Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: L. Wu, G. Deng and Y. Liang , *Org. Biomol. Chem.*, 2017, DOI: 10.1039/C7OB01638G.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/obc

Dynamic Article Links ▶
View Article Online
DOI: 10.1039/C7OB01638G

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

COMMUNICATION

Synthesis of Dibenzo[*a*,*c*]carbazoles from 2-(2-Halophenyl)-indoles and Iodobenzenes via Palladium-Catalyzed Dual C–H Functionalization

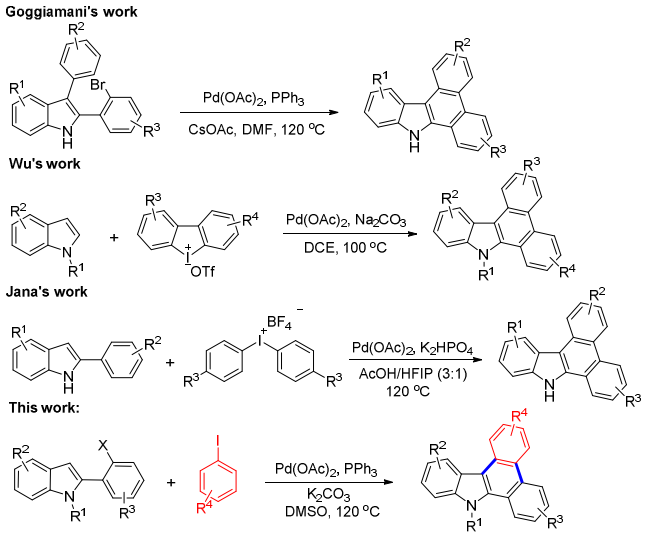
Lijun Wu, Guobo Deng* and Yun Liang*

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

An efficient palladium-catalyzed strategy for the synthesis of dibenzo[*a*,*c*]carbazole derivatives has been developed. In the presence of $Pd(OAc)_2$, 2-(2-halophenyl)-indoles and iodobenzenes proceeded smoothly to obtain the corresponding dibenzo[*a*,*c*]carbazoles in moderate to good yields. This methodology constructs two new C-C bonds via a palladium-catalyzed dual C-H functionalization.

Carbazoles are an important class of heterocycle due to their widespread application in many fields.[1] Among these, fused carbazoles have received much attention, since fused carbazoles moieties are frequently found in natural products and biologically active compounds. such as CDK inhibitors,[2] antitumor,[3] antiestrogenic properties[4] and potential DNA intercalating drugs.[5] Therefore, great efforts have been made to develop methods for the effective synthesis of this useful structural skeleton in recent years.[6] Traditional strategies for the synthesis of fused carbazoles are as follows: (a) transition-metel-catalyzed intermolecular cyclization reactions of indole derivatives,[7] (b) tandem cyclization of diynes,[8] (c) intramolecular cyclization of prefunctionalized indoles.[9] These methods are useful for the synthesis of some fused carbazoles. Regrettably, there are few reports on the synthesis of dibenzo[*a*,*c*]carbazoles.

Recently, methods based on palladium catalysis have gained great attention as they offer some strategies for the synthesis of dibenzo[*a*,*c*]carbazoles (Scheme 1). For instance, Goggiamani has recently reported the synthesis of dibenzo[*a*,*c*]carbazoles from 2-(2-bromoaryl)-3-arylidole.[10] Wu and co-workers have reported a new route to synthesise dibenzo[*a*,*c*]carbazoles through dual C-H functionalization of indoles with cyclic diaryliodoniums.[11] More recently, Jana and co-workers have also demonstrated that 1,4-Pd migration can be a powerful tool for the synthesis of dibenzo[*a*,*c*]carbazoles.[12] Those methods are very effective for the construction of some dibenzo[*a*,*c*]carbazoles, however, the development of novel and expeditious methods of synthesizing dibenzo[*a*,*c*]carbazoles are still highly desirable and remain a challenge. Our previous work indicated that benzo[*a*]carbazoles were able to be obtained from vinylindoles with arynes.[13] As part of our ongoing studies on the development of fused carbazoles chemistry, we continue to explore the feasibility of synthesizing dibenzo[*a*,*c*]carbazoles. Herein, we report an efficient and mild palladium-catalyzed cross-coupling tandem reaction of 2-(2-halophenyl)-indoles with iodobenzenes, affording the corresponding dibenzo[*a*,*c*]carbazole derivatives in moderate to good yields.



