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One-pot synthesis of carbazoles by palladium-catalyzed *N*-arylation and oxidative coupling†

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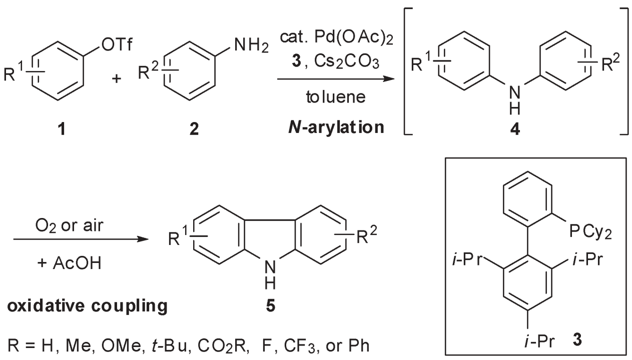
One-pot *N*-arylation and oxidative coupling can be promoted by a common palladium catalyst in the presence of appropriate additives: palladium-catalyzed *N*-arylation of anilines with aryl triflates under the standard conditions followed by addition of acetic acid under oxygen or air atmosphere afforded various types of functionalized carbazoles in good to excellent yields.

Palladium-catalyzed C–H activation of an aromatic group using aryl halides or triflates has received considerable attention in recent years, due to the wide-ranging need for the construction of fused aromatic ring systems using nonfunctionalized aryl groups.[1–3] A palladium(II)-mediated oxidative biaryl coupling reaction that activates two C–H bonds is more attractive in that a carbon–carbon bond can be directly formed from two nonfunctionalized aromatic carbon atoms with high atom economy. Formation of heterocycles through this type of intramolecular dehydrogenative coupling was first reported by Yoshimoto *et al.*[4] and Åkermark *et al.*,[5] by use of a stoichiometric amount of palladium(II) acetate.[6,7] Recent contributions to the catalytic version of this reaction in the presence of an appropriate co-oxidant such as cupric acetate,[8] *tert*-butyl hydroperoxide,[9] catalytic $Sn(OAc)_2$–oxygen,[10] or oxygen[10] significantly improved the potential synthetic utility of this type of transformation, although some catalytic reactions suffer from low yields.

We envisioned that one-pot Buchwald–Hartwig *N*-arylation[11,12] and oxidative biaryl coupling reaction in the presence of a common palladium catalyst[13] would serve as an attractive synthetic route to highly-functionalized carbazoles, which constitute an important class of compounds that exist in many biologically-active natural products.[14,15] Although a related carbazole synthesis by the reaction of haloanilines and halobenzenes through sequential palladium-catalyzed *N*-arylation and aromatic C–H activation has already been reported,[16] there are no precedents for a direct carbazole synthesis *via* oxidative biaryl coupling reaction that activates two C–H bonds. Herein we present the first direct construction of carbazoles **5** by coupling of readily available aryl triflates **1** and anilines **2**, through one-pot palladium-catalyzed *N*-arylation and oxidative coupling in the presence of molecular oxygen or air (Scheme 1).

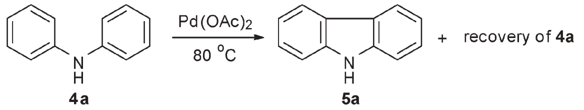


Scheme 1 Direct synthesis of carbazoles by one-pot *N*-arylation and oxidative coupling.

We first optimized reaction conditions in the oxidative coupling step (Table 1). In good accordance with Åkermark's observation,[10] oxygen proved to be effective to give **5a** in 91% yield (entry 1). We found that air, one of the ideal oxidants in practical use, appropriately promotes the coupling reaction, giving rise to a comparable result (90% yield, entry 2). By lowering the catalyst loading from 10 mol% to 5 mol%, the yield of the desired carbazole was slightly decreased (85%; see ESI†). Although the palladium-catalyzed *N*-arylation generally requires less polar solvents, solvents such as toluene were found to be ineffective for the oxidative carbazole formation (entry 3). In view of the addition of acetic acid to the reaction mixture after *N*-arylation, we investigated the carbazole formation in a mixed solvent including toluene and found that toluene–acetic acid (1 : 4) works well for this transformation under either oxygen or air (entries 5 and 6).

