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Palladium-catalyzed phosphorylation of arylsulfonium salts with P(O)H compounds *via* C–S bond cleavage†

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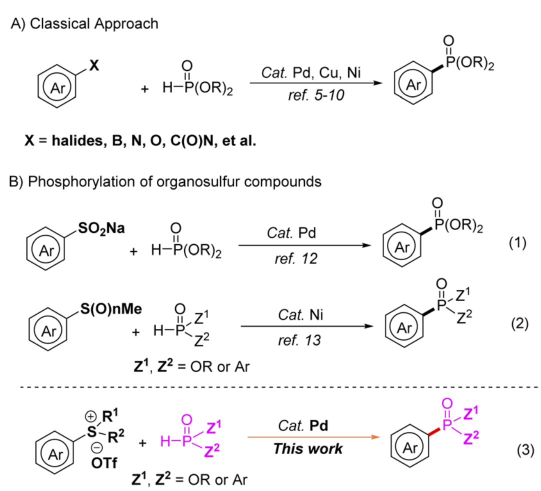
Herein we report a novel palladium-catalyzed phosphorylation of arylsulfonium salts with P(O)H compounds *via* C–S bond cleavage under mild conditions. The protocol provides a pragmatic strategy applicable to the synthesis of diverse arylphosphonates.

Arylphosphonates are ubiquitous constituents of numerous biologically active compounds, agrochemicals and functional materials,[1] and also play an important role in organometallic catalysis[2] and organocatalysis[3] in organic synthesis. Ever since the pioneering work by Hirao and co-workers in the 1980s,[4] various methods catalyzed or mediated by transition-metals for the synthesis of arylphosphonates have been developed. The cross-coupling reactions of P(O)H compounds with various aryl partners that have been reported so far include aryl halides,[5] aryl boron reagents,[6] aryl oxygen derivatives,[7] aryl nitrogen reagents,[8] and aryl amide derivatives,[9] *etc.* (Scheme 1A).[10]

It is well known that organosulfur compounds have been of great importance in organic synthesis because of their accessibility and intriguing reactivity. As a valuable transformation of organosulfur compounds, transition-metal catalyzed C–S bond cleavage has attracted much attention.[11] In this regard, Wang's group developed a novel palladium-catalyzed phosphonation of sodium arylsulfinates with H-phosphonate diesters in 2014 (Scheme 1B, eqn (1)).[12] And then, Han's group developed the nickel-catalyzed phosphinylation of C–S bonds forming C–P bonds by using sulfides, sulfoxides and sulfones as substrates (Scheme 1B, eqn (2)).[13] As a good choice for the aryl source, arylsulfonium salts are easily available, easy to handle, and reasonably reactive, they show great potential for transition metal-catalyzed transformation such as arylation, alkenylation, alkynylation, borylation, alkoxycarbonylation, and carboxylation,[14] which can be viewed as an activated form of the inert C–S bond. As a continuation of our interest in the Ar–P bond construction,[15] herein we wish to report palladium-catalyzed phosphorylation of arylsulfonium salts with P(O)H compounds (Scheme 1B, eqn (3)).

We commenced our investigation by studying the reaction conditions of arylsulfonium salts **1a** with diethyl phosphonate **2a** (Table 1). A series of Pd catalysts, including $PdCl_2$, $Pd_2(dba)_3$, $Pd(dppf)Cl_2$, $Pd(PPh_3)_2Cl_2$, $Pd(acac)_2$, and $Pd(OAc)_2$ were examined in the presence of X-phos (5 mol%), K_3PO_4 (1.0 equiv.) in *N*,*N*-dimethylformamide (DMF) at 80 °C (Table 1, entries 1–6), which were found to be effective, thus affording the desired product **3a**. Among these Pd catalysts, $Pd(OAc)_2$ turned out to be the best catalyst for the reaction, affording the desired product in a yield of 58% (Table 1, entry 6). Subsequently, a survey of different phosphine ligands revealed that XPhos was the best choice (Table 1, entries 7–12). In order to improve the reaction yield, we opted to continue our optimization studies using different bases (Table 1, entries 13–16), but no better reactivity was achieved. Furthermore, the effect of the solvent was also probed (Table 1, entries 17–23). To our delight, *i*PrOH was found to be suitable for the reaction, affording the desired product **3a** in 72% yield (Table 1, entry 22).



