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Pd(II)-catalyzed intramolecular C–H activation/C–C cross coupling for the synthesis of carbazoles from diaryl acetamides

Sichang Wang, Hui Mao, Zhangqin Ni, Yuanjiang Pan *

Department of Chemistry, Zhejiang University, Hangzhou 310027, China

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ABSTRACT

Pd(II)-catalyzed intramolecular C–H activation/C–C cross coupling within *N*,*N*-diphenyl-acetamides allows the efficient formation of differently substituted carbazoles. In this cross-dehydrogenative coupling, many different functional groups are tolerated and the starting material *N*,*N*-diphenyl-acetamides can be easily prepared in one step from commercially available acetanilides and iodobenzenes.

Transition metal-catalyzed C–H activation reactions are among the most popular processes in modern organic synthesis.[1] Catalytically efficient activation of aromatic C–H bonds leading to useful organic reactions such as new C–C bond formation is of considerable interest for the chemical and pharmaceutical industries and remains a long-term challenge to chemists.[2–5] C–H functionalization is the most sustainable and straightforward method to construct complicated structures and has received significant attention in the past several decades.[6] Chemists continue to develop increasingly efficient methods for the construction of biaryl molecules by C–H activation.

Carbazole alkaloids are attractive synthetic targets for they display a variety of biological activities.[7–9] The indigenous application of the stem bark of the curry-leaf tree as folk medicine led to the discovery of antibacterial, antifungal, and antiviral properties of this class of natural products.[10,11] Carbazole derivatives have also been extensively applied as organic materials and have been investigated for the development of optoelectronic applications such as polymeric light-emitting diodes (PLED) and organic light-emitting devices (OLED).[12,13] In view of these important applications, we set out to develop a metal-catalyzed synthesis of carbazoles. The use of pivalic acid as solvent results in improved reproducibility, higher yields, and broader scope for the intramolecular aryl–aryl coupling.[14] The development of better conditions for the transformation of diarylacetamides into carbazoles is greatly appealing. Instead of expensive pivalic acid, herein, acetic acid is used as the reaction solvent together with Ag_2O as oxidant, which also leads to higher yields.

The requisite biaryl amines **3** were synthesized from acetanilides **1** and iodobenzenes **2** as model substrates by an Ullmann C–N cross-coupling reaction (Scheme 1).[15]

A combination of a palladium catalyst and a reoxidant was used to investigate the conversion of *N*,*N*-diphenyl-acetamide **3a** to *N*-acetyl carbazole **4a** (Table 1). Preliminary results suggested that the use of a combination of 5% $Pd(OAc)_2$ and a stoichiometric amount of $Cu(OAc)_2/Ag_2O$ or $CsCO_3/Ag_2O$ at 120 °C under an atmosphere of air after 14 h provided a near quantitative yield of **4a** in acetic acid (Table 1, entries 9 and 10). No product was observed in the absence of $Pd(OAc)_2$ (Table 1, entry 14), suggesting that Ag_2O mediated the reoxidation of the reduced palladium species. Other commercially available palladium precatalysts (Table 1, entries 1–4) were less efficient than $Pd(OAc)_2$ in affecting the transformation. Other reoxidants (Table 1, entries 7–12) were also evaluated in various palladium-catalyzed oxidative coupling reactions.[14] Results show that a stoichiometric amount of Ag_2O (Table 1, entry 13) was sufficient to mediate the reoxidation process and deliver **4a** in comparable yields.

Next, the scope and limitations of this cascade reaction were examined. The proposed method was tested on substrates causing electronic variations on each ring of the diarylacetamides. Various biarylacetamides bearing electron-donating (OMe) or -withdrawing groups (Cl, F, CF_3 and NO_2) on the aromatic ring were treated with palladium acetate to produce corresponding carbazoles in moderate to good yields (Table 2, entries 2–15). For example, when monosubstituted electron-rich diphenylacetamides were treated with palladium acetate and silver oxide in acetic acid, good yields (up to

* Corresponding author.
E-mail address: cheyjpan@zju.edu.cn (Y. Pan).

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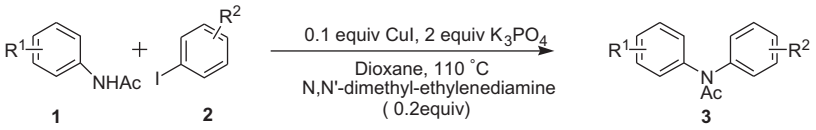
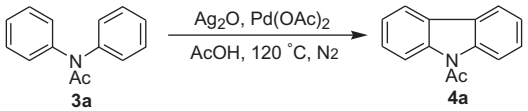


Scheme 1. Synthesis of biaryl acetamides by Ullmann C–N cross-coupling.

