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Palladium-catalyzed desulfitative C–P coupling of arylsulfinate metal salts and H-phosphonates†

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Catalyzed by palladium(II) chloride, a diverse range of arylsulfinate sodium, potassium, lithium, silver, zinc, and copper salts undergo desulfination/C–P coupling with H-phosphonates, in the presence of silver(I) carbonate as oxidant, to produce useful arylphosphonates under microwave irradiation.

The synthesis of organophosphorus compounds has received significant interest due to their widespread applications in catalysis,[1] synthesis,[2] medicinal chemistry,[3] and materials chemistry.[4] Among the manifold reported methods, the transition-metal-catalyzed cross-coupling reaction has been one of the most powerful carbon–phosphorus bond-forming strategies.[5] Since the seminal work reported by Tavs and Hirao independently,[6] versatile efficient catalytic systems have been developed for the preparation of arylphosphonates. In this context, the aryl substrate scope has been expanded from aryl halides to triflates, mesylates, tosylates, phenols, diazonium salts, boronic acids, and cyano compounds.[7]

Recently, increasing attention has been attracted to desulfitative coupling *via* releasing SO_2 from sulfinate metal salts, RSO_2Na[8] or $(RSO_2)_2Zn$.[9] In contrast to current research in which sulfinates are mainly used to participate in sulfonylation reactions,[10] desulfitative coupling reactions have been well demonstrated in desulfitative Heck reactions,[8d] tandem desulfination/C–H activations,[8e,9,11] biaryls synthesis,[11c,12] aryl ketones synthesis,[8f,g] additions,[13] and diarylmethanes synthesis.[14] However, until now, this type of reaction is limited to the C–C bond formations. As similar with the decarboxylative couplings,[15] we envisioned that the resulting aryl metallic intermediate from arylsulfinate metal salt generated in the presence of palladium catalyst might also react with nucleophiles. Considering the great importance of organophosphorus compounds, we wish to develop an efficient desulfitative C–P coupling reaction of arylsulfinate metal salts and H-phosphonates, and have achieved the preliminary results.[16] While this manuscript was under review, a similar work has been published focusing on desulfitative C–P coupling of sodium arylsulfinates by Wang group.[17] Differing from Wang's work, a microwave-promoted method was applied to our desulfitative C–P coupling, and the scope of arylsulfinate metal salts was also investigated.

Our initial investigations focused on the $PdCl_2$-catalyzed desulfitative phosphonation of sodium *p*-toluenesulfinate **1a** with diethyl phosphite **2a** under microwave irradiation. Ag^I salts are known as efficient oxidants in the Pd-catalyzed oxidative couplings,[18] thus we chose silver salts as oxidants to take part in this reaction. As shown in Table 1, we were gratified to find that the use of 20 mol% of $PdCl_2$ and 1 equivalent of Ag_2CO_3 in toluene at 120 °C provided a 8% yield of the desired product **3a** (Table 1, entry 1). Besides the desulfitative homocoupling product **4**,[11a,12a] the reduction/arylation product **5** and reduction/phosphorylation product **6**[19] were also generated because of the reductive properties of phosphites.[20] Similar product distribution was obtained when xylene was used as the solvent (entry 2). When the reaction in other common solvents (*e.g.*, EtOAc, THF, DCE, and DMF) was carried out, **3a** was produced in moderate yield, and the phosphorothioate ester **6** was effectively controlled (entries 3–6). By employing Myers' solvent system,[21] the reaction yield was slightly improved to 68% (entry 7). Due to the competing reduction reactions, we anticipated that the yield might be mended through increasing the amount of the oxidant. To our delight, the augment of the dose of Ag_2CO_3 to 2 equivalents gave **3a** in 96% isolated yield (entry 8). Moving to other silver salts (*e.g.*, Ag_2O, $AgNO_3$, Ag_2MoO_4, and AgOAc) resulted in lower yield (entries 9–12). Running the reaction in DMSO afforded the coupled product in 80% yield (entry 13). 20% yield of **3a** was obtained in the absence of Ag_2CO_3 whether or not the reaction was ran in air atmosphere (entries 14–15), which indicating that the oxygen had no effect on reaction. Absence of $PdCl_2$ showed none of the

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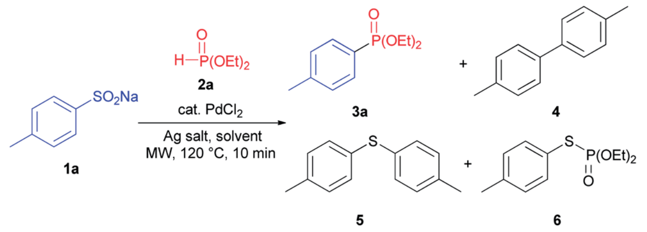
† Electronic supplementary information (ESI) available: Experimental procedures and characterization data of all compounds and copies of NMR spectra. See DOI: 10.1039/c4ra01270d

