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# Mechanistic Studies on the Palladium-Catalyzed Direct C-5 Arylation of Imidazoles: The Fundamental Role of the Azole as a Ligand for Palladium

Luca Alessandro Perego,[a,b,*] Laurence Grimaud,[b,*] and Fabio Bellina[a,*]

[a] Dipartimento di Chimica e Chimica Industriale, University of Pisa, via Moruzzi 3, 56124 Pisa, Italy
E-mail: fabio.bellina@unipi.it

[b] Département de Chimie, Ecole Normale Supérieure – PSL Research University, Sorbonne Universités – UPMC Univ Paris 06, CNRS UMR 8640 PASTEUR, 24, rue Lhomond, 75005 Paris, France
E-mail: luca.perego@ens.fr or laurence.grimaud@ens.fr

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**Abstract:** An in-depth mechanistic study on the palladium-catalyzed direct arylation of imidazoles at the C-5 position is presented. The interactions of triphenylphosphine ($PPh_3$)-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 have 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 these species to effect the C–H arylation of dmim at room temperature in the presence of acetate is also demonstrated.

**Keywords:** C–C coupling; C–H activation; nitrogen heterocycles; palladium; reaction mechanism

## 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.

**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, ...

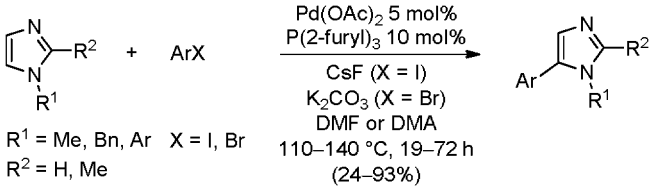
**b. Direct arylation reactions:**

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

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

Among the wide variety of arylheteroarenes, arylazoles are important structural units, often found in natural products and their synthetic analogues,[4] pharmaceuticals,[5] and organic functional materials,[6] 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 that appeared before 2000,[7–9] we established an efficient and general protocol for the direct arylation of imidazoles with high regioselectiviy for the C-5 position.[10] 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 (*N*,*N*-dimethylacetamide) at 110 °C for *N*-methylimidazole and at 140 °C for *N*-benzyl- and *N*-arylimidazoles (Scheme 2).[10] $PPh_3$,[9]




**Scheme 2.** C-5 regioselective arylation of imidazoles.[10]

$AsPh_3$,[11] $PCy_3$,[12,13] and P(*n*-Bu)$Ad_2$[14] can also be used as ligands. Procedures using $[Pd(phen)_2](PF_6)_2$[15] or bulky NHC-Pd complexes[14,16] 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,[17] while the second used $(n\text{-Bu})_4NOAc$ as the base for the C-5 direct arylation of several azoles (1-methylpyrazole, oxazole, thiazole, 1-methyl-1*H*-imidazole) under comparatively mild conditions[18] (70–110 °C).[19]

Despite the synthetic relevance of Pd-catalyzed direct arylation reactions, relatively little attention has been devoted to understanding their mechanisms. Moreover, as well outlined in the reviews compiled by Echavarren[20a] and Fagnou[20b] in 2010, and by Gorelsky[20c] 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 an $S_EAr$-type mechanism,[9] 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 metallation-deprotonation (CMD) mechanism has been proposed by Fagnou and Gorelsky for the C–H functionalization of a number of heterocycles.[20b,c,23] According to this mechanistic hypothesis, the carboxylate anion acts as a "proton shuttle" and assists the simultaneous metallation 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.[20b,c,22,23] Hartwig and Tan have prepared and characterized the complex {(2-Me-$C_6H_4$)Pd[P(*t*-$Bu)_3$](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 species are not competent in the direct arylation of benzene. This conclusion was also supported by DFT calculations.[24] On the other hand, Ozawa and co-workers showed that a $PPh_3$-ligated aryl-Pd species can effect the direct arylation of a variety of substrates.[25] Hartwig and co-workers have also highlighted the key role of a cyclometallated species {Pd(OAc)[(*t*-$Bu)_2PCMe_2$-$CH_2$]}, formed by C–H activation of P(*t*-$Bu)_3$ 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 $\beta$-selective arylation of thiophenes.[27] The C-2 regioselectivity observed in some cases for the functionalization of 1,3-azoles has been linked to the enhancement of the C-2–H acidity upon Pd-coordination through the pyridine-like nitrogen. A proton abstraction mechanism called "non-concerted metallation deprotonation" (nCMD) was thus proposed,[28] while a deprotonation–ring opening pathway has been demonstrated for the C-2 arylation of benzoxazole.[29] Evidence for free-radical processes has also been put forward in a limited number of cases.[15,30]

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 insights useful to develop new and more efficient catalytic systems in terms of activity under mild conditions, selectivity and functional group tolerance.

