[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 coupling reactions, there is no need to presynthesize either one or both of the reagents from the parent hydrocarbons, making the processes more sustainable. An extraordinary progress has been made in the last decade to extend the scope of these reactions and the number of available catalyst systems 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 advisable. The most common pathway for breaking the C-H bond is the so called concerted metalation-deprotonation mechanism (CMD) where a coordinated base, commonly a 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 that have a suitable structure to play this dual role have been successfully used in Pd-catalyzed C-C couplings involving C-H activation. Most prominent are the N-monoprotected aminoacids introduced by the group of J. –Q. Yu, that are efficient in several transformations of C(sp^2)H and C(sp^3)H bonds,[4] including enantioselective couplings.[5] The involvement of the OAc or Boc protecting groups of the coordinated ligand in the C-H cleavage has been proposed as one of the reasons for the

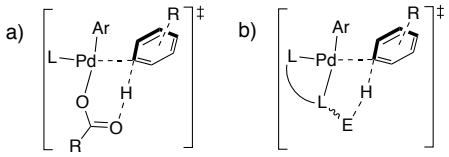


Figure 1. Representation of CMD transition states for a C-H activation by a carboxylate (a) or a basic group, E, on the ligand (b).

success of these ligands, 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 hydrogenation reactions,[9,10] 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.[11] Related monodentate pyridone derivatives have also been recently used to accelerate coupling reactions of arenes.[12] Again, the involvement of the ligand in the C-H activation step is plausible and has just been supported by DFT calculations.[12d]

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.[13,14] 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 and 2, Table 1).[13] 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). The amount of ligand and base can be reduced with no erosion of the reaction yield (cf. entries 2 and 5, Table 1), but the use of a base

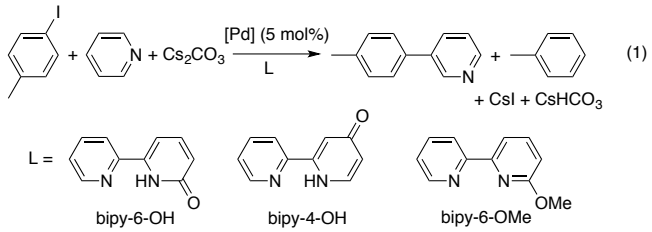


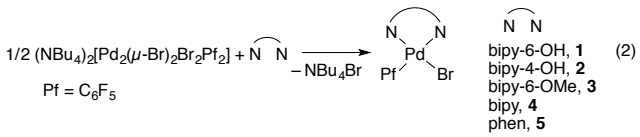
Table 1. Direct arylation of pyridine with *p*-iodo toluene using different precatalyst.[a]

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-6-OH (6)	1	88 (97)	90 (100)
6	**1**	-	1	80 (100)	

a) Reaction conditions: ArI (0.5 mmol), pyridine (3.0 mL), [Pd] (5 mol %), Cs_2CO_3 as base, 140 ˚C. b) Determined by integration of ^{1}H NMR signals (methyl region). The formation of ArH (toluene) accounts for the differences between crude yield and conversion. The coupling product is a mixture of regioisomers: o:m:p = 1:14:1.

different to Cs_2CO_3 or a lower temperature strongly decreased the yield (see SI for control experiments and additional data). The well-defined precursor $[Pd(bipy\text{-}6\text{-}OH)Br(C_6F_5)]$ (**1**) was also tested instead of the $Pd(OAc)_2$/ligand mixture. **1** is a plausible model intermediate in the catalytic reaction, after oxidative addition of the ArX, and it also catalyzes the reaction (entry 6, Table 1). The synthetic route used for complex **1** and other analogous $[PdBr(C_6F_5)(N\text{-}N)]$ 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 scope and regioselectivity (meta-substitution) as those reported for the $Pd(OAc)_2$/phen catalytic system,[13] but it is 5-8 times faster (usually 6 h vs 30-48 h, Scheme 1). Aryl iodides with electron withdrawing groups such as *p*-$CF_3C_6H_4I$ are even faster and the reaction is complete in 2 h. As shown in Scheme 2, the direct arylation of other arenes catalyzed by **1** can also be accomplished in short reaction times. This reaction does not work with N-chelating ligands such as bipy or phen.



