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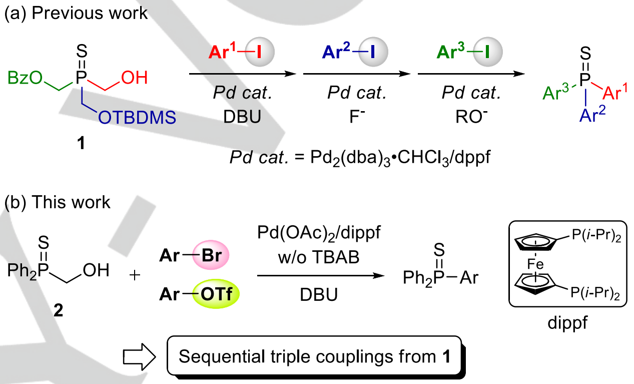
Pd-Catalyzed P–C Cross-Coupling of Aryl Bromides and Triflates with Hydroxymethylphosphine Sulfide Derivatives

Hidetoshi Ohta, Qian Xue, and Minoru Hayashi*

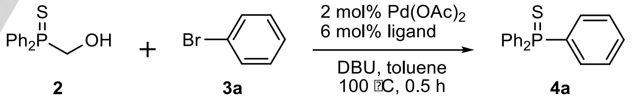
Abstract: The development of a versatile process for phosphine synthesis has attracted considerable interest because organophosphines are indispensable for organic synthesis. Previously, we developed a Pd-catalyzed P–C coupling reaction for hydroxymethylphosphine sulfide derivatives with various aryl iodides as a method for preparing a variety of triarylphosphine derivatives. However, the catalyst system for aryl iodides did not activate aryl bromides and triflates, which are more readily available than aryl iodides. Herein, we report a new and effective catalyst system for the P–C coupling of various aryl bromides and triflates with hydroxymethylphosphine sulfides. An application of the new method was demonstrated with the sequential synthesis of an unsymmetrically substituted triarylphosphine sulfide using multiple couplings of an orthogonally protected precursor.

Tertiary phosphines play an important role in organic synthesis as reagents, organocatalysts, and ligands in transition metal catalysis.[1] Therefore, considerable effort has been devoted to developing efficient and versatile synthetic methodologies for preparing tertiary phosphines.[2–7] However, it remains difficult to introduce several different substituents onto a single phosphorus atom in a selective manner.[8] Previously, we reported a Pd-catalyzed deformylative P–C coupling reaction that allowed the stepwise and selective introduction of several aromatic substituents onto a single phosphorus atom using unsymmetric phosphine sulfide **1** with protected and unprotected hydroxymethyl groups [Scheme 1(a)].[9] The resulting triarylphosphine sulfides were easily purified because of their air stability and low polarity. They were subsequently converted to the corresponding phosphines by reducing the P=S bond.[10] Therefore, the P–C coupling provides a highly versatile method for synthesizing a wide range of triarylphosphines. A drawback to the disclosed P–C coupling method is the requirement of expensive aryl iodides as the coupling partner. Our P–C coupling reaction would be more valuable if less expensive and more widely available aryl bromides could be used. Aryl triflates, which are readily prepared from the corresponding phenol derivatives, would also be attractive coupling partners. However, both aryl bromides and aryl triflates are less reactive than aryl iodides and could not be activated with our first-generation catalyst, $Pd_2(dba)_3{\cdot}CHCl_3$/dppf. Herein, we disclose a novel catalyst for enabling the P–C coupling of hydroxymethylphosphine sulfide **2** with various aryl bromides and triflates: $Pd(OAc)_2$/dippf was found to be highly effective [Scheme 1(b)]. The versatility of the second-generation approach was demonstrated with a site-selective triple coupling sequence from **1** to produce an unsymmetrically substituted triarylphosphine sulfide.



Scheme 1. P–C coupling of hydroxymethylphosphine sulfide derivatives.

Table 1. Survey of ligands for the coupling of aryl bromides.[a,b]



Entry	Ligand	Yield [%][c]	Entry	Ligand	Yield [%][c]
1	Dippf	93	13	PPh_3	0
2	Dppf	45	14	P(*o*-tol)$_3$	0
3	(*S*)-(*R*)-Josiphos	27	15	P(*n*-Bu)$_3$	0
4	Dtbpf	0	16	P(*n*-Octyl)$_3$	0
5	(*S*)-(−)-Binap	33	17	PCy_3	0
6	Xantphos	9	18	P(*t*-Bu)$_3$	0
7	Dppe	0	19	PCy_2H	0
8	Dppp	0	20	$P(NMe_2)_3$	0
9	Dppb	0	21	JohnPhos	0
10	Dcype	0	22	Cy-JohnPhos	0
11	Dppbz	0	23	SPhos	0
12	(*S*,*S*)-Chiraphos	0	24	IPr	0

