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# Development and applications of new protocols for the Pd-catalyzed direct arylation of azoles with aryl halides

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*All things are ready, if our minds be so.*

*(W. Shakespeare)*

*Dedicated to me…*

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To my family: thank you.

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# ABSTRACT

Our own interest in the development of new and convenient protocols for the highly regioselective synthesis of (hetero)arylazoles via palladium-catalyzed intermolecular direct (hetero)arylation reactions of azoles with (hetero)aryl halides prompted us to design general and selective procedures for the synthesis of 5-aryl-1-methyl-1*H*-pyrazoles (**21**), 5-aryl-oxazoles (**30**), 5-aryl-thiazoles (**31**) and 5-aryl-1-methyl-1*H*-imidazoles (**32**), that were obtained by regioselective Pd-catalyzed direct C-5 arylation reactions of the corresponding azoles. In particular, we demonstrated that a variety of 5-aryl-1-methyl-1*H*-pyrazoles (**21**) can be prepared in moderate-to-good yields by a highly regioselective procedure involving the $Pd(OAc)_2$-catalyzed direct C-5 arylation of commercially available 1-methyl-1*H*-pyrazole (**15**) with activated, unactivated and deactivated, *para*- and *ortho*-substituted aryl bromides **26** in the presence of $Bu_4NOAc$ as the base in DMA at 70 °C.

Then, we applied these unprecedented reaction conditions promoted by $Bu_4NOAc$ to the direct C-5 arylation of oxazole (**4**), thiazole (**8**) and 1-methyl-1*H*-imidazole (**12**). With our pleasure, we found that a variety of 5-aryl-oxazoles (**30**) and 5-aryl-thiazoles (**31**) can be prepared in high yields and selectivities performing the reactions at only 70 °C. Moreover, 5-aryl-1*H*-imidazoles (**32**) can be efficiently synthesized in terms of activity and selectivity by using the same reaction conditions, but rising the reaction temperature at 110 °C.

Next, our attention was focused on a preliminary screening of the selective direct C-5 arylation of 1-phenyl-1*H*-pyrazole (**23**) with bromotoluene **26a**, chosen as model coupling partners. During this screening we observed the formation of three main products: 1-phenyl-5-*p*-tolyl-1*H*-pyrazole (**36a**), 1-(4'-methyl-[1,1'-biphenyl]-2-yl)-1*H*-pyrazole (**37a**) and 1-(4'-methyl-[1,1'-biphenyl]-2-yl)-5-(*p*-tolyl)-1*H*-pyrazole (**38a**). At the end of this in-depth study, we found that the best conditions for the C-5 direct arylation of commercially available compound **23** with bromotoluene **26a** consist in the use of $PdCl_2(MeCN)_2$ as the precatalyst in the presence of $K_2CO_3$ as base, pivalic acid and $Bu_4NBr$ as additives in DMA at 110 °C. Under these conditions, the required 1-phenyl-5-*p*-tolyl-1*H*-pyrazole (**36a**) was obtained in 43 % GLC yield with a selectivity higher than 80 %.

Direct arylation of azoles promoted by $Bu_4NOAc$ was also employed as key-step for the synthesis of useful organic materials. Firstly, we synthesized the 2,5-diaryl substituted oxazoles balsoxin (**39a**) and texaline (**39b**), two bioactive compounds isolated from the plant *Amyris* spp. in the Caribbean. In order to prepare these compounds, we tested a one-pot sequential diarylation of oxazole (**4**) with different aryl bromides by pairing the C-5 arylation procedure promoted by $Bu_4NOAc$ for the first step with the protocol for the direct C-2 arylation mediated by CuI, previously reported by our research group, for the second-one.

Balsoxin (**39a**) and texaline (**39b**) were obtained with an overall yield of 39 and 38 %, respectively.

After that, we focused our attention on the synthesis of resveratrol analogues **48** and **49**. The 2,5-diarylated imidazoles **48** were obtained by applying again the one-pot sequential procedure, this time starting from the 1-methyl-1*H*-imidazole (**12**). Compounds **49** (the relative unprotected derivatives of 2,5-diaryl-imidazoles **48**) were also synthesized by reacting compounds **48** with $BBr_3$ in $CH_2Cl_2$ at -60 °C. The biological activity of molecules **48** and **49** was then evaluated and we found that they show cytotoxic activity against the 60 human tumoral cell line panel of the *National Cancer Institute* of USA. Moreover, in a separate screening, compound **49b** resulted to be a NQO2 inhibitor *in vitro* and showed cytotoxicity higher than resveratrol (**44**).

Finally, we devoted part of our synthetic efforts to the preparation of new *push-pull* fluorophores, consisting in unsymmetrically substituted *p*-phenylene-linked imidazole-benzimidazoles **50**, imidazole-benzothiazoles **51** and thiazole-benzothiazoles **52**. In this context, we used a two-step procedure that involved the palladium-catalyzed direct C-5 arylation of azoles with aryl bromides promoted by $Bu_4NOAc$ developed in this Ph.D. work for the first step, and the ligandless direct arylation at the C-2 position promoted by CuI with aryl bromides previously developed by Bellina's group for the second step. Afterwards, their spectroscopic properties were evaluated by analysing their absorbance and emission spectra. Compounds **50**, **51** and **52** presented high quantum yields and Stokes shifts up to 114 nm.

As regards the final part of this Ph.D. work, it was carried out at the University of York, in collaboration with Professor Ian Fairlamb. We synthesize three new $Cu^I$-NHC: (1,3-dibenzylbenzo[*d*]imidazolin-2-ylidene)copper(I) bromide (**64a**), (1,3-diphenylbenzo[*d*]imidazolin-2-ylidene)copper(I) bromide (**64b**), and (1,3-bis(2,4,6-trimethylphenyl)imidazolin-2-yliden)copper(I) chloride (**65**). We demonstrated that **64b** undergoes a direct reaction with PhI (**2**), both in the presence and in the absence of $Pd(OAc)_2$, to give the arylated product (1,3-diphenyl)-2-phenylbenzo[*d*]imidazolium bromide (**86b**).

The studies summarized above have been the subject of the following publications and communications:

**Articles**

I. F. Bellina, M. Lessi and C. Manzini, ***Mild palladium-catalyzed regioselective direct arylation of azoles promoted by tetrabutylammonium acetate***, *Eur. J. Org. Chem.*, **2013**, 5621-5630.

II. M. Lessi, C. Manzini, P. Minei, L. A. Perego, J. Bloino, F. Egidi, V. Barone, A. Pucci, F. Bellina, ***Synthesis and optical properties of imidazole-based fluorophores having high quantum yields***, *ChemPlusChem*, **2014**, *79*, 366-370.

III. F. Bellina, N. Guazzelli, M. Lessi, C. Manzini, ***Imidazole analogues of resveratrol: synthesis and cancer cell growth evaluation***, submitted to *Tetrahedron*, November **2014**.

IV. T. J. Williams, B. R. M. Lake, C. E. Willans, N. A. Rajabi, A. Ariafard, C. Manzini, F. Bellina, A. C. Whitwood, I. J. S. Fairlamb, ***Mechanistic elucidation of the arylation of non-spectator* N*-heterocyclic carbenes at copper using a combined experimental and computational approach***, submitted to *Organometallics*.

**Oral and poster communications**

I. 10th meeting of Gruppo Interdivisionale di Chimica Organometallica (Co.G.I.C.O.) in Padova (Italy), **2012**. Poster: C. Manzini, F. Bellina, ***Palladium-catalyzed direct C-H arylation of pyrazole derivatives: first results***.

II. XXV International Conference of Organometallic Chemistry in Lisbon, (Portugal), **2012**. Oral communication: F. Bellina, A. Gini, M. Lessi, C. Manzini, L. Perego, ***Recent advances in selective direct arylation of azoles***.

III. 10th PhD Day of Consorzio Interuniversitario di Reattività Chimica e Catalisi (CIRCC) in Pisa (Italy), **2013**. Oral communication: C. Manzini, F. Bellina, N. Guazzelli, M. Lessi, L. Perego, ***Development and applications of a new mild protocol for the regioselective Pd-catalyzed direct arylation of azoles***.

IV. 9th International School of Organometallic Chemistry (ISOC), in Camerino (Italy), **2013**. Flash presentation and Poster: C. Manzini, F. Bellina, N. Guazzelli, M. Lessi, L. A. Perego, ***Mild regioselective Palladium-catalyzed direct C-H arylation of azoles***.

V. 14th Tetrahedron Symposium, in Vienna (Austria), **2013**. Poster: F. Bellina, N. Guazzelli, M. Lessi, C. Manzini, L. Perego, ***Mild ligandless regioselective palladium-catalyzed direct arylation of azoles***.

VI. European Winter School on Physical Organic Chemistry (e-WISPOC 2014), in Bressanone (Italy), **2014**. Poster: G. Marianetti, M. Lessi, C. Manzini, L. A. Perego, C. Pezzetta, P. Minei, A. Pucci, G. Ruggeri, F. Bellina, ***Azole-based fluorophores via regioselective Pd-catalyzed direct C-H arylation reactions***.

VII. XXXIX International Summer School on Organic Synthesis *"A. Corbella"*, in Gargnano (Italy), **2014**. Oral Communication: C. Manzini, N. Guazzelli, M. Lessi, G. Marianetti, L. A. Pergo, C. Pezzetta, P. Minei, A. Pucci, G. Ruggeri, F. Bellina, ***Regioselective palladium-catalyzed direct C-H arylation of azoles***.

VIII. 2nd International Symposium of C-H Activation, in Rennes (France), **2014**. Short lecture: C. Manzini, F. Bellina, M. Lessi, N. Guazzelli, G. Marianetti, L. A. Perego, C. Pezzetta, P. Minei, A. Pucci, G. Ruggeri, ***Regioselective palladium-catalyzed direct arylation of azoles***.

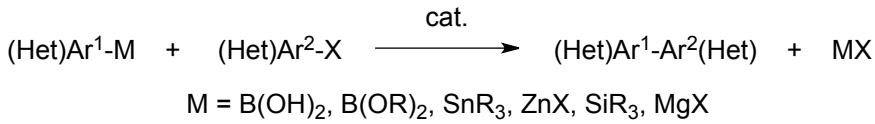
# INTRODUCTION

Arylazoles are important structural units, frequently found in natural products [1] pharmaceutics,[2] agrochemicals[3] and organic functional materials.[4] Due to their widespread applications, the development of straightforward functional group-tolerant synthetic methods for their preparation has attracted considerable attention.[5]

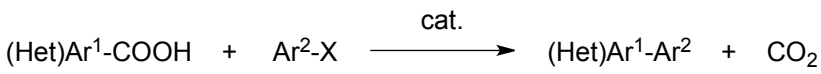
Many cross-coupling strategies have been developed so far for the formation of heteroaryl-(hetero)aryl bonds, with high yields, excellent selectivities and high functional group tolerance under mild conditions. The most common approach was the use of the traditional cross-coupling reactions promoted by transition metal catalysts (Scheme 1a).[6] However, these methods suffer from lack of atom- and step-economy, as they involve the preactivation of both the coupling partners that afterwards lead to the formation of additional waste.

An alternative to this approach consists of a Pd-catalyzed decarboxylative cross-coupling reaction between haloarenes and heteroaryl carboxylic acids (Scheme 1b).[7] In this case, the regioselectivity of the reaction is ensured by the carboxylic function and only carbon dioxide (apart from HX) is produced as waste.

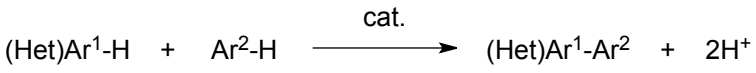
**a**. Traditional cross-coupling reactions:



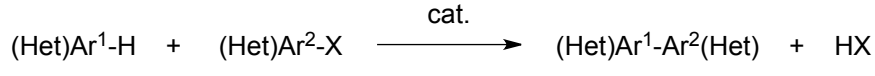

**b**. Decarboxylative cross-coupling reactions:




**c**. Oxidative coupling:




**d**. Direct arylation with (hetero)aryl halides:




**Scheme 1**

Recognizing the value of arylheteroarenes and the potential for improvement, several research groups have been looking for ways to reduce reliance in the substrate preactivation. Among the methodologies proposed, the oxidative coupling of heteroarenes[8] represents the simplest and most convenient approach because it involves the coupling of two (hetero)aryl C-H bonds (Scheme 1c), especially when these transformations can be performed with molecular oxygen as the terminal oxidant. However, achieving regioselectivity in intermolecular oxidative arylation reactions still represents an obstacle.

An eco-friendly and economic alternative to these approaches involves the use of a (hetero)arene and a (hetero)aryl halide (Scheme 1d). The development and applications of transition metal-catalyzed direct arylation reactions of heteroarenes with aryl halides or pseudohalides have attracted a great attention.[9,10] In fact, these reactions do not involve the use of stoichiometric amounts of organometallic reagents and result in a smaller number of reaction steps to achieve the required cross-coupling products with a concurrent reduction of waste.

After the first examples of the Pd-catalyzed direct arylation that appeared in the 1980s,[11] this synthetic approach has had a significant impact on the construction of (hetero)aryl-(hetero)aryl bonds over the last decade.

This introduction is intended to enlighten the reader on the direct intermolecular transition metal-catalyzed arylation reactions of heteroaromatic compounds. The direct intermolecular arylation of π-electron-rich heteroarenes, in particular azoles, with aryl halides will be discussed in more details because it represents the main subject area of this Ph.D. thesis.

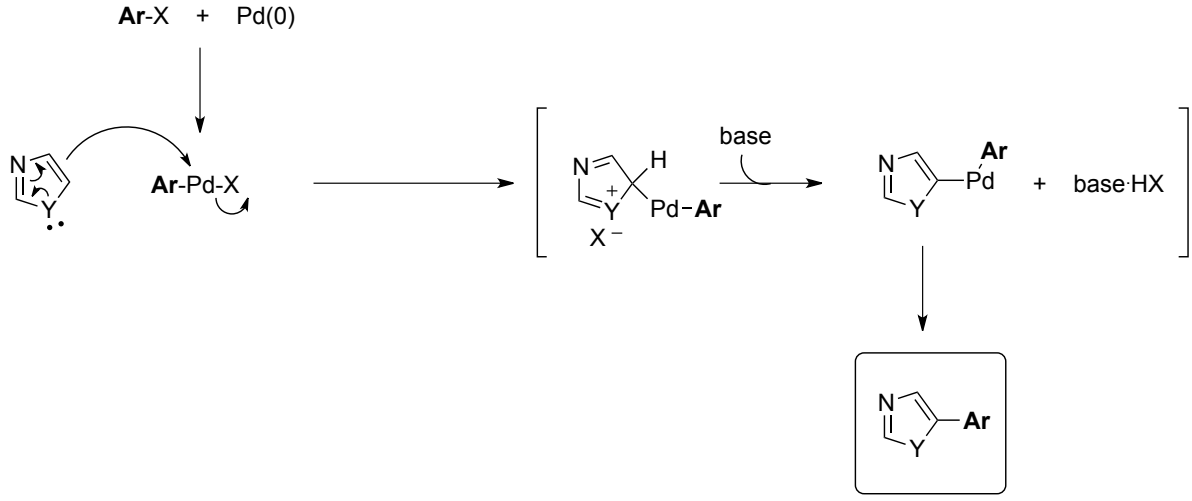
## 1. Direct arylation of azoles with aryl halides: mechanistic pathways (and the regioselectivity quest).

Many transition metals were used so far in the direct arylation of azoles with aryl halides, as Pd,[12] Cu,[13] Ni,[14] and Rh.[15] Palladium-catalyzed arylation reactions have particularly been investigated and we decided to focus our attention on them in this Ph.D. work. As regard the direct arylation of π-electron-rich heteroaromatics, it should be noted that the electronic bias inherent in their structure is often enough to control the regioselectivity of the activation of heteroaryl C-H bonds and obviates the need for the presence of directing groups.[9] Consequently, the regioselectivity of these reactions primarily depends on the type of

heterocycle, but also on the electronic nature of the catalyst employed. However, other parameters such as the nature of the solvent, the additives and the steric characteristics of the catalyst have been used to affect the regioselectivity of direct arylation reactions.[9]

As regards the azoles it is worthy of mention that, whereas few examples have been reported for the direct intermolecular arylation of π-deficient heteroaromatics such as pyridine,[16] azine, and diazine *N*-oxides,[17] the use of π-electron-rich heteroaromatics in these Pd-catalyzed $Csp^2$-$Csp^2$ bond forming reactions has been featured prominently.[9,10d,e] In fact, from a strategic prospective, the latent reactivity of a C-H bond of an electron-rich nucleus may mimic that of an organometallic compound in the transmetalation step of the catalytic cycle of traditional cross-coupling reactions.[18]

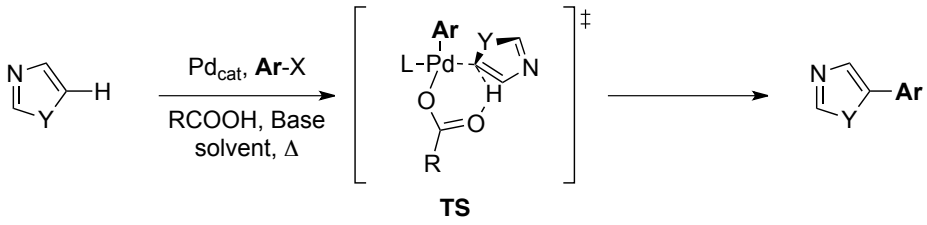
Many research groups have devoted their efforts in last decade in the development of various methodologies for the direct arylations of π-electron-rich heteroaromatics with aryl halides, and in the mechanistic interpretation of the C-H bond cleavage.[19] The first mechanism that has been suggested for the palladium-catalyzed direct arylation of heteroaromatics under the standard conditions (a metal-phosphine catalyst and carbonate/carboxylate base) was the electrophilic aromatic substitution ($S_EAr$), as depicted for 1,3 azoles in Scheme 2.[20]




**Scheme 2**

Thus, according to this mechanistic hypothesis, the regioselectivity appears to be mainly governed by the electron density of the substrate, as demonstrated by the fact that the Pd-catalyzed arylation reactions of electron-rich heteroarenes with aryl halides generally occur at the site with the highest nucleophilic character.[20]

Nevertheless, another reaction mechanism, the concerted metalation-deprotonation pathway (CMD), has more recently suggested and it has become the considerable alternative to the electrophilic aromatic substitution for the direct arylation of electron-rich heteroaromatic nuclei (Scheme 3).




**Scheme 3**

In the CMD transition state (**TS**, Scheme 3), a carboxylate ligand of the metal catalyst abstracts a proton from a C-H bond while, at the same time, a metal carbon bond is being formed.[19,21]

From a distortion-interaction analysis performed for several C-H bonds of different (hetero)arenes by Fagnou and co-workers, it emerged that the CMD energy barrier in the Pd-catalyzed direct arylation of heteroarenes depends on different contributions (Figure 1): an energetic cost (distortion energy, $E_{dist}$) associated with the distortion of the catalyst and the (hetero)arene from their ground state structures (**I** and **II**) to their geometries (**III** and **IV**) in the TS structure **V**, and an energetic gain (electronic interaction energy, $E_{int}$) resulting from the electronic interaction of fragments **III** and **IV** to form the TS structure **V**.

These factors allowed the authors to classify the (hetero)arenes into three categories (Figure 2).[19,21] Class I includes (hetero)arenes for which the regioselectivity of C-H bond metalation is controlled by the difference in the arene distortion energies, $E_{dist}$(ArH). 1-Methyl-pyrazole, for instance, belongs to class I and its C5-H bond is more reactive than C3-H and C4-H bonds in the CMD process due to the lower distortion energy of this heterocycle at its C5 site.

Class II includes (hetero)arenes for which catalyst-arene electronic interaction energies define the most reactive C-H bonds. The three 1,3-azoles 1-methyl-imidazole, oxazole and thiazole, belong to the second class, and calculations showed that their C5-H bonds are more reactive than the others in the CMD process due to a more negative interaction energy at their C5 site.

Class III includes (hetero)arenes for which both the arene distortion and catalyst-arene interaction energies enhance the CMD cleavage of a given C-H bond. An example of such heteroarenes is thiophene, for which $C_{\alpha}$-H bonds are more reactive than $C_{\beta}$-H bonds in the

CMD process due to a lower arene distortion energy at the $C_\alpha$ site and the more favourable catalyst-arene interaction energy at the $C_\alpha$ site.

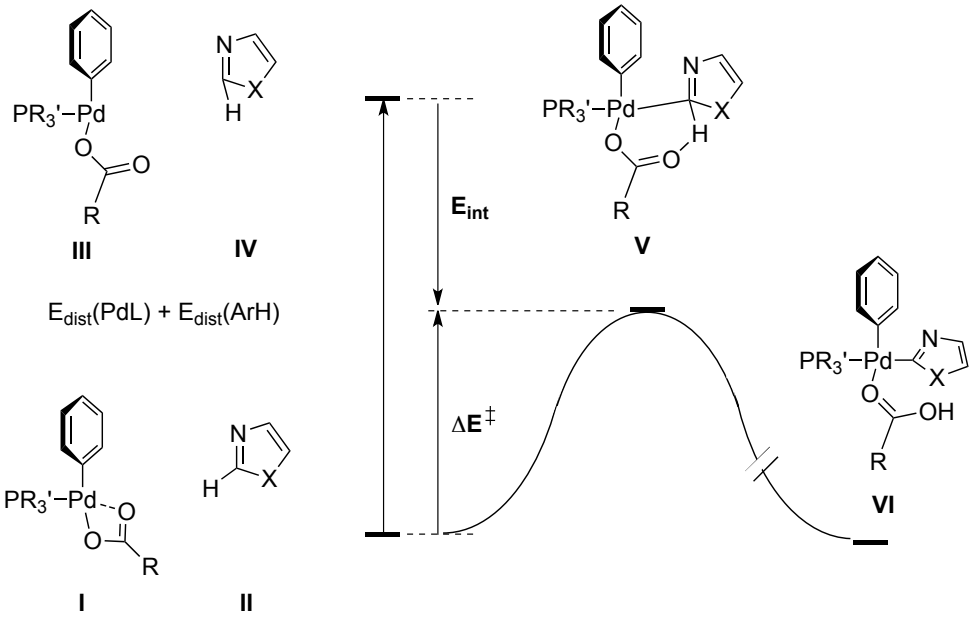



**Figure 1**: Distortion-interaction analysis for the CMD transition states. The TS structure for the C-H bond cleavage at the C-2 site of azole is shown as an example.

Moreover, it can happen that in special situations when properties of the metal catalyst are tuned to lower the activation barriers for alternative reaction pathways and/or to increase the CMD activation barriers, other mechanisms can be at play. For example, it has recently been shown that Heck-type arylation becomes the lowest-energy pathway of thiophene using the Pd-catalyst with the bulky fluorinated phosphine ligand $P(OCH(CF_3)_2)_3$.[22] Instead of $C_\alpha$ arylation that is characteristic for the CMD pathway,[21] this Heck-type arylation pathway leads to $C_\beta$ arylation. It cannot be excluded that other substrates as azoles may undergo this mechanism when an appropriate reaction system has been found.

From what has just reported above, it is clear that both of the hypotheses of $S_EAr$ and/or CMD mechanism would justify the observed C-5 selectivity on the azoles when they react with aryl halides in the presence of a palladium catalyst. On the other hand, since Miura and co-workers reported their seminal paper in 1998,[20a] it emerged that the selectivity on the azole nucleus could be addressed also on the C-2 site, by using Cu(I) as additive to palladium catalyst or even as catalyst itself. As just said, the addition of a stoichiometric or catalytic amount of Cu(I) salts to palladium catalyst significantly increases the reactivity of the C-2 position providing the 2-arylated products.[23]

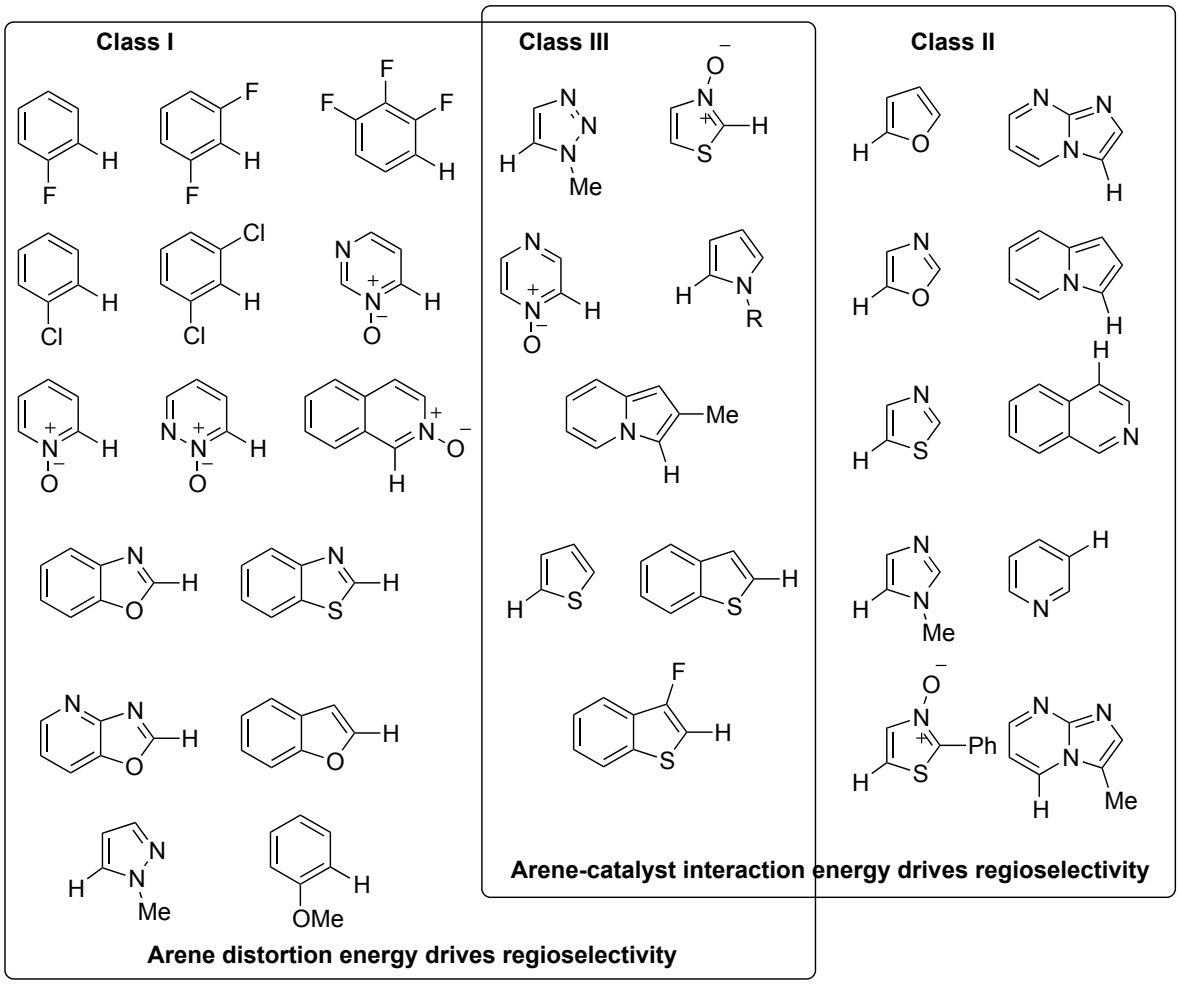
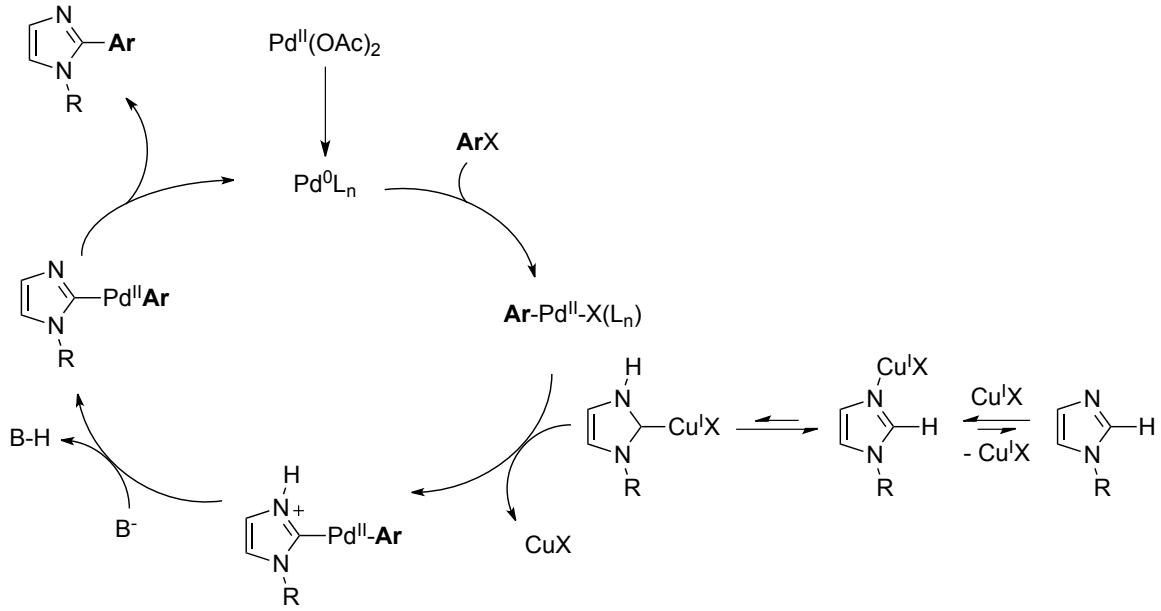



**Figure 2:** Classification of (hetero)arene substrates in terms of contributions to regioselectivity of C-H bond metalation via the CMD pathway based on their reactivity with the $[Pd(C_6H_5)(PR'_3)(OAc)]$ catalyst. C-H bonds with the lowest activation energies for the CMD cleavage are shown.[19,21]

Mechanistic proposal were made by our research group in 2006 in order to explain the selectivity showed by 1,3-azoles when they are reacted wit aryl halides under the classical direct arylation conditions but in the presence of a copper(I) salt.[23c] The C-2 selectivity is thought to derive from a more classical cross-coupling type mechanism which hinged upon the pre-coordination of the substrate to Cu(I), akin to alkyne coordination in the Sonogashira reaction. This complex is proposed to be in equilibrium with an organocuprate, which could undergo transmetalation with loss of CuX to produce the product after reductive elimination (Scheme 4).[23a]

This proposed mechanism is supported by the influence of the electronic properties of the imidazole system upon reaction rates. For imidazoles bearing electron-withdrawing aryl groups, such as phenylmethylsulfinate, a rate enhancement was observed, whilst longer reaction times were required with electron-donating substituents.




**Scheme 4**

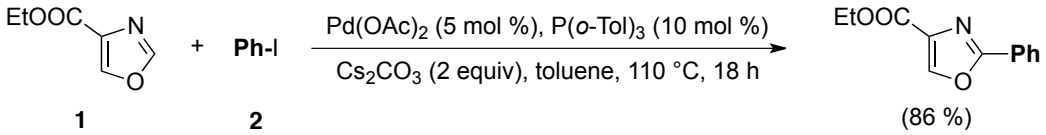
The electronic effects of the substituent alter the acidity of the C2-H proton, and subsequently the rate of cuprate formation. The reduction in selectivity with an increased Pd loading also supports this, as the formation of the cuprate should be the rate determining step, due the high reactivity of organocopper reagents, for the C2-arylation pathway. This proposed mechanism suggests that the reaction should be catalytic in copper but upon lowering the copper(I) stoichiometry, a greatly increased quantity of C5-arylation is observed. An equilibrium between the imidazoylcuprate and free copper(I) iodide, which can be biased by using an excess of copper(I) iodide, was postulated to explain these observations. This would indicate that the equilibrium between the cuprated species and free copper(I) iodide, and the factors which affect this, are key to reaction progression.[23a]

## 2. Pd-catalyzed direct arylation of 1,3-azoles with aryl halides.

### 2.1. Oxazole derivatives.

The first examples of the selective C-5 arylation reaction of oxazole with chloropyrazines and pyridyl triflate in the presence of $Pd(PPh_3)_4$ as the pre-catalyst system and KOAc as the base in DMA at reflux were reported by Ohta[24] in 1992. On the other hand, the C-2 phenylation of ethyl oxazole-4-carboxylate (**1**) reported by Hoarau's group in 2005

represents the first example of a selective direct C-2 arylation of oxazole derivatives (Scheme 5).[25]

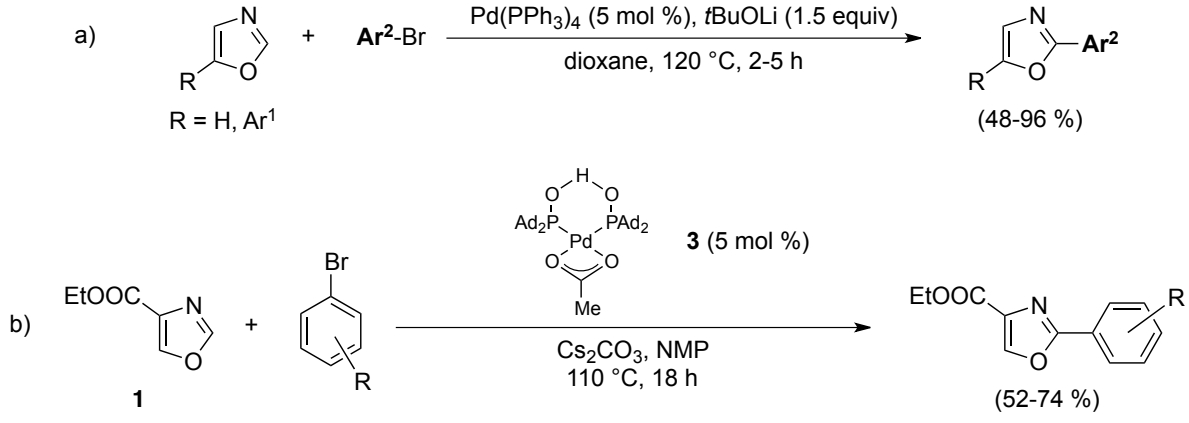



**Scheme 5**

As this last example, most of the papers published so far were focused on the arylation at the C-2 position of oxazole and its benzocondensed derivative. In 2008, Doucet showed that oxazole is prone to be arylated with 4-*t*-butyl-bromobenzene in the presence of $Cs_2CO_3$ (2 equiv), $PdCl(C_3H_5)$(dppb) (5 mol %) in DMF at 150 °C for 20 h, to give the 2-(4-*t*-butylphenyl)-oxazole in 69 % yield,[26] and Bhanage reported the arylation of oxazole with 4-iodobenzene and 4-bromoanisole with $K_3PO_4$ (2 equiv), in the presence of palladium bis(2,2,6,6-tetramethyl-3,5-heptanedionate) (10 mol %) in NMP at 125 °C for 36 h, to give the 2-arylated products in 62 and 63 % yield, respectively.[27]

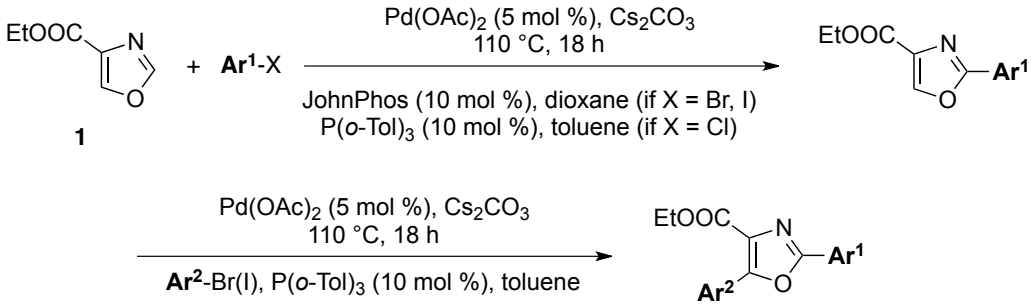
In the same year, Doucet reported another methodology for the arylation of heteroaromatics with aryl triflates, and he proposed that benzoxazole may undergo the C-2 arylation in the presence of 5 mol % $Pd(OAc)_2$, 10 mol % $PPh_3$, KOAc as base, in DMF at 150 °C giving the 2-arylated benzoxazole derivatives in 57-86 % isolated yield.[28]

After these studies, Besselièvre and co-workers reported the arylation at the C-2 position of unsubstituted and 5-substituted aryl oxazoles with aryl bromides (Scheme 6a)[29] and, in 2011, Ackermann et al. showed that ethyl oxazole-4-carboxylate (**1**) reacts with several aryl bromides in the presence of 5 mol % of the palladium(II) complex **3** (Scheme 6b).[30]




**Scheme 6**

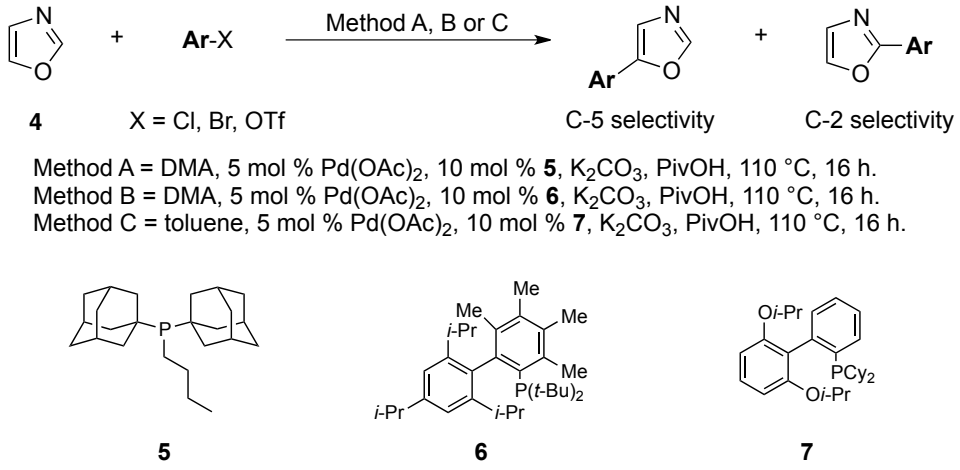
In 2008, Hoarau's group reported a sequential C-2 and C-5 diarylation of **1**. As regard the arylation at the C-2 position, the authors have extended the scope of the reaction to several aryl halides different from iodobenzene (**2**) (see Scheme 5).[25] In the first step the oxazole reacted at its C-2 position in the presence of $Pd(OAc)_2$ (5 mol %), $Cs_2CO_3$ as base, at 110 °C for 18 h. JohnPhos (10 mol %) in dioxane was employed as ligand when aryl bromides and iodides were used, while with aryl chlorides P(*o*-Tol)$_3$ (10 mol %) in toluene was selected. The subsequent arylation on the 2-substitited azole obtained with aryl bromides and iodides was performed under the same reaction conditions, but using 10 mol % P(*o*-Tol)$_3$ in toluene (Scheme 7).[31]




**Scheme 7**

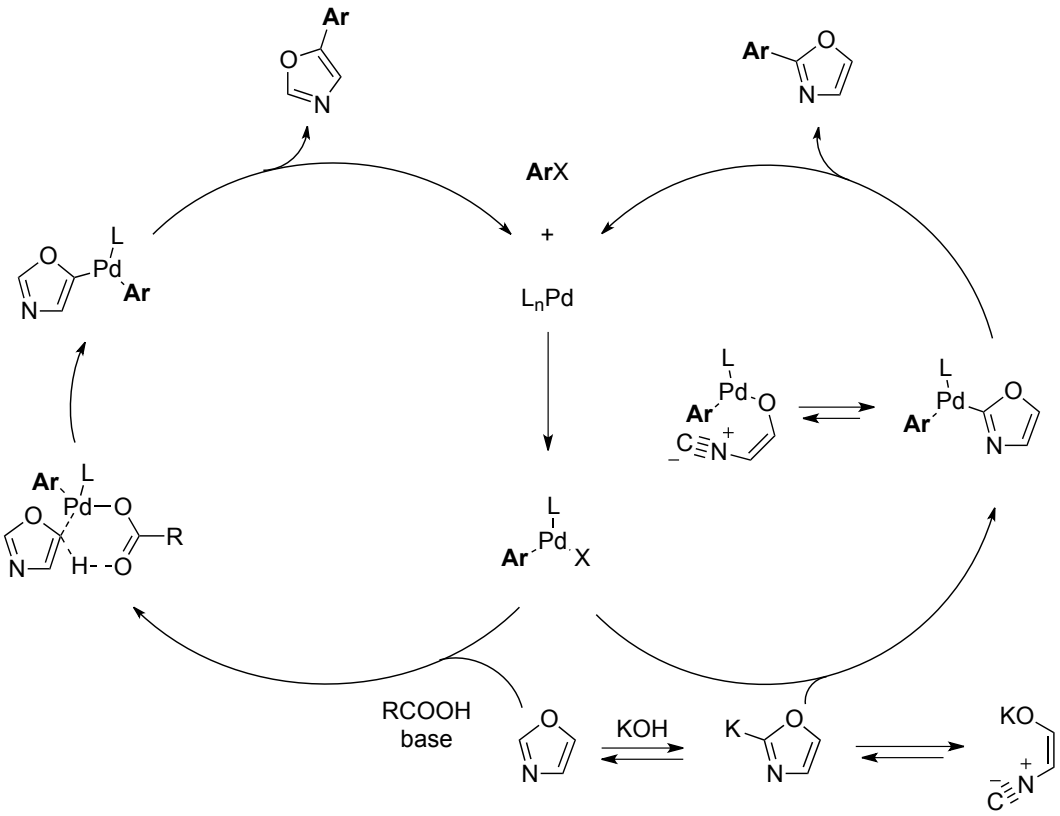
An eco-friendly procedure was reported by Doucet and co-workers for the C-2 arylation of (benz)oxazole using carbonates, that are polar, aprotic, nontoxic and biodegradable, as reaction solvents.[32] In particular, they found that the benzoxazole reacts with electron-rich and electron-poor aryl bromides, *para*-, *meta*-, and *ortho*-substituted, in the presence of $PdCl(C_3H_5)$(dppb) (1 mol %) and $Cs_2CO_3$ as base, in diethylcarbonate at 130 °C (yields from 25 up to 92 %).[32]

In 2010 Strotman and co-workers showed that it is possible to achieve a regioselective arylation at the C-5 or at the C-2 of unsubstituted oxazole (**4**) using aryl chlorides, bromides or triflates. They developed three different methods depending on the nature of the electrophile that reacts with compound **4** and on the arylation site (C-5 or C-2). These methods are summarized in Scheme 8.[33] The authors reported that a good C-5 selectivity may be reached by using the method A with aryl chlorides and method B, which differs from the previous only for the nature of palladium ligand, with aryl bromides and triflates.




**Scheme 8**

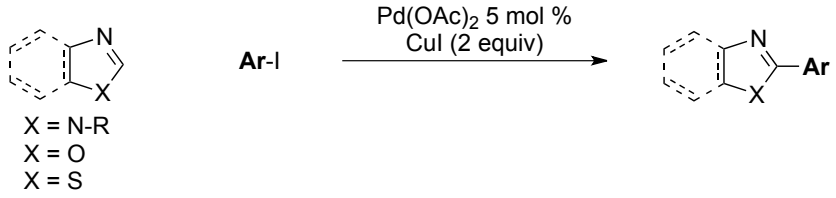
Otherwise, the C-2 selectivity can be achieved with aryl chlorides, aryl bromides and triflates by using the method C. The hypothesis of mechanism suggested by Strotman *et al*. involves two different pathways that may explain the selectivity (Scheme 9). They proposed that the C-5 arylation goes through a CMD mechanism, which is thought to require the intermediacy of a Pd-carboxylate complex **A** (Scheme 9, left cycle)[33]




**Scheme 9**

Moreover, they examined direct arylation of oxazole with bromobenzene using a variety of bases, with or without PivOH and they found that with strong bases like KOH or KO*t*Bu, the reactions favoured the C-2 selectivity, regardless of the catalyst, solvent or presence of PivOH. Given the reasonable acidity of the C-2 proton of oxazole,[34] the authors thought plausible that reaction at this center may occur through formal deprotonation.[23d,35] Either the potassium oxazole species or the dominant ring-opened enolate tautomer[36] could react with an ArPdX species. Therefore, they proposed the catalytic cycle reported in Scheme 9 (right cycle) to account for the differences in regioselectivity that they observed with different bases. Both catalytic cycles begin with oxidative addition of the aryl halide to a Pd(0) complex. In the presence of PivOH and weak bases, the ArPdX species would form an ArPd(OPiv) intermediate which could undergo CMD with oxazole at C-5. Alternatively, when strong bases are employed, a potassium-oxazole species (or ring-opened tautomer) may directly attack ArPdX, forming an ArPd(2-oxazole) intermediate.

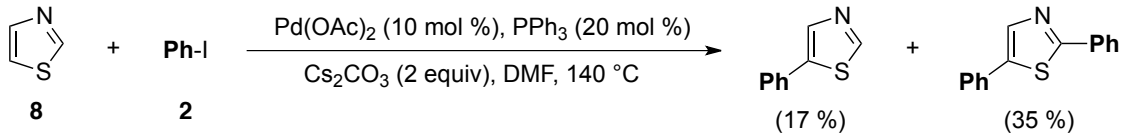
Finally, it is worth mentioning that our research group dedicated several papers on the palladium/copper catalyzed direct arylation at the C-2 position of azoles. We found that the 1,3-azoles and their benzocondensed derivatives can be selectivity arylated at their C2-H bonds in the presence of $Pd(OAc)_2$ (5 mol%), CuI (2 equiv) in DMF at 140 °C with aryl iodides in moderate-to-very good yields (Scheme 10).[23b,c37]




**Scheme 10**

## 2.2. Thiazole derivatives.

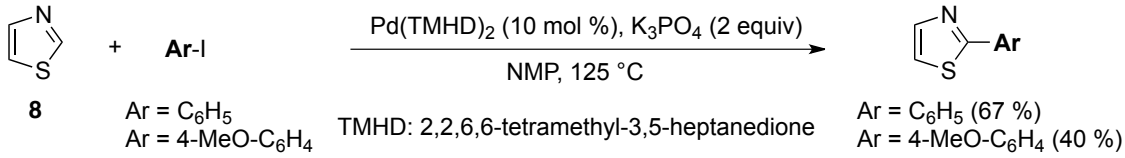
In 1992, Ohta reported the first selective $Pd(PPh_3)_4$-catalyzed direct C-5 arylation of thiazole (**8**) with chloropyrazines in the presence of KOAc as base in DMA at reflux.[24] Six years later, Miura found out that the treatment of thiazole (**8**) with iodobenzene (**2**) using $Pd(OAc)_2/PPh_3$ as the pre-catalyst system and $Cs_2CO_3$ as base afforded a mixture of 5-monophenylated and 2,5-diphenylated products (Scheme 11).[20a]




**Scheme 11**

Subsequently, in 2003, he showed that diarylation at the C-5 and the C-2 position of thiazole (**8**) can be achieved efficiently by $Pd(OAc)_2$-catalyzed direct arylation with aryl bromides employing a bulky phosphine ligand such as P(*t*-Bu)$_3$, in the presence of $Cs_2CO_3$ as base in DMF at 150 °C.[38]

As regards the selective monoarylation of thiazole ring, it should be noted that in 2000 Kondo reported the selective monoarylation of **8** both at C-5 and C-2 positions using iodobenzoate immobilized on an insoluble polymer support.[39] However it is worth noting that, save the selective C-5 arylation of thiazole with aryl iodides in the presence of KOAc as base and catalytic amounts of $Pd(OH)_2$/C in DMA at 140 °C,[40] most of the procedures developed for the direct C-5 arylation of thiazole ring with (hetero)aryl iodides,[41] bromides,[42] chlorides[43] and triflates[28] involves 2-substituted thiazole derivatives. On the other hand, only one example of selective Pd-catalyzed C-2 arylation of thiazole has been reported (Scheme 12).[27]



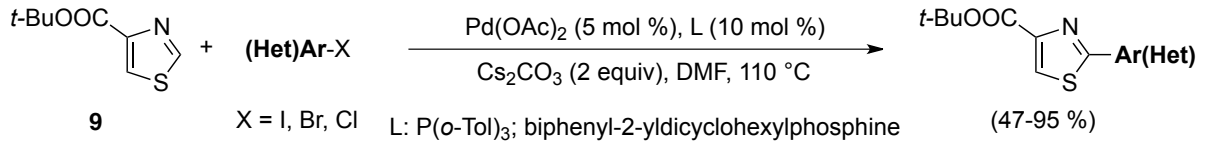

**Scheme 12**

As shown in Scheme 12, when the reaction of thiazole with iodobenzene and iodoanisole was carried out in the presence of palladium bis(2,2,6,6-tetramethyl-3,5-heptanedionate) as catalyst and $K_3PO_4$ in NMP at 125 °C, 2-monoarylation occurred selectively.

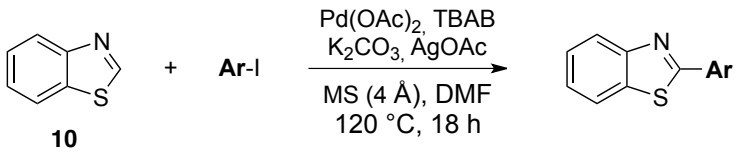
In 2008, Hourau and co-workers[44] reported the Pd-catalyzed selective C-2 arylation of *tert*-butyl 4-thiazolecarboxylate (**9**) with (hetero)aryl halides (Scheme 13).

Regarding the C-2 arylation, Ranu reported a methodology for the direct arylation of benzothiazole (**10**) with aryl iodides promoted by palladium(0) nanoparticles under ligand-free conditions. The reaction system involves the use of $Pd(OAc)_2$ as palladium source and TBAB (tetrabutylammonium bromide) as stabilizer for Pd nanoparticles formed *in situ*,

$K_2CO_3$, AgOAc, molecular sieves (4 Å) in DMF at 120 °C to give the 2-aryl-benothiazole derivative (Scheme 14).[45]

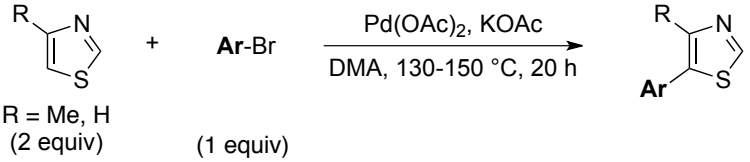



**Scheme 13**




**Scheme 14**

In 2009, Doucet's group showed that the 4-methyl-thiazole and *C*-unsubstituted thiazole can undergo monoarylation selectively at the C-5 position with aryl bromides when they are treated with $Pd(OAc)_2$ and KOAc, in DMA at 130-150 °C for 20 h (Scheme 15).[46] The 2-arylated or 2,5-diarylated thiazoles were not detected.



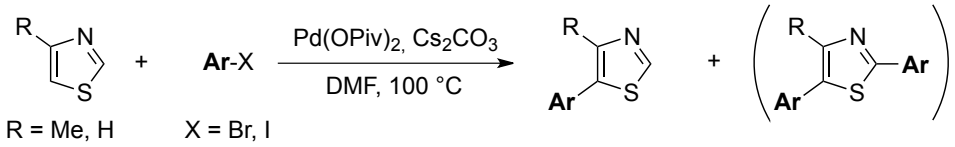

**Scheme 15**

It is interesting to note that, in order to favour the monoarylated product and to increase the conversion of the reaction, 2 equiv of the azole were used though this substrate is more expensive than the aryl bromides used as coupling partners.

Rault and coworkers reported in 2009 that a small library of 5-arylthiazole might be regioselectively obtained in 27-63 % yields by reacting thiazole (**8**) with electron-rich, electron poor and heteroaryl bromides.[47] The couplings were carried out in the presence of 5 mol % $Pd(PPh_3)_4$ and 3 equiv of KOAc. However, a strong molar excess (5 equiv) of azole was once again required to attain good regioselectivity, and drastic reaction conditions (150 °C in a sealed tube) were necessary to reduce reaction times. Interestingly, the same authors evidenced in their paper that the ligandless conditions previously reported for the same coupling (2 equiv

of **8**, 1 equiv of aryl bromide, 2 equiv of KOAc, 0.4 mol % $Pd(OAc)_2$, DMA, 130 °C in sealed tube) gave poorer results in their hands.[46]

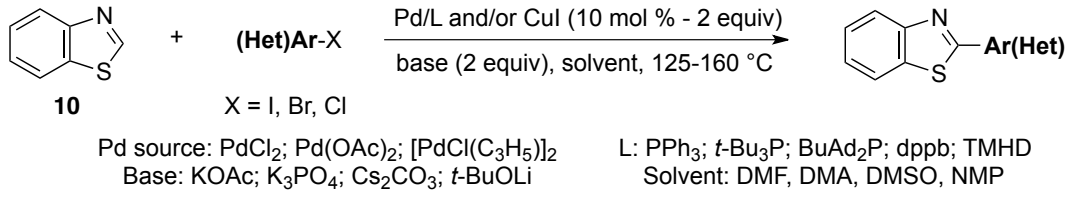
Moreover, Shi and co-workers published that 4-methyl-thiazole and thiazole can be selectively arylated ad the C-5 position when treated with $Pd(OPiv)_2$ (10 mol %), $Cs_2CO_3$ (1 equiv), in DMF at 100 °C in the presence of aryl iodides and bromides (Scheme 16).[48]




**Scheme 16**

A wide variety of aryl iodides, regardless of the electron-deficient to -rich nature, were successfully applied for this regioselective arylation, along with sterically hindered aryl halides (isolated yields ranging from 24 to 93 %). Small amounts of the corresponding 2,5-diarylated derivatives as byproducts were also detected under these reaction conditions. Furthermore, it was found that the reaction proceed smoothly also in the presence of aryl bromides, giving the respective 5-aryl-4-methyl-thiazoles in 47-71 % yield. The *C*-unsubstituted thiazole was found to be reactive towards aryl iodides, giving the monoarylation products in 18-60 % isolated yield.[48]

It is interesting to note that several Pd- and Pd/Cu-catalyzed procedures developed for the direct arylation of thiazole derivatives have also been successfully employed for the synthesis of 2-arylbenzothiazoles by direct C-2 arylation of benzothiazole (**10**) with aryl halides.[20a,20f,24,27,38,41,42a]

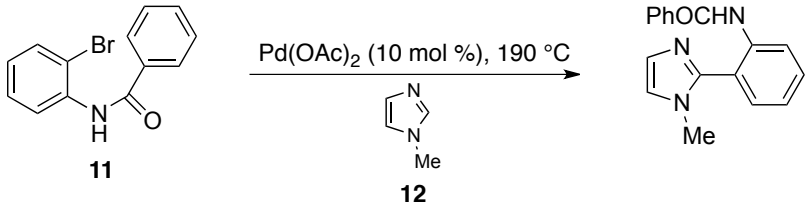



**Scheme 17**

As shown in Scheme 17, the Pd- and/or CuI-catalyzed direct C-2 arylation of benzothiazole have been found to invariably require stoichiometric amounts of a base, polar aprotic solvents and high reaction temperatures.

