Synthetic Methods

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Tetraarylphosphonium Halides as Arylating Reagents in Pd-Catalyzed Heck and Cross-Coupling Reactions**

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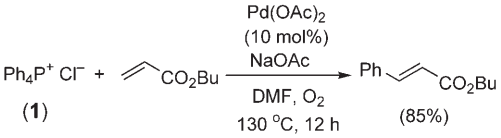
Transition-metal-catalyzed olefination and cross-coupling reactions have become one of the most powerful tools in organic synthesis.[1] While aryl, alkenyl, alkynyl, and, more recently, alkyl halides are typically employed as coupling reagents, a variety of different types of pseudohalide species have been also investigated as useful electrophiles. Among these, representative recent examples are carboxylic acids,[2] acid anhydrides,[3] aryl esters,[4] sulfonates,[5] phosphonic acids,[6] sulfonium ions,[7] and ammonium salts.[8] Although metal-mediated C–P bond cleavage of organophosphorus species was previously investigated,[9] the use of such compounds in cross-coupling reactions has been relatively underdeveloped. Yamamoto and co-workers suggested that quaternary phosphonium iodide ($Ph_4P^+I^-$) oxidatively adds to Pd^0 complexes through P-aryl bond cleavage and they showed briefly that one phenyl group was transferred to react with activated olefins, although in low yields (32–36 %).[10] Reetz et al. reported that the efficiency of the Heck reaction with normally unreactive aryl halides was significantly improved by the presence of phosphonium halides.[11] Additionally, several research groups described mechanistic details for the observed aryl–aryl interchange process between phosphinyl- and Pd-bound aryl groups in cross-coupling reactions that relied on the composition of the products[12] and theoretical considerations.[13] Herein, we describe our recent studies on the utility of tetraarylphosphonium halides as arylating reagents in Heck and cross-coupling reactions, as well as providing spectroscopic details on the activation process.[14]

At the outset of our studies, we attempted to optimize the reaction conditions for the Pd-catalyzed olefination reaction using tetraarylphosphonium ions. When tetraphenylphosphonium chloride (**1**) was treated with *n*-butyl acrylate (3.0 equiv) in the presence of $Pd(OAc)_2$ (10 mol %) and sodium acetate (3.0 equiv), *n*-butyl *trans*-cinnamate was isolated in 85 % yield [Eq. (1)], which thus clearly suggested that the C–P bond of **1** is activated catalytically in agreement with the previous report.[10] We envisioned that the employment of electrospray ionization mass spectrometry (ESI-MS) could lead us to trace the activation process because it allows facile detection of highly unstable and/or sensitive metal-containing intermediates.[15]



(1)

When **1** was treated with 0.5 equivalents of $[Pd_2(dba)_3]$ (dba = *trans,trans*-dibenzylideneacetone) at 100 °C, a set of ion peaks were detected in the ESI-mass spectra which were attributed to transient metal species resulting from the activation of the P–phenyl bond of **1** (Figure 1). It was observed that a dba ligand in the complex was gradually displaced by acetonitrile to give a series of peaks for $[(PPh_3)_2PhPd(CH_3CN)_m]$ ($m = 1$–3) at the expense of phosphonium ion (Figure 1, all *m/z* values are reported on the basis of the ^{106}Pd isotope).[16] When $Pd(OAc)_2$ was employed instead of $[Pd_2(dba)_3]$, the activation process occurred more slowly and the corresponding peaks started to appear only after a few hours under the same conditions. The fact that a complex of Pd^0 is more active than a Pd^{II} species for the activation is in a good agreement with the generally accepted assumption that Pd^{II} precursors are reduced initially into Pd^0 complexes, which are catalytically active in most cross-coupling reactions.[17]

Pd-mediated cleavage of the P–C bond of tetraarylphosphonium ions was further supported by the isolation and characterization of an oxidatively inserted palladium species. When $Ph_4P^+Cl^-$ (**1**) was treated with 0.5 equivalents of $[Pd_2(dba)_3]$ in the presence of PPh_3, a transparent solid **2** was isolated (54 %) that revealed a square-planar geometry with two triphenylphosphine groups positioned *trans* to each other (Figure 2). The bond lengths and angles of **2** are within comparable range of those previously reported, although the same palladium species was prepared starting from a different precursor by a ligand-exchange method.[18] When the isolated Pd complex **2** was treated with *n*-butyl acrylate,[19] reaction occurred readily in the presence of sodium acetate at temperatures over 80 °C to afford butyl cinnamate in 55 %.[20] This result led us to postulate that phosphonium species play a dual role, as a source of the arylating group and as a stabilizing ligand on palladium complexes, upon release of phosphine from the phosphonium ions.

