

Rate and Mechanism of the Heck Reactions of Arylpalladium Complexes Ligated by a Bidentate P,P Ligand with an Electron-Rich Alkene (Isobutyl Vinyl Ether)

Christian Amatore,* Béatrice Godin, Anny Jutand,* and Frédéric Lemaître

Département de Chimie, Ecole Normale Supérieure, UMR CNRS-ENS-UPMC 8640, 24, Rue Lhomond, F-75231 Paris Cedex 5, France

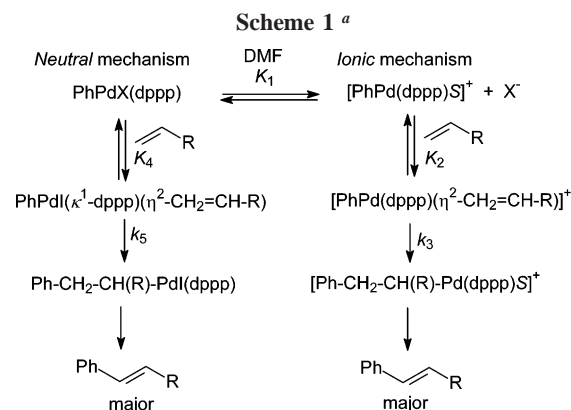
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Two main intermediate complexes, $\text{PhPd}(\text{OAc})(\text{dppp})$ and $\text{PhPdI}(\text{dppp})$, are generated in palladium-catalyzed Heck reactions performed from PhI and an acetate salt used as a base, in DMF. Both complexes react with the electron-rich alkene isobutyl vinyl ether ($\text{CH}_2=\text{CHO}^i\text{Bu}$) exclusively by an ionic mechanism, i.e., via the cationic complex $[\text{PhPd}(\text{dppp})(\text{DMF})]^+$ formed by dissociation of AcO^- or I^- from the parent complexes, as already established for the reaction of $\text{PhPd}(\text{OAc})(\text{dppp})$ with styrene and methyl acrylate and the reaction of $\text{PhPdI}(\text{dppp})$ with styrene. A mechanism is proposed which rationalizes the regioselectivity observed when reacting the electron-rich isobutylvinyl ether in palladium-catalyzed Heck reactions.

Introduction

In a previous work¹ we established that the mechanism of the reaction of an electron-deficient alkene (methyl acrylate) or styrene with the complexes $\text{PhPdX}(\text{dppp})$ ($\text{X} = \text{I}, \text{OAc}$; $\text{dppp} = 1,3\text{-bis}(\text{diphenylphosphino})\text{propane}$) formed in Heck reactions^{2,3} was substrate dependent. Indeed, $\text{PhPd}(\text{OAc})(\text{dppp})$ reacts with styrene and methyl acrylate exclusively by a ionic mechanism: i.e., via the cationic complex $[\text{PhPd}(\text{dppp})(\text{DMF})]^+$ formed upon dissociation of the acetate ion ligand. The complex $\text{PhPdI}(\text{dppp})$ reacts with styrene exclusively via an ionic mechanism, but the neutral and ionic mechanisms were shown to compete in parallel in the reaction with methyl acrylate (Scheme 1).¹ The linear alkene (β -arylation) is formed as the major product.

Heck reactions performed from electron-rich alkenes have been well-developed by Hallberg et al.⁴ Conditions have been optimized for the formation of the branched alkene (α -arylation)



^a The mechanism is purely ionic when $\text{X} = \text{OAc}$, $\text{R} = \text{Ph}$, CO_2Me or $\text{X} = \text{I}$, $\text{R} = \text{Ph}$. Ionic and neutral mechanisms are in parallel when $\text{X} = \text{I}$, $\text{R} = \text{CO}_2\text{Me}$.

* To whom correspondence should be addressed. Fax: 33 1 44 32 33 25. E-mail: Anny.Jutand@ens.fr (A.J.); christian.amatore@ens.fr (C.A.).

(1) Amatore, C.; Godin, B.; Jutand, A.; Lemaître, F. *Chem. Eur. J.* **2007**, *13*, 2002–2011.

(2) For reviews on Heck reactions: (a) de Mejeire, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379–2411. (b) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2–7. (c) Shibasaki, M.; Vogl, E. M. *J. Organomet. Chem.* **1999**, *576*, 1–15. (d) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–3066. (e) Larhed, M.; Hallberg, A. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002; Vol. I, Chapter IV.2, pp 1133–1178. (f) Farina, V. *Adv. Synth. Catal.* **2004**, *346*, 1553–1582.