Keeping these 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.

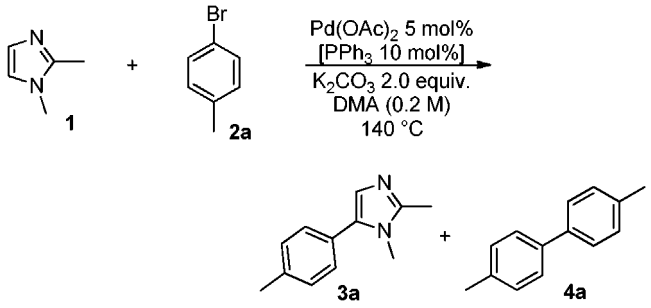
## Results and Discussion

### Kinetic Isotope Effect

As discussed previously, direct arylation reactions of imidazoles at the C-5 position are usually carried out with a precatalyst composed of a Pd(II) salt, usually $Pd(OAc)_2$, and either a phosphine[9–11,31] or no added ligand[6e,17,18] (the so-called *ligandless conditions*). Customarily, a 1:2 molar ratio between Pd and a monodentate ligand is employed.[9–11,31]

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-products formed by N or C-2 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

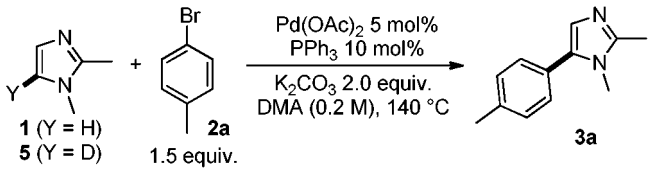



**Scheme 3.** Model reaction.

140 °C (Scheme 3). The formation of the C-5 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.

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 the Supporting Information, §2.2 for the experimental procedure). First, the reactions involving dmim **1** and 5-D-dmim **5** were performed separately (Scheme 4). 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 ($k_H = 2.1 \cdot 10^{-2}$ min$^{-1}$ and $k_D = 0.77 \cdot 10^{-2}$ 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 C-5–H bond under our conditions, as observed for other direct arylation reactions.[31,33]




**Scheme 4.** Reactions for KIE determination.

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:

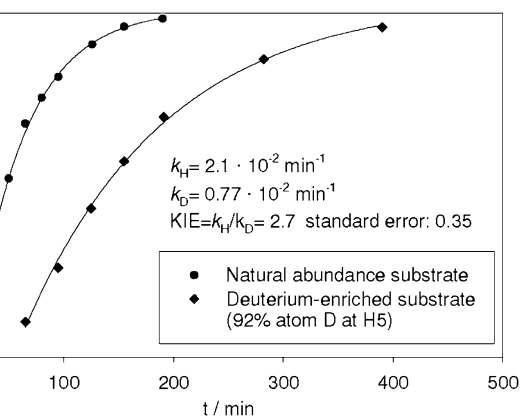



**Figure 1.** Determination of KIE for the reactions in Scheme 4. Experimental points are shown together with exponential fit: $[\mathbf{3a}] = A + C_\infty(1 - e^{-kt})$. Parameter $A$ has been included because an induction period has been excluded from the fitted data (*vide infra*).

$$KIE = \frac{k_H}{k_D} = \frac{\log\left(\frac{[1]}{[1]_0}\right)}{\log\left(\frac{[5]}{[5]_0}\right)} = 2.32$$

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-$C_6H_4$Br and $k_H/k_D = 2.40$ for 4-$CF_3$-$C_6H_4$Br (see the Supporting Information, §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 those 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 the Supporting Information, §1.3).

## 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 ex-

periment (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).

