Letter

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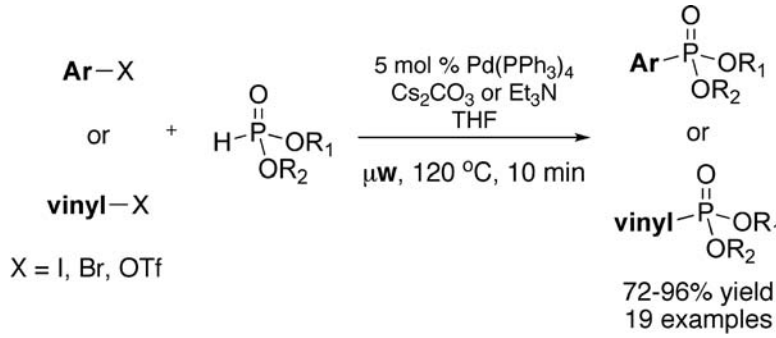


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# Microwave-Assisted Palladium-Catalyzed Cross-Coupling of Aryl and Vinyl Halides with H-Phosphonate Diesters

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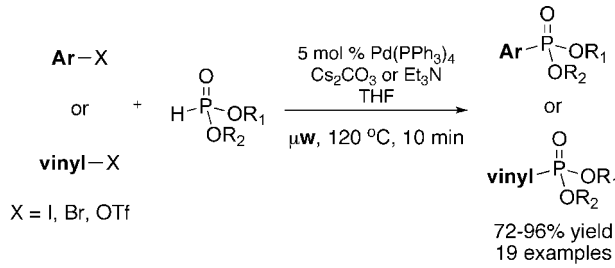
## ABSTRACT




**A general and efficient method for the microwave-assisted formation of the C−P bond was developed. Using a prevalent palladium catalyst, $Pd(PPh_3)_4$, a quantitative cross-coupling of various H-phosphonate diesters with aryl and vinyl halides was achieved in less than 10 min. The reactions occurred with retention of configuration at the phosphorus center and in the vinyl moiety. Using this protocol, several C-phosphonates, including those bearing nucleoside and cholesteryl moieties, were prepared in high yields.**

Aryl- and vinylphosphonates are valuable intermediates in organic synthesis[1,2] and also find numerous practical applications.[3,4] Compounds containing arylphosphonate moieties are used, e.g., in designing fuel cell membranes,[3] materials with special optical properties,[5] and those bearing a vinylphosphonate function, are established building blocks in polymer sciences[6] and in the synthesis of heterocyclic compounds.[7] In recent years there has been a growing interest in these classes of phosphorus compounds in medicinal chemistry[8−10] and nucleic acid chemistry[11,12] due to biological activity that the presence of a C−P bond can confer to many organic compounds.

Access to aryl- and vinylphosphonates improved considerably when, in addition to the traditional synthetic meth-

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ods,[1,8,13] Hirao and co-workers introduced a Pd-catalyzed cross-coupling reaction of H-phosphonates with aryl and vinyl halides.[14−16] After further development and modifications, this method constitutes the current state of the art in the synthesis of C($sp^2$)−P bonds.[17]

In recent years, application of microwaves to synthetic organic chemistry has become increasingly popular and attracted considerable practical[18,19] and theoretical attention.[20] Among various chemical transformations investigated,[19] the palladium-catalyzed cross-coupling reactions have been recognized as an exceptionally successful area of application of this controllable thermal source for conducting organic reactions. Both the C−C bond forming cross-coupling reactions, as well as those for the C−N and C−O bond formation using the Buchwald−Hartwig chemistry,[21] were efficiently carried out under microwave irradiation conditions.[19,22]

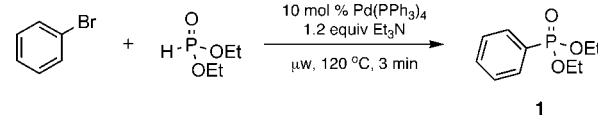
In contrast, the use of microwaves to facilitate cross-coupling reactions involving phosphorus nucleophiles still remains largely unexplored. Only recently, a single report on a Pd-catalyzed microwave-assisted coupling of H-phosphonate and H-phosphinate derivatives with aryl triflate (yields ca. 19−52%), during synthesis of progesterone antagonists, has appeared.[9]

