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Suzuki-Miyaura Cross-Coupling Reaction Catalyzed by 4,4'-^{t}Bu$_2$-2,2'-dipyridyl-palladium(II) Dichloride Complex in Aqueous Solvent Under Aerobic Condition

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4,4'-*di*-^{t}Bu-2,2'-dipyridylpalladium(II) dichloride complex [(^{t}Bubpy)PdCl$_2$] showed high efficiency for the Suzuki coupling reaction of aryl iodide and bromide with phenylboronic acid in alcohol solvent under aerobic condition. All reactions gave the isolated coupling products in moderate to excellent yields.

Keywords: Suzuki-Miyaura reaction, Cross-coupling, Bipyridine, Palladium chloride.

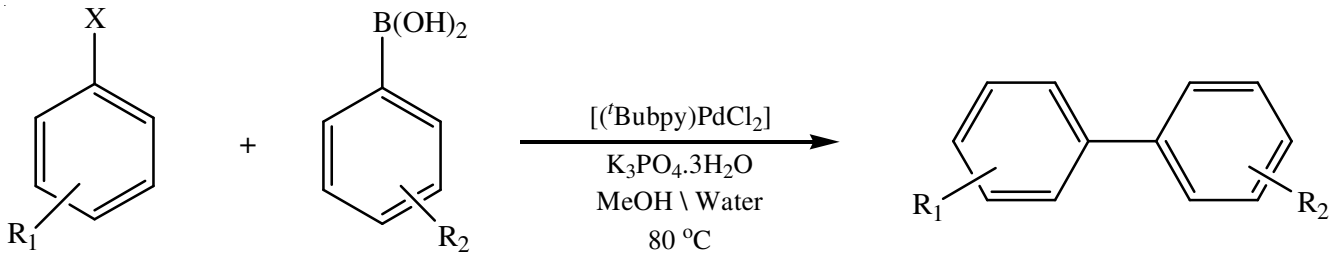
INTRODUCTION

The discovery of palladium catalyzed organic reactions has drawn the attention of chemists to use them in formation of C-C bonds[1-3]. Among them, Suzuki-Miyaura cross-coupling reaction catalyzed by Pd-complexes is a powerful tool for biaryls and heterobiaryl synthesis[4-8]. This reaction can be the key step in the synthesis of pharmaceutical mediates or in natural products, ligands, polymer and in advanced materials[9-11].

It is known that the reaction of Suzuki-Miyaura is dependent on the type of ligands[12-14]. Bulky and electron-rich phosphine ligands have been used widely in palladium-catalyzed Suzuki-Miyaura coupling reactions and excellent results have been reported[15-17]. However, most of the phosphines ligands are sensitive to air and moisture, which causes a limit in their use[18-20]. Therefore, number of phosphine-free ligands such as N-heterocyclic carbenes were employed[21-24]. In addition, ligands containing donor atoms such as N or O and S become important in cross-coupling reaction due to their high stability to air, non-toxic and easy to handle[25-29]. One of the most interesting N-donor ligand is 4,4'-*di*-^{t}Bu-2,2'-bipyridine, which has been used as an effective ligand in C-H borylation of arenes and hetero arenes[30,31]. Interestingly, no report mentioned the use of 4,4'-*di*-^{t}Bu-2,2'-bipyridine palladium(II) dichloride complex, [(^{t}Bubpy)PdCl$_2$], **1**, in Suzuki reaction. But there are examples of 2,2'-bipyridine with palladium, which used as a ligand in cationic Pd-bipyridine to catalyzed the addition of phenylboronic acid to β,β-disubstituted enones or as cationic 4,4'-*bis*(bromomethyl)-2,2'-bipyridine with palladium to catalyzed Suzuki reaction in water[32,33]. Accordingly, we are exploring the catalytic effect of **1** on the coupling of aryliodides or bromides with phenylboronic acid in alcoholic solvent under atmospheric condition. Preliminary results suggested that **1** can be a good precursor catalyst under atmospheric condition only in a mixing aqueous solvent such as MeOH/H$_2$O and in the presence of stoichiometric amount of K$_3$PO$_4$·3H$_2$O at 80 °C. Series of symmetrical and asymmetrical biaryls have been synthesized according to (**Scheme-I**).

