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Short communication

Palladium-catalyzed non-directed C–H bond arylation of difluorobenzenes and dichlorobenzenes bearing benzoxazole or benzothiazole

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ABSTRACT

We report, herein, on palladium-catalyzed direct arylation of difluorobenzenes and dichlorobenzenes bearing benzoxazole or benzothiazole moieties, which don't act as directing groups. With moderate electron-withdrawing substituents on the aryl bromides as coupling partners, the reaction proceeds nicely using phosphine-free $PdCl_2$ catalyst, and potassium pivalate/dimethylacetamide (PivOK/DMA) as catalytic system. The reaction was regioselective and occurred at the less hindered *ortho*-positions of fluorine or chlorine atoms.

1. Introduction

Difluorobenzenes substituted by benzoxazole or benzothiazole units are an important class of ligands. As example, the cyclometalated iridium complex **I** is a photoluminescent complex involved in the construction of organic light emitting diodes [1–3]. The blue-light-emitting zinc material **II** has been synthesized from 2-(5-fluoro-hydroxyphenyl)benzothiazole [4]. The iridium catalyst **III**, with two 2-(3,5-difluorophenyl)benzoxazole ligands, displays a high activity in water splitting [5]. In addition, the motifs benzothiazole and benzoxazole are present in many pharmaceuticals. As example, 2-(benzothiazol-2-yl)-*N*,*N*-bis(2-chloroethyl)-5-fluorobenzenamine (**IV**) displays high activity against human cervical cancer cell lines [6,7], and 2-(3-fluorophenyl)-1-(1-(3-fluorophenyl)-1,2,3-triazol-4-yl)methylbenzimidazole (**V**) exhibits antitubercular properties [8] (Fig. 1).

Nowadays, the functionalization of C–H bonds is an important research area, as such methodologies provide an atom economic access to complex molecules [9–13]. Since the pioneering work of Fagnou and co-workers on palladium-catalyzed direct arylation of electron-deficient polyfluorobenzenes, this methodology proved as one of the most reliable and easiest access to (poly)fluorobiphenyls (Fig. 2a) [14]. Their work induced emulation in direct arylation of electron-deficient arenes [11]. Among other improvements, a particular attention has focused on the use of alternative coupling partners to aryl halides (e.g., tosylates [15–17], diaryliodonium salts [18], boronic acids [19,20], $ArSO_2Na$ [21], carboxylic acid [22] or simple arenes under oxidative conditions [23]), or the use of other catalytic systems [24,25]. In order to address the lower reactivity of less-electron deficient fluorobenzenes [14,26,27], directing group (e.g., carboxylic acid) strategy has been employed [28,29]. On the other hand, benzoxazole unit has been employed as a directing group for the regioselective C2 arylation of phenyl using a palladium catalyst in the presence of silver carbonate in trifluoroacetic acid (Fig. 2b) [30,31]. A similar procedure was reported by Ding, Peng and co-workers for the direct C2 arylation of 2-arylbenzothiazole (Fig. 2c) [32]. To the best of our knowledge, the reactivity of dihalogenophenyls bearing a benzoxazole or a benzothiazole as potential directing groups in palladium-catalyzed direct arylation has never been reported. Furthermore, the reactivities and regioselectivities in palladium-catalyzed direct arylation of such substrates needed to be investigated (Fig. 2d).

2. Results and discussion

We selected 2-(3,5-difluorophenyl)benzoxazole and 4-bromobenzonitrile as model substrates, and we used our previous optimized reaction conditions described for the direct arylation of 3-substituted fluorobenzenes, namely, 5 mol% $PdCl(C_3H_5)(dppb)$ catalyst in the presence of KOAc as base in DMA at 150 °C (Table 1, entry 1) [33]. We were pleased to find that the reaction occurred regioselectively at the C–H

