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# Palladium-Catalyzed Direct Arylation *via* $sp^2$ and $sp^3$ C-H Activation of (hetero)Aromatics and Hydrocarbons for C-C Bond Formation

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DMF N,N-dimethylformamide

THF Tetrahydrofurane

NMP N-methyl-2-pyrrolidone

MW Microwave

DMA N,N-dimethylacetamide

DMAc N,N-dimethylacetamide

DMSO Dimethyl sulfoxide

dppb 1,4-bis(dipheynylphosphino)butane

CMD Concerted metallation-deprotonation

dba Dibenzylideneacetone

$S_EAr$ Electrophilic aromatic substitution

TS Transition state

GC Gas chromatography

NMR Nuclear magnetic resonance

dppm Bis(diphenylphosphino)methane

DEC Diethylcarbonate

MeTHF Methyl tetrahydrofurane

CPME Cyclopentylmethyl ether

dppe 1,2-bis(diphenylphosphino)ethane

OTf Triflate

TBAF Tetra-*n*-butylammonium fluoride

t-amylOH Tertpentyl alcohol

Ph-BPin arylboronic acid pinacol esters

Phen·$H_2O$ phenanthroline hydrate

$BuAd_2P$ bulky n-butyl-di-1-adamantylphosphine

TEMPO 2,2,6,6-tetramethylpiperidine 1-oxyl

TBAI Tetrabutylammonium iodide

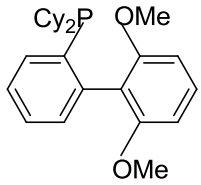
SEM [2-(trimethylsilyl)ethoxy]-methyl

PMB *para*-Methoxybenzyl

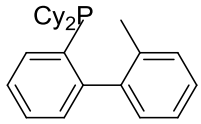
Bn Benzyl

DHC-18-C-6 Dicyclohexano-18-crown-6

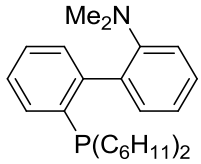
S-Phos



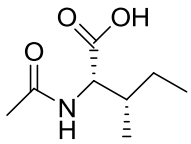

M-Phos




DavePhos




Ac-Ile-OH



# *General Introduction*

Biaryls and aryl-heterocycles are important key units in optical products, natural compounds, or pharmaceutical agents. The direct catalytic C-H bond functionalisation of (hetero)aromatics with aromatic halide is attractive as this synthetic methodology would offer cleaner, more economical and greener processes as direct arylation reactions provide only an acid (HX) associated to a required base as by-product and therefore presents advantages both in terms of atom-economy and relatively inert wastes. Palladium-catalyzed C-H activation/C-C bond-forming reactions have emerged as a promising tool for synthetic transformations for the assembly of carbon-carbon bonds. Despite much success has been obtained with palladium(0)/(II) catalysts, there are still many challenges to overcome, such as the control of regioselectivity at multi C-H sites, the exploration of new directing ligands, the development of $sp^3$ C-H bond functionalization.

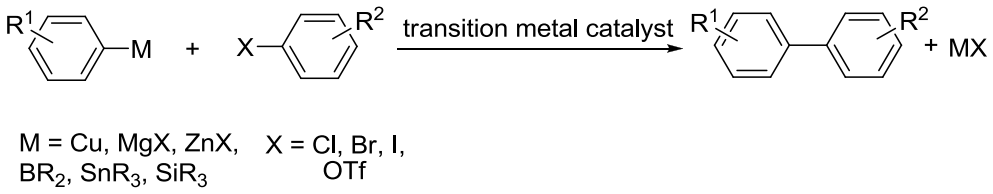
Herein, we would like to report highly effective coupling reactions involving $sp^2$ and $sp^3$ C-H bond activation by using palladium-catalyzed direct arylation of (hetero)aromatics with aryl halides. In **chapter 1**, the recent literatures about C-H bond arylation to form $sp^2$ C-$sp^2$ C and $sp^3$ C-$sp^2$ C bond *via* palladium catalysts will be emphasized. And then in **chapter 2**, we will describe the palladium-catalysed direct C2-arylation of benzothiophene with aryl bromides in the absence of phosphine ligand. The influence of C3-substituent on benzothiophene will also be discussed. In **chapter 3**, we will report the direct polyarylation of 1-methylpyrrole and 1-phenylpyrrole. The access to symmetrical 2,5-diarylated compounds from most reactive C-H bonds at C2, C5 positions of pyrrole derivatives and the sequential C2 arylation followed by C5 arylation to form non-symmetrically substituted 2,5-diarylpyrroles will be studied. To examine the reactivity of less reactive C-H bonds, we will report in the **chapter 4** the direct arylation of polychlorobenzenes. The reactivity of polychlorobenzene *vs* polyfluorobenzenes for palladium-catalysed direct arylation will be compared. The system of $PdCl(C_3H_5)$(dppb)/KOAc will be employed to promote the direct arylation of some polychlorobenzenes with aryl bromides. **Chapter 5** will describe palladium-catalyzed selective $sp^2$ and $sp^3$ C-H bond activation of guaiazulene which is a medical product separated from the lactarius indigo mushroom. This methodology show the solvent and base-controlled selectivity toward $sp^2$ C2-arylation (KOAc in ethylbenzene), $sp^2$ C3-arylation (KOAc in DMAc) and $sp^3$ C4-Me arylation ($CsOAc/K_2CO_3$ in DMAc).

# *Chapter 1: Literature survey on recent palladium-catalyzed C-H bond functionalization for C-C bond formation*

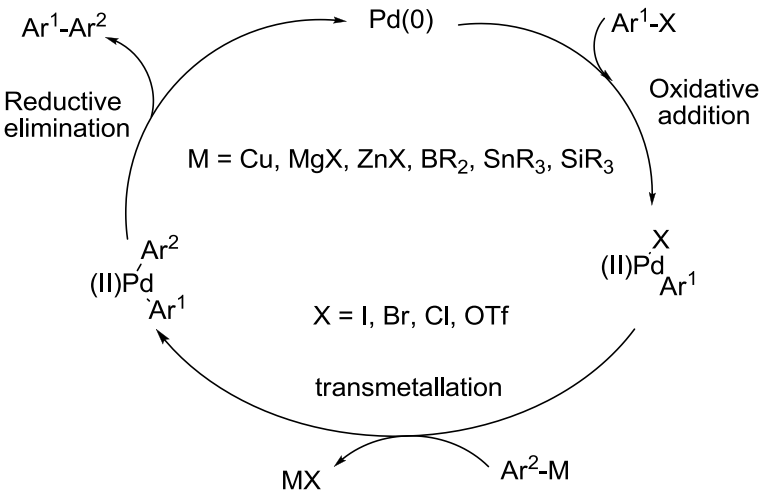
# Chapter 1: Literature survey on recent palladium-catalyzed C-H bond functionalization for C-C bond formation

## 1.1 Introduction

The formation of carbon-carbon (C-C) bond is a very important way to construct organic species. In 1855, the first discovery of the C-C bond formation for the synthesis of symmetrical alkenes via radical process encourages numerous innovations in organic chemistry. Especially in 1972, an important discovery of cross-coupling reaction was reported, employing the Grignard reagents and an organic halide, for generating C-C bonds by using nickel or palladium based catalysts, which is named Tamao-Kumada-Corriu coupling reaction.[1] Subsequently, a myriad development of this powerful synthetic transformation such as Negishi coupling,[2] Stille coupling,[3] Suzuki-Miyaura coupling,[4] Sonagashira coupling,[5] has been witnessed during the last decades. Due to their significant contribution on homogenous metal catalyzed cross coupling reactions in organic synthesis,[6] Richard F. Heck, Ei-ichi Negishi, Akira Suzuki were awarded the 2010 Nobel Prize. However these couplings still have still some fundamental drawbacks, as they required an additional synthetic operations for access to organometallic substrates RM (M = Cu, MgX, ZnX, $BR_2$, $SnR_3$, $SiR_3$, etc.), and produce a stoichiometric amount of metal waste from the arene-activating groups upon completion of the cross-coupling reaction (Scheme 1.1). Hence, when organometallic reagents are insufficiently stable to participate in the coupling reaction, more efficient environmentally-friendly process for the preparation of biaryls are needed.[7,8]

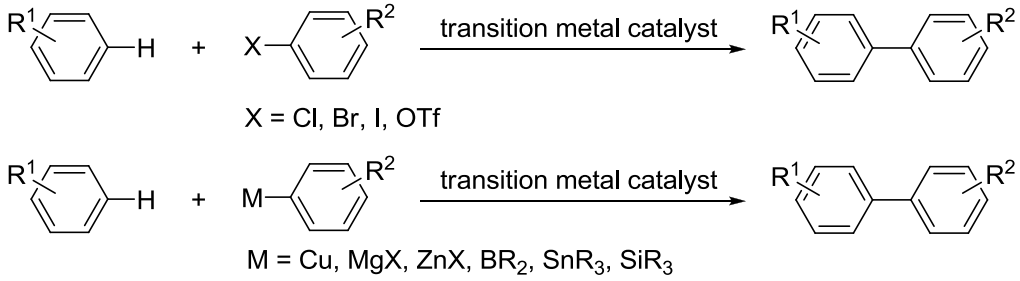



**Scheme 1.1**. Biaryl synthesis *via* traditional-metal-catalyzed cross-coupling reactions.




**Scheme 1.2**. General catalytic cycle of classical cross-coupling reactions.

The present challenge is to perform the direct conversion of C-H bonds without producing intermediate C-Metal bonds. To assess this possibility, the plausible catalytic cycle of these classical cross-coupling reactions is depicted in Scheme 1.2,[9] which involves: (I) oxidative addition of aryl halides or pseudohalide $Ar^1$-X to a palladium(0) complex yielding $Ar^1PdX$; (II) transmetallation between $Ar^1PdX$ and $Ar^2M$ generating $Ar^1Pd(II)Ar^2$ and MX; (III) reductive elimination gives coupling compound $Ar^1$-$Ar^2$ and regenerates the Pd(0) complex. In this catalytic cycle, the rate-limiting step is often the oxidative addition, especially with unactivated aryl bromides and aryl chlorides as substrates.[10] Therefore, replacement of Ar-X with Ar-H in the coupling reaction requires the generation of ArPd(II)X intermediate directly from Ar-H compound as one possibility, and similarly, arenes (C-H) could be used to replace the aryl metals (C-M) (Scheme 1.3).




**Scheme 1.3**. Transition metal-catalyzed C-C bond formation *via* C-H activation.

Over the past decades, significant advances has been made in the transition-metal-catalyzed C-C bond formation through C-H activation (for reviews see 11-16). In this direct C-H bond activation, one of the preactivated reaction partners is replaced by a simple C-H containing compound, which is not only just of academic interest but also attractive for industrial applications, since only one preactivated reaction partner is needed. Obviously, the cost of the reaction will be reduced by using cheap starting material, and the waste of the reaction can also be greatly reduced to benefit the environment.

Various transition metals (Pd, Rh, Ru, Cu, Fe, etc.) have been shown to be effective for cross-coupling reactions involving C-H bond activation in recent years.[17-22] The field of palladium, which has emerged as the preferred catalysts to promote the C-H bond cleavage in catalytic direct C-C bond formations, has been developed since the pioneering work of Fagnou[23], Yu[24], and Ackermann[25].

In this chapter, the recent progress of palladium(0)/(II)-catalyzed functionalization of $sp^2$ C-H bond and $sp^3$ C-H bonds for the selective formation of C-C bonds are summarized.

## 1.2 Palladium-catalyzed $sp^2$ C-H bond activation for C-C bond formation

Palladium-catalyzed direct intra- and inter-molecular arylation of (hetero)arenes is proposed to occur in general *via* oxidative addition of the transition metal into the aryl halide, followed by one of a number of possible key C-C bond-forming steps (Figure 1.1): (1) an electrophilic palladation or electrophilic aromatic substitution at the metal ($S_EAr$)[26] would involve a rate-determining nucleophilic attack by the arene on an electrophilic Pd(II)-aryl species followed by rapid deprotonation of the resulting Wheland intermediate; subsequent reductive elimination of the biaryl from Pd(II) would form the desired C-C bond as well as regenerate the active catalyst; (2) a concerted $S_E3$ process,[27] or a $\sigma$-bond metathesis;[28] (3) the Heck-type pathway is characterized by *syn*-addition of a palladium-carbon bond across a double bond of the aromatic coupling partner; while *anti*-$\beta$-hydride elimination is a high-energy process, the formation of a $\pi$-allyl species is often proposed, which could then isomerize to allow for a lower energy *syn*-$\beta$-hydride elimination,[29] or (4) the C-H bond oxidative addition of a Pd(II) species to a Pd(IV) species through an insertion into a C-H bond of an aromatic coupling partner;[30] (5) a Concerted

metallation-deprotonation (CMD) pathway, for simple or electron-deficient aromatics, is the lowest energy process, which was consistent with experimental observations.[31] In a CMD pathway, the Pd-C bond formation occurs concurrently with the cleavage of the C-H bond of the arene to afford a Pd(II) diaryl species. This is then followed by reductive elimination of the biaryl product, regenerating the active catalyst. This CMD pathway was validated for C-C bond formation at C($sp^2$)-H bonds. Importantly, the concerted nature of this process opens the door for similar reactivity at non-acidic C($sp^3$)-H bonds which cannot react in a stepwise fashion.[32] This part will highlight the developments in both the intramolecular and intermolecular direct arylations. Where appropriate, additional mechanistic discussion will be presented.

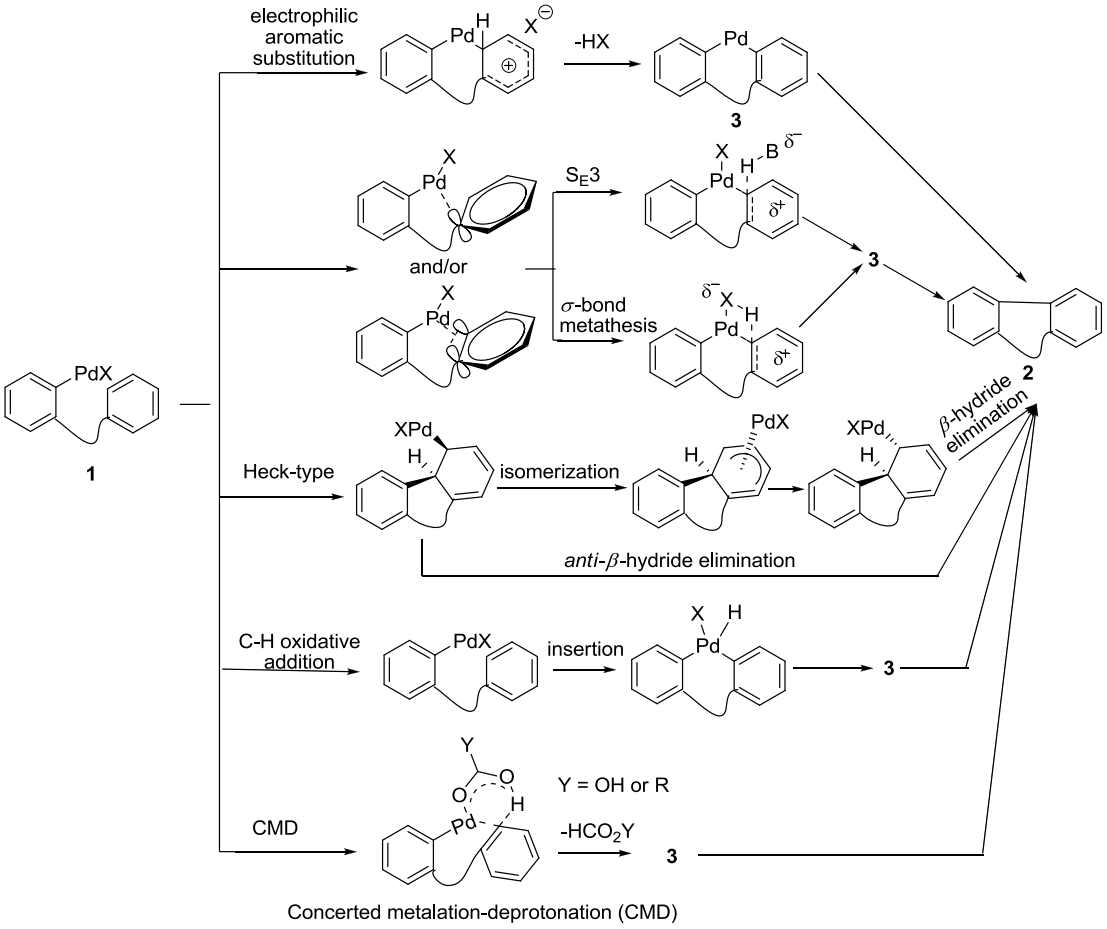



**Figure 1.1.** Five possible direct arylation mechanisms.

## 1.2.1 Palladium-catalyzed aryl-aryl bond formation

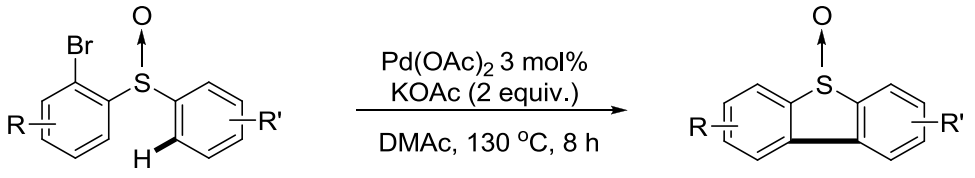
Palladium-catalyzed arylation directly *via* C-H bond cleavage using aryl halides as coupling partners is very often employed in the synthesis of biaryl molecules, which skeletons are found in

a wide range of important compounds, including natural products and functional organic materials.[33,34]

### 1.2.1.1 Palladium-catalyzed intramolecular aryl-aryl bond formation

This section deals with the intramolecular C-C bond formation leading to complex biaryl moieties with extended $\pi$-conjugated systems *via* single or double C-H bond activation(s).

Colobert and co-workers used phosphine-free palladium acetate as the catalyst to access dibenzothiophene-S-oxide scaffolds using easily accessible 2-bromo-diaryl sulfoxides (Scheme 1.4).[35] They employed $Pd(OAc)_2$ (3 mol%) and KOAc (2 equiv.) as base in polar solvent DMAc to form the cyclization products in high yields.

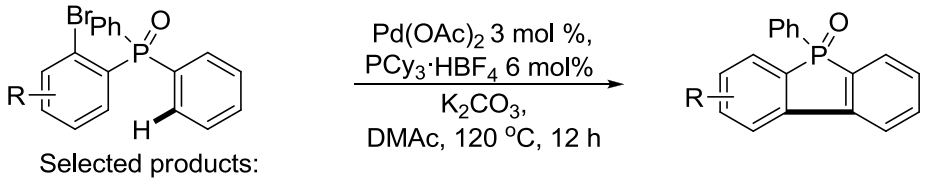



Selected products:

R = *p*-Ac, R' = H (86%); R = *m*-F, R' = *p*-Me (85%); R = *p*-Ac, R' = *p*-Me (88%)

**Scheme 1.4**. Sulfoxide-directed cyclometalation *via* Pd(0)-catalysis.

The dibenzophosphole oxides were obtained by Cui's group *via* palladium-catalyzed direct arylation reaction from the readily available *ortho*-halodiarylphosphine oxides. The optimized reaction conditions are as follows, $Pd(OAc)_2$ (3 mol%) associated to $PCy_3{\cdot}HBF_4$ (6 mol%) as the catalyst, DMAc as the solvent and $K_2CO_3$ (1.5 equiv.) as the base. This catalytic system tolerates both electron-rich and electron-poor aryl bromides and affords the cyclized products in good to excellent yields (Scheme 1.5).[36]

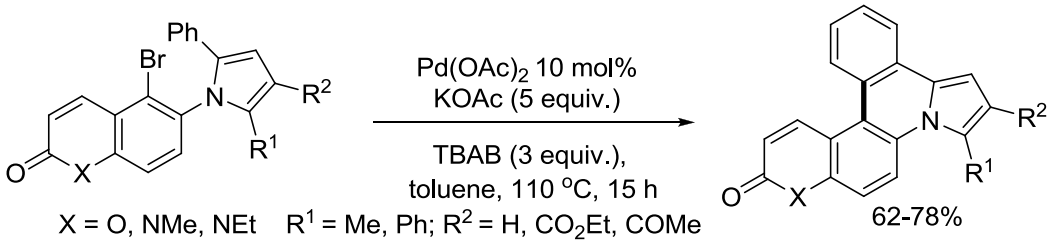



Selected products:

R = H (98%); R = *m*-OMe (96%); R = *p*-Cl (94%); R = *p*-$CO_2$Et (90%); R = *p*-CN, (83%)

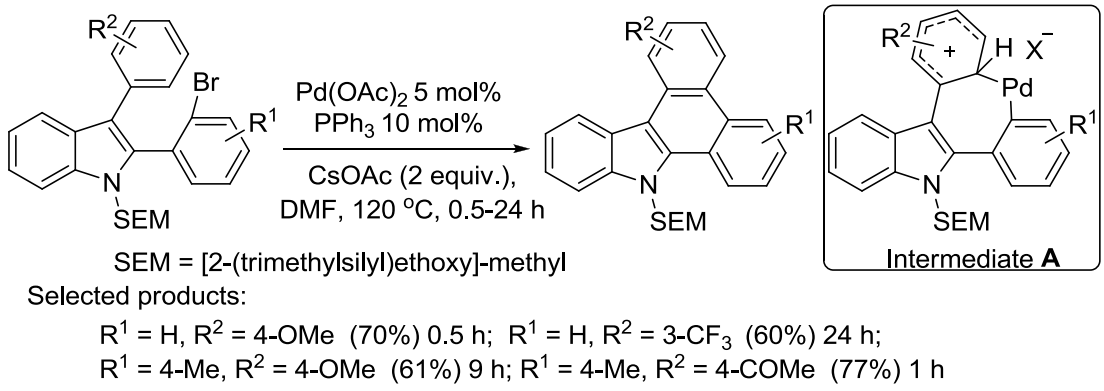
**Scheme 1.5**. Phosphine oxide-directed cyclometalation *via* Pd-catalysis.

Intramolecular palladium-catalyzed C-H activation of *N*-aryl-pyrrole in toluene was carried out by Hazra and co-workers in 2012 (Scheme 1.6).[37] This protocol was simple and efficient for the synthesis of polycyclic heterocycles in good yields using $Pd(OAc)_2$ as a catalyst, potassium acetate as a base in the presence of TBAB at 110 $^oC$. Hazra and co-workers noticed that $Cs_2CO_3$ or $K_2CO_3$ provided lower yields compared to KOAc, and $PPh_3$ offered a somewhat negative result.



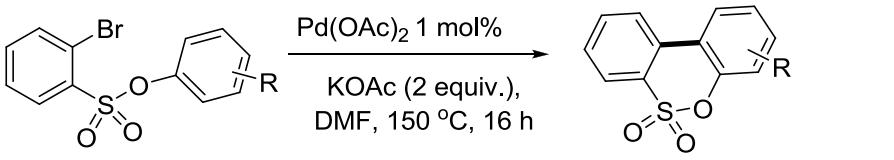

**Scheme 1.6**. Palladium-catalyzed intramolecular arylation of *N*-aryl-pyrrole.

Iazzetti and co-workers studied the intramolecular cross-coupling reaction of 2-(2-bromoaryl)-3-arylindoles (Scheme 1.7).[38] This methodology provides a general route for the synthesis of dibenzo[a,c]carbazoles in almost quantitative yields. Palladium acetate with $PPh_3$ as ligand catalyzes intramolecular biaryl coupling. This process most probably involves electrophilic aromatic substitutions.




**Scheme 1.7**. Palladium-catalyzed intramolecular arylation of 2-(2-bromoaryl)-3-arylindoles.

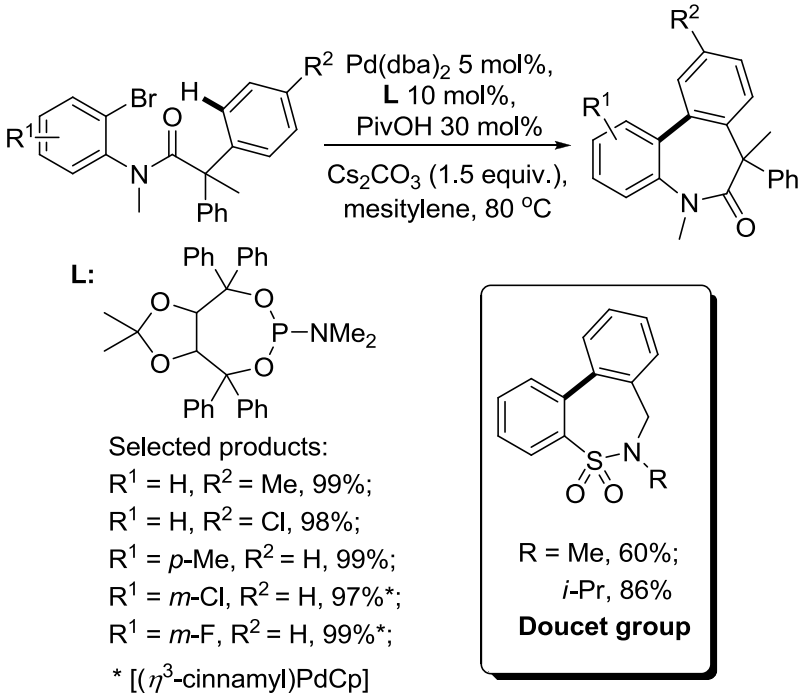
In the same year, Doucet and co-workers envisioned a simple access to synthesize the functionalized sultones from 2-bromobenzenesulfonic acid phenyl esters in the presence of a phosphine-free palladium acetate catalyst (1 mol%) (Scheme 1.8).[39] In this case, electron-donating substituents on the phenol moiety favored the reaction, whereas electron-withdrawing substituents are unfavourable.




Selected products: R = 4-OMe, 96%; 4-$NO_2$, 0%; *o*-benzyl, 80%; 4-Cl, 62%

**Scheme 1.8**. The synthesis of sultones *via* Pd-catalysis.

Up till now, there are few reported examples for the formation of seven-membered ring *via* $sp^2$ C-H activation.[40] This gap is attributed to the difficult formation of intermediate eight-membered palladacycles.[40a,41] Doucet and co-workers prepared two seven-membered ring compounds (Scheme 1.9)[39] from *N*-benzyl-2-bromo-*N*-methylbenzenesulfonamides as shown in Scheme 1.8. Last year, Cramer and co-workers established a procedure to sythesize dibenzazepinones *via* the palladium-catalyzed intramolecular direct C-H arylation. This reaction proceeded smoothly with palladium dibenzylideneacetone $Pd(dba)_2$ (5 mol%) and monodentate phosphine ligand **L** (10 mol%) in mesitylene (Scheme 1.9).[41] Mechanistically, a less preferred palladacycle (eight-membered versus six-membered), unique selectivity for the $C(sp^2)$-H (**2s**) over the $C(sp^3)$-H (**3s**) arylation was observed (Figure 1.2).




**Scheme 1.9**. Seven-membered ring formation *via* Pd-catalysis.

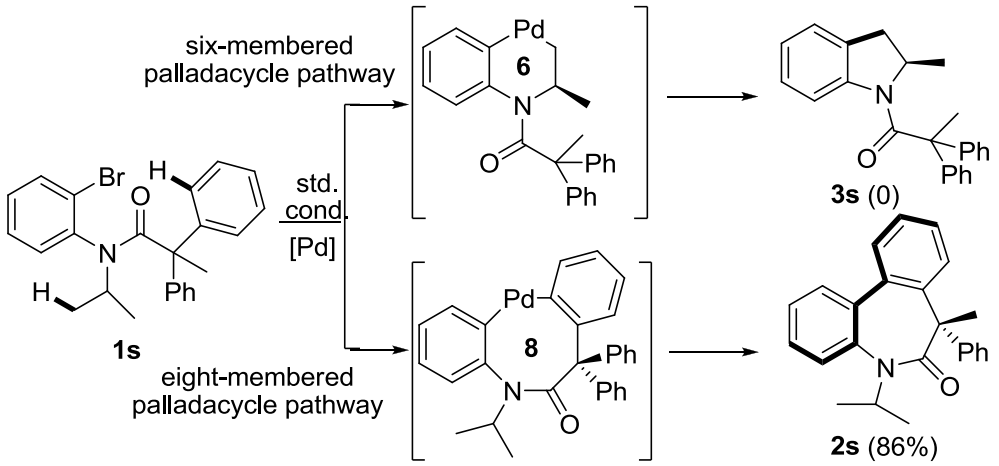
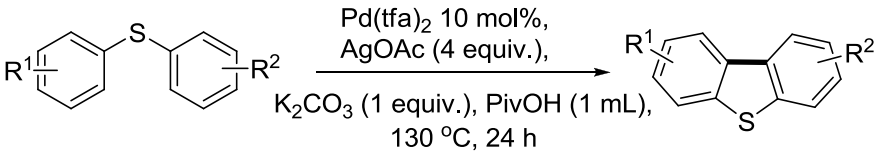



**Figure 1.2**. Regioselective C-H arylation of **1s**.

The dibenzothiophenes have been prepared by reduction of dibenzothiophene-S-oxide scaffolds[35] mentioned above. This year, Zhou and co-workers established the palladium-catalyzed direct intramolecular arylation of dibenzothiophenes from diaryl sulfides *via* double C-H bonds activation (Scheme 1.10).[42] This procedure was carried out in the system of $Pd(tfa)_2$ (tfa = trifluoroacetate) (10 mol%) rather than $Pd(OAc)_2$, AgOAc (4 equiv.), and $K_2CO_3$ (1 equiv.) in PivOH at 130 $^oC$ for 24 h. The diaryl sulfides bearing electron-rich substituents proceeded better (74-87%) than those with electron-deficient substituents (51-68%). Higher reactivity of the electron-rich substrates suggests that electrophilic aromatic substitution ($S_EAr$) would be responsible for C-H activation, rather than CMD pathway.




Selected products:
$R^1 = R^2 = H$, 86%; $R^1 = R^2 = 4\text{-OMe}$, 83%;
$R^1 = H$, $R^2 = 4\text{-F}$, 48%; $R^1 = 4\text{-OMe}$, $R^2 = 4\text{-Cl}$, 68%

**Scheme 1.10**. Palladium-catalyzed intramolecular arylation of dibenzothiophenes *via* double C-H bonds.

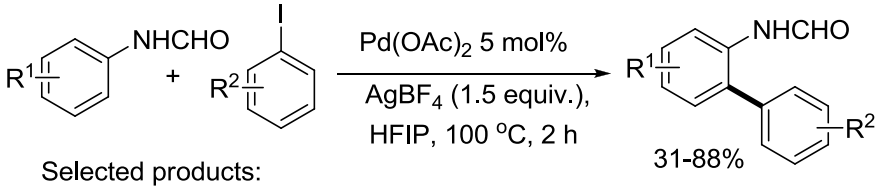
### 1.2.1.2 Palladium-catalyzed intermolecular aryl-aryl bond formation

This part which focuses on single or double C-H bonds activation leading to intermolecular biaryl synthesis, will be divided into two categories: (i) in the presence of directing group, and (ii) in the absence of directing group.

(i) To overcome uncontrolled site selectivity, a number of examples of C-C bond forming reaction with directing groups have been described in recent years. This section explains the effect of directing group assisting the activation of *ortho* aromatic C-H bond.

*N*-containing moieties like pyridine,[43] amides,[44-46] guanidine,[47] 1,2,3-triazole,[48] free-amine,[49] *N*,*N*-dimethylaminomethyl,[50] and phosphoramidate[51] have been employed in the efficient chelation-assisted C-H arylation. The regioselectivity of *ortho*-arylation with pyridine, amide, free-amine, and carboxylate as directing group has been addressed in recent review by Hussain[35] and Zhang[52].

The synthesis of biaryl formanilide *via* palladium-catalyzed C-H activation has been reported by Huang and co-workers (Scheme 1.11).[46] This formamide-directed *ortho*-arylation protocol employed the system of $Pd(OAc)_2$ (5 mol %) as the catalyst, $AgBF_4$ (1.5 equiv) as the oxidant under HFIP (1,1,1,3,3,3-hexafluoro-2-propanol) (0.2 mL). Aryl iodides bearing electron-rich groups afforded the arylation products in higher yields (64-76%), whereas the electron-deficient aryl iodides led to a dramatic decrease in yields at higher temperature with AgTFA as the oxidant (44-52%).




Selected products:

$R^1$ = *o*-Me, $R^2$ = *p*-Me 70%; $R^1$ = *o*-Me, $R^2$ = *p*-Cl 65%; $R^1$ = *o*-Me, $R^2$ = *p*-$NO_2$ 44%*;
$R^1$ = *o*-Et, $R^2$ = H 80%; * AgTFA (1.5 equiv.), TFA, 110 °C, 5 h

**Scheme 1.11**. Palladium-catalyzed formamide-directed *ortho*-arylation of formanilide.

Formamide-directed electrophilic palladation generates a palladacycle intermediate **A**. Then, oxidative addition of aryl iodide to Pd(II) **A** gives a Pd(IV) intermediate **B**, followed by reductive elimination to afford the arylation product and Pd(II). Silver salt not only acts as a halide scavenger to improve the transformation under the reaction condition but also acts as an oxidant (Figure 1.3).

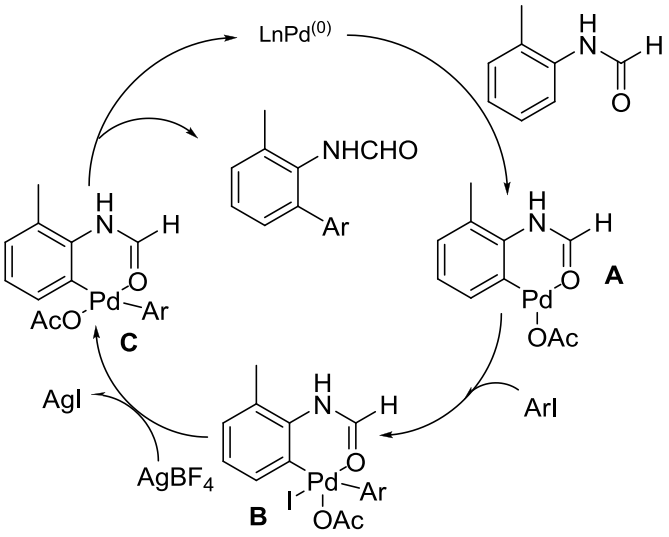
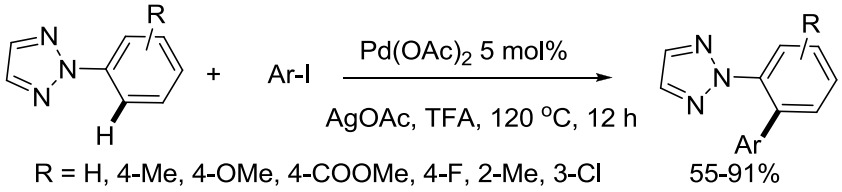


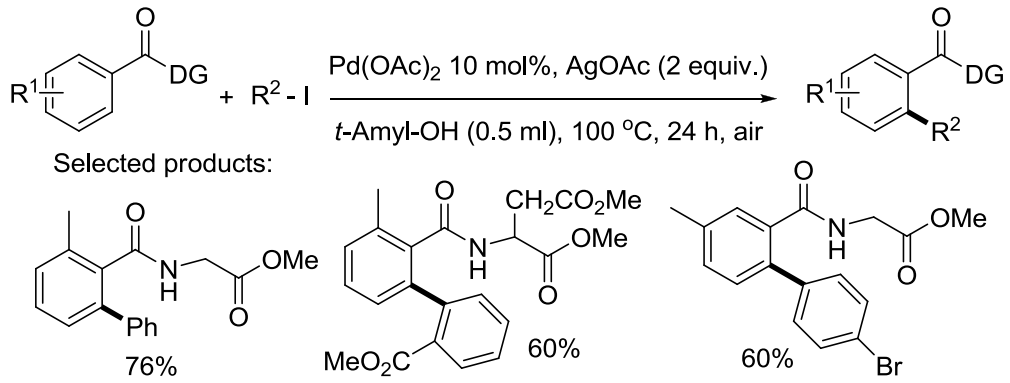

**Figure 1.3**. Proposed reaction mechanism.

Recently, Kuang and co-workers simplified the protocol for the arylation of 2-aryl-1,2,3-triazoles by using ligand-free palladium acetate (5 mol%) (Scheme 1.12).[48] A nitrogen atom in 1,2,3-triazole coordinated to Pd(II) species forming a pallacycle. Trifluoroacetate presumably participated in the aromatic proton abstraction to generate an aryl palladium intermediate. This process was followed by the oxidative addition of aryl iodides to form Pd(IV) species. Reductive elimination of Pd(IV) species in the presence of AgOAc and TFA gave the desired compounds and regenerated of the Pd(II) catalyst. The electron-rich or -deficient aryl iodides were well tolerated, resulting in excellent yields (61-91%).



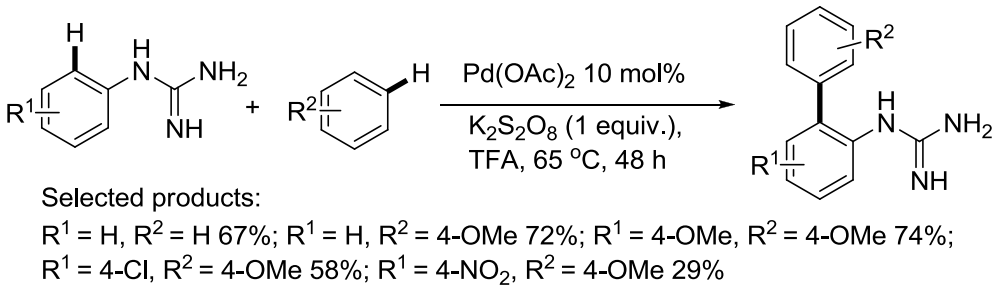

**Scheme 1.12.** Palladium-catalyzed azole-directed *ortho*-arylation of 2-aryl-1,2,3-triazoles.

Another application of palladium catalysts has been shown in the regioselective *ortho*-arylation of *N*-benzoyl $\alpha$-amino esters with aryl iodides using $\alpha$-amino ester as a directing group (Scheme 1.13).[53] Chatani and co-workers found that the steric hindrance of the $\alpha$-substituent dramatically affected the arylation selectivity. Aryl iodides and bromo/iodo alkyl compounds that contain no $\beta$-hydrogen could be used as coupling partners with similar regioselectivities.



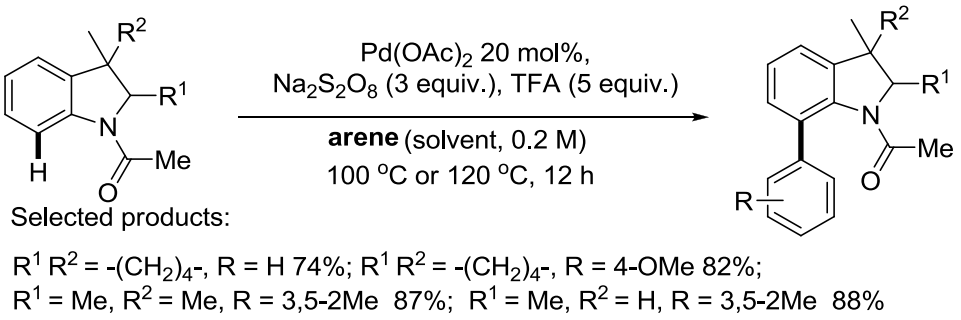

**Scheme 1.13**. Palladium-catalyzed $\alpha$-amino ester-directed *ortho*-arylation of *N*-benzoyl $\alpha$-amino esters.

In 2012, Yu and co-workers reported an efficient route to synthesize biologically active products through palladium-catalysed *ortho*-arylation of arylguanidine with electron-rich arenes, affording a variety of aryl guanidines (Scheme 1.14).[47] The reaction was carried out by using 10 mol% $Pd(OAc)_2$ in addition of 3 equiv. of $K_2S_2O_8$ (potassium persulfate), in the presence of TFA at 65 $^oC$ for 48 h.



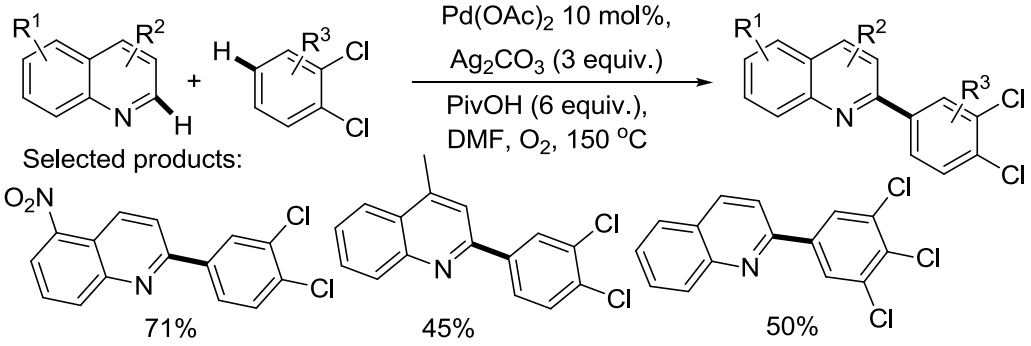

**Scheme 1.14.** Palladium-catalyzed guanidine-directed *ortho*-arylation of arylguanidine.

Continuously, palladium-catalyzed *ortho*-arylation of acetylated indoline with arenes to afford a variety of 7-aryl-indolines in moderate to good yields (40-93%) *via* dehydrogenative C-H/C-H cross coupling, was reported by Oestreich and co-workers (Scheme 1.15).[54] In this case, the introduction of the aryl group at C-7 position was directed by the acetyl group present on indoline in the presence of $Pd(OAc)_2$ as a catalyst, $Na_2S_2O_8$ as the terminal oxidant and TFA as an additive, and *o*-xylene as a solvent at 100 $^oC$.




**Scheme 1.15.** Palladium-catalyzed acetyl-directed *ortho*-arylation of indolines.

The synthesis of C3-arylated quinoline was disclosed by Kapur and co-workers in a two-step procedure.[55] Later on, Huang and co-workers developed a novel Pd-catalyzed C2-arylation of quinolones with chlorobenzenes (Scheme 1.16).[56] This protocol employed $Pd(OAc)_2$ (10 mol%) as the catalyst, $Ag_2CO_3$ (3 equiv.) and $O_2$ as the oxidants, in addition of PivOH (6 equiv.) in DMF at 150 °C for 30 h. The electron-deficient quinoline partners were tolerated except C8-$NO_2$ group.



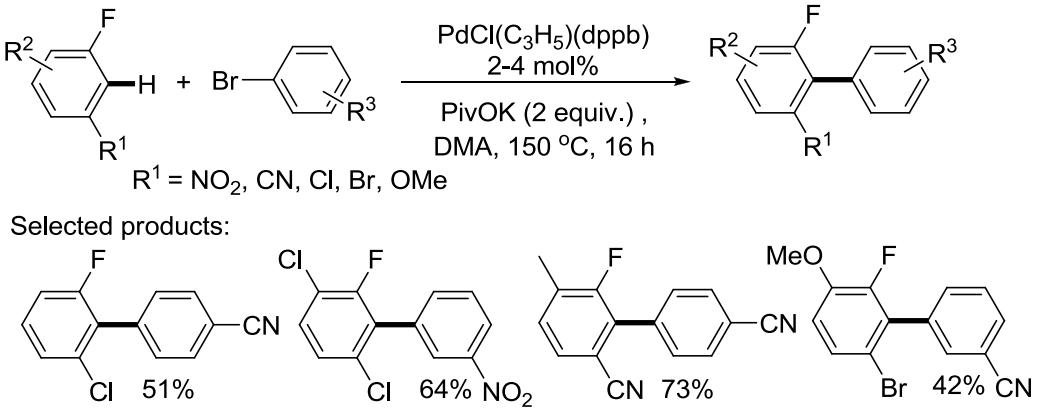

**Scheme 1.16**. Palladium-catalyzed C2-arylation of quinolines.

(ii) The absence of directing groups on most aromatic substrates makes C-H bond activation challenging.[57] Although some high yielding methods have been developed,[58] achieving high site selectivity is still a challenge.[59] Polyfluorobiaryl substructures are prevalent in medicinal chemistry and numerous functional materials. The arylation of polyfluorobenzenes with differently substituted aryl *via* palladium-catalyzed C-H activation has been developed during recent years.[35,60] The details about polyfluorobiaryl will be addressed in Chapter 4. Here, only recent examples will be discussed.

Liu and co-workers reported the highly selective arylation of polyfluorobenzenes with arene bromides bearing electron-rich or -deficient substituents by well-defined $Pd(OAc)_2/PCy_3$ in the

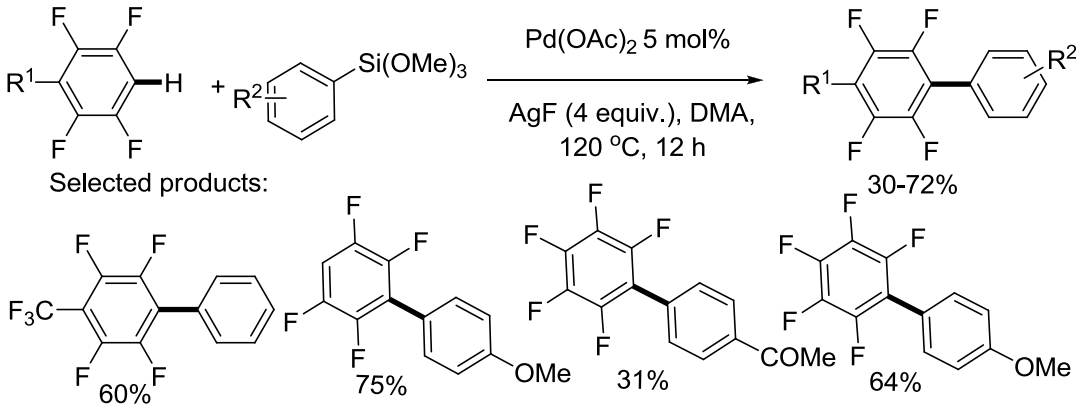
presence of $Cs_2CO_3$ as the base and toluene as solvent at 80 °C in good to excellent yield.[61]

Especially, the regio-selectivity of the arylation of monofluorobenzene was studied in Doucet's group. They found that C2-arylations of fluorobenzenes with electron-withdrawing substituents at C3 proceeded efficiently with the system of $PdCl(C_3H_5)(dppb)$ (2-4 mol%) as the catalyst, PivOK (2 equiv.) as the base in DMA at 150 °C for 16 h (Scheme 1.17).[62]




**Scheme 1.17**. Palladium-catalyzed C2-arylation of unactive monofluorobenzene.

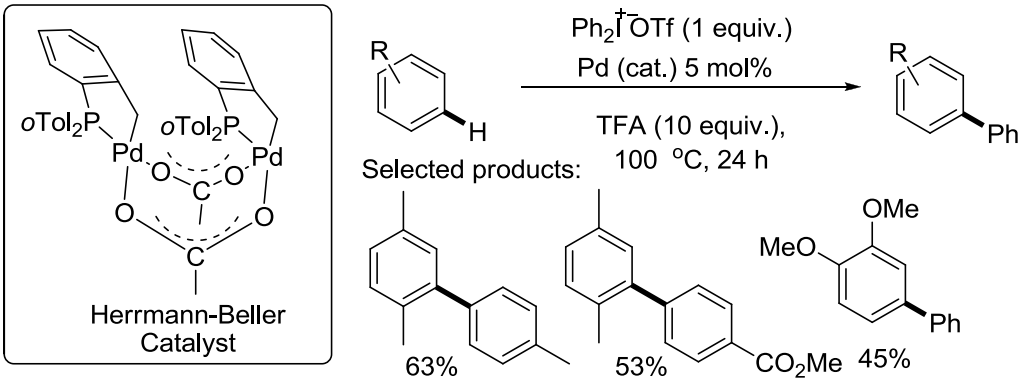
Su and co-workers expanded the scope of coupling partners to aryl trimethoxysilanes. This methodology was carried out with $Pd(OAc)_2$ (5 mol%) in addition to AgF (4 equiv.) as the oxidant in DMA at 120 °C (Scheme 1.18).[63] Pentafluorobenzene and tetrafluorobenzene tolerated diverse functional groups on aryl trimethoxysilanes.




**Scheme 1.18**. Palladium-catalyzed direct arylation of polyfluorobenzenes.

The direct arylation of unactive arenes *via* palladium-catalyzed C-H bond activation was reported by Greaney and co-workers. The arylation of simple arenes with diaryliodonium salts was achieved (Scheme 1.19).[64] The Herrmann-Beller palladacycle was a precatalyst and

stoichiometric TFA enhanced the electrophilicity of the palladium catalyst.




**Scheme 1.19**. Palladium-catalyzed direct arylation of unactive arenes.

## 1.2.2 Aryl-heteroaryl bond formation

Heteroaryls attached with aryl or heteroaryl groups represent privileged structural motifs that are utilized in functional organic materials, as well as in bioactive compounds and pharmaceuticals.[65] Palladium-catalyzed direct arylation with activated heteroaryl C-H bonds provides a desirable and atom-economical alternative to standard cross-coupling reactions for the construction of new C-C bonds.[66] The two mechanisms that have received most attention are the electrophilic aromatic substitution ($S_EAr$) and the CMD pathway. It is generally accepted that electron-rich heteroarenes react through a $S_EAr$ mechanism due to their high nucleophilicity. In Fagnou's group, the C-H cleavage of a wide range of (herero)aromatic has been identified through the CMD pathway (Figure 1.4), experimentally and computationally.[23c,23e] During this direct (hetero)arylation process, the site-selectivity among the multitude C-H bonds is always the key challenge.[67] This section deals with the regioselectivities of arylation of heteroarenes *via* palladium-catalyzed single C-H bond or double C-H bonds activation.

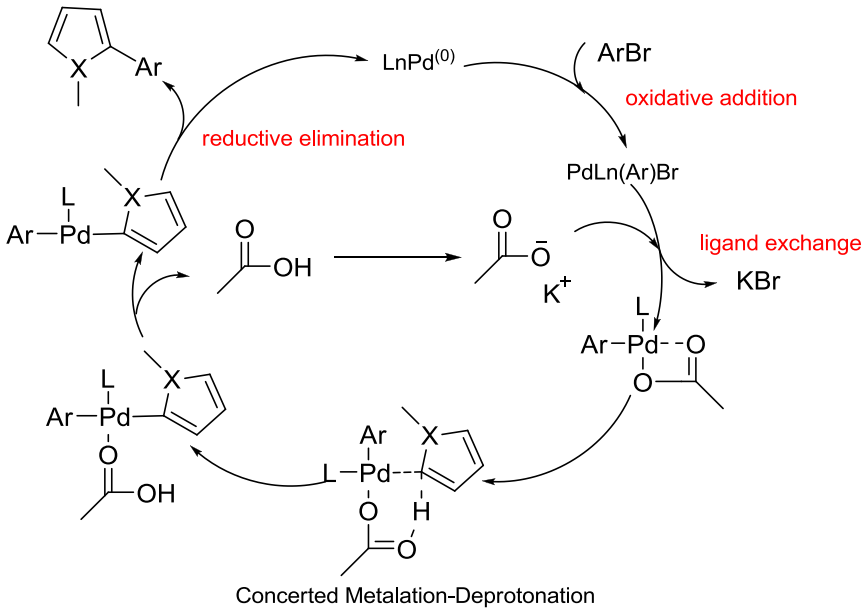



**Figure 1.4**. The general CMD pathway for the C-H activation of (hetero)aromatics.

### 1.2.2.1 Palladium-catalyzed direct intermolecular arylation of heteroarenes

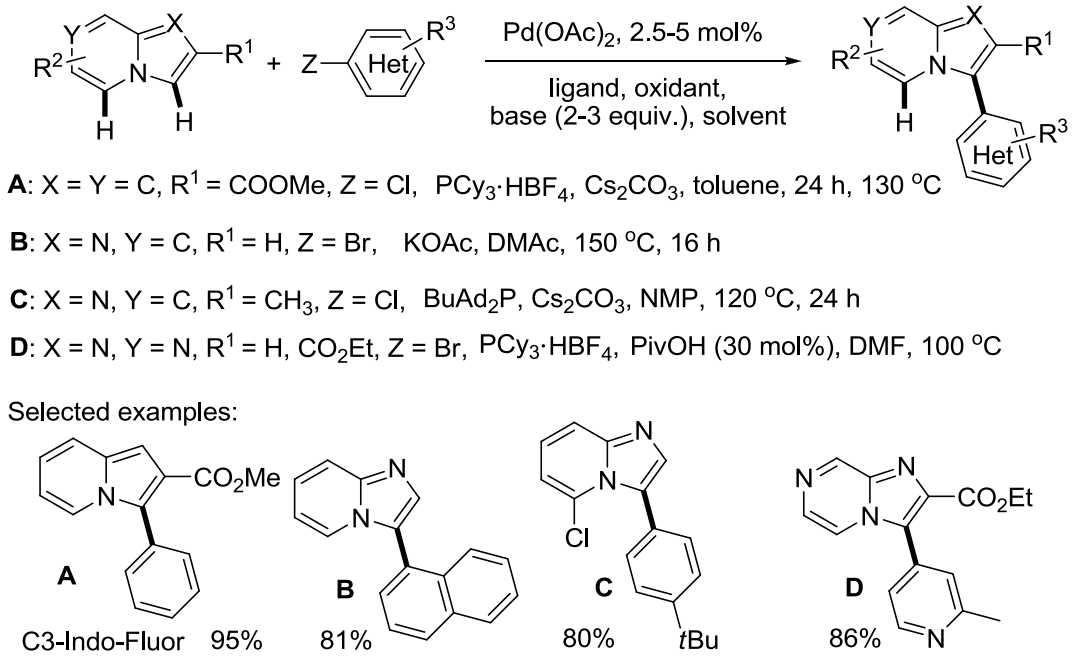
### a) Palladium-catalyzed direct arylation of heteroarenes with aryl halides

(i) Selective C3-arylation of heteroarenes.

The synthesis of full-color-tunable fluorescent indolizine core named C3-Indo-Fluor (Scheme 1.20) was achieved by You and co-workers. They employed $Pd(OAc)_2$ (5 mol%) coordinated with $PCy_3 \cdot HBF_4$ (10 mol%) as the catalyst, cesium carbonate as the base in toluene to obtain C3-arylated indolizines with chlorobenzenes bearing electron-rich, -poor, or sterically hindered groups in good yields (Scheme 1.20 **A**).[68]

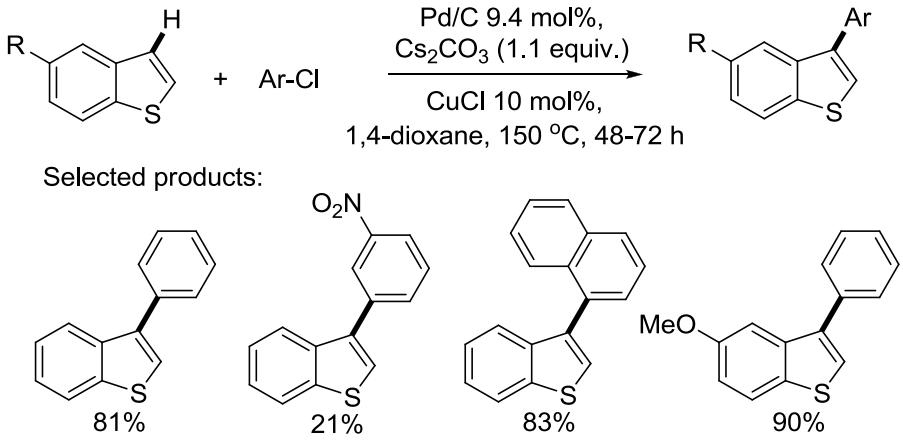
The selective C3-arylation of related imidazo[1,2-a]pyridines with aryl bromides were performed in Doucet's group by using low-loading (0.1-0.01 mol%) palladium acetate without any ligand, and patasium acetate (2 equiv.) as the base in DMA at 150 $^{o}$C for 16 h (Scheme 1.20 **B**).[69] This system was also suitable for differently substituted arylbromides with high selectivity. Cao and co-workers employed aryl chlorides as aryl halides by adding phosphine ligands with cessium carbonate as the base, in NMP at lower temperature (120 $^{o}$C) (Scheme 1.20 **C**).[70] By changing pyridine part to pyrazine, Huestis and co-workers used the similar conditions as You's[68] in the presence of oxidative PivOH in polar solvent DMF to expand the scope of C3-arylation, as well as

the subsequent C5 direct arylation for aryl and heteroaryl bromides (Scheme 1.20 **D**).[71]




**Scheme 1.20**. Palladium-catalyzed direct C-H (Hetero)arylation of *N*-Heterocycles.

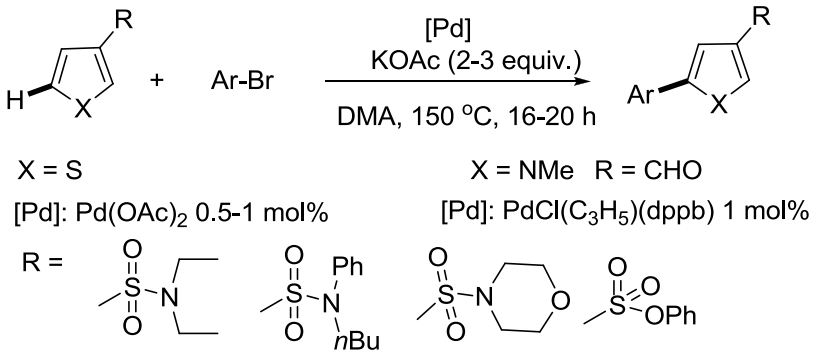
Last year, Glorius and co-workers established an efficient route to selectively arylate the less reactive C3-position of benzo[*b*]thiophene with various aryl chlorides (Scheme 1.21).[72] This protocol employed heterogeneous Pd/C as the catalyst in addition of copper salts enhancing the reactivity. Electron-rich, electron-neutral and sterically encumbered aryl chlorides gave coupling products in typically excellent yields.




**Scheme 1.21**. Pd/C catalyzed C3-arylation of benzo[*b*]thiophene.

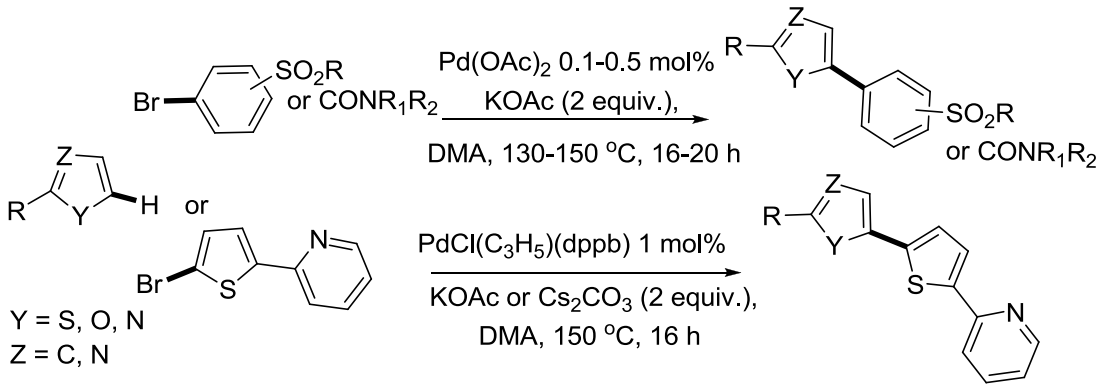
(ii) Selective C5 or C2 -arylation of heteroarenes.

Concerning the similar reactivity of several C-H bonds on most heterocycles, Doucet and co-workers eatablished mainly two systems to control the regioselectivity of arylation.[73] They used $Pd(OAc)_2$ or $PdCl(C_3H_5)(dppb)$ as the catalyst, acetate or carbonate salts as the base in polar solvent DMA to selectively achieve desired arylated compounds. The C5-arylation of thiophene and pyrrole bearing blocking substituents at C2 could be performed with high regioselectivity. The arylation of thiophenes bearing $SO_2NR_2$ substituents at C3 was found to proceed regioselectively at C5 (Scheme 1.22).[73a,73f] The aryl bromides for C5-arylated-3-acetylpyrrole were tolerated with the sterical groups.




**Scheme 1.22**. Palladium-catalyzed C5-arylation of thiophenes.

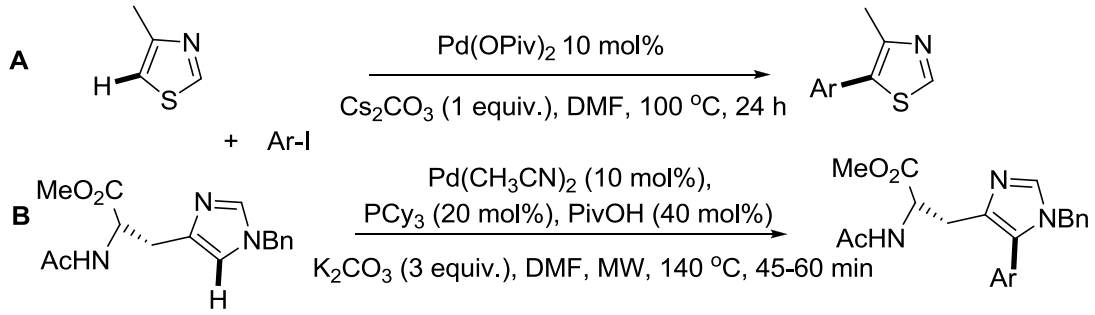
These systems were also employed for the C5-arylation of heterocycles with bromobenzene bearing $SO_2R$ (at C4 or C2)[73b] or amide substituents[73c], and 5-bromothiophen-2-ylpyridine[73f] (Scheme 1.23).




**Scheme 1.23**. Palladium-catalyzed C5-arylation of C2-blocked heterocycles.

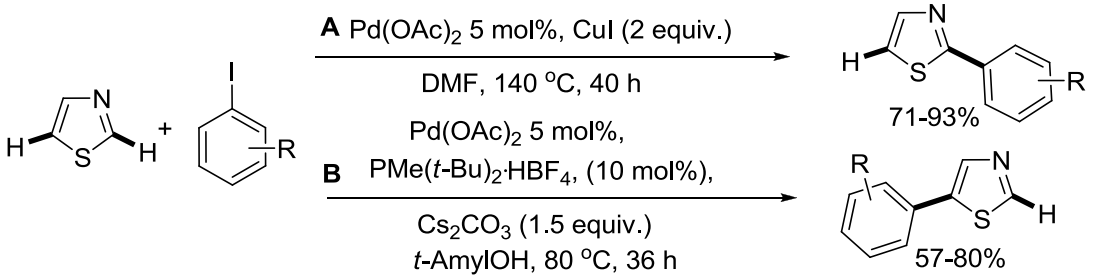
In 2013, the direct C5-arylation of thiazole and *N*-protected imidazole bearing C4-subsituent was reported by Shi and Jain, respectively. Shi and co-workers employed ligand-free $Pd(OPiv)_2$

(10 mol%) as the catalyst with $Cs_2CO_3$ (1 equiv.) in DMF at 100 °C to arylate thiazole with various aryl iodides and bromides in good yields (Scheme 1.24 **A**).[74] Meanwhile, Jain and co-workers used the system of $Pd(CH_3CN)_2$ (10 mol%) in the presence of $PCy_3$ (20 mol%) as the catalyst, PivOH as the oxidant, under the MW irridation. The C5-arylated *N*-protected imidazoles were obtained in 1 h with moderate to good yields (61-86%) (Scheme 1.24 **B**).[75]




**Scheme 1.24**. Palladium-catalyzed C5-arylation of C3-substituent heterocycles.

This year, Itami and co-workers developed a methodology to selectively form C2, C5, or C4-arylated thiazoles with aryl halides or aryl boronic acid.[76b] The C2-arylated thiazoles were obtained in good yields using $Pd(OAc)_2$ (5 mol%) combined with copper salts (Scheme 1.25 **A**). By adding the ligand $PMe(t\text{-}Bu)_2{\cdot}HBF_4$ (10 mol%) and $Cs_2CO_3$ (1.5 equiv.), in *t*-AmylOH (Tertpentyl alcohol) at 80 °C for 36 h, the C5-arylated thiazoles were obtained selectively (Scheme 1.25 **B**).

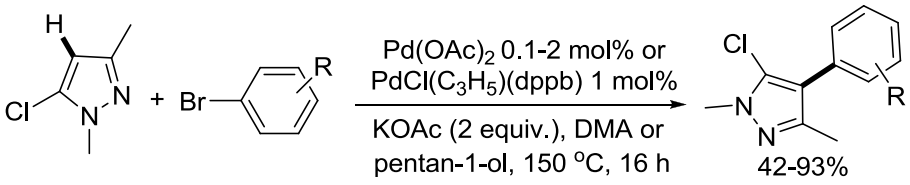



**Scheme 1.25**. Palladium-catalyzed C2- or C5- arylation of thiazole.

(ii) Selective C4 -arylation of heteroarenes.

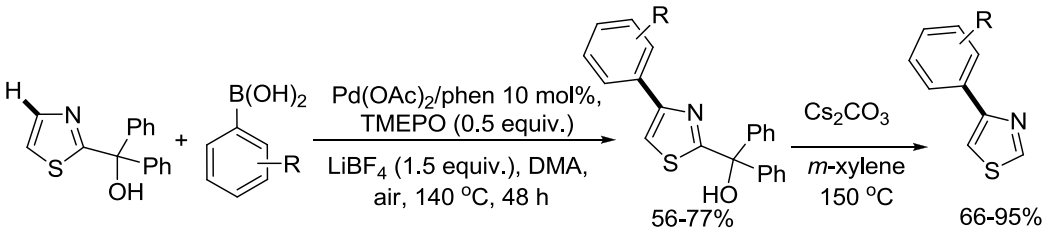
The selective C4-arylation of pyrazole was achieved in Doucet's group by blocking carbon C5 with a chloro substituent with their established conditions (Scheme 1.22 or 1.23). The electron-deficient aryl bromides could be compatible with ligand-free $Pd(OAc)_2$ catalytic system, whereas $PdCl(C_3H_5)$(dppb) also promoted the coupling of electron-rich aryl bromides (Scheme

1.26).[77]




**Scheme 1.26**. Palladium-catalyzed C4-arylation of pyrazole.

As mentioned in ref 76, Itami and co-workers also optimized the conditions for C4-arylation of thiazoles. They utilized $Pd(OAc)_2$ (5 mol%) in addition of phen (10 mol%), TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl) (0.5 equiv.), $LiBF_4$ (1.5 equiv.) in DMAc under air at 100 $^oC$ for 48 h to prepare the C4-arylated thiazoles after deprotection at C2-position (Scheme 1.27).[76b]



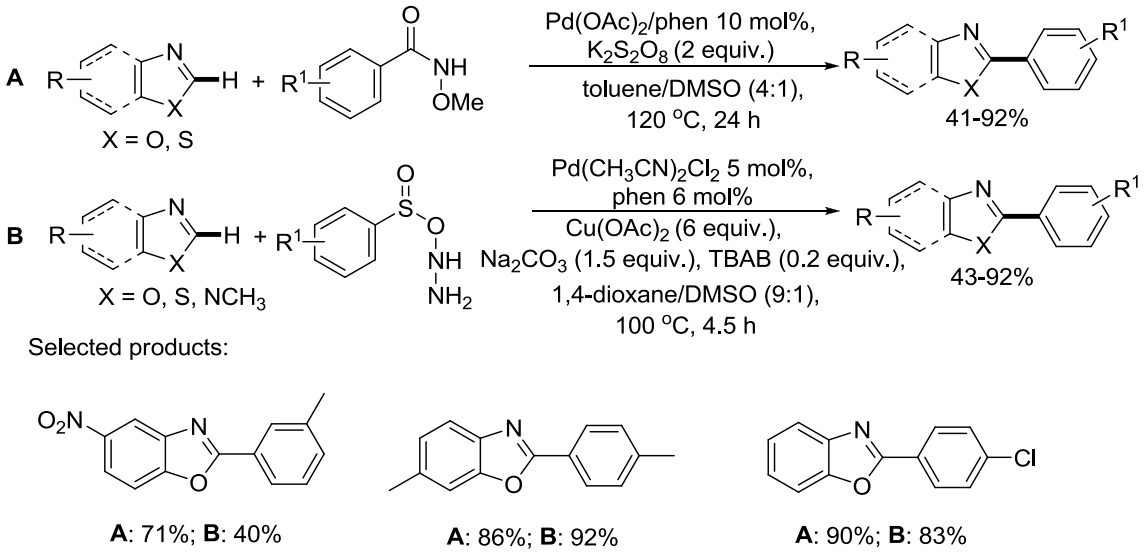

**Scheme 1.27**. Palladium-catalyzed C4-arylation of thiazole with aryl boronic acid.

## b) Palladium-catalyzed direct arylation of heteroarenes with various aryl derivatives

Aryl halides are important coupling partners for transition metal-catalyzed direct arylation of heteroaromatics. However, the reactivity of other various arylating reagents has also been explored for this type of reactions, such as, arylsilanes, aryl boronic acid,[76] aryl trifluoroborates, diazonium salts,[78] ArC(O)X (X = OH, NHOR, OR)[79] and $ArSO_2Y$ (Y = H, Na, $NHNH_2$, Cl),[80] (ref 34). Here, we would like to introduce some examples of palladium-catalyzed decarbonylation and desulfination cross-coupling reactions.