EXPERIMENTAL

All reactions were carried out under an air condition. All compounds were obtained from Aldrich Chemical Company,



Scheme-I: [(^{t}Bubpy)PdCl$_2$] catalyzed Suzuki-Miyaura cross-coupling reaction

tested for purity by GC/MS and used without further purification. NMR spectra were recorded at ambient temperature on Bruker Avance 400 and 600. Proton and carbon spectra were referenced to external $SiMe_4$ *via* residual protons in the deuterated solvents or solvent resonance respectively. Elemental analyses were carried out by Perkin-Elmer 2400 series-II elemental analyzer in the Department of Chemistry at King Abdul Aziz University. GC-MS analyses were performed on a Shamadzu Series II gas chromatograph equipped with a 5971 mass selective detector. A fused silica capillary column (10 m or 12 m cross-linked 5 % phenylmethylsilicone) was used and the oven temperature was ramped from 50 to 280 °C at a rate of 20 °C/min. UHP grade helium was used as the carrier gas. All complexes [(^{t}Bupby)$PdCl_2$], [(MeObpy)$PdCl_2$], [(bpy)$PdCl_2$], [(Mebpy)$PdCl_2$] and [$PdCl_2(PhCN)_2$] were prepared according to literatures[34-36].

Typical procedure for Suzuki reaction of aryl iodo or bromides with arylboronic acids: All reactions were performed under aerobic conditions. To a mixture of the appropriate aryl bromide/iodiede (1 equiv.), phenylboronic acid or 4-methoxyphenyl boronic acid (50 mg, 0.41 mmol), $K_3PO_4{\cdot}3H_2O$ (3 equiv. 320 mg, 1.20 mmol) in the presence of 1 or 2 mol % (2 mg, 4.50×10^{-3} mmol or 4 mg, 8.98×10^{-3} mmol) of complex [(^{t}Bubpy)$PdCl_2$] and methanol/water (20/4 mL) was added. The reaction mixture was heated to 80 °C with vigorous stirring for 2, 4 or 16 h. Then, the mixture was cooled to room temperature and extracted with diethyl ether (3 × 30 mL) and washed with 5 mL of EtOAc. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel. The yields were based on aryl halide.

4-Methoxyl-biphenyl[37]: (73.1 mg, 0.40 mmol, 98 %), ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.80 (d, $J_{H\text{-}H}$ = 8.4 Hz, 2H), 7.51-7.54 (m, 2H), 7.42-7.39 (m, 2H), 7.28-7.32 (m, 1H), 6.96-6.99 (m, 2H), 3.85 (s, 3H,OCH_3). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 159.10, 140.80, 133.72, 128.71, 128.14, 126.72, 126.64, 114.14, 55.33. GC-MS (70 Ev) *m/z* (relt.): 184 M^+ ($C_{13}H_{12}O$), 169 $[M\text{-}Me]^+$ ($C_{12}H_9O$). Anal. calcd. for $C_{13}H_{12}O$: C, 84.75; H, 6.57. Found: C 84.55; H 6.55. m.p. (85-86 °C), (lit. 84.0-85.0 °C).

4-Nitro-biphenyl[37]: (67.3 mg, 0.34 mmol, 90 %), ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.73 (d, $J_{H\text{-}H}$ = 8 Hz, 2H), 7.69 (d, $J_{H\text{-}H}$ = 8 Hz, 2H), 7.59 (d, $J_{H\text{-}H}$ = 7.2 Hz, 2H), 7.49 (t, $J_{H\text{-}H}$ = 7.2 Hz, 2H), 7.43 (t, $J_{H\text{-}H}$ = 7.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 145.65, 139.14, 132.60, 130.08, 129.10, 128.65, 127.73, 127.22. GC-MS (70 Ev) *m/z* (relt.): 199 M^+ ($C_{12}H_9NO_2$), 183 $[M\text{-}O]^+$ ($C_{12}H_9NO$). Anal. calcd. for $C_{12}H_9NO_2$: C 72.35; H 4.55; N 7.03. Found: C 72.13; H 4.51; N 7.12. m.p. (112-113 °C), (lit. 115-116 °C).

4-Nitro-4'-methoxy biphenyl[37]: (60 mg, 0.26 mmol, 98 %),^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.00-7.03 (m, 2H), 8.26-8.28 (m, 2H), 7.70-7.78 (m,, 2H), 7.58-7.60 (m, 2H), 3.87 (s, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 160.41, 147.21, 146.50, 131.06, 128.58, 127.08, 124.15, 114.59, 55.43. GC-MS (70 Ev) *m/z* (relt.): 229 M^+ ($C_{13}H_{11}NO_3$), 198 $[M\text{-}OMe]^+$ ($C_{13}H_8NO$). Anal. calcd. for $C_{13}H_{11}NO_3$: C 68.11; H 4.84; N 6.11. Found: C 67.97; H 4.83; N 6.20. m.p. (107-108 °C).