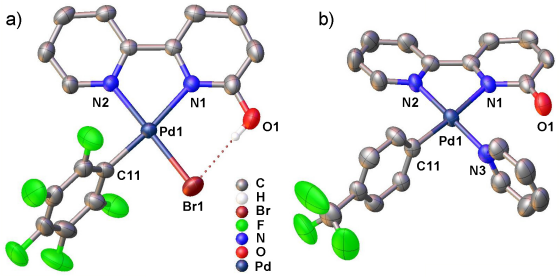
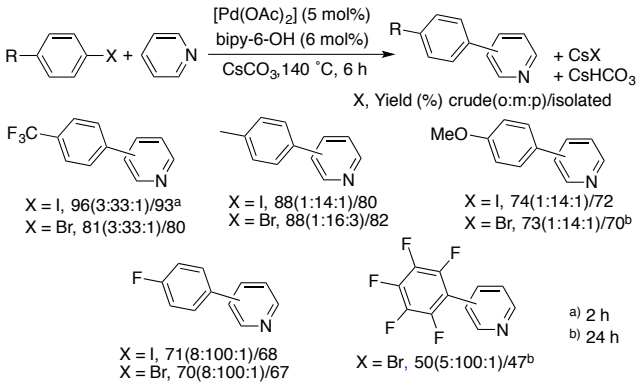
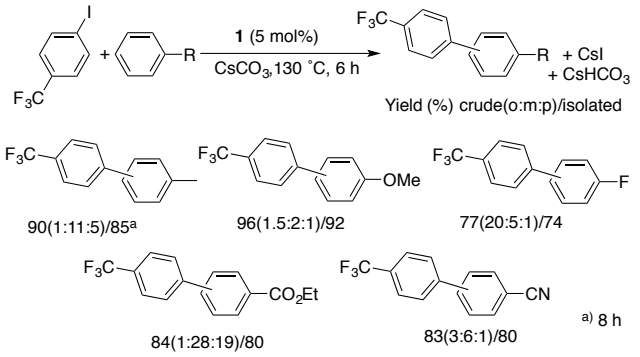


Figure 2. Molecular structures of complexes: **1** (a) and **10** (b). ORTEP plots (40% probability ellipsoids) are shown. Hydrogen atoms are omitted for clarity except that of the OH group in **1**, that shows a H-bond with the Br ligand.

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



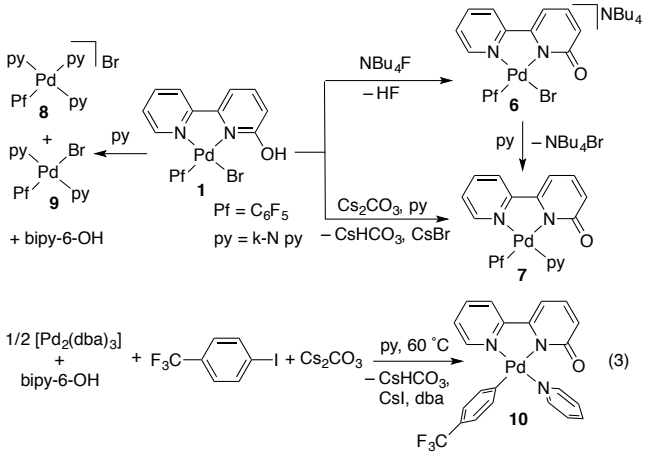
Scheme 2. Direct arylation of arenes catalyzed by bipy-6-OH palladium complexes.



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 completely displaced by the coordinating solvent (Scheme 3). 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 mixture formed by **1** in this solvent, or when the independently synthesized **6** is dissolved in pyridine (Scheme 3 and Figure S8 for the molecular structure of **7**). An analogous complex **10** was prepared by oxidative addition of *p*-$CF_3C_6H_4I$ to Pd(0) in pyridine in the presence of Cs_2CO_3 (Eq. 3 and Figure 2b).

