Letter

Palladium–Catalyzed Regioselective C–H Bond Arylations of Benzoxazoles and Benzothiazoles at the C7 Position

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Palladium–Catalyzed Regioselective C–H Bond Arylations of Benzoxazoles and Benzothiazoles at the C7 Position

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ABSTRACT: We report herein, a very simple catalytic system for the direct arylation of benzoxazole and benzothiazole derivatives at C7 position, namely, phosphine-free $PdCl_2$ associated to PivOK in NMP at 150 °C. (Thio)phenoxy chelation-assisted Pd-catalyzed C–H bond cleavage, from an opened intermediate, was proposed to explain this unique regioselectivity. This reaction allows the synthesis of 2-amino-6-arylphenols through the ring opening of the benzoxazole.

KEYWORDS . Arylation – Catalysis – C–H Activation – Palladium – Benzoxazole

Over the past decades, transition metal-catalyzed regioselective C–C bond formation methodologies led to a radical change in the synthesis of complex organic molecules such as pharmaceuticals or materials.[1] Among them, C–H bond arylation reactions have emerged as one of the most powerful tools for the direct C–C bond formation with greater atom economy.[2] In addition, such methodology allows in some cases novel regioselectivities affording products which were not easily accessible using more conventional methods. Most of the regioselective C–H bond arylations required the presence of an *ortho*-directing group such as amides, carboxylic acids, imines, pyridine, etc.[3] Other methods for the control of the regioselectivity of arylations rely on the proton acidity *via* a concerted-metalation-deprotonation (CMD) pathway.[4] Usually arylations of 2-phenylbenzothiazoles or 2-phenylbenzazoles *via* C–H bond activation would take place preferentially at the *ortho*-position of the phenyl ring, due to a directing effect of the benzoxazolyl or benzothiazolyl groups (Fig. 1a).[5] To overcome this regioselectivity and provide an original access to C7 arylated benzoxazole the presence of an additional directing group is required. As example, in the course of their study on the synthesis of c-Met kinase inhibitors, Cho *et al.* reported a direct arylation of a 2-arylbenzoxazole at C7 position through palladium catalysis (Fig. 1b).[6] This uncommon regioselectivity could arise from the presence of the hydroxy group at the C6 position, which acts as an *ortho*-directing group. Phenoxy group has been firstly introduced as directing group by Miura for palladium-promoted C–H bond arylation of 2-arylphenols through a aryl(aryloxy)palladium intermediate.[7] Moreover, when a larger excess of aryl iodide (4 eq.) was used, diarylation was also possible. However, to the best of our knowledge, there is no other example of transition metal-catalyzed C7 arylation of benzoxazoles or benzothiazoles, especially without the use of an additional directing group. On the other hand, during their investigations on palladium-catalyzed C2 direct arylation of benzoxazole, Zhuravlev and co-worker have demonstrated a ring opening pathway (Fig. 1c).[8] Based on this equilibrium between an opened and a closed form of benzoxazole –which is also found at high temperature with 2-substituted benzoxazoles–[9] we postulate that 2-phenylbenzoxazole could be transitorily opened, under proper conditions, leading to a phenoxy group, which could act as directing group in palladium catalysis promoting a regioselective direct C7 arylation of benzoxazole (Fig 1d). Similar intermediate should be operative with 2-substituted benzothiazole.

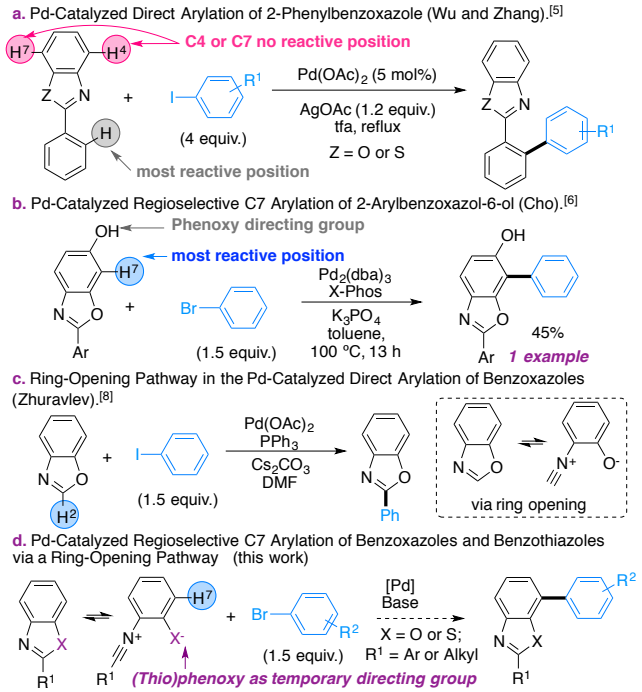


Figure 1. Pd-Catalyzed C–H Arylation of Benzoxazoles.

