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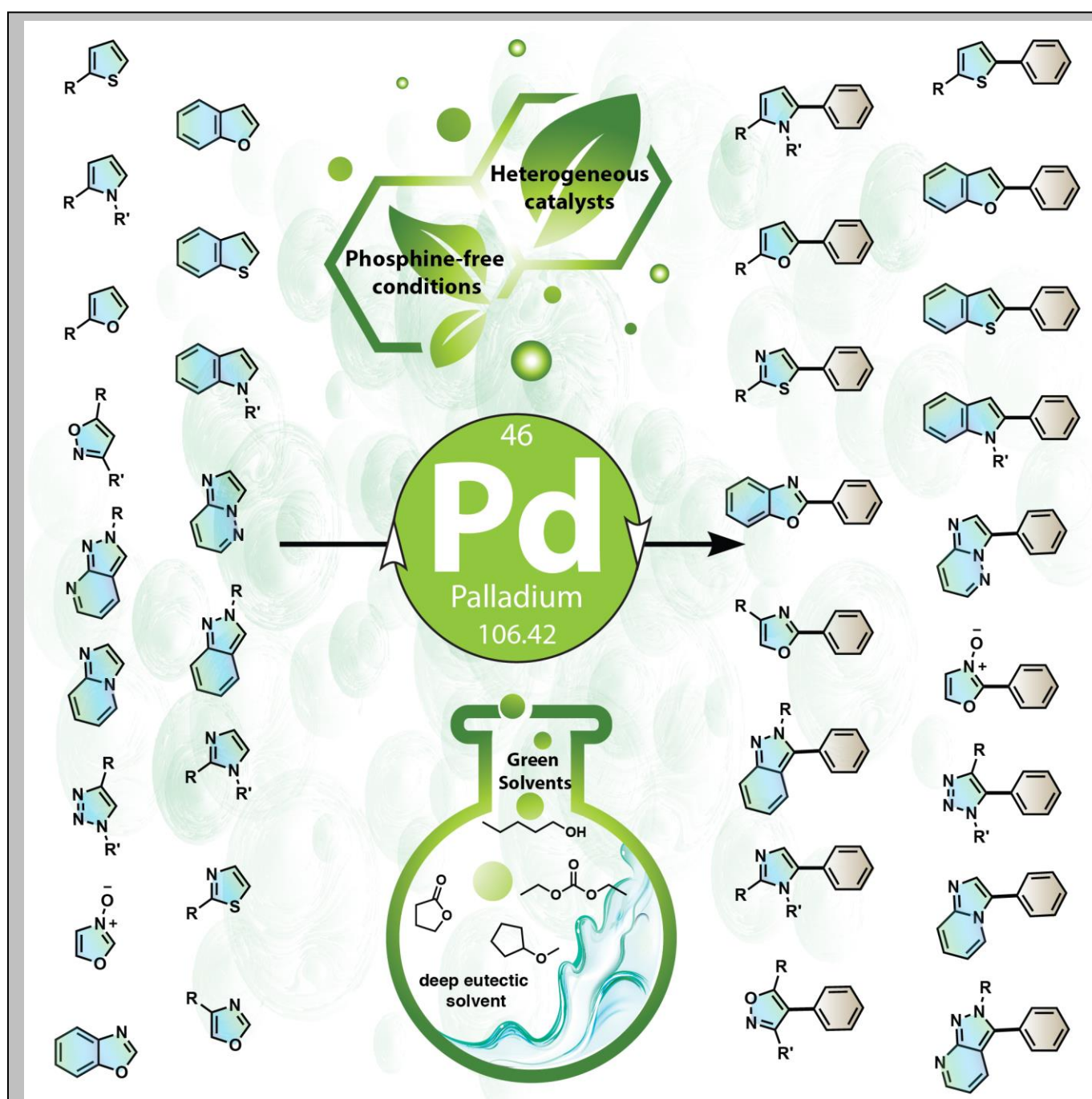
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# Environmentally Benign Arylations of 5-Membered Ring Heteroarenes by Pd-Catalyzed C-H Bonds Activations

Shuxin Mao,<sup>[a]</sup> Haoran Li,<sup>[a]</sup> Xinzhe Shi,<sup>[a]</sup>  
Jean-François Soulé,<sup>\*[a]</sup> and Henri Doucet<sup>†\*[a]</sup>



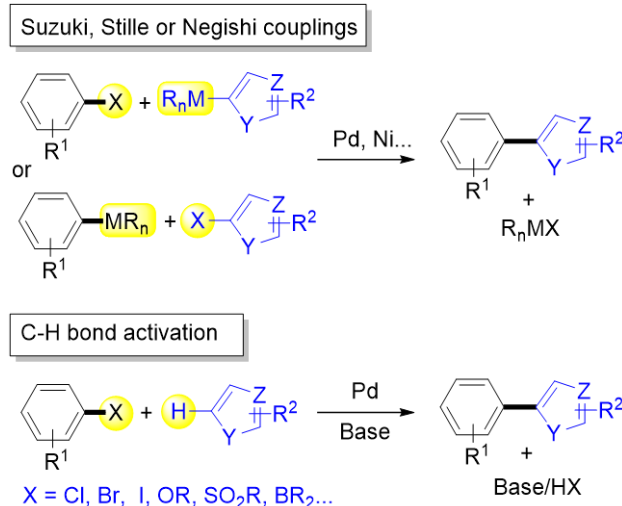
**Abstract:** The palladium-catalyzed functionalization of 5-membered ring heteroaromatics, *via* a C-H bonds activation, for access to arylated heteroaromatics represent a very attractive alternative to more classical cross-coupling reactions, as it saves steps and reduces the amount of wastes. Despite these advantages, these transformations initially suffered from major limitations in terms of sustainable chemistry concerning the reaction media, the nature of the catalyst, the catalyst loading, the aryl source or the regioselectivity control. Tremendous improvements allowing more sustainable reaction conditions using greener solvents, new aryl sources or employing easily removable catalysts and lower catalyst loadings have been described during the last decades. This review summarizes some of the most important contributions made in these directions.

## 1. Introduction

(Hetero)aryl-substituted heteroarenes are important units in pharmaceutical chemistry and in material science.<sup>1</sup> Therefore, the development of effective methods employing sustainable reaction conditions for the arylation of heteroaryl derivatives is an important research area. Transition metal catalyzed reactions such as Suzuki, Stille or Negishi cross-couplings can be employed for the formation of C(aryl)-C(heteroaryl), bonds (Scheme 1, top).<sup>2</sup> These transformations have largely contributed to the development of very convenient procedures for the preparation of a very wide variety of arylated heteroarenes. However, such transformations require the synthesis of organometallic derivatives and produces organometallic wastes. Since the seminal work reported in 1982 by Nakamura, Tajima and Sakai<sup>3</sup> and in 1985 by Ohta et al.,<sup>4</sup> on the Pd-catalyzed direct arylation of 5-membered ring heteroaromatics, the transition-metal catalyzed direct functionalization of C-H bonds of heteroarenes has emerged as a very attractive alternative to cross-coupling reactions for the functionalization of (hetero)arenes.<sup>5</sup> These reactions generally led to lower E factors (E-factor = mass of waste per mass of product), as the only by-product which is generated is formally HX (for the reaction performed using aryl halides as reaction partners) (Scheme 1, bottom).

Initially, despite its obvious advantages in terms of “green chemistry”,<sup>6</sup> palladium catalyzed C-H bond functionalization for access to arylated 5-membered ring heteroarenes suffered from several environmental problems such as 1) the use of quite toxic solvents, 2) the use of high catalyst loadings and the presence of expensive and/or quite toxic ligands, 3) the use of coupling partners which are not very attractive in terms of green chemistry, 4) the formation of mixtures of regioisomers due to

the similar reactivity's of several C-H bonds, and 5) the use of high reaction temperatures. Therefore, the development of more sustainable procedures for such reactions was needed. During the last two decades, several improvements allowing more sustainable reaction conditions using greener solvents, more attractive aryl sources, employing more easily removable catalysts and lower catalyst loadings have been described. In this review, we will outline some of the contributions on the Pd-catalyzed direct arylations of heteroaromatics dealing with environmental issues of these reactions such as the nature of the catalyst, solvent and coupling partners, catalyst loadings, and regioselectivities of the reactions.



**Scheme 1.** Classical cross-coupling reactions vs direct arylations.

Shuxin Mao was born in P.R. China. He joined the international master's program

“Catalysis, Molecules and Green Chemistry” in the University of Rennes 1 (France) in 2017. He performed his master's research training in H. Doucet and J. F. Soulé team in the University of Rennes 1. His work focuses on the C-H bond functionalization using palladium catalysis and green chemistry.

Haoran Li was born in P.R. China. He joined the international master's program

“Catalysis, Molecules and Green Chemistry” in the University of Rennes 1 (France) in 2015. He performed his master's research training in Prof. C. Darcel's team in the University of Rennes 1. He currently works towards a PhD degree of ENSCR under the supervision of Dr. Henri Doucet. He received a grant from the China Scholarship Council (CSC) in 2017. His work focuses on the C-H bond functionalization using palladium catalysis.

[a] S. Mao, H. Li, X. Shi, Dr. J.-F. Soulé, Dr. H. Doucet  
CNRS, ISCR-UMR 6226  
Univ Rennes  
F-35000 Rennes, France  
E-mail: jean-francois.soule@univ-rennes1.fr, henri.doucet@univ-rennes1.fr

Xinzhe Shi was born in P.R. China. She joined the international master's program "Catalysis, Molecules and Green Chemistry" in the University of Rennes 1 (France) receiving grants from the Foundation Rennes 1 in 2015. She performed her master's research training in H. Doucet and J. F. Soulé team. She currently works towards a PhD degree of University of Rennes 1 under the supervision of Dr. Henri Doucet and Dr. Jean-François Soulé. Her work focuses on the C-H bond functionalization using palladium catalysis.

Jean-François Soulé completed his PhD in 2007 working on the Petasis reaction applied on the synthesis of biological interest molecules under the supervision of the Prof. Jean-Marie Beau, at the Institut de Chimie des Substances Naturelles, Gif-sur- Yvette (France). In 2010, he joined the group of the Prof. Shu Kobayashi at the University of Tokyo (Japan) as a postdoctoral fellow. In October 2013, he was appointed as "Chargé de Recherche" CNRS at the University of Rennes 1. His main interest focuses on the development of sustainable chemistry, notably, transition-metals catalyzed C-H functionalization.

Henri Doucet received his PhD in chemistry working with Prof. P. H. Dixneuf and Dr. C. Bruneau at Rennes 1 University (France) in 1994. After post-doctoral appointments at Oxford university (UK) with Prof. J. M. Brown; and Nagoya university, (Japan) with Prof. R. Noyori, he moved to the University of Marseille (France) as CNRS researcher in the group of Prof M. Santelli. In 2006 he moved to Rennes 1 University. His research interests include organic synthesis by metal-catalyzed processes and green chemistry.

## 2. Reactions in green solvents

For palladium-catalyzed C-H bond functionalizations of heteroarenes, high boiling point polar aprotic solvents such as *N*-methylpyrrolidone (NMP), dimethylformamide (DMF), 1,4-dioxane, and especially dimethylacetamide (DMA) were initially considered as the solvents of choice. However, all these solvents are classified as undesirable in terms of green chemistry.<sup>6</sup> Greener solvents for the Pd-catalyzed C-H bond functionalization of (hetero)arenes were thus strongly needed.

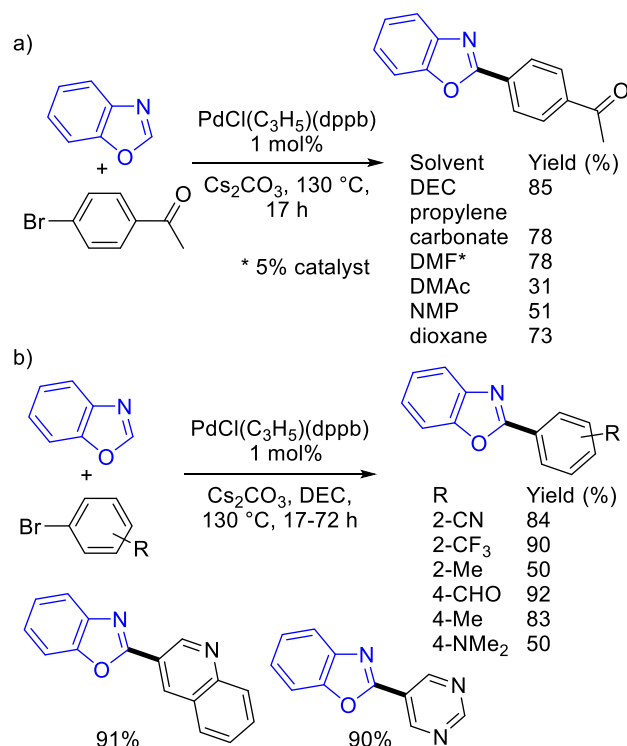
### 2.1. Reactions in dialkyl carbonates

Dialkyl carbonates such as the highly polar propylene carbonate or the less polar dimethyl- and diethyl-carbonates have been used as solvents in metal-catalyzed reactions.<sup>7</sup> These solvents

display several advantages including a high biodegradability and a low environmental impact during their synthesis. They are currently prepared *via* transition metal catalyzed carbonylation of methanol<sup>8</sup> or using CO<sub>2</sub>.<sup>9</sup> For these reasons, carbonate solvents are attracting increasing attention as alternative solvents in homogeneous catalysis.<sup>10</sup>

In order to evaluate the suitability of carbonates as solvents for Pd-catalyzed direct arylations of heteroarenes, reactions employing benzoxazole and 4-bromoacetophenone have been performed in diethyl carbonate (DEC).<sup>11</sup> The direct arylation proceeded nicely affording the coupling product in 85% yield using 1 mol% PdCl(C<sub>3</sub>H<sub>5</sub>)(dppb) as catalyst (Scheme 2, a). Interestingly, lower amounts of side-products were detected in DEC than for the reactions performed in DMF, DMA, NMP or dioxane. The same reaction using propylene carbonate also proceeded, but afforded a lower yield.

