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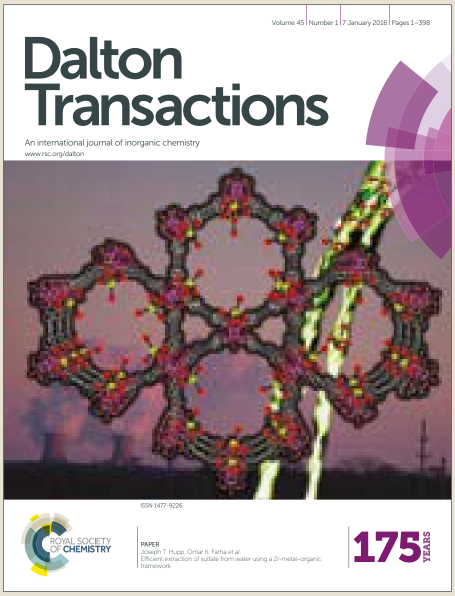

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Synthesis of Zwitterionic Palladium Complexes and Their Application as Catalysts in Cross-Coupling Reactions of Aryl, Heteroaryl and Benzyl Bromides with Organoboron Reagents in Neat Water

*V. Ramakrishna and N. Dastagiri Reddy**

Department of Chemistry, Pondicherry University, Pondicherry 605014, India

*Corresponding author. E–mail: ndreddy.che@pondiuni.edu.in

Abstract: *N*-(3-Chloro-2-quinoxalinyl)-*N′*-arylimidazolium salts (aryl = 2,6-diisopropylphenyl [HL1Cl]Cl, aryl = mesityl [HL2Cl]Cl) have been synthesized by treating 2,3-dichloroquinoxaline with corresponding *N'*-arylimidazole in neat. Facile reactions of these imidazolium salts with $Pd(PPh_3)_4$ and $Pd_2(dba)_3/PPh_3$ (dba = dibenzyledene acetone) at 50 ^oC have afforded zwitterionic palladium(II) complexes $[Pd(HL1)(PPh_3)Cl_2]$ (**I**) and $[Pd(HL2)(PPh_3)Cl_2]$ (**II**) in excellent yields. **I** and **II** have been tested for their ability to catalyze Suzuki-Miyaura cross coupling (SMC) reactions in neat water/K_2CO_3 and are found to be highly active for carrying out these reactions between aryl bromides and organoboron reagents. Further, the scope of the catalyst **I** was also examined by employing (hetero)aryl bromides, hydrophilic aryl bromides, benzyl bromides and various organoboron reagents. More than 80 aryl/benzyl

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bromide-arylboronic acid combinations were screened in neat water/K_2CO_3 and found that **I** is a versatile catalyst, which produced the biaryls/diarylmethanes in excellent yields. A TON of 82,000 was achieved by using **I**. Studies on the mechanism have also been carried out to investigate the involvement of carbene complexes in the catalytic path. Poison tests and two phase test were also conducted and the results are reported.

Key words: 2,3-dichloroquinoxaline; N-heterocyclic carbene; Pd-NHC; Suzuki-Miyaura coupling; zwitterion

Introduction

Palladium–catalyzed Suzuki-Miyaura cross-coupling (SMC) reaction of aryl and benzyl halides with nucleophilic organoboron reagents has been extensively utilized in the construction of unsymmetrical biaryl and diarylmethane derivatives.[1] These structural units are widely found in biologically active compounds, herbicides, natural products, conducting polymers and liquid crystalline materials.[2] In 1979, Suzuki reported Pd catalyzed sp^2(C)–sp^2(C) cross coupling reactions and several years later in 1994, Keay demonstrated sp^3(C)–sp^2(C) coupling.[3] The SMC cross-coupling has emerged as an efficient methodology over Kumada,[4] Hiyama,[5] Stille[6] and Negishi[7] coupling reactions owing to the advantages of the organoboron reagents, which are used in SMC reactions. Organoboron reagents are less toxic, commercially available, thermally stable, not sensitive to air/moisture, and have high tolerance toward the functional groups in substrates.[8] In the literature, a variety of methods have been developed for the SMC reactions such as microwave-heating,[9] ultrasonic-irradiation,[10] ligand-free methodology,[11] water-soluble catalysis,[12] nano catalysis,[13] and the addition of organic co-solvents,[14] surfactants or phase-transfer reagents.[15] Over the past few years, there has been a growing interest to exploit water as

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a solvent for the SMC reactions.[16] Water being an ideal solvent from a green chemistry perspective has a greater scope as an alternative to organic solvent as it is inexpensive, readily available, renewable, non-flammable and non-toxic. Moreover, if water is used as a solvent, the desiccation of the substrates is not required and the products can easily be separated.[17]

Traditionally, sulfonate, carboxylate, and ammonium groups have been incorporated into ligands in order to improve the water solubility of metal complexes.[18] In this context, zwitterionic metal complexes have received considerable attention. The most common among the zwitterionic metal complexes are of two types. One is with a formal cationic charge on the metal center and an associated anionic ancillary ligand. The other type is with a formal anionic charge on the metal center and an associated cationic ancillary ligand.[19] Though several zwitterionic complexes of Pd are known in the literature, only a few of them have been studied for their catalytic activity.[18c,h,20] Recently, a few such complexes with a formal negative charge on Pd have been reported in the literature (Figure 1, **a** - **e**). However, except for **c**, catalytic activity of these complexes has not been explored.[20a-f] Lee and his co-workers have reported that **c** is highly active in carrying out the SMC reactions in aqueous medium (4:1 dioxane/water).[20f] Hence, we became interested in synthesizing zwitterionic Pd(II) complexes with formal anionic charge on the metal. Herein, we report the facile synthesis of zwitterionic palladium(II) complexes (Figure 1) and their efficiency as catalysts in water mediated sp^2(C)–sp^2(C) and sp^3(C)–sp^2(C) carbon coupling reactions.

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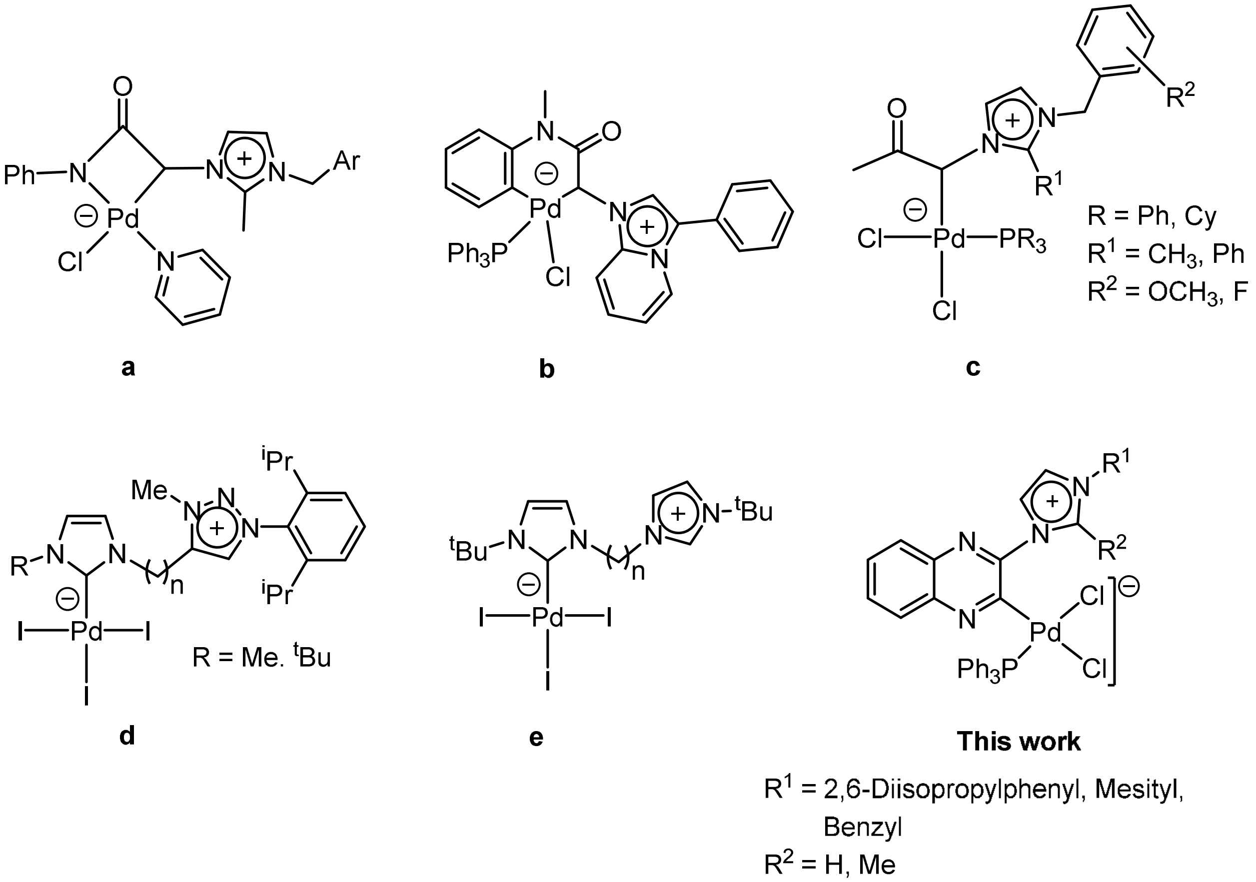

Figure 1 Examples of zwitterionic anionic Pd(II) complexes derived from imidazole or triazole derivatives

Results and Discussion

N-(3-Chloro-2-quinoxalinyl)-*N′*-arylimidazolium salts [HL1Cl]Cl (aryl = 2,6-diisopropylphenyl) and [HL2Cl]Cl (aryl = mesityl) were prepared as ligand precursors from inexpensive reactants 2,3-dichloroquinoxaline and the corresponding *N′*-arylimidazoles in a single step in very high yields (Scheme 1). These salts were characterized by NMR spectroscopy. The ^{1}H NMR spectrum in DMSO-d_6 displayed a singlet in downfield region (~10.60 and ~10.80 ppm), characteristic to the acidic NC**H**N proton. Further, the solid state structure of the imidazolium salt [HL2Cl]PF_6 was confirmed from single crystal X-ray diffraction analysis and