It is important to note that C7-arylated benzoxazole could be further easily deprotected to give a general access to 2-amino-6-arylphenols. This motif is very interesting because it forms the core of a range of marketed biologically active compounds (Fig. 2). For examples, Eltrombapag is an oral medication commercialized by GSK for the treatment of chronic hepatic C infection.[10] Totrombopag, also developed by GSK, is a back-up compound for eltrombopag. Garenoxacin is a quinolone antibiotic for the treatment of some bacterial infections. However, the synthesis of the 2-amino-6-arylphenols, which are key intermediates of these drugs remain challenging. They are generally obtained in 5 steps, with poor overall yields, from 2-bromophenol *via* nitration reaction and Suzuki cross-coupling.[11]

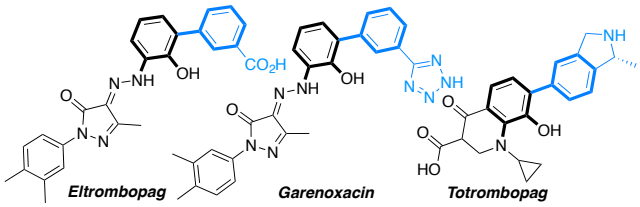
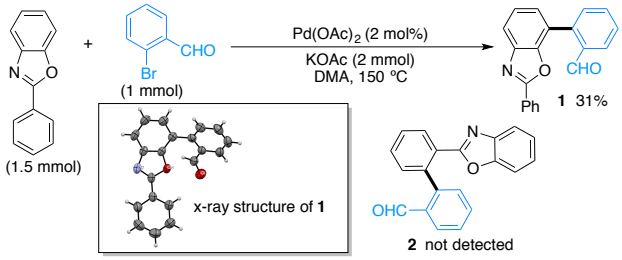


Figure 2. Marketed Drugs Containing 2-Amino-6-arylphenols.

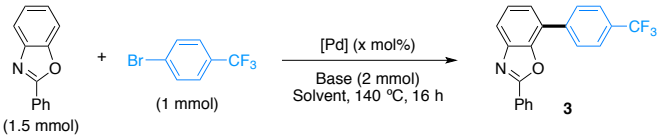
Recently, we reported the palladium-catalyzed direct arylation of benzoxazole or benzothiazole derivatives, in which such functional groups had not displayed any *ortho*-directing effect.[12] In the course of our investigation on the reactivity of 2-arylbenzoxazole, we also employed 2-phenylbenzoxazole as starting material using our previous optimized reaction conditions (*i.e.*, $Pd(OAc)_2$, 2 eq. of KOAc, in DMA at 150 °C) (Scheme 1). To our surprise, we obtained the unexpected C7 arylation product **1** as unique product in 31% yield.[13] This result was quite remarkable, as the previously reported conditions only afforded the arylated product **2**, resulting from the benzoxazoyl directed arylation (Fig. 1a).[5a, 5b] In addition other synthetic approaches generally involved multistep synthesis or/and poor regioselectivities.[14] Only a few heterocycles display reactive C7–H or C4–H bonds using palladium catalysis (i.e., indazoles,[15] pyrazolo[1,5-a]pyrimidines,[16]).



Scheme 1. Preliminary Result

Then, we chose 1-bromo-4-(trifluoromethyl)benzene as more reactive coupling partner to screen the influence of several parameters of this reaction (Table 1). The same reaction conditions allowed the synthesis of C7 arylated benzoxazole **3** in 35% yield (entry 1). First, the influence of other solvents was evaluated (entries 2-5). Lower yields were obtained when the reaction was performed in DMSO or DMF and no reaction occurred in a non-polar solvent such as xylene. Interestingly, when NMP was used as solvent, a higher yield of 56% in **3** was obtained (entry 5). We also examined other palladium sources (entries 6-8). $PdCl_2$ affords a higher 68% yield in **3**, whereas both $PdCl(C_3H_5)(dppb)$ and $Pd_2(dba)_3$ led to lower yields. The use of PivOK improved the yield in **3** to 79% (entry 9). As proposed by Fagnou and co-workers, the superior activity of PivOK could come from its better proton-shuttle character in CMD mechanism, which makes the C–H bond cleavage easier. No yield improvement was observed using other bases such as K_2CO_3, Cs_2CO_3, *t*-BuOK, or AdOK (entries 10-13). The change of the stoichiometry of the reaction, namely, 1 eq. of 2-phenylbenzoxazole and 1.5 eq. of 1-bromo-4-(trifluoromethyl)benzene allowed the formation of desired product **3** in higher 85% yield (entry 14). When dried conditions were used, no reaction occurred; whereas the addition of 4 eq. of water promoted the reaction (entries 14-17).[17, 18]