It is observed in the catalytic coupling of *p*-$CF_3C_6H_4I$ and pyridine, pointing to **10** as the catalyst resting state in the reaction. Both **7** and **10** catalyze the direct arylation of pyridine and their activities are equal to that of complex **1** (94-96% crude yield in 2 h in the reaction of *p*-$CF_3C_6H_4I$ and pyridine).

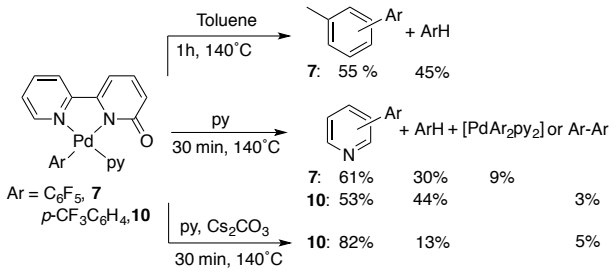
Scheme 3. Behavior of 1 in pyridine as solvent.



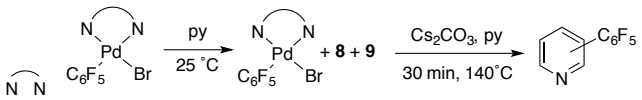
When complex **10** was heated up to 140 ˚C in pyridine the formation of the Ar-Py coupling product was observed as the major product (Scheme 4). This clearly indicates that the ligand is capable of assisting the C-H cleavage. The acid generated in the reaction is responsible for the formation of the reduction product ArH, either directly or through the generation of a Pd-H moiety by protonation of Pd(0), and subsequent H transmetalation.[15] In the presence of Cs_2CO_3 the amount of ArH is reduced and the coupling product 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(sp^2)-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. As it has been discussed above the anionic bipy-6-O is coordinated to palladium in pyridine. 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 C_6F_5-py upon heating in the presence of a base, not even the better coordinating bipy-4-OH or phen (see Scheme 5, and Table S4).

Scheme 4. Cleavage of the C(sp^2)-H bond by the coordinated Bipy-6-O.

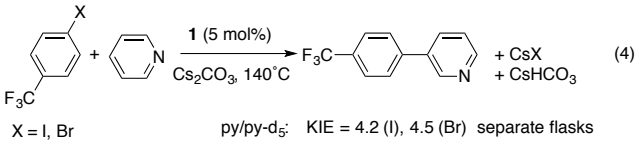


Scheme 5. Decomposition of complexes 1-5 in pyridine



bipy-6-OH, **1**	**1** (0%)	61%
bipy-4-OH, **2**	**2** (38%)	0%
bipy-6-OMe, **3**	**3** (0%)	0%
bipy, **4**	**4** (9%)	0%
phen, **5**	**5** (95%)	0%

Kinetic measurements were carried out on the coupling reaction shown in Eq. 4 using ^{19}F NMR (see supporting information for details). Complex **1** was used as precatalyst but it is transformed in **7** when dissolved in pyridine in the presence of Cs_2CO_3; therefore complex **7** is the actual catalyst used. No induction time was observed in any of our 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*-$CF_3C_6H_4$, *p*-$OMeC_6H_4$. 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-d_5 (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 catalytic reaction. The process involves the rearrangement of the coordinated κ–N to an η^2-pyridine followed by the C-H cleavage assisted by the ligand (Figure 3 and Figure S59). The calculated KIE = 3.58 is also consistent with our experimental results. Calculations show that the meta C-H cleavage is clearly favored by 1.6 and 3.1 kcal mol^{-1} over the para or ortho positions respectively (see Figure S57).[16]

