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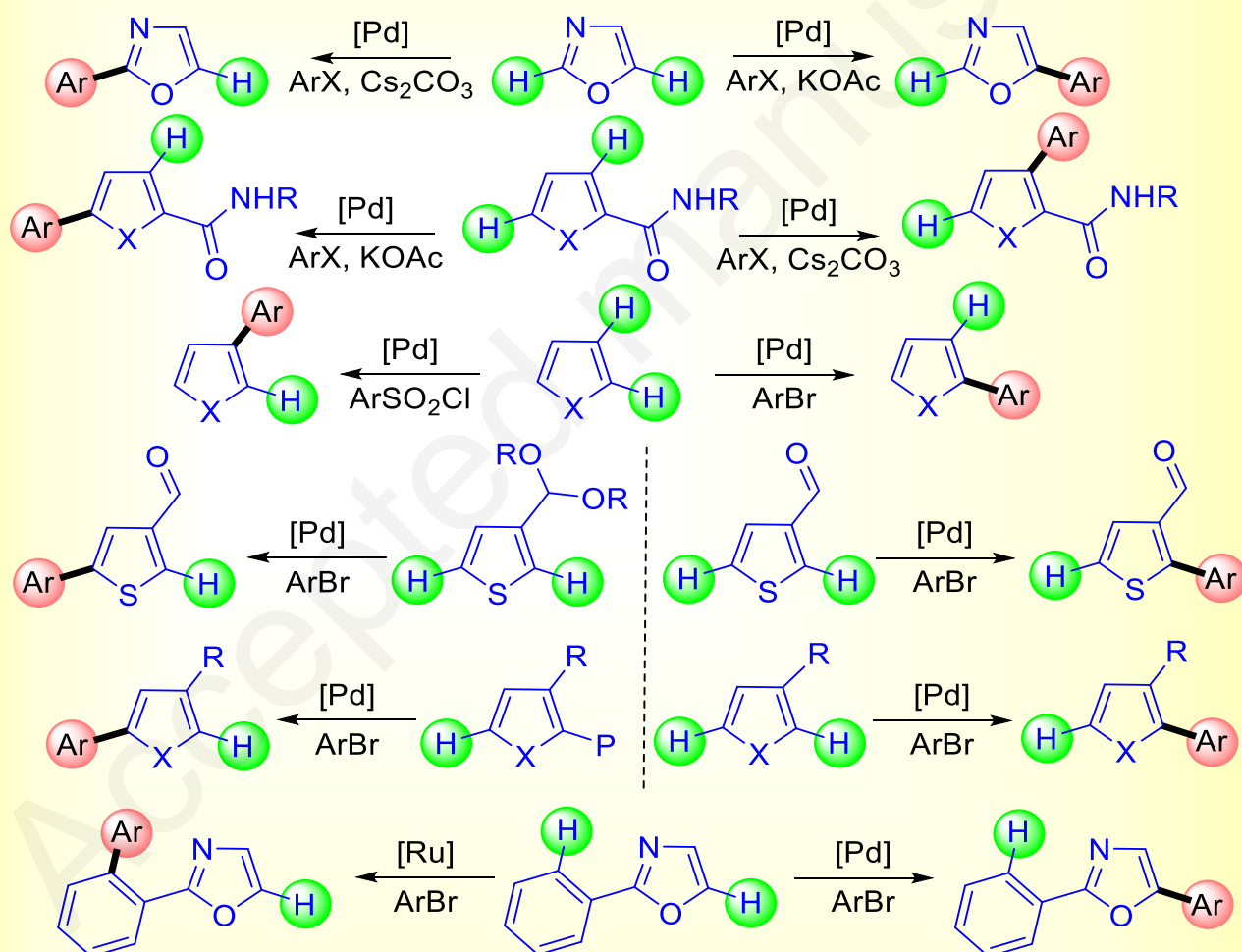
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## Effective tools for the metal-catalyzed regiodivergent direct arylations of (hetero)arenes

Hai-Yun Huang,<sup>[a]</sup> Amal Benzai,<sup>[a]</sup> Xinzhe Shi,<sup>[a]</sup>  
and Henri Doucet\*<sup>[a]</sup>

### Regiodivergent direct arylations



**Abstract:** The direct functionalization of two different C-H bonds of the same organic molecule using different procedures - also called regiodivergent C-H bond functionalization - currently represents an important research topic in organic chemistry, as it demonstrates the versatility of C-H bond functionalization methodology. Over the last decade, the number of tools to control such regiodivergent C-H bond functionalizations has increased significantly. In this account, we will present the various tools that allowed us to arylate different positions of various (hetero)arenes, *via* a C-H bond functionalization, using palladium or ruthenium catalysis.

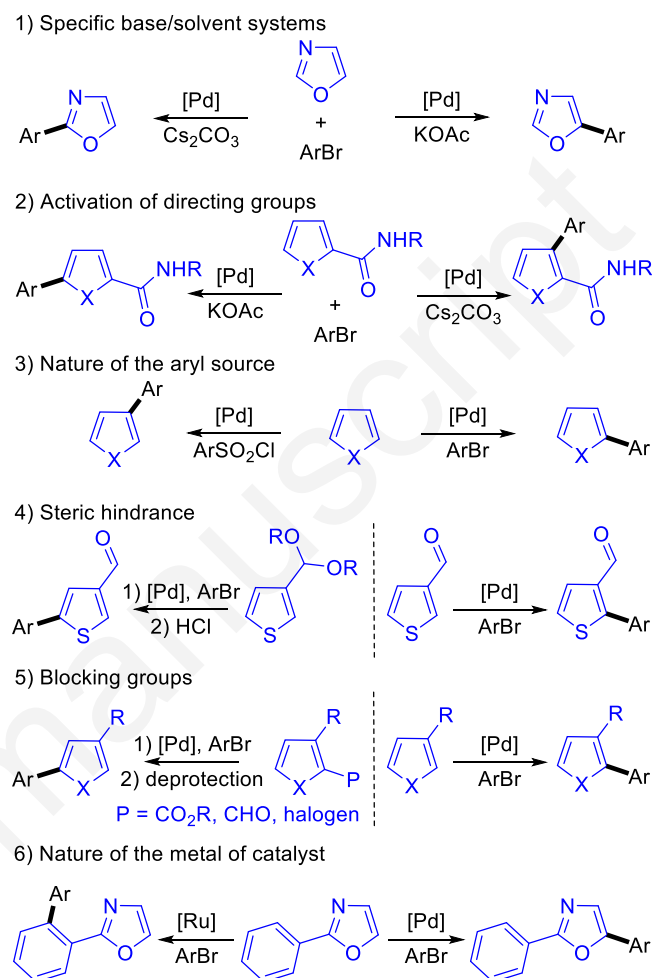
## 1. Introduction

When specific C-H bonds of organic molecules such as arenes or heteroarenes can be directly functionalized *via* catalytic reactions, it provides straightforward methods for the synthesis of (hetero)aromatic derivatives. Since the first reports in 1982 by Nakamura, Tajima and Sakai and in 1985 by Ohta et al. on the arylation of heteroarenes, and the reports by Oi, Inoue et al. in 2001 and Fagnou et al. in 2006 on the arylation of 2-arylpyridines, 2-arylazoles, polyfluorobenzenes and pyridines, the metal-catalyzed so called "direct arylation" *via* the C-H bond functionalization of 5- and 6-membered ring (hetero)aromatics with aryl (pseudo)halides, has emerged as one of the most powerful methods allowing a simple access to (hetero)biaryls.<sup>[1-3]</sup> The chief advantages of such protocol is that 1) the major by-product is HX associated to a base instead of metallic or boron salts with classical coupling procedures, and 2) no prior preparation of organometallics such as organozinc or boron derivatives is required, reducing the number of synthesis steps.

