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Shedding Light on the Precatalytic Mixture of $Pd(OAc)_2$ and Cooperating Bipyridone Ligands for the C—H Functionalization of Arenes

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The use of a mixture of a precursor palladium compound and a ligand as precatalyst is a common practice in metal catalyzed organic synthesis. In general, little attention is paid to how these mixtures develop into the active species, but this is crucial for an efficient catalysis. We describe here the complexes that are obtained from $Pd(OAc)_2$ and $PdCl_2$ and the chelating bipyridones [2,2′- bipyridin]-6(1*H*)-one (bipy-6-OH) and 1,10-phenanthrolin-2(1*H*)-one (phen-2-OH). This type of ligands plays a cooperating role in the C—H activation step and are useful in many Pd-catalyzed C—H functionalization reactions. Both monomeric and dimeric complexes were obtained. The catalytic performance observed when using the isolated, well defined Pd-ligand complexes and the $Pd(OAc_2)$/ligand mixtures in a model direct arylation of toluene have been analyzed, as well as the plausible pathway for the generation of Pd(0) active species under catalytic conditions.

1. Introduction

The use of a precatalytic mixture of a commercially available metal salt and a suitable ligand is common practice in organometallic catalysis. It is convenient and easy from the operational point of view. The way this precatalytic mixture evolves to the actual active species is often an obscure issue. However, these off-cycle processes are important to determine the nature and concentration of the active species in the catalytic cycle.

Many of the most challenging catalytic reactions nowadays rely on the use of cooperating ligands, that is, ligands that participate in the bond-forming or bond-cleavage steps, being chemically modified and changing its coordination mode to the metal.[1] Often, these ligands have several donor atoms and play the cooperating role via the modification of their structure and their charge by proton transfer reactions. This leads to a more complex coordination behavior toward the metal and makes the determination of the nature of the catalyst from the precatalytic mixtures more complicated. Among those challenging reactions, Pd-catalyzed C—H functionalization processes generally use cooperating ligands, most prominently mono-protected amino acids (MPAA) and pyridone-type derivatives.[2–4] The latter are becoming quite important both as monodentate ligands,[5] and as part of chelating ligands where the 2-pyridone fragment is included.[6–10] They assist the C—H cleavage by being involved in the concerted metalation deprotonation transition state for the C—H activation (Figure 1). The studies on the species that are formed from pyridones and common palladium precursors in catalysis are scant. In particular, the reactions with the trimeric $Pd(OAc)_2$, the most common commercially available palladium precursor in catalysis, are interesting considering this complex bears a carboxylate ligand which may act as a base as well as a mono- or bidentate ligand. A few palladium complexes with pyridone ligands have been structurally characterized. For example, the reaction of nonchelating pyridones (py—OH) with palladium acetate in the presence of base has been reported to lead to oligomeric complexes, either di-,[11,12] or trinuclear,[13,14] containing κ^2-N,O bridging motifs (Figure 2) and also monomeric derivatives when an excess of pyridone ligand is used.[15,16] Computational analysis of the complexes formed by interaction of palladium acetate and 3,5-disubstituted 2-pyridones predict a more stable dimeric complex with κ^2-N,O pyridone bridges than the monomeric species.[17]

We analyze here the reactions of the chelating ligands [2,2′- bipyridin]-6(1*H*)-one (bipy-6-OH) and 1,10-phenanthrolin-2(1*H*)-one (phen-2-OH) with palladium precursors $Pd(OAc)_2$ and $PdCl_2$. Bipy-6-OH and phen-2-OH are useful cooperating ligands in the palladium catalyzed direct C—H arylation of simple arenes,[18] pyridine,[6] unprotected anilines,[19] as well as in the oxidative Heck reaction of arenes.[20] They and their close derivatives are present in the catalyst toolbox for C—H functionalization reactions.[8] Well-defined palladium complexes [PdAr(L-L)L′] (L-L = bipy-6-OH; L′ = Br; L-L = bipy-6-O; L′ = py, aniline) can be used as precatalysts, but usually the mixture $Pd(OAc)_2$ + ligand is also efficient. Since these ligands can act as L,L ligands in their protonated form, L,X ligands if they are deprotonated (Figure 3), we wondered what species would be formed from this mixture under different conditions and how they can influence

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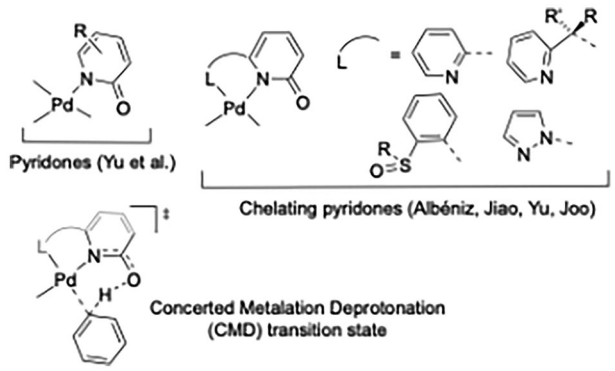


Figure 1. Pyridone-type ligands and their cooperating role in the C—H activation step.

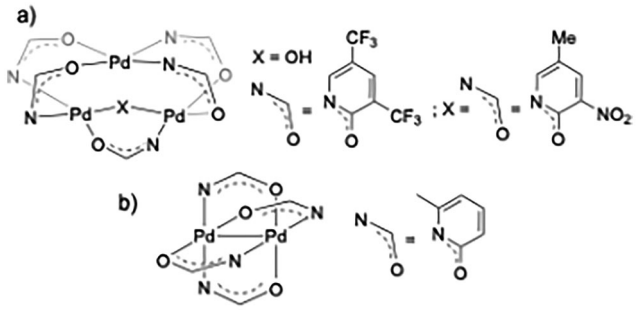


Figure 2. Examples of palladium complexes formed from $Pd(OAc)_2$ and nonchelating pyridone ligands. (a) Refs.[13, 14] (b) Refs.[11, 12].