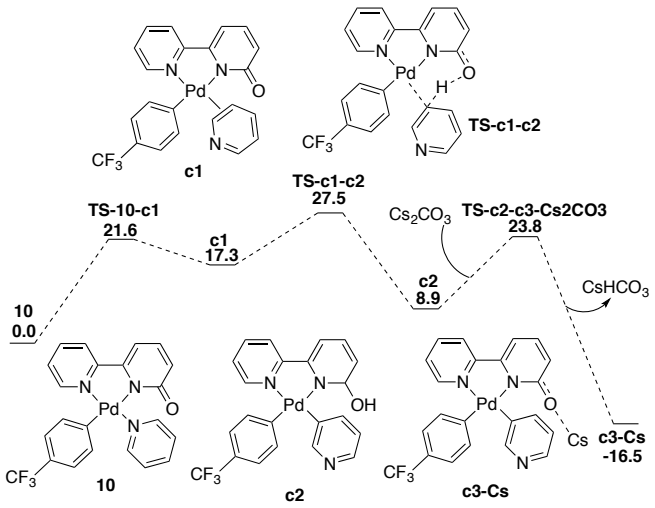
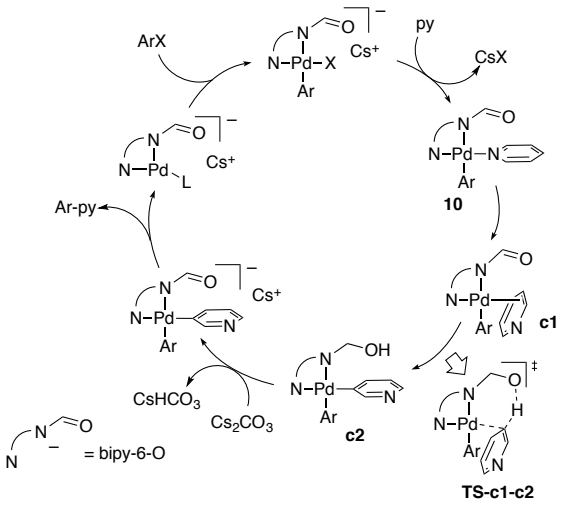


Figure 3. Free energy profile for the bipy-6-O assisted cleavage of the meta C-H bond of pyridine. Energies in kcal/mol.

The alternative pathway corresponding to a C-H cleavage assisted by Cs_2CO_3 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 (see Figure S56).

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 calculations show that the reductive elimination from an anionic [Pd(bipy-6-O)Ar(σ–pyridyl)]$^-$ is clearly more favorable than from a neutral [Pd(bipy-6-OH)Ar(σ–pyridyl)] (Figure S58). This finding and the fact that the neutral bipy-6-OH is easily displaced on Pd(II) by free pyridine in excess support the occurrence of anionic coordinated bipy-6-O throughout the cycle.

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. Thus, 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 and chelating ligand can be used without compromising the coordination of the substrates to the metal. The mechanism proposed by Yu's group using the Pd/phen catalytic system for the direct arylation of pyridine involves a Pd(II)/Pd(IV) cycle.[13] A mechanism analogous to that in Scheme 6 would require an additional coordination site for the base and could only be operative if an external H abstraction by the base takes place, which might also be feasible, but more energy demanding.

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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REFERENCES

(1) (a) Campeau, L. C.; Fagnou, K. Palladium-catalyzed direct arylation of simple arenes in synthesis of biaryl molecules. *Chem. Commun.* **2006**, 1253–1264. (b) Ackermann, L.; Vicente, R.; Kapdi, A. R.; Transition-Metal-Catalyzed Direct Arylation of (Hetero)Arenes by C-H Bond Cleavage. *Angew. Chem. Int. Ed.* **2009**, *48*, 9792–9826. (c) Lyons, T. W.; Sanford, M. S.; Palladium-Catalyzed Ligand-Directed C-H Functionalization Reactions. *Chem. Rev.* **2010**, *110*, 1147–1169. (d) Yang, Y.; Lan, J.; You, J. Oxidative C−H/C−H Coupling Reactions between Two (Hetero)arenes. *Chem. Rev.* **2017**, *117*, 8787−8863. (e) He, J.; Wasa, M.; Chan, K. S. L.; Shao, Q. Yu, J. –Q. Palladium-Catalyzed Transformations of Alkyl C−H Bonds. *Chem. Rev.* **2017**, *117*, 8754−8786. (f) Newton, C. G.; Wang, S. –G.; Oliveira, C. C.; Cramer, N. Catalytic Enantioselective Transformations Involving C−H Bond Cleavage by Transition-Metal Complexes. *Chem. Rev.* **2017**, *117*, 8908−8976.

