Pd(0)-Catalyzed Phosphorus−Carbon Bond Formation. Mechanistic and Synthetic Studies on the Role of the Palladium Sources and Anionic Additives

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Received August 6, 2007

$Pd(PPh_3)_4$, $Pd(dba)_2$, $Pd(OAc)_2$, and $PdCl_2$, have been evaluated as possible Pd(0) sources for the palladium-catalyzed P−C bond formation via a cross-coupling of aryl halides with H-phosphonate diesters. It was found that the most efficient catalytic system can be generated from $Pd(OAc)_2$ with a key role being played by Pd(II) and Pd(0) species with coordinated acetate ions. The reactivity of differently ligated Pd(II) complexes was determined, and ^{31}P NMR spectroscopy studies were carried out to provide mechanistic interpretations for the observed differences between the catalytic systems.

Introduction

Organometallic chemistry has been one of the most rapidly growing areas of chemistry over the past decades. Among various chemical transformations catalyzed by transition metals, cross-coupling reactions became an irreplaceable tool in organic synthesis, especially since, in addition to the traditional carbon−carbon bond formation,[1] a new field of a cross-coupling with heteroatom nucleophiles emerged.[2] Although, the pioneering work by the Buchwald and Hartwig groups on nitrogen nucleophiles[3−5] in the mid-1990s is usually recognized as the beginning of this kind of chemistry, the first report on the palladium-catalyzed coupling of vinyl bromides with H-phosphonates as nucleophiles appeared in 1980.[4] This reaction was further extended by other researchers to aryl halides[6] and triflates,[7] as well as to vinyl triflates.[8] On the side of nucleophiles, phosphinates,[9] including H-phosphinates,[10] phosphine oxides,[11] phosphines,[12] and boranophosphines[13] were successfully employed as substrates for this kind of coupling.

The development in the field of organometallic chemistry has been driven by two major areas of its applications: the synthesis of substituted, especially chiral, phosphine ligands, and natural product synthesis.[14] Due to mildness of the reaction conditions, Pd-catalyzed cross-couplings provide access to a large number of compounds, with diverse structural features, that cannot be obtained in other ways.[15] In natural product synthesis, nucleic acids and their analogues became attractive synthetic targets for the transition-metal-catalyzed reactions, due to the growing interest in modified oligonucleotides as potential antisense/antigene agents.[16] In recent years several reports from this[17] and other[18−20] laboratories appeared on the synthesis of phosphorus-modified nucleic acid analogues via the palladium-catalyzed cross-coupling reactions.

The extensive progress in exploration of scope of the reactants that can be coupled using transition metals was not, however, paralleled by the development of new catalytic systems. In a majority of cases, $Pd(PPh_3)_4$ was used as a catalyst, as in original procedures reported by Hirao in the early 1980s.[4−6] Among a few exceptions are reports on using other palladium sources (e.g., $Pd(OAc)_2$,[10,18] $Pd(PPh_3)_2Cl_2$[21]) or different ligands (dppp,[22] dppb,[23] dppf[20]); however, the changes introduced were the result

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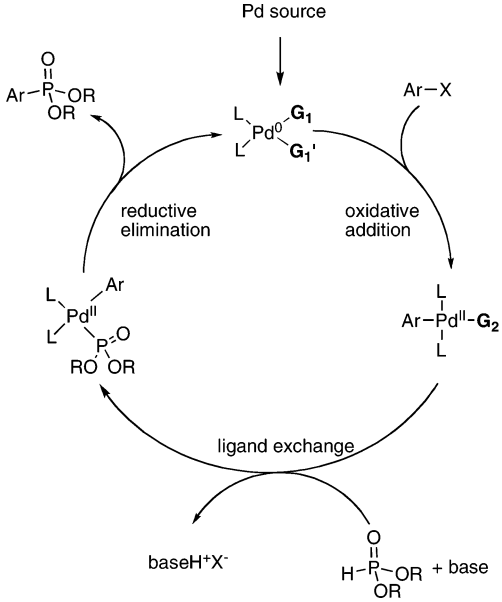
Scheme 1. Mechanism of Palladium-Catalyzed Cross-Coupling between Aryl Halide and H-Phosphonate[a]



[a] Depending on palladium source and additives $\mathbf{G_1}$, $\mathbf{G_1'}$ = L (PPh_3), dba, X^-, OAc^-, solvent; $\mathbf{G_2}$ = X^-, OAc^-, solvent.

Table 1. Reactivity of Palladium(0) Complexes in Oxidative Addition with Iodobenzene as a Function of the Palladium Precursors and Various Additives (L = PPh_3)[a]

entry	Pd(0) precursor	reactive species (S = solvent)	K_{obs} ($M^{-1}s^{-1}$) in THF (DMF)
1	Pd^0L_4	SPd^0L_2[b]	16[c] (16)[c] (25)[d]
2	Pd^0L_4+AcO^-	$Pd^0L_2(OAc)^-$	(21)[d]
3	$Pd(OAc)_2$ +5L	$Pd^0L_2(OAc)^-,H^+$	(41)[d]
4	$Pd(OAc)_2$ +5L +3Et_3N	$Pd^0L_2(OAc)^-$	(22)[d]
5	$Pd(OAc)_2$ +3L	$Pd^0L_2(OAc)^-,H^+$	(140)[d]
6	$Pd(OAc)_2$ +3L +3Et_3N	$Pd^0L_2(OAc)^-$	(65)[d]
7	$PdBr_2L_2$ +2e	$Pd^0L_2Br^-$	400[c]
8	$PdBr_2L_2$ +2e +$n$$Br^-$	$Pd^0L_2Br_2^-$	50[c]
9	$PdCl_2L_2$ +2e	$Pd^0L_2Cl^-$	530[c]
10	$PdCl_2L_2$ +2e +$n$$Cl^-$	$Pd^0L_2Cl_2^-$	72[c]
11	$PdCl_2L_2$ +2e +50Li^+	Pd^0L_2Cl,Li	1320[c]
12	$PdCl_2L_2$ +2e +Zn^{2+}	Pd^0L_2Cl,ZnCl	1480[c]
13	$Pd^0(dba)_2$ + 2L	SPd^0L_2[b]	2.7[c] (1.9)[c]

[a] All data from refs 24 and 25. [b] Transient species present at trace concentration. [c] 20 °C. [d] 25 °C.

of screening with various reaction conditions rather than a better understanding of the underlying mechanisms.