(3) For Heck reactions catalyzed by palladium ligated to dppp, see: (a) Cabri, W.; Candiani, I.; Bedeshi, A. *J. Org. Chem.* **1990**, *55*, 3654–3655. (b) Cabri, W.; Candiani, I.; DeBernardinis, S.; Francalanci, F.; Penco, S.; Santi, R. *J. Org. Chem.* **1991**, *56*, 5796–5800. (c) Cabri, W.; Candiani, I.; Bedeshi, A.; Santi, R. *Tetrahedron Lett.* **1991**, *32*, 1753–1756. (d) Cabri, W.; Candiani, I.; Bedeshi, A.; Penco, S.; Santi, R. *J. Org. Chem.* **1992**, *57*, 1481–1486. (e) Cabri, W.; Candiani, I.; Bedeshi, A.; Santi, R. *J. Org. Chem.* **1992**, *57*, 3558–3563. (f) Herrmann, W. A.; Brossmer, C.; Öfele, K.; Beller, M.; Fisher, M. *J. Mol. Catal., A* **1995**, *103*, 133–146. (g) Larhed, M.; Hallberg, A. *J. Org. Chem.* **1996**, *61*, 9582–9584. (h) Larhed, M.; Hallberg, A. *J. Org. Chem.* **1997**, *62*, 7858–7862. (i) Vallin, K. S. A.; Larhed, M.; Johansson, K.; Hallberg, A. *J. Org. Chem.* **2000**, *65*, 4537–4542. (j) Qadir, M.; Möchel, T.; Hii, K. K. *Tetrahedron* **2000**, *56*, 7975–7979. (k) Vallin, K. S. A.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2001**, *66*, 4340–4343. (l) Vallin, K. S. A.; Zhang, Q. S.; Larhed, M.; Curran, D. P.; Hallberg, A. *J. Org. Chem.* **2003**, *68*, 6639–6645.

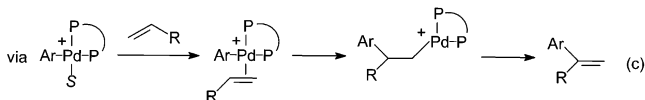
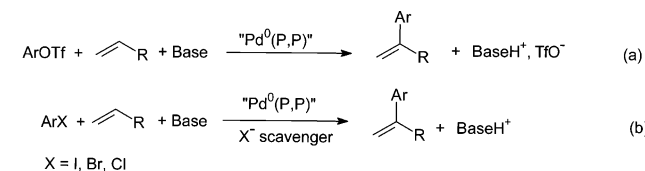
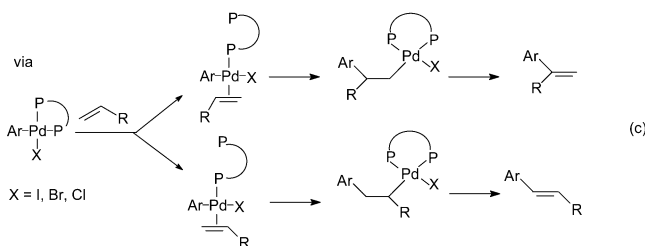
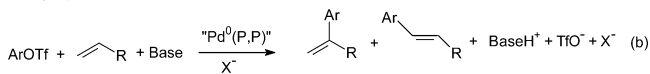
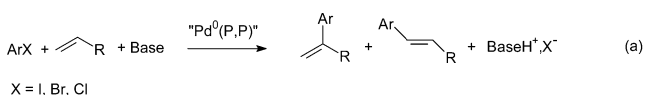
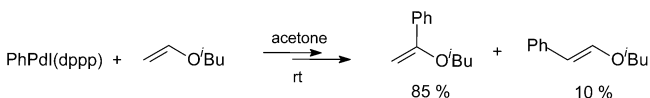
as the major product. The regioselectivity of Heck reactions is thought to be affected by the type of mechanism: ionic versus neutral.⁵ As proposed by Hayashi et al.⁶ and Cabri et al.,^{2b,3d,e} branched alkenes are mainly produced from electron-rich alkenes under the conditions of the ionic mechanism (Scheme 2c):⁷ i.e., from cationic $[\text{ArPd}(\text{P},\text{P})\text{S}]^+$ ($\text{S} = \text{solvent}$) generated in the oxidative addition of neutral Pd^0 complexes ligated by a

(4) For an early review on Heck reactions performed from electron-rich alkenes see: Daves, G. D., Jr.; Hallberg, A. *Chem. Rev.* **1989**, *89*, 1433–1445.

(5) For recent theoretical approaches on the regioselectivity in Heck reactions, see: (a) Von Schenck, H.; Akermarck, B.; Svensson, M. *J. Am. Chem. Soc.* **2003**, *125*, 3503–3508. (b) Deeth, R. J.; Smith, A.; Brown, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 7144–7151.

(6) Ozawa, F.; Kubo, A.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 1417–1419. (b) Hayashi, T.; Kubo, A.; Ozawa, F. *Pure Appl. Chem.* **1992**, *64*, 421–427. (c) Ozawa, F.; Kubo, A.; Matsumoto, Y.; Hayashi, T. *Organometallics* **1993**, *12*, 4188–4196.

