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Palladium-Catalyzed Direct Synthesis of Carbazoles via One-Pot *N*-Arylation and Oxidative Biaryl Coupling: Synthesis and Mechanistic Study

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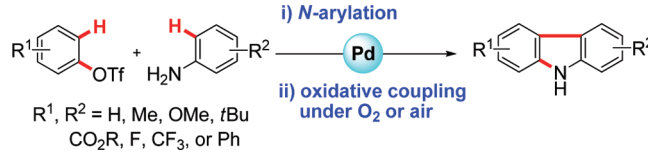


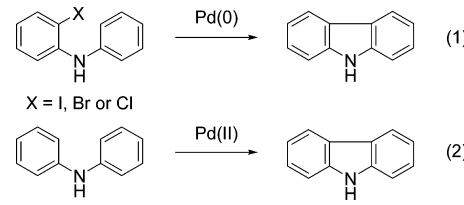
An efficient catalytic system has been developed for the synthesis of carbazoles by one-pot *N*-arylation and oxidative biaryl coupling. A significant substituent effect of the diarylamine intermediate on oxidative coupling was observed. Mechanistic studies of oxidative coupling, including trapping of reaction intermediates and kinetic isotope effect experiments, are also presented.

Introduction

Nitrogen heterocycles are found in many biologically active compounds and also useful as drug-like templates. Carbazoles have various biological activities (e.g., antibacterial, anti-inflammatory, antitumor).[1] They also exhibit useful properties as organic materials, such as hole-transporting, photoconductive effects, and photorefractive effects.[2] Developing a reliable methodology to obtain carbazoles with multiple functionalities in a single step is desirable because most methods of synthesizing carbazoles require several steps.[3] In view of synthesizing carbazoles in an atom-economical manner, we focused on one-pot synthesis of carbazoles through a palladium-catalyzed C−H arylation reaction.[4−6]

Palladium-catalyzed intramolecular C−H arylation of *N*-phenyl-2-haloaniline derivatives is a useful method for the synthesis of carbazoles (eq 1, Scheme 1).[7] The oxidative biaryl coupling reaction, originally reported by Yoshimoto[8] and Åkemark[9a] using palladium(II) (eq 2, Scheme 1), can be an atom-economical approach to carbazoles, particularly if the reaction proceeds catalytically.[10−12] As related reactions to eq 1, Scheme

SCHEME 1. Synthesis of Carbazole by Palladium-Catalyzed C−H Activation



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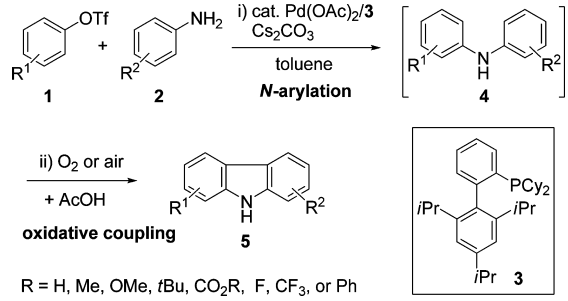
1, direct syntheses of carbazoles by cascade Buchwald−Hartwig *N*-arylation−C−H arylation using *o*-haloanilines/halobenzenes[13] and anilines/*o*-dihalobenzenes[14] were recently reported. These contributions prompted us to develop a more atom-economical, direct synthetic method of carbazoles. We present the full account of our palladium-catalyzed carbazole synthesis by direct coupling of aryl triflates and anilines through one-pot *N*-arylation[15] and oxidative biaryl coupling reaction in the presence of a common palladium catalyst and molecular oxygen or air (Scheme 2).[16] Some mechanistic considerations regarding the oxidative coupling shown in eq 2, Scheme 1, are also discussed.

SCHEME 2. One-Pot Synthesis of Carbazoles by *N*-Arylation and Oxidative Biaryl Coupling



Results and Discussion

Synthesis of Various Carbazoles by One-Pot *N*-Arylation and Oxidative Biaryl Coupling. Our preliminary investigation revealed that acetic acid or a mixed solvent containing acetic acid were the solvents of choice for the oxidative biaryl coupling reaction, whereas the commonly used solvents for the *N*-arylation reaction (toluene, dioxane, DMF) were ineffective.[16,17] Carbazole formation was therefore carried out in a mixed solvent containing acetic acid, which was added after *N*-arylation in toluene. We chose the triflate as a leaving group for *N*-arylation because a halide anion in the reaction vessel poisons the palladium catalyst in the oxidative coupling reaction.[10b,18,19] Results of the direct synthesis of carbazoles with phenyl triflates and anilines are summarized in Table 1.

