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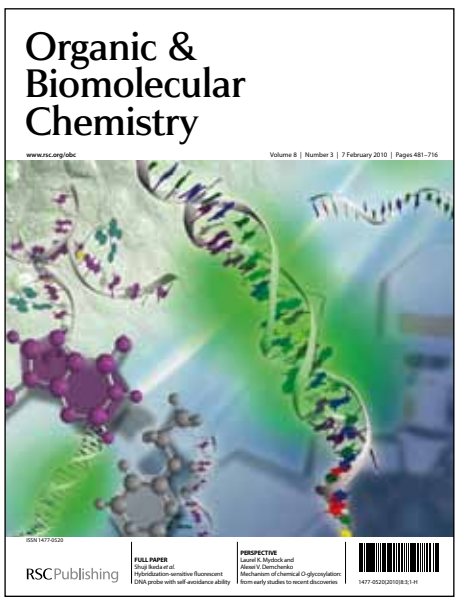

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Dibenzo[*a,c*]carbazoles from 2-(2-bromoaryl)-3-arylindoles via a palladium-catalyzed intramolecular C-H functionalization/C-C bond formation process

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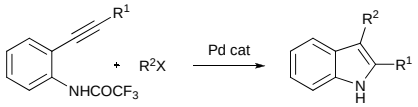
The palladium-catalyzed cyclization of 2-(2-bromoaryl)-3-arylindoles provides a new versatile approach to dibenzo[*a,c*]carbazoles. The reaction tolerates a variety of useful substituents including chloro, nitro, ether, cyano, keto, and ester groups.

The palladium-catalyzed reaction of alkynyltrifluoroacetanilides with organopalladium intermediates generated in situ from palladium(0) species and (hetero)aryl and vinylic halides or triflates, alkyl halides, alkynyl halides, and allylic esters has been proved to be a powerful and versatile tool for the construction of the substituted indole ring (Scheme 1).[1]



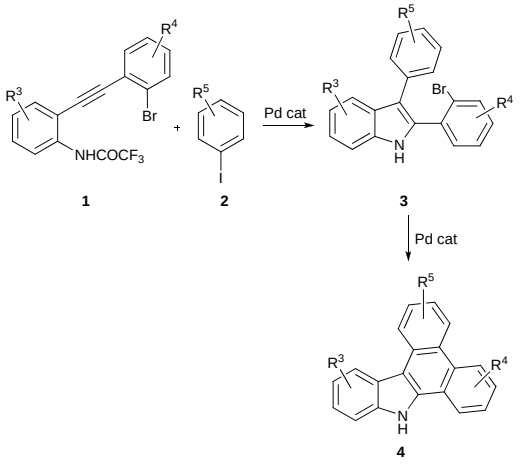
R^1 = H, alkyl, alkenyl, (hetero)aryl
R^2 = (hetero)aryl and alkentyl halide or triflate, alkyl halide, allylic ester

Scheme 1. Palladium-catalyzed synthesis of indoles from trifluoroacetanilides.

As part of our ongoing studies in this area, we hypothesized that in the presence of appropriate functional groups this indole synthesis might be exploited to provide a new ready access to condensed carbazoles. In particular, 2-[(2-bromoaryl)ethynyl]trifluoroacetanilides **1** were selected as suitable substrates for the construction of the dibenzo[*a,c*]carbazole ring through a process based on an aminopalladation/reductive elimination reaction followed by an intramolecular C-H functionalization/C-C bond formation step (Scheme 2).

The stimulus for this study has been provided by the growing importance of condensed (hetero)aromatic rings in organic material science[2] and by their biological acitivity.[3] In this context, carbazole derivatives are particularly attractive.[4] For example, bisindolecarbazoles exhibit blue emission[5] and dibenzocarbazole derivatives show photorefractivity properties.[6] The pyridocarbazole ring has been proposed as an appropriate skeleton to design DNA intercalating drugs[7] and indolo,pyrrolocarbazoles have been shown to possess CDK inhibitory properties.[8] In addition, combining our indole synthesis with a cyclization based on a C-H functionalization/C-C bond formation reaction appeared particularly attractive to us. Indeed, direct transition metal-catalyzed functionalization of (hetero)arenes via the activation of inert C-H bonds has attracted a great deal of attention in recent years.[9] Intensive investigations in this area have shown the great potential of this chemistry as an extremely convenient alternative to classical cross-coupling reactions based on preactivated (hetero)arenes.