Scheme 1 Synthesis Approaches to Dibenzo[a,c]carbazoles

Our investigation began with the reaction of 2-(2-iodophenyl)-1-methyl-1*H*-indole **1a** with iodobenzene **2a** to determine the optimal reaction conditions, and the results were summarized in Table 1. In the presence of $Pd(OAc)_2$ as the catalyst and NaOAc as base, substrate **1a** and **2a** were converted into the desired product 9-methyl-9*H*-dibenzo[*a*,*c*]carbazole **3aa** in 22% yield. Inspired by this result, a series of base (including NaOAc, CsF, K_2CO_3, Cs_2CO_3, Na_2CO_3) were examined (entries 1-5). K_2CO_3 gave the best results, and the desired product of dibenzo[*a*,*c*]carbazole was obtained in 81% yield. Subsequently, a number of other Pd catalysts, such as $PdCl_2$, $Pd_2(dba)_3$ and $Pd(PPh_3)_4$ were tested (entries 3 and 6-8). The results indicated

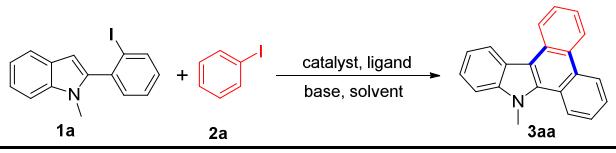
Key Laboratory of the Assembly and Application of Organic Functional Molecules, Hunan Normal University, Changsha, Hunan 410081, China. Fax: +86(0731)88872533; E-mail: gbdeng@hunnu.edu.cn. and yliang@hunnu.edu.cn.

† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

View Article Online
DOI: 10.1039/C7OB01638G

that $Pd(OAc)_2$ was the best one for this cascade reaction. Notably, control experiments showed that no formation of the desired product **3aa** occurred in the absence of a Pd catalysts (entry 9). To improve the reaction performance, the effects of ligands (including P(*o*-tol)$_3$, PPh_3, dppp, dppf, *X*-phos) were also examined (entries 10-14). PPh_3 achieved the best result, and the desired product **3aa** was obtained in 86% yield (entry 11). Solvents such as DMF, toluene and DMSO were also evaluated (entries 3 and 15-17), and a 92% yield of **3aa** was afforded when DMSO was used (entry 17). Finally, the temperature screening indicated that 120 °C was the most suitable temperature for this protocol (entries 18-19). Thus, the optimized reaction conditions were as follows: **1a** (0.3 mmol), **2a** (0.36 mmol), $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), K_2CO_3 (0.9 mmol), DMSO (2 mL), under an air atmosphere in sealed schlenk tube at 120 °C for 12 hours.

Table 1 Optimization of reaction conditions[a]



