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Preparation of Arylphosphonates by Palladium(0)-Catalyzed Cross-Coupling in the Presence of Acetate Additives: Synthetic and Mechanistic Studies

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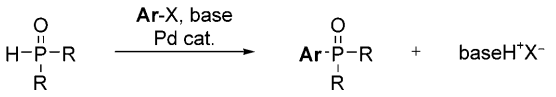
Abstract: An efficient protocol for the synthesis of arylphosphonate diesters *via* a palladium-catalyzed cross-coupling of H-phosphonate diesters with aryl electrophiles, promoted by acetate ions, was developed. A significant shortening of the cross-coupling time in the presence of the added acetate ions was achieved for bidentate and monodentate supporting ligands, and for different aryl electrophiles (iodo, bromo and triflate derivatives). The reaction conditions were optimized in terms of amount of the catalyst, supporting ligands, and source of the acetate ion used. Various arylphosphonates, including those of potential biological significance, were synthesized using this newly developed protocol. Some mechanistic aspects of the investigated reactions are also discussed.

Keywords: acetate additives; arylphosphonates; H-phosphonate diesters; nucleotide analogues; palladium-catalyzed cross-coupling

Introduction

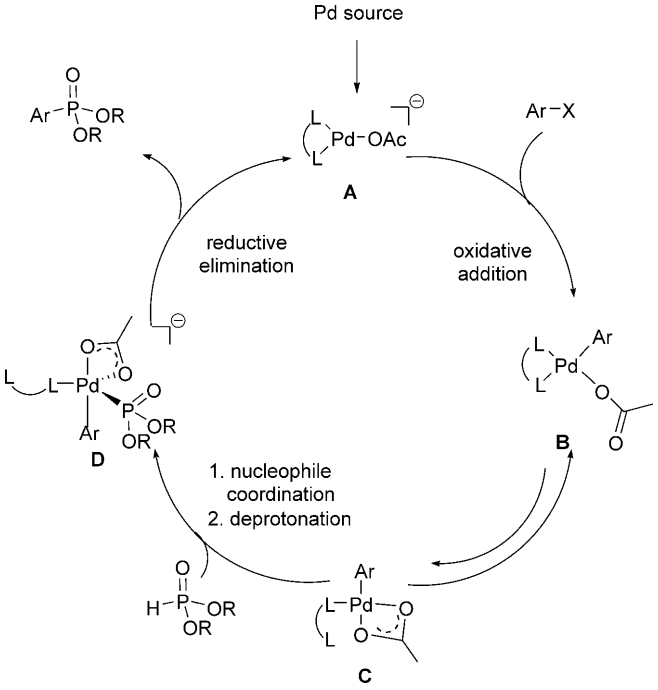
Since its introduction in the early 1980s by Hirao et al., the cross-coupling reaction of aryl halides with H-phosphonate diesters catalyzed by $Pd(PPh_3)_4$,[1] has been used for the preparation of various organophosphorus compounds.[2] Relatively mild reaction conditions and the possibility to synthesize arylphosphonates in a stereospecific manner,[3] contributed to popularity of the method.[4,5,6,7] Nevertheless, increasing applications of aryl- and vinylphosphonates in material sciences[6,8] and biological chemistry,[5,7,9–15] caused a demand for improved protocols for the C–P bond forming cross-coupling reactions, to simplify synthesis of complex organic compounds.

To enhance efficiency of the C–P bond formation (Scheme 1), other supporting ligands than triphenylphosphine used by Hirao et al.,[1] were investigated [for example, dppp,[16] dppb,[17] $PPh_2(m\text{-}C_6H_4SO_3M)$[18]], and the most efficient was found to be a wide-bite-angle ligand,[19] 1,1′-bis(diphenylphosphino)ferrocene (dppf).[12,20–22] In this type of cross-coupling reactions the base has to be used in a stoichiometric amount. The most commonly used one is triethylamine,[23] however, due to possible dealkylation of sensitive H-phosphonate diesters, it is often replaced by less nucleophilic tertiary amines[22,24] or propylene oxide.[9,12,20] For special reaction conditions, for example, biphasic conditions[25] or for the reactions involving microwave heating,[26] using inorganic bases such as K_2CO_3 and Cs_2CO_3 can be advantageous. As far as the palladium source is concerned, it was found that in contrast to $Pd(PPh_3)_4$ used in Hirao's original procedure,[1] catalytic systems generated *in situ* from $Pd(OAc)_2$ and appropriate phosphine ligands, were usually superior in terms of reactivity for promoting the C–P bond formation.[9,11,20–22,24,27]



Scheme 1. A palladium-catalyzed C–P bond-forming cross-coupling reaction.

All these improvements, for which a mechanistic basis has been provided in recent years,[19,27,28,29–31] lend themselves into a modified catalytic cycle for the palladium-mediated formation of the C–P bond as shown in Scheme 2.



Scheme 2. A catalytic cycle for a palladium-promoted cross-coupling between aryl halides and H-phosphonate diesters involving acetate ligated palladium complexes.