4-Cyano biphenyl[38]: (67.3 mg, 0.38 mmol, 99 %), ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.30 (d, $J_{H\text{-}H}$ = 8.4 Hz, 2H), 7.74 (d, $J_{H\text{-}H}$ = 8.4 Hz, 2H), 7.62 (d, $J_{H\text{-}H}$ = 7.2 Hz, 2H), 7.49 (t, $J_{H\text{-}H}$ = 7.2 Hz, 2H), 7.45 (t, $J_{H\text{-}H}$ = 7.2 Hz, ^{1}H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 147.63, 147.02, 138.74, 129.154, 128.92, 127.81, 127.79, 124.12, 117. GC-MS (70 Ev) *m/z* (relt.): 179 M^+ ($C_{13}H_9N$), 153 $[M\text{-}CN]^+$ ($C_{12}H_9$). Anal. calcd. for $C_{13}H_9N$: C 87.12; H 5.06; N 7.82. Found: C 86.97; H 5.03; N 7.88. m.p. (86-88 °C), lit. m.p. (83-85 °C).

4-Cyano-4'-methoxy biphenyl[39]: (62.6 mg, 0.30 mmol, 98 %), ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.68-7.71 (m, 2H), 7.63-7.66 (m, 2H), 7.53-7.56 (m, 2H), 6.99-7.02 (m, 2H), 3.86 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 160.17, 145.22, 132.76, 132.58, 128.37, 127.11, 119.12, 114.60 (CN), 110.07, 55.41. GC-MS (70 Ev) *m/z* (relt.): 209 ($C_{14}H_{11}NO$), 195 $[M\text{-}N]^+$ ($C_{14}H_{11}O$). Anal. calcd. for $C_{14}H_{11}NO$: C 80.36; H 5.30; N 6.69. Found: C 80.14; H 5.28; N 6.77. m.p. (102-103 °C), (lit. 101-102 °C).

4-Acetyl biphenyl[38]: (74 mg, 0.38 mmol, 99 %), ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8 (d, $J_{H\text{-}H}$ = 8.4 Hz, 2H), 7.69 (d, $J_{H\text{-}H}$ = 8.4 Hz, 2H), 7.62-7.64 (m, 2H), 7.46-7.49 (m, 2H), 7.39-7.42 (m, 1H), 2.64 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 196.50 (CO), 146, 140.08, 136.06, 129.15, 129.11, 128.43, 127.47, 127,43, 26.86, (CH_3). GC-MS (70 Ev) m/z (relt.): 196 M^+ ($C_{14}H_{12}O$), 182 $[M\text{-}CH_2]^+$ ($C_{13}H_{10}O$). Anal. calcd. for $C_{14}H_{12}O$: C 85.68; H 6.16. Found: C 85.55; H 6.13. m.p. (119-120 °C).

4-Phenyl benzaldehyde[40]: (60 mg, 0.33 mmol, 98 %), ^{1}H NMR ($CDCl_3$, 600 MHz) δ 10.06 (s, 1H, CHO), 7.95-7.97 (m, 2H), 7.75-7.78 (m, 2H), 7.63-7.65 (m, 2H), 7.47-7.50 (m, 2H), 7.41-7.44 (m, 1H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 192.03 (CO), 147.22, 139.70, 135.14, 130.30, 129.02, 128.48, 127.70, 127.37. GC-MS (70 Ev) *m/z* (relt.): 182 M^+ ($C_{13}H_{10}O$), 153 $[M\text{-}CHO]^+$ ($C_{12}H_9$). Anal. calcd. for $C_{13}H_{10}O$: C 85.69; H 5.53. Found C 85.57; H 5.50. m.p. (85-86 °C).

4-(4'-Methoxyphenyl)benzaldehyde[41]: (60 mg, 0.28 mmol, 98 %), ^{1}H NMR ($CDCl_3$, 600 MHz) δ 10.03 (s, 1H), 7.00-7.02 (m, 2H), 7.92-7.94 (m, 2H), 7.2 (d, $J_{H\text{-}H}$ = 7.8 Hz, 2H), 7.58-7.61 (m, 2H), 3.87 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 191.97 (CO), 160.08, 146.79, 134.63, 132.04, 130.34, 128.51, 127.06, 114.45, 55.40 (OCH_3). GC-MS (70 ev) *m/z* (relt.): 212 M^+ ($C_{14}H_{12}O_2$), 181 $[M\text{-}OCH_3]^+$ ($C_{13}H_9O$). Anal. calcd. for $C_{14}H_{12}O_2$: C 79.22; H 5.70. Found: C 79.07; H 5.66. m.p. (103-104 °C).