(2) (a) Biswas, B.; Sugimoto, M.; Sakaki, S. C-H Bond Activation of Benzene and Methane by $M(\eta^2\text{-}O_2CH)_2$ (M = Pd or Pt). A Theoretical Study. *Organometallics* **2000**, *19*, 3895-3908. (b) Davies, D. L.; Donald, S. M. A.; Macgregor, S. A. Computational Study of the Mechanism of Cyclometalation by Palladium Acetate. *J. Am. Chem. Soc.* **2005**, *127*, 13754-13755. (c) García-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. Proton Abstraction Mechanism for the Palladium-Catalyzed Intramolecular Arylation. *J. Am. Chem. Soc.* **2006**, *128*, 1066-1067. (d) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. Catalytic Intermolecular Direct Arylation of Perfluorobenzenes. *J. Am. Chem. Soc.* **2006**, *128*, 8754-8756.

(3) (a) Ackermann, L. Carboxylate-Assisted Transition-Metal-Catalyzed C-H Bond Functionalizations: Mechanism and Scope. *Chem. Rev.* **2011**, *111*, 1315–1345. (b) Davies, D. L. Macgregor, S. A.; McMullin, C. L. Computational Studies of Carboxylate-Assisted C−H Activation and Functionalization at Group 8−10 Transition Metal Centers. *Chem. Rev.* **2017**, *117*, 8649−8709.

(4) (a) Wang, D. –H.; Engle, K. M.; Shi, B. –F.; Yu, J. –Q. Ligand-Enabled Reactivity and Selectivity in a Synthetically Versatile Aryl C–H Olefination. *Science*, **2010**, *327*, 315-319. (b) Engle, K. M.; Wang, D. –H.; Yu, J. –Q. Ligand-Accelerated C-H Activation Reactions: Evidence for a Switch of Mechanism. *J. Am. Chem. Soc.* **2010**, *132*, 14137-14151**.** (c) Engle, K. M.; Thuy-Boun, P. S.; Dang, M.; Yu, J. -Q. Ligand-Accelerated Cross-Coupling of $C(sp^2)$-H Bonds with Arylboron Reagents. *J. Am. Chem. Soc.* **2011**, *133*, 18183–18193. (d) Tang, R. –Y.; Li, G.; Yu, J. –Q. Conformation-induced remote meta-C–H activation of amines. *Nature*, **2014**, *507*, 215-220.

(5) (a) Shi, B. –F.; Maugel, N.; Zhang, Y. –H. Yu, J. –Q. Pd^{II}-Catalyzed Enantioselective Activation of $C(sp^2)$-H and $C(sp^3)$-H Bonds Using Monoprotected Amino Acids as Chiral Ligands. *Angew. Chem. Int. Ed.* **2008**, *47*, 4882–4886. (b) Shi, B. –F.; Zhang, Y. –H.; Lam, J. K.; Wang, D. –H.; Yu, J. –Q. Pd(II)-Catalyzed Enantioselective C-H Olefination of Diphenylacetic Acids. *J. Am. Chem. Soc.* **2010**, *132*, 460-461. (c)

Xiao, K. –J.; Chu, L.; Yu, J. –Q. Enantioselective C-H Olefination of α-Hydroxy and α-Amino Phenylacetic Acids by Kinetic Resolution. *Angew. Chem. Int. Ed.* **2016**, *55*, 2856-2860.