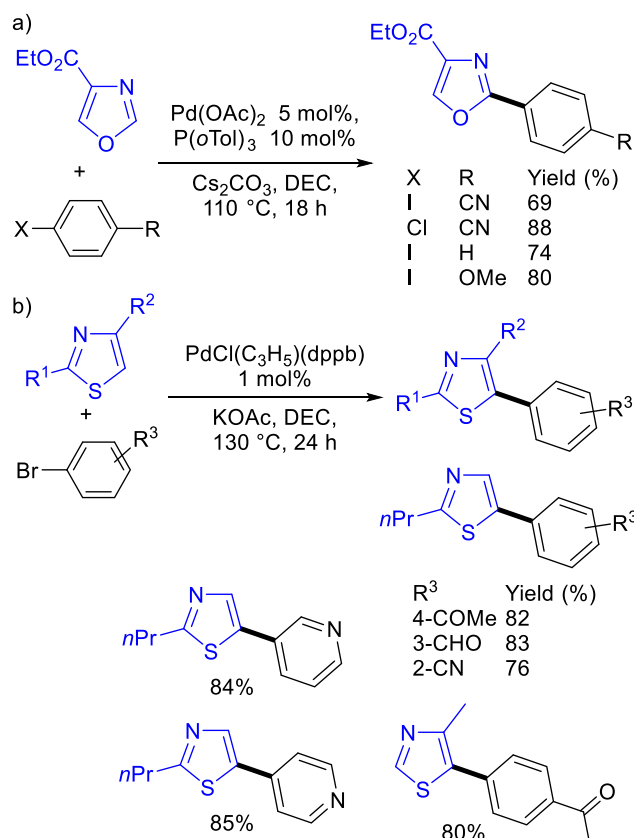
The scope of this procedure was examined (Scheme 2, b).<sup>11</sup> Electron-deficient aryl bromides and also bromo-substituted heteroarenes gave the expected coupling products in high yields. Moreover, in all cases the stability of 2-arylbenzoxazoles appeared to be higher in DEC than in DMF.



**Scheme 2.** Selected examples of coupling of benzoxazole with (hetero)aryl bromides in DEC.

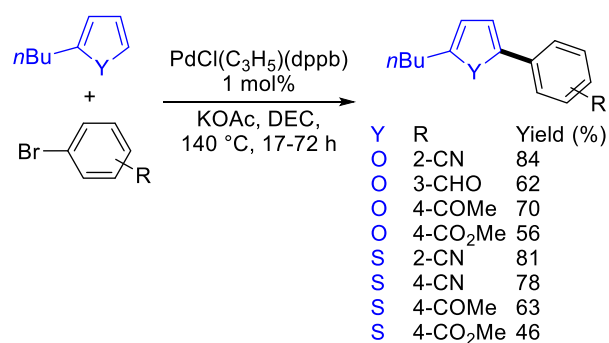
The reactivity of ethyl oxazole-4-carboxylate in Pd-catalyzed C2-arylation with a set of aryl halides using DEC as solvent was also evaluated.<sup>11</sup> Reaction with 4-iodoanisole or 4-chlorobenzonitrile using 5 mol% Pd(OAc)<sub>2</sub> associated to 10 mol% P(*o*Tol)<sub>3</sub> as the catalytic system afforded the desired C2-

arylated oxazoles in 80% and 88% yields, respectively with preservation of the regioselectivity of the reaction at the C2-position (Scheme 3, a). The reactivity of a few thiazole derivatives in DEC was also studied (Scheme 3, b). They were successfully regioselectively arylated at C5-position.<sup>11b</sup> Moreover, very high yields of coupling products were obtained.



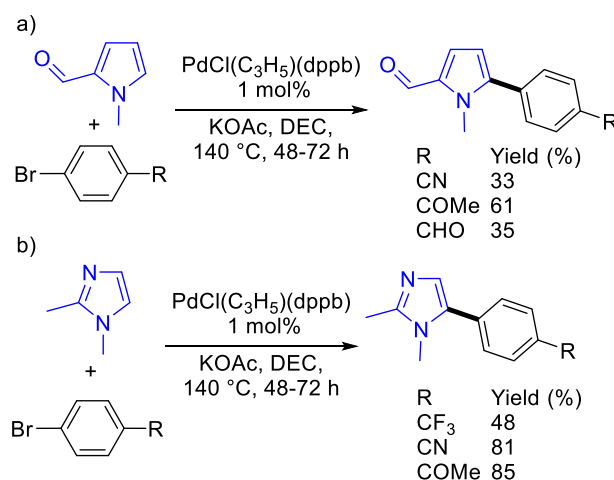
**Scheme 3.** Selected examples of coupling of ethyl oxazole-4-carboxylate and thiazoles with aryl halides in DEC.

The functionalization of furan derivatives is an important research topic in sustainable chemistry, as some of them can be prepared from agricultural wastes. The reaction of 2-*n*-butylfuran with electron-deficient aryl bromides using 1 mol% PdCl(C<sub>3</sub>H<sub>5</sub>)(dppb) catalyst in DEC gave regioselectively the C5-arylated furans in 56-84% yields (Scheme 4).<sup>11b</sup> However, due to its moderate reactivity, a high reaction temperature of 140 °C had to be employed. The reactivities of 2-*n*-butylthiophene and 2-*n*-butylfuran in DEC were found to be similar. At 140 °C, a variety of aryl bromides was coupled with 2-*n*-butylthiophene in moderate to good yields.<sup>11b</sup>



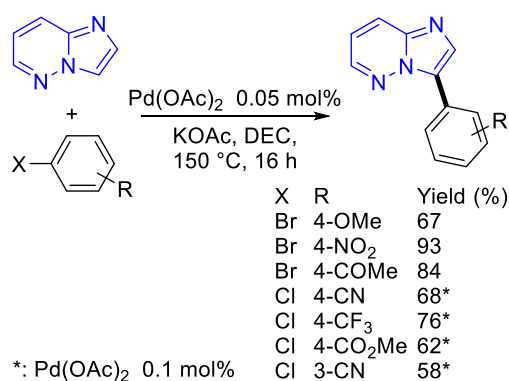
**Scheme 4.** Selected examples of coupling of 2-*n*-butylfuran and 2-*n*-butylthiophene with aryl bromides in DEC.

1-Methyl-2-formylpyrrole displayed a poor reactivity for direct arylation in DEC, and low to moderate yields were obtained due to poor conversions of the aryl bromides (Scheme 5, a).<sup>11b</sup> Conversely, the direct C5-arylation of 1,2-dimethylimidazole in DEC was found to proceed quite nicely, although the reaction was slower than in DMA (Scheme 5, b). High conversions of 4-bromoacetophenone and 4-bromobenzonitrile and good yields in C5-arylation products were obtained. In DMA, complete conversions were observed in 17 h using 0.5-0.1 mol% Pd(OAc)<sub>2</sub> catalyst.<sup>12</sup>



**Scheme 5.** Selected examples of coupling of 1-methyl-2-formylpyrrole and 1,2-dimethylimidazole with aryl bromides in DEC

Our group reported in 2016 that phosphine-free Pd(OAc)<sub>2</sub> catalyzes very efficiently the direct arylation of imidazo[1,2-*b*]pyridazine at C3-position in DEC using very low catalyst loadings (Scheme 6).<sup>13</sup> The reactions were performed employing as little as 0.1-0.05 mol% catalyst with a set of aryl bromides and specific electron-deficient aryl chlorides.



**Scheme 6.** Selected examples of coupling of imidazo[1,2-*b*]pyridazine with aryl halides in DEC.

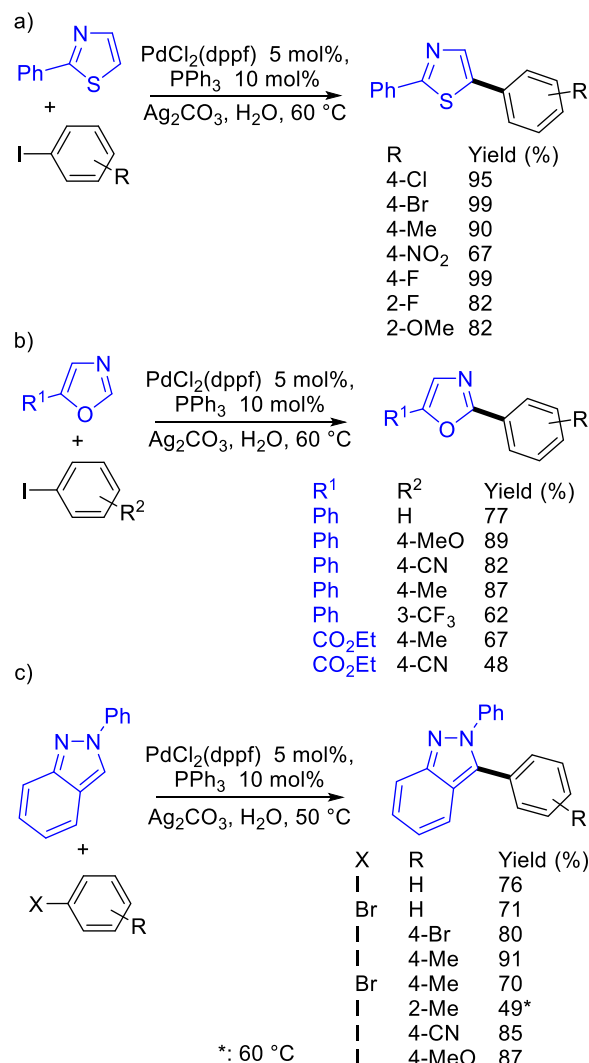
In summary, dialkyl carbonates and in particular DEC can be advantageously employed as alternative greener solvents for the Pd-catalyzed direct arylation of heteroaromatic derivatives. In several cases, cleaner reactions were observed than those performed in more classical solvents for such couplings such as DMA or DMF. The major drawback regarding the use of carbonates as solvents for these reactions is a decrease of the catalytic efficiency, requiring longer reaction times and/or higher catalyst loadings.

## 2.2. Reactions using water

Water might be regarded as the ideal green solvent, as it is non-toxic and non-flammable, although its recycling is generally expensive.<sup>14</sup> A limitation when using water as the solvent for catalytic transformations is the solubility and stability of catalysts and substrates. In some cases, the use of amphiphiles and water soluble ligands may circumvent some solubility issues.

In 2007, Greaney et al. described several examples of Pd-catalyzed direct arylations of heteroaromatics “on water”.<sup>15-18</sup> They observed, using this solvent, very clean direct C5-arylations of thiazoles with high conversions of aryl iodides after 24 h at 60 °C (Scheme 7, a).<sup>15</sup> These results are consistent with a S<sub>E</sub>Ar mechanism. According to the authors, there are several advantages of performing such reactions using “on-water” chemistry: 1) an increase of the reaction rate, 2) a convenient ease of operation, 3) an improved safety profile due to the good heat capacity of water and 4) an easier work-up. Moreover, in some cases, the product directly sublimed out of the aqueous mixture. They also employed this methodology with a benzimidazole and benzothiazole.<sup>15</sup> These substrates were also efficiently arylated “on water” with iodobenzene using again PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>/PPh<sub>3</sub> as catalyst, Ag<sub>2</sub>CO<sub>3</sub> as base at 60 °C (yields >99%). Using the same reaction conditions, they observed good reactivity of 2-aryloxazoles, providing good to excellent yields of the desired 2,5-diarylated oxazoles.<sup>16</sup> They also studied the synthesis of 2,5-disubstituted oxazoles *via* C2-direct arylation of

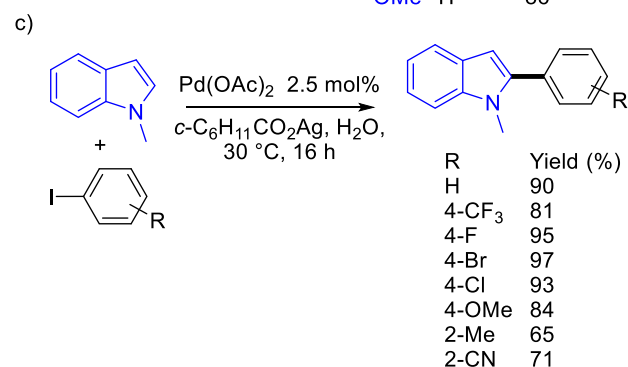
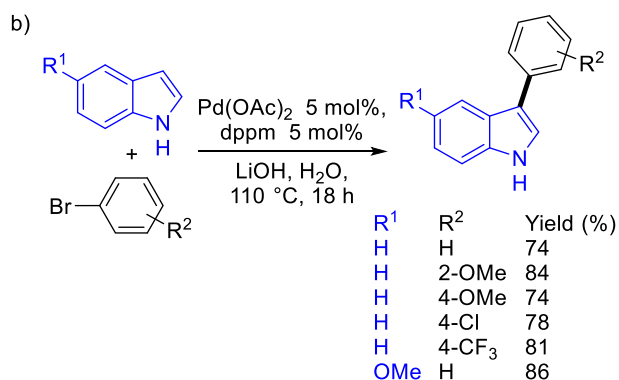
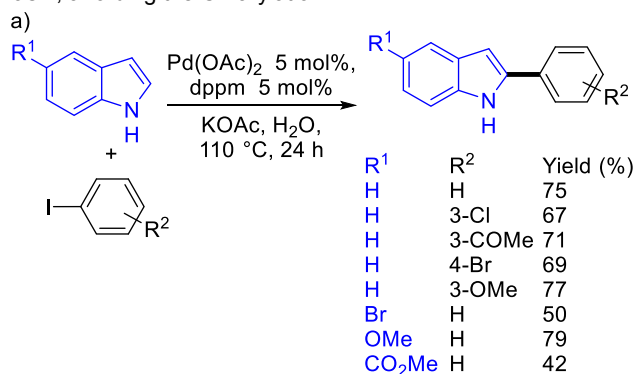
5-substituted oxazoles with a set of iodobenzenes (Scheme 7, b).<sup>17</sup> 2-Phenylindazole was also an very reactive substrate, undergoing “on water” arylation with a set of aryl halides at only 50 °C (Scheme 7, c).<sup>18</sup> It should be mentioned that for these reactions, the substrates and catalyst were premixed prior to the addition of water, as good mixing was crucial for effective arylations.



