

Suzuki cross-coupling reactions catalyzed by palladium complex of an inexpensive phosphinite, 2-diphenylphosphinoxynaphthyl

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Abstract

A facile and less expensive monophosphinite ligand 2-(diphenylphosphinoxy)-naphthyl, $C_{10}H_7OPPh_2$ (**1**) has been synthesized from the reaction of β -naphthol with chlorodiphenylphosphine. The mixture of $Pd(OAc)_2$ and **1** catalyzes the Suzuki cross-coupling of a variety of aryl halides with aryl boronic acids at room temperature or at 60 °C, giving generally high yields even under low catalytic loads. The effect of solvent, base and catalyst loading on the coupling reaction of aryl halide with arylboronic acid is also described.

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Keywords: Phosphine; Phosphinite; Suzuki cross-coupling reaction; Palladium; Metal complexes

1. Introduction

The palladium-catalyzed Suzuki cross-coupling reaction of aryl halides with arylboronic acids, is one of the most powerful tool for the preparation of unsymmetrical biaryl compounds [1], which has been applied to many areas, including herbicides [2] and natural product syntheses [3]. Triarylphosphine/Pd complexes have been the most commonly employed catalysts for the Suzuki reaction [1a]. Recently, improved catalyst systems for Suzuki coupling reactions have been described. Sterically demanding, electron rich phosphines, such as tri-*t*-butylphosphines and its analogs [4], di(*t*-butyl)aryl and dicyclohexylarylphosphines [5] have shown excellent activities in the Suzuki reaction for a variety of substrates. However, the major drawback of these catalyst systems is that the phosphine ligands are comparatively difficult to make or are rather more expensive. We were therefore interested in continuing our studies on high activity catalysts derived from inexpensive, easily synthesized ligand sets.

Bedford et al. [6] and Zapf and Beller [7] have shown that the phosphinites and even the electron-poor phosphites show very high activity in Suzuki and Heck coupling reactions. How-

ever, in these cases, the precatalyst or catalyst formed in situ are palladacyclic or orthopalladated complexes, which are known to be better catalysts than the other ordinary phosphinite coordinated *cis* or *trans* non-orthopalladated complexes. Very few reports are known where non-orthopalladated aryl-diphenylphosphinite complexes are used for Suzuki coupling reaction and those were generally carried out at drastic conditions [8]. In view of this and as a continuation of our work [9] in designing new phosphorus based ligands for exploring their organometallic chemistry and catalytic utility in organic synthesis [10], herein we report Suzuki cross-coupling reactions catalyzed by palladium complex of an inexpensive monophosphinite, 2-(diphenylphosphinoxy)-naphthyl (**1**) under mild conditions. A full report on the effect of solvent, base and catalyst loading on the coupling reaction of aryl halide with arylboronic acid is also described.

2. Experimental

2.1. Materials and methods

All experimental manipulations were carried out under an atmosphere of dry nitrogen or argon using standard Schlenk techniques. Solvents were dried and distilled prior to use by conventional methods. Ph_2PCl was purchased from Lancaster and all other chemicals were obtained from commercial sources

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and were used without further purification. The ^1H and $^{31}\text{P}\{^1\text{H}\}$ NMR (δ in ppm) spectra were obtained on a Varian VXR 300 spectrometer operating at frequencies of 300 and 121 MHz, respectively. The spectra were recorded in CDCl_3 solutions with CDCl_3 as an internal lock and TMS as internal standard and 85% H_3PO_4 was used as an external standard for $^{31}\text{P}\{^1\text{H}\}$ NMR, respectively. Positive shifts lie downfield of the standard. Microanalysis was carried out on a Carlo Erba Model 1106 elemental analyzer. GC analyses were performed on a Perkin-Elmer Clarus 500 GC fitted with packed column. Q-ToF Micro-mass experiments were carried out using Waters Q-ToF micro (YA-105).

