Domino Reactions

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Domino N–H/C–H Bond Activation: Palladium-Catalyzed Synthesis of Annulated Heterocycles Using Dichloro(hetero)arenes**

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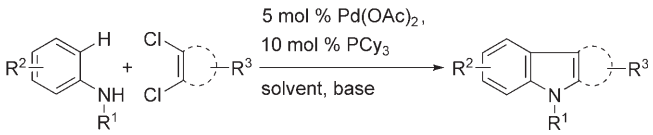
Methodologies for the regioselective formation of $C(sp^2)$–$C(sp^2)$ linkages are mainly based on transition-metal-catalyzed coupling reactions between organometallic reagents and organic (pseudo)halides.[1,2] The organometallic compounds are often not commercially available and their use gives rise to the formation of undesired by-products. Accordingly, focus has shifted to direct arylation reactions through cross-coupling of C–H bonds as an economical and ecologically benign alternative.[3] Significant progress was accomplished by recently developed methodologies for the general use of readily available, but less reactive aryl chlorides[4] in intra-[5–7] and intermolecular[8,9] direct arylation reactions.[10] However, only one elegant, albeit limited, domino[11,12] process was reported that consists of a transition-metal-catalyzed traditional coupling of a bromide and a C–H bond arylation with a chloride.[5,7,13]

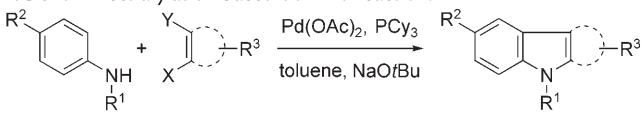
Herein, we report a novel palladium-catalyzed domino reaction[14] for the synthesis of annulated heterocycles. This approach involves an amination and a direct arylation by using readily available anilines and 1,2-dihalo(hetero)arenes[15] and importantly allows for the functionalization of substrates bearing chlorides as the only leaving groups (Scheme 1). Furthermore, different from previously reported C–H bond arylation-based carbazole[16,17] syntheses,[5,6a,7,12] the direct synthesis of carbazoles with a free NH moiety is efficiently accomplished.

To probe the viability of the envisioned domino reaction, palladium complexes derived from numerous ligands were screened with various 1,2-dihaloarenes and Ph_2NH in toluene as solvent. Optimization studies revealed that the most efficient process was accomplished when using PCy_3 as the ligand (Cy = cyclohexyl). Importantly, the approach was found to be applicable not only to bromides (Table 1, entries 1–3) but also to less-reactive chlorides (Table 1, entry 4). Notably, even inexpensive 1,2-dichlorobenzene gave rise to the desired carbazole efficiently (Table 1, entry 5). As carbolines are ubiquitous in biologically active compounds, it is important to note that heterocyclic halides[18] could be employed with comparable efficacy (Table 1, entry 6). Further, an indole derivative was efficiently accessible through a direct vinylation with a 1,2-dihaloalkene (Table 1, entries 7 and 8).

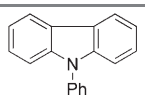
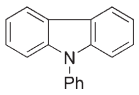
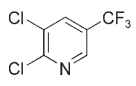
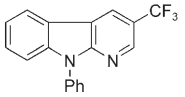
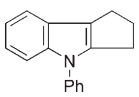
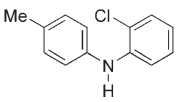


Scheme 1. Direct arylation-based synthesis of annulated heterocycles.

Table 1: Direct arylation-based domino reaction.[a]



1 2 3

Entry	Halide	Product	Yield [%]
1		 **3c**	96
2			94[b]
3			94[c]
4		 **3c**	88
5			85
6		 **3b**	93
7		 **3a**	77
8			78[c]
9[d]		 **4**	94

[a] R^1 = Ph, R^2 = H, unless otherwise stated (see entry 9). Reaction conditions: **1** (1.20 mmol), **2** (1.00 mmol), $Pd(OAc)_2$ (5.0 mol%), PCy_3 (10.0 mol%), NaO*t*Bu (3.00 mmol), PhMe (10 mL), 105 °C, 18 h; yields of isolated product. [b] PPh_3 (10 mol%) instead of PCy_3. [c] *N*,*N*′-Bis(2,6-diisopropylphenyl)imidazolium chloride (10 mol%) instead of PCy_3. [d] R^1 = H, R^2 = Me.

