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FULL PAPER

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Water Soluble Benzimidazole Containing Ionic Palladium(II) Complex for Rapid Microwave-Assisted Suzuki Reaction of Aryl Chlorides

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In this paper a water soluble benzimidazole – Pd complex used for Suzuki reaction under conventional heating and microwave heating. To increase the activity of complex, ionic group change with bulky TBA^+ and $Bmim^+$ groups. To determine whether the reaction is homogeneous or heterogeneous, Hg(0) poisoning tests, hot filtration tests and CS_2 poisoning tests were performed.

KEYWORDS
Benzimidazole, Green Chemistry, Microwave, Palladium Complex, Suzuki Reaction

1 | INTRODUCTION

Palladium catalyzed Suzuki reaction is one of the most important methods for the formation of new C–C bonds and very powerful tool in organic synthesis. Due to popularity of Suzuki reaction, Akira Suzuki won Nobel Prize 2010.[1] Suzuki reaction can be performed with using three distinctive steps. In the first step, an aryl halide reacts with the palladium(0) through an oxidative addition. After that a transmetallation reaction occurs which yields palladium(II) complex and coupled products. The last step includes reductive elimination of the products. Unfortunately, this very useful reaction has some limitations. Reaction needs high loadings for Pd catalysts and activity on aryl-chlorides are very low. The high C–Cl bond strength compared with C–Br and C–I bonds disfavors oxidative addition step[2]. On the other hand, aryl chlorides are more widely available and generally less expensive than aryl bromides and aryl iodides. That's why research on Suzuki reactions are focused on using aryl chlorides as a substrate instead of aryl bromides and iodides. To activate aryl chlorides several successful catalysts like palladacycles,[3] palladium-phosphine complexes[4] and palladium-carbene complexes[5] were used. Also our recent study proved that bulky group protected ferrocene-diimine complexes with microwave irradiation can catalyze aryl chlorides rapidly.[6]

Herein we report a convenient and environmentally friendly method for Suzuki coupling reaction of unreactive aryl chlorides with using water as a solvent and microwave irradiation for heating. We replaced ionic potassium with tetrabutylammonium bromide (TBA^+) and **1**-Butyl-3-methylimidazolium hexafluorophosphate ($Bmim^+$) to protect active Pd(0) species.[7] Water was selected for the reaction media because aqueous reaction conditions offer a safe, economic and environmentally benign alternative in organic syntheses.[8] Microwave irradiation serves several advantages including reduction of reaction times and electricity costs.[9] As a result, modified complex C managed to couple several aryl chlorides with several boronic acids under MW irradiation with high conversion approximately in 15 minutes.

2 | EXPERIMENTAL

2.1 | General

All reagents and solvents were obtained from commercial sources and used without further purification. Melting points were determined by BÜCHI Melting point B-540 apparatus. ^{1}H and ^{13}C-NMR spectra were recorded on a Bruker Ultra Shield Plus, Ultra long time 400 MHz NMR spectrometer. Elemental analysis data were performed on a LECO CHNS analyzer (for C, H, N). FT-IR spectra were recorded on Perkin Elmer FT-IR 100 spectrometer. ESI MS spectra were obtained from the AB SCIEX 4000 Q TRAP. MALDI-TOF mass spectra were obtained from a Voyager DE matrix assisted laser desorption/ionization time-of-flight spectrometer. Gas chromatographic analyses were performed on an Agilent 6890 N instrument equipped with a WCOT HP-1 fused silica capillary column. Microwave irritation were carried out with modified Bosch Micro Combi commercial microwave oven (850 W).

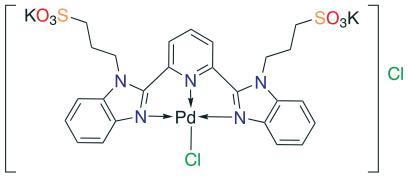
2.2 | Synthesis of Potassium 2,6-bis(1-(3-propylsulfonate)benzimidazol-2'-yl) pyridine, L

The ligand was synthesized by the reaction of 2,6-bis(NH-benzimidazol-2-yl)pyridine [10] with 1,3-propanesulfonate in DMSO as reported by Po *et al.*[11] as illustrated in Scheme 1.