Table 1. Optimization of the Reaction Conditions.

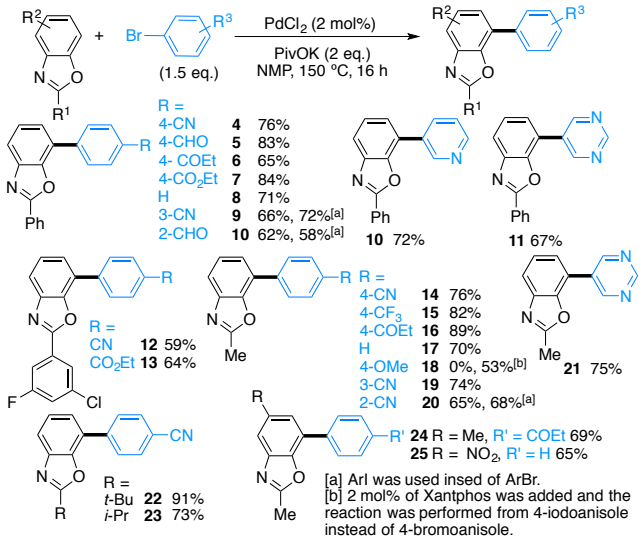


Entry	[Pd] (x mol%)	Base	Solvent	Yield in **3** (%)
1	$Pd(OAc)_2$ (2)	KOAc	DMA	38
2	$Pd(OAc)_2$ (2)	KOAc	DMSO	14
3	$Pd(OAc)_2$ (2)	KOAc	DMF	35
4	$Pd(OAc)_2$ (2)	KOAc	xylene	0
5	$Pd(OAc)_2$ (2)	KOAc	NMP	56
6	$PdCl_2$ (2)	KOAc	NMP	68
7	$PdCl(C_3H_5)(dppb)$ (2)	KOAc	NMP	14
8	$Pd_2(dba)_3$ (1)	KOAc	NMP	18
9	$PdCl_2$ (2)	PivOK	NMP	79
10	$PdCl_2$ (2)	K_2CO_3	NMP	8
11	$PdCl_2$ (2)	Cs_2CO_3	NMP	34
12	$PdCl_2$ (2)	*t*BuOK	NMP	21
13	$PdCl_2$ (2)	AdOK	NMP	62
14[a]	$PdCl_2$ (2)	PivOK	NMP	85
15[b]	$PdCl_2$ (2)	PivOK	NMP	28
16[b, c]	$PdCl_2$ (2)	PivOK	NMP	N.R.
17[b, c, d]	$PdCl_2$ (2)	PivOK	NMP	72

[a] 1 mmol. of 2-phenylbenzoxazole and 1.5 mmol. of 1-bromo-4-(trifluoromethyl)benzene. [b] Dried NMP and PivOK. [c] Molecular sieves 4 Å (200 mg). [d] 4 mmol. of water.