After the *N*-arylation of aniline **2a** with phenyl triflate **1a** under the Buchwald−Hartwig conditions was completed (monitored by TLC), acetic acid was added and the reaction mixture subjected to an oxygen atmosphere to afford the desired carbazole **5aa** in 69% yield (Table 1, entry 1).[20] Air proved to be a good co-oxidant and **5aa** was obtained in 67% yield, although a slightly longer reaction time was required (entry 2). We next examined the reaction of various triflates and anilines under oxygen conditions. The reaction of phenyl triflates **1b−d** bearing an electron-donating group at the para position resulted in low yields of the carbazoles **5ba−da** due to their instability under the reaction conditions (entries 3−5).[21] The reaction of triflates **1e−i** with an electron-withdrawing group at the para position resulted in better yields of carbazoles (50−74%, entries 6−10) than those of the electron-rich triflates **1b−d**. When using meta-substituted phenyl triflates **1j−m**, the biaryl coupling reaction selectively proceeded at the less hindered position of the triflates, leading to 2-substituted carbazoles **5ja−ma** (entries 11−15). The electron-deficient triflate **1m** gave poor results (34%, entry 15) in contrast with the reaction of the para-substituted electron-deficient triflates **1e−i** (entries 6−10). By using air in place of oxygen as the co-oxidant, the desired carbazole **5ja** was obtained in 82% yield (entry 12). The reaction of the ortho-substituted triflates **1n** and **1o** led to the desired carbazoles **5na** and **5oa** in only 20% and 27% yields, presumably due to steric hindrance as well as fewer reactive carbons in the cyclization step (entries 16 and 17).[12c] Introduction of a substituent to aniline such as the trifluoromethyl group, the methoxycarbonyl group, and the phenyl group was tolerated (entries 18−20). Regioisomeric trifluoromethylated diphenyl-

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(16) A portion of this study was already reported in a preliminary communication: Watanabe, T.; Ueda, S.; Inuki, S.; Oishi, S.; Fujii, N.; Ohno, H. *Chem. Commun.* **2007**, 4516–4518.

(17) Quite recently, it has been reported that pivalic acid works well as the reaction solvent for oxidative biaryl coupling, see ref 10c.

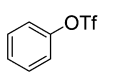
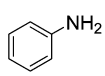
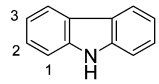
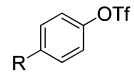
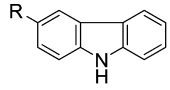
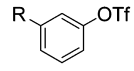
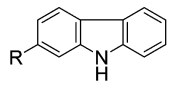
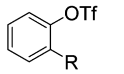
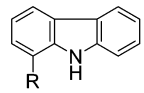
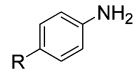
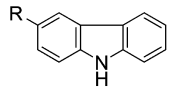
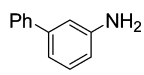
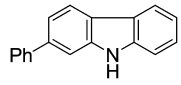
(18) Indeed, the treatment of diphenylamine in AcOH under oxygen atomosphere with palladium dichloride or palladium acetate/tetrabutylammonium bromide led to recovery of the starting material.

(19) Ligand screening for *N*-arylation is given in the Supporting Information.

(20) When *N*-methyl anisidine was used, the corresponding *N*-methyl carbazole was obtained in ca. 7% yield. In this case, demethylated carbazole was formed in ca. 3% yield as a byproduct under the oxidative coupling process. Use of *N*-phenylaniline (diphenylamine) in place of aniline was ineffective in the oxidative coupling step after *N*-arylation.

(21) High reactivity of electron-rich carbazoles was described in ref 10c.

TABLE 1. Synthesis of Monosubstituted Carbazoles[a]

entry	triflate	aniline	temp (°C),[b] time (h)[b]	yield (%)[c]
				
1	**1a**	**2a**	100, 9	**5aa** 69[d]
2			100, 17[e]	67
		**2a**		
3	**1b** (R = Me)		100, 6.5	**5ba** 46
4	**1c** (R = OMe)		90, 20.5	**5ca** 26
5	**1d** (R = *t*Bu)		100, 5	**5da** 43
6	**1e** (R = CO_2Me)		120, 29	**5ea** 64[f]
7	**1f** (R = CO_2Bn)		120, 7	**5fa** 74
8	**1g** (R = COMe)		120, 80	**5ga** 50[g]
9	**1h** (R = F)		100, 37	**5ha** 57
10	**1i** (R = Ph)		120, 9	**5ia** 65
		**2a**		
11	**1j** (R = Me)		100, 5	**5ja** 62
12			100, 22.5[e]	82
13	**1k** (R = OMe)		100, 23	**5ka** 53
14	**1l** (R = *t*Bu)		100, 9	**5la** 62
15	**1m** (R = CF_3)		120, 31	**5ma** 34
		**2a**		
16	**1n** (R = Me)		120, 29	**5na** 20
17	**1o** (R = CO_2Me)		120, 50	**5oa** 27[h]
	1a			
18		**2b** (R = CF_3)	100, 5	**5ab** 72[i]
19		**2c** (R = CO_2Me)	120, 29	**5ea** 66
				
