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Pyrrole as a Directing Group: Regioselective Pd(II)-Catalyzed Alkylation and Benzylation at the Benzene Core of 2-Phenylpyrroles

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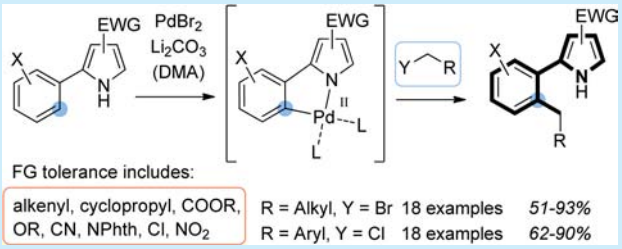
Supporting Information

ABSTRACT: Pyrrole has been employed for the first time as a directing group in the Pd(II)-catalyzed *ortho*-functionalization of C(sp^2)−H bonds. A variety of substituted 2-phenylpyrroles were successfully methylated, alkylated, or benzylated in the *ortho*-position of the benzene ring, yielding the respective 2-substituted pyrrol-2-yl benzenes (36 examples, 51−93% yield). Neither additives nor additional ligands were required to perform the reaction, which was routinely conducted with $PdBr_2$ as the catalyst and Li_2CO_3 as the base. Mechanistically, there is evidence that precoordination of palladium to the pyrrole enables the regioselective *ortho*-attack.



In recent years, the directed transition-metal-catalyzed alkylation of arenes has emerged as a powerful tool for the formation of C_{aryl}−C_{alkyl} carbon−carbon bonds.[1,2] Alkylation occurs preferably in the *ortho*-position to a given functional group, complementing the classic Friedel−Crafts alkylation approach.[3] Moreover, it facilitates the introduction of primary alkyl groups, which is notoriously difficult by Friedel−Crafts-type chemistry. Since strongly basic or acidic conditions are not required for transition-metal-catalyzed alkylation methods, they can be applied at a late stage in a synthetic sequence. Given the plethora of directing groups that have been described over the years to render a directed alkylation possible, it is surprising to note that the pyrrole group has so far not been employed for this purpose.

Substituted 2-phenylpyrroles represent a large compound class and have been extensively investigated over the years. A massive array of data has been generated, in particular, related to their use in medicinal chemistry.[4,5] In addition, there are several natural products that exhibit an *ortho*-alkylated 2-phenylpyrrole as a core structure, including the lamellarins,[6] robustivine,[7] telisatin,[8] oleracein E,[9] leptocarpine,[10] and triketramine (Figure 1).[11] An approach for the regioselective introduction of an alkyl group into 2-phenylpyrroles was therefore highly desirable. We have now found that when using a simple catalyst system (Li_2CO_3 as base, $PdBr_2$ as catalyst), it is possible to perform selective, high-yielding alkylation and benzylation reactions at the *ortho*-position of the benzene ring in 2-phenylpyrroles. Regioselective monoalkylation reactions at various electron-deficient pyrroles are possible with functionalized primary alkyl bromides or benzyl chlorides. The reaction enables a late-stage functionalization reaction of 2-phenylpyrroles under mild conditions. Our preliminary results are summarized in this communication.

A major obstacle to overcome when attempting an alkylation of free (i.e., N-unprotected) 2-phenylpyrroles is their high

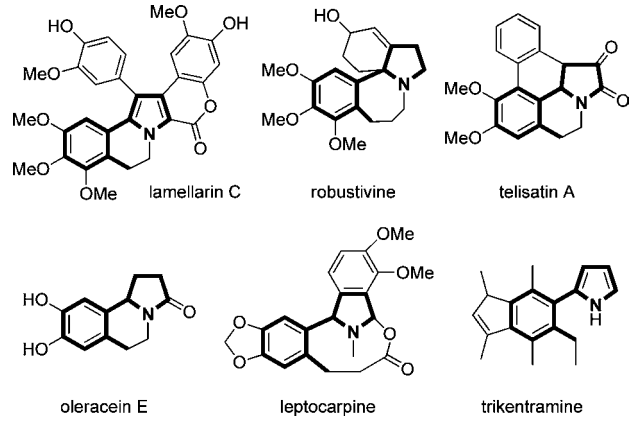


Figure 1. Representative natural products exhibiting an *ortho*-alkylated 2-phenylpyrrole skeleton.