The data obtained for the ligand are in good agreement with the reported data. M.p. 265 °C. FT-IR (ATR, ν/cm^{-1}): 3020 (C-H$_{ar}$), 2936 (C-H$_{al}$), 1571 (C=N), 1437, 1418 (C=C), 1179, 1033 (S=O). ^{1}H-NMR (dmso-d_6, δ_{ppm}): 8.32 (2H, d, J = 7.68), 8.21 (1H, m), 7.76 (4H, m), 7.31 (4H, m), 4.90 (4H, t, J = 7.10), 2.26 (4H, t, J = 7.39), 2.0 (4H, m). ESI-MS (m/z): [M+K]$^{+}$: 670.

2.3 | Synthesis of Chloro-2-6-bis(1-(3-propylsulfonate)benzimidazol-2'-yl) pyridinepalladium(II)chloride, [Pd(L)]Cl, C

The complex was obtained as yellow solid in 75% yield by the reaction of **L** with K_2PdCl_4 in DMSO by the similar procedure as reported for Pt(II) complex (Scheme 2).[11] Elemental analysis calcd (%) for



SCHEME 2 The molecular structure of the Pd complex

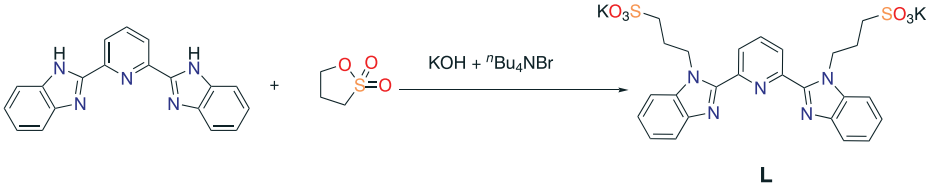
$C_{25}H_{23}Cl_2K_2N_5O_6PdS_2{\cdot}3H_2O$: C, 34.79; H, 3.39; N, 8.11; found: C, 34.9; H, 3.1; N, 7.9. IR (ATR, ν/cm^{-1}): 3099 (aromatic C-H), 2933 (aliphatic C-H), 523 (C=N), 1485,1442 (C=C), 1160, 1031 (S=O). ^{1}H-NMR (dmso-d_6, δ_{ppm}): 8.76 (2H, d, J = 7.35), 8.45 (1H, t, J = 7.48), 7.91 (2H, d, J = 7.17), 7.27 (2H, d, J = 7.41), 7.35 (4H, m), 4.74 (4H, m), 2.65 (4H, t, J = 7.17), 2.11 (4H, m). MALDI TOFF MS m/z 773.9 [M]$^{+}$.

2.4 | General Procedure for the Suzuki Coupling Reaction

The aryl chloride (1.0 mmol), phenylboronic acid (1.2 mmol), K_2CO_3 (5 mmol), **C** (0.02 mmol) and H_2O (10 ml) were added to a teflon capped Schlenk tube (50 ml) and irradiated at 850 W for 10 min in a microwave oven. After cooling to room temperature, the reaction mixture was extracted with ethyl acetate – acetone (5:1 v/v, 20 ml x 2). The organic phase was dried over $MgSO_4$. The solvent was removed by evaporation under reduced pressure to afford the biaryls. The product was purified by column chromatography on silica gel using petroleum ether-ethyl acetate (30:1 v/v) as the eluent to give an analytically pure product.