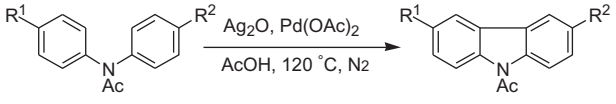
Table 1
Screening of reaction conditions for synthesis carbazole[a]



Entry	Pd(mol %)	Oxidant(equiv)	Solvent	Temperature (°C)	Time (h)	Yield[b] (%)
1	$Pd(OAc)_2$(5)	$Cu(OAc)_2$(2), $CsCO_3$(2)	Toluene	120	14	0
2	$PdCl_2$(5)	$Cu(OAc)_2$(2), $CsCO_3$(2)	Toluene	110	12	0
3	$Pd(OAc)_2$(5)	$Cu(OAc)_2$(2), Ag_2O(2)	TFA	120	14	0
4	$PdCl_2$(5)	$Cu(OAc)_2$(2), $CsCO_3$(2)	TFA	110	12	0
5	$Pd(OAc)_2$(5)	$Cu(OAc)_2$(2), $CsCO_3$(2)	DMF	120	14	0
6	$Pd(OAc)_2$(5)	$Cu(OAc)_2$(2),$CsCO_3$(2)	Dioxane	100	14	0
7	$Pd(OAc)_2$(5)	$Cu(OAc)_2$(2), $CsCO_3$(2)	AcOH	120	14	40
8	$Pd(OAc)_2$(5)	$Cu(OAc)_2$(2)	AcOH	120	14	13
9	$Pd(OAc)_2$(5)	$Cu(OAc)_2$(2), Ag_2O(2)	AcOH	120	14	60
10	$Pd(OAc)_2$(5)	$CsCO_3$(2), Ag_2O(2)	AcOH	120	14	68
11	$Pd(OAc)_2$(5)	$CsCO_3$(2)	AcOH	120	14	43
12	$Pd(OAc)_2$(5)	Na_2CO_3(2)	AcOH	120	14	40
13	$Pd(OAc)_2$(5)	Ag_2O(1)	AcOH	120	14	70
14		Ag_2O(1)	AcOH	120	14	0

[a] All reactions were performed with *N*,*N*-diphenyl-acetamides (0.3 mmol), oxidant (0.3 mmol) and catalyst (5–8 mol %) in 2 mL of solvent under nitrogen atmosphere.
[b] Isolated yield after silica gel chromatography.

Table 2
Scope and limitations of palladium(II)-catalyzed carbazole formation from diarylacetamides[a]



