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A Direct Palladium-Catalyzed Route to Selectively Substituted Carbazoles through Sequential C–C and C–N Bond Formation: Synthesis of Carbazomycin A

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Abstract: The present paper offers a synthetically simple one-pot procedure for the catalytic preparation of the biologically interesting class of carbazoles. The new procedure is based on the combined catalysis of palladium and norbornene starting from *o*-substituted iodoarenes and *N*-sulfonylated or *N*-acetylated *o*-bromoanilines. A well-known member of this class, carbazomycin A, has been successfully prepared.

Keywords: carbazoles; catalysis; C–H activation; norbornene; palladium

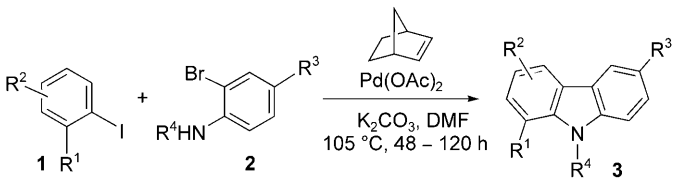
Carbazoles are interesting structures present in a wide variety of pharmaceuticals and natural products with useful biological activities.[1] Carbazole derivatives also find applications as organic materials.[2]

We describe here a one-pot catalytic procedure and its application to the synthesis of antibiotic carbazomycin A.[3]

Recently reported methods to prepare these compounds are based on the *N*-arylation of aniline derivatives[4] followed by ring closure through either C–H activation *via* metallacycles[5] or oxidative biaryl coupling[6] in the presence of a Pd catalyst. Buchwald et al. reported a different approach based on the ability of 2-acetaminobiphenyl and Pd to achieve sequential C–H activation and intramolecular C–N bond formation.[7] A significant alternative to these strategies is offered by the combination of intermolecular aryl-aryl with intramolecular *N*-aryl coupling.[8] With this in mind we wondered whether our Pd-catalyzed cross-coupling method of *o*-substituted aryl iodides with aryl bromides[9] could be utilized for the synthesis of selectively substituted carbazoles in the presence of a suitably placed amino group.

Our experiments were unsuccessful, however, until we discovered that use of the benzenesulfonyl or tosyl-substituted amino group allowed us to carry out an efficient ring closure to carbazole. The reaction gave 1-substituted carbazoles in good to excellent yields (Table 1).

Table 1. Synthesis of carbazoles.[a]



Entry	R^1, R^2	R^3	R^4	Time [h]	**3** Yield [%][b]
1	Me, H	H	Ts	48	**3a**, 93
2	Me, 4-Me	H	Ts	60	**3b**, 91
3[c]	Me, 4-OMe + 3-Me	H	Ts	120	**3c**, 98
4	Et, H	H	Ts	48	**3d**, 94
5	*i*-Pr, H	H	Ts	65	**3e**, 82
6	-$(CH)_4$-	H	Ts	72	**3f**, 87
7	Me, H	Me	Ts	72	**3g**, 94
8	Me, H	Cl	Ts	48	**3h**, 90
9	Me, H	H	SO_2Ph	96	**3i**, 92

[a] *Reaction conditions:* aryl iodide (1.1 equiv.), aryl bromide (1.0 equiv.), norbornene (0.25 equiv.), $Pd(OAc)_2$ (5 mol%), K_2CO_3 (2.2 equiv.) in DMF at 105 °C under N_2 for the time needed for Pd black precipitation; $0.2 \cdot 10^{-2}$ mmol $Pd(OAc)_2$/mL DMF.

[b] Isolated yield based on the charged amount of aryl bromides. Conversion of aryl iodides is over 99% and that of aryl bromides ranges from 87 to 99%.

[c] 0.5 equiv. of norbornene.

