Late stage Pd-catalyzed C-H bond functionalization: A powerful tool for the one step access to arylated Cyproheptadine and cyclobenzaprine derivatives

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Late stage Pd-catalyzed C-H bond functionalization: A powerful tool for the one step access to arylated Cyproheptadine and Cyclobenzaprine derivatives

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Abstract— The reactivity of Cyproheptadine and Cyclobenzaprine in Pd-catalyzed arylation *via* C-H bond functionalizations was investigated. From Cyproheptadine using aryl bromides as aryl sources and 5 mol% of a palladium catalyst, the C10-arylated Cyproheptadine derivatives were regioselectively obtained. The highest yields were obtained with electron-rich aryl bromides, but the reaction tolerated useful functional groups on the aryl bromide such as dimethylamino, methoxy, hydroxyl, alkyl, aryl, fluoro, chloro and trifluoromethyl. Cyclobenzaprine was also reactive under the same reaction conditions.

Keywords: palladium, C-H bond functionalization, Cyproheptadine, Cyclobenzaprine, aryl bromides

1. Introduction

The dibenzo[*a*,*d*][7]annulene unit (Fig 1, top) can be found in several drugs. For example, Cyproheptadine is used to treat allergic reactions and cyclical vomiting syndrome; whereas Cyclobenzaprine is employed as muscle relaxer medication to relieve skeletal muscle spasms (Fig. 1, bottom). Moreover, Cyproheptadine might be useful for breast cancer treatment [1,2]. Amitriptyline, which can be prepared by reduction of the C_{10}=C_{11} double bond of Cyclobenzaprine [3], is one of the most efficient drugs used in the treatment of depression (Fig. 1, bottom) [4]. Therefore, the development of a methodology employing the so-called late stage C-H bond functionalization allowing the easy access in one step to a wide variety of derivatives of these drugs containing useful functional groups has potential in pharmaceutical chemistry.

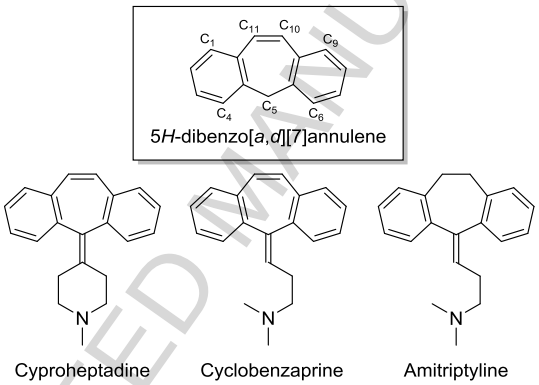
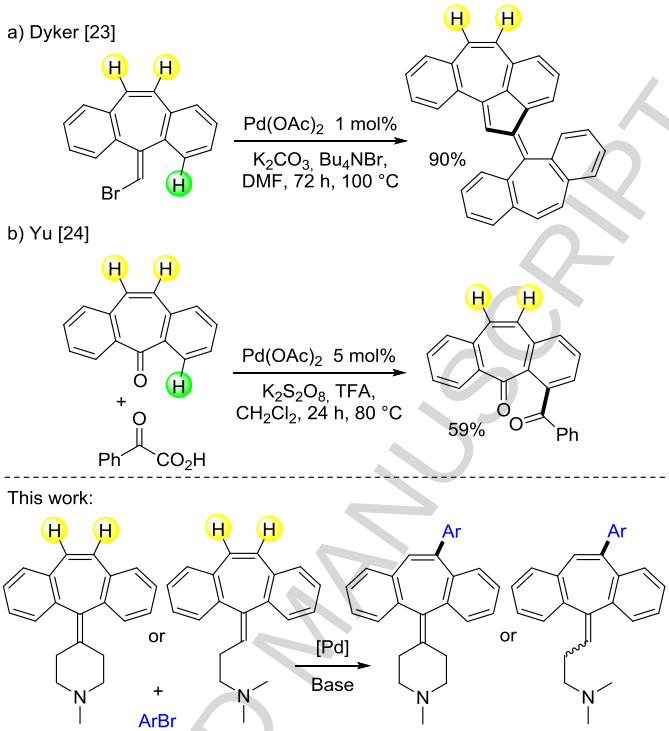