As it is apparent from the intermediates involved (**A**–**D**, Scheme 2), an acetate ligand plays a crucial role in all stages of the catalytic cycle. Initially, the higher reactivity of catalytic systems generated *in situ* from $Pd(OAc)_2$ was ascribed to increased reactivity of anionic palladium(0) complexes ligated by acetate ions (species **A**) in the oxidative addition,[28,29,30] however, more detailed studies revealed that participation of acetate ions in the ligand exchange (intermediates **B** and **C**) and the reductive elimination (intermediate **D**) steps[27,31] is also of crucial importance.

As to the accelerating effect of acetate in the ligand exchange and the reductive elimination, apparently it originates from the unique ability of acetate ion to act as a bidentate κ^2-ligand (intermediates **C** and **D** in Scheme 2).[31] Due to this, the rate of incorporation of phosphorus nucleophile into a palladium(II) complex (i.e., ligand substitution or transmetallation process) is greatly facilitated *via* intramolecular displacement of one of the phosphine ligands by an oxygen atom of the adjacent acetate. The intermediate formed (**C**) is highly reactive and coordinates an H-phosphonate diester, followed by its deprotonation to form an equilibrium mixture of type **D** intermediates, from which reductive elimination occurs. Due to the presence of an acetate ligand these Pd-phosphonate complexes are highly fluxional and the reductive elimination is accelerated by a constant supply of species containing aryl and phosphonate moieties in the *cis* arrangement, necessary for this process.[31]

On the basis of these mechanistic findings, we set out to develop an efficient protocol for the synthesis of arylphosphonates *via* a palladium-catalyzed cross-coupling reaction between H-phosphonate diesters and ArX (X = I, Br, or triflate) in the presence of external acetate ion additives. In this paper we show that the profound accelerating effect of acetate additives is a universal phenomenon and is compatible with a broad spectrum of supporting phosphine ligands. The developed protocol employs substoichiometric amounts of inorganic acetate and its efficiency was demonstrated in the synthesis of various complex arylphosphonate derivatives.

Results and Discussion

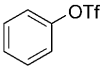
Although by using $Pd(OAc)_2$ as a palladium source all steps of a cross-coupling reaction are accelerated due to introduction of an acetate ion, the observed differences in reactivity are usually small (see Table 1, entry 1 *vs.* 2 for aryl halides).[24,27] This phenomenon we traced back to competition between acetate and halide anions for a palladium center[27] in intermediates of type **A** and **B** (Scheme 2). Since concentration of halides gradually increases during the course of the reaction, less reactive halide-palladium complexes are formed, and for this reason, an accelerating effect of the acetate is only observed at the initial stages of the cross-coupling reaction, when the concentration of halides is low. To remedy this problem, we carried out our screening experiments using stoichiometric amounts of acetate, as our previous mechanistic studies indicated that external addition of acetate increases the overall rate of a cross-coupling reaction.[27]

Effect of Stoichiometric OAc^- Additive on the C–P Bond Forming Reaction with Different Phosphine Ligands

We started our study with an examination of how external acetate ions additives influence the rates of the C–P bond formation, as a function of a leaving group in an electrophilic aromatic substrate and phosphine supporting ligands used. Of particular interest was the behavior of bidentate phosphines, since the postulated mechanisms for ligand substitution and reductive elimination steps (Scheme 2) implied that, at least at some stages of the reaction, only one phosphorus atom of the chelating ligand had to be engaged in complexation (e.g., intermediate **C**). Although preliminary experiments proved that it was the case for dppp,[31] other bidentate phosphines might not permit such a mechanistic pathway.

Thus, to evaluate the compatibility of acetate additives with common supporting phosphine ligands, we

Table 1. Effect of OAc^- additives on the cross-coupling using different phosphine ligands.[a,b]

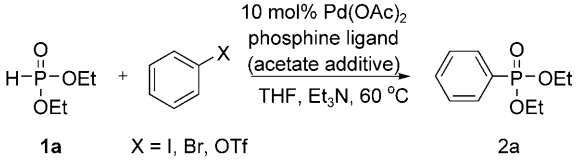
Entry	Pd source/Ligand	OAc^- additive[c]	Reaction time [h][d]		
					
1	$Pd(PPh_3)_4$	no	8	18	23
2	$Pd(OAc)_2+PPh_3$	no	7	16	5
3	$Pd(OAc)_2+PPh_3$	yes	1	2.5	3
4	$Pd(OAc)_2$+dppp	no	10	25	3
5	$Pd(OAc)_2$+dppp	yes	0.5	2	0.75
6	$Pd(OAc)_2$+dppb	no	21	26	2
7	$Pd(OAc)_2$+dppb	yes	1	3	1
8	$Pd(OAc)_2$+dppf	no	6	14	1
9	$Pd(OAc)_2$+dppf	yes	0.75	2	0.75
10	$Pd(OAc)_2$+BINAP	no	26	21	0.75
11	$Pd(OAc)_2$+BINAP	yes	1.5	2	0.5

[a] **Abbreviations:** dppp = 1,3-bis(diphenylphosphino)propane, dppb = 1,4-bis(diphenylphosphino)butane, dppf = 1,1′-bis(diphenylphosphino)ferrocene, BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (racemic).