In this context, stimulated by mechanistic reports by Jutand and Amatore on the Pd-catalyzed reactions,[24−26] we set out to perform a comparative study of different palladium(0) precursors to evaluate their efficiency in promoting the P−C bond formation and to explore the effect of anionic additives on these reactions. The latter possibility was suggested by Jutand and Amatore, who have shown that rates of oxidative additions, a common step for all cross-coupling reactions (Scheme 1), were strongly influenced by species brought into the reaction mixture with the palladium source, or by external additives, such as halide or acetate ions, dba, bases, and Lewis acids (Table 1).

It is clearly visible from the data presented in Table 1 that the highest rates of the oxidative additions were achieved in the presence of Brønsted and, especially, Lewis acids (Table 1, entries 5, 11, and 12).[27] Unfortunately, in the case of phosphorus nucleophiles acidic additives are incompatible with the reaction systems due to high basicity of the generated phosphorus(III)-centered anions; however, use of the halides (Table 1, entries 7−10) or acetate ions (Table 1, entry 6) remained a viable alternative. Jutand and Amatore investigated the influence of halides and acetate only on the oxidative addition step,[24,26] but we assumed that these anionic species may coordinate also to the palladium(II) species, thus influencing as well rates of the second step in the catalytic cycle, namely, ligand substitution by the phosphorus nucleophile (Scheme 1).

In this paper we present our studies on different palladium sources with respect to their ability to catalyze the cross-coupling reaction between phenyl halides and diethyl H-phosphonate. Additionally, effects of the added halide and acetate ions on rates of the investigated reactions were studied using ^{31}P NMR spectroscopy, and mechanistic explanations for the observed variations in catalytic efficiency of the reaction systems generated from different palladium precursors are provided.

Results and Discussion

Pd(0)-based catalysts that are required for palladium-catalyzed cross-coupling reactions can be either prepared from pure Pd(0) compounds or generated *in situ* from the appropriate Pd(II) precursors. Using various sources of palladium may lead to reagent systems that differ in their catalytic efficiency due to the presence of differently ligated Pd(0) species.

Comparison of Different Palladium Sources. The most commonly used palladium sources in the cross-coupling and the Heck reactions are $Pd(PPh_3)_4$, $Pd(dba)_2$, $Pd(OAc)_2$, and $PdCl_2$. The former two already contain palladium(0), whereas the other two compounds are palladium(II) salts that must be reduced prior entering the catalytic cycle. In the case of $Pd(OAc)_2$, the added phosphine ligands usually play the role of a reducing agent,[28,29] while $PdCl_2$ or its ligated form $Pd^{II}L_2Cl_2$ can be reduced by tertiary amines[30] or the organometallic nucleophile itself.[31]

For the purpose of our study we chose iodobenzene and bromobenzene as model aryl halides and diethyl H-phosphonate ($(EtO)_2P(O)H$) as the phosphorus nucleophile. All four palladium sources were used with an appropriate amount of PPh_3 as a ligand.[32] The reactions were carried with 10 mol % of a catalyst loading, in THF at 60 °C using Et_3N as a base (Scheme 2). The progress of the reactions was monitored by ^{31}P NMR spectroscopy, and the obtained results are summarized in Table 2.

For both bromo- and iodobenzene the shortest reaction times were found when the reaction was carried out in the presence of a catalyst generated from $Pd(OAc)_2$. $Pd(PPh_3)_4$, a catalyst

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[32] We decided to generate $Pd^{II}(PPh_3)_2Cl_2$ complex *in situ* from $PdCl_2$ and 2 equiv of PPh_3 rather than to use premade complex. According to our observations (^{31}P NMR) the complex is formed quantitatively within 30 min in THF at 60 °C and is smoothly reduced with Et_3N in the presence of an aryl halide.

Scheme 2. Model Cross-Coupling Reaction Used in the Study

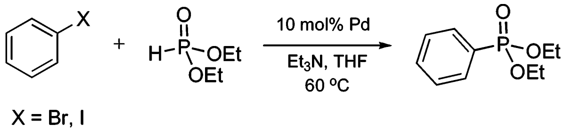
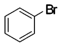
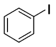


Table 2. Comparison of Different Palladium Sources in a Cross-coupling Reaction between $(EtO)_2P(O)H$ and Bromo- or Iodobenzene (Scheme 2)[a]

Entry	Palladium source (+ ligand)	Reaction time	
			
1	$Pd(PPh_3)_4$	18 h	8 h
2	$Pd(OAc)_2 + 3PPh_3$[b]	16 h	7 h
3	$Pd(dba)_2 + 2PPh_3$	24 h	10 h
4	$PdCl_2 + 2PPh_3$	No reaction	No reaction

[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. [b] A 15 min palladium reduction performed prior to the addition of Ph−X and $(EtO)_2P(O)H$.

commonly used for this purpose, gave slightly longer reaction times, while using $Pd(dba)_2$ as the palladium source resulted in the slowest reactions (Table 2). It is important to note that in the instance of $Pd(OAc)_2$ it was necessary to perform the palladium reduction prior to the addition of phenyl halide and $(EtO)_2P(O)H$; otherwise no product (diethyl phenylphosphonate) was formed. Somewhat surprisingly, also no product formation was observed with $PdCl_2$ used as a palladium source, irrespective of how the reduction was carried out.

The observed differences in efficiency of the catalytic systems generated from $Pd(PPh_3)_4$, $Pd(OAc)_2$, and $Pd(dba)_2$ are in agreement with the reactivity of the corresponding Pd(0) species in the oxidative addition step (Table 1) of the investigated reactions. However, the reason why the catalytic system generated from $PdCl_2$ was inactive in the studied cross-coupling reactions remained unclear. Also, the phenomenon that when the reduction of $Pd(OAc)_2$ was carried out in the presence of an aryl halide and the H-phosphonate diester, no product formation was observed seemed puzzling. To address these issues we decided to perform more detailed mechanistic investigations using ^{31}P NMR spectroscopy.

Complexation of the Generated Pd(0) Species by Diethyl H-Phosphonate. The $Pd(OAc)_2$ Case. Since it is known that neither Et_3N nor aryl halides interfere with the reduction of $Pd^{II}(OAc)_2$ by PPh_3 to form $Pd^0(PPh_3)_2(OAc)^-$, a reactive species involved in the oxidative addition step,[29] then it was apparent that $(EtO)_2P(O)H$ prevented its formation or somehow deactivated it.