20	**1a**	**2d**	120, 16	**5ad** 60

[a] Reaction conditions: triflate **1** (1.0 equiv), aniline **2** (1.1 equiv), $Pd(OAc)_2$ (10 mol %), **3** (15 mol %), Cs_2CO_3 (1.2 equiv), toluene (0.5 M), 100 °C, 1−2 h, then O_2 (1 atm), AcOH (0.125 M). [b] Conditions for oxidative coupling. [c] Isolated yield. [d] When *N*-arylation was conducted for 24 h, a similar result (62% yield) was obtained. [e] Air was used in place of O_2. [f] *N*-Arylation product was obtained in 28% yield. [g] *N*-Arylation product was obtained in 49% yield. [h] *N*-Arylation product was obtained in 68% yield. [i] *N*-Arylation product was obtained in 23% yield.

amine intermediates should be formed in entries 15 and 18, but a remarkable difference in the yield of carbazoles was observed (34% for **5ma** and 72% for **5ab**).

The results shown in Table 1 indicate that the reactivity in the oxidative biaryl coupling step is strongly influenced by the substitution pattern of diarylamine intermediates because *N*-arylation proceeded almost quantitatively in many cases.[22] Furthermore, the product yields are not dependent on the reaction time of *N*-arylation (for example, 69% of **5aa** with 1 h; 62% of **5aa** with 24 h, entry 1). The reactivity of diarylamines

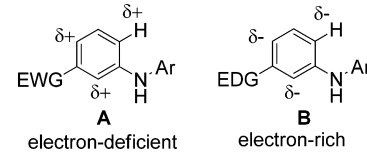


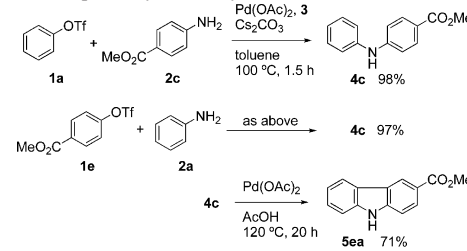
FIGURE 1. Electronic state in the C−H activation site.

of type **A** (Figure 1), having an electron-withdrawing group at the meta position, to palladium(II) was remarkably low (entry 15), whereas diarylamines having an electron-withdrawing group at the para position gave moderate-to-good results (50−74%, entries 6−8).[23] These results can be attributed to the electron density of the C−H activation site; more direct influence of the electron-withdrawing group at the meta position would reduce the electron density of the reaction site as shown in **A**, thereby lowering the reactivity of **A** toward the electron-deficient palladium(II). The higher reactivity of diarylamine of type **B** bearing an electron-donating group at the meta position can be explained by the higher electron density at the C−H activation site compared with the ortho- or para-substituted ones (entries 3, 11, and 16).

We next examined the one-pot reaction using a combination of substituted triflates and anilines (Table 2). Among the triflates **1b**, **1j**, and **1n** bearing a methyl group at the para, meta, and ortho position, respectively (entries 1, 2, and 4), *m*-methylated triflate **1j** gave the carbazole in the highest yield (>99%, entry 2) by the reaction with aniline **2c** having a *p*-methoxycarbonyl group under an oxygen atmosphere. A comparable result with entry 2 was obtained by using air as the co-oxidant (93%, entry 3). Combination of phenyl triflates **1k**, **1l**, **1m**, and **1j** bearing an electron-donating group at the meta position and anilines **2c**−**g** bearing an electron-withdrawing group at the para position gave good results to afford the corresponding carbazoles in yields of 71−95% (entries 5−9). Substitution of aniline by the *o*-methoxycarbonyl group lowered the yield to 52% (entry 10). A trace amount of carbazole **5ec** was obtained by combination of **1e** and **2c** both having an electron-withdrawing group at the para position. The reaction of triflate and aniline both having a *m*-methyl group led to the desired carbazole **5ji** in 43% yield, along with 30% of diarylamine after 30.5 h at 100 °C (entry 12).