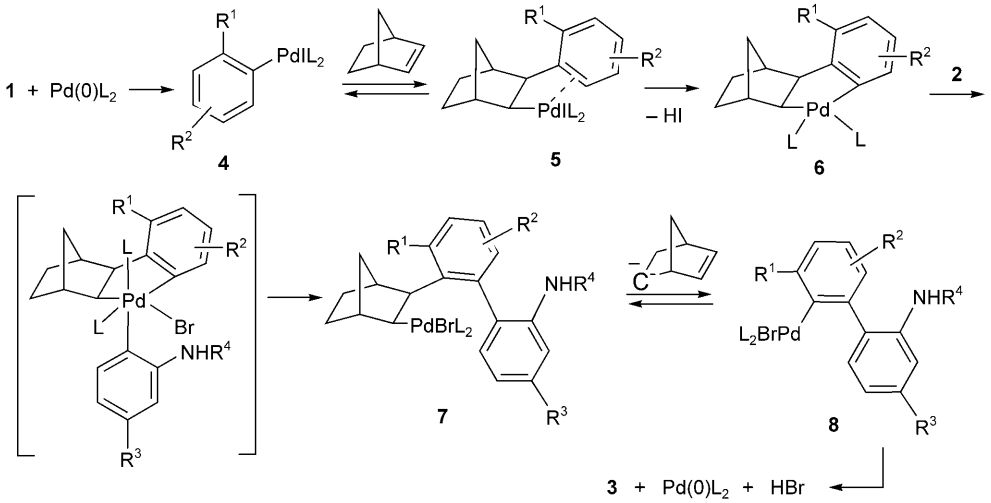
Aryl iodides bearing either a single *o*-methyl group or an additional one in the *para* position (entries 1 and 2) reacted with *o*-bromo-*N*-tosylaniline to afford the desired carbazoles **3a** and **3b** in excellent yields. An even better result was attained using 2,3-dimethyl-4-methoxyiodobenzene with the same *o*-bromo-*N*-tosylaniline, the corresponding carbazole **3c** being isolated in 98% yield. It is worth noting that compound **3c** is the sulfonylated 4-deoxycarbazomycin B, a degradation product of the natural alkaloid carbazomycin B.[1] Replacing the *o*-methyl group with an ethyl or an isopropyl one led to compounds **3d** and **3e** in 94 and 82% yields, respectively (entries 4 and 5). 1-Iodonaphthalene behaved well and gave compound **3f** in 87% yield (entry 6). When *o*-iodotoluene was allowed to react with *o*-bromo-*N*-tosylaniline, containing either a *p*-methyl or *p*-chloro substituent, the expected carbazoles **3g** and **3h** were isolated in 94 and 90% yields, respectively (entries 7 and 8). *o*-Bromo-*N*-benzenesulfonylaniline in place of *o*-bromo-*N*-tosylaniline coupled with *o*-iodotoluene to give compound **3i** in 92% yield (entry 9). Under the standard conditions the reaction did not proceed in the absence of norbornene and no carbazole was obtained, thus confirming that, according to the reaction pathway proposed in Scheme 1, C–C bond formation takes place before formation of the C–N bond.

The key intermediate palladacycle **6** is formed by oxidative addition of the aryl iodide to Pd(0)[10] followed by stereoselective insertion of norbornene to give the *cis,exo*-arylnorbornylpalladium complex **5**.[11] This species undergoes ring closure to metallacycle **6**[12] by electrophilic aromatic substitution involving C–H activation.[13] *o*-Bromo-*N*-tosylaniline **2** then reacts with **6**, likely through the Pd(IV) species shown in brackets,[14] to afford **7**, which results from selective attack of the aryl group of **2** onto the aromatic site of palladacycle **6**. At this point, owing to the steric effect exerted by the two *ortho* substituents, norbornene is expelled, thus becoming available for a new catalytic cycle, and the biphenylylpalladium intermediate **8** is formed, where the amido group (NHR^4) is in an appropriate position for an intramolecular amidation reaction leading to compound **3** and Pd(0).

It is worth noting that the aryl bromide **2** wins the competition with the aryl iodide **1** for reaction with palladacycle **6**. This preference may be due to a chelation effect.

The amount of norbornene is crucial for the success of the reaction since a high concentration favors its insertion but at the same time prevents its deinsertion. We were pleased to find that, contrary to what is usually observed for other Pd/norbornene-catalyzed coupling reactions,[15] the yield of carbazoles **3** improved on decreasing the amount of norbornene, good results being obtained even with 0.10 equiv. The reaction became slower, however, and longer reaction times were required (120 h to obtain compound **3a** in 88% yield).

Certain substituted substrates were found to be rather reluctant to undergo the reaction and the addition of triphenylphosphine (TPP) was needed to obtain acceptable results (Table 2). Thus *o*-trifluoromethyliodobenzene ($R^1 = CF_3$) and *o*-bromo-*N*-tosylaniline (Table 2, entry 1) reacted at 120 °C in the presence of TPP to give **3j** in 65% yield together with 10% of the corresponding deprotected carbazole **3k**, desulfonylation occurring under the reaction conditions.[16] Analogously *o*-bromo-*p*-nitro-*N*-tosylaniline ($R^3 = NO_2$) reacted with *o*-iodotoluene under similar conditions giving the deprotected carbazole **3l** in 58% yield (entry 2). Apparently the *p*-nitro group negatively affects the reactivity of the amido group towards ring closure. TPP (with 1 equiv. of norbornene) was also required when the acetamide ($R^4 = Ac$) was used in place of the sulfonamide, leading to the de-



Scheme 1. Proposed reaction pathway.

