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A Tandem Cross-Coupling/S_NAr Approach to Functionalized Carbazoles

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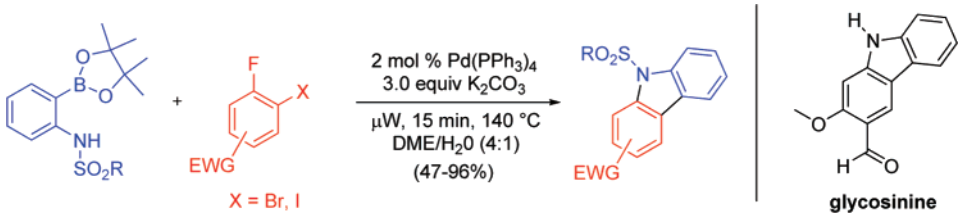
ABSTRACT



A novel route to functionalized carbazoles utilizing a tandem Suzuki cross-coupling/S_NAr protocol is described. This process was found to be compatible with a variety of electron-withdrawing groups including aldehydes, esters, and sulfones. Using this method, a concise total synthesis (four steps, 50% overall yield) of the carbazole alkaloid glycosinine was achieved.

The carbazole ring system is present in a variety of naturally occurring medicinally active substances.[1] Both synthetic and natural carbazole derivatives have been shown to exhibit a broad range of biological activity including the inhibition of CDK-5[2] and antimicrobial/anti-inflammatory activities.[3,4] Carbazole-containing molecules have also been widely used as organic materials.[5] Due to these interesting properties, a number of synthetic approaches to the carbazole framework have been described.[6] To the best of our knowledge, there exists only a single report where both a carbon−nitrogen and carbon−carbon bond of a functionalized carbazole were constructed in a one-pot tandem process.[6b] Although this protocol proceeded in modest to high yields, it required prolonged heating at elevated temperatures (3 h at 160 °C) and was sometimes complicated by the formation of isomeric products.

Prompted by the diverse biological activities, we aimed to identify a novel metal-catalyzed microwave-assisted protocol that would allow for the rapid entry into the carbazole scaffold. Herein, we present a high yielding, one-pot synthesis of functionalized carbazoles utilizing a tandem Suzuki cross-coupling/S_NAr strategy (CC−S_NAr).

Our proposed approach is shown in Scheme 1. Cross-coupling of an aniline-derived boronic ester (**1**) with an appropriately substituted dihalide (**2**) using microwave-assisted palladium catalysis would provide diaryl intermedi-

(1) (a) Knölker, H.-J.; Reddy, K. R. *Chem. Rev.* **2002**, *102*, 4303. (b) Knölker, H.-J. *Top. Curr. Chem.* **2005**, *244*, 115.

(2) Potterat, O.; Puder, C.; Bolek, W.; Wagner, K.; Ke, C.; Ye, Y.; Gillardon, F. *Pharmazie* **2005**, *60*, 637.

(3) Roy, M. K.; Thalang, V. N.; Trakoontivakorn, G.; Nakahara, K. *Br. J. Pharmacol.* **2005**, *145*, 145.

(4) Hsu, M.-J.; Chao, Y.; Chang, Y.-H.; Ho, F.-M.; Huang, L.-J.; Huang, Y.-L.; Luh, T.-Y.; Chen, C.-P.; Lin, W.-W. *Biochem. Pharmacol.* **2005**, *70*, 102.

(5) (a) Zhang, Y.; Wada, T.; Sasabe, H. *J. Mater. Chem.* **1998**, *8*, 809. (b) Grazulevicius, J. V.; Strohriegl, P.; Pielichowski, J.; Pielichowski, K. *Prog. Polym. Sci.* **2003**, *28*, 1297. (c) Thomas, K. R. J.; Lin, J. T.; Tao, Y.-T.; Ko, C.-W. *J. Am. Chem. Soc.* **2001**, *123*, 9404. (d) Díaz, J. L.; Dobarro, A.; Villacampa, B.; Velasco, D. *Chem. Mater.* **2001**, *13*, 2528.