### 2.3. Imidazole derivatives.

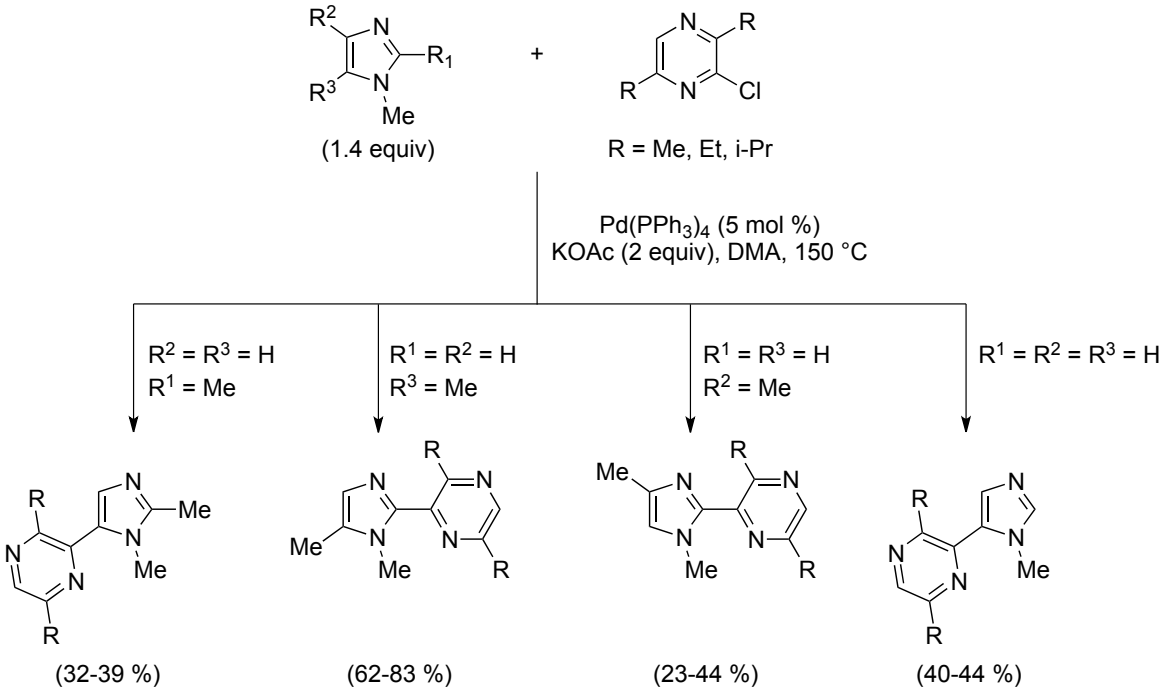
In 1984, Ames found that the Pd-catalyzed intramolecular arylation of *N*-(2-bromophenyl)benzamide (**11**) in 1-methyl-1*H*-imidazole (**12**) at 190 °C did not furnish the required phenanthridone but, surprisingly, gave a 2-arylated-1-methyl-1*H*-imidazole (Scheme 18).[11c]



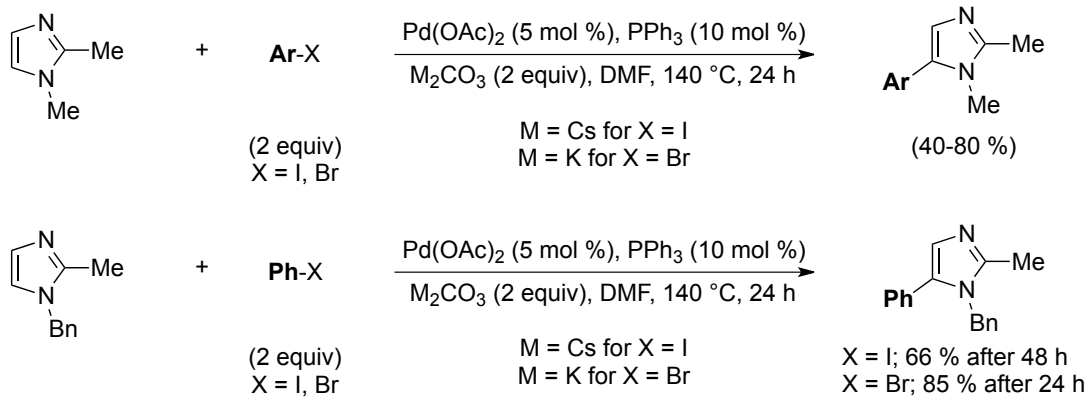

**Scheme 18**

Eight years later, the first important study on the Pd-catalyzed direct arylation of *N*-methylimidazole derivatives was reported by Ohta and co-workers[24] who employed chloropyrazines as the arylating agents (Scheme 19). It should be noted that 1-methyl-1*H*-imidazole (**12**) could be arylated with complete C-5 selectivity, albeit in modest yields.[24]

In 1998, Miura and co-workers performed an extensive study focused on the Pd-catalyzed direct arylation of a variety of azoles, including imidazoles, thiazoles and oxazoles, with aryl halides.[20a] These authors observed that in the $Pd(OAc)_2/PPh_3$-catalyzed direct arylation of 1,2-dimethyl- and 1-benzyl-2-methyl-1*H*-imidazole in DMF at 140 °C, both aryl halide and base played an important role in the arylation. In particular, the relatively soluble base $Cs_2CO_3$ was effective when aryl iodides were used, while $K_2CO_3$ was as effective as $Cs_2CO_3$ for direct arylations performed with aryl bromides (Scheme 20).[20a]



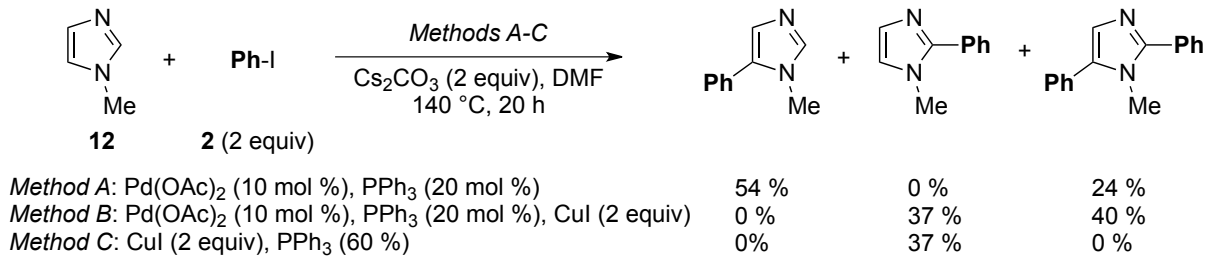

**Scheme 19**




**Scheme 20**

Interestingly, they also found that the regioselectivity of the reaction between iodobenzene (**2**) and 1-methyl-1*H*-imidazole (**12**) could be controlled by the nature of the catalyst system (Scheme 21).[20a] In fact, in the presence of the sole palladium precatalyst, the arylation preferentially occurred at the C-5 position (*Method A*, Scheme 21), but the addition of a stoichiometric amount of Cu(I) salt significantly increased the reactivity of the C-2 position providing the 2-arylated product in 37 % yield (*Method B*, Scheme 21). Moreover, large amounts of 2,5-diphenyl-1-methyl-1*H*-imidazole were also obtained when the reaction was performed under the experimental conditions reported as *Methods A* and *B* (Scheme 21). Nevertheless, when the reaction was carried out with 2 equiv of CuI and in the absence of a

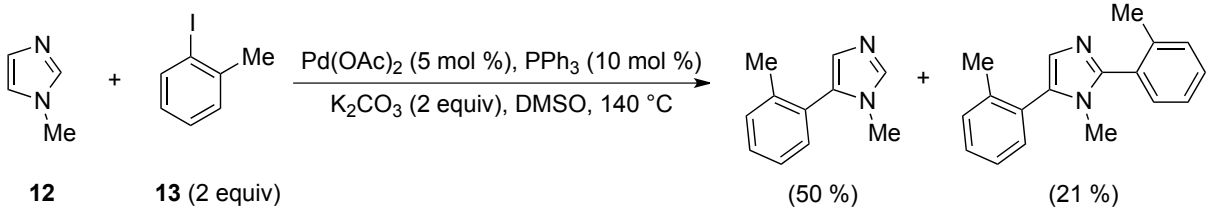
palladium salt, the C-2 arylated product was exclusively obtained (*Method C*, Scheme 21).[20a]




**Scheme 21**

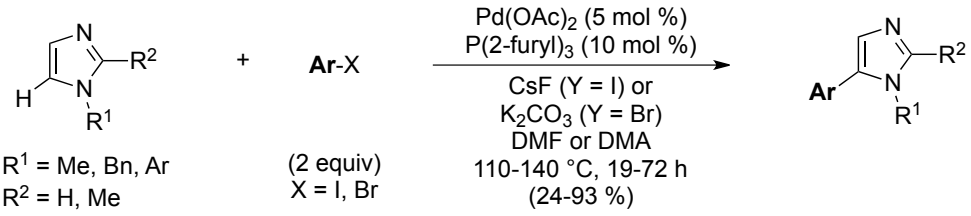
In 2000, Kondo *et al*.[39] performed the regioselective palladium-catalyzed monoarylation of azoles including 1-methyl-1*H*-imidazole (**12**) using iodobenzoate immobilized on an insoluble polymer support. Similarly to what described by Miura in 1998,[20a] the positional selectivity for the coupling reactions was found to be dramatically influenced by the presence of CuI, and no diarylation was observed in both cases.[39]

On the other hand, according to Miura's results,[20a] Mori recently found that the $Pd(OAc)_2/PPh_3$-catalyzed arylation of 1-methyl-1*H*-imidazole (**12**) with 2-iodotoluene (**13**) in DMSO at 140 °C provided a mixture of the corresponding 5-arylated and 2,5-diarylated products in 50 and 21% yield, respectively (Scheme 22).[49]



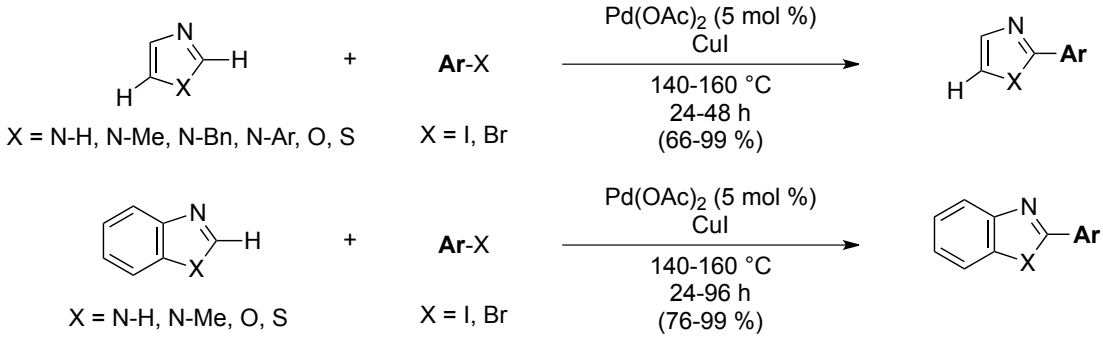

**Scheme 22**

Between 2005 and 2009 our research group developed a generally applicable and selective method for the direct arylation of several *N*-substituted imidazoles at the C-5 position with aryl iodides and bromides. These conditions were suitable for *N*-methyl-, *N*-benzyl, *N*-aryl-imidazoles and involved 5 mol % $Pd(OAc)_2$, 10 mol % P(2-furyl)$_3$, CsF as base for aryl iodides and $K_2CO_3$ for aryl bromides, in DMF or DMA as solvent at 110 °C for *N*-methyl-imidazole and at 140°C for *N*-benzyl- and *N*-aryl imidazoles (Scheme 23).[23b-d,37a,50]




**Scheme 23**

In the same years, the authors focused their attention also on the selective arylation of the imidazole ring at the C-2 position. Starting from Miura's work of 1998 described above,[20a] and after an extensive optimization, they were able to find that by using a $Pd(OAc)_2$/CuI system, *N*-substituted- and, for the very first time, free *NH*-imidazoles can be arylated at the C-2 position even in the absence of an inorganic base (Scheme 24). The reactions can be performed both with aryl iodides and bromides, at 140 °C (if X = I) or at 160 °C (if X = Br).[23b-d,37a,50a,b]



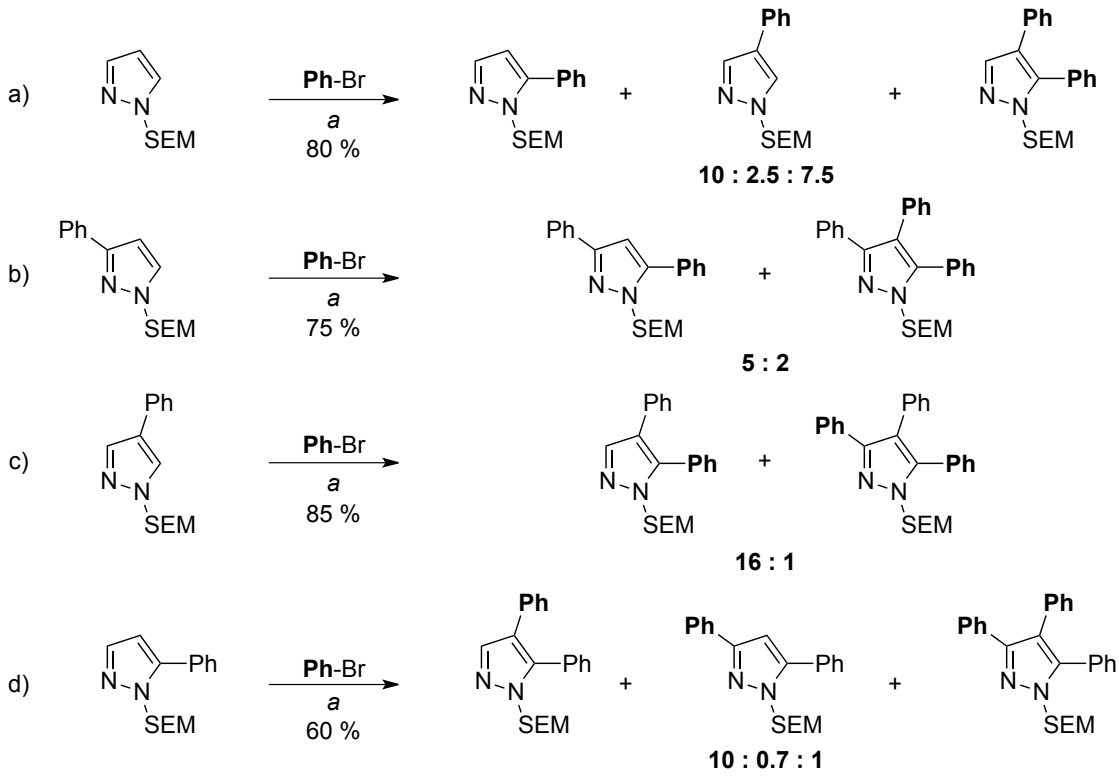

**Scheme 24**

In 2009, also Doucet and co-workers reported a methodology for the Pd-catalyzed direct arylation at the C-5 position of *N*-methyl-imidazole **12** with aryl bromides. By using ligandless conditions, $Pd(OAc)_2$ (0.1 mol %) as a low amount of catalyst precursor, KOAc (2 equiv) as base, DMA as solvent, 150 °C as reaction temperature, they were able to synthesize several 5-aryl-1*H*-imidazoles in moderate to good yields.[51]

## 2.4. Pyrazole derivatives.

Compared to the 1,3-azoles, pyrazole has been scarcely studied to date in the area of transition metal-catalyzed direct arylation with aryl halides,[52] because it is difficult to gain a

reasonable regioselectivity. In 2009, Sames and co-workers developed the first catalytic method for the intermolecular *C*-arylation of pyrazoles and explored its regioselectivity trends.[53] They chose to examine SEM-protected pyrazoles as the substrates [SEM: 2-(trimethylsilyl)ethoxy-methyl] due to the stability of this protecting group under the catalytic arylation conditions as well as the ability of SEM group to be transposed from one nitrogen to another, enabling sequential arylations. Systematic examination of the reaction parameters (metal catalyst, ligand, base, and solvent) for the coupling of SEM-pyrazole and bromobenzene led the authors to develop a robust method which uses the following conditions: 5 mol % $Pd(OAc)_2$, 7.5 mol % $PBuAd_2$, 3 equiv $K_2CO_3$, 25 mol % PivOH in DMA as solvent and heating at 140 °C (Scheme 25).[53]

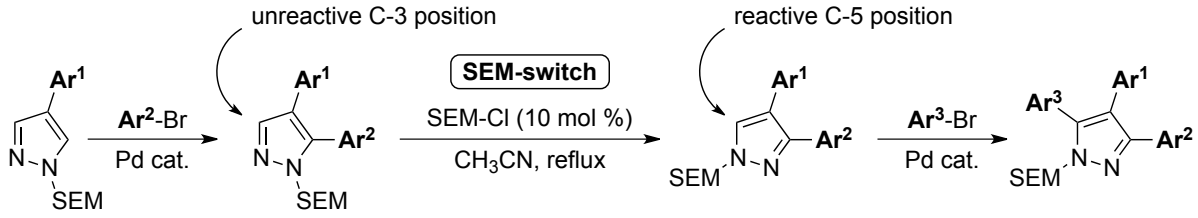



*a*: Pyrazole, PhBr (1.5 equiv), $Pd(OAc)_2$ (5 mol %), P(*n*Bu)$Ad_2$ (7.5 mol %), $K_2CO_3$ (3 equiv), PivOH (25 mol %), 2.5 M DMA, 140 °C for 12 h.

**Scheme 25**

The *C*-unsubstituted SEM-pyrazole when submitted to the catalytic conditions gave a mixture of mono- and diarylated products, whose relative amounts evidenced the higher reactivity of the 5-position in comparison with the 4-position, and the very low reactivity of the 3-position (C-H arylation: C-5 > C-4 >> C-3) (Scheme 25a). This trend was confirmed by examining the reaction of 1-SEM-3-phenylpyrazole, which gave a 5:2 ratio of 1-SEM-3,5-diphenylpyrazole

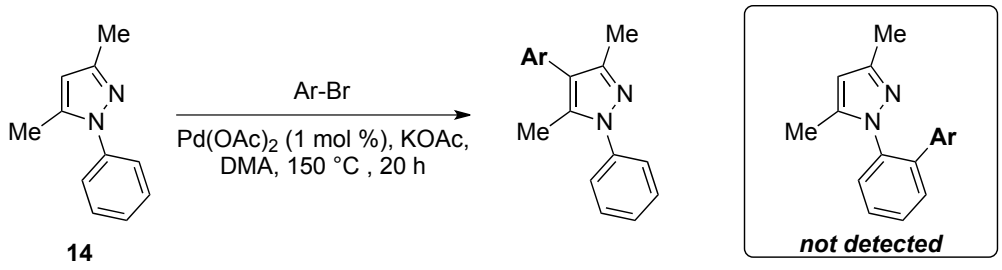
and 1-SEM-3,4,5-triphenylpyrazole (Scheme 25b). In contrast, 1-SEM-4-phenylpyrazole was arylated at C-5 with high selectivity to provide 1-SEM-4,5-diphenylpyrazole in 80 % yield (Scheme 25c). The regioisomer resulting from arylation at the C-3 was not detected, and only a small amount of the bisarylated product, 1-SEM-3,4,5-triphenylpyrazole, was formed. Arylation of 1-SEM-5-phenylpyrazole was also selective, taking place at the C-4 to afford 1-SEM-4,5-diphenylpyrazole as the major product (Scheme 25d). These results demonstrated that arylation at the C-3 is ineffective, which is consistent with the low reactivity of this site, whereas arylation occurs at both C-4 and C-5, with a preference for the latter. According to Sames and co-workers, it is well established that C-4 of pyrazole is the most nucleophilic position and readily undergoes electrophilic substitution, whereas the 5-position carries the most acidic C-H bond which can be selectively deprotonated by strong bases.[53,54] Then, by using the conditions reported above, they were able to synthesize various triarylated SEM-protected pyrazoles exploiting the SEM-switch approach (Scheme 26).[53]




**Scheme 26**

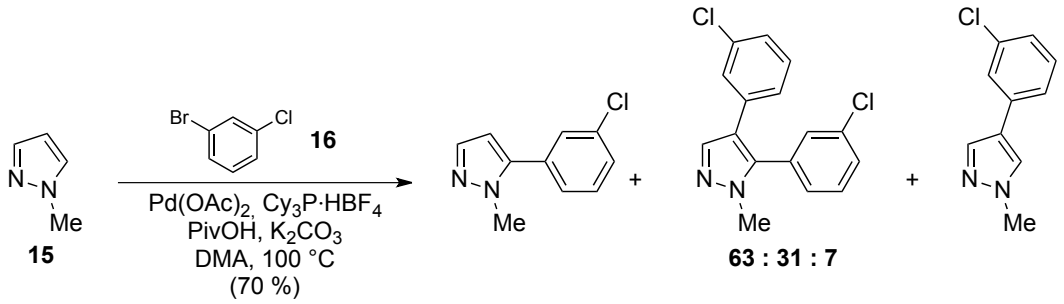
Between 2010 and 2012, Doucet and co-workers devoted their attention to the direct arylation at the C-4 position of 1,3,5-trisubstituted pyrazoles with aryl bromides.[55] By using this strategy they assured the formation of only one product and avoided regioselectivity problems due to the arylation at the remaining C-H bonds of the pyrazole ring. Moreover, in the paper published in 2010,[55a] they showed that also 1-phenyl-3,5-dimethyl-pyrazole (**14**) can be arylated under their ligandless procedure to give the respective 4-arylated pyrazoles in 58-80 % isolated yields without detecting any arylation product at the phenyl ring bound to the N-atom due to the well-known *ortho*-directing properties of the pyrazole nucleus (Scheme 27).

In 2010, Mateos and Mendiola reported a methodology to quickly access 5-aryl-1-methyl-pyrazoles. For that purpose, they started a research effort exploring the C-H activation methodology on the *N*-methylpyrazole ring mediated by Pd complexes.[56]




**Scheme 27**

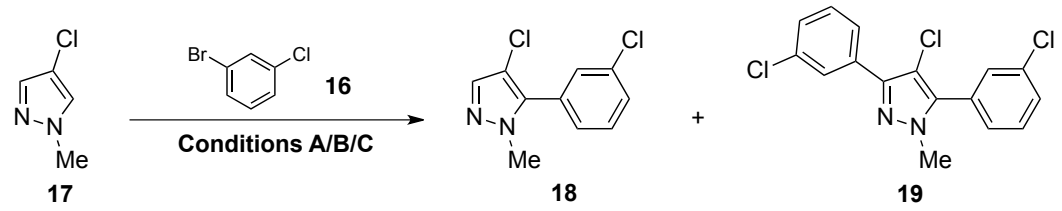
1-Methylpyrazole (**15**) was initially selected as starting material for direct C-H activation. Experimental conditions reported in the literature by Fagnou *et al.*[57] were applied to 3-bromochlorobenzene (**16**), and a mixture of three different arylated pyrazole derivatives were isolated (Scheme 28).




**Scheme 28**

A general reactivity rule could be stated for **15** based on experimental results: C-5 > C-4 >> C-3 (the same relationship was found by Sames and co-workers with SEM-protected pyrazole, as reported above).[53]

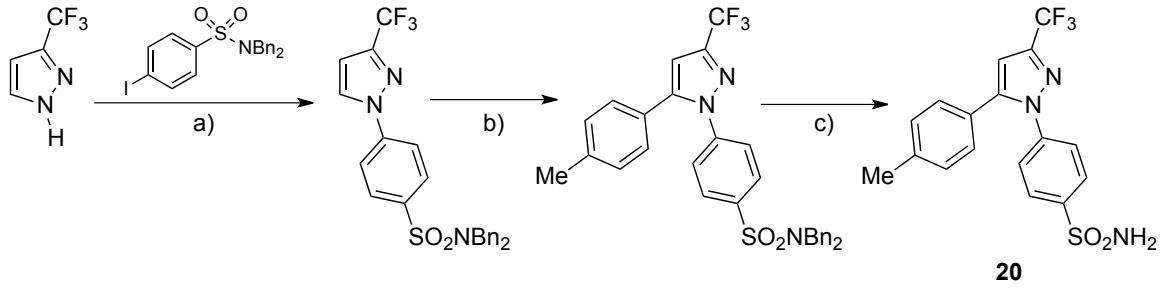
Afterwards, they were able to find a set of experimental conditions to successfully arylate 4-chloro-1-methylpyrazole (**17**). With the objective of obtaining the best combination of conversion and selectivity, two different protocols were found: a) based on conversion: $Pd(OAc)_2$, DavePhos, $Bu_4NOAc$, isobutyric acid, NMP at 100 °C; b) based on selectivity: $Pd(OAc)_2$, $^tBu_3P{\cdot}HBF_4$, $Bu_4NOAc$, isobutyric acid, NMP at 100 °C (Scheme 29).[56] These conditions were then applied to prepare a small library of 5-aryl-chloropyrazoles in moderate to excellent yields with both electron-rich and electron-poor aryl bromides (10-94 %).




**Conditions A**: $Pd(OAc)_2$, DavePhos, $Bu_4NOAc$, Isobutyric acid, NMP at 100 °C; 94 % yield (**18**), 96:4 (**18**:**19**)
**Conditions B**: $Pd(OAc)_2$, *t*BuP·$HBF_4$, $Bu_4NOAc$, Isobutyric acid, NMP at 100 °C; 91 % yield (**18**), 93:7 (**18**:**19**)
**Conditions C**: $Pd(OAc)_2$, DavePhos, $Bu_4NOAc$, Isobutyric acid, NMP at 150 °C; 80 % yield (**18**), 85:15 (**18**:**19**)

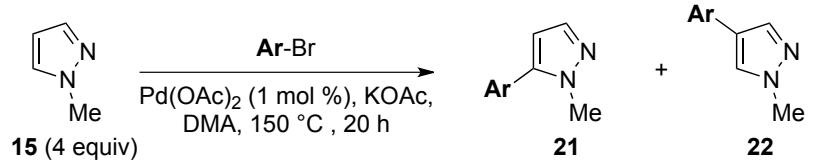
**Scheme 29**

On the other hand, the Fagnou's conditions[57] were also applied by Gaulier's group to the key step of their short synthetic route to Celecoxib **20** (Scheme 30).[58]




**Scheme 30:** Reagent and conditions: a) CuI, *N*,*N*-dimethylcyclohexylamine, $K_3PO_4$, 1,4-dioxane, 115 °C, 50 h, 73 %; b) 1-bromo-4-methylbenzene, $Pd(OAc)_2$, $PBuAd_2$, $K_2CO_3$, PivOH, DMA, 140 °C, 50 h, 66 %; c) $H_2SO_{4conc}$, rt, 2 h, 69 %.

Moreover, Doucet and co-workers reported the first optimized ligandless procedure for the Pd-catalyzed arylation of the *C*-unsubstituted 1-methyl pyrazole (**15**) with a wide variety of aryl bromides.[59] They observed that the direct arylation favours the C-5 selectivity when **15** was treated with an aryl bromide, in the presence of $Pd(OAc)_2$ (1 mol %), KOAc (2 equiv) in DMA at 150 °C for 20 h (Scheme 31).

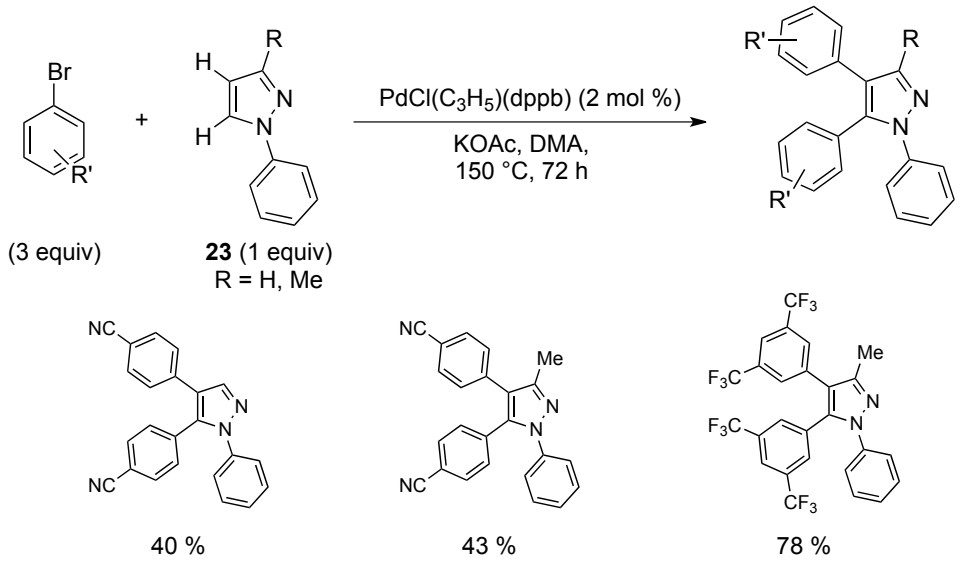



**Scheme 31**

However, despite the large excess of 1-methylpyrazole (4 equiv) employed, they observed the formation of a mixture of monoarylation products, the 5-arylated (**21**) and the 4-arylated

pyrazoles (**22**). Moderate to good yields were obtained (38-65 %), with a C-5 selectivity ranging between 51-87 %.

Recently, the same research group showed that it is possible to achieve a double arylation of 1-methylpyrazole (**15**) both at the C-4 and C-5 positions,[60] changing a little the conditions reported in 2011.[59] They modified the pyrazole/aryl bromide ratio from 4:1 to 1:3, then they used 2 mol % of $PdCl(C_3H_5)(dppb)$ as catalyst precursor instead of $Pd(OAc)_2$ and 6 equiv of KOAc instead of 2. With this methodology they synthesized several 4,5-diarylated 1-methyl-pyrazoles in 28-81 % isolated yield. Moreover, in the same work, it is reported the first double arylation of 1-phenyl-pyrazole (**23**) with aryl bromides (Scheme 32).

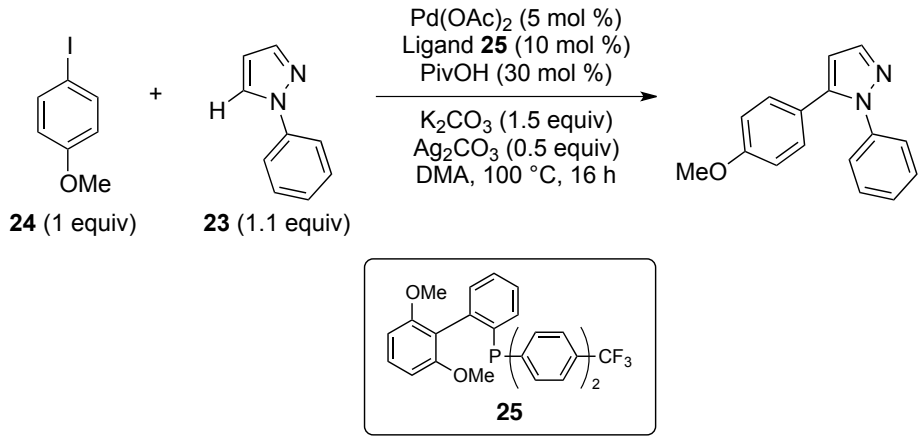



**Scheme 32**

With these reaction conditions and a pyrazole/aryl bromide ratio 1:3, they synthesized three 4,5-diaryl-1-phenyl pyrazoles in 40 to 78 % isolated yield.[60]

As regards the Pd-catalyzed direct C-H arylation of 1-phenyl-pyrazole (**23**) on the heteroaromatic ring, no paper was published so far about a specific procedure aimed at synthesizing a monoarylated 1-phenyl-pyrazole. The first example of direct monoarylation at the C-5 position of **23** was reported by Daugulis and co-workers in 2008 when they proposed a copper-catalyzed procedure for the arylation of several heteroarenes, including **23**.[13a] This methodology involved the use of 10 mol % CuI/phenantroline catalyst system, $Et_3COLi$ as the base in DMPU at 125 °C for the arylation of 1-phenyl pyrazole (**23**) with iodobenzene (**2**), to give the 1,5-diphenyl pyrazole in 52 % isolated yield.

Two years later, René and Fagnou published a procedure for the C-H arylation of heteroaromatics with aryl iodides, and they found that **23** reacted with iodoanisole (**24**) in the presence of 5 mol % $Pd(OAc)_2$, 10 mol % ligand **25**, PivOH (30 mol %), $K_2CO_3$ (1.5 equiv), $Ag_2CO_3$ (0.5 equiv) in DMA at 100 °C for 16 h (Scheme 33).[61]




**Scheme 33**

## 3. Aims of this Ph.D. thesis.

This Ph.D. thesis was performed in order to broaden the substrate scope of the direct arylation reactions of azoles and, particularly, to design and develop convenient and efficient protocols for the highly regioselective synthesis of (hetero)arylazoles by Pd-catalyzed intermolecular arylation reactions of azoles with (hetero)aryl halides.

Specifically, the aims of the present study were:

1) to design and develop a general and highly selective procedure for the Pd-catalyzed direct C-5 arylation of 1-methyl-1*H*-pyrazole (**15**) with (hetero)aryl bromides;
2) to acquire this new general method for the highly selective synthesis of 5-aryl-1-methyl-1*H*-pyrazoles;
3) to verify if the general method of Pd-catalyzed direct C-5 arylation of 1-methyl-1*H*-pyrazole (**15**) can be also applied to the selective C-5 arylation of 1,3-azoles and to synthesize a small library of 5-aryl-oxazoles, 5-aryl-thiazoles and 5-aryl-1*H*-imidazoles;
4) to design a new general and selective procedure for the Pd-catalyzed direct arylation of 1-phenyl-1*H*-pyrazole (**23**) with aryl bromides;

5) to apply the methodologies developed to the synthesis of compounds of interest as bioactive molecules and fluorophores;
6) to synthesize *N*-heterocyclic copper carbenes and to study their role in the Pd/Cu mediated arylation with aryl iodides.

For the sake of clarity, the data concerning the topics covered in this Ph.D. thesis have been organized in four chapters. The results of the study concerning the Pd-catalyzed C-5 arylation reactions of 1-methyl-1*H*-pyrazole (**15**) and 1-phenyl-1*H*-pyrazole (**23**), the synthesis of 5-aryl-1-methyl-1*H*-pyrazoles, 5-aryl-oxazoles, 5-aryl-thiazoles and 5-aryl-1-methyl-1*H*-imidazoles have been reported and commented in **Chapter 1**. In **Chapter 2** we have reported the applications of the developed procedure for the selective C-5 direct arylation of 1,3-azoles with aryl bromides. **Chapter 3** deals with the results obtained in the synthesis and the study of the role of NHC-copper carbenes in the Pd/Cu mediated arylation reaction. This part of the Ph.D. was carried out at the University of York (United Kingdom) under the supervision of Professor Ian J. S. Fairlamb. Finally, **Chapter 4** deals with the Experimental Part.

# CHAPTER 1

## *Pd-catalyzed direct arylation of C-unsubstituted azoles with aryl halides*[62]

As mentioned in the **Introduction**, there are relatively few methods that appear to be generally applicable to the palladium-catalyzed regioselective direct arylation of the broadest range of *simple C-unsubstituted azoles*. In contrast with methods that perform the direct arylation on *C*-substituted azoles,[9,10b,23b,50c,54,63] in which the desired groups have to be introduced at the early stage of the synthesis to grant the required selectivity, the arylation of unsubstituted azoles allows the introduction of aryl moieties on the parent azole frameworks in a late stage of the synthesis.

In their seminal paper of 1998 on direct arylation of azoles, Miura and co-workers reported that 1-methyl-1*H*-imidazole (**12**) and thiazole (**8**) may be regioselectively arylated at their C-5 position with aryl bromides or iodides at 140 °C in DMF in the presence of $Pd(OAc)_2$ (10 mol %), $PPh_3$ (20 mol %) and 2 equiv of $K_2CO_3$ (for bromides) or $Cs_2CO_3$ (for iodides) (see Scheme 20).[20a] However, this method suffers from regioselectivity problems and, as our research group demonstrated later,[50e] $PPh_3$ may be involved in undesired aryl-aryl exchange reactions with the aryl moiety of the halides. In 2009 Fagnou and co-workers demonstrated that thiazole and 1-benzyl-1,2,3-triazole are able to undergo regioselective C-5 arylation when treated with aryl bromides and $K_2CO_3$ in DMA at 100 °C, in the presence of 2 mol % $Pd(OAc)_2$ and 4 mol % $PCy_3{\cdot}HBF_4$.[57] The coupling required also 30 mol % of pivalic acid which, according to the authors, granted faster reactions. Unfortunately, very low yields were observed when 1-methyl-1*H*-imidazole was used as the coupling partner, and the protocol proved to be unsuitable for the direct arylation of imidazole, 1-benzyl-1*H*-imidazole and isoxazole. Finally, it is worth mentioning that in a series of papers Doucet and co-workers described a phosphine-free method for the direct C-5 arylation of 1-methyl-1*H*-imidazole (**12**),[51] thiazole (**8**)[46] and 1-methyl-1*H*-pyrazole (**15**)[59] with aryl bromides, in the presence of 2 equiv of KOAc, and with a low loading of $Pd(OAc)_2$ (0.1-1 mol %). This method provides the required 5-arylated azoles in low to satisfactory yields, but it suffers in general from regioselectivity problems when the arylation involves 1-methyl-1*H*-pyrazole (**15**) despite a 4:1 molar ratio between this expensive azole and aryl bromides.[59] Moreover, this protocol shares with all the others high reaction temperatures (130-150 °C), which constitute a serious issue when thermolable substrates have to be used,[64] and may cause security problems during scale-up because sealed vessels are generally required.

As reported in the **Introduction**, recent theoretical investigations revealed that a concerted metalation/deprotonation (CMD) pathway is of relevance for the Pd-catalyzed direct arylation of azoles.[19,65] In this mechanistic hypothesis, $Pd(OAc)_2$ is generally the transition-metal precatalyst, and a carboxylate (or carbonate) anion plays a fundamental role in the C-H cleavage, which occurs in the rate-determining step of this model, simultaneously with carbon-palladium bond formation. In the light of these theoretical findings, and based on our knowledge of Pd-catalyzed direct arylations of π-electron-rich heteroarenes,[23c-d,34,50c-e] we reasoned that common reaction conditions should be found for different azoles if they really share the same mechanistic pathway when treated with aryl halides. In the CMD mechanism the choice of an appropriate base represents an important element of catalyst design. For this reason, in this Ph.D. work we decided to devote particular attention to study the influence of the anionic base and its counter cation[66] on the outcome of the direct arylation of azoles during a re-examination of all the reaction parameters. More specifically, we focused our attention on the development of an efficient procedure for the palladium-catalyzed direct arylation of 1-methyl-1*H*-pyrazole (**15**), oxazole (**4**), thiazole (**8**) and 1-methyl-1*H*-imidazole (**12**) with aryl bromides. We were also aware that, often, the presence of substituents of different nature on the *N*-atom of the heterocycles, as alkyl or aryl groups, can influence the reactivity of the whole catalytic systems.[23b,23d,37a,50a,50c-d] In fact, in order to get the best efficiency and selectivity for a specific *N*-substituted heteroarenes, we often need to find a specific solvent/catalyst/base reaction system. For this reason we devoted the last part of the thesis also on the preliminary screening of the direct arylation of 1-phenyl-1*H*-pyrazole (**23**).

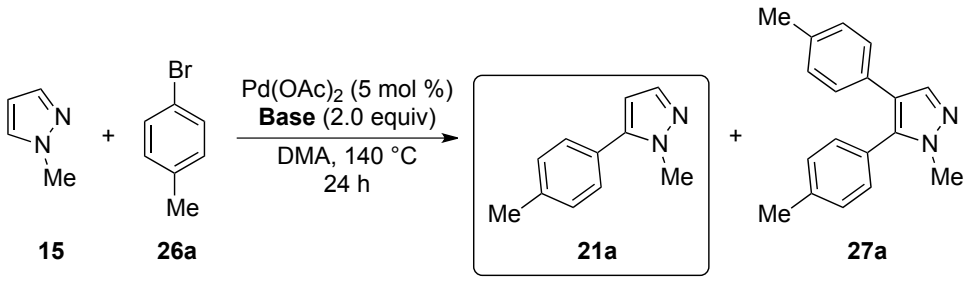
## 1. Synthesis of 5-aryl-1-methyl-1*H*-pyrazoles (21) *via* Pd-catalyzed direct arylation of 1-methyl-1*H*-pyrazole (15).[62]

At the outset of our studies, we decided to investigate the synthesis of 5-aryl-1-methyl-1*H*-pyrazoles (**21**) starting from the Pd-catalyzed direct C-5 arylation of 1-methyl-1*H*-pyrazole (**15**) with aryl bromides. As mentioned in the **Introduction**, the regioselective synthesis of *C*-monoarylated pyrazoles represents a challenging target, and previous studies by Sames on SEM-protected pyrazole,[53] by Mateos and Mendiola[56] and by Doucet[59] on **15** clearly indicated the difficulties in performing a clean monoarylation on simple *C*-unsubstituted pyrazoles. In fact, the different protocols used so far to perform the direct C-5 arylation reactions of **15** meet

with limited success because of modest yields,[53,56] low regioselectivity[53,56] or the use of a large excess of the expensive precursor.[59]

With the aim to overcome these limitations, at the beginning of this Ph.D. work, we focused our attention on the Pd-catalyzed direct arylation of 1-methyl-1*H*-pyrazole (**15**) with 4-bromotoluene (**26a**), chosen as a model-coupling partner. We decided to perform the reactions starting from 1 mmol of **15** and 1.5 equiv of **26a** in the presence of 5 mol % of the catalyst precursor, 2 equiv of a suitable base, in 5 mL of an appropriate solvent. We also set the reaction temperature at 140 °C and the reactions were followed for 24 h.

At first the impact of the base was evaluated, using $Pd(OAc)_2$ (5 mol %) as the catalyst and DMA as the solvent (Scheme 34).

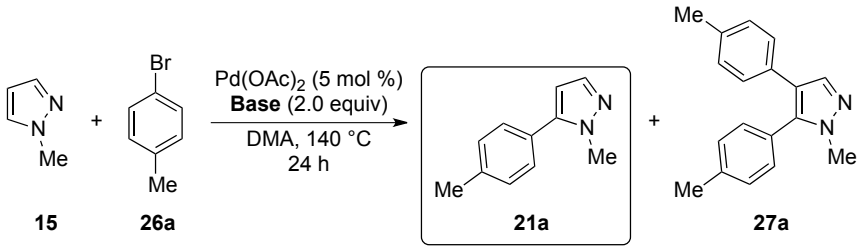



**Scheme 34**

The results of this preliminary screening are reported in Table 1. A mixture of the 5-arylated pyrazole **21a** and the corresponding 4,5-diarylated derivative **27a** was invariably observed when the GLC yield of **21a** was higher than 10 % (entries 5-9, Table 1), while **27a** was not detected in the crude reaction mixtures when lower GLC yields were recorded (entries 1-4 and 10-11, Table 1). Moreover, the crude reaction mixtures were found to be contaminated by significant amounts of 4,4'-dimethyl-1,1'-biphenyl (**28a**), derived from a Pd-catalyzed Ullmann-type reductive coupling of **26a** (Figure 3).[67] The structures of the products **21a**, **27a** and **26a** were all confirmed by $^{1}$H-NMR, $^{13}$C-NMR and GC-MS analyses.

These results, along with the detection of traces (if any) of the other two isomeric 3- and 4-monoarylated pyrazoles (**29a** and **22a** respectively, Figure 3), confirmed the higher reactivity of the 5-position relative to the 4-position, while the 3-position resulted essentially unreactive.[53]

**Table 1**: Screening of the bases for the direct C-5 arylation of 1-methyl-1*H*-pyrazole (**15**) with 4-bromotoluene (**26a**).




| Entry[a] | Base | Yield of 21a (%)[b] | 21a:27a |
|---|---|---|---|
| 1 | NaOAc | 6 | 100:0 |
| 2 | KOAc | 8 | 100:0 |
| 3 | CsOAc | 7 | 100:0 |
| 4 | AgOAc | 1 | 100:0 |
| **5** | **$Bu_4NOAc$** | **49** | **86:14** |
| 6[c] | $Bu_4NOAc$ | 44 | 89:11 |
| 7 | $K_2CO_3$ | 19 | 85:15 |
| 8 | $KHCO_3$ | 18 | 86:14 |
| 9 | $K_3PO_4$ | 24 | 90:10 |
| 10 | KF | 4 | 90:10 |
| 11 | KO$^t$Bu | 6 | 100:0 |

[a] Unless otherwise stated, the reactions were carried out using **15** (1.0 mmol), **26a**, (1.5 equiv), $Pd(OAc)_2$ (5 mol %), DMA (5 mL) for 24 h at 140 °C. [b] GLC yield. [c] Reaction carried out in the presence of 0.3 equiv of pivalic acid.

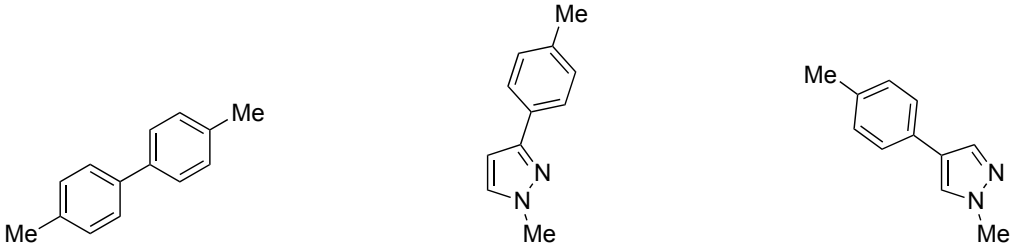



**Figure 3**: 4,4'-Dimethyl-1,1'-biphenyl (**28a**), 1-methyl-3-(*p*-tolyl)-1*H*-pyrazole (**29a**) and 1-methyl-4-(*p*-tolyl)-1*H*-pyrazole (**22a**).

Although the selectivity of the arylation was little influenced by the base, its chemical nature had a deep impact on the efficiency of the coupling reaction. In particular, the yield of **21a** seems to be related to a specific cation/anion pair and not to a particular anion or cation (compare for example, entries 1-5, or entries 2 and 7-11, Table 1). From these data it clearly emerges that $Bu_4NOAc$ represents the best choice in terms of chemical yield (49 %) for the

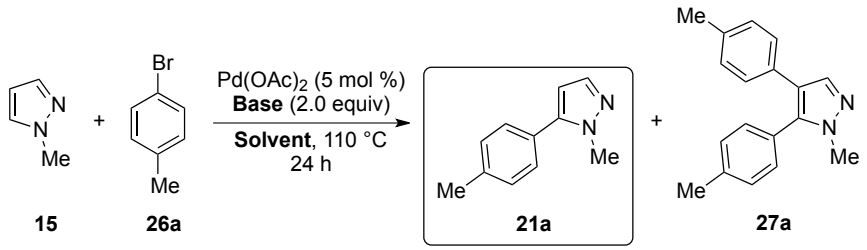
regioselective direct 5-arylation of **15** with **26a** in DMA (entry 5, Table 1). Potassium-containing bases $K_2CO_3$, $KHCO_3$, and $K_3PO_4$ also showed activity, albeit with a significant lower product yields (entries 7-9, Table 1). All the other bases were ineffective at 140 °C in DMA, including KOAc, a base frequently used to promote the direct arylation of azoles and that, in particular, was previously employed in the direct arylation of **15** with aryl bromides at 150 °C in the same solvent.[59] Note also the result obtained when $Bu_4NOAc$ was used in combination with 30 mol % of pivalic acid (entries 6, Table 1), which as already stated at the beginning of this chapter, is an additive commonly used in direct arylation reactions in combination with inorganic bases.[9,10b,23b,50c,50e,54,57] In this case we observed a yield lower than that obtained when the same reaction was carried out in the absence of this carboxylic acid (entries 5, Table 1).

Then, we attempted to improve the yield of the arylation reaction, so the effects of the nature of the solvent were examined. The reaction temperature for this second screening was set at 110 °C to allow a better comparison between solvents with boiling points lower than 140 °C. We also tried to compare the three bases that gave the best results in terms of efficiency in order to observe if the trend of the results reported in Table 1 could be kept also in solvents different from DMA (Table 2).

From the data summarized in Table 2, it clearly emerges that the *N*,*N*-dimethylacetamide (DMA) is a better solvent than toluene and dioxane for all the three bases (entries 1, 5 and 9, Table 2). In light of the results obtained in the reactions with $K_3PO_4$ and $K_2CO_3$ in toluene (entries 2 and 6, Table 2), we thought that the low solubility of the inorganic bases in this solvent could influence the effectiveness of the arylation; therefore we tried to exploit the capability of a transfer agent to improve the solubility of inorganic bases in organic solvents[68] as we previously reported in the procedure for the direct C-3 arylation of (NH)-indoles with aryl bromides.[69] The use of a lipophilic quaternary ammonium salt such $BnBu_3NCl$ could have favoured the solubility of $K_3PO_4$ and $K_2CO_3$ in toluene. Unfortunately, both the catalytic systems resulted inactive with these reaction conditions (entries 3 and 7, Table 2). It is clear that $Bu_4NOAc$ results the most efficient base in promoting this arylation and it is interesting to observe that, when we used this organic base, the **21a**:**27a** molar ratio was always higher than 80 % (entries 9-13, Table 2). Furthermore, DMA gave the best result in terms of efficiency among the polar solvents as *N*-methyl-pyrrolidone (NMP) and dimethylformamide (DMF) (entries 9, 12-13, Table 2). Finally, we tried to improve the low efficiency demonstrated by KOAc (entry 2, Table 1) by performing the arylation of **15** in the presence of 1.0 equiv of

$Bu_4NCl$ (entry 14, Table 2), but the yield of **21a** remained lower than that obtained by using $Bu_4NOAc$.

**Table 2**: Screening of the solvents for the direct C-5 arylation of 1-methyl-1*H*-pyrazole (**15**) with 4-bromotoluene (**26a**).



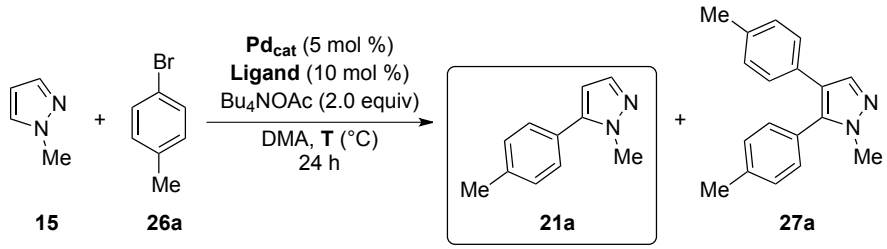

| Entry[a] | Base | Solvent | Yield of 21a (%)[b] | 21a:27a |
|---|---|---|---|---|
| 1 | $K_3PO_4$ | DMA | 15 | 89:11 |
| 2 | $K_3PO_4$ | Toluene | 3 | 100:0 |
| 3[c] | $K_3PO_4$ | Toluene | 3 | 100:0 |
| 4 | $K_3PO_4$ | Dioxane | - | - |
| 5 | $K_2CO_3$ | DMA | 19 | 83:17 |
| 6 | $K_2CO_3$ | Toluene | 9 | 80:20 |
| 7[c] | $K_2CO_3$ | Toluene | - | - |
| 8 | $K_2CO_3$ | Dioxane | - | - |
| **9** | **$Bu_4NOAc$** | **DMA** | **52 (52)[d]** | **82:18** |
| 10 | $Bu_4NOAc$ | Toluene | 45 | 93:7 |
| 11 | $Bu_4NOAc$ | Dioxane | 39 | 92:8 |
| 12 | $Bu_4NOAc$ | NMP | 50 (47)[e] | 83:17 |
| 13 | $Bu_4NOAc$ | DMF | 34 | 91:9 |
| 14[f] | KOAc | DMA | 34 | 88:12 |

[a] Unless otherwise stated the reactions were carried out using **15** (1.0 mmol %), **26a**, (1.5 equiv), $Pd(OAc)_2$ (5 mol %), solvent (5 mL), for 24 h at 110 °C. [b] GLC yield. In parentheses, isolated yield. [c] Reaction was carried out in the presence of 0.2 equiv of $BnBu_3NCl$. [d] 1-Methyl-4,5-di-(*p*-tolyl)-1*H*-pyrazole (**27a**) was also isolated in 12 % yield. [e] 1-Methyl-4,5-di-(*p*-tolyl)-1*H*-pyrazole (**27a**) was also isolated in 10 % yield. [f] Reaction carried out in the presence of 1.0 equiv of $Bu_4NCl$.

Taking into account these results, we studied the influence of the palladium pre-catalyst and the ligand on the efficiency and selectivity of our model reaction (Table 3). As regards the catalyst precursor, the best results were obtained by using $Pd(OAc)_2$ (entry 9, Table 2) and $PdCl_2$ (entry 3, Table 3), with poorer results in terms of yield obtained with $Pd_2(dba)_3$ and $PdCl_2(MeCN)_2$ (entries 1 and 2, Table 3). The reaction was also successful with reduced palladium loading (entry 4, Table 3), but we proceeded with 5 mol % of $Pd(OAc)_2$ for

convenience. Afterwards, we examined the role of the ligand and we observed that monodentate phosphines (entries 5-12, Table 3) were found to be more efficient than bidentate ligands (entries 13-16, Table 3). However, in general, their presence did not increase the activity and the selectivity of the catalytic system, irrespective of the electronic and/or steric properties of the ligand itself.

**Table 3**: Screening of the catalyst precursors, the ligands and the reaction temperature for the direct C-5 arylation of 1-methyl-1*H*-pyrazole (**15**) with 4-bromotoluene (**26a**).

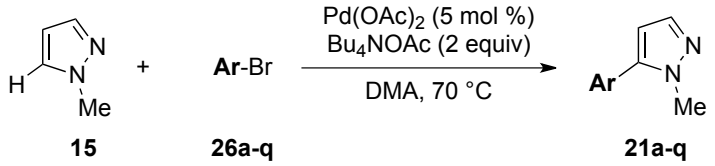



| Entry[a] | Catalyst | Ligand | Temperature (°C) | Yield of 21a (%)[b] | 21a:27a |
|---|---|---|---|---|---|
| 1 | $Pd_2(dba)_3$ | - | 110 | 38 | 91:9 |
| 2 | $PdCl_2(MeCN)_2$ | - | 110 | 46 | 87:13 |
| 3 | $PdCl_2$ | - | 110 | 52 (51)[c] | 84:16 |
| 4[d] | $Pd(OAc)_2$ | - | 110 | 40 | 75:25 |
| 5 | $Pd(OAc)_2$ | $PPh_3$ | 110 | 42 | 85:15 |
| 6 | $Pd(OAc)_2$ | P(*o*-Tol)$_3$ | 110 | 50 | 87:13 |
| 7 | $Pd(OAc)_2$ | P(*t*Bu)$_2$biphenyl | 110 | 39 | 68:32 |
| 8 | $Pd(OAc)_2$ | $PCy_3$ | 110 | 42 | 78:22 |
| 9 | $Pd(OAc)_2$ | P(*t*Bu)$_3$·$HBF_4$ | 110 | 30 | 79:21 |
| 10 | $Pd(OAc)_2$ | $PBuAd_2$ | 110 | 47 | 77:23 |
| 11 | $Pd(OAc)_2$ | P(2-furyl)$_3$ | 110 | 14 | 93:7 |
| 12 | $Pd(OAc)_2$ | $AsPh_3$ | 110 | 39 | 83:17 |
| 13 | $Pd(OAc)_2$ | Xantphos | 110 | 38 | 76:24 |
| 14 | $Pd(OAc)_2$ | dppb | 110 | 40 | 76:24 |
| 15 | $Pd(OAc)_2$ | dppf | 110 | 28 | 82:18 |
| 16 | $Pd(OAc)_2$ | Oxydiphenylene($PPh_2$)$_2$ | 110 | 38 | 76:24 |
| **17** | **$Pd(OAc)_2$** | **-** | **70** | **62 (58)**[e] | **84:16** |
| 18 | $Pd(OAc)_2$ | - | 40 | - | - |

[a] Unless otherwise stated the reactions were carried out using **15** (1.0 mmol %), **26a**, (1.5 equiv), $Pd_{cat}$ (5 mol %), ligand (10 mol %) (if any), DMA (5 mL), for 24 h at 110 °C. [b] GLC yield. In parentheses, isolated yield. [c] 1-Methyl-4,5-di-(*p*-tolyl)-1*H*-pyrazole (**27a**) was also isolated in 10 % yield. [d] Reaction performed by using 1 mol % of $Pd(OAc)_2$. [e] 1-Methyl-4,5-di-(*p*-tolyl)-1*H*-pyrazole (**27a**) was also isolated in 12 % yield.

Due to the fact that the yield obtained with $Bu_4NOAc$ as the base was slightly higher at 110 °C than at 140 °C (compare entry 9, Table 2 with entry 5, Table 1), we decided to lower further the reaction temperature and we found, with our pleasure, that an even better chemical yield was obtained when **15** was treated with **26a** in the presence of $Bu_4NOAc$ and $Pd(OAc)_2$ in DMA at only 70 °C (entry 17, Table 3). However, an attempt to carry out the same reaction at 40 °C was unsuccessful, and the precursors were recovered unchanged after 24 h (entry 18, Table 3).

The good results obtained in the preparation of **21a** from **15** and **26a** under the experimental conditions reported in entry 17 of Table 3 prompted us to extend this mild procedure to the selective preparation of 5-aryl-1*H*-pyrazoles **21** starting from **15** and commercially available *para*- and *ortho*-substituted aryl bromides **26a-q** by using 5 mol % $Pd(OAc)_2$ as the catalyst and 2 equi $Bu_4NOAc$ as the base in DMA at 70 °C (Scheme 35). The results are reported in Table 4.