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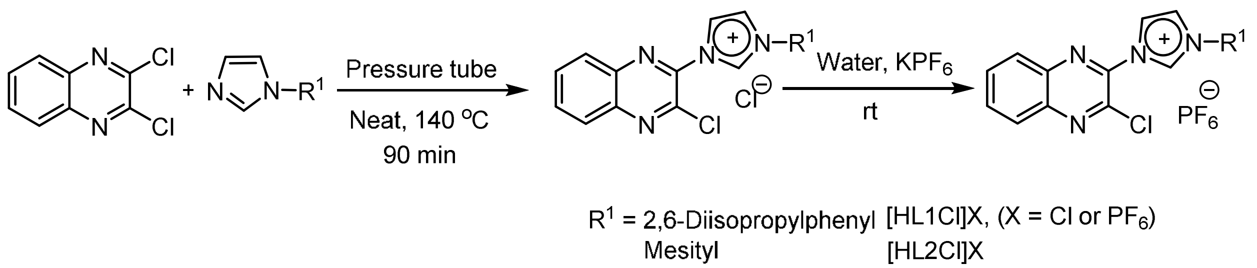
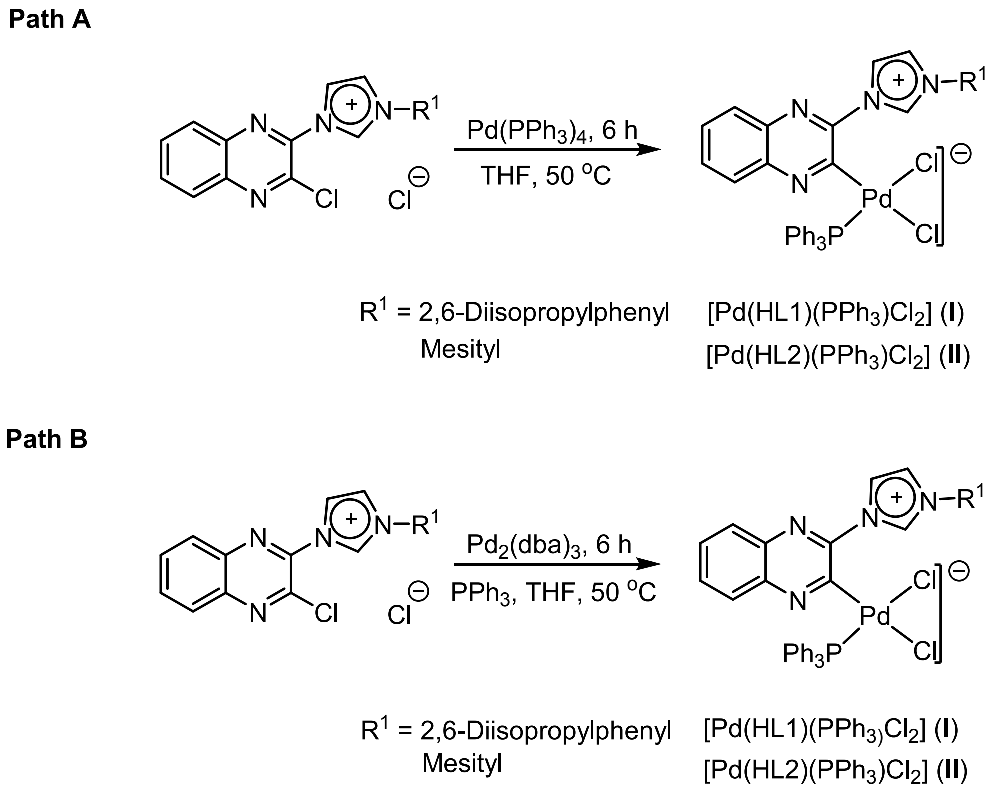
an ORTEP diagram of the molecular structure is shown in Figure S1 (see Electronic Supplementary Information).



Scheme 1 Synthesis of imidazolium salts



Scheme 2 Synthesis of zwitterionic Pd(II) complexes

The Pd(II) complexes were synthesized by the reaction of the imidazolium salts with commercially available $Pd(PPh_3)_4$ or $Pd_2(dba)_3/PPh_3$ in THF at 50 °C (Scheme 2). The C−Cl bond is oxidatively added to Pd(0) to afford pale/bright yellow zwitterionic Pd(II) complexes $[Pd(HL1)(PPh_3)Cl_2]$ (**I**) and $[Pd(HL2)(PPh_3)Cl_2]$ (**II**), which were characterized using NMR spectroscopy and elemental analysis. While the presence of the imidazolium group and PPh_3 was

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evident from the ^{1}H NMR spectra, the ^{31}P NMR spectra confirmed the coordination of PPh_3 to Pd. In order to explore the structural features of these complexes, single crystal X-ray diffraction analysis was performed on single crystals grown from saturated solutions of the complexes in acetonitrile at 0 °C. The ORTEP diagrams depicting the molecular structures of **I** and **II** are given in Figure 2 and the selected bond parameters are listed in Table 1. The structures reveal that the metal in both the complexes is in slightly distorted square planar geometry and coordinated by an *ortho*-heteroaryl carbon of the quinoxaline ring, triphenyl phosphine and two chloride ions. The quinoxaline ring is almost orthogonal to the coordination plane of the metal with a dihedral angle of 87.50^o in **I** and 81.46^o & 86.55^o in **II**. The imidazolium ring is also not coplanar with the quinoxaline ring and the dihedral angle between the planes is 23.33^o in **I** and 32.59^o & 32.66^o in **II**. The structure further reveals that both **I** and **II** are *cis* complexes. The Pd−C bond length was found to be 1.988(2) Å in **I** and 2.003(5) Å & 1.997(5) Å in **II**, which is in accordance with the reports in the literature.[20c,f]

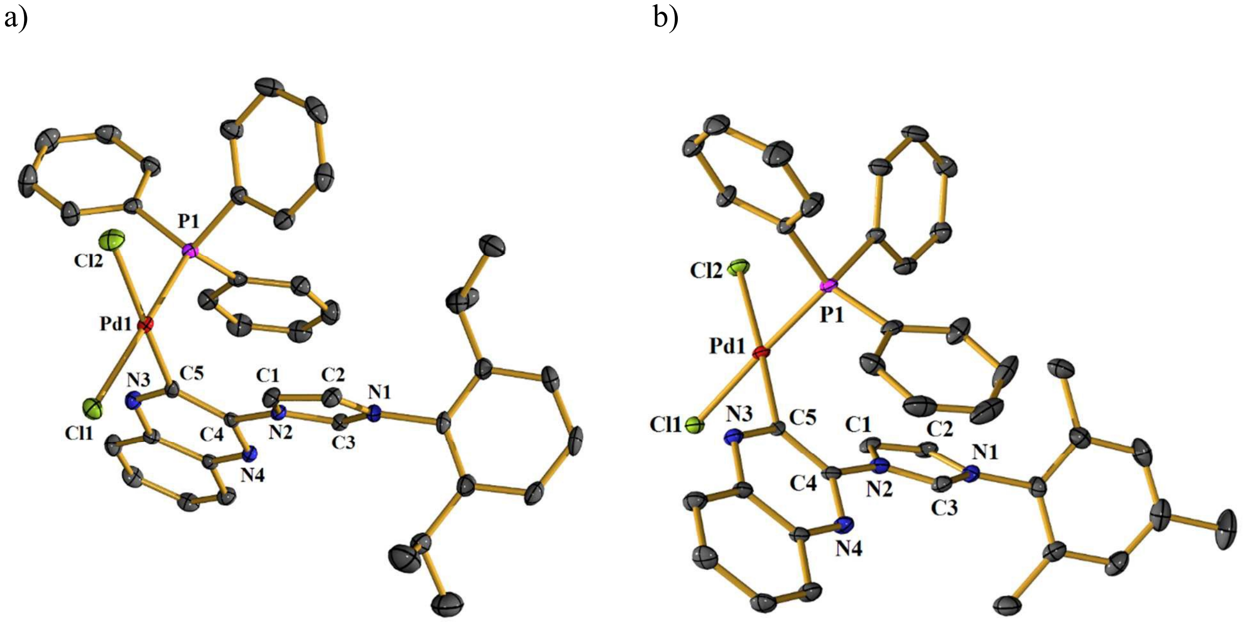

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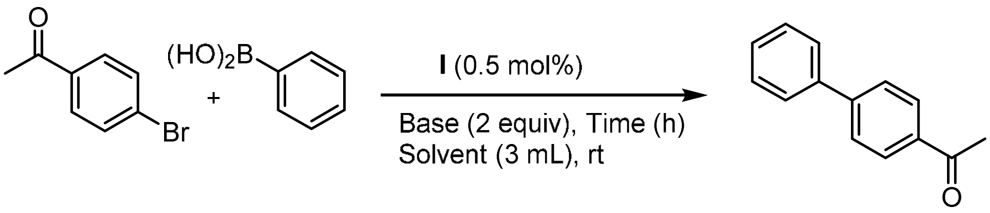
Figure 2 a) Molecular structure of **I**, b) molecular structure of **II**. All hydrogen atoms and solvent molecules have been removed for clarity. Thermal ellipsoids are drawn at 50% probability level.

Table 1 Selected bond parameters of [Pd(HL1)(PPh_3)Cl_2] (**I**) and [Pd(HL2)(PPh_3)Cl_2] (**II**).