Initially, in most cases, only the "most reactive" C-H bond of (hetero)arenes could be functionalized.<sup>[1]</sup> However, C-H bond functionalization will be really synthetically useful for pharmaceutical or organic material chemists when it will be possible to activate a specific C-H bond on molecules. Therefore, the discovery of conditions allowing the regioselective functionalization of several C-H bonds of the same molecule, also called regiodivergent functionalization, is a very important aspect of the current researches dealing with metal-catalyzed C-H bond arylation.

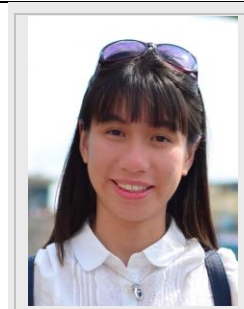
Since two decades, several tools have been discovered allowing to functionalize more than one C-H bond of the same (or very similar) (hetero)arenes giving rise to different bi(hetero)aryls. For example, such regiodivergent functionalizations are possible by 1) the use of specific base/solvent systems, 2) the activation of directing groups, 3) changing the nature of the aryl source, 4) exploiting the steric hindrance of one of the coupling partners, 5) the use of blocking groups, and 6) changing the metal catalyst (Fig 1). In this account, we will summarize our results dealing with the functionalization of two different C-H bonds of various

(hetero)arenes based on these six tools.



**Figure 1.** Tools for the regiodivergent metal-catalyzed direct arylations.

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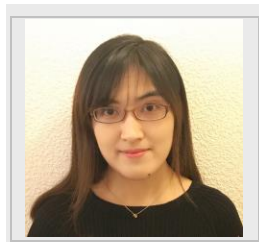


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Henri Doucet received his PhD in chemistry working with Prof. P. H. Dixneuf and Dr. C. Bruneau at Rennes 1 University (France) in 1994. After post-doctoral appointments at Oxford university (UK) with Prof. J. M. Brown; and Nagoya university, (Japan) 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. Nature of the base or solvent

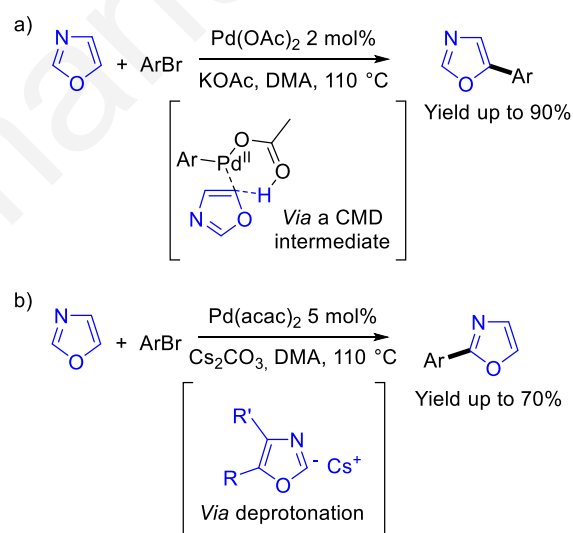
The nature of the base in the C-H bond cleavage step is very important.<sup>[1]</sup> In several cases, a quite strong base may directly deprotonate the substrate; while a weaker base may play the dual role of base and ligand in the metal-assisted C-H bond cleavage step.<sup>[4]</sup> Therefore, with specific substrates, two different C-H bonds could be functionalized by changing only the base or the base/solvent combination.

### 2.1. Carbonates and acetates

In 2010, Strotman, Chobanian et al. reported conditions for the regiodivergent Pd-catalyzed direct arylation of oxazoles (C2- vs C5-arylations).<sup>[5]</sup> They found that the C5-arylation is preferred in DMA associated to 10 mol% 2-di-*tert*-butylphosphino-3,4,5,6-tetramethyl-2',4',6'-triisopropyl-1,1'-biphenyl as ligand; whereas, C2-arylation regioselectively took place in xylene associated to 10 mol% 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl ligand. In both cases, K<sub>2</sub>CO<sub>3</sub>/PivOH was employed as base/additive, and the regioselectivity was controlled by changing the ligand/solvent system.

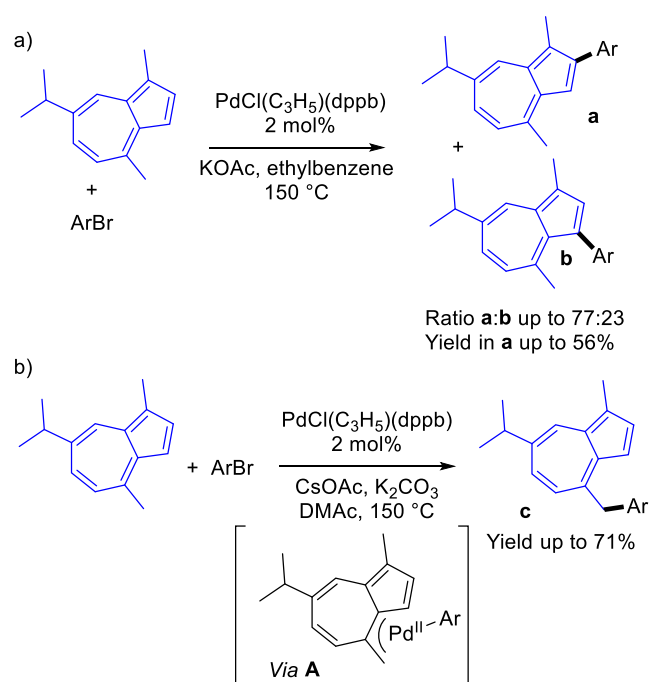
However, the free energy of activation for Pd-catalyzed direct arylation of oxazole *via* Concerted Metalation Deprotonation (CMD) pathway (Scheme 1) which has been calculated by Gorelsky<sup>[6]</sup> reveals that it is higher for the C-H bond flanked by two heteroelements (25.3 kcal mol<sup>-1</sup>) than for the C-H bond at C5-position (23.5 kcal mol<sup>-1</sup>). Therefore, we expected to be able to control the regioselectivity of the arylation of oxazole in favor of C5-arylation using acetates as base/ligand (CMD pathway); whereas C2-arylations were expected *via* the deprotonation of the more acidic C2-position of oxazole using stronger bases.

Indeed, in 2019 we reported that the regioselectivity of the direct arylation of oxazole can be controlled using the appropriate base.<sup>[7]</sup> From phosphine-free Pd(OAc)<sub>2</sub> catalyst associated to KOAc, regioselective C5-arylations, which likely proceed *via* a CMD mechanism, were observed (Scheme 1, a). By contrast, the Pd(acac)<sub>2</sub> catalyst associated to Cs<sub>2</sub>CO<sub>3</sub> as the base led regioselectively to the C2-arylated oxazoles probably *via* a base-deprotonation of oxazole (Scheme 1, b). A wide variety of (hetero)aryl bromides was tolerated by these two sets of conditions.



**Scheme 1.** Conditions for regiodivergent Pd-catalyzed direct arylations of oxazole.

Guaiazulene that features the azulene skeleton is a constituent of pigments in the *Lactarius indigo* mushrooms. As guaiazulene does not contain any reactive function, its modification *via* catalyzed C-H bond functionalization is a very appealing tool. A few years ago, we demonstrated that both the sp<sup>2</sup> and sp<sup>3</sup> direct arylations of guaiazulene were possible when appropriate reaction conditions were employed.<sup>[8]</sup> The use of KOAc in ethylbenzene led to the C2-arylated guaiazulenes **a** (Scheme 2, a); whereas a mixture of CsOAc/K<sub>2</sub>CO<sub>3</sub> selectively promoted the sp<sup>3</sup> direct arylation at C4-Me to give 4-benzylguaiazulenes **c** (Scheme 2, b). The formation of 4-benzylguaiazulenes **c** might arise from the formation of an allyl-palladium intermediate such **A**. The higher base concentration in solution due to the better solubility of CsOAc compared to KOAc might favor this reaction pathway.