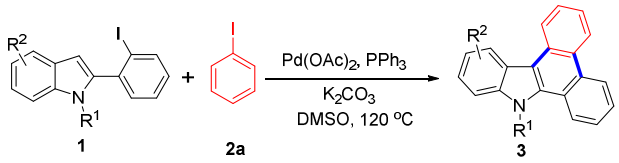
1a 2a 3aa

Entry	Catalyst	Ligand	Base	Solvent	yield/**3aa**[b]
1	$Pd(OAc)_2$		NaOAc	DMA	22
2	$Pd(OAc)_2$		CsF	DMA	72
3	$Pd(OAc)_2$		K_2CO_3	DMA	81
4	$Pd(OAc)_2$		$CsCO_3$	DMA	57
5	$Pd(OAc)_2$		$NaCO_3$	DMA	63
6	$PdCl_2$		K_2CO_3	DMA	71
7	$Pd_2(dba)_3$		K_2CO_3	DMA	65
8	$Pd(Ph_3)_4$		K_2CO_3	DMA	67
9			K_2CO_3	DMA	0
10	$Pd(OAc)_2$	P(o-tol)$_3$	K_2CO_3	DMA	84
11	$Pd(OAc)_2$	PPh_3	K_2CO_3	DMA	86
12	$Pd(OAc)_2$	dppp	K_2CO_3	DMA	83
13	$Pd(OAc)_2$	dppf	K_2CO_3	DMA	46
14	$Pd(OAc)_2$	X-phos	K_2CO_3	DMA	78
15	$Pd(OAc)_2$	PPh_3	K_2CO_3	DMF	83
16	$Pd(OAc)_2$	PPh_3	K_2CO_3	Tol	Trace
17	$Pd(OAc)_2$	PPh_3	K_2CO_3	DMSO	92
18[c]	$Pd(OAc)_2$	PPh_3	K_2CO_3	DMSO	93
19[d]	$Pd(OAc)_2$	PPh_3	K_2CO_3	DMSO	42

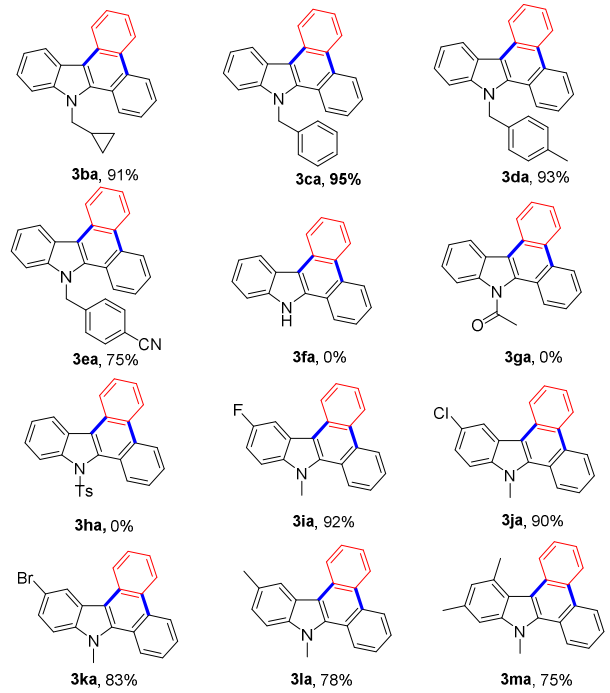
[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.36 mmol), Pd salt (5 mol %), ligand (10 mol %), base (0.9 mmol), solvent (2 mL), under air atmosphere in sealed Schlenk tube, at 140 °C for 12 h. [b] Isolated yields. [c]120 °C. [d] 80 °C.

With the optimized conditions in hand, a series of substituted 2-(2-iodophenyl)-indoles were examined, and the results are summarized in Table 2. First, the substituents on the nitrogen atom were screened. The results showed that a range of electron-donating substituents including cyclopropylmethyl, benzyl or substituted benzyl substrates could be smoothly transformed into the corresponding desired products (**3ba**–**3ea**) in excellent yields under the optimized conditions. For example, cyclopropylmethyl substituted substrate **1b** regioselectively formed 9-(cyclopropylmethyl)-9*H*-dibenzo[*a*,*c*]carbazole **3ba** in 91% yield. Substrate **1d** with an electron-donating methyl group and substrate **1e** with an electron-withdrawing CN group both showed high reactivity, giving **3da** and **3ea** in 93% and 75% yield respectively. It is regrettable that group free and electron-withdrawing substituted substrates are unfavourable to this tandem reaction. Subsequently, our study focused on the substitution effect on the aryl ring of indole **1** (products **3ia**-**3ma**). It is noteworthy that a halo group, such as Cl and Br, on the aromatic ring is amenable to the optimal conditions, thereby providing an opportunity for additional modifications at the halo-genated position (**3ja** and **3ka**).Substrate **1m** with methyl at the 4 and 6 positions were also viable for constructing **3ma** in 75% yield.