[b] *Reaction conditions:* 0.30 mmol **1a**, 0.33 mmol PhX, 0.36 mmol Et_3N, 3 mL THF, 60 °C; entry 1: 0.03 mmol $Pd(PPh_3)_3$; entries 2–11: 0.03 mmol $Pd(OAc)_2$, 0.09 mmol monodentate or 0.06 mmol bidentate ligand; 15 min, palladium reduction was performed before addition of **1a** and PhX.

[c] 0.30 mmol *n*-$Bu_4N(OAc)$.

[d] >95% conversion monitored by ^{31}P NMR spectroscopy.



Scheme 3. A model reaction for an acetate-promoted cross-coupling.

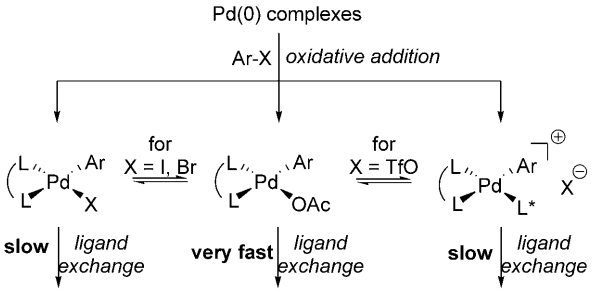
performed a series of model reactions in which diethyl H-phosphonate (**1a**) was coupled with iodobenzene, bromobenzene, and phenyl triflate (Scheme 3).

In all cases 10 mol% of the palladium pre-catalyst, in the form of $Pd(OAc)_2$ [except for the benchmark reaction with $Pd(PPh_3)_4$ – Table 1, entry 1], was used, together with an appropriate phosphine that acted both as a reducing agent for palladium and a supporting ligand for the catalyst formed.[30,32]

Each reaction was carried out separately in the absence and in the presence of *n*-$Bu_4N(OAc)$ (1 equiv.), and the progress of the reactions was monitored by ^{31}P NMR spectroscopy. The completion times for these cross-coupling reactions (>95% conversion into phenylphosphonate **2a**) are presented in Table 1.

As it is apparent from the data in Table 1, the reactivities of PhI, PhBr and PhOTf in a cross-coupling reaction catalyzed by $Pd(PPh_3)_4$ (entry 1) paralleled their relative rates of oxidative addition.[33] By using $Pd(OAc)_2$ as the palladium source (entry 2; 0.2 equiv. of OAc^- is introduced to the reaction mixture with this pre-catalyst), a slight acceleration of the product formation was observed for PhI and PhBr, whereas for PhOTf, this effect was significantly stronger (shortening of the reaction time from 23 to only 5 h). A completely different picture emerged upon external addition of acetate to the reaction mixture (entry 3). In this instance, a significant shortening of the reaction time was observed for the aryl halides, while for phenyl triflate, the effect was only moderate (from 5 to 3 h). This pattern of reactivity was observed for all ligands investigated (Table 1, even number entries *vs.* odd number ones).

On the whole, the data in Table 1 are consistent with the catalytic cycle in Scheme 2 and point to the importance of the acetate-mediated ligand exchange process that seems to operate for all the bidentate supporting phosphine ligands. Crucial to the final outcome of these reactions is probably an equilibrium system shown in Scheme 4 that controls amounts of



Scheme 4. Equilibria between palladium(II) complexes that undergo ligand exchange with H-phosphonate diesters. L* stands for a neutral ligand, for example, solvent molecule or diphosphine monoxide.[30] For monodentate ligands the presented Pd(II) complexes have the *trans* configuration.

different Pd(II) complexes in the reaction mixture that undergo ligand exchange with phosphorus nucleophiles (H-phosphonate diesters).

A dramatic accelerating effect of acetate observed in the reactions involving phenyl triflate can be ascribed to a weak bonding of the triflate anion to a palladium(II) center.[33] Due to this, even in presence of a substoichiometric amount of acetate ions [introduced to the reaction mixture along with $Pd(OAc)_2$], the equilibrium is apparently shifted towards the reactive acetate-ligated species (Scheme 4). For PhI and PhBr, however, relatively high affinity of halides *vs.* OAc^- towards Pd(II)[29] caused that highly reactive acetate-ligated Pd(II) species were formed in significant amounts only at the beginning of the reaction, when the concentration of halide ions was low. As the reactions progressed, the dominant Pd(II) species became those with ligated halides, and this slowed down the ligand exchange process, and in consequence, the whole cross-coupling. In contrast to this, when a stoichiometric amount of acetate was present in the reaction mixture (external addition), then throughout the reaction the dominant Pd(II) species contained ligated acetate. This secured high rates of the individual steps and made the differences between reactions involving various aryl substrates (aryl halides *vs.* aryl triflate), small.

