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Palladium-catalyzed Mizoroki–Heck coupling reactions using sterically bulky phosphite ligand

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ABSTRACT

A new catalytic system based on palladium-phosphite for Mizoroki–Heck coupling reactions of aryl iodide and bromide is described. An air-stable phosphite ligand afforded the desired products with high yields in the palladium-catalyzed Mizoroki–Heck reactions. The coupling of aryl iodides was optimized with 0.5 mol% Pd(OAc)$_2$, 1 mol% phosphite **2**, and K_2CO_3 in DMF solvent. For the coupling of aryl bromides, 1 mol% Pd(OAc)$_2$ and 5 mol% phosphite **2** were required with Na_2CO_3 as base. As a coupling partner alkene, *n*-butyl acrylate, *t*-butyl acrylate, styrene and *N*-*t*-butyl acrylamide all showed good yields.

Palladium-catalyzed carbon–carbon bond forming reactions have received much attention in research into organic synthesis for decades [1]. The most general reaction types are Kumada [2,3], Nigishi [4,5], Suzuki–Miyaura [6,7], Stille-Migita [8,9], Hiyama [10], Sonogashira [11,12] and Mizoroki–Heck reactions [13–15], using organometallic reagents such as Mg, Zn, B, Sn, Si and Cu as the coupling partner, except for the Mizoroki–Heck reaction, which is the coupling reaction of aryl and alkenyl halides with alkene derivatives. Since the first report by Mizoroki and Heck, numerous studies have investigated the development of this type of reaction. Like other type of palladium-catalyst coupling reactions, Mizoroki–Heck reaction's activity is also highly dependent on the nature of the ligand, for example, its electronic and steric effect [16]. Therefore, most studies have focused on the development of suitable ligand systems. Recently, sterically bulky monodentate phosphine [17,18] and *N*-heterocycle carbene [19,20] have been developed and afforded high activity. However, alkyl phosphine ligands are not stable toward oxygen and moisture, and most of the *N*-heterocyclic carbene ligands required a cumbersome synthetic step. To overcome these problems, we have examined sterically bulky phosphite ligands as shown in Fig. 1. Whereas phosphite compound **1** has been employed as a ligand in the palladium- or nickel-catalyzed reactions, including Mizoroki–Heck reaction [21,22], phosphite **2** has received less attention. Recently, we reported the Hiyama reaction [23] and homocoupling of aryl halides [24] using palladium-phosphite **2** catalytic system. In order to expand the scope of palladium-catalyzed coupling reaction using phosphite **2**, we attempted to apply phosphite **2** as a ligand in the Mizoroki–Heck reaction.

To investigate the reactivity of phosphite as ligand, we first employed 4-iodotoluene and *n*-butyl acrylate as the standard substrates. Their coupling reactions were carried out under a variety of palladium sources, bases and solvents. The results are summarized in Table 1. Among the tested bases, potassium carbonate was the most effective base for the coupled product (entry 1), while other bases such as Cs_2CO_3, Na_2CO_3 and K_3PO_4 gave acceptable yields of 97%, 94% and 90%, respectively (entries 2–4). Replacement of inorganic bases by organic base such as DBU afforded low product yield (entry 5). All the tested palladium sources showed good reactivities independent of their oxidative state (entries 6–8). Polar solvents gave the desired product in moderate to good yields (entries 9 and 10); however, no coupled product was formed in nonpolar solvents such as *p*-xylene (entry 11). As the reaction temperature was decreased to 80 °C, 4-iodotoluene was not completely converted (entry 12). Therefore, the optimized condition for the Mizoroki–Heck reaction of aryl iodide substrate is 0.5 mol% Pd(OAc)$_2$, 1.0 mol% phosphite **2**, 1.5 eq. K_2CO_3 and DMF at 120 °C for 3 h. This optimized condition was then applied to the aryl bromide substrate such as 4-bromotoluene. However, the product yield was very low yield even at a palladium-catalyst loading of 2.5 mol% and a reaction temperature of 140 °C (entry 13). To increase the product yield, we investigated the reaction condition for the aryl bromide substrates and found that the base is the most important factor in the Mizoroki–Heck reaction of 4-bromotoluene