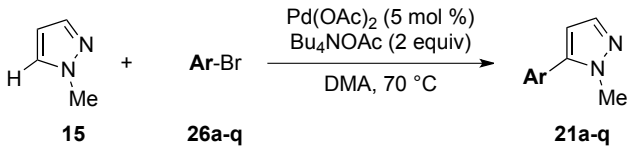



**Scheme 35**

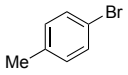
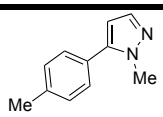
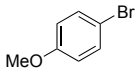
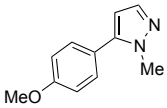
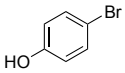
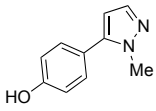
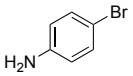
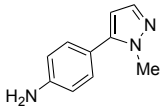
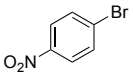
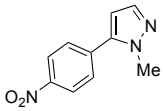
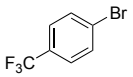
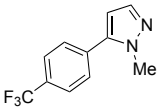
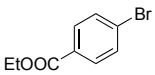
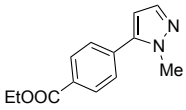
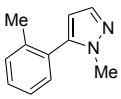
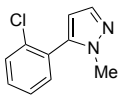
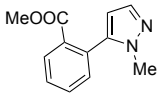
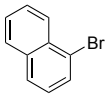
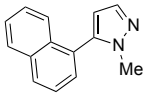
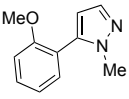
Good chemical yields and C-5 regioselectivity were observed with electron-rich *para*-substituted aryl bromides **26a** and **26b** (entries 1 and 2, Table 4), and similar C-5 regioselectivity but slightly lower yields were observed with electron-poor *para*-substituted aryl bromides **26e-g** as the electrophilic partners (entries 5-7, Table 4). Similarly to our observations during the preliminary screenings, the crude reaction mixtures were contaminated by the corresponding 4,5-diarylated pyrazoles **27** (detected by GLC and GC-MS); smaller amounts (16-18%) of **27** were produced with deactivated bromides **26a-b** than with activated bromide **26e-g** (20-30 %).

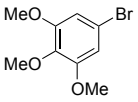
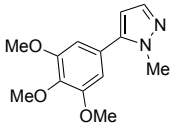
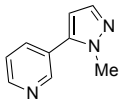
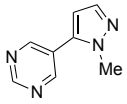
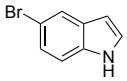
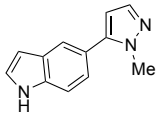
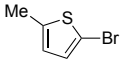
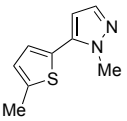
In contrast to the results reported by Doucet and coworkers,[59] a good selectivity was observed irrespective of the electronic nature of the *para*-substitutent on the aryl bromide **26**. In fact, we argued that the possibility of lowering the reaction temperature from 150 °C to 70 °C due to the successful use of $Bu_4NOAc$ enhanced the kinetic discrimination among the C-H bonds with different dissociation energies ($\Delta G^{act}$ at 298 K for C-H bond cleavage in **15**: C-3 31.3, C-4 28.5, C-5 27.3 kcal·mol$^{-1}$).[19]

**Table 4**: Scope of the ligandless Pd-catalyzed direct C-5 arylation of 1-methyl-1*H*-pyrazole (**15**) with aryl bromides **26a-q** promoted by $Bu_4NOAc$.




**15** **26a-q** **21a-q**

| Entry[a] | Aryl bromide (26) | | Reaction time (h)[b] | Product 21 | | Yield (%)[c] | C-5 Selectivity[d] |
|---|---|---|---|---|---|---|---|
| 1 | **26a** |  | 24 | **21a** |  | 58 | 0.84 |
| 2 | **26b** |  | 23 | **21b** |  | 58 | 0.84 |
| 3 | **26c** |  | 48 | **21c** |  | 28 | 1.00 |
| 4 | **26d** |  | 24 | **21d** |  | - | - |
| 5 | **26e** |  | 46 | **21e** |  | 46 | 0.70 |
| 6 | **26f** |  | 48 | **21f** |  | 30 | 0.70 |
| 7 | **26g** |  | 48 | **21g** |  | 41 | 0.80 |
| 8 | **26h** |  | 24 | **21h** |  | 47 | 0.78[e] |
| 9 | **26i** |  | 24 | **21i** |  | 42 | 0.73[f] |
| 10 | **26j** |  | 24 | **21j** |  | - | - |
| 11 | **26k** |  | 24 | **21k** |  | 50 | 0.76[e] |
| 12 | **26l** |  | 24 | **21l** |  | - | - |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 13 | **26m** |  | 24 | **21m** |  | - | - |
| 14[g] | **26n** |  | 65 | **21n** |  | 33 | 0.60 |
| 15 | **26o** |  | 24 | **21o** |  | - | - |
| 16 | **26p** |  | 24 | **21p** |  | - | - |
| 17 | **26q** |  | 72 | **21q** |  | 11 | 0.88 |

[a] The reactions were carried out by using pyrazole **15** (1 mmol) and aryl bromide **26** (1.5 equiv) at 70 °C in the presence of $Pd(OAc)_2$ (5 mol %) and $Bu_4NOAc$ (2 equiv) in DMA (5 mL). [b] The reactions were stopped when the conversion was higher than 95 %, or when they did not progress further. [c] Isolated yield. [d] 5-Arylated pyrazole **21** (% GLC) with respect to all arylated products formed. Unless otherwise stated, the main byproduct was the corresponding diarylated pyrazole **27**. [e] The crude reaction mixture was contaminated by ca. 7 % of a regioisomeric monoarylated derivative. [f] The crude reaction mixture was contaminated by ca. 14 % of a regioisomeric monoarylated derivative. [g] The reaction was performed at 110 °C.

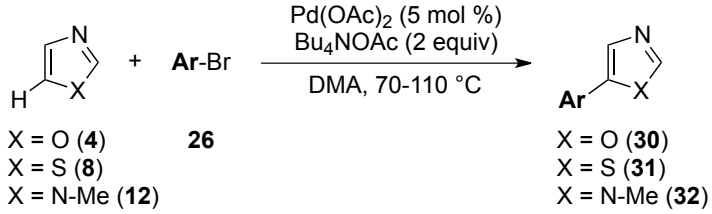
As a consequence, a strong molar excess of **15** was not necessary to secure a high regioselectivity. This simple combination of $Pd(OAc)_2$ and $Bu_4NOAc$ proved to be tolerant to some sterically hindered bromides without the need to force reaction conditions. In fact, 2-bromotoluene (**26h**), 2-chloro-1-bromobenzene (**26i**), and 1-naphthyl bromide (**26k**) reacted readily with **15** at 70 °C to give the corresponding 5-arylated pyrazoles **21h**, **21i** and **21k** in 47, 42 and 50 % isolated yields, respectively (entries 8-9 and 11, Table 4). Note, in these reactions, variable amounts (7-14 %) of a monoarylated regioisomeric pyrazole (presumably the C-4 isomer)[59] were also detected in the crude reaction mixtures.

On the other hand, methyl-2-bromobenzoate (**26j**), 2-bromoanisole (**26l**) and 5-bromo-1,2,3-trimethoxybenzene (**26m**) (entries 10 and 12-13, Table 4) did not react in this mild conditions with 1-methyl-pyrazole as well as 5-bromopyrimidine (**26o**) and the NH-free 5-bromo indole (**26p**) (entries 15-16, Table 4). No monoarylation product was also detected employing unprotected 4-bromoaniline (**26d**) (entry 4, Table 4). Otherwise, it is worth of noting that, for the first time, unprotected 4-bromophenol (**26c**) was used in a Pd-catalyzed direct arylation and 4-(1-methyl-1*H*-pyrazol-5-yl)-phenol (**21c**) was isolated in 28 % yield (entry 3, Table 4) by the reaction of **26c** with 1-methyl-pyrazole (**15**) after 48 h at 70 °C. Finally, heteroaryl bromides as

3-bromopyridine (**26n**) and 2-bromo-5-methylthiophene (**26q**) also reacted with compound **15** even if with low reactivity, giving 33 and 11 % isolated yields respectively.

## 2. Synthesis of 5-aryl-oxazoles (30), 5-aryl-thiazoles (31) and 5-aryl-1-methyl-1*H*-imidazoles (32) *via* Pd-catalyzed direct arylation of oxazole (4), thiazole (8) and 1-methyl-1*H*-imidazole (12) promoted by $Bu_4NOAc$.[62]

Having successfully demonstrated the viability of the $Pd(OAc)_2$-catalyzed regioselective direct 5-arylation of **15** with bromides **26** in the presence of $Bu_4NOAc$ as base, we proceeded to broaden the scope of this arylation reaction by applying the optimized reaction conditions of entry 17 of Table 3 to the synthesis of different classes of monoarylated azoles (Scheme 36).

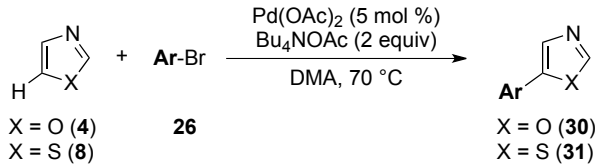


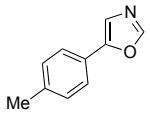
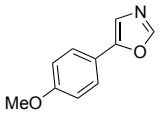
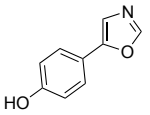
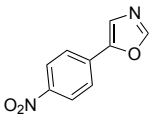
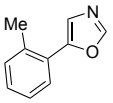
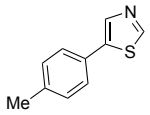
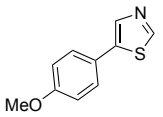
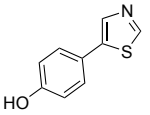
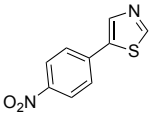
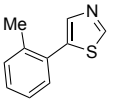

**Scheme 36**

We found that 1,3-azoles can react at the 5-position with a variety of activated and deactivated aryl bromides **26** (Table 5 and Table 6).

In detail, oxazole (**4**) and thiazole (**8**) were efficiently and regioselectively converted into the corresponding 5-arylated derivatives **30** and **31**, respectively, by reacting with 1.5 equiv of aryl bromides **26a-c**, **26e** and **26h**. Deactivated bromides **26a-b**, activated 1-bromo-4-nitrobenzene (**26e**) and *ortho*-substituted bromotoluene (**26h**) gave yields ranging from 49 to 72 % and high selectivities when treated with **4** (entries 1-2 and 4-5, Table 5), whereas the corresponding 5-arylated thiazoles **31a-b**, **31e** and **31h** were obtained in isolated yields of 59-70 % with C-5 selectivities up to 100 % (entries 6-7 and 9-10, Table 5).

**Table 5**: Scope of the ligandless Pd-catalyzed direct C-5 arylation of oxazole (**4**) and thiazole (**8**) with aryl bromides **26a-c**, **26e** and **26h** promoted by $Bu_4NOAc$.




| Entry[a] | Time (h)[b] | Product | | Yield (%)[c] | C-5 Selectivity[d] |
|---|---|---|---|---|---|
| 1 | 5 | **30a** |  | 58 | 0.86 |
| 2 | 24 | **30b** |  | 49 | 0.88 |
| 3 | 48 | **30c** |  | 36 | 0.95 |
| 4 | 24 | **30e** |  | 57 | 0.89 |
| 5 | 24 | **30h** |  | 72 | 0.83 |
| 6 | 21 | **31a** |  | 65 | 0.86 |
| 7 | 48 | **31b** |  | 67 | 1.00 |
| 8 | 48 | **31c** |  | 17 | 1.00 |
| 9 | 48 | **31e** |  | 70 | 0.94 |
| 10 | 29 | **31h** |  | 59 | 0.89 |

[a] The reactions were carried out by using azoles **4** and **8** (1 mmol) and aryl bromide **26** (1.5 equiv) at 70 °C in the presence of $Pd(OAc)_2$ (5 mol %) and $Bu_4NOAc$ (2 equiv) in DMA (5 mL). [b] The reactions were stopped when the conversion was higher than 95 % or when they did not progress further. [c] Isolated yield. [d] 5-Monoarylated azole (% GLC) with respect to all arylated products formed.

Even with these two azoles, unprotected 4-bromophenol (**26c**) was used for the Pd-catalyzed direct arylation and 4-(oxazole-5-yl)phenol (**30c**) and 4-(thiazole-5-yl)phenol (**31c**) were isolated in 36 and 17 % yield, respectively (entries 3 and 8, Table 5) by the reaction of **26c** with oxazole (**4**) and thiazole (**8**) after 48 h at 70 °C.

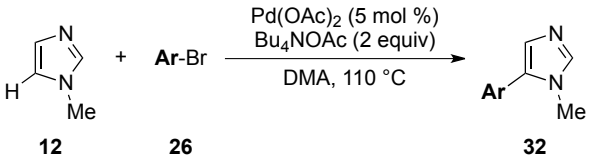
Note that this convenient synthetic method for the direct 5-arylation of **4** and **8** competes favourably with previously reported protocols. In fact, as reported in the **Introduction**, Strotman et al. investigated the regioselective direct 5-arylation of oxazole (**4**) with (hetero)aryl bromides in DMA for 16 h at 110 °C in a sealed vial in the presence of $Pd(OAc)_2$ (5 mol %), 3 equiv of $K_2CO_3$ and 0.4 equiv of pivalic acid, but a two-fold excess of **4** was required to gain high regioselectivities (90-100 %) and 10 mol % of the air sensitive di(1-adamantyl)-*n*-butylphosphane (**5**) was employed as the Pd ligand (see Scheme 8).[33] As regards thiazole (**8**), Rault and co-workers reported a small library of 5-arylthiazole **31** regioselectively obtained (27-63 % isolated yields) by treating **8** with electron-rich, electron-poor and heteroaryl bromides.[47] However, a strong molar excess of 5 equiv of **8** was once again required to attain good regioselectivity and drastic reaction conditions were necessary to reduce reaction times.

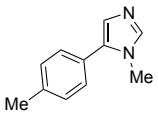
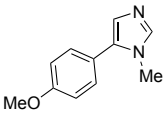
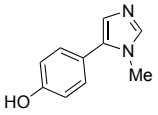
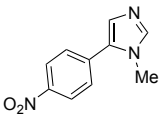
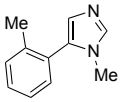
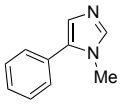
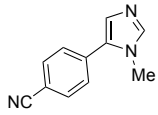
A highly efficient direct 5-arylation was also achieved when 1-methyl-1*H*-imidazole (**12**) was treated with several aryl bromides using the same reaction conditions promoted by $Bu_4NOAc$ but setting the reaction temperature to 110 °C (Table 6).

Yields higher than 80 % resulted from the reaction of **12** with electron-rich 4-bromotoluene (**26a**) and 4-bromoanisole (**26b**) (entries 1-2, Table 6); however electron-neutral bromobenzene (**26r**), electron-poor 4-bromobenzonitrile (**26s**), and 1-bromo-4-nitrobenzene (**26e**) were also used as coupling partners (75, 69 and 45 % isolated yields, respectively; entries 6, 7 and 4, Table 6). As we observed for pyrazole **15** and also the parent 1,3-azoles **4** and **8**, the reaction proved to be tolerant towards the *ortho*-substituted aryl bromide, 2-bromotoluene (**26h**); in fact, 1-methyl-5-(2-methylphenyl)-1*H*-imidazole (**32h**) was isolated in a satisfactory 68 % yield (entry 5, Table 6). Invariably, very good regioselectivity was observed, with typically less than 10 % (GLC) of the corresponding 2,5-diarylated imidazoles found to contaminate the crude reaction mixtures. Finally, the reaction between the unprotected 4-bromophenol (**26c**) and 1-methyl-1*H*-imidazole (**12**) did not occur (entry 3, Table 6).

Note that this new protocol for the regioselective 5-arylation of **12** gave identical regioselectivities but higher isolated yields than the procedure reported by our research group in 2008, in which we employed $Pd(OAc)_2$ (5 mol %) and $P(2\text{-furyl})_3$ (10 mol %) as catalyst system, 2 equiv of $K_2CO_3$ as base, and DMF as solvent at 110 °C.[50c]

**Table 6**: Scope of the ligandless Pd-catalyzed direct C-5 arylation of 1-methyl-1*H*-imidazole (**12**) with aryl bromides **26a-c**, **26e**, **26h** and **26r-s** promoted by $Bu_4NOAc$.




| Entry[a] | Time (h)[b] | Product | | Yield (%)[c] | C-5 Selectivity[d] |
|---|---|---|---|---|---|
| 1 | 22 | **32a** |  | 81 | 0.90 |
| 2 | 24 | **32b** |  | 82 | 0.97 |
| 3 | 24 | **32c** |  | - | - |
| 4 | 24 | **32e** |  | 45 | 1.00 |
| 5 | 24 | **32h** |  | 68 | 0.91 |
| 6 | 24 | **32r** |  | 75 | 0.97 |
| 7 | 23 | **32s** |  | 69 | 0.92 |

[a] The reactions were carried out by using azole **12** (1 mmol) and aryl bromide **26** (1.5 equiv) at 110 °C in the presence of $Pd(OAc)_2$ (5 mol %) and $Bu_4NOAc$ (2 equiv) in DMA (5 mL). [b] The reactions were stopped when the conversion was higher than 95 % or when they did not progress further. [c] Isolated yield. [d] 5-Monoarylated azole (% GLC) with respect to all arylated products formed.

For comparison, imidazole **32b** was obtained in 49 % yield by applying our older method, and *ortho*-substituted aryl bromides did not react at all. The use of $Bu_4NOAc$ at 110 °C in DMA also gave better results than those reported by Doucet and co-workers in 2009.[51] In that case, their harsh low catalyst loading method [$Pd(OAc)_2$ (0.5-0.01 mol %), 2 equiv of KOAc in DMA at 150 °C] gave significantly lower yields when electron-rich aryl bromides **26a** and **26b** were used (40 and 42 % isolated yields, respectively), whereas results similar to those reported

here were described when a typical electron-poor aryl bromide, 4-bromobenzonitrile (**26s**), was used (76 % yield).

## 3. Mechanistic hypothesis of the palladium-catalyzed direct arylation of azoles with aryl bromides promoted by $Bu_4NOAc$.[62]

From our data it emerges that the experimental order of reactivity for the three 1,3-azoles, that is oxazole > thiazole > 1-methyl-1*H*-imidazole, parallels the calculated Gibbs free energy for the cleavage of the C5-H bond for a CMD reaction mechanism[19] ($\Delta G^{act}$ at 298 K: oxazole 23.5, thiazole 23.7, 1-methyl-1*H*-imidazole 25.0 kcal·mol$^{-1}$). This experimental order of reactivity is distinctly different to that reported for common electrophilic substitution reactions carried out in nonacidic media (1-methyl-1*H*-imidazole > oxazole > thiazole),[70] which allows us to reasonably exclude an alternative $S_EAr$ mechanistic pathway, which has also been postulated for direct arylations involving these heteroaromatics.[20a]

Undoubtedly, the efficiency and very high regioselectivity demonstrated by this ligand-free protocol at mild reaction temperatures and without the need of employing a strong molar excess of the heteroaromatic partner has to be attributed to the use of $Bu_4NOAc$ as the base. Its efficacy in promoting such ligand-free direct arylations, in our opinion, may be motivated not only by the well-known ability of ammonium salts to act as metal stabilizers in the absence of phosphines or other ancillary ligands (the so-called "Jeffery conditions"),[69,71,72] but also by the fact that organic ionic bases have good solubility and are fully ionized in organic solvents.[73] In fact, we noted that arylations involving $Bu_4NOAc$ gave yellow to deep-orange solutions (Figure 4), in contrast to the reactions carried out in the presence of inorganic bases, which usually give dark-brown heterogeneous reaction mixtures. These last features may lead, as a consequence, to an improved availability in solution of the acetate anion,[74] which can then play better its key-role in the concerted metalation/deprotonation pathway (CMD) postulated for these Pd-catalyzed reactions (Figure 5), as already mentioned.[19]

In particular, the role of $Bu_4NOAc$ may be of relevance in the anionic ligand-exchange step that may occur at the aryl palladium intermediate **I**, producing the palladium acetate intermediate **II**, which then may follow the CMD pathway *via* a six-membered transition state **TS**. DFT calculations evidenced that this path is energetically more favourable than a pathway

involving a σ-bond metathesis, in which the bromine atom induces deprotonation via **TS-I** (Figure 6).[75]

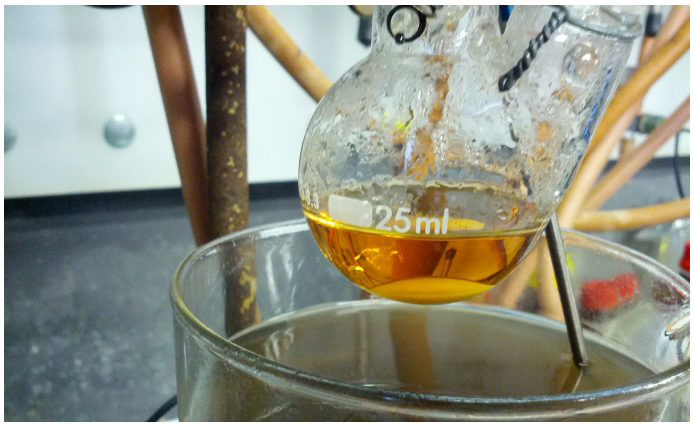



**Figure 4**: A typical crude reaction mixture from a $Bu_4NOAc$-promoted direct arylation, after 24 h at 110 °C.

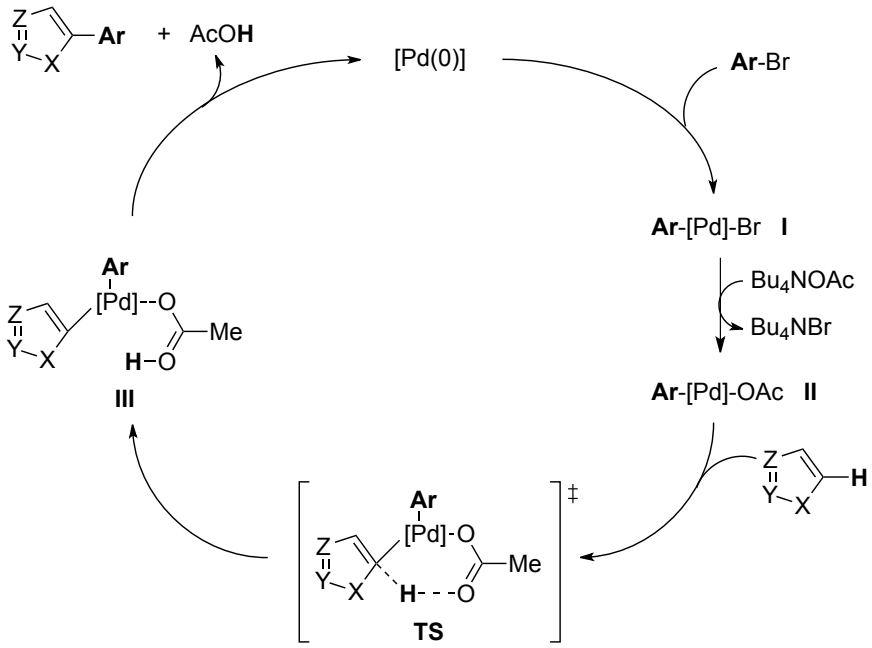



**Figure 5**: Proposed CMD pathway for the ligand-free Pd-catalyzed direct 5-arylation of azoles with aryl bromides mediated by $Bu_4NOAc$. Coordinating species around Pd (such as solvent molecules or ammonium salts) have been omitted for semplicity.

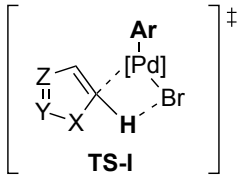
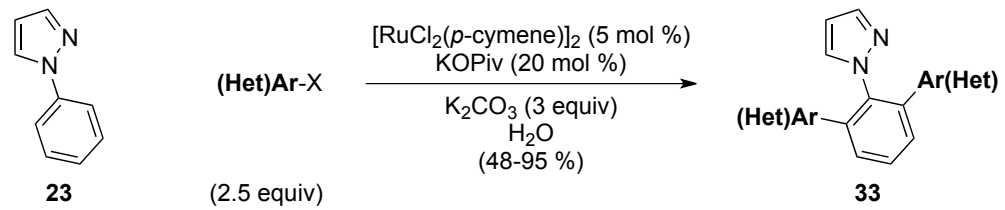



**Figure 6**: Structure of intermediate **TS-I**.

Hence, if the lower-energy pathway involves a bromine/acetate exchange, this may become a limiting step for the entire process when bases that are poorly soluble in the reaction media are employed, and may explain the efficiency of $Bu_4NOAc$ in promoting this class of C-C bond-forming reaction.

## 4. Preliminary screening on the palladium-catalyzed direct arylation of 1-phenyl-1*H*-pyrazole (23).

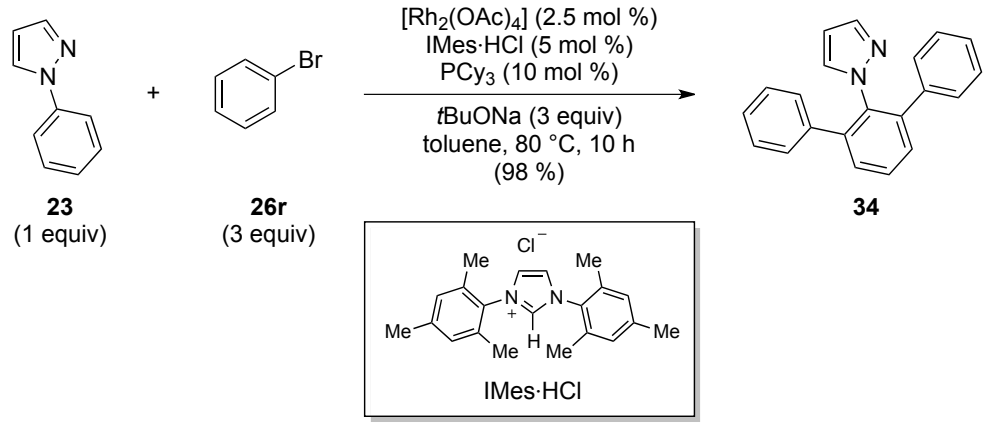
Our next challenge, after the study of the reactivity of the 1-methyl-1*H*-pyrazole with aryl bromides, was to focus our attention to the direct arylation of 1-phenyl-1*H*-pyrazole (**23**). To the best of our knowledge, nothing about the palladium-catalyzed direct arylation of compounds **23** with aryl bromides to give the monoarylated product has been reported so far. This compound presents increased regioselectivity challenges in the reaction of palladium-catalyzed direct arylation, because the pyrazole nucleus is a well-known *ortho*-directing substrate and, as a consequence, also the *ortho* C-H bonds of the N-1 phenyl ring may be involved in carbon-carbon bond forming reactions with aryl halides. Actually, most of the publications on the *ortho*-direct arylation of **23** with aryl halides does not involve palladium, but describes successful ruthenium-[76] and rhodium-catalyzed[77] cross couplings. For examples, Dixneuf and co-workers reported that 5 mol % [{$RuCl_2$(*p*-cymene)}$_2$] catalyst can efficiently perform the direct *ortho*-arylation of 1-phenyl-pyrazole **23** with aryl chlorides in refluxing water in the presence of KOPiv (20 mol %) and $K_2CO_3$ (3 equiv) to give the diarylated products **33** (Scheme 37).[76a]




**Scheme 37**

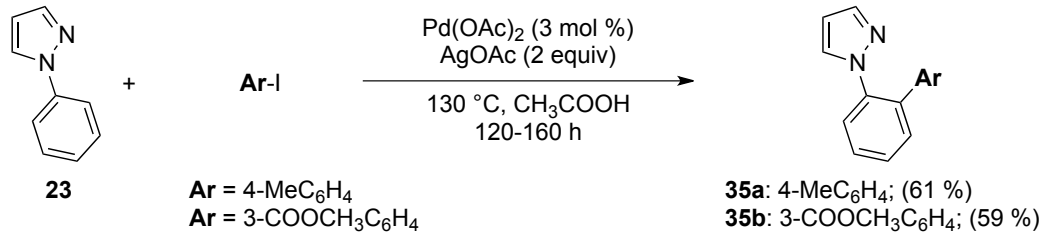
In 2009, Chang's group developed a procedure for a rhodium-catalyzed chelation-assisted direct arylation at the $sp^2$ C-H bonds of *N*-based arenes with aryl bromides.[77] The reactivity of rhodium catalyst was dramatically increased by the simultaneous employment of

an electron-rich *N*-heterocyclic carbene and $PCy_3$ ligands as reported in Scheme 38. The 1-([1,1':3',1''-terphenyl]-2'-yl)-1*H*-pyrazole (**34**) was obtained in 98 % isolated yield with these reaction conditions.




**Scheme 38**

The direct arylation at the *ortho*-position of the phenyl ring of compound **23** can be achieved also with a palladium catalyst, as it has been described by Daugulis in 2005.[78] He reported that 1-phenyl-1*H*-pyrazole (**23**) can be monoarylated at the C-1' position of the phenyl ring when it is treated with 5 equiv of aryl iodide in the presence of 3 mol % $Pd(OAc)_2$, 2 equiv AgOAc in acetic acid as the solvent for 120-160 h at 130 °C. The monoarylated products **35** were obtained in 59 and 61 % isolated yields (Scheme 39).

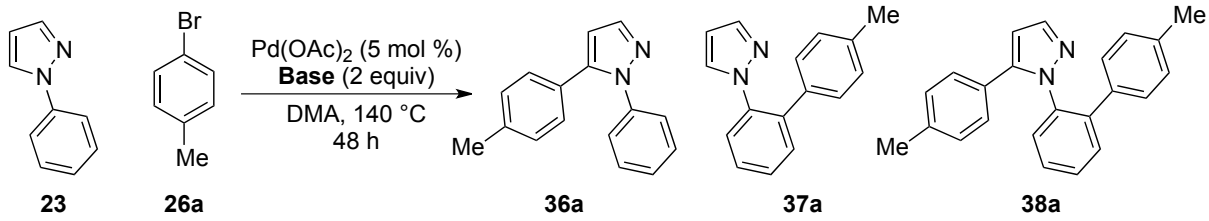



**Scheme 39**

On the other hand, nothing about the C3-H, C4-H or C5-H direct arylation on the *C*-unsubstituted 1-phenyl-pyrazole **23** has been published. Only Doucet and co-workers reported the diarylation of **23** with aryl bromides in a paper published very recently in 2014,[60] (see Scheme 32) but no regioselective monoarylation has been achieved.

For these reasons, in the last part of this Ph.D. work, we focused our attention on a preliminary screening of the palladium-catalyzed direct arylation of **23** with aryl bromides. More specifically, we chose the palladium-catalyzed direct arylation of 1-phenyl-1*H*-pyrazole (**23**) with 4-bromotoluene (**26a**) as a model reaction. We decided to perform the reactions starting from 1 mmol of **23** and 1.5 mmol of **26a** in the presence of 5 mol % of the catalyst precursor, 2 equiv of a suitable base, in 5 mL of an appropriate solvent. We also set the reaction temperature at 140 °C and the reactions were followed for 48 h.

At first the impact of the base was evaluated, using $Pd(OAc)_2$ (5 mol %) as the catalyst precursor and DMA as the solvent (Scheme 40).

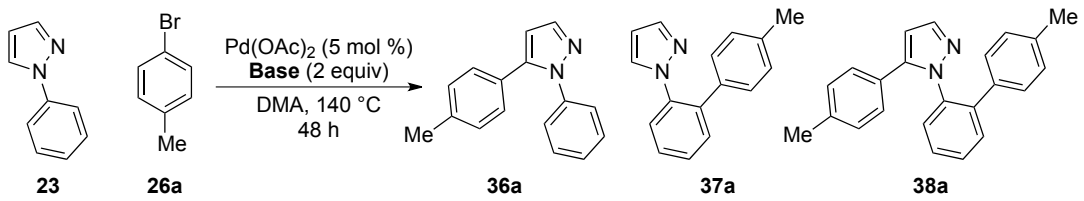



**Scheme 40**

The results of this preliminary screening are reported in Table 7. A mixture of the 5-arylated pyrazole **36a**, the corresponding *ortho*-arylated-pyrazole **37a** and the *ortho*-5-diarylated derivative **38a** was invariably observed when the GLC yield of **36a** was higher than 10 % (entries 4-6 and 9-10, Table 7), while **38a** was not detected or detected in a very small amount in the crude reaction mixture when lower GLC yields were recorded (entries 1-3 and 7, Table 7). Moreover, the crude reaction mixtures were found to be contaminated by significant amounts of 4,4'-dimethyl-1,1'-biphenyl **28a**, derived from the Pd-catalyzed Ullmann-type reductive coupling of **26a** (see Figure 3).[67]

From the data summarized in Table 7, it clearly emerged that carbonates ($Ag_2CO_3$ excluded) are the best in terms of efficiency (entries 5-6 and 9-10, Table 7). In contrast to that observed for 1-methylpyrazole, $Bu_4NOAc$ resulted ineffective for the direct arylation of **23**, and with KOAc gave yield lower than 10 % (entries 1-2, Table 7). The addition of pivalic acid did not contribute to an increase of the chemical yield but it enhanced the selectivity of the 5-arylated product **36a** both with KOAc and $K_2CO_3$ (entries 3 and 6, Table 7). Interestingly, $K_3PO_4$ seemed to promote the arylation at the *ortho*-position of the phenyl ring of **23** (entry 4, Table 7) while a stronger base, as *t*BuOLi, did not result effective for this reaction (entry 11, Table 7).

**Table 7**: Screening of the bases for the direct C-5 arylation of 1-phenyl-1*H*-pyrazole (**23**) with 4-bromotoluene (**26a**).




**23** **26a** **36a** **37a** **38a**

| Entry[a] | Base | Yield of 36a (%)[b] | 36a:37a:38a |
|---|---|---|---|
| 1 | $Bu_4NOAc$ | < 10 | 72:28:0 |
| 2 | KOAc | < 5 | 68:32:0 |
| 3[c] | KOAc | < 5 | 100:0:0 |
| 4 | $K_3PO_4$ | 11 | 22:52:26 |
| **5** | **$K_2CO_3$** | **(22)** | **49:23:28** |
| **6**[c] | **$K_2CO_3$** | **24** | **57:14:29** |
| 7[d] | $K_2CO_3$ | < 10 | 39:56:5 |
| 8 | $Ag_2CO_3$ | - | - |
| 9[c] | $Na_2CO_3$ | 17 | 49:37:14 |
| 10[c] | $Cs_2CO_3$ | 19 | 51:40:9 |
| 11 | *t*BuOLi | - | - |

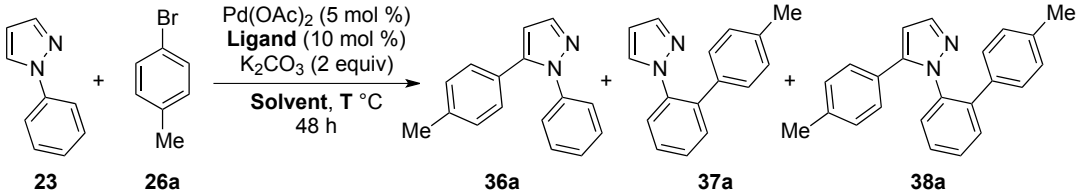
[a] Unless otherwise stated, the reactions were carried out using **23** (1.0 mmol), **26a** (1.5 equiv), $Pd(OAc)_2$ (5 mol %), base (2.0 equiv) in DMA (5 mL) for 48 h at 140 °C. [b] GLC yields. In parenthesis, isolated yields. [c] Reaction was carried out in the presence of 30 mol % PivOH. [d] Reaction was carried out in the presence of 10 mol % CuI.

In light of the better chemical yields and the regioselectivity obtained with $K_2CO_3$ in this preliminary screening, we decided to study the influence of the solvent and a possible role of the ligand on the efficiency and selectivity of our model reaction (Table 8). The reaction temperature for this second screening was kept at 140 °C except for toluene and dioxane wherein the reactions were performed at 110 and 100 °C, respectively.

From the results reported in Table 8, it clearly emerges that toluene, dioxane, NMP and dimethylsulfoxide (entries 1-4, Table 8), resulted ineffective in this reaction. Chlorobenzene and DMF showed a slight activity, giving both the 5-arylated products **36a** in 18 % chemical yields (entries 5-6, Table 8). Anyway, from the data summarized in Table 7 and Table 8 it is clear that the dimethylacetamide (DMA) is the best solvent in terms of efficiency and regioselectivity (entries 5-6 and 10, Table 7). Afterwards we examined the influence of the ligand on the palladium-catalyzed direct arylation of **23** with **26a** in DMA in the presence of 2

equiv of $K_2CO_3$. Low-to-moderate yields were obtained both with monodentate phosphines (entries 7-13, Table 8) and bidentate phosphines (entries 14-15, Table 8).

**Table 8**: Screening of the solvents and the ligands for the direct C-5 arylation of 1-phenyl-1*H*-pyrazole (**23**) with 4-bromotoluene (**26a**).




| Entry[a] | Ligand | Solvent | Yield of 36a (%)[b] | 36a:37a:38a |
|---|---|---|---|---|
| 1[c] | - | Toluene[d] | - | - |
| 2 | - | Dioxane[e] | < 2 | 100:0:0 |
| 3 | - | NMP | < 5 | 49:51:0 |
| 4 | - | DMSO | - | - |
| 5 | - | Chlorobenzene | 18 | 100:0:0 |
| 6 | - | DMF | 18 | 48:37:15 |
| 7 | $PPh_3$ | DMA | 21 | 40:27:33 |
| 8 | P(*o*-Tol)$_3$ | DMA | 10 | 15:74:11 |
| 9 | P(2-furyl)$_3$ | DMA | 17 | 38:43:19 |
| 10 | $PCy_3$ | DMA | 23 | 44:26:30 |
| 11 | P(*t*Bu)$_3$·$HBF_4$ | DMA | 20 | 40:36:24 |
| 12 | $PBuAd_2$ | DMA | 21 | 58:31:11 |
| 13[c] | $PBuAd_2$ | DMA | (21) | 57:18:25 |
| 14 | dppf | DMA | 22 | 48:34:18 |
| 15 | Xantphos | DMA | 21 | 44:32:24 |

[a] Unless otherwise stated, the reactions were carried out using **23** (1.0 mmol), **26a** (1.5 equiv), $Pd(OAc)_2$ (5 mol %), ligand (10 mol %) (if any), $K_2CO_3$ (2.0 equiv) in solvent (5 mL) for 48 h at 140 °C. [b] GLC yields. In parenthesis, isolated yields. [c] Reaction was carried out in the presence of 30 mol % PivOH. [d] Reaction was carried out at 110 °C. [e] Reaction was carried out at 100 °C.

Among the monodentate, $PPh_3$, $PCy_3$ and $PBuAd_2$ resulted the most efficient, giving **36a** in 21, 23 and 21 % chemical yields, respectively (entries 7, 10 and 12, Table 8). Bidentate phosphines also gave similar results, but just $PBuAd_2$ showed the highest C-5 selectivity (58 %). The addition of 30 mol % of pivalic acid in the presence of $PBuAd_2$ did not contribute to rise the chemical yield, but changed the **37a**/**38a** ratio with a higher production of compounds

**38a** (entry 13, Table 8). Anyway, the yields and the selectivities obtained in entries 12 and 13 of Table 8 were perfectly comparable with the reactions performed without the ligand of Table 7 (entries 5 and 6).

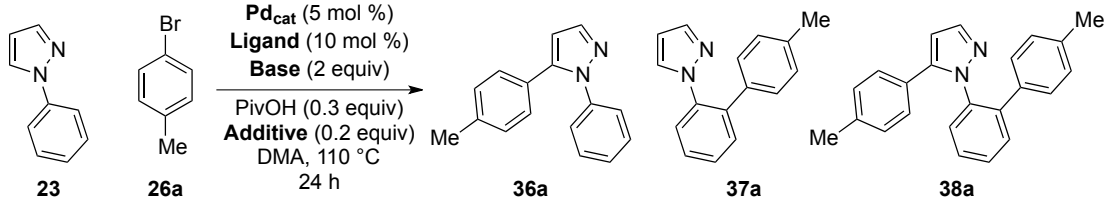
At the end of this second screening we argued if it might be possible to achieve better yields and selectivities by lowering the reaction temperature, and afterwards we observed the role of the palladium precatalyst in this reaction. The results of the third screening were reported in Table 9. We decided to add a 30 mol % PivOH to the reactions we performed for this last screening because it resulted to be beneficial for the selectivity, even if it did not contribute effectively to enhance the chemical yield of 5-arylpyrazole **36a**. Moreover, as we can observe from entries 5 and 6 of Table 7 or entries 12 and 13 of Table 8, pivalic acid increases the production of diarylated derivative **38a** relative to the *ortho*-arylated derivative **37a**, and this fact can be exploited from a purification point of view. In fact, the diarylated product **38a** is easier to separate from compound **36a** than the isomer **37a**.

At the beginning of this last screening we decided to set the reaction temperature at 110 °C. We had an increase of both the yield and the selectivity of compound **36a** with a regioselectivity higher than 71 % (entry 1, Table 9). Taking into account this result, we studied the influence of the palladium precatalyst on the model reaction.

All the palladium complexes we tried showed a catalytic activity. More specifically, $Pd(PPh_3)_4$ and $PdCl_2$(dppb) gave product **36a** in 16 and 19 % chemical yield, respectively, with a selectivity of 61 and 48 % (entries 2-3, Table 9). Then, we used $PdCl_2(MeCN)_2$ and, with our pleasure, we observed that it led to a yield of 29 % for the 5-arylated-pyrazole **36a** with a selectivity (82 %) higher than all the other trials we performed so far for 1-penyl-1*H*-pyrazole (**23**) (entry 4, Table 9). In light of these results, we decided to proceed with the screening by using the $PdCl_2(MeCN)_2$ as the palladium source for the direct arylation of **23** with **26a**.

After that, we wanted to verify if modifying the **23**/**26a** ratio it was possible to achieve better performances in terms of efficiency and regioselectivity. Unfortunately, the presence of 2 equiv of the aryl bromide **26a** did not influence the yield of the product **36a** (entry 5, Table 9) and, on the other hand, acted on the selectivity favouring the formation of the diarylated derivative **38a**. Then, we note with our delight that the difficult substrate **23** could be converted in **36a** with a better chemical yield by adding a phase transfer reagent (20 mol %). Both $BuBu_3NCl$ and $Bu_4NBr$ can promote the direct arylation of **23** with 4-bromotoluene (**26a**) with 35 and 38 % GLC yield, respectively, if the **23**/**26a** ratio is 1/1.5 (entries 6 and 9, Table 9) and with 40 and 43 % GLC yield, respectively, when the **23**/**26a** ratio is 1/2 (entries 7 and 10, Table 9).

**Table 9**: Screening of the reaction temperature, the palladium precatalyst, the presence of additive and **23**/**26a** molar ratio for the direct arylation of 1-phenyl-1*H*-pyrazole (**23**) with 4-bromotoluene (**26a**).

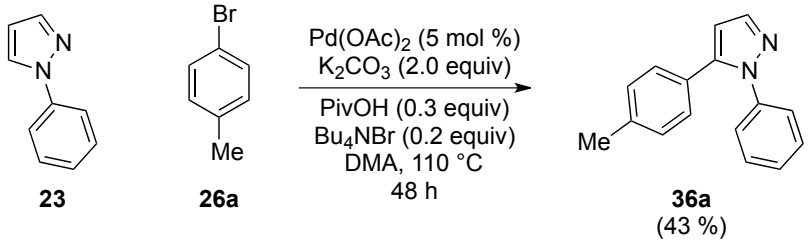



| Entry[a] | Catalyst | Base | Additive | 23/26a ratio | T (°C) | Yield of 36a (%)[b] | 36a:37a:38a |
|---|---|---|---|---|---|---|---|
| 1 | $Pd(OAc)_2$ | $K_2CO_3$ | - | 1/1.5 | 110 | 29 | 71:22:7 |
| 2 | $Pd(PPh_3)_4$ | $K_2CO_3$ | - | 1/1.5 | 110 | 16 | 61:28:11 |
| 3 | $PdCl_2$(dppb) | $K_2CO_3$ | - | 1/1.5 | 110 | 19 | 48:40:12 |
| 4 | $PdCl_2(MeCN)_2$ | $K_2CO_3$ | - | 1/1.5 | 110 | 29 (27) | 82:13:5 |
| 5 | $PdCl_2(MeCN)_2$ | $K_2CO_3$ | - | 1/2 | 110 | 28 | 73:14:13 |
| 6 | $PdCl_2(MeCN)_2$ | $K_2CO_3$ | $BnBu_3NCl$ | 1/1.5 | 110 | 35 | 69:14:13 |
| 7 | $PdCl_2(MeCN)_2$ | $K_2CO_3$ | $BnBu_3NCl$ | 1/2 | 110 | 40 | 77:15:8 |
| 8 | $PdCl_2(MeCN)_2$ | $K_2CO_3$ | $BnBu_3NCl$ | 1/1.5 | 70 | - | - |
| 9 | $PdCl_2(MeCN)_2$ | $K_2CO_3$ | $Bu_4NBr$ | 1/1.5 | 110 | 38 (29) | 78:11:11 |
| 10 | $PdCl_2(MeCN)_2$ | $K_2CO_3$ | $Bu_4NBr$ | 1/2 | 110 | 43 | 70:12:18 |
| 11 | $PdCl_2(MeCN)_2$ | $K_2CO_3$ | $Bu_4NBr$ | 1/1 | 110 | 31 | 80:10:10 |
| 12[c] | $PdCl_2(MeCN)_2$ | $K_2CO_3$ | $Bu_4NBr$ | 1/1.5 | 110 | 33 | 78:12:10 |
| **13** | **$PdCl_2(MeCN)_2$** | **$K_2CO_3$** | **$Bu_4NBr$** | **2/1** | **110** | **43 (38)** | **83:17:0** |
| 14 | $PdCl(C_3H_5)$dppb | KOAc | - | 1/1.5 | 150 | 6 | 69:31:0 |

[a] Unless otherwise stated, the reactions were carried out using **23** and **26a** with the ratio reported for each entries, $Pd_{cat}$ (5 mol %), ligand (10 mol %) (if any), base (2 equiv), PivOH (30 mol %), additive (if any) (20 mol %) in DMA (5 mL) for 48 h at 110 °C. [b] GLC yields. In parenthesis, isolated yields. [c] Reaction was carried out in the presence of 10 mol % $Pd(OAc)_2$.

We also tried to lower further the reaction temperature to 70 °C by using $BuBn_3NCl$ as phase transfer agent that could have favoured the solubility in these conditions. Unfortunately, the system resulted ineffective (entry 8, Table 9). Afterwards, among the two-phase transfer agents, we decided to keep going with the $Bu_4NBr$, that gave a better yield and the best selectivity for compound **36a**. We changed again the **23**/**26a** ratio and we found that when this was 1/1, the yield of the 5-arylated-pyrazole **36a** resulted to be 31 % with a selectivity of 80 % (entry 11, Table 9), while when it was 2/1 the yield of **36a** reached the 43 % with a regioselectivity of 83 % and no detection of diarylated product **38a** (entry 13, Table 9). Moreover, the addition of a double amount of $PdCl_2(MeCN)_2$ did not contribute to an increase of the chemical yield of derivative **36a** (entry 12, Table 9).

Finally, with the recent publication of Doucet's work on the palladium catalyzed direct arylation of pyrazoles with aryl bromides in hands,[60] we wanted to verify if the conditions they reported for 1-phenyl-1*H*-pyrazole (**23**) could be suitable for our substrate (see Scheme 32). Hence, 1 mmol of **23** and 1.5 equiv of 4-bromotoluene (**26a**) reacted in the presence of 2 mol % $PdCl(C_3H_5)$dppb as the catalyst that we previously synthesized in our lab. Then, 2 mmol of KOAc were also added in DMA and the reaction was carried out at 150 °C for 72 h. Nevertheless, we got the product **36a** in only 6 % chemical yield (entry 14, Table 9).
Therefore, the conditions we finally obtained from this long screening involved 2 equiv of 1-phenyl-1*H*-pyrazole (**23**), 1 equiv of aryl bromide (**26a**), 5 mol % $PdCl_2(MeCN)_2$, 30 mol % PivOH, 20 mol % $Bu_4NBr$, 2 equiv $K_2CO_3$ in DMA at 110 °C (Scheme 41).




**Scheme 41**

A scope of the reaction will be planned in the future in order to verify the viability of our new procedure, when *ortho*- and *para*-substituted electron-rich and electron-poor aryl bromides are used with several 1-aryl-1*H*-pyrazoles.

## 5. Conclusions.

In conclusion, we have successfully established a new and versatile procedure for the regioselective synthesis of 5-aryl-1-methyl-1*H*-pyrazoles (**21**) by using a Pd-catalyzed direct arylation reaction promoted by $Bu_4NOAc$ as base. In particular, we showed that a large number of 5-aryl-1-methyl-1*H*-pyrazoles (**21**) can be prepared by reacting 1 equiv of the heterocycle with 1.5 equiv of the aryl bromide of interest (**26**) in the presence of $Bu_4NOAc$ as base in DMA at 70 °C.

Then, with our pleasure, we found that the reaction conditions developed for the synthesis of 5-aryl-1-methyl-pyrazoles (**21**) could be used for the preparation of 5-aryl-

oxazoles (**30**), 5-aryl-thiazoles (**31**) and 5-aryl-1-methyl-1*H*-imidazoles (**32**). More specifically, we synthesizes a small library of 5-aryl-oxazoles (**30**) and 5-aryl-thiazoles (**31**) by using the reaction conditions promoted by $Bu_4NOAc$ and performing the reactions at 70 °C; on the other hand, we were also able to prepared several 5-aryl-1-methyl-1*H*-imidazoles (**32**) by using this new methodology, carrying out the reactions at 110 °C.

We have also hypothesized a possible mechanism that involves a CMD pathway for the Pd-catalyzed direct arylation reaction of azoles promoted by $Bu_4NOAc$. We attributed the efficiency and the very high regioselectivity demonstrated by this ligand-free protocol at mild reaction temperatures to the efficacy of $Bu_4NOAc$ in promoting such ligand-free direct arylations, for the well-known ability of ammonium salts to act as metal stabilizers in the absence of phosphanes or other ancillary ligands and also by the fact that organic ionic bases have good solubility and are fully ionized in organic solvents.

Finally, we undertook a preliminary screening for the development of a regioselective procedure for the palladium-catalyzed direct arylation of 1-phenyl-1*H*-pyrazole (**23**) with aryl bromides. We chose the reaction between **23** and 4-bromotoluene (**26a**) as a model reaction and we found that they can react in the presence of $PdCl_2(MeCN)_2$ as catalyst precursor, pivalic acid and $Bu_4NBr$ as additives, with $K_2CO_3$ as the base in DMA at 110 °C with a selectivity of the 5-aryl-1*H*-pyrazole **36a** of 83 %, with a chemical yield of 43 %.

# CHAPTER 2

## *Applications of the palladium-catalyzed regioselective direct arylation of azoles with aryl bromides promoted by $Bu_4NOAc$*

As a consequence of the development of the new procedure for the direct arylation of pyrazole and the three 1,3-azoles promoted by $Bu_4NOAc$, we decided to focus our attention also on the possible applications of this methodology to the synthesis of useful organic materials. However, in order to achieve these purposes we had also to take into account other synthetic procedures, in particular the methodology that our research group previously reported for the arylation of 1,3-azoles at the C-2 position.

## 1. One-pot synthesis of bioactive Balsoxin (39a) and Texaline (39b).[62]

We started our purpose with the synthesis of two bioactive compounds, balsoxin (**39a**) and texaline (**39b**), (Figure 7).

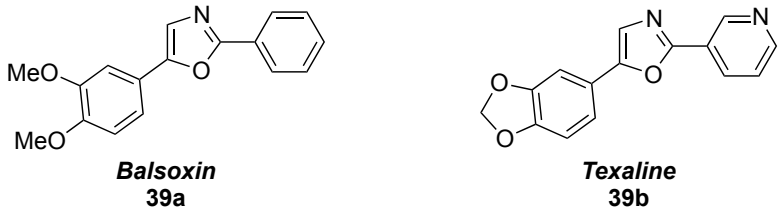
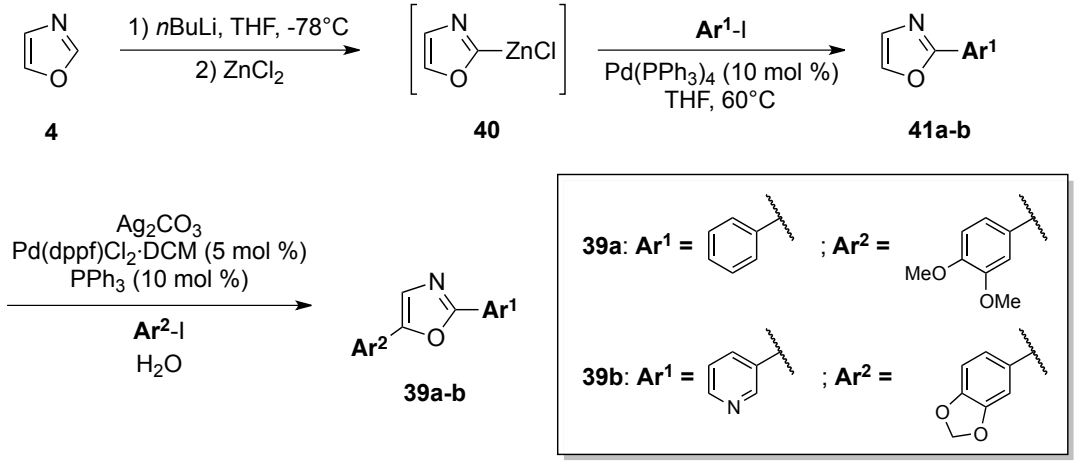



**Figure 7**: Structures of balsoxin (**39a**) and texaline (**39b**).

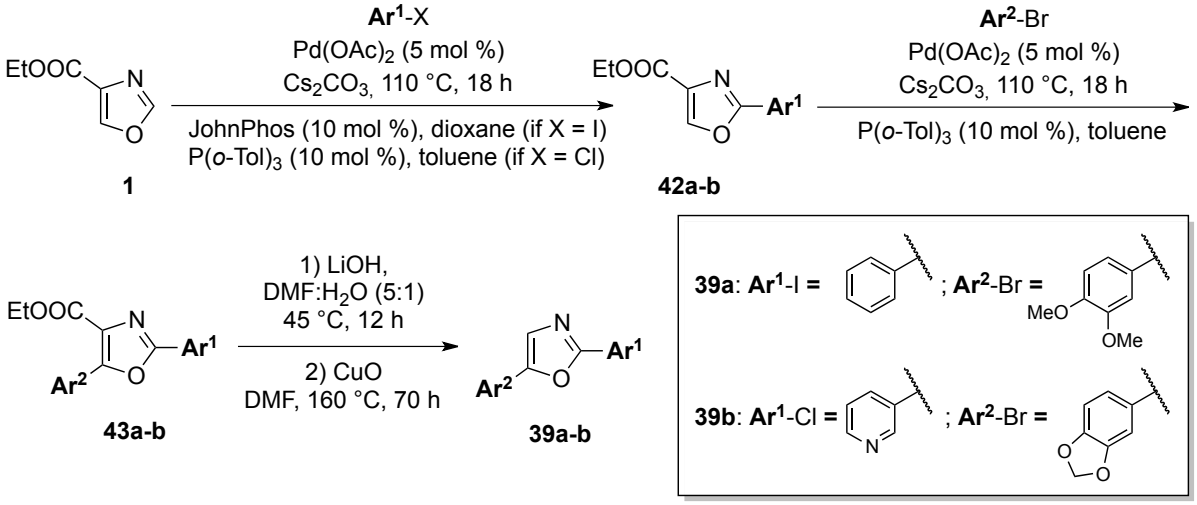
Balsoxin and texaline are natural products isolated from the plant species *Amyris* in the Caribbean, [79] with texaline reported to have antimycrobacterial activity against *Mycrobacterium tuberculosis*, *M. avium* and *M. kansasii*.[80] These molecules are often used as classical models of application of new procedures for direct arylation of azoles.[14c,31,81] For example, in 2008 Greaney and co-workers reported a three-steps synthesis of **39a** and **39b** in which they proposed, for the last step, a new Pd-catalyzed methodology for the C-5 arylation of the 2-arylate oxazoles carried out in water (Scheme 42).[81a] In the first reaction, they functionalized the 2-position of the oxazole (**4**) using a Negishi cross-coupling protocol developed by Reeder and co-workers.[82] Following lithiation with *n*BuLi at -78 °C, solid $ZnCl_2$ was added to form the zincate **40**, which subsequently underwent Pd-catalyzed coupling with the appropriate aryl iodides at 60 °C to give the 2-arylated products **41**. Then,

they reacted compounds **41** with the suitable aryl iodides that yielded balsoxin (**39a**) and texaline (**39b**) in 68 and 58 %, respectively (Scheme 42).




