Palladium-Catalyzed C−P Bond Formation: Mechanistic Studies on the Ligand Substitution and the Reductive Elimination. An Intramolecular Catalysis by the Acetate Group in Pd^{II} Complexes

Marcin Kalek[†] and Jacek Stawinski*[,†,‡]

Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, S-106 91 Stockholm, Sweden, and Institute of Bioorganic Chemistry, Polish Academy of Sciences, Noskowskiego 12/14, 61-704 Poznan, Poland

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Ligand substitution and reductive elimination of the palladium-catalyzed C−P bond forming cross-coupling were investigated in depth. It was found that for $PhPd^{II}(PPh_3)_2X$ (X = I, Br, Cl) complexes, a step commonly referred to as ligand substitution commenced with coordination of an H-phosphonate diester, followed by its deprotonation to form an equilibrium mixture of penta- and tetracoordinate palladiumphosphonate intermediates, from which reductive elimination of the product (diethyl phenylphosphonate) occurred. For the acetate counterpart, $PhPd^{II}(PPh_3)_2(OAc)$, the incorporation of a phosphonate moiety to the complex was preceded by a rate-determining removal of the supporting phosphine ligand, facilitated by an intramolecular catalysis by the acetate group. Both the reaction steps, i.e., formation of palladiumphosphonate intermediates and reductive elimination, were significantly faster for the acetate versus halides containing Pd^{II} complexes investigated. Similar observations were found to be true also for bidentate ligand complexes $[(dppp)Pd^{II}(Ph)X]$; however, in this instance, a single palladiumphosphonate intermediate, $(dppp)Pd^{II}(Ph)(PO(OEt)_2)$, could be observed by ^{31}P NMR spectroscopy. The synthetic and kinetic studies on the cross-coupling reaction of diethyl H-phosphonate with phenyl halides permitted us to elucidate a crucial catalytic role of an acetate group in Pd^{II} complexes and to propose two distinctive catalytic cycles, which complemented traditional Pd^0/Pd^{II} schemes, for the palladium-mediated C−P bond formation.

Introduction

Palladium-catalyzed cross-coupling reactions constitute extremely useful tools in organic synthesis,[1] and their applications have significantly broadened when, in addition to classical carbon−carbon bond forming transformations, new variants of the reaction with heteroatom nucleophiles have been developed.[2] Among these, several palladium-catalyzed cross-couplings using phosphorus nucleophiles[3,4] attracted considerable attention due to their possible applications in the synthesis of modified nucleic acids[5] and chiral phosphine ligands.[6]

Despite some controversies,[7,8] there is a consensus that palladium-catalyzed cross-coupling reactions with heteroatom nucleophiles follow a three-step catalytic cycle, which for the example of H-phosphonates, is depicted in Scheme 1.

Most of mechanistic studies on catalytic cycles as that shown in Scheme 1, using experiemental[9,10] and computational[11] techniques, have been focused on oxidative addition, a common step of a variety of important cross-coupling reactions. The reductive elimination steps, in which the C−N,[12,13] C−O,[12,14] C−S,[12,15,16] and C−P[17−19] bonds can be produced, received

* Corresponding author. Tel: (+46) 0816 2485. Fax: (+46) 0815 4908. E-mail: js@organ.su.se.
[†] Stockholm University.
[‡] Polish Academy of Sciences.

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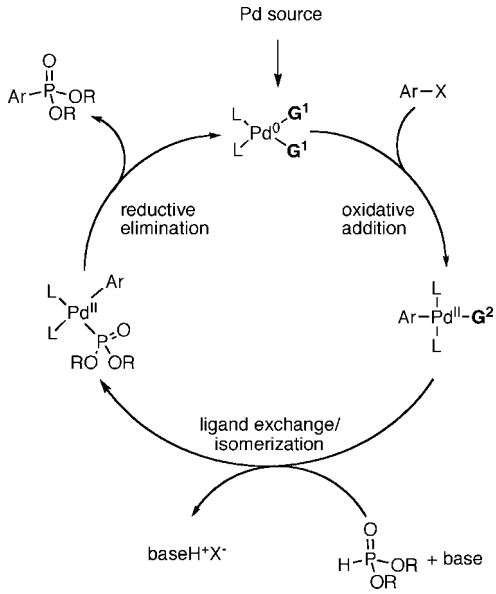
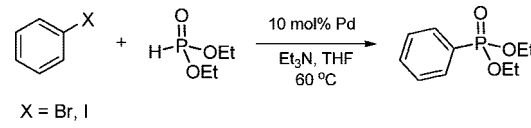
Scheme 1. Generic Mechanism for the Palladium-Catalyzed Cross-Coupling between Aryl Halide and H-Phosphonate Diesters (G^1 = L, dba, X^-, OAc^-, solvent; G^2 = X^-, OAc^-, solvent)



less attention, and the studies were confined mainly to complexes containing bidentate ligands. It is assumed that, similarly to the palladium-catalyzed C−C bond formation,[20,21] in these reactions a *cis* arrangement of the eliminated groups secured by bidentate ligands facilitates carbon−heteroatom bond formation in this step. Even less information is available for the process of ligand substitution during cross-coupling reactions with the heteroatom nucleophiles, with notable exceptions of the work by Jutand et al.[16] on an intimate mechanism of thiol transfer to the Pd^{II} center and that by Hartwig, Blackmon, and Buchwald el al.,[7] on a mechanism of the palladium-catalyzed C−N bond formation.[22]

There are several interesting practical and mechanistic aspects of d^8-metallophosphonate chemistry, in which H-phosphonate derivatives play a pivotal role. In addition to acting as nucleophiles in the cross-coupling reactions, H-phosphonates (or other species containing the P−H bond) can undergo oxidative addition to transition metals, and the complexes formed may follow hydrophosphorylation[4,23,24] and transfer hydrogenation[4,23,25] reaction pathways. H-Phosphonate derivatives can also act as air-stable HASPO (heteroatom-substituted secondary phosphine oxides) preligands,[26] forming palladium(0) complexes that are active in oxidative addition of aryl halides and that can be used as catalysts for other cross-coupling reactions.[26,27] This type of reactivity, however, is highly undesirable when H-phosphonates themselves are intended to be substrates in Pd(0)-catalyzed cross-coupling reactions.[28]

Table 1. Effect of Anionic Additives on the Cross-Coupling of Diethyl H-Phosphonate with Bromo- and Iodobenzene[a,b]



X = Br, I

Entry	Palladium source (+ ligand and additive)	Reaction time (Br)	Reaction time (I)
1	$Pd(PPh_3)_4$	18 h	8 h
2	$Pd(PPh_3)_4 + 10Cl^-$	11 h	2.5 h
3	$Pd(PPh_3)_4 + 10Br^-$	10 h	4 h
4	$Pd(OAc)_2 + 3PPh_3$	16 h	7 h
5	$Pd(OAc)_2 + 3PPh_3 + 10Cl$	11 h	2 h
6	$Pd(OAc)_2 + 3PPh_3 + 10Br^-$	11 h	4 h
7	$Pd(OAc)_2 + 3PPh_3 + 10OAc^-$	2.5 h	1 h

[a] Experimental conditions: 0.1 M $(EtO)_2P(O)H$, 1.1 equiv of Ph-X, 1.2 equiv of Et_3N, THF, 60 °C, 10 mol % Pd, anions were added as corresponding n-Bu_4N^+ salts. [b] All data from ref. 28.

Our recent studies on the influence of palladium sources and anionic additives on the rate and efficiency of the cross-coupling between H-phosphonates and aryl halides led to the discovery of an intriguing phenomenon, namely, that the rate of ligand substitution was strongly dependent on the leaving group in Pd^{II} complexes and followed the order $OAc^- \gg Cl^-, Br^- > I^-$.[28] It was argued that exceptionally high rates of ligand substitution for the acetate derivatives could account for a remarkable acceleration of the overall cross-coupling reactions observed in the presence of OAc^- ions (Table 1).[29]

Inspired by the idea that a ligand substitution step may be responsible for the overall rate of cross-coupling reactions (Table 1), we set out to perform in-depth investigations on this process, using as a model reaction the palladium-catalyzed cross-coupling between aryl halides and diethyl H-phosphonate. In this paper, we describe our studies on a mechanism of a ligand substitution in palladium(II) complexes containing monodentate and bidentate ligands, as well as reductive eliminations from the palla-

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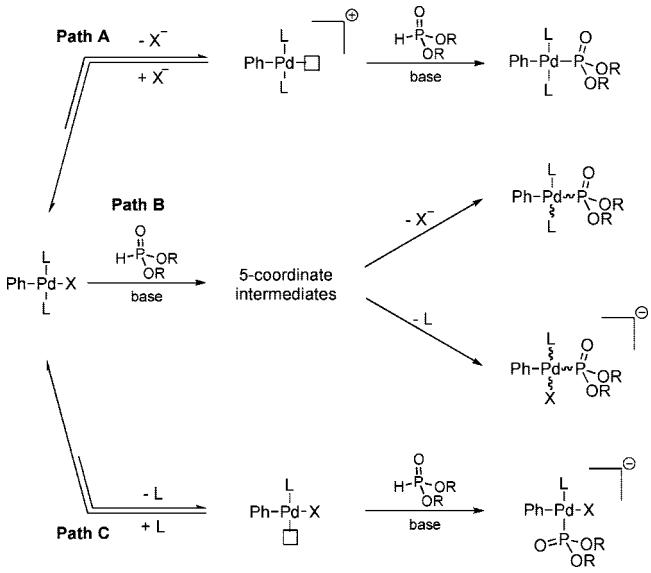
(29) OAc^- ions also accelerate the oxidative addition to Pd^0; however, their effect on this step of the catalytic cycle is expected to be lower than that of Cl^- and Br^-. See also ref 9.

Scheme 2. Possible Reaction Pathways for the Ligand Substitution in $PhPdL_2X$ Complexes with an H-Phosphonate Diester As a Nucleophile (L = PPh_3)



diumphosphonate intermediates formed. In particular, a mechanistic role of leaving groups in palladium(II) complexes is addressed in detail, and a plausible explanation, supported by experimental data, for the dramatic acceleration of the cross-coupling reactions in the presence of acetate ions is proposed.