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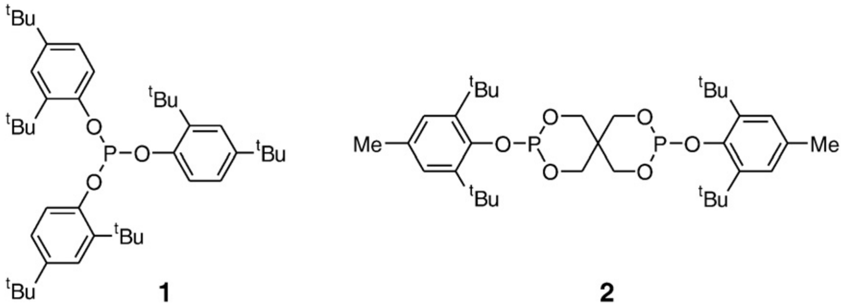

1 2

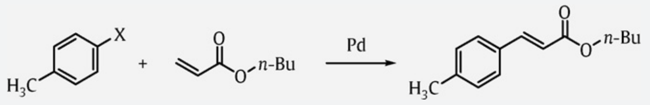
Fig. 1. Phosphite compounds.

and *n*-butyl acrylate. Among the tested bases, only Na_2CO_3 showed an acceptable product yield (64%) (entry 15), whereas the other inorganic bases, which showed good reactivity for aryl iodide, afforded low yields. To improve the reaction yield, we varied the content of palladium and ligand and maximized the coupled product yield at 81% with 1 mol% palladium and 5 mol% phosphate (entry 18). Despite the doubling of the mole ratio of the catalyst, the yield was not improved (entry 17). As expected, when the reaction was carried out without the phosphite ligand, the desired product was formed with very low yield (entry 19).

On the basis of the optimized conditions, we next carried out the Heck coupling reactions with a variety of aryl iodides and alkene derivatives (Table 2) [25]. The coupling reactions of *n*-butyl acrylate and aryl iodides showed good yields (entries 1–7). The electron neutral aryl iodide afforded the desired product with 94% yield (entry 1). In the case of iodoanisole derivatives, sterically hindered 2-iodoanisole showed a slightly lower yield than 4-iodoanisole (entries 3 and 4). Aryl iodides having an electron withdrawing substituent gave the coupled product in good yields, and showed chemoselectivity to iodide (entry 6). The iodonaphthalene required a longer reaction time than the other substrates, and afforded the desired product with 98% yield in 12 h. The coupling reactions of 4-iodotoluene and other alkene derivatives such as *t*-butyl acrylate, *N*-*t*-butylacrylamide and styrene showed good yields (entries 8, 9 and 10).

Next, a variety of aryl bromides was employed as coupling partner with *n*-butyl acrylate in the Heck reaction using the palladium-phosphite **2** catalytic system. The results are summarized in Table 3 [26]. Electron neutral aryl bromide, bromobenzene, gave the desired coupled product in 70% yield (entry 1). Aryl bromides containing an electron donating group produced the corresponding coupled product in moderate yields (entries 2–7). Among the bromoanisole derivatives, 2-bromoanisole exhibited the lowest yield (entry 3). However, the heteroaromatic bromides 3-bromopyridine and 2-bromothiophene afforded the desired coupled product in good yield of 87% and 70%,

Table 1
The optimized reaction condition for palladium-catalyzed Mizoroki–Heck reaction.[a]

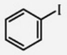
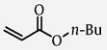
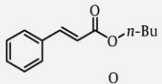
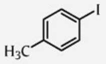
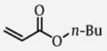
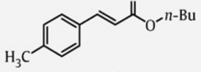
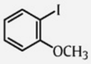
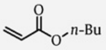
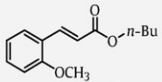
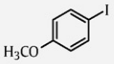
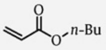
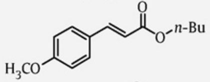
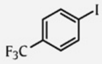
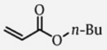
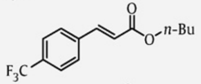
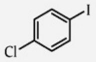
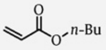
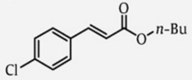
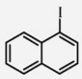
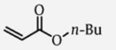
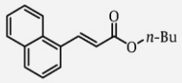
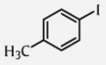
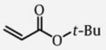
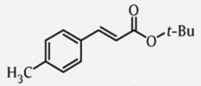
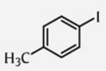
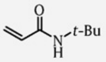
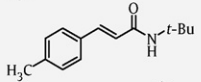
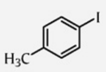
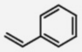
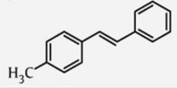


