

Communication

[2, 2'-Bipyridin]-6(1H)-one, a Truly Cooperating Ligand in the Palladium-Mediated C-H Activation Step: Experimental Evidence in the Direct C-3 Arylation of Pyridine

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[2, 2'-Bipyridin]-6(1*H*)-one, a Truly Cooperating Ligand in the Palladium-Mediated C-H Activation Step: Experimental Evidence in the Direct C-3 Arylation of Pyridine

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Supporting Information Placeholder

ABSTRACT: The ligand [2, 2'-bipyridin]-6(1*H*)-one (bipy-6-OH) has a strong accelerating effect in the Pd-catalyzed direct arylation of pyridine or arenes. The isolation of relevant intermediates and the study of their decomposition unequivocally show that the deprotonated coordinated ligand acts as a base and assists the cleavage of the C-H bond. Mechanistic work indicates that the direct arylation of pyridine with this ligand occurs through a Pd(0)/Pd(II) cycle. Because of this dual ligand-intramolecular base role, there is no need of an available coordination site on the metal for an external base, a difficulty encountered when chelating ligands are used in coupling reactions that involve a C-H cleavage step.

Palladium-catalyzed cross coupling reactions that use arenes or alkanes as coupling partners are extremely interesting since, in contrast to classic C-C couplings, there is no need to pre-synthesize the reagents from the parent hydrocarbons, making the processes more sustainable. Extraordinary progress has been made to extend the scope of these reactions and the number of available catalysts is now large.¹ The cleavage of the strong and kinetically sluggish C-H bond is not easy and mechanistic studies show that, generally, this step is rate determining in the catalysis. As a consequence, higher temperatures and long reaction times are often required, so more active catalysts are highly desirable. The most common pathway for breaking the C-H bond is the so called concerted metalation-deprotonation (CMD) where a coordinated base, usually carboxylate or carbonate, and the arene form a 6-membered cyclic transition state leading to a palladium aryl and the protonated base (Figure 1, a).^{2,3} We have been exploring ligands that could favor the CMD transition state by incorporating the basic moiety into the ligand. This has kinetic advantages since the coordination of an external base to the metal is not needed, so it does not compete with the substrate for the metal coordination sphere and, at the same time, the ligand provides an effective high local concentration of base playing a bifunctional or cooperating role (Figure 1, b).

Ligands with a suitable structure to play this dual role have been successfully used in Pd-catalyzed couplings involving C-H activation. Most prominent are the N-monoprotected aminoacids introduced by J. -Q. Yu et al. that are efficient in several transformations of C(sp²)H and C(sp³)H bonds,⁴ including enantioselective couplings.⁵ The involvement of the protecting groups of the ligand in the C-H cleavage has been proposed as one of the

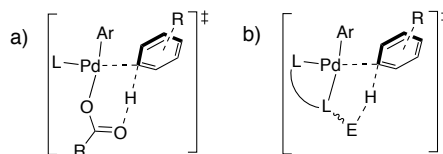


Figure 1. Representation of CMD transition states for C-H activation by a carboxylate (a) or a basic group, E, on the ligand (b).

reasons for their success, and calculations as well as some indirect gas-phase MS evidence showed that it is feasible.⁶ However, other computational reports favor a C-H cleavage by an external base over an internal assistance of the ligand.⁷ There is no clear-cut experimental data that demonstrate the H abstraction by the ligand in these or any other catalysts. We report here and experimentally support the cooperating effect in the C-H cleavage of arenes of [2, 2'-bipyridin]-6(1*H*)-one (bipy-6-OH), whose deprotonated form effectively brings about the C-H cleavage of an arene. This and related ligands have been used before in Ir-,⁸ or Ru-catalyzed hydrogen transfer reactions,^{9,10} other applications,¹¹ and by Duan et al. in oxidative Heck reactions of arenes where they attribute the improvement in the catalysis to a different reason: the anionic nature of the deprotonated ligand that favors the dissociation of an acetate.¹² Monodentate pyridone derivatives have also been recently used to accelerate coupling reactions of arenes.¹³ Again, the involvement of the ligand in the C-H activation step is plausible and has just been supported by DFT calculations.^{13d}