Table 2. Synthesis of carbazoles requiring the addition of TPP.[a]

Entry	R^1, R^2	R^3	R^4	Time [h]	**3** Yield [%][b]
1	CF_3, H	H	Ts	65	**3j**, 65 **3k** (R^4 = H), 10
2	Me, H	NO_2	Ts	59	**3l** (R^4 = H), 58
3	Me, H	H	Ac	48	**3m** (R^4 = H), 67
4	2,5-Me	H	Ac	48	**3n** (R^4 = H), 50

[a] *Reaction conditions:* aryl iodide (1.1 equiv.), aryl bromide (1.0 equiv.), norbornene (0.25 equiv. in entries 1 and 2; 1 equiv. in entries 3 and 4), $Pd(OAc)_2$ (5 mol%), TPP (10 mol%), K_2CO_3 (2.2 equiv.) in DMF at 120 (entries 1 and 2) and 105 °C (entries 3 and 4) under N_2 for the time needed for Pd black precipitation; $0.2 \cdot 10^{-2}$ mmol Pd-$(OAc)_2$/mL DMF.

[b] Isolated yield on the charged amount of aryl bromides. Conversion of aryl iodides and bromides is over 99% and 95%, respectively.

protected carbazole **3m** in 67% yield (entry 3). On the other side, the acetamide was needed with a 5-substituted iodide such as 2,5-dimethyliodobenzene (entry 4), which gave no reaction with the sulfonamide. Carbazole **3n** was obtained in modest yield, however. The coupling reaction between palladacycle **6** and the sulfonylated bromoaniline **2** (Scheme 1) would indeed be sterically more difficult in the presence of an R^2 substituent (coming from a 5-substituted aryl iodide) *ortho* to the Pd–C bond of the palladacycle.

Using TPP we could thus make possible the ring closure to carbazole for some substrates which were hardly or poorly reactive under the general conditions we had previously established.

Aryl iodides bearing functional groups such as the methoxy, amino, mono- and dimethylamino and the hydroxy ones in the *ortho* position inhibited the formation of compound **3.**

All these observations turned out to be quite useful for working out an efficient synthesis of the biologically important antibiotic carbazomycin A[1,3] (**11**, Scheme 2). In agreement with what is observed for the 5-substituted aryl iodides, compound **9** hardly coupled with *o*-bromo-*N*-tosylaniline in the presence of $Pd(OAc)_2$/TPP at 120 °C but reacted with *o*-bromo-*N*-acetylaniline even at 105 °C in the presence of the same catalyst to give **11** in a satisfactory 70% yield, the substitution effect being more favorable than with two Me groups only in 2 and 5 positions (Table 2, entry 4).

To the best of our knowledge this compound has never been obtained by means of Pd catalysis, the method of choice involving the use of the cyclohexadienyliron tricarbonyl cation.[3e]

In conclusion, we have described a new Pd- and norbornene-catalyzed sequential synthesis of 1-substituted carbazoles by C–C and C–N cross coupling starting from simple and readily available aryl halides. Beside the mechanistic interest the present procedure offers a valid complementary alternative to the previously reported methods. The straightforward and efficient synthesis of carbazomycin A further adds to the potentiality of the method.

Experimental Section

General Procedure for the Reaction of an *ortho*-Substituted Aryl Iodide and an *ortho*-Bromo-*N*-arylsulfonyl- or acetylaniline

A Schlenk-type flask, equipped with a magnetic stirring bar, was charged with $Pd(OAc)_2$ (5 mg, 0.022 mmol), norbornene (10 mg, 0.11 mmol), the desired aryl iodide and bromide (0.48 and 0.44 mmol, respectively) in DMF (10 mL) and K_2CO_3 (138 mg, 1.0 mmol). The reaction mixture was stirred at 105–120 °C for the time needed for Pd black precipitation. When needed TPP (11.5 mg, 0.044) was added. After cooling to room temperature, the organic layer was diluted with EtOAc (30 mL) and extracted three times with a solution of NaCl (25 mL). The organic layer was dried over Na_2SO_4, the solvent was removed under reduced pressure and the resulting residue was purified by flash chromatography on silica gel using mixtures of hexane-EtOAc as eluent (97:3 for sulfonylated carbazoles, 95:5 for unprotected carbazoles **3k**, **3m**, **3n** and 80:20 for **3l**).

Acknowledgements

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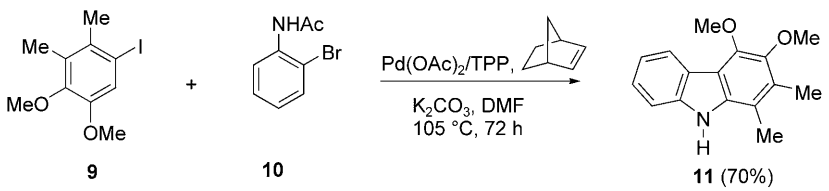

Scheme 2. Synthesis of carbazomycin A.

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