(6) (a) Yamamoto, M.; Matsubara, S. *Chem. Lett.* **2007**, *36*, 172. (b) Bedford, R. B.; Betham, M. *J. Org. Chem.* **2006**, *71*, 9403. (c) Liu, C.-Y.; Knochel, P. *Org. Lett.* **2005**, *7*, 2543. (d) Smitrovich, J. H.; Davies, I. W. *Org. Lett.* **2004**, *6*, 533. (e) Knölker, H.-J.; Wolpert, M. *Tetrahedron* **2003**, *59*, 5317 and references cited therein. (f) Bringmann, G.; Tasler, S.; Endress, H.; Peters, K.; Peters, E. M. *Synthesis* **1998**, *10*, 1501. (g) Kuwahara, A.; Nakano, K.; Nozaki, K.; *J. Org. Chem.* **2005**, *70*, 413. (h) Gilchrist, T. L. *Heterocyclic Chemistry*; Pitman Publishing Ltd.: London, 1985. (i) Sundberg, R. J. *Comp. Heterocycl. Chem. II* **1996**, *2*, 119. (j) Moody, C. J. *Synlett* **1994**, 681. (k) Bergman, J.; Pelcman, B. *Pure Appl. Chem.* **1990**, *62*, 1967. (l) Soderberg, B. C. G. *Curr. Org. Chem.* **2000**, *4*, 727. (m) Lin, G.; Zhang, A. *Tetrahedron Lett.* **1999**, *40*, 341. (n) Pedersen, J. M.; Bowman, W. R.; Elsegood, M. R. J.; Fletcher, A. J.; Lovell, P. J. *J. Org. Chem.* **2005**, *70*, 10615. (o) Larock, R. C.; Berrios-Pena, N.; Narayanan, K. *J. Org. Chem.* **1990**, *55*, 3447. (p) Rocca, P.; Marsais, F.; Godard, A.; Queguiner, G. *Tetrahedron* **1993**, *49*, 49. (q) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560.

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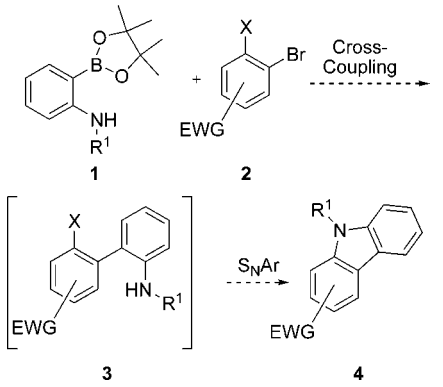
Scheme 1. Proposed One-Pot CC−S_NAr Route to Carbazoles

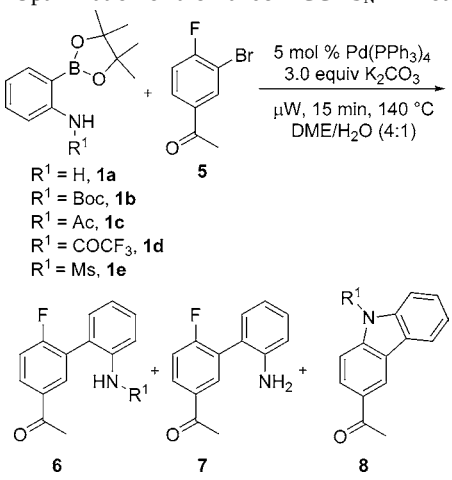


ate **3**. Intramolecular S_NAr cyclization of intermediate **3** would provide carbazole **4**.

Initially, our efforts focused on the reaction of unsubstituted boronic ester **1a** (Table 1) with 3-bromo-4-fluoroacetophenone (**5**) using a microwave-assisted cross-coupling protocol (5 mol % of $Pd(PPh_3)_4$, 3 equiv of K_2CO_3, 4:1 DME/water, 140 °C, 15 min).[7] Unfortunately, only cross-coupled material was observed (i.e., **6**/**7**) (Table 1, entry 1).[8] We rationalized that modulating the pK_a of the aniline by the addition of an electron-withdrawing group would increase the possibility of in situ cyclization. To this end, our first attempt involved using Boc derivative **1b**; however, only biaryl derivative **6** was observed (entry 2). Acetylated derivatives (**1c** and **1d**) were also subjected to the cross-coupling procedure (entries 3 and 4). As with the Boc derivative, the major products were derived from cross-coupling (**6**); however, significant amounts of cleavage products were also seen (i.e., **7**). Since the hydrolysis of the electron-withdrawing group was observed under these conditions, we hypothesized that a more stable group would allow for productive in situ cyclization. Indeed, when the methylsulfonyl (Ms) derivative **1e** (entry 5) was exposed to **5**, carbazole **8** was formed in quantitative conversion.