Table 2 Variation of 2-(2-iodophenyl)-indoles [a,b]



1 2a 3



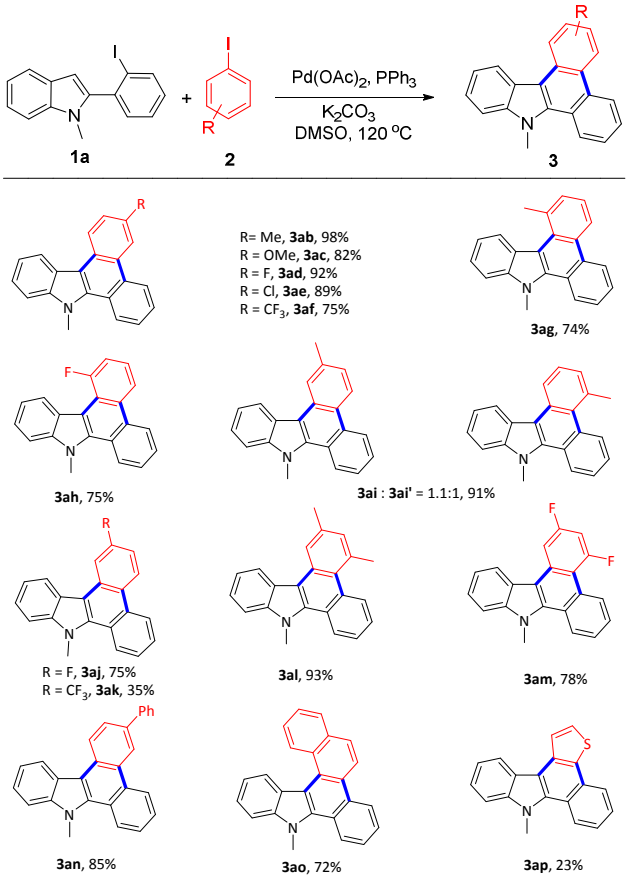
[a] Reaction conditions: **1** (0.3 mmol), **2a** (0.36 mmol), $Pd(OAc)_2$ (5 mol %), K_2CO_3 (0.9 mmol), DMSO (2 mL), 120 °C and 12 h in air atmosphere. [b] Isolated yields.

We next explored the possibility of employing substituted iodobenzenes as substrates to react with **1a**, and the results are summarized in Table 3. The corresponding dibenzo[*a*,*c*]carbazoles were obtained in good to perfect yields.

View Article Online
DOI: 10.1039/C7OB01638G

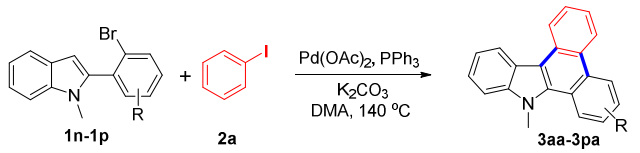
Initially, the *para*-substituent of the aryl moiety was screened. To our delight, substrates **2b**-**2f**, bearing electron-donating or electron-deficient groups on the aryl ring, were compatible under the standard conditions. Substrate **2b** with a methyl group, for instance, underwent the reaction with 2-(2-iodophenyl)-1-methyl-1*H*-indole **1a**, affording **3ab** in 98% yield. Good yield was still achieved from substrate **2f** with a CF_3 group. As expected, a series of the ortho-substituted (R = Me, F) or meta-substituted (R = Me, F, CF_3) iodobenzenes furnished the transformation producing the desired dibenzo[*a*,*c*]carbazoles in moderate to high yields. However, two regioisomers generated from substrate **2i**, in a 1.1:1 ratio. The results showed that the electron-donating groups substrates displayed higher reactivity than the electron-withdrawing groups substrates. Furthermore, Substrates **2l** and **2m** with two substituents at the 3 and 5 positions were also viable for constructing **3al** and **3am** in 93% and 78% yield respectively. Moreover, diphenyl and naphthyl iodides could be successfully converted into poly-cyclicring products (**3an**-**3ao**) in good yields. Thiophenyl iodides were tolerated under the reaction conditions, although the reaction yield was relatively low.