(6) (a) Cheng, G. –J.; Yang, Y. –F.; Liu, P.; Chen, P.; Sun, T. –Y.; Li, G.; Zhang, X.; Houk, K. N.; Yu, J. –Q.; Wu, Y. D. Role of N-Acyl Amino Acid Ligands in Pd(II)-Catalyzed Remote C−H Activation of Tethered Arenes. *J. Am. Chem. Soc.* **2014**, *136*, 894−897. (b) Cheng, G. –J.; Chen, P.; Sun, T. –Y.; Zhang, X.; Yu, J. –Q.; Wu, Y. –D. A Combined IM-MS/DFT Study on [Pd(MPAA)]-Catalyzed Enantioselective C-H Activation: Relay of Chirality through a Rigid Framework. *Chem. Eur. J.* **2015**, *21*, 11180 -11188. (c) Haines, B. E.; Yu, J. –Q.; Musaev, D. G. Enantioselectivity Model for Pd-Catalyzed C−H Functionalization Mediated by the Mono-N-protected Amino Acid (MPAA) Family of Ligands. *ACS Catal.* **2017**, *7*, 4344−4354.

(7) (a) Musaev, D. G.; Kaledin, A.; Shi, B. –F.; Yu, J. –Q. Key Mechanistic Features of Enantioselective C−H Bond Activation Reactions Catalyzed by [(Chiral Mono-N-Protected Amino Acid)− Pd(II)] Complexes. *J. Am. Chem.Soc.* **2012**, *134*, 1690−1698. (b) Cong, X.; Tang, H.; Wu, C. Zeng, X. Role of Mono-N-protected Amino Acid Ligands in Palladium(II)-Catalyzed Dehydrogenative Heck Reactions of Electron-Deficient (Hetero)arenes: Experimental and Computational Studies. *Organometallics* **2013**, *32*, 6565−6575. (c) Haines B. E.; Musaev, D. G. Factors Impacting the Mechanism of the Mono-N-Protected Amino Acid Ligand-Assisted and Directing-Group-Mediated C−H Activation Catalyzed by Pd(II) Complex. *ACS Catal.* **2015**, *5*, 830−840. (d) Plata, R. E.; Hill, D. E.; Haines, B. E.; Musaev, D. G.; Chu, L.; Hickey, D. P.; Sigman, M. S.; Yu, J. Q.; Blackmond, D. G. A Role for Pd(IV) in Catalytic Enantioselective C−H Functionalization with Monoprotected Amino Acid Ligands under Mild Conditions. *J. Am. Chem. Soc.* **2017**, *139*, 9238−9245.

(8) (a) Wang, W. –H. Muckerman, J. T.; Fujita, E.; Himeda, Y. Mechanistic Insight through Factors Controlling Effective Hydrogenation of CO_2 Catalyzed by Bioinspired Proton-Responsive Iridium(III) Complexes. *ACS Catal.* **2013**, *3*, 856-860. (b) Zeng, G.; Sakaki, S.; Fujita, K.; Sano, H; Yamaguchi, R. Efficient Catalyst for Acceptorless Alcohol Dehydrogenation: Interplay of Theoretical and Experimental Studies. *ACS Catal.* **2014**, *4*, 1010-1020. (c) Fujita, K.; Tanaka, Y.; Kobayashi, M.; Yamaguchi, R. Homogeneous Perdehydrogenation and Perhydrogenation of Fused Bicyclic N-Heterocycles Catalyzed by Iridium Complexes Bearing a Functional Bipyridonate Ligand. *J. Am. Chem. Soc.* **2014**, *136*, 4829-4832. (d) Wang, R.; Ma, J.; Li, F. Synthesis of α-Alkylated Ketones via Tandem Acceptorless Dehydrogenation/α-Alkylation from Secondary and Primary Alcohols Catalyzed by Metal−Ligand Bifunctional Iridium Complex [Cp*Ir(2,2′- bpyO)(H_2O)]. *J. Org. Chem.* **2015**, *80*, 10769−10776.