Results and Discussion

Ligand Substitution in $PhPdL_2X$ Complexes (X = halide). Palladium(II) complexes are tetracoordinated, 16-electron, square-planar species, in which ligand substitution can occur via two distinct reaction pathways: (i) an associative path, involving pentacoordinated, 18-electron square-pyramidal and trigonal-bipyramidal intermediates (or transition states), or (ii) a dissociative path, which proceeds via tricoordinated, 14-electron, T-shaped species.[30,31]

For *trans*-$PhPd^{II}(PPh_3)_2X$ (X = I, Br, Cl) complexes, which are intermediates implicated in the above-discussed cross-coupling reactions, two dissociative mechanisms (paths A and C) and an associative one (path B) (Scheme 2) can be considered for the ligand substitution with an H-phosphonate nucleophile.

Path A is initiated by a reversible dissociation of the halide anion to form a 14-electron unsaturated complex, which undergoes reaction with an H-phosphonate diester in the presence of base, to produce a *trans* palladium phosphonate complex. In path B, an H-phosphonate coordinates to the starting palladium complex, forming five-coordinate intermediates (isomeric square pyramids and trigonal bipyramids), which can release either the halide or PPh_3, leading to the corresponding phosphonate complexes with different possible geometries (see further in the text). Finally, in path C, the initial reversible dissociation of a phosphine ligand is followed by the addition of an H-phosphonate diester, and after deprotonation, an anionic *cis* palladium phosphonate complex is formed. In addition to these, there is a solvent-assisted substitution pathway possible, in which solvent molecules act as nucleophiles replacing first the halide or PPh_3 (an associative pathway), and this is followed by the replacement of the coordinated solvent molecule by a phosphonate moiety.[30,32] Such a mechanism can be kinetically indistinguishable from those in path A or C, but stereochemistry of the palladium phosphonate complexes formed can be different.

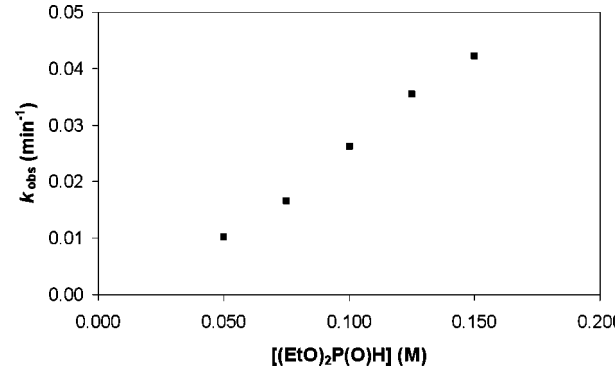


Figure 1. Dependence of the rate of $PhPd(PPh_3)_2I$ decay on concentration of $(EtO)_2P(O)H$ in THF at 40 °C (initial [$PhPd(PPh_3)_2I$] = 5 mM, [Et_3N] = 50 mM).

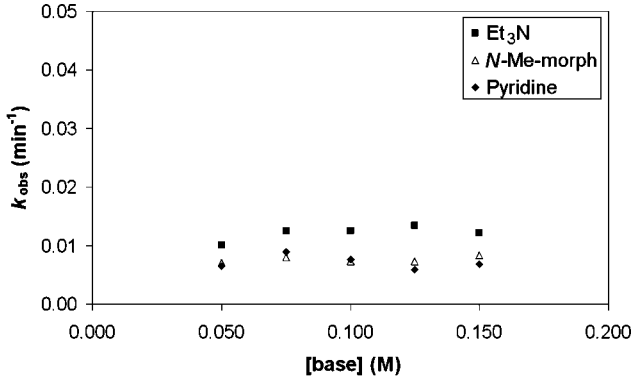


Figure 2. Dependence of the rate of $PhPd(PPh_3)_2I$ decay on concentration and the kind of base in THF at 40 °C (initial [$PhPd(PPh_3)_2I$] = 5 mM, [$(EtO)_2P(O)H$] = 50 mM).

To evaluate a possible participation of the above-presented mechanisms during ligand substitution with H-phosphonate diesters, we measured rates of decay of $PhPd(PPh_3)_2X$ complexes (X = I, Br, Cl) under various experimental conditions, using ^{31}P NMR spectroscopy. In all kinetic runs the initial concentration of the palladium complexes was 5 mM. Diethyl H-phosphonate and triethylamine were used as a model phosphorus nucleophile and a base, respectively, and their concentrations were varied from 50 to 150 mM (10- to 30-fold excess over Pd^{II} complexes). To avoid palladium black formation from low-ligated Pd^0 species, generated by reductive elimination of diethyl phenylphosphonate from Pd^{II} complexes, 1 equiv of PPh_3 per the Pd complex (5 mM; except for the experiments with variable amounts of PPh_3) was added to the reaction mixtures. Under such conditions, and with high excess of the H-phosphonate and a base, first-order kinetics with respect to $PhPd^{II}(PPh_3)_2X$ was observed in all instances, with excellent reproducibility of the measured rate constants.

Figures 1−3 show the observed first-order rate constants for the decay of complex $PhPd(PPh_3)_2I$, as a function of concentrations of $(EtO)_2P(O)H$, the base used, and PPh_3, respectively. As it was apparent from the presented data, the reaction showed

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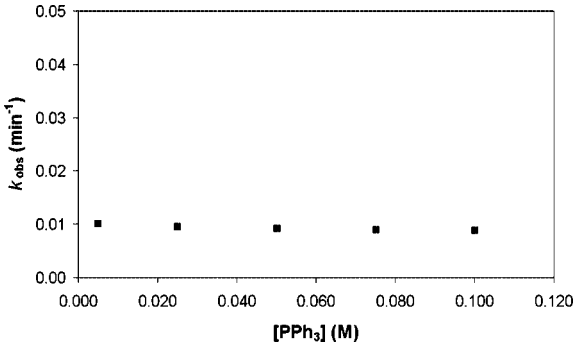

Figure 3. Dependence of the rate of $PhPd(PPh_3)_2I$ decay on concentration of PPh_3 in THF at 40 °C (initial $[PhPd(PPh_3)_2I] = 5$ mM, $[(EtO)_2P(O)H] = [Et_3N] = 50$ mM).

Table 2. Observed First-Order Rate Constants (k_{obs}) of the Decay of $PhPd(PPh_3)_2X$ Complexes at 40 °C (initial $[PhPd(PPh_3)_2X] = 5$ mM, $[(EtO)_2P(O)H] = [Et_3N] = 50$ mM)

entry	palladium(II) complex	solvent	k_{obs} (min^{-1})
1	$PhPd(PPh_3)_2I$	THF	0.0101
2	$PhPd(PPh_3)_2I$	toluene	0.0138
3	$PhPd(PPh_3)_2Br$	THF	0.0192
4	$PhPd(PPh_3)_2Cl$	THF	0.0336

a linear dependence on the H-phosphonate concentration (Figure 1), but was rather insensitive to the amounts of the base or PPh_3 used (Figures 2 and 3). Therefore, the experimentally determined rate law for the ligand substitution in the studied complexes was as follows:

$$-\frac{d[PhPd(PPh_3)_2X]}{dt} = k_{obs}[PhPd(PPh_3)_2X] \quad (1)$$

where

$$k_{obs} = k[(EtO)_2P(O)H] \quad (2)$$

One should note that although for the reactions investigated base is an indispensable reaction component, it does not enter into the kinetic equation. This, and the fact that using bases of various strengths[33] resulted only in mediocre changes in the reaction rates (Figure 2), suggested that deprotonation of the H-phosphonate diester occurred at a kinetically unimportant step of the reaction (after the rate-determining step; also, *vide infra*). To ascertain further that the P−H bond breaking did not influence the overall reaction rate, we measured a kinetic isotope effect, using the deuterated H-phosphonate $[(EtO)_2P(O)D]$.[34] The obtained value of $k_H/k_D = 1.17 \pm 0.05$ was indeed very small and excluded the possibility of a significant degree of P−H bond breaking in the rate-determining step.

The rate constants measured for the complexes bearing different halide ligands (Table 2) were in perfect agreement with the previously reported qualitative results.[28] Comparable values of the rate constants for the reaction in toluene and THF (Table 2, entries 1 and 2) indicated no involvement of a solvent-assisted substitution mechanism, and the lack of inhibitory effect of the added PPh_3 ruled out path C (Scheme 2) as a possible mechanism.

To evaluate a possible participation of the second dissociative pathway (Scheme 2, path A) in the ligand substitution step, one should take into account the affinity order of halide anions toward a Pd^{II} center. It was determined previously that, contrary to the hard−soft acid base principle prediction, the affinity of halides to the palladium in $PhPd(PPh_3)_2X$ complexes decreases in the order Cl > Br > I.[35,36] Thus, if the ligand substitution would indeed follow path A, the fastest reaction should be expected for the iodide-ligated complex, followed by the bromide and chloride derivatives, according to relative concentrations of free cationic 14-electron species $[PhPd(PPh_3)_2^+]$ produced from these complexes. However, the data in Table 2 display an opposite order of reactivity, and this, to high probability, excludes path A as a plausible reaction mechanism.

Analysis of the reaction pathways for the ligand substitution in $PhPd(PPh_3)_2X$ complexes (Scheme 2) showed that apparently only path B was consistent with the observed linear dependence of the rate on $(EtO)_2P(O)H$ concentration, and it correctly predicted the absence of the influence from PPh_3. Also the trend in reactivity of Pd^{II} complexes bearing different halides (Table 2) can be satisfactorily explained on the basis of this mechanism. The first step of the reaction, a coordination of the H-phosphonate diester to $PhPd(PPh_3)_2X$, should be facilitated by low electron density at the palladium center, and since this step is kinetically important, the reaction rates were expected to follow the electronegativity order of the halogen atoms (Cl > Br > I) present in these complexes (Table 2).

The role of base in this reaction (Figure 2) deserves some comment since deprotonation of the H-phosphonate diester is a chemically important step. One can envisage two scenarios for this process (Scheme 3): (i) a base-mediated, rapid pre-equilibrium between the H-phosphonate and its anion, followed by attack of the generated phosphorus nucleophile on the palladium complex (path B1), and (ii) an initial coordination of the H-phosphonate diester to the Pd^{II} complex, followed by abstraction of the phosphorus-bonded proton by a base (path B2).

