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SYNTHESIS OF DICHLORO-PALLADIUM-4-(2,5-DIBROMO IMIDAZOLYL)-2′-AMINO PYRIDYL COMPLEX AS PRE-CATALYST AND ITS APPLICATION IN SUZUKI-MIYAURA CROSS COUPLING REACTION.

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Abstract

4-(2,5-Dibromoimidazolyl)-2′-aminopyridyl form complex with Na_2PdCl_4 in methanol. 1 mmol% of the complex was utilized in Suzuki-Miyaura cross coupling reaction to prepare substituted biphenyls and terphenyls in good to excellent yields.

Introduction

For many years catalyzed by transition metals have been most powerful convenient tools in modern organic synthesis, for example, the Suzuki-Miyaura (SM)[1] cross coupling reaction. Transition metal catalyzed cross coupling reactions have had a major impact on the construction of C-C bonds functionalized biaryl system[2]. Although many different types of ligands have been discovered for these types of reactions. For example the development of catalysts not including phosphane ligands is of special interest due to environmental concerns. As reported in several scientific papers, it is very difficult to separate the remaining phosphane moiety during work-up process[3]. Moreover, many ligands are often air-sensitive or expensive, which places significant limits on their synthetic applications.

In recent past palladacycles as catalyst in cross coupling reactions have been described[4]. There are also homogeneous catalysts, which are reusable, very stable and enhanced activity has been reported[5]. The complexes of palladium(II) salts with the dipyridine-based ligands of type 1 have shown to be efficient catalysts for C-C bond forming reactions[6]. Farther more, we have reported a new pyridine oxime ligands-based palladium catalyst **2**, for the C-C coupling reactions[7]. (β-oxoiminato) (phosphanyl) palladium complexes[8] **3** have been found to be very active as catalyst in Suzuki-Miyaura coupling reactions. Recently, R. Franzen[9] has reported the diimine or diamine-palladium complexes **4** & **5** for the synthesis of chlorinated biphenyl by Suzuki cross-coupling reactions. Abu-Surrah et.al.[10] have recently reported pyrazole-based schiff bases of palladium (II) complex **6**, having biological activity. Latestly, M. A. Hashem has reported two dipyridyl-palladium complexes **7** & **8**[11], which are easily prepared in good yield with high purity and promote the Suzuki-Miyaura cross coupling reaction. In continuation of our work on pyridine based palladacycles, we report here another dibromoimidazolyl-pyridyl-palladium complex **9**, which is easily prepared in good yield and this palladium complex

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promote the Suzuki-Miyaura cross coupling reaction in the preparation of substituted biphenyls, phenylnaphthyl and terphenyls in good to excellent yields.

