

Pd-catalyzed C-H bond functionalization of heterocycles and fluorobenzenes : a simple access to poly(hetero)aromatic compounds

Haiyun Huang

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Par
Haiyun HUANG

Pd-catalyzed C-H bond functionalization of heterocycles and fluorobenzenes: a simple access to poly(hetero)aromatic compounds

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Xiao-Feng Wu Prof. LIKAT, Rostock Allemagne et Dalian Institute of Chemical Physics, Chine

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Co-dir. de thèse : Soulé Jean-François CR CNRS, Univ. Rennes1

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If you are lucky enough to have lived in Paris as a young man, then wherever you go for the rest of your life, it stays with you, for Paris is a movable feast.

- Ernest Hemingway

But for me, it’s even luckier, I could have chance to live in Rennes for five years while I am young. Five years, which it’s long enough for me to love the city and to love the people who lives here.

Rennes is not large, almost every corner carries a small story of us. We strolled through the flowers and explored the spring, betting with classmates, blowing dandelions up in one breath to roam the summer. The colorful autumn on campus and the rare snowy winter here. Wearing headphones in the morning and listening to "Un, Deux, Trois, Quatre..." all the way to school for practicing French. The round-bottom flask reflects a beautiful rainbow in the evaporator at sunset.

Being far from home for the first time, I gained a lot of emotions, full of knowledge and full of love.

How time flies! I have made it all the way from inside a fresh hand master student in the final year of my doctoral studies. There are many things I am appreciative of, and I am grateful and thankful for everyone I have met here.

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should go to Disneyland or Astérix theme park for holiday, recommend the new LEGO of Harry Potter, and talk about the snowy scenery of Rennes and the beaches of his vacation. He is a very lovely person. He has enough trust in his students, he believes in our own pace and never rushes me to submit data. I am really grateful to have such a boss and appreciate his cultivation of me during these years. I also hope that he can also get the Nobel Prize so that I can brag to my students about my Nobel Prize boss.

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General Introduction

General Introduction

Aryl-(hetero)aryl bond formation is one of the most fundamental transformations in organic chemistry. It allows the elaboration of poly(hetero)aryls, which are useful as pharmaceuticals, photo-materials and agrochemicals. The palladium-catalyzed direct arylation of the (hetero)arenes *via* C-H bond activation has emerged as one of the most efficient tools for the access to bi-(hetero)aryls. Direct C-H bond functionalization exhibits several advantages compared to classical cross-coupling reactions, since such reactions avoid the pre-functionalization of one of the coupling partners, reducing the number of synthesis steps and also waste generation.

Since the beginning of the 21st century, significant progresses have been made in transition-metal-catalyzed direct functionalization of heteroarenes. Particularly, palladium-catalyzed direct C-H arylations of heteroarenes have been extensively studied. Although a variety of catalytic systems have been applied in these reactions, the substrate scope is still quite limited. 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. In the past few years, our group carried out researches to develop the arylation of (hetero)aromatics *via* C-H bond functionalization for the access to a wider diversity of substrates. All these results had a positive effect on my research and provided many new directions.

The first chapter will summarize a few general mechanistic information on palladium catalyzed C-H bond arylation and detail some literature on direct arylation related to this PhD research work. The results of our laboratory dealing with the functionalization of different C-H bonds of various (hetero)arenes based on several tools will be emphasized. This first chapter should give a better understanding of this PhD work, as one of the main objective of this thesis was to develop new regioselective Pd-catalyzed reactions with C-H bond transformations. To achieve this

target, C-H bond (hetero)arenes functionalization methodology was applied to the synthesis of several (hetero)biaryls. These results are summarized in the chapters 2 to 6.

The discovery of simple methods for the modification of bioactive molecules such as Lilolidine is an important research area. The chapter 2, deals with the regioselective Pd-catalyzed direct C1- and C2-arylations of Lilolidine for access to 5,6-dihydro pyrrolo[3,2,1-*ij*]quinoline derivatives.

Fluoro-substituents are very important functional groups in pharmaceutical and also material chemistry. The reactivity of the diverse polyfluoroalkoxy substituents on benzene was evaluated using Pd-catalyzed direct arylation. This study will be discussed in the chapter 3.

The metal-catalyzed direct functionalization of 5-membered ring (hetero)arenes is a very powerful synthetic tool for the synthesis of valuable polyheteroaromatics. However, the presence of specific functional groups on heterocycles may result in selectivity issues potentially challenging to handle with. The chapter 4, deal with the reactivity of 2-alkoxythiazoles as heteroaryl sources for the access to 2-alkoxy-5-arylthiazoles and also to 3-alkyl-5-arylthiazol-2(3H)-ones by *O*- to *N*-alkyl migratory rearrangement as they exhibit useful physical or biological properties.

In chapter 5, we report on the site-selectivity of the Pd-catalyzed direct arylation of a difluorobenzo[*d*]imidazole and the scope of this new transformation was also studied.

In the final chapter (chapter 6), starting from a set of *N*-methyl-*N*-(polyfluorobenzyl) acetamides and a *N*-methyl-*N*-(polyfluorobenzyl)

benzamide as reactants, we studied the reactivity and regioselectivity for the direct arylation of benzene units containing both fluoro and *N*-methyl tertiary amide substituents. We will describe the access to a variety of *N*-protected-methylamine substituted (poly)fluorobiphenyls using a variety of aryl bromides as the coupling partners.

Chapter 1:

Review on effective tools for the metal-catalyzed regiodivergent direct arylations of (hetero)arenes

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Review on effective tools for the metal-catalyzed regiodivergent direct arylations of (hetero)arenes

1.1 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.[1-3] The chief advantages of such protocol are 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.[1] 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. 1.1).

In this chapter which was published as a review in the Chemical Record, we summarize the results of our laboratory dealing with the functionalization of two different C-H bonds of various (hetero)arenes based on these six tools. This review was written in collaboration with A. Benzai, X. Shi, and H. Doucet: "H.-Y. Huang, A. Benzai, X. Shi, H. Doucet, *Chem. Rec.* **2021**, *21*, 343-356."

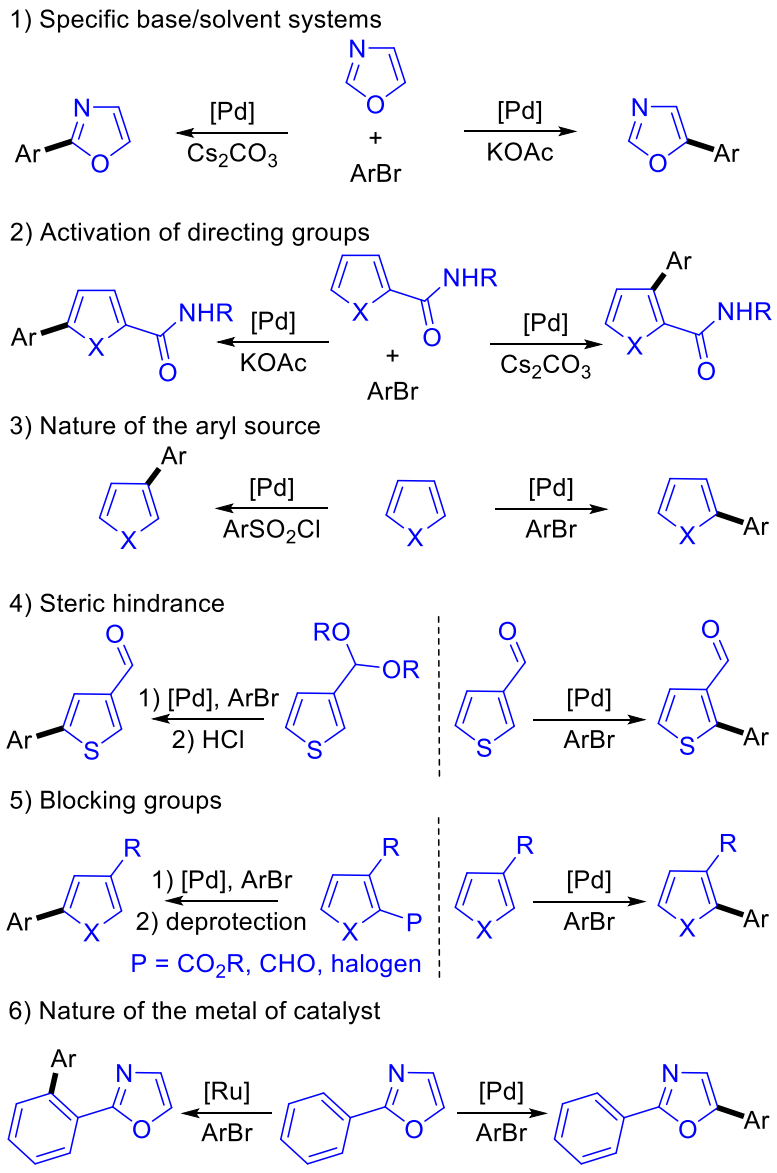


Figure 1.1. Tools employed in our laboratory for the regiodivergent metal-catalyzed direct arylations.

1.2 Nature of the base or solvent

The nature of the base in the C-H bond cleavage step is very important.[1] 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.[4] Therefore, with specific substrates, two different C-H bonds could be functionalized by changing only the base or the base/solvent combination.

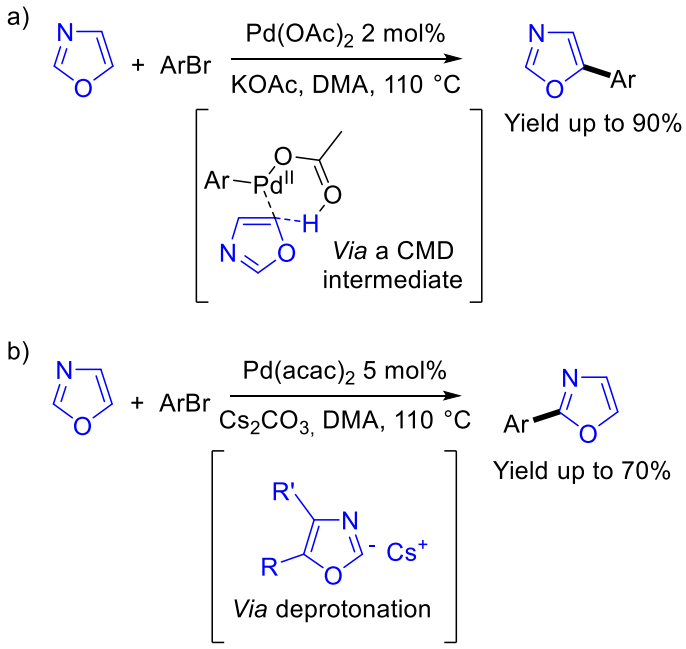
1.2.1. Carbonates and acetates

In 2010, Strotman, Chobanian et al. reported conditions for the regiodivergent Pd-catalyzed direct arylation of oxazoles (C2- *vs* C5-arylations).[5] 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_2CO_3/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 1.1) which has been calculated by Gorelsky[6] reveals that it is higher for the C-H bond flanked by two heteroelements (25.3 kcal mol^{-1}) than for the C-H bond at C5-position (23.5 kcal mol^{-1}). Therefore, our group 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 our group reported that the regioselectivity of the direct arylation of oxazole can be controlled using the appropriate base.[7] From phosphine-free

$Pd(OAc)_2$ catalyst associated to KOAc, regioselective C5-arylations, which likely proceed *via* a CMD mechanism, were observed (Scheme 1.1, a). By contrast, the $Pd(acac)_2$ catalyst associated to Cs_2CO_3 as the base led regioselectively to the C2-arylated oxazoles probably *via* a base-deprotonation of oxazole (Scheme 1.1, b). A wide variety of (hetero)aryl bromides was tolerated by these two sets of conditions.

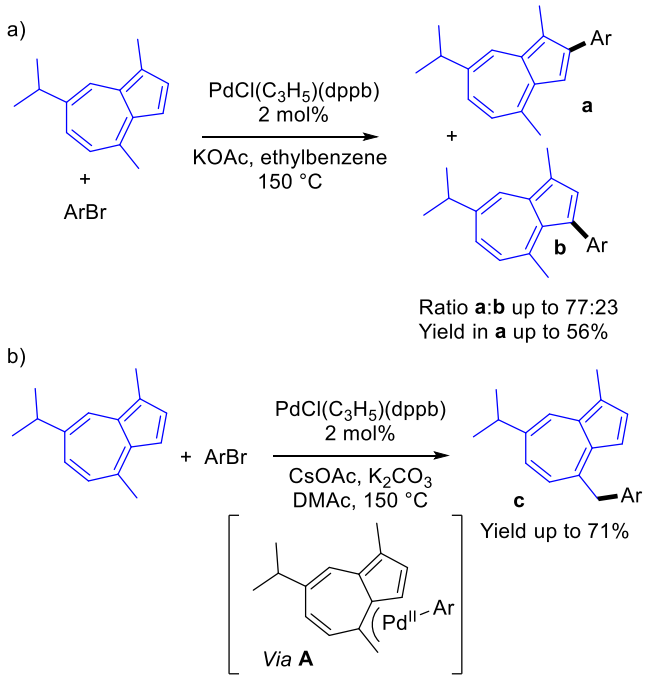


Scheme 1.1. Conditions for regiodivergent Pd-catalyzed direct arylations of oxazole.

Guaiazulene that feature 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, our group demonstrated that both the sp^2 and sp^3 direct arylations of guaiazulene were possible when appropriate reaction conditions were employed.[8] The use of KOAc in ethylbenzene led to the C2-arylated guaiazulenes **a** (Scheme 1.2, a); whereas a mixture of $CsOAc/K_2CO_3$ selectively promoted the sp^3 direct arylation at C4-Me to give 4-benzylguaiazulenes **c** (Scheme 1.2, 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.



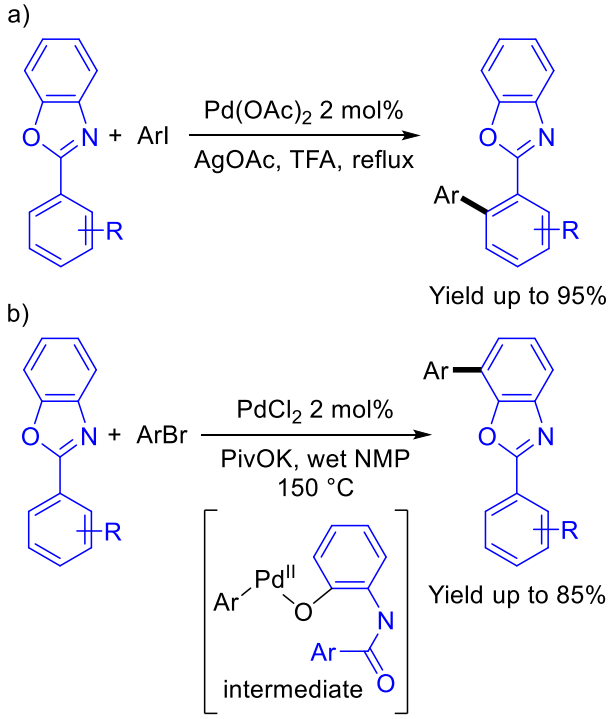
Scheme 1.2. Conditions for regiodivergent Pd-catalyzed direct arylations of guaiazulene.

1.2.2. 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 $Pd(OAc)_2$ 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 1.3, a).[9]

In 2016, our group reinvestigated the Pd-catalyzed direct arylation of 2-arylbenzoxazoles.[10] We found that the use of PivOK as the base in wet NMP instead of AgOAc/TFA, using $PdCl_2$ as the catalyst source allowed the regioselective arylation of 2-arylbenzoxazoles at the unexpected C7-position (Scheme 1.3, 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 1.3, b) followed by reductive elimination.

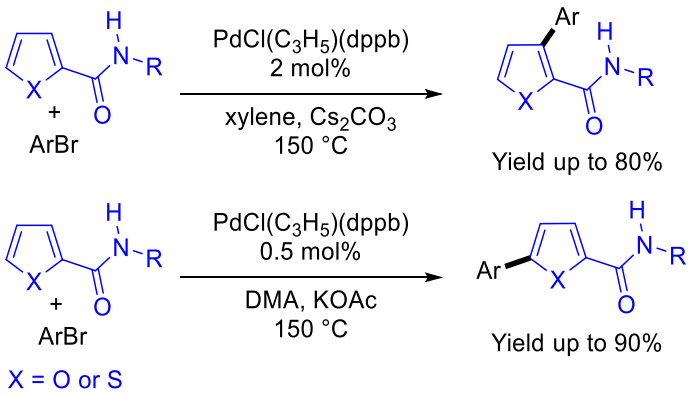


Scheme 1.3. Conditions for regiodivergent Pd-catalyzed direct arylations of 2-arylbenzoxazoles.

1.3 On/off directing groups

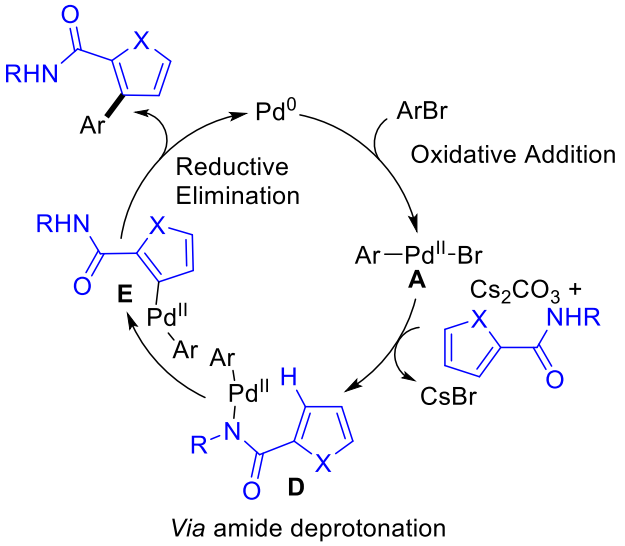
Some specific functional groups can be activated using appropriate reaction conditions to control the site-selectivity of the arylation. For example, a secondary carboxanilide function can be deprotonated with quite strong bases favoring its coordination to palladium resulting in the modification of 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.[11] Then, the regiodivergent arylation at either the C3- or C5-positions of furans and thiophenes containing secondary carboxamides at C2-position was described by our group.[12] 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_2CO_3 base with xylene solvent regioselectively provided the C3-arylated furans and thiophenes (Scheme 1.4). 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.

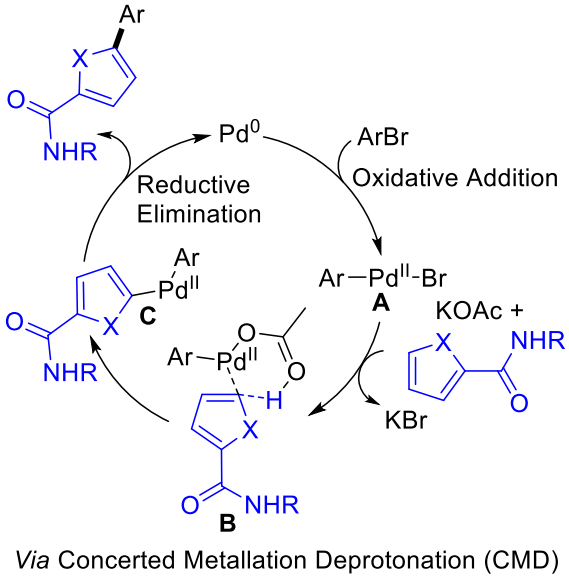


Scheme 1.4. Regiodivergent arylations of furans and thiophenes bearing secondary carboxamides.

The formation of the C3-arylated heteroarenes in the presence of Cs_2CO_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 1.5). Conversely, the C5-arylation observed with KOAc probably proceeds *via* a CMD mechanism (Scheme 1.6).



Scheme 1.5. Plausible mechanism for C3-arylation.



Scheme 1.6. Plausible mechanism for C5-arylation.

1.4 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.

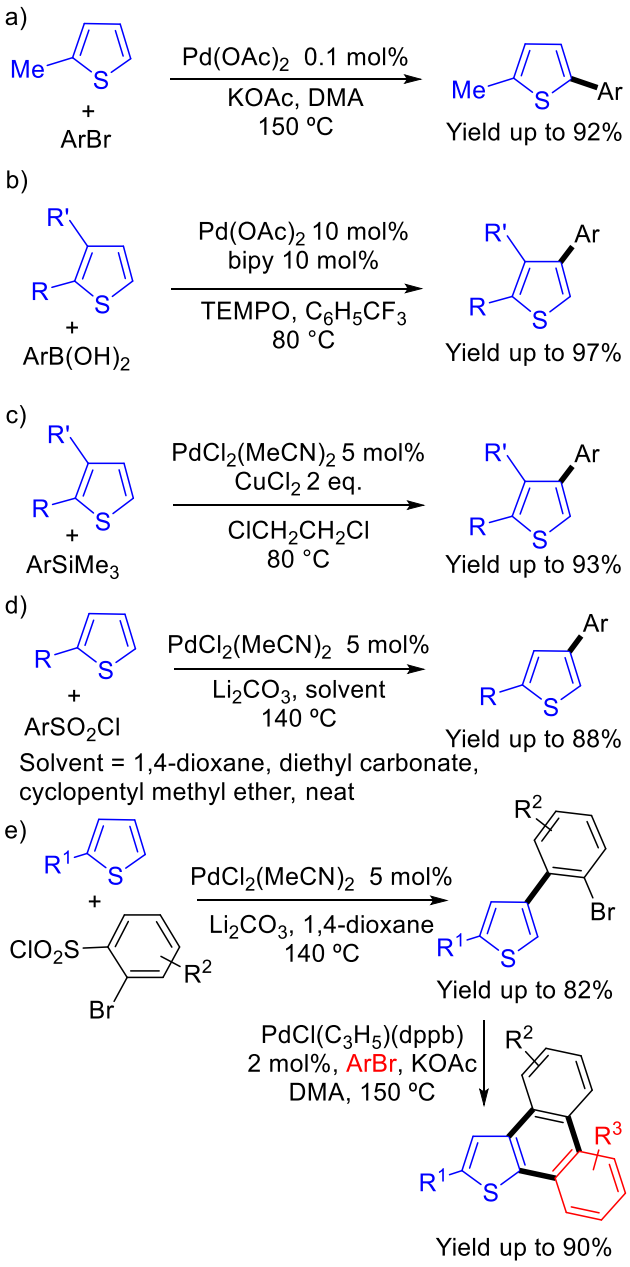
1.4.1. Regiodivergent arylations of thiophenes

The Pd-catalyzed direct arylation of thiophenes with aryl halides generally occurs regioselectively at C2- or C5-positions (α-arylations) (Scheme 1.7, a).[13] However, a few groups succeeded to obtain C3- or C4-arylated (β-arylated) thiophenes using other aryl sources. In 2011, Studer, Itami et al. developed a method for the β-arylations of thiophenes using arylboronic acids as the aryl source under Pd/TEMPO catalysis (Scheme 1.7, b).[14] Then, in 2012 Oi *et al.* reported a procedure for the β-arylation of thiophenes using aryltrimethylsilanes as the coupling partners in the presence of $PdCl_2(MeCN)_2$ catalyst with $CuCl_2$ as oxidant (Scheme 1.7, c).[15] Glorius et al. also reported conditions allowing the β-arylation of thiophenes using aryliodonium salts as the aryl source and Pd/C catalyst.[16a] A room temperature procedure for the β-arylation of thiophenes using aryl iodides, Ag_2CO_3 base in 1,1,1,3,3,3-hexafluoroisopropan-2-ol has also been reported by Larrosa et al. in 2016.[16b]

In 2014, our group investigated the reactivity of benzenesulfonyl chlorides as the aryl source for the arylation of thiophenes (Scheme 1.7, d).[17a] $PdCl_2(MeCN)_2$ or $Pd(OAc)_2$ catalysts in the presence of 3 equivalents of Li_2CO_3 as base in 1,4-dioxane without additives or ligands regioselectively provided the β-arylated thiophenes in high yields. It should be mentioned that the reaction tolerated chloro-, bromo- and iodo-substituents on the benzenesulfonyl chlorides.[17a,17b] Moreover, these

desulfitative cross-couplings could be performed in diethylcarbonate or cyclopentyl methyl ether as green and renewable solvents or even in neat conditions.[17c] Our group also recently successfully employed heterogeneous 10% Pd/C catalyst for the direct *β*-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.[17d] The regioselectivities with Pd/C catalyst were similar to those observed with the homogeneous palladium catalysts $Pd(OAc)_2$ or $PdCl_2(MeCN)_2$ 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 *β*-arylthiophenes. For these desulfitative couplings, albeit no mechanistic investigation has been performed, a mechanism pathway was suggested, 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.[17e]

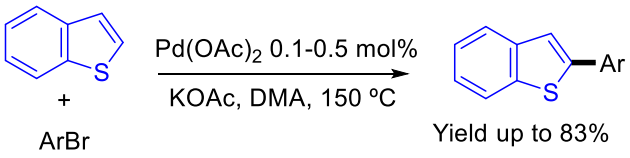
Our group applied this methodology to the synthesis of polyaromatic hydrocarbon containing a sulfur atom (Scheme 1.7, e).[17f] The strategy involved a Pd-catalyzed desulfitative regioselective C4-arylation of thiophenes with 2-bromobenzenesulfonyl chlorides followed by a Pd-promoted one-pot cascade C-H 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 1.7. Selected examples of regiodivergent arylations of thiophenes.

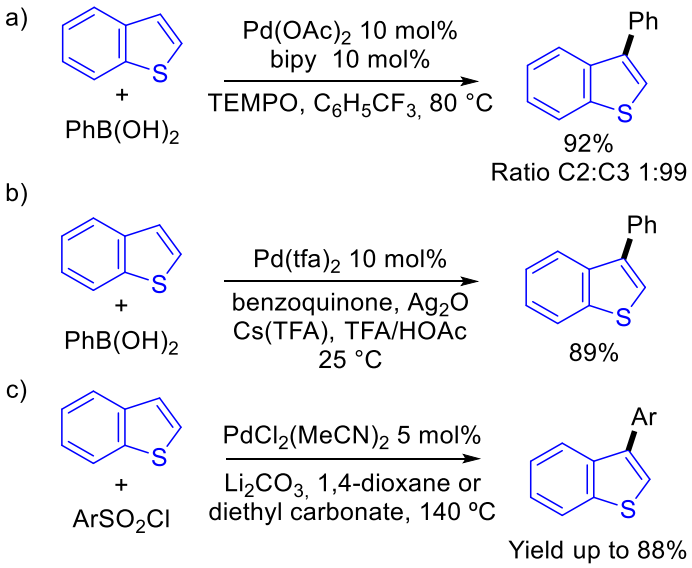
1.4.2. Regiodivergent arylations of benzothiophenes

The reactivity of benzothiophenes is quite similar to thiophenes, and they can be regioselectively arylated by aryl bromides at their C2-position (*α*-arylation) using $Pd(OAc)_2$ catalyst and KOAc base in DMA, probably *via* a CMD mechanism (Scheme 1.8).[18]



Scheme 1.8. Procedure for the C2-arylations of benzothiophenes

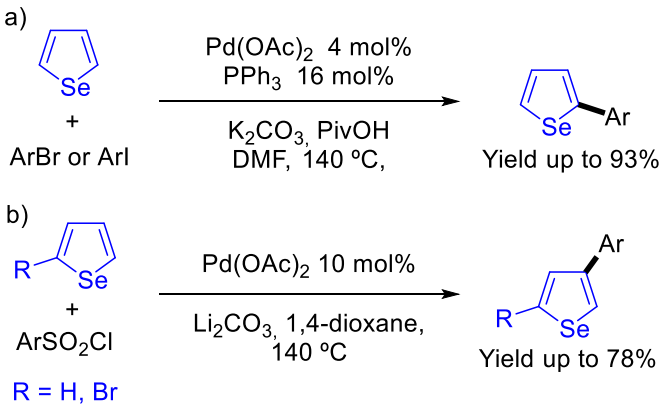
However, some procedures promoting the regioselective *β*-arylations of benzothiophenes, have also been reported (Scheme 1.9). Studer and Itami applied their procedure - phenylboronic acid as aryl source under Pd/TEMPO catalysis - for the *β*-arylations of benzothiophene (Scheme 1.9, a).[19] Then, in 2013, Bach and Schnapperelle found that $Pd(TFA)_2$ catalyst in trifluoroacetic acid, in the presence of Ag_2O, cesium trifluoroacetate, benzoquinone, with phenylboronic acid as the aryl source also promoted the *β*-arylation of benzothiophene (Scheme 1.9, b).[20] Our group also described a procedure for the Pd-catalyzed direct *β*-arylation of benzothiophenes (Scheme 1.9, c).[17a,17c] Using again benzenesulfonyl chlorides as the aryl source, $PdCl_2(MeCN)_2$ catalyst in the presence of Li_2CO_3 as base using 1,4-dioxane or diethyl carbonate as the solvent, the *β*-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.[17d] Moreover, our conditions tolerated a wide scope of functional groups on the benzenesulfonyl chloride such as methoxy, cyano, chloro or bromo.



Scheme 1.9. Selected examples of C3-arylations of benzothiophenes.

1.4.3. Regiodivergent arylations of selenophenes

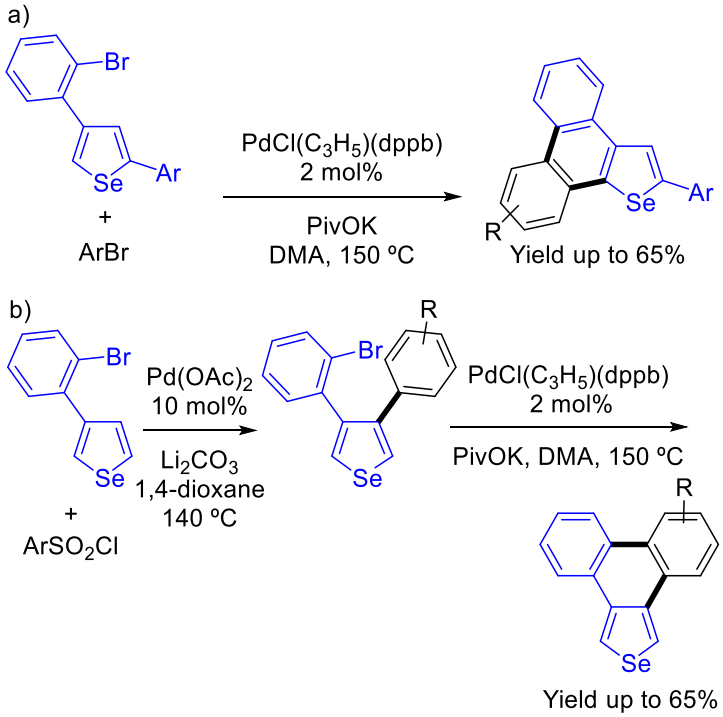
Schneider et al. reported in 2014, that the Pd-catalyzed direct arylation of selenophene occurs regioselectively at C2-position (*α*-arylation) in the presence of aryl halides and K_2CO_3 associated to PivOH as base (Scheme 1.10, a). This regioselectivity probably arises from CMD mechanism.[21] Then, 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 (*β*-arylation) instead of C2-position (Scheme 1.10, b).[22a] The C3- or C4-arylated selenophenes were regiospecifically obtained using 10 mol% $Pd(OAc)_2$ catalyst and 3 equiv. of Li_2CO_3 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 1.10. Selected examples of regiodivergent arylations of selenophenes.

Our group recently applied this methodology to the synthesis of planar *π*-extended selenium containing molecules.[22b] 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 1.11, a), or phenanthro[*c*]selenophenes (Scheme 1.11, b).



Scheme 1.11. Application to the synthesis of π-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 β-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 α-arylations, and so far this tool is effective only for (benzo)thiophenes and selenophenes.

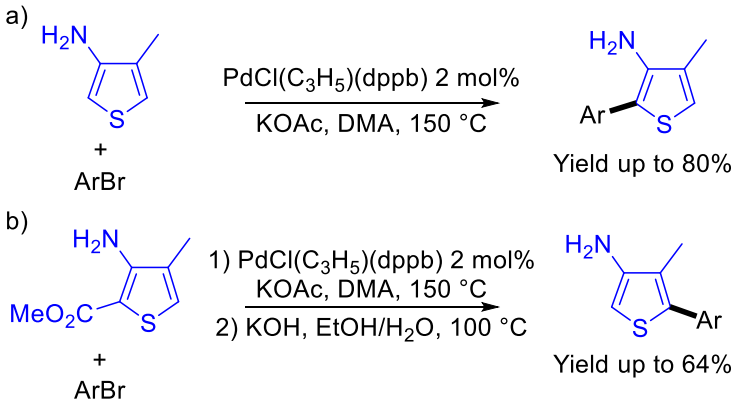
1.5 Blocking group

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 substituents at C2-position of 3-hexylthiophene, the regioselectivity of the Pd-catalyzed direct arylation was diverted to produce alternative C5-arylated thiophenes.[23] 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.

1.5.1. 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, our group has 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 1.12).[24] 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 1.12, a). Conversely, the coupling of bromobenzenes with methyl 3-amino-4-methylthiophene-2-carboxylate gave the C5-arylated thiophenes (Scheme 1.12, b). The simple treatment of such 5-arylthiophenes by KOH in EtOH/H_2O gave the decarboxylated

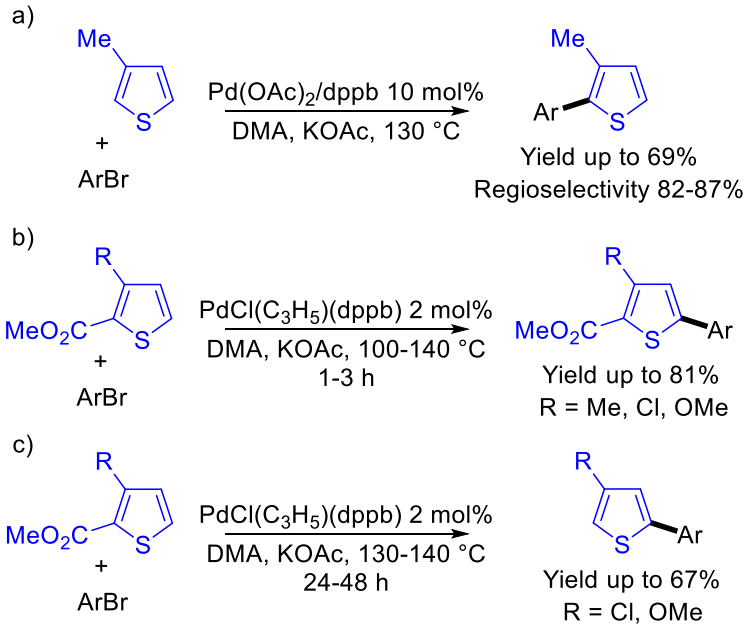
thiophenes. It should be mentioned that both thiophene substrates are commercially available.



Scheme 1.12. 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 $Pd(OAc)_2$/dppb catalyst affords the C2-arylated thiophenes in 82-87% regioselectivity (Scheme 1.13, a).[25]

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 1.13, b).[26] 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 1.13, c).



Scheme 1.13. Regiodivergent arylations of thiophene derivatives using an ester as blocking group.

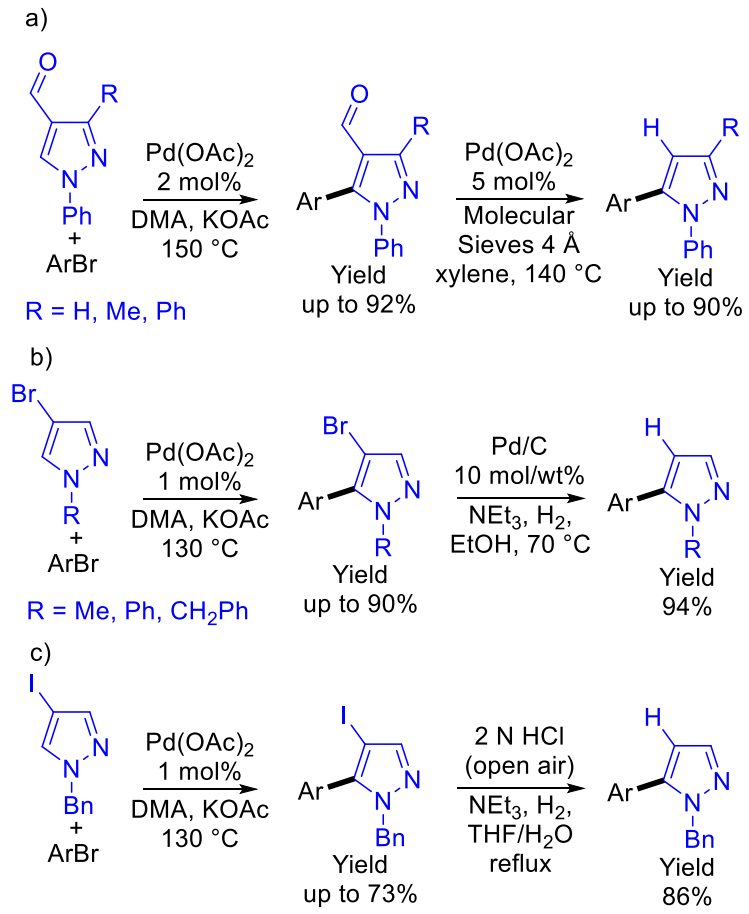
1.5.2. Formyl and halo substituents

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.[27] 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.[28]

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

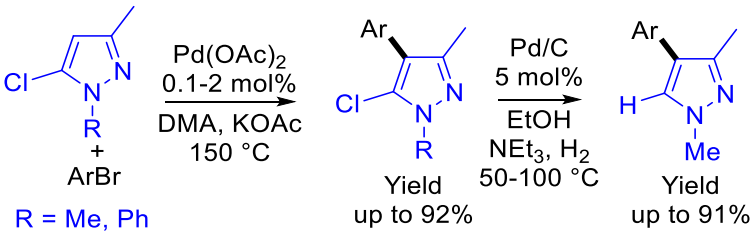
underwent Pd-catalyzed direct arylation reaction to provide regioselectively the 5-aryl-substituted pyrazoles (Scheme 1.14, a). The reaction proceeded in moderate to high yields using 2 mol% of $Pd(OAc)_2$ catalyst.[29]

Our group also employed bromo- and iodo-substituents as blocking groups at C4-position of pyrazoles (Scheme 1.14, b and c).[30] These C4-halosubstituted *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, our group 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 1.14. C5-arylations of pyrazoles using formyl or halogen substituents as blocking groups.

In order to obtain regioselectively C4-arylated pyrazoles, our group also studied the potential of an ester substituent as a temporary C5 blocking group.[31] 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% $Pd(OAc)_2$ catalyst, the 5-chloropyrazoles led to high yields in the desired C4-arylated pyrazoles (Scheme 1.15).[32] Moreover, the dechlorination of these 4-aryl-5-chloropyrazoles proceeded nicely using Pd/C catalyst.



Scheme 1.15. C4-arylations of pyrazoles using a chloro substituent as blocking group.

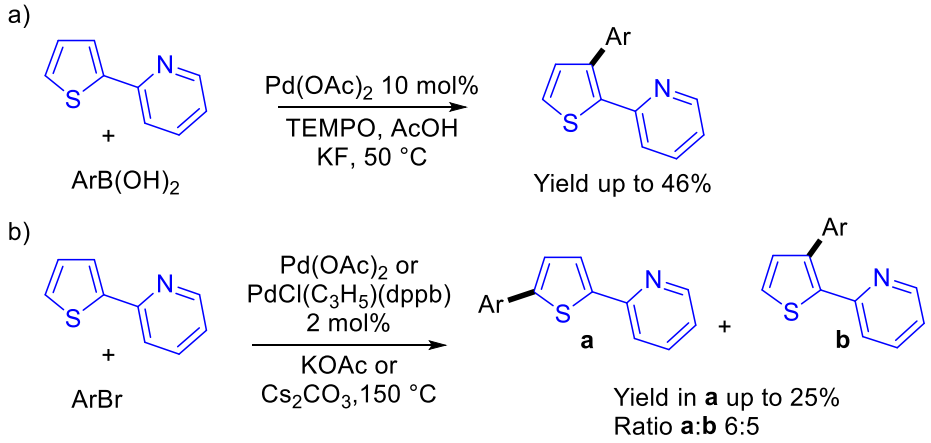
1.5.3. Protection *via* cyclometalation

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 opto-electronic 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 $Pd(OAc)_2/P[p\text{-}(CF_3)C_6H_4]_3$ as catalytic system and TEMPO as a stoichiometric oxidant (Scheme 1.16, a).[33] 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.

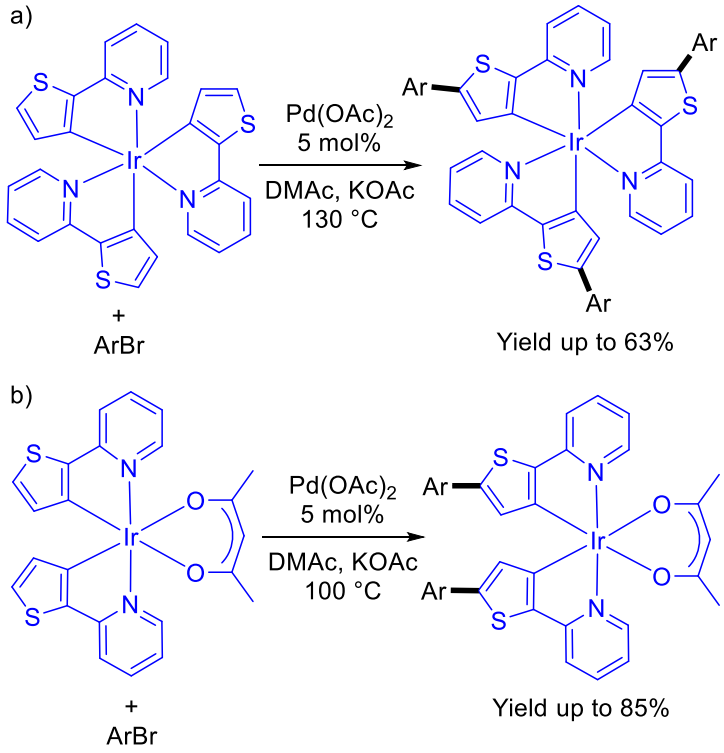
Our group studied the Pd-catalyzed direct coupling of 2-thienylpyridine using aryl bromides instead of arylboronic acids (Scheme 1.16, b).[34] The results show that the reaction is not regioselective, as both the C3- and C5-positions of the thienyl ring were arylated, and these two regioisomers were 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 1.16. Regioselectivity of the arylations of 2-pyridylthiophene.

In order to inhibit the pyridine ring nitrogen atom coordination mechanism, our group performed the direct arylation of thienylpyridine ligands on bis- or tris-cyclometallated iridium complexes (Scheme 1.17).[35] We found that the iridium-coordinated 2-thiophen-2-ylpyridines could de directly arylated with aryl bromides regioselectively at the thienyl C5-position using 5 mol% $Pd(OAc)_2$ 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 Ir complexes in only one step.

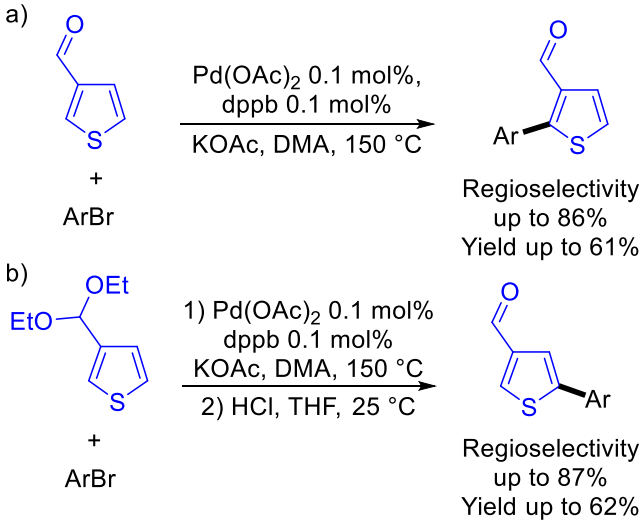


Scheme 1.17. C5-Arylations of metallated 2-pyridylthiophene.

1.6 Steric hindrance

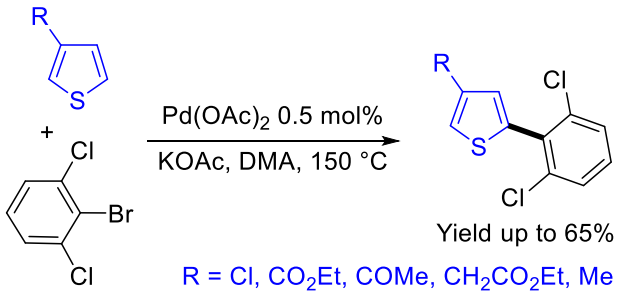
As explained in the scheme 13, in most cases, 3-substituted thiophenes such as 3-alkylthiophene or 3-cyanothiophene are arylated at their C2-position.[25] However, the regioselectivity of the arylation of 3-substituted thiophenes is strongly influenced by the steric hindrance of both coupling partners. For example from 3-acetylthiophene and 9-bromoanthracene, the C5-arylated thiophene was obtained in 90% regioselectivity.[1f,25] 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.[36] Indeed, we observed that the arylation of 3-formylthiophene with aryl bromides occurs mainly at the C2-position (regioselectivities 76-86%) (Scheme 1.18, a). Conversely, with more congested 3-formylthiophene diethylacetal, the arylation occurred mainly at the C5-position (regioselectivities 64-88%) (Scheme 1.18, b). Treatment of the 5-arylated 3-formylthiophene diethylacetals by HCl gives the corresponding C5-arylated 3-formylthiophenes.



Scheme 1.18. Regioselectivity of the arylations of 3-formylthiophene and 3-formylthiophene diethylacetal.

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.[37] 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 1.19). However, we didn't succeed to remove the two chloro substituents of the benzene unit after the coupling reaction.



Scheme 1.19. Regioselectivity of the arylations of 3-substituted thiophene with 2-bromo-1,3-dichlorobenzene.

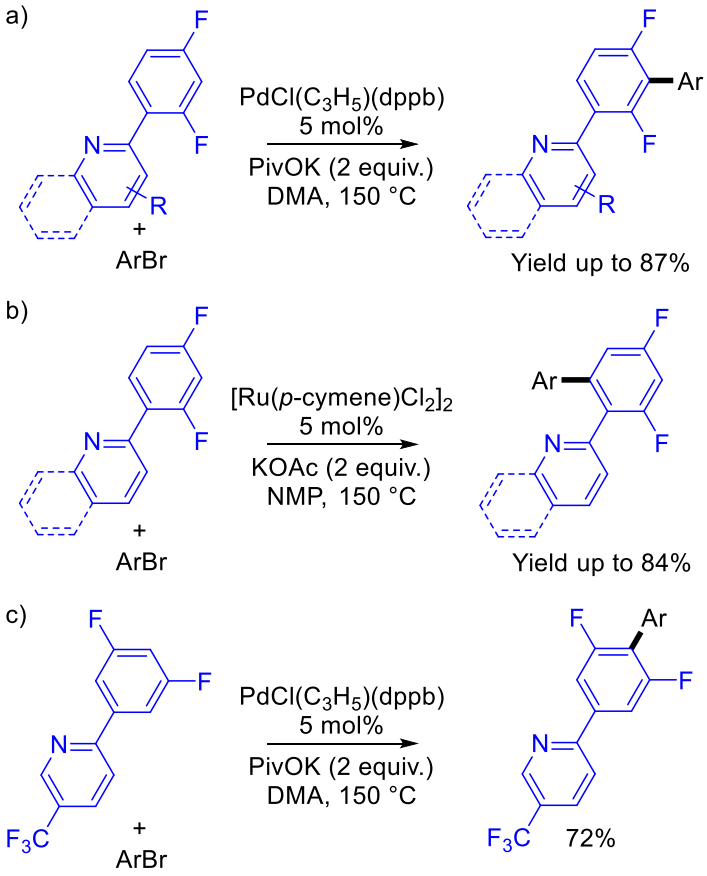
1.7 Nature of the metal of catalysts

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.

1.7.1. Arylation of 2-(difluorophenyl)pyridines and quinolines

In 2019, our group reported the regiodivergent C-H bond arylation of polyfluorinated 2-arylpyridines and 2-arylquinolines (Scheme 1.19).[38a] 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 1.20, a). The best results were obtained with $PdCl(C_3H_5)$(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 $Pd(OAc)_2$ catalyst). The base which plays a critical role in CMD mechanism has an important influence on the reactions yields. Using very soluble base, KOPiv, 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 1.20, b). Using 5 mol % of $[Ru(p\text{-cymeme})Cl_2]_2$ associated to KOAc, the arylation proceeded in >95:5 selectivity, and in good yields.

In 2020, our group 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 1.20, a and c).

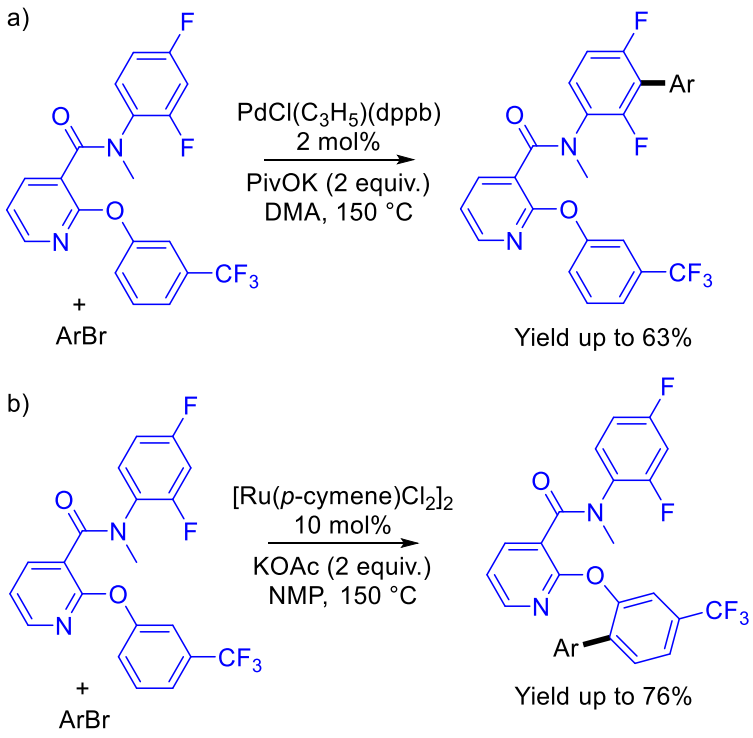


Scheme 1.20. Regiodivergent Pd- or Ru-catalyzed direct arylations of 2-(difluorophenyl)pyridines and quinolines.

1.7.2. Arylation of Diflufenican

Diflufenican, which is an herbicide, contains a 1,3-difluorobenzene ring and a pyridine ring (Scheme 1.21). 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.[39] 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 1.21, 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 1.21, b). With these two procedures, the arylated Diflufenican derivatives were obtained in moderate to good yields.

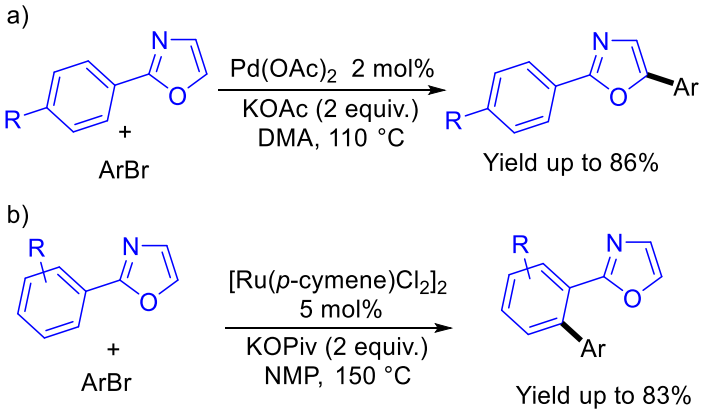


Scheme 1.21. Regiodivergent Pd- or Ru-catalyzed direct arylations of Diflufenican.

1.7.3. Arylation of 2-aryloxazoles

Our group also studied the reactivity of 2-aryloxazoles using Pd and Ru catalysts.[40] From 2-aryloxazoles and a set of electron-rich or -poor aryl bromides, in

the presence of $Pd(OAc)_2$ catalyst, the 2,5-diaryloxazoles were obtained with complete regioselectivity and high yields (Scheme 1.22, 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 1.22, b). For these reactions, $[Ru(p\text{-cymene})Cl_2]_2$ was employed as the catalyst and KOPiv as the base.[41]



Scheme 1.22. Regiodivergent Pd- or Ru-catalyzed direct arylations of 2-aryloxazoles.

1.8 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.

1.9 References

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Chapter 2:

Regioselective Pd-catalyzed direct C1- and C2-arylations of Lilolidine for access to 5,6-dihydropyrrolo[3,2,1-*ij*]quinoline derivatives

Chapter 2

Regioselective Pd-catalyzed direct C1- and C2-arylations of Lilolidine for access to 5,6-dihydropyrrolo[3,2,1-ij]quinoline derivatives

2.1 Introduction

Lilolidine (Fig. 2.1, left), which is a commercially available compound, contains a 5,6-dihydropyrrolo[3,2,1-*ij*]quinoline skeleton found in several bioactive molecules. For example, Tivantinib (Fig. 2.1, middle) exhibits MET inhibitor properties [1]; whereas Tarazepide (Fig. 2.1, right) is being investigated for the treatment of gastrointestinal diseases. Other Lilolidine derivatives also exhibit properties for the treatment of cancers [2-5]. Therefore, the discovery of simple methods for the preparation of Lilolidine derivatives is an important research area in pharmaceutical chemistry.