**Scheme 42**

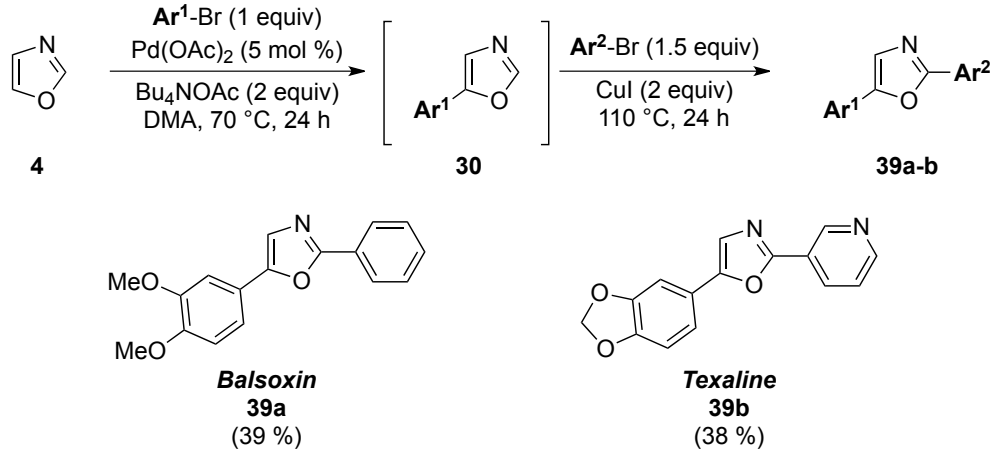
Another example was reported by Hoarau's group that used the methodology showed in Scheme 7 of **Introduction**.[31] They proposed a three-steps procedure to synthesize balsoxin (**39a**) and texaline (**39b**) starting from the ethyl oxazole-4-carboxylate (**1**) that reacted with the appropriate aryl halides and gave the 2-arylated oxazoles **42**. These compounds reacted in the second step with the respective aryl bromides to yield the 2,5-diarylated products **43**. The final products balsoxin (**39a**) and texaline (**39b**) were obtained after decarboxylation reaction with an overall yield of 43 and 62 %, respectively (Scheme 43).[31]




**Scheme 43**

Therefore, since the two compounds are 2,5-diaryl substituted oxazoles, we argued that it might be possible to achieve the one-pot sequential 5- and 2-diarylation of 1,3-azoles with different aryl bromides by pairing the C-5 arylation procedure promoted by $Bu_4NOAc$ for the first step with the protocol for the direct C-2 arylation mediated by CuI, previously reported by Bellina and co-workers, for the second one.[23c-d,37]

To probe the feasibility of this approach, we attempted the one-pot synthesis of the two bioactive natural 2,5-diaryloxazoles, balsoxin (**39a**) and texaline (**39b**) (Scheme 44).




**Scheme 44**

In the first step, 1.1 equiv of oxazole (**4**) were treated with 1 equiv of 4-bromo-1,2-dimethoxybenzene (**26t**) or 5-bromobenzo[*d*][1,3]dioxole (**26u**) at 70 °C in DMA in the presence of $Pd(OAc)_2$ as catalyst and $Bu_4NOAc$ as base. The reactions were carried out for 24 h. After that, without any purification of the intermediates **30**, we added 1.5 equiv of bromobenzene (**26r**) or 3-bromopyridine (**26n**) along with 2 equiv of CuI. The use of 5 mol % $Pd(OAc)_2$ and 2 equiv of $Bu_4NOAc$ as initial quantities proved to be effective for the sequential reactions, and no additional catalyst or base was necessary in the second step. After 24 h at 110 °C, the required balsoxin (**39a**) and texaline (**39b**) were isolated in 39 and 38 % yield, respectively (Scheme 44).

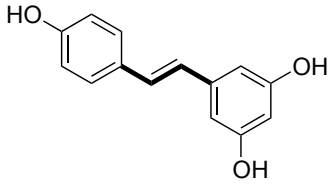
The analysis $^1$H-NMR, $^{13}$C-NMR and GC-MS confirmed the structure of compounds **39**.

It is noteworthy that the second step of the procedure was carried out at only 110 °C instead of 140 °C, that is the temperature generally used in the Pd/Cu catalyzed direct arylation of 1,3-azoles.[23c-d,37]

## 2. One pot synthesis of resveratrol derivatives (48).

Once we found that it was possible to achieve the one-pot sequential 5- and 2-diarylation of oxazole (**4**), we dedicated part of our efforts in the synthesis of imidazole analogues of resveratrol (**44**).

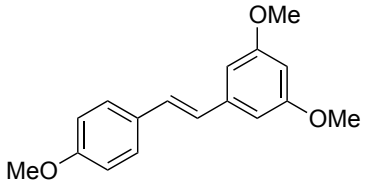
Resveratrol or ((*E*)-5-(4-hydroxystyryl)benzene-1,3-diole (**44**) is a natural fitoalexine that shows beneficial effects on the human health, including anti-oxidant,[83] anti-obesity,[84] anti-viral,[85] anti-diabetic,[86] anti-inflammatory,[87] cardiovascular protective[88] and anti-tumoral[89] effects based on *in vitro* and animal models[90,91] (Figure 8). It is produced by at least 72 species of plants distributed among 31 genera and 12 families in response to stress, injury, fungal infection, and UV irradiation.[89a,90] Anyway, the problem to use resveratrol is connected to its easy degradation after it has been assumed, for instance, with the nutrition. In fact, many biological matrices convert *in vivo* the hydroxy groups into derivatives that are rapidly metabolized, or the double bond may undergo reduction or stereomutation from *trans* to *cis* isomer.




***Resveratrol***
**44**

**Figure 8**: Structure of resveratrol (**44**).

A method to avoid these problems could be to convert resveratrol in its respective analogues. One of the simplest synthetic strategies to get resveratrol analogues is the conversion of one or more hydroxy groups in the respective methylethers. This can obviate the formation *in vivo* of conjugates and enhance the biological availability of the molecule. For instance, the 3,5,4'-trimethoxy-stylbene (**45**) (Figure 9) is one of the analogues that has been recently prepared and tested on the cell line HL-60 of human promyelocytic leukemia and has shown cytotoxic activity higher than resveratrol.[92]

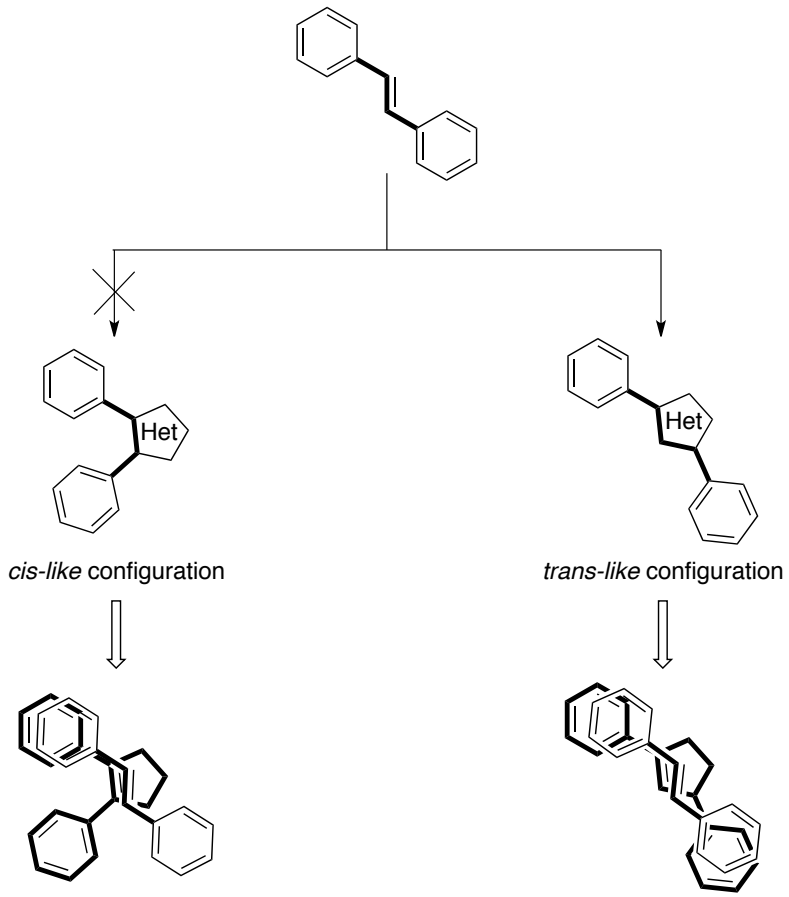



**45**

**Figure 9**: 3,5,4'-Trimethoxy-stylbene (**45**), a resveratrol analogues with protected hydroxy groups.

Otherwise, analogues in which the double bond is substituted by unsaturated systems more resistant to reduction, or in which the double bond is embedded in stable cyclic structure has been reported in literature. Anyway, the *trans* configuration of the two aromatic moiety was always kept, being fundamental for the maintenance of the biological activity.[93]

In order to avoid the chemical modification of the *trans* double bond, we decided to prepare cyclic analogues of resveratrol (**44**), in which this stereodefined bond has been embedded into an imidazolic nucleus (Scheme 45).[94]




**Scheme 45**

In particular, our research group focused the attention on the synthesis of 1,4-diaryl-1*H*-imidazoles (**46**), 2,4-diaryl-1-methyl-1*H*-imidazoles (**47**) and 2,5-diaryl-1-methyl-1*H*-imidazoles (**48**) (Figure 10). In these three classes of compounds, the aryl groups are linked in a 1,3-fashion, in order to keep the required *trans* geometry.[94]

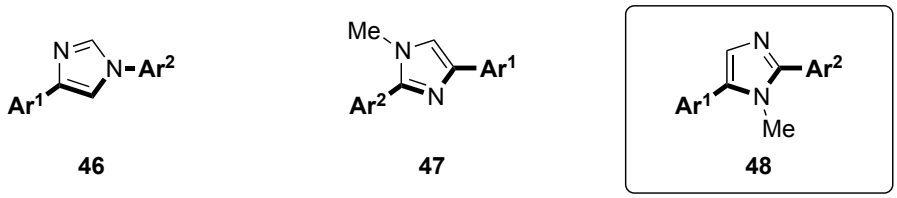
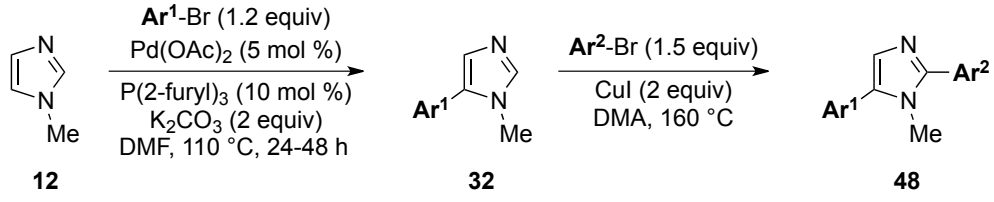



**Figure 10**: Structures of 1,4-diaryl-1*H*-imidazoles (**46**), 2,4-diaryl-1-methyl-1*H*-imidazoles (**47**) and 2,5-diaryl-1-methyl-1*H*-imidazoles (**48**).

As regard this Ph.D. work, we decided to focus our synthetic efforts on compounds **48** (Figure 10) and then to evaluate their biological activity.

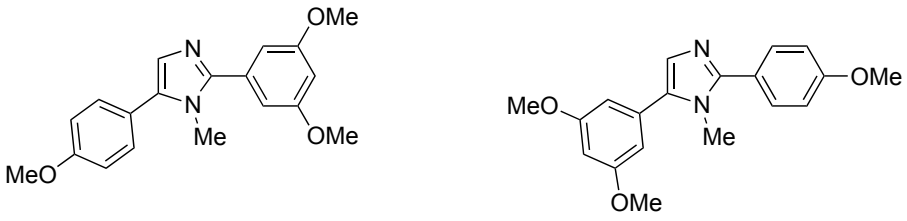
The 2,5-diaryl-1-methyl-1*H*-imidazoles (**48**) were already synthesized in our laboratory by using a simple two-steps procedure starting from 1-methyl-1*H*-imidazole (**12**) (Scheme 46). The first reaction consisted in a C-5 direct arylation of **12** with aryl bromides that, as reported by our research group in 2008, involved the use of $Pd(OAc)_2$ and $P(2\text{-furyl})_3$ as catalytic system, $K_2CO_3$ as base, DMA as solvent, at a reaction temperature of 110 °C.[50c] The required 2,5-diarylated imidazoles **48** were then obtained by base-free and ligandless C-2 direct arylation of the prepared 5-arylated imidazoles **32** with an aryl bromide, in the presence of a Pd/Cu catalyst system at 160 °C (Scheme 46).[23c-d,37]




**Scheme 46**

In light of the fact that we succeeded in the synthesis of balsoxin (**39a**) and texaline (**39b**) with a one-pot approach, by applying the reaction conditions promoted by $Bu_4NOAc$, we decided also to try a one-pot sequential C-5 and C-2 diarylation sequence starting from 1-methyl-1*H*-imidazole (**12**), in order to synthesize the resveratrol analogues. In this way, we

would have shorted the preparation time and, more likely, enhanced the isolated yield by avoiding one of the two purification steps (see paragraph 1 of **Chapter 2**).
In particular, the resveratrol analogues **48a-b** that have been prepared are reported in Figure 11.

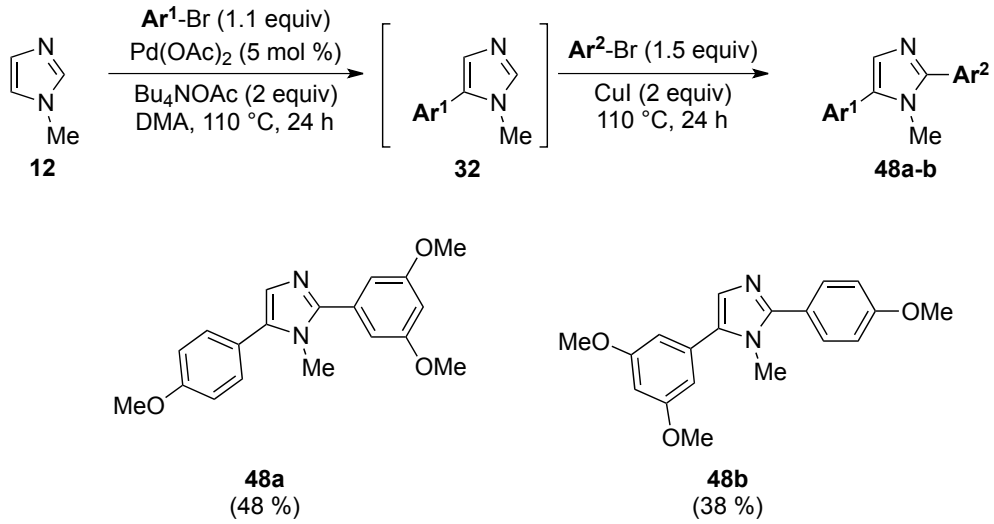



**48a** **48b**

**Figure 11**: 2,5-Diaryl-1-methyl-1*H*-imidazoles **48**: resveratrol analogues.

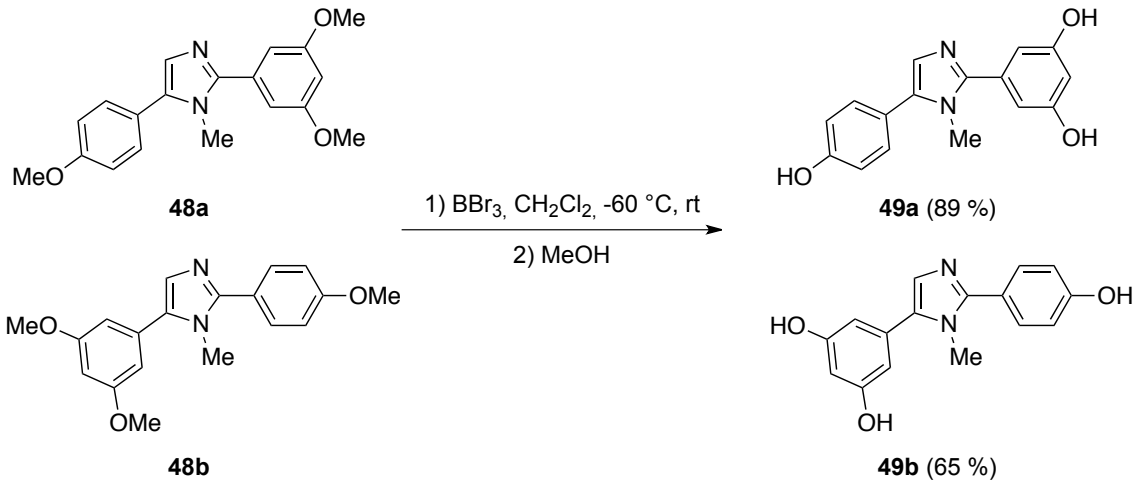
The approach we used was the same adopted for the synthesis of balsoxin and texaline, as reported in paragraph 1 of this chapter. We started the synthesis by using the reaction conditions developed during this Ph.D. work. In details, 1 equiv of imidazole **12** was treated with 1.1 equiv of 4-bromoanisole (**26b**) or 5-bromo-1,3-dimethoxy-benzene (**26v**) at 110 °C in DMA in the presence of $Pd(OAc)_2$ as catalyst and $Bu_4NOAc$ as base. The reactions were carried out until the disappearance of the precursors. After this time, without any purification of the intermediates **32**, 1.5 equiv of 5-bromo-1,3-dimethoxy-benzene (**26v**) or 4-bromoanisole (**26b**) were added along with 2 equiv of CuI. The use of 5 mol % $Pd(OAc)_2$ and 2 equiv of $Bu_4NOAc$ as initial quantities proved again to be effective for the sequential reactions, and no additional catalyst or base was necessary in the second step. After 24 h at 110 °C, the required resveratrol analogues **48a** and **48b** were isolated in 48 and 38 % yield, respectively (Scheme 47). The analysis $^{1}$H-NMR, $^{13}$C-NMR and GC-MS confirmed the structure of compounds **48**.

The yields obtained with this one-pot approach resulted better than those resulting from the application of the two-steps method shown in Scheme 46. This last procedure led to compounds **48a** and **48b** in 21 and 24 % of overall yields, respectively.[94] Therefore, our better results confirmed the efficiency of the one-pot methodology.




**Scheme 47**

Finally, compounds **48** were unprotected to give resveratrol analogues **49**. To a solution of derivatives **48** in $CH_2Cl_2$, 6.75 equiv of $BBr_3$ in $CH_2Cl_2$ were added at -60 °C. Then the mixtures obtained were heated and left at room temperature for 48 h. The resveratrol analogues **49a-b** were isolated by crystallization after work-up in 80 and 65 % of yield (Scheme 48).




**Scheme 48**

Compounds **48a** and **49a** and others prepared in our laboratory by using the two-steps procedure, with the $Pd(OAc)_2$ / P(2-furyl)$_3$ system (Figure 12, compounds **48c-e**), were sent to the *National Cancer Institute* (NCI, Bethesda, USA).

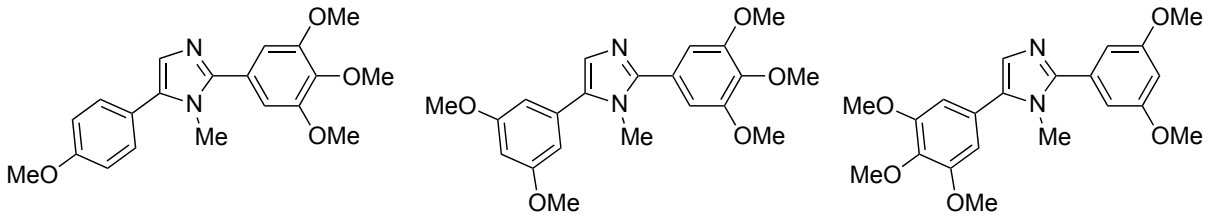



**Figure 12**: Structures of compounds **48c**, **48d** and **48e**.

They verified the cytotoxicity of molecules **48** and **49** *in vitro* applying them to their 60 human tumoral cell line panel representing leukemia, melanoma, cancer of the lung, colon, brain, ovary, breast, prostate and kidney.[94,95] Compounds **48** and **49** were tested initially at a single high dose ($10^{-5}$ M) in the full NCI 60 cell panel. Then, those-ones that satisfied pre-determined threshold inhibition criteria in a minimum number of cell lines should have been advanced to the full 5-dose assay. The threshold inhibition criteria for progression to the 5-dose screen was selected to efficiently capture compounds with anti-proliferative activity based on careful analysis of historical DTP screening data (the threshold criteria is periodically updated by NCI as additional data becomes available).

The results of the one-dose assay are reported in Figure 13 as the mean graph mid-point (MGM) values, which are based on a calculation of the percent average of growth of the treated cells compared to the untreated control cells. Results from Figure 13 indicate that compound **48a** was found to be the most cytotoxic against the NCI panel, but none of these compounds was further evaluated in the following 5-doses assay. It is interesting to observe that the only presence of free phenolic groups typical of **44** does not secure the bioactivity of these analogues. In fact, as demonstrated by the results for compound **49a**, the presence of free hydroxy groups may also deplete the activity when compared to that displayed by the corresponding *O*-methylated analogue **48a**.

The data summarized in Figure 14 allow a in-depth analysis of the one-dose screening results, and put better in evidence the fact that **48a** is the most active compound among the selected five derivatives, against all the nine different types of human tumors.

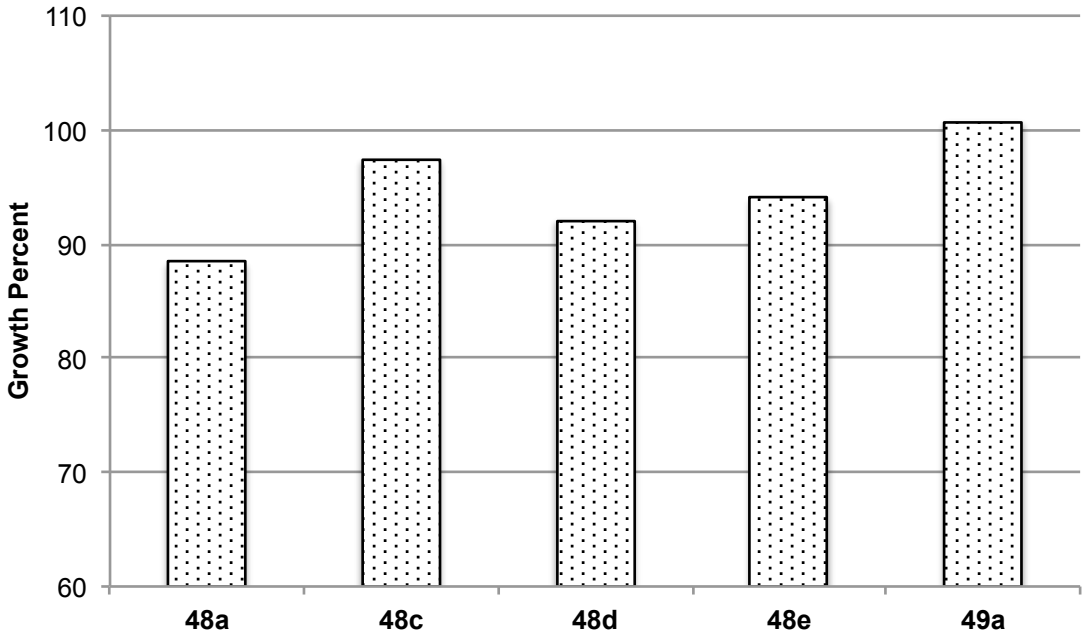



**Figure 13**: NCI 60 human tumor cell line screening (one dose): mean growth (%) for all tested cell lines.

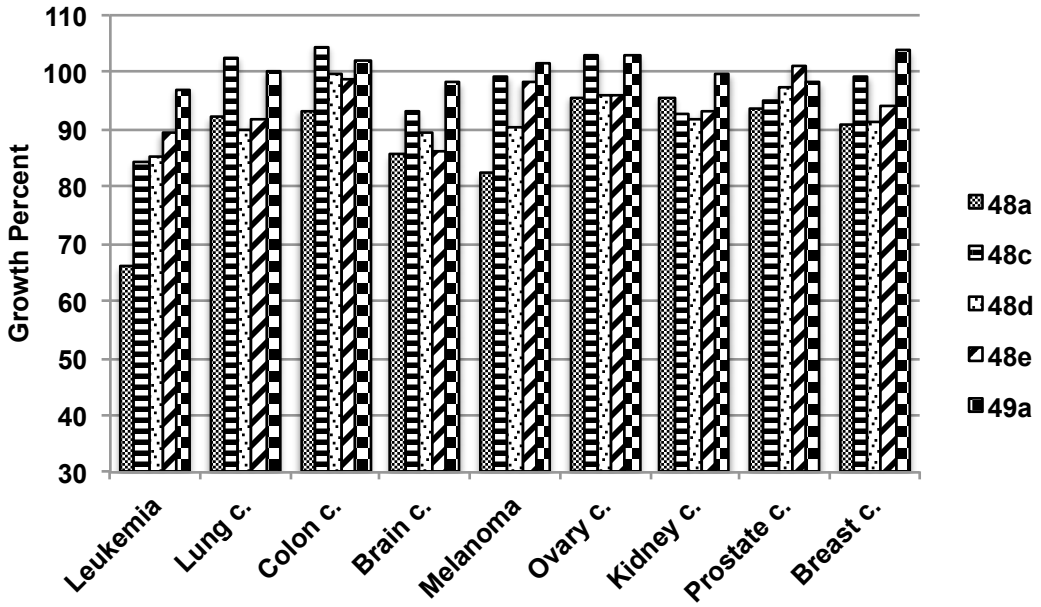
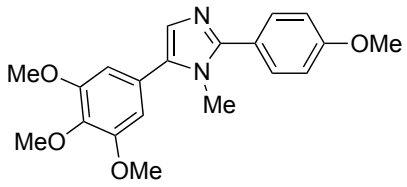



**Figure 14**: NCI 60 human tumor cell lines screening (one dose): mean values (%) for the nine tumor panels.

All the compounds we sent showed growth-inhibition of one or more cell line.

Moreover, compound **49b** resulted a NQO2[96] inhibitor *in vitro*, as confirmed by Professor Ian Stratford of University of Manchester. He evaluated the ability of resveratrol analogues **48a-e**, **49a-b** and **48f** (see Figure 15) to inhibit the NQO2, in order to identify a

pharmacological tool useful to study the physiological role of this protein in the tumoral cells. Compound **49b** showed the ability to inhibit NQO2 at nano-molar concentrations. The $IC_{50}$ value for **49b** was 613.4 nM ± 1.4 while resveratrol (**44**) showed $IC_{50}$ 891 nM ± 1.9. It is noteworthy that the analogues containing methoxy groups did not showed any activity toward NQO2.[94]




**48f**

**Figure 15**: Structure of **48f**.

## 3. Synthesis and optical properties of fluorophores 50, 51 and 52.

Another application of our methodology was the synthesis of fluorophores, that are fluorescent molecular entities[97] and show a wide range of uses from technology to chemical and biological analysis. This is due to the properties of the fluorescence emission, which are strongly influenced by structural modifications and surrounding media, allowing a precise and selective tuning and monitoring thereof. The properties usually observed are spectrum shape, peak position, quantum yield and lifetime; more specific techniques make use of other properties, such as quenching, fluorescence anisotropy and excimer formation.[98]

Especially the dependence of the fluorescence emission from the micro-environment around the fluorophores (type of solution, presence of other interacting species, polymer surfaces, crystalline structures) and any possible interaction of the excited species therewith is largely employed to get information on local parameters: physical, structural or chemical. In this context it is used the term fluorescent probe (or indicator in the case of chemical parameters like pH and the concentration of a species). When the fluorophores is covalently bound to a target molecule, and the aim is to visualize or localize such species, the term fluorescent label or tracer is used. Fluorescent probes and tracers provide a wealth of information on various subjects: polymers, solid surfaces, surfactant solutions, biological membranes, vesicles, proteins, nucleic acids and living cells.[98] The most typical applications of fluorescent probes and tracers are: pH indicators, probes for polarity, molecular thermometers, pressure sensitive

paints, molecular sensors for ion and molecule recognition and autofluorescence and fluorescent labels in biology.

Fluorophores are largely used as probes and tracers, but there is also a wide range of applications in materials science. The so-called *push-pull* fluorophores are a particular class of compounds in this context. The "model" of *push-pull* compounds is a D-π-A fluorophore composed of a π-conjugated backbone end-capped with two different groups: a strong electron-donor group D (usually -OR or $-NR_2$ groups) and a strong electron-acceptor group A (usually -CN, -COR or $-CF_3$ groups) (Scheme 49). Polarizability and optical properties of these systems depend primarily on their chemical structure, in particular the electronic behaviour of the A and D groups and the nature and length of the π-linker.[4c]


**Scheme 49**: Typical structure of *push-pull* fluorophores.

This type of structure and functionalization allows intramolecular (or internal) charge transfer (ICT) between the D and the A moieties during electron transitions.[98,99] Excitation of the fluorophores induces the promotion of one electron from an orbital to another. If the initial and final orbitals are separated in space, condition reachable with *push-pull* fluorophores for the presence of the D and A groups, the electronic transition occurs with an almost instantaneous change in the dipole moment of the fluorophores. This causes a different range of responses of the system depending on the degree of polarity of the solvent employed. Furthermore, relaxation towards an ICT state can be accompanied by conformational changes of the fluorophore.

The D-π-A structure provides interesting advantages over other similar materials; first of all ease of synthesis and possibility to tune properties like absorption spectra, HOMO-LUMO levels and degree of ICT from proper choices of D-A couples, a π-skeleton and substitutions. Furthermore, they usually show chemical and thermal stability, good solubility in organic solvents and/or polymeric matrices and ease of chemical ligation to polymer support.[4c,100]

In the design of *push-pull* systems, great attention has been given to five- and six-membered heterocycles, used as suitable π-conjugated backbones. Heteroaromatic fluorophores with electron-donor and -acceptor architectures have attracted growing interest for both understanding of fundamental chemistry and physics and promising applications in

diverse fields, ranging from solar energy conversion,[100] to optoelectronic devices[101] and chromogenic materials.[102] The main advantages lie in their high chemical and thermal robustness, good solubility in common organic solvents and availability. Furthermore, heteroatoms can enhance the donor/acceptor character of the groups (playing the part of auxiliary donors or acceptors) and improve the overall polarizability of the chromophore.

Imidazole in particular has been studied as part of π-conjugated backbones. The role of imidazole in π-backbones and synthetic routes towards these systems have been recently reviewed by Bureš and Kulhánek.[4c] It possesses two nitrogen atoms of different electronic nature, has good characteristic of stability and can be easily synthesized and further functionalized at positions N-1, C-2, C-4 and C-5. Other azoles, like oxazole and thiazole, have similar properties and could thus be substitutes of imidazole. The most important factors that affect D-A interactions are the extent of electronic donation or attraction by the D/A groups (i.e. the strength of the groups), the length and electronic nature of the a π-linker and the fluorophores overall planarity, thus these are properties most often tuned to obtain the desired behaviour. The entire azole moiety may behave as an electron donor or acceptor depending on the D/A substitutions.

Our proposal in this Ph.D. work was to exploit again the methodologies developed for the transition metal catalyzed regioselective C-H functionalization of the azole nuclei (among which the procedure promoted by $Bu_4NOAc$), and to apply them to the construction of novel, previously difficulty accessible complex azole-based molecular structures. In particular, we focused our attention on the synthesis of unsymmetrical derivatives of structure **50**, **51** and **52** (Figure 16) and to characterize the main spectroscopic properties thereof.

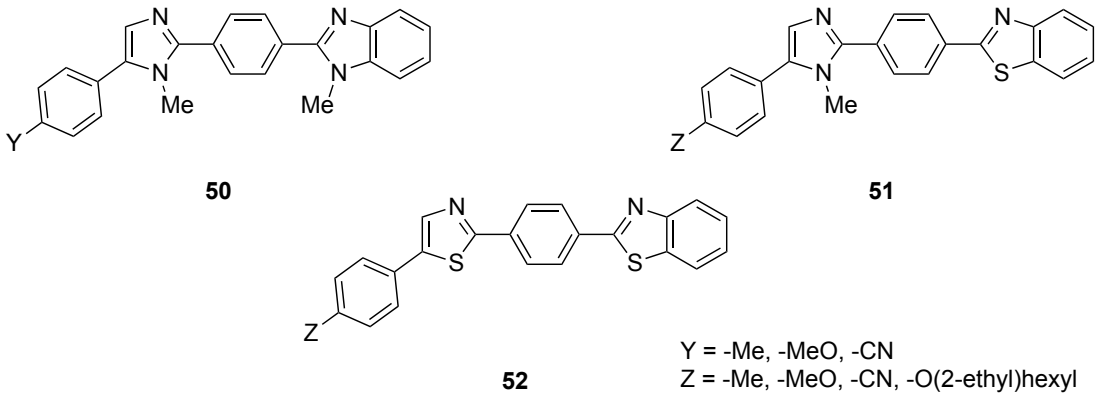



**Figure 16**: General structures of *push-pull* fluorophores **50**, **51** and **52**.

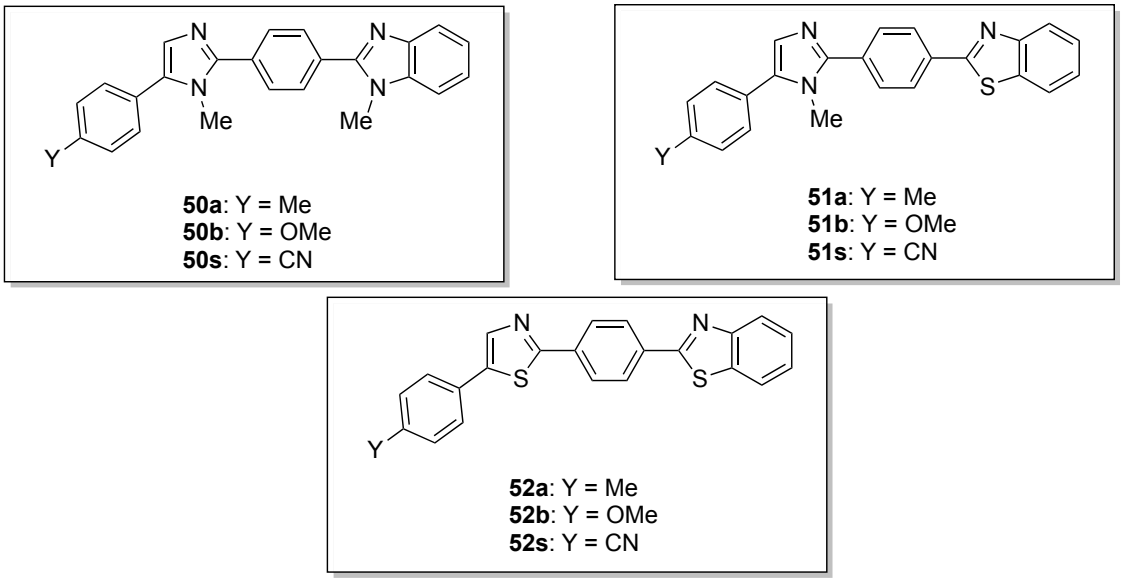
Azoles possess a wide range of interesting properties such as acid-base character, transition metal-binding activity, thermal and chemical robustness, and tautomerism. Imidazole and benzimidazole moieties have been utilized as suitable π-conjugated spacers in charge-transfer chromophores and useful DNA-binding probes for fluorescence microscopy and flow cytometry.[103]

To the best of our knowledge, no study has been published on unsymmetrically substituted *p*-phenylene-linked bis-imidazoles and thiazoles. Nevertheless, they seems promising in terms of optical properties, such as large Stokes shifts and high fluorescence quantum yields, as can be inferred by comparison with similar compounds already described in literature.[104] Moreover, unsymmetrical derivatives are likely to have enhanced ICT upon excitation in comparison to symmetrical compounds.

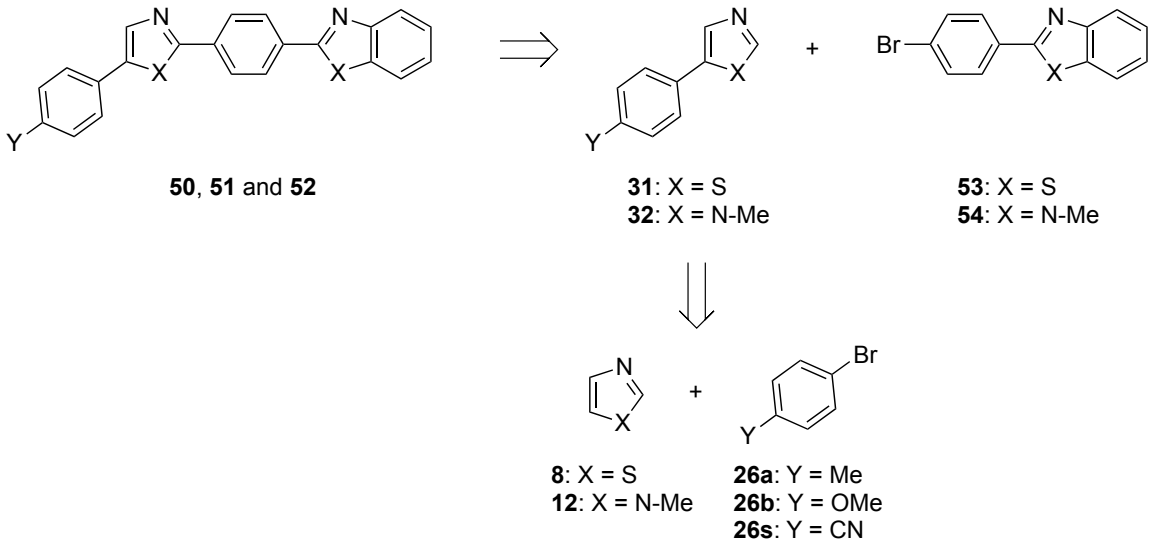
In our research group, we focused our attention on the synthesis of compounds **50**,[105] **51** and **52** (Scheme 50). We decided to modify the structures by changing the azoles in these three derivatives with the aim of evaluating the influence of the presence of two nitrogen atoms and of their partial or total replacement with sulphur on the physical and spectroscopic properties of the resulting fluorophores.

We selected a methyl, a methoxy and a cyano group as substituents on the terminal phenyl ring of compounds **50-52**, since they are typical examples of electron-neutral, electron-releasing and electron-withdrawing groups, respectively (Hammett's $\sigma_p$ constants:[106] CN +0.66; Me -0.17; MeO -0.27). For this reason, they are likely to be representative of other similar substituents as concerns both synthetic issues and spectroscopic properties. We focused on *p*-substituted derivatives to avoid synthetic complications due to the steric hindrance while keeping conjugation between the X group and the π-skeleton.

For the synthesis of the 5-aryl-thiazoles **31** and 5-aryl-imidazoles **32** (see Scheme 50) we used the palladium-catalyzed direct C5-H arylation reaction mediated by $Bu_4NOAc$ developed in this Ph.D. work.[62] We started from 1 equiv of thiazole (**8**) or 1-methyl-1*H*-imidazole (**12**) and 1.5 equiv of 4-bromotoluene (**26a**), 4-bromoanisole (**26b**) and 4-bromobenzonitrile (**26s**) that reacted in the presence of 2 equiv of $Bu_4NOAc$ in DMA at 70 and 110 °C (see **Chapter 1**). The 5-arylated products, **31** and **32**, were purified and isolated after flash chromatography with the yields reported in Table 10.




*Retrosynthetic pathway:*

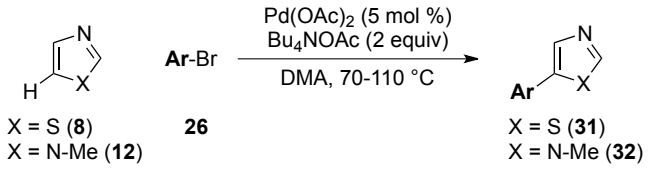


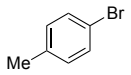
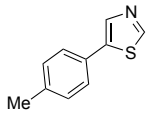
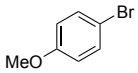
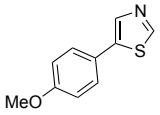
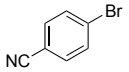
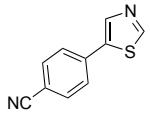
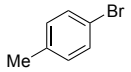
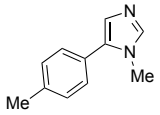
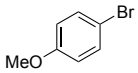
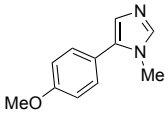
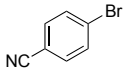
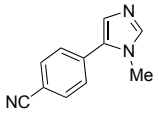

**Scheme 50**

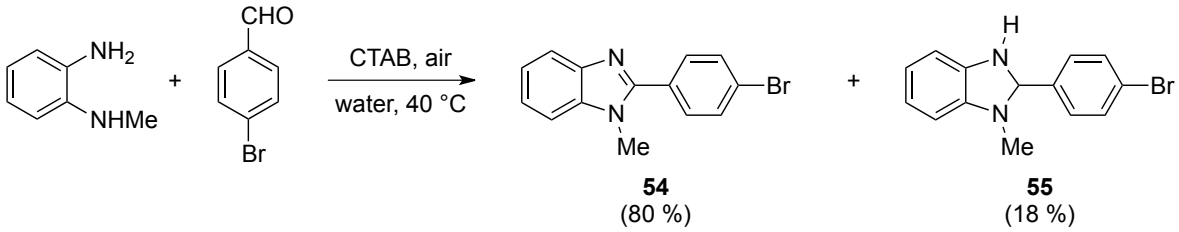
As regards the preparation of the brominated benzimidazole derivative **54**, which represents the common precursor to compounds **50**, we chose to follow the procedure described by Chakrabarty and co-workers[107] because of its simplicity, mild conditions, efficiency and atom economy. The authors used cetylpyridinium bromide (CPB) as a phase transfer catalyst, but we decided to replace it with cetyltrimethylammonium bromide (CTAB), which was available in our laboratory. The reaction so conducted failed to give reasonable amounts of pure product. Although the conversion was quantitative, it only afforded mixtures of the required compound **54** and of the non-aromatic benzimidazoline **55** (identified by the

means of $^1$H-NMR analyses) which could not be separated by fractional crystallization from common solvents (Scheme 51).

**Table 10**: Synthesis of 5-aryl-thiazoles (**31**) and 5-aryl-imidazoles (**32**) with the ligandless Pd-catalyzed direct C-5 arylation of thiazole (**8**) and 1-methyl-1*H*-imidazole (**12**) with aryl bromides **26a**, **26b** and **26s** promoted by $Bu_4NOAc$ (for the conditions, see **Chapter 1**).

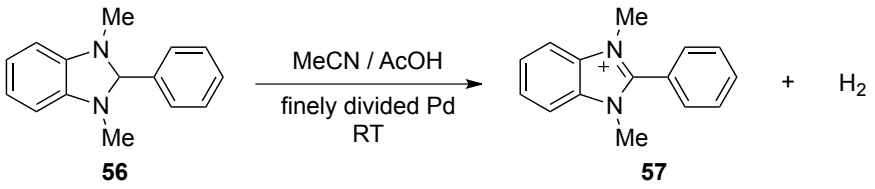



| Aryl bromide (26) | | 5-aryl-azole | | Reaction time (h) | Isolated yield (%) |
|---|---|---|---|---|---|
| **26a** |  | **31a** |  | 21 | 65 |
| **26b** |  | **31b** |  | 48 | 67 |
| **26s** |  | **31s** |  | 56 | 61 |
| **26a** |  | **32a** |  | 22 | 81 |
| **26b** |  | **32b** |  | 24 | 82 |
| **26s** |  | **32s** |  | 24 | 69 |




**Scheme 51**

It is worth mentioning that we were unable to distinguish **54** from **55** by TLC or by GLC. We guessed that **55** aromatizes to give the corresponding benzimidazole **54** at high temperatures (e.g. in the GLC injector) or under air on TLC plates. $^{1}$H-NMR spectroscopy was thus to be used to follow the progress of the reaction. The aromatization of benzimidazolines is indeed a thermodynamically favoured process. For example, 1,3-dimethyl-2-phenylbenzimidazoline (**56**) is known to spontaneously lose molecular hydrogen at room temperature in the presence of metallic Pd, $Pd(OAc)_2$ or Wilkinson's catalyst in protic solvents, to give the corresponding imidazolium salt (**57**), and it has also been investigated as an hydrogen storage medium (Scheme 52).[108]



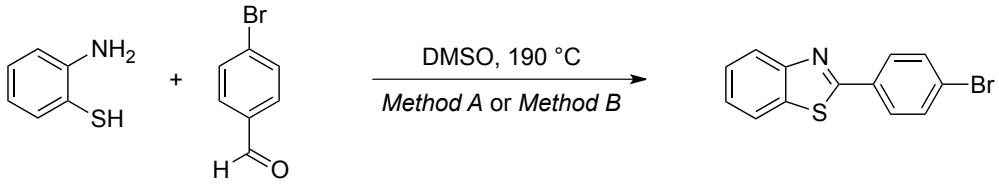

**56** **57**

**Scheme 52**

Since the separation of compound **54** from the byproduct **55** was neither easily accomplished nor desirable in terms of atom economy, we investigated the possibility of oxidizing the crude mixture of products to convert **55** in **54**.

Considering that Lin and Yang[109] obtained excellent yields of benzimidazoles by simple heating *o*-phenylenediamines with aldehydes in dioxane at 100 °C in the presence of air, we refluxed overnight the crude reaction mixture containing **54** and **55** dissolved in the minimum amount of dioxane sparged with air. The required product **54** was thus successfully recovered in 79 % yield after recrystallization from $CH_2Cl_2$/hexane.

On the other hand, as regards the 2-(4-bromophenyl)benzo[*d*]thiazole (**53**), which represents the most common precursor to compounds **51** and **52**, Qin and Yang in 2007[110] (*Method A*) and Ji in 2010[111] (*Method B*) reported two efficient protocols for its preparation trough a condensation of *o*-aminothiophenol (**58**) with *p*-bromobenzaldehyde (**59**) in DMSO (reflux at 190 °C). The two conditions differ for concentration and reaction time, as reported in Scheme 53.




**58** **59** **53**

*Method A*: concentration 2 mL / mmol, under Ar, 30 min., yield 92 %
*Method B*: concentration 30 mL / mmol, 2 h, yield 88 %.

**Scheme 53**

We chose to follow the method used by Ji for its simplicity and efficacy (*Method B*). The condensation was carried out with 5 mmol of **59**, 6.25 mmol of **58** and 150 mL of DMSO, at 190 °C for 2 h, that gave a 92 % isolated yield of **53**.

The products **53** and **54** were both characterized by $^{1}$H-NMR, $^{13}$C-NMR and GC-MS analysis.

Following the previously reported good results obtained by our research group with the C-2 arylation of imidazoles under base-free conditions in ligandless Pd-catalysis,[23c,37,50d] we also performed the reactions without any added base. Compounds **50**, **51** and **52** were purified and isolated after flash chromatography with the yields reported in Table 11.

Even though the temperature had to be raised to 160 °C, the reactions were remarkably clean and no difficulty removable byproducts were detected in the crude reaction mixture.

All the intermediates were characterized by NMR spectroscopy and mass spectrometry, with satisfactory results.

Emission and absorption have been obtained for compounds **50**, **51** and **52**. For compounds **50** the measurements were performed both in THF[105] and $CHCl_3$ while for **51** and **52** just in $CHCl_3$ because of solubility problems of these compounds in THF.

As regards the bis-imidazoles derivatives **50**, we can observe that, when the measurement are performed in THF, there is a little difference in the absorption spectrum between derivatives **50a** and **50b**, while **50s** is red-shifted of about 10 nm (Figure 17, Table 12). The emission spectrum becomes progressively red-shifted in order **50a** and **50b** and the Stokes shift increases in the same direction (95 nm and 103 nm, respectively). The cyano derivative **50s** displays a significantly lower Stokes shift (82 nm) in comparison with the other two compounds.

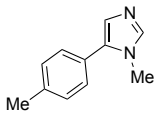
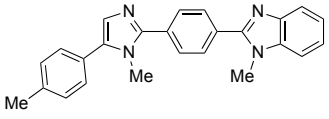
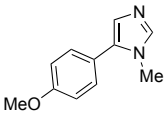
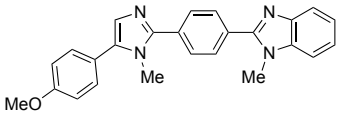
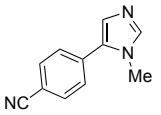
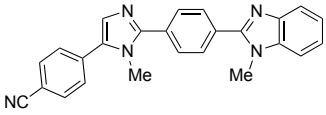
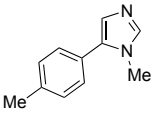
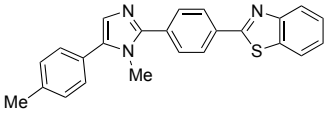
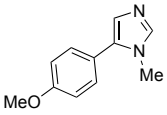
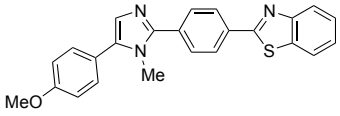
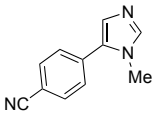
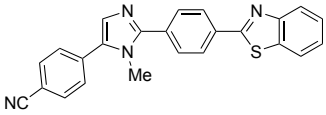
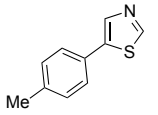
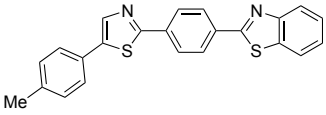
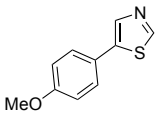
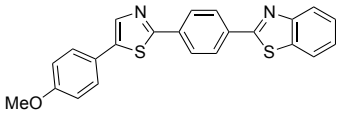
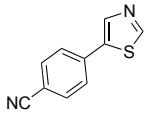
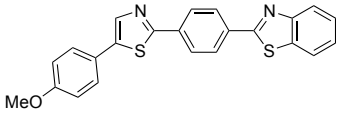
Absorption maximum wavelengths ($\lambda_{abs}$), fluorescence maximum wavelengths ($\lambda_{em}$), Stokes shifts (*S*), molar extinction coefficients ($\varepsilon$), fluorescence quantum yields ($\Phi_f$) and brightness values (*B*) for compounds **50** are summarized in Table 12.

**Table 11**: Synthesis of 2,5-diaryl-azoles **50**, **51** and **52** with the ligandless Pd/Cu-catalyzed direct C-2 arylation of 5-aryl-azoles **31** and **32** with aryl bromides **53** and **54**.


**32a**: Y = Me
**32b**: Y = OMe
**32c**: Y = CN

**43**

**38a**: Y = Me; (88 %)
**38b**: Y = MeO; (66 %)
**38s**: Y = CN; (42 %)

| 5-aryl-azole | | 2,5-diarylazole | | Isolated yield (%) |
|---|---|---|---|---|
| **32a** |  | **50a** |  | 88 |
| **32b** |  | **50b** |  | 66 |
| **32s** |  | **50s** |  | 42 |
| **32a** |  | **51a** |  | 66 |
| **32b** |  | **51b** |  | 66 |
| **32s** |  | **51s** |  | 83 |
| **31a** |  | **52a** |  | 25 |
| **31b** |  | **52b** |  | 72 |
| **31s** |  | **52s** |  | 53 |

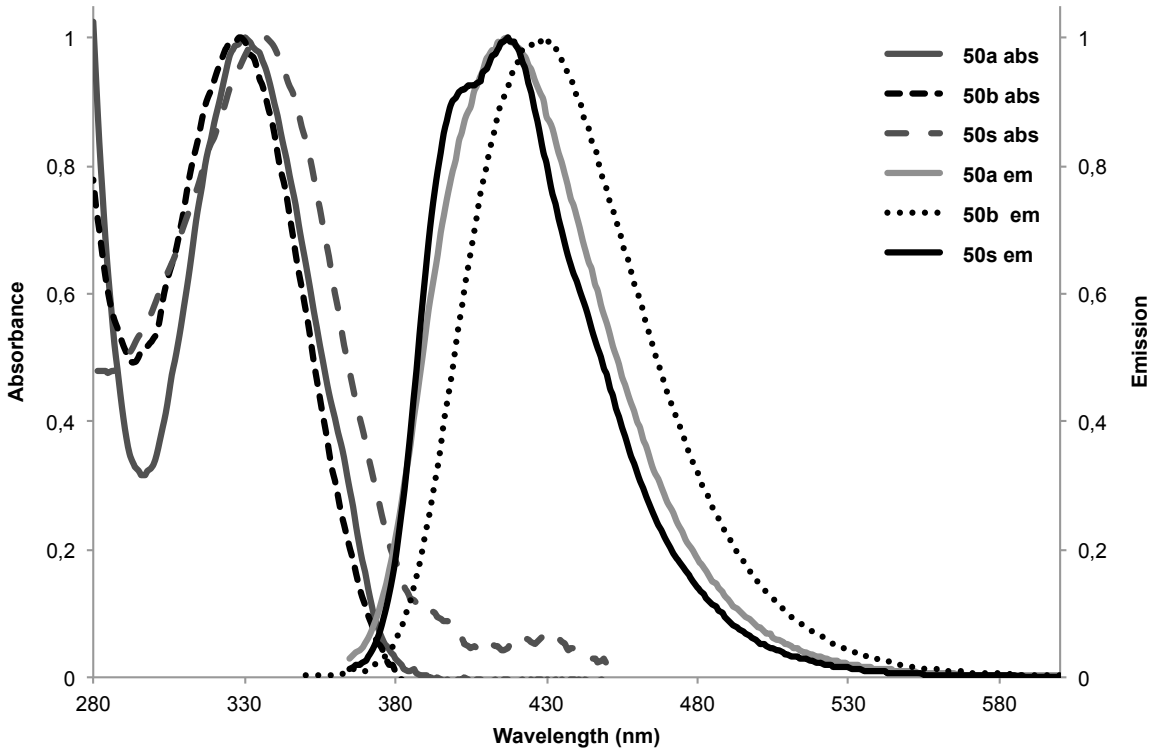



**Figure 17**: Absorbance (left) and emission (right) spectra of 5 μM compounds **50** solutions in THF; absorbance and emission values are normalized.

The same tendency for the absorption spectrum still remains when the values were determined in $CHCl_3$. The red-shift has again the order **50a**, **50b** and **50s** as we can see from Figure 18 and the **50s** resulted to be shifted of about 8 nm. The emission spectra also showed the same trend of THF analyses. Their three fluorescence maximum wavelengths are red-shifted again in order **50s**, **50a** and **50b**, even though in this case the values of **50s** and **50a** differ for only 1 nm. The Stokes shift increases in the direction: **50s**, **50a** and **50b** (87 nm, 100 nm and 107 nm, respectively) (Table 12).

The fluorescence quantum yields (Φ) of the three fluorophores were also determined in order to have a quantitative picture but, at the moment of the writing of this thesis, it could be detected only for THF (Table 12). All molecules resulted strong emitters with quantum yields comprised between 83 % and 90 %. The lowest Φ corresponds to **50s**, which is characterized by the lowest *S* (82 nm) and the highest overlapping between absorbance and emission (Figure 17). The product of ε and Φ was also calculated for making comparisons between the different fluorophores. This parameter is defined as the brightness (*B*) of the dye, which accounts for both the amount of light absorbed and the quantum efficiency of the fluorophore. *B* values of around 30000 $M^{-1}cm^{-1}$ are among the highest calculated for fluorophores in the

same wavelength region (for example, pyrene brightness = 32000 $M^{-1}cm^{-1}$).[112] As regards the quantum yields in $CHCl_3$ we are waiting the results very soon in order to complete the table of values.