Figure 1 Structures of 5*H*-dibenzo[*a*,*d*][7]annulene, Cyproheptadine, Cyclobenzaprine and Amitriptyline

During the last decades, the metal-catalyzed C–H bond functionalization of a broad range of the sp^2 C-H bonds [5-14] including cyclic alkenes [15-21] were demonstrated to be extremely effective for the access to sophisticated structures. With cyclic alkenes, in general the reaction likely proceed *via* a Heck type mechanism. However, as the Heck type β-H elimination step is not possible with these substrates – as the hydrogen involved in the β-hydride elimination process is *anti* with respect to the Pd-C bond – , a *syn* β'-hydride elimination may occur in some cases [22]. These methodologies are very attractive in terms of late-stage functionalization as it does not require the preparation of an organometallic or a boron derivative of one of the coupling partners. A few examples of metal-catalyzed C–H bond functionalization of the C4-position of dibenzo[*a*,*d*][7]annulene units have been reported [23-26]. For example, in 1996, Dyker described one example of C4-functionalization of a 5-methylene-5H-dibenzo[*a*,*d*][7]annulene *via* Pd-catalysis (Scheme 1, a) [23]. In 2017, Yu et al. reported

conditions for the intermolecular C4-acylation of 5H-dibenzo[*a*,*d*][7]annulen-5-one with 2-oxo-2-phenylacetic acid using 5 mol% $Pd(OAc)_2$ catalyst (Scheme 1, b) [24]. In 2016, Nakamura, Ilies et al. methylated the C4-position of 5H-dibenzo[*a*,*d*][7]annulen-5-one with $AlMe_3$ using a Fe-catalyst [25], and very recently, Sundara-raju et al. described conditions for the Co-catalyzed C4-alkylation of this annulen-5-one with a maleimide [26].



Scheme 1 Pd-catalyzed C-H bond functionalizations of dibenzo[*a*,*d*][7]annulene units and of Cyproheptadine and Cyclobenzaprine.

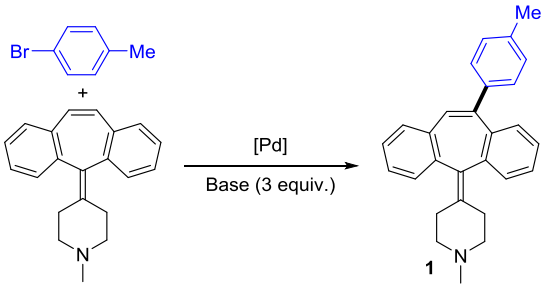
To our knowledge, the Pd-catalyzed C-H bond functionalization of Cyproheptadine and Cyclobenzaprine has not yet been described and needed to be investigated. Herein, we report on the reactivity of Cyproheptadine and Cyclobenzaprine in palladium-catalyzed arylations *via* a C-H bond functionalization using a variety of aryl bromides as the aryl source.

2. Results and discussion

First, we examined the reactivity of Cyproheptadine in Pd-catalyzed direct arylation in the presence KOAc as base using DMA as the solvent (Table 1), as we had previously observed that these reaction conditions allowed the coupling of fulvene, acenaphthylene or dibenzo[*b*,*f*]azepine derivatives with aryl bromides [11,12]. Reactions performed with 5 mol% $Pd(OAc)_2$ or $PdCl_2(MeCN)_2$ as the catalysts at 150 °C during 16 or 48 h using 4-bromotoluene as the aryl source regioselectively afforded the C10-