Table 3 Synthesis of 2-aminobenzothiazolones from substituted *o*-iodophenyl isocyanides[a]



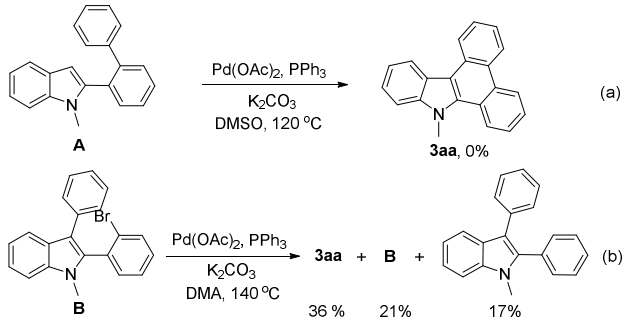
[a] Reaction conditions: **1a** (0.3 mmol), **2** (0.36 mmol), $Pd(OAc)_2$ (5 mol %), K_2CO_3 (0.9 mmol), DMSO (2 mL), 120 °C and 12 h in air atmosphere. [b] Isolated yields.

To extend the substrate scope of this cyclization methodology, the different substituted 2-(2-bromophenyl)-1-methyl-1*H*-indoles and iodobenzene were screened (Scheme 2). In the presence of $Pd(OAc)_2$ as the catalyst and K_2CO_3 as base, 2-(2-bromophenyl)-1-methyl-1*H*-indole **1n** and **2a** were converted into the desired product 9-methyl-9*H*-dibenzo[*a*,*c*]carbazole **3aa** in 70% yield. Compared with 2-(2-iodophenyl)-1-methyl-1*H*-indoles, the activities of 2-(2-bromophenyl)-1-methyl-1*H*-indoles were slightly lower in terms of yield. The *m*-OMe-substituted and *m*-Cl-substituted substrates **1o** and **1p** formed the corresponding dibenzo[*a*,*c*]-carbazoles **3na** and **3oa** in 51% and 52% yield respectively.



Scheme 2 Variation of 2-(2-bromophenyl)-indoles

To shed light on the possible mechanism of the reaction, several control experiments were carried out, as shown in Scheme 3. First, using 2-([1,1'-biphenyl]-2-yl)-1-methyl-1*H*-indole **A** was tested under standard condition and it can't be converted into the desired product 9-methyl-9*H*-dibenzo[*a*,*c*]carbazole **3aa**. Notably, 2-(2-bromophenyl)-1-methyl-3-phenyl-1*H*-indole **B** were tested under standard condition (Scheme 2). To our delight, **B** was converted into the desired product 9-methyl-9*H*-dibenzo[*a*,*c*]carbazole **3aa** in 36% yield. The results implied that **B** was the intermediate among this cross-coupling tandem reaction.