nucleophilicity at the nitrogen atom. N-Alkylation occurs readily[12] and renders the nitrogen atom inaccessible to direct the approach of a transition metal. In recent work on the regioselective alkylation of free indoles and pyrroles, we found that N-alkylation can be avoided by the use of weak bases in the presence of a suitable palladium catalyst.[13] We therefore started preliminary experiments by employing $PdCl_2(MeCN)_2$ as a potential palladium catalyst and K_2HPO_4 as a base. Ethyl 2-(*ortho*-tolyl)pyrrole-4-carboxylate (**1a**) was chosen as a representative 2-phenylpyrrole and butyl bromide as the alkylating agent (Table 1, EWG = electron-withdrawing group). We found, under these conditions at 70 °C in DMA as the solvent, a low but notable butylation to product **2a** (entry 1). Increasing the reaction temperature led to an improved

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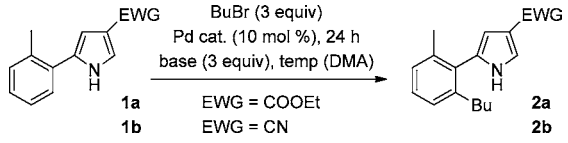
Table 1. Optimization of the Pd-Catalyzed Butylation of 1a



entry	temp (°C)	Pd source	base	conv[a] (%)	yield[a] (%)
1	70	$PdCl_2(MeCN)_2$	K_2HPO_4	15	10
2	90	$PdCl_2(MeCN)_2$	K_2HPO_4	39	22
3	110	$PdCl_2(MeCN)_2$	K_2HPO_4	41	14
4	90	$PdCl_2(PPh_3)_2$	K_2HPO_4	5	–
5	90	$PdBr_2$	K_2HPO_4	43	31
6	90	$PdBr_2$	$CsHCO_3$	87	23[b]
7	90	$PdBr_2$	$KHCO_3$	69	46[b]
8	90	–	$KHCO_3$	36	–
9	90	$PdBr_2$	$NaHCO_3$	44	40
10	90	$PdBr_2$	Li_2CO_3	40	39
11[c]	90	$PdBr_2$	Li_2CO_3	52	48
12[c,d]	90	$PdBr_2$	Li_2CO_3	83	78[d]
13[e]	90	$PdBr_2$	Li_2CO_3	4	4

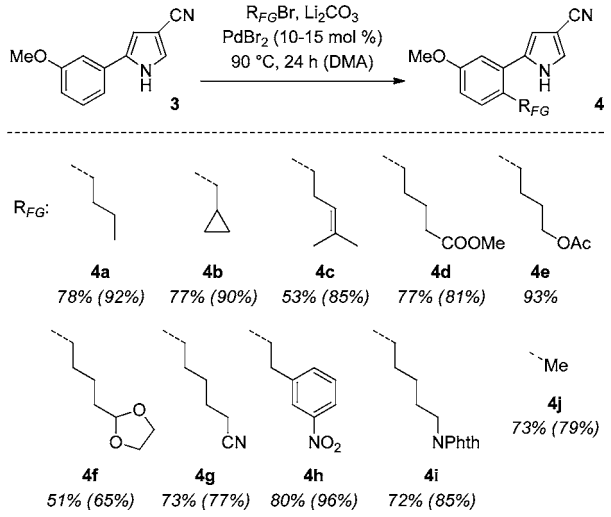
[a]Determined by GLC using dodecane as an internal standard. [b]Difference between conversion and yield is mainly due to formation of N-alkylation product. [c]15 mol % of $PdBr_2$ was used. [d]Reaction was performed on a preparative scale with **1b** instead of **1a**. The reaction product was the 4-cyano analogue of **2a**, compound **2b**. [e]Butyl iodide was used as the butylating reagent.