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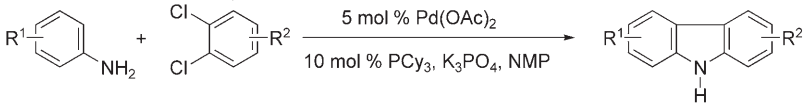
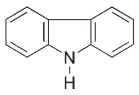
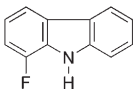
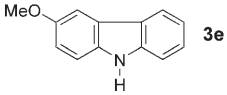
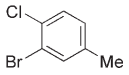
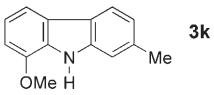
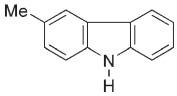
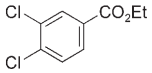
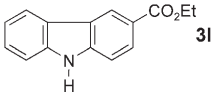
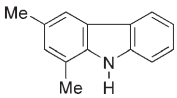
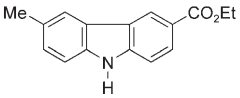
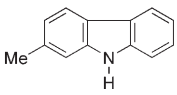
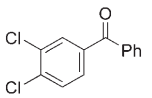
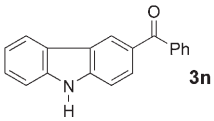
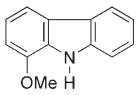
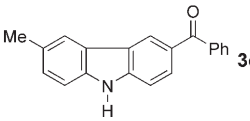
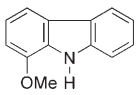
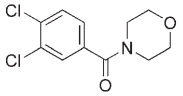
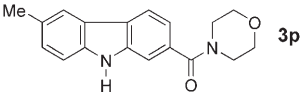
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

Table 2: Synthesis of carbazoles with a free NH moiety.[a]



1 **2** **3**

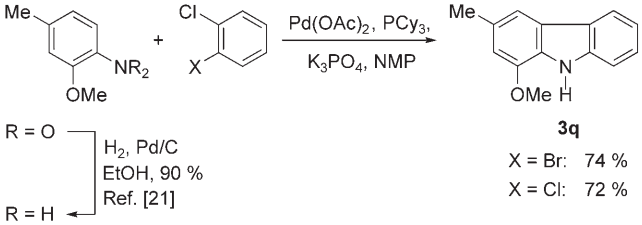
Entry	R^1	Chloride	Product	Yield [%]	Entry	R^1	Chloride	Product	Yield [%]
1	H		 **3d**	81	8	2-F		 **3j**	80
2	4-MeO		 **3e**	71	9	2-MeO		 **3k**	80
3	4-Me		 **3f**	77	10	H		 **3l**	62
4	2,4-Me_2		 **3g**	63	11	4-Me		 **3m**	57
5	3-Me		 **3h**	75	12	H		 **3n**	77
6	2-MeO		 **3i**	64	13	4-Me		 **3o**	76
7	2-MeO		 **3i**	68	14	4-Me		 **3p**	71

[a] Reaction conditions: **1** (1.2 mmol), **2** (1.0 mmol), $Pd(OAc)_2$ (5.0 mol%), PCy_3 (10.0 mol%), K_3PO_4 (2.2–3.0 mmol), NMP (10 mL), 130°C, 18 h; yields of isolated product.

Various carbazoles with activities of relevance to biology display a free NH moiety.[16] Unfortunately, the previously reported direct arylation-based domino carbazole synthesis proved not to be applicable to the use of primary anilines. Therefore, C–H bond arylation-based approaches to naturally occurring carbazoles had to employ lengthy and inefficient protection/deprotection strategies.[6a,7,12] No direct arylation was accomplished under the reaction conditions highlighted in Table 1 when applied to primary anilines (Table 1, entry 9).