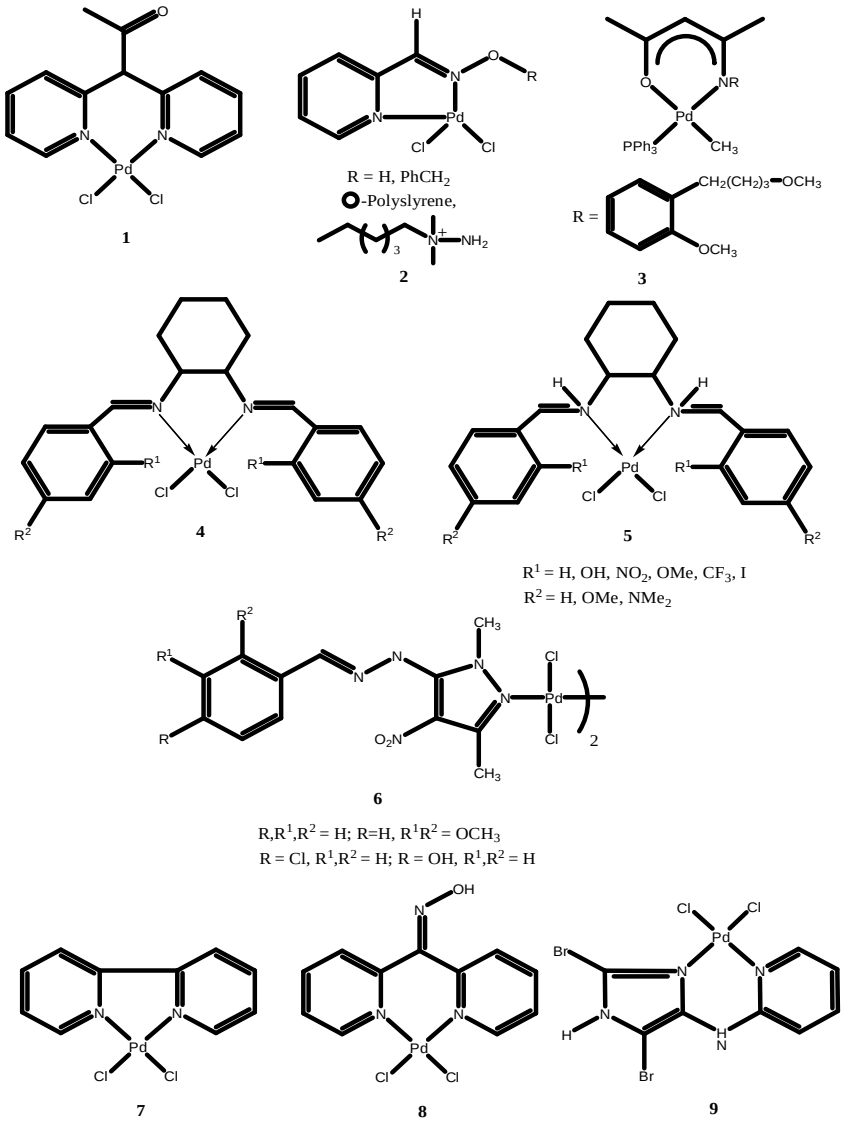


Fig. 1.

Experimental

NMR spectra were recorded on Bruker WH 400 MHz spectrometer in the Bangladesh Council of Scientific and industrial Research (BCSIR) laboratories, Dhaka, Bangladesh and Leibniz Institute of Plant Biochemistry, Weinberg-3, D-06120 Halle (Salle), Germany using tetramethylsilane as the internal standard. Mass spectra were recorded with JEOL AX 505 mass spectrometer with JMA 5000 mass data system on Leibniz Institute of Plant Biochemistry, Weinberg-3, D-06120, Halle (Salle), Germany. The thin layer chromatography (TLC) was performed on precoated aluminum plates (Merck 60 F_{254} silica gel) and detected by UV light and in iodine chamber. Column chromatography was performed with Merck silica gel 60, 70-230 mesh ASTM. Yields of the product are the isolated yield after column chromatography. All solvents were dried and purified by usual techniques.

*General procedure for the preparation of ligand, 4(2,5-dibromoimidazolyl)-2′-aminopyridine(**11**)*

Preparation of 2, 4, 5-tribromoimidazole (10)

Imidazole (10 mmol), N-bromosuccinimide (30.2 mmol), silica gel (0.8 g) and dichloromethane (10 mL) were mixed under nitrogen at room temperature for 3 hours. Product was taken in 10 mL methanol and filtered to remove silica gel. The methanolic solution was evaporated in a rotary evaporator to get a solid product. The solid was further washed twice with 10 mL distilled water each time and dried over anhydrous silica-gel to isolate pure white crystals of 2,4,5-tribromoimidazole , m.p 217-219°C (2.96 g, 97%), spectral data are given in Table 1.

A mixture of 2,4,5-Tribromoimidazole (6 mmol), 2-aminopyridine (15 mmol), potassium carbonate (12 mmol), palladium catalyst **7** (24 mmol%) in dioxane (50 mL) was refluxed for 25 hours at 100°C temperature. The reaction mixture was worked up with water (10 mL) and ethyl acetate (10 mL) and was filtered to remove the solid catalyst and potassium carbonate. It was then extracted further with ethyl acetate (10 mL). Ethyl acetate extract was dried over anhydrous sodium sulfate. The solvent was removed in a rotary evaporator. The crude product was column cromatographed over a silica gel eluting with petroleum ether-ethyl acetate (1:1) solvent mixture to obtain pure product of 4-(2,5-dibromoimidazolyl)-2′-aminopyridine, m.p. 144-145°C (373 mg, 20%), spectral data are given in Table 1.