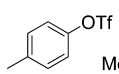
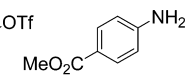
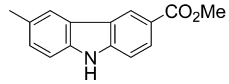
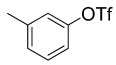
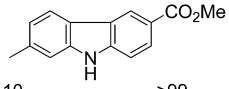
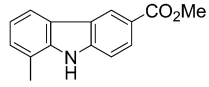
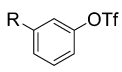
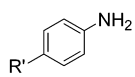
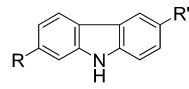
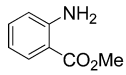
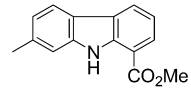
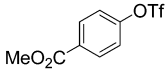
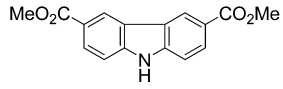
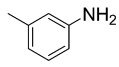
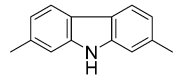
We next explored the one-pot reaction triflate **1j** with aniline **2j**, both having a meta substituent (Scheme 3). In contrast with the reaction using other meta-substituted components such as **1j**−**m**, **2d**, and **2i** leading to single carbazoles by the oxidative coupling at the less hindered position (Tables 1 and 2),

(22) Almost the same results were obtained when the one-pot *N*-arylation−oxidative coupling was performed separately. For example, the stepwise reactions of **1a** and **2c** gave 70% yield of **5ea** in 2 steps (compare with entry 19: 66%). The stepwise and one-pot reaction of **1e** and **2a** also gave comparable results (69% and 64%, respectively, see entry 6).



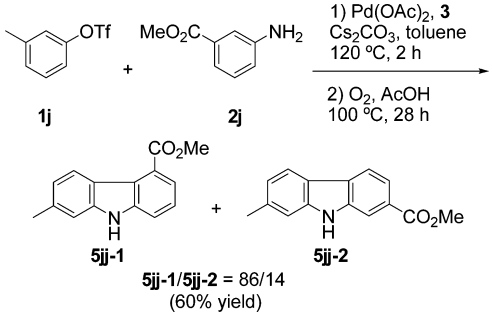
(23) Although the exact reason for the positive effect of an electron-withdrawing group at the para position on the carbazole formation is unclear, the increased acidity of the releasing proton may be one possible explanation.

TABLE 2. Synthesis of Disubstituted Carbazoles[a]

entry	triflate	aniline	temp (°C),[b] time (h)[b]	yield (%)[c]
1	 **1b**	 **2c**	80, 22.5	 **5bc** 78
2	 **1j**	**2c**	100, 10	 **5jc** >99
3			100, 23[d]	93
4	 **1n**	**2c**	120, 23	 **5nc** 56
5	 **1k** (R = OMe)	 **2c**	100, 8	 **5kc** 80
6	**1l** (R = *t*Bu)	**2c**	100, 11	**5lc** 95
7	**1j**	**2e** (R' = COMe)	100, 49	**5je** 78
8	**1j**	**2f** (R' = F)	100, 8	**5jf** 71
9	**1j**	**2g** (R' = CF_3)	100, 5	**5jg** 78
10	**1j**	 **2h**	120, 71	 **5jh** 52[e]
11	 **1e**	**2c**	120, 24	 **5ec** trace[f]
12	**1j**	 **2i**	100, 30.5	 **5ji** 43[g]

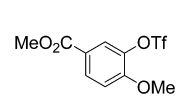
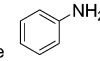
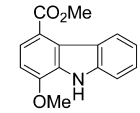
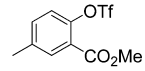
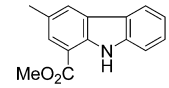
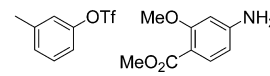
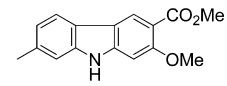
[a] Reaction conditions: triflate **1** (1.0 equiv), aniline **2** (1.1 equiv), $Pd(OAc)_2$ (10 mol %), **3** (15 mol %), Cs_2CO_3 (1.2 equiv), toluene (0.5 M), 100 °C, 1−2 h, then O_2 (1 atm), AcOH (0.125 M). [b] Conditions for oxidative coupling. [c] Isolated yield. [d] Air was used in place of O_2. [e] *N*-Arylation product was obtained in 33% yield. [f] *N*-Arylation product was obtained in 89% yield. [g] *N*-Arylation product was obtained in 30% yield.

SCHEME 3. Regioselectivity on the Reaction of 1j with 2j



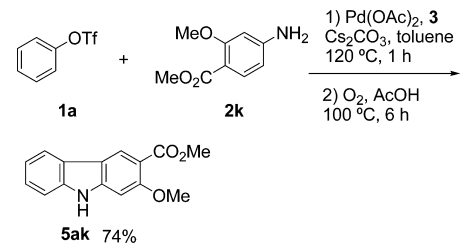
regioisomeric two products **5jj-1** and **5jj-2** (86:14) were obtained in 60% yield. Oxidative coupling proceeded predominantly at the more hindered ortho position of the ester group, whereas at the methylbenzene moiety the less hindered para position of the methyl group reacted exclusively. This can be rationalized by the coordinating effect of the carbonyl oxygen to palladium(II)[24,25] and/or the electronic effect of the ester group, which promotes proton abstraction on the C−H activation step.[7e,5j,26,27]

