

# Preparation of benzylphosphonates *via* a palladium(0)-catalyzed cross-coupling of H-phosphonate diesters with benzyl halides. Synthetic and mechanistic studies†‡§

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We have developed a new, efficient method for the synthesis of benzylphosphonate and benzylphosphonothioate diesters *via* a palladium(0)-catalyzed cross-coupling reaction between benzyl halides and H-phosphonate or H-phosphonothioate diesters, using Pd<sub>2</sub>(dba)<sub>3</sub>(CHCl<sub>3</sub>) as a palladium source and Xantphos as a supporting ligand. Some mechanistic aspects of these reactions were investigated using <sup>31</sup>P NMR spectroscopy.

## Introduction

Analogues of naturally occurring phosphorus-containing compounds possessing P–C bonds (C-phosphonates and C-phosphinates) exhibit enhanced stability to hydrolysis and enzymatic digestion, and therefore, have attracted attention as potential pesticides and therapeutics.<sup>1</sup> A prominent group among these compounds are benzylphosphonates, that show a vast array of biological activity,<sup>2,3</sup> and are frequently used as prodrugs.<sup>3</sup> In the antisense/antigene research area, the recently synthesized benzylphosphonate-modified oligonucleotides turned out to be superior inhibitors against the hepatitis-C virus to the corresponding phosphorothioates or methylphosphonates.<sup>4</sup>

For the formation of the P–C(sp<sup>3</sup>) bond, the most common approaches are probably those involving the Michaelis–Arbuzov<sup>5</sup> and Michaelis–Becker<sup>6</sup> reactions. Although quite general in scope, these methods usually require harsh reaction conditions<sup>7</sup> that are unsuitable for the synthesis of biologically interesting, complex molecules.<sup>8</sup> Due to this, for the preparation of oligonucleoside benzylphosphonates, the only method of practical value makes use of benzylphosphonous dichloride as a precursor, but it is lengthy and, because of a facile ligand exchange at the phosphorus centre, complex reaction mixtures are usually formed.<sup>9</sup>

Recent studies in our<sup>10,11</sup> and other<sup>12</sup> laboratories have shown that the application of transition metal chemistry enables a mild synthesis of aryl- and vinylphosphonates, even in the case of sensitive nucleotide analogues.

Herein, we describe our synthetic and mechanistic investigations aimed at broadening the scope of methods for P–C bond formation by cross-coupling of benzyl halides with

H-phosphonate diesters catalyzed by Pd(0). Despite the vast interest in the area of palladium-catalyzed cross-coupling using heteroatom nucleophiles,<sup>13</sup> only a few examples of a P–C(sp<sup>3</sup>) bond formation have been reported so far.<sup>14</sup>

## Results and discussion

### Synthesis of benzylphosphonate and benzylphosphonothioate diesters

In a preliminary account of this work,<sup>15</sup> we reported on the preparation of benzylphosphonates using a palladium(0)-catalyzed cross-coupling of H-phosphonate diesters and benzyl halides. By screening various ligands, we found that only large bite angle phosphines efficiently promoted the formation of benzylphosphonates, and the best catalytic system consisted of Pd(OAc)<sub>2</sub>/Xantphos and *N,N*-diisopropylethylamine (DIPEA) as a base.

Although the Pd(OAc)<sub>2</sub>/Xantphos system worked well, further studies showed that the results were not completely reproducible (variations in yields), and we traced this back to the reduction step of the Pd(II) precursor.<sup>16</sup> Since the reduction has to be carried out in the presence of a controlled amount of water,<sup>15,16</sup> partial hydrolysis of the substrates may occur due to the high lability of H-phosphonate diesters under basic conditions.

We envisaged that the synthesis of benzylphosphonates would be simpler to conduct if the reduction step could be omitted by using Pd(0) as a palladium source. Since Pd(PPh<sub>3</sub>)<sub>4</sub> was not suitable for this purpose,<sup>15</sup> we tried tris(dibenzylideneacetone)dipalladium(0)(chloroform) [Pd<sub>2</sub>(dba)<sub>3</sub>(CHCl<sub>3</sub>)] and Xantphos as a supporting ligand. We found that cross-coupling of diethyl H-phosphonate with benzyl bromide catalyzed by Pd<sub>2</sub>(dba)<sub>3</sub>(CHCl<sub>3</sub>) and Xantphos in THF (reflux) showed the same efficiency and kinetics as that with Pd(OAc)<sub>2</sub>/Xantphos (see the ESI<sup>†</sup>), and thus, this catalyst system (Fig. 1) has been adopted for the present studies.<sup>17</sup>

In Table 1, the results of cross-coupling of various benzyl halide derivatives with diethyl H-phosphonate are summarised. The optimal reaction conditions consisted of using 1.2 equiv. of a benzyl halide relative to diethyl H-phosphonate, 1.2 equiv.

