

Elucidating Reactivity Differences in Palladium-Catalyzed Coupling Processes: The Chemistry of Palladium Hydrides

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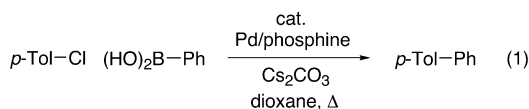
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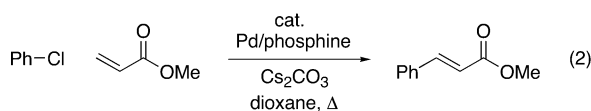
Tremendous progress has recently been described in the development of highly active palladium-based catalysts for cross-coupling reactions of aryl halides and sulfonates.¹ For example, a broad range of couplings of previously “unreactive” aryl chlorides can now be achieved through the use of any of an array of ligands (e.g., aryldialkylphosphines, trialkylphosphines, and carbenes).²

Compared with *cross-coupling* processes, advances in the development of more reactive catalysts for *Heck arylations*³ have been limited—to date, only Pd/P(*t*-Bu)₃ has been shown to serve as an efficient catalyst for couplings of a variety of aryl chlorides and olefins under relatively mild conditions.^{4,5} This dichotomy in progress between cross-couplings and Heck arylations is intriguing in light of the traditional view that the poor reactivity of aryl chlorides in coupling processes is due to their reluctance to oxidatively add to Pd(0) complexes.⁶ Were this the only significant barrier to success, then palladium/ligand combinations that have proved effective for cross-couplings of aryl chlorides should also be effective for Heck reactions of these compounds.

Equations 1 and 2 provide an illustration of this inability to simply extrapolate from success in cross-couplings to success in Heck arylations. Thus, whereas in our 1998 study of the Suzuki reaction we observed that PCy₃ and P(*t*-Bu)₃ furnish comparably active catalysts for the cross-coupling of an aryl chloride (eq 1),⁷ in our 1999 investigation of the Heck reaction, we found Pd/PCy₃ to be ineffective under conditions in which Pd/P(*t*-Bu)₃ is active (eq 2).^{4b,8}

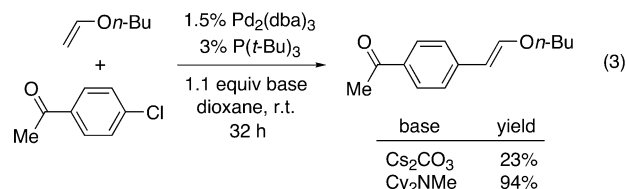


phosphine	yield
PCy ₃	75%
P(<i>t</i> -Bu) ₃	86%

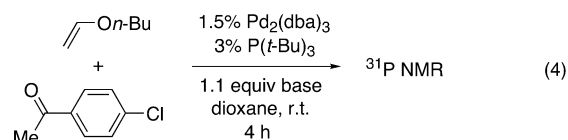


phosphine	yield
PCy ₃	<2%
P(<i>t</i> -Bu) ₃	56%

In the standard catalytic cycle for Heck arylations, the role of the Brønsted base is to mediate reductive elimination of HX from L₂PdHX to regenerate a Pd(0) adduct (Figure 1).³ In our earlier studies of Pd/P(*t*-Bu)₃-catalyzed Heck reactions, we determined that the choice of base has a large impact on the efficiency of the process (e.g., eq 3).^{4a} We have now monitored these arylations by ³¹P NMR spectroscopy, and we have discovered that the resting state of the catalytic reaction depends on the Brønsted base: in the presence of Cs₂CO₃, L₂PdHCl is the only detectable palladium–phosphine complex, whereas in the case of Cy₂NMe only PdL₂ is observed (eq 4).⁹ To the best of our knowledge, the arylation mediated by Cs₂CO₃ represents the first time that a palladium hydride has been identified during the course of a catalyzed Heck reaction.¹⁰



base	yield
Cs ₂ CO ₃	23%
Cy ₂ NMe	94%

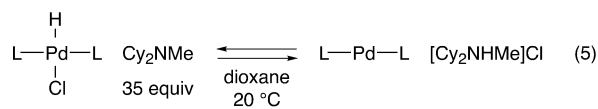


base	L ₂ PdHCl : PdL ₂
Cs ₂ CO ₃ (~8% conversion)	>98 : <2
Cy ₂ NMe (~30% conversion)	<2 : >98

L = P(*t*-Bu)₃

The ³¹P NMR data in eq 4 indicate that Cs₂CO₃ is not especially effective at regenerating Pd(0) from L₂PdHCl, correlating with the lower coupling activity of Pd/P(*t*-Bu)₃ in the presence of this particular Brønsted base. Interestingly, discussions of the Heck reaction rarely focus on the Pd(0)-regeneration step of the catalytic cycle; indeed, we are not aware of any mechanistic work that has specifically explored reductive elimination of H–X within the context of reactivity studies of Heck arylation catalysts.^{11,12}

