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Palladium-Catalyzed Synthesis of Functionalized Tetraarylphosphonium Salts

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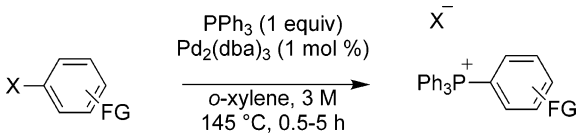

X = Br, 12 examples (45-96%)
I, 10 examples (88-95%)
OTf, 5 examples (83-97%)
FG = alcohols, ketones, aldehydes phenols

An efficient method to synthesize functionalized tetraarylphosphonium salts is described. This palladium-catalyzed coupling reaction between aryl iodides, bromides, or triflates and triphenylphosphine generates phosphonium salts in high yields. The coupling is compatible with a variety of functional groups such as alcohols, ketones, aldehydes, phenols, and amides.

Introduction

Phosphonium salts have gained major importance in recent years. They are versatile compounds that have been used as catalyst transfer agents,[1] organic reagents,[2] ionic liquids,[3] conducting agents,[4] and flame-proofing agents.[5,6] Aryl-substituted phosphonium salts, which are lipophilic cations, have become increasingly popular in cellular biology.[7] Alkyltriarylphosphonium salts have been shown to accumulate in mitochondria of specific organs[8] and have thus been studied as anticancer agents[9,10] and as drug carriers.[11] Some tetraarylphosphonium (TAP) salts also possess some significant bioactivity;[10] however, their preparation is very tedious. Furthermore, there is no simple or general catalytic method for the synthesis of functionalized TAP.[12]

Our group has recently reported the use of functionalized TAP as solubility control groups for reagents and synthesis. The covalent binding of TAP to a reagent or catalyst renders the latter soluble in solvents such as dichloromethane. The supported reagent or catalyst is then easily separated from the reaction

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product by precipitation upon an etheral solvent such such as diethyl ether. A number of TAP-supported reagents such as triphenylphosphine and diazocarboxylate derivatives[13] and tin reagents[14] were prepared and utilized in various reactions. We have also used TAP as a soluble support in the synthesis of small molecules to allow isolation by a precipitation.[15]

The classical methods for the preparation of TAP typically employ metal-free conditions which require high temperature and/or harsh reaction conditions.[16,17]

More conveniently, the synthesis of TAP was accomplished with transition metal catalysts and reagents. Nickel(II)-mediated synthesis of TAP requires high nickel loading (50 mol %)[18] or an *o*-imine substituent.[19] Nickel(0)-catalyzed reactions are effective only with strongly electron-donating substituents on the aryl halide component (OMe, NMe_2),[20] high catalyst loading (10−35 mol %), and/or tedious purification.[1b,c] Palladium-catalyzed formation of TAP[21] was first reported by Heck, who observed the presence of TAP as a byproduct in a palladium-catalyzed reaction.[22] Subsequently, Migita developed a palladium-catalyzed (using $Pd(OAc)_2$) synthesis of TAP limited to aryl iodides.[23] To date, no efficient method is known for the palladium-catalyzed synthesis of TAP from aryl bromides or triflates.[24] Herein, we report a palladium-catalyzed reaction for the synthesis of functionalized TAP from aryl bromides, iodides, and triflates.

SCHEME 1. Preliminary Results

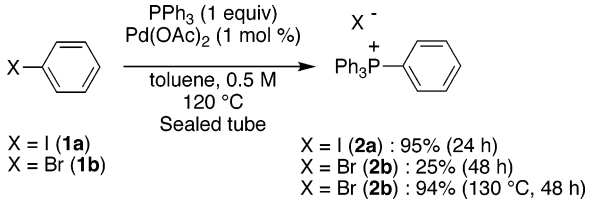
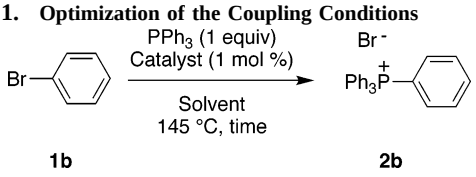