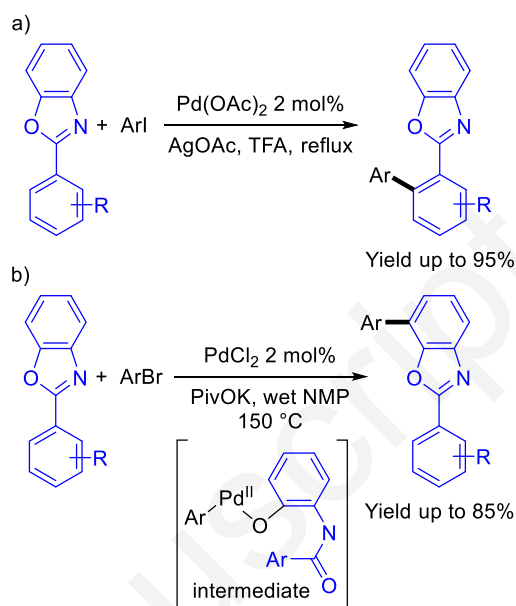


**Scheme 2.** Conditions for regioselective Pd-catalyzed direct arylations of guaiazulene.

## 2.2. AgOAc/TFA vs PivOK/NMP

In 2008, Wu et al. reported that the arylations of 2-phenylbenzoxazoles, *via* a C-H bond activation, using AgOAc/TFA and Pd(OAc)<sub>2</sub> as reaction conditions took place preferentially at the *ortho*-position of the phenyl ring, due to a directing effect of the nitrogen atom of the benzoxazolyl unit (Scheme 3, a).<sup>[9]</sup>

In 2016, we reinvestigated the Pd-catalyzed direct arylation of 2-arylbenzoxazoles.<sup>[10]</sup> We found that the use of PivOK as the base in wet NMP instead of AgOAc/TFA, using PdCl<sub>2</sub> as the catalyst source allowed the regioselective arylation of 2-arylbenzoxazoles at the unexpected C7-position (Scheme 3, b). Mechanistic studies suggest that, under these conditions, the formation of an open form of benzoxazole is the key factor for the control of the regioselectivity, with a coordination of the phenoxy group to palladium (see intermediate in the scheme 3, b) followed by reductive elimination.

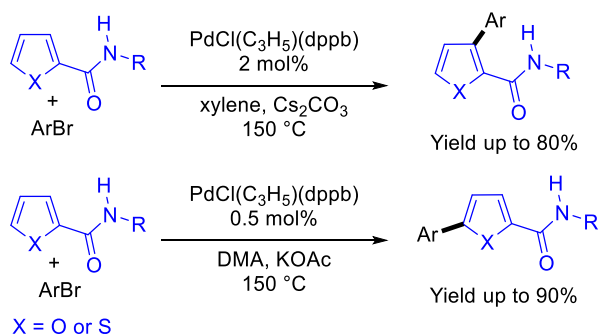


**Scheme 3.** Conditions for regioselective Pd-catalyzed direct arylations of 2-arylbenzoxazoles.

## 3. On/off directing groups

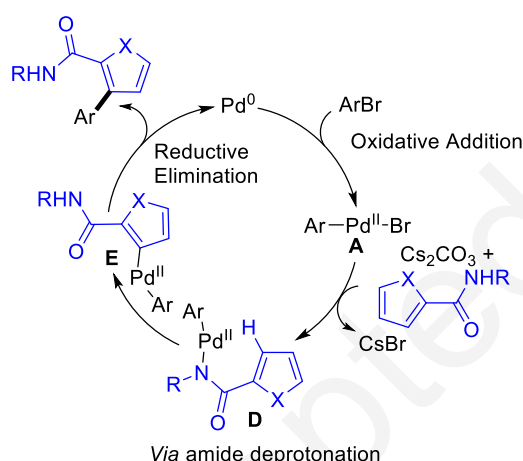
Some specific functional groups can be activated using appropriate reaction conditions to control the site-selectivity of the arylation. For example, a secondary carboxanilide function can be deprotonated with quite strong bases favoring its coordination to palladium resulting in the modification of the regioselectivity of the reaction.

The first example of C3-arylation of a thiophene derivative substituted at C2-position by a carboxanilide function was reported by Miura *et al.*, using phenyltriflate as the aryl source.<sup>[11]</sup> Then, the regioselective arylation at either the C3- or C5-positions of furans and thiophenes containing secondary carboxamides at C2-position was described by our group.<sup>[12]</sup> The nature of the base proved to be crucial for the regiocontrol of the arylation. The direct arylation occurred regioselectively at the C5-position in the presence of KOAc; whereas the use of Cs<sub>2</sub>CO<sub>3</sub> base with xylene solvent regioselectively provided the C3-arylated furans and thiophenes (Scheme 4). The regioselectivity of the arylation also depends on the carboxanilide function, as with tertiary amides only the C5-arylated products were obtained whatever the base.

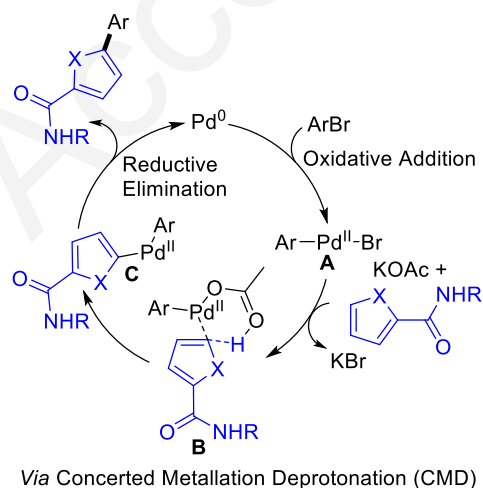


**Scheme 4.** Regiodivergent arylations of furans and thiophenes bearing secondary carboxamides.

The formation of the C3-arylated heteroarenes in the presence of  $\text{Cs}_2\text{CO}_3$  base likely comes from a coordination-assisted mechanism *via* amide deprotonation by the base followed by migration of the palladium at C3-position of the thiophene or furan rings (Scheme 5). Conversely, the C5-arylation observed with KOAc probably proceeds *via* a CMD mechanism (Scheme 6).



**Scheme 5.** Plausible mechanism for C3-arylation.



**Scheme 6.** Plausible mechanism for C5-arylation.

## 4. Aryl source

With some heteroarenes, the use of alternative aryl sources to aryl halides as the coupling partners allowed to obtain other regioisomers. This strategy has been used by some groups including ours for the arylation of (benzo)thiophenes and selenophenes.

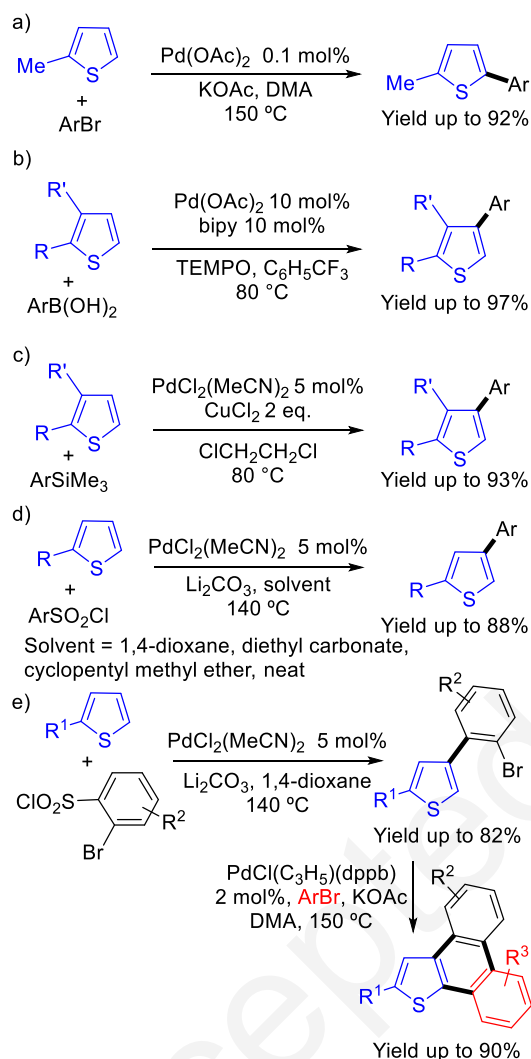
### 4.1. Regiodivergent arylations of thiophenes