Thus, we conducted an optimization study with primary anilines, with a particular focus on the use of 1,2-dichloroarenes. We found that *N*-methylpyrrolidinone (NMP) as solvent, K_3PO_4 as base,[19] and PCy_3 as ligand allowed the envisioned transformation, giving rise to carbazoles **3** in high yields (Table 2). Under these reaction conditions, numerous regioselectively substituted carbazoles **3** were obtained starting from the corresponding electron-rich (Table 2, entries 1–7) or electron-deficient (Table 2, entry 8) primary anilines **1**. Highly regioselective reactions were also observed for substituted 1,2-dihaloarenes (Table 2, entries 9–14).[20] The mild reaction conditions allowed for the synthesis of functionalized carbazoles (Table 2, entries 10–14).

Finally, we applied our protocol to an efficient synthesis of naturally occurring murrayafoline A[16] (**3q**; Scheme 2). Hence, easily accessible 2-methoxy-4-methylaniline[21] delivered the desired product **3q** in high yield through the palladium-catalyzed domino reaction, even when using inexpensive 1,2-dichlorobenzene.



Scheme 2. Efficient synthesis of murrayafoline A (**3q**).

In summary, we have reported a novel palladium-catalyzed domino synthesis of annulated heterocycles that consists of an amination and a direct C–H bond arylation with readily available anilines and 1,2-dihalo(hetero)arenes. Notably, this approach constitutes an unprecedented direct

arylation-based domino process that is applicable to substrates bearing only chlorides as leaving groups. The efficiency of the protocol is shown by an economical synthesis of murrayafoline A (**3q**) from 1,2-dichlorobenzene.

Experimental Section

Representative procedure—synthesis of murrayafoline A (**3q**): A solution of $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 5.0 mol%), PCy_3 (28.9 mg, 0.10 mmol, 10 mol%), finely powdered K_3PO_4 (467 mg, 2.20 mmol), 2-methoxy-4-methylaniline[21] (165 mg, 1.20 mmol), and 1,2-dichlorobenzene (424 mg, 1.20 mmol) in dry NMP (10.0 mL) was stirred for 18 h at 130 °C under N_2. Et_2O (25 mL) and H_2O (25 mL) were added to the reaction mixture at ambient temperature. The separated aqueous phase was extracted with Et_2O (2 × 75 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. The remaining residue was purified by column chromatography on silica gel (*n*-pentane/Et_2O, 50:1→30:1) to yield murrayafoline A (**3q**) as an off-white solid (152 mg, 72%).

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Keywords: C–C coupling · C–H activation · domino reactions · heterocycles · palladium