Based on the results of the oxidative coupling, we next investigated the one-pot carbazole formation, through Buchwald–Hartwig *N*-arylation[11,12] and oxidative coupling reaction, using

Table 1 Optimization of reaction conditions[a]



Entry	Oxidant (1 atm)	Solvent (0.1 M)	Time (h)	Yield (%)[b] 5a	4a
1	O_2	AcOH	24	91	—
2	Air	AcOH	24	90	—
3	O_2	toluene	24	15	62
4	O_2	toluene–AcOH (1 : 1)	24	12	84
5	O_2	toluene–AcOH (1 : 4)	36	80	—
6	Air	toluene–AcOH (1 : 4)	36	64	—

[a] Reactions carried out with 10 mol% of $Pd(OAc)_2$. [b] HPLC yield (absolute calibration curve method).

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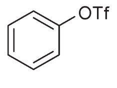
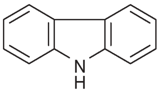
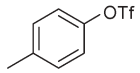
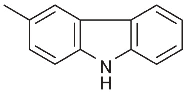
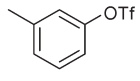
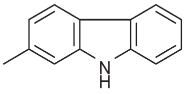
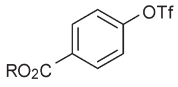
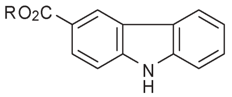
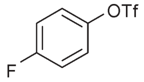
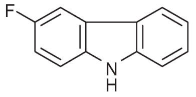
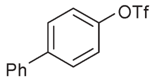
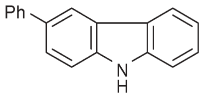
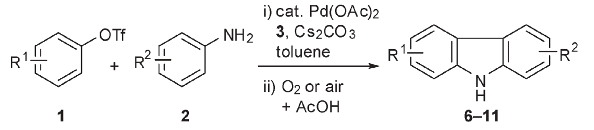
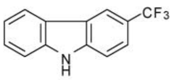
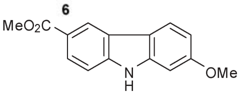
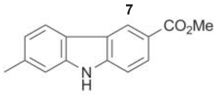
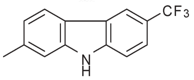
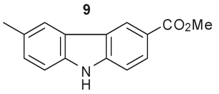
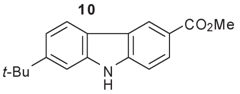
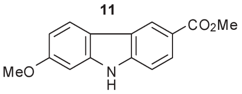
Table 2 Reaction of aryl triflates with aniline[a]

Entry	Triflate	T (°C)	Time (h)	Product	Yield (%)[b]
1	 **1a**	100[c]	10	 **5a**	69
2[d]		100	18		67
3	 **1b**	100	8	 **5b**	46
4	 **1c**	100	7.5	 **5c**	62
5[d]		100	24		82[e]
6	 **1d** (R = Me) **1e** (R = Bn)	120	30	 **5d** (R = Me) **5e** (R = Bn)	64[f]
7		120	8		63
8	 **1f**	100	38	 **5f**	57
9	 **1g**	120	10	 **5g**	65

[a] Reaction conditions: aryl triflate **1** (1.0 equiv.), aniline **2a** (1.1 equiv.), $Pd(OAc)_2$ (10 mol%), **3** (15 mol%), Cs_2CO_3 (1.2 equiv.), toluene (0.5 M), 100 °C, then O_2 (1 atm), AcOH (0.125 M). [b] Yields of isolated products. [c] When the reaction was performed at 80 °C, **5a** and **4a** were obtained in 55% and 15% yields, respectively. [d] Air was used in place of O_2. [e] Average isolated yield from two experiments. [f] *N*-arylation product, methyl 4-(phenylamino)benzoate, was obtained in 28% yield.

