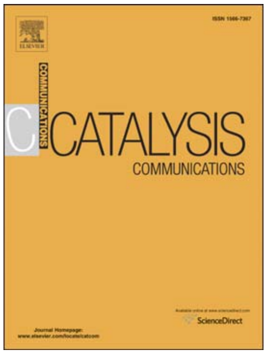

An efficient and recyclable thermoregulated phosphine-palladium catalyst for the carbonylative Suzuki coupling of aryl halides with arylboronic acids in water

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PII: S1566-7367(15)30042-X
DOI: doi: 10.1016/j.catcom.2015.08.008
Reference: CATCOM 4405

To appear in: *Catalysis Communications*

Received date: 18 July 2015
Revised date: 5 August 2015
Accepted date: 6 August 2015

Please cite this article as: Yuanping Hao, Jingyang Jiang, Yanhua Wang, Zilin Jin, An efficient and recyclable thermoregulated phosphine-palladium catalyst for the carbonylative Suzuki coupling of aryl halides with arylboronic acids in water, *Catalysis Communications* (2015), doi: 10.1016/j.catcom.2015.08.008

An efficient and recyclable thermoregulated phosphine-palladium catalyst for the carbonylative Suzuki coupling of aryl halides with arylboronic acids in water

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Abstract:

An efficient protocol has been developed for the carbonylative Suzuki coupling of aryl halides using the thermoregulated phosphine-palladium as a reusable catalyst in pure water. This protocol was applied to a wide variety of hindered and functionalized aryl iodides and bromides with arylboronic acids, to afford the desired biaryl ketones in good to high yields. The palladium catalyst was easily recovered in the aqueous phase and reused up to eight cycles without a significant decrease in its activity.

Keywords:

carbonylation, Suzuki coupling, palladium, thermoregulated phosphine, water

1.Introduction

Biaryl ketones are important building blocks in numerous natural products, pharmaceuticals, photosensitizers, and advanced organic materials [1-6]. Among many well-documented synthetic strategies [7,8], the palladium-catalyzed carbonylative Suzuki coupling of aryl-X compounds, carbon monoxide, and arylboronic acids is a powerful and convenient tool for the synthesis of biaryl ketones [9,10], due to that boronic acids are generally nontoxic and air- and moisture-stable

[11]. Therefore, many efforts have been devoted to the advancement of this transformation over the past few decades [12-16]. However, the vast majority of the work has been carried out in organic solvents (e.g. toluene, anisole). Only a handful of reports on the carbonylative Suzuki coupling reaction focus on the use of environmentally benign solvents, such as aqueous solvent [17-19], and polyethylene glycol (PEG) [20]. Among them, the use of water as a promising medium to replace organic solvents has attracted increasing attention for reasons of economy, safety and environmental concerns [21,22]. To this end, there is still considerable room for progress toward efficient catalytic systems for the carbonylative Suzuki coupling reaction in water. Although water-based catalytic system can facilitate catalyst/product separation and catalyst reuse, most of organic substrates are insoluble in water, resulting in poor reactivity. To solve this problem, many attempts have been made, such as adding organic co-solvents or phase transfer agents, and so on [23].

A water/organic biphasic system termed thermoregulated phase transfer catalysis (TRPTC) offers an attractive alternative approach which can combine the advantages of homogeneous catalysis for reactivity and heterogeneous catalysis for catalyst recovery [24-28]. In a typical TRPTC process, a suitable organic solvent is necessary as a co-solvent for the efficient aqueous/organic biphasic catalysis. To date, a limited number of reports exist on pure water-based thermoregulated biphasic catalytic reactions. Our group has previously developed a type of phosphine ligands containing PEG moieties ($Ph_2P(CH_2CH_2O)_nCH_3$) possessing the capability of phase-transferring between aqueous phase and organic phase based on the cloud point (C_p) as a nonionic surfactant, which were shown to be very efficient and versatile thermoregulated ligands for palladium-catalyzed cross-coupling reactions and cobalt-catalyzed hydroformylation in water [29-32]. Larpent and co-workers reported the use of a thermoresponsive PEG-supported dipyridyl ligand in the thermoregulated biphasic palladium-catalyzed Heck reaction in water [33]. These thermoregulated systems are based on the inverse temperature dependent solubility of PEG residues in water that allows the transfer of the catalyst into the organic phase (substrate phase) during the reaction at high temperature and the separation of the catalyst in the aqueous phase once cooled to room temperature, and further reuse. Considering the fact that there are no reports on TRPTC for aqueous carbonylative Suzuki coupling reactions, in this paper, a thermoregulated phosphine ligand $Ph_2P(CH_2CH_2O)_nCH_3$($n \approx 22$) was employed in palladium-catalyzed carbonylative Suzuki coupling of aryl iodides and bromides with arylboronic acids using water as a sole solvent.