Table 1 Optimization of the reaction between **1a** and **2a**[a]



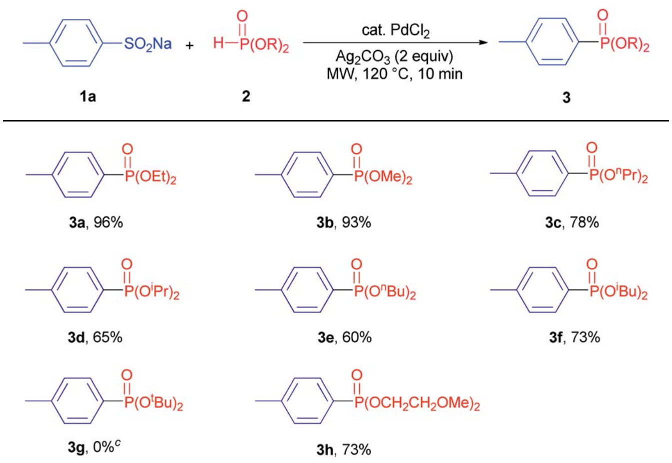
Entry	Ag salt (equiv.)	Solvent	Yield of **3a**[b] (%)	**3a/4/5/6**[b,c] (%)
1	Ag_2CO_3 (1)	Toluene	8	14/0/3/83
2	Ag_2CO_3 (1)	Xylene	10	16/4/6/74
3	Ag_2CO_3 (1)	EtOAc	63	84/4/11/1
4	Ag_2CO_3 (1)	THF	66	80/0/16/4
5	Ag_2CO_3 (1)	DCE	44	57/13/22/8
6	Ag_2CO_3 (1)	DMF	64	77/2/17/4
7[d]	Ag_2CO_3 (1)	DMF–DMSO	68	82/0/10/8
8[d]	Ag_2CO_3 (2)	DMF–DMSO	99 (96[e])	94/5/1/0
9[d]	Ag_2O (2)	DMF–DMSO	81	90/8/0/0
10[d]	$AgNO_3$ (2)	DMF–DMSO	33	67/31/2/0
11[d]	Ag_2MoO_4 (2)	DMF–DMSO	43	64/3/13/10
12[d]	AgOAc (2)	DMF–DMSO	4	11/0/13/76
13	Ag_2CO_3 (2)	DMSO	80	86/10/4/0
14[d]	—	DMF–DMSO	20	46/4/34/16
15[d,f]	—	DMF–DMSO	21	52/4/37/7
16[d,g]	Ag_2CO_3 (2)	DMF–DMSO	~0	4/44/41/10
17[d,h]	Ag_2CO_3 (2)	DMF–DMSO	40	66/0/34/0

[a] Reaction conditions: **1a** (0.36 mmol), **2a** (0.3 mmol), $PdCl_2$ (20 mol%), Ag salt, solvent (2 mL), MW irradiation at 120 °C for 10 min. [b] GC-MS analysis of crude reaction mixture. [c] Ratio of these four peaks was determined by area normalization method. [d] DMF–DMSO = 19/1 (v/v). [e] Isolated yield in parentheses. [f] Carried out in Ar. [g] In the absence of $PdCl_2$. [h] Carried out under conventional heating condition at 120 °C for 10 h.

phosphonation product **3a** (entry 16), Therefore, $PdCl_2$ and Ag_2CO_3 might have a synergetic action in the desulfination. When the reaction was operated under conventional heating condition for 10 h, only 40% of **3a** was generated (entry 17).

The scope of this desulfitative C–P coupling with respect to the H-phosphonates has been investigated (Table 2). Moderate to good yields could be obtained with various H-phosphonates (**3a–3f**, **3h**). The strong steric hindrance of the H-phosphonates led to inhibition of the reaction (**3g**).