We chose the direct arylation of pyridine as a model reaction to test the performance of the ligand and study its catalytic behavior. This useful reaction was reported by J. -Q. Yu using a Pd(OAc)₂/phenanthroline precatalyst mixture and allows to selectively functionalize pyridine at the meta position.^{14,15} The reaction is carried out in the coordinating pyridine as reagent and solvent, so it is also a good test to evaluate the coordination ability of the ligand. Under these conditions, most monodentate ligands do not compete favorably with the substrate for coordination to the metal. Table 1 shows the results obtained in the reaction depicted in Eq. 1. Bipy-6-OH has a strong accelerating effect when compared to 1,10-phenanthroline (phen) used in the original report (entries 1-2, Table 1).¹⁴ The presence of an OH group in a position close to the metal center (6-OH) is crucial. A methoxy group has no beneficial effect (entry 3, Table 1) and the regioisomeric bipy-4-OH, with similar electronic features than bipy-6-OH, leads to an inactive catalyst (entry 4, Table 1).

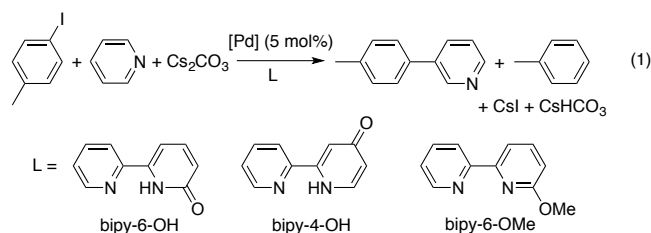
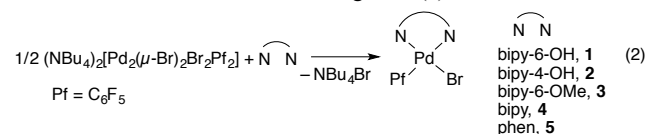


Table 1. Direct arylation of pyridine with *p*-iodotoluene using different precatalyst.^a

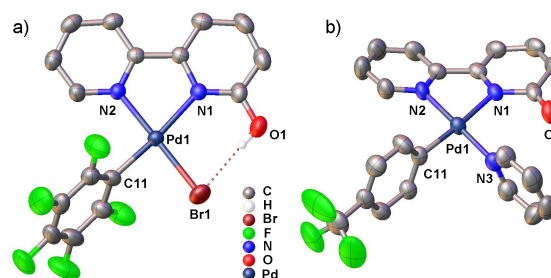
Entry	[Pd]	L (mol%)	Base:ArI mol ratio	%Crude yield (% conversion), ^b 6 h	%Crude yield (% conversion), ^b 24 h
1	[Pd(OAc) ₂]	phen (15)	3	5 (5)	82 (86)
2	[Pd(OAc) ₂]	bipy-6-OH (15)	3	64 (74)	90 (100)
3	[Pd(OAc) ₂]	bipy-6-OMe (15)	3	0 (0)	15 (24)
4	[Pd(OAc) ₂]	bipy-4-OH (15)	3	0 (0)	0 (0)
5	[Pd(OAc) ₂]	bipy (15)	3	1 (2)	6 (7)
6	[Pd(OAc) ₂]	bipy-6-OH (6)	1	88 (97)	90 (100)
7	1	-	1	80 (100)	

a) Reaction conditions: ArI (0.5 mmol), pyridine (3.0 mL), [Pd] (5 mol%), Cs₂CO₃, 140 °C. b) Determined by ¹H NMR (methyl region). The formation of ArH (toluene) accounts for the differences between crude yield and conversion. Ar-py is a mixture of regioisomers: o:m:p = 1:14:1.

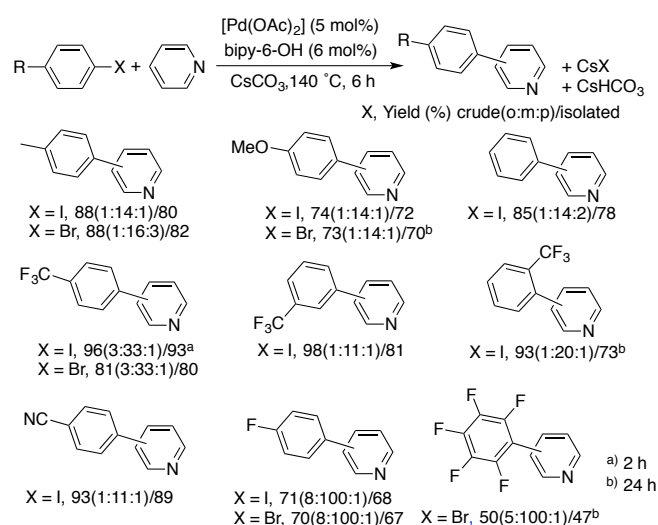
The amount of ligand and base can be reduced with no erosion of the yield (cf. entries 2 and 6, Table 1), but the use of a base different to Cs₂CO₃ or a lower temperature strongly decreased the yield (see SI for control experiments and additional data). The well-defined precursor [Pd(bipy-6-OH)Br(C₆F₅)] (**1**) was also tested. **1** is a plausible model intermediate in the catalytic reaction, after oxidative addition of ArX, and it also catalyzes the reaction (entry 7, Table 1). The synthetic route used for **1** and other analogous [PdBr(C₆F₅)(N-N)] complexes is collected in Eq. 2, and the molecular structure of **1** is shown in Figure 2 (a).