2. Experimental

2.1 General procedure for the carbonylative Suzuki coupling reaction.

A 75 mL autoclave equipped with a Teflon liner and a magnetic stirrer bar was charged with $Pd(OAc)_2$ (4.48 mg, 2.0×10^{-2} mmol), **L** (46.7 mg, 4.0×10^{-2} mmol) and H_2O (6 mL) and the mixture was stirred at room temperatures for 0.5 h under N_2. Then iodobenzene (113μL, 1 mmol), phenylboronic acid (134 mg, 1.1 mmol), Na_2CO_3 (106 mg, 1 mmol), and *n*-decane (0.1 mL, GC internal standard) were added. Once sealed, the autoclave was purged three times with CO, and pressurized to 1 atm of CO. The reaction mixture was stirred at 100 °C for 2 h. After reaction, the mixture was extracted with diethyl ether (3 × 5 mL). The combined organic layer was concentrated in vacuo and the product was purified by column chromatography.

In the recycling experiment, the aqueous phase containing the catalyst was subjected to a second run by charging it with the same substrates as mentioned above, and the reaction performed under the same conditions.

3. Results and discussion

The carbonylative Suzuki coupling of iodobenzene with phenylboronic acid in the presence of CO (1 atm) in water was chosen as the model reaction and different parameters were evaluated to optimize the reaction conditions (Table 1). Initially, the effect of temperature on the carbonlative Suzuki coupling was studied. The results indicated that the preferred temperature was 100 °C, since a complete conversion of iodobenzene with 97% selectivity into the desired benzophenone could be obtained after 2 h (Table 1, entry 3). Further increasing the temperature from 100 °C to 110 °C, the selectivity of the expected product decreased from 97% to 93% due to the increased amount of the direct coupling product (Table 1, entry 4). Generally, the base is an important factor that determines the efficiency of the carbonylative Suzuki coupling reaction. Here, suitable bases may suppress the rate of transmetallation to form the Ar-Pd-Ar intermediate and favor the insertion of CO into the Ar-Pd-X species [9]. Among the bases evaluated, Na_2CO_3 was found to be superior compared with other bases (Table 1, entries 5-13). K_3PO_4 and triethylamine also led to good product selectivity on decreasing the amount from 2 equiv to 1 equiv (1 equiv, 93-96% versus 2 equiv, 68-76%, Table 1, entries 10-13). In the case of **L**/Pd molar ratio study, it was found that deviation from the 2:1 ratio resulted in a significantly drop in activity. Most likely, for lower amounts of ligand, the system is not stable enough to give a satisfactory conversion (Table 1, entry 14). On the contrary, when higher amounts of ligand are used, the coordination sphere of the palladium center is likely too hindered to allow a good activity (Table 1, entry 15). Therefore, the optimized conditions were obtained as listed in entry 5 (Table 1).

Encouraged by this result, the scope of the reaction with a range of aryl iodides was explored. As demonstrated in Table 2, the presented method shows high yields up to 93% for electron-donating substituents such as methyl (Table 2, entries 2-4) or methoxy (Table 2, entries 5-6) on the iodoaryl partner including *ortho*-substituted examples. Sterically hindered 1-iodonaphthalene was effectively converted into the corresponding product in 87% yield (Table 2, entry 7). *meta*-, *para*-Fluoro and chloro-substituted aryl iodides provided the corresponding biaryl ketones, good partners for further functionalization, in 81-85% yields (Table 2, entries 8-11). Aryl iodides containing strong electron-withdrawing groups are known to be prone to undergo noncarbonylative coupling to biaryl byproducts [9,34]. Here, *para*-nitro and carbonyl-substituted iodoarenes furnished the desired products in 61% and 68% yields even under an increased CO pressure of 5 atm, respectively (Table 2, entries 12-13). Heteroaryl iodide such as 2-iodothiophene was successfully employed in this reaction to provide the corresponding product in 75% yield (Table 2, entry 14). This aqueous protocol for the carbonylative Suzuki coupling reaction could also be performed with more challenging aryl bromides (Table 2, entries 15-17).

