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Pd(OAc)₂ and (DHQD)₂PHAL as simple, efficient and recyclable/reusable catalyst system for Suzuki–Miyaura cross-coupling reactions in H₂O at room temperature

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Suzuki–Miyaura cross-coupling reaction catalyzed by Pd(OAc)₂ and (DHQD)₂PHAL is a very simple, mild and efficient protocol for the synthesis of biaryls/heterobiaryls in neat H₂O at room temperature. The catalyst system is recyclable/reusable and can be employed in several consecutive runs without significant loss in catalytic activity.

The cross-coupling of organo–boron compounds with organic halides or related electrophiles provide one of the most straightforward methodologies for various carbon–carbon bond formations. The Suzuki–Miyaura¹ reaction has gained prominence in the last few years because the conditions developed for the cross-coupling reaction have many desirable features for large-scale synthesis and are amenable to the industrial synthesis of pharmaceuticals and fine chemicals. It is one of the most significant and versatile tools for the synthesis of biologically active compounds ranging from the synthesis of novel materials to industrial manufacturing of many agrochemicals, pharmaceuticals, liquid crystals and biologically active natural products.² Generally, the phosphine ligands are used to complex and activate the palladium species, and excellent results have been reported for the palladium-catalyzed Suzuki–Miyaura cross-coupling reaction for effective phosphine ligands.³ However, phosphine ligands are sensitive to air and moisture, restricting the reuse of the catalyst and leading to undesirable residues under aqueous reaction conditions, which places significant limits on their synthetic applications to this coupling reaction.⁴ Therefore, the development of phosphine-free catalytic systems to overcome the above difficulties is considered to be one of the most challenging and demanding fields in organic synthesis.

Recently, highly efficient conversions have been reported for Suzuki–Miyaura couplings that are based on the use of bulky electron-rich ligands which provides extra stabilization to the rate determining transition state in palladium-catalyzed reactions.⁵ Literature reports also reveal the necessity of promoters such as ionic additives (NaCl, Na₂SO₄, LiCl *etc.*), β-cyclodextrin, TBAB, FeCl₃, ZnCl₂, CuI to name a few to enhance the rate of Suzuki–Miyaura cross-coupling reactions.⁶ Further concern in such reactions, is the

complete or at least partial replacement of organic solvents by environmental benign reaction media.⁷ With an increasing awareness on the use of cleaner green chemistry processes, tremendous efforts have been made for the development of organic reactions in water because it provides noteworthy advantages compared with most organic solvents both from an economic and an environmental point of view.⁸ All the above points encouraged us to develop a simple, efficient and greener method of Suzuki–Miyaura cross-coupling reaction with wide applicability. Therefore, we wish to report herein our preliminary result to develop a more active and reusable catalyst system for Suzuki–Miyaura cross-coupling reactions under very mild and environmental friendly conditions. Our attempt was to evaluate a phosphine-free systems in palladium catalysis and therefore (DHQD)₂PHAL (**Figure 1**) had been chosen as a ligand for this purpose.

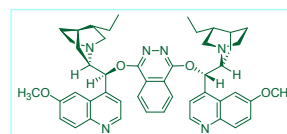
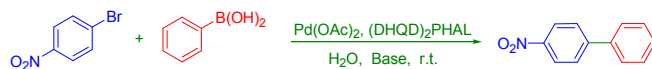


Figure 1. (DHQD)₂PHAL

Our initial investigation was directed toward exploring the reaction conditions for the model cross-coupling of phenyl boronic acid with 4-nitrobromobenzene. Considering the key role of base in the formation of active palladium intermediates and/or promoting transmetalation during the catalytic cycle of Suzuki–Miyaura cross-coupling reaction,⁹ different bases including sodium/potassium inorganic salts and organic base were screened (**Table 1**, Entries 1–11). It was found that, K₂CO₃ was superior and giving an excellent yield in absence of any organic solvents/ promoters (**Table 1**, Entry 4). Presence of water as a reaction media increases solubility of the bases, which is responsible for the activation of boronic acid resulting in enhancing the rate of the reaction in aqueous medium. Likewise, we did an experiment in the absence of base, no cross-coupling product was observed, which confirmed the necessity of base for the smooth Suzuki–Miyaura cross-coupling (**Table 1**, Entry 10). In order to demonstrate the effect of (DHQD)₂PHAL in this reaction, we performed a reaction of 4-nitrobromobenzene and

phenylboronic acid in the absence of (DHQD)₂PHAL under the same reaction conditions, but the yield obtained was very low (30 %, **Table 1**, Entry 11).