2.2. Synthesis of 2-(diphenylphosphinoxy)-naphthyl, $\text{C}_{10}\text{H}_7\text{OPPh}_2$ (**1**)

A solution of Ph_2PCl (6.2 mL, 34.6 mmol) in 50 mL of diethyl ether was added dropwise to a mixture of β -naphthol (5 g, 34.6 mmol), Et_3N (4.8 mL, 34.6 mmol) and catalytic amount of 4-dimethylaminopyridine (DMAP) (0.002 g), also in diethyl ether (150 mL) at 0°C and the reaction mixture was stirred at room temperature for 16 h. The white suspension was filtered through celite to remove amine hydrochloride, filtrate was concentrated and cooled to 0°C to give white crystalline product **1**. It was recrystallized from CH_2Cl_2 /petroleum ether mixture at 25°C to get analytically pure product. Yield: 93% (10.6 g). Mp: $72\text{--}74^\circ\text{C}$. Anal. Calcd. for $\text{C}_{22}\text{H}_{17}\text{OP}$: C, 80.47; H, 5.22%. Found: C, 79.99; H, 5.23%. ^1H NMR (300 MHz, CDCl_3): δ 7.76 (s, 1H, Ar), 7.74 (d, 1H, Ar), 7.31–7.73 (m, 5H, Ar, 10H, OPPh_2). $^{31}\text{P}\{^1\text{H}\}$ NMR (121.4 MHz, CDCl_3): δ 109.1 (s).

2.3. General procedure for coupling reactions of aryl halides with boronic acid

In two-necked flask under an atmosphere of nitrogen was placed correct amount of catalyst from stock solution (made up by mixing $\text{Pd}(\text{OAc})_2$ and **1** in toluene). It was dried under vacuum and 5 mL of methanol or toluene was added to the flask. After stirring for 5 min, aryl halide (0.5 mmol), aryl boronic acid (0.75 mmol) and K_2CO_3 (0.138 g, 1 mmol) were added. The mixture was then stirred at room temperature or at required temperature for 2 h (6 h in case of aryl chlorides). The solvent was then removed under reduced pressure. The resultant resid-

ual mixture was diluted with water (10 mL) and Et_2O (10 mL), followed by extraction twice (2×6 mL) with Et_2O . The combined organic fraction was dried over MgSO_4 . An aliquot was taken with a syringe and subjected to GC. The conversion to the coupled product was determined by GC analysis using aryl halide or dodecane as internal standard.

3. Results and discussion

3.1. Preparation of 2-(diphenylphosphinoxy)-naphthyl (**1**)

Reaction of β -naphthol with one equivalent of chlorodiphenylphosphine in diethyl ether in the presence of triethylamine and a catalytic amount of 4-dimethylaminopyridine (DMAP) at 0°C affords the monophosphinite, $\text{C}_{10}\text{H}_7\text{OPPh}_2$ (**1**) in 93% yield (Scheme 1).

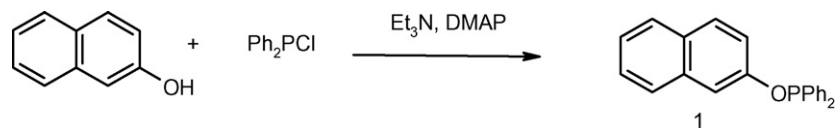
The $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum of **1** shows a single resonance at 109.1 ppm. Elemental analysis of **1** is in good agreement with the calculated values.

3.2. Catalytic Suzuki cross-coupling reactions

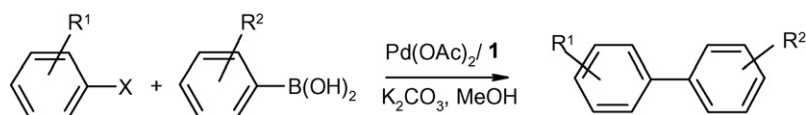
Based on our recent success [10] with palladium(II) acetate and bisphosphinite as a catalyst system in Suzuki reactions of aryl bromides here we employed a similar protocol, 2-(diphenylphosphinoxy)-naphthyl (**1**) for the Suzuki coupling reactions of aryl halides with arylboronic acids (Scheme 2). We have also investigated the effects of catalyst loading, base employed and the solvents used on the coupling of 4-bromoacetophenone with phenylboronic acid in order to optimize the reaction conditions.

