Suzuki–Miyaura Coupling Reactions Using Phosphite Ligands

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Abstract: A new catalytic system based on palladium phosphites for Suzuki coupling reactions of aryl bromides is described. An air-stable catalytic system effectively promotes Suzuki couplings of aryl bromides with a range of boronic acids to afford diaryl products in high yields.

Key words: cross-coupling, palladium, phosphorus, Suzuki–Miyaura coupling, phosphite

The synthesis of biaryls has received increasing attention due to their important role in natural products, agrochemicals, pharmaceuticals, and new materials.[1] The Suzuki reaction of organoboron compounds with aryl halides provides a most straightforward and powerful tool for such synthetic strategies.[2] Compared to other organometallic nucleophiles such as orgnomagnesium, organozinc, and organotin, the key advantages of organoboranes are their stability to heat, oxygen, and water, in addition to the ease of handling and separation process.[3]

To extend the Suzuki–Miyaura coupling reaction for fine chemical applications, numerous studies have been reported in the literature including the use of phase-transfer complex,[4] low palladium loading,[5] reaction under microwave irradiation,[6] phosphine-free catalyst system,[7] and iron catalyst system.[8] Despite these recent advances, there still remains improvement for a general protocol that could be employed as a practically useful process with broadened scope of this transformation.

Usually, the Suzuki–Miyaura reaction is mediated by a palladium–phosphine complex as catalyst. Most research has focused on the development of efficient ligands to obtain high catalytic activity. Recently sterically bulky and electron-rich phosphine lgiands[9] and carbene-type ligands[10] have been reported to display high activity in Suzuki–Miyaura coupling of aryl halides. They showed good reactivity to even aryl chlorides, which are the most challenging substrates. However, most alkylphosphine ligands including P(t-Bu)$_3$, are sensitive to oxygen and moisture. Therefore they require an inert environment for carrying out the reaction. In case of carbene-type ligands, most of them should be prepared through multistep synthesis in spite of their increased stability.

In contrast to the phosphine ligands, much less attention has been paid to phosphite ligands, although they are very cheap and stable to air and moisture. Recently, we have developed new catalytic systems based on phosphite ligands and employed them in the palladium or nickel catalyzed-transformations.[11] All phosphites, which were employed in the transformations, have been widely used as antioxidants.[12] Phosphite compound **1** showed good activity in Hiyama reaction[11a] and the homocoupling of aryl halides,[11b] and phosphite **3** (Figure 1) was found as the best ligand in the dehalogenation[11c] and aminocarbonylation.[11d]

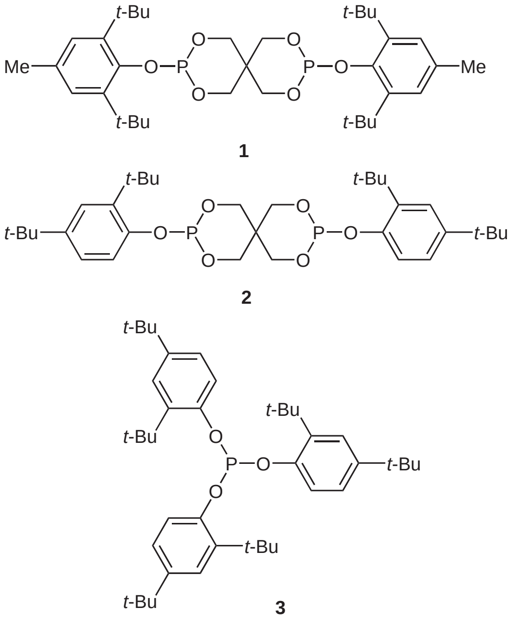

Figure 1 Phosphite ligands **1**–**3**

To the best of our knowledge, phosphite compounds have never been employed as ligands in Suzuki cross-coupling reaction, although a variety of new ligands have been developed and employed in this transformation.[13] Therefore, we report here the recent development of Suzuki cross-coupling reaction using phosphite ligands as important progress of practical utility.