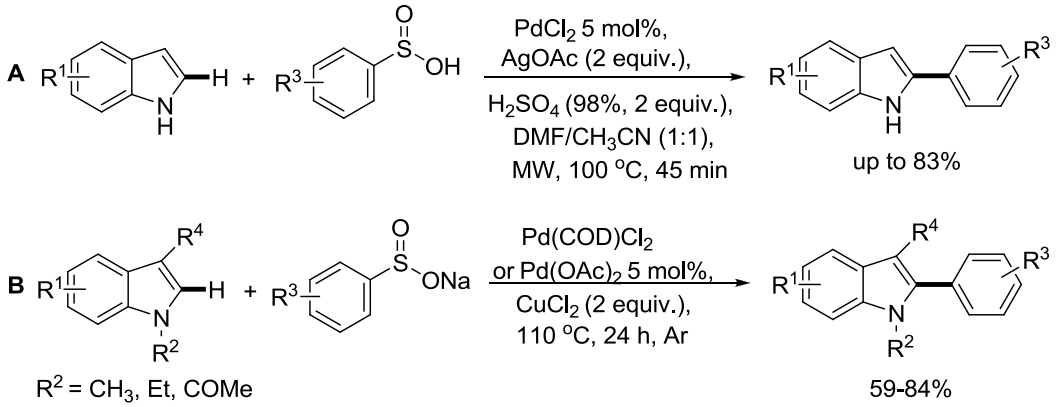
Wang[79] and Li[80c] simultaneously reported the palladium-catalyzed arylation of azoles using ArC(O)NHOR and $ArSO_2NHNH_2$, respectively. Wang used $Pd(OAc)_2$ (5 mol%)/1,10-phenanthroline in conjunction with $K_2S_2O_8$ as an oxidant *via* decarbonylation (Scheme 1.28 **A**) while $Pd(CH_3CN)_2Cl_2$ (5 mol%)/Phen $H_2O$ (6 mol%) with $Cu(OAc)_2$ as the oxidant in the presence of TBAB (Tetrabutylammonium bromide) *via*

desufinative-denitrogenation was used by Li (Scheme 1.28 **B**). They found that aryl-coupling species bearing electron-withdrawing and -donating groups were tolerated under these conditions. The higher reactivity of electron-deficient benzoxazoles with 3-bromotoluene was allowed to avoid the use of copper salts.




**Scheme 1.28**. Palladium-catalyzed C2-arylation of (ox)azoles.

Later on, Wang and co-workers broadened the direct arylation of free (NH)-indoles with arylsulfinic acid with silver acetate as an oxidant and $H_2SO_4$ as an additive using microwave (Scheme 1.29 **A**).[80a] This catalytic system enabled rapid and effective access to a variety of 2-arylated (NH)-indole products. Similarly, Deng and co-workers also demonstrated the reactivity of arylsufinic acid sodium salts as coupling partners, with *N*-substituent indoles in cross-coupling reactions using $Pd(COD)Cl_2$ or $Pd(OAc)_2$ (5 mol%) with $CuCl_2{\cdot}2H_2O$ as the oxidant in toluene/dioxane (1:1) (Scheme 1.29 **B**).[80b]




**Scheme 1.29**. Palladium-catalyzed desulfitative direct C2-arylation of indoles.

The Pd(II) catalyst reacts with the indole **1** in the C-2 position to form a Ar-Pd(II)-X intermediate **A** (X=OAc), which is subsequently displaced by sulfinic acid **2** to form intermediate **B**. This intermediate species undergoes desulfination to generate the aryl-palladium complex **C**. A reductive elimination of **C** affords the desired product **3** and the Pd(0) catalyst is reoxidized to Pd(II) by $CuCl_2$, thus closing the catalytic cycle (Figure 1.5). Various arylsufinic acid sodium salts with or without substituents selectively coupled with indoles and exclusively afforded the C-2 arylated indole adducts.

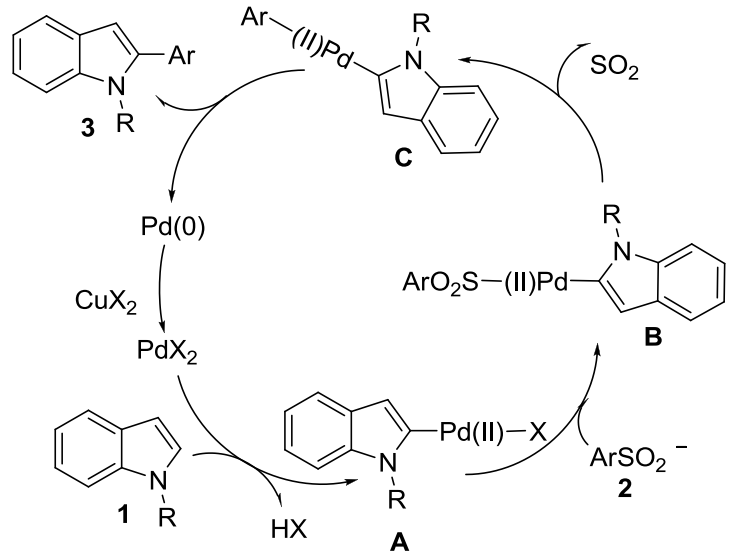
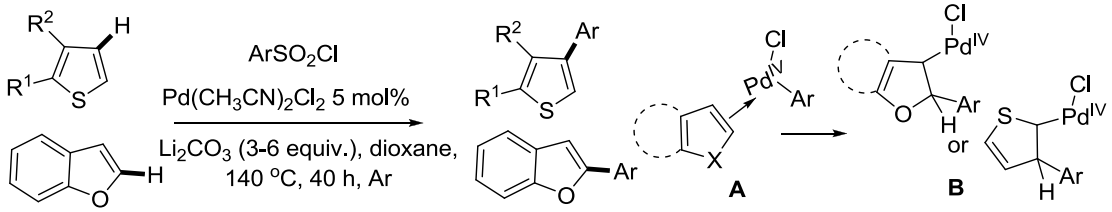



**Figure 1.5**. Proposed mechanism for C2-arylation of indoles.

$ArSO_2Cl$ has been recently applied as the coupling partners for the palladium-catalyzed desulfitative direct arylation of thiophene and benzofuran derivatives in Doucet's group. The reaction proceeds with easily accessible ligand-free $Pd(MeCN)_2Cl_2$ catalyst and $Li_2CO_3$ as base

and tolerates a wide variety of substituents on the benzenesulfonyl chloride (Scheme 1.30).[80d,80e]

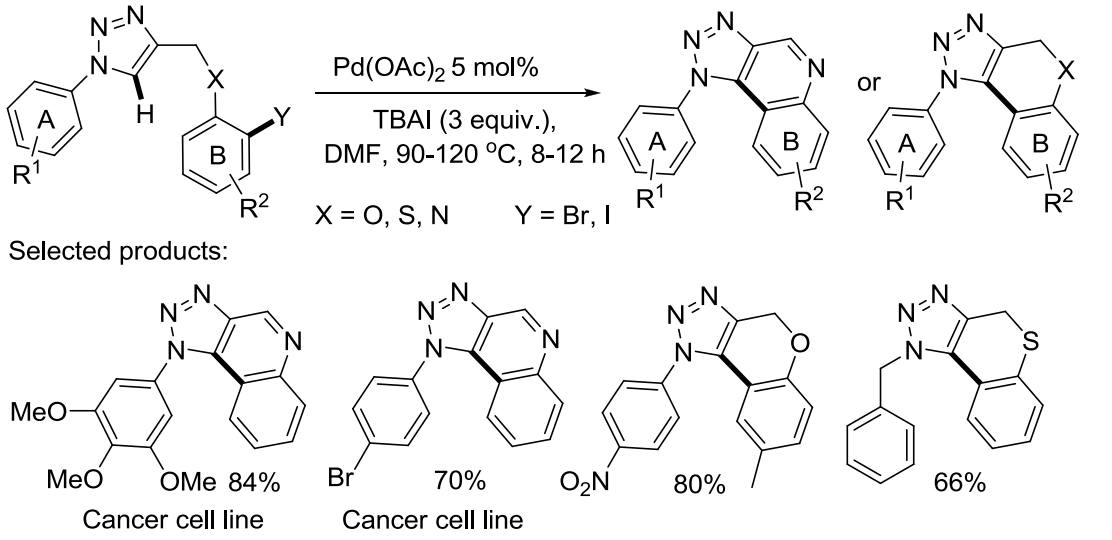
Mechanistically, the oxidative addition of the benzenesulfonyl chloride to Pd(II) affords the Pd(IV) species followed by elimination of $SO_2$. The coordination of heteroring gives imtermediate **A**. The migration of the aryl group to the *β*-carbon atom of thiophene or *α*-carbon atom of benzofuran leads **B**. Finally, base-assisted proton abstraction results the desired products and regenerates the Pd(II) species.




**Scheme 1.30**. Palladium-catalyzed desulfitative direct C2-arylated benzofuran and C3- arylated thiophene.

## 1.2.2.2 Palladium-catalyzed direct intramolecular arylation of heteroarenes

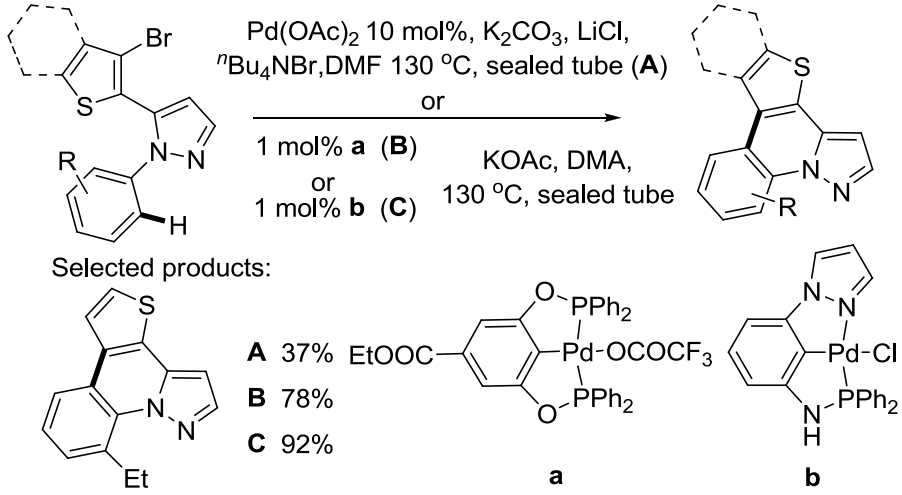
This section is about the intramolecular C-C bond formation leading to complex bi(hetero)aryl moieties *via* single C-H bond activation. The synthesis of some fused heterocycles *via* palladium-catalysis in DMF were carried out by Wang and co-workers in 2013 (Scheme 1.31).[81] This protocol was simple and efficient for the synthesis of quinoline fused triazoles in good yields using ligand-free $Pd(OAc)_2$ as the catalyst and TBAI (tetrabutylammonium iodide) at 120 °C.




**Scheme 1.31**. The synthesis of quinoline fused triazoles *via* Pd-catalysis.

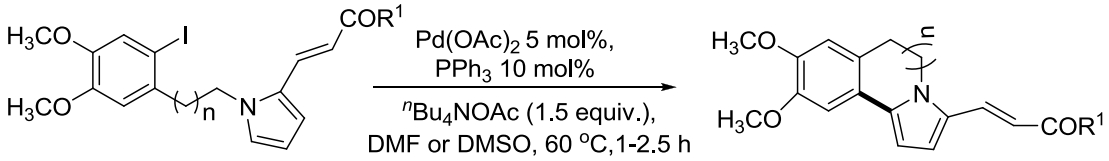
Wang and co-workers observed that TBAI accelerated the reaction rate in the absence of ligand.

SanMartin and co-workers studied the palladium-catalyzed intramolecular cross-coupling of 1-aryl-5-(benzo)thienylpyrazoles (Scheme 1.32).[82] They presented three methodologies of general applicability for the key intramolecular C-H heteroarylation of arenes. The latter two palladacycles (Scheme 1.32 **a** and **b**) act better at low-loadings.




**Scheme 1.32**. The synthesis of pyrazolo(benzo)thienoquinolines *via* Pd-catalysis.

Recently, Lete and co-workers found that the intramolecular palladium-catalyzed reaction of *N*-(arylalkyl)pyrroles can be applied for the selective synthesis of medium-sized rings by choosing the appropriate catalytic systems to direct the reaction to the pyrrole nucleus (Scheme 1.33).[83] The six- or seven-member ring, were selectively formed through $Pd(OAc)_2$ with $PPh_3$ or dppp in DMF.




n = 1: $R^1 = NEt_2$, (99%); $R^1$ = OBn, (84%); n = 2: $R^1 = NEt_2$, (84%); $R^1$ = OBn, (70%)

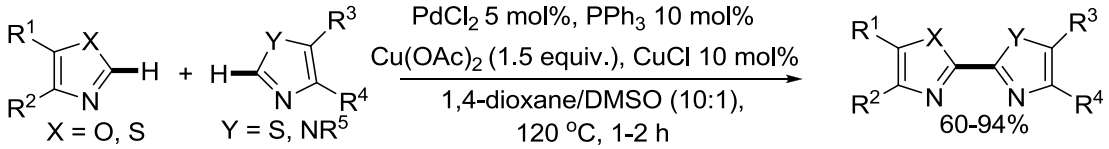
**Scheme 1.33**. The formation of six- or seven-member ring *via* Pd-catalysis.

### 1.2.2.3 Palladium-catalyzed bi(hetero)aryl C-C bond formation *via* double C-H bonds

The transition metal-catalyzed direct arylation *via* single C-H bond cleavage has been enormously developed. C-C Bond formation *via* double C-H activation has been also extensively

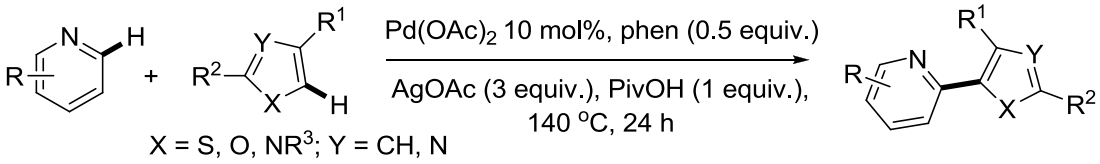
studied in recent years. This section concerns palladium-catalyzed inter- or intra-molecular bi(hetero)aryl C-C bond formation *via* double C-H bond activations.

You and co-workers reported an efficient palladium-catalyzed dehydrogenative cross-coupling between two azoles with closely related structures at the C2 and C2' positions in the presence of $PdCl_2$ (5 mol%) associated with $PPh_3$ (10 mol%) and $Cu(OAc)_2$ (1.5 equiv.) in combination with CuCl (10 mol%) in 1,4-dioxane/DMSO at 120 °C for 1-2 h (Scheme 1.34).[84] This method gave highly selective oxidative cross-coupling of structurally similar azoles forming unsymmetrical bisazoles.



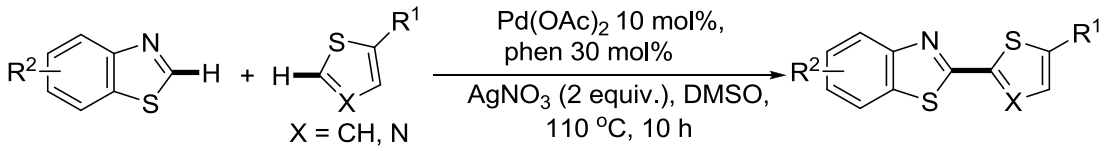

**Scheme 1.34**. Palladium-catalyzed unsymmetrical biazoles at C2 and C2' positions.

Later on, they developed a method to couple pyridines with heteroarenes catalyzed by $Pd(OAc)_2$/phen with silver salts as the oxidants in PivOH at 140 °C (Scheme 1.35),[85] yielding *ortho*-arylated products of pyridine and related azine. They noticed that the activated azine *N*-oxide was not necessary in this system.



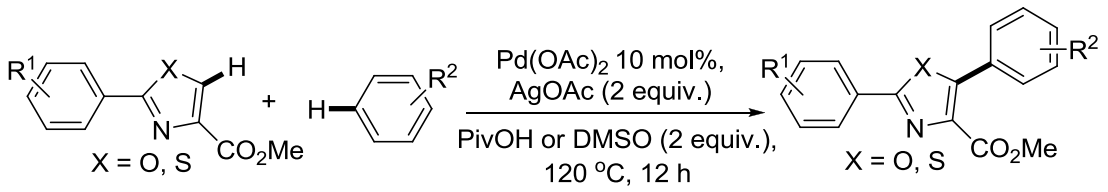

**Scheme 1.35**. Palladium-catalyzed C2-heteroarylation of pyridine and related azine.

Yang and co-workers extended the scope of unsymmetrical biheteroaryls. They improved the conditions by using $Pd(OAc)_2$/phen with silver salts as the oxidants in DMSO at 110 °C (Scheme 1.36).[86] Notably, the direct C-2 heteroarylation of benzothiazoles with the S-atom containing five-membered aromatic heterocycles was successful even in air.



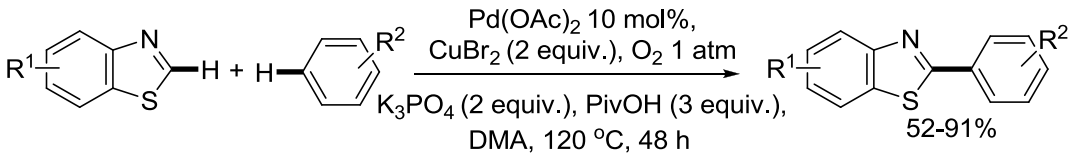

**Scheme 1.36**. Palladium-catalyzed direct C-2 heteroarylation of benzothiazoles.

Almost at the same time, Yao and co-workers disclosed the direct C5-arylation of azole-4-carboxylates with simple unactivated arenes by using $Pd(OAc)_2$ as a catalyst and AgOAc as an oxidant in the presence of PivOH in arene at 120 °C (Scheme 1.37).[87] This protocol tolerates electron-rich or -deficient groups on arenes with moderate to good yields (44-92%). The coupling yields for *p*-xylene could be remarkably improved by employing DMSO as solvent and PivOH as an additive (80%/51%).




**Scheme 1.37**. Palladium-catalyzed direct C5-arylation of azole-4-carboxylates with simple unactivated arenes.

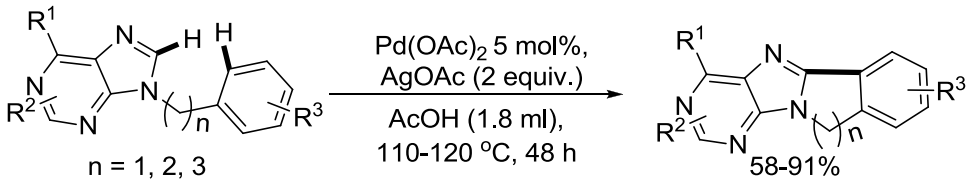
Su and co-workers replaced azole-4-carboxylates with benzoxazole, while keeping palladium in action, accelerated by $CuBr_2$ in cross-coupling reactions with unactivated arenes (Scheme 1.38).[88] The combination of $K_3PO_4$ and PivOH improved the yield, and $CuBr_2$ not only worked as an oxidant but also as a Lewis acid by coordination to benzoxazole, hence increasing C-H acidity of benzoxazole.




**Scheme 1.38**. Palladium-catalyzed direct C5-arylation of benzoxazole with simple unactivated arenes.

Li and co-workers developed a novel and convenient method for highly efficient intramolecular cyclization of purines and benzimidazoles catalysed by $Pd(OAc)_2$ to synthesize *N*-fused heterocycles (Scheme 1.39).[89] This intramolecular direct double C-H activation is conducted under normal acidic conditions without any base or ligand. A range of medium and large rings

were formed from purine or benzimidazole containing substrates.




**Scheme 1.39**. Palladium-catalyzed intramolecular cyclization of purines and benzimidazoles *via* bi C-H bonds.

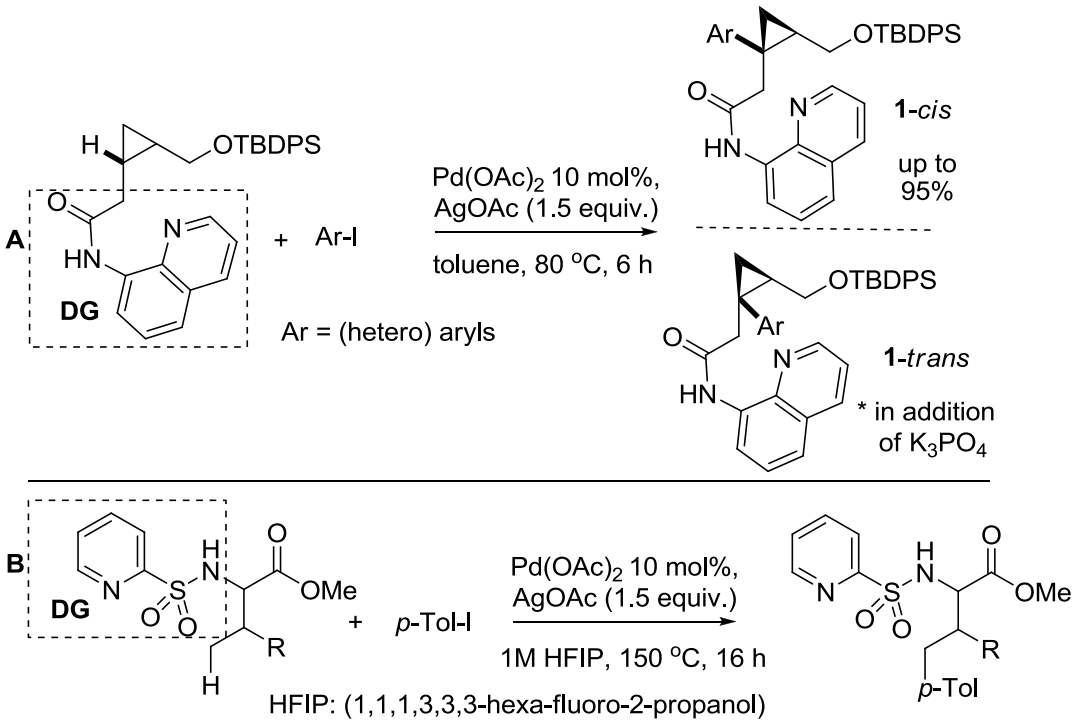
## 1.3 Palladium-catalyzed functionalization of $sp^3$ C-H bonds

The functionalization of relatively unreactive C-H bonds remains an area of intense interest within organic chemistry, particularly from the viewpoint of sustainability and efficiency in organic synthesis. It usually requires more acidic protons, the directing groups or the controlling ligands to accelerate the cleavage of $sp^3$ C-H bonds. This section deals with the effect to inter- and intra-molecular ($sp^3$-$sp^2$) C-C formation *via* palladium-catalyzed direct C-H activation.

### 1.3.1 Palladium-catalyzed intermolecular ($sp^3$-$sp^2$) C-C formation

The chiral quaternary carbon center on cyclopropanes was constructed by palladium-catalyzed tertiary C($sp^3$)-H arylation of cyclopropanes *via* directing group-mediated C-H activation using aryl iodides as a coupling partner in Shuto's group (Scheme 1.40 **A**).[90] The tertiary C($sp^3$)-H bond activation of ***1***-*cis* occurred under the conditions with $Pd(OAc)_2$ (10 mol %) and AgOAc (1.5 equiv) in toluene at 80 °C, while, in the presence of $K_3PO_4$ (1 equiv.), ***1***-*trans* could be obtained.

At the same time, Carretero and co-workers described palladium-catalyzed direct $\gamma$-C($sp^3$)-H activation of amino acid esters bearing a removable *N*-(2-pyridyl)sulfonyl directing group (Scheme 1.40 **B**).[91] A variety of *N*-(2-pyridyl) sulfonamide amino acid derivatives including $\alpha$-quaternary amino acids, $\beta$-amino acids, and dipeptide substrates, react with iodoarenes in the presence of $Pd(OAc)_2$ to provide $\gamma$-arylated products in synthetically useful yields.




**Scheme 1.39**. Palladium-catalyzed direct arylation of C($sp^3$)-H compounds with directing-group.

To facilitate the intermolecular arylation of unactivated C($sp^3$)−H bonds (those with pKa > 30[92]) in the absence of directing groups, Walsh group established one general method for the functionalization of weakly acidic $sp^3$-hybridized C−H bonds (pKa's 28−35 in DMSO) *via* deprotonative cross-coupling processes (DCCP).[93] Substrates employed to date include diarylmethanes,[93a,93b] sulfoxides,[93c] sulfones,[93d] amides,[93e,93g] phosphine oxides,[93f] and most recently phosphonates.[93h]

For the arylation of diarylmethanes, Walsh and co-workers found that the combination of $Pd(OAc)_2$ and NiXantphos as an excellent precatalyst system with alkali metal-bis (trimethylsilyl) amide base ($MN(SiMe_3)_2$, M = Li, Na, K), in CPME at room temperature afforded the desired triarylmethane products (Scheme 1.41 **A**).[93a,93b] They emphasized that ($MN(SiMe_3)_2$, M = Li, Na) failed to show trace conversion in the absence of additives, while, only a single base, $KN(SiMe_3)_2$ worked for benzylation.

The direct *α*-arylation of unactivated sulfones and sulfoxides with aryl bromides were obtained by using the monodentate, bulky, and electron-rich phosphine ligand (Figure 1.6 **L2**), which was introduced by Kwong and co-workers[94] (Scheme 1.41 **B** and **C**). In this case, LiO*t*Bu performed

better for the arylation and provided the monoarylation products with very good selectivity. Aryl chlorides also participated in the reaction when catalyzed by *in situ* formation of a Buchwald-type second-generation precatalyst (Scheme 1.41 **P1**)[95] in the presence of $H_2O$ as an additive.

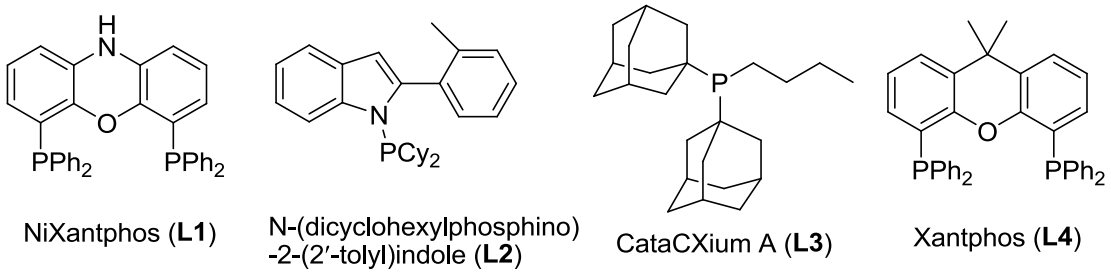
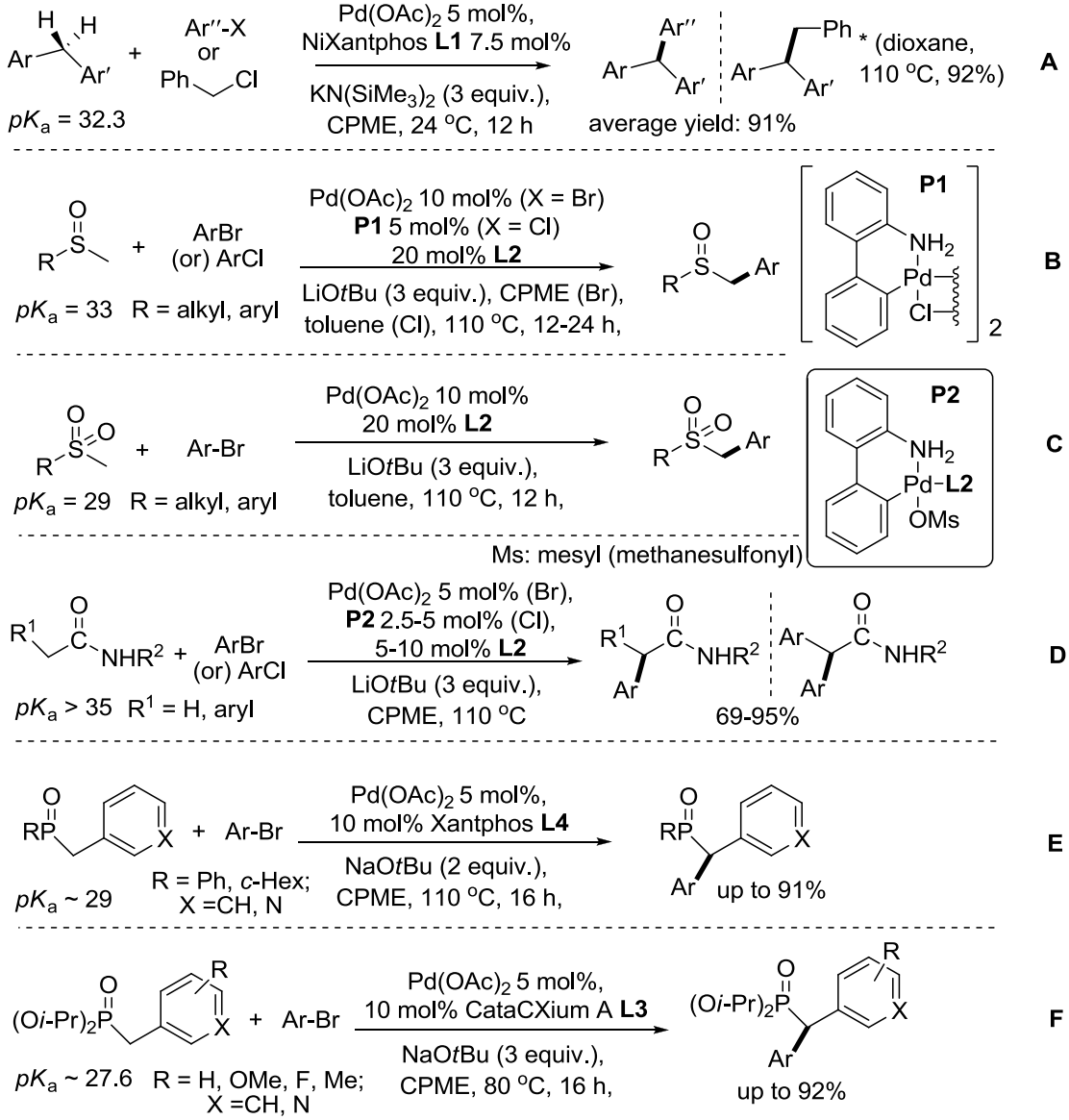



**Figure 1.6**. Ligands for $\alpha$-arylation in DCCP.

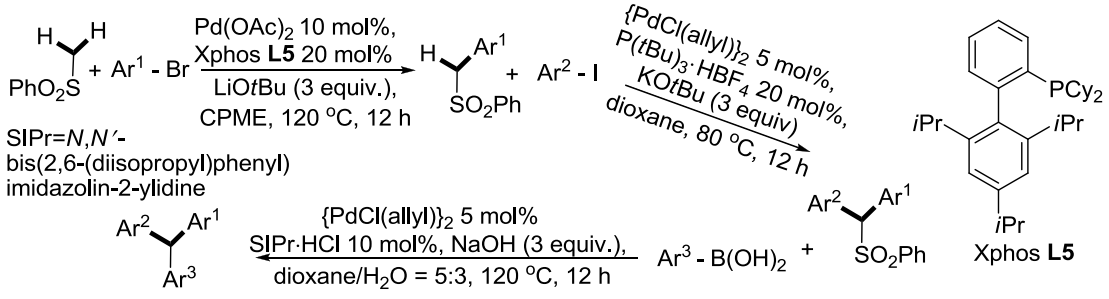



**Scheme 1.41**. Palladium-catalyzed α-arylation of unactive C($sp^3$)–H bonds (pKa's 28–35 in DMSO).

Continuously, Walsh and co-workers disclosed that the *α*-(mono or di)arylation of acetamides with aryl bromides could be performed under the same conditions with sulfoxides (Scheme 1.41 **C**), while, the third generation indole phosphines-based precatalyst (Scheme 1.41 **P2**) effectively catalyzed the direct *α*-arylation of acetamides with aryl chlorides (Scheme 1.41 **D**). The chemoselectivity between mono- and bis-arylated products was effectively controlled by base and solvent combinations.

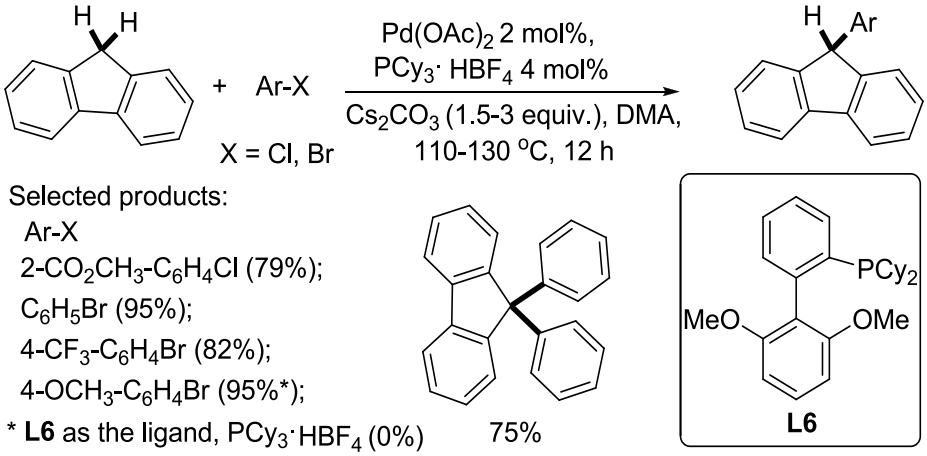
The *α*-arylation of benzylic phosphine oxides and phosphonates was also studied by replacing phosphine ligand **L2** with Xantphos **L4** and CataCXium A **L3** (Figure 1.6), respectively, accessing the desired products with NaO*t*Bu as the base in good selectivity. It was pointed out that this DCCP process involved direct C-H deprotonation of the substrate by base without the participation of palladium catalyst.

Base on the pioneering work of Walsh and co-workers about the arylation of sulfone.[93d] Crudden and co-workers developed a route for the formation of triarylmethane by palladium-catalyzed sequential arylation of methyl phenyl sulfone (Scheme 1.42).[96] The use of $Pd(OAc)_2$ and XPhos (Scheme 1.42) as the catalyst precursors resulted in exclusive mono-arylation, which is crucial for the introduction of three different aryl groups. The second arylation was carried out with various iodoarenes by palladium dimer $\{PdCl(allyl)\}_2$ (5 mol%) in addition of $P(tBu)_3 \cdot HBF_4$ (20 mol%) with KO*t*Bu (3 equiv) in dioxane at 80 °C for 12 h. The difficult desulfonylative arylation with the nucleophile partner arylboronic acid was successful with the use of the *N*-heterocyclic carbene SIPr·HCl salts and aqueous solutions of NaOH yielding the products. Aryl boronic acids with an electron-donating group, all reacted in high yields. The selectivity for the electron-poor substrates increased at higher temperature (150 °C).




**Scheme 1.42**. Synthesis of triarylmethanes through Pd-catalyzed sequential arylations.

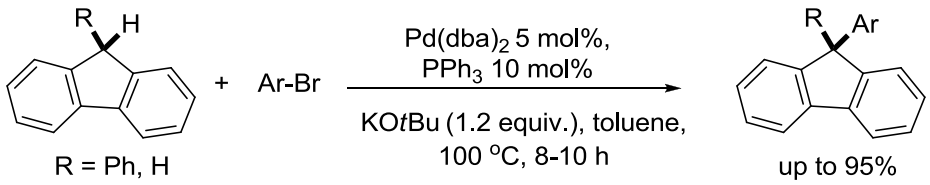
The mono- and multiarylations of methylene-bridged arenes to construct quaternary carbon center, was also established by Wu and co-workers. This protocol employed $Pd(OAc)_2$ in combination with phosphine ligands as the catalyst with $Cs_2CO_3$ as the base in DMA at 130 $^oC$ (Scheme 1.43).[97] They noted that the electronic properties of haloarenes strongly influence the reaction efficiency.




**Scheme 1.43**. The synthesis of 9-arylfluorene derivatives *via* Pd-catalyst.

The coupling products of electron-rich aryl halides were dramatically improved by using **L6** ligand instead of $PCy_3{\cdot}HBF_4$.

Later on, the conditions and the scope for access to arylfluorenes were further developed in Huang's group by using $Pd(dba)_2$ (5 mol%), $PPh_3$ (10 mol%), and stronger base KO*t*Bu in toluene at 100 $^oC$ for 8-10 h (Scheme 1.44).[98] Various functional groups (such as F, Cl, OMe) on aryl bromides could be well tolerated and quaternary carbon center was easily built, although, negligible amount of diarylfluorenes were observed when 2-bromotoluene (45%), 1-bromonaphthalene (58%), and heterocycles (39-65%) were employed as substrates under the standard conditions.




**Scheme 1.44**. Direct synthesis of unsymmetric diarylfluorenes *via* Pd-catalyst.

### 1.3.2 Palladium-catalyzed intramolecular ($sp^3$-$sp^2$) C-C formation

The mechanism of palladium(0)-catalyzed synthesis of fused four- or five-membered heterocycles by intramolecular C($sp^3$)-H arylations from aryl halides has been studied in detail both computationally and experimentally, and a common picture can be drawn from these data (Figure 1.7).[99] Oxidative addition of the aryl halide to a $Pd^0$ complex is followed by ligand exchange with carbonate or pivalate. Then C-H bond activation occurs *via* the now widely accepted base-induced, and CMD pathway to give a five- or six-membered palladacycle which, upon reductive elimination, furnishes the four- or five-membered ring product, respectively. This mechanism, which is analogous to the one already proposed for C($sp^2$)–H arylation reactions, probably applies to most Pd-catalyzed C($sp^3$)-H activation reactions involving a carbonate or carboxylate base. The regioselectivity of the above C($sp^3$)-H bond arylations (Figure 1.7) were also shown to occur preferentially at primary C–H bonds *vs.* secondary and tertiary positions.[97,98]

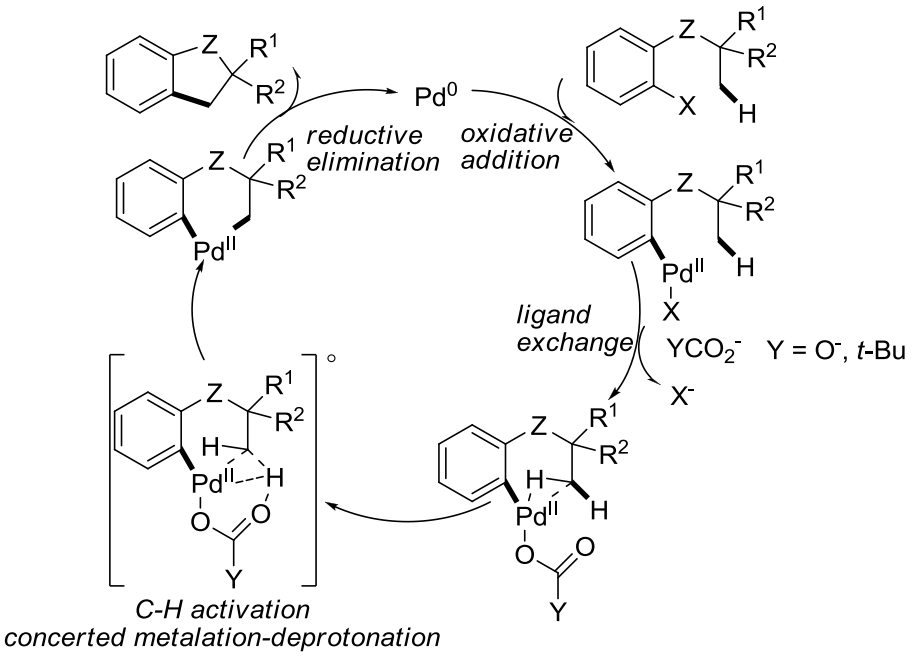
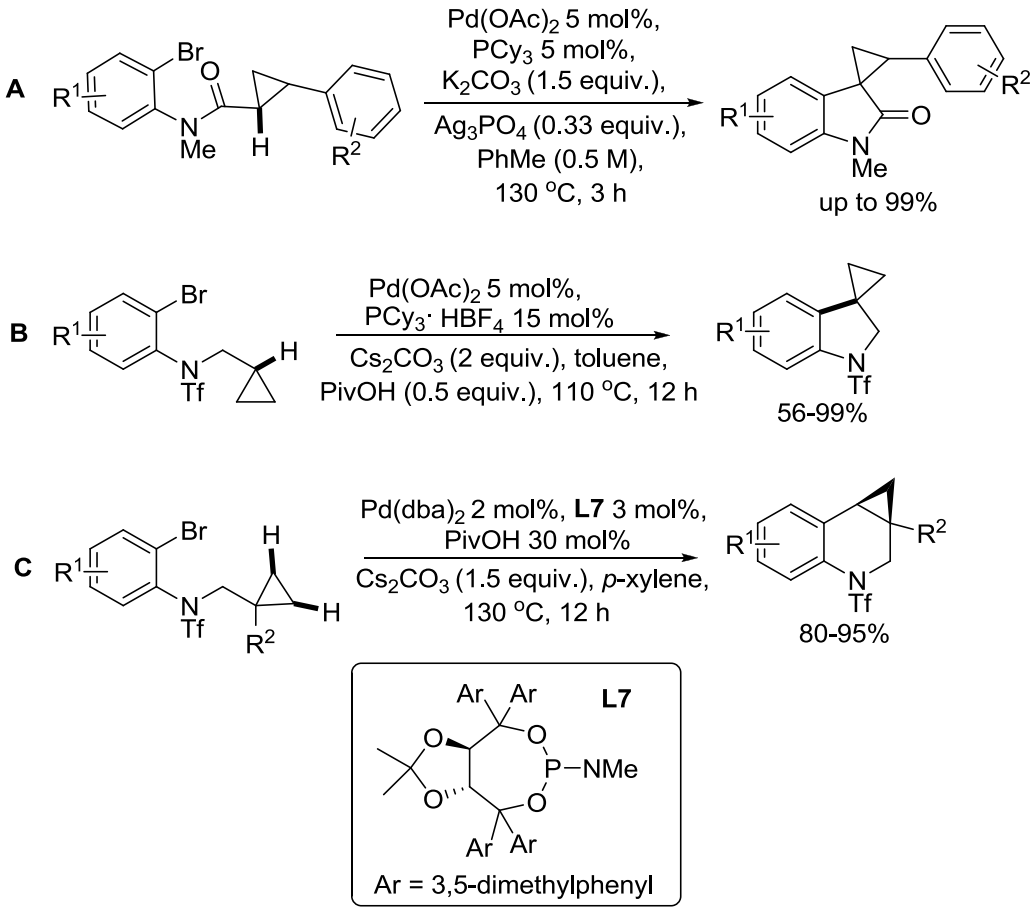



**Figure 1.7**. A common mechanism for Pd(0)-catalyzed intramolecular arylation of aryl halides for the synthesis of fused heterocycles.[99e]

The details about palladium-catalyzed intramolecular ($sp^3$-$sp^2$) C-C formation will be addressed in Chapter 5, and here, we would like to give some examples of palladium(0)-catalyzed C-H functionalization of methine C($sp^3$)-H bond. Charette and co-workers described the direct arylation of cyclopropanes *via* a Pd-catalyzed, Ag-mediated process (Scheme 1.45 **A**).[100] A range

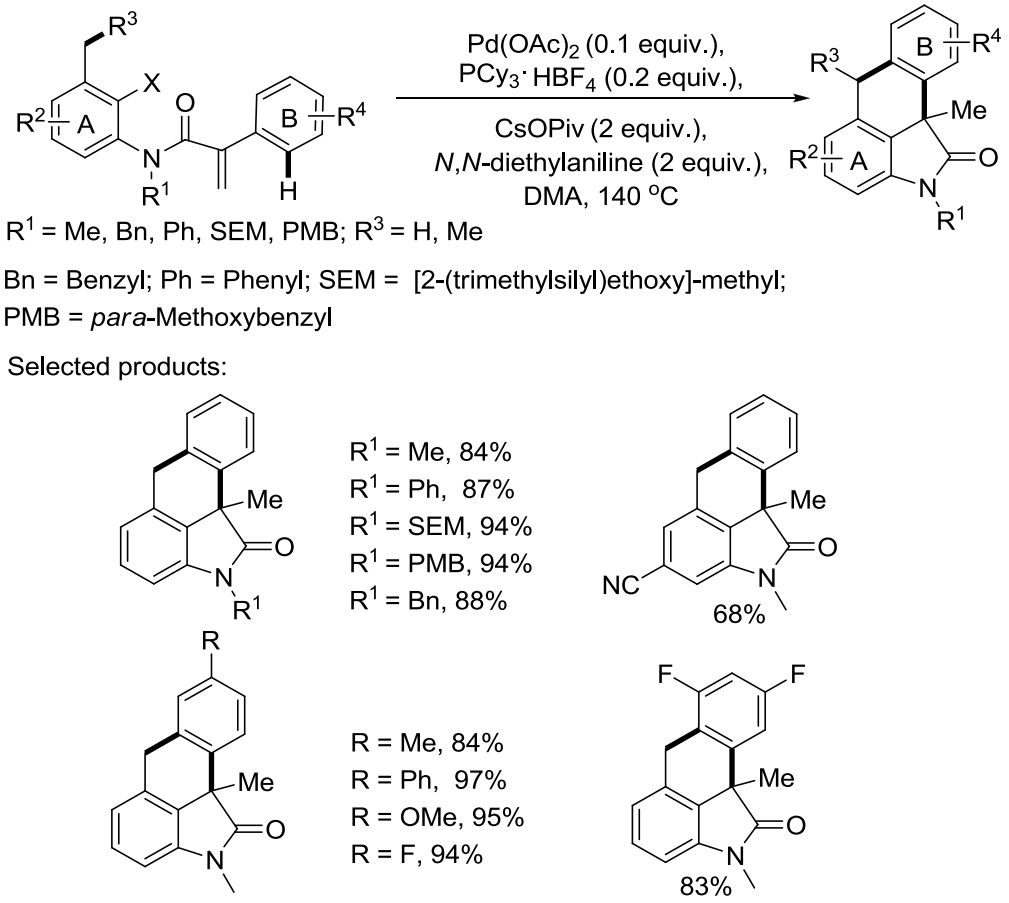
of functional groups on the aryl ring containing the halide or on the cyclopropane unit were tolerated with good to excellent yields (62-99%). The mechanism studies identified C-H cleavage as the rate-determining step.

Another procedure for palladium-catalyzed methine C-H bond arylation was carried out by Cramer group with PivOH in the absence of silver salts (Scheme 1.45 **B**).[101] Common electron-donating and -withdrawing groups are well tolerated in the *ortho*-, *meta*-, and *para*-position. Aryl chlorides can be employed as well, though slightly higher reaction temperatures were required. To extend the applications, Cramer and co-workers afterwards optimized the conditions for the intramolecular C($sp^3$)-H functionalizations of unbranched cyclopropylmethyl anilines.[102] Consequently, the terahydroquinoline scaffold was formed with excellent selectivities with the system of $Pd(dba)_2$ in conjunction with lignd **L7**, coordinated with PivOH and $Cs_2CO_3$ as the base in *p*-xylene. Notably, the cooperative effect between the chiral phosphine ligand and the carboxylate base is a great handle to tune the selectivity.




**Scheme 1.44**. Palladium-catalyzed intramolecular arylation of C($sp^3$)-H activation.

Later, Zhu and co-workers reported an effective route for [3,4]-fused oxindole formation catalyzed by $Pd(OAc)_2$ (0.1 equiv.) coordinated with the ligand $PCy_3 \cdot HBF_4$ (0.2 equiv.), and CsOPiv (2 equiv.) as the base in DMA at 140 °C *via* a domino process (Scheme 1.45).[103] The tertiary amine *N*,*N*-diethylaniline as the best additive was proven to be essential to ensure the occurrence of the domino process and double cyclization with good to excellent yields.




**Scheme 1.45**. Palladium-catalyzed [3,4]-fused oxindoles formation through $sp^2$ and $sp^3$ C-H bond activation *via* a domino process.

Mechanistically, the fused oxindoles were accessed *via* domino processes incorporating a C-H functionalization, and more specifically a C($sp^3$)-H activation step, which is shown in Figure 1.8. Oxidative addition of **1** to palladium(0) and subsequent intramolecular carbopalladation gives the $\sigma$-alkyl/Pd(II) intermediate **A**. This palladium species is ideally positioned to activate the neighboring aromatic C($sp^2$)-H bond, thus leading to the five-membered palladacycle **D** *via* a hypothetical CMD intermediate **C**. A formal proton transfer from **D** results in a 1,4-palladium shift from the alkyl to the aryl position. Thus generated Pd(II)/aryl species **E**, after C-C bond

rotation, is expected to activate the neighboring C4 methyl group to furnish the seven-membered palladacycle **F**, affording the tetracyclic oxindole **2** by reductive elimination with concurrent regeneration of the palladium(0) species.

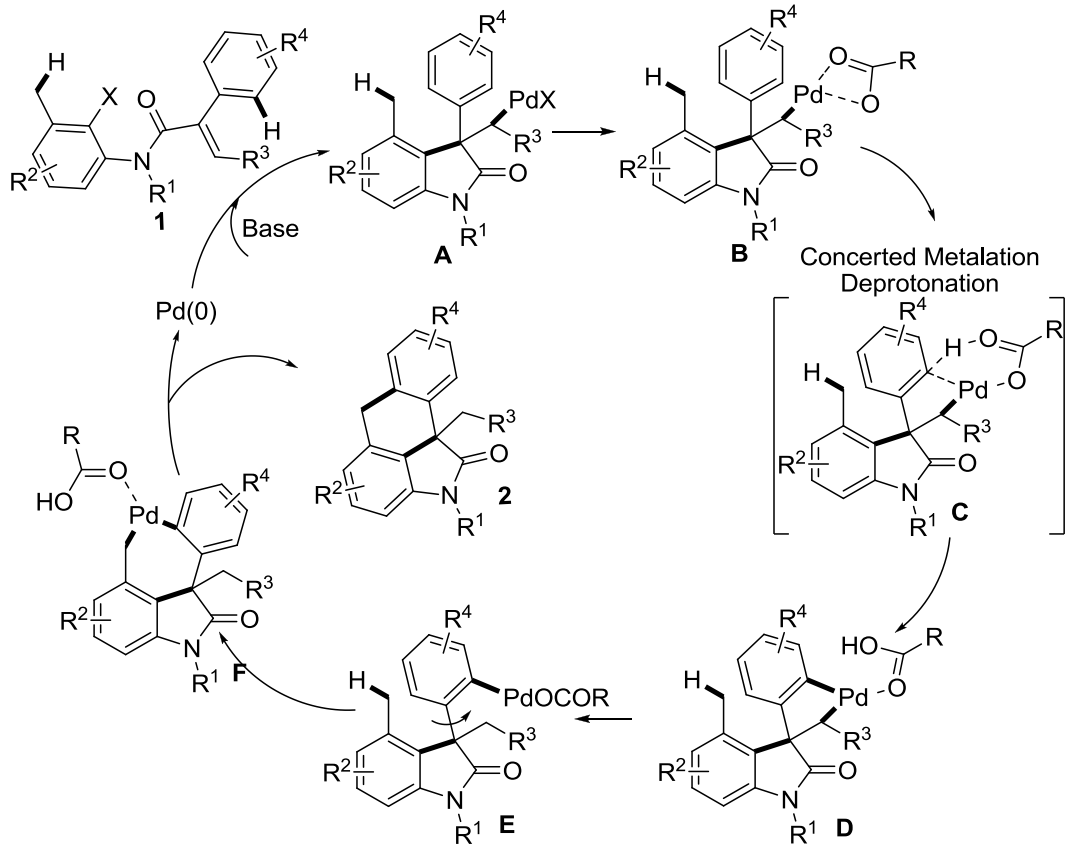



**Figure 1.8**. Synthesis of [3,4]-fused oxindoles by a domino carbopalladation/1,4-palladium migration/C($sp^3$)-H activation sequence.

## 1.4 Conclusion

The above recent successful reactions demonstrate a tremendous development in the field of palladium-catalyzed C-H bond activation for the C-C bond formation from 2012 to April 2014.

The direct *ortho*-arylation with (hetero)arylhalides of arenes containing directing groups has been developed using palladium catalysts *via* single and double C-H bond activation leading to the synthesis of biaryls. Some unactive C-H activation of fluorobenzenes and simple arenes were performed *via* classical CMD pathway. Only few seven-membered rings *via* a eight-membered ring intermediate with respect to previous six- or seven-membered cyclometallated intermediate were formed.

Palladium complex can be an efficient catalyst for the arylation of heterocycles with aryl halides, aryl boronic acids, aryl carbonates and also aryl sulfinates. The reactivity and regioselectivity can be controlled by the catalyst, ligand, base or solvent. The challenging double C-H bond activation *via* inter- or intra-molecular avoiding installation of additional functionalities and reducing organic waste has been greatly improved.

The palladium(0)/(II)-catalyzed $sp^3$ C-H bond functionalization has also made impressive progress. The inter- or intra-molecular $sp^3$ C-H arylation with arylhalides *via* DCCP or CMD pathway could successfully form $sp^3$ C- $sp^2$ C bonds. The $sp^3$ C-H activation will probably progress in the near future.

Despite the success recently obtained with palladium(0)/(II) or (II)/(IV) catalysts, there are still many challenges to overcome, such as the control of regioselectivity at other C-H sites than at the *ortho*-positions of functional groups, the exploration of new directing ligands, and the development of $sp^3$ C-H bond functionalization. This is one of the main reasons why it is necessary to make efforts to develop this C-H bond activation process and develop new applications. In this thesis, the focuses are on palladium catalyzed arylation of $sp^2$ and $sp^3$ C-H bond arylation with aryl halides.

## 1.5 Reference


1. *(a)* K. Tamao, K. Sumitani, M. Kumada, *J. Am. Chem. Soc.* **1972**, *94*, 4374; *(b)* R. J. P. Corriu, J. P. Masse, *J. Chem. Soc., Chem. Commun.* **1972**, 144.
2. A. O. King, N. Okukado, E.-i. Negishi, *J. Chem. Soc., Chem. Commun.* **1977**, 683.
3. D. Milstein, J. K. Stille, *J. Am. Chem. Soc.* **1978**, *100*, 3636.
4. N. Miyaura, K. Yamada, A. Suzuki, *Tetrahedron Lett.* **1979**, *20*, 3437.
5. K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.* **1975**, *16*, 4467.
6. http://www.nobelprize.org/nobel_prizes/chemistry/laureates/2010/
7. *(a)* G. Vasapollo, G. Mele, A. Maffei, R. D. Sole, *Appl. Organomet. Chem.* **2003**, *17*, 835; *(b)* J. Bayardon, J. Holz, B. Schäffner, V. Andrushko, S. Verevkin, A. Preetz, A. Börner, *Angew. Chem. Int. Ed.* **2007**, *46*, 5971; *(c)* A. M. Berman, J. C. Lewis, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2008**, *130*, 14926.
8. *(a)* V. Ritleng, C. Sirlin, M. Pfeffer, *Chem. Rev.* **2002**, *102*, 1731; *(b)* D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174; *(c)* D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624.
9. N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457.
10. U. Christmann, R. Vilar, *Angew. Chem. Int. Ed.* **2005**, *44*, 366.
11. G. P. McGlacken, L. M. Bateman, *Chem. Soc. Rev.* **2009**, *38*, 2447.
12. S. Rousseaux, B. Liégault, K. Fagnou, Modern Tools for the Synthesis of Complex Bioactive Molecules, *Wiley-VCH* , **2012**, 1.
13. L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315.
14. *(a)* K. M. Engle, J.-Q. Yu, Organic Chemistry-Breakthroughs and Perspectives, *chapter 8*, p 279; *(b)* Z. Shi, C. Zhang, C. Tang, N. Jiao, *Chem. Soc. Rev.* **2012**, *41*, 3381.
15. G. Yan, X. Wu, M. Yang, *Org. Biomol. Chem.* **2013**, *11*, 5558.
16. R. Rossi, F. Bellina, M. Lessi, C. Manzini, *Adv. Synth. Catal.* **2014**, *356*, 17.
17. Selected reviews about Pd: *(a)* R. Giri, B.-F. Shi, K. M. Engle, N. Maugel, J.-Q. Yu, *Chem. Soc. Rev.* **2009**, *38*, 3242; *(b)* X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2009**, *48*, 5094; *(c)* T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010,** *110*, 1147; *(d)* M. Wasa, K. M. Engle, J.-Q. Yu, *Isr. J. Chem.* **2010**, *50*, 605; *(e)* D. R. Stuart, K, Fagnou,

Topics in Organometallic Chemistry, p 91; *(f)* B.-J. Li, Z.-J. Shi, *Chem. Soc. Rev.* **2012**, *41*, 5588; *(g)* N. I. Nikishkin, J. Huskens, W. Verboom, *Org. Biomol. Chem.* **2013**, *11*, 3583; *(h)* R. Giri, S. Thapa, A. Kaflea, *Adv. Synth. Catal.* **2014**, *356*, 1395.

18. Selected reviews about Rh: *(a)* C. Wang, H. Chen, Z. Wang, J. Chen, Y. Huang, *Angew. Chem. Int. Ed.* **2012**, *51*, 7242; *(b)* Z. Qi, X. Li, *Angew. Chem. Int. Ed.* **2013**, *52*, 8995; *(c)* H. U. Vora, A. P. Silvestri, C. J. Engelin, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2014**, *53*, 2683.
19. Selected reviews about Ru: *(a)* Y. Kommagalla, K. Srinivas, C. V. Ramana, *Chem. Eur. J.* **2014**, *20*, 1. *(b)* S. D. Sarkar, W. Liu, S. I. Kozhushkov, L. Ackermann, *Adv. Synth. Catal.* **2014**, *356*, 1461.
20. Selected reviews about Copper: *(a)* Y. Tan, J. M. Muñoz-Molina, G. C. Fu, J. C. Peters, *Chem. Sci.* 2014, **5**, 2831; *(b)* Y. Shen, J. Chen, M. Liu, J. Ding, W. Gao, X. Huang, H. Wu, *Chem. Commun.* **2014**, *50*, 4292; *(c)* W. Qian, H. Wang, J. Allen, *Angew. Chem.* **2013**, 125, 11198; *(d)* G. Danoun, A. Tlili, F. Monnier, M. Taillefer, *Angew. Chem. Int. Ed.* **2012**, *51*, 12815.
21. Selected reviews about Iron: *(a)* M. Bordeaux, A. Galarneau, J. Drone, *Angew. Chem. Int. Ed.* **2012**, *51*, 10712. *(b)* D.-C. Samet Gülak, A. J. Wangelin, *Angew. Chem. Int. Ed.* **2012**, *51*, 1357.
22. Others: S. Tanaka, D. Tanaka, G. Tatsuta, K. Murakami, S. Tamba, A. Sugie, A. Mori, *Chem. Eur. J.* **2013**, *19*, 1658.
23. Selected examples: *(a)* L.-C. Campeau, D. R. Stuart, J.-P. Leclerc, M. Bertrand-Laperle, E. Villemure, H.-Y. Sun, S. Lasserre, N. Guimond, M. Lecavallier, K. Fagnou, *J. Am. Chem. Soc.* **2009**, *131*, 3291; *(b)* D. Lapointe, K. Fagnou, *Org. Lett.* **2009**, *11*, 4160; *(c)* H.-Y. Sun, S. I. Gorelsky, D. R. Stuart, L.-C. Campeau, K. Fagnou, *J. Org. Chem.* **2010**, *75*, 8180; *(d)* O. Renéé, K. Fagnou, *Org. Lett.* **2010**, *12*, 2116; *(e)* D. Lapointe, T. Markiewicz, C. J. Whipp, A. Toderian, K. Fagnou, *J. Org. Chem.* **2011**, *76*, 749; *(f)* S. Gorelsky, D. Lapointe, K. Fagnou, *J. Org. Chem.* **2012**, *77, 658.*
24. Selected examples: *(a)* M. Wasa, K. S. L. Chan, X. G. Zhang, J. He, M. Miura, J.-Q. Yu, *J. Am. Chem. Soc.* **2012**, *134, 18570*; *(b)* M. Ye, A. Edmunds, J. Morris, D. Sale, Y. Zhang, J.-Q. Yu, *Chem. Sci.* **2013**, *4, 2374; (c)* T. M. Figg, M. Wasa, J.-Q. Yu, D. G. Musaev, *J. Am. Chem. Soc.* **2013**, *135, 14206; (d)* J. He, S. Li, Y. Deng, H. Fu, B. N. Laforteza, J. E.

Spangler, A. Homs, J.-Q. Yu, *Science* **2014**, *343*, *1216*.

25. Selected examples: *(a)* L. Ackermann, S. Barfüßer, C. Kornhaaß, A. R. Kapdi, *Org. Lett.* **2011**, *13*, 3082; *(b)* L. Ackermann, V. P. Mehta, *Chem. Eur. J.* **2012**, *18*, 10230; *(c)* W. Ma, L. Ackermann, *Chem. Eur. J.* **2013**, *19*, 13925.
26. *(a)* S. Yanagisawa, T. Sudo, R. Noyori, K. Itami, *J. Am. Chem. Soc.* **2006**, *128*, 11748; *(b)* S. Chuprakov, N. Chernyak, A. S. Dudnik, V. Gevorgyan, *Org. Lett.* **2007**, *9*, 2333; *(c)* X. Zhao, C. S. Yeaung, V. M. Dong, *J. Am. Chem. Soc.* **2010**, *132*, 5837.
27. H. Zollinger, *Adv. Phys. Org. Chem.* **1964**, *2*, 162.
28. *(a)* E. J. Hennessy, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 12084; *(b)* A. J. Mota, A. Dedieu, C. Bour, J. Suffert, *J. Am. Chem. Soc.* **2005**, *127*, 7171; *(c)* D. L. Davies, S. A. Donald, S. A. Macgregor, *J. Am. Chem. Soc.* **2005**, *127*, 13754.
29. M. S. McClure, B. Glover, E. McSorley, A. Millar, M. H. Osterhout, F. Roschanger, *Org. Lett.* **2001**, *3*, 1677.
30. M. A. Campo, Q. Huang, T. Yao, Q. Tian, R. C. Larock, *J. Am. Chem. Soc.* **2003**, *125*, 11506.
31. *(a)* M. Lafrance, C. N. Rowley, T. K. Woo, K. Fagnou, *J. Am. Chem. Soc.* **2006**, *128*, 8754; *(b)* L.-C. Campeau, D. R. Stuart, J.-P. Leclerc, M. Bertrand-Laperle, E. Villemure, H.-Y. Sun, S. Lasserre, N. Guimond, M. Lecavallier, K. Fagnou, *J. Am. Chem. Soc.* **2009**, *131*, 3291; *(c)* B. Biswas, M. Sugimoto, S. Sakaki, *Organometallics* **2000**, *19*, 3895; *(d)* D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174.
32. S. Rousseaux, S. I. Gorelsky, B. K. W. Chung, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*,10692.
33. A. Lei, H. Zhang, in: C-H and C-X Bond Functionalization: Transition Metal Mediation, **2013**, chapter 9, p 310.
34. I. Hussaina, T. Singh, *Adv. Synth. Catal.* **2014**, 356, 1661.
35. T. Wesch, A. Berthelot-Bréhier, F. R. Leroux, F. Colobert, *Org. Lett.* **2013**, *15*, 2490.
36. Y. Cui, L. Fu, J. Cao, Y. Deng, J. Jiang, *Adv. Synth. Catal.* **2014**, *356*, 1217.
37. B. Roy, R. N. De, S. Hazra, *Monatsh Chem* **2012**, *143*, 119.
38. S. Cacchi, G. Fabrizi, A. Goggiamani, A. Iazzetti, *Org. Biomol. Chem.* **2012**, *10*, 9142.
39. C. B. Bheeter, J. K. Bera, H. Doucet, *Adv. Synth. Catal.* **2012**, *354*, 3553.