The Pd-catalyzed direct arylation of thiophenes with aryl halides generally occurs regioselectively at C2- or C5-positions ( $\alpha$ -arylations) (Scheme 7, a).<sup>[13]</sup> However, a few groups succeeded to obtain C3- or C4-arylated ( $\beta$ -arylated) thiophenes using other aryl sources. In 2011, Studer, Itami et al. developed a method for the  $\beta$ -arylations of thiophenes using arylboronic acids as the aryl source under Pd/TEMPO catalysis (Scheme 7, b).<sup>[14]</sup> Then, in 2012 Oi et al. reported a procedure for the  $\beta$ -arylation of thiophenes using aryltrimethylsilanes as the coupling partners in the presence of  $\text{PdCl}_2(\text{MeCN})_2$  catalyst with  $\text{CuCl}_2$  as oxidant (Scheme 7, c).<sup>[15]</sup> Glorius et al. also reported conditions allowing the  $\beta$ -arylation of thiophenes using arylidonium salts as the aryl source and Pd/C catalyst.<sup>[16a]</sup> A room temperature procedure for the  $\beta$ -arylation of thiophenes using aryl iodides,  $\text{Ag}_2\text{CO}_3$  base in 1,1,1,3,3,3-hexafluoroisopropan-2-ol has also been reported by Larrosa et al. in 2016.<sup>[16b]</sup>

In 2014, our group investigated the reactivity of benzenesulfonyl chlorides as the aryl source for the arylation of thiophenes (Scheme 7, d).<sup>[17a]</sup>  $\text{PdCl}_2(\text{MeCN})_2$  or  $\text{Pd}(\text{OAc})_2$  catalysts in the presence of 3 equivalents of  $\text{Li}_2\text{CO}_3$  as base in 1,4-dioxane without additives or ligands regioselectively provided the  $\beta$ -arylated thiophenes in high yields. It should be mentioned that the reaction tolerated chloro-, bromo- and iodo-substituents on the benzenesulfonyl chlorides.<sup>[17a,17b]</sup> Moreover, these desulfurative cross-couplings could be performed in diethylcarbonate or cyclopentyl methyl ether as green and renewable solvents or even in neat conditions.<sup>[17c]</sup> We also recently successfully employed heterogeneous 10% Pd/C catalyst for the direct  $\beta$ -arylation of thiophene derivatives with a range of benzenesulfonyl chlorides. These couplings likely proceed *via* the formation of homogeneous catalytically active soluble clusters or nanoparticles from Pd/C.<sup>[17d]</sup> The regioselectivities with Pd/C catalyst were similar to those observed with the homogeneous palladium catalysts  $\text{Pd}(\text{OAc})_2$  or  $\text{PdCl}_2(\text{MeCN})_2$  when benzenesulfonyl chlorides were employed as the aryl sources. Due to the very wide availability of diversely functionalized benzenesulfonyl chlorides, these aryl sources should be very attractive to organic chemists for access to  $\beta$ -arylthiophenes. For these desulfurative couplings, albeit no mechanistic investigation has been performed, we have suggested a mechanism pathway, based on a Pd(II)/Pd(IV) catalytic system, as it is known that benzenesulfonyl chlorides can transform Pd(II) into Pd(IV) by oxidative addition even at room temperature.<sup>[17e]</sup>

We applied this methodology to the synthesis of polyaromatic hydrocarbon containing a sulfur atom (Scheme 7, e).<sup>[17f]</sup> The

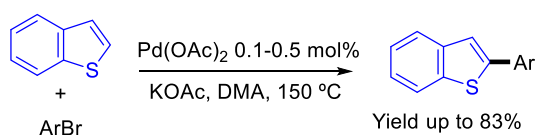
strategy involved a Pd-catalyzed desulfitative regioselective C4-arylation of thiophenes with 2-bromobenzenesulfonyl chlorides followed by a Pd-promoted one-pot cascade C-H bond direct C5-arylation of the thiophene ring followed by a cyclization reaction. A wide range of diversely substituted thio-containing polyaromatic hydrocarbon was synthesized in high yields by this method.



**Scheme 7.** Selected examples of regiodivergent arylations of thiophenes.

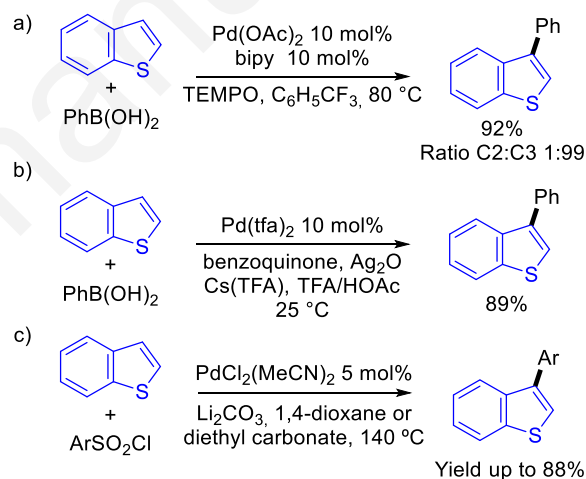
#### 4.2. Regiodivergent arylations of benzothiophenes

The reactivity of benzothiophenes is quite similar to thiophenes, and they can be regioselectively arylated by aryl bromides at their C2-position ( $\alpha$ -arylation) using Pd(OAc)<sub>2</sub> catalyst and KOAc base in DMA, probably *via* a CMD mechanism (Scheme 8).<sup>[18]</sup>



**Scheme 8.** Procedure f for the C2-arylations of benzothiophenes

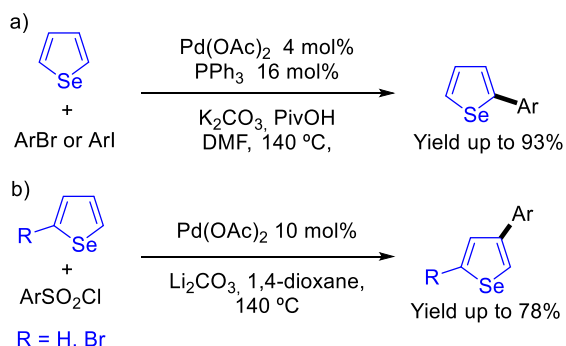
However, some procedures promoting the regioselective  $\beta$ -arylations of benzothiophenes, have also been reported (Scheme 9). Studer and Itami applied their procedure - phenylboronic acid as aryl source under Pd/TEMPO catalysis - for the  $\beta$ -arylations of benzothiophene (Scheme 9, a).<sup>[19]</sup> Then, in 2013, Bach and Schnapperelle found that Pd(TFA)<sub>2</sub> catalyst in trifluoroacetic acid, in the presence of Ag<sub>2</sub>O, cesium trifluoroacetate, benzoquinone, with phenylboronic acid as the aryl source also promoted the  $\beta$ -arylation of benzothiophene (Scheme 9, b).<sup>[20]</sup> Our group also described a procedure for the Pd-catalyzed direct  $\beta$ -arylation of benzothiophenes (Scheme 9, c).<sup>[17a,17c]</sup> Using again benzenesulfonyl chlorides as the aryl source, PdCl<sub>2</sub>(MeCN)<sub>2</sub> catalyst in the presence of Li<sub>2</sub>CO<sub>3</sub> as base using 1,4-dioxane or diethyl carbonate as the solvent, the  $\beta$ -arylated benzothiophenes were obtained in high regioselectivities and good yields. In several cases, 10% Pd/C catalyst has also proven to be an effective catalyst for these desulfitative couplings.<sup>[17d]</sup> Moreover, our conditions tolerated a wide scope of functional groups on the benzenesulfonyl chloride such as methoxy, cyano, chloro or bromo.