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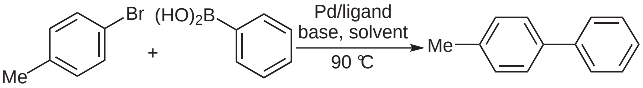
As a starting point for the development of the methodology, we chose the coupling between 4-bromotoluene and phenylboronic acid in the presence of palladium catalyst with a variety of phosphite ligands as a model reaction. The results are summarized in Table 1. As the findings in our previous study,[11a] a Pd-to-ligand ratio of 1:1 gave the best result. Among the phosphite ligands screened, phosphite **1** showed the highest yield as expected from the results in Hiyama reaction (entry 1). Thus, we investigated the effect of various reaction parameters (palladium catalyst, base, solvent, catalyst loading, and temperature) over the yields of the coupling reactions. $Pd(acac)_2$ was found to be superior to other palladium source such as $Pd(OAc)_2$, $Pd(MeCN)_2Cl_2$, and $Pd_2(dba)_3$ (entries 1, 4–6). K_3PO_4, which is commonly employed with dialkylbiarylphosphine ligands[9a] to accelerate the Suzuki–Miyaura reaction gave very low yield (entry 7). K_2CO_3, Cs_2CO_3, KF, and CsF showed moderate efficiency, giving the product in 70, 73, 60, and 63% yield, respectively (entries 8–11). Na_2CO_3 was found to be the best base for this transformation. The reaction proceeded well in polar solvents, such as NMP (*N*-methyl-2-pyrrolidinone) and DMA (dimethylacetamide) in 89 and 75% yield, respectively (entries 1 and 15). The yield decreased in less polar solvents such as toluene (entry 12). It was found that the presence of water was critical in obtaining high yields of the desired product. Thus, the optimized reaction conditions were found to consist of 1,4-dioxane–H_2O (10:1) as solvent, Na_2CO_3 as base, phosphite **1** as ligand, and $Pd(acac)_2$ as catalyst (entry 16).

In an effort to explore the scope of this method, we have screened the coupling of representative aryl bromides with arylboronic acids. The reaction system is generally applicable for a variety of substrates as illustrated in Table 2. The coupling reaction is very tolerant of functional groups for aryl bromides, and the reactions with both electron-withdrawing and electron-donating substituents gave the desired biaryl products in good to excellent yields. In case of bromoanisole derivatives, all substrates showed good yields (entries 3–5).

1-Bromonaphthalene gave higher yield than 2-bromonaphthalene (entries 6 and 7). Heteroaryl bromides such as 2-bromothiophene and 3-bromopyridine afforded the desired coupling product in high yields, however, 2-bromopyridine showed somewhat low yield (entries 8–10). Activated aryl bromides afforded coupled products in excellent yields, especially, *ortho*-substituted phenyl bromides such as 2-nitrophenyl bromide and 2-bromobiphenyl showed very high yields (entries 11 and 16). Sterically hindered aryl bromides such as bromomesitylene were coupled with phenylboronic acid and 2-tolylboronic acid to give the desired biaryl products in 85 and 74% yield, respectively (entries 17 and 18). Aryl bromides bearing electron-donating group (entries 19–22) and electron-withdrawing group (entries 23 and 24) were coupled with a variety of arylboronic acids to give the products in good to excellent yields. We attempted to extend this catalytic system to aryl chlorides, which are more challenging substrates. However, only activated aryl chlorides afforded the desired product in 25% yield. Substrates bearing electron-donating and electron-neutral groups showed very low yields. Longer reaction time and high catalyst loading did not significantly improve the yield of the product in either case.

Table 1 Reaction Conditions for Optimized Suzuki–Miyaura Reaction Using Phosphite Ligands[a]



Entry	Pd/L	Base	Solvent	Yield (%)[b]
1	$Pd(acac)_2$/**1**	Na_2CO_3	NMP	89
2	$Pd(acac)_2$/**2**	Na_2CO_3	NMP	38
3	$Pd(acac)_2$/**3**	Na_2CO_3	NMP	5
4	$Pd(OAc)_2$ /**1**	Na_2CO_3	NMP	25
5	$Pd(MeCN)_2Cl_2$/**1**	Na_2CO_3	NMP	56
6	$Pd_2(dba)_3$/**1**	Na_2CO_3	NMP	52
7	$Pd(acac)_2$/**1**	K_3PO_4	NMP	5
8	$Pd(acac)_2$/**1**	K_2CO_3	NMP	70
9	$Pd(acac)_2$/**1**	Cs_2CO_3	NMP	73
10	$Pd(acac)_2$/**1**	KF	NMP	60
11	$Pd(acac)_2$/**1**	CsF	NMP	63
12	$Pd(acac)_2$/**1**	Na_2CO_3	toluene	5
13	$Pd(acac)_2$/**1**	Na_2CO_3	diglyme	31
14	$Pd(acac)_2$/**1**	Na_2CO_3	THF	38
15	$Pd(acac)_2$/**1**	Na_2CO_3	DMA	75
16	$Pd(acac)_2$/**1**	Na_2CO_3	dioxane–H_2O	94

[a] Reaction conditions: 4-bromotoluene (1.0 mmol), $PhB(OH)_2$ (1.1 mmol), Pd (2 mol%), ligand (2 mol%), and solvent (3.0 mL).

[b] The yield was determined by GC by comparison with an internal standard (naphthalene).