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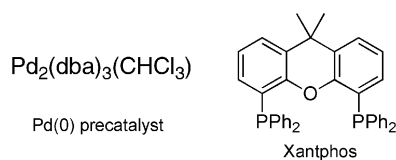
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**Fig. 1** A catalyst system for the synthesis of benzylphosphonates.

of *N,N*-diisopropylethylamine (DIPEA) in the presence of 5% of the Pd catalyst, and 5% of the supporting ligand in THF, under reflux. These, in most cases, secured a complete conversion (<sup>31</sup>P NMR spectroscopy) into the corresponding benzylphosphonates within 4 h, and only for the 5-chloromethylfuran derivative (entry 10), the reaction time had to be extended to 6 h with a simultaneous increasing of the catalyst load to 8% Pd. Consistent with our previous findings, no visible differences in reactivity have been observed between Cl vs. Br derivatives, and electronic features of the substituents in the aromatic ring did not appreciably affect the rates of the cross-coupling reactions investigated.

Compared with our previously developed reaction conditions [Pd(OAc)<sub>2</sub>/Xantphos],<sup>15</sup> using Pd<sub>2</sub>(dba)<sub>3</sub>(CHCl<sub>3</sub>) permitted us, in most cases, to lower the catalyst load from 10 to 5 mol% of Pd, and to reduce the amount of the supporting ligand from 20 to 5 mol%. Also, the overall reproducibility of the cross-coupling reactions in terms of yields was significantly improved with this new catalyst system.

To demonstrate the generality of the developed synthetic protocol, various H-phosphonate diesters with diverse structural features were subjected to a cross-coupling reaction with benzyl chloride. The results are summarised in Table 2.

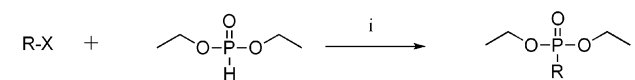
As was observed for diethyl H-phosphonate, cross-coupling of asymmetrically substituted dialkyl, alkyl glyceryl and alkyl cholesteryl H-phosphonate diesters with benzyl chloride (Table 2, entries 1–3) occurred smoothly, affording the corresponding benzylphosphonates **11–13** in good isolated yields.

Previously, we showed that benzylation of dithymidyl H-phosphonate diesters occurred stereospecifically with, most likely, retention of configuration at the phosphorus center.<sup>15</sup> To address a possible issue of coordination of palladium by functional groups present in complex organic molecules, we next investigated benzylation of dinucleoside H-phosphonate diesters bearing four standard heterocyclic bases present in DNA (adenine, cytosine, guanine and thymine derivatives; Table 2, entries 4–7). No deterioration of the catalyst system could be observed, as judged from similar kinetics of the cross-coupling reaction as those for simple diethyl H-phosphonate. In all instances, the benzylation of dinucleoside H-phosphonates was uneventful, and the corresponding benzylphosphonates **14–17** were obtained as a *ca.* 1 : 1 mixture of the diastereomers in high yields.

Efficient cross-coupling of H-phosphonate diesters with benzyl halides prompted us to investigate *P*-benzylation of H-phosphonothioate diesters as a possible entry to new phosphate analogues, namely benzylphosphonothioates (reaction scheme in Table 3).

As representative compounds, diethyl and nucleoside ethyl H-phosphonothioate diesters (Table 3) were subjected to

**Table 1** Synthesis of diethyl benzylphosphonate derivatives



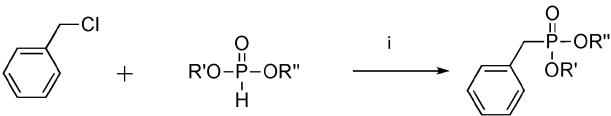
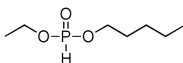
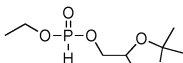
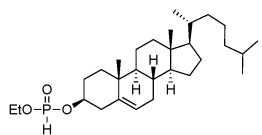
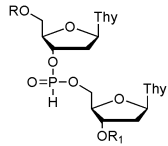
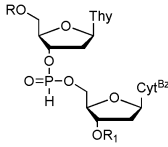
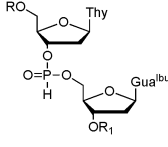
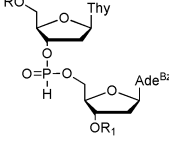
Entry	R-X	<chem>CCOP(=O)(OR)OCC</chem>	Conv. (%) <sup>a</sup>	Yield (%) <sup>b</sup>
1		<b>1</b>	99	89
2		<b>2</b>	99	88
3		<b>3</b>	99	87
4		<b>4</b>	99	96
5		<b>5</b>	99	90
6		<b>6</b>	99	86
7		<b>7</b>	96	92
8 <sup>c</sup>		<b>8</b>	99	92
9 <sup>c</sup>		<b>9</b>	99	99
10 <sup>d</sup>		<b>10</b>	99 <sup>d</sup>	90

*i* = 2.5 mol% Pd<sub>2</sub>(dba)<sub>3</sub>(CHCl<sub>3</sub>), 5 mol% Xantphos, 1.2 equiv. *N,N*-diisopropylethylamine, THF, 4 h under reflux.<sup>a</sup> Determined by <sup>31</sup>P NMR spectroscopy. <sup>b</sup> Isolated yield. <sup>c</sup> 2.5 equiv. of the base was used. <sup>d</sup> 4 mol% Pd<sub>2</sub>(dba)<sub>3</sub>(CHCl<sub>3</sub>), 8 mol% Xantphos, 6 h.

cross-coupling with benzyl chloride. In the absence of a Pd(0) catalyst, no diethyl benzylphosphonothioate formation could be observed upon reflux overnight of equimolar amounts of diethyl H-phosphonothioate and benzyl chloride in THF, in the presence of *N,N*-diisopropylethylamine (1.3 equiv.). However, using the reaction conditions developed for the cross-coupling of H-phosphonate diesters [Pd<sub>2</sub>(dba)<sub>3</sub>(CHCl<sub>3</sub>) + Xantphos], clean formation of the corresponding benzylphosphonothioate diesters **18** and **19** (Table 3, entries 1 and 3, respectively), was observed.