(7) For studies on the ionic mechanism see: (a) Brown, J. M.; Hii, K. K. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 657–659. (b) Hii, K. K.; Claridge, T. D. W.; Brown, J. M. *Angew. Chem., Int. Ed.* **1997**, *36*, 984–987. (c) Deeth, R. J.; Smith, A.; Hii, K. K.; Brown, J. M. *Tetrahedron Lett.* **1998**, *39*, 3229–3232. (d) Ludwig, M.; Strömberg, S.; Svensson, M.; Akermarck, B. *Organometallics* **1999**, *18*, 970–975. (e) Hii, K. K.; Claridge, T. D. W.; Giernoth, R.; Brown, J. M. *Adv. Synth. Catal.* **2004**, *346*, 983–988.

Scheme 2. Ionic Mechanism for Heck Reactions with Electron-Rich Alkenes (R = EDG)

Scheme 3. Neutral Mechanism for Heck Reactions (R = EDG)

Scheme 4


bidentate P,P ligand with aryl triflates (Scheme 2a)^{2b,e,3,5} or with aryl halides in presence of an halide scavenger (Ag^+ ,^{8a} Ti^+ ,^{3c,8b} or K^+ ^{3k}) (Scheme 2b).

As shown by Cabri et al.,^{2b,3d} a mixture of branched and linear products is formed when Heck reactions are performed from electron-rich alkenes under the conditions of the neutral mechanism (Scheme 3c): i.e., when neutral $\text{ArPdX}(\text{P},\text{P})$ complexes are formed in the oxidative addition of $\text{Pd}^0(\text{P},\text{P})$ complexes with aryl halides (Scheme 3a) or with aryl triflates in the presence of halide ions (Scheme 3b).

The cationic complexes $[\text{ArPd}(\text{P},\text{P})\text{S}]^+$ may also be generated in an equilibrium from neutral $\text{ArPdX}(\text{P},\text{P})$ complexes and may even be more reactive than $\text{ArPdX}(\text{P},\text{P})$, as established in our previous work (Scheme 1).¹ On the other hand, the cationic complexes $[\text{ArPd}(\text{P},\text{P})\text{S}]^+$ may not be generated at high concentrations as soon as anions are present, as occurs during catalytic reactions. Indeed, we have shown that $\text{PhPd}(\text{OAc})$ -(dppp) is formed when oxidative additions are performed in presence of a large excess of acetate ions used as a base in some Heck reactions.⁹ Moreover, $\text{PhPdI}(\text{dppp})$ (**1a**) and $\text{PhPd}(\text{OAc})$ -(dppp) (**1b**) are involved in an equilibrium where their respective anions are exchanged.¹

(8) (a) Karabelas, K.; Westerlund, C.; Hallberg, A. *J. Org. Chem.* **1985**, *50*, 3896–3900. (b) Grigg, R.; Loganathan, V.; Santhakumar, V.; Teasdale, A. *Tetrahedron Lett.* **1991**, *32*, 687–690.

(9) Amatore, C.; Jutand, A.; Thuilliez, A. *Organometallics* **2001**, *20*, 3241–3249.

(10) For the kinetic laws, see ref 1.

The purpose of this work is to establish the mechanism of the reaction of $\text{PhPdX}(\text{dppp})$ (X = I, OAc) (formed in the first steps of Heck reactions) with an electron-rich alkene (isobutyl vinyl ether) under the conditions of real catalytic Heck reactions (base, ions released in the reaction, ionic strength, etc.).

Results and Discussion

Mechanism of the Reaction of $\text{PhPdI}(\text{dppp})$ (1a**) with $\text{CH}_2=\text{CHO}^i\text{Bu}$ in DMF.** The reaction of $\text{PhPdI}(\text{dppp})$ (**1a**) with $\text{CH}_2=\text{CHO}^i\text{Bu}$ was first monitored by ^1H NMR in acetone- d_6 using 10 equiv of isobutyl vinyl ether in the absence of any base at room temperature. The initially yellow solution of **1a** turned progressively to brown after the addition of isobutyl vinyl ether. The branched product $\text{CH}_2=\text{C}(\text{Ph})\text{O}^i\text{Bu}$ was generated in 85% yield (Scheme 4) in a slow reaction (1 week), together with the linear product (*E*)- $\text{PhCH}=\text{CHO}^i\text{Bu}$ (10%), indicative of a regioselectivity of 9/1 in favor of the branched product in acetone.

