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Efficient Suzuki cross-coupling reactions using bulky phosphines

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Abstract

A series of phosphines, P(biphenyl)$_n$Ph$_{3-n}$ has been used as co-catalyst in the palladium catalyzed Suzuki cross-coupling reaction of aryl-bromides and -chlorides. The effects of the phosphine, palladium source, base, solvent and promoter salt were investigated. High conversions and turnovers were obtained in all studied phosphines, particularly using P(biphenyl)Ph$_2$ which can be interpreted by the contribution of steric and electronic effects.

Keywords: Suzuki coupling reaction; Phosphine; Palladium catalyst

1. Introduction

In recent years, palladium catalyzed Suzuki cross-coupling reactions (Scheme 1) have increasingly employed for construction of unsymmetrical biaryl units which have wide range of applications such as pharmaceutical, herbicides, natural products as well as engineering [1–6]. The key advantages of the Suzuki coupling compared to other coupling methods [7–12], are the mild reaction conditions and the commercial availability of the diverse boronic acids that are environmentally safer than the other organometallic reagents [13]. In addition, the handling and removal of boron-containing byproducts is easy when compared to other organometallic reagents, especially in a large-scale synthesis [14].

While PPh$_3$ is an available co-catalyst [15], it usually requires elevated reaction temperatures to function efficiently, and tend to be unreactive towards aryl-chloride substrates [16]. Also, PPh$_3$ tends to produce phenyl–aryl coupling byproducts [17]. Excellent and instructive Buchwald's reports [3] on the reactivity of bulky phosphines encouraged us to use biphenyl phosphines in the Suzuki reactions. Herein, we wish to report the high conversions and turnovers in the Suzuki cross-coupling reactions of phenylboronic acid with some aryl-halides (Scheme 2). Interestingly, the conversion shows an optimum in the middle of bulkiness and basicity order of the studied phosphines.

2. Experimental

2.1. Materials and techniques

All chemicals were purchased from Fluka and/or Merck companies. ^{1}H (400 MHz), ^{13}C (100 MHz) and ^{31}P (162 MHz) NMR spectra were recorded on a Bruker Avance Spectrometer. Shimadzu GC 14-A and thin layer chromatography on precoated silica gel fluorescent 254 nm (0.2 mm) were used for monitoring the reactions. Conversions were determined by GC, based on bromoacetophenone. Turnovers were defined as mol of product per mol of catalyst. Elemental analysis was performed using CHN Herause rapid model. The cross-coupling biphenyl product was characterized by its ^{1}H NMR spectrum and melting points.

2.2. Preparation of P(biph)$_3$ (***III***): typical procedure [18]

To a freshly prepared diethyl ether solution of 4-lithiobiphenyl (33 mmol, 5.3 g) at −78 °C was added freshly distilled PCl$_3$ (10 mmol, 1.38 g) in 5 ml of anhydrous diethyl ether dropwise with stirring over 20 min. After stirring at −78 °C (at this temperature organolithium reagent has sufficient stabil-

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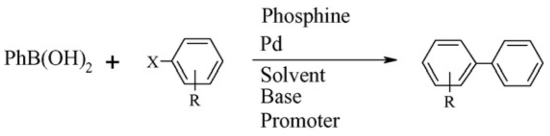


Scheme 1. The Suzuki–Miyaura cross-coupling reaction.