Table 3 Reaction of aryl triflates with substituted anilines[a]



Entry	Triflate (R^1)	Aniline (R^2)	T (°C)	Time (h)	Product	Yield (%)[b]
1	**1a** (H)	**2b** (4-CF_3)	100	6	 **6**	72[c]
2	**1d** (4-CO_2Me)	**2c** (3-OMe)	100	17	 **7**	68
3	**1c** (3-Me)	**2d** (4-CO_2Me)	100	11	 **8**	>99
4[d]			100	24		93
5	**1c** (3-Me)	**2b** (4-CF_3)	100	6	 **9**	78
6	**1b** (4-Me)	**2d** (4-CO_2Me)	80	24	 **10**	78
7	**1h** (3-*t*-Bu)	**2d** (4-CO_2Me)	100	12	 **11**	95
8[d]			100	24		88
9	**1i** (3-OMe)	**2d** (4-CO_2Me)	100	9	 **7**	80

[a] Reaction conditions: aryl 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, then O_2 (1 atm), AcOH (0.125 M). [b] Yields of isolated products. [c] *N*-arylation product, *N*-(4-trifluoromethylphenyl)aniline was obtained in 23% yield. [d] Air was used in place of O_2.

various aryl triflates **1a–g** and aniline **2a**. The results are summarized in Table 2. Typically, *N*-arylation of aniline **2a** with an aryl triflate **1a** was conducted in toluene by use of the standard procedure using palladium acetate (10 mol%) and phosphine ligand **3** (15 mol%).[17] After completion of the *N*-arylation determined by TLC, acetic acid was added and an oxygen balloon was connected to the reaction flask (oxygen conditions) or subjected to air by an open system (air conditions). As we expected, the one-pot reaction of phenyl triflate **1a** with aniline **2a** using the oxygen conditions gave the desired carbazole **5a** in 69% yield (entry 1). Moreover, under the air conditions, **5a** was obtained in 67% yield, although a slightly longer reaction time was required (entry 2). 3-Methylated triflate **1c** (entry 4) was more reactive than the 4-substituted one **1b** (entry 3) to afford carbazole **5c** regioselectively under the oxygen conditions. Of note, the reaction of **1c** under the air conditions furnished an even better yield in a prolonged reaction time (82%, entry 5) than that under the oxygen conditions (62%, entry 4). Triflates **1d–g** bearing an electron-withdrawing substituent also gave moderate yields of 3-substituted carbazoles **5d–g** (entries 6–9). It should be clearly noted that the use of aryl halides interfered with the oxidative coupling by concomitantly generating halide anion in *N*-arylation, as described by Åkermark and co-workers.[10a,18]

The one-pot reaction of various aryl triflates with substituted anilines was then investigated (Table 3). The reaction of phenyl triflate **1a** with electron-deficient 4-(trifluoromethyl)aniline **2b** (entry 1) gave a comparable result to that obtained by the reaction of electron-deficient triflates **1d–g** with aniline **2a** (Table 2, entries 6–9). The reaction of electron-deficient triflate **1d** with electron-rich aniline **2c** gave the desired carbazole **7** in 68% yield (entry 2). The combination of 3-methylated triflate **1c** with 4-(methoxycarbonyl)aniline **2d** gave the desired carbazole **8** in quantitative yield (entry 3). Similarly, good results were obtained using electron-rich triflates and electron-deficient anilines (entries 4–9). It was proven that the desired carbazoles can be obtained in high yields by the reaction of aryl triflates substituted by an electron-donating group at the 3-position such as **1c**, **1h** or **1i**, especially with anilines substituted by an electron-withdrawing group such as **2b** and **2d** (entries 3, 5, 7, and 9). Also in these reactions, air oxidation appropriately promoted the desired coupling reaction (entries 4 and 8). It is noteworthy that, although 3-substituted aryl triflates could give two regioisomers, the C–H activation exclusively proceeded at the sterically less-hindered aromatic carbon of the triflate to afford carbazoles as the single isomer. In many cases, *N*-arylation proceeded almost quantitatively, so the yield of carbazoles was mainly dependent on the reactivity of the resulting diarylamines in the C–H activation step.

In conclusion, we have developed an efficient atom-economic synthetic route from aryl triflates and anilines to functionalized carbazoles in a one-flask reaction. This study first demonstrated that a common palladium catalyst with different additives promotes sequential *N*-arylation and oxidative C–H activation, besides careful examination of interesting substituent effects on the reactivity. Application of this method to the total synthesis of biologically-active natural products and an investigation of the reaction mechanism of C–H activation are now in progress.

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