Bond lengths [Å]				Bong angles [^{o}]			
	I	**II**	**II***		**I**	**II**	**II***
Pd1−P1	2.2454(6)	2.2588(14)	2.2626(14)	C5−Pd1−Cl1	88.93(6)	86.38(14)	87.50(14)
Pd1−C5	1.988(2)	2.003(5)	1.997(5)	C5−Pd1−P1	89.61(6)	90.98(14)	91.36(14)
Pd1−Cl1	2.3771(5)	2.3796(13)	2.3838(13)	Cl1−Pd1−Cl2	93.40(2)	92.07(5)	91.05(5)
Pd1−Cl2	2.3981(5)	2.3942(12)	2.3918(12)	P1−Pd1−Cl2	88.03(2)	90.58(5)	90.09(5)
N2−C4	1.442(3)	1.441(7)	1.440(6)	P1−Pd1−Cl1	177.37(2)	177.33(5)	178.83(5)
C4−C5	1.438(3)	1.431(7)	1.432(7)	C5−C4−N2	121.57(18)	122.3(4)	120.8(4)
N4−C4	1.300(0)	1.305(6)	1.304(7)	N4−C4−N2	112.93(18)	112.5(4)	114.2(4)
N3−C5	1.316(3)	1.307(6)	1.311(6)	C5−Pd1−Cl2	177.47(6)	177.65(15)	178.47(14)
N1−C3	1.332(3)	1.334(7)	1.332(7)	N3−C5−Pd1	116.78(15)	116.5(3)	115.6(4)

* Two molecules are present in the asymmetric unit of **II**

Table 2 Optimization of reaction conditions[a]



Entry	Base	Solvent	Time (h)	[b]Yield (%)
1	K_2CO_3	1,4-dioxane	5	81
2	K_2CO_3	1,4-dioxane/water (2:1)	8	92
3	K_2CO_3	1,4-dioxane/water (1:2)	5	95
4	K_2CO_3	DMF/water (1:2)	5	94
5	K_2CO_3	Isopropanol/water (1:2)	5	95
6	K_2CO_3	DMSO/water (1:2)	5	85
7	K_2CO_3 or Na_2CO_3	water	3	96
8	NaOAc	water	3	61
9	KOAc	water	3	55
10	NaOH	water	3	28
11	KOH	water	3	21

[a] Reaction conditions: 4-bromoacetophenone (1.0 mmol), phenylboronic acid (1.2 mmol), K_2CO_3 (2.0 mmol), solvent (3 mL), [Pd] (0.5 mol%), at room temperature, in air. [b] Isolated yield after column chromatography.

As the main aim of designing and synthesizing **I** and **II** is to use them as catalysts for the SMC reactions in aqueous medium, a number of experiments were carried out using them as catalysts under various conditions. It has been well established that the combination of the solvent and the base play a significant role in SMC reactions.[21] Therefore, the probe began with optimizing a model reaction between 4-bromoacetophenone and phenylboronic acid in various solvent/base combinations in the presence of 0.5 mol% of the catalysts at rt. The results of the reactions using **I** have been illustrated in Table 2. **II** also showed similar activity. It was observed that all the reactions, wherever there was a combination of water and K_2CO_3, afforded the cross coupling product in excellent yields (Table 2, entries 2-7). The best combination was found to be neat water and K_2CO_3 (or Na_2CO_3) with yields reaching near quantitative in 3 h (Table 2, entry 7). The catalysts could not perform well with the combination of strong bases and H_2O, which is reflected in low yields of the product. Organotrifluoroborates, which can easily be prepared by the treatment of a boronic acid with potassium hydrogen fluoride, have advantages over boronic acid such as greater stability to air and moisture, easy isolation and no trimer formation.[22] To the best of our knowledge, there are only a few articles reported in the literature, which describe the SMC reactions in aqueous medium utilizing organotrifluoroborates in place of boronic acids.[23] Hence, we further investigated the aforementioned optimized SMC reaction using potassium phenyltrifluoroborate in place of phenylboronic acid. Though at room temperature the reaction in water with K_2CO_3 as base yielded only 80% of the cross coupled product, when the reaction was conducted at 70 °C the yield was quantitative in 3 h. All these probe reactions were conducted

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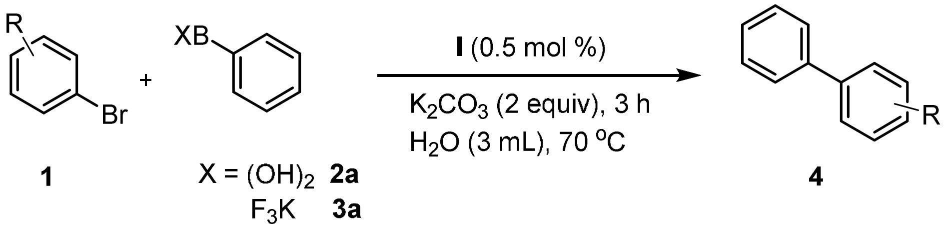
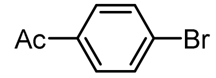
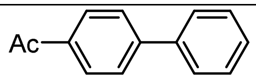
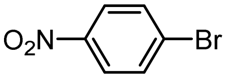
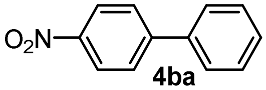
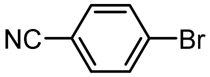
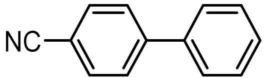
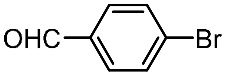
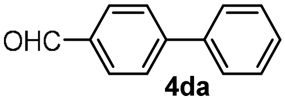
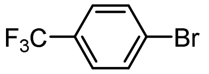
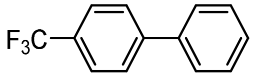
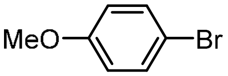
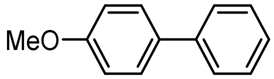
using both the catalysts **I** and **II** separately and found that they are equally efficient. The fact that none of these reactions produced homocoupling by-products make these palladium complexes highly efficient catalyst precursors for the SMC reactions.

Table 3 Suzuki-Miyaura cross-coupling reaction of substituted aryl bromides with phenylboronic acid and potassium phenyltrifluoroborate in neat water[a]



Entry	Aryl bromide **1**	Organoboron reagent	Biaryl **4**	[b]Yield (%)
1	 **1a**	**2a** **3a**	 **4aa**	98 (**2a**)[c] 98 (**3a**)
2	 **1b**	**2a** **3a**	 **4ba**	97 (**2a**)[c] 95 (**3a**)
3	 **1c**	**2a** **3a**	 **4ca**	98 (**2a**)[c] 97 (**3a**)
4	 **1d**	**2a** **3a**	 **4da**	96 (**2a**)[c] 98 (**3a**)
5	 **1e**	**2a** **3a**	 **4ea**	95 (**2a**) 94 (**3a**)
6	 **1f**	**2a** **3a**	 **4fa**	95 (**2a**) 96 (**3a**)

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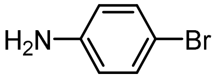
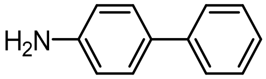
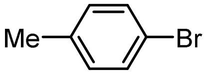
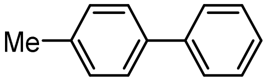
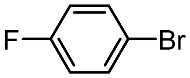
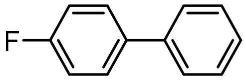
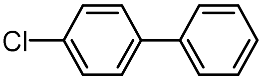
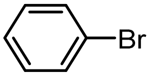
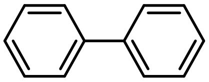
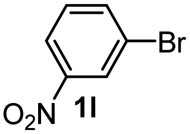
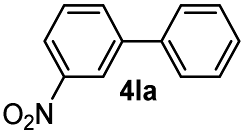
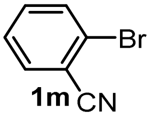
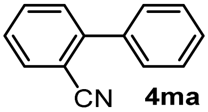
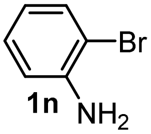
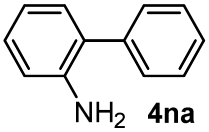
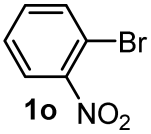
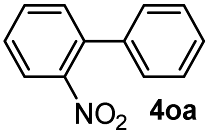
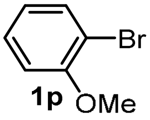
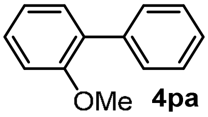
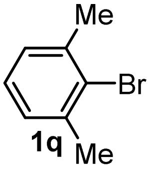
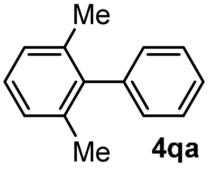
7	 **1g**	**2a** **3a**	 **4ga**	95 (**2a**) 93 (**3a**)
8	 **1h**	**2a** **3a**	 **4ha**	95 (**2a**) 93 (**3a**)
9	 **1i**	**3a**	 **4ia**	96
10	 **1j**	**3a**	 **4ja**	97
11	 **1k**	**2a** **3a**	 **4ka**	97 (**2a**) 95 (**3a**)
12	 **1l**	**2a** **3a**	 **4la**	96 (**2a**) 94 (**3a**)
13	 **1m**	**2a** **3a**	 **4ma**	95 (**2a**) 93 (**3a**)
14	 **1n**	**2a** **3a**	 **4na**	93 (**2a**) 92 (**3a**)
15	 **1o**	**2a** **3a**	 **4oa**	95 (**2a**) 93 (**3a**)
16	 **1p**	**3a**	 **4pa**	94
17	 **1q**	**3a**	 **4qa**	91[c,d]

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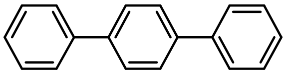
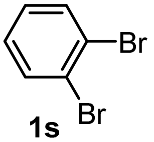
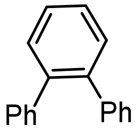
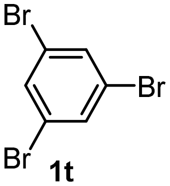
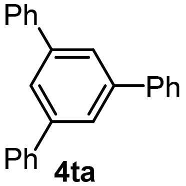
18	 **1r**	**2a** **3a**	 **4ra**	95 (**2a**) 93 (**3a**)
19	 **1s**	**2a** **3a**	 **4sa**	94 (**2a**)[c,d] 92 (**3a**)[c,d]
20	 **1t**	**2a** **3a**	 **4ta**	95 (**2a**) 94 (**3a**)

[a]Reaction conditions: 1/n mmol of aryl bromide (n = number of bromine atoms on aryl ring), organoboron reagent (**2a** or **3a**) (1.2 mmol), K_2CO_3 (2.0 mmol), H_2O (3 mL), [Pd] (0.5 mol%), reaction time of 3 h, in air. [b]Isolated yield (purity of the isolated product was confirmed by ^1H NMR), [c]at rt. [d]Isolated yields after column chromatography.