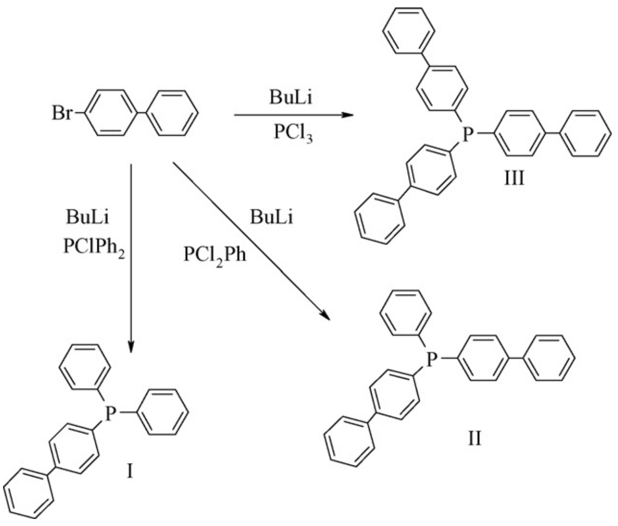
ity and activity) for 30 min, the reaction mixture was allowed to warm to room temperature. After stirring at room temperature for 1.5 h, the reaction mixture was hydrolyzed with HCl (1N, 10 ml), followed by addition of chloroform and then, the organic solution was separated and dried over $MgSO_4$. The solvent was removed at reduced pressure. The residue was washed with methanol (4× 5 ml), to yield the crude product (4.12 g, 84.1%). The crude product was recrystallized from a chloroform/hexane (1/4) to yield desired pure product (3.85 g, 78.6%).

In order to prepare $P(biph)_2Ph$ (**II**), and $P(biph)Ph_2$ (**I**), similar procedures were used using solutions of 4-biphenyllithium (22 mmol, 3.52 g and 11 mmol, 1.76 g, respectively) in dry diethyl ether and solutions of PCl_2Ph (10 mmol, 1.78 g) or $PClPh_2$ (10 mmol, 2.25 g) in dry diethyl ether instead of PCl_3. The yields of pure products were 3.11 g (75.1%) for (**II**) and 2.63 g (77.8%) for (**III**), respectively.

Characterization data of phosphines—**I**, ^{1}H NMR ($CDCl_3$): δ 7.10–7.40 (m); $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ −5.89 (s); anal. calc. for $C_{24}H_{19}P$: C, 85.21%, H, 5.62%, found: C, 84.84%, H, 5.68%, mp = 135–137 °C; **II**, ^{1}H NMR ($CDCl_3$): δ 7.10–7.40 (m); $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ −9.68 (s); anal. calc. for $C_{30}H_{23}P$: C, 86.96%, H, 5.56%, found: C, 87.12%, H, 5.65%, mp = 152–154 °C; **III**, ^{1}H NMR ($CDCl_3$): δ 7.15–7.35 (m); $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ −12.36 (s); anal. calc. for $C_{36}H_{27}P$: C, 88.16%, H, 5.51%, found: C, 88.24%, H, 5.48%, mp = 169–171 °C.

2.3. *Preparation of n-BuPyBF$_3$Cl: typical procedure*

Pyridine (96 g, 1.2 mol) in 10% molar excess was refluxed with *n*-BuCl (105 g, 1.1 mol) for 72 h in dark. The reaction mixture was cooled and the solid obtained was recrystallized from MeCN/EtOAc, filtered under vacuum, washed with EtOAc and quickly transferred to a bottle while still moist with solvent. The excess solvent was then removed under vacuum. Then 1 mol BF_3 was added to *n*-BuPyCl (0.5 mol) at room temperature under N_2 to give the desired ionic liquid.



Scheme 2. The route for the synthesis of phosphines.

Table 1
Effects of phosphines on Suzuki coupling reactions[a]

Entry	Halide	$Pd(OAc)_2$ (mol%)	Phosphine	Time (h)	Conversion[b] (%)	TON
1	Br	1	**I**	1	100	100
2	Br	1	**II**	1	100	100
3	Br	1	**III**	5	85	85
4	Cl	1	**I**	5	82	82
5	Cl	1	**II**	12	70	70
6	Cl	1	**III**	5	67	67
7	Br	0.001	**I**	12	75	75000
8	Br	0.001	**II**	24	55	55000
9	Br	0.001	**III**	24	40	40000
10	Cl	0.001	**I**	24	45	45000
11	Cl	0.001	**II**	24	36	36000
12	Cl	0.001	**III**	24	15	15000

[a] Reaction conditions: 1.0 mmol 4-haloacetophenone, 4 mol% phosphine, 1.5 mmol $PhB(OH)_2$, 2.0 mmol K_3PO_4, 5 ml toluene, 1 ml water, 100 °C.

[b] Determined by GC based on aryl-halide.