A striking feature of these cross-coupling reactions was, however, a significantly longer reaction time than that for H-phosphonate derivatives (18–19 h vs. 4 h), even after increasing the catalyst load to 10% Pd (Table 3, entries 1 and 3). In contrast to these, when benzyl bromide was used as a reactant, the cross-coupling to the corresponding

**Table 2** Synthesis of diverse benzylphosphonate diesters

				
Entry	$\text{R}'\text{O}-\text{P}(=\text{O})(\text{H})-\text{OR}''$	$\text{R}'\text{O}-\text{P}(=\text{O})(\text{H})-\text{OR}''$	Conv. (%) <sup>a</sup>	Yield (%) <sup>b</sup>
1		<b>11</b>	99	88
2		<b>12</b>	99	74
3		<b>13</b>	99	88
4		<b>14</b>	99	88
5		<b>15</b>	99	85
6		<b>16</b>	99	80
7		<b>17</b>	99	81

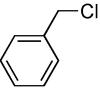
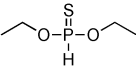
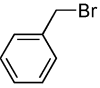
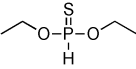
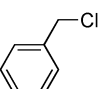
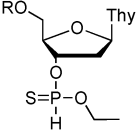
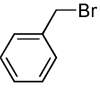
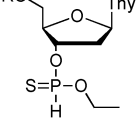
R = *t*-butyldiphenylsilyl; R<sub>1</sub> = 4,4'-dimethoxytrityl; Thy = thymine-1-yl; Cyt<sup>Bz</sup> = *N*<sup>4</sup>-benzoylcytosine-1-yl; Gua<sup>ibu</sup> = *N*<sup>2</sup>-isobutyrylguanine-9-yl; Ade<sup>Bz</sup> = *N*<sup>6</sup>-benzoyladenine-9-yl. *i* = 2.5 mol% Pd<sub>2</sub>(dba)<sub>3</sub>(CHCl<sub>3</sub>), 5 mol% Xantphos, 1.2 equiv. *N,N*-diisopropylethylamine, THF, 4 h under reflux.<sup>a</sup> Determined by <sup>31</sup>P NMR spectroscopy. <sup>b</sup> Isolated yield.

benzylphosphonothioates **18** and **19** became very fast and the reactions went to completion within 2 h (Table 3, entries 2 and 4).

Previously, we observed similar differences in reactivity between H-phosphonate and H-phosphonothioate diesters in Pd-catalyzed cross-coupling arylation reactions.<sup>11</sup> Since the

P–H bond in H-phosphonothioate diesters is more acidic than that of the corresponding H-phosphonate derivatives,<sup>18</sup> one should, in principle, expect a faster reaction for H-phosphonothioate diesters, due to more efficient generation of a phosphorus nucleophile under the reaction conditions. It seems that the reactivity pattern of H-phosphonothioate

**Table 3** Cross-coupling of H-phosphonothioate diesters with benzyl halides

$\text{R-X} + \text{R}'\text{O}-\text{P}(\text{S})(\text{H})-\text{OR}'' \xrightarrow{i} \text{C}_6\text{H}_5\text{CH}_2-\text{P}(\text{S})(\text{OR}')(\text{OR}'')$						
Entry	R-X	R'O-P(S)(H)-OR''	R'O-P(S)(H)-OR''	Time/h	Conv. (%) <sup>a</sup>	Yield (%) <sup>b</sup>
1			<b>18</b>	19	99	88
2			<b>18</b>	2	99	79
3			<b>19</b>	18	99	78
4			<b>19</b>	2	99	83

R = *t*-butyldiphenylsilyl; Thy = thymine-1-yl. *i* = Entries 1 and 3: 2.5 mol% Pd<sub>2</sub>(dba)<sub>3</sub>(CHCl<sub>3</sub>), 5 mol% Xantphos; entries 2 and 4: 5 mol% Pd<sub>2</sub>(dba)<sub>3</sub>(CHCl<sub>3</sub>), 10 mol% Xantphos; 1.2 equiv. *N,N*-diisopropylethylamine, THF, under reflux.<sup>a</sup> Determined by <sup>31</sup>P NMR spectroscopy. <sup>b</sup> Isolated yield.

diesters with benzyl halides follows that of aryl halides,<sup>11</sup> *i.e.* the catalytic cycle is most efficient for electrophilic substrates that undergo rapid oxidative addition to Pd(0) complexes (also, *vide infra*).