To expand the scope of the catalyst **I**, we further studied the SMC reactions of the organoboron reagents [phenylboronic acid (**2a**) and potassium phenyltrifluoroborate (**3a**)] with the aryl bromides containing various substituents including diverse functional groups. The products were separated by simply filtering the reaction mixture if they are solids and in case of semi-solids and oily substances they were extracted with diethyl ether. However, in few cases column chromatography was needed to purify the products. It was observed that the products that were separated by filtering the reaction mixture were found to contain traces of Pd black, which was removed by dissolving them in ethyl acetate and filtering the solution through a plug of silica or celite. The results of these coupling reactions are furnished in Table 3. All the substituted aryl bromides, irrespective of the nature of the substituent, afforded the desired products in excellent yields. When phenylboronic acid was employed, except in four cases (Table 3, entries 1–4), all the 20 aryl bromides screened required higher temperature (70 ^oC) for

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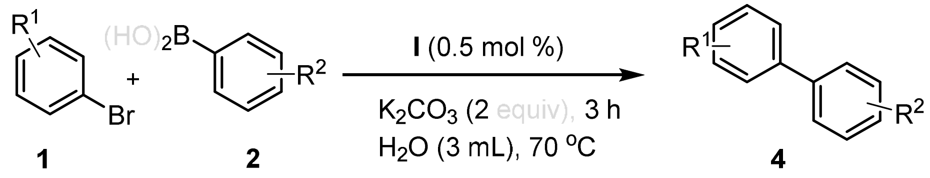
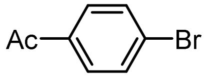
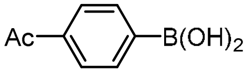
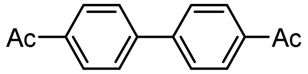
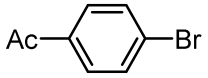
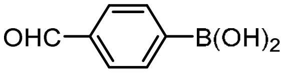
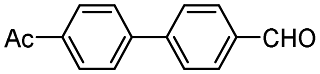
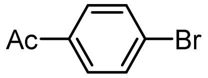
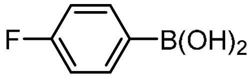
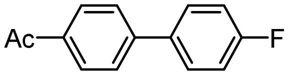
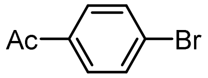
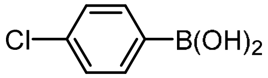
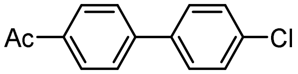
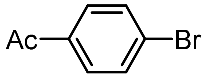
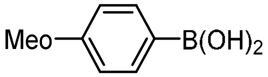
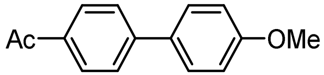
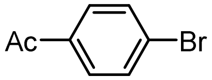
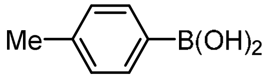
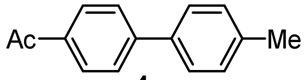
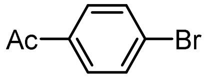
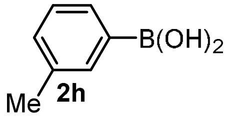
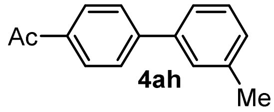
the completion of the reaction in 3 h. However, all the reactions involving potassium phenyltrifluoroborate took place only at 70 °C to afford the cross coupled products in excellent yields. Moderately hindered aryl bromides also underwent quantitative coupling with **2a** and **3a** (Table 3, entries 13–17). Two terphenyls and one quarterphenyl were synthesized successfully using dibromo- and tribromobenzene in high yields respectively (Table 3, entries 18–20).

Table 4 Suzuki-Miyaura coupling of substituted phenylboronic acids with aryl bromides in neat water[a]



Entry	Aryl halide 1	Boronic acid	Biaryl 4	[b]Yield (%)
1	 **1a**	 **2b**	 **4ab**	98
2	 **1a**	 **2c**	 **4ac**	95
3	 **1a**	 **2d**	 **4ad**	95
4	 **1a**	 **2e**	 **4ae**	96
5	 **1a**	 **2f**	 **4af**	91[c]
6	 **1a**	 **2g**	 **4ag**	98
7	 **1a**	 **2h**	 **4ah**	93

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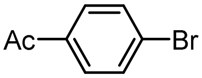
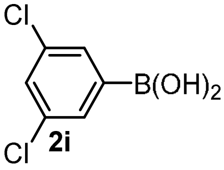
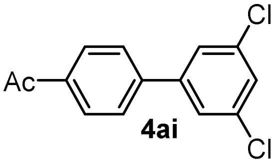
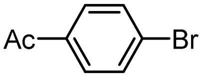
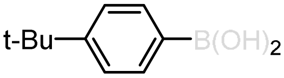
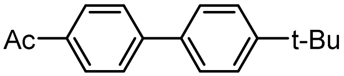
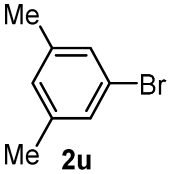
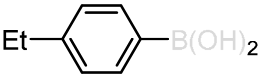
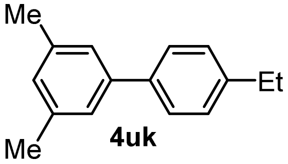
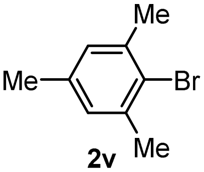
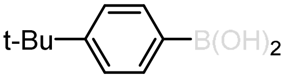
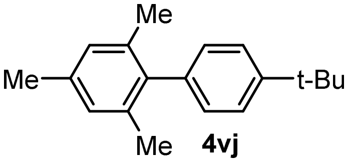
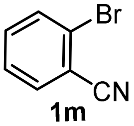
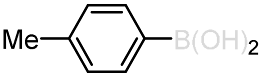
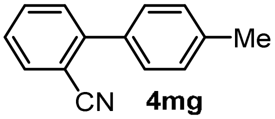
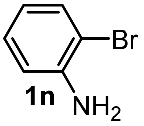
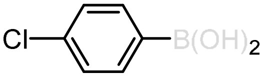
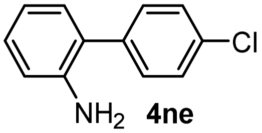
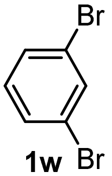
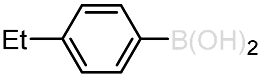
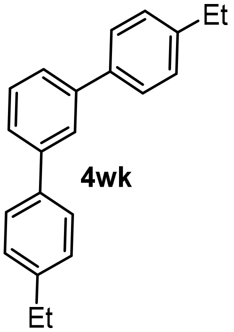
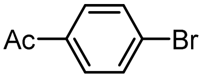
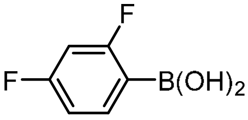
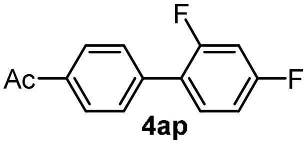
8	 **1a**	 **2i**	 **4ai**	96
9	 **1a**	 **2j**	 **4aj**	95
10	 **2u**	 **2k**	 **4uk**	96
11	 **2v**	 **2j**	 **4vj**	95
12	 **1m**	 **2g**	 **4mg**	93
13	 **1n**	 **2e**	 **4ne**	92[c]
14	 **1w**	 **2k**	 **4wk**	96
15	 **1a**	 **2p**	 **4ap**	55

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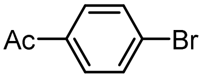
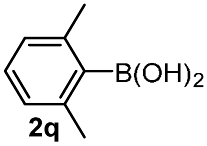
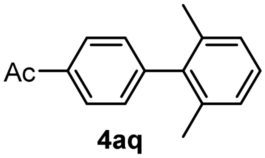
16	 **1a**	 **2q**	 **4aq**	Nil

[a]Reaction conditions: 1/n mmol of aryl bromide (n = number of bromine atoms on aryl ring), arylboronic acid (1.2 mmol), K_2CO_3 (2.0 mmol), H_2O (3 mL), [Pd] (0.5 mol%), at 70 ºC, reaction time of 3 h, in air. [b]Isolated yield (purity of the isolated product was confirmed by ^{1}H NMR). [c]Isolated yield after column chromatography.

The SMC reactions were also conducted on a wide variety of arylboronic acids using **I** to examine the scope of the catalyst. In most of these reactions (Table 4 entries 1–9), 4-bromoacetophenone (**1a**) was employed, but a few other substituted aryl bromides (Table 4, entries 10–14) were also used to crosscheck the applicability of the catalyst for various boronic acid-bromobenzene combinations. In all the cases, the reaction was completed in 3 h at 70 ^{o}C and excellent yields of the cross coupled products were obtained. However, when the reactions were conducted at room temperature the yields were low (50 - 70%). Further, when the moderately hindered boronic acid 2,4-difluorophenylboronic acid (Table 4, entry 15) was used with 4-bromoacetophenone, the yield was drastically reduced to 55%. Sterically demanding 2,6-dimethylphenylboronic acid (Table 4, entry 16) afforded no cross coupled product. These results and also entry 17 in Table 4 suggest that the catalytic efficiency of the complex **I** does not depend on the steric crowd on the aryl bromide, but is highly sensitive to the bulkiness of the boronic acid. In some of the cases (Table 4, entries 9, 10, 11 and 14), formation of <10% of homo-coupled products of boronic acid was also observed and hence the cross-coupled products were purified by column chromatography.