TABLE 3. Synthesis of Multisubstituted Carbazoles[a]

entry	triflate	aniline	temp (°C),[b] time (h)[b]	yield (%)[c]
1	 **1p**	 **2a**	120, 23	 **5pa** 19
2	 **1q**	**2a**	120, 19	 **5qa** 42
3	 **1j**	**2k**	100, 9	 **5jk** 71

[a] Reaction conditions: triflate **1** (1.0 equiv), aniline **2** (1.1 equiv), $Pd(OAc)_2$ (10 mol %), **3** (15 mol %), Cs_2CO_3 (1.2 equiv), toluene (0.5 M), 100 °C, 1−2 h, then O_2 (1 atm), AcOH (0.125 M). [b] Conditions for oxidative coupling. [c] Isolated yield.

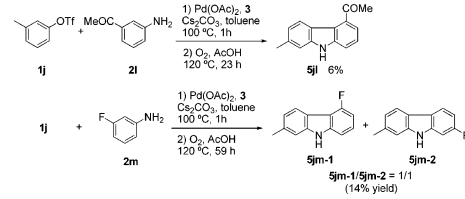
SCHEME 4. One-Pot Synthesis of Clausine L 5ak



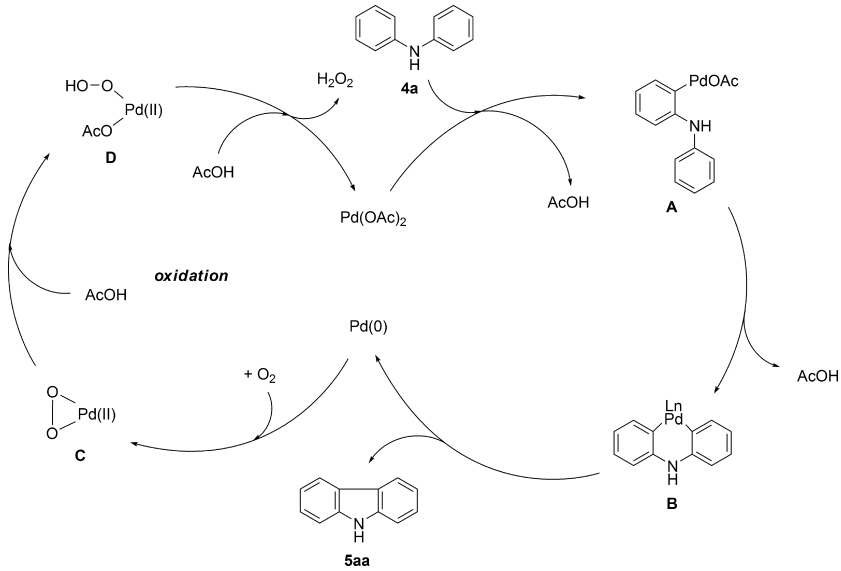
We next investigated the reaction of disubstituted triflates/anilines to synthesize multisubstituted carbazoles (Table 3). The reaction of the disubstituted triflate **1p** having an *o*-methoxy group gave a 2,5-disubstituted carbazole **5pa** in only 19% yield (entry 1), which was in good agreement with the result obtained with the *o*-methylated triflate **1n** (20%; Table 1, entry 16). Reactions using the disubstituted triflate **1q** (entry 2) or

(24) Related coordination effects were also reported in palladium-catalyzed intramolecular C−H activation: (a) Teijido, B.; Fernández, A.; López-Torres, M.; Castro-Juiz, S.; Suárez, A.; Ortigueira, J. M.; Vila, J. M.; Fernández, J. J. *J. Organomet. Chem.* **2000**, *598*, 71–79. (b) Harayama, T.; Kawata, Y.; Nagura, C.; Sato, T.; Miyagoe, T.; Abe, H.; Takeuchi, Y. *Tetrahedron Lett.* **2005**, *46*, 6091–6094. (c) Ueda, S.; Nagasawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 6411–6413.

(25) In the coupling reaction with **1j**, 3-aminoacetophenone **2l** and 3-fluoroaniline **2m** showed similar regioselectivity to **2j**, although the product yields were lower.



SCHEME 5. Possible Catalytic Cycle in Oxidative Coupling



disubstituted aniline **2k** (entry 3) proceeded to afford substituted carbazoles **5qa** and **5jk** in acceptable yields (42% and 71%, respectively). The anti-platelet natural carbazole Clausine L **5ak**[28] was obtained in 74% yield by direct coupling of triflate **1a** and aniline **2k** (Scheme 4).