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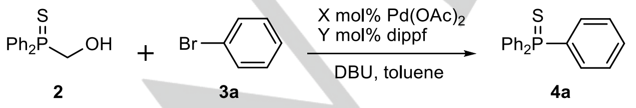
[a] Reaction conditions: **2** (0.25 mmol), **3a** (1.2 eq), $Pd(OAc)_2$ (2 mol%), ligand (6 mol%), DBU (2.0 eq), toluene (2.5 mL), 100 °C, 0.5 h. [b] The formal names and structures of all the ligands can be found in the Supporting Information. [c] Calculated from the ^{31}P NMR ratio.

In most transition-metal catalyzed reactions, the organic ligands surrounding a metal center have considerable influence on catalytic performance.[11] Therefore, we first investigated the effect of various ligands in the reaction of **2** with phenyl bromide (**3a**) (Table 1). The catalyst generated from $Pd(OAc)_2$ and dippf showed high catalytic activity, yielding triphenylphosphine sulfide (**4a**) in 93% yield (entry 1). Other ferrocenylphosphine ligands, dppf and Josiphos, were less effective, yielding **4a** in 45% and 27% yields, respectively (entries 2 and 3). In contrast, the reaction with dtbpf gave no coupling adduct (entry 4). Binap and xantphos yielded low amounts of **4a** (entries 5 and 6). A wide selection of other ligands were screened, including bidentate phosphines (entries 7–12), monodentate phosphines (entries 13–23), and an *N*-heterocyclic carbene (entry 24), which did not yield **4a**. Thus, we determined that dippf was the best ligand for the P–C coupling of **2** with **3a**.

Next, we optimized the reaction conditions to allow the reaction to proceed at lower temperatures and Pd loadings (Table 2). The reaction rates decreased when the temperatures decreased: **4a** was obtained in 74% yield at 80 °C and in 41% yield at 60 °C (entries 1 and 2). In the reaction at 60 °C, a significant increase in the yield was not observed with longer reaction time (entry 3), suggesting that the catalytically active Pd species became deactivated. Increasing the amounts of dippf from 6 mol% to 8 mol% prevented the reduction in catalytic activity, producing **4a** almost quantitatively after 4 h (entry 4). Unfortunately, the reaction at 40 °C provided **4a** in much lower yield, even after 24 h (entry 5). Thus, we set the optimum reaction temperature at 60 °C. Efficient P–C coupling at lower Pd loadings was achieved by adjusting the substrate concentration. When the Pd loading was reduced from 2 mol% to 1 mol%, the yield of **4a** decreased to 39% (entry 6); however, **4a** was obtained quantitatively by increasing the substrate concentration from 0.1 mol/L to 0.5 mol/L (entry 7). Similarly, the reaction at 0.5 mol% Pd loading was possible by increasing the concentration of **2** from 0.5 mol/L to 1 mol/L, giving **4a** in quantitative yield (entries 8 and 9).

Table 2. Optimization of conditions for the coupling of aryl bromides.[a]

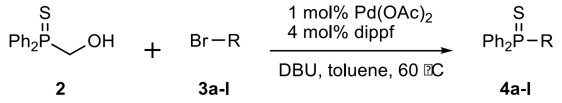


Entry	Temp.	Time	mol% of cat.		Conc. of **2**	Yield
	[°C]	[h]	X	Y	[mol/L]	[%][b]
1	80	0.5	2	6	0.1	74
2	60	0.5	2	6	0.1	41
3	60	12	2	6	0.1	46
4	60	4	2	8	0.1	98
5	40	24	2	8	0.1	13
6	60	4	1	4	0.1	39
7	60	4	1	4	0.5[c]	99
8	60	24	0.5	2	0.5[c]	0
9	60	4	0.5	2	1[d]	>99

[a] Reaction conditions: **2** (0.25 mmol), **3a** (1.2 eq), $Pd(OAc)_2$ (X mol%), dippf (Y mol%), DBU (2.0 eq), toluene (2.5 mL). [b] Calculated from the ^{31}P NMR ratio. [c] The reaction was performed on a 1.0 mmol scale of **2** with 2.0 mL of toluene. [d] The reaction was performed on a 2.0 mmol scale of **2** with 2.0 mL of toluene.