Entry	X	Pd	Pd/L (mol%)	Base	Solvent	Temp	Conv. (%)[b]	Yield (%)[b]
1	I	$Pd(OAc)_2$	0.5/1	K_2CO_3	DMF	120	100	99
2	I	$Pd(OAc)_2$	0.5/1	Cs_2CO_3	DMF	120	100	97
3	I	$Pd(OAc)_2$	0.5/1	Na_2CO_3	DMF	120	100	94
4	I	$Pd(OAc)_2$	0.5/1	K_3PO_4	DMF	120	94	90
5	I	$Pd(OAc)_2$	0.5/1	DBU	DMF	120	30	21
6	I	$Pd_2(dba)_3$	0.5/1	K_2CO_3	DMF	120	100	98
7	I	$Pd(CH_3CN)_2Cl_2$	0.5/1	K_2CO_3	DMF	120	100	99
8	I	$Pd(acac)_2$	0.5/1	K_2CO_3	DMF	120	100	98
9	I	$Pd(OAc)_2$	0.5/1	K_2CO_3	DMAc	120	77	72
10	I	$Pd(OAc)_2$	0.5/1	K_2CO_3	DMSO	120	97	94
11	I	$Pd(OAc)_2$	0.5/1	K_2CO_3	*p*-xylene	120	3	0
12	I	$Pd(OAc)_2$	0.5/1	K_2CO_3	DMF	80	90	87
13	Br	$Pd(OAc)_2$	2.5/5	K_2CO_3	DMF	140	35	15
14	Br	$Pd(OAc)_2$	2.5/5	Cs_2CO_3	DMF	140	37	25
15	Br	$Pd(OAc)_2$	2.5/5	Na_2CO_3	DMF	140	75	64
16	Br	$Pd(OAc)_2$	2.5/5	K_3PO_4	DMF	140	16	9
17	Br	$Pd(OAc)_2$	2/10	Na_2CO_3	DMF	140	100	68
18	Br	$Pd(OAc)_2$	1/5	Na_2CO_3	DMF	140	100	81
19	Br	$Pd(OAc)_2$	1/0	Na_2CO_3	DMF	140	11	5

[a] Reaction condition: 4-halotoluene (0.3 mmol), *n*-butyl acrylate (0.4 mmol), base (0.45 mmol), catalytic amount of palladium and phosphite **2** were reacted.

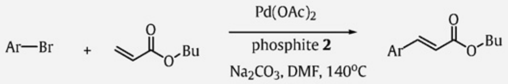
[b] Determined by GC with internal standard (naphthalene).

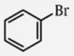
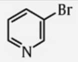
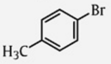
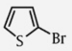
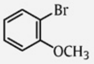
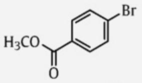
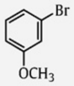
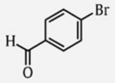
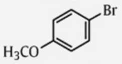
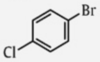
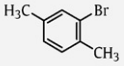
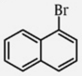
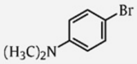
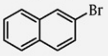
Table 2
The Mizoroki–Heck reaction of aryl iodides and alkene derivatives[a].

Entry	ArI	Alkenes	Products[b]	Yield (%)[c]
1				94
2				99
3				73
4				95
5				96
6				92
7				98[d]
8				96
9				89
10				95

[a]Reaction condition: ArI (3.0 mmol), alkene (4.0 mmol), $Pd(OAc)_2$ (0.015 mmol), phosphite **2** (0.03 mmol), K_2CO_3 (4.5 mmol) and DMF (15.0 mL) were stirred at 120 °C for 6 h. [b]All compounds were characterized by comparing the results of gas chromatography (GC) analysis, ^1H and ^{13}C NMR spectra with authentic samples or literature data. [c]Isolated yield. [d]Reaction time was 12 h.

Table 3
The Mizoroki–Heck reaction of Aryl bromides and *n*-butyl acrylate[a,b].