First we checked if diethyl H-phosphonate can form complexes with $Pd^{II}(OAc)_2$. Since reduction of $Pd^{II}(OAc)_2$ by PPh_3 is an intramolecular reaction that involves intermediacy of $Pd^{II}(PPh_3)_2(OAc)_2$,[29] a competing complexation by the H-phosphonate present could prevent formation of this species and, consequently, the palladium reduction. To this end, to a THF solution of $Pd(OAc)_2$, 10 equiv of the H-phosphonate were added, and the reaction mixture was checked by ^{31}P NMR spectroscopy. Unfortunately, in neither the presence nor the absence of Et_3N, no additional resonances, except those of the H-phosphonate diester ($\delta_P = 6.9$ ppm, $^1J_{PH} = 650$ Hz, $^3J_{PH} = 8.2$ Hz, dt), could be detected. However, when similar experiments were repeated with the added PPh_3 (3 equiv), the $Pd^{II}(PPh_3)_2(OAc)_2$ complex ($\delta_P = 14.9$ ppm) was smoothly formed without any interference from the H-phosphonate, which meant that the reaction is not quenched at the level of the Pd(II) species. As the reaction proceeded, the signal from $Pd^{II}(PPh_3)_2(OAc)_2$ gradually decreased and a new resonance due to Ph_3PO ($\delta_P = 23.9$ ppm), indicating that the palladium reduction occurred, was formed. However, in contrast to the reference reaction that was run in the absence of the H-phosphonate diester, the broad peak due to the reduced $Pd^0(PPh_3)_2(OAc)^-$ species ($\delta_P = -4.7$ ppm)[29] did not appear, but instead a new signal at 95.5 ppm emerged. The intensity of this new peak grew with time at the expense of the H-phosphonate signal. Integration of the signal at 95.5 ppm in relation to time showed that it was always approximately two times bigger then the signal of Ph_3PO. In the ^1H-coupled ^{31}P NMR spectra no $^1J_{PH}$ coupling constant characteristic for H-phosphonates was present, indicating a lack of the P−H bond.

As for the chemical reactivity of an intermediate resonating at 95.5 ppm, the addition of excess of iodobenzene to the reaction mixture at 60 °C did not result in any changes in the ^{31}P NMR spectrum over 1 h, meaning that this species did not undergo oxidative addition. However, upon addition of 20 equiv of PPh_3 the intensity of the signal at 95.5 ppm started slowly to decrease with time, demonstrating the complex was probably a Pd(0) species in an equilibrium with $Pd^0(PPh_3)_n$ complexes.[33] Additionally, for the stoichiometric reaction, when $Pd(OAc)_2$, iodobenzene, and the H-phosphonate diester were present in equimolar amounts, the intermediate resonating at 95.5 ppm was not formed and the reaction proceeded to the desired product, diethyl phenylphosphonate, even when the reduction of $Pd(OAc)_2$ with 3 equiv of PPh_3 was carried out in the presence of the H-phosphonate.

All these observations allow us to propose a plausible mechanism explaining the behavior of the catalytic system generated from $Pd(OAc)_2$ (Scheme 3). In the case of performing the reaction with a preceding palladium reduction, the ordinary reaction pathway is followed (path A in Scheme 3).[29] In this instance, the intermediate $Pd^0(PPh_3)_2(OAc)^-$ formed is resistance to complexation by diethyl H-phosphonate, but it undergoes an oxidative addition with phenyl halide and, thus, may be involved in the catalytic cycle. However, if the palladium reduction is performed in the presence of the excess of $(EtO)_2P(O)H$, the H-phosphonate may intercept the short-living, low-ligated intermediate $Pd^0(PPh_3)(OAc)^-$,[29] forming a complex ($\delta_P = 95.5$ ppm),[34] which is unreactive toward phenyl halide in the oxidative addition and, thus, cannot enter into the catalytic cycle (path B, Scheme 3).[35] Under stoichiometric reaction conditions, when the palladium catalysts and the H-phosphonate diester are present in equimolar (or close to it) amounts, the intermediate resonating at 95.5 ppm is not formed and the reaction proceeds to the desired product, diethyl phenylphosphonate (Scheme 2), even when the reduction of $Pd(OAc)_2$ with a phosphine is carried out in the presence of the H-phosphonate. These indicate that the low-ligated intermediate $Pd^0(PPh_3)(OAc)^-$ formed during the reduction of $Pd(OAc)_2$ can be intercepted by the H-phosphonate only when the latter is present in large excess, as

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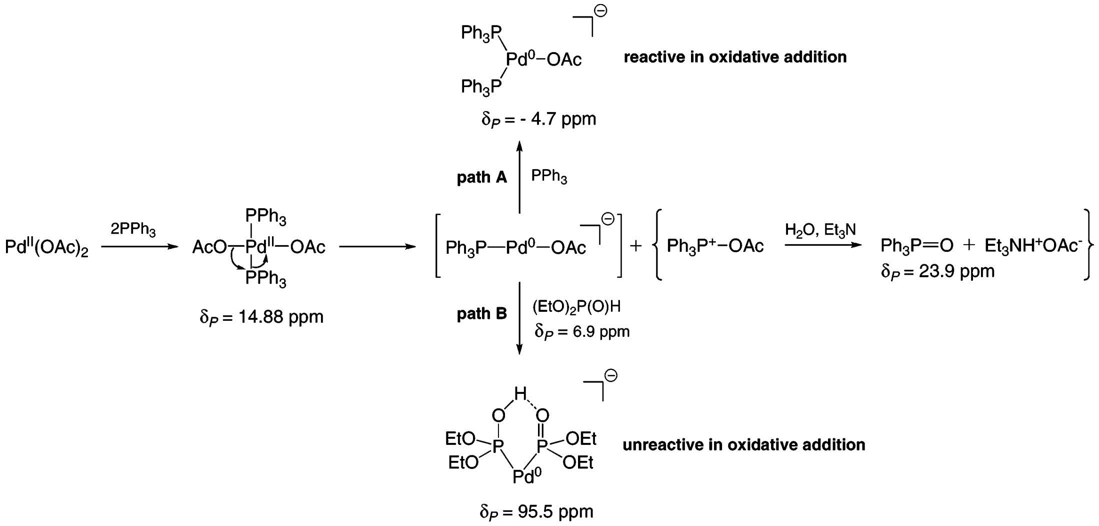
[33] Due to a rapid exchange of the phosphine moiety, only one weighed average signal at $\delta_P = -4.8$ ppm for these complexes and free PPh_3 was observed.