2.4. *General procedure for the Suzuki cross-coupling (entry 1, Table 1)*

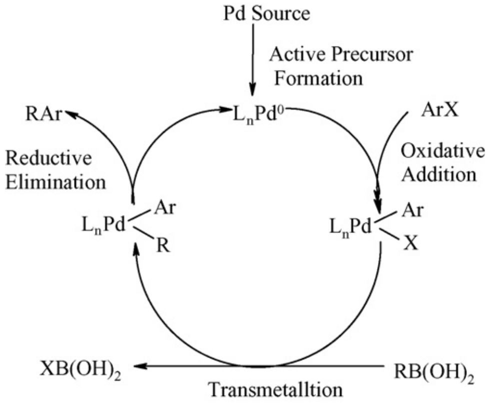
Reaction tube was charged with $PhB(OH)_2$ (1.5 mmol), K_3PO_4 (2 mmol), and **I** (4 mol%) under a dry nitrogen atmosphere. A solution of 4-bromoacetophenone (1.0 mmol in 2 ml of freshly dried toluene) along with a solution of palladium acetate (1 mol% in 3 ml of freshly dried toluene) was added through a rubber septum. After addition of water (1 ml), the resulting mixture was heated at 100 °C for 1 h. After extraction with ether, the organic phase was dried over $MgSO_4$. The solvent was evaporated and a crude product was obtained. For determination of conversions and yields by GC, a small portion of the crude product was added to a solution of hexadecane as internal standard in CH_2Cl_2 (1 ml). To isolate the product, the crude product was purified by chromatography with hexane/ethylacetate (6:1). Yield 0.172 g (87.6%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.65 (s, 3H, methyl of acetyl), 7.35–7.47 (m, 3H), 7.6–7.65 (m, 2H), 7.70 (d, 2H, *J* = 8 Hz), 8.0 (d, 2H, *J* = 8 Hz). mp = 119–120 °C.

3. Results and discussion

3.1. *Effect of the phosphines on cross-coupling reactions*

All three phosphines have excellent reactivity in the presence of Bu_4NBr promoter and high catalyst concentration (Table 1). However, at lower catalyst loading and/or less reactive aryl-chlorides, the order of reactivity for the phosphines is as follows:

$P(biph)Ph_2 > P(biph)_2Ph > P(biph)_3$



Scheme 3. General mechanism for Suzuki cross-coupling reaction.

Recent mechanistic studies have appeared that monoligated palladium species play an important role in the cross-coupling reactions [19]. To understand the role of the phosphines, it is important to consider the mechanism step by step (Scheme 3). The first step is the generation of catalytically active P–Pd(0) species from the corresponding Pd(**II**) precursor; mechanistic investigation reveal that, in this step, increasing the bulkiness and basicity of the phosphines, enhances the rate of phosphine dissociation and reduction of Pd. After generation of the active catalyst, the oxidative addition of aryl-halide to the Pd(0) center takes place which is favored by electron-rich and less bulky phosphines. Following a transmetalation reaction, the final step is the reductive elimination of the product, the rate of which is usually increased by the coordination of less basic and more bulky phosphines.

The ^{31}P NMR chemical shifts are excellent basis for obtaining information about the electron density of the phosphines [20] (Eq. (1)):

$$\delta = -3.3 + \sum \sigma_n^{\mathrm{p}} \quad (n = 1 - 3) \tag{1}$$

where σ^{p} is the contribution of biphenyl in decreasing the ^{31}P chemical shift from the reference value (PPh$_3$: $\delta = -3.3$ ppm, 85% H_3PO_4). The negative increment value for biphenyl (−3.097 calculated based on Eq. (1) show that the electron donating ability of the phosphine increases with increasing the number of biphenyl substituents on the phosphorus atom (Table 2).

Steric characteristics of the phosphines were studied using the Tolman's cone angle [21] (Table 2). The cone angles of P(biph)Ph$_2$ and P(biph)$_2$Ph were determined according to linear increment of the cone angle from PPh$_3$ to P(biph)$_3$ per each biphenyl substituent (Eq. (2)):

$$\Theta = 145 + \sum \delta_n^{\mathrm{p}} \quad (n = 1 - 3) \tag{2}$$

where, δ^{p} is the contribution of biphenyl in increasing the cone angle from the reference value (PPh$_3$: $\Theta = 145°$). The positive increment value for biphenyl (18.3° calculated based on Eq. (2) show that the bulkiness of the phosphine increases with increasing the number of biphenyl substituents on the phosphorus atom (Table 2).