Due to the synthetic and practical importance of aryl- and vinylphosphonate derivatives, we describe herein our systematic investigations on the reaction conditions for the microwave-assisted palladium-catalyzed C−P bond formation. Although a plethora of ligands for the cross-coupling reactions involving palladium have been developed, and some of them were successfully applied in the reactions with H-phosphonate nucleophiles,[23] a catalyst of choice for this kind of chemistry remains $Pd(PPh_3)_4$.[17] In line with these, we set out to develop a general-purpose protocol for the synthesis of aryl- and vinylphosphonates under microwave conditions, using this one-component Pd(0) catalyst.

For the purpose of optimization of the experimental conditions, we chose as a model reaction coupling between bromobenzene and diethyl H-phosphonate. All experiments were performed in standard, sealed microwave vessels, under an inert gas atmosphere.

First, screening of various common solvents was carried out by comparing a degree of conversion into diethyl phenylphosphonate during 3 min at 120 °C, using $^{31}P$ NMR spectroscopy (Table 1).

**Table 1.** Solvent Screening[a]




1

| entry | solvent | conversion[b] (%) |
|---|---|---|
| 1 | THF | 39 |
| 2 | DMSO | 65[c] |
| 3 | acetone | 29 |
| 4 | dioxane | 30 |
| 5 | DMF | 38 |
| 6 | NMP | 51[c] |
| 7 | toluene | 28 |

[a] Reaction conditions: 0.1 M $(EtO)_2P(O)H$, 1.1 equiv of Ph-Br; after initial heating, the reaction temperature was maintained for 3 min at 120 °C. [b] Determined by $^{31}P$ NMR spectroscopy. [c] At concentrations higher than 0.1 M, starting material decomposition was observed.

As is apparent from Table 1, the reaction proceeded reasonably well in all solvents tested. Although the best results were obtained for DMSO and NMP (Table 1, entries 2 and 6), severe side reactions occurred when the concentration of the reactants was increased to 0.25 M (a concentration range convenient for preparative syntheses). In DMSO, the starting H-phosphonate was oxidized to a P(V) species, probably via a Swern-type oxidation (formation of $Me_2S$), while in NMP, a partial cleavage of one of the ethyl groups from $(EtO)_2P(O)H$ was observed. Therefore, as a solvent for the further studies, THF was selected (Table 1, entry 1), due to its good efficiency in the coupling reaction and easy handling during the workup procedure.

In the next step of the screening procedure, different bases were examined for their ability to promote the cross-coupling of the model substrates (Table 2). The best results were obtained for $Et_3N$[15] and $Cs_2CO_3$[24] (Table 2, entries 1 and 4). These bases secured ca. 40% conversion into phenylphosphonate **1** within 3 min at 120 °C, while the other carbonates investigated, as well as $K_3PO_4$ and propylene oxide, were by far less efficient.

Attempted increasing of the coupling rate, by applying temperatures higher than 120 °C, failed due to progressing

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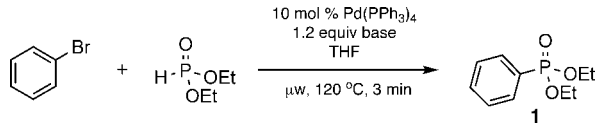
(24) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144–1157.

**Table 2.** Base Screening[a]




| entry | base | conversion[b] (%) |
|---|---|---|
| 1 | $Et_3N$ | 39 |
| 2 | $Na_2CO_3$ | 16 |
| 3 | $K_2CO_3$ | 7 |
| 4 | $Cs_2CO_3$ | 40 |
| 5 | $K_3PO_4$ | 10 |
| 6 | propylene oxide | 4 |

[a] Reaction conditions: 0.1 M $(EtO)_2P(O)H$, 1.1 equiv of Ph-Br; after initial heating, the reaction temperature was maintained for 3 min at 120 °C. [b] Determined by $^{31}P$ NMR spectroscopy.

decomposition of the starting material (diethyl H-phosphonate) and the reaction product.