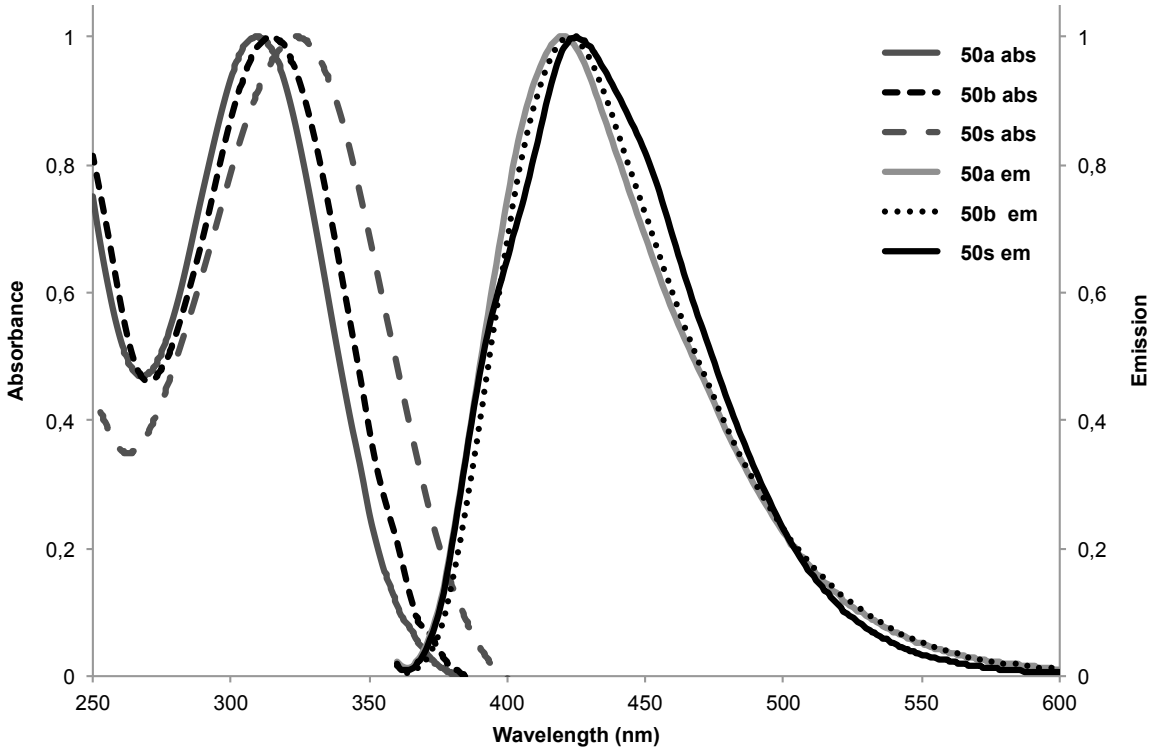



**Figure 18**: Absorbance (left) and emission (right) spectra of 5 μM compounds **50** solutions in $CHCl_3$; absorbance and emission values are normalized.

Absorption and emission spectra for the **51** and **52** series were measured in $CHCl_3$ as stated before (Figure 19 and Figure 20). Compounds **51** and **52** show a little difference in their absorption spectra between compounds of the same series, while there is a big difference in the position of the peak of absorbance between the two series **51** and **52**.

Compounds **51** display the maximum of absorbance around 345 nm while compounds **52** display the maximum at about 370 nm. We can also observe a big difference with the series of derivatives **50** that showed their maximum around 315 nm. Emission spectra are instead approximately in the same region, giving to compounds **51** a greater Stokes shift than **52** (see Table 12). A common trend can be observed in the two series on the positions of the emission maximum: **51b** and **52b** with the methoxy group on the phenyl substituent show the greater shifts, that decrease passing to **51a** and **52a** with the methyl group and then to **51s** and **52s**

with the cyano group. The electronic effect of these substituents on the Stokes shift is the similar effect observed for compounds **50** in THF.[105]

**Table 12**: Spectroscopic properties of fluorophores **50**, **51** and **52** dissolved in $CHCl_3$.

| | $\lambda_{abs}$ [nm] | ε [$M^{-1}cm^{-1}$] | $\lambda_{em}$ [nm] | *S* [nm] | $\Phi_f$[a] | *B* [$M^{-1}cm^{-1}$][b] |
|---|---|---|---|---|---|---|
| **50a** | 316 | 27600 | 416 | 100 | n.d.[c] | n.c.[d] |
| | 320[e] | 31000[e] | 415[e] | 95 | 0.88 | 27280 |
| **50b** | 320 | 24900 | 427 | 107 | n.d.[c] | n.c.[d] |
| | 325[e] | 36000[e] | 428[e] | 103 | 0.90 | 32400 |
| **50s** | 328 | 25300 | 415 | 87 | n.d.[c] | n.c.[d] |
| | 335[e] | 39000[e] | 397[e] | 82 | 0.83 | 32370 |
| **51a** | 342 | 32000 | 442 | 100 | 0.81 | 25920 |
| **51b** | 345 | 32000 | 457 | 112 | 0.90 | 28800 |
| **51s** | 343 | 42000 | 426 | 83 | 0.80 | 33600 |
| **52a** | 367 | 43000 | 443 | 76 | 0.59 | 25370 |
| **52b** | 372 | 38800 | 460 | 88 | 0.55 | 21340 |
| **52s** | 372 | 47500 | 436 | 64 | 0.61 | 28975 |

[a] Fluorescence quantum yield (Φ) was determined relative to quinine sulphate in 0.1 M $H_2SO_4$ (Φ = 0.54). [b] The brightness (*B*) values of fluorophores were calculated as the product of the absorption coefficient ε and Φ. [c] Φ values in $CHCl_3$ not detected. [d] *B* values in $CHCl_3$ not calculated. [e] Absorbance, emission and ε values were determined in THF. For compounds **51** and **52** the values were determined only in $CHCl_3$ because of solubility problems in THF.

From Table 12 it emerges that compounds **51** possess higher quantum yields with bigger Stokes shifts than **52**, but generally lower molar extinction coefficients. The lower quantum yields of compounds **52** may be ascribed to the "heavy atom effect": it is well known that the presence of heavy atoms in aromatic molecules results in fluorescence quenching, making non-radiative relaxation pathways easier, and this may be the effect of the additional sulphur atom.[98]

Compounds **50** showed Stokes shifts, molar extinction coefficients and quantum yields comparable with those obtained for compounds **51**. However, spectra of compounds **51** are slightly red-shifted compared to those of compounds **50**.[105]

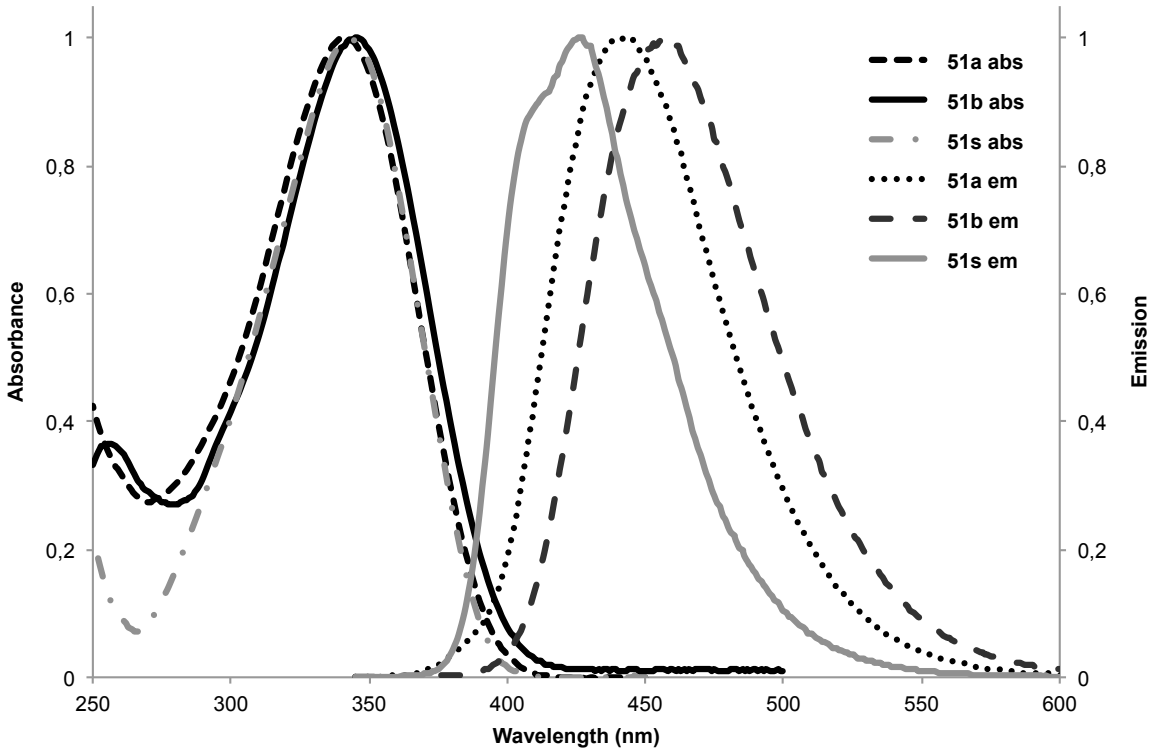



**Figure 19**: Absorbance (left) and emission (right) spectra of 5 μM compounds **51** solutions in $CHCl_3$; absorbance and emission values are normalized.

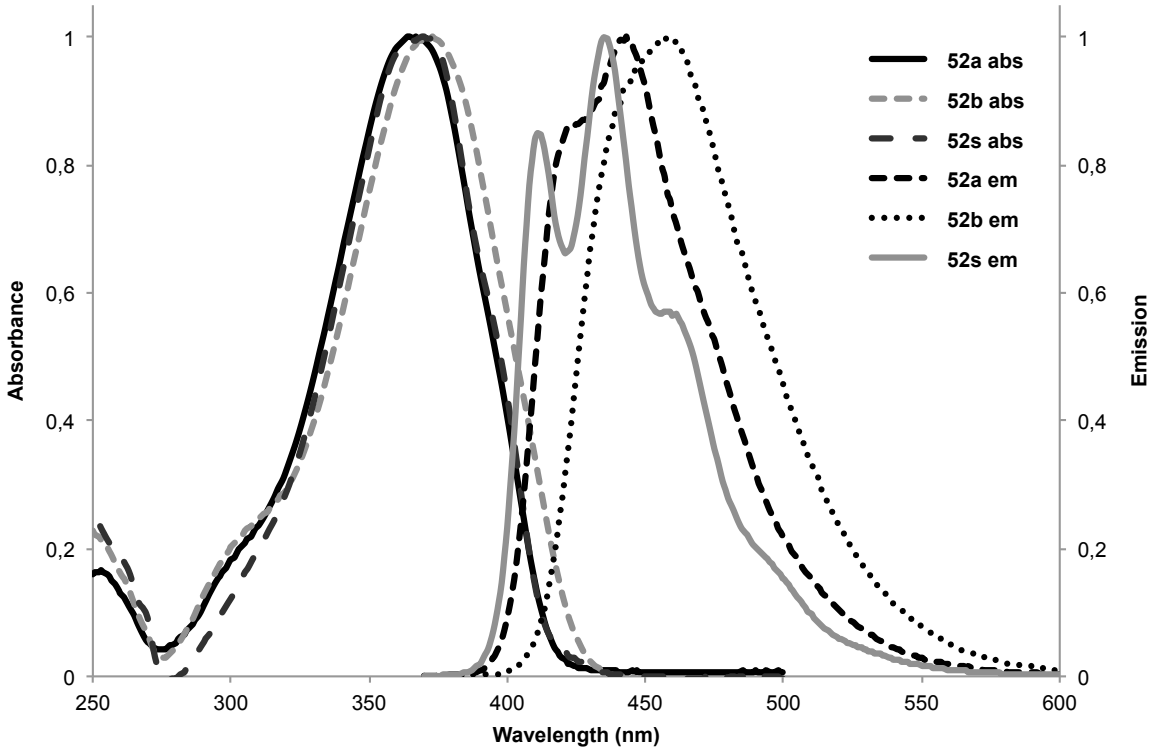
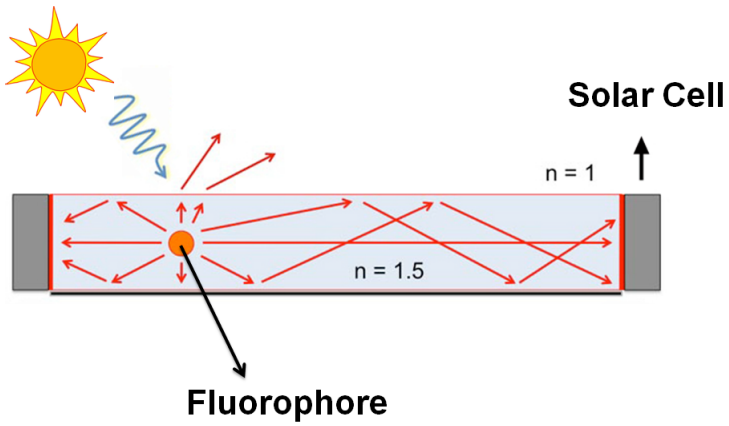



**Figure 20**: Absorbance (left) and emission (right) spectra of 5 μM compounds **52** solutions in $CHCl_3$; absorbance and emission values are normalized.

The idea of designing fluorophores of structure **50-52** was directed in the prospective of improving the characteristic of standard photovoltaic (PV) systems, and the sunlight concentration is one of the most promising approaches. Luminescent solar concentrators (LSCs) have been proposed as alternative photovoltaic (PV) devices, as they require less semi-conductor material per unit of generated power, compared with conventional PV-technologies. While initially introduced as a means for better exploitation of high efficiency solar cells and therefore for cost reduction, recently the focus has shifted towards LSCs as a promising concept for integration of PV into buildings.[113] LSCs are essentially thin sheets of transparent plastics, in which luminescent species are dispersed (Figure 21).

**a)**




**b)**

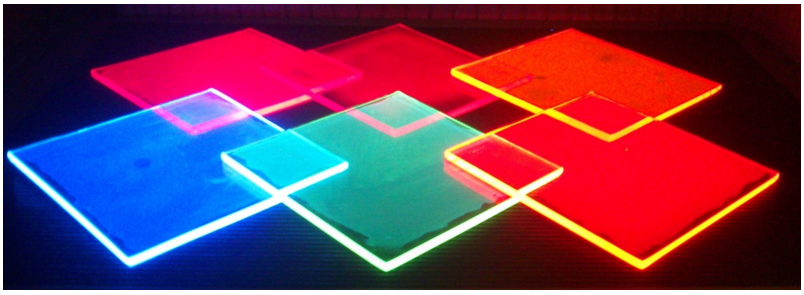


**Figure 21**: a) Schematic representation of a LSC; b) Examples of LSC of fluorophores of different nature.

Long and slim solar cells are attached to the small side faces such that their collection surface is directed to the plastic plate. Sunlight enters the sheet through the large top face and is absorbed by the dispersed fluorophore in polymeric matrix, which re-emit light (Figure 21a). The wavelength of the re-emitted light is different from the incoming wavelength, just like the propagation direction. Because of this change in direction a large fraction of the re-emitted light cannot leave the plate through the plastic-air interface, as it is in the regime of total internal reflection (TIR). Therefore the light is wave-guided until it reaches the solar cell. The

wavelength of the re-emitted light depends on the choice of the fluorophore, which has to be ideally chosen such that the emission band matches the maximum of the spectral response of the solar cell (Figure 21b). The solar cell will thus operate with a higher efficiency than under broad-spectrum illumination.

Despite several attempts, LSC power conversion efficiency (~7%) remains too low for most practical applications due to a number of loss mechanisms attributed to non-radiative energy dissipation and self-absorption by the fluorophore. In the perspective of extensive LSC applications, the fundamental open issue is the development of high quantum yield and photo-stable dyes, which can meet the LSC requirements for commercialization.

As regards our compounds, fluorophores **50** exhibit bright blue-green emissions in the solid state (Figure 22 and Figure 23). Powders of **50a** and **50s** emit significantly red-shifted fluorescence relative to **50b** and the THF solutions. This phenomenon may be attributed to the higher electronic coupling resulting from aggregation of their respective molecules or planarization of their chromophoric backbone owing to the increased conjugation.

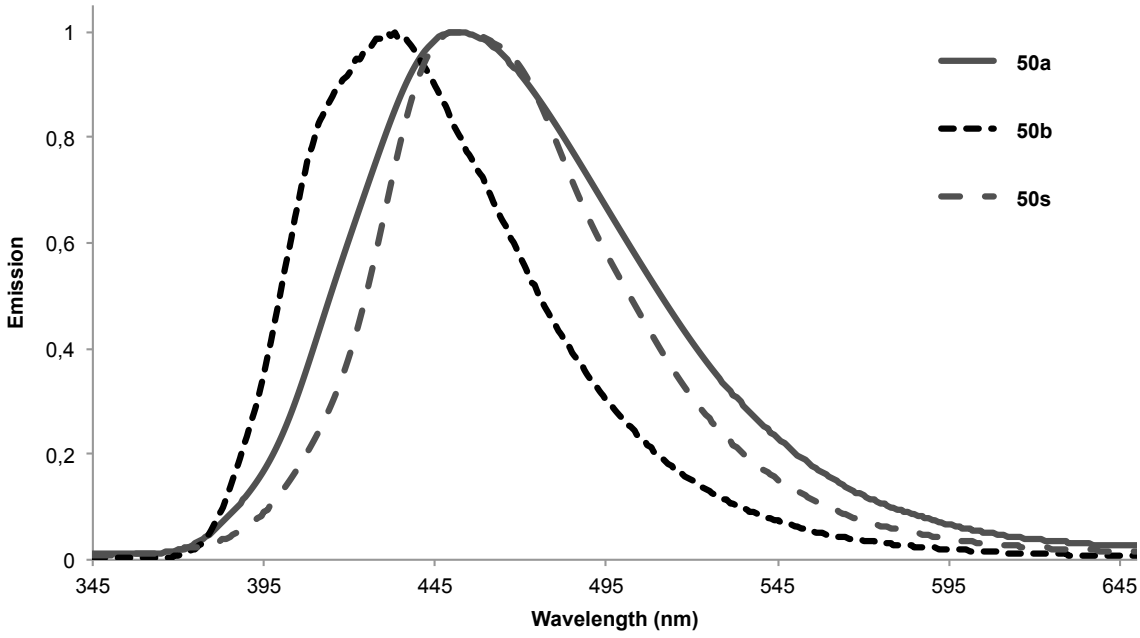



**Figure 22**: Normalized emission spectra of solid dyes **50**.


**Figure 23**: Pictures of the different solid samples of compounds **50** taken under illumination at 366 nm.

Fluorescence is well retained in the solid state even for derivatives **51** and **52** (bright blu-green colour under UV exposure).

As a last application of this Ph.D. work, we synthesized two compounds, **50w** and **51w** (Figure 24) with the (2-ethyl)-hexyloxy substituent, in order to obtain a better solubility in organic solvents and to achieve good affinity with polymeric matrices. We did not focus on the synthesis of the bis-thiazole compounds because derivatives **52** showed lower quantum yields and Stokes shifts than the relatives **50** and **51**.

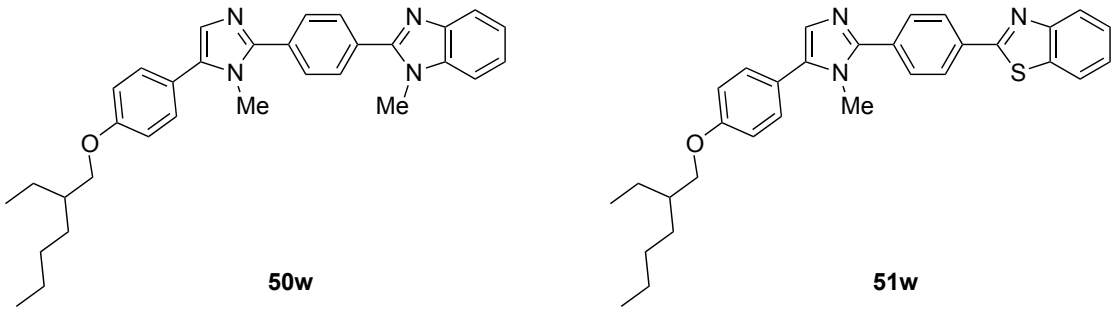


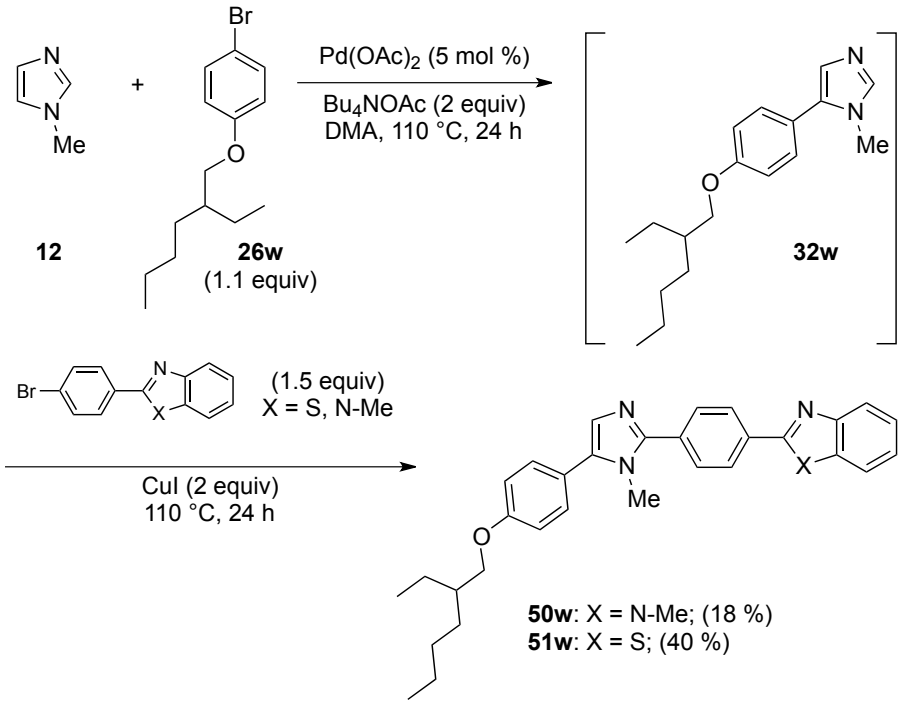

**Figure 24**: Structures of compounds **50w** and **51w**.

Once more, we wanted to apply the one-pot approach used for balsoxin (**39a**) and texaline (**39b**) and the resveratrol analogues **48** (see paragraphs 1 and 2 of **Chapter 2**) for the synthesis of **50w** and **51w**.

Hence, 1 equiv of 1-methyl-1*H*-imidazole (**12**) was treated with 1.1 equiv of 4-bromo-(2-ethyl)-hexyloxybenzene (**26w**) at 70 °C in DMA in the presence of 5 mol % $Pd(OAc)_2$ as catalyst and $Bu_4NOAc$ as base. The two reactions were carried out for 24 h. After that, without any purification of the intermediates **32w**, 1.5 equiv of 2-(4-bromophenyl)-1-methyl-1*H*-benzo[*d*]imidazole (**50**) or of 2-(4-bromophenyl)benzo[*d*]thiazole (**49**) were added along with 2 equiv of CuI. The use of 5 mol % $Pd(OAc)_2$ and 2 equiv of $Bu_4NOAc$ as initial quantities proved to be effective for the sequential reactions, and no additional catalyst or base was necessary in the second step. After 24 h at 110 °C, the required compounds **50w** and **51w** were isolated in 18 and 40 % yield, respectively (Scheme 54).

Compounds **50w** and **51w** were purified by crystallization and the analysis $^{1}$H-NMR and $^{13}$C-NMR confirmed the structure of these compounds. Optical properties of **50w** and **51w** were evaluated and are reported in Table 13.

These results are perfectly concordant with those found for **50** and **51** series (see Table 12).




**Scheme 54**

**Table 13**: Spectroscopic properties of fluorophores **50w** and **51w**.

| | $\lambda_{abs}$ [nm] | ε [$M^{-1}cm^{-1}$] | $\lambda_{em}$ [nm] | *S* [nm] | $\Phi_f$[a] | *B* [$M^{-1}cm^{-1}$][b] |
|---|---|---|---|---|---|---|
| **50w** | 321[c] | 30000[c] | 426[c] | 105 | 0.99 | 29700 |
| **51w** | 343[d] | 30000[d] | 457[d] | 114 | 0.76 | 22800 |

[a] Fluorescence quantum yield (Φ) was determined relative to quinine sulphate in 0.1 M $H_2SO_4$ (Φ = 0.54). [b] The brightness (*B*) values of fluorophores were calculated as the product of the absorption coefficient ε and Φ. [c] Absorbance, emission and ε values were determined in THF. [d] Absorbance, emission and ε values were determined in $CHCl_3$.

Compound **50w** properties were determined in THF solutions. It shows an absorbance spectrum with a maximum around 321 nm, very similar to **50a** and **50b** with the methyl and the methoxy group; its emission spectrum resulted with the fluorescence maximum wavelength around 426 nm, with a Stokes shift of 105 nm, higher than the other **50** compounds, as well as the quantum yield (Table 13). As regards compounds **51w**, its optical properties were determined in $CHCl_3$ because of solubility problems. Even for compound **51w** the results were concordant with those reported in Table 12. The absorbance spectrum has the maximum wavelength of about 343 nm, perfectly overlapping with the absorbances found for compounds **51**. The fluorescence emission has the maximum around 457 nm, giving the highest Stokes shift detected so far for all the compounds **50**-**52** (114 nm). Its quantum yield resulted to be slightly lower than the others of the **51** series (0.79) (Table 13).

# 4. Conclusions.

In conclusion, we applied the palladium-catalyzed direct arylation of azoles with aryl bromides mediated by $Bu_4NOAc$ to the synthesis of some biologically active compounds and organic functional materials.

We firstly tried to synthesize two natural compounds, balsoxin (**39a**) and texaline (**39b**), that are 2,5-diaryl-oxazoles. We decided to use a one-pot approach by applying the reaction conditions promoted by $Bu_4NOAc$, as regarded the first step, and the ligandless procedure for the direct arylation at the C-2 position of 1,3-azoles with aryl bromides in the presence of CuI developed by our group, for the second one. We were able to synthesized compounds **39a** and **39b** in 39 and 38 % yield, respectively, with only one purification step.

Then, by using the same one-pot methodology, we prepared two resveratrol analogues **48a** and **48b**, starting from 1-methyl-1*H*-imidazole (**12**). The compounds were synthesized in 48 and 38 % isolated yield, respectively; we also prepared the relative unprotected derivatives **49a** and **49b** that we got in 89 and 65 % yield. Molecules **48** and **49** showed cytotoxic activity against the 60 human tumoral cell line panel of the *National Cancer Institute* of USA and moreover, compound **49b** resulted to be a NQO2 inhibitor *in vitro* as confirmed by Professor Ian Stratford of University of Manchester and showed cytotoxicity higher than resveratrol (**44**).

As last application, we devoted a part of our synthetic efforts to the preparation of new *push-pull* fluorophores **50**, **51** and **52**. We used a two-step procedure, that involved the palladium-catalyzed direct arylation of azoles with aryl bromides in the presence of $Bu_4NOAc$ for the first step and the ligandless direct arylation at the C-2 position promoted by CuI with aryl bromides of Bellina's group for the second step. We synthesized compounds **50**-**52** with overall yields ranging from 16 to 71 %. Then, we evaluated their spectroscopic properties, by analysing their absorbance and emission spectra. Molecules **50**-**52** presented quantum yields comprise between 55 and 99 % with Stokes shifts up to 114 nm. They will be used in the development of luminescent solar concentrators (LSC) that represents an attractive alternative to the standard photovoltaic systems (PV) because their simplicity of the materials and their low costs.

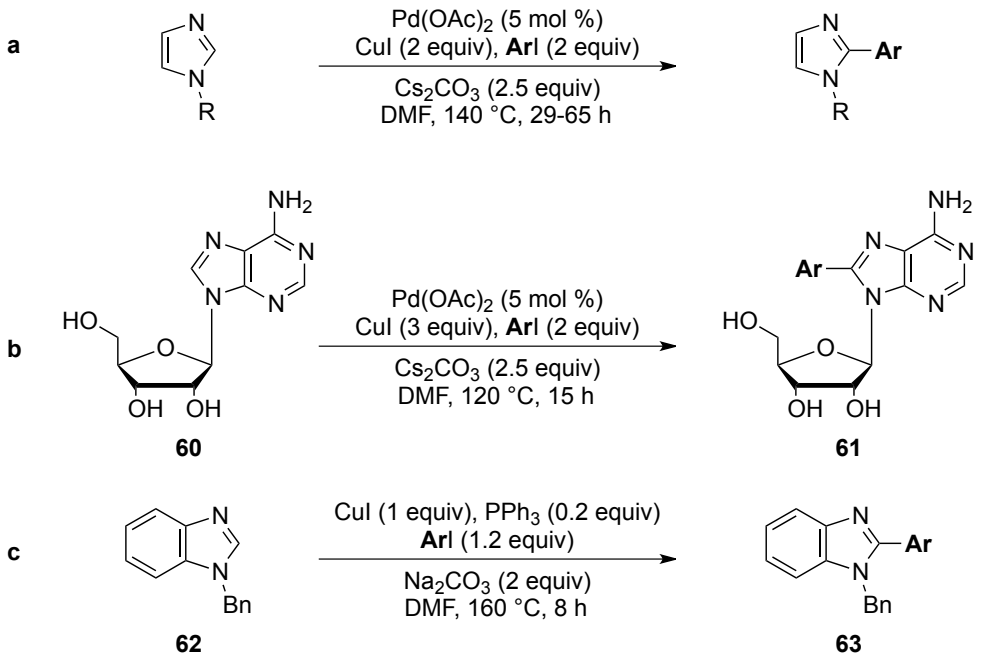
# CHAPTER 3

# *Synthesis of N-heterocyclic copper carbenes and study of their role in Pd/Cu mediated systems*

*This part of the Ph.D. thesis was carried out at the University of York, in collaboration with Professor Ian J. S. Fairlamb.*

The development of Pd/Cu-mediated approaches for the functionalization of (benz)azoles and related purines has greatly diversified the arylated derivatives that can be accessed.[23a-b,50a] For these processes, it is often beneficial to use stoichiometric quantitites of a Cu salt with Pd acting as a catalyst; however, the mechanism of these reaction is not fully understood.

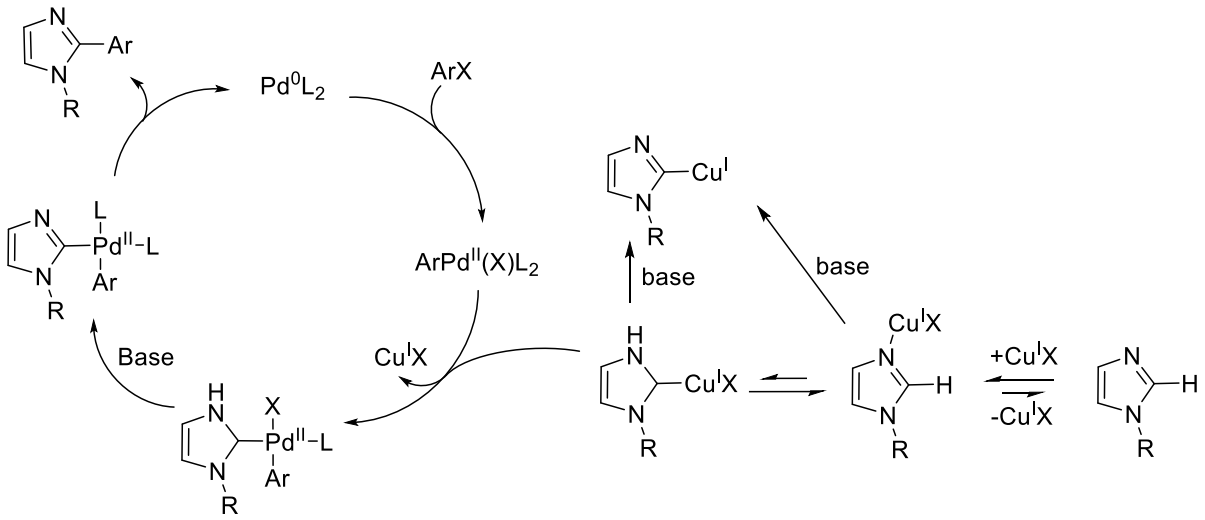
As already discussed in the **Introduction** of this thesis, our research group have developed a procedure for the functionalization of imidazoles to synthesize 2-arylimidazoles, which proceed in DMF at high temperatures (Scheme 55a).[23c-d,37,50c-e] Another example of reaction involving a Pd/Cu catalytic system was reported by Fairlamb's group in 2008. Here, adenosine **60** can be functionalized using a similar route to give 8-aryladenosine **61** (Scheme 55b).[64,114]




**Scheme 55**: Leading examples of C-H bonds functionalization reactions at heteroarenes.

Moreover, the functionalization of a benzimidazole (**62**) to give a 2-arylbenzimidazole (**63**) has been shown to proceed in the absence of Pd and using 1 equiv of CuI, though higher reaction temperatures were employed in this reaction (Scheme 55c).[13b] Interestingly, Miura and co-workers commented in their work that the arylation of 1-methyl-benzimidazoles works considerably better with CuI alone than using Pd/Cu together (the reason for this outcome was stated as unclear at the time).[20a]

As reported in the Scheme 4 of **Introduction** a mechanism for the Pd/Cu-mediated reactions have been proposed, with suggestions of initial intermediates involving *N*-coordination of $Cu^I$ to imidazole, organocuprate formation and the involvement of $Cu^I$-NHCs.[23c-d,37,50c-e,64,114] Metal-NHCs have also been postulated in intramolecular Rh-catalyzed C-H functionalization of benzimidazoles,[115] and in intermolecular Rh-catalyzed C-H functionalization of heterocycles.[116] A pathway bringing the proposed Pd/Cu-mediated mechanism together is shown in Scheme 56, which involves the transmetalation of an NHC ligand from $Cu^I$ to $Pd^{II}$, allowing reductive elimination to form the arylated imidazole. It has also been established that well-defined Pd nanoparticles are forms under these reaction conditions, with their role most likely as a reservoir of $Pd^0$,[117] akin to Heck-type coupling reactions.[118,119]

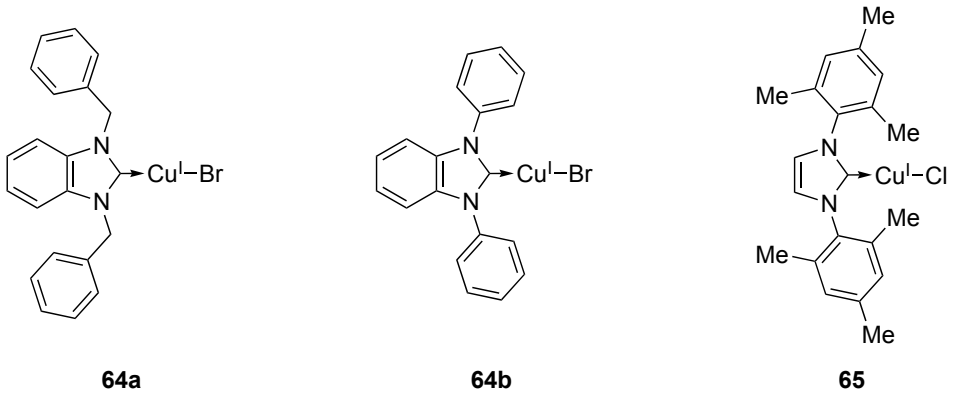



**Scheme 56**: Proposed reaction mechanism for the C-H bond functionalization of (benz)imidaoles/purines, mediated by Pd and Cu. The $Pd^0L_2$ is likely in equilibrium with higher order Pd nanoparticles (not shown).[117]

Unfortunately, under working conditions the proposed intermediate species in Scheme 56 are difficult to detect and synthesize, especially at $Cu^I$. Very recent studies by Hahn and co-workers have demonstrated that related organoplatinate caffeine-derived species can be

formed by an alternative synthetic route involving oxidative addition of $Pt^0$ into a C-Br bond.[120] Subsequent protonation gave an $Pt^{II}$-NHC complex of the type $Pt^{II}(X)_2(NHC)L$. While this study confirms the potential of such M-NHC species as intermediates, the reactivity of these complexes toward aryl halides, for example, has not been studied so far.

In order to verify if $Cu^I$-NHC species can be arylated by reaction with aryl iodide (in the presence and absence of Pd), we decided to synthesize and study compounds **64a**, **64b** and **65** as model systems (Figure 25). In compound **64a**, the *N*-benzyl substituent provides modest steric protection at the carbene centre, and is similar to typical substrates (see compound **62** in Scheme 55). The second benzyl substituent, however, takes the place of a proton. Then, the effect of steric bulk around the carbene centre was investigated by exchanging the benzyl substituent with phenyl (compound **64b**) and the mesityl group (compound **65**).




**64a** **64b** **65**

**Figure 25**: $Cu^I$-NHC complexes **64a**, **64b** and **65** examined in C-2 functionalization.

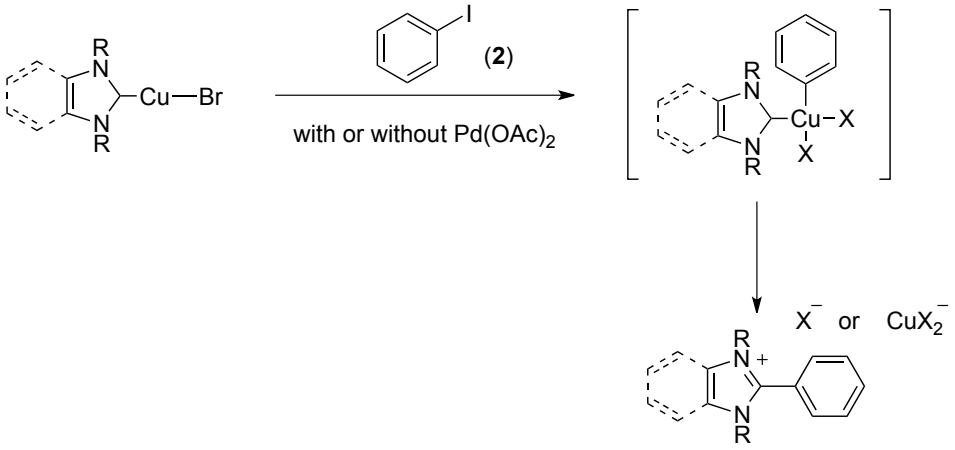
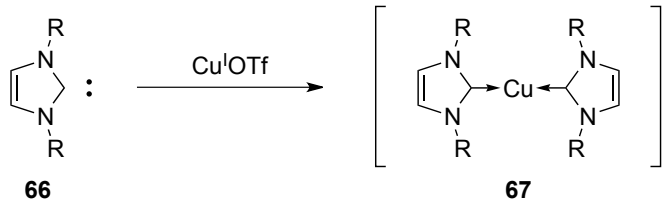



**Figure 26**: Reaction of $Cu^I$-NHC complexes with PhI (**2**) in the presence and absence of $Pd(OAc)_2$ (the latter *via* a $Cu^{III}$ species).

A key question arising from this study is whether the NHC ligand acts in either a non-interfering and supporting manner as a spectator ligand or participates as an actor and hence substrate. Although metal NHC complexes are generally robust species, reductive elimination can occur from $Ni^{II}$ and $Pd^{II}$ complexes containing NHC and aryl or alkyl ligands.[121] Therefore, this study would allow us to understand whether reductive elimination is feasible at Cu *via* a higher oxidation state intermediate (Figure 26)

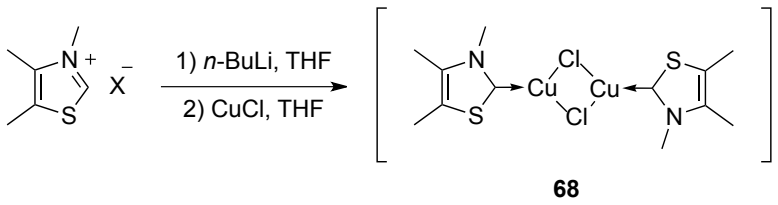
## 1. Synthesis and characterisation of $Cu^{I}$-NHC complexes 64a, 64b and 65.

NHC-$Cu^{I}$ complexes have been shown to have important roles in catalysis,[122] and demonstrated cytotoxic activity.[123] The first NHC-$Cu^{I}$ complex (**67**) was isolated by Arduengo and co-workers starting from carbene **66** and $Cu^{I}OTf$ (Scheme 57).[124] Nolan and co-workers have used similar complexes, with $PF_6$ or $BF_4$ as counter anions, as very efficient and selective pre-catalysts for the hydrosilylation of carbonyl compounds.[125]



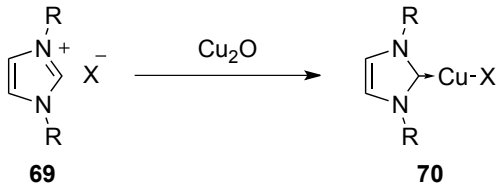

**Scheme 57**

The first monocarbene complex was studied by Raubenheimer and co-workers. These thiazole-derived carbene complexes (**68**) existed as chloride dimers in the solid-state (for an example see Scheme 58). This methodology was extended to a greater variety of thiazolylidene and *N*-methylimidazolylidene scaffolds.[126]




**Scheme 58**

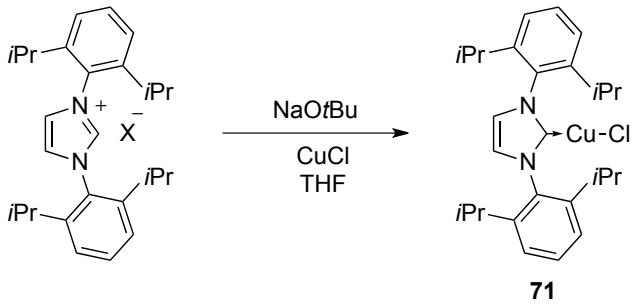
In 2001, Danopoulous and co-workers synthesised pyridine-*N*-functionalised $Cu^{I}$ complexes from imidazolium bromides and $Cu_2O$.[127] Dependent on substituents and recrystallisation conditions, these complexes existed as monomers, dimers and polymers. Douthwaite and co-workers used this method in the synthesis of carbene-phenoximine complexes.[128] Cazin and co-workers demonstrated that this "green" approach (the only by-product being water) to Cu(NHC)s **70** formation could be applied to a variety of imidazolium salts **69**, including Mes, Pr, and Cy as R substituents in different solvents ($CH_2Cl_2$, toluene, $H_2O$) (Scheme 59).[129]




**69** **70**

**Scheme 59**

Buchwald and co-workers synthesised the first NHC-Cu complex of the form (NHC)CuX (**71**), where X is a halide, *via* the simple reaction of free carbene with $Cu^{I}Cl$ (Scheme 60).[130] The resulting complex was found to be air and moisture stable, and demonstrated to be useful as a catalyst in the conjugative reduction of α,β-unsaturated carbonyl compounds.




**71**

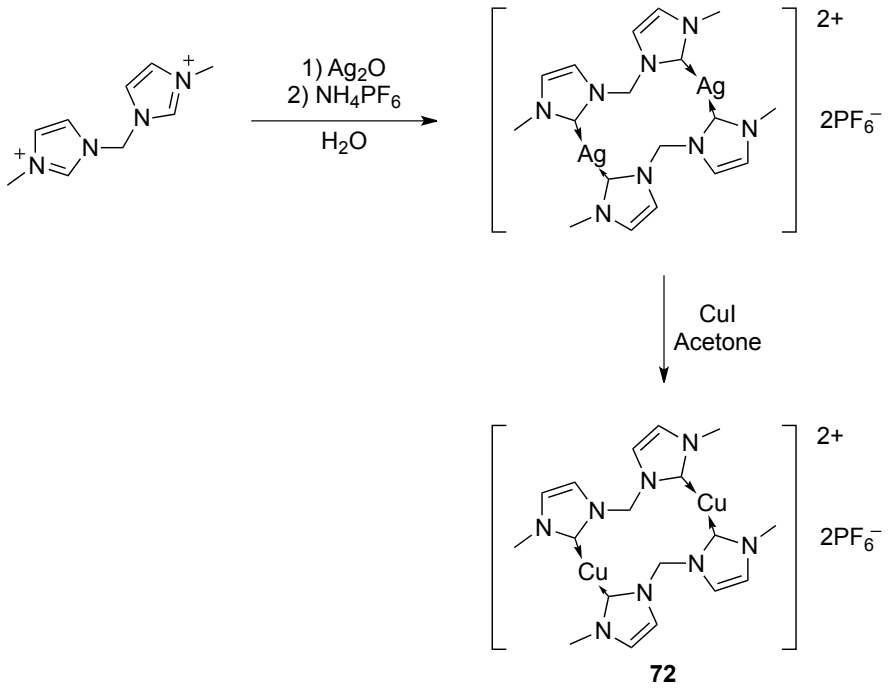
**Scheme 60**

In similar work by Nolan and co-workers, the reduction of carbonyls was performed by (NHC)CuCl complexes formed *in situ* from the parent imidazolium salt.[131] Lebel has utilized Nolan's catalysts in the synthesis of styrenes and aliphatic alkenes from carbonyls.[132] Nolan later demonstrated the utility of Cu(NHC)X complexes in the hydrosilylation of ketones and

"click" chemistry,[133] and in the direct C-H bond carboxylation of arenes.[134]

Albrecht and co-workers, after a study of a comprehensive library of *bis*-NHC-CuI complexes, demonstrated that substituents play an important role in stability.[135] Their complexes demonstrated that aryl (Mes or Dipp) produced the most stable CuI complexes, whilst alkyl substituents (including seemingly more hindered NHCs such as *i*Pr) induced rapid demetallation in the presence of water. Albrecht used these complexes in a novel ligand transfer to Ru. Furst and Cazin demonstrated that Cu(NHC)X complexes could also be used as carbene transfer reagents to $Au^{I}$ and $Pd^{II}$.[136]

Tsubomura and co-workers have synthesised a bi-metallic NHC-$Cu^{I}$ complex **72** (Scheme 61).[137] They also demonstrated these complexes could be produced *via* transmetallation from $Ag^{I}$. These complexes were considered for applications as luminescent materials in light emitting diodes. Similar bi-metallic complexes with a carbene/metal ratio 1:1 were reported by Hoffman and co-workers.[138]

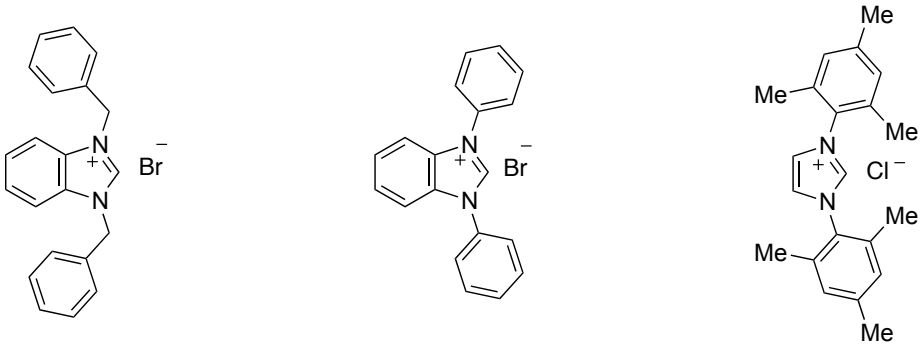



**72**

**Scheme 61**

### 1.1. Synthesis of the (benz)imidazolium salts 73a, 73b and 74.

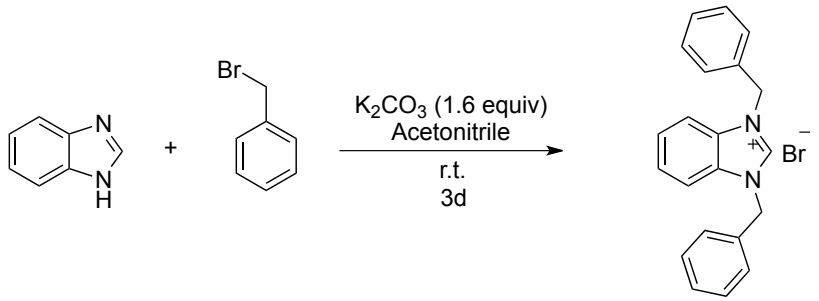
We began the synthesis of compounds **64a**, **64b** and **65** by preparing the relative (benz)imidazolium salts **73a**, **73b** and **74** (Figure 27).




**73a** **73b** **74**

**Figure 27**: Structures of (benz)imidazolium salts **73a**, **73b** and **74**.

As regard the dibenzylbenzo[*d*]imidazolium bromide **73a**, it was achieved by reacting the benzimidazole (**75**) (1 equiv) and 2 equiv of benzyl bromide (**76**) with 1.6 equiv of $K_2CO_3$ in acetonitrile as the solvent at room temperature for 3 days (Scheme 62).[139] After a simple aqueous work-up, we were able to isolate the benzimidazolium bromide **73a** in 99 % chemical yield. The structure of **73a** was confirmed by $^1$H-NMR, $^{13}$C-NMR and ESI-MS analyses.

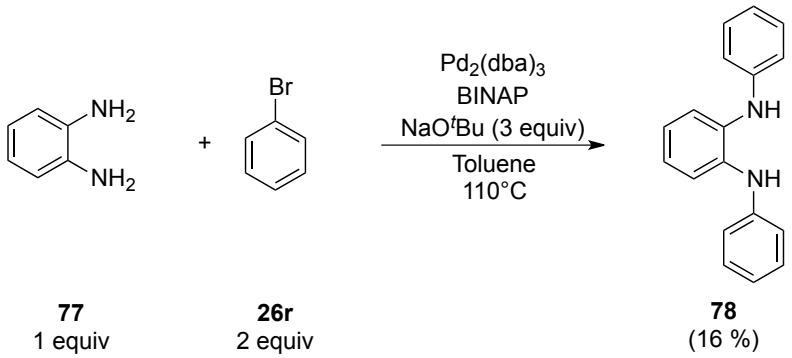



**75** 1 equiv **76** 2 equiv **73a** (99 %)

**Scheme 62**

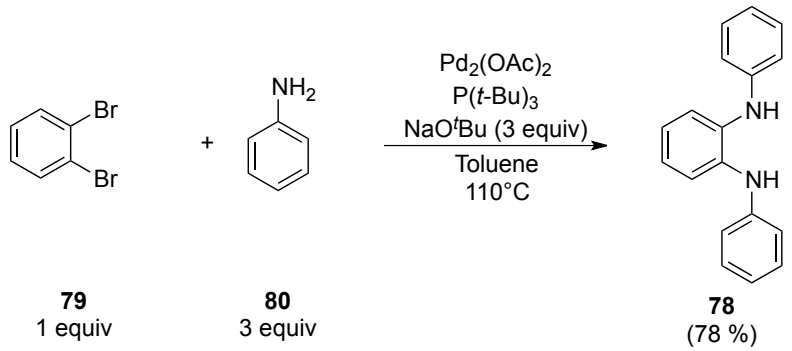
For the synthesis of 1,3-diphenyl-1*H*-benzo[*d*]imidazol-3-ium bromide (**73b**), we needed to prepare the *N*,*N*-diphenylbenzene-1,2-diamine (**78**) as the reaction precursor. Initially, we tried to synthesize **78** starting from benzene-1,2-diamine (**77**) and bromobenzene (**26r**) as reported by Sun and co-workers in 2013.[140] Hence, 1 equiv of compound **77** and 2 equiv of **26r** reacted under nitrogen atmosphere in the presence of 5 mol % of $Pd_2(dba)_3$, 7.5 mol % BINAP as ligand, 3 equiv of NaO*t*Bu in toluene at 110 °C as reported in Scheme 63.

The reaction was followed by TLC and compound **78** was obtained in only 16 % isolated yield after work-up and a difficult purification by flash cromatography.




**Scheme 63**

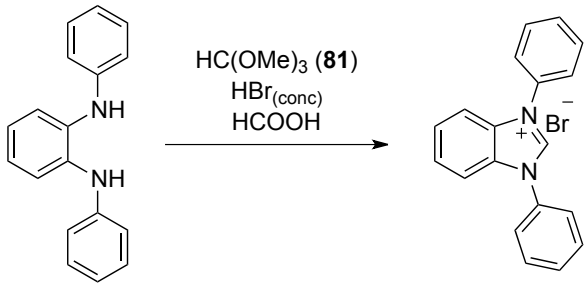
Because of the scarce chemical yield of *N*,*N*-diphenylbenzene-1,2-diamine (**78**), we thought to change the procedure and decided to apply the Harlan's group methodology reported in 2004 that started from the inverted substrates.[141] More specifically, under nitrogen atmosphere, 1 equiv of 1,2-dibromobenzene (**79**) reacted with 3 equiv of aniline (**80**) in the presence of 2.5 mol % $Pd(OAc)_2$, 7.5 mol % P*t*$Bu_3$ and 3 equiv NaO*t*Bu in toluene at reflux temperature. The reaction was left overnight and after work-up and a recrystallization process, compound **78** was isolated in 78 % yield (Scheme 64). The structure of **78** was then confirmed by the analysis of $^{1}$H-NMR, $^{13}$C-NMR and ESI-MS spectra.




**Scheme 64**

Once we prepared the precursor **78** we had to synthesize the relative benzimidazolium bromide **73b**. The procedure we exploited to have the cyclization of the diamine **78** was reported by Zou and co-workers in 2005 where they reported the preparation of 1,3-diphenyl-benzimidazolium chloride.[142] They reacted compound **78** with trimethyl ortoformate (**81**) in

the presence of $HCl_{conc}$ and catalytic HCOOH. Hence, we wondered if replacing the $HCl_{conc}$ with $HBr_{conc}$ it might be possible to get the same product, but as a bromide salt. For this reason, at a solution of *N*,*N*-diphenylbenzene-1,2-diamine (**78**) in trimethyl orthoformate (**81**), $HBr_{conc}$ and catalytic HCOOH were added and the reaction mixture was heated at 80 °C for 2 h as reported in Scheme 65. Afterwards, the product **73b** was purified by crystallization and isolated with 99 % chemical yield. Its structure was then confirmed by the analysis of $^{1}$H-NMR, $^{13}$C-NMR and ESI-MS spectra.




**Scheme 65**

The 1,3-dimesityl-1*H*-imidazol-3-ium chloride (**74**) was not prepared in our laboratory because it was commercially available; for this reason it was used directly as a precursor for the synthesis of copper carbene **65**.

We devoted part of our synthetic efforts also on the preparation of the relative benzocondensed derivative of compound **74**, the 1,3-dimesityl-1*H*-benzo[*d*]imidazol-3-ium bromide (**73c**) (Figure 28), in order to add compound **64c** to the library of benzimidazolium copper-carbenes to study.

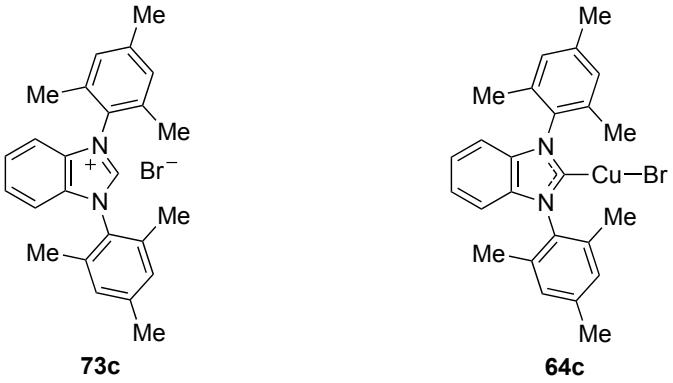
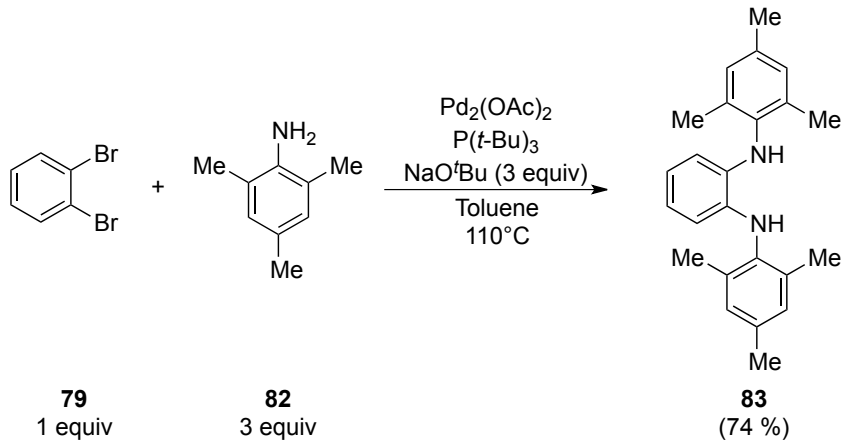



**Figure 28**: Structure of 1,3-dimesityl-1*H*-benzo[*d*]imidazol-3-ium bromide (**73c**) and its relative copper-carbene **64c**.