conversion but also induced significant N-alkylation, as indicated by the decrease in yield for **2a** (entries 2 and 3, footnote *b*). An extensive variation of the palladium catalyst led to the conclusion that phosphane coordination is detrimental to its catalytic properties (e.g., entry 4), while $PdBr_2$ showed improved reactivity and selectivity versus $PdCl_2(MeCN)_2$ (entry 5). The degree of N-alkylation could be lowered by adapting the base strength. In the order $CsHCO_3 < KHCO_3 < NaHCO_3 < Li_2CO_3$, there was a decrease of N-alkylation (entries 6, 7, 9, and 10) and an increase (entries 6 and 7) in yield for the C-alkylation product **2a**. If $PdBr_2$ was omitted, only N-alkylation was observed (entry 8). The relative low conversion even under optimized conditions could be improved by increasing the amount of catalyst to 15 mol % (entry 11) and by increasing the acidity of the pyrrole. 4-Cyano-2-(*ortho*-tolyl)pyrrole (**1b**) reacted on a preparative scale (entry 12) to the butylated product **2b** in a high yield of 78% (94% based on conversion). When butyl bromide was replaced with butyl iodide, the selectivity remained high but conversion ceased almost completely (entry 13).

To evaluate the functional group tolerance of the 2-phenylpyrrole alkylation, we chose 4-cyano-2-(*meta*-methoxyphenyl)pyrrole (**3**) as the substrate. As with the *ortho*-substituted 2-phenylpyrroles **1a** and **1b**, exclusive monoalkylation was observed in the *ortho*-position relative to the pyrrole unit. Pyrrole alkylation was not observed. Employing 10 mol % of $PdBr_2$, butylation product **4a** was obtained in 78% yield (Scheme 1; yields in brackets are based on conversion). For all other methylation (product **4j**) and alkylation reactions, the catalyst loading was raised to 15 mol % to increase conversion. Functional group tolerance was established toward cyclopropyl (product **4b**), alkenyl (**4c**), ester (**4d**), acetoxy (**4e**), acetal (**4f**), cyano (**4g**), nitro (**4h**), and protected (Phth = phthaloyl) amino groups (**4i**).

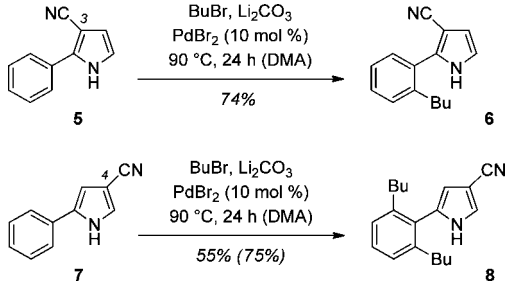
The higher electron-withdrawing power of the cyano group resulted—as it did for **1b** versus **1a**—in an improved reactivity

Scheme 1. Pd-Catalyzed Alkylation of 3 with Various Functionalized Alkyl Bromides (FG = Functional Group)



compared to that of the ethoxycarbonyl analogue of **3**. If the cyano group was positioned at carbon atom C3 of the pyrrole, it showed an activity similar to that at C4 (Scheme 2, **5**→**6**). In

Scheme 2. Pd-Catalyzed Butylation of Cyano-Substituted 2-Phenylpyrroles 5 and 7



addition, it rendered a second alkylation impossible because rotation around the C_{aryl}–$C_{pyrrole}$ bond is restricted. After monoalkylation, the second *ortho*-position in **6** cannot be exposed to the directing group. In contrast to this result, double alkylation was observed for 4-cyano-2-phenylpyrrole (**7**), and product **8** was obtained in good yield.

For benzylation reactions of 2-phenylpyrroles, it was sufficient to employ the respective chlorides as electrophiles (Scheme 3; yields based on conversion). A catalyst loading of 10 mol % guaranteed complete (**9a**,**c**–**e**,**g**–**i**) or high conversion (**9b**,**f**). As observed in the alkylation reactions, the presence of an EWG in position C3 of the pyrrole core avoided double benzylation, and monobenzylated products **9e**–**g** were obtained. A total of eight further benzylation reactions with FG-substituted benzyl chlorides was performed (74–90% yield). Details can be found in the Supporting Information.

