Mechanistic Studies on the Pd-Catalyzed Direct Arylation of Imidazoles at C5: Role of the Substrate as a Ligand for Pd

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Abstract: A detailed mechanistic study on the Pd-catalyzed direct arylation of imidazoles at the C5 position is presented. The interactions of PPh_3-ligated aryl-Pd species with 1,2-dimethyl-1*H*-imidazole (dmim) have been studied in detail. In contrast with previous suggestions, phosphine-ligated organo-Pd species are not active and the reaction proceeds through imidazole-ligated organo-Pd intermediates. The kinetics of the oxidative addition of aryl halides with dmim-ligated Pd^0 species has been characterized in a $Pd(dba)_2$/dmim model system. A thorough study of the equilibria involving novel $[ArPd(dmim)_2X]$ complexes (X=I, OAc) and the unexpected cationic $[ArPd(dmim)_3]^+$ is also reported. The ability of those species to effect the C-H arylation of dmim at room temperature in the presence of acetate is also demonstrated.

Introduction

Palladium-catalyzed reactions have become the method of choice for the preparation of unsymmetrical (hetero)biaryls.[1] A general approach to this subject is the use of the now well-established Pd-catalyzed cross-coupling protocols (Scheme 1, a). However, these methods are not atom- and step-economical, since they require the preactivation of both coupling partners. Moreover, they generate a stoichiometric quantity of potentially toxic metal-containing waste.

A more economical and environmentally-friendly approach, which may also be suitable for the late-stage diversification of functionalized molecules,[2] is the palladium-catalyzed direct arylation of heteroarenes with aromatic electrophiles (Scheme 1, b).[3] This strategy is based on the activation of a C-H bond and does not require the use of a stoichiometric amount of a preformed organometallic reagent. Excellent regioselectivity can often be attained thanks to the presence of heteroatoms in the aromatic nucleus, which are able to differentiate unlike C-H bonds by electronic effects and metal-coordinating ability.

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a. Traditional cross-coupling reactions:

$$(Het)Ar^1M + (Het)Ar^2X \xrightarrow{\text{cat. Pd}} (Het)Ar^1\text{-}(Het)Ar^2 + MX$$

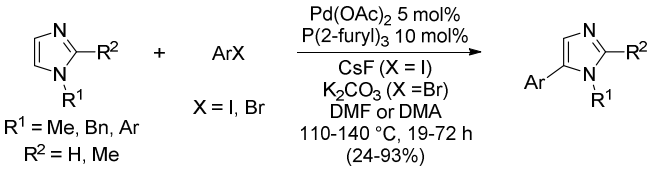
M = $B(OH)_2$, $B(OR)_2$, SnR_3, ZnX, SiR_3, MgX, …

b. Direct arylation reactions:

$$(Het)Ar^1H + (Het)Ar^2X \xrightarrow{\text{cat. Pd}} (Het)Ar^1\text{-}(Het)Ar^2 + HX$$

Scheme 1. Comparison between traditional Pd-catalyzed cross-couplings and direct arylation reactions.

Among the wide variety of aryl-heteroarenes, arylazoles are important structural units, often found in natural products and their synthetic analogues,[5] pharmaceuticals,[6] and organic functional materials,[7] so in the last few years we became interested in the development of straightforward and convenient methods for their synthesis. Inspired by some seminal reports appeared before 2000,[8-10] we established an efficient and general protocol for the direct arylation of imidazoles with high regioselectiviy for the C5 position.[11] These conditions involve the use of 5 mol% $Pd(OAc)_2$, 10 mol% P(2-furyl)$_3$, CsF or K_2CO_3 as the base, in DMF or DMA at 110 °C for *N*-methyl-imidazole and at 140°C for *N*-benzyl- and *N*-aryl imidazole (Scheme 2).[11] PPh_3[10], $AsPh_3$,[12] PCy_3[13,14], and P^{n}BuAd$_2$[15] can also be used as ligands. Procedures using $[Pd(phen)_2](PF_6)_2$[16] or bulky NHC-Pd complexes[15,17] as precatalysts have also been described. Two ligand-free protocols have been reported: the first one employed KOAc and 0.01-0.5% $Pd(OAc)_2$ at 150 °C,[18] while the second used ^{n}Bu$_4$NOAc as the base for the C5 direct arylation of several azoles (*1*-methylpyrazole, oxazole, thiazole, 1-methyl-1*H*-imidazole) under comparatively mild conditions (70-110 °C).[19,20]



Scheme 2. C5-Regioselective arylation of imidazoles.[11]

Despite the synthetic relevance of Pd-catalyzed direct arylation reactions, relatively few attention has been devoted to their mechanistic understanding. Moreover, as well outlined in the reviews compiled by Echavarren[4a] and Fagnou[4b] in 2010, and by Gorelsky[4c] in 2013, the mechanistic studies performed so far have been generally focused only on the C-H bond-breaking step, mainly because it is responsible for the experimentally observed regioselection among different (hetero)aromatic C-H bonds.

Early workers in this field generally believed that C-H bond activation of these electron-rich heteroaromatics takes place by a S_EAr-type mechanism[10], indeed convincing evidence has been

found for a number of related cases.[21] After the ground-breaking discovery of the key role of carboxylates in the functionalization of unsubstituted benzene[22], a concerted metalation-deprotonation (CMD) mechanism has been proposed by Fagnou and Gorelsky for the C-H functionalization of a number of heterocycles.[4b,4c,23] According to this mechanistic hypothesis, the carboxylate anion acts as a "proton shuttle" and assists the simultaneous metalation and deprotonation of the arene while still coordinated to Pd, thus there is no proper Wheland intermediate.[22,23]

Phosphine-ligated arylpalladium carboxylates are typically proposed to react with arenes to form the diaryl-palladium complexes through the CMD pathway.[4b,4c,22,23] Hartwig and Tan have prepared and characterized the complex [(2-Me-C_6H_4)Pd(P^tBu_3)(OPiv)].[24] Inconsistently with previous proposals, they showed that these isolated organopalladium species do not react readily with benzene to form the arylation product in more than trace amounts and that phosphine-ligated are not competent species in the direct arylation of benzene. This conclusion was also supported by DFT calculations.[24] On the other hand, Ozawa and coworkers showed that a PPh_3-ligated aryl-Pd species can effect the direct arylation of a variety of substrates[25]. Hartwig and coworkers have also highlighted the key role of a cyclometalated species [Pd(OAc)($^tBu_2PCMe_2$-CH_2)], formed by C-H activation of P^tBu_3 in the direct arylation of pyridine-*N*-oxides and benzothiophene.[26] A Heck-type carbopalladation-dehydropalladation pathway has been proposed to explain some peculiarities of a *β*-selective arylation of thiophenes[27]. The C2 regioselectivity observed in some cases for the functionalization of 1,3-azoles has been linked to the enhancement of the C2-H acidity upon Pd-coordination through the pyridine-like nitrogen. A proton abstraction mechanism called "non-Concerted Metalation Deprotonation" (nCMD) was thus proposed,[28] while a deprotonation-ring opening pathway has been demonstrated for the C2 arylation of benzoxazole.[29] Evidence for free-radical processes has also been put forward in a limited number of cases.[30]

However, none of the studies summarized above is able to explain the great influence of experimental parameters (ratios between substrates, choice of base and solvent, addition of ligands) on the outcome of the coupling reaction. In our opinion, an in-depth study of the mechanisms of direct arylation reactions may give insight useful to develop new and more efficient catalytic systems in terms of activity under mild conditions, selectivity and functional group tolerance.

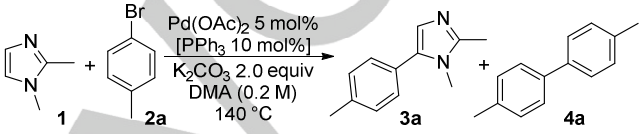
Keeping those premises in mind, we undertook a detailed mechanistic study of the Pd-catalyzed direct arylation of imidazoles with a broad focus on the whole catalytic cycle. Our results evidenced that PPh_3-ligated aryl-Pd species are not able to perform the C-H functionalization of imidazoles, while novel imidazole-coordinated organo-Pd complexes are active even at room temperature.

Results and Discussion

Kinetic isotope effect

As discussed previously, direct arylation reactions of imidazoles at the C5 position are usually carried out with a precatalyst mixture composed of a Pd^{II} salt, usually $Pd(OAc)_2$, and either a phosphine[10-12, 31] or no added ligand[7e,18,19] (the so-called *ligandless conditions*). Customarily, a 1 : 2 molar ratio between Pd and monodentate ligand is employed.[10-12, 31]

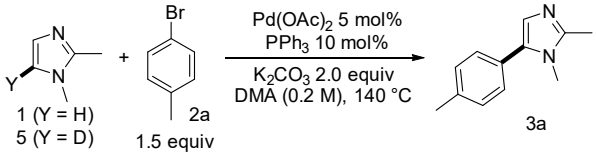
For our mechanistic studies we selected a simple model system. 1,2-Dimethyl-1*H*-imidazole (dmim, **1**) was chosen in order not to have by-producs formed by *N*- or *C2*- arylation. 4-Bromotoluene (**2a**) was used as the coupling partner along with $Pd(OAc)_2$ (5 mol%) as the precatalyst, PPh_3 (10 mol%) as the ligand, and K_2CO_3 as the base in anhydrous DMA at 140 °C (Scheme 3). The formation of the C5-arylated product **3a** and of the by-product 4,4'-bitolyl (**4a**), as well as the disappearance of starting materials dmim (**1**) and **2a** was followed by GLC analysis of aliquots withdrawn periodically from the reaction mixture using naphthalene as an internal standard.