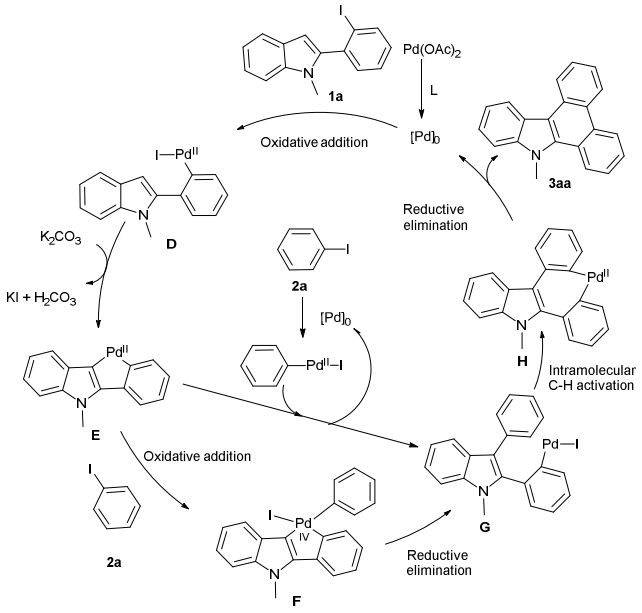


Scheme 3 Control experiment

Based on the above observations and previous mechanistic studies,[12,15,16] a plausible mechanism is proposed in scheme 4. First, the active Pd (0) is presumably generated in situ from the palladium acetate during the reaction and formed Pd(Ⅱ) complex **D** by oxidative addition of **1a**.[12,16] Then, intermediate **E** is obtained by the electrophilic cyclization reaction of intermediate **D**.[15a,16] Subsequently, the five membered carbo-palladacyle **E** undergoes a second oxidative addition with iodobenzene to form intermediate **F**.[15b,c,d] Selective reductive elimination of the intermediate **F** would afford the intermediate

View Article Online
DOI: 10.1039/C7OB01638G

G. Another way to get intermediate **G** may be transmetalation-type exchange of aryl ligands with the phenylpalladium(Ⅱ) species. Finally, intramolecular C-H activation of **G** and reductive elimination of **H** afford the desired product **3aa**.[12,15b,c,d,16]



Scheme 4 Possible Mechanism

In summary, we have demonstrated a novel palladium-catalyzed cross-coupling tandem reaction of *N*-substituted-(2-halophenyl)indoles and iodobenzenes. This methodology allows formation of two new C-C bonds via a palladium-catalyzed dual C-H functionalization. Furthermore, this method provides an efficient approach to synthesize dibenzo[*a*,*c*]carbazoles, which are ubiquitous structural units in a number of biologically active compounds.

Acknowledgment

This work was supported by the Natural Science Foundation of China (21572051，21602057), Ministry of Education of the People's Republic of China (213027A), Education Department of Hunan Province (15A109) for financial support.

Notes and references

1 (a) W. Maneerat, T. Ritthiwigrom, S. Cheenpracha, T. Promgool, K. Yossathera, S. Deachathai, W. Phakhodee and S. Laphookhieo, *J. Nat. Prod.,* 2012, **75**, 741. (b) A. W. Schmidt, K. R. Reddy and H. J. Knölker, *Chem. Rev.*, 2012, **112**, 3193. (c) S. H. Kim, I. Cho, M. K. Sim, S. Park and S. Y. Park, *J. Mater. Chem.,* 2011, **21**, 9139. (d) C. M. Amb, A. L. Dyer and J. R. Reynolds, *Chem. Mater.,* 2011, **23**, 397. (e) A. R. Howard-Jones and C. T. Walsh, *J. Am. Chem. Soc.*, 2009, **128**, 12289. (f) A. C. Grimsdale, K. Leok Chan, R. E. Martin, P. G. Jokisz and A. B. Holmes, *Chem. Rev.,* 2009, **109**, 897. (g) J. Cao, T. Kopajtic, J. L. Katz and A. H. Newman, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 5238. (h) S. Routier, J. Y. Mérour, N. Dias, A. Lansiaux, C. Bailly, O. Lozach and L. Meijer, *J. Med. Chem.*, 2006, **49**, 789. (i) D. E. Gingrich, S. X. Yang, G. W. Gessner, T. S. Angeles, R. L and Hudkins, *J. Med. Chem.*, 2005, **48**, 3776. (j) K. Brunner, A. van Dijken, H. Börner, J. J. Bastiaansen, N. M. Kiggen and B. M. Langeveld, *J. Am. Chem. Soc.*, 2004, **126**, 6035. (k) S. Wakim, J. Bouchard, N. Blouin, A. Michaud and M. Leclerc, *Org. Lett.*, 2004, **6**, 3413. (l) H. E. Katz, Z. Bao and S. L. Gilat, *Acc. Chem. Res.,* 2001, **34**, 359.