arylated Cyproheptadine **1** in 17-27% yields (Table 1, entries 1- 3). No arylations at other positions of Cyproheptadine were observed by GC/MS analysis of the crude mixtures. Then, the influence of a set of phosphine ligands on the reaction was examined. Higher yields in **1** were obtained with PPh_3 and dppb than with the electron-rich PCy_3 ligand (Table 1, entries 4-7). The use of $PdCl(C_3H_5)$(dppb) [27] as the catalyst afforded **1** in a higher yield of 41% (Table 1, entry 8). Other bases (K_2CO_3, Cs_2CO_3, CsOAc, NaOAc or DBU) and other solvents (DMF, NMP and xylene), afforded **1** in lower yields (Table 1, entries 9-16). Using a shorter reaction time (16 h instead of 48 h), **1** was obtained in a similar yield; whereas after 4 h the yield in **1** dropped to 34% due to a partial conversion of 4-bromotoluene (Table 1, entries 17 and 18). The use of 4-iodotoluene instead of 4-bromotoluene with $PdCl(C_3H_5)$(dppb) catalyst afforded **1** in only 11% yield, and the formation of a large amount of 4,4'-dimethyl-1,1'-biphenyl due to the homo-coupling of 4-iodotoluene was observed (Table 1, entry 19). On the other hand, with 4-chlorotoluene as aryl source, product **1** was obtained in 19% due to a poor conversion of this aryl chloride (Table 1, entry 20).

Table 1. Influence of the reaction conditions on the coupling of Cyproheptadine with 4-bromotoluene

