Organic & Biomolecular Chemistry

Accepted Manuscript

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View Article Online
DOI: 10.1039/C8OB01386A

Journal Name

COMMUNICATION

Pd-Catalyzed cascade cyclization of *o*-alkynylanilines via C-H/C-N bond cleavage leading to dibenzo[*a*,*c*]carbazoles

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

DOI: 10.1039/x0xx00000x

www.rsc.org/

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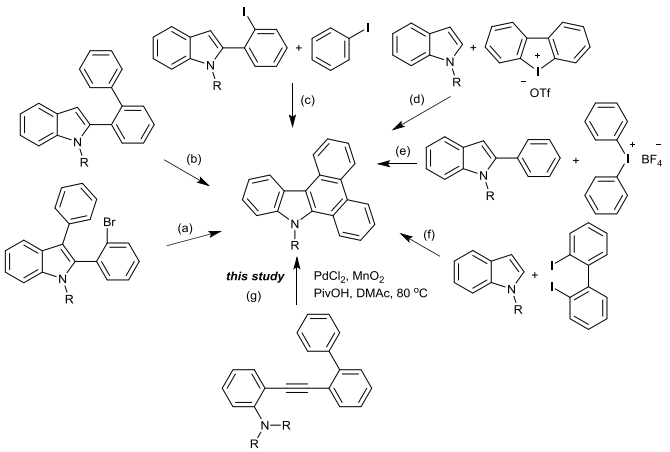
A new and efficient Pd-catalyzed cascade cyclization of biaryl-tethered *o*-alkynylanilines has been reported for the formation of the dibenzo[*a*,*c*]carbazole derivatives. The use of the alkyl-substituted tertialy anilines together with the combination of the $PdCl_2$ catalyst with the MnO_2 oxidant and PivOH are vital for giving rise to the 5-*endo* cyclization, C-N bond cleavage, C-H bond activation in a cascade manner to produce the corresponding prodcuts with structural diversity.

Introduction

The structurally and electronically intriguing features of carbazole and its derivatives make them particularly attractive in both pharmaceuticals and functional materials.[1] The carbazole derivatives are of great interests in pharmacological activities, such as antibiotic and antifungal activities,[2,3] DNA intercalating drugs,[4] CDK inhibitory properties.[5] Moreover, the carbazoles derivatives have been proved to be a promising electron donating units for organic optoelectronic materials in organic photovoltaics and organic light-emitting diodes.[6] Among them, the fused cabazole derivatives of dibenzo[*a*,*c*]carbazoles (DBCs) are expected to exhibit potential biological activities and distinct optoelectronic properties due to the carbazole moiety and the extended π-system. However, in comparison with a number of the carbazole synthetic methods,[1] the synthetic methodologies for constructing DBCs are limited. So far, the reported synthetic methods of DBCs are mainly focused on the Pd-catalyzed cyclization of prefunctionalized indoles. For example, intramolecular C-H/C-Br coupling of 2-(2-bromoaryl)-3-arylindoles[7] and C-H/C-H coupling of 2-(biphenyl-2-yl)-1*H*-indole,[8] and tandem cross-coupling reaction of 2-(2-halophenyl)-indoles with iodobenzenes[9] have been reported as major synthetic methods (Scheme 1a-c). In addition, the Pd-catalyzed dual or triple C-H functionalization of indoles with cyclic and acyclic diaryliodiniums, and annulative π-extension reaction of indole with 2,2'-diiodobiphenyl have been developed independently by the Wu, Jana, and Itami groups as a new synthetic strategy of DBCs (Scheme 1d-f).[10-12] A general and facile synthetic method other than starting from prefunctionalized indoles towards structurally diverse DBCs is still highly desirable.