#### Mechanistic aspects of the Pd-catalysed benzylphosphonate synthesis

Benzyl bromides are usually much more reactive in oxidative addition to Pd(0) complexes than the corresponding chlorides,<sup>19</sup> and thus, the similar reaction times observed for the Pd-catalyzed benzylation of H-phosphonate diesters with various benzyl halides suggested that oxidative addition was probably not the rate determining step of the catalytic cycle. The slower reaction of electron-deficient benzyl halides *vs.* electron-rich ones<sup>15</sup> also lends support for this hypothesis.<sup>20</sup> Since Stockland *et al.*<sup>21</sup> reported that reductive elimination from metal phosphonate complexes is significantly accelerated in the presence of large bite angle phosphine ligands, the high efficiency of Xantphos (and to a lesser extent, other bidentate ligands<sup>15</sup>) in the investigated reactions pointed to the kinetic importance of later steps in the catalytic cycle.

To gain some insight into mechanistic aspects of these cross-coupling reactions, <sup>31</sup>P NMR experiments were carried out (Fig. 2 and 3). To this end, the catalyst precursor, Pd<sub>2</sub>(dba)<sub>3</sub>(CHCl<sub>3</sub>), was dissolved in THF at 40 °C, and an equimolar amount of Xantphos was added. The <sup>31</sup>P NMR spectrum revealed the rapid formation of a Pd(0)–Xantphos complex, as was apparent from the appearance of two resonances at *ca.* 8.5 and 10.5 ppm (Fig. 2a). Upon addition of benzyl bromide (1 equiv.), these signals disappeared within 5 min, and a new resonance at *ca.* 11.5 ppm, assigned to an oxidative addition product of benzyl bromide to the Pd(0)–Xantphos complex [a benzylpalladium(II) complex], emerged (Fig. 2b). When this reaction mixture was then treated with diethyl H-phosphonate and *N,N*-diisopropylethylamine (5 equiv. of both reactants), the intensity of the signal at *ca.* 11.5 ppm was gradually decreasing in time with the simultaneous formation of the elimination product, diethyl benzylphosphonate (signal at *ca.* 26 ppm; Fig. 2c). After 1 h at 40 °C, *ca.* 24% of the benzylphosphonate product was formed, but heating for additional 10 min at 60 °C brought the reaction to completion (Fig. 2d and e).

An analogous  $^{31}\text{P}$  NMR experiment was also carried out with benzyl chloride, instead of benzyl bromide, and fragments of the corresponding spectra are shown in Fig. 3. It is clearly visible that benzyl chloride underwent significantly slower oxidative addition than benzyl bromide, and after 30 min at 40 °C, only traces of a benzylpalladium(II) complex (signal at *ca.* 11.5 ppm) could be detected (Fig. 3b).

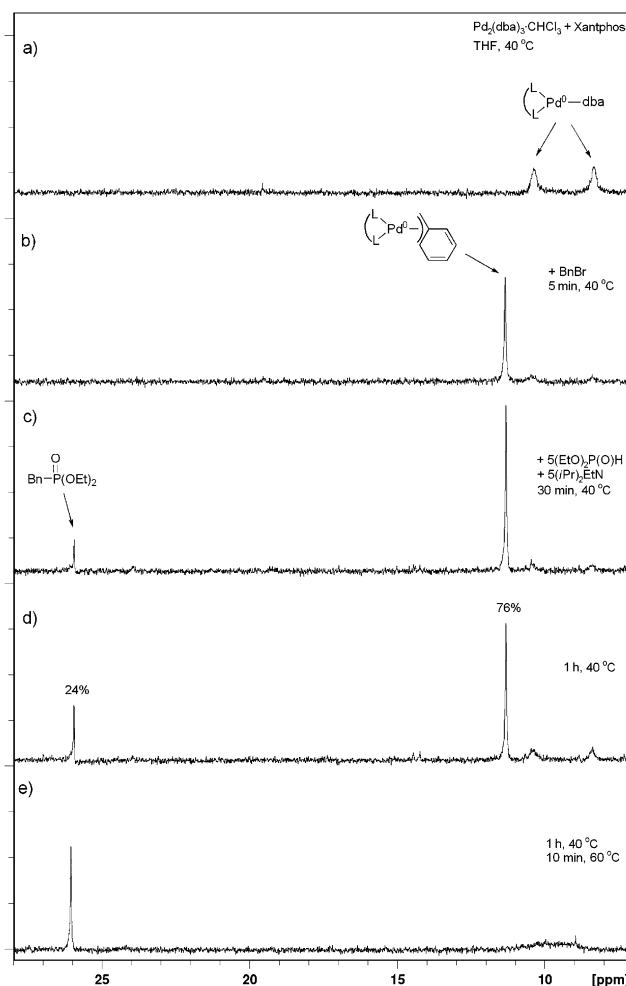
Upon heating of the reaction mixture, the intensity of the signal at *ca.* 11.5 ppm was gradually increasing, with a simultaneous broadening of the signals due to the Pd(0)–Xantphos complex. When the benzylpalladium(II) complex became the major product (Fig. 3d), diethyl H-phosphonate and *N,N*-diisopropylethylamine (5 equiv. of both reactants) were added to the reaction mixture. This, after 1 h at 40 °C, resulted in 52% conversion of the benzylpalladium(II) complex into diethyl benzylphosphonate (signal at *ca.* 26 ppm; Fig. 3e and f).