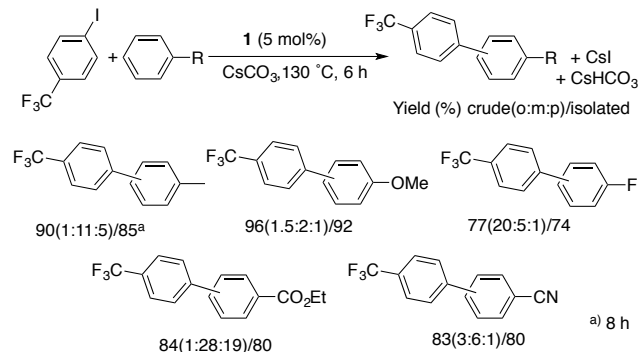
The synthesis of aryl pyridines catalyzed by **1** or a Pd(OAc)₂/bipy-6-OH mixture shows the same regioselectivity (meta-substitution) as those reported for the Pd(OAc)₂/phen catalytic system,¹⁴ but it is faster (6 h vs 30–48 h, Scheme 1 and SI for kinetic details). Aryl iodides with electron withdrawing groups such as *p*-CF₃C₆H₄I are even faster and the reaction is complete in 2 h. The direct arylation of other arenes catalyzed by **1** can also be accomplished in short reaction times (Scheme 2). This reaction does not work with N-chelating ligands such as bipy or phen in the same reaction conditions.



Scheme 1. Direct arylation of pyridines catalyzed by bipy-6-OH palladium complexes.



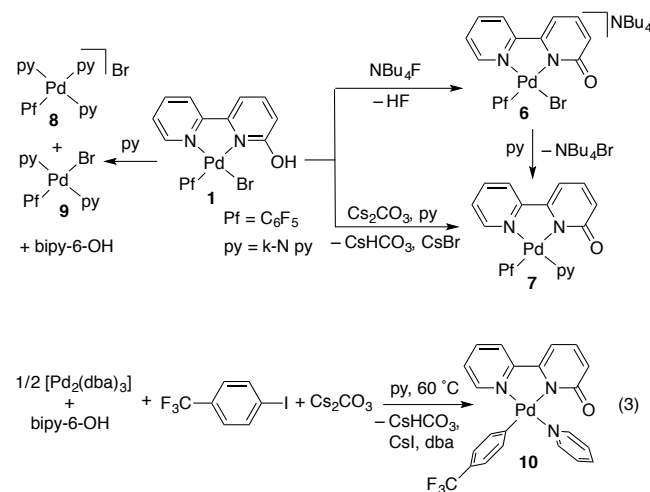
Scheme 2. Direct arylation of arenes catalyzed by bipy-6-OH palladium complexes.



The direct arylation of pyridine was studied in detail, starting with the behavior of complex **1** under conditions relevant to the catalysis. When **1** is dissolved in pyridine, the chelating bipy-6-OH is displaced by the solvent (Scheme 3 and Figure S2). The deprotonated bipy-6-O is a better ligand and complex **7** is the only species observed in pyridine either when a base is added to the mix-

ture formed by **1**+pyridine, or when the independently synthesized **6** is dissolved in pyridine (Scheme 3, Figure S2 and Figure S17 for the molecular structure of **7**). An analogous complex **10** was prepared by oxidative addition of *p*-CF₃C₆H₄I to Pd(0) in pyridine in the presence of Cs₂CO₃ (Eq. 3 and Figure 2b). It is observed in the catalytic coupling of *p*-CF₃C₆H₄I and pyridine, pointing to **10** as the catalyst resting state in the reaction (Figure S1). Both **7** and **10** are efficient catalysts and their activities are equal to that of complex **1** (94-96% crude yield in 2 h in the reaction of *p*-CF₃C₆H₄I and pyridine).