**Scheme 9.** Selected examples of C3-arylations of benzothiophenes.

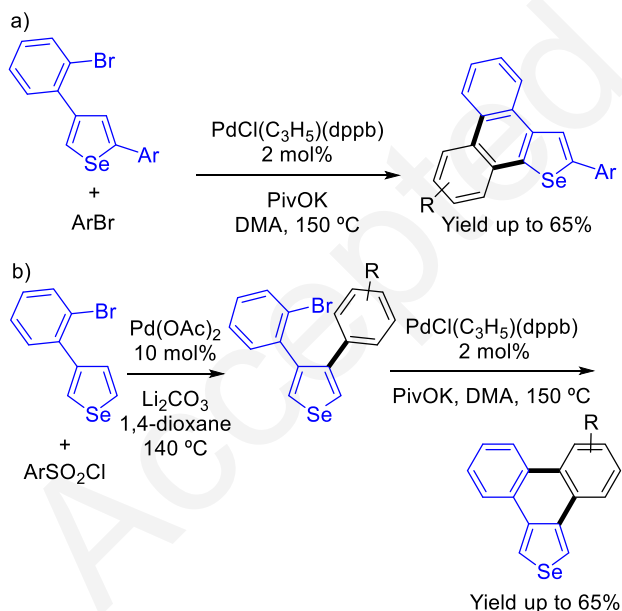
#### 4.3. Regiodivergent arylations of selenophenes

Schneider et al. reported in 2014, that the Pd-catalyzed direct arylation of selenophene occurs regioselectively at C2-position ( $\alpha$ -arylation) in the presence of aryl halides and K<sub>2</sub>CO<sub>3</sub> associated to PivOH as base (Scheme 10, a). This regioselectivity probably arises from CMD mechanism.<sup>[21]</sup> Then, in 2017 our group found that using benzenesulfonyl chlorides as the aryl source instead of aryl halides, Pd-catalyzed desulfitative arylation of selenophenes occurs at C3- or C4-positions ( $\beta$ -arylation) instead of C2-position (Scheme 10, b).<sup>[22a]</sup> The C3- or C4-arylated selenophenes were regioselectively obtained using 10 mol% Pd(OAc)<sub>2</sub> catalyst and 3 equiv. of Li<sub>2</sub>CO<sub>3</sub> in 1,4-dioxane. Interestingly, good yields were also obtained with benzenesulfonyl chlorides containing halo-substituents including bromo and iodo. In addition, 2-bromo-4-arylselenophenes were regioselectively obtained from 2-bromoselenophene. In the course of these reactions, no C-Br bond cleavage was observed.



**Scheme 10.** Selected examples of regiodivergent arylations of selenophenes.

We recently applied this methodology to the synthesis of planar  $\pi$ -extended selenium containing molecules.<sup>[22b]</sup> Combinations of Pd-catalyzed C-H bond arylations of 3-(2-bromophenyl)selenophene with either aryl bromides or benzenesulfonyl chlorides followed by intramolecular C-H bond arylations allowed the extension of the selenophene-containing aromatic skeleton at the [b]-, or [c]-junctions to give either phenanthro[b]selenophenes (Scheme 11, a), or phenanthro[c]selenophenes (Scheme 11, b).



**Scheme 11.** Application to the synthesis of  $\pi$ -extended selenium containing molecules.

In summary, the use of some alternative aryl sources to aryl halides for the arylation of specific heteroarenes allows to modify the regioselectivity of the arylation in favor of  $\beta$ -arylation. However, for such reactions higher catalyst loadings had to be employed than for the reactions with the system acetate or

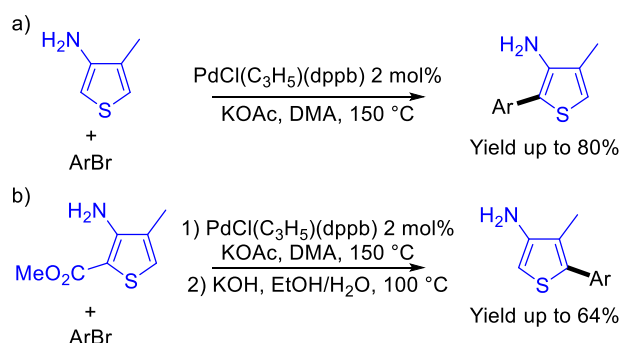
pivalate in DMA which promotes the  $\alpha$ -arylations, and so far this tool is effective only for (benzo)thiophenes and selenophenes.

## 5. Blocking group

The use of removable or synthetically useful blocking groups on substrates is an effective strategy for modifying the arylation site of (hetero)arenes. The introduction of chloride substituents as blocking groups on various heteroarenes in order to arylate specific positions has been described in 2010 by Fagnou *et al.* For example, through the introduction of a chloride substituent at C2-position of 3-hexylthiophene, the regioselectivity of the Pd-catalyzed direct arylation was diverted to produce alternative C5-arylated thiophenes.<sup>[23]</sup> The use of blocking groups to obtain alternative regioisomers is not very attractive in many cases, as it may be required to introduce and then to remove such groups adding two steps to the synthesis scheme. However, this methodology may be synthetically useful in very specific cases, such as when the blocking group is readily present in commercial compounds, when it is easily eliminated during the coupling reaction, or when it is useful in the next steps to access the final target.

### 5.1. Esters substituents

Esters are particularly interesting blocking groups because they are present on many commercial compounds and their removal of heteroarenes is often very easy. For example, we have reported the regiodivergent arylation of a thiophene substituted at C3- and C4-positions by two different functions using ester as blocking group at C2-position (Scheme 12).<sup>[24]</sup> From 3-amino-4-methylthiophene the direct arylation with both electron-deficient and electron-rich aryl bromides afforded regioselectively the C2-arylated products in good yields (Scheme 12, a). Conversely, the coupling of bromobenzenes with methyl 3-amino-4-methylthiophene-2-carboxylate gave the C5-arylated thiophenes (Scheme 12, b). The simple treatment of such 5-arythiophenes by KOH in EtOH/H<sub>2</sub>O gave the decarboxylated thiophenes. It should be mentioned that both thiophene substrates are commercially available.



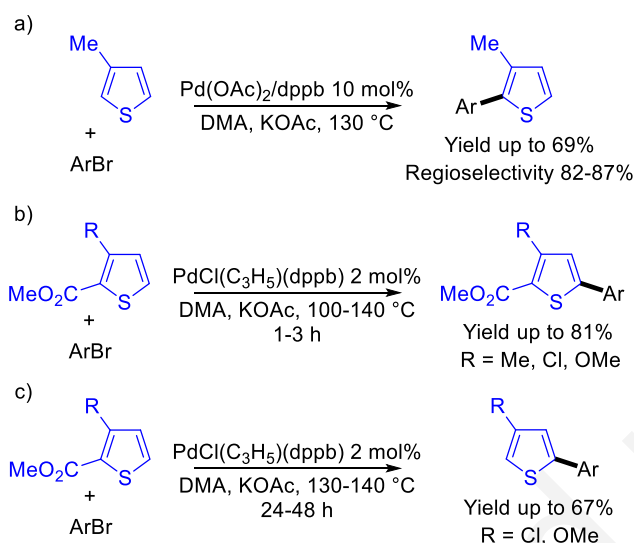
**Scheme 12.** Regiodivergent arylations of thiophene derivatives using an ester as blocking group.