The first type of a mechanism, which involves generation of a phosphonate anion, was the most obvious option, since phosphorus acid diesters in the H-phosphonate form, cannot act as phosphorus nucleophiles. The second type of a mechanism, i.e. coordination of a neutral nucleophile followed by its deprotonation, however, was postulated for the ligand substitutions involving thiols[16] and, in a slightly different kind of palladium-catalyzed reaction, also for alcohols.[37] In the instance of H-phosphonates derivatives, which do not have a lone electron pair on the phosphorus atom, the association process would have to involve either oxygen electron pairs or the P═O double bond, as tentatively depicted in Scheme 3.

To verify which of the two possible pathways operated in our reactions, the predicted rate laws for path B1 and path B2 were compared with the experimentally determined one.

For path B1, the following rate expression for the disappearance of the $PhPd(PPh_3)_2X$ complex can be derived:

$$-\frac{d[PhPd(PPh_3)_2X]}{dt} = \frac{Kk_1[(EtO)_2P(O)H][base][PhPd(PPh_3)_2X]}{[baseH^+]} \quad (3)$$

Although, the assumed rapid equilibrium between the H-phosphonate and its anion would explain the lack of a primary

(33) pK_a values for the corresponding conjugated acids in water: Et_3NH^+ 10.8, *N*-Me-morpholineH^+ 7.4, pyridineH^+ 5.2.

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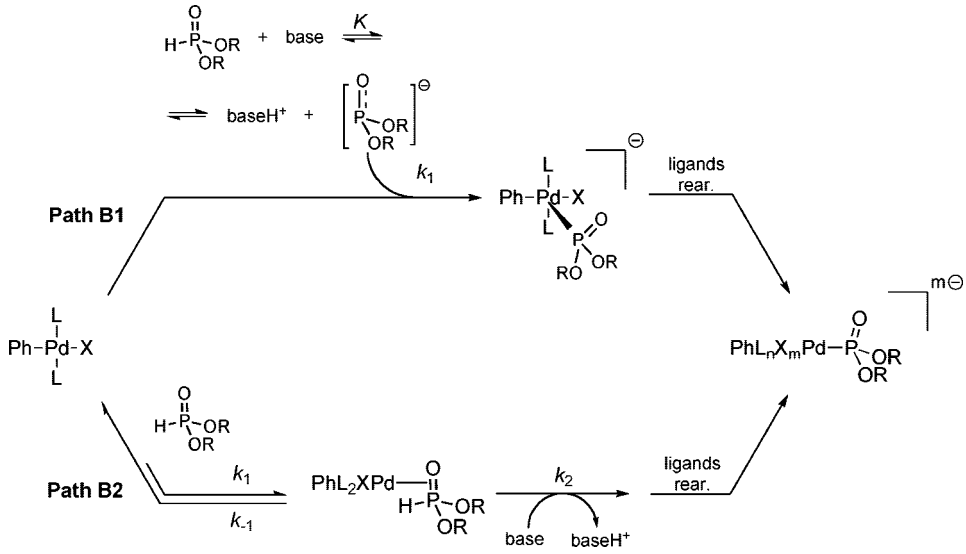
(37) Ozawa, F.; Kawasaki, N.; Okamoto, H.; Yamamoto, T.; Yamamoto, A. *Organometallics* **1987**, *6*, 1640–1651.

Scheme 3. Possible Associative Pathways for Ligand Substitution in $PhPdL_2X$ Complexes with an H-Phosphonate Diester as a Nucleophile (L = PPh_3)



kinetic isotope effect for the reaction investigated, the rate law (3) was inconsistent with the experimental data since it predicted (i) a first-order dependence on base concentration; (ii) a linear dependence of the rate on the equilibrium constant K; and (iii) an inverse dependence of the ligand exchange rates on concentration of the conjugated acid ($baseH^+$).[38]

For path B2 (Scheme 3), application of a steady-state approximation led to the following rate law:

$$-\frac{d[PhPd(PPh_3)_2X]}{dt} = \frac{k_1k_2[(EtO)_2P(O)H][base][PhPd(PPh_3)_2X]}{k_{-1} + k_2[base]} \quad (4)$$

In this form, the rate expression (4) was inconsistent with the experimental results (dependence on base concentration). However, assuming that the proton abstraction step could be much faster than the collapse of the complex $[PhPd(PPh_3)_2X + (EtO)_2P(O)H]$ back into the starting materials ($k_{-1} \ll k_2[base]$), then consistent with a small kinetic isotope effect observed, eq 4 would simplify to

$$-\frac{d[PhPd(PPh_3)_2X]}{dt} = k_1[(EtO)_2P(O)H][PhPd(PPh_3)_2X] \quad (5)$$

The resulting rate law (5) is identical to the experimentally determined one (eq 1) and lends support for path B2, with the rate-determining step being coordination of the H-phosphonate diester by the Pd^{II} complex, as a possible mechanism for the studied reaction.

Since the experimentally obtained rate constant k (eqs 1 and 2) corresponded to elementary second-order rate constant k_1 for nucleophilic attack of the H-phosphonate diester on the palladium center (Scheme 3), it was possible to determine thermodynamic activation parameters for this step. The highly negative value of the entropy of activation ($\Delta S^{\ddagger} = -72.2$ J mol^{-1} K^{-1}) determined from the Eyring plot[39] supported the associative character of this initial event in the ligand substitution step.

Table 3. Observed First-Order Rate Constants (k_{obs}) of the Decay of (dppp)Pd(Ph)X Complexes at 40 °C in THF (initial [(dppp)Pd(Ph)X] = 5 mM, $[(EtO)_2P(O)H] = [Et_3N] = 50$ mM)

entry	palladium(II) complex	k_{obs} (min^{-1})
1	(dppp)Pd(Ph)I	0.0581
2	(dppp)Pd(Ph)Br	0.1060
3	(dppp)Pd(Ph)Cl	0.1697

After having established the mechanistic basis for the ligand exchange for halide-containing complexes with monodentate ligands [*trans*-$PhPd(PPh_3)_2X$], we investigated the analogous reaction in the presence of bidentate ligands, which are known to force *cis* geometry of Pd^{II} complexes. As a model bidentate ligand, we chose 1,3-bis(diphenylphosphino)propane (dppp), due to its similar stereoelectronic properties to PPh_3.[40] In Table 3, the observed rate constants for the decay of (dppp)Pd(Ph)X complexes bearing various halide substituents, determined under the same reaction conditions as those used for the PPh_3 complexes, are shown. As apparent from the presented data, the rate constants for ligand substitution in complexes bearing this bidentate ligands were noticeably higher, but followed the same order of reactivity as those for the $PhPd(PPh_3)_2X$ complexes (Table 2). These may suggest that also complexes with bidentate ligands follow an analogous associative mechanistic pathway of ligand substitution as that described above for their monodentate phosphine counterparts.

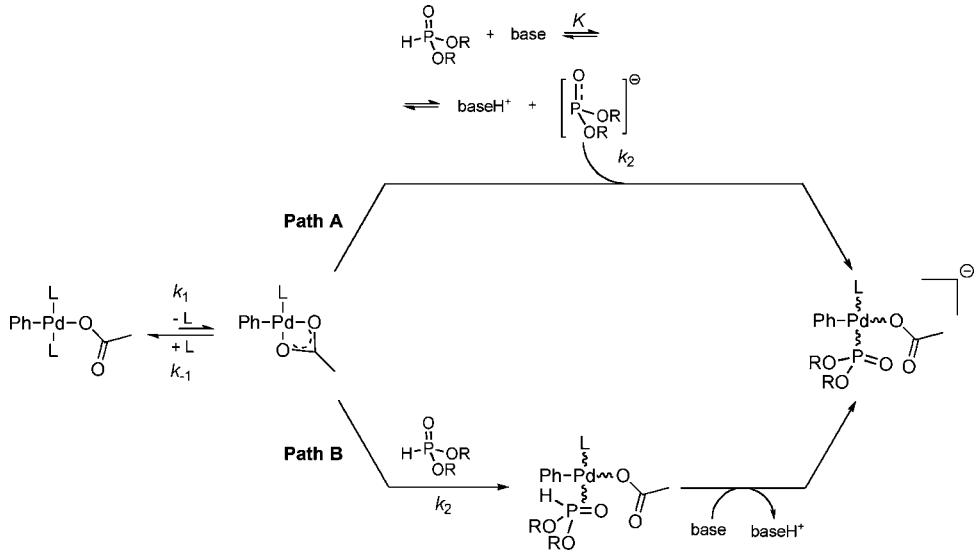
Ligand Substitution in $PhPdL_2(OAc)$ Complexes. As it was mentioned in the Introduction, the $PhPd(PPh_3)_2(OAc)$ complex exhibited a remarkably high reactivity in ligand substitution reactions with H-phosphonate nucleophiles.[28] This phenomenon cannot be explained on the basis of the mechanism discussed in the previous section for the halide complexes using the electronegativity argument, and thus for the acetate complexes probably a distinct mechanism was operating. Path A (Scheme 2), which involved the initial dissociation of an anion, seemed to be unlikely due to similar affinity of OAc^- and I^- ions to

(38) The rates of ligand exchange reactions between $PhPdL_2X$ and diethyl H-phosphonate diester were independent of the base concentration (when used in over stoichiometric amount) and were fairly insensitive to the base strength (*vide supra*). If the reactions were affected by the presence of the conjugated acids as predicted by eq 3, the first-order decay of $PhPdL_2X$, would not be observed due to increasing concentration of these species during the course of the reaction.

(39) See the Supporting Information.

(40) Palladium reduction and oxidative addition processes have also been studied in detail for complexes with dppp. See: Amatore, C.; Jutand, A.; Thuilliez, A. *Organometallics* **2001**, *20*, 3241–3249.