Further tuning of the reaction conditions led us to decrease the catalyst load to 5 mol % of $Pd(PPh_3)_4$ and extend the heating time to 10 min. These conditions, when applied to the preparative syntheses of aryl- and vinylphosphonate diesters (Table 3), secured a complete conversion (as determined by $^{31}P$ NMR) to the corresponding products for all of the tested combinations of different aryl and vinyl halides and *H*-phosphonate diesters.

As is apparent from data in Table 3, the substrates bearing different leaving groups (iodide, bromide, and triflate; Table 3, entries 1−3) were all efficiently coupled under the microwave irradiation conditions. It is worth mentioning that, using conventional heating, the reactions from entries 1 and 2 went to completion within 2.5 to 18 h (depending on the specific method used[15,25]), but catalytic efficiency under microwave irradiation vs conventional heating was similar.

Aryl groups with electron-donating and electron-withdrawing substituents (entries 7 and 8) and H-phosphonate diesters bearing different alkyl groups (entries 4−6) also coupled efficiently under these reaction conditions.

As far as the size of the aryl group is concerned, four arylphosphonates with larger aryl moieties were also synthesized in good isolated yields (entries 9−12). Additionally, a heteroaromatic derivative, 3-bromopyridine, was successfully coupled with diethyl H-phosphonate, producing the corresponding pyridylphosphonate **11** (entry 13). Importantly, the NMR spectra of the isolated products from entries 7−13 showed that the attachment point of the phosphorus atom was the same as that of the halide in the starting materials.

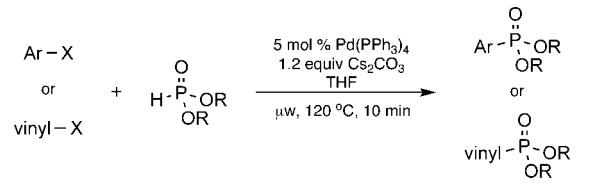
Finally, three vinyl bromides were used for a cross-coupling reaction with diethyl H-phosphonate (entries 14−16). Also in these instances the yields of the isolated products were high and for vinylphosphonates **13** and **14**, the substituent arrangement at the double bond was preserved.[14]

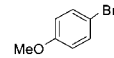
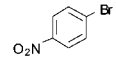
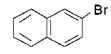
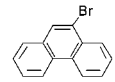
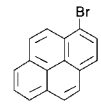
To demonstrate compatibility of the developed microwave-assisted cross-coupling conditions with more complex, functionalized systems, we carried out a P-arylation of cholesteryl ethyl H-phosphonate with bromobenzene (Scheme 1). The reaction was uneventful and afforded the expected cholesteryl ethyl phenylphosphonate **15** in an isolated yield of 86%.

As a second example of more complex systems, we chose a cross-coupling of a dinucleoside H-phosphonate with iodobenzene, to produce a compound with a phenylphosphonate internucleotide linkage (Scheme 2).

The important feature of dinucleoside H-phosphonates is that, in contrast to the ethyl cholesteryl diester, their P-diastereoisomers, possessing opposite configurations at