4-Trifluoromethyl biphenyl[42]: (73.6 mg, 0.33 mmol, 99 %), ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.69 (s, 3H), 7.59-7.61 (m, 2H), 7.45-7.49 (m, 2H), 7.39-7.42 (m, 2H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 144.95, 139.99, 129.67, 129.45, 129.22, 128.39, 127.63, 127.49. GC-MS (70 ev) *m/z* (relt.): 222 M^+ ($C_{13}H_9F_3$), 201 $[M\text{-}H_2F]^+$ ($C_{13}H_7F_3$). Anal. calcd. for $C_{13}H_9F_3$ C 70.27; H 4.08. Found: C 70.12; H 4.03. m.p. (69-70 °C).

4-Trifluoromethyl-4'-methoxy biphenyl[39]: (60.4 mg, 0.24 mmol, 99 %), ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.64-7.67 (m, 4H), 7.53-7.56 (m, 2H), 7.99-.027 (m, 2H), 3.86 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 158.82, 143.27, 131.17, 127.32, 125.84, 124.65, 124.63, 113.40, 54.36 (OCH_3). GC-MS (70 ev) *m/z* (relt.): 252 M^+ ($C_{14}H_{11}F_3O$), 237 $[M\text{-}Me]^+$ ($C_{13}H_8F_3O$). Anal. calcd. for $C_{14}H_{11}F_3O$: C 66.66; H 4.40. Found: C 66.44, H 4.39. m.p. (121-122 °C) (lit. 124-125°C).

3,5-*bis*(Trifluoromethyl)biphenyl: (70.5 mg, 0.24 mmol, 99 %), ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.01 (s, 2H), 7.85 (s,

1H), 7.60-7.62 (m, 2H), 7.50-7.53 (m, 2H), 7.45-7.48 (m, 1H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 137.20, 136.60, 131.80, 129.0, 127.50, 127.42, 127.40, 121.00. GC-MS (70 ev) *m/z* (relt.): 290 M^+ ($C_{14}H_8F_6$), 271 [Me-M]$^+$ ($C_{14}H_8F_5$). Anal. calcd. for $C_{14}H_8F_6$: C 57.94; H 2.78. Found: C 57.77; H 2.74.

4-Phenyl benzoic acid[43]: (74.7 mg, 0.38 mmol, 99 %), ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.18 (d, J_{H-H} = 8.4 Hz, 2H), 7.70 (d, J_{H-H} = 8.4Hz, 2H), 7.63-7.65 (m, 2H), 7.47 (t, J_{H-H} = 7.6 Hz, 2H), 7.40-7.43 (m, 1H), 1.74 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 170.74 (CO), 146.45, 139.85, 130.73, 128.96, 128.29, 127.85, 127.32, 127.18. GC-MS (70 ev) *m/z* (relt.): 198 M^+ ($C_{13}H_{10}O_2$), 169 [M-COH]$^+$ (C12H9O). Anal. Calcd. for C13H10O2: C 78.77; H 5.09. Found: C 78.56; H 5.01. m.p. (25-26°C).

4-(4'-Methoxyphenyl)benzoate: (74.1 mg, 0.31 mmol, 99 %), ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.12 (d, J_{H-H} = 8.4, 2H), 6.65 (d, J_{H-H} = 8.4, 2H), 7.58-7.60 (m, 2H), 6.99-7.02 (m, 2H), 3.87 (s, 3H, OCH_3), 1.44 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 167 (CO), 160.90, 140.91, 130.22, 129.40, 128.90, 128. 47, 127.30, 114.60, 56.00 (OCH_3), 50.40 (C $OOCH_3$). GC-MS (70 ev) m/z (relt.) 242 M^+ ($C_{15}H_{14}O_3$), 227 [M-Me]$^+$ ($C_{14}H_{11}O_3$). Anal. calcd. For $C_{14}H_{12}O_3$: C 73.67; H 5.30. Found: C 73.54; H 5.22. m.p. (253-255 °C).