[34] Structures for an intermediate resonating at $\delta_P = 95.5$ shown in Scheme 3 and the related intermediates in Scheme 5 are only tentative. These, and other low ligated intermediates discussed in this paper are, most likely stabilized *via* coordination of solvent molecules (that are omitted from the structures) and may have geometries different from those shown in the schemes.

[35] One should note that the $Pd^0(PPh_3)(OAc)^-$ species apparently cannot be formed during the reductive elimination step of the catalytic cycle; otherwise, the H-phosphonate present would intercept it and arrest the catalytic reaction.

Scheme 3. Formation of Catalytically Active Pd(0) Complex from $Pd(OAc)_2$ and PPh_3 (Path A) and Suppression of Its Formation in the Presence of $(EtO)_2P(O)H$ Excess (Path B)



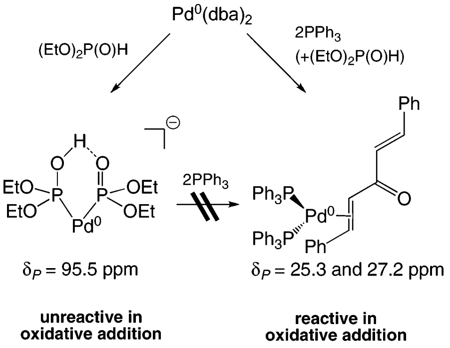
it is the case for the catalytic reaction. Indeed, we found that even with a 4 molar excess of $(EtO)_2P(O)H$ (it corresponds to a catalytic reaction with 25% Pd), the reduction of $Pd(OAc)_2$ could be carried out in the presence of the H-phosphonate without compromising the efficiency of the overall cross-coupling reaction.

The $Pd(dba)_2$ Case. The complexation of palladium(0) by H-phosphonate diesters or secondary phosphine oxides is a known phenomenon,[36] and in many cases $Pd(dba)_2$ is used as the palladium source to obtain such complexes.[36,37] Although, some of the H-phosphonate Pd(0)-ligated species are able to undergo oxidative addition and thus catalyze cross-coupling reactions,[37] apparently the one with $(EtO)_2P(O)H$ as a ligand is not, as it was discussed above. However, in the studied cross-coupling reaction (Scheme 2), when $Pd(dba)_2$ was used as the palladium source (Table 2, entry 3), a full conversion of the starting material into diethyl phenylphosphonate was observed, indicating that apparently complexation of the Pd(0) species by the H-phosphonate diester did not occur in this instance.

Indeed, in the ^{31}P NMR spectrum of a solution prepared by dissolving in THF solid $Pd(dba)_2$, PPh_3 (2 equiv), and $(EtO)_2P(O)H$ (10 equiv), only the signals characteristic to $Pd^0(dba)(PPh_3)_2$ ($\delta_P = 25.3$ and 27.2 ppm)[38] were present. However, in the absence of the phosphine, the peak at 95.5 ppm appeared, indicating formation of the Pd(0) H-phosphonate complex. Similarly as for $Pd(OAc)_2$, once this species was formed, it was persistent to recomplexation by the added PPh_3 (2 equiv).

Our findings regarding the behavior of the catalytic system derived from $Pd(dba)_2$ are summarized in Scheme 4. It seems that, in a THF solution, $Pd(dba)_2$ efficiently undergoes ligand exchange with PPh_3, forming catalytically active species $Pd^0(dba)(PPh_3)_2$, even in the presence of a large excess of $(EtO)_2P(O)H$. Consequently, this reaction system worked under both catalytic and stoichiometric conditions, although rates of the cross-coupling reactions were rather low (Table 2). On the other hand, when the phosphine was absent, the dba ligands were replaced by two H-phosphonate molecules forming a complex resonating at 95.5 ppm in the ^{31}P NMR spectrum. Identical chemical shifts of this complex and the one obtained from $Pd(OAc)_2$ suggested that there were no other ligands, except those of H-phosphonates and solvent molecules, associated with the palladium.

Scheme 4. Behavior of $Pd(dba)_2$ in the Presence of PPh_3 and/or $(EtO)_2P(O)H$



The $PdCl_2$ Case. Finally, we studied the possibility of palladium(0) complexation by the diethyl H-phosphonate when the $PdCl_2$ was used as a palladium source. As it is apparent from Table 2 (entry 4), the system based on $PdCl_2$ was inefficient in promoting the investigated cross-coupling reactions. In light of the previous discussion, the most likely reason for this was the formation of a catalytically inactive Pd(0) H-phosphonate complex.

To check this hypothesis, $PdCl_2$, PPh_3 (2 equiv), Et_3N (10 equiv), and $(EtO)_2P(O)H$ (10 equiv) were dissolved in THF, and progress of the reaction was followed by ^{31}P NMR spectroscopy. Initially, the formation of $Pd^{II}(PPh_3)_2Cl_2$ could be observed ($\delta_P = 23.6$ ppm); however, as the reduction process progressed, concentration of this species gradually decreased and simultaneously two new signals at 81.4 and 95.5 ppm, in the approximate ratio 3:2, appeared. The signal at 95.5 ppm was assigned to the already discussed Pd(0) H-phosphonate complex, and the one at 81.4 ppm could originate from a similar species but having additionally one Cl^- ion ligated.

The following experiment was carried out to verify this assumption: the Pd(0) diethyl H-phosphonate complex ($\delta_P =$ 95.5 ppm) was generated from $Pd(dba)_2$ and $(EtO)_2P(O)H$ in THF, as described in the previous section. To this mixture, a solution of $n\text{-}Bu_4N^+Cl^-$ in THF was added in small portions, and a ^{31}P NMR spectrum was registered after each addition. As expected, a gradual disappearance of the signal at 95.5 ppm