Stimulated by the above observations, we initiated an investigation of base-mediated reductive elimination of HCl from L₂PdHCl adducts (L = P(*t*-Bu)₃ and PCy₃). The results of this study surprised us: for the P(*t*-Bu)₃-derived complex, reaction with Cy₂NMe leads to the anticipated elimination to cleanly generate PdL₂ (Δ*G*[‡] = 22 kcal/mol at 20 °C), whereas for the analogous PCy₃ adduct the equilibrium favors L₂PdHCl (eq 5).¹³



ligand	L ₂ PdHCl : PdL ₂
P(<i>t</i> -Bu) ₃	<2 : >98
PCy ₃	>98 : <2

Although we had expected that there might be a *kinetic* impediment to base-mediated reductive elimination from L₂PdHCl complexes (e.g., due to the low solubility of a particular Brønsted base), we had not anticipated that, for some adducts, Cy₂NMe-induced elimination would not be favored *thermodynamically*. Of course, one potential explanation for the divergent reactivity illustrated in eq 5 is the different steric demand of P(*t*-Bu)₃ and PCy₃.¹⁴ To obtain a clearer picture of this possibility, we crystallographically characterized the two L₂PdHCl complexes (Figure 2).¹⁵ In the case of the PCy₃ adduct, the P–Pd–P geometry is linear (180°). In contrast, for the P(*t*-Bu)₃ complex, the P–Pd–P angle is 161°; specifically, the P(*t*-Bu)₃ ligands are bent away from Cl, at the cost of increased interaction between the two phosphines and with the hydride. These

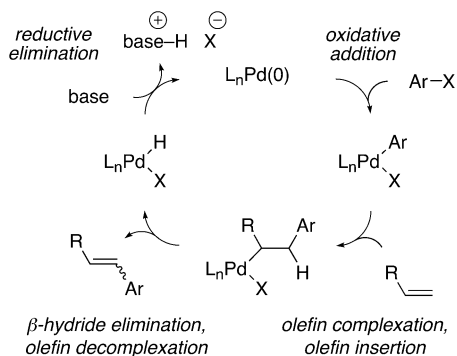


Figure 1. Generalized catalytic cycle for Heck arylations.

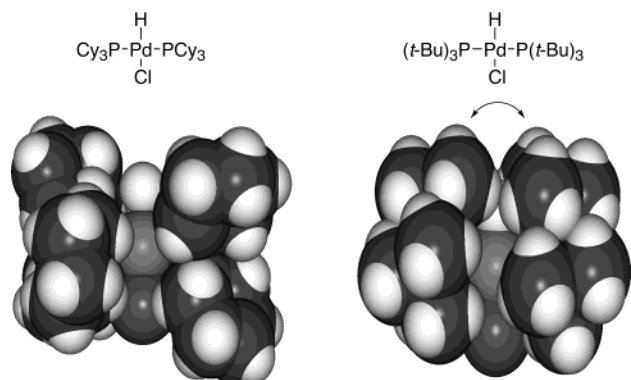
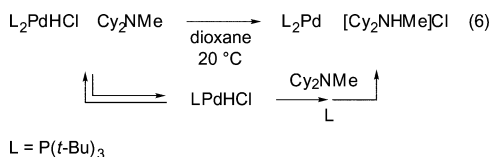


Figure 2. Space-filling (van der Waals radii) models based on the X-ray crystal structures of L_2PdHCl (left: $\text{L} = \text{PCy}_3$; right: $\text{L} = \text{P}(t\text{-Bu})_3$).

unfavorable steric effects are relieved upon reductive elimination to generate $\text{Pd}(\text{P}(t\text{-Bu})_3)_2$, thereby providing a driving force for this process.

On the basis of these data, we postulate that the comparatively low activity of Pd/PCy_3 as a catalyst for Heck reactions of aryl chlorides (e.g., eq 2) may be attributable in part to the relative reluctance of $(\text{PCy}_3)_2\text{PdHCl}$ to undergo reductive elimination in the presence of Cy_2NMe , the critical $\text{Pd}(0)$ -regenerating step of the catalytic cycle (Figure 1). For $(\text{P}(t\text{-Bu})_3)_2\text{PdHCl}$, on the other hand, loss of HCl is favored and facile.

We have examined the kinetics of the Cy_2NMe -mediated reductive elimination of HCl from L_2PdHCl ($\text{L} = \text{P}(t\text{-Bu})_3$; eq 6). The rate of the reaction is first order in L_2PdHCl , zero order in Cy_2NMe , and inhibited by the addition of $\text{P}(t\text{-Bu})_3$.¹⁶ These data are consistent with a mechanism for reductive elimination that involves an initial dissociation of L from L_2PdHCl (eq 6).