40. *(a)* B. S. Bhakuni, A. Kumar, S. J. Balkrishna, J. A. Sheikh, S. Konar, S. Kumar, *Org. Lett.* **2012**, *14*, 2838; *(b)* C. S. Nervig, P. J. Waller, D. Kalyani, *Org. Lett.* **2012**, *14*, 4838; *(c)* W.-Y. Wang, X. Feng, B.-L. Hu, C.-L. Deng, X.-G. Zhang, *J. Org. Chem.* **2013**, *78*, 6025; *(d)* M. Sickert, H. Weinstabl, B. Peters, X. Hou, M. Lautens, *Angew. Chem. Int. Ed.* **2014**, *53*, 5147.
41. T. Saget, N. Cramer, *Angew. Chem. Int. Ed.* **2013**, *52*, 7865.
42. R. Che, Z. Wu, Z. Li, H. Xiang, X. Zhou, *Chem. Eur. J.* **2014**, 20, 7258.
43. *(a)* M. Koley, N. Dastbaravardeh, M. Schnürch, M. D. Mihovilovic, *ChemCatChem* **2012**, *4*, 1345; *(b)* S. R. Neufeldt, M. S. Sanford, *Adv. Synth. Catal.* **2012**, *354*, 3517; (c) B. Liu, Y. Huang, J. Lan, F. Song, J. You, *Chem. Sci.* **2013**, *4*, 2136; *(d)* J.-H. Chu, C.-C. Wu, D.-H. Chang, Y.-M. Lee, M.-J. Wu, *Organometallics* **2013**, *32*, 272.
44. D.-D. Li, T.-T. Yuan, G.-W. Wang, *J. Org. Chem.* **2012**, *77*, 3341.
45. F. Yang, F. Song, W. Li, J. Lan J. You, *RSC Adv.* **2013**, *3*, 9649.
46. C. Wan, J. Zhao, M. Xu, J. Huang, *J. Org. Chem.* **2014**, *79*, 4751.
47. J. Shao, W. Chen, M. A. Giulianotti, R. A. Houghten, Y. Yu, *Org. Lett.* **2012**, *14*, 5452.
48. S. Shi, W. Liu, P. He, C. Kuang, *Org. Biomol. Chem.* **2014**, *12*, 3576.
49. Z. Liang, J. Yao, K. Wang, H. Li, Y. Zhang, *Chem. Eur. J.* **2013**, *19*, 16825.
50. R. Feng, J. Yao, Z. Liang, Z. Liu, Y. Zhang, *J. Org. Chem.* **2013**, *78*, 3688.
51. B. C. Chary, S. Kim, Y. Park, J. Kim, P. H. Lee, *Org. Lett.* **2013**, *15*, 2692.
52. *(a)* Z. Wu, S. Chen, C. Hu, Z. Li, H. Xiang, X. Zhou, *ChemCatChem* **2013**, *5*, 2839; *(b)* G. Shia, Y. Zhang, *Adv. Synth. Catal.* **2014**, *356*, 1419.
53. L. C. Misal. Castro, N. Chatani, *Chem. Eur. J.* **2014**, *20*, 4548.
54. L.-Y. Jiao, M. Oestreich, *Chem. Eur. J.* **2013**, *19*, 10845.
55. V. K. Tiwari, G. G. Pawar, R. Das, A. Adhikary, M. Kapur, *Org. Lett.* **2013**, *15*, 3310.
56. X. Ren, P. Wen, X. Shi, Y.Wang, J. Li, S. Yang, H. Yan, G. Huang, *Org. Lett.* **2013**, *15*, 5194.
57. *(a)* N. Kuhl, M. N. Hopkinson, J. Wencel-Delord, F. Glorius, *Angew. Chem. Int. Ed.* **2012**, *51*, 10236; *(b)* W. Liu, F. Tian, X. Wang, H. Yu, Y. Bi, *Chem. Commun.* **2013**, *49*, 2983.
58. *(a)* L. T. Ball, G. C. Lloyd-Jones, C. A. Russell, *Science* **2012**, *337*, 1644; *(b)* D. W. Robbins, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2013**, *52*, 933; *(c)* I. A. Sanhueza, A. M.

Wagner, M. S. Sanford, F. Schoenebeck, *Chem. Sci.* **2013**, *4*, 2767; *(d)* L. J. Durak, J. C. Lewis, *Organometallics* **2014**, *33*, 620.

59. S. R. Neufeldt, M. S. Sanford, *Acc. Chem. Res.* **2012**, *45*, 936.
60. *(a)* B. Liu, Z. Wang, N. Wu, M. Li, J. You, J. Lan, *Chem. Eur. J.* **2012**, *18*, 1599; *(b)* J. C. Bernhammer, H. V. Huynh, *Organometallics* **2012**, *31*, 5121. *(c)* F. Chen, Q.-Q. Min, X. Zhang, *J. Org. Chem.* **2012**, *77*, 2992; *(d)* D. S. Lee, P. Y. Choy, C. M. So, J. Wang, C. P. Laua, F. Y. Kwong, *RSC Adv.* **2012**, *2*, 9179; *(e)* S. Lentijo, G. Aullon, J. A. Miguel, P. Espinet, *Dalton Trans.* **2013**, *42*, 6353; *(f)* M. Wakioka, Y. Kitano, F. Ozawa, *Macromolecules* **2013**, *46*, 370; *(g)* H. Zhao, J. Shen, J. Guo, R. Ye, H. Zeng, *Chem. Commun.* **2013**, *49*, 2323.
61. X. Ma, Y. Liu, P. Liu, J. Xie, B. Dai, Z. Liu, *Appl. Organometal. Chem.* **2014**, *28*, 180.
62. T. Yan, L. Zhao, M. He, J.-F. Soulé, C. Bruneau, H. Doucet, *Adv. Synth. Catal.* **2014**, *356*, 1586.
63. H. Fan, Y. Shang, W. Su, *Eur. J. Org. Chem.* **2014**, 3323.
64. T. E. Storr, M. F. Greaney, *Org. Lett.* **2013**, *15*, 1410.
65. N. Yang, L. Dong, Z. Su, C. Hu, *RSC Adv.* **2013**, *3*, 20772.
66. M. C. Bryan, B. Dillon, L. G. Hamann, G. J. Hughes, M. E. Kopach, E. A. Peterson, M. Pourashraf, I. Raheem, P. Richardson, D. Richter, H. F. Sneddon, *J. Med. Chem.* **2013**, *56*, 6007.
67. *(a)* S. R. Neufeldt, M. S. Sanford, *Acc. Chem. Res.* **2012**, *45*, 936; *(b)* J. M. Schulman, A. A. Friedman, J. Panteleev, M. Lautens, *Chem. Commun.* **2012**, *48*, 55; *(c)* S. I. Gorelsky, *Organometallics*, **2012**, *31*, 794; *(d)* D. Roy, S. Mom, S. Royer, D. Lucas, J.-C. Hierso, H. Doucet, *ACS Catal.* **2012**, *2*, 1033; *(e)* L. G. Mercier, M. Leclerc, *Acc. Chem. Res.* **2013**, *46*, 1597; *(f)* L. Wang, B. Verbelen, C. Tonnelé, D. Beljonne, R. Lazzaroni, V. Leen, W. Dehaena, N. Boens, *Photochem. Photobiol. Sci.* **2013**, *12*, 835; *(g)* S. Chen, Y. Liao, F. Zhao, H. Qi, S. Liu, G.-J. Deng, *Org. Lett.* **2014**, *16*, 1618; *(h)* L. Zhang, P. Li, C. Liu, J. Yang, M. Wang, L. Wang, *Catal. Sci. Technol.* **2014**, *4*, 1979.
68. B. Liu, Z. Wang, N. Wu, M. Li, J. You, J. Lan, *Chem. Eur. J.* **2012**, *18*, 1599.
69. H. Fu, L. Chen, H. Doucet, *J. Org. Chem.* **2012**, *77*, 4473.
70. H. Cao, Y. Lin, H. Zhan, Z. Du, X. Lin, Q.-M. Liang, H. Zhang, *RSC Adv.* **2012**, *2*, 5972.

71. B. M. Johnson, M. P. Huestis, *Eur. J. Org. Chem.* **2014**, 1589.

72. D.-T. D. Tang, K. D. Collins, F. Glorius, *J. Am. Chem. Soc.* **2013**, *135*, 7450.

73. $Pd(OAc)_2$ as the catalyst: *(a)* C. B. Bheeter, J. K. Berab, H. Doucet, *RSC Adv.* **2012**, *2*, 7197; *(b)* C. B. Bheeter, R. Jin, J. K. Berab, H. Doucet, *RSC Adv.* **2013**, *3*, 5987; *(c)* L. Chen, C. Bruneau, P. H. Dixneuf, H. Doucet, *ChemCatChem* **2013**, *5*, 1956; *(d)* I. Smari, C. Youssef, K. Yuan, A. Beladhria, H. B. Ammar, B. B. Hassine, H. Doucet, *Eur. J. Org. Chem.* **2014**, 1778; $PdCl(C_3H_5)$(dppb) as the catalyst: *(e)* L. Chen, C. Bruneau, P. H. Dixneuf, H. Doucet, *Green Chem.* **2012**, *14*, 1111; *(f)* Y. Xu, L. Zhao, Y. Li, H. Doucet, *Adv. Synth. Catal.* **2013**, *355*, 1423; *(g)* J. Laroche, K. Beydoun, V. Guerchais, H. Doucet, *Catal. Sci. Technol.* **2013**, *3*, 2072.

74. X.-W. Liu, J.-L. Shi, J.-X. Yan, J.-B. Wei, K. Peng, L. Dai,C.-G. Li, B.-Q. Wang, Z.-J. Shi, *Org. Lett.* **2013**, *15*, 5774.

75. A. Mahindra, N. Bagra, R. Jain, *J. Org. Chem.* **2013**, *78*, 10954.

76. *(a)* K. Yamaguchi, H. Kondo, J. Yamaguchi, K. Itami, *Chem. Sci.* **2013**, *4*, 3753; *(b)* S. Tani, T. N. Uehara, J. Yamaguchi, K. Itami, *Chem. Sci.* **2014**, *5*, 123.

77. T. Yan, L. Chen, C. Bruneau, P. H. Dixneuf, H. Doucet, *J. Org. Chem.* **2012**, *77*, 7659.

78. A. F. P. Biajoli, E. T. da P, C. R. D. Correia, *RSC Adv.* **2012**, *2*, 11930.

79. C. Li, P. Li, J. Yang, L. Wang, *Chem. Commun.* **2012**, *48*, 4214.

80. *(a)* T. Miao, P. Li, G.-W. Wang, L. Wang, *Chem. Asian J.* **2013**, *8*, 3185; *(b)* M. Wu, J. Luo, F. Xiao, S. Zhang, G.-J. Deng, H.-A. Luo, *Adv. Synth. Catal.* **2012**, *354*, 335; *(c)* X. Yu, X. Li, B. Wan, *Org. Biomol. Chem.* **2012**, *10*, 7479; *(d)* K. Yuan, H. Doucet, *Chem. Sci.* **2014**, *5*, 392; *(e)* L. Loukotova, K. Yuan, H. Doucet, *ChemCatChem* **2014**, *6*, 1303.

81. C.-Yu Chen, C.-H. Yang, W.-P. Hu, J. K. Vandavasi, M. I. Chung, J.-J. Wang, *RSC Adv.* **2013**, *3*, 2710.

82. F. Churruca, S. Hernández, M. Perea, R. SanMartin, E. Domínguez, *Chem. Commun.* **2013**, *49*, 1413.

83. E. Coya, N. Sotomayor, E. Lete, *Adv. Synth. Catal.* **2014**, 356, 1853.

84. J. Dong, Y. Huang, X. Qin, Y. Cheng, J. Hao, D. Wan, W. Li, X. Liu, J. You, *Chem. Eur. J.* **2012**, *18*, 6158.

85. B. Liu, Y. Huang, J. Lan, F. Song, J. You, *Chem. Sci.* **2013**, *4*, 2163.

86. X. Chen, X. Huang, Q. He, Y. Xie, C. Yang, *Chem. Commun.* **2014**, *50*, 3996.

87. Z. Li, L. Ma, J. Xu, L. Kong, X. Wu, H. Yao, *Chem. Commun.* **2012**, *48*, 3763.

88. G. Wu, J. Zhou, M. Zhang, P. Hu, W. Su, *Chem. Commun.* **2012**, *48*, 8964.

89. G. Meng, H.-Y. Niu, G.-R. Qu, J. S. Fossey, J.-P. Li, H.-M. Guo, *Chem. Commun.* **2012**, *48*, 9601.

90. N. Hoshiya, T. Kobayashi, M. Arisawa, S. Shuto, *Org. Lett.* **2013**, *15*, 6202.

91. N. Rodr ́guez, J. A. Romero-Revilla, M. Á. Fern ández-Ib áñez, J. C. Carretero, *Chem. Sci.* **2013**, *4*, 175.

92. O. Baudoin, *Chem. Soc. Rev.* **2011**, *40*, 4902.

93. *(a)* J. Zhang, A. Bellomo, A. D. Creamer, S. D. Dreher, P. J. Walsh, *J. Am. Chem. Soc.* **2012**, *134*, 13765; *(b)* A. Bellomo, J. Zhang, N. Trongsiriwat, P. J. Walsh, *Chem. Sci.* **2013**, *4*, 849; *(c)* T. Jia, A. Bellomo, K. EL Baina, S. D. Dreher, P. J. Walsh, *J. Am. Chem. Soc.* **2013**, *135*, 3740; *(d)* B. Zheng, T. Jia, P. J. Walsh, *Org. Lett.* **2013**, *15*, 1690; *(e)* B. Zheng, T. Jia, P. J. Walsh, *Org. Lett.* **2013**, *15*, 4190; *(f)* S. Montel, T. Jia, P. J. Walsh, *Org. Lett.* **2014**, *16*, 130; *(g)* B. Zheng, T. Jia, P. J. Walsh, *Adv. Synth. Catal.* **2014**, *356*, 165; *(h)* S. Montel, L. Raffier, Y. He, P. J. Walsh, *Org. Lett.* **2014**, *16*, 1446.

94. C. M. So, C. P. Lau, F. Y. Kwong, *Org. Lett.* **2007**, *9*, 2795.

95. N. C. Bruno, M. T. Tudge, S. L. Buchwald, *Chem. Sci.* **2013**, *4*, 916.

96. M. Nambo, C. M. Crudden, *Angew. Chem. Int. Ed.* **2014**, *53*, 742.

97. J.-J. Chen, S. Onogi, Y.-C. Hsieh, C.-C. Hsiao, S. Higashibayashi, H. Sakurai, Y.-T. Wu, *Adv. Synth. Catal.* **2012**, *354*, 1551.

98. X. Cao, W. Yang, C. Liu, F. Wei, K. Wu, W. Sun, J. Song, L. Xie, W. Huang, *Org. Lett.* **2013**, *15*, 3102.

99. *(a)* M. Lafrance, S. I. Gorelsky, K. Fagnou, *J. Am Chem. Soc.* **2007**, *129*, 14570; *(b)* S. Rousseaux, S. I. Gorelsky, B. K. W. Chung, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 10692; *(c)* S. Rousseaux, M. Davi, J. Sofack-Kreutzer, C. Pierre, C. E. Kefalidis, E. Clot, K. Fagnou, O. Baudoin, *J. Am. Chem. Soc.* **2010**, *132*, 10706; *(d)* C. E. Kefalidis, O. Baudoin, E. Clot, *Dalton Trans.* **2010**, 10528.

100. C. L. Ladd, D. S. Roman, A. B. Charette, *Org. Lett.* **2013**, *15*, 1350.

101. T. Saget, D. Perez, N. Cramer, *Org. Lett.* **2013**, *15*, 1354.

102. T. Saget, N. Cramer, *Angew. Chem. Int. Ed.* **2012**, *51*, 12842.

103. T. Piou, A. Bunescu, Q. Wang, L. Neuville, J. Zhu, *Angew. Chem. Int. Ed.* **2013**, *52*, 12385.

# *Chapter 2: Phosphine-free palladium-catalyzed direct C2-arylation of benzothiophenes with aryl bromides*

# Chapter 2: Phosphine-free palladium-catalyzed direct C2-arylation of benzothiophenes with aryl bromides

## 2.1 Introduction

Benzothiophene derivatives are of considerable interest for pharmaceutical chemistry due to their biological activities. For example, the 2-arylbenzothiophene derivative Raloxifene is used in the prevention of osteoporosis (Figure 2.1). Therefore, the development of simple and convenient processes using readily accessible benzothiophene derivatives for the synthesis of arylated benzothiophenes is highly desirable.

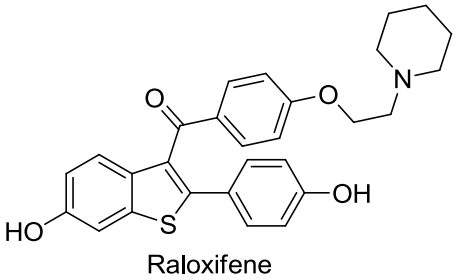
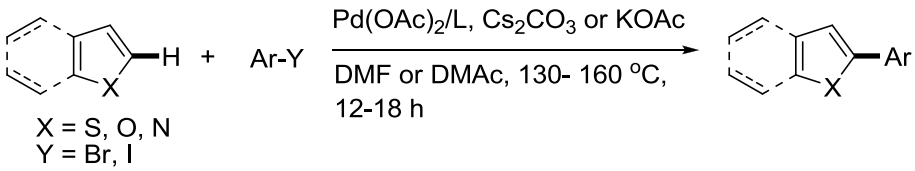



**Figure 2.1**. Example of bioactive 2-arylbenzothiophene.

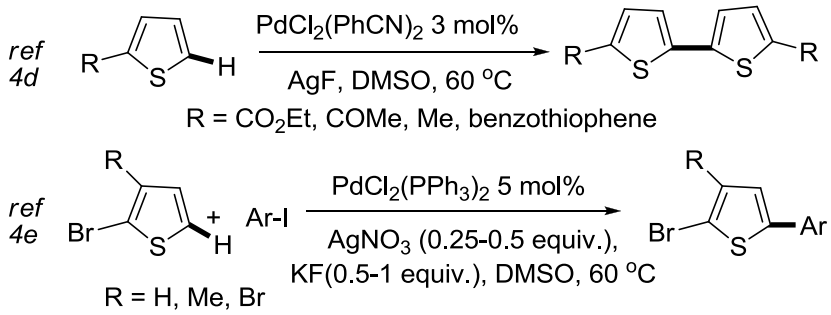
As explained in the chapter 1, the palladium-catalyzed direct arylation of several heteroaromatics such as furans, thiophenes or pyrroles *via* a C–H bond activation using aryl halides has led to success in recent years.[1-4](Scheme 2.1)



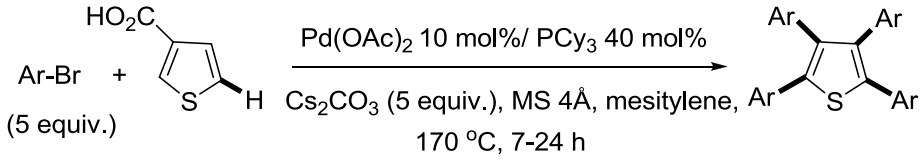

**Scheme 2.1**. Palladium-catalyzed direct arylation of heteroaromatics.

In Mori group, well-defined bithiophene units, were formed *via* palladium-catalyzed C-H activation in the presence of silver salts under mild conditions (Scheme 2.2).[4d,4e] Concerning polyarylation *via* such reactions, Miura demonstrated that 3-thiophenecarboxylic acids could undergo perarylation accompanied by cleavage of the three C-H bonds and decarboxylation, with

excess of aryl bromides, through palladium catalysts, to give the corresponding tetraarylated products in good yields (Scheme 2.3).[4g]

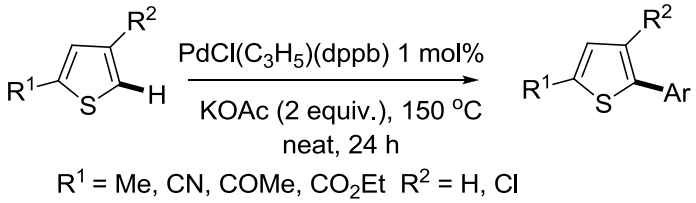



**Scheme 2.2.** Palladium-catalyzed arylation of thiophene substrates in the presence of silver salts.



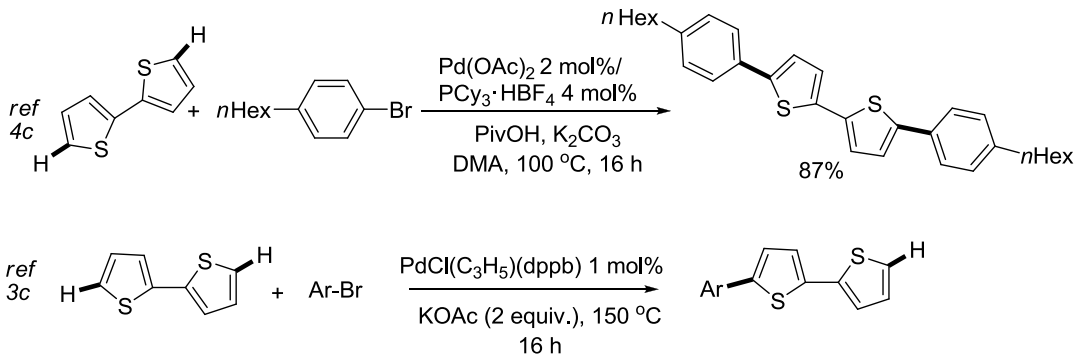

**Scheme 2.3.** Palladium-catalyzed tetraarylation of 3-thiophenecarboxylic acids.

Similarly, Doucet and co-workers used $PdCl(C_3H_5)(dppb)$ (1 mol%) catalyst with potassium acetate (2 equiv.), to obtain the 5-arylated thiophenes in high regioselectivity using a variety of aryl bromides (Scheme 2.4).[3f]




**Scheme 2.4.** Palladium-catalyzed 5-arylation of thiophenes under slovent-free conditions.

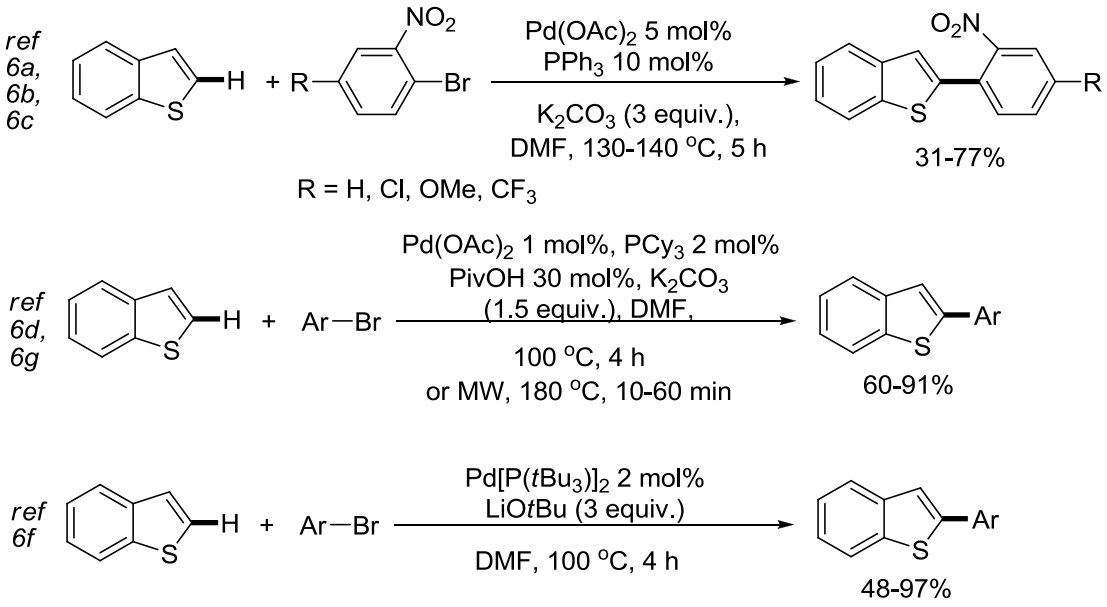
Useful thiophene-based organic electronic meterials were also assembled *via* direct C-H bond activation in Fagnou and Doucet group. They employed palladium acetate (2 mol%) with $PCy_3 \cdot HBF_4$ (4 mol%) and $PdCl(C_3H_5)(dppb)$ (1 mol%), respectively, for access to 5,5′-diarylated and 5-monoarylated 2,2′-bithiophenyl derivatives in good yields (Scheme 2.5).[3c,4c]



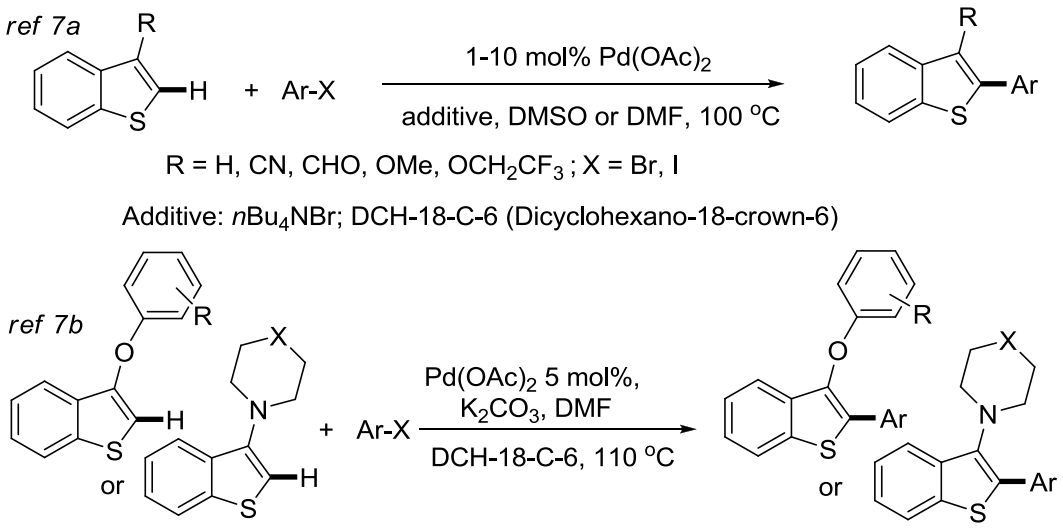

**Scheme 2.5.** Palladium-catalyzed mono- or di- arylations of bithiophene.

Such couplings are very attractive compared to classical palladium-catalyzed reactions such as Stille, Suzuki or Negishi couplings[5] as they do not require the preliminary synthesis of organometallic derivatives.

If the direct arylation of thiophene derivatives has been extensively discribed, on the other hand, only a few examples of such direct arylations using benzothiophenes have been reported.[6,7] Moreover, the reported procedures either require 1-10 mol% palladium catalyst associated to 1-20 mol% of phosphine ligands (Scheme 2.6)[6] or employed a stoichiometric amount of quaternary ammonium salts or crown ethers as stabilizing agents producing important amount of wastes (Scheme 2.7) .[7]



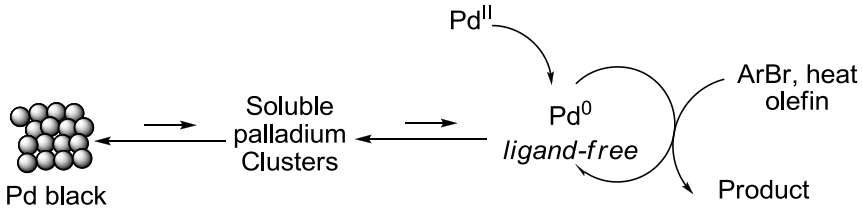

**Scheme 2.6**. Palladium-catalyzed C2-arylation of benzothiophenes.




**Scheme 2.7**. Phosphine-free palladium-catalyzed C2-arylation of benzothiophenes.

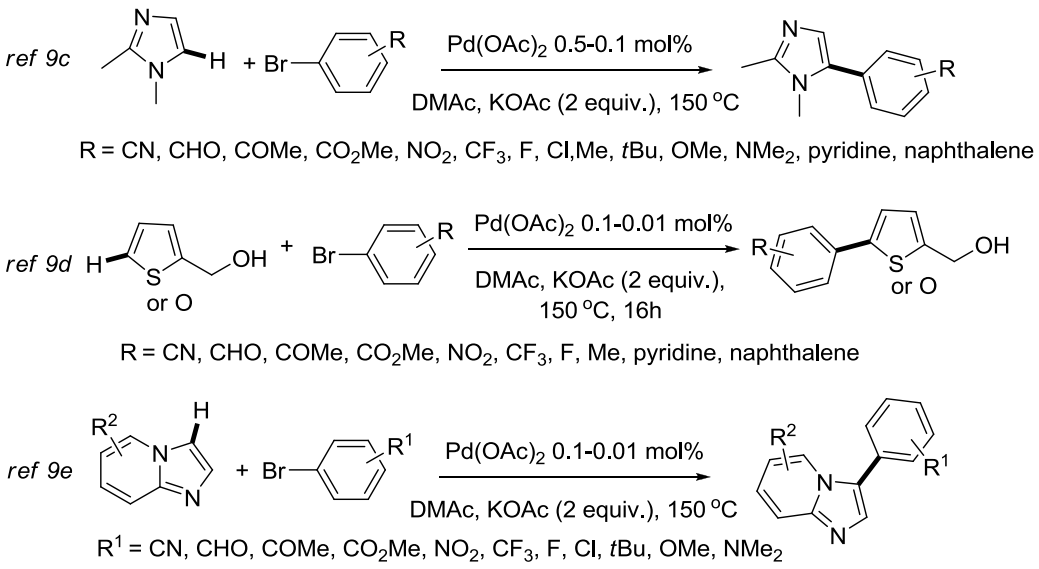
To our knowledge, the palladium-catalyzed direct arylation of benzothiophenes using ligand-free catalyst without stabilizing agent has not been reported to date. The use of such conditions would be very attractive for industrial application, as it would reduce both the cost and wastes formation of such couplings.

In 2003, de Vries and co-workers described extremely exciting results for the Heck and Suzuki reactions using a low loading (0.1-0.01 mol%) of ligand-free catalyst $Pd(OAc)_2$ (Scheme 2.8).[8] They have demonstrated that, at elevated temperature, when $Pd(OAc)_2$ is employed as the catalyst precursor, soluble palladium(0) colloids or nanoparticles are formed, and then the Heck or Suzuki reaction takes place.




**Scheme 2.8**. Ligand-free $Pd(OAc)_2$ catalyzed Heck and Suzuki reactions at low loading.

Our laboratory has recently reported that the use of the "de Vries conditions" allows the coupling or several heteroaromatics such as pyrroles,[9b] imidazoles,[9c] furans,[9d] thiophenes[9d] or imidazopyridines[9e] using a very low loading (0.1-0.01 mol%) of ligand-free $Pd(OAc)_2$ catalyst (Scheme 2.9).[9]




**Scheme 2.9**. Ligand-free $Pd(OAc)_2$ catalyzed the coupling of heteroaromatics at low loading.

However, so far, such procedure has not been employed for the direct arylation of benzothiophenes.[10]

In this chapter, we will describe the coupling of benzothiophene derivatives with a variety of electronically and sterically diverse aryl and heteroaryl bromides using low loadings of ligand-free $Pd(OAc)_2$ catalyst.

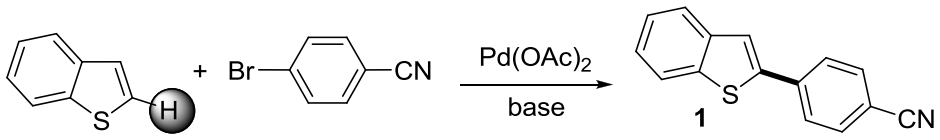
## 2.2 Results and discussions

### 2.2.1 Palladium catalyzed direct C2-arylation of benzothiophenes

#### 2.2.1.1 Optimization for palladium-catalyzed direct C2-arylation of benzothiophene

First, we examined the influence of the reaction conditions for the coupling of benzothiophene with 4-bromobenzonitrile (Scheme 2.10, Table 2.1). Starting form a slight excess of benzothiophene (1.5 equiv.) with respect to the aryl bromide, in the presence of 0.5 mol% $Pd(OAc)_2$ as the catalyst, KOAc as the base, and DMAc as the solvent at 150 $^{o}$C, the desired product **1** was obtained in 69% yield, whereas, a lower catalyst loading of 0.1 mol% gave **1** in only 55% yield due to a partical conversion of the aryl bromide (Table 2.1, entries 1 and 2). The influence of a few other bases was also examined; however, NaOAc, CsOAc, KF or carbonates led to lower yields of **1** (Table 2.1, entries 3-8). Then, we explored the influence of a few other

solvents. Moderated yields were obtained in diethyl carbonate or cyclopentyl methyl ether (Table 2.1, entries 11 and 12). On the other hand, the use of only 0.1 mol% $Pd(OAc)_2$ in DMF gave **1** in 59% yield (Table 2.1, entry 9).




**Scheme 2.10**. Palladium-catalyzed direct C2-arylation of benzothiophene with 4-bromobenzonitrile.

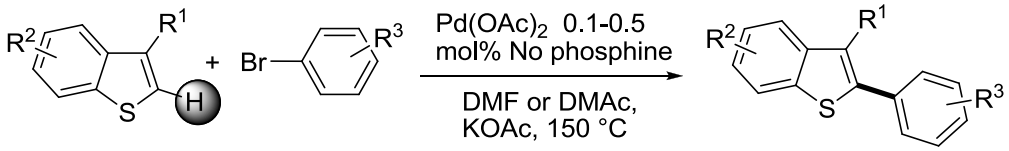
**Table 2.1**. Influence of the reaction conditions for palladium-catalyzed direct C2-arylation of benzothiophene with 4-bromobenzonitrile.

| Entry | $Pd(OAc)_2$ (mol%) | Solvent | Base | Conv. (%) | Yield in **1** (%) |
|---|---|---|---|---|---|
| 1 | 0.5 | DMAc | KOAc | 100 | 69 |
| 2 | 0.1 | DMAc | KOAc | 67 | 55 |
| 3 | 0.1 | DMAc | CsOAc | 12 | - |
| 4 | 0.1 | DMAc | NaOAc | 43 | 37 |
| 5 | 0.1 | DMAc | $Na_2CO_3$ | 25 | 18 |
| 6 | 0.1 | DMAc | $K_2CO_3$ | 7 | 6 |
| 7 | 0.1 | DMAc | $Cs_2CO_3$ | 90 | 0[a] |
| 8 | 0.1 | DMAc | KF | 36 | 30 |
| 9 | 0.1 | DMF | KOAc | 80 | 59[b] |
| 10 | 0.5 | NMP | KOAc | 70 | 55[b] |
| 11 | 0.5 | DEC | KOAc | 54 | 48[b] |
| 12 | 0.5 | CPME | KOAc | 51 | 42[b] |

| | | | | | |
|---|---|---|---|---|---|
| 13 | 0.5 | pentan-1-ol | KOAc | 10 | -[b] |

Conditions: $Pd(OAc)_2$, 4-bromobenzonitrile (1 mmol), benzothiophene (1.5 mmol), base (2 mmol), 150 °C, 16 h, under argon, conversion of 4-bromobenzonitrile. [a] Formation of 4-bromobenzamide. [b] Catalyst is a solution prepared with 1 mg of $Pd(OAc)_2$ in 1 mL of DMAc. DEC: diethyl carbonate; CPME: cyclopentyl methyl ether.

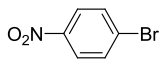
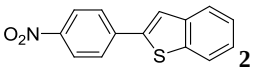
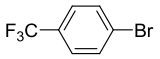
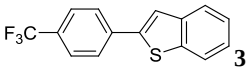
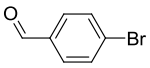
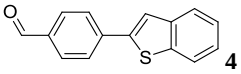
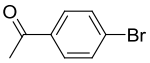
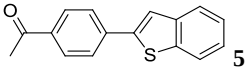
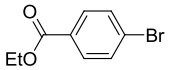
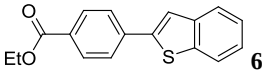
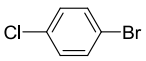
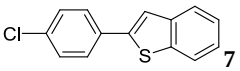
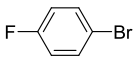
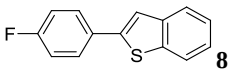
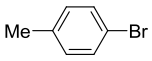
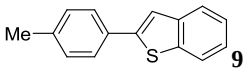
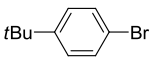
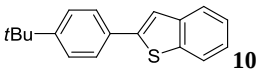
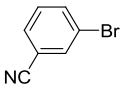
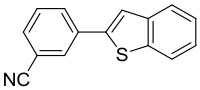
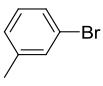
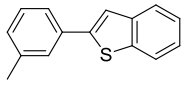
### 2.2.1.2 Scope for palladium-catalyzed 2-arylation of benzothiophene

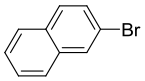
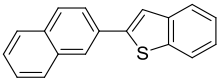
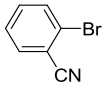
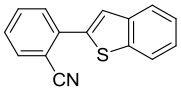
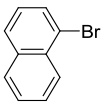
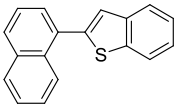
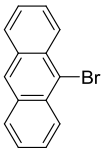
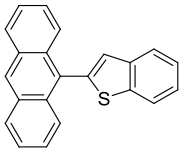
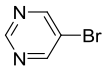
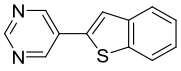



**Scheme 2.11**. Palladium-catalyzed direct arylation of benzothiophene derivatives with (hetero)aryl bromides.

We then studied the scope of 2-arylation of benzothiophene using 0.1 or 0.5 mol% $Pd(OAc)_2$ catalyst, KOAc as the base and either DMF or DMAc as the solvent (Scheme 2.11, Table 2.2). A good yield in **4** was obtained from 4-bromobenzaldehyde using only 0.1 mol% $Pd(OAc)_2$ (Table 2.2, entry 4). However, in most cases, higher loading of $Pd(OAc)_2$ 0.5 mol% had to be employed to observe high conversions of the aryl bromides and good yields of coupling products. For example, with this catalyst loading, 4-trifluoromethylbromobenzene, 4-bromoacetophenone, ethyl 4-bromobenzoate, 4-chlorobromobenzene or 4-fluorobromobenzene gave the expected C2-arylated benzothiophenes **3**, **5-8** in 61-80% yields (Table 2.2, entries 3, 5-12). With these reactants, very similar yields were obtained using DMF or DMAc as the solvent. It should be noted that no cleavage of the C-Cl bond of 4-chlorobromobenzene was observed under these reaction conditions allowing further transformations. In the presence of the electron-rich aryl bromides, 4-bromotoluene and 4-*tert*-butylbromobenzene, moderate yields in **9** and **10** were obtained, due to partial conversion of these aryl bromides (Table 2.2, entries 13 and 14).

**Table 2.2**. Palladium-catalyzed arylation of benzothiophene with (hetero)aryl bromides.

| Entry | Aryl halide | Product | Catalyst loading (mol%) | Yield (%) |
|---|---|---|---|---|
| 1 |  |  **2** | 0.1 | 51 |
| 2 |  |  **3** | 0.1 | 22 |
| 3 | | | 0.5 | 61 |
| 4 |  |  **4** | 0.1 | 72 |
| 5 |  |  **5** | 0.5 | 66 |
| 6 | | | 0.5 | 63[a] |
| 7 |  |  **6** | 0.5 | 76 |
| 8 | | | 0.5 | 77[a] |
| 9 |  |  **7** | 0.5 | 73 |
| 10 | | | 0.5 | 71[a] |
| 11 |  |  **8** | 0.5 | 80 |
| 12 | | | 0.5 | 73[a] |
| 13 |  |  **9** | 0.5 | 55 |
| 14 |  |  **10** | 0.5 | 32 |
| 15 |  |  **11** | 0.1 | 60 |
| 16 |  |  **12** | 0.5 | 60 |

| | | | | |
|---|---|---|---|---|
| 17 |  |  **13** | 0.1 | 62 |
| 18 |  |  **14** | 0.1 | 73 |
| 19 |  |  **15** | 0.5 | 82[a] |
| 20 |  |  **16** | 0.5 | trace |
| 21 | | | 0.5 | 83[a] |
| 22 |  |  **17** | 0.1 | 66 |

Conditions: Catalyst is a solution prepared with 1 mg of $Pd(OAc)_2$ in 1 mL of DMAc (0.001 or 0.005 equiv.), benzothiophene (1.5 equiv.), aryl bromide (1 equiv.), KOAc (2 equiv.), DMF, 150 ℃, 16 h, isolated yields.

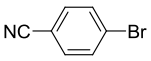
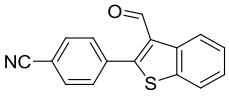
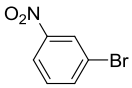
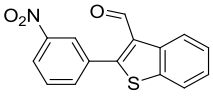
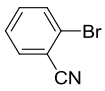
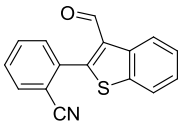
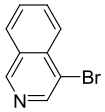
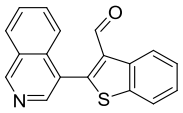
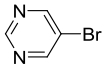
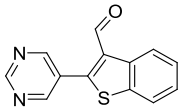
[a] Solvent: DMAc.

With such substrates, the use of palladium associated to phosphine ligands should be preferred. A few *meta*- and *ortho*-substituted aryl bromides were also employed. 2- and 3-bromobenzonitriles gave **11** and **14** in 60% and 73% yields, respectively in the presence of 0.1 mol% $Pd(OAc)_2$ (Table 2.2, entries 15 and 18). Both 1- and 2-bromonaphthalene gave the expected products **15** and **13** (Table 2.2, entries 17 and 19). However, from 1-bromonaphthalene, a higher yield in **15** was obtained when using DMAc as the solvent. A similar tendency was observed with 9-bromoanthracene. In DMF, a very low yield in **16** was observed by GC/MS analysis due to the formation of several unidentified side-products; whereas a very clean reaction was observed in DMAc to give **16** in 83% yield (Table 2.2, entries 20 and 21). Therefore, for challenging aryl bromides, the use of DMAc as the solvent should be preferred. We also examined the coupling of 5-bromopyrimidine with benzothiophene. The desired product **22** was isolated in 66% yield (Table 2.2, entry 22). For all these reactions, no arylation at C3 of benzothiophene was detected.

### 2.2.1.3 Scope for palladium-catalyzed 2-arylation of benzothiophene-3-carbaldehyde

We then studied the reactivity of benzothiophene-3-carbaldehyde with some aryl bromides (Table 2.3). We observed that using 0.1 mol% $Pd(OAc)_2$ as the catalyst and 4-bromobenzonitrile as coupling partner in DMF, the 2-arylated benzothiophene **18** was obtained in low yield (Table 2.3, entry 1). Moreover, the formation of the homocoupling product biphenyl-4,4′-dicarbonitrile was also observed.

**Table 2.3**. Palladium-catalyzed C2-arylation of benzothiophene-3-carbaldehyde with (hetero)aryl bromides (Scheme 2.11).

| Entry | Aryl halide | Product | Catalyst loading (mol%) | Yield (%) |
|---|---|---|---|---|
| 1 | | | 0.1 | 13[a] |
| 2 |  |  **18** | 0.5 | 33[a] |
| 3 | | | 0.5 | 65 |
| 4 |  |  **19** | 0.5 | 78 |
| 5 |  |  **20** | 0.5 | 77 |
| 6 |  |  **21** | 0.5 | 65 |
| 7 |  |  **22** | 0.5 | 61 |

Conditions: benzothiophene-3-carbaldehyde (1.5 equiv.), aryl bromide (1 equiv.), KOAc (2 equiv.), DMAc, 150 ℃, 16 h, isolated yields. [a] In DMF with a solution of catalyst prepared with 1 mg of $Pd(OAc)_2$ in 1 mL of DMAc.

The use of a higher catalyst loading allowed to improve the yield in **18** to 33%, but some

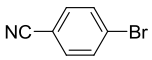
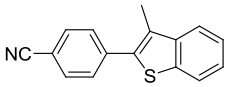
formation of unidentified side-products was observed, and again, some formation of biphenyl-4,4′-dicarbonitrile was detected by GC-MS (Table 2.3, entry 2). On the other hand, in DMAc, using 0.5 mol% $Pd(OAc)_2$, a clean reaction was observed, and **18** was isolated in 65% yield (Table 2.3, entry 3). The stability of benzothiophene-3-carbaldehyde in DMF appears to be limited. From the more congested substrate 2-bromobenzonitrile, a good yield in **20** was also obtained in DMAc (Table 2.3, entry 5). A similar reactivity of 3-bromonitrobenzene, 4-bromoisoquinoline or 5-bromopyrimidine was observed in DMAc to give **19**, **21** and **22** in 61-78% yields (Table 2.2, entries 4, 6 and 7).

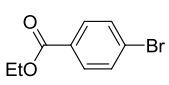
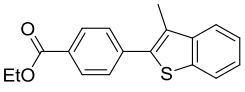
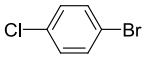
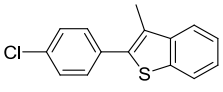
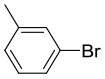
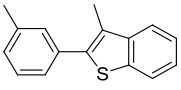
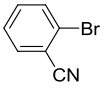
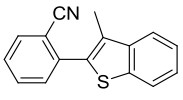
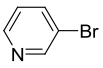
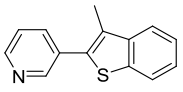
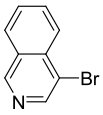
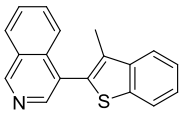
### 2.2.1.4 Scope for palladium-catalyzed 2-arylation of 3-methylbenzothiophene

With 3-methylbenzothiophene in DMAc, very clean reactions were observed in all cases using various aryl bromides and 0.1-0.5 mol% $Pd(OAc)_2$ catalyst (Table 2.4). The electron-deficient aryl bromides, 4-bromobenzonitrile and ethyl 4-bromobenzoate gave **23** and **24** in 88 and 81% yields, respectively using 0.5 mol% $Pd(OAc)_2$ catalyst (Table 2.4, entries 1 and 2). A high yield in **25** resulting from selective cleavage of the C-Br bond was also obtained from 4-chlorobromobenzene (Table 2.4, entries 3 and 4). The use of only 0.1 mol% $Pd(OAc)_2$ led to a high conversion of this aryl bromide.

Again, no cleavage of the C-Cl bond was observed allowing further transformations. A slightly lower yield was obtained for the coupling of the electron-rich aryl bromide: 3-bromotoluene (Table 2.4, entry 5). It should be noted that both 3-bromopyridine and 4-bromoisoquinoline could be coupled with 3-methylbenzothiophene to give **28** and **29** in high yields using only 0.1 mol% $Pd(OAc)_2$ (Table 2.4, entries 7 and 8).

**Table 2.4**. Palladium-catalyzed C2-arylation of 3-methylbenzothiophene with (hetero)aryl bromides (Scheme 2.11).

| Entry | Aryl halide | Product | Catalyst loading (mol%) | Yield (%) |
|---|---|---|---|---|
| 1 |  |  **23** | 0.5 | 88 |

| | | | | |
|---|---|---|---|---|
| 2 |  |  **24** | 0.5 | 81 |
| 3 |  |  **25** | 0.1 | 72 |
| 4 | | | 0.5 | 88 |
| 5 |  |  **26** | 0.5 | 66 |
| 6 |  |  **27** | 0.5 | 79 |
| 7 |  |  **28** | 0.1 | 70 |
| 8 |  |  **29** | 0.1 | 61 |

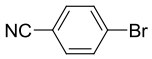
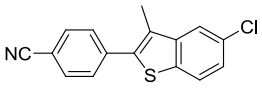
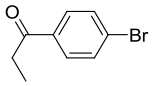
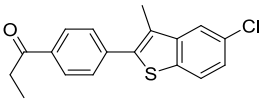
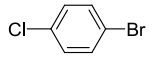
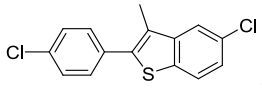
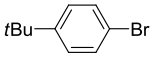
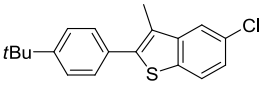
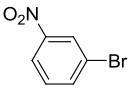
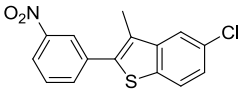
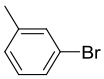
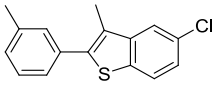
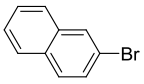
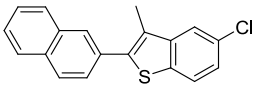
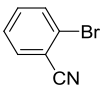
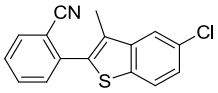
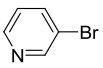
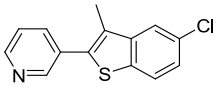
Conditions: $Pd(OAc)_2$ (0.001 or 0.005 equiv.), 3-methylbenzothiophene (1.5 equiv.), aryl bromide (1 equiv.), KOAc (2 equiv.), DMAc, 150 ℃, 16 h, isolated yields.

### 2.2.1.5 Scope for palladium-catalyzed 2-arylation of 5-chloro-3-methyl-benzothiophene

The reactivity of 5-chloro-3-methylbenzothiophene with a set of (hetero)aryl bromides was also examined using 0.1-0.5 mol% $Pd(OAc)_2$ catalyst (Table 2.5). In all cases, high yields of the desired coupling products **30**-**38** were obtained, except with the electron-rich, 4-*tert*-butylbromobenzene. For example, from 4-chlorobromobenzene, 3-nitrobromobenzene or 2-bromobenzonitrile and 0.1 mol% $Pd(OAc)_2$, the products **32**, **34** and **37** were obtained in 82-85% yields (Table 2.5, entries 3, 5 and 8).

**Table 2.5**. Palladium-catalyzed C2-arylation of 5-chloro-3-methylbenzothiophene with (hetero)aryl bromides (Scheme 2.11).

| Entry | Aryl halide | Product | Catalyst loading (mol%) | Yield (%) |
|---|---|---|---|---|

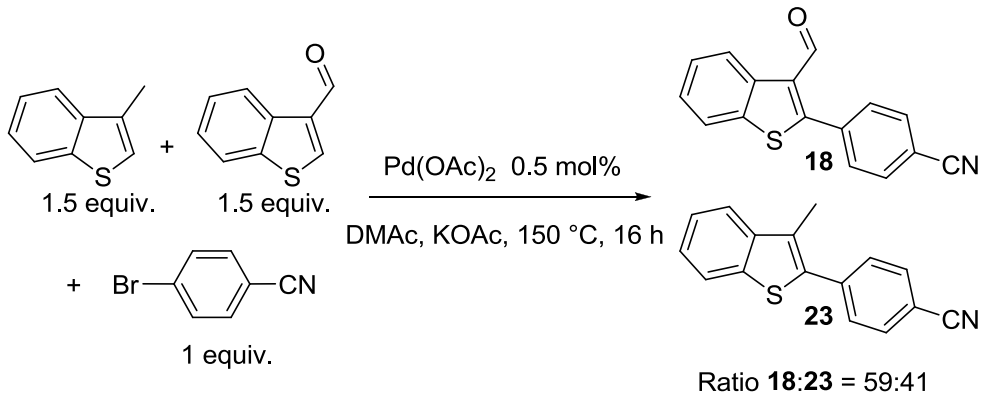
| | | | | |
|---|---|---|---|---|
| 1 |  |  **30** | 0.5 | 78 |
| 2 |  |  **31** | 0.5 | 83 |
| 3 |  |  **32** | 0.1 | 85 |
| 4 |  |  **33** | 0.1 | 58 |
| 5 |  |  **34** | 0.1 | 83 |
| 6 |  |  **35** | 0.5 | 80 |
| 7 |  |  **36** | 0.1 | 88 |
| 8 |  |  **37** | 0.1 | 82 |
| 9 |  |  **38** | 0.1 | 76 |

Conditions: $Pd(OAc)_2$ (0.001 or 0.005 equiv.), 5-chloro-3-methylbenzothiophene (1.5 equiv.), aryl bromide (1 equiv.), KOAc (2 equiv.), DMAc, 150 ℃, 16 h, isolated yields.

### 2.2.1.6 The competitive reaction for the reactivity of C3-substituent benzothiophenes

In order to have a better insight of the influence of the benzothiophenes C3-substituents on their reactivity, we performed a competitive experiment using an equimolar mixture of 3-methylbenzothiophene and benzothiophene-3-carbaldehyde in the presence of

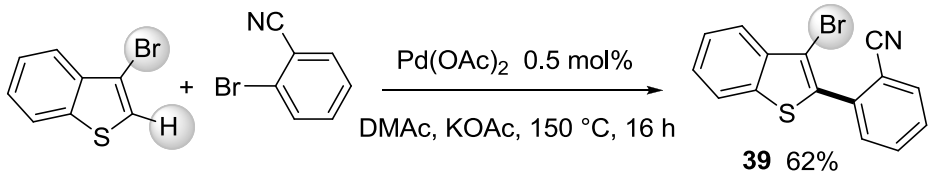
4-bromobenzonitrile and 0.5 mol% $Pd(OAc)_2$ (Scheme 2.12). We observed the formation of a mixture of the products **23** and **18** in a 41:59 ratio. This result indicates that the presence of electron-donating or electron-withdrawing substituents at C3 of benzothiophenes only has a minor influence on their reactivities.




**Scheme 2.12**. Competitive experiments using a mixture of 3-methylbenzothiophene and benzothiophene-3-carbaldehyde.

### 2.2.1.7 Palladium catalyzed direct C2 arylation of 3-bromobenzothiophene

To our knowledge, the direct arylation at C2 of 3-bromobenzothiophene has not been reported. So far, the coupling of such reactants to prepare 3-arylbenzothiophenes employs organozinc intermediates.[11] We observed that using 3-bromobenzothiophene and 2-bromobenzonitrile in a 1.5:1 ratio and again 0.5 mol% $Pd(OAc)_2$ catalyst, the desired product **39** was obtained in 62% yield without cleavage of the C-Br bond of the benzothiophene derivative.

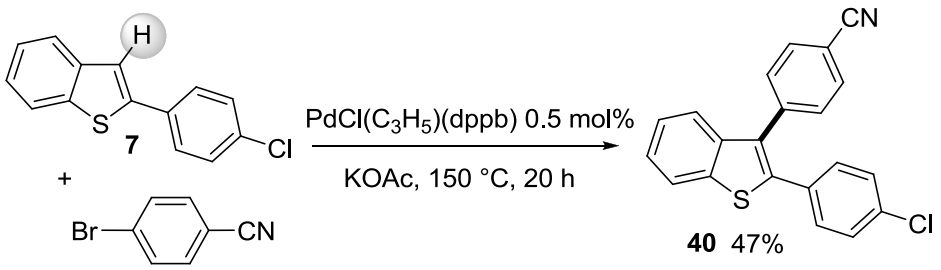



**Scheme 2.13**. Palladium-catalyzed direct arylation of 3-bromobenzothiophene with 2-bromobenzonitrile.

### 2.2.2 Palladium catalyzed direct C3- arylation of 2-(4-Chlorophenyl) -benzo[*b*]thiophene (7)

Finally, the palladium-catalyzed C3 direct arylation of **7** was examined (Scheme 2.14). The use of 0.5 mol% $Pd(OAc)_2$ catalyst gave **40** as traces. On the other hand, in the presence of 0.5 mol% $PdCl(C_3H_5)$(dppb) catalyst, **40** was isolated in 47% yield, without cleavage of the C-Cl bond of

the aryl substituent, showing the beneficial effect of the phosphine ligand in this case.




**Scheme 2.14**. Palladium-catalyzed direct C3 arylation of 2-arylbenzothiophene **7** with 4-bromobenzonitrile.

## 2.3 Conclusion

In summary, we have demonstrated that using as low as 0.1-0.5 mol% of $Pd(OAc)_2$ as the catalyst precursor, the direct 2-arylation *via* C-H bond activation of benzothiophenes proceeds in moderate to high yields. This procedure gave the best results using electron-deficient aryl bromides. Several functions such as formyl, acetyl, propionyl, nitro, nitrile, chloro, fluoro or trifluoromethyl are tolerated. Congested aryl bromides such as 9-bromoanthracene, also gave satisfactory results. This ligand-free low catalyst loading procedure is economically and environmentally attractive, as there is no need to eliminate phosphine derivatives at the end of the reaction; and as with this C-H bond activation procedure, no preparation of an organometallic derivative is required, reducing the number of steps and therefore the mass of waste products. The major waste is the relatively non-toxic AcOH/KBr instead of metallic salts with more classical metal-catalyzed coupling reactions. For these reasons, the methodology developed here is very promising for the sustainable synthesis of 2-arylbenzothiophenes.

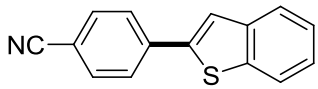
## 2.4 Experimental details

All reactions were performed in Schlenck tubes under argon. Potassium acetate 99+ was used. Benzothiophenes and aryl bromides were used without purification. $^{1}H$ (400 MHz, 25 °C), $^{13}C$ (100 MHz, 25 °C) spectra were recorded in $CDCl_3$ solutions. Chemical shifts are reported in ppm relative to $CDCl_3$ ($^{1}H$: 7.29 and $^{13}C$: 77.0). Flash chromatography was performed on silica gel (230-400 mesh).

**General procedure for the preparation of 1-40**

As a typical experiment, the reaction of the aryl bromide (1 mmol), benzothiophene (1.5 mmol) and KOAc (0.196 g, 2 mmol) at 150 ℃ during 16 h in DMF or DMAc (4 mL) in the presence of $Pd(OAc)_2$ (0.224 mg, 0.001 mmol) or (1.12 mg, 0.005 mmol) prepared as a solution in DMAc (1 mg of $Pd(OAc)_2$ in 1 mL of DMAc) under argon affords the coupling product after evaporation of the solvent and purification on silica gel.

**2-(4-Cyanophenyl)-benzo[*b*]thiophene 1**[6g]

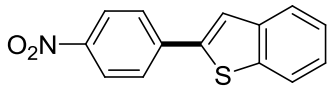



From 4-bromobenzonitrile (0.182 g, 1 mmol) and benzothiophene (0.201 g, 1.5 mmol), **1** was obtained in 69% (0.162 g) yield as a yellow solid (mp. 181-182 $^{o}$C).

Eluent pentane: diethylether 20:1

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.1 Hz, 1H), 7.72 (d, *J* = 7.9 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.55 (s, 1H), 7.30 (t, *J* = 7.3 Hz, 1H), 7.28 (t, *J* = 7.3 Hz, 1H).

**2-(4-Nitrophenyl)-benzo[*b*]thiophene 2**[6g]

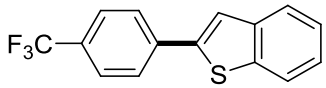



From 4-bromonitrobenzene (0.202 g, 1 mmol) and benzothiophene (0.201 g, 1.5 mmol), **2** was obtained in 51% (0.130 g) yield as a yellow solid (mp. 214-216 $^{o}$C).

Eluent pentane: diethylether 20:1

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, *J* = 8.4 Hz, 2H), 7.82-7.70 (m, 4H), 7.64 (s, 1H), 7.33 (t, *J* = 7.3 Hz, 1H), 7.31 (t, *J* = 7.3 Hz, 1H).

**2-[4-(Trifluoromethyl)phenyl]-benzo[*b*]thiophene 3**[6f]

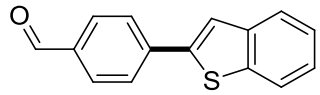


From 1-bromo-4-trifluoromethylbenzene (0.225 g, 1 mmol) and benzothiophene (0.201 g, 1.5 mmol), **3** was obtained in 61% (0.170 g) yield as a colorless solid (mp. 215-216 $^{o}$C).

Eluent pentane: diethylether 20:1

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.80-7.70 (m, 4H), 7.61 (d, *J* = 8.2 Hz, 2H), 7.56 (s, 1H), 7.32 (t, *J* = 7.3 Hz, 1H), 7.28 (t, *J* = 7.3 Hz, 1H).

**4-Benzo[*b*]thiophen-2-ylbenzaldehyde 4**[1]

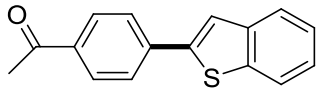


From 4-bromobenzaldehyde (0.185 g, 1 mmol) and benzothiophene (0.201 g, 1.5 mmol), **4** was obtained in 72% (0.171 g) yield as a yellow solid (mp. 170-172 $^{o}$C).

Eluent pentane: diethylether 20:1

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 9.97 (s, 1H), 7.87 (d, *J* = 8.3 Hz, 2H), 7.80 (d, *J* = 8.3 Hz, 2H), 7.80-7.72 (m, 2H), 7.63 (s, 1H), 7.32 (t, *J* = 7.3 Hz, 1H), 7.28 (t, *J* = 7.3 Hz, 1H).

**1-(4-Benzo[*b*]thiophen-2-yl-phenyl)-ethanone 5**[1]

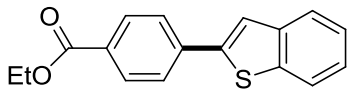


From 4-bromoacetophenone (0.199 g, 1 mmol) and benzothiophene (0.201 g, 1.5 mmol), **5** was obtained in 66% (0.166 g) yield as a yellow solid (mp. 208-209 $^{o}$C).

Eluent pentane: diethylether 10:1

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, *J* = 8.3 Hz, 2H), 7.80-7.68 (m, 4H), 7.59 (s, 1H), 7.30 (t, *J* = 7.3 Hz, 1H), 7.27 (t, *J* = 7.3 Hz, 1H), 2.55 (s, 3H).

**Ethyl 4-benzo[*b*]thiophen-2-yl-benzoate 6**[6d]

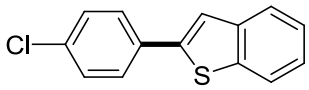



From ethyl 4-bromobenzoate (0.229 g, 1 mmol) and benzothiophene (0.201 g, 1.5 mmol), **6** was obtained in 76% (0.214 g) yield as a white solid (mp. 175-176 $^{o}$C).

Eluent pentane: diethylether 20:1

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, *J* = 8.3 Hz, 2H), 7.74 (d, *J* = 7.0 Hz, 1H), 7.70-7.65 (m, 3H), 7.56 (s, 1H), 7.30 (t, *J* = 7.3 Hz, 1H), 7.27 (t, *J* = 7.3 Hz, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 1.34 (t, *J* = 7.2 Hz, 3H).

**2-(4-Chlorophenyl)-benzo[*b*]thiophene 7**[6d]

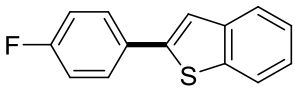



From 1-bromo-4-chlorobenzene (0.191 g, 1 mmol) and benzothiophene (0.201 g, 1.5 mmol), **7** was obtained in 73% (0.178 g) yield as a white solid (mp. 199-201 $^{o}$C).

Eluent pentane

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 7.0 Hz, 1H), 7.70 (d, *J* = 7.0 Hz, 1H), 7.56 (d, *J* = 8.3 Hz, 2H), 7.44 (s, 1H), 7.32 (d, *J* = 8.3 Hz, 2H), 7.30-7.20 (m, 2H).

**2-(4-Fluorophenyl)-benzo[*b*]thiophene 8**[6d]

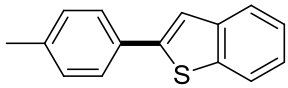



From 1-bromo-4-fluorobenzene (0.175 g, 1 mmol) and benzothiophene (0.201 g, 1.5 mmol), **8** was obtained in 80% (0.182 g) yield as a white solid (mp. 165-166 $^{o}$C).

Eluent pentane

$^1$H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 7.7 Hz, 1H), 7.68 (d, *J* = 7.7 Hz, 1H), 7.58 (dd, *J* = 8.6, 4.8 Hz, 2H), 7.37 (s, 1H), 7.27 (t, *J* = 7.3 Hz, 1H), 7.23 (t, *J* = 7.3 Hz, 1H), 7.03 (t, *J* = 8.6 Hz, 2H).

**2-(4-Methylphenyl)-benzo[*b*]thiophene 9**[6g]

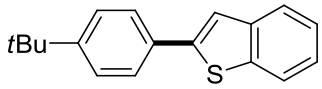



From 4-bromotoluene (0.171 g, 1 mmol) and benzothiophene (0.201 g, 1.5 mmol), **9** was obtained in 55% (0.123 g) yield as a white solid (mp. 165-167 $^o$C).

Eluent pentane

$^1$H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 7.8 Hz, 1H), 7.68 (d, *J* = 7.8 Hz, 1H), 7.53 (d, *J* = 8.3 Hz, 2H), 7.42 (s, 1H), 7.26 (t, *J* = 7.3 Hz, 1H), 7.23 (t, *J* = 7.3 Hz, 1H), 7.20 (d, *J* = 8.3 Hz, 2H), 2.32 (s, 3H).

**2-(4-*tert*-Butylphenyl)-benzo[*b*]thiophene 10**[6d]

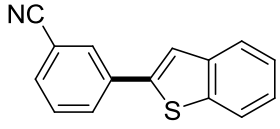



From 1-*tert*-butylbromobenzene (0.213 g, 1 mmol) and benzothiophene (0.201 g, 1.5 mmol), **10** was obtained in 32% (0.085 g) yield as a white solid (mp. 165-167 $^o$C).

Eluent pentane

$^1$H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 7.8 Hz, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.53 (d, *J* = 8.3 Hz, 2H), 7.42 (s, 1H), 7.36 (d, *J* = 8.3 Hz, 2H), 7.24 (t, *J* = 7.3 Hz, 1H), 7.21 (t, *J* = 7.3 Hz, 1H), 1.27 (s, 9H).

**2-(3-Cyanophenyl)-benzo[*b*]thiophene 11**[12a]

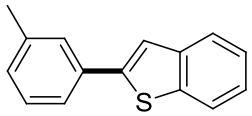


From 3-bromobenzonitrile (0.182 g, 1 mmol) and benzothiophene (0.201 g, 1.5 mmol), **11** was obtained in 60% (0.141 g) yield as a colorless oil.

Eluent pentane: diethylether 20:1

$^1$H NMR (400 MHz, $CDCl_3$): δ 7.88 (s, 1H), 7.81 (d, *J* = 7.9 Hz, 1H), 7.76 (d, *J* = 7.8 Hz, 1H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.51 (d, *J* = 7.9 Hz, 1H), 7.50 (s, 1H), 7.43 (t, *J* = 7.8 Hz, 1H), 7.30 (t, *J* = 7.3 Hz, 1H), 7.27 (t, *J* = 7.3 Hz, 1H).

**2-*m*-Tolylbenzo[*b*]thiophene 12**[12b]

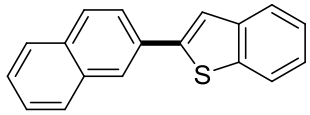


From 3-bromotoluene (0.171 g, 1 mmol) and benzothiophene (0.201 g, 1.5 mmol), **12** was obtained in 60% (0.134 g) yield as a white solid (mp. 116-118 $^o$C).

Eluent pentane

$^1$H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 7.7 Hz, 1H), 7.69 (d, *J* = 7.5 Hz, 1H), 7.50-7.40 (m, 3H), 7.25-7.20 (m, 3H), 7.08 (d, *J* = 7.4 Hz, 1H), 2.34 (s, 3H).

**2-Naphthalen-2-yl-benzo[*b*]thiophene 13**[6d]

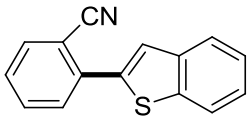


From 2-bromonaphthalene (0.207 g, 1 mmol) and benzothiophene (0.201 g, 1.5 mmol), **13** was obtained in 62% (0.161 g) yield as a colorless solid (mp. 210-212 $^o$C).

Eluent pentane

$^1$H NMR (400 MHz, $CDCl_3$): δ 8.07 (s, 1H), 7.85-7.70 (m, 6H), 7.60 (s, 1H), 7.47-7.37 (m, 2H), 7.29 (t, *J* = 7.8 Hz, 1H), 7.23 (t, *J* = 7.3 Hz, 1H).

**2-Benzo[*b*]thiophen-2-yl-benzonitrile 14**

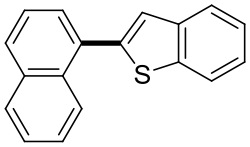



From 2-bromobenzonitrile (0.182 g, 1 mmol) and benzothiophene (0.201 g, 1.5 mmol), **14** was obtained in 73% (0.171 g) yield as a white solid (mp 119-121 ℃).

Eluent pentane: diethylether 20:1

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.80-7.72 (m, 3H), 7.67 (d, *J* = 7.7 Hz, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.52 (t, *J* = 7.3 Hz, 1H), 7.36-7.23 (m, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 140.3, 140.2, 139.2, 137.5, 134.5, 133.0, 130.2, 128.2, 125.3, 124.8, 124.5, 124.4, 122.1, 118.7, 110.5. Elemental analysis: calcd (%) for $C_{15}H_9NS$ (235.30): C 76.56, H 3.86; found: C 76.65, H 4.02.

