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.

Keywords: Arylation, Palladium, C-H Bond Activation, Heterocycles, Fluorine Chemistry.

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 synthetized 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)methylbenzoimidazole (**V**) exhibits antitubercular properties.[8]

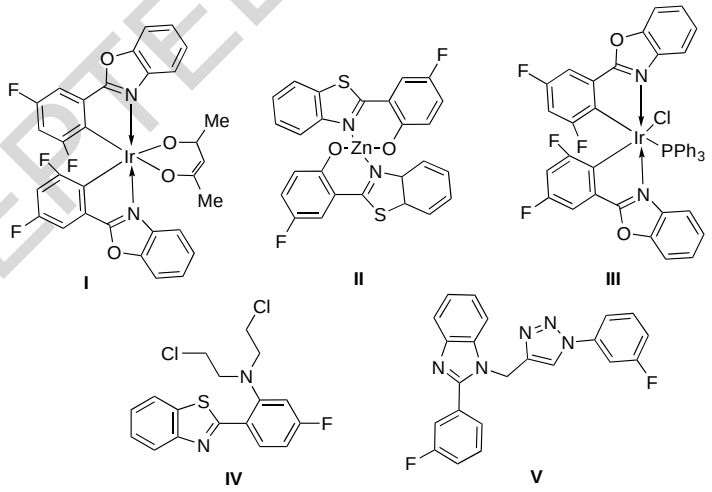


Figure 1. Relevant Structures Containing Difluorobenzenes Substituted by a Benzoxazole or a Benzothiazole

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 (Figure 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 condi-

tions[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 have been employed.[28, 29] On other hand, benzoxazole unit has been employed as directing group for the regioselective C2 arylation of phenyl using a palladium catalyst in the presence of silver carbonate in trifluoroacetic acid (Figure 2b).[30, 31] A similar procedure was reported by Ding, Peng and co-workers for the direct C2 arylation of 2-arylbenzothiazole (Figure 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 (Figure 2d).