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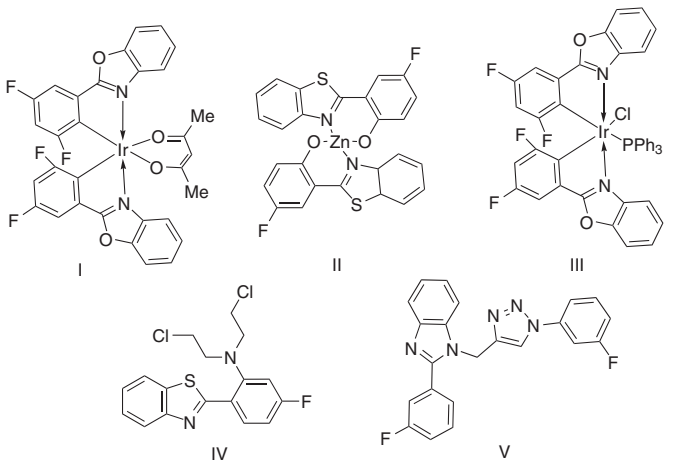
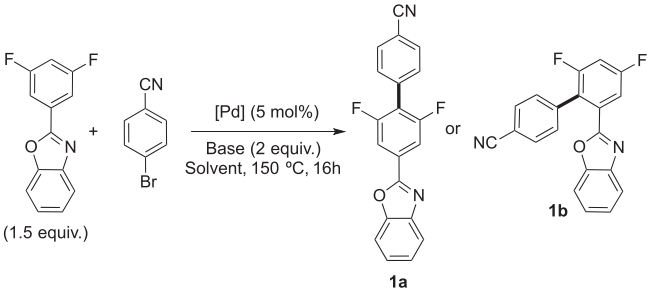


Fig. 1. Relevant structures containing difluorobenzenes substituted by a benzoxazole or a benzothiazole.

bond flanked by the two fluorine atoms to afford the regioisomer **1a** in 53% yield. It is important to note that the regioisomer **1b**, resulting from a benzoxazolyl directed C–H bond arylation, was not detected. This result (i.e., the most acidic C–H bond reacts preferentially) suggests that, under these reaction conditions, a concerted metalation–deprotonation mechanism is operative instead of a directed C–H bond activation process. Then, we employed other palladium sources. Phosphine-free $Pd(OAc)_2$ gave a lower 45% yield, whereas using 5 mol% $PdCl_2$ a higher yield of 57% was obtained (Table 1, entries 2 and 3). $Pd_2(dba)_3$ catalyst was also effective for this reaction, albeit **1a** was isolated in a lower yield (Table 1, entry 4). Then, we investigated the effect of the base on this transformation. Potassium carbonate led to a very low yield in **1a** due to a low conversion (Table 1, entry 5). The highest yield in **1a** was obtained using PivOK as base with 75% isolated yield of **1a** (Table 1, entry 6). As proposed by Fagnou and co-workers [14], PivOK certainly acts as a proton-shuttle in the CMD mechanism and facilitates the C–H bond cleavage. PivONa exhibits a slightly lower efficiency, probability because of its lower solubility in DMA (Table 1, entry 7). Notably, a lower amount of catalyst (i.e., 2 mol% $PdCl_2$) gave lower yield in **1a** (Table 1, entry 8). Finally, other solvents were tested for the direct arylation of 2-(3,5-difluorophenyl)benzoxazole. DMF and DMSO were completely ineffective for this reaction as only starting materials and bromoarene homocoupling were detected (Table 1, entries 9 and 10). Then, we used xylene as non-polar and non-coordinating solvent in order to favor the benzoxazolyl directed C–H bond activation process; however no reaction occurred (Table 1, entry 11). It should be mentioned that when the reaction was performed from 3,5-difluorobenzaldehyde instead of 2-(3,5-difluorophenyl)benzoxazole, no coupling product was detected (Table 1, entry 12).

Table 1
Optimization of the reaction conditions.



