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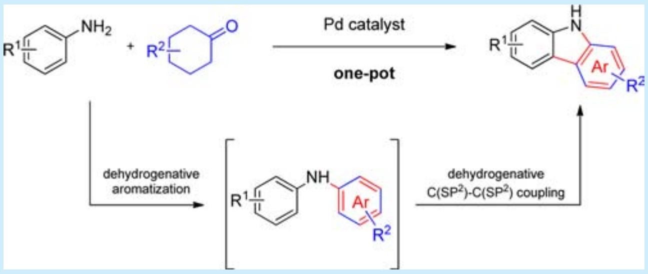
Ligand-Free Pd-Catalyzed Domino Synthesis of Carbazoles via Dehydrogenative Aromatization/C(sp^2)−C(sp^2) Coupling Sequence

Lixian Wen,[†] Lin Tang,[†] Yu Yang, Zhenggen Zha, and Zhiyong Wang*

Hefei National Laboratory for Physical Sciences at Microscale, CAS Key Laboratory of Soft Matter Chemistry and Department of Chemistry & Collaborative Innovation Center of Suzhou Nano Science and Technology, University of Science and Technology of China, Hefei, Anhui 230026, P. R. China

S *Supporting Information*

ABSTRACT: A palladium-catalyzed domino reaction via a dehydrogenative aromatization and a dual C(sp^2)−H functionalization process for one-pot synthesis of carbazoles under ligand-free conditions has been developed. On the basis of the catalytic system, carbazoles can be synthesized in moderate to good yields from facile arylamines and cyclic ketones, which presents straightforward and practical C(sp^2)−C(sp^2) bond formation.



Carbazoles are significant structural motifs due to their widespread applications in medicine and the dye industry, as well as their supramolecular recognition.[1] Much effort has been made toward their construction using Fischer−Borsche cyclization, Heck-type coupling reactions, iron-mediated cyclization, and alternative amination.[2−6] However, these methods generally suffer from limitations of substrate generality and availability. In this context, a more straightforward and practical protocol for the synthesis of carbazoles is highly desirable.

Transition-metal-catalyzed functionalization of the C−H bond has emerged as a powerful tool for C−C bond formation. Accordingly, recent years have witnessed intense interest in the conversion of various C−H bonds to C−C bonds.[7] Among these reactions, ligands are necessary in order to improve the reactions' activity.[8] Therefore, C−H bond functionalization for highly selective C−C bond formation under ligand-free conditions remains a challenge in synthetic methodology. Encouraged by previous work on the dual C(sp^2)−H bond dehydrogenative functionalization,[9] we herein report an efficient palladium-catalyzed domino reaction of arylamines and cyclic ketones for synthesizing carbazoles via a dehydrogenative aromatization C(sp^2)−C(sp^2) coupling in the absence of a ligand.

We began our research using aniline **1a** and cyclohexanone **2a** as the model substrates to optimize the reaction conditions (Table 1). To investigate the effect of solvents on this reaction, various solvents were screened. Compared with DMF, DMSO, AcOH, and CF_3SO_3H, PivOH proved to be the optimal solvent, affording the corresponding product **3aa** in 69% yield (entries 1−5). Subsequently, different catalysts were tested. When $Pd(OAc)_2$ was employed as the catalyst, **3aa** could be obtained in 74% yield, whereas a low yield of **3aa** was obtained when $Pd(PPh_3)_4$ and $Pd(acac)_2$ served as the catalysts (entries 6−8). Among various oxidants, $Cu(OAc)_2$ still proved optimal (entries 8−14). The strategy to decrease the amount of copper salt in O_2 atmosphere was examined, but a trace amount of the product was observed (entry 15). In addition, the reaction atmosphere and temperature were optimized, and no higher yield was obtained (entries 16−18).