Table 2 Desulfitative phosphonation of **1a** with various H-phosphonates[a,b]

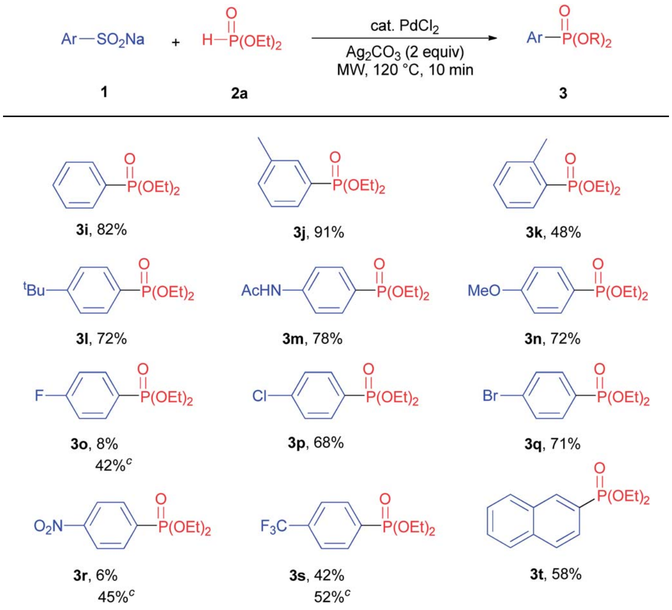


[a] Reaction conditions: **1a** (0.36 mmol), **2** (0.3 mmol), $PdCl_2$ (20 mol%), Ag_2CO_3 (2 equiv.), DMF–DMSO (v/v = 19/1, 2 mL), MW irradiation at 120 °C for 10 min. [b] Isolated yields. [c] Only biaryl **4** was observed by GC-MS.

We have also explored functional group tolerance with respect to the substituents on the sodium arylsulfinate (Table 3). Both electron-rich groups and electron-withdrawing groups performed well under our standard reaction conditions. Sodium arylsulfinates with a *m*-methyl substitution gave a yield of 91% (**3j**). Versatile groups on the *para*-position of the arylsulfinates, such as ^{t}Bu, AcNH, MeO, and halides, gave the products in good yields (**3l–3n**, **3p** and **3q**). It was noteworthy that the bromo substituent tolerated well in this reaction (**3q**). However, much diethyl pyrophosphate was produced when *p*-fluoro, *p*-nitro, and *p*-trifluoromethyl arylsulfinate sodium salts were employed as the substrates. Using DMSO as the solvent could eliminate these disadvantages and gave the products in moderate yields (**3o**, **3r** and **3s**). Sodium 2-naphthalenesulfinate provided the corresponding product in 58% yield (**3t**).

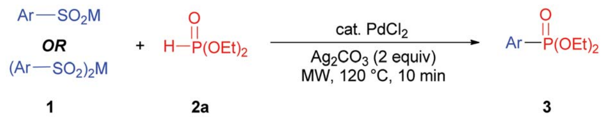
This catalytic system was also effective for other metal salts of arylsulfinate, including Li, K, Ag, Zn, and Cu. As depicted in Table 4, the reaction of these arylsulfinate metal salts with diethyl phosphite gave the coupled product in moderate to

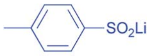
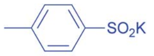
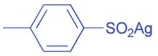
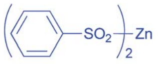
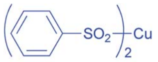
Table 3 Desulfitative arylation of **2a** with various arylsulfinate sodium salts[a,b]



[a] Reaction conditions: **1a** (0.36 mmol), **2** (0.3 mmol), $PdCl_2$ (20 mol%), Ag_2CO_3 (2 equiv.), DMF–DMSO (v/v = 19/1, 2 mL), MW irradiation at 120 °C for 10 min. [b] Isolated yields. [c] DMSO (2 mL).

Table 4 Desulfitative arylation of **2a** with arylsulfinate metal salts[a]



Entry	Arylsulfinate	Product	Yield[b] (%)
1	 **1u**	**3a**	36
2	 **1v**	**3a**	86
3	 **1w**	**3a**	44
4	 **1x**	**3b**	93
5	 **1y**	**3b**	31

[a] Reaction conditions: **1u–w** (0.36 mmol) or **1x** and **1y** (0.18 mmol), **2a** (0.3 mmol), $PdCl_2$ (20 mol%), Ag_2CO_3 (2 equiv.), DMF–DMSO (v/v = 19/1, 2 mL), MW irradiation at 120 °C for 10 min. [b] Isolated yields.

excellent yields (entries 1–5). Among these metal salts, zinc arylsulfinate turned out to be the most appropriate substrate for the catalytic system (entry 4).

In summary, we have developed a new type of desulfitative coupling for the preparation of arylphosphonates and have demonstrated its functional group tolerance and substrate scope. The versatile arylsulfinate metal salts (M = Na, Li, K, Ag, Zn, and Cu) used pave the way for the application of desulfitative C–P couplings. Full details of the mechanism and further scope of these transformations will be forthcoming.

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