In the course of the Pd-catalyzed arylation of 3-substituted thiophenes, position C2 is generally the most reactive. For example, the arylation of 3-methylthiophene in the presence of



$\text{Pd}(\text{OAc})_2/\text{dppb}$  catalyst affords the C2-arylated thiophenes in 82-87% regioselectivity (Scheme 13, a).<sup>[25]</sup>

Our group also examined the potential of esters as blocking groups at the C2-position of a range of 3-substituted thiophenes in order to control the regioselectivity for the direct arylation at C5-position (Scheme 13, b).<sup>[26]</sup> The reactions performed at 100-140 °C during 1-3 h proceeded nicely providing the C5-arylated thiophenes in good yields. Such C5-arylations can be followed by easy decarboxylation. We also observed that at 130-140 °C, a slow decarboxylation reaction of some of the arylated ester-substituted thiophenes occurs. It was therefore possible to perform both catalytic C5-arylation and decarboxylation in one pot using a slightly higher reaction temperature and a longer time (24-48 h) (Scheme 13, c).



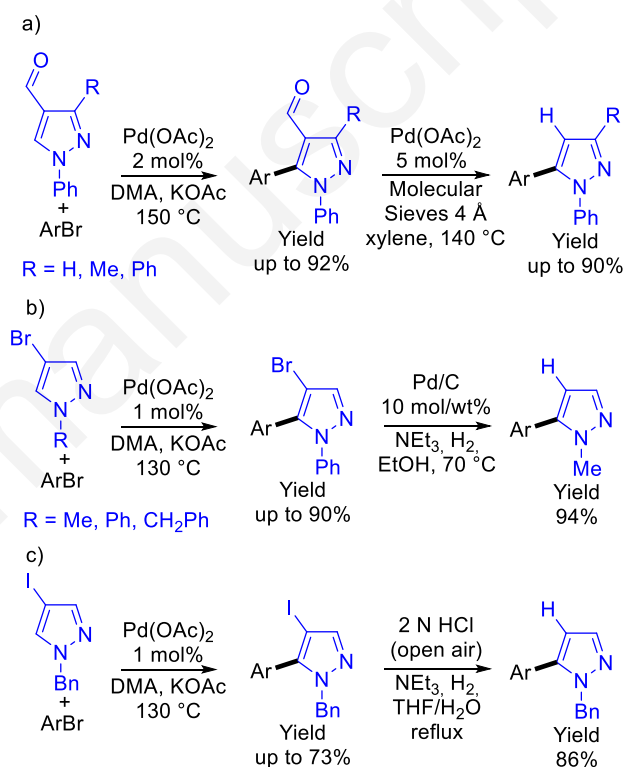
**Scheme 13.** Regiodivergent arylations of thiophene derivatives using an ester as blocking group.

## 5.2. Formyl and halo substituents

The Pd-catalyzed direct arylation of pyrazoles is quite challenging due to the lack of regioselectivity of these coupling reactions. In 2009, Sames et al. determined the regioselectivity of such arylations, and their results indicated a higher reactivity at the C5-position relative to the C4-position and a very low reactivity at the C3-position.<sup>[27]</sup> In most cases, they obtained mixtures of C4-, C5-arylated, and C4,C5-diarylated pyrazoles. In order to obtain regioselective C5-arylations, some groups introduced removable substituents at the C4-position of pyrazoles such as a chloro.<sup>[28]</sup>

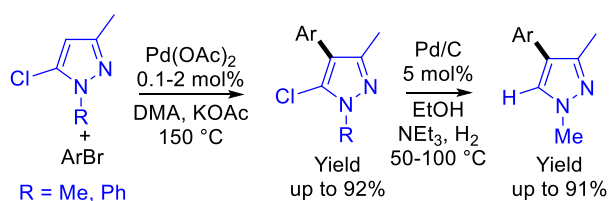
Our group studied the potential of a formyl substituent as blocking group at the C4-position of pyrazoles. This blocking group is very appealing as a wide variety of 4-formylpyrazoles can be easily prepared from hydrazine derivatives, ketones and DMF, and as the formyl group removal of 4-formylpyrazoles using a palladium catalyst is a straightforward reaction. Indeed, we observed that 4-formylpyrazoles underwent Pd-catalyzed direct arylation reaction to provide regioselectively the 5-aryl-substituted pyrazoles (Scheme 14, a). The reaction proceeded in moderate to high yields using 2 mol% of  $\text{Pd}(\text{OAc})_2$  catalyst.<sup>[29]</sup>

We also employed bromo- and iodo-substituents as blocking groups at C4-position of pyrazoles (Scheme 14, b and c).<sup>[30]</sup> These C4-halo-substituted *N*-protected pyrazole derivatives were regioselectively arylated at the C5-position using aryl bromides as the aryl source. The reaction was found to be highly chemoselective as the C-Br or C-I bonds on the pyrazole ring were not involved during the C-H bond arylation process. These reactions proceeded in moderate to very high yields with electron-deficient aryl bromides or heteroaryl bromides. In addition, we also showed that the bromo- or iodo-substituents of the arylated pyrazoles could either be employed for the preparation of C4,C5-diarylated pyrazoles, or a selective debromination or deiodination could be performed to afford the halogen-free 5-arylated pyrazole.



**Scheme 14.** C5-arylations of pyrazoles using formyl or halogen substituents as blocking groups.

In order to obtain regioselectively C4-arylated pyrazoles, we also studied the potential of an ester substituent as a temporary C5 blocking group.<sup>[31]</sup> However, the C4-arylation of ethyl 2,5-dimethylpyrazole-3-carboxylate proceeded in low yield. Then we turned our attention to the use of a chloro blocking group at the C5-position of pyrazole. In the presence of only 0.1-0.5 mol%  $\text{Pd}(\text{OAc})_2$  catalyst, the 5-chloropyrazoles led to high yields in the desired C4-arylated pyrazoles (Scheme 15).<sup>[32]</sup> Moreover, the dechlorination of these 4-aryl-5-chloropyrazoles proceeded nicely using Pd/C catalyst.



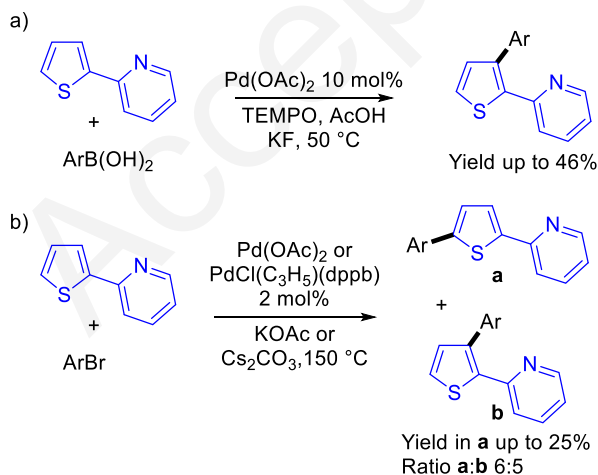
**Scheme 15.** C4-arylations of pyrazoles using a chloro substituent as blocking group.

### 5.3. Protection *via* cyclometalation

Aryl-substituted nitrogen-based compounds containing heterocycles, such as aryl-thienylpyridines have attracted increased interest due to their coordination properties making them important building blocks for the preparation of optoelectronic devices. However, the arylation of 2-pyridylthiophene at the C5-position of thienyl ring is quite challenging due to the coordination properties of the pyridine unit.

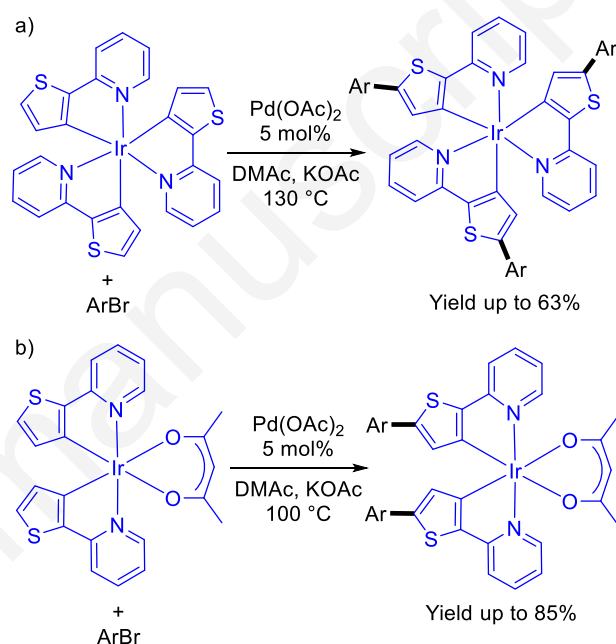
For example, Studer et al. reported in 2008 the oxidative coupling of 2-pyridylthiophene with arylboronic acids using  $\text{Pd}(\text{OAc})_2/\text{P}[\text{p}(\text{CF}_3)\text{C}_6\text{H}_4]_3$  as catalytic system and TEMPO as a stoichiometric oxidant (Scheme 16, a).<sup>[33]</sup> In the course of this reaction, the 2-pyridyl unit acts as a directing group to mediate the arylation regioselectively at the C3-position of the thiophene ring.