The P–C coupling of **2** with various aryl bromides was investigated (Table 3). In the presence of 1 mol% Pd catalyst, **2** was coupled with **3a**, *p*-tolyl bromide (**3b**), and *m*-tolyl bromide (**3c**) for 4 h to produce the corresponding products **4a**–**4c** in 95%, 96%, and 97% isolated yields, respectively (entries 1–3). Sterically hindered *o*-tolyl bromide (**3d**) produced **4d** in 71% yield after 24 h (entry 4). The reaction of electron-rich *p*-anisyl bromide (**3e**) required a higher reaction temperature (80 °C) and Pd loading (2 mol% Pd), providing **4e** in 74% yield (entry 5). The reaction of various electron-poor aryl bromides (**3f**–**3j**) possessing cyano, formyl, methoxycarbonyl, and nitro groups yielded **4f**–**4j** in 90–94% yield (entries 6–10). Furthermore, a heteroaryl bromide, 2-thienyl bromide (**3k**), was converted to the corresponding product (**4k**) in 92% yield (entry 11). For the reactions of **3a**, **3b**, **3f**, and **3i,** a lower catalyst loading (0.5 mol% Pd) was possible, producing the corresponding products in high yields (entries 1, 2, 6, and 9).

Table 3. P–C coupling of various aryl bromides.[a]



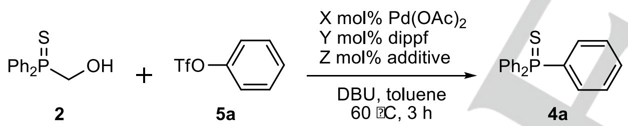
Entry	R-Br	Time [h]	Product	Yield [%][b]
1	Ph- (**3a**)	4	**4a**	95 (96)[c]
2	*p*-CH_3-C_6H_4- (**3b**)	4	**4b**	96 (95)[c]
3	*m*-CH_3-C_6H_4- (**3c**)	4	**4c**	97
4	*o*-CH_3-C_6H_4- (**3d**)	24	**4d**	71
5	*p*-CH_3O-C_6H_4- (**3e**)	24	**4e**	74[d]
6	*p*-NC-C_6H_4- (**3f**)	5	**4f**	91 (93)[c]
7	*p*-OHC-C_6H_4- (**3g**)	9	**4g**	90
8	*o*-OHC-C_6H_4- (**3h**)	15	**4h**	92

9	*p*-CH_3O_2C-C_6H_4- (**3i**)	5	**4i**	94 (92)[c]
10	*p*-O_2N-C_6H_4- (**3j**)	7	**4j**	91
11	2-Thienyl- (**3k**)	6	**4k**	92

[a] Reaction conditions: **2** (0.50-1.0 mmol), **3a–3l** (1.2 eq), $Pd(OAc)_2$ (1 mol%), dippf (4 mol%), DBU (2.0 eq), toluene (2 mL per 1.0 mmol of **2**), 60 °C. [b] Isolated yield. [c] The reaction was performed on a 1.6 mmol scale of **2** with $Pd(OAc)_2$ (0.5 mol%), dippf (2 mol%), and toluene (1.6 mL). [d] The reaction was performed on a 0.50 mmol scale of **2** with $Pd(OAc)_2$ (2 mol%), dippf (8 mol%), and toluene (5 mL) at 80 °C.

We also investigated the P–C coupling of aryl triflates using the $Pd(OAc)_2$/dippf catalyst (Table 4). The addition of a halide salt was necessary to accomplish the reaction.[12] As shown in entry 1, the reaction of **2** with phenyl triflate (**5a**) did not occur without any halide additives (entry 1). By adding LiCl and LiBr, the coupling reaction proceeded to give **4a** in 19% and 44% yields, respectively (entries 2 and 3). Quantitative formation of **4a** was achieved using TBAB as the halide ion source (entry 4). Furthermore, the Pd loading could be reduced from 2 mol% to 1 mol% by increasing the substrate concentration (entry 5). Under optimized conditions, various aryl triflates such as **5a**, *p*-tolyl triflate (**5b**), *p*-anisyl triflate (**5c**), and *p*-cyanophenyl triflate (**5d**) could be converted to the corresponding products in 91–96% isolated yields (Table 5).

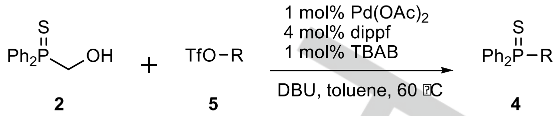
Table 4. Survey of additives for the coupling of aryl triflates.[a]



Entry	Additive	mol% of cat.			Conc. of **2**	Yield
		X	Y	Z	[mol/L]	[%][b]
1	None	2	8	—	0.1	0[c]
2	LiCl	2	8	2	0.1	19
3	LiBr	2	8	2	0.1	44
4	TBAB	2	8	2	0.1	>99
5	TBAB	1	4	1	0.5[d]	>99

[a] Reaction conditions: **2** (0.40 mmol), **5a** (1.2 eq), $Pd(OAc)_2$ (X mol%), dippf (Y mol%), additive (Z mol%), DBU (2.0 eq), toluene (4 mL), 60 °C, 3 h. [b] Calculated from the ^{31}P NMR ratio. [c] The reaction was carried out for 24 h. [d] The reaction was performed on a 0.80 mmol scale of **2** with 1.6 mL of toluene.