Entry	ArBr	Yield (%)^{c}	Entry	ArBr	Yield (%)^{c}
1		70	8		87
2		81	9		70
3		35	10		96
4		56	11		76
5		40	12		99
6		46	13		98
7		65	14		99

[a] Reaction condition: ArBr (3.0 mmol), *n*-butyl acrylate (4.0 mmol), Pd(OAc)$_2$ (0.03 mmol), phosphite **2** (0.15 mmol), Na$_2$CO$_3$ (4.5 mmol) and DMF (15.0 mL) were stirred at 140 °C for 12 h. [b] All compounds were characterized by comparing the results of gas chromatography (GC) analysis, ^{1}H and ^{13}C NMR spectra with authentic samples or literature data. [c] Isolated yield.

respectively (entries 8 and 9). Activated aryl bromides, which have an electron donating group, showed good yields (entries 10–12). This catalytic system showed good chemoselectivity. In the case of 4-bromochlorobenzene, the coupling reaction occurred only at the bromide site. All naphthyl bromides showed excellent yields (entries 13 and 14).

Based on the previous report, we suggested that the larger π-acceptor ability of the phosphite moiety increases the reaction rates, and the sterically bulky group in phoshite might give the positive effect in the reductive elimination step [27]. To investigate the coordination manner of phosphite **2** in the Mizoroki–Heck coupling reaction, NMR experiment was carried out. When Pd(OAc)$_2$ and phosphite **2** were treated with the molar ratio of 1 to 2 in the mixture of DMF-d$_7$ and CDCl$_3$, only one peak was observed and no free phosphorus peak in ^{31}P NMR [28]. Which means that phosphite **2** might coordinate to the palladium, and stabilize the complex. The exact coordination manner is not identified at this point. Further studies of coordination manner are in progress in our laboratory.

In conclusion, we first employed sterically bulky phosphite **2** as a ligand in the Heck coupling reactions and investigated its catalytic activity with palladium in the coupling of aryl iodides or bromides with alkene derivatives. The coupling of aryl iodides was optimized with 0.5 mol% Pd(OAc)$_2$ and 1 mol% phosphite **2** and most of the inorganic bases showed good reactivities. However, 1 mol% Pd(OAc)$_2$ and 5 mol% phosphite **2** were needed for the coupling of aryl bromides, and only Na$_2$CO$_3$ afforded the desired product in high yield. *N*-Butyl acrylate, *t*-butyl acrylate, *N*-*t*-butyl acrylamide and styrene were used as alkene derivatives, and all showed good reactivities. To the best of our knowledge, phosphite **2** has never been reported as a ligand in Heck Coupling Reactions. This catalytic system can be used without resort to dry reagents or anaerobic conditions. In addition, considering given the very low cost of arylphosphites as ligands, this method has a promising potential as a convenient route for functionalizing aryl alkene compounds.

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[25] Typical Experimental Procedure: Pd(OAc)$_2$ (3.4 mg, 0.015 mmol), phosphite **2** (19.0 mg, 0.030 mmol), aryl iodide (3.0 mmol) and alkene (4.0 mmol) were combined with K$_2$CO$_3$ (622 mg, 4.5 mmol) in DMF (10.0 mL). The resulting mixture was placed in an oil bath at 120 °C for 6 h. The reaction was poured into 20 mL of saturated aqueous ammonium chloride and extracted with Et$_2$O (3×20 mL). The combined ether extracts were washed with brine (60 mL), dried over MgSO$_4$, and filtered. The solvent was removed under vacuum. The crude product was purified by flash chromatography (15% ethyl acetate in hexane).
[26] Typical Experimental Procedure: Pd(OAc)$_2$ (3.4 mg, 0.015 mmol), phosphite **2** (19.0 mg, 0.030 mmol), aryl bromide (3.0 mmol) and alkene (4.0 mmol) were combined with Na$_2$CO$_3$ (477 mg, 4.5 mmol) in DMF (10.0 mL). The resulting mixture was placed in an oil bath at 140 °C for 8 h. The reaction was poured into 20 mL of saturated aqueous ammonium chloride and extracted with Et$_2$O (3×20 mL). The combined ether extracts were washed with brine (60 mL), dried over MgSO$_4$, and filtered. The solvent was removed under vacuum. The crude product was purified by flash chromatography (15% ethyl acetate in hexane).
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[28] ^{31}P NMR (DMF-d$_7$/CDCl$_3$) phosphite **2**: δ124.83; The complex of Pd(OAc)$_2$ and phosphite **2**: $\delta-9.23$.