Scheme 3. Behavior of **1** in pyridine.

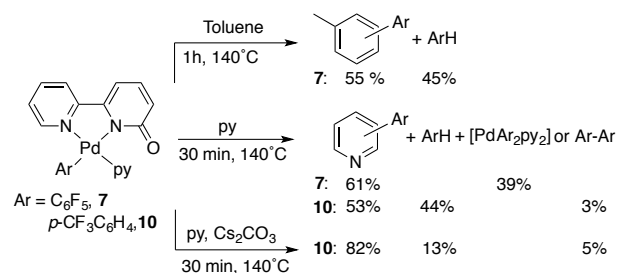


When complex **10** was heated up to 140 °C in pyridine the formation of the Ar-py coupling product was observed as the major product (Scheme 4). This indicates that the ligand is capable of assisting the C-H cleavage. The acid generated in the reaction is responsible for the formation of the reduction product ArH, either directly or through the generation of a Pd-H moiety by protonation of Pd(0), and subsequent H transmetalation in a dimer.¹⁶ In the presence of Cs₂CO₃ the amount of ArH is reduced and Ar-py was observed in 82% yield. The behavior of **7** upon heating in pyridine is analogous and it decomposes to give 61% yield of Ar-py. Interestingly, when **7** was heated in toluene the Ar-Tol coupling product was also observed (Scheme 4). Therefore, bipy-6-O is a strongly coordinating ligand that efficiently cooperates in the cleavage of the C(sp²)-H bond.

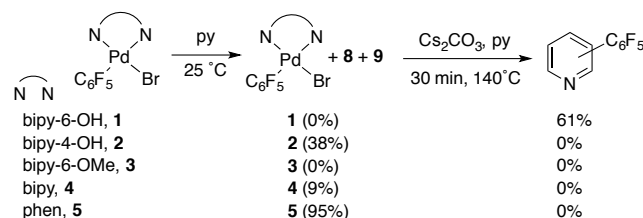
As shown in Scheme 5, when complexes **1-5** are dissolved in pyridine, all the bipyridine neutral ligands are substituted by the solvent and the amount of complex that remains unaltered gives the following trend in coordination ability: bipy-6-OH ≈ bipy-6-OMe < bipy < bipy-4-OH < phen ≈ bipy-6-O ≈ bipy-4-O. As it has been discussed above the anionic bipy-6-O is coordinated to palladium in pyridine and the same behavior was observed for the anionic bipy-4-O (Figure S6). The low activity of bipy-6-OMe in the catalysis could be attributed to its low coordination ability in the catalytic conditions. However, none of the ligands in complexes **2-5** assist the C-H cleavage and they do not form the coupling product C₆F₅-py upon heating in the presence of base, not even the better coordinating bipy-4-OH or phen (Scheme 5 and Table S4).¹⁷

Kinetic measurements were carried out on the coupling reaction shown in Eq. 4 using ¹⁹F NMR (see SI for details). Complex **1** was used as precatalyst but it is transformed into **7** when dissolved in pyridine in the presence of Cs₂CO₃; therefore complex **7** is the actual catalyst used. No induction time was observed in any of our

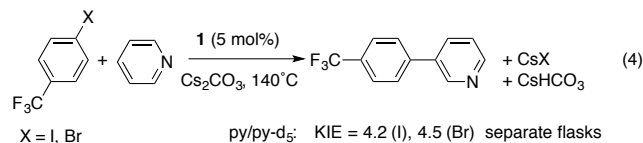
Scheme 4. Cleavage of the C(sp²)-H bond by the coordinated bipy-6-O.



Scheme 5. Decomposition of complexes **1-5** in pyridine



experiments. The reaction is first order in the palladium complex and zero order in the aryl halide. Other aryl halides were also studied and the reaction rate is independent on the ArX concentration for X = Br, I and Ar = *p*-CF₃C₆H₄, *p*-OMeC₆H₄. The amount of free halide does not have any influence in the reaction rate. In contrast, there is a clear kinetic isotope effect when the reactions were carried using pyridine or pyridine-d₅ (Eq. 4).