Scheme 1 Reported Pd-catalyzed synthetic methods of dibenzo[*a*,*c*]carbazoles from indoles and our method from *o*-alkynylanilines. (a) Intramolecular C-H/C-Br coupling: $Pd(OAc)_2/PPh_3$, CsOAc, DMF, 120 °C. (b) Intramolecular C-H/C-H coupling: $Pd(OPiv)_2$, $Cu(OPiv)_2$, DMF, 150 °C, (c) Tandem reaction with iodobenzene; $Pd(OAc)_2/PPh_3$, K_2CO_3, DMSO, 120 °C. (d) Dual C-H functionalization with cyclic diaryliodoniums: $Pd(OAc)_2$, Na_2CO_3, DCE, 100 °C. (e) Triple C-H functionalization with diaryliodoniums: $Pd(OAc)_2$, K_2HPO_4, AcOH, HFIP, 110 °C. (f) Annulative π-extension reaction with 2,2'-diiodobiphenyl: $Pd(MeCN)_4(BF_4)_2$ (5 mol%), AgOPiv, TfOH, $(CH_2Cl)_2$, 50 °C. (g) This study: intramolecular cascade cyclization of biaryl-tethered *o*-alkynylanilines.

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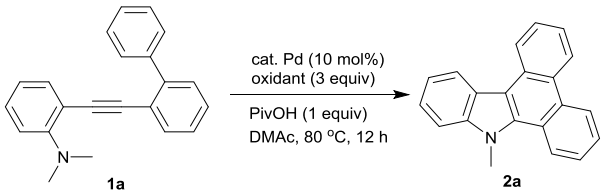
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

The Pd-catalyzed heteroannulation of *o*-alkynylanilines has been proved to be a powerful and attractive synthetic methodology for the construction of a variety of functional indoles and fused indole derivatives.[13] In particular, the tandem cyclization of *o*-alkynylanilines bearing a *N*,*N*-dialky moiety under Pd-catalyzed oxidative conditions has been emerged to be promising synthetic strategy for constructing various functional indoles and indole-fused polyheterocycles.[14] On the other hand, we recently demonstrated that bis-biarylalkynes could undergo a Pd(II)-catalyzed dual C-H activation for constructing 9,9'-bifluorenylidenes under the $PdCl_2/MnO_2$/PivOH oxidation conditions via the formation of a palladacycle species.[15a] In light of the pioneering indole synthetic methods[14] and our recent interests in the Pd-catalyzed C-H functionalization for constructing highly fused π-conjugated polycycles,[15] we reasoned that if a biary-tethered *o*-alkynylaniline having a suitable *N*,*N*-dialky group is employed under the Pd(II)-catalyzed oxidative conditions, the DBC scaffold could be formed through an intramolecular cascade cyclization involving 5-*endo* cyclization, *N*-dealkylation, and C-H bond activation. Herein, we report a new Pd-catalyzed cascade cyclization of the biaryl-tethered *o*-alkynylanilines towards construction of structurally intriguing DBCs under $PdCl_2/MnO_2$/PivOH oxidative systems. To the best of our knowledge, this is the first DBC synthetic method from the *o*-alkynylaniline substrates (Scheme 1f).[16]

Table 1 Optimization of reaction conditions[a]



Entry	Cat. Pd	Oxidant	**2a** (%)[b]	**1a** (%)[b]
1	$PdCl_2$	MnO_2	95 (93)	0
2	$Pd(PPh_3)_2Cl_2$	MnO_2	90	0
3	$Pd(OAc)_2$	MnO_2	94	0
4	$Pd(OPiv)_2$	MnO_2	42	56
5	$Pd(CH_3CN)_4(BF_4)_2$	MnO_2	68	23
6	$Pd_2(dba)_3$	MnO_2	52	41
7[c]	$PdCl_2$	MnO_2	49	28
8	$PdCl_2$	_	24	68
9	$PdCl_2$	$CuCl_2$	5	10
10	$PdCl_2$	$Cu(OAc)_2$	78	0
11	$PdCl_2$	AgOAc	76	24
12	$PdCl_2$	*o*-chloranil	0	0
13	$PdCl_2$	O_2 (1 atm)	70	6

[a] Reaction conditions: **1a** (0.3 mmol), Pd catalyst (10 mol%), oxidant (3 equiv), PivOH (1 equiv) in DMAc (1.5 mL) at 80 °C for 12 h. [b] ^{1}H NMR yield determined using CH_2Br_2 as an internal standard. Isolated yield is in parenthesis. [c] Without PivOH.

