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Triphenylphosphine chalcogenides as efficient ligands for room temperature palladium(II)-catalyzed Suzuki–Miyaura reaction

Pankaj Das *, Utpal Bora, Archana Tairai, Chandan Sharma

Department of Chemistry, Dibrugarh University, Dibrugarh 786004, Assam, India

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ABSTRACT

A simple catalytic system based on $PdCl_2$ and triphenylphosphine chalcogenides (PPh_3X; X = O, S, Se) is found to be highly effective (up to 97% isolated yield) in the room temperature Suzuki–Miyaura reactions. Under the same experimental conditions, triphenylphosphine chalcogenides as ligands show superior activities compared to free triphenylphosphine.

The palladium-catalyzed Suzuki–Miyaura reaction of aryl halides with aryl boronic acids has proven to be one of the most powerful strategies for synthesizing diversified biaryls, which constitute an important class of compounds for pharmaceutical, material, and agricultural chemistry.[1] It is a well-known fact in Suzuki–Miyaura reaction that the activity and selectivity of a catalyst depend on the steric and electronic properties of the ligand attached to the metal. Thus, right choice of ligand plays a crucial role in such catalysis. Among different ligand systems, the phosphine-based ligands such as commercially available triarylphosphines,[1a,2] hemilabile-type phosphine (P–O[3]/P,N[4]/P–S[5] donor), sterically crowded biphenyl-type phosphines[6], and other electron-rich phosphines[7] have been extensively used as ligand precursors for this reaction. However, the main drawbacks associated with such phosphine-based ligands are that in majority of cases they require an elevated temperature for effective catalytic activity and tend to be inactive toward aryl chlorides as substrate.[7e,f] Nevertheless, there exist some reports where some functionalized phosphine ligands have effectively catalyzed Suzuki–Miyaura reaction at room temperature.[3d,4b] But, due to the trivalent nature of the phosphorous atom they are very much sensitive to air and often requires an air-free condition to maximize the catalytic performance, thus, causing significant inconvenience in handling.[8] On the contrary, the ligand containing pentavalent phosphorous are relatively robust and insensitive to air and have got very less attention in Suzuki–Miyaura reaction, although such type of ligands are found to be effective in many palladium-catalyzed reaction under mild conditions.[9–12] Thus, in this Letter we wish to report our preliminary result in the use of easily accessible[9] and commercially available triphenylphosphine chalcogenides (PPh_3X; X = O(**L1**); S(**L2**); Se(**L3**)) as ligands in palladium(II)-catalyzed Suzuki–Miyaura reaction of aryl boronic acid with aryl bromide/chloride at room temperature.

To investigate the effectiveness of these ligands, **L1**–**L3**, in Suzuki–Miyaura reaction, the reaction of 4-bromonitrobenzene with phenylboronic acid was chosen as a model reaction using DMF as a solvent, K_2CO_3 as a base, and the reactions were performed in aerobic condition at room temperature in the presence of palladium(II) complexes as catalysts generated in situ from $PdCl_2$ and ligands **L1**–**L3** in 1:2 molar ratio. The results are summarized in Table 1. It has been seen from Table 1 that, even in the absence of any ligand, the coupling reaction proceeded with good yield (entry 1) accompanied with significant amount of homodiaryl compound as a byproduct. But, the use of the ligands **L1–L3** in our reaction conditions gave the desired product in improved yield (Table 1, entries 3, 5, and 7) along with significant reduction of the side product formation. Among the three ligands, the phosphine oxide (**L1**) shows the highest activity (Table 1, entry 3) whereas the phosphine selenide (**L3**) shows the lowest activity (Table 1, entry 7). Usually, in Suzuki–Miyaura reaction, the in situ-generated catalytic species and pre-formed catalyst often give different results[7g,13] and to compare the activities of the in situ catalyst with pre-formed catalyst we have synthesized Pd(II) complexes of the type, $[PdCl_2(PPh_3X)_2]$ **1L1**–**1L3** (X = O, S, Se).[14] Though the Pd(II) complexes **1L1–1L3** were reported in the literature[15], to the best of our knowledge, there is no report on the catalytic activity of these ligands in Suzuki–Miyaura reaction. From the results depicted in Table 1, it is shown that the use of the pre-formed complexes **1L1–1L3** as a catalyst resulted in higher yield

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* Corresponding author. Fax: +91 373 2370323.
E-mail address: pankajd29@yahoo.com (P. Das).