TABLE 1. Optimization of the Coupling Conditions



entry	precatalyst	solvent (concn, M)	time (h)	yield (%)[a]
1	$Pd(OAc)_2$	*o*-xylene (0.5)	48	80
2	$Pd(PPh_3)_4$	*o*-xylene (0.5)	48	82
3[b]	$Pd_2(dba)_3$	*o*-xylene (0.5)	48	86
4	Pd on C	*o*-xylene (0.5)	48	20
5[c]	$PdCl_2$	*o*-xylene (0.5)	48	9
6[b,d]	$Pd_2(dba)_3$	*o*-xylene (0.5)	48	94[e]
7[b,f]	$Pd_2(dba)_3$	*o*-xylene (0.5)	48	49
8	$Pd_2(dba)_3$	*o*-xylene (1)	4	56
9	$Pd_2(dba)_3$	*o*-xylene (2)	4	83
10	$Pd_2(dba)_3$	*o*-xylene (3)	4	91
11	$Pd_2(dba)_3$	*o*-xylene (4)	4	70
12	$Pd_2(dba)_3$	*o*-xylene (3)	5	95
13	$Pd_2(dba)_3$	*p*-xylene (3)	5	92
14	$Pd_2(dba)_3$	ethylbenzene (3)	5	88
15	$Pd_2(dba)_3$	benzonitrile (3)	5	91
16[g]	$Pd_2(dba)_3$	*o*-xylene (3)	5	54
17[h]	$Pd_2(dba)_3$	*o*-xylene (3)	5	80

[a] Isolated yield. [b] 0.5 mol % was used with $Pd_2(dba)_3$. [c] 0.02 equiv of Et_3N was added. [d] 0.5 equiv of triphenylphosphine was used instead of 1 equiv. [e] Yield based on the limiting reagent: triphenylphosphine. [f] 2 equiv of triphenylphosphine was used instead of 1 equiv. [g] The reaction was run at 125 °C. [h] The reaction was run at 135 °C.

Results and Discussion

We began our studies using the method described by Migita (Scheme 1).[23] Excellent yields were obtained with iodobenzene; however, only trace amounts (ca. 10%) of phosphonium salt **2b** were obtained after 24 h at 120 °C. Increasing the reaction time to 48 h led to only a slight improvement in yield (25%). Interestingly, increasing the temperature to 130 °C gave a 94% yield of phosphonium **2b** albeit in 48 h (Scheme 1).

Encouraged by these results, we undertook a careful optimization of the coupling reaction between triphenylphosphine and bromobenzene (Table 1). Several palladium pre-catalysts [$Pd(OAc)_2$, $PdCl_2$, $Pd_2(dba)_3$, Pd/C] were screened (entries 1−5) and $Pd_2(dba)_3$ produced the best yield (entry 3). Varying the amount of triphenylphosphine showed that lowering it to 0.5

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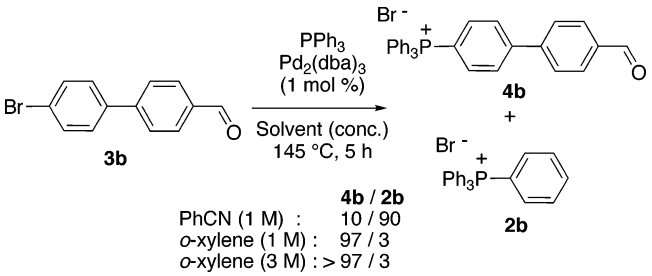
SCHEME 2. Reaction with Functionalized Aryl Bromides