Table 5 Synthesis of biaryls containing heteroaromatic ring catalyzed by **I**[a]

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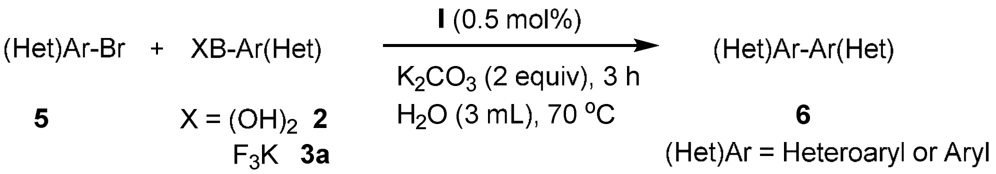
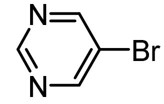
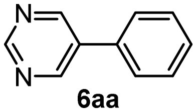
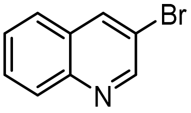
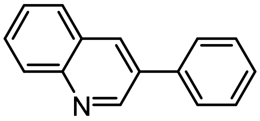
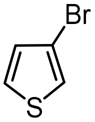
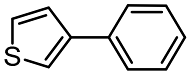
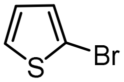
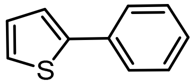
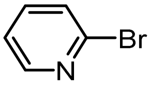
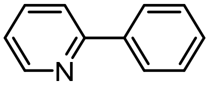
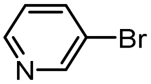
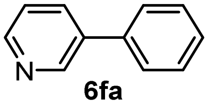
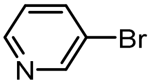
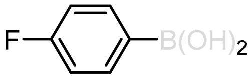
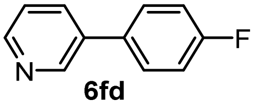
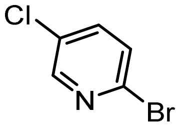
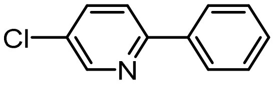


Entry	Aryl bromide **5**	Organoboron reagent	Biaryl **6**	[b]Yield (%)
1	 **5a**	**2a** **3a**	 **6aa**	92 (**2a**) 95 (**3a**)
2	 **5b**	**2a** **3a**	 **6ba**	92 (**2a**) 90 (**3a**)
3	 **5c**	**2a** **3a**	 **6ca**	92 (**2a**) 93 (**3a**)
4	 **5d**	**2a** **3a**	 **6da**	95 (**2a**) 93 (**3a**)
5	 **5e**	**2a** **3a**	 **6ea**	95 (**2a**) 96 (**3a**)
6	 **5f**	**3a**	 **6fa**	96
7	 **5f**	 **2d**	 **6fd**	92
8	 **5g**	**2a**	 **6ga**	94[c]

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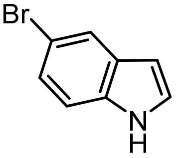
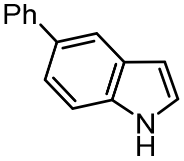
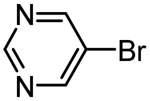
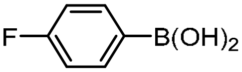
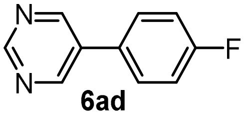
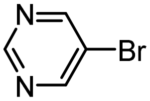
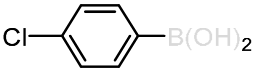
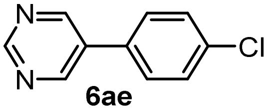
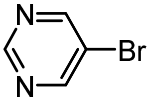
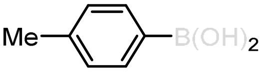
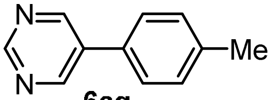
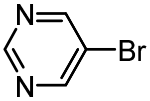
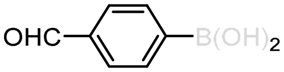
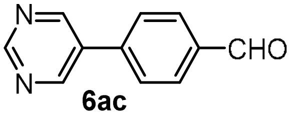
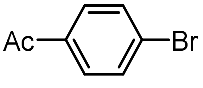
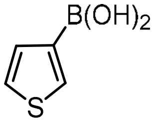
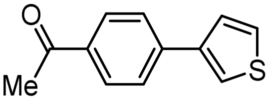
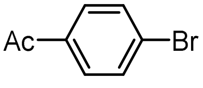
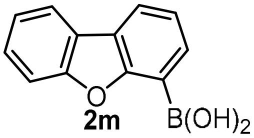
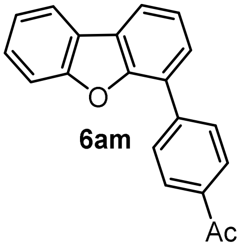
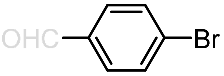
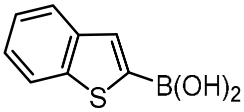
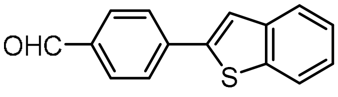
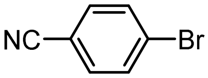
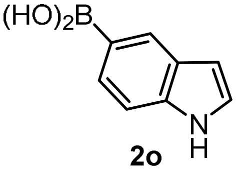
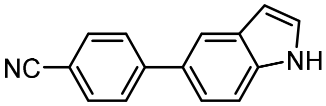
9	 **5h**	**2a**	 **6ha**	93^{c}
10	 **5a**	 **2d**	 **6ad**	95
11	 **5a**	 **2e**	 **6ae**	96
12	 **5a**	 **2g**	 **6ag**	93
13	 **5a**	 **2c**	 **6ac**	96
14	 **1a**	 **2l**	 **6al**	92^{c}
15	 **1a**	 **2m**	 **6am**	88^{c}
16	 **1d**	 **2n**	 **6dn**	65^{c}
17	 **1c**	 **2o**	 **6co**	85^{c}

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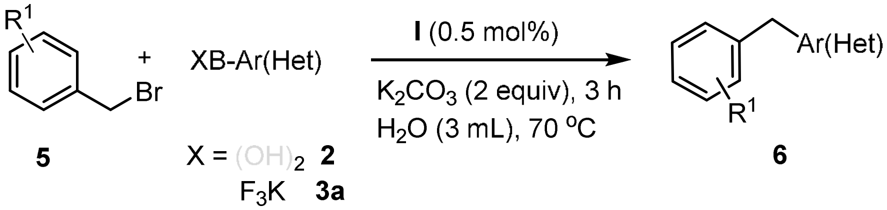
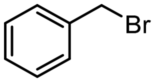
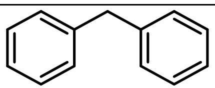
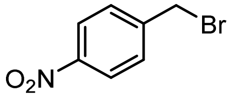
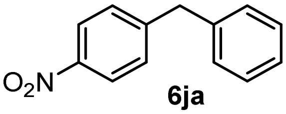
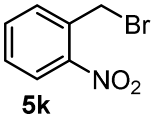
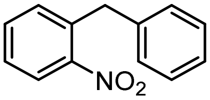
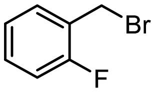
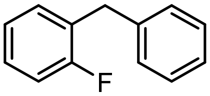
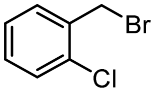
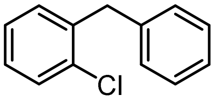
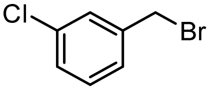
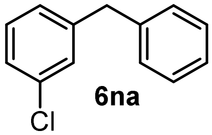
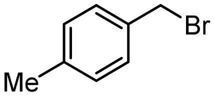
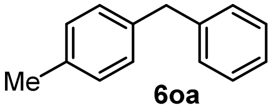
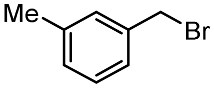
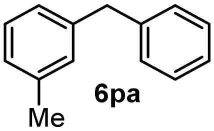
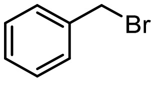
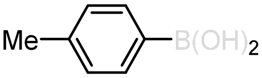
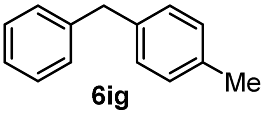
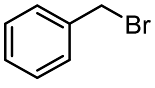
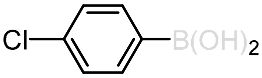
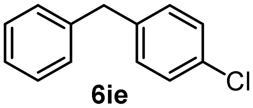
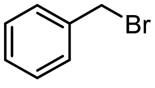
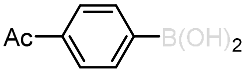
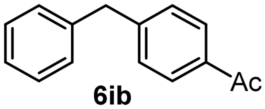
[a]Reaction conditions: aryl bromide (1.0 mmol), organoboron reagent (1.2 mmol), K_2CO_3 (2.0 mmol), H_2O (3 mL), [Pd] (0.5 mol%), at 70 ºC, reaction time of 3 h, in air. [b]Isolated yield (purity of the isolated product was confirmed by ^1H NMR). [c]Isolated yield after column chromatography.

Aryl-heteroaryl and heteroaryl-heteroaryl moieties are commonly present in drugs and bioactive natural products.[1] Synthesis of such systems through the SMC reaction is quite challenging owing to the ligating ability of the heteroatoms, which can lead to the catalyst deactivation by forming stable Pd(II) complexes. Hence the literature on their synthesis is limited to only a few articles. Reports on such reactions in water are even less.[24] In the present investigation, we also examined the ability of **I** to bring about the coupling between heteroaryl bromides and organoboron reagents and in few cases between aryl bromides and heteroarylboronic acids under the said optimized reaction conditions (Table 5). Except the reaction between 4-bromobenzaldehyde and benzothiophene-2-boronic acid (Table 5, entry 16), which gave the corresponding cross coupled product in moderate yield, all the reactions yielded the biaryls in excellent yields. It is noteworthy that indole-5-boronic acid, without any protection of NH group, also underwent coupling with 4-bromobenzonitrile in water and produced the corresponding biaryl in very good yield (Table 5, entry 17).

