C–H Activation

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Chemoselective Benzylic C–H Activations for the Preparation of Condensed N-Heterocycles**

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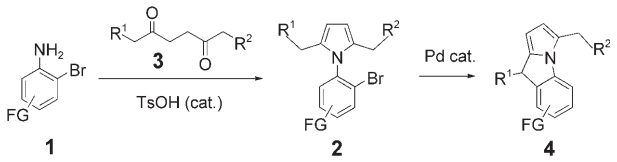
Dedicated to Professor Siegfried Blechert on the occasion of his 60th birthday

The preparation of complex polycyclic heterocycles is an important synthetic goal because of the utility of these molecules as potential pharmaceuticals.[1] One of the most efficient approaches for preparing polycyclic molecules is to use domino reactions.[2] Especially attractive are reaction sequences that involve C–H activation reactions[3] since such reactions preclude the presence of additional functionalities in the substrate. A range of Ru-,[4] Rh-,[5] Pt-,[6] and Pd-[7] catalyzed C–H activations for heterocycle synthesis have been recently described.[8] Since a variety of 2-bromoanilines **1** can be readily converted into N-arylpyrrole derivatives of type **2** by the reaction with a 1,4-diketone **3**, we envisaged that a subsequent C–H activation would afford condensed heterocycles of type **4** (Scheme 1).



Scheme 1. Preparation of tricyclic N-heterocycles of type **4**. FG = functional group; Ts = 4-toluenesulfonyl.

We therefore heated pyrrole **2a** with $Pd(OAc)_2$ (5 mol%) and various ligands in toluene and in the presence of a base for trapping HBr (100 °C, 20 h, Table 1). Preliminary experiments showed that polar solvents such as DMF led to complex reaction mixtures, but nonpolar solvents such as toluene gave much better results. Strongly chelating ligands such as dppe and dppp did not lead to the formation of **4a**; however, PPh_3 (10 mol%) led to the 9*H*-pyrrolo[1,2-*a*]indole **4a** with 45% conversion after 20 h at 100 °C, (entries 1–3 in Table 1). When

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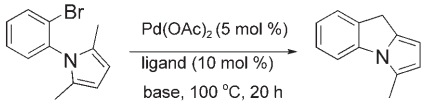
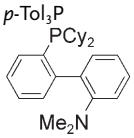
Table 1: Pd-catalyzed cyclization of the pyrrole derivative **2a** leading to the tricyclic heterocycle **4a**.



2a **4a**

Entry	Ligand[a]	Base	Conv. [%][b]
1	dppe	Cs_2CO_3	0
2	dppp	Cs_2CO_3	0
3	PPh_3	K_2CO_3	45
4	PPh_3	Cs_2CO_3	73
5	*o*-Tol_3P	Cs_2CO_3	0
6	*o*-$Furyl_3P$	Cs_2CO_3	8
7	*m*-Tol_3P	K_2CO_3	27
8	*m*-Tol_3P	Cs_2CO_3	100
9	*p*-Tol_3P	K_2CO_3	15
10	*p*-Tol_3P	Cs_2CO_3	100[c]
11		Cs_2CO_3	67

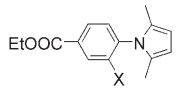
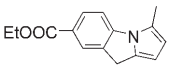
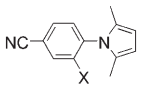
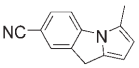
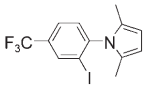
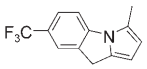
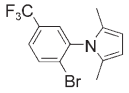
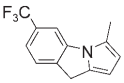
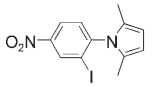
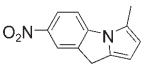
[a] dppe = ethane-1,2-diylbis(diphenylphosphane); dppp = propane-l,2-diylbis(diphenylphosphane); Tol = tolyl; Cy = cyclohexyl. [b] The conversion was determined by GC analysis of reaction aliquots. [c] Conversion after 12 h at 110°C.