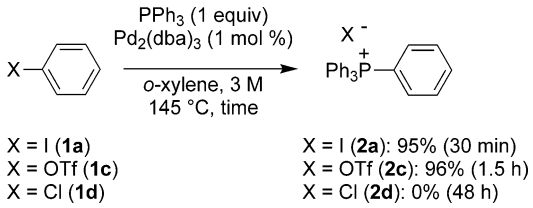


equiv accelerated the reaction (entry 6) while increasing it to 2 equiv gave lower yield (entry 7). However, a one-to-one ratio of bromobenzene and triphenylphosphine was kept for the rest of the optimization. The concentration of the reaction was also found to be extremely important for further improvement (entries 8−11) since varying the concentration of reagent from 0.5 to 3 M gave a nearly quantitative yield of desired TAP **2b** in only 5 h (entry 12). Since the phosphonium salt generated is not soluble in *o*-xylene, product isolation requires a simple filtration of the reaction mixture followed by diethyl ether (or *tert*-butyl methyl ether) trituration of the solid to remove any traces of unreacted starting material. A screening of the solvent indicated that other aromatic solvents could be used such as benzonitrile. In the latter, the reaction is homogeneous, which makes the isolation of the product and the solvent removal less practical. This solvent, however, could not be used with functionalized substrates (vide infra). The optimal temperature was shown to be 145 °C (entries 10, 16, and 17).

When two sets of optimized conditions (Table 1, entries 12 and 15) were applied to a substituted aryl bromide, an important side reaction was observed when benzonitrile was used as solvent (Scheme 2). The palladium-catalyzed coupling of 4-bromo-4′-formylbiphenyl (**3b**) with triphenylphosphine in benzonitrile led to the desired product **4b** that was contaminated with significant amounts of tetraphenylphosphonium bromide (**2b**). It is believed that this side product is formed from the oxidative addition of Pd(0) into the phosphonium−phenyl bond, followed by the reductive elimination with triphenylphosphine to afford phosphonium **2b**.[25] Chang has recently shown that tetraarylphosphonium salts can be used as electrophilic partners in several palladium-catalyzed processes.[26] This reaction has been utilized as a key feature to make phosphines.[27] Fortunately, the formation of this byproduct was completely suppressed when switching the solvent from benzonitrile to *o*-xylene. It is believed that the heterogeneous nature of the reaction in *o*-xylene plays a key role in the minimization of the byproduct formation by making the phosphonium salt less available to undergo further oxidative addition with palladium(0).

These optimized conditions were effective not only with aryl bromides but also with aryl iodides and triflates (Scheme 3). Excellent yields of the desired products were obtained in shorter

SCHEME 3. Reaction with Other Activated Aryl



reaction times for aryl iodides and triflates. In addition to making aryl bromides react, these reaction conditions give better yield in shorter reaction time (30 min vs 25 h) compare to Migita's condition.[23] However, aryl chlorides did not react under these conditions.

To explore the scope of the reaction, several aryl bromides, iodides, and triflates were subjected to the optimized reaction conditions (Table 2).

Various TAP salts containing an aryl group bearing an electron-donating substituent at the meta or para position were prepared in excellent yields (products **9**, **10**, **12**, and **13**). Aryl halides bearing ortho substituents could not be efficiently coupled with triphenylphosphine under these conditions. Several functional groups such as alcohols (entry 2), aldehydes (entry 3), amides (entry 4), and ketones (entry 8) are well tolerated under the reaction conditions. The reactions proceeded very well with aryl bromides, iodides, or triflates, but the reaction times were significantly shorter with the latter. When a dibromo compound was used as a starting material, it was possible to stop the reaction at the monophosphonium stage (see compounds **5** and **14**), a process that was not possible to achieve using Horner's conditions.[18] Functional groups that are so far not tolerated include carboxylic acids and esters.

It is also possible to use the monobromoaryltriphenylphosphonium salt in a subsequent palladium-catalyzed cross-coupling reaction. For example, Stille coupling of aryl bromide **5** with Fu's condition[28] afforded phosphonium salt **15** in 89% yield (Scheme 4). Phosphonium **15** is an intermediate in the synthesis of supported tin reagents that previously required 5 steps from commercially available 4,4′-dibromobiphenyl using Horner's procedure.[18]

In conclusion, we have developed an efficient method to generate functionalized TAP. The palladium-catalyzed reaction gives excellent yields for the coupling reaction of aryl halides or triflates and triphenylphosphine. Aryl iodides, triflates, and bromides can be efficiently used under the reaction condition. The ease of purification by simple precipitation/filtration also makes this method very convenient. Efforts to increase the functional group tolerance are under study and will be reported in due course.