A catalytic cycle of the oxidative biaryl coupling is shown in Scheme 5. The first C−H activation of diarylamine **4aa**, generated by *N*-arylation of the aniline **1a** with the phenyl triflate **2a**, with palladium(II) would give the *o*-palladation intermediate **A**. The second C−H activation releasing acetic acid gives palladacycle **B**, reductive elimination of which would produce carbazole **5aa** and palladium(0). Aerobic reoxidation of palladium(0) has been reported,[29] with formation a η^2-peroxido palladium(II) species **C**,[30] protonolysis with acetic acid affording palladium(II) hydroperoxide **D**,[31] and ligand exchange with acetate liberating H_2O_2 regenerating catalytically active palladium(II) species.[32−34]

Mechanism of the Oxidative Coupling Step. As shown in Scheme 6, C−H activation in the first step would produce the *o*-palladation intermediate **E** and/or **F** through electrophilic substitution (path A), σ-bond metathesis (path B), or oxidative addition (path C).[5,6,35] The carbopalladation pathway (path G) can also be involved in the second C−H activation,[36] besides paths D−F as presented in *o*-palladation (paths A−C).[37] Two C−H activation steps can proceed in different reaction mechanisms because the electronic and steric nature of palladium(II) in the first and second C−H activation is considerably different. We conducted trapping and deuterium experiments to obtain some mechanistic information of the two palladation steps.

It is known that the reaction of electron-rich arenes with alkenes in the presence of palladium(II) affords vinylarenes through palladation of arenes followed by a Heck-type reaction.[9b,f] Using this chemistry, we expected that the first palladation intermediate of type **E** and/or **F** (Scheme 6) could be trapped by an appropriate alkene to give the Heck-type product bearing the alkenyl group on the more reactive benzene ring. This would help to determine the mechanism of the first palladation. The reaction of diarylamine **4b** with methyl (*Z*)-3-phenylacrylate in the presence of a stoichiometric amount of palladium acetate in acetic acid at 100 °C

(26) García-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, *129*, 6880–6886.

(27) It is likely that this biaryl coupling reaction needs to keep a balance between both electron-donating and -withdrawing groups. Thus, electron-withdrawing groups can (1) facilitate path E (σ-bond methathesis) by increasing the acidity of aromatic C-H protons, (2) decrease nucleophilicity of the aromatic carbon (when meta-substituted ones), and (3) stabilize the arylpalladium complex **B** (Scheme 5) by coordination (when there is an *o*-methoxycarbonyl group), and (4) stabilize the carbazoles. On the other hand, electron-donating groups can (1) decrease the acidity of the aromatic proton to suppress path E (σ-bond methathesis), (2) increase the nucleophilicity of the aromatic carbon, and (3) destabilize the carbazoles. We would like to express our sincere appreciation to the reviewer.

(28) For isolation of clausine L, see: (a) Wu, T.-S.; Huang, S.-C.; Lai, J.-S.; Teng, C.-M.; Ko, F.-N.; Kuoh, C.-S. *Phytochemistry* **1993**, *32*, 449–451. For synthesis of clausine L, see: (b) Forke, R.; Jäger, A.; Knölker, H.-J. *Org. Biomol. Chem.* **2008**, *6*, 2481–2483.

(29) (a) Stahl, S. S.; Thorman, J. L.; Nelson, R. C.; Kozee, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 7188–7189. (b) Ackerman, L. J.; Sadighi, J. P.; Kurtz, D. M.; Labinger, J. A.; Bercaw, J. E. *Organometallics* **2003**, *22*, 3884–3890. (c) Konnick, M. M.; Guzei, I. A.; Stahl, S. S. *J. Am. Chem. Soc.* **2004**, *126*, 10212–10213. (d) Mueller, J. A.; Goller, C. P.; Sigman, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9724–9734. (e) Rogers, M. M.; Wendlandt, J. E.; Guzei, I. A.; Stahl, S. S. *Org. Lett.* **2006**, *8*, 2257–2260. (f) Gligorich, K. M.; Cummings, S. A.; Sigman, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 14193–14195. (g) Iwai, Y.; Gligorich, K. M.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2008**, *47*, 3219–3222. For reviews, see: (h) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400–3420. (i) Gligorich, K. M.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2006**, *45*, 6612–6615.

(30) For related η^2-peroxido palladium(II) intermediates, see: Wilke, G.; Schott, H.; Heimbach, P. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 92–93.

(31) (a) Muto, S.; Ogata, H.; Kamiya, Y. *Chem. Lett.* **1975**, *4*, 809–812. (b) Muto, S.; Kamiya, Y. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 2587–2589.

(32) Palladium(II) hydride pathway cannot be ruled out (insertion of O_2 into H-Pd-X followed by protonation of the resulting HOO-Pd-X with acetic acid releasing H_2O_2), see: (a) Takehira, K.; Hayakawa, T.; Orita, H.; Shimizu, M. *J. Mol. Catal.* **1989**, *53*, 15–21. (b) Hosokawa, T.; Murahashi, S. *Acc. Chem. Res.* **1990**, *23*, 49–54. (c) Hosokawa, T.; Nakahira, T.; Takano, M.; Murahashi, S. *J. Mol. Catal.* **1992**, *74*, 489–498. (d) Nishimura, T.; Onoue, T.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1999**, *64*, 6750–6755. See also, refs 29h and 29i.