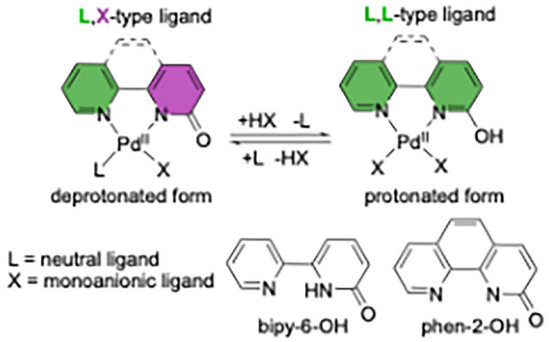


Figure 3. Bipyridone ligands used in this work and coordination modes.

the performance of the catalytic reaction. We describe here the systematic study of these reactions, a catalytic test of their activity in a C—H functionalization reaction and a plausible route for the generation of the active species.

2. Results and Discussion

2.1. Palladium Complexes Formed from the Mixture $Pd(OAc)_2$ and Bipyridone Ligands

The reaction of equimolar amounts of bipy-6-OH and $Pd(OAc)_2$ in a polar aprotic solvent such as CH_2Cl_2 or *N*,*N*-dimethylacetamide (DMA) at room temperature led after several hours to the dimeric

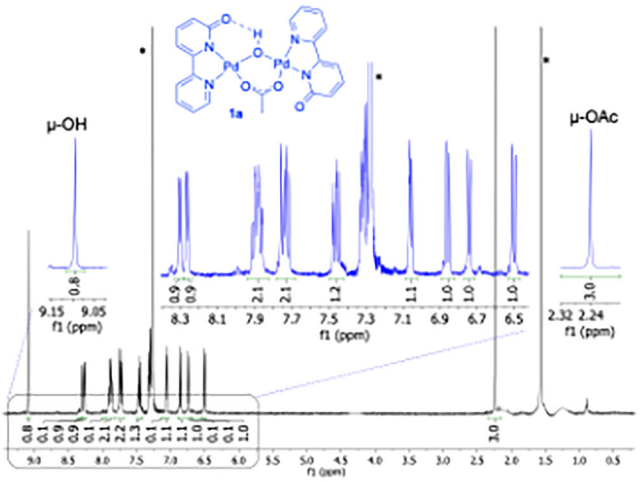
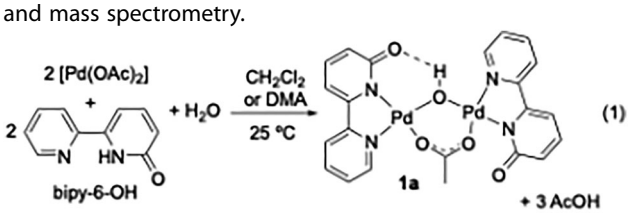


Figure 4. ^1H NMR spectrum in $CDCl_3$ of complex 1a at 298 K. * Signals corresponding to residual H_2O and $CHCl_3$.

palladium complex **1a** with mixed acetate-hydroxide bridges (Equation 1). The presence of adventitious water is surely the source of the hydroxo moiety (see below). The structure of **1a** has been determined by a combination of conductivity measurements, ^1H, 2D-^1H DOSY, gHSQC, and gHMBC NMR experiments, and mass spectrometry.



The conductivity value obtained for **1a** is very low ($\Lambda_M = 3.4$ S cm^2 mol^{-1}) showing a neutral complex in solution. The ^1H NMR unveils two sets of signals for the inequivalent bipy-6-O ligands, along with only one signal for the methyl group of the acetate ligand and a broad singlet at 9.1 ppm (Figure 4). This signal has been assigned to a hydroxo bridge (μ-OH), probably H-bonded to the carbonyl group of one of the bipy-O ligands as indicated by the high chemical shift of the signal in ^1H NMR. This has also been observed in the related dimer [Pd_2(bipy-6-O)$_2$(C_5F_5)$_2$(μOH$_2$)],[18a] and the high chemical shift value here contrasts with the high field signals usually observed for non H-bonded palladium bridging hydroxo complexes (about 0 to −5 ppm).[21,22] The μ-OH moiety undergoes fast exchange with free water as shown by the strong decrease in the intensity of the signal at 9.1 ppm upon addition of D_2O to a solution of **1a** in $CDCl_3$ (Figure S24). The IR spectrum of the complex shows clear absorptions for the hydroxo group (3466 cm^{-1}) as well as a low ν(CO) band at 1601 cm^{-1} for the acetate group, characteristic of a bridging situation, about 40 cm^{-1} lower than that for a monodentate arrangement.[23]

The molecular weight of **1a** was estimated by 2D-DOSY experiments using internal standards for calibration (see Supporting Information for details). The results obtained by 2D DOSY (DMSO-d_6 as a solvent) along with the mass spectrum (ESI-TOF) corroborate that the dimeric structure in Equation 1 is present in solution. The molecular structure of complex **1a** could not be

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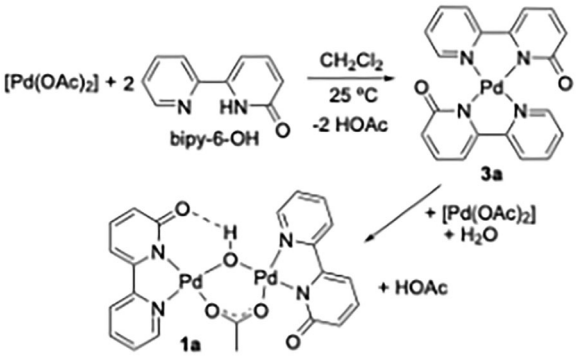


Scheme 1. Complexes formed by reaction of bipy-6-OH and $Pd(OAc)_2$.

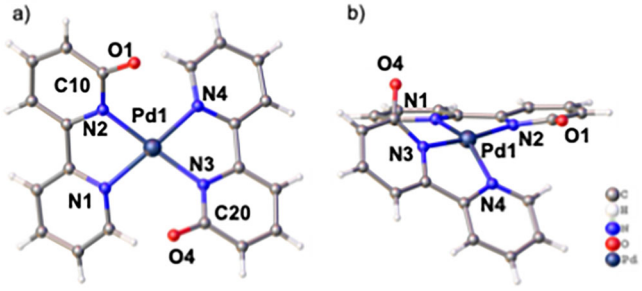
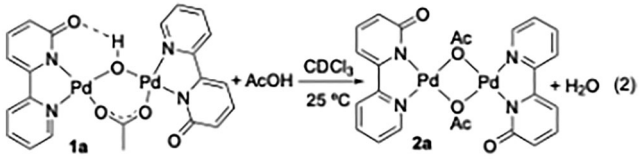


Figure 5. Molecular structure of complex **3a** (the cocrystallized water molecules and chloroform are omitted for clarity): (a) upper view showing the trans stereochemistry. (b) Lateral view showing the highly distorted coordination geometry. Selected distances (Å): Pd1–N1, 2.0500(19); Pd1–N2, 2.014(2); Pd1–N3, 2.024(2); Pd1–N4, 2.040(2); O1–C10, 1.263(3); O4-C20, 1.259(4). Selected angles (°): N2-Pd1-N1, 79.27(8); N3-Pd1-N4, 79.49(9); N1-Pd1-N4, 153.14(9); N2-Pd1-N3, 173.39(8).

determined by X-ray diffraction, but the stereochemistry corresponds to a *trans*-**1a** complex because of the ^{1}H NMR pattern: Two inequivalent bipy-6-O ligands are clearly observed, and this fact does not fit with the *cis*-**1a** isomer (equivalent bipyridones).