The generality of this method appears to be rather broad, tolerating a wide variety of electron-withdrawing groups (Table 2, entries 1−9).[9] It was found that *para*-toluenesulfonyl (Ts) derivative (**1f**) also cleanly delivered the desired carbazole (entries 2 and 11). Subjecting 3-bromo-4-chloroacetophenone to boronic ester **1a** resulted in only a 29% isolated yield, although significant amounts of the intermediate diaryl chloride were also observed (entry 10). While this tandem process proceeded smoothly with an electron-withdrawing group ortho to the fluoride (entry 11), the

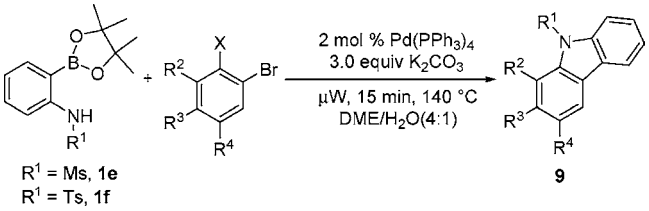
Table 1. Optimization of the Tandem CC−S_NAr Protocol



entry	R^1	**6**[a]	**7**[a]	**8**[a]
1	H	100	0	0
2	Boc	100	0	0
3	Ac[b]	70	30	0
4	$COCF_3$	60	40	0
5	Ms	0	0	100

[a] Ratios determined by HPLC. [b] The corresponding boronic acid was used.

Table 2. $Pd(PPh_3)_4$-Catalyzed CC−S_NAr Approach to Carbazoles



entry	**9**	R^1	X	R^2	R^3	R^4	yield[a] (%)
1	**9a**	Ms	F	H	H	COMe	95
2	**9b**	Ts	F	H	H	COMe	86
3	**9c**	Ms	F	H	H	CO_2Me	88
4	**9d**	Ms	F	H	H	$CONMe_2$	47[b]
5	**9e**	Ms	F	H	H	CHO	87
6	**9f**	Ms	F	H	H	(*E*)-CH=CH−CO_2Me	78
7	**9g**	Ms	F	H	H	CN	90
8	**9h**	Ms	F	H	H	NO_2	96
9	**9i**	Ms	F	H	H	SO_2Me	81
10	**9a**	Ms	Cl	H	H	COMe	29[c]
11	**9j**	Ts	F	CO_2Me	H	H	83
12	**9k**	Ms	F	H	CO_2Me	H	0
13	**9l**	Ms	F	H	H	H	0[d]

[a] Isolated yield, reported as an average of two runs. [b] Required an additional 15 min at 170 °C. [c] The intermediate biaryl chloride was isolated in 56% yield. [d] The intermediate biaryl fluoride was isolated in 93% yield.

(7) Using these conditions, 3-bromoacetophenone underwent cross-coupling with boronic ester **1a** in quantitative yield.

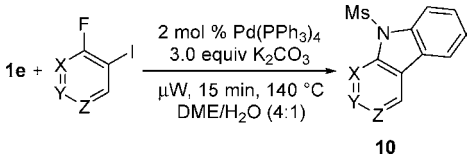
(8) A variety of conditions were employed including elevated temperatures (up to 200 °C for 30 min) and stronger bases (such as NaOH).

(9) This process is also compatible with conventional heating. Carbazole **9a** was formed in 99% yield when boronic ester **1a** was exposed to 3-bromo-4-fluoroacetophenone at 90 °C for 12 h.

corresponding meta isomer failed under the standard conditions (entry 12).

Substituted pyridines were also subjected to the CC−S_NAr coupling protocol (Table 3). While both the 2- and 4-fluoro-

Table 3. CC−S_NAr-Mediated Formation of Pyridoindoles



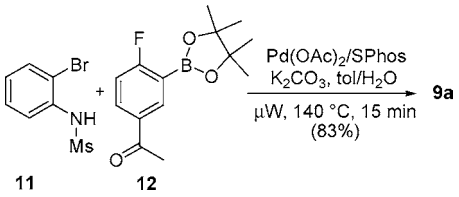
entry	10	X	Y	Z	yield[a] (%)
1	**10a**	N	C	C	97[b]
2	**10b**	C	N	C	trace
3	**10c**	C	C	N	90[c]

[a] Isolated yield, reported as an average of two runs. [b] The corresponding bromofluoride was used. [c] The HCl salt of the iodofluoride and 4.0 equiv of K_2CO_3 were used.

pyridine derivatives delivered the carbazoles in high yield (Table 3, entries 1 and 3), the 3-fluoro isomer produced only trace amounts (entry 2). These results, combined with data in Table 2, demonstrate the need for an electron-withdrawing group at either the ortho or para position relative to the fluorine.