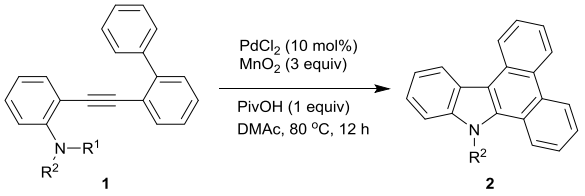
Results and discussion

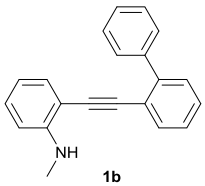
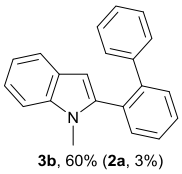
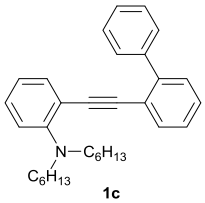
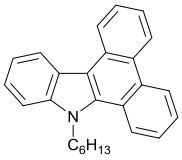
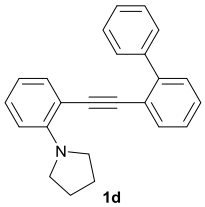
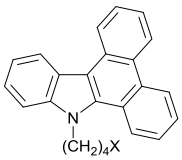
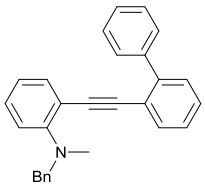
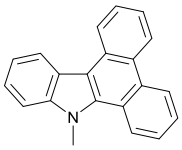
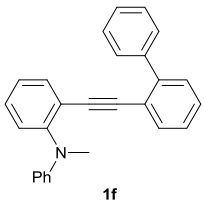
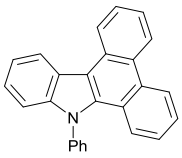
The optimization results using 2-(biphenyl]-2-ylethynyl)-*N*,*N*-dimethylaniline **1a** as a starting substrate are summarized in Table 1. When **1a** was subjected with our previously developed oxidative condition[15a] of $PdCl_2$ (10 mol%), MnO_2 (3 equiv), and PivOH (1 equiv), the corresponding DBC **2**a was obtained in a high yield of 95% (entry 1). $Pd(PPh_3)_2Cl_2$ and $Pd(OAc)_2$ were also proved to be effective for producing high yields of **2a** by combination with the MnO_2 oxidant and the PivOH additive (entries 2 and 3). Other catalysts such as $Pd(OPiv)_2$, $Pd(CH_3CN)_4(BF_4)_2$, and $Pd_2(dba)_3$ were examined to be less effective, which afforded **2a** in moderate yields along with the recovered **1a** (entries 4-6). The reaction of **1**a in the absence of PivOH dramatically decreased the yield of **2a** (entry 7), suggesting that PivOH may play an important role in both demethylation and C-H bond activation processes. Moreover, the reaction without using an oxidant gave a poor yield of **2a** (entry 8), indicating that the use of oxidants are indispensable for achieving a high yield of **2a** in the present cascade cyclization. Consequently, various oxidants were tested in the presence of the $PdCl_2$ catalyst and PivOH. The use of $CuCl_2$ resulted in decomposition of **1a** with a low yield of **2a**, while $Cu(OAc)_2$ and AgOAc were efficient oxidants to afford **2a** in 78% and 76% yields, respectively (entries 9-11). *o*-Chloranil was tested to be an unsuitable oxidant, which resulted in a complete decomposition of **1a** without forming **2a** (entry 12). Interestingly, the green oxidant of O_2 (1 atm) could lead to the corresponding product **2a** in 70% yield (entry 13). It was noted that among the solvents tested, the polar solvents such as diemthylacetamide (DMAc, 95%), dimethylformamide (79%), acetonitrile (77%), 1,4-dioxane (74%), and 1,2-dichloroethane (72%), gave much higher yields of **2a** than the use of the nonpolar solvent of toluene (34%).

Under the optimized reaction conditions, the *N*-substituent effect on the reaction efficiency has been studied (Table 2). The reaction with the secondary aniline **1b** produced the 2-biaryl-substituted indole **3b** as a major product along with the corresponding product **2a** in 3% yield due to the facile protonation of the corresponding indole-Pd species after the 5-*exo* cyclization, indicating that the use of the tertiary aniline substrates is crucial for the successful implementation of the current cascade cyclization (entry 1). The *N*,*N*-dihexylaniline **1c** was also a suitable substrate for producing the corresponding hexyl-protected DBC **2c** in 89% yield at a higher reaction temperature of 100 °C (entry 2). When the pyrrolidine-substituted aniline **1d** was used, the corresponding pyrrolidine ring-opened pivalate ester **2d** was formed a major product together with the chlorinated product **2d'** as a minor product (entry 3), suggesting that the dealkylation might be assisted by the nucleophilic attack of PivOH. The reaction with the *N*-benzyl-*N*-methylaniline **1e** produced the corresponding methyl-protected DBC **2a** as a sole product without forming the benzyl-protected DBC, indicating the facile deprotection property of the benzyl moiety (entry 4). The reaction with the *N*-phenyl-*N*-methylaniline **1f** produced the phenyl-protected DBC **2f** as a single product in 67% yield (entry 5), indicating the advantage of the present method for introducing varied *N*-protecting groups.