The kinetics of the reaction of **1a** with $\text{CH}_2=\text{CHO}^i\text{Bu}$ in DMF (containing 10% acetone- d_6) in the absence of base was monitored by ^{31}P NMR spectroscopy using a capillary of $\text{H}_3\text{-PO}_4$ (80% in water) as an internal standard, by following the disappearance of the two doublets of $\text{PhPdI}(\text{dppp})$ ¹ after addition of excess $\text{CH}_2=\text{CHO}^i\text{Bu}$. The observed rate constant k_{obs} (obtained from the slope of the linear plot of $\ln x - x + 1$ (x = molar fraction of unreacted **1a**) against time)¹⁰ varied linearly with the isobutyl vinyl ether concentration up to 6 M, attesting to a first-order reaction for the alkene (Figure 1). Beyond that concentration, the observed rate constant k_{obs} no longer depended

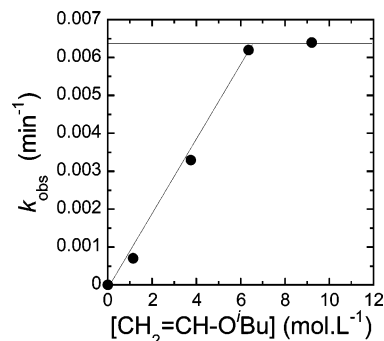


Figure 1. Kinetics of the reaction of $\text{PhPdI}(\text{dppp})$ (**1a**; $C_0 = 11.5$ mM) in DMF at 25 °C with isobutyl vinyl ether: reaction order of the alkene, determined by the plot of k_{obs} against alkene concentration.

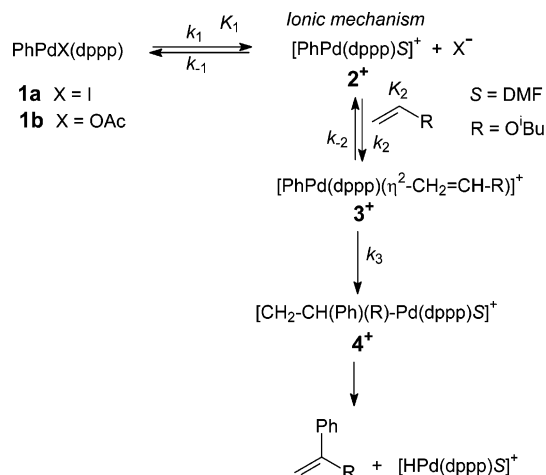
Scheme 5


Table 1. Rate Constants of the Reaction of PhPdX(dppp) (X = I, OAc) with Alkenes^a

X	k_1 (s ⁻¹)	$K_1K_2k_3$ (s ⁻¹)		
		CH ₂ =CHCO ₂ Me	CH ₂ =CHO ⁱ Bu	CH ₂ =CHPh
OAc	$[1.6(\pm 0.1)] \times 10^{-4 b}$	$[1.5(\pm 0.1)] \times 10^{-6 b}$	$[1.2(\pm 0.1)] \times 10^{-7}$	$[6.6(\pm 0.1)] \times 10^{-8 b}$
I	$[1.1(\pm 0.1)] \times 10^{-4 b}$	$[1.0(\pm 0.1)] \times 10^{-6 b}$	$[1.7(\pm 0.1)] \times 10^{-7}$	$[3.8(\pm 0.1)] \times 10^{-8 b}$
I	$[1.1(\pm 0.1)] \times 10^{-4}$			

^a See Scheme 5 for the definitions of k_1 and $K_1K_2k_3$. ^b See ref 1.

on the alkene concentration, attesting to a zero-order reaction (Figure 1).

Such kinetic behavior is similar to that observed in our previous work¹ in the reaction of PhPd(OAc)(dppp) with CH₂=CHCO₂Me and characterizes the ionic mechanism depicted in Scheme 5.

Two kinetic laws derived from eq 1 are involved: eq 2 at low alkene concentrations and eq 3 at high alkene concentrations (X = I, R = OⁱBu).¹⁰

$$\text{rate} = \frac{k_1k_2k_3[\mathbf{1}][\text{CH}_2=\text{CHR}]}{k_{-1}k_{-2}[\text{X}^-] + k_2k_3[\text{CH}_2=\text{CHR}]} \quad (1)$$

$$\text{rate} = \frac{k_1k_2k_3[\mathbf{1}][\text{CH}_2=\text{CHR}]}{k_{-1}k_{-2}[\text{X}^-]} \quad (2)$$

$$\text{rate} = k_1[\mathbf{1}] \quad (3)$$

The reaction of **1a** with CH₂=CHOⁱBu was limited by the dissociation of PhPdI(dppp) to [PhPd(dppp)(DMF)]⁺ and I⁻ at high alkene concentrations. The limiting value of k_{obs} gives $k_1 = 1.1 \times 10^{-4} \text{ s}^{-1}$ (DMF, 25 °C) according to eq 3. As it should be, this value is exactly the same as that previously determined in the reaction of PhPdI(dppp) with methyl acrylate in our previous work (Table 1).¹ The slope of the increasing part of the curve in Figure 1 gives the value $K_1K_2k_3 = 1.7 \times 10^{-7} \text{ s}^{-1}$ (DMF, 25 °C) (Table 1).