Further investigation of the scope of this catalytic system was carried out for the carbonylative Suzuki coupling reaction between different aryl iodides and other arylboronic acids (Table 3). Under the applied reaction conditions, the reaction of methyl-, methoxy-, fluoro-, and cyano-substituted arylboronic acids with various aryl iodides proceeded smoothly, to give the expected biaryl ketones in 71-92% yields. 4,4’-Difluorobenzophenone, a key intermediate in the synthesis of denagliptin used for the treatment of Type Ⅱ diabetes [35], was produced in 84% yield (Table 3, entry 13). It was also desirable to expand the scope of the method for heterocyclic boronic acids. Thus, 2-thiopheneboronic acid reacted with iodobenzene and 4-iodotoluene, and the desired heteroaryl ketones were obtained in 79% and 71% yields, respectively (Table 3, entries 4 and 7).

Next, the reactivity and selectivity of dihalobenzenes were also investigated (Scheme 1). Under low CO pressure (1 atm), 1,4-diiodobenzene reacted at 100 °C to give mainly compound **1** in 61% selectivity, which results from the combination of carbonylative coupling and direct coupling (Table 4, entry 1). Higher CO pressure and lower temperature induced the selectivity formation of the diketone, which is important intermediate for advanced functional materials [2,3], but with rather low activity (Table 4, entry 3). In the case of 4-bromoiodobenzene, under 5 atm of CO pressure, the corresponding diketone was obtained with 87% selectivity (Table 4, entry 4).

In addition, under the reaction conditions used for aryl bromides, 1,2-diphenylethanone was obtained in 72% yield in the carbonylative coupling of benzyl chloride with phenylboronic acid. Further investigation on the scope of the aqueous carbonylative coupling reaction is underway in our laboratory.

In order to evaluate the recyclability of the catalyst, the reusability experiments were carried out for the model reaction under the optimized conditions. According to the unique feature of thermoregulated biphasic catalysis, the catalysts would recover their water solubility and return into the aqueous phase via cooling to room temperature. Then the product was simply extracted with diethyl ether, and the aqueous solution containing recycled catalyst was directly reused in the next run by adding fresh substrates. The palladium catalyst could be recycled effectively in eight cycles (Fig. 1). The total leaching of Pd into the organic phase after eight times was observed to be 5.7 wt.% by inductively coupled plasma atomic emission spectroscopic (ICP-AES) analysis (see Supplementary data).

4. Conclusions

In summary, the thermoregulated system has been successfully applied to palladium-catalyzed carbonylative Suzuki coupling of aryl iodides and bromides with arylboronic acids in pure water for the first time. This system tolerates a variety of functional groups on both coupling partners, and the corresponding biaryl ketones were obtained in 61%-93% yields. 1,4-Dihalobenzene can also undergo successive carbonylative Suzuki coupling reactions. Notably, the catalytic system is based on environmentally benign solvent and can be recycled up to eight times.