K_2CO_3 was replaced by Cs_2CO_3 (1.2 equiv), the conversion increased to 73% (entry 4, Table 1). Sterically hindered ligands such as *o*-Tol_3P and *o*-$Furyl_3P$ were not suitable (entries 5 and 6, Table 1), but *m*-Tol_3P afforded 27% conversion in the presence of K_2CO_3 and 100% conversion with Cs_2CO_3. The best result was obtained with *p*-Tol_3P; reaction in the presence of Cs_2CO_3 gave 100% conversion within 12 h at 110°C (entries 7–10, Table 1). Interestingly, when the hindered phosphine 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl was used,[9] we observed a conversion of 67% (entry 11, Table 1).

Based on these optimized reaction conditions, we prepared a large range of 9*H*-pyrrolo[1,2-*a*]indoles (Table 2). The 2-iodo- and 2-bromo-*N*-arylpyrrole derivatives **2b** and **2c** underwent ring closure smoothly providing the tricyclic product **4b** in 81% and 83% yield, respectively, showing that the use of aryl iodides and bromides leads to similar results (entries 1 and 2 in Table 2). The ester function was well tolerated in this ring closure. Also, the cyano-substituted iodide **2d** and bromide **2e** furnished the expected product **4c** in 70% and 60% yield, respectively (entries 3 and 4, Table 2) under the standard conditions. Trifluoromethyl-substituted substrates, which may be of importance for the preparation of pharmaceutically relevant heterocycles, reacted readily and led to the tricyclic products **4d** (77%) and **4e** (65%) (entries 5 and 6, respectively). Only a nitro substituent complicated the reaction and furnished the 9*H*-pyrrolo-[1,2-*a*]indole **4f** in only 33% yield (entry 7, Table 2).

In the case of unsymmetrical 2,5-disubstituted derivatives, an interesting selectivity was observed. Thus, the N-arylpyrrole derivative **5** underwent preferentially a chemoselective activation of the phenyl ring over the methyl substituent,

Table 2: Preparation of 9*H*-pyrrolo[1,2-*a*]indoles of type **4**.

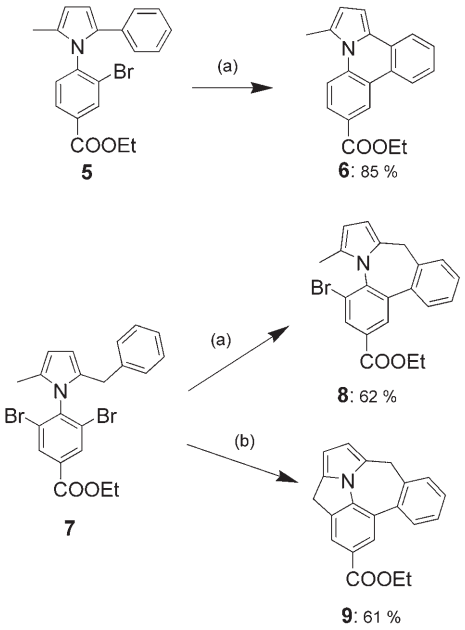
Entry	Product of type **2**	Product of type **4**	Yield [%][a]
			
1	**2b**: X = I	**4b**	81
2	**2c**: X = Br	**4b**	83
			
3	**2d**: X = I	**4c**	70
4	**2e**: X = Br	**4c**	60
			
5	**2f**	**4d**	77
			
6	**2g**	**4e**	65
			
7	**2h**	**4f**	33

[a] Yield of isolated, analytically pure product.

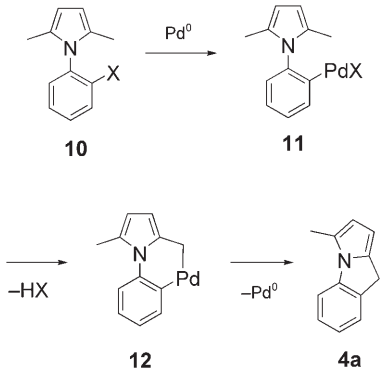
leading to the pyrrolo[1,2-*f*]phenanthridine derivative **6** in 85% yield (Scheme 2). A stepwise cyclization was observed with the dibromo derivative **7**. Under the standard conditions only the phenyl C–H bond was activated, resulting in formation of a seven-membered ring (**8**, 62%). Forcing reaction conditions (110°C, 24 h) led to a second cyclization with the formation of the pentacyclic compound **9** in 61% yield (Scheme 2).