The addition of acetic acid to **1a** generates a new symmetric complex which has been tentatively assigned to $[Pd_2(\mu\text{-}OAc)_2(bipy\text{-}6\text{-}O)_2]$ (**2a**) (Equation 2). This experiment illustrates the basic behavior of the μ-OH group.



An excess of bidentate or monodentate ligands are sometimes used in catalysis (mol ratio ligand:Pd > 1 or 2). The reaction of $Pd(OAc)_2$ and bipy-6-OH in a Pd:ligand = 1:2 mol ratio leads to the monomeric **3a** with two deprotonated coordinated bipy-6-O ligands (Scheme 1). The stereochemistry of **3a** was unequivocally determined by crystal X-ray diffraction. The coordination of the second bipy-6-O to the metal generates a very distorted square planar geometry with a tilted bipy-6-O so the *trans* carbonylmoieties can alleviate the steric clash with the pyridine ring of the other ligand (Figure 5). Three molecules of water are trapped in the crystal lattice which establish hydrogen bonds with the carbonyl groups (see Supporting Information). Interestingly, when an equimolecular amount of $Pd(OAc)_2$ was added to isolated complex **3a**, a reorganization in solution was observed to afford complex **1a** at room temperature (Scheme 1). This indicates a strong tendency to form the thermodynamically stable dimeric structure when the mol ratio Pd:Ligand is 1:1.

Since the interconversion between complexes **1a**–**3a** is possible we decided to monitor the reaction of $Pd(OAc)_2$ and bipy-6-OH in a mol ratio Pd:ligand = 1:1 to see how these species appear and evolve. Several experiments were carried out in chloroform with different amounts of water present, and they were followed up by ^{1}H NMR looking at the aromatic region of the ligand. As the free ligand disappeared, a mixture of complexes **1a**–**3a** was formed (Figure 6). The presence of water strongly increases the reaction rate to give complex **1a** as major product (cf. reaction times in Figure 6a,b vs. Figure 6c). The monomeric bis ligand species **3a** is formed at the beginning of the reaction but it is transformed in **1a** efficiently, as long as enough water is present (Figure 6b,c). When the reaction was carried out avoiding the presence of water (dry $CDCl_3$ under nitrogen) the rearrangement of **3a** and $Pd(OAc)_2$ occurs slowly and **3a** is the main component of the mixture (Figure 6a). Both dimeric complexes **1a** and **2a** were formed, the latter being favored by the presence of acetic acid formed in the reaction media as shown in Equation 2.

Considering that C—H functionalization reactions commonly require high temperatures, most of the solvents used have high boiling points. Thus, we decided to study the reaction of bipy-6-OH with $Pd(OAc)_2$ in DMSO-d_6 and DMA, and the results are collected in Table 1. The almost complete formation of complex **1a** takes place in DMSO in the first 10 min at room temperature and it is stable in solution since no decomposition was observed after 24 h. The reaction in DMA is slower than in DMSO and only complex **3a** (26 %) can be observed in the first 10 min at room temperature. After 3 h at 298 K the amount of **3a** increases (56 %) and the reaction of **3a** with the remaining $Pd(OAc)_2$ also occurs leading to **1a** (44 %). Complex **1a** is the only species observed in DMA when the reaction time is extended to 24 h. These experiments tell us that the bipy-6-OH complexation and the subsequent reorganization reaction that leads to a complex with a ratio Pd:bipy-6-O = 1:1 is analogous in different solvents but occurs faster in DMSO. The higher coordination ability of DMSO and its slightly higher polarity than DMA may influence the outcome, including the solubility of the products. Also, the amount of water present, which could be different depending on the solvent, can influence this rate, as observed in Figure 6.

An analogous behavior was observed for phen-2-OH with some differences in the reaction rates. When $Pd(OAc)_2$ and phen-2-OH were mixed in CH_2Cl_2 or DMA at room temperature only complex **3b** was observed starting from a Pd:Ligand ratio both 1:1 and 1:2. When the ratio is 1:1, half of the palladium source, palladium acetate, is available in the reaction media but no reorganization was observed when the reaction mixture was allowed to stand for 24 h at room temperature or it was heated at 60 °C in CH_2Cl_2 (Scheme 2). The reorganization to a new dimeric complex **1b** took place only upon heating in DMA at 120 °C for 10 min (Scheme 2). Thus, the formation of complex **3b** is kinetically preferred whereas complex **1b** is the thermodynamic product. The

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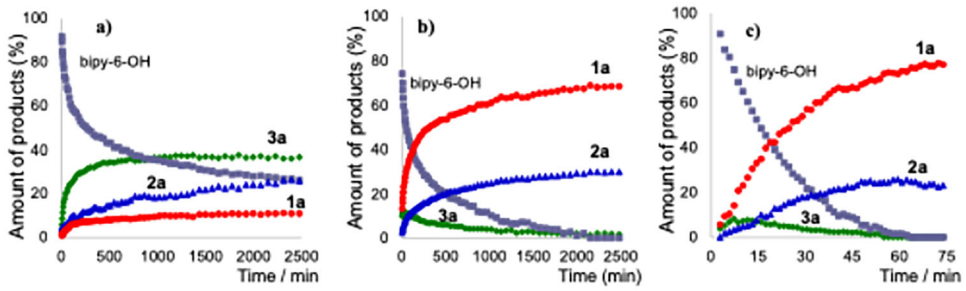
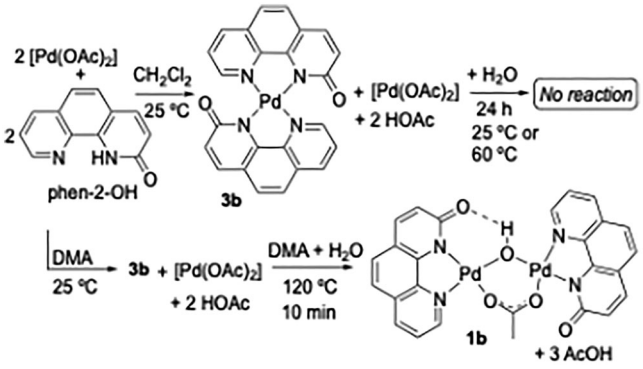