Having successfully verified the viability of Harlan's procedure for the synthesis of *N,N*,-diphenyl-1,2-diamine (**78**) , we applied the same reaction conditions to the preparation of *N,N*-dimesythylbenzene-1,2-diamine (**83**), that should have been used afterwards as precursor of compound **73c**. This time we started from 1 equiv of 1,2-dibromobenzene (**79**) and 3 equiv of 2,4,6-trimethylaniline (**82**) as reported in (Scheme 66).[141,143] Compound **83** was achieved after work-up and recrystallization step in 74 % isolate yield. The structure of **83** was then confirmed by $^{1}$H-NMR, $^{13}$C-NMR and ESI-MS analyses.

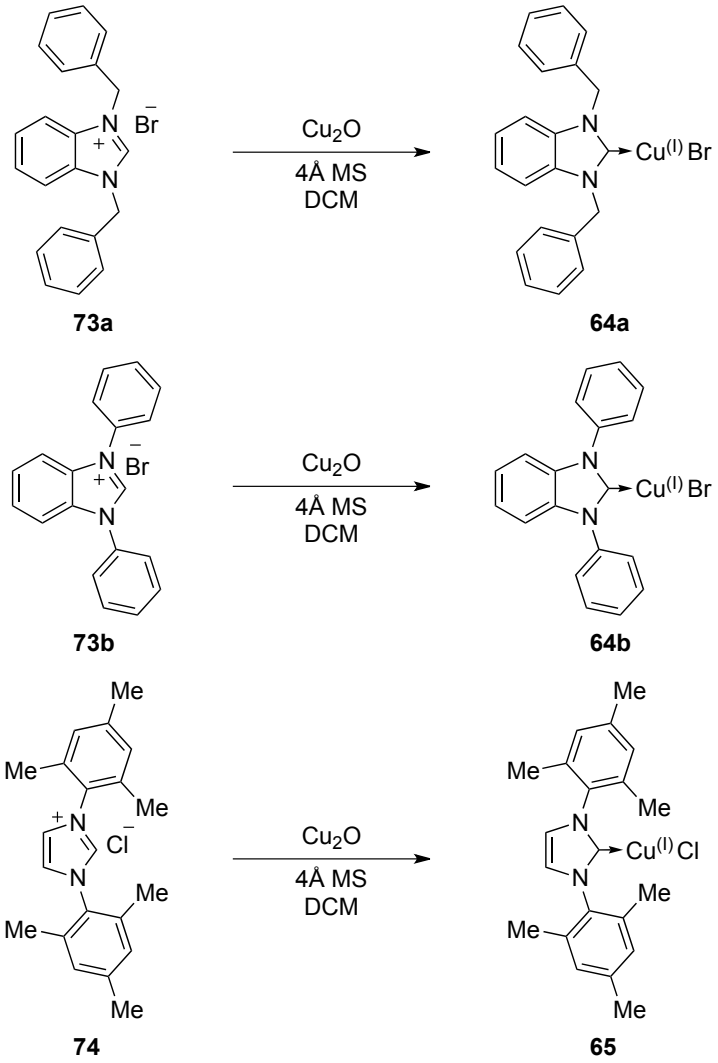



**Scheme 66**

Therefore, we repeated again the cyclization reaction we applied for the preparation of compound **73b**, by adding the *N,N*-dimesythylbenzene-1,2-diamine (**83**) in trimethyl orthoformate (**81**) with $HBr_{conc}$ and catalytic formic acid at 80 °C for 2 h.[142] Unfortunately, we were not able to synthesize the benzimidazolium bromide **73c** with this procedure, even though we tried to extend the reaction time. We also tried to perform the reaction in the microwave, setting the standard reaction time and temperature and even increasing them until 24 h and 110 °C. Compound **73b** was not reachable again, more likely because of the steric hindrance of the *ortho*-substituent of the mesytil rings that obstruct the cyclization of the trymethyl orthoformate **81**. For these reasons we decided to focus our attention only on the imidazolium chloride **74**.

### 1.2. Synthesis of copper carbenes 64a, 64b and 65.

The copper carbenes **64a**, **64b** and **65** were all synthesized in a quantitative manner by reacting the (benz)imidazolium salts **73a**, **73b** and **74** with $Cu_2O$ in anhydrous $CH_2Cl_2$ as reported in Scheme 67.




**Scheme 67**

Products **64a**, **64b** and **65** were all characterized by $^{1}$H-NMR, $^{13}$C-NMR and mass-spectra analyses.

Single crystals of complex **64b** suitable for X-ray diffraction analysis were grown *via* the vapour diffusion of diethyl ether into a solution of the product in dichloromethane. The molecule crystallizes as a one-dimensional polymer propagated by the formation of bromide

bridges ($\mu^2$-Br) along the chrystallographic b-axis between neighbouring NHC-Cu-Br units (Figure 29).

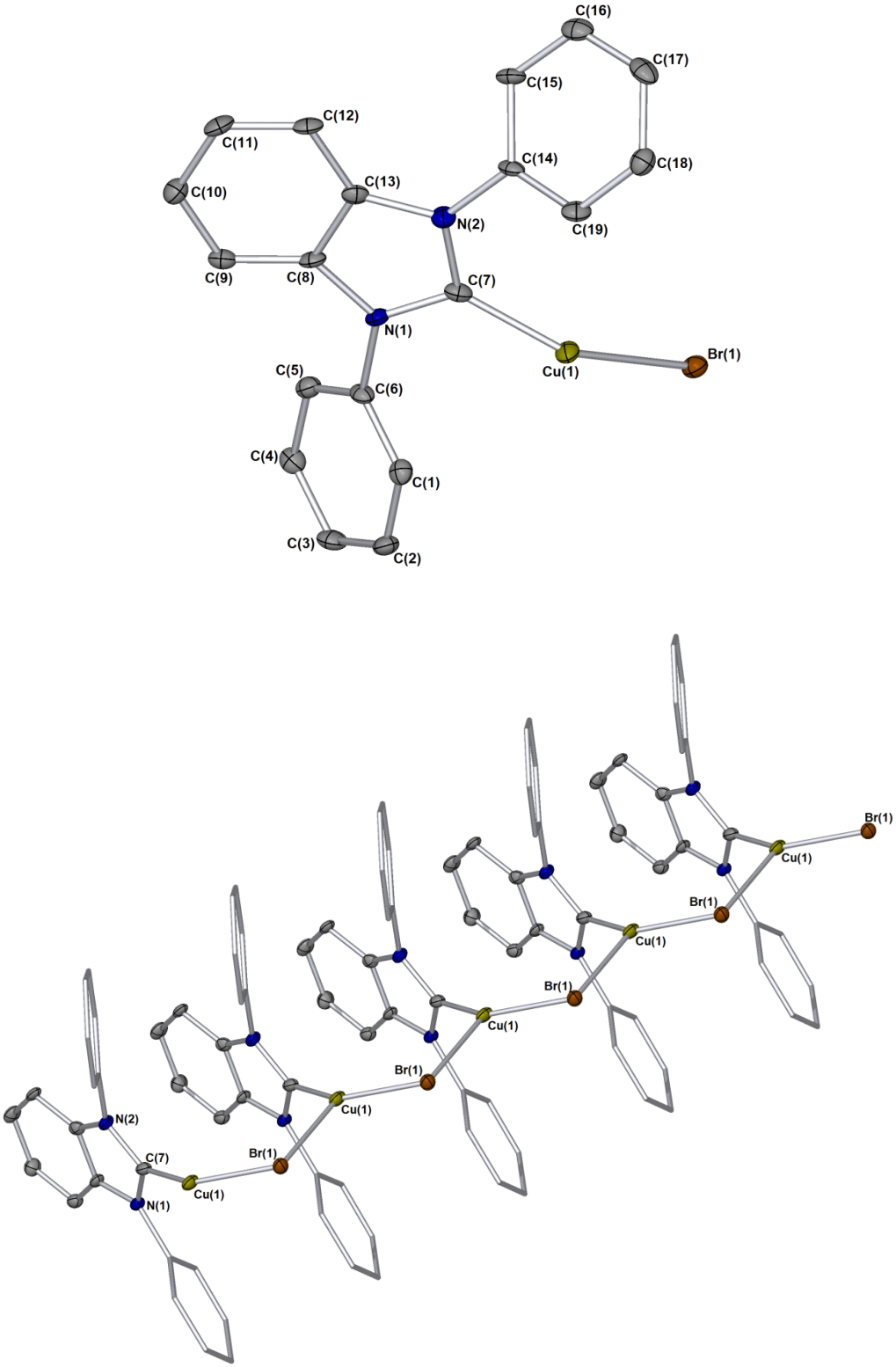
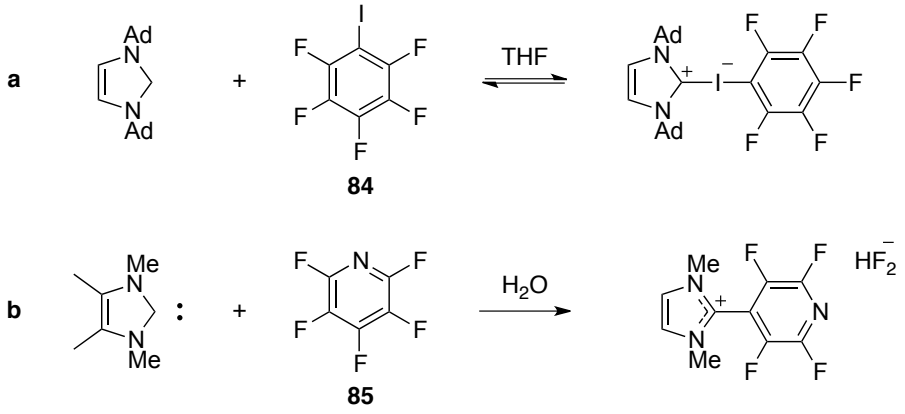



**Figure 29**: Single crystal X-ray structure of **64b**. Hydrogen atoms are omitted for clarity. Thermal ellipsoids are set to 50 % probability.

Each monomer of the polymer is separated by a distance of 3.89 Å, corresponding to the length of the b-axis of the unit cell. Such ligand-unsupported zigzag (metal-halide)$_n$ chains are rare and, to our knowledge, are unprecedented in Cu$^I$-NHC chemistry. Moreover, π-π stacking interactions between the phenyl rings are evident throughout the crystal lattice.

## 2. Reaction of Cu$^I$-NHC complexes 64a, 64b and 65 with PhI (2), with and without Pd(OAc)$_2$.

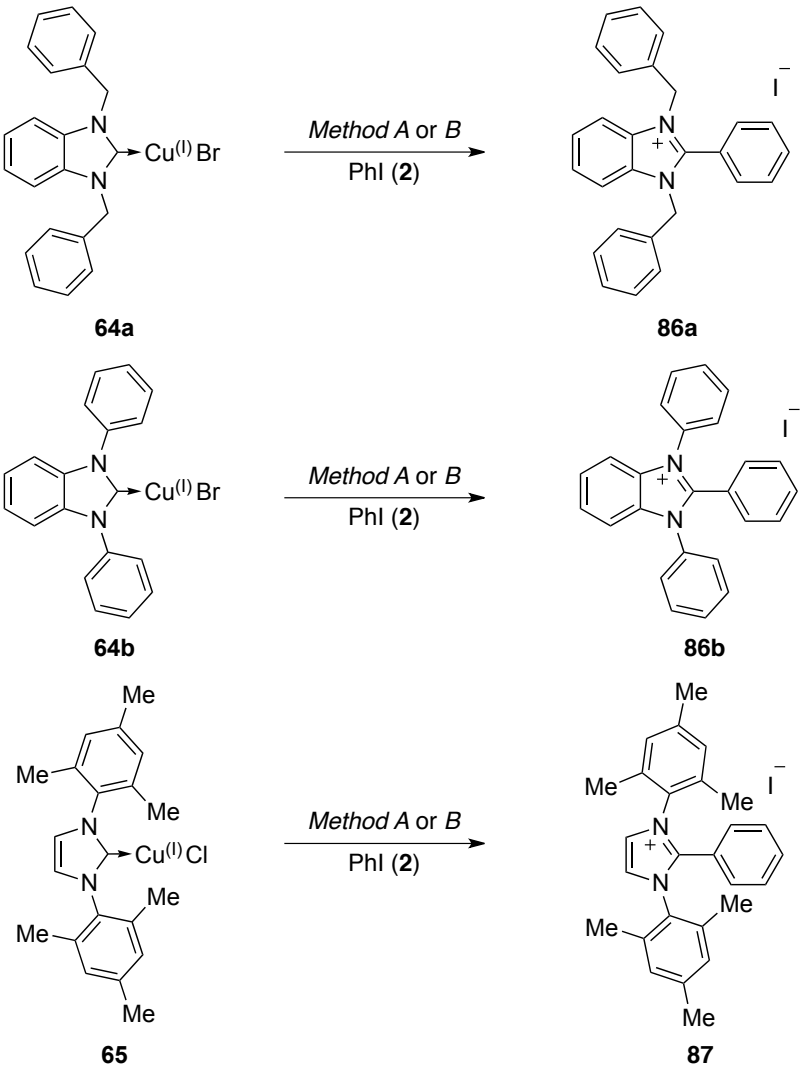
Reactions of NHC with (hetero)aryl halides have been of interest since the early work of Arduengo and co-workers who showed that an imidazole-2-ylidene in the presence of iodopentafluorobenzene (**84**) is in equilibrium with an iodoimidazolium adduct (Scheme 68a).[144] Arnold *et al*. studied a more structurally complex system resulting in cleavage of the C-I bond in **84**, leading to C-I bond formation at the carbene carbon.[145] However, no reaction was noted with PhI (**2**), which contains a slightly stronger C-I bond. On the other hand, Henkel and co-workers observed displacement of the 4-fluoro substituent in perfluoropyridine (**85**) by an imidazole-2-ylidene (Scheme 68b).[146]




**Scheme 68**: Examples of previous work assessing the reactivity of NHCs toward aryl halides in the absence of transition metal.[144,146]

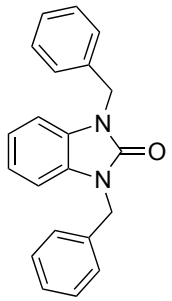
In order to understand whether Cu$^I$-NHC **64a**, **64b** and **65** can enter into a reaction with PhI (**2**), reactions of Cu$^I$-NHCs with PhI were conducted in benzene at 90 °C, in the absence (*Method A*) and presence (*Method B*) of Pd(OAc)$_2$ (Scheme 69).

Arylations of compound **64a** with the two methods were already performed before this Ph.D. work started.[147] When compound **64a** was treated with *Method A*, three species were observed in the $^1$H-NMR spectrum: compound **64a** it-self (54.3 %), the arylated product **86a** (30.5 %) and the side-product 1,3-dibenzyl-2-benzimidazolone (**88**) (15.2 %) (Figure 30). On the other hand, the same reaction in the presence of $Pd(OAc)_2$ produced compound **86a** in 42.6 % (conversion by $^1$H-NMR). Moreover, in this latter reaction 6.4 % 1,3-dibenzyl-2-benzimidazolone (**88**) was detected by NMR analysis together with a signal attributable to a *cis*-$Pd(NHC)_2Br_2$ complex (**89**), with the diastereotopy determined by molecular simmetry, that is with the two NHC ligands in *cis*-arrangement (Figure 30).[147]

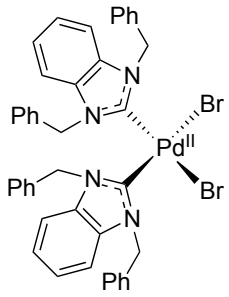



**Scheme 69**: Assessing the reactivity of $Cu^I$-NHCs toward PhI (**2**). *Method A*: **2** (5 equiv), $C_6H_6$, 90 °C, 24 h. *Method B*: **2** (5 equiv), $Pd(OAc)_2$ (1 equiv), $C_6H_6$, 90 °C, 24 h. Note that the anion, here depicted as $I^-$, could also be either $Br^-$, $CuX_2$ or $Cu_2X_4$ anions (where X = Br or I).

This observation provides evidence that, in the presence of $Pd(OAc)_2$, the $Cu^I$-NHC acts as a transmetallating agent, with arylation likely occurring from Pd. The formation of imidazolone compounds in $Cu^I$-NHC chemistry has been observed previously, and is thought to occur due to trace oxygen in the reaction.[148]




**88**




**89**

**Figure 30**: On the left: structure of 1,3-dibenzyl-2-benzimidazolone (**88**); on the right: postulated structure of *cis*-$Pd(NHC)_2Br_2$ (**89**) obtained from the transemtallation reaction of $Pd(OAc)_2$ with complex **64a** in benzene.[147]

In this Pd.D. work, we focused our attention on the arylation of copper carbenes **64b** and **65** with PhI (**2**) in the absence and presence of $Pd(OAc)_2$. The reagents were added to a Young's NMR tube under anhydrous conditions, heated at 90 °C, and followed by $^1$H-NMR spectroscopy. After 24 h, the benzene was removed from the reaction *in vacuo* and the reaction mixture was analysed in $CD_3CN$ to enable direct comparison with authentic starting material and product.

Firstly, the arylation of **64b** in the absence of $Pd(OAc)_2$ (*Method A*) was carried out. The $^1$H-NMR spectra are reported in Figure 31. We observed the depletion of $Cu^I$-NHC **64b** after 24 h in $C_6D_6$ at 90 °C in the presence of 5 equiv of PhI (**2**) (Figure 31d) and the formation of the precipitating product **86b** from the solution as a white solid.

As regard the arylation in the presence of $Pd(OAc)_2$ (*Method B*), we could observe that after the addition of the palladium complex there is a rearrangement of the signals of the carbene **64b** (Figure 32c). Arylation was found to proceed with complex **64b** at 90 °C, with starting complex **64b** being fully consumed after 2 hours (Figure 32d). The arylated imidazolium product **86b** precipitated from solution in quantitative yield (isolated yield > 99 %).

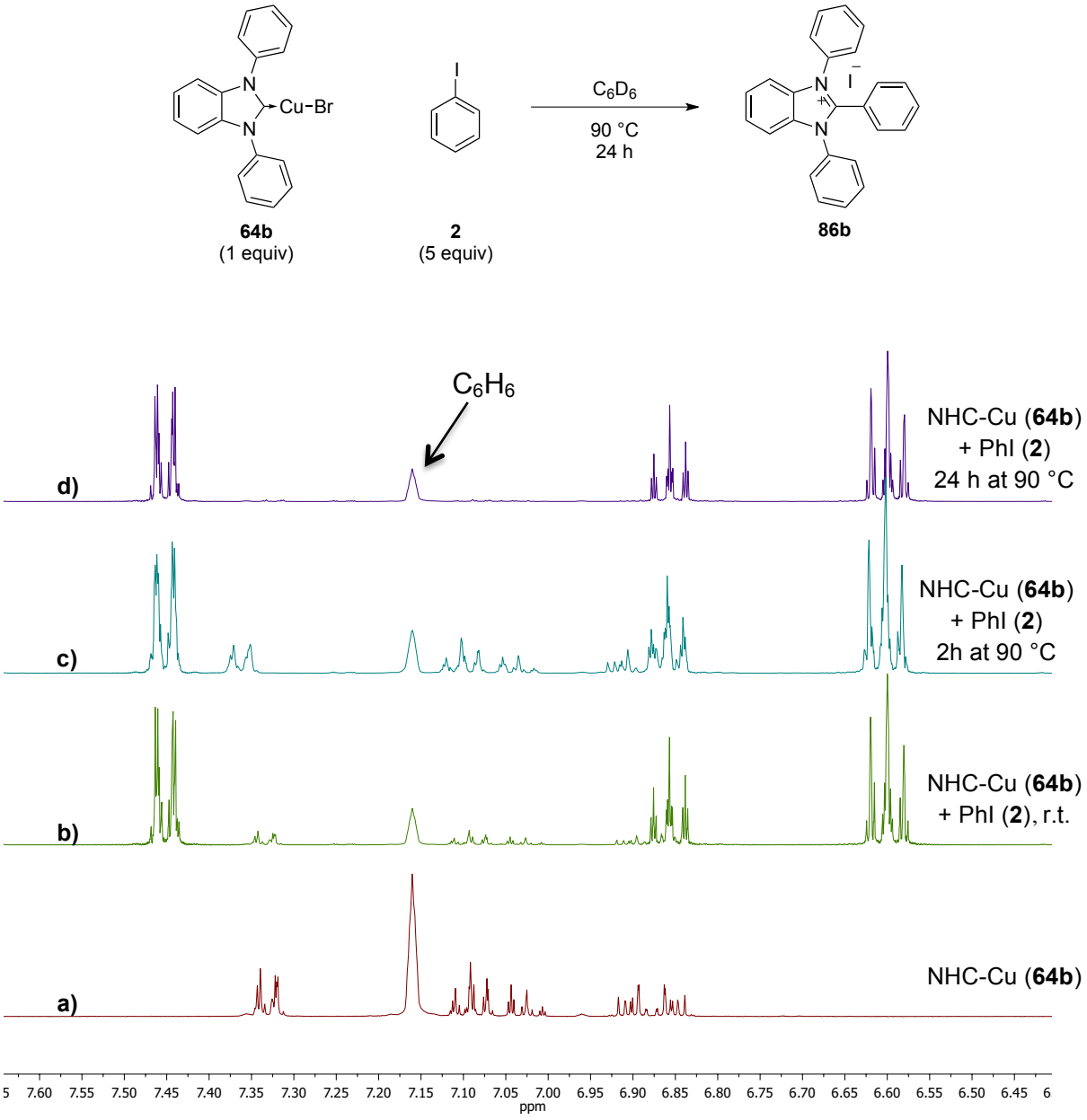



**Figure 31**: $^{1}$H-NMR spectra showing reaction outcome of Cu$^{I}$-NHC **64b** with PhI (**2**) in the absence of $Pd(OAc)_2$. a) $^{1}$H-NMR spectrum of compound **64b** in $C_6D_6$; b) $^{1}$H-NMR spectrum of compound **64b** after the addition of PhI in $C_6D_6$ (**2**) at room temperature; c) $^{1}$H-NMR spectrum of compound **64b** with PhI (**2**) after 2 h at 90 °C in $C_6D_6$; d) $^{1}$H-NMR spectrum of compound **64b** with PhI (**2**) after 24 h at 90 °C in $C_6D_6$.

In the absence of $Pd(OAc)_2$ a similar outcome was recorded, with quantitative conversion to **86b** after 24 h. A single crystal of **86b** was grown from acetonitrile and the X-ray diffraction structure determined (Figure 33). The unit cell contains two independent molecules, with each positively-charged arylated imidazolium species being charge balanced by a Cu$^{I}$-containing $Cu_2I_4^{2-}$ anion. The bonds connecting the phenyl moieties to the imidazolium rings were measured as 1.480(7) and 1.472(7) Å for C(7)-C(8) and C(32)-C(33) respectively. The bond

angles around N(2)-C(7)-C(8) and N(3)-C(32)-N(33) are 126.2(5) and 127.8(5)° respectively. The N(2)-C(7)-C(8)-C(9) and N(3)-C(32)-C(33)-C(38) torsion angles lie at 63.8(8) and 68.5(7)° respectively.

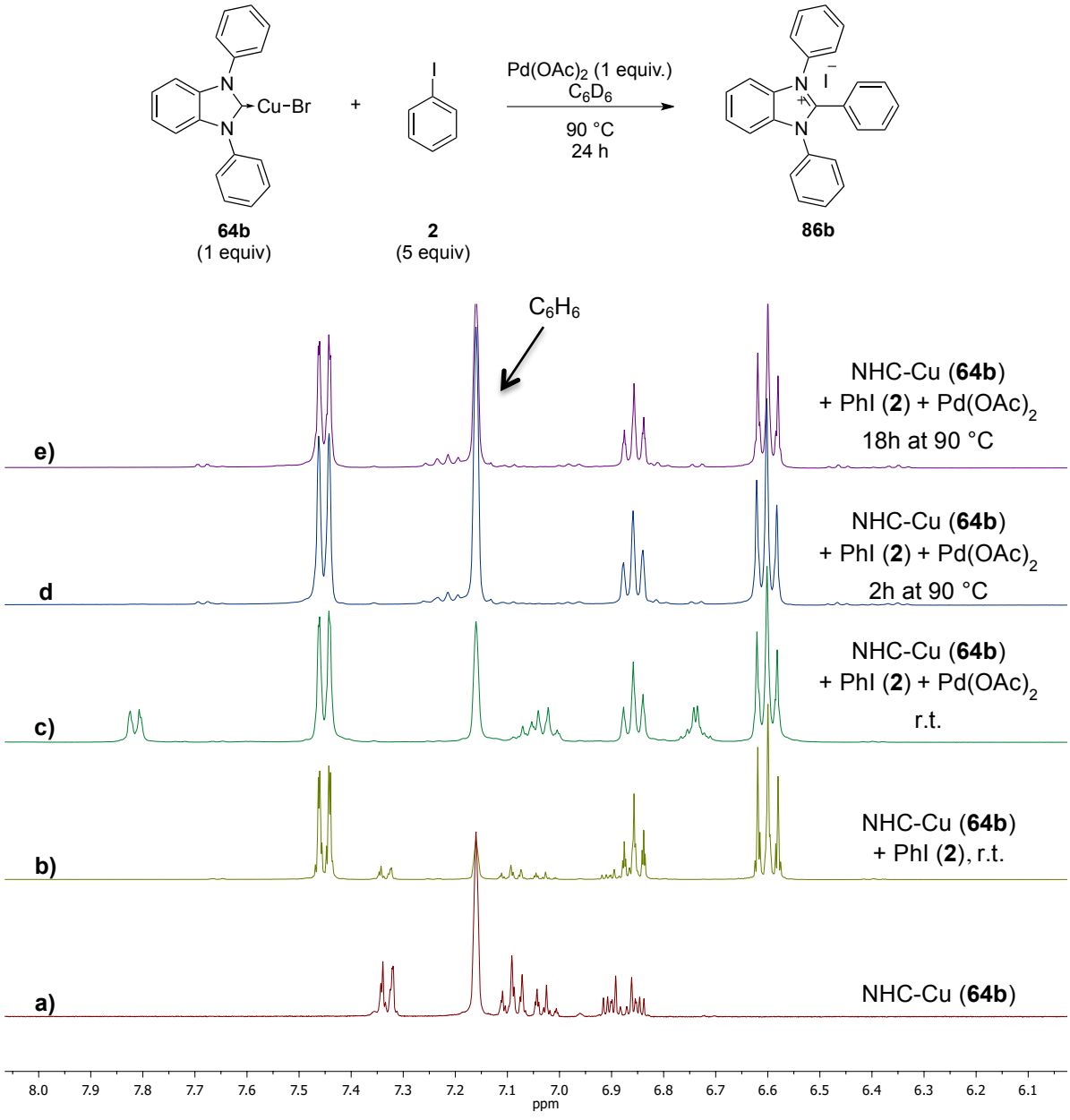



**Figure 32**: $^{1}$H-NMR spectra showing reaction outcome of Cu$^{I}$-NHC **64b** with PhI (**2**) in the presence of $Pd(OAc)_2$. a) $^{1}$H-NMR spectrum of compound **64b** in $C_6D_6$; b) $^{1}$H-NMR spectrum of compound **64b** after the addition of PhI in $C_6D_6$ (**2**) at room temperature; c) $^{1}$H-NMR spectrum of compound **64b** with PhI (**2**) after the addition of $Pd(OAc)_2$ in $C_6D_6$ at room temperature; d) $^{1}$H-NMR spectrum of compound **64b** with PhI (**2**) in the presence of $Pd(OAc)_2$ after 2 h at 90 °C in $C_6D_6$; e) $^{1}$H-NMR spectrum of compound **64b** with PhI (**2**) in the presence of $Pd(OAc)_2$ after 24 h at 90 °C in $C_6D_6$.

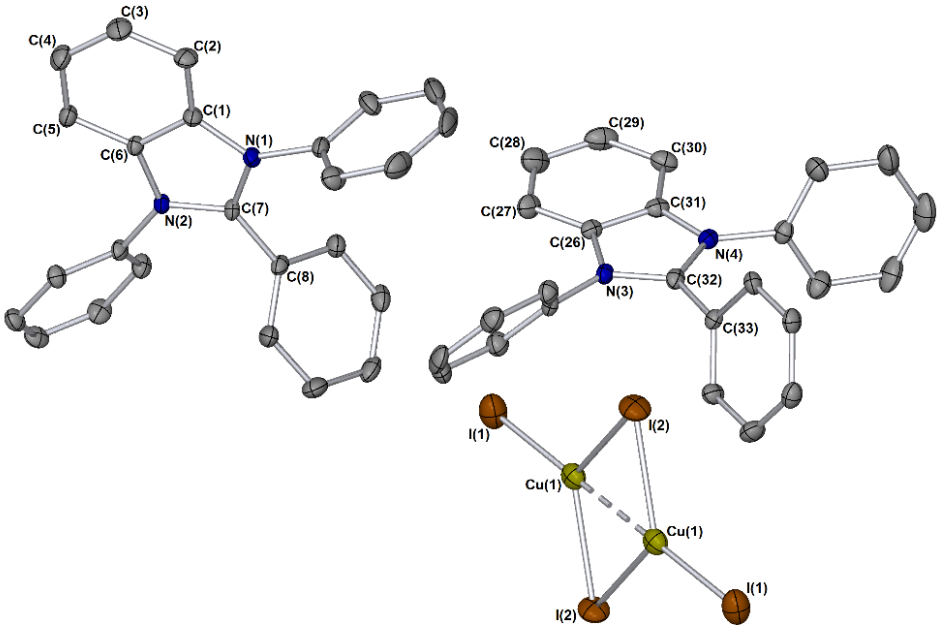



**Figure 33**: Single crystal X-ray structure of **86b** (two indipendent organic fragments accompany the $Cu_2I_4^{2-}$ anion shown in the figure above). Hydrogen atoms are omitted for clarity. Thermal ellipsoids are set to 50 % probability.

On the other hand, studying reactions with complex **64b** at room temperature, a different outcome was recorded. Although no reaction was observed in the absence of $Pd(OAc)_2$ (Figure 31b), in the presence of $Pd(OAc)_2$ *trans*-[Pd(NHC)-$\kappa^1$-Br-$\mu_2$-Br]$_2$ (**90**) was formed quantitatively (as shown by $^1$H-NMR spectroscopic analysis). Single crystals of the $Pd^{II}$-NHC complex were grown *via* slow evaporation from dichloromethane. The structure shows a dinuclear $Pd^{II}$-NHC complex, with each $Pd^{II}$ center coordinated by one carbene, one terminal bromide atom and two μ-bromide atoms (Figure 34). The C(1)-Pd(1) and C(20)-Pd(2) bond distances were measured at 1.941(6) and 1.931(6) Å respectively, which are comparable to other Pd-NHC complexes exhibiting bridging bromide atoms in the solid-state.[149] The *trans*-C(1)-Pd(1)-Br(2) angle is 176.56(17)° and C(20)-Pd(2)-Br(1) is 176.44(16)°.

We then applied the two reaction conditions to complex **65**. Arylation in the absence of $Pd(OAc)_2$ did not occur after 24 h at 90 °C as we can see from Figure 35d. The $^1$H-NMR and the mass-spectroscopy analyses of the NMR sample confirmed the results.

As we saw for compound **64b**, we observed the depletion of **65** when we applied *Method B* in the presence of $Pd(OAc)_2$ as soon after 2 hours at 90 °C in $C_6D_6$ (Figure 36d). ESI-MS of the dried reaction mixture after 24 hours confirmed that at least a partial arylation of compound **65** occurred. The NMR analysis of the crude product was not helpful to confirm the structure

of the product **87** and further investigations will be planned in order to have a quantification of the yield.

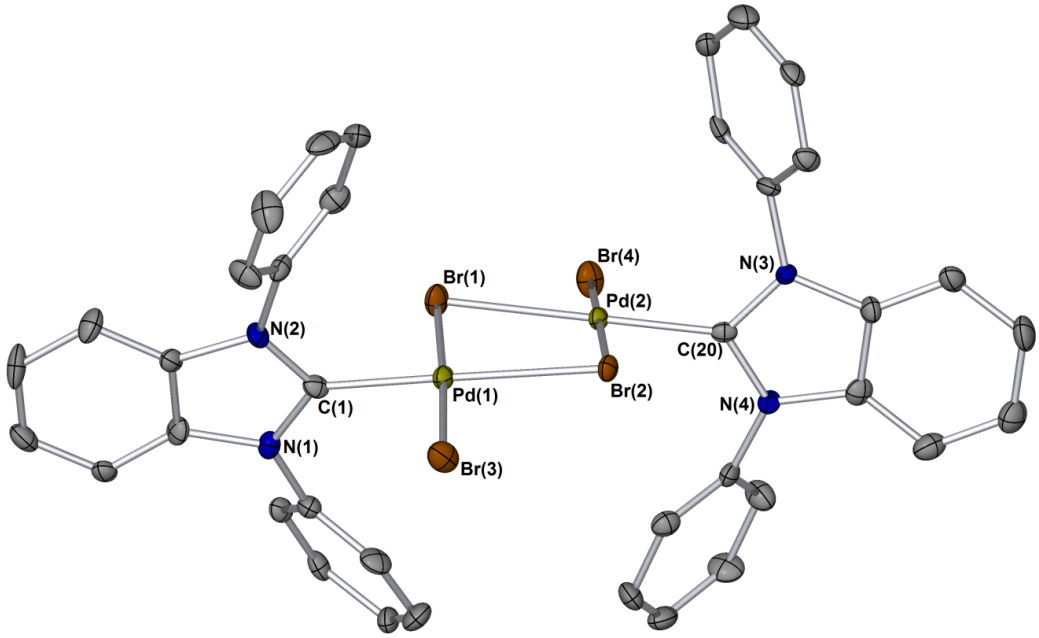



**Figure 34**: Single crystal X-ray structure of *trans*-[Pd(NHC)-$\kappa^1$-Br-$\mu_2$-Br]$_2$ (**90**). Hydrogen atoms are omitted for clarity. Thermal ellipsoids are set to 50% probability.

However, considering the *a*-values (describing the steric effects for various substituents) for benzyl and phenyl groups, the latter is considerably larger (Bn = 1.35 and Ph = 3).[150] It is therefore surprising that arylation occurs in higher yield for the *N*-phenyl derivative **64b** to give **86b**. Furthermore, increasing the steric bulk to *N*-mesityl hinders the arylation reaction. This indicates that the electronic effects of the *N*-substituent are likely to play an important part in the arylation reaction.

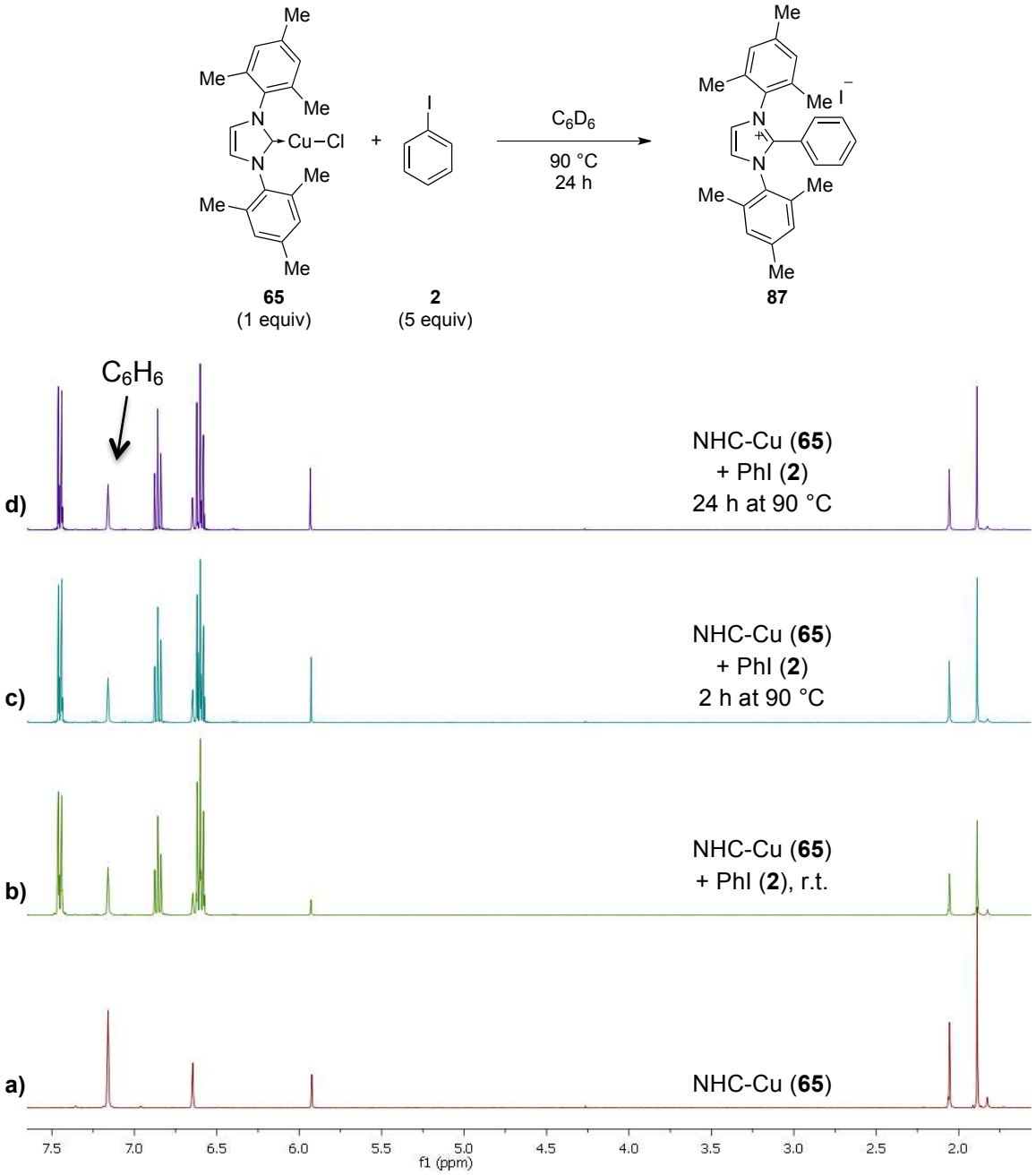



**Figure 35**: $^{1}$H-NMR spectra showing reaction outcome of Cu$^{I}$-NHC **65** with PhI (**2**) in the absence of $Pd(OAc)_2$. a) $^{1}$H-NMR spectrum of compound **65** in $C_6D_6$; b) $^{1}$H-NMR spectrum of compound **65** after the addition of PhI in $C_6D_6$ (**2**) at room temperature; c) $^{1}$H-NMR spectrum of compound **65** with PhI (**2**) in the presence after 2 h at 90 °C in $C_6D_6$; d) $^{1}$H-NMR spectrum of compound **65** with PhI (**2**) after 24 h at 90 °C in $C_6D_6$.

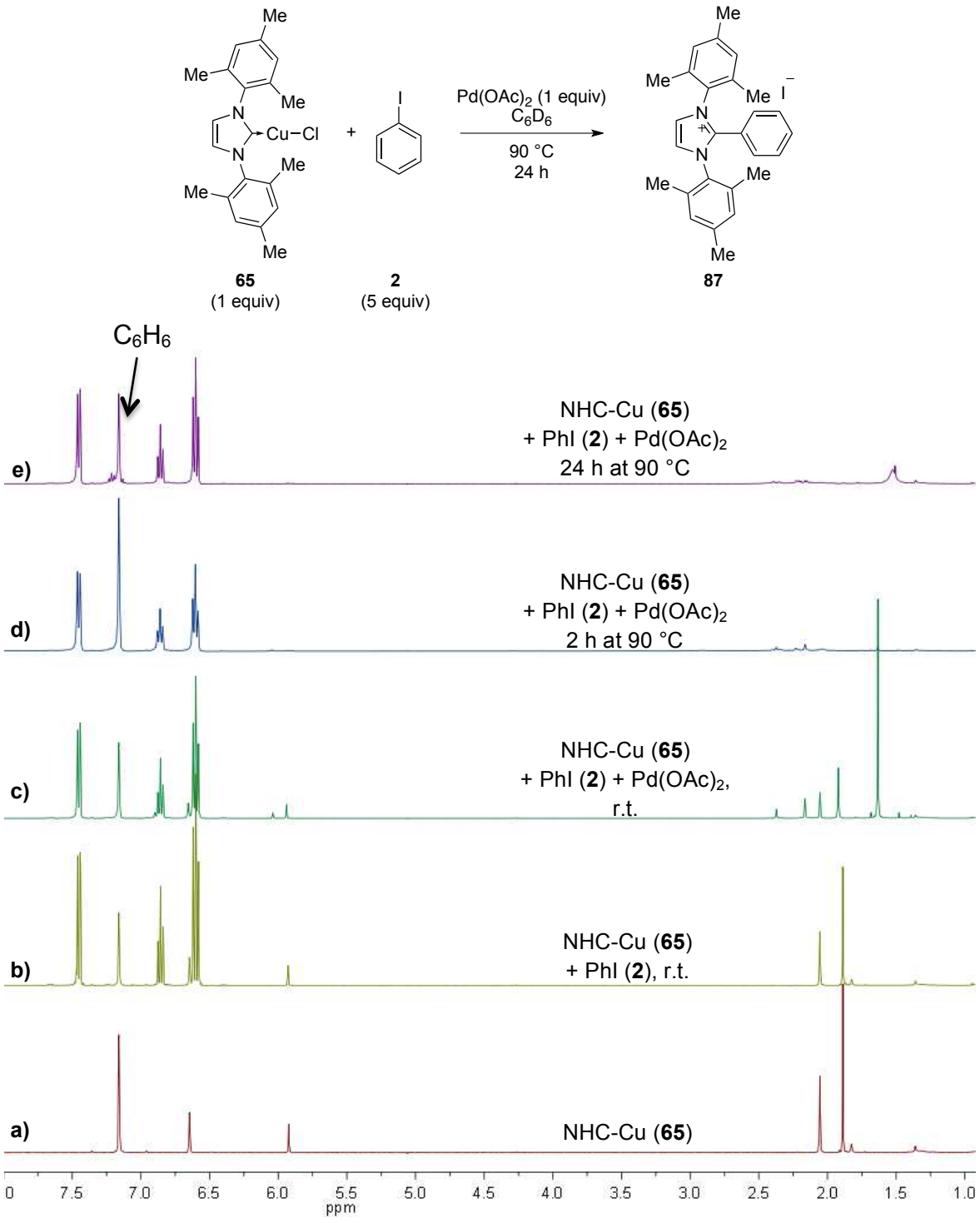
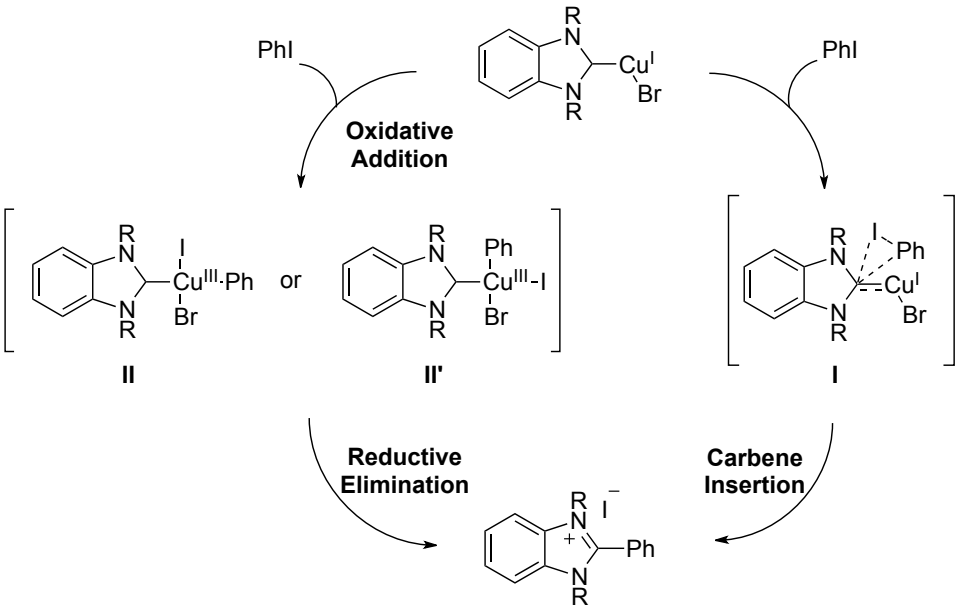



**Figure 36**: $^{1}$H-NMR spectra showing reaction outcome of Cu$^{I}$-NHC **65** with PhI (**2**) in the presence of $Pd(OAc)_2$. a) $^{1}$H-NMR spectrum of compound **65** in $C_6D_6$; b) $^{1}$H-NMR spectrum of compound **65** after the addition of PhI in $C_6D_6$ (**2**) at room temperature; c) $^{1}$H-NMR spectrum of compound **65** with PhI (**2**) after the addition of $Pd(OAc)_2$ in $C_6D_6$ at room temperature; d) $^{1}$H-NMR spectrum of compound **65** with PhI (**2**) in the presence of $Pd(OAc)_2$ after 2 h at 90 °C in $C_6D_6$; e) $^{1}$H-NMR spectrum of compound **65** with PhI (**2**) in the presence of $Pd(OAc)_2$ after 24 h at 90 °C in $C_6D_6$.

## 3. DFT calculations – assessment of the reaction pathway for arylation in the absence of Pd.

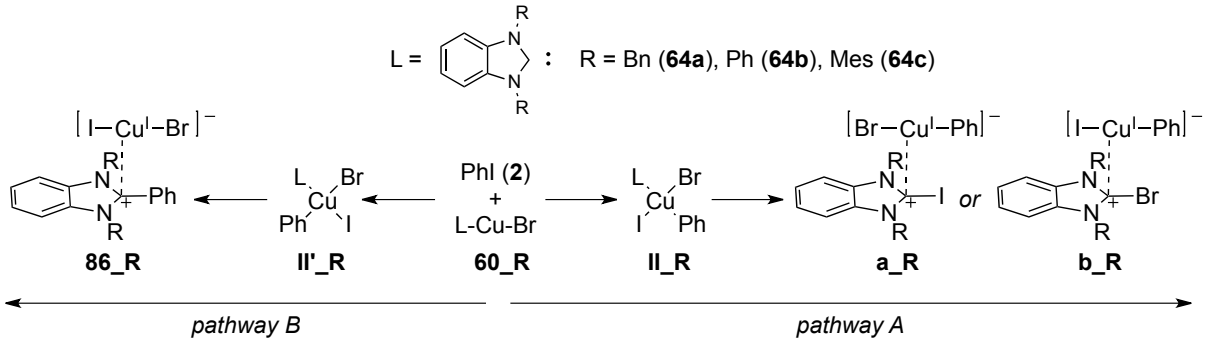
Given that the direct reaction of $Cu^{I}$-NHC complexes with iodobenzene (**2**) is possible in the absence of Pd to give arylated products (reactivity order **64b** > **64a** >> **65**), density functional theory (DFT) was used to understand potential reaction pathways for this process. The first pathway that we consider was a carbene insertion mechanism (*via* **I**, Scheme 70) akin to that reported by Pérez and co-workers.[151] A second plausible pathway involves a $Cu^{I}/Cu^{III}$ oxidative addition/reductive elimination process (*via* **II** and **II'**, Scheme 70), as suggested by Ribas and co-workers.[152]




**Scheme 70**: Possible mechanism pathways for the reaction of a $Cu^{I}$-NHC with PhI.

To better understand the feasibility of some of these mechanistic proposal and the effect of steric bulk of the *N*-substituent on reactivity, DFT calculations were conducted at the M06 level of theory for different NHC ligands (L) with L = benzyl (Bn), phenyl (Ph) and mesityl (Mes). Calculations were made in collaboration with the University of Leeds, the Azad University and the University of Tasmania. They were conducted initially on the structure of carbenes **64a**, **64b** and **64c** in order to find a possible trend of the reactivity of these copper-carbenes in the arylation with PhI (**2**) in the absence of Pd.

Initial calculations revealed that the carbene insertion pathway was unfeasible, and the oxidative addition/reductive elimination sequence was found to be most likely. For example, PhI (**2**) can oxidatively add to $Cu^{I}$ to give two different $Cu^{III}$ species **II_R** and **II'_R**, where the former has a phenyl group that is *trans* to the NHC ligand and the latter where the phenyl group is *cis* to the NHC ligand (Scheme 71). Interestingly, these two intermediate species (**II_R** and **II'_R**) were computed to be competitive. Crucially, the oxidative addition reactions are endoergonic, supporting the fact that the oxidation state of +3 at copper is unstable.




**Scheme 71**: Possible mechanistic pathways for the reaction of a $Cu^{I}$-NHC with PhI (**2**) to form halo-imidazolium (*pathway A*) or phenyl-imidazolium (*pathway B*).

The intermediate **II_R** can undergo the C-I (or C-Br) reductive elimination process to produce **a_R** or **b_R** (Scheme 71, *pathway A*). The formation of halo-imidazolium salts from Cu-NHCs has recently been reported by Willans and co-workers, with the presence of a $Cu^{II}$-NHC and excess $CuBr_2$ appearing to drive the successive disproportionation and reductive elimination reaction.[153] In the case of this work, calculations indicate that the C-I (or C-Br) couplings are energetically unfavorable (shown in Figure 37 for R = Bn, *pathway A*), explaining why the C-I and C-Br couplings are not observed experimentally under the conditions described earlier. By contrast, the intermediate **II'_R** (Scheme 71, *pathway B*) can undergo the C-C reductive elimination to produce the initial product **86_R**. The corresponding reaction is entirely exoergonic and has a small activation barrier of 2.8 kcal/mol for R = Ph, of 6.0 kcal/mol for R = Mes (Figure 38) and of 5.7 kcal/mol for R = Bn (Figure 37).

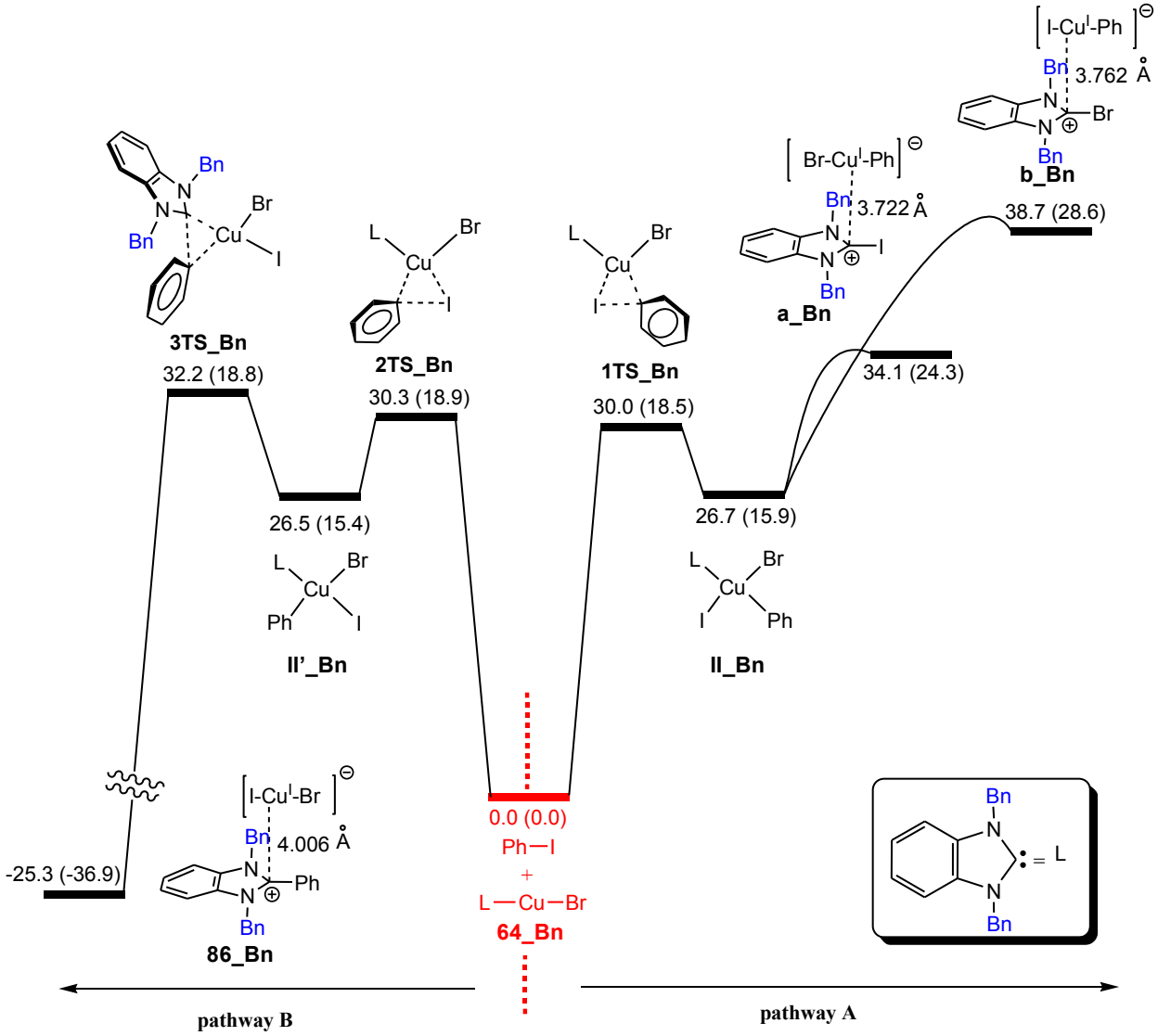



**Figure 37**: The calculated energy profile for C-I, C-Br and C-C couplings starting from **64_Bn** + PhI (**2**) *via* the oxidative addition/reductive elimination mechanism. The relative Gibbs energies and electronic energies (in parentheses) obtained from the M06/BS2//B3LYP/BS1 calculations in toluene are given in kcal/mol.

Interestingly, the stability of **II'_R** is affected by the steric bulk of the R groups; for the less bulky R groups such as Bn and Ph, intermediate **II'_R** is relatively stable (Figure 37 and Figure 38), and as a result the C-C reductive elimination reactions can occur with overall energy barriers being accessible under the reaction conditions: 32.2 and 27.5 kcal/mol for R = Bn and Ph, respectively. For comparability, we also computed a pathway for the hypothetical coompound **64c** where R = Mes (Figure 38). In this case the C-C reductive elimination requires an overall activation barrier of 39.4 kcal/mol, which is too high in energy. This is presumably due to the steric bulk of the Mes groups decreasing the stability of intermediate

**II'_Mes**, in turn, leading to an increase in the overall activation barrier of the C-C reductive elimination reaction.