In summary, we have shown that sterically bulky phosphite **1** exhibits good activity as a ligand in the palladium-catalyzed Suzuki–Miyaura coupling reactions. This catalytic system was not sensitive to oxygen or moisture; no change in their efficiencies was observed even if the coupling reactions were carried out under aerobic conditions. In addition, considering the cost and the stability of phosphite as ligand, this method provides a convenient route to synthesize the biaryl compounds.

Table 2 Suzuki–Miyaura Reaction of Aryl Halides with Arylboronic Acids[a]

$$Ar^1X + Ar^2B(OH)_2 \xrightarrow[\substack{Na_2CO_3,\ dioxane–H_2O \\ 90\ ^\circ C}]{Pd(acac)_2/phosphite\ \mathbf{1}} Ar^1—Ar^2$$

Entry	Ar^1X	$Ar^2B(OH)_2$	Yield (%)[b]
1	PhBr	$PhB(OH)_2$	98
2	$4\text{-}MeC_6H_4Br$	$PhB(OH)_2$	94
3	$2\text{-}MeOC_6H_4Br$	$PhB(OH)_2$	76
4	$3\text{-}MeOC_6H_4Br$	$PhB(OH)_2$	84
5	$4\text{-}MeOC_6H_4Br$	$PhB(OH)_2$	85
6	1-bromonaphthalene	$PhB(OH)_2$	98
7	2-bromonaphthalene	$PhB(OH)_2$	76
8	2-bromothiophene	$PhB(OH)_2$	88
9	2-bromopyridine	$PhB(OH)_2$	45
10	3-bromopyridine	$PhB(OH)_2$	85
11	$2\text{-}O_2NC_6H_4Br$	$PhB(OH)_2$	98
12	$4\text{-}O_2NC_6H_4Br$	$PhB(OH)_2$	94
13	$4\text{-}MeCOC_6H_4Br$	$PhB(OH)_2$	95
14	$4\text{-}MeOCOC_6H_4Br$	$PhB(OH)_2$	91
15	$4\text{-}HOC_6H_4Br$	$PhB(OH)_2$	88
16	$2\text{-}PhC_6H_4Br$	$PhB(OH)_2$	99
17	mesityl bromide	$PhB(OH)_2$	85
18	mesityl bromide	$2\text{-}MeC_6H_4B(OH)_2$	74
19	$2\text{-}MeOC_6H_4Br$	$2\text{-}MeC_6H_4B(OH)_2$	70
20	$4\text{-}MeC_6H_4Br$	$4\text{-}MeOC_6H_4B(OH)_2$	72
21	$4\text{-}MeC_6H_4Br$	$4\text{-}MeCOC_6H_4B(OH)_2$	81
22	$4\text{-}MeC_6H_4Br$	$4\text{-}MeC_6H_4B(OH)_2$	73
23	$4\text{-}MeCOC_6H_4Br$	$2\text{-}MeC_6H_4B(OH)_2$	98
24	$4\text{-}MeCOC_6H_4Br$	$4\text{-}MeC_6H_4B(OH)_2$	98
25	PhCl	$PhB(OH)_2$	5 (8)[c]
26	$4\text{-}MeCOC_6H_4Cl$	$PhB(OH)_2$	25 (27)[c]
27	$4\text{-}MeOC_6H_4Cl$	$PhB(OH)_2$	5 (5)[c]

[a] Reaction conditions: Ar^1X (1.0 equiv), $Ar^2B(OH)_2$ (1.1 equiv), $Pd(acac)_2$ (2 mol%), phsophite **1** (2 mol%), Na_2CO_3 (1.2 equiv), 1,4-dioxane–H_2O (10:1, 0.3 M), 12 h at 90 °C under aerobic conditions (time is not optimized).

[b] The isolated yields of compounds are an average of at least two runs. All compounds are characterized by comparison of ^1H NMR spectra with literature data.

[c] Amount of $Pd(acac)_2$ and phosphite **1** used: 5 mol% each.

All reagents were obtained from commercial suppliers and used without further purification.

Suzuki–Miyaura Coupling Reaction Using Phosphite Ligand 1; General Procedure

$Pd(acac)_2$ (0.06 mmol), phosphite **1** (0.06 mmol), aryl halide (3.0 mmol), and aryl boronic acid (3.3 mmol) were combined with Na_2CO_3 (3.6 mmol) in a round-bottomed flask. 1.4-Dioxane (10.0 mL) and H_2O (1.0 mL) were added, and the flask was sealed with a septum. The resulting mixture was placed in an oil bath at 90 °C until the starting material was consumed, as determined by GC and TLC. The reaction was poured into aq sat. NH_4Cl (20 mL) and extracted with Et_2O (3 × 20 mL). The combined Et_2O extracts were washed with brine (60 mL), dried ($MgSO_4$), and filtered. The solvent was removed under vacuum, and the resulting crude product was purified by flash choromatography on silica gel. The product was eluted with 5% EtOAc in hexane (Table 2).

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