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Palladium(II) complex with a potential N₄-type Schiff-base ligand as highly efficient catalyst for Suzuki–Miyaura reactions in aqueous media

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ABSTRACT

Two new air-stable palladium(II) complexes containing a N₄-Schiff-base ligand have been synthesized and investigated as catalysts for the Suzuki–Miyaura reactions. The binuclear complex **2** has proven to be an excellent catalyst for additive-free Suzuki–Miyaura reactions of aryl bromides in neat water at room temperature and aryl chlorides in aqueous-glycerol at 80 °C. Satisfactory to excellent yields of biaryls are obtained with a wide range of substrates with relatively low loading of catalyst.

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During the last two decades, ligand promoted palladium-mediated Suzuki-Miyaura cross-coupling reaction has exemplified one of the most important processes in organic chemistry.¹ Among the different ligands, phosphine-based ligands are still considered to be the most preferred ligand system for Suzuki-reaction.² However, the phosphine ligands are toxic and sensitive to air and moisture which pose significant limitations on their uses. On the contrary, nitrogen-based ligands are generally non-toxic, robust in nature, insensitive to air/moisture, easy-to-handle, and have the potentiality to overcome some of the drawbacks faced by traditional phosphine ligands. Hence, the recent endeavors to search for nitrogen based ligands developed several attractive alternatives such as N-heterocyclic carbenes,³ amines,⁴ oxime-based palladacycles,⁵ etc. Although significant progress has been achieved in developing efficient catalysts that worked under mild reaction conditions with challenging substrates including aryl chlorides, it still remains a major challenge to carry out the Suzuki-Miyaura reactions in water. Due to environmental and economical concerns, many research groups,⁶ including the groups of Leadbeater,^{6a,6b} Shaughnessy,^{4c} Eppinger,^{2j} Zhang,^{6c} Vanelle,^{6d} and Turkman,^{3e,6e} have developed several catalytic systems for Suzuki reactions in water. However, majority of these catalytic systems required either elevated temperatures^{4c,6g,6h} and/or addition of a organic co-solvent,⁶ⁱ and/or the addition of tetrabutylammoniumbromide (TBAB) as phase transfer catalyst,^{6a–6d} even with aryl bromides or iodides as substrates. It may be noted that the use of TBAB not only makes the work-up procedure more complicated but also produces waste when it is used in excess.^{6b} Thus, from academic and industrial view points, the development of new catalytic systems that can promote the Suzuki–Miyaura reactions in aqueous medium under mild reaction conditions without using any additive would be highly advantageous.

For decades, Schiff-bases have played a key role as chelating multidentate ligands in coordination chemistry and catalysis because of their easy synthesis, high stability under a variety of oxidative and reductive conditions, etc.⁷ Moreover, electronic and steric properties of Schiff-bases could be easily tuned by properly selecting the condensing partners. Indeed, there have been few reports about employment of Schiff-base ligands in palladium-catalyzed Suzuki-Miyaura reactions.8 However, almost in all the cases the reactions were carried out in toxic organic solvents such as DMF,^{8a–8f} toluene,^{8g} THF,^{8g} etc. In addition, these catalysts often required a temperature in the range of 100–120 °C for activating aryl bromides-iodides and usually failed to activate aryl chlorides as substrates.^{8a-8d,8f} To our knowledge, only recently, Bowes et. al.^{8h} developed a Schiff-base derived catalyst that was used in water, however only moderate vields were obtained with arvl bromides or arvl iodides as substrates even after refluxing the reaction mixture for a few hours with 2 mol % catalyst. Thus, in order to extend the scope of Schiff-base ligands further in Suzuki-Miyaura



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Scheme 1.

Complex 1/2 (0.2 mol%)

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Table 1

Screening of solvents for room temperature Suzuki-Miyaura reactions^a of 4-bromoanisole with phenylboronic acid using complex 1 and 2 as catalysts

$MeO \longrightarrow Br + B(OH)_2 \xrightarrow{Complex 1/2 (0.2 mol s),} OMe$							
Entry	Solvent	Time (h)	Yield ^{b,c} (%)				
			Complex 1	Complex 2			
1	H ₂ O	12	12	98			
2	ⁱ PrOH	8	36	98			
3	ⁱ PrOH–H ₂ O (1:1)	4	56	99			
4	ⁱ PrOH–H ₂ O (1:1)	12	66	99			
5	n-BuOH	24	52	95			
6	MeOH	24	58	98			
7	DMF	24	26	76			
8	THF	24	26	62			
9	Toluene	24	22	68			

^a Reaction condition: 1.0 mmol 4-bromoanisole, 1.10 mmol phenylboronic acid, 3.0 mmol K₂CO₃, solvent (6 ml).