**Scheme 7.** Selected examples of on water couplings of heteroarenes with aryl halides.

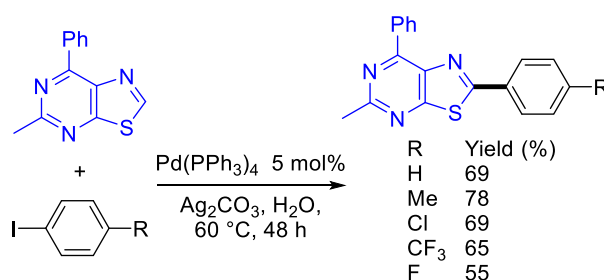
Djakovitch et al. described in 2010 an “on water” Pd-catalyzed site-selective arylation of (*NH*)-indoles.<sup>19</sup> Their methodology allowed the access to C2- or C3-arylated indoles depending on the reaction conditions (Scheme 8, a and b). They found that the use of the appropriate halide/base partners is the key element to control C2- vs C3-arylation. In the presence of iodobenzene, the use of 5 mol% Pd(OAc)<sub>2</sub> associated to dppm ligand as the catalyst and KOAc as the base, exhibit both high

activity and regioselectivity (>20/1) toward 2-arylindoles (Scheme 8, a). This methodology was found to be general, affording the coupling products in 42-79% yields. This group also developed a procedure for the regioselective C3-arylation of indoles, since a dramatical base effect on the regioselectivity was observed during their optimization of the C2-arylation protocol. The use of LiOH·H<sub>2</sub>O as the base associated to bromobenzene instead of iodobenzene provided the arylated indoles in 6.5:1 regioselectivity, in favor of 3-phenylindole (Scheme 8, b). The “on water” C2-arylation of indoles has also been reported by Larrosa et al. (Scheme 8, c).<sup>20</sup> They employed a phosphine-free palladium-catalyst, Ag-cyclohexanoate as the base and aryl iodides as aryl source. It should be mentioned that these couplings were performed at 30 °C. The first step of both catalytic cycles would be an electrophilic palladation at the C3-position of indoles. With LiOH as base, rearomatization followed by reductive elimination would give C3-arylated indoles. Conversely, a migration of palladium from C3-position to C2-position could be favored by the presence of the weak base AcOK, affording the C2-arylation.



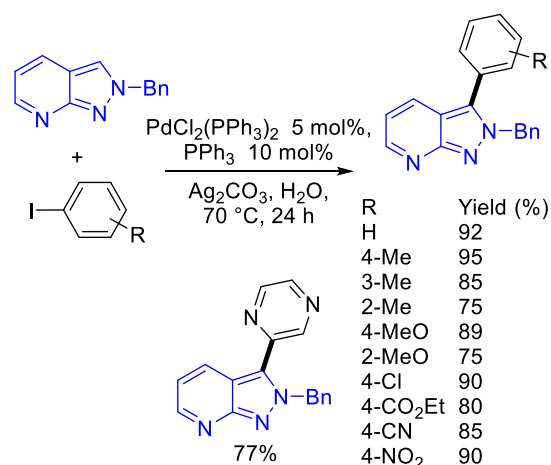
**Scheme 8.** Selected examples of on water C2- or C3-arylations of indoles with aryl halides.

Li, Sun et al. developed in 2012 a Pd-catalyzed system for the direct arylation of thiazolo[5,4-*d*]pyrimidines with iodobenzenes using water as the solvent (Scheme 9).<sup>21</sup> For these reactions, Pd(PPh<sub>3</sub>)<sub>4</sub> was used as catalyst and Ag<sub>2</sub>CO<sub>3</sub> as the base. Again, a quite low reaction temperature (60 °C) could be employed.



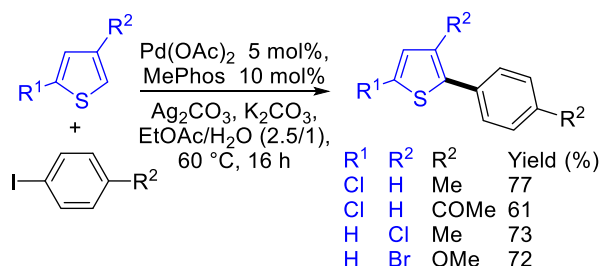
**Scheme 9.** Selected examples of on water arylations of thiazolo[5,4-*d*]pyrimidines with aryl iodides.

In 2017, the on water Pd-catalyzed direct arylation of 2*H*-pyrazolo[3,4-*b*]pyridines using aryl iodides as aryl source was described by El Kazzouli, Suzenet, Guillaumet et al. (Scheme 10).<sup>22</sup> The C3-arylated pyrazolopyridines were obtained in good to excellent yields using only 5 mol% of PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> catalyst in the presence of 10 mol% PPh<sub>3</sub>. This procedure tolerated a variety of functional groups on the aryl bromide. Moreover, again quite low reaction temperature conditions (70 °C) were employed.



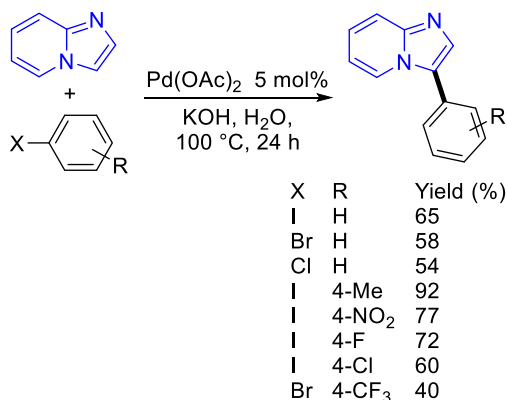
**Scheme 10.** Selected examples of on water C3-arylations of 2*H*-pyrazolo[3,4-*b*]pyridines with aryl iodides.

Biphasic conditions using water were also found to be suitable for the direct arylation of thiophene derivatives. In 2010, René and Fagnou employed H<sub>2</sub>O/EtOAc as biphasic system for access to a variety of bi(hetero)aryls.<sup>23</sup> For example, 2-chlorothiophene was regioselectively arylated at C5 position at only 60 °C (Scheme 11). This methodology demonstrates the potential of water as co-solvent in the development of reactions using milder conditions.



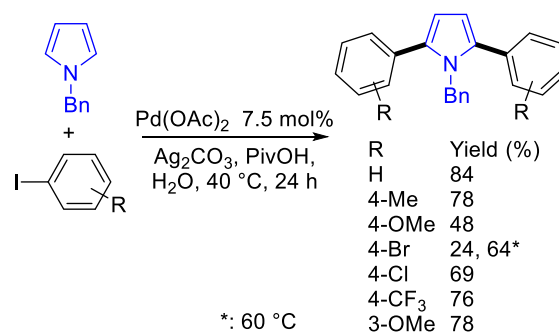
**Scheme 11.** Coupling of halothiophenes with aryl iodides using a biphasic system.

In 2017, a very simple procedure for the “on water” arylation of imidazo[1,2-*a*]pyridines with aryl halides has been reported by Rode et al. (Scheme 12).<sup>24</sup> Phosphine-ligand free Pd(OAc)<sub>2</sub> associated to KOH were used as catalyst and base. In most cases, aryl iodides were employed as the aryl source, but aryl bromides and in a few cases aryl chlorides could also be employed, affording the 3-arylimidazo[1,2-*a*]pyridines in moderate to high yields.



**Scheme 12.** Selected examples of on water couplings of imidazo[1,2-*b*]pyridine with aryl halides.

The Pd-catalyzed 2,5-diarylation of pyrroles with aryl iodides on water has been described by Chung et al. (Scheme 13).<sup>25</sup> The reaction proceeded in good to high yields under low temperature (40 °C) with a phosphine-free catalyst.

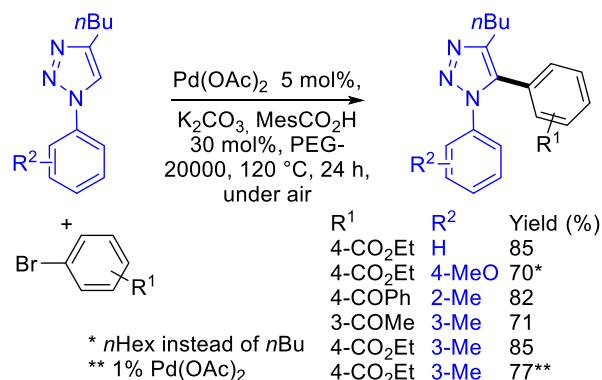


**Scheme 13.** Selected examples of on water couplings of pyrroles with aryl iodides.

In summary, water was shown to be a suitable solvent for C-H bond arylation or diarylation of a range of heteroaromatic compounds. Rate enhancements were observed for some reactions; moreover, low reaction temperatures were successfully employed in many cases. However, in this solvent, expensive silver salts were quite often used as base/additive; whereas, in carbonates as solvents, the less expensive potassium carbonate base could be employed. In addition, for large scale applications, the viability of water as solvent is debatable due to the poor solubility of most substrates, products, catalysts and ligands in this solvent.

### 2.3. Reactions in polyethylene glycols

Polyethylene glycols (PEGs) are also considered as green media due to their low toxicity and recyclability.<sup>26</sup> In 2009, Ackerman group reported the use of PEGs as solvents for the Pd-catalyzed direct arylations of 1,2,3-triazoles with aryl bromides (Scheme 14).<sup>27</sup> Better yields were obtained in PEG-20000 than in PEG-2000. The best reaction conditions, involved PEG-20000 solvent and a phosphine ligand-free palladium catalyst modified by a carboxylic acid. Several functional groups on the aryl bromide were tolerated, which allowed the preparation of diversely substituted *N*-aryltriazoles in high yields.



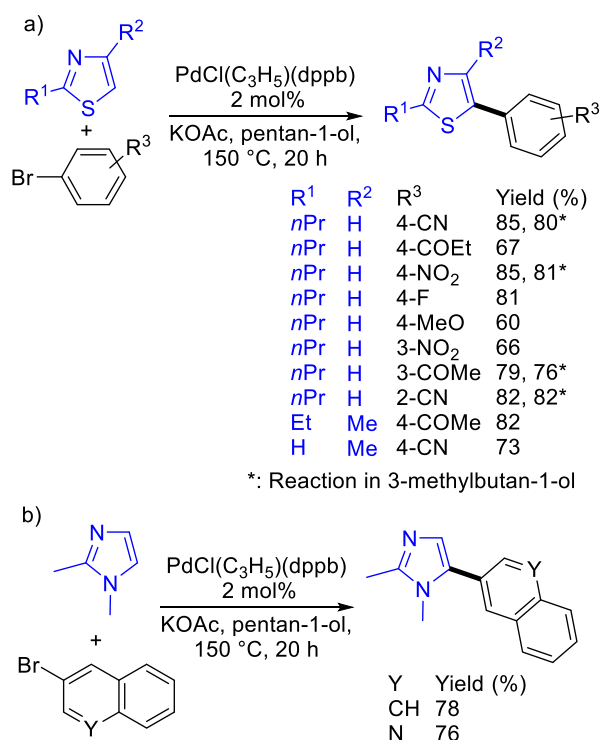
**Scheme 14.** Selected examples of coupling of triazoles with various aryl bromides in PEG-20000.