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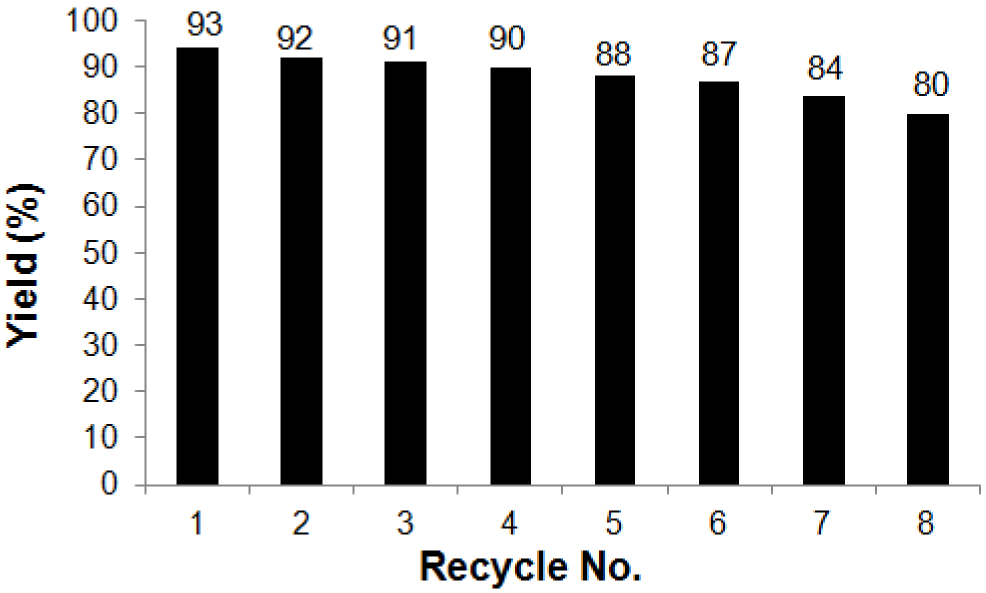
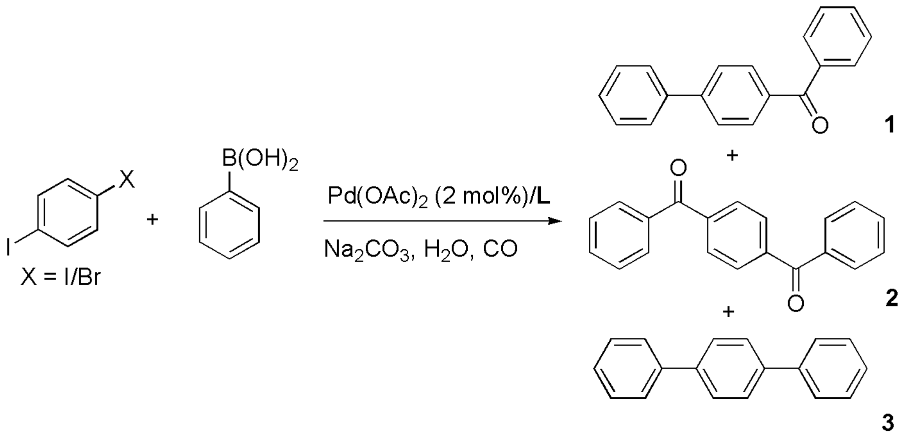
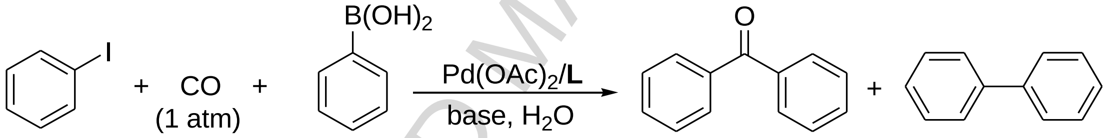

100
90
80
70
60
50
40
30
20
10
0
Yield (%)
93
92
91
90
88
87
84
80
1
2
3
4
5
6
7
8
Recycle No.

Fig. 1



Scheme 1

Table 1. Thermoregulated phosphine-palladium catalyzed carbonylative Suzuki coupling of iodobenzene with phenylboronic acid[a].



Entry	Base (equiv)	Temp. (°C)	Conversion[b] (%)	Selectivity[c] (%)
1	Na_2CO_3 (2)	80	89	99
2	Na_2CO_3 (2)	90	96	98
3	Na_2CO_3 (2)	100	100	97
4	Na_2CO_3 (2)	110	100	93
5	Na_2CO_3 (1)	100	100	99
6	K_2CO_3 (1)	100	99	96
7	Cs_2CO_3 (1)	100	98	95
8	$NaHCO_3$ (1)	100	77	99
9	NaOAc (1)	100	49	99
10	$K_3PO_4{\cdot}3H_2O$ (2)	100	100	68
11	$K_3PO_4{\cdot}3H_2O$ (1)	100	99	96
12	Et_3N (2)	100	100	76
13	Et_3N (1)	100	100	93
14	Na_2CO_3 (1)	100	76	95[d]
15	Na_2CO_3 (1)	100	88	98[e]

[a] Reaction conditions: iodobenzene (1.0 mmol), phenylboronic acid (1.1 mmol), $Pd(OAc)_2$ (2.0 mol%), **L**/Pd = 2:1 (molar ratio), H_2O (6 mL), CO (1 atm), 2 h. Each entry is the result of two tests.