2-Hydroxy-4-(4'-methoxyphenyl)benzaldehyde: (57.8 mg, 0.25 mmol, 79 %), ^{1}H NMR ($CDCl_3$, 600 MHz) δ 10.96 (s, 1H, CHO), 9.96 (s, 1H, OH), 7.72 (d, J_{H-H} = 8.4 Hz, 1H), 6.98-7 (m, 2H), 7.71-7.73 (m, 1H), 7.70 (d, J_{H-H} = 2.4 Hz, 2H), 7.47-7.49 (m, 2H), 3.86 (s, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 196.75 (CO), 160.50, 159.16, 135.46, 133.04, 131.89, 131.35, 127.66, 120.67, 118.04, 114.38, 55.38 (OCH_3). GC-MS (70 ev) *m/z* (relt.): 228 M^+ ($C_{14}H_{12}O_3$), 211 [M-OH]$^+$ ($C_{14}H_{11}O_2$). Anal. calcd. for $C_{14}H_{12}O_3$: C 73.67; H 5.30. Found: C 73.55; H 5.24. m.p. (114-115 °C).

2-Methoxy bipheny[44]: (52.3 mg, 0.28 mmol, 70 %), ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.55-7.58 (m, 2H), 7.43-7.46 (m, 2H) 7.37-7.35 (m, 3H), 7.05-7.08 (m, 1H), 7.032-7.01 (m, 1H), 3.85 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 160.29, 143.06, 141.70, 130.06, 129, 127.40, 127.30, 121.10, 114.60, 112.98, 55.80. GC-MS (70 ev) *m/z* (relt.): 184 M^+ ($C_{13}H_{12}O$), 169 [M-Me]$^+$ ($C_{12}H_9$). Anal. calcd. for $C_{13}H_{12}O$: C 84.75; H 6.57. Found: C 84.57; H 6.55.

3-Methoxyl biphenyl[45]: (21.0 mg, 0.11 mmol, 28 %), ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.65 (d, J_{H-H} = 7.2 Hz, 2H), 7.48 (t, J_{H-H} = 7.8 Hz, 2H), 7.42-7.39 (m, 2H), 7.23 (d, J_{H-H} = 7.8 Hz, 1H), 7.18 (s, 1H), 6.95 (d, J_{H-H} = 8.4 Hz, 1H), 3.92 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 160.50, 143.16, 141.40, 134.17, 129.00, 128.40, 127.30, 126.80, 114.54, 112.90, 55.70 (OCH_3). GC-MS (70 ev) *m/z* (relt.): 184 M^+ ($C_{13}H_{12}O$), 169 [M-Me]$^+$ ($C_{12}H_9$). Anal. calcd. for $C_{13}H_{12}O$: C 84.75; H 6.57. Found: C 84.66; H 6.53.

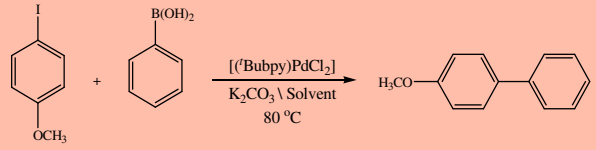
2-Methyl biphenyl[38]: (38.3 mg, 0.23 mmol, 51 %), ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.56-7.59 (m, 2H), 7.44-7.41 (m, 4H) 7.31-7.35 (m, 2H), 7.16 (d, J_{H-H} = 7.6 Hz, 1H), 2.39 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 142.2, 142.1, 137.30, 136.60, 129.70, 129.00, 127.40, 127.30, 126.00, 136.70, 20.2 (CH_3). GC-MS (70 ev) *m/z* (relt.): 168 M^+ ($C_{13}H_{12}$), 153 [M-CH_3]$^+$ ($C_{13}H_{12}$). Anal. calcd. for $C_{13}H_{12}$: C 92.81; H 7.19. Found: C 92.79; H 7.14.

3-Methyl biphenyl[38]: 30.6 mg, 0.18 mmol, 41 %), ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.57-7.60 (m, 2H), 7.41-7.45 (m, 2H), 7.35-7.37 (m, 1H), 7.32-7.35 (m, 1H), 7.17-7.20 (m, 1H), 7.13 (t, J_{H-H} = 6.6 Hz, 1H), 6.88-6.91 (dd, J_{H-H} = 8.4, 8.4 Hz, 1H), 3.87 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 143.1, 141.2 141.40, 136.56, 129, 127.90, 127.12, 119.70, 113.40, 112.90, 21.20 (CH_3). GC-MS (70 ev) *m/z* (relt.): 168 M^+ ($C_{13}H_{12}$), 153 [M-CH_3]$^+$ ($C_{13}H_{12}$). Anal. calcd. for $C_{13}H_{12}$: C 92.81; H 7.19. Found: C 92.66; H 7.16.