With the standard conditions in hand, the scope of the arylamines was extended (Scheme 1). On the basis of experimental results, the electronic properties had a slight effect on the reaction. Substrates with electron-donating groups (**1b**−**e**) and electron-withdrawing groups (**1f,h,j,k**) on the phenyl ring gave the corresponding products in good yields.[10] However, low yield was observed when the chloro substituent located on the phenyl ring, which could be attributed to the side reaction of Buchwald−Hartwig amination (**1g**). On the other hand, **3ia** was afforded only in a yield of 46%, perhaps due to the poor nucleophilicity of **1i**.[11] Furthermore, we investigated the influence of the steric effect on the yields and regioselectivities. The results indicated that the methyl substituent at different positions of the phenyl ring had little impact on the yields (**3ba,la,ma**). Interestingly, the reaction showed excellent regioselectivity (>99:1) when the substrates were *m*-tolylamine **1m** and pyridin-3-ylamine (**1q**), whereas, the ratio of **3oa**/**3pa** was decreased to 2:3 when R1 was replaced by methoxyl.

Subsequently, the scope of the cyclohexanone was examined as shown in Scheme 2. Both electron-rich and electron-deficient ketones could be employed as the substrates, and the reaction could be carried out smoothly, affording the products in good yields (**3ba,da,ea,as**). The steric hindrance of the substituents had a negative influence on the reaction (**3ba,la** and **3ma,na**).

There are two possible pathways for this reaction.[12] To obtain more direct evidence, several control experiments were carried out (Scheme 3).[9k,13] First, a small amount of diphenylamine

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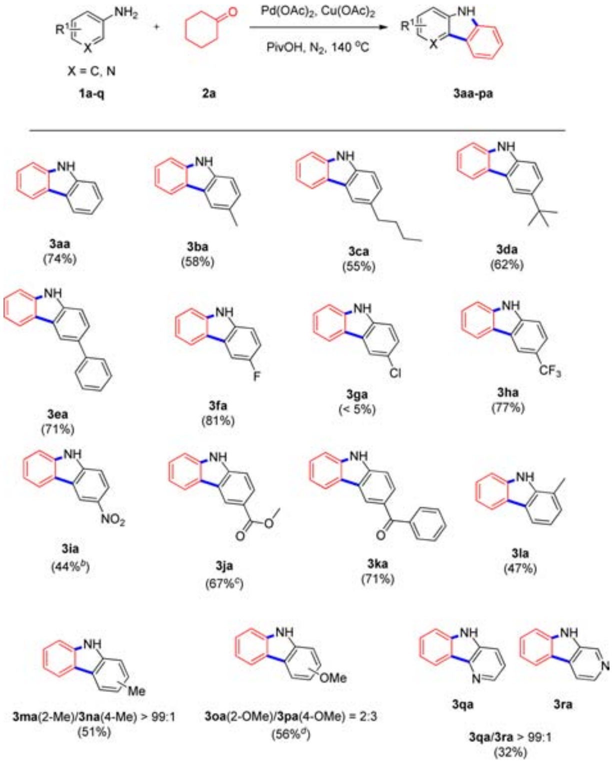
Table 1. Optimization of Reaction Conditions[a]

entry	catalyst	oxidant	solvent	yield[b] (%)
1	$PdCl_2$	$Cu(OAc)_2$	DMF	nd
2	$PdCl_2$	$Cu(OAc)_2$	DMSO	trace
3	$PdCl_2$	$Cu(OAc)_2$	AcOH	15
4	$PdCl_2$	$Cu(OAc)_2$	CF_3SO_3H	nd
5	$PdCl_2$	$Cu(OAc)_2$	PivOH	69
6	$Pd(PPh_3)_4$	$Cu(OAc)_2$	PivOH	12
7	$Pd(acac)_2$	$Cu(OAc)_2$	PivOH	31
8	$Pd(OAc)_2$	$Cu(OAc)_2$	PivOH	74
9	$Pd(OAc)_2$	$CuCl_2$	PivOH	trace
10	$Pd(OAc)_2$	$CuBr_2$	PivOH	8
11	$Pd(OAc)_2$	CuO	PivOH	63
12	$Pd(OAc)_2$	AgOAc	PivOH	trace
13	$Pd(OAc)_2$	DDQ	PivOH	trace
14	$Pd(OAc)_2$	$K_2S_2O_8$	PivOH	nd
15[c]	$Pd(OAc)_2$	O_2	PivOH	trace
16[d]	$Pd(OAc)_2$	$Cu(OAc)_2$	PivOH	62
17[e]	$Pd(OAc)_2$	$Cu(OAc)_2$	PivOH	65