By comparing the reactions carried out in the absence of external acetate additives, for most ligands (Table 1, entries 2, 4, 6 and 8) iodobenzene reacted faster than its bromo counterpart. The exception was, however, BINAP (entry 10) for which a faster cross-coupling reaction was observed with bromo- *vs.* iodobenzene. A possible explanation for this could be that palladium(II) complexes containing bromide undergo faster ligand substitution (*ca.* 2 times) by H-phosphonate diesters than those in with iodide,[31] and thus, in this particular case, not oxidative addition but ligand exchange, became a turnover limiting step of the catalytic cycle. Upon addition of external acetate to such a BINAP-mediated reaction (Table 1, entry 11), however, a significant accelerating effect was observed and the cross-coupling reaction with iodobenzene became faster (slightly) than that with bromobenzene.

The above results show that the ligand exchange process has the largest impact on the overall reaction kinetics in the C–P bond forming cross-coupling with H-phosphonate diesters, although, the rate of oxidative addition also matters. Slow cross-couplings in the absence of acetate indicate that H-phosphonates exhibit relatively weak nucleophilicity towards the palladium(II) center. The most probable reason for that is that, unlike amines, alcohols or thiols, these compounds do not bear a lone electron pair on the heteroatom forming bond to the metal. Hence, a preceding association must take place first, most probably with participation of the phosphoryl oxygen.[31]

To conclude this part, it seems that a mechanism presented in Scheme 2 operates for various bidentate supporting phosphine ligands. Relative rates of the cross-coupling reactions observed for different aryl electrophiles are understandable. The most affected by the external addition of acetate are the reactions in which the ligand substitution could be enhanced to the highest degree, that is, those involving PhBr and PhI as electrophiles. For PhOTf, since the reaction already proceeds mainly *via* the acetate-ligated species even in the presence substoichiometric amounts of OAc^- introduced with $Pd(OAc)_2$, the further addition of acetate ions has only a minor effect.

Finally, since for the cross-coupling reactions in the presence of acetate all phosphine ligands investigated showed similar efficiency, it means that differences observed in the absence of this additive reflect the ability of the supporting ligands to facilitate a ligand exchange process. In this respect, the most efficient seemed to be monodentate PPh_3 and the wide-bite-angle phosphine dppf (Table 1, entries 2 and 8), and the latter was used in our further studies.

Effect of Amount and Source of the Acetate Additives on the Cross-Coupling Reactions

Since preliminary experiments with external acetate additives indicated a complex relationship between the accelerating effect and the amount and the source of the acetate ion used, more detail investigations were carried out to find optimal reaction conditions.

To this end a cross-coupling reaction between diethyl H-phosphonate **1a** and bromobenzene, catalyzed by the $Pd(OAc)_2$/dppf was carried out using different amounts of the acetate additive and its various sources. The results are summarized in Table 2.

To assess how the amount of the external acetates affects efficiency of our cross-coupling reaction, we used the well soluble in organic solvent *n*-$Bu_4N(OAc)$ as an acetate source. Entry 1 in Table 4 shows the results for our reference reaction where no external acetate additive was introduced, and entry 2, for the reaction in the presence of 1 equivalent of *n*-$Bu_4N(OAc)$. By carrying out experiments with different amounts of acetate ions we noticed that the reactions were fastest with 1 equivalent of *n*-$Bu_4N(OAc)$, but then slowed down, and with 5 equivalents of the added *n*-$Bu_4N(OAc)$, no product formation could be observed (Table 2, entry 3). The same phenomenon we observed for other acetate salt soluble in organic solvents, $Et_3NH(OAc)$ (Table 2, entries 4 and 5). A smaller accelerating effect exerted by this salt *vs.* *n*-$Bu_4N(OAc)$ (Table 2 entry 4 *vs.* 2) originated probably from a partial hydrogen bonding of AcO^- with Et_3NH^+, that lowered its effective activity.

Table 2. Effect of different acetate additives on the cross-coupling of diethyl H-phosphonate **1a** with PhBr, using $Pd(OAc)_2$ dppf.[a]

Entry	Pd loading (mol%)	Acetate additive (equiv.)	Reaction time [h][b]
1	10	none	14
2	10	*n*-$Bu_4N(OAc)$ (1)	2
3	10	*n*-$Bu_4N(OAc)$ (5)	no reaction
4	10	$Et_3NH(OAc)$ (1)	3.5
5	10	$Et_3NH(OAc)$ (5)	no reaction
6	10	LiOAc (1)	5
7	10	NaOAc (1)	4
8	10	CsOAc (1)	3.5
9	10	KOAc (1)	3.5
10	10	KOAc (0.5)	3
11	10	KOAc (0.2)	4
12	10	KOAc (0.1)	3
13	5.0	KOAc (0.1)	4
14	2.5	KOAc (0.1)	2.5
15	1.0	KOAc (0.1)	4.5

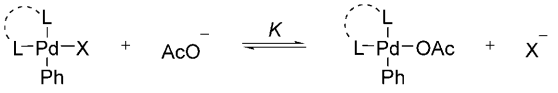
[a] *Reaction conditions:* 0.30 mmol **1a**, 0.33 mmol PhBr, 0.36 mmol Et_3N, 3 mL THF, 60 °C; 15 min, palladium reduction was performed before addition of **1a** and PhX.
[b] >95% conversion monitored by ^{31}P NMR spectroscopy.