During the course of optimization of the conditions for olefination with phosphonium halides, it was found that higher yields (ca. 20 %) were obtained when the reaction was carried out under atmospheric oxygen relative to those performed under N_2.[21] It is thought that oxygen oxidizes liberated triphenylphosphine into its oxide, thus driving the reaction to completion more readily. Indeed, a side product of triphenylphosphine oxide was seen to be generated (> 80 %) during the olefination reaction under an O_2 atmosphere

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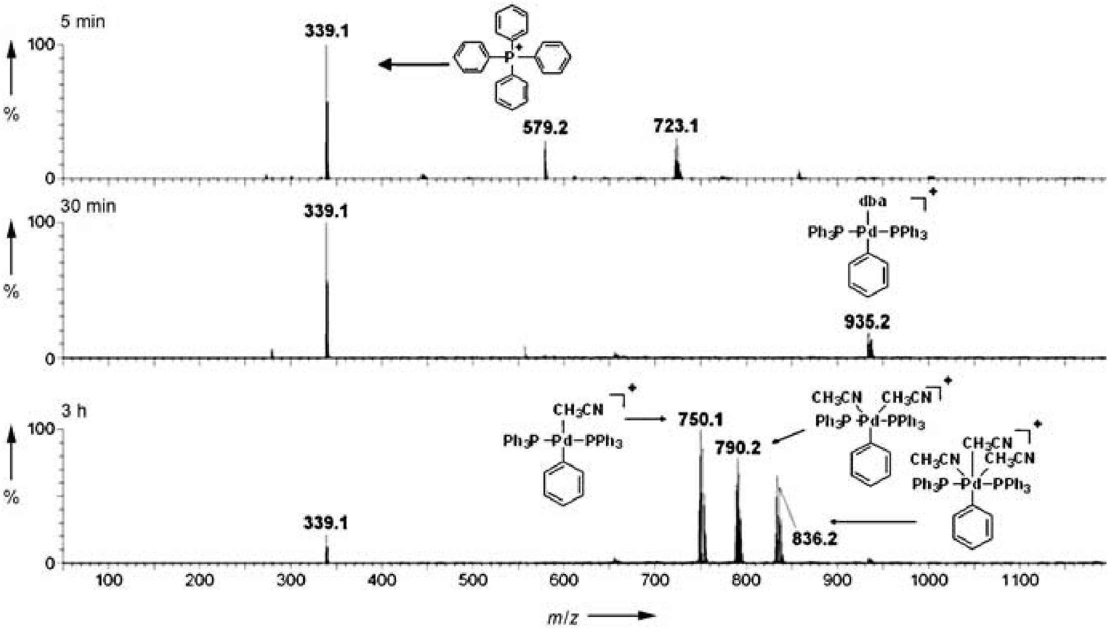


Figure 1. ESI mass spectra obtained from the treatment of tetraphenylphosphonium chloride (**1**) with $[Pd_2(dba)_3]$ (0.5 equiv) at 100 °C.

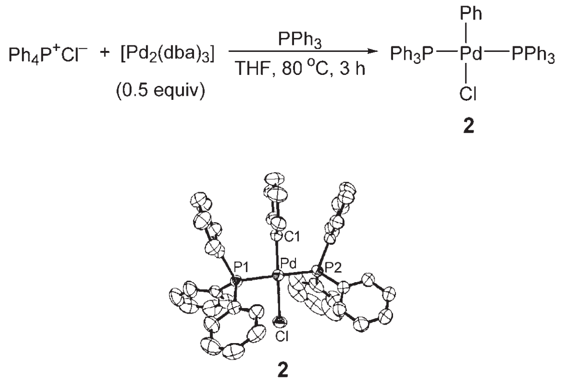
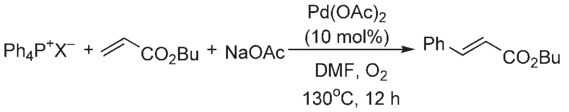


Figure 2. Preparation and X-ray crystal structure of **2**.