Scheme 1 Transition metal-catalyzed phosphorylation reactions.

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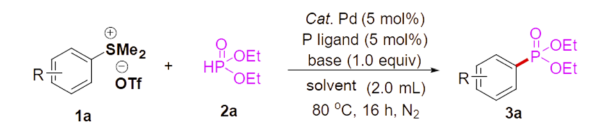
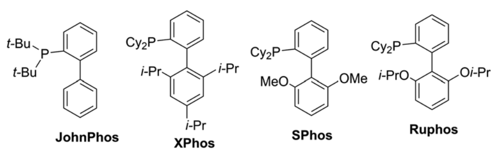
Table 1 Optimization of the reaction conditions[a,b]



Entry	Cat.	P ligand	Base	Solvent	Yield[b] (%)
1	$PdCl_2$	XPhos	K_3PO_4	DMF	40
2	$Pd_2(dba)_3$	XPhos	K_3PO_4	DMF	10
3	$Pd(dppf)Cl_2$	XPhos	K_3PO_4	DMF	35
4	$Pd(PPh_3)_2Cl_2$	XPhos	K_3PO_4	DMF	10
5	$Pd(acac)_2$	XPhos	K_3PO_4	DMF	19
6	$Pd(OAc)_2$	XPhos	K_3PO_4	DMF	58
7	$Pd(OAc)_2$	dppe	K_3PO_4	DMF	5
8	$Pd(OAc)_2$	PPh_3	K_3PO_4	DMF	6
9	$Pd(OAc)_2$	dppp	K_3PO_4	DMF	15
10	$Pd(OAc)_2$	JohnPhos	K_3PO_4	DMF	20
11	$Pd(OAc)_2$	SPhos	K_3PO_4	DMF	32
12	$Pd(OAc)_2$	Ruphos	K_3PO_4	DMF	30
13	$Pd(OAc)_2$	XPhos	K_2HPO_4	DMF	50
14	$Pd(OAc)_2$	XPhos	Cs_2CO_3	DMF	23
15	$Pd(OAc)_2$	XPhos	$NaHCO_3$	DMF	25
16	$Pd(OAc)_2$	XPhos	Et_3N	DMF	21
17	$Pd(OAc)_2$	XPhos	K_3PO_4	DMSO	43
18	$Pd(OAc)_2$	XPhos	K_3PO_4	DMA	31
19	$Pd(OAc)_2$	XPhos	K_3PO_4	Dioxane	Trace
20	$Pd(OAc)_2$	XPhos	K_3PO_4	MeCN	58
21	$Pd(OAc)_2$	XPhos	K_3PO_4	EtOH	46
22	$Pd(OAc)_2$	XPhos	K_3PO_4	iPrOH	72
23	$Pd(OAc)_2$	XPhos	K_3PO_4	*t*AmOH	63