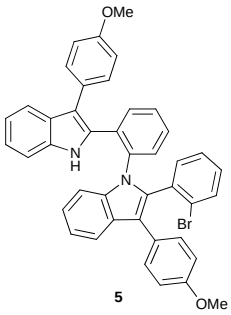
Herein we report the results of this study.



Scheme 2. Synthesis dibenzo[*a,c*]carbazoles from 2-[(2-bromoaryl)ethynyl]trifluoroacetanilides.

2-[(2-Bromoaryl)ethynyl]trifluoroacetanilides **1** were prepared by reacting 2-ethynylanilines[10] with 1-bromo-2-iodoarenes or 2-bromoarylacetylenes with 2-iodoanilines [$PdCl_2(PPh_3)_2$, CuI, $(i\text{-Pr})_2NH$, DMF, 0 °C to rt] and, subsequently, the resultant cross-coupling products with trifluoroacetic anhydride. Compounds **1** were then converted into 2,3-diarylindoles **3** upon treatment with aryl iodides in the presence of $Pd(PPh_3)_4$ and Cs_2CO_3 in MeCN at 80 °C.

Initial attempts to cyclize 2-[(2-bromoaryl)ethynyl]trifluoroacetanilides **1** to the corresponding carbazole derivatives **4** examined the reaction of **3a** (R^3 = R^4 = H; R^5 = 4-MeO) using $Pd(OAc)_2$ as the source of Pd(0) species. Unfortunately, disappointing results were obtained with a variety of ligands [PPh_3 , dppe, P(*t*-Bu)$_3$, the latter prepared in situ from $HP(Bu\text{-}t)_3BF_4$[11]], bases (K_2CO_3, K_2CO_3/MgO, CsOAc), solvents (DMF, toluene), and reaction temperatures (80-120 °C). Formation of only traces of the desired carbazole was observed in several cases along with the N-arylation byproduct **5**.

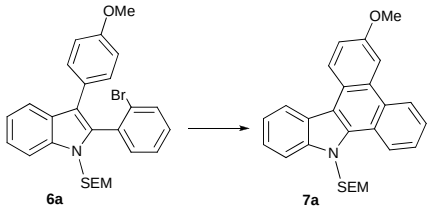


5

To avoid the formation of N-arylation byproducts, we decided to protect the indole NH group. Using **3a** as the substrate, the introduction of several protecting groups was explored. Tosyl chloride and 1-bromo-2-(2-methoxyethoxy)ethane failed to give the desired protected indoles. Isovaleryl chloride, ethyl chlorocarbonate, and benzyl choride afforded the corresponding indole derivatives in 65, 66, and 75% yield, respectively. We were pleased to find that an excellent result could be obtained with 2-(trimethylsilyl)ethoxymethyl chloride (SEM-Cl). The SEM derivative **6a** was isolated in 95% yield upon treatement of **3a** with SEM-Cl in the presence of NaH in DMF at room temperature for 1h.

With an efficient procedure for the protection of the starting indole in hands, the cyclization of **6a** to the corresponding carbazole **7a** was next investigated.