Entry	[Pd]	Base	Solvent	Yield 1a (%)
1	$PdCl(C_3H_5)(dppb)$	KOAc	DMA	53
2	$Pd(OAc)_2$	KOAc	DMA	45
3	$PdCl_2$	KOAc	DMA	57
4	$Pd_2(dba)_3$	KOAc	DMA	32
5	$PdCl_2$	K_2CO_3	DMA	12
6	$PdCl_2$	PivOK	DMA	75
7	$PdCl_2$	PivONa	DMA	67
8[a]	$PdCl_2$	PivOK	DMA	56
9	$PdCl_2$	PivOK	DMF	0
10	$PdCl_2$	PivOK	DMSO	0
11	$PdCl_2$	PivOK	Xylene	0
12[b]	$PdCl_2$	PivOK	DMA	0

[a] The reaction was performed using 2 mol% of $PdCl_2$.
[b] The reaction was performed from 3,5-difluorobenzaldehyde.

With the optimized conditions in hands, we turned our attention to the scope and limitation of this palladium-catalyzed non-directed C–H bond arylation. Firstly, we performed the C4 direct arylation of 2-(3,5-difluorophenyl)benzoxazole with a set of aryl bromides (Scheme 1). Other aryl bromides containing electron-withdrawing *para*-substituents, such as 4-bromoacetophenone or ethyl 4-bromobenzoate, smoothly reacted to afford the desired C4-arylated products **2** and **3** in 82% and 84% yields, respectively. Not surprisingly, 2-bromobenzonitrile, which has a low steric profile and higher Hammett constant that 4-bromobenzonitrile (0.71 vs 0.66) [34], exhibited a higher reactivity to give the desired product **4** in 89% yield. However, more bulky 2-bromobenzaldehyde led to the C4-arylated compound **5** in only 67% yield. Then, we investigated the reactivity of a set of six-membered ring heteroaryl bromides. 3-Bromopyridine reacts with 2-(3,5-difluorophenyl)benzoxazole to give the C4-arylated product **6** in moderate 46% yield. The arylated products **7** and **8** – resulting from the cross-coupling with 3-bromoquinoline and 5-bromopyrimidine – were isolated in high 73% and 71% yields, respectively. However, it is important to note that ligand-free $PdCl_2$/PivOK system did not allow the use of aryl bromides bearing electron-donating substituents due to a slower oxidative addition process.

Next, we studied the reactivity of 2-(3,5-difluorophenyl) benzothiazole in palladium-catalyzed C–H bond arylation (Scheme 2). Interestingly, unlike benzoxazole, benzothiazole exhibits directing

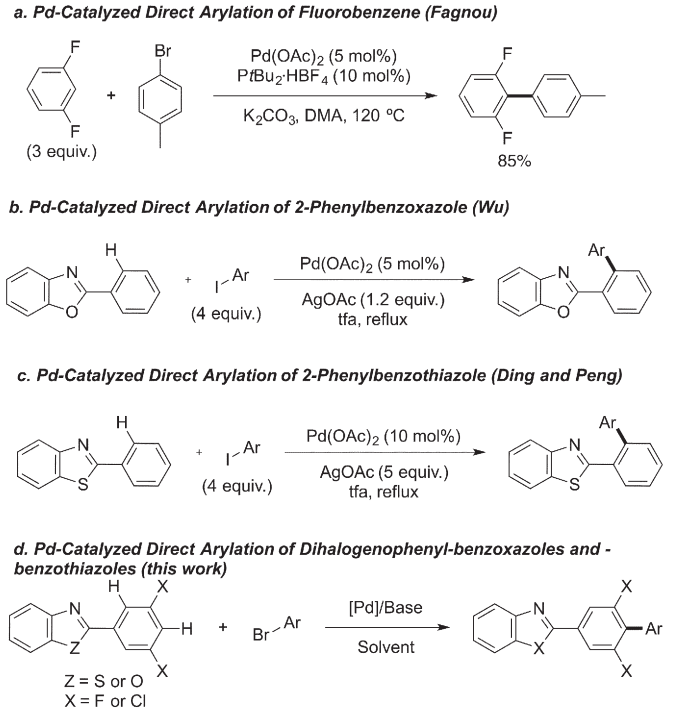


Fig. 2. Previous palladium-catalyzed intermolecular direct arylations of fluorobenzenes, 2-arylbenzothiazoles or 2-arylbenzoxazoles.