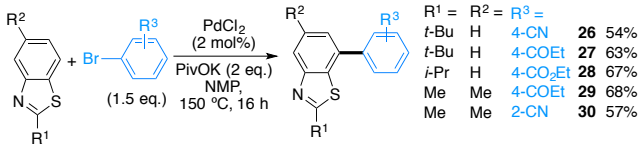
With the optimized reaction conditions in hands, we turned our attention to the substrate scope for these direct C7 arylations of benzoxazole derivatives (Scheme 2). First, aryl bromides with 4-nitrile, 4-formyl, 4-propionyl or 4-ester substituents have been successfully reacted with 2-phenylbenzoxazole to afford the C7 arylated benzoxazoles **4**-**7** in 62-85% yields. The reaction also proceeded in high yield using bromobenzene. 3-Bromobenzonitrile afforded the desired product **9** in 66% yield. The reaction was found to be slightly steric factor dependent, as 2-bromobenzaldehyde afforded the desired product **1** in 62% yield. 3-Bromopyridine and 5-bromopyrimidine were also successfully employed affording the C-7 arylated benzoxazoles **10** and **11** in 72% and 65% yields, respectively. Functional groups on the C2-aryl of the benzoxazole were tolerated. Indeed, 2-(3-chloro-5-fluorophenyl)benzoxazole was regioselectively arylated at C7 position with aryl bromides affording the desired products **12** and **13** in 59% and 64% yields, respectively. Direct arylation of a 3-chloro-5-fluorobenzene moiety was not operative in NMP.[18] Benzoxazoles substituted by an alkyl group at C2 position were also arylated at C7 position in very high yields. For example, from 2-methybenzoxazole and a set of aryl bromides including heteroaryl bromides, the C7-arylated products **14**-**21** were obtained in 53-89% yields. The electron-rich aryl bromide 4-bromoanisole was not reactive under these conditions. However, from 4-iodoanisole and in the presence of a diphosphine ligand, the desired coupling product **18** was isolated in 53% yield.[18] A benzoxazole bearing a *tert*-butyl group at C2 position displayed a high reactivity, as **22** was obtained in very high yield, albeit an isopropyl substituent also afforded the C7-arylated product **23** but in 73% yield. It is im-

portant to note that this reaction was not sensitive to the electronic properties of benzoxazole ring, as benzoxazoles substituted by methyl or nitro groups at C5 position afforded the desired C7 arylated products **24** and **25** in 69% and 65% yields, respectively. For reactions in which lower yields were obtained (i.e., products **9**, **10**, **20**), aryl iodides instead of aryl bromides were also employed. However, similar yields were obtained showing that the lower yields obtained with these electron-deficient aryl bromides do not arise from a slow oxidative additive addition to palladium.



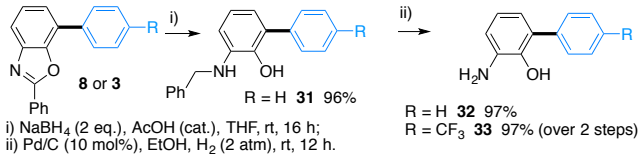
Scheme 2. Scope of the Pd-Catalyzed Benzoxazoles C7 Arylations.

We also investigated the reactivity of benzothiazoles (Scheme 3). We were pleased to find that the reaction proceeded well with 2-alkylbenzothiazoles. 2-*Tert*-butyl- or 2-*iso*-propylbenzothiazoles were arylated using 2 mol% of $PdCl_2$ in the presence of KOAc as base in NMP to afford the C7 arylated products **26**-**29** in 54-63% yields. 2,5-Dimethylbenzothiazole was also arylated at the C7 position in good yield. However, 2-phenylbenzothiazole displayed no reactivity under these conditions, probably due to the formation of a chelate complex with the palladium species.



Scheme 3. Scope of the Pd-Catalyzed Benzothiazoles C7 Arylations.

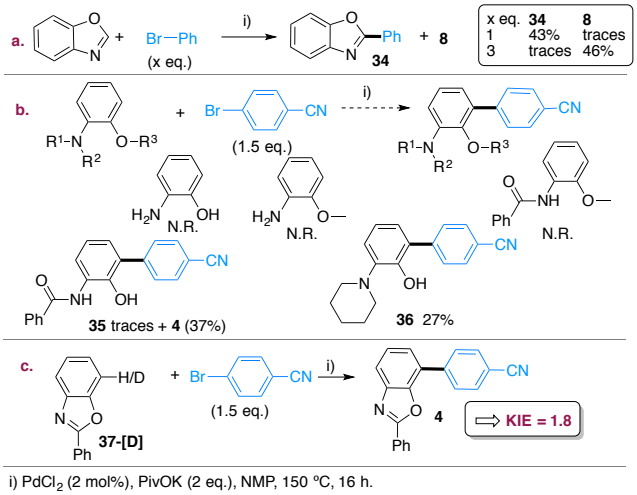
The potential of this methodology for the access to C6 arylated 2-aminophenols, which are useful building blocks in pharmaceuticals, was then investigated (Scheme 4).[19]



Scheme 4. Deprotection of Benzoxazoles.

The 2,7-diphenylbenzoxazole **8** has been deprotected using $NaBH_4$ to furnish the *N*-benzyl-2-amino-6-phenylphenol **31** in 96% yield. Then, debenzylation using Pd/C under H_2 atmosphere allowed the formation of the aminophenol **31** in excellent 97% yield. This sequence reaction was also conducted from **3**, without the isolation of the intermediate, to give the 2-amino-6-arylphenol **33** in 97% yield.