The coordinated bipy-6-O ligand is capable of bringing about the C-H cleavage of arenes as shown by the decomposition of complexes **7** or **10** (Scheme 4). DFT calculations at the M06 level on this step using complex **10** show that the C-H cleavage assisted by the ligand requires an activation energy of 27.5 kcal mol⁻¹, consistent with the temperature and reaction times required for the catalysis. The process involves the rearrangement of the coordinated κ-N to η²-pyridine followed by C-H cleavage assisted by the ligand (Figure 3 and Figure S78). The calculated KIE = 3.58 is also consistent with the experimental results. Calculations show that the meta C-H cleavage is favored by 1.6 and 3.1 kcal mol⁻¹ over the para or ortho positions respectively (Figure S76).¹⁸ The alternative pathway corresponding to a C-H cleavage assisted by Cs₂CO₃ was explored but the barrier for this process is higher (30.9 kcal mol⁻¹) than the ligand assisted pathway and it involves the previous substitution of the coordinated pyridine by the carbonate (Figure S75).

With these data the plausible catalytic cycle is represented in Scheme 6. The oxidative addition of ArX to a Pd(0) complex in the presence of the ligand and the base is possible (Eq. 3) and it is fast in catalytic conditions. The substitution of the halide by pyridine is also fast (Scheme 3) to give complex **10**, observed during the reaction, as the resting state of the catalyst. The subsequent ligand-assisted C-H cleavage is the rate-determining step and the product-forming reductive elimination follows to give a Pd(0) that re-enters the cycle. The fact that the neutral bipy-6-OH is easily

displaced on Pd(II) by free pyridine in excess supports the occurrence of anionic coordinated bipy-6-O throughout the cycle.¹⁹

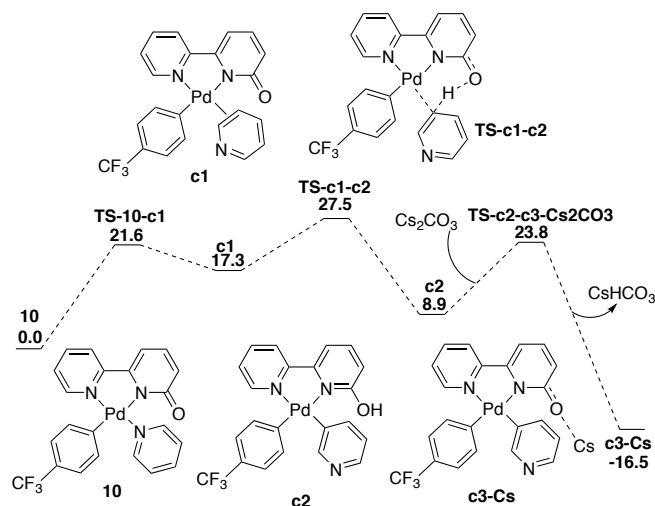
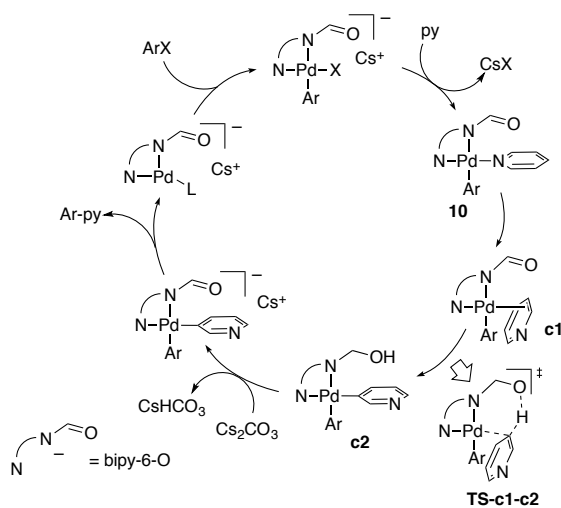


Figure 3. Free energy profile for the bipy-6-O assisted cleavage of the meta C-H bond of pyridine. Energies in kcal mol⁻¹.

Scheme 6. Catalytic cycle for the direct arylation of pyridine.



In conclusion, we have experimentally tested that the chelating anionic ligand 2, 2'-bipyridin-6-onate is an effective cooperating ligand for the coupling of arenes. The coordination of a base is not required for C-H activation since this role is played by the ligand. The direct arylation follows a Pd(0)/Pd(II) catalytic cycle where only two available coordination sites on the metal are necessary and therefore this strongly bound chelating ligand can be used without compromising the coordination of the substrates to the metal.

ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization, kinetic and X-ray structure determination data, selected spectra, and computational details including cartesian coordinates and calculated potential energies

(PDF). A combined CIF file for complexes **1**, **7** and **10**. The Supporting Information is available free of charge on the ACS Publications website.

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Notes

The authors declare no competing financial interests.

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