The occurrence of the ionic mechanism was further confirmed by the acceleration of the reaction by the ionic strength, as observed when the reaction was performed in the presence of increasing amounts of ⁿBu₄NBF₄ (Figure 2a), which favored the dissociation of PhPdI(dppp) to [PhPd(dppp)(DMF)]⁺ and I⁻. On the other hand, the reaction was found to be slower upon addition of increasing amounts of ⁿBu₄NI, at constant ionic strength, as maintained by the addition of adequate amounts of ⁿBu₄NBF₄ so that [ⁿBu₄NI] + [ⁿBu₄NBF₄] = 575 mM. The plot of k_{obs} against the reciprocal of iodide ion concentration was linear (Figure 2b), attesting to a reaction order of -1 for I⁻, as predicted by the kinetic law in eq 2. The slope of this straight line gives a value of $K_1K_2k_3 = 5 \times 10^{-6} \text{ s}^{-1}$, which, in comparison to that found at no ionic strength ($K_1K_2k_3 = 1.7 \times 10^{-7} \text{ s}^{-1}$; vide supra), shows that at high ionic strength the decelerating effect observed in the presence of iodide ions is highly compensated by the great accelerating effect due to the ionic strength.

Mechanism of the Reaction of PhPd(OAc)(dppp) (1b) with CH₂=CHOⁱBu in DMF. The reaction of PhPd(OAc)(dppp) (**1b**) with CH₂=CHOⁱBu was followed by ³¹P NMR spectroscopy. The pale pink solution of PhPd(OAc)(dppp) (**1b**) turned brown after addition of CH₂=CHOⁱBu, whereas the two doublets of PhPd(OAc)(dppp) slowly disappeared over time. Two new doublets slowly appeared at 20.84 ($J_{\text{PP}} = 49.6 \text{ Hz}$) and -0.245 ppm ($J_{\text{PP}} = 49.6 \text{ Hz}$). At the end of the reaction, such doublets disappeared after addition of iodobenzene (10 equiv), indicating that they characterize a Pd(0) complex, likely

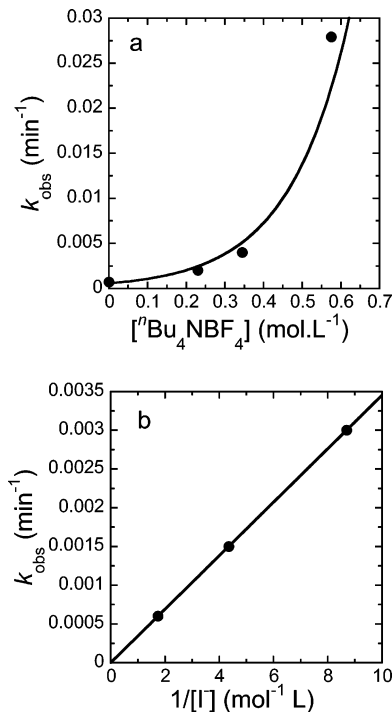


Figure 2. (a) Kinetics of the reaction of PhPdI(dppp) (**1a**; $C_0 = 11.5 \text{ mM}$) with isobutyl vinyl ether (1.15 M) at high ionic strength in DMF at 25 °C: plot of k_{obs} against ⁿBu₄NBF₄ concentration. (b) Kinetics of the reaction of PhPdI(dppp) (**1a**; $C_0 = 11.5 \text{ mM}$) with isobutyl vinyl ether (1.15 M) in the presence of ⁿBu₄NI at constant ionic strength in DMF at 25 °C: plot of k_{obs} against 1/[ⁿBu₄NI].