Scheme 3. Model reaction

First, kinetic isotope effect (KIE) experiments were performed. KIE studies have been applied to a great variety of metal-mediated C-H activation processes and these efforts have been reviewed recently.[32]

For this purpose, 5-deuterio-1,2-dimethyl-1*H*-imidazole (5-D-dmim, **5**) was synthesized with 92% deuterium incorporation by low temperature halogen-lithium exchange, followed by quenching with CH_3OD (see SI §2.2 for the experimental procedure). First, the reactions involving dmim **1** and 5-D-dmim **5** were performed separately. If an initial induction period was excluded, the amount of **3a** formed fitted an exponential rise to maximum with respect to time (R^2>0.998, Figure 1). The two first-order apparent rate constants were determined from the fit parameters (k_H = 2.1·10^{-2} min^{-1} and k_D. = 0.77·10^{-2} min^{-1}, Figure 1). The ratio of these independently determined rate constants (i.e., k_H/k_D) gives 2.7 as KIE value (standard error: 0.35). This result proves unambiguously that the turnover-limiting step of the catalytic cycle involves the cleavage of the imidazole C5-H bond under our conditions, as observed for other direct arylation reactions.[31, 33]



Scheme 4. Reactions for KIE determination.

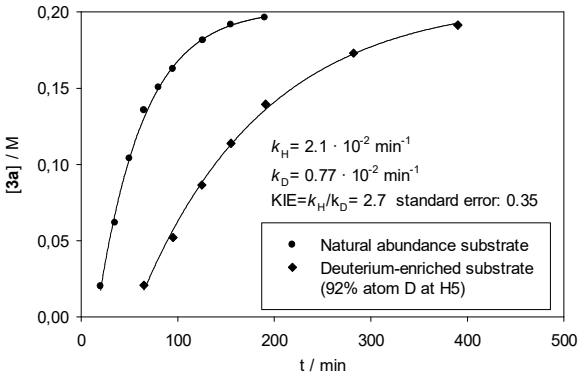


Figure 1. Determination of KIE for the reactions in Scheme 4. Experimental points are shown together with exponential fit: [**3a**]=*A*+*C*$_\infty$(1-e^{-kt}). Parameter *A* has been included because an induction period has been excluded from the fitted data (*vide infra*).

Secondly, competition experiments were performed introducing both **1** and **5** in the same flask to determine KIE from the initial and final concentrations of **1** and **2** (as assessed by GLC-MS analysis), assuming first order kinetics in the imidazole substrate, with the following formula:

$$\mathrm{KIE} = \frac{k_\mathrm{H}}{k_\mathrm{D}} = \frac{\log\left(\frac{[\mathbf{1}]}{[\mathbf{1}]_0}\right)}{\log\left(\frac{[\mathbf{5}]}{[\mathbf{5}]_0}\right)} = 2.32$$

The value obtained is rather consistent with the one determined by the two separated reactions, and it is not greatly influenced by varying the aryl bromide ArBr: k_H/k_D=2.23 for 4-MeO-C_6H_4Br and k_H/k_D=2.40 for 4-CF_3-C_6H_4Br (see SI, §1.2).

Electronic effects

The influence of the electronic character of the imidazole substrate on the reaction kinetics was also investigated. A variety of 1-aryl-2-methylimidazoles bearing diverse substituents on the aryl ring have been prepared. Relative reaction rates for the arylation under conditions close to the one reported in Scheme 3 were assessed by competition experiments in order to obtain a Hammett plot. Unfortunately no correlation was evident, but electron-poor substrates reacted faster than electron-rich ones (for data and experimental details, see SI §1.3), so the reaction overall has a slightly nucleophilic character.

Induction period and role of PPh_3

In order to understand why an induction period is observed at the beginning of the reaction, the model experiment (Scheme 3) was performed either with PPh_3 as ligand or without any added ligand and the formation of the coupling product **3a** was followed with time (Figure 2).

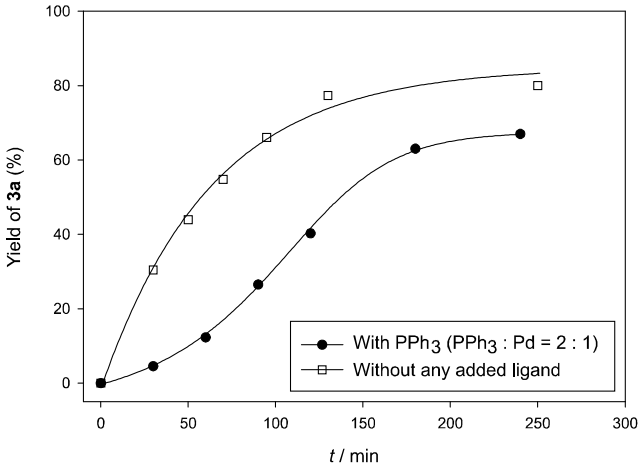
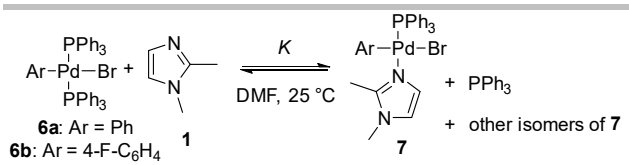


Figure 2. Kinetic curve for the formation of **3** under the conditions reported in Scheme 3.

At the beginning, the reaction in the presence of PPh_3 was significantly slower. A 50% yield was reached in slightly less than 2 h and the homocoupling product **4a** was formed in a 6% GLC yield.[32] However, under ligandless conditions, the reaction was faster, reaching 50% yield in about 1 h and the by-product **4a** was formed just in trace amounts (< 1% GLC yield).[34]

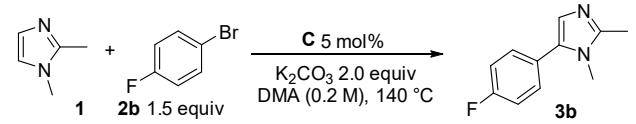
The existence of an induction period in the presence of PPh_3 suggests that this ligand has an inhibiting effect on the catalytic reaction. It is well-known that a mixture of $Pd(OAc)_2$ and PPh_3 rapidly undergoes a redox reaction, even at room temperature, with the formation of Pd^0 species and $[PPh_3OAc]^+$ (hydrolysed to PPh_3O by adventitious water).[35] This reaction accounts for the depletion of one of the two added equivalents of PPh_3 (with respect to Pd). When the model reaction was performed under the conditions of Scheme 3 but 4-bromotoluene (**2a**) was replaced with 4-fluorobromobenzene (**2b**), reaction monitoring by ^{19}F and ^{31}P NMR spectroscopy showed that one of the two equivalents of PPh_3 is oxidized to PPh_3O just after mixing the reactants at room temperature, while the second equivalent is more slowly oxidized at 140 °C. The expected coupling product **3b** is not formed in sizeable quantity until a substantial amount of PPh_3 has been depleted (for details, see SI §1.4).[36]

In order to confirm that PPh_3-ligated palladium species are not active in the reaction under study, we characterized the behaviour of some PPh_3-ligated aryl-palladium complexes in the presence of dmim and tested their reactivity. First, the interaction of *trans*-[ArPd(PPh_3)$_2$Br] (**6**)[37] (**6a:** Ar = Ph, **6b:** Ar = 4-F-C_6H_4) with dmim in DMF was studied by ^{31}P NMR spectroscopy. Analogously to what described in the literature for primary and secondary aliphatic amines,[38] dmim displaces one of the PPh_3 ligands to give a mixture of isomeric [ArPd(PPh_3)(dmim)Br] species (Scheme 5). As no change in the ^{31}P spectrum was observed after the addition of a large excess of ^{n}Bu$_4$NBr, most likely bromide is not displaced and no cationic complex forms. The displacement of a second PPh_3 ligand is much more difficult. The values of the overall equilibrium constant *K* (Scheme 5) have been estimated by quantitative ^{31}P-NMR spectroscopy (see SI, §1.5) and were found to be lower than 1 (*K* = 0.068 for Ar = Ph, *K* = 0.050 for Ar = 4-F-C_6H_4).[39]



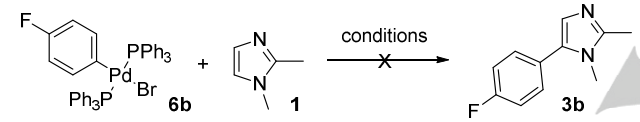
Scheme 5. Displacement of PPh_3 by dmim in *trans*-[ArPd(PPh_3)$_2$Br].