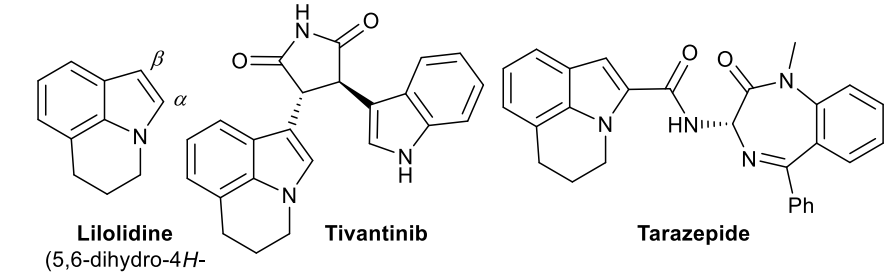
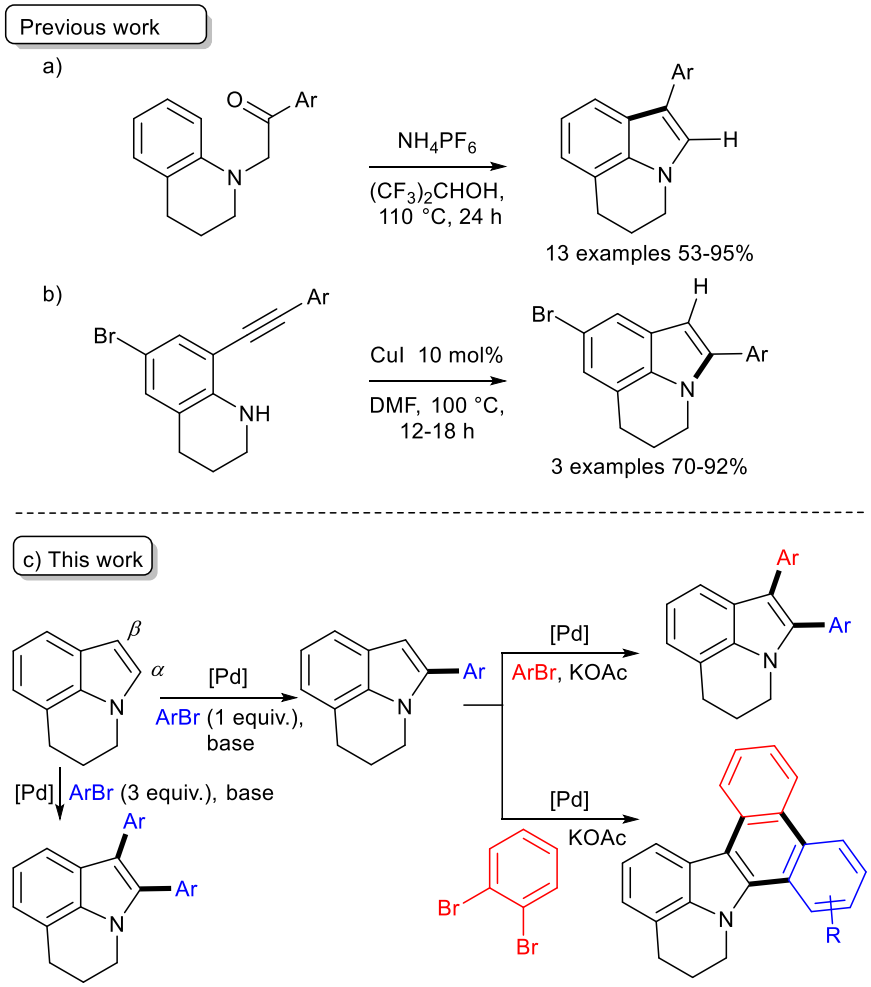


Figure 2.1. Structures of Lilolidine, Tivantinib and Tarazepide.

To our knowledge, so far only a few methods allow the synthesis of Lilolidines arylated at α- [6,7] or β- [8-13] positions of the nitrogen atom. In 2014, Chen, Tang et al. reported that NH_4PF_6 promotes the cyclodehydration of α-amino carbonyl compounds, leading to the formation of β-arylated 5,6-dihydropyrrolo [3,2,1-*ij*]quinoline derivatives [6] (Scheme 2.1, a). Three α-arylated 5,6-dihydro pyrrolo[3,2,1-*ij*]quinoline derivatives have been prepared by Pal et al. *via* the cyclization of 8-arylethynyl-1,2,3,4-tetrahydroquinolines [9] (Scheme 2.1, b). The best results were obtained using 10 mol% of CuI catalyst in DMF at 100 °C.

The late stage C-H bond functionalization of molecules represents a powerful method for the easy screening of the biological properties of compounds containing a bioactive unit. Since the seminal work by Ohta et al. on the Pd-catalyzed C-H bond functionalization of heteroarenes such as thiophenes, furans, pyrroles and indoles [14,15], this methodology has been widely applied for the preparation of new aryl-substituted heteroarenes [16-21]. Several results dealing with the C-H bond functionalization of indoles have been reported allowing to prepare either α- [22-31] or β-arylated [32-37] indoles, depending on the reaction conditions. However, to the best of our knowledge, no example of regioselective α- or β-arylations *via* the C-H bond functionalization of Lilolidine has been reported so far (Scheme 2.1, c).



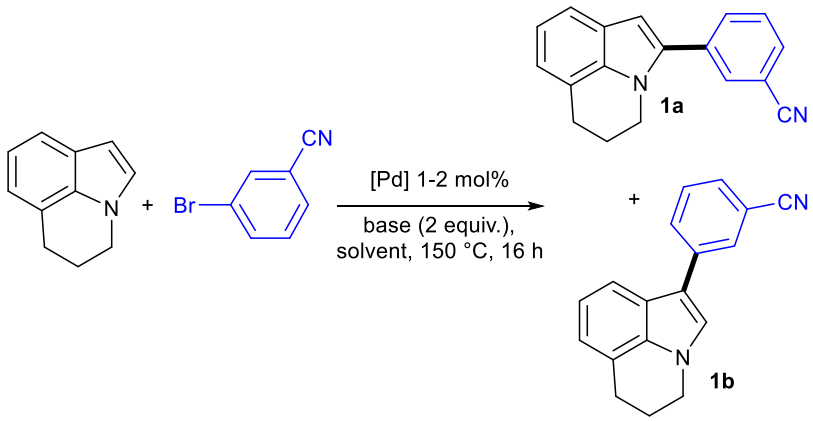
Scheme 2.1. Access to α- and β-arylated Lilolidine derivatives.

In this chapter, we report i) on the simple access to α-arylated 5,6-dihydropyrrolo[3,2,1-*ij*]quinolines using an air-stable Pd-catalyst associated to an inexpensive base, ii) on the sequential access to α,β-diarylated 5,6-dihydropyrrolo[3,2,1-*ij*]quinolines containing identical or different aryl groups at α- and β-positions *via* two-fold Pd-catalyzed C-H bond functionalizations, iii) on the synthesis of 5,6-dihydrodibenzo[*a*,*c*]pyrido[3,2,1-*jk*]carbazoles *via* three successive C-H bond functionalization steps (Scheme 2.1, c).

2.2 Results and discussion

Based on our previous results on the arylation of heteroaromatics [38], we initially employed 1 mol% $Pd(OAc)_2$ catalyst associated to KOAc as the base in DMA at 150 °C as the reaction conditions to promote the coupling of Lilolidine with 3-bromobenzonitrile (Table 2.1). Under these conditions, a mixture of the α- and β-arylated Lilolidines **1a** and **1b** was obtained in 64:36 ratio. Then, the influence of some bases on the regioselectivity with $Pd(OAc)_2$ catalyst was examined. With CsOAc a similar regioselectivity than with KOAc was obtained; whereas, the use of NaOAc afforded the products **1a** and **1b** in 85:15 ratio, but with a moderate conversion of 3-bromobenzonitrile (Table 2.1, entries 2 and 3). High regioselectivities in favor of isomer **1a** (85-90%) were also obtained using K_2CO_3 and Na_2CO_3, but partial conversions of 3-bromobenzonitrile were observed (Table 2.1, entries 4-6). In order to improve the conversions of the aryl bromide, the thermally more stable $PdCl(C_3H_5)$(dppb) catalyst [39] was employed. With K_2CO_3 and Na_2CO_3, the conversion of 3-bromobenzonitrile was not improved; whereas using NaOAc, a complete conversion of the aryl bromide was observed (Table 2.1, entries 8-10). Moreover, the regioselectivity in favor of α-arylated Lilolidine was improved to 93% affording **1a** in 83% yield. The use of KOAc associated to $PdCl(C_3H_5)$(dppb) catalyst also afforded the regioisomer **1a** in a quite good regioselectivity and yield (Table 2.1, entry 11). The higher conversions observed in the presence of acetate bases compared to carbonate bases (Table 2.1, entries 4-6 and 8-11) might be due to an easier coordination of acetates to palladium which favors the Concerted Metallation Deprotonation (CMD) mechanism [40]. The regioselectivities observed using acetate bases are consistent with a CMD mechanism.

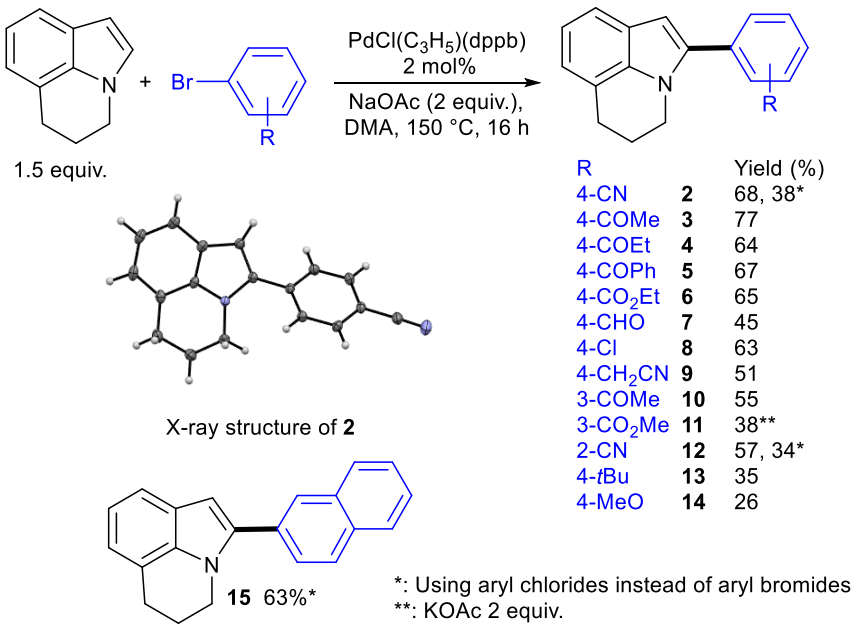
Table 2.1. Influence of the reaction conditions for palladium-catalyzed direct coupling of Lilolidine with 3-bromobenzonitrile.



Entry	Catalyst (mol%)	Base	Conv. (%)	Ratio **1a**:**1b**	Yield in **1a** (%)
1	$Pd(OAc)_2$ (1)	KOAc	100	64:36	63
2	$Pd(OAc)_2$ (1)	CsOAc	100	69:31	58
3	$Pd(OAc)_2$ (1)	NaOAc	65	85:15	43
4	$Pd(OAc)_2$ (1)	K_2CO_3	40	90:10	37
5	$Pd(OAc)_2$ (1)	Cs_2CO_3	0	-	-
6	$Pd(OAc)_2$ (1)	Na_2CO_3	33	85:15	nd
7	$Pd(OAc)_2$ (1)	KOAc	0[a]	-	-
8	$PdCl(C_3H_5)(dppb)$ (2)	K_2CO_3	42	90:10	nd
9	$PdCl(C_3H_5)(dppb)$ (2)	Na_2CO_3	35	91:9	nd
10	$PdCl(C_3H_5)(dppb)$ (2)	NaOAc	100	93:7	83
11	$PdCl(C_3H_5)(dppb)$ (2)	KOAc	100	82:18	68

Conditions: Lilolidine (1.5 mmol), 3-bromobenzonitrile (1 mmol), base (2 mmol), DMA, under argon, 16 h, 150 °C, isolated yields. [a] In xylene.

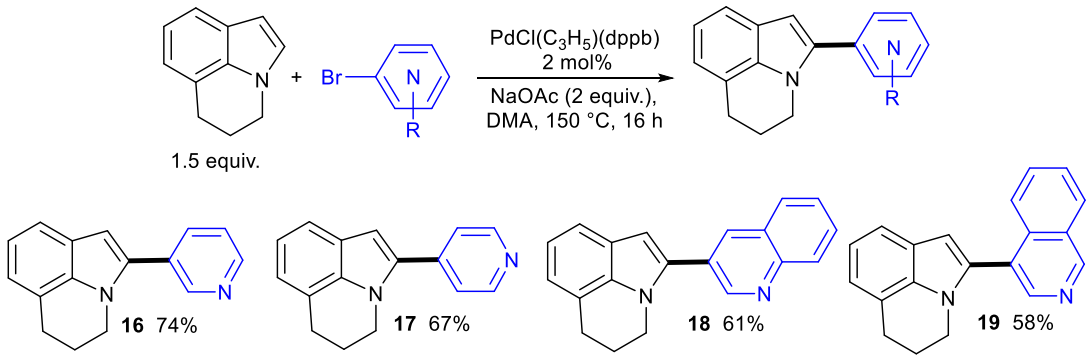
Then, a set of aryl bromides was reacted with Lilolidine using 2 mol% $PdCl(C_3H_5)$(dppb) catalyst, NaOAc or KOAc as bases in DMA at 150 °C (Scheme 2.2). We initially studied the reactivity of electron-deficient aryl bromides. Acetyl, propionyl, benzoyl and ester *para*-substituents on the aryl bromides were tolerated affording the target products **2**-**6** in 64-77% yields. The structure of **2** was confirmed by X-ray analysis. A lower yield of **7** was obtained for the reaction of 4-bromobenzaldehyde with Lilolidine due to the formation of degradation products. Good yields in **8** and **9** were obtained from 4-chloro- and 4-acetonitrile-substituted aryl bromides. In all cases, with these *para*-substituted aryl bromides, high regioselectivities in favor of the α-arylations were observed. The *meta*-substituted 3-bromoacetophenone and methyl 3-bromobenzoate also afforded the α-arylated Lilolidines **10** and **11** with high regioselectivities. Conversely, with the more sterically hindered aryl source 2-bromobenzonitrile, a mixture of α- and β-arylated Lilolidine derivatives was obtained (ratio α:β 69:31). The reactivity of two electron-rich aryl bromides was also examined. With 4-*tert*-butylbromobenzene and 4-bromoanisole, the target products **13** and **14** were obtained with high regioselectivities, but in low yields due to a partial conversion of these aryl bromides. It should be mentioned that the use of aryl chlorides instead of aryl bromides did not allowed to improve the regioselectivities or the reaction yields. With 4-chlorobenzonitrile, product **2** was obtained in 80% regioselectivity and in 38% yield; whereas the use of 2-chlorobenzonitrile afforded **12** in 62% regioselectivity and in 34% yield. In both cases, partial conversions of the aryl chlorides were observed.



R		Yield (%)
4-CN	**2**	68, 38*
4-COMe	**3**	77
4-COEt	**4**	64
4-COPh	**5**	67
4-CO_2Et	**6**	65
4-CHO	**7**	45
4-Cl	**8**	63
4-CH_2CN	**9**	51
3-COMe	**10**	55
3-CO_2Me	**11**	38**
2-CN	**12**	57, 34*
4-*t*Bu	**13**	35
4-MeO	**14**	26

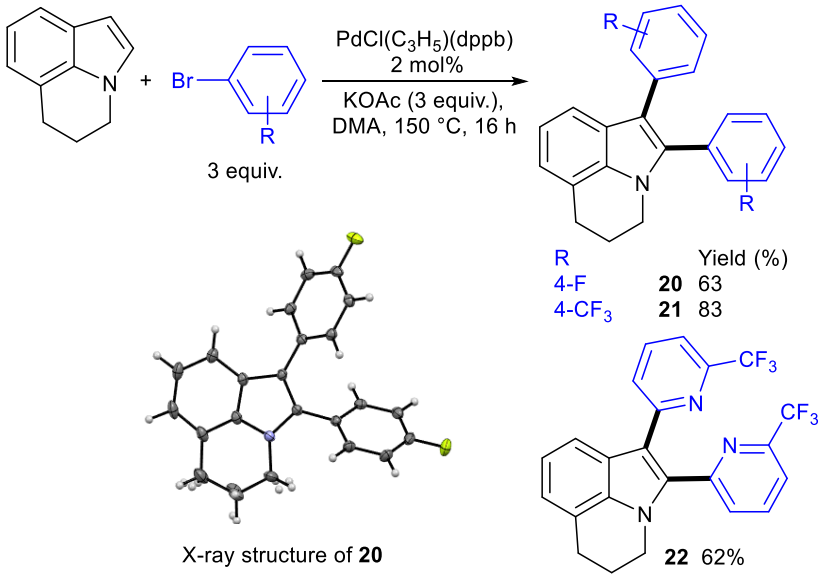
Scheme 2.2. Synthesis of α-arylated Lilolidine derivatives.

Pyridines and quinoline heterocycles are very important structures in pharmaceutical chemistry as more than 100 currently marketed drugs contain these units. Therefore, the reactivity of 3- and 4-bromo-substituted pyridines, 3-bromoquinoline and 4-bromoisoquinoline for the α-arylation of Lilolidine was also studied (Scheme 2.3). In all cases, the desired *N*-containing coupling products **16**-**19** were obtained in high regioselectivities and in 58-74% yields.



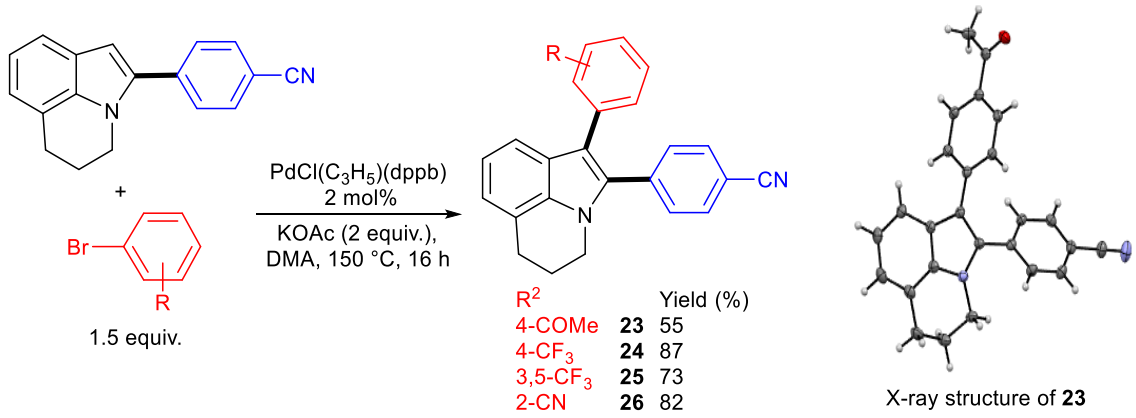
Scheme 2.3. Synthesis of α-arylated Lilolidine derivatives using heteroaryl bromides.

Then, the one pot synthesis of α,β-di(hetero)arylated 5,6-dihydropyrrolo [3,2,1-*ij*]quinolines was attempted (Scheme 2.4). The use of a larger amount of aryl bromides (3 equiv.) provided the target diarylated Lilolidines **20**-**22** in good yields. Under these conditions, the mono-arylated Lilolidines were detected in very low yields by GC/MS analysis of the crude mixtures. The structure of **20** was confirmed by X-ray diffraction.



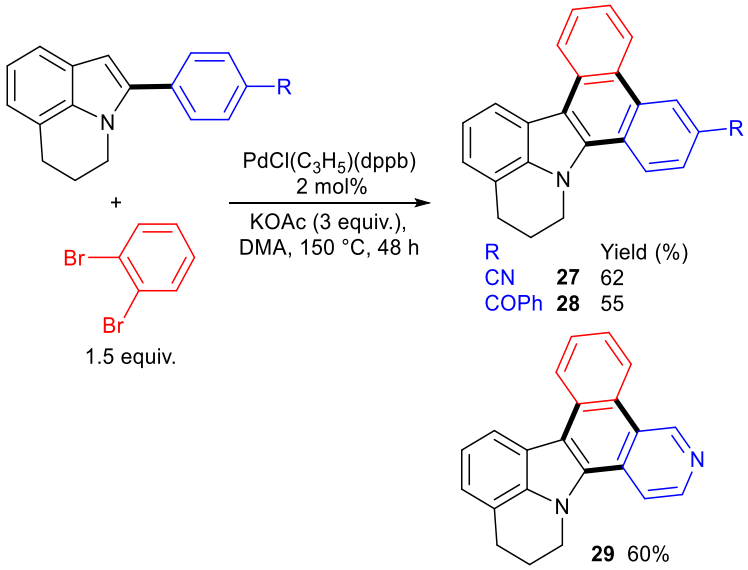
Scheme 2.4. Synthesis of α,β-di(hetero)arylated Lilolidine derivatives.

As α-arylated Lilolidines can be easily obtained under the reaction conditions of the scheme 2, the synthesis of α,β-diarylated 5,6-dihydropyrrolo [3,2,1-*ij*]quinolines containing two different aryl groups at α- and β-positions *via* sequential Pd-catalyzed C-H bond functionalization steps was studied (Scheme 2.5). The reaction of 1 equiv. of 4-(5,6-dihydropyrrolo[3,2,1-*ij*] quinolin-2-yl)benzonitrile **2** and 1.5 equiv. of a set of aryl bromides using again 2 mol% $PdCl(C_3H_5)(dppb)$ catalyst associated to KOAc provided the desired diarylated Lilolidines **23**-**26** in 55-87% yields. The structure of **23** was confirmed by X-ray diffraction.



Scheme 2.5. Synthesis of *α,β*-diarylated Lilolidine derivatives *via* successive direct arylations.

Finally, the synthesis of 5,6-dihydrodibenzo[*a*,*c*]pyrido[3,2,1-*jk*]carbazoles *via β*-arylation of the previously obtained *α*-arylated Lilolidines followed by an intramolecular Pd-catalyzed direct arylation was examined (Scheme 2.6). The reaction of compound **2** with 1,2-dibromobenzene in the presence of 2 mol% $PdCl(C_3H_5)$(dppb) catalyst and KOAc as base afforded the desired carbazole **27** in moderate yield after 16 h due to a partial conversion of **2**. However, the use of a longer reaction time (48 h) allowed to reach an almost complete conversion of **2**, and the carbazole **27** was isolated in 62% yield. A slightly lower yield in the carbazole **28** was obtained from (4-(5,6-dihydropyrrolo[3,2,1-*ij*] quinolin-2-yl)phenyl)(phenyl)methanone **5** and 1,2-dibromobenzene. This sequential C-H bond arylation strategy was also effective for the synthesis of the carbazole **29** from the pyridine *α*-substituted Lilolidine **17**.



Scheme 2.6. Synthesis of 5,6-dihydrodibenzo[*a*,*c*]pyrido[3,2,1-*jk*]carbazoles *via* successive direct arylations.

2.3 Conclusion

The late stage Pd-catalyzed C-H bond functionalization allows to prepare (di)arylated Lilolidine derivatives in only one or two steps. The α-arylated Lilolidines were generally obtained in high regioselectivities and in good yields using aryl bromides as easily available aryl sources, acetates as inexpensive bases and $PdCl(C_3H_5)$(dppb) as air-stable catalyst. The reaction tolerated a wide variety of useful functional groups such as nitrile, formyl, acetyl, propionyl, benzoyl, esters, chloro, or acetonitrile on the aryl bromide and the heteroaryl bromides 3- or 4-bromopyridines and 3-bromoquinoline. From these α-arylated Lilolidines, a second Pd-catalyzed direct arylation at β-position gave rise to α,β-diarylated Lilolidines with two different aryl units. The one pot access to α,β-diarylated Lilolidines with two identical aryl groups was also possible by using a larger amount of aryl bromide. The synthesis of 5,6-dihydrodibenzo[*a*,*c*]pyrido[3,2,1-*jk*]carbazoles from Lilolidine *via* three successive direct C-H bond arylations also proceed nicely. Therefore, this methodology provides a straightforward access to a wide variety of α- and β-(hetero)aryl substituted Lilolidines allowing to tune or modify their biological properties.

2.4 Experimental details

General.

All reactions were performed in Schlenk tubes under argon. DMA analytical grade were not distilled before use. Sodium acetate or potassium acetate 99+ were used. Commercial Lilolidine (>98%) and aryl bromides were used without purification. ^{1}H (400 MHz), ^{13}C (100 MHz) spectra were recorded in $CDCl_3$ solutions. Chemical shifts are reported in ppm relative to $CDCl_3$ (^{1}H: 7.26 and ^{13}C: 77.16). Flash chromatography was performed on silica gel (230-400 mesh).

Preparation of the $PdCl(C_3H_5)$(dppb) catalyst [39]:

An oven-dried 40 mL Schlenk tube equipped with a magnetic stirring bar under argon atmosphere, was charged with $[Pd(C_3H_5)Cl]_2$ (182 mg, 0.5 mmol) and dppb (426 mg, 1 mmol). 10 mL of anhydrous dichloromethane were added, then, the solution was stirred at room temperature for twenty minutes. The solvent was removed under reduced pressure. The yellow powder was used without purification. ^{31}P NMR (81 MHz, $CDCl_3$) δ = 19.3 (s).

General procedure for the synthesis of the α-arylated Lilolidine derivatives 1a and 2-22:

As a typical experiment, the reaction of the aryl bromide (1 mmol), Lilolidine (0.236 g, 1.5 mmol), NaOAc (0.164 g, 2 mmol) or KOAc (0.196 g, 2 mmol) (see schemes) at 150 ^{o}C during 16 h in DMA (2 mL) in the presence of $PdCl(C_3H_5)$(dppb) (12.2 mg, 0.02 mmol) under argon afford the corresponding arylation product after evaporation of the solvent and purification on silica gel.

3-(5,6-Dihydropyrrolo[3,2,1-*ij*]quinolin-2-yl)benzonitrile (1a):

From 3-bromobenzonitrile (0.182 g, 1 mmol) and Lilolidine (0.236 g, 1.5 mmol), **1a** was obtained in 83% (0.214 g) yield as a white solid: mp 176-178 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (s, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.57 (t, *J* = 7.9 Hz, 1H), 7.47 (d, *J* = 7.9 Hz, 1H), 7.07 (t, *J* = 7.2 Hz, 1H), 6.98 (d, *J* = 7.1 Hz, 1H), 6.61 (s, 1H), 4.21 (t, *J* = 5.7 Hz, 2H), 3.04 (t, *J* = 5.1 Hz, 2H), 2.24 (quint., *J* = 5.7 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.3, 135.8, 134.3, 132.8, 131.8, 130.9, 129.7, 125.9, 122.4, 120.5, 119.7, 118.7, 118.3, 113.1, 102.1, 44.0, 25.0, 23.3.

Elemental analysis: calcd (%) for $C_{18}H_{14}N_2$ (258.32): C 83.69, H 5.46; found: C 83.45, H 5.32.

4-(5,6-Dihydropyrrolo[3,2,1-*ij*]quinolin-2-yl)benzonitrile (2):

From 4-bromobenzonitrile (0.182 g, 1 mmol) and Lilolidine (0.236 g, 1.5 mmol), **2** was obtained in 68% (0.175 g) yield as a yellow solid: mp 201-203 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.5 Hz, 2H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.47 (d, *J* = 7.9 Hz, 1H), 7.05 (t, *J* = 7.9 Hz, 1H), 6.99 (d, *J* = 7.9 Hz, 1H), 6.66 (s, 1H), 4.24 (t, *J* = 5.7 Hz, 2H), 3.04 (t, *J* = 5.1 Hz, 2H), 2.23 (quint., *J* = 5.7 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.8, 137.4, 136.1, 132.5, 128.8, 125.9, 122.4, 120.6, 119.9, 119.0, 118.4, 110.9, 102.8, 44.3, 25.0, 23.3.

Elemental analysis: calcd (%) for $C_{18}H_{14}N_2$ (258.32): C 83.69, H 5.46; found: C 83.78, H 5.30.

1-(4-(5,6-Dihydropyrrolo[3,2,1-*ij*]quinolin-2-yl)phenyl)ethan-1-one (3):

From 4-bromoacetophenone (0.199 g, 1 mmol) and Lilolidine (0.236 g, 1.5 mmol), **3** was obtained in 77% (0.212 g) yield as a yellow solid: mp 139-141 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, *J* = 8.5 Hz, 2H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.48 (d, *J* = 7.9 Hz, 1H), 7.07 (t, *J* = 7.9 Hz, 1H), 6.99 (d, *J* = 7.9 Hz, 1H), 6.67 (s, 1H), 4.26 (t, *J* = 5.7 Hz, 2H), 3.04 (t, *J* = 5.1 Hz, 2H), 2.65 (s, 3H), 2.23 (quint., *J* = 5.7 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 197.6, 138.7, 137.5, 136.0, 135.9, 128.8, 128.5, 126.0, 122.4, 120.4, 119.5, 118.3, 102.2, 44.2, 26.8, 25.1, 23.3.

Elemental analysis: calcd (%) for $C_{19}H_{17}NO$ (275.35): C 82.88, H 6.22; found: C 83.02, H 6.30.

1-(4-(5,6-Dihydropyrrolo[3,2,1-*ij*]quinolin-2-yl)phenyl)propan-1-one (4):

From 4-bromopropiophenone (0.213 g, 1 mmol) and Lilolidine (0.236 g, 1.5 mmol), **4** was obtained in 64% (0.184 g) yield as a white solid: mp 147-149 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, *J* = 8.5 Hz, 2H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.48 (d, *J* = 7.9 Hz, 1H), 7.07 (t, *J* = 7.9 Hz, 1H), 6.98 (d, *J* = 7.9 Hz, 1H), 6.66 (s, 1H), 4.26 (t, *J* = 5.7 Hz, 2H), 3.11-3.00 (m, 4H), 2.23 (quint., *J* = 5.7 Hz, 2H), 1.27 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 200.4, 138.8, 137.3, 135.9, 135.7, 128.5, 128.4, 126.0, 122.4, 120.3, 119.5, 118.3, 102.1, 44.2, 32.0, 25.1, 23.3, 8.4.

Elemental analysis: calcd (%) for $C_{20}H_{19}NO$ (289.38): C 83.01, H 6.62; found: C 82.89, H 6.67.

Other regioisomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, *J* = 8.5 Hz, 2H), 7.82-7.74 (m, 3H), 7.41 (s, 1H), 7.14 (t, *J* = 7.9 Hz, 1H), 6.99 (d, *J* = 7.9 Hz, 1H), 4.23 (t, *J* = 5.7 Hz, 2H), 3.10-2.99 (m, 4H), 2.29 (quint., *J* = 5.7 Hz, 2H), 1.26 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 200.4, 141.3, 135.3, 133.8, 128.9, 126.3, 125.0, 123.7, 122.5, 121.1, 119.6, 117.7, 115.6, 44.5, 31.7, 24.8, 22.9, 8.6.

(4-(5,6-Dihydropyrrolo[3,2,1-*ij*]quinolin-2-yl)phenyl)(phenyl)methanone (5):

From 4-bromobenzophenone (0.261 g, 1 mmol) and Lilolidine (0.236 g, 1.5 mmol), **5** was obtained in 67% (0.226 g) yield as a yellow solid: mp 159-161 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, *J* = 8.5 Hz, 2H), 7.88 (d, *J* = 8.5 Hz, 2H), 7.70 (d, *J* = 8.3 Hz, 2H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.57-7.47 (m, 3H), 7.09 (t, *J* =

7.7 Hz, 1H), 7.00 (d, *J* = 7.0 Hz, 1H), 6.70 (s, 1H), 4.29 (t, *J* = 5.7 Hz, 2H), 3.06 (t, *J* = 5.1 Hz, 2H), 2.25 (quint., *J* = 5.7 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 196.2, 138.7, 137.7, 136.9, 136.3, 135.9, 132.5, 130.6, 130.1, 128.4, 128.2, 126.0, 122.3, 120.3, 119.4, 118.2, 102.1, 44.2, 25.0, 23.3.

Elemental analysis: calcd (%) for $C_{24}H_{19}NO$ (337.42): C 85.43, H 5.68; found: C 85.28, H 5.29.

Ethyl 4-(5,6-Dihydropyrrolo[3,2,1-*ij*]quinolin-2-yl)benzoate (6):

From ethyl 4-bromobenzoate (0.229 g, 1 mmol) and Lilolidine (0.236 g, 1.5 mmol), **6** was obtained in 65% (0.198 g) yield as a white solid: mp 109-111 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, *J* = 8.4 Hz, 2H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 7.9 Hz, 1H), 7.07 (t, *J* = 7.9 Hz, 1H), 6.98 (d, *J* = 7.9 Hz, 1H), 6.66 (s, 1H), 4.43 (q, *J* = 7.5 Hz, 2H), 4.25 (t, *J* = 5.7 Hz, 2H), 3.04 (t, *J* = 5.1 Hz, 2H), 2.23 (quint., *J* = 5.7 Hz, 2H), 1.44 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.5, 138.8, 137.2, 135.9, 130.0, 129.4, 128.3, 126.0, 122.3, 120.3, 119.4, 118.2, 102.0, 61.2, 44.2, 25.1, 23.3, 14.5.

Elemental analysis: calcd (%) for $C_{20}H_{19}NO_2$ (305.38): C 78.66, H 6.27; found: C 78.89, H 6.36.

4-(5,6-Dihydropyrrolo[3,2,1-*ij*]quinolin-2-yl)benzaldehyde (7):

From 4-bromobenzaldehyde (0.185 g, 1 mmol) and Lilolidine (0.236 g, 1.5 mmol), **7** was obtained in 45% (0.117 g) yield as a yellow solid: mp 143-145 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.06 (s, 1H), 7.96 (d, *J* = 8.5 Hz, 2H), 7.73 (d, *J* = 8.5 Hz, 2H), 7.49 (d, *J* = 7.9 Hz, 1H), 7.07 (t, *J* = 7.9 Hz, 1H), 6.99 (d, *J* = 7.9 Hz, 1H), 6.70 (s, 1H), 4.27 (t, *J* = 5.7 Hz, 2H), 3.05 (t, *J* = 5.1 Hz, 2H), 2.24 (quint., *J* = 5.7 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 191.8, 138.9, 138.4, 136.1, 135.2, 130.2, 128.8, 126.0, 122.4, 120.5, 119.7, 118.4, 102.7, 44.3, 25.1, 23.3.

Elemental analysis: calcd (%) for $C_{18}H_{15}NO$ (261.32): C 82.73, H 5.79; found: C 82.89, H 5.64.

2-(4-Chlorophenyl)-5,6-dihydropyrrolo[3,2,1-ij]quinoline (8):

From 4-bromochlorobenzene (0.191 g, 1 mmol) and Lilolidine (0.236 g, 1.5 mmol), **8** was obtained in 63% (0.168 g) yield as a white solid: mp 147-149 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, *J* = 8.5 Hz, 2H), 7.44 (d, *J* = 7.9 Hz, 1H), 7.43 (d, *J* = 8.5 Hz, 2H), 7.04 (t, *J* = 7.9 Hz, 1H), 6.95 (d, *J* = 7.9 Hz, 1H), 6.54 (s, 1H), 4.19 (t, *J* = 5.7Hz, 2H), 3.03 (t, *J* = 5.1 Hz, 2H), 2.22 (quint., *J* = 5.7 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.8, 135.5, 133.8, 131.4, 129.9, 128.9, 126.0, 122.2, 120.2, 119.1, 118.1, 101.1, 43.9, 25.1, 23.3.

Elemental analysis: calcd (%) for $C_{17}H_{14}ClN$ (267.76): C 76.26, H 5.27; found: C 76.39, H 5.41.

2-(4-(5,6-Dihydropyrrolo[3,2,1-*ij*]quinolin-2-yl)phenyl)acetonitrile (9):

From 2-(4-bromophenyl)acetonitrile (0.196 g, 1 mmol) and Lilolidine (0.236 g, 1.5 mmol), **9** was obtained in 51% (0.139 g) yield as a yellow solid: mp 130-132 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, *J* = 8.5 Hz, 2H), 7.48 (d, *J* = 7.9 Hz, 1H), 7.42 (d, *J* = 8.5 Hz, 2H), 7.07 (t, *J* = 7.9 Hz, 1H), 6.98 (d, *J* = 7.9 Hz, 1H), 6.58 (s, 1H), 4.21 (t, *J* = 5.7 Hz, 2H), 3.80 (s, 2H), 3.04 (t, *J* = 5.1 Hz, 2H), 2.23 (quint., *J* = 5.7 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 139.0, 135.5, 132.8, 129.3, 129.2, 128.3, 126.0, 122.2, 120.2, 119.1, 118.0, 117.8, 101.1, 43.9, 25.1, 23.5, 23.3.

Elemental analysis: calcd (%) for $C_{19}H_{16}N_2$ (272.35): C 83.79, H 5.92; found: C 83.58, H 5.69.

1-(3-(5,6-Dihydropyrrolo[3,2,1-*ij*]quinolin-2-yl)phenyl)ethan-1-one (10):

From 3-bromoacetophenone (0.199 g, 1 mmol) and Lilolidine (0.236 g, 1.5 mmol), **10** was obtained in 55% (0.151 g) yield as a yellow solid: mp 159-161 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (s, 1H), 7.96 (d, *J* = 8.5 Hz, 1H), 7.76 (d, *J* = 7.8 Hz, 1H), 7.57 (t, *J* = 7.9 Hz, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.06 (t, *J* = 7.9 Hz, 1H), 6.97 (d, *J* = 7.9 Hz, 1H), 6.62 (s, 1H), 4.22 (t, *J* = 5.7 Hz, 2H), 3.04 (t, *J* = 5.1 Hz, 2H), 2.66 (s, 3H), 2.23 (quint., *J* = 5.7 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 197.9, 138.9, 137.6, 135.6, 133.5, 133.1, 129.1, 128.4, 127.5, 126.0, 122.3, 120.3, 119.2, 118.1, 101.4, 43.9, 26.9, 25.1, 23.3.

Elemental analysis: calcd (%) for $C_{19}H_{17}NO$ (275.35): C 82.88, H 6.22; found: C 82.78, H 6.08.

Methyl 3-(5,6-dihydropyrrolo[3,2,1-*ij*]quinolin-2-yl)benzoate (11):

From methyl 3-bromobenzoate (0.215 g, 1 mmol) and Lilolidine (0.236 g, 1.5 mmol), **11** was obtained in 38% (0.110 g) yield as a yellow solid: mp 146-148 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (s, 1H), 8.05 (d, *J* = 8.5 Hz, 1H), 7.76 (d, *J* = 8.5 Hz, 1H), 7.54 (t, *J* = 7.8 Hz, 1H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.06 (t, *J* = 7.9 Hz, 1H), 6.97 (d, *J* = 7.9 Hz, 1H), 6.62 (s, 1H), 4.24 (t, *J* = 5.7 Hz, 2H), 3.97 (s, 3H), 3.04 (t, *J* = 5.1 Hz, 2H), 2.23 (quint., *J* = 5.7 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0, 138.8, 135.6, 133.2, 133.0, 130.7, 129.6, 128.9, 128.7, 126.0, 122.3, 120.3, 119.1, 118.1, 101.3, 52.4, 43.9, 25.1, 23.3.

Elemental analysis: calcd (%) for $C_{19}H_{17}NO_2$ (291.35): C 78.33, H 5.88; found: C 78.60, H 6.04.

2-(5,6-Dihydropyrrolo[3,2,1-*ij*]quinolin-2-yl)benzonitrile (12):

From 2-bromobenzonitrile (0.182 g, 1 mmol) and Lilolidine (0.236 g, 1.5 mmol), **12** was obtained in 57% (0.147 g) yield as a white solid: mp 225-227 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (dd, *J* = 7.8, 0.8 Hz, 1H), 7.67 (td, *J* = 7.8, 1.3 Hz, 1H), 7.56 (d, *J* = 7.9 Hz, 1H), 7.52-7.44 (m, 2H), 7.07 (t, *J* = 7.9 Hz, 1H), 6.99 (d, *J* = 7.9 Hz, 1H), 6.73 (s, 1H), 4.11 (t, *J* = 5.7 Hz, 2H), 3.05 (t, *J* = 5.1 Hz, 2H), 2.25 (quint., *J* = 5.7 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 136.4, 135.7, 135.2, 133.9, 132.6, 131.0, 128.2, 125.9, 122.4, 120.4, 119.8, 118.6, 118.5, 112.9, 103.9, 43.6, 25.0, 23.1.

Elemental analysis: calcd (%) for $C_{18}H_{14}N_2$ (258.32): C 83.69, H 5.46; found: C 83.76, H 5.51.

The regioisomers 2-(5,6-Dihydropyrrolo[3,2,1-*ij*]quinolin-1-yl)benzonitrile was also isolated in 19% yield (31% selectivity): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 7.9 Hz, 1H), 7.75 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.66 (s, 1H), 7.63 (td, *J* = 7.7, 1.2 Hz, 1H), 7.60 (d, *J* = 7.9 Hz, 1H), 7.31 (td, *J* = 7.9, 1.1 Hz, 1H), 7.12 (t, *J* = 7.9 Hz, 1H), 7.01 (d, *J* = 7.5 Hz, 1H), 4.26 (t, *J* = 5.7 Hz, 2H), 3.05 (t, *J* = 5.1 Hz, 2H), 2.30 (quint., *J* = 5.7 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 139.7, 134.7, 134.2, 132.9, 129.6, 126.4, 125.7, 124.2, 122.5, 121.1, 120.0, 119.6, 117.1, 112.4, 110.1, 44.6, 24.8, 22.9.

2-(4-(*tert*-Butyl)phenyl)-5,6-dihydropyrrolo[3,2,1-*ij*]quinoline (13):

From 4-*tert*-butylbromobenzene (0.213 g, 1 mmol) and Lilolidine (0.236 g, 1.5 mmol), **13** was obtained in 35% (0.101 g) yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52-7.49 (m, 4H), 7.44 (d, *J* = 7.9 Hz, 1H), 7.04 (t, *J* = 7.9 Hz, 1H), 6.93 (d, *J* = 7.9 Hz, 1H), 6.57 (s, 1H), 4.27 (t, *J* = 5.7Hz, 2H), 3.06 (t, *J* = 5.1 Hz, 2H), 2.24 (quint., *J* = 5.7 Hz, 2H), 1.41 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.8, 140.1, 135.4, 130.0, 128.5, 126.2, 125.6, 122.1, 119.9, 118.6, 117.8, 100.3, 43.9, 34.8, 31.5, 25.2, 23.3.

Elemental analysis: calcd (%) for $C_{21}H_{23}N$ (289.42): C 87.15, H 8.01; found: C 87.39, H 7.78.

2-(4-Methoxyphenyl)-5,6-dihydropyrrolo[3,2,1-*ij*]quinoline (14):

From 4-bromoanisole (0.187 g, 1 mmol) and Lilolidine (0.236 g, 1.5 mmol), **14** was obtained in 26% (0.068 g) yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 7.9 Hz, 1H), 7.03 (t, *J* = 7.9 Hz, 1H), 6.99 (d, *J* = 8.0 Hz, 2H), 6.92 (d, *J* = 7.9 Hz, 1H), 6.48 (s, 1H), 4.19 (t, *J* = 5.7Hz, 2H), 3.87 (s, 3H), 3.02 (t, *J* = 5.1 Hz, 2H), 2.20 (quint., *J* = 5.7 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4, 140.0, 135.2, 130.0, 126.2, 125.4, 122.1, 119.9, 118.5, 117.7, 114.2, 99.9, 55.5, 43.8, 25.1, 23.3.

Elemental analysis: calcd (%) for $C_{18}H_{17}NO$ (263.34): C 82.10, H 6.51; found: C 82.39, H 6.54.

2-(Naphthalen-2-yl)-5,6-dihydropyrrolo[3,2,1-*ij*]quinoline (15):

From 2-bromonaphthalene (0.207 g, 1 mmol) and Lilolidine (0.236 g, 1.5 mmol), **15** was obtained in 63% (0.178 g) yield as a yellow solid: mp 147-149 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (bs, 1H), 7.93 (d, *J* = 8.5 Hz, 1H), 7.91-7.87 (m, 2H), 7.70 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.57-7.47 (m, 3H), 7.06 (t, *J* = 7.4 Hz, 1H), 6.69 (dd, *J* = 7.0, 1.0 Hz, 1H), 6.67 (s, 1H), 4.31 (t, *J* = 5.7 Hz, 2H), 3.06 (t, *J* = 5.1 Hz, 2H), 2.25 (quint., *J* = 5.7 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 140.1, 135.6, 133.5, 132.8, 130.3, 128.3, 128.2, 127.9, 127.4, 126.9, 126.6, 126.4, 126.2, 122.2, 120.1, 118.9, 118.0, 101.2, 44.1, 25.2, 23.4.

Elemental analysis: calcd (%) for $C_{21}H_{17}N$ (283.37): C 89.01, H 6.05; found: C 88.78, H 6.20.

2-(Pyridin-3-yl)-5,6-dihydropyrrolo[3,2,1-*ij*]quinoline (16):

From 3-bromopyridine (0.158 g, 1 mmol) and Lilolidine (0.236 g, 1.5 mmol), **16** was obtained in 74% (0.173 g) yield as a yellow solid: mp 99-101 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.84 (d, *J* = 1.3 Hz, 1H), 8.62 (dd, *J* = 4.6, 1.2 Hz, 1H), 7.86 (dt, J = 7.9, 2.0 Hz, 1H), 7.48 (d, *J* = 7.9 Hz, 1H), 7.40 (dd, J = 7.8, 4.8 Hz, 1H), 7.07 (t, *J* = 7.9 Hz, 1H), 6.98 (d, *J* = 7.9 Hz, 1H), 6.62 (s, 1H), 4.22 (t, *J* = 5.7 Hz, 2H), 3.04 (t, *J* = 5.1 Hz, 2H), 2.24 (quint., *J* = 5.7 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.4, 148.7, 136.2, 135.7, 128.9, 126.0, 123.5, 122.3, 120.4, 119.4, 118.2, 101.8, 43.9, 25.0, 23.2.

Elemental analysis: calcd (%) for $C_{16}H_{14}N_2$ (234.30): C 82.02, H 6.02; found: C 81.78, H 5.85.

Other regioisomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.95 (s, 1H), 8.47 (d, *J* = 3.9 Hz, 1H), 7.98 (d, *J* = 7.9 Hz, 1H), 7.72 (d, *J* = 8.1 Hz, 1H), 7.37-7.32 (m, 2H), 7.11 (t, *J* = 7.9 Hz, 1H), 6.99 (d, *J* = 7.9 Hz, 1H), 4.24 (t, *J* = 5.7 Hz, 2H), 3.04 (t, *J* = 5.1 Hz, 2H), 2.29 (quint., *J* = 5.7 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 147.9, 146.4, 135.2, 133.9, 124.2, 123.8, 123.7, 122.5, 121.0, 119.6, 117.2, 112.9, 44.5, 24.8, 22.9.

2-(Pyridin-4-yl)-5,6-dihydropyrrolo[3,2,1-*ij*]quinoline (17):

From 4-bromopyridine (0.158 g, 1 mmol) and Lilolidine (0.236 g, 1.5 mmol), **17** was obtained in 67% (0.157 g) yield as a yellow solid: mp 111-113 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.67 (d, *J* = 6.0 Hz, 2H), 7.51-7.44 (m, 3H), 7.07 (t, *J* = 7.9 Hz, 1H), 6.99 (d, *J* = 7.9 Hz, 1H), 6.73 (s, 1H), 4.28 (t, *J* = 5.7 Hz, 2H), 3.04 (t, *J* = 5.1 Hz, 2H), 2.24 (quint., *J* = 5.7 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.2, 140.3, 136.8, 136.2, 125.8, 122.6, 122.5, 120.5, 119.9, 118.5, 102.8, 44.3, 25.0, 23.3.

Elemental analysis: calcd (%) for $C_{16}H_{14}N_2$ (234.30): C 82.02, H 6.02; found: C 81.85, H 6.14.

2-(Quinolin-3-yl)-5,6-dihydropyrrolo[3,2,1-*ij*]quinoline (18):

From 3-bromoquinoline (0.208 g, 1 mmol) and Lilolidine (0.236 g, 1.5 mmol), **18** was obtained in 61% (0.173 g) yield as a yellow solid: mp 151-153 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.17 (d, J = 2.0 Hz, 1H), 8.27 (d, J = 2.0 Hz, 1H), 8.17 (d, *J* = 8.4 Hz, 1H), 7.89 (d, *J* = 8.4 Hz, 1H), 7.76 (t, *J* = 7.5 Hz, 1H), 7.61 (t, *J* = 7.5 Hz, 1H), 7.52 (d, *J* = 7.9 Hz, 1H), 7.10 (t, *J* = 7.9 Hz, 1H), 7.00 (d, *J* = 7.9 Hz, 1H), 6.75 (s, 1H), 4.31 (t, *J* = 5.7 Hz, 2H), 3.07 (t, *J* = 5.1 Hz, 2H), 2.27 (quint., *J* = 5.7 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.8, 147.3, 136.8, 135.8, 134.4, 129.8, 129.5, 128.0, 127.8, 127.4, 126.1, 122.3, 120.4, 119.5, 118.3, 102.2, 44.0, 25.0, 23.3.

Elemental analysis: calcd (%) for $C_{20}H_{16}N_2$ (284.36): C 84.48, H 5.67; found: C 84.29, H 5.57.

2-(Isoquinolin-4-yl)-5,6-dihydropyrrolo[3,2,1-*ij*]quinoline (19):

From 4-bromoisoquinoline (0.208 g, 1 mmol) and Lilolidine (0.236 g, 1.5 mmol), **19** was obtained in 58% (0.165 g) yield as a yellow solid: mp 155-157 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.33 (s, 1H), 8.63 (s, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 7.89 (d, *J* = 8.2 Hz, 1H), 7.76-7.63 (m, 2H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.13 (t, *J* = 7.6 Hz, 1H), 7.03 (d, *J* = 7.9 Hz, 1H), 6.68 (s, 1H), 3.91 (t, *J* = 5.7 Hz, 2H), 3.07 (t, *J* = 5.1 Hz, 2H), 2.21 (quint., *J* = 5.7 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 152.9, 144.4, 135.4, 135.3, 134.2, 131.1, 128.4, 128.0, 127.6, 126.1, 125.1, 124.2, 122.1, 120.3, 119.2, 118.0, 103.6, 43.2, 25.0, 23.1.

Elemental analysis: calcd (%) for $C_{20}H_{16}N_2$ (284.36): C 84.48, H 5.67; found: C 84.39, H 5.71.

Other regioisomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.24 (s, 1H), 8.68 (s, 1H), 8.17 (d, *J* = 8.6 Hz, 1H), 8.04 (d, *J* = 8.4 Hz, 1H), 7.68-7.60 (m, 2H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.32 (s, 1H),

7.08 (t, *J* = 7.6 Hz, 1H), 7.02 (d, *J* = 7.9 Hz, 1H), 4.28 (t, *J* = 5.7 Hz, 2H), 3.09 (t, *J* = 5.1 Hz, 2H), 2.24 (quint., *J* = 5.7 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 151.0, 143.4, 134.9, 134.7, 130.1, 128.7, 127.9, 127.2, 127.1, 125.9, 125.7, 125.5, 122.3, 120.5, 119.2, 117.8, 111.3, 44.4, 24.8, 23.0.

General procedure for the synthesis of the *α,β*-diarylated Lilolidine derivatives 20-22:

As a typical experiment, the reaction of the aryl bromide (3 mmol), Lilolidine (0.157 g, 1 mmol), KOAc (0.294 g, 3 mmol) at 150 °C during 16 h in DMA (5 mL) in the presence of $PdCl(C_3H_5)$(dppb) (12.2 mg, 0.02 mmol) under argon afford the corresponding diarylation product after evaporation of the solvent and purification on silica gel.

1,2-Bis(4-fluorophenyl)-5,6-dihydropyrrolo[3,2,1-ij]quinoline (20):

From 4-bromofluorobenzene (0.525 g, 3 mmol) and Lilolidine (0.157 g, 1 mmol), **20** was obtained in 63% (0.217 g) yield as a white solid: mp 177-179 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, *J* = 7.9 Hz, 1H), 7.33-7.22 (m, 4H), 7.13-7.05 (m, 3H), 7.03-6.95 (m, 3H) 4.06 (t, *J* = 5.7 Hz, 2H), 3.06 (t, *J* = 5.1 Hz, 2H), 2.25 (quint., *J* = 5.7 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.6 (d, *J* = 248.3 Hz), 161.2 (d, *J* = 244.5 Hz), 135.0, 134.4, 132.5 (d, *J* = 8.1 Hz), 131.5 (d, *J* = 3.2 Hz), 131.2 (d, *J* = 7.7 Hz), 127.7 (d, *J* = 3.2 Hz), 125.0, 122.2, 120.6, 119.5, 116.9, 115.8 (d, *J* = 21.5 Hz), 115.4 (d, *J* = 21.2 Hz), 113.8, 43.3, 25.2, 23.1.

Elemental analysis: calcd (%) for $C_{23}H_{17}F_2N$ (345.39): C 79.98, H 4.96; found: C 80.21, H 4.89.

1,2-Bis(4-(trifluoromethyl)phenyl)-5,6-dihydropyrrolo[3,2,1-ij]quinoline (21):

From 4-bromobenzotrifluoride (0.676 g, 3 mmol) and Lilolidine (0.157 g, 1 mmol), **21** was obtained in 83% (0.369 g) yield as a white solid: mp 220-222 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, *J* = 8.1 Hz, 2H), 7.59 (d, *J* = 7.9 Hz, 1H), 7.55 (d, *J* = 8.1 Hz, 2H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.41 (d, *J* = 8.1 Hz, 2H), 7.15 (t, *J* = 7.9 Hz, 1H), 7.06 (d, *J* = 7.9 Hz, 1H), 4.09 (t, *J* = 5.7 Hz, 2H), 3.08 (t, *J* = 5.1 Hz, 2H), 2.26 (quint., *J* = 5.7 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 139.1, 135.2, 135.0, 134.8, 131.1, 130.3 (q, *J* = 32.4 Hz), 129.8, 127.7 (q, *J* = 32.4 Hz), 125.8 (q, *J* = 3.8 Hz), 125.5 (q, *J* = 3.8 Hz), 124.9, 124.5 (q, *J* = 271.7 Hz), 124.2 (q, *J* = 272.3 Hz), 122.5, 121.2, 120.2, 117.0, 114.3, 43.6, 25.1, 23.1.