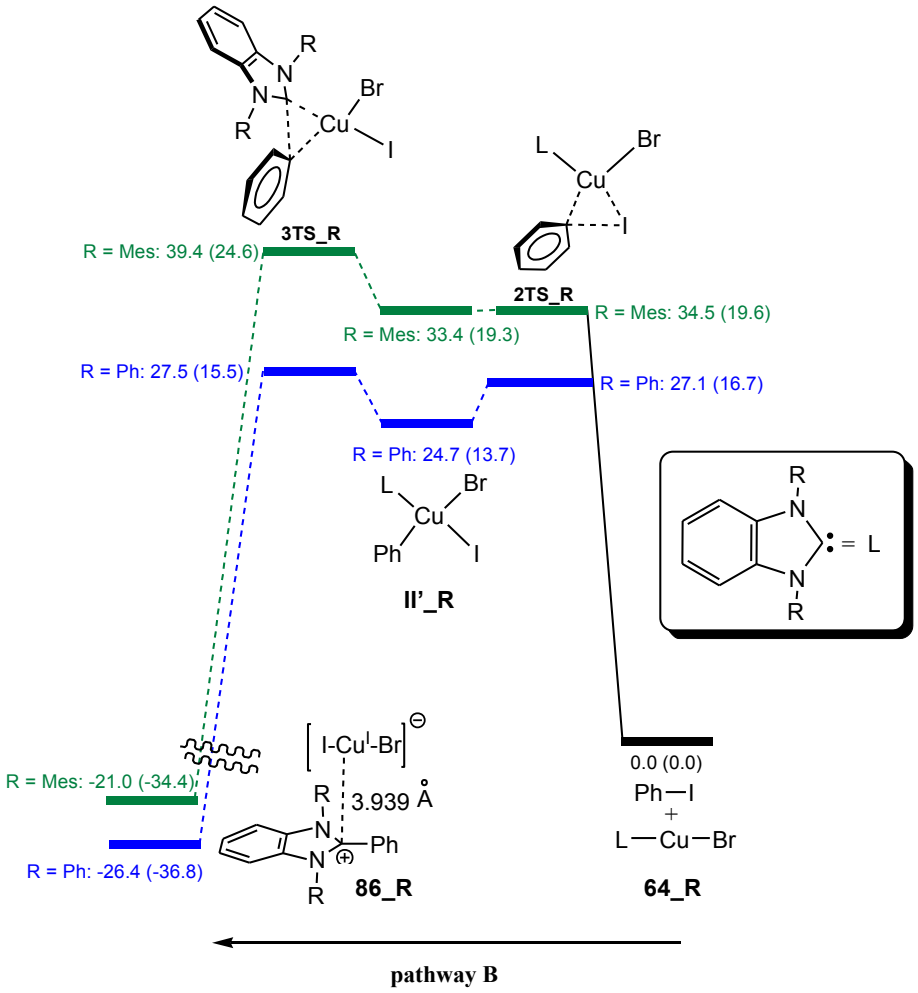
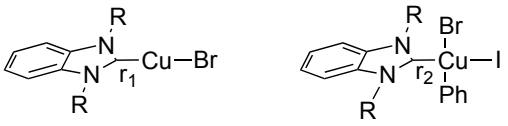



**Figure 38**: The calculated energy profile for C-C couplings starting from **64_R** + PhI (**2**) (R = Ph, Mes) *via* the oxidative addition/reductive elimination mechanism. The relative Gibbs energies and electronic energies (in parentheses) obtained from the M06/BS2//B3LYP/BS1 calcultaions in toluene are given in kcal/mol.

The calculations showed also that the Cu-C(NHC) bonds are lengthened upon going from **64_R** to **II′_R** (Figure 39). Although, the lengthening of the Cu-C(NHC) bond for the cases of R = Bn (0.039 Å) and R = Ph (0.043 Å) is comparable, it is more significant for R = Mes (0.118 Å). This result suggests that the *steric* hindrance of the mesityl groups renders the Cu-NHC bond in **II′_Mes** significantly weak, thereby leading to a more destabilization of **II′_R** relative to **64_R**, ultimately diminishing the reactivity of **64_Mes**.



**64_R** **II'_R**

| R | $r_1$(Å) | $r_2$(Å) | $\Delta r = r_2 - r_1$ |
|---|---|---|---|
| **Bn** | 1.933 | 1.972 | 0.039 |
| **Ph** | 1.933 | 1.976 | 0.043 |
| **Mes** | 1.925 | 2.043 | 0.118 |

**Figure 39**: The calculated Cu-C(NHC) bond distances for **64_R** ($r_1$) and **II'_R** ($r_2$) and the CuC(NHC) distance variations ($\Delta r$) upon moving from **64_R** to **II'_R**.

As already specified in paragraph 1.1 of this chapter, we were not able to synthesize the Cu-NHC **64c** in order to verify the viability of the computational calculations. Therefore, analyses on the imidazolium derivative **65** were afterwards made.

Calculations on derivative **65** were run (Figure 40) and from these data we could observe that with the imidazole ring the activation barrier resulted to be even higher than the parent benzimidazole system **64c**, being of 7 kcal/mol.

The reaction with $Pd(OAc)_2$ involves transmetalation of the NHC ligand from $Cu^I$ to $Pd^{II}$, which is well established. Indeed, as noted earlier, the arylation[121a-c] and alkylation[121e] of NHC ligands at $Pd^{II}$ are reported.

## 4. Conclusions.

In conclusion, we have demonstrated that after $Cu^I$-NHC complex **64a**, even **64b** undergoes a direct reaction with PhI (**2**), in the presence and absence of $Pd(OAc)_2$, to give arylated product **86b**. Arylation of complex **65** was also observed in the presence of $Pd(OAc)_2$ but more investigations are necessary in order to verify the yield and to characterized the arylation product.

DFT calculations show that the energy barrier for direct arylation from complex **65**, is too high due to steric bulk destabilizing the intermediates; hence the ligand requires transfer to $Pd^{II}$ to enable the reaction to proceed.

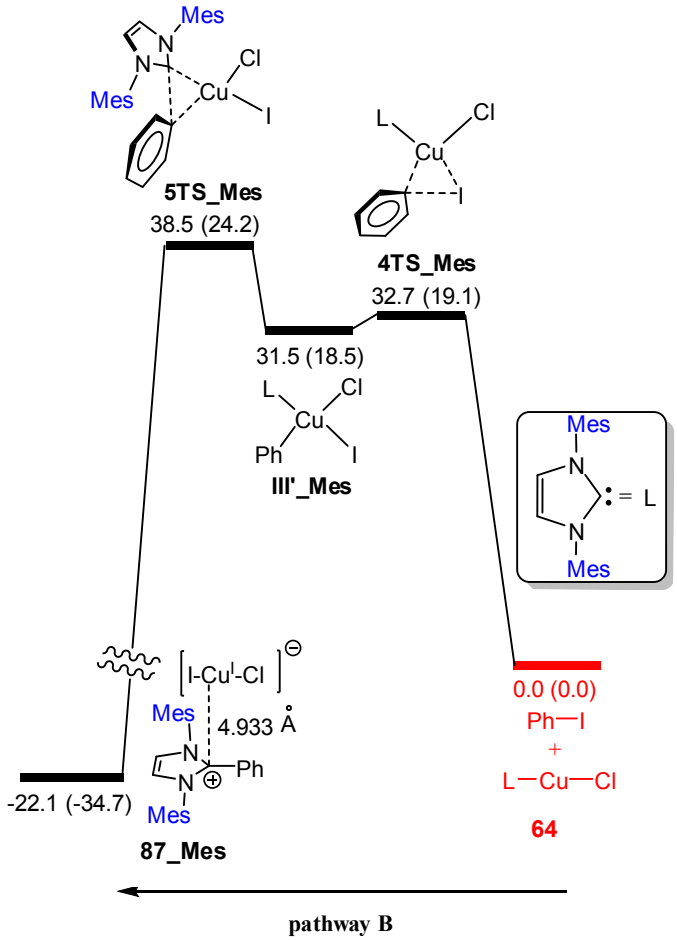



**Figure 40**: The calculated energy profile for C-C coupling starting from **65** + PhI (**2**) *via* the oxidative addition/reductive elimination mechanism. The relative Gibbs energies and electronic energies (in parentheses) obtained from the M06/BS2//B3LYP/BS1 calculations in toluene are given in kcal/mol.

Although these reactions are less effective in the absence of $Pd(OAc)_2$, our work represents the first successful reaction of Cu-NHCs with an aryl halide, and provides a valuable insight into the effect of *N*-substituent in these reactions. This study indicates that $Cu^I$-NHC species are viable intermediates in catalytic C-H bond functionalization processes involving (benz)azoles.

Finally, the DFT studies have demonstrated that an oxidative addition/reductive elimination pathway involving $Cu^{III}$ species is energetically feasible.

# CHAPTER 4

# *Experimental part*

*As regards **Chapter 1** and **Chapter 2**:*

GLC analyses were performed on a Dani GC 1000 instrument with a PTV injector, that was equipped with a Dani DDS 1000 data station. Two types of capillary columns, an Alltech AT-35 bonded FSOT column (30 m x 0.25 mm i.d.) and an Alltech AT-1 bonded FSOT column (30 m x 0.25 mm. i.d.) were used. Fluka precoated 60 F254 aluminium silica gel sheets were used for TLC analyses. Purifications by flash-cromatography were performed using silica gel Merck 60 (particle size 0.040-0.063 mm). GLC-MS analyses were performed using an Agilent 6890 Network GC system interfaced with an Agilent 5973 Network mass selective detector. NMR spectra were recorded at room temperature on a Varian Gemini 200 at 200 MHz ($^{1}$H) and 50.3 MHz ($^{13}$C), and we referred to TMS or to the residual protons of deuterated solvents.

All reactions with air- and water-sensitive materials were performed under argon and in flame-dried glassware when it was necessary, by standard syringe and septa technique. The completion of the reactions and the composition of the reaction mixtures were established on the basis of GLC and GLC-MS analyses of samples of the crude reaction mixtures filtered through a short plug of celite and eluted with additional AcOEt or $CH_2Cl_2$.

Dimethylacetamide (DMA) and $CH_2Cl_2$ were distilled from $CaH_2$. Anhydrous toluene, dimethylformamide (DMF), dioxane, *N*-methylpyrrolidinone (NMP) were commercially available (**Aldrich**) and were used as received. Pivalic acid and pyridine were distilled before the use. All the chemicals, unless specified, are commercially available from **Aldrich**. Oxazole (**4**), thiazole (**8**), 1-methyl-1*H*-imidazole (**12**), 1-methyl-1*H*-pyrazole (**15**), 1-phenyl-1*H*-pyrazole (**23**), 4-bromotoluene (**26a**), 4-bromoanisole (**26b**), 4-bromophenol (**26c**), 4-bromoaniline (**26d**) (**Carlo Erba**), 4-nitro-benzene (**26e**), 1-bromo-4-(trifluoromethyl)benzene (**26f**), ethyl-4-bromobenzoate (**26g**), 2-bromotoluene (**26h**), 1-bromo-2-chlorobenzene (**26i**), methyl-2-bromobenzoate (**26j**), 1-bromonaphtalene (**26k**), 2-bromoanisole (**26l**), 5-bromo-1,2,3-trimethoxybenzene (**26m**) (**Alfa Aesar**), 3-bromopyridine (**26n**), 5-bromopyrimidine (**26o**), 5-bromo-1*H*-indole (**26p**), 2-bromo-5-methylthiophene (**26q**), bromobenzene (**26r**) (**Carlo Erba**), 4-bromobenzonitrile (**26s**), 4-bromo-1,2-dimethoxybenzene (**26t**) (**Fluka**), 5-bromobenzo[*d*][1,3]dioxole (**26u**), 5-bromo-1,3-dimethoxybenzene (**26v**), $Pd(OAc)_2$, $Pd_2(dba)_2$, $PdCl_2$, $PdCl_2$(dppb), CuI, P(2-furyl)$_3$, $PPh_3$,

P(*o*-Tol)$_3$, PBuAd$_2$ (**5**) (**Stream Chemicals**), PCy$_3$ (**Stream Chemicals**), P(*t*Bu)$_2$biphenyl (**Stream Chemicals**), P(*t*Bu$_3$)·HBF$_4$ (**Lancaster**), Xantphos, Oxydiphenylene(PPh$_2$)$_2$, dppb, dppf, phenantroline, naphtalene (**Riedel-de Haën**), Ag$_2$CO$_3$, Na$_2$CO$_3$, Cs$_2$CO$_3$, K$_2$CO$_3$ (**Carlo Erba**), KHCO$_3$ (**Carlo Erba**), Bu$_4$NOAc, NaOAc, CsOAc, KOAc, AgOAc (**Fluka**), K$_3$PO$_4$ (**Riedel-de Haën**), KF, *t*BuOK, BnBu$_3$NCl, Bu$_4$NBr and BnEt$_3$NCl, were commercially available and were used without further purification.
PdCl$_2$(MeCN)$_2$ was prepared according to the literature.[154]

*As regards **Chapter 3**:*

All air sensitive procedures were carried out using Schlenk techniques (high vacuum, liquid nitrogen trap on a standard in-house built dual line). When necessary a glove (dry) box was used (<0.5 ppm $O_2$). Room temperature upper and lower limits are stated as 13-25 °C, but typically 21-23 °C was recorded. Commercial chemicals were purchased from Sigma-Aldrich® and Alfa Aesar® and used directly unless otherwise stated in the text. TLC analysis was carried out on Merck TLC aluminium sheets (silica gel 60 F254) and visualized with UV light (at 254 nm), iodine vapour or an aqueous solution of potassium permanganate. Flash chromatography was run on silica gel 60 according to the method reported by W. C. Still *et al.*[155] Melting points were recorded using a Stuart digital SMP3 machine and are uncorrected values. NMR spectra were obtained in the solvent indicated, using a JEOL ECX400 (400 MHz and 101 MHz for $^1$H and $^{13}$C, respectively). Chemical shifts are reported in ppm and were referenced to the residual undeuterated solvent of the deuterated solvent used. Spectra were typically run at a temperature of 300 K. All $^{13}$C NMR spectra were obtained with $^1$H decoupling. NMR spectra were processed using MestrNova software (version 8.01). The spectra given below were saved as either .BMP or .PNG files in MestrNova and inserted directly into a Microsoft Word Document. For the $^1$H NMR spectra the resolution varies from 0.15 to 0.5 Hz; the coupling constants have been quoted to ±0.5 Hz in all cases for consistency. $^1$H NMR chemical shifts are quoted to 2 decimal places; $^{13}$C NMR chemical shifts are quoted to 1 decimal place. Numbers were rounded to the nearest value, *e.g.* 1.237 ≈ 1.24, 1.232 ≈ 1.23.
MS spectra were measured using a Bruker Daltronics micrOTOF MS, Agilent series 1200LC with electrospray ionization (ESI and APCI) or on a Thermo LCQ using electrospray

ionization, with < 5 ppm error recorded for all HRMS samples. LIFDI mass spectrometry was carried out using a Waters GCT Premier MS Agilent 7890A GC (usually for analysis of organometallic compounds when ESI or APCI are not satisfactory ionization methods). Mass spectral data is quoted as the *m/z* ratio along with the relative peak height in brackets (base peak = 100).

**X-Ray crystallography.** Diffraction data were collected at 110 K on a Bruker Smart Apex diffractometer with Mo-$K_\alpha$ radiation ($\lambda$ = 0.71073 Å) using a SMART CCD camera. Diffractometer control, data collection and initial unit cell determination was performed using "SMART" (v5.625 Bruker-AXS). Frame integration and unit-cell refinement software was carried out with "SAINT+" (v6.22, Bruker AXS). Absorption corrections were applied by SADABS (v2.03, Sheldrick). Structures were solved by direct methods using SHELXS-97 (Sheldrick, 1990) and refined by full-matrix least squares using SHELXL-97 (Sheldrick, 1997). All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed using a "riding model" and included in the refinement at calculated positions.

**DFT calculations.** Gaussian 09[156] was used to fully optimize all structures of Chapter 3 at the B3LYP level of density functional theory (DFT).[157] The effective core potential of Hay and Wadt with a double-$\xi$ valence basis set (LANL2DZ)[158] was chosen to describe Cu and I. The 6-31G(d) basis set was used for other atoms.[159] Polarization functions for Cu ($\xi_f$ = 3.525) and I ($\xi_d$ = 0.289) were also added.[160] This basis set combination will be referred to as BS1. Frequency calculations were carried out at the same level of theory as for structural optimization. IRC[161] calculations were used to confirm the connectivity between transition structures and minima. Because recent studies have established that M06[162] predicts the activation energies more accurately than B3LYP,[163] we carried out single-point energy calculations for all the structures with a larger basis set (BS2) at the M06 level. BS2 utilizes the quadruple-$\zeta$ valence def2-QZVP[164] basis set on Pt and the 6-311+G(2d,p) basis set on other atoms. The solvation energies were calculated using BS2 on optimized geometries with the CPCM solvation model using DMF as solvent.[165] To estimate the corresponding Gibbs free energies, $\Delta G$, the entropy corrections were calculated at the B3LYP/BS1 level, adjusted by the method proposed by Okuno[166] and finally added to the M06/BS2 total energies. We have used the potential and Gibbs free energies obtained from the M06/BS2//B3LYP/BS1 calculations in DMF unless otherwise stated.

# 1. General procedure for the screening of the reaction conditions for the Pd-catalyzed C-5 arylation of 1-methyl-1*H*-pyrazole (15) with 4-bromotoluene (26a).

A mixture of 1-methyl-1*H*-pyrazole (**15**) (83 μL, 82 mg, 1.0 mmol), palladium catalyst (0.05 mmol), ligand (if any) (0.10 mmol), 4-bromotoluene (**26a**) (0.26 g, 1.5 mmol), base (2.0 mmol) in the selected solvent (5 mL) was stirred under argon for 24 h at the temperature reported in Table 1-Table 3. After cooling to room temperature, the crude reaction mixture was diluted with AcOEt, naphthalene was added as internal standard, and the resulting mixture was analyzed by GLC and GLC-MS. Table 1-Table 3 summarize the results of this screening.

## 1.1. 1-Methyl-5-(*p*-tolyl)-1*H*-pyrazole (21a) and 1-methyl-4,5-di-*p*-tolyl-1*H*-pyrazole (27a).

The crude reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (70:30 + 0.1 % $Et_3N$) as eluent. Concentration of the first eluted chromatographic fractions allowed isolation of compound **27a** (23 mg, 12 % yield, entry 9, Table 2) as a pale-yellow solid, m.p. 162–164 °C. $^1$H NMR (200 MHz, $CDCl_3$): δ = 7.70 (s, 1H), 7.20 (m, 4H), 7.04 (m, 4H), 3.79 (s, 3H), 2.41 (s, 3H), 2.28 (s, 3H) ppm. $^{13}$C NMR (50.3 MHz, $CDCl_3$): δ = 139.7, 138.5, 137.3, 135.4, 130.2, 129.9, 129.4, 129.0, 127.5, 127.1, 120.7, 31.2, 21.4, 21.0 ppm. MS (EI): m/z (%) = 263 (21), 262 (100), 261 (19), 247 (10), 232 (6), 202 (4), 189 (4), 130 (4). $C_{18}H_{18}N_2$ (262.35): calcd. C 82.41, H 6.92, N 10.68; found C 82.84, H 6.89, N 10.73.

Concentration of the last eluted chromatographic fractions allowed isolation of compound **21a** (89 mg, 52 %, entry 9, Table 2) as a light-yellow oil. $^1$H NMR (200 MHz, $CDCl_3$): δ 7.49 (d, *J* = 1.9 Hz, 1H), 7.27 (m, 4H), 6.26 (d, *J* = 1.9 Hz, 1H), 3.87 (s, 3H), 2.39 (s, 3H) ppm. $^{13}$C NMR (50.3 MHz, $CDCl_3$) δ 143.4, 138.3, 138.2, 129.2 (2C), 128.5 (2C), 127.7, 105.7, 37.4, 21.2 ppm. MS (EI): m/z (%) = 173 (13), 172 (100), 171 (33), 157 (9), 144 (10), 130 (9), 128 (9), 115 (9). The spectral properties of this compound are in agreement with those previously reported.[167] This compound was also obtained in isolated yield of 47 % from

the Pd-catalyzed reactions of **15** and **26a** carried out at 110 °C (entry 12, Table 2) or in 58 % from the reaction at 70 °C (entry 17, Table 3).

### 1.2. General procedure for the palladium-catalyzed direct 5-arylation of 1-methyl-1*H*-pyrazole (15), oxazole (4), thiazole (8), and 1-methyl-1*H*-imidazole (12) with aryl bromides 26a–s.

$Pd(OAc)_2$ (11.2 mg, 0.05 mmol), $Bu_4NOAc$ (0.60 g, 2.0 mmol), and aryl bromide **26** (1.5 mmol), if a solid, were placed in a flame-dried reaction vessel. The reaction vessel was fitted with a silicon septum, evacuated, and back-filled with argon. This sequence was repeated twice. DMA (5 mL), aryl bromide **26** (1.5 mmol), if a liquid, and the appropriate azole **15**, **4**, **8**, or **12** (1.0 mmol) were then added successively under a stream of argon by syringe at room temperature. The resulting mixture was stirred at 70 °C (for azoles **15**, **4**, and **8**) or at 110 °C (for azole **12**) under argon for the period of time reported in Table 3. After cooling to room temperature, the reaction mixture was diluted with EtOAc, filtered through a plug of Celite, and eluted with additional EtOAc and $CH_2Cl_2$. The filtrate was concentrated under reduced pressure and the residue purified by flash chromatography on silica gel. This procedure was used to prepare compounds **21b-q**, **30a-h**, **31a-h**, **32a-h** and **32r-s** (Table 4-Table 6).

#### 1.2.1. 5-(4-Methoxyphenyl)-1-methyl-1*H*-pyrazole (21b).

The crude reaction product, which was obtained by Pd-catalyzed reaction of **15** with **26b** (entry 2, Table 4), was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (60:40 + 0.1% $Et_3N$) as eluent to give **21b** (0.11 g, 58 %) as a yellow oil. $^1H$ NMR (200 MHz, $CDCl_3$): δ 7.48 (d, $J$ = 1.9 Hz, 1H), 7.32 (m, 2H), 6.97 (m, 2H), 6.24 (d, $J$ = 1.9 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H) ppm. $^{13}C$ NMR (50.3 MHz, $CDCl_3$): δ 159.1, 138.3, 133.0, 129.5 (2C), 127.1, 121.8, 113.9 (2C), 55.1, 32.1 ppm. MS (EI): m/z (%) = 189 (13), 188 (100), 174 (7), 173 (61), 145 (10). The spectral properties of this compound are in agreement with those previously reported.[59]

### 1.2.2. 4-(1-Methyl-1*H*-pyrazol-5-yl)phenol (21c).

The crude reaction product, which was obtained by Pd-catalyzed reaction of **15** with **26c** (entry 3, Table 4), was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (1:1) as eluent to give **21c** (48 mg g, 28 %) as a white solid, m.p. 180-184 °C. $^1$H NMR (200 MHz, $CDCl_3$): δ 8.75 (br, 1H), 7.57 (d, *J* = 1.8 Hz, 1H), 7.28 (m, *J* = 8.4 Hz, 2H), 6.98 (m, *J* = 8.4 Hz, 2H), 6.29 (d, *J* = 1.8 Hz, 1H), 3.89 (s, 3H) ppm. $^1$H NMR (200 MHz, $CD_3OD/CDCl_3$): δ 7.47 (d, *J* = 1.8 Hz, 1H) 7.25 (d, *J* = 8.4 Hz, 2H), 6.92 (d, *J* = 8.4 Hz, 2H), 6.24 (d, *J* = 1.8 Hz, 1H), 3.84 (s, 3H). $^{13}$C NMR (50.3 MHz, $CD_3OD/CDCl_3$): δ 157.3, 144.0, 138.1, 129.9 (2C), 121.3, 115.4 (2C), 105.4, 36.9. MS (EI): m/z (%) = 175 (12), 174 (100), 173 (25), 131 (11), 119 (12). $C_{10}H_{10}N_2O$ (174.20): calcd. C 68.95, H 5.79, N 16.08; found C 69.01, H 3.90, N 12.29.

### 1.2.3. 1-Methyl-5-(4-nitrophenyl)-1*H*-pyrazole (21e).

The crude reaction product, which was obtained by Pd-catalyzed reaction of **15** with **26e** (entry 5, Table 4), was purified by flash chromatography on silica gel with a mixture of $CH_2Cl_2$ and acetone (98:2) as eluent to give **21e** (0.20 g, 46 %) as a yellow solid, m.p. 75-77°C. $^1$H NMR (200 MHz, $CDCl_3$): δ 8.33 (m, 2H), 7.65 (m, 2H), 7.57 (d, *J* = 1.9 Hz, 1H), 6.47 (d, *J* = 1.9 Hz, 1H), 3.98 (s, 3H) ppm. $^{13}$C NMR (50.3 MHz, $CDCl_3$): δ 147.6, 141.4, 139.0, 136.9, 129.4 (2C), 124.0 (2C), 107.4, 38.0 ppm. MS (EI): m/z (%) = 204 (12), 203 (100), 173 (20), 103 (11), 89 (10). The physical and spectral properties of this compound are in agreement with those previously reported.[59]

### 1.2.4. 5-[4-(Trifluoromethyl)phenyl]-1-methyl-1*H*-pyrazole (21f).

The crude reaction product, which was obtained by Pd-catalyzed reaction of **15** with **26f** (entry 6, Table 4), was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (85:15 + 0.1% $Et_3N$) as eluent to give **21f** (68 mg, 30 %) as a pale-yellow oil. $^1$H NMR (200 MHz, $CDCl_3$): δ 7.72 (m, 2H), 7.55 (m, 2H), 7.54 (d, *J* = 1.9 Hz, 1H), 6.37 (d, *J* = 1.9 Hz, 1H), 3.92 (s, 3H) ppm. $^{13}$C NMR (50.3 MHz, $CDCl_3$): δ 142.0, 138.7, 134.3, 130.1, 129.0 (2C), 125.6 (q, *J* = 3.7 Hz, 2C), 123.9 (q, *J* = 272 Hz, $CF_3$), 106.6, 37.6 ppm.

MS (EI): m/z (%) = 227 (13), 226 (100), 225 (47), 207 (9), 198 (9). $C_{11}H_9F_3N_2$ (226.20): calcd. C 58.41, H 4.01, N 12.38; found C 58.35, H 3.99, N 12.42.

### 1.2.5. Ethyl 4-(1-methyl-1*H*-pyrazol-5-yl)benzoate (21g).

The crude reaction product, which was obtained by Pd-catalyzed reaction of **15** with **26g** (entry 7, Table 4), was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (80:20) as eluent to give **21g** (95 mg, 41 %) as a yellow oil. $^1$H NMR (200 MHz, $CDCl_3$): δ 8.13 (m, 2H), 7.53 (d, *J* = 1.6 Hz, 1H), 7.51 (m, 2H), 6.38 (d, *J* = 1.6 Hz, 1H), 4.41 (q, *J* = 7.2 Hz, 2H), 3.92 (s, 3H), 1.42 (t, *J* = 7.2 Hz, 3H) ppm. $^{13}$C NMR (50.3 MHz, $CDCl_3$): δ 165.9, 142.4, 138.6, 134.8, 130.2, 129.8 (2C), 128.4 (2C), 106.5, 61.1, 37.7, 14.3 ppm. MS (EI): m/z (%) = 231 (11), 230 (78), 202 (24), 186 (16), 185 (100). $C_{13}H_{14}N_2O_2$ (230.27): calcd. C 67.81, H 6.13, N 12.17; found C 67.89, H 6.11, N 12.21.

### 1.2.6. 1-Methyl-5-(*o*-tolyl)-1*H*-pyrazole (21h).

The crude reaction product, which was obtained by Pd-catalyzed reaction of **15** with **26h** (entry 8, Table 4), was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (70:30 + 0.1% $Et_3N$) as eluent to give **21h** (80 mg, 47 %) as a pale-yellow oil. $^1$H NMR (200 MHz, $CDCl_3$): δ 7.53 (d, *J* = 1.9 Hz, 1H), 7.28 (m, 4H), 6.19 (d, *J* = 1.9 Hz, 1H), 3.65 (s, 3H), 2.16 (s, 3H) ppm. $^{13}$C NMR (50.3 MHz, $CDCl_3$): δ 142.3, 138.2, 137.4, 130.4, 130.1 (2C), 128.9, 125.6, 106.2, 36.5, 19.8 ppm. MS (EI): m/z (%) = 172 (100), 171 (57), 144 (70), 128 (16), 115 (20). $C_{11}H_{12}N_2$ (172.23): calcd. C 76.71, H 7.02, N 16.27; found C 76.65, H 7.06, N 16.22.

### 1.2.7. 5-(2-Chlorophenyl)-1-methyl-1*H*-pyrazole (21i).

The crude reaction product, which was obtained by Pd-catalyzed reaction of **15** with **26i** (entry 9, Table 4), was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (90:10 + 0.1 % $Et_3N$) as eluent to give **21i** (82 mg, 42 %) as a pale-yellow oil. $^1$H NMR (200 MHz, $CDCl_3$): δ 7.54 (d, *J* = 1.9 Hz, 1H), 7.34 (m, 5H), 6.27 (d, *J* = 1.9 Hz, 1H), 3.72 (s, 3H) ppm. $^{13}$C NMR (50.3 MHz, $CDCl_3$): δ 140.2, 138.2, 134.2, 131.8, 130.3,

129.94, 129.71, 126.7, 106.9, 36.9 ppm. MS (EI): m/z (%) = 194 (32), 193 (23), 192 (100), 191 (33), 156 (12). $C_{10}H_9ClN_2$ (192.65): calcd. C 62.35, H 4.71, N 14.54; found C 62.40, H 4.69, N 14.59.

### 1.2.8. 1-Methyl-5-(1-naphthyl)-1*H*-pyrazole (21k).

The crude reaction product, which was obtained by Pd-catalyzed reaction of **15** with **26k** (entry 11, Table 4), was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (80:20 + 0.1 % of $Et_3N$) as eluent to give **21k** (0.11 g, 50 %) as a pale-yellow solid, m.p. 87-90 °C. $^1$H NMR (200 MHz, $CDCl_3$): δ 7.88 (m, 2H), 7.63 (d, *J* = 1.8 Hz, 1H), 7.47 (m, 5H), 6.34 (d, *J* = 1.8 Hz, 1H), 3.61 (s, 3H) ppm. $^{13}$C NMR (50.3 MHz, $CDCl_3$): δ 141.2, 138.4, 133.4, 132.00, 129.2, 128.3, 128.2, 128.1, 126.7, 126.1, 125.2, 124.9, 107.5, 36.9 ppm. MS (EI): m/z (%) = 209 (16), 208 (100), 207 (40), 180 (23), 153 (27). The spectral properties of this compound are in agreement with those previously reported.[59]

### 1.2.9. 3-(1-Methyl-1*H*-pyrazol-5-yl)pyridine (21n).

The crude reaction product, which was obtained by Pd-catalyzed reaction of **15** with **26n** (entry 14, Table 4), was purified by flash chromatography on silica gel with a mixture of AcOEt and MeOH (90:10) as eluent to give **21n** (53 mg, 33 %) as a brown oil. $^1$H NMR (200 MHz, $CDCl_3$): δ 8.71-8.65 (m, 2H), 7.79-7.74 (m, 1H), 7.55 (d, *J* = 1.6 Hz, 1H), 7.46-7.39 (m, 1H), 6.38 (d, J = 1.8 Hz, 1H), 3.91 (s, 3H). $^{13}$C NMR (50.3 MHz, $CDCl_3$): δ 149.8, 149.0, 141.1, 137.9 136.5, 122.6, 122.1, 106.3, 39.2 ppm. MS (EI): m/z (%) = 160 (11), 159 (100), 158 (20), 131 (51), 104 (12). The spectral properties of this compound are in agreement with those previously reported.[168]

### 1.2.10. 1-Methyl-5-(5-methylthiophen-2-yl)-1*H*-pyrazole (26q)

The crude reaction product, which was obtained by Pd-catalyzed reaction of **15** with **26q** (entry 17, Table 4), was purified by flash chromatography on silica gel with a mixture of AcOEt and MeOH (90:10) as eluent to give **21q** (19.5 mg, 11 %) as a brown oil. $^1$H NMR (200 MHz, $CDCl_3$): δ 7.45 (d, *J* = 1.8 Hz, 1H), 6.95 (d, *J* = 3.6 Hz, 1H), 6.77 (dq, $J^l$ = 3.4 Hz,

$J^2$ = 1 Hz, 1H), 6.33 (d, $J$ = 2.2 Hz, 1H), 3.96 (s, 3H), 2.52 (d, $J$ = 1 Hz, 3H) ppm. $^{13}$C NMR (50.3 MHz, $CDCl_3$): δ 141.3, 138.4, 136.9, 129.0, 126.8, 125.8, 106.4, 37.8, 15.3 ppm. MS-(EI): m/z (%) = 179 (13), 178 (100), 177 (49), 163 (8), 145 (8).

### 1.2.11. 5-(*p*-Tolyl)oxazole (30a).

The crude reaction product, which was obtained by Pd-catalyzed reaction of **4** with **26a** (entry 1, Table 5), was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (90:10) as eluent to give **30a** (92 mg, 58 %) as a yellow solid, m.p. 38-41 °C. $^1$H NMR (200 MHz, $CDCl_3$): δ 7.88 (s, 1H), 7.51 (m, 2H), 7.28 (s, 1H), 7.19 (m, 2H), 2.35 (s, 3H) ppm. $^{13}$C NMR (50.3 MHz, $CDCl_3$): δ 151.7, 150.2, 138.7, 129.5 (2C), 124.9, 124.3 (2C), 120.6, 21.4 ppm. MS (EI): m/z (%) = 159 (100), 131 (26), 130 (38), 104 (34), 103 (21), 91 (21). The spectral properties of this compound are in agreement with those previously reported.[169]

### 1.2.12. 5-(4-Methoxyphenyl)oxazole (30b).

The crude reaction product, which was obtained by Pd-catalyzed reaction of **4** with **26b** (entry 2, Table 5), was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (80:20) as eluent to give **30b** (85 mg, 49 %) as a yellow solid, m.p. 45-48 °C. $^1$H NMR (200 MHz, $CDCl_3$): δ 7.89 (s, 1H), 7.57 (m, 2H), 7.23 (s, 1H), 6.94 (m, 2H), 3.82 (s, 3H) ppm. $^{13}$C NMR (50.3 MHz, $CDCl_3$): δ 159.7, 151.4, 149.7, 125.8 (2C), 120.5, 119.9, 114.2 (2C), 55.3 ppm. MS (EI): m/z (%) = 176 (11), 175 (100), 160 (37), 132 (27), 77 (22). The spectral properties of this compound are in agreement with those previously reported.[33]

### 1.2.13. 4-(Oxazol-5-yl)phenol (30c).

The crude reaction product, which was obtained by Pd-catalyzed reaction of **4** with **26c** (entry 3, Table 5), was purified by flash chromatography on silica gel with a mixture of toluene and THF (80:20) as eluent to give **30c** (58 mg, 36 %) as a colorless solid, m.p. 229-230 °C. $^1$H NMR (200 MHz, [$D_6$]DMSO): δ 9.85 (s, OH), 8.35 (s, 1H), 7.56 (m, 2H), 7.47 (s,

1H), 6.89 (m, 2H) ppm. $^{13}$C NMR (50.3 MHz, [$D_6$]DMSO): δ 157.6, 150.8, 150.6, 125.6 (2C), 119.4, 118.5, 115.6 (2C) ppm. MS (EI): m/z (%) = 161 (100), 133 (20), 121 (19), 106 (30), 105 (29). $C_9H_7NO_2$ (161.16): calcd. C 67.07, H 4.38, N 8.69; found C 66.91, H 4.40, N 8.62.

### 1.2.14. 5-(4-Nitrophenyl)oxazole (30e).

The crude reaction product, which was obtained by Pd-catalyzed reaction of **4** with **26e** (entry 4, Table 5) was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (80:20) as eluent to give **30e** (0.11 g, 57 %) as a yellow solid, m.p. 135-137 °C. $^1$H NMR (200 MHz, $CDCl_3$): δ 8.31 (m, 2H), 8.06 (s, 1H), 7.84 (m, 2H), 7.59 (s, 1H) ppm. $^{13}$C NMR (50.3 MHz, $CDCl_3$): δ 151.9, 149.5, 147.4, 133.4, 124.9 (2C), 124.7, 124.5 (2C) ppm. MS (EI): m/z (%) = 190 (100), 160 (43), 132 (25), 89 (91), 63 (21). The spectral properties of this compound are in agreement with those previously reported.[170]

### 1.2.15. 5-(*o*-Tolyl)oxazole (30h).

The crude reaction product, which was obtained by Pd-catalyzed reaction of **4** with **26h** (entry 5, Table 5), was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (90:10) as eluent to give **30h** (0.11 g, 72 %) as a pale-yellow oil. $^1$H NMR (200 MHz, $CDCl_3$): δ 7.96 (s, 1H), 7.67 (m, 1H), 7.27 (m, 4H), 2.48 (s, 3H) ppm. $^{13}$C NMR (50.3 MHz, $CDCl_3$): δ 150.8, 150.1, 134.9, 131.0, 128.5, 127.0, 126.9, 126.1, 124.1, 21.7 ppm. MS (EI): m/z (%) = 159 (100), 132 (35), 131 (44), 130 (49), 104 (36). The spectral properties of this compound are in agreement with those previously reported.[33]

### 1.2.16. 5-(*p*-Tolyl)thiazole (31a).

The crude reaction product, which was obtained by Pd-catalyzed reaction of **8** with **26a** (entry 6, Table 5), was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (90:10 + 0.1 % Et3N) as eluent to give **31a** (0.11 g, 65 %) as a pale-yellow solid, m.p. 82-84 °C. $^1$H NMR (200 MHz, $CDCl_3$): δ 8.69 (s, 1H), 8.02 (s, 1H), 7.44 (m, 2H), 7.18 (m, 2H), 2.35 (s, 3H) ppm. $^{13}$C NMR (50.3 MHz, $CDCl_3$): δ 151.4, 139.3, 138.4, 138.3, 129.6 (2C), 128.1, 126.7 (2C), 21.2 ppm. MS (EI): m/z (%) = 176 (12), 175

(100), 148 (32), 147 (43), 115 (17). The spectral properties of this compound are in agreement with those previously reported.[171]

### 1.2.17. 5-(4-Methoxyphenyl)thiazole (31b).

The crude reaction product, which was obtained by Pd-catalyzed reaction of **8** with **26b** (entry 7, Table 5), was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (92:8) as eluent to give **31b** (0.13 g, 67 %) as a bright-yellow solid, m.p. 89-92 °C. $^{1}$H NMR (200 MHz, $CDCl_3$): δ 8.68 (s, 1H), 7.97 (s, 1H), 7.48 (m, 2H), 6.92 (m, 2H), 3.82 (s, 3H) ppm. $^{13}$C NMR (50.3 MHz, $CDCl_3$): δ 159.8, 151.2, 139.2, 138.0, 128.2 (2C), 123.6, 114.5 (2C), 55.4 ppm. MS (EI): m/z (%) = 191 (100), 176 (58), 149 (20), 148 (27), 121 (20). The spectral properties of this compound are in agreement with those previously reported.[47]

### 1.2.18. 4-(Thiazol-5-yl)phenol (31c).

The crude reaction product, which was obtained by Pd-catalyzed reaction of **8** with **26c** (entry 8, Table 5), was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (60:40) as eluent to give **31c** (29 mg, 17 %) as a yellow solid, 205-210 °C. $^{1}$H NMR (200 MHz, $CD_3OD$): δ 8.85 (s, 1H), 7.99 (s, 1H), 7.48 (m, 2H), 6.84 (m, 2H) ppm. $^{13}$C NMR (50.3 MHz, $CDCl_3$): δ 159.3, 153.1, 141.1, 138.0, 129.3 (2C), 123.3, 117.0 (2C) ppm. MS (EI): m/z (%) = 178 (13), 177 (100), 150 (37), 121 (23), 77 (10). The spectral properties of this compound are in agreement with those previously reported.[172]

### 1.2.19. 5-(4-Nitrophenyl)thiazole (31e).

The crude reaction product, which was obtained by Pd-catalyzed reaction of **8** with **26e** (entry 9, Table 5), was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (80:20) as eluent to give **31e** (0.14 g, 70 %) as a yellow solid, m.p. 139-141 °C. $^{1}$H NMR (200 MHz, $CDCl_3$): δ 8.93 (s, 1H), 8.29 (m, 2H), 8.26 (s, 1H), 7.76 (m, 2H) ppm. $^{13}$C NMR (50.3, $CDCl_3$): δ 154.2, 147.4, 141.1, 137.4, 127.4 (2C), 126.2, 124.5 (2C) ppm. MS (EI): m/z (%) = 206 (100), 176 (26), 148 (20), 133 (27), 89 (53). $C_9H_6N_2O_2S$

(206.22): calcd. C 52.42, H 2.93, N 13.58; found C 52.35, H 2.95, N 13.63.

### 1.2.20. 5-(*o*-Tolyl)thiazole (31h).

The crude reaction product, which was obtained by Pd-catalyzed reaction of **8** with **26h** (entry 10, Table 5), was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (90:10) as eluent to give **31h** (0.10 g, 59 %) as a pale-yellow oil. $^{1}$H NMR (200 MHz, $CDCl_3$): δ 8.79 (s, 1H), 7.84 (s, 1H), 7.27 (m, 4H), 2.37 (s, 3H) ppm. $^{13}$C NMR (50.3 MHz, $CDCl_3$): δ 152.5, 141.5, 137.3, 136.3, 130.7, 130.6, 130.1, 128.5, 126.0, 21.0 ppm. MS (EI): m/z (%) = 176 (12), 175 (95), 148 (49), 147 (100), 115 (52). $C_{10}H_9NS$ (175.25): calcd. C 68.53, H 5.18, N 7.99; found C 68.59, H 5.15, N 8.06.

### 1.2.21. 4-(Thiazol-5-yl)benzonitrile (31s).

The crude reaction product, which was obtained by Pd-catalyzed reaction of **8** with **26s** (Table 10), was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (90:10) as eluent to give **31s** (113 mg, 61 %) as a yellow solid, m.p. 101-102 °C [Lit. 102 °C].[47] $^{1}$H NMR (200 MHz, $CDCl_3$): δ 8.86 (s, 1H), 8.19 (s, 1H), 7.70 (m, 4H) ppm. $^{13}$C NMR (50.3 MHz, $CDCl_3$): δ 153.7, 140.5, 137.2, 132.7, 135.3, 127.1, 118.2, 111.6 ppm. MS (EI): m/z (%) = 187 (%), 186 (100), 160 (10), 115 (10), 114 (12). The spectral properties of this compound are in agreement with those previously reported.[46]

### 1.2.22. 1-Methyl-5-(*p*-tolyl)-1*H*-imidazole (32a).

The crude reaction product, which was obtained by Pd-catalyzed reaction of **12** with **26a** (entry 1, Table 6), was purified by flash chromatography on silica gel with a mixture of $CH_2Cl_2$ and MeOH (96:4) as eluent to give **32a** (0.14 g, 81 %) as a yellow oil. $^{1}$H NMR (200 MHz, $CDCl_3$): δ 7.49 (s, 1H), 7.26 (m, 2H), 7.25 (m, 2H), 7.07 (s, 1H), 3.63 (s, 3H), 2.39 (s, 3H) ppm. $^{13}$C NMR (50.3 MHz, $CDCl_3$): δ 138.7, 137.6, 133.3, 129.3 (2C), 128.3 (2C), 127.6, 126.7, 32.4, 21.2 ppm. MS (EI): m/z (%) = 173 (13), 172 (100), 171 (17), 144 (14), 130 (16). The spectral properties of this compound are in agreement with those previously reported.[51]

### 1.2.23. 5-(4-Methoxyphenyl)-1-methyl-1*H*-imidazole (32b).

The crude reaction product, which was obtained by Pd-catalyzed reaction of **12** with **26b** (entry 2, Table 6), was purified by flash chromatography on silica gel with a mixture of $CH_2Cl_2$ and MeOH (96:4) as eluent to give **32b** (0.15 g, 82 %) as a light-yellow solid, m.p. 73-75 °C. $^1$H NMR (200 MHz, $CDCl_3$): δ 7.48 (s, 1H), 7.30 (m, 2H), 7.02 (s, 1H), 6.96 (m, 2H), 3.83 (s, 3H), 3.61 (s, 3H) ppm. $^{13}$C NMR (50.3 MHz, $CDCl_3$): δ 159.1, 138.3, 132.3, 129.6 (2C), 127.1, 121.8, 113.9 (2C), 55.1, 32.1 ppm. MS (EI): m/z (%) = 189 (12), 188 (100), 174 (10), 173 (82), 145 (17). The spectral properties of this compound are in agreement with those previously reported.[50c]

### 1.2.24. 1-Methyl-5-(4-nitrophenyl)-1*H*-imidazole (32e).

The crude reaction product, which was obtained by Pd-catalyzed reaction of **12** with **26e** (entry 4, Table 6), was purified by flash chromatography on silica gel with a mixture of $CH_2Cl_2$ and MeOH (96:4) as eluent to give **32e** (92 mg, 45 %) as a yellow-orange solid, m.p. 169-171 °C. $^1$H NMR (200 MHz, $CDCl_3$): δ 8.30 (m, 2H), 7.63 (s, 1H), 7.61 (m, 2H), 7.28 (s, 1H), 3.81 (s, 3H) ppm. $^{13}$C NMR (50.3 MHz, $CDCl_3$): δ 146.7, 140.1, 136.2, 131.3, 130.2, 128.1 (2C), 124.1 (2C), 33.1 ppm. MS (EI): m/z (%) = 203 (100), 173 (19), 130 (17), 103 (16), 89 (32). The spectral properties of this compound are in agreement with those previously reported.[173]

### 1.2.25. 1-Methyl-5-(*o*-tolyl)-1*H*-imidazole (32h).

The crude reaction product, which was obtained by Pd-catalyzed reaction of **12** with **26h** (entry 5, Table 6), was purified by flash chromatography on silica gel with a mixture of $CH_2Cl_2$ and MeOH (98:2) as eluent to give **32h** (0.12 g, 68 %) as a light-brown oil. $^1$H NMR (200 MHz, $CDCl_3$): δ 7.55 (s, 1H), 7.27 (m, 4H), 6.97 (s, 1H), 3.42 (s, 3H), 2.19 (s, 3H) ppm. $^{13}$C NMR (50.3 MHz, $CDCl_3$): δ 138.0, 137.8, 131.9, 131.0, 130.1, 129.0, 128.7 (2C), 127.9, 125.6 (2C), 31.6, 20.0 ppm. MS (EI): m/z (%) = 172 (100), 171 (24), 144 (50), 131 (24), 130 (62). $C_{11}H_{12}N_2$ (172.23): calcd. C 76.71, H 7.02, N 16.27; found C 76.77, H 6.99, N 16.24.

### 1.2.26. 1-Methyl-5-phenyl-1*H*-imidazole (32r).

The crude reaction product, which was obtained by Pd-catalyzed reaction of **12** with **26r** (entry 6, Table 6), was purified by flash chromatography on silica gel with a mixture of $CH_2Cl_2$ and MeOH (96:4) as eluent to give **32r** (0.12 g, 75 %) as a pale-yellow oil. $^1$H NMR (200 MHz, $CDCl_3$): δ = 7.42 (s, 1H), 7.32 (m, 5H), 7.01 (s, 1H), 3.58 (s, 3H) ppm. $^{13}$C NMR (50.3 MHz, $CDCl_3$): δ = 139.1, 128.8, 128.7 (2C), 128.5 (2C), 128.1, 127.9, 127.0, 32.5 ppm. MS (EI): m/z (%) = 158 (100), 130 (17), 116 (13), 103 (12), 89 (12). The spectral properties of this compound are in agreement with those previously reported.[50c]

### 1.2.27. 4-(1-Methyl-1*H*-imidazol-5-yl)benzonitrile (32s).

The crude reaction product, which was obtained by Pd-catalyzed reaction of **12** with **26s** (entry 7, Table 6), was purified by flash chromatography on silica gel with a mixture of $CH_2Cl_2$ and MeOH (96:4) as eluent to give **32s** (0.13 g, 69 %) as a light-yellow solid, m.p. 148-151 °C. $^1$H NMR (200 MHz, $CDCl_3$): δ = 7.73 (m, 2H), 7.59 (s, 1H), 7.53 (m, 2H), 7.22 (s, 1H), 3.75 (s, 3H) ppm. $^{13}$C NMR (50.3 MHz, $CDCl_3$): δ = 140.5, 134.3, 132.5 (2C), 131.6, 129.8, 128.3 (2C), 118.5, 111.2, 33.0 ppm. MS (EI): m/z (%) = 159 (12), 158 (100), 130 (16), 116 (13), 103 (13), 89 (12). The spectral properties of this compound are in agreement with those previously reported.[51]

## 2. General procedure for the screening of the reaction conditions for the Pd-catalyzed C-5 arylation of 1-phenyl-1*H*-pyrazole (23) with 4-bromotoluene (26a).

A mixture of 1-phenyl-1*H*-pyrazole (**23**) (0.13 mL, 0,14 g, 1.0 mmol), palladium catalyst (0.05 mmol), ligand (if any) (0.10 mmol) 4-bromotoluene (**26a**) (0.26 g, 1.5 mmol), base (2.0 mmol), pivalic acid (if any) (34 μL, 31 mg, 0.3 mmol), phase transfer agent (if any) (0.2 mmol) in the selected solvent (5 mL) was stirred under argon for 24 h at the temperature reported in Table 7-Table 9. After cooling to room temperature, the crude reaction mixture was diluted with AcOEt, naphthalene was added as internal standard, and the resulting

mixture was analyzed by GLC and GLC-MS. Table 7-Table 9 summarize the results of this screening.

### 2.1. 1-Phenyl-5-(*p*-tolyl)-1*H*-pyrazole (36a), 1-(4'-methyl-[1,1'-biphenyl]-2-yl)-1*H*-pyrazole (37a) and 1-(4'-methyl-[1,1'-biphenyl]-2-yl)-5-(*p*-tolyl)-1*H*-pyrazole (38a).

The crude reaction mixture was concentrated under reduced pressure and the residue was purified by a first flash chromatography on silica gel with a mixture of toluene and AcOEt (95:5) as eluent. Then, after the concentration from the forth to the fifth eluted chromatographic fractions, these were newly purified by a second flash chromatography on silica gel with a mixture of petroleum ether and THF (95:5) as eluent. Concentration of the first eluted chromatographic fractions allowed isolation of compound **37a** as a pale-yellow oil. $^{1}$H NMR (200 MHz, $CDCl_3$): δ 7.64 (d, *J* = 2 Hz, 1H), 7.62-7.57 (m, 1H), 7.46-7.44 (m, 3H), 7.11-7.08 (m, 3H), 7.01-6.97 (m, 2H), 6.20 (t, *J* = 2 Hz, 1H), 2.34 (s, 3H) ppm. $^{13}$C NMR (50.3 MHz, $CDCl_3$): δ 140.4, 138.7, 137.4, 136.8, 135.7, 131.5, 131.2, 129.4, 128.5, 128.4, 128.3, 126.7, 106.5, 21.4 ppm. MS (EI): m/z (%) = 234 (35), 233 (100), 218 (6), 191 (6), 165 (7), 116 (7). The spectral properties of this compound are in agreement with those previously reported.[174]

Concentration of the second eluted chromatographic fractions allowed isolation of compound **36a** (90 mg, 38 %, entry 13, Table 9) as a light-yellow oil. $^{1}$H NMR (200 MHz, $CDCl_3$): δ 7.71 (d, *J* = 2 Hz, 1H), 7.40-7.22 (m, 5H), 7.15-7.02 (m, 4H) 6.47 (d, *J* = 2 Hz, 1H) 2.33 (s, 3H) ppm. $^{13}$C NMR (50.3 MHz, $CDCl_3$): δ 143.0, 140.2, 138.0, 129.1, 128.8, 128.6, 127.7, 127.3, 125.2, 107.6, 21.3 ppm (11 of 12 carbons were observed). MS (EI): m/z (%) = 235 (18), 234 (100), 233 (68), 219 (10), 77 (13). The spectral properties of this compound are in agreement with those previously reported.[175] This compound was also obtained in isolated yield of 22 % from the Pd-catalyzed reactions of **23** and **26a** carried out at 140 °C (entry 5, Table 7) or in 21 %, 27 % and 29 % from the reactions at 110 °C (entry 13, Table 8 and entries 4 and 9,Table 9).

Concentration of the third eluted chromatographic fractions allowed isolation of compound **38a** as a light-pink solid, m.p. 115-120 °C. $^{1}$H NMR (200 MHz, $CDCl_3$): δ 7.71-

7.61 (m, 2H), 7.51-7.39 (m, 2H), 7.32-7.27 (m, 1H), 6.85 (d, *J* = 7.2 Hz, 4H), 6.51 (dd, *J* = 8.4 Hz, 4H), 6.25 (d, *J* = 1.8 Hz, 1H), 2.27 (s, 3H), 2.26 (s, 3H) ppm. $^{13}$C NMR (50.3 MHz, $CDCl_3$) δ: 139.3, 139.0, 138.0, 136.8, 135.1, 130.7, 129.5, 129.3, 128.7, 128.0, 127.7, 106.1, 29.9, 21.3 ppm. MS (EI): m/z (%) = 325 (14), 324 (65), 323 (100), 234 (18), 233 (98). $C_{23}H_{20}N_2$ (324.42): calcd. C 85.15, H 6.21, N 8.63; found C 84.98, H 6.32, N 8.70.

### 2.2. Preparation of PdCl($C_3H_5$)dppb catalyst.

A 50 mL double-necked round-bottom flask, equipped with a magnetic bar, was charged with 25 mL of distilled water in which argon was bubbled. After this time, the flask was opened under argon flow; $PdCl_2$ (0,18, 1 mmol) and KCl (0.15 g, 2 mmol) were added in turn; and the flask was sealed with a rubber septum. The mixture was allowed to stir for 1 h, and an excess of allyl chloride (3-chloroprop-1-ene) (0.25 mL, 0.23 g, 3 mmol) was then injected through the septum. The mixture was allowed to stir for 24 h. After this time, the reaction mixture was extracted with three portions of chloroform (3 x 30 mL), and the organic layers were gathered, dried over $MgSO_4$, filtered, and reduced to yield the intermediate product $[Pd(C_3H_5)Cl]_2$ as a crystalline yellow solid.[176] An oven dried 50 mL Schlenk tube equipped with a magnetic stirring bar under argon atmosphere was then charged with $[Pd(C_3H_5)Cl]_2$ (0.12 mg, 0.33 mmol) and dppb (0.28 g, 0.66 mmol). 7 mL of anhydrous $CH_2Cl_2$ were added, then the solution was stirred at room temperature for 20 minutes. The solvent was removed under vacuum. The yellow product [PdCl($C_3H_5$)dppb] was used without purification.[177]

## 3. One-pot synthesis of Balsoxin (39a) and Texaline (39b).

### 3.1. 5-(3,4-Dimethoxyphenyl)-2-phenyloxazole (Balsoxin, 39a).

$Pd(OAc)_2$ (11.2 mg, 0.05 mmol) and $Bu_4NOAc$ (0.60 g, 2.0 mmol) were added to a flame-dried reaction vessel. The reaction vessel was fitted with a silicone septum, evacuated, and back-filled with argon. This sequence was repeated twice. DMA (5 mL), 4-bromo-1,2-dimethoxy-benzene (**26t**) (0.14 mL, 0.22 g, 1.0 mmol), and oxazole (**4**) (72 mL, 76 mg, 1.1 mmol) were then added successively under a stream of argon by syringe at room temperature.