If allyl chloride was employed as reagent instead of benzyl chloride, etheno-bridged tricyclic products were isolated (Scheme 4). Pyrrole **3** gave product **10** in 59% yield (88% based on conversion). Apparently, a Pd-induced pyrrole addition[14] follows the initial allylation reaction. An ethano bridge could be installed at 3-nitro-2-phenylpyrrole (**11**) upon treatment with 2-chloroethyl bromide under standard conditions. The propano bridge, which is relevant to the synthesis of

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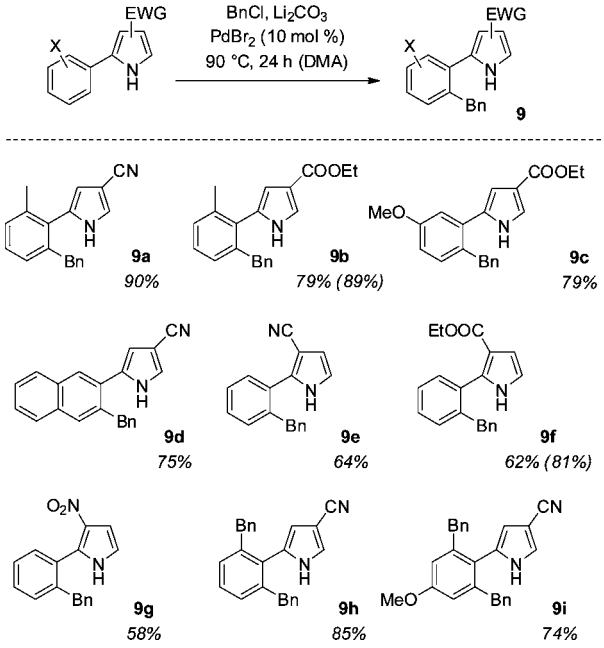
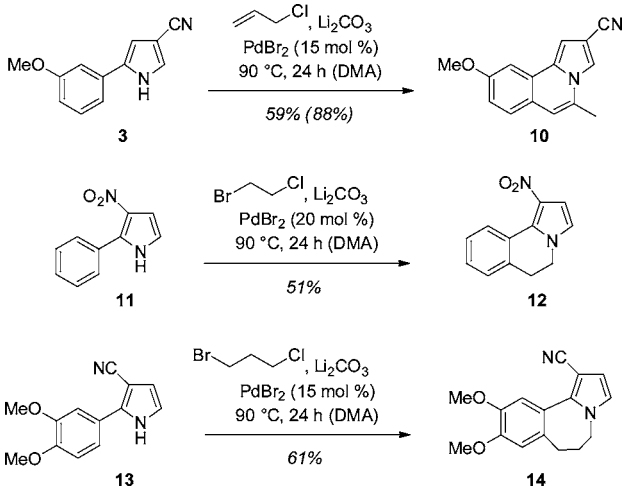
Scheme 3. Pd-Catalyzed Benzylation of Various EWG-Substituted 2-Phenylpyrroles



Scheme 4. Pd-Catalyzed Domino Reaction: *ortho*-Alkylation and Cyclization



naturally occurring pyrrolobenzazepines (e.g., robustivine, Figure 1), was readily established with 3-chloropropyl bromide as the alkylating agent (e.g., **13**→**14**).

Mechanistically, evidence was collected showing that the NH group at the pyrrole core is crucial for the C−H activation reaction. If the N-methylated derivative of ethyl 2-(*meta*-methoxyphenyl)pyrrole-4-carboxylate (**15a**), pyrrole **15b** (Figure 2), was subjected to the conditions of the benzylation reaction, there was no indication of a reaction. If compound **15a** was treated with a base (K_2CO_3 or Li_2CO_3) and $PdBr_2$ in the absence of an alkylating reagent, a new species was detected by ^{1}H NMR spectroscopy,[15] which lacked the pyrrole NH proton and one proton at the methoxyphenyl core. Chemical shift data (Figure 2) support the depicted structure assignment for this species as palladacycle **16** (L = ligand).

This intermediate is likely formed by *ortho*-palladation at the methoxyphenyl ring after initial Pd-mediated deprotonation of