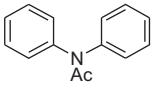
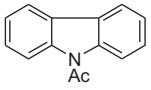
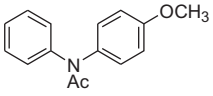
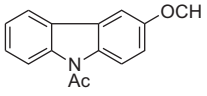
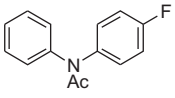
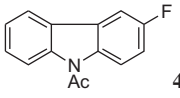
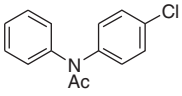
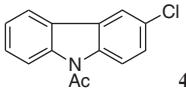
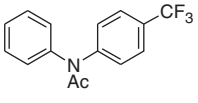
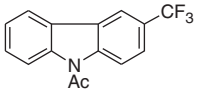
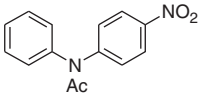
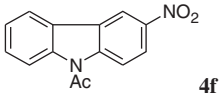
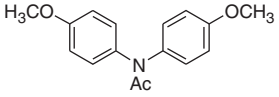
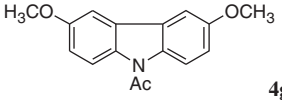
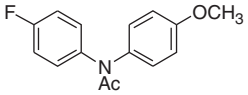
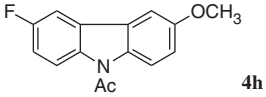
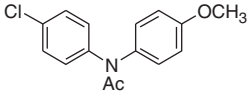
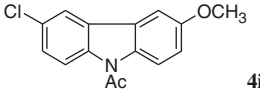
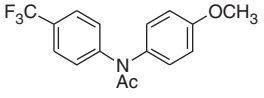
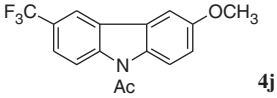
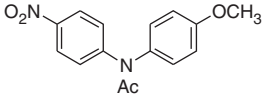
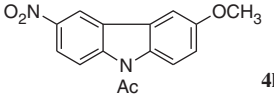
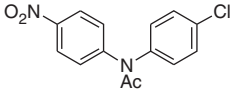
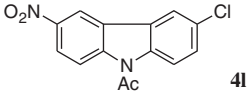
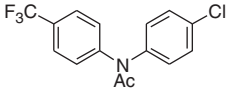
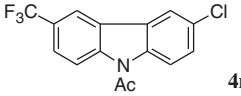
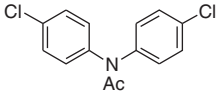
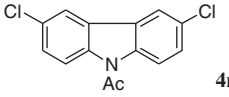
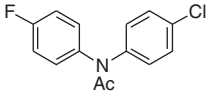
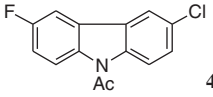
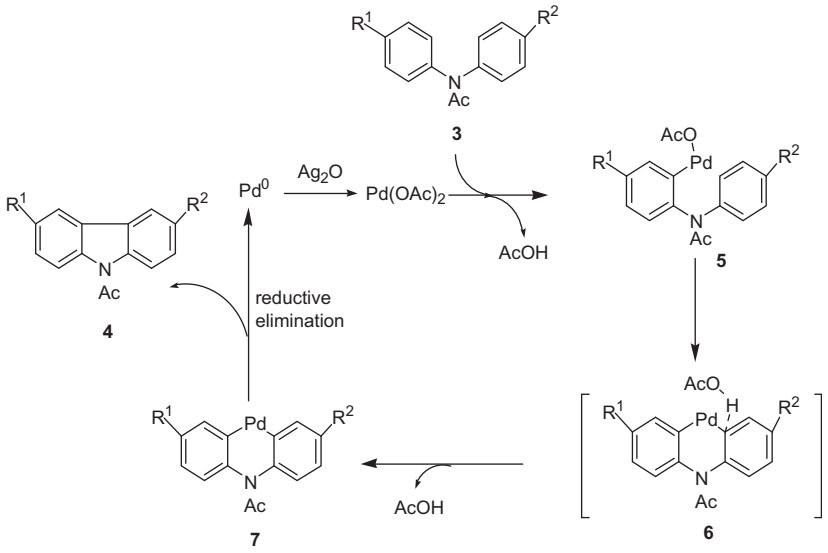
Entry	Diarylamine	Product	Yield[b] (%)
1		 **4a**	70
2		 **4b**	68
3		 **4c**	55
4		 **4d**	60
5		 **4e**	43
6		 **4f**	60

Table 2 (*continued*)

Entry	Diarylamine	Product	Yield[b] (%)
7		 **4g**	76
8		 **4h**	53
9		 **4i**	66
10		 **4j**	48
11		 **4k**	68
12		 **4l**	58
13		 **4m**	40
14		 **4n**	58
15		 **4o**	53

[a] All reactions were performed with *N*,*N*-diphenyl-acetamides (0.3 mmol), Ag_2O (0.3 mmol) and $Pd(OAc)_2$ (5–8 mol %) in 2 mL of solvent under nitrogen atmosphere.
[b] Isolated yield after silica gel chromatography.



Scheme 2. Proposed pathway for carbazole synthesis.

68%) were obtained for the preparation of carbazole products (Table 2, entry 2). However, diarylacetamides with electron-withdrawing groups afforded the product with reduced yields (Table 2, entries 3–6). In addition, carbazoles with good yields were obtained when a series of disubstituted diphenylamines were employed (Table 2, entries 7–15).

Based on these results, a tandem mechanism is proposed to explain the intramolecular C–H activation to the aryl ring (Scheme 2).[14] First, substrate **3** and palladium(II) acetate could form a Pd(II) intermediate **5** with the release of one molecule of acetic acid. Palladium(II) intermediate **6** then loses one molecule acetic acid to provide a six-membered cyclic palladium(II) complex **7**. After reductive elimination, the Pd(II)-containing six-membered ring of **7** produces the carbazole product **4** and a Pd(0) species, which is reoxidized to Pd(II) acetate in the presence of Ag_2O to complete the catalytic cycle.

In summary, an efficient way to produce substituted carbazoles has been developed through a tandem C–H activation in this work. The products can be assembled in a simple two-step protocol from readily available reagents. Considering its excellent reaction efficiency, wide substrate scope, and very mild reaction conditions, this present intramolecular oxidative C–H coupling will be an attractive route to the practical synthesis of carbazoles. Further studies on the mechanism and applications are underway in our laboratory.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.11.082.

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