Complex **6b** was tested under catalytic conditions and turned out to be a competent precatalyst, providing a yield comparable to the one obtained with $Pd(OAc)_2$, albeit in a longer reaction time (Scheme 6). Prolonged heating (140 °C, 2.5 h) of a mixture of **6b** (0.02 M in DMF) in a NMR tube with 1.0 equiv if dmim and 2.0 equiv of Cs_2CO_3 provoked precipitation of palladium black without formation of desired coupling product. AgOAc and CsOAc also failed to promote the reaction (Scheme 7).



for **C** = $Pd(OAc)_2$, reaction time 4 h: 70% (isolated yield)
for **C** = trans-[(4-C_6H_4)Pd(PPh_3)$_2$Br] (**6b**) 24 h: 74% (^{19}F NMR yield)

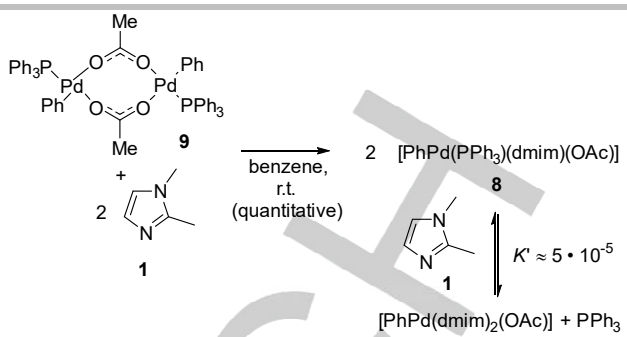
Scheme 6. Comparison of $Pd(OAc)_2$ and *trans*-[ArPd(PPh_3)$_2$Br] as precatalysts.



Conditions: a) Cs_2CO_3 2.0 equiv, DMF (0.02 M), 120 °C
b) AgOAc 1.0 equiv, Cs_2CO_3 2.0 equiv, DMF (0.02 M), 120 °C
c) CsOAc 2.0 equiv, DMF (0.02 M), 120 °C

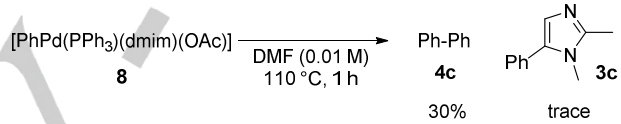
Scheme 7. Attempted reaction of *trans*-[ArPd(PPh_3)$_2$Br] with dmim.

A complex of composition [PhPd(PPh_3)(dmim)(OAc)] (**8**), which should be structurally very close to a transition state proposed on the basis of DFT calculations,[40] was prepared by the reaction of the bridged acetate complex [PhPd(PPh_3)(μ-OAc)]$_2$ (**9**)[41] with 2.0 equiv of dmim (Scheme 8).[42] Upon treatment of **8** with a large excess of dmim (100 equiv), uncoordinated PPh_3 appeared in the ^{31}P NMR spectrum. The thermodynamic constant *K'* for this equilibrium (Scheme 8) has been estimated from ^{31}P NMR data and the value obtained ($5.5 \cdot 10^{-5}$ at 25 °C) points out that the displacement of this phosphine ligand is much more difficult than the removal of one PPh_3 from [ArPd(PPh_3)$_2$Br] (**6**), with a value about three orders of magnitude lower.[43] Such behaviour can be rationalized in terms of the so-called *thermodynamic trans effect* or *trans influence*.[44]



Scheme 8. Synthesis of complex **8** and its PPh_3-displacement equilibrium.

The reactivity of **8** was then investigated in DMF at 120 °C under various conditions. Heated alone, it gave a 30% yield of biphenyl, but only traces of the expected coupling product, 5-Ph-dmim (**3c**) (Scheme 9). Addition of an excess of dmim **1** or other coordinating bases (nBu$_4$NOAc, DBU, iPr$_2$NH, see details in the SI, §1.6) promoted the formation of **3c** together with high amounts of PhPh, differently from what happens in the catalytic process.[45] These results suggest that **8** is an unlikely intermediate of the catalytic reaction.



Scheme 9. Thermal decomposition of [PhPd(PPh_3)(dmim)(OAc)] (**8**)

The observation of an induction period in the catalytic reaction in the presence of PPh_3 and the poor reactivity of isolated aryl-Pd complexes featuring one or two PPh_3 ligands advocate that the latter are not reactive intermediates of the catalytic cycle. The higher efficiency of the catalytic reaction under study with ligands with lower donating ability than PPh_3, such as $AsPh_3$[12] and P(2-furyl)$_3$,[11a, 46] is most likely due to the ease with which they can be displaced by the imidazole substrate. The direct arylation of azoles at C5 can also be performed under mild conditions (70°C for oxazole and thiazole, 110 °C for *N*-protected imidazole) without any added ligand when the soluble base ^{n}Bu$_4$NOAc is employed, thus underlining the strong inhibitory effect of phosphine ligands.[19]

Oxidative addition with dmim-ligated Pd^0

Given the importance of phosphine-free conditions for the reaction under study, the feasibility of oxidative addition with dmim as the sole ligand of the Pd^0 species was investigated. Among the different methods tested, dmim-ligated Pd^0 was obtained by displacement of dba ligands from $Pd(dba)_2$ in the presence of an excess of dmim in dichloromethane. The instantaneous colour change from purple-violet to orange-yellow prompted us to study the system by UV-Vis spectroscopy. It appeared that with 20 equiv of dmim the spectrum is virtually indistinguishable from the one of a solution of dba in an amount compatible with a complete displacement of the dba ligands (see SI, §1.7).

A similar behaviour was observed by cyclic voltammetry (CV) performed in DMF at a steady gold disk electrode. A solution of $Pd(dba)_2$ in DMF (2.0 mM) gives two reduction peaks R1 and R2 (Figure 3). R2 is assigned to the reduction of free, uncoordinated dba, as can be inferred by comparison with an authentic sample.[47] On adding increasing amounts of dmim to this solution,

R2 progressively increases and R1 gradually disappears. The maximum reduction current of R2 is proportional to the concentration of free dba, so the amount of free dba in solution can be readily estimated.[47] With 10 equiv of dmim all dba is apparently displaced from Pd, since R2 doubles after the addition of an authentic sample of dba. The small reduction peak R1 (less than 20% of R2) is assigned to the reduction of dba bound to palladium, because it is maximum when no dmim is present and disappears when dba is completely displaced.

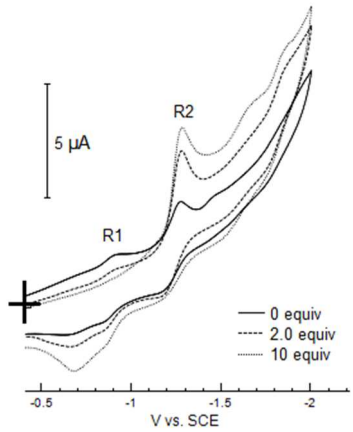


Figure 3. Cyclic voltammetry of $Pd(dba)_2$ (2.0 mM in DMF), in the presence of varying amounts of dmim, as shown in the inset. Conditions: steady gold disk electrode (⌀ = 1.0 mm), scan rate 0.1 V/s, 25 °C, supporting electrolyte $^{n}Bu_4NBF_4$ 0.3 M.

While dba is progressively displaced, a barely noticeable oxidation wave O1 becomes apparent in the presence of excess dmim (Figure 4, left), which can be attributed to a dmim-ligated Pd^0 species. On adding one equivalent of PhI to the solution containing $Pd(dba)_2$ (2.0 mM) and 10 equiv of dmim, the wave O1 disappears and a new large wave O2 appears, which is assigned to the oxidation of iodide anion by comparison with a solution of $^{n}Bu_4NI$ (Figure 4, right). These experiments clearly indicate that dmim-ligated Pd^0 species are active towards the oxidative addition of PhI, and the process is quite fast at room temperature. As the oxidative addition product features free iodide anions it should have a cationic character, at least in the presence of excess dmim (Scheme 10).

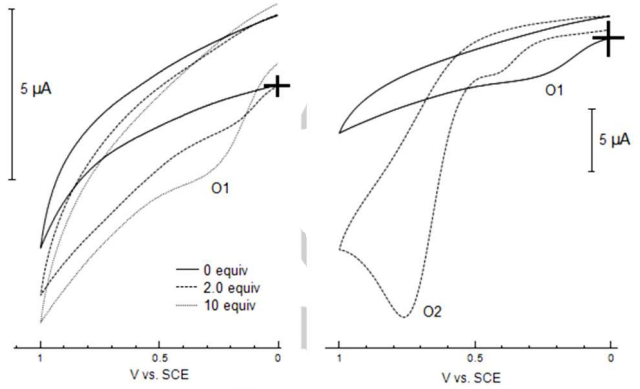
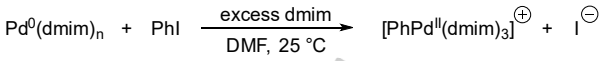


Figure 4 – Left: voltammetric oxidation of $Pd(dba)_2$ (2.0 mM in DMF), in the presence of varying amounts of dmim, as shown in the inset. Right: voltammetric oxidation of $Pd(dba)_2$ (2 mM in DMF), in the presence of 10 equiv of dmim, before (solid line) and after (dashed line) addition of 1.0 equiv of PhI. Conditions: steady gold disk electrode (⌀ = 1.0 mm), scan rate 0.1 V/s, 25 °C, supporting electrolyte $^{n}Bu_4NBF_4$ 0.3 M.