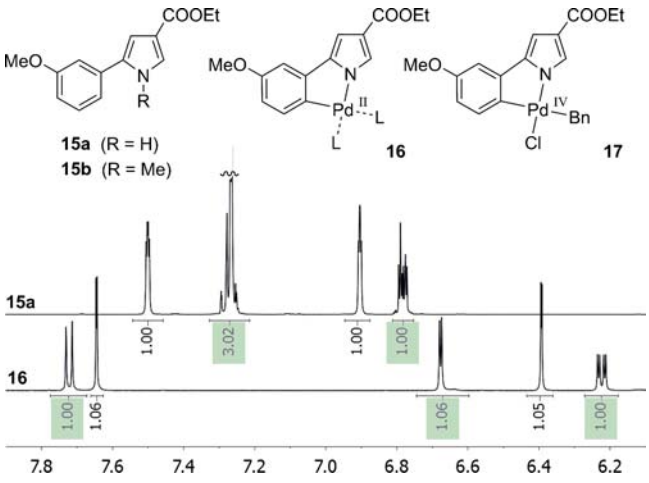
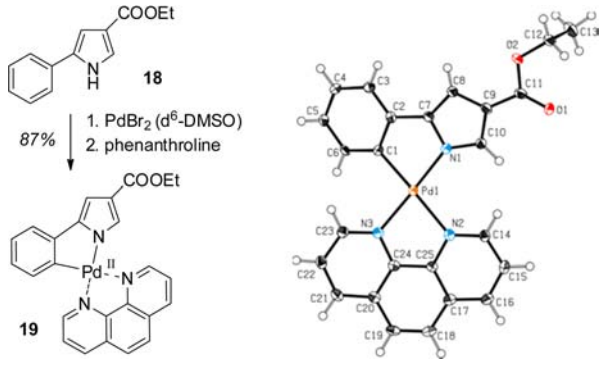


Figure 2. Top: Structure of pyrroles **15** and of catalytic intermediates **16** (L = ligand) and **17**. Bottom: Partial view of the ^{1}H NMR spectrum of intermediate **16** obtained upon treatment of **15a** with K_2CO_3 (1.2 equiv) and $PdBr_2$ (1.2 equiv) at 60 °C in DMSO-d_6. Starting material **15a** reveals four proton signals for the 2-(*para*-methoxyphenyl) group, while one proton signal is absent in intermediate **16** (integration in gray). The two pyrrole protons at C3 and C5 appear as a doublet of doublets (dd) in **15a** but as a doublet (d) in **16**, indicating the loss of the NH proton.

the pyrrole NH proton. The reaction is reversible, as shown by addition of pyrrole **3** to the solution of **16** in DMSO-d_6. An equilibrium mixture of two *ortho*-palladated pyrrole species was detected in conjunction with the free pyrroles **3** and **15a**. Further reaction course is suggested to involve an oxidative addition of alkyl bromide or benzyl chloride (BnCl) at intermediate **16** to form Pd^{IV} complex **17** (shown as a product of the BnCl reaction; ligands omitted).[16] Subsequent reductive elimination leads to C−C bond formation and liberation of the catalyst. The existence of *ortho*-palladated 2-phenylpyrroles such as **16** was further corroborated by the preparation of stable phenanthroline complex **19** (Scheme 5). Upon treatment of ethyl 2-phenyl-

Scheme 5. Preparation of Phenanthroline Complex 19 (Left) and Its Crystal Structure (Right)



pyrrole-4-carboxylate (**18**) with $PdBr_2$ under the conditions employed for the C−H activation of compound **15a** and upon addition of phenanthroline, a crystalline material could be obtained. Product **19** was isolated in 87% yield and was structurally characterized by single-crystal X-ray analysis (see Supporting Information). The structure, which features a square-planar palladium center and a carbon−palladium bond with a

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length of 2.01 Å, lends further credibility to the hypothesis of an initial pyrrole-directed C−H activation reaction.

In summary, the pyrrole nucleus has been shown to be an effective handle to mediate Pd-catalyzed C−H activation reactions at adjacent C(sp^2) centers. 2-Phenylpyrroles were selectively alkylated and benzylated at the *ortho*-position of the benzene core. A palladacycle, in which the pyrrole nitrogen atom and the *ortho*-carbon atom of the phenyl group are bound to palladium, is a likely intermediate of the catalytic cycle. Its structure could be determined by X-ray crystallographic analysis of the respective phenanthroline complex. Given the abundance of 2-phenylpyrroles, the reaction should be useful for late-stage functionalization reactions. Ongoing work is devoted to an in-depth exploration of the alkylation reaction and to an expansion of the directing group properties of pyrrole to other C−H activation reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00141.

Experimental procedures, analytical data for all new compounds, and NMR spectra (PDF)
X-ray data for **19** (CIF)

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Notes

The authors declare no competing financial interest.

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