Table 1. Cyclization of **6a** to **7a.** [a]



6a **7a**

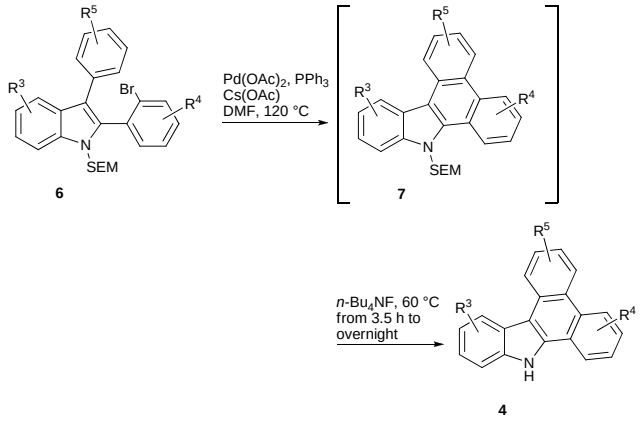
Entry	Ligand (equiv)	Base	Time (h)	T (°C)	Yield % of **7a** [b]
1	dppe (0.05)	K_2CO_3	7	100	25[c]
2	dppe (0.1)	K_2CO_3	8	120	23[d]
3	dppe (0.2)	K_2CO_3	23	120	37[e]
4	dppe (0.1)	CsOAc	7	120	40[f]
5	dppe (0.2)	CsOAc	1.5	120	89
6	PPh_3 (0.2)	CsOAc	0.5	120	97

[a] Reactions were carried out under a nitrogen atmosphere on a 0.25 mmol scale in 5 mL of DMF using 0.05 equiv of $Pd(OAc)_2$, a phosphine ligand, and 2 equiv of base. [b] Yields are given for isolated products. [c] The starting material was recovered in 74% yield. [d] The starting material was recovered in 49% yield. [e] The starting material was recovered in 37% yield. [f] The starting material was recovered in 25% yield.

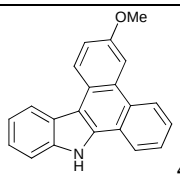
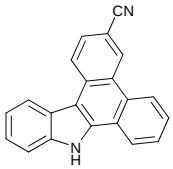
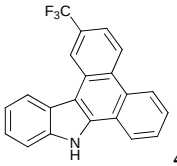
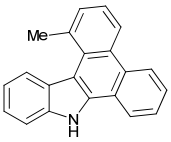
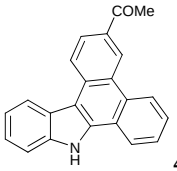
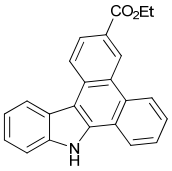
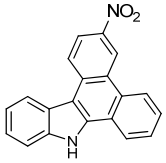
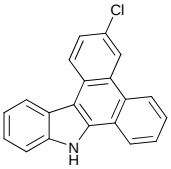
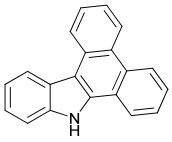
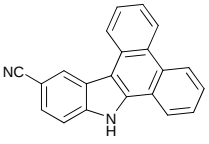
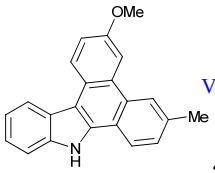
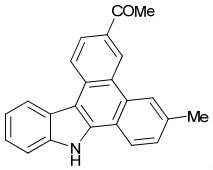
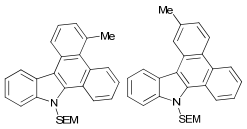
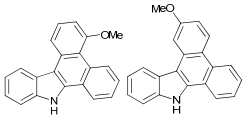
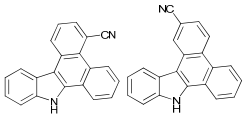
As shown in Table 1, the best result both in term of yield and reaction time was observed using PPh_3 and Cs(OAc) in DMF at 120 °C (entry 6). The protecting group could be readily removed by treating the N-SEM carbazole with a THF solution of *n*-Bu_4NF at 60 °C. Furthermore, the cyclization/deprotection sequence could be successfully performed, omitting the isolation of the intermediate protected carbazole, by adding the reagents required for the deprotection step to a crude mixture following the cyclization of **7a** that had been concentrated under reduced pressure. Under these conditions, the correspondiong free NH carbazole was isolated in 70% overall yield.