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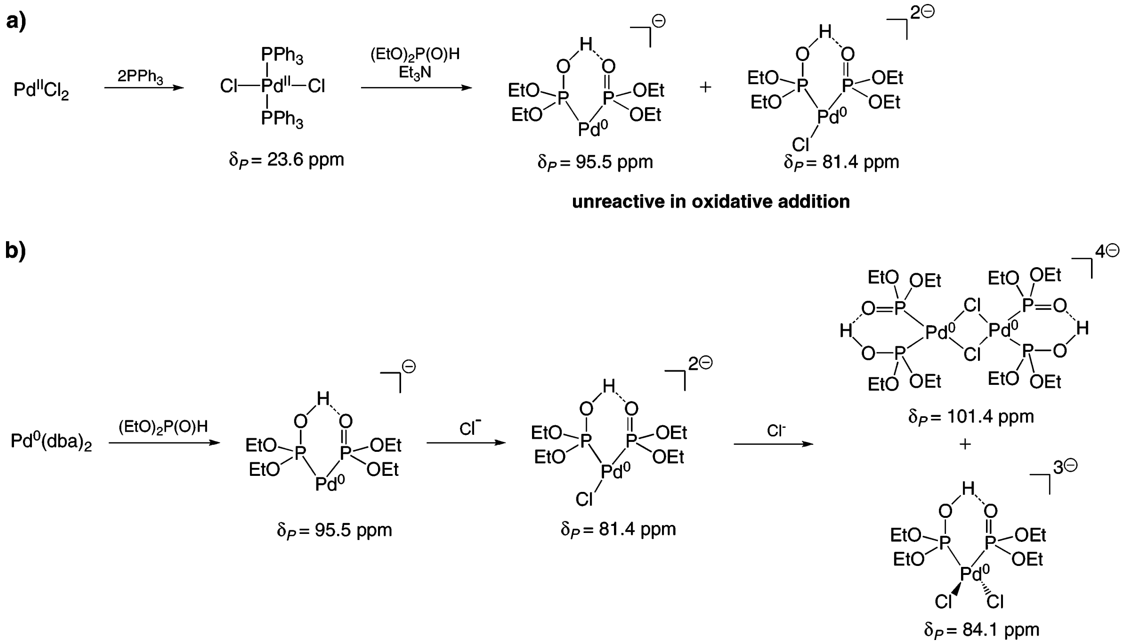
Scheme 5 [a]



[a] (a) Formation of Pd(0) diethyl H-phosphonate complexes from $PdCl_2$ as the palladium source. (b) Formation of Pd(0) diethyl H-phosphonate complexes ligated with Cl^- (putative structures).

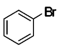
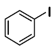
and formation of the signal at 81.4 ppm were observed. With an increasing concentration of Cl^-, also additional signals at 101.4 and 84.1 ppm appeared, and after addition of a total 20 equiv of Cl^-, the latter signal was the only one remaining, except that from the excess of $(EtO)_2P(O)H$ (peak at $\delta_P = 6.9$ ppm).These results can be interpreted in the following way. Using $PdCl_2$ as the palladium source leads to the formation of a complex resonating at 95.5 ppm (Scheme 5a) that, at the concentration of Cl^- brought into the system with $PdCl_2$, is partially ligated by a single chloride ion, giving rise to an additional resonance signal at 81.4 ppm (3:2 ratio). With the added chloride anions, there is a possibility to form other Pd(0) diethyl H-phosphonate complexes ligated by more Cl^-. Putative structures of such complexes, a dinuclear (resonating at 101.4 ppm) and mononuclear one (resonating at 84.1 ppm), are presented in Scheme 5b.

All these Pd(0) H-phosphonate complexes were unreactive in the oxidative addition of aryl halides; therefore $PdCl_2$ seems to be incompatible as the palladium source in the cross-coupling with the H-phosphonate is investigated, under neither catalytic nor stoichiometric conditions.

Effect of Anion Additives on the Rate of the Cross-Coupling between Phenyl Halides and Diethyl H-Phosphonate. After having established the phenomenon of Pd(0) complexation with diethyl H-phosphonate, and how and when it may interfere with the cross-coupling reactions, we investigated the effects of different anionic additives on the rate of the reaction presented in Scheme 2. Due to incompatibility of the $PdCl_2$ reagent system and low reactivity of $Pd(dba)_2$ in the investigated reactions (Table 2), further studies were performed only with $Pd(PPh_3)_4$ and $Pd(OAc)_2$ as the palladium sources.

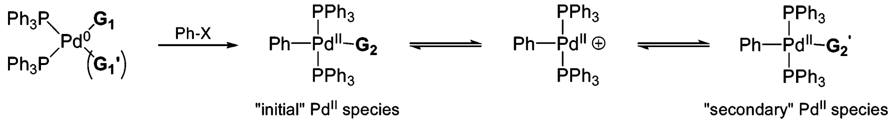
According to the data shown in Table 1, the oxidative addition step of the catalytic cycle is accelerated in the presence of Cl^-, Br^-, and OAc^-, due to formation of very reactive, electron-rich anionic Pd(0) species ligated with these anions. Taking into account that bromides and iodides are produced in the course of the reactions with bromobenzene and iodobenzene, respectively, a 10-fold excess of tetra-*n*-butylammonium salts with a given anionic part was used to suppress competition from these Br^- or I^- anions. By having such high anion concentrations, formation of the most reactive Pd(0) species ligated with a single halide is most likely compromised (Table 1, entry 7 vs 8 for Br^- and entry 9 vs 10 for Cl^-); however, we considered the homogeneity of the reacting forms to be more important at the current stage of these studies. As it is apparent from data in Table 3, upon additions of Cl^-, Br^-, and OAc^-, the times for completion of all the reactions investigated became shorter, approximately to the same extent, irrespective of the palladium source used. The most notable effect was that of the acetate ions, for which a remarkable acceleration (Table 3, entry 7), much higher than those for chlorides or bromides (Table 3, entries 2, 5 and 3, 6 respectively), was observed. These surprising results suggested that the role of the added anions was not limited to the oxidative addition but that these additives also strongly influenced other steps in the catalytic cycle that might ultimately lead to the change of a rate-determining step.

Table 3. Effect of Anionic Additives on the Reaction Times of $(EtO)_2P(O)H$ with Bromo- or Iodobenzene (Scheme 2)[a]

Entry	Palladium source (+ ligand and additive)	Reaction time A 	B 
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	$Pd(OAc)_2 + 3PPh_3$ [b]	16 h	7 h
5	$Pd(OAc)_2 + 3PPh_3 + 10Cl^-$ [b]	11 h	2 h
6	$Pd(OAc)_2 + 3PPh_3 + 10Br^-$ [b]	11 h	4 h
7	$Pd(OAc)_2 + 3PPh_3 + 10OAc^-$ [b]	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 $n\text{-}Bu_4N^+$ salts. [b] A 15 min palladium reduction performed prior to addition of Ph−X and $(EtO)_2P(O)H$.