Scheme 4. Plausible Pathways for the Ligand Substitution in the $PhPdL_2(OAc)$ Complex with an H-Phosphonate Diesters as a Nucleophile (L = PPh_3)



the palladium(II) center.[36] One should, however, consider the other dissociative pathway (path C, Scheme 2), but in a slightly modified version, namely, with the carbonyl oxygen atom of the acetate group acting as an intramolecular nucleophilic catalyst in substitution of one of the phosphine ligands (Scheme 4). The intermediate, bearing a bidentate acetate group, formed in this reaction step, would then coordinate directly the H-phosphonate diester (Scheme 4, path B) or react with its anion (Scheme 4, path A) to give a ligand substitution product. An intramolecular nucleophilic catalysis by the acetate group would explain high rate acceleration observed in such reactions, due to favorable entropy changes, similarly as during neighboring group participation processes. Feasibility of this reaction pathway is supported by a number of reports describing metal complexes bearing bidentate (κ^2) acetate or amidate ligands, which have been observed in solution, solid state, and as reaction intermediates.[41] The involvement of analogous species was also claimed for certain palladium-catalyzed Heck reactions.[9,36]

To verify a possible intermediacy of bidentate acetate complexes in ligand substitution involving the palladium acetate complexes (Scheme 4, paths A and B), we measured rates of the disappearance of $PhPd(PPh_3)_2(OAc)$ as a function of PPh_3, $(EtO)_2P(O)H$, and Et_3N concentrations. Due to high reaction rates, the measurements were conducted at 15 °C.

It was found that with an excess of PPh_3, $(EtO)_2P(O)H$, and Et_3N, the decay of $PhPd(PPh_3)_2(OAc)$ followed first-order kinetics (^{31}P NMR experiments). A plot in Figure 4, $1/k_{obs}$ versus concentration of PPh_3, showed a linear relationship, with a positive slope and nonzero *y*-intercept, which indicated inhibition of the reaction by the phosphine ligand. The plot of $1/k_{obs}$ versus $1/[(EtO)_2P(O)H]$ was also linear, with a nonzero *y*-intercept (Figure 5), and the reaction was found to be independent of the base (Et_3N) concentration (Figure 6).

To find out which of the reaction pathways in Scheme 4 was compatible with the experimental kinetic data, we derived rate laws for path A and path B. After application of a steady-state approximation to the reaction sequence in path A, the following rate law for the decay of the $PhPd(PPh_3)_2(OAc)$ complex was obtained:

$$-\frac{d[PhPd(PPh_3)_2(OAc)]}{dt} = \frac{k_1k_2K\dfrac{[(EtO)_2P(O)H][base]}{[baseH^+]}[PhPd(PPh_3)_2(OAc)]}{k_{-1}[PPh_3] + k_2K\dfrac{[(EtO)_2P(O)H][base]}{[baseH^+]}} \quad (6)$$

$$\frac{1}{k_{obs}} = \frac{k_{-1}[PPh_3][baseH^+]}{k_1k_2K[(EtO)_2P(O)H][base]} + \frac{1}{k_1} \quad (7)$$

Equation 7 correctly predicts the relationships of $1/k_{obs}$ versus $[PPh_3]$ (Figure 4) and versus $1/[(EtO)_2P(O)H]$ (Figure 5). However, as for the corresponding halide complexes (Scheme 3, path B1, and eq 3), the existence of the pre-equilibrium between the H-phosphonate diester and its anion implied that also a base concentration entered into the rate law (7), and thus the relationships $1/k_{obs}$ versus 1/[base], should be identical to that of $1/k_{obs}$ versus $1/[(EtO)_2P(O)H]$ (Figure 5). Since the rate of the reaction investigated was not affected by changes in the concentration of Et_3N (Figure 6), path A in Scheme 4 was inconsistent with our kinetic data.

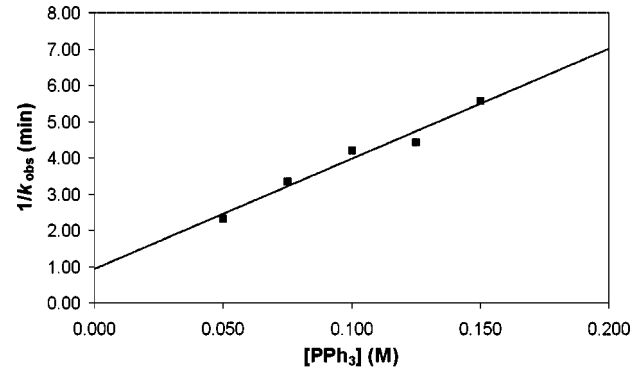


Figure 4. Plot of $1/k_{obs}$ versus PPh_3 concentration for the decay of $PhPd(PPh_3)_2(OAc)$ in THF at 15 °C (initial $[PhPd(PPh_3)_2(OAc)]$ = 5 mM, $[(EtO)_2P(O)H] = [Et_3N]$ = 50 mM).

(41) (a) Tackett, J. E. *Appl. Spectrosc.* **1989**, *43*, 483–489. (b) Harvey, M.; Baggio, S.; Baggio, R.; Mombru, A. W. *Acta Crystallogr.* **1999**, *C55*, 308–310. (c) Ikawa, T.; Barder, T. E.; Biscoe, M. R.; Buchwald, L. S. *J. Am. Chem. Soc.* **2007**, *129*, 13001–13007. (d) Fujita, K. i.; Yamashita, M.; Puschmann, F.; Alvarez-Falcon, M. M.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 9044–9045.

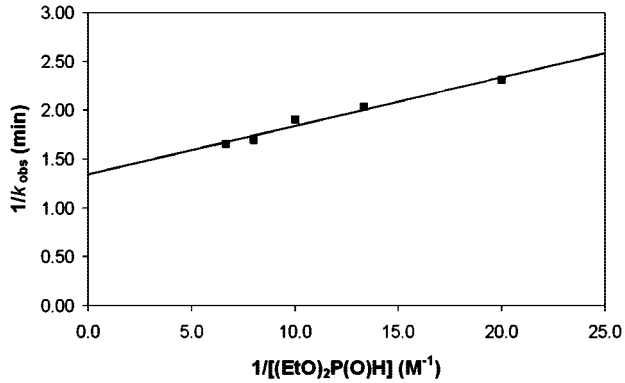


Figure 5. Plot of $1/k_{obs}$ vs $1/[(EtO)_2P(O)H]$ for the decay of $PhPd(PPh_3)_2(OAc)$ in THF at 15 °C (initial $[PhPd(PPh_3)_2(OAc)] = 5$ mM, $[PPh_3] = [Et_3N] = 50$ mM).

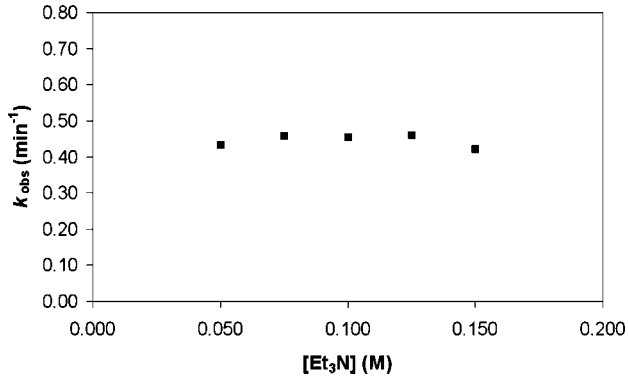


Figure 6. Dependence of the rate of $PhPd(PPh_3)_2(OAc)$ decay on the concentration of Et_3N in THF at 15 °C (initial $[PhPd(PPh_3)_2(OAc)] = 5$ mM, $[(EtO)_2P(O)H] = [PPh_3] = 50$ mM).

Instead, the second mechanistic pathway, namely, path B (Scheme 4), turned out to be in good agreement with the results shown in Figures 4−6:

$$-\frac{d[PhPd(PPh_3)_2(OAc)]}{dt} = \frac{k_1k_2[(EtO)_2P(O)H][PhPd(PPh_3)_2(OAc)]}{k_{-1}[PPh_3] + k_2[(EtO)_2P(O)H]} \quad (8)$$

$$\frac{1}{k_{obs}} = \frac{k_{-1}[PPh_3]}{k_1k_2[(EtO)_2P(O)H]} + \frac{1}{k_1} \quad (9)$$

For this mechanism, base concentration was not present in the rate law (8), since the P−H bond breaking occurred after the rate-determining step and thus was kinetically insignificant. Equation 9 correctly predicted also the observed linear dependencies of $1/k_{obs}$ versus $[PPh_3]$ and versus $1/[(EtO)_2P(O)H]$. Nonzero *y*-intercepts for these reactions, which corresponded to $1/k_1$, indicated that the rate law (8) could not be simplified by dropping the $k_2[(EtO)_2P(O)H]$ term in the denominator. In mechanistic terms this means that the intermediate bidentate acetate complex (Scheme 4) reacted with comparable rates both "backward" with PPh_3 and "forward" with the H-phosphonate. Actually, by plugging into eq 9 the measured values of k_{obs}, the known concentrations of the reactants, and k_1 (from the intercept), the k_2/k_{-1} ratio could be calculated. The obtained value of ∼0.9 showed that the transient bidentate acetate complex formed was not selective toward different nucleophiles, as one would expect for a highly reactive intermediate.

To support further the proposed mechanism for the ligand substitution in the $PhPd(PPh_3)_2(OAc)$ complex (path B in Scheme 4), we determined the thermodynamic activation parameters for the initial step of the reaction, namely, the dissociation of the phosphine ligand (Scheme 4). To this end, k_1 rate constants were determined at three temperatures (5 and 10 °C in addition to 15 °C; from intercepts of the plots $1/k_{obs}$ versus PPh_3)[39] and plugged into the Eyring equation.[39] A highly positive entropy of activation ($\Delta S^{\ddagger} = 53.3$ J mol^{-1} K^{-1}) obtained confirmed a dissociative character of this key step of the reaction.

Finally, we attempted to measure the ligand substitution rate for a complex containing an acetate group and a bidentate ligand, (dppp)Pd(Ph)(OAc). Unfortunately, the reaction was too fast to be followed by means of ^{31}P NMR spectroscopy (completion in <3 min). Anyway, the very high rate for this reaction suggested that probably a mechanism analogous to that described above (Scheme 4, path B) operated also for this bidentate phosphine complex. Such a mechanism would imply that, at least at some stages of the reaction, only one phosphorus atom of the dppp ligand would be engaged in the complexation. Recent studies on reactivity of dppf palladium(II) complexes with sulfur nucleophiles[16] lend support for such a scenario (also, *vide infra*).