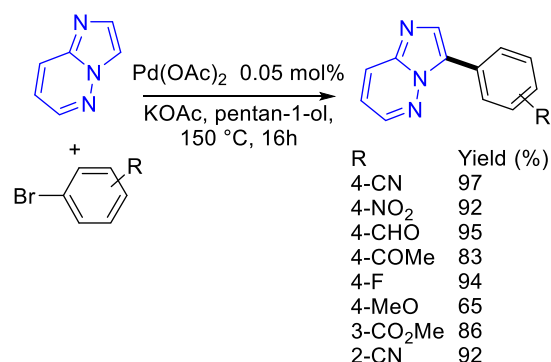
## 2.4. Reactions in alcohols

Pentan-1-ol and also 3-methylbutan-1-ol, which are biodegradable, are moderately soluble in water, but miscible with most classical organic solvents, are not considered as hazardous air pollutant solvents. These solvents can be prepared by fermentation or by the reduction of 1-valeraldehyde or 3-methylbutyraldehyde. Exposure to small amounts of these alcohols is unlikely to exhibit any adverse health effects, as they are found in several beverages such as beer. Therefore, these alcohols can be considered as "green" solvents compared to DMA, NMP or 1,4-dioxane.

In 2011, our group reported that thiazoles and imidazoles can be arylated at C5-position with a range of aryl bromides using 3-methylbutan-1-ol or pentan-1-ol as the solvents with 2 mol% of PdCl(C<sub>3</sub>H<sub>5</sub>)(dppb) catalyst (Scheme 15).<sup>28</sup> We also investigated the C3-arylation of imidazo[1,2-*b*]pyridazines in pentan-1-ol (Scheme 16).<sup>13</sup> These reactions proceeded with very high turnover numbers using only 0.05 mol% of phosphine-free Pd(OAc)<sub>2</sub> as catalyst precursor. The reaction conditions allowed the use of a several substituents on the aryl bromide. It should be mentioned that with some heteroaromatics, the direct arylations using alcohols as the solvents also proceeded using the heterogeneous Pd/C catalyst (see scheme 28).



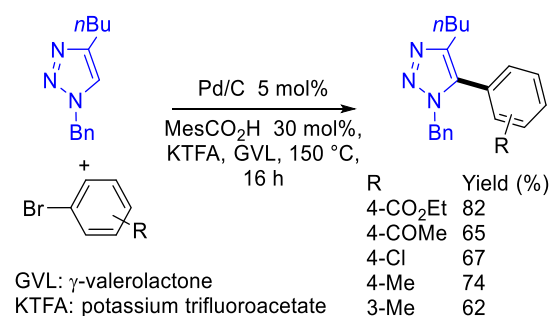
**Scheme 15.** Selected examples of coupling of heteroarenes with aryl bromides in alcohols.



**Scheme 16.** Selected examples of coupling of imidazo[1,2-*b*]pyridazines with aryl bromides in alcohols.

2.5. Reactions in  $\gamma$ -valerolactone

$\gamma$ -Valerolactone (GVL) is a renewable chemical, which can be prepared by hydrogenative cyclization of levulinic acid. GVL features a good safety profile, (high boiling and flash points, low toxicity, and low formation of peroxides). Therefore, it also represents a "green" alternative to DMA, DMF and NMP for palladium-catalyzed reactions.<sup>29</sup> In 2016, GVL has been evaluated by Ackermann, Vaccaro et al. for the direct arylation of 1,2,3-triazoles (Scheme 17).<sup>30</sup> They employed Pd/C (5 mol%) as catalyst and aryl bromides as aryl source, and obtained the C5-arylated 1,2,3-triazoles in good yields.



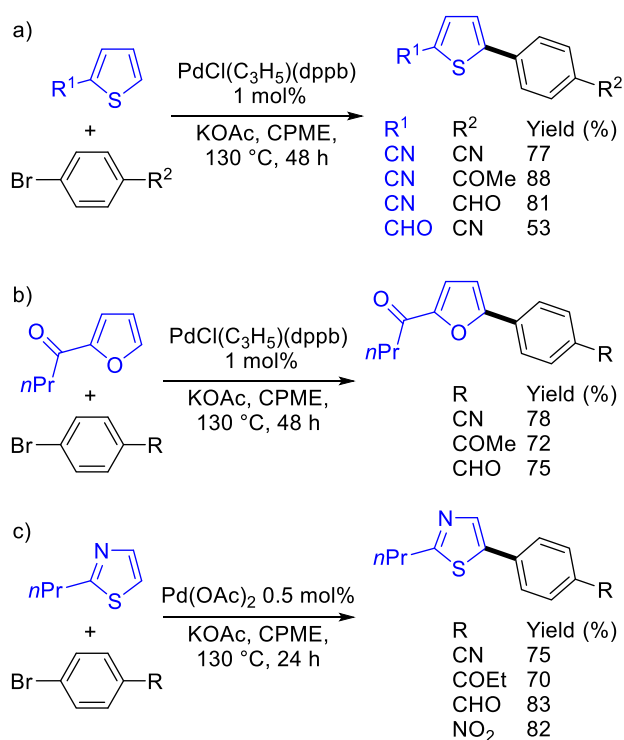
**Scheme 17.** Selected examples of coupling of triazoles with aryl bromides in  $\gamma$ -valerolactone.

## 2.6. Reactions in cyclopentyl methyl ether

Ethers such as cyclopentyl methyl ether (CPME) have also been employed as the solvents for Pd-catalyzed direct arylations. The use of CPME for the preparation of arylated heteroarenes is attractive in terms of sustainable chemistry, as this solvent presents several advantageous features including a limited miscibility in water, and low formation of peroxides (compared to THF or diisopropyl ether). Moreover, CPME can be prepared by

the addition of methanol to cyclopentene, which produces no apparent waste.<sup>31</sup> Therefore, the use of CPME as solvent in coupling reactions is in agreement with several principles of the "green chemistry".<sup>6</sup>

In 2011, our group reported that CPME can be used for the direct arylation of specific heteroaromatics (Scheme 18).<sup>32</sup> The direct C5-arylation of thiophenes, furans or thiazoles using aryl bromides as reaction partners was found to proceed in moderate to high yields in the presence of 1 mol% of PdCl(C<sub>3</sub>H<sub>5</sub>)(dppb) catalyst in CPME at 130 °C. A wide range of functions on the aryl bromide was tolerated. Conversely, in this solvent, very low to moderate yields in coupling products were obtained from imidazoles and isoxazoles.

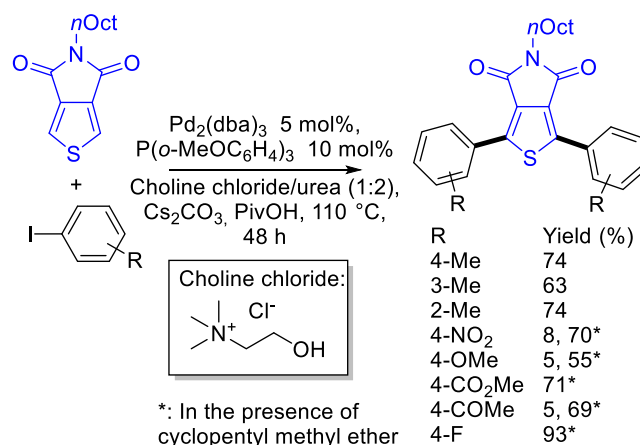


**Scheme 18.** Selected examples of coupling of heteroarenes with aryl bromides in CPME.

## 2.7. Reactions in deep eutectic solvents

Deep eutectic solvents are composed of quaternary ammonium salts which are complexed with an organic molecule such as amides, acids, urea or polyols. They currently attract attention as a new class of environmentally friendly media. When these two components are mixed, hydrogen-bond interactions provide an eutectic mixture with 1) a melting point which is lower than those of the two components employed and 2) unusual solvent properties due to the hydrogen bonding. Other important advantages of deep eutectic solvents are the low cost and low toxicity of some of them.

In 2017, Farinola et al. described the direct arylation of 5-octylthieno[3,4-c]pyrrole-4,6-dione with aryl iodides in a deep eutectic solvent prepared from choline chloride and urea (Scheme 19).<sup>33</sup> These reactions were performed in non-anhydrous conditions in air with Pd<sub>2</sub>(dba)<sub>3</sub> associated to P(*o*-MeOC<sub>6</sub>H<sub>4</sub>)<sub>3</sub> as catalyst with a mixture of Cs<sub>2</sub>CO<sub>3</sub> and PivOH as base. In some cases, cyclopentyl methyl ether was added to the reaction mixture to increase the reactions yields.

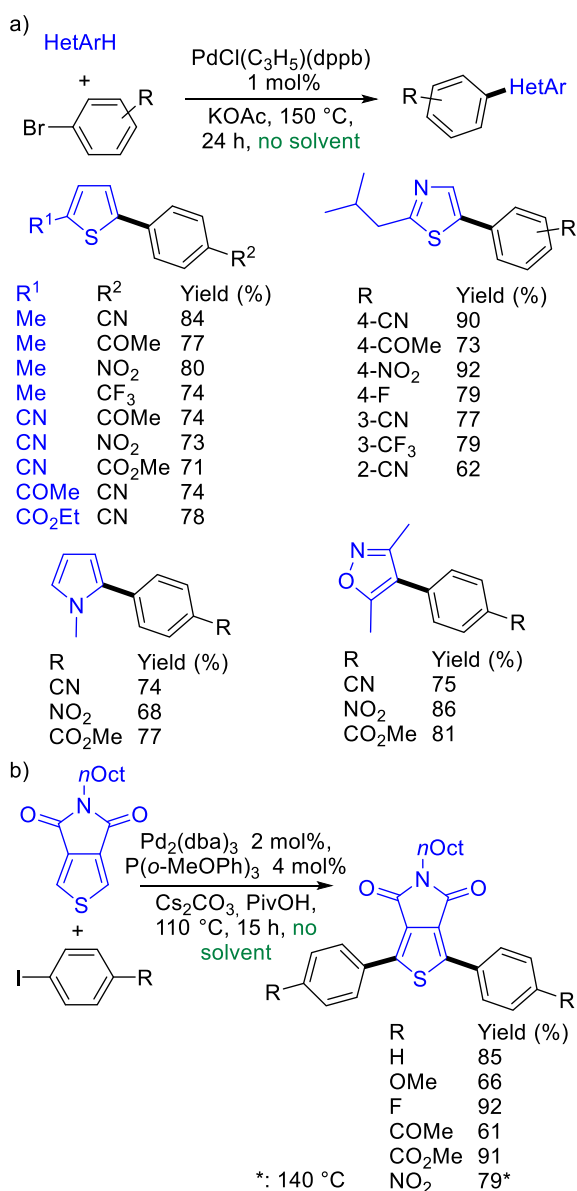


**Scheme 19.** Selected examples of coupling of heteroarenes with aryl bromides in deep eutectic solvents.

## 2.8. Solvent-free reactions

Solvent-free reactions are also very attractive to deal with toxicity and hazards associated with the use of solvents. Moreover, it generally simplifies purification procedures at the end of the reaction. In 2012, our group reported that Pd-catalyzed direct arylations of some heteroaromatics with aryl bromides can be performed using neat conditions (Scheme 20, a).<sup>34a</sup> In the presence of 1 mol% of palladium catalysts and KOAc as the base, the arylation of several heteroaromatics such as thiophenes, thiazoles, pyrroles or isoxazoles using bromobenzenes as reaction partners proceeded in moderate to high yields. However, these solvent-free conditions were limited to the use of electron-deficient aryl bromides. Moreover, poor yields were obtained with some heteroarenes such as furans. Due to the poor coordination properties of furans, they are probably not as good stabilizing agent for palladium species than thiazoles or thiophenes.

In 2018, Farinola et al. extended the scope of the solvent-free direct arylation to thienopyrrolodione, diketopyrrolopyrroles, benzodithiophene derivatives, and to fluorinated heteroarenes.<sup>34b</sup> The reactions were performed with aryl iodides and tolerated several functional groups on both the coupling partners (Scheme 20, b).