DOI: 10.1039/C8OB01386A

Table 2 Study of the *N*-substituent effect[a]

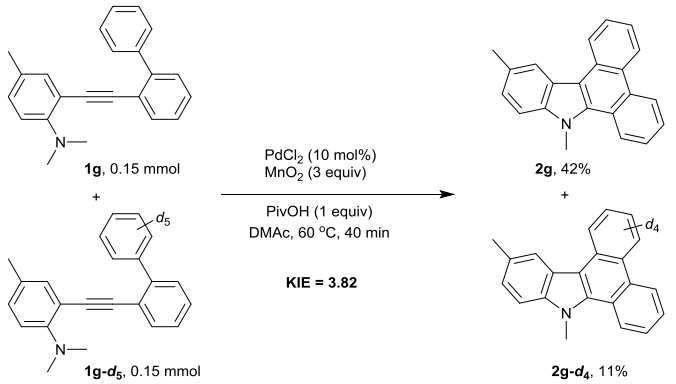


Entry	1	2 (%)[b]
1	 **1b**	 **3b**, 60% (**2a**, 3%)
2	 **1c**	 **2c**, 89% (100 °C)
3	 **1d**	 **2d**, X = OPiv, 70% **2d'**, X = Cl, 10%
4	 **1e**	 **2a**, 30%
5	 **1f**	 **2f**, 67% (24 h)

[a] Reaction conditions: **1** (0.3 mmol), $PdCl_2$ (10 mol%), MnO_2 (3 equiv), PivOH (1 equiv) in DMAc (1.5 mL) at 80 °C for 12 h. [b] Isolated yields.

Next, we investigated the electronic effect of substituents on the aniline and biphenyl moieties (Table 3). The reactions with *o*-alkynylanilines **1g** and **1h** having an electron-donating methyl group at the 4- and 5-positions of the aniline moiety, respectively, did not affect the efficiency for achieving good yields of the corresponding DBCs **2g** and **2h**, while the perdeuterated aniline **1g'** required a prolonged reaction time (12 h) for consumption of the starting substrate under the standard conditions (entries 1-3). Similarly, the *o*-alkynylanilines **1i-k** bearing electron-poor substituents such as F and CF_3 at the 4- or 5-position of the aniline moiety also did not show significant efficiency differences (entries 4-6), indicating the negligible electronic effect of the aniline moiety on the nucleophilic 5-*exo* cyclization process. Similar electronic effect was also observed from the reaction with substrates with the substituents on the biphenyl group. For example, the reactions with the anilines **1l** and **1m** having an electron-rich methyl substituent and an electron-poor Cl substituent at the 4'-position of the biphenyl group, respectively, afforded the corresponding products **2l** and **2m** in similarly high yields within 6 hours (entries 7 and 8). Interestingly, the biphenyl-tethered 10-alkynylphenanthren-9-amine **1n** also proceeded the present cascade cyclization efficiently, giving rise to the highly π-extended tetrabenzo[*a*,*c*,*g*,*i*]carbazole **2n** in 87% yield (entry 9).[12] The reaction also showed a high compatibility with the heterocycle-composed biaryl moiety. For example, the reaction with *o*-alkynylaniline **1o** bearing 3-phenylbenzo[*b*]thiophene at the alkynyl terminus produced the corresponding benzothiphene-fused carbazole **2o** in 67% yield (entry 10).