(33) For related palladium-catalyzed aerobic oxidation, see: (a) Dams, M.; De Vos, D. E.; Celen, S.; Jacobs, P. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3512–3515. (b) Stoltz, B. M. *Chem. Lett.* **2004**, *33*, 362–367.

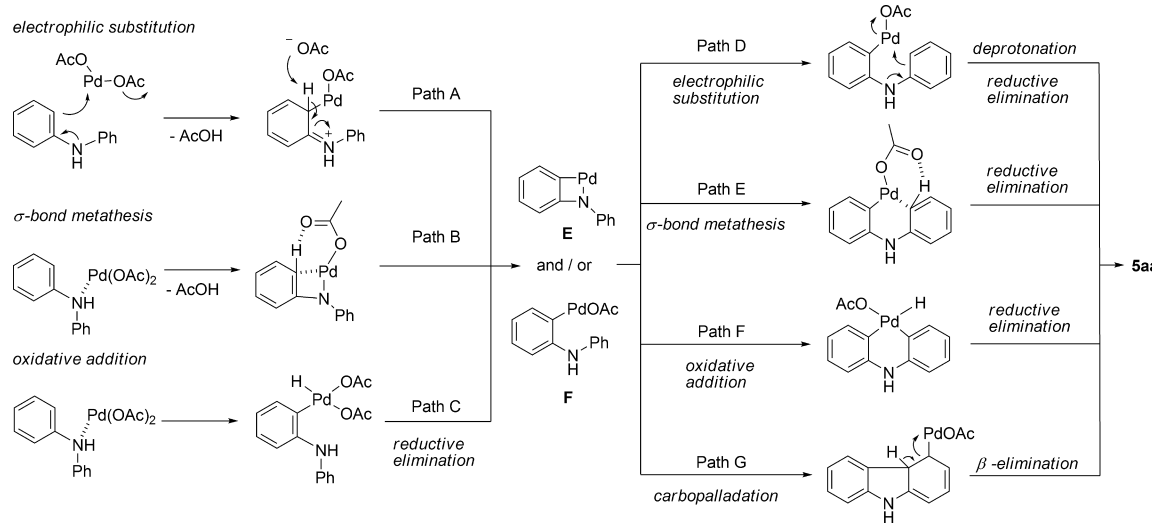
(34) Alternative Pd(II)/Pd(IV) catalytic cycle requires stronger oxidants than oxygen, such as $PhI(OAc)_2$ and oxone, see: Desai, L. V.; Sanford, M. S. *Angew. Chem., Int. Ed* **2007**, *46*, 5737–5740. See also, refs 11f and 12e.

(35) Ryabov, A. D. *Chem. Rev.* **1990**, *90*, 403–424, See also, refs **5a**, **5c**, **5e**, and **6b**.

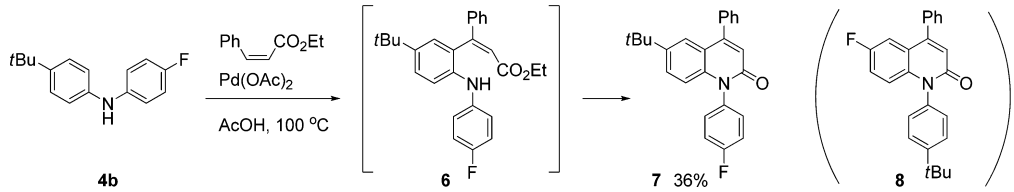
(36) The carbopalladation intermediate would have the wrong stereochemistry for the well-accepted *syn*-elimination of H-Pd-OAc. However, a stereomutation of the benzylic proton or *anti*-elimination cannot be completely ruled out, see: (a) Grigg, R.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S.; Worakun, T. *Tetrahedron* **1990**, *46*, 4003–4018. (b) McClure, M. S.; Glover, B.; McSorley, E.; Millar, A.; Osterhout, M. H.; Roschangar, F. *Org. Lett.* **2001**, *3*, 1677–1680.

(37) (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238. (b) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848–10849. (c) Pascual, S.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *Tetrahedron* **2008**, *64*, 6021–6029.