Figure 6. Plots of amount of products (% of ligand in each compound) versus time for the reactions of $Pd(OAc)_2$ and bipy-6-OH (mol ratio Pd:ligand = 1:1): (a) Dry-$CDCl_3$ (solvent dried with CaH_2 and kept under nitrogen). (b) $CDCl_3$ as received. (c) $CDCl_3$+drop of water (please note the different time scale in the *x*-axis of the plot).

Table 1. Complexes formed by reaction of bipy-6-OH and $Pd(OAc)_2$ (1:1 mol ratio) in different solvents.[a)]

Time, T	DMSO[b)]	DMA[b)]
10 min, 25 °C	**1a** (91 %), **3a** (9 %).	**3a** (26 %), bipy-6-OH (74 %)
3 h, 25 °C	**1a** (100 %)	**3a** (56 %), **1a** (44 %)
24 h, 25 °C	**1a** (100 %)	**1a** (100 %)

[a)] Reaction conditions: bipy-6-OH (2.5 mg, 0.014 mmol), $Pd(OAc)_2$ (3.26 mg, 0.014 mmol), and solvent (0.6 mL).
[b)] Amount of products (% of ligand in each compound) determined by ^1H NMR in the reaction mixture. See spectra in the Supporting information.

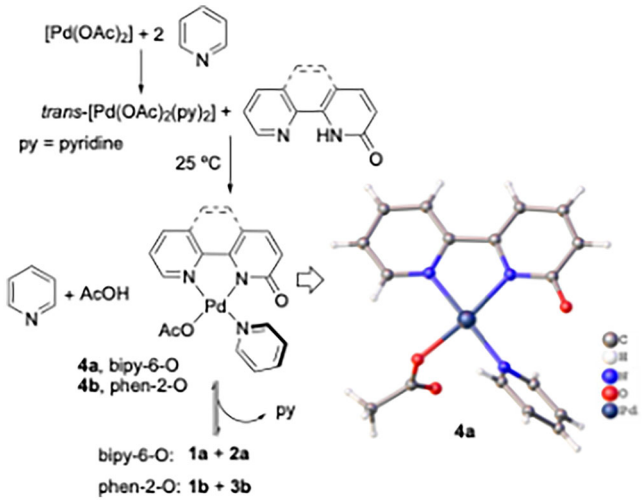


Scheme 2. Complexes formed by reaction of phen-2-OH and $Pd(OAc)_2$.

very low solubility of complex **3b** could be responsible for the slower rearrangement of the phen-2-OH products when compared to bipy-6-OH. In the same way as observed for the latter ligand, the reactions in Scheme 2 are faster when DMSO was used as solvent at room temperature and **1b** was formed as major product (80%) after 10 min and **1b** was the only product observed after 24 h.

Thus, the dimeric complexes **1** are the thermodynamically preferred species from a mixture of $Pd(OAc)_2$ and the chelating bipy-6-OH and phen-2-OH. In contrast to the monodentate pyridines in Figure 2, no species with κ^2-N,O pyridone bridges were detected.

Monomeric complexes containing a ratio Pd:bipyridone = 1:1 can only be obtained in the presence of an additional ligand



Scheme 3. Complexes formed in the presence of pyridine.

such as pyridine. Thus, the reaction of the in situ preformed *trans*-$[Pd(OAc)_2(py)_2]$, by mixing $Pd(OAc)_2$ and an excess of pyridine, with an equimolecular amount of bipyridone ligand led to the formation of complexes **4a** and **4b** (Scheme 3). In both cases, the acetate deprotonates the bipyridone ligand to afford a neutral [Pd(L-X)(OAc)(py)] complex (L–X = bipy-6-O or phen-2-O). The molecular structure of complex **4a** was determined by X-ray diffraction and it shows the acetate ligand coordinated in a monodentate fashion (κ^1-OAc) in a *trans* position to the carbonyl group of the bipy-6-O (Scheme 3). Complexes **4a**,**b** are more soluble in common organic solvents than the dimeric **1a**,**b**. However, the dissociation of pyridine is a very facile process and isolated samples of **4a**,**b** led to a mixture of species in solution (Scheme 3 and Figures S9 and S10 in the Supporting Information). The addition of an excess of pyridine to this mixture shifts the dissociation equilibrium toward **4**.

In the reactions with palladium acetate, the deprotonation of the ligand occurs to generate a monoanionic bipy-6-O or phen-2-O ligand (L, X-type coordination) and acetic acid. In contrast, when $PdCl_2$ is used as precursor, the absence of a base affords the monomeric Pd(II) complexes **5a**,**b** with the ligands bound in their protonated form (L, L-type coordination) (Scheme 4). The molecular structure of complex **5a** shows a hydrogen bond between the OH of the ligand and the closest chlorine atom.

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Scheme 4. Complexes formed by reaction of $PdCl_2$ and bipyridones.