These results show that the activation of a methyl substituent is not easy and is not facilitated by the presence of a further phenyl substituent; the benzyl substituent of compound **7** did not undergo a C–H activation at the benzylic position but on the phenyl ring despite the formation of a seven-membered ring. The additional phenyl ring has rather a deleterious steric influence. These considerations led us to propose the following tentative reaction sequence for the cyclization reaction. The *N*-(2-haloaryl)pyrrole derivative **10** undergoes first an oxidative addition of Pd^0 generated in situ, leading to the Pd^{II} species **11** (Scheme 3). Concomitant C–H activation and HX elimination provides the palladacycle **12**, which after reductive elimination provides the 9*H*-pyrrolo-[1,2-*a*]indole **4a**.

Remarkably, this activation of the 2-methyl substituent of pyrroles[10] can be extended to *N*-acyl-2,5-pyrrole derivatives such as **13a–c**. Under the usual conditions, these readily available amides are converted to the pyrrolo[1,2-*b*]isoquinolines **14a–c** in yield of 75–81% (Scheme 4). Nonaromatic N-acylpyrroles such as **15a–c** undergo the same type of



Scheme 2. Chemoselective C–H activation. Reaction conditions: a) $Pd(OAc)_2$ (5 mol%), *p*-Tol_3P (10 mol%), Cs_2CO_3 (1.2 equiv), 110°C, 12 h; b) $Pd(OAc)_2$ (5 mol%), *p*-Tol_3P (10 mol%), Cs_2CO_3 (2.2 equiv), 110°C, 24 h.



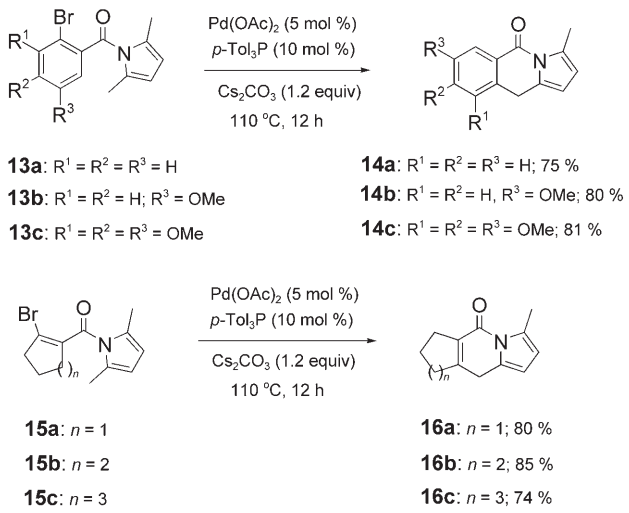
Scheme 3. Tentative reaction sequence for the ring closure.

cyclization with a C–H activation, leading to the heterocycles **16a–c** in 74–85% yield and demonstrating the broad scope of this type of ring closure (Scheme 4).

In summary, we have reported new Pd-catalyzed cyclizations leading to condensed N-heterocycles. The key step of these ring closures is a chemoselective intramolecular C–H activation of a methyl group at position 2 of a pyrrole ring. Further studies on the reaction mechanism and scope are currently underway in our laboratories.

Experimental Section

Synthesis of **4b** starting **2c** (entry 2 of Table 2): A mixture of the aryl bromide **2c** (322 mg, 1.0 mmol), $Pd(OAc)_2$ (11 mg, 5 mol%), tri(*p*-tolyl)phosphine (30 mg, 10 mol%), and Cs_2CO_3 (391 mg, 1.2 mmol) was heated at 110°C in toluene (5 mL) under N_2 in a sealed tube for 12 h. After the reaction mixture had cooled to room temperature,



Scheme 4. Preparation of tricyclic heterocycles starting from N-acylpyrroles.

water (10 mL) was added. The mixture was extracted with diethyl ether (3 × 30 mL), and the combined extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography (hexane/diethyl ether 10:1) provided **4b** (200 mg, 83% yield) as a white solid, m.p. 77.9–78.9°C.

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