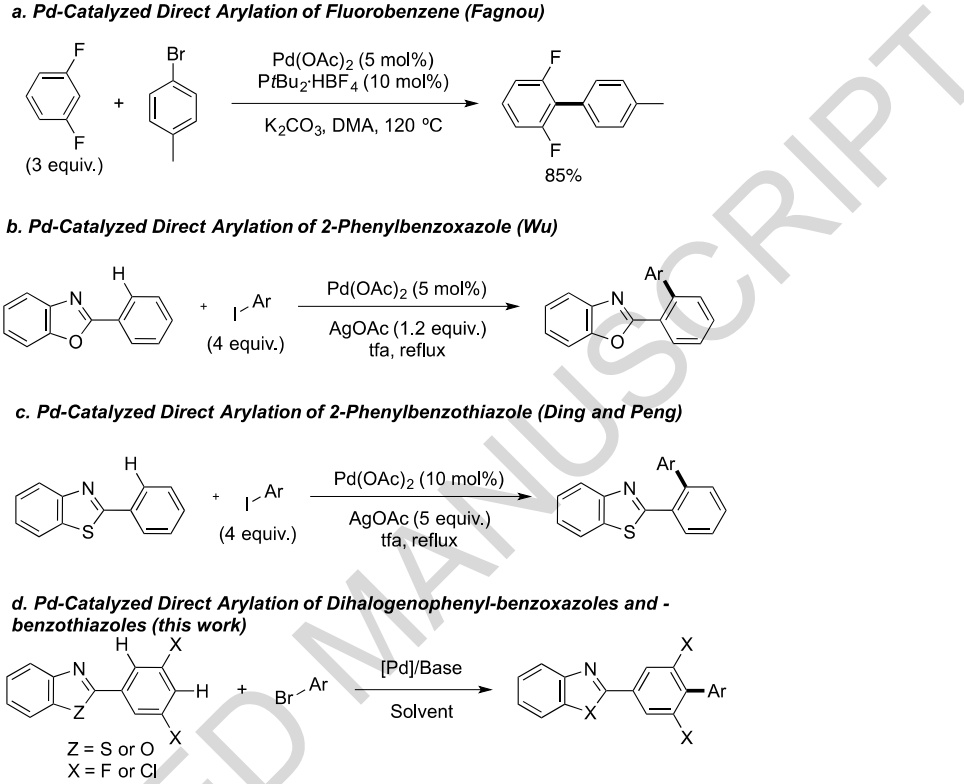


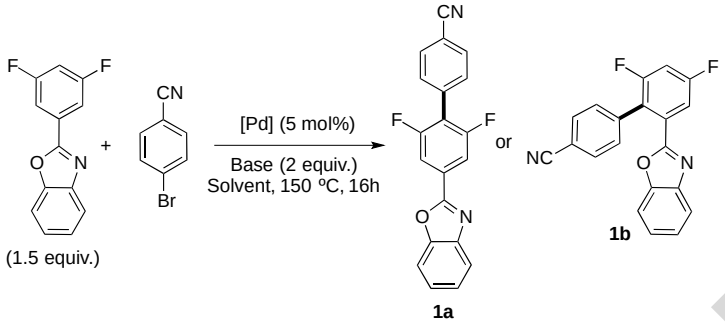
Figure 2. Previous Palladium-Catalyzed Intermolecular Direct Arylations of Fluorobenzenes, 2-Arylbenzothiazoles or 2-Arylbenzoxazoles.

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 ºC (Table 1, entry 1).[33] We were pleased to find that the reaction occurred regioselectively at the C–H 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).

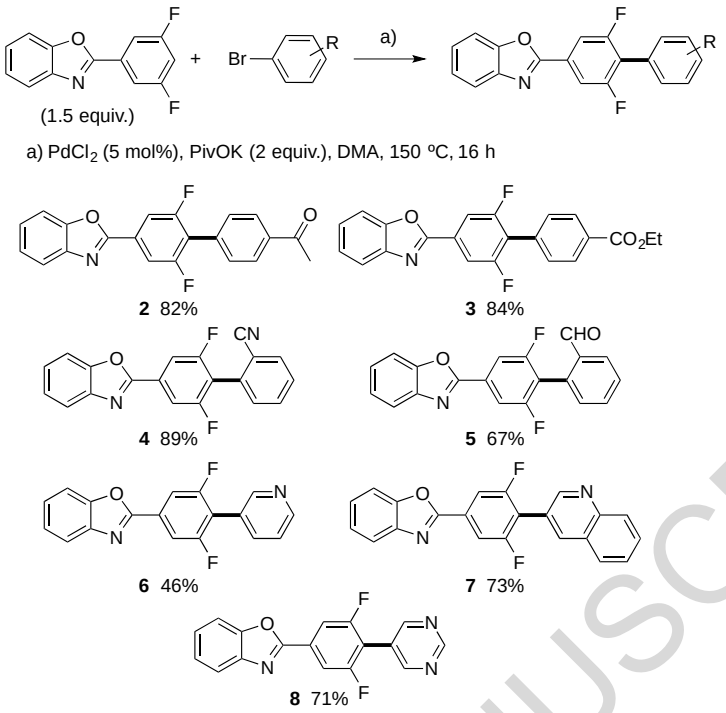
Table 1. Optimization of the Reaction Conditions



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

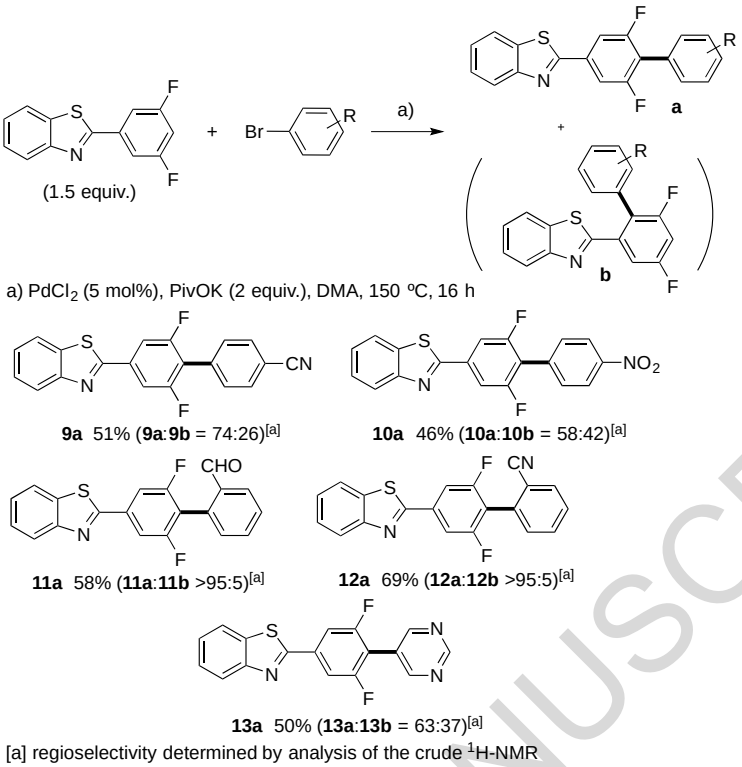
[a]The reaction was performed using 2 mol% of $PdCl_2$.
[b]The reaction was performed from 3,5-difluorobenzaldehyde.