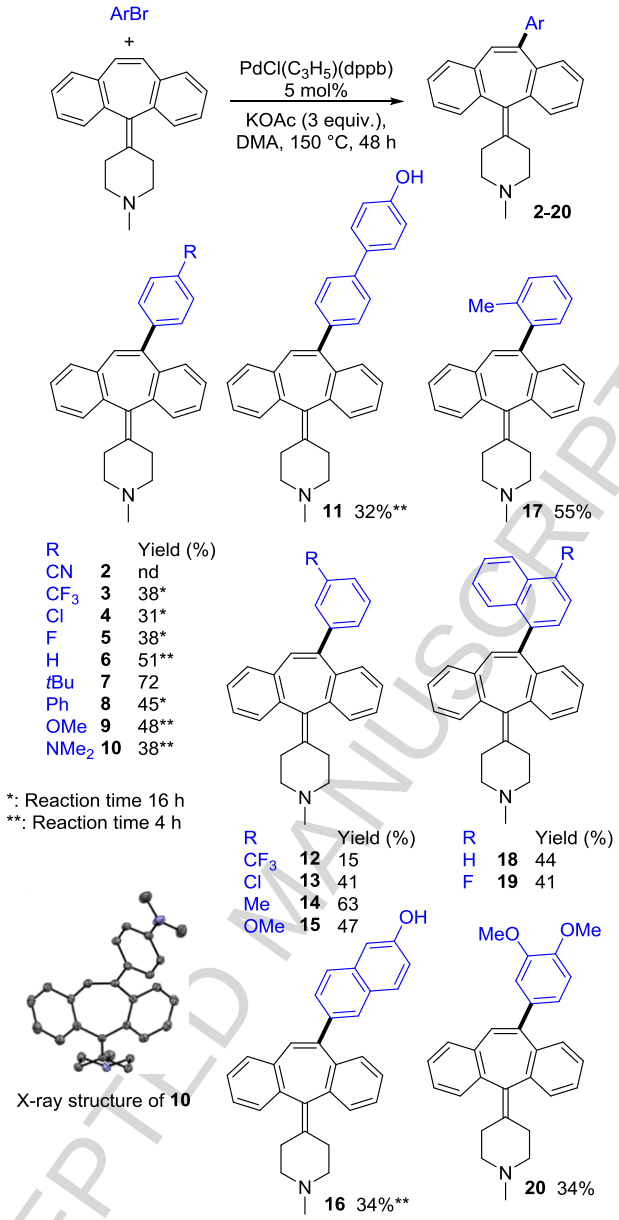


Entry	Catalyst (mol%)	Solvent	Base	Yield (%)
1	$Pd(OAc)_2$	DMA	KOAc	24
2	$Pd(OAc)_2$	DMA	KOAc	17[a]
3	$PdCl_2(MeCN)_2$	DMA	KOAc	27
4	$Pd(OAc)_2$ / 2 PPh_3	DMA	KOAc	20[a]
5	$Pd(OAc)_2$ / 2 PCy_3	DMA	KOAc	6[a]
6	$Pd(OAc)_2$ / dppe	DMA	KOAc	14[a]
7	$Pd(OAc)_2$ / dppb	DMA	KOAc	24[a]
8	$PdCl(C_3H_5)$(dppb)	DMA	KOAc	41
9	$PdCl(C_3H_5)$(dppb)	DMA	K_2CO_3	0
10	$PdCl(C_3H_5)$(dppb)	DMA	Cs_2CO_3	0
11	$PdCl(C_3H_5)$(dppb)	DMA	CsOAc	5
12	$PdCl(C_3H_5)$(dppb)	DMA	NaOAc	8
13	$PdCl(C_3H_5)$(dppb)	DMA	DBU	5[a]
14	$PdCl(C_3H_5)$(dppb)	DMF	KOAc	0
15	$PdCl(C_3H_5)$(dppb)	NMP	KOAc	5
16	$PdCl(C_3H_5)$(dppb)	xylene	KOAc	0
17	$PdCl(C_3H_5)$(dppb)	DMA	KOAc	39[a]
18	$PdCl(C_3H_5)$(dppb)	DMA	KOAc	34[b]
19	$PdCl(C_3H_5)$(dppb)	DMA	KOAc	11[a,c]
20	$PdCl(C_3H_5)$(dppb)	DMA	KOAc	19[a,d]

Conditions: Catalyst (0.05 equiv.), Cyproheptadine (1 equiv.), 4-bromotoluene (2 equiv.), base (3 equiv.), 48 h, 150 °C, isolated yields of **1**. [a] 16 h. [b] 4 h. [c] From 4-iodotoluene. [d] From 4-chlorotoluene.

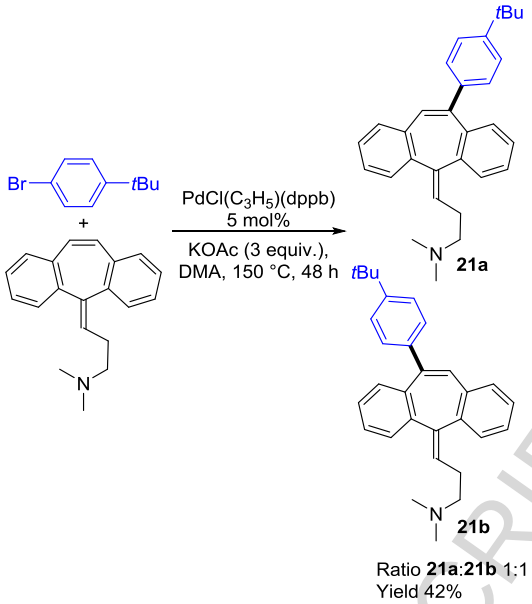
Then, the scope of the coupling of Cyproheptadine with a set of aryl bromides in the presence of 5 mol% $PdCl(C_3H_5)$(dppb), KOAc as the base in DMA at 150 °C was investigated (Scheme 2). No formation of the desired product **2** was detected with the highly electron-deficient 4-bromobenzonitrile. Conversely, low yields in the target products **3**-**5** were obtained for the reactions with the less electron-deficient 4-bromobenzotrifluoride, 4-bromochlorobenzene and 4-bromofluorobenzene, although complete conversions of these aryl bromides were observed. With these three aryl bromides, the formation of large amounts of aryl bromide homo-coupling products and unidentified degradation products was observed by NMR analysis of the crude mixtures. Higher yields were obtained for the reactions with electron-neutral or -rich aryl bromides. From bromobenzene, the C10-phenyl substituted Cyproheptadine **6** was obtained in 51% yield. Aryl bromides bearing *tert*-butyl, phenyl or methoxy *para*-substituents afforded the target products **7**-**9** in 45-72% yields. Even 4-bromo-*N*,*N*-dimethylaniline was reactive providing the product **10** in 38% yield. The structure of **10** was confirmed by X-ray analysis. From a 4-bromobiphenyl bearing a free OH group, the desired product **11** was obtained in moderate yield. Interestingly, the OH group remained untouched allowing further transformations. The low reactivity of electron-poor aryl halides compared to electron-rich aryl halides had already been observed for related Pd catalyzed reactions [28].