Table 1. Effects of bases in the Suzuki–Miyaura reactions of 4-nitrobromobenzene with phenylboronic acid in the presence of Pd(OAc)₂ and (DHQD)₂PHAL catalytic system^a



Entry	Base	Time (h)	Yield ^b (%)
1	Na ₃ PO ₄ ·12H ₂ O	12	38
2	Na ₂ HPO ₄	12	35
3	K ₃ PO ₄	12	30
4	K ₂ CO ₃	2	88
5	Na ₂ CO ₃	6	68
6	CS ₂ CO ₃	12	65
7	NaOH	24	38
8	KOH	24	35
9	Et ₃ N	24	Trace
10	–	24	No reaction
11	K ₂ CO ₃	24	30 ^c

^a Reaction conditions: 4-nitrobromobenzene (1 mmol), phenylboronic acid (1.2 mmol), Pd(OAc)₂ (0.01 mmol), (DHQD)₂PHAL (0.01 mmol), base (1.2 mmol) in H₂O (3 mL) at room temperature.

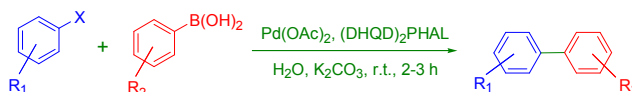
^b Yield of isolated product.

^c Without the ligand

After attaining the optimal reaction conditions, we then examined the applicability of the present catalytic system to the Suzuki–Miyaura cross-coupling of various aryl bromides and different aryl boronic acids (**Table 2**). A wide range of electronically and structurally diverse aryl bromides were readily converted to the corresponding coupled products with different substituted aryl boronic acids in excellent yields at room temperature. It was observed that the aryl halides with electron-deficient boronic acids showed slightly reduced product yields, compared to those of the electron-neutral and electron-rich boronic acids (**Table 2**, Entries 11 & 12). Various aryl bromides bearing electron-withdrawing groups such as nitro, cyano, aldehyde and acetyl moieties, and electron releasing groups such as methyl and methoxy moieties react with different substituted aryl boronic acids to afford biaryls in excellent yields (**Table 2**, Entries 1–12). It is worth to note that the amount of homo-coupling products of aryl boronic acids were almost negligible in this protocol.

To further extend the scope of the catalyst system, we next employed some heterocyclic systems as Suzuki–Miyaura coupling partners. Typically, high catalyst loading is required to overcome catalyst deactivation through heteroatom coordination. It may be noted that under slightly extended reaction time, with the 1 mol % of Pd(OAc)₂ and 1 mol% (DHQD)₂PHAL catalytic conditions, pyridine, thiophene, and indole substrates all afforded their cross-coupled products in high isolated yields (**Table 2**, Entries 13–15). We had have run all the reactions in three times to confirm the reproducibility of results and also yields of the desired products (**Table 2**, Entries 1–15).

Table 2. Pd(OAc)₂ and (DHQD)₂PHAL catalysed Suzuki–Miyaura cross-coupling reaction of aryl/heteroaryl halides with aryl boronic acids in H₂O at room temperature^a



Entry	ArX	ArB(OH) ₂	Time (h)	Yield ^b (%)
1			2 ^c , 2 ^d , 2 ^e	88 ^c , 88 ^d , 86 ^e
2			2 ^c , 2 ^d , 2 ^e	89 ^c , 88 ^d , 88 ^e
3			2 ^c , 2 ^d , 2 ^e	87 ^c , 86 ^d , 86 ^e
4			2 ^c , 2 ^d , 2.5 ^e	86 ^c , 85 ^d , 85 ^e
5			2 ^c , 2 ^d , 2 ^e	88 ^c , 87 ^d , 87 ^e
6			2 ^c , 2.5 ^d , 2.5 ^e	85 ^c , 85 ^d , 83 ^e
7			2 ^c , 2 ^d , 2.5 ^e	88 ^c , 86 ^d , 84 ^e
8			2 ^c , 2.5 ^d , 2.5 ^e	82 ^c , 82 ^d , 80 ^e
9			3 ^c , 3 ^d , 3 ^e	80 ^c , 79 ^d , 77 ^e
10			2 ^c , 2.5 ^d , 2.5 ^e	85 ^c , 85 ^d , 82 ^e
11			2 ^c , 2.5 ^d , 2.5 ^e	65 ^c , 64 ^d , 64 ^e
12			2.5 ^c , 2.5 ^d , 2.5 ^e	62 ^c , 62 ^d , 60 ^e
13			3 ^c , 3 ^d , 3 ^e	82 ^c , 80 ^d , 78 ^e
14			3 ^c , 3 ^d , 3 ^e	85 ^c , 85 ^d , 79 ^e
15			3 ^c , 3 ^d , 3 ^e	80 ^c , 78 ^d , 75 ^e

^a Reaction conditions: arylhalide (1 mmol), arylboronic acid (1.2 mmol), Pd(OAc)₂ (0.01 mmol), (DHQD)₂PHAL (0.01 mmol), K₂CO₃ (1.2 mmol) in H₂O (3 mL) at room temperature.

