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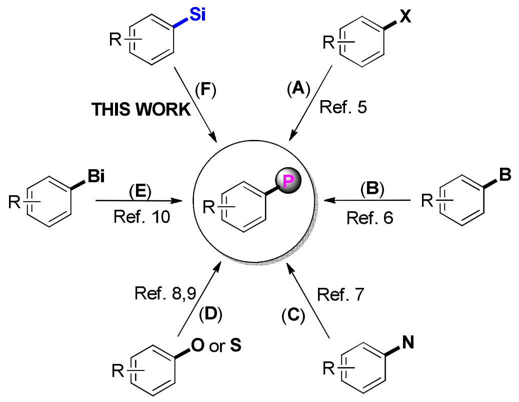
Construction of Ar-P bond by Pd-catalyzed oxidative cross-coupling of arylsilanes with H-phosphonates via C-Si bond cleavage

Haiqing Luo,* Haidong Liu, Xingwei Chen, Keke Wang, Xuzhong Luo and Kejun Wang*

A novel and efficient methodology that allows for the construction of Ar-P bond via the Pd-catalyzed oxidative cross-coupling reaction of various arylsilanes with H-phosphonates leading to valuable arylphosphonates has been developed.

Arylphosphonates have attracted much attention due to their wide applications in various aspects such as the preparation of P ligands, pharmaceutical intermediates and agricultural pesticides.[1] Many studies have revealed that organic compounds usually show certain changes of their physical, chemical, and biological properties when phosphorus-containing units were introduced.[2] With a traditional method, arylphosphonates were synthesized by the coupling of phosphorous chloride with organolithiums or Gringard reagents.[3] But a serious problem limiting its application was that both of the organometallic reagents were very unstable and dangerous. In 1980s, Hirao and co-workers reported their pioneering work on the palladium-catalyzed oxidative cross-coupling of dialkyl phosphonates with aryl halides.[4] Subsequently, significant advances were made to form the Ar-P bond construction by the reaction of H-phosphonates with various coupling partners via the bond cleavages of C-X (Scheme 1A),[5] C-B (Scheme 1B),[6] C-N (Scheme 1C),[7] C-O or C-S (Scheme 1D),[8, 9] and C-Bi (Scheme 1E),[10] *etc.*[11]



Scheme 1 Methods for synthesis of arylphosphonates.

Since the Hiyama cross-coupling reaction was first reported in 1988,[12] arylsilanes, being a new choice as the aryl resource, exhibited many unique advantages,[13] including nontoxicity, high stability, environmental benignity and easy operation in synthesis. However, to the best of our knowledge, this promising, attractive coupling remains totally unexplored in the field of Ar-P bond construction involving arylsilanes. Therefore, developing a mild, efficient and environmentally benign Ar-P bond construction method to access valuable arylphosphonates via C-Si bond cleavage is still desirable. In view of the importance of arylphosphonates[14] and also as a continuation of our interest in this arylsilanes-based coupling recation,[15] we herein report a construction of Ar-P bond by the palladium-catalyzed oxidative cross-coupling of arylsilanes with H-phosphonates via C-Si bond cleavage (Scheme 1F).

At the outset of the investigation, we explored the Pd-catalyzed oxidative cross-coupling of triethoxy(phenyl)silane **1a** with diethyl phosphon-ate under the oil bath heating conditions. One of the key points of the Hiyama coupling reaction is to find an appropriate fluorine source to break the C-Si bond. Then, different fluorine sources such as tetrabutylammonium fluoride (TBAF), KF, AgF, and CsF were examined in the presence of 5 mol% $Pd(PPh_3)_2Cl_2$ in dimethyl sulfoxide (DMSO) at 80 °C (Table 1, entries 1-4). To our delight, KF and CsF were both found to be effective, affording the desired cross-coupling product **3a**, and KF turned out to be the better choice (Table 1, entry 2). The effect of solvent was investigated (table1 entries 5-8), DMSO, dichloroethane (DCE) and (DMF) were found to be suitable for the reaction. However, trace amounts or no desired product (n.d.p) could be detected by using dioxane and tetrahydrofuran (THF). We were very pleased to found that the DMF was the best solvent for this reaction; affording the desired product in a yield of 84% (Table 1, entry 9). Followed, various palladium catalysts (Table 1, entries 9-12) were examined;

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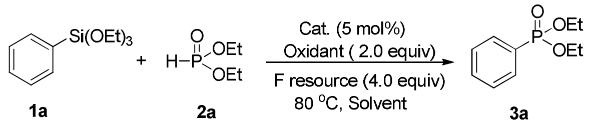
the results revealed that $Pd(PPh_3)_2Cl_2$ and $Pd(MeCN)_2Cl_2$ were both found to be effective in this reaction. Other oxidants, including AgOAc, $Cu(OAc)_2$, $K_2S_2O_8$ and BQ were also tested (Table 1, entries 15-18). To our surprise, Ag_2CO_3 was the only suitable oxidant for this reaction. Further study indicated that the yield of **3a** was significantly decreased when the reaction temperature was reduced to 60 °C (Table 1, entry 20); however, almost the same yield was obtained while the reaction was carried out at 100 °C (Table 1, entry 21). At last, control experiments were conducted (Table 1, entries 5, 14, 19), and observed no desired product in the absence of $Pd(PPh_3)_2Cl_2$, Ag_2CO_3 or KF.