**2-Naphthalen-1-ylbenzothiophene 15**[6g]

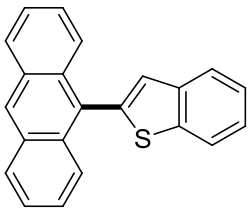



From 1-bromonaphthalene (0.207 g, 1 mmol) and benzothiophene (0.201 g, 1.5 mmol), **15** was obtained in 82% (0.213 g) yield as a white solid (mp. 105-106 $^{o}$C).

Eluent pentane

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, *J* = 8.0 Hz, 1H), 7.83-7.75 (m, 3H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.54 (d, *J* = 7.0 Hz, 1H), 7.45-7.22 (m, 6H).

**2-Anthracen-9-yl-benzo[*b*]thiophene 16**[12c]

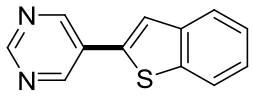



From 9-bromoanthracene (0.257 g, 1 mmol) and benzothiophene (0.201 g, 1.5 mmol), **16** was obtained in 83% (0.257 g) yield as a yellow solid (mp. 225-227 $^{o}$C).

Eluent pentane

$^1$H NMR (400 MHz, $CDCl_3$): δ 8.49 (s, 1H), 7.99 (d, *J* = 8.4 Hz, 2H), 7.90-7.82 (m, 4H), 7.45-7.30 (m, 7H).

**5-Benzo[*b*]thiophen-2-yl-pyrimidine 17**

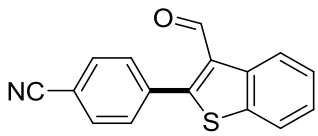


From 5-bromopyrimidine (0.159 g, 1 mmol) and benzothiophene (0.201 g, 1.5 mmol), **17** was obtained in 66% (0.140 g) yield as a colorless solid (mp 128-130 ℃).

Eluent pentane: diethylether 10:1

$^1$H NMR (400 MHz, $CDCl_3$): δ 9.09 (s, 1H), 8.95 (s, 2H), 7.79 (d, *J* = 7.7 Hz, 1H), 7.75 (d, *J* = 7.5 Hz, 1H), 7.56 (s, 1H), 7.32 (t, *J* = 7.4 Hz, 1H), 7.29 (t, *J* = 7.4 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 157.8, 153.9, 140.1, 139.9, 136.1, 128.7, 125.5, 125.1, 124.2, 122.5, 121.9. Elemental analysis: calcd (%) for $C_{12}H_8N_2S$ (212.27): C 67.90, H 3.80; found: C 67.99, H 3.64.

**4-(3-Formylbenzo[b]thiophen-2-yl)-benzonitrile 18**[7a]

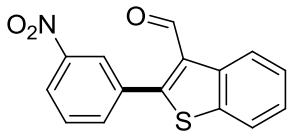


From 4-bromobenzonitrile (0.182 g, 1 mmol) and benzothiophene-3-carbaldehyde (0.243 g, 1.5 mmol), **18** was obtained in 65% (0.171 g) yield as a yellow solid (mp. 165-167 $^o$C).

Eluent pentane: diethylether 5:1

$^1$H NMR (400 MHz, $CDCl_3$): δ 9.97 (s, 1H), 8.71 (d, *J* = 8.1 Hz, 1H), 7.81 (d, *J* = 7.9 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.48 (t, *J* = 7.3 Hz, 1H), 7.42 (t, *J* = 7.3 Hz, 1H).

**2-(3-Nitrophenyl)-benzo[*b*]thiophene-3-carbaldehyde 19**

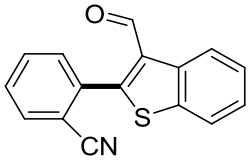


From 3-bromonitrobenzene (0.202, 1 mmol) and benzothiophene-3-carbaldehyde (0.243 g, 1.5 mmol), **19** was obtained in 78% (0.221 g) yield as a yellow solid (mp 136-138 ℃).

Eluent pentane: diethylether 5:1

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 9.99 (s, 1H), 8.72 (d, *J* = 8.1 Hz, 1H), 8.40 (d, *J* = 1.7 Hz, 1H), 8.32 (d, *J* = 8.3 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.4867 (t, *J* = 7.3 Hz, 1H), 7.50 (t, *J* = 7.3 Hz, 1H), 7.45 (t, *J* = 7.3 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 185.4, 156.3, 148.4, 138.2, 136.8, 136.2, 133.4, 131.1, 130.0, 126.7, 126.5, 125.4, 125.1, 124.6, 121.8. Elemental analysis: calcd (%) for $C_{15}H_9NO_3S$ (283.30): C 63.59, H 3.20; found: C 63.42, H 3.04.

**2-(3-Formylbenzo[*b*]thiophen-2-yl)-benzonitrile 20**[7a]

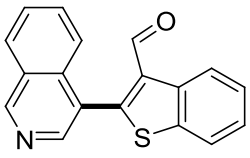


From 2-bromobenzonitrile (0.182 g, 1 mmol) and benzothiophene-3-carbaldehyde (0.243 g, 1.5 mmol), **20** was obtained in 77% (0.202 g) yield as a lolorless oil.

Eluent pentane: diethylether 20:3

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 9.83 (s, 1H), 8.71 (d, *J* = 8.1 Hz, 1H), 7.81 (d, *J* = 7.8 Hz, 1H), 7.79 (d, *J* = 7.8 Hz, 1H), 7.67 (t, *J* = 7.8 Hz, 1H), 7.60-7.55 (m, 2H), 7.49 (t, *J* = 7.3 Hz, 1H), 7.43 (t, *J* = 7.3 Hz, 1H).

**2-Isoquinolin-4-yl-benzo[*b*]thiophene-3-carbaldehyde 21**

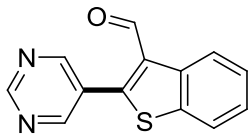


From 4-bromoisoquinoline (0.208 g, 1 mmol) and benzothiophene-3-carbaldehyde (0.243 g, 1.5 mmol), **21** was obtained in 65% (0.188 g) yield as a yellow solid (mp 132-134 ℃).

Eluent pentane: diethylether 2:1

$^1$H NMR (400 MHz, $CDCl_3$): δ 9.67 (s, 1H), 9.32 (s, 1H), 8.76 (d, *J* = 8.1 Hz, 1H), 8.61 (s, 1H), 8.02 (d, *J* = 7.6 Hz, 1H), 7.83 (d, *J* = 7.6 Hz, 1H), 7.79 (d, *J* = 7.6 Hz, 1H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.62 (t, *J* = 7.7 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 185.8, 154.4, 154.1, 144.6, 139.0, 136.4, 135.3, 133.1, 132.0, 128.2, 128.1, 126.6, 126.3, 125.3, 124.3, 121.7. Elemental analysis: calcd (%) for $C_{18}H_{11}NOS$ (289.35): C 74.72, H 3.83; found: C 74.60, H 3.98.

**2-Pyrimidin-5-yl-benzo[*b*]thiophene-3-carbaldehyde 22**

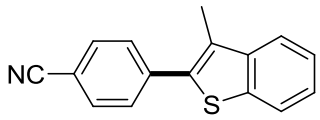



From 5-bromopyrimidine (0.159 g, 1 mmol) and benzothiophene-3-carbaldehyde (0.243 g, 1.5 mmol), **22** was obtained in 61% (0.146 g) yield as a yellow solid (mp 151-153 ℃).

Eluent pentane: diethylether 2:1

$^1$H NMR (400 MHz, $CDCl_3$): δ 10.00 (s, 1H), 9.30 (s, 1H), 8.94 (s, 2H), 8.70 (d, *J* = 8.1 Hz, 1H), 7.83 (d, *J* = 8.1 Hz, 1H), 7.50 (t, *J* = 8.1 Hz, 1H), 7.44 (t, *J* = 8.1 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 184.6, 159.3, 157.0, 150.7, 138.4, 136.8, 131.7, 126.9, 126.7, 125.3, 121.9. Elemental analysis: calcd (%) for $C_{13}H_8N_2OS$ (240.28): C 64.98, H 3.36; found: C 65.14, H 3.47.

**4-(3-Methylbenzo[*b*]thiophen-2-yl)-benzonitrile 23**

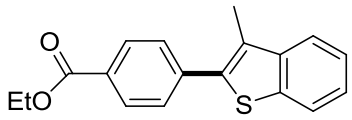



From 4-bromobenzonitrile (0.182 g, 1 mmol) and 3-methyl-benzothiophene (0.222 g, 1.5 mmol), **23** was obtained in 88% (0.219 g) yield as a white solid (mp 125-127 ℃).

Eluent pentane: diethylether 10:1

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 7.5 Hz, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.36 (t, *J* = 7.3 Hz, 1H), 7.30 (t, *J* = 7.3 Hz, 1H), 2.40 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 141.0, 139.6, 139.1, 135.7, 132.3, 130.2, 129.4, 125.2, 124.6, 122.6, 122.3, 118.7, 111.3, 12.8. Elemental analysis: calcd (%) for $C_{16}H_{11}NS$ (249.33): C 77.07, H 4.45; found: C 77.01, H 4.35.

**Ethyl 4-(3-methylbenzo[*b*]thiophen-2-yl)-benzoate 24**

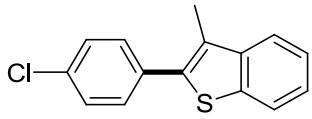



From ethyl 4-bromobenzoate (0.229 g, 1 mmol) and 3-methyl-benzothiophene (0.222 g, 1.5 mmol), **24** was obtained in 81% (0.240 g) yield as a yellow oil.

Eluent pentane

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, *J* = 8.2 Hz, 2H), 7.76 (d, *J* = 7.5 Hz, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.54 (d, *J* = 8.2 Hz, 2H), 7.35 (t, *J* = 7.3 Hz, 1H), 7.29 (t, *J* = 7.3 Hz, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 2.41 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 166.3, 141.1, 139.3, 139.1, 136.8, 129.8, 129.6, 129.5, 128.6, 124.7, 124.3, 122.4, 122.2, 61.1, 14.4, 12.8. Elemental analysis: calcd (%) for $C_{18}H_{16}O_2S$ (296.38): C 72.94, H 5.44; found: C 72.80, H 5.32.

**2-(4-Chlorophenyl)-3-methylbenzo[*b*]thiophene 25**



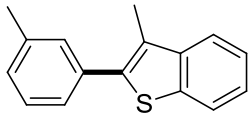

From 1-bromo-4-chlorobenzene (0.191 g, 1 mmol) and 3-methyl-benzothiophene (0.222 g, 1.5 mmol), **25** was obtained in 88% (0.227 g) yield as a white solid (mp 87-89 ℃).

Eluent pentane

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 7.5 Hz, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.39 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 1H), 7.27 (t, *J* = 7.3 Hz, 1H), 2.36 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ 141.1, 138.9, 136.7, 133.9, 133.2, 130.9, 128.8, 127.9, 124.5, 124.3, 122.2, 122.1, 12.6. Elemental analysis: calcd (%) for $C_{15}H_{11}ClS$ (258.77): C 69.62, H 4.28; found: C 69.79, H 4.09.

**3-Methyl-2-*m*-tolyl-benzo[*b*]thiophene 26**

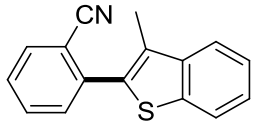



From 3-bromotoluene (0.171 g, 1 mmol) and 3-methyl-benzothiophene (0.222 g, 1.5 mmol), **26** was obtained in 66% (0.157 g) yield as a colourless oil.

Eluent pentane

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 7.8 Hz, 1H), 7.61 (d, *J* = 7.9 Hz, 1H), 7.35-7.18 (m, 5H), 7.10-7.05 (m, 1H), 2.36 (s, 3H), 2.32 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 141.3, 138.9, 138.3, 138.2, 134.7, 130.4, 128.6, 128.5, 127.3, 126.9, 124.3, 124.1, 122.2, 122.1, 21.5, 12.7. Elemental analysis: calcd (%) for $C_{16}H_{14}S$ (238.35): C 80.63, H 5.92; found: C 80.74, H 5.99.

**2-(3-Methylbenzo[b]thiophen-2-yl)-benzonitrile 27**

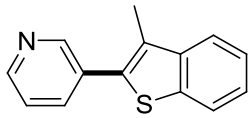



From 2-bromobenzonitrile (0.182 g, 1 mmol) and 3-methyl-benzothiophene (0.222 g, 1.5 mmol), **27** was obtained in 79% (0.197 g) yield as a white solid (mp 122-124 ℃).

Eluent pentane: diethylether 10:1

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 7.5 Hz, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.68 (d, *J* = 7.8 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 7.48 (d, *J* = 7.2 Hz, 1H), 7.41 (t, *J* = 7.3 Hz, 1H), 7.36 (t, *J* = 7.3 Hz, 1H), 7.31 (t, *J* = 7.3 Hz, 1H), 2.30 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 140.3, 139.6, 138.4, 133.3, 133.1, 132.5, 132.0, 131.2, 128.6, 125.1, 124.5, 122.7, 122.2, 117.9, 113.9, 13.0. Elemental analysis: calcd (%) for $C_{16}H_{11}NS$ (249.33): C 77.07, H 4.45; found: C 77.40, H 4.57.

**3-(3-Methylbenzo[b]thiophen-2-yl)-pyridine 28**

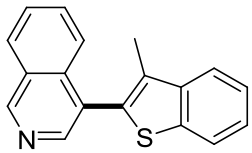



From 3-bromopyridine (0.158 g, 1 mmol) and 3-methyl-benzothiophene (0.222 g, 1.5 mmol), **28** was obtained in 70% (0.157 g) yield as a white solid (mp 210-212 ℃).

Eluent pentane: diethylether 10:1

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.73 (d, *J* = 1.2 Hz, 1H), 8.53 (d, *J* = 3.6 Hz, 1H), 7.80-7.70 (m, 2H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.40-7.23 (m, 3H), 2.39 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 150.2, 148.8, 140.9, 139.1, 136.8, 133.9, 130.9, 129.0, 124.8, 124.4, 123.4, 122.4, 122.2, 12.6. Elemental analysis: calcd (%) for $C_{14}H_{11}NS$ (225.31): C 74.63, H 4.92; found: C 74.57, H 4.69.

**4-(3-Methylbenzo[*b*]thiophen-2-yl)-isoquinoline 29**

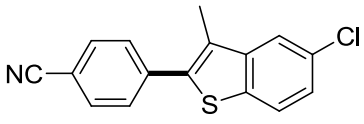



From 4-bromoisoquinoline (0.208 g, 1 mmol) and 3-methyl-benzothiophene (0.222 g, 1.5 mmol), **29** was obtained in 61% (0.168 g) yield as a yellow oil.

Eluent pentane: diethylether 10:3

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 9.24 (s, 1H), 8.53 (s, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.81 (d, *J* = 7.7 Hz, 1H), 7.75-7.70 (m, 2H), 7.65-7.55 (m, 2H), 7.40 (t, *J* = 7.8 Hz, 1H), 7.33 (t, *J* = 7.8 Hz, 1H), 2.16 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 153.0, 144.8, 140.4, 139.9, 135.2, 131.9, 131.3, 131.0, 128.3, 128.0, 127.5, 125.9, 125.0, 124.7, 124.4, 122.3, 122.2, 12.7. Elemental analysis: calcd (%) for $C_{18}H_{13}NS$ (275.37): C 78.51, H 4.76; found: C 78.51, H 4.87.

**4-(5-Chloro-3-methylbenzo[*b*]thiophen-2-yl)-benzonitrile 30**

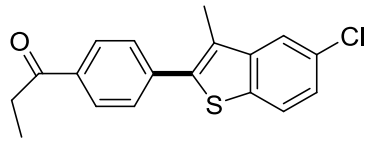


From 4-bromobenzonitrile (0.182 g, 1 mmol) and 5-chloro-3-methylbenzothiophene (0.274 g, 1.5 mmol), **30** was obtained in 78% (0.221 g) yield as a white solid (mp 164-166 ℃).

Eluent pentane: diethylether 50:3

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.70-7.63 (m, 4H), 7.56 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 8.5 Hz, 1H), 2.37 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 142.1, 139.0, 137.7, 137.2, 132.4, 130.9, 130.2, 128.7, 125.5, 123.3, 122.2, 118.6, 111.7, 12.8. Elemental analysis: calcd (%) for $C_{16}H_{10}ClNS$ (283.78): C 67.72, H 3.55; found: C 67.81, H 3.41.

**1-[4-(5-Chloro-3-methylbenzo[*b*]thiophen-2-yl)-phenyl]-propan-1-one 31**

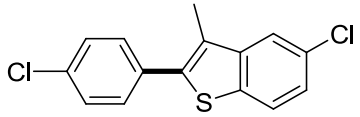



From 4-bromopropiophenone (0.213 g, 1 mmol) and 5-chloro-3-methylbenzothiophene (0.274 g, 1.5 mmol), **31** was obtained in 83% (0.261 g) yield as a white solid (mp 136-138 ℃).

Eluent pentane

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, *J* = 8.3 Hz, 2H), 7.62-7.58 (m, 2H), 7.51 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 8.5 Hz, 1H), 2.91 (q, *J* = 7.5 Hz, 2H), 2.34 (s, 3H), 1.16 (t, *J* = 7.5 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 200.1, 142.4, 138.8, 137.1, 136.1, 130.7, 129.7, 128.3, 128.1, 125.1, 123.2, 122.1, 31.9, 12.8, 8.3. Elemental analysis: calcd (%) for $C_{18}H_{15}ClOS$ (314.83): C 68.67, H 4.80; found: C 68.49, H 4.89.

**5-Chloro-2-(4-chlorophenyl)-3-methylbenzo[*b*]thiophene 32**

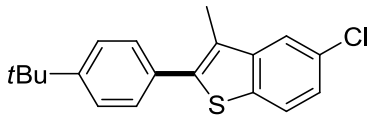



From 1-bromo-4-chlorobenzene (0.191 g, 1 mmol) and 5-chloro-3-methylbenzothiophene (0.274 g, 1.5 mmol), **32** was obtained in 85% (0.249 g) yield as a white solid (mp 137-138 ℃).

Eluent pentane

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, *J* = 8.2 Hz, 1H), 7.58 (s, 1H), 7.40-7.30 (m, 4H), 7.20 (d, *J* = 8.3 Hz, 1H), 2.30 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 142.4, 138.7, 136.9, 134.2, 132.7, 130.9, 130.7, 128.9, 127.4, 124.9, 123.2, 121.9, 12.6. Elemental analysis: calcd (%) for $C_{15}H_{10}Cl_2S$ (293.21): C 61.44, H 3.44; found: C 61.59, H 3.31.

**2-(4-*tert*-Butylphenyl)-3-methyl-benzo[*b*]thiophene 33**

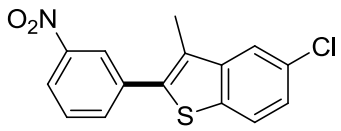



From 1-*tert*-butylbromobenzene (0.213 g, 1 mmol) and 5-chloro-3-methylbenzothiophene (0.274 g, 1.5 mmol), **33** was obtained in 58% (0.182 g) yield as a white solid (mp 134-136 ℃).

Eluent pentane

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.2 Hz, 1H), 7.60 (s, 1H), 7.45-7.35 (m, 4H), 7.22 (d, *J* = 8.3 Hz, 1H), 2.36 (s, 3H), 1.30 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 151.2, 142.6, 140.3, 136.9, 131.3, 130.4, 129.3, 126.6, 125.6, 124.4, 123.1, 121.7, 34.8, 31.3, 12.6. Elemental analysis: calcd (%) for $C_{19}H_{20}ClS$ (314.87): C 72.47, H 6.08; found: C 72.27, H 6.29.

**5-Chloro-3-methyl-2-(3-nitrophenyl)-benzo[*b*]thiophene 34**

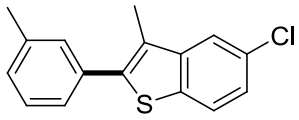



From 3-bromonitrobenzene (0.202, 1 mmol) and 5-chloro-3-methylbenzothiophene (0.274 g, 1.5 mmol), **34** was obtained in 83% (0.251 g) yield as a yellow solid (mp 176-177 ℃).

Eluent pentane: diethylether 10:1

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.30 (s, 1H), 8.16 (d, *J* = 8.3 Hz, 1H), 7.75 (d, *J* = 7.7 Hz, 1H), 7.68-7.60 (m, 2H), 7.57 (t, *J* = 8.0 Hz, 1H), 7.26 (d, *J* = 8.5 Hz, 1H), 2.37 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 148.4, 142.1, 137.0, 136.0, 135.5, 131.0, 129.7, 128.7, 125.5, 124.3, 123.3, 122.8, 122.2, 12.6. elemental analysis: calcd (%) for $C_{15}H_{10}ClNO_2S$ (303.76): C 59.31, H 3.32; found: C 59.50, H 3.48.

**5-Chloro-3-methyl-2-*m*-tolyl-benzo[*b*]thiophene 35**

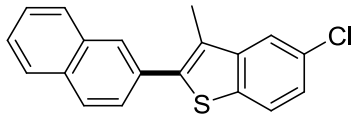



From 3-bromotoluene (0.171 g, 1 mmol) and 5-chloro-3-methylbenzothiophene (0.274 g, 1.5 mmol), **35** was obtained in 80% (0.218 g) yield as a colourless oil.

Eluent pentane

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, *J* = 8.3 Hz, 1H), 7.56 (s, 1H), 7.30-7.05 (m, 5H), 2.31 (s, 3H), 2.30 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 142.6, 140.4, 138.4, 137.0, 134.2, 130.5, 130.3, 128.9, 128.6, 126.8, 126.7, 124.6, 123.1, 121.8, 21.5, 12.7. Elemental analysis: calcd (%) for $C_{16}H_{13}ClS$ (272.79): C 70.45, H 4.80; found: C 70.32, H 4.68.

**5-Chloro-3-methyl-2-naphthalen-2-yl-benzo[*b*]thiophene 36**

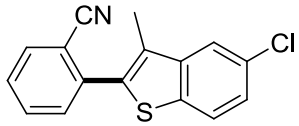



From 2-bromonaphthalene (0.207 g, 1 mmol) and 5-chloro-3-methylbenzothiophene (0.274 g, 1.5 mmol), **36** was obtained in 88% (0.271 g) yield as a white solid (mp 128-129 ℃).

Eluent pentane

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.85 (s, 1H), 7.80-7.70 (m, 3H), 7.65-7.55 (m, 2H), 7.51 (d, *J* = 8.3 Hz, 1H), 7.43-7.38 (m, 2H), 7.19 (d, *J* = 8.4 Hz, 1H), 2.34 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 142.6, 140.2, 137.2, 133.3, 132.8, 131.7, 130.6, 128.9, 128.3, 128.2, 127.8, 127.3, 127.2, 126.7, 126.6, 124.7, 123.2, 121.9, 12.8. Elemental analysis: calcd (%) for $C_{19}H_{13}ClS$ (308.83): C 73.89, H 4.24; found: C 74.08, H 4.01.

**2-(5-Chloro-3-methyl-benzo[*b*]thiophen-2-yl)-benzonitrile 37**

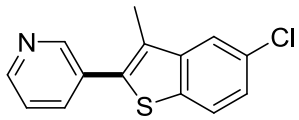


From 2-bromobenzonitrile (0.182 g, 1 mmol) and 5-chloro-3-methylbenzothiophene (0.274 g, 1.5 mmol), **37** was obtained in 82% (0.232 g) yield as a white solid (mp 161-163 ℃).

Eluent pentane: diethylether 10:1

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.3 Hz, 1H), 7.68-7.60 (m, 2H), 7.58 (t, *J* = 7.7 Hz, 1H), 7.50-7.40 (m, 2H), 7.25 (d, *J* = 8.6 Hz, 1H), 2.25 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 141.5, 137.8, 137.6, 135.1, 133.4, 132.6, 131.9, 130.8, 130.6, 128.9, 125.5, 123.2, 122.4, 117.8, 113.8, 12.9. Elemental analysis: calcd (%) for $C_{16}H_{10}ClNS$ (283.78): C 67.72, H 3.55; found: C 67.57, H 3.59.

**3-(5-Chloro-3-methylbenzo[*b*]thiophen-2-yl)-pyridine 38**

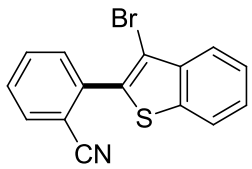



From 3-bromopyridine (0.158 g, 1 mmol) and 5-chloro-3-methylbenzothiophene (0.274 g, 1.5 mmol), **38** was obtained in 76% (0.197 g) yield as a white solid (mp 116-118 ℃).

Eluent pentane: diethylether 2:1

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.58 (d, *J* = 1.1 Hz, 1H), 8.52 (d, *J* = 3.8 Hz, 1H), 7.69 (d, *J* = 7.9 Hz, 1H), 7.60-7.55 (m, 2H), 7.27 (dd, *J* = 7.7, 4.9 Hz, 1H), 7.20 (dd, *J* = 8.5, 1.8 Hz, 1H), 2.30 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 150.1, 149.2, 142.1, 137.1, 136.7, 136.0, 130.8, 130.4, 128.4, 125.1, 123.4, 123.2, 122.1, 12.5. Elemental analysis: calcd (%) for $C_{14}H_{10}ClNS$ (259.75): C 64.73, H 3.88; found: C 64.50, H 3.99.

**2-(3-Bromobenzothiophen-2-yl)-benzonitrile 39**



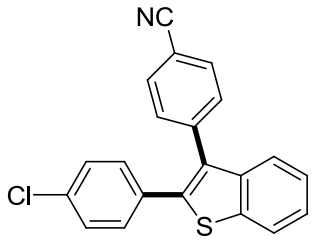

From 2-bromobenzonitrile (0.182 g, 1 mmol), 3-bromo-benzothiophene (0.319 g, 1.5 mmol), KOAc (0.196 g, 2 mmol) at 150 ℃ during 16 h in DMAc (4 mL) in the presence of $Pd(OAc)_2$

(1.12 mg, 0.005 mmol), **40** was obtained in 62% (0.195 g) yield as a brown solid (mp 174-176 ℃).

Eluent pentane

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.63 (td, *J* = 7.7, 1.1 Hz, 1H), 7.55 (d, *J* = 7.2 Hz, 1H), 7.49 (td, *J* = 7.7, 1.1 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 1H), 7.39 (t, *J* = 7.7 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 138.6, 138.1, 136.7, 133.8, 133.5, 132.6, 132.0, 129.4, 126.2, 125.6, 124.1, 122.3, 117.5, 114.0, 109.1. Elemental analysis: calcd (%) for $C_{15}H_8BrNS$ (314.20): C 57.34, H 2.57; found: C 57.50, H 2.86.

**4-[2-(4-Chlorophenyl)-benzo[*b*]thiophen-3-yl]-benzonitrile 40**




From 2-(4-chlorophenyl)-benzothiophene **7** (0.244 g, 1 mmol), 4-bromobenzonitrile (0.364 g, 2 mmol), KOAc (0.392 g, 4 mmol) at 150 ℃ during 20 h in DMAc (4 mL) in the presence of $PdCl(C_3H_5)$(dppb) (3.1 mg, 0.005 mmol) **40** was obtained in 47% (0.162 g) yield as a white solid (mp 178-180 ℃).

Eluent pentane: diethylether 2:1

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, *J* = 7.0 Hz, 1H), 7.64 (d, *J* = 8.3 Hz, 2H), 7.46 (d, *J* = 7.0 Hz, 1H), 7.37 (d, *J* = 8.3 Hz, 2H), 7.35-7.25 (m, 2H), 7.19 (d, *J* = 8.5 Hz, 2H), 7.12 (d, *J* = 8.5 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 140.3, 139.8, 139.7, 139.0, 134.5, 132.6, 132.0, 131.6, 131.2, 130.9, 128.9, 125.2, 125.0, 122.8, 122.4, 118.7, 111.4. Elemental analysis: calcd (%) for $C_{21}H_{12}ClNS$ (345.85): C 72.93, H 3.50; found: C 72.80, H 3.66.

## 2.5 Reference


1. A. Ohta, Y. Akita, T. Ohkuwa, M. Chiba, R. Fukunaga, A. Miyafuji, T. Nakata, N. Tani, Y. Aoyagi, *Heterocycles* **1990**, *31*, 1951.
2. For reviews on palladium-catalyzed C-H bond functionalization: *(a)* L. Ackermann, R. Vincente, A. R. Kapdi, *Angew. Chem. Int. Ed.* **2009**, *48*, 9792; *(b)* X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2009**, *48*, 5094; *(c)* J. Roger, A. L. Gottumukkala, H. Doucet, *ChemCatChem* **2010**, *2*, 20; *(d)* C. Fischmeister, H. Doucet, *Green. Chem.* **2011**, *13*, 741; *(e)* J. Wencel-Delord, F. Glorius, *Nature Chem.* **2013**, *5*, 369.
3. For selected recent contributions on direct arylation of thiophenes from our laboratory: *(a)* F. Derridj, J. Roger, S. Djebbar, H. Doucet, *Org. Lett.* **2010**, *12*, 4320; *(b)* L. Chen, J. Roger, C. Bruneau, P. H. Dixneuf, H. Doucet, *Chem. Commun.* **2011**, *47*, 1872; *(c)* K. Si Larbi, S. Djebbar, H. Doucet, *Eur. J. Inorg. Chem.* **2011**, 3493; *(d)* K. Beydoun, H. Doucet, *Eur J. Org. Chem.* **2012**, 6745; *(e)* K. Beydoun, M. Zaarour, J. A. G. Williams, H. Doucet, V. Guerchais. *Chem. Commun.* **2012**, *48*, 1260; *(f)* S. Bensaid, H. Doucet, *ChemSusChem* **2012**, *5*, 1559.
4. For selected examples of palladium-catalyzed direct arylation of thiophenes from other groups: Fagnou group: *(a)* M. Parisien, D. Valette, K. Fagnou, *J. Org. Chem.* **2005**, *70*, 7578; *(b)* L.-C. Campeau, M. Bertrand-Laperle, J.-P. Leclerc, E. Villemure, S. Gorelsky, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 3276; *(c)* D. J. Schipper, K. Fagnou, *Chem. Mater.* **2011**, *23*, 1594; Mori group: *(d)* K. Masui, H. Ikegami, A. Mori, *J. Am. Chem. Soc.* **2004**, *126*, 5074; *(e)* K. Kobayashi, A. Sugie, M. Takahashi, K. Masui, A. Mori, *Org. Lett.* **2005**, *7*, 5083; Others: *(f)* G. L. Turner, J. A. Morris, M. F. Greaney, *Angew. Chem., Int. Ed.* **2007**, *46*, 7996; *(g)* M. Nakano, H. Tsurugi, T. Satoh, M. Miura, *Org. Lett.* **2008**, *10*, 1851; *(h)* C. Pierre, O. Baudoin, *Org. Lett.* **2011**, *13*, 1816; *(i)* L. Théveau, C. Verrier, P. Lassalas, T. Martin, G. Dupas, O. Querolle, L. Van Hijfte, F. Marsais, C. Hoarau, *Chem. Eur. J.* **2011**, *17*, 14450.
5. *(a)* J. J. Li, G. W. Gribble, *Palladium in Heterocyclic Chemistry*, Pergamon: Amsterdam, **2000**; *(b)* E. Negishi, Ed. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Wiley-Interscience: New York, **2002**; Part III, p 213.
6. For examples of intermolecular direct arylation of benzothiophenes using palladium associated to phosphine ligands as catalyst: *(a)* J. Fournier Dit Chabert, G. Chatelain, S.

Pellet-Rostaing, D. Bouchu, M. Lemaire, *Tetrahedron Lett.* **2006**, *47*, 1015; *(b)* E. David, S. Pellet-Rostaing, M. Lemaire, *Tetrahedron* **2007**, *63*, 8999; *(c)* E. David, J. Lejeune, S. Pellet-Rostaing, J. Schulz, M. Lemaire, J. Chauvin, A. Deronzier, *Tetrahedron Lett.* **2008**, *49*, 1860; *(d)* B. Liegault, D. Lapointe, L. Caron, A. Vlassova, K. Fagnou, *J. Org. Chem.* **2009**, *74*, 1826; *(e)* O. Rene, K. Fagnou, *Adv. Synth. Catal.* **2010**, *352*, 2116; *(f)* S. Tamba, Y. Okubo, S. Tanaka, D. Monguchi, A. Mori, *J. Org. Chem.* **2010**, *75*, 6998; *(g)* M. Baghbanzadeh, C. Pilger, C. O. Kappe, *J. Org. Chem.* **2011**, *76*, 8138.

7. For examples of intermolecular direct arylation of benzothiophenes using 5 mol% $Pd(OAc)_2$ associated to a stoechiometric amount of quaternary ammonium salts or crown ethers as stabilizing agents: *(a)* J. Fournier Dit Chabert, L. Joucla, E. David, M. Lemaire, *Tetrahedron* **2004**, *60*, 3221; *(b)* E. David, J. Perrin, S. Pellet-Rostaing, J. Fournier dit Chabert, M. Lemaire, *J. Org. Chem.* **2005**, *70*, 3569; *(c)* E. David, C. Rangheard, S. Pellet-Rostaing, M. Lemaire, *Synlett* **2006**, 2016; *(d)* J. Fournier dit Chabert, B. Marquez, L. Neville, L. Joucla, S. Broussous, P. Bouhours, E. David, S. Pellet-Rostaing, B. Marquet, N. Moreau, M. Lemaire, *Bioorg. Med. Chem.* **2007**, *15*, 4482.
8. *(a)* A. H. M. de Vries, J. M. C. A. Mulders, J. H. M. Mommers, H. J. W. Henderickx, J. G. de Vries, *Org. Lett.* **2003**, *5*, 3285; *(b)* M. T. Reetz, J. G. de Vries, *Chem. Commun.* **2004**, 1559; *(c)* A. mardanov, L. mieder-van de Vondervoort, A. H. M. de Vries, J. G. de Vries, *Adv. Synth. Catal.* **2004**, *346*, 1812; *(d)* J. G. de Vries, *Dalton Trans.* **2006**, 421.
9. For direct arylations of heteroaromatics with aryl halides using ligand-less palladium catalysts: *(a)* X. Wang, D. V. Gribkov, D. Sames, *J. Org. Chem.* **2007**, *72*, 1476; *(b)* J. Roger, H. Doucet, *Adv. Synth. Catal.* **2009**, *351*, 1977; *(c)* J. Roger, H. Doucet, *Tetrahedron* **2009**, *65*, 9772; *(d)* J. Roger, F. Požgan, H. Doucet, *Adv. Synth. Catal.* **2010**, *352*, 696; *(e)* H. Y. Fu, L. Chen, H. Doucet, *J. Org. Chem.* **2012**, *77*, 4473.
10. For recent examples of 2-arylbenzothiophene synthesis: Z. Duan, S. Ranjit, X. Liu. *Org. Lett.* **2010**, *12*, 2430.
11. *(a)* M. Mosrin, G. Monzon, T. Bresser, P. Knochel, *Chem. Commun.* **2009**, 5615; *(b)* H. Zhao, J. W. Dankwardt, S. G. Koenig, S. P. Singh, *Tetrahedron Lett.* **2012**, *53*, 166.
12. *(a)* G. Chelucci, S. Baldino, A. Ruiu, *J. Org. Chem.* **2012**, *77*, 9921; *(b)* Y. Uozumi, Y. Nakai, *Org. Lett.* **2002**, *4*, 2997; *(c)* A. B. Biro. A. Kotschy, *Eur. J. Org. Chem.* **2007**, 1364.

# *Chapter 3: Palladium-catalyzed direct polyarylations of pyrrole derivatives*

# Chapter 3: Palladium-catalyzed direct polyarylations of pyrrole derivatives

## 3.1 Introduction

The aryl-pyrrole compounds constitute a common structure in natural products, pharmacologically active compounds and organic materials.[1] Monopyrollic compounds are observed in increasing number of bioactive compounds. For example, rhazinilam (**1**, Figure 3.1)[2] and its fomyl-derivative rhazinal (**2**, Figure 3.1)[3], derived from plant, are recognised as rather potent spindle-toxins.[3a] The arylated pyrroles present important bioactivities, such as, C2, C3 and C5 triarylated pyrrole (**3**, Figure 3.1)[4] has been reported to be a glucagon receptor antagonist. 3,4-Diarylated pyrroles including lamellarin (**4**, Figure 3.1), separated from various marine organisms, also show considerable potential for the treatment of various cancers.[5]

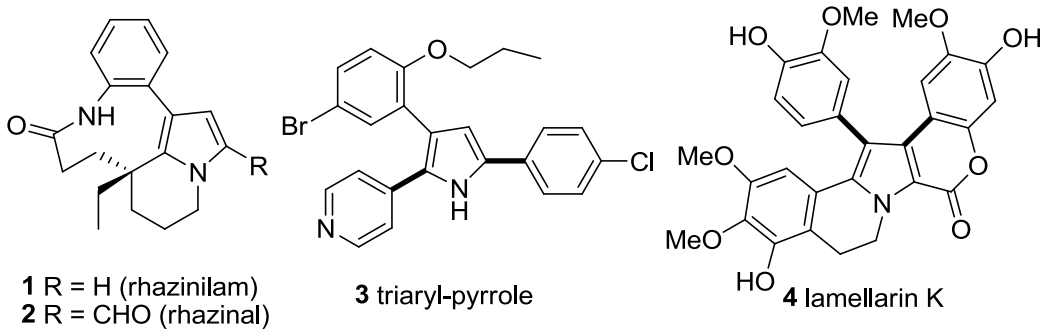
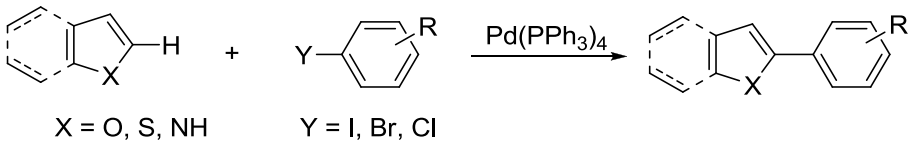


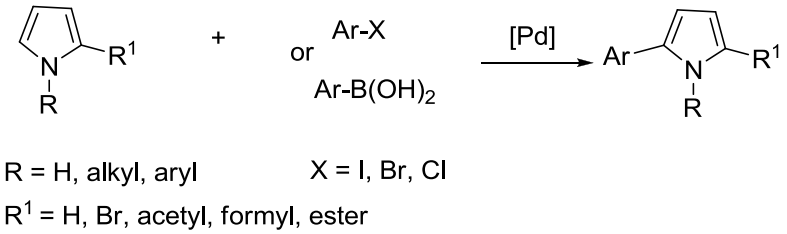

**Figure 3.1**. Examples of pyrrole-containing bioactive compounds.

As depicted in the previous chapters, the classical palladium-catalyzed reactions such as Stille, Suzuki or Negishi couplings allow the formation of a wide variety of polyaryls.[6] However, for these couplings, the preliminary synthesis of (poly)organometallic derivatives is required, and such synthesis might be tricky, especially with heteroarenes. Moreover, these reactions provide a stoichiometric amount of metallic side products, from which undesired contamination could be potentially harmful for pharmaceutical, agrochemical and related biological applications. As early as 1985, Ohta and co-workers reported that the arylation of several heteroaromatics,[7] including pyrroles, with aryl halides proceed, in moderate to good yields, *via* a C-H bond activation,[8,9] using $Pd(PPh_3)_4$ as the catalyst (Scheme 3.1).




**Scheme 3.1**. $Pd(PPh_3)_4$ catalyzed arylation of heteroaromatics.

Since these results, the palladium-catalyzed direct arylation of pyrroles with aryl halides has proved to be a very powerful method for the synthesis of a wide variety of arylated pyrroles (Scheme 3.2).[10-14]




**Scheme 3.2**. Palladium-catalyzed arylation of pyrroles.

In the course of the palladium-catalyzed direct arylations of pyrroles, the most reactive positions are generally the carbons C2 and C5; whereas, the positions C3 and C4 display a poor reactivity (Fig. 3.2).[8g]

In most cases, intramolecular arylations[11] or intermolecular C5-arylations of C2-substituted pyrroles[12,13] have been reported.

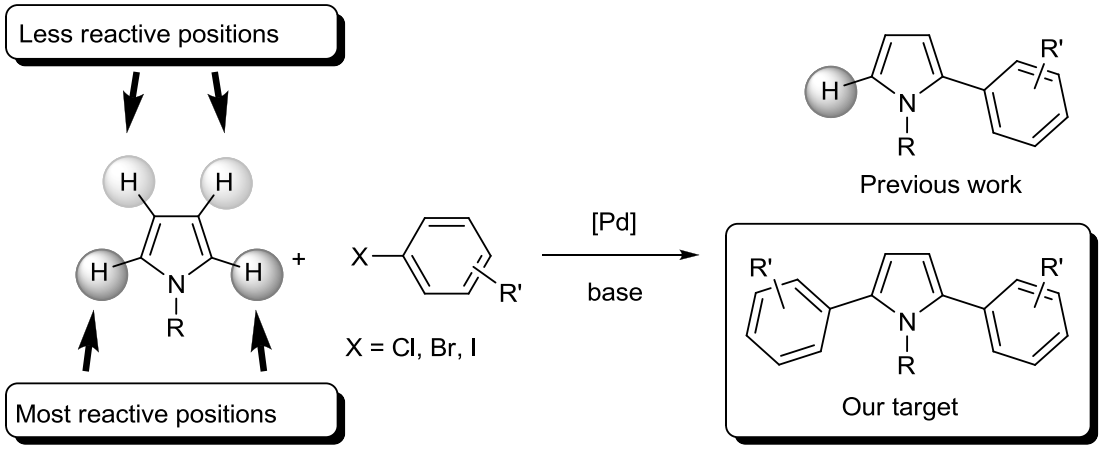
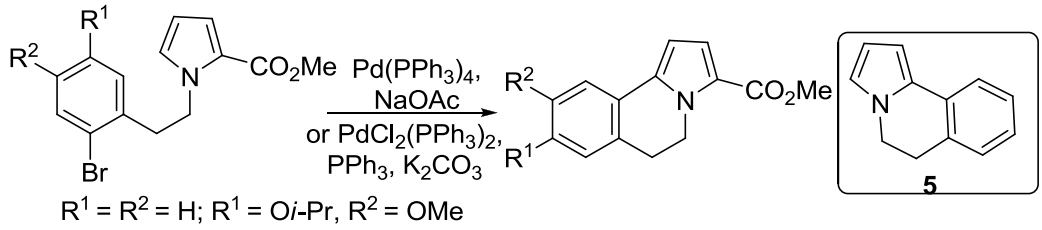


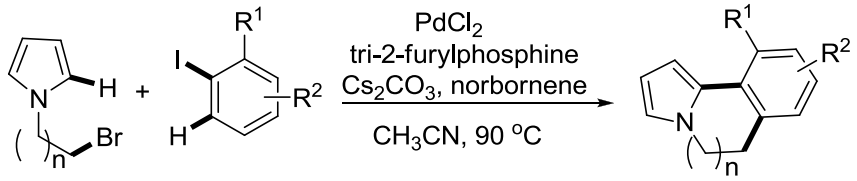

**Figure 3.2**. Regioselectivity of the arylation of pyrroles.

The intramolecular arylation of pyrrole derivatives has been employed for access to

5,6-dihydro-pyrrolo[2,1-*a*]isoquinoline framework **5** (Scheme 3.3) since its unique tricyclic structure has been found in bioactive lamellarins (**4**, Figure 3.1). Álvarez and Olsen reported a concise and efficient route to **5** (Scheme 3.3) by using $Pd(PPh_3)_4$ or $PdCl_2(PPh_3)_2$ as the catalyst *via* C2-arylation (Scheme 3.3).[5,10b] In 2006, Lautens and co-workers reported a strategy, based on a palladium-catalyzed/norbornene-mediated sequential aromatic alkylation/aryl-heteroaryl coupling reaction and involving an aromatic $sp^2$ C-H functionalization as the key step (Scheme 3.4).[10c] The cyclization of similar tricycle compounds was also achieved in Cuny's group by using palladium acetate and $Cs_2CO_3$ in the presence of Xantphos.[10e]

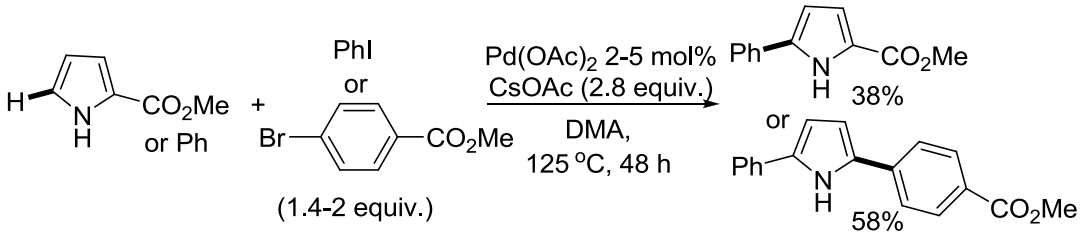



**Scheme 3.3**. Palladium-catalyzed cyclization of pyrrole *via* C2-arylation.




**Scheme 3.4**. Palladium-catalyzed aryl-heteroaryl coupling reaction.

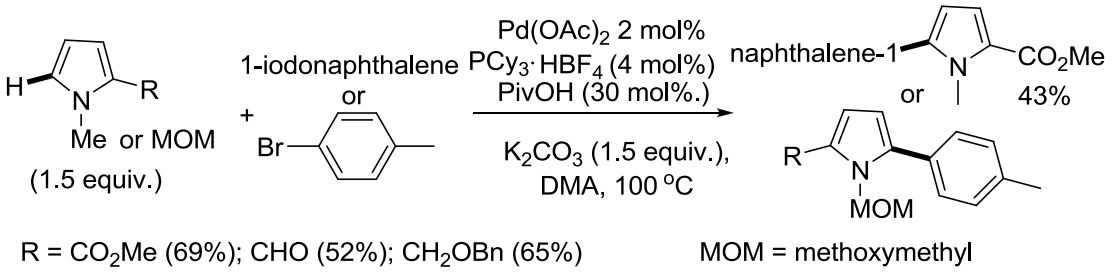
The palladium-catalyzed intermolecular C5-arylation of C2-substituted pyrrole compounds was studied in Sames group[12b,12c] and Fagnou group[12d,12g]. Sames described a phosphine-free palladium catalytic system for the C5-arylation of free (N-H) pyrroles (Scheme 3.5).[12c]



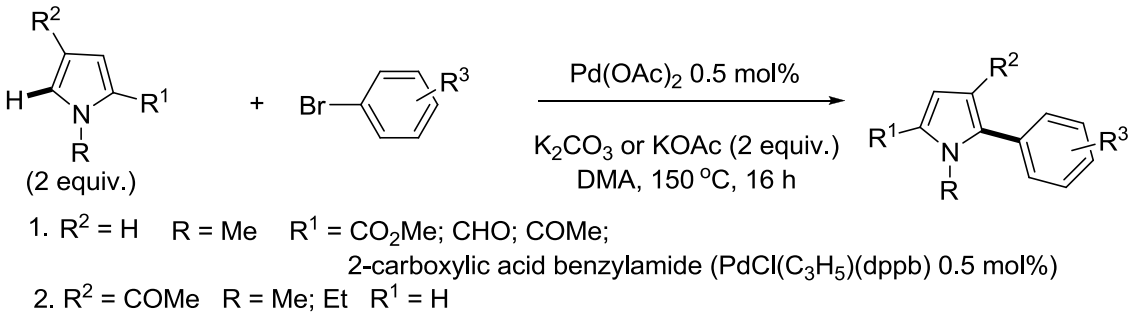

**Scheme 3.5**. Palladium-catalyzed C5-arylation of free (N-H) pyrroles.

Similarly, Fagnou and co-workers described the C5-arylation of *N*-protected pyrroles using palladium acetate in the presence of phosphine ligand and pivalate (Scheme 3.6).[12d] Similar work

has been developed in Doucet' group, but using low loadings of phosphine-free palladium catalyst with a wide variety of aryl bromides with high regioselectivities (Scheme 3.7).[12e-12h]

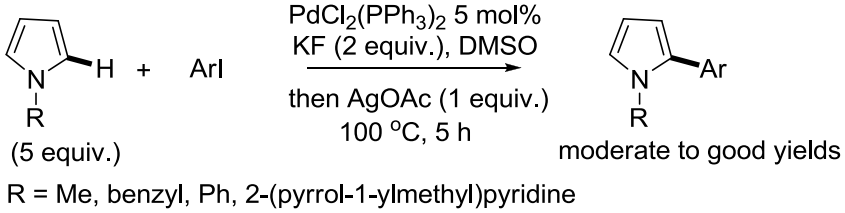



**Scheme 3.6**. Palladium-catalyzed C5-arylation of *N*-protected pyrroles.

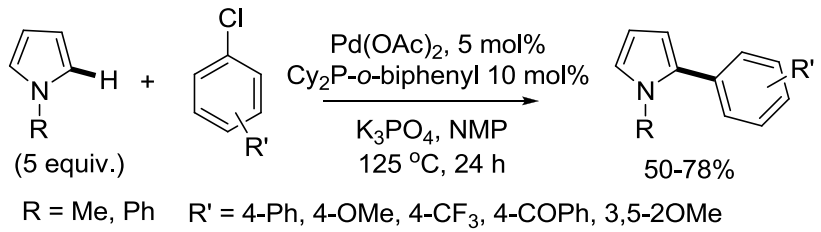



**Scheme 3.7** . Palladium-catalyzed C5-arylation of *N*-protected pyrroles under phosphine-free conditions.

The *mono*-arylation at C2 of some non-substituted 1-alkylpyrroles or 1-arylpyrroles has also been described (Scheme 3.2).[14] Gryko and co-workers investigated the conditions to perform the regioselective arylation of C2-position of *N*-substituted pyrroles by using $PdCl_2(PPh_3)_2$ and silver acetate (Scheme 3.8).[14a] Daugulis extended the substrate scope to aryl chlorides, by employing palladium acetate (5 mol%) with 2-(dicyclohexylphosphino)biphenyl ligand (10 mol%) using an excess of *N*-methylpyrrole (Scheme 3.9).[4]

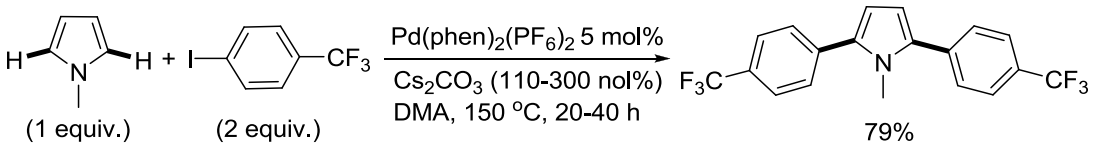



**Scheme 3.8**. Palladium-catalyzed *mono*- C2-arylation of non-substituted 1-alkylpyrroles or 1-arylpyrroles.



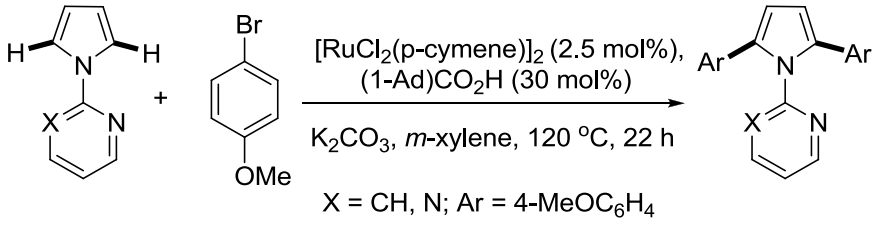

**Scheme 3.9**. Palladium-catalyzed monoarylation of *N*-protected pyrrole with aryl chloride.

On the other hand, to our knowledge, only one example of palladium-catalyzed *di*-arylation of a pyrrole has been described (Scheme 3.10).[15] From 1-methylpyrrole and 4-(trifluoromethyl)phenyliodide using 5 mol% Pd(1,10-phenanthroline)$_2$(PF$_6$)$_2$ as the catalyst, Shibahara and co-workers obtained the 2,5-diarylated 1-methylpyrrole in 79% yield.



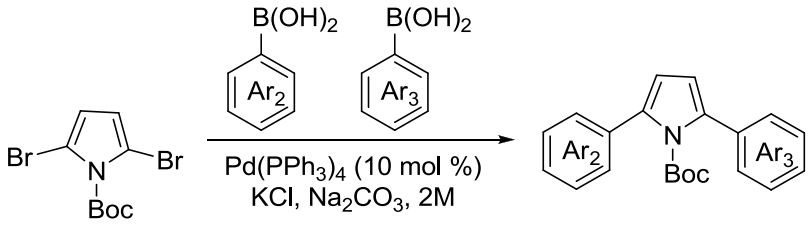

**Scheme 3.10**. One example for palladium-catalyzed *di*-arylation of a pyrrole.

It should be noted that, Ackermann and co-workers, have also reported an elegant regioselective 2,5-diarylation of a *N*-pyridylpyrrole and also of a *N*-pyrimidylpyrrole using a ruthenium catalyst (Scheme 3.11).[16] For these reactions, the pyridyl or pyrimidyl substituent on the nitrogen atom act as a directing group to favor the regioselective arylations at both C2 and C5 positions of the pyrrole.




**Scheme 3.11**. Ruthenium-catalyzed arylation of pyrroles.

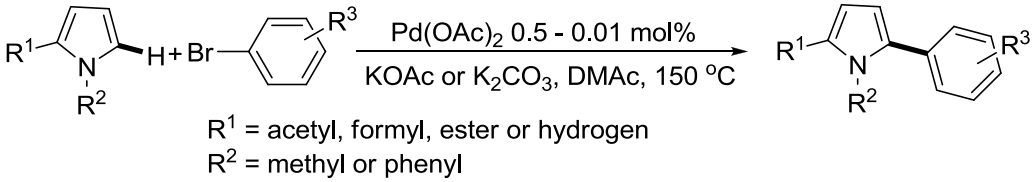
However, to date, Suzuki, Stille or Negishi couplings reactions remain the most classical methods to prepare polyarylated pyrrole derivatives.[17] For example, in 2009, Dauban and co-workers described the 2,5-diarylation of a 2,5-dibromopyrrole using Suzuki coupling (Scheme 3.12).[17d]




**Scheme 3.12**. Palladium-catalyzed 2,5-diarylation of a 2,5-dibromopyrrole *via* Suzuki coupling.

As only one example of palladium-catalyzed direct *di*-arylation of pyrrole derivatives has been reported, the discovery of a procedure allowing a more general access to symmetrically or non-symmetrically substituted 2,5-diarylpyrroles is desirable.

Recently our laboratory has reported that the reaction of pyrroles bearing various substituents at C2 with aryl bromides using $Pd(OAc)_2$ as the catalyst, KOAc as the base and DMAc as the solvent led to the C5 arylated heteroaromatics in high yields.[18] Our laboratory has also reported a few examples of *mono*-arylation of 1-methylpyrrole (Scheme 3.13).




**Scheme 3.13**. Palladium-catalyzed *mono*-arylation of 1-methylpyrrole.

In this chapter, starting from 1-methylpyrrole or 1-phenylpyrrole as reactants, we would like to report the access to: i) symmetrical 2,5-diarylated pyrroles with a set of aryl bromides; ii) 2,3,4,5-tetraarylated pyrroles; iii) unsymmetrically 2,5-diarylated pyrroles *via* sequential C2 catalytic arylation followed by C5 different catalytic arylation.

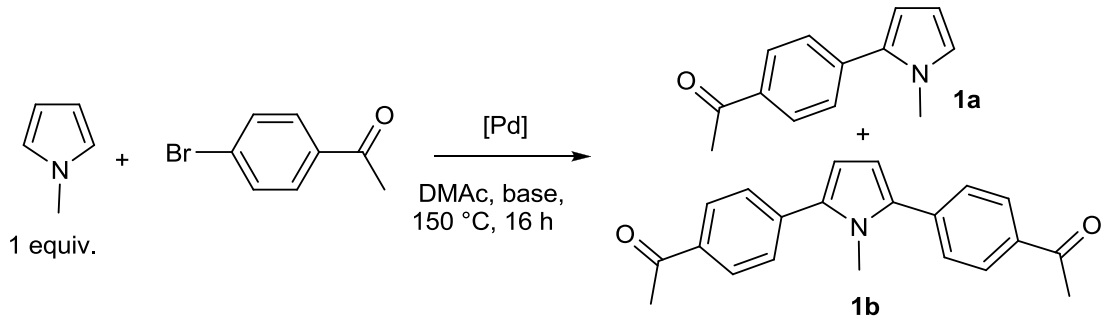
## 3.2 Results and Discussions

### 3.2.1 Synthesis of palladium-catalyzed symmetrical 2,5-diarylation of pyrroles

#### 3.2.1.1 Optimization of palladium-catalyzed 2,5-diarylation of pyrroles

First, we have considered the reaction of 1-methylpyrrole with 4-bromoacetophenone to reach the formation of the 2,5-diarylated pyrrole **1b** (Scheme 3.14). We observed that from 2.2 equiv. of

4-bromoacetophenone and 1 equiv. of 1-methylpyrrole, with 4 equiv. of KOAc as the base and DMAc as the solvent, using only 0.1 mol% $Pd(OAc)_2$ as the catalyst, the 2,5-diarylated pyrrole **1b** was only obtained in low yield due to the formation of a mixture of mono- and diarylated pyrroles **1a** and **1b** (Table 3.1, entry 1). The use of an higher $Pd(OAc)_2$ loading (1 mol%) (Table 3.1, entry 2) did not allow to improve the yield in **1b** (Table 3.1, entry 2). This result reveals that the concentration of active Pd species is relatively similar with these two different concentrations of $Pd(OAc)_2$. For this ligand-free procedure, under relatively high palladium concentrations, so-called "palladium black", which is inactive for such catalyzed reactions, forms very rapidly. Consequently, the conversions of aryl bromides and the yields of coupling products are not increased even with a higher catalyst loading.




**Scheme 3.14**. Palladium-catalyzed 2,5-diarylation of 1-methylpyrrole with 4-bromoacetophenone.

Therefore, we employed 1 mol% $PdCl(C_3H_5)(dppb)$, which forms less rapidly "palladium black", as the catalyst, as we recently demonstrated it was one of the best catalyst for the direct arylation of some thiophenes.[9b] A higher yield of 42% in **1b** was obtained when 2.5 equiv. of 4-bromoacetophenone were employed with this catalyst (Table 3.1, entry 3). Then, we employed a larger excess of 4-bromoacetophenone. With 3 equiv. of this aryl bromide a higher yield of 46% in **1b** was obtained; whereas the use of 4 equiv. led to a lower yield of 30% (Table 3.1, entries 4 and 5).

**Table 3.1.** Influence of reaction parameters for the palladium-catalyzed direct 2,5-diarylation of 1-methylpyrrole with 4-bromoacetophenone (Scheme 3.14).[a]

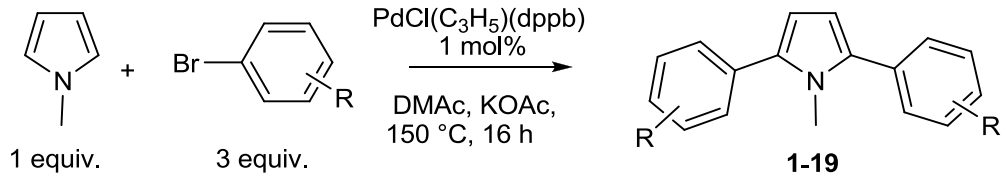
| Entry | Catalyst (mol%) | Equiv. of 4-bromoacetophenone | Yield in **1b** (%) |
|---|---|---|---|
| 1 | $Pd(OAc)_2$ (0.1) | 2.2 | 27 |

| | | | |
|---|---|---|---|
| 2 | $Pd(OAc)_2$ (1) | 2.5 | 21 |
| 3 | $PdCl(C_3H_5)$(dppb) (1) | 2.5 | 42 |
| 4 | $PdCl(C_3H_5)$(dppb) (1) | 3 | 46 |
| 5 | $PdCl(C_3H_5)$(dppb) (1) | 4 | 30 |

[a] 1-methylpyrrole (1 equiv.), KOAc (4 equiv.), DMAc, 150 °C, 16 h, isolated yields in **1b**.

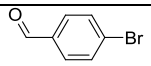
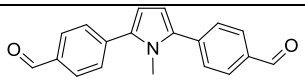
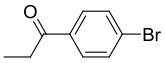
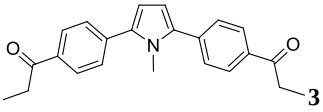
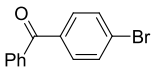
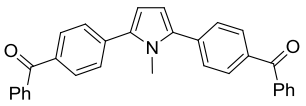
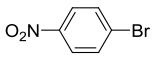
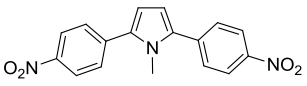
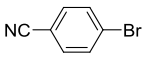
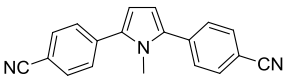
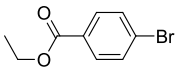
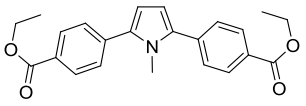
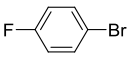
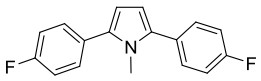
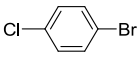
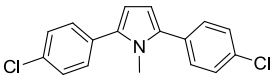
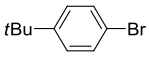
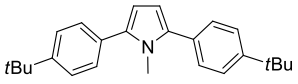
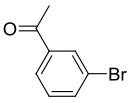
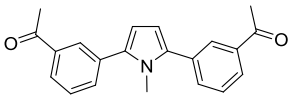
### 3.2.1.2 Scope for palladium-catalyzed direct 2,5-diarylation of 1-methylpyrrole with aryl bromides

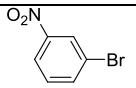
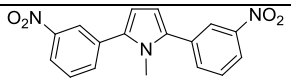
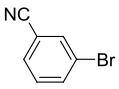
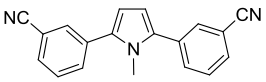
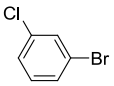
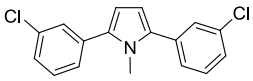
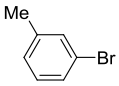
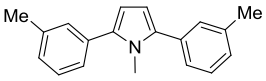
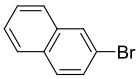
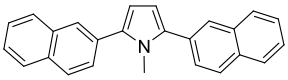
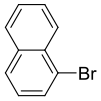
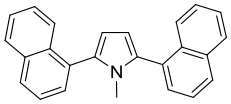
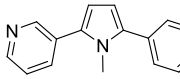
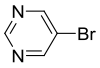
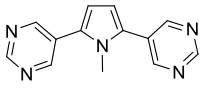
We examined the scope of this procedure using *para*-, *meta*- or *ortho*-substituted aryl bromides and also heteroaryl bromides (Scheme 3.15, Table 3.2). The electron-deficient *para*-substituted aryl bromides, 4-bromobenzaldehyde, 4-bromopropiophenone, 4-bromobenzophenone, 4-bromonitrobenzene or 4-bromobenzonitrile reacted with 1-methylpyrrole to give the expected products **2**-**6** in 58-69% yields (Table 3.2, entries 1-5). A high yield of 81% for **7** was obtained using ethyl 4-bromobenzoate (Table 3.2, entry 6). From 4-chlorobromobenzene, **9** was obtained in 62% yield (Table 3.2, entry 8). In the course of this reaction, no cleavage of the C-Cl bond was observed, allowing further transformations. Surprisingly, even the electron-rich aryl bromide, 4-*tert*-butylbromobenzene was successfully coupled with 1-methylpyrrole to give **10** in 52% yield (Table 3.2, entry 9). A set of *meta*-substituted aryl bromides was also employed. The best yields were obtained from 3-bromoacetophenone and 3-bromonitrobenzene to give **11** and **12** in 78 and 80% yields, respectively (Table 3.2, entries 10 and 11). Lower yields were obtained in the presence of 3-bromobenzonitrile, 3-chlorobromobenzene or 3-bromotoluene (Table 3.2, entries 12-14). 1- and 2-bromonaphthalenes also gave the desired products **16** and **17** in 65 and 68% yields (Table 3.2, entries 15 and 16). We also employed heteroaryl bromides. The first attempt to prepare **18** from 3-bromopyridine led to a mixture of di- and tri-arylated pyrrole, and **18** was only isolated in 41% yield (Table 3.2, entry 17). However, the use of only 2.3 equiv. instead of 3 equiv. of 3-bromopyridine allows to obtain **18** in a higher yield of 62% (Table 3.2, entry 18). A more selective reaction was observed in the presence of 5-bromopyrimidine to give **19** in 71% yield (Table 3.2, entry 19).




**Scheme 3.15**. Palladium-catalyzed 2,5-diarylation of 1-methylpyrrole.

**Table 3.2**. Scope of the palladium-catalyzed direct 2,5-diarylation of 1-methylpyrrole (Scheme 3.15).[a]

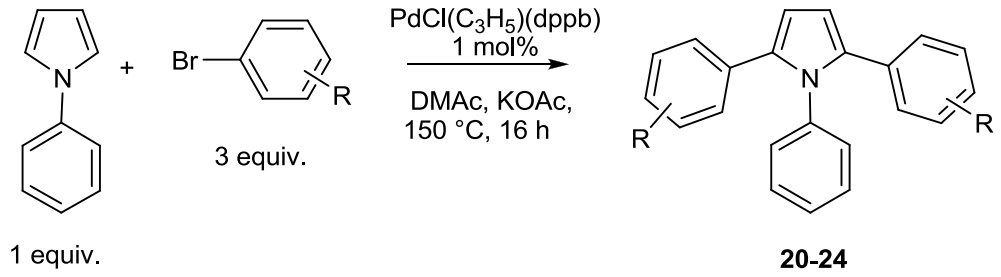
| Entry | Aryl bromide | Product | Yield (%) |
|---|---|---|---|
| 1 |  |  **2** | 69 |
| 2 |  |  **3** | 60 |
| 3 |  |  **4** | 62 |
| 4 |  |  **5** | 67 |
| 5 |  |  **6** | 58 |
| 6 |  |  **7** | 81 |
| 7 |  |  **8** | 69 |
| 8 |  |  **9** | 62 |
| 9 |  |  **10** | 52 |
| 10 |  |  **11** | 78 |

| | | | |
|---|---|---|---|
| 11 |  |  **12** | 80 |
| 12 |  |  **13** | 61 |
| 13 |  |  **14** | 63 |
| 14 |  |  **15** | 62 |
| 15 |  |  **16** | 65 |
| 16 |  |  **17** | 68 |
| 17 |  |  **18** | 41 |
| 18 | | | 62[b] |
| 19 |  |  **19** | 71 |

[a] $PdCl(C_3H_5)(dppb)$ (0.01 equiv.), aryl bromide (3 equiv.), 1-methylpyrrole (1 equiv.), KOAc (4 equiv.), DMAc, 150 ℃, 16 h, isolated yields. [b] 3-bromopyridine 2.3 equiv.

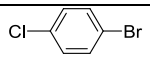
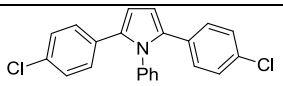
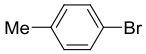
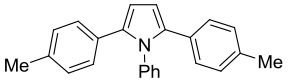
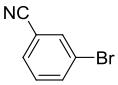
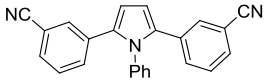
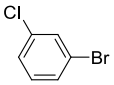
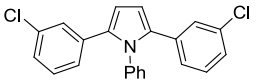
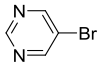
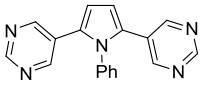
### 3.2.1.3 Scope for palladium-catalyzed direct 2,5-diarylation of 1-phenylpyrrole with aryl bromides

Then, arylation reactions of 1-phenylpyrrole with aryl bromides were examined (Scheme 3.16, Table 3.3). With this reactant, again only the C2 and C5 diarylated pyrroles **20**-**24** were isolated. However, lower yields with 1-methylpyrrole were obtained. First, we studied the reactivity of two para-substituted aryl bromides. In the presence of 4-chlorobromobenzene or 4-bromotoluene, the products **20** and **21** were obtained in 35 and 33% yields, respectively (Table 3.3, entries 1 and 2). Higher yields of 54 and 52% were obtained in the presence of the meta-substituted aryl bromides, 3-bromobenzonitrile or 3-chlorobromobenzene (Table 3.3, entries 3 and 4). Finally, from 5-bromopyrimidine, **24** was formed in 51% yield.