^b Isolated yield.

^c Yields are of average of two runs.

reactions, we have synthesized and characterized two new palladium complexes with a previously reported⁹ N₄-type Schiff-base ligand 1,2-bis(2'-pyridylmethylenediamino)benzene (L). It is noteworthy to mention that the N₄-ligand L due to the presence of multiple bonding sites is expected to increase the steric congestion around the metal center which is considered to be the vital step facilitating the reductive elimination step in the cross-coupling mechanism. The catalytic activities of the complexes have been explored for Suzuki–Miyaura reactions of aryl bromides and iodides in aqueous condition and aryl chlorides in aqueousglycerol.

The palladium complexes $[Pd(OAC)_2L](1)$ and $[Pd_2(OAC)_4L](2)$ were prepared¹⁰ by treating $[Pd(OAC)_2]$ with the ligand L in 1:1 and 2:1 molar ratio, respectively (Scheme 1). The complexes **1** and **2** were isolated as yellow solids which are stable to air both in solid state and in solution. The identities of the complexes were fully established by elemental analyses, ESI-mass, FTIR, and ¹H and ¹³C NMR spectroscopy.¹⁰ The elemental analyses values and the appearances of molecular ion peaks in the ESI-mass spectra of complexes **1** and **2** support their proposed compositions. In the FTIR spectra, the *v*C=N stretching bands in complexes **1** and **2** appeared at 1631 and 1664 cm⁻¹ respectively and, in comparison with the free ligand (1618 cm⁻¹) these values were shifted toward

higher wave numbers indicating coordination of imine nitrogen with palladium. In addition to imine shifting, the $v_{Py}(C=N)$ stretching band in the complex **2** has also been shifted about 9 cm⁻¹, indicating the involvement of pyridine nitrogen in coordination. In the ¹H NMR spectra, signals due to imine protons appeared as singlets at δ 8.58 and 8.34 ppm, respectively for complexes **1** and **2**. The coordination of pyridine nitrogen in the complex **2** resulted in a downfield shift of 1.54 ppm of the α -proton resonance of pyridine compared to the corresponding signal of the complex **1**. A similar downfield shift was also observed in the corresponding carbon of the ¹³C NMR spectra of complex **2**. However, no prominent shift was observed in the imine or other aromatic carbon resonances.

To evaluate the efficiencies of the complexes **1** and **2** as catalysts for the Suzuki–Miyaura reaction¹¹, initially we have screened a relatively activated substrate, *p*-bromoanisole with phenylboronic acid. The reactions were conducted in water at room temperature with K_2CO_3 as base with 0.2 mol % catalysts and the results are depicted in Table 1. We are very much delighted to see that the desired biphenyls were isolated in nearly quantitative yields within 12 h with complex **2** as catalyst (entry 1). However, under similar experimental condition, complex **1** was found to be almost ineffective in water producing only poor yields (entry 1). Nevertheless, the yield with complex **1** could be

Table 2

Suzuki-Miyaura cross-coupling reactions^a of various aryl bromides and iodides with arylboronic acids using complex 2 as catalyst



Entry	R	R′	Х	Time (h)	Yield ^{b,c} (%)
1	4-NO ₂	Н	Br	12	98
2	4-NO ₂	4-Cl	Br	24	96
3	4-NO ₂	4-Me	Br	16	94
4	4-COMe	Н	Br	6	98
5	4-CHO	Н	Br	12	92
6	Н	Н	Br	6	96
7	Н	4-Me	Br	6	98
8	4-Me	Н	Br	6	99
9	4-OMe	Н	Br	12	99
10	4-OMe	4-Cl	Br	24	92
11	4-OMe	4-Me	Br	16	98
12	2-Me	Н	Br	24	86
13	2-OMe	Н	Br	24	92
14	1,3-Dimethyl	Н	Br	24	82
15	Н	Н	Ι	2	98
16	4-OMe	Н	Ι	2	98

^a Reaction condition: 1.0 mmol aryl halide, 1.10 mmol arylboronic acid, 3.0 mmol,K₂CO₃, water (6 ml).

^b Isolated yield.

^c Yields are of average of two runs.