2.2. Catalytic Reactions

To evaluate the catalytic activity of the synthesized palladium complexes the direct arylation reaction of toluene with aryl halides, was chosen as a model reaction (Equation 3).[18] As previously reported, three regioisomers were obtained (*o*:*m*:*p*) in different ratios, the *ortho*-isomer being generally disfavored (see Tables S1 and S2 in the Supporting Information). The reaction was carried out using the arene as reagent and solvent (toluene for this particular case) but, in order to decrease the amount of arene used, DMA can be chosen as cosolvent with toluene in a ratio 1:1 (v/v). The cosolvent has a significant accelerating effect in this arylation reaction as has been studied before.[18a]

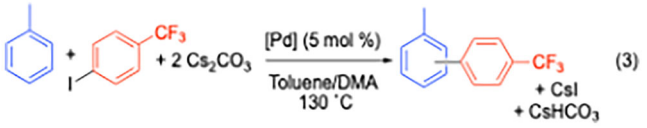

Table 2 collects the crude yields of the cross-coupling aryltolyl products using different precatalysts. The reaction requires the presence of the cooperating bipyridone ligands (cf. entries 1–5, Table 2) since the deprotonated pyridone moiety is essential to assist the C—H activation step in this reaction (see below). When toluene was used as reagent and solvent, the precatalytic mixture of $Pd(OAc)_2$ and bipy-6-OH leads to the arylated product in good yield but rather long reaction time (91 % yield in 24 h, entry 5, Table 2). The reaction rate is not influenced by the addition of a small amount of water (entry 6, Table 2). Significant differences were observed when the preformed bipy-6-OH complexes described above were used, that is, **1a**, **3a**, and **5a**. Complex **4a** was not tested since as a catalyst precursor it is likely to be a mixture of species rather than a unique complex, as a result of the facile dissociation of pyridine mentioned above.

The dimeric complex **1a** showed the highest catalytic activity and affords an 82 % yield of the crosscoupling product in just 6 h (entry 7, Table 2). Complex **5a** is also quite active (65 % yield in 6 h, entry 9, Table 2) and even if the ligand is bound in its L, L-type coordination mode the presence of a base under catalytic conditions can induce the facile deprotonation to the L–X coordination mode.

In contrast, complex **3a**, which presents two chelating bipy-6-O ligands bound to the palladium center shows an activity similar to the $Pd(OAc)_2$/bipy-6-OH mixture (cf. entries 5, 8 in Table 2). These results show that a preformed Pd-precatalyst with one coordinated bipy-6-O ligand per palladium is optimal to accelerate the overall reaction and get shorter reaction times in a non-polar reaction medium. Both the mixture $Pd(OAc)_2$/bipy-6-OH or complex **3a** need a reorganization process which is slow in toluene and it is probably influenced by the lower solubility of the species in this solvent. The presence of water in this nonpolar solvent does not accelerate the process as we have observed for the reorganization processes in the more polar $CDCl_3$ (Figure 6).

The complexes bearing phen-2-OH as a ligand show lower activity than the bipy-6-OH derivatives, probably due to the lower solubility of the phen-2-O palladium species. In this case, there is only a small advantage in using a preformed palladium species vs. the mixture of $Pd(OAc)_2$ + phen-2-OH. (entries 10–13, Table 2).

All reactions give excellent yields when DMA was used as cosolvent and the reaction time is significantly reduced to 6 h (entries 14–21, Table 2). The accelerating effect of polar and moderately coordinating solvents such as DMA in the direct arylation of toluene has been studied before with well-defined precatalysts bearing the bipy-6-OH ligand.[18a] Under these catalytic conditions, there is no significant difference in catalytic performance when using the mixture $Pd(OAc)_2$ + ligand or the preformed complexes. As shown in Table 1 and Scheme 2 the reorganization reactions needed to form complexes **1** from palladium acetate and the corresponding ligand are faster in polar solvents such as DMA, making both precatalysts equivalent in practice. Consistent to this, the aerobic olefination of toluene that we reported before in DMA as solvent,[20] can also be carried out using complex **1a** as precatalyst with similar results as the mixture $Pd(OAc)_2$ + bipy-6-OH (Scheme 5a). In the same vein, when the polar pyridine is used as substrate and solvent in the regioselective *meta* direct arylation of pyridine both **1a** and the precatalytic mixture $Pd(OAc)_2$ + bipy-6-OH are equally effective (Scheme 5b).[6]

The mechanism for the direct arylation of toluene with cooperating bipyridone ligands has been studied and the simplified catalytic cycle proposed is shown in Scheme 6.[6,18a] This is a Pd(0)/Pd(II) cycle where intermediate **A** is the result of an oxidative addition of the aryl halide (p-$CF_3C_6H_4I$) on Pd(0) species. Since all the precatalyst employed in Table 2 are Pd(II) species, an off-cycle decomposition of the starting precatalyst to generate Pd(0) species, capable to start the catalytic cycle, is necessary. Many catalytic reactions that involve Pd(0) use Pd(II) complexes as precatalysts.[24] Some of these complexes are metalacycles or organometallic complexes especially designed to decompose easily to Pd(0).[25] For more common precursors, pathways for reduction involve a phosphine ligand, which forms the corresponding phosphine oxide,[21] or an alcohol when used as solvent or additive via β-H elimination to give an unstable palladium hydride.[26]

None of the common pathways are feasible here and therefore we analyzed the decomposition of the precatalyst that could give some insight into the activation process. When the dimeric complex **1a** was heated in toluene at 130 °C for 2 h, Pd black was formed in the reaction medium. A white solid was

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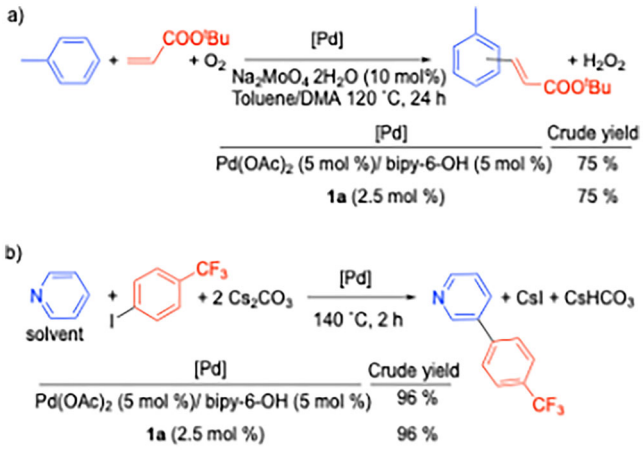
Table 2. Direct arylation of toluene with *p*-$CF_3C_6H_4I$ using different catalysts according to Equation 3.[a]