In summary, we have described a series of studies that provide insight into the Heck arylation process. Specifically, we have detected, for the first time, the postulated palladium-hydride intermediate (L_2PdHX) in the catalytic cycle. We have determined that the base-mediated $\text{Pd}(0)$ -regeneration step ($\text{L}_2\text{PdHX} \rightarrow \text{PdL}_2$) of the cycle can be kinetically slow and thermodynamically unfavorable. This reductive elimination process is remarkably sensitive to the structure of L (PCy_3 vs $\text{P}(t\text{-Bu})_3$), which we believe, on the basis of crystallographic studies, may be a consequence of steric effects. Finally, we have correlated slow rates of Heck arylation with reluctant reductive elimination of L_2PdHX , furnishing a possible rationaliza-

tion for our observed Brønsted-base (Cs_2CO_3 vs Cy_2NMe) and ligand (PCy_3 vs $\text{P}(t\text{-Bu})_3$) effects. Additional mechanistic studies of palladium-catalyzed coupling processes, as well as the development of Heck-type reactions of alkyl electrophiles, are underway.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (2) For a review of palladium-catalyzed coupling reactions of aryl chlorides, see: Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176–4211.
- (3) For an overview, see: Negishi, E.-i., Ed. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Wiley-Interscience: New York, 2002; Chapter IV.
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- (5) Other catalysts that effect Heck couplings of aryl chlorides have been described, but relatively high reaction temperatures are required and a limited range of reaction partners has been explored. For some early examples, see ref 2.
- (6) For discussions, see: (a) Grushin, V. V.; Alper, H. In *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Springer-Verlag: Berlin, 1999; pp 193–226. (b) Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047–1062.
- (7) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387–3388.
- (8) This difference in reactivity has been confirmed by others; for example, see: Galardon, E.; Ramdeehul, S.; Brown, J. M.; Cowley, A.; Hii, K. K.; Jutand, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1760–1763.
- (9) In contrast, for Heck reactions catalyzed by palladacycles, the resting state of the catalytic cycle is a species derived from the oxidative addition of Ar-X to $\text{Pd}(0)$: Rosner, T.; Le Bars, J.; Pfaltz, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2001**, *123*, 1848–1855.
- (10) In a recent review of Hydridopalladium Complexes [Hii, K. K. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., Ed.; Wiley-Interscience: New York, 2002; Chapter II.2.5], Hii has noted that hydridopalladium complexes “have never been detected under true catalytic conditions...The involvement of these species in the β -hydrogen elimination step is...only implied based on mechanistic considerations.”
- (11) Jeffery has postulated that the success of the “Jeffery conditions” for Heck reactions of aryl and vinyl iodides ($\text{Pd}(\text{OAc})_2$, HCO_3^- , R_4NX) may be attributable in part to efficient regeneration of $\text{Pd}(0)$: Jeffery, T. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI: London, 1996; Vol. 5, pp 153–260.
- (12) For reviews of palladium-hydride chemistry, see: (a) Hii, K. K. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., Ed.; Wiley-Interscience: New York, 2002; Chapter II.2.5. (b) Grushin, V. V. *Chem. Rev.* **1996**, *96*, 2011–2033.
- (13) Notes: (a) To mimic the stoichiometry of a palladium-catalyzed Heck reaction, we employ a large excess (35 equiv) of Cy_2NMe . (b) The equilibrium ratios provided in eq 5 were confirmed by treating PdL_2 with $[\text{Cy}_2\text{NHMe}]\text{Cl}$ (1 equiv) in the presence of Cy_2NMe (34 equiv).
- (14) Electronic considerations do not appear to furnish a suitable explanation, since $\text{P}(t\text{-Bu})_3$ is generally regarded as more electron-donating than PCy_3 , which should lead to a more stable $\text{Pd}(\text{II})$ complex.
- (15) Notes: (a) The hydrides in the crystal structures have not been located but are modeled for illustrative purposes (see the Supporting Information for details). (b) Pd-P bond lengths for L_2PdHCl : 2.3058(8) Å for $\text{L} = \text{PCy}_3$; 2.361(11) Å for $\text{L} = \text{P}(t\text{-Bu})_3$.
- (16) Notes: (a) During the course of the reductive elimination, no intermediate is evident by ^{31}P NMR spectroscopy. (b) A preliminary kinetics study indicates that $k_{\text{H}}/k_{\text{D}} \approx 1.0\text{--}1.5$ for reactions of $\text{L}_2\text{PdHCl}/\text{L}_2\text{PdDCl}$.

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