



## Palladium-catalyzed cross-couplings of allylic phosphates

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### ABSTRACT

A range of palladium-catalyzed cross-coupling reactions can be performed using allylic phosphates as electrophiles. Both conventional heating and microwave irradiation can be used.

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Introduction of allylic and benzylic structural units into organic molecules represents a special case of organotransition metal-catalyzed cross-coupling reactions, as the reactive centers of these units are located at  $sp^3$ -hybridized carbon atoms. While the allylation of enolates with  $\pi$ -allylpalladium complexes (the Tsuji–Trost reaction) has found widespread use in organic synthesis,<sup>1</sup> other cross coupling reactions of allylic species, such as Suzuki, Stille, Hiyama, and Negishi, are much less frequent, and the yields are, in general, modest. Standard precursors of organometallic species include halides, acetates, carbonates, and sulfonates, while phosphates were seldom used for this purpose. Recently, it has been shown that benzylic phosphates represent a useful class of precursors for the Suzuki–Miyaura,<sup>2</sup> as well as for the copper-mediated Kumada cross coupling.<sup>3</sup> This prompted us to investigate whether the allylic phosphates could be used for a range of palladium-catalyzed cross-couplings—a possibility that, to the best of our knowledge, has not been systematically studied. Several reports exist, however, on cobalt,<sup>4</sup> or copper<sup>5</sup>-mediated couplings of allylic phosphates with arenemetals, as well as on their palladium-mediated metallo-ene reaction<sup>6</sup> and alkoxyacylation.<sup>7</sup>

Several allylic phosphates were prepared from the corresponding alcohols and diethylchlorophosphate, according to the previously described procedures.<sup>8</sup> It should be noted that cinnamyl phosphates are more susceptible to hydrolysis on silica, with respect to ordinary allylic phosphates; therefore, their purification should be fast. These phosphates were then submitted to the reaction conditions suitable for cross-coupling reactions. After some

experimentation, it was established that no single reaction protocol would be suitable for all couplings, and that the choice of the catalyst (ligand) and the reaction conditions depends on the type of reaction to perform. The results of these experiments are represented in Table 1. The Hiyama coupling was tried first. We found that, using in situ-prepared tetrakis(triphenylphosphine)palladium, in the presence of TBAF as activator, in hot DMF,<sup>9</sup> reasonable yields of coupling products could be obtained (entries 1, 3, and 4). As expected, the coupling occurred regioselectively (attack at the less substituted end), with the *E*-configuration of the products. The next experiments focused on the Stille reaction. Here, lithium chloride was used instead of an organic ligand, and the reactions were performed at room temperature,<sup>10</sup> to afford the expected products in 50–68% yields (entries 5–7). We next turned to the Suzuki–Miyaura reaction. Somewhat surprisingly, the use of ligands such as triphenylphosphine or dppf resulted in low yields of the desired products. The best results were obtained with biaryl monophosphine ligands, such as 2-(dicyclohexylphosphino)biphenyl (cyclohexylJohnPhos) and XPhos. Reactions with the latter were much faster (45 min vs 16 h; compare entries 11 and 12); however, a serious side reaction in the presence of XPhos was the formation of diallyl ethers, therefore the former ligand was preferred. Couplings were also performed using a recently reported modification of the Suzuki–Miyaura reaction, where cyclic triolborate salts are used as superior synthetic equivalents of more conventional boranes, or boronates.<sup>11</sup> These reactions were run under very mild conditions (without organic ligand, in the presence of water and atmospheric oxygen, at room temperature, in essentially neutral reaction medium), and provided the expected products in good yields (entries 16–18). Entry 14 represents a useful alternative to

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**Table 1**  
Various Pd-catalyzed couplings of allylic phosphate

Entry	Reactants	Conditions	Products	Yields (%)	
<i>Hiyama coupling</i>					
1			A		72
2			B		85
3			A		63
4			A		50
<i>Stille coupling</i>					
5			C		68
6			C		55
7			C		50
<i>Suzuki–Miyaura coupling</i>					
8			D		76 (87)
9			E		70
10			D		47
11			E		46
12			F		52
13			D		45
14			D		65
15			D		56 (36% with PPh3)
16			G		82

(continued on next page)