Table 1. Optimization of reaction conditions for the Pd-catalyzed oxidative cross-coupling of arylsilanes **1a** with diethyl phosphonate **2a** [a]

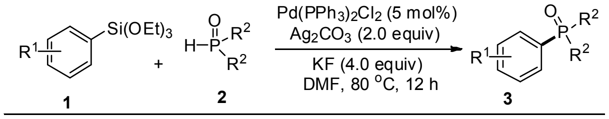


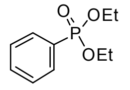
Entry	Pd Cat.	Oxidant	F source	solvent	Yield(%)[b]
1	$Pd(PPh_3)_2Cl_2$	Ag_2CO_3	TBAF	DMSO	n.d.p
2	$Pd(PPh_3)_2Cl_2$	Ag_2CO_3	KF	DMSO	31
3	$Pd(PPh_3)_2Cl_2$	Ag_2CO_3	AgF	DMSO	trace
4	$Pd(PPh_3)_2Cl_2$	Ag_2CO_3	CsF	DMSO	22
5	$Pd(PPh_3)_2Cl_2$	Ag_2CO_3	-	DMSO	n.d.p
6	$Pd(PPh_3)_2Cl_2$	Ag_2CO_3	KF	THF	n.d.p
7	$Pd(PPh_3)_2Cl_2$	Ag_2CO_3	KF	DCE	23
8	$Pd(PPh_3)_2Cl_2$	Ag_2CO_3	KF	Dioxane	n.d.p
9	$Pd(PPh_3)_2Cl_2$	Ag_2CO_3	KF	DMF	84
10	$Pd(OAc)_2$	Ag_2CO_3	KF	DMF	n.d.p
11	$PdCl_2$	Ag_2CO_3	KF	DMF	n.d.p
12[c]	$PdCl_2$	Ag_2CO_3	KF	DMF	60
13	$Pd(MeCN)_2Cl_2$	Ag_2CO_3	KF	DMF	29
14	-	Ag_2CO_3	KF	DMF	n.d.p
15	$Pd(PPh_3)_2Cl_2$	AgOAc	KF	DMF	trace
16	$Pd(PPh_3)_2Cl_2$	$Cu(OAc)_2$	KF	DMF	n.d.p
17	$Pd(PPh_3)_2Cl_2$	$K_2S_2O_8$	KF	DMF	n.d.p
18	$Pd(PPh_3)_2Cl_2$	BQ	KF	DMF	n.d.p
19	$Pd(PPh_3)_2Cl_2$	-	KF	DMF	n.d.p
20[d]	$Pd(PPh_3)_2Cl_2$	Ag_2CO_3	KF	DMF	56
21[e]	$Pd(PPh_3)_2Cl_2$	Ag_2CO_3	KF	DMF	83

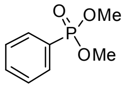
[a] Unless otherwise noted, the reaction conditions are as follows: **1a** (0.5 mmol), **2a** (0.25 mmol), 5 mol % Pd catalyst, Oxidant (0.5 mmol), F resource (0.5 mmol), Solvent (4 mL). [b] Isolated yield after purification by flash column chromatography on silica gel, n.d.p and trace was determined by TLC. [c] 20 mol % PPh_3 was added. [d] The reaction temperature was 60 °C. [e] The reaction temperature was 100 °C.

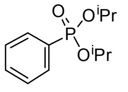
With the optimized reaction conditions in hand, we next proceeded to explore the scope of the construction of Ar-P bond with a series of H-phosphonate diesters and arylsilanes. The results are summarized in Table 2. Firstly, it can be seen that triethoxyphenylsilane is better than trimethoxyphenylsilane to give the desired phosphonated product diethyl phenylphosphonate **3a**. In general, the H-phosphonate diesters with different alkyl groups can all react smoothly with triethoxyphenylsilane to afford the corresponding cross-coupling reaction products in moderate to excellent yields (**3a-d**). To further evaluate the substrate scope, a series of arylsilanes were used to test the reaction with diethyl phosphonate **2a** under the optimized reaction conditions (**3e-r**). Various phenylsilanes bearing different electron-donating group have good compatibility under these reaction conditions (**3e-k**). Notably, *meta*-methyl (**1e**), *ortho*-methyl (**1f**), 3,5-dimethyl (1h) and *meta*-methoxyl (**1j**) were all tolerated well illustrating that steric hindrance is not very evident on this transformation. In addition, benzo[d][1,3]dioxol-5-yltriethoxy-silane, triethoxy(naphthalen-1-yl)silane and [1,1'-biphenyl]-4-yltri-ethoxysilane were also tested for their reactions with **2a**, and the results were satisfactory to give the corresponding phosphonated products **3k**, **3l** and **3m** in yields of 80%, 66% and 84%, respectively. However, arylsilanes with an