2.5 | Optimization of Coupling Reaction

Because of its simplicity, coupling reaction between chlorobenzene (1.0 mmol) and phenylboronic acid (1.2 mmol) with using **C** 0.1 mol %) as a catalyst was chosen as a model reaction for the optimization. To compare the advantage of microwave heating over conventional heating and to understand the effect of ionic groups, a series of experiments were established (Table 1). To optimize the reaction time, K_2CO_3 was used as a base which is very effective in related systems.[12] For



SCHEME 1 Synthetic pathway of the ligand

TABLE 1 Effect of Conventional Heating vs MW

Entry	Catalyst	Yield*	
		80 °C	MW
1	Li_2PdCl_4	13	22
2	$PdCl_2$	10	16
3	C	42	72
4[a]	C-TBAB	69	96
5[b]	C-Bmim	61	91

Reaction Conditions: 1 mmol chlorobenzene, 1.2 mmol phenylboronic acid, 2 mmol of K_2CO_3, 0.1 mol% catalyst, 80 °C for conventional heating or 850 W microwave irradiation, 5 ml H_2O. Reaction time = 2 h for conventional heating, 15 min for microwave irradiation. [a] 0.5 mmol TBAB added. [b] 0.5 mmol Bmim added.

*GC yields.

base optimization, K_2CO_3, Na_2CO_3, Cs_2CO_3, K_3PO_4, and NaOMe were tested (Table 2).

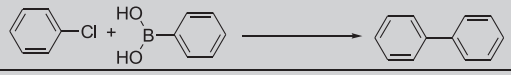
2.6 | PPh_3 and CS_2 Poisoning Test

To the coupling reaction of chlorobenzene and phenylboronic acid, **C** (0.1 mol %) was added as a catalyst and PPh_3 or CS_2 (1 mol %) was added under optimized conditions. The product biphenyl was obtained with 100 % conversion after 2 hours.

2.7 | Mercury (Hg) Poisoning Test

The Hg poisoning test is very significant to understand whether the reaction is homogeneous or heterogeneous. Before the coupling reaction carried out, excess Hg (Hg: Pd:400:1) was taken in the reaction flask. Thereafter the coupling reactions of phenylboronic acid (1.2 mmol) with chlorobenzene (1.0 mmol) using **C** (0.1 mol%) and nanoparticles (0.4 mol%) isolated from **C** as a catalyst under the optimized conditions were carried out in the flask. As a result the product biphenyl was obtained 72% yield after 2 h even in the presence of excess Hg.

TABLE 2 Optimization Results of Suzuki Coupling



Entry	Base	M.W (Watt)	Time(min)	Yield*
1	K_2CO_3	850	5	23
2	K_2CO_3	850	10	58
3	K_2CO_3	850	15	72
4	K_2CO_3	850	20	74
5	K_2CO_3	600	15	51
6	K_2CO_3	360	15	NA
7	Na_2CO_3	850	15	36
8	Cs_2CO_3	850	15	79
9	K_3PO_4	850	15	41
10	NaOMe	850	15	29

Reaction conditions: [a]Arylchloride (1.0 mmol), phenylboronic acid (1.2 mmol), 0,1 mol% C-K, 2 mmol base, H_2O (5 ml).* GC yields.

2.8 | Hot Filtration Test

Reactions with **C** were subjected to a hot filtration test. Coupling reaction of phenylboronic acid (1.2 mmol) with chlorobenzene (1.0 mmol) catalyzed with **C** (0.1 mol%) under the optimized conditions was filtered hot through G4 sintered glass crucible which contains 1.5 g celite until the conversion reach 20% (monitored by GC). The conversion was monitored in the filtrate with time, continued and reached a maximum (71%) after 2 h.

3 | RESULTS AND DISCUSSIONS

3.1 | Characterization of the Ligand (L) and the palladium(II) complex (C)