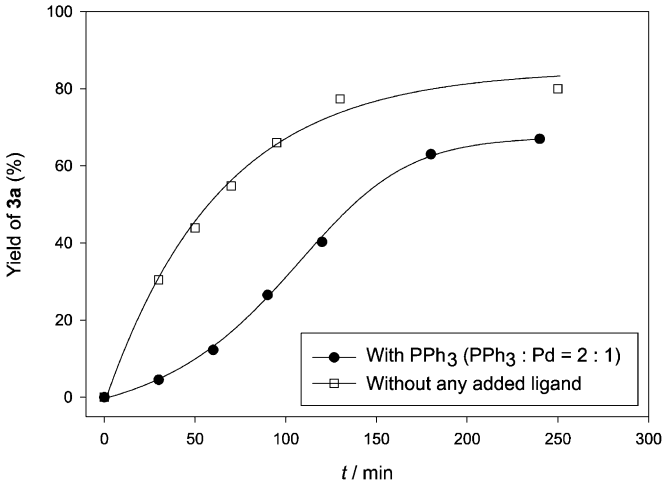
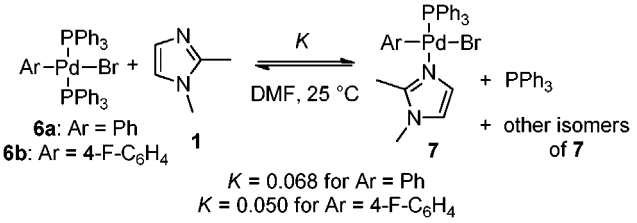



**Figure 2.** Kinetic curve for the formation of **3a** under the conditions reported in Scheme 3.

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 byproduct **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 $[AcOPPh_3]^+$ (hydrolyzed to $Ph_3PO$ 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 with 4-bromotoluene (**2a**) replaced by 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 $Ph_3PO$ 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 a sizeable quantity until a substantial amount of $PPh_3$ has been depleted (for details, see the Supporting Information §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*-$[ArPd(PPh_3)_2Br]$ (**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 is 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 **7** (Scheme 5). As no change in the $^{31}P$ NMR

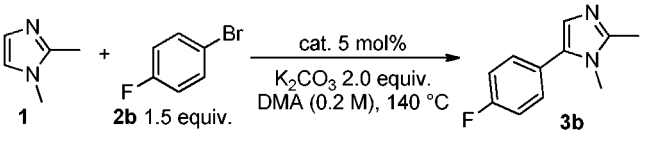



**Scheme 5.** Displacement of $PPh_3$ by dmim in *trans*-$[ArPd(PPh_3)_2Br]$.

spectrum was observed after the addition of a large excess of $(n\text{-}Bu)_4NBr$, 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 the Supporting Information, §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]

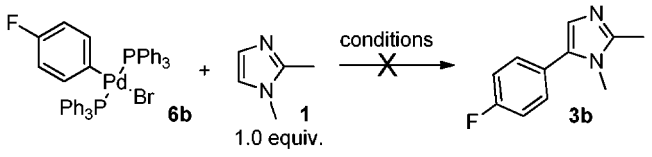
Complex **6b** was tested under catalytic conditions and turned out to be a competent precatalyst, providing a yield comparable to the one obtained with $Pd(OAc)_2$, albeit in a longer reaction time (Scheme 6). Prolonged heating (140 °C, 2.5 h) of a mixture of **6b** (0.02 M in DMF) in an NMR tube with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

A complex with the composition $[PhPd(PPh_3)(dmim)(OAc)]$ (**8**), which should be structurally very close to a transition state proposed on the basis of DFT calculations,[23b] was prepared by the reaction of the bridged acetate complex




cat. = $Pd(OAc)_2$, reaction time 4 h: 70% (isolated yield)
cat. = *trans*-[(4-F-$C_6H_4$)$Pd(PPh_3)_2Br$] (**6b**) 24 h: 74% ($^{19}F$ NMR yield)

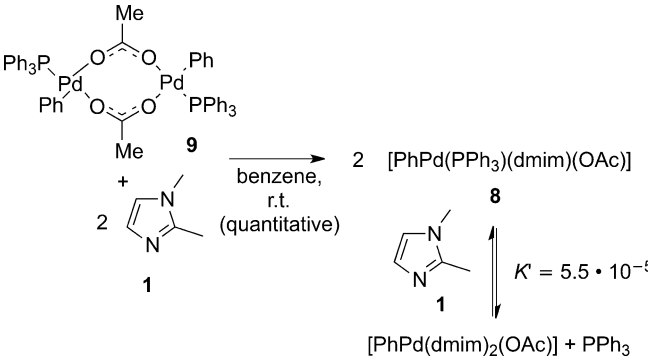
**Scheme 6.** Comparison of $Pd(OAc)_2$ and *trans*-$[ArPd(PPh_3)_2Br]$ as precatalysts.