Table 6. Suzuki-Miyaura *sp*^{3}(C)–*sp*^{2}(C) cross-coupling of benzyl bromides with aryl boronic acids and potassium phenyltrifluoroborate[a]



DOI: 10.1039/C7DT01433C

Entry	Benzyl bromide **5**	Organoboron reagent	Methylene bridged biaryl **6**	[b]Yield (%)
1	 **5i**	**3a**	 **6ia**	98
2	 **5j**	**3a**	 **6ja**	96
3	 **5k**	**3a**	 **6ka**	92
4	 **5l**	**3a**	 **6la**	91
5	 **5m**	**3a**	 **6ma**	94
6	 **5n**	**3a**	 **6na**	93
7	 **5o**	**3a**	 **6oa**	94
8	 **5p**	**3a**	 **6pa**	97
9	 **5i**	 **2g**	 **6ig**	92
10	 **5i**	 **2e**	 **6ie**	95
11	 **5i**	 **2b**	 **6ib**	92[c]

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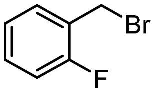
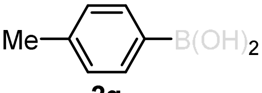
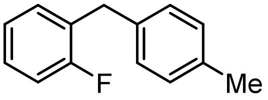
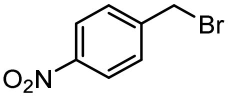
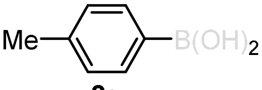
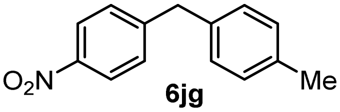
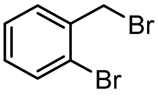
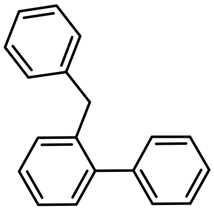
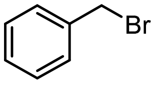
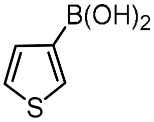
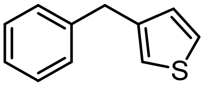
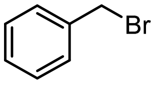
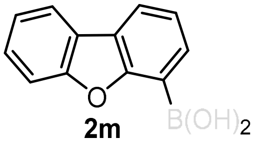
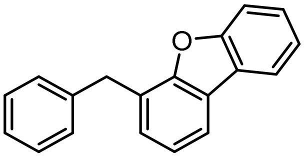
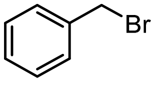
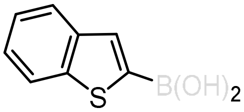
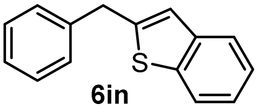
12	 **5l**	 **2g**	 **6lg**	92
13	 **5j**	 **2g**	 **6jg**	93
14[d]	 **5q**	**2a** **3a**	 **6qa**	95 (**2a**) 94 (**3a**)
15	 **5i**	 **2l**	 **6il**	93
16	 **5i**	 **2m**	 **6im**	91[c]
17	 **5i**	 **2n**	 **6in**	85[c]

[a]Reaction conditions: benzyl bromide (1.0 mmol), organoboron reagent (**2** or **3a**, 1.2 mmol), K_2CO_3 (2.0 mmol), H_2O (3 mL), [Pd] (0.5 mol%), at 70 ºC, reaction time of 3 h, in air. [b]Isolated yield (Purity of the isolated product was confirmed by ^{1}H NMR). [c]Isolated yield after column chromatography. [d]Organoboron reagent (**2** or **3a**, 2.4 mmol)

Further, the catalyst **I** was also probed to carry out sp^3(C)−sp^2(C) coupling between a series of benzyl bromides and organoboron reagents **2** and **3a** (Table 6). The resultant diarylmethane derivatives constitute an important class of building blocks in the synthesis of supramolecules and bio-active organic molecules. A thorough literature search revealed that only

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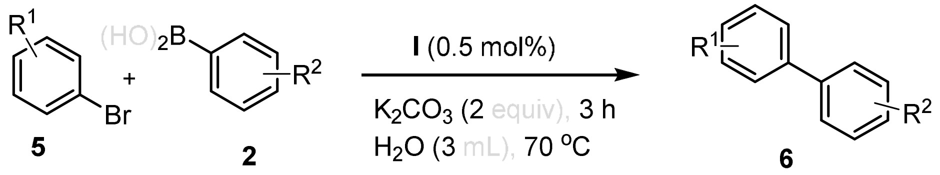
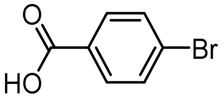
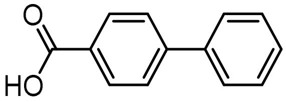
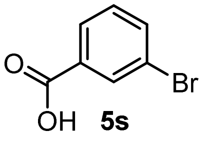
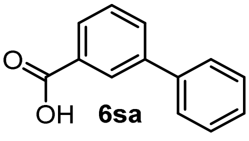
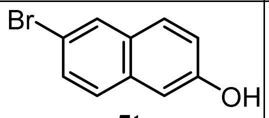
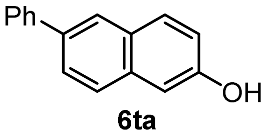
a few examples of aqueous-phase SMC reactions of benzyl halides have been reported so far.[25] In this study, a series of eight benzyl bromides were studied for their coupling reaction with potassium phenyltrifluoroborate **3a** and few arylboronic acids including heteroarylboronic acids using **I** as a catalyst in water at 70 °C. All the reactions produced diarylmethanes in very good yields, which can be seen in Table 6. Initially, selected benzyl bromides were screened with **3a** (Table 6, entries 1−8). Upon successful applicability of **I** in carrying out *sp*^{3}(C)–*sp*^{2}(C) coupling in these substrates, the catalyst was tested further for its ability to catalyze the reactions between various combinations of benzyl bromides and arylboronic acids (Table 6, entries 9−13). Even the heteroaryl boronic acids employed in this study also produced very good yields (Table 6, entries 15−17). In case of 2-bromobenzyl bromide both *sp*^{3}(C)–*sp*^{2}(C) and *sp*^{2}(C) *sp*^{2}(C) couplings took place when slightly more than two equivalents of organoboron reagent (**2a** or **3a**) were used under similar conditions (Table 6, entry 14).

Table 7 Suzuki-Miyaura coupling of hydrophilic aryl bromides with arylboronic acids[a]



Entry	Aryl halide **5**	Boronic acid **2**	Biaryl **6**	[b]Yield (%)
1	 **5r**	**2a**	 **6ra**	98
2	 **5s**	**2a**	 **6sa**	97
3	 **5t**	**2a**	 **6ta**	98

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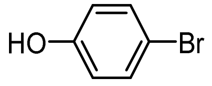
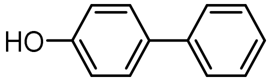
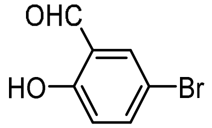
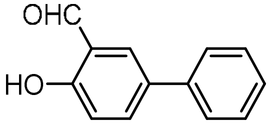
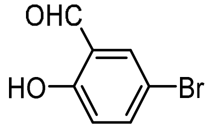
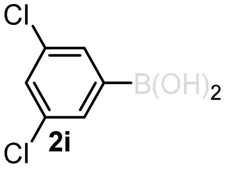
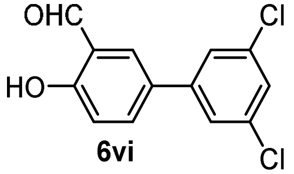
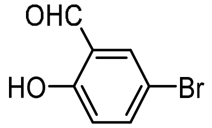
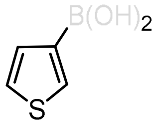
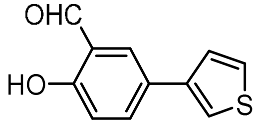
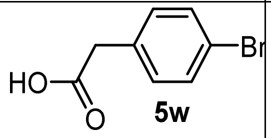
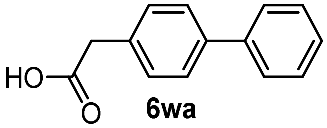
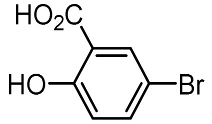
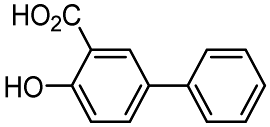
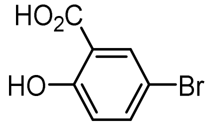
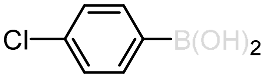
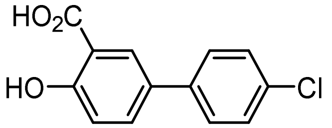
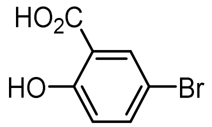
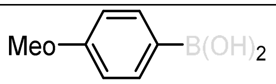
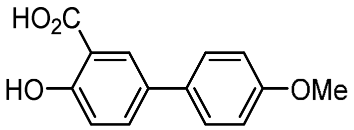
4	 **5u**	**2a**	 **6ua**	97
5	 **5v**	**2a**	 **6va**	98
6	 **5v**	 **2i**	 **6vi**	95^{c}
7	 **5v**	 **2l**	 **6vl**	98
8	 **5w**	**2a**	 **6wa**	98
9	 **5x**	**2a**	 **6xa**	98
10	 **5x**	 **2e**	 **6xe**	97
11	 **5x**	 **2f**	 **6xf**	98

[a]Reaction conditions: aryl bromide (1.0 mmol), arylboronic acid (**2**) (1.2 mmol), K_2CO_3 (2.0 mmol), H_2O (3 mL), [Pd] (0.5 mol%), at 70 ºC, reaction time of 3 h, in air. [b]Isolated yield (the

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purity of the isolated product was confirmed by ^{1}H NMR). ^{c}Isolated yield after column chromatography.