**Scheme 3.16**. Palladium-catalyzed 2,5-diarylation of 1-phenylpyrrole.

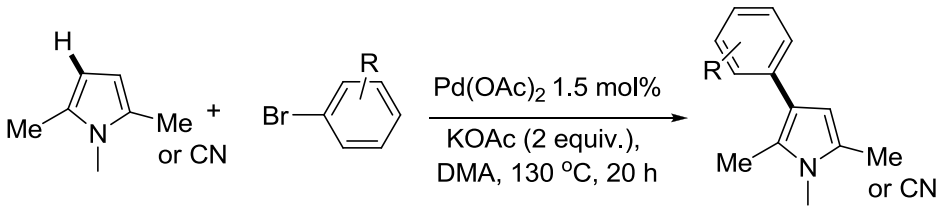
**Table 3.3**. Scope of the palladium-catalyzed direct 2,5-diarylation of 1-phenylpyrrole (Scheme 3.16).[a]

| Entry | Aryl bromide | Product | Yield (%) |
|---|---|---|---|
| 1 |  |  **20** | 35 |
| 2 |  |  **21** | 33 |
| 3 |  |  **22** | 54 |
| 4 |  |  **23** | 52 |
| 5 |  |  **24** | 51 |

[a] $PdCl(C_3H_5)(dppb)$ (0.01 equiv.), aryl bromide (3 equiv.), 1-phenylpyrrole (1 equiv.), KOAc (4 equiv.), DMAc, 150 ℃, 16 h, isolated yields.

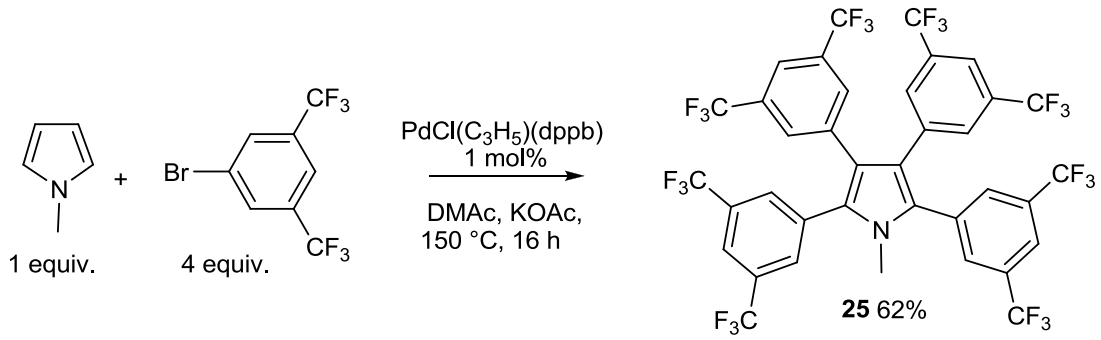
## 3.2.2 Synthesis of palladium-catalyzed 2,3,4,5-tetraarylated pyrroles

The arylation of less active C3- or C4- position of 2,5-substituted pyrrole was obtained in our laboratory by using $Pd(OAc)_2$ (1.5 mol%) , with KOAc (2 equiv.), in the absence of ligand, in DMA at 130 $^oC$ for 20 h (Scheme 3.17).[19] Aryl bromides with electron-deficient and sterically hindered substituents were well tolerated. However, we never succeed in getting the multiarylated compounds in one step.




**Scheme 3.17**. Palladium-catalyzed C3- or C4- arylation of pyrrole.

However, we found that the reactivity of 3,5-bis(trifluoromethyl)bromobenzene with 1-methylpyrrole was quite unusual as compared to the other aryl bromides. The reaction of 3 equiv. of this aryl bromide with 1-methylpyrrole led to a mixture of di-, tri- and even some tetraarylated pyrrole according to GC/MS analysis. Therefore, in order to obtain more selectively the 2,3,4,5-tetraarylated pyrrole **25**, we employed 4 equiv. of this aryl bromide. Under these conditions, **25** was the major product of the reaction with 85% selectivity and 62% yield (Scheme 3.18).




**Scheme 3.18**. Palladium-catalyzed tetraarylation of 1-methylpyrrole.

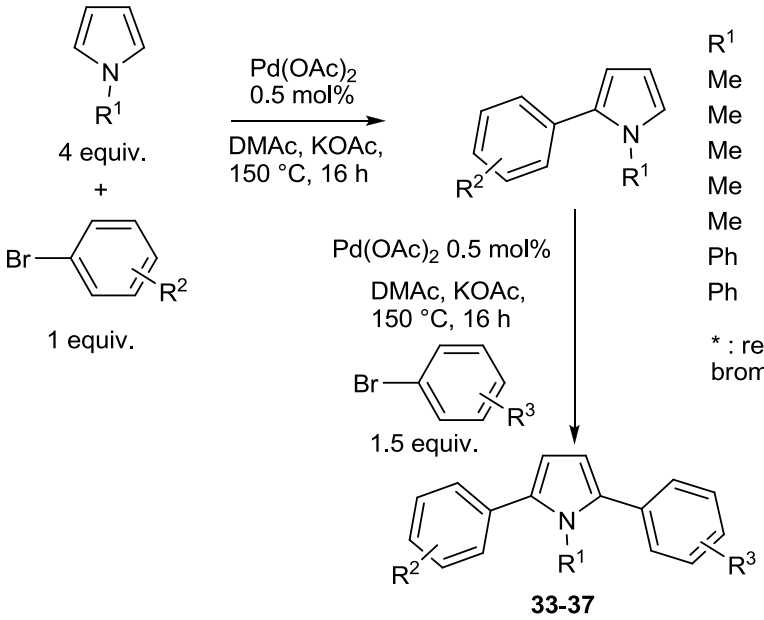
### 3.2.3 Synthesis of palladium-catalyzed unsymmetrically 2,5-diarylated pyrroles

#### 3.2.3.1 Synthesis of palladium-catalyzed C2-arylated pyrroles

We studied the sequential C2 arylation followed by C5 different arylation of pyrroles to prepare non-symmetrical 2,5-diarylpyrroles (Scheme 3.19, Table 3.4). The yields of palladium-catalyzed direct C5 arylations of 2-arylpyrroles certainly depends on the electronic properties of both the aryl substituent on pyrroles and on the aryl bromide. Therefore, we initially compared the yields of reactions using the two possible combination of starting materials to prepare a specific 2,5-diarylpyrrole. For both steps we employed 0.5 mol% $Pd(OAc)_2$ as the catalyst as we

previously observed that such phosphine-free conditions allows efficient direct monoarylation of some pyrrole derivatives.[18]

For the first step (Scheme 3.19, top), the electron deficient aryl bromides, 4-bromobenzonitrile or 4-bromonitrobenzene gave very selectively the mono-C2-arylated products **26**, **30** and **31**. The C2,C5-diarylated pyrroles were only produced as traces. A high yield in **29** was also obtained from 2-bromonaphthalene. On the other hand, surprisingly the reactions with 4-bromotoluene and 4-tert-butylbromobenzene gave mixtures of mono- and di-arylated pyrroles (mono:di ratio = 75:25) although we employed a 1:4 ratio of aryl bromide and pyrrole derivative. The second arylation of pyrroles appears to be favored by the presence of electron donating groups on the aryls of 2-arylpyrroles.




| $R^1$ | $R^2$ | Prod. | Yield (%) |
|---|---|---|---|
| Me | 4-CN | **26** | 83 |
| Me | 4-Me | **27** | 66 |
| Me | 4-*t*Bu | **28** | 56 |
| Me | * | **29** | 89 |
| Me | 4-$NO_2$ | **30** | 81 |
| Ph | 4-CN | **31** | 80 |
| Ph | 4-Me | **32** | 52 |

* : reaction with 2-bromonaphthalene

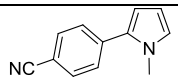
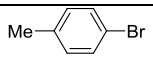
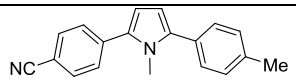
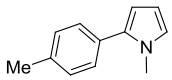
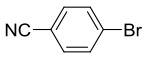
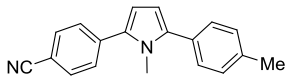
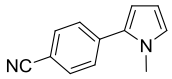
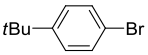
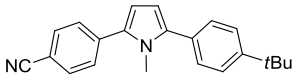
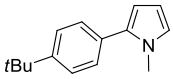
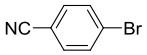
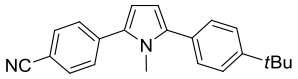
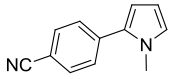
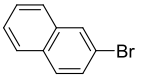
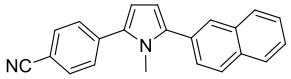
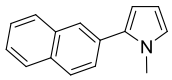
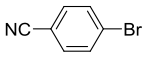
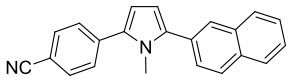
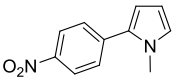
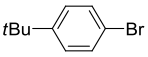
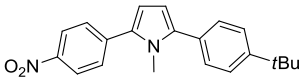
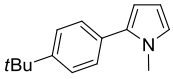
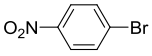
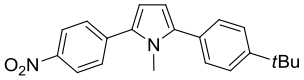
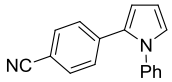
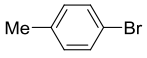
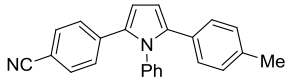
**Scheme 3.19**. Palladium-catalyzed sequential 2,5-diarylation of 1-methylpyrrole.

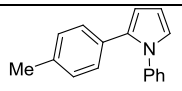
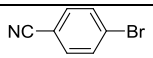
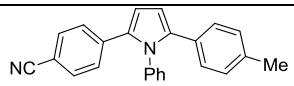
### 3.2.3.2 Scope of palladium-catalyzed sequential C5 different arylation of C2-arylated pyrroles

For the C5 arylation step, we observed that the reaction of 4-bromotoluene with **26** gave **33** in 52% yield, whereas, the reaction of 4-bromobenzonitrile with **27** led to **33** in 71% yield (Table 3.4, entries 1 and 2). Product **34** was also obtained in much higher yield by coupling of 4-bromobenzonitrile with **28**, than using 4-tert-butylbromobenzene and **26** (Table 3.4, entries 3 and 4). On the other hand, very similar yields in **35** were obtained using both reaction pathways

(Table 3.4, entries 5 and 6). For the Synthesis of **36** and **37**, the best yields were again obtained when using the most electron-deficient aryl bromide for the second step (Table 3.4, entries 7-10). In summary, for the synthesis of such non-symmetrical 2,5-diarylpyrroles, by this procedure, high yields were obtained for both steps with electron-deficient aryl bromides. On the other hand, with electron-rich aryl bromides moderate yields were obtained due to the formation of some 2,5-diarylpyrroles for the reaction with 1-methylpyrrole or due to the poor reactivity of such aryl bromides for the C5 arylation of some 2-arylpyrroles.

**Table 3.4.** Scope of the palladium-catalyzed direct sequential 2,5-diarylation of 1-methyl- or 1-phenyl-2-arylpyrroles (Scheme 3.19). [a]

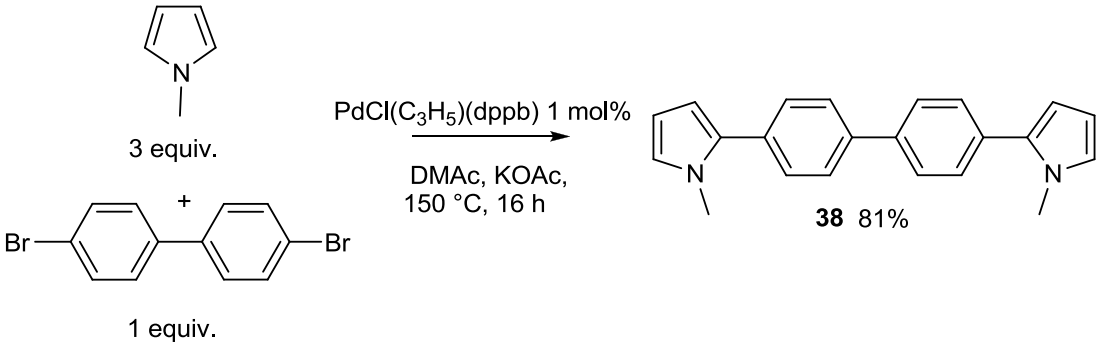
| Entry | Pyrrole | Aryl bromide | Product | Yield (%) |
|---|---|---|---|---|
| 1 |  **26** |  |  **33** | 52 |
| 2 |  **27** |  |  **33** | 71 |
| 3 |  **26** |  |  **34** | 32 |
| 4 |  **28** |  |  **34** | 74 |
| 5 |  **26** |  |  **35** | 87 |
| 6 |  **29** |  |  **35** | 90 |
| 7 |  **30** |  |  **36** | 42 |
| 8 |  **28** |  |  **36** | 80 |
| 9 |  **31** |  |  **37** | 55 |

| | | | | | |
|---|---|---|---|---|---|
| 10 |  **32** |  |  **37** | | 86 |

[a] $Pd(OAc)_2$ (0.005 equiv.), aryl bromide (1.5 equiv.), 1-methyl- or 1-phenyl-2-arylpyrrole (1 equiv.), KOAc (2 equiv.), DMAc, 150 ℃, 16h, isolated yields.

### 3.2.4 Synthesis of 4,4'-diheteroarylation of 4,4'-dibromobiphenyl

The 4,4′-diheteroarylation of 4,4′-dibromobiphenyl was also studied (Scheme 3.19). From 3 equiv. of 1-methylpyrrole and 1 equiv. of 4,4′-dibromobiphenyl in the presence of 1 mol% $PdCl(C_3H_5)(dppb)$, the desired product **38** was produced in 81% yield (Scheme 3.20).




**Scheme 3.20**. Palladium-catalyzed arylation of 1-methylpyrrole with 4,4′-dibromobiphenyl.

## 3.3 Conclusion

In summary, in this chapter we have demonstrated that the palladium-catalyzed direct diarylation at C2 and C5 of 1-methylpyrrole or 1-phenylpyrrole using 1 mol% $PdCl(C_3H_5)(dppb)$ as the catalyst and KOAc as the base proceed with both electron-poor and some electron-rich aryl bromides. A variety of substituents on the aryl bromide such as ester, acetyl, formyl, propionyl, benzoyl, nitro, nitrile, chloro, fluoro or *tert*-butyl are tolerated. The sequential C2 arylation of 1-methylpyrrole or 1-phenylpyrrole followed by C5 arylation reveals that electron-deficient aryl bromide should preferably be employed. It should be noted that from 3,5-bis(trifluoromethyl)bromobenzene and 1-methylpyrrole, the 2,3,4,5-tetrarylated product was formed in good yield. To our knowledge this is the first example of a catalyzed direct tetraarylation of a pyrrole. Moreover, these arylations were performed using only 0.5-1 mol% of air-stable catalyst. The major by-products of these reactions are a base associated to HBr, and the method avoids the preliminary preparation of a requisite (poly)organometallic derivative, reducing

the number of steps to prepare these compounds. For these reasons, this process gives an economically viable and environmentally attractive access to polyarylated pyrrole derivatives.

## 3.4 Experimental Details

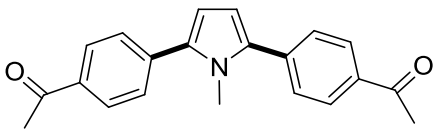
DMAc (*N*,*N*-dimethylacetamide) (99%) was purchased from Acros. KOAc (99%), $[Pd(C_3H_5)Cl]_2$ (56.5%) and dppb [1,4-bis(diphenylphosphino)butane] (98%) were purchased from Alfa Aesar and used as received without any further purification.

**Preparation of the $PdCl(C_3H_5)$(dppb) catalyst:**[20] 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 yellow powder was used without purification. $^{31}P$ NMR (81 MHz, $CDCl_3$) $\delta$ = 19.3 (s).

**General procedure for the Synthesis of 1-24**

As a typical experiment, the reaction of the aryl bromide (3 mmol), 1-methylpyrrole (0.081 g, 1 mmol) or 1-phenylpyrrole (0.143 g, 1 mmol), and KOAc (0.392 g, 4 mmol) at 150 ℃ for 16 h in DMAc (3 mL) in the presence of $PdCl(C_3H_5)$(dppb) (6.1 mg, 0.01 mmol) under argon afforded the corresponding diarylation product after extraction with dichloromethane, evaporation and filtration on silica gel.

**2,5-Bis(4-acetylphenyl)-1-methylpyrrole 1b**

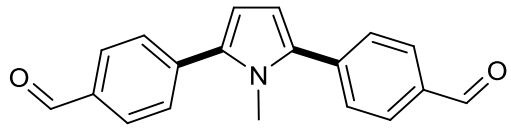



From 4-bromoacetophenone (0.597 g, 3 mmol) and 1-methylpyrrole (0.081 g, 1 mmol), **1** was obtained in 46% (0.146 g) yield as a yellow solid.

Eluent pentane: diethylether 4:3

$^{1}$H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.95 (d, *J* = 7.8 Hz, 4H), 7.50 (d, *J* = 7.8 Hz, 4H), 6.39 (s, 2H), 3.61 (s, 3H), 2.56 (s, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): δ 197.5, 137.5, 137.3, 135.3, 128.7, 128.2, 110.7, 35.0, 26.6. Elemental analysis: calcd (%) for $C_{21}H_{19}NO_2$ (317.38): C 79.47, H 6.03, N 4.41; found: C 79.69, H 6.09, N 4.31.

**2,5-Bis(4-formylphenyl)-1-methylpyrrole 2**

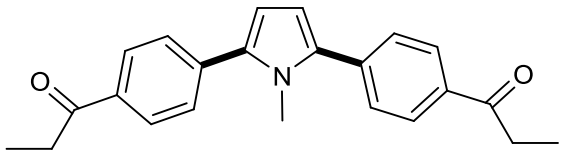



From 4-bromobenzaldehyde (0.555 g, 3 mmol) and 1-methylpyrrole (0.081 g, 1 mmol), **2** was obtained in 69% (0.200 g) yield as a brown solid.

Eluent pentane: diethylether 4:3

$^{1}$H NMR (400 MHz, $CDCl_3$, 25 °C): δ 9.96 (s, 2H), 7.87 (d, *J* = 7.0 Hz, 4H), 7.57 (d, *J* = 7.0 Hz, 4H), 6.43 (s, 2H), 3.63 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): δ 191.6, 138.7, 137.6, 134.7, 130.1, 128.6, 111.4, 35.2. Elemental analysis: calcd (%) for $C_{19}H_{15}NO_2$ (289.33): C 78.87, H 5.23, N 4.84; found: C 78.96, H 5.35, N 4.89.

**2,5-Bis(4-propionylphenyl)-1-methylpyrrole 3**

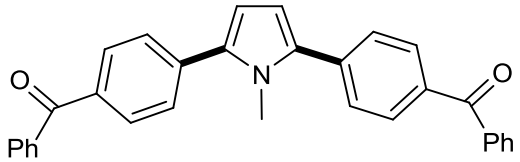



From 4-bromopropiophenone (0.639 g, 3 mmol) and 1-methylpyrrole (0.081 g, 1 mmol), **3** was obtained in 60% (0.207 g) yield as a grass green solid.

Eluent pentane: diethylether 3:1

$^{1}$H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.96 (d, *J* = 7.0 Hz, 4H), 7.50 (d, *J* = 7.0 Hz, 4H), 6.38 (s, 2H), 3.61 (s, 3H), 2.96 (q, *J* = 7.5 Hz, 4H), 1.19 (t, *J* = 7.5 Hz, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): δ 200.2, 137.4, 137.3, 135.1, 128.4, 128.3, 110.6, 34.9, 31.7, 8.3. Elemental analysis: calcd (%) for $C_{23}H_{23}NO_2$ (345.43): C 79.97, H 6.71, N 4.05; found: C 80.11, H 6.64, N 3.89.

**{4-[5-(4-Benzoyl-phenyl)-1-methylpyrrol-2-yl]-phenyl}-phenyl-methanone 4**

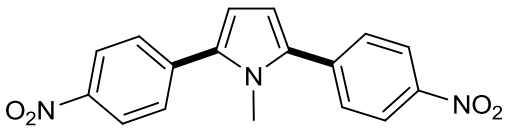



From 4-bromobenzophenone (0.783 g, 3 mmol) and 1-methylpyrrole (0.081 g, 1 mmol), **4** was obtained in 62% (0.273 g) yield as a brown solid.

Eluent pentane: diethylether 5:1

$^{1}$H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.83 (d, *J* = 7.6 Hz, 4H), 7.78 (d, *J* = 7.6 Hz, 4H), 7.60-7.50 (m, 6H), 7.44 (t, J = 7.6 Hz, 4H), 6.42 (s, 2H), 3.67 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): δ 196.1, 137.7, 137.3, 137.1, 135.7, 132.4, 130.6, 130.0, 128.3, 128.0, 110.7, 35.0. Elemental analysis: calcd (%) for $C_{31}H_{23}NO_2$ (441.52): C 84.33, H 5.25, 3.17; found: C 84.21, H 5.01, N 3.28.

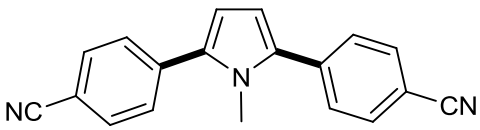
**2,5-Bis(4-nitrophenyl)-1-methylpyrrole 5:**[21]




From 4-bromonitrobenzene (0.606 g, 3 mmol) and 1-methylpyrrole (0.081 g, 1 mmol), **5** was obtained in 67% (0.216 g) yield as a brown solid.

Eluent pentane: diethylether 1:1

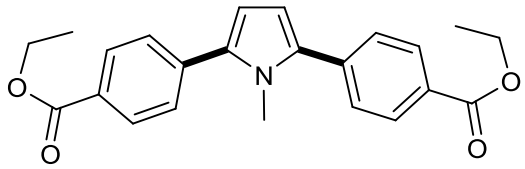
**2,5-Bis(4-cyanophenyl)-1-methylpyrrole 6:**[10g]




From 4-bromobenzonitrile (0.546 g, 3 mmol) and 1-methylpyrrole (0.081 g, 1 mmol), **6** was obtained in 58% (0.164 g) yield as a brown solid.

Eluent pentane: diethylether 2:1

**2,5-Bis(ethyl 4-benzoate)-1-methylpyrrole 7**

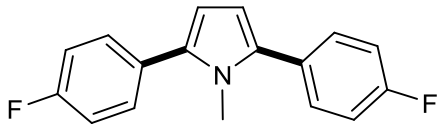


From ethyl 4-bromobenzoate (0.687 g, 3 mmol) and 1-methylpyrrole (0.081 g, 1 mmol), **7** was obtained in 81% (0.305 g) yield as a brown solid.

Eluent pentane: diethylether 3:1

$^{1}$H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.03 (d, *J* = 7.0 Hz, 4H), 7.47 (d, *J* = 7.0 Hz, 4H), 6.37 (s, 2H), 4.33 (q, *J* = 7.5 Hz, 4H), 3.59 (s, 3H), 1.34 (t, *J* = 7.5 Hz, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): δ 166.4, 137.3, 137.2, 129.8, 128.7, 128.1, 110.4, 61.0, 34.9, 14.4. Elemental analysis: calcd (%) for $C_{23}H_{23}NO_4$ (377.43): C 73.19, H 6.14, N 3.71; found: C 73.04, H 6.10, N 3.88.

**2,5-Bis(4-fluorophenyl)-1-methylpyrrole 8**

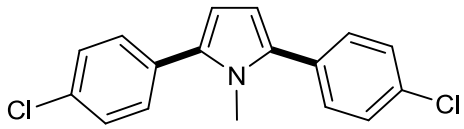


From 4-fluorobromobenzene (0.525 g, 3 mmol) and 1-methylpyrrole (0.081 g, 1 mmol), **8** was obtained in 69% (0.186 g) yield as a red-brown solid.

Eluent pentane

$^{1}$H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.34 (dd, *J* = 8.6, 5.4 Hz, 4H), 7.04 (t, *J* = 8.6 Hz, 4H), 6.19 (s, 2H), 3.47 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): δ 162.0 (d, *J* = 246.8 Hz), 135.7, 130.4 (d, *J* = 8.0 Hz), 129.6, 115.4 (d, *J* = 21.5 Hz), 108.6, 33.9. Elemental analysis: calcd (%) for $C_{17}H_{13}F_2N$ (269.29): C 75.82, H 4.87, N 5.20; found: C 75.90, H 4.74, N 5.39.

**2,5-Bis(4-chlorophenyl)-1-methylpyrrole 9**

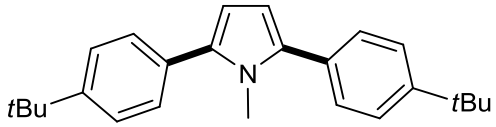



From 4-bromochlorobenzene (0.574 g, 3 mmol) and 1-methylpyrrole (0.081 g, 1 mmol), **9** was obtained in 62% (0.187 g) yield as a colorless solid.

Eluent pentane

$^{1}$H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.30 (s, 8H), 6.22 (s, 2H), 3.48 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): δ 136.1, 132.9, 131.8, 129.9, 128.7, 109.2, 34.3. Elemental analysis: calcd (%) for $C_{17}H_{13}Cl_2N$ (302.20): C 67.57, H 4.34, N 4.63; found: C 67.47, H 4.30, N 4.50.

**2,5-Bis(4-*tert*-butylphenyl)-1-methylpyrrole 10**

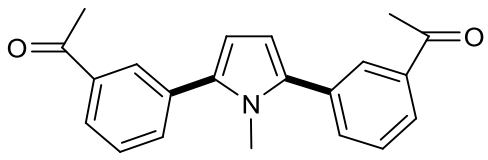



From 4-*tert*-butylbromobenzene (0.639 g, 3 mmol) and 1-methylpyrrole (0.081 g, 1 mmol), **10** was obtained in 52% (0.179 g) yield as a yellow solid.

Eluent pentane

$^{1}$H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.36 (d, *J* = 7.0 Hz, 4H), 7.33 (d, *J* = 7.0 Hz, 4H), 6.21 (s, 2H), 3.54 (s, 3H), 1.29 (s, 18H). $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): δ 149.7, 136.6, 130.8, 128.4, 125.3, 108.3, 34.6, 34.3, 31.4. Elemental analysis: calcd (%) for $C_{25}H_{31}N$ (345.52): C 86.90, H 9.04, N 4.05; found: C 86.98, H 9.18, N 4.23.

**2,5-Bis(3-acetylphenyl)-1-methylpyrrole 11**

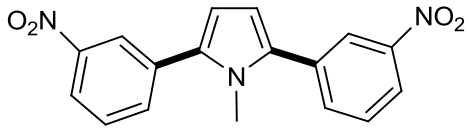



From 3-bromoacetophenone (0.597 g, 3 mmol) and 1-methylpyrrole (0.081 g, 1 mmol), **11** was obtained in 78% (0.247 g) yield as a yellow solid.

Eluent pentane: diethylether 4:3

$^{1}$H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.99 (s, 2H), 7.83 (d, *J* = 7.5 Hz, 2H), 7.60 (d, *J* = 7.5 Hz, 2H), 7.46 (t, *J* = 7.5 Hz, 2H), 6.31 (s, 2H), 3.55 (s, 3H), 2.58 (s, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): δ 198.0, 137.4, 136.4, 133.8, 133.1, 128.9, 128.4, 126.8, 109.5, 34.3, 26.7. Elemental analysis: calcd (%) for $C_{21}H_{19}NO_2$ (317.38): C 79.47, H 6.03, N 4.41; found: C 79.35, H 6.11, N 4.65.

**2,5-Bis(3-nitrophenyl)-1-methylpyrrole 12**

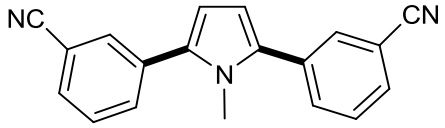



From 3-bromonitrobenzene (0.606 g, 3 mmol) and 1-methylpyrrole (0.081 g, 1 mmol), **12** was obtained in 80% (0.258 g) yield as a orange solid.

Eluent pentane: diethylether 1:1

$^{1}$H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.27 (s, 2H), 8.12 (d, *J* = 7.9 Hz, 2H), 7.74 (d, *J* = 7.9 Hz, 2H), 7.55 (t, *J* = 7.5 Hz, 2H), 6.39 (s, 2H), 3.61 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): δ 148.5, 135.7, 134.5, 134.2, 129.6, 123.1, 121.8, 110.7, 34.5. Elemental analysis: calcd (%) for $C_{17}H_{13}N_3O_4$ (323.30): C 63.15, H 4.05, N 13.00; found: C 63.31, H 4.14, N 12.89.

**2,5-Bis(3-cyanophenyl)-1-methylpyrrole 13**



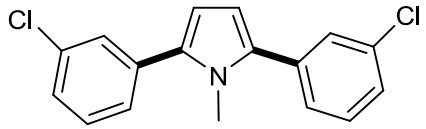

From 3-bromobenzonitrile (0.546 g, 3 mmol) and 1-methylpyrrole (0.081 g, 1 mmol), **13** was obtained in 61% (0.172 g) yield as a white solid.

Eluent pentane: diethylether 2:1

$^{1}$H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.67 (s, 2H), 7.62 (d, *J* = 7.9 Hz, 2H), 7.52 (d, *J* = 7.9 Hz, 2H), 7.48 (t, *J* = 7.5 Hz, 2H), 6.31 (s, 2H), 3.53 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): δ

135.6, 134.3, 132.7, 131.8, 130.5, 129.5, 118.6, 113.0, 110.5, 34.4. Elemental analysis: calcd (%) for $C_{19}H_{13}N_3$ (283.33): C 80.54, H 4.62, N 14.83; found: C 80.68, H 4.78, N 14.99.

**2,5-Bis(3-chlorophenyl)-1-methylpyrrole 14**

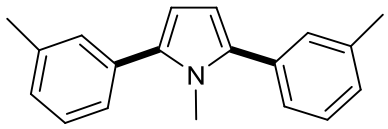



From 3-bromochlorobenzene (0.574 g, 3 mmol) and 1-methylpyrrole (0.081 g, 1 mmol), **14** was obtained in 63% (0.190 g) yield as a yellow solid.

Eluent pentane

$^1$H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.36 (s, 2H), 7.30-7.22 (m, 4H), 7.19 (t, *J* = 7.5 Hz, 2H), 6.24 (s, 2H), 3.51 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): δ 136.0, 135.0, 134.4, 129.8, 128.6, 127.0, 126.7, 109.6, 34.4. Elemental analysis: calcd (%) for $C_{17}H_{13}Cl_2N$ (302.20): C 67.57, H 4.34, N 4.63; found: C 67.69, H 4.48, N 4.82.

**2,5-Bis(*m*-tolyl)-1-methylpyrrole 15**

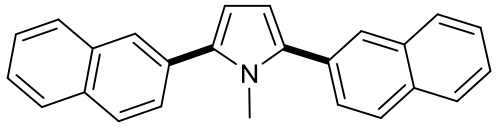



From 3-bromotoluene (0.513 g, 3 mmol) and 1-methylpyrrole (0.081 g, 1 mmol), **15** was obtained in 62% (0.162 g) yield as a red-brown solid.

Eluent pentane: diethylether 100:1

$^1$H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.30-7.15 (m, 6H), 7.05 (d, *J* = 7.8 Hz, 2H), 6.22 (s, 2H), 3.51 (s, 3H), 2.33 (s, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): δ 138.0, 136.9, 133.6, 129.5, 128.3, 127.6, 125.8, 108.6, 34.3, 21.5. Elemental analysis: calcd (%) for $C_{19}H_{19}N$ (261.36): C 87.31, H 7.33, N 5.36; found: C 87.47, H 7.14, N 5.47.

**1-Methyl-2,5-dinaphthalen-2-ylpyrrole 16**

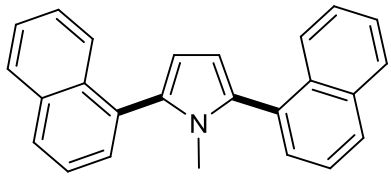


From 2-bromonaphthalene (0.621 g, 3 mmol) and 1-methylpyrrole (0.081 g, 1 mmol), **16** was obtained in 65% (0.216 g) yield as a brown solid.

Eluent pentane: diethylether 100:3

$^{1}$H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.88 (s, 2H), 7.85-7.80 (m, 6H), 7.60 (d, *J* = 7.8 Hz, 2H), 7.45-7.40 (m, 4H), 6.41 (s, 2H), 3.69 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): δ 137.3, 133.5, 132.3, 130.9, 128.0, 127.9, 127.7, 127.1, 127.0, 126.4, 125.9, 109.5, 34.7. Elemental analysis: calcd (%) for $C_{25}H_{19}N$ (333.43): C 90.06, H 5.74, N 4.20; found: C 90.11, H 5.60, N 4.11.

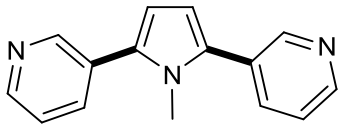
**1-Methyl-2,5-dinaphthalen-1-ylpyrrole 17**[22]



From 1-bromonaphthalene (0.621 g, 3 mmol) and 1-methylpyrrole (0.081 g, 1 mmol), **17** was obtained in 68% (0.227 g) yield as a brown solid.

Eluent pentane: diethylether 100:1

**2,5-Bis(pyridin-3-yl)-1-methylpyrrole 18**

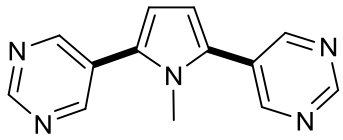


From 3-bromopyridine (0.363 g, 2.3 mmol) and 1-methylpyrrole (0.081 g, 1 mmol), **18** was obtained in 62% (0.146 g) yield as a brown solid.

Eluent dichlomethane: methanol 20:1

$^{1}$H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.69 (s, 2H), 8.50 (d, *J* = 4.9 Hz, 2H), 7.70 (d, *J* = 7.7 Hz, 2H), 7.30 (dd, *J* = 7.7, 4.9 Hz, 2H), 6.34 (s, 2H), 3.56 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): δ 149.5, 148.2, 135.7, 134.0, 129.1, 123.4, 110.2, 34.1. Elemental analysis: calcd (%) for $C_{15}H_{13}N_3$ (235.28): C 76.57, H 5.57, N 17.86; found: C 76.69, H 5.40, N 17.69.

**2,5-Bis(pyrimidin-5-yl)-1-methylpyrrole 19**

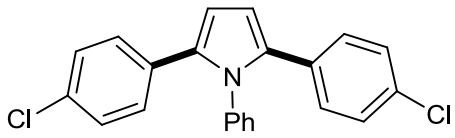



From 5-bromopyrimidine (0.477 g, 3 mmol) and 1-methylpyrrole (0.081 g, 1 mmol), **19** was obtained in 71% (0.168 g) yield as a yellow solid.

Eluent dichlomethane: methanol 100:1

$^{1}$H NMR (400 MHz, $CDCl_3$, 25 °C): δ 9.12 (s, 2H), 8.80 (s, 4H), 6.44 (s, 2H), 3.60 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): δ 157.2, 155.8, 131.1, 127.1, 111.5, 34.0. Elemental analysis: calcd (%) for $C_{13}H_{11}N_5$ (237.26): C 65.81, H 4.67, N 29.52; found: C 65.79, H 4.79, N 29.68.

**2,5-Bis(4-chlorophenyl)-1-phenylpyrrole 20**

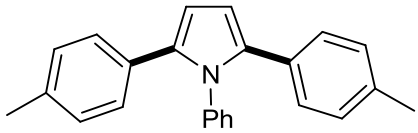



From 4-bromochlorobenzene (0.574 g, 3 mmol) and 1-phenylpyrrole (0.143 g, 1 mmol), **20** was obtained in 35% (0.127 g) yield as a white solid.

Eluent pentane: diethylether 100:1

$^{1}$H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.25-7.15 (m, 5H), 7.07 (d, *J* = 7.9 Hz, 4H), 6.89 (d, *J* = 7.9 Hz, 4H), 6.39 (s, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): δ 138.5, 134.9, 132.3, 131.5, 129.8, 129.1, 128.8, 128.2, 127.7, 110.3. Elemental analysis: calcd (%) for $C_{22}H_{15}Cl_2N$ (364.27): C 72.54, H 4.15, N 3.85; found: C 72.39, H 4.07, N 4.02.

**2,5-Bis(4-methylphenyl)-1-phenylpyrrole 21**

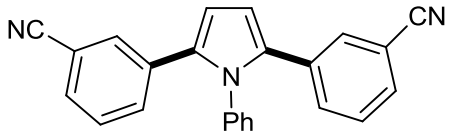



From 4-bromotoluene (0.513 g, 3 mmol) and 1-phenylpyrrole (0.143 g, 1 mmol), **21** was obtained in 33% (0.107 g) yield as a white solid.

Eluent pentane: diethylether 100:1

$^{1}$H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.17-7.10 (m, 3H), 7.00-6.92 (m, 2H), 6.90-6.80 (m, 8H), 6.35 (s, 2H), 2.18 (s, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): δ 139.2, 135.8, 135.7, 130.5, 129.0, 128.7, 128.6, 128.5, 127.1, 109.5, 21.1. Elemental analysis: calcd (%) for $C_{24}H_{21}N$ (323.43): C 89.12, H 6.54, N 4.33; found: C 89.20, H 6.68, N 4.25.

**2,5-Bis(3-cyanophenyl)-1-phenylpyrrole 22**

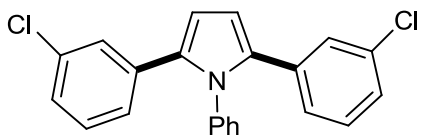



From 3-bromobenzonitrile (0.546 g, 3 mmol) and 1-phenylpyrrole (0.143 g, 1 mmol), **22** was obtained in 54% (0.186 g) yield as a white solid.

Eluent pentane: diethylether 10:1

$^{1}$H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.40-7.10 (m, 10H), 6.97-6.90 (m, 3H), 6.48 (s, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): δ 137.7, 134.3, 134.0, 132.6, 131.8, 129.9, 129.5, 128.8, 128.6, 128.5, 118.6, 112.4, 111.4. Elemental analysis: calcd (%) for $C_{24}H_{15}N_3$ (345.40): C 83.46, H 4.38, N 12.17; found: C 83.61, H 4.17, N 12.35.

**2,5-Bis(3-chlorophenyl)-1-phenylpyrrole 23**

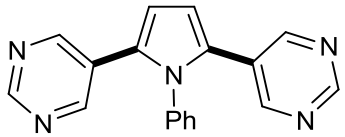


From 3-bromochlorobenzene (0.574 g, 3 mmol) and 1-phenylpyrrole (0.143 g, 1 mmol), **23** was obtained in 52% (0.189 g) yield as a white solid.

Eluent pentane

$^{1}$H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.25-7.15 (m, 3H), 7.05-6.90 (m, 8H), 6.77 (d, *J* = 7.9 Hz, 2H), 6.42 (s, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): δ 138.3, 134.8, 134.7, 133.8, 129.1, 129.0, 128.8, 128.5, 127.9, 126.7, 126.4, 110.7. Elemental analysis: calcd (%) for $C_{22}H_{15}Cl_2N$ (364.27): C 72.54, H 4.15, N 3.85; found: C 72.66, H 4.25, N 3.64.

**2,5-Bis(pyrimidin-5-yl)-1-phenylpyrrole 24**

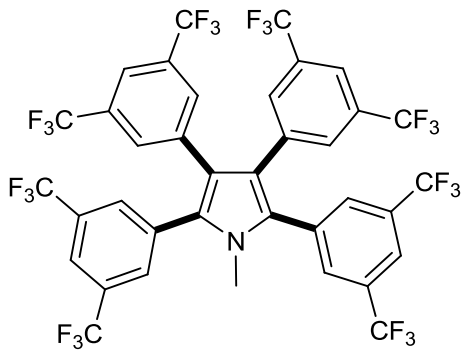



From 5-bromopyrimidine (0.477 g, 3 mmol) and 1-phenylpyrrole (0.143 g, 1 mmol), **24** was obtained in 51% (0.152 g) yield as a white solid.

Eluent pentane: diethylether 9:2

$^{1}$H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.93 (s, 2H), 8.35 (s, 4H), 7.40-7.28 (m, 3H), 7.03 (d, *J* = 7.8 Hz, 2H), 6.62 (s, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): δ 156.5, 155.4, 137.0, 130.7, 130.1, 129.3, 128.6, 126.8, 112.1. Elemental analysis: calcd (%) for $C_{18}H_{13}N_5$ (299.33): C 72.23, H 4.38, N 23.40; found: C 72.31, H 4.24, N 23.19.

**2,3,4,5-Tetrakis-(3,5-bis-trifluoromethylphenyl)-1-methylpyrrole 25**



The reaction of 3,5-bis-(trifluoromethyl)bromobenzene (1.172 g, 4 mmol), 1-methylpyrrole (0.081 g, 1 mmol) and KOAc (0.392 g, 4 mmol) at 150 ℃ for 16 h in DMAc (3 mL) in the presence of $PdCl(C_3H_5)(dppb)$ (6.1 mg, 0.01 mmol) under argon afforded, after extraction with dichloromethane, evaporation and filtration on silica gel, the tetraarylation product **25** in 62% (0.576) yield as a yellow solid.

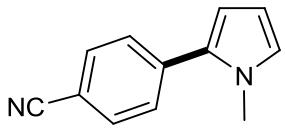
Eluent pentane

$^1$H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.84 (s, 2H), 7.11 (s, 4H), 7.56 (s, 2H), 7.26 (s, 4H), 3.46 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): δ 135.1, 132.7, 132.6 (q, $J$ = 33.9 Hz), 131.9 (q, $J$ = 33.5 Hz), 131.3, 130.9 (m), 130.2 (m), 122.6 (q, $J$ = 272.7 Hz), 122.5 (q, $J$ = 272.7 Hz), 122.4 (m), 121.8, 120.5 (m), 33.8. Elemental analysis: calcd (%) for $C_{37}H_{15}F_{24}N$ (929.48): C 47.81, H 1.63, N 1.51; found: C 47.99, H 1.97, N 1.36.

**General procedure for the Synthesis of 26-32**

As a typical experiment, the reaction of the aryl bromide (1 mmol), 1-methylpyrrole (0.324 g, 4 mmol) or 1-phenylpyrrole (0.572 g, 4 mmol), and KOAc (0.196 g, 2 mmol) at 150 ℃ for16 h in DMAc (3 mL) in the presence of $Pd(OAc)_2$ (1.1 mg, 0.005 mmol) under argon afforded the corresponding arylation product after extraction with dichloromethane, evaporation and filtration on silica gel.

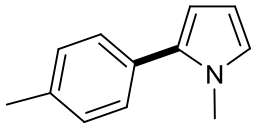
**4-(1-Methylpyrrol-2-yl)-benzonitrile 26**[18]




From 4-bromobenzonitrile (0.182 g, 1 mmol) and 1-methylpyrrole (0.324 g, 4 mmol), **26** was obtained in 83% (0.151 g) yield as a white solid (mp 102-103 ℃).

Eluent pentane: diethylether 9:2

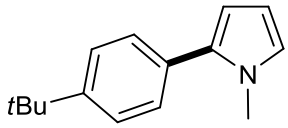
**1-Methyl-2-*p*-tolylpyrrole 27**[23]



From 4-bromotoluene (0.171 g, 1 mmol) and 1-methylpyrrole (0.324 g, 4 mmol), **27** was obtained in 66% (0.113 g) yield as a colorless oil.

Eluent pentane

**2-(4-*tert*-Butylphenyl)-1-methylpyrrole 28**

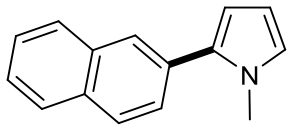


From 4-*tert*-butylbromobenzene (0.213 g, 1 mmol) and 1-methylpyrrole (0.324 g, 4 mmol), **28** was obtained in 56% (0.119 g) yield as a colorless oil.

Eluent pentane: diethylether 10:1

$^{1}$H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.33 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.3 Hz, 2H), 6.61 (s, 1H), 6.15-6.06 (m, 2H), 3.57 (s, 3H), 1.27 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): δ 149.7, 134.6, 130.5, 128.4, 125.3, 123.3, 108.4, 107.7, 35.1, 34.6, 31.4. Elemental analysis: calcd (%) for $C_{15}H_{19}N$ (213.32): C 84.46, H 8.98, N 6.57; found: C 84.5, H 8.79, N 6.40.

**1-Methyl-2-naphthalen-2-ylpyrrole 29**



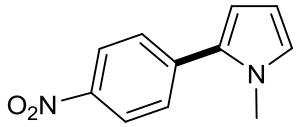
From 2-bromonaphthalene (0.207 g, 1 mmol) and 1-methylpyrrole (0.324 g, 4 mmol), **29** was obtained in 89% (0.184 g) yield as a yellow oil.

Eluent pentane: diethylether 100:1

$^{1}$H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.07-8.00 (m, 4H), 7.77 (d, *J* = 7.8 Hz, 1H), 7.71-7.62 (m, 2H), 6.94 (m, 1H), 6.61 (m, 1H), 6.50 (m, 1H), 3.86 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, 25 ℃):

δ 134.6, 133.5, 132.2, 130.8, 128.0, 127.9, 127.7, 127.2, 127.0, 126.4, 125.9, 124.0, 109.2, 108.0, 35.3. Elemental analysis: calcd (%) for $C_{15}H_{13}N$ (207.27): C 86.92, H 6.32, N 6.76; found: C 86.99, H 6.24, N 6.64.

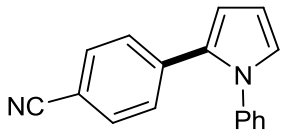
**1-Methyl-2-(4-nitrophenyl)-pyrrole 30**[23]




From 4-bromonitrobenzene (0.202 g, 1 mmol) and 1-methylpyrrole (0.324 g, 4 mmol), **30** was obtained in 81% (0.164 g) yield as a yellow solid (mp 114-115 ℃).

Eluent pentane: diethylether 9:2

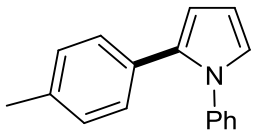
**4-(1-Phenylpyrrol-2-yl)-benzonitrile 31**[18]




From 4-bromobenzonitrile (0.182 g, 1 mmol) and 1-phenylpyrrole (0.536 g, 4 mmol), **31** was obtained in 80% (0.195 g) yield as a white solid (mp 125-126 ℃).

Eluent pentane: diethylether 9:2

**1-Phenyl-2-*p*-tolylpyrrole 32**[18]



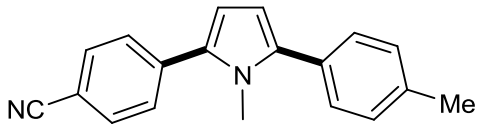

From 4-bromotoluene (0.171 g, 1 mmol) and 1-phenylpyrrole (0.536 g, 4 mmol), **32** was obtained in 52% (0.121 g) yield as a colorless oil.

Eluent pentane: diethylether 100:1

**General procedure for the Synthesis of 33-37**

As a typical experiment, the reaction of the aryl bromide (1.5 mmol), pyrrole derivative (1 mmol) and KOAc (0.196 g, 2 mmol) at 150 °C for 16 h in DMAc (3 mL) in the presence of $PdOAc)_2$ (1.12 mg, 0.005 mmol) under argon afforded the corresponding arylation product after extraction with dichloromethane, evaporation and filtration on silica gel.

**4-(1-Methyl-5-*p*-tolylpyrrol-2-yl)-benzonitrile 33**

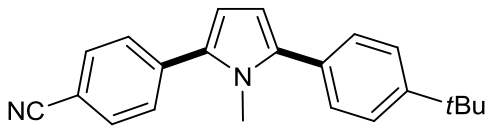



From 4-bromobenzonitrile (0.273 g, 1.5 mmol) and 1-methyl-2-*p*-tolylpyrrole **27** (0.171 g, 1 mmol), **33** was obtained in 71% (0.223 g) yield as a white solid.

Eluent pentane: diethylether 100:1

$^1$H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.61 (d, *J* = 7.8 Hz, 2H), 7.49 (d, *J* = 7.8 Hz, 2H), 7.28 (d, *J* = 7.8 Hz, 2H), 7.18 (d, *J* = 7.8 Hz, 2H), 6.36 (d, *J* = 3.7 Hz, 1H), 6.24 (d, *J* = 3.7 Hz, 1H), 3.55 (s, 3H), 2.34 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): δ 139.2, 137.9, 137.3, 134.7, 132.3, 130.0, 129.3, 128.8, 128.3, 119.1, 110.8, 109.5, 109.1, 34.6, 21.2. Elemental analysis: calcd (%) for $C_{19}H_{16}N_2$ (272.34): C 83.79, H 5.92, N 10.29; found: C 83.97, H 5.99, N 10.36.

**4-[5-(4-*tert*-Butylphenyl)-1-methylpyrrol-2-yl]-benzonitrile 34**



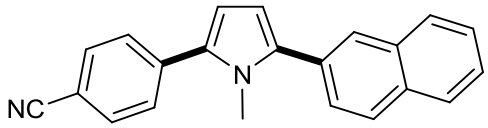

From 4-bromobenzonitrile (0.273 g, 1.5 mmol) and 2-(4-*tert*-butyl-phenyl)-1-methylpyrrole **28** (0.213 g, 1 mmol), **34** was obtained in 74% (0.232 g) yield as a white solid.

Eluent pentane: diethylether 100:1

$^1$H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.61 (d, *J* = 7.8 Hz, 2H), 7.49 (d, *J* = 7.8 Hz, 2H), 7.39 (d, *J* = 7.8 Hz, 2H), 7.32 (d, *J* = 7.8 Hz, 2H), 6.36 (d, *J* = 3.7 Hz, 1H), 6.24 (d, *J* = 3.7 Hz, 1H), 3.56 (s, 3H), 1.29 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): δ 150.5, 139.2, 137.9, 134.6, 132.3, 130.0,

128.6, 128.2, 125.5, 119.1, 110.8, 109.5, 109.2, 34.7, 31.3. Elemental analysis: calcd (%) for $C_{22}H_{22}N_2$ (314.42): C 84.04, H 7.05, N 8.91; found: C 83.89, H 7.18, N 8.67.

**4-(1-Methyl-5-naphthalen-2-ylpyrrol-2-yl)-benzonitrile 35**

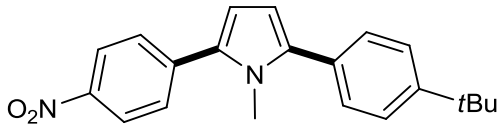



From 4-bromobenzonitrile (0.273 g, 1.5 mmol) and 1-methyl-2-naphthalen-2-ylpyrrole **29** (0.207 g, 1 mmol), **35** was obtained in 90% (0.277 g) yield as a yellow solid.

Eluent pentane: diethylether 9:2

$^1$H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.89-7.78 (m, 4H), 7.63 (d, *J* = 7.8 Hz, 2H), 7.55-7.50 (m, 3H), 7.50-7.40 (m, 2H), 6.41 (d, *J* = 3.7 Hz, 1H), 6.39 (d, *J* = 3.7 Hz, 1H), 3.63 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): δ 139.2, 137.8, 135.3, 133.4, 132.5, 132.4, 130.2, 128.4, 128.2, 128.0, 127.7, 127.5, 126.9, 126.6, 126.2, 119.1, 111.1, 110.0, 109.7, 34.9. Elemental analysis: calcd (%) for $C_{22}H_{16}N_2$ (308.38): C 85.69, H 5.23, N 9.08; found: C 85.88, H 5.41, 8.98.

**2-(4-*tert*-Butylphenyl)-1-methyl-5-(4-nitrophenyl)-pyrrole 36**

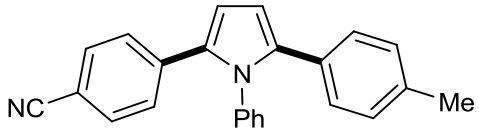



From 4-bromonitrobenzene (0.303 g, 1.5 mmol) and 2-(4-*tert*-butylphenyl)-1-methylpyrrole **28** (0.213 g, 1 mmol), **36** was obtained in 80% (0.267 g) yield as a brown solid.

Eluent pentane: diethylether 100:1

$^1$H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.18 (d, *J* = 7.8 Hz, 2H), 7.52 (d, *J* = 7.8 Hz, 2H), 7.39 (d, *J* = 7.8 Hz, 2H), 7.32 (d, *J* = 7.8 Hz, 2H), 6.42 (d, *J* = 3.7 Hz, 1H), 6.26 (d, *J* = 3.7 Hz, 1H), 3.58 (s, 3H), 1.29 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): δ 150.6, 145.8, 139.9, 139.8, 134.4, 129.8, 128.6, 127.9, 125.5, 124.0, 111.6, 109.5, 34.8, 34.7, 31.3. Elemental analysis: calcd (%) for $C_{21}H_{22}N_2O_2$ (334.41): C 75.42, H 6.63, N 8.38; found: C 75.58, H 6.54, N 8.24.

**4-(1-Phenyl-5-p-tolylpyrrol-2-yl)-benzonitrile 37**

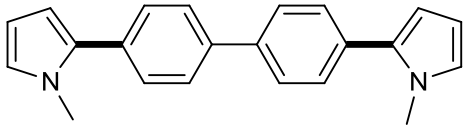



From 4-bromobenzonitrile (0.273 g, 1.5 mmol) and 1-phenyl-2-*p*-tolyl-1-pyrrole **32** (0.233 g, 1 mmol), **37** was obtained in 86% (0.287 g) yield as a yellow solid.

Eluent pentane: diethylether 100:1

$^{1}$H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.34 (d, *J* = 7.8 Hz, 2H), 7.25-7.15 (m, 3H), 7.02 (d, *J* = 7.8 Hz, 2H), 7.00-6.96 (m, 2H), 6.92 (d, *J* = 7.8 Hz, 2H), 6.86 (d, *J* = 7.8 Hz, 2H), 6.52 (d, *J* = 3.7 Hz, 1H), 6.86 (d, *J* = 3.7 Hz, 1H), 2.21 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): δ 138.6, 137.9, 137.7, 136.6, 133.3, 131.7, 129.7, 129.1, 128.8, 128.7, 128.6, 128.2, 127.8, 119.1, 111.9, 110.3, 109.0, 21.1. Elemental analysis: calcd (%) for $C_{24}H_{18}N_2$ (334.41): C 86.20, H 5.43, N 8.38; found: C 86.01, H 5.59, N 8.40.

**4,4′-Bis(1-methylpyrrol-2-yl)-biphenyl 38**




From 4,4′-dibromobiphenyl (0.312 g, 1 mmol), 1-methylpyrrole (0.243 g, 3 mmol) and KOAc (0.392 g, 4 mmol) at 150 ℃ for 16 h in DMAc (3 mL) in the presence of $PdCl(C_3H_5)$(dppb) (6.1 mg, 0.01 mmol), **38** was obtained in 81% (0.253 g) yield as a yellow solid.

Eluent pentane: diethylether 10:2

$^{1}$H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.59 (d, *J* = 8.2 Hz, 4H), 7.42 (d, *J* = 8.2 Hz, 4H), 6.67 (m, 2H), 6.22 (m, 2H), 6.16 (m, 2H), 3.65 (s, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): δ 138.9, 134.2, 132.3, 128.9, 126.9, 123.9, 108.9, 107.9, 35.2. Elemental analysis: calcd (%) for $C_{22}H_{20}N_2$ (312.41): C 84.58, H 6.45, N 8.97; found: C 84.69, H 6.69, N 8.79.

## 3.5 Reference


1. V. A. Vaillard, R. A. Rossi, S. E. Martin, *Org. Biomol. Chem.*, **2011**, *9*, 4927.
2. K.-H. van Pée, J. M. Ligon, *Nat. Prod. Rep.* **2000**, *17*, 157.
3. *(a)* M. G. Banwell, T. E. Goodwin, S. Ng, J. A. Smith, D. J. Wong, *Eur. J. Org. Chem.* **2006**, 3043; *(b)* K. T. De Silva, A. H. Ratcliffe, G. F. Smith, G. N. Smith, *Tetrahedron Lett.* **1972**, *13*, 913.
4. E. T. Nadres, A. Lazareva, O. Daugulis, *J. Org. Chem.* **2011**, *76*, 471.
5. D. Pla, A. Marchal, C. A. Olsen, F. Albericio, M. Álvarez, *J. Org. Chem.* **2005**, *70*, 8231.
6. *(a)* J. J. Li, G. W. Gribble, Palladium in Heterocyclic Chemistry, Pergamon: Amsterdam **2000**; *(b)* E. Negishi, Ed. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Wiley-Interscience: New York, **2002**; Part III, p 213.
7. *(a)* Y. Akita, A. Inoue, K. Yamamoto, A. Ohta, T. Kurihara, M. Shimizu, *Heterocycles* **1985**, *23*, 2327; *(b)* A. Ohta, Y. Akita, T. Ohkuwa, M. Chiba, R. Fukunaga, A. Miyafuji, T. Nakata, N. Tani, Y. Aoyagi, *Heterocycles* **1990**, *31*, 1951.
8. *(a)* T. Satoh, M. Miura, *Chem. Lett.* **2007**, *36*, 200; *(b)* L.-C. Campeau, D. R. Stuart, K. Fagnou, *Aldrichimica Acta* **2007**, *40*, 35; *(c)* I. V. Seregin, V. Gevorgyan, *Chem. Soc. Rev.* **2007**, *36*, 1173; *(d)* B.-J. Li, S.-D. Yang, Z.-J. Shi, *Synlett* **2008**, 949; *(e)* F. Bellina, R. Rossi, *Tetrahedron* **2009**, *65*, 10269; *(f)* L. Ackermann, R. Vicente, A. Kapdi, *Angew. Chem. Int. Ed.* **2009**, *48*, 9792; *(g)* J. Roger, A. L. Gottumukkala, H. Doucet, *ChemCatChem* **2010**, *2*, 20; *(h)* C.-L. Sun, B.-J. Li, Z.-J. Shi, *Chem. Commun.* **2010**, *46*, 677; *(i)* C. Fischmeister, H. Doucet, *Green Chem.* **2011**, *13*, 741.
9. For selected recent examples of palladium-catalyzed direct arylations of heteroaromatics from our laboratory: *(a)* R. V. Smaliy, M. Beaupérin, H. Cattey, P. Meunier, J.-C. Hierso, J. Roger, H. Doucet, Y. Coppel, *Organometallics* **2009**, *28*, 3152; *(b)* F. Derridj, J. Roger, S. Djebbar, H. Doucet, *Org. Lett.* **2010**, *12*, 4320; *(c)* J. Roger, F. Pozgan, H. Doucet, *Adv. Synth. Catal.* **2010**, *352*, 696; *(d)* L. Chen, J. Roger, C. Bruneau, P. H. Dixneuf, H. Doucet, *Chem. Commun.* **2011**, *47*, 1872; *(e)* K. Beydoun, H. Doucet, *ChemSusChem* **2011**, *4*, 526; *(f)* K. Si Larbi, H. Y. Fu, N. Laidaoui, K. Beydoun, M. Miloudi, D. El Abed, S. Djebbar, H. Doucet, *ChemCatChem* **2012**, *4*, 815.

10. For examples of palladium-catalyzed intramolecular direct 2- or 5-arylations of pyrroles: *(a)* T. Honma, K. Hayashi, T. Aoyama, N. Hashimoto, T. Machida, K. Fukasawa, T. Iwama, C. Ikeura, M. Ikuta, I. Suzuki-Takahashi, Y. Iwasawa, T. Hayama, S. Nishimura, H. Morishima, *J. Med. Chem.* **2001**, *44*, 4615; *(b)* C. A. Olsen, N. Parera, F. Albericio, M. Alvarez, *Tetrahedron Lett.* **2005**, *46*, 2041; *(c)* C. Blaszykowski, E. Aktoudianakis, C. Bressy, D. Alberico, M. Lautens, *Org. Lett.*, **2006**, *8*, 2043; *(d)* S. Lage, U. Martinez-Estibalez, N. Sotomayor, E. Lete, *Adv. Synth. Catal.* **2009**, *351*, 2460; *(e)* J. K. Laha, G. D. Cuny, *J. Org. Chem.* **2011**, *76*, 8477.
11. For examples of palladium-catalyzed direct intermolecular 2- or 5-arylations of pyrrolyl salts: *(a)* L. Filippini, M. Gusmeroli, P. Riva, *Tetrahedron Lett.* **1992**, *33*, 1755; *(b)* R. D. Rieth, N. P. Mankad, E. Calimano, J. P. Sadighi, *Org. Lett.* **2004**, *6*, 3981; *(c)* D. L. Swartz, A. L. Odom, *Organometallics* **2006**, *25*, 6125.
12. For examples of palladium-catalyzed direct intermolecular 5-arylations of substituted pyrroles: *(a)* M. Romero, Y. Harrak, J. Basset, L. Ginet, P. Constans, M. D. Pujol, *Tetrahedron* **2006**, *62*, 9010; *(b)* B. B. Toure, B. S. Lane, D. Sames, *Org. Lett.* **2006**, *8*, 1979; *(c)* X. Wang, D. V. Gribkov, D. Sames, *J. Org. Chem.* **2007**, *72*, 1476; *(d)* B. Liégaut, D. Lapointe, L. Caron, A. Vlassova, K. Fagnou, *J. Org. Chem.* **2009**, *74*, 1826; *(e)* J. J. Dong, J. Roger, C. Verrier, T. Martin, R. Le Goff, C. Hoarau, H. Doucet, *Green Chem.* **2010**, *12*, 2053; *(f)* O. Rene, K. Fagnou, *Adv. Synth. Catal.* **2010**, *352*, 2116; *(g)* N. Laidaoui, J. Roger, A. Miloudi, D. El Abed, H. Doucet, *Eur. J. Org. Chem.* **2011**, 4373; *(h)* Y. Xu, L. Zhao, Y. Li, H. Doucet, *Adv. Synth. Catal.* **2013**, *355*, 1423.
13. For examples of iridium-catalyzed direct intermolecular arylations of pyrroles: B. Join, T. Yamamoto, K. Itami, *Angew. Chem, Int. Ed.* **2009**, *48*, 3644.
14. For examples of palladium-catalyzed direct intermolecular 2-arylations of non-substituted pyrroles: *(a)* D. T. Gryko, O. Vakuliuk, D. Gryko, B. Koszarna, *J. Org. Chem.* **2009**, *74*, 9517; *(b)* F. Jafarpour, S. Rahiminejadan, H. Hazrati, *J. Org. Chem.* **2010**, *75*, 3109; *(c)* C. B. Bheeter, J. K. Bera, H. Doucet, *Tetrahedron Lett.* **2012**, *53*, 509.
15. For an example of palladium-catalyzed direct intermolecular 2,5-diarylation of a pyrrole: F. Shibahara, E. Yamaguchi, T. Murai, *Chem. Commun.* **2010**, *46*, 2471.
16. For examples of ruthenium-catalyzed direct intermolecular 2,5-diarylations of pyrroles: L. Ackermann, A. V. Lygin, *Org. Lett.* **2011**, *13*, 3332.

17. For examples of palladium-catalyzed 2,5-diarylation of pyrroles via Suzuki, Negishi or Stille couplings: *(a)* A. Dhanabalan, J. Knol, J. C. Hummelen, R. A. J. Janssen, *Synth. Metals* **2001**, *119*, 519; *(b)* H. Gour, S. Jain, S. K. Arora, N. Sinha, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3592; *(c)* T. T. Dang, R. Ahmad, T. T. Dang, H. Reinke, P. Langer, *Tetrahedron Lett.* **2008**, *49*, 1698; *(d)* F. Beaumard, P. Dauban, R. H. Dodd, *Org. Lett.* **2009**, *11*, 1801; *(e)* S.-M. T. Toguem, O. Fatunsin, A. Villinger, P. Langer, *Tetrahedron Lett.* **2011**, *52*, 3732.
18. J. Roger, H. Doucet, *Adv. Synth. Catal.* **2009**, *351*, 1977.
19. Y. Fall, H. Doucet, M. Santelli, *ChemSusChem* **2009**, *2*, 153.
20. T. Cantat, E. Génin, C. Giroud, G. Meyer, A. Jutand, *J. Organomet. Chem.* **2003**, *687*, 365.
21. R. K. Arafa, R. Brun, K. A. Werbovetz, F. A. Tanious, W. D. Wilson, D. W. Boykin, *Heterocycl. Commun.* **2004**, *10*, 423.
22. Y. V. Shurukhin, N. A. Klyuev, I. I. Grandberg, *Zh. Org. Khim.* **1985**, *21*, 2057.
23. F. Bilodeau, M.-C. Brochu, N. Guimond, K. H. Thesen, P. Forgione, *J. Org. Chem.* **2010**, *75*, 1550.

# *Chaper 4: Reactivity of C-H bonds of polychlorobenzenes in palladium-catalyzed direct arylations of with aryl bromides*

# Chaper 4: Reactivity of C-H bonds of polychlorobenzenes in palladium-catalyzed direct arylations of with aryl bromides

## 4.1 Introduction

### 4.1.1 A short survey about direct arylation of polyfluorobenzenes with aryl halides

As explained in chapter 2 and chapter 3, the direct arylation of (hetero)aromatics with aryl halides or pseudo halides, *via* a C-H bond activation, provides a simpler access to the corresponding aryl-(hetero)aryl derivatives.[1,2] The formation of biphenyl derivatives *via* C-H bond activation has attracted less attention, due to the lower reactivity of C-H bonds of most benzene derivatives.

In 2006, Fagnou and co-workers reported the first intermolecular metal-catalyzed direct arylation reaction using polyfluorobenzene derivatives (Scheme 4.1 **A**).[3] The presence of fluoro substituents on benzene appears to efficiently promote such couplings allowing the one step access to polyfluorobiphenyls. This procedure is of particular interest as many fluorobenzenes are readily available commercially at an affordable cost, and as fluoro-substituted biphenyls are important substructures in both bio- and material-chemistry.