(9) (a) Nieto, I.; Livings, M. S.; Sacci III, J. B.; Reuther, L. E.; Zeller, M.; Papish, E. T. Transfer Hydrogenation in Water via a Ruthenium Catalyst with OH Groups near the Metal Center on a bipy Scaffold. *Organometallics* **2011**, *30*, 6339−6342. (b) Moore, C. M.; Szymczak, N. K. 6,6'-Dihydroxy terpyridine: a proton-responsive bifunctional ligand and its application in catalytic transfer hydrogenation of ketones. *Chem. Commun.,* **2013**, *49*, 400-402. (c) Roy, B. C.; Chakrabarti, K.; Shee, S.; Paul, S.; Kundu, S. Bifunctional Ru^{II}-Complex-Catalysed Tandem C-C Bond Formation: Efficient and Atom Economical Strategy for the Utilisation of Alcohols as Alkylating Agents. *Chem. Eur. J.* **2016**, *22*, 18147 – 18155.

(10) Khusnutdinova, J. R.; Milstein, D. Metal–Ligand Cooperation. *Angew. Chem. Int. Ed.* **2015**, *54*, 12236-12273

(11) Ying, C. –H.; Yan, S. –B.; Duan, W. –L. 2-Hydroxy-1,10-phenanthroline vs 1,10-Phenanthroline: Significant Ligand Acceleration Effects in the Palladium-Catalyzed Oxidative Heck Reaction of Arenes. *Org. Lett.* **2014**, *16*, 500-503. (b) Ying, C. –H.; Duan, W. –L. Palladium-catalyzed direct C–H allylation of arenes without directing groups. *Org. Chem. Front.* **2014**, *1*, 546–550

(12) (a) Wang, P.; Li, G. –C.; Jain, P.; Farmer, M. E.; He, J.; Shen, P. –X.; Yu, J. –Q. Ligand-Promoted meta-C−H Amination and Alkynylation. *J. Am. Chem. Soc.* **2016**, *138*, 14092−14099. (b) Shi, H.; Wang, P.; Suzuki, S.; Farmer, M. E.; Yu, J. –Q. Ligand Promoted meta-C−H Chlorination of Anilines and Phenols. *J. Am. Chem. Soc.* **2016**, *138*, 14876−14879. (c) Wang, P.; Farmer, M. E.; Yu, J. –Q. Ligand-Promoted meta-C–H Functionalization of Benzylamines. *Angew. Chem. Int. Ed.* **2017**, *56*, 5125 – 5129. (d) Wang, P.; Verma, P.; Xia, G.; Shi, J.; Qiao, J. X.; Tao, S.; Cheng, P. T. W.; Poss, M. A.; Farmer, M. E.; Yeung, K. –S.; Yu, J. –Q. Ligand-accelerated non-directed C–H functionalization of arenes. *Nature*, **2017**, *551*, 489-493.

(13) Ye, M.; Gao, G- -L. Edmunds, A. J. F.; Worthington, P. A.; Morris, J. A.; Yu, J. –Q. Ligand-Promoted C3-Selective Arylation of Pyridines with Pd Catalysts: Gram-Scale Synthesis of (±)-Preclamol. *J. Am. Chem. Soc.* **2011**, *133*, 19090–19093.

(14) For a complete account of the methods for direct functionalization of pyridines: Murakami, K.; Yamada, S.; Kaneda, T.; Itami, K. C−H Functionalization of Azines. *Chem. Rev.* **2017**, *117*, 9302−9332.

(15) (a) Albéniz, A. C.; Espinet, P.; Lin, Y. –S. Involvement of Intramolecular Hydride Transfer in the Formation of Alkanes from Palladium Alkyls. *Organometallics*, **1997**, *16*, 4030-4032. (b) Martín-Ruiz, B.; Pérez-Ortega, I.; Albéniz, A. C. *Organometallics*, **2018**, *37*, 1665−1670.

(16) Petit, A.; Flygare, J.; Miller, A. T.; Winkel, G.; Ess, D. H. Transition-State Metal Aryl Bond Stability Determines Regioselectivity in Palladium Acetate Mediated C H Bond Activation of Heteroarenes. *Org. Lett.* **2012**, *14*, 3680-3683.

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