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 Hammet 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 allowed the use of aryl bromides bearing electron-donating substituents due to a slower oxidative addition process.



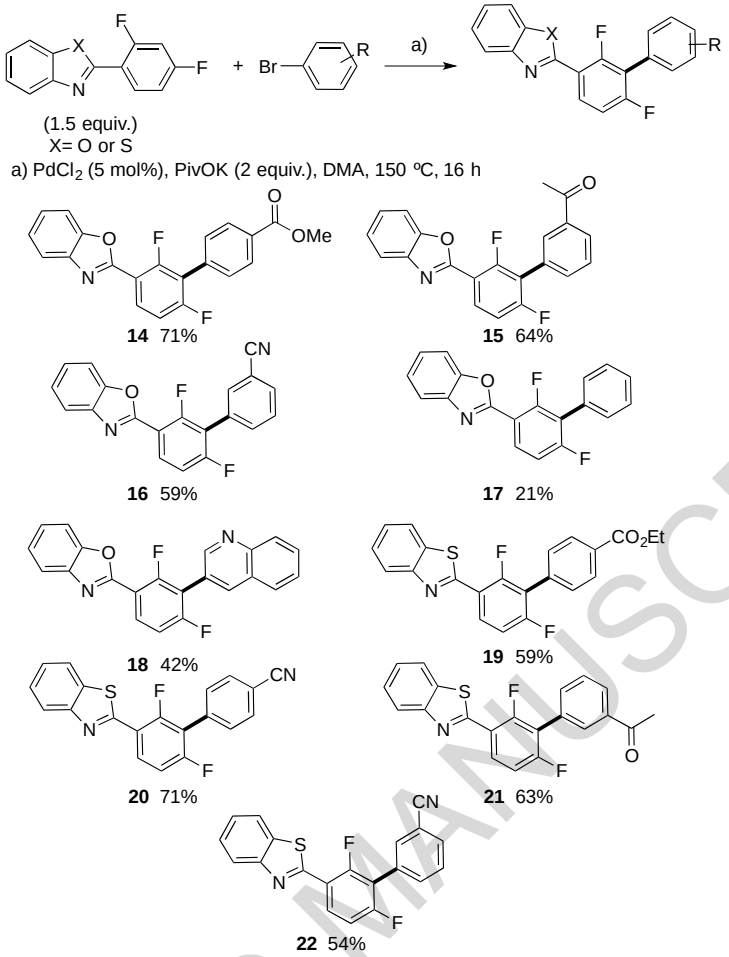
Scheme 1. Scope of Aryl Bromides for Pd-catalyzed Direct Arylation of 2-(3,5-Difluorophenyl)benzoxazole.

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 group properties. Indeed, the reaction between 2-(3,5-difluorophenyl)benzothiazole and 4-bromobenzonitrile afforded a mixture of the C4- and C2-arylated products **9a** and **9b** in 74:26 ratio. The major regioisomer **9a**, which results from the non-directed C–H bond activation (i.e., the C–H bond flanked by the two fluorine atoms), was isolated in 51% yield. A similar reactivity and regioselectivity trend was observed with 4-bromonitrobenzene. From 2-bromobenzaldehyde or 2-bromobenzonitrile, only the regioisomers **11a** and **12a** arising from C4-arylation were isolated in 58% and 69% yields, respectively. Using 5-bromopyrimidine as coupling partner, the reaction was not regioselective and a mixture of both regioisomers **13a** and **13b** was obtained in 63:37 ratio. The major regioisomer **13a**, resulting from the non-directed C–H bond activation, was isolated in pure form in 50% yield.



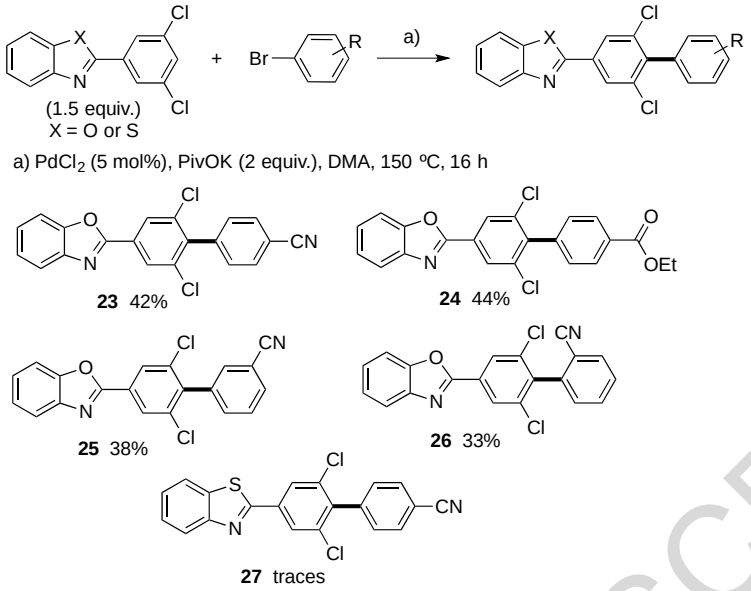
Scheme 2. Pd-catalyzed Direct Arylation of 2-(3,5-Difluorophenyl)benzothiazole