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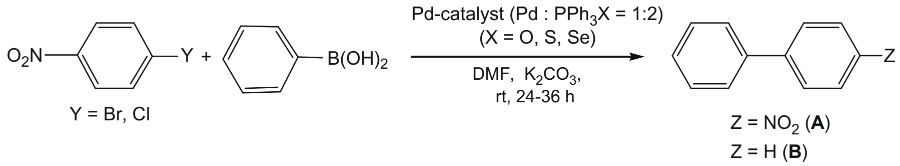
Table 1
Effect of different catalyst on Suzuki–Miyaura reaction[a] at room temperature[16]



Entry	Substrate (Y)	Catalyst	Yield[a] (%)[b]	
			A	B[c]
1	Br	$PdCl_2$	65	25
2	Br	$PdCl_2/PPh_3$	75	Nil
3	Br	$PdCl_2/2PPh_3O$	90	Trace
4	Br	$[PdCl_2(PPh_3O)_2]$	97	7
5	Br	$PdCl_2/2PPh_3S$	86	Trace
6	Br	$[PdCl_2(PPh_3S)_2]$	95	6
7	Br	$PdCl_2/2\ PPh_3Se$	80	Trace
8	Br	$[PdCl_2(PPh_3Se)_2]$	92	Trace
9	Cl	$PdCl_2$	13	nil
10	Cl	$PdCl_2/2\ PPh_3O$	60	Trace
11	Cl	$[PdCl_2(PPh_3O)_2]$	76	Trace
12	Cl	$PdCl_2/2PPh_3S$	50	21
13	Cl	$[PdCl_2(PPh_3S)_2]$	68	12
14	Cl	$PdCl_2/2PPh_3Se$	48	Trace
15	Cl	$[PdCl_2(PPh_3Se)_2]$	54	16

[a] Reaction conditions: 0.5 mmol of Ar-Y, 0.55 mmol of Ar-$B(OH)_2$, 1.5 mmol K_2CO_3, $PdCl_2$ (2 mol %), ligand (4 mol %), DMF (3 ml), reaction time for Ar-Br is 24 h and for Ar-Cl is 36 h.

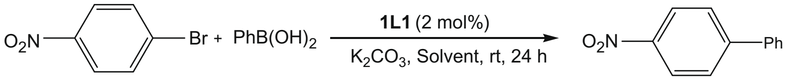
[b] Isolated yield.

[c] Determined with respect to initial amount of Ar-$B(OH)_2$ used.

of the desired product compared to that of the in situ catalyst (Table 1, entries 3 vs 4, 5 vs 6, 7 vs 8). Although the reason for these differences in activities is not clear, one possible explanation could be the slow rate of formation of the in situ complex at room temperature, as the syntheses of the complexes require forcing conditions (refluxing in acetonitrile for few hours).[14] In order to confirm the influence of O, S, and Se as donors a controlled experiment was performed using PPh_3 as a ligand and the reaction was done under an inert atmosphere to avoid any aerial oxidation of phosphine to phosphine oxide. Our results showed a significant decrease in isolated yield when PPh_3 was used as a ligand (Table 1, entry 2) compared to the triphenylphosphine chalcogenide ligand **L1–L3** (Table 1, entries 3, 5, 7) indicating superior reactivity of these pentavalent phosphorous-based ligands over trivalent phosphine. The effect of triphenylphosphine chalcogenides **L1–L3** ligands was much more prominent when we used aryl chloride as a substrate. For instance, when we carried out the Suzuki–Miyaura reaction in air under ligand-free condition using 4-chloronitrobenzene, only 13% of the product was isolated (Table 1, entry 9). However the use of the phosphine chalcogenide ligand **L1–L3** along with $PdCl_2$ leads to dramatic rise in the product yields (Table 1, entries 10, 12, 14). Similar to the aryl bromide, also in this case the pre-formed catalyst show better results compared to the catalytic species generated in situ (Table 1, entries 10 vs 11, 12 vs 13, 14 vs 15). Although a longer reaction time and reduced yields of the products were obtained for aryl chlorides compared to those of aryl bromides (Table 1, entries 3–8 vs 10–15) as a substrate, these results were very significant as we were able to use aryl chlorides as substrates in the Suzuki–Miyaura reaction at room temperature**.** To study the effect of solvents in our system, we examined the reaction between 4-bromonitrobenzene with phenylboronic acid in the presence of various solvents by using the triphenylphosphine chalcogenide complex **1L1** as a catalyst and the results are summarized in Table 2. The reaction was found to proceed in both protic and aprotic solvents although significant variations in yields were noticed. The best result was obtained when DMF was used as a solvent and no product formation was observed when water was used as a solvent (Table 2, entries 3 and 5).

To evaluate the scope and limitations of the current procedure, reactions of a wide array of electronically diverse aryl bromides and chlorides with phenyl boronic acid were examined using pre-

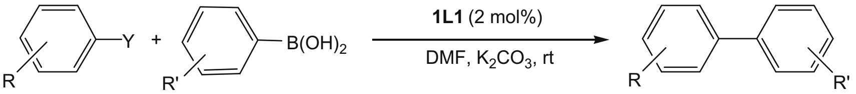
Table 2
Effect of solvents in the Suzuki–Miyaura reaction of 4-bromonitrobenzene



Entry	Solvent	Yield[a] (%)
1	THF	57
2	CH_3CN	59
3	DMF	97
4	*i*-PrOH	62
5	H_2O	No reaction
6	*i*-PrOH/H_2O, 1:1	90
7	DMF/H_2O, 1:1	66

[a] Isolated yield.