The observed inhibition of the cross-coupling reaction by a high concentration of acetate ions was not completely unexpected, in light of the involvement of acetate ions in various reactions steps (see, Scheme 2). The ^{31}P NMR experiments revealed that under such reaction conditions acetate ions apparently interfered with the oxidative addition step as no arylpalladium(II) complex formation could be observed upon addition of bromobenzene to a model reaction mixture containing a palladium(0) complex $Pd(PPh_3)_4$ and 50 equivalents of *n*-$Bu_4N(OAc)$.[34] On the other hand, a high concentration of the acetate probably did not affect significantly the reduction step of $Pd(OAc)_2$ with PPh_3 as judged from the formation of the corresponding phosphine oxide (^{31}P NMR experiment).

Although using *n*-$Bu_4N(OAc)$ secured homogenous reaction conditions, its high price, hydroscopic properties, and problems with its removal during work-up, prompted us to look for other sources of acetate anions. To this end we investigated various alkali metal acetates (Li, Na, Cs, and K) (Table 2, entries 6–9). Interestingly, although these salts were only sparingly soluble in THF under reflux ($<1\ mg\,mL^{-1}$), they gave a reasonable shortening of the reaction time. Since the reactions occurred under heterogeneous conditions and the concentration of acetate ions was controlled by the solubility factor, using smaller amounts of these salts (e.g., entries 9–12 for KOAc), did not affect the reaction time (within the experimental error).

What was somewhat unclear about using alkali metal acetates as external additives, however, was a significant shortening of the reaction time achieved with a small amount of acetate ions present in the reaction mixtures (e.g., entry 12 *vs.* 2 in Table 2). If we assume that concentration of Pd(II) complexes ligated with acetate is controlled by Eq. (1) (L = mono- or bidentate ligand, X = halide),[29] the expressions for the corresponding equilibrium constant [Eqs. (2) and (3)] indicate that a favorable ratio of acetate *vs.* halide ligated complexes is controlled by the ratio of $[OAc^-]/[X^-]$ in the reaction media. Under homogenous reaction conditions, this can be increased only by higher concentrations of the added acetate, while under heterogeneous conditions, also by removal of the halides from the reaction solution.

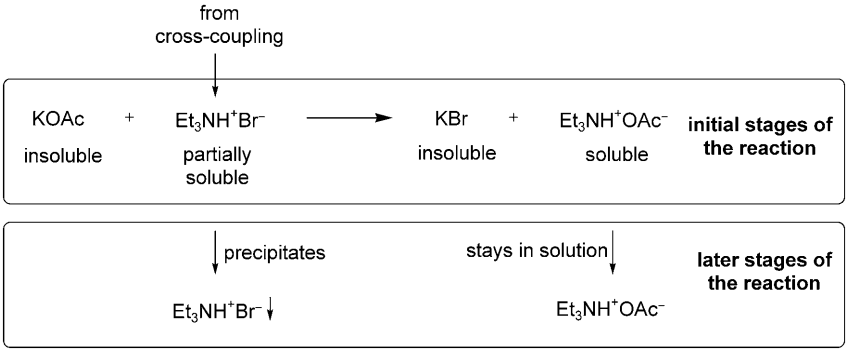
A postulated model for such a scenario is depicted in Scheme 5. At the beginning of a cross-coupling re-



(1)

$$K = \frac{[PhL_2Pd(OAc)][X^-]}{[PhL_2PdX][OAc^-]} \quad (2)$$

$$\frac{[PhL_2Pd(OAc)]}{[PhL_2PdX]} = K\frac{[OAc^-]}{[X^-]} \quad (3)$$



Scheme 5. A mechanism for maintaining a favorable ratio $[OAc^-]/[Br^-]$ in the reaction mixture when using KOAc as an acetate source.

action bromides are removed from the reaction media *via* precipitation of insoluble in organic solvents potassium bromide, and at some point (e.g., 10% conversion for entry 12, or 20% conversion for entry 11), the whole amount of AcO^- ions is in solution in the form of $Et_3NH(OAc)$. As the reaction progresses, the bromides produced are still removed from the solution, this time in the form of an Et_3NHBr precipitate. In consequence, the ratio $[OAc^-]/[Br^-]$ remained steady for the most part of the reaction and secured a fast cross-coupling, even when only 10 mol% KOAc additive was used for the reaction.

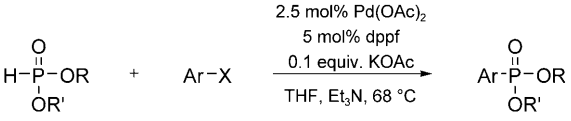
Further experiments showed that for a given amount of the added acetate it was possible to reduce the amount of the catalyst even 10-fold, without affecting significantly the efficiency of the reaction (Table 2, entries 13–15). We found that for synthetic purposes 2.5 mol% of Pd in combination with 0.1 equivalent of KOAc (Table 2, entry 14) was the best choice.