Biaryls containing hydrophilic functional groups are intermediates in many pharmaceutical compounds and liquid crystal materials. Due to the low solubility of these hydrophilic bromides in common organic solvents, high polar solvents like DMF, dimethyl acetamide and DMSO are frequently used for constructing hydrophilic biaryls *via* the SMC route.[26] The major problem in using these solvents lies in difficulty in extracting and purifying the products. Whereas, when water is used as solvent, the biaryls can easily be separated in pure form without any loss especially when the conversion is quantitative. So far there is only one report available in the literature, which describes the synthesis of hydrophilic functionalized biaryls through water mediated SMC reactions. The authors demonstrated that $[PdCl_2(NH_2CH_2COOH)_2]/K_2CO_3$ system showed excellent activity in catalyzing the SMC reactions of a wide variety of water soluble aryl bromides with boronic acids at room temperature.[27] In the present work, **I** was also tested for its ability to catalyze the SMC reactions between hydrophilic aryl bromides and arylboronic acids in neat water and found that it was a highly efficient catalyst, which produced the biaryls in almost quantitative yields (Table 7). Out of the 11 biaryls synthesized only one compound required purification by column chromatography and all the other biaryls were obtained in pure form by neutralizing the reaction mixture with 4N HCl followed by filtration. The anti-inflammatory drug felbinac (Table 7, entry 8) was synthesized with >98% purity (as per ^{1}H NMR analysis) just by neutralization and filtration. Most of the synthetic procedures currently used for making this drug require column chromatography or other purification methods.[28] Several arylboronic acid/hydrophilic aryl bromide combinations were screened and found that the biaryls were produced in almost

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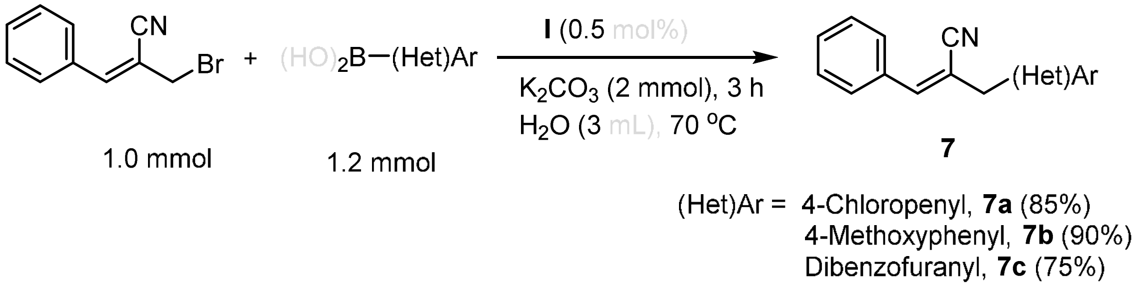
quantitative yields. Identical conditions were also explored for coupling 2-(bromomethyl)-3-phenylacrylonitrile with aryl or heteroarylboronic acids, as depicted in Scheme 3. The corresponding cross coupled products **7a**, **7b** and **7c** were obtained in excellent yields.



Scheme 3 Suzuki-Miyaura coupling of 2-(bromomethyl)-3-phenylacrylonitrile

For an economically viable synthesis of fine chemicals, a low loading catalyst is needed.[29] In this regard, we probed **I** and **II** for their ability to execute the SMC reaction between 4-bromoacetophenone and phenylboronic acid at various catalyst loadings at rt and also at 70 °C. The results, which are given in Table S1 (see electronic supplementary information (ESI)) indicate that the catalysts **I** and **II** are equally efficient and even with the loading as low as 0.001 mol% (500 times lower than the optimized loading), afforded the cross coupled product in 82% yield at 70 °C in 24 h with excellent TONs (82,000 with **I** and 80,000 with **II**).

Insights into mechanism

In order to understand the mechanistic path of these reactions, an NMR tube reaction was conducted between the imidazolium complex **I** and K_2CO_3 in D_2O at rt under ultra-sonication. The ^1H NMR recorded after 10 minutes showed no signals due to the insolubility of the contents of the reaction mixture in water. The water was syringed out and the residue was dissolved in $CDCl_3$ to obtain a ^1H NMR spectrum, which showed full conversion of the imidazolium complex to a carbene complex $[Pd(L1)(PPh_3)Cl]$ (**III**). Later, the carbene complexes **III** and $[Pd(L2)(PPh_3)Cl]$ (**IV**) were synthesized from **I** and **II** respectively using DMAP as a base in

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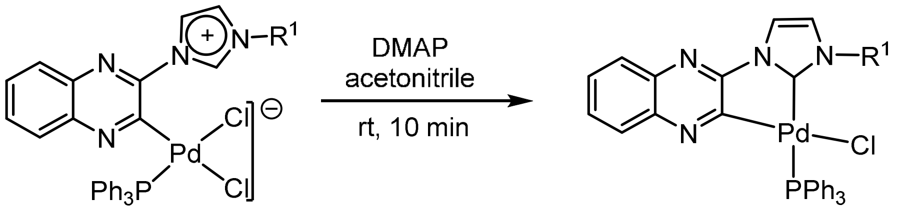
acetonitrile at rt (Scheme 4). **III** and **IV** were isolated and characterized by using NMR spectroscopy and elemental analysis.



R^1 = 2,6-Diisopropylphenyl [Pd(L1)(PPh$_3$)Cl] (**III**)
Mesityl [Pd(L2)(PPh$_3$)Cl] (**IV**)

Scheme 4 Synthesis of *ortho*-palladated-NHC-phosphine complexes

The solid state structure of **III** was determined by single crystal X-ray analysis. An ORTEP diagram along with the selected bond parameters is given in Figure 3. The molecular structure of the carbene complex shows the ligand is *ortho* chelated to palladium forming a palladacycle. Triphenylphosphine occupies the position *trans* to the carbene carbon. The geometry around the metal is a distorted square planar with the maximum deviation from the ideal bond angle occurring within the chelate ring (C3−Pd1−C5 = 80.34^o).

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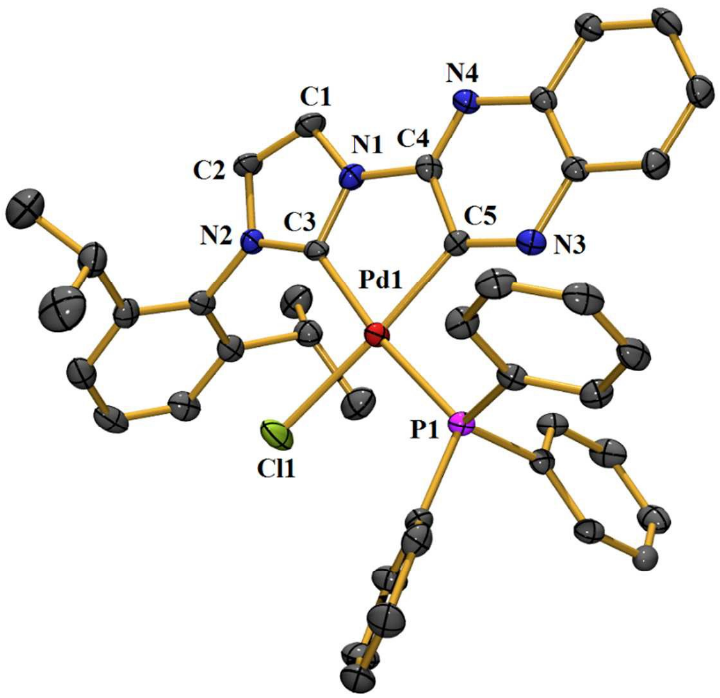

Figure 3 Molecular structure of [Pd(L1)(PPh$_3$)Cl] (**III**). All hydrogen atoms have been omitted for clarity. Thermal ellipsoids are drawn at 50% probability level. Selected bond lengths [Å]: Pd1−P1 2.3216(11), Pd1−Cl1 2.3454(12), Pd1−C5 2.006(4), Pd1−C3 2.044(4), C5−C4 1.457(6), C5−N3 1.308(5), N2−C3 1.354(5), N1−C3 1.342(5), N4−C4 1.282(5), N2−C4 1.413(5). Selected bond angles [^{o}]: P1−Pd1−Cl1 91.64(4), C5−Pd1−P1 92.70(11), C3−Pd1−Cl1 95.32(11), C5−Pd1−C3 80.34(15), C5−C4−Pd1 114.6(3), N2−C3−Pd1 114.1(3), , C3−N2−C4 118.2(3), N2−C4−C5 112.4(3), N3−C5−Pd1 128.6(3), N1−C3−Pd1 141.3(3).

At first, it was felt that these carbene complexes were involved in the reaction path. Therefore, **III** was employed in the SMC reaction (with or without base) under similar conditions used for the reactions catalyzed by the imidazolium complexes **I** and **II**. However, the carbene complex catalyzed reactions took much longer time (26 h) for the completion of the reaction compared to those catalyzed by the imidazolium complexes (3 h). This observation rules out the involvement of a carbene complex in the mechanistic path. To confirm further, two

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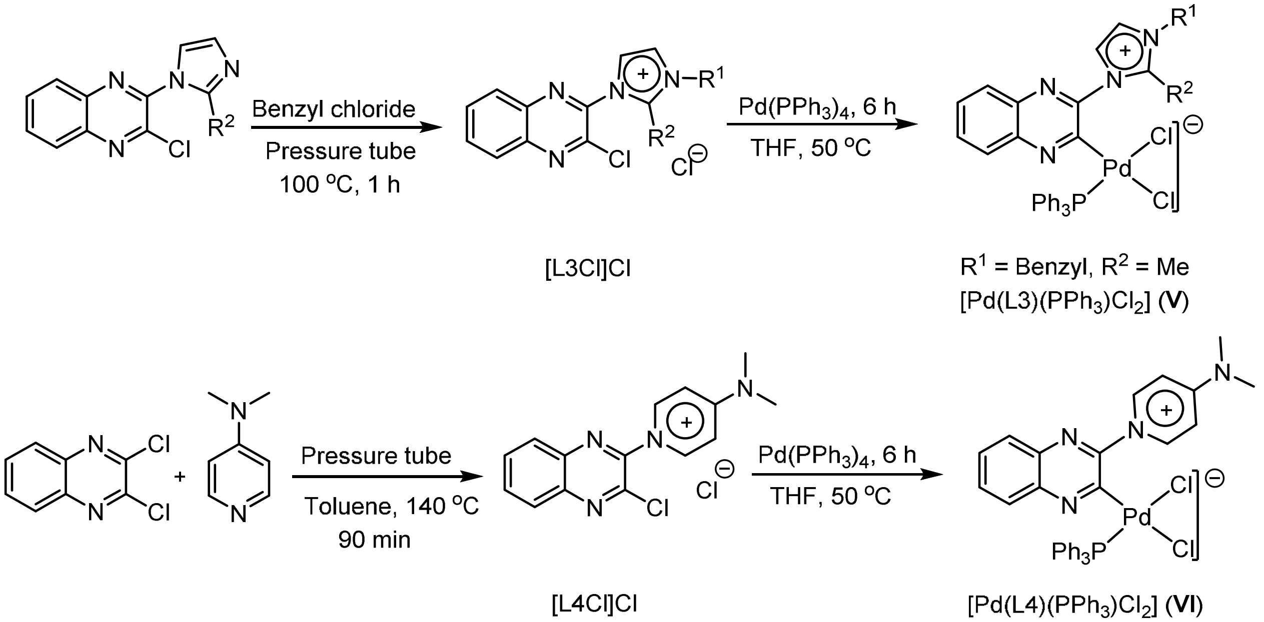
zwitterionic complexes of Pd(II) (complexes **V** and **VI**) in which there is no possibility of formation of a carbene complex were designed and synthesized (Scheme 5). In complex **V**, C3 position of imidazolium ring is blocked by a methyl group. Imidazolium ring in the complex **I** is replaced with *N*,*N*-dimethyl-4-aminopyridinium ring to obtain complex **VI**. The ligand precursor of **VI** has been structurally characterized and an ORTEP diagram is given in the electronic supplementary information. Both the complexes were well characterized by using NMR technique before employing them as catalysts for the SMC reactions. In case of **V**, the structure was further confirmed by single crystal X-ray analysis and an ORTEP diagram along with the selected bond parameters is given in Figure 4. It was found that these zwitterionic complexes were as active as **I** and **II**, and took much less time than the carbene complexes for the completion of the SMC reactions under similar conditions. These results further confirm that the SMC reactions catalyzed by **I** do not depend on the formation of a carbene complex.