Elemental analysis: calcd (%) for $C_{25}H_{17}F_6N$ (445.41): C 67.42, H 3.85; found: C 67.56, H 3.99.

1,2-Bis(6-(trifluoromethyl)pyridin-2-yl)-5,6-dihydropyrrolo[3,2,1-*ij*]quinoline (22):

From 2-bromo-6-trifluoromethylpyridine (0.678 g, 3 mmol) and Lilolidine (0.157 g, 1 mmol), **22** was obtained in 62% (0.277 g) yield as a yellow solid: mp 143-145 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85-7.77 (m, 3H), 7.75 (t, *J* = 7.8 Hz, 1H), 7.65 (dd, *J* = 6.3, 2.5 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.46 (d, *J* = 7.7 Hz, 1H), 7.17 (t, *J* = 7.9 Hz, 1H), 7.06 (d, *J* = 7.9 Hz, 1H), 4.31 (t, *J* = 5.7 Hz, 2H), 3.05 (t, *J* = 5.1 Hz, 2H), 2.25 (quint., *J* = 5.7 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.5, 151.9, 148.0 (q, *J* = 34.6 Hz), 137.4, 135.2, 135.1, 129.8, 126.2, 124.6, 123.0, 121.8, 121.7 (q, *J* = 273.8 Hz), 121.6 (q, *J* = 273.0 Hz), 120.8, 119.1 (m), 118.0, 116.9 (m), 114.9, 44.1, 25.1, 23.1.

Elemental analysis: calcd (%) for $C_{23}H_{15}F_6N_3$ (447.38): C 61.75, H 3.38; found: C 61.79, H 3.50.

General procedure for the synthesis of the α,β-diarylated Lilolidine derivatives 23-29: As a typical experiment, the reaction of the aryl bromide (1.5 mmol), 5,6-dihydropyrrolo[3,2,1-*ij*]quinolin-2-yl derivative **2**, **5** or **17** (1 mmol), KOAc (0.192 g, 2 mmol) at 150 ºC during 16 h in DMA (2 mL) in the presence of $PdCl(C_3H_5)(dppb)$ (12.2 mg, 0.02 mmol) under argon afford the corresponding arylation product after evaporation of the solvent and purification on silica gel.

4-(1-(4-Acetylphenyl)-5,6-dihydropyrrolo[3,2,1-*ij*]quinolin-2-yl)benzonitril e (23):

From 4-bromoacetophenone (0.299 g, 1.5 mmol) and 4-(5,6-dihydropyrrolo[3,2,1-*ij*]quinolin-2-yl)benzonitrile **2** (0.258 g, 1 mmol), **23** was obtained in 55% (0.207 g) yield as a yellow solid: mp 243-245 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, *J* = 8.5 Hz, 2H), 7.68 (d, *J* = 8.5 Hz, 2H), 7.60 (d, *J* = 7.9 Hz, 1H), 7.45 (d, *J* = 8.5 Hz, 2H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.15 (t, *J* = 7.9 Hz, 1H), 7.07 (d, *J* = 7.9 Hz, 1H), 4.10 (t, *J* = 5.7 Hz, 2H), 3.08 (t, *J* = 5.1 Hz, 2H), 2.60 (s, 3H), 2.27 (quint., *J* = 5.7 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 197.7, 140.3, 136.4, 135.0, 134.7, 134.5, 132.5, 131.4, 129.7, 128.8, 124.8, 122.6, 121.4, 120.5, 118.6, 117.2, 115.2, 111.9, 43.7, 26.7, 25.1, 23.0.

Elemental analysis: calcd (%) for $C_{26}H_{20}N_2O$ (376.46): C 82.95, H 5.36; found: C 82.99, H 5.58.

4-(1-(4-(Trifluoromethyl)phenyl)-5,6-dihydropyrrolo[3,2,1-*ij*]quinolin-2-yl) benzonitrile (24):

From 4-bromobenzotrifluoride (0.338 g, 1.5 mmol) and 4-(5,6-dihydropyrrolo[3,2,1-*ij*]quinolin-2-yl)benzonitrile **2** (0.258 g, 1 mmol), **24** was obtained in 87% (0.350 g) yield as a white solid: mp 239-241 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.5 Hz, 2H), 7.61 (d, *J* = 7.9 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.48 (d, *J* = 8.5 Hz, 2H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.18 (t, *J* = 7.9 Hz, 1H), 7.10 (d, *J* = 7.9 Hz, 1H), 4.14 (t, *J* = 5.7 Hz, 2H), 3.12 (t, *J* = 5.1 Hz, 2H), 2.30 (quint., *J* = 5.7 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.9, 136.3, 134.9, 134.4, 132.5, 131.3, 129.9, 128.0 (q, *J* = 32.4 Hz), 125.6 (q, *J* = 3.7 Hz), 124.8, 124.6 (q, *J* = 271.8 Hz), 122.6, 121.3, 120.5, 118.6, 117.0, 114.9, 111.9, 43.6, 25.1, 23.0.

Elemental analysis: calcd (%) for $C_{25}H_{17}F_3N_2$ (402.42): C 74.62, H 4.26; found: C 74.39, H 4.36.

4-(1-(3,5-Bis(trifluoromethyl)phenyl)-5,6-dihydropyrrolo[3,2,1-*ij*]quinolin-2-yl)benzonitrile (25):

From 1,3-bis(trifluoromethyl)-5-bromobenzobenzene (0.440 g, 1.5 mmol) and 4-(5,6-dihydropyrrolo[3,2,1-*ij*]quinolin-2-yl)benzonitrile **2** (0.258 g, 1 mmol), **25** was obtained in 73% (0.343 g) yield as a white solid: mp 209-211 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74-7.67 (m, 5H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 8.5 Hz, 2H), 7.18 (t, *J* = 7.4 Hz, 1H), 7.10 (d, *J* = 7.2 Hz, 1H), 4.11 (t, *J* = 5.7 Hz, 2H), 3.09 (t, *J* = 5.1 Hz, 2H), 2.28 (quint., *J* = 5.7 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.4, 135.6, 134.9, 134.8, 132.7, 131.9 (q, *J* = 33.0 Hz), 131.3, 129.4, 124.4, 123.2 (q, *J* = 272.5 Hz), 122.8, 121.8, 120.8, 119.4 (q, *J* = 4.0 Hz), 118.4, 116.5, 113.2, 112.4, 43.7, 25.0, 23.0.

Elemental analysis: calcd (%) for $C_{26}H_{16}F_6N_2$ (470.42): C 66.38, H 3.43; found: C 66.20, H 3.54.

2-(2-(4-Cyanophenyl)-5,6-dihydropyrrolo[3,2,1-*ij*]quinolin-1-yl)benzonitrile (26):

From 2-bromobenzonitrile (0.272 g, 1.5 mmol) and 4-(5,6-dihydropyrrolo[3,2,1-*ij*]quinolin-2-yl)benzonitrile **2** (0.258 g, 1 mmol), **26** was obtained in 82% (0.294 g) yield as a white solid: mp 195-197 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66-7.53 (m, 5H), 7.41-7.34 (m, 4H), 7.13 (t, *J* = 7.2 Hz, 1H), 7.06 (d, *J* = 7.2 Hz, 1H), 4.31-4.18 (m, 1H), 4.18-4.05 (m, 1H), 3.14-3.05 (m, 2H), 2.40-2.27 (m, 1H), 2.27-2.21 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 139.1, 136.0, 135.5, 134.8, 133.8, 132.8, 132.4, 132.2, 131.1, 127.1, 125.3, 122.6, 121.3, 120.5, 118.7, 118.6, 117.0, 113.6, 112.6, 111.7, 73.9, 25.0, 23.1.

Elemental analysis: calcd (%) for $C_{25}H_{17}N_3$ (359.43): C 83.54, H 4.77; found: C 83.31, H 4.40.

5,6-Dihydrodibenzo[a,c]pyrido[3,2,1-*jk*]carbazole-10-carbonitrile (27):

From 1,2-dibromobenzene (0.354 g, 1.5 mmol) and 4-(5,6-dihydropyrrolo[3,2,1-*ij*]quinolin-2-yl)benzonitrile **2** (0.258 g, 1 mmol), **27** was obtained in 62% (0.206 g) yield as a yellow solid: mp 262-264 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.02 (s, 1H), 8.78 (d, *J* = 8.1 Hz, 1H), 8.60 (d, *J* = 8.3 Hz, 1H), 8.53 (d, *J* = 8.5 Hz, 1H), 8.34 (d, *J* = 8.1 Hz, 1H), 7.78 (t, *J* = 7.9 Hz, 1H), 7.73 (d, *J* = 8.5 Hz, 1H), 7.60 (t, *J* = 7.9 Hz, 1H), 7.33 (t, *J* = 7.8 Hz, 1H), 7.24 (d, *J* = 7.0 Hz, 1H), 4.77 (t, *J* = 5.7 Hz, 2H), 3.12 (t, *J* = 5.1 Hz, 2H), 2.36 (quint., *J* = 5.7 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.5, 132.2, 130.6, 130.1, 129.2, 128.5, 127.6, 126.2, 125.6, 124.4, 124.1, 123.5, 123.4, 122.8, 122.3, 121.2, 120.9, 120.0, 119.8, 115.9, 108.3, 46.8, 25.1, 23.7.

Elemental analysis: calcd (%) for $C_{24}H_{16}N_2$ (332.41): C 86.72, H 4.85; found: C 86.49, H 4.98.

(5,6-Dihydrodibenzo[*a*,*c*]pyrido[3,2,1-*jk*]carbazol-10-yl)(phenyl)methanone (28):

From 1,2-dibromobenzene (0.354 g, 1.5 mmol) and (4-(5,6-dihydropyrrolo[3,2,1-*ij*]quinolin-2-yl)phenyl)(phenyl)methanone **5**

(0.337 g, 1 mmol), **28** was obtained in 55% (0.226 g) yield as a yellow solid: mp 126-128 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.30 (s, 1H), 8.85 (d, *J* = 7.8 Hz, 1H), 8.74-8.67 (m, 2H), 8.40 (d, *J* = 8.1 Hz, 1H), 8.12 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.95 (d, *J* = 7.9 Hz, 2H), 7.79 (t, *J* = 7.8 Hz, 1H), 7.68 (t, *J* = 7.9 Hz, 1H), 7.63-7.53 (m, 3H), 7.34 (d, *J* = 7.2 Hz, 1H), 7.28-7.21 (m, 1H), 4.96 (t, *J* = 5.7 Hz, 2H), 3.17 (t, *J* = 5.1 Hz, 2H), 2.42 (quint., *J* = 5.7 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 196.7, 138.2, 137.5, 133.7, 133.0, 132.5, 130.6, 130.3, 129.9, 128.6, 127.9, 127.3, 127.0, 126.9, 126.7, 124.1, 124.0, 123.7, 122.9, 122.8, 121.9, 121.5, 120.7, 119.9, 115.5, 46.9, 25.2, 23.8.

Elemental analysis: calcd (%) for $C_{30}H_{21}NO$ (411.50): C 87.56, H 5.14; found: C 87.39, H 4.95.

13,14-Dihydrobenzo[*c*]dipyrido[4,3-a:3',2',1'-*jk*]carbazole (29):

From 1,2-dibromobenzene (0.354 g, 1.5 mmol) and 2-(pyridin-4-yl)-5,6-dihydropyrrolo[3,2,1-*ij*]quinoline **17** (0.234 g, 1 mmol), **29** was obtained in 60% (0.185 g) yield as a yellow solid: mp 239-241 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.16 (bs, 1H), 8.90-8.79 (m, 2H), 8.77 (bs, 1H), 8.42-8.32 (m, 2H), 7.80 (t, *J* = 7.6 Hz, 1H), 7.65 (t, *J* = 7.6 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.26 (d, *J* = 7.0 Hz, 1H), 4.91 (t, *J* = 5.7 Hz, 2H), 3.17 (t, *J* = 5.1 Hz, 2H), 2.43 (quint., *J* = 5.7 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 147.6, 144.6, 137.6, 131.1, 130.6, 128.2, 125.6, 124.6, 124.1, 122.9, 122.8, 122.4, 121.2, 120.9, 120.1, 116.7, 46.4, 25.0, 23.6.

Elemental analysis: calcd (%) for $C_{22}H_{16}N_2$ (308.38): C 85.69, H 5.23; found: C 85.50, H 4.96.

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Chapter 3:

Pd-catalyzed direct arylations of heteroarenes with polyfluoroalkoxy-substituted bromobenzenes

Chapter 3

Pd-catalyzed direct arylations of heteroarenes with polyfluoroalkoxy-substituted bromobenzenes

3.1 Introduction

Many important drugs contain a (polyfluoroalkoxy)benzene unit (Fig. 3.1). For example, Sonidegib is an anticancer agent for treating basal-cell carcinoma, Lumacaftor is employed to treat Mucoviscidose. Difamilast is a topical, selective, nonsteroidal PDE4 inhibitor developed for the treatment of atopic dermatitis.[1] Therefore, the development of simple procedures allowing to have access to polyfluoroalkoxy-substituted benzene derivatives using inexpensive reagents in a few steps is of great interest to researchers working in the field of pharmaceutical chemistry.

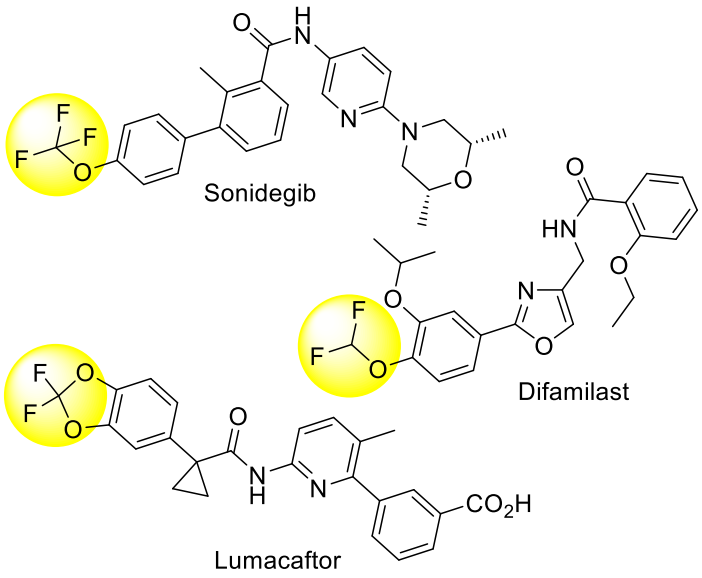
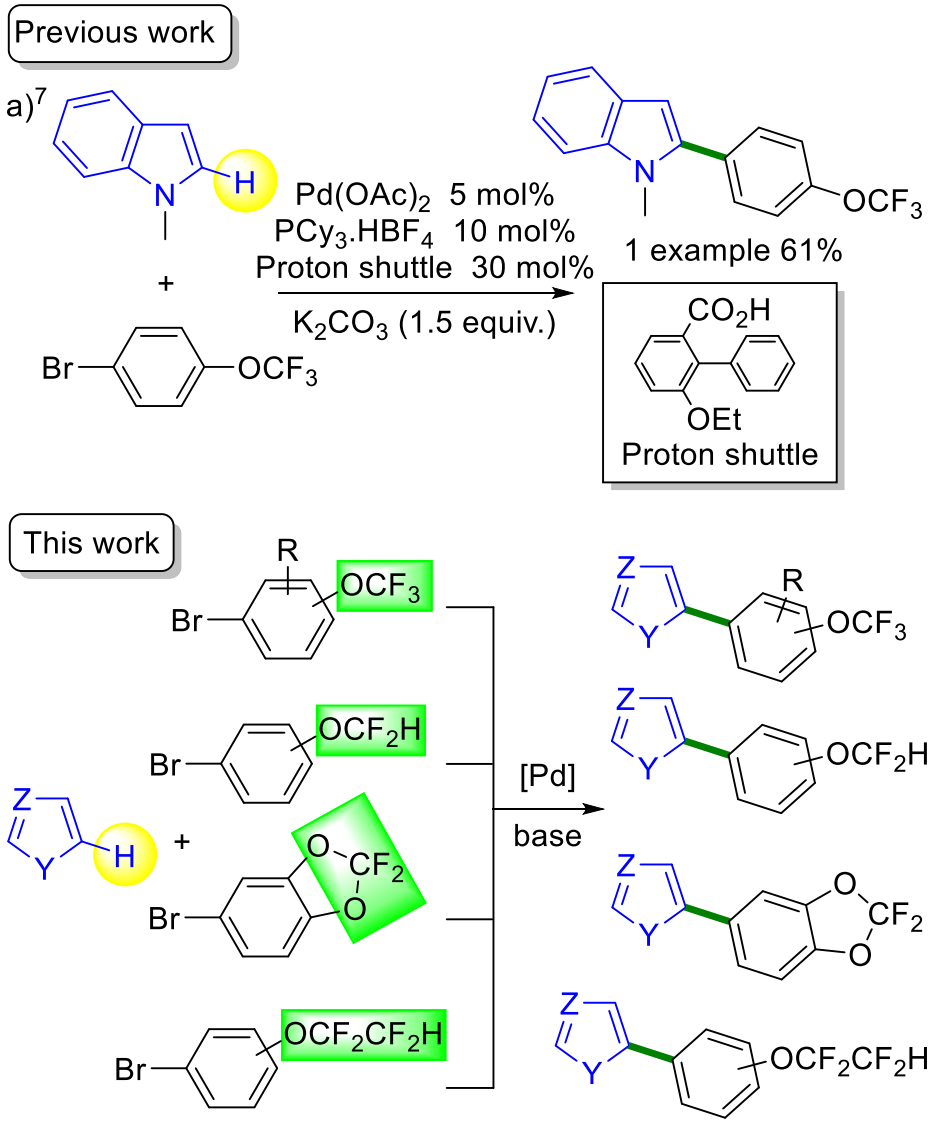


Figure 3.1. Selected examples of drugs containing a di- or a tri-fluoroalkoxybenzene unit

In 1985, Ohta and co-workers reported the arylation of heteroarenes *via* the functionnalization of C-H bonds using aryl halides as aryl sources and Pd-catalysts.[2] Since these seminal results, the so-called "direct arylation" has been demonstrated to be an extremely effective method for the synthesis of arylated heteroarenes.[3,4] For such arylations, a wide variety of aryl halides have been employed. However, so far only a few examples using halophenols have been described and in most cases, expensive bases such as silver salts were used or low yields were obtained.[5] In addition, iodo- and bromo-phenols are in several cases not easy to handle because they generally have very unpleasant odors. Moreover, the transformation of phenols into di- or tri-methoxybromobenzenes is a tedious reaction as it employs expensive difluoromethyl sources such as trimethyl(bromodifluoromethyl)silane,[6a] difluorobromoacetic acid,[6b] diethyl bromodifluoromethylphosphonate,[6c] or trifluoromethyl sources such as 2'-(trifluoromethoxy)[1,1'-biphenyl]-2-diazonium,[6d] or trimethylsilyltrifluoromethane,[6e] and often affords the desired products in moderate yields.

Therefore, the direct use of (polyfluoroalkoxy)bromobenzene derivatives for the synthesis of heteroarenes bearing (polyfluoroalkoxy)benzene units has potential for pharmaceutical chemistry. To the best of our knowledge, the Pd-catalyzed direct arylations of heteroarenes by (difluoromethoxy)bromobenzenes, 2- and 3-(trifluoromethoxy)bromobenzenes or (polyfluoroethoxy)benzenes has not been reported yet; whereas only one example using 1-bromo-4-(trifluoromethoxy)benzene has been described (Scheme 3.1, top).[7] This coupling reaction was performed using 5 mol% $Pd(OAc)_2$ and 10 mol% PCy_3 as catalyst system in the presence of a 2-arylbenzoic acid (30 mol%) as proton shuttle. In most cases, for such reactions, the more reactive 1-iodo-4-(trifluoromethoxy)benzene was used, or a high loading of an expensive ligand had to be employed.[8,9]

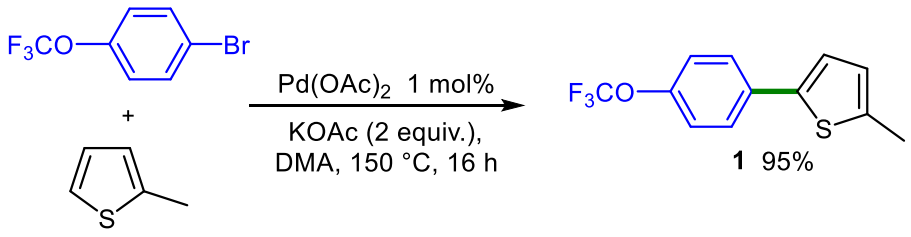
Herein, we report on the reactivity of *o*/*m*/*p* polyfluoromethoxy-substituted bromobenzenes and also a difluorobenzo[*d*][1,3]dioxoles and a (tetrafluoroethoxy) benzene in Pd-catalyzed direct arylation of heteroaromatics (Scheme 3.1, bottom).



Scheme 3.1. Pd-catalyzed direct arylations of heteroarenes by di-, tri- and tetra-(fluoro)alkoxy-substituted bromobenzenes

3.2 Results and discussions

Using reaction conditions similar to those employed with other aryl bromides,[10] we first examined the reactivity of 2-methylthiophene[11] (1.5 equiv.) with 1-bromo-4-(trifluoromethoxy)benzene (1 equiv.) (Scheme 3.2). In the presence of 1 mol% $PdCl(C_3H_5)(dppb)$ catalyst with KOAc as the base in DMA at 150 °C, the expected C5-arylated thiophene **1** was regioselectively obtained in 93% yield and a complete conversion of the aryl bromide was observed. The use of phosphine-free catalyst $Pd(OAc)_2$ (1 mol%) also afforded **1** in a very high yield of 95%. The use of lower reaction temperatures (120 or 100 °C) gave the product **1** in similar yields (94% and 92%), and at 80 °C, **1** was obtained in only 77% yield due to a partial conversion of the aryl bromide. Conversely, very low yields in **1** were obtained using diethyl carbonate, cyclopentyl methyl ether or pentan-1-ol as the solvents due to poor conversions of the aryl bromide.

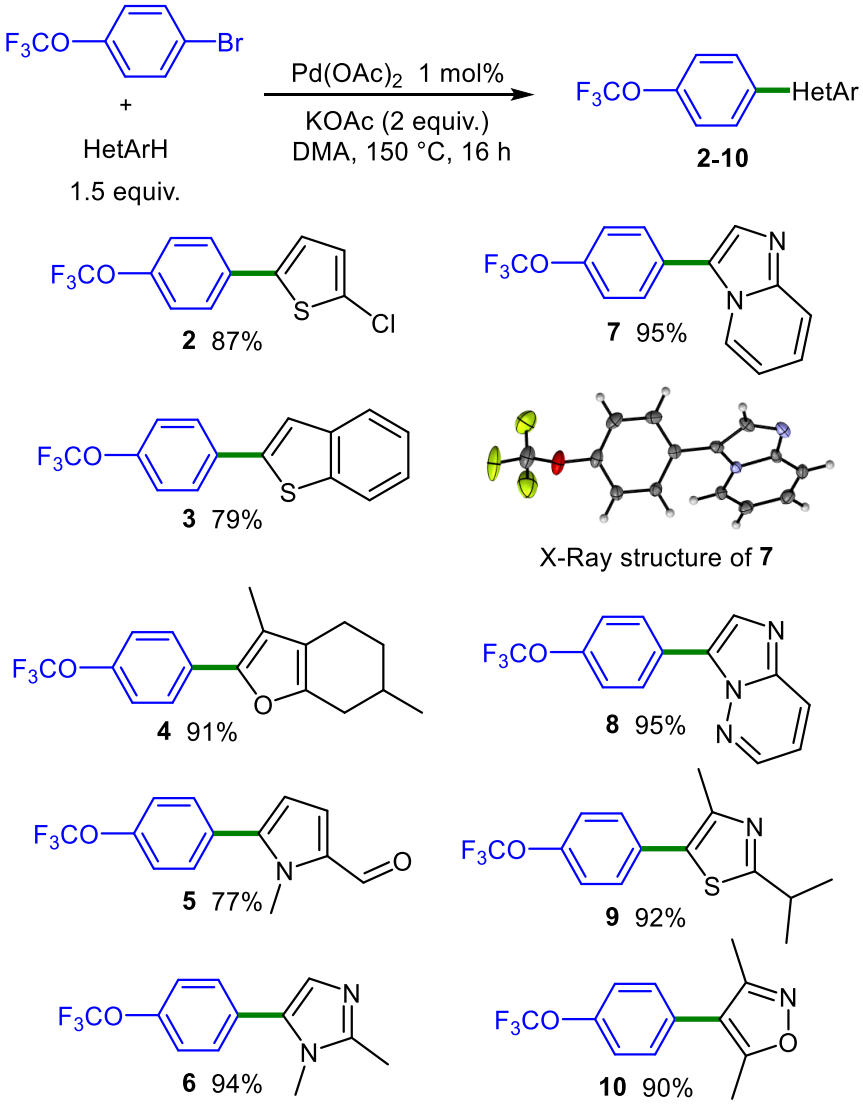


Variation to above conditions	Yield (%)
$PdCl(C_3H_5)(dppb)$ 1 mol%	93
CsOAc	85 (conv. 90%)
120 °C	94
100 °C	92
80 °C	77
diethyl carbonate	8 (conv. 12%)
cyclopentyl methyl ether	6 (conv. <10%)
pentan-1-ol	2 (conv. <10%)

Scheme 3.2. Direct arylation of 2-methylthiophene using 1-bromo-4-(trifluoromethoxy)benzene.

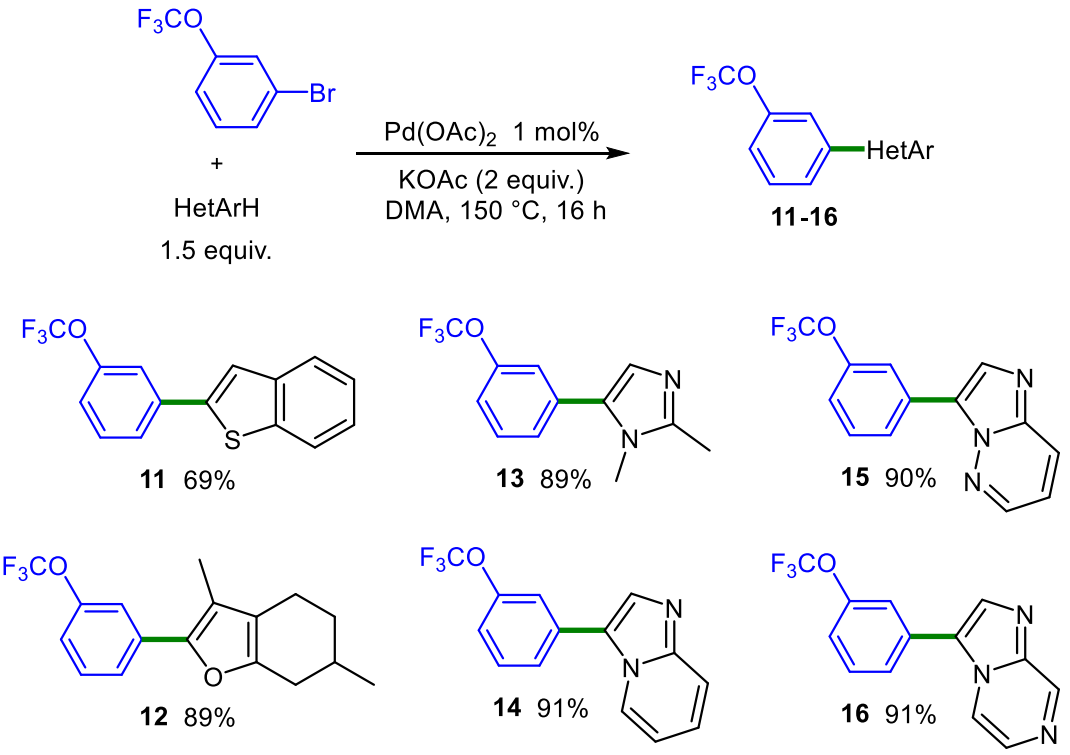
Then, a set of heteroarenes[12] was reacted with 1-bromo-4-(trifluoromethoxy) benzene using 1 mol% $Pd(OAc)_2$ with KOAc in DMA (Scheme 3.3) With

2-chlorothiophene and benzothiophene, the desired products **2** and **3** were obtained in 87% and 79% yield, respectively. 2-Formylpyrrole and 1,2-dimethylimidazole afforded the C5-arylated heteroarenes **5** and **6** in 77% and 94% yield, respectively. The arylation of imidazo[1,2-*a*]pyridine and imidazo[1,2-*b*] pyridazine, which are important units in pharmaceutical chemistry, with 1-bromo-4-(trifluoromethoxy)benz -ene was also successful giving rise to products **7** and **8** in almost quantitative yields. The structure of **7** was confirmed by X-ray analysis.[13] Finally, a thiazole derivative was arylated at C5-position and an isoxazole at C4-position affording the products **9** and **10** in 92% and 90% yield, respectively.



Scheme 3.3. Direct arylations of a set of heteroarenes with 1-bromo-4-(trifluoromethoxy)benzene.

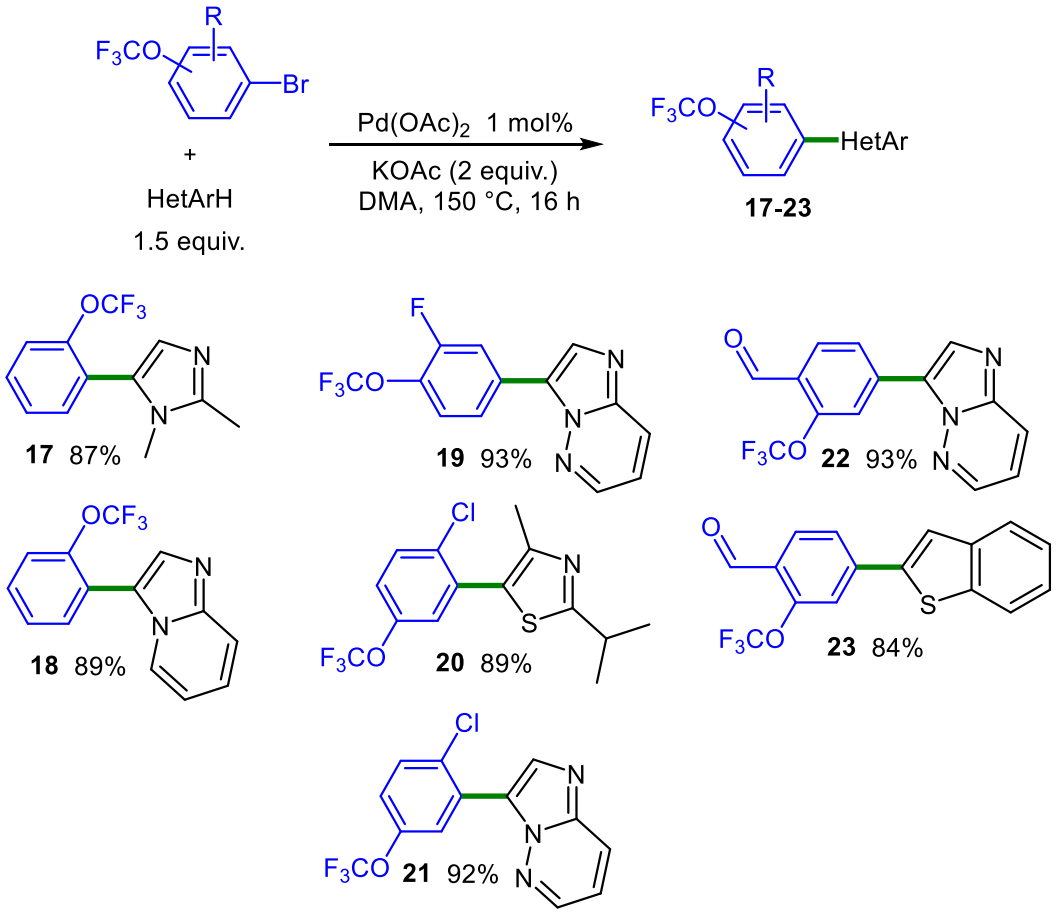
Then, the behavior of 3-bromo and 2-bromo substituted (trifluoromethoxy)benzenes was investigated (Scheme 3.4). The reaction of 1-bromo-3-(trifluoromethoxy) benzene with benzothiophene, menthofuran and 1,2-dimethylimidazole gave the expected products **11**-**13** in 69-89% yields. Imidazo[1,2-*a*]pyridine, imidazo[1,2-*b*]pyridazine and imidazo[1,2-*a*]pyrazine also reacted nicely with this aryl bromide affording the products **14**-**16** in 90-91% yields.



Scheme 3.4. Direct arylations of a set of heteroarenes with 1-bromo-3-(trifluoromethoxy)benzene.

A minor influence of the steric hindrance on the reaction was observed, and the coupling of 1-bromo-2-(trifluoromethoxy)benzene with 1,2-dimethylimidazole and imidazo[1,2-*a*]pyridine gave the products **17** and **18** in similar yields than for the reaction with the *meta*-bromo substituted (trifluoromethoxy)benzene (Scheme 3.5). The influence or a few additional substituents on the bromo(trifluoromethoxy) benzenes was also studied. 1-Bromo-3-fluoro-4-(trifluoromethoxy)benzene using imidazo[1,2-*b*]pyridazine as coupling partner delivered the product **19** in 93% yield. A chloro-substituent was also tolerated, providing the products **20** and **21** in very high

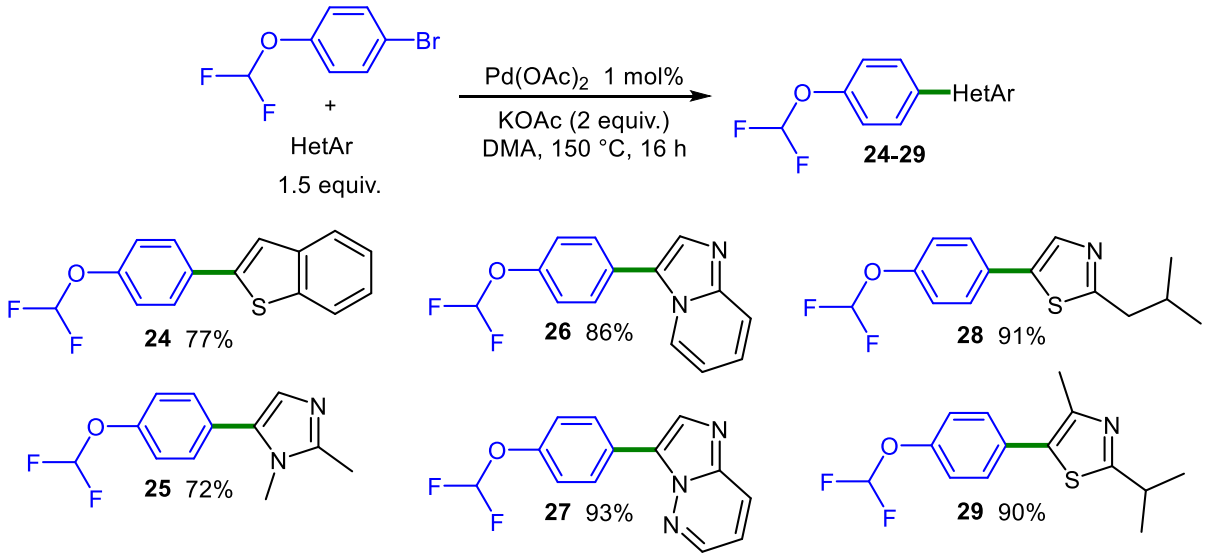
yields without cleavage of the C-Cl bond. 4-Bromo-2-(trifluoromethoxy) benzaldehyde also reacted nicely giving rise to the compounds **22** and **23** in 93% and 84% yield, respectively.



Scheme 3.5. Direct arylations of a set of heteroarenes with 1-bromo-2-(trifluoromethoxy)benzene or functionalized bromo(trifluoromethoxy)benzenes.

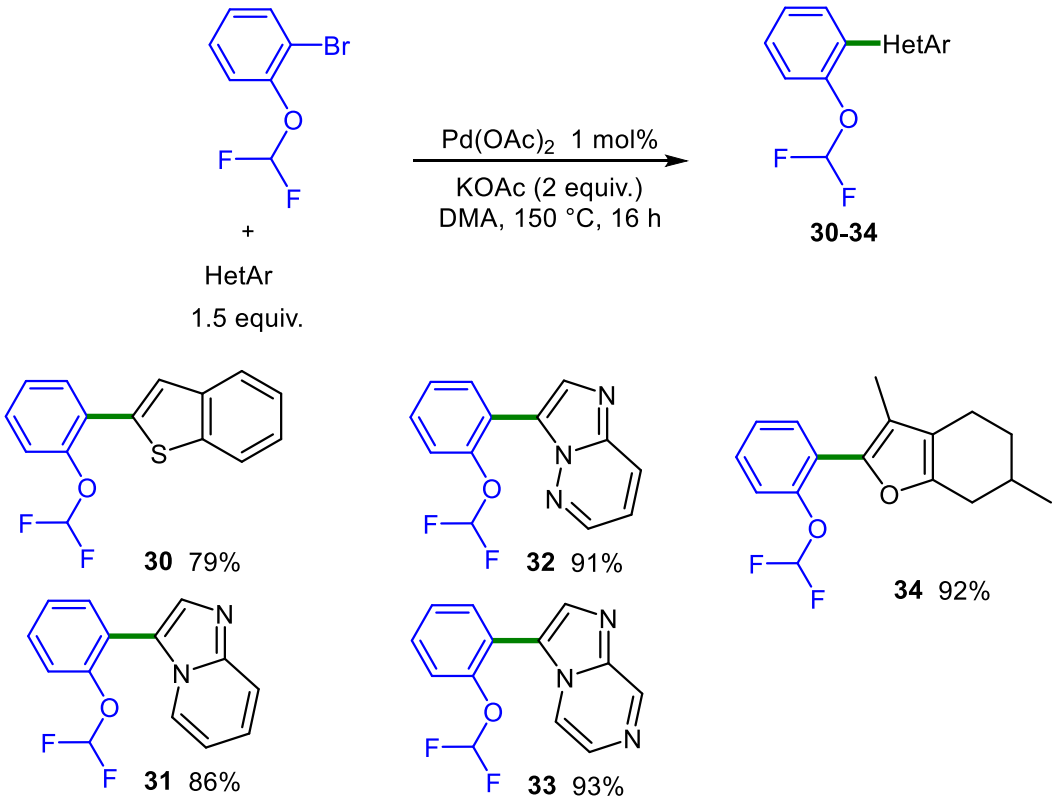
The reactivity of bromo-substituted (difluoromethoxy)benzenes in direct arylation of heteroaromatics was also studied (Scheme 3.6). Again, the use of only 1 mol% $Pd(OAc)_2$ catalyst promoted very efficiently such reactions. From benzothiophene and 1-bromo-4-(difluoromethoxy)benzene, the C2-arylated benzothiophene **24** was regioselectively obtained in 77% yield. The nitrogen containing heteroaromatics 1,2-dimethylimidazole, imidazo[1,2-*a*]pyridine and imidazo[1,2-*b*]pyridazine afforded the products **25-27** in 72-93% yields. The reactivity of two thiazoles

derivatives was also examined. In both cases, the C5-arylated thiazoles **28** and **29** were obtained in very high yields.



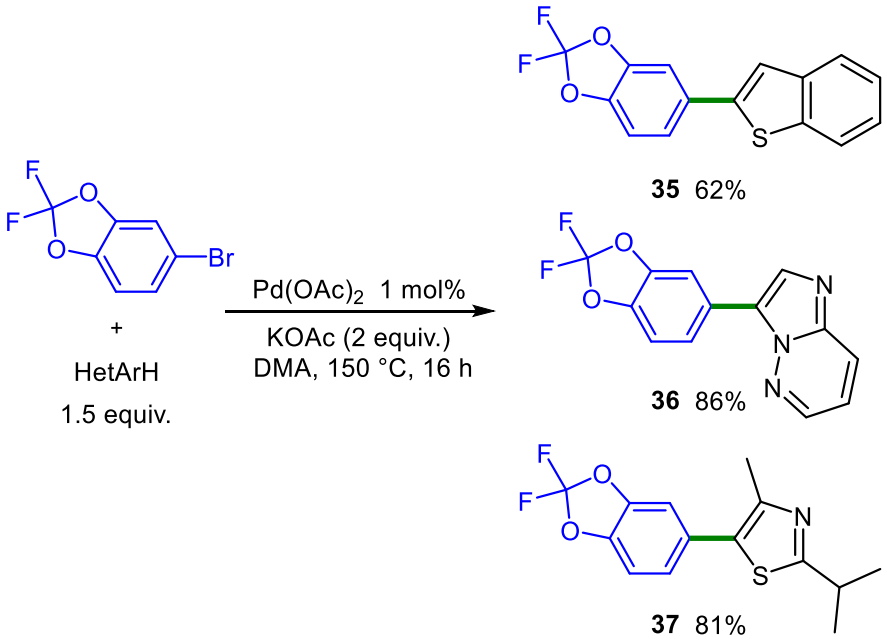
Scheme 3.6. Direct arylations of a set of heteroarenes with 1-bromo-4-(difluoromethoxy)benzene.

The more sterically hindered 1-bromo-2-(difluoromethoxy)benzene exhibit a similar reactivity than 1-bromo-4-(difluoromethoxy)benzene (Scheme 3.7). Its coupling with benzothiophene, imidazo[1,2-*a*]pyridine, imidazo[1,2-*b*]pyridazine, imidazo [1,2-*a*]pyrazine and menthofuran gave the products **30**-**34** in 79-93% yields.



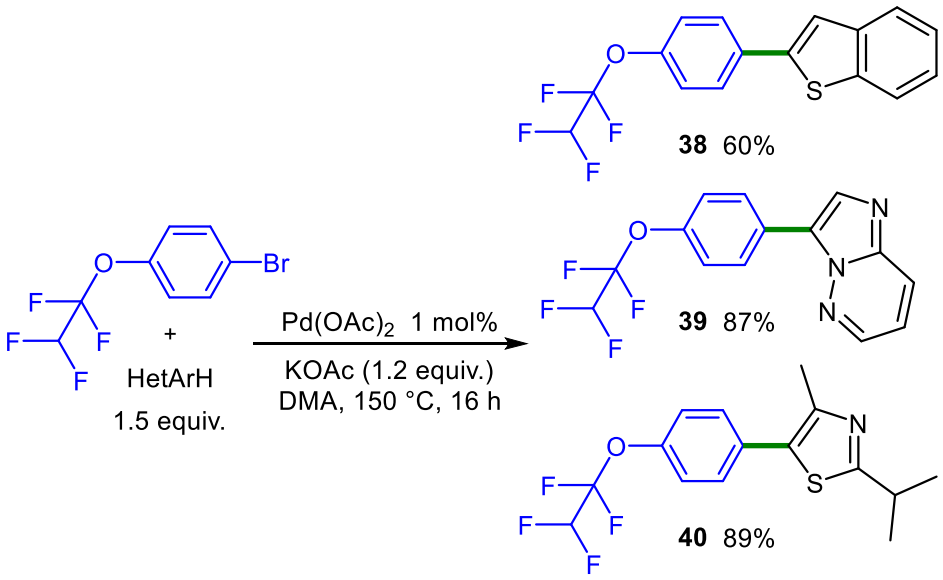
Scheme 3.7. Direct arylations of a set of heteroarenes with 1-bromo-2-(difluoromethoxy)benzene.

The introduction of a difluorobenzo[*d*][1,3]dioxole unit on heteroarenes is particularly interesting because of their presence on important pharmaceutical compounds such as Lumacaftor (see fig. 3.1). The reactivity of 5-bromo-2,2-difluorobenzo [*d*][1,3]dioxole in direct arylation is described in the scheme 3.8. Again, the reactions proceeded nicely in the presence of 1 mol% $Pd(OAc)_2$ and KOAc, giving rise to the target products **35-37** in good to high yields. No decomposition of the dioxolane moiety was observed in the course of these couplings.



Scheme 3.8. Direct arylations of a set of heteroarenes with 5-bromo-2,2-difluorobenzo[*d*][1,3]dioxole.

Finally, the reactivity of 1-bromo-4-(1,1,2,2-tetrafluoroethoxy)benzene in direct arylation was evaluated (Scheme 3.9). Again, in the presence of benzothiophene, imidazo[1,2-*b*]pyridazine and a thiazole derivative, the target products **38**-**40** were isolated in 60-89% yield. No cleavage of the quite acidic C-H bond of the tetrafluoroethoxy unit was observed, although such deprotonations have already been observed in the presence of a strong base.[14]



Scheme 3.9. Direct arylations of a set of heteroarenes with 1-bromo-4-(1,1,2,2-tetrafluoroethoxy)benzene.

3.3 Conclusion

In summary, di- and tri-fluoromethoxy substituents at *o*/*m*/*p* positions on bromobenzenes are well tolerated in Pd-catalyzed direct arylations. Phosphine-free $Pd(OAc)_2$ catalyst with KOAc base was successfully employed to promote the direct arylation of a wide range of heteroaromatics with these fluoro-containing aryl bromides. High yields in the arylated heteroaromatics were obtained in most cases using (benzo)thiophenes, thiazoles, imidazoles, pyrroloquinolines, imidazopyridines, isoxazoles, furans and pyrroles. Difluorobenzo[*d*][1,3]dioxole and 1,1,2,2-tetrafluoroe thoxy)benzene units were also successfully introduced on heteroaromatics under the same reaction conditions. To our knowledge, these are the first examples of direct arylations of heteroaromatics using (difluoromethoxy)benzenes, difluorobenzo [*d*][1,3]dioxoles, 2- and 3-(trifluoromethoxy)benzenes and tetrafluoroethoxybenzenes. The use of these polyfluoroalkoxy-substituted bromobenzenes in direct arylation is certainly more attractive than the use of bromophenols, as they display a much higher reactivity, as many of them are commercially available, and as there is no need to introduce a polyfluoroalkyl group to obtain the (polyfluoroalkoxy)benzenes. For these reasons, this procedure provides an economically viable and environmentally very attractive access to heteroarenes bearing a (polyfluoroalkoxy)benzene unit.

3.4 Experimental details

Typical experiment for coupling reactions: The reaction of the aryl bromide (1 mmol), heteroaromatic (1.5 mmol) and KOAc (0.196 g, 2 mmol) in the presence of $Pd(OAc)_2$ (0.0024 g, 1 mol%) in DMA under argon at 150 °C during 16 h, affords the corresponding product after cooling, evaporation of the solvent and filtration on silica gel (pentane/ether).

2-Methyl-5-(4-(trifluoromethoxy)phenyl)thiophene (1):

1-Bromo-4-(trifluoromethoxy)benzene (0.241 g, 1 mmol) and 2-methylthiophene (0.147 g, 1.5 mmol) affords **1** in 95% (0.245 g) yield as a yellow solid: mp 105-107 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, *J* = 8.5 Hz, 2H), 7.20 (d, *J* = 8.5 Hz, 2H), 7.08 (d, *J* = 3.5 Hz, 1H), 6.75-6.72 (m, 1H), 2.51 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.2 (q, *J* = 1.8 Hz), 140.5, 140.4, 133.7, 126.8, 126.5, 123.7, 121.5 (q, *J* = 1.0 Hz), 120.5 (q, *J* = 257.0 Hz), 15.6.

LRMS calcd for M^+ $C_{12}H_9F_3OS$ 258, found 258.

2-Chloro-5-(4-(trifluoromethoxy)phenyl)thiophene (2):

1-Bromo-4-(trifluoromethoxy)benzene (0.241 g, 1 mmol) and 2-chlorothiophene (0.178 g, 1.5 mmol) affords **2** in 87% (0.243 g) yield as a yellow solid: mp 63-65 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, *J* = 8.5 Hz, 2H), 7.22 (d, *J* = 8.5 Hz, 2H), 7.04 (d, *J* = 3.7 Hz, 1H), 6.89 (d, *J* = 3.7 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.8 (q, *J* = 1.8 Hz), 141.4, 132.6, 130.0, 127.4, 127.0, 123.0, 121.7 (q, *J* = 1.0 Hz), 120.6 (q, *J* = 257.5 Hz).

LRMS calcd for M^+ $C_{11}H_6ClF_3OS$ 278, found 278.

2-(4-(Trifluoromethoxy)phenyl)benzo[*b*]thiophene (3):

1-Bromo-4-(trifluoromethoxy)benzene (0.241 g, 1 mmol) and benzothiophene (0.201 g, 1.5 mmol) affords **3** in 79% (0.232 g) yield as a white solid: mp 185-187 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 8.2 Hz, 1H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.73 (d, *J* = 8.5 Hz, 2H), 7.52 (s, 1H), 7.38 (t, *J* = 7.8 Hz, 1H), 7.34 (t, *J* = 7.8 Hz, 1H), 7.30 (d, *J* = 8.5 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.2 (q, *J* = 1.8 Hz), 142.6, 140.7, 139.7, 133.2, 128.0, 124.8, 124.7, 123.9, 122.4, 121.6 (q, *J* = 1.0 Hz), 120.7 (q, *J* = 257.5 Hz), 120.3.

LRMS calcd for M^+ $C_{15}H_9F_3OS$ 294, found 294.

3,6-Dimethyl-2-(4-(trifluoromethoxy)phenyl)-4,5,6,7-tetrahydrobenzofuran (4):

1-Bromo-4-(trifluoromethoxy)benzene (0.241 g, 1 mmol) and menthofuran (0.225 g, 1.5 mmol) affords **4** in 91% (0.282 g) yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, *J* = 8.5 Hz, 2H), 7.23 (d, *J* = 8.5 Hz, 2H), 2.74 (dd, *J* = 16.3, 6.3 Hz, 1H), 2.50-2.37 (m, 2H), 2.30-2.21 (m, 1H), 2.16 (s, 3H), 2.00-1.83 (m, 2H), 1.48-1.35 (m, 1H), 1.12 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.1, 147.3 (q, *J* = 1.8 Hz), 145.7, 131.4, 126.1, 121.2, 120.1 (q, *J* = 1.0 Hz), 120.7 (q, *J* = 257.5 Hz), 116.9, 31.5, 31.4, 29.8, 21.6, 20.2, 9.9.

LRMS calcd for M^+ $C_{17}H_{17}F_3O_2$ 310, found 310.

1-Methyl-5-(4-(trifluoromethoxy)phenyl)-pyrrole-2-carbaldehyde (5):

1-Bromo-4-(trifluoromethoxy)benzene (0.241 g, 1 mmol) and 2-formylpyrrole (0.142 g, 1.5 mmol) affords **5** in 77% (0.207 g) yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.59 (s, 1H), 7.45 (d, *J* = 8.5 Hz, 2H), 7.31 (d, *J* = 8.5 Hz, 2H), 6.97 (d, *J* = 4.0 Hz, 1H), 6.30 (d, *J* = 4.0 Hz, 1H), 3.92 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 179.9, 149.5 (q, *J* = 1.8 Hz), 142.7, 133.4, 130.8, 129.9, 124.5, 121.2 (q, *J* = 1.0 Hz), 120.2 (q, *J* = 257.7 Hz), 111.1, 34.4.

LRMS calcd for M^+ $C_{13}H_{10}F_3NO_2$ 269, found 269.

1,2-Dimethyl-5-(4-(trifluoromethoxy)phenyl)imidazole (6):

1-Bromo-4-(trifluoromethoxy)benzene (0.241 g, 1 mmol) and 1,2-dimethylimidazole (0.144 g, 1.5 mmol) affords **6** in 94% (0.241 g) yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, *J* = 8.5 Hz, 2H), 7.28 (d, *J* = 8.5 Hz, 2H), 6.96 (s, 1H), 3.52 (s, 3H), 2.45 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.7 (q, *J* = 1.8 Hz), 146.5, 132.3, 130.0, 129.4, 126.4, 121.3 (q, *J* = 1.0 Hz), 120.6 (q, *J* = 257.5 Hz), 31.4, 13.7.

LRMS calcd for M^+ $C_{12}H_{11}F_3N_2O$ 256, found 256.

3-(4-(Trifluoromethoxy)phenyl)imidazo[1,2-*a*]pyridine (7):[9d]

1-Bromo-4-(trifluoromethoxy)benzene (0.241 g, 1 mmol) and imidazo[1,2-*a*]pyridine (0.177 g, 1.5 mmol) affords **7** in 95% (0.264 g) yield as a white solid: mp 101-103 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, *J* = 7.0 Hz, 1H), 7.69 (s, 1H), 7.67 (d, *J* = 7.0 Hz, 1H), 7.57 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.21 (dd, *J* = 6.9, 7.8 Hz, 1H), 6.82 (t, *J* = 6.9 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.9 (q, *J* = 1.8 Hz), 146.4, 132.9, 129.5, 128.1, 124.6, 124.4, 123.1, 121.8 (q, *J* = 1.0 Hz), 120.3 (q, *J* = 257.5 Hz), 118.4, 112.9.

LRMS calcd for M^+ $C_{14}H_9F_3N_2O$ 278, found 278.

3-(4-(Trifluoromethoxy)phenyl)imidazo[1,2-*b*]pyridazine (8):

1-Bromo-4-(trifluoromethoxy)benzene (0.241 g, 1 mmol) and imidazo[1,2-*b*]pyridazine (0.179 g, 1.5 mmol) affords **8** in 95% (0.265 g) yield as a yellow solid: mp 93-95 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 (d, *J* = 4.2 Hz, 1H), 8.09 (d, *J* = 8.5 Hz, 2H), 8.04 (s, 1H), 8.03 (dd, *J* = 9.1, 0.9 Hz, 1H), 7.33 (d, *J* = 8.5 Hz, 2H), 7.07 (dd, *J* = 9.1, 4.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.7 (q, *J* = 1.8 Hz), 143.1, 140.4, 133.1, 128.3, 127.4, 126.3, 121.3 (q, *J* = 0.8 Hz), 120.4 (q, *J* = 257.5 Hz), 116.6.