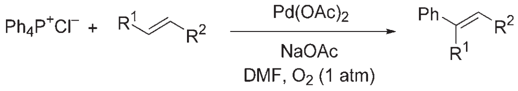
[Eq. (1)]. Whereas sodium acetate turned out to be most effective of the various bases examined, it was interesting to observe that olefination proceeds even in the absence of an external base, albeit with moderate yields (53 % from the reaction of Equation (1) under such conditions).[22] Additionally, the efficiency of the reaction was dependent on the nature of the counteranions of the phosphonium salts [Eq. (2)]. Whereas reactions with phosphonium species that bear chloride ions gave the highest yield, other halide salts such as bromide and iodide resulted in reduced yields. However, upon addition of LiCl (2.0 equiv) in a reaction with $Ph_4P^+Br^-$, the efficiency was recovered to the same level as with $Ph_4P^+Cl^-$.

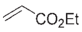
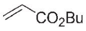
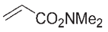
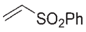
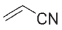
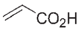
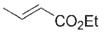
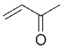


(2)

X = Cl: 85%
I: 57%
Br: 57%
Br: 82% (2 equiv of LiCl)

Table 1: Heck olefinations with **1**.[a]



Entry	Alkene	Yield [%][b]
1	 CO_2Et	72
2	 CO_2Bu	85
3	 CO_2NMe_2	98
4	 SO_2Ph	74
5[c]	 $PO(OEt)_2$	76
6	 CN	70[d]
7	 CO_2H	71
8	 CO_2Et	59
9		70

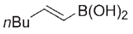
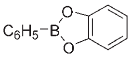
[a] Reaction conditions: alkenes (3.0 equiv), catalyst (10 mol %), NaOAc (3.0 equiv), 130 °C, 12 h under O_2 (1 atm). [b] Yield of isolated product. [c] 3.0 equivalents of Cs_2CO_3 was used instead of NaOAc. [d] $E/Z = 4{:}1$.

Under the optimized conditions, the olefination of **1** was examined with a range of alkenes (Table 1).[23] Whereas reactions with acrylic esters, amides, vinyl sulfone, and vinyl phosphonate proceeded efficiently to afford the corresponding olefinated products exclusively in the *E* form, olefination with acrylonitrile produced cinnamonitrile with modest selectivity ($E/Z = 4{:}1$). Notably, acrylic acid was also readily coupled with **1** to afford (*E*)-cinnamic acid in good yield.[24]

The use of phosphonium species in the Suzuki–Miyaura reaction was next investigated (Table 2). While electronic and steric variations on organoboron compounds have negligible

Table 2: Suzuki coupling reactions with **1**.[a]

$$Ph_4P^+Cl^- + R{-}B(OR')_2 \xrightarrow[\text{NaOAc, DMF, } N_2]{Pd(OAc)_2} Ph{-}R$$

Entry	Organoborane	Yield [%][b]
1	$C_6H_5\text{-}B(OH)_2$	77
2	$4\text{-Ac-}C_6H_4\text{-}B(OH)_2$	80
3	$4\text{-MeO-}C_6H_4\text{-}B(OH)_2$	95
4	$2\text{-Me-}C_6H_4\text{-}B(OH)_2$	83
5	$4\text{-Br-}C_6H_4\text{-}B(OH)_2$	70
6	$4\text{-CHO-}C_6H_4\text{-}B(OH)_2$	75
7		91
8		63
9		70

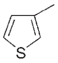
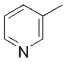
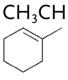
[a] Reaction conditions: organoboranes (1.5 equiv), catalyst (10 mol%), NaOAc (3.0 equiv), 100 °C, 12 h under N_2. [b] Yield of isolated product.

