Oxidative Heck-Type Reaction Involving Cleavage of a Carbon−Phosphorus Bond of Arylphosphonic Acids

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In recent years, cleavage of a carbon−phosphorus bond with transition metals has been a topic in the organometallic chemistry. Several reactions involving C−P bond fission have appeared in the literature.[1,2] However, application of such a process in organic synthesis is not well documented. Furthermore, exploitation of phosphonic acids in C−P bond cleavage remained unexplored.[2,3]

The Heck reaction, in which aromatic halides are coupled with alkenes under Pd(0) catalysis, is a powerful tool in organic synthesis.[4] Recently, oxidative Heck-type reactions, which exploit arylmetals such as arylborane,[5] -stannane,[6] -silane,[7] -bismuth,[8] and -antimony,[9] have been extensively investigated.[10] Herein we disclose a Pd-catalyzed oxidative Heck-type reaction which makes use of arylphosphonic acid as a source of an aryl group (Scheme 1). This reaction involves cleavage of a carbon−phosphorus bond of an arylphosphonic acid **1**. To our best knowledge, this is the first report on a C−P bond activation of arylphosphonic acid under transition metal catalysis.

We investigated the Heck-type reaction of 4-methoxyphenylphosphonic acid (**1a**) with styrene in the presence of a palladium catalyst (10 mol %) in 1,4-dioxane at 100 °C (Table 1). Initially, we found that the use of TBAF (3.0 equiv, THF solution) and Me$_3$-NO·2H$_2$O (3.0 equiv) afforded 4-methoxystilbene (**2a**) in 53% yield (entry 1). Naturally, no reaction proceeded without a catalyst (entry 2). As a palladium source, Pd(OAc)$_2$ proved to be most effective. The use of PdCl$_2$ or PdCl$_2$(PPh$_3$)$_2$ lowered the yield (entries 3 and 4), and Pd(PPh$_3$)$_4$ is not effective at all (entry 5). A phosphine ligand retards or inhibits the reaction. A choice of an oxidant is essential, and Me$_3$NO·2H$_2$O was the best among oxidants we examined (entries 6−8). The use of TBAF is also crucial (entry 9). As the reaction solvent, toluene is comparable to 1,4-dioxane (entry 10). Although the reduced amount of Pd(OAc)$_2$ (5 mol %) retarded the reaction (entry 16), a prolonged reaction period (24 h) achieved quantitative conversion (entry 17). After optimization, we picked up the conditions of entry 17 as the standard. Interestingly, the use of diethyl arylphosphonates instead of arylphosphonic acids provided none of expected products under the same reaction conditions.

With the optimized reaction conditions in hand, we examined the reaction of a variety of arylphosphonic acids with alkenes. The results are summarized in Table 2. Both electron-rich and -deficient styrenes can be used as the alkene. Acrylic esters and amides also provided good results. Phenyl-, 2-methylphenyl-, 4-methoxyphenyl-, and 1-naphthylphosphonic acids react with alkenes to provide the desired products in good yields (entries 1−13). Substituents at the ortho position do not affect the reactivity (entries 6−8). An electron-withdrawing group on the phenyl ring retards the reaction (entries 14−20), and prolonged reaction time is required to obtain satisfactory yields. Bis-coupling proceeds with *p*-phenylenediphosphonic acid (entries 19 and 20). Alkenylphosphonic acids such as (*E*)-β-styrylphosphonic acid also react with alkenes under the same conditions to afford conjugated dienes in good yields (entries 21 and 22).
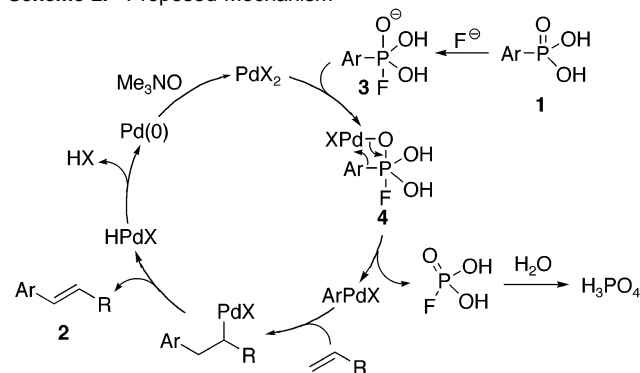
Scheme 1
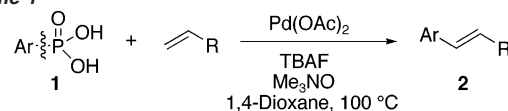
Scheme 2. Proposed Mechanism