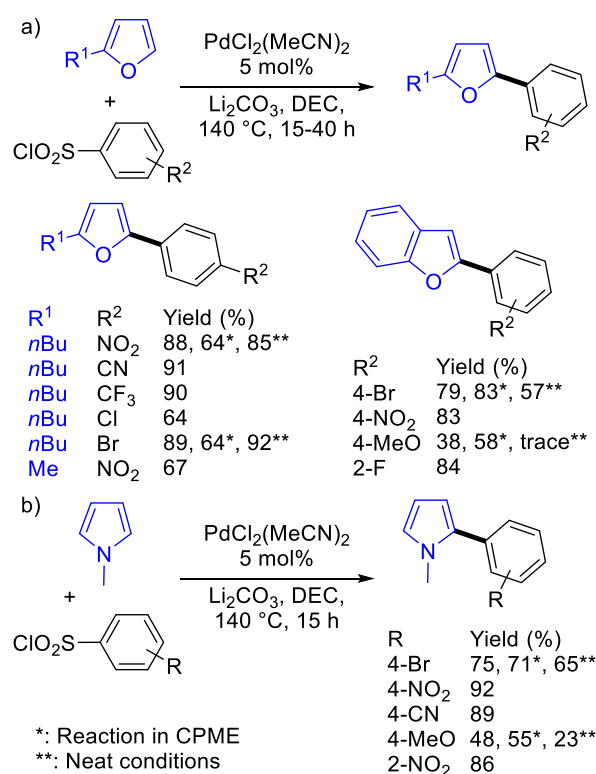


**Scheme 20.** Selected examples of solvent-free couplings of heteroarenes with aryl halides.

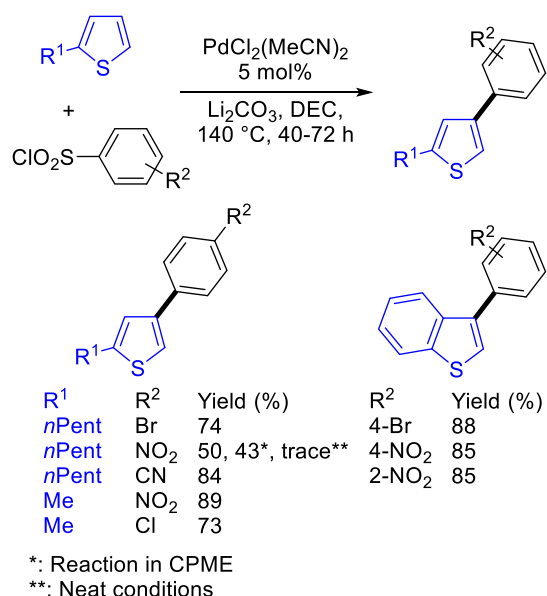
## 2.9. Green solvents associated to benzenesulfonyl chlorides as aryl source

In recent years, a few groups reported that benzenesulfonyl chlorides can be employed as alternative coupling partners in Pd-catalyzed direct arylation of heteroarenes.<sup>35</sup> The first example of such direct desulfurative-couplings was reported in 2009 by Dong et al., who arylated benzoquinoline in high yield using a palladium catalyst associated to Ag and Cu salts in 1,4-dioxane.<sup>36</sup> The advantages of RSO<sub>2</sub>Cl derivatives are that many of them are easily available, and that they are easy to handle. Moreover, the generation of SO<sub>2</sub> in the course of desulfurative

couplings is not an important issue for industrial processes, as SO<sub>2</sub> is added to some foods. In 2015, we reported the Pd-catalyzed regioselective direct arylation of a variety of heteroarenes using benzenesulfonyl chlorides as coupling partners.<sup>37</sup> We found that, in the presence of 5 mol% PdCl<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub> as the catalyst precursor, these reactions could be performed in DEC, in CPME or even using neat conditions in a few cases, instead of 1,4-dioxane (Schemes 21 and 22). Under these solvent-free conditions, the reaction proceeds with furan derivatives at C5-positions and with benzofuran and pyrrole derivatives at C2-positions (Scheme 21). Conversely, the arylation of thiophenes and benzothiophenes did not proceed using neat-conditions; whereas, in DEC the arylation occurred at C3- and C4-positions, respectively (Scheme 22).



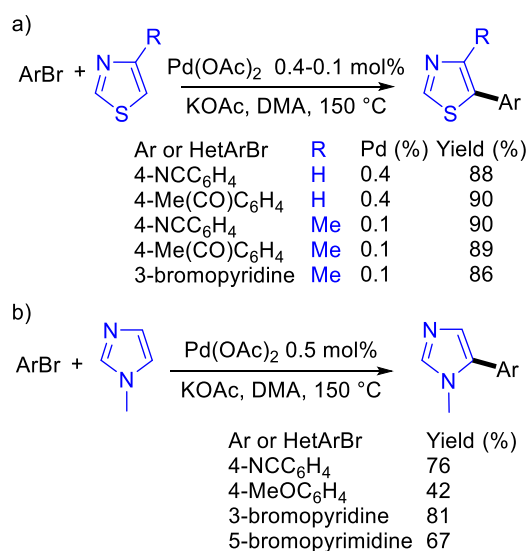
**Scheme 21.** Selected examples of coupling at C2-position of heteroarenes with benzenesulfonyl chlorides in green solvents or using neat conditions.



**Scheme 22.** Selected examples of coupling at C3-position of heteroarenes with benzenesulfonyl chlorides in green solvents.

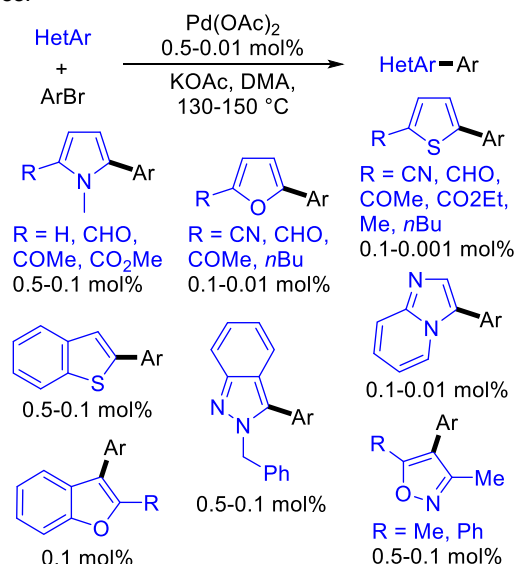
### 3. Phosphine-free low catalyst loadings

One of the major disadvantages of metal-catalyzed C-H bond activation reactions compared to Suzuki or Negishi couplings is the relatively high catalyst loadings which are often employed. In most cases, direct arylations were initially performed using 1–10 mol% palladium catalyst. Moreover, very often palladium salt was associated to 1–20 mol% of mono- or di-phosphines as ligands.<sup>5</sup> From 2008,<sup>38</sup> our group reported the low-loading and phosphine-free Pd-catalyzed direct arylation of several heteroarenes such as thiazoles<sup>39</sup> or imidazoles.<sup>40</sup> The use of only 0.5–0.1 mol% Pd(OAc)<sub>2</sub> with KOAc as base in DMA at 150 °C was found to promote very efficiently and regioselectively the direct C5-arylation of thiazole derivatives (Scheme 23, a). These conditions also allowed to obtain the C5-arylated imidazoles in almost complete regioselectivity and in high yields with electron-deficient aryl bromides (Scheme 23, b). Conversely, with this procedure, moderate yields were often obtained with electron-rich aryl bromides and aryl chlorides were unreactive.



**Scheme 23.** Selected examples of phosphine-free and low-catalyst loadings direct arylations of thiazoles and imidazoles.

Then, our group extended the low-loading and phosphine-free Pd-catalyzed direct arylation to several heteroarenes such as pyrroles,<sup>41a</sup> furans,<sup>41b</sup> thiophenes,<sup>41c</sup> isoxazoles,<sup>41d</sup> benzofurans,<sup>41e</sup> imidazo[1,2-*a*]pyridines,<sup>41f</sup> benzothiophenes,<sup>41g</sup> and indazoles,<sup>41h</sup> (Scheme 24). It should be noted that with most heterocycles, a wide range of functional groups on the bromobenzene was tolerated. This phosphine-free low catalyst loading procedure is economically attractive, due to the low catalyst cost and as there is no need to remove phosphine residues.



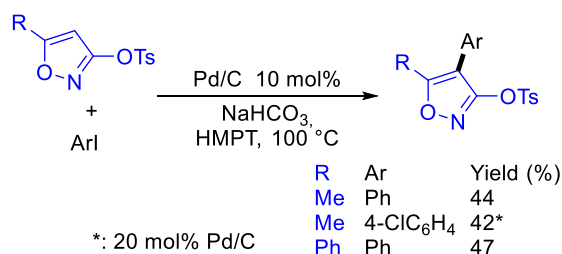
**Scheme 24.** Phosphine-free and low-catalyst loadings direct arylations of heteroarenes.

## 4. Heterogeneous catalysis

Heterogeneous and solid-supported catalysts are very attractive in terms of "green chemistry" as the catalyst can generally be removed very easily at the end of the reaction by simple filtration, as the catalyst can be recycled in some cases and due to the reduced contamination of products by metal residues.<sup>42</sup>

### 4.1. Reactions with Pd/C catalyst

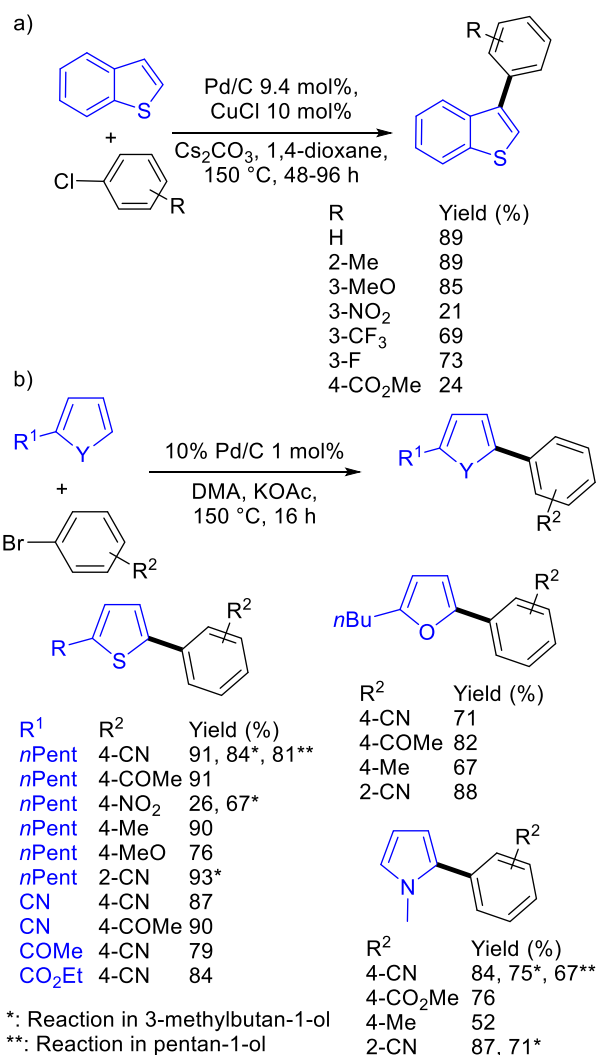
The first examples of Pd-catalyzed direct arylations of heteroarenes using an heterogeneous catalyst were reported in 1982 by Nakamura, Tajima and Sakai (Scheme 25).<sup>3</sup> They employed Pd/C catalyst with NaHCO<sub>3</sub> as base, and HMPT as the solvent. The reaction was limited to the use of isoxazoles as heteroarenes.



**Scheme 25.** Selected examples of Pd/C as catalyst for C4-arylation of isoxazoles.

In 2013, Glorius and co-workers described the first example of direct arylation of benzothiophenes using a heterogeneous catalyst (Scheme 26, a). They discovered that, with Pd/C catalyst associated to 10 mol% of CuCl, the less reactive  $\beta$ -position of benzothiophene was regioselectively arylated with a very high  $\alpha/\beta$  selectivity (>99%).<sup>43a</sup> Electron-deficient, -excessive or -neutral chlorobenzenes afforded the coupling products in good to excellent yields. From the sterically encumbered 2-chlorotoluene, a high yield in the 3-tolylbenzothiophene derivative was also obtained. Their mechanistic investigation suggests that the active catalyst is probably heterogeneous, as the use of homogeneous Pd-complexes provided exclusively  $\alpha$ -arylations.

Very recently, our group reported that only 1 mol% of the Pd/C catalyst promotes the direct arylations of a wide range of heteroaromatics using aryl bromides as coupling partners (Schemes 26, b).<sup>44</sup> With this catalyst and KOAc as the base in DMA, without additives or co-catalysts, the direct arylation of 2-substituted thiophenes and furans proceeded highly regioselectively at C5-position in moderate to very high yields. We also described the C2-arylation of 1-methylpyrrole using Pd/C catalyst.