Experimental Section

Typical Procedure for the Synthesis of TAP Iodides. Iodobenzene (1.22 g, 669 μL, 6 mmol, 1.0 equiv), $Pd_2(dba)_3$ (55.0 mg, 0.06 mmol, 1 mol %) weighted in a glovebox, and triphenylphosphine (1.57 g, 6.0 mmol, 1 equiv) were mixed together in a dry 50 mL tube under inert atmosphere (Argon) of a combinatorial chemistry kit equipped with a condenser. To this mixture were added dry *o*-xylene (2 mL, 3 M) and a magnetic stir bar. The reaction mixture was heated to reflux for 1 h under argon. The phosphonium salts precipitated as the reaction proceeded. After 1

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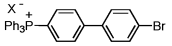
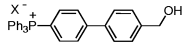
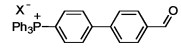
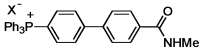
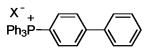
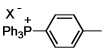
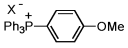
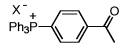
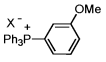
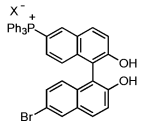
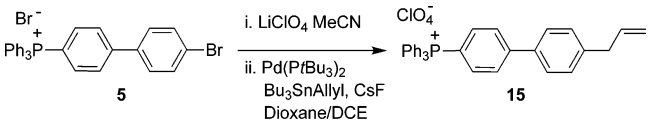
TABLE 2. Scope of the Coupling Reaction

entry			X=Br	yield (%)[b] X=I	X=OTf
1		**5**	96[e]	--	--
2		**6**	96	89[c]	--
3		**4**	95	92[c]	--
4		**7**	80	83[c]	--
5		**8**	93	89	--
6		**9**	93	92	88[d]
7		**10**	98	94	97
8		**11**	41	40	--
9		**2**	95	95	96
10		**12**	88	88[c]	83[d]
11		**13**	91	95	93
12		**14**	89[e]	--	--

[a] Reaction times: 5 h for aryl bromide, 1 h for aryl iodide, and 2 h for aryl triflates. [b] Isolated yields. [c] 2 h of reaction time. [d] 3 h of reaction time. [e] Monophosphonium salt was formed exclusively.

SCHEME 4. Utility of TAP 5



h, the tube was cooled to room temperature, 20 mL of diethyl ether was added, and the resulting suspension was stirred at room temperature for 2 min. The precipitate was filtered on Celite and silica gel and washed with 50 mL of diethyl ether. The phosphonium salt was dissolved with DCM into a 200 mL round-bottomed flask. The organic phase was concentrated under reduced pressure to afford **2a** as a pure white solid (2.66 g, 95% yield): mp >250 °C (346);[23] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90−7.81 (m, 4H), 7.76−7.69 (m, 8H), 7.60−7.53 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.8 (d, J = 3.0 Hz, 4C), 134.4 (d, J = 10.3 Hz, 8C), 130.8 (d, J = 12.9 Hz, 8C), 117.4 (d, J = 89.6 Hz, 4C); ^{31}P NMR (122 MHz, $CDCl_3$) δ 23.3; IR 3065 (br), 3062, 1585, 1483, 1435, 1262, 1141, 1107, 1030, 995, 905 (film) cm^{-1}; HRMS (ES, Pos) calcd for $C_{24}H_{20}P_1$ [M]$^+$ 339.1302, found 339.1288; HRMS (ES, Neg) calcd for ^{127}I [M]$^-$ 126.9056, found 126.9050.