By comparing the spectra in Fig. 2b and 3b, it became apparent that oxidative addition of benzyl bromide to the Pd(0)–Xantphos complex was significantly faster than that of benzyl chloride, but the added diethyl H-phosphonate reacted faster with the benzylpalladium(II) complex produced from benzyl chloride than with that from benzyl bromide (Fig. 2d *vs.* Fig. 3e). Thus, the observed similar reaction times for cross-coupling of benzyl chlorides and benzyl bromides with H-phosphonate diesters were apparently due to the fact that a faster ligand exchange/reductive elimination step in the instance of benzyl chloride derivatives made up for the slow oxidative addition step. In light of this, it seemed likely that the turnover limiting step for the Pd(0)-catalyzed cross-coupling of benzyl chlorides with H-phosphonates was apparently the oxidative addition step, while for the corresponding bromides, it was the reaction of H-phosphonate with a benzylpalladium(II) complex.

In this context, the structural features of benzylpalladium(II) complexes, produced in the oxidative addition step, were also pertinent. Although for benzylpalladium(II) complexes a structure analogous to that of arylpalladium(II) complexes was initially proposed<sup>22</sup> ( $\eta^1$ -type complexes), recent crystallographic data provided evidence for an  $\eta^3$ -coordination of the benzyl group.<sup>23,24</sup> In solution, however, a rapid  $\eta^3$ – $\eta^1$ – $\eta^3$  isomerization was proposed for such complexes, with the dominant form being  $\eta^3$ -benzylpalladium(II).<sup>24,25</sup>

Since  $\eta^3$ -benzylpalladium(II) complexes are structurally related to  $\eta^3$ -allylpalladium complexes, it was assumed that nucleophilic substitution with nitrogen, oxygen or carbon nucleophiles occurs analogously to the Tsuji–Trost reaction,<sup>26</sup> *i.e.* via an  $\eta^3$ -benzylpalladium intermediate.<sup>24,25,27,28</sup> Although this probably is the case for heteroatom and carbon nucleophiles with a negative charge or a lone electron pair on the nucleophilic atom, the situation can be different for H-phosphonate nucleophiles. In this instance, the nucleophilic species, a phosphite anion (generated *in situ* by the added base), is usually present only in tiny amounts<sup>29</sup> and, as we demonstrated for arylpalladium(II) complexes, the rate determining step for ligand substitution is coordination of the P=O group to the Pd(II) complex.<sup>30</sup>

We suggest that a similar mechanism also operates for benzylpalladium(II) complexes, and the reaction involves



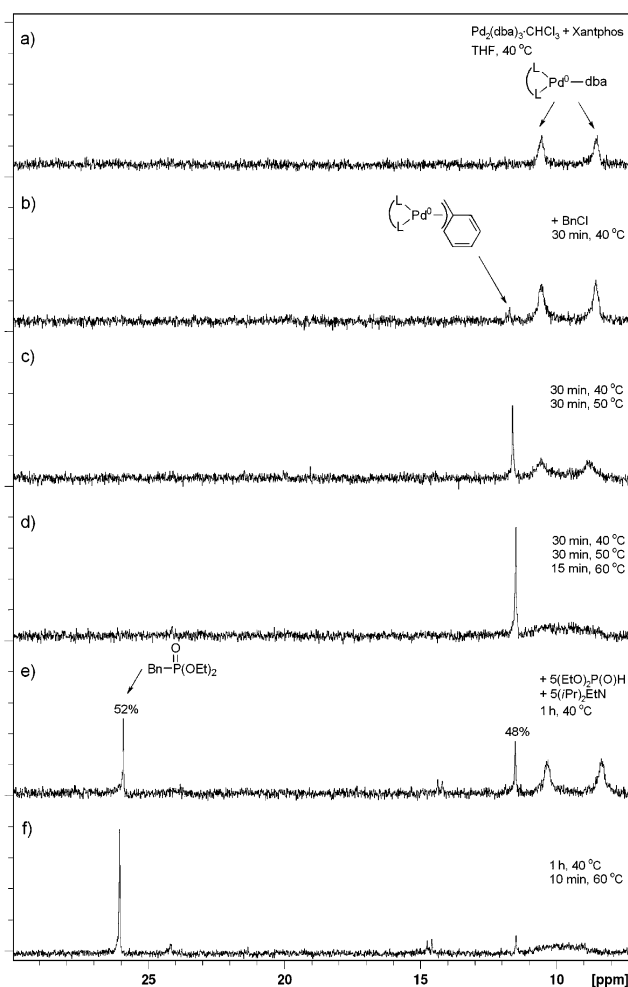
**Fig. 2**  $^{31}\text{P}$  NMR spectra showing the oxidative addition of equimolar amounts of benzyl bromide to  $\text{Pd}_2(\text{dba})_3(\text{CHCl}_3)/\text{Xantphos}$  (1 : 2 mol ratio), followed by the reaction of added diethyl H-phosphonate (5 equiv.) and *N,N*-diisopropylethylamine (5 equiv.).