LRMS calcd for M^+ $C_{13}H_8F_3N_3O$ 279, found 279.

2-Isopropyl-4-methyl-5-(4-(trifluoromethoxy)phenyl)thiazole (9):

1-Bromo-4-(trifluoromethoxy)benzene (0.241 g, 1 mmol) and 2-isopropyl-4-methylthiazole (0.212 g, 1.5 mmol) affords **9** in 92% (0.277 g) yield as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8.5 Hz, 2H), 7.25 (d, *J* = 8.5 Hz, 2H), 3.27 (sept., *J* = 7.6 Hz, 1H), 2.44 (s, 3H), 1.40 (d, *J* = 7.6 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.9, 148.6 (q, *J* = 1.8 Hz), 147.5, 131.5, 130.6, 129.0, 121.2 (q, *J* = 1.0 Hz), 120.5 (q, *J* = 257.4 Hz), 33.5, 23.3, 16.2.

LRMS calcd for M^+ $C_{14}H_{14}F_3NOS$ 301, found 301.

3,5-Dimethyl-4-(4-(trifluoromethoxy)phenyl)isoxazole (10):

1-Bromo-4-(trifluoromethoxy)benzene (0.241 g, 1 mmol) and 2,4-dimethylisoxazole (0.145 g, 1.5 mmol) affords **10** in 90% (0.231 g) yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (s, 4H), 2.41 (s, 3H), 2.27 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.6, 158.6, 148.7 (q, *J* = 1.8 Hz), 130.6, 129.4, 121.5 (q, *J* = 1.0 Hz), 120.4 (q, *J* = 257.4 Hz), 115.7, 11.7, 10.9.

LRMS calcd for M^+ $C_{12}H_{10}F_3NO_2$ 257, found 257.

2-(3-Trifluoromethoxy)phenyl)benzo[*b*]thiophene (11):

1-Bromo-3-(trifluoromethoxy)benzene (0.241 g, 1 mmol) and benzothiophene (0.201 g, 1.5 mmol) affords **11** in 69% (0.203 g) yield as a white solid: mp 113-115 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 8.2 Hz, 1H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.63 (d, *J* = 8.3 Hz, 1H), 7.58 (s, 1H), 7.56 (bs, 1H), 7.45 (t, *J* = 8.1 Hz, 1H), 7.40-7.32 (m, 2H), 7.20 (d, *J* = 8.3 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.9 (q, *J* = 1.8 Hz), 142.5, 140.6, 139.8, 136.5, 130.5, 125.0, 124.9, 124.0, 122.5, 120.7, 120.6 (q, *J* = 257.5 Hz), 120.5 (q, *J* = 0.8 Hz), 119.6, 119.1 (q, *J* = 0.8 Hz).

LRMS calcd for M^+ $C_{15}H_9F_3OS$ 294, found 294.

3,6-Dimethyl-2-(3-(trifluoromethoxy)phenyl)-4,5,6,7-tetrahydrobenzofuran (12):

1-Bromo-3-(trifluoromethoxy)benzene (0.241 g, 1 mmol) and menthofuran (0.225 g, 1.5 mmol) affords **12** in 89% (0.276 g) yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, *J* = 8.0 Hz, 1H), 7.47 (s, 1H), 7.38 (t, *J* = 7.7 Hz, 1H), 7.05 (d, *J* = 8.2 Hz, 1H), 2.74 (dd, *J* = 16.3, 6.3 Hz, 1H), 2.50-2.33 (m, 2H), 2.30-2.21 (m, 1H), 2.18 (s, 3H), 2.01-1.83 (m, 2H), 1.48-1.35 (m, 1H), 1.12 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.4, 149.7 (q, *J* = 1.8 Hz), 145.4, 134.5, 129.9, 123.0, 120.7 (q, *J* = 257.5 Hz), 120.3, 118.1, 117.7, 117.3, 31.5, 31.3, 29.8, 21.6, 20.1, 10.0.

LRMS calcd for M^+ $C_{17}H_{17}F_3O_2$ 310, found 310.

1,2-Dimethyl-5-(3-(trifluoromethoxy)phenyl)imidazole (13):

1-Bromo-3-(trifluoromethoxy)benzene (0.241 g, 1 mmol) and 1,2-dimethylimidazole (0.144 g, 1.5 mmol) affords **13** in 89% (0.228 g) yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (t, *J* = 7.7 Hz, 1H), 7.23 (d, *J* = 8.2 Hz, 1H), 7.17-7.10 (m, 2H), 6.93 (s, 1H), 3.48 (s, 3H), 2.38 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.4 (q, *J* = 1.8 Hz), 146.7, 132.5, 132.0, 130.1, 126.7, 126.6, 120.7, 120.6 (q, *J* = 257.4 Hz), 119.8, 31.3, 13.6.

LRMS calcd for M^+ $C_{12}H_{11}F_3N_2O$ 256, found 256.

3-(3-(Trifluoromethoxy)phenyl)imidazo[1,2-*a*]pyridine (14):

1-Bromo-3-(trifluoromethoxy)benzene (0.241 g, 1 mmol) and imidazo[1,2-*a*]pyridine (0.177 g, 1.5 mmol) affords **14** in 91% (0.253 g) yield as a white solid: mp 63-65 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (d, *J* = 7.0 Hz, 1H), 7.70 (s, 1H), 7.65 (d, *J* = 7.0 Hz, 1H), 7.55-7.43 (m, 2H), 7.39 (s, 1H), 7.26-7.21 (m, 1H), 7.20 (dd, *J* = 6.9, 7.8 Hz, 1H), 6.82 (t, *J* = 6.9 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.9 (q, *J* = 1.8 Hz), 146.5, 133.2, 131.4, 130.8, 126.1, 124.7, 124.3, 123.1, 120.5 (q, *J* = 257.5 Hz), 120.4 (q, *J* = 1.0 Hz), 120.2 (q, *J* = 1.0 Hz), 118.5, 113.1.

LRMS calcd for M^+ $C_{14}H_9F_3N_2O$ 278, found 278.

3-(3-(Trifluoromethoxy)phenyl)imidazo[1,2-*b*]pyridazine (15):

1-Bromo-3-(trifluoromethoxy)benzene (0.241 g, 1 mmol) and imidazo[1,2-*b*]pyridazine (0.179 g, 1.5 mmol) affords **15** in 90% (0.251 g) yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.44 (d, *J* = 4.2 Hz, 1H), 8.11-7.97 (m, 4H), 7.50 (t, *J* = 8.1 Hz, 1H), 7.22 (d, *J* = 8.1 Hz, 1H), 7.09 (dd, *J* = 9.1, 4.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.5 (q, *J* = 1.8 Hz), 143.0, 140.5, 133.3, 130.5, 130.0, 127.0, 126.1, 124.8, 120.6 (q, *J* = 257.5 Hz), 120.0 (q, *J* = 0.8 Hz), 119.1 (q, *J* = 0.8 Hz), 116.7.

LRMS calcd for M^+ $C_{13}H_8F_3N_3O$ 279, found 279.

3-(3-(Trifluoromethoxy)phenyl)imidazo[1,2-*a*]pyrazine (16):

1-Bromo-3-(trifluoromethoxy)benzene (0.241 g, 1 mmol) and imidazo[1,2-*a*]pyrazine (0.179 g, 1.5 mmol) affords **16** in 91% (0.254 g) yield as a yellow solid: mp 84-86 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.12 (d, *J* = 1.3 Hz, 1H), 8.19 (dd, *J* = 4.7, 1.4 Hz, 1H), 7.90 (d, *J* = 4.7 Hz, 1H), 7.87 (s, 1H), 7.57 (t, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.40 (s, 1H), 7.30 (dd, *J* = 8.2, 2.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.0, 144.8, 141.6, 135.0, 131.1, 130.4, 129.9, 126.2, 125.4, 121.3, 120.5 (q, *J* = 258.1 Hz), 120.4, 116.1.

LRMS calcd for M^+ $C_{13}H_8F_3N_3O$ 279, found 279.

1,2-Dimethyl-5-(2-(trifluoromethoxy)phenyl)imidazole (17):

1-Bromo-2-(trifluoromethoxy)benzene (0.241 g, 1 mmol) and 1,2-dimethylimidazole (0.144 g, 1.5 mmol) affords **17** in 87% (0.223 g) yield as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46-7.39 (m, 1H), 7.37-7.33 (m, 3H), 6.93 (s, 1H), 3.37 (s, 3H), 2.44 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 147.9 (q, *J* = 1.5 Hz), 146.2, 132.8, 130.0, 128.1, 127.5, 127.0, 124.3, 120.9 (q, *J* = 1.5 Hz), 120.7 (q, *J* = 257.4 Hz), 31.2, 13.8.

LRMS calcd for M^+ $C_{12}H_{11}F_3N_2O$ 256, found 256.

3-(2-(Trifluoromethoxy)phenyl)imidazo[1,2-*a*]pyridine (18):

1-Bromo-2-(trifluoromethoxy)benzene (0.241 g, 1 mmol) and imidazo[1,2-*a*]pyridine (0.177 g, 1.5 mmol) affords **18** in 89% (0.247 g) yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, *J* = 7.0 Hz, 1H), 7.68 (s, 1H), 7.64 (d, *J* = 7.0 Hz, 1H), 7.53-7.34 (m, 4H), 7.18 (dd, *J* = 6.9, 7.8 Hz, 1H), 6.76 (t, *J* = 6.9 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 147.1 (q, *J* = 1.5 Hz), 146.2, 134.1, 132.0, 130.2, 127.4, 124.6, 124.1, 122.6, 121.3 (q, *J* = 1.5 Hz), 120.4, 120.3 (q, *J* = 258.5 Hz), 118.0, 112.4.

LRMS calcd for M^+ $C_{14}H_9F_3N_2O$ 278, found 278.

3-(3-Fluoro-4-(trifluoromethoxy)phenyl)imidazo[1,2-*b*]pyridazine (19):

1-Bromo-3-fluoro-4-(trifluoromethoxy)benzene (0.259 g, 1 mmol) and imidazo[1,2-*b*]pyridazine (0.179 g, 1.5 mmol) affords **19** in 93% (0.276 g) yield as a yellow solid: mp 99-101 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 (d, *J* = 4.2 Hz, 1H), 8.12-8.05 (m, 2H), 8.03 (d, *J* = 9.1 Hz, 1H), 7.83 (d, *J* = 8.5 Hz, 1H), 7.40 (t, *J* = 8.5 Hz, 1H), 7.12 (dd, *J* = 9.1, 4.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 154.6 (d, *J* = 251.8 Hz), 143.2, 140.7, 136.7 (dq, *J* = 12.6, 2.0 Hz), 133.6, 129.2 (d, *J* = 8.0 Hz), 126.4, 126.3, 124.0 (d, *J* = 0.6 Hz), 122.7 (d, *J* = 3.7 Hz), 120.6 (qd, *J* = 259.0, 0.7 Hz), 117.0, 115.3 (d, *J* = 21.2 Hz).

LRMS calcd for M^+ $C_{13}H_7F_4N_3O$ 297, found 297.

5-(2-Chloro-5-(trifluoromethoxy)phenyl)-2-isopropyl-4-methylthiazole (20):

1-Bromo-2-chloro-5-(trifluoromethoxy)benzene (0.275 g, 1 mmol) and 2-isopropyl-4-methylthiazole (0.212 g, 1.5 mmol) affords **20** in 89% (0.299 g) yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, *J* = 8.8 Hz, 1H), 7.23 (s, 1H), 7.17 (d, *J* = 8.8 Hz, 1H), 3.28 (sept., *J* = 7.6 Hz, 1H), 2.27 (s, 3H), 1.41 (d, *J* = 7.6 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 177.4, 150.1, 147.4 (q, *J* = 2.0 Hz), 133.2, 133.0, 131.2, 125.2 (q, *J* = 1.0 Hz), 122.1 (q, *J* = 1.0 Hz), 118.7, 120.4 (q, *J* = 258.2 Hz), 33.5, 23.2, 16.0.

LRMS calcd for M^+ $C_{14}H_{13}ClF_3NOS$ 335, found 335.

3-(2-Chloro-5-(trifluoromethoxy)phenyl)imidazo[1,2-*b*]pyridazine (21):

1-Bromo-2-chloro-5-(trifluoromethoxy)benzene (0.275 g, 1 mmol) and imidazo[1,2-*b*]pyridazine (0.179 g, 1.5 mmol) affords **21** in 92% (0.289 g) yield as a yellow solid: mp 85-87 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (d, *J* = 4.2 Hz, 1H), 8.08 (s, 1H), 8.04 (dd, *J* = 9.1, 1.6 Hz, 1H), 7.65 (d, *J* = 2.7 Hz, 1H), 7.56 (d, *J* = 8.8 Hz, 1H), 7.21 (dd, *J* = 3.0, 1.2 Hz, 1H), 7.11 (dd, *J* = 9.2, 4.5 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 147.5 (q, *J* = 2.0 Hz), 143.2, 139.8, 135.3, 132.2, 131.4, 129.0, 126.2, 125.0, 124.2 (q, *J* = 0.9 Hz), 122.2 (q, *J* = 0.9 Hz), 120.4 (d, *J* = 259.0 Hz), 117.3.

LRMS calcd for M^+ $C_{13}H_7ClF_3N_3O$ 313, found 313.

4-(Imidazo[1,2-*b*]pyridazin-3-yl)-2-(trifluoromethoxy)benzaldehyde (22):

4-Bromo-2-(trifluoromethoxy)benzaldehyde (0.269 g, 1 mmol) and imidazo[1,2-*b*]pyridazine (0.179 g, 1.5 mmol) affords **22** in 92% (0.286 g) yield as a yellow solid: mp 123-125 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.32 (s, 1H), 8.47 (dd, *J* = 4.4, 1.6 Hz, 1H), 8.32-8.27 (m, 1H), 8.20 (s, 1H), 8.09 (dm, *J* = 9.1 Hz, 1H), 8.04 (dd, *J* = 9.1, 1.7 Hz, 1H), 7.99 (d, *J* = 8.2 Hz, 1H), 7.16 (dd, *J* = 9.2, 4.5 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 186.8, 151.2 (q, *J* = 2.0 Hz), 143.4, 141.5, 136.0, 134.9, 129.2, 127.0, 126.4, 125.9, 124.5, 120.5 (q, *J* = 259.2 Hz), 118.4 (q, *J* = 1.3 Hz), 117.6.

LRMS calcd for M^+ $C_{14}H_8F_3N_3O_2$ 307, found 307.

4-(Benzo[*b*]thiophen-2-yl)-2-(trifluoromethoxy)benzaldehyde (23):

4-Bromo-2-(trifluoromethoxy)benzaldehyde (0.269 g, 1 mmol) and benzothiophene (0.201 g, 1.5 mmol) affords **23** in 84% (0.270 g) yield as a yellow solid: mp 94-96 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.37 (s, 1H), 8.02 (d, *J* = 8.1 Hz, 1H), 7.89-7.82 (m, 2H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.72 (s, 1H), 7.67-7.65 (m, 1H), 7.43-7.37 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 186.9, 151.4, 141.9, 141.0, 140.3, 129.8, 127.6, 125.8, 125.3, 125.2, 124.5, 122.8, 122.6, 120.5 (q, *J* = 259.2 Hz).

LRMS calcd for M^+ $C_{16}H_9F_3O_2S$ 322, found 322.

2-(4-(Difluoromethoxy)phenyl)benzo[*b*]thiophene (24):

1-Bromo-4-(difluoromethoxy)benzene (0.223 g, 1 mmol) and benzothiophene (0.201 g, 1.5 mmol) affords **24** in 77% (0.213 g) yield as a pink solid: mp 197-199 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 8.2 Hz, 1H), 7.78 (d, *J* = 8.2 Hz, 1H), 7.71 (d, *J* = 8.5 Hz, 2H), 7.50 (s, 1H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.33 (t, *J* = 7.8 Hz, 1H), 7.19 (d, *J* = 8.5 Hz, 2H), 6.55 (t, *J* = 73.7 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 151.2 (t, *J* = 3.0 Hz), 143.0, 140.8, 139.6, 131.9, 128.0, 124.8, 124.6, 123.8, 122.4, 120.2 (t, *J* = 0.8 Hz), 119.8, 115.9 (t, *J* = 260.6 Hz).

LRMS calcd for M^+ $C_{15}H_{10}F_2OS$ 276, found 276.

5-(4-(Difluoromethoxy)phenyl)-1,2-dimethylimidazole (25):

1-Bromo-4-(difluoromethoxy)benzene (0.223 g, 1 mmol) and 1,2-dimethylimidazole (0.144 g, 1.5 mmol) affords **25** in 72% (0.171 g) yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, *J* = 8.2 Hz, 2H), 7.18 (d, *J* = 8.2 Hz, 2H), 6.94 (s, 1H), 6.55 (t, *J* = 73.7 Hz, 1H), 3.51 (s, 3H), 2.45 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.7 (t, *J* = 3.0 Hz), 146.3, 132.6, 130.2, 128.1, 126.3, 120.0 (t, *J* = 0.8 Hz), 115.9 (t, *J* = 260.5 Hz), 31.4, 13.9.

LRMS calcd for M^+ $C_{12}H_{12}F_2N_2O$ 238, found 238.

3-(4-(Difluoromethoxy)phenyl)imidazo[1,2-*a*]pyridine (26):

1-Bromo-4-(difluoromethoxy)benzene (0.223 g, 1 mmol) and imidazo[1,2-*a*]pyridine (0.177 g, 1.5 mmol) affords **26** in 86% (0.224 g) yield as a white solid: mp 87-89 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, *J* = 7.0 Hz, 1H), 7.64 (s, 1H), 7.63 (d, *J* = 7.0 Hz, 1H), 7.50 (d, *J* = 8.5 Hz, 2H), 7.25 (d, *J* = 8.5 Hz, 2H), 7.16 (dd, *J* = 6.9, 7.8 Hz, 1H), 6.77 (t, *J* = 6.9 Hz, 1H), 6.57 (t, *J* = 73.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.8 (t, *J* = 3.0 Hz), 146.2, 132.7, 129.6, 126.6, 124.6, 124.4, 123.1, 120.4 (t, *J* = 0.8 Hz), 118.3, 115.8 (t, *J* = 260.6 Hz), 112.7.

LRMS calcd for M^+ $C_{14}H_{10}F_2N_2O$ 260, found 260.

3-(4-(Difluoromethoxy)phenyl)imidazo[1,2-*b*]pyridazine (27):

1-Bromo-4-(difluoromethoxy)benzene (0.223 g, 1 mmol) and imidazo[1,2-*b*]pyridazine (0.179 g, 1.5 mmol) affords **27** in 93% (0.243 g) yield as a yellow solid: mp 113-115 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (d, *J* = 4.2 Hz, 1H), 8.08-7.97 (m, 4H), 7.23 (d, *J* = 8.5 Hz, 2H), 7.05 (dd, *J* = 9.1, 4.4 Hz, 1H), 6.56 (t, *J* = 73.7 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.8 (t, *J* = 2.8 Hz), 143.0, 140.2, 132.8, 128.4, 127.6, 126.1, 126.0, 119.8, 116.5, 115.9 (t, *J* = 260.5 Hz).

LRMS calcd for M^+ $C_{13}H_9F_2N_3O$ 261, found 261.

5-(4-(Difluoromethoxy)phenyl)-2-isobutylthiazole (28):

1-Bromo-4-(difluoromethoxy)benzene (0.223 g, 1 mmol) and 2-isobutylthiazole (0.212 g, 1.5 mmol) affords **28** in 91% (0.257 g) yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (s, 1H), 7.51 (d, *J* = 8.5 Hz, 2H), 7.14 (d, *J* = 8.5 Hz, 2H), 6.52 (t, *J* = 73.7 Hz, 1H), 2.88 (d, *J* = 7.6 Hz, 2H), 2.20-2.15 (m, 1H), 1.02 (d, *J* = 7.6 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 150.8 (t, *J* = 2.8 Hz), 137.9, 137.3, 129.2, 128.1, 120.2 (t, *J* = 0.8 Hz), 115.8 (t, *J* = 260.5 Hz), 42.6, 29.9, 22.4.

LRMS calcd for M^+ $C_{14}H_{15}F_2NOS$ 283, found 283.

5-(4-(Difluoromethoxy)phenyl)-2-isopropyl-4-methylthiazole (29):

1-Bromo-4-(difluoromethoxy)benzene (0.223 g, 1 mmol) and 2-isopropyl-4-methylthiazole (0.212 g, 1.5 mmol) affords **29** in 90% (0.255 g) yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, *J* = 8.5 Hz, 2H), 7.16 (d, *J* = 8.5 Hz, 2H), 6.54 (t, *J* = 73.7 Hz, 1H), 3.28 (sept., *J* = 7.6 Hz, 1H), 2.44 (s, 3H), 1.41 (d, *J* = 7.6 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.7, 150.6 (t, *J* = 2.9 Hz), 147.2, 130.7, 130.0, 129.3, 119.8 (t, *J* = 0.8 Hz), 115.9 (t, *J* = 260.5 Hz), 33.5, 23.4, 16.2.

LRMS calcd for M^+ $C_{14}H_{15}F_2NOS$ 283, found 283.

2-(2-(Difluoromethoxy)phenyl)benzo*[b]*thiophene (30):

1-Bromo-2-(difluoromethoxy)benzene (0.223 g, 1 mmol) and benzothiophene (0.201 g, 1.5 mmol) affords **30** in 79% (0.218 g) yield as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95-7.84 (m, 2H), 7.81-7.75 (m, 2H), 7.48-7.27 (m, 5H), 6.57 (t, *J* = 7.3 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.1 (t, *J* = 2.5 Hz), 140.2, 140.1, 138.3, 130.7, 129.4, 126.7, 126.1, 124.8, 124.6, 124.0, 123.9, 122.1, 120.3, 116.3 (t, *J* = 260.4 Hz).

LRMS calcd for M^+ $C_{15}H_{10}F_2OS$ 276, found 276.

3-(2-(Difluoromethoxy)phenyl)imidazo[1,2-*a*]pyridine (31):

1-Bromo-2-(difluoromethoxy)benzene (0.223 g, 1 mmol) and imidazo[1,2-*a*]pyridine (0.177 g, 1.5 mmol) affords **31** in 86% (0.224 g) yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, *J* = 6.0 Hz, 1H), 7.66 (s, 1H), 7.62 (d, *J* = 9.0 Hz, 1H), 7.48-7.36 (m, 2H), 7.32-7.26 (m, 2H), 7.15 (dd, *J* = 8.1, 1.3 Hz, 1H), 6.74 (t, *J* = 6.8 Hz, 1H), 6.31 (t, *J* = 73.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.7 (t, *J* = 2.6 Hz), 146.1, 133.8, 132.0, 130.2, 126.0, 124.5, 124.4, 121.4, 121.0, 119.9, 117.8, 115.5 (t, *J* = 261.6 Hz), 112.1.

LRMS calcd for M^+ $C_{14}H_{10}F_2N_2O$ 260, found 260.

3-(2-(Difluoromethoxy)phenyl)imidazo[1,2-*b*]pyridazine (32):

1-Bromo-2-(difluoromethoxy)benzene (0.223 g, 1 mmol) and imidazo[1,2-*b*]pyridazine (0.179 g, 1.5 mmol) affords **32** in 91% (0.238 g) yield as a white solid: mp 85-87 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.02 (s, 1H), 7.97 (dd, *J* = 9.1, 1.7 Hz, 1H), 7.90 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.45-7.22 (m, 3H), 7.02 (dd, *J* = 9.1, 4.4 Hz, 1H), 6.50 (t, *J* = 73.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.0 (t, *J* = 2.5 Hz), 142.8, 139.6, 134.9, 131.0, 129.8, 125.9, 125.4, 124.0, 120.7 (t, *J* = 0.9 Hz), 119.4 (t, *J* = 0.8 Hz), 116.7, 116.2 (t, *J* = 259.5 Hz).

LRMS calcd for M^+ $C_{13}H_9F_2N_3O$ 261, found 261.

3-(2-(Difluoromethoxy)phenyl)imidazo[1,2-*a*]pyrazine (33):

1-Bromo-2-(difluoromethoxy)benzene (0.223 g, 1 mmol) and imidazo[1,2-*a*]pyrazine (0.179 g, 1.5 mmol) affords **33** in 93% (0.243 g) yield as a white solid: mp 98-100 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.13 (d, *J* = 0.7 Hz, 1H), 7.91-7.84 (m, 3H), 7.55-7.48 (m, 2H), 7.42-7.33 (m, 2H), 6.37 (t, *J* = 73.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.8 (t, *J* = 2.5 Hz), 144.2, 141.5, 135.9, 132.0, 131.1, 129.6, 126.3, 122.7, 120.2, 120.0, 117.7, 115.5 (t, *J* = 262.9 Hz).

LRMS calcd for M^+ $C_{13}H_9F_2N_3O$ 261, found 261.

2-(2-(Difluoromethoxy)phenyl)-3,6-dimethyl-4,5,6,7-tetrahydrobenzofuran (34):

1-Bromo-2-(difluoromethoxy)benzene (0.223 g, 1 mmol) and menthofuran (0.225 g, 1.5 mmol) affords **34** in 92% (0.268 g) yield as a yellow solid: mp 54-56 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (dd, *J* = 7.4, 1.9 Hz, 1H), 7.36-7.21 (m, 3H), 6.44 (t, *J* = 75.0 Hz, 1H), 2.74 (dd, *J* = 16.3, 6.3 Hz, 1H), 2.50-2.37 (m, 2H), 2.30-2.21 (m, 1H), 2.01 (s, 3H), 2.00-1.97 (m, 1H), 1.93-1.86 (m, 1H), 1.50-1.37 (m, 1H), 1.13 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.8, 148.2, 142.9, 130.7, 128.7, 125.8, 124.9, 121.1, 119.3, 118.8, 116.7 (t, *J* = 258.7 Hz), 31.6, 31.4, 29.8, 21.7, 20.3, 9.6.

LRMS calcd for M^+ $C_{17}H_{18}F_2O_2$ 292, found 292.

5-(Benzo[*b*]thiophen-2-yl)-2,2-difluorobenzo[*d*][1,3]dioxole (35):

5-Bromo-2,2-difluorobenzo[*d*][1,3]dioxole (0.237 g, 1 mmol) and benzothiophene (0.201 g, 1.5 mmol) affords **35** in 62% (0.180 g) yield as a white solid: mp 151-153 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.46 (s, 1H), 7.45-7.40 (m, 2H), 7.40-7.30 (m, 2H), 7.11 (d, *J* = 8.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.5 (t, *J* = 0.8 Hz), 143.8 (t, *J* = 0.9 Hz), 142.8, 140.6, 139.6, 131.8 (t, *J* = 255.6 Hz), 131.0, 124.9, 124.8, 123.8, 122.4, 122.3, 120.1, 109.9, 107.9.

LRMS calcd for M^+ $C_{15}H_8F_2O_2S$ 290, found 290.

3-(2,2-Difluorobenzo[*d*][1,3]dioxol-5-yl)imidazo[1,2-*b*]pyridazine (36):

5-Bromo-2,2-difluorobenzo[*d*][1,3]dioxole (0.237 g, 1 mmol) and imidazo[1,2-*b*]pyridazine (0.179 g, 1.5 mmol) affords **36** in 86% (0.236 g) yield as a yellow solid: mp 113-115 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.04-7.98 (m, 2H), 7.88 (d, *J* = 1.7 Hz, 1H), 7.71 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.15 (d, *J* = 8.4 Hz, 1H), 7.08 (dd, *J* = 9.1, 4.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.1 (t, *J* = 0.8 Hz), 143.3 (t, *J* = 0.9 Hz), 143.1, 140.3, 132.9, 131.8 (t, *J* = 255.6 Hz), 127.4, 126.3, 124.8, 122.9, 116.6, 109.8, 108.3.

LRMS calcd for M^+ $C_{13}H_7F_2N_3O_2$ 275, found 275.

5-(2,2-Difluorobenzo[*d*][1,3]dioxol-5-yl)-2-isopropyl-4-methylthiazole (37):

5-Bromo-2,2-difluorobenzo[*d*][1,3]dioxole (0.237 g, 1 mmol) and 2-isopropyl-4-methylthiazole (0.212 g, 1.5 mmol) affords **37** in 81% (0.240 g) yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15-7.05 (m, 3H), 3.28 (sept., *J* = 7.6 Hz, 1H), 2.42 (s, 3H), 1.41 (d, *J* = 7.6 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.9, 147.6, 144.0, 143.3, 131.8 (t, *J* = 255.6 Hz), 129.1, 128.7, 124.9, 110.6, 109.6, 33.5, 23.3, 16.1.

LRMS calcd for M^+ $C_{14}H_{13}F_2NO_2S$ 297, found 297.

2-(4-(1,1,2,2-Tetrafluoroethoxy)phenyl)benzo[*b*]thiophene (38):

1-Bromo-4-(1,1,2,2-tetrafluoroethoxy)benzene (0.273 g, 1 mmol) and benzothiophene (0.201 g, 1.5 mmol) affords **38** in 60% (0.196 g) yield as a white solid: mp 201-203 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 7.5 Hz, 1H), 7.79 (d, *J* = 7.5 Hz, 1H), 7.73 (d, *J* = 8.8 Hz, 2H), 7.52 (s, 1H), 7.40-7.29 (m, 2H), 7.27 (d, *J* = 8.8 Hz, 2H), 5.94 (tt, *J* = 53.1, 2.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.8 (t, *J* = 1.7 Hz), 142.8, 140.7, 139.7, 133.0, 127.9, 124.8, 124.7, 123.8, 122.4, 122.2, 120.2, 116.5 (tt, *J* = 272.1, 28.7 Hz), 107.8 (tt, *J* = 251.8, 41.3 Hz).

LRMS calcd for M^+ $C_{16}H_{10}F_4OS$ 326, found 326.

3-(4-(1,1,2,2-Tetrafluoroethoxy)phenyl)imidazo[1,2-*b*]pyridazine (39):

1-Bromo-4-(1,1,2,2-tetrafluoroethoxy)benzene (0.273 g, 1 mmol) and imidazo[1,2-*b*]pyridazine (0.179 g, 1.5 mmol) affords **39** in 87% (0.270 g) yield as a yellow solid: mp 79-81 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.05 (d, *J* = 8.8 Hz, 2H), 8.01 (s, 1H), 7.98 (dd, *J* = 9.1, 1.7 Hz, 1H), 7.30 (d, *J* = 8.8 Hz, 2H), 7.03 (dd, *J* = 9.1, 4.4 Hz, 1H), 5.94 (tt, *J* = 53.1, 2.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.3 (t, *J* = 1.7 Hz), 143.0, 140.3, 132.9, 128.1, 127.4, 127.1, 126.1, 121.8, 116.5 (tt, *J* = 272.1, 28.7 Hz), 107.8 (tt, *J* = 251.8, 41.4 Hz).

LRMS calcd for M^+ $C_{14}H_9F_4N_3O$ 311, found 311.

2-Isopropyl-4-methyl-5-(4-(1,1,2,2-tetrafluoroethoxy)phenyl)thiazole (40):

1-Bromo-4-(1,1,2,2-tetrafluoroethoxy)benzene (0.273 g, 1 mmol) and 2-isopropyl-4-methylthiazole (0.212 g, 1.5 mmol) affords **40** in 89% (0.296 g) yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.5 Hz, 2H), 7.23 (d, *J* = 8.5 Hz, 2H), 5.92 (tt, *J* = 53.1, 2.8 Hz, 1H), 3.27 (sept., *J* = 7.6 Hz, 1H), 2.44 (s, 3H), 1.40 (d, *J* = 7.6 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.7, 148.2 (t, *J* = 1.7 Hz), 147.4, 131.2, 130.5, 129.1, 121.8, 116.6 (tt, *J* = 272.1, 28.7 Hz), 107.8 (tt, *J* = 251.8, 41.4 Hz), 33.5, 23.3, 16.2.

LRMS calcd for M^+ $C_{15}H_{15}F_4NOS$ 333, found 333.

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Chapter 4:

Pd-catalyzed C–H Bond Arylation and *O*- to *N*-alkyl Migratory Rearrangement of 2-Alkoxythiazoles: A One Pot Access to 2-Alkoxy-5-arylthiazoles or 3-Alkyl-5-arylthiazol-2(3H)-ones

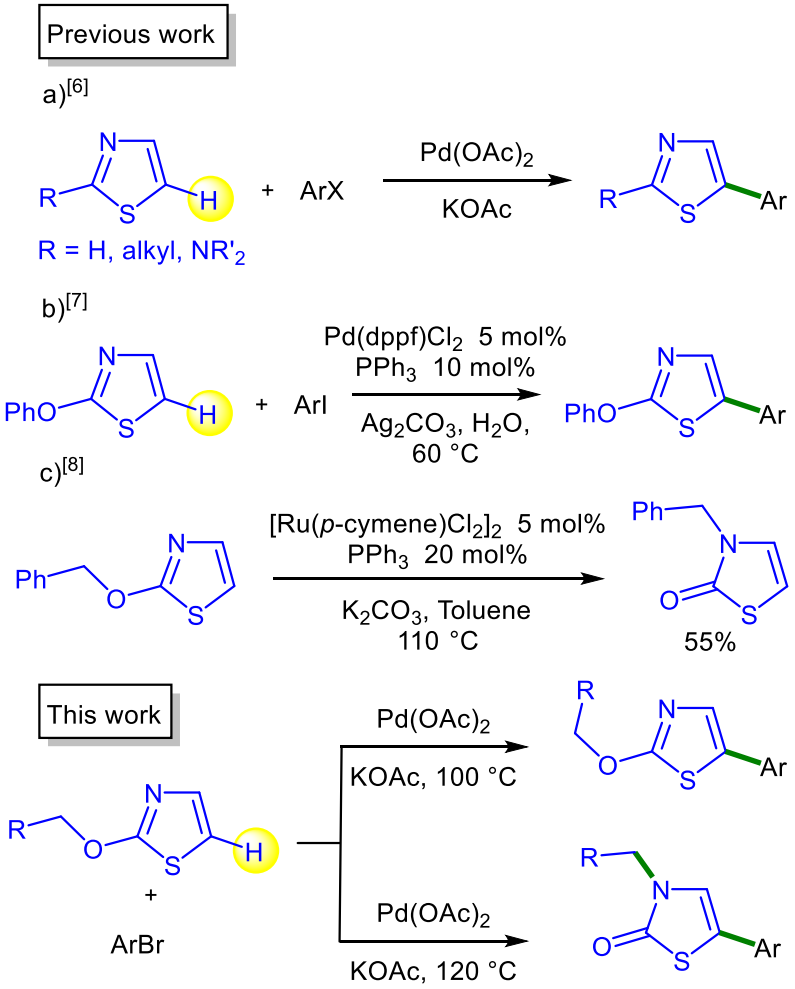
Chapter 4:

Pd-catalyzed C–H Bond Arylation and *O*- to *N*-alkyl Migratory Rearrangement of 2-Alkoxythiazoles: A One Pot Access to 2-Alkoxy-5-arylthiazoles or 3-Alkyl-5-arylthiazol-2(3H)-ones

4.1 Introduction

As seen in the previous chapters, the metal-catalyzed direct functionalization of 5-membered ring (hetero)arenes is a very powerful synthetic tool for the synthesis of valuable polyheteroaromatics.[1] However, the presence of specific functional groups on heterocycles may result in selectivity issues potentially challenging to handle with. In the C–H bond functionalization of 5-membered ring heteroarenes such as thiazoles, palladium-catalyzed direct C5-arylation is strongly favored.[2,3] Several procedures for the Pd-catalyzed direct arylation of 2-alkylthiazoles have been reported (Scheme 4.1, a).[4] Conversely, only a few examples of Pd-catalyzed direct arylations of thiazoles bearing an heteroelements at C2-position have been described.[5] Some direct arylations of 2-amine or 2-amide-substituted thiazoles have been reported.[6] By sharp contrast, Pd-catalyzed direct arylation reactions with thiazoles containing an OR substituent at C2-position are limited to the use of 2-phenoxythiazole (Scheme 4.1, b).[7]

In this context, in 2011, Dong et al. also studied the reactivity of 2-(benzyloxy)thiazole in Ru-catalyzed *O*- to *N*-alkyl migratory rearrangement.[8] 3-Benzylthiazol-2(3H)-one was obtained in 55% yields using 5 mol% [Ru(*p*-cymene)Cl_2]$_2$ associated to 20 mol% PPh_3 as catalytic system and K_2CO_3 base (Scheme 4.1, c). Therefore, we were interested in the reactivity of 2-alkoxythiazoles as heteroaryl sources for the access to 2-alkoxy-5-arylthiazoles and also to 3-alkyl-5-arylthiazol-2(3H)-ones by *O*- to *N*-alkyl migratory rearrangement as they exhibit useful physical or biological properties.[9] (Scheme 4.1, bottom).



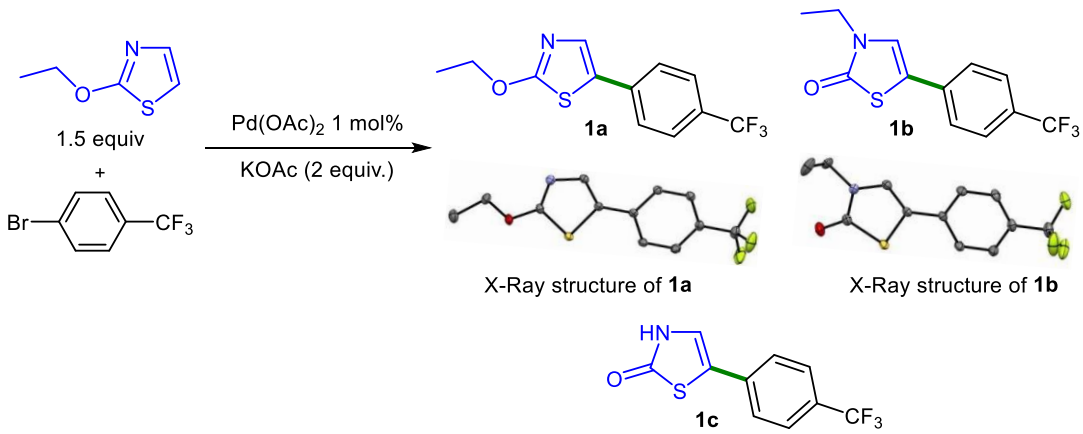
Scheme 4.1. Direct arylations of thiazoles and *O*- to *N*-alkyl migratory rearrangement.

Accordingly, we report in this chapter general and simple conditions for: *i*) the Pd-catalyzed regioselective C5-arylation of 2-alkoxythiazoles *via* C–H bond functionalization, *ii*) the preparation of 3-alkyl-5-arylthiazol-2(3H)-ones *via* one pot C5-arylation and *O*- to *N*-alkyl migratory rearrangement of 2-alkoxythiazoles. We found the decisive role of the reaction temperature at the origin of the *O*- to *N*-alkyl migratory rearrangement. The substrate scope for such arylation reactions is described.

4.2 Results and discussion

Under standard C–H bond functionalization conditions,[10] we examined the reaction outcome of the coupling of 2-ethoxythiazole with 4-(trifluoromethyl)bromobenzene using 1 mol% of $Pd(OAc)_2$ catalyst, and 2 equiv. of KOAc as the base in DMA during 6h (Table 4.1, entry 4). Under these conditions, an intractable mixture of C5-arylated thiazole **1a**, 3-ethyl-5-arylthiazol-2(3H)-ones **1b**, with traces of 5-arylthiazol-2(3H)-ones **1c** was obtained (Ratio **1a**:**1b**:**1c** 67:24:9). The *O*- to *N*-alkyl migratory rearrangement at the origin of the formation of **1b** is a known reaction previously reported by Dong et al. (see scheme 4.1, c).[8] The structures of **1a** and **1b** was confirmed by X-ray analysis.[11] The C5-arylated thiazole **1a** was the major compound using shorter reaction times (1h-4h) (Table 4.1, entries 1-3). Conversely, a longer reaction time (16h) allowed to obtain **1b** in 83% selectivity and in 61% yield (Table 4.1, entry 5). Using a lower reaction temperature (100°C), a good selectivity in favor of the formation of **1a** was observed (Ratio **1a**:**1b**:**1c** 90:4:6). At this temperature, the migratory rearrangement products were observed in very low yield. The influence of solvents was examined; however, both pentan-1-ol and cyclopentyl methyl ether led to low yields in **1a** due to a poor conversion of the aryl bromide and **1b** was not detected (Table 4.1, entries 7 and 8). The use of dry DMA at 100 or 120°C gave similar ratio of **1a**:**1b**:**1c** than the use of 99+ DMA (Table 4.1, entries 9 and 10).

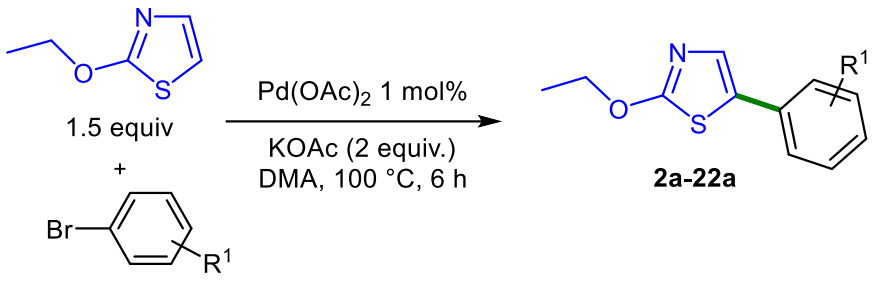
Table 4.1. Influence of the reaction conditions on the selectivity of the C–H bond arylation of 2-ethoxythiazole.[a]



Entry	Solvent	Temp. (°C)	Time (h)	Conv. (%)	Ratio **1a**:**1b**:**1c**	Yield in **1a** or **1b** (%)
1	DMA	120	1	27	98:0:2	nd
2	DMA	120	2	48	96:0:4	nd
3	DMA	120	4	78	89:5:6	nd
4	DMA	120	6	96	67:24:9	nd
5	DMA	120	16	100	3:83:14	61 of **1b**
6	DMA	100	6	94	90:4: 6	66 of **1a**
7	pentan-1-ol	120	16	<15	100:0:0	nd
8	CPME	120	16	<15	100:0:0	nd
9	Dry DMA	120	16	94	68:21:11	nd
10	Dry DMA	100	6	92	92:3:5	nd

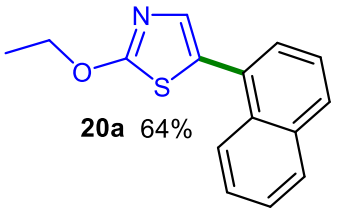
[a] $Pd(OAc)_2$ 1 mol%, 2-ethoxythiazole (1.5 equiv.), 4-bromobenzotrifluoride (1 equiv.), conversion based on consumption of 4-bromobenzotrifluoride.

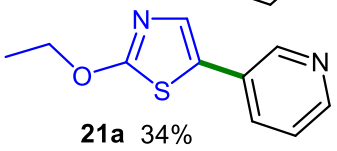
Based on the conditions for selective C5-C–H thiazole arylation without migration: 1 mol% $Pd(OAc)_2$ catalyst, KOAc base at 100 °C during 6 h, the substrate scope and the functional group tolerance using 2-ethoxythiazole as the reaction partner was investigated (Scheme 4.2). First, the influence of *para*-substituents on the aryl bromide was determined (Scheme 4.2). Using 4-bromonitrobenzene or 4-bromobenzonitrile as the aryl sources, good yield of 63% and 78% in **2a** and **3a** were obtained. The reaction tolerates several other functional groups on the aryl bromide such as acetyl, formyl, propionyl, chloro, fluoro or phenyl, affording the 5-arylthiazoles **4a**-**9a** in 63-88% yields. For the reaction with 4-bromochlorobenzene, the C-Cl bond remained untouched potentially allowing for further functionalization. Conversely, the electron-rich 4-bromotoluene led to **10a** in a lower yield of 54%, and 4-bromoanisole gave the expected product **11a** in a very low yield due to a poor conversion of this aryl bromide. With this substrate, the use of 100 °C as the reaction temperature is not sufficient to promote efficiently the oxidative addition to palladium, but the use of a higher reaction temperature afforded the product **11b** in larger amount; whereas, **11a** was still obtained in very low yield. Formyl, acetyl or fluoro *meta*-substituents on the aryl bromide were well tolerated, and the expected 5-aryl thiazoles **12a**-**14a** were obtained in 56-77% yields. The presence of *ortho*-substituents on the aryl bromide may significantly influence the arylation yields due to steric factors. The use of 2-bromobenzonitrile, 2-bromonitrobenzene or 2-bromobenzaldehyde gave the 5-arylthiazoles **15a**-**17a** in notably high yields. The arylation of 2-ethoxythiazole by 2-fluorobromobenzene also proceeded in high yield. Conversely, the use of 2-bromotoluene gave the product **19a** in only 16% yield due to a very low conversion of this aryl bromide. Using the heteroaryl bromides, 3-bromopyridine and 3-bromoquinoline, the yields in the desired coupling products **21a** and **22a** were moderate to good.

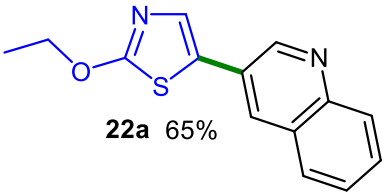


R^1		Yield (%)
4-NO_2	**2a**	63
4-CN	**3a**	78
4-COMe	**4a**	80
4-CHO	**5a**	88
4-COEt	**6a**	84
4-Cl	**7a**	83
4-F	**8a**	63
4-Ph	**9a**	68
4-Me	**10a**	54
4-OMe	**11a**	13
3-CHO	**12a**	56
3-COMe	**13a**	77
3-F	**14a**	68
2-CN	**15a**	75
2-NO_2	**16a**	72
2-CHO	**17a**	85
2-F	**18a**	81
2-Me	**19a**	16*

*: 64h



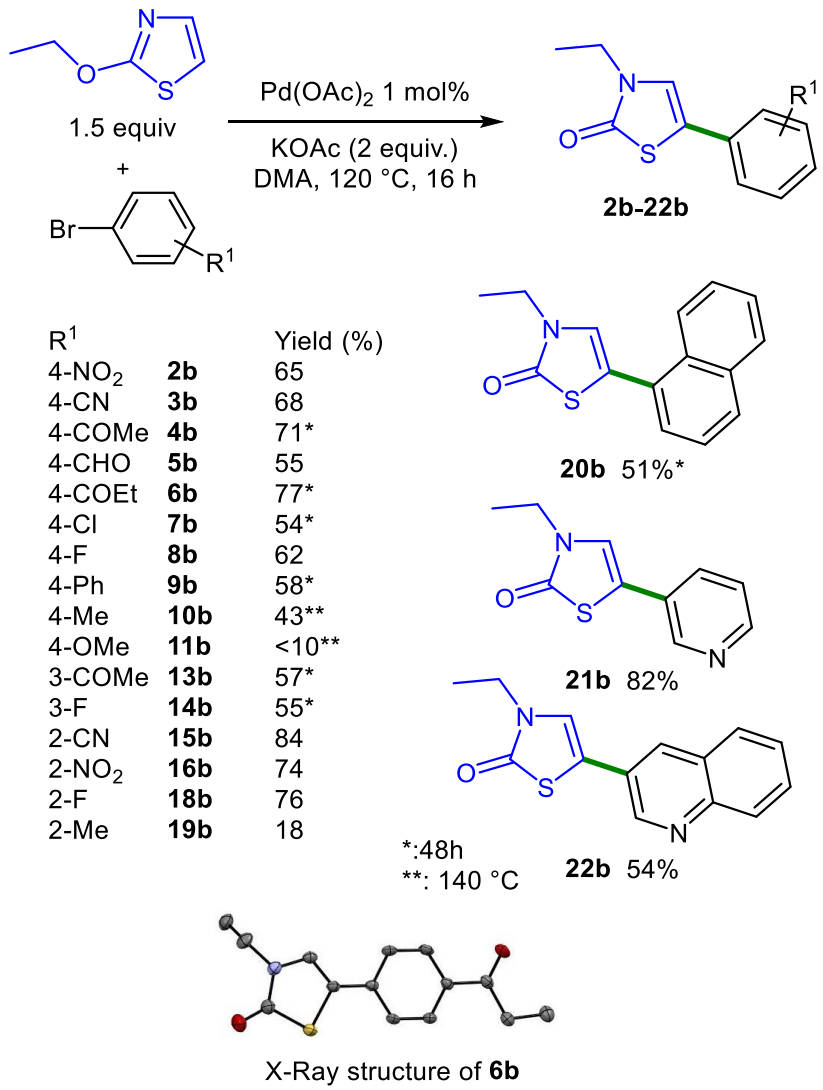




Scheme 4.2. Scope of C5-arylation of 2-ethoxythiazole.

The scope of the one pot preparation of 3-ethyl-5-arylthiazol-2(3H)-ones **b** was also studied using 120 °C as the reaction temperature and again 1 mol% $Pd(OAc)_2$ catalyst and KOAc base during 16-48 h (Scheme 4.3). Pleasingly, under these conditions in most cases, high selectivities favoring the formation of the desired 3-ethyl-5-arylthiazol-2(3H)-ones **b** were observed. Direct arylation with *O*- to *N*-alkyl migratory rearrangement from bromoarenes bearing nitro, cyano, acetyl, formyl, propionyl, chloro or fluoro *para*-substituents, gave the expected 5-arylthiazol-2(3H)-ones **2b**-**8b** in 54-77% yields. The structure of **6b** was confirmed by X-Ray analysis. [11] Again, the use of the electron-rich aryl bromide 4-bromotoluene led to a lower yield in the desired product **10b** and a higher reaction temperature (140 °C) had to be employed, as at 120 °C a mixture of **10a** and **10b** was obtained. Substituents at *meta*-position on the aryl bromide were also well tolerated, with 3-bromoacetophenone and 3-fluorobenzene giving the products **13b** and **14b** in

57% and 55% yield, respectively. In general, the use of more hindered aryl bromides afforded the 5-arylthiazol-2(3H)-ones in high yields. 2-Cyano-, 2-nitro- and 2-fluoro substituted aryl bromides gave the products **15b**, **16b** and **18b** in 74-84% yields. We examined the opportunity to extend the reaction to heteroaryl bromides. Both 3-bromopyridine and 3-bromoquinoline gave the desired biheteroaryls **21b** and **22b** with high selectivity and good yields.

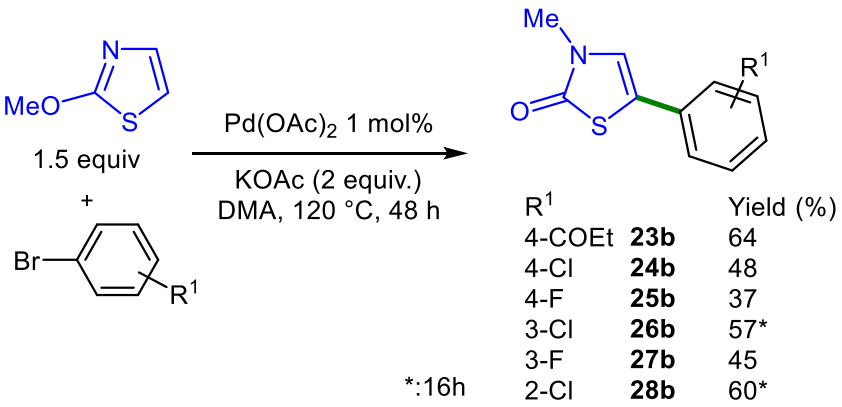


R^1		Yield (%)
4-NO_2	**2b**	65
4-CN	**3b**	68
4-COMe	**4b**	71*
4-CHO	**5b**	55
4-COEt	**6b**	77*
4-Cl	**7b**	54*
4-F	**8b**	62
4-Ph	**9b**	58*
4-Me	**10b**	43**
4-OMe	**11b**	<10**
3-COMe	**13b**	57*
3-F	**14b**	55*
2-CN	**15b**	84
2-NO_2	**16b**	74
2-F	**18b**	76
2-Me	**19b**	18

Scheme 4.3. Scope of C5-arylation of 2-ethoxythiazole with a *O*- to *N*-ethyl migratory rearrangement.

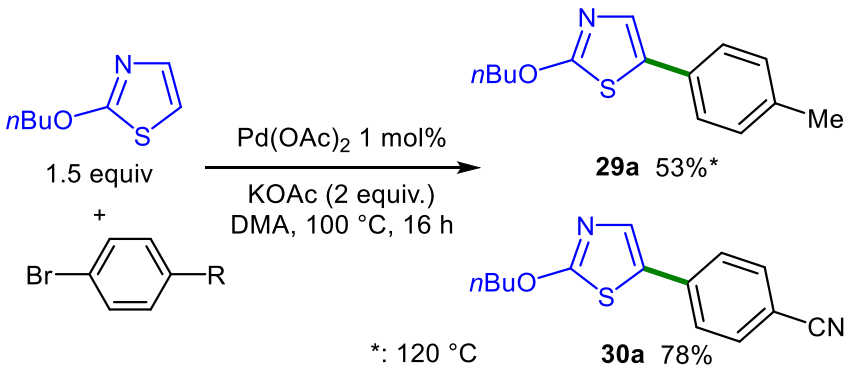
Several reactions using 2-methoxythiazole as the reaction partner were also performed at 120 °C in order to prepare 3-methyl-5-arylthiazol-2(3H)-ones (Scheme

4.4). Similar or lower yields in the desired products **23b**-**28b** than with 2-ethoxythiazole were obtained. However, the methyl migration step was slower and a long reaction time (48h) was generally required to reach complete migration.



Scheme 4.4. Scope of C5-arylation of 2-methoxythiazole with a *O*- to *N*-methyl migratory rearrangement.