The synthesis of the ligand was previously reported and fully characterized. The IR spectrum clearly indicates the presence of sulfonate groups with the characteristic stretching modes of S=O at 1179 and 1033 cm^{-1}, respectively. In addition, the presence of the aromatic CH band at 3020 cm^{-1}, and the corresponding aliphatic CH stretching bands at 2936 and 2876 cm^{-1} confirm the attachment of the polysulfonate groups to the benzimidazole moieties. The molecular structure was further confirmed by the ESI MS in which the observed major peak at *m/z* 670 assigned to the $[M+K+H]^+$ for $C_{25}H_{23}N_5O_6S_2K_3$.. Furthermore, the compound was also characterized by ^{1}H-NMR as shown in Figure 1. The data are very identical to the reported data.[11] As depicted in Figure 1, the protons belong to the benzimidazole rings appear as multiplets at 7.31 and 7.76 ppm, respectively. The protons on the pyridine ring appear as a doublet at 8.32 ppm, and as a multiplet at 8.21 ppm, respectively. The protons belong to the propyl group appear in the aliphatic regions as expected at 2.00 ppm as a multiplet for the middle CH_2, 2.26 ppm as a triplet for CH_2SO_3 and 4.90 ppm as a triplet for CH_2N, respectively as shown in Figure 1. The integral value of total number of 23 protons is confirmed the molecular structure.

The Pd complex, **C** was fully characterized by elemental analysis. FTIR, ^{1}H-NMR and MALDI TOFF MS. The infrared spectrum of the complex is very much akin to that of the ligand. The characteristic stretching modes of the S=O group are observed at 1031 and 1160 cm^{-1}, respectively. The aromatic CH and aliphatic CH stretching bands are observed at 3099 and 2933 cm^{-1}, respectively. The molecular structure was clearly

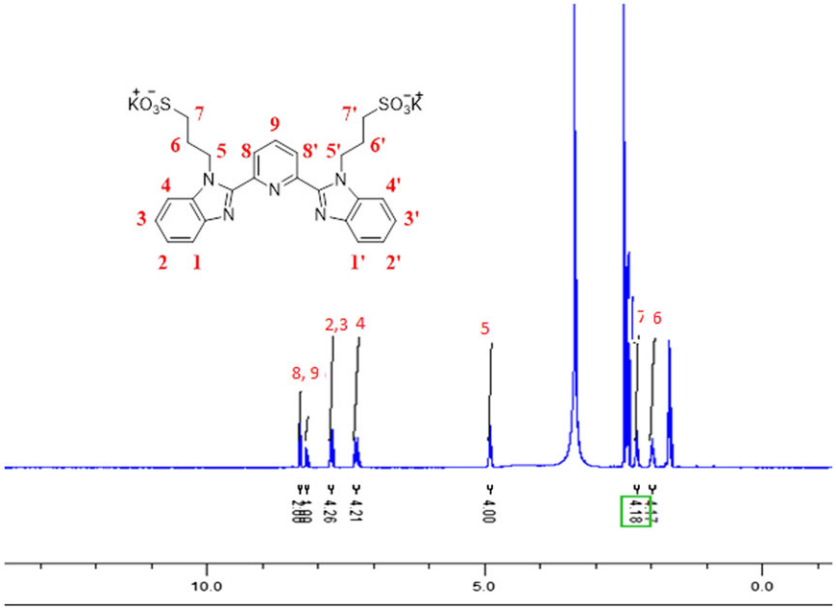


FIGURE 1 ^{1}H-NMR Spectrum of **L**

confirmed by the MALDI TOFF MS *m/z* 773.0 $[M\text{-}Cl]^+$ for $C_{25}H_{23}ClKN_5O_6PdS_2$ (calc.: 773.9). The ^{1}H-NMR spectrum of the complex (Figure 2) is very much similar to that of the free ligand. The protons of the benzimidazole rings slightly deshielding as appeared doublets at 7.27 and 7.91 ppm, and as a triplet at 7.35 ppm, respectively. The pyridine protons also underwent deshielding as a doublet at 8.76 ppm and as a triplet at 8.45 ppm in comparison to that of the free ligand. The propyl protons show insignificant deshielding upon coordination to Pd(II) ion, and they appear at 2.11, 2.65 and 4.74 ppm, respectively with same pattern as the free ligand. The total number of 23 protons is identical to the ^{1}H-NMR integral value.