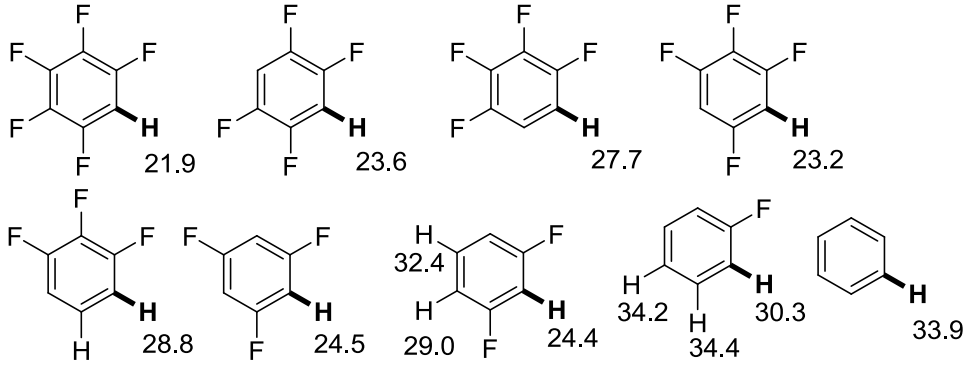



**Figure 4.1**. Gibbs free energies of activation ($\Delta G_{298\ K}$) of the cleavage of C-H bonds for different (poly)fluorobenzenes in the CMD process using the [Pd($C_6H_5$)($PMe_3$)(OAc)] catalyst.[4]

From competitive experiments with different perfluoroarenes (*i.e.*, pentafluorobenzene,

tetrafluorobenzenes, trifluorobenzene and difluorobenzene), the authors observed that the reactivity increases with the number of fluorine atoms, which is in accordance with calculated datas shown in Fig. 4.1.[4,5]

In other words, more electron-deficient arenes react preferentially. Based on this inversion of reactivity compared to the direct arylation occurring *via* $S_EAr$ mechanism and with the help of density functional theory (DFT) calculations, the authors proposed a mechanism, where the C-H bond activation occurred through CMD by a coordinated base (Figure 4.2). Two different bases have been considered in this mechanism: bromide ligand on $(PR_3)$Pd-Br (Figure 4.2, Mechanism **C1**) and carbonate ligand on $(PR_3)$Pd-$HCO_3$ (Figure 4.2, Mechanism **C2**). The mechanism **C2**, proton abstraction assisted by a carbonate, was found to have the lowest reaction barrier.

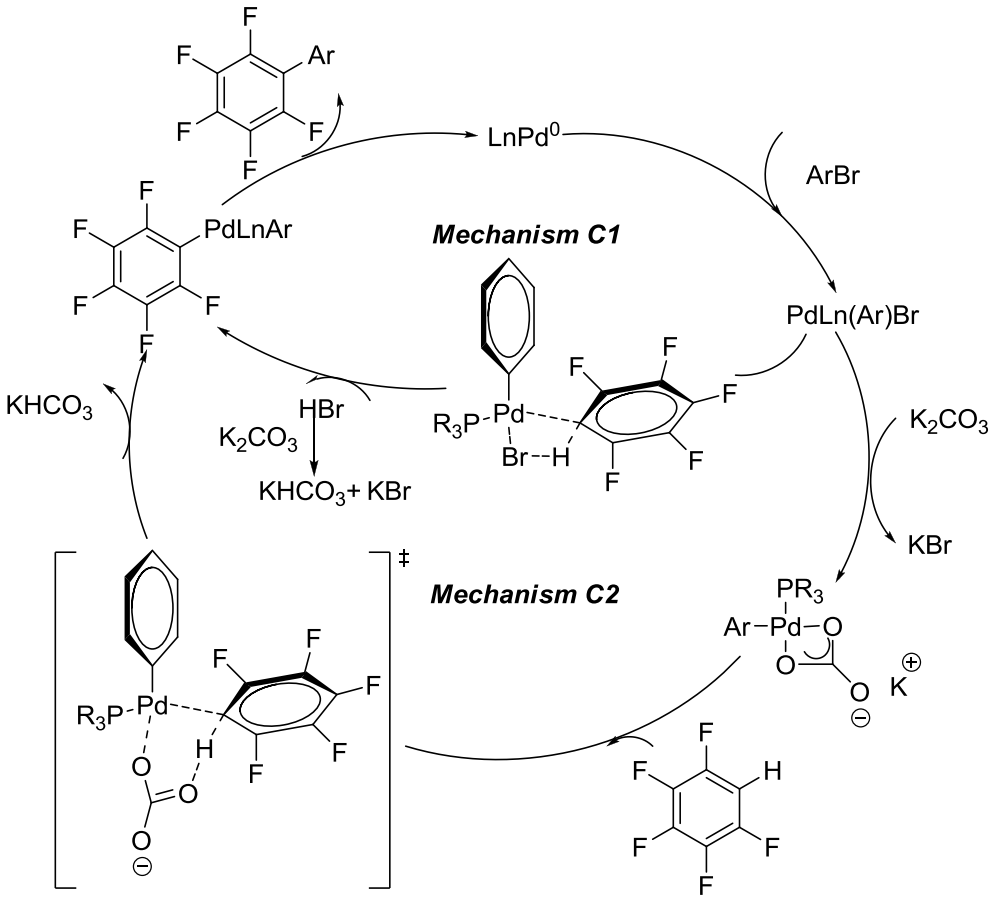
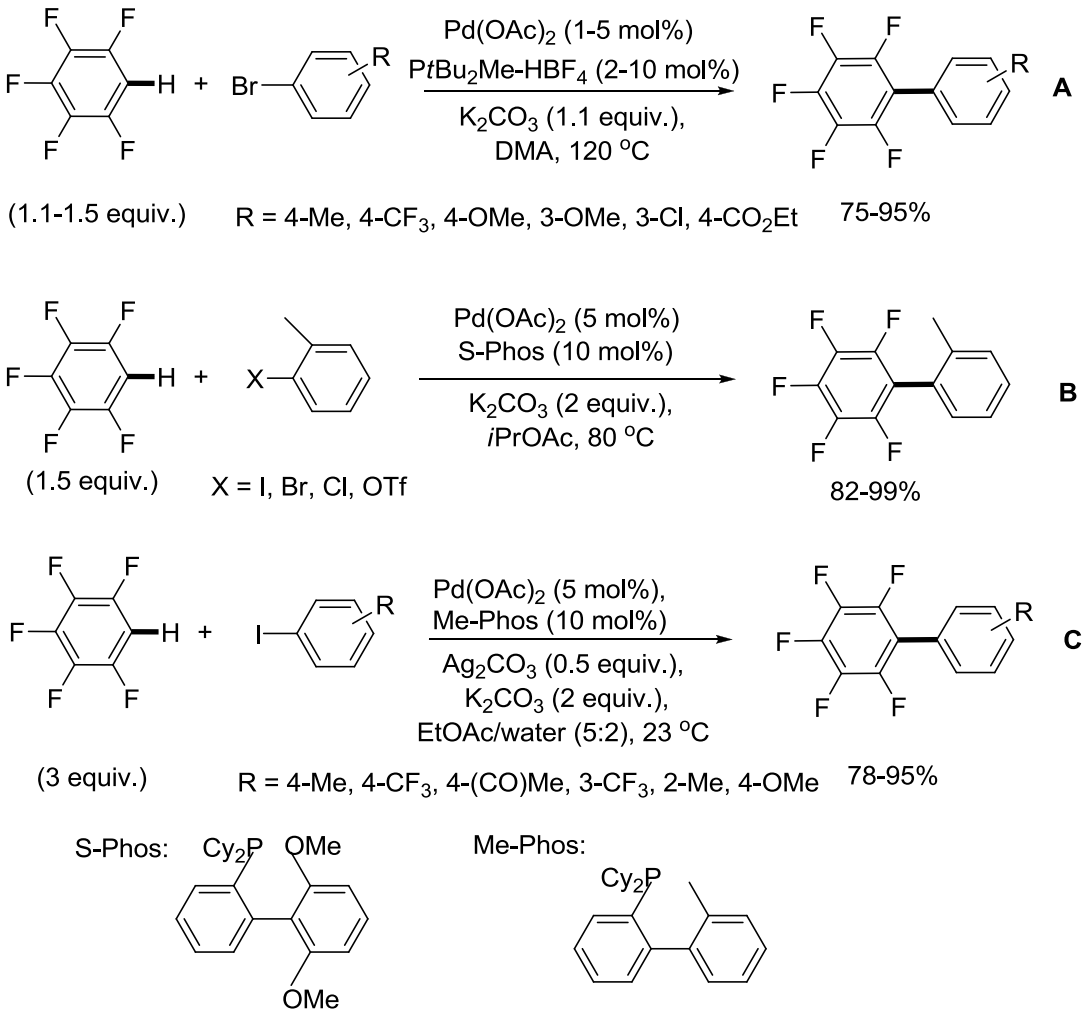



**Figure 4.2**. Proposed catalytic cycle of perfluorobenzene direct arylation.[3]

1. Pentafluorobenzene ($C_6F_5H$) is most reactive in the family of poly-fluoroarene; moreover, no regioselectivity issue exists with this compound.

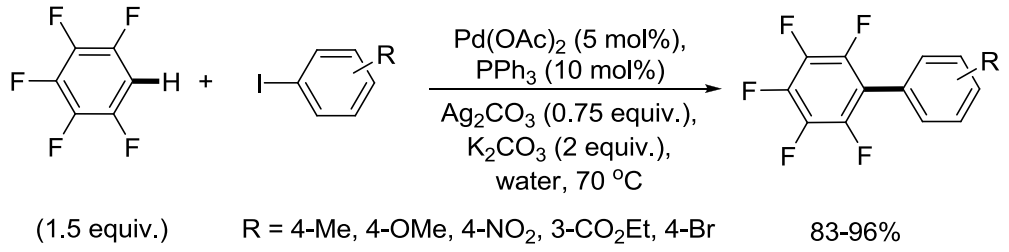
Fagnou and co-workers continued to investigate this area with aryl-chlorides and *ortho*-substituted aryl-bromides, which display poor reactivity under the previous conditions.[6] The use of the 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (S-Phos) in isopropyl acetate (*i*PrOAc) instead of P*t*Bu$_2$Me-HBF$_4$ in DMA and lower temperature 80 $^{o}$C, *ortho*-substituted aryl halides or triflates gave good yields into the desired cross-coupling products (Scheme 4.1 **B**). In later work, the authors again optimized the reaction conditions and found that the reaction could be performed at room temperature in a mixture of water and ethyl acetate (EtOAc/water, 5:2) (Scheme 4.1 **C**). These mild biphasic conditions were successfully applied to a wide range of aryl iodides.




**Scheme 4.1**. Palladium-catalyzed direct arylation of pentafluorobenzene ($C_6F_5H$).

A similar work was reported by Zhang, using triphenyl phosphine as ligand instead of Me-Phos with aryl iodides (Scheme 4.2).[7] The reaction temperature is higher (70 ℃) than that in Fagnou's

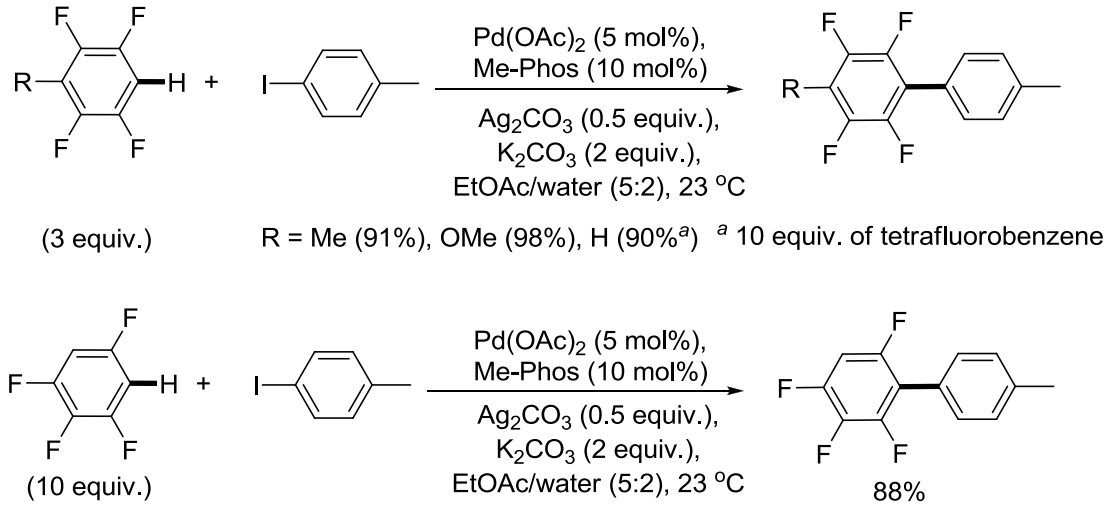
conditions, but, the reaction proceeded in water, only.




**Scheme 4.2**. Palladium-catalyzed direct arylation of pentafluorobenzene ($C_6F_5H$).

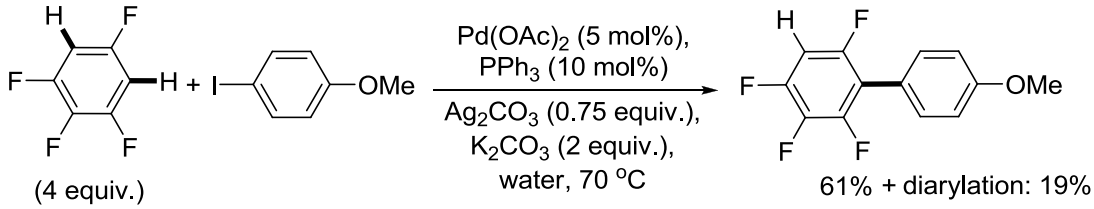
2. The reactivity of 1,2,4,5-tetrafluorobenzenes and 1,2,3,5-tetrafluorobenzenes was found to be in general relatively similar to pentafluorobenzene.

In Fagnou group, the direct arylation of tetrafluorobenzenes was also examined, under the conditions above (Scheme 4.1). The biphasic conditions EtOAc/water using $Ag_2CO_3$ as the base promotes the palladium-catalyzed direct mono-arylation of tetrafluorobenzenes at room temperature in the presence of a huge excess of tetrafluoroarenes (10 equiv.) (Scheme 4.3).[8]




**Scheme 4.3**. Palladium-catalyzed mono-arylation of 1,2,4,5-tetrafluorobenzenes and 1,2,3,5-tetrafluorobenzenes.

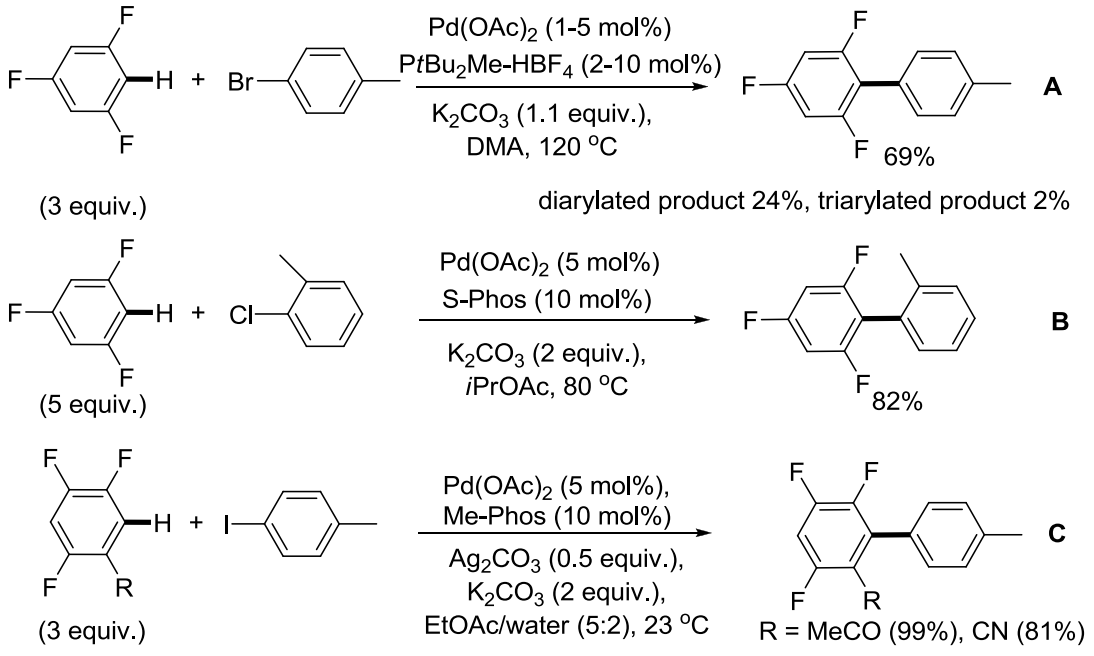
With Zhang' system, the direct arylation with non-substituted tetrafluorobenzenes (4 equiv.) were performed (Scheme 4.4).[7]




**Scheme 4.4**. Palladium-catalyzed direct arylation with non-substituted tetrafluorobenzenes.

3. The major challenge of trifluorobenzenes is to control the mono-arylation as well as the regioselectivity for the metal-catalyzed direct arylation, as it might contain several C-H bonds susceptible to react.

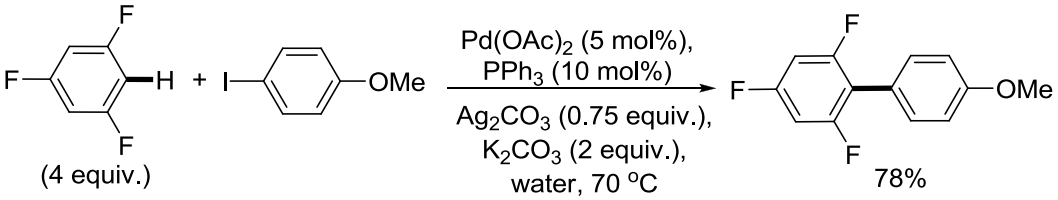
In Fagnou and co-workers' investigation, di-arylated product and trace amount of tri-arylated product were obtained under the first described conditions (Scheme 4.1 **A**).[3] Using the milder conditions described in the Scheme 4.1 **B**, only mono-arylated product from the *ortho*-chlorotoluene was obtained (Scheme 4.5, **B**).[6] Using the conditions described in the Scheme 4.1 **C**, *i.e.*, in water media with aryl iodide at 23 °C, substituted trifluorobenzene derivatives reacts with a sole regioselectivity (Scheme 4.5, **C**).[8] Electron-withdrawing substituents have probably been selected in order to enhance the reactivity of fluorinated arenes.




**Scheme 4.5**. Palladium-catalyzed direct mono-arylation of trifluorobenzenes.

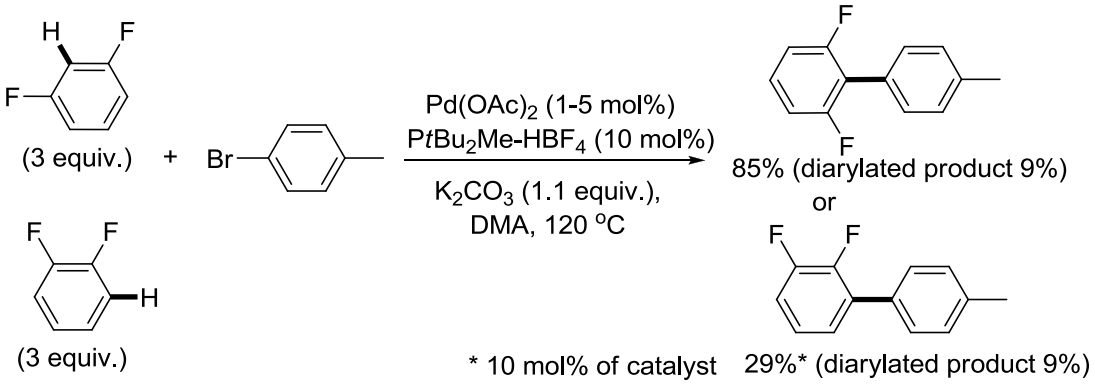
Zhang has reported one example of coupling of 1,3,5-trifluorobenzene and

1-iodo-4-methoxybenzene using the conditions described in the Scheme 4.2. Four equivalents of the trifluorinated substrate have been used, probably to avoid the formation of di- and tri-arylated products (Scheme 4.6).[7]



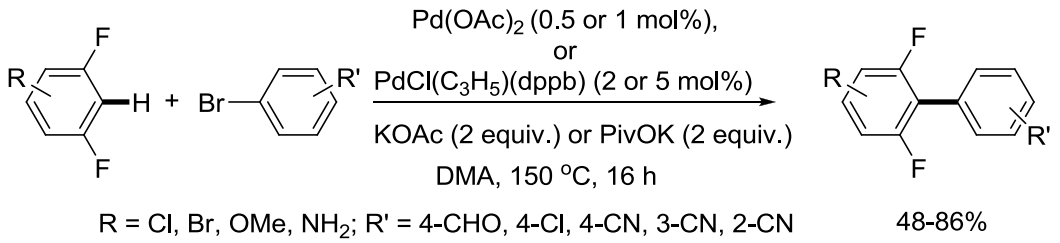

**Scheme 4.6**. Palladium-catalyzed arylation of 1,3,5-trifluorobenze with 1-iodo-4-methoxybenzene.

4. The direct arylation of difluorobenzenes is more challenging for both reactivity and regioselectivity issues. Among the three different conditions described by Fagnou for the intermolecular direct arylation of electron-deficient arenes, only the first has been applied to difluorinated arenes (Scheme 4.7).[3] However, di-arylated products were also obtained in both cases.



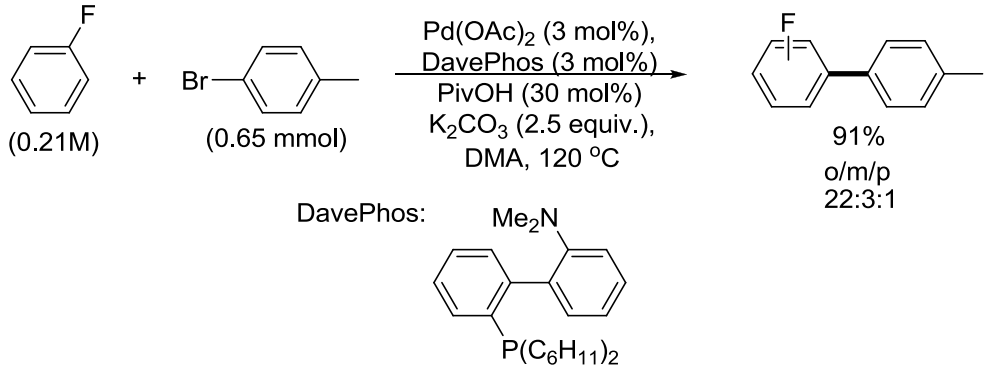

**Scheme 4.7**. Palladium-catalyzed direct arylation of difluorobenzenes.

In 2013, Doucet and co-workers have specifically studied the reactivity of 4-substituted 1,3-difluorobenzenes for the palladium-catalyzed direct arylations (Scheme 4.8).[9] The reaction smoothly proceeded under the standard reaction conditions, and in all cases, the arylations occurred only between the two fluorine atoms.



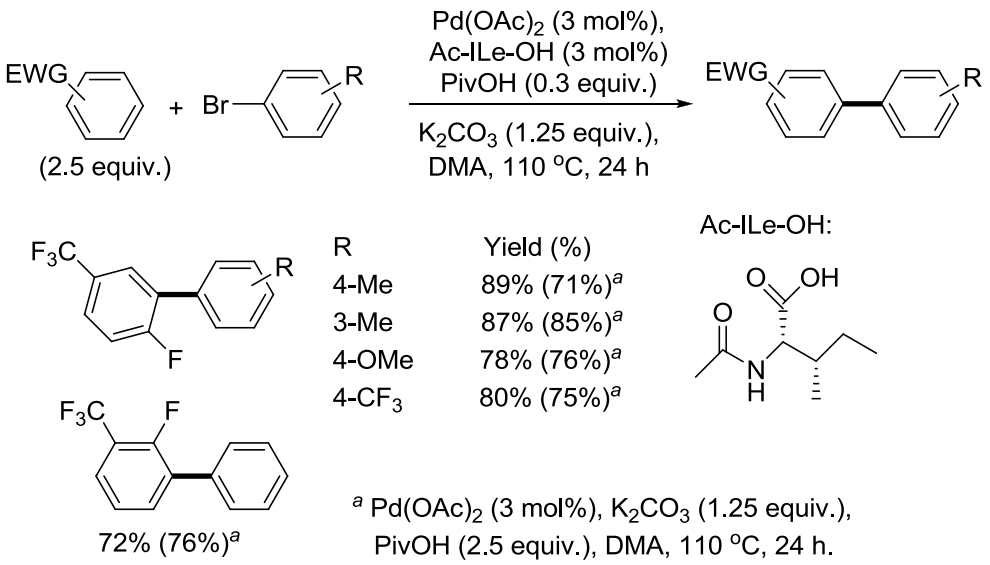

**Scheme 4.8**. Palladium-catalyzed direct arylations of 4-substituted 1,3-difluorobenzenes.

5. The intermolecular direct arylation with monofluoroarene is less widely described, due to their lower reactivity in CDM type reaction arising from the relatively low acidity of the C-H bonds. Fagnou and Lafrance optimized the reaction conditions: the fluorobenzene reacted in high yield, albeit its large excess (similar as solvent conditions); the arylation mainly occurred at the *ortho*-position to the fluorine atom (Scheme 4.9).[3]




**Scheme 4.9**. Palladium-catalyzed arylation of monofluorobenzene.

To enhance the reactivity of mono-fluorobenzene for the direct arylation with aryl bromide, other electron-withdrawing substituents, namely fluoro-(trifluoromethyl) benzene has been used as the substrate (Scheme 4.10).[10] The desired coupling products with good to excellent yields were obtained with unique regioselectivity. And, in addition to the C-H bond activation at *ortho*-position to the fluorine atom, the $CF_3$ substituent activated the C-H bond at the *meta*-position.




**Scheme 4.10**. Palladium-catalyzed direct arylation of substituted monofluorobenzene with aryl bromide.

## 4.1.2 A short introduction about direct arylation of polychlorobenzenes

Several (poly)chlorobenzene derivatives display important biological properties. For example, Lamotrigine is an anticonvulsant used in the treatment of epilepsy, Hexachlorophene is a disinfectant used in soaps, and Ambigol A also has antimicrobial activity. Besides, Dicloxacillin, Clobuzarit and Tanomastat play the role as antibiotic, antirheurnatic and protease inhibitor, respectively (Fig. 4.3). Therefore, the discovery of general simple routes for access to a variety of (poly)chlorobenzene derivatives has potential in medicinal chemistry.

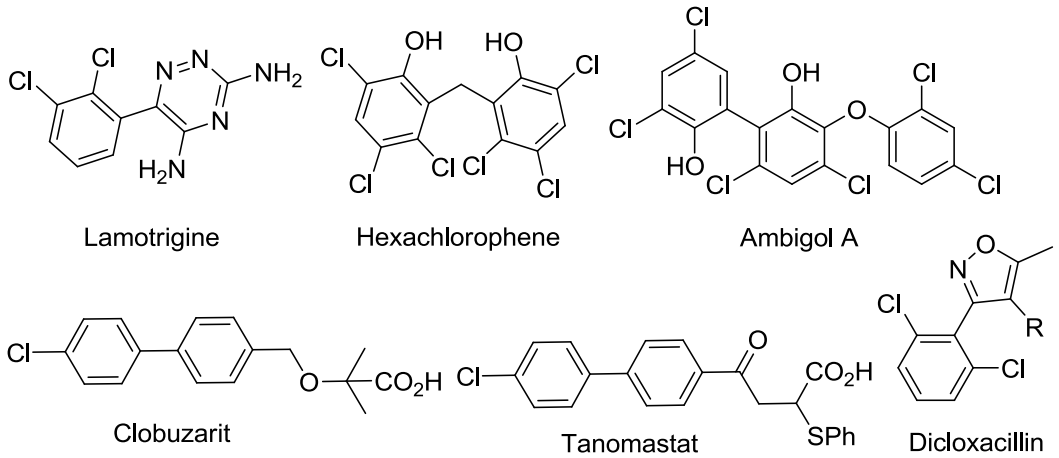
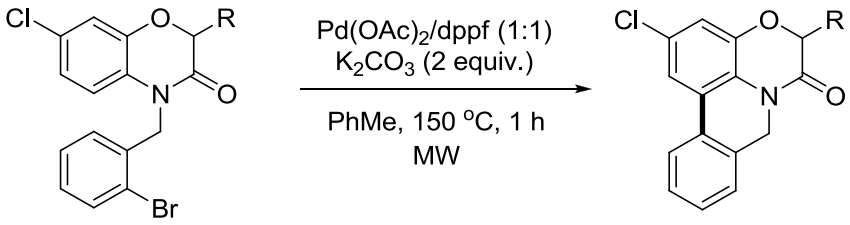



**Figure 4.3**. Examples of bioactive (poly)chlorobenzenes.

The direct coupling of (poly)chlorobenzenes with aryl halides *via* a C-H bond

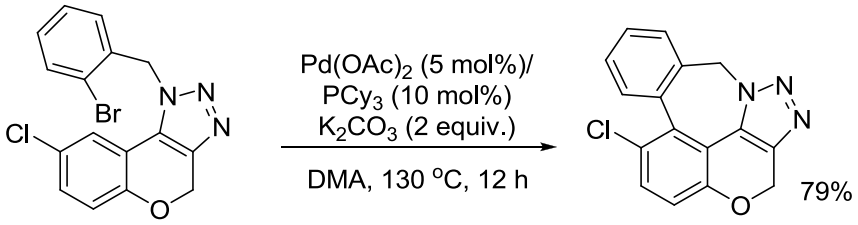
activation/functionalization has attracted much less attention, due to the lower reactivity of C-H bonds than in polyfluorobenzenes.[11-13]

Two examples of intramolecular direct arylations using chlorobenzene have been reported in the literature. In 2007, Dai and co-workers synthesized novel fuzed heterocycles, using palladium-catalyzed direct arylation assisted by microwave (Scheme 4.11).[11a]




**Scheme 4.11**. Palladium-catalyzed intramolecular direct arylations of chlorobenzene *via* MW.

In Swamy group, a new fuzed pentacyclic compound (Scheme 4.12)[11b] was prepared by a palladium-catalyzed cyclization following a Fagnou' protocol[12].




**Scheme 4.12**. Palladium-catalyzed cyclization of fuzed pentacyclic compound.

For the palladium-catalyzed intermolecular arylation with chlorobenzenes, only aryl iodides, were used as the coupling partners. Recently, Wang and co-workers reported the 2-arylation of 4-chlorobenzamide or 6-arylation of 3,4-dichlorobenzamide (Fig. 4.4, top).[13b] They demonstrated that the amide group directed the arylation at the less hindered *ortho*-position of the amide. Similarly, Larrosa and co-workers described that the carboxylic acid group in 2,4-dichlorobenzoic acid allowed for direct arylation at C6 (Fig. 4.4, bottom).[13c]

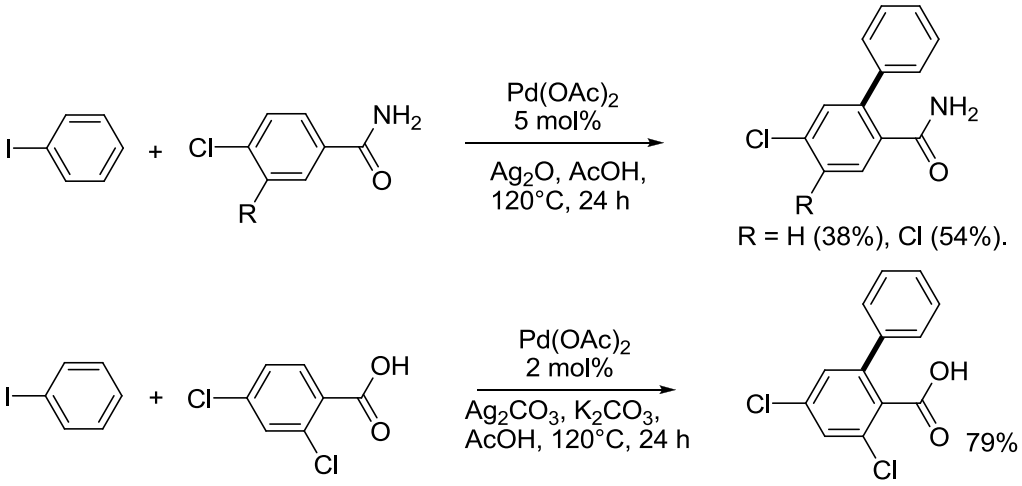
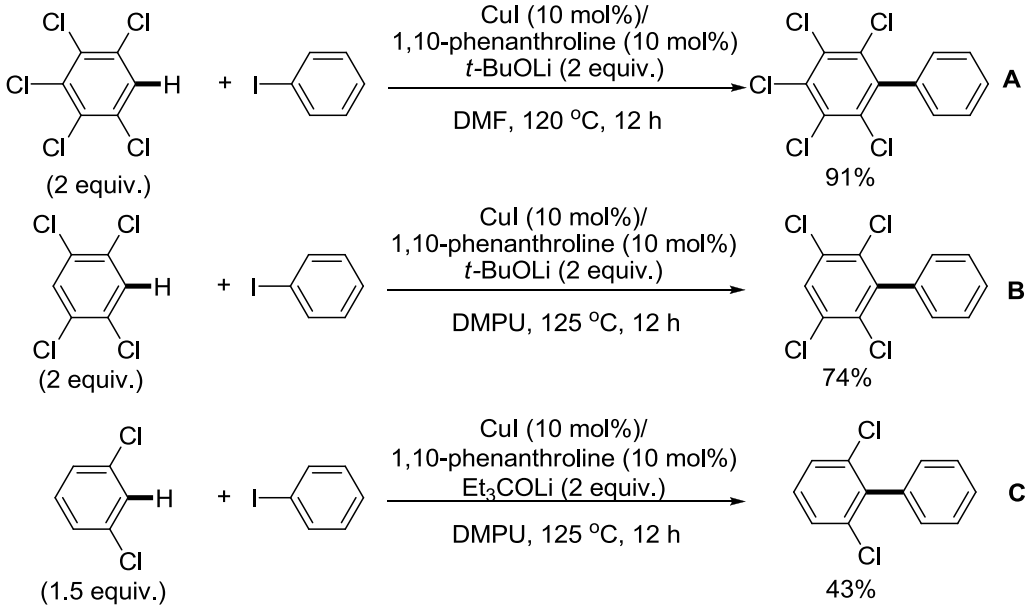



**Figure 4.4**. Reported Pd-catalyzed direct arylations of mono- and di-chlorobenzenes.[13b,13c]

In Daugulis group, a method for copper-catalyzed regioselective mono-arylation of polychlorobenzenes has been established (Scheme 4.13).[14] Penta- and tetrachlorobenzenes were phenylated in excellent yields with iodobenzene using copper(I) iodide (10 mol%), 1,10-phenanthroline (10 mol%), and *t*-BuOLi (2 equiv.) as the base (Scheme 4.13 **A** and **B**). Less reactive 1,3-dichlorobenzene is regioselectively phenylated in an acceptable 43% yield by employing $Et_3COLi$ as the base (Scheme 4.13 **C**).




**Scheme 4.13**. Copper-catalyzed mono-arylation of polychlorobenzenes.

The Gibbs free energies of activation for direct arylation *via* CMD[4,15] pathway of several polychlorobenzenes have been calculated by Gorelsky (Fig. 4.5).[4] A lower reactivity of

pentachlorobenzene compared to pentafluorobenzene could be expected as the energies of activation ($\Delta G_{298\ K}$) for the cleavage of C-H bonds are 27.2 and 21.9, respectively. Similarly, 1,3,5-trichlorobenzene was expected to be less reactive than 1,3,5-trifluorobenzene (energies: 28.5 vs 24.5); and for 1,3-dichlorobenzene, the most reactive C-H should be the C2 position. However, as these calculated reactivities have not yet been confirmed by experiments, the outcome of the reaction of polychlorobenzenes with aryl halides in the presence of palladium-catalysts was quite unpredictable and needed to be investigated.

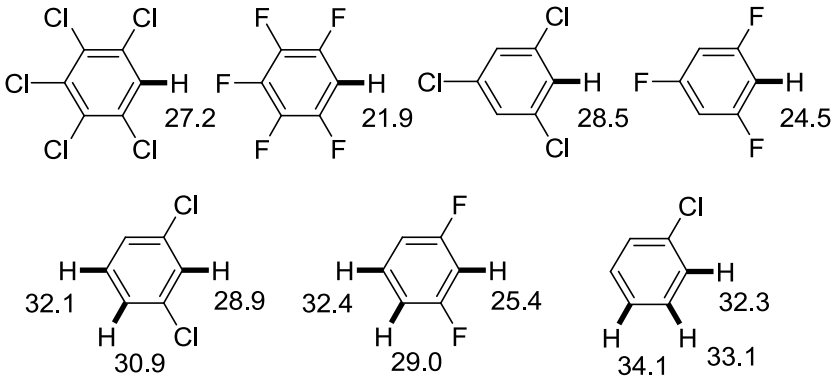



**Figure 4.5**. Gibbs free energies of activation ($\Delta G_{298\ K}$) of the cleavage of C-H bonds for different polyhaloarenes in the CMD process using the [Pd($C_6H_5$)($PMe_3$)(OAc)] catalyst.[4]

In this chapter, we wish to report on (i) the influence of chloro-substituents on benzene on the reactivity and regioselectivity of the palladium-catalyzed direct arylation with aryl halides; (ii) the scope of the reaction using a set of aryl bromides.

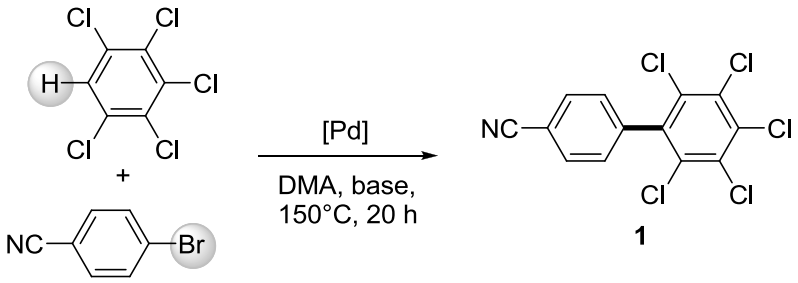
## 4.2 Results and discussions

### 4.2.1 The examination of the reactivity for polychlorobenzenes

#### 4.2.1.1 Optimization for palladium-catalyzed direct arylation of poly-chlorobenzene

Commercially available pentachlorobenzene and 4-bromobenzonitrile were employed as the test substrates (Scheme 4.14, Table 4.1). We initially examined the influence of the nature of the base on the yield of this reaction using 2 mol% of PdCl($C_3H_5$)(dppb) as the catalyst and DMA as the solvent, as such conditions were previously found operative for some direct arylations of (hetero)aromatics.[2b] In all cases, a partial conversion of 4-bromobenzonitrile was observed. In the

presence of NaOAc, KOAc or $K_2CO_3$ as bases, very similar yields of **1** were obtained; whereas, CsOAc was less effective (Table 4.1, entries 1-4). The ratio of the reactants also appeared to have a minor influence on the yield (Table 4.1, entries 2,5). Another catalyst precursor was also employed. However, the use of phosphine-free $Pd(OAc)_2$ led to **1** in similar yield 25% (Table 4.1, entry 6).




**Scheme 4.14**. Influence of the reaction conditions for the palladium-catalyzed direct arylation of pentachlorobenzene with 4-bromobenzonitrile.

**Table 4.1**. Influence of the reaction conditions for the palladium-catalyzed direct arylation of pentachlorobenzene with 4-bromobenzonitrile (Scheme 4.14).

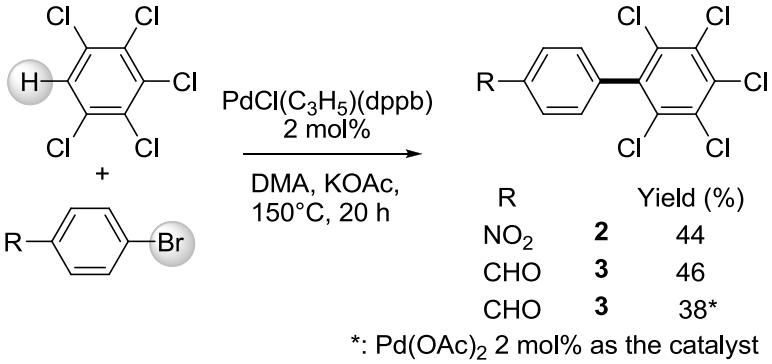
| Entry | Ratio ArBr : $C_6HCl_5$ | Catalyst (mol%) | Base | Yield in **1** (%) |
|---|---|---|---|---|
| 1 | 1:1.5 | $PdCl(C_3H_5)(dppb)$ (2) | NaOAc | 23 |
| 2 | 1:1.5 | $PdCl(C_3H_5)(dppb)$ (2) | KOAc | 24 |
| 3 | 1:1.5 | $PdCl(C_3H_5)(dppb)$ (2) | CsOAc | 8 |
| 4 | 1:1.5 | $PdCl(C_3H_5)(dppb)$ (2) | $K_2CO_3$ | 21 |
| 5 | 1:3 | $PdCl(C_3H_5)(dppb)$ (2) | KOAc | 25 |
| 6 | 1:1.5 | $Pd(OAc)_2$ (2) | KOAc | 25 |

Conditions: base (4 equiv.), DMA, 20 h, 150 ℃.

### 4.2.1.2 The reactivity of pentachlorobenzene

The influence of two other bromobenzene substituents on the reactivity for the coupling with pentachlorobenzene was then examined (Scheme 4.15). In the presence of the electron-deficient

aryl bromides, 4-bromonitrobenzene or 4-bromobenzaldehyde, the products **2** and **3** were obtained in 44% and 46% yields, respectively when $PdCl(C_3H_5)(dppb)$ was employed as the catalyst. The use of $Pd(OAc)_2$ catalyst gave **3** in a lower yield. Again, in all cases, only a partial conversion of the aryl bromide and pentachlorobenzene was observed.

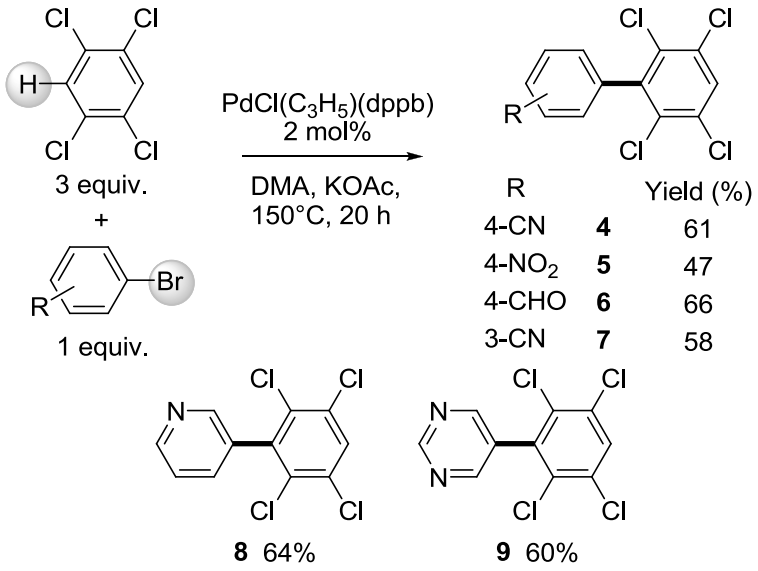



**Scheme 4.15**. Direct arylations of pentachlorobenzene with aryl bromides.

### 4.2.1.3 The reactivity of 1,2,4,5-tetrachlorobenzene

### a) Scope of direct arylation for 1,2,4,5-tetrachlorobenzene

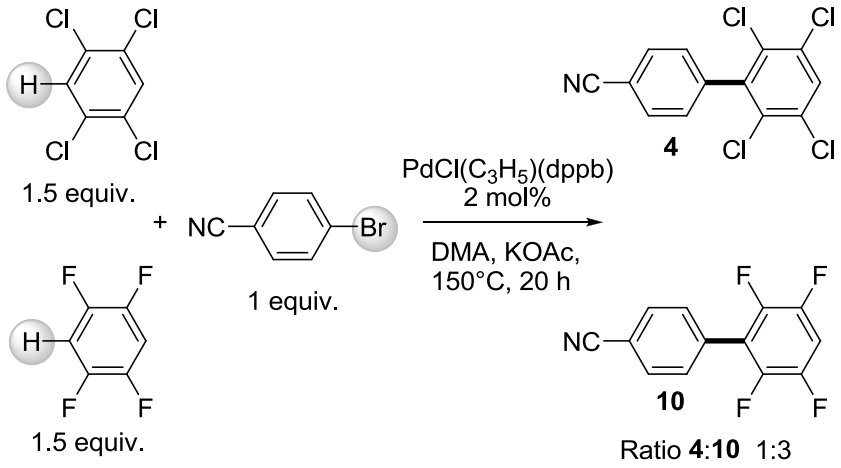
The reactivity of 1,2,4,5-tetrachlorobenzene was found to be slightly higher than pentachlorobenzene (Scheme 4.16). For these couplings, in order to avoid the formation of 1,4-di-arylated tetrachlorobenzenes, 3 equiv. of 1,2,4,5-tetrachlorobenzene were employed. In the presence of aryl bromides substituted at C4 by nitrile, nitro or formyl substituents, the desired mono-arylation products **4**-**6** were obtained in 47-66% yields, and no significant amount of di-arylation products was formed. From 3-bromobenzonitrile, a similar yield of 58 % for **7** was obtained. We also found that the coupling of 3-bromopyridine, or 5-bromopyrimidine proceeded quite nicely to give **8** and **9** in 64% and 60% yields, respectively.




**Scheme 4.16**. Direct arylation of 1,2,4,5-tetrachlorobenzene with various aryl bromides.

## b) The competitive experiment between 1,2,4,5-tetrachlorobenzene and 1,2,4,5-tetrafluorobenzene

In order to gain more insights on the reactivity of chloro- *vs* fluoro-substituted benzenes, we compared the reactivity of tetrachloro- and tetrafluorobenzenes. An equimolar mixture of 1,2,4,5-tetrachlorobenzene and 1,2,4,5-tetrafluorobenzene reacted with 4-bromobenzonitrile gave a mixture of products **4** and **10** in a 1:3 ratio (Scheme 4.17).



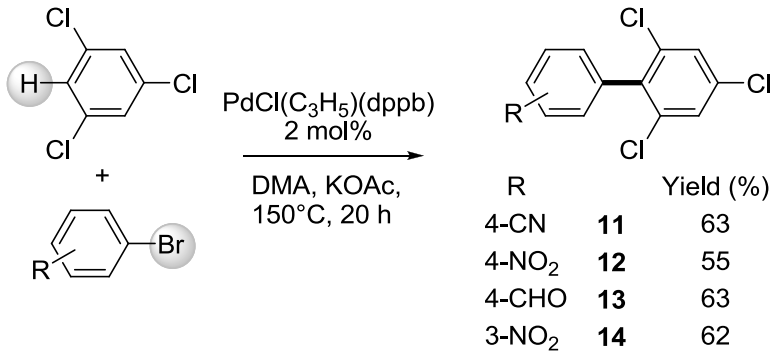

**Scheme 4.17**. Competitive experiment for palladium-catalyzed direct arylation using an equimolar mixture of 1,2,4,5-tetrachlorobenzene and 1,2,4,5-tetrafluorobenzene.

Moreover, some formation of di-arylation product of 1,2,4,5-tetrafluorobenzene was also detected by GC/MS analysis; whereas, no di-arylation of 1,2,4,5-tetrachlorobenzene was observed.

This result confirms that 1,2,4,5-tetrachlorobenzene is less reactive than 1,2,4,5-tetrafluorobenzene for Pd-catalyzed direct arylation.

### 4.2.1.4 The reactivities of 1,3,5-trichlorobenzene and 1,2,3-trichlorobenzene

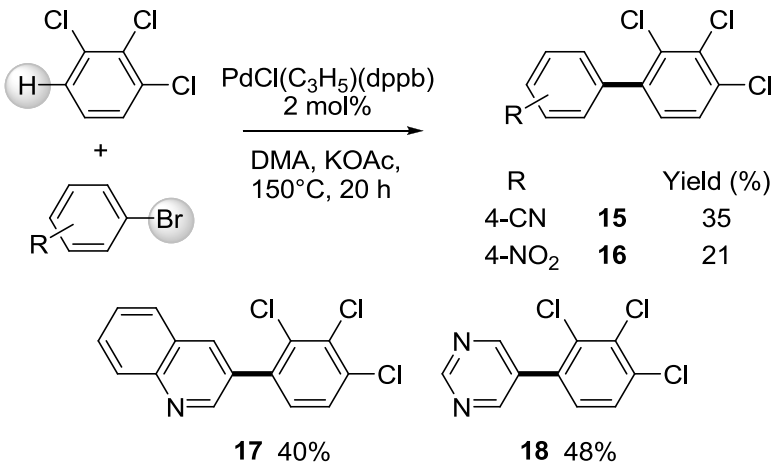
Gorelsky had calculated a Gibbs free energies of activation for direct arylation of 1,3,5-trichlorobenzene of 28.5 (Fig. 4.5).[15c] Under similar conditions, the desired arylation products **11-14** were obtained in higher yields with 1,3,5-trichlorobenzene than with pentachlorobenzene (Scheme 4.18). Very similar yields were obtained from cyano-, nitro- or formyl-substituted bromobenzenes.




| R | | Yield (%) |
|---|---|---|
| 4-CN | **11** | 63 |
| 4-$NO_2$ | **12** | 55 |
| 4-CHO | **13** | 63 |
| 3-$NO_2$ | **14** | 62 |

**Scheme 4.18**. Direct arylation of 1,3,5-trichlorobenzene with various aryl bromides.

1,2,3-Trichlorobenzene reacted with 4-bromobenzonitrile and 4-bromonitrobenzene, respectively, gave **15** and **16** in poor yields (Scheme 4.19). Noteworthily, the reaction was regioselective in favor of the formation of the 4-arylated products. Better yields were obtained for the coupling with 3-bromoquinoline and 5-bromopyrimidine, as the desired products **17** and **18** were obtained in 40 and 48% yields, respectively.

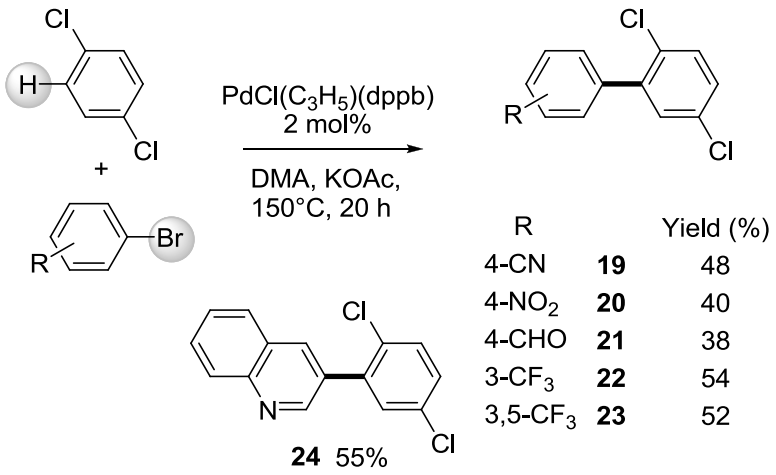



**Scheme 4.19**. Direct arylation of 1,2,3-trichlorobenzene with various aryl bromides.

### 4.2.1.5 The reactivities of 1,4-dichlorobenzene and 1,3-dichlorobenzene

### a) Scope of direct arylation for 1,4-dichlorobenzene

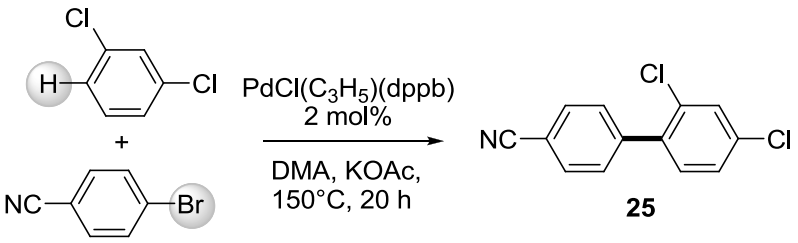
Unexpectedly, quite good yields were obtained for the coupling of 1,4-dichlorobenzene with aryl bromides. From 4-bromobenzonitrile, **19** was obtained in 48% yield (Scheme 4.20). Both 3-trifluoromethylbromobenzene and 3,5-bis(trifluoromethyl)bromobenzene also gave the expected products **22** and **23** in quite good yields, 54% and 52%, respectively. The best yield was obtained in the presence of 3-bromoquinoline to give **24** in 55% yield.




**Scheme 4.20**. Direct arylation of 1,4-dichlorobenzene with various aryl bromides.

### b) The test of reactivity for 1,3-dichlorobenzene

According to Gorelsky, for 1,3-dichlorobenzene, the carbon 2 should be more reactive than carbon 4 (energies: 28.5 vs 24.5) (Fig. 4.5).[4] Our first attempt of coupling of 1,3-dichlorobenzene with 4-bromobenzonitrile using $PdCl(C_3H_5)$(dppb) catalyst and KOAc as base in DMA led to a mixture of two regioisomers according to GC/MS analysis. Surprisingly, the major product of the reaction was the C4-arylated 1,3-dichlorobenzene **25** with a selectivity of 66% (Scheme 4.21, table 4.2). Arylation at the less reactive C4 position might be due to the steric hindrance of the chloro substituents. The influence of several reaction parameters has been studied, but in all cases, the same regioselectivity was obtained. However, the reactions performed in DMF or NMP led to lower yields of **25** due to the formation of side-products; whereas, $Pd(OAc)_2$ gave a lower conversion.




**Scheme 4.21**. Direct arylation of 1,3-dichlorobenzene with 4-bromobenzonitrile.

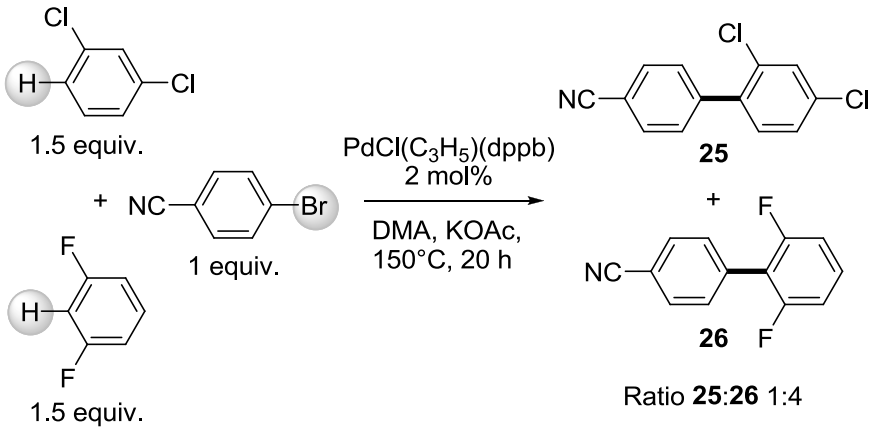
**Table 4.2**. Influence of the reaction conditions for the palladium-catalyzed direct arylation of 1,3-dichlorobenzene with 4-bromobenzonitrile (Scheme 4.21).

| Entry | Catalyst (mol%) | Solvent | Conv. (%) | Yield in **25** (%) |
|---|---|---|---|---|
| 1 | $PdCl(C_3H_5)$(dppb) (2) | DMA | 57 | 34 |
| 2 | $PdCl(C_3H_5)$(dppb) (2) | DMF | 64 | 25 |
| 3 | $PdCl(C_3H_5)$(dppb) (2) | NMP | 56 | 26 |
| 4 | $Pd(OAc)_2$ (2) | DMA | 47 | - |
| 5 | $Pd(OAc)_2$ (2) / dppe (2) | DMA | 69 | 33 |
| 6 | $Pd(OAc)_2$ (2) / dppb (2) | DMA | 54 | - |

Conditions: 4-bromobenzonitrile (1 equiv.), 1,3-dichlorobenzene (3 equiv.), KOAc (4 equiv.), 20 h, 150 ℃, conv. of 4-bromobenzonitrile, in all cases **25** was obtained in 66% regioselectivity.

### c) Competitive reaction between 1,3-dichlorobenzene and 1,3-difluorobenzene

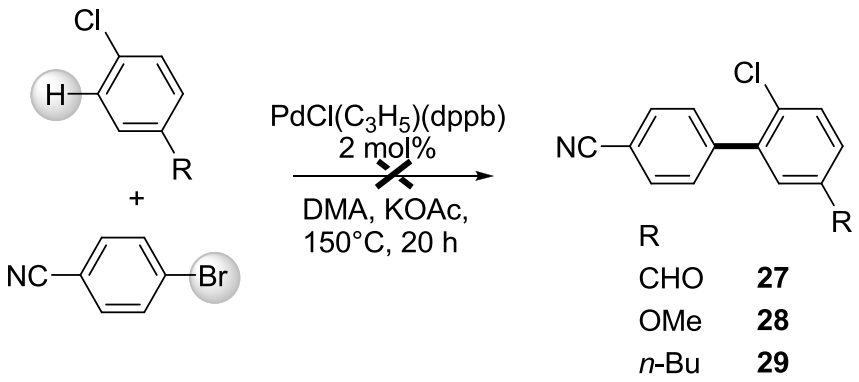
The reaction of an equimolar mixture of 1,3-dichlorobenzene and 1,3-difluorobenzene using the same reaction conditions gave a mixture of the 2-arylated 1,3-difluorobenzene **26** and the 4-arylated 1,3-dichlorobenzene **25** in a 4:1 ratio (Scheme 4.22). Again, the fluorobenzene derivative is more reactive than the chlorobenzene derivative. Moreover, the regioselectivities of these two reactions were different; the less sterically demanding fluoro substituents making possible the calculated arylation at C2 (Fig. 4.5).




**Scheme 4.22**. Competitive experiment for palladium-catalyzed direct arylation using an equimolar mixture of 1,3-dichlorobenzene and 1,3-difluorobenzene.

### 4.2.1.6 The reactivities of 4-substituted chlorobenzenes

The reactivity of three 4-substituted chlorobenzenes with 4-bromobenzonitrile as coupling partner using similar reaction conditions was also examined (Scheme 4.23). However, the presence of electron-withdrawing or -donating substituents on chlorobenzene led to unreacted aryl bromide, and no formation of the target products **27**-**29** was detected.

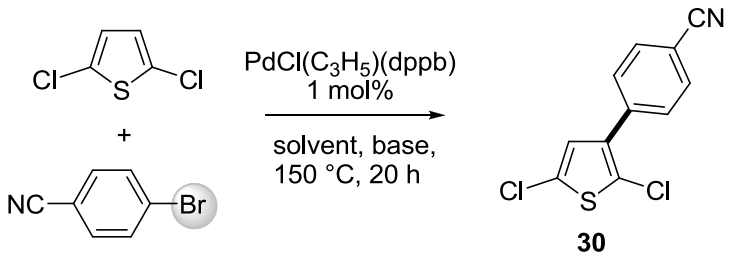



**Scheme 4.23**. Attempts of direct arylation of 4-substituted chlorobenzenes with 4-bromobenzonitrile.

## 4.2.2 The examination of the reactivity for 2,5-dichlorothiophene

### 4.2.2.1 Optimization for palladium-catalyzed arylation of 2,5-dichlorothiophene

We also examined the reactivity of 2,5-dichlorothiophene for direct arylation (Schemes 4.24 and 4.25). The influence of a few reaction parameters has been examined. The best yield in **30** was obtained using 1 mol% $PdCl(C_3H_5)$(dppb) catalyst in DMF with KOAc as the base. However, quite similar results were obtained in DMA or using 2 mol% $Pd(OAc)_2$/dppb as catalyst.




**Scheme 4.24**. Direct arylation of 2,5-dichlorothiophene with various aryl bromides.

**Table 4.3**. Influence of the reaction conditions for the palladium-catalyzed direct arylation of 2,5-dichlorothiophene with 4-bromobenzonitrile (Scheme 4.24).

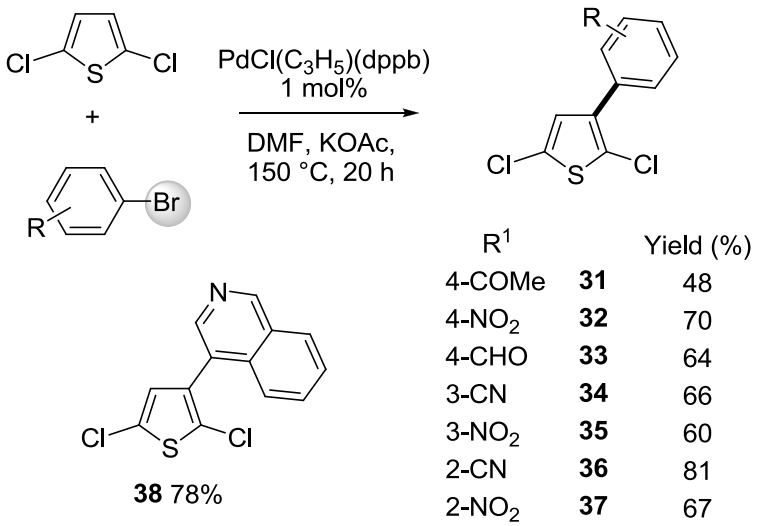
| Entry | Catalyst (mol%) | Base | Solvent | Conv. (%) | Yield in **30** (%) |
|---|---|---|---|---|---|
| 1 | $PdCl(C_3H_5)$(dppb) (1) | KOAc | DMA | 70 | 56 |
| 2 | $PdCl(C_3H_5)$(dppb) (2) | KOAc | DMA | 78 | 60 |
| 3 | $PdCl(C_3H_5)$(dppb) (1) | CsOAc | DMA | 30 | - |

| | | | | | |
|---|---|---|---|---|---|
| 4 | $PdCl(C_3H_5)(dppb)$ (1) | KOAc | NMP | 60 | 50 |
| 5 | $PdCl(C_3H_5)(dppb)$ (1) | KOAc | DMF | 87 | 63 |
| 6 | $PdCl(C_3H_5)(dppb)$ (0.5) | KOAc | DMF | 44 | - |
| 7 | $Pd(OAc)_2$ (2)/dppb (2) | KOAc | DMF | 88 | 62 |

Conditions: 4-bromobenzonitrile (1 equiv.), 2,5-dichlorothiophene (2 equiv.), base (4 equiv.), 20 h, 150 ℃, conv. of 4-bromobenzonitrile.

### 4.2.2.2 Scope of direct arylation for 2,5-dichlorothiophene

The reaction tolerates a variety of substituents on the aryl bromide such as acetyl, formyl, nitrile or nitro (Scheme 4.25). The best yields were obtained for the reactions with 2-bromobenzonitrile and 4-bromoisoquinoline. With these reactants, the desired products **36** and **38** were obtained in 81 and 78% yields, respectively. On the other hand, from 4-bromoacetophenone, **31** was only produced in 48% yield due to the formation of unidentified side-products.




| $R^1$ | | Yield (%) |
|---|---|---|
| 4-COMe | **31** | 48 |
| 4-$NO_2$ | **32** | 70 |
| 4-CHO | **33** | 64 |
| 3-CN | **34** | 66 |
| 3-$NO_2$ | **35** | 60 |
| 2-CN | **36** | 81 |
| 2-$NO_2$ | **37** | 67 |

**Scheme 4.25**. Direct arylation of 2,5-dichlorothiophene with various aryl bromides.

## 4.3 Conclusion

In summary, we report herein the first examples of palladium-catalyzed direct *ortho*-arylation of polychlorobenzene derivatives with aryl bromides using chloro-substituent as a directing group. The reactivity of polychlorobenzenes was found to be lower than the corresponding

polyfluorobenzene derivatives as calculated by Gorelsky. The influence of the number and positions of chloro-substituents on benzene on their reactivity was studied. The steric properties of chloro-substituents likely partially modify the reactivity of this family of compounds. Although moderate yields were obtained in several cases, this method gives access to functionalized polychlorobiphenyls in only one step.

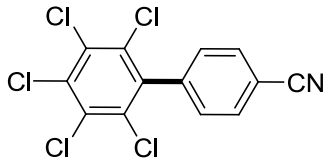
## 4.4 Experimental details

**General Remarks:** All reactions were performed in Schlenk tubes under argon. DMA of analytical grade was used without any distillation. Potassium acetate 99+ was used. Commercial aryl halide derivatives were used without purification. $^{1}H$ (300 and 400 MHz), $^{13}C$ (75 and 100 MHz) spectra were recorded in $CDCl_3$ solutions. Chemical shifts are reported in ppm relative to $CDCl_3$ ($^{1}H$: 7.26 and $^{13}C$: 77.0). Flash chromatography was performed on silica gel (230-400 mesh).

**General procedure for the Syntheses of compounds 1-31**

As a typical experiment, the reaction of the aryl bromide (1 mmol), polychlorobenzene derivative (1.5 or 3 mmol) and KOAc (0.392 g, 4 mmol) at 150 ℃ for 20 h in DMA (4 mL) in the presence of $PdCl(C_3H_5)$(dppb) (12.2 mg, 0.02 mmol) under argon afforded the coupling product after evaporation of the solvent and purification on silica gel.

**2′,3′,4′,5′,6′-Pentachlorobiphenyl-4-carbonitrile 1**

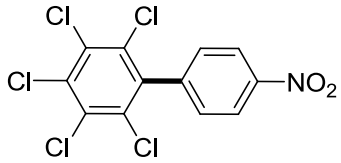



From 4-bromobenzonitrile (0.182 g, 1 mmol) and pentachlorobenzene (0.375 g, 1.5 mmol), **1** was obtained in 25% (0.088 g) yield as a yellow solid.

Eluent pentane: diethylether 20:1

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 141.3, 138.4, 134.2, 132.6, 132.4, 132.2, 130.0, 118.2, 113.0. Elemental analysis: calcd (%) for $C_{13}H_4Cl_5N$ (351.44): C 44.43, H 1.15; found: C 44.50, H 1.22.

**2,3,4,5,6-Pentachloro-4′-nitrobiphenyl 2**[17]

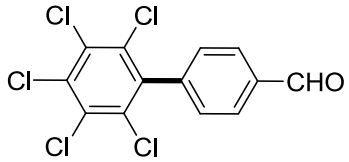



From 4-bromonitrobenzene (0.202 g, 1 mmol) and pentachlorobenzene (0.375 g, 1.5 mmol), **2** was obtained in 44% (0.163 g) yield as a white solid.

Eluent pentane

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.39 (d, *J* = 8.9 Hz, 2H), 7.43 (d, *J* = 8.9 Hz, 2H).

**2′,3′,4′,5′,6′-Pentachlorobiphenyl-4-carbaldehyde 3**

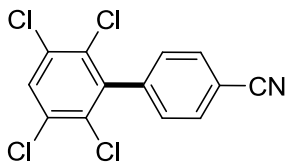



From 4-bromobenzaldehyde (0.185 g, 1 mmol) and pentachlorobenzene (0.375 g, 1.5 mmol), **3** was obtained in 46% (0.163 g) yield as a white solid.

Eluent pentane: diethylether 100:1

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 10.12 (s, 1H), 8.04 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 191.5, 142.8, 139.1, 136.4, 133.9, 132.3, 132.2, 130.0, 129.8. Elemental analysis: calcd (%) for $C_{13}H_5Cl_5O$ (354.44): C 44.05, H 1.42; found: C 44.14, H 1.60.

**2′,3′,5′,6′-Tetrachlorobiphenyl-4-carbonitrile 4**

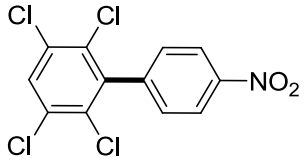


From 4-bromobenzonitrile (0.182 g, 1 mmol) and 1,2,4,5-tetrachlorobenzene (0.647 g, 3 mmol), **4** was obtained in 61% (0.193 g) yield as a white solid.

Eluent pentane: diethylether 10:1

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.0 Hz, 2H), 7.62 (s, 1H), 7.27 (d, *J* = 8.0 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 141.6, 140.7, 132.5, 132.4, 131.4, 130.9, 130.0, 118.3, 112.8. Elemental analysis: calcd (%) for $C_{13}H_5Cl_4N$ (317.00): C 49.26, H 1.59; found: C 49.40, H 1.49.