We investigated then the regioselectivity of 2-(2,4-difluorophenyl)benzoxazole and 2-(2,4-difluorophenyl)benzothiazole in palladium-catalyzed direct arylation with aryl bromides as coupling partners (Scheme 3). We found that using 2-(2,4-difluorophenyl)benzoxazole as substrate, the direct arylation again occurred regioselectively at the C–H bond flanked by the two fluorine atoms. Using methyl 4-bromobenzoate, the desired C3-arylated product **14** was isolated in 71% yield. *Meta*-substituted aryl bromides such as 3-bromoacetophenone or 3-bromobenzonitrile also displayed high reactivities and the desired biphenyls **15** and **16** were isolated in 64% and 59% yields, respectively. Under these reaction conditions, bromobenzene smoothly reacted to provide **17** in only 21% yield. We imputed this lack of reactivity to the slow oxidative addition rate of this electron-rich aryl bromide. Heteroaryl bromides, such as 3-bromoquinoline, afforded the desired product **18** in 42% yield. We should note that in all cases, no arylation at C6-position of phenyl moiety was detected in the crude mixture. In contrast to the reaction with 3,5-difluorobenzene bearing a benzothiazole at C1 –in which, two regioisomers were obtained (Scheme 2)–, the reaction with 2,4-difluorobenzene bearing a benzothiazole at C1 afforded a single regioisomer. Indeed, when the reaction was performed from 2-(2,4-difluorophenyl)benzothiazole and ethyl 4-bromobenzoate, only the regioisomer **19** was obtained in 59% yield. The arylation took place at the C–H bond between the two fluorine atoms, whereas the benzothiazolyl directed C–H bond activation process is not operative. Similar regioselectivity and reactivity trend was observed with other 4- and 3-substituted aryl bromides affording regioselectively the desired arylated products **20**, **21**, and **22** in 71%, 63%, and 54% yields, respectively.



Scheme 3. Pd-catalyzed Direct Arylation of 2,4-Difluorophenyls Bearing a Benzoxazole or a Benzothiazole

We had previously demonstrated that polychlorobenzenes react quite similarly to polyfluorobenzenes in palladium-catalyzed direct arylation.[35] Indeed, the arylation occurred at the most acidic position, albeit for some specific cases, in which the steric hindrance was the most important factor. Therefore, we investigated the reactivity of 3,5-dichlorobenzenes bearing benzoxazole or benzothiazole motifs. From 2-(3,5-dichlorophenyl)benzoxazole using 5 mol% of $PdCl_2$ in the presence of PivOK as base in DMA, the arylation occurred regioselectively at the most acidic position, namely, the C–H bond between the two chlorine atoms. The C–H bonds at *ortho*-positions to the benzoxazole remained untouched. Using a set of aryl bromides, the C4-arylated product **23-26** were isolated in 33-44% yields. On the other hand, the 3,5-dichlorophenyl substituted by a benzothiazole moiety at C1 was found to be unreactive under these reaction conditions.



Scheme 4. Pd-catalyzed Direct Arylation of 3,5-Dichlorophenyls Bearing a Benzoxazole or a Benzothiazole

3. Conclusion

In summary, we have demonstrated that palladium-catalyzed direct arylation of electron-deficient arenes such as 3,5-difluorobenzene, 2,4-difluorobenzene or 3,5-dichlorobenzene bearing benzoxazole or benzothiazole units, reacted preferentially *via* the activation of the most acidic C–H bond, whereas the C–H bonds at *ortho*-position of benzoxazole was not activated. In the case of 2-(3,5-difluorophenyl)benzothiazole, the benzothiazole unit acts as a directing group and mixtures of both C2- and C4-regioisomers were obtained. The non-directed C-H bond functionalization proceeds with ligand-free $PdCl_2$ catalyst and PivOK as base in DMA. This procedure tolerates a wide variety of substituents on the aryl bromides such as nitro, cyano, ester, ketone, formyl and also pyridine derivatives. This strategy allows the regioselective *para*- or *meta*-arylations without the use of directing groups. Moreover, it could find further applications in ligand synthesis for the tuning of organic light emitting diodes.

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Abstract