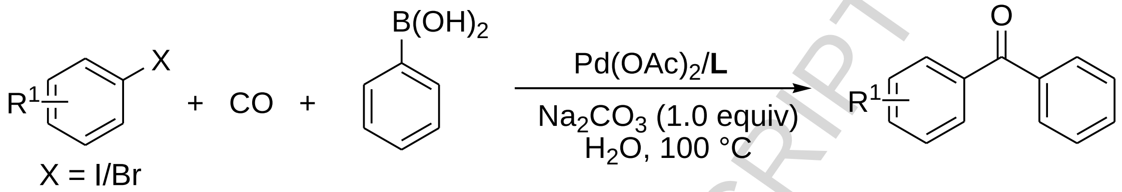
[b] Conversion was determined by GC on the basis of iodobenzene using *n*-decane as internal standard.

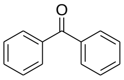
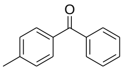
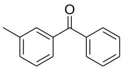
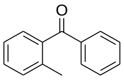
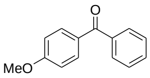
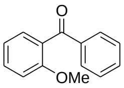
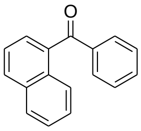
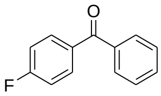
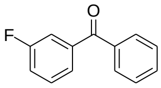
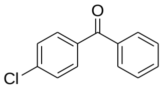
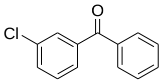
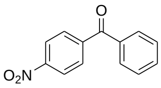
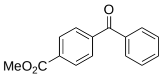
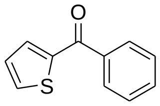
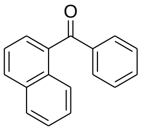
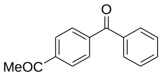
[c] Selectivity for carbonylated product, diphenyl accounts for the balance.

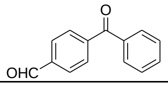
[d] **L**/Pd = 1:1 (molar ratio).

[e] **L**/Pd = 4:1 (molar ratio).

Table 2. Carbonylative Suzuki coupling of various aryl halides with phenylboronic acid[a].



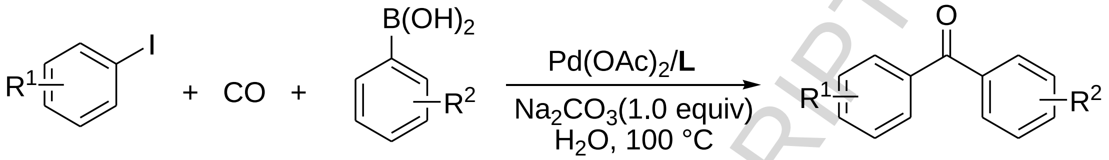
Entry	R^1	X	P(CO) (atm)	Time (h)	Product	Yield[b] (%)
1	-	I	1	2		93
2	4-Me	I	1	5		90
3	3-Me	I	1	7		88
4	2-Me	I	1	10		91
5	4-OMe	I	1	5		93
6	2-OMe	I	1	12		66
7	1-Iodonaph	-	1	10		87
8	4-F	I	1	8		84
9	3-F	I	1	10		82
10	4-Cl	I	1	8		85
11	3-Cl	I	1	8		81
12	4-NO_2	I	5	3		61
13	4-CO_2Me	I	5	9		68
14	2-Iodothiophene	-	5	10		75
15	1-Bromonaph	-	5	20		73
16	4-COMe	Br	5	20		71

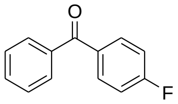
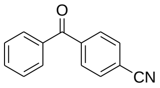
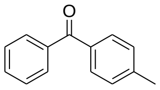
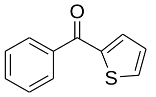
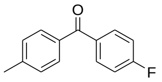
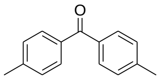
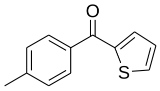
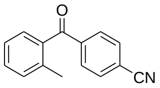
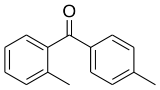
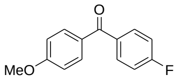
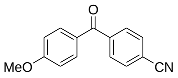
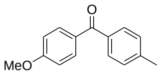
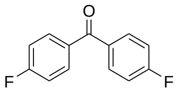
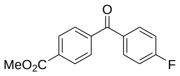
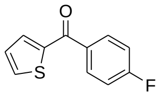
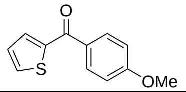
17	4-CHO	Br	5	20		69

[a] Reaction conditions: aryl halide (1 mmol), phenylboronic acid (1.1 mmol), Pd(OAc)$_2$ (2 mol%), **L** (4 mol%), Na$_2$CO$_3$ (1 equiv), H$_2$O (6 mL), 100 °C.

[b] Isolated yields.