The resulting mixture was stirred at 70 °C under argon for 24 h. CuI (0.38 g, 2.0 mmol) and bromobenzene (**26r**) (0.16 mL, 0.24 g, 1.5 mmol) were then sequentially added to the resulting deep-orange solution under a stream of argon. The reaction mixture was heated to 110 °C and stirred at this temperature for 8 h. After cooling to room temperature, the reaction mixture was diluted with AcOEt and poured into a saturated aqueous $NH_4Cl$ solution. The resulting mixture was basified with a few drops of aqueous $NH_4OH$, stirred in the open air for 0.5 h, and then extracted with AcOEt. The organic extract was washed with water, dried, and concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (70:30) as eluent. The chromatographic fractions containing the required compound were collected and concentrated to give **39a** (0.11 g, 39 %) as a light-yellow solid, m.p. 97–98 °C. $^1$H NMR (200 MHz, $CDCl_3$): δ 8.11 (m, 2H), 7.49 (m, 3H), 7.35 (s, 1H), 7.30 (dd, *J* = 1.9, 8.4 Hz, 1H), 7.20 (d, *J* = 1.9 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 3.99 (s, 3H), 3.94 (s, 3H) ppm. $^{13}$C NMR (50.3 MHz, $CDCl_3$): δ 160.5, 151.1, 149.3, 149.2, 130.1, 128.7, 127.4, 126.1, 122.1, 121.0, 117.2, 111.4, 107.3, 55.99, 55.95 ppm. MS (EI): m/z (%) = 282 (20), 281 (100), 266 (23), 238 (11), 107 (11). The spectral properties of this compound are in agreement with those previously reported.[81b]

### 3.2. 5-(Benzo[*d*][1,3]dioxol-5-yl)-2-(pyridin-3-yl)oxazole (Texaline, 39b).

$Pd(OAc)_2$ (11.2 mg, 0.05 mmol) and $Bu_4NOAc$ (0.60 g, 2.0 mmol) were added to a flame-dried reaction vessel. The reaction vessel was fitted with a silicon septum, evacuated, and back-filled with argon. This sequence was repeated twice. DMA (5 mL), 5-bromo-benzo[*d*][1,3]dioxole (**26u**) (0.12 mL, 0.20 g, 1.0 mmol), and oxazole (**4**) (72 mL, 76 mg, 1.1 mmol) were then added successively under a stream of argon by syringe at room temperature. The resulting mixture was stirred at 70 °C under argon for 48 h. CuI (0.38 g, 2.0 mmol) and 3-bromopyridine (**26n**) (0.15 mL, 0.24 g, 1.5 mmol) were then sequentially added to the resulting brown solution under a stream of argon. The reaction mixture was heated to 110 °C and stirred at this temperature for 24 h. After cooling to room temperature, the reaction mixture was diluted with AcOEt and poured into a saturated aqueous $NH_4Cl$ solution. The resulting mixture was basified with a few drops of aqueous $NH_4OH$, stirred in the open air for 0.5 h, and then extracted with AcOEt. The organic extract was washed with water, dried, and concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (50:50) as eluent. The chromatographic

fractions containing the required compound were collected and concentrated to give **39b** (0.10 g, 38 %) as a light- yellow solid, m.p. 167–169 °C. $^{1}$H NMR (200 MHz, $CDCl_3$): δ 9.30 (br. s, 1H), 8.67 (d, *J* = 3.7 Hz, 1H), 8.31 (dt, *J* = 8.0, 1.9 Hz, 1H), 7.40 (dd, *J* = 8.0, 4.8 Hz, 1H), 7.32 (s, 1H), 7.22 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.14 (d, *J* = 1.6 Hz, 1H), 6.87 (d, *J* = 8.1 Hz, 1H), 6.01 (s, 2H) ppm. $^{13}$C NMR (50.3 MHz, $CDCl_3$): δ 158.2, 152.0, 150.9, 148.4, 148.3, 147.5, 133.3, 123.8, 123.7, 122.6, 121.8, 118.7, 109.0, 105.0, 101.6 ppm. MS (EI): m/z (%) = 267 (16), 266 (100), 181 (11), 153 (27), 63 (9). The spectral properties of this compound are in agreement with those previously reported.[81b]

## 4. General procedure for the synthesis of resveratrol derivatives 48 by sequential one-pot C-5 and C-2 direct arylations.

$Pd(OAc)_2$ (11.2 mg, 0.05 mmol) and $Bu_4NOAc$ (0.60 g, 2.0 mmol) were added to a flame-dried reaction vessel. The reaction vessel was fitted with a silicon septum, evacuated, and back-filled with argon. This sequence was repeated twice. DMA (5 mL), an aryl bromide **26b** or **26v** (1.0 mmol), and 1-methyl-1*H*-imidazole (**12**) (93 mL, 90.3 mg, 1.1 mmol) were then added successively under a stream of argon by syringe at room temperature. The resulting mixture was stirred at 110 °C under argon for 24 h. CuI (0.38 g, 2.0 mmol) and an aryl bromide **26v** or **26b** (1.5 mmol) were then sequentially added to the resulting brown solution under a stream of argon. The reaction mixture was heated to 110 °C and stirred at this temperature for 24 h. After cooling to room temperature, the reaction mixture was diluted with AcOEt and poured into a saturated aqueous $NH_4Cl$ solution. The resulting mixture was basified with a few drops of aqueous $NH_4OH$, stirred in the open air for 0.5 h, and then extracted with AcOEt. The organic extract was washed with water, dried, and concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel. The chromatographic fractions containing the required compound were collected and concentrated. This procedure was employed to prepare 2,5-diaryl-1-methyl-1*H*-imidazoles **48a** and **48b** in 48 and 38% yield, respectively.

### 4.1. 2-(3,5-Dimethoxyphenyl)-5-(4-methoxyphenyl)-1-methyl-1H-imidazole (48a).

The crude reaction product obtained by Pd-catalyzed and Cu-mediated one pot

sequential direct arylation reactions involving 4-bromoanisole (**26b**) in the first step and 5-bromo-1,3-dimethoxy-benzene (**26v**) in the second step was purified by flash chromatography on silica gel with a mixture of AcOEt and toluene (60:40) as eluent to give **48a** (0.16 g, 48%) as a light yellow solid, m.p. 121–123 °C. $^{1}$H NMR (200 MHz, $CDCl_3$) δ 7.33 (m, 2H), 7.10 (s, 1H), 6.95 (m, 2H), 6.81 (d, *J* = 2.0 Hz, 2H), 6.49 (t, *J* = 2.0 Hz, 1H), 3.80 (s, 9H), 3.62 (s, 3H). $^{13}$C NMR (50.3 MHz $CDCl_3$) δ 160.5 (2C), 159.3, 148.4, 135.2, 132.5, 129.9 (2C), 126.6, 122.3, 114.0 (2C), 106.6 (2C), 100.8, 55.4 (2C), 55.2, 33.6. MS (EI): m/z (%) = 325 (21), 324 (100), 323 (59), 309 (22), 294 (7). $C_{19}H_{20}N_2O_3$ (324.37): calcd. C 70.35, H 6.21, N 8.64; found C 71.98, H 6.19, N 8.85.

### 4.2. 5-(3,5-Dimethoxyphenyl)-2-(4-methoxyphenyl)-1-methyl-1H-imidazole (48b).

The crude reaction product obtained by Pd-catalyzed and Cu-mediated one pot sequential direct arylation reactions involving 5-bromo-1,3-dimethoxy-benzene (**26v**) in the first step and 4-bromoanisole (**26b**) in the second step was purified by flash chromatography on silica gel with a mixture of AcOEt and toluene (90:10) as eluent to give **48b** (0.12 g, 38%) as a light yellow oil; $^{1}$H NMR (200 MHz, $CDCl_3$) δ 7.61 (m, 2H), 7.17 (s, 1H), 7.00 (m, 2H), 6.58 (d, *J* = 2.2 Hz, 2H), 6.48 (t, *J* = 2.2 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 6H), 3.65 (s, 3H); $^{13}$C NMR (50.3 MHz, $CDCl_3$) δ 160.8 (2C), 159.9, 149.6, 135.2, 132.0, 130.1 (2C), 127.2, 123.2, 113.9 (2C), 106.7 (2C), 106.7, 99.7, 55.4 (2C), 55.3, 33.8; MS (EI): m/z (%) = 325 (21), 324 (100), 323 (28), 309 (23), 281 (6). $C_{19}H_{20}N_2O_3$ (324.37): calcd. C 70.35, H 6.21, N 8.64; found C 72.46, H 6.17, N 8.91.

## 5. General procedure for the synthesis of resveratrol derivatives 49 by demethylation with $BBr_3$.

To a solution of *O*-methoxyphenyl imidazoles **48** (0.3 mmol) in dry $CH_2Cl_2$ (40 ml), which was stirred at -78 °C, was added a 1 M solution of $BBr_3$ in $CH_2Cl_2$ (2.7 ml, 2.7 mmol). The reaction mixture was allowed to warm up to room temperature and stirred at this temperature for 48 h. After cooling to 0 °C, the reaction mixture was diluted with methanol (1.5 mL), and AcOEt (10 mL) and a 10% aqueous solution of NaOH (10 mL) were

sequentially added. The organic phase was recovered and acidified with a 10% solution of HCl cooled at 0 °C. The formed precipitated was collected by filtration and dried *in vacuo*, to give the title compounds chemically pure. This procedure was employed to prepare polyphenolic imidazoles **49a** and **49b** in 89 and 65% yield, respectively.

### 5.1. 5-(5-(4-Hydroxyphenyl)-1-methyl-1*H*-imidazol-2-yl)benzene-1,3-diol (49a).

Pale grey solid, m.p. 175-178 °C. $^{1}$H NMR (200 MHz, $CD_3OD$): δ 7.30 (m, 2H), 6.96 (s, 1H), 6.89 (m, 2H), 6.56 (s, 2H), 6.37 (s, 1H), 3.60 (s, 3H). $^{13}$C NMR (200 MHz, $CD_3OD$): δ 159.8 (2C), 158.8, 149.8, 136.8, 133.2, 131.3 (2C), 125.8, 122.1, 116.6 (2C), 108.5 (2C), 104.3, 34.0. MS (EI): m/z $[M + H]^+$ = 283, $[M - H]^-$ = 281. $C_{16}H_{14}N_2O_3$ (282.29): calcd. C 68.08, H 5.00, N 9.92; found C 65.72, H 4.95, N 10.07.

### 5.2. 5-(2-(4-Hydroxyphenyl)-1-methyl-1*H*-imidazol-5-yl)benzene-1,3-diol (49b).

Pale brown solid, m.p. 181-184 °C. $^{1}$H NMR (200 MHz, $CD_3OD$): δ 7.49 (m, 2H), 7.05 (s, 1H), 6.92 (m, 2H), 6.42 (s, 2H), 6.33 (s, 1H), 3.64 (s, 3H). $^{13}$C NMR (200 MHz, $CD_3OD$): δ 159.9 (3C), 150.4, 136.7, 132.5, 131.5 (2C), 125.4, 121.9, 116.5 (2C), 108.2 (2C), 103.5, 34.3. MS (EI): m/z $[M + H]^+$ = 283, $[M - H]^-$ = 281. $C_{16}H_{14}N_2O_3$ (282.29): calcd. C 68.08, H 5.00, N 9.92; found C 65.72, H 5.04, N 9.64.

## 6. Synthesis of fluorophores 50, 51 and 52.

### 6.1. 2-(4-Bromophenyl)benzo[*d*]thiazole (53).

A three–necked 500 mL flask equipped with air condenser and magnetic stirrer was charged with 2-aminothiophenol (**58**) (0.67 mL, 0.78 g, 6.25 mmol), 4-bromobenzaldehyde (**59**) (0.93 g, 5 mmol) and DMSO (150 mL). The mixture was stirred under air at reflux of the solvent (190 °C). The progress of the reaction was monitored by GLC and after 2 h the conversion was complete. The reaction mixture was poured into water and the resulting white-greenish precipitate was recovered by filtration, purified by crystallization in ethanol giving **53** as a

white solid (1.34 g, 92 %), m.p. 51-53 °C [Lit. 52-53 °C]. $^1$H NMR (200 MHz, $CD_3Cl_3$): δ 8.09-8.05 (m, 1H), 8.00-7.89 (m, 3H), 7.66-7.60 (m, 2H), 7.51 (dt, $J^1$ = 8 Hz, $J^2$ = 1.4 Hz, 1H), 7.40 (dt, $J^1$ = 8 Hz, $J^2$ = 1.4 Hz, 1H) ppm. MS (EI): m/z (%) = 291 (100), 290 (20), 289 (99), 210 (30), 108 (19). The spectral properties of this compound are in agreement with those previously reported.[110,111]

### 6.2. 2-(4-Bromophenyl)-1-methyl-1*H*-benzo[*d*]imidazole (54).

A 250 mL flask equipped with an air condenser and a magnetic stirrer was charged with *N*-methyl-1,2-benzendiamine (2.27 mL, 20 mmol), 4-bromobenzaldehyde (**59**) (3.7 g, 20 mmol), cetyltrimethylammonium bromide (346.5 mg, 1 mmol) and deionized water (100 mL). The mixture was stirred under air at 40 °C. The progress of the reaction was monitored by $^1$H NMR spectroscopy. After 88 h the conversion was judged complete and the reaction mixture was saturated with NaCl and extracted with AcOEt (100 mL + 3 x 50 mL). The combined organic extracts were dried on anhydrous sodium sulphate and concentrated under reduced pressure yielding a mixture containing 65 % of the required compound **54** and 35 % of the benzimidazolines (**55**), as estimated by $^1$H NMR analysis.
The crude reaction mixture was dissolved into 250 mL of dioxane. Air was bubbled into the solution for 15 minutes. The solution was refluxed overnight and then the solvent was removed under reduced pressure. The residue was purified by recrystallization from $CH_2Cl_2$/hexane. The required **54** was recovered as a light brown needles (4.52 g, 79 %), m.p. 112-114 °C [lit. 115-116 °C]. $^1$H NMR (300 MHz, $CDCl_3$): δ 7.84-7.66 (m, 1H), 7.67-7.65 (m, 4H), 7.40-7.31 (m, 3H), 3.85 (s, 3H) ppm. MS (EI): m/z (%) = 288 (79), 287 (100), 286 (82), 285 (91), 206 (37). The spectral properties of this compound are in agreement with those previously reported.[178]

### 6.3. General procedure for the synthesis of 2-(4-aryl-1-methyl-1*H*-imidazol-2-yl)phenyl)-1-methyl-1*H*-benzo[*d*]imidazoles (50).

A two-necked flask equipped with a magnetic stirrer and a reflux condenser was charged with the appropriate 5-aryl-1-methyl-1*H*-imidazole **32** (0.75 mmol), 2-(4-bromophenyl)-1-methyl-1*H*-benzo[*d*]imidazole **54** (323 mg, 1.13 mmol), $Pd(OAc)_2$ (8.4 mg, 0.04 mmol) and CuI (286 mg, 1.50 mmol). The apparatus was fitted with a silicone septum, evacuated and backfilled with argon three times. Anhydrous DMA (4 mL) was added by

syringe against a positive pressure of argon. The reaction mixture was stirred at 160 °C. The degree of completion of the reaction and the composition of the reaction mixture was established on the basis of GLC and GLC-MS analyses of samples of the crude reaction mixtures diluted in $CH_2Cl_2$ and washed with saturated $NH_4Cl$ solution to which a few drops of concentrated aqueous ammonia had been added. After cooling at room temperature, the reaction mixture was diluted with $CH_2Cl_2$ (200 mL) and poured into a saturated aqueous $NH_4Cl$ solution to which 5 mL of concentrated aqueous ammonia had been added. The resulting mixture was stirred in the open air for 30 minutes and then extracted with $CH_2Cl_2$. The organic extracts were washed with saturated brine, dried, filtered over Celite and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with $CH_2Cl_2$ and MeOH (95:5) as eluent. The chromatographic fractions containing the required compound **50** were collected and concentrated under reduced pressure. The solid compound so obtained was triturated with $Et_2O$, isolated by filtration and dried under vacuum. This procedure was employed to prepare compounds **50**.[23c,37a,50d]

### 6.3.1. 1-Methyl-2-(4-(1-methyl-5-*p*-tolyl-1*H*-imidazol-2-yl)phenyl)-1*H*-benzo[*d*]imidazole (50a).

The reaction between **54** and **32a** according to the general procedure (92 h) gave **50a** as an off-white amorphous solid (250.8 mg, 88 %), m.p. 245-252 °C. $^1$H NMR (200 MHz, $CDCl_3$): δ 7.93-7.82 (m, 5H), 7.44-7.28 (m, 7H), 7.23 (s, 1H), 3.92 (s, 3H), 3.73 (s, 3H), 2.42 (s, 3H) ppm. $^{13}$C NMR (50.3 MHz, $CDCl_3$): δ 153.3, 143.2, 138.3, 136.9, 136.3, 132.3, 130.5, 129.9, 129.1, 128.9, 127.7, 127.3, 123.2, 122.8, 120.2, 109.9, 34.2, 32.1, 21.6 ppm. MS (EI): m/z (%) = 379 (25), 378 (100), 377 (66). $C_{25}H_{22}N_4$ (378.47): calcd. C 79.34, H 5.86; found C 79.01, H 5.89.

### 6.3.2. 2-(4-(5-(Methoxyphenyl)-1-methyl-1*H*-imidazol-2-yl)phenyl)-1-methyl-1*H*-benzo[*d*]imidazole (50b).

The reaction between **54** and **32b** according to the general procedure (72 h) gave **50b** as an off-white amorphous solid (195 mg, 66 %), m.p. 265-269 °C. $^1$H NMR (200 MHz, $CDCl_3$): δ 7.89-7.82 (m, 5H), 7.42-7.31 (m, 5H), 7.19 (s, 1H), 7.01 (d, $J$ = 8.5 Hz, 2H), 3.93 (s, 3H), 3.87 (s, 3H), 3.72 (s, 3H) ppm. $^{13}$C NMR (50.3 MHz, $CDCl_3$): δ 159.6, 153.2, 148.0, 143.0,

136.7, 135.9, 132.3, 130.2, 129.5, 129.3, 128.7, 128.4, 127.4, 123.0, 122.6, 120.4, 119.9, 119.5, 114.3, 109.6, 55.6, 34.0, 29.7 ppm. MS (EI): m/z (%) = 395 (27), 394 (100), 393 (51). $C_{25}H_{22}N_4O$ (394.47): calcd. C 76.12, H 5.62; found C 76.63, H 5.58.

### 6.3.3. 4-(1-Methyl-2-(4-(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)phenyl)-1*H*-imidazol-5-yl)benzonitrile (50s).

The reaction between **54** and **32s** according to the general procedure (92 h) gave **50s** as an off-white amorphous solid (123 mg, 42 %), m.p. 279-282 °C. $^1$H NMR (200 MHz, $CDCl_3$): δ 7.96-7.75 (m, 7H), 7.60 (d, *J* = 8.3 Hz, 1H), 7.44-7.33 (m, 4H), 3.93 (s, 3H), 3.77 (s, 3H) ppm. $^{13}$C NMR (50.3 MHz, $CDCl_3$): δ 153.0, 150.3, 143.1, 136.9, 134.7, 134.4, 133.0, 131.7, 131.1, 130.0, 129.8, 129.3, 128.7, 123.4, 122.9, 120.1, 118.8, 111.6, 110.0, 34.6, 32.2 ppm. MS (EI): m/z (%) = 391 (27), 389 (100), 388 (83). $C_{25}H_{19}N_5$ (389.45): calcd. C 77.10, H 4.92; found C 76.96, H 4.96.

## 6.4. General procedure for the synthesis of 2-(4-(5-aryl-1-methyl-1*H*-imidazol-2-yl)phenyl)benzo[*d*]thiazoles (51) and 2-(4-(5-arylthiazol-2-yl)phenyl)benzo[*d*]thiazoles (52).

The appropriate 5-aryl-thiazole **31** (0.5 mmol) or 5-aryl-1-methyl-1*H*-imidazole **32** (0.5 mmol), 2-(4-bromophenyl)benzo[*d*]thiazole **53** (218 mg, 0.75 mmol) were placed in a two-necked flask equipped with a reflux condenser and a magnetic stirrer. The apparatus was fitted with a silicone septum, evacuated and backfilled with argon three times. Anhydrous DMA (3.5 mL) was then added by syringe against a positive pressure of argon. The reaction mixture was stirred at 160 °C under argon for 72 h, then it was cooled to room temperature and diluted with 100 mL of AcOEt. To the resulting mixture, 100 mL of a saturated $NH_4Cl$ solution and 5 mL of concentrated ammonia were added, and the biphasic mixture was stirred in the open air for 30 minutes. The two phases were separated and the aqueous phase was extracted with AcOEt (3 x 50 mL). The organic extract was washed with water (2 x 50 mL), dried and concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel. Compounds **51** and **52** were obtained following this protocol.

### 6.4.1. 2-(4-(1-Methyl-5-(*p*-tolyl)-1*H*-imidazol-2-yl)phenyl)benzo[*d*]thiazole (51a).

The crude reaction product obtained by Pd- and Cu-mediated reaction of **32a** and **53** was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (60:40) as eluent to give **51a** as an iridescent yellow-greenish solid (122 mg, 66 %), m.p. 204-206 °C. $^{1}$H NMR (200 MHz, $CDCl_3$): δ 8.21 (d, *J* = 8.0 Hz, 2H), 8.10 (d, *J* = 8.0 Hz, 1H), 7.93 (d, *J* = 7.6 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.56-7.23 (m, 8H), 3.74 (s, 3H), 2.42 (s, 3H) ppm. $^{13}$C NMR (50.3 MHz, $CDCl_3$): δ 167.2, 154.1, 148.1, 138.0, 136.2, 135.1, 133.4, 133.2, 129.5, 129.0, 128.8, 128.6, 127.7, 127.0, 126.4, 125.3. 123.3, 121.6, 34.0, 21.3 ppm. MS (EI): m/z (%) = 383 (9), 382 (30), 381 (100), 380 (49), 190 (14).

### 6.4.2. 2-(4-(5-(4-Methoxyphenyl)-1-methyl-1*H*-imidazol-2-yl)phenyl)benzo[*d*]thiazole (51b).

The crude reaction product obtained by Pd- and Cu-mediated reaction of **32b** and **53** was purified adding a mixture of toluene and AcOEt (70:30), filtrating the barely soluble product and performing a flash chromatography on silica gel of the filtrate to give **51b** as a yellow solid (141 mg, 66 %), m.p. 244-248 °C. $^{1}$H NMR (200 MHz, $CDCl_3$): δ 8.21 (d, *J* = 8.4 Hz, 2H), 8.10 (d, *J* = 8.0 Hz, 1H), 7.95-7.84 (m, 3H), 7.55-7.37 (m, 4H), 7.20 (s, 1H), 7.01 (d, *J* = 8.8 Hz, 2H), 3.87 (s, 3H), 3.71 (s, 3H) ppm. $^{13}$C NMR (50.3 Hz, $CDCl_3$): δ 167.2, 159.5, 154.1, 147.9, 135.9, 135.1, 133.4, 133.3, 130.2, 129.0, 127.7, 127.5, 126.4, 125.3, 123.3, 122.3, 121.7, 114.3, 55.4, 34.0 ppm. MS (EI): m/z (%) = 398 (30), 397 (100), 396 (27), 382 (15), 198 (13).

### 6.4.3. 4-(2-(4-(Benzo[*d*]thiazole-2-yl)phenyl)-1-methyl-1*H*-imidazol-5-yl)benzonitrile (51s).

The crude reaction product obtained by Pd- and Cu-mediated reaction of **32s** and **53** was purified by flash chromatography on silica gel with a mixture of toluene and AcOEt (40:60) as eluent to give **51s** as a yellow solid (153 mg, 83 %), m.p. 217-220 °C. $^{1}$H NMR (200 MHz, $CDCl_3$): δ 8.24 (d, *J* = 8.0 Hz, 2H), 8.11 (d, *J* = 7.4 Hz, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 2H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.62-7.37 (m, 5H), 3.78 (s, 3H) ppm. $^{13}$C NMR (50.3 Hz, $CDCl_3$): δ 166.9, 154.1, 150.0, 135.1, 134.4, 134.3, 134.0, 132.7, 132.4,

129.7, 129.3, 128.5, 127.8, 126.5, 125.5, 123.4, 121.7, 118.5, 111.4, 34.4 ppm. MS (EI): m/z (%) = 394 (9), 393 (27), 392 (100), 391 (66), 196 (10).

### 6.4.4. 2-(4-(5-(*p*-Tolyl)thiazole-2-yl)phenyl)benzo[*d*]thiazole (52a).

The crude reaction product obtained by Pd- and Cu-mediated reaction of **31a** and **53** was purified adding a mixture of toluene and AcOEt (95:5), filtrating an insoluble residual and performing a flash chromatography on silica gel of the filtrate to give **52a** as a yellow solid (47 mg, 25 %), m.p. 207-210 °C. $^{1}$H NMR (200 MHz, $CDCl_3$): δ 8.21-8.16 (m, 2H), 8.12-8.06 (m, 3H), 8.03 (s, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.56-7.40 (m, 4H), 7.24 (d, *J* = 8.0 Hz, 2H), 2.40 (s, 3H) ppm. $^{13}$C NMR spectrum was not recorded due to the very low solubility of the compound in common organic solvents. MS (EI): m/z (%) = 385 (26), 384 (100), 192 (12), 148 (26), 147 (31).

### 6.4.5. 2-(4-(5-(4-Methoxyphenyl)thiazole-2-yl)phenyl)benzo[*d*]thiazole (52b).

The crude reaction product obtained by Pd- and Cu-mediated reaction of **31b** and **53** was purified by (i) filtration of a solid component and treatment of it with hot $CH_2Cl_2$ to obtain a clean product and (ii) flash chromatography on silica gel of the filtrate with a mixture of $CH_2Cl_2$ and AcOEt (96:4) as eluent to give **52b** as an iridescent yellow solid (143 mg, 72 %), m.p. 196-199 °C. $^{1}$H NMR (200 MHz, $CDCl_3$): δ 8.20-8.05 (m, 5H), 7.97-7.91 (m, 2H), 7.58-7.37 (m, 4H), 6.96 (d, *J* = 8.8 Hz, 2H), 3.86 (s, 3H) ppm. $^{13}$C NMR spectrum was not recorded due to the very low solubility of the compound in common organic solvents. MS (EI): m/z (%) = 400 (100), 281 (22), 207 (38), 149 (32), 44 (24).

### 6.4.6. 4-(2-(4-(Benzo[*d*]thiazole-2-yl)phenyl)thiazole-5-yl)benzonitrile (52s).

The crude reaction product obtained by Pd- and Cu-mediated reaction of **31s** and **53** was purified by (i) filtration of a solid component and treatment of it with hot $CH_2Cl_2$ to obtain a clean product and (ii) flash chromatography on silica gel of the filtrate with a mixture of toluene and AcOEt (90:10) as eluent to give **52s** as a yellow solid (96 mg, 53 %), m.p. 233-235 °C. $^{1}$H NMR (200 MHz, aquired at 40 °C, $CDCl_3$): δ 8.23-8.08 (m, 6H), 7.93 (d, *J* = 7.6 Hz, 1H), 7.71 (s, 4H), 7.56-7.38 (m, 2H) ppm. $^{13}$C NMR spectrum was not recorded due to

the very low solubility of the compound in common organic solvents. MS (EI): m/z (%) = 397 (12), 396 (29), 395 (100), 197 (8), 159 (52).

## 7. One-pot synthesis of fluorophores 50w and 51w.

$Pd(OAc)_2$ (11.2 mg, 0.05 mmol) and $Bu_4NOAc$ (0.60 g, 2.0 mmol) were added to a flame-dried reaction vessel. The reaction vessel was fitted with a silicone septum, evacuated, and back-filled with argon. This sequence was repeated twice. DMA (5 mL), 1-bromo-4-((2-ethylhexyl)oxy)benzene **26w** (0.31 g, 1.1 mmol), and 1-methyl-1*H*-imidazole (**12**) (80 μ, 82 mg, 1 mmol) were then added successively under a stream of argon by syringe at room temperature. The resulting mixture was stirred at 110 °C under argon for 24 h. CuI (0.38 g, 2.0 mmol) and the aryl bromide **53** or **54** (1.5 mmol) were then sequentially added to the resulting solution under a stream of argon. The reaction mixture was heated to 110 °C and stirred at this temperature for 24 h. After cooling to room temperature, the reaction mixture was diluted with AcOEt and poured into a saturated aqueous $NH_4Cl$ solution. The resulting mixture was basified with a few drops of aqueous $NH_4OH$, stirred in the open air for 0.5 h, and then extracted with AcOEt. The organic extract was washed with water, dried, and concentrated under reduced pressure, and the residue was purified by recrystallization. This procedure was employed to prepare 2,5-diaryl-1-methyl-1*H*-imidazoles **50w** and **51w** in 18 and 40% yield, respectively.

### 7.1. 1-Bromo-4-((2-ethylhexyl)oxy)benzene (26w).[179]

In a 500 mL three-necked flask, $K_2CO_3$ (8.29 g, 60 mmol) and 4-bromophenol (**26c**) (6.92 g, 40 mmol) were added to acetone (93 mL) and the mixture was heated at refluxing temperature. After 30 minutes, 2-ethyl-hexyl bromide (10.7 mL, 11.6 g, 60 mmol) was dropped into the reaction mixture. After the reaction was complete, it was cooled to room temperature, washed with $H_2O$ and extracted with $Et_2O$ The organic layers were washed with brine, exctracted again and dried with anhydrous magnesium sulphate ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by distillation (131.8 °C, 2 mmHg) and compound **26w** was obtained as a colourless oil (6.72 g, 59 %). $^1$H NMR (200 MHz, $CDCl_3$): δ 7.33 (m, 2H), 6.76 (m, 2H), 3.77 (d, $J$ = 5.4 Hz, 2H), 1.69 (ept, $J$ = 6

Hz, 1H), 1.53-1.21 (m, 8H), 0.94-0.87 (m, 6H) ppm. The spectral properties of this compound are in agreement with those previously reported.[180]

### 7.2. 2-(4-(5-(4-((2-Ethylhexyl)oxy)phenyl)-1-methyl-1*H*-imidazol-2-yl)phenyl)-1-methyl-1*H*-benzo[*d*]imidazole (50w).

The crude reaction product obtained by Pd-catalyzed and Cu-mediated one pot sequential direct arylation reactions involving 1-bromo-4-((2-ethylhexyl)oxy)benzene (**26w**) in the first step and 2-(4-bromophenyl)-1-methyl-1*H*-benzo[*d*]imidazole (**54**) (1.5 mmol) in the second step was purified by crystallization from $CH_2Cl_2$/hexaneto give **50w** (91 mg, 18%) as a iridescent white solid, m.p. 201-204 °C. $^1$H NMR (200 MHz, $CDCl_3$): δ 7.96-7.82 (m, 5H), 7.44-7.28 (m, 5H), 7.19 (s, 1H), 7.00 (d, *J* = 8.8 Hz, 2H) 3.91-3.88 (m, 5H), 3.70 (s, 3H), 1.82-1.68 (m, 1H), 1.58-1.26 (m, 8H), 0.99-0.89 (m, 6H) ppm. $^{13}$C NMR (50.3 MHz $CDCl_3$) δ 167.2, 159.5, 154.2, 147.8, 136.1, 135.2, 133.5, 133.4, 130.2, 129.0, 127.7, 127.4, 126.4, 125.4, 123.4, 122.1, 121.7, 114.9, 70.8, 39.5, 33.9, 30.7, 29.2, 24.0, 23.1, 14.1, 13.8, 11.2. ppm. $C_{32}H_{36}N_4O$ (492.65): calcd. C 78.01, H 7.37, N 11.37; found C 77.89, N 7.12, N 11.57.

### 7.3. 2-(4-(5-(4-((2-Ethylhexyl)oxy)phenyl)-1-methyl-1*H*-imidazol-2-yl)phenyl)benzo[*d*]thiazole (51w).

The crude reaction product obtained by Pd-catalyzed and Cu-mediated one pot sequential direct arylation reactions involving 1-bromo-4-((2-ethylhexyl)oxy)benzene (**26w**) in the first step and 2-(4-bromophenyl)benzo[*d*]thiazole (**53**) (1.5 mmol) in the second step was purified by crystallization from $CH_2Cl_2$/hexane to give **51w** (340 mg, 40%) as a yellow solid, m.p. 65-67 °C. $^1$H NMR (200 MHz, $CDCl_3$): δ 8.20 (d, *J* = 8 Hz, 2H), 8.09 (d, *J* = 8.2 Hz, 1H), 7.93-7.84 (m, 3H), 7.54-7.35 (m, 4H),7.19 (s, 1H), 7.00 (d, *J* = 8.4 Hz, 2H), 3.91-3.81 (m, 2H), 3.71 (s, 3H), 1.85-1.63 (m, 1H), 1.60-1.26 (m, 8H), 0.98-0.92 (m, 6H) ppm. $^{13}$C NMR (50.3 MHz $CDCl_3$) δ 159.3, 153.0, 147.9, 142.9, 136.6, 135.9, 132.2, 130.1 (2C), 129.5 (2C), 128.7 (2C), 127.3, 122.9, 122.5, 122.0, 119.8, 114.8 (2C), 109.6, 70.6, 39.4, 33.8, 31.8, 30.6, 29.7, 29.1, 23.9, 23.1, 14.2, 11.2 ppm. $C_{31}H_{33}N_4O$ (495.68): calcd. C 75.12, H 6.71, N 8.48; found C 75.34, H 6.49, N 8.80.

# 8. Synthesis of Cu-NHC 64a, 64b, 65.

## 8.1. Synthesis of benzimidazolium salts 73a and 73b.

### 8.1.1. 1,3-Dibenzyl-1*H*-benzo[*d*]imidazol-3-ium bromide (73a).[139]

To a round-bottom flask was added benzimidazole (**75**) (10 g, 85 mmol), benzyl bromide (**76**) (20 mL, 29 g, 170 mmol), $K_2CO_3$ (17.5 g, 127 mmol) and acetonitrile (200 mL). This mixture was stirred for 3 d at ambient temperature. Solvent was removed under reduced pressure. Water (200 mL) was added, and the mixture stirred. The reaction mixture was filtered to give product **73a** as a white solid (31.9 g, 99% yield), m.p. 228-229 °C [Lit. 210-212 °C]. $^1$H NMR (400 MHz, $(CD_3)_2SO$): δ 9.98 (s, 1H), 7.96-7.90 (m, 2H), 7.64-7.57 (m, 2H), 7.50-7.46 (m, 4H), 7.43-7.33 (m, 6H), 5.75 (s, 4H). $^{13}$C NMR (101 MHz, $(CD_3)_2SO$): δ 134.0, 131.1, 129.0, 128.8, 128.3, 126.8, 114.0, 50.0 (note: C2 not observed). ESI-MS: *m/z* = 299 [M-Br]. ESI-HRMS: *m/z* = 299.1539 [M-Br]. $C_{21}H_{19}N_2$: calcd. 229.1543.

### 8.1.2. *N*,*N*-Diphenylbenzene-1,2-diamine (78).[141]

In a two-necked flask under nitrogen atmosphere, $Pd(OAc)_2$ (32 mg, 0.143 mmol) and solid $P^tBu_3$ (85 mg, 0.421 mmol) were combined in toluene (15 mL) and stirred for 5 min. Dibromobenzene (**79**) (0.65 mL, 5.39 mmol) was added followed by aniline (**80**) (1.46 mL, 16 mmol) and $NaO^tBu$ (1.538 g, 16 mmol). Upon addition of the $NaO^tBu$ a brown colour was observed. The reaction mixture was heated to 110 °C for 14 h. After several hours a precipitated formed. The flask was opened and the reaction mixture was quickly quenched with an aqueous $NH_4Cl_{sat}$ solution (30 mL). Then, other 15 mL of toluene were added and the organic layer was separated and washed with deionized water (2 x 30 mL). The aqueous layer was washed with fresh toluene (3 x 15 mL) and the organic phases were collected. The toluene layer was dried over $MgSO_4$ for 1 h, then filtered and concentrated under vacuum.
The solid obtained was dissolved in 6 mL of toluene again; hexane was added until a precipitate formed. The solution was cooled overnight at -20 °C. Dark purple crystals were isolated. The product **78** was crystallized again from EtOH as white off solid (1.091 g, 78 % yield), m.p. 111-114 °C [Lit. 109 °C].[181] $^1$H NMR (400 MHz, $CDCl_3$): δ 7.33-7.24 (m, 6H), 7.01-6.90 (m, 8H), 5.64 (s, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$): δ 144.08, 135.07, 129.50,

123.16, 120.76, 120.40, 117.40. ESI-HRMS: *m/z* = 261.1394 [M + $H^+$]. $C_{18}H_{17}N_2$: calcd. 261.1386.

### 8.1.3. 1,3-Diphenyl-1*H*-benzo[*d*]imidazol-3-ium bromide (73b).

To a 50 mL round bottom flask, N,N-diphenylbenzene-1,2-diamine (**78**) (260 mg, 1 mmol), trimethyl orthoformate (**81**) (7 mL), $HBr_{conc.}$ (0.2 mL) and formic acid (1 drop) were added. The resulting mixture was stirred under nitrogen at 80 °C for 2 h. Once the reaction was cooled, the solvent was removed and the solid residue of compound **73b** was purified by recrystallization from AcOEt/$CH_2Cl_2$ to provide slight yellow microcrystals (350 mg, 99 % yield), m.p. compound **73b** starts to decompose around 235 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ 11.06 (s, 1H), 8.19 (d, *J* = 8 Hz, 4H), 7.82-7.78 (m, 2H), 7.73-7.69 (m, 6H), 7.66-7.63 (m, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$): δ 141.6, 132.77, 131.74, 131.20, 130.80, 128.29, 125.71, 114.20. ESI-HRMS: *m/z* = 271.1237 [M + Br]. $C_{19}H_{15}N_2^+$: calcd. 271.1230. IR (solid-state ATR, $cm^{-1}$): 3156, 3066, 2995, 2898, 2787, 1588, 1548, 1478, 1356, 1308, 1255, 1226, 1081, 754, 691, 619, 571, 495, 433.

## 8.2. Synthesis of $Cu^I$-NHC 64a, 64b and 65.

### 8.2.1. (1,3-Dibenzylbenzo[*d*]imidazolin-2-ylidene)copper(I) bromide (64a).

A Schlenk flask was charged with 1,3-dibenzylbenzo[*d*]imidazolium bromide (**73a**) (389 mg, 1 mmol), $Cu_2O$ (286 mg, 2 mmol) and 4Å MS. These were dried and degassed thoroughly *in vacuo*. Anhydrous $CH_2Cl_2$ (20 mL) was added via cannula and the mixture was stirred at reflux for 24 h. After this time, the mixture was allowed to cool and was removed from the filtrate *in vacuo* to give the product **64a** as a white crystalline solid (440 mg, 99% yield). $^1$H NMR (500 MHz, $CD_2Cl_2$): δ 7.40-7.32 (m, 12H), 7.30-7.27 (m, 2H), 5.69 (s, 4H). $^{13}$C NMR (126 MHz, $CD_2Cl_2$): δ 135.9, 129.6, 129.0, 128.0, 124.7, 112.5, 53.4 (7 of the 9 carbon environments observed). $C_{21}H_{18}BrCuN_2$: calcd. C 57.09, H 4.11, N 6.34; found C 56.90, H 4.05, N 6.15. LIFDI-MS: *m/z* (%) 440 (67) [$^{63}Cu^{79}BrM$], 441 (12) [$^{63}Cu^{79}Br^{13}CM$], 442 (100) [$^{63}Cu^{81}BrM$ and $^{65}Cu^{79}BrM$], 442 (22) [$^{63}Cu^{81}Br^{13}CM$ or $^{65}Cu^{79}Br^{13}CM$], 443 (28) [$^{65}Cu^{81}BrM$] (observed as monomer only).

### 8.2.2. (1,3-Diphenylbenzo[d]imidazolin-2-ylidene)copper(I) bromide (64b).

A Schlenk flask was charged with 1,3-diphenylbenzimidazolium bromide (**73b**) (527 mg, 1.5 mmol), $Cu_2O$ (429 mg, 3 mmol) and 4Å MS. These were dried and degassed thoroughly *in vacuo*. Anhydrous $CH_2Cl_2$ (30 mL) was added via cannula and the mixture was stirred at reflux for 24 h. After this time, the mixture was allowed to cool and was removed from the filtrate *in vacuo* to give the product as a white-off solid (630 mg, 99 % yield), m.p. 205-208 °C. $^1$H NMR (400 MHz, $CD_2Cl_2$): δ 7.78-7.75 (m, 4H), 7.70-7.65 (m, 4H), 7.64-7.60 (m, 2H), 7.56-7.51 (m, 2H), 7.48-7.43 (m, 2H). $^1$H NMR (400 MHz, $CD_3CN$): δ 7.77-7.74 (m, 4H), 7.69-7.60 (m, 6H), 7.55-7.50 (m, 2H), 7.48-7.44 (m, 2H). $^{13}$C NMR (101 MHz, $CD_2Cl_2$): δ 138.04, 134.61, 130.61, 130.06, 126.60, 125.52, 112.78 (only 7 of 8 resonance observed). ESI-HRMS: *m/z* = 603.1616 (observed as a dimer, 2 NHC linked to the same Cu, calcd. for $C_{38}H_{28}CuN_4$). LIFDI-MS: *m/z* (%) 603.21 (100), 605.23 (45), 606.23 (18). IR (solid-state ATR, $cm^{-1}$): 3041, 2962, 1590, 1482, 1357, 1259, 1047, 796, 740, 693, 603, 501.

### 8.2.3. (1,3-Bis(2,4,6-trimethylphenyl)imidazolin-2-yliden)copper(I) chloride (65).

A Schlenk flask was charged with 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride (**74**) (511 mg, 1.5 mmol), $Cu_2O$ (429 mg, 3 mmol) and 4Å MS. These were dried and degassed thoroughly *in vacuo*. Anhydrous $CH_2Cl_2$ (30 mL) was added via cannula and the mixture was stirred at reflux for 24 h. After this time, the mixture was allowed to cool and was removed from the filtrate *in vacuo* to give the product as a white-off solid (600 mg, 99 % yield). $^1$H NMR (400 MHz, $CD_2Cl_2$): δ 7.11 (s, 2H), 7.07 (s, 4H), 2.38 (s, 6H), 2.12 (s, 12 H). $^{13}$C NMR (101 MHz, $CD_2Cl_2$): δ 140.19, 135.80, 135.36, 129.87, 122.98, 21.44, 18.13 (only 7 of 8 resonance observed).

## 9. Reaction of $Cu^I$-NHC complexes 64a, 64b and 65 with PhI (2), with and without $Pd(OAc)_2$.

### 9.1. Arylation procedure: *Method A*.

To a Young's NMR tube in the glove-box was added Cu(NHC)Br (**64b** or **65**) (0.0145 mmol) and dissolved in anhydrous $C_6D_6$ (0.7 ml) (distilled from Na). A $^1$H NMR spectrum (400 MHz) was recorded. In the glove-box, PhI (**2**) (8 μL, 14.7 mg, 0.0724 mmol) was added to the $C_6D_6$ solution. A $^1$H NMR spectrum was recorded and the sample was then heated to 90 $^o$C. $^1$H NMR spectra were recorded at 2 h and 24 h to monitor any chemical change. The $C_6D_6$ solvent was removed *in vacuo* and the solid (no mass loss) was re-dissolved in $CD_3CN$ (for ease of referencing with authentic standards of the potential products), and a $^1$H NMR spectrum recorded.

### 9.2. Arylation procedure: *Method B*.

To a Young's NMR tube in the glove-box was added Cu(NHC)Br (**64b** or **65**) (0.0145 mmol) dissolved in anhydrous $C_6D_6$ (0.7 ml) (distilled from Na). A $^1$H NMR spectrum (400 MHz) was then recorded. In the glove-box, PhI (**2**) (8 μL, 14.7 mg, 0.0724 mmol) was added, followed by a second $^1$H NMR spectrum. In the glove-box, $Pd(OAc)_2$ (3 mg, 0.0146 mmol) was added, followed by a third $^1$H NMR spectrum. The sample was then heated to 90 $^o$C for 24 h. Concomitant Pd black and product precipitation occurred, preventing any further *in situ* spectroscopic analysis. The solvent was removed *in vacuo* to give a brown solid (no mass loss), which was analysed by ESI-MS. This brown solid was re-dissolved in $CD_3CN$ (for ease of referencing with authentic standards of the potential products), and a $^1$H NMR spectrum recorded.

### 9.3. (1,3-Diphenyl)-2-phenylbenzo[*d*]imidazolium copper(II)diiodide (86b).

A Schlenk flask was charged in the glovebox with (1,3-diphenylbenzo[*d*]imidazolin-2-ylidene)copper(I) bromide (**64b**) (60 mg, 0.145 mmol), PhI (**2**) (80 μL, 0.724 mmol) and dry $C_6H_6$. Then, the reaction was heated at 90 °C. After 24 h the product **86b** precipitated as a white solid (51 mg, 99 % yield), m.p. 274-277 °C. $^1$H NMR (400 MHz, $CD_3CN$): δ 7.77-7.72 (m, 2H), 7.67-7.57 (m, 12H), 7.51-7.47 (m, 1H), 7.45-7.42 (m, 2H), 7.36-7.32 (m, 2H). $^{13}$C NMR (101 MHz, $CD_3CN$): δ 137.48, 133.86, 133.63, 133.56, 132.17, 132.09, 131.40, 129.84, 129.05, 128.49, 122.11, 114.46. ESI-HRMS: *m/z* = 347.1552, (calc. for $C_{25}H_{19}N_2^+$ 347.1543). IR (solid-state ATR, $cm^{-1}$): 3042, 1591, 1494, 1442, 1166, 1028, 750, 695, 584, 506.

# APPENDIX A

## Preliminary screening on the palladium-catalyzed direct arylation of 1-phenyl-1H-pyrazole (23): supplementary reactions.

As already stated in the **Chapter 1**, in Table 14 and Table 15 are reported all the data on the preliminary study of the Pd-catalyzed direct arylation of 1-phenyl-1*H*-pyrazole (**23**). The entries in bold are the supplementary reactions to those reported in Table 8 and Table 9.

From the data summarized in Table 14 it clearly emerges as $Cs_2CO_3$ resulted completely ineffective in toluene as well as in dioxane and in *N*-methyl-pyrrolidone (NMP) (entries 1-3, Table 14). Moreover, in order to verify that $Bu_4NOAc$ be effective or not for this reaction model even in the presence of ligands, we tried to perform the direct arylation of **23** with **26a** in the presence of P(o-Tol)$_3$, P(tBu)$_3$·HBF$_4$ and PBuAd$_2$ (entries 19-21, Table 14). Only P(tBu)$_3$·HBF$_4$ showed a slight activity giving a yield lower than 10 %, while other two phosphines did not showed activity.

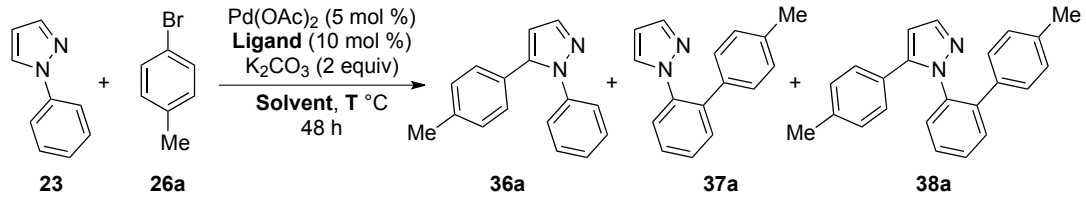
In addition to all the reactions performed, we also wanted to verify if, with a lower temperature, $Bu_4NOAc$ and $Cs_2CO_3$ could promote the direct arylation of 1-phenyl-1*H*-pyrazole (**23**) with 4-bromotoluene (**26a**). Once more, the two bases did not result effective for our reaction model (entries 1-2, Table 15). Furthermore, the addition of the PBuAd$_2$ at 110 °C did not contribute to an enhancement of the yield of **36a** (entry 4, Table 15), and also the selectivity resulted comparable with that obtained in entry 3.

When we found that $PdCl_2(MeCN)_2$ resulted the best catalyst, we also tested three type of ligands with this palladium catalyst. The PBuAd$_2$ did not influence significantly both the yield and the regioselectivity of compound **36a**. Then, we attempt to use *N*-containing ligands, as phenantroline or pyridine, because we wanted to verify if the presence of the nitrogen on the ligand could inhibit the *ortho*-arylation on the phenyl ring of **23** directed by the N-2 atom of pyrazole system. As we can note from entry 9 of Table 15, pyridine gave the product in 29 % yield but the selectivity of 5-aryl-pyrazole **36a** did not experience an enhancement. Moreover, phenantroline resulted to be ineffective for the promotion of our model reaction taking to a yield of only 5 %.

With the choice of $PdCl_2(MeCN)_2$ as the new catalyst precursor, we wanted to verify if it was possible to have some change in the yield or in the regioselectivity by rising again the reaction temperature to 140 °C. The reactions in the presence and in the absence of pyridine as ligand gave a yield of 30 and 35 %, respectively, but we observed again that with a higher reaction

temperature the selectivity decrease significantly (entries 11-12, Table 15). Finally, even though we changed the catalyst precursor, the $Bu_4NOAc$ still remained ineffective for our model reaction (entry 13, Table 15).

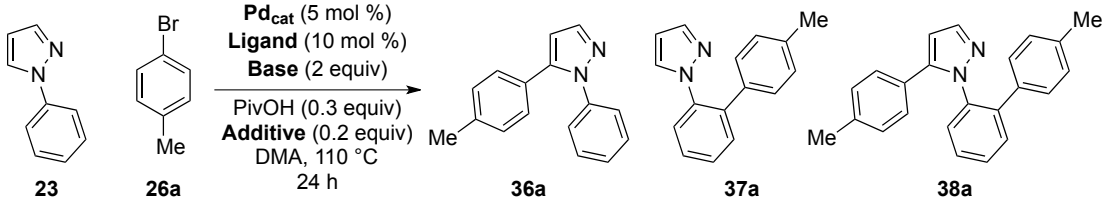
**Table 14**: Screening of the solvents and the ligands for the direct C-5 arylation of 1-phenyl-1*H*-pyrazole (**23**) with 4-bromotoluene (**26a**).




| Entry[a] | Ligand | Base | Solvent | Yield of 36a (%)[b] | 36a:37a:38a |
|---|---|---|---|---|---|
| **1**[c] | **-** | **$Cs_2CO_3$** | **Toluene**[d] | **-** | **-** |
| **2** | **-** | **$Cs_2CO_3$** | **Dioxane**[e] | **-** | **-** |
| **3** | **-** | **$Cs_2CO_3$** | **NMP** | **-** | **-** |
| 4[c] | - | $K_2CO_3$ | Toluene[d] | - | - |
| 5 | - | $K_2CO_3$ | Dioxane[e] | < 2 | 100:0:0 |
| 6 | - | $K_2CO_3$ | NMP | < 5 | 49:51:0 |
| 7 | - | $K_2CO_3$ | DMSO | - | - |
| 8 | - | $K_2CO_3$ | Chlorobenzene | 18 | 100:0:0 |
| 9 | - | $K_2CO_3$ | DMF | 18 | 48:37:15 |
| 10 | $PPh_3$ | $K_2CO_3$ | DMA | 21 | 40:27:33 |
| 11 | P(*o*-Tol)$_3$ | $K_2CO_3$ | DMA | 10 | 15:74:11 |
| 12 | P(2-furyl)$_3$ | $K_2CO_3$ | DMA | 17 | 38:43:19 |
| 13 | $PCy_3$ | $K_2CO_3$ | DMA | 23 | 44:26:30 |
| 14 | P(*t*Bu)$_3$·$HBF_4$ | $K_2CO_3$ | DMA | 20 | 40:36:24 |
| 15 | $PBuAd_2$ | $K_2CO_3$ | DMA | 21 | 58:31:11 |
| 16[c] | $PBuAd_2$ | $K_2CO_3$ | DMA | (21) | 57:18:25 |
| 17 | dppf | $K_2CO_3$ | DMA | 22 | 48:34:18 |
| 18 | Xantphos | $K_2CO_3$ | DMA | 21 | 44:32:24 |
| **19** | **P(*o*-Tol)$_3$** | **$Bu_4NOAc$** | **DMA** | **-** | **-** |
| **20** | **P(*t*Bu)$_3$·$HBF_4$** | **$Bu_4NOAc$** | **DMA** | **< 10** | **66:25:9** |
| **21** | **$PBuAd_2$** | **$Bu_4NOAc$** | **DMA** | **-** | **-** |

[a] Unless otherwise stated, the reactions were carried out using **23** (1.0 mmol), **26a** (1.5 equiv), $Pd(OAc)_2$ (5 mol %), ligand (10 mol %) (if any), base (2 equiv) in solvent (5 mL) for 48 h at 140 °C. [b] GLC yields. In parenthesis, isolated yields. [c] Reaction was carried out in the presence of 30 mol % PivOH. [d] Reaction was carried out at 110 °C. [e] Reaction was carried out at 100 °C.

**Table 15**: Screening of the reaction temperature, the palladium precatalyst, the presence of additive and **23/26a** molar ratio for the direct arylation of 1-phenyl-1*H*-pyrazole (**23**) with 4-bromotoluene (**26a**).




**23** **26a** **36a** **37a** **38a**

| Entry[a] | Catalyst | Base | Ligand | Additive | 23/26a ratio | T (°C) | Yield of 36a (%)[b] | 36a:37a:38a |
|---|---|---|---|---|---|---|---|---|
| **1**[c] | **$Pd(OAc)_2$** | **$Bu_4NOAc$** | **-** | **-** | **1/1.5** | **110** | **< 10** | **83:17:0** |
| **2** | **$Pd(OAc)_2$** | **$Cs_2CO_3$** | **-** | **-** | **1/1.5** | **110** | **-** | **-** |
| 3 | $Pd(OAc)_2$ | $K_2CO_3$ | - | - | 1/1.5 | 110 | 29 | 71:22:7 |
| **4** | **$Pd(OAc)_2$** | **$K_2CO_3$** | **$PBuAd_2$** | **-** | **1/1.5** | **110** | **29** | **77:15:8** |
| 5 | $Pd(PPh_3)_4$ | $K_2CO_3$ | - | - | 1/1.5 | 110 | 16 | 61:28:11 |
| 6 | $PdCl_2$(dppb) | $K_2CO_3$ | - | - | 1/1.5 | 110 | 19 | 48:40:12 |
| 7 | $PdCl_2(MeCN)_2$ | $K_2CO_3$ | - | - | 1/1.5 | 110 | 29 (27) | 82:13:5 |
| **8** | **$PdCl_2(MeCN)_2$** | **$K_2CO_3$** | **$PBuAd_2$** | **-** | **1/1.5** | **110** | **25** | **84:11:5** |
| **9** | **$PdCl_2(MeCN)_2$** | **$K_2CO_3$** | **Pyridine[d]** | **-** | **1/1.5** | **110** | **29** | **77:15:8** |
| **10** | **$PdCl_2(MeCN)_2$** | **$K_2CO_3$** | **Phenantroline[d]** | **-** | **1/1.5** | **110** | **5** | **79:21:0** |
| **11** | **$PdCl_2(MeCN)_2$** | **$K_2CO_3$** | **-** | **-** | **1/1.5** | **140** | **30** | **60:14:26** |
| **12** | **$PdCl_2(MeCN)_2$** | **$K_2CO_3$** | **Pyridine[d]** | **-** | **1/1.5** | **140** | **35** | **59:13:28** |
| **13** | **$PdCl_2(MeCN)_2$** | **$Bu_4NOAc$** | **-** | **-** | **1/1.5** | **110** | **< 5** | **91:9:0** |
| 14 | $PdCl_2(MeCN)_2$ | $K_2CO_3$ | - | - | 1/2 | 110 | 28 | 73:14:13 |
| 15 | $PdCl_2(MeCN)_2$ | $K_2CO_3$ | - | $BnBu_3NCl$ | 1/1.5 | 110 | 35 | 69:14:13 |
| 16 | $PdCl_2(MeCN)_2$ | $K_2CO_3$ | - | $BnBu_3NCl$ | 1/2 | 110 | 40 | 77:15:8 |
| 17 | $PdCl_2(MeCN)_2$ | $K_2CO_3$ | - | $BnBu_3NCl$ | 1/1.5 | 70 | - | - |
| 18 | $PdCl_2(MeCN)_2$ | $K_2CO_3$ | - | $Bu_4NBr$ | 1/1.5 | 110 | 38 (29) | 78:11:11 |
| 19 | $PdCl_2(MeCN)_2$ | $K_2CO_3$ | - | $Bu_4NBr$ | 1/2 | 110 | 43 | 70:12:18 |
| 20 | $PdCl_2(MeCN)_2$ | $K_2CO_3$ | - | $Bu_4NBr$ | 1/1 | 110 | 31 | 80:10:10 |
| 21[e] | $PdCl_2(MeCN)_2$ | $K_2CO_3$ | - | $Bu_4NBr$ | 1/1.5 | 110 | 33 | 78:12:10 |
| 22 | $PdCl_2(MeCN)_2$ | $K_2CO_3$ | - | $Bu_4NBr$ | 2/1 | 110 | 43 (38) | 83:17:0 |
| 23 | $PdCl(C_3H_5)$dppb | KOAc | - | - | 1/1.5 | 150 | 6 | 69:31:0 |

[a] Unless otherwise stated, the reactions were carried out using **23** and **26a** with the ratio reported for each entries, $Pd_{cat}$ (5 mol %), ligand (10 mol %) (if any), base (2 equiv), PivOH (30 mol %), additive (if any) (20 mol %) in DMA (5 mL) for 48 h at 110 °C. [b] GLC yields. In parenthesis, isolated yields. [c] Reaction was carried out in the absence of PivOH. [d] Reaction was carried out with a Pd/Ligand ratio 1:1. [e] Reaction was carried out in the presence of 10 mol % $Pd(OAc)_2$.

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