Our group studied the Pd-catalyzed direct coupling of 2-thienylpyridine using aryl bromides instead of arylboronic acids (Scheme 16, b).<sup>[34]</sup> The results show that the reaction is not regioselective, as both the C3- and C5-positions of the thienyl ring were arylated, and these two regioisomers were formed in an almost equimolar mixture, whatever the reaction conditions employed. The formation of the C3-arylated product likely arises from the coordination of the nitrogen atom of the pyridine ring to the palladium center; whereas, C5-arylation probably proceed *via* a concerted metallation-deprotonation mechanism.



**Scheme 16.** Regioselectivity of the arylations of 2-pyridylthiophene.

In order to inhibit the pyridine ring nitrogen atom coordination mechanism, we performed the direct arylation of thienylpyridine ligands on bis- or tris-cyclometallated iridium complexes (Scheme 17).<sup>[35]</sup> We found that the iridium-coordinated 2-thiophen-2-ylpyridines could be directly arylated with aryl bromides regioselectively at the thienyl C5-position using 5 mol%  $\text{Pd}(\text{OAc})_2$  catalyst. Since our goal for the arylation of 2-thiophen-2-ylpyridines was to prepare ligands for the synthesis of cyclometallated iridium complexes, the use of iridium to block the C3-position of the thienyl ring is very practical. This late-stage functionalization methodology opens new simple routes to a variety of Ir complexes in only one step.



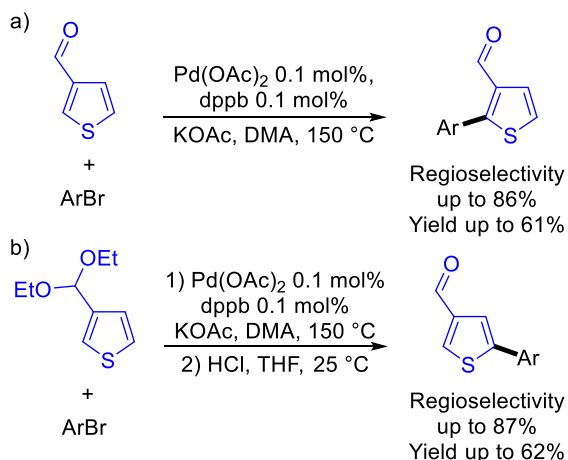
**Scheme 17.** C5-Arylations of metallated 2-pyridylthiophene.

## 6. Steric hindrance

As explained in the scheme 13, in most cases, 3-substituted thiophenes such as 3-alkylthiophene or 3-cyanothiophene are arylated at their C2-position.<sup>[25]</sup> However, the regioselectivity of the arylation of 3-substituted thiophenes is strongly influenced by the steric hindrance of both coupling partners. For example from 3-acetylthiophene and 9-bromoanthracene, the C5-arylated thiophene was obtained in 90% regioselectivity.<sup>[11,25]</sup> Therefore, by using specific functional groups we expected to be able to obtain regiodivergent arylations.

Both 3-formylthiophene and 3-formylthiophene diethylacetal are commercially available at an affordable cost. In 2010, our group studied the regioselectivity of the arylation of these two thiophene derivatives, as we expected to observe a significant change in the regioselectivity of the arylation with these two substrates.<sup>[36]</sup> Indeed, we observed that the arylation of 3-formylthiophene with aryl bromides occurs mainly at the C2-position (regioselectivities 76-86%) (Scheme 18, a). Conversely, with more congested 3-formylthiophene diethylacetal, the arylation occurred mainly at the C5-position (regioselectivities 64-88%) (Scheme 18, b). Treatment of the 5-arylated 3-

formylthiophene diethylacetals by HCl gives the corresponding C5-arylated 3-formylthiophenes.



**Scheme 18.** Regioselectivity of the arylations of 3-formylthiophene and 3-formylthiophene diethyl acetal.

The use of congested 2-bromo-1,3-dichlorobenzene as the coupling partner also allowed to control the regioselectivity of the arylation of 3-substituted thiophene derivatives in favor of the C5-position.<sup>[37]</sup> For example, the coupling of 2-bromo-1,3-dichlorobenzene with thiophenes bearing chloro, acetyl or methyl at C3-position afforded regioselectively in all cases the C5-arylated thiophenes (Scheme 19). However, we didn't succeed to remove the two chloro substituents of the benzene unit after the coupling reaction.



**Scheme 19.** Regioselectivity of the arylations of 3-substituted thiophene with 2-bromo-1,3-dichlorobenzene.

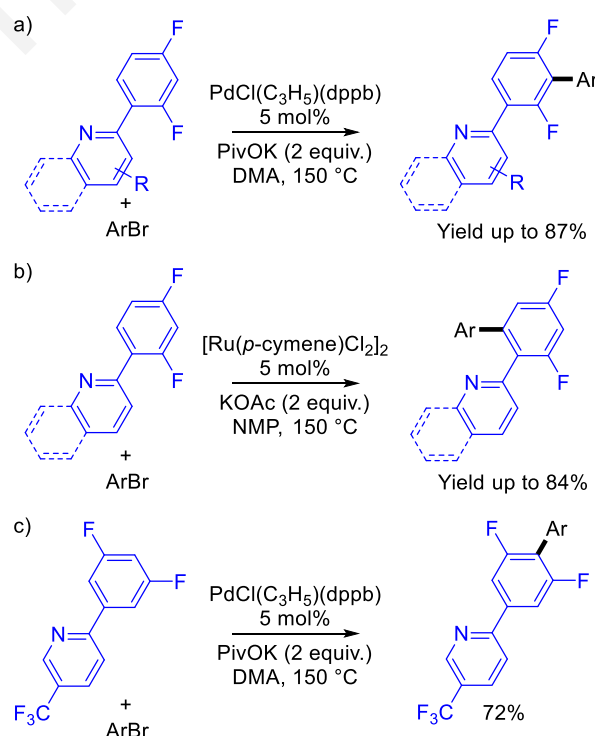
## 7. Nature of the metal of catalysts

One of the most obvious method to control the site-selectivity of the arylation of (hetero)arenes is the use of different metals as catalysts. Pd-catalysis is very effective for the arylation of heteroarenes and polyfluorobenzenes. By contrast, the Ru-catalyzed direct arylations mostly relies on the coordination of the nitrogen atom of pyridines, diazines or *N*-containing 5-membered ring heteroarenes. Therefore, substrates containing these two types of units may lead to regiodivergent arylations. In our group, we studied the reactivity of such substrates in three different cases.

### 7.1. Arylation of 2-(difluorophenyl)pyridines and quinolines

In 2019, we reported the regiodivergent C-H bond arylation of polyfluorinated 2-arylpyridines and 2-arylquinolines (Scheme 19).<sup>[38a]</sup> The use of a palladium catalyst promoted the functionalization of the C-H bond of the aryl flanked by two fluorine atoms which is the most acidic position (Scheme 20, a). The best results were obtained with PdCl(C<sub>3</sub>H<sub>5</sub>)(dppb) catalyst. The use of this diphosphine palladium catalyst, might inhibit the formation of the regioisomer arising from nitrogen atom coordination, by preventing the coordination of the pyridine unit to palladium. With this catalyst, the regioselectivity was greatly improved to a 92:8 ratio (vs 76:24 with Pd(OAc)<sub>2</sub> catalyst). The base which plays a critical role in CMD mechanism has an important influence on the reactions yields. Using very soluble base, KO<sup>i</sup>Piv, full conversions of the aryl bromides were observed with good yields. Conversely, a Ru(II) complex promoted the C-H bond arylation at the *ortho*-position of the aryl unit of 2-arylpyridines or 2-arylquinolines *via* coordination of the nitrogen atom to ruthenium (Scheme 20, b). Using 5 mol % of [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> associated to KOAc, the arylation proceeded in >95:5 selectivity, and in good yields.