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.

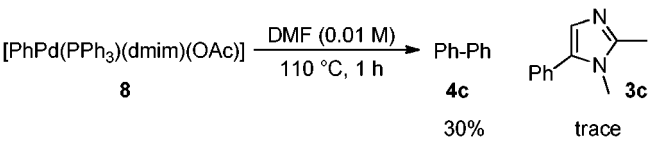
**Scheme 7.** Attempted reaction of *trans*-[ArPd($PPh_3$)$_2$Br] with dmim.

[PhPd($PPh_3$)(μ-OAc)]$_2$ (**9**)[40] with 2.0 equiv. of dmim (Scheme 8).[41] 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.[42] Such a behaviour can be rationalized in terms of the so-called *thermodynamic trans effect* or *trans influence*.[43]




**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




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

bases [($n$-Bu)$_4$NOAc, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, ($i$-Pr)$_2$NH, see details in the Supporting Information, §1.6] promoted the formation of **3c** together with high amounts of PhPh, differently from what happens in the catalytic process.[44] These results suggest that **8** is an unlikely intermediate of the catalytic reaction.

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 $AsPh_3$[11] and P(2-furyl)$_3$,[10a,45] is most likely due to the ease with which they can be displaced by the imidazole substrate. The direct arylation of azoles at C-5 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.[18]

## 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 (*trans*,*trans*-dibenzylideneacetone) 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 the Supporting Information, §1.7, Figure S6).

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 uncoordinated dba, as can be inferred by comparison with an authentic sample.[46] 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.[46] 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

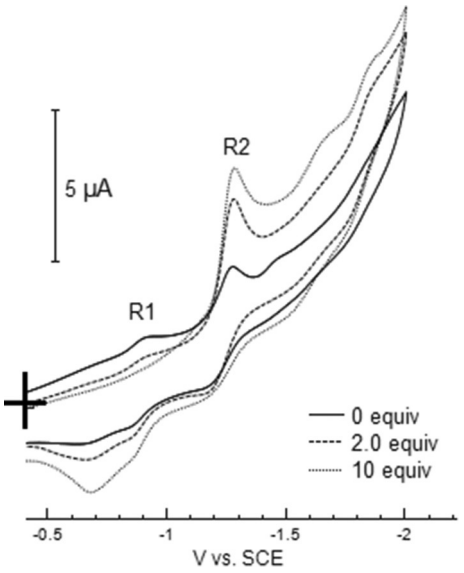



**Figure 3.** Cyclic voltammetry of $Pd(dba)_2$ (2.0 mM in DMF), in the presence of varying amounts of dmim, as shown in the inset. *Conditions:* steady gold disk electrode (ø = 1.0 mm), scan rate 0.1 $V s^{-1}$, 25 °C, supporting electrolyte ($n$-$Bu)_4NBF_4$ 0.3 M.

at a maximum when no dmim is present and disappears when dba is completely displaced.

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 the basis of $^1H$ NMR data (see the Supporting Information, §1.7, Figure S7) we tentatively propose a stoichiometry of $Pd(dmim)_3$ for the latter complex. 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).

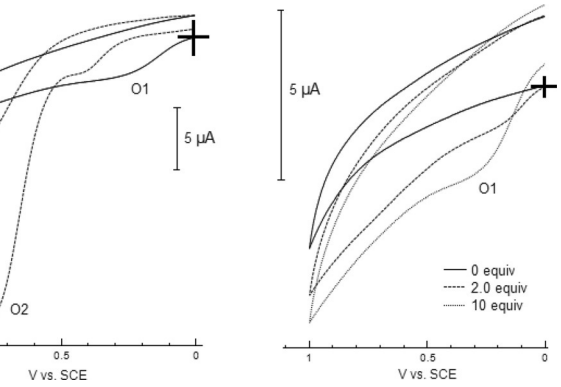
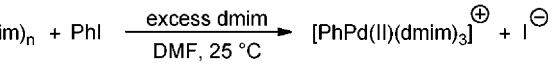