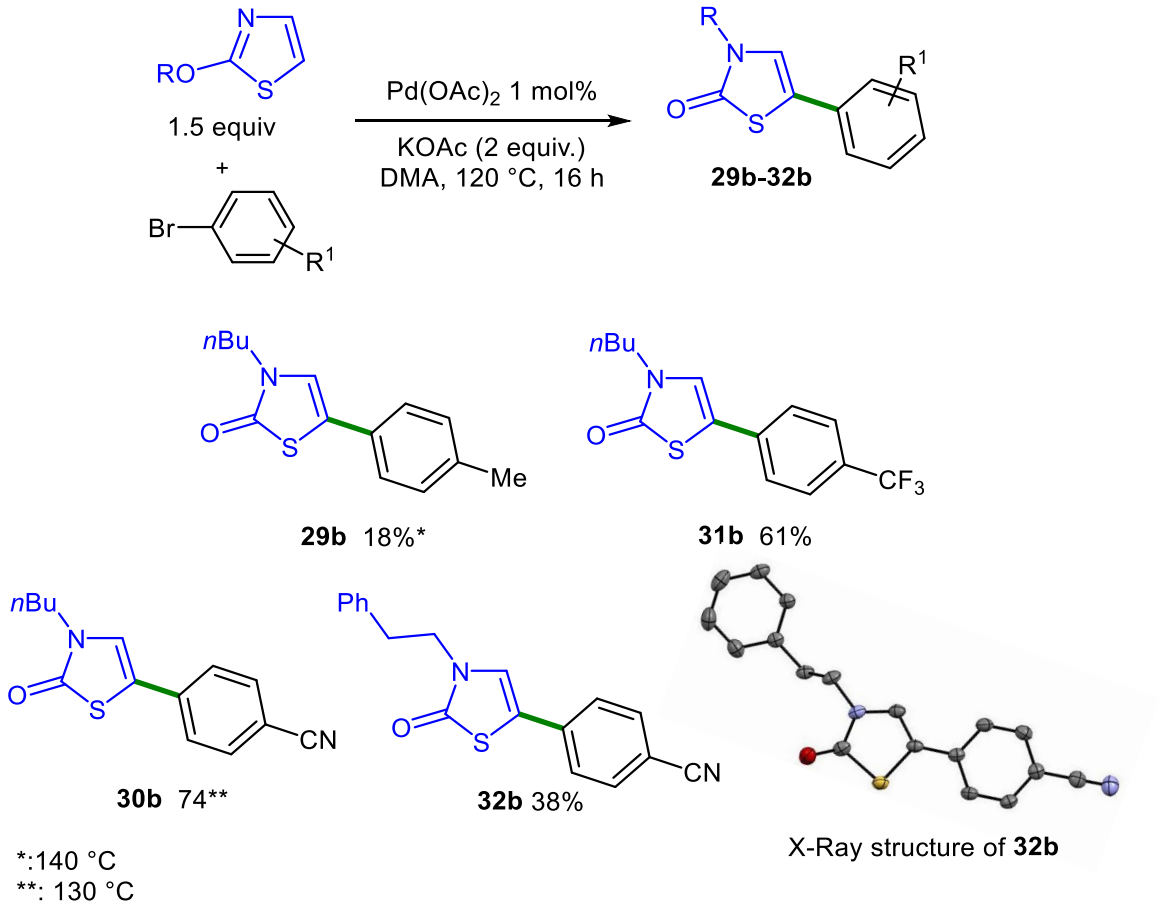
The reactivity of 2-*n*butoxythiazole is quite similar to 2-ethoxythiazole (Schemes 4.5 and 4.6). At 100-120°C, the C5-arylated thiazoles **29a** and **30a** were obtained in 53% and 78% yield, respectively.



Scheme 4.5. Scope of C5-arylation of 2-*n*butoxythiazole.

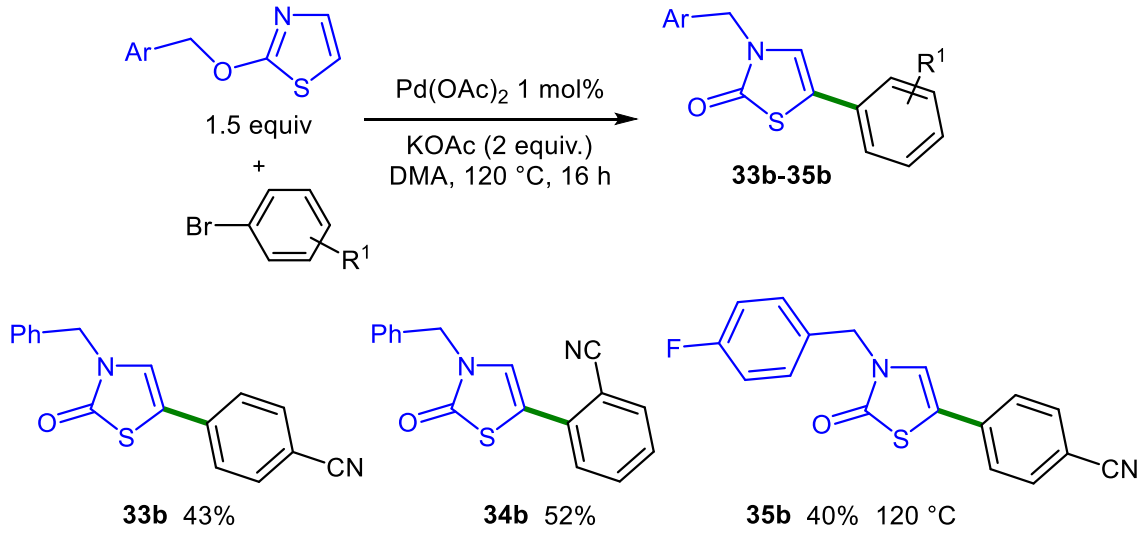
Again, using more elevated temperatures (120-140°C), the *O*- to *N*-butyl migratory rearrangement occurred, giving rise to the products **29b**-**31b** (Scheme 4.6). Better yields were obtained using electron-deficient aryl bromides. The migration of

the phenethyl group of 2-phenethoxythiazole was slower, and the product **32b** was only obtained in 38% yield. The structure of **32b** was confirmed by X-Ray analysis.[11]



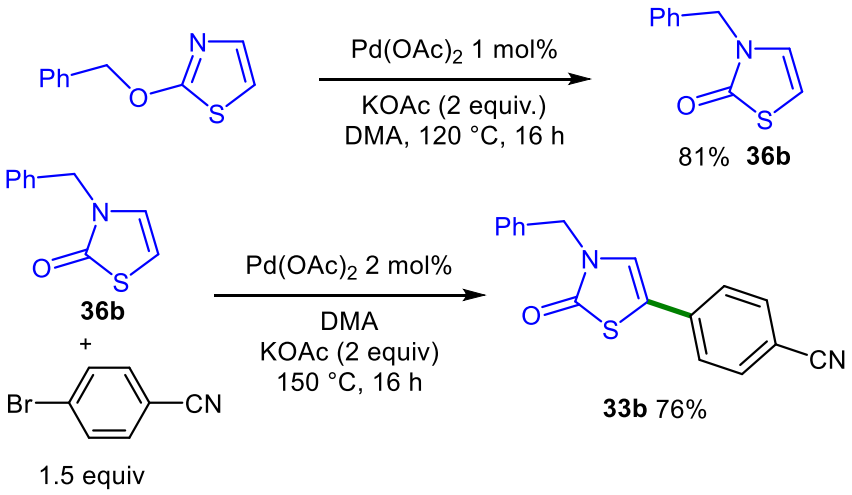
Scheme 4.6. Scope of the C5-arylation of 2-*n*butoxythiazole or 2-phenethoxythiazole with a *O*- to *N*-alkyl migratory rearrangement.

Since benzyl is common protecting group of heteroarenes,[12] the reactivity 2-(benzyloxy)thiazole was examined (Scheme 4.7). In the presence of 2- or 4-bromobenzonitriles, the products **33b** and **34b** were obtained in moderate yields. The reaction also tolerated a 4-fluorobenzyl group on thiazole.



Scheme 4.7. Scope of the C5-arylation of 2-benzyloxythiazole with a *O*- to *N*-benzyl migratory rearrangement.

The reactivity of 2-(benzyloxy)thiazole in the absence of aryl bromide using the direct arylation conditions was also examined and provided the *O*- to *N*-alkyl migratory rearrangement product 3-benzylthiazol-2(3H)-one **36b** in 81% yield, indicating that during the direct arylation reaction, a partial *O*- to *N*-alkyl rearrangement may occur (Scheme 4.8). We thus examined the reactivity of 3-benzylthiazol-2(3H)-one **36b** in Pd-catalyzed direct arylation. In the presence of 4-bromobenzonitrile, the expected product **33b** was obtained in 76% yield, revealing that the formation of the 3-alkyl-5-arylthiazol-2(3H)-ones **b** may arise from the direct arylation of both 2-alkylthiazoles and 3-alkylthiazol-2(3H)-ones.



Scheme 4.8. 2-(Benzyloxy)thiazole *O*- to *N*-alkyl migratory rearrangement and Pd-catalyzed direct arylation of 3-benzylthiazol-2(3H)-one **36b**

4.3 Conclusion

Overall, we disclosed simple general conditions for the palladium-catalyzed C-H bond functionalization of 2-alkoxythiazoles allowing the access to *i*) 2-alkoxy-5-arylthiazoles *via* direct C5-arylation or *ii*) 3-alkyl-5-arylthiazol-2(3H)-ones *via* one pot C5-arylation with a *O*- to *N*-alkyl migratory rearrangement. The selectivity of the reaction was found to strongly depend on the reaction temperature and time, as the *O*- to *N*-alkyl migratory rearrangement required a temperature > 100 °C. This temperature-dependent selectivity was applied to the synthesis of 2-alkoxythiazoles and 3-alkyl-5-arylthiazolones using a wide scope of aryl bromides including heteroaryl bromides. With ligand-free air-stable $Pd(OAc)_2$ catalyst and inexpensive KOAc base in DMA, the C5-arylated thiazoles and 3-alkyl-5-arylthiazolones were obtained in good yields with aryl bromides bearing nitrile, nitro, acetyl, formyl, trifluoromethyl, chloro or fluoro substituents. Due to the wide availability of diversely substituted aryl bromides at an affordable cost, such simple reaction conditions should be very attractive for synthetic chemists, giving a robust access to both 2-alkoxy-5-arylthiazoles and 3-alkyl-5-arylthiazol-2(3H)-ones.

4.4 Experimental details

General: $Pd(OAc)_2$ (99%) was purchased from Aldrich. DMA (99+%) extra pure and KOAc (99%) were purchased from ACROS. 2-Methoxythiazole and 2-ethoxythiazole were purchased from Fluorochem. These compounds were not purified before use.

Procedure A, typical experiment for the synthesis of C5-arylated thiazoles: (products **1a**-**30a**): The reaction of the aryl bromide (1 mmol), thiazole derivative (1.5 mmol) and KOAc (0.196 g, 2 mmol) in the presence of $Pd(OAc)_2$ (2.2 mg, 1 mol%) in DMA (5 mL) under argon at 100-120 °C (see schemes) during 6-64 h (see schemes), affords the C5-arylated thiazoles after cooling, evaporation of the solvent and filtration on silica gel (pentane/ether).

Procedure B, typical experiment for the synthesis of C5-arylated thiazoles: (products **1b**-**35b**): The reaction of the aryl bromide (1 mmol), thiazole derivative (1.5 mmol) and KOAc (0.196 g, 2 mmol) in the presence of $Pd(OAc)_2$ (2.2 mg, 1 mol%) in DMA (5 mL) under argon at 120-140 °C (see schemes) during 16-48 h (see schemes), affords the C5-arylated thiazoles after cooling, evaporation of the solvent and filtration on silica gel (pentane/ether).

2-Ethoxy-5-(4-(trifluoromethyl)phenyl)thiazole (1a)

Following procedure A, 4-bromobenzotrifluoride (0.225 g, 1 mmol) and 2-ethoxythiazole (0.194 g, 1.5 mmol) affords **1a** in 66% (0.180 g) yield as a white solid: mp 101-103 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, *J* = 8.2 Hz, 2H), 7.53 (d, *J* = 8.2 Hz, 2H), 7.40 (s, 1H), 4.51 (q, *J* = 7.3 Hz, 2H), 1.47 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.6, 135.7, 133.8, 129.5 (q, *J* = 32.8 Hz), 129.4, 126.1 (q, *J* = 3.8 Hz), 125.5, 124.1 (q, *J* = 272.0 Hz), 68.0, 14.6.

HRMS calcd for $[M+Na]^+$ $C_{12}H_{10}F_3NOSNa$ 296.0327, found: 296.0327.

3-Ethyl-5-(4-(trifluoromethyl)phenyl)thiazol-2(3H)-one (1b)

Following procedure B, 4-bromobenzotrifluoride (0.225 g, 1 mmol) and 2-ethoxythiazole (0.194 g, 1.5 mmol) affords **1b** in 61% (0.166 g) yield as a white solid: mp 91-93 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, *J* = 8.2 Hz, 2H), 7.42 (d, *J* = 8.2 Hz, 2H), 6.96 (s, 1H), 3.83 (q, *J* = 7.3 Hz, 2H), 1.37 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 135.2, 129.5 (q, *J* = 32.8 Hz), 126.1 (q, *J* = 3.8 Hz), 124.9, 124.0 (q, *J* = 272.0 Hz), 120.8, 117.2, 40.8, 14.8.

HRMS calcd for $[M+Na]^+$ $C_{12}H_{10}F_3NOSNa$ 296.0327, found: 296.0330.

5-(4-(Trifluoromethyl)phenyl)thiazol-2(3H)-one (1c)

Following procedures A or B, this compound was isolated as a side-product in low yield as a side-product.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.24 (s, 1H), 7.63 (d, *J* = 8.2 Hz, 2H), 7.45 (d, *J* = 8.2 Hz, 2H), 6.98 (s, 1H).

LRMS calcd for M^+ $C_{10}H_6F_3NOS$ 245, found 245.

2-Ethoxy-5-(4-nitrophenyl)thiazole (2a)

Following procedure A, 4-bromonitrobenzene (0.202 g, 1 mmol) and 2-ethoxythiazole (0.194 g, 1.5 mmol) affords **2a** in 63% (0.157 g) yield as a yellow solid: mp 174-176 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, *J* = 8.7 Hz, 2H), 7.56 (d, *J* = 8.7 Hz, 2H), 7.50 (s, 1H), 4.52 (q, *J* = 7.3 Hz, 2H), 1.47 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.5, 146.7, 138.7, 135.3, 128.0, 125.9, 124.6, 68.3, 14.6.

HRMS calcd for $[M+Na]^+$ $C_{11}H_{10}N_2O_3SNa$ 273.0304, found: 273.0302.

2-Ethoxy-5-(4-nitrophenyl)thiazole (2b)

Following procedure B, 4-bromonitrobenzene (0.202 g, 1 mmol) and 2-ethoxythiazole (0.194 g, 1.5 mmol) affords **2b** in 65% (0.162 g) yield as a yellow solid: mp >200 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, *J* = 8.7 Hz, 2H), 7.46 (d, *J* = 8.7 Hz, 2H), 7.08 (s, 1H), 3.86 (q, *J* = 7.3 Hz, 2H), 1.39 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 146.7, 138.1, 124.9, 124.6, 122.4, 116.4, 41.0, 14.8.

HRMS calcd for $[M+Na]^+$ $C_{11}H_{10}N_2O_3SNa$ 273.0304, found: 273.0306.

4-(2-Ethoxythiazol-5-yl)benzonitrile (3a)

Following procedure A, 4-bromobenzonitrile (0.182 g, 1 mmol) and 2-ethoxythiazole (0.194 g, 1.5 mmol) affords **3a** in 78% (0.179 g) yield as a white solid: mp 105-107 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, *J* = 8.2 Hz, 2H), 7.47 (d, *J* = 8.2 Hz, 2H), 7.41 (s, 1H), 4.48 (q, *J* = 7.3 Hz, 2H), 1.43 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.8, 136.5, 134.6, 132.8, 128.9, 125.8, 118.7, 110.6, 68.0, 14.5.

HRMS calcd for $[M+Na]^+$ $C_{12}H_{10}N_2OSNa$ 253.0406, found: 253.0405.

4-(3-Ethyl-2-oxo-2,3-dihydrothiazol-5-yl)benzonitrile (3b)

Following procedure B, 4-bromobenzonitrile (0.182 g, 1 mmol) and 2-ethoxythiazole (0.194 g, 1.5 mmol) affords **3b** in 68% (0.156 g) yield as a yellow solid: mp 101-103 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, *J* = 8.2 Hz, 2H), 7.41 (d, *J* = 8.2 Hz, 2H), 7.02 (s, 1H), 3.83 (q, *J* = 7.3 Hz, 2H), 1.37 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 136.2, 132.8, 125.0, 121.8, 118.6, 116.6, 110.7, 40.9, 14.7.

HRMS calcd for $[M+Na]^+$ $C_{12}H_{10}N_2OSNa$ 253.0406, found: 253.0407.

1-(4-(2-Ethoxythiazol-5-yl)phenyl)ethan-1-one (4a)

Following procedure A, 4-bromoacetophenone (0.199 g, 1 mmol) and 2-ethoxythiazole (0.194 g, 1.5 mmol) affords **4a** in 80% (0.198 g) yield as a white solid: mp 85-87 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, *J* = 8.2 Hz, 2H), 7.50 (d, *J* = 8.2 Hz, 2H), 7.44 (s, 1H), 4.51 (q, *J* = 7.3 Hz, 2H), 2.60 (s, 3H), 1.46 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 197.3, 174.7, 136.7, 135.9, 134.1, 129.8, 129.3, 125.6, 68.0, 26.7, 14.6.

HRMS calcd for $[M+Na]^+$ $C_{13}H_{13}NO_2SNa$ 270.0559, found: 270.0562.

5-(4-Acetylphenyl)-3-ethylthiazol-2(3H)-one (4b)

Following procedure B, 4-bromoacetophenone (0.199 g, 1 mmol) and 2-ethoxythiazole (0.194 g, 1.5 mmol) affords **4b** in 71% (0.175 g) yield as a yellow solid: mp 166-168 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, *J* = 8.2 Hz, 2H), 7.40 (d, *J* = 8.2 Hz, 2H), 7.00 (s, 1H), 3.83 (q, *J* = 7.3 Hz, 2H), 2.59 (s, 3H), 1.37 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 197.2, 170.5, 136.2, 136.0, 129.2, 124.6, 121.0, 117.5, 40.8, 26.7, 14.8.

HRMS calcd for $[M+Na]^+$ $C_{13}H_{13}NO_2SNa$ 270.0559, found: 270.0560.

4-(2-Ethoxythiazol-5-yl)benzaldehyde (5a)

Following procedure A, 4-bromobenzaldehyde (0.185 g, 1 mmol) and 2-ethoxythiazole (0.194 g, 1.5 mmol) affords **5a** in 88% (0.205 g) yield as a white solid: mp 90-92 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.95 (s, 1H), 7.83 (d, *J* = 8.2 Hz, 2H), 7.55 (d, *J* = 8.2 Hz, 2H), 7.45 (s, 1H), 4.49 (q, *J* = 7.3 Hz, 2H), 1.44 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 191.3, 174.9, 138.0, 135.1, 134.5, 130.5, 129.5, 125.9, 68.0, 14.5.

HRMS calcd for $[M+Na]^+$ $C_{12}H_{11}NO_2SNa$ 256.0403, found: 256.0404.

4-(3-Ethyl-2-oxo-2,3-dihydrothiazol-5-yl)benzaldehyde (5b)

Following procedure B, 4-bromobenzaldehyde (0.185 g, 1 mmol) and 2-ethoxythiazole (0.194 g, 1.5 mmol) affords **5b** in 55% (0.128 g) yield as a yellow solid: mp 138-140 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.98 (s, 1H), 7.86 (d, *J* = 8.2 Hz, 2H), 7.47 (d, *J* = 8.2 Hz, 2H), 7.05 (s, 1H), 3.84 (q, *J* = 7.3 Hz, 2H), 1.38 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 191.3, 170.4, 137.6, 135.3, 130.6, 124.9, 121.6, 117.4, 40.9, 14.8.

HRMS calcd for $[M+Na]^+$ $C_{12}H_{11}NO_2SNa$ 256.0403, found: 256.0406.

1-(4-(2-Ethoxythiazol-5-yl)phenyl)propan-1-one (6a)

Following procedure A, 4-bromopropiophenone (0.213 g, 1 mmol) and 2-ethoxythiazole (0.194 g, 1.5 mmol) affords **6a** in 84% (0.219 g) yield as a white solid: mp 130-132 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, *J* = 8.2 Hz, 2H), 7.48 (d, *J* = 8.2 Hz, 2H), 7.41 (s, 1H), 4.49 (q, *J* = 7.3 Hz, 2H), 2.96 (q, *J* = 7.3 Hz, 2H), 1.45 (t, *J* = 7.3 Hz, 3H), 1.21 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 199.9, 174.6, 136.4, 135.6, 133.9, 129.8, 128.9, 125.5, 67.9, 31.8, 14.6, 8.35.

HRMS calcd for $[M+Na]^+$ $C_{14}H_{15}NO_2SNa$ 284.0716, found: 284.0718.

3-Ethyl-5-(4-propionylphenyl)thiazol-2(3H)-one (6b)

Following procedure B, 4-bromopropiophenone (0.213 g, 1 mmol) and 2-ethoxythiazole (0.194 g, 1.5 mmol) affords **6b** in 77% (0.201 g) yield as a yellow solid: mp 125-127 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, *J* = 8.2 Hz, 2H), 7.38 (d, *J* = 8.2 Hz, 2H), 7.00 (s, 1H), 3.82 (q, *J* = 7.3 Hz, 2H), 2.97 (q, *J* = 7.3 Hz, 2H), 1.37 (t, *J* = 7.3 Hz, 3H), 1.21 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 199.9, 170.4, 136.0, 135.7, 128.8, 124.6, 120.9, 117.5, 40.8, 31.8, 14.8, 8.3.

HRMS calcd for $[M+Na]^+$ $C_{14}H_{15}NO_2SNa$ 284.0716, found: 284.0714.

5-(4-Chlorophenyl)-2-ethoxythiazole (7a)

Following procedure A, 4-bromochlorobenzene (0.191 g, 1 mmol) and 2-ethoxythiazole (0.194 g, 1.5 mmol) affords **7a** in 83% (0.198 g) yield as a white solid: mp 79-81 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 7.28 (s, 1H), 4.49 (q, *J* = 7.3 Hz, 2H), 1.45 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.9, 133.4, 132.6, 130.6, 129.7, 129.3, 127.1, 67.8, 14.6.

HRMS calcd for $[M+Na]^+$ $C_{11}H_{10}ClNOSNa$ 262.0064, found: 262.0065.

5-(4-Chlorophenyl)-3-ethylthiazol-2(3H)-one (7b)

Following procedure B, 4-bromochlorobenzene (0.191 g, 1 mmol) and 2-ethoxythiazole (0.194 g, 1.5 mmol) affords **7b** in 54% (0.129 g) yield as a white solid: mp 101-103 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (d, *J* = 8.2 Hz, 2H), 7.26 (d, *J* = 8.2 Hz, 2H), 6.82 (s, 1H), 3.81 (q, *J* = 7.3 Hz, 2H), 1.36 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 133.5, 130.3, 129.3, 126.1, 119.4, 117.6, 40.7, 14.8.

HRMS calcd for $[M+Na]^+$ $C_{11}H_{10}ClNOSNa$ 262.0064, found: 262.0063.

2-Ethoxy-5-(4-fluorophenyl)thiazole (8a)

Following procedure A, 4-bromofluorobenzene (0.175 g, 1 mmol) and 2-ethoxythiazole (0.194 g, 1.5 mmol) affords **8a** in 63% (0.140 g) yield as a white solid: mp 67-69 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (dd, *J* = 8.3, 5.2 Hz, 2H), 7.22 (s, 1H), 7.05 (t, *J* = 8.2 Hz, 2H), 4.48 (q, *J* = 7.3 Hz, 2H), 1.45 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7, 162.3 (d, *J* = 247.5 Hz), 132.1, 129.9, 128.3, 127.7 (d, *J* = 8.0 Hz), 116.1 (d, *J* = 21.9 Hz), 67.8, 14.6.

HRMS calcd for $[M+Na]^+$ $C_{11}H_{10}FNOSNa$ 246.0359, found: 256.0359.

3-Ethyl-5-(4-fluorophenyl)thiazol-2(3H)-one (8b)

Following procedure B, 4-bromofluorobenzene (0.175 g, 1 mmol) and 2-ethoxythiazole (0.194 g, 1.5 mmol) affords **8b** in 62% (0.138 g) yield as a white solid: mp 81-83 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (dd, *J* = 8.3, 5.2 Hz, 2H), 7.05 (t, *J* = 8.2 Hz, 2H), 6.75 (s, 1H), 3.81 (q, *J* = 7.3 Hz, 2H), 1.36 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 162.4 (d, *J* = 247.5 Hz), 128.0 (d, *J* = 3.4 Hz), 126.7 (d, *J* = 8.1 Hz), 118.8, 117.8, 116.1 (d, *J* = 22.0 Hz), 40.6, 14.8.

HRMS calcd for $[M+Na]^+$ $C_{11}H_{10}FNOSNa$ 246.0359, found: 256.0361.

5-([1,1'-Biphenyl]-4-yl)-2-ethoxythiazole (9a)

Following procedure A, 4-bromobiphenyl (0.233 g, 1 mmol) and 2-ethoxythiazole (0.194 g, 1.5 mmol) affords **9a** in 68% (0.191 g) yield as a yellow solid: mp 137-139 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63-7.57 (m, 4H), 7.52 (d, *J* = 8.2 Hz, 2H), 7.48-7.42 (m, 2H), 7.39-7.32 (m, 2H), 4.51 (q, *J* = 7.3 Hz, 2H), 1.47 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.8, 140.5, 140.4, 132.2, 131.1, 130.6, 129.0, 127.7, 127.6, 127.0, 126.3, 67.6, 14.6.

HRMS calcd for $[M+Na]^+$ $C_{17}H_{15}NONa$ 304.767, found: 304.0767.

5-([1,1'-Biphenyl]-4-yl)-2-ethoxythiazole (9b)

Following procedure B, 4-bromobiphenyl (0.233 g, 1 mmol) and 2-ethoxythiazole (0.194 g, 1.5 mmol) affords **9b** in 58% (0.163 g) yield as a yellow solid: mp 162-164 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, *J* = 8.2 Hz, 4H), 7.49-7.31 (m, 5H), 6.88 (s, 1H), 3.83 (q, *J* = 7.3 Hz, 2H), 1.38 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 140.7, 140.3, 130.7, 129.0, 127.8, 127.7, 127.0, 125.3, 119.0, 118.5, 40.6, 14.8.

HRMS calcd for $[M+Na]^+$ $C_{17}H_{15}NOSNa$ 304.0767, found: 304.0764.

2-Ethoxy-5-(*p*-tolyl)thiazole (10a)

Following procedure A, 4-bromotoluene (0.171 g, 1 mmol) and 2-ethoxythiazole (0.194 g, 1.5 mmol) affords **10a** in 54% (0.118 g) yield as a white solid: mp 36-38 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, *J* = 8.1 Hz, 2H), 7.28 (s, 1H), 7.18 (d, *J* = 8.1 Hz, 2H), 4.50 (q, *J* = 7.3 Hz, 2H), 2.37 (s, 3H), 1.47 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.4, 137.5, 131.6, 131.0, 129.7, 129.2, 125.9, 67.5, 21.3, 14.6.

HRMS calcd for $[M+Na]^+$ $C_{12}H_{13}NOSNa$ 242.0610, found: 242.0611.

3-Ethyl-5-(*p*-tolyl)thiazol-2(3H)-one (10b)

Following procedure B at 140 °C, 4-bromotoluene (0.171 g, 1 mmol) and 2-ethoxythiazole (0.194 g, 1.5 mmol) affords **10b** in 43% (0.094 g) yield as a yellow solid: mp 81-83 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.1 Hz, 2H), 7.16 (d, *J* = 8.1 Hz, 2H), 6.77 (s, 1H), 3.81 (q, *J* = 7.3 Hz, 2H), 2.35 (s, 3H), 1.36 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 137.8, 129.8, 128.9, 124.9, 119.0, 118.3, 40.5, 21.3, 14.8.

HRMS calcd for $[M+Na]^+$ $C_{12}H_{13}NOSNa$ 242.0610, found: 242.0611.

2-Ethoxy-5-(4-methoxyphenyl)thiazole (11a)

Following procedure A, 4-bromoanisole (0.187 g, 1 mmol) and 2-ethoxythiazole (0.194 g, 1.5 mmol) affords **11a** in 13% (0.030 g) yield as a white solid: mp 78-80 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, *J* = 8.2 Hz, 2H), 7.18 (s, 1H), 6.90 (d, *J* = 8.2 Hz, 2H), 4.48 (q, *J* = 7.3 Hz, 2H), 3.82 (s, 3H), 1.45 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.8, 159.4, 131.0, 127.4, 124.7, 114.5, 67.5, 55.5, 14.7.

HRMS calcd for $[M+Na]^+$ $C_{12}H_{13}NO_2SNa$ 258.0559, found: 258.0560.

3-(2-Ethoxythiazol-5-yl)benzaldehyde (12a)

Following procedure A, 3-bromobenzaldehyde (0.185 g, 1 mmol) and 2-ethoxythiazole (0.194 g, 1.5 mmol) affords **12a** in 56% (0.130 g) yield as a yellow solid: mp 66-68 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.03 (s, 1H), 7.92 (s, 1H), 7.76 (d, *J* = 7.8 Hz, 1H), 7.68 (d, *J* = 7.8 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.40 (s, 1H), 4.50 (q, *J* = 7.3 Hz, 2H), 1.46 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 192.0, 174.3, 137.1, 133.3, 133.2, 131.5, 129.8, 129.4, 128.9, 126.4, 67.9, 14.6.

HRMS calcd for $[M+Na]^+$ $C_{12}H_{11}NO_2SNa$ 256.0403, found: 256.0403.

1-(3-(2-Ethoxythiazol-5-yl)phenyl)ethan-1-one (13a)

Following procedure A, 3-bromoacetophenone (0.199 g, 1 mmol) and 2-ethoxythiazole (0.194 g, 1.5 mmol) affords **13a** in 77% (0.190 g) yield as a yellow solid: mp 58-60 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (s, 1H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.59 (d, *J* = 8.2 Hz, 1H), 7.41 (t, *J* = 7.8 Hz, 1H), 7.36 (s, 1H), 4.47 (q, *J* = 7.3 Hz, 2H), 2.59 (s, 3H), 1.43 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 197.7, 174.0, 137.8, 132.9, 132.7, 130.2, 129.3, 127.4, 125.3, 67.7, 26.7, 14.5.

HRMS calcd for $[M+Na]^+$ $C_{13}H_{13}NO_2SNa$ 270.0559, found: 270.0559.

5-(3-Acetylphenyl)-3-ethylthiazol-2(3H)-one (13b)

Following procedure B, 3-bromoacetophenone (0.199 g, 1 mmol) and 2-ethoxythiazole (0.194 g, 1.5 mmol) affords **13b** in 57% (0.141 g) yield as a yellow solid: mp 113-115 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (s, 1H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.52-7.41 (m, 2H), 6.95 (s, 1H), 3.82 (q, *J* = 7.3 Hz, 2H), 2.62 (s, 3H), 1.37 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 197.7, 170.5, 137.8, 132.4, 129.4, 129.3, 127.6, 124.1, 120.0, 117.7, 40.7, 26.8, 14.8.

HRMS calcd for $[M+Na]^+$ $C_{13}H_{13}NO_2SNa$ 270.0559, found: 270.0561.

2-Ethoxy-5-(3-fluorophenyl)thiazole (14a)

Following procedure A, 3-bromofluorobenzene (0.175 g, 1 mmol) and 2-ethoxythiazole (0.194 g, 1.5 mmol) affords **14a** in 68% (0.151 g) yield as a white solid: mp 60-62 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.25 (m, 2H), 7.20 (d, *J* = 8.0 Hz, 1H), 7.13 (dt, *J* = 8.0, 1.2 Hz, 1H), 6.95 (dd, *J* = 8.0, 1.4 Hz, 1H), 4.48 (q, *J* = 7.3 Hz, 2H), 1.45 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.8, 163.1 (d, *J* = 247.0 Hz), 134.2 (d, *J* = 8.3 Hz), 133.0, 130.6 (d, *J* = 8.7 Hz), 129.6, 121.6 (d, *J* = 2.9 Hz), 114.4 (d, *J* = 21.3 Hz), 112.7 (d, *J* = 23.0 Hz), 67.8, 14.6.

HRMS calcd for $[M+Na]^+$ $C_{11}H_{10}FNOSNa$ 246.0359, found: 246.0358.

3-Ethyl-5-(3-fluorophenyl)thiazol-2(3H)-one (14b)

Following procedure B, 3-bromofluorobenzene (0.175 g, 1 mmol) and 2-ethoxythiazole (0.194 g, 1.5 mmol) affords **14b** in 55% (0.123 g) yield as a yellow solid: mp 68-70 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.28 (m, 1H), 7.10 (d, *J* = 8.0 Hz, 1H), 7.03 (dt, *J* = 8.0, 1.2 Hz, 1H), 6.99 (dd, *J* = 8.0, 1.4 Hz, 1H), 6.86 (s, 1H), 3.82 (q, *J* = 7.3 Hz, 2H), 1.37 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 163.2 (d, *J* = 247.0 Hz), 133.9 (d, *J* = 8.3 Hz), 130.7 (d, *J* = 8.7 Hz), 120.6 (d, *J* = 3.0 Hz), 119.9, 117.6, 114.7 (d, *J* = 21.3 Hz), 111.8 (d, *J* = 22.2 Hz), 40.7, 14.8.

HRMS calcd for $[M+Na]^+$ $C_{11}H_{10}FNOSNa$ 246.0359, found: 246.0359.

2-(2-Ethoxythiazol-5-yl)benzonitrile (15a)

Following procedure A, 2-bromobenzonitrile (0.182 g, 1 mmol) and 2-ethoxythiazole (0.194 g, 1.5 mmol) affords **15a** in 75% (0.172 g) yield as a white solid: mp 64-66 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.58 (s, 1H), 7.57 (td, *J* = 7.8, 1.3 Hz, 1H), 7.46 (d, *J* = 8.2 Hz, 1H), 7.36 (td, *J* = 7.8, 1.3 Hz, 1H), 4.51 (q, *J* = 7.3 Hz, 2H), 1.45 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.2, 136.7, 135.1, 134.4, 133.1, 129.5, 127.8, 126.1, 118.6, 110.1, 68.0, 14.6.

HRMS calcd for $[M+Na]^+$ $C_{12}H_{10}N_2OSNa$ 253.0406, found: 253.0408.

2-(3-Ethyl-2-oxo-2,3-dihydrothiazol-5-yl)benzonitrile (15b)

Following procedure B, 2-bromobenzonitrile (0.182 g, 1 mmol) and 2-ethoxythiazole (0.194 g, 1.5 mmol) affords **15b** in 84% (0.193 g) yield as a white solid: mp 60-62 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, *J* = 8.2 Hz, 1H), 7.58 (t, *J* = 7.8 Hz, 1H), 7.40-7.31 (m, 3H), 3.84 (q, *J* = 7.3 Hz, 2H), 1.37 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 134.5, 133.4, 128.5, 127.6, 124.1, 118.8, 114.0, 108.6, 40.9, 14.7.

HRMS calcd for $[M+Na]^+$ $C_{12}H_{10}N_2OSNa$ 253.0406, found: 253.0406.

2-Ethoxy-5-(2-nitrophenyl)thiazole (16a)

Following procedure A, 2-bromonitrobenzene (0.202 g, 1 mmol) and 2-ethoxythiazole (0.194 g, 1.5 mmol) affords **16a** in 72% (0.180 g) yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 8.2 Hz, 1H), 7.60 (t, *J* = 7.8 Hz, 1H), 7.53-7.45 (m, 2H), 7.11 (s, 1H), 4.50 (q, *J* = 7.3 Hz, 2H), 1.46 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.7, 149.4, 136.2, 132.7, 132.4, 129.1, 125.9, 124.3, 123.8, 68.0, 14.6.

HRMS calcd for $[M+Na]^+$ $C_{11}H_{10}N_2O_3SNa$ 273.0304, found: 273.0305.

3-Ethyl-5-(2-nitrophenyl)thiazol-2(3H)-one (16b)

Following procedure B, 2-bromonitrobenzene (0.202 g, 1 mmol) and 2-ethoxythiazole (0.194 g, 1.5 mmol) affords **16b** in 74% (0.185 g) yield as a yellow solid: mp 67-69 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.2 Hz, 1H), 7.60 (t, *J* = 7.8 Hz, 1H), 7.49-7.43 (m, 2H), 6.69 (s, 1H), 3.80 (q, *J* = 7.3 Hz, 2H), 1.34 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 149.2, 132.5, 131.9, 129.1, 125.7, 124.4, 123.2, 112.0, 40.8, 14.8.

HRMS calcd for $[M+Na]^+$ $C_{11}H_{10}N_2O_3SNa$ 273.0304, found: 273.0306.

2-(2-Ethoxythiazol-5-yl)benzaldehyde (17a)

Following procedure A, 2-bromobenzaldehyde (0.185 g, 1 mmol) and 2-ethoxythiazole (0.194 g, 1.5 mmol) affords **17a** in 85% (0.198 g) yield as a yellow solid: mp 72-74 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.23 (s, 1H), 7.99 (d, *J* = 8.2 Hz, 1H), 7.60 (td, *J* = 7.8, 1.4 Hz, 1H), 7.52-7.43 (m, 2H), 7.03 (s, 1H), 4.52 (q, *J* = 7.3 Hz, 2H), 1.47 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 191.5, 175.6, 137.6, 134.8, 134.6, 133.9, 131.6, 128.7, 128.4, 125.0, 68.0, 14.6.

HRMS calcd for $[M+Na]^+$ $C_{12}H_{11}NO_2SNa$ 256.0403, found: 256.0403.

2-Ethoxy-5-(2-fluorophenyl)thiazole (18a)

Following procedure A, 2-bromofluorobenzene (0.175 g, 1 mmol) and 2-ethoxythiazole (0.194 g, 1.5 mmol) affords **18a** in 81% (0.180 g) yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (s, 1H), 7.46 (td, *J* = 7.6, 2.0 Hz, 1H), 7.25-7.20 (m, 1H), 7.17-7.09 (m, 2H), 4.51 (q, *J* = 7.3 Hz, 2H), 1.47 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.8, 159.0 (d, *J* = 249.0 Hz), 135.5 (d, *J* = 7.6 Hz), 128.8 (d, *J* = 8.2 Hz), 128.4 (d, *J* = 3.5 Hz), 124.7 (d, *J* = 3.4 Hz), 124.0, 120.0 (d, *J* = 13.5 Hz), 116.3 (d, *J* = 22.1 Hz), 67.9, 14.7.

HRMS calcd for $[M+Na]^+$ $C_{11}H_{10}FNOSNa$ 246.0359, found: 246.0361.

3-Ethyl-5-(2-fluorophenyl)thiazol-2(3H)-one (18b)

Following procedure B, 2-bromofluorobenzene (0.175 g, 1 mmol) and 2-ethoxythiazole (0.194 g, 1.5 mmol) affords **18b** in 76% (0.169 g) yield as a yellow solid: mp 54-56 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.18 (m, 2H), 7.16-7.10 (m, 2H), 7.09 (s, 1H), 3.82 (q, *J* = 7.3 Hz, 2H), 1.37 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 159.4 (d, *J* = 249.5 Hz), 128.5 (d, *J* = 8.6 Hz), 127.7 (d, *J* = 3.5 Hz), 124.8 (d, *J* = 3.5 Hz), 123.5 (d, *J* = 14.6 Hz), 119.7 (d, *J* = 12.2 Hz), 116.2 (d, *J* = 22.0 Hz), 112.5 (d, *J* = 3.1 Hz), 40.7, 14.8.

HRMS calcd for $[M+Na]^+$ $C_{11}H_{10}FNOSNa$ 246.0359, found: 246.0359.

2-Ethoxy-5-(*o*-tolyl)thiazole (19a)

Following procedure A, 2-bromotoluene (0.171 g, 1 mmol) and 2-ethoxythiazole (0.194 g, 1.5 mmol) affords **19a** in 16% (0.035 g) yield as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (d, *J* = 7.9 Hz, 1H), 7.30-7.17 (m, 3H), 7.07 (s, 1H), 4.51 (q, *J* = 7.3 Hz, 2H), 2.41 (s, 3H), 1.47 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.8, 136.6, 134.6, 131.2, 130.9, 130.6, 128.3, 126.2, 67.6, 21.2, 14.7.

HRMS calcd for $[M+Na]^+$ $C_{12}H_{13}NOSNa$ 242.0610, found: 242.0609.

3-Ethyl-5-(*o*-tolyl)thiazol-2(3H)-one (19b)

Following procedure B, 2-bromotoluene (0.171 g, 1 mmol) and 2-ethoxythiazole (0.194 g, 1.5 mmol) affords **19b** in 18% (0.039 g) yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.15 (m, 4H), 6.53 (s, 1H), 3.82 (q, *J* = 7.3 Hz, 2H), 2.42 (s, 3H), 1.37 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5, 136.5, 131.1, 131.0, 129.9, 128.5, 126.4, 121.4, 117.9, 40.4, 21.2, 14.8.

HRMS calcd for $[M+Na]^+$ $C_{12}H_{13}NOSNa$ 242.0610, found: 242.0612.

2-Ethoxy-5-(naphthalen-1-yl)thiazole (20a)

Following procedure A, 1-bromonaphthalene (0.207 g, 1 mmol) and 2-ethoxythiazole (0.194 g, 1.5 mmol) affords **13a bis** in 64% (0.164 g) yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25-8.19 (m, 1H), 7.92-7.83 (m, 2H), 7.56-7.44 (m, 4H), 7.23 (s, 1H), 4.55 (q, *J* = 7.3 Hz, 2H), 1.51 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.8, 135.5, 133.9, 132.2, 129.2, 129.0, 128.7, 128.5, 127.8, 126.8, 126.3, 125.5, 125.4, 67.6, 14.7.

HRMS calcd for $[M+Na]^+$ $C_{15}H_{13}NOSNa$ 278.0610, found: 278.0614.

3-Ethyl-5-(naphthalen-1-yl)thiazol-2(3H)-one (20b)

Following procedure B, 1-bromonaphthalene (0.207 g, 1 mmol) and 2-ethoxythiazole (0.194 g, 1.5 mmol) affords **20b** in 51% (0.130 g) yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, *J* = 8.0 Hz, 1H), 7.92-7.83 (m, 2H), 7.56-7.44 (m, 4H), 6.71 (s, 1H), 3.88 (q, *J* = 7.3 Hz, 2H), 1.41 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 134.0, 131.9, 129.4, 129.2, 128.7, 128.2, 126.9, 126.4, 125.5, 125.1, 122.1, 116.6, 40.5, 14.9.

HRMS calcd for $[M+Na]^+$ $C_{15}H_{13}NOSNa$ 278.0610, found: 278.0607.

2-Ethoxy-5-(pyridin-3-yl)thiazole (21a)

Following procedure A, 3-bromopyridine (0.158 g, 1 mmol) and 2-ethoxythiazole (0.194 g, 1.5 mmol) affords **21a** in 34% (0.070 g) yield as a yellow solid: mp 132-134 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.72 (bs, 1H), 8.51 (bs, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.37 (s, 1H), 7.32 (dd, *J* = 8.0, 4.8 Hz, 1H), 4.51 (q, *J* = 7.3 Hz, 2H), 1.46 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.6, 148.3, 146.6, 133.7, 133.3, 128.6, 126.9, 123.9, 68.0, 14.6.

HRMS calcd for $[M+Na]^+$ $C_{10}H_{10}N_2OSNa$ 229.0406, found: 229.0404.

3-Ethyl-5-(pyridin-3-yl)thiazol-2(3H)-one (21b)

Following procedure B, 3-bromopyridine (0.158 g, 1 mmol) and 2-ethoxythiazole (0.194 g, 1.5 mmol) affords **21b** in 82% (0.169 g) yield as a yellow solid: mp 87-89 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.68 (bs, 1H), 8.51 (bs, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.32 (dd, *J* = 8.0, 4.8 Hz, 1H), 6.95 (s, 1H), 3.84 (q, *J* = 7.3 Hz, 2H), 1.38 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 148.3, 145.6, 132.5, 128.3, 124.0, 120.5, 115.0, 40.8, 14.8.

HRMS calcd for $[M+Na]^+$ $C_{10}H_{10}N_2OSNa$ 229.0406, found: 229.0404.

2-Ethoxy-5-(quinolin-3-yl)thiazole (22a)

Following procedure A, 3-bromoquinoline (0.208 g, 1 mmol) and 2-ethoxythiazole (0.194 g, 1.5 mmol) affords **22a** in 65% (0.166 g) yield as a yellow solid: mp 115-117 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.07 (d, *J* = 2.2 Hz, 1H), 8.11 (d, *J* = 8.0 Hz, 1H), 8.09 (d, *J* = 2.2 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.70 (t, *J* = 8.0 Hz, 1H), 7.57 (t, *J* = 8.0 Hz, 1H), 7.51 (s, 1H), 4.54 (q, *J* = 7.3 Hz, 2H), 1.48 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.5, 147.9, 147.0, 133.8, 131.8, 129.7, 129.3, 128.0, 127.8, 127.6, 127.5, 125.6, 68.0, 14.6.

HRMS calcd for $[M+Na]^+$ $C_{14}H_{12}N_2OSNa$ 279.0562, found: 279.0564.

3-Ethyl-5-(quinolin-3-yl)thiazol-2(3H)-one (22b)

Following procedure B, 3-bromoquinoline (0.208 g, 1 mmol) and 2-ethoxythiazole (0.194 g, 1.5 mmol) affords **22b** in 54% (0.138 g) yield as a yellow solid: mp 164-166 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.00 (s, 1H), 8.10 (d, *J* = 8.0 Hz, 1H), 7.94 (d, *J* = 2.2 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.71 (t, *J* = 8.0 Hz, 1H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.08 (s, 1H), 3.87 (q, *J* = 7.3 Hz, 2H), 1.41 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 147.0, 146.6, 134.3, 131.1, 129.8, 129.2, 127.9, 127.8, 125.7, 120.7, 115.7, 40.9, 14.8.

HRMS calcd for $[M+Na]^+$ $C_{14}H_{12}N_2OSNa$ 279.0562, found: 279.0563.

3-Methyl-5-(4-propionylphenyl)thiazol-2(3H)-one (23b)

Following procedure B, 4-bromopropiophenone (0.213 g, 1 mmol) and 2-methoxythiazole (0.173 g, 1.5 mmol) affords **23b** in 64% (0.158 g) yield as a yellow solid: mp 144-146 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, *J* = 8.3 Hz, 2H), 7.39 (d, *J* = 8.3 Hz, 2H), 6.96 (s, 1H), 2.99 (q, *J* = 7.6 Hz, 2H), 3.42 (s, 3H), 1.23 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 199.9, 170.9, 135.9, 135.8, 128.9, 124.6, 122.1, 117.5, 32.5, 31.9, 8.4.

HRMS calcd for $[M+Na]^+$ $C_{13}H_{13}NO_2SNa$ 270.0559, found: 270.0559.

5-(4-Chlorophenyl)-3-methylthiazol-2(3H)-one (24b)

Following procedure B, 4-bromochlorobenzene (0.192 g, 1 mmol) and 2-methoxythiazole (0.173 g, 1.5 mmol) affords **24b** in 48% (0.108 g) yield as a yellow solid: mp 146-148 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.3 Hz, 2H), 6.82 (s, 1H), 3.41 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 133.6, 130.2, 129.3, 126.1, 120.7, 117.5, 32.4.

HRMS calcd for $[M+Na]^+$ $C_{10}H_8ClNOSNa$ 247.9907, found: 247.9907.

5-(4-Fluorophenyl)-3-methylthiazol-2(3H)-one (25b)

Following procedure B, 4-bromofluorobenzene (0.175 g, 1 mmol) and 2-methoxythiazole (0.173 g, 1.5 mmol) affords **25b** in 37% (0.77 g) yield as a yellow solid: mp 125-127 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (dd, *J* = 8.3, 5.2 Hz, 2H), 7.07 (t, *J* = 8.2 Hz, 2H), 6.73 (s, 1H), 3.38 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 162.3 (d, *J* = 247.5 Hz), 127.9 (d, *J* = 3.4 Hz), 126.7 (d, *J* = 8.1 Hz), 120.2, 117.7, 116.2 (d, *J* = 22.0 Hz), 32.4.

HRMS calcd for $[M+Na]^+$ $C_{10}H_8FNOSNa$ 232.0203, found: 232.0204.

5-(3-Chlorophenyl)-3-methylthiazol-2(3H)-one (26b)

Following procedure B, 3-bromochlorobenzene (0.192 g, 1 mmol) and 2-methoxythiazole (0.173 g, 1.5 mmol) affords **26b** in 57% (0.128 g) yield as a yellow solid: mp 138-140 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.32 (m, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.28 (t, *J* = 7.9 Hz, 1H), 7.22 (d, *J* = 7.8 Hz, 1H), 6.87 (s, 1H), 3.42 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 135.1, 133.4, 130.4, 127.8, 124.8, 123.1, 121.3, 117.1, 32.4.

HRMS calcd for $[M+Na]^+$ $C_{10}H_8ClNOSNa$ 247.9907, found: 247.9905.

3-Methyl-5-(3-fluorophenyl)thiazol-2(3H)-one (27b)

Following procedure B, 3-bromofluorobenzene (0.175 g, 1 mmol) and 2-methoxythiazole (0.173 g, 1.5 mmol) affords **27b** in 45% (0.094 g) yield as a white solid: mp 116-118 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.28 (m, 1H), 7.10 (d, *J* = 8.0 Hz, 1H), 7.03 (dt, *J* = 8.0, 1.2 Hz, 1H), 6.99 (dd, *J* = 8.0, 1.4 Hz, 1H), 6.84 (s, 1H), 3.39 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 163.2 (d, *J* = 247.0 Hz), 133.7 (d, *J* = 8.3 Hz), 130.7 (d, *J* = 8.7 Hz), 121.2, 120.6 (d, *J* = 3.0 Hz), 117.3 (d, *J* = 2.9 Hz), 114.7 (d, *J* = 21.3 Hz), 111.8 (d, *J* = 22.2 Hz), 32.4.

HRMS calcd for $[M+Na]^+$ $C_{10}H_8FNOSNa$ 232.0203, found: 232.0205.

5-(2-Chlorophenyl)-3-methylthiazol-2(3H)-one (28b)

Following procedure B, 2-bromochlorobenzene (0.192 g, 1 mmol) and 2-methoxythiazole (0.173 g, 1.5 mmol) affords **28b** in 60% (0.135 g) yield as a white solid: mp 79-81 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.33 (dd, *J* = 7.8, 1.9 Hz, 1H), 7.27 (t, *J* = 7.9 Hz, 1H), 7.23 (t, *J* = 7.8 Hz, 1H), 6.99 (s, 1H), 3.40 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4, 132.1, 130.9, 130.4, 130.1, 129.0, 127.3, 124.8, 114.8, 32.4.

HRMS calcd for $[M+Na]^+$ $C_{10}H_8ClNOSNa$ 247.9907, found: 247.9908.

2-Butoxy-5-(*p*-tolyl)thiazole (29a)

Following procedure A, 4-bromotoluene (0.171 g, 1 mmol) and 2-*n*butoxythiazole (0.235 g, 1.5 mmol) at 120 °C, affords **29a** in 53% (0.131 g) yield as a yellow solid: mp 57-59 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, *J* = 8.1 Hz, 2H), 7.28 (s, 1H), 7.18 (d, *J* = 8.1 Hz, 2H), 4.43 (t, *J* = 7.3 Hz, 2H), 2.37 (s, 3H), 1.81 (quint., *J* = 7.2 Hz, 2H), 1.55 (sext., *J* = 7.2 Hz, 2H), 1.00 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.6, 137.5, 131.6, 131.0, 129.7, 129.3, 125.9, 71.5, 31.0, 21.3, 19.2, 13.9.

HRMS calcd for $[M+Na]^+$ $C_{14}H_{17}NOSNa$ 270.0923, found: 270.0922.

3-Butyl-5-(*p*-tolyl)thiazol-2(3H)-one (29b)

Following procedure B, 4-bromotoluene (0.171 g, 1 mmol) and 2-*n*butoxythiazole (0.235 g, 1.5 mmol) at 140 °C, affords **29b** in 18% (0.044 g) yield as a yellow solid: mp 61-63 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.1 Hz, 2H), 7.16 (d, *J* = 8.1 Hz, 2H), 6.75 (s, 1H), 3.74 (t, *J* = 7.3 Hz, 2H), 2.35 (s, 3H), 1.71 (quint., *J* = 7.2 Hz, 2H), 1.41 (sext., *J* = 7.2 Hz, 2H), 0.97 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 137.8, 129.8, 128.9, 124.9, 118.8, 118.7, 45.3, 31.6, 21.3, 20.0, 13.8.

HRMS calcd for $[M+Na]^+$ $C_{14}H_{17}NOSNa$ 270.0923, found: 270.0921.

4-(2-Butoxythiazol-5-yl)benzonitrile (30a)

Following procedure A, 4-bromobenzonitrile (0.182 g, 1 mmol) and 2-*n*butoxythiazole (0.235 g, 1.5 mmol) at 120 °C, affords **30a** in 78% (0.201 g) yield as a white solid: mp 86-88 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, *J* = 8.1 Hz, 2H), 7.49 (d, *J* = 8.1 Hz, 2H), 7.42 (s, 1H), 4.43 (t, *J* = 7.3 Hz, 2H), 1.79 (quint., *J* = 7.2 Hz, 2H), 1.53 (sext., *J* = 7.2 Hz, 2H), 0.97 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.1, 136.6, 134.7, 132.8, 128.9, 125.9, 118.7, 110.6, 72.0, 30.9, 19.1, 13.8.

HRMS calcd for $[M+Na]^+$ $C_{14}H_{14}N_2OSNa$ 281.0719, found: 281.0720.