3.2 | Optimization Results

According to the base optimization results K_2CO_3 was chosen as the reaction base whereas other alternatives need more reaction times for high conversion or found totally ineffective. The reaction time was optimized 15 min. for 850 W microwave irradiation and 2 h for conventional heating at 80 °C where necessary. The optimum concentration of catalyst **C** was found to be 0.1 mol%.

3.3 | Influence of the Complex on Suzuki reaction

Table 3 summarizes the effect of catalyst on Suzuki reaction. It is very clear from the results that, the sulfonate group has a great effect on Suzuki coupling reaction. This is because of the stabilization effect of big groups on active Pd(0) nanoparticles. To prove its efficiency, TBAB was added to the reaction media.[13] The catalytic activity of **C**, which showed the moderate activity, increased suddenly when TBAB was added as an additive and the conversion increased from 72 to 99% (Table 3, entry 1). **C-TBA** which the ion was TBA^+, showed the highest activity. Differences between the ions, K^+ and TBA^+ can be explained by the stabilization effects of bulky groups. Also, $Bmim^+$ (**C-Bmim**) showed the same stabilization effect like TBA^+ ion. Significantly **C** (with $\mathbf{K^+}$, $\mathbf{TBA^+}$ and $\mathbf{Bmim^+}$) was able to couple inactivated electron rich aryl chlorides with various boronic acids in high yields (Table 3, entry 2-4). Also sterically hindered substrates were tested. Suzuki reactions using sterically demanding substrates are difficult and generally occur with the formation of unwanted homocoupling products.[14] As shown in Table 3 (entries 4-7) sterically hindered biaryls could be obtained in high yields. Also other functional groups were tested and those groups underwent the coupling reaction efficiently (Table 3, entries 8-10).

It is very important to determine whether the reaction is homogeneous or heterogeneous. Hg(0) poisoning test is one of the well-known test and easy to perform on C-C coupling reactions. Hg(0) amalgamates strongly bind to Pd(0), Rh(0) and Ni(0) based complexes, thereby blocking the access of the active site to the substrate. Thus, Pd(0) species can possibly be poisoned by adding excess Hg(0) to the reaction mixture during the reaction. If the catalytic reaction stops after addition of Hg(0), the reaction mechanism follows a heterogeneous pathway. It follows homogeneous pathway if mercury does not suppress the pathway.[15] In this work we performed the Hg poisoning experiment in a coupling reaction between chlorobenzene and phenylboronic acid (1 mol% **C,** 2 mmol K_2CO_3, dioxan, 50 °C). Under these conditions 50% conversion achieved after 30 min, and then Hg (400 equiv.) was added. In all cases the reaction did not stop (86%

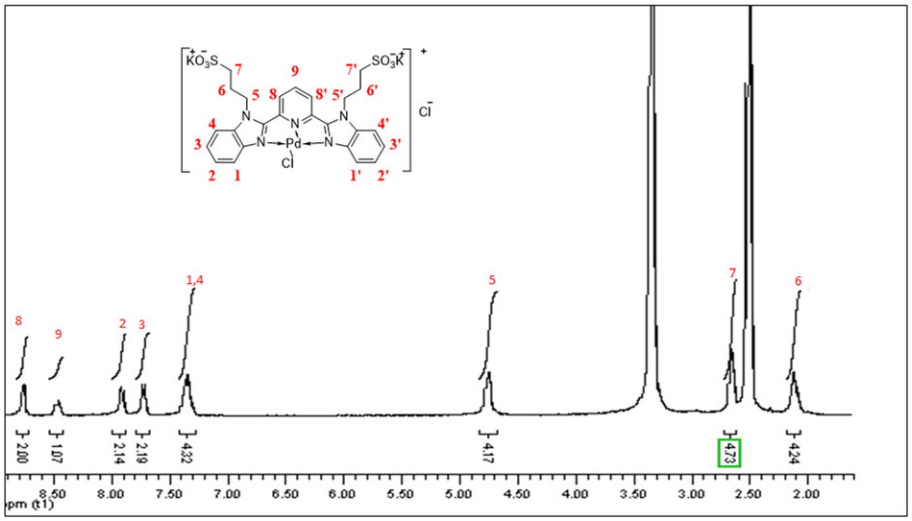
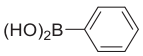
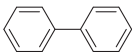
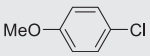
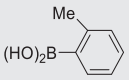
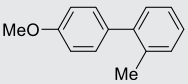
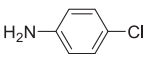
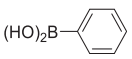
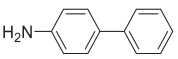
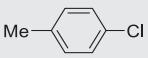
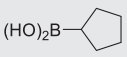
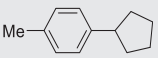
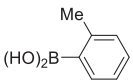
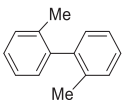
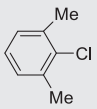
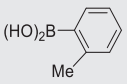
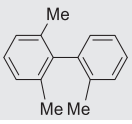
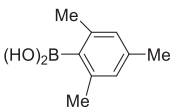
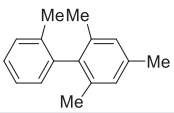
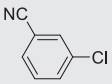
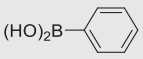
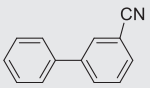
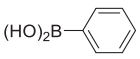
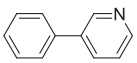
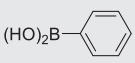
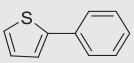