In order to further understand the mechanistic details, the deuterium isotope experiment was carried out (Scheme 2). An intermolecular competing reaction with a 1:1 mixture of the protonated **1g** and the perdeuterated **1g-*d*$_5$** under the standard conditions in the same reaction vessel at 60 °C for 40 min produced the corresponding DBC products **2g** and **2g-*d*$_4$** with a kinetic isotope effect (KIE) value of 3.82. This high KIE value clearly indicates that the C-H activation step should be the rate-determining. Moreover, the high KIE value also implies that the demethylation presumably takes place prior to the C-H bond activation,[14c,17] because if the C-H bond activation take place with the indolium intermediate **B** (see Scheme 3), the lower KIE value is expected due to the electron-deficient nature of the intermediate **B**.



Scheme 2 Intermolecular competing reaction between **1g** and **1g-*d*$_5$** in the same reaction vessel.

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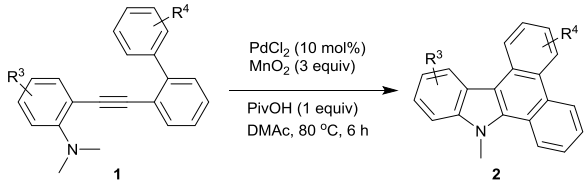
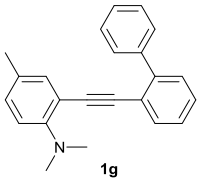
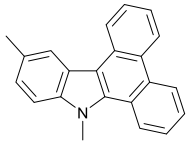
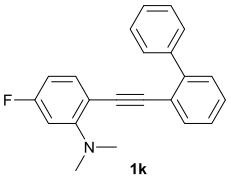
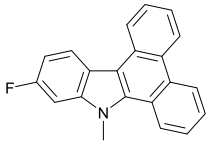
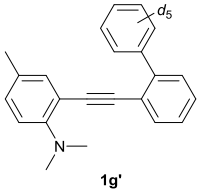
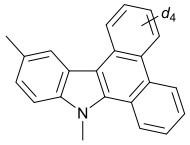
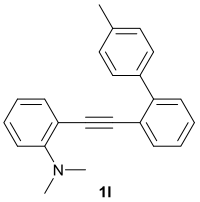
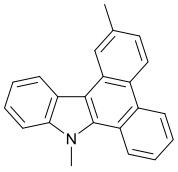
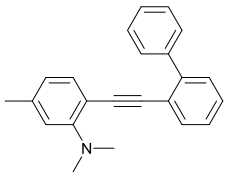
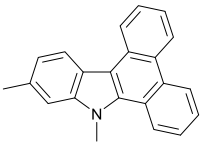
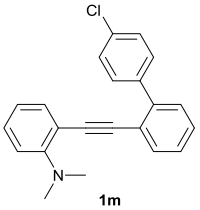
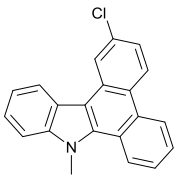
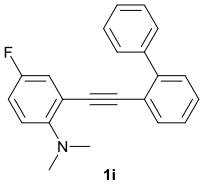
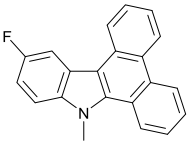
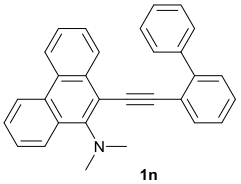
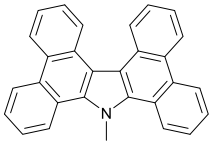
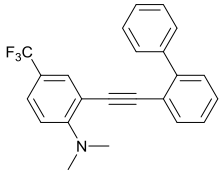
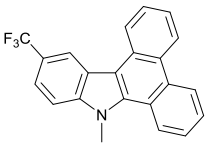
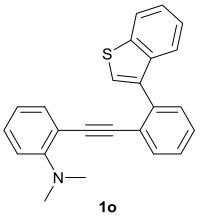
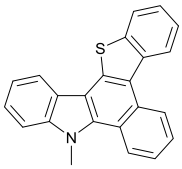
Table 3 Synthesis of various dibenzo[*a*,*c*]carbazole derivatives[a]