coordination of the P=O function of an H-phosphonate diester to  $\eta^1$ -benzylpalladium(II) (A) on the way to benzyl-(phosphonate)palladium(II) complex B, rather than a nucleophilic attack of the phosphite anion on  $\eta^3$ -benzylpalladium(II) complex to afford the final product (see Scheme 1). Although due to rapid  $\eta^3$ – $\eta^1$ -equilibria in benzylpalladium(II) complexes<sup>28</sup> it was difficult to find out which form of these complexes reacted with H-phosphonate diesters (only one signal observed in the  $^{31}\text{P}$  NMR spectra, see Fig. 2 and 3), the higher reactivity of benzylpalladium(II) complexes generated from benzyl chlorides *vs.* benzyl bromides pointed to the kinetic importance of  $\eta^1$ -benzylpalladium(II) forms. This would be in line with the order of reactivity of aryl-(halide)palladium(II) complexes, for which higher rates of ligand substitution were observed for chloride *vs.* bromide derivatives.<sup>31</sup>

In light of the above, we tentatively formulated a catalytic cycle for the Pd-catalyzed cross-coupling of benzyl halides with H-phosphonate diesters as depicted in Scheme 1.

The cycle is analogous to that generally assumed for the synthesis of arylphosphonates<sup>10,30–32</sup> and involves the



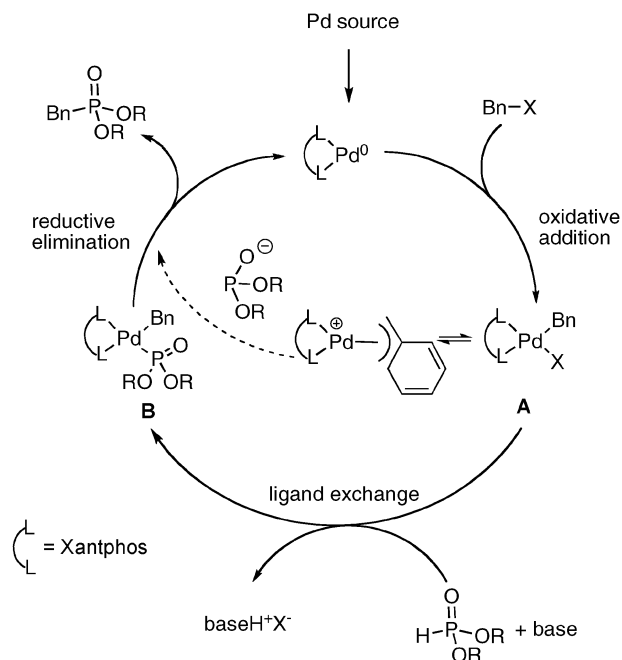


**Fig. 3**  $^{31}\text{P}$  NMR spectra showing the oxidative addition of equimolar amounts of benzyl chloride to  $\text{Pd}_2(\text{dba})_3(\text{CHCl}_3)/\text{Xantphos}$  (1 : 2 mol ratio), followed by the reaction of added diethyl H-phosphonate (5 equiv.) and *N,N*-diisopropylethylamine (5 equiv.).

generation of benzylpalladium(II) complex **A**, followed by a ligand exchange step to produce benzyl(phosphonate)-palladium(II) complex **B**, from which a reductive elimination of the product benzylphosphonate diesters occurs. Although in the case of H-phosphonate diesters, it is most likely the  $\eta^1$ -benzylpalladium(II) species **A** that undergoes a ligand exchange to produce intermediate **B**, for more reactive phosphorus nucleophiles (e.g. alkali metal phosphite salts), the nucleophilic attack may occur directly on the benzylic carbon of the  $\eta^3$ -benzylpalladium(II) complex (see Scheme 1).

A similar catalytic cycle probably also operates for the cross-coupling of H-phosphonothioate diesters, as judged from the  $^{31}\text{P}$  NMR experiments on the formation of diethyl benzylphosphonothioate diester from diethyl H-phosphonothioate and benzyl bromide (see the ESI $^\dagger$ ).

As a final part of these investigations, we wanted to find out why triphenylphosphine ( $\text{PPh}_3$ ) was a highly inefficient ligand in the Pd-catalyzed synthesis of benzylphosphonates using benzyl halides and H-phosphonate diesters. $^{15}$  To this end, we carried out a  $^{31}\text{P}$  NMR experiment, analogous to that in