*Complex formation of the ligand, **11** with Na_2PdCl_4 to obtain complex **9***

4-(2, 5-Dibromoimidazolyl)-2′-aminopyridine, **11** (0.7843 mmol), sodium tetrachloro-palladate (1.56 mmol) in methanol was refluxed for 16 hours. Mixture was filtered in a

sintered crucible, washed further 2 times with methanol. On drying in a desiccator yellow solid of complex **9**, (388mg, 100%) was obtained, spectral data are given in Table. 1

General procedure of Suzuki-Miyaura cross-coupling utilizing the complex 9

Arylboronic acid (1.5 mmol), arylhalide (1.0 mmol), catalyst **9** (1 mmol%), base K_2CO_3 (2 mmol) and toluene (3-4 mL) were mixed together in air. The mixture was refluxed at 105°C for 2-4 hours. The mixture was cooled to room temperature, work-up with H_2O (10 mL) and ethyl acetate (10 mL) was added; any residual solids present were filtered. To the filtrate ethyl acetate was added again and shaken well. The two layers were separated. The aqueous layer was again extracted with either ethyl acetate or dichloromethane and combined with the original organic layer. The organic phase was dried over anhydrous sodium sulfate. The solvent was removed in rotary evaporator. The crude product was column chromatographed over a silica gel eluting with petroleum ether-ethyl acetate solvent mixture to obtain pure product. Yields were calculated from these isolated products. Spectral data of the isolated compounds **14 a-i** are given in Table-2.

Table 1. Spectral data for products the ligand 10, 11 and complex 9

Compound	^{1}H-NMR (δ, ppm)	Mass spectra
2, 4,5-Tribromoimidazole[a], **10**	^{1}H-NMR(CD_3OD): No peak , because of the rapid exchange of N-H proton with deuterium(D)	303.7,305.7,307.7, 309.7(molecular ion peak , isotopic ratio of 1:2:2:1)
4-(2,5-Dibromoimidazolyl)-2'-aminopyridine, **11**	^{1}H-NMR($CDCl_3$): 9.36(1H, broad, [N-H]-1), 9.27 (1H, broad, [N-H]-4),8.21 (1H d, J=8Hz, H-6'), 8.00 (1H,d,J=8Hz, H-3'), 7.94(1H, d,J=8Hz, H-5'), 7.64(1H, d, J=8Hz, H-4')	315,317,319[M^+-H, two bromine isotopic pattern]; 223,225,227[M^+ -Aminopyridyl]; 156[M^+-2HBr], 143,145,118,120
Pd-complex, **9**	1H-NMR(DMSO): 9.39(1H, broad,[N-H]-4), 8.35(1H,d, j=8Hz,H-6'),8.23 (1H, d,J=8Hz, H-3'), 7.99(1H,t, J=8Hz,H-4'), 7.46 (1H,broad,[N-H]-1), 6.65(1H,t,J=8Hz,H-5')	492, 494, 496, 498, 500, 502 [M^+ , with Br_2Cl_2 isotopic pattern]; 391, 393, 395, 397 [M^+-HBr-NH_3, isotopic pattern]; 348 350,352,354 [M^+-PdCl]; 302,304,306,308 [M^+-$PdCl_2$-NH]; 258,260,262,223,225

a.^{13}C-NMR (CD_3OD) spectra of 2, 4,5-Tribromoimidazole: 110(C-4,5), 118(C-2)

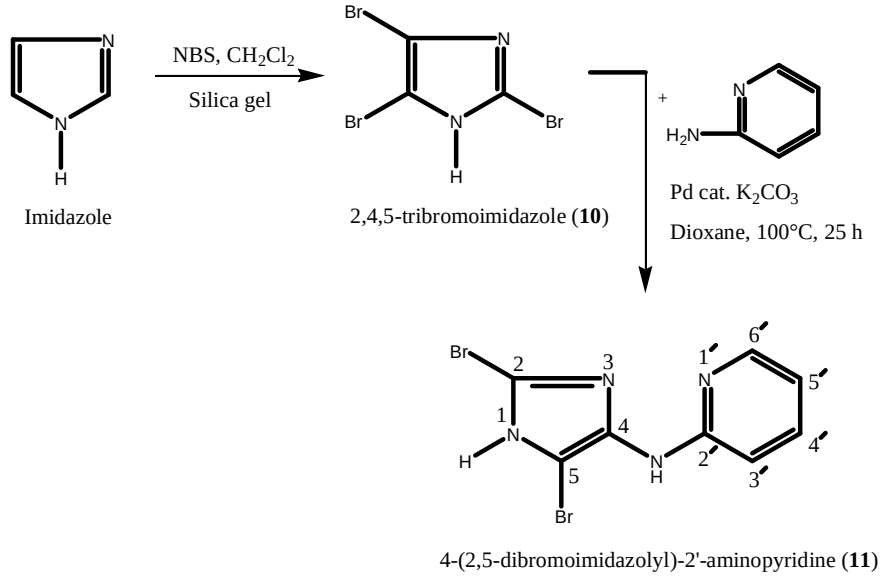
Table 2. Spectral data for products 14a-i.