4-(3-Butyl-2-oxo-2,3-dihydrothiazol-5-yl)benzonitrile (30b)

Following procedure B, 4-bromobenzonitrile (0.182 g, 1 mmol) and 2-*n*butoxythiazole (0.235 g, 1.5 mmol) at 130 °C, affords **30b** in 74% (0.191 g) yield as a white solid: mp 136-138 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.3 Hz, 2H), 7.41 (d, *J* = 8.3 Hz, 2H), 6.99 (s, 1H), 3.78 (t, *J* = 7.3 Hz, 2H), 1.73 (quint., *J* = 7.2 Hz, 2H), 1.42 (sext., *J* = 7.2 Hz, 2H), 0.97 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 136.2, 132.9, 125.0, 122.2, 118.7, 116.5, 110.8, 45.7, 31.5, 19.9, 13.7.

HRMS calcd for $[M+Na]^+$ $C_{14}H_{14}N_2OSNa$ 281.0719, found: 281.0721.

3-Butyl-5-(4-(trifluoromethyl)phenyl)thiazol-2(3H)-one (31b)

Following procedure B, 4-bromobenzotrifluoride (0.225 g, 1 mmol) and 2-*n*butoxythiazole (0.235 g, 1.5 mmol) at 120 °C, affords **31b** in 61% (0.183 g) yield as a yellow solid: mp 98-100 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, *J* = 8.3 Hz, 2H), 7.42 (d, *J* = 8.3 Hz, 2H), 6.94 (s, 1H), 3.77 (t, *J* = 7.3 Hz, 2H), 1.72 (quint., *J* = 7.2 Hz, 2H), 1.42 (sext., *J* = 7.2 Hz, 2H), 0.97 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 135.2, 129.5 (q, *J* = 32.8 Hz), 126.1 (q, *J* = 3.8 Hz), 124.9, 124.0 (q, *J* = 272.0 Hz), 121.2, 116.9, 45.6, 31.5, 19.9, 13.7.

HRMS calcd for $[M+Na]^+$ $C_{14}H_{14}F_3NOSNa$ 324.0640, found: 324.0642.

4-(2-Oxo-3-phenethyl-2,3-dihydrothiazol-5-yl)benzonitrile (32b)

Following procedure B, 4-bromobenzonitrile (0.182 g, 1 mmol) and 2-phenethoxythiazole (0.308 g, 1.5 mmol) at 120 °C, affords **32b** in 38% (0.116 g) yield as a yellow solid: mp 146-148 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, *J* = 8.3 Hz, 2H), 7.36-7.23 (m, 5H), 7.19 (d, *J* = 8.3 Hz, 2H), 6.58 (s, 1H), 4.01 (t, *J* = 7.3 Hz, 2H), 3.03 (t, *J* = 7.3 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 137.5, 136.1, 132.8, 129.0, 128.9, 127.2, 125.0, 122.5, 118.6, 115.9, 110.8, 47.5, 35.5.

HRMS calcd for $[M+Na]^+$ $C_{18}H_{14}N_2ONaS$ 329.0719, found: 329.0720.

4-(3-Benzyl-2-oxo-2,3-dihydrothiazol-5-yl)benzonitrile (33b)

Following procedure B, 4-bromobenzonitrile (0.182 g, 1 mmol) and 2-(benzyloxy)thiazole (0.286 g, 1.5 mmol) affords **33b** in 43% (0.126 g) yield as a white solid: mp >200 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, *J* = 8.2 Hz, 2H), 7.44-7.27 (m, 7H), 6.90 (s, 1H), 4.95 (s, *2*H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 136.0, 135.5, 132.9, 129.3, 128.7, 128.1, 125.1, 121.6, 118.6, 117.1, 111.1, 49.1.

HRMS calcd for $[M+Na]^+$ $C_{17}H_{12}N_2OSNa$ 315.0562, found: 315.0562.

2-(3-Benzyl-2-oxo-2,3-dihydrothiazol-5-yl)benzonitrile (34b)

Following procedure B, 2-bromobenzonitrile (0.182 g, 1 mmol) and 2-(benzyloxy)thiazole (0.286 g, 1.5 mmol) affords **34b** in 52% (0.152 g) yield as a yellow solid: mp 98-100 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.57 (td, *J* = 8.0, 1.2 Hz, 1H), 7.41-7.30 (m, 8H), 4.96 (s, *2*H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 135.5, 134.5, 134.4, 133.4, 129.2, 128.6, 128.5, 128.2, 127.8, 124.2, 118.6, 114.3, 108.8, 49.2.

HRMS calcd for $[M+Na]^+$ $C_{17}H_{12}N_2OSNa$ 315.0562, found: 315.0564.

4-(3-(4-Fluorobenzyl)-2-oxo-2,3-dihydrothiazol-5-yl)benzonitrile (35b)

Following procedure B, 4-bromobenzonitrile (0.182 g, 1 mmol) and 2-((4-fluorobenzyl)oxy)thiazole (0.313 g, 1.5 mmol) affords **35b** in 40% (0.124 g) yield as a yellow solid: mp 147-149 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, *J* = 8.2 Hz, 2H), 7.37(d, *J* = 8.2 Hz, 2H), 7.30 (dd, *J* = 8.6, 4.9 Hz, 2H), 7.08 (t, *J* = 8.6 Hz, 2H), 6.90 (s, 1H), 4.91 (s, *2*H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 162.8 (d, *J* = 247.8 Hz), 135.9, 132.9, 131.3 (d, *J* = 3.2 Hz), 129.9 (d, *J* = 8.3 Hz), 125.2, 121.4, 118.6, 117.3, 116.3 (d, *J* = 21.8 Hz), 111.2, 48.4.

HRMS calcd for $[M+Na]^+$ $C_{17}H_{11}FN_2ONa$ 333.0468, found: 333.0468.

3-Benzylthiazol-2(3H)-one (36b)[13]

The reaction of 2-(benzyloxy)thiazole (0.191 g, 1 mmol) and KOAc (0.196 g, 2 mmol) in the presence of $Pd(OAc)_2$ (2.2 mg, 1 mol%) in DMA (5 mL) under argon at 120 °C during 16 h, affords **36b** after cooling, evaporation of the solvent and filtration on silica gel (pentane/ether 4/1) in 81% (0.155 g) yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.21 (m, 5H), 6.48 (d, *J* = 5.4 Hz, 1H), 6.09 (d, *J* = 5.4 Hz, 1H), 4.86 (s, *2*H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 136.0, 129.0, 128.2, 127.9, 124.3, 101.6, 48.7.

4.5 References

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Chapter 5:

Regiocontrolled palladium-catalyzed direct C2-arylation of a difluorobenzo[*d*]imidazole

Chapter 5

Regiocontrolled palladium-catalyzed direct C2-arylation of a difluorobenzo[*d*]imidazole

5.1 Introduction

Fluoro-substituted benzimidazole units can be found in several important drugs (Fig. 5.1).[1] For example, Abemaciclib is a drug for the treatment of advanced or metastatic breast cancers which was designated as a "breakthrough therapy" for breast cancer by the U.S. Food and Drug Administration in October 2015 (Fig. 5.1, left). Selumetinib[1a] and Binimetinib[1b] are also an anti-cancer drugs developed to treat various cancers.

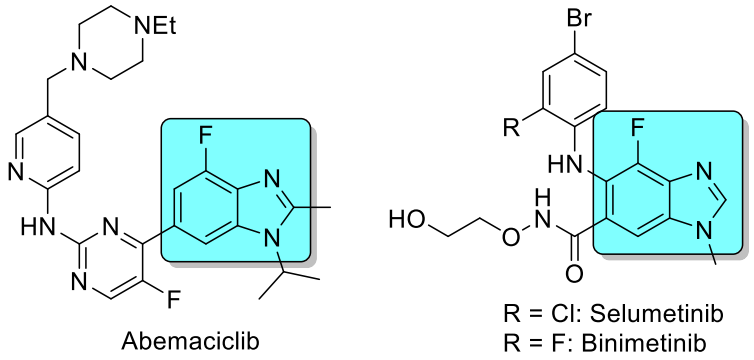
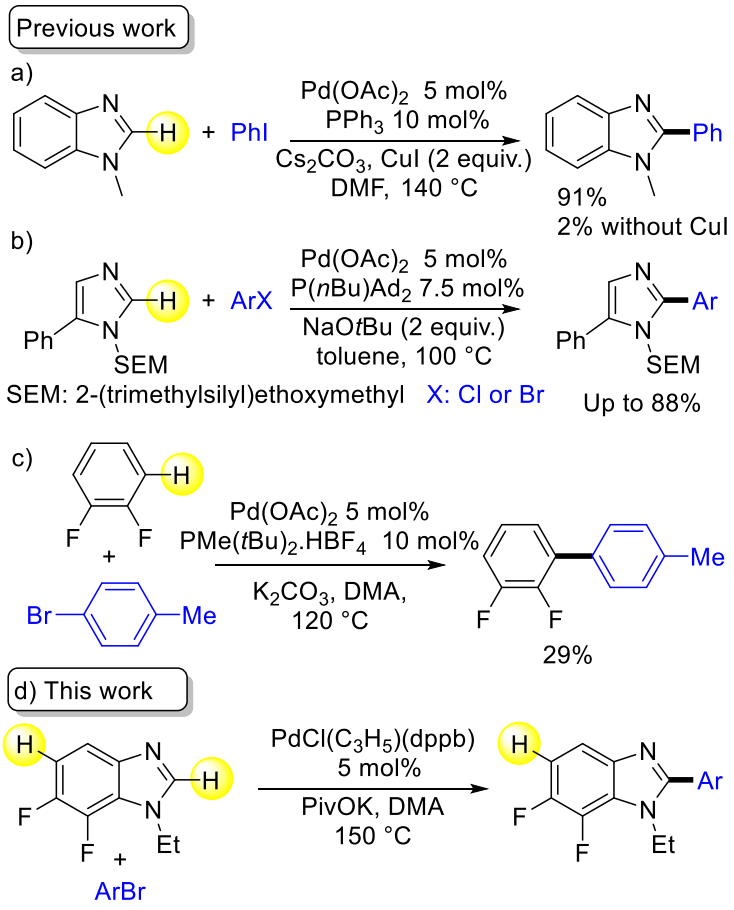


Figure 5.1. Representative examples of drugs containing a fluorobenzimidazole unit.

As explained in the previous chapters, since the seminal work by Ohta et al. in 1990 on the Pd-catalyzed arylation of a wide range of 5-membered ring heteroaromatics such as pyrroles, indoles or thiophenes, *via* a C-H bond functionalization,[2] the so-called direct arylation of heteroarenes has been demonstrated to be a very effective tool to access (hetero)biaryls.[3,4] When this methodology can be employed to the late-stage functionalization of drugs, it provides a very convenient method for the access to a library of compounds in only a few steps

allowing an easier screening of the biological properties of a family of compounds with a specific unit.

The first example of Pd-catalyzed direct arylation of a benzimidazole[5] was reported by Miura and co-workers who obtained 2-phenylbenzimidazole from 1-methylbenzo[*d*]imidazole and iodobenzene using $Pd(OAc)_2$ as the catalyst (Scheme 5.1, a).[5a] In 2010, Sames et al. described a general Pd-catalyzed approach to arylated imidazoles (Scheme 5.1, b).[5f] For the C2-arylation of imidazoles, they employed $Pd(OAc)_2$/P(*n*Bu)Ad_2 associated to NaO*t*Bu as the base. Polyfluorobenzenes are also a very important class of substrates in Pd-catalyzed direct arylation, as many of them allow to obtain the corresponding biaryls in good yields.[6-8] Even 1,2-difluorobenzene was found to afford the corresponding difluorobiaryl using $Pd(OAc)_2$/PMe(*t*Bu)$_2$ and K_2CO_3 as the catalytic system with 4-bromotoluene as coupling partner (Scheme 5.1, c).[8a]



Scheme 5.1. Pd-catalyzed direct arylations of benzimidazoles and difluorobenzenes with aryl halides.

According to Gorelsky calculations, the arylation of polyfluorobenzene rings using aryl halides as the aryl source likely proceed *via* a concerted metallation deprotonation (CMD) mechanism.[9] The energy of activation of C-H bonds flanked by a fluoro substituent is higher for fluorobenzene (30.3 kcal mol^{-1}), than for 1,2,3-trifluorobenzene (28.8 kcal mol^{-1}) (Fig. 5.2, top left). Therefore, for 1,2-difluorobenzene it should be located between these two values.[9b] Gorelsky also calculated the energy of activation for C2-arylation of 1-methylimidazole via a CMD mechanism (26.5 kcal mol^{-1}) (Fig. 5.2, top right). Conversely, for (benzo)imidazoles, according to Gandon and Hoarau computational study the presence of a coordinating nitrogen atom may be involved in the mechanism.[10] The azole coordination on palladium would strongly favor a non-concerted metallation deprotonation (*n*CMD) mechanism (Fig. 5.2, bottom right). Their calculations using a carbonate as base/ligand gives an energy of activation of 27.1 for the *n*CMD and 29.7 for the CMD mechanisms.[10] Therefore, from a polyfluoro-substituted benzimidazole, a regioselective arylation at the C2-position was conceivable. However, to the best of our knowledge, the Pd-catalyzed direct arylation methodology has not been applied to the synthesis of fluoro-substituted imidazoles yet. In this chapter, we report on the site-selectivity of the Pd-catalyzed direct arylation of a difluorobenzo[*d*]imidazole and on the scope of the reaction (Scheme 5.1, d). This work was performed in collaboration with H. Li.

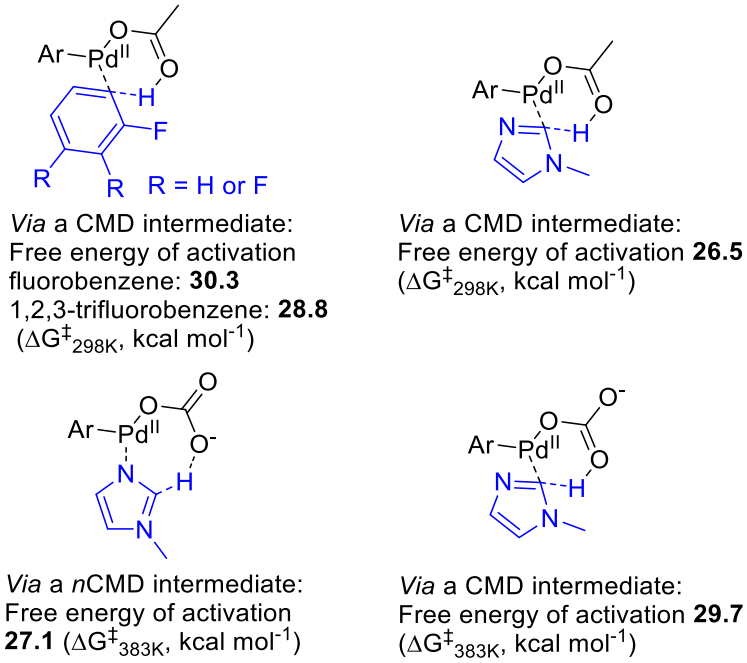
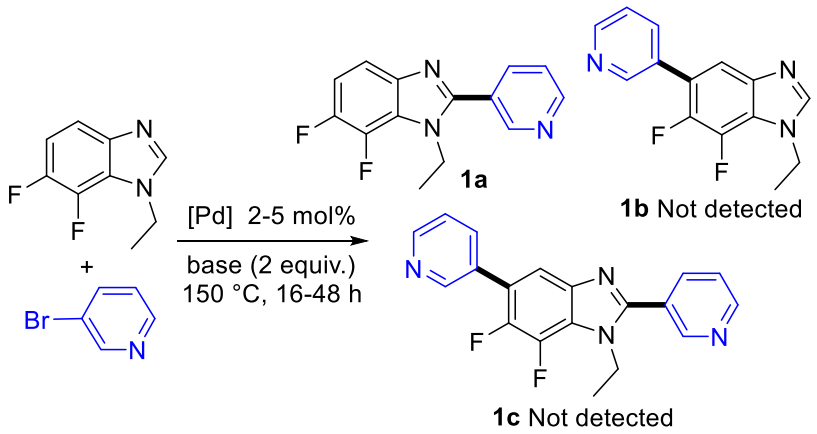


Figure 5.2 DFT calculated intermediates and energies of activation for the direct arylation of (poly)fluorobenzenes and imidazoles.

5.2 Results and Discussion

Based on our previous results on palladium-catalyzed direct arylation,[11] we first examined the regioselectivity of the arylation of 1-ethyl-6,7-difluorobenzo [*d*]imidazole with 1.5 equiv. of 3-bromopyridine. In the presence of 2 mol% $PdCl(C_3H_5)(dppb)$[12] catalyst and KOAc base at 150 °C in DMA, the C2-arylated imidazole **1a** was regioselectively obtained in 22% yield (Table 5.1, entry 1). Under these conditions, the difluorobenzene ring remained untouched. The use of Cs_2CO_3 as the base instead of KOAc provided **1a** in a very low yield; whereas, the use of PivOK using a longer reaction time improved to yield to 40% (Table 5.1, entries 2-4). The yield in **1a** was not improved by using xylene, DMF or NMP as the solvents (Table 5.1, entries 5-7). Phosphine-free catalyst $Pd(OAc)_2$ (2 mol%) gave **1a** in only 32%, but a higher loading of $PdCl(C_3H_5)(dppb)$ catalyst (5 mol%) afforded **1a** in 53% yield (Table 5.1, entries 8 and 9). The use CuI as additive or of KOPiv and Cs_2CO_3 as a mixture of bases did not improved the reaction yield (Table 5.1, entries 10 and 11). Although an excess of 3-bromopyridine was employed (1.5 equiv.), in the course of these reactions no formation of C5-arylated or C2,C5-diarylated products **1b** and **1c** was observed.

Table 1 Influence of the reaction conditions for the palladium-catalysed direct coupling of 1-ethyl-6,7-difluorobenzo[*d*]imidazole with 3-bromopyridine.



Entry	Catalyst (mol %)	Base	Solvent	Time (h)	Yield in **1a** (%)
1	$PdCl(C_3H_5)(dppb)$ (2)	KOAc	DMA	16	22
2	$PdCl(C_3H_5)(dppb)$ (2)	Cs_2CO_3	DMA	16	<5
3	$PdCl(C_3H_5)(dppb)$ (2)	KOPiv	DMA	16	25
4	$PdCl(C_3H_5)(dppb)$ (2)	KOPiv	DMA	48	40
5	$PdCl(C_3H_5)(dppb)$ (2)	KOPiv	xylene	48	15
6	$PdCl(C_3H_5)(dppb)$ (2)	KOPiv	NMP	48	20
7	$PdCl(C_3H_5)(dppb)$ (2)	KOPiv	DMF	48	34
8	$Pd(OAc)_2$ (2)	KOPiv	DMA	48	32
9	$PdCl(C_3H_5)(dppb)$ (5)	KOPiv	DMA	48	53
10	$PdCl(C_3H_5)(dppb)$ (5)	KOPiv (2 equiv.) + CuI (2 equiv.)	DMA	48	42[a]
11	$PdCl(C_3H_5)(dppb)$ (5)	KOPiv + Cs_2CO_3	DMA	48	41

Conditions: 1-Ethyl-6,7-difluorobenzo[*d*]imidazole (1 mmol), 3-bromopyridine (1.5 mmol), base (2 mmol), 150 °C, isolated yields. [a] The formation of a large amount of insoluble salt was also observed.

Then, the influence of substituents on the aryl bromide for the C2-arylation of 1-ethyl-6,7-difluorobenzo[*d*]imidazole was studied using 5 mol% $PdCl(C_3H_5)(dppb)$ catalyst and PivOK in DMA at 150 °C (Scheme 5.2). We first employed

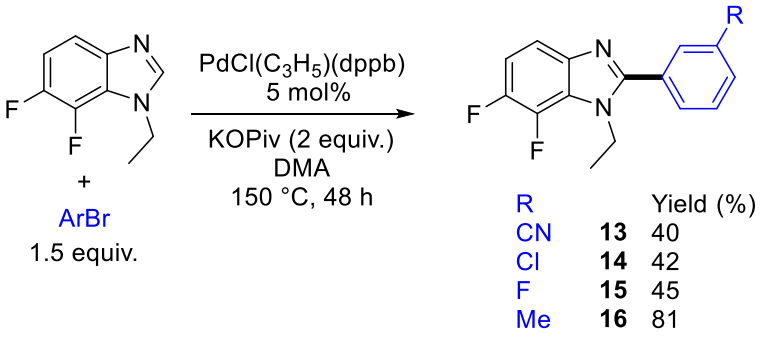
electron-deficient *para*-substituted aryl bromides. A cyano substituent at the C4-position afforded product **2** in 50%; whereas, 4-bromobenzaldehyde gave the expected C2-arylated benzimidazole **3** in only 22% yield due to the formation of degradation products. Benzoyl, trifluoromethyl, chloro and fluoro *para*-substituents on the aryl bromide were tolerated giving rise to products **4**-**7** in 36-43% yields. Under these reaction conditions, no cleavage of the C-Cl bond was observed. The electron-neutral bromobenzene and slightly electron-rich 4-bromotoluene and 4-*tert*-butylbromobenzene gave the desired coupling products **8**-**10** in 39-56% yields revealing that with these aryl bromides, the oxidative addition step is not the rate limiting step of the catalytic cycle. Conversely, the use of more electron-rich 4-bromoanisole led to the C2-arylated benzimidazole **12** in only 20% yield, due to a poor conversion.



R		Yield (%)
CN	**2**	50
CHO	**3**	22
COPh	**4**	42
CF_3	**5**	41
Cl	**6**	36
F	**7**	43
H	**8**	39
Me	**9**	56
*t*Bu	**10**	42
Ph	**11**	44
OMe	**12**	20

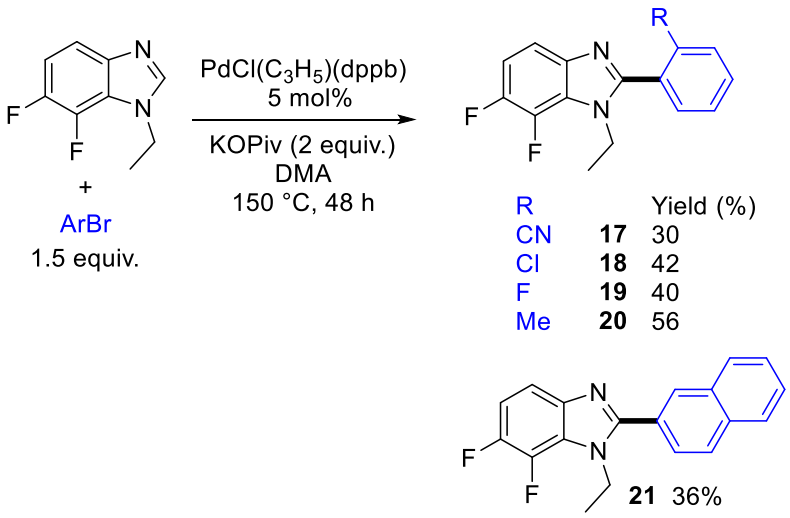
Scheme 2 Scope of the Pd-catalyzed direct C2-arylations of 1-ethyl-6,7-difluorobenzo[*d*]imidazole using *para*-substituted aryl bromides.

We also studied the influence of *meta*-substituents on the aryl bromide (Scheme 5.3). With Cyano-, chloro or fluoro-substituted aryl bromides, moderate yields in the expected products **13**-**15** were obtained; whereas more electron-rich 3-bromotoluene gave **16** in 81% yield.



Scheme 5.3. Scope of the Pd-catalyzed direct C2-arylations of 1-ethyl-6,7-difluorobenzo[*d*]imidazole using *meta*-substituted aryl bromides

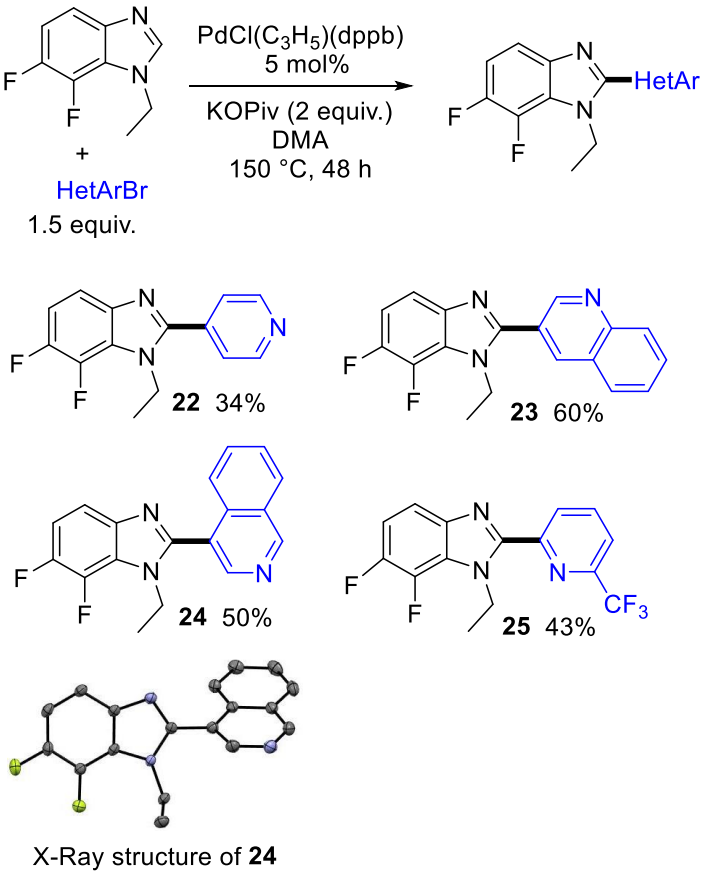
With more sterically hindered *ortho*-substituted aryl bromides, such as 2-bromobenzonitrile and 2-bromochlorobenzene, the arylated benzimidazole derivatives **17** and **18** were obtained in 30% and 42% yield, respectively (Scheme 5.4). Again the use of more-electron rich 2-bromotoluene gave the target product **20** in a higher yield of 56%. A moderate yield in **21** was obtained from 2-bromonaphthalene.



Scheme 5.4. Scope of the Pd-catalyzed direct C2-arylations of 1-ethyl-6,7-difluorobenzo[*d*]imidazole using ortho-substituted aryl bromides and 2-bromonaphthalene

The *N*-containing 6-membered ring heterocycles are present in many very important drugs.[13] Therefore, the reactivity of 4-bromopyridine, 3-bromoquinoline

and also 4-bromoisoquinoline was also studied (Scheme 5). In all cases, the desired coupling products **22**-**24** were obtained. The structure of **24** was confirmed by X-ray analysis.[14] 2-Bromo-6-(trifluoromethyl)pyridine was also found to be reactive leading to the desired arylation product **25** in 43% yield. It should be mentioned that in all cases, no other regioisomers were detected by GC/MS analysis of the crude mixtures confirming that the difluoro-substituted ring is unreactive under these conditions.



Scheme 5.5. Scope of the Pd-catalyzed direct C2-arylations of 1-ethyl-6,7-difluorobenzo[*d*]imidazole using various heteroaryl bromides

Based on our experimental results – e.g. better yields using PivOK base which is a base of choice for CMD mechanism than with Cs_2CO_3 usually employed for *n*CMD process - and on the energies of activation of the figure 2, a CMD mechanism seems to be slightly favored. However, the coordination of the imidazole unit to palladium cannot be excluded.

5.3 Conclusion

In summary, we report herein the first examples of metal-catalyzed C-H bond functionalizations of a fluoro-substituted benzimidazole. The arylation occurred regiospecifically at the C2-position of benzimidazole; whereas, the C-H bond flanked by a fluorine atom remained untouched. This selectivity might be due to the coordination of one of the nitrogen atoms of difluorobenzo[*d*]imidazole to palladium. Low to moderate yields for C2-arylated difluorobenzimidazole were obtained using aryl bromides bearing useful functional groups such as nitrile, benzoyl, formyl, chloro, fluoro, trifluoromethyl or methoxy. Nitrogen-containing heteroaryl bromides were also tolerated. Therefore, this direct arylation methodology which employs easily available reactants, catalyst and base, provides a straightforward access to fluoro-substituted 2-arylbenzimidazoles allowing to tune or modify easily their properties.

5.4. Experimental details

General:

All reactions were carried out under an inert atmosphere with standard Schlenk techniques. ^{1}H NMR spectra were recorded on Bruker GPX (400 MHz) spectrometer. Chemical shifts (δ) were reported in parts per million relative to residual chloroform (7.26 ppm for ^{1}H; 77.16 ppm for ^{13}C), constants were reported in Hertz. ^{1}H NMR assignment abbreviations were the following: singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), doublet of triplets (dt), and multiplet (m). ^{13}C NMR spectra were recorded at 100 MHz on the same spectrometer and reported in ppm. All reagents were weighed and handled in air.

Preparation of the $PdCl(C_3H_5)$(dppb) catalyst: [12]

An oven-dried 40 mL Schlenk tube equipped with a magnetic stirring bar under argon atmosphere, was charged with $[Pd(C_3H_5)Cl]_2$ (182 mg, 0.5 mmol) and dppb (426 mg, 1 mmol). 10 mL of anhydrous dichloromethane was added, then the solution was stirred at room temperature for twenty minutes. The solvent was removed in vacuum. The yellow powder was used without purification. ^{31}P NMR (81 MHz, $CDCl_3$): δ 19.3 (s).

General procedure for the synthesis of C2-arylated 1-ethyl-6,7-difluoro -benzo[*d*]imidazole:

To a 25 mL oven dried Schlenk tube, aryl bromide (1.5 mmol), 1-ethyl-6,7-difluoro-benzo[*d*]imidazole (0.182 g, 1 mmol), KOPiv (0.280 g, 2 mmol), DMA (2 mL) and $PdCl(C_3H_5)$(dppb) (30.5 mg, 0.05 mmol) were successively added. The reaction mixture was evacuated by vacuum-argon cycles (5 times) and stirred at 150 °C (oil bath temperature) for 48 hours. After cooling the reaction at room temperature and concentration, the crude mixture was purified by silica column chromatography to afford the C2-arylated 1-ethyl-6,7-difluorobenzo[*d*]imidazoles.

1-Ethyl-6,7-difluoro-2-(pyridin-3-yl)benzo[*d*]imidazole (1a):

Following general procedure, 3-bromopyridine (0.237 g, 1.5 mmol) and 1-ethyl-6,7-difluoro-benzo[*d*]imidazole (0.182 g, 1 mmol), affords **1a** in 53% (0.137 g) yield as a white solid: mp 96-98 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.96 (s, 1H), 8.78 (d, *J* = 4.3 Hz, 1H), 8.05 (d, *J* = 6.2 Hz, 1H), 7.55-7.49 (m, 2H), 7.13 (ddd, *J* = 11.1, 8.8, 7.4 Hz, 1H), 4.38 (q, *J* = 7.6 Hz, 2H), 1.52 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 151.9 (d, *J* = 2.2 Hz), 151.2, 149.7, 147.1 (dd, *J* = 241.4, 10.9 Hz), 141.6 (d, *J* = 2.1 Hz), 137.2 (dd, *J* = 239.7, 17.7 Hz), 137.0, 126.1, 124.4 (dd, *J* = 5.9, 5.2 Hz), 123.7, 115.5 (dd, *J* = 7.9, 4.2 Hz), 112.2 (d, *J* = 21.0 Hz), 41.7 (d, *J* = 3.5 Hz), 16.9 (d, *J* = 3.3 Hz).

LRMS calcd for M^+ $C_{14}H_{11}F_2N_3$ 259, found 259.

HRMS calcd for $[M+Na]^+$ $C_{14}H_{11}F_2N_3Na$ 282.0813, found 282.0810.

4-(1-Ethyl-6,7-difluorobenzo[*d*]imidazol-2-yl)benzonitrile (2):

Following general procedure, 4-bromobenzonitrile (0.273 g, 1.5 mmol) and 1-ethyl-6,7-difluoro-benzo[*d*]imidazole (0.182 g, 1 mmol), affords **2** in 50% (0.142 g) yield as a yellow solid: mp 168-170 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (s, 4H), 7.51 (ddd, *J* = 9.1, 3.8, 1.2 Hz, 1H), 7.16 (ddd, *J* = 11.1, 8.8, 7.4 Hz, 1H), 4.38 (q, *J* = 7.6 Hz, 2H), 1.52 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 152.6 (d, *J* = 2.4 Hz), 147.2 (dd, *J* = 241.4, 10.9 Hz), 141.4, 137.4 (dd, *J* = 239.7, 17.7 Hz), 134.0, 132.7, 130.1, 124.5 (dd, *J* = 5.9, 5.2 Hz), 118.2, 115.5 (dd, *J* = 7.9, 4.2 Hz), 114.1, 112.8 (d, *J* = 21.0 Hz), 41.9 (d, *J* = 3.5 Hz), 16.8 (d, *J* = 3.3 Hz).

LRMS calcd for M^+ $C_{16}H_{11}F_2N_3$ 283, found 283.

HRMS calcd for $[M+Na]^+$ $C_{16}H_{11}F_2N_3Na$ 306.0813, found 306.0803.

4-(1-Ethyl-6,7-difluorobenzo[*d*]imidazol-2-yl)benzaldehyde (3):

Following general procedure, 4-bromobenzaldehyde (0.277 g, 1.5 mmol) and 1-ethyl-6,7-difluoro-benzo[*d*]imidazole (0.182 g, 1 mmol), affords **3** in 22% (0.063 g) yield as a white solid: mp 140-142 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.13 (s, 1H), 8.06 (d, *J* = 8.3 Hz, 2H), 7.90 (d, *J* = 8.3 Hz, 2H), 7.51 (ddd, *J* = 9.1, 3.8, 1.2 Hz, 1H), 7.16 (ddd, *J* = 11.1, 8.8, 7.4 Hz, 1H), 4.40 (q, *J* = 7.6 Hz, 2H), 1.52 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 191.5, 153.5, 147.1 (dd, *J* = 241.4, 10.9 Hz), 141.5, 137.4 (dd, *J* = 239.7, 17.7 Hz), 135.3, 130.2, 130.1, 124.6 (m), 115.6 (dd, *J* = 7.9, 4.2 Hz), 112.4 (d, *J* = 21.0 Hz), 41.8 (d, *J* = 3.5 Hz), 16.8 (d, *J* = 3.3 Hz).

LRMS calcd for M^+ $C_{16}H_{12}F_2N_2O$ 286, found 286.

HRMS calcd for $[M+Na]^+$ $C_{16}H_{12}F_2N_2ONa$ 309.0810, found 309.0813.

(4-(1-Ethyl-6,7-difluorobenzo[*d*]imidazol-2-yl)phenyl)(phenyl)methanone (4):

Following general procedure, 4-bromobenzophenone (0.392 g, 1.5 mmol) and 1-ethyl-6,7-difluoro-benzo[*d*]imidazole (0.182 g, 1 mmol), affords **4** in 42% (0.152 g) yield as a white solid: mp 162-164 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, *J* = 8.2 Hz, 2H), 7.88-7.80 (m, 4H), 7.64 (t, *J* = 7.8 Hz, 1H), 7.55-7.51 (m, 3H), 7.16 (ddd, *J* = 11.1, 8.8, 7.4 Hz, 1H), 4.42 (q, *J* = 7.6 Hz, 2H), 1.53 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 196.1, 153.8 (d, *J* = 1.8 Hz), 147.2 (dd, *J* = 241.4, 10.9 Hz), 141.5 (d, *J* = 1.8 Hz), 139.1, 137.3 (dd, *J* = 239.7, 17.7 Hz), 137.2, 133.3, 133.0, 130.5, 130.2, 129.4, 128.6, 124.5 (m), 115.5 (dd, *J* = 7.9, 4.2 Hz), 112.3 (d, *J* = 21.0 Hz), 41.8 (d, *J* = 3.5 Hz), 16.8 (d, *J* = 3.3 Hz).

LRMS calcd for M^+ $C_{22}H_{16}F_2N_2O$ 362, found 362.

HRMS calcd for $[M+Na]^+$ $C_{22}H_{16}F_2N_2ONa$ 385.1123, found 385.1124.

1-Ethyl-6,7-difluoro-2-(4-(trifluoromethyl)phenyl)benzo[*d*]imidazole (5):

Following general procedure, 4-bromobenzotrifluoride (0.338 g, 1.5 mmol) and 1-ethyl-6,7-difluoro-benzo[*d*]imidazole (0.182 g, 1 mmol), affords **5** in 41% (0.134 g) yield as a yellow solid: mp 126-128 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 8.3 Hz, 2H), 7.81 (d, *J* = 8.3 Hz, 2H), 7.51 (ddd, *J* = 9.1, 3.8, 1.2 Hz, 1H), 7.15 (ddd, *J* = 11.1, 8.8, 7.4 Hz, 1H), 4.37 (q, *J* = 7.6 Hz, 2H), 1.51 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 153.4, 147.2 (dd, *J* = 241.4, 10.9 Hz), 141.5, 137.4 (dd, *J* = 239.7, 17.7 Hz), 133.2, 132.2 (q, *J* = 32.8 Hz), 129.9, 126.0 (q, *J* = 1.8 Hz), 124.5 (m), 124.4 (q, *J* = 272.4 Hz), 115.6 (dd, *J* = 7.9, 4.2 Hz), 112.3 (d, *J* = 21.0 Hz), 41.7 (d, *J* = 3.5 Hz), 16.8 (d, *J* = 3.3 Hz).

LRMS calcd for M^+ $C_{16}H_{11}F_5N_2$ 326, found 326.

HRMS calcd for $[M+Na]^+$ $C_{16}H_{11}F_5N_2Na$ 349.0735, found 349.0721.

2-(4-Chlorophenyl)-1-ethyl-6,7-difluorobenzo[*d*]imidazole (6):

Following general procedure, 4-bromochlorobenzene (0.287 g, 1.5 mmol) and 1-ethyl-6,7-difluoro-benzo[*d*]imidazole (0.182 g, 1 mmol), affords **6** in 36% (0.105 g) yield as a white solid: mp 127-129 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J* = 8.3 Hz, 2H), 7.53 (d, *J* = 8.3 Hz, 2H), 7.50 (ddd, *J* = 9.1, 3.8, 1.2 Hz, 1H), 7.12 (ddd, *J* = 11.1, 8.8, 7.4 Hz, 1H), 4.35 (q, *J* = 7.6 Hz, 2H), 1.49 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 153.7, 147.1 (dd, *J* = 241.4, 10.9 Hz), 140.9, 137.6 (dd, *J* = 239.7, 17.7 Hz), 136.8, 130.8, 129.4, 127.7, 124.3 (m), 115.2 (dd, *J* = 7.9, 4.2 Hz), 112.3 (d, *J* = 21.0 Hz), 41.7 (d, *J* = 3.5 Hz), 16.7 (d, *J* = 3.3 Hz).

LRMS calcd for M^+ $C_{15}H_{11}ClF_2N_2$ 292, found 292.

HRMS calcd for $[M+Na]^+$ $C_{15}H_{11}ClF_2N_2Na$ 315.0471, found 315.0472.

1-Ethyl-6,7-difluoro-2-(4-fluorophenyl)benzo[*d*]imidazole (7):

Following general procedure, 4-fluorobromobenzene (0.263 g, 1.5 mmol) and 1-ethyl-6,7-difluoro-benzo[*d*]imidazole (0.182 g, 1 mmol), affords **7** in 43% (0.119 g) yield as a yellow solid: mp 86-88 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (dd, *J* = 8.2, 5.5 Hz, 2H), 7.50 (dd, *J* = 8.8, 3.8 Hz, 1H), 7.25 (t, *J* = 7.8 Hz, 2H), 7.14 (ddd, *J* = 11.1, 8.8, 7.4 Hz, 1H), 4.36 (q, *J* = 7.6 Hz, 2H), 1.49 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.1 (d, *J* = 248.1 Hz), 153.8 (d, *J* = 2.0 Hz), 147.1 (dd, *J* = 241.4, 10.9 Hz), 140.4, 137.3 (dd, *J* = 239.7, 17.7 Hz), 131.6 (d, *J* = 8.5 Hz), 125.1 (d, *J* = 3.1 Hz), 124.1 (dd, *J* = 5.9, 5.2 Hz), 116.4 (d, *J* = 22.0 Hz), 115.0 (dd, *J* = 7.9, 4.2 Hz), 112.3 (d, *J* = 21.0 Hz), 41.8 (d, *J* = 3.5 Hz), 16.7 (d, *J* = 3.3 Hz).

LRMS calcd for M^+ $C_{15}H_{11}F_3N_2$ 276, found 276.

HRMS calcd for $[M+Na]^+$ $C_{15}H_{11}F_3N_2Na$ 299.0766, found 299.0758.

1-Ethyl-6,7-difluoro-2-phenylbenzo[*d*]imidazole (8):

Following general procedure, bromobenzene (0.263 g, 1.5 mmol) and 1-ethyl-6,7-difluoro-benzo[*d*]imidazole (0.182 g, 1 mmol), affords **8** in 39% (0.101 g) yield as a yellow solid: mp 90-92 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71-7.66 (m, 2H), 7.55-7.52 (m, 3H), 7.49 (ddd, *J* = 9.1, 3.8, 1.2 Hz, 1H), 7.11 (ddd, *J* = 11.1, 8.8, 7.4 Hz, 1H), 4.36 (q, *J* = 7.6 Hz, 2H), 1.49 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.1, 147.0 (dd, *J* = 241.4, 10.9 Hz), 141.6, 137.4 (dd, *J* = 239.7, 17.7 Hz), 130.3, 129.7, 129.4, 129.0, 124.3 (m), 115.2 (dd, *J* = 7.9, 4.2 Hz), 111.8 (d, *J* = 21.0 Hz), 41.6 (d, *J* = 3.5 Hz), 16.7 (d, *J* = 3.3 Hz).

LRMS calcd for M^+ $C_{15}H_{12}F_2N_2$ 258, found 258.

HRMS calcd for $[M+Na]^+$ $C_{15}H_{12}F_2N_2Na$ 281.0728, found 281.0738.

1-Ethyl-6,7-difluoro-2-(*p*-tolyl)benzo[*d*]imidazole (9):

Following general procedure, 4-bromotoluene (0.257 g, 1.5 mmol) and 1-ethyl-6,7-difluoro-benzo[*d*]imidazole (0.182 g, 1 mmol), affords **9** in 56% (0.152 g) yield as a white solid: mp 134-136 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, *J* = 8.3 Hz, 2H), 7.47 (dd, *J* = 9.1, 3.8 Hz, 1H), 7.34 (d, *J* = 8.3 Hz, 2H), 7.10 (ddd, *J* = 11.1, 8.8, 7.4 Hz, 1H), 4.35 (q, *J* = 7.6 Hz, 2H), 2.45 (s, 3H), 1.48 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.3, 146.9 (dd, *J* = 241.4, 10.9 Hz), 141.2, 140.5, 137.4 (dd, *J* = 239.7, 17.7 Hz), 129.7, 129.3, 124.3, 124.3 (m), 115.1 (dd, *J* = 7.9, 4.2 Hz), 111.7 (d, *J* = 21.0 Hz), 41.6 (d, *J* = 3.5 Hz), 21.6, 16.7 (d, *J* = 3.3 Hz).

LRMS calcd for M^+ $C_{16}H_{14}F_2N_2$ 272, found 272.

HRMS calcd for $[M+Na]^+$ $C_{16}H_{14}F_2N_2Na$ 295.1017, found 295.1001.

2-(4-(*tert*-Butyl)phenyl)-1-ethyl-6,7-difluorobenzo[*d*]imidazole (10):

Following general procedure, 4-*tert*-butylbromobenzene (0.320 g, 1.5 mmol) and 1-ethyl-6,7-difluoro-benzo[*d*]imidazole (0.182 g, 1 mmol), affords **10** in 42% (0.132 g) yield as a yellow solid: mp 120-122 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.3 Hz, 2H), 7.54 (d, *J* = 8.3 Hz, 2H), 7.47 (dd, *J* = 9.1, 3.8 Hz, 1H), 7.10 (ddd, *J* = 11.1, 8.8, 7.4 Hz, 1H), 4.38 (q, *J* = 7.6 Hz, 2H), 1.49 (t, *J* = 7.6 Hz, 3H), 1.38 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.3 (d, *J* = 2.2 Hz), 153.6, 146.9 (dd, *J* = 241.4, 10.9 Hz), 141.5, 137.4 (dd, *J* = 239.7, 17.7 Hz), 129.2, 126.8, 125.9, 124.3 (m), 115.1 (dd, *J* = 7.9, 4.2 Hz), 111.7 (d, *J* = 21.0 Hz), 41.6 (d, *J* = 3.5 Hz), 35.1, 31.4, 16.8 (d, *J* = 3.3 Hz).

LRMS calcd for M^+ $C_{19}H_{20}F_2N_2$ 314, found 314.

HRMS calcd for $[M+Na]^+$ $C_{19}H_{20}F_2N_2Na$ 337.1487, found 337.1473.

2-([1,1'-Biphenyl]-4-yl)-1-ethyl-6,7-difluorobenzo[*d*]imidazole (11):

Following general procedure, 4-bromobiphenyl (0.350 g, 1.5 mmol) and 1-ethyl-6,7-difluoro-benzo[*d*]imidazole (0.182 g, 1 mmol), affords **11** in 44% (0.147 g) yield as a white solid: mp 142-144 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81-7.74 (m, 4H), 7.67 (d, *J* = 8.3 Hz, 2H), 7.55-7.46 (m, 3H), 7.41 (t, *J* = 7.8 Hz, 1H), 7.12 (ddd, *J* = 11.1, 8.8, 7.4 Hz, 1H), 4.42 (q, *J* = 7.6 Hz, 2H), 1.53 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 154.8 (d, *J* = 2.2 Hz), 147.0 (dd, *J* = 241.4, 10.9 Hz), 143.1, 141.4 (d, *J* = 2.4 Hz), 140.1, 137.4 (dd, *J* = 239.7, 17.7 Hz), 129.9, 129.1, 128.3, 128.1, 127.6, 127.3, 124.3 (m), 115.2 (dd, *J* = 7.9, 4.2 Hz), 111.8 (d, *J* = 21.0 Hz), 41.7 (d, *J* = 3.5 Hz), 16.8 (d, *J* = 3.3 Hz).

LRMS calcd for M^+ $C_{21}H_{16}F_2N_2$ 334, found 334.

HRMS calcd for $[M+H]^+$ $C_{21}H_{17}F_2N_2$ 335.1354, found 335.1356.

1-Ethyl-6,7-difluoro-2-(4-methoxyphenyl)benzo[*d*]imidazole (12):

Following general procedure, 4-bromoanisole (0.280 g, 1.5 mmol) and 1-ethyl-6,7-difluoro-benzo[*d*]imidazole (0.182 g, 1 mmol), affords **12** in 20% (0.058 g) yield as a yellow solid: mp 110-112 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.4 Hz, 2H), 7.49 (dd, *J* = 8.3, 2.9 Hz, 1H), 7.10 (ddd, *J* = 11.1, 8.8, 7.4 Hz, 1H), 7.05 (d, *J* = 8.4 Hz, 2H), 4.36 (q, *J* = 7.6 Hz, 2H), 3.89 (s, 3H), 1.49 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 161.3, 155.0 (d, *J* = 2.2 Hz), 147.0 (dd, *J* = 241.4, 10.9 Hz), 141.2 (d, *J* = 2.1 Hz), 137.4 (dd, *J* = 239.7, 17.7 Hz), 130.9, 124.2 (m), 121.6, 114.8 (dd, *J* = 7.9, 4.2 Hz), 114.5, 111.7 (d, *J* = 21.0 Hz), 55.6, 41.6 (d, *J* = 3.5 Hz), 16.7 (d, *J* = 3.3 Hz).

LRMS calcd for M^+ $C_{16}H_{14}F_2N_2O$ 288, found 288.

HRMS calcd for $[M+H]^+$ $C_{16}H_{15}F_2N_2O$ 289.1147, found 289.1147.

3-(1-Ethyl-6,7-difluorobenzo[*d*]imidazol-2-yl)benzonitrile (13):

Following general procedure, 3-bromobenzonitrile (0.273 g, 1.5 mmol) and 1-ethyl-6,7-difluoro-benzo[*d*]imidazole (0.182 g, 1 mmol), affords **13** in 40% (0.113 g) yield as a white solid: mp 142-144 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (s, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.68 (t, *J* = 7.8 Hz, 1H), 7.50 (ddd, *J* = 9.1, 3.8, 1.2 Hz, 1H), 7.14 (ddd, *J* = 11.1, 8.8, 7.4 Hz, 1H), 4.37 (q, *J* = 7.6 Hz, 2H), 1.52 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 152.3, 147.3 (dd, *J* = 241.4, 10.9 Hz), 141.3, 137.4 (dd, *J* = 239.7, 17.7 Hz), 133.7, 133.6, 133.0, 131.1, 130.0, 124.5 (dd, *J* = 5.9, 5.2 Hz), 118.0, 115.5 (dd, *J* = 7.9, 4.2 Hz), 113.7, 112.6 (d, *J* = 21.0 Hz), 41.9 (d, *J* = 3.5 Hz), 16.8 (d, *J* = 3.3 Hz).

LRMS calcd for M^+ $C_{16}H_{11}F_2N_3$ 283, found 283.

HRMS calcd for $[M+Na]^+$ $C_{16}H_{11}F_2N_3Na$ 306.0813, found 306.0804.

2-(3-Chlorophenyl)-1-ethyl-6,7-difluorobenzo[*d*]imidazole (14):

Following general procedure, 3-bromochlorobenzene (0.287 g, 1.5 mmol) and 1-ethyl-6,7-difluoro-benzo[*d*]imidazole (0.182 g, 1 mmol), affords **14** in 42% (0.123 g) yield as a yellow solid: mp 116-118 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (bs, 1H), 7.59 (d, *J* = 8.1 Hz, 1H), 7.57-7.47 (m, 3H), 7.14 (ddd, *J* = 11.1, 8.8, 7.4 Hz, 1H), 4.39 (q, *J* = 7.6 Hz, 2H), 1.52 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 153.5, 147.1 (dd, *J* = 241.4, 10.9 Hz), 141.4, 137.3 (dd, *J* = 239.7, 17.7 Hz), 135.1, 131.4, 130.5, 130.2, 129.6, 127.4, 124.3 (m), 115.4 (dd, *J* = 7.9, 4.2 Hz), 112.1 (d, *J* = 21.0 Hz), 41.7 (d, *J* = 3.5 Hz), 16.7 (d, *J* = 3.3 Hz).

LRMS calcd for M^+ $C_{15}H_{11}ClF_2N_2$ 292, found 292.

HRMS calcd for $[M+Na]^+$ $C_{15}H_{11}ClF_2N_2Na$ 315.0471, found 315.0475.

1-Ethyl-6,7-difluoro-2-(3-fluorophenyl)benzo[*d*]imidazole (15):

Following general procedure, 3-fluorobromobenzene (0.263 g, 1.5 mmol) and 1-ethyl-6,7-difluoro-benzo[*d*]imidazole (0.182 g, 1 mmol), affords **15** in 45% (0.124 g) yield as a white solid: mp 81-83 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55-7.45 (m, 3H), 7.42 (d, *J* = 8.3 Hz, 1H), 7.24 (t, *J* = 7.8 Hz, 1H), 7.10 (ddd, *J* = 11.1, 8.8, 7.4 Hz, 1H), 4.38 (q, *J* = 7.6 Hz, 2H), 1.50 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.9 (d, *J* = 248.1 Hz), 153.5, 147.3 (dd, *J* = 241.4, 10.9 Hz), 141.3, 137.3 (dd, *J* = 239.7, 17.7 Hz), 131.5 (d, *J* = 8.0 Hz), 130.7 (d, *J* = 8.4 Hz), 125.1 (d, *J* = 3.1 Hz), 124.3 (dd, *J* = 5.9, 5.2 Hz), 117.4 (d, *J* = 21.0 Hz), 116.7 (d, *J* = 23.1 Hz), 115.4 (dd, *J* = 7.9, 4.2 Hz), 112.2 (d, *J* = 21.0 Hz), 41.7 (d, *J* = 3.5 Hz), 16.7 (d, *J* = 3.3 Hz).

LRMS calcd for M^+ $C_{15}H_{11}F_3N_2$ 276, found 276.

HRMS calcd for $[M+Na]^+$ $C_{15}H_{11}F_3N_2Na$ 299.0766, found 299.0756.

1-Ethyl-6,7-difluoro-2-(*m*-tolyl)benzo[*d*]imidazole (16):

Following general procedure, 3-bromotoluene (0.257 g, 1.5 mmol) and 1-ethyl-6,7-difluoro-benzo[*d*]imidazole (0.182 g, 1 mmol), affords **16** in 81% (0.220 g) yield as a yellow solid: mp 96-98 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (s, 1H), 7.47 (dd, *J* = 9.1, 3.8 Hz, 1H), 7.45 (d, *J* = 8.3 Hz, 2H), 7.42 (t, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 8.2 Hz, 1H), 7.10 (ddd, *J* = 11.1, 8.8, 7.4 Hz, 1H), 4.36 (q, *J* = 7.6 Hz, 2H), 2.45 (s, 3H), 1.48 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.3, 147.0 (dd, *J* = 241.4, 10.9 Hz), 141.4, 139.0, 137.4 (dd, *J* = 239.7, 17.7 Hz), 131.1, 130.3, 129.5, 128.8, 126.3, 124.2 (m), 115.1 (dd, *J* = 7.9, 4.2 Hz), 111.8 (d, *J* = 21.0 Hz), 41.6 (d, *J* = 3.5 Hz), 21.6, 16.7 (d, *J* = 3.3 Hz).

LRMS calcd for M^+ $C_{16}H_{14}F_2N_2$ 272, found 272.

HRMS calcd for $[M+Na]^+$ $C_{16}H_{14}F_2N_2Na$ 295.1017, found 295.1002.