[1] M. Beller, C. Bolm, *Transition Metals for Organic Synthesis*, 2nd ed., Wiley-VCH, Weinheim, **2004**.
[2] A. de Meijere, F. Diederich, *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed., Wiley-VCH, Weinheim, **2004**.
[3] G. Dyker, *Handbook of C-H Transformations*, Wiley-VCH, Weinheim, **2005**.
[4] A. F. Littke, G. C. Fu, *Angew. Chem.* **2002**, *114*, 4350–4386; *Angew. Chem. Int. Ed.* **2002**, *41*, 4176–4211.
[5] R. B. Bedford, C. S. J. Cazin, *Chem. Commun.* **2002**, 2310–2311.
[6] a) L.-C. Campeau, M. Parisien, A. Jean, K. Fagnou, *J. Am. Chem. Soc.* **2006**, *128*, 581–590; b) L. Wang, P. B. Shevlin, *Org. Lett.* **2000**, *2*, 3703–3705.
[7] R. B. Bedford, M. Betham, C. S. J. Cazin in *Handbook of C-H Transformations* (Ed.: G. Dyker), Wiley-VCH, Weinheim, **2005**, pp. 238–245.
[8] L. Ackermann, *Org. Lett.* **2005**, *7*, 3123–3125.
[9] For the use of tosylates, see: L. Ackermann, A. Althammer, R. Born, *Angew. Chem.* **2006**, *118*, 2681–2685; *Angew. Chem. Int. Ed.* **2006**, *45*, 2619–2622.
[10] For a review, see: L.-C. Campeau, K. Fagnou, *Chem. Commun.* **2006**, 1253–1264, and references therein.
[11] L. F. Tietze, G. Brasche, K. M. Gericke, *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, **2006**.
[12] For a recent tandem reaction involving an intramolecular direct arylation with an aryl chloride, see: J.-P. Leclerc, M. André, K. Fagnou, *J. Org. Chem.* **2006**, *71*, 1711–1714.
[13] For representative examples of elegant domino reactions involving direct arylation reactions with iodides and bromides, see: a) G. Dyker, J. Körning, P. G. Jones, P. Bubenitschek, *Angew. Chem.* **1993**, *105*, 1805–1807; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1733–1735; b) H. A. Wegner, L. T. Scott, A. de Meijere, *J. Org. Chem.* **2003**, *68*, 883–887; c) M. A. Campo, Q. Huang, T. Yao, Q. Tian, R. C. Larock, *J. Am. Chem. Soc.* **2003**, *125*, 11506–11507; d) F. Faccini, E. Motti, M. Catellani, *J. Am. Chem. Soc.* **2004**, *126*, 78–79; e) C. Bressy, D. Alberico, M. Lautens, *J. Am. Chem. Soc.* **2005**, *127*, 13148–13149; f) C.-G. Dong, Q.-S. Hu, *Angew. Chem.* **2006**, *118*, 2347–2350; *Angew. Chem. Int. Ed.* **2006**, *45*, 2289–2292; g) L. F. Tietze, F. Lotz, *Eur. J. Org. Chem.* **2006**, 4676–4684; h) D. J. Cárdenas, B. Martin-Matute, A. M. Echavarren, *J. Am. Chem. Soc.* **2006**, *128*, 5033–5040, and references therein.
[14] For a stepwise carbazole synthesis using 2-bromo-1-iodobenzene, see: a) T. Iwaki, A. Yasuhara, T. Sakamoto, *J. Chem. Soc. Perkin Trans. 1* **1999**, 1505–1510; b) I. C. F. R. Ferreira, M.-J. R. P. Queiroz, G. Kirsch, *Tetrahedron* **2003**, *59*, 3737–3742, and references therein.
[15] 2-Chloro-1-iodoarenes were previously used for indole syntheses, which are based on a Sonogashira coupling and an amination reaction: a) L. Ackermann, *Org. Lett.* **2005**, *7*, 439–442; b) L. T. Kaspar, L. Ackermann, *Tetrahedron* **2005**, *61*, 11311–11316.
[16] H.-J. Knölker, K. R. Reddy, *Chem. Rev.* **2002**, *102*, 4303–4428.
[17] Selected recent palladium-catalyzed carbazole syntheses: a) H.-J. Knölker, J. Knöll, *Chem. Commun.* **2003**, 1170–1171; b) K. Nozaki, K. Takahashi, K. Nakano, T. Hiyama, H.-Z. Tang, M. Fujiki, S. Yamaguchi, K. Tamao, *Angew. Chem.* **2003**, *115*, 2097–2099; *Angew. Chem. Int. Ed.* **2003**, *42*, 2051–2053; c) W. C. P. Tsang, N. Zheng, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 14560–14561; d) M. P. Krahl, A. Jäger, T. Krause, H.-J. Knölker, *Org. Biomol. Chem.* **2006**, *4*, 3125–3219, and references therein.
[18] Under the reaction conditions outlined in Table 1, 2,3-dibromothiophene and Ph_2NH led to 72% yield of isolated product.
[19] Under otherwise identical reaction conditions, the use of K_2CO_3 as base and DMA as solvent gave only 6% conversion (GC analysis) to the desired product for the transformation described in Table 2, entry 3.
[20] The regiochemistry of carbazoles **3** was unambiguously established by various 2D NMR experiments and a single-crystal X-ray diffraction analysis of **3b**, **3k**, **3m**, **3o**, and **3p**.
[21] H.-J. Knölker, M. Bauermeister, *J. Chem. Soc. Chem. Commun.* **1990**, 664–665.