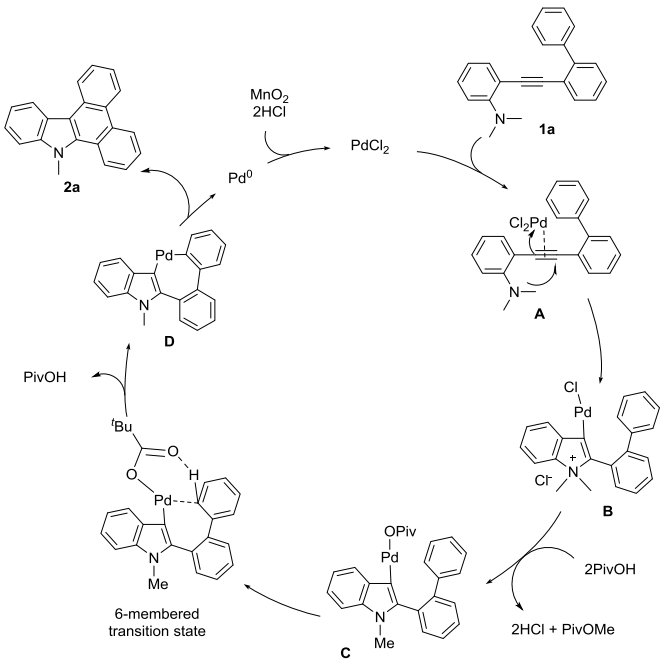


1		**1g**		**2g**, 78%	6		**1k**		**2k**, 82%
2		**1g'**		**2g'**, 76% (12 h)	7		**1l**		**2l**, 81%
3		**1h**		**2h**, 70%	8		**1m**		**2m**, 87%
4		**1i**		**2i**, 78%	9		**1n**		**2n**, 87% (12 h)
5		**1j**		**2j**, 97%	10		**1o**		**2o**, 67% (12 h)

[a] Reaction conditions: **1** (0.3 mmol), $PdCl_2$ (10 mol%), MnO_2 (3 equiv), PivOH (1 equiv) in DMAc (1.5 mL) at 80 °C for 6 h. [b] Isolated yield.

On the basis of the experimental evidences, the plausible reaction mechanism is outlined in Scheme 3. The coordination of the Pd(II) catalyst with the alkyne moiety of **1a** leads to the 5-*endo* cyclization to form a indolium-Pd intermediate **B**. Subsequently, the nucleophilic attack of PivOH to the activated *N*-methyl group in the intermediate **B** results in a demethylation reaction and a counter anion exchange of Pd(II) to yield the indole-Pd(OPiv) intermediate **C** with releasing HCl and PivOMe.

The *ortho*-C-H activation of the intermediate **C** through a pivalate-assisted transition state affords the seven-membered palladacycle **D**. Subsequent reductive elimination of the intermediate **D** produces the corresponding product **2a** and the Pd(0) species. The Pd(0) species can be oxidized by MnO_2 in the presence of HCl, regenerating the active $PdCl_2$ catalyst.[15a]



Scheme 3 Plausible reaction mechanism.

Conclusions

In conclusion, we have developed for the first time a new and efficient DBC synthetic methodology from the biaryl-tethered *o*-alkynylanilines under the Pd-catalyzed oxidative conditions. The present reaction proceeds through a cascade process involving 5-*endo* cyclization, demethylation, and *ortho*-C-H activation, producing the corresponding DBC derivatives, tetrabenzocarbazole, and benzothiophene-fused carbazole in good to high yields. The present cascade cyclization provides a general and useful synthetic method for constructing various DBC structures, which will be further extended to the synthesis of valuable bioactive compounds and highly π-extended carbazole-fused functional materials.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We are grateful to the National Natural Science Foundation of China (No. 21372035, 21573032, and 21602026) and the China Postdoctoral Science Foundation (No. 2016M590226) for their financial support. TJ thanks Japan Society for Promotion of Science (JSPS) KAKENHI Grant Number 15KK0180 on Fostering Joint International Research.

DOI: 10.1039/C8OB01786A

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DOI: 10.1039/C8OB01386A

Table of Contents

Pd-Catalyzed cascade cyclization of *o*-alkynylanilines via C-H/C-N bond cleavage leading to dibenzo[*a*,*c*]carbazoles

Sheng Zhang, Hengmin Ma, Hon Eong Ho, Yoshinori Yamamoto, Ming Bao* and Tienan Jin*

A new and efficient Pd-catalyzed cascade cyclization of biaryl-tethered *o*-alkynylanilines has been reported for the formation of dibenzo[*a*,*c*]carbazole derivatives.