To sum up this part, we demonstrated that a successful implementation of the mechanistic findings concerning the acetate-promoted catalytic cycle in Scheme 2 can be achieved in two different ways: *via* the addition of stoichiometric amounts of soluble in organic solvents acetates [for example, $n\text{-}Bu_4N(OAc)$ or $Et_3NH(OAc)$], or by using sub-stoichiometric amounts of the acetate additives with a simultaneous removal of halides from the reaction media. Both methods secured a favorable ratio $[OAc^-]/[X^-]$ and provided comparable acceleration of the Pd-catalyzed cross-coupling reactions of H-phosphonate diesters with aryl electrophiles. The latter approach, however, seems to be preferable for preparative purposes as it permits one to carry out the reaction with a lower catalyst load.

Synthesis of Arylphosphonate Diesters Promoted by the Acetate Additive

The above studies led us to the reaction conditions shown in Scheme 6 that we successfully used in the synthesis of various arylphosphonates with diverse structural features both in the aryl and in the ester moieties (Table 3, Table 4, and Table 5).

All the reactions in Table 3, Table 4, and Table 5 were run to >95% conversion (^{31}P NMR spectroscopy) and the products were isolated by silica gel chromatography.



Scheme 6. Optimized reaction conditions for the synthesis of arylphosphonate diesters.

First, aryl substrates containing different leaving groups, namely iodobenzene, bromobenzene and phenyl triflate, were coupled with diethyl H-phosphonate.

As is apparent form entries 1–3 (Table 3), all of them showed comparable reactivity in the cross-coupling reactions in the presence of acetate ions. Dimethyl H-phosphonate (Table 3, entry 4) reacted with bromobenzene similarly to diethyl H-phosphonate (3 h for the completion), but the presence of two isopropyl groups (entry 5) in the H-phosphonate moiety visibly slowed down the cross-coupling reactions (10 h), most likely due to the steric hindrance.

Then, cross-couplings with aryl bromides bearing polycyclic aromatic moieties were investigated (Table 3, entries 6–9). 2-Bromonaphthalene (entry 6) reacted similarly to bromobenzene (*ca.* 2 h), but its positional isomer, 1-bromonaphthalene (entry 7), 9-bromophenanthrene (entry 8), and 1-bromopyrene (entry 9), underwent cross-coupling with diethyl H-phosphonate significantly slower (23–32 h), probably due to highly unfavorable interactions with the peri-hydrogen atoms. This slow kinetics, however, did not affect the efficiency of the reactions, and the isolated yields of the corresponding arylphosphonates formed were rather high. In line with the importance of steric factors in this type of reactions, a very slow cross-coupling was observed for *o*-bromotoluene (Table 3, entry 13).

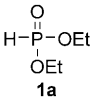
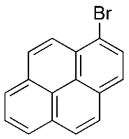
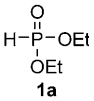
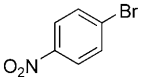
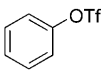
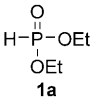
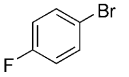
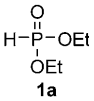
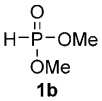
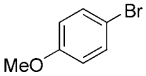
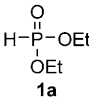
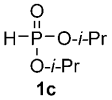
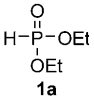
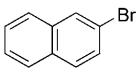
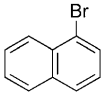
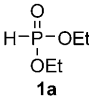
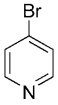
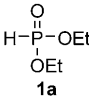
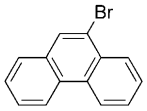
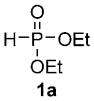
Concerning the influence of electronic factors, the cross-coupling was rather insensitive to the presence of electron-withdrawing substituents in the aromatic ring of the electrophilic substrates (e.g., *p*-nitro- and *p*-fluorobromobenzene, entries 10 and 11, respectively), but the introduction of a strongly electron-donating *p*-methoxy group (entry 12), significantly slowed down the reaction (10 h).

Since pyridylphosphonates emerged recently as potential, biologically important nucleotide analogues,[7,15] we carried out two cross-coupling reactions involving 3-bromopyridine (entry 14) and 4-bromopyridine (entry 15). The reactions proceeded smoothly and the corresponding diethyl pyridylphosphonates were isolated in high yields (>90%).

Looking for a possible chemoselectivity in this type of cross-coupling reactions, we investigated aromatic dihalides as electrophilic substrates (Table 4).

To this end we reacted *p*-bromoiodobenzene (Table 4, entry 1) and 2,5-dibromopyridine (Table 4, entry 2) with diethyl H-phosphonate under the developed reaction conditions. In both instances the reactions were high yielding and completely chemoselective. For bromoiodobenzene, it was the iodine atom that was replaced by the phosphorus nucleophile forming diethyl 4-bromophenylphosphonate, and for dibromopyridine, the bromine at the C-2 position of

Table 3. Acetate-promoted cross-coupling of aryl halides with H-phosphonate diesters.[a]