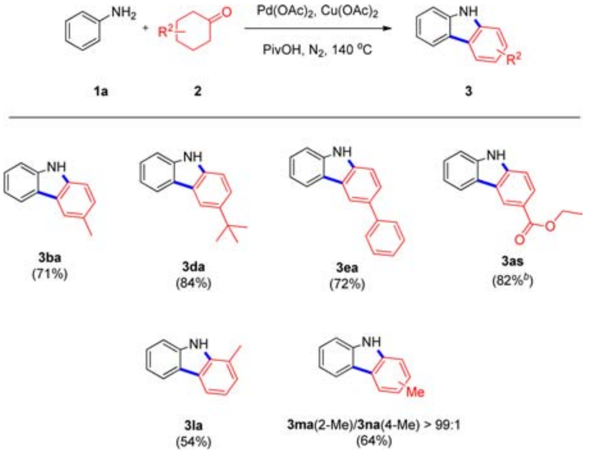
[a] Unless otherwise noted, all reactions were performed with **1a** (0.35 mmol), **2a** (0.25 mmol), catalyst (10 mol %), and oxidant (6 equiv) in solvent (1.5 mL) at 140 °C for 24 h sealed under N_2 atmosphere. [b] Isolated yield. [c] 20 mol % of $Cu(OAc)_2$ was used, and the reaction was carried out under O_2 atmosphere. [d] The reaction was carried out under 120 °C. [e] The reaction was carried out under air atmosphere.

Scheme 1. Scope of Anilines[a]



[a] Unless otherwise noted, all reactions were performed with **1** (0.35 mmol), **2a** (0.25 mmol), Pd(OAc)2 (10 mol %), and Cu(OAc)2 (6 equiv) in PivOH (1.5 mL) at 140 °C for 24 h sealed under N_2 atm; yield of isolated product. [b] $LiOH{\cdot}H_2O$ (0.35 mmol) as the base. [c] Two milliliters of PivOH and toluene (v/v = 1:1) as the solvent. [d] PivOK (0.35 mmol) as the base.

Scheme 2. Scope of Cyclohexanones[a]



[a] Unless otherwise noted, all reactions were performed with **1a** (0.35 mmol), **2** (0.25 mmol), $Pd(OAc)_2$ (10 mol %), and $Cu(OAc)_2$ (6 equiv) in PivOH (1.5 mL) at 140 °C for 24 h sealed under N_2 atmosphere; yield of isolated product. [b] Two milliliters of PivOH and toluene (v/v = 1:1) as the solvent.

could be detected in the reaction mixture, which indicated that it perhaps was the intermediate of the reaction. Moreover, a primary kinetic isotopic effect (KIE) value of 2.45 was observed for the competition reaction between diphenylamine and diphenylamine-d_5, which revealed that the C−H bond cleavage was involved in the rate-determining step.[14a,b] However, when cyclopentanone was used as the substrate, no product was obtained, proving that the feasibility of aromatization is essential to this reaction. Interestingly, when 4,4-dimethylcyclohexanone, which cannot be aromatized, was employed as substrate, a methyl rearrangement product was obtained,[15] which showed that only dual aryl C(sp^2)−C(sp^2) formation was achieved under the standard conditions.

On the basids of the above discoveries and previous works,[9] a plausible reaction mechanism was proposed, as shown in Scheme 4. First, the reaction starts with a condensation to give an enamine[14e] followed by palladation to generate a palladium(II) species **IV**.[14f−h] Subsequently, tautomerization and *β*-hydride elimination will liberate a cyclic diene intermediate **VI** and a Pd(0) species. The latter could be oxidized to Pd(II) in the presence of Cu(II). The intermediate **4a** will be formed from the diene species **VI** in a second oxidation. Afterward, the reaction is boosted by fast electrophilic palladation of **4a** with $Pd(OPiv)_2$ to generate intermediate **VIII**. Further intramolecular C−H cleavage takes place to generate **X** via transition state **IX**, which is considered as the rate-determining step.[14a,b] The following reductive elimination affords product carbazole and generates a Pd(0) species, which is oxidized to a Pd(II) species by Cu(II) to finish the catalytic cycle.