2 T. A. Engler, K. Furness, S. Malhotra, C. Sanchez-Martinez, C. Shih, W. Xie, G. X. Zhu, X. Zhou, S. Conner, M. M. Faul, K. A. Sullivan, S. P. Kolis, H. B. Broks, B. Patel, R. M. Schultz, T. B. Dehahn, K. Kirmani, C. D. Spencer, S. A. Watkins, E. l. Considine, J. A. Dempsey, C. A. Ogg, N. B. Stamm, B. D. Anderson, R. M. Campbell, V. Vasudevan and M. L. Lytle, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 2261.

3 A. Segall, H. Pappa, R. Casaubon, G. Martin, R. Bergoc and M. T. Pizzorno, *Eur. J. Med. Chem.*, 1995, **30**, 165.

4 E. Von Angerer and J. Prekajac, *J. Med. Chem.*, 1986, **29**, 380.

5 E. Lescot, G. Muzard, J. Markovits, J. Belleney, B. P. Roques and J. B. Le Pecq, *J. Med. Chem.*, 1986, **29**, 1731.

6 (a) Y. Wu, P. Sun, K. Zhang, T. Yang, H. Yao and A. Lin, *J. Org. Chem.*, 2016, **81**, 2166. (b) F. Sha, Y. Tao, C.-Y. Tang, F. Zhang and X.-Y. Wu, *J. Org. Chem.*, 2015, **80**, 8122. (c) Y. Su, H. Zhou, J. Chen, J. Xu, X. Wu, A. Lin and H. Yao, *Org. Lett.*, 2014, **16**, 4884. (d) S. Protti, A. Palmieri, M. Petrini, M. Fagnoni, R. Ballini and A. Albini, *Adv. Synth. Catal.*, 2013, **355**, 643. (e) R. Xie, Y. Ling and H. Fu, *Chem. Commun.*, 2012, **48**, 12210. (f) J. Zhou, W. Yang, B. Wang, H. Ren, *Angew. Chem. Int. Ed.*, 2012, **51**, 12293. (g) X.-F. Xia, N. Wang, L.-L. Zhang, X. R. Song, X.-Y. Liu, Y.-M. Liang, *J. Org. Chem.*, 2012, **77**, 9163. (h) F. Xiao, Y. Liao, M. Wu and G.-J. Deng, *Green Chem.*, 2012, **14**, 3277. (i) C.-C. Chen, S.-C. Yang and M.-J. Wu, *J. Org. Chem.*, 2011, **76**, 10269. (j) K. Hirano, Y. Inaba, K. Takasu, S. Oishi, Y. Takemoto, N. Fujii and H. Ohno, *J. Org. Chem.*, 2011, **76**, 9068. (k) N. Della Ca, G. Sassi and M. Catellani, *Adv. Synth. Catal.*, 2008, **350**, 2179. (l) T. Tsuchimoto, H. Matsubayashi, M. Kaneko, Y. Nagase, T. Miyamura and E. Shirakawa, *J. Am. Chem. Soc.*, 2008, **130**, 15823. (m) X.-X. Li, W.-Z. Song and W.-P. Tang, *J. Am. Chem. Soc.*, 2013, **135**, 16797. (n) W.-Z. Song, X.-X. Song, X.-X. Li, K. Yang, X.-L. Zhao, D. A. Glazier, B.-M. Xi and W.-P. Tang, *J. Org. Chem.*, 2016, **81**, 2930.