^b Yield of isolated product.

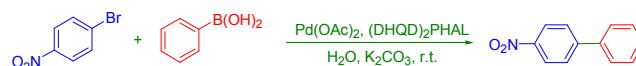
^c 1st run

^d 2nd run

^e 3rd run

In order to highlight the synthetic usefulness of this protocol we turned to an investigation on the recycling of our catalytic system. The results obtained in our experiment confirmed that it was possible to recycle and reuse the catalytic medium after extraction of products with diethyl-ether for at least five times without losing significant catalytic activity (**Table 3**, Entries 1–5).

Table 3. Recyclability of the catalytic system^a



Entry	Run	Time (h)	Yield ^b (%)
1	1 st	2	88
2	2 nd	2	88
3	3 rd	2	86
4	4 th	2.5	86
5	5 th	3	85

^a Reaction conditions: 4-nitrobromobenzene (1 mmol), phenylboronic acid (1.2 mmol), Pd(OAc)₂ (0.01 mmol), (DHQD)₂PHAL (0.01 mmol), K₂CO₃ (1.2 mmol) in H₂O (3 mL) at room temperature.

^b Yield of isolated product.

The reaction was shown to be operationally simplistic and proceed efficiently at room temperature; addition of a catalytic amount of Pd(OAc)₂ followed by (DHQD)₂PHAL, exhibits the best catalytic system in the presence of K₂CO₃ as the base at room temperature without using any promoters/ additives/ organic media. (DHQD)₂PHAL or hydroquinidine 1,4-phthalazinediyl diether which was first introduced by Sharpless *et al.*¹⁰ for asymmetric dihydroxylation of alkenes is a commercially available and air stable multidentate ligand with two potential coordination sites (N and O atoms) offering certain advantages. It is believed that additional coordination sites in the ligand as a stabilizing group during the course of a metal-mediated reaction could improve the catalytic efficiency of the complex.¹¹ In addition, a combination of several factors may be responsible for the unique success of this ligand: (i) its electron-rich nature enhances the rate of oxidative addition and (ii) its steric bulk enhances the rate of reductive elimination. Subsequently, the proper selection of the solvent and base is significant for the success of this process.

In conclusion, we herein presented an improved aqueous protocol with broad applicability regarding the range of substrates and functional group tolerance. Suzuki–Miyaura reaction of diverse aryl/heteroaryl halides and various electron-neutral, electron-rich and electron-deficient aryl boronic acids can be performed under phosphine/organic solvent free conditions, based on Pd(OAc)₂ and (DHQD)₂PHAL in H₂O at room temperature. More importantly, the catalyst system is recyclable/reusable several times without significant loss of catalytic activity.

Experimental

Starting materials and solvents were purchased from common commercial sources and were used without additional purification. ¹H NMR and ¹³C NMR spectra were recorded at 500 MHz or 300 MHz using TMS as internal standard. Mass spectroscopy data of the product of Suzuki reaction was collected on a MS–EI instrument. Infrared spectra were obtained from a FTIR spectrometer.

In a 50 mL round bottomed flask, a mixture of aryl halide (1 mmol), arylboronic acid (1.2 mmol), Pd(OAc)₂ (0.01 mmol), (DHQD)₂PHAL (0.01 mmol) and K₂CO₃ (1.2 mmol) in H₂O (3 mL) and the mixture was stirred at room temperature for a time period as mentioned in Table 3. The progress of the reaction was monitored by TLC. After completion of the reaction it was extracted with diethyl ether (3 x 10 mL) and washed with water. The combined ether extract was dried over anhydrous Na₂SO₄. The filtrate was concentrated under reduced pressure. The product was purified by column chromatography over silica gel using hexane/ethyl acetate (9:1 v/v) to get the desired coupling product. The products were characterized by IR and NMR.

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Notes and references

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Graphical Abstract:

Pd(OAc)₂ and (DHQD)₂PHAL as simple, efficient and recyclable/reusable catalyst system for Suzuki–Miyaura cross–coupling reactions in H₂O at room temperature

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