Scheme 6. Formation of Three Pd(II) Species That Might Be Involved in Ligand Exchange Reaction with the H-Phosphonate



Entry	Ph-X	Added anion	$\mathbf{G_1}$ (Pd⁰ complex)	$\mathbf{G_2}$ ("initial" Pd^II complex)	$\mathbf{G_2'}$ ("secondary" Pd^II complex)	Respective entries in Table 3
1	Ph-Br	--	Br	Br	--	1A
2	Ph-I	--	--	I	--	1B
3	Ph-Br	Cl^-	Cl	Br	Cl	2A, 5A[a]
4	Ph-I	Cl^-	Cl	I	Cl	2B, 5B[a]
5	Ph-Br	Br^-	Br	Br	--	3A, 6A[a]
6	Ph-I	Br^-	Br	I	Br	3B, 6B[a]
7	Ph-Br	OAc^-	OAc	OAc	Br	7A
8	Ph-I	OAc^-	OAc	OAc	I	7B

[a] OAc^- brought with $Pd(OAc)_2$ can be neglected due to low concentration

Qualitative Comparison of Reactivity of Different Phenylpalladium(II) Species with $(EtO)_2P(O)H$ in the Ligand Substitution Step. Since the data from Table 3 cannot be explained on the grounds of rates of the oxidative additions (Table 1) or the reductive eliminations (the same intermediate for all the reactions, Scheme 1), we assumed that the observed differences must originate from distinct reactivities of the Pd(II) species during the ligand substitution step.

The square planar palladium(II) complexes formed in the course of the oxidative addition, depending on the kind of anionic additives present, can be differently ligated[24] and thus may show different reactivities (Scheme 6). For example, the initial Pd(II) complex, formed directly in the oxidative addition,[39] can bear an acetate group brought from the Pd(0) complex ($\mathbf{G_2}$ = OAc in Pd(II) complex if $\mathbf{G_1}$ = OAc in the preceding Pd(0) complex)[40] or alternatively a halide brought from Ar−X, if Pd(0) was ligated by another halide [$\mathbf{G_2}$ = X in Pd(II) complex if $\mathbf{G_1}$ = Cl or Br in the preceding Pd(0) complex].[41] In the presence of anionic additives, $\mathbf{G_2}$ in the initial Pd(II) complex may undergo exchange, probably via a dissociative mechanism or/and produce the cationic $PhPd^{II}(PPh_3)_2^+$ complex *via* a dissociative pathway.[40] Therefore, during a cross-coupling reaction, three distinct Pd(II) species might be involved in the formation of a phenyl-H-phosphonate-palladium(II) intermediate, from which reductive elimination occurs. These are the "initial" Pd(II) complex formed in the oxidative addition, cationic $PhPd^{II}(PPh_3)_2^+$ intermediate, and "secondary" Pd(II) complex ligated by another anion present in the reaction mixture. Scheme 6 summarizes the Pd(0) and Pd(II) species that can be present in the reaction mixtures from Table 3.

To establish relative reactivities of the Pd(II) complexes ligated with different anions in the reaction with $(EtO)_2P(O)H$, we performed ^{31}P NMR investigations. We decided to generate simultaneously two Pd(II) complexes, ligated with different anions, and observed their decay upon addition of $(EtO)_2P(O)H$. Such competitive experiments have advantages over looking for the reactivity of a single reactive species, on two counts. First, they resemble the real catalytic reaction conditions, with all other components being present, and with both the "initial" and the "secondary" Pd(II) complexes having a possibility of reacting with the H-phosphonate. Second, since the Pd(II) complexes are in equilibrium, this method would provide information about relative rates of the complexes' equilibration and their reactions with the H-phosphonate.

First, a 1:1 mixture of Pd(II) complexes ligated with I^- and Br^- was prepared, and the reaction of the produced species with diethyl H-phosphonate was followed by ^{31}P NMR spectroscopy (Figure 2a). To this end, $PhPd^{II}(PPh_3)_2I$ was generated in THF at 60 °C (1 min) from equimolar amounts of iodobenzene and $Pd(PPh_3)_4$, and to these, 0.5 equiv Br^- (as $n\text{-}Bu_4N^+$ salt) was added. After equilibration at 60 °C for 15 min, a 1:1 mixture of $PhPd^{II}(PPh_3)_2I$ and $PhPd^{II}(PPh_3)_2Br$ was obtained.[42] At this point 10 equiv Et_3N was added, followed by 10 equiv of $(EtO)_2P(O)H$, and the mixture was incubated at 60 °C (Figure 2a). It was clearly visible that the peak due to $PhPd^{II}(PPh_3)_2Br$ disappeared faster than that of $PhPd^{II}(PPh_3)_2I$, indicating higher reactivity of the former species under the reaction conditions. The complex with ligated bromide almost completely disappeared within 45 min after addition of the H-phosphonate, while its iodide counterpart was still present in the solution.

Similar experiments were performed with ca. 1:1 mixtures of $PhPd^{II}(PPh_3)_2I$ and $PhPd^{II}(PPh_3)_2Cl$ (Figure 2b) and $PhPd^{II}(PPh_3)_2I$ with $PhPd^{II}(PPh_3)_2(OAc)$ (Figure 2c). Both $PhPd^{II}(PPh_3)_2Cl$ and $PhPd^{II}(PPh_3)_2(OAc)$ complexes appeared to be more reactive than $PhPd^{II}(PPh_3)_2I$; however, a huge difference in reactivity between these two species was observed. While $PhPd^{II}(PPh_3)_2Cl$ displayed a comparable reactivity to that for $PhPd^{II}(PPh_3)_2Br$ (Figure 2b vs 2a, respectively) as judged from the rates of disappearance of their ^{31}P NMR signals (ca 45 min), the signal originating from $PhPd^{II}(PPh_3)_2(OAc)$ could not be detected after 1 min (the time required to place NMR tube back into the spectrometer and register the spectra) after addition of $(EtO)_2P(O)H$ (Figure 2c). Unfortunately, due to almost identical ^{31}P NMR chemical shifts of $PhPd^{II}(PPh_3)_2Br$ and $PhPd^{II}(PPh_3)_2Cl$ we were not able to determine relative reactivities of these two palladium(II) species.

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(39) To be specific, a complex formed first in the oxidative addition is assumed to be a trigonal bipyramid $PhPd^{II}(PPh_3)_2G_1X$ that, in the presence of a minute amount of free PPh_3 (which is the case for $Pd(PPh_3)_4$ or $Pd(OAc)_2 + 3PPh_3$), quickly collapses to *trans*-$PhPd^{II}(PPh_3)_2G_2$ with the expulsion of G_1 or X. For details, see refs 24 (review), 40 (G_1 = OAc), and 41 (G_1 = Cl).