**2,3,5,6-Tetrachloro-4′-nitrobiphenyl 5**

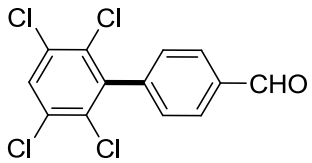



From 4-bromonitrobenzene (0.202 g, 1 mmol) and 1,2,4,5-tetrachlorobenzene (0.647 g, 3 mmol), **5** was obtained in 47% (0.158 g) yield as a yellow solid.

Eluent pentane: diethylether 10:1.

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.29 (d, *J* = 8.9 Hz, 2H), 7.64 (s, 1H), 7.43 (d, *J* = 8.9 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 148.0, 143.4, 140.4, 132.5, 131.4, 131.0, 130.3, 124.0. Elemental analysis: calcd (%) for $C_{12}H_5Cl_4NO_2$ (336.98): C 42.77, H 1.50; found: C 42.64, H 1.38.

**2′,3′,5′,6′-Tetrachlorobiphenyl-4-carbaldehyde 6**

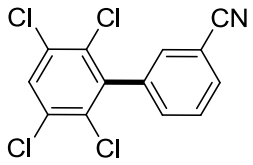



From 4-bromobenzaldehyde (0.185 g, 1 mmol) and 1,2,4,5-tetrachlorobenzene (0.647 g, 3 mmol), **6** was obtained in 66% (0.211 g) yield as a white solid.

Eluent pentane: diethylether 10:1

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 10.03 (s, 1H), 7.94 (d, *J* = 8.4 Hz, 2H), 7.61 (s, 1H), 7.32 (d, *J* = 8.4 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 191.6, 143.0, 141.3, 136.3, 132.3, 131.5, 130.7, 130.0, 129.9. Elemental analysis: calcd (%) for $C_{13}H_6Cl_4O$ (320.00): C 48.79, H 1.89; found: C 48.62, H 2.04.

**2′,3′,5′,6′-Tetrachlorobiphenyl-3-carbonitrile 7**

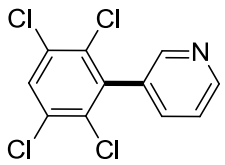



From 3-bromobenzonitrile (0.182 g, 1 mmol) and 1,2,4,5-tetrachlorobenzene (0.647 g, 3 mmol), **7** was obtained in 58% (0.184 g) yield as a white oil.

Eluent pentane: diethylether 100:3

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, *J* = 7.8 Hz, 1H), 7.63 (s, 1H), 7.55 (t, *J* = 7.8 Hz, 1H), 7.46 (s, 1H), 7.39 (d, *J* = 7.8 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 141.2, 138.3, 133.6, 132.7, 132.4, 132.3, 131.8, 130.9, 129.6, 118.2, 113.2. Elemental analysis: calcd (%) for $C_{13}H_5Cl_4N$ (317.00): C 49.26, H 1.59; found: C 49.21, H 1.64.

**3-(2,3,5,6-Tetrachlorophenyl)-pyridine 8**

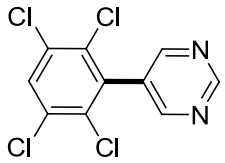



From 3-bromopyridine (0.158 g, 1 mmol) and 1,2,4,5-tetrachlorobenzene (0.647 g, 3 mmol), **8** was obtained in 64% (0.187 g) yield as a yellow solid.

Eluent pentane: diethylether 10:2

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.68 (bs, 1H), 8.47 (bs, 1H), 7.64 (s, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.47 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 148.5, 148.4, 138.5, 138.1, 132.5, 132.2, 131.2. Elemental analysis: calcd (%) for $C_{11}H_5Cl_4N$ (292.97): C 45.10, H 1.72; found: C 45.27, H 1.89.

**5-(2,3,5,6-Tetrachlorophenyl)-pyrimidine 9**

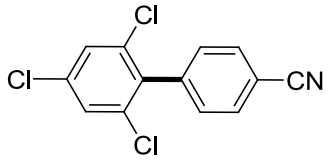



From 5-bromopyrimidine (0.159 g, 1 mmol) and 1,2,4,5-tetrachlorobenzene (0.647 g, 3 mmol), **9** was obtained in 60% (0.176 g) yield as a yellow solid.

Eluent pentane: diethylether 10:1

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 9.24 (s, 1H), 8.61 (s, 2H), 7.67 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 158.5, 157.0, 135.7, 132.7, 132.2, 131.7, 131.6. Elemental analysis: calcd (%) for $C_{10}H_4Cl_4N_2$ (293.96): C 40.86, H 1.37; found: C 40.77, H 1.27.

**2′,4′,6′-Trichlorobiphenyl-4-carbonitrile 11**

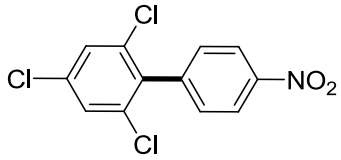



From 4-bromobenzonitrile (0.182 g, 1 mmol) and 1,3,5-trichlorobenzene (0.544 g, 3 mmol), **11** was obtained in 63% (0.178 g) yield as a yellow oil.

Eluent pentane: diethylether 10:1

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.1 Hz, 2H), 7.39 (s, 2H), 7.30 (d, *J* = 8.1 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 140.5, 136.3, 135.0, 134.9, 132.2, 130.6, 128.3, 118.5, 112.5. Elemental analysis: calcd (%) for $C_{13}H_6Cl_3N$ (282.55): C 55.26, H 2.14; found: C 55.11, H 2.07.

**2,4,6-Trichloro-4′-nitrobiphenyl 12**

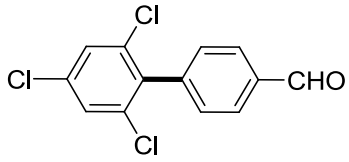


From 4-bromonitrobenzene (0.202 g, 1 mmol) and 1,3,5-trichlorobenzene (0.544 g, 3 mmol), **12** was obtained in 55% (0.166 g) yield as a white oil.

Eluent pentane: diethylether 100:1

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, *J* = 8.7 Hz, 2H), 7.39 (s, 2H), 7.36 (d, *J* = 8.7 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 146.8, 141.3, 135.0, 134.1, 133.9, 129.9, 127.4, 122.7. Elemental analysis: calcd (%) for $C_{12}H_6Cl_3NO_2$ (302.54): C 47.64, H 2.00; found: C 47.80, H 1.88.

**2′,4′,6′-Trichlorobiphenyl-4-carbaldehyde 13**

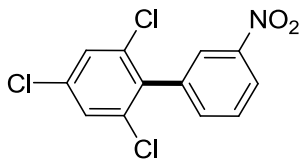



From 4-bromobenzaldehyde (0.185 g, 1 mmol) and 1,3,5-trichlorobenzene (0.544 g, 3 mmol), **13** was obtained in 63% (0.180 g) yield as a white solid.

Eluent pentane

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 10.02 (s, 1H), 7.93 (d, *J* = 8.1 Hz, 2H), 7.39 (s, 2H), 7.35 (d, *J* = 8.1 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 191.7, 142.0, 136.9, 136.1, 135.0, 134.7, 130.5, 129.7, 128.3. Elemental analysis: calcd (%) for $C_{13}H_7Cl_3O$ (285.55): C 54.68, H 2.47; found: C 54.49, H 2.67.

**2,4,6-Trichloro-3′-nitrobiphenyl 14**

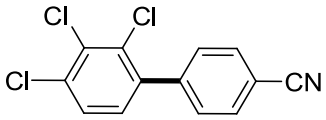



From 3-bromonitrobenzene (0.202 g, 1 mmol) and 1,3,5-trichlorobenzene (0.544 g, 3 mmol), **14** was obtained in 62% (0.187 g) yield as a yellow solid.

Eluent pentane: diethylether 10:1

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, *J* = 8.7 Hz, 1H), 8.08 (s, 1H), 7.59 (t, *J* = 8.0 Hz, 1H), 7.51 (d, *J* = 8.7 Hz, 1H), 7.41 (s, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 148.3, 137.3, 135.9, 135.7, 135.3, 135.2, 129.5, 128.4, 125.0, 123.5. Elemental analysis: calcd (%) for $C_{12}H_6Cl_3NO_2$ (302.54): C 47.64, H 2.00; found: C 47.61, H 1.97.

**2′,3′,4′-Trichlorobiphenyl-4-carbonitrile 15**

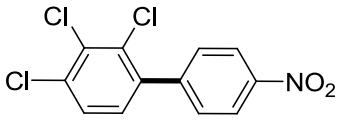



From 4-bromobenzonitrile (0.182 g, 1 mmol) and 1,2,3-trichlorobenzene (0.544 g, 3 mmol), **15** was obtained in 35% (0.099 g) yield as a white solid.

Eluent pentane: diethylether 100:1

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.0 Hz, 2H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 8.3 Hz, 1H), 7.09 (d, *J* = 8.3 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 143.1, 139.1, 134.4, 132.8, 132.6, 132.1, 130.1, 128.8, 128.5, 118.4, 112.2. Elemental analysis: calcd (%) for $C_{13}H_6Cl_3N$ (282.55): C 55.26, H 2.14; found: C 55.08, H 2.22.

**2,3,4-Trichloro-4′-nitrobiphenyl 16**

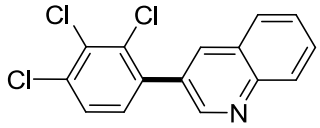



From 4-bromonitrobenzene (0.202 g, 1 mmol) and 1,2,3-trichlorobenzene (0.544 g, 3 mmol), **16** was obtained in 21% (0.063 g) yield as a white solid.

Eluent pentane: diethylether 100:1

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, *J* = 8.9 Hz, 2H), 7.50 (d, *J* = 8.9 Hz, 2H), 7.43 (d, *J* = 8.3 Hz, 1H), 7.12 (d, *J* = 8.3 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 147.7, 144.9, 138.8, 134.6, 132.9, 132.6, 130.3, 128.8, 128.5, 123.6. Elemental analysis: calcd (%) for $C_{12}H_6Cl_3NO_2$ (302.54): C 47.64, H 2.00; found: C 47.49, H 1.89.

**3-(2,3,4-Trichlorophenyl)-quinoline 17**

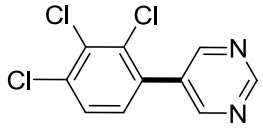



From 3-bromoquinoline (0.208 g, 1 mmol) and 1,2,3-trichlorobenzene (0.544 g, 3 mmol), **17** was obtained in 40% (0.123 g) yield as a white solid.

Eluent pentane: diethylether 10:3

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.89 (s, 1H), 8.15-8.10 (m, 2H), 7.82 (d, *J* = 8.1 Hz, 1H), 7.73 (t, *J* = 8.0 Hz, 1H), 7.56 (t, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 8.3 Hz, 1H), 7.21 (d, *J* = 8.3 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 150.2, 146.9, 137.4, 136.5, 134.3, 133.3, 132.8, 131.7, 130.5, 129.4, 129.0, 128.6, 128.1, 127.5, 127.4. Elemental analysis: calcd (%) for $C_{15}H_8Cl_3N$ (308.59): C 58.38, H 2.61; found: C 58.28, H 2.57.

**5-(2,3,4-Trichlorophenyl)-pyrimidine 18**

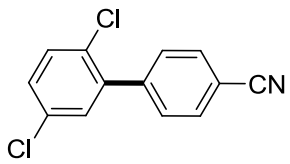



From 5-bromopyrimidine (0.159 g, 1 mmol) and 1,2,3-trichlorobenzene (0.544 g, 3 mmol), **18** was obtained in 48% (0.124 g) yield as a brown solid.

Eluent pentane: diethylether 10:3

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 9.21 (s, 1H), 8.76 (s, 2H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 158.1, 156.7, 135.2, 133.9, 133.2, 128.9, 128.8. Elemental analysis: calcd (%) for $C_{10}H_5Cl_3N_2$ (259.52): C 46.28, H 1.94; found: C 46.41, H 2.01.

**2′,5′-Dichlorobiphenyl-4-carbonitrile 19**

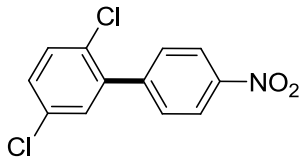


From 4-bromobenzonitrile (0.182 g, 1 mmol) and 1,4-dichlorobenzene (0.441 g, 3 mmol), **19** was obtained in 48% (0.119 g) yield as a white solid.

Eluent pentane: diethylether 10:1

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 8.0 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 9.0 Hz, 1H), 7.28-7.23 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 142.6, 140.0, 133.0, 132.0, 131.4, 130.8, 130.6, 130.1, 129.6, 118.5, 112.1. Elemental analysis: calcd (%) for $C_{13}H_7Cl_2N$ (248.11): C 62.93, H 2.84; found: C 62.74, H 2.71.

**2,5-Dichloro-4′-nitrobiphenyl 20**[18]

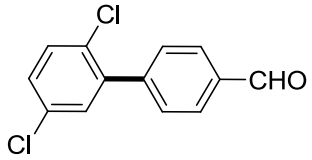



From 4-bromonitrobenzene (0.202 g, 1 mmol) and 1,4-dichlorobenzene (0.441 g, 3 mmol), **20** was obtained in 40% (0.107 g) yield as a white oil.

Eluent pentane: diethylether 10:1

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, *J* = 8.3 Hz, 2H), 7.53 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 9.0 Hz, 1H), 7.30-7.23 (m, 2H).

**2′,5′-Dichlorobiphenyl-4-carbaldehyde 21**



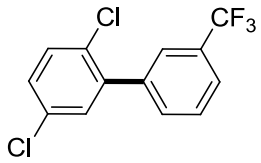

From 4-bromobenzaldehyde (0.185 g, 1 mmol) and 1,4-dichlorobenzene (0.441 g, 3 mmol), **21** was obtained in 38% (0.095 g) yield as a yellow oil.

Eluent pentane: diethylether 100:3

$^{1}$H NMR (400 MHz, $CDCl_3$): 10.02 (s, 1H), 7.90 (d, *J* = 8.0 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 9.0 Hz, 1H), 7.28 (d, *J* = 2.4 Hz, 1H), 7.25 (dd, *J* = 9.0, 2.4 Hz, 1H). $^{13}$C NMR (100

MHz, $CDCl_3$): 191.8, 144.1, 140.7, 135.8, 132.9, 131.3, 130.9, 130.7, 130.1, 129.6, 129.3. Elemental analysis: calcd (%) for $C_{13}H_8Cl_2O$ (251.11): C 62.18, H 3.21; found: C 62.10, H 3.08.

**2,5-Dichloro-3′-trifluoromethylbiphenyl 22**

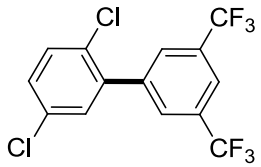



From 3-trifluoromethylbromobenzene (0.225 g, 1 mmol) and 1,4-dichlorobenzene (0.441 g, 3 mmol), **22** was obtained in 54% (0.157 g) yield as a white oil.

Eluent pentane

$^1$H NMR (400 MHz, $CDCl_3$): δ 7.61 (s, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.50 (t, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 9.0 Hz, 1H), 7.28 (d, *J* = 2.4 Hz, 1H), 7.25 (dd, *J* = 9.0, 2.4 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 140.4, 138.8, 132.9, 132.7, 133.2, 131.0, 130.8 (q, *J* = 32.0 Hz), 129.2, 128.7, 128.5, 126.1 (q, *J* = 3.9 Hz), 124.9 (q, *J* = 3.7 Hz), 124.0 (q, *J* = 271.9 Hz). Elemental analysis: calcd (%) for $C_{13}H_7Cl_2F_3$ (291.10): C 53.64, H 2.42; found: C 53.82, H 2.28.

**2,5-Dichloro-3′,5′-bis-trifluoromethylbiphenyl 23**

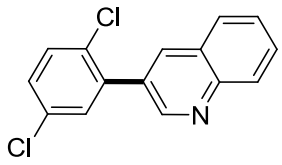



From 1-bromo-3,5-bis(trifluoromethyl)benzene (0.293 g, 1 mmol) and 1,4-dichlorobenzene (0.441 g, 3 mmol), **23** was obtained in 52% (0.187 g) yield as a white solid.

Eluent pentane

$^1$H NMR (400 MHz, $CDCl_3$): δ 7.86 (s, 1H), 7.82 (s, 2H), 7.39 (d, *J* = 9.0 Hz, 1H), 7.32-7.25 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 140.0, 138.8, 133.2, 131.7 (q, *J* = 33.0 Hz), 131.4, 130.9, 130.7, 130.0, 129.6 (m), 123.1 (q, *J* = 271.5 Hz), 122.0 (q, *J* = 3.8 Hz). Elemental analysis: calcd (%) for $C_{14}H_6Cl_2F_6$ (359.09): C 46.83, H 1.68; found: C 46.74, H 1.79.

**3-(2,5-Dichlorophenyl)-quinoline 24**

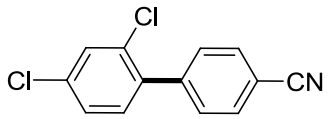



From 3-bromoquinoline (0.208 g, 1 mmol) and 1,4-dichlorobenzene (0.441 g, 3 mmol), **24** was obtained in 55% (0.151 g) yield as a yellow solid.

Eluent pentane: diethylether 10:3

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.94 (s, 1H), 8.20 (s, 1H), 8.16 (d, *J* = 8.1 Hz, 1H), 7.83 (d, *J* = 8.1 Hz, 1H), 7.74 (t, *J* = 7.9 Hz, 1H), 7.57 (t, *J* = 7.9 Hz, 1H), 7.41 (d, *J* = 9.0 Hz, 1H), 7.38 (d, *J* = 2.4 Hz, 1H), 7.29 (dd, *J* = 9.0, 2.4 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 149.4, 145.7, 137.8, 137.6, 133.2, 131.5, 131.4, 131.3, 131.2, 131.0, 129.8, 128.2, 128.1, 127.8, 127.6. Elemental analysis: calcd (%) for $C_{15}H_9Cl_2N$ (274.14): C 65.72, H 3.31; found: C 65.67, H 3.17.

**2′,4′-Dichlorobiphenyl-4-carbonitrile 25**

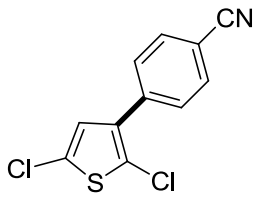



From 4-bromobenzonitrile (0.182 g, 1 mmol) and and 1,3-dichlorobenzene (0.441 g, 3 mmol), **25** was obtained in 34% (0.084 g) yield as a white solid.

Eluent pentane

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 8.0 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 1.9 Hz, 1H), 7.28 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.18 (d, *J* = 8.3 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 142.8, 137.2, 135.0, 133.0, 132.0, 131.7, 130.2, 130.1, 127.5, 118.6, 111.9. Elemental analysis: calcd (%) for $C_{13}H_7Cl_2N$ (248.11): C 62.93, H 2.84; found: C 63.07, H 3.04.

**4-(2,5-Dichlorothiophen-3-yl)-benzonitrile 30**

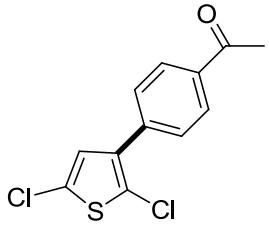



From 4-bromobenzonitrile (0.182 g, 1 mmol) and 2,5-dichlorothiophene (0.306 g, 2 mmol), **30** was obtained in 63% (0.160 g) yield as a yellow solid.

Eluent pentane: diethylether 9:1

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.0 Hz, 2H), 7.63 (d, *J* = 8.0 Hz, 2H), 6.91 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 137.7, 136.2, 132.4, 129.0, 127.4, 126.8, 123.6, 118.5, 111.7. Elemental analysis: calcd (%) for $C_{11}H_5Cl_2NS$ (254.14): C 51.99, H 1.98; found: C 52.12, H 2.14.

**1-[4-(2,5-Dichlorothiophen-3-yl)-phenyl]-ethanone 31**

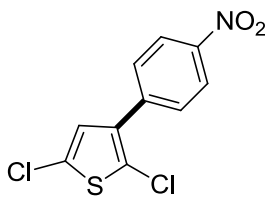



From 4-bromoacetophenone (0.199 g, 1 mmol) and 2,5-dichlorothiophene (0.306 g, 2 mmol), **31** was obtained in 48% (0.130 g) yield as a brown solid.

Eluent pentane: diethylether 10:1

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, *J* = 8.0 Hz, 2H), 7.62 (d, *J* = 8.0 Hz, 2H), 6.94 (s, 1H), 2.63 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 197.4, 137.8, 137.0, 136.3, 128.6, 128.5, 127.1, 127.0, 123.0, 26.6. Elemental analysis: calcd (%) for $C_{12}H_8Cl_2OS$ (271.16): C 53.15, H 2.97; found: C 53.29, H 3.09.

**2,5-Dichloro-3-(4-nitrophenyl)-thiophene 32**

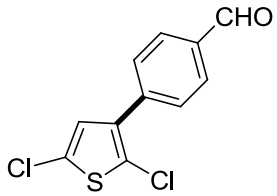


From 4-bromonitrobenzene (0.202 g, 1 mmol) and 2,5-dichlorothiophene (0.306 g, 2 mmol), **32** was obtained in 70% (0.192 g) yield as a brown solid.

Eluent pentane: diethylether 10:1

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.29 (d, *J* = 8.5 Hz, 2H), 7.69 (d, *J* = 8.5 Hz, 2H), 6.95 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 147.2, 139.5, 135.8, 129.2, 127.6, 126.8, 123.9, 123.8. Elemental analysis: calcd (%) for $C_{10}H_5Cl_2NO_2S$ (274.12): C 43.81, H 1.84; found: C 43.98, H 1.89.

**4-(2,5-Dichlorothiophen-3-yl)-benzaldehyde 33**

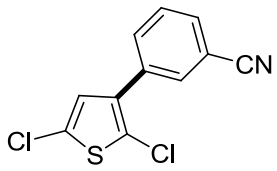



From 4-bromobenzaldehyde (0.185 g, 1 mmol) and 2,5-dichlorothiophene (0.306 g, 2 mmol), **33** was obtained in 64% (0.164 g) yield as a yellow solid.

Eluent pentane: diethylether 10:1

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 10.05 (s, 1H), 7.94 (d, *J* = 8.0 Hz, 2H), 7.69 (d, *J* = 8.0 Hz, 2H), 6.95 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 191.6, 139.1, 136.8, 135.5, 129.9, 128.9, 127.2, 127.0, 123.3. Elemental analysis: calcd (%) for $C_{11}H_6Cl_2OS$ (257.14): C 51.38, H 2.35; found: C 51.09, H 2.20.

**3-(2,5-Dichlorothiophen-3-yl)-benzonitrile 34**

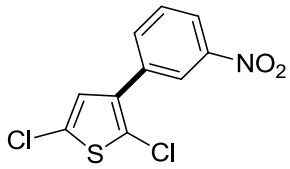



From 3-bromobenzonitrile (0.182 g, 1 mmol) and and 2,5-dichlorothiophene (0.306 g, 2 mmol), **34** was obtained in 66% (0.168 g) yield as a white solid.

Eluent pentane: diethylether 9:1

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.81 (s, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 6.90 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 135.7, 134.5, 132.6, 131.8, 131.4, 129.5, 127.4, 126.8, 123.2, 118.4, 112.9. Elemental analysis: calcd (%) for $C_{11}H_5Cl_2NS$ (254.14): C 51.99, H 1.98; found: C 52.20, H 2.17.

**2,5-Dichloro-3-(3-nitrophenyl)-thiophene 35**

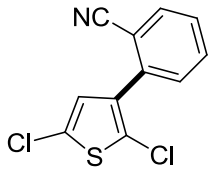



From 3-bromonitrobenzene (0.202 g, 1 mmol) and 2,5-dichlorothiophene (0.306 g, 2 mmol), **35** was obtained in 60% (0.164 g) yield as a yellow solid.

Eluent pentane: diethylether 10:1

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.39 (s, 1H), 8.22 (d, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.62 (t, *J* = 7.6 Hz, 1H), 6.96 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 148.4, 135.6, 134.8, 134.2, 129.6, 127.5, 126.8, 123.5, 123.3, 122.8. Elemental analysis: calcd (%) for $C_{10}H_5Cl_2NO_2S$ (274.12): C 43.81, H 1.84; found: C 43.67, H 1.70.

**2-(2,5-Dichlorothiophen-3-yl)-benzonitrile 36**

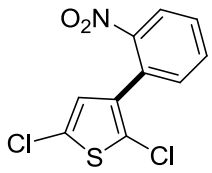



From 2-bromobenzonitrile (0.182 g, 1 mmol) and and 2,5-dichlorothiophene (0.306 g, 2 mmol), **36** was obtained in 81% (0.205 g) yield as a white solid.

Eluent pentane: diethylether 10:1

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.0 Hz, 1H), 7.67 (t, *J* = 7.6 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 1H), 6.94 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 136.8, 134.9, 133.4, 132.7, 130.7, 128.7, 127.2, 127.1, 125.0, 117.6, 112.5. Elemental analysis: calcd (%) for $C_{11}H_5Cl_2NS$ (254.14): C 51.99, H 1.98; found: C 52.07, H 1.84.

**2,5-Dichloro-3-(2-nitrophenyl)-thiophene 37**

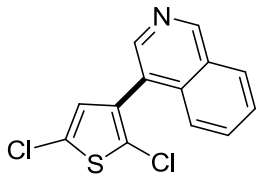



From 2-bromonitrobenzene (0.202 g, 1 mmol) and 2,5-dichlorothiophene (0.306 g, 2 mmol), **37** was obtained in 67% (0.183 g) yield as a yellow solid.

Eluent pentane: diethylether 10:1

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, *J* = 8.0 Hz, 1H), 7.67 (t, *J* = 7.6 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 1H), 6.77 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 148.8, 134.1, 132.9, 132.3, 129.5, 128.2, 127.0, 126.8, 124.7, 123.9. Elemental analysis: calcd (%) for $C_{10}H_5Cl_2NO_2S$ (274.12): C 43.81, H 1.84; found: C 44.03, H 1.97.

**4-(2,5-Dichlorothiophen-3-yl)-isoquinoline 38**




From 4-bromoisoquinoline (0.208 g, 1 mmol) and 2,5-dichlorothiophene (0.306 g, 2 mmol), **38** was obtained in 78% (0.218 g) yield as a brown solid.

Eluent pentane: diethylether 9:1

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 9.29 (s, 1H), 8.49 (s, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 7.75-7.60 (m, 3H), 6.90 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 153.0, 143.8, 134.1, 134.0, 130.9, 128.4, 128.1,

127.5, 127.0, 125.1, 124.9, 124.4. Elemental analysis: calcd (%) for $C_{13}H_7Cl_2NS$ (280.17): C 55.73, H 2.52; found: C 55.49, H 2.31.

## 4.5 Reference


1. *(a)* D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174; *(b)* T. Satoh, M. Miura, *Chem. Lett.* **2007**, *36*, 200; *(c)* I. V. Seregin, V. Gevorgyan, *Chem. Soc. Rev.* **2007**, *36*, 1173; *(d)* L.-C. Campeau, D. R. Stuart, K. Fagnou, *Aldrichim. Acta* **2007**, *40*, 35; *(e)* B.-J. Li, S.-D. Yang, Z.-J. Shi, *Synlett* **2008**, 949; *(f)* F. Bellina, R. Rossi, *Tetrahedron* **2009**, *65*, 10269; *(g)* L. Ackermann, R. Vincente, A. R. Kapdi, *Angew. Chem. Int. Ed.* **2009**, *48*, 9792; *(h)* X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2009**, *48*, 5094; *(i)* C. Fischmeister, H. Doucet, *Green Chem.* **2011**, *13*, 741; *(j)* L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315; *(k)* N. Kuhl, M. N. Hopkinson, J. Wencel-Delord, F. Glorius, *Angew. Chem. Int. Ed.* **2012**, *51*, 10236; *(l)* J. Wencel-Delord, F. Glorius, *Nature Chem.* **2013**, *5*, 369.
2. For selected recent contributions on direct arylations of (hetero)aromatics from our laboratory: *(a)* K. Beydoun, M. Zaarour, J. A. G. Williams, H. Doucet, V. Guerchais, *Chem. Commun.* **2012**, *48*, 1260; *(b)* F. Derridj, J. Roger, S. Djebbar, H. Doucet, *Adv. Synth. Catal.* **2012**, *354*, 747; *(c)* L. Zhao, C. Bruneau, H. Doucet, *Chem. Commun.* **2013**, *49*, 5598; *(d)* J. Laroche, K. Beydoun, V. Guerchais, H. Doucet, *Catal. Sci. Technol.* **2013**, *3*, 2072.
3. M. Lafrance, C. N. Rowley, T. K. Woo, K. Fagnou, *J. Am. Chem. Soc.* **2006**, *128*, 8754.
4. S. I. Gorelsky, *Coord. Chem. Rev.* **2013**, *257*, 153.
5. S. I. Gorelsky, *Organometallics* **2012**, *31*, 4631.
6. O. René, K. Fagnou, *Org. Lett.* **2010**, *12*, 2116.
7. M. Lafrance, D. Shore, K. Fagnou, *Org. Lett.* **2006**, *8*, 5097.
8. F. Chen, Q.-Q. Min, X. Zhang, *J. Org. Chem.* **2012**, *77*, 2992.
9. T. Yan, C. B. Bheeter, H. Doucet, *Eur. J. Org. Chem.* **2013**, *2013*, 7152.
10. Y.-N. Wang, X.-Q. Guo, X.-H. Zhu, R. Zhong, L.-H. Cai, X.-F. Hou, *Chem. Commun.* **2012**, *48*, 10437.
11. For Pd-catalyzed intramolecular arylations of chlorobenzenes: *(a)* J. Wu, L. Nie, J. Luo, W.-M. Dai, *Synlett* **2007**, 2728; *(b)* M. Nagarjuna Reddy, K. C. Kumara Swamy, *Eur. J. Org. Chem.* **2012**, 2013.

*12.* L.-C. Campeav, M. Parisien, A. Jean, K. Fagnou, *J. Am. Chem. Soc.* **2006**, *128*, 581.

13. For Pd-catalyzed intermolecular direct arylations of chlorobenzenes: *(a)* H. Liu, B. Yin, Z. Gao, Y. Li, H. Jiang, *Chem. Commun.* **2012**, *48*, 2033; *(b)* D.-D. Li, T.-T. Yuan, G.-W. Wang, *J. Org. Chem.* **2012**, *77*, 3341; *(c)* C. Arroniz, A. Ironmonger, G. Rassias, I. Larrosa, *Org. Lett.* **2013**, *15*, 910; For Pd-catalyzed decarboxylative coupling with chlorobenzene: *(d)* H.-Q. Luo, W. Dong, T.-P. Loh, *Tetrahedron Lett.* **2013**, *54*, 2833.
14. For copper-catalyzed direct arylation of polychlorobenzene: H.-Q. Do, R. M. K. Khan, O. Daugulis, *J. Am. Chem. Soc.* **2008**, *130*, 15185.
15. *(a)* D. Garcia-Cuadrado, P. de Mendoza, A. A. C. Braga, F. Maseras, A. M. Echavarren, *J. Am. Chem. Soc.* **2007**, *129*, 6880; *(b)* S. I. Gorelsky, D. Lapointe, K. Fagnou, *J. Org. Chem.* **2012**, *77*, 658.
16. T. Cantat, E. Génin, C. Giroud, G. Meyer, A. Jutand, *J. Organomet. Chem.* **2003**, *687*, 365.
17. J. M. Birchall, R. N. Haszeldine, H. Woodfine, *J. Chem. Soc., Perkin Trans. 1* **1973**, *10*, 1121.
18. H. Jasch, S. B. Hoefling, M. R. Heinrich, *J. Org. Chem.* **2012**, *77*, 1520.

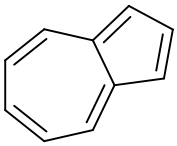
# *Chapter 5: A Straightforward Access to Guaiazulene Derivatives using Palladium-Catalyzed $sp^2$ or $sp^3$ C-H Bond Functionalization*

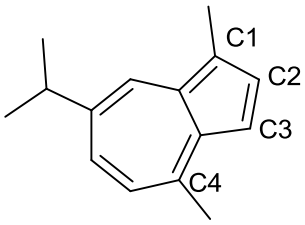
# Chapter 5: A Straightforward Access to Guaiazulene Derivatives using Palladium-Catalyzed $sp^2$ or $sp^3$ C-H Bond Functionalization

## 5.1 Introduction

Azulene and also guaiazulene that feature the azulene skeleton (Fig. 5.1) are both constituents of pigments in the lactarius indigo mushrooms. They are also present in some corals and in chamomile oil. Guaiazulene is used as a cosmetic color additive (blue color) and as a drug against ulcer. It also provides anti-inflammatory and pain relief benefits, and is used treating skin irritation caused by over-exposure to the sun. Guaiazulene is also a strong antioxidant, an antiviral and has been shown to be effective in suppressing both warts and cold sores. Because of its rose-like scent, it is used as a fragrance in some formulations. It is also employed as a volatile dye. Due to these multiple uses, the discovery of simple access to guaiazulene derivatives would be very useful.[1]

Azulenes display unique structural and electronic properties.[2,3] Their large dipole moment arises from the electron drift from its seven-membered ring to its five-membered ring, which leads to its aromatic delocalization energy being 5 times lower than that of benzene.[3]



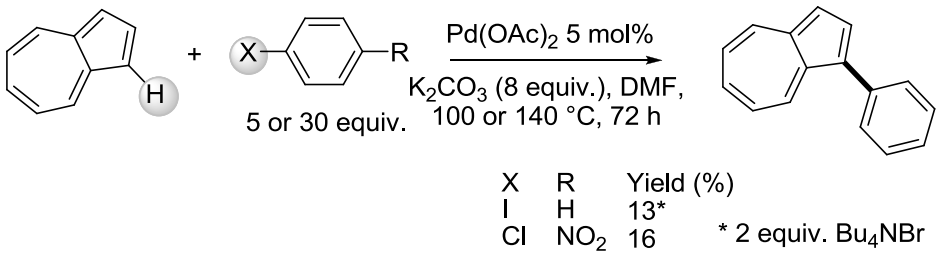



Azulene Guaiazulene

**Figure 5.1**. Structures of Azulene and Guaiazulene

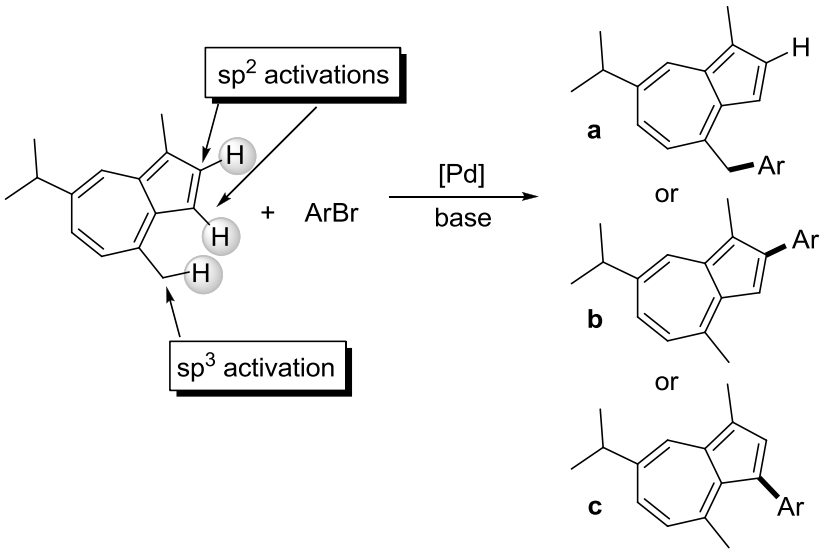
As guaiazulene does not present any reactive function, its modification requires the activation of C-H bonds. The palladium-catalyzed direct arylation or vinylation of heteroaromatics has recently emerged as a very powerful method for the preparation of substituted (hetero)aromatics.[4-10] However, there are still limitations for these reactions in terms of substrate scope. If the coupling of various aryl halides with heteroarenes has been largely described, on the other hand, the coupling of azulenes with aryl halides via palladium-catalyzed C-H bond

functionalization has attracted much less attention, as only two examples of such reaction have been described (Scheme 5.1). It has been reported by Dyker and co-workers that the direct arylation at C1 of azulene with iodobenzene or 4-chloronitrobenzene proceeded in quite low yields using 5 mol% $Pd(OAc)_2$ catalyst (Scheme 5.1).[11] For these coupling reactions 5-30 equiv. of aryl halide were employed.




**Scheme 5.1**. Previous work about palladium-catalyzed direct arylation of azulene.

The palladium-catalyzed direct arylation would allow the preparation of arylated guaiazulenes in only one step, with low amount of wastes, which represents a considerable advantage (Scheme 5.2). In addition, such couplings are expected to present a high functional group tolerance, which would allow a straightforward modification of the nature of the substituents and hence of the properties of the resulting guaiazulene derivatives.

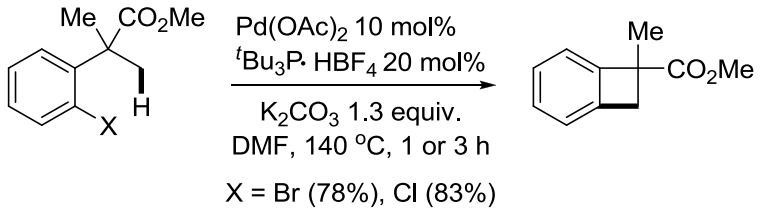



**Scheme 5.2**. Palladium-catalyzed direct arylation of guaiazulene.

As guaiazulenes present several type of $sp^2$ and $sp^3$ C-H bonds, their reactivities towards palladium-catalyzed direct arylation were unpredictable.

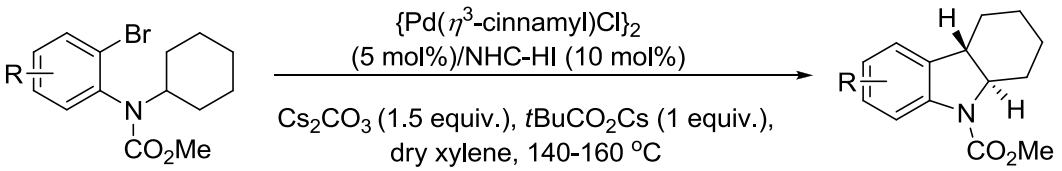
The palladium-catalyzed $sp^2$ C-H bond functionalization has already been described in chapters 2, 3 and 4. The $sp^3$ C-H bond functionalization of unactivated C-H bonds[12] has attracted less attention. Herein, some selected intramolecular[13] and intermolecular[14] activation reactions of $sp^3$ C-H bond without directing groups will be emphasized.

The intramolecular $sp^3$ C-H activation, could successfully give rise to the formation of valuable four-membered[13a,13b], five-membered[13b-13e], and six-membered[13f] rings. Fagnou and Baudoin found that employing a combination of $Pd(OAc)_2$ and $t$Bu$_3$P as the catalyst, $K_2CO_3$ as the base, and DMF as the solvent, a variety of substituted benzocyclobutenes were obtained efficiently *via* intramolecular $sp^3$ C-H activation of methyl group (Scheme 5.3).[13a,13b]



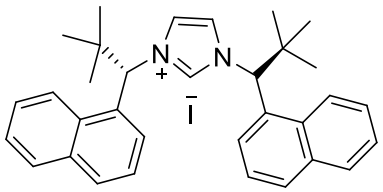

**Scheme 5.3**. Pd(0)-catalyzed synthesis of benzocyclobutenes by $sp^3$ C-H activation.

In 2011, Kündig and co-workers disclosed the synthesis of (fuzed)indolines by palladium(0)-catalayzed intramolecular C($sp^3$)-H arylation, using chiral *N*-heterocyclic carbenes (NHC) (10 mol%) as the ligands, in the presence of cesium pivalate and cesium carbonate in xylenes as solvent at 140-160 °C (Scheme 5.4).[13c] Highly enantioenriched *trans*-fuzed indolines were obtained with good yields. In the same year, Kagan reported a similar work by using commercially available chiral diphosphines instead of chiral NHC ligands (Scheme 5.5).[13d]

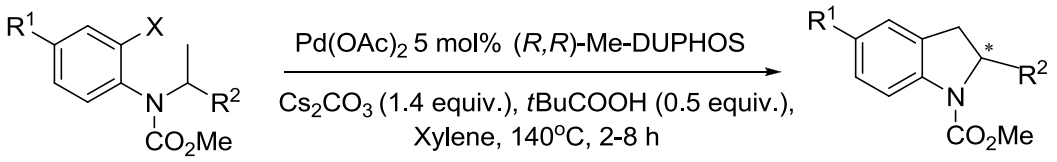



| R | Yield (%) | R | Yield (%) |
|---|---|---|---|
| H | 84 | 4-$CO_2$Me | 82 |
| 4-MeO | 84 | 5-MeO | 55 |
| 4-Ph | 88 | 5-F | 70 |
| 4-F | 81 | 6-F | 68 |
| 4-Cl | 30 | 4,6-dimethyl | 88 |
| 4-Br | 0 | | |

NHC-HI:

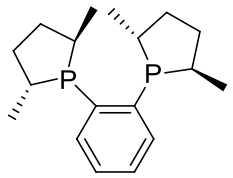



**Scheme 5.4**. Pd(0)-NHC-catalyzed synthesis of indolines by $sp^3$ C-H activation.



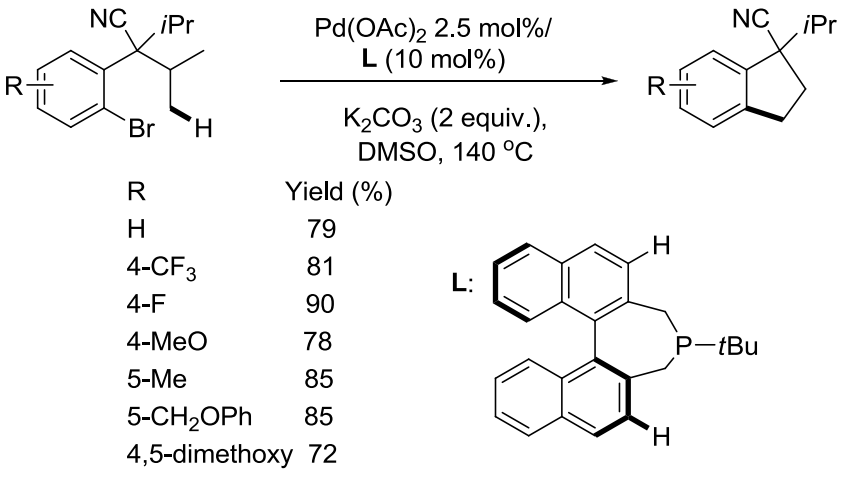

| $R^1$ | $R^2$ | X | Yield (%) |
|---|---|---|---|
| H | Me | Br | 97 |
| H | Me | I | 82 |
| H | Me | Cl | 0 |
| H | Et | Br | 65 |
| F | Me | Br | 84 |

(*R,R*)-Me-DUPHOS



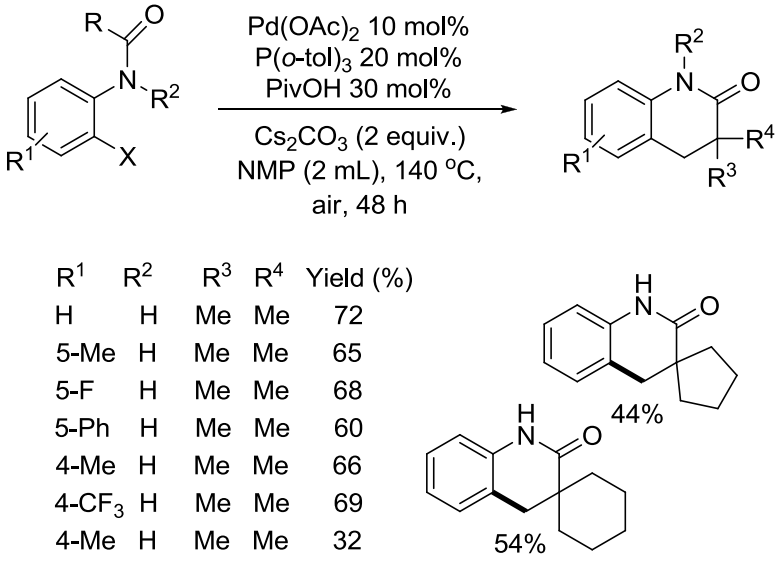

**Scheme 5.5**. Pd(0)-catalyzed synthesis of indolines by $sp^3$ C-H activation.

Inspired by the synthesis of indolines, Baudoin and co-workers reported their results on the synthesis of indanes by use of a similar type of reaction (Scheme 5.6).[13e] They found that the binepine ligands appeared to be more efficient and stereoselective than NHC[13c] and diphosphine ligands[13d]. DMSO as the solvent could significantly improve the cyclization of indane analogues instead of adding pivalate.




**Scheme 5.6**. Pd(0)-catalyzed synthesis of indanes by intramolecular $sp^3$ C-H activation.

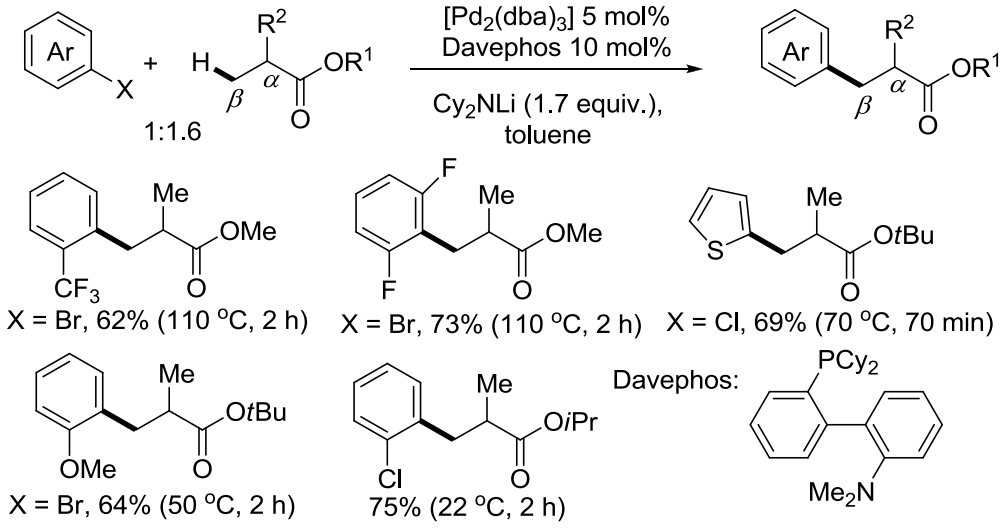
Recently, Shi and co-workers published a successful method for the formation of six-membered rings by an oxidative-addition-initiated strategy through direct C($sp^3$)-H bond activation. The phosphine ligand P(*o*-tol)$_3$ with substantial steric hindance was found to enhance the efficiency. The 3,3-disubstituted 3,4-dihydroquinolinone derivatives were obtained under palladium acetate with the polar solvent NMP, in the presence of pivalate acid (30 mol%), in air (Scheme 5.7).[13f]




**Scheme 5.7**. Pd(0)-catalyzed synthesis of six-membered derivatives by $sp^3$ C-H activation.

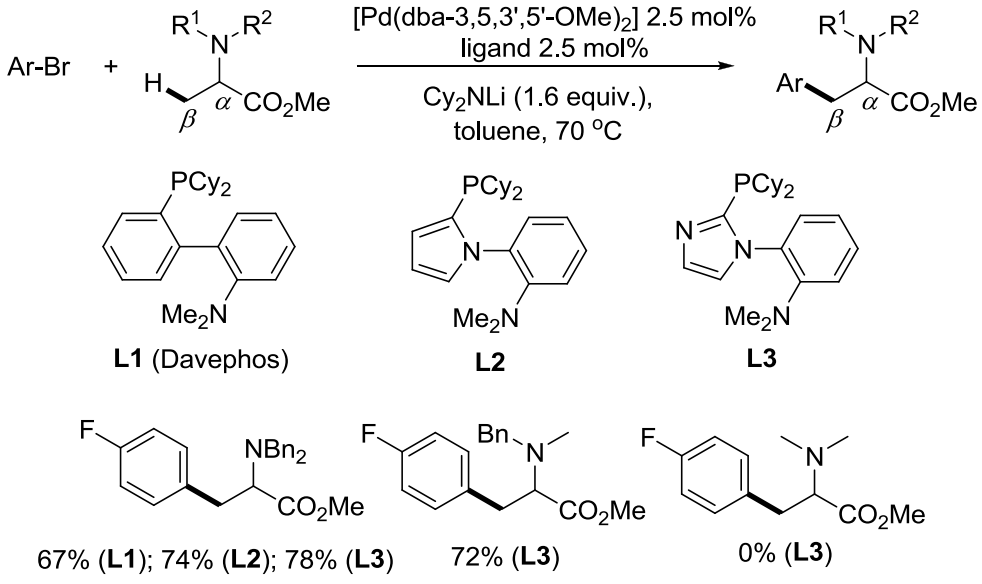
In recent years, Baudoin and co-workers have reported a mild and efficient strategy to achieve intermolecular *β*-arylated compounds of unactivated $sp^3$ C-H bonds of carboxylic esters and *α*-aminoesters in the presence of an appropriate Pd(0) catalyst. In the first example, with the palladium catalyst, composed of $Pd_2(dba)_3$ and Davephos, the aryl bromides bearing an electron

withdrawing group in the *ortho*-position,[14c] the *β*-arylation of carboxylic esters proceed with lithium dicyclohexylamide ($Cy_2NLi$) as an additive (Scheme 5.8).[14a]




**Scheme 5.8**. Pd(0)-catalyzed intermolecular *β*-arylation of carboxylic esters *via* $sp^3$ C-H activation.

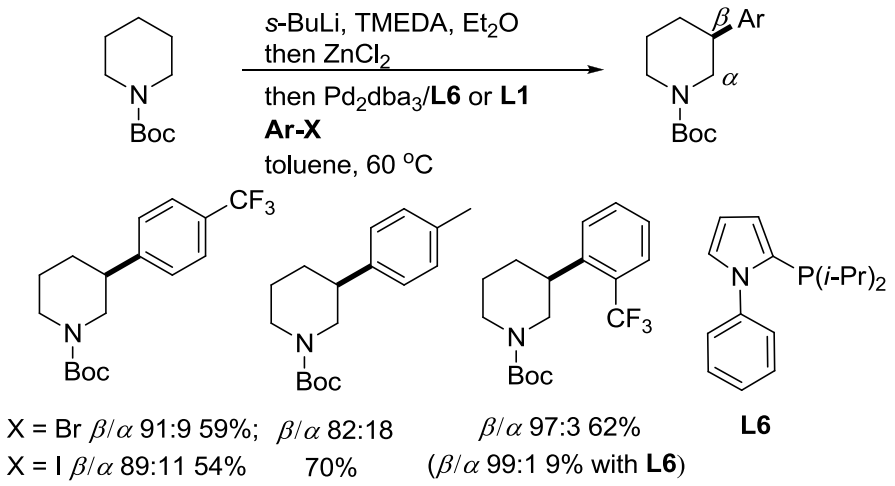
In their later research, they found that replacing the Davephos ligand by nitrogen heterocycles (pyrrole **L2** and imidazole **L3**) had a positive impact on the yield for various aryl bromides and that the presence of a tertiary *α*-amino group strongly favored *β*-arylation (Scheme 5.9).[14b]



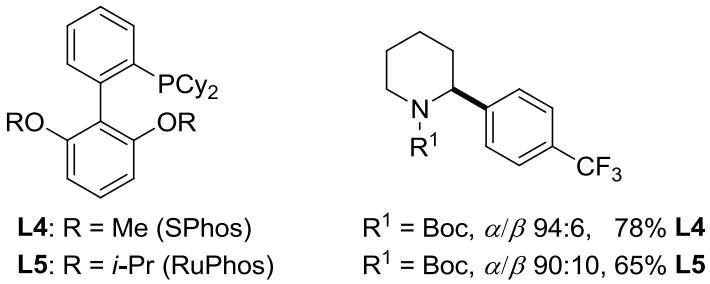

**Scheme 5.9**. Pd(0)-catalyzed intermolecular *β*-arylation of *α*-amino esters *via* $sp^3$ C-H activation.

Last year, Baudoin and co-workers obtained successfully *β*-selective C($sp^3$)-H arylation of *N*-Boc-piperidines with ligand control. They explained that the flexible biarylphosphines (**L1** and **L8**) ligand provided the desired *β*-arylated products with a variety of aryl electrophiles (Scheme

5.10), whereas more rigid biarylphosphines furnished the more classical $\alpha$-arylated products (Scheme 5.11).[14d]




**Scheme 5.10**. Ligand controlled $\beta$-arylation of Boc-piperidines *via* $sp^3$ C-H activation.




**Scheme 5.11**. Ligand controlled $\alpha$-arylation of Boc-piperidines *via* $sp^3$ C-H activation.

In this chapter, we would like to report on (i) the influence of the reaction conditions for the palladium-catalyzed direct coupling of aryl bromides with guaiazulene, and (ii) show the scope of the $sp^2$ or $sp^3$ functionalization of guaiazulene.

## 5.2 Results and discussion

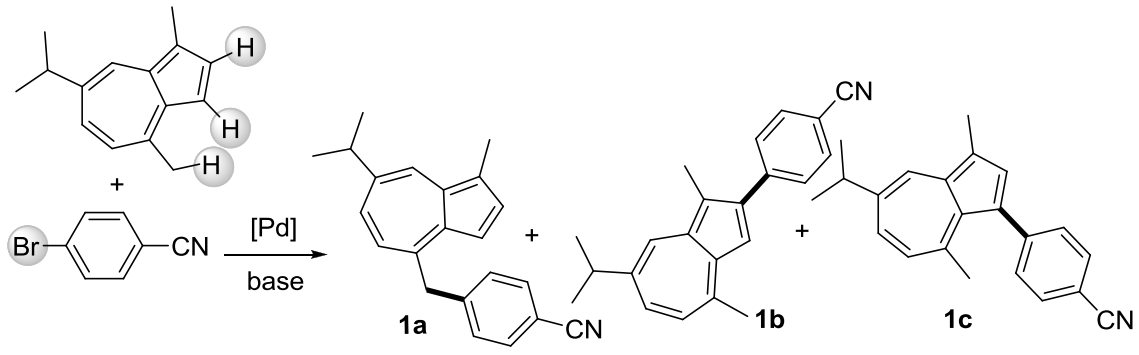
### 5.2.1 Optimization of palladium-catalyzed direct arylation of guaiazulene

Keeping in mind the reaction conditions employed for the direct arylation of heteroaromatics in our previous works,[6] we initially examined the influence of the nature of base and their cation for the coupling of guaiazulene with 4-bromobenzonitrile using 2 mol% $PdCl(C_3H_5)$(dppb) as catalyst and DMAc as solvent (Table 5.1). The use of $K_2CO_3$ as base did not result in the formation of the target coupling products (Table 5.1, entry 1); whereas, $Cs_2CO_3$ afforded a mixture of the coupling

products **1b** and **1c** in 33:67 ratio (Table 5.1, entry 2). On the other hand, the use of mixtures of bases: CsOAc + $K_2CO_3$ or $Cs_2CO_3$ led to a complete modification of the regioselectivity of the arylation with an exclusive $sp^3$ C-H bond functionalization[5,8-10] of the seven membered ring methyl substituent to give 4-benzylguaiazulene **1a** in 61% or 67% yields (Table 5.1, entries 3, 5 and 6). It should be noted that the intermolecular $sp^3$ palladium-catalyzed arylations of unactivated C-H bonds without participation of a directing group are quite scarce.[5c,10] A similar selectivity was observed for the reactions performed in DMF, diethyl carbonate or cyclopentyl methyl ether, but with a low productivity in carbonate and ether solvents (Table 5.1, entries 7-9). CsOAc as the only base also gave quite selectively isomer **1a** (Table 5.1, entry 10). On the other hand, the use of KOAc/$K_2CO_3$ or KOAc/$Cs_2CO_3$ as mixtures of bases led to a mixture of **1b** and **1c** without formation of **1a** showing the crucial role of cations in the reaction (Table 5.1, entries 11 and 12).[15]

Then, in order to favor the formation of **1b** and **1c**, we employed KOAc as the only base. No formation of **1a** was detected, and a mixture of **1b** and **1c** was obtained in a 15:85 ratio (Table 5.1, entry 14). This difference of selectivity might be due to the higher solubility of CsOAc. A similar selectivity was observed in NMP; whereas, a less polar solvent such as ethylbenzene gave **1b** and **1c** in a 53:47 ratio (Table 5.1, entries 15 and 16). A similar influence of the nature of the solvent on the regioselectivity of the arylation of 3-substituted furans has already been reported.[16] A minor influence of the nature of the catalyst on the regioselectivity of this reaction was observed (Table 5.1, entries 18-20).

**Table 5.1**. Influence of the reaction conditions for palladium-catalyzed direct coupling of 7-isopropyl-1,4-dimethylazulene (guaiazulene) with 4-bromobenzonitrile.




| Entry | Catalyst (mol %) | Base (equiv.) | Solvent | Ratio **1a**:**1b**:**1c** | Conv. (%) | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | $PdCl(C_3H_5)(dppb)$ (2) | $K_2CO_3$ (4) | DMAc | - | 100 | |
| 2 | $PdCl(C_3H_5)(dppb)$ (2) | $Cs_2CO_3$ (4) | DMAc | 0:33:67 | 64 | |
| 3 | $PdCl(C_3H_5)(dppb)$ (2) | CsOAc (4) + $K_2CO_3$ (4) | DMAc | **100**:0:0 | 100 | 61 of **1a** |
| 4 | $PdCl(C_3H_5)(dppb)$ (0.5) | CsOAc (4) + $K_2CO_3$ (4) | DMAc | 92:8:0 | 100 | |
| 5 | $PdCl(C_3H_5)(dppb)$ (2) | CsOAc (4) + $Cs_2CO_3$ (4) | DMAc | **100**:0:0 | 100 | |
| 6 | $PdCl(C_3H_5)(dppb)$ (2) | CsOAc (1) + $K_2CO_3$ (1) | DMAc | **100**:0:0 | 100 | 67 of **1a** |
| 7 | $PdCl(C_3H_5)(dppb)$ (2) | CsOAc (4) + $K_2CO_3$ (4) | DMF | 100:0:0 | 100 | |
| 8 | $PdCl(C_3H_5)(dppb)$ (2) | CsOAc (4) + $K_2CO_3$ (4) | DEC | 100:0:0 | 10 | |

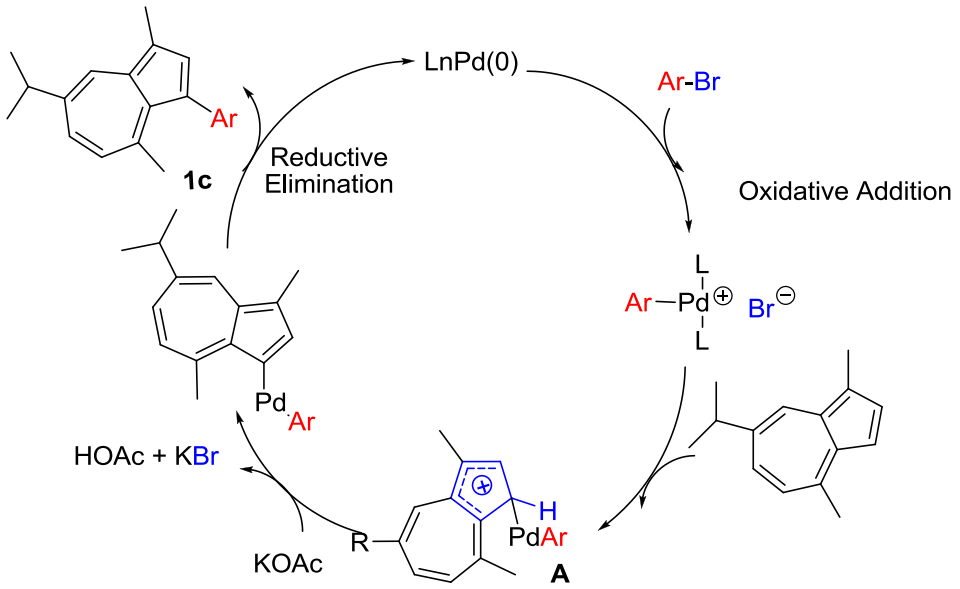
| | | | | | | |
|---|---|---|---|---|---|---|
| 9 | $PdCl(C_3H_5)(dppb)$ (2) | CsOAc (4) + $K_2CO_3$ (4) | CPME | 100:0:0 | 9 | |
| 10 | $PdCl(C_3H_5)(dppb)$ (2) | CsOAc (4) | DMAc | 96:4:0 | 60 | |
| 11 | $PdCl(C_3H_5)(dppb)$ (2) | KOAc (4) + $K_2CO_3$ (4) | DMAc | 0:25:75 | 100 | |
| 12 | $PdCl(C_3H_5)(dppb)$ (2) | KOAc (4) + $Cs_2CO_3$ (4) | DMAc | 0:30:70 | 100 | |
| 13 | $PdCl(C_3H_5)(dppb)$ (2) | KOH (4) + $K_2CO_3$ (4) | DMAc | 0:31:69 | 43 | |
| 14 | $PdCl(C_3H_5)(dppb)$ (2) | KOAc (8) | DMAc | 0:15:**85** | 100 | 51 of **1c** |
| 15 | $PdCl(C_3H_5)(dppb)$ (2) | KOAc (8) | NMP | 0:18:82 | 100 | |
| 16 | $PdCl(C_3H_5)(dppb)$ (2) | KOAc (8) | ethylbenzene | 0:**53**:47 | 100 | 38 of **1b** |
| 17 | $PdCl(C_3H_5)(dppb)$ (2) | KOAc (8) | xylene | 0:**47**:53 | 55 | |
| 18 | $Pd(OAc)_2$ (10) | KOAc (8) | DMAc | 0:20:80 | 100 | |
| 19 | $Pd(OAc)_2$ (2)/$PCy_3$ (4) | KOAc (8) | DMAc | 0:19:81 | 100 | |
| 20 | $Pd(OAc)_2$ (2)/dppe (2) | KOAc (8) | DMAc | 0:18:82 | 100 | |

Conditions: catalyst: [Pd], 7-isopropyl-1,4-dimethylazulene (1.5 mmol), 1-bromobenzonitrile (1 mmol), under argon, 16 h, 150 ℃, GC and NMR conversions, isolated yields.