Thus, based on above mentioned discussion, P(biph)$_3$ is the most basic and bulky ligand in the phosphine series studied; the higher reactivity of P(biph)Ph$_2$ may be attributed to an optimum contribution of electronic and steric effects. Such optimum is more consistent with oxidative addition as rate the determining step.

3.2. *Effect of the catalyst*

The key compound in the reaction is the catalyst. Thus, we employed Pd(OAc)$_2$, Pd(dba), Pd$_2$(dba)$_3$ (dba, dibenzilidene acetone), Pd/C. PdCl$_2$, and Pd(PPh$_3$)$_4$ as catalyst for initial optimizations. The results (Table 3) show that all palladium derivatives have similar reactivity in high catalyst loading. These catalysts show their differences in reactivity only in the lower concentration. The 10^{-3} mol% solutions of Pd(OAc)$_2$, Pd(dba) and Pd$_2$(dba)$_3$ show higher reactivity compared to other palladium catalyst. The slow reaction of Pd(PPh$_3$)$_4$ and PdCl$_2$ may be due to slow initial dissociation (for Pd(PPh$_3$)$_4$) and reduction (for PdCl$_2$) pre steps [22]. The formation of some byproducts such as self coupling products, and coupling products of phosphine-bound phenyls are attributed for low yield of Pd(PPh$_3$)$_4$ [17]. The phenyl group of the PPh$_3$ becomes incorporated in the products giving scrambled derivatives. Under oxygen-free conditions, homo-coupling products can be avoided [23]. In the case of palladium acetate, preheating of the palla-

Table 2
Steric and electronic effects of the phosphines

Phosphine	Θ (°)	^{31}P chemical shift (ppm)
III	200[a]	−12.36
II	182[b]	−9.68
I	163[b]	−5.89
PPh$_3$	145[a]	−3.3

[a] From Ref. [21].
[b] Calculated based on Eq. (2).

Table 3
Effects of catalyst on the Suzuki coupling reactions[a]

Entry	Catalyst (mol%)	Time (h)	Conversion[b] (%)	TON
1	Pd(OAc)$_2$ (1)	1	100	100
2	Pd(PPh$_3$)$_4$ (1)	1	100	100
3	PdCl$_2$ (1)	1	96	96
4	Pd(dba)$_2$ (1)	1	100	100
5	Pd$_2$(dba)$_3$ (1)	1	100	100
6	Pd/C (1)	1	95	95
7	Pd(OAc)$_2$ (0.1)	1	95	950
8	Pd(OAc)$_2$ (0.01)	1	75	7500
9	Pd(OAc)$_2$ (0.01)	6	95	9500
10	Pd(OAc)$_2$ (0.001)	12	75	75000
11	Pd(PPh$_3$)$_4$ (0.001)	12	50	50000
12	PdCl$_2$ (0.001)	12	42	42000
13	Pd(dba)$_2$ (0.001)	12	68	68000
14	Pd$_2$(dba)$_3$ (0.001)	12	70	70000
15	Pd/C (0.001)	12	60	60000

[a] Reaction conditions: 1.0 mmol 4-bromoacetophenone, 4 mol% P(biph)Ph$_2$, 1.5 mmol PhB(OH)$_2$, 2.0 mmol K$_3$PO$_4$, 5 ml toluene, 1 ml water, 100 °C.
[b] Determined by GC based on aryl-halide.

Table 4
Effect of the base on Suzuki coupling reactions[a]

Entry	Base	Conversion[b] (%)	TON
1	K_3PO_4	100	100
2	KF	65	65
3	Cs_2CO_3	100	100
4	Na_2CO_3	85	85
5	NEt_3	70	70
6	K_2CO_3	90	90

[a] Reaction conditions: 1.0 mmol 4-bromoacetophenone, 1 mol% $Pd(OAc)_2$, 4 mol% $P(biph)(Ph)_2$, 1.5 mmol $PhB(OH)_2$, 2.0 mmol base, 5 ml toluene, 1 ml water, 100 °C, 1 h.