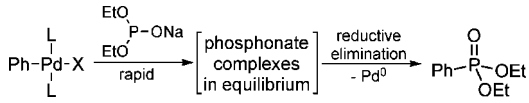
Intermediate Phosphonate Pd^{II} Complexes Bearing PPh_3 Ligands and the C−P Bond-Forming Reductive Elimination Step. The so far discussed results focused on a ligand substitution step and revealed various ways in which palladium(II) complexes, formed in the course of oxidative addition, might react with H-phosphonate diesters, depending on the anion (Cl^-, Br^-, I^-, AcO^-) initially ligated to the Pd^{II} center. However, an important issue that has not been addressed yet was the structure of palladium phosphonate complexes formed in ligand substitution steps, from which a reductive elimination of diethyl phenylphosphonate occurred (Scheme 5).

Scheme 5

In the instance of halide-containing complexes (Scheme 2, path B), the possible square-planar palladium phosphonate products may be neutral (a halide anion departs and two PPh_3 ligands remain; two isomers) or anionic species (a halide anion stays and PPh_3 departs; three isomers). For the Pd^{II} complex with an acetate group, the square-planar palladium phosphonate complex formed (Scheme 4) should be an anionic species with three different possible configurations. It was also possible that, before the reductive elimination took place, a ligand exchange and isomerization of palladium phosphonate complexes occurred. These could be induced by PPh_3, halide, or acetate ions present in the reaction mixture and would add further to the complexity of the intermediate complexes formed. Some of these intermediates might be formed preferentially, either on kinetic or thermodynamic grounds, but only those having phenyl and phosphonate ligands in *cis* configuration should be able to undergo reductive elimination.[20,21] The latter issue could be quite complex for cross-coupling reactions performed in the presence of monodentate ligands, such as PPh_3.

To obtain mechanistic insight into the reductive elimination step, we decided to generate palladium phosphonate intermediates from $PhPd(PPh_3)_2X$ (X = I, Br, Cl, OAc) complexes using different phosphorus-nucleophiles and to follow both the product formation and the decay of the palladium phosphonate intermediates by ^{31}P NMR spectroscopy (Schemes 5 and 6).

Scheme 6. Rapid *in Situ* Generation of the Equilibrating Pd^{II} Phosphonate Complexes via the Reaction of PhPd(PPh$_3$)$_2$X with (EtO)$_2$PONa and the Following Reductive Elimination (L = PPh$_3$)



Analysis of the cross-coupling reactions involving phosphorus nucleophiles by ^{31}P NMR spectroscopy was facilitated by the fact that phosphine ligands present in different complexes, and also the reactants and the products, could be observed simultaneously. In Figures 7−10, the filled squares represent the first-order decays of PhPd(PPh$_3$)$_2$X complexes in the presence of excess (EtO)$_2$P(O)H and Et$_3$N, and the filled diamonds in the same figures represent the amounts of the reductive elimination product [(EtO)$_2$P(O)Ph)] formed.

As apparent from the data for PhPd(PPh$_3$)$_2$Br and PhPd(PPh$_3$)$_2$Cl complexes (Figures 8 and 9, respectively), the reductive elimination product formation lagged behind the disappearance of the starting palladium complexes; that is, the amount of diethyl phenylphosphonate formed after a given time was less than expected from the substrate consumption. What was important, in the ^{31}P NMR spectra of these reaction mixtures, there were no other signals than those from PhPd(PPh$_3$)$_2$X, (EtO)$_2$P(O)H, (EtO)$_2$P(O)Ph, and PPh$_3$-ligated Pd^0 species. The "missing" amount of the cross-coupling product (calculated as the difference of the integrals of the (EtO)$_2$P(O)Ph and PhPd(PPh$_3$)$_2$X signals), which should correspond to

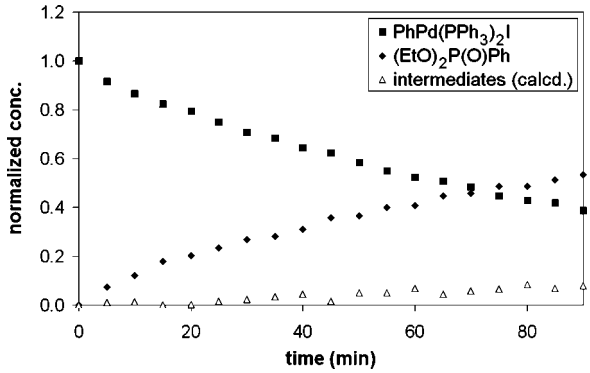


Figure 7. Reaction of PhPd(PPh$_3$)$_2$I with (EtO)$_2$P(O)H in THF at 40 °C (initial [PhPd(PPh$_3$)$_2$I] = 5 mM, [(EtO)$_2$P(O)H] = [Et$_3$N] = 50 mM).

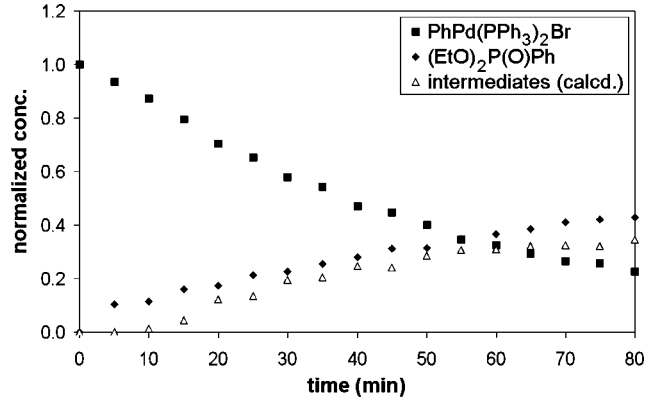


Figure 8. Reaction of PhPd(PPh$_3$)$_2$Br with (EtO)$_2$P(O)H in THF at 40 °C (initial [PhPd(PPh$_3$)$_2$Br] = 5 mM, [(EtO)$_2$P(O)H] = [Et$_3$N] = 50 mM).

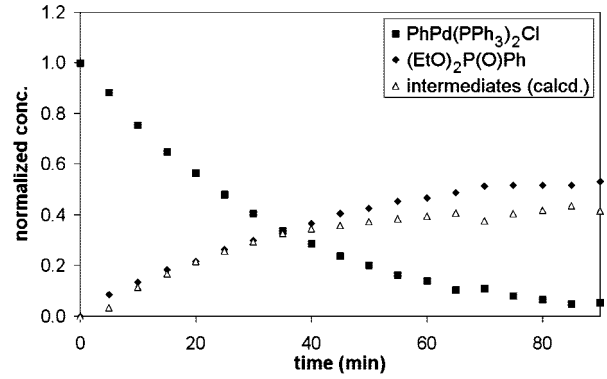


Figure 9. Reaction of PhPd(PPh$_3$)$_2$Cl with (EtO)$_2$P(O)H in THF at 40 °C (initial [PhPd(PPh$_3$)$_2$Cl] = 5 mM, [(EtO)$_2$P(O)H] = [Et$_3$N] = 50 mM).

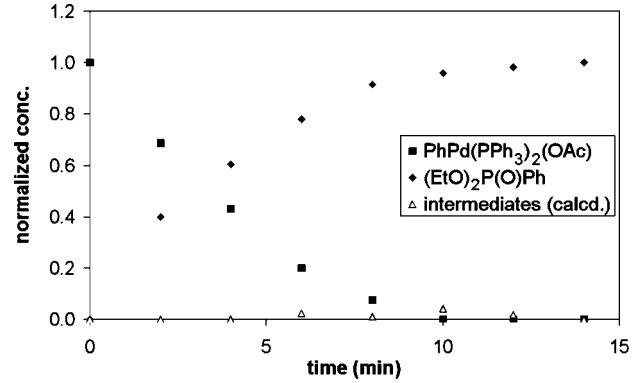


Figure 10. Reaction of PhPd(PPh$_3$)$_2$(OAc) with (EtO)$_2$P(O)H in THF at 15 °C (initial [PhPd(PPh$_3$)$_2$(OAc)] = 5 mM, [(EtO)$_2$P(O)H] = [Et$_3$N] = 50 mM).

"intermediates" in Scheme 5, is shown in the graphs as open triangles. The fact that these intermediates, although present in a relatively large concentration, were not detectable by the ^{31}P NMR spectroscopy could be due to their involvement in a complex equilibria system and extensive splitting pattern of the resonances (due to coupling of nonequivalent phosphorus atoms of phosphine and phosphonate ligands), which could ultimately lead to broadening of the signals into the baseline. A similar phenomenon, ascribed to a dynamic solution behavior of square-planar palladium complexes, was already reported for Pd^{II} phosphonate species containing triarylphosphines.[19] Interestingly, this effect of accumulation of equilibrating palladium phosphonate intermediates was observed mainly for PhPd(PPh$_3$)$_2$-Br and PhPd(PPh$_3$)$_2$Cl complexes (Figures 8, 9) and to a smaller extent for PhPd(PPh$_3$)$_2$I (Figure 7).

Due to expected difficulties in dealing with a series of sequential reactions that could lead to complex kinetic expressions, we decided to study the reductive elimination from an equilibrium mixture of palladium phosphonates, rapidly generated from PhPd(PPh$_3$)$_2$X and a powerful phosphorus nucleophile, namely, sodium diethyl phosphite [(EtO)$_2$PONa]. Such a technique has been used for studying other reductive elimination processes.[13−15,17,19]

To this end, to a solution of PhPd(PPh$_3$)$_2$I in THF containing PPh$_3$ (the presence of PPh$_3$ was necessary to avoid Pd black precipitation, *vide supra*) was added 0.9 equiv of (EtO)$_2$PONa, and progress of the reaction was followed by ^{31}P NMR spectroscopy. The first spectrum recorded (<1 min) revealed the presence of only a sharp, residual signal of PhPd(PPh$_3$)$_2$I (∼10%), while the resonances due to (EtO)$_2$PONa and PPh$_3$

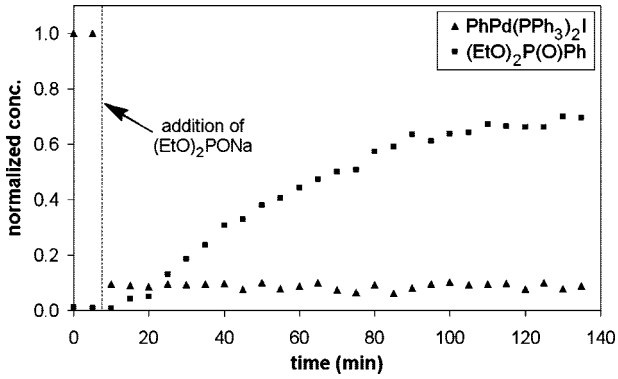


Figure 11. Generation of the equilibrating Pd^{II} phosphonate complexes by the addition of $(EtO)_2PONa$ to a solution of $PhPd(PPh_3)_2I$ and the following reductive elimination of $(EtO)_2P(O)Ph$ in THF at 40 °C (initial $[PhPd(PPh_3)_2I] = 5$ mM).