3.2.1. Effect of catalyst loading on coupling reaction

It is significant to accomplish good yields using minimum amounts of catalysts. Therefore, we have examined the effect of catalyst loading on a convenient coupling between 4-bromoacetophenone and phenylboronic acid at room temperature. Good yields were obtained from normal catalyst loads down to a level of 0.01 mol% (Table 1). A moderate yields (48% and 43%) were obtained even at catalyst loading as low as 0.005 and 0.0025 mol% with a TON of 9600 and 17,200, respectively. These are the indications of an effective catalytic system that merits more downstream explorations.

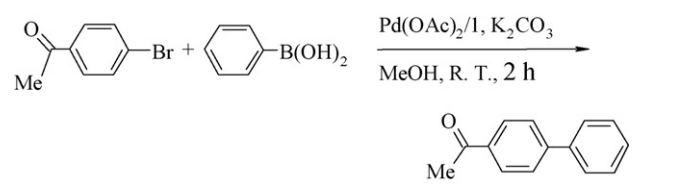


Scheme 1.



Scheme 2.

Table 1
Influence of low catalyst loading on the coupling reaction^a



Entry	Amount of catalyst (mol%) Pd(OAc) ₂ /1	Conversion (%)	TON ^a
1	0.05	100	2000
2	0.02	99	4950
3	0.01	87	8700
4	0.005	48	9600
5	0.0025	43	17200

^a In units of [(mol product)/(mol Pd)].

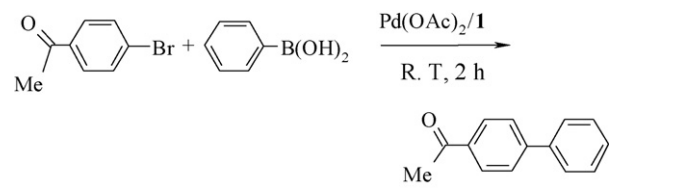
3.2.2. Effect of base on coupling reaction

To examine the effect of base, a series of bases were taken into consideration for the coupling between 4-bromoacetophenone and phenylboronic acid. The most common and inexpensive bases such as K₂CO₃, Na₂CO₃, Et₃N were found to be more effective (Table 2). Surprisingly, Cs₂CO₃ is found to be less effective in the present system although it is a common base for several Pd/phosphine Suzuki reactions [11]. Similarly, we found the commonly used KF is also less effective in the present studies although which is found to be an efficient base for Pd₂(dba)₃/phosphine Suzuki type catalytic reactions [12]. This may be due to the relatively less basic nature of phosphinite as compared to phosphines.

3.2.3. Effect of solvent on coupling reaction

An investigation of the influence of the solvents on coupling between 4-bromoacetophenone and phenylboronic acid was carried out with a range of solvent systems (Table 3). It was observed that the more polar solvent such as methanol gave near quantitative yield with in 1 h. This may be due to the high complex

Table 2
Effect of base on the coupling reaction^a

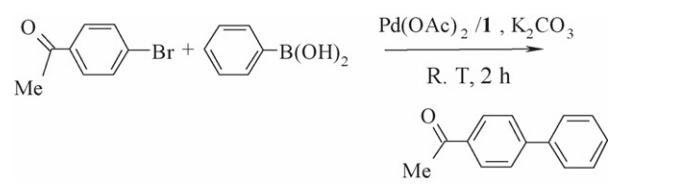


Entry	Base	Yield (%) ^b
1	K ₂ CO ₃	100
2	Na ₂ CO ₃	99
3	Et ₃ N	97
4	Cs ₂ CO ₃	75
5	KOH	73
6	KF	61

^a Reaction conditions: 0.5 mmol of 4-bromoacetophenone, 0.75 mmol of phenylboronic acid, 1 mmol of base, 0.05 mol% of Pd(OAc)₂/1, 5 mL of MeOH.