**Figure 4.** *Left:* voltammetric oxidation of $Pd(dba)_2$ (2.0 mM in DMF), in the presence of varying amounts of dmim, as shown in the inset. *Right:* voltammetric oxidation of $Pd(dba)_2$ (2 mM in DMF), in the presence of 10 equiv. of dmim, before (solid line) and after (dashed line) addition of 1.0 equiv. of PhI. *Conditions:* steady gold disk electrode (∅ = 1.0 mm), scan rate 0.1 $V s^{-1}$, 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 resulting product allowed to use conductimetry to follow the reaction kinetics.[47] First, the dependence of the rate for the oxidative addition of PhI (1.0 equiv.) varying the concentration of dmim was studied. Final conductivity $\kappa_\infty$ 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.[48]

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. Taking 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

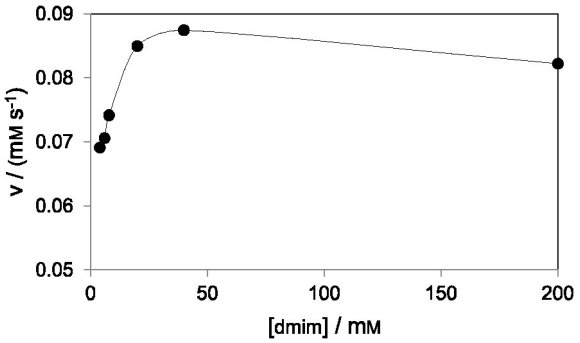



**Figure 5.** Initial rates $v$ for the oxidative addition of PhI (2.0 mM) with $Pd(dba)_2$ (2.0 mM in DMF) in the presence of varying amounts of dmim, as measured by conductimetry, temperature: 25 °C.

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 the Supporting Information, §1.7, Figure S8).

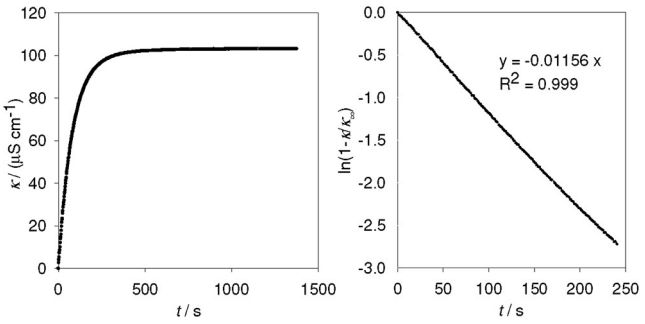



**Figure 6.** *Left:* oxidative addition of 4-bromobenzonitrile (**10**) (50 equiv.) to $Pd(dba)_2$ (2.0 mM in DMF) in the presence of dmim (20 equiv.), as followed by monitoring the conductivity $\kappa$. *Right:* same data, represented with a semilogarithmic plot. Temperature: 25 °C.

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.

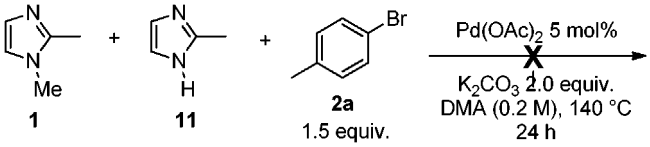
Oxidative addition occurs faster when unsubstituted imidazole is used instead of dmim. This observation

**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-$C_6H_4$Br (**10**) | 0.117 |
| Imidazole | PhI | 30.2 |

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).

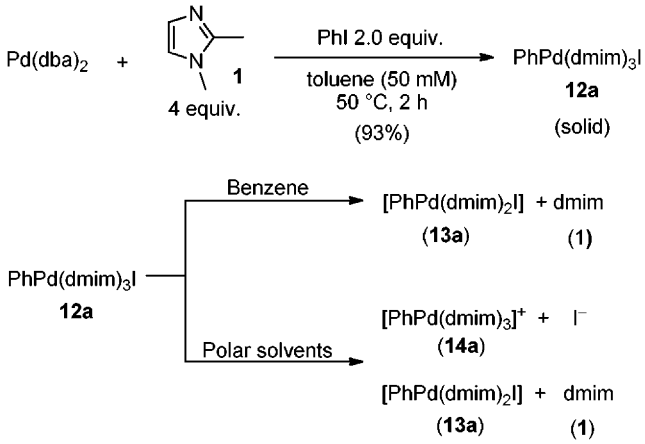



**Scheme 11.** Attempted direct arylation of a mixture of dmim and 2-methyl-1*H*-imidazole.

## 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 $^1H$ 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 $^1H$ NMR spectrum of **12a** is shown in Figure 7). The cationic complex $[PhPd(dmim)_3]^+$ (**14a**) alone has been characterized in $CDCl_3$ solution