[b] Determined by GC based on aryl-halide.

dium catalyst to about 60 °C, significantly increases the conversion of Suzuki reaction. Therefore, based on experimental data, $Pd(OAc)_2$ was selected as palladium source.

3.3. *Effect of the base*

It is known that the base is involved in several steps of the catalytic cycle, most notably in the transmetallation step where, hydrolysis of the Ar-PdL_2–X intermediate to more reactive Ar-PdL_2–OR is known to accelerate the rate [24]. A good to excellent conversion was observed in most of the bases (Table 4) except KF and NEt_3. In the case of the phosphine **I**, the conversion of the reaction shows a dramatic decrease using the Na_2CO_3. Among the studied bases, K_3PO_4 has proved to be the base of choice.

3.4. *Effect of the solvent*

Among the commonly used organic solvents (toluene, DMF, THF, and dioxane), the best results were obtained with toluene and dioxane and in some extent with DMF (Table 5). During the initial optimizations, we found that the reactions proceed in high yields only in the presence of water. In the water-free system, negligible coupling was observed, but addition of incremental amounts of water led to a very high conversion of aryl-halides. Interestingly, reactions in two ionic liquids, butylpyridiniumechlorotriflouroborate, $BuPyBF_3Cl$, and butylimidazoliumechlorotriflouroborate, $BmimBF_3Cl$, led to good conversion.

Table 5
Effects of the solvent on Suzuki coupling reactions[a]

Entry	Solvent	*T* (°C)	Conversion[b] (%)	TON
1	Toluene	100	100	100
2	Dioxane	100	100	100
3	DMF	100	85	85
4	THF	70	74	74
5	DMSO	100	55	55
6	DME	80	65	65
7	$BuPyBF_3Cl$	r.t.	80	80
8	$BmimBF_3Cl$	r.t.	85	85

[a] Reaction conditions: 1.0 mmol 4-bromoacetophenone, 1 mol% $Pd(OAc)_2$, 4 mol% $P(biph)(Ph)_2$, 1.5 mmol $PhB(OH)_2$, 2.0 mmol K_3PO_4, 5 ml solvent, 1 ml water, 100 °C, 1 h.

[b] Determined by GC based on aryl-halide.

Table 6
Effects of the promoter on Suzuki coupling reactions[a]

Entry	Base	Promoter	*T* (°C)	Time (h)	Conversion[b] (%)	TON
1	KF	–	100	1	65	65
2	KF	Bu_4NBr	100	1	95	95
2	NEt_3	–	100	1	70	70
3	NEt_3	Bu_4NBr	100	1	85	85
5	K_3PO_4	–	r.t.	10	75	75
6	K_3PO_4	Bu_4NBr	r.t.	10	95	95

[a] Reaction conditions: 1.0 mmol 4-bromoacetophenone, 1 mol% $Pd(OAc)_2$, 4 mol% $P(biph)(Ph)_2$, 1.5 mmol $PhB(OH)_2$, 2.0 mmol base, 0.4 mmol Bu_4NBr, 5 ml toluene, 1 ml water.

[b] Determined by GC based on aryl-halide.

These results are most important from environmental and industrial points of view [25]. Using ionic liquids, it is often possible to recycle the active palladium catalyst by simple extraction of biphenyl product and inorganic salts from the ionic liquid, which forms a tri-phasic system on adding water and a nonpolar solvent such as hexane [26]. We found that the recycled catalyst was able to recharge the reaction for three successive times and in all cases gave yields of over 70%. Also, addition of 2 mol% of the phosphine in each recycling step, retain the yield with no significant change.