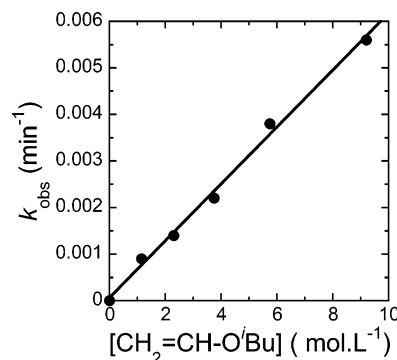
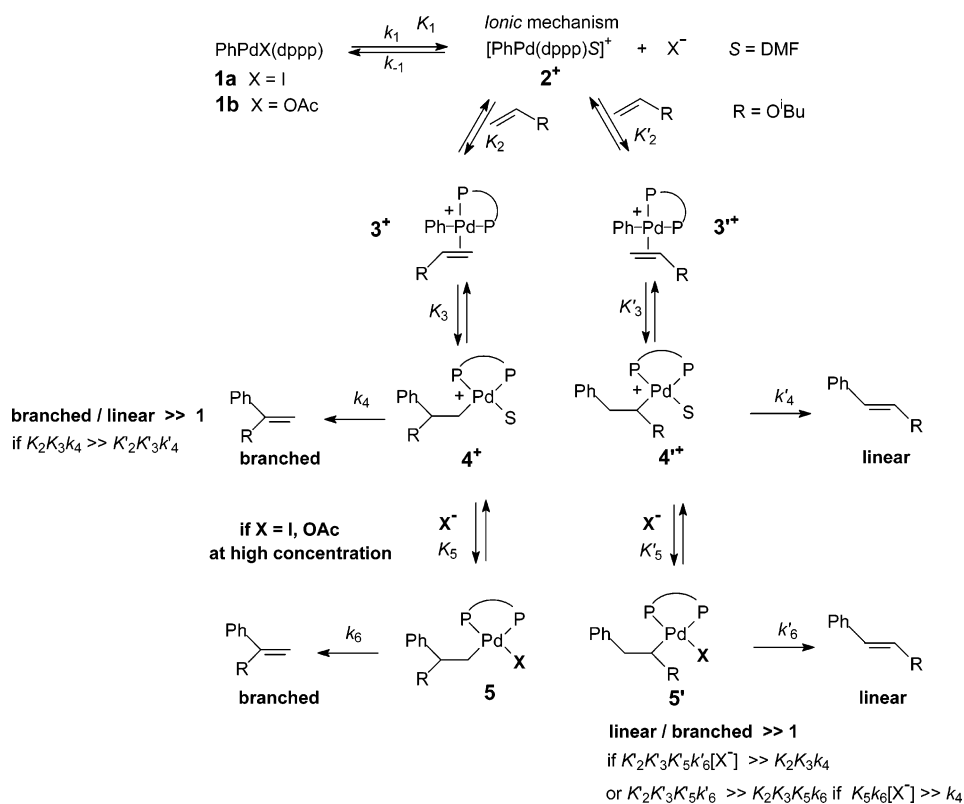


Figure 3. Kinetics of the reaction of PhPd(OAc)(dppp) (**1b**; $C_0 = 12.2 \text{ mM}$) in DMF at 25 °C with isopropyl vinyl ether: reaction order of the alkene, determined by the plot of k_{obs} against alkene concentration.

(η^2 -CH₂=CHOⁱBu)Pd⁰(dppp), which has been thus produced in the absence of any base.¹¹

The reaction of **1b** with CH₂=CHOⁱBu was first-order over the whole concentration range investigated here (Figure 3). The reaction was thus never limited by the dissociation of PhPd(OAc)(dppp) to [PhPd(dppp)(DMF)]⁺ and AcO⁻, in agreement

(11) Similar doublets were also observed in the reaction of **1b** with CH₂=CHCO₂Me at 17.93 ($J_{\text{PP}} = 49.5 \text{ Hz}$) and 0.16 ppm ($J_{\text{PP}} = 49.5 \text{ Hz}$).

Scheme 6. Tentative Mechanism To Rationalize the Regioselectivity of Heck Reactions

with the fact that this dissociation is easier than that of I^- from $\text{PhPdI}(\text{dppp})$ (compare the respective values of k_1 determined in our previous work¹ and reported here in Table 1). The reaction was accelerated upon increasing the ionic strength by addition of ${}^n\text{Bu}_4\text{NBF}_4$ and decelerated by addition of ${}^n\text{Bu}_4\text{NOAc}$ at constant ionic strength, confirming that $\text{PhPd}(\text{OAc})(\text{dppp})$ reacted with $\text{CH}_2=\text{CHO}^i\text{Bu}$ via the ionic mechanism of Scheme 5. The value of $K_1K_2k_3$ was determined from the slope of the straight line in Figure 3 (Table 1).

Comparison of the rate constants determined in this work (Table 1, entries in boldface type) with those determined in our previous work¹ shows that the reaction of $\text{PhPdI}(\text{dppp})$ with $\text{CH}_2=\text{CHO}^i\text{Bu}$ was faster than that of $\text{CH}_2=\text{CHPh}$ but surprisingly slower than that of $\text{CH}_2=\text{CHCO}_2\text{Me}$ at identical concentrations, in DMF. The same reactivity order was observed when $\text{PhPd}(\text{OAc})(\text{dppp})$ was considered.

Discussion and Conclusion

$\text{PhPdI}(\text{dppp})$ and $\text{PhPd}(\text{OAc})(\text{dppp})$ (formed together in Heck reactions performed from phenyl iodide with an acetate salt as a base) react with isobutyl vinyl ether exclusively by a ionic mechanism: i.e., via the cationic complex $[\text{PhPd}(\text{dppp})(\text{DMF})]^+$ formed by dissociation of the iodide or acetate ion, respectively. Comparison with our previous work¹ exhibits the following orders of reactivity.