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

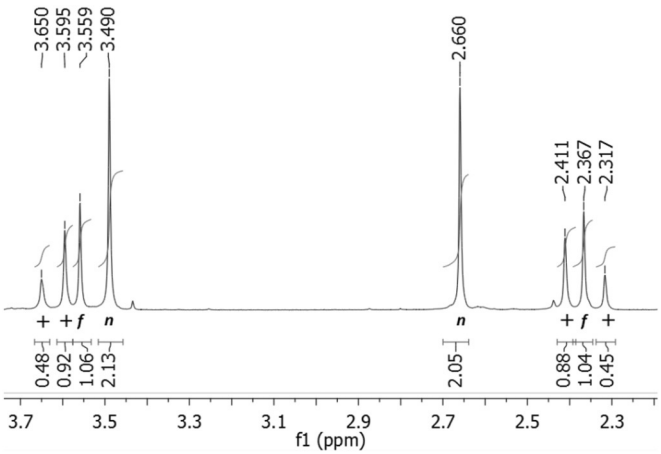
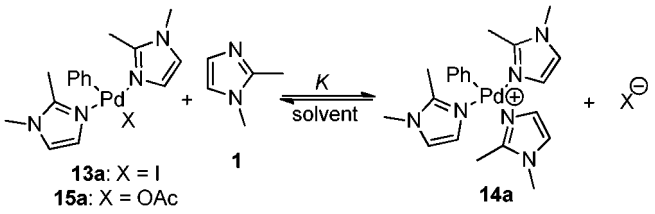



**Figure 7.** Aliphatic region of the $^1H$ NMR spectrum of a solution of $[PhPd(dmim)_3I]$ (**12a**) in $CDCl_3$ at 25 °C. Assignments: + $[PhPd(dmim)_3]^+$ (**14a**), ***f*** free uncoordinated dmim (**1**), ***n*** $[PhPd(dmim)_2I]$ (**13a**).

by $^1H$, $^{13}C$ and $^{19}F$ NMR spectroscopies with $TfO^-$ as counterion after anion exchange with AgOTf. Detailed spectral analyses are reported in the Supporting Information, §1.8.

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 excess 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[49] (80:20 ratio) (Table 2, see the Supporting Information, §1.9 for experimental details).



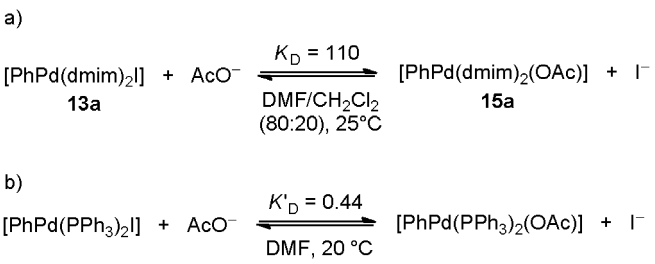

**Scheme 13.** Ionization equilibrium for **13a** and **15a**.

**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 | $CH_2Cl_2$ | $6.3\cdot10^{-3}$ |
| I | $DMF/CH_2Cl_2$ 80:20 vol. | 8.6 |
| OAc | $DMF/CH_2Cl_2$ 80:20 vol. | $8.1\cdot10^{-2}$ |

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 $(n\text{-}Bu)_4NOAc$ 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),[50] thus the softer




**Scheme 14.** Anion exchange equilibrium between **13a** and **15a**, and the same for the $PPh_3$-ligated analogous complexes (data from ref.[50]).

$[PhPd(PPh_3)_2]^+$ moiety binds preferentially the soft anion $I^-$, while the harder $[PhPd(dmim)_2]^+$ has more affinity for hard $AcO^-$.[51] This observation points out that dmim-ligated organopalladium complexes may have very different properties from their $PPh_3$-ligated analogues and generalizations based on the behaviour of the latter are to be considered with great caution.