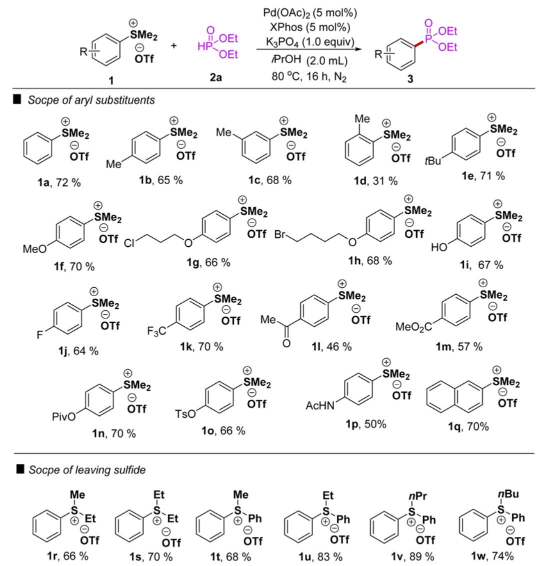


[a] **1a** (0.36 mmol), **2a** (0.30 mmol), cat. Pd (5 mo%), ligand (5 mo%), base (0.3 mmol), solvent (2.0 mL), 80 °C, 16 h, under N_2. [b] Isolated yield.

Having the optimized conditions established in hand, we then proceeded to explore the scope of the phosphorylation of various arylsulfonium salts with diethyl phosphonate **2a**. The results were summarized in Table 2, in general moderate to good yields were obtained under the optimized reaction conditions. The phosphorylation reaction had shown excellent tolerance to both electron-withdrawing and electron-donating groups as aromatic substituents, including alkyl (**1b–d**), alkoxyl (**1f–h**), fluoro (**1j**), trifluoromethyl (**1k**), acetyl (**1l**), ester (**1m–o**), and acetamido groups (**1p**). For the substrate of arylsulfonium salts with the naphthalene group, the reaction gave the desired product in 70% yield. Surprisingly, the phosphorylation reaction could be conducted in the presence of unprotected active hydroxyl group (**1i**), affording 67% yield. The diminished yield in the case of **1d** may be attributed to steric hindrance. The desired products were also obtained in good yields regardless of the alkyl substituents on the sulfonium moiety (**1r–s**). In addition, different substituents (**1r–w**) at the sulfur atom to evaluate the reactivity of leaving group on the Pd-catalyzed phosphorylation, several dialkyl-(phenyl) or alkyl(diphenyl)sulfonium triflates were tested under the optimized conditions. To our delight, the desired products were obtained in good to excellent yields (**1t–v**), in which ethyl- and propyl(diphenyl)-sulfonium triflates were more suitable, afforded **3a** in 83%, and 89% yields, respectively.

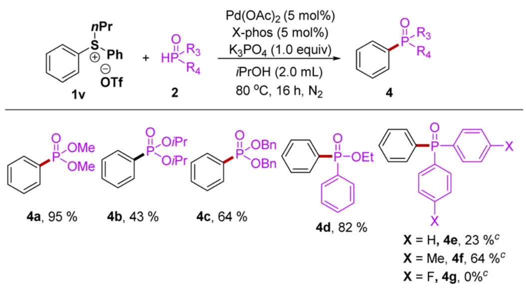
For further evaluation of the substrate scope, different P(O)H compounds were used to test the reaction. As shown in Scheme 3, the H-phosphonate diesters with different alkyl groups can all react smoothly with arylsulfonium salt **1v** to afford the corresponding phosphorylation product (**4a–c**) in moderate to good yields. Ethyl phenylphosphinate (**4d**) had good compatibility under the optimized conditions to give the corresponding products in 82% yield. Next, some di-*p*-tolylphosphine oxides were subjected to the reaction at 110 °C, diphenyl- and di-*p*-

Table 2 Scope of the catalytic phosphorylation of arylsulfonium salts[a,b]



[a] **1** (0.36 mmol), **2a** (0.30 mmol), $Pd(OAc)_2$ (5 mo%), XPhos (5 mo%), K_3PO_4 (0.3 mmol), iPrOH (2.0 mL), 80 °C, 16 h, under N_2. [b] Isolated yield.