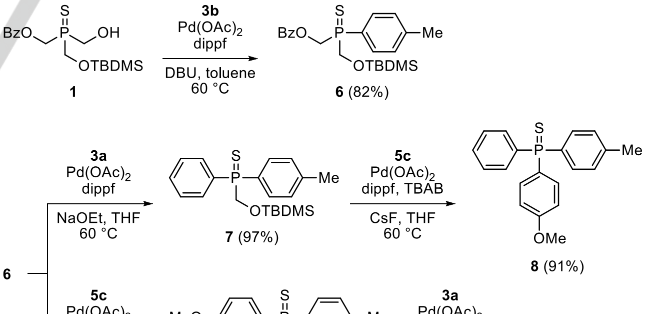
Table 5. P–C coupling of various aryl triflates. [a]



Entry	R-	Time [h]	Product	Yield [%][b]
1	Ph- (**5a**)	3	**4a**	94
2	*p*-CH_3-C_6H_4- (**5b**)	3	**4b**	95
3	*p*-CH_3O-C_6H_4- (**5c**)	4	**4e**	96
4	*p*-NC-C_6H_4- (**5d**)	4	**4f**	91

[a] Reaction conditions: **2** (0.80 mmol), **5** (1.2 eq), $Pd(OAc)_2$ (1 mol%), dippf (4 mol%), TBAB (1 mol%), DBU (2.0 eq), toluene (1.6 mL), 60 °C. [b] Isolated yield.

The newly developed P–C coupling of aryl bromides and triflates catalyzed by $Pd(OAc)_2$/dippf was applied to the stepwise synthesis of an unsymmetrically substituted triarylphosphine sulfide from **1** (Scheme 2). With our first-generation catalyst, we already showed that **1** can be selectively coupled with various aryl iodides by selecting the appropriate base [see Scheme 1(a)].[9] Similarly, the hydroxymethyl group in **1** was successfully converted to a *p*-tolyl group using P–C coupling with bromide **3b** under the DBU-mediated conditions described above, providing **6** in 82% isolated yield. The obtained **6** reacted efficiently with **3a** and **5c** in a stepwise and site-selective manner by selecting the coupling conditions and was finally converted to triarylphosphine sulfide **8** via **7** or **9**.



Scheme 2. Sequential triple P–C coupling from **1**. Isolated yields are shown in parentheses. Details of the reaction conditions: see the Supporting Information.

In summary, we have developed the P–C coupling of hydroxymethylphosphine sulfide derivatives with various aryl bromides and triflates, which are significantly more accessible than aryl iodides. The new catalytic system was successfully applied to the sequential triple coupling of orthogonally protected precursor **1** to yield an unsymmetrically substituted triarylphosphine sulfide. Further improvements to our P–C coupling protocol and a synthetic application to functional materials are currently underway.

Experimental Section

General procedure for the P–C coupling of aryl bromides and triflates with hydroxymethylphosphine sulfide derivatives: A solution (toluene or THF) of Pd(OAc)$_2$ (0.5-5 mol%) and dippf (2-20 mol%) was stirred at r.t. for 0.5 h under Ar. To this catalyst solution was added successively a hydroxymethylphosphine sulfide derivative, aryl bromide or triflate (1.2 eq), solvent (toluene or THF), and base (2.0 eq). The reaction mixture was stirred at 60-80 °C for 0.5-24 h under Ar. After cooling to r.t., the mixture was quenched with aqueous 1N HCl. The resulting mixture was extracted with ethyl acetate, and the combined organic layer was dried and evaporated to dryness. The residue was purified by column chromatography on silica gel to give the product.

Acknowledgements

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Keywords: P–C coupling • aryl bromide • aryl triflate • hydroxymethylphosphine sulfide derivative• Pd catalyst

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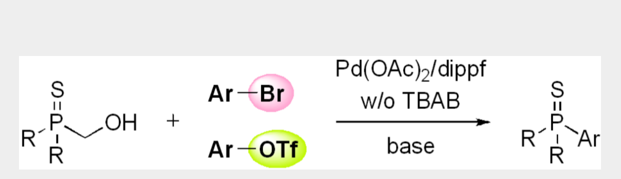

A powerful method for the versatile phosphine synthesis: The P–C coupling of hydroxymethylphosphine sulfide derivatives with various aryl bromides and triflates to yield triarylphosphine sulfides has been developed. The new method was successfully applied to the sequential triple coupling of an orthogonally protected precursor to give an unsymmetrically substituted triarylphosphine sulfide.

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