**Table 3.** Microwave-Assisted Synthesis of Aryl- and Vinylphosphonate Diesters[a]

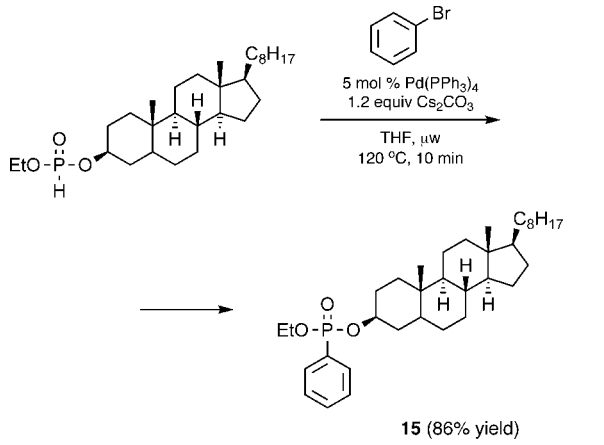



| entry | aryl or vinyl halide | R | product | isolated yield (%) |
|---|---|---|---|---|
| 1 |  | Et | **1** | 90 |
| 2 |  | Et | **1** | 73 |
| 3 |  | Et | **1** | 83 |
| 4 |  | Me | **2** | 77 |
| 5 |  | *i*-Pr | **3** | 87 |
| 6 |  | Bn | **4** | 74 |
| 7 |  | Et | **5** | 84 |
| 8 |  | Et | **6** | 96 |
| 9 |  | Et | **7** | 73 |
| 10 |  | Et | **8** | 86 |
| 11 |  | Et | **9** | 72 |
| 12 |  | Et | **10** | 77 |
| 13 |  | Et | **11** | 86 |
| 14 |  | Et | **12** | 84 |
| 15 |  | Et | **13** | 91 |
| 16 |  | Et | **14** | 88 |

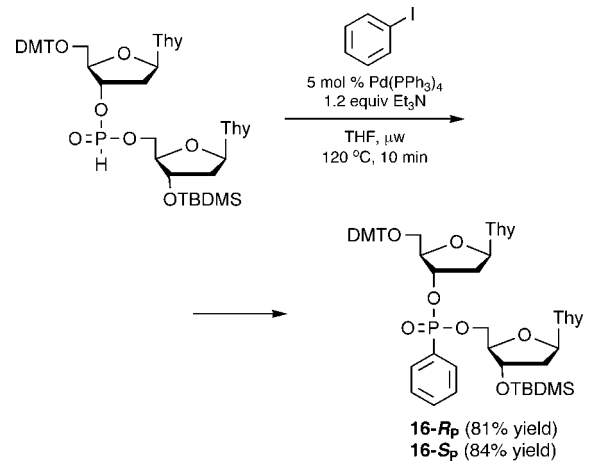
[a] Reaction conditions: 0.25 M H-phosphonate diester, 1.1 equiv of Ar-X or vinyl-X; after initial heating, reaction temperature was maintained for 10 min at 120 °C.

(25) Kalek, M.; Stawinski, J. *Organometallics* **2007**, *26*, 5840–5847.

**Scheme 1**




**Scheme 2**[a]




[a]DMT = 4,4′-dimethoxytrityl, TBDMS = *tert*-butyldimethylsilyl, Thy = thymin-1-yl.

the phosphorus atom, are easily available.[12,26] This opened a possibility to verify if the microwave heating did not deteriorate a complete stereospecificity of this reaction (retention of the configuration) observed under conventional heating.[27,28]

Somewhat surprisingly, application of the previously developed reaction conditions to a dinucleoside H-phosphonate resulted in no phosphorus resonance signals in the $^{31}$P NMR spectra. We speculated that this might be due to absorption of the substrate on the solid $Cs_2CO_3$. To alleviate this problem, we replaced $Cs_2CO_3$ with $Et_3N$. This latter base, during our screening (Table 2, entry 1 vs 4) showed similar efficiency to $Cs_2CO_3$, and it was also used before for the cross-coupling reactions under the conventional heating conditions.[28,29] It was rewarding to see that with $Et_3N$ used as a base both diastereomers of dinucleoside H-phosphonate could be successfully coupled with iodobenzene, without any noticeable decomposition. Additionally, the complete stereospecificity of the reaction was observed, since each of the diastereomers of the dinucleoside *H*-phosphonate was exclusively transformed into a single diastereomer of the product **16** (Scheme 2; see the Supporting Information for details).

In summary, we have developed a convenient and general method for the microwave-assisted preparation of aryl- and vinylphosphonates based on a Pd-catalyzed cross-coupling. The procedure is highly efficient and provides rapid access to a broad spectrum of phosphonate diesters, including more complex compounds, as was illustrated in the synthesis of cholesteryl (**15**) and dinucleoside (**16**) derivatives. Regarding stereochemistry, the reaction is completely stereospecific (most likely retention of configuration at the phosphorus center[27,28]), and in addition, the configuration in the vinyl moiety is preserved.[14]

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

**Supporting Information Available:** Synthetic experimental procedures, characterization data, and NMR spectra for products **1**−**16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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