3.5. *Effect of the promoter*

Comparison of the results revealed that the salt additive Bu_4NBr has a beneficial effect on the cross-coupling of aryl-chlorides especially, in the case of $Pd(OAc)_2$, and $PdCl_2$ (Table 6). Recently, Herrman and Böhm have reported a substantial improve of Heck coupling of aryl-chlorides in the presence of Bu_4NBr [27]. The role of the additive in not well understood but it is suggested that it is involved in the stabilization of anionic palladium species such as $[\text{Hal-Pd-ligand}]^-$ [28], or facilitation of the solvation of the organic substrates and activating the boronic acid by formation of $[ArB(OH)_3]^-[R_4N]^+$ [29]. Reetz and Westermann recently reported that Bu_4NBr is able to stabilize colloidal palladium nanoparticles that act as catalysts in the Suzuki coupling of aryl-bromides [30].

Table 7
The effect of temperature on Suzuki coupling reactions[a]

Entry	*T* (°C)	Time (h)	Conversion[b] (%)	TON
1	100	1	100	100
2	80	1	96	96
3	50	1	70	70
4	r.t.	1	35	35
5[c]	r.t.	1	90	45
6	r.t.	10	75	75
7	r.t.	24	95	95

[a] Reaction conditions: 1.0 mmol 4-bromoacetophenone, 1 mol% $Pd(OAc)_2$, 4 mol% $P(biph)(Ph)_2$, 1.5 mmol $PhB(OH)_2$, 2.0 mmol K_3PO_4, 5 ml toluene, 1 ml water, 100 °C.

[b] Determined by GC based on aryl-halide.

[c] Two mole percent $Pd(OAc)_2$ and 8 mol% $P(biph)(Ph)_2$.

Table 8
Suzuki coupling of aryl-halides[a]

Entry	Halide	R	Time (h)	Conversion[b] (%)	Yield [c](%)	mp (°C)	
						Found	Reported[d]
1	Br	4-COMe	1	100	87.6	119–120	120–121
2	Br	H	1	95	83.5	70–71	71
3	Br	4-Me	1	92	80.3	48–49	49–50
4	Br	4-OMe	1	86	78.4	90–91	91–92
5	Br	4-Ph	1	100	90.5	211–212	213
6	Cl	4-COMe	5	82	75.4	118–119	120–121
7	Cl	H	5	80	74.2	69–71	71
8	Cl	4-Me	5	75	68.5	48–49	49–50
9	Cl	4-OMe	5	71	64.2	89–90	91–92

[a] Reaction conditions: 1.0 mmol aryl-halide, 1 mol% $Pd(OAc)_2$, 4 mol% $P(biph)Ph_2$, 1.5 mmol $PhB(OH)_2$, 2.0 mmol K_3PO_4, 5 ml toluene, 1 ml water, 100 °C.
[b] Determined by GC based on aryl-halide.
[c] Isplated yield.
[d] From Ref. [33].

3.6. Effect of temperature on the Suzuki reaction

Although the reactions give excellent yields at the high temperatures, but running the reaction in a wide range of temperatures shows that, the Suzuki cross-coupling reactions can be employed in mild conditions (Table 7). The reactions need longer times at lower temperatures. On addition of salt promoter, the reaction yields increase substantially. Also, increasing the amount of the catalyst, improve the reaction yields.

3.7. Comparison of aryl-bromide and -chloride reaction

There are some drawbacks with the Pd-mediated Suzuki cross-coupling reaction in that only aryl-bromides and iodides can be used effectively. Recent progress on increasing the rate of aryl-chlorides resulted in overcoming this problem [31]. Stronger C–Cl bond strength is responsible to slower rate of reaction of aryl-chlorides, because oxidative addition step was suggested often the rate-determining step in cross-coupling catalytic cycles [24]. Efficiency of the obtained optimum conditions was investigated for a series of aryl-halides. Table 8 shows that $P(biph)Ph_2/Pd(OAc)_2$ is a high reactive catalyst system which can catalyze the Suzuki cross-coupling of even extremely electron-rich such as 4-chloroanisole (Table 8, entry 7) as well as less active aryl-bromides. The less reactive aryl-chloride seems to need more reaction times.

4. Conclusion

The new method described here appears to be highly competitive with other methods reported in the literature, and in some cases, better results are obtained, especially in terms of catalyst loading, reaction time and yields. In addition, preparation of the phosphines used in this method is easier than other methods [32].

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