Based on Gorelsky calculations,[20] the difference between the Gibbs free energies of activation ($\Delta G^{\ddagger}298K$) for the cleavage of the C4–H and C7–H bonds of benzoxazole or benzothiazole via a CMD pathway does not explain the complete regioselectivity on this reaction. Nevertheless, we cannot completely deny a potential effect of the C2 benzoxazole substituent. Then, in order to have a better understanding of the reaction mechanism, a set of control experiments was carried out. As expected from the previous literature,[21] unsubstituted benzoxazole in the presence of 1 equiv. of PhBr was arylated at C2 position affording **34** in 43% yield; however, in presence of 3 equiv. of PhBr, the diarylated product **8** was isolated in 46% yield (Scheme 5.a). No reaction occurred using unprotected 2-aminophenol, 2-methoxyaniline and *N*-(2-methoxyphenyl)benzamide. Using *N*-benzoyl aminophenol as starting material, we found that the arylation occurred at the C–H bond adjacent to the OH function; however, a cyclization reaction also took place to give the benzoxazole **4** in 37% yield with trace amount of the arylated product **35**. No arylation product arising from an amide directed reaction was detected. From 2-(piperidin-1-yl)phenol, in which amine was protected (no cyclization to form a benzoxazole was possible) the arylated product **36** was regioselectively obtained in 27% yield (Scheme 5.b). All these control experiments seem to support a phenoxy directed arylation mechanism *via* an isomerization between opened and closed benzoxazole forms which may occur at high temperature.[22] However, we cannot completely deny a SEAr mechanism, which has been proposed by Hartwig in the case of iridium-catalyzed C7 borylation of benzoxazoles.[23] Finally, an intermolecular kinetic isotopic effect (KIE, k_H/k_D) of 1.8 was determined from two parallel reactions. This result suggest that the C–H bond cleavage is the "turnover-limiting step" of this catalytic reaction (Scheme 5.c).[24]



Scheme 5. Control Experiments and Kinetic Isotopic Effect.

Finally, a plausible catalytic cycle is shown in Fig. 3. We propose a catalytic cycle involving phenoxy chelation-assisted palladium-catalyzed regioselective C–H bond cleavage (intermediate **E**), resulting from an equilibrium between the closed (**C**) and the opened (**D**) forms of benzoxazole.[25] A similar mechanism might also be operative from benzothiazole with a sulfur chelation-assisted C–H bond activation. Such opened transition states have

been previously mentioned in the direct functionalization of benzoxazoles or azoles at the C2 positions.[8, 26]

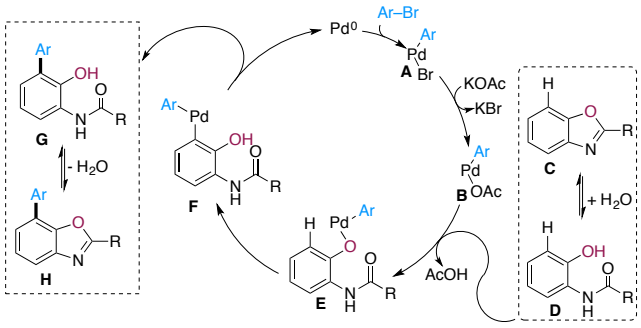


Figure 3. Proposed Mechanism.

In summary, we discovered that a simple catalytic system, namely, phosphine-free of $PdCl_2$ with PivOK as base in NMP, allowed the regioselective arylation of both benzoxazoles and benzothiazoles at unexpected C7-position. Mechanistic studies suggest that an open form of benzoazoles with a palladium coordination to the phenoxy group is the key factor for the control of the regioselectivity. We believe that this methodology is the first one allowing a simple access to C7-arylated benzoazoles and 2-amino-6-arylphenols. As this procedure tolerates a wide substrate scope, it should find further applications in drug and material designs.

ASSOCIATED CONTENT

Supporting Information. Reaction procedure and spectra are available free of charge via the Internet at http://pubs.acs.org.

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13.The regioselectivity of the reaction was determined by X-Ray analysis after recrystallization of 1 in cyclohexane (CCDC 1435542).

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17.NMP containing up to 5% of water; when the use of NMP containing >5% of water led to lower yields.

18.See the supporting information for more details.

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25.Water seems to be necessary for that equilibrium (table 1, entries 16 and 17) and should come from the solvant.

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