(40) Amatore, C.; Carré, E.; Jutand, A.; M'Barki, M. A.; Meyer, G. *Organometallics* **1995**, *14*, 5605−5614.

(41) Amatore, C.; Jutand, A.; Suarez, A. *J. Am. Chem. Soc.* **1993**, *115*, 9531−9541.

(42) The affinity of anions to $Pd(PPh_3)_2(Ph)-X$ decreases in the order $Cl^- > Br^- > I^- \approx OAc^-$, and large differences in equilibria constants enable a practically quantitative replacement of the anion lower in the row with the one which is higher. See also refs 24 and 40.

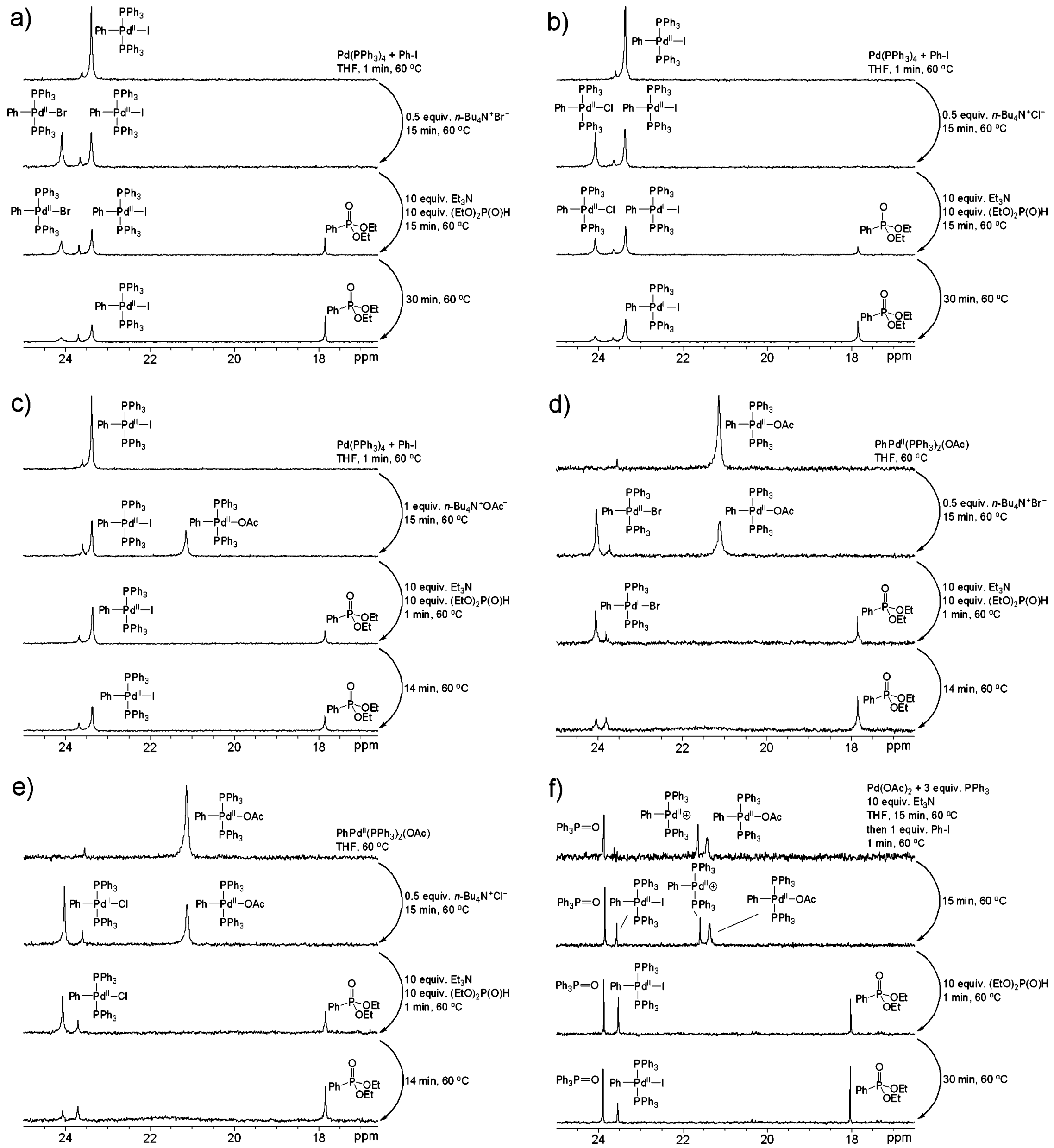

Figure 1. ^{31}P NMR competition experiments between Pd(II) species ligated with different anions in reaction with $(EtO)_2P(O)H$: (a) Br$^-$ vs I$^-$; (b) Cl$^-$ vs I$^-$; (c) I$^-$ vs OAc$^-$; (d) Br$^-$ vs OAc$^-$; (e) Cl$^-$ vs OAc$^-$; I$^-$ vs OAc$^-$ vs cationic species. Small signal at 23.7 ppm originates from contamination with Ph_3PO.

Attempted generation of mixtures of $PhPd^{II}(PPh_3)_2(OAc)$ with $PhPd^{II}(PPh_3)_2Br$ and with $PhPd^{II}(PPh_3)_2Cl$ failed due to large differences in the corresponding equilibrium constants,[43] and thus we had to use premade $PhPd^{II}(PPh_3)_2(OAc)$ as a starting material (Figure 2d and 2e). In both cases the complex ligated with OAc$^-$ displayed much higher reactivity than its halide counterparts. Similarly as in the experiment shown in Figure 2c, the signal due to $PhPd^{II}(PPh_3)_2(OAc)$ disappeared within the time required to register the ^{31}P NMR spectrum (~1 min), again demonstrating a remarkably high rate of reaction between this species and the H-phosphonate.