Entry	Aryl halide	H-phosphonate (**1**)	Reaction time [h][b]	Product [%][c]	Entry	Aryl halide	H-phosphonate (**1**)	Reaction time[b]	Product [%][c]
1		 **1a**	3	**2a** (81)	9		 **1a**	32	**2g** (82)
2		 **1a**	2.5	**2a** (75)	10		 **1a**	4	**2h** (98)
3		 **1a**	3	**2a** (79)	11		 **1a**	3	**2i** (91)
4		 **1b**	3	**2b** (72)	12		 **1a**	10	**2j** (90)
5		 **1c**	10	**2c** (95)	13		 **1a**	32	**2k** (63)
6		 **1a**	2	**2d** (85)	14		 **1a**	1.5	**2l** (92)
7		 **1a**	36	**2e** (97)	15		 **1a**	5	**2m** (94)
8		 **1a**	23	**2f** (92)					

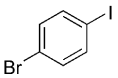
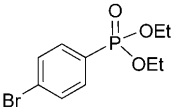
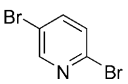
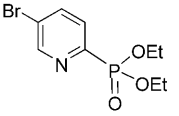
[a] *Reaction conditions:* 0.03 mmol $Pd(OAc)_2$, 0.06 mmol dppf, 1.5 mmol Et_3N, and 0.13 mmol KOAc in 5 mL THF, 68 °C, 15 min; then 1.25 mmol **1** and 1.38 mmol ArX were added.
[b] >95% conversion monitored by ^{31}P NMR spectroscopy.
[c] Isolated yield.

the pyridine ring reacted selectively to produce diethyl 5-bromopyridin-2-ylphosphonate.

As a final part of these investigations we tested the efficacy of the developed cross-coupling method in the synthesis of more complex arylphosphonate diesters (Table 5) that are of potential importance to medicinal chemistry[10,35] and nucleic acids-based therapeutics.[13,15,36]

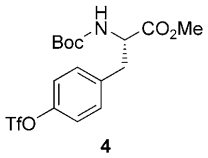
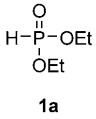
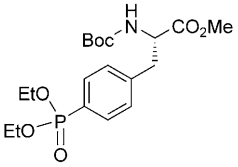
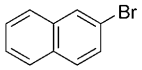
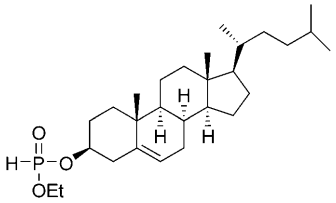
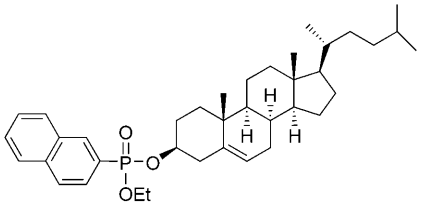
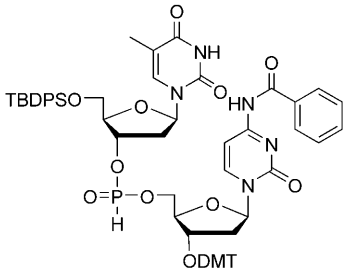
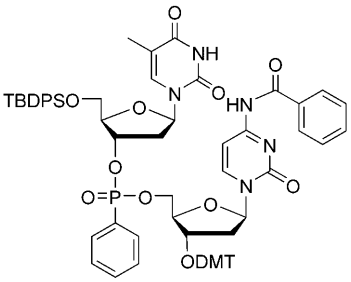
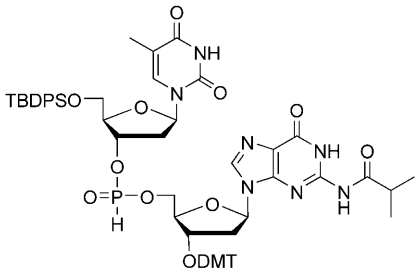
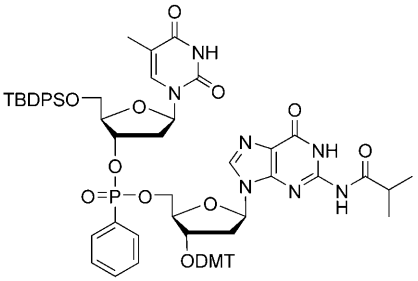
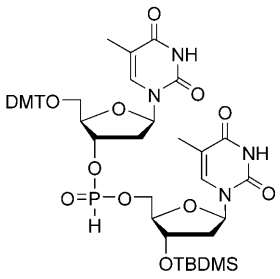
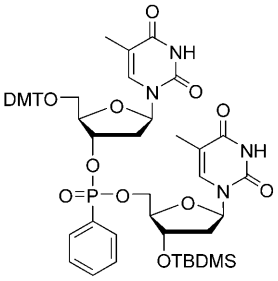
In entry 1 (Table 5), a protected tyrosine triflate derivative **4** in the reaction with diethyl H-phosphonate was successfully converted into the corresponding arylphosphonate **9** in high yield. Entry 2 (Table 5) shows the transformation of cholesteryl H-phosphonate diester **5** into the highly lipophilic 2-naphthylphosphonate derivative **10**. Also various dinucleoside H-phosphonates **6**–**8** (Table 5, entries 3–5) reacted efficiently with bromobenzene to produce the corresponding dinucleoside phenylphosphonates. The reac-

Table 4. Selective acetate-promoted cross-coupling of aryl dihalides with **1a**.[a]

Entry	Aryl halide	Reaction time [h][b]	Product	Yield [%][c]
1		2	 **3a**	96
2		3	 **3b**	83

[a] *Reaction conditions:* 0.03 mmol $Pd(OAc)_2$, 0.06 mmol dppf, 1.5 mmol Et_3N, and 0.13 mmol KOAc in 5 mL THF, 68 °C, 15 min; then 1.25 mmol **1** and 1.25 mmol ArX were added.
[b] >95% conversion monitored by ^{31}P NMR spectroscopy.
[c] Isolated yield.