Compound	^{1}H-NMR ($CDCl_3$) (δ, ppm)
14a	2.63(3H,s,CH_3), 7.37(1H,t,J=7.2Hz,H-4'),7.47(2H,t,J=7.6Hz,H- 3',5')7.63 (2H,d,J=8.4Hz,H-2',6'),7.68(2H,d,J=8.0Hz,H-3,5),8.03(2H,d,J=8.4Hz, H-2,6)
14b	7.45(1H,dt,J=7.6Hz,J=1.6Hz,H-4'),7.49(2H,dd,J=7.2Hz,7.6Hz,H 3',5'),7.63(2H, dd,J=7.2Hz,J=1.6Hz,H-2',6'),7.73(2H,d,J=8.8Hz,H-3,5),8.29(2H,d,J=8.8Hz,H-2,6)
14c	2.40(3H,s,CH_3),7.26(2H,d,J=8.0Hz,H-2,6),7.31(1H,t,J=7.6Hz,H-4'), 7.43(2H,t,J=7.6Hz,H-3',5'),7.50(2H,d,J=8Hz,H-3,5),7.60(2H,d,J=7.2Hz,H-2',6')
14d	7.13(1H,dt,H-6'),7.25(1H,s,H-2'),7.30(1H,dt,J=8Hz,H4'),7.69(1H,m,J=7.6Hz, H-5'), 8.08(2H,d,J=7.6Hz,H-3,5),8.29(2H,d,J=8.8Hz,H-2,6)
14e	7.36(2H,dt,J_0=7.6Hz,J_m=1.6Hz,H-4,4'),7.46(4H,t,J=7.6Hz,H-3,3',5,5') 7.62(4H,dd,J_0=7.6Hz,J_m=1.2Hz,H-2,2',6,6')
14f	7.39(2H,t,J=7.6hz,H-4',4"),7.48(4H,t,H-3',3",5',5"),7.55(1H,t,H=5), 7.61(2H,dd,H-4,6),7.69(4H,dd,J=7.2Hz,J_m=1.6Hz,H-2',2",6',6"),7.84(1H,t,H=2)
14g	7.35(2H,tt,J_0=7.2Hz,J_m=1.2Hz,H-4',4"),7.46(4H,t,J=7.2Hz,H-3',3",5',5") 7.65(4H,d,d,J_0=7.2Hz,H-2',2",6',6"),7.68(4H,s,h-2,3,5,6)
14h	7.39(1H,d,J=7.2Hz,J=7.6Hz,H-4'),7.48(2H,dt,J=7.2Hz,J=7.6Hz,H-3',5'),7.61(2H,d,J=8.4Hz,h-2',6'),7.69(4H,s,(br),H-2,3,5,6)
14i	7.39(1H,t,J=7.6Hz,H-4'),7.47-7.53(4H,m,H-5,6,7,8),7.74(2H,d,J=7.6Hz,H-3,4), 7.76(1H,dd,J_0=9.6Hz,J_m=1.6Hz,H-3'/5'),7.86(1H,dd,J_0=9.2Hz,J_m=2Hz,H-3',5'), 7.91(2H, t, H-2', 6'), 8.05(1H, s, H-1)

Results and Discussion

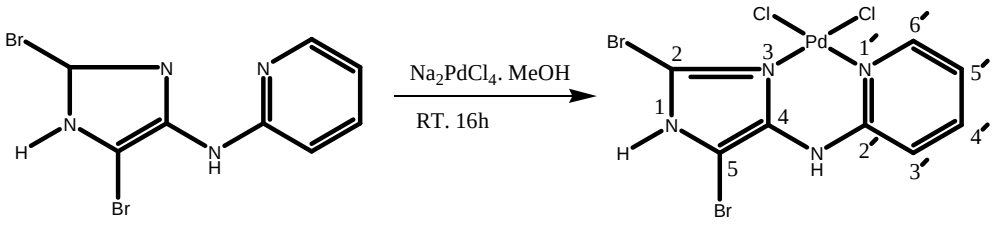
Preparation of the ligand, 11

The heterocyclic ligand, **11** was prepared from imidazole over tribromoimidazole, **10** followed by reaction with 2-aminopyridine, in 20% yield.