### Reactivity of dmim-Ligated Arylpalladium Species – Direct Arylation at Room Temperature

The reactivity of dmim-ligated arylpalladium 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, $(n\text{-}Bu)_4NOAc$] 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.[a]

| Entry | Additive(s) | GLC yields | |
|---|---|---|---|
| | | 5-Ph-dmim (**3c**) | PhPh (**4c**) |
| 1 | none | 0 | 64% |
| 2 | DBU 2.0 equiv. | 22% | 30% |
| 3 | AgOAc 1.0 equiv. | 95% | 5% |
| 4 | $(n\text{-}Bu)_4NOAc$ 2.0 equiv. | 94% | 6% |
| 5 | DBU 2.0 equiv., AgOAc 1.0 equiv. | 99% | 1% |

[a] Yields were determined using a calibration curve with tetradecane as an internal standard. Product identity has been confirmed by co-injection of an authentic sample.

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 $[(4\text{-}F\text{-}C_6H_4)Pd(dmim)_2(OAc)]$ (**15b**) in $CHCl_3$ was prepared by the reaction of isolated $(4\text{-}F\text{-}C_6H_4)Pd(dmim)_3I$ (**12b**) with AgOAc and treated with $(n\text{-}Bu)_4NOAc$ (20 equiv.) at room temperature. A comparatively fast reaction ensued and palladium black was deposited along with formation of coupling product **3b**, as proven 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 C-5 position can happen at room temperature. Reports on the direct arylation of other aromatic nuclei under catalytic conditions at room temperature are sparse.[52]

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

| Entry | Additive(s) | Residual **15b** | NMR Yields | |
|---|---|---|---|---|
| | | | **3b** | **4b** |
| 1 | $(n\text{-}Bu)_4NOAc$ 20 equiv. | 26% | 71% | 3% |
| 2 | dmim 10 equiv. | 65% | 32% | 3% |
| 3 | $(n\text{-}Bu)_4NOAc$ 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 metallation–deprotonation reaction mechanism with acetate acting as an outer-sphere base.[53]

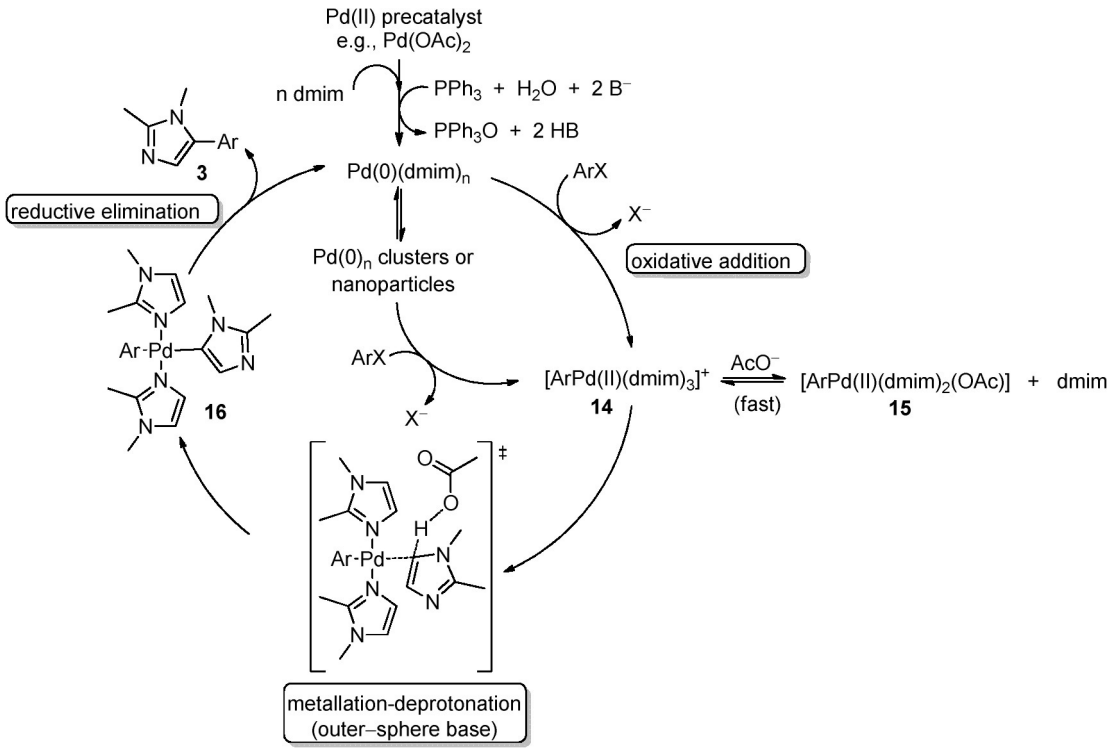
On the basis of our experimental findings, we can reasonably propose the revised mechanism depicted in Scheme 15, featuring dmim-ligated complexes only. The structure of imidazole-ligated Pd(0) is not known at present. As metallic Pd is always formed along with the coupling product under stoichiometric 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 arylpalladium species (**16**), which in turn undergoes product-forming reductive elimination probably after a *trans-cis* isomerization process, as usually assumed.

