaction generality. The further work to solve regioselectivity with cyclic unsymmetrical idodoniums is undergoing and will be reported in a due course.

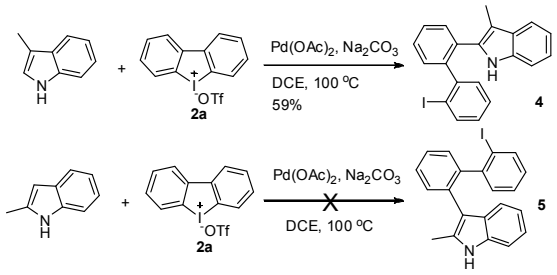
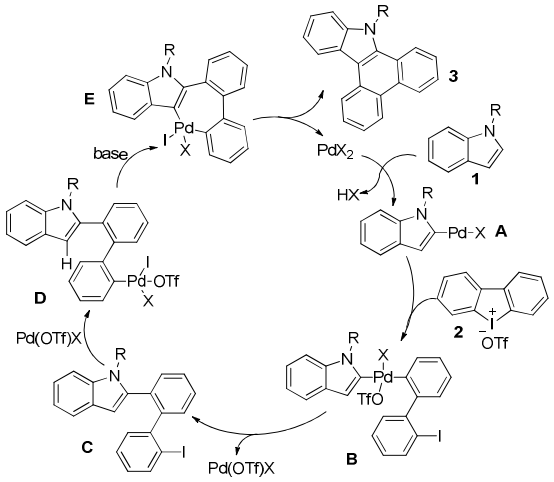


Figure 2. Arylation of 2 or 3 positioned methylindole with **2a**.

To explore the mechanism of the reaction, 2-methylindole and 3-methylindole were employed to study which position of the indoles would be firstly arylated by cyclic iodoniums (Figure 2). In our experiments, only 3-methylindole was found to be arylated in the C2 position to give **4** while the 2-methylindole failed the arylation. This finding implied that the palladation of indole occurred at C2 position initially. Base on our observation and Sanfords's report,[17] we proposed a mechanism (Scheme 2) in which a $Pd^{II/IV}$ catalytic cycle was involved. The reaction was initiated via C2 electrophilic palladation of indole with Pd (II) species. Then, oxidative addition of cyclic iodonium **2** to **A** would afford Pd (IV) intermediate **B** that consequently underwent reductive elimination, resulting in C2 arylated product **C**. With recycled Pd (II) catalyst, a second oxidative addition transformed **C** to Pd (IV) intermediate **D** that continued a palladium metallation of C3 position of indole with ease, driven by the formation of a seven-member intermediate **E**. A final reductive elimination led to the formation of dibenzocarbazoles **3**.



Scheme 2. The proposed mechanism

Conclusions

In summary, we have developed an efficient method to prepared a range of dibenzocarbazoles at modest yields from cyclic diaryliodoniums with *N*-substituted or free indoles. The reaction is atom and step economical, involving dual C-H activation/arylation of indoles. Two C-C bonds and one ring were formed in one single operation. In our method, $Pd(OAc)_2$ was employed as catalyst and no additional expensive ligands were needed. The reaction was not sensitive to air and convenient to handle. A number of functional groups were tolerated, providing opportunities for further transformation. Due to their drug-like properties, a biological evaluation and screening of these synthetic dibenzocarbazoles are under way.

Notes and references

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