2-(1-Ethyl-6,7-difluorobenzo[*d*]imidazol-2-yl)benzonitrile (17):

Following general procedure, 2-bromobenzonitrile (0.273 g, 1.5 mmol) and 1-ethyl-6,7-difluoro-benzo[*d*]imidazole (0.182 g, 1 mmol), affords **17** in 30% (0.085 g) yield as a white solid: mp 104-106 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, *J* = 8.3 Hz, 1H), 7.78 (t, *J* = 7.8 Hz, 1H), 7.70-7.64 (m, 2H), 7.53 (ddd, *J* = 9.1, 3.8, 1.2 Hz, 1H), 7.16 (ddd, *J* = 11.1, 8.8, 7.4 Hz, 1H), 4.27 (q, *J* = 7.6 Hz, 2H), 1.39 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.9, 147.3 (dd, *J* = 241.4, 10.9 Hz), 140.5, 137.3 (dd, *J* = 239.7, 17.7 Hz), 133.8, 133.3, 133.0, 131.2, 130.7, 124.0 (m), 117.0, 115.9 (dd, *J* = 7.9, 4.2 Hz), 113.9, 112.4 (d, *J* = 21.0 Hz), 41.8 (d, *J* = 3.5 Hz), 16.6 (d, *J* = 3.3 Hz).

LRMS calcd for M^+ $C_{16}H_{11}F_2N_3$ 283, found 283.

HRMS calcd for $[M+Na]^+$ $C_{16}H_{11}F_2N_3Na$ 306.0813, found 306.0811.

2-(2-Chlorophenyl)-1-ethyl-6,7-difluorobenzo[*d*]imidazole (18):

Following general procedure, 2-bromochlorobenzene (0.287 g, 1.5 mmol) and 1-ethyl-6,7-difluoro-benzo[*d*]imidazole (0.182 g, 1 mmol), affords **18** in 42% (0.123 g) yield as a yellow solid: mp 98-100 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57-7.46 (m, 4H), 7.42 (t, *J* = 8.1 Hz, 1H), 7.12 (ddd, *J* = 11.1, 8.8, 7.4 Hz, 1H), 4.17 (q, *J* = 7.6 Hz, 2H), 1.33 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 152.2, 147.1 (dd, *J* = 241.4, 10.9 Hz), 141.5 (d, *J* = 2.3 Hz), 137.3 (dd, *J* = 239.7, 17.7 Hz), 134.5, 132.1, 131.8, 130.1, 129.3, 127.2, 123.5 (m), 115.5 (dd, *J* = 7.9, 4.2 Hz), 111.8 (d, *J* = 21.0 Hz), 41.5 (d, *J* = 3.5 Hz), 16.4 (d, *J* = 3.3 Hz).

LRMS calcd for M^+ $C_{15}H_{11}ClF_2N_2$ 292, found 292.

HRMS calcd for $[M+Na]^+$ $C_{15}H_{11}ClF_2N_2Na$ 315.0471, found 315.0470.

1-Ethyl-6,7-difluoro-2-(2-fluorophenyl)benzo[*d*]imidazole (19):

Following general procedure, 2-fluorobromobenzene (0.263 g, 1.5 mmol) and 1-ethyl-6,7-difluoro-benzo[*d*]imidazole (0.182 g, 1 mmol), affords **19** in 40% (0.110 g) yield as a yellow solid: mp 80-82 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68-7.51 (m, 3H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.27 (t, *J* = 7.8 Hz, 1H), 7.17 (ddd, *J* = 11.1, 8.8, 7.4 Hz, 1H), 4.24 (q, *J* = 7.6 Hz, 2H), 1.40 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2 (d, *J* = 250.0 Hz), 150.0 (d, *J* = 2.0 Hz), 147.1 (dd, *J* = 241.4, 10.9 Hz), 141.5 (m), 137.3 (dd, *J* = 239.7, 17.7 Hz), 132.7 (d, *J* = 8.23 Hz), 132.4 (d, *J* = 2.3 Hz), 124.9 (d, *J* = 3.5 Hz), 123.5 (m), 116.3 (d, *J* = 21.5 Hz), 115.4 (dd, *J* = 7.9, 4.2 Hz), 112.1 (d, *J* = 21.0 Hz), 41.8 (d, *J* = 3.5 Hz), 16.3 (d, *J* = 3.3 Hz).

LRMS calcd for M^+ $C_{15}H_{11}F_3N_2$ 276, found 276.

HRMS calcd for $[M+Na]^+$ $C_{15}H_{11}F_3N_2Na$ 299.0766, found 299.0758.

1-Ethyl-6,7-difluoro-2-(*o*-tolyl)benzo[*d*]imidazole (20):

Following general procedure, 2-bromotoluene (0.257 g, 1.5 mmol) and 1-ethyl-6,7-difluoro-benzo[*d*]imidazole (0.182 g, 1 mmol), affords **20** in 56% (0.152 g) yield as a yellow solid: mp 102-104 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (dd, *J* = 9.1, 3.8 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.38-7.29 (m, 3H), 7.11 (ddd, *J* = 11.1, 8.8, 7.4 Hz, 1H), 4.12 (q, *J* = 7.6 Hz, 2H), 2.24 (s, 3H), 1.32 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 154.6 (d, *J* = 2.2 Hz), 147.0 (dd, *J* = 241.4, 10.9 Hz), 141.5, 138.1, 137.4 (dd, *J* = 239.7, 17.7 Hz), 130.7, 130.3, 130.0, 129.2, 126.0, 123.3 (m), 115.1 (dd, *J* = 7.9, 4.2 Hz), 111.6 (d, *J* = 21.0 Hz), 41.1 (d, *J* = 3.5 Hz), 19.8, 16.5 (d, *J* = 3.3 Hz).

LRMS calcd for M^+ $C_{16}H_{14}F_2N_2$ 272, found 272.

HRMS calcd for $[M+Na]^+$ $C_{16}H_{14}F_2N_2Na$ 295.1017, found 295.1007.

1-Ethyl-6,7-difluoro-2-(naphthalen-2-yl)benzo[d]imidazole (21):

Following general procedure, 2-bromonaphthalene (0.311 g, 1.5 mmol) and 1-ethyl-6,7-difluoro-benzo[*d*]imidazole (0.182 g, 1 mmol), affords **21** in 36% (0.111 g) yield as a yellow solid: mp 110-112 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (s, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 7.97-7.90 (m, 2H), 7.78 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.64-7.47 (m, 3H), 7.15 (ddd, *J* = 11.1, 8.8, 7.4 Hz, 1H), 4.44 (q, *J* = 7.6 Hz, 2H), 1.52 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.1 (d, *J* = 2.2 Hz), 147.0 (dd, *J* = 241.4, 10.9 Hz), 141.5 (d, *J* = 1.8 Hz), 137.3 (dd, *J* = 239.7, 17.7 Hz), 133.9, 133.1, 129.6, 128.8, 128.7, 128.0, 127.6, 127.1, 126.8, 126.1, 124.4 (m), 115.2 (dd, *J* = 7.9, 4.2 Hz), 111.9 (d, *J* = 21.0 Hz), 41.8 (d, *J* = 3.5 Hz), 16.7 (d, *J* = 3.3 Hz).

LRMS calcd for M^+ $C_{19}H_{14}F_2N_2$ 308, found 308.

HRMS calcd for $[M+H]^+$ $C_{19}H_{15}F_2N_2Na$ 309.1198, found 309.1198.

1-Ethyl-6,7-difluoro-2-(pyridin-4-yl)benzo[*d*]imidazole (22):

Following general procedure, 4-bromopyridine hydrochloride (0.292 g, 1.5 mmol), 1-ethyl-6,7-difluoro-benzo[*d*]imidazole (0.182 g, 1 mmol) and KOPiv (0.294 g, 3 mmol) affords **22** in 34% (0.087 g) yield as a yellow solid: mp 92-94 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.84 (d, *J* = 5.8 Hz, 2H), 7.65 (d, *J* = 5.8 Hz, 2H), 7.53 (ddd, *J* = 9.1, 3.8, 1.2 Hz, 1H), 7.16 (ddd, *J* = 11.1, 8.8, 7.4 Hz, 1H), 4.42 (q, *J* = 7.6 Hz, 2H), 1.55 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 152.0, 150.5, 147.3 (dd, *J* = 241.4, 10.9 Hz), 141.5 (d, *J* = 2.0 Hz), 137.5, 137.4 (dd, *J* = 239.7, 17.7 Hz), 124.6 (t, *J* = 6.0 Hz), 123.6, 115.8 (dd, *J* = 7.9, 4.2 Hz), 112.5 (d, *J* = 21.0 Hz), 41.8 (d, *J* = 3.5 Hz), 16.8 (d, *J* = 3.3 Hz).

LRMS calcd for M^+ $C_{14}H_{11}F_2N_3$ 259, found 259.

HRMS calcd for $[M+Na]^+$ $C_{14}H_{11}F_2N_3Na$ 282.0813, found 282.0812.

3-(1-Ethyl-6,7-difluorobenzo[*d*]imidazol-2-yl)quinoline (23):

Following general procedure, 3-bromoquinoline (0.312 g, 1.5 mmol) and 1-ethyl-6,7-difluoro-benzo[*d*]imidazole (0.182 g, 1 mmol), affords **23** in 60% (0.185 g) yield as a yellow solid: mp 97-99 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.27 (d, *J* = 2.2 Hz, 1H), 8.57 (d, *J* = 2.2 Hz, 1H), 8.24 (d, *J* = 8.4 Hz, 1H), 7.97 (d, *J* = 8.4 Hz, 1H), 7.87 (t, *J* = 7.9 Hz, 1H), 7.69 (t, *J* = 7.9 Hz, 1H), 7.56 (ddd, *J* = 9.1, 3.8, 1.2 Hz, 1H), 7.17 (ddd, *J* = 11.1, 8.8, 7.4 Hz, 1H), 4.47 (q, *J* = 7.6 Hz, 2H), 1.58 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 152.2 (d, *J* = 2.5 Hz), 149.7, 148.5, 147.3 (dd, *J* = 241.4, 10.9 Hz), 141.8, 137.3 (dd, *J* = 239.7, 17.7 Hz), 137.2, 131.2, 129.7, 128.5, 127.9, 127.3, 124.6 (m), 123.1, 115.5 (dd, *J* = 7.9, 4.2 Hz), 112.3 (d, *J* = 21.0 Hz), 41.9 (d, *J* = 3.5 Hz), 16.9 (d, *J* = 3.3 Hz).

LRMS calcd for M^+ $C_{18}H_{13}F_2N_3$ 309, found 308.

HRMS calcd for $[M+Na]^+$ $C_{18}H_{13}F_2N_3Na$ 332.0970, found 332.0956.

4-(1-Ethyl-6,7-difluorobenzo[*d*]imidazol-2-yl)isoquinoline (24):

Following general procedure, 4-bromoisoquinoline (0.312 g, 1.5 mmol) and 1-ethyl-6,7-difluoro-benzo[*d*]imidazole (0.182 g, 1 mmol), affords **24** in 50% (0.154 g) yield as a yellow solid: mp 92-94 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.43 (s, 1H), 8.70 (s, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 7.80-7.67 (m, 3H), 7.56 (ddd, *J* = 9.1, 3.8, 1.2 Hz, 1H), 7.17 (ddd, *J* = 11.1, 8.8, 7.4 Hz, 1H), 4.21 (q, *J* = 7.6 Hz, 2H), 1.34 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 154.8, 150.9, 147.3 (dd, *J* = 241.4, 10.9 Hz), 144.3, 141.9, 137.3 (dd, *J* = 239.7, 17.7 Hz), 134.9, 132.0, 128.4, 128.3, 128.2, 124.4, 123.9 (m), 121.3, 115.6 (dd, *J* = 7.9, 4.2 Hz), 111.9 (d, *J* = 21.0 Hz), 41.7 (d, *J* = 3.5 Hz), 16.8 (d, *J* = 3.3 Hz).

LRMS calcd for M^+ $C_{18}H_{13}F_2N_3$ 309, found 308.

HRMS calcd for $[M+Na]^+$ $C_{18}H_{13}F_2N_3Na$ 332.0970, found 332.58.

1-Ethyl-6,7-difluoro-2-(6-(trifluoromethyl)pyridin-2-yl)benzo[*d*]imidazole (25):

Following general procedure, 2-bromo-6-(trifluoromethyl)pyridine (0.339 g, 1.5 mmol) and 1-ethyl-6,7-difluoro-benzo[*d*]imidazole (0.182 g, 1 mmol), affords **25** in 43% (0.141 g) yield as a yellow solid: mp 115-117 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.61 (d, *J* = 8.0 Hz, 1H), 8.07 (t, *J* = 7.8 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.54 (dd, *J* = 9.1, 3.8 Hz, 1H), 7.17 (ddd, *J* = 11.1, 8.8, 7.4 Hz, 1H), 4.99 (q, *J* = 7.6 Hz, 2H), 1.64 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.1, 149.3 (d, *J* = 2.2 Hz), 147.6 (dd, *J* = 241.4, 10.9 Hz), 147.5 (q, *J* = 35.3 Hz), 140.8 (d, *J*= 2.2 Hz), 138.6, 137.7 (dd, *J* = 239.7, 17.7 Hz), 127.2 (d, *J* = 0.7 Hz), 125.6 (m), 121.5 (q, *J* = 274.1 Hz), 120.6 (q, *J* = 2.6 Hz), 115.7 (dd, *J* = 7.9, 4.2 Hz), 112.6 (d, *J* = 21.0 Hz), 43.4 (d, *J* = 3.5 Hz), 16.4.

LRMS calcd for M^+ $C_{15}H_{10}F_5N_3$ 327, found 327.

HRMS calcd for $[M+Na]^+$ $C_{15}H_{10}F_5N_3Na$ 350.0687, found 350.0683.

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Chapter 6:

Reactivity of *N*-Methyl-*N*-(Polyfluorobenzyl)acetamides and *N*-Methyl-*N*-(Polyfluorobenzyl)benzamides in Pd-Catalyzed C–H Bond Arylation

Chapter 6

Reactivity of *N*-Methyl-*N*-(Polyfluorobenzyl)acetamides and *N*-Methyl-*N*-(Polyfluorobenzyl)benzamides in Pd-Catalyzed C–H Bond Arylation

6.1 Introduction

Polyfluorinated benzylamines are widely used as pharmaceuticals, agrochemicals, and imaging materials (Figure 6.1).[1] As examples, Taradenacin, which is an antimuscarinic agent, contains a 3,4,5-trifluorobenzylamine group. The difluorinated benzylamine Larotrectinib is a drug for the treatment of cancer, and the Baloxavir marboxil is an antiviral medication for treatment of influenza A and influenza B. Pexmetinib, which includes a 3-fluorobenzylamine group, is an anti-inflammatory drug and Trelagliptin is a drug used for the treatment of type 2 diabetes. Previous methods for the synthesis of fluorinated aromatics, e.g., Balz−Schiemann reaction, often required harsh reaction conditions,[2] which limit the scope of this transformation.[3] More recently, fluoroaromatics were prepared from aryl (pseudo)halides or aryl metallic derivatives *via* transition-metal-catalyzed fluorinations.[4] However, this strategy required to employ prefunctionalized starting materials. The C–H bond fluorination has also been reported but required the preinstallation of directing groups and/or the use of expensive fluorine sources.[5] The discovery of simple and efficient methods to access to fluorinated molecules with broad molecular diversity remains an important challenge for both academic research groups and chemical companies.

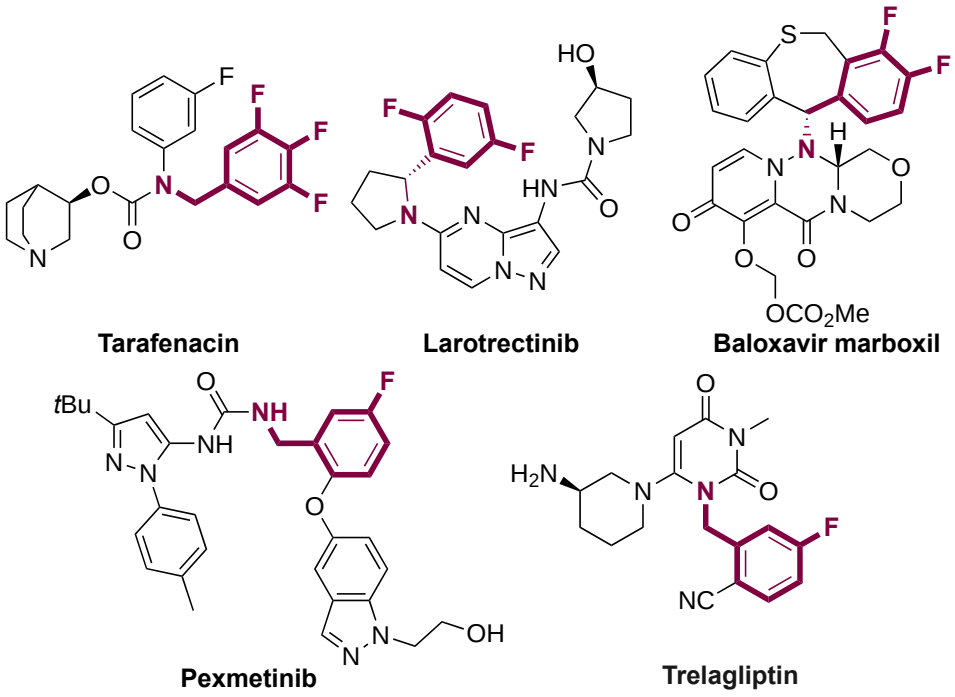


Figure 6.1. Relevant Pharmaceuticals Containing a (Poly)fluorinated Benzylamine Scaffold.

Recently, transition metal catalyzed-regioselective C–H bond functionalization has emerged as a suitable tool to access molecular diversity with a minimum number of manipulations.[6] In 2006, Fagnou and co-workers reported the first example of palladium-catalyzed C–H bond arylation of (poly)fluorobenzene derivatives using aryl halides as coupling partners (Figure 6.2 a).[7] The reaction generally took place at *ortho*-position of fluorine atoms allowing to prepare fluorinated biphenyls in good yields from commercially available fluorinated raw materials. However, the regioselectivity can be affected by the presence of an additional substituent leading to mixtures of *para*- or *meta*-fluorobiphenyl derivatives.[8] We have shown that using Pd/KOPiv/DMA as catalytic system, (poly)fluorobenzene bearing a benzoxazole,[9] a pyridine[10] or an amide[11] group reacted preferentially at the C–H bond flanked by two fluorine atoms (Figure 6.2 b). To the best of our knowledge, no example of Pd-catalyzed C–H bond arylation of polyfluorinated benzylamines was reported, so far. Such substrates are challenging because previous reports have shown that benzylamine derivatives such as sulfinyl isobutyramide,[12] picolinamide,[13]

pyrazine-2-carboxamide preferentially react at the *ortho*-position of the methylamine group (Figure 6.2 c).

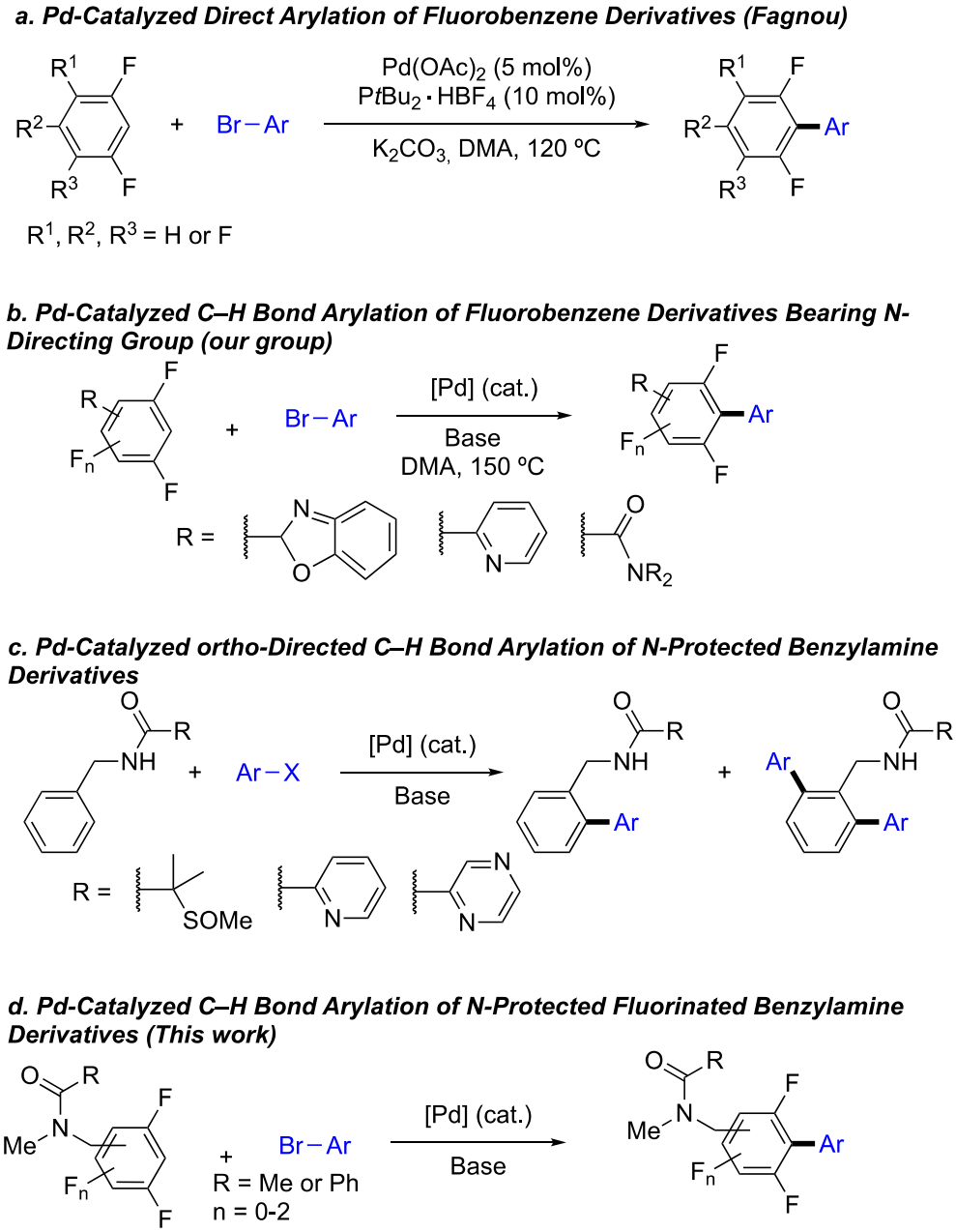


Figure 6.2. Pd-Catalyzed C–H bond Arylation of Polyfluorinated Benzylamines.

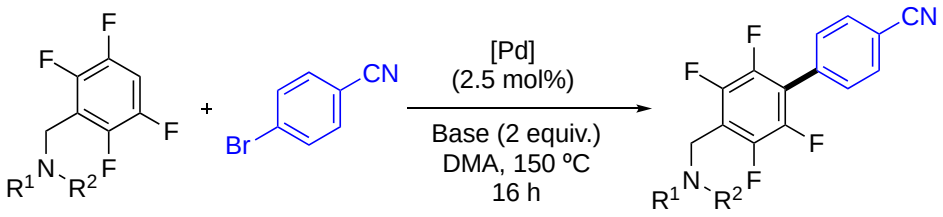
In this chapter, starting from a set of *N*-methyl-*N*-(polyfluorobenzyl)acetamides and a *N*-methyl-*N*-(polyfluorobenzyl)benzamide as reactants, we report (i) on the reactivity and regioselectivity for the direct arylation of benzene units containing both fluoro and *N*-methyl tertiary amide substituents; (ii) on the access to a variety of *N*-protected-methylamine substituted (poly)fluorobiphenyls using a variety of aryl

bromides as coupling partners (Figure 6.2 d). this work was done in collaboration with Mohamed Elhadi Benhalouche and Abdellah Miloudi from Oran university.

6.2 Results and Discussion

We firstly investigated the reactivity of non-protected (2,3,5,6-tetrafluorophenyl) methanamine (**a**) in Pd-catalyzed C–H bond arylation with 4-bromobenzonitrile (Table 6.1, entry 1). Using our previous reaction conditions for C–H bond arylation of polyfluorobenzene derivatives [namely, 2.5 mol% of $Pd(OAc)_2$ associated to 2 equivalents of KOAc in DMA at 150 ºC], the desired biphenyl product **1a** was not obtained. A similar reactivity trend was observed with *N*-(2,3,5,6-tetrafluorobenzyl) acetamide (**b**) (Table 6.1, entry 2). The lack of reactivity of these two substrates might be explained by the presence of NH function, which could inhibit the palladium activity. Therefore, we decided to investigate the reactivity of *N*-methyl-*N*-(2,3,5,6-tetrafluorobenzyl)acetamide (**c**). We were pleased to find that under the same reaction conditions, the desired biphenyl product **1c** was obtained in 45% yield (Table 6.1, entry 3). Next, we explored the effect of several reaction parameters (i.e., base, palladium sources and solvent). The use of K_2CO_3 as base inhibited the reaction, while the use of PivOK as base slightly improved the yield of **1c** to 58% (Table 6.1, entries 4 and 5). In both cases, we observed partial conversions of 4-bromobenzonitrile; therefore, other sources of palladium were tested. No improvement was observed using 2.5 mol% $PdCl_2(CH_3CN)_2$, whereas the use of a palladium diphosphine catalyst [$PdCl(C_3H_5)$(dppb)] gives **1c** in 89% yield with a full conversion of the aryl bromide (Table 6.1, entries 6 and 7). A partial conversation was obtained using only 1 mol% of this Pd catalyst (Table 6.1, entry 8). No improvement was observed by changing DMA to DMF or xylene (Table 6.1, entries 9 and 10).

Table 6.1. Reactivity of (2,3,5,6-tetrafluorophenyl)methanamine (**a**), *N*-(2,3,5,6-Tetrafluorobenzyl)acetamide (**b**), *N*-Methyl-*N*-(2,3,5,6-Tetrafluorobenzyl)acetamide (**c**) in Pd-Catalyzed C–H Bond Arylation with 4-Bromobenzonitrile



a $R^1 = R^2 = H$
b $R^1 = H$, $R^2 = Ac$
c $R^1 = Me$, $R^2 = Ac$
(1.5 equiv.)

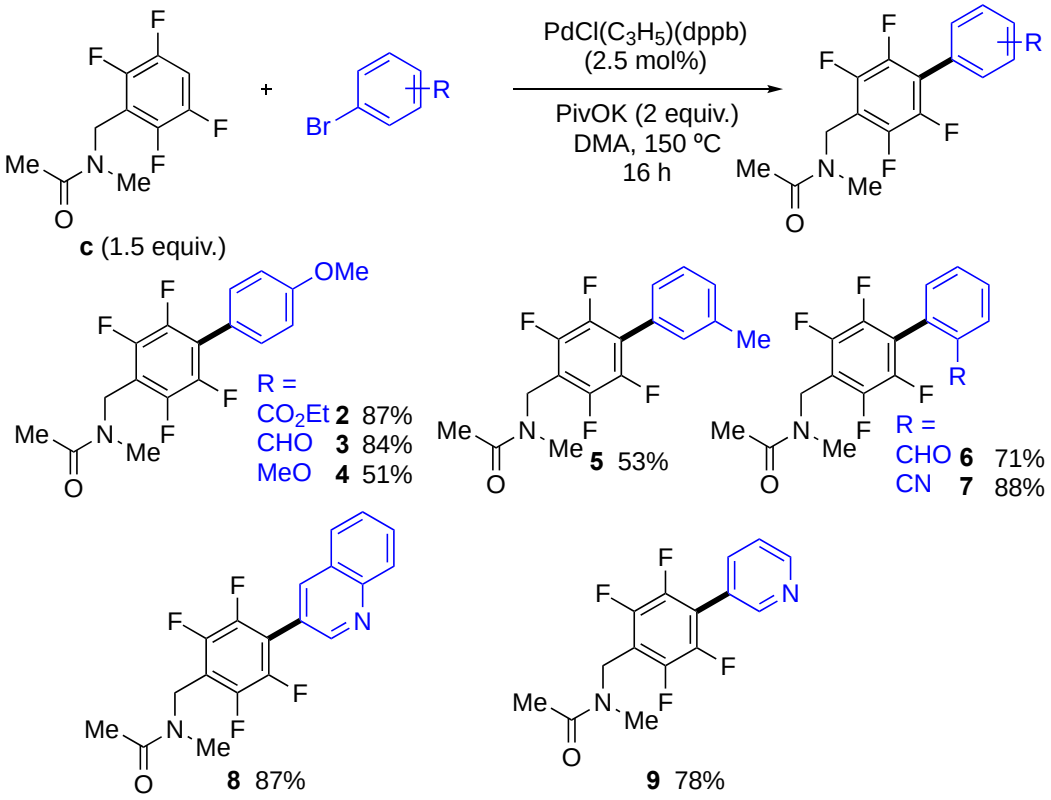
1a $R^1 = R^2 = H$
1b $R^1 = H$, $R^2 = Ac$
1c $R^1 = Me$, $R^2 = Ac$

Entry	Reactant **a**, **b** or **c**	[Pd] Catalyst	Base	Yield (%)
1	**a**	$Pd(OAc)_2$	KOAc	0
2	**b**	$Pd(OAc)_2$	KOAc	0
3	**c**	$Pd(OAc)_2$	KOAc	45
4	**c**	$Pd(OAc)_2$	K_2CO_3	0
5	**c**	$Pd(OAc)_2$	PivOK	58
6	**c**	$PdCl_2(CH_3CN)_2$	PivOK	41
7	**c**	$PdCl(C_3H_5)$(dppb)	PivOK	89
8[a]	**c**	$PdCl(C_3H_5)$(dppb)	PivOK	76
9[b]	**c**	$PdCl(C_3H_5)$(dppb)	PivOK	21
10[c]	**c**	$PdCl(C_3H_5)$(dppb)	PivOK	0

[a] using 1 mol% of Pd catalyst; [b] in DMF; [c] in Xylene

Having determined the best conditions to arylate the C–H bond of *N*-methyl-*N*-(2,3,5,6-tetrafluorobenzyl)acetamide (**c**), we turned our attention to the scope of aryl bromides (Scheme 1). Other aryl bromides bearing an electron-withdrawing substituent at the *para*-positions –such as ethyl ester and formyl groups– nicely reacted to afford the biphenyl products **2** and **3** in 87% and 84% yield,

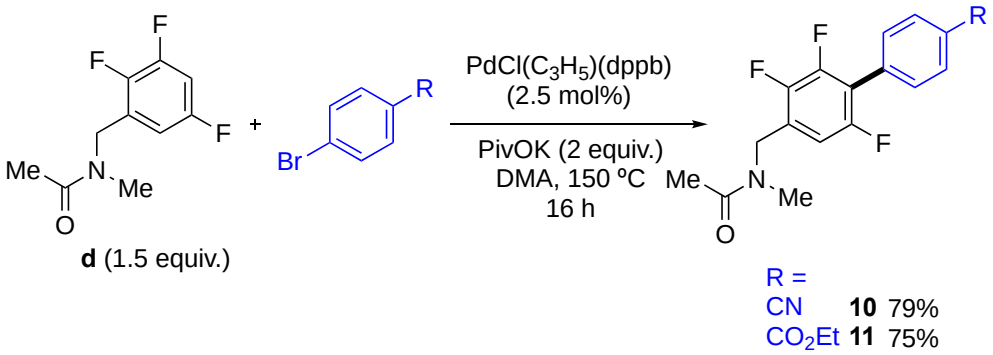
respectively. The reaction was more sluggish when 4-bromoanisole was employed, as the desired acetamide **4** was isolated in only 51% yield due to a partial conversion of this electron-rich aryl bromide. Similarly, the coupling between **c** and 3-bromotoluene led to the formation of **5** in 53% yield. The reaction was not very sensitive to steric factors as 2-bromobenzaldehyde and 2-bromobenzonitrile reacted nicely with **c** to give the biphenyl products **6** and **7** in 87% and 78% yield, respectively. The reaction also tolerated the use of nitrogen-containing heteroaryl bromides such as 3-bromoquinoline and 3-bromopyridine, as the products **8** and **9** were isolated in good to excellent yields.



Scheme 6.1. Scope of (Hetero)Aryl Bromides in Pd-Catalyzed C–H Bond Arylation of *N*-Methyl-*N*-(2,3,5,6-Tetrafluorobenzyl)acetamide (**c**)

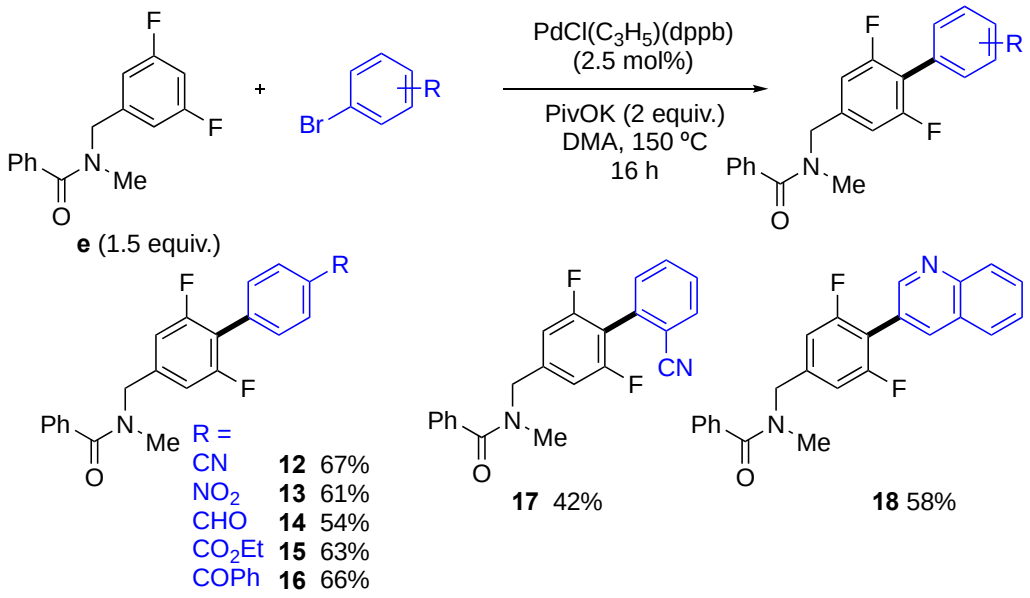
Then, we investigated the reactivity of *N*-methyl-*N*-(2,3,5-trifluorobenzyl) acetamide (**d**) in Pd-catalyzed C–H bond arylation with aryl bromides (Scheme 6.2). Although this substrate bears two C–H bonds, the reaction regioselectively occurred only at the C–H bond flanked by the two-fluorine atoms affording the biphenyls **10**

and **11** in good yields from 4-bromobenzonitile and ethyl 4-bromobenzoate, respectively. A similar regioselectivity has been previously observed with 6-substituted 1,2,4-trifluorobenzene derivatives.[7a, 10] This regioselectivity might be assigned to a lower Gibbs free energies of activation ($\Delta G^{\neq}$) of the cleavage of C–H bond adjacent to two fluorine atoms in Concerted Metalation Deprotonation (CMD) process.[14]



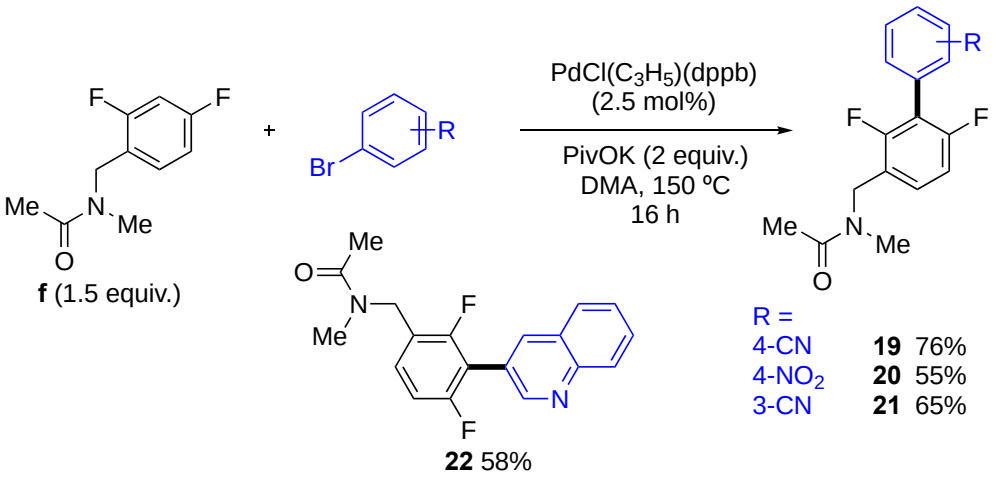
Scheme 6.2. Scope of Aryl Bromides in Pd-Catalyzed C–H Bond Arylation of *N*-Methyl-*N*-(2,3,5-Trifluorobenzyl)acetamide (**d**)

We also explored the reactivity of *N*-(3,5-difluorobenzyl)-*N*-methylbenzamide (**e**) in Pd-catalyzed C–H bond arylation with aryl bromides (Scheme 6.3). In the line with the previous reports on arylation of 1,3-difluorobenzene derivatives,[7a, 9-10] reaction between the difluorinated benzyl-*N*-methylbenzamide **e** and 4-bromobenzonitrile led to the single regioisomer **12** in 67% yield. The arylation again took place at the C–H bond flanked by the two fluorine atoms. The coupling reactions with other aryl bromides *para*-substituted by an electron withdrawing group (e.g., nitro, formyl, ethyl ester or benzoyl) afforded the 2,6-difluoro-[1,1'-biphenyl] derivatives **13-16** in 54-66% yields. From *N*-(3,5-difluorobenzyl)-*N*-methylbenzamide (**e**) and 2-bromobenzonitrile the desired coupling product **17** was isolated in only 42% yield. Moreover, 3-bromoquinoline was successfully employed as aryl source to provide an efficient access to the 2-(2,6-difluorophenyl)quinoline derivative **18** in 58% yield.



Scheme 6.3. Scope of (Hetero)Aryl Bromides in Pd-Catalyzed C–H Bond Arylation of *N*-(3,5-Difluorobenzyl)-*N*-Methylbenzamide (**e**)

The reactivity and regioselectivity was not sensitive to the substitution pattern of the fluorine atoms, provided that the C–H bond remained flanked by two fluorine atoms (Scheme 6.4). As example, *N*-(2,4-difluorobenzyl)-*N*-methylacetamide (**f**) underwent C–H bond arylation in the presence of 2.5 mol% of $Pd(OAc)_2$ associated to 2 equivalents of KOAc in DMA at 150 ºC. The biphenyl products **19**-**21** were regioselectively obtained in 55-76% yields from 4-bromobenzonitrile, 1-bromo-4-nitrobenzene and 3-bromobenzonitrile. Again 3-bromoquinoline displayed good reactivity affording the 3-arylquinoline **22** in 58% yield.



Scheme 6.4. Scope of (Hetero)Aryl Bromides in Pd-Catalyzed C–H Bond Arylation of *N*-(2,4-Difluorobenzyl)-*N*-Methylacetamide (**f**)

6.3 Conclusion

In summary, we have demonstrated that palladium-catalyzed direct arylation of electron-deficient arenes such as 1,2,4,5-tetrafluorobenzyl, 1,2,4-trifluorobenzyl, or 1,3-difluorobenzyl, bearing *N*-methylacetamide or *N*-methylbenzamide groups, always reacted *via* the cleavage of the C–H bond flanked by two fluorine atoms, whereas the C–H bonds at *ortho*-position of *N*-methylacetamide or *N*-methylbenzamide remained untouched. These fluorine-directed C–H bond functionalizations proceed with an easy to handle diphosphine palladium catalyst and PivOK as base in DMA. This procedure tolerates a wide variety of substituents on the aryl bromides such as nitro, cyano, ester, ketone, formyl and heteroaryl bromides with pyridinyl or quinolyl units. The reaction is not limited to activated aryl bromides, as electron donating substituents such as methoxy and methyl are also tolerated. Owing to the importance of polyfluorinated benzylamines and polyfluorinated biphenyls in pharmaceutical and material sciences, this methodology could find applications in late-stage modifications *via* regioselective C–H bond arylation to discover new active fluorinated molecules.

6.4 Experimental details

General:

All reactions were carried out under argon atmosphere with standard Schlenk-tube techniques. HPLC grade DMA was stored under argon and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AV III 400 MHz NMR spectrometer equipped with BBFO probehead. Chemical shifts (d) were reported in parts per million relative to residual chloroform (7.26 ppm for ^{1}H ; 77.0 ppm for ^{13}C), constants were reported in Hertz. ^{1}H NMR assignment abbreviations were the following: singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), doublet of triplets (dt), and multiplet (m). All reagents were weighed and handled in air.

Preparation of the $PdCl(C_3H_5)$(dppb) catalyst:[15]

An oven-dried 40 mL Schlenk tube equipped with a magnetic stirring bar under argon atmosphere, was charged with $[Pd(C_3H_5)Cl]_2$ (182 mg, 0.5 mmol) and dppb (426 mg, 1 mmol). 10 mL of anhydrous dichloromethane were added, then, the solution was stirred at room temperature for twenty minutes. The solvent was removed in vacuum. The powder was used without purification.

^{31}P NMR (81 MHz, $CDCl_3$) δ = 19.3 (s).

General procedure A for synthesis of *N*-methyl-*N*-(poly fluorobenzyl)acetamides (c-d and f) and *N*-(3,5-difluorobenzyl)-*N*-methyl-benzamide (e):

To a DMF (10 mL) solution of sodium hydride (60% dispersion in mineral oil) (0.719 g, 0.431 g corrected for mineral oil, 18 mmol, 1.2 equiv) was slowly added a solution of solution of *N*-methylacetamide (1.22 g, 16.8 mmol, 1.12 equiv) or *N*-methylbenzamide (2.27 g, 16.8 mmol, 1.12 equiv) in DMF (8 mL). After 30 min at room temperature, polyfluorobenzylbromide (15 mmol, 1 equiv) was added concurrently over 1 h. A water bath was used to maintain the temperature below

40 °C. The resulting mixture was stirred overnight at room temperature and then poured into a mixture of 20% NH_4Cl (50 mL), and Et_2O (50 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (2 x 50 mL). The organic layers were combined and washed with H_2O (3x 50 mL) and then brine (50 mL). The organic layer was dried (Na_2SO_4), and the solvent was removed to afford a residue. The crude mixture was purified by silica column chromatography to afford the desired arylated product.

***N*-Methyl-*N*-(2,3,5,6-tetrafluorobenzyl)acetamide (c):**

Following the general procedure **A** using 3-(bromomethyl)-1,2,4,5-tetrafluorobenzene (3.64 g, 15 mmol), the residue was purified by flash chromatography on silica gel (heptane-EtOAc, 70-30) to afford the desired compound **c** (3.25 g, 92%) as a yellow solid (Mp = 85-97 ºC):

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.08 – 6.86 (m, 1H), 4.80 & 3.55 (s, 2H), 2.91 & 2.73 (s, 3H), 2.15 & 1.98 (s, 3H). Observed complexity is due to the mixture of rotamers.

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.4 & 170.2, 145.7 (dm, *J* = 250.4 Hz), 145.1 145.7 (dm, *J* = 250.4 Hz), 116.5 & 115.6 (t, *J* = 17.0 Hz), 106.2 & 105.2 (t, *J* = 22.7 Hz), 42.3 & 39.2, 35.8 & 32.0, 21.4 & 20.9. Observed complexity is due to the mixture of rotamers.

Elemental analysis: calcd (%) for $C_{10}H_9F_4NO$ (235.18): C 51.07, H 3.86; found: C 51.21, H 4.03.

***N*-Methyl-*N*-(2,3,5-trifluorobenzyl)acetamide (d):**

Following the general procedure **A** using 3-(bromomethyl)-2,4,5-trifluorobenzene (3.38 g, 15 mmol), the residue was purified by flash chromatography on silica gel (heptane-EtOAc, 70-30) to afford the desired compound **d** (3.06 g, 94%) as a colorless oil:

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.88 – 6.56 (m, 2H), 4.55 & 4.52 (s, 2H), 2.95 & 2.87 (s, 3H), 2.08 & 2.07 (s, 3H). Observed complexity is due to the mixture of rotamers.

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 171.0 & 170.8, 157.8 (dm, *J* = 250.1 Hz), 150.1 (dm, *J* = 250.1 Hz), 145.5 (dm, *J* = 245.8 Hz), 127.8 (dd, *J* = 8.6, 13.8 Hz), 111.1 & 109.2 (td, *J* = 3.2, 24.1 Hz), 104.4 (dd, *J* = 20.9, 27.6 Hz), 48.00 & 44.0, 36.1 & 33.6, 21.6 & 21.1. Observed complexity is due to the mixture of rotamers.

Elemental analysis: calcd (%) for $C_{10}H_{10}F_3NO$ (217.19): C 55.30, H 4.64; found: C 55.48, H 4.87.

***N*-(3,5-Difluorobenzyl)-*N*-methylbenzamide (e):**

Following the general procedure **A** using 1-(bromomethyl)-3,5-difluorobenzene (3.11 g, 15 mmol), the residue was purified by flash chromatography on silica gel (heptane-EtOAc, 70-30) to afford the desired compound **e** (3.60 g, 92%) as a colorless oil:

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.44 – 7.28 (m, 6H), 6.87 – 6.80 (m, 1H), 6.78 – 6.69 (m, 1H), 4.71 & 4.47 (s, 2H), 2.94 & 2.86 (s, 3H). Observed complexity is due to the mixture of rotamers.

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.5 & 172.0, 163.5 (dm, *J* = 249.1 Hz), 141.2 (m), 135.8, 130.0, 128.7, 127.2, 110.7(m), 103.2 (m), 50.5, 37.4. Observed complexity is due to the mixture of rotamers.

Elemental analysis: calcd (%) for $C_{15}H_{13}F_2NO$ (261.27): C 68.96, H 5.02; found: C 69.19, H 6.15.

***N*-(2,4-difluorobenzyl)-*N*-methylacetamide (f):**

Following the general procedure **A** using 1-(bromomethyl)-2,4-difluorobenzene (3.11 g, 15 mmol), the residue was purified by flash chromatography on silica gel (heptane-EtOAc, 70-30) to afford the desired compound **f** (2.69 g, 90%) as a colorless oil:

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.31 & 7.11 (q, *J* = 6.9, 7.6 Hz, 1H), 6.92 – 6.72 (m, 2H), 4.57 & 4.51 (s, 2H), 2.96 & 2.90 (s, 3H), 2.15 & 2.11 9s, 3H). Observed complexity is due to the mixture of rotamers.

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.6 (2), 162.1 &161.8 (dd, *J* = 14.2, 248.1 Hz), 160.6 & 161.0 (dd, *J* = 11.8, 248.2 Hz), 131.2 (m), 129.0 (dd, *J* = 5.8, 9.7 Hz), 128.0 & 126.6, 120.1 & 119.3 (d, *J* = 3.7 Hz), 111.2 & 111.1 (d, *J* = 21.1 Hz), 103.9 & 103.2 (t, *J* = 25.7 Hz), 47.5 & 43.3, 35.5 & 32.9, 21.3 & 20.8. Observed complexity is due to the mixture of rotamers.

Elemental analysis: calcd (%) for $C_{10}H_{11}F_2NO$ (199.20): C 60.30, H 5.57; found: C 60.45, H 5.29.

General procedure B for synthesis of fluorinated biphenyls:

To a 25 mL oven dried Schlenk tube, (polyfluorobenzyl)acetamide (0.75 mmol), (hetero)arylbromide (0.5 mmol), PivOK (140 mg, 1 mmol), DMA (2 mL) and $PdCl(C_3H_5)$(dppb) (7.7 mg, 0.012 mmol) were successively added. The reaction mixture was evacuated by vacuum-argon cycles (5 times) and stirred at 150 ºC (oil bath temperature) for 16 h (see tables and schemes). After cooling the reaction at room temperature and concentration, the crude mixture was purified by silica column chromatography to afford the desired arylated product.

***N*-((4'-Cyano-2,3,5,6-tetrafluoro-[1,1'-biphenyl]-4-yl)methyl)-*N*-methylacetamide (1c):**

Following the general procedure **B** using *N*-methyl-*N*-(2,3,5,6-tetrafluorobenzyl)acetamide (**c**) (176 mg, 0.75 mmol) and 4-bromobenzonitrile (91 mg, 0.5 mmol), the residue was purified by flash chromatography on silica gel (heptane-EtOAc, 70-30) to afford the desired compound **1c** (150 mg, 89%) as a white solid (Mp = 130-132 ºC):

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.81 – 7.74 (m, 2H), 7.61 – 7.54 (m, 2H), 4.79 & 4.69 (s, 2H), 3.01 & 2.90 (s, 3H), 2.29 & 2.11 (s, 3H). Observed complexity is due to the mixture of rotamers.

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.8 & 170.5, 147.7 (dm, *J* = 252.2 Hz), 143.5 (dm, *J* = 246.2 Hz), 132.5 & 132.4, 132.1 & 131.7 (brs), 131.0, 118.3, 118.2 & 118.0, 116.5 & 115.3 (t, *J* = 17.2 Hz), 113.5 & 113.2, 42.7 & 40.1, 36.6 & 32.6, 21.8 & 21.3. Observed complexity is due to the mixture of rotamers.

Elemental analysis: calcd (%) for $C_{17}H_{12}F_4N_2O$ (336.29): C 60.72, H 3.60; found: C 60.89, H 3.56.

Ethyl 2',3',5',6'-tetrafluoro-4'-((*N*-methylacetamido)methyl)-[1,1'-biphenyl] -4-carboxylate (2):

Following the general procedure **B** using *N*-methyl-*N*-(2,3,5,6-tetrafluoro benzyl)acetamide (**c**) (176 mg, 0.75 mmol) and ethyl 4-bromobenzoate (115 mg, 0.5 mmol), the residue was purified by flash chromatography on silica gel (heptane-EtOAc, 60-40) to afford the desired compound **2** (167 mg, 87%) as a yellow solid (Mp = 102-105 ºC):

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.17 – 8.08 (m, 2H), 7.55 – 7.44 (m, 2H), 4.74 & 4.66 (s, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 3.05 & 2.99 (s, 3H), 2.11 & 2.06 (s, 3H), 1.38 (t, *J* = 6.7 Hz, 3H). Observed complexity is due to the mixture of rotamers.

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.7 & 170.5, 166.1 & 166.0, 145.8 (dm, *J* = 252.2 Hz), 143.7 (dm, *J* = 247.8 Hz), 131.8 & 131.4 (brs), 131.5 & 131.2, 130.2, 129.9, 129.8, 120.3 & 119.3 (t, *J* = 16.4 Hz), 115.6 & 114.6 (t, *J* = 17.2 Hz), 61.4 & 61.3, 42.6 & 39.8, 36.3 & 32.6, 21.8 & 21.3, 14.4. Observed complexity is due to the mixture of rotamers.

Elemental analysis: calcd (%) for $C_{19}H_{17}F_4NO_3$ (383.35): C 59.53, H 4.47; found: C 59.62, H 4.71.

***N*-Methyl-*N*-((2,3,5,6-tetrafluoro-4'-formyl-[1,1'-biphenyl]-4-yl)methyl)acetamide (3):**

Following the general procedure **B** using *N*-methyl-*N*-(2,3,5,6-tetrafluorobenzyl)acetamide (**c**) (176 mg, 0.75 mmol) and 4-bromobenzaldehyde (93 mg, 0.5 mmol), the residue was purified by flash

chromatography on silica gel (heptane-EtOAc, 50-50) to afford the desired compound **3** (143 mg, 84%) as a yellow solid (Mp = 93-95 ºC):

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 10.10 & 10.08 (s, 1H), 8.05 – 7.96 (m, 2H), 7.70 – 7.60 (m, 2H), 4.76 & 4.69 (s, 2H), 3.09 & 2.92 (s, 3H), 2.31 & 2.13 (s, 3H). Observed complexity is due to the mixture of rotamers.

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 191.7 & 191.6, 170.8 & 170.6, 145.8 (dm, *J* = 252.2 Hz), 143.9 (dm, *J* = 249.1 Hz), 136.8 & 136.6, 133.5 & 133.0, 131.0 (m), 129.9 & 129.9, 118.9 & 116.1 (t, *J* = 16.3 Hz), 42.7 & 40.0, 36.5 & 32.6, 21.8 & 21.3. Observed complexity is due to the mixture of rotamers.

Elemental analysis: calcd (%) for $C_{17}H_{13}F_4NO_2$ (339.29): C 60.18, H 3.86; found: C 60.02, H 4.06.

***N*-Methyl-*N*-((2,3,5,6-tetrafluoro-4'-methoxy-[1,1'-biphenyl]-4-yl)methyl)acetamide (4):**

Following the general procedure **B** using *N*-methyl-*N*-(2,3,5,6-tetrafluorobenzyl)acetamide (**c**) (176 mg, 0.75 mmol) and 4-bromoanisole (94 mg, 0.5 mmol), the residue was purified by flash chromatography on silica gel (heptane-EtOAc, 70-30) to afford the desired compound **4** (87 mg, 51%) as a white solid (Mp = 108-110 ºC):

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.44 – 7.37 (m, 2H), 7.06 – 6.99 (m, 2H), 4.76 & 4.66 (s, 2H), 3.86 & 3.86 (s, 3H), 3.04 & 2.90 (s, 3H), 2.30 & 2.12 (s, 3H). Observed complexity is due to the mixture of rotamers.

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.6 & 170.5, 145.7 (dm, *J* = 252.2 Hz), 143.8 (dm, *J* = 251.1 Hz), 131.4 (m), 120.0 (t, *J* = 16.5 Hz), 119.4, 119.0, 114.2, 114.1, 114.0 & 113.8, 55.4 & 44.3, 42.5 & 39.3, 36.0 & 32.4, 21.8 & 21.2. Observed complexity is due to the mixture of rotamers.

Elemental analysis: calcd (%) for $C_{17}H_{15}F_4NO_2$ (341.31): C 59.83, H 4.43; found: C 59.98, H 4.21.