Scheme 10. Oxidative addition of PhI with dmim-ligated Pd^0

The ionic nature of the product allowed to use conductimetry to follow reaction kinetics.[48] First, the dependence of the rate for the oxidative addition of PhI (1.0 equiv) varying the concentration of dmim was studied. Final conductivity κ_∞ did not change for several hours, suggesting that the product was chemically stable. Initial rates were estimated as $v = c\,\kappa/\kappa_\infty$, where c is the initial concentration of the limiting reagent. The apparent initial rate v steeply increases until the concentration of added dmim is 20 mM (10 equiv). The rate does not change significantly when more dmim is added (up to 100 equiv), this behaviour is consistent with the complete displacement of dba from Pd^0 at high concentration of dmim (> 10 equiv) and the reactivity of imidazole-ligated Pd^0 towards PhI. (Figure 5).

The latter observation suggests that the dissociation of one of the dmim ligands is either not required for the oxidative addition to take place or it is fast enough not to affect the rate of oxidative addition. This scenario is very different from the oxidative addition of aryl halides to $Pd(PPh_3)_4$. Indeed, the latter compound gives rise to $Pd(PPh_3)_3$ as the main species in solution and a further ligand dissociation is required for oxidative addition to take place, since the reactive intermediate is the 14-electron complex $Pd(PPh_3)_2$. Overall, the reaction has order -1 with respect to PPh_3, in accordance to a pre-equilibrium regimen.[49]

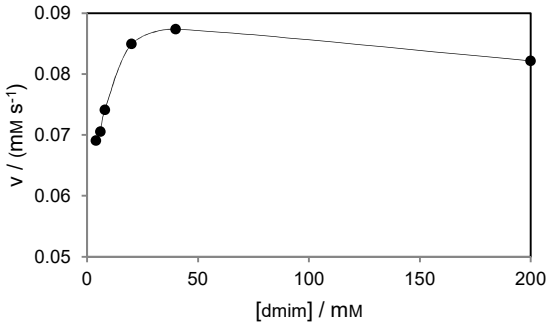


Figure 5. Initial rates v for the oxidative addition of PhI (2.0 mM) with $Pd(dba)_2$ (2.0 mM in DMF) in the presence of varying amounts of dmim, as measured by conductimetry, temperature: 25 °C.

Further work was carried out replacing PhI with 4-bromobenzonitrile (**10**). Oxidative addition using 50 equiv of **10** with respect to $Pd(dba)_2$ (2.0 mM in DMF) in the presence of dmim (20 equiv) is slower and more amenable to conductimetric measurements. Taken into account the kinetic law for the appearance of the complex resulting from oxidative addition for a pseudo-first order reaction $C(t) = C_\infty\,(1 - e^{-kt})$, the quantity $\ln[1 - C(t)/C_\infty]$ was plotted as a function of time (t) and k was calculated as the slope of the resulting graph. Under those conditions, the semilogarithmic plot traced as described before is linear for at least four half-lives (R^2>0.999, Figure 6), implying that the oxidative addition reaction is first order with respect to Pd. Apparent rate constants were also measured in a similar fashion at different concentrations of **10**. The reaction is first order also with respect to this reagent (see SI, §1.7).

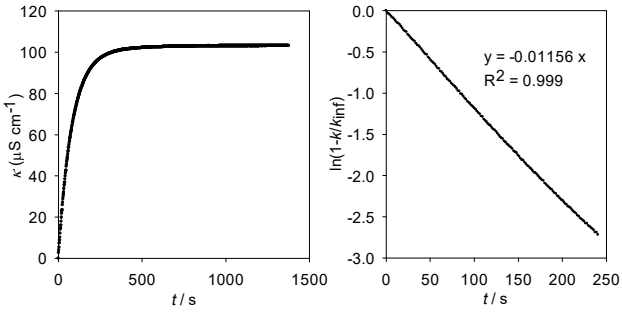


Figure 6. Left: oxidative addition of 4-bromobenzonitrile (**10**) (50 equiv) to $Pd(dba)_2$ (2.0 mM in DMF) in the presence of dmim (20 equiv), as followed by monitoring the conductivity *κ*. Right: same data, represented with a semilogarithmic plot. Temperature: 25 °C.

We can conclude that the kinetic law for the oxidative addition of ArX to dmim-ligated Pd^0 species, generated in situ by displacement of dba from $Pd(dba)_2$ with excess dmim, is simply $dP/dt = k[Pd][ArX]$ in which *P* stands for the concentration of the formed product and [Pd] is the total concentration of Pd^0 species. Some values of *k* are summarized in Table 1. It is noteworthy that this reaction is comparatively fast, even at room temperature.

Table 1 – Rate constants for the oxidative additions of ArX to $Pd(dba)_2$ in DMF in the presence of 20 equiv of imidazole derivative, which is enough to displace quantitatively dba and make *in situ* imidazole-ligated Pd^0, $dP/dt = k[Pd][ArX]$. All data are referred to 25 °C and are deduced from conductimetric measurements.

Imidazole derivative	ArX	*k* ($M^{-1}s^{-1}$)
dmim (**1**)	PhI	21.8
dmim (**1**)	4-CN-C_6H_4Br (**10**)	0.117
Imidazole	PhI	30.2

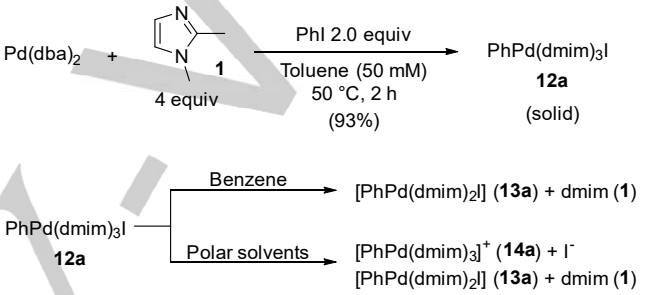
Oxidative addition occurs faster when unsubstituted imidazole is used instead of dmim. This observation suggests that the impossibility to perform the direct arylation of *N*-unprotected imidazoles is not due to inhibition of the oxidative addition step. To the best of our knowledge, no reaction of this kind has been reported in the literature so far.

In our hands, a 1:1 mixture of dmim and 2-methyl-1*H*-imidazole (**11**) subjected to standard direct arylation conditions did not give any trace of coupling product (as assessed by GLC-MS of the crude reaction mixture), thus showing that not only the *N*-unsubstituted imidazole is not a substrate for the reaction, but it is also a catalytic poison (Scheme 11).

Scheme 11. Attempted direct arylation of a mixture of dmim and 2-methyl-1*H*-imidazole.

Characterization of dmim-ligated arylpalladium species

The use of a less polar solvent as toluene for the reaction of $Pd(dba)_2$ with PhI in the presence of dmim allowed the isolation of a solid of composition $PhPd(dmim)_3I$ (**12a**) in excellent yield (Scheme 12). This solid dissolved to some extent in benzene-d_6 and behaved as a 1:1 mixture of dmim (**1**) and $[PhPd(dmim)_2I]$ (**13a**), as determined by ^{1}H-NMR spectroscopy and comparison of the chemical shifts with an authentic sample of dmim. However, in more polar solvents ($CDCl_3$, acetone-d_6, DMF-d_7) complex spectra were obtained, indicating the presence of two species in equilibrium: a cationic $[PhPd(dmim)_3]^+$ (**14a**) and a neutral complex $[PhPd(dmim)_2I]$ (**13a**). About 30% of the complex is in the ionic form in $CDCl_3$ at room temperature (the interpreted aliphatic section of the ^{1}H NMR spectrum of **12a** is shown in Figure 7). The cationic complex $[PhPd(dmim)_3]^+$ (**14a**) alone has been characterized in $CDCl_3$ solution by ^{1}H, ^{13}C and ^{19}F NMR spectroscopies with TfO^- as counterion after anion exchange with AgOTf. Detailed spectral analyses are reported in the SI, §1.8.



Scheme 12. Synthesis of $PhPd(dmim)_3I$ (**12a**) and its ionization in different solvents.

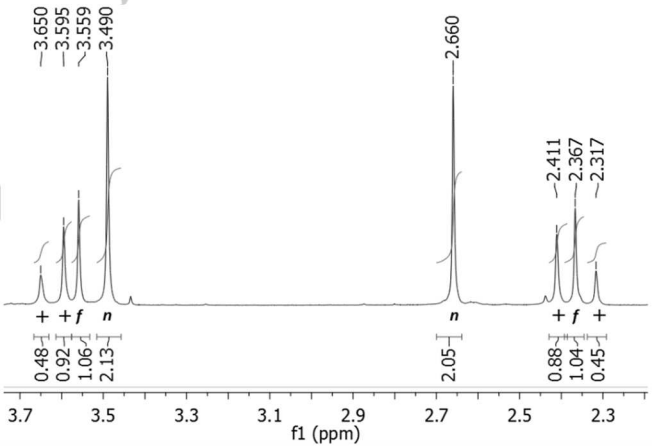
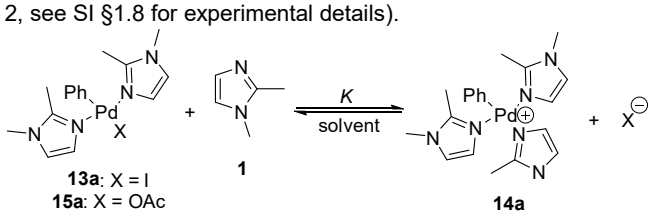


Figure 7. Aliphatic region of the ^{1}H NMR spectrum of a solution of $[PhPd(dmim)_3I]$ (**12a**) in $CDCl_3$ at 25 °C. Assignments: + $[PhPd(dmim)_3]^+$ (**14a**), ***f*** free uncoordinated dmim (**1**), ***n*** $[PhPd(dmim)_2I]$ (**13a**).