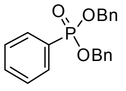
Table 2. Construction of Ar-P bond by Pd-catalyzed oxidative cross-coupling of arylsilanes with H-phosphonates [a,b]

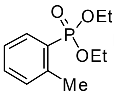


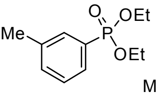

3a, 84%, 72%[c]

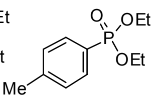

3b, 54%

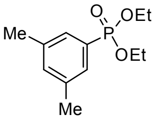

3c, 93%

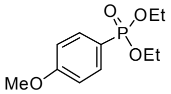

3d, 66%

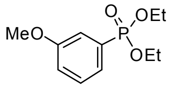

3e, 50%

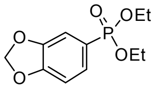

3f, 94%

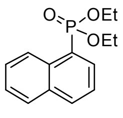

3g, 75%

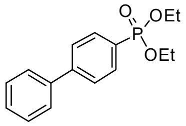

3h, 68%

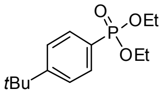

3i, 84%

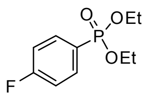

3j, 88%

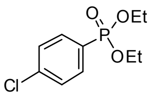

3k, 80%

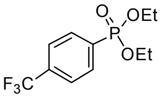

3l, 66%

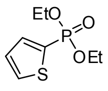

3m, 84%

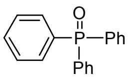

3n, 63%

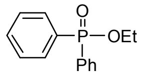

3o, 41%[c]


3p, 53%[d]


3q, 31%[d]


3r, 35%[d]


3s, trace[e]

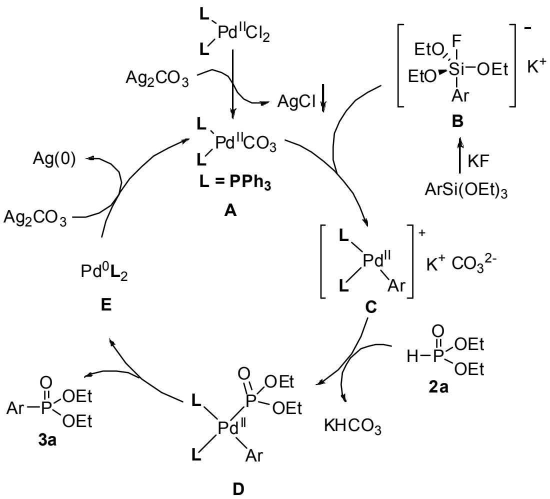

3t, trace[e]

[a] Unless otherwise noted, the reaction conditions are as follows: **1** (0.5 mmol), **2** (0.25 mmol), 5 mol % $Pd(PPh_3)_2Cl_2$, Ag_2CO_3 (0.5 mmol), KF (1.0

mmol), DMF (4 mL). [b] All the yields refer to isolated yields. [c] Trimethoxy(phenyl)-silane was used. [d] The reaction temperature was 100 °C. [e] Detected by ^{1}H NMR spectra or GC-Ms.

electron-withdrawing group in the aromatic ring (**1o**-**q**) and triethoxy(thiophen-2-yl)silane presented relatively lower reactivity (**1r**). Furthermore, we applied the same tactic to the synthesis of triphenylphosphine **3s** and ethyl diphenylphosphinate **3t**, but it is a pity that only trace products were detected by ^{1}H NMR or GC-Ms.

A plausible mechanism for construction Ar-P bond reaction via C-Si bond cleavage was proposed as shown in Scheme 2. The reaction is initiated via the C-Si activation reaction to give intermediate **B** by the nucleophilic attack of a fluoride ion on silicon, which has been established by Hiyama.[16] Due to easy to generate the AgCl precipitation, $Pd(PPh_3)_2Cl_2$ can react with Ag_2CO_3 to generate $Pd(PPh_3)_2CO_3$. Then, the intermediate **B** reacted with $Pd(PPh_3)_2CO_3$ to generate $ArPd^{II}(PPh_3)_2KCO_3$ and followed by the nucleophilic coordination of diethyl phosphonate **2a** to species **C**, which affords intermediate **D**[6c,9a]. Subsequently, reductive elimination from **D** produces arylphosphonate **3a** and Pd(0) species. Finally, Pd(0) is oxidized by Ag_2CO_3 to regenerate the catalytically active $Pd(PPh_3)_2CO_3$ and finishes the catalytic cycle.



Scheme 2. Proposed mechanism for Pd-catalyzed oxidative cross-coupling of arylsilanes with H-phosphonates.

In summary, we have demonstrated a Pd-catalyzed oxidative cross-coupling reaction for construction of Ar-P bond by using enviomentally friendly arylsilanes and H-phosphonates. This reaction constitutes an efficient method for the synthesis of valuable arylphosphonates. Mechanistically, this approach involves oxidation and reductive elimination progress as the two key steps to afford the target product. This protocol is the first example of a transition metal-catalyzed Ar-P bond formation of various arylsilanes with H-phosphonates via aryl C-Si bond cleavage; this reaction may be found useful in applications of organic synthesis.

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