***N*-Methyl-*N*-((2,3,5,6-tetrafluoro-3'-methyl-[1,1'-biphenyl]-4-yl)methyl)acetamide (5):**

Following the general procedure **B** using *N*-methyl-*N*-(2,3,5,6-tetrafluorobenzyl)acetamide (**c**) (176 mg, 0.75 mmol) and 3-bromotoluene (85 mg, 0.5 mmol), the residue was purified by flash chromatography on silica gel (heptane-EtOAc, 60-40) to afford the desired compound **5** (86 mg, 53%) as a yellow solid (Mp = 48-50 ºC):

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.49 – 7.33 (m, 1H), 7.29 – 7.21 (m, 3H), 4.76 & 4.66 (s, 2H), 3.04 & 2.91 (s, 3H), 2.40 (s, 3H), 2.30 & 2.12 (s, 3H). Observed complexity is due to the mixture of rotamers.

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.6 & 170.4, 145.7 (dm, *J* = 246.9 Hz), 143.8 (dm, *J* = 245.6 Hz), 138.5 & 128.3, 130.6 (m), 130.2 (m), 128.7 & 128.6, 128.6 & 128.5, 127.2 & 126.8, 121.1 & 120.4 (t, *J* = 16.9 Hz), 114.5 & 113.5 (t, *J* = 17.3 Hz), 42.5 & 39.5, 36.0 & 32.4, 21.7 & 21.4, 21.6 & 21.2. Observed complexity is due to the mixture of rotamers.

Elemental analysis: calcd (%) for $C_{17}H_{15}F_4NO$ (325.31): C 62.77, H 4.65; found: C 62.81, H 4.86.

***N*-Methyl-*N*-((2,3,5,6-tetrafluoro-2'-formyl-[1,1'-biphenyl]-4-yl)methyl)acetamide (6):**

Following the general procedure **B** using *N*-methyl-*N*-(2,3,5,6-tetrafluorobenzyl)acetamide (**c**) (176 mg, 0.75 mmol) and 2-bromobenzaldehyde (93 mg, 0.5 mmol), the residue was purified by flash chromatography on silica gel (heptane-EtOAc, 40-60) to afford the desired compound **6** (120 mg, 71%) as a colorless oil:

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.93 & 9.92 (s, 1H), 8.03 (d, *J* = 7.6 Hz, 1H), 7.78 – 7.59 (m, 2H), 7.44 – 7.35 (m, 1H), 4.78 & 4.70- (s, 2H), 3.08 &2.93 (s, 3H), 2.30 & 2.13 (s, 3H). Observed complexity is due to the mixture of rotamers.

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 190.5, 170.8 & 170.6, 145.5 (dm, *J* = 249.3 Hz), 143.8 (dm, *J* = 247.8 Hz), 134.3, 134.1 (m), 132.1 & 131.8, 130.9, 130.4 &

130.2, 127.9 & 127.9 (t, *J* = 2.9 Hz), 118.7 & 117.2 (d, *J* = 17.8 Hz), 116.1 & 114.7 (d, *J* = 18.3 Hz), 42.7 & 39.8, 36.4 & 32.6, 21.8 & 21.1. Observed complexity is due to the mixture of rotamers.

Elemental analysis: calcd (%) for $C_{17}H_{13}F_4NO_2$ (339.29): C 60.18, H 3.86; found: C 60.22, H 4.01.

***N*-((2'-Cyano-2,3,5,6-tetrafluoro-[1,1'-biphenyl]-4-yl)methyl)-*N*-methylacetamide (7):**

Following the general procedure **B** using *N*-methyl-*N*-(2,3,5,6-tetrafluorobenzyl)acetamide (**c**) (176 mg, 0.75 mmol) and 2-bromobenzonitrile (91 mg, 0.5 mmol), the residue was purified by flash chromatography on silica gel (heptane-EtOAc, 70-30) to afford the desired compound **7** (148 mg, 88%) as a colorless oil:

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.89 – 7.81 (m, 1H), 7.79 – 7.70 (m, 1H), 7.66 – 7.58 (m, 1H), 7.53 – 7.44 (m, 1H), 4.79 & 4.71 (s, 2H), 3.08 & 2.93 (s, 3H), 2.17 & 2.14 (s, 3H). Observed complexity is due to the mixture of rotamers.

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.8 & 170.6, 145.7 (dm, *J* = 249.3 Hz), 143.5 (dm, *J* = 247.8 Hz), 133.5 (m), 133.1 (m), 131.7 & 131.6, 131.2 (t, *J* = 3.3 Hz), 130.2, 130.0, 117.5, 117.0 (m), 114.0, 42.8 & 29.9, 36.5 & 32.7, 21.9 & 21.4. Observed complexity is due to the mixture of rotamers.

Elemental analysis: calcd (%) for $C_{17}H_{12}F_4N_2O$ (336.29): C 60.72, H 3.60; found: C 60.91, H 3.82.

***N*-Methyl-*N*-(2,3,5,6-tetrafluoro-4-(quinolin-3-yl)benzyl)acetamide (8):**

Following the general procedure B using *N*-methyl-*N*-(2,3,5,6-tetrafluorobenzyl)acetamide (**c**) (176 mg, 0.75 mmol) and 3-bromoquinoline (104 mg, 0.5 mmol), the residue was purified by flash chromatography on silica gel (heptane-EtOAc, 60-40) to afford the desired compound **8** (158 mg, 87%) as yellow solid (Mp = 104-106 ºC):

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.01 – 8.93 (m, 1H), 8.34 – 8.26 (m, 1H), 8.19 – 8.10 (m, 1H), 7.93 – 7.86 (m, 1H), 7.83 – 7.75 (m, 1H), 7.66 – 7.56 (m, 1H), 4.78 & 4.70 (s, 2H), 3.09 & 2.93 (s, 3H), 2.31 & 2.13 (s, 3H). Observed complexity is due to the mixture of rotamers.

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.7 & 170.4, 150.4 & 150.2 (t, *J* = 2.7 Hz), 147.9 & 147.8, 145.8 (dm, *J* = 250.6 Hz), 144.0 (dm, *J* = 247.8 Hz), 137.7 & 137.7, 130.9 & 130.7, 129.4 & 129.4, 128.2, 127.5, 127.4 (m), 120.9 & 120.5, 117.9 & 116.9 (t, *J* = 16.6 Hz), 116.0 & 114.8 (t, *J* = 17.2 Hz), 42.6 & 39.8, 36.3 & 32.5, 21.7 & 21.2. Observed complexity is due to the mixture of rotamers.

Elemental analysis: calcd (%) for $C_{19}H_{14}F_4N_2O$ (362.33): C 62.98, H 3.89; found: C 63.12, H 4.09.

***N*-Methyl-*N*-(2,3,5,6-tetrafluoro-4-(pyridin-3-yl)benzyl)acetamide (9):**

Following the general procedure **B** using *N*-methyl-*N*-(2,3,5,6-tetrafluorobenzyl)acetamide (**c**) (176 mg, 0.75 mmol) and 3-bromopyridine (79 mg, 0.5 mmol), the residue was purified by flash chromatography on silica gel (heptane-EtOAc, 70-30) to afford the desired compound **9** (122 mg, 78%) as a yellow solid (Mp = 84-86 ºC):

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 – 8.68 (m, 1H), 8.68 – 8.65 (m, 1H), 7.83 – 7.74 (m, 1H), 7.47 – 7.36 (m, 1H), 4.78 & 4.68 (s, 2H), 3.07 & 2.90 (s, 3H), 2.29 & 2.11 (s, 3H). Observed complexity is due to the mixture of rotamers.

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.8 & 170.5, 150.5 (m), 150.3, 145.8 (dm, *J* = 250.6 Hz), 143.8 (dm, *J* = 247.8 Hz), 137.5, 124.0, 123.7 & 123.6, 117.8 & 116.8 (t, *J* = 16.6 Hz), 116.1 & 114.9 (t, *J* = 17.2 Hz), 42.7 & 39.9, 26.4 & 32.6, 21.8 & 21.1. Observed complexity is due to the mixture of rotamers.

Elemental analysis: calcd (%) for $C_{15}H_{12}F_4N_2O$ (312.27): C 57.70, H 3.87; found: C 57.89, H 3.62.

***N*-((4'-Cyano-2,3,6-trifluoro-[1,1'-biphenyl]-4-yl)methyl)-*N*-methylacetamide (10):**

Following the general procedure **B** using *N*-methyl-*N*-(2,3,5-trifluorobenzyl)acetamide (**d**) (163 mg, 0.75 mmol) and 4-bromobenzonitrile (91 mg, 0.5 mmol), the residue was purified by flash chromatography on silica gel (heptane-EtOAc, 70-30) to afford the desired compound **10** (126 mg, 79%) as a yellow oil:

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.80 – 7.70 (m, 2H), 7.63 – 7.43 (m, 2H), 7.05 – 6.76 (m, 1H), 4.66 & 4.63 (s, 2H), 3.08 & 2.00 (s, 3H), 2.17 (s, 3H). Observed complexity is due to the mixture of rotamers.

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 171.3 & 171.1, 154.8 (dm, *J* = 247.4 Hz), 147.6 (ddd, *J* = 7.1, 15.2, 252.2 Hz), 146.0 (ddd, *J* = 3.7, 13.9, 245.0 Hz), 133.2 & 132.8, 132.3 & 132.2, 131.0 (m), 127.7 (dd, *J* = 8.8, 14.2 Hz), 118.5 & 118.4, 117.2 (dd, *J* = 14.7, 20.2 Hz), 112.9 & 112.6, 111.6 & 109.5 (td, *J* = 3.4, 25.5 Hz), 48.2 & 44.5, 36.6 & 34.0, 21.8 & 21.4. Observed complexity is due to the mixture of rotamers.

Elemental analysis: calcd (%) for $C_{17}H_{13}F_3N_2O$ (318.29): C 64.15, H 4.12; found: C 64.21, H 4.01.

Ethyl 2',3',6'-trifluoro-4'-((*N*-methylacetamido)methyl)-[1,1'-biphenyl]-4-carboxylate (11): Following the general procedure **B** using *N*-methyl-*N*-(2,3,5-trifluorobenzyl)acetamide (**d**) (163 mg, 0.75 mmol) and ethyl 4-bromobenzoate (115 mg, 0.5 mmol), the residue was purified by flash chromatography on silica gel (heptane-EtOAc, 70-30) to afford the desired compound **11** (135 mg, 75%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.16 – 8.07 (m, 2H), 7.57 – 7.46 (m, 2H), 6.94 & 6.78 (ddd, *J* = 2.1, 5.4, 9.7 Hz, 1H), 4.66 & 4.62 (s, 2H), 4.40 (q, *J* = 5.8, 6.6 Hz, 2H), 3.06 & 2.99 (s, 3H), 2.17 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H). Observed complexity is due to the mixture of rotamers. ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 171.3 & 171.0, 166.2, & 166.1, 155.0 (dm, *J* = 249.4 Hz),

147.7 (ddd, *J* = 7.5, 14.9, 251.4 Hz), 146.0 (ddd, *J* = 3.7, 13.9, 244.3 Hz), 132.9 & 132.5, 130.9 & 130.7, 130.2 (m), 129.7 & 129.6, 126.8 & 126.2 (dd, *J* = 8.8, 14.1 Hz), 118.2 (dd, *J* = 15.0, 20.5 Hz), 111.4 & 109.4 (td, *J* = 3.4, 25.6 Hz), 61.3, 48.2 & 44.3, 36.5 & 34.0, 21.8 & 21.4, 14.3. Observed complexity is due to the mixture of rotamers. Elemental analysis: calcd (%) for $C_{19}H_{18}F_3NO_3$ (365.35): C 62.46, H 4.97; found: C 62.58, H 5.10.

***N*-((4'-Cyano-2,6-difluoro-[1,1'-biphenyl]-4-yl)methyl)-*N*-methylbenzamide (12):**

Following the general procedure **B** using *N*-(3,5-difluorobenzyl)-*N*-methylbenzamide (**e**) (196 mg, 0.75 mmol) and 4-bromobenzonitrile (91 mg, 0.5 mmol), the residue was purified by flash chromatography on silica gel (heptane-EtOAc, 60-30) to afford the desired compound **12** (121 mg, 67%) as a white solid (Mp = 123-125 ºC):

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.75 (d, *J* = 8.5 Hz, 2H), 7.59 (d, *J* = 8.2 Hz, 2H), 7.51 – 7.42 (m, 5H), 7.08 – 6.79 (m, 2H), 4.77 & 4.55 (s, 2H), 3.09 & 2.99 (s, 3H). Observed complexity is due to the mixture of rotamers.

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 171.7, 159.8 (d, *J* = 253.4 Hz), 140.9, 135.4, 131.9, 131.0, 129.9, 128.5, 127.0, 118.5, 111.9, 111.4, 50.3, 37.5.

Elemental analysis: calcd (%) for $C_{22}H_{16}F_2N_2O$ (362.38): C 72.92, H 4.45; found: C 73.08, H 4.21.

***N*-((2,6-Difluoro-4'-nitro-[1,1'-biphenyl]-4-yl)methyl)-*N*-methylbenzamide (13):**

Following the general procedure **B** using *N*-(3,5-difluorobenzyl)-*N*-methylbenzamide (**e**) (196 mg, 0.75 mmol) and 1-bromo-4-nitrobenzene (101 mg, 0.5 mmol), the residue was purified by flash chromatography on silica gel (heptane-EtOAc, 60-40) to afford the desired compound **13** (117 mg, 61%) as yellow solid (Mp = 150-152 ºC):

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.31 (d, *J* = 8.8 Hz, 2H), 7.66 (d, *J* = 8.7 Hz, 2H), 7.52 – 7.40 (m, 5H), 7.09 – 6.83 (m, 2H), 4.77 & 4.57 (brs, 2H), 3.08 & 3.00 (brs, 3H). Observed complexity is due to the mixture of rotamers.

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.0, 160.1 (d, *J* = 249.2 Hz), 147.7, 141.2, 135.6, 131.4, 130.2, 128.7, 127.2 (m), 124.1, 123.7, 123.6, 111.4 (m), 50.6, 37.3. Elemental analysis: calcd (%) for $C_{21}H_{16}F_2N_2O_3$ (362.38): C 65.97, H 4.22; found: C 66.12, H 4.45.

***N*-((2,6-Difluoro-4'-formyl-[1,1'-biphenyl]-4-yl)methyl)-*N*-methylbenzamide (14):**

Following the general procedure **B** using *N*-(3,5-difluorobenzyl)-*N*-methylbenzamide (**e**) (196 mg, 0.75 mmol) and 4-bromobenzaldehyde (93 mg, 0.5 mmol), the residue was purified by flash chromatography on silica gel (heptane-EtOAc, 70-30) to afford the desired compound **14** (98 mg, 54%) as a yellow oil:

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 10.07 (s, 1H), 7.97 (d, *J* = 8.3 Hz, 2H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.56 – 7.37 (m, 5H), 7.12 – 6.76 (m, 2H), 4.77 & 4.55 (s, 2H), 3.08 & 2.99 (s, 3H). Observed complexity is due to the mixture of rotamers.

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 191.9, 172.9, 160.2 (d, *J* = 252.3 Hz), 140.6, 138.3, 136.0, 135.8 (d, *J* = 11.3 Hz), 131.1, 130.2, 130.2 (d, *J* = 7.9 Hz), 129.7, 128.7, 127.1, 126.8, 111.4, 103.0, 52.9, 37.6.

Elemental analysis: calcd (%) for $C_{22}H_{17}F_2NO_2$ (365.38): C 72.32, H 4.69; found: C 72.21, H 4.56.

Ethyl 2',6'-difluoro-4'-((*N*-methylbenzamido)methyl)-[1,1'-biphenyl]-4-carboxylate (15):

Following the general procedure **B** using *N*-(3,5-difluorobenzyl)-*N*-methylbenzamide (**e**) (196 mg, 0.75 mmol) and ethyl 4-bromobenzoate (115 mg, 0.5 mmol), the residue was purified by flash

chromatography on silica gel (heptane-EtOAc, 60-40) to afford the desired compound **15** (129 mg, 63%) as a colorless oil:

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.13 (d, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 8.2 Hz, 2H), 7.48 – 7.41 (m, 5H), 7.06 – 6.81 (m, 2H), 4.76 & 4.60 (s, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 3.09 & 2.98 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H). Observed complexity is due to the mixture of rotamers.

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 171.9, 166.4, 160.3 (d, *J* = 251.8 Hz), 140.2, 135.8, 133.6, 130.4, 130.1, 128.6, 128.7, 127.2 (brm), 111.2 (m), 61.2, 50.5, 37.6, 14.5.

Elemental analysis: calcd (%) for $C_{24}H_{21}F_2NO_3$ (409.43): C 70.41, H 5.17; found: C 70.58, H 5.29.

***N*-((4'-Benzoyl-2,6-difluoro-[1,1'-biphenyl]-4-yl)methyl)-*N*-methylbenzamide (16):**

Following the general procedure **B** using *N*-(3,5-difluorobenzyl)-*N*-methylbenzamide (**e**) (196 mg, 0.75 mmol) and 4-bromobenzophenone (131 mg, 0.5 mmol), the residue was purified by flash chromatography on silica gel (heptane-EtOAc, 60-40) to afford the desired compound **16** (145 mg, 66%) as a brown oil:

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.96 – 7.80 (m, 4H), 7.68 – 7.56 (m, 4H), 7.56 – 7.39 (m, 6H), 6.95 (d, *J* = 6.4 Hz, 2H), 4.78 & 4.68 (s, 2H), 3.09 & 2.99 (s, 3H). Observed complexity is due to the mixture of rotamers.

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 196.2, 171.9, 160.2 (d, *J* = 250.2 Hz), 140.3, 137.5, 137.3, 135.7, 135.5, 133.3, 132.6, 130.3, 130.1, 130.1, 130.0, 128.6, 128.4, 127.2, 111.2 (m), 54.7 & 50.5, 37.6 & 33.5. Observed complexity is due to the mixture of rotamers.

Elemental analysis: calcd (%) for $C_{28}H_{21}F_2NO_2$ (441.48): C 76.18, H 4.79; found: C 75.98, H 4.51.

***N*-((2'-Cyano-2,6-difluoro-[1,1'-biphenyl]-4-yl)methyl)-*N*-methylbenzamide (17):**

Following the general procedure **B** using *N*-(3,5-difluorobenzyl)-*N*-methylbenzamide (**e**) (196 mg, 0.75 mmol) and 2-bromobenzonitrile (91 mg, 0.5 mmol), the residue was purified by flash chromatography on silica gel (heptane-EtOAc, 60-40) to afford the desired compound **17** (76 mg, 42%) as a yellow oil:

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.80 (d, *J* = 7.6 Hz, 1H), 7.69 (td, *J* = 1.3, 7.7 Hz, 1H), 7.54 (dt, *J* = 1.0, 7.6 Hz, 1H), 7.49 (d, *J* = 7.7 Hz, 2H), 7.46 – 7.41 (m, 4H), 7.09 – 6.86 (m, 2H), 4.79 & 4.56 (s, 2H), 3.09 & 2.00 (s, 3H). Observed complexity is due to the mixture of rotamers.

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.5 & 172.1, 160.2 (d, *J* = 254.7 Hz), 141.7, 135.6, 133.2, 132.7, 131.8, 130.1, 129.1, 128.7, 127.2, 117.7, 114.1, 111.8 (m), 110.2 (m), 54.7 & 50.5, 37.7 & 31.1. Observed complexity is due to the mixture of rotamers.

Elemental analysis: calcd (%) for $C_{22}H_{16}F_2N_2O$ (362.38): C 72.92, H 4.45; found: C 73.13, H 4.58.

***N*-(3,5-Difluoro-4-(quinolin-3-yl)benzyl)-*N*-methylbenzamide (18):**

Following the general procedure **B** using *N*-(3,5-difluorobenzyl)-*N*-methylbenzamide (**e**) (196 mg, 0.75 mmol) and 3-bromoquinoline (104 mg, 0.5 mmol), the residue was purified by flash chromatography on silica gel (heptane-EtOAc, 60-40) to afford the desired compound **18** (113 mg, 58%) as a yellow solid (Mp = 154-156 ºC):

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.00 (s, 1H), 8.30 (s, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 7.9 Hz, 1H), 7.81 – 7.73 (m, 1H), 7.64 – 7.57 (m, 1H), 7.54 – 7.39 (m, 5H), 7.11 – 6.84 (m, 2H), 4.80 & 4.58 (s, 2H), 3.11 & 3.01 (s, 3H). Observed complexity is due to the mixture of rotamers.

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 171.8 (brs), 160.4 (d, *J* = 252.0 Hz), 151.1, 147.5 & 147.4, 140.5 (brs), 137.4, 135.6 & 135.3, 130.1, 130.0, 129.3 & 129.2, 128.5,

128.1 & 127.9, 127.6, 127.3 & 127.0, 122.4, 114.1 (t, *J* = 21.2 Hz), 111.4 (d, *J* = 24.7 Hz), 110.3 (m), 54.4 & 50.4, 37.4 & 33.4. Observed complexity is due to the mixture of rotamers.

Elemental analysis: calcd (%) for $C_{24}H_{18}F_2N_2O$ (388.42): C 74.21, H 4.67; found: C 74.28, H 4.51.

***N*-((4'-Cyano-2,6-difluoro-[1,1'-biphenyl]-3-yl)methyl)-*N*-methylacetamide (19):**

Following the general procedure **B** using *N*-(2,4-difluorobenzyl)-*N*-methylacetamide (**f**) (149 mg, 0.75 mmol) and 4-bromobenzonitrile (91 mg, 0.5 mmol), the residue was purified by flash chromatography on silica gel (heptane-EtOAc, 50-50) to afford the desired compound **19** (114 mg, 76%) as a yellow oil:

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.80 – 7.70 (m, 2H), 7.64 – 7.54 (m, 2H), 7.37 & 7.17 (td, *J* = 6.4, 8.4 Hz, 1H), 7.05 & 6.98 (td, *J* = 1.3, 9.0 Hz, 1H), 4.62 & 4.57 (s, 2H), 3.05 & 2.95 (s, 3H), 2.17 & 2.14 (s, 3H). Observed complexity is due to the mixture of rotamers.

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 171.1 & 171.0, 158.9 (dd, *J* = 6.4, 250.0 Hz), 157.7 (dd, *J* = 6.5, 249.6 Hz), 134.2 & 133.7, 132.5 – 132.1 (m), 131.4 – 130.9 (m), 128.6 (dd, *J* = 6.3, 10.1 Hz), 121.1 & 120.4 (dd, *J* = 3.8, 16.6 Hz), 118.7 & 118.6, 116.5 (t, *J* = 18.7 Hz), 112.3 & 112.0 (d, *J* = 3.9 Hz), 112.2 (m), 48.4 & 44.5 (d, *J* = 4.5 Hz), 36.4 & 33.6 (d, *J* = 1.3 Hz), 21.9 & 21.4. Observed complexity is due to the mixture of rotamers.

Elemental analysis: calcd (%) for $C_{17}H_{14}F_2N_2O$ (300.31): C 67.99, H 4.70; found: C 68.23, H 4.67.

***N*-((2,6-Difluoro-4'-nitro-[1,1'-biphenyl]-3-yl)methyl)-*N*-methylacetamide (20):**

Following the general procedure **B** using *N*-(2,4-difluorobenzyl)-*N*-methylacetamide (**f**) (149 mg, 0.75 mmol) and 1-bromo-4-nitrobenzene (101 mg, 0.5 mmol),, the residue was purified by flash

chromatography on silica gel (heptane-EtOAc, 40-60) to afford the desired compound **20** (88 mg, 55%) as a brown solid (Mp = 90-93 ºC):

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.34 – 8.28 (m, 2H), 7.64 (d, *J* = 8.7 Hz, 2H), 7.39 &7.20 (td, *J* = 6.4, 8.4 Hz, 1H), 7.07 & 7.00 (t, *J* = 8.8 Hz, 1H), 4.63 & 4.59 (s, 2H), 3.04 & 2.96 (s, 3H), 2.17 & 2.15 (s, 3H). Observed complexity is due to the mixture of rotamers.

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 171.2, 159.0 (dm, *J* = 250.4 Hz), 157.8 (dm, *J* = 251.6 Hz), 147.8 & 147.7, 136.2 & 135.6, 131.5, 128.7 (m), 123.6 (m), 121.3 (d, *J* = 16.7 Hz), 116.1 (t, *J* = 18.6 Hz), 112.2 (m), 48.4 & 44.5, 36.5 & 33.7, 21.9 & 21.5. Observed complexity is due to the mixture of rotamers.

Elemental analysis: calcd (%) for $C_{16}H_{14}F_2N_2O_3$ (320.30): C 60.00, H 4.41; found: C 60.29, H 4.42.

***N*-((3'-Cyano-2,6-difluoro-[1,1'-biphenyl]-3-yl)methyl)-*N*-methylacetamide (21):**

Following the general procedure **B** using *N*-(2,4-difluorobenzyl)-*N*-methylacetamide (**f**) (149 mg, 0.75 mmol) and 3-bromobenzonitrile (91 mg, 0.5 mmol), the residue was purified by flash chromatography on silica gel (heptane-EtOAc, 50-50) to afford the desired compound **21** (98 mg, 65%) as a yellow oil:

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.76 (s, 1H), 7.74 – 7.65 (m, 2H), 7.63 – 7.52 (m, 1H), 7.38 & 7.17 (td, *J* = 6.5, 8.4 Hz, 1H), 7.05 & 6.99 (td, *J* = 1.3, 9.0 Hz, 1H), 4.63 & 4.58 (s, 2H), 3.03 & 2.96 (s, 3H), 2.17 & 2.15 (s, 3H). Observed complexity is due to the mixture of rotamers.

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 171.2 & 171.1, 159.0 (dd, *J* = 6.4, 249.7 Hz), 157.8 (dd, *J* = 6.5, 249.4 Hz), 134.9 & 134.8, 134.0 & 133.9, 132.1 & 131.9, 131.1 (dd, *J* = 6.3, 10.1 Hz), 133.7 & 130.3, 129.4 & 129.3, 128.4 (dd, *J* = 6.3, 10.1 Hz), 121.1 & 120.4 (dd, *J* = 3.8, 16.6 Hz), 118.6 & 118.4, 116.1 (t, *J* = 18.8 Hz), 113.0 & 112.8, 112.3 & 112.1 (d, *J* = 3.9 Hz), 112.2 & 112.0 (d, *J* = 3.9 Hz), 48.4 & 44.5 (d, *J*

= 4.5 Hz), 36.4 & 33.7 (d, *J* = 1.4 Hz), 21.9 & 21.4. Observed complexity is due to the mixture of rotamers.

Elemental analysis: calcd (%) for $C_{17}H_{14}F_2N_2O$ (300.31): C 67.99, H 4.70; found: C 67.91, H 4.65.

_N_-(2,4-Difluoro-3-(quinolin-3-yl)benzyl)-_N_-methylacetamide (22):

Following the general procedure **B** using *N*-(2,4-difluorobenzyl)-*N*-methylacetamide (**f**) (149 mg, 0.75 mmol) and 3-bromoquinoline (104 mg, 0.5 mmol), the residue was purified by flash chromatography on silica gel (heptane-EtOAc, 50-50) to afford the desired compound **22** (95 mg, 58%) as a yellow oil:

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.30 (d, *J* = 2.3 Hz, 1H), 8.47 (d, *J* = 2.1 Hz, 1H), 8.19 (d, *J* = 8.5 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.78 (ddd, *J* = 1.4, 6.9, 8.4 Hz, 1H), 7.71 – 7.58 (m, 1H), 7.39 – 7.28 & 7.18 – 7.08 (m, 1H), 6.95 – 6.73 (m, 1H), 4.58 & 4.51 (s, 2H), 2.97 & 2.91 (s, 3H), 2.16 & 2.13 (s, 3H). Observed complexity is due to the mixture of rotamers.

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 171.0, 162.4 (dd, *J* = 11.8, 248.5 Hz), 161.2 (dd, *J* = 11.9, 248.3 Hz), 149.7 & 147.8, 134.0, 131.8 (dd, *J* = 5.9, 9.6 Hz), 130.9, 130.1, 129.5, 129.1 (dd, *J* = 5.8, 9.7 Hz), 128.2, 128.0, 127.6, 120.4 (d, *J* = 11.5 Hz), 111.8 & 111.7 (dd, *J* = 3.8, 21.1 Hz), 104.5 & 103.5 (t, *J* = 25.4 Hz), 48.1 & 43.9 (d, *J* = 3.8 Hz), 36.1 & 22.6, 21.9 & 21.4. Observed complexity is due to the mixture of rotamers.

Elemental analysis: calcd (%) for $C_{19}H_{16}F_2N_2O$ (326.35): C 69.93, H 4.94; found: C 70.22, H 5.28.

6.5 References

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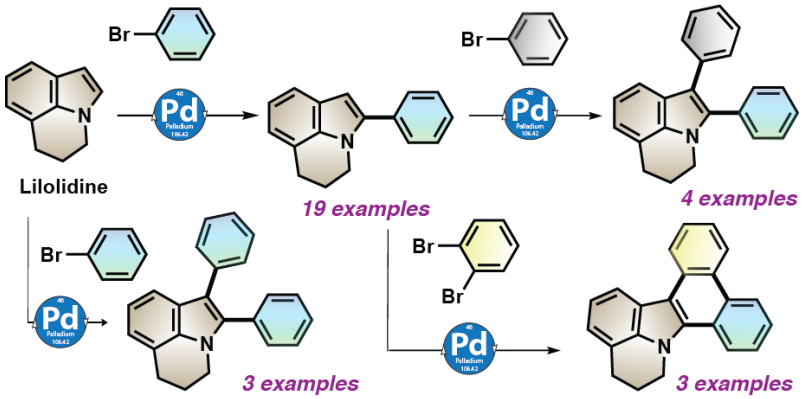
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General conclusion

General conclusion

Palladium-catalyzed sp^2 C-H bond functionalizations now represent one of the most reliable methodology for the access to biaryls *via* a carbon-carbon bond formation. In this thesis, we succeeded to enlarge the substrate scope of such reactions using economically viable conditions.

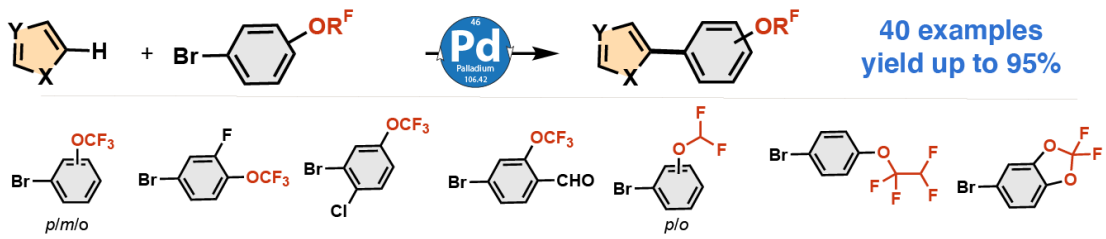
In the chapter 2, Pd-catalyzed C-H bond functionalization of Lilolidine was investigated. The use of a palladium-diphosphine catalyst associated to acetate bases in DMA was found to promote the regioselective arylation at α-position of the nitrogen atom of Lilolidine with a wide variety of aryl bromides. From these α-arylated Lilolidines, a second arylation at β-position gives the access to α,β-diarylated Lilolidines containing two different aryl groups. The one pot access to α,β-diarylated Lilolidines with two identical aryl groups is also possible using a larger amount of the aryl bromide. The synthesis of 5,6-dihydrodibenzo[*a*,*c*]pyrido[3,2,1-*jk*] -carbazoles from Lilolidine *via* three successive direct arylations is also described. Therefore, this methodology provides a straightforward access to several Lilolidine derivatives from commercially available compounds *via* one, two or three C-H bond functionalization step allowing to tune their biological properties (Scheme 1).



Scheme 1 Access to α- and β-arylated Lilolidine derivatives.

In the chapter 3, the reactivity of di-, tri- and tetra-fluoroalkoxy-substituted

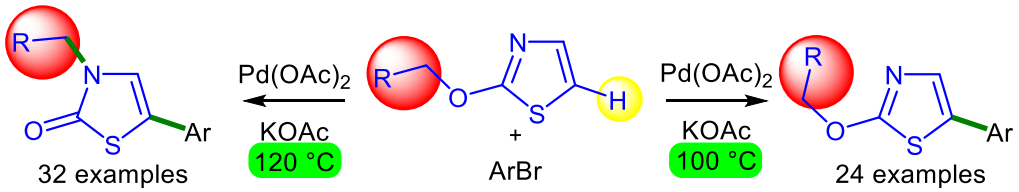
bromobenzenes in the direct arylation of 5-membered ring heteroarenes using palladium catalysis was explored. High yields in arylated heteroarenes were obtained using only 1 mol% of $Pd(OAc)_2$ catalyst with KOAc as inexpensive base. Similar yields were obtained with *o*/*m*/*p* trifluoromethoxy-, *o*/*p* difluoromethoxy-, and tetrafluoroethoxy-substituents on the aryl bromide. A bromo-substituted difluorobenzo[*d*][1,3]dioxole was also successfully coupled. The major side-products of the reaction are HBr/KOAc. Therefore, this synthetic scheme is very attractive for the access to such polyfluoroalkoxy-containing arylated heteroaromatics in terms of cost, simplicity and low environmental impact, compared to reactions involving arylation of heteroarenes with bromophenols followed by polyfluoroalkylation (Scheme 2).



Scheme 2. Pd-catalyzed direct arylations of heteroarenes by di-, tri- and tetra-(fluoro)alkoxy-substituted bromobenzenes

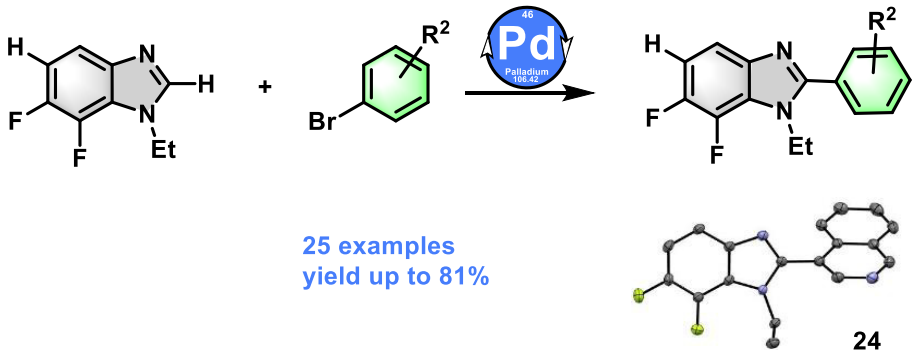
The Pd-catalyzed direct arylation of thiazole or 2-alkylthiazoles is a well-known reaction affording the corresponding 5-arylthiazoles in very high yields. Conversely, the reactivity of 2-alkoxythiazoles has not been described yet. In chapter 4, we report conditions for the Pd-catalyzed regioselective C5-arylation of 2-alkoxythiazoles. Moreover, we also found reactions conditions allowing to obtain 3-alkyl-5-arylthiazol-2(3H)-ones *via* a one pot direct arylation with *O*- to *N*-alkyl migratory rearrangement. The judicious choice of the reaction temperature allows to control the selectivity of the reaction. In general, at 100 °C, 5-arylthiazoles were the major products; whereas, at 120 °C 3-alkyl-5-arylthiazol-2(3H)-ones were obtained with good selectivities. The arylation reaction is promoted by a ligand-free air-stable palladium catalyst and a simple and inexpensive base without oxidant or further

additives, and tolerates a variety of useful substituents on the aryl bromide and also heteroaryl bromides (Scheme 3).



Scheme 3. Direct arylations of 2-alkoxythiazoles and *O*- to *N*-alkyl migratory rearrangement.

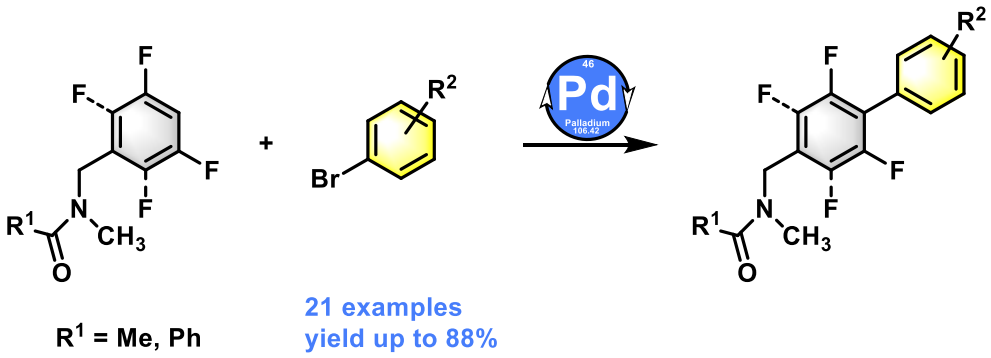
In the chapter 5, conditions for the regioselective palladium-catalyzed direct arylation of a 6,7-difluorobenzo[*d*]imidazole using aryl bromides as the coupling partners are described. The site selectivity of the arylation was found to be in favor of the C2-carbon of the difluorobenzo[*d*]imidazole; whereas the difluoro-substituted ring remained untouched, even in the presence of an excess of aryl bromide. This method tolerates a variety of substituents at *para*-, *meta*- and *ortho*-positions on the aryl bromide and also *N*-containing heteroaryl bromides (Scheme 4).



Scheme 4. Pd-catalyzed direct arylations of a 6,7-difluorobenzo[*d*]imidazole with aryl halides.

In the chapter 6, the influence of fluoro substituents on the aryl group of *N*-methyl-*N*-benzylacetamides and *N*-methyl-*N*-benzylbenzamides on the

regioselectivity of palladium-catalyzed direct arylations was studied. With these (poly)fluoro-substituted tertiary benzamides, the arylations regioselectively proceed at the C-H bond flanked by two fluoro substituents using 2.5 mol% of an air-stable palladium catalyst and PivOK/*N*,*N*-dimethylacetamide (DMA) as the reaction conditions. For these reactions, a variety of substituents on the aryl bromide, such as ester, propionyl, acetyl, formyl, nitro, nitrile, methoxy, or methyl, was tolerated. Nitrogen-containing heteroaryl bromides were also successfully used. These results reveal that under our reaction conditions, fluoro substituents act as better directing groups than amides in palladium-catalyzed direct arylations (Scheme 5).



Scheme 5. Pd-catalyzed C–H bond arylation of polyfluorinated benzylamines.

The above-presented results highlight the importance to study synthetically useful and appealing compounds in C-H bond functionalization together with Pd catalyst. In the future, for the short- and long-term, research efforts to follow-up the contributions reported in this PhD thesis could be the following:

- The study of luminescence and photochromism, it should be noted that a range of functionalities such as nitrile, nitro or trifluoromethyl on the aryl bromide are tolerated. Such functional groups tolerance allows easier modification of the electronic structures and, in consequence, of the photophysical properties of the molecules. This strategy leds to the formation of a new class of emitters with appealing photophysical properties.

- The application of new strategies relying on green chemistry by using cheaper metals like Fe, the exploitation of ligand-free or solvent-free (or neat) reaction conditions.

UNIVERSITÉ DE RENNES 1

Titre : Fonctionnalisation de liaisons C-H d'hétérocycles et de fluorobenzènes catalysée par le Pd : Un accès simple a des composés poly(hétéro)aromatiques.

Mots clés : Fonctionnalisation de liaisons C-H, Arylation directe, Palladium, Catalyse, Hétéroarènes

Résumé : Dans le premier chapitre de ma thèse, j'ai résumé des informations mécanistiques générales sur la fonctionnalisation de liaisons C-H sp^2 catalysée par le palladium, et j'ai détaillé certains résultats de la littérature sur l'arylation directe des (hétéro)arènes.

Dans les chapitres 2-6, j'ai décris les résultats que nous avons obtenus en utilisant le palladium comme catalyseur dans l'arylation directe de différents (hétéro)aromatiques afin de fonctionnaliser des liaisons C-H spécifiques.

Tout d'abord, j'ai étudié la fonctionnalisation de liaisons C-H de la Lilolidine en utilisant un catalyseur palladium-diphosphine. Ces résultats sont résumés dans le chapitre 2.

Ensuite, j'ai exploré la réactivité de bromobenzènes di-, tri- et tétra-fluoroalkoxy-substitués dans l'arylation directe d'hétéroarènes à 5 chaînons en utilisant la catalyse au palladium. Ces résultats sont présentés dans le chapitre 3.

Dans le chapitre 4, je décris des conditions permettant la C5-arylation régiosélective de 2-alkoxythiazoles catalysée par le Pd. Nous avons constaté que le choix judicieux de la température de réaction permet de contrôler la sélectivité.

Dans le chapitre 5, nous décrivons l'arylation directe régiosélective catalysée par le palladium d'un 6,7-difluorobenzo[*d*]imidazole en utilisant des bromures d'aryle comme partenaires de couplage.

Enfin, dans le chapitre 6, nous avons étudié l'influence des substituants fluoro sur le groupe aryle des *N*-méthyl-*N*-benzylacétamides et *N*-méthyl-*N*-benzylbenzamides sur la régiosélectivité de l'arylation directe catalysée par le palladium.

Title : Pd-catalyzed C-H bond functionalization of heterocycles and fluorobenzenes: A simple access to poly(hetero)aromatic compounds.

Keywords : C-H bonds functionalization, Direct arylation, Palladium, Catalysis, Hereroarenes

Abstract : In the first chapter of my thesis, I summarized general mechanistic information on palladium-catalyzed sp^2 C-H bond functionalization and detailed several literature results on the direct arylation of (hetero)arenes.

In the chapters 2-6. I describe the results we obtained using palladium as catalyst in the direct arylation of different (hetero)aromatics to functionalize specific C-H bonds.

First, I studied the C-H bond functionalization of Lilolidine using a palladium-diphosphine catalyst. These results are summarized in the chapter 2.

Then, I explored the reactivity of *di*-, *tri*- and *tetra*-fluoroalkoxy-substituted bromobenzenes in the direct arylation of 5-membered ring heteroarenes using palladium catalysis. These results are reported in the chapter 3.

In the chapter 4, I report conditions for the Pd-catalyzed regioselective C5-arylation of 2-alkoxythiazoles. We found that the judicious choice of the reaction temperature allows to control the selectivity.

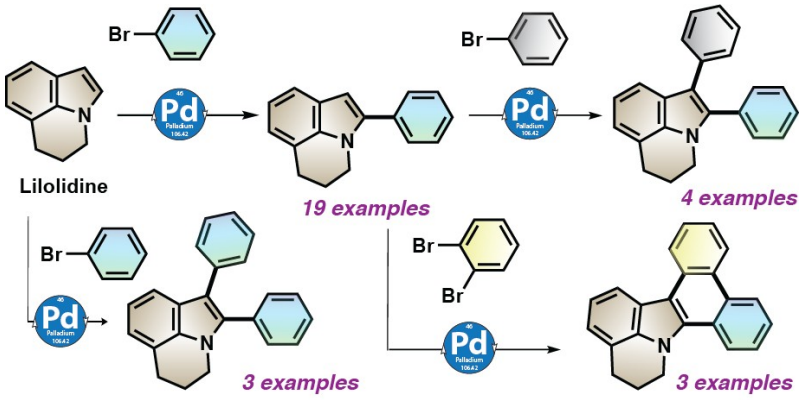
In the chapter 5, We describe the regioselective palladium-catalyzed direct arylation of a 6,7-difluorobenzo[*d*]imidazole using aryl bromides as the coupling partners.

Finally, in the chapter 6, We studied the influence of fluoro-substituents on the aryl group of *N*-methyl-*N*-benzylacetamides and *N*-methyl-*N*-benzylbenzamides on the regioselectivity of the Pd-catalyzed arylation.

Résumé

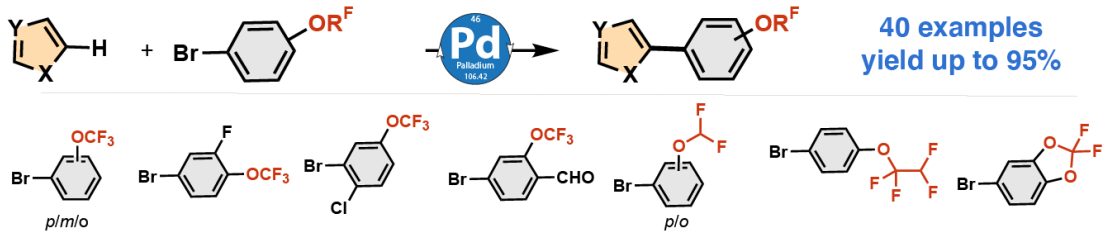
Les fonctionnalisations de liaisons C-H sp2 catalysées par le palladium représentent aujourd'hui l'une des méthodologies les plus fiables pour accéder aux biaryles via la formation de liaisons carbone-carbone. Dans cette thèse, nous avons réussi à élargir la gamme de substrats pour ces réactions en utilisant des conditions économiquement viables.

Dans le chapitre 2, la fonctionnalisation de la liaison C-H de la Lilolidine catalysée par le Pd a été étudiée. L'utilisation d'un catalyseur palladium-diphosphine associé à des bases acétates dans le DMA s'est avérée favoriser l'arylation régiosélective en position α de l'atome d'azote de la Lilolidine avec une grande variété de bromures d'aryle. A partir de ces Lilolidines α-arylées, une seconde arylation en position *β* donne accès à des Lilolidines *α,β*-diarylées contenant deux groupes aryles différents. L'accès en un pot aux Lilolidines *α,β*-diarylées avec deux groupes aryles identiques est également possible en utilisant une plus grande quantité de bromure d'aryle. La synthèse de 5,6-dihydrodibenzo[a,c]pyrido[3,2,1-*jk*]
-carbazoles à partir de Lilolidine via trois arylations directes successives est également décrite. Par conséquent, cette méthodologie fournit un accès direct à plusieurs dérivés de la Lilolidine à partir de composés disponibles dans le commerce via une, deux ou trois étapes de fonctionnalisation de la liaison C-H permettant d'ajuster leurs propriétés biologiques (Schéma 1).



Schéeme 1 Accès aux dérivés de Lilolidine *α*- et *β*-arylés.

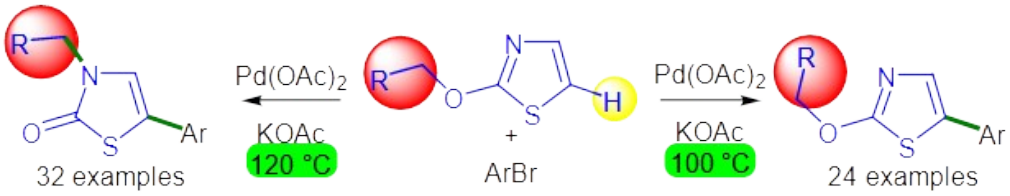
Dans le chapitre 3, la réactivité des bromobenzènes di-, tri- et tétra-fluoroalkoxy-substitués dans l'arylation directe d'hétéroarènes à 5 membres en utilisant la catalyse au palladium a été explorée. Des rendements élevés en hétéroarènes arylés ont été obtenus en utilisant seulement 1 mol% de catalyseur Pd(OAc)2 avec KOAc comme base peu coûteuse. Des rendements similaires ont été obtenus avec des substituants o/m/p trifluorométhoxy-, o/p difluorométhoxy-, et tétrafluoroéthoxy sur le bromure d'aryle. Un difluorobenzo[d][1,3]dioxole bromo-substitué a également été couplé avec succès. Les principaux produits secondaires de la réaction sont HBr/KOAc. Par conséquent, ce schéma de synthèse est très intéressant pour l'accès à de tels hétéroaromatiques arylés contenant des polyfluoroalcoxy en termes de coût, de simplicité et de faible impact environnemental, par rapport aux réactions impliquant l'arylation d'hétéroarènes avec des bromophénols suivie d'une polyfluoroalkylation (schéma 2).



Scheme 2. Arylations directes d'hétéroarènes catalysées par Pd au moyen de bromobenzènes di-, tri- et tétra-(fluoro)-alcoxy-substitués

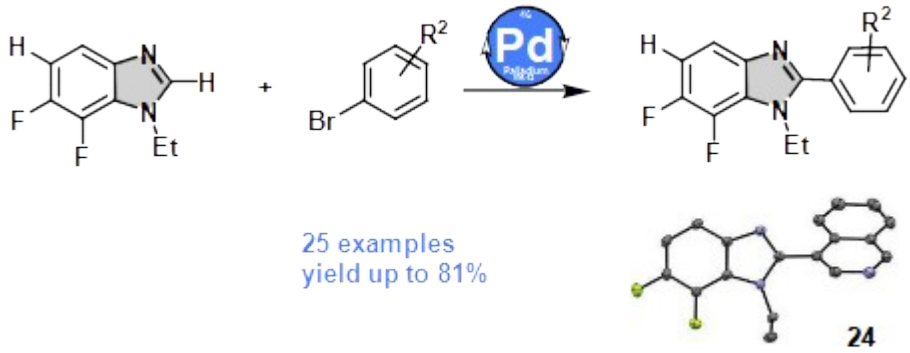
L'arylation directe de thiazoles ou de 2-alkylthiazoles catalysée par Pd est une réaction bien connue qui permet d'obtenir les 5-arylthiazoles correspondants avec des rendements très élevés. En revanche, la réactivité des 2-alkoxythiazoles n'a pas encore été décrite. Dans le chapitre 4, nous rapportons les conditions de la C5-arylation régiosélective des 2-alkoxythiazoles catalysée par Pd. De plus, nous avons également trouvé des conditions de réaction permettant d'obtenir des 3-alkyl-5-arylthiazol-2(3H)-ones via une arylation directe en un pot avec réarrangement migratoire de O- à N-alkyle. Le choix judicieux de la température de réaction permet de contrôler la sélectivité de la réaction. En général, à 100 °C, les 5-arylthiazoles sont les produits

majeurs ; alors qu'à 120 °C, les 3-alkyl-5-arylthiazol-2(3H)-ones sont obtenues avec de bonnes sélectivités. La réaction d'arylation est favorisée par un catalyseur au palladium sans ligand et stable à l'air et une base simple et peu coûteuse sans oxydant ni autres additifs, et tolère une variété de substituants utiles sur le bromure d'aryle et également sur les bromures d'hétéroaryle (schéma 3).



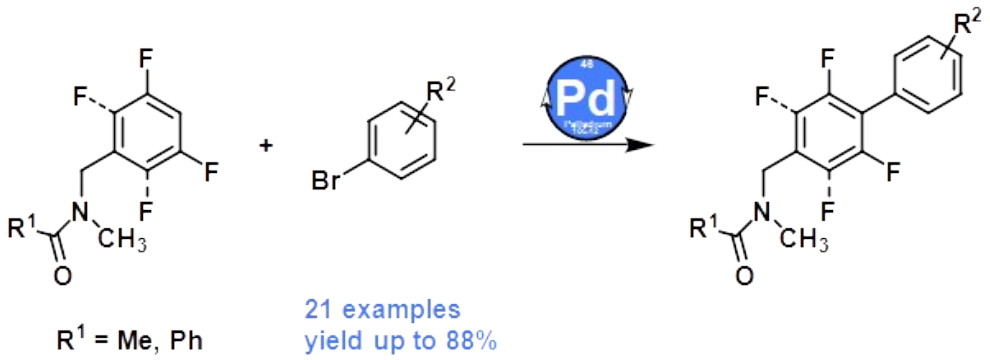
Scheme 3. Arylations directes de 2-alkoxythiazoles et réarrangement migratoire de O- à N-alkyle.

Dans le chapitre 5, les conditions pour l'arylation directe régiosélective catalysée par le palladium d'un 6,7-difluorobenzo[d]imidazole en utilisant des bromures d'aryle comme partenaires de couplage sont décrites. La sélectivité du site de l'arylation s'est avérée être en faveur du carbone C2 du difluorobenzo[d]imidazole, alors que le cycle difluoro-substitué est resté intact, même en présence d'un excès de bromure d'aryle. Cette méthode tolère une variété de substituants en positions para, méta et ortho sur le bromure d'aryle et également les bromures d'hétéroaryle contenant de l'azote (schéma 4).



Scheme 4. Arylations directes catalysées par Pd d'un 6,7-difluorobenzo[d]imidazole avec des halogénures d'aryle.

Dans le chapitre 6, l'influence des substituants fluoro sur le groupe aryle des *N*-méthyl-*N*-benzylacétamides et *N*-méthyl-*N*-benzylbenzamides sur la régiosélectivité des arylations directes catalysées par le palladium a été étudiée. Avec ces benzamides tertiaires (poly)fluorés, les arylations se déroulent de manière régiosélective au niveau de la liaison C-H flanquée de deux substituants fluorés en utilisant 2,5 % en moles d'un catalyseur au palladium stable à l'air et PivOK/*N,N*-diméthylacétamide (DMA) comme conditions de réaction. Pour ces réactions, une variété de substituants sur le bromure d'aryle, tels que ester, propionyle, acétyle, formyle, nitro, nitrile, méthoxy ou méthyle, était tolérée. Les bromures d'hétéroaryle contenant de l'azote ont également été utilisés avec succès. Ces résultats révèlent que dans nos conditions de réaction, les substituants fluoro agissent comme de meilleurs groupes directeurs que les amides dans les arylations directes catalysées par le palladium (Schéma 5).



Scheme 5. Arylation des liaisons C-H des benzylamines polyfluorées catalysée par Pd.

Les résultats présentés ci-dessus soulignent l'importance d'étudier des composés utiles et attrayants d'un point de vue synthétique dans la fonctionnalisation des liaisons C-H avec le catalyseur Pd. Dans l'avenir, à court et à long terme, les efforts de recherche pour suivre les contributions rapportées dans cette thèse de doctorat pourraient être les suivants :

Dans l'étude de la luminescence et du photochromisme, il faut noter qu'une gamme de fonctionnalités telles que nitrile, nitro ou trifluorométhyle sur le bromure d'aryle sont tolérées. Cette tolérance des groupes fonctionnels permet de modifier plus facilement les structures électroniques et, par conséquent, les propriétés photophysiques des molécules. Cette stratégie conduit à la formation d'une nouvelle classe d'émetteurs aux propriétés photophysiques attrayantes.

L'application de nouvelles stratégies reposant sur la chimie verte en utilisant des métaux moins chers comme le Fe, l'exploitation de conditions de réaction sans ligand ou sans solvant (ou pur).