FIGURE 2 ^{1}H-NMR Spectrum of **C**

TABLE 3 Suzuki cross- couplings between aryl halides and boronic acids using **C** as the catalyst

Entry	Aryl Halide	Boronic Acid	Product	Yield %* C-K	Yield %* C-TBAB	Yield %* C-Bmim
1				72	99	96
2				68	96	92
3				67	91	87
4				70	91	86
5				63	86	81
6				60	85	80
7				66	90	92
8				82	99	98
9				79	99	96
10				77	91	81

Conditions: 1.0 mmol arylchloride, 1.2 mmol eq. aryl boronic acid, 2 mmol K_2CO_3, 0.1% **Complex**, 850 W M.W. irradiation, 15 min, 5 ml H_2O.

*GC yields.

conversion after 1 hour), indicating that monometallic species are the true active species rather than Pd nanoparticles or cluster particles. Hg(0) was not quenched the reaction because these Pd(0) species were protected by the ligand. Hg(0) poisoning experiments are not enough to determine the process as being homogeneous or

heterogeneous. Therefore, we performed CS_2 poisoning and hot filtration experiments. To determine the number of catalytically active metal atoms and provide evidence as to the nature of the catalyst we used CS_2 poisoning procedure.[16] CS_2 poisoning experiments were performed between chlorobenzene and phenylboronic acid using the same conditions that were used in the Hg test. Under these conditions, 50% conversion was achieved after 30 min. Different amounts of CS_2 in dioxane were added (0, 0.5, 1 or 1.5 equiv. of CS_2) to different experiment sets and reactions were screened by GC for 2 days. It was found that 1.5 equiv. CS_2 were necessary to completely terminate the reaction, which also indicates that the catalyst is of a molecular nature. Hot filtration experiments were also performed.[17] Once a 50% conversion was achieved by the coupling reaction between chlorobenzene and phenylboronic acid, the reaction was filtered through a sintered glass filter containing cellulose to remove the metal particles. It was found that the filtrate was catalytically active (84% conversion) and no coupling product was obtained using the Pd retained in the cellulose. These results also support the activity of the presence of a soluble catalyst (homogeneous catalyst).

4 | CONCLUSION

We have developed a new water soluble Pd catalyst containing sulfonated imidazole ligand that showed excellent Suzuki Coupling reactivity with aryl chlorides in water under MW irradiation. Good to excellent yields of cross coupling products were obtained when the ionic groups exchanged with bulky TBA^+ and $Bmim^+$ ions. In addition, poisoning tests indicate that the homogeneous molecular palladium species containing imidazole ligand is responsible for the catalytic activity.

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