In view of the relevance of acetate for the mechanism of the reaction under study, the substitution of iodide in $PhPd(dmim)_3I$ (**12a**) with AgOAc was attempted. Any effort to isolate a complex in the solid state invariably failed because of the precipitation of metallic palladium and extensive decomposition while removing the solvent (even in high vacuum at 0 °C). However, $[PhPd(dmim)_2(OAc)]$ (**15a**) turned out to be quite stable in dilute benzene solution and could be characterized *in situ* by NMR and mass spectrometry.

We next studied the equilibria between **13a**/**15a** and the cationic form $[PhPd(dmim)_3]^+$ (**14a**) in the presence of dmim

(Scheme 13). Once again, conductimetry was performed to access the thermodynamic constants for these two equilibria in pure CH_2Cl_2 and in a DMF/CH_2Cl_2 mixture[50] (80:20 ratio) (Table 2, see SI §1.8 for experimental details).



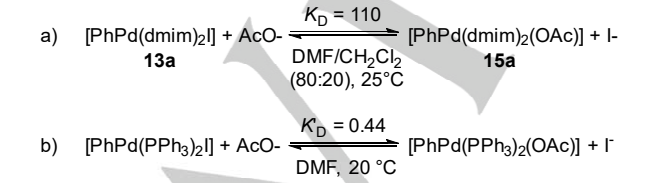
Scheme 13. Ionization equilibrium for **13a** and **15a**.

Table 2. Equilibrium constants for the reaction in Scheme 13, as deduced from conductivity measurements (on 2.0 mM solutions in the specified solvents, 25 °C).

X	Solvent	*K*
I	CH_2Cl_2	0.20
OAc	CH_2Cl_2	$6.3 \cdot 10^{-3}$
I	DMF/CH_2Cl_2 80:20 vol.	8.6
OAc	DMF/CH_2Cl_2 80:20 vol.	$8.1 \cdot 10^{-2}$

The equilibrium constant K_D for the displacement of iodide by acetate at 25 °C (Scheme 14, a) can be estimated from the data in Table 2 as $K_D=K_I/K_{OAc}$: K_D=32 in CH_2Cl_2 and K_D=110 in DMF/ CH_2Cl_2 (80:20).

From these data it follows that the $[PhPd(dmim)_2]^+$ moiety has a greater affinity for AcO^- than for I^-. This suggests that the main palladium species present in solution during the direct arylation of dmim is most likely $[ArPd(dmim)_2(OAc)]$ (**15a**), especially when the very efficient, soluble base $^nBu_4NOAc$ is used,[19] generating high concentrations of free acetate. The comparison with the PPh_3-ligated analogues $[PhPd(PPh_3)_2X]$ (X = I, OAc) is also interesting. The equilibrium constant for the I^-/AcO^- exchange is K'_D=0.44 at 20 °C (Scheme 14, b),[51] thus the softer $[PhPd(PPh_3)]^+$ moiety binds preferentially the soft anion I^-, while the harder $[PhPd(dmim)_2]^+$ has more affinity for hard AcO^-.[52] This observation points out that dmim-ligated organopalladium complexes may have very different properties from their PPh_3-ligated analogues and generalization based on the behaviour of the latter are to be considered with great caution.



Scheme 14. Anion exchange equilibrium between **13a** and **15a**, and the same for the PPh3-ligated analogous complexes (data from ref. 51).

Reactivity of dmim-ligated aryl-palladium species – direct arylation at room temperature

The reactivity of dmim-ligated aryl palladium species generated from **12a** was next investigated in the presence of different additives (Table 3). It is worth noting that **12a** alone does not evolve to the coupling product **3c**. However, DBU (2.0 equiv) addition promoted the formation of **3c** although in modest yield. In the presence of added acetates (AgOAc, $^nBu_4NOAc$) almost quantitative yields of **3c** were obtained.

Table 3. Reactions of $PhPd(dmim)_3I$ (**12a**) (as a 10 mM solution in DMF, 110 °C, 1 h) in the presence of additives – yields determined by GLC, using tetradecane as an internal standard.

Entry	Additive(s)	5-Ph-dmim (**3c**) GLC yield	PhPh (**4c**) GLC yield
1	None	0	64%
2	DBU 2.0 equiv	22%	30%
3	AgOAc 1.0 equiv	95%	5%
4	$^nBu_4NOAc$ 2.0 equiv	94%	6%
5	DBU 2.0 equiv, AgOAc 1.0 equiv	99%	1%

Taking into account these preliminary results, we speculated that acetate was a key element for an efficient reaction to take place, even at lower temperature. For convenience, a solution of $[(4\text{-F-}C_6H_4)Pd(dmim)_2(OAc)]$ (**15b**) in $CHCl_3$ was prepared by the reaction of isolated $(4\text{-F-}C_6H_4)Pd(dmim)_3I$ (**12b**) with AgOAc and treated with $^nBu_4NOAc$ (20 equiv) at room temperature. A comparatively fast reaction ensued and palladium black was deposited along with formation of coupling product **3b**, as proved by ^{19}F NMR analyses. The effect of added dmim (10 equiv) was also evaluated and the best results were obtained with both the additives (Table 4).

These results are remarkable since, to the best of our knowledge, there is no system described in the literature in which direct arylation of azoles at the C5 position can happen at room temperature. Reports on the direct arylation of other aromatic nuclei under catalytic conditions at room temperature are sparse.[53]

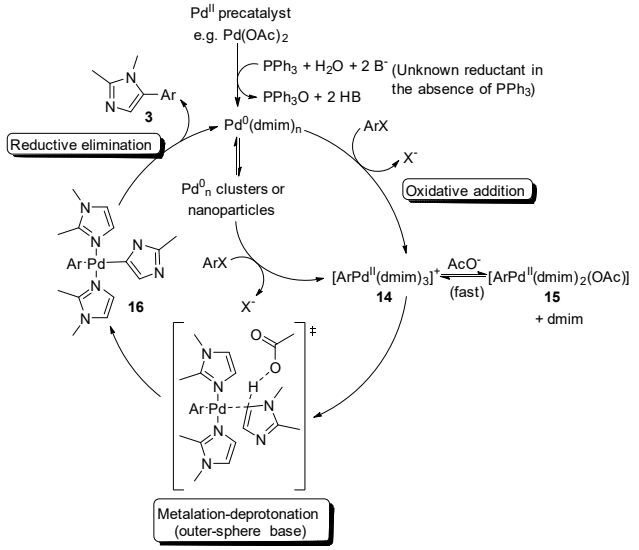
Table 4 – Reactions of $[(4\text{-F-}C_6H_4)Pd(dmim)_2(OAc)]$ (**15b**) (generated *in situ* as a 10 mM solution in $CHCl_3$ from $(4\text{-F-}C_6H_4)Pd(dmim)_3I$ (**12b**) and AgOAc, room temperature, 16 h) in the presence of additives – yields determined by ^{19}F NMR.

Entry	Additive(s)	Residual **15b**	NMR yield of **3b**	NMR yield of $(4\text{-F-}C_6H_4)_2$ (**4b**)
1	$^nBu_4NOAc$ 20 equiv	26%	71%	3%
2	dmim 10 equiv	65%	32%	3%
3	$^nBu_4NOAc$ 20 equiv + dmim 10 equiv	6%	92%	2%

As the addition of dmim increases the rate of product formation, the actual reactive species should be the cationic complex $[ArPd(dmim)_3]^+$ (**14**). In a first approach, the addition of acetate should slow the reaction down, since it decreases the concentration of **14** by shifting the equilibrium towards the less reactive $[ArPd(dmim)_2(OAc)]$ (**15**) (Scheme 15). However, the rate enhancement observed by the addition of AcO^- is consistent with a metalation-deprotonation reaction mechanism with acetate acting as an outer-sphere base.[54]

On the basis of our experimental findings, we can reasonably propose the revised mechanism depicted in Scheme 15, featuring dmim-ligated complexes only. The structure of imidazole-ligated Pd^0 is not known at present. As metallic Pd is always formed along with the coupling product under

stoichiometric conditions, we cannot exclude a role of heterogeneous species as a Pd^0 reservoir. Oxidative addition occurs and the Ar-Pd^{II} complexes so formed (**14**, **15**) evolve to a 5-imidazolyl aryl palladium species (**16**), which in turn undergoes product-forming reductive elimination probably after a *trans-cis* isomerization process, as usually assumed.



Scheme 15. Revised catalytic cycle for the direct arylation of imidazoles.

Conclusions

We have established that phosphine-ligated aryl-Pd complexes are highly unlikely active intermediates in the direct arylation of imidazoles at C5. This is in contrast with what is commonly assumed for the specific case of imidazole derivatives.[40] Our findings parallel what reported by Hartwig for the direct arylation of unfunctionalized benzene,[24] but the case of basic heterocycles such as the azoles is fundamentally different, since the latter compounds can themselves act as ligands.