Scheme 5 Synthesis of zwitterionic Pd(II) complexes **V** and **VI**

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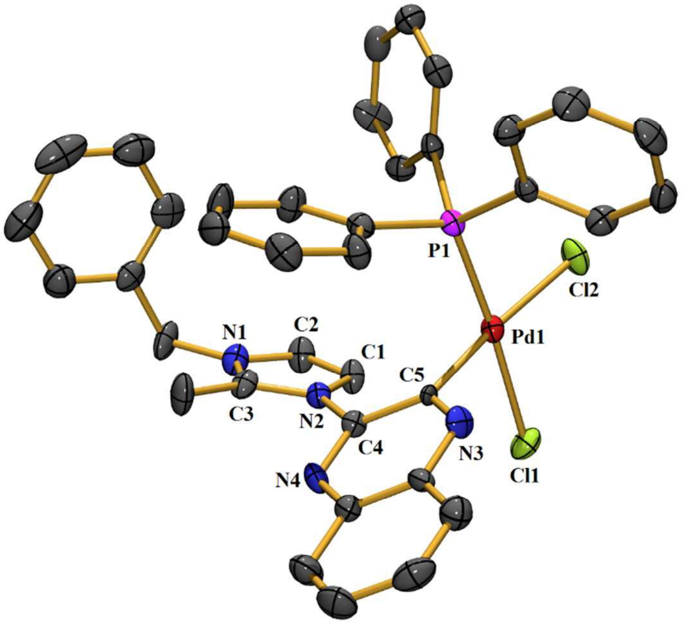

Figure 4 Molecular structure of [Pd(L3)(PPh$_3$)Cl$_2$] (**V**). All hydrogen atoms and solvent molecules have been removed for clarity. Thermal ellipsoids are drawn at 50% probability level. Selected bond lengths [Å]: Pd1−P1 2.243(2), Pd1−C5 1.985(7), Pd1−Cl1 2.394(2), Pd1−Cl2 2.417(2), N2−C4 1.445(9), C4−C5 1.446(10), N4−C4 1.286(9), N3−C5 1.303(9), N1−C3 1.358(10). Selected bond angles [°]: C5−Pd1−Cl1 83.1(2), C5−Pd1−P1 91.7(2), Cl1−Pd1−Cl2 94.83(8), P1−Pd1−Cl2 90.39(8), P1−Pd1−Cl1 174.78(8), C5−C4−N2 120.3(6), N4−C4−N2 114.3(6), C5−Pd1−Cl2 175.2(2), N3−C5−Pd1 117.4(5).

It has been reported in the literature that the most likely active species in SMC reactions is a Pd(0) species.[30] Recently, Braga, Navarro and their co-workers carried out computational studies on the plausible pathway in Heck coupling reactions catalyzed by an ionic complex [TBA][(NHC)PdCl$_3$] and suggested *in situ* formation of [(NHC)Pd(0)Cl]$^-$, which is the active species in the reaction.[31] Lee *et al*. observed the formation of two and three coordinated Pd(II) species in ES-MS spectra of catalyst precursors, and speculated that these species could generate L$_n$Pd(0), which plays a key role in the catalytic cycle.[20f] Similar to their observation, we also

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noticed that all the imidazoium complexes and the dimethylaminopyridinium complex showed corresponding three coordinated species $[PdL(PPh_3)Cl]^+$ [m/z = 761.16 (**I**–Cl), 719.11(**II**–Cl), 705.10 (**V**–Cl) and 655.08 (**VI**–Cl)] when they were subjected to ES-MS. In addition, the ES-MS spectra also showed peaks corresponding to $[M–2Cl–H]^+$, presumably due to the formation of a two coordinated species $[Pd(L–H^+)(PPh_3)]^+$ with the loss of two $Cl^–$ ions and an acidic proton on the imidazolium/pyridinium ion. As with the literature report, these results also suggest the possibility of *in situ* formation of two/three coordinated Pd(II), which have the potential to generate the active species $L(PPh_3)Pd(0)$.

In order to probe the nature of the catalysis (homogeneous *vs* heterogeneous) in these reactions, poisoning tests and a two phase test were carried out. The details of these experiments are given in the ESI. Though the poisoning tests conducted on **I** and **VI** with the addition of Hg and the addition of PPh_3 at room temperature adversely affected the reactions, the reactions conducted at 70 ^{o}C afforded excellent yields. In a two phase test, a mixture of 4-bromoacetophenone and freshly prepared immobilized aryl bromide were treated with an excess of phenylboronic acid in the presence of **I** as a catalyst and K_2CO_3 in water at 70 ºC. The ^{1}H NMR analysis of the products after hydrolyzing the immobilized phase indicated that the immobilized aryl bromide was also converted to the cross coupled product to the extent of 52%. These results indicate that the catalysis is largely homogeneous.

In most of the reactions reported in this article, formation of Pd black was observed during the course of the reaction. In order to find out if the Pd black is involved in catalysis, it was isolated from the reaction mixture by filtering on a 0.2 µm filter paper followed by washing the precipitate with ethyl acetate and used as a catalyst under the optimized conditions. The Pd black was unable to initiate the Suzuki-Miyaura reaction. It is noteworthy that the filtrate from

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the reaction mixture too was found to be catalytically inactive, which indicates that neither the active catalyst nor the precatalyst are present in the reaction medium at the end of the reaction.

Conclusion

In summary, two imidazolium substituted quinoxaline based organopalladium complexes **I** and **II** were synthesized and structurally characterized. These complexes are found to be excellent catalysts for carrying out Suzuki-Miyaura cross-coupling reactions in neat water. The results of a series of experiments conducted using **I** clearly indicate that it has the advantages of i) being highly efficient in neat water medium, which enables easy separation of products (just filtration is enough in most cases), ii) needing no organic base (only a cheap inorganic base K_2CO_3 is required), iii) demanding no phase transfer catalyst, iv) requiring only low catalyst loading resulting in high turnover number (82,000), v) producing cross-coupled products in almost quantitative yields and no homo-coupled products in most cases, vi) being versatile: as demonstrated in the synthesis of biaryls with variety of functional groups, heterobiaryls and hydrophilic biaryls. Though initially it appeared that these catalysts may form carbene complexes as active catalysts, subsequent experiments conducted using carbene complexes obtained from these catalysts showed that they were less efficient than the imidazolium complexes and thus rule out their involvement in the catalytic cycle. PPh_3 and mercury poisoning tests on **I** and **VI**, and a two phase test involving an immobilized aryl bromide using **I** suggest that the catalysis is largely homogeneous. Currently, we are examining the complexes, which are reported in this article, for their catalytic activity in the SMC reactions of aryl chlorides. The preliminary reactions carried out on **I** showed positive results and the details will be discussed elsewhere. Studies are ongoing on the synthesis of water soluble catalysts for cross coupling reactions.

Structural Determination

Single crystals of [HL2Cl](PF_6), [L4Cl]Cl, [Pd(HL1)(PPh_3)Cl_2] (**I**), [Pd(HL2)(PPh_3)Cl_2] (**II**), [Pd(L1)(PPh_3)Cl] (**III**) and [Pd(L3)(PPh_3)Cl_2] (**V**) were mounted on a glass fiber in paraffin oil and then brought into a cold nitrogen stream of a low-temperature device so that the oil solidified. Data collection were performed on an OXFORD XCALIBUR diffractometer, equipped with a CCD area detector, using graphite-monochromated Mo K_α (λ = 0.71073 Å) radiation and a low temperature device. All calculations were performed using SHELXS-97 and SHELXL-97.[32] The structures were solved by direct methods and successive interpretation of the difference Fourier maps, followed by full-matrix least-squares refinement (against F^2). All non-hydrogen atoms were refined anisotropically. The contribution of the hydrogen atoms in their calculated positions was included in the refinement using a riding model. Upon convergence, the final Fourier difference map of the X-ray structures showed no significant peaks.

All the data sets were collected to 2Θ values > 50° but they were cut off to $2\Theta = 50°$ during the refinement. Relevant data concerning the crystallographic data, data collection, and refinement details are summarized in Table S1 (see ESI). Crystallographic information files (CIF) for the structures reported in this paper have also been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 1415075-1415080. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail, deposit@ccdc.cam.ac.uk).

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†Electronic supplementary information (ESI) available: Detailed experimental procedure for all the experiments, analytical data, ^{1}H, ^{13}C, ^{31}P NMR and ES-MS spectra. Details of experiments on catalyst loading, poison tests and a two phase test. Molecular structures of **[**HL2Cl](PF$_6$) and [L4Cl]Cl and their selected bond parameters, and the crystal data of all structurally characterized compounds.

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Graphical Abstract for the Table of Contents

Manuscript title:	Synthesis of Zwitterionic Palladium Complexes and Their Application as Catalysts in Cross-Coupling Reactions of Aryl, Heteroaryl and Benzyl Bromides with Organoboron Reagents in Neat Water
Authors:	V. Ramakrishna and N. Dastagiri Reddy

The zwitterionic Pd(II) complexes of imidazolium substituted quinoxaline based were synthesized and found to be excellent catalysts for carrying out Suzuki-Miyaura cross-coupling reactions in neat water.