This protocol was then used when the process was extended to include other N-SEM indoles **6**. Our preparative results are summarized in Table 2. Several carbazole derivatives bearing a variety of useful functional groups have been prepared in good to excellent yield. Cyano, keto, ester, nitro, and chloro substituents are well tolerated. With indoles bearing meta substituents on the aryl ring at the C3 position, two regioisomeric carbazole derivatives can form and the nature of the substituents was found to play an important role in controlling the composition of the reaction mixture. In the presence of 3-Me or 3-MeO groups almost equimolar amounts of the two regioisomers are formed (Table 2, entries 13 and 14). However, with the more steric demanding 3-CF_3 group the new C-C bond is formed regioselectively at the less crowded ortho position (Table 2, entry 3). No evidence of the regioisomeric derivative was attained. Interestingly, with **6o**, bearing a meta cyano substituent, the new C-C bond is formed preferentially at the more crowded ortho position (Table 2, entry 15). Such a behavior may be accounted for by the coordination of the cyano group to the palladium atom of the arylpalladium complex formed *in situ* via oxidative addition. The resultant intermediate would exert a directing effect on the cyclization step.

Table 2. Sequential synthesis of carbazoles **4** from N-SEM indoles **6**. [a][b]

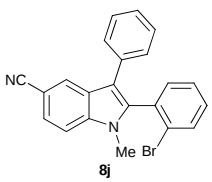


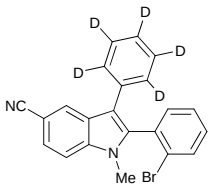
6 **7** **4**

Entry	N-SEM Indole **6**			T (h)[d]	Product Yield %[c]
	R^3	R^4	R^5		
1	H	H	4-MeO	0.5	 **4a** (70)
2	H	H	4-CN	7	 **4b** (92)
3	H	H	3-CF_3	24	 **4c** (60)
4	H	H	2-Me	0.5	 **4d** (84)
5	H	H	4-MeCO	5	 **4e** (65)
6	H	H	4-EtOCO	24	 **4f** (65)
7	H	H	4-NO_2	5	 **4g** (73)
8	H	H	4-Cl	24	 **4h** (80)
9	H	H	H	9	 **4i** (62)
10	5-CN	H	H	1	 **4j** (75)
11	H	4-Me	4-MeO	9	 **4k** (61)
12	H	4-Me	4-MeCO	1	 **4l** (77)
13	H	H	3-Me		 **7m** **7m'** (50:50) **7m +7m'**(95)
14	H	H	3-MeO		 **4n** **4n'** (45:55) **4n +4n'**(60)
15	H	H	3-CN		 **4o** **4o'** (75:25) **4o + 4o'** (55)

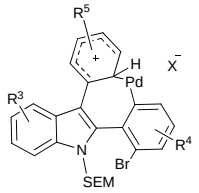
[a] The numbering of the substituents refers to the starting N-SEM indoles. [b] Reactions were carried out under a nitrogen atmosphere on a 0.25 mmol scale in 5 mL of DMF at 120 °C using 0.05 equiv of $Pd(OAc)_2$, 0.2 equiv of PPh_3, and 2 equiv of Cs(OAc). [c] Reaction times refer to the cyclization step. [d] Yields refer to the cyclization/deprotection sequence and are given for isolated products.

As to the mechanism of the cyclization step, an intermolecular competition experiment using **8j** and the corresponding indole containing a deuterium labeled 3-phenyl substituent **8jD** suggests that a hydrogen-abstraction step is not involved in the rate-limiting step.


8j


8jD

No isotope effect was observed when these two compounds were subjected to cyclization conditions supporting the view that the reaction proceeds through an electrophilic aromatic substitution involving the intermediate **A**.[12]



A

To sum up, this paper describes a general protocol for the synthesis of dibenzo[*a*,*c*]carbazoles from 2-(2-bromoaryl)-3-arylindoles, readily available from 2-[(2-bromoaryl)ethynyl]trifluoroacetanilides. The reaction tolerates a variety of useful substituents including chloro, nitro, ether, cyano, keto, and ester groups and proceeds through an intramolecular palladium-catalyzed C-H functionalization/C-C bond formation process that most probably involves an electrophilic aromatic substitution.

Acknowledgment

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Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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