We have demonstrated a facile oxidative addition reaction of aryl halides with imidazole-ligated Pd^0, giving rise to $[ArPd(dmim)_3]^+$ in the presence of excess dmim. We studied the equilibria of the latter complex with acetate and iodide, generating $[ArPd(dmim)_2X]$ (X = I, OAc). Dmim-ligated Ar-Pd species are active towards the direct arylation of dmim at room temperature in the presence of AcO^- as a base. Preliminary data point out that C-H bond cleavage may occur by a metalation-deprotonation mechanism involving cationic $[ArPd(dmim)_3]^+$ with AcO^- acting as an outer-sphere base.[54]

Further studies are underway in order to confirm the mechanism we proposed, both experimentally and computationally. We are confident that our findings will be helpful for the development of enhanced catalytic systems for the C-H functionalization of heteroarenes, possibly active under very mild conditions and with ample functional group tolerance.

Experimental Section

Synthesis of $PhPd(dmim)_3I$ (12a)

A 50 mL round-bottom flask with a side arm equipped with a magnetic stirrer was charged with $Pd(dba)_2$ (575 mg, 1.0 mmol) and conditioned under Ar. Deaerated toluene (20 mL) and dmim **1** (355 µL, 4.0 mmol) were added. The colour of the solution changed from violet to orange-yellow, and the starting material dissolved completely. When colour change ceased, iodobenzene (224 µL, 2.0 mmol) was introduced. Within a minute after the addition of the iodide a brownish, sticky mass was formed and adhered to the wall of the flask. After vigorous stirring for 2 h at 50 °C this material was converted to an off-white solid with crystalline appearance.

The reaction mixture was filtered on a sintered glass funnel and washed thoroughly with Et_2O (3 x 20 mL). The solid material was dissolved in acetone (20 mL) and the resulting solution was filtered through a short pad of diatomaceous earth. Removal of the solvents at reduced pressure gave the title compound in the form of a white crystalline powder (554 mg, 93%).

This complex behaves like a 1:1 mixture of *trans*-$[PhPd(dmim)_2I]$ (**13a**) and uncoordinated dmim in benzene. ^1H NMR (300 MHz, benzene-d_6): δ = 7.34-7.32 (m, 4H, Pd-bound dmim C5-H and 2,6-C_6H_5Pd), 7.16 (s, 1H, free dmim C5-H), 7.06-6.98 (m, 2H, 3,5-C_6H_5Pd), 6.90-6.86 (m, 1H, 4-C_6H_5Pd), 6.27 (d, J = 1.2 Hz, 1H, free dmim C4-H), 5.76 (d, J = 1.5 Hz, 2H, Pd-bound dmim C4-H), 2.45 (s, 3H, free dmim, N-CH_3), 2.37 (s, 6H, Pd-bound dmim N-CH_3), 1.95 (s, 3H, free dmim C-CH_3), 1.91 (s, 6H, Pd-bound dmim C-CH_3) ppm. ESI-MS (positive ion mode, MeCN) *m/z* (%): [477.7 (1), 476.6 (10), 475.6 (45), 474.6 (19), 471.4 (62), 470.5 (64), 469.5 (25)] $[PhPd(dmim)_3^+]$, [420.5 (8), 416.4 (20), 414.5 (13)] $[PhPd(MeCN)(dmim)_2^+]$, [380.5 (8), 379.4 (42), 377.3 (76), 376.3 (22), 375.3 (100), 374.3 (86), 373.3 (39), 371.4 (4)] $[PhPd(dmim)_2^+]$, 97.2 (69) $[dmimH^+]$. ESI-MS (negative ion mode, MeCN) *m/z* (%): 127.0 (100) $[I^-]$.

The low solubility of this complex prevented to get ^{13}C NMR data. Solubility in $CDCl_3$ is higher, but a complex ^1H spectrum is obtained because there is an equilibrium between $[PhPd(dmim)_3]^+$ (**14a**) and $[PhPd(dmim)_2I]$ (**13a**). Here follow the spectral data for the cationic complex $[PhPd(dmim)_3]^+$ (**14a**), which has been obtained by exchanging I^- for TfO^- by treatment of a solution of the title compound with excess AgOTf. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.01 (br s, 2H, *cis*-dmim C4-H), 6.94-6.92 (m, 2H, Ph-Pd), 6.88 (br s, 1H, *trans*-dmim C4-H), 6.88-6.81 (m, 4H, PhPd (3H) + *trans*-dmim C5-H), 6.73 (d, J = 1.2 Hz, 2H, *cis*-dmim C5-H), 3.62 (s, 3H, *trans*-dmim N-CH_3), 3.53 (s, 3H, *cis*-dmim N-CH_3), 2.60 (br s, 6H, *cis*-dmim C-CH_3), 2.46 (br s, 3H, *trans*-dmim C-CH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 146.3, 145.9, 145.8, 135.2, 127.6, 126.6, 126.0, 123.5, 121. 8, 121.7, 34.2, 33.8, 13.9, 12.6 ppm. $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$): δ = -78.2 ppm.

$PhPd(dmim)_2(OAc)$ (**15a**)

The title compound can be prepared by treatment of a solution of the corresponding iodide (**12a**) in benzene with an excess of AgOAc and removal of the AgI thus formed by filtration through a short plug of diatomaceous earth. Any attempt to isolate the title compound in the solid state invariably failed because of extensive decomposition while removing the solvent (even in high vacuum at 0 °C). Said complex, however, is quite stable as a dilute solution in benzene and can be characterized as such, together with some free dmim, which does not interfere. ^1H NMR (300 MHz, benzene-d_6): δ = 7.53 (d, J = 1.5 Hz, 2H, dmim C5-H), 7.48 (dd, J = 8.1, 1.2 Hz, 2H, 2,6-C_6H_5Pd), 7.03-6.99 (m. 2H, 3,5-C_6H_5Pd). 6.92-6.87 (m, 1H, 4-C_6H_5Pd), 5.79 (d, J =1.5 Hz, 2H, dmim C4-H), 2.39 (s, 6H, N-CH_3), 2.27 (br s, 3H, AcO^-), 1.96 (s, 6H, C-CH_3) ppm. ESI-MS (positive ion mode, MeCN) *m/z* (%): [476.5 (10), 475.6 (37), 474.6 (23), 471.5 (74), 470.5 (54), 469.5 (22)][$PhPd(dmim)_3^+$], [420.5 (8), 416.5 (20), 414.5 (13)] $[PhPd(MeCN)(dmim)_2^+]$, [380.5 (10), 379.3 (56), 377.3 (100), 376.4 (33), 375.3 (97), 374.3 (92), 373.3 (56)] $[PhPd(dmim)_2^+]$, 257.3 (31), 255.4 (59) 97.2 (69) $[dmimH^+]$. ESI-MS (negative ion mode, MeCN) *m/z* (%): 59.3 (100) $[AcO^-]$.

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Keywords: Palladium • Nitrogen Heterocycles • C-H Activation • Reaction Mechanism • C-C Coupling

[1] I. Cepanec, *Synthesis of Biaryls*, Elsevier, **2004**.

[2] J. Wencel-Delord, F. Glorius, *Nat. Chem.* **2013**, *5*, 369–375.

[3] For reviews on direct arylation reactions, see: a) L.-C. Campeau, D. R. Stuart, K. Fagnou, *Aldrichimica Acta* **2007**, *40*, 35–41; b) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174–238; c) T. Satoh, M. Miura, *Chem. Lett.* **2007**, *36*, 200–205; d) I. V Seregin, V. Gevorgyan, *Chem. Soc. Rev.* **2007**, *36*, 1173–1193; e) I. J. S. Fairlamb, *Chem. Soc. Rev.* **2007**, *36*, 1036–1045; f) L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem. Int. Ed. Engl.* **2009**, *48*, 9792–9826; g) F. Bellina, R. Rossi, *Tetrahedron* **2009**, *65*, 10269–10310; h) G. P. Chiusoli, M. Catellani, M. Costa, E. Motti, N. Della Ca', G. Maestri, *Coord. Chem. Rev.* **2010**, *254*, 456–469; i) O. Daugulis, *Top. Curr. Chem.* **2010**, *292*, 57–84; j) Y.-X. Su, L.-P. Sun, *Mini Rev. Org. Chem.* **2012**, *9*, 87–117; k) M. He, J.-F. Soulé, H. Doucet, *ChemCatChem* **2014**, *6*, 1824–1859; l) I. Hussain, T. Singh, *Adv. Synth. Catal.* **2014**, *356*, 1661–1696; m) R. Rossi, F. Bellina, M. Lessi, C. Manzini, *Adv. Synth. Catal.* **2014**, *356*, 17–117; n) R. Rossi, F. Bellina, M. Lessi, C. Manzini, L. A. Perego, *Synthesis* **2014**, *46*, 2833–2883.

[4] For reviews on the mechanism of direct arylation reactions, see: a) M. Livendahl, A. M. Echavarren, *Isr. J. Chem.* **2010**, *50*, 630–651; b) D. Lapointe, K. Fagnou, *Chem. Lett.* **2010**, *39*, 1118–1126; c) S. I. Gorelsky, *Coord. Chem. Rev.* **2013**, *257*, 153–164.