Table 5. Synthesis of some biologically relevant arylphosphonate derivatives.[a,b]

Entry	Aryl derivative	H-phosphonate diester	Reaction time [h][c]	Product	Yield [%][d]
1	 **4**	 **1a**	2.5	 **9**	86
2[e]		 **5**	5	 **10**	71
3[e]		 **6**	1.5	 **11**	54
4[e]		 **7**	7	 **12**	60
5		 **8-R_P** **8-S_P**	5.5	 **13-R_P** **13-S_P**	63 (**13-R_P**) 56 (**13-S_P**)

[a] **Abbreviations:** TBDPS = *tert*-butyldiphenylsilyl, TBDMS = *tert*-butyldimethylsilyl, DMT = 4,4′-dimethoxytrityl.
[b] *Reaction conditions:* 0.01 mmol $Pd(OAc)_2$, 0.02 mmol dppf, 0.48 mmol Et_3N, and 0.04 mmol KOAc in 4 mL THF, 68 °C, 15 min; then 0.40 mmol H-phosphonate and 0.44 mmol ArX were added.
[c] > 95% conversion monitored by ^{31}P NMR spectroscopy.
[d] Isolated yield.
[e] Mixture of the H-phosphonate diastereoisomers (*ca.* 1:1) was used.

tion time varied depending on nucleosidic composition and the protecting groups present, but it did not exceed 7 h. Although in all instances the ^{31}P NMR spectroscopy indicated a complete conversion into the corresponding phenylphosphonates **11**–**13**, the isolated yields were lower than for other arylphosphonates, due to loses during purifications.

To find out if the involvement of acetates in a catalytic cycle (Scheme 2) does not erode stereochemistry at the phosphorus center, separate diastereomers of dithymidine H-phosphonate **8** (**8**-R_P and **8**-S_P) were subjected to a cross-coupling with bromobenzene (Table 5, entry 13). The ^{31}P NMR spectra revealed that the reactions were completely stereospecific (**8**-R_P→**13**-R_P and **8**-S_P→**13**-S_P) and thus confirmed that the developed procedure did not compromise the usual stereospecificity of this type of cross-coupling reactions.[3,5,7,37]

Conclusions

We have developed a mild, and efficient procedure for the synthesis of arylphosphonates that makes use of an acetate-promoted, palladium-catalyzed cross-coupling reaction of aryl halides (or triflates) with H-phosphonate diesters. The reaction conditions of the new protocol were optimized in terms of the supporting ligands, kinds and amounts of the acetate additive, and the catalyst load. The method seems to be rather general, accepts a wide range of electrophilic aryl (iodide, bromide and triflate) derivatives, and H-phosphonate substrates (simple alkyl, cholesteryl, dinucleosides), and may provide a convenient entry to complex arylphosphonate diesters of biological importance.

Experimental Section

General

All reagents and solvents were of analytical grade, obtained from commercial suppliers and used without further purification. THF was dried using a VAC solvent purifier system. All reactions were carried out using standard Schlenk techniques. Column chromatography was preformed on silica gel (Grace Davison, Davsil, 0.035–0.070 mm). The NMR spectra were registered using a Bruker Avance II 400 MHz instrument. The chemical shifts are reported in ppm, relative to solvent peaks (^{1}H, ^{13}C) or 2% H_3PO_4 solution in D_2O (^{31}P NMR). Assignment of the NMR signals was done on the basis of 2D correlation experiments (COSY, HSQC).

Experimental Procedure for the Acetate-Promoted Preparation of Arylphosphonates

$Pd(OAc)_2$ (7 mg, 0.03 mmol), dppf (33 mg, 0.06 mmol) and KOAc (13 mg, 0.13 mmol) were placed in the reaction vessel. The vessel was sealed and filled with N_2, by applying 2 cycles of vacuum, followed by N_2. THF was introduced *via* a septum (5 mL), followed by triethylamine (1.50 mmol, 152 mg, 208 μL), and the mixture was stirred and heated at 68 °C After 15 min, H-phosphonate (1.25 mmol) and aryl halide (1.38 mmol) were added (in the case of solid reagents, they were dissolved in a small amount of THF). After heating at 68 °C for the time indicated in Table 3, the solvent was evaporated and the product purified by silica gel chromatography (depending on the case, pentane-AcOEt mixture from 1:1 to 1:9 was used as an eluent).

Supporting Information

Characterization data for the synthesized arylphosphonates (Table 3, Table 4, and Table 5) and their ^{1}H, ^{13}C, and ^{31}P NMR spectra are available as Supporting Information.

Acknowledgements

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