Table 4. Observed First-Order Rate Constants (k_{obs}) of the Reductive Elimination of $(EtO)_2P(O)Ph$ from the Mixtures of Equilibrating Pd^{II} Phosphonate Complexes, Generated from Different $PhPd(PPh_3)_2X$ Precursors and $(EtO)_2PONa$, in THF at 40 °C (initial $[PhPd(PPh_3)_2X] = 5$ mM)

entry	$PhPd(PPh_3)_2X$ precursor and amount of PPh_3 added	k_{obs} (min^{-1})
1	$PhPd(PPh_3)_2I + PPh_3$	0.0141
2	$PhPd(PPh_3)_2Br + PPh_3$	0.0077
3	$PhPd(PPh_3)_2Cl + PPh_3$	0.0074
4	$PhPd(PPh_3)_2I + 10PPh_3$	0.0346
5	$PhPd(PPh_3)_2Br + 10PPh_3$	0.0291
6	$PhPd(PPh_3)_2Cl + 10PPh_3$	0.0121
7	$PhPd(PPh_3)_2(OAc) + PPh_3$	0.7412

disappeared completely (Scheme 6).[42] Such an appearance of the ^{31}P NMR spectrum suggested that the expected equilibrium mixture of palladium phosphonate complexes was, indeed, rapidly formed and that free PPh_3 [but not $PhPd(PPh_3)_2I$] was engaged into this equilibria system. After ca. 10 min, a signal of the expected reductive elimination product, $(EtO)_2P(O)Ph$, started to emerge, together with a broad peak from PPh_3 ligated to Pd^0 species. The formation of $(EtO)_2P(O)Ph$ displayed first-order kinetics (Figure 11), and the corresponding rate constant could be determined (Table 4, entry 1). A similar behavior was observed for the other $PhPd(PPh_3)_2X$ complexes (X = Br, Cl, and OAc),[39] and the rate constants for a reductive elimination from these complexes are listed in Table 4. Also, the effect of added PPh_3 on rates of the reductive eliminations was investigated (Table 4).

The data in Table 4 revealed two important features of the reductive elimination process. First, the rate of a reductive elimination depends on the anion present in the precursor complex, and second, the addition of PPh_3 accelerates the reaction. These findings suggested that a reductive elimination could occur from pentacoordinate intermediates (probably, *tbp*) containing a halide anion or that the departure of a halide anion to form a square-planar complex, from which the elimination occurs, was the rate-determining step for the process.

The trend of reactivity found for the halides (Table 4, entries 1−3) explained the postulated accumulation of the intermediate palladium phosphonate complexes during reactions of $PhPd(PPh_3)_2X$ with $(EtO)_2P(O)H$ (Figures 7−9) and the observed lag in the product formation when X = Cl and Br. This was consistent with the fact that rates of coordination of $(EtO)_2P(O)H$ by $PhPd(PPh_3)_2X$ (Scheme 5, the first step) decreased in the order X = Cl > Br > I (Table 2), while those of the reductive elimination (Scheme 5, the second step) decreased in an opposite direction (I > Br > Cl). For X = Cl or Br, the intermediate Pd^{II} phosphonate complexes were quickly formed, but collapsed slowly to the product, whereas for X = I, formation of the intermediate complexes was slower than the subsequent reductive elimination step.

According to theoretical studies, the concerted reductive elimination is symmetry allowed and can occur from both square-planar (*sq*)[21] and trigonal bipyramid (*tbp*)[43] complexes, provided that the eliminated ligands occupy the adjacent positions (*cis* in *sq* and equatorial-apical in *tbp* complexes). Assuming that the phenyl group and a phosphonate ligand cannot dissociate from palladium(II) complexes, the postulated equilibria of palladium phosphonate species were thus due to exchange of halide anions, PPh_3, and/or spatial rearrangements of the ligands. There are 5 *sq* and 11 *tbp* reasonable (neutral or monoanionic) structures possible, interconverting via 13 transient square-pyramids.[39] Nine of them (3 *sq* and 6 *tbp*) fulfill the geometrical requirements for a reductive elimination; however, due to stereoelectronic effects, these structures may differ significantly in their ability to undergo reductive elimination.

From electronic and structural points of view, more susceptible to reductive elimination are complexes with low electron density and bulky spectator ligands present.[44] In light of this, pentacoordinate palladium complexes containing halides should exhibit rather low reactivity in reductive elimination, due to both net negative charge present and small steric demands for spherical halide anions. However, if the halide anion is expelled, the resulting complexes, ligated only by phenyl, a phosphonate, and 2 or 3 PPh_3 molecules (2 *sq* and 3 *tbp* structures), should be more susceptible to reductive elimination. We believe that the observed trend in reactivity of Pd^{II} phosphonate complexes in reductive elimination as a function of the halide present, i.e., I > Br > Cl, originated from the different affinity of these anions toward the Pd^{II} center. A weakly bound I^- was expected to be more easily replaced by PPh_3 than a strongly bound Cl^-, and in the presence of excess phosphine ligand, the equilibrium should be shifted toward the neutral, more sterically hindered species, from which reductive elimination should be facilitated.

Finally, there was a case of a remarkably fast reductive elimination when the acetate group was present in the precursor complex [$PhPd(PPh_3)_2(OAc)$; Table 4, entry 7]. Since this reaction was more than an order of magnitude faster than that for the most reactive halide derivative [$PhPd(PPh_3)_2I$; Table 4, entries 1 and 4] it seemed that a distinct mechanism might operate for the acetate-containing palladium complexes. For $PhPd(PPh_3)_2(OAc)$, the addition of $(EtO)_2PONa$ triggered a rapid reaction, with only a small lag in the diethyl phenylphosphonate formation. This indicated that both steps of the reaction in Scheme 6, i.e., the reaction of $PhPd(PPh_3)_2(OAc)$ with the phosphorus nucleophile and the reductive elimination from the intermediate palladium phosphonate complexes formed, were fast.

The high reactivity of $PhPd(PPh_3)_2(OAc)$ in ligand substitution was discussed above, and it was assigned to generation of

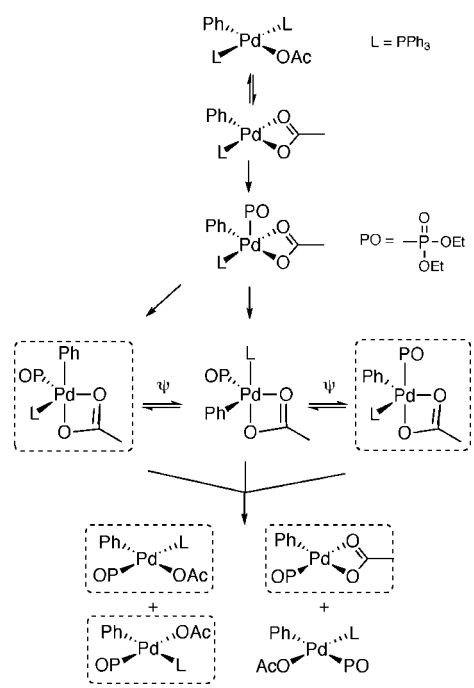
(42) A rapid reaction of $(EtO)_2PONa$ indicates that the H-phosphonate anion can efficiently act a nucleophile in the ligand substitution at the Pd^{II} center. This means that path B1 in Scheme 3 is a possible mechanism for the reaction. However, no involvement of this mechanism when Et_3N, *N*-methylmorpholine, and pyridine were used as bases shows that these bases generate only negligible amount of the H-phosphonate anion, and thus under standard reaction conditions apparently only path B2 is operating.

(43) Braterman, P. S.; Cross, R. J.; Young, G. B. *J. Chem. Soc., Dalton Trans.* **1976**, 1306–1310.

(44) Zuidema, E.; van Leeuwen, P. W. N. M.; Bo, C. *Organometallics* **2005**, *24*, 3703–3710.

(45) Amatore, C.; Carre, E.; Jutand, A.; M'Barki, M. A. *Organometallics* **1995**, *14*, 1818–1826.

Scheme 7. Putative Penta- and Tetracoordinate Palladium Phosphonate Species Formed from the $PhPd(PPh_3)_2(OAc)$ Complex[a]



[a] Complexes from which reductive elimination is allowed are marked with dashed rectangles (charges are omitted for clarity).

a highly reactive κ^2-acetate species (Scheme 4). However, the enhanced reactivity observed in the reductive elimination step of the acetate-containing complexes was less obvious, and we ascribed it to some unique features of the generated palladium phosphonate intermediates bearing an acetate group. Since ^{31}P NMR spectroscopy did not provide any insight into chemical structures of these intermediates, we could only speculate that coordination of $(EtO)_2PONa$ to a κ^2-acetate species should result in formation of negatively charged, pentacoordinate (*tbp*) intermediates, in which the κ^2-acetate group might span the equatorial and the apical position of *tbp* (Scheme 7). Since it was rather unlikely that a κ^2-ligand could be expelled from the complex, we considered two scenarios for the reductive elimination step. In one of them, from the pool of generated pentacoordinate intermediates, four square-planar palladium phosphonates could be formed (Scheme 7). A reductive elimination of the product (diethyl phenylphosphonate), with generation of $LPd^0(OAc)^{-}$[45] or κ^2-$Pd^0(OAc)^-$ species, might occur from three of these interconverting (via pentacoordinate species) complexes.