Entry	Toluene/DMA(v/v ratio)	[Pd] (mol %)	Ar–Tol Crude Yield, %, (React. Time)[b]
1	1/0	–	- (24 h)
2	1/0	$Pd(OAc)_2$ (5)	- (24 h)
3	1/0	$Pd(OAc)_2$ (5) + bipy (5)	0 (6 h), 1 (24 h)
4	1/0	$Pd(OAc)_2$ (5) + 1,10-phen (5)	0 (6 h), 1 (24 h)
5	1/0	$Pd(OAc)_2$ (5) + bipy-6-OH (5)	20 (6 h), 91 (24 h)
6[c]	1/0	$Pd(OAc)_2$ (5) + bipy-6-OH (5)	12 (6 h), 94 (24 h)
7	1/0	**1a** (2.5)	82 (6 h)
8	1/0	**3a** (5)	18 (6 h), 94 (24 h)
9	1/0	5a (5)	65 (6 h), 89 (24 h)
10	1/0	$Pd(OAc)_2$ (5) + phen-2-OH (5)	6 (6 h), 18 (24 h)
11	1/0	**1b** (2.5)	15 (6 h), 29 (24 h)
12	1/0	**3b** (5)	3 (6 h), 50 (24 h)
13	1/0	5b (5)	4 (6 h), 19 (24 h)
14	1/1	$Pd(OAc)_2$ (5) + bipy-6-OH (5)	96 (6 h)
15	1/1	**1a** (2.5)	93 (6 h)
16	1/1	**3a** (5)	95 (6 h)
17	1/1	5a (5)	88 (6 h)
18	1/1	$Pd(OAc)_2$ (5) + phen-2-OH (5)	79 (6 h)
19	1/1	**1b** (2.5)	93 (6 h)
20	1/1	**3b** (5)	97 (6 h)
21	1/1	5b (5)	88 (6 h)

[a] Reaction conditions: *p*-$CF_3C_6H_4I$ (0.34 mmol), toluene (3 mL) or toluene/DMA (1.5/1.5 mL), [Pd] (5 mol %), Cs_2CO_3 (0.68 mmol), and 130 °C.
[b] Crude yields determined by ^{19}F NMR of the reaction mixture. The reduction product of the aryl iodide (ArH) and the homocoupling derivative (Ar–Ar) are the observed byproducts.
[c] H_2O (50 µL) was added.



Scheme 5. (a) Aerobic olefination of toluene and (b) direct arylation of pyridine with different precatalysts.

obtained from the reaction mixture and its analysis by mass spectrometry (GC–MS) and ^1H NMR indicated the presence of six different regioisomeric biphenyl products from the dimerization of toluene (Scheme 7). This experiment proves that the C—H activation of two molecules of toluene followed by a reductive elimination to give the homocoupling product is a feasible pathway to decompose complex **1a** to Pd(0)species that initiate the catalytic cycle.

3. Conclusion

The complexes obtained by reaction of the bipyridone ligands bipy-6-OH and phen-2-OH with $Pd(OAc)_2$ exhibit an anionic L, X-type coordination mode to Pd(II). Despite the Pd:Ligand ratio used, the formation of the neutral monomeric $[Pd(L\text{-}X)_2]$ (L–X = bipy-6-O, phen-2-O, **3**) occurs first. This is the only product observed for a ratio Pd:ligand = 1:2. If the ratio Pd:Ligand is 1:1, a subsequent ligand reorganization of complexes **3a,b** with the remaining $Pd(OAc)_2$ is possible, leading to the formation of dimeric complexes $[Pd_2(L\text{-}X)_2(\mu\text{-}OAc)(\mu\text{-}OH)]$ (L–X = bipy-6-O, phen-2-O, **1**) which have been isolated and characterized. The formation of complexes **1** is faster in the more coordinating and polar DMSO and, in the case of the ligand bipy-6-OH,

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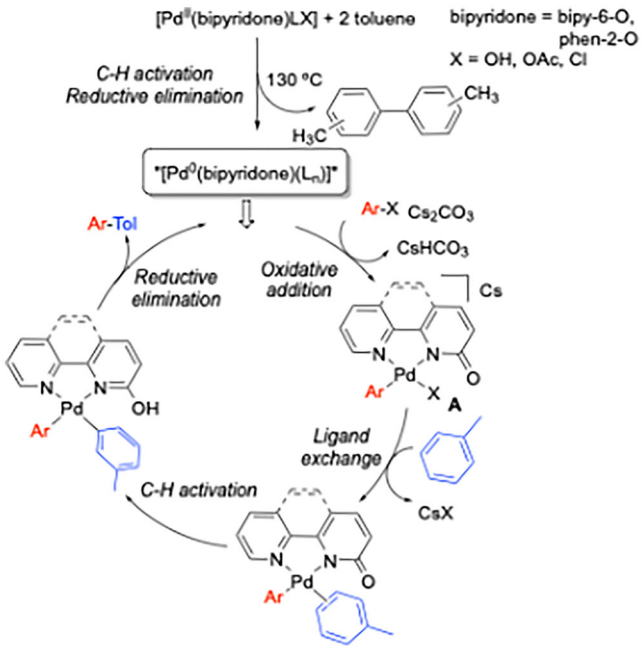
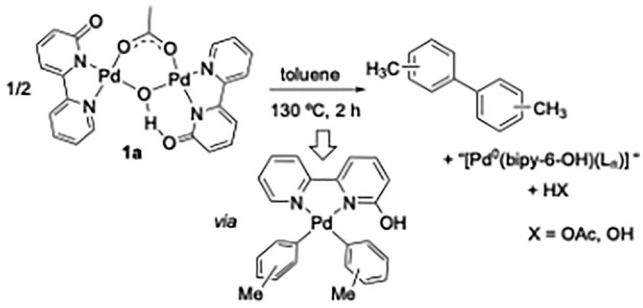


Scheme 6. Catalytic cycle for the arylation of toluene with Pd(II) precursors bearing bipyridone cooperating ligands.



Scheme 7. Decomposition of **1a** in toluene.

water accelerates the reaction and influences the distribution of palladium complexes. Phen-2-OH, usually forming less soluble complexes, shows a more reluctant behavior, requiring high temperatures for the reorganization to take place. In contrast to palladium acetate, the reaction with $PdCl_2$ as metal precursor affords a neutral L, L-coordination mode for the bipyridone ligands leading to complexes [Pd(L-L)Cl_2] (L–L = bipy-6-OH **5a**; phen-2-OH, **5b**).