## Conclusions

We have established that phosphine-ligated aryl-Pd complexes are highly unlikely active intermediates in the direct arylation of imidazoles at C-5. This is in contrast with what is commonly assumed for the specific case of imidazole derivatives.[23b] Our findings parallel what was 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),




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

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 metallation–deprotonation mechanism involving cationic $[ArPd(dmim)_3]^+$ with $AcO^-$ acting as an outer-sphere base.[53]

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 argon. Degassed 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 PhI 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 $Et_2O$ (3×20 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; yield: 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-$d_6$): $\delta$ = 7.34–7.32 (m, 4H, Pd-bound dmim C-5-H and 2,6-$C_6H_5Pd$), 7.16 (s, 1H, free dmim C-5-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 C-4-H), 5.76 (d, $J$ = 1.5 Hz, 2H, Pd-bound dmim C-4-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-$CH_3$); 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 us 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, $CDCl_3$): $\delta$ = 7.01 (br s, 2H, *cis*-dmim C-4-H), 6.94–6.92 (m, 2H, Ph-Pd),

6.88 (br s, 1H, *trans*-dmim C-4-H), 6.88–6.81 [m, 4H, PhPd (3H) + *trans*-dmim C-5-H], 6.73 (d, $J=1.2$ Hz, 2H, *cis*-dmim C-5-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-$CH_3$); $^{13}$C NMR (75.5 MHz, $CDCl_3$): $\delta=146.3$, 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; $^{19}$F{$^1$H} NMR (282 MHz, $CDCl_3$): $\delta=-78.2$.

### 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. $^1$H NMR (300 MHz, benzene-$d_6$): $\delta=7.53$ (d, $J=1.5$ Hz, 2H, dmim C-5-H), 7.48 (dd, $J=8.1$, 1.2 Hz, 2H, 2,6-$C_6H_5$Pd), 7.03–6.99 (m. 2H, 3,5-$C_6H_5$Pd). 6.92–6.87 (m, 1H, 4-$C_6H_5$Pd), 5.79 (d, $J=1.5$ Hz, 2H, dmim C-4-H), 2.39 (s, 6H, N-$CH_3$), 2.27 (br s, 3H, $AcO^-$), 1.96 (s, 6H, C-$CH_3$); 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) [$AcO^-$].

## Acknowledgements

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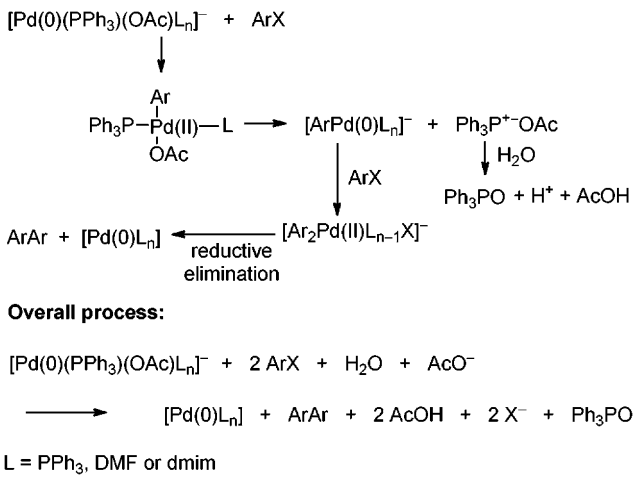


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