The reactivity of four *meta*-substituted aryl bromides was also examined. Again, the "quite strong" electron-withdrawing substituent CF_3 on the aryl bromide led to the coupling product **12** a in lower yield than the chloro-, methyl- and methoxy-substituted aryl bromides which afforded the products **13**-**15** in 41-63% yields. Unprotected 6-bromo-2-naphthol and the more hindered 2-bromotoluene, 1-bromonaphthalene and 1-bromo-4-fluoronaphthalene were also found to be useful substrates for this reaction, as the products **16**-**19** were obtained in 34-55% yields. Finally, the dimethoxy-substituted aryl bromide, 4-bromoveratrole provided the C10-arylated Cyproheptadine derivative **20** in 34% yield.



Scheme 2 Palladium-catalyzed C10-arylations of Cyproheptadine.

By contrast, the direct arylation of Cyclobenzaprine with 1-bromo-4-*tert*-butylbenzene produced an equimolar mixture of the two regioisomeric compounds **21a** and **21b** in 42% yield (Scheme 3).



Scheme 3 Palladium-catalyzed direct arylations of Cyclobenzaprine.

These two regioisomers were separated by silica gel column chromatography, and the structures of **21a** and **21b** were assigned by NMR analysis. Relevant spatial proximities (determined by NOESY experiments) are shown in figure 2 (see supporting information for more details). Structure of **21a** is supposed to be twisted since a correlation is seen between protons from the aryl of *t*Bu-aryl group and *N*-methyl. It can be seen from the X-ray solid structure of **10** that the NMe_2-aryl group and the methyl-piperidine moiety are located on the same side of the tricyclic part. For **21a**, methyl-piperidine is replaced by a *N*,*N*-dimethylethanamine unit which is likely to be much more flexible.

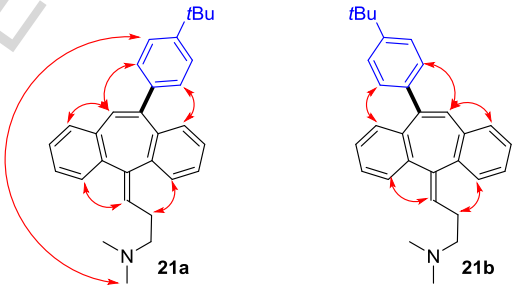


Figure 2 Relevant NOESY correlations observed for compounds **21a** and **21b**

In summary, we report here the first method allowing to prepare C10-arylated Cyproheptadine derivatives. As this method employs the so-called late-stage C-H bond functionalization methodology, no preparation of specific starting materials is required allowing an easy tuning of the steric and electronic properties of the introduced

aryl group. Moreover, these arylation were performed using the air-stable $PdCl(C_3H_5)$(dppb) catalyst precursor associated to KOAc as inexpensive base, and tolerated useful functional groups on the aryl bromide such as di-methylamino, methoxy, hydroxyl, alkyl, aryl, fluoro, chloro and trifluoromethyl. We also describe the catalytic C10/C11-arylation of Cyclobenzaprine. In the course of this reaction an equimolar mixture of the two regioi-somers which could be separated by column chromatography was formed. Such late-stage functionalizations of important drugs should allow a fast screening of the influence of aryl groups at C10-position on their biological properties. This work should also lead to the development of new synthetic pathways by functionalizing the C10/C11 positions of these drugs through the use of different coupling partners.

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*Highlights

- First regioselective arylations at the C10-position of Cyproheptadine
- One step access to Cyproheptadine congeners
- Good functional group tolerance
- Air and moisture tolerant Pd-catalyst

Graphical abstract