[5] a) F. Bellina, S. Cauteruccio, S. Monti, R. Rossi, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5757–5762; b) K. Higuchi, T. Kawasaki, *Nat. Prod. Rep.* **2007**, *24*, 843–868; c) P. K. Cheplogoi, D. A. Mulholland, P. H. Coombes, M. Randrianarivelojosia, *Phytochemistry* **2008**, *69*, 1384–1288; d) B. I. Morinaka, J. R. Pawlik, T. F. Molinski, *J. Org. Chem.* **2010**, *75*, 2453–2460; e) V. Kumar, K. Kaur, G. K. Gupta, A. K. Sharma, *Eur. J. Med. Chem.* **2013**, *69*, 735–753; f) S. A. Ohnmacht, P. Mamone, A. J. Culshaw, M. F. Greaney, *Chem. Commun.* **2008**, 1241–1243; g) F. Bellina, N. Guazzelli, M. Lessi, C. Manzini, *Tetrahedron* **2015**, *71*, 2298–2305.

[6] Two recent examples: a) J. Gising, M. T. Nilsson, L. R. Odell, S. Yahiaoui, M. Lindh, H. Iyer, A. M. Sinha, B. R. Srinivasa, M. Larhed, S. L. Mowbray, et al., *J. Med. Chem.* **2012**, *55*, 2894–2898; b) R. Selig, M. Goettert, V. Schattel, D. Schollmeyer, W. Albrecht, S. Laufer, *J. Med. Chem.* **2012**, *55*, 8429–8439.

[7] a) J. Lim, T. A. Albright, B. R. Martin, O. Š. Miljanić, *J. Org. Chem.* **2011**, *76*, 10207–10219; b) C. Wang, H. Dong, W. Hu, Y. Liu, D. Zhu, *Chem. Rev.* **2012**, *112*, 2208–2267; c) J. Kulhánek, F. Bureš, *Beilstein J. Org. Chem.* **2012**, *8*, 25–49; d) Z. Chi, X. Zhang, B. Xu, X. Zhou, C. Ma, Y. Zhang, S. Liu, J. Xu, *Chem. Soc. Rev.* **2012**, *41*, 3878–3896; e) M. Lessi, C. Manzini, P. Minei, L. A. Perego, J. Bloino, F. Egidi, V. Barone, A. Pucci, F. Bellina, *ChemPlusChem* **2014**, *79*, 366–370.

[8] D. E. Ames, A. Opalko, *Tetrahedron* **1984**, *40*, 1919–1925.

[9] Y. Aoyagi, A. Inoue, I. Koizumi, R. Hashimoto, K. Tokunaga, K. Gohma, J. Komatsu, K. Sekine, A. Miyafuji, al. et, *Heterocycles* **1992**, *33*, 257–272.

[10] S. Pivsa-Art, T. Satoh, K. Yoshiki, M. Masahiro, M. Nomura, Y. Kawamura, M. Miura, *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467–473.

[11] a) F. Bellina, S. Cauteruccio, A. Di Fiore, C. Marchetti, R. Rossi, *Tetrahedron* **2008**, *64*, 6060–6072; b) F. Bellina, S. Cauteruccio, A. Di Fiore, R. Rossi, *Eur. J. Org. Chem.* **2008**, 5436–5445; c) F. Bellina, R. Rossi, *Adv. Synth. Catal.* **2010**, *352*, 1223–1276.

[12] F. Bellina, S. Cauteruccio, L. Mannina, R. Rossi, S. S. Viel, *J. Org. Chem.* **2005**, *70*, 3997–4005

[13] B. Liégault, D. Lapointe, L. Caron, A. Vlassova, K. Fagnou, B. Liegault, *J. Org. Chem.* **2009**, *74*, 1826–1834.

[14] M. Baghbanzadeh, C. Pilger, C. O. Kappe, *J. Org. Chem.* **2011**, *76*, 8138–8142.

[15] J. M. Joo, B. B. Touré, D. Sames, B. B. Toure, *J. Org. Chem.* **2010**, *75*, 4911–4920.

[16] F. Shibahara, E. Yamaguchi, T. Murai, *J. Org. Chem.* **2011**, *76*, 2680–2693.

[17] P. V. Kumar, W.-S. Lin, J.-S. Shen, D. Nandi, H. M. Lee, *Organometallics* **2011**, *30*, 5160–5169.

[18] J. Roger, H. Doucet, *Tetrahedron* **2009**, *65*, 9772–9781.

[19] F. Bellina, M. Lessi, C. Manzini, *European J. Org. Chem.* **2013**, *2013*, 5621–5630.

[20] A comparative table of published reaction conditions is reported in the SI, §1.1.

[21] For some Pd-catalyzed C-H activation reaction of aromatic compounds which seems to proceed by a S_EAr-type mechanism, see: a) M. Catellani, G. P. Chiusoli, *J. Organomet. Chem.* **1992**, *425*, 151–154; b) B. Martín-Matute, C. Mateo, D. J. Cárdenas, A. M. Echavarren, *Chem. Eur. J.* **2001**, *7*, 2341–2348; c) C.-H. Park, V. Ryabova, I. V Seregin, A. W. Sromek, V. Gevorgyan, *Org. Lett.* **2004**, *6*, 1159–1162; d) J.-X. Wang, J. A. McCubbin, M. Jin, R. S. Laufer, Y. Mao, A. P. Crew, M. J. Mulvihill, V. Snieckus, *Org. Lett.* **2008**, *10*, 2923–2926; e) B. S. Lane, M. A. Brown, D. Sames, *J. Am. Chem. Soc.* **2005**, *127*, 8050–8057; f) S. Chuprakov, N. Chernyak, A. S. Dudnik, V. Gevorgyan, *Org. Lett.* **2007**, *9*, 2333–2936; g) A. Sugie, K. Kobayashi, Y. Suzaki, K. Osakada, A. Mori, *Chem. Lett.* **2006**, *35*, 1100–1101.

[22] M. Lafrance, K. Fagnou, *J. Am. Chem. Soc.* **2006**, *128*, 16496–16497.

[23] a) S. I. Gorelsky, D. Lapointe, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 10848–10849; b) S. I. Gorelsky, D. Lapointe, K. Fagnou, *J. Org. Chem.* **2012**, *77*, 658–668.

[24] Y. Tan, J. F. Hartwig, *J. Am. Chem. Soc.* **2011**, *133*, 3308–3311.

[25] a) M. Wakioka, Y. Nakamura, Q. Wang, F. Ozawa, *Organometallics* **2012**, *31*, 4810–4816; b) M. Wakioka, Y. Nakamura, Y. Hihara, F. Ozawa, S. Sakaki, *Organometallics* **2013**, *32*, 4423–4430; c) M. Wakioka, Y. Nakamura, Y. Hihara, F. Ozawa, S. Sakaki, *Organometallics* **2014**, *33*, 6247–6252.

[26] Y. Tan, F. Barrios-Landeros, J. F. Hartwig, *J. Am. Chem. Soc.* **2012**, *134*, 3683–3686.

[27] a) K. Ueda, S. Yanagisawa, J. Yamaguchi, K. Itami, *Angew. Chemie Int. Ed.* **2010**, *49*, 8946–8949; b) S.-Y. Tang, Q.-X. Guo, Y. Fu, *Chem. Eur. J.* **2011**, *17*, 13866–13876.

[28] a) C. C. Verrier, T. Martin, C. Hoarau, F. Marsais, *J. Org. Chem.* **2008**, *73*, 7383–7386; b) T. Martin, C. Verrier, C. Hoarau, F. Marsais, *Org. Lett.* **2008**, *10*, 2909–2912; c) L. Théveau, C. Verrier, P. Lassalas, T. Martin, G. Dupas, O. Querolle, L. Van Hijfte, F. Marsais, C. Hoarau, *Chem. Eur. J.* **2011**, *17*, 14450–14563; d) C. Verrier, P. Lassalas, L. Théveau, G. Quéguiner, F. Trécourt, F. Marsais, C. Hoarau, *Beilstein J. Org. Chem.* **2011**, *7*, 1584–1601; e) L. Théveau, O. Querolle, G. Dupas, C. Hoarau, *Tetrahedron* **2013**, *69*, 4375–4380.

[29] R. S. Sanchez, F. A. Zhuravlev, *J. Am. Chem. Soc.* **2007**, *129*, 5824–5285.

[30] a) F. Shibahara, E. Yamaguchi, T. Murai, *Chem. Commun.* **2010**, *46*, 2471–2473; b) F. Shibahara, E. Yamaguchi, T. Murai, *J. Org. Chem.* **2011**, *76*, 2680–2693.

[31] F. Bellina, S. Cauteruccio, R. Rossi, *J. Org. Chem.* **2007**, *72*, 8543–8546.

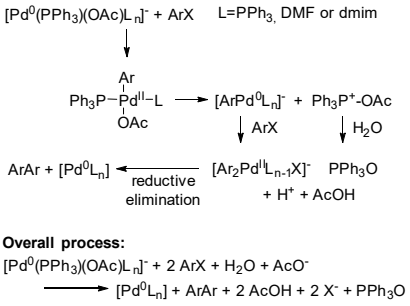
[32] a) E. M. Simmons, J. F. Hartwig, *Angew. Chem. Int. Ed. Engl.* **2012**, *51*, 3066–3072; b) M. A. Sierra, M. Gómez-Gallego, *Chem. Rev.* **2011**, *111*, 4857–4963.