Table 1 (continued)

Entry	Reactants	Conditions	Products	Yields (%)
17		G		72
18		G		40
<i>Negishi coupling</i>				
19		H		40

## Reagents and conditions:

- (A) Pd(OAc)<sub>2</sub> (10 mol %), PPh<sub>3</sub> (20 mol %), TBAF (200 mol %), DMF, Ar, 90 °C, 24 h;  
 (B) Pd(OAc)<sub>2</sub> (10 mol %), PPh<sub>3</sub> (20 mol %), TBAF (200 mol %), DMF, Ar, mw, 300 W, 25 min (120 °C);  
 (C) Pd(dba)<sub>2</sub> (5 mol %), LiCl (300 mol %), DMF, Ar, rt, 24 h;  
 (D) Pd(dba)<sub>2</sub> (1 mol %), CyJohnPhos (4 mol %), K<sub>3</sub>PO<sub>4</sub>·3H<sub>2</sub>O (200 mol %), toluene, Ar, 90 °C, 16 h;  
 (E) Pd(dba)<sub>2</sub> (1 mol %), K<sub>3</sub>PO<sub>4</sub>·3H<sub>2</sub>O (200 mol %), toluene, Ar, mw, 300 W, 25 min (120 °C);  
 (F) Pd(dba)<sub>2</sub> (1 mol %), XPhos (4 mol %), K<sub>3</sub>PO<sub>4</sub> anhyd (200 mol %), toluene, Ar, 90 °C, 45 min;  
 (G) Pd(OAc)<sub>2</sub> (5 mol %), DMF, H<sub>2</sub>O, rt, 2 h;  
 (H) Pd<sub>2</sub>dba<sub>3</sub> (2.5 mol %), dppf (5 mol %), THF, 70 °C, 16 h.

the geranylation of phenols, a transformation that was previously performed under strongly acidic conditions where side reactions were also possible.<sup>12</sup> Finally, the formation of cinnamyl benzene in the reaction of cinnamyl phosphate with phenylzinc chloride showed that allylic phosphates could serve as reaction partners for the Negishi coupling, although the yield in this reaction was not high (entry 19).

Couplings were also performed under microwave irradiation, which brought about a significant shortening of the reaction times, with the yields comparable to those obtained with conventional heating.<sup>13</sup> For example, the Hiyama coupling, which required 24 h at 90 °C, was complete within 25 min under mw irradiation (entry 2; see also entries 9 and 11).

To summarize, allylic phosphates can be used as electrophiles in a range of palladium-catalyzed cross-couplings. The straightforward preparation of these derivatives from the corresponding alcohols, coupled with their good reactivity, makes them potentially useful precursors for cross coupling reactions.

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## Supplementary data

Detailed experimental procedures and the complete spectral data of all new compounds are provided. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.026.

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- Typical experimental procedure (Suzuki coupling)*: A 12 mL glass tube was charged with cinnamyl phosphate (100 mg; 0.37 mmol), phenylboronic acid (54 mg; 0.44 mmol), K<sub>3</sub>PO<sub>4</sub>·2H<sub>2</sub>O (131 mg; 56 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (11 mg, 5 mol %), toluene (3 mL), and a piece of Weflon. This tube was placed in a Teflon outer jacket and secured with a Teflon top containing a ceramic thermo well, with the fiber-optic probe inside. The sample was irradiated for 5 min (multimode type irradiation) with 300 W power, in order to reach 120 °C, and was maintained at that temperature for 20 min more, with magnetic stirring. The reaction mixture was then cooled to room temperature, diluted with diethyl ether, and filtered through a cotton plug. The organic extract was washed with water, dried over anhydrous MgSO<sub>4</sub>, filtered, concentrated under reduced pressure, and purified by column chromatography on SiO<sub>2</sub>, to provide 50 mg (72%) of (E)-1,3-diphenylpropene as a colorless oil, spectral data identical to previously reported in: Baker, L.; Minehan, T. *J. Org. Chem.* **2004**, *69*, 3957–3960; Correia, R.; DeShong, P. *J. Org. Chem.* **2001**, *66*, 7159–7165, and Lawrence, N. J.; Muhammad, F. *Tetrahedron* **1998**, *54*, 15345–15360.