In summary, we have developed an efficient method to synthesize carbazoles by a Pd-catalyzed domino reaction in the absence of ligand, which was performed with good functional group tolerance. Moreover, the starting material of this reaction is much easier to obtain, and the complicated separate procedure can be avoided. A Pd-catalyzed Csp^2−Csp^2 coupling mechanism was confirmed. Further studies to extend this transformation are ongoing.

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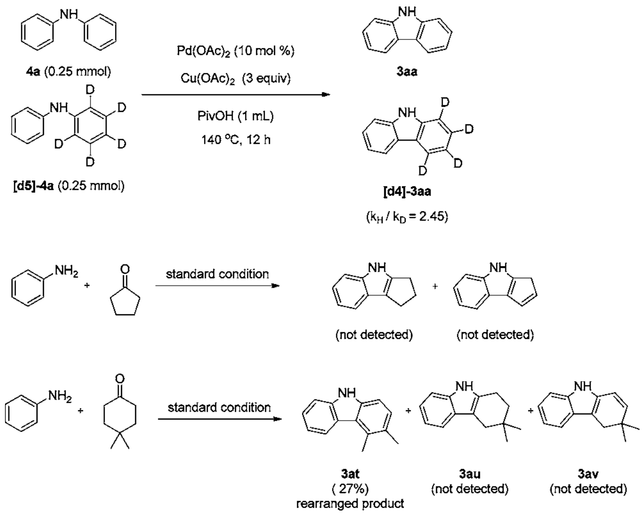
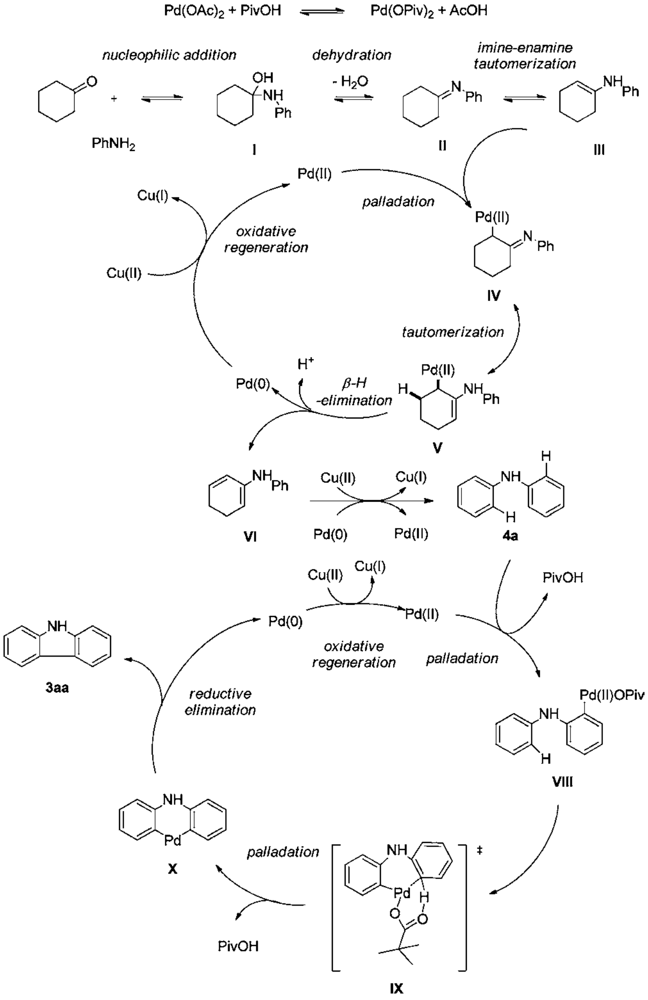
Scheme 3. Control Experiments



Scheme 4. Possible Reaction Pathway



ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00193.

Experimental procedures, characterization data, and ^{1}H NMR, ^{13}C NMR of products (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: zwang3@ustc.edu.cn.

Author Contributions

†L.W. and L.T. contributed equally.

Notes

The authors declare no competing financial interest.

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