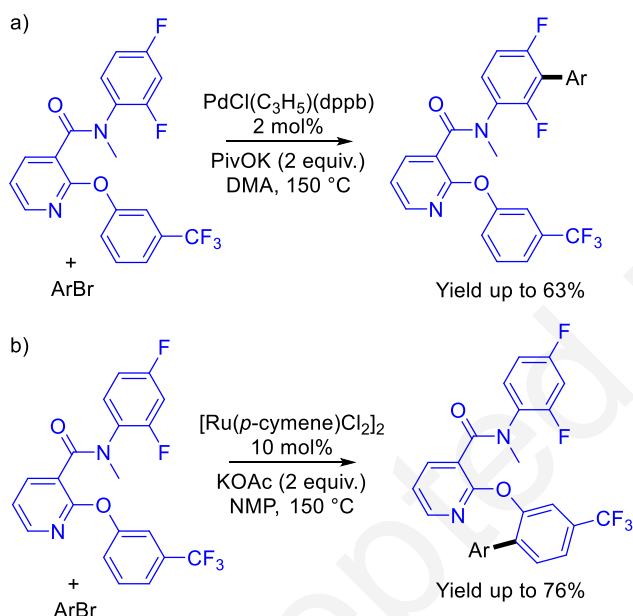
In 2020, we applied this strategy to the arylation of the phenyl ring of 2-(2,4-difluorophenyl)-5-(trifluoromethyl)pyridine and 2-(3,5-difluorophenyl)-5-(trifluoromethyl)pyridine for the access to two families of Ir(III) complexes, charge-neutral and cationic species which show bright photoluminescence. The reaction was regioselective since only the C3- or C4-positions of the difluorinated phenyl rings were readily functionalized (Scheme 20, a and c).



**Scheme 20.** Regiodivergent Pd- or Ru-catalyzed direct arylations of 2-(difluorophenyl)pyridines and quinolines.

## 7.2. Arylation of Diflufenican

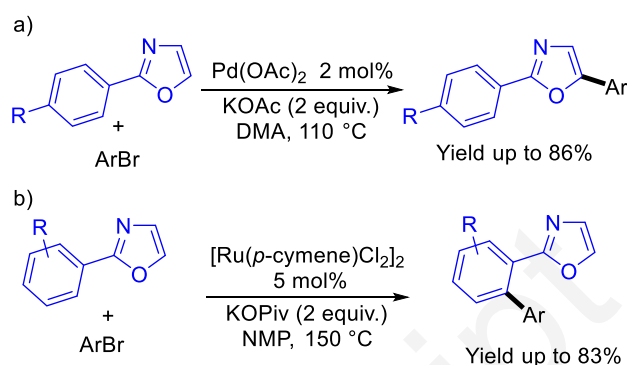
Diflufenican, which is an herbicide, contains a 1,3-difluorobenzene ring and a pyridine ring (Scheme 21). Therefore, it also represents a very interesting molecule in terms of site-selectivity for the metal-catalyzed C-H bond functionalization. When appropriate reaction conditions are employed, the Pd- and Ru-catalyzed C-H bond functionalization of Diflufenican protected as a tertiary amide afforded two different families of compounds.<sup>[39]</sup> With a Pd-catalyst, Diflufenican was regioselectively arylated at the C-H position flanked by two fluorine atoms (most acidic position); whereas, no arylation of the trifluoromethylbenzene ring was detected under these reaction conditions (Scheme 21, a). In sharp contrast, with a Ru-catalyst, the arylation regioselectively occurred at the less hindered *ortho*-position of the ether function of the trifluoromethylbenzene ring via the coordination of the pyridine ring to ruthenium (Scheme 21, b). With these two procedures, the arylated Diflufenican derivatives were obtained in moderate to good yields.



**Scheme 21.** Regiodivergent Pd- or Ru-catalyzed direct arylations of Diflufenican.

## 7.3. Arylation of 2-aryloxazoles

We also studied the reactivity of 2-aryloxazoles using Pd and Ru catalysts.<sup>[40]</sup> From 2-aryloxazoles and a set of electron-rich or -poor aryl bromides, in the presence of Pd(OAc)<sub>2</sub> catalyst, the 2,5-diaryloxazoles were obtained with complete regioselectivity and high yields (Scheme 22, a). Conversely, the Ru-catalyzed direct arylation of 2-aryloxazoles occurred at the aryl unit via coordination of the nitrogen atom of oxazole to ruthenium (Scheme 22, b). For these reactions, [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> was employed as the catalyst and KO<sup>t</sup>Piv as the base.<sup>[41]</sup>



**Scheme 22.** Regiodivergent Pd- or Ru-catalyzed direct arylations of 2-aryloxazoles.

## 8. Conclusion

In summary, in several cases, the metal-catalyzed C-H bond functionalization for the arylation of (hetero)arenes is not limited to only one “most reactive” C-H bond of the substrates. The use of several tools which include the use of various aryl sources, the modification of some of the reaction conditions such as the base and solvent, the introduction of blocking groups, the use of directing functional groups such as amides, the nature of the metal catalyst allowed to modify the site selectivity for several substrates resulting in regiodivergent arylations. The steric hindrance of the substrates can also be employed to control the regioselectivity of the reactions. Therefore, metal-catalyzed direct arylation now represents a powerful method to access arylated (hetero)aromatics. However, many challenges remain, as in some cases, mixtures of regioisomers and/or low yields were obtained. In several cases, more efficient catalysts allowing lower catalyst loadings need to be discovered in order to provide more economically attractive procedures. Concerning the different mechanisms involved in changing regioselectivity, a large number of questions remain unanswered. Determining more clearly the mechanistic reasons leading to the different observed regioselectivities would certainly improve further the efficiency and scope of such reactions. Moreover, in the near future, there are no doubts that new tools will be discovered allowing to functionalize more and more C-H bonds of several (hetero)arenes making this reaction an unavoidable synthesis method in the preparation of poly(hetero)aryls.

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**Keywords:** regiodivergence • arylation • C-H bond functionalization • catalysis • palladium

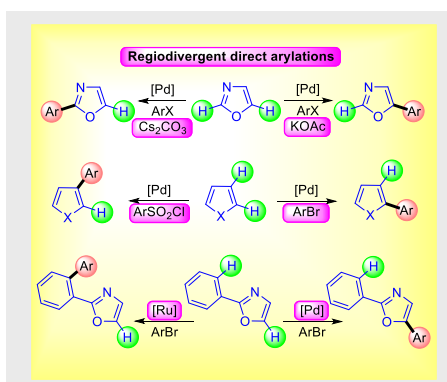
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## Entry for the Table of Contents

## PERSONAL ACCOUNT

Over the past decade, several synthetic tools allowing the direct arylation of two different C-H bonds of the same organic molecule - also called regiodivergent arylation - have been described. In this account, we summarize our results using the different tools that have allowed us to arylate different positions of various (hetero)arenes, via the functionalization of C-H bonds, using palladium or ruthenium catalysis.



Hai-Yun Huang,<sup>[a]</sup> Amal Benzai,<sup>[a]</sup> Xinzhe Shi,<sup>[a]</sup> and Henri Doucet<sup>\*[a]</sup>

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Effective tools for the metal-catalyzed regiodivergent direct arylations of (hetero)arenes