Typical Procedure for the Synthesis of TAP Bromides. Bromobenzene (942 mg, 632 μL, 6 mmol, 1.0 equiv), $Pd_2(dba)_3$ (55.0 mg, 0.06 mmol, 1 mol %) weighted in a glovebox, and triphenylphosphine (1.57 g, 6.0 mmol, 1 equiv) were mixed together under inert atmosphere (Argon) in a dry 50 mL tube of a combinatorial chemistry kit equipped with a condenser. To this mixture were added dry *o*-xylene (2 mL, 3 M) and a magnetic stir bar. The reaction mixture was heated to reflux for 5 h under argon. The phosphonium salts precipitated as the reaction proceeded. After 5 h, the tube was cooled to room temperature, 20 mL of diethyl ether was added, and the resulting suspension was stirred at room temperature for 2 min. The precipitate was filtered on Celite and silica gel and washed with 50 mL of diethyl ether. The phosphonium salt was dissolved with DCM into a 200 mL round-bottomed flask. The organic phase was concentrated under reduced pressure to afford pure **2b** as a pure white solid (2.39 g, 95% yield). Mp >250 °C (288);[23] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90−7.81 (m, 4H), 7.76−7.69 (m, 8H), 7.60−7.53 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.8 (d, J = 3.0 Hz, 4C), 134.4 (d, J = 10.3 Hz, 8C), 130.8 (d, J = 12.9 Hz, 8C), 117.4 (d, J = 89.6 Hz, 4C); ^{31}P NMR (122 MHz, $CDCl_3$) δ 23.3; IR 3065 (br), 3062, 1585, 1483, 1435, 1262, 1141, 1107, 1030, 995, 905 (film) cm^{-1}; HRMS (ES, Pos) calcd for $C_{24}H_{20}P_1$ [M]$^+$ 339.1302, found 339.1288; LRMS (ES, Neg) calcd for ^{79}Br [M]$^-$ 78.9, found 79.0; calcd for ^{81}Br [M]$^-$ 80.9, found 81.0.

Typical Procedure for the Synthesis of TAP Triflates. Phenyl trifluoromethanesulfonate (1.36 g, 6 mmol, 1.0 equiv), $Pd_2(dba)_3$ (55.0 mg, 0.06 mmol, 1 mol %) weighted in a glovebox, and triphenylphosphine (1.57 g, 6.0 mmol, 1 equiv) were mixed together in a dry 50 mL tube under inert atmosphere (argon) of a combinatorial chemistry kit equipped with a condenser. To this mixture were added dry *o*-xylene (2 mL, 3 M) and a magnetic stir bar. The reaction mixture was heated to reflux for 1 h under argon. The phosphonium salts precipitated as the reaction proceeded. After 1 h, the tube was cooled to room temperature, 20 mL of diethyl ether was added and the resulting suspension was stirred at room temperature for 2 min. The precipitate was filtered on Celite and silica gel and washed with 50 mL of diethyl ether. The phosphonium salt was dissolved with DCM into a 200 mL round-bottomed flask. The organic phase was concentrated under reduced pressure to afford **2c** as a pure white solid (2.81 g, 96% yield): mp >250 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90−7.81 (m, 4H), 7.76−7.69 (m, 8H), 7.60−7.53 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.8 (d, J = 3.0 Hz, 4C), 134.4 (d, J = 10.3 Hz, 8C), 130.8 (d, J = 12.9 Hz, 8C), 117.4 (d, J = 89.6 Hz, 4C); ^{31}P NMR (122 MHz, $CDCl_3$) δ 23.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ −79.5; IR 3065 (br), 3062, 1585, 1483, 1435, 1262, 1141, 1107, 1030, 995, 905 (film) cm^{-1}; HRMS (ES, Pos) calcd for $C_{24}H_{20}P_1$ [M]$^+$ 339.1302, found 339.1288; HRMS (ES, Neg) calcd for CF_3SO_3 [M]$^-$ 148.9532, found 148.9525.

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Supporting Information Available: Experimental procedures for the preparation of all the compounds and characterization data for each reaction and detailed structural assignment. This material is available free of charge via the Internet at http://pubs.acs.org.

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