Table 3. Carbonylative Suzuki coupling of various aryl iodides with arylboronic acids[a].



Entry	R^1	R^2	Time (h)	Product	Yield[b] (%)
1	-	4-F	6		87
2	-	4-CN	7		81
3	-	4-Me	7		90
4	-	2-Thiophene	6		79
5	4-Me	4-F	6		91
6	4-Me	4-Me	15		92
7	4-Me	2-Thiophene	7		71
8	2-Me	4-CN	6		87
9	2-Me	4-Me	13		76
10	4-OMe	4-F	6		86
11	4-OMe	4-CN	6		80
12	4-OMe	4-Me	7		83
13	4-F	4-F	8		84
14	4-CO$_2$Me	4-F	7		73[c]
15	2-Iodothiophene	4-F	8		76[c]
16	2-Iodothiophene	4-OMe	8		85[c]

[a] Reaction conditions: aryl halide (1 mmol), arylboronic acids (1.1 mmol), Pd(OAc)$_2$ (2 mol%), **L**

(4 mol%), Na_2CO_3 (1 equiv), H_2O (6 mL), CO (1 atm), 100 °C.

[b] Isolated yields.

[c] CO (5 atm).

Table 4. Carbonylative Suzuki coupling of 1,4-dihalobenzenes[a].

Entry	X	Temp. (°C)	P(CO) (atm)	Time (h)	Conv.[b] (%)	Selet.[b] of **1**	Selet.[b] of **2**	Selet.[b] of **3**
1	I	100	1	6	100	63	22	15
2	I	100	8	4	100	42	58	0
3	I	80	8	36	100	7	93 (81)	0
4	Br	100	5	30	100	12	88	0

[a] Reaction conditions: 1,4-dihalobenzene (1 mmol), phenylboronic acid (2.2 mmol), $Pd(OAc)_2$ (2 mol%), **L** (4 mol%), Na_2CO_3 (2 equiv), H_2O (6 mL).

[b] Conversions of 1,4-dihalobenzenes and selectivities of **1**-**3** was determined by GC-MS; the value in parentheses refers to isolated yields of the corresponding product.

Table 1. Thermoregulated phosphine-palladium catalyzed carbonylative Suzuki coupling of iodobenzene with phenylboronic acid[a].

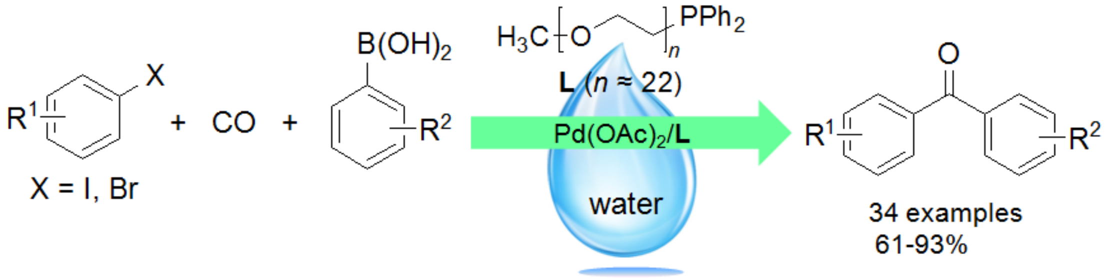
Table 2. Carbonylative Suzuki coupling of aryl halides with phenylboronic acid[a].

Table 3. Carbonylative Suzuki coupling of aryl iodides with arylboronic acids[a].

Table 4. Carbonylative Suzuki coupling of 1,4-dihalobenzenes[a].

Scheme 1. Carbonylative Suzuki coupling of 1,4-dihalobenzenes.

Fig. 1. Catalyst reusability study. Reaction conditions: iodobenzene (1 mmol), phenylboronic acid (1.1 mmol), $Pd(OAc)_2$ (2 mol%), **L**/Pd = 2:1 (molar ratio), Na_2CO_3 (1 equiv), H_2O (6 mL), CO (1 atm), 100 °C, 2 h, isolated yield.



Graphical abstract

Highlights

The carbonylative Suzuki coupling reaction was carried out in pure water.

Thermoregulated phosphine-palladium catalyst was used.

The catalyst exhibited high catalytic activity for the synthesis of biaryl ketones.

Both aryl halides (I,Br) and benzyl chloride were suitable substrates.

The palladium catalyst can be simply recovered and efficiently reused up to 8 runs.