[33] For some Pd-catalyzed direct arylation reaction for which no KIE is observed see ref. [21d], [25c], and the following: a) I. V Seregin, V. Ryabova, V. Gevorgyan, *J. Am. Chem. Soc.* **2007**, *129*, 7742–7743; b) J. J. Priego, S. Gutierrez, R. Ferritto, H. B. Broughton, S. Gutiérrez, *Synlett* **2007**, *2007*, 2957–2960; c) F. Shibahara, E. Yamaguchi, T. Murai, *Chem. Commun.* **2010**, *46*, 2471–2473.

Form some examples of direct arylation reactions for which non-negligible KIE has been measured, see ref. [22], [24], [25c], and the

following: d) B. S. Lane, M. A. Brown, D. Sames, *J. Am. Chem. Soc.* **2005**, *127*, 8050–8057; e) H. Y. Sun, S. I. Gorelsky, D. R. Stuart, L. C. Campeau, K. Fagnou, *J. Org. Chem.* **2010**, *75*, 8180–8189.

[34] In the presence of PPh_3 the homocoupling product **4** is formed mainly at the beginning of the reaction time (see SI §1.4, Figure S2), when the appearance of the coupling product **3** is still very slow and dmim is being consumed at a slow rate. Actually, the quantity of **4** remains almost constant after the induction period until the conversion of dmim is complete. All these observations led us to postulate that **4** could result from the evolution of the intermediate complex $[ArPd^{II}(PPh_3)(OAc)L]$ (L stands for a generic ligand here, L=PPh_3, dmim or DMF) formed after oxidative addition of ArX with the Pd^0 species generated by the oxidation of the first equivalent of PPh_3 (Scheme below). Indeed, it could further evolve through reductive elimination of $[AcOPPh_3]^+$, analogously to what shown previously for $[Pd(OAc)_2(PPh_3)_2]$ (see ref. 35). The resulting Pd^0 species $[ArPd^0L_n]^-$ could add another molecule of ArX giving the reductive elimination-prone complex $[Ar_2Pd^{II}L_{n-1}X]^-$. Elimination of ArAr would give back Pd^0. Overall, ArX acts as an oxidising agent for PPh_3 and it is reduced to ArAr. See also: C. Amatore, E. Carré, A. Jutand, H. Tanaka, R. Quinghua, S. Torii, *Chem. Eur. J.* **1996**, *2*, 957-966.



[35] a) C. Amatore, A. Jutand, M. A. M'Barki, *Organometallics* **1992**, *11*, 3009–3013; b) C. Amatore, E. Carre, A. Jutand, M. A. M'Barki, *Organometallics* **1995**, *14*, 1818–1826.

[36] At present, it is not clear how does the homocoupling product **4** forms in the absence of PPh_3. However, it is well-known that heating aryl halides in DMF with a palladium catalyst in the presence of bases leads to homocoupling or dehalogenation products. For a reference, see: W. M Seganish, M.E. Mowery, S. Riggleman, P. DeShong, *Tetrahedron* **2005**, *61*, 2117–2121.

[37] P. Fitton, E. A. Rick, *Organomet. Chem.* **1971**, *28*, 287–291.

[38] Jutand, A.; Negri, S.; Principaud, A. *Eur. J. Inorg. Chem.* **2005**, 631–635.

[39] This *K* value is of comparable magnitude to those reported in the literature for the displacement of PPh_3 from $[ArPd(PPh_3)_2X]$ by a secondary amine (see ref 38).

[40] S. I. Gorelsky, D. Lapointe, K. Fagnou, *J. Org. Chem.* **2012**, *77*, 658–68.

[41] a) V. V. Grushin, H. Alper, *Organometallics* **1993**, *12*, 1890–1901; b) V. V. Grushin, C. Bensimon, H. Alper, *Organometallics* **1995**, *14*, 3259–3263.

[42] For as similar synthesis involving benzothiazole instead of dmim, see ref. 25b.

[43] It should be noted that the displacement of AcO^- by dmim is also possible, both in the starting complex and in the product (see next section for a determination of the thermodynamic constant for the latter case). The value of *K'* is, thus, to be understood as an *apparent constant* for the displacement of PPh_3 from all the PPh_3-containing species present in equilibrium.

[44] For a review: a) T. G. Appleton, H. C. Clark, L. E. Manzer, *Coord. Chem. Rev.* **1973**, *10*, 335–422.
It is, indeed, a quite general fact that two soft ligands (with invariably high *trans* influence, as PPh_3 in the specific case) destabilize each other with respect to the substitution with a harder ligand (with less *trans* influence, such as dmim). This phenomenon has been called *antisymbiosis* by R.G. Pearson in the framework of the HSAB (Hard-Soft Acid and Bases) concept. See also: b) R. G. Pearson, *Inorg. Chem.*, **1973**, *12*, 712–713.

[45] A DMF solution of **8** was also heated in the presence of various additives (^{n}Bu$_4$NOAc, DBU, ^{i}Pr$_2$NH). In all the cases, total yields exceeded 100% because of the participation of the Ph groups of PPh_3 through C-P bond activation. Under catalytic conditions, only trace amounts of PhPh could be detected. Moreover, a substantial amount of PPh_3 is converted to $OPPh_3$ while **8** evolved.

[46] N. G. Andersen, BA. Keay, *Chem. Rev.* **2001**, *101*, 997–1030.

[47] C. Amatore, A. Jutand, F. Khalil, M. A. M'Barki, L. Mottier, *Organometallics* **1993**, *12*, 3168–3178.

[48] a) A. Jutand, A. Mosleh, *Organometallics* **1995**, *14*, 1810–1817; b) A. Jutand, S. Négri, *Organometallics* **2003**, *22*, 4229–4237; C. Amatore, A. A. Bahsoun, A. Jutand, G. Meyer, A. Ndedi Ntepe, L. Ricard, *J. Am. Chem. Soc.* **2003**, *125*, 4212–4222.

[49] J.-F. Fauvarque, F. Pflüger, M. Troupel, *J. Organomet. Chem.* **1981**, *208*, 419–427.

[50] The use of pure DMF as a solvent was difficult for X=OAc, since troubles were encountered with the removal of silver salts from this solvent while preparing the required solution of $[PhPd(dmim)_2(OAc)]$ (**15a**). The latter complex was thus prepared in a small volume of CH_2Cl_2, silver salts were removed, DMF was added and the conductimetry experiment performed. As reported before, it was not possible to isolate the complex in a pure state because of its ready decomposition.

[51] K'_D can be calculated from the ionization constants reported by Amatore and Jutand for $[PhPd(PPh_3)_2X]$ (X = I, OAc) in DMF. See: C. Amatore, E. Carré, A. Jutand *Acta Chem. Scand.* **1998**, *52*, 100–106.

[52] This is a consequence of the general concept known as *chemical symbiosis*. See the following ref.: C. K. Jorgensen, *Inorg. Chem.* **1964**, *3*, 1201–1202.

[53] Some examples of Pd-catalyzed direct arylation reactions that occur at room temperature: a) N. R. Deprez, D. Kalyani, A. Krause, M. S. Sanford *J. Am. Chem. Soc.* **2006**, *128*, 4972–4973; b) S. Islam, I. Larrosa, *Chem. Eur. J.* **2013**, *19*, 15093–15096; b) F. A. Zhuravlev, *Tetrahedron Lett.* **2006**, *47*, 2929–2932; c) F. Gao, F.; Kim, B.-S.; Walsh, P. J. *Chem. Commun.*. **2014**, *50*, 10661–10664; d) O. René, K. Fagnou, *Org. Lett.* **2010**, *12*, 2116–2119; e) L.-C. Campeau, M. Bertrand-Laperle, J.-P. Leclerc, E. Villemure, S. Gorelsky, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 3276–3277.

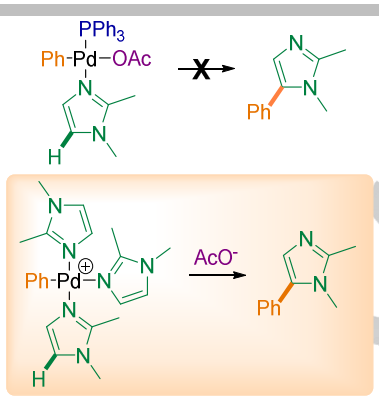
[54] Similar observations have been made for Ru-catalyzed arylation of some arenes functionalized with metal-directing groups: a) E. Ferrer Flegeau, C. Bruneau, P. H. Dixneuf, A. Jutand, *J. Am. Chem. Soc.* **2011**, *133*, 10161–10170; b) I. Fabre, N. von Wolff, G. Le Duc, E. Ferrer Flegeau, C. Bruneau, P. H. Dixneuf, A. Jutand, *Chem. Eur. J.* **2013**, *19*, 7595–7604.

Entry for the Table of Contents (Please choose one layout)

Layout 1:

FULL PAPER

Substrate and Ligand as the same time: The Pd-catalyzed direct arylation of imidazoles at C5 cannot proceed through PPh_3-ligated organo-Pd intermediates. These heteroarenes act themselves as ligands for Pd: novel imidazole-ligated aryl-Pd complexes have been isolated and characterized. These species are able to undergo C-H activation under very mild conditions in the presence of acetate anions.



L. A. Perego, F. Bellina*, L. Grimaud**

Page No. – Page No.

Mechanistic Studies on the Pd-Catalyzed Direct Arylation of Imidazoles at C5: Role of the Substrate as a Ligand for Pd