The activity as precatalysts of the isolated complexes has been tested in the direct arylation of toluene and compared to the mixture $Pd(OAc)_2$/bipy-6-OH. When the catalytic reaction is carried out in a polar solvent such as the mixture toluene/DMA, there is no significant difference in the yield and rate among the precatalysts used, most probably because of the rapid Pd/Ligand coordination-reorganization in the medium to form the active species. However, when the reaction is run in a non-polar, non-coordinating solvent (neat toluene) complexes with a coordinated anionic bipy-6-O in a ratio Pd:ligand = 1:1 (**1a** and **5a**) show faster reactions than the precatalyst mixture of $Pd(OAc)_2$/bipy-6-OH. This shows that the precoordination of one bipyridone ligand to the metal facilitates the formation of the active species. Therefore, we expect that complexes **1a** and **5a**, easy to synthesize, can be convenient and effective precatalysts in C—H functionalization reactions in non-polar solvents. The Pd(II) precatalyst can be transformed into Pd(0) species, active in the direct arylation reaction, via C—H activation of two arene molecules and reductive elimination under catalytic conditions.

4. Experimental Section

4.1. General Considerations

^{1}H and ^{13}C{^{1}H} spectra were recorded on Agilent MR-500 spectrometer at the *Laboratorio de Técnicas Instrumentales* (LTI) of the UVa. Chemical shifts (in δ units, ppm) were referenced to $SiMe_4$ (^{1}H and ^{13}C). The spectral data were recorded at 298 K unless otherwise noted. Homonuclear (^{1}H-COSY, ^{1}H-2D-DOSY) and heteronuclear (^{1}H-^{13}C HSQC and HMBC) experiments were used to help with the signal assignments. Elemental analyses were carried out in a Thermo Scientific FLASH 2000 microanalyzer (at the Parque Científico Tecnológico of the UBU, Burgos). Infrared spectra were recorded (in the range 4000–200 cm^{-1}) on a PerkinElmer FT-IR Spectrum Frontier with an ATR diamond accessory. Conductivity measurements were carried out by a Mettler Toledo MC226 conductimeter. Acetone was chosen as a solvent for the measurements. The values of the molar conductivities were compared to the reported values for different electrolytes.[27] Solvents were dried using a solvent purification system SPS PS-MD-5 (ether, hexane, THF, and CH_2Cl_2) or distilled from appropriate drying agents under nitrogen prior to use and stored over 3 Å or 4 Å molecular sieves (pyridine, *N,N*-dimethylacetamide and $CDCl_3$). $Pd(OAc)_2$, 2,2′-bipyridine, 1,10-phenanthroline are commercially available and were purchased from Johnson Matthey, Sigma–Aldrich, or Alfa Aesar. All commercial reagents and solvents were used as received unless otherwise indicated. [2,2′-bipyridin]-6(1*H*)-one (bipy-6-OH),[28] and 1,10-phenanthrolin-2(1*H*)-one (phen2OH),[29] were prepared according to the procedures in the literature.

4.2. Synthesis of Bipy-6-OH Complexes

[Pd_2(μ-OAc)(μ-OH)(bipy-6-O)$_2$] (1a). [2,2′-Bipyridin]-6(1*H*)-one (bipy-6-OH) (100 mg, 0.581 mmol) was added to $Pd(OAc)_2$ (130.4 mg, 0.581 mmol) in DMA (2 mL). The mixture became yellow, and a yellow precipitate was observed. The suspension was stirred at room temperature for 16 h and then Et_2O (5 mL) was added to the suspension. The yellow solid was filtered, washed with Et_2O (3 × 2 mL) and air-dried. Yield: 160 mg (87%). ^{1}H NMR (499.73 MHz, $CDCl_3$): δ 9.08 (s, 1H, H^7), 8.29 (dd, J = 5.7, 1 Hz, 1H, $H^{6'}$ or $H^{13'}$), 8.25 (d, J = 5.7, 1 Hz, 1H, $H^{13'}$ or $H^{6'}$), 7.87 (m, 2H, $H^{4'}$, $H^{11'}$), 7.72 (m, 2H, $H^{3'}$, $H^{10'}$), 7.45 (m, 1H, H^4), 7.36-7.29 (m, 3H, $H^{5'}$, $H^{12'}$, H^{11}), 7.04 (d, J = 8.8 Hz, 1H, H^3), 6.85 (d, J = 8.8 Hz, 1H, H^5), 6.73 (d, J = 6.8 Hz, 1H, H^{10}), 6.49 (d, J = 8.8 Hz, 1H, H^{12}), 2.23 (s, 3H, H^{15}). ^{13}C {^{1}H} NMR (125.58 MHz, δ, $CDCl_3$): 178.6 (C^{14}), 172.9 (C^{13}) 170.3 (C^6), 159.4 ($C^{9'}$), 158.1 ($C^{2'}$), 153 (C^2), 149.8 ($C^{6'}$ or $C^{13'}$), 149.5 (C^9), 147.1 ($C^{13'}$ or $C^{6'}$), 138.7 ($C^{4'}$, $C^{11'}$), 137.6 (C^4), 136.5 (C^{11}), 124.6 ($C^{5'}$ or $C^{12'}$), 123.8 ($C^{12'}$or $C^{5'}$), 123.4 (C^{12}), 120.8 ($C^{3'}$, $C^{10'}$) 120.7 (C^5), 109.5 (C^3) 106.1 (C^{10}), 23.3 (C^{15}). IR (neat, cm^{-1}): ν (μ-OH, st) 3466; (μ-OAc) 1601, 1470. HRMS (ESI-TOF) m/z calcd for $C_{20}H_{15}N_4O_3Pd_2$ [[Pd_2(μ-OH)(bipy-6-O)$_2$]$^+$]$^+$ 570.9222. Found 570.9233. Λ_M = 3.4 Scm^2/mol. Anal. calcd for $C_{22}H_{18}N_4O_5Pd_2$: C, 41.86 %; H, 2.87 %; N, 8.87%. Found C, 41.68 %; H, 3.09 %; N, 8.83%.