Table 3

Suzuki-Miyaura cross-coupling reactions^a of various aryl chlorides with arylboronic acids using complex 2 as catalyst

$R' = R' = B(OH)_2 = Complex 2 (1 mol%),$ $R' = B(OH)_2 = B(OH)_2 = Complex 2 (1 mol%),$ $R' = B(OH)_2 = R'$ $R' = R'$ $R' = R'$							
Entry	R	R′	Solvent	Yield ^{b,c} (%)			
1	4-NO ₂	Н	H ₂ O	12 ^d			
3	4-NO ₂	Н	ⁱ PrOH	65			
4	4-NO ₂	Н	ⁱ PrOH–H ₂ O (1:1)	56			
5	4-NO ₂	Н	Glycerol	36			
6	4-NO ₂	Н	Glycerol-H ₂ O (1:1)	82			
7	4-NO ₂	4-Cl	Glycerol $-H_2O(1:1)$	56			
8	4-NO ₂	4-Me	Glycerol $-H_2O(1:1)$	68			
9	4-COMe	Н	Glycerol $-H_2O(1:1)$	76			
10	Н	Н	Glycerol $-H_2O(1:1)$	86			
11	4-Me	Н	Glycerol $-H_2O(1:1)$	74			
12	4-OMe	Me	Glycerol $-H_2O(1:1)$	62			
13	2-OMe	Н	Glycerol– $H_2O(1:1)$	Trace			
14	2-Me	Н	Glycerol– $H_2O(1:1)$	12			

^a Reaction condition: 1.0 mmol aryl chloride, 1.10 mmol arylboronic acid, 3.0 mmol, K₂CO₃, solvent (6 ml).

^b Isolated yield.

^c Yields are of average of two runs.

^d Reaction performed at room temperature.

improved considerably using ⁱPrOH as co-solvent with water (in 1:1 proportion) (entry 4). The ⁱPrOH–water (1:1) combination was also found to be a very effective solvent for complex **2** and quantitative biphenyl formation was achieved in a much shorter time when we compared with neat water as solvent (entry 1 vs entry 3). Outstanding yields with complex **2** were also achieved with the other protic solvents such as ⁱPrOH, ⁿBuOH, and MeOH (entries 2, 5, and 6). However, non-protic solvents such as DMF, THF, and toluene gave relatively poorer yields (entries 7–9).

Encouraged by the results of 2 for initial screening reaction in water, the cross-coupling reactions of a wide variety of aryl bromides in the presence of complex 2 were undertaken in water and the results are displayed in Table 2. In general, bromo benzene and other aryl bromides with electron-withdrawing and electron-donating substituents underwent the coupling reactions with phenylboronic acid in nearly quantitative yields. No significant differences were observed in yield when phenylboronic acid was replaced by *p*-chloroboronic acid (entries 2 and 10) and *p*tolylboronic acid (entries 3, 7, and 11), although some differences in the reaction times were noticed. In general, reactions are much slower with *p*-chloroboronic acid (entries 2 and 10) compared to phenyl (entries 1 and 9) or tolylboronic acid (entries 3 and 11). It is interesting to note that our catalyst can also tolerate sterically demanding substrates such as 2-bromotoluene, 2-bromoanisole, and 2-bromo-1,3-dimethylbenzene (entries 12, 13, and 14), and gave the desired products in good yields. Similar to aryl bromides, aryl iodides as substrates react with phenylboronic acid to give the corresponding coupling products in quantitative yields (entries 15 and 16). As expected, reactions with aryl iodides are much quicker compared to the corresponding aryl bromides.

Unfortunately, the reaction condition was not compatible with aryl chloride as substrate as only very poor yield was obtained in the reaction between *p*-chloronitrobenzene with phenylboronic acid even after increasing the catalyst loading up to 1 mol % (Table 3, entry 1). However, a search for an alternative condition revealed that use of glycerol as co-solvent with water (in 1:1 proportion) at a relatively elevated temperature (80 °C) significantly improved the product formation (Table 3, entry 6). It may be mentioned that glycerol has already been recognized as a sustainable solvent as it has all the desirable properties of a green solvent such as low flammability, high availability, low toxicity, biodegradability, obtained from renewable feedstock, etc.¹² Indeed, chlorobenzene (entry 10) or aryl chlorides containing electron withdrawing substituents such as *p*-chloronitrobenzene/*p*-chloroacetophenone (entries 6 and 9) and electron donating substituents such as *p*-chloroanisole/p-chlorotoluene (entries 11 and 12) reacted smoothly with phenylboronic acid affording the desired biphenyls in moderateto-good yields. However, aryl chlorides with electron donating substituent at the ortho-position are reluctant to react with phenylboronic acid and very poor yield was obtained (entries 13 and 14). Noteworthy to mention that although we have obtained relatively less yields of coupling products with aryl chlorides compared to aryl bromides as substrates, these results are quite significant as we are able to use aryl chlorides as substrates in the Suzuki-Miyaura reaction using environmentally-benign reaction media using reasonably low catalyst loading (1 mol %). In general aryl chlorides are difficult substrates for coupling reactions because of stronger C-Cl bond strength. To activate such chlorides most of the existing catalytic systems still rely on phosphines as ligands and usually operate at drastic reaction conditions (e.g., up to 130 °C, Pd: up to 4 mol %) in environmentally least preferred reaction media such as DMF, toluene, etc.^{2a,2e,2h,2l} Nevertheless, there also exist very few outstanding catalysts derived from N-based ligands that smoothly performed cross-coupling reactions with aryl chlorides.3b,3f,13