Table 1. Optimization of the Reaction Conditions[a]

entry	catalyst (mol %)	oxidant (equiv)	TBAF (equiv)	solvent	time (h)	yield (%)[b]
1	Pd(OAc)$_2$ (10)	Me$_3$NO (3)	3	dioxane	2	53
2	none	Me$_3$NO (3)	3	dioxane	2	0
3	PdCl$_2$ (10)	Me$_3$NO (3)	3	dioxane	2	45
4	PdCl$_2$(PPh$_3$)$_2$ (10)	Me$_3$NO (3)	3	dioxane	2	33
5	Pd (PPh$_3$)$_4$ (10)	Me$_3$NO (3)	3	dioxane	2	0
6	Pd(OAc)$_2$ (10)	none	3	dioxane	2	0
7	Pd(OAc)$_2$ (10)	CuCl$_2$ (3)	3	dioxane	2	0
8	Pd(OAc)$_2$ (10)	NMO (3)	3	dioxane	2	38
9	Pd(OAc)$_2$ (10)	Me$_3$NO (3)	0	dioxane	2	19
10	Pd(OAc)$_2$ (10)	Me$_3$NO (3)	3	toluene	2	55
11	Pd(OAc)$_2$ (10)	Me$_3$NO (3)	3	DMF	2	37
12	Pd(OAc)$_2$ (10)	Me$_3$NO (3)	3	dioxane	8	84
13	Pd(OAc)$_2$ (10)	Me$_3$NO (2)	3	dioxane	8	79
14	Pd(OAc)$_2$ (10)	Me$_3$NO (3)	2	dioxane	8	87
15	Pd(OAc)$_2$ (10)	Me$_3$NO (3)	1	dioxane	8	76
16	Pd(OAc)$_2$ (5)	Me$_3$NO (3)	2	dioxane	8	67
17	Pd(OAc)$_2$ (5)	Me$_3$NO (3)	2	dioxane	24	100
18	Pd(OAc)$_2$ (5)	Me$_3$NO (3)	2	toluene	24	99

[a] The mixture of 4-methoxyphenylphosphonic acid (0.3 mmol), styrene (0.36 mmol), palladium catalyst, oxidant, TBAF (1 M THF solution), and solvent (3 mL) is stirred at 100 °C. [b] NMR yields with dibenzyl ether as an internal standard.

Formation of phosphoric acid in the reaction mixture was confirmed with ^{31}P NMR spectroscopy. Although the mechanism of this reaction is not clear at this stage, we propose the following mechanism as illustrated in Scheme 2. Due to the strong affinity between fluoride and phosphorus,[11,12] the nucleophilic attack of a

Table 2. Oxidative Heck-Type Reaction of Arylphosphonic Acids[a]

Entry	Arylphosphonic acid	Olefin	Yield (%)
1	Ph–P(OH)$_2$ (O)	=\Ph (styrene)	95
2		4-Cl styrene	87
3		4-OMe styrene	92
4		O^{t}Bu acrylate	82
5		NMe$_2$ acrylamide	73[b]
6	2-Me-C$_6$H$_4$P(OH)$_2$	styrene	100
7		4-Cl styrene	75
8		O^{t}Bu acrylate	88
9	MeO-C$_6$H$_4$-P(OH)$_2$	styrene	100
10		4-Cl styrene	79
11		O^{t}Bu acrylate	96
12	naphthyl-P(OH)$_2$	styrene	85
13		O^{t}Bu acrylate	85
14	2-CF$_3$-C$_6$H$_4$-P(OH)$_2$	styrene	67
15		4-OMe styrene	65
16		O^{t}Bu acrylate	68 (71)[c]
17	EtOC(O)-C$_6$H$_4$-P(OH)$_2$	styrene	54
18		O^{t}Bu acrylate	49 (57)[c] (59)[d]
19[e]	(HO)$_2$P-C$_6$H$_4$-P(OH)$_2$	styrene	42
20[e]		O^{t}Bu acrylate	52 (76)[c]
21	Ph-CH=CH-P(OH)$_2$	styrene	66
22		O^{t}Bu acrylate	71

[a] The mixture of arylphosphonic acid (0.3 mmol), alkene (0.36 mmol), Pd(OAc)$_2$ (0.015 mmol), Me$_3$NO·2H$_2$O (0.9 mmol), TBAF (0.6 mmol, 1 M THF solution), and 1,4-dioxane (3 mL) is stirred at 100 °C for 24 h. [b] Pd(OAc)$_2$ (0.03 mmol) is used. [c] Reaction time is 64 h. [d] Toluene is employed as a solvent. [e] Diphosphonic acid (0.15 mmol) is used.

fluoride ion to an arylphosphonic acid generates a pentacoordinated phosphorus compound **3**.[13,14] Ligand exchange on palladium

provides the intermediate **4**. An aryl transfer from phosphorus to palladium yields arylpalladium species, which then reacts with an alkene to afford the Heck product **2** and Pd(0) species via β-elimination. Oxidation of Pd(0) with Me$_3$NO regenerates Pd(II) species.

In conclusion, we have found that the reaction of arylphosphonic acids with a variety of alkenes provides the Heck-type adducts in the presence of a catalytic amount of Pd(OAc)$_2$. The reaction requires an oxidant and TBAF as the activator and proceeds via carbon−phosphorus bond cleavage.

Supporting Information Available: General procedures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) After submission of our manuscript, the oxidative Heck-type reaction with carboxylic acids has been reported. Myers, A. G.; Tanaka, D.; Mannion, M. R. *J. Am. Chem. Soc.* **2002**, *124*, 11250.
(11) The dissociation energy of a P−F bond is 117 kcal/mol.
(12) **Caution**: A combination of phosphorous compounds and fluoride can be highly toxic in the absence of water. The use of anhydrous reaction conditions should be avoided.
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(14) An addition of TBAF (1.0 equiv) to a solution of phenylphosphonic acid in 1,4-dioxane causes an upfield shift of a signal by about 10 ppm in ^{31}P NMR spectrum. However, no coupling between ^{31}P and ^{19}F could be observed.

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