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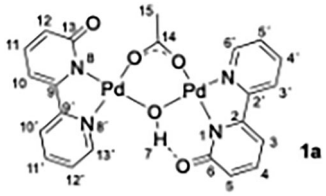
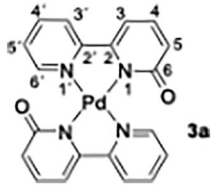
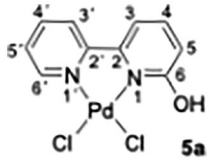


Pd(bipy-6-O)$_2$] (3a). [2,2′-Bipyridin]-6(1*H*)-one (bipy-6-OH) (192.3 mg, 1.11 mmol) was added to a solution of $Pd(OAc)_2$ (125.1 mg, 0.557 mmol) in CH_2Cl_2 (15 mL). The mixture was stirred at room temperature for 1 h. During this time the orange solution became yellow and a precipitate was observed. The solvent was evaporated to *c.a.* 5 mL and Et_2O (10 mL) was added to the suspension. The yellow solid was filtered, washed with Et_2O (3 × 5 mL), acetone (3 × 5 mL) and air-dried. Yield: 181 mg (72%). Crystals suitable for X-ray diffraction studies were obtained by slow evaporation of a solution of the complex in $CHCl_3$. ^{1}H NMR (499.73 MHz, δ, $CDCl_3$): 9.15 (dd, J = 5.7, 1.1 Hz, 1H, $H^{6'}$), 7.86 (td, J = 7.6, 1.5 Hz, 1H, H^4), 7.70 (d, J = 8.2 Hz, 1H, $H^{3'}$), 7.31 (dd, J = 8.5, 6.9 Hz, 1H, $H^{4'}$), 7.21 (td, J = 6.8, 1.5 Hz, 1H, $H^{5'}$), 6.66 (dd, J = 6.8, 1.0 Hz, 1H, H^5), 6.51 (dd, J = 8.5, 1.0 Hz, 1H, H^3). ^{13}C {^{1}H} NMR (125.58 MHz, δ, $CDCl_3$): 169.4 (C^6), 160.4 ($C^{2'}$), 153.7 ($C^{6'}$), 153.3 (C^2), 138.9 ($C^{4'}$) 137.2 (C^4) 123.7 ($C^{5'}$), 122.1 (C^5), 120.2 ($C^{3'}$), 105.9 (C^3). IR (neat, cm^{-1}): ν (CO, st) 1616 cm^{-1}. A sample of the isolated complex was analyzed and it was found to contain several water molecules in its formulation. Anal. calcd for $C_{20}H_{14}N_4O_2Pd \cdot 6\ H_2O$: C, 43.14 %; H, 4.71 %; N, 10.06 %. Found C, 43.70 %; H, 4.48 %; N, 10.17 %.



[Pd(bipy-6-OH)Cl$_2$] (5a). [2,2′-Bipyridin]-6(1*H*)-one (bipy-6-OH) (72.0 mg, 0.41 mmol) was added to a solution of $PdCl_2$ (74.1 mg, 0.41 mmol) in CH_2Cl_2 (30 mL). The mixture was stirred at reflux for 16 h. During this time, the brown suspension became yellow and a precipitate was observed. The yellow solid was filtered, washed with cold $CH_2Cl_2$2 (3 x 5 mL), Et_2O (3 x 5 mL) and air-dried. Yield: 105 mg (72 %). ^{1}H NMR (499.73 MHz, δ, DMSO-d6): 11.97 (br, 1H, OH), 9.10 (d, J = 5.4 Hz, 1H, H6′), 8.47 (d, J = 8.1 Hz, 1H, H3′), 8.29 (td, J = 7.7, 1.2 Hz, 1H, H4′), 8.14 (t, J = 7.2 Hz, 1H, H4), 8.08 (br, 1H, H3), 7.72 (t, J = 7.7 Hz, 1H, H5′), 7.07 (d, J = 8.0 Hz, 1H, H5). 13C {^{1}H} NMR (125.58 MHz, δ, DMSO-d6): 167.3 (C^6), 158.3 ($C^{2'}$), 153.8 (C^2), 143.6 (C^4), 141.8 ($C^{4'}$), 127.1 ($C^{5'}$), 124.4 ($C^{3'}$), 117.1 (C^5), 116.5 (C^3), 105.1 ($C^{6'}$). IR (neat, cm^{-1}): ν (OH, st) 3078; ν (Pd-Cl), 337, 329. Anal. calcd. for: $C_{10}H_8Cl_2N_2OPd$: C, 34.36 %; H, 2.31%; N, 8.01%. found: C, 33.99%; H, 2.40%; N, 7.67%.



The analogous phen-2-OH complexes were prepared by similar procedures (see Supporting Information).

4.3. Catalytic Reactions

4.3.1. General Procedure for Direct Arylation of Toluene

Method A; toluene as solvent): $Pd(OAc)_2$ (3.8 mg, 0.017 mmol), bipy-6-OH (2.93 mg, 0.017 mmol), and cesium carbonate (222 mg, 0.68 mmol) were introduced in a Schlenk flask with a screw cap in a nitrogen atmosphere. Then, toluene (3 mL) and the aryl iodide (*p*-$CF_3C_6H_4I$) (51 µL, 0.34 mmol) were added. The mixture was kept in a preheated-bath at 130 °C for 6–24 h. After this time, the conversion was checked by ^{19}F NMR of the crude mixture. The crude yields are collected in Table 2. The spectral data of the three isomers found conform to the characterization data in the literature: 3-methyl-4′-(trifluoromethyl)-1,1′-biphenyl,[6,30] 4-methyl-4′-(trifluoromethyl)-1,1′-biphenyl,[6,31] and 2-methyl-4′-(trifluoro-methyl)-1,1′-biphenyl.[6,31]

Method B; *N,N*-dimethylacetamide (DMA) as cosolvent: $Pd(OAc)_2$ (3.8 mg, 0.017 mmol), bipy-6-OH (2.93 mg, 0.017 mmol) and cesium carbonate (222 mg, 0.68 mmol) were introduced in a Schlenk flask with a screw cap in a nitrogen atmosphere. Then, toluene (1.5 mL), *N,N*-dimethylacetamide (1.5 mL) and the aryl iodide (*p*-$CF_3C_6H_4I$) (51 µL, 0.34 mmol) were added. The mixture was kept in a preheated-bath at 130 °C for 6–24 h. After this time, the conversion and yield were checked by ^{19}F NMR of the crude mixture.

Additional experimental information, characterization data, and spectra for the compounds and details for the X-ray structure determinations (pdf) can be found in the Supporting Information.

Supporting Information

For additional experimental details, X-ray diffraction and characterization data see the Supporting Information. Deposition Numbers 2426928 (for **3a**), 2426929 (for **4a**), and 2426930 (for **5a**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Arene functionalization · C—H activation · Cooperating ligands · Palladium · Precatalyst

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