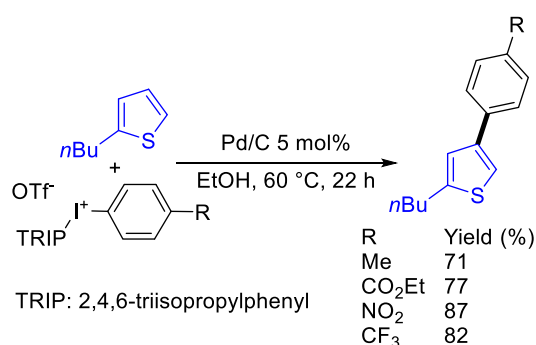


**Scheme 26.** Selected examples of Pd/C as catalyst for arylations of heteroarenes.

### 4.2. Reactions with Pd/C catalyst in green solvents

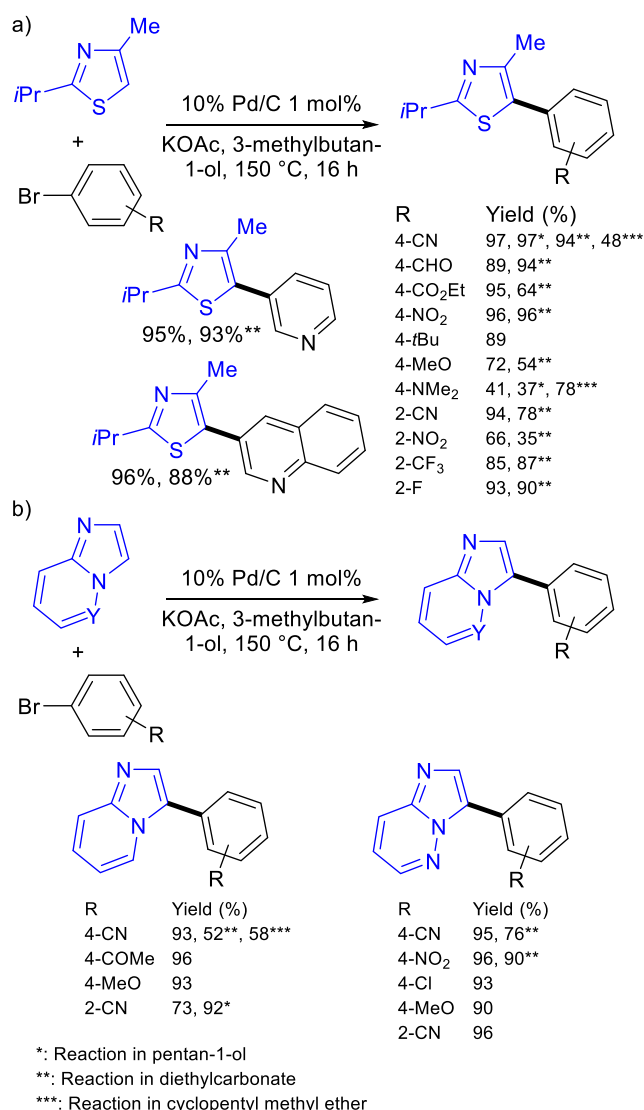
We have seen in the section 2.5, that Pd/C (5 mol%) catalyst was successfully employed by Ackermann, Vaccaro et al. for the direct C5-arylation of 1,2,3-triazoles using  $\gamma$ -valerolactone as green solvent (Scheme 17).<sup>30</sup>

In 2014, Glorius group extended the scope of Pd/C catalyst using green solvents to the C4-arylation of thiophenes employing arylidonium salts as aryl source instead of aryl chlorides, but without copper salt as additive (Scheme 27).<sup>43b</sup> These reactions were performed in ethanol at only 60 °C.



**Scheme 27.** Selected examples of Pd/C as catalyst for  $\beta$ -arylations of (benzo)thiophenes.

Our group also reported that with specific heteroarenes such as thiazoles, imidazo[1,2-*a*]pyridine and imidazo[1,2-*b*]pyridazine, these arylations with Pd/C catalyst proceeded in “green” solvents such as 3-methylbutan-1-ol (Scheme 28).<sup>44</sup> For example, the arylation of 2-isopropyl-4-methylthiazole with 4-bromobenzonitrile in 3-methylbutan-1-ol using 1 mol% of 10% Pd/C catalyst afforded the C5-arylated thiazole in 97% yield. Both electron-poor and electron-excessive aryl bromides were employed. This environmentally friendly protocol was also employed for the arylation of 2-isopropyl-4-methylthiazole with 3-bromopyridine or 3-bromoquinoline.



**Scheme 28.** Selected examples of Pd/C as catalyst for arylations of thiazoles, imidazo[1,2-*a*]pyridine and imidazo[1,2-*b*]pyridazine in green solvents.

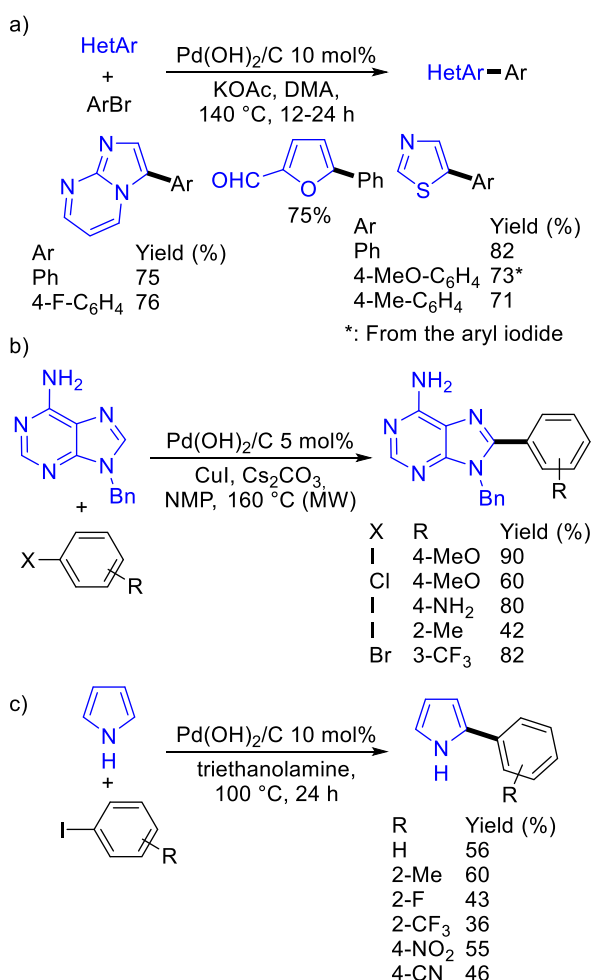
### 4.3. Reactions with Pd(OH)<sub>2</sub>/C catalyst

Fagnou et al. demonstrated in 2005 that Pd(OH)<sub>2</sub>/C (Pearlman's catalyst) is also very effective in intermolecular direct arylation reactions (Scheme 29, a).<sup>45</sup> Imidazo[1,2-*a*]pyrimidine was arylated regioselectively at the C3-position in good yields in the presence of 10 mol% Pd(OH)<sub>2</sub>/C and aryl bromides as aryl sources. Arylation of thiazole was selective at the C5-position; whereas, the coupling of 2-furaldehyde with bromobenzene afforded a 12:1 mixture of C5- vs C3-arylated products. They also examined the reactivity of a few other heterocycles such as imidazoles and benzothiazole with this catalyst. However, the arylation products were produced in less than 10% yields. According to the authors, a soluble palladium species *via*

leaching from the carbon support act as the active catalyst for these reactions.

Four years later, Alami et al. reported the C8-arylation of free-NH<sub>2</sub> adenines using 5 mol% Pd(OH)<sub>2</sub>/C catalyst in the presence of a stoichiometric amount of CuI using microwave heating (Scheme 29, b).<sup>46</sup> This protocol proved to be very effective to prepare 8-aryladenine derivatives without protection of the amino group. Moreover, a range of aryl halides including the less reactive aryl chlorides was successfully employed.

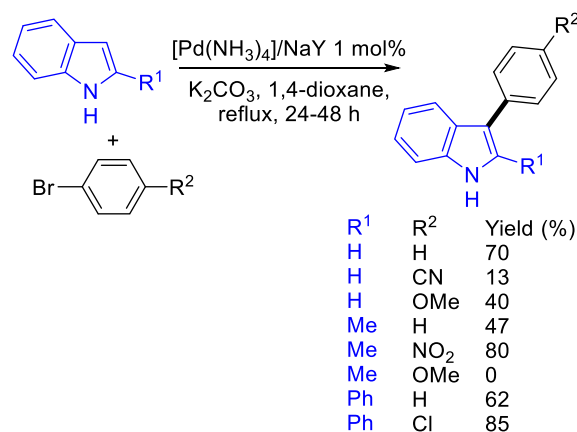
The Pd(OH)<sub>2</sub>/C-catalyzed direct C2-arylation of free NH-pyrrole has been reported by Jafarpour et al. in 2010 (Scheme 29, c).<sup>47</sup> This method provides a simple access to a 2-aryl-1H-pyrroles; however, aryl iodides were employed as aryl sources, and moderate yields were often obtained.



**Scheme 29.** Selected examples of Pd(OH)<sub>2</sub>/C as catalyst for arylations of heteroarenes.

#### 4.4. Reactions using Pd-nanoparticles or zeolites

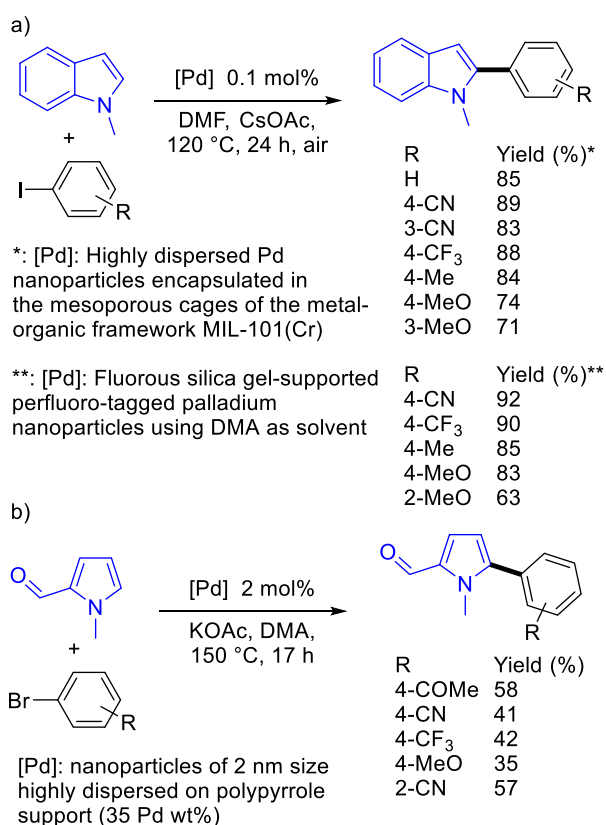
In 2008, Djakovitch et al. reported a heterogeneously Pd-catalyzed procedure for the C3-arylation of 2-substituted indoles (Scheme 30).<sup>48</sup> The catalyst was prepared by ion exchange of a NaY zeolite using a 0.1 M aqueous solution of [Pd(NH<sub>3</sub>)<sub>4</sub>]<sup>2+</sup>, 2 Cl<sup>-</sup>. In general, aryl bromides bearing electron-withdrawing substituent gave the highest yields.



**Scheme 30.** Selected examples using zeolite as catalyst support for arylations of heteroarenes.

In 2011, Cao et al. prepared highly dispersed Pd-nanoparticles encapsulated in the mesoporous cages of the metal-organic framework of MIL-101(Cr).<sup>49</sup> In the presence of only 0.1 mol% of this catalyst and CsOAc as base in DMF, the arylation of indoles proceeded regioselectively at the C2-position in high yields with a variety of iodobenzenes; whereas, the reactions with bromobenzenes and chlorobenzenes were sluggish (Scheme 31, a). Fluorous silica gel-supported perfluoro-tagged palladium nanoparticles have also been used as catalyst for the direct C2-arylation of indoles (Scheme 31, a).<sup>50</sup>

In 2011 and 2016, Hierso et al. employed palladium nanoparticles of 2 nm size highly dispersed on a polypyrrole support (35 Pd wt%) for the C5-arylation of thiophenes, furans, pyrroles and imidazoles (Scheme 31, b).<sup>51, 52</sup> The catalyst could be recovered and reused. According to the authors, the active species of this catalytic system likely come from the releasing of molecular or colloidal soluble palladium species.



**Scheme 31.** Selected examples using nanoparticles as catalysts for arylations of heteroarenes.

In summary, the use of heterogeneous catalysts represents a very attractive ecofriendly approach for such reactions. However, in many cases, these couplings were performed in the presence of toxic reaction solvents such as 1,4-dioxane, NMP, DMF or DMA.

## 5. Use of aryl chlorides as coupling partners

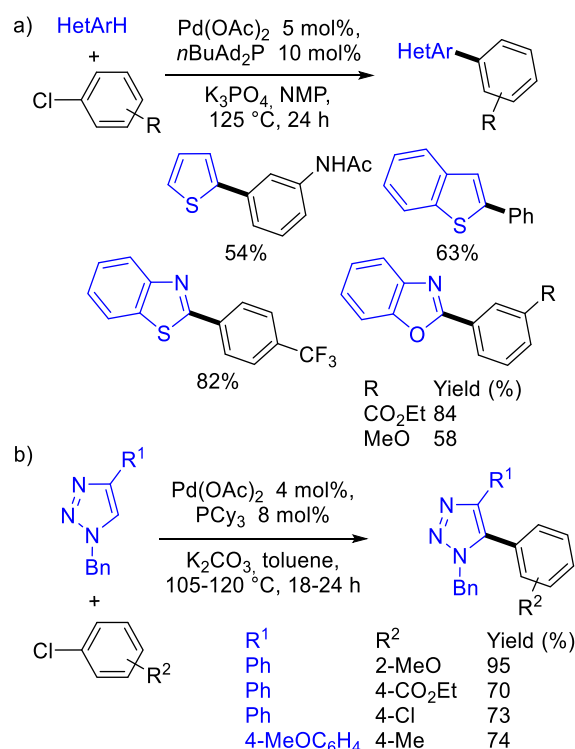
Pd-catalyzed direct arylations of heteroarenes are usually performed using aryl bromides, aryl iodides, aryl triflates, iodonium salts and benzenesulfonyl chlorides<sup>5</sup> as the coupling partners. Conversely, aryl chlorides remain quite uncommon aryl sources, despite the fact that among all coupling partners, they are certainly among the most useful substrates due to their low cost and to the wide diversity of easily available compounds. With a few exceptions,<sup>43a</sup> aryl chlorides are generally unreactive under the conditions employed to couple other starting materials such as aryl bromides or iodides. However, monodentate electron-rich phosphine-ligands associated to palladium, catalytic systems based on a chelating di- or poly-phosphines or the use of carbenes as ligands were found to promote a limited number

of coupling reactions based on mostly electron-deficient aryl chlorides, chlorotoluenes, chloroanisoles and chloro-substituted heteroarenes.<sup>53-56</sup>

### 5.1. Reactions using monodentate phosphine ligands

In 2007 Daugulis et al. reported the first general procedure for the direct arylation of heteroarenes using aryl chlorides (Scheme 32, a).<sup>53a</sup> They employed the electron-rich and bulky *n*butyldi-1-adamantylphosphine ligand associated to Pd(OAc)<sub>2</sub> and K<sub>3</sub>PO<sub>4</sub> as base. A set of five-membered ring heterocycles including (benzo)thiophenes, benzofurans, (benzo)thiazoles, benzoxazoles, imidazoles and caffeine were successfully employed. Three years later, they extended the scope of the arylation with aryl chlorides to pyrroles and furans using Pd(OAc)<sub>2</sub>/P(Cy)<sub>2</sub>(*o*-biphenyl) as catalyst.<sup>53b</sup> A similar procedure, using Cs<sub>2</sub>CO<sub>3</sub> as base was reported by Cao et al. for the C3-arylation of imidazo[1,2-*a*]pyridines with aryl chlorides.<sup>54</sup>

In 2008, Ackermann et al. employed a mixture of Pd(OAc)<sub>2</sub> and PCy<sub>3</sub> as catalyst precursor for the C5-arylation of triazoles with aryl chlorides (Scheme 32, b).<sup>55</sup> These reactions were performed in toluene using K<sub>2</sub>CO<sub>3</sub> as base, and tolerated a variety of substituents on the aryl chloride including electron-donating substituents such as 4-methyl and 2-methoxy.