^b Conversion to coupled product determined by GC, based on aryl halides; average of two runs.

Table 3
Effect of the solvent on the coupling reaction^a



Entry	Solvent	Yield (%) ^b
1	MeOH	100
2	Toluene	82
3	THF	63
4	Acetone	57
5	CH ₃ CN	26
6	Dioxane	24

^a Reaction conditions: 0.5 mmol of 4-bromoacetophenone, 0.75 mmol of phenylboronic acid, 1 mmol of K₂CO₃, 0.05 mol% of Pd(OAc)₂/1.

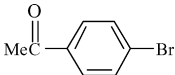
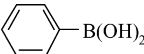
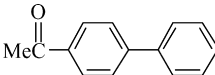
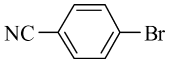
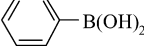
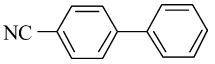
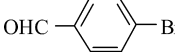
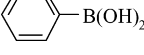
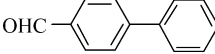
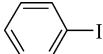
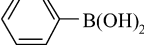
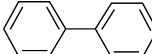
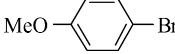
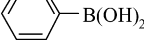
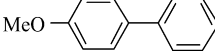
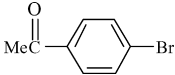
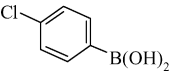
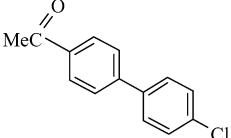
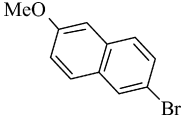
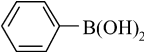
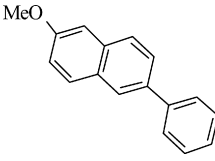
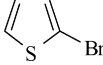
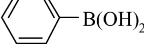
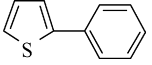
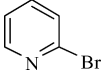
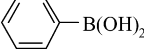
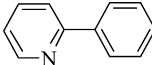
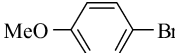
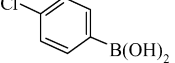
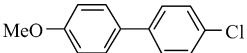
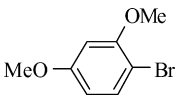
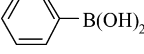
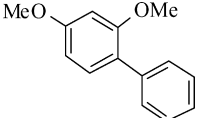
^b Conversion to coupled product determined by GC, based on aryl halides; average of two runs.

solubility. Although, non-polar solvent such as toluene also gives good yield but it takes more time for the reaction. The reactions in acetonitrile and dioxane resulted in very poor yields.

3.2.4. Coupling reactions of aryl bromides and aryl iodides with arylboronic acids

After optimizing the reaction conditions, we have carried out the coupling reactions of several substrates with arylboronic acids. It is found that Pd(OAc)₂/1 mixture is a highly active catalyst in the Suzuki cross-coupling of aryl halides with arylboronic acids in methanol using K₂CO₃ as a base. As shown in Table 4, 4-bromoacetophenone couples with phenylboronic acid in the presence of 0.05 mol% of Pd(OAc)₂/1 mixture and two equivalent of K₂CO₃ to give near quantitative yield of 4-acetylbiphenyl in methanol at room temperature (entry 1). The use of deactivated electron rich aryl bromide (e.g. entry 5) as well as activated, electron-poor ones (entries 1 and 2) also resulted in high yields. Generally, these coupling reactions can be satisfactorily carried out at room temperature. When there is a need to improve the yield, reaction can be carried out at elevated temperatures (60 °C) (entries 5 and 7). We also studied the coupling of some heterocycles or highly substituted aryl bromides with boronic acids. For example, coupling of 2-bromothiophene and 2-bromopyridine with phenylboronic acid in presence of 0.1 mol% of Pd(OAc)₂/1 at 60 °C gave the corresponding coupling products in moderate yields (entries 8 and 9). However, coupling of 2,4-dimethoxy phenylbromide with phenylboronic acid gives only 36% of conversion. The high efficiency of Pd(OAc)₂/1 at room temperature or at 60 °C makes this a valuable catalyst for thermally sensitive substrates. There have been few reports on efficient Suzuki cross-coupling reactions of aryl bromides at room temperature mostly using Pd/phosphine systems [4b,5a,b]. Although, Pd/phosphinite is known for Suzuki cross-coupling reactions, most of them are carried out at higher temperature, where active catalytic species is orthopalladated complex formed in situ [6b,7]. Some non-orthopalladated phosphinite complexes [PdCl₂{PPh₂(OAr)}₂]