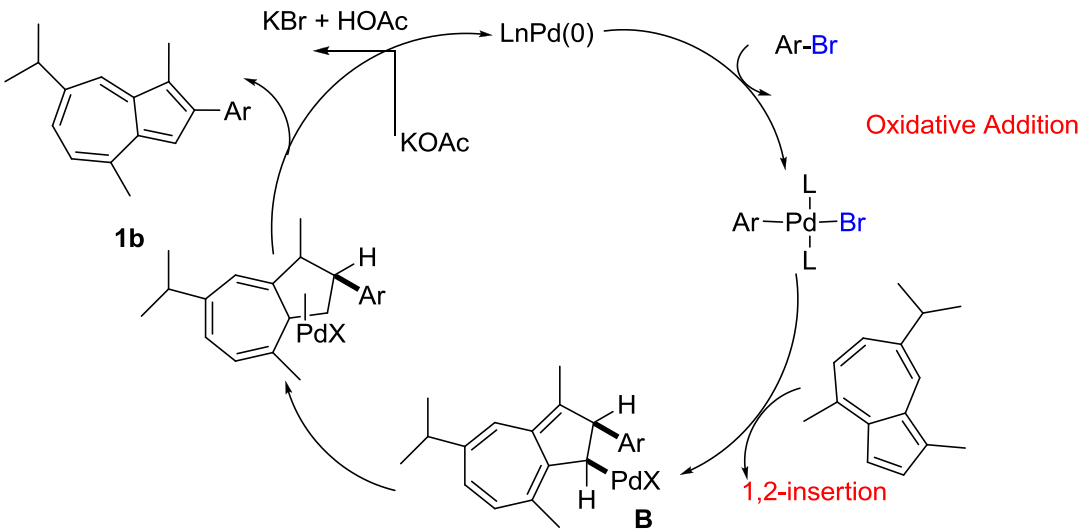
### 5.2.2 The Examination of mechanisms for $sp^2$ or $sp^3$ C-H activation of guaiazulene

In all cases, the first step of the catalytic cycle is certainly the oxidative addition of the aryl bromide to Pd(0) to afford a Pd(II) intermediate. The arylation which takes place at the electron-rich C3 position to form **1c** in DMAc suggests an electrophilic aromatic substitution

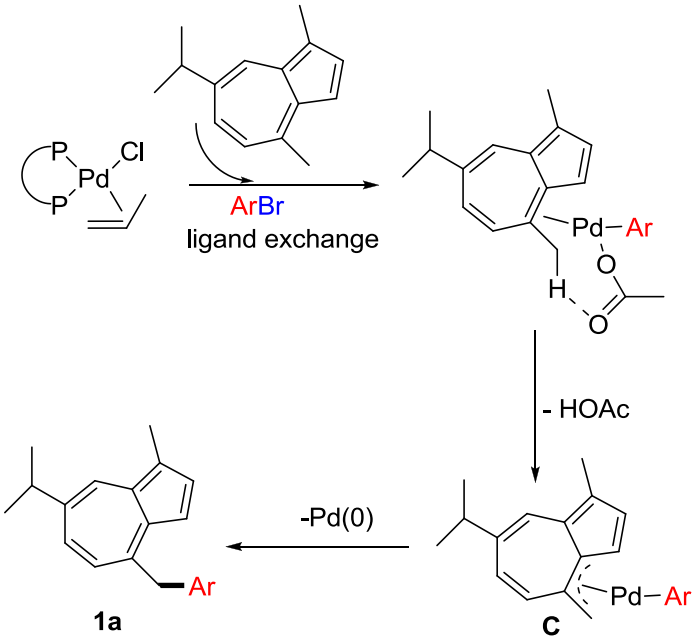
mechanism from an electrophilic cationic Pd-species **A**, although a concerted-metallation-deprotonation mechanism is also possible[11,17] (Scheme 5.12). The non-polar solvent ethylbenzene certainly favors neutral Pd-species **B** and therefore an Heck type mechanism with formation of a Pd-C bond at C3 and arylation at C2 to form **1b** followed.[16] (Scheme 5.13) The 4-benzylguaiazulene **1a** more likely results from formation of an allyl-palladium intermediate **C** (Scheme 5.14). The higher base concentration in solution due to the better solubility of CsOAc compared to KOAc might favor this reaction pathway.[18,19] The Pd-catalyzed activation of benzylic C-H bonds has already been reported.[9b]




**Scheme 5.12**. Proposed mechanism of C3 ($sp^2$)-H bond arylation.



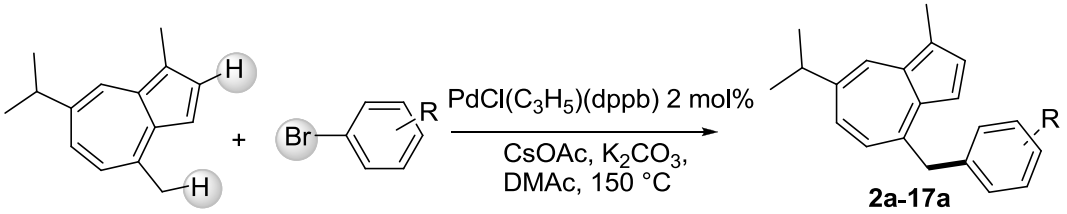

**Scheme 5.13**. Proposed mechanism of C2 ($sp^2$)-H bond arylation.



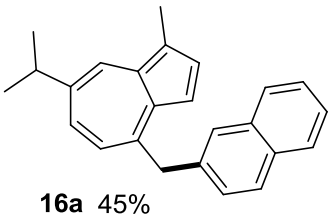

**Scheme 5.14**. Proposed mechanism of C4-Me ($sp^3$)-H bond arylation.

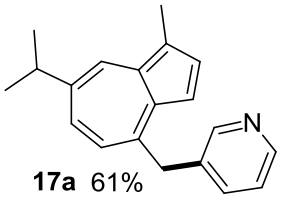
### 5.2.3 Scope for palladium-catalyzed direct C($sp^3$)-H arylation of guaiazulene

Using CsOAc/$K_2CO_3$ as bases (Table 5.1, entry 3), the scope of the $sp^3$ C-H bond functionalization was examined using various aryl bromides (Scheme 5.15). Moderate yields of 45% and 46% in **2a** and **3a** were obtained by coupling of guaiazulene with 4-bromobenzaldehyde and 4-bromopropiophenone. Higher yields of 67% and 68% in **4a** and **5a** were obtained from ethyl 4-bromobenzoate and 4-(trifluoromethyl)bromobenzene. The desired coupling products **6a** and **7a** were also obtained using 4-bromochlorobenzene and 4-fluorobromobenzene as the coupling partners. It should be noted that no cleavage of the C-Cl bond was observed in the course of the reaction with 4-bromochlorobenzene allowing further transformations. Lower yields in **8a** and **9a** were obtained from the electron rich, 4-bromotoluene and 4-*tert*-butylbromobenzene due to the formation of some unidentified side-products. Then, we examined the reactivity of a few *meta*-substituted aryl bromides. Again, the best results were obtained with the trifluoromethyl- and chloro-substituted bromobenzenes to give **12a** and **13a** in 71 and 69% yields, respectively, whereas, moderate yields of **11a** and **14a** were obtained with 3-bromoacetophenone or 3-bromotoluene. 2-Bromofluorobenzene was also found to be a suitable substrate for this reaction to give **15a** in 63% yield. Finally, the reactivity of 3-bromopyridine was examined. The desired 4-benzylguaiazulene **17a** was obtained in 61% yield.




| R | Product | Yield (%) |
|---|---|---|
| 4-CHO | **2a** | 45 |
| 4-COEt | **3a** | 46 |
| 4-$CO_2$Et | **4a** | 67 |
| 4-$CF_3$ | **5a** | 68 |
| 4-Cl | **6a** | 66 |
| 4-F | **7a** | 52 |
| 4-Me | **8a** | 42 |
| 4-*t*Bu | **9a** | 48 |
| 3-CN | **10a** | 54 |
| 3-COMe | **11a** | 51 |
| 3-$CF_3$ | **12a** | 71 |
| 3-Cl | **13a** | 69 |
| 3-Me | **14a** | 54 |
| 2-F | **15a** | 63 |

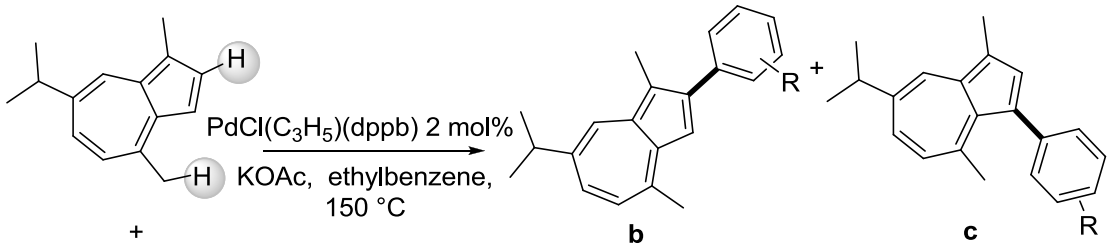


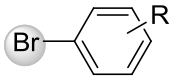




**Scheme 5.15**. Palladium-catalyzed direct $sp^3$ arylation of guaiazulene.

### 5.2.4 Scope for palladium-catalyzed $sp^2$ C2 or C3-arylation of guaiazulene

As the C2-arylation of guaiazulene was also possible using KOAc as the base in ethylbenzene (Table 5.1, entry 15), the scope of this coupling was also examined (Scheme 5.16). The use of less electron-deficient aryl bromides than 4-bromobenzonitrile led to **b** isomer in higher regioselectivity. From 4-chlorobromobenzene or 4-fluorobromobenzene, products **6b** and **7b** were obtained both in 77% regioselectivities and in 53 and 51% yields, respectively. Similar regioselectivities in favor of the formation of the C2-arylated guaiazulene were observed with 3- or 4-bromotoluene or bromobenzene to give **8b**, **14b** and **18b** in 54-56% yields. The reactivity of electron-rich 3-bromotoluene for C3-arylation of guaiazulene was also examined using KOAc as the base in DMAc (Scheme 5.16). Product **14c** was obtained in a lower selectivity of 63% and in 38% yield, as compared to the reaction with the electron-poor 4-bromobenzonitrile which gave **1c** in 51% yield (Table 5.1, entry 13).




| R | ratio **b**:**c** | Major Product | Yield of **b** (%) |
|---|---|---|---|
| 4-Cl | 77:23 | **6b** | 53 |
| 4-F | 77:23 | **7b** | 51 |
| 4-Me | 70:30 | **8b** | 56 |
| 3-Me | 76:24 | **14b** | 54 |
| H | 75:25 | **18b** | 56 |
| 3-Me | 37:63 | **14c** | 38 of **c*** |

* DMAc as the solvent

**Scheme 5.16**. Palladium-catalyzed direct $sp^2$ C2- or C3-arylation of guaiazulene.

## 5.3 Conclusion

In summary, we have demonstrated that both the $sp^2$ and $sp^3$ direct arylations of guaiazulene are possible when appropriate reaction conditions are employed. The use of a mixture of $CsOAc/K_2CO_3$ selectively promotes the $sp^3$ direct arylation at C4-Me of guaiazulene to give 4-benzylguaiazulenes; whereas KOAc in DMAc led quite selectively to the C3 arylated compounds and KOAc in ethylbenzene to the C2 arylated guaiazulenes. These conditions offer routes for fast and direct access to arylated guaiazulenes. It should be noted that this protocol is applicable to a range of functional moieties, including reactive ones, on the aryl bromide. Such functional group tolerance allows the easy modification of these derivatives, a strategy enabling the tuning of their properties.

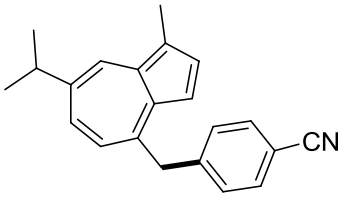
## 5.4 Experimental details

All reactions were perfomed in Schlenck tubes under argon. DMAc or ethylbenzene of analytical grade were used without any distillation. Potassium acetate 99+, cesium acetate and potassium carbonate 99% were used. Commercial guaiazulene and aryl bromides were used as recieved. $^1H$ (400 or 500 MHz), $^{13}C$ (100 or 125 MHz) spectra were recorded in $CDCl_3$ solutions. Chemical shifts are reported in ppm relative to $CDCl_3$ ($^1H$: 7.29 and $^{13}C$: 77.0). Flash chromatography was performed on silica gel (230-400 mesh) using pentane\ether.

**General procedure for the synthesis of 1a-17a**

As a typical experiment, reaction of the aryl bromide (1 mmol), 7-isopropyl-1,4-dimethylazulene (0.296 g, 1.5 mmol), CsOAc (0.767 g, 4 mmol) and $K_2CO_3$ (0.552 g, 4 mmol) at 150 $^oC$ for 16 h in DMAc (5 mL) in the presence of $PdCl(C_3H_5)(dppb)$ (12.2 mg, 0.02 mmol) under argon afforded the corresponding arylation products after extraction with dichloromethane, evaporation and filtration on silica gel.

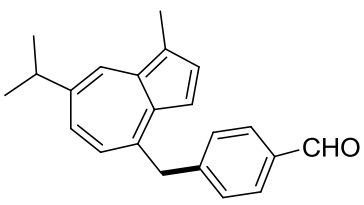
**4-(7-Isopropyl-1-methylazulen-4-ylmethyl)-benzonitrile 1a**




From 4-bromobenzonitrile (0.182 g, 1 mmol), 7-isopropyl-1,4-dimethylazulene (0.296 g, 1.5 mmol), CsOAc (0.767 g, 4 mmol) and $K_2CO_3$ (0.552 g, 4 mmol) in the presence of $PdCl(C_3H_5)(dppb)$ (12.2 mg, 0.02 mmol) **1a** was obtained in 61% (0.182 g) yield as a blue oil. Eluent pentane: diethylether 10:1

$^1H$ NMR (400 MHz, CDCl3): δ 8.16 (s, 1H), 7.58 (d, *J* = 3.2 Hz, 1H), 7.45 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 9.7 Hz, 1H), 7.29 (d, *J* = 8.3 Hz, 2H), 7.20 (d, *J* = 3.2 Hz, 1H), 6.86 (d, *J* = 9.7 Hz, 1H), 4.46 (s, 2H), 3.02 (sept., *J* = 6.8 Hz, 1H), 2.60 (s, 3H), 1.29 (d, *J* = 6.8 Hz, 6H). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 146.2, 144.2, 140.7, 137.3, 137.2, 136.8, 135.1, 133.7, 132.3, 129.2, 126.0, 125.0, 119.0, 113.1, 110.1, 43.3, 38.3, 24.7, 12.9. Elemental analysis: calcd (%) for $C_{22}H_{21}N$ (299.41): C 88.25, H 7.07; found: C 88.10, H 7.14.

**4-(7-Isopropyl-1-methylazulen-4-ylmethyl)-benzaldehyde 2a**

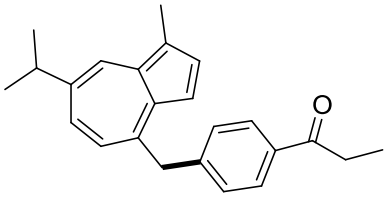



From 4-bromobenzaldehyde (0.185 g, 1 mmol), 7-isopropyl-1,4-dimethylazulene (0.296 g, 1.5 mmol), CsOAc (0.767 g, 4 mmol) and $K_2CO_3$ (0.552 g, 4 mmol) in the presence of

$PdCl(C_3H_5)$(dppb) (12.2 mg, 0.02 mmol) **2a** was obtained in 45% (0.136 g) yield as a blue oil. Eluent pentane: diethylether 10:1

$^1$H NMR (400 MHz, $CDCl_3$): δ 9.87 (s, 1H), 8.15 (s, 1H), 7.68 (d, *J* = 8.0 Hz, 2H), 7.59 (d, *J* = 3.2 Hz, 1H), 7.40-7.33 (m, 3H), 7.23 (d, *J* = 3.2 Hz, 1H), 6.89 (d, *J* = 10.7 Hz, 1H), 4.49 (s, 2H), 3.02 (sept., *J* = 6.8 Hz, 1H), 2.60 (s, 3H), 1.29 (d, *J* = 6.8 Hz, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 191.9, 147.9, 144.8, 140.5, 137.4, 137.1, 136.8, 135.1, 134.8, 133.7, 130.0, 129.2, 125.9, 125.1, 113.1, 43.5, 38.3, 24.7, 12.9. Elemental analysis: calcd (%) for $C_{22}H_{22}O$ (302.41): C 87.38, H 7.33; found: C 87.57, H 7.50.

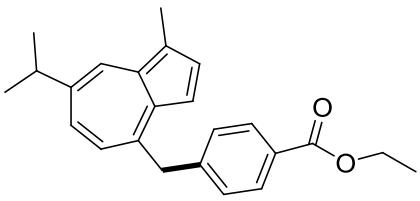
**1-[4-(7-Isopropyl-1-methylazulen-4-ylmethyl)-phenyl]-propan-1-one 3a**



From 4-bromopropiophenone (0.213 g, 1 mmol), 7-isopropyl-1,4-dimethylazulene (0.296 g, 1.5 mmol), CsOAc (0.767 g, 4 mmol) and $K_2CO_3$ (0.552 g, 4 mmol) in the presence of $PdCl(C_3H_5)$(dppb) (12.2 mg, 0.02 mmol) **3a** was obtained in 46% (0.152 g) yield as a blue oil. Eluent pentane: diethylether 10:1

$^1$H NMR (400 MHz, $CDCl_3$): δ 8.15 (s, 1H), 7.77 (d, *J* = 8.0 Hz, 2H), 7.58 (s, 1H), 7.35 (d, *J* = 10.7 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.17 (s, 1H), 6.89 (d, *J* = 10.7 Hz, 1H), 4.46 (s, 2H), 3.00 (sept., *J* = 6.8 Hz, 1H), 2.86 (q, *J* = 7.6 Hz, 2H), 2.60 (s, 3H), 1.29 (d, *J* = 6.8 Hz, 6H), 1.12 (t, *J* = 7.6 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 200.4, 146.0, 145.2, 140.4, 137.5, 137.0, 136.7, 135.1, 135.1, 133.6, 128.8, 128.3, 125.8, 125.1, 113.1, 43.2, 38.3, 24.7, 12.9, 8.3. Elemental analysis: calcd (%) for $C_{24}H_{26}O$ (330.46): C 87.23, H 7.93; found: C 87.14, H 7.99.

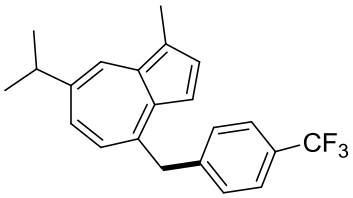
**Ethyl 4-(7-isopropyl-1-methylazulen-4-ylmethyl)-benzoate 4a**



From ethyl 4-bromobenzoate (0.229 g, 1 mmol), 7-isopropyl-1,4-dimethylazulene (0.296 g, 1.5 mmol), CsOAc (0.767 g, 4 mmol) and $K_2CO_3$ (0.552 g, 4 mmol) in the presence of $PdCl(C_3H_5)$(dppb) (12.2 mg, 0.02 mmol) **4a** was obtained in 67% (0.232 g) yield as a blue oil. Eluent pentane: diethylether 10:1

$^1$H NMR (400 MHz, $CDCl_3$): δ 8.14 (s, 1H), 7.84 (d, *J* = 8.1 Hz, 2H), 7.57 (d, *J* = 3.5 Hz, 1H), 7.33 (d, *J* = 10.7 Hz, 1H), 7.28-7.22 (m, 3H), 6.87 (d, *J* = 10.7 Hz, 1H), 4.46 (s, 2H), 4.25 (q, *J* = 7.6 Hz, 2H), 3.00 (sept., *J* = 6.8 Hz, 1H), 2.60 (s, 3H), 1.30-1.25 (m, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 166.5, 145.9, 145.3, 140.3, 137.5, 137.0, 136.7, 135.1, 133.6, 129.8, 128.7, 128.6, 125.8, 125.1, 113.1, 60.8, 43.2, 38.3, 24.7, 14.3, 12.9. Elemental analysis: calcd (%) for $C_{24}H_{26}O_2$ (346.46): C 83.20, H 7.56; found: C 83.34, H 7.40.

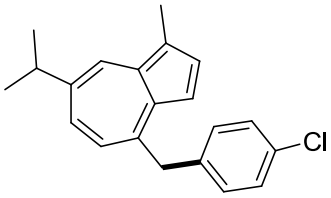
**7-Isopropyl-1-methyl-4-(4-trifluoromethylbenzyl)-azulene 5a**




From 4-(trifluoromethyl)bromobenzene (0.225 g, 1 mmol), 7-isopropyl-1,4-dimethylazulene (0.296 g, 1.5 mmol), CsOAc (0.767 g, 4 mmol) and $K_2CO_3$ (0.552 g, 4 mmol) in the presence of $PdCl(C_3H_5)$(dppb) (12.2 mg, 0.02 mmol) **5a** was obtained in 68% (0.233 g) yield as a blue oil. Eluent pentane: diethylether 10:1

$^1$H NMR (400 MHz, $CDCl_3$): δ 8.14 (s, 1H), 7.58 (d, *J* = 3.6 Hz, 1H), 7.40 (d, *J* = 8.1 Hz, 2H), 7.34 (d, *J* = 10.7 Hz, 1H), 7.29 (d, *J* = 8.1 Hz, 2H), 7.23 (d, *J* = 3.6 Hz, 1H), 6.87 (d, *J* = 10.7 Hz, 1H), 4.45 (s, 2H), 3.00 (sept., *J* = 6.8 Hz, 1H), 2.59 (s, 3H), 1.28 (d, *J* = 6.8 Hz, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 145.0, 144.7, 140.5, 137.5, 137.1, 136.8, 135.1, 133.7, 128.9, 128.6 (q, *J* = 32.2 Hz), 125.9, 125.3 (q, *J* = 3.7 Hz), 125.1, 124.2 (q, *J* = 271.9 Hz), 113.1, 43.0, 38.3, 24.7, 13.0. Elemental analysis: calcd (%) for $C_{22}H_{21}F_3$ (342.40): C 77.17, H 6.18; found: C 77.25, H 6.07.

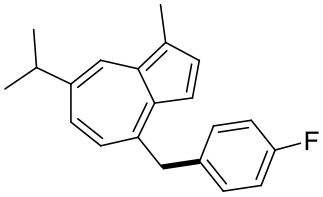
**4-(4-Chlorobenzyl)-7-isopropyl-1-methyl-azulene 6a**



From 4-bromochlorobenzene (0.191 g, 1 mmol), 7-isopropyl-1,4-dimethylazulene (0.296 g, 1.5 mmol), CsOAc (0.767 g, 4 mmol) and $K_2CO_3$ (0.552 g, 4 mmol) in the presence of $PdCl(C_3H_5)$(dppb) (12.2 mg, 0.02 mmol) 6a was obtained in 66% (0.203 g) yield as a blue oil. Eluent pentane

$^1$H NMR (400 MHz, $CDCl_3$): δ 8.14 (s, 1H), 7.58 (d, *J* = 3.6 Hz, 1H), 7.34 (d, *J* = 9.7 Hz, 1H), 7.24 (d, *J* = 3.6 Hz, 1H), 7.10 (s, 4H), 6.87 (d, *J* = 9.7 Hz, 1H), 4.38 (s, 2H), 3.00 (sept., *J* = 6.8 Hz, 1H), 2.60 (s, 3H), 1.28 (d, *J* = 6.8 Hz, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 145.7, 140.3, 139.1, 137.4, 136.9, 136.7, 135.1, 133.5, 132.0, 130.0, 128.6, 125.7, 125.0, 113.0, 42.5, 38.3, 24.7, 12.9. Elemental analysis: calcd (%) for $C_{21}H_{21}Cl$ (308.84): C 81.67, H 6.85; found: C 81.40, H 6.99.

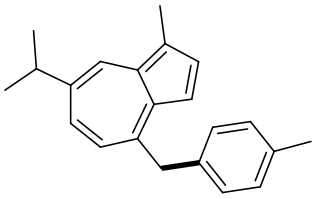
**4-(4-Fluorobenzyl)-7-isopropyl-1-methyl-azulene 7a**



From 4-bromofluorobenzene (0.175 g, 1 mmol), 7-isopropyl-1,4-dimethylazulene (0.296 g, 1.5 mmol), CsOAc (0.767 g, 4 mmol) and $K_2CO_3$ (0.552 g, 4 mmol) in the presence of $PdCl(C_3H_5)$(dppb) (12.2 mg, 0.02 mmol) **7a** was obtained in 52% (0.152 g) yield as a blue oil. Eluent pentane: diethylether 20:1

$^1$H NMR (400 MHz, $CDCl_3$): δ 8.13 (s, 1H), 7.58 (d, *J* = 3.7 Hz, 1H), 7.34 (d, *J* = 9.3 Hz, 1H), 7.27 (d, *J* = 3.7 Hz, 1H), 7.17-7.12 (m, 2H), 6.90-6.80 (m, 3H), 4.39 (s, 2H), 3.00 (sept., *J* = 6.8 Hz, 1H), 2.60 (s, 3H), 1.28 (d, *J* = 6.8 Hz, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 161.7 (d, *J* = 246.5 Hz), 146.1, 140.2, 137.4, 136.9, 136.6, 136.2, 135.1, 133.5, 130.0 (d, *J* = 7.9 Hz), 125.7, 125.0, 115.2 (d, *J* = 21.3 Hz), 112.9, 42.4, 38.3, 24.7, 12.9. Elemental analysis: calcd (%) for $C_{21}H_{21}F$ (292.39): C 86.26, H 7.24; found: C 86.15, H 7.16.

**7-Isopropyl-1-methyl-4-(4-methylbenzyl)-azulene 8a**

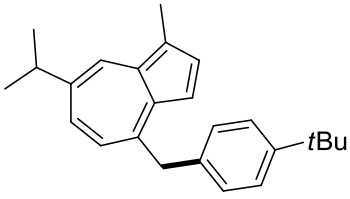



From 4-bromotoluene (0.171 g, 1 mmol), 7-isopropyl-1,4-dimethylazulene (0.296 g, 1.5 mmol), CsOAc (0.767 g, 4 mmol) and $K_2CO_3$ (0.552 g, 4 mmol) in the presence of $PdCl(C_3H_5)$(dppb) (12.2 mg, 0.02 mmol) **8a** was obtained in 42% (0.121 g) yield as a blue oil.

Eluent pentane

$^1$H NMR (400 MHz, $CDCl_3$): δ 8.12 (s, 1H), 7.57 (s, 1H), 7.32 (d, *J* = 10.7 Hz, 1H), 7.18 (s, 1H), 7.09 (d, *J* = 8.0 Hz, 2H), 6.98 (d, *J* = 8.0 Hz, 2H), 6.90 (d, *J* = 10.7 Hz, 1H), 4.39 (s, 2H), 2.99 (sept., *J* = 6.8 Hz, 1H), 2.59 (s, 3H), 2.21 (s, 3H), 1.27 (d, *J* = 6.8 Hz, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 146.8, 139.9, 137.6, 137.5, 136.7, 136.5, 135.7, 135.1, 133.3, 129.1, 128.6, 125.5, 125.1, 112.9, 42.7, 38.2, 24.7, 21.0, 12.9. Elemental analysis: calcd (%) for $C_{22}H_{24}$ (288.43): C 91.61, H 8.39; found: C 91.75, H 8.30.

**4-(4-*tert*-Butylbenzyl)-7-isopropyl-1-methyl-azulene 9a**

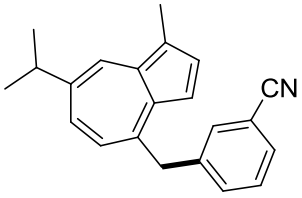


From 4-*tert*-butylbromobenzene (0.213 g, 1 mmol), 7-isopropyl-1,4-dimethylazulene (0.296 g, 1.5 mmol), CsOAc (0.767 g, 4 mmol) and $K_2CO_3$ (0.552 g, 4 mmol) in the presence of $PdCl(C_3H_5)$(dppb) (12.2 mg, 0.02 mmol) **9a** was obtained in 48% (0.158 g) yield as a blue oil.
Eluent pentane

$^1$H NMR (400 MHz, $CDCl_3$): δ 8.12 (s, 1H), 7.57 (d, *J* = 3.2 Hz, 1H), 7.35-7.25 (m, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 6.93 (d, *J* = 10.7 Hz, 1H), 4.39 (s, 2H), 2.98 (sept., *J* = 6.8 Hz, 1H), 2.59 (s, 3H), 1.27 (d, *J* = 6.8 Hz, 6H), 1.20 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 149.0, 146.8, 139.9, 137.7, 137.5, 136.7, 136.5, 135.2, 133.4, 128.3, 125.5, 125.4, 125.3, 113.0,

42.7, 38.3, 34.4, 31.4, 24.8, 13.0. Elemental analysis: calcd (%) for $C_{25}H_{30}$ (330.51): C 90.85, H 9.15; found: C 90.74, H 9.20.

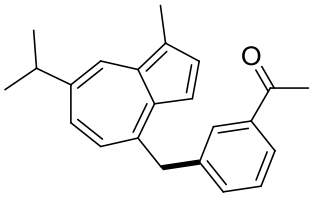
**3-(7-Isopropyl-1-methylazulen-4-ylmethyl)-benzonitrile 10a**




From 3-bromobenzonitrile (0.182 g, 1 mmol), 7-isopropyl-1,4-dimethylazulene (0.296 g, 1.5 mmol), CsOAc (0.767 g, 4 mmol) and $K_2CO_3$ (0.552 g, 4 mmol) in the presence of $PdCl(C_3H_5)$(dppb) (12.2 mg, 0.02 mmol) **10a** was obtained in 54% (0.161 g) yield as a blue oil. Eluent pentane: diethylether 10:1

$^1$H NMR (400 MHz, $CDCl_3$): δ 8.16 (s, 1H), 7.59 (d, *J* = 3.6 Hz, 1H), 7.50-7.30 (m, 4H), 7.24 (t, *J* = 7.7 Hz, 1H), 7.20-7.15 (m, 1H), 6.87 (d, *J* = 10.7 Hz, 1H), 4.43 (s, 2H), 3.02 (sept., *J* = 6.8 Hz, 1H), 2.60 (s, 3H), 1.30 (d, *J* = 6.8 Hz, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 144.3, 142.1, 140.7, 137.3, 137.2, 136.9, 135.1, 133.8, 133.0, 132.0, 130.1, 129.2, 126.1, 124.9, 118.9, 113.0, 112.5, 42.8, 38.2, 24.7, 12.9. Elemental analysis: calcd (%) for $C_{22}H_{21}N$ (299.41): C 88.25, H 7.07; found: C 88.01, H 7.17.

**1-[3-(7-Isopropyl-1-methylazulen-4-ylmethyl)-phenyl]-ethanone 11a**

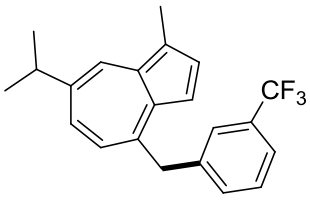



From 3-bromoacetophenone (0.199 g, 1 mmol), 7-isopropyl-1,4-dimethylazulene (0.296 g, 1.5 mmol), CsOAc (0.767 g, 4 mmol) and $K_2CO_3$ (0.552 g, 4 mmol) in the presence of $PdCl(C_3H_5)$(dppb) (12.2 mg, 0.02 mmol) **11a** was obtained in 51% (0.161 g) yield as a blue oil. Eluent pentane: diethylether 10:1

$^1$H NMR (400 MHz, $CDCl_3$): δ 8.14 (s, 1H), 7.86 (s, 1H), 7.67 (d, *J* = 7.7 Hz, 1H), 7.59 (d, *J* = 3.6 Hz, 1H), 7.30-7.20 (m, 4H), 6.9 (d, *J* = 10.7 Hz, 1H), 4.47 (s, 2H), 3.00 (sept., *J* = 6.8 Hz, 1H),

2.60 (s, 3H), 2.48 (s, 3H), 1.28 (d, *J* = 6.8 Hz, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 198.3, 145.5, 141.2, 140.3, 137.4, 137.3, 136.9, 136.8, 135.1, 133.6, 133.3, 128.7, 128.4, 126.5, 125.8, 125.0, 113.0, 43.1, 38.3, 26.7, 24.7, 12.9. Elemental analysis: calcd (%) for $C_{23}H_{24}O$ (316.44): C 87.30, H 7.64; found: C 87.48, H 7.51.

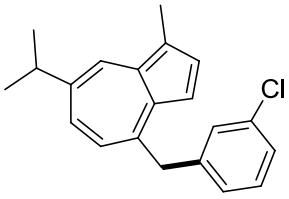
**7-Isopropyl-1-methyl-4-(3-trifluoromethyl-benzyl)-azulene 12a**



From 3-(trifluoromethyl)bromobenzene (0.225 g, 1 mmol), 7-isopropyl-1,4-dimethylazulene (0.296 g, 1.5 mmol), CsOAc (0.767 g, 4 mmol) and $K_2CO_3$ (0.552 g, 4 mmol) in the presence of $PdCl(C_3H_5)$(dppb) (12.2 mg, 0.02 mmol) **12a** was obtained in 71% (0.243 g) yield as a blue oil. Eluent pentane: diethylether 10:1

$^1$H NMR (400 MHz, $CDCl_3$): δ 8.15 (s, 1H), 7.58 (d, *J* = 1.6 Hz, 1H), 7.50 (s, 1H), 7.40-7.30 (m, 3H), 7.30- 7.20 (m, 2H), 6.87 (d, *J* = 10.7 Hz, 1H), 4.46 (s, 2H), 3.00 (sept., *J* = 6.8 Hz, 1H), 2.60 (s, 3H), 1.28 (d, *J* = 6.8 Hz, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 145.0, 141.5, 140.4, 137.5, 137.1, 136.8, 135.1, 133.6, 132.0, 130.8 (q, *J* = 32.0 Hz), 128.9, 125.9, 125.3 (s, *J* = 3.8 Hz), 124.9, 124.1 (q, *J* = 272.3 Hz), 123.2 (q, *J* = 3.7 Hz), 113.0, 42.9, 38.3, 24.7, 12.9. Elemental analysis: calcd (%) for $C_{22}H_{21}F_3$ (342.40): C 77.17, H 6.18; found: C 77.45, H 6.24.

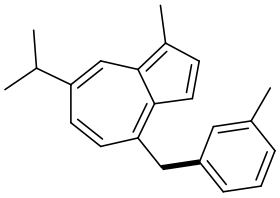
**4-(3-Chlorobenzyl)-7-isopropyl-1-methyl-azulene 13a**



From 3-bromochlorobenzene (0.191 g, 1 mmol), 7-isopropyl-1,4-dimethylazulene (0.296 g, 1.5 mmol), CsOAc (0.767 g, 4 mmol) and $K_2CO_3$ (0.552 g, 4 mmol) in the presence of $PdCl(C_3H_5)$(dppb) (12.2 mg, 0.02 mmol) **13a** was obtained in 69% (0.212 g) yield as a blue oil. Eluent pentane

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.22 (s, 1H), 7.66 (d, *J* = 3.6 Hz, 1H), 7.42 (d, *J* = 10.7 Hz, 1H), 7.33 (d, *J* = 3.6 Hz, 1H), 7.27 (s, 1H), 7.20-7.15 (m, 3H), 6.96 (d, *J* = 10.7 Hz, 1H), 4.46 (s, 2H), 3.09 (sept., *J* = 6.8 Hz, 1H), 2.68 (s, 3H), 1.36 (d, *J* = 6.8 Hz, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 145.3, 142.6, 140.3, 137.5, 137.0, 136.7, 135.1, 134.2, 133.6, 129.7, 128.7, 126.9, 126.5, 125.8, 125.0, 113.0, 42.9, 38.3, 24.7, 13.0. Elemental analysis: calcd (%) for $C_{21}H_{21}Cl$ (308.84): C 81.67, H 6.85; found: C 81.79, H 6.70.

**7-Isopropyl-1-methyl-4-(3-methylbenzyl)-azulene 14a**

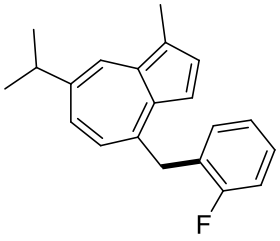


From 3-bromotoluene (0.171 g, 1 mmol), 7-isopropyl-1,4-dimethylazulene (0.296 g, 1.5 mmol), CsOAc (0.767 g, 4 mmol) and $K_2CO_3$ (0.552 g, 4 mmol) in the presence of $PdCl(C_3H_5)$(dppb) (12.2 mg, 0.02 mmol) **14a** was obtained in 54% (0.155 g) yield as a blue oil.

Eluent pentane

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.12 (s, 1H), 7.57 (s, 1H), 7.35-7.25 (m, 2H), 7.10-6.95 (m, 3H), 6.95-6.88 (m, 2H), 4.38 (s, 2H), 2.98 (sept., *J* = 6.8 Hz, 1H), 2.59 (s, 3H), 2.20 (s, 3H), 1.27 (d, *J* = 6.8 Hz, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 146.7, 140.5, 139.9, 138.1, 137.7, 136.8, 136.5, 135.1, 133.4, 129.5, 128.4, 127.0, 125.8, 125.5, 125.2, 113.0, 43.1, 38.3, 24.8, 21.4, 13.0. Elemental analysis: calcd (%) for $C_{22}H_{24}$ (288.43): C 91.61, H 8.39; found: C 91.77, H 8.57.

**4-(2-Fluorobenzyl)-7-isopropyl-1-methyl-azulene 15a**

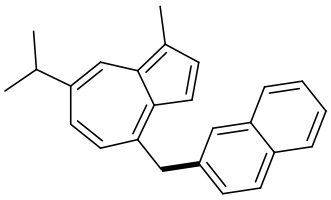



From 2-bromofluorobenzene (0.175 g, 1 mmol), 7-isopropyl-1,4-dimethylazulene (0.296 g, 1.5 mmol), CsOAc (0.767 g, 4 mmol) and $K_2CO_3$ (0.552 g, 4 mmol) in the presence of

$PdCl(C_3H_5)$(dppb) (12.2 mg, 0.02 mmol) **15a** was obtained in 63% (0.184 g) yield as a blue oil. Eluent pentane: diethylether 10:1

$^1$H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, *J* = 2.0 Hz, 1H), 7.57 (s, 1H), 7.34 (dd, *J* = 10.4, 2.0 Hz, 1H), 7.15- 6.80 (m, 6H), 4.44 (s, 2H), 2.99 (sept., *J* = 6.8 Hz, 1H), 2.59 (s, 3H), 1.28 (d, *J* = 6.8 Hz, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 160.8 (d, *J* = 246.0 Hz), 145.1, 140.3, 137.5, 136.9, 136.7, 135.0, 133.5, 130.6 (d, *J* = 4.2 Hz), 127.9 (d, *J* = 8.1 Hz), 127.2 (d, *J* = 15.7 Hz), 125.6, 124.7, 124.0 (d, *J* = 3.5 Hz), 115.2 (d, *J* = 22.3 Hz), 112.9, 38.3, 35.4, 24.7, 12.9. Elemental analysis: calcd (%) for $C_{21}H_{21}F$ (292.39): C 86.26, H 7.24; found: C86.44, H 7.51.

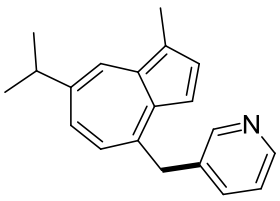
**7-Isopropyl-1-methyl-4-naphthalen-2-ylmethylazulene 16a**



From 2-bromonaphthalene (0.207 g, 1 mmol), 7-isopropyl-1,4-dimethylazulene (0.296 g, 1.5 mmol), CsOAc (0.767 g, 4 mmol) and $K_2CO_3$ (0.552 g, 4 mmol) in the presence of $PdCl(C_3H_5)$(dppb) (12.2 mg, 0.02 mmol) **16a** was obtained in 45% (0.146 g) yield as a blue oil. Eluent pentane

$^1$H NMR (400 MHz, $CDCl_3$): δ 8.15 (s, 1H), 7.70-7.60 (m, 4H), 7.59 (d, *J* = 3.6 Hz, 1H), 7.40-7.28 (m, 5H), 6.94 (d, *J* = 10.7 Hz, 1H), 4.58 (s, 2H), 3.00 (sept., *J* = 6.8 Hz, 1H), 2.61 (s, 3H), 1.27 (d, *J* = 6.8 Hz, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 146.3, 140.1, 138.2, 137.7, 136.9, 136.6, 135.1, 133.6, 133.4, 132.2, 128.1, 127.7, 127.6, 127.3, 127.0, 125.9, 125.6, 125.4, 125.2, 113.0, 43.3, 38.3, 24.7, 13.0. Elemental analysis: calcd (%) for $C_{25}H_{24}$ (324.46): C 92.54, H 7.46; found: C 92.67, H 7.66.

**3-(7-Isopropyl-1-methylazulen-4-ylmethyl)-pyridine 17a**




From 3-bromopyridine (0.158 g, 1 mmol), 7-isopropyl-1,4-dimethylazulene (0.296 g, 1.5 mmol), CsOAc (0.767 g, 4 mmol) and $K_2CO_3$ (0.552 g, 4 mmol) in the presence of $PdCl(C_3H_5)(dppb)$ (12.2 mg, 0.02 mmol) **17a** was obtained in 61% (0.168 g) yield as a blue oil.

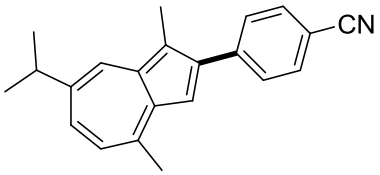
Eluent pentane

$^1$H NMR (400 MHz, $CDCl_3$): δ 8.55 (s, 1H), 8.35 (d, *J* = 3.8 Hz, 1H), 8.14 (s, 1H), 7.59 (d, *J* = 3.6 Hz, 1H), 7.44 (d, *J* = 7.7 Hz, 1H), 7.35 (d, *J* = 10.7 Hz, 1H), 7.25 (d, *J* = 3.6 Hz, 1H), 7.04 (dd, *J* = 7.7, 4.0 Hz, 1H), 6.88 (d, *J* = 10.7 Hz, 1H), 4.40 (s, 2H), 3.00 (sept., *J* = 6.8 Hz, 1H), 2.60 (s, 3H), 1.28 (d, *J* = 6.8 Hz, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 149.9, 147.8, 144.8, 140.5, 137.3, 137.1, 136.8, 136.1, 135.8, 135.1, 133.6, 125.9, 124.9, 123.4, 113.0, 40.4, 38.3, 24.7, 12.9. Elemental analysis: calcd (%) for $C_{20}H_{21}N$ (275.39): C 87.23, H 7.69; found: C 87.45, H 7.87.

**General procedure for the synthesis of 1b, 6b-8b, 14b and 18b**

As a typical experiment, reaction of the aryl bromide (1 mmol), 7-isopropyl-1,4-dimethylazulene (0.296 g, 1.5 mmol), and KOAc (0.784 g, 8 mmol) at 150 $^o$C for 16 h in ethylbenzene (5 mL) in the presence of $PdCl(C_3H_5)(dppb)$ (12.2 mg, 0.02 mmol) under argon afforded the corresponding arylation product after extraction with dichloromethane, evaporation and filtration on silica gel.

**4-(7-Isopropyl-1,4-dimethylazulen-2-yl)-benzonitrile 1b**

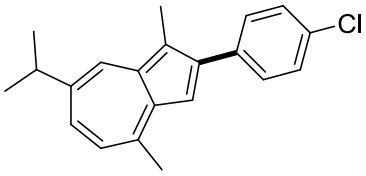



From 4-bromobenzonitrile (0.182 g, 1 mmol), 7-isopropyl-1,4-dimethylazulene (0.296 g, 1.5 mmol), KOAc (0.784 g, 8 mmol) in ethylbenzene in the presence of $PdCl(C_3H_5)(dppb)$ (12.2 mg, 0.02 mmol) **1b** was obtained in 38% (0.114 g) yield (containing around 10% of **1c**) as a blue oil. Eluent pentane: diethylether 100:1

$^1$H NMR (400 MHz, $CDCl_3$): δ 8.21 (s, 1H), 7.67 (s, 4H), 7.37 (d, *J* = 10.6 Hz, 1H), 7.25 (bs, 1H), 7.01 (d, *J* = 10.6 Hz, 1H), 3.04 (sept., *J* = 6.8 Hz, 1H), 2.81 (s, 3H), 2.63 (s, 3H), 1.31 (d, *J* = 6.8 Hz, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 145.6, 145.2, 143.3, 141.5, 137.9, 136.8, 135.6, 134.4,

132.1, 130.2, 126.3, 121.6, 119.2, 113.2, 110.3, 38.4, 24.8, 24.2, 11.6. Elemental analysis: calcd (%) for $C_{22}H_{21}N$ (299.41): C 88.25, H 7.07; found: C 88.20, H 7.21.

**2-(4-Chlorophenyl)-7-isopropyl-1,4-dimethylazulene 6b**

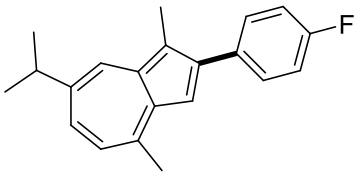


From 4-bromochlorobenzene (0.191 g, 1 mmol), 7-isopropyl-1,4-dimethylazulene (0.296 g, 1.5 mmol), KOAc (0.784 g, 8 mmol) in ethylbenzene in the presence of $PdCl(C_3H_5)(dppb)$ (12.2 mg, 0.02 mmol) **6b** was obtained in 53% (0.163 g) yield as a blue oil.

Eluent pentane: diethylether 100:1

$^1$H NMR (400 MHz, $CDCl_3$): δ 8.18 (s, 1H), 7.51 (d, *J* = 8.5 Hz, 2H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.33 (d, *J* = 10.6 Hz, 1H), 7.24 (s, 1H), 6.99 (d, *J* = 10.6 Hz, 1H), 3.02 (sept., *J* = 6.8 Hz, 1H), 2.77 (s, 3H), 2.62 (s, 3H), 1.30 (d, *J* = 6.8 Hz, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 146.8, 144.2, 141.1, 137.8, 136.9, 136.7, 134.7, 133.6, 133.0, 130.9, 128.6, 126.0, 121.3, 113.2, 38.4, 24.8, 24.2, 11.6. Elemental analysis: calcd (%) for $C_{21}H_{21}Cl$ (308.84): C 81.67, H 6.85; found: C 81.68, H 6.97.

**2-(4-Fluorophenyl)-7-isopropyl-1,4-dimethylazulene 7b**



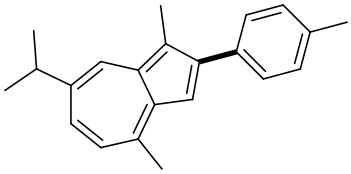
From 4-bromofluorobenzene (0.175 g, 1 mmol), 7-isopropyl-1,4-dimethylazulene (0.296 g, 1.5 mmol), KOAc (0.784 g, 8 mmol) in ethylbenzene in the presence of $PdCl(C_3H_5)(dppb)$ (12.2 mg, 0.02 mmol) **7b** was obtained in 51% (0.149 g) yield as a blue oil.

Eluent pentane: diethylether 100:1

$^1$H NMR (400 MHz, $CDCl_3$): δ 8.18 (s, 1H), 7.55 (dd, *J* = 7.9, 5.6 Hz, 2H), 7.33 (d, *J* = 10.6 Hz,

1H), 7.24 (s, 1H), 7.10 (t, *J* = 8.4 Hz, 2H), 6.99 (d, *J* = 10.6 Hz, 1H), 3.02 (sept., *J* = 6.8 Hz, 1H), 2.78 (s, 3H), 2.62 (s, 3H), 1.31 (d, *J* = 6.8 Hz, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 162.2 (d, *J* = 246.5 Hz), 147.2, 143.9, 141.0, 137.8, 136.7, 134.5, 134.4, 133.4, 131.1 (d, *J* = 7.9 Hz), 125.9, 121.2, 115.3 (d, *J* = 21.3 Hz), 113.3, 38.4, 24.8, 24.2, 11.6. Elemental analysis: calcd (%) for $C_{21}H_{21}F$ (292.39): C 86.26, H 7.24; found: C 86.48, H 7.34.

**7-Isopropyl-1,4-dimethyl-2-p-tolylazulene 8b**

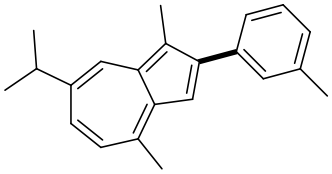


From 4-bromotoluene (0.171 g, 1 mmol), 7-isopropyl-1,4-dimethylazulene (0.296 g, 1.5 mmol), KOAc (0.784 g, 8 mmol) in ethylbenzene in the presence of $PdCl(C_3H_5)$(dppb) (12.2 mg, 0.02 mmol) **8b** was obtained in 56% (0.161 g) yield as a blue oil.

Eluent pentane

$^1$H NMR (400 MHz, $CDCl_3$): δ 8.17 (s, 1H), 7.50 (d, *J* = 8.5 Hz, 2H), 7.31 (d, *J* = 10.6 Hz, 1H), 7.23 (d, *J* = 8.5 Hz, 2H), 7.20 (s, 1H), 6.97 (d, *J* = 10.6 Hz, 1H), 3.03 (sept., *J* = 6.8 Hz, 1H), 2.78 (s, 3H), 2.65 (s, 3H), 2.36 (s, 3H), 1.31 (d, *J* = 6.8 Hz, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 148.3, 143.5, 140.8, 137.8, 136.8, 136.6, 135.5, 134.2, 133.1, 129.6, 129.1, 125.7, 121.3, 113.5, 38.4, 24.8, 24.2, 21.3, 11.6. Elemental analysis: calcd (%) for $C_{22}H_{24}$ (288.43): C 91.61, H 8.39; found: C 91.78, H 8.24.

**7-Isopropyl-1,4-dimethyl-2-m-tolylazulene 14b**

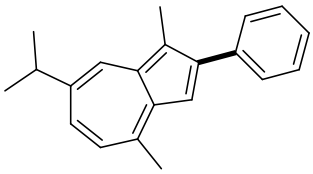


From 3-bromotoluene (0.171 g, 1 mmol), 7-isopropyl-1,4-dimethylazulene (0.296 g, 1.5 mmol), KOAc (0.784 g, 8 mmol) in ethylbenzene in the presence of $PdCl(C_3H_5)$(dppb) (12.2 mg, 0.02 mmol) **14b** was obtained in 54% (0.156 g) yield as a blue oil.

Eluent pentane

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, *J* = 1.7 Hz, 1H), 7.45-7.25 (m, 5H), 7.31 (d, *J* = 10.6 Hz, 1H), 7.10 (d, *J* = 7.1 Hz, 1H), 6.97 (d, *J* = 10.6 Hz, 1H), 3.03 (sept., *J* = 6.8 Hz, 1H), 2.78 (s, 3H), 2.64 (s, 3H), 2.38 (s, 3H), 1.30 (d, *J* = 6.8 Hz, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 148.5, 143.7, 140.8, 138.4, 137.9, 137.8, 136.6, 134.3, 133.3, 130.4, 128.2, 127.8, 126.8, 125.7, 121.4, 113.7, 38.4, 24.8, 24.2, 21.6, 11.6. Elemental analysis: calcd (%) for $C_{22}H_{24}$ (288.43): C 91.61, H 8.39; found: C 91.79, H 8.49.

**2-(4-Phenyl)-7-isopropyl-1,4-dimethylazulene 18b**



From bromobenzene (0.157 g, 1 mmol), 7-isopropyl-1,4-dimethylazulene (0.296 g, 1.5 mmol), KOAc (0.784 g, 8 mmol) in ethylbenzene in the presence of $PdCl(C_3H_5)$(dppb) (12.2 mg, 0.02 mmol) **18b** was obtained in 56% (0.153 g) yield as a blue oil.

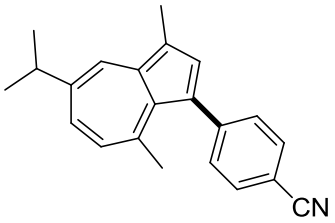
Eluent pentane

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.18 (s, 1H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.41 (t, *J* = 8.5 Hz, 2H), 7.33-7.25 (m, 3H), 6.98 (d, *J* = 10.6 Hz, 1H), 3.03 (sept., *J* = 6.8 Hz, 1H), 2.78 (s, 3H), 2.65 (s, 3H), 1.31 (d, *J* = 6.8 Hz, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 148.3, 143.8, 140.9, 138.5, 137.8, 136.7, 134.4, 133.4, 129.7, 128.4, 127.0, 125.8, 121.4, 113.6, 38.4, 24.8, 24.2, 11.6. Elemental analysis: calcd (%) for $C_{21}H_{22}$ (274.40): C 91.92, H 8.08; found: C 92.02, H 7.99.

**General procedure for the synthesis of 1c and 14c**

As a typical experiment, reaction of the aryl bromide (1 mmol), 7-isopropyl-1,4-dimethylazulene (0.296 g, 1.5 mmol), and KOAc (0.784 g, 8 mmol) at 150 $^{o}$C for 16 h in DMAc (5 mL) in the presence of $PdCl(C_3H_5)$(dppb) (12.2 mg, 0.02 mmol) under argon afforded the corresponding arylation product after extraction with dichloromethane, evaporation and filtration on silica gel.

**4-(5-Isopropyl-3,8-dimethylazulen-1-yl)-benzonitrile 1c**

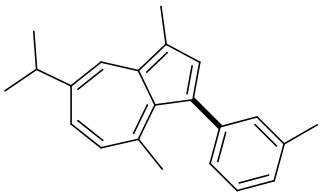


From 4-bromobenzonitrile (0.182 g, 1 mmol), 7-isopropyl-1,4-dimethylazulene (0.296 g, 1.5 mmol), KOAc (0.784 g, 8 mmol) in DMAc in the presence of $PdCl(C_3H_5)$(dppb) (12.2 mg, 0.02 mmol) **1c** was obtained in 51% (0.153 g) yield as a green oil.

Eluent pentane: diethylether 100:1

$^1$H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, *J* = 2.1 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.46 (s, 1H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.36 (dd, *J* = 10.7, 2.1 Hz, 1H), 6.92 (d, *J* = 10.7 Hz, 1H), 3.02 (sept., *J* = 6.8 Hz, 1H), 2.59 (s, 3H), 2.33 (s, 3H), 1.30 (d, *J* = 6.8 Hz, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 146.4, 145.7, 141.0, 139.7, 138.5, 135.3, 134.2, 132.2, 131.1, 131.0, 127.7, 127.0, 124.7, 119.4, 109.2, 37.9, 27.9, 24.6, 12.8. Elemental analysis: calcd (%) for $C_{22}H_{21}N$ (299.41): C 88.25, H 7.07; found: C 88.24, H 7.25.

**7-Isopropyl-1,4-dimethyl-3-*m*-tolylazulene 14c**




From 3-bromotoluene (0.171 g, 1 mmol), 7-isopropyl-1,4-dimethylazulene (0.296 g, 1.5 mmol), KOAc (0.784 g, 8 mmol) in DMAc in the presence of $PdCl(C_3H_5)$(dppb) (12.2 mg, 0.02 mmol) **14c** was obtained in 38% (0.110 g) yield as a green oil.

Eluent pentane: diethylether 100:1

$^1$H NMR (400 MHz, $CDCl_3$): δ 8.26 (d, *J* = 2.1 Hz, 1H), 7.47 (s, 1H), 7.28 (dd, *J* = 10.7, 2.1 Hz, 1H), 7.22- 7.03 (m, 4H), 6.82 (d, *J* = 10.7 Hz, 1H), 3.00 (sept., *J* = 6.8 Hz, 1H), 2.60 (s, 3H), 2.34

(s, 3H), 2.32 (s, 3H), 1.30 (d, *J* = 6.8 Hz, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 146.1, 141.4, 140.1, 139.6, 137.7, 136.6, 134.8, 133.7, 131.6, 131.5, 129.5, 127.8, 127.1, 126.7, 126.6, 124.0, 37.9, 27.6, 24.7, 21.5, 12.8. Elemental analysis: calcd (%) for $C_{22}H_{24}$ (288.43): C 91.61, H 8.39; found: C 91.87, H 8.17.

## 5.5 References


1. *(a)* M. Gordon, *Chem. Rev.* **1952**, *50*, 127; *(b)* V. B. Mochalin, Y. N. Porshnev, *Russ. Chem. Rev.* **1977**, *46*, 530; *(c)* S. E. Estdale, R. Brettle, D. A. Dunmur, C. M. Marson, *J. Mater. Chem.* **1997**, *7*, 391; *(d)* A. L. Crombie, J. L. Jr. Kane, K. M. Shea, R. L. Danheiser, *J. Org. Chem.* **2004**, *69*, 8652; *(e)* S. Carret, A. Blanc, Y. Coquerel, M. Berthod, A. E. Greene, J.-P. Deprés, *Angew. Chem. Int. Ed.* **2005**, *44*, 5130; *(f)* F. Wang, T. T. Lin, C. He, H. Chi, T. Tang, Y.-H. Lai, *J. Mater. Chem.* **2012**, *22*, 10448.
2. For the specific polarity and aromaticity of azulenes: *(a)* A. G. Anderson, B. M. Steckler, *J. Am. Chem. Soc.* **1959**, *81*, 4941; *(b)* H. Möllerstedt, M. C. Piqueras, R. Crespo, H. Ottosson, *J. Am. Chem. Soc.* **2004**, *126*, 13938.
3. M. J. S. Dewar, The Molecular Orbital Theory of Organic Chemistry, McGraw-Hill, New York, **1969**.
4. For general reviews on C-H bond functionalization: *(a)* D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174; *(b)* T. Satoh, M. Miura, *Chem. Lett.* **2007**, *36*, 200; *(c)* B.-J. Li, S.-D. Yang, Z.-J. Shi, *Synlett* **2008**, 949; *(d)* C. Lewis, R. G. Bergman, J. A. Ellman, *Acc. Chem. Res.* **2008**, *41*, 1013; *(e)* F. Bellina, R. Rossi, *Tetrahedron* **2009**, *65*, 10269; *(f)* L. Ackermann, R. Vicente, A. Kapdi, *Angew. Chem. Int. Ed.* **2009**, *48*, 9792; *(g)* O. Daugulis, H.-Q. Do, D. Skabashov, *Acc. Chem. Res.* **2009**, *42*, 1074; *(h)* X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2009**, *48*, 5094; *(i)* J. Roger, A. L. Gottumukkala, H. Doucet, *ChemCatChem* **2010**, *2*, 20; *(j)* N. Kuhl, M. N. Hopkinson, J. Wencel-Delord, F. Glorius, *Angew. Chem. Int. Ed.* **2012**, *51*, 10236; *(k)* J. Wencel-Delord, F. Glorius, *Nature Chem.* **2013**, *5*, 369.
5. For reviews on $sp^3$ C-H bond functionalization: *(a)* R. Giri, B.-F. Shi, K. M. Engle, N. Maugel, J.-Q. Yu, *Chem. Soc. Rev.* **2009**, *38*, 3242; *(b)* F. Bellina, R. Rossi, *Chem. Rev.* **2010**, *110*, 1082; *(d)* H. Li, B.-J. Li, Z.-J. Shi, *Catal. Sci. Technol.* **2011**, *1*, 191.
6. For selected recent examples of palladium-catalyzed direct arylation from our laboratory: *(a)* L. Chen, J. Roger, C. Bruneau, P. H. Dixneuf, H. Doucet, *Chem. Commun.* **2011**, *47*, 1872; *(b)* M. Baloch, R. Jacob Roy, D. Roy, K. Beydoun, H. Doucet, *RSC Adv.* **2011**, *1*,

1527; *(c)* K. Beydoun, M. Zaarour, J. A. G. Williams, H. Doucet, V. Guerchais, *Chem. Commun.* **2012**, *48*, 1260.

7. A. Ohta, Y. Akita, T. Ohkuwa, M. Chiba, R. Fukunaga, A. Miyafuji, T. Nakata, N. Tani, Y. Aoyagi, *Heterocycles* **1990**, *31*, 1951.
8. For selected examples of formation of 5- or 6-membered rings *via* intramolecular palladium-catalyzed direct $sp^3$ C-H arylations of unactivated C-H bonds: *(a)* G. Dyker, *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1023; *(b)* O. Baudoin, A. Herrbach, F. Guéritte, *Angew. Chem., Int. Ed.* **2003**, *42*, 5736; *(c)* M. Lafrance, S. I. Gorelsky, K. Fagnou, *J. Am. Chem. Soc.* **2007**, *129*, 14570; *(d)* H. Ren, Z. Li, P. Knochel, *Chem. Asian J.* **2007**, *2*, 416; *(e)* T. Watanabe, S. Oishi, N. Fujii, H. Ohno, *Org. Lett.* **2008**, *10*, 1759; *(f)* A. Salcedo, L. Neuville, J. Zhu, *J. Org. Chem.* **2008**, *73*, 3600; *(g)* C.-H. Hsiao, Y.-K. Lin, C.-J. Liu, T.-C. Wu, Y.-T. Wu, *Adv. Synth. Catal.* **2010**, *352*, 3267; *(h)* J. Sofack-Kreutzer, N. Martin, A. Renaudat, R. Jazzar, O. Baudoin, *Angew. Chem. Int. Ed.* **2012**, *51*, 10399; *(i)* E. Larionov, M. Nakanishi, D. Katayev, C. Besnard, E. P. Kündig, *Chem. Sci.* **2013**, *4*, 1995.
9. For selected examples of formation of C-C bonds *via* intermolecular palladium-catalyzed heteroatom-directed direct $sp^3$ C-H arylations of unactivated C-H bonds with diaryliodoniums or aryl halides: *(a)* D. Kalyani, N. R. Deprez, L. V. Desai, M. S. Sanford, *J. Am. Chem. Soc.* **2005**, *127*, 7330; *(b)* D. Shabashov, O. Daugulis, *Org. Lett.* **2005**, *7*, 3657; *(c)* B. V. S. Reddy, L. R. Reddy, E. J. Corey, *Org. Lett.* **2006**, *8*, 3391; *(d)* R. Giri, N. Maugel, J.-J. Li, D.-H. Wang, S. P. Breazzano, L. B. Saunders, J.-Q. Yu, *J. Am. Chem. Soc.* **2007**, *129*, 3510; *(e)* L.-C. Campeau, D. J. Schipper, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 3266; *(f)* J. J. Mousseau, A. Larivée, A. B. Charette, *Org. Lett.* **2008**, *10*, 1641; *(g)* M. Wasa, K. M. Engle, J.-Q. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 9886; *(h)* Y. Feng, G. Chen, *Angew. Chem. Int. Ed.* **2010**, *49*, 958; *(i)* I. Bassoude, S. Berteina-Raboin, S. Massip, J.-M. Leger, C. Jarry, E. M. Essassi, G. Guillaumet, *Eur. J. Org. Chem.* **2012**, 2572.
10. For example of formation of C-C bonds *via* intermolecular palladium-catalyzed non-directed direct $sp^3$ C-H arylations of unactivated C-H bonds with aryl halides: T. Niwa, H. Yorimitsu, K. Oshima, *Org. Lett.* **2007**, *9*, 2373.
11. G. Dyker, S. Borowski, J. Heiermann, J. Körning, K. Opwis, G. Henkel, M. Köckerling, *J. Organomet. Chem.* **2000**, *606*, 108.

12. O. Baudoin, *Chem. Soc. Rev.* **2011**, *40*, 4902.
13. For selected examples of intramolecular C($sp^3$)-H activation reactions: *(a)* M. Chaumontet, R. Piccardi, N. Audic, J. Hitce, J.-L. Peglion, E. Clot, O. Baudoin, *J. Am. Chem. Soc.* **2008**, *130*, 15157; *(b)* S. Rousseaux, M. Davi, J. Sofack-Kreutzer, C. Pierre, C. E. Kefalidis, E. Clot, K. Fagnou, O. Baudoin, *J. Am. Chem. Soc.* **2010**, *132*, 10706; *(c)* M. Nakanishi, D. Katayev, C. Besnard, E. P. Kündig, *Angew. Chem. Int. Ed.* **2011**, *50*, 7438; *(d)* S. Anas, A. Cordi, H. B. Kagan, *Chem. Commun.* **2011**, *47*, 11483; *(e)* N. Martin, C. Pierre, M. Davi, R. Jazzar, O. Baudoin, *Chem. Eur. J.* **2012**, *18*, 4480; *(f)* J.-X. Yan, H. Li, X.-W. Liu, J.-L. Shi, X. Wang, Z.-J. Shi, *Angew. Chem. Int. Ed.* **2014**, *53*, 1.
14. *(a)* A. Renaudat, L. Jean-Gérard, R. Jazzar, C. E. Kefalidis, E. Clot, O. Baudoin, *Angew. Chem. Int. Ed.* **2010**, *49*, 7261; *(b)* S. Aspin, A.-S. Goutierre, P. Larini, R. Jazzar, O. Baudoin, *Angew. Chem. Int. Ed.* **2012**, *51*, 10808; *(c)* P. Larini, C. E. Kefalidis, R. Jazzar, A. Renaudat, E. Clot, O. Baudoin, *Chem. Eur. J.* **2012**, *18*, 1932; *(d)* A. Millet, P. Larini, E. Clotb, O. Baudoin, *Chem. Sci.* **2013**, *4*, 2241.
15. C. Amatore, A. Jutand, G. Le Duc, *Chem. Eur. J.* **2012**, *18*, 6616.
16. B. Glover, K. A. Harvey, B. Liu, M. J. Sharp, M. F. Tymoschenko, *Org. Lett.* **2003**, *5*, 301.
17. *(a)* D. L. Davies, S. M. A. Donald, S. A. Macgregor, *J. Am. Chem. Soc.* **2005**, *127*, 13754; *(b)* D. Garcia-Cuadrado, P. de Mendoza, A. A. C. Braga, F. Maseras, A. M. Echavarren, *J. Am. Chem. Soc.* **2007**, *129*, 6880; *(c)* D. Lapointe, K. Fagnou, *Chem. Lett.* **2010**, *39*, 1118.
18. For deprotonation at C4-Me of guaiazulene with a strong base: S. Kurokawa, *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2311.
19. Heating of guaiazulene at 150 °C with 4 equiv. both of CsOAc and $K_2CO_3$ in DMAc in the presence of 4 equiv. of MeOD or $D_2O$, without palladium catalyst did not show any incorporation of deuterium.

# *General Conclusion*

The Palladium-catalyzed arylation through C-H bond activation gives a very simple access to relatively complex molecules in only one step. The major by-products are AcOH/KBr instead of metallic salts with more classical coupling procedures such as Suzuki, Stille or Negishi reactions. Moreover, no preparation of an organometallic derivative is required, reducing the number of steps and consequently the amount of waste to prepare these compounds. Moreover low catalyst loading procedure is also economically and environmentally attractive. The regioselectivity is always an important issue in the presence of multi C-H bonds but several methods allow to control the regioselectivity of C-H bond cross couplings.

In summary, in chapter 2, we have demonstrated that a variety of benzothiophenes are successfully arylated *via* palladium-catalyzed direct arylation reactions, including those that possess electron withdrawing group (formyl), electron donating group (methyl) or bromo group at C3. Using as little as 0.5-0.1 mol% of $Pd(OAc)_2$ as the catalyst precursor, the direct C2-arylation of benzothiophene derivatives generally proceeds in high yields. A wide variety of functional groups on the aryl bromide such as nitrile, nitro, acetyl, formyl, ester, chloro, fluoro or trifluoromethyl was tolerated.

We demonstrated in chapter 3 that the C2 and C5 positions of pyrroles are more reactive for C-H bond functionalization than the C3 and C4 positions, the formation of 2,5-diarylpyrroles was found to proceed quite selectively in the presence of 3 equiv. of a variety of aryl bromide. Non-symmetrically 2,5-diarylpyrroles *via* sequential C2 arylation followed by C5 arylation could also proceed smoothly. The coupling products with electron-deficient aryl bromides were obtained in higher yields. Excess 3,5-bis(trifluoromethyl)benzene was efficient to achieve tetraarylation of 1-methylpyrrole in good yield.

We observed in chapter 4 that the reactivity of polychlorobenzenes was lower than that of polyfluorobenzenes. $PdCl(C_3H_5)$(dppb)/KOAc system was found to promote the direct arylation of some polychlorobenzenes with aryl bromides. The best yields were obtained for the coupling of 1,2,4,5-tetrachlorobenzene or 1,3,5-trichlorobenzene with electron-deficient aryl bromides. The C3 arylation of 2,5-dichlorothiophene was also found to proceed nicely.

We also described in chapter 5 that both the palladium-catalyzed $sp^2$ and $sp^3$ direct arylations of guaiazulene are possible when appropriate reaction conditions are employed. The use of a mixture of $CsOAc/K_2CO_3$ in DMAc selectively promotes the $sp^3$ direct arylation at C4-Me of guaiazulene to give 4-benzylguaiazulenes; whereas KOAc in DMAc leads quite selectively to the C3- arylated compounds likely *via* $S_EAr$ process and KOAc in ethylbenzene favoring the Heck type mechanism affords the C2- arylated guaiazulenes. These conditions offer routes for fast and direct access to arylated guaiazulenes. The reaction tolerates various substituents such as formyl, acetyl, propionyl, fluoro, trifluoromethyl, fluoro or even chloro on the aryl bromide.

## Palladium-catalyzed direct arylation *via* $sp^2$ and $sp^3$ C-H activation of hetero(aromatics) and hydrocarbons for C-C bond formation

During this thesis, we were interested in the $sp^2$ and $sp^3$ C-H bond activation catalyzed by palladium catalysts for the preparation of (hetero)aryl-aryls and biaryls. This method is considered as cost effective and environmentally attractive compared to the classical couplings such as Suzuki, Heck, or Negishi. First we described the palladium-catalyzed direct C2-arylation of benzothiophene in the absence of phosphine ligand with high selectivity. We also demonstrated that it is possible to active both C2 and C5 C-H bonds for access to 2,5-diarylated compounds in one step, and also to non-symmetrically substituted 2,5-diarylpyrroles *via* sequential C2 arylation followed by C5 arylation. We also studied the reactivity of polychlorobenzenes *via* palladium-catalyzed C-H activation. We finally examined the palladium-catalysed selective $sp^2$ and $sp^3$ C-H bond activation of guaiazulene. The selectivity depends on the solvent and base: $sp^2$ C2-arylation (KOAc in ethylbenzene), $sp^2$ C3-arylation (KOAc in DMAc) and $sp^3$ C4-Me arylation ($CsOAc/K_2CO_3$ in DMAc). Through this method, a challenging $sp^3$ C-H bond was activated.

**Keywords:** Arylation; Heteroaromatics; Palladium; C-H activation; Atom-Economy; Biaryls; $sp^3$ and $sp^2$ C-H bond activation; Aryl halides; Homogeneous catalysis.

## Arylations directe catalysées au palladium *via* activation de liaisons C-H de type $sp^2$ et $sp^3$ d'hétéro(aromatiques) et d'hydrocarbures pour la formation de liaisons C-C

Au cours de cette thèse, nous nous sommes intéressés à l'activation de liaisons $sp^2$ et $sp^3$ C-H catalysée par le palladium pour la préparation d'(hétéro)aryl-aryles et de biaryles. Cette méthode est considérée comme attractive pour l'environnement par rapport aux méthodes classiques, tels que Suzuki, Heck, ou Negishi. Tout d'abord, nous avons décrit que la C2-arylation directe de benzothiophènes peut être effectuée par un catalyseur du palladium en l'absence de ligand phosphine avec une grande sélectivité. Nous avons également démontré qu'il est possible d'activer les positions C2 et C5 de pyrroles pour accéder en une seule étape a des 2,5-diarylpyrroles. Des 2,5-diarylpyrroles non-symétriques ont été formés par arylation séquentielle en C2 suivie par une arylation en C5. Nous avons également étudié la réactivité de polychlorobenzenes pour l'activation de liaisons C-H catalysé au palladium. Nous avons finalement étudié l'activation $sp^2$ et $sp^3$ sélective catalysé au palladium de liaisons C-H du guaiazulene. La sélectivité de la réaction dépend du solvant et de la base : C2-arylation (KOAc en éthylbenzène), C3-arylation (KOAc dans le DMAc) et C4-Me arylation ($CsOAc/K_2CO_3$ dans le DMAc). Grâce à cette méthode, une liaison $sp^3$ C-H peu réactive a été activée.

**Mots clés:** Arylation; Hétéroaromatiques; Palladium; Activation de liaison C-H; Economie d'atomes; Biaryls; Activation de liaison $sp^3$ et $sp^2$ C-H; Halogénures d'aryle; Catalyse Homogène.

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