Scheme 1

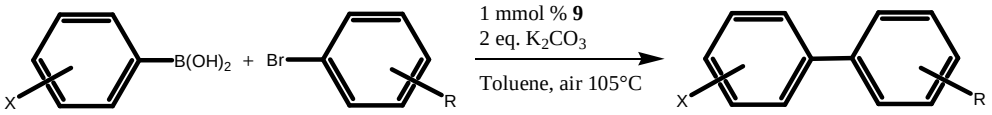
The Pd-catalyst was easily prepared from 4-(2, 5-Dibromoimidazolyl)-2′-aminopyridine, **11** by refluxing with Na_2PdCl_4 in MeOH over night (Scheme-2). The complex formation is quantitative.



Scheme 2

The Pd complex, **9** was characterized from the ^{1}H-NMR data analysis (Table-1). Complex **9** contains six protons of different types. The broad peak at δ9.39 ppm is assigned for the N-H proton of amino group and another broad peak at δ7.46 ppm is for N-H proton of imidazole ring. The peaks at δ8.35, δ8.23 ppm as doublets were assigned for H-6′ for H-3′ proton respectively. The peaks at δ 7.99 and δ 6.65ppm as triplets for H-4′ and H-5′ respectively. The ESI MS value at 492, 494, 496,498,500,502 with relative intensities (38, 100,89, 32) with Br_2Cl_2 isotopic pattern and the base peak at 302,304, 306, 308 for (H-$PdCl_2$-NH) confirming the Pd-complex formation.

With the Pd catalyst **9** in hand, we first tested the Suzuki-Miyaura coupling reaction of 4-bromoacetophenone with phenyl boronic acid in the presence of K_2CO_3 as a model reaction. The reaction was done in toluene at 100-105°C with 1 mmol% of **9**. The reaction leads to 81% of the product,4-phenylacetophenone **14a**, in 2 hours and all of the starting material was converted into the product,(Scheme-**3**, Table-**3**, Entry **1**). We repeated the SM coupling reaction of phenyl boronic acid with electron withdrawing substituent (-NO_2) in aryl bromides (Table-**3**, Entry **2**), the coupling was excellent. We continue the SM coupling reactions with other boronic acids (fluoro-substituted) (Table-**3**, Entry-**4**), the yield was very good. The spectroscopic data for compounds **14a-i** is given in table -**2.** The reaction of phenylboronic acids with 1, 3-aryliodide and 4-dibromides were also very good.



1.5 equiv. **12** 1 equiv. **13** **14**

Scheme 3

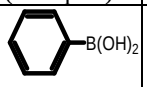
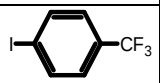
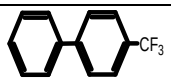
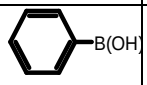
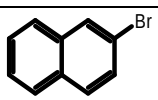
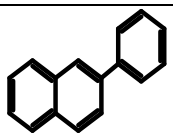
Table 3. Suzuki-Miyaura coupling of aryl halides with aryl boronic acid

Entry	Arylboronic acid, **12** X= Substituents	Arylhalides **13** R=substituents	T°C	**9**(mmol%)	Time(h)	Product **14**	Yield (%)
1	H	4-$COCH_3$	105	1	2.0	a	81
2	H	4-NO_2	105	1	1.5	b	100
3	H	4-CH_3	105	1	2.0	c	95
4	3- F	4-NO_2	105	1	2.5	d	96
5	H	H	105	1	2.0	e	95
6	H	3-Br	105	1	2.0	f	95
7	H	4-Br	105	1	2.0	g	88

Boronic acid was also used for the coupling with iodo aryl halide (Table-**4**,Entry **1**); good result was obtained. The coupling with bromonaphthalene also leads to the production of **14i** in good yield (Table-**4**, Entry **2)**. The spectroscopic data for compounds **14h**, **14i** is given in Table-**2**.

From the above results we find that Pd complex **9** shows outstanding performance. The complex **9** is very stable to oxygen and moisture; no change in its activity was observed, when it was exposed to air and water.

Table 4. SM coupling of aryl iodide and 2-bromonaphthalane with phenyl boronic acid in presence of complex **9**

Entry	Phenylboronic acid (1.5 equiv.)	Arylhalides (1 equiv.)	Product **14**	T°C	**9**(mmol %)	Time (h)	Product **14**	Yield (%)
1				105	1	1.5	h	95
1				105	1	3.0	i	96

Conclusion

We have shown in the above results and discussion section that the Pd complex **9** is a highly efficient catalyst for Suzuki-Miyaura coupling reactions. This is applicable in normal aerial conditions and is very stable in various reaction conditions. We are now investigating the activity of this catalyst in other reactions.

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