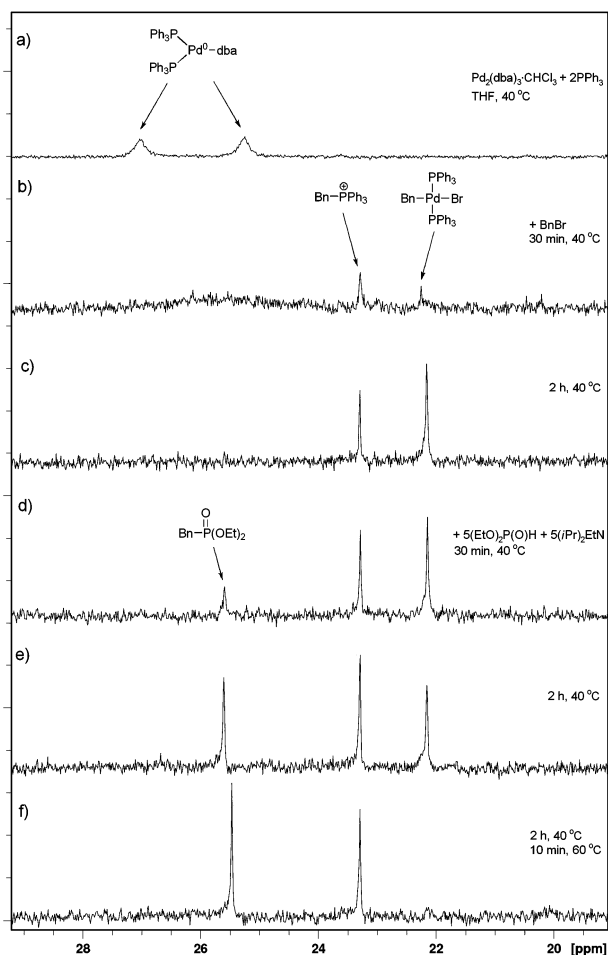


**Scheme 1** A catalytic cycle for palladium(0)-mediated benzylphosphonate formation.

Fig. 2, but using  $\text{PPh}_3$  instead of Xantphos as the supporting ligand (Fig. 4). When benzyl bromide was added to the *in situ* generated catalyst system [from  $\text{Pd}_2(\text{dba})_3(\text{CHCl}_3)$  and  $\text{PPh}_3$ , Fig. 4a], the slow formation of a benzylpalladium(II) complex (signal at *ca.* 22 ppm), accompanied by benzylation of the phosphine ligand (benzyltriphenylphosphonium salt, signal at *ca.* 23 ppm), was observed (Fig. 4b). The reaction was almost complete after *ca.* 2 h (Fig. 4c), and the addition of diethyl H-phosphonate and *N,N*-diisopropylethylamine initiated formation of the product, diethyl benzylphosphonate (signal at *ca.* 25.5 ppm, Fig. 4d). It took 2 h at 40 °C, and an additional 10 min at 60 °C, to bring this reaction to completion. During this time, the signal due to benzylation of the ligand (*ca.* 23 ppm) remained unchanged (Fig. 4e and f).

As is apparent from these experiments, oxidative addition of benzyl bromide to the  $\text{Pd}(0)$  complex in the presence of  $\text{PPh}_3$  was significantly slower than that in the presence of Xantphos. Also, formation of the product from the benzylpalladium(II) complex was much slower in the presence of  $\text{PPh}_3$  than in the reaction with Xantphos. These pointed to a beneficial role of Xantphos as the supporting ligand in the benzylphosphonate synthesis, that not only accelerated the reductive elimination, but also facilitated the oxidative addition step.

Concerning a competing benzylation of  $\text{PPh}_3$  by benzyl bromide, since this reaction occurred to a significant extent with a stoichiometric ratio of reactants, one can anticipate that under catalytic reaction conditions, this may completely inactivate the supporting ligand. Although using benzyl chloride would lessen this problem, the oxidative addition of benzyl chloride to  $\text{Pd}(0)$  in the presence of  $\text{PPh}_3$  was found to be very sluggish, and no benzylpalladium(II) formation could be detected in THF at 40 °C after 2.5 h (results not shown).



**Fig. 4**  $^{31}\text{P}$  NMR spectra showing the oxidative addition of equimolar amounts of benzyl bromide to  $\text{Pd}_2(\text{dba})_3(\text{CHCl}_3)/\text{PPh}_3$  (1:4 mol ratio), followed by the reaction of added diethyl H-phosphonate (5 equiv.) and *N,N*-diisopropylethylamine (5 equiv.).

In separate experiments, we also checked a possible benzylation of the Xantphos ligand with benzyl halides (for details, see the ESI $^\dagger$ ). With 10 equiv. of benzyl chloride in THF at 60 °C, no benzylation of Xantphos could be detected after reaction overnight. In contradiction to this, under analogous reaction conditions, benzyl bromide effected monobenzylation of Xantphos with similar kinetics to those of benzylation of  $\text{PPh}_3$  ( $t_{1/2}$  = 95 and 100 min, respectively). Apparently, due to the fast oxidative addition of benzyl bromide to  $\text{Pd}(0)$ -Xantphos complexes, no benzylation of Xantphos could be detected in the experiment depicted in Fig. 2, in contrast to an analogous experiment with  $\text{PPh}_3$  in Fig. 4 that showed significant benzylation of the supporting ligand.

## Conclusions

We have developed a new, general method for efficient preparation of benzylphosphonate diesters *via* the  $\text{Pd}(0)$ -catalyzed cross-coupling reaction of benzyl chlorides or bromides with H-phosphonate diesters using  $\text{Pd}_2(\text{dba})_3(\text{CHCl}_3)/\text{Xantphos}$  as a catalyst system. The reaction is rather general, accepts a

wide range of benzyl derivatives and H-phosphonate diesters, and is also applicable to the synthesis of benzylphosphonothioate analogues of phosphate esters. The  $^{31}\text{P}$  NMR studies revealed that for a cross-coupling involving benzyl bromides, the turnover-limiting step of the catalytic cycle is probably the ligand exchange/reductive elimination step, while for less reactive benzyl chlorides, it is the oxidative addition. Xantphos, as a supporting ligand, seems to facilitate both the oxidative addition and the reductive elimination step.