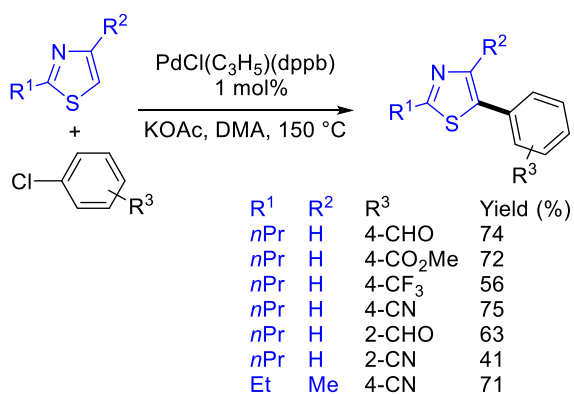


**Scheme 32.** Selected examples using monodentate phosphine-ligands for direct arylations with aryl chlorides.



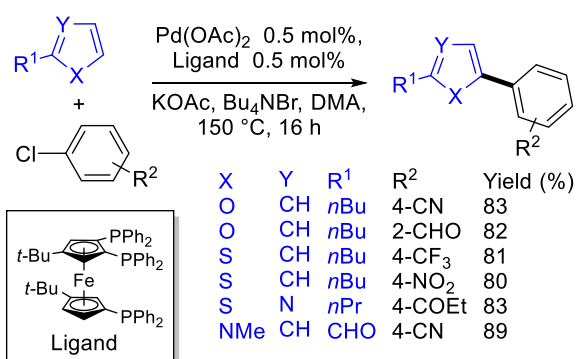
## 5.2. Reactions using bi- and poly-dentate phosphine ligands

In 2007, our group reported the C5-arylation of thiazoles with aryl chlorides using 1 mol% of the air-stable  $\text{PdCl}(\text{dppb})(\text{C}_3\text{H}_5)$  complex as catalyst with KOAc as base (Scheme 33).<sup>56</sup> These reaction conditions tolerated a range of electron-withdrawing substituents on the aryl chloride, but were ineffective with electron-rich aryl chlorides.



**Scheme 33.** Selected examples using bidentate phosphine-ligand for direct arylations with aryl chlorides.

Our group in association with Hierso's group also described the efficiency of an air-stable ferrocenyl triphosphane ligand in the direct arylation of heteroarenes with aryl chlorides (Scheme 34).<sup>57</sup> A variety of heteroaromatic compounds such as furans, thiophenes, pyrroles, and thiazoles were tolerated by this procedure. Moreover, catalyst loadings ranging between 0.1 and 0.5 mol% could be employed. This procedure tolerated useful functional groups on the aryl chloride.

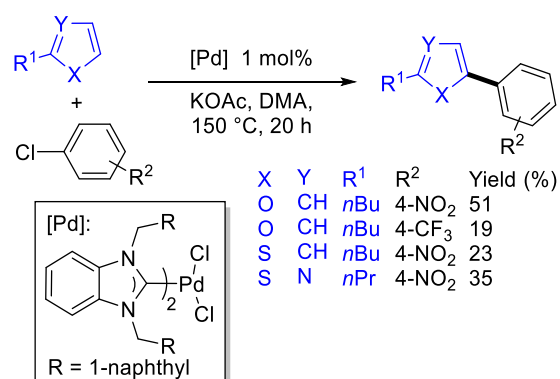


**Scheme 34.** Selected examples using polydentate phosphine-ligand for direct arylations with aryl chlorides.

## 5.3. Reactions using carbene ligands

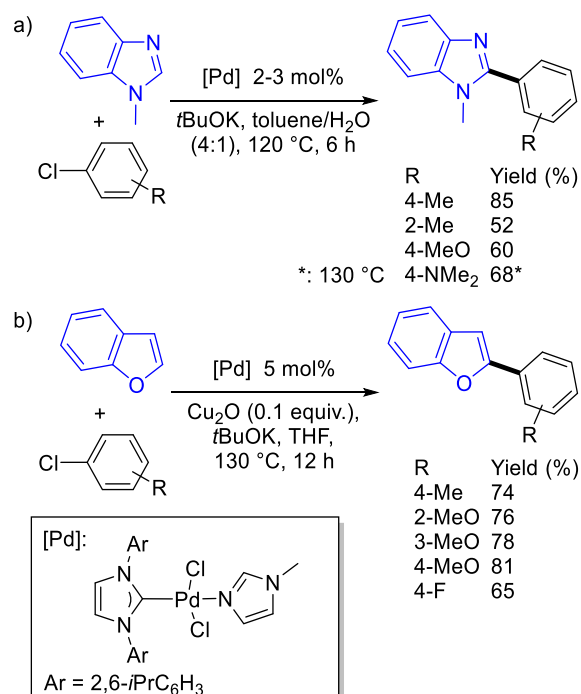
Several carbene ligands have also been employed to promote reactions with aryl chlorides.<sup>58-61</sup> However, in several cases

such as in the presence of benzimidazole-based carbenes, moderate yields were obtained and the reaction was limited to the use of electron-poor chlorobenzenes (Scheme 35).<sup>58</sup>



**Scheme 35.** Selected examples using carbene-ligands for direct arylations with aryl chlorides.

Shao et al. reported in 2014, that benzimidazoles were efficiently arylated by aryl chlorides in the presence of a NHC-Pd(II) complex (Scheme 36, a).<sup>59</sup> Under the best conditions, even strongly deactivated aryl chlorides such as chloroanilines were successfully coupled with benzimidazoles in good to high yields. One year later, they extended the use of this catalyst to the regioselective C2-arylation of benzofuran with chloroanisoles, 4-chlorotoluene and 4-chlorofluorobenzene (Scheme 36, b).<sup>60</sup>



**Scheme 36.** Selected examples using carbene-ligands for direct arylations with aryl chlorides.

Palladium(II) acetate complexes bearing PCy<sub>3</sub> and carbene ligands, Pd(L)(PCy<sub>3</sub>)(OAc)<sub>2</sub> (L = 1,3-disubstituted imidazol-2-ylidenes), prepared by Lee *et al.* were also efficient in catalyzing the arylations of heteroarenes with aryl chlorides.<sup>61</sup> A variety of substituents was tolerated.

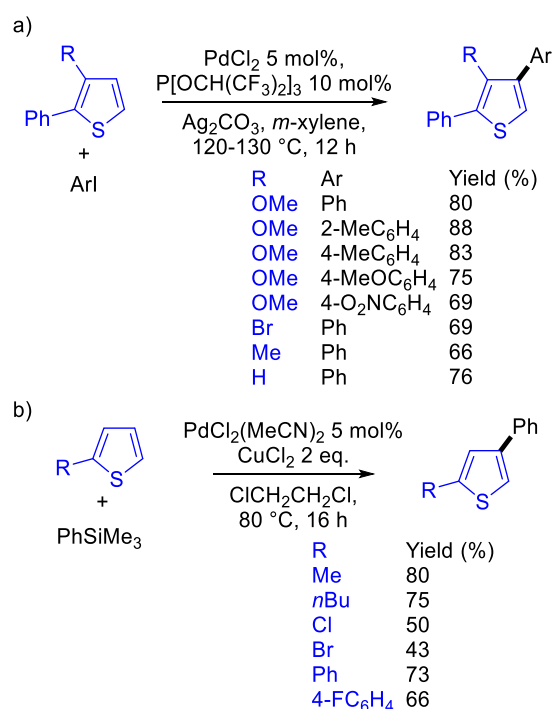
Despite these remarkable achievements, more sustainable catalytic systems employing less toxic solvents and lower amounts of palladium catalysts and/or less sophisticated ligands promoting the coupling of a wider array of aryl chlorides to different classes of heteroaromatics are still needed.

## 6. Regioselectivity

The control of the regioselectivity of the direct arylations of heterocycles is also a very important aspect of these reactions in terms of green chemistry, as it allows the access to the desired regioisomers without pre-functionalization. We have seen in the section 2.2 (see scheme 8) that Djakovitch *et al.* were able to control the regioselectivity of the arylation of indoles in favor of C2- or C3-positions by changing the reaction conditions using water as the solvent.<sup>19</sup> The palladium-catalyzed direct C2- and/or C5-arylations of most heteroaromatics such as (benzo)thiophenes, (benzo)furans, pyrroles, thiazoles, oxazoles, selenophenes or imidazoles are general favored. Since two decades, several groups investigated the influence of catalysts, reaction conditions and nature of aryl sources in order to modify of the regioselectivity of these arylations.

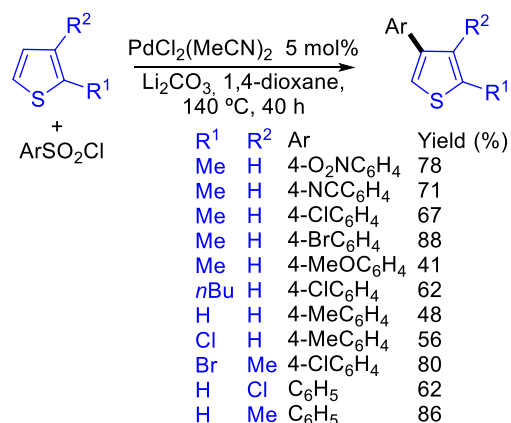
### 6.1. $\beta$ -Arylations of thiophenes

The palladium-catalyzed direct arylation of unsubstituted thiophene using simple palladium salts associated to acetates as bases regioselectively occurs at  $\alpha$ -position.<sup>5f</sup> In 2009, Itami *et al.* discovered the first catalytic system which promoted the  $\beta$ -regioselective arylations of thiophene derivatives (Scheme 37, a). These  $\beta$ -functionalizations were obtained using PdCl<sub>2</sub> associated to a phosphite ligand P[OCH(CF<sub>3</sub>)<sub>2</sub>]<sub>3</sub>, Ag<sub>2</sub>CO<sub>3</sub> as base in xylene with aryl iodides as aryl sources.<sup>62</sup> Both electron-withdrawing and electron-donating substituents on the iodobenzene were tolerated. In 2012 Oi *et al.* also described a procedure for the  $\beta$ -arylation of thiophenes. They found that the use of PdCl<sub>2</sub>(MeCN)<sub>2</sub> catalyst with CuCl<sub>2</sub> as oxidant using aryltrimethylsilanes as coupling partners afforded the C4-arylated thiophenes (Scheme 37, b).<sup>63</sup> Thiophenes bearing halogen substituents at C2-position could also be employed without loss of the halogen substituent, providing regioselectively 2-chloro- or 2-bromo-4-phenylthiophenes. Glorius *et al.* also reported conditions allowing the C4-arylation of thiophenes using arylidonium salts as aryl source using Pd/C catalyst (see scheme 26, b).<sup>43b</sup>



Scheme 37. Selected examples of  $\beta$ -arylations of thiophenes.