Table 3
Suzuki–Miyaura reaction[a] of various substrates



Entry	Y	R	R′	Time[b] (h)	Yield[c] (%)
1	Br	H	H	24	82
2	Br	4-CHO	H	16	90
3	Br	4-NO_2	H	16	97
4	Br	4-COOH	H	18	92
5	Br	4-COOMe	H	18	91
6	Br	4-OMe	H	30	72
7	Cl	H	H	36	45
8	Cl	4-CHO	H	30	64
9	Cl	4-COOH	H	30	43
10	Cl	4-COOMe	H	30	46
11	Cl	4-NO_2	H	30	76
12	Cl	4-OMe	H	36	32
13	Br	4-NO_2	4-OMe	16	82
14	Br	4-NO_2	3-NO_2	18	76
15	Cl	4-NO_2	4-OMe	36	56
16	Cl	4-NO_2	3-NO_2	36	58

[a] Reaction conditions: Ar-Y (0.5 mmol), Ar-$B(OH)_2$ (0.55 mmol), $[PdCl_2(PPh_3O)_2]$ (2 mol %) K_2CO_3 (1.5 mmol), DMF (3 ml).

[b] Reactions were monitored by TLC.

[c] Isolated yield.

formed triphenylphosphine oxide complex **1L1** as a catalyst (Table 3). It is seen from Table 3 that in general, the aryl bromides with electron-withdrawing substituents such as NO_2, CHO, and CO_2Me (entries 2–5) underwent the coupling reactions in nearly quantitative yields (90–97%) whereas the corresponding aryl chlorides (entries 8–11) gave the desired products in good to moderate yield (upto 76%). The nonactivated aryl bromides such as 4-bromobenzene and 4-bromoanisole also gave the coupling products in reasonably good yields (Table 3, entries 1 and 6). However, the nonactivated aryl chlorides such as 4-chlorobenzene and 4-chloroanisole gave only 45% and 32% yields, respectively (Table 3, entries 7 and 12). Besides phenylboronic acid, other boronic acids such as 4-tolylboronic acid and 3-nitrophenylboronic acid were successfully used to yield the desired products in high yields (Table 3, entries 13–16).

In conclusion, we have developed a simple catalytic system based on $PdCl_2$ and triphenylphosphine chalcogenides (PPh_3X; X = O, S, Se) for Suzuki–Miyaura reaction of aryl halides with aryl boronic acid at room temperature. The aryl bromides and the less reactive aryl chlorides underwent the coupling reaction in good-to-excellent yields. Under the same experimental conditions, triphenylphosphine chalcogenides as ligands are more active compared to the free triphenylphosphine.

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14. *Synthesis of $[PdCl_2(PPh_3O)_2]$:* A solution of ligand PPh_3O (0.34 mmol) in 10 ml of acetonitrile was added drop by drop to a solution of $PdCl_2$ (0.17 mmol) in 10 ml of acetonitrile. The reaction was refluxed for 3 h, during which a yellow precipitate was formed. After filtration, the residue was washed with acetonitrile and then dried under vacuum to get the complex **1L1** as bright yellow powder (yield: 96%); mp: 179 °C; Anal. Calcd for $C_{36}H_{30}Cl_2P_2O_2Pd$: C, 58.93; H, 4.09%. Found: C, 59.41; H, 4.13%. IR (KBr/cm^{-1}): 1165 (ν(PO). NMR (300 MHz, in $CDCl_3$), ^1H: 7.70–7.27 (m, C_6H_5); $^{31}P\{^1H\}$: 36.81(s). The complexes **1L2** and **1L3** were also synthesized by a similar procedure and the identities of the complexes were confirmed by melting point determination and infra red spectra.[15a]
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16. *General procedure for the Suzuki–Miyaura reaction:* An oven-dried round-bottomed flask was charged with a mixture of aryl halide (0.5 mmol), arylboronic acid (0.55 mmol), K_2CO_3 (1.5 mmol) $PdCl_2$ (2 mol %), and ligand (4 mol %), and the mixture was stirred in DMF (3 ml) at room temperature for required time. After completion, the reaction mixture was diluted with water (20 ml) and extracted with ether (20 ml × 3). The combined extract was

washed with brine (20 ml × 3) and dried over Na_2SO_4. After evaporation of the solvent under reduced pressure, the residue was chromatographed (silica gel, ethyl acetate/hexane, 1:9) to obtain the desired products. The products were confirmed by comparing the ^1H NMR and mass spectral data with authentic samples.