In conclusion, we have developed a simple and highly efficient phosphine-free catalytic system that can perform the Suzuki– Miyaura cross-coupling reactions of aryl bromides and iodides in aqueous media at room temperature, and for aryl chlorides in aqueous-glycerol at 80 °C. High product yields, use of environment-friendly reaction media, relatively mild reaction condition, use of nitrogen-based ligand, no TBAB was required, etc. are some of the most significant advantages of our present catalytic system.

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- 10. (a) Synthesis of complex 1: A solution of the ligand L (0.075 g, 2.62 mmol) in 20 ml acetonitrile was added dropwise to a solution of $[Pd(OAc)_2]$ (0.17 g, 2.62 mmol) in 15 ml acetonitrile. After refluxing the reaction mixture for 6 h, the yellow precipitate was filtered. The residue was washed with hexane and recrystallized from dichloromethane and finally complex 1 was obtained as a bright yellow solid. Yield: 82%; Anal. Calcd for C₂₂H₂₀N₄O₄Ql-d: C: 51.72; H: 3.94; N: 10.96. Found: C, 51.91; H, 3.91; N, 10.92. MS-ESI (MeOH): m/z: 510 [M]*; Selected IR frequencies (cm⁻¹, KBr): 1631 ($v_{C=N}$: imine), 1589 ($v_{C=N}$: pyridine), 1676 (v_{coo} : acetate); ¹H NMR (400 MHz, CDCl₃) δ [ppm: 2.18 (s, 6H,CH₃) 8.58 (s, 2H, CH=N), 7.47 (d, 2H, Py, *J* = 8.0 Hz), 7.89–6.91 (m, 10H, Ph+Py). ¹³C NMR (100.62 MHz, CDCl₃) δ [ppm: 182.01 (COO), 152.85 (CH=N), 23.54 (CH₃), 124.59–150.61 (Ph+Py); (b) Synthesis of complex 2: complex 2 was prepared by following the same procedure for synthesizing complex 1 using ligand L and Pd(OAc)₂ in 1:2 molar ratio. Yield: 86%; Anal. Calcd for C₂₆H₂₆Ha₂O₈Q₉Pd₂: C: 42.46; H: 3.56; N: 7.61. Found: C, 42.26; H, 3.53; N, 7.58. MS-ESI (MeOH): m/z: 734 [M–1]*; Selected IR frequencies (cm⁻¹, KBr): 1664 ($v_{C=N}$: imine), 1581($v_{C=N}$: pyridine), 1698 ($v_{C=0}$: acetate); ¹H NMR (400 MHz, CDCl₃) δ (ppm): 2.21 (s, 6H, CH₃), 2.14 (s, 6H, CH₃) 9.01 (d, 2H, Py, *J* = 5.2 Hz), 8.34 (s, 2H, CH=N), 7.30–8.24 (m, 10H, Ph+Py); ¹³C NMR (100.62 MHz, CDCl₃) δ (ppm) 198.01 (COO), 172.60 (CH=N), 29.70 (CH₃), 22.60 (CH₃) 125.60–158.01 (Ph+Py).
- 11. General procedure for the Suzuki-Miyaura reaction: A 50 ml round bottom flask was charged with a mixture of aryl halide (0.5 mmol), arylboronic acid (0.55 mmol), k_2CO_3 (1.5 mmol), and Pd catalyst (0.2 mol% for aryl bromide or 1 mol% for aryl chloride) and the mixture was stirred for required times at room temperature in water (6 ml) for aryl bromides/at 80 °C in aqueous-glycerol (6 ml) for aryl chlorides. After completion, the reaction mixture was diluted with water (20 ml) and extracted with ether (20 ml \times 3). The combined extract was washed with brine (20 ml \times 3) and dried over Na₂SO₄. After evaporation of the solvent under reduced pressure, the residue was chromatographed (silica gel, ethyl acetate/hexane 1:9) to obtain the desired product. The products were confirmed by comparing the ¹H NMR and mass spectral data with authentic samples.
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