7 (a) T. Nanjo, S.Yamamoto, C. Tsukano and Y. Takemoto, *Org. Lett.*, 2013, **15**, 3754. (b) X.-F. Xia, N. Wang, L.-L. Zhang, X.-R. Song, X.-Y. Liu and Y.-M. Liang, *J. Org. Chem.*, 2012, **77**, 9163. (c) R. Xie, Y. Ling and H. Fu, *Chem. Commun.*, 2012, **48**, 12210. (d) J. García-Fortanet, F. Kessler and S. L. Buchwald, *J. Am. Chem. Soc.*, 2009, **131**, 6676. (e) X. Cai and V. Snieckus, *Org. Lett.*, 2004, **6**, 2293.

8 (a) C.-C. Chen, S.-C. Yang and M.-J. Wu, *J. Org. Chem.*, 2011, ***76***, 10269. (b) C.-C. Chen, L.-Y. Chin, S.-C. Yang and M.-J. Wu, *Org. Lett.*, 2012, **14**, 5652.

9 J. Yang, Q. Zhang, W. Zhang and W. Yu, *RSC Adv.*, 2014, **4**, 13704.

10 S. Cacchi, G. Fabrizi, A. Goggiamani and A. Iazzetti, *Org. Biomol. Chem.,* 2012, **10**, 9142.

11 Y. Wu, X. Peng, B. Luo, F. Wu, B. Liu, F. Song, P. Huang and S.-J. Wen, *Org. Biomol. Chem.,* 2014, **12**, 9777.

12 S. K. Bhunia, A. Polley, R. Natarajan and R. Jana, *Chem. Eur. J.*, 2015, **21**, 16786.

13 L. J. Wu, H. Huang, P. Dang, Y. Liang and S. F. Pi, *RSC Adv.,* 2015, **5**, 64354.

14 (a) Z. Gao, Z. Wang, T. Shan, Y. Liu, F. Shen, Y. Pan and Y. Ma, *Org. Electron.*, 2014, **11**, 2667. (b) N. Yoshikai and Y. Wei, *Asian J. Org. Chem.*, 2013, **2**, 466. (c) A. W. Schmidt, K. R. Reddy and H. J. Knölker, *Chem. Rev.*, 2012, **112**, 3193. (d) S. Routier, P. Peixoto, J. Y. Mérour, G. Coudert, N. Dias, C. Bailly, D. H. Caignard, *J. Med. Chem.*, 2005, **48**, 1401.

15 (a) B. S. Lane, M. A. Brown and D. Sames, *J. Am. Chem. Soc.*, 2005, **127**, 8050. (b) G. Maestri, E. Motti, N. Della Ca', M. Malacria, E. Derat and M. Catellani, *J. Am. Chem. Soc.,* 2011, **133**, 8574. (c) R. Ferraccioli, D. Carenzi, O. Rombol`a and M. Catellani, *Org. Lett.*, 2004, **6**, 4759. (d) E. Motti, N. Della C`a, D. Xu, A. Piersimoni, E. Bedogni, Z. M. Zhou and M. Catellani, *Org. Lett.*, 2012, **14**, 5792.

16 A. Kumar, S. S. Shinde, D. K. Tiwari, B. Sridhar and P. R. Likhar, *RSC Adv.,* 2016, **6**, 43638.

View Article Online
DOI: 10.1039/C7OB01638G

Synthesis of Dibenzo[*a*,*c*]carbazoles from 2-(2-Halophenyl)-indoles and Iodobenzenes via Palladium-Catalyzed Dual C–H Functionalization

Lijun Wu, Guobo Deng* and Yun Liang*

We report an efficient approach to synthesize dibenzo[*a*,*c*]carbazoles via Palladium-Catalyzed Cross-Coupling Tandem Reaction.