For the various complexes $\text{PhPdX}(\text{dppp})$ (X = I, OAc): $\text{CH}_2=\text{CHCO}_2\text{Me} > \text{CH}_2=\text{CHO}^i\text{Bu} > \text{CH}_2=\text{CHPh}$.

For the various alkenes: $[\text{PhPd}(\text{dppp})(\text{DMF})]^+ \gg \text{PhPdX}(\text{dppp})$ (X = I, OAc)

The reaction of isobutyl vinyl ether with $\text{PhPdX}(\text{dppp})$ (X = I, OAc) is slower than the previous reaction in which $\text{PhPdX}(\text{dppp})$ species are formed: i.e., the oxidative addition of iodobenzene (used at the same concentration as that of isobutyl vinyl ether) with a Pd(0) complex generated from

$\text{Pd}(\text{OAc})_2$ and dppp .⁹ The carbopalladation (reaction of phenylpalladium(II) complexes with alkenes) remains therefore the rate-determining step of the overall catalytic Heck reaction.

We have established in the present work that neutral $\text{ArPdX}(\text{dppp})$ (X = I, OAc) reacts with isobutyl vinyl ether via the cationic complex $[\text{PhPd}(\text{dppp})(\text{DMF})]^+$ by a pure ionic mechanism, in contradiction with the hypothesis by Cabri et al., which proposes that neutral $\text{ArPdI}(\text{dppp})$ complexes may be the reactive species in the so-called neutral mechanism (Scheme 3).^{2b} The regioselectivity (major branched product) observed here when isobutyl vinyl ether is reacted is that expected for the "textbook" ionic mechanism (Scheme 2c). However, the mechanism proposed here in Scheme 5, establishing the exclusive reactivity of cationic complexes generated from neutral $\text{ArPdX}(\text{dppp})$ complexes, cannot explain why the regioselectivity of the Heck reaction performed with electron-rich alkenes is so sensitive to the experimental conditions. This was explained by the textbook mechanisms proposed in Schemes 2 and 3, thought to favor the formation of either reactive cationic or reactive neutral arylpalladium complexes (Schemes 2 and 3, respectively). On the other hand, the role of the base able to deliver anions (acetates, carbonates) is bypassed in those mechanisms. One must therefore imagine a more elaborate mechanism to rationalize the regioselectivity observed in Heck reactions (Scheme 6). The complexation of the alkene to the reactive cationic complex $[\text{PhPd}(\text{dppp})(\text{DMF})]^+$ (**2⁺**) may generate the two conformational isomers **3⁺** and **3'⁺** and, henceforth, the two complexes **4⁺** and **4'⁺** after a reversible carbopalladation step.¹² The branched product is formed as a major product if $K_2K_3k_4 \gg K'_2K'_3k'_4$, the equilibrium **3⁺**/**4⁺** and **3'⁺**/**4'⁺** being fast enough (Scheme 6, upper left mechanism).¹³ This is supported by DFT calculations reported by Brown et

(12) For a reversible alkene insertion into a Pt-alkyl bond in a cationic $[\text{RPt}(\text{dmpc})]^+$ complex, see: Flood, T. C.; Bitler, S. P. *J. Am. Chem. Soc.* **1984**, *106*, 6076–6077.

al.^{5b} If the anions X^- (I^- , AcO^-) are present at high concentration, the cationic complexes 4^+ and $4'^+$ may be reversibly quenched as neutral complexes 5 and $5'$, respectively. The linear product will be thus formed as a major product whenever $K'_2K'_3K'_5k'_6[X^-] \gg K_2K_3k_4$ or $K'_2K'_3K'_5k'_6 \gg K_2K_3K_5k_6$ if $K_5k_6[X^-] \gg k_4$ (Scheme 6, lower right mechanism).

According to this proposition, the major branched product would be formed in a reaction involving either pure cationic $[PhPd(dppp)(DMF)]^+$ or neutral $PhPdX(dppp)$ (reacting via the cationic complex), both in the absence of extra anions (I^- , AcO^-) or at very low concentration (upper left part of Scheme 6). The linear product would be formed as the major compound when the reaction is performed from either cationic $[PhPd(dppp)(DMF)]^+$ or neutral $PhPdX(dppp)$ (reacting via the cationic complex) in the presence of a large excess of anions (I^- , AcO^-) (lower right part of Scheme 6), as often occurs in real catalytic reactions.