Finally, we became interested in comparing the reactivity of $PhPd^{II}(PPh_3)_2(OAc)$ with that of $PhPd^{II}(PPh_3)_2^+$ (Figure 2f). For this purpose, $Pd(OAc)_2$, PPh_3 (3 equiv), and Et_3N (10 equiv) were dissolved in THF and incubated for 15 min at 60 °C, to ensure a complete palladium reduction to take place. The subsequent addition of iodobenzene (1 equiv) resulted in a rapid reaction producing a mixture of the "initial" palladium(II) complex $PhPd^{II}(PPh_3)_2(OAc)$ ($\delta_P = 21.2$ ppm) and a complex with dissociated ligand $PhPd^{II}(PPh_3)_2^+$ ($\delta_P = 21.5$ ppm). After 15 min at 60 °C, the equilibrated reaction mixture contained $PhPd^{II}(PPh_3)_2(OAc)$, $PhPd^{II}(PPh_3)_2I$, and $PhPd^{II}(PPh_3)_2^+$ (Figure 2f) and the addition of $(EtO)_2P(O)H$ (10 equiv) caused a rapid disappearance of both $PhPd^{II}(PPh_3)_2(OAc)$ and $PhPd^{II}(PPh_3)_2^+$ species (^{31}P NMR spectroscopy). The decay of the remaining $PhPd^{II}(PPh_3)_2I$ was slow and roughly similar to that observed in the previous experiments (Figure 2a and 2b). At this stage of investigations we could not conclude if the rapid disappearance of $PhPd^{II}(PPh_3)_2^+$ indicated that this species reacted directly with the H-phosphonate or that it was involved in rapid equilibrium with the highly reactive $PhPd^{II}$(PPh3)$_2$(OAc).[43]

To sum up this part, the reactivity of the Pd(II) species in the ligand substitution reaction with diethyl H-phosphonate

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[43] Interestingly, $PhPd^{II}(PPh_3)_2(OAc)$ and $PhPd^{II}(PPh_3)_2^+$ showed comparable or lower reactivity to that of $PhPd^{II}(PPh_3)_2I$ in the reaction with styrene (*syn*-insertion step of the Heck reaction). See also ref 41.

decreases in the following order ($PhPd^{II}(PPh_3)_2^+$), $PhPd^{II}(PPh_3)_2(OAc) \gg PhPd^{II}(PPh_3)_2Cl$, $PhPd^{II}(PPh_3)_2Br > PhPd^{II}(PPh_3)_2I$, and in light of these, we can propose the following rationalization for the results and the trends observed in Table 3.

Using $Pd(OAc)_2$ as a palladium source in cross-coupling reactions involving phosphorus nucleophiles should, in principle, increase efficiency of the reaction, compared to that catalyzed by $Pd(PPh_3)_4$, due to higher reactivity, in both the oxidative addition and the ligand substitution steps, the generated intermediates $Pd^0(PPh_3)_2(OAc)^-$ and $PhPd^{II}(PPh_3)_2(OAc)$. However, in practice, both systems show similar efficiency in the investigated reaction as it is apparent from entry 4 vs 1 in Table 3. This is apparently due to the fact that, in the course of the reaction, the concentration of the halide anion released from Ar−X builds up, and thus the amount of the initially formed reactive species $Pd^0(PPh_3)_2(OAc)^-$ and $PhPd^{II}(PPh_3)_2(OAc)$ is rapidly depleted in the reaction mixture. As a result, the efficiencies of both catalytic systems become similar, since the initial acceleration observed in the case of a system based on $Pd(OAc)_2$ results only in a small shortening of the total reaction time.

Performing the reaction with Br^- or Cl^- as additives (Table 3, entries 2, 3, 5, and 6) leads to exclusive formation of Pd(0) species ligated by these anions, and this results in an acceleration at the level of the oxidative addition. The ligand substitution step is also affected; however, since the reactivities of $PhPd^{II}(PPh_3)_2Cl$ and $PhPd^{II}(PPh_3)_2Br$ are only slightly higher than that of $PhPd^{II}(PPh_3)_2I$, these have only a mediocre contribution to the overall acceleration. Thus, it seems that using $Pd(OAc)_2$ together with the halide as additives (Table 3, entries 5 and 6) does not provide any advantages in terms of efficiency but adds technical complicacy due to necessity of performing a separate palladium reduction step.

Finally, when the acetate additive is used (Table 3, entry 7), the reactive species $Pd^0(PPh_3)_2(OAc)^-$ and $PhPd^{II}(PPh_3)_2(OAc)$ are present throughout the reaction, accelerating both the oxidative addition and the ligand substitution steps, and lend themselves to a remarkable shortening of the cross-coupling reaction time.

Conclusions

In summary, we studied several aspects of the cross-coupling reaction between a model phosphorus nucleophile, diethyl H-phosphonate, and aryl halides. Regarding the palladium source, it was demonstrated that the best results were obtained with $Pd(OAc)_2$. When using this compound as a Pd(0) precursor, a preceding palladium reduction must be performed to avoid an interference from the complexation of the Pd(0) species by the H-phosphonate. For the same reason $PdCl_2$ turned out to be inefficient in cross-coupling reactions, at least for the H-phosphonate investigated.

This study also showed that it was possible to efficiently accelerate the cross-coupling reactions via the addition of different anions, e.g., halides or acetate, that strongly influenced the ligand substitution step. It was also found that the reactivity of the Pd(II) species in the ligand substitution reaction with diethyl H-phosphonate decreased in the following order: $PhPd^{II}(PPh_3)_2^+$, $PhPd^{II}(PPh_3)_2(OAc) \gg PhPd^{II}(PPh_3)_2Cl$, $PhPd^{II}(PPh_3)_2Br > PhPd^{II}(PPh_3)_2I$.

Palladium(II) species ligated with the acetate ion exhibited remarkably high reactivity, leading to an unprecedented acceleration of the overall cross-coupling reaction between aryl halides and H-phosphonate diesters. This phenomenon might be of importance in synthetic organic chemistry, and further studies are in progress in this laboratory.

Experimental Section

Bromobenzene, n-Bu_4NBr, iodobenzene, $Pd(dba)_2$, PPh_3 (all from Aldrich), n-Bu_4NCl, n-Bu_4NOAc, Et_3N (all from Alfa), $Pd(PPh_3)_4$ (Apollo Scientific), $(EtO)_2P(O)H$ (Janssen Chimica), $PdCl_2$, and $Pd(OAc)_2$ (Lancaster) were commercial grades and were used without further purification.

Complex $PhPd^{II}(PPh_3)_2(OAc)$ was prepared according to the published procedure.[40] THF was freshly distilled from sodium/benzophenone under an Ar atmosphere.

All experiments were carried out under an Ar atmosphere in 10 mm NMR tubes equipped with septa, using standard Schlenk techniques. NMR spectra were recorded on Bruker Avance II 500 MHz instrument. Chemical shifts are reported in ppm, relative to 2% H_3PO_4 solution in D_2O (external standard).

The reactant ratios and the experimental conditions for the investigated reactions are given in the appropriate tables and in the text.

Acknowledgment. Financial support from the Swedish Research Council is gratefully acknowledged.

OM700797K