Since the underlying chemistry of the method is different from that of the Michaelis–Arbuzov and the Michaelis–Becker reactions, this new protocol expands the range of synthetic methods available for the preparation of biologically important C-phosphate analogues.

## Experimental

### General

All reagents were of analytical grade, obtained from commercial suppliers and were used without further purification. Dinucleoside H-phosphonates $^{33}$  and H-phosphonothioate diesters $^{34}$  were synthesized from the appropriate H-phosphonate $^{35}$  and H-phosphonothioate $^{36}$  monoesters and alcohols according to standard coupling procedures. THF was dried using a VAC solvent purifier system. All reactions were carried out using standard Schlenk techniques. Column chromatography was performed on silica gel (DAVISIL, 35–70 micron).  $^1\text{H}$ ,  $^{13}\text{C}$  and  $^{31}\text{P}$  NMR spectra were recorded at 400, 100 and 162 MHz, respectively, in  $\text{CDCl}_3$  on a Bruker Avance II 400 MHz spectrometer.  $^1\text{H}$  NMR spectra were referenced to internal tetramethylsilane (TMS, 0.00 ppm) or  $\text{CHCl}_3$  (7.26 ppm),  $^{13}\text{C}$  NMR spectra to the center-line of  $\text{CDCl}_3$  (77.16 ppm), and  $^{31}\text{P}$  NMR spectra to external 2%  $\text{H}_3\text{PO}_4$  in  $\text{D}_2\text{O}$ . Coupling constants,  $J$ , are reported in Hz. For integration of the  $^{31}\text{P}$ -NMR signals, a long pulse delay (3 s) and a broadband proton decoupling during the acquisition time, were used. For characterisation data and NMR spectra of products in Tables 1–3, see the ESI $^\dagger$ .

### Syntheses

**General procedure for the synthesis of benzylphosphonates 1–9 and 11–13.**  $\text{Pd}_2(\text{dba})_3(\text{CHCl}_3)$  (0.025 mmol, 26 mg), Xantphos (0.050 mmol, 29 mg), solid benzyl halide (1.2 mmol), solid H-phosphonate diester (1.0 mmol) and THF (5 mL) were placed in a two-neck flask equipped with a reflux condenser. The apparatus was filled with nitrogen by applying two cycles of vacuum/ $\text{N}_2$ . The mixture was heated to reflux and *N,N*-diisopropylethylamine (for compounds 1–7 and 10–13: 1.2 mmol, 155 mg, 210  $\mu\text{L}$ ; for compounds 8 and 9: 2.2 mmol, 310 mg, 420  $\mu\text{L}$ ), liquid benzyl halide (1.2 mmol) and liquid H-phosphonate diester (1.0 mmol) were added. The mixture was refluxed for 4 h, concentrated under vacuum, and the product purified by silica gel chromatography or by extraction (see the ESI $^\dagger$  for details).

**Ethyl 5-diethylphosphonomethylfuran-2-carboxylate (10).** The Reaction was carried out similarly to that described for compounds 1–9 and 11–13, except for the use of 0.04 mmol

(41.4 mg)  $\text{Pd}_2(\text{dba})_3(\text{CHCl}_3)$ , 0.08 mmol Xantphos (46 mg), and 6 h heating under reflux.

**General procedure for the synthesis of dinucleoside benzylphosphonates 14–17.**  $\text{Pd}_2(\text{dba})_3(\text{CHCl}_3)$  (0.0125 mmol, 13 mg), Xantphos (0.025 mmol, 15 mg), a suitable protected dinucleoside H-phosphonate (0.5 mmol) and THF (5 mL) were placed in a two-neck flask equipped with a reflux condenser. The apparatus was filled with nitrogen by applying two cycles of vacuum/ $\text{N}_2$ , and *N,N*-diisopropylethylamine (0.6 mmol, 78 mg, 105  $\mu\text{L}$ ) and benzyl chloride (0.6 mmol, 76 mg, 69  $\mu\text{L}$ ) were added. The mixture was refluxed for 4 h, concentrated under vacuum and purified by silica gel chromatography using pentane–EtOAc (1:1, v/v) with a gradient of MeOH (2.5–10%).

**Diethyl benzylphosphonothioate (18).** The reaction was carried out starting from benzyl bromide and diethyl H-phosphonothioate similarly to the procedure described for compounds 1–9 and 11–13, except for 2 h heating under reflux. The product was purified by silica gel chromatography using pentane–EtOAc (20:1, v/v).

**5'-O-(tert-Butyldiphenylsilyl)thymidin-3'-yl ethyl benzylphosphonothioate—mixture of diastereoisomers (19).** The reaction was carried out starting from benzyl bromide and 5'-O-(tert-butyldiphenylsilyl)thymidin-3'-yl ethyl H-phosphonothioate, similarly to the method described for compounds 14–17, except for 3 h heating under reflux. The product was purified by silica gel chromatography, using a linear gradient of MeOH (0–10%) in  $\text{CH}_2\text{Cl}_2$ .

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