Table 3 Scope of the catalytic phosphorylation of P(O)H compounds[a,b]



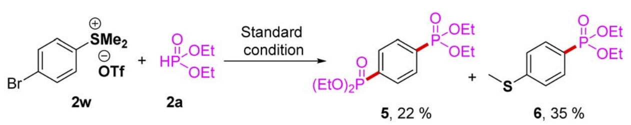
[a] **1v** (0.36 mmol), **2** (0.30 mmol), $Pd(OAc)_2$ (5 mo%), XPhos (5 mo%), K_3PO_4 (0.3 mmol), iPrOH (2.0 mL), 80 °C, 16 h, under N_2. [b] Isolated yield. [c] $T = 110$ °C.

tolylphosphine oxides show reactivity to afford the corresponding products **4e** and **4f** in 23% and 64% yield, respectively. Unfortunately, bis(4-fluorophenyl)-phosphine oxide was incompatible to the current catalytic system (**4g**) (Table 3).

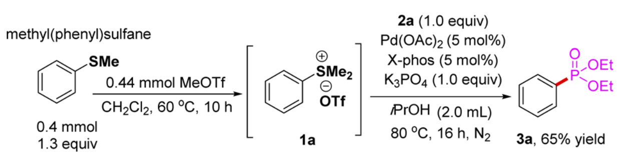
Interestingly, the (4-bromophenyl)dimethylsulfonium **2w** was used to test the reaction, unexpected diphosphorylation product **5** and phosphorylation product bearing 4-methylthio group **6** were obtained, respectively in 22% and 35% yield (Scheme 2).

To prove the synthetic utility of the strategy, one-pot phosphorylation method was investigation. Treatment of methyl(phenyl)sulfane with MeOTf in 1,2-dichloroethane (DCE) afforded the corresponding aryl sulfonium salts **1a** (confirmed with ^{1}H NMR). After removal of all volatiles under a reduced pressure, one-pot phosphorylation was performed in the presence of $Pd(OAc)_2$, XPhos, diethyl phosphonate **2a**, K_3PO_4, and iPrOH. We are pleased to find that the reaction proceeded smoothly to provide the desired product **3a** in 61% yield.

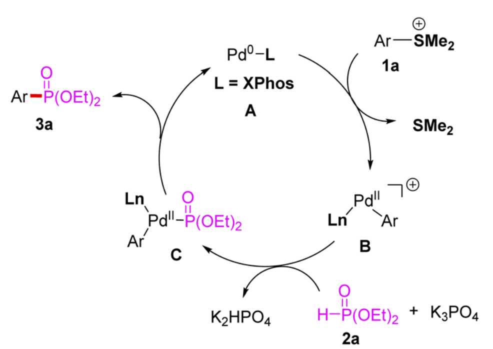
A plausible mechanism for the phosphorylation of arylsulfonium salts with P(O)H compounds was proposed as shown in Scheme 4. First, palladium(0) species **A** was generated from the reduction of palladium(II) with phosphine ligand by the aid of K_3PO_4.[16] Then, arylsulfonium **1a** would undergo oxidative addition with **A** to form cationic arylpalladium(II) **B**,[17] followed by ligand exchange of diethyl phosphonate **2a** with species **B** led to the generation of intermediate **C** in base condition.[13]



Scheme 2 Phosphorylation of the (4-bromophenyl)dimethyl sulfonium.



Scheme 3 One-pot phosphorylation of aryl sulfide.



Scheme 4 Plausible reaction mechanism.

Subsequently, reductive elimination from **C** afforded arylphosphonate **3a** and palladium (0) species **A** and the catalytic cycle was completed.

In summary, we have developed a palladium-catalyzed phosphorylation of arylsulfonium salts with P(O)H compounds. The transformation proceeded under mild reaction conditions and had advantages include good functional group tolerance, a wide scope of substrates, and easily available arylsulfonium salts. Mechanistically, this approach involves oxidative addition and reductive elimination processes as the two key steps to afford the desired product. The protocol provides pragmatic strategy applicable to the synthesis of diverse arylphosphonates.

Conflicts of interest

There are no conflicts to declare.

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