Table 4
Suzuki cross-coupling of aryl halides with boronic acids catalyzed by Pd(OAc)₂/1

Entry	Aryl halide	Boronic acid	Product	Conditions ^a	Yield (%) ^b
1				0.05 mol% RT	100
2				0.05 mol% RT	>99
3				0.05 mol% RT	98
4				0.05 mol% RT	93
5				0.05 mol% RT	89 (99) ^c
6				0.1 mol% RT	87
7				0.1 mol% 60 °C	55 (79) ^c
8				0.1 mol% 60 °C	73
9				0.1 mol% 60 °C	58
10				0.1 mol% 60 °C	52
11				0.1 mol% 60 °C	36

^a Reaction conditions: ArX (0.5 mmol), ArB(OH)₂ (0.75 mmol), K₂CO₃ (1 mmol), MeOH (5 mL), time 2 h.

^b Conversion to coupled product determined by GC, based on aryl halides (or dodecane); average of two runs.

^c At 60 °C, 2 h.

are reported for Suzuki reaction, where the active catalyst is believed to be hydrolyzed form of ligand, i.e. P(OH)Ph₂ [8]. In the present investigation, the reactions have been carried out under mild conditions, and at present we are not sure about the active catalytic species. Similar Pd/phosphinite systems for Suzuki reaction at room temperature are not seen in the literature.

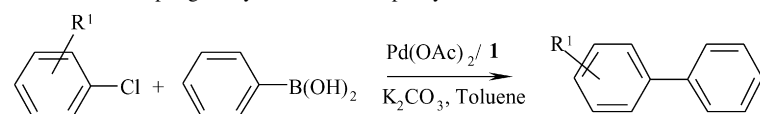
The activity of Pd(OAc)₂/1 is found to be superior to that of Pd(OAc)₂/phosphine used by Semeril et al. where coupling reaction between 4-bromoanisole or 2-bromo,6-

methoxynaphthalene with phenylboronic acid was carried out in presence of 2 mol% of catalyst at 110 °C in DMF as solvent [13].

3.2.5. Coupling reaction of aryl chlorides with phenylboronic acid

A series of reactions were carried out using stubborn aryl chlorides with phenylboronic acid in presence of 2 mol% of Pd(OAc)₂/1 mixture (Table 5). Use of activated aryl chlorides such as 2-chlorobenzaldehyde or 4-chlorobenzonitrile in toluene

Table 5
Suzuki cross-coupling of aryl chlorides with phenyl boronic acid^a



Entry	Aryl halide	Boronic acid	Product	Yield (%) ^b
1				78
2				59
3				29
4				20
5				9

^a Reaction conditions: ArCl (0.5 mmol), PhB(OH)₂ (0.75 mmol), K₂CO₃ (1 mmol), Pd(OAc)₂/1 (2 mol%). Toluene (5 mL), 110 °C, time, 6 h.

^b Conversion to coupled product determined by GC, based on aryl chloride (or dodecane); average of two runs.

at 110 °C gives moderate yields, where as other inactivated aryl chlorides such as 2-chlorotoluene gives poor yield.

4. Conclusion

In summary, a versatile and inexpensive monophosphinite ligand **1** was synthesized. We have shown that Pd(OAc)₂/**1** is an efficient catalytic system for Suzuki coupling of various aryl halides under mild conditions with excellent turnover numbers. Further utility of this ligand in other catalytic transformations is under active investigation in our laboratory.

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