According to this new mechanism in Scheme 6, we can explain the regioselectivity of Heck reactions recently reported by Xiao et al.¹⁴ Heck reactions catalyzed by $Pd(OAc)_2$ associated with $dppp$ and performed from the electron-rich alkene (*n*-butyl vinyl ether) and aryl halides (without any halide scavenger: i.e., under the conditions of the neutral "textbook" mechanism of Scheme 3a) gave a mixture of branched and linear products in DMF, whereas the branched product was exclusively produced in ionic liquids.¹⁴ Whatever the medium, the cationic complex $[ArPd(dppp)S]^+$ is always the most intrinsically reactive complex. In DMF, a mixture of branched and linear products was produced because the halide ions released at high concentration in the course of the catalytic reaction reacted with the cationic complexes of types 4^+ and $4'^+$ to give the neutral complexes 5 and $5'$, at the origin of the mixture of branched and linear products. At high ionic strength, as in ionic liquids, the dissociation of $ArPdX(dppp)$ toward the reactive cationic complex $[ArPd(dppp)S]^+$ is favored, its concentration is increased, and consequently, the reaction is faster. More importantly, however, the reaction of halide ions (released in the course of the catalytic reaction) with the cationic complexes of types 4^+ and $4'^+$ is slowed down by the high ionic strength (no need for halide scavengers), inhibiting the formation of complexes 5 and $5'$ (lower part of Scheme 6). The regioselectivity of the reaction in ionic liquids (major branched product) is thus given by the upper left part of Scheme 6 (via complex 4^+).

In conclusion, the regioselectivity of Heck reactions performed in DMF from electron-rich alkenes is sensitive to the presence of anions, halide, or acetate (see Scheme 6). However, even in the presence of anions, the carbopalladation step always

proceeds from cationic $[ArPd(dppp)(S)]^+$ complexes and not from neutral $ArPdX(dppp)$ complexes.

Experimental Section

General Methods. ³¹P NMR spectra were recorded on a Bruker spectrometer (101 MHz) in DMF containing 10% of acetone-*d*₆. A capillary tube containing H₃PO₄ (85% in water) was introduced into the NMR tube to serve as an internal standard for the kinetic studies. ¹H NMR spectra were recorded on a Bruker spectrometer (250 MHz).

Chemicals. DMF was distilled from calcium hydride under vacuum and kept under argon. Isobutyl vinyl ether, ⁿBu₄NI, ⁿBu₄NOAc, and ⁿBu₄NBF₄ were obtained from commercial sources. The complexes $PhPdI(dppp)$ and $PhPd(OAc)(dppp)$ were synthesized according to the literature.^{7d,1}

Typical Procedure for the Reaction of $PhPdI(dppp)$ (1a**) and $PhPd(OAc)(dppp)$ (**1b**) with Isobutyl Vinyl Ether.** The reaction was performed in a Schlenk tube under argon. To a yellow solution of 5.6 mg (7.7 μmol) of **1b** (or 4.6 mg (6.5 μmol) of **1a**) in 400 μL of acetone-*d*₆ was added 1 μL (11.2 μmol) of isobutyl vinyl ether at room temperature. The yellow solution of **1b** turned progressively red. The ¹H NMR spectra showed the progressive disappearance of the signal of the Ph group linked to the Pd(II) center of **1b**. After 1 week, a black solution was obtained, **1b** was no longer observed and the branched product 1-phenylisobutyl vinyl ether was formed as the major product together with the linear product (*E*)-2-phenylisobutyl vinyl ether. The excess isobutyl vinyl ether was eliminated under vacuum. A 1 μL amount (9.3 μmol) of 1,1,2,2-tetrachloroethane was then added as an internal standard to determine the amount of product formed in the reaction: branched (85% yield), linear (10% yield).

Typical Procedure for the Kinetics of the Reaction of $PhPdI(dppp)$ (1a**) with Isobutyl Vinyl Ether As Monitored by ³¹P NMR Spectroscopy.** The reaction was performed as above, starting from 5 mg (6.9 μmol) of **1a** and various amounts of isobutyl vinyl ether. ⁿBu₄NBF₄ was added before the isobutyl vinyl ether to probe the effect of the ionic strength on the kinetics. In other experiments, known amounts ⁿBu₄NI were added before the isobutyl vinyl ether to probe the effect of the iodide ions on the kinetics.

Similar reactions were performed from $PhPd(OAc)(dppp)$ (**1b**). ⁿBu₄NOAc was used to probe the decelerating effect of acetate ions on the kinetics.

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(13) According to this mechanism, the value of $K_1K_2k_3$ determined in this work (Scheme 5) would in fact be that of $K_1K_2K_3k_4$ (Scheme 6).

(14) (a) Xu, L. J.; Chen, W. P.; Ross, J.; Xiao, J. L. *Org. Lett.* **2001**, *3*, 295–297. (b) Mo, J.; Xu, L.; Xiao, J. *J. Am. Chem. Soc.* **2005**, *127*, 751–760. (c) Mo, J.; Xiao, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 4152–4157.