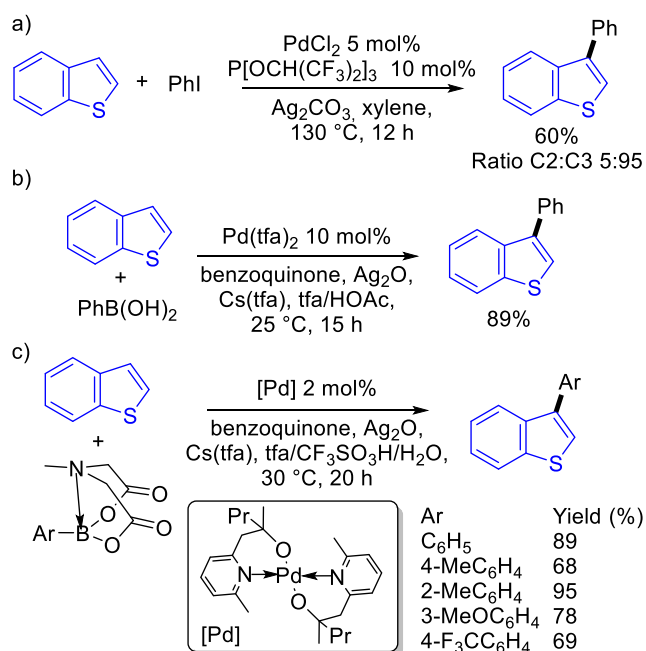
In 2014, our group reported that the Pd-catalyzed direct desulfurative arylation of thiophenes using benzenesulfonyl chlorides as aryl source also takes place at the C4-position (Scheme 38, see also scheme 22).<sup>64</sup> PdCl<sub>2</sub>(MeCN)<sub>2</sub> in the presence of 3 equivalents of Li<sub>2</sub>CO<sub>3</sub> as base without additives or ligands provided the arylated thiophenes in high yields with a wide substrate scope, which included sensitive functional groups on the benzenesulfonyl chloride such as cyano, nitro, bromo, or chloro. It also tolerated chloro- and bromo-substituents on thiophenes.



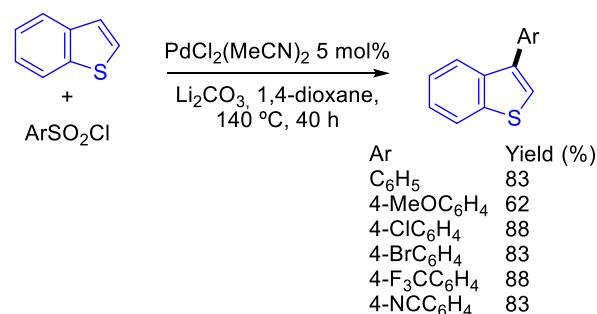
Scheme 38. Selected examples of  $\beta$ -arylations of thiophenes.

6.2.  $\beta$ -Arylations of benzothiophenes

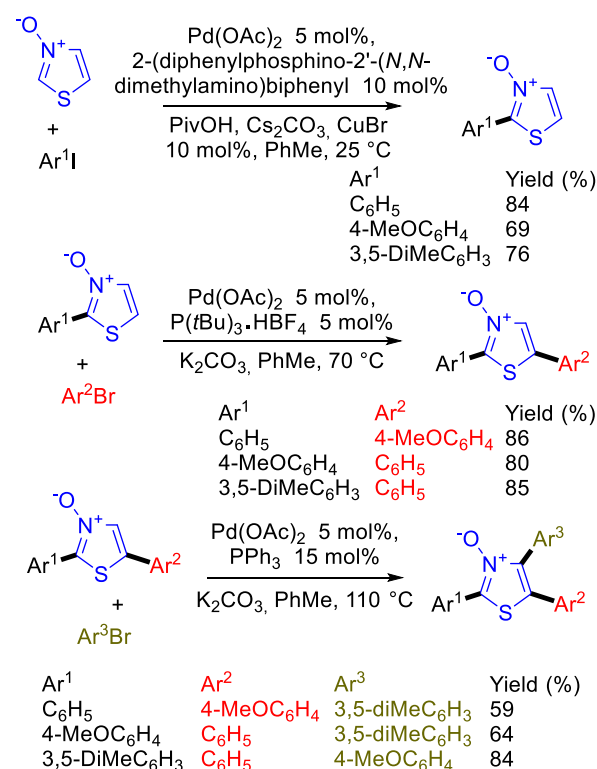
Benzothiophene can be easily arylated at C2-position in the presence of  $\text{Pd}(\text{OAc})_2$  catalyst and KOAc base.<sup>5f</sup> However, procedures allowing the regioselective C3-arylations of benzothiophenes, without using blocking or directing groups have also been reported (Scheme 39). Again, the first one was reported by Itami *et al.* in 2010 (Scheme 39, a).<sup>62b</sup> The regioselective coupling at C3-position was observed using again  $\text{PdCl}_2/\text{P}[\text{OCH}(\text{CF}_3)_2]_3$  catalyst,  $\text{Ag}_2\text{CO}_3$  as base in xylene with aryl iodides. Bach and Schnapperelle also discovered a procedure promoting the C3-arylation of benzothiophene (Scheme 39, b).<sup>65</sup> Using  $\text{Pd}(\text{tfa})_2$  catalyst in trifluoroacetic acid as the solvent, in the presence of  $\text{Ag}_2\text{O}$ , cesium trifluoroacetate, benzoquinone, and phenylboronic acid as aryl source, a highly regioselective C3-arylation of benzothiophene was obtained. Using so-called MIDA boronates as the coupling partners instead phenylboronic acid, the C3-arylated benzothiophenes were also regioselectively obtained in high yields (Scheme 39, c).<sup>66</sup> Glorius *et al.* also reported a procedure for the arylation at  $\beta$ -position of benzothiophenes using Pd/C catalyst in the presence of 10 mol% CuCl (see Scheme 26, a).<sup>43a</sup>

Scheme 39. Selected examples of  $\beta$ -arylations of benzothiophene.

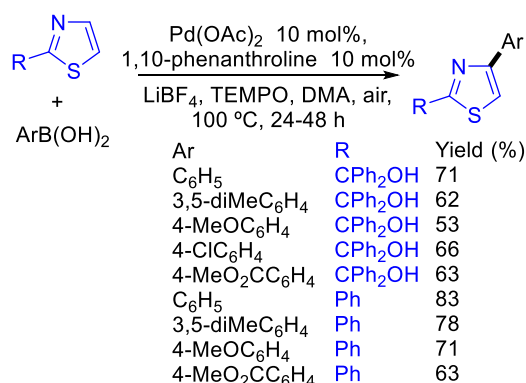
In 2014, our group described the Pd-catalyzed direct desulfurative arylation of benzothiophenes with benzenesulfonyl chlorides as aryl source (Scheme 40, see also scheme 22).<sup>64</sup>  $\text{PdCl}_2(\text{MeCN})_2$  in the presence of  $\text{Li}_2\text{CO}_3$  as base gave access to the C3-arylated benzothiophenes in high regioselectivities and with a wide substrate scope, which included useful functional groups such as cyano or bromo.

Scheme 40. Selected examples of  $\beta$ -arylations of benzothiophene6.3.  $\beta$ -Arylations of thiazoles

In 2005, Fagnou *et al.* described the programmed 2,4,5-triarylation of thiazole derivatives (Scheme 41).<sup>67</sup> The use of thiazole *N*-oxide instead of thiazole considerably enhances the reactivity of the thiazole ring system with C2>C5>C4 arylation order. The reaction of thiazole *N*-oxides with aryl iodides at room temperature afforded regioselectively thiazoles arylated at C2-position. Their reaction with bromobenzenes at 70 °C provided the C2,C5-diarylated thiazoles. Finally, the arylations at C4-position gave complete functionalization of the thiazole.

Scheme 41. Selected examples of regioselective polyarylations of thiazoles *N*-oxide.

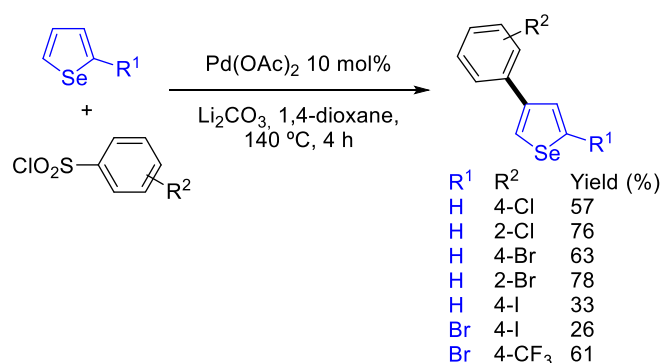
As seen in some of the previous sections, the Pd-catalyzed direct arylation of thiazoles preferentially occurs at C5-position (C2-position for thiazole *N*-oxide), whereas, the C4-position remained untouched. In 2011, Itami and co-workers discovered that the reactivity order on thiazoles could be modified by using arylboronic acids as aryl source under specific reaction conditions (Scheme 42).<sup>68</sup> The use of 2-phenylthiazole and arylboronic acids with Pd(OAc)<sub>2</sub> / 1,10-phenanthroline catalyst, TEMPO and LiBF<sub>4</sub> additives in DMA under air regioselectively provided the 4-arylthiazoles in 53–83% yields. Electron-withdrawing and -donating substituents on the arylboronic acid were tolerated. Their experiments and theoretical calculations suggest that these C4-arylations probably occurred *via* a Heck-like mechanism.



**Scheme 42.** Selected examples of  $\beta$ -arylations of thiazoles.

#### 6.4. $\beta$ -Arylations of selenophenes

The Pd-catalyzed direct arylation of selenophene in the presence of aryl halides and K<sub>2</sub>CO<sub>3</sub> associated to PivOH as base, occurs at C2-position.<sup>69</sup> Our group reported in 2017 that the Pd-catalyzed desulfurative arylation of selenophenes using benzenesulfonyl chlorides as aryl source occurs at C3- or C4-positions instead of C2-position (Scheme 43).<sup>70</sup> From selenophene using 10 mol% Pd(OAc)<sub>2</sub> catalyst and 3 equiv. of Li<sub>2</sub>CO<sub>3</sub> as the base in 1,4-dioxane, in all cases, the C3-arylated selenophenes were regioselectively produced. Satisfactory yields were obtained in the presence of benzenesulfonyl chlorides containing halo-substituents including bromo and iodo. Moreover, from 2-bromoselenophene, the 2-bromo-4-arylselenophenes were regioselectively obtained without C-Br bond cleavage.



**Scheme 43.** Selected examples of  $\beta$ -arylations of selenophenes.

In summary, the use of appropriate reaction conditions now allows to control the regioselectivity of the arylation of several heterocycles. However, for  $\beta$ -arylations of (benzo)thiophenes, thiazoles and selenophenes, high catalyst loadings and quite toxic solvents were employed (DMA, 1,4-dioxane, toluene, xylene).

## 7. Conclusions

During the last decades, several results dealing with various green aspects of the direct arylation of heteroaromatics have been reported. The variety of green solvents promoting this reaction has been significantly increased. Dialkyl carbonates, aliphatic alcohols or water were shown to be suitable solvents for most of these transformations. Cyclopentyl methyl ether,  $\gamma$ -valerolactone, or deep eutectic solvents promoted the arylation of specific heteroaromatics. PEGs have also been used for Pd-catalyzed direct arylations. These solvents allowed the recycling of the catalysts. The reactions rates are generally lower in these solvents, but in some cases they allowed cleaner reactions, and in general, the work-up procedure is simpler, resulting in a decreased waste production and also in time saving. In a few cases, the use of neat conditions was also possible. Initially, direct arylations of heteroaromatics were in most cases performed using quite high catalyst loadings associated to phosphine ligands. During the last decades, most heterocycles were found to be very reactive using a low loading (< 1 mol%) of phosphine-free Pd(OAc)<sub>2</sub> catalyst. Moreover, several heterogeneous catalysts such as Pd/C, Pd(OH)<sub>2</sub>/C or Pd-nanoparticles, which can be easily removed at the end of the reaction by filtration, were found to promote very efficiently some of these direct arylations. Finally, for several heteroaromatics, the use of alternative reaction conditions or aryl sources were found to drastically modify the regioselectivity of some arylations allowing the access to alternative regioisomers without pre-functionalizations. It also permitted the programmed synthesis of polyarylated heteroaromatics *via* successive arylations. For these reasons, Pd-catalyzed direct arylations now represents an economically viable and environmentally attractive access to arylated heterocycles. However, several challenges remain, as in most cases, high reaction temperature had to be employed to

promote the C-H bond cleavage or the oxidative addition of the aryl halides. Moreover, in several cases, more efficient catalysts allowing lower catalyst loadings or permitting to activate more effectively aryl chlorides are needed in order to provide economically attractive procedures.

## Acknowledgements

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**Keywords:** catalysis • palladium • heteroarenes • C-H bond activation • arylation • green solvents

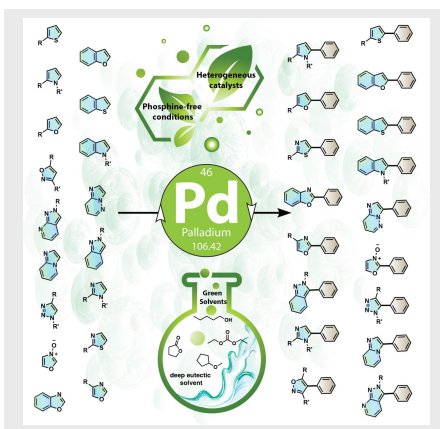
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## Entry for the Table of Contents

## REVIEW

The Pd-catalyzed (hetero)arylation of 5-membered ring heteroaromatics, via a C-H bonds activation step, represents a very attractive synthetic route for access to arylated heteroaromatics. Initially such reactions suffered from major limitations with regards to green chemistry. Tremendous improvements allowing more sustainable reaction conditions have been described during the last decades. This review summarizes some of the most important contributions made in these directions.



Shuxin Mao, Haoran Li, Xinzhe Shi, Jean-François Soulé,\* and Henri Doucet\*

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**Environmentally Benign Arylations of 5-Membered Ring Heteroarenes by Pd-Catalyzed C-H Bonds Activations**