In the second scenario (Scheme 7), reductive elimination of diethyl phenylphosphonate might take place directly from pentacoordinate palladium phosphonate intermediates. In our opinion, reductive elimination from pentacoordinate intermediates containing an acetate group is a viable option on three counts. First, due to expected positional preference, the κ^2-acetate group should occupy a equatorial-apical position in *tbp*, and thus the number of *tbp*'s formed, should be limited to three. Second, from the initial *sp* complex bearing a phosphonate group in the vertex position, two *tbp*'s (both with a κ^2-acetate group spanning the equatorial and the apical position) could be formed. One of them would have the groups to be eliminated in a favorable position for reductive elimination, an equatorial-apical position, while from the other *tbp*, such an arrangement of the ligands could be attained after one pseudorotation, using either the phenyl or the phosphonate moiety as a pivot of pseudorotation. Two *tbp*'s from which the reductive elimination is permitted are marked with dashed rectangles in Scheme 7. Due to steric demands for a bulky PPh_3, this ligand should show preference for an equatorial position in *tbp*, and thus formation of *tbp* species with an apical-equatorial arrangement of the groups to be eliminated should be energetically favored. Third, *tbp*'s bearing κ^2-acetate in the equatorial-apical position are expected to be distorted, and this may facilitate their collapse, with expulsion of the reductive elimination product.

Scheme 8. *In Situ* Generation of $(dppp)Pd(Ph)(PO(EtO)_2)$ Complex via the Reaction of (dppp)Pd(Ph)X (X = I, Br, Cl) with $(EtO)_2PONa$ and the Following Reductive Elimination

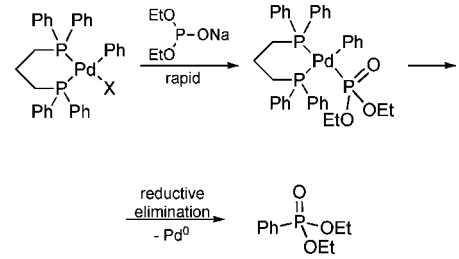


Table 5. Observed First-Order Rate Constants (k_{obs}) for the Reductive Elimination of $(EtO)_2P(O)Ph$ from the Palladium Phosphonate Intermediate, Generated from (dppp)Pd(Ph)X and $(EtO)_2PONa$, in THF at 40 °C (initial [(dppp)Pd(Ph)X] = 5 mM)

entry	(dppp)Pd(Ph)X precursor and amount of PPh_3 added	k_{obs} (min^{-1})
1	(dppp)Pd(Ph)I + PPh_3	0.0568
2	(dppp)Pd(Ph)Br + PPh_3	0.0499
3	(dppp)Pd(Ph)Cl + PPh_3	0.0500
4	(dppp)Pd(Ph)I + 10PPh_3	0.0497
5	(dppp)Pd(Ph)(OAc) + PPh_3	0.4013

Intermediate Phosphonate Pd^{II} Complexes Bearing dppp Ligand and the C−P Bond-Forming Reductive Elimination Step. To clarify certain aspects of the reductive elimination steps studied, we conducted additional experiments on complexes bearing a bidentate ligand (dppp). In this instance, in contradistinction to the monodentate complexes of type $PhPd(PPh_3)_2X$, treatment of (dppp)Pd(Ph)X (X = I, Br, Cl) complexes with $(EtO)_2PONa$ provided palladium phosphonate species with a well-defined ^{31}P NMR characteristic (three groups of resonances in the region of chemical shifts of ca. 0, 4, and 82 ppm). This complex was formed irrespective of the halide present in the parent compound (Scheme 8), and on the basis of the chemical shift values and the splitting pattern of the signals, its structure was assigned as $(dppp)Pd(Ph)(PO(EtO)_2)$.[39]

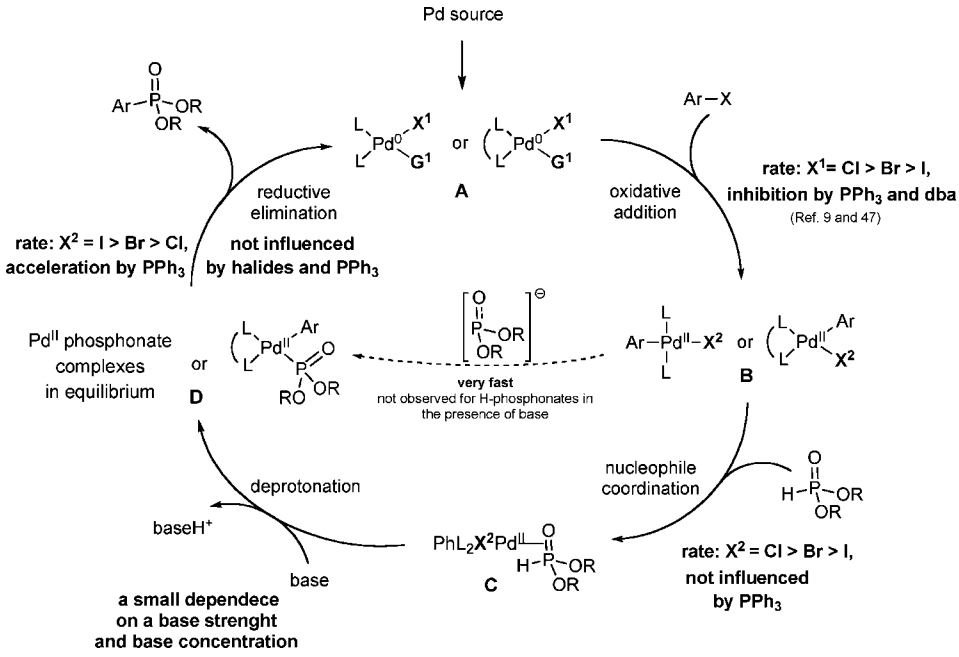
Apparently, the entropically driven chelating effect of the dppp ligand made this Pd^{II} phosphonate complex by far less fluxional compared to complexes with monodentate PPh_3 ligands, and formation of this complex was in agreement with the earlier reports on analogous Pd^{II} phosphonate complexes bearing bidentate ligands.[17−19,46]

For the $(dppp)Pd(Ph)(PO(EtO)_2)$ complex, generated from different precursors, a reductive elimination of diethyl phenylphosphonate was investigated, and the first-order rate constants were determined. These are listed in Table 5, together with the rate constant for the reaction when a 10 M excess of PPh_3 was used (Table 5, entry 4).

For all the precursor complexes bearing different halides, similar rate constants were obtained. Since the addition of extra PPh_3 did not influence significantly the rate of this reaction, it

(46) Stockland, R. A.; Maher, D. L.; Anderson, G. K.; Rath, N. P. *Polyhedron* **1999**, *18*, 1067–1075.

Scheme 9. Proposed Catalytic Cycle for the Palladium-Mediated Cross-Coupling of H-Phosphonates with Aryl Halides[a]



[a] Structures to the left and to the right refer to PPh_3 or a bidentate ligand, respectively. Complexes' charges are omitted for clarity.

seemed that the reductive elimination probably occurred directly from this *cis*-configured (dppp)Pd(Ph)($PO(EtO)_2$) complex.

As to the acetate-containing complex (dppp)Pd(Ph)(OAc), also in this instance it behaved differently form the halide complexes of type (dppp)Pd(Ph)X. First, it reacted an order of magnitude faster than the other bidentate complexes investigated (Table 5, entry 5), and second, the expected palladium phosphonate (dppp)Pd(Ph)($PO(EtO)_2$) could not be detected by ^{31}P NMR spectroscopy. Instead, upon addition of $(EtO)_2PONa$ to the reaction mixture, the signal from the (dppp)Pd(Ph)(OAc) complex disappeared immediately, and a fast formation of the reductive elimination product [$(EtO)_2P(O)Ph$] was observed. This phenomenon appeared to be similar to that observed for the reaction of $PhPd(PPh_3)_2X$ complexes with $(EtO)_2PONa$ and pointed to the formation of an equilibrium mixture of palladium phosphonate complexes.

Although structures of such complexes remained cryptic, one can speculate that the acetate group in (dppp)Pd(Ph)(OAc) can open the six-membered ring system of the dppp ligand and form a highly reactive bidentate (κ^2) acetate species, analogous to that shown in Scheme 4. This could coordinate the phosphorus nucleophile $(EtO)_2PONa$ and generate a mixture of pentacoordinate palladium phosphonate intermediates. However, in contrast to the halide-containing complexes, which can expel a halide anion and collapse to (dppp)Pd(Ph)($PO(EtO)_2$), complexes with κ^2-acetate ligands probably could not eliminate the acetate group and thus remained highly fluxional. Since the presence of a κ^2-acetate ligand in pentacoordinate complexes will confer significant distortions to *tbp* geometry, the reactivities of such complexes are expected to be high, and a reductive elimination may thus occur directly from these species (*vide supra*).

Irrespective of the mechanistic details, which remain to be clarified, an important feature of the acetate group as a ligand in palladium complexes is its ability to form bidentate (κ^2) acetate species, both for square-planar and pentacoordinate complexes, which may have enhanced reactivity in ligand substitution and reductive elimination reactions.