SCHEME 6. Possible Reaction Mechanism of Oxidative Coupling



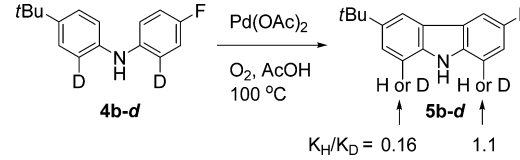
SCHEME 7. Scavenging of Intermediate by the Oxidative Heck Reaction



provided the lactam **7** in 36% yield, formed by *o*-alkenylation at the arene bearing a *tert*-butyl group followed by lactam formation (Scheme 7).[38] The regioisomeric lactam **8** (*o*-alkenylation product at the fluorobenzene) as well as the carbazole were not observed. The yield of the lactam **7** was insufficient, but this result suggests that the first C−H activation predominantly proceeds at the electron-rich arene rather than electron-deficient fluorobenzene moiety.[39,40] Because the electron-rich aromatic carbon readily undergoes carbazole formation (Figure 1), the first C−H activation would probably proceed by the electrophilic mechanism (Scheme 6, path A). This is in good agreement with the electronic state of palladium species: palladium(II) acetate is electronically more deficient than the arylpalladium acetate **A** that would be the active species in the second C−H activation (Scheme 5).

We investigated the kinetic isotope effect (KIE) of the oxidative biaryl coupling using diarylamine **4b-*d***[41] having a deuterium at the ortho position of the amino group in each arene (Scheme 8). In the oxidative coupling of the diarylamine **4b-*d***, values of $K_H/K_D = 0.16$ (*tert*-butylbenzene side) and $K_H/K_D = 1.1$ (fluorobenzene side) were observed. These results indicate that the deuterium atom on the fluorobenzene would not be involved in the rate-determining step. Because the fluorobenzene would participate in the second C−H activation step as described above (Scheme 7), σ-bond metathesis (path E) and oxidative addition (path F), which both require participation of the *o*-deuterium/hydrogen in the transition state, would be less important pathways in the second C−H activation. Considering that diarylamine derived from the 3-methyphenyl triflate **1j** and 3-methylaniline **2i** showed low reactivity toward oxidative coupling to give the carbazole **5ji** (43%) and the diarylamine (30%) (Table 2, entry 12), involvement of electrophilic substitution (Path D) in the second C−H activation is unlikely. The results presented here can be explained by path A (electrophilic substitution) in the first palladation and path G (carbopalladation) in the second palladation, but participation of other pathways cannot be completely excluded.

SCHEME 8. Investigation of KIE



Conclusions

We developed an efficient method for construction of various functionalized carbazoles by one-pot *N*-arylation−oxidative biaryl coupling from readily available anilines and phenyl triflates. Oxidative C−H activation is remarkably influenced by substituents on the aromatic rings. Important information for understanding the mechanism of palladium(II)-catalyzed oxidative biaryl coupling was provided by conducting *o*-olefination and deuterium experiments.

(38) The structure of **7** was confirmed by comparison of its spectral data with the authentic sample prepared by a separete route, see the Supporting Information.

(39) The possibility that 3-phenylacrylate present in the reaction mixture might affect the reactivity of the palladium catalyst cannot be ruled out.

(40) The first palladation at the fluorobenzene moiety followed by 1,4-palladium shift might be possible. However, the palladium shift process would produce a regioisomeric mixture, see: (a) Campo, M. A.; Zhang, H.; Yao, T.; Ibdah, A.; McCulla, R. D.; Huang, Q.; Zhao, J.; Jenks, W. S.; Larock, R. C. *J. Am. Chem. Soc.* **2007**, *129*, 6298–6307. See also: (b) Mota, A. J.; Dedieu, A.; Bour, C.; Suffert, J. *J. Am. Chem. Soc.* **2005**, *127*, 7171–7182.

(41) For synthesis of **4b-*d***, see the Supporting Information.

Experimental Section

General Procedure for the Synthesis of Carbazoles (Table 2, Entry 1). Toluene (0.4 mL) was added to a flask containing 4-methylphenyl triflate (**1b**) (48.0 mg, 0.20 mmol), 4-(methoxycarbonyl)aniline (**2c**) (33.3 mg, 0.22 mmol), $Pd(OAc)_2$ (4.49 mg, 10 mol %), ligand **3** (14.3 mg, 15 mol %), and Cs_2CO_3 (84.7 mg, 0.24 mmol) under an argon atmosphere. The mixture was stirred at 100 °C for 1.5 h, then stirred at room temperature for 5 min. AcOH (1.6 mL) was added to the mixture and an oxygen balloon connected to the reaction vessel. The reaction mixture was stirred at 80 °C for 22.5 h. After cooling, the reaction mixture was diluted with ethyl acetate, washed with saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo. Crude material was purified by flash chromatography with hexane/ethyl acetate (15:1) to afford the desired carbazole **5bc** (37.4 mg, 78% yield).

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Supporting Information Available: Characterization data for all novel compounds, as well as NMR spectra for all the carbazoles synthesized. This material is available free of charge via the Internet at http://pubs.acs.org.

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