To further expand the potential utility of this method, the coupling of fluorinated boronic esters with bromo anilines (**11** and **12**) was investigated (Scheme 2). Unfortunately,

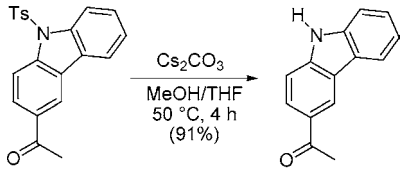
Scheme 2. $Pd(OAc)_2$/SPhos-Catalyzed CC−S_NAr Approach to Carbazoles



exposure to the general CC−S_NAr conditions failed to produce synthetically useful quantities of the desired carbazole (presumably due to the electron poor nature of the boronic ester). After exploring a variety of conditions, the combination of 2 mol % of $Pd(OAc)_2$ and 4 mol % of 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (SPhos) proved to be optimal.[10] This catalytic system, in combination with K_2CO_3 (3 equiv) and a toluene/water solvent mixture, delivered carbazole **9a** in 83% yield after only 15 min of microwave irradiation.

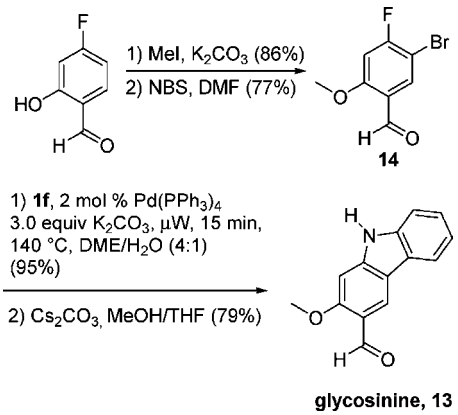
Although the aniline boronic ester **1a** (Table 1, entry 1) failed to undergo the desired CC−S_NAr coupling, the same compound could be accessed by removal of the sulfonamide functionality. For example, exposing tosylated carbazole **9b** to Cs_2CO_3 in a mixture of THF and MeOH provided **9m** in 91% yield (Scheme 3).[11,12]

Scheme 3. Formation of Carbazole **9m**



To demonstrate the utility of this method in natural product synthesis, we developed a facile route to the carbazole alkaloid glycosinine (**13**) (Scheme 4).[13] Methylation and

Scheme 4. Total Synthesis of Glycosinine



bromination of 4-fluoro-2-hydroxybenzaldehyde delivered **14**. Boronic ester **1f** cleanly reacted with **14** using the general $Pd(PPh_3)_4$ catalyzed CC−S_NAr coupling protocol to deliver the tosylated carbazole in near quantitative yield. Deprotection using Cs_2CO_3 produced glycosinine (**13**) (four steps, 50% overall yield). This synthesis compares favorably to the previously reported route (six steps, 19% overall yield).[14]

To the best of our knowledge, this process constitutes a novel approach to the synthesis of functionalized carbazoles. Given the high yield, short reaction times, operational simplicity, and functional group compatibility, this protocol will provide convenient access to a variety of carbazole-containing molecules. Furthermore, using this method an efficient total synthesis of the carbazole alkaloid glycosinine was achieved.

(10) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685.

(11) Bajwa, J. S.; Chen, G.-P.; Prasad, K.; Repiè, O.; Blacklock, T. J. *Tetrahedron Lett.* **2006**, *47*, 6425.

(12) The methylsulfonyl group of **9a** can also be removed, although it required more forcing conditions (KOH, MeOH, 70 °C, 12 h).

(13) Lange, G. L.; Ruangrungsi, N.; Ariyaprayoon, J.; Lange, G. L.; Organ, M. G. *J. Nat. Prod.* **1990**, *53*, 946.

(14) Knölker, H.-J.; Gösmann, H.; Hofmann, C. *Synlett* **1996**, *8*, 737.

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Supporting Information Available: Experimental procedures, compound characterization data, and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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