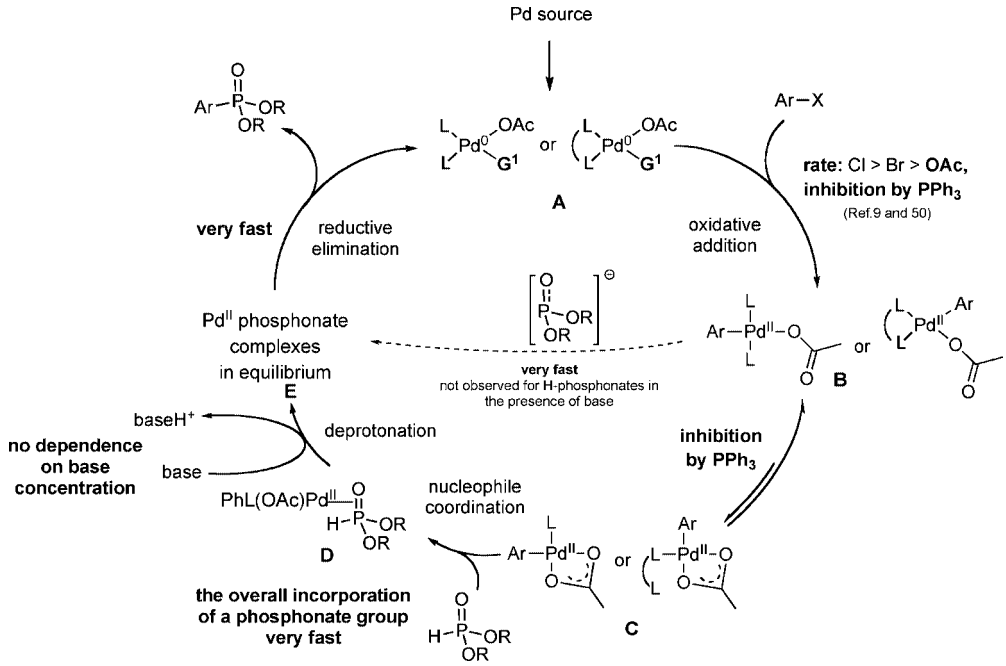
Mechanisms for the Palladium-Catalyzed C−P Bond Formation. The above mechanistic studies on ligand substitution and reductive elimination, appended with the existing knowledge about oxidative addition, lend themselves to a more detailed picture of two catalytic cycles for the palladium-mediated C−P bond formation, which are summarized in Schemes 9 and 10.

Scheme 9 depicts a catalytic cycle for the reaction in which halide anions are involved. This is by far the most common situation for cross-coupling reactions using aryl halides, since even in the absence of external halide additives, these anions are released during the course of the reaction and can interact with various palladium species at different stages of the cycle.

The first step, oxidative addition of an aryl halide to Pd^0 catalyst **A**, results in formation of arylpalladium complexes **B**. Reactivity of the palladium catalyst **A** in this step depends on the halide anions ligated to this species ($\mathbf{X}^1$ in Scheme 8) and decreases in the order Cl > Br > I. Additional ligation of PPh_3 or dba ($\mathbf{G}^1$) lowers the reactivity of catalytic species **A**.[9,47] The next step, a reaction of arylpalladium **B** with a nucleophile, usually referred to as a ligand substitution, in the case of phosphorus nucleophiles is better described as a nucleophile coordination step. This affords pentacoordinate species **C**, which has to undergo deprotonation by a base to form penta- or four-coordinated palladium phosphonate complexes **D**. This pathway is followed by H-phosphonate diesters and related phosphorus nucleophiles that do not have a lone electron pair on the phosphorus atom. The reactivity of Pd^{II} complexes **B**, irrespective of denticity of the supporting ligand used (mono- or bidentate), follows the same trend as that for the oxidative addition; namely, the reaction is fastest when $\mathbf{X}^2 = Cl$, followed by Br and I. These two steps of the cycle are responsible for the overall acceleration of the cross-coupling reaction when chlorides or bromides are added to the reaction mixture (Table 1, entries 2, 3, 5, and 6).

(47) Amatore, C.; Jutand, A. *Coord. Chem. Rev.* **1998**, *178−180*, 511–528.

Scheme 10. Proposed Catalytic Cycle for the Palladium-Mediated Cross-Coupling of H-Phosphonates with Aryl Halides, Involving Acetate As a Ligand[a]



[a] Structures to the left and to the right refer to PPh_3 or a bidentate ligand, respectively. Complexes' charges are omitted for clarity.

A nucleophile coordination step, which produces pentacoordinate complex **C**, is usually slow compared to the subsequent deprotonation, and thus the strength of a base used for the reaction and its concentration practically do not significantly affect the rates of the palladium phosphonates **D** formation.[48] Importantly, the whole incorporation process of a phosphonate ligand into complexes **D** is not influenced by PPh_3 ligand concentration.

For phosphorus nucleophiles that do not require deprotonation [e.g., $(EtO)_2PONa$], direct nucleophilic attack on Pd^{II} complexes **B** is possible.[49] This reaction is very fast and produces palladium phosphonates **D**. Now, depending on the denticity of the supporting ligand used, there are two scenarios. For monodentate ligand PPh_3, the Pd^{II} phosphonates **D** are involved in a complex equilibria system of penta- and tetracoordinate species, powered by the halide anions and PPh_3 present. Reductive elimination of the product $Ar-P(O)(OR)_2$ from such an equilibrating mixture of palladium phosphonate complexes is highest if I^- ions are engaged in the equilibria and somewhat slower for Br^- and Cl^-. The added PPh_3 accelerates further this reductive elimination.

For bidentate phosphines used as supporting ligands, less fluxional, tetracoordinate Pd^{II} phosphonate complexes **D**, with defined *cis* configuration of an aryl and a phosphonate group, are formed. Rates of reductive elimination from such complexes are not affected by the kind and concentration of the halide anions present, nor the added PPh_3.

The above catalytic cycle is modified to large extent when the acetate ion is involved in complexation of palladium species at different stages of a cross-coupling reaction, and this is shown in Scheme 10.

The acetates can be brought to the reaction mixture together with the palladium source [e.g., $Pd(OAc)_2$] or may be introduced as an external additive. Due to rather weak affinity of the acetate ion to Pd^0 ($Cl^- > Br^- > OAc^- > I^-$) or Pd^{II} ($Cl^- > Br^- > OAc^- \sim I^-$) centers, the halides released during the course of a cross-coupling reaction may effectively compete with acetate ions, and ultimately, the reaction may switch to the "halide cycle" (Scheme 9). This is usually manifested in a gradual slowing of the cross-coupling reaction. However, if the reaction is carried out in the presence of externally added acetate anions (e.g., *n*-Bu_4NOAc), a remarkable shortening in the reaction time is observed (Table 1, entry 7).

In this acetate type of catalytic cycle, the oxidative addition of aryl halides to Pd^0 catalyst **A** bearing an acetate group is slower than a reaction with a palladium catalyst with coordinated halides (Scheme 9) and is also inhibited by the added PPh_3.[50] The observed overall acceleration of cross-coupling reactions upon addition of acetate anions is due to mechanistic changes in steps leading from arylpalladium **B** to palladium phosphonate **E** complexes (collectively referred to as a ligand substitution) and in the reductive elimination step.

The presence of an acetate group in Pd^{II} complexes **B** (Scheme 10), formed in oxidative addition, opens a new mechanistic pathway for the reaction with H-phosphonate diesters. Namely, the acetate may act as an internal nucleophile and expel the phosphine ligand, producing highly reactive intermediates of type **C**, with a κ^2-acetate ligand. From this species, after coordination of an H-phosphonate diester to produce a pentacoordinate complex **D**, and its subsequent deprotonation, an equilibrium mixture of palladium phosphonates **E** is formed. Since κ^2-acetate complexes **C** and arylpalladium **B** are in equilibrium, and a nucleophile coordination to

(48) Base is, however, an indispensable reactant component and has to be used in stoichiometric amounts in cross-coupling reactions involving H-phosphonate diesters.

(49) This pathway is not observed for cross-coupling reactions of dialkyl H-phosphonate diesters in the presence of a base, due to negligible concentration of the corresponding H-phosphonate anions under the reaction conditions. However, for more acidic H-phosphonate or H-phosphinate derivatives, this pathway cannot be excluded.

(50) Jutand, A.; Mosleh, A. *Organometallics* **1995**, *14*, 1810–1817.

C is apparently a rate-determining step (cf. Scheme 4), the generation of palladium phosphonate complexes **E** is inhibited by the added PPh_3. Due to high reactivity of κ^2-acetate complexes **C**, the overall incorporation of a phosphonate moiety to form palladium phosphonates **E** is very fast compared to that in the halide type of catalytic cycle (Scheme 9). For phosphorus nucleophiles, which do not require prior deprotonation, an alternative, direct path from arylpalladium complexes **B** to palladium phosphonates **E** is also available. Irrespective of the reaction path involved and denticity of the supporting ligands used, palladium phosphonates **E** in this instance are formed as an equilibrium mixture of penta- and tetracoordinate species. The reductive elimination from such palladium phosphonate complexes is extremely fast, most likely due to the ability of the acetate group to form highly reactive, pentacoordinate palladium κ^2-acetate species.

Conclusions

In summary, we investigated in detail the ligand substitution and the reductive elimination steps of the palladium-catalyzed cross-coupling reaction of aryl halides with diethyl H-phosphonate under various experimental conditions. It was found that what was usually referred to as a ligand substitution step for $PhPd(PPh_3)_2X$ (X = Cl, Br, I) complexes involved a coordination of an H-phosphonate diester in a rate-determining step, followed by deprotonation to form an equilibrium mixture of penta- and tetracoordinated palladium phosphonate intermediates.

Generation of palladium phosphonate intermediates from $PhPd(PPh_3)_2(OAc)$ was significantly faster than that observed for $PhPd(PPh_3)_2X$ and involved the intermediacy of highly reactive κ^2-acetate complexes.

Rates of a reductive elimination of diethyl phenylphosphonate from palladium phosphonate intermediates depended strongly on the kind of arylpalladium complexes used for their generation, and for $PhPd(PPh_3)_2(OAc)$, it was an order of magnitude higher than that observed for the halide-containing complexes.

These findings, together with kinetic experiments, enabled us to clarify some important mechanistic features of an acetate group present in palladium(II) complexes and to propose two catalytic cycles for the formation of the C−P bond via a palladium-mediated cross-coupling of aryl halides with H-phosphonate diesters, depending on whether halides versus acetates were dominant ligands.

Studies on synthetic applications of a remarkable rate enhancement of the C−P bond formation by acetate ions are in progress in our laboratory.

Acknowledgment. Financial support of the Swedish National Research Council is gratefully acknowledged.

Supporting Information Available: Experimental synthetic procedures, protocols for the kinetic measurements, raw kinetic data, the Eyring plots and a graph used to obtain k_1 values, full isomerization scheme for phosphonate complexes with PPh_3 as ligand, and ^{31}P NMR spectra of *in situ* generated (dppp)Pd(Ph)-$(PO(EtO)_2)$ complex. This material is available free of charge via the Internet at http://pubs.acs.org.

OM800641N