effects on efficiency, several functional groups were tolerated under the reaction conditions. As demonstrated in entry 9, a boronic ester derived from catechol was also employed as an efficient coupling partner with **1**. Although the exact reason is not clear at present, the effect of oxygen observed in the Heck olefination was not observed in case of Suzuki and Sonogashira reactions (see below).[25]

In the Sonogashira-type reaction, tetraarylphosphonium halides were also readily employed as efficient arylating reagents with a wide range of alkynes (Table 3). In a similar manner as observed in Heck and Suzuki reactions, the alkynylation was not significantly affected by aryl substituents. Note that coupling of **1** with 1-phenyl-2-(trimethylsilyl)-acetylene, an internal alkyne, was also carried out efficiently (98 % yield) when 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride was employed as an additive (10 mol %).

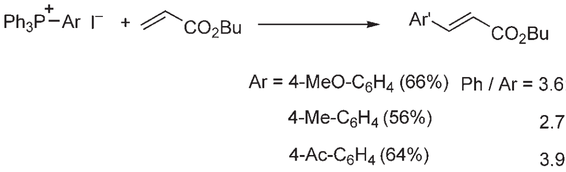
Table 3: Sonogashira coupling reactions with **1**.[a]

$$Ph_4P^+Cl^- + {\equiv}{-}R \xrightarrow[\text{Et}_3\text{N, DMF, } N_2]{Pd(OAc)_2} Ph{-}{\equiv}{-}R$$

Entry	Alkyne	Yield [%][b]
1	C_6H_5	99
2	$4\text{-F-}C_6H_4$	86
3	$4\text{-Me-}C_6H_4$	62
4	$4\text{-PhO-}C_6H_4$	99
5		62
6		77
7	$HO(CH_2)_3$	64
8	$CH_3CH(OH)CH_2$	63
9		77
10	$(i\text{Pr})_3Si$	99

[a] Reaction conditions: alkynes (3.0 equiv), catalyst (5 mol%), Et_3N (2.0 equiv), 100 °C, 12 h under N_2. [b] Yield of isolated product.

When differently substituted tetraarylphosphonium halides[26] were used in olefinations, a selective aryl transfer was not observed [Eq. (3)]. Independent of the electronic nature of the aryl substituents, a mixture of unsubstituted (major) and substituted cinnamates (minor) were produced with a ratio of 3–4:1. The rather statistical aryl transfer in the Heck olefination was also observed in Suzuki and Sonogashira reactions. These results can be presumably attributed to fast aryl–aryl interchange processes between phosphinyl- and Pd-bound aryl groups that are generated upon cleavage of the C–aryl bond of the heterogeneously substituted phosphonium species.



(3)

In summary, conditions have been optimized for the Pd-catalyzed reactions of tetraarylphosphonium halides with olefins, organoborons, and alkynes that demonstrate the utility of the phosphonium species as facile arylating reagents. Characterization of reaction intermediates by ESI mass spectrometry and X-ray crystallography add important knowledge to the Pd-mediated activation pathway of the C–P bond of phosphonium precursors.

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[21] Although the intermediate $[Pd^0(PPh_3)_2]$ species that is generated at the end of the catalytic cycle is known to be very sensitive to oxygen,[1] the present results suggest that its oxidative addition with the phosphonium salts might be faster than its reaction with oxygen. We thank one reviewer for indicating this.

[22] One reviewer suggested that triphenylphosphine, which is liberated during the reaction, may serve as a base, although the same role by chloride ion cannot be ruled out at present.

[23] Although the reported yields were obtained from reactions with $Pd(OAc)_2$ catalyst (10 mol%), use of $[Pd_2(dba)_3]$ (5 mol%) resulted in almost comparable results.

[24] When tetra-*p*-tolylphosphonium chloride was employed, *n*-butyl *trans*-3-(4-methylphenyl)acrylate was obtained in 99% yield.

[25] Suzuki and Sonogashira reactions under oxygen atmosphere afforded significantly lower yields relative to those obtained under N_2; see the Supporting Information for details.

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