RESULTS AND DISCUSSION

Effect of solvents on the [(^{t}Bubpy)PdCl$_2$] catalyzed Suzuki-Miyaura reaction: In initial investigation, we examined the coupling reaction of the model substrate 4-iodoanisole (1 equiv.) with phenylboronic acid (1 equiv.) using **1** (1 mol %) as a catalyst and K_2CO_3 (3 equiv.) as a base with different solvents at 80 ºC for 16 h as shown in Table-1. For instance, the polar solvents gave the coupling product good to excellent yield; this may be due to the high complex solubility. The biphenyl product obtained in methanol resulted in excellent yield (98 %) (Table-1, Entry-1) and a nearly quantitative conversion was obtained from the reactions in ethanol (92 %) (Table-1, Entry- 2). In contrast, when DMF was used as solvent, low yield of the biaryl product were obtained, 46 %, (Table-1, Entry-3). Whereas the nonpolar solvent toluene gave a poor yield (42 %) (Table-1, Entry-4), but 1,4-dioxane and water showed no activity for the reaction (Table-1, Entries-5, 6). Therefore methanol was chosen for further study because it was readily available, low cost and had a higher efficiency.

TABLE-1
EFFECT OF SOLVENTS ON THE [(^{t}Bubpy)PdCl$_2$] CATALYZED SUZUKI–MIYAURA REACTION[a]



Entry	Solvent	Time (h)	Yield[b] (%)
1	Methanol	16	97
2	Ethanol	16	92
3	DMF	16	46
4	Toluene	16	42
5	1,4-Dioxane	16	0
6	Water	16	0

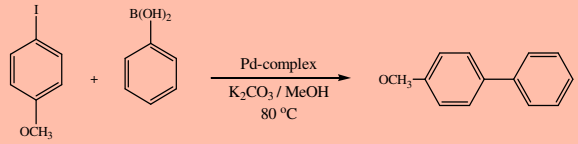
[a]Conditions: Phenylboronic acid 1 equiv (50.0 mg, 0.41 mmol), 4-iodoanisole 1 equiv (96.0 mg, 0.41 mmol), K_2CO_3 3 equiv (171 mg, 1.24 mmol), Catalyst (^{t}BubpyPdCl$_2$) 1 mol % (2.00 mg, 4.50 × 10^{-3} mmol), 80 ºC, [b]Isolated yields

Effect of Pd-complex containing substituted 2,2'-dipyridyl ligands on Suzuki-Miyaura reaction: From Table-1, we observe that MeOH is the best solvent for the coupling reaction. Therefore, we used the same previous model with MeOH as a solvent to explore the catalytic effect of series of palladium complexes containing substituted 2,2'-dipyridyl derivatives such as 4,4'-MeO_2-2,2'-dipyridyl-palladium(II) dichloride complex, [(MeObpy)PdCl$_2$] (**2**), 2,2'-dipyridyl-palladium(II) dichloride complex [(bpy)PdCl$_2$] (**3**) and 4,4'-Me_2-2,2'-

dipyridyl-palladium(II) dichloride complex [(Mebpy)$PdCl_2$] (**4**), on the coupling of 4-iodoanisole with phenylboronic acid in the presence of 1 mol % of catalyst and K_2CO_3 as a base with MeOH as a solvent at 80 °C, Table-2.

Under the optimized conditions shown in Table-2, the best results were obtained when complex **1** containing 4,4'-$^tBu_2$-2,2'-dipyridyl was used as the ligand for the reaction; the isolated yield of biaryl product was 97 % (Table-2, Entry-1). Complex **2** containing 4,4'-MeO_2-2,2'-dipyridyl as ligand also gave good yield of biaryl product, 90 %, (Table-2, Entry-2). However, our results showed a significant decrease in isolated yield when complex **3** containing 2,2'-dipyridyl was used as a ligand and the coupling product was 86 % (Table-2, Entry-3). Complex **4** containing 4,4'-Me_2-2,2'-dipyridyl also showed less activity for the reaction, the yield of biaryl product was only 66 % (Table-2, Entry-4). Nevertheless, when $PdCl_2(PhCN)_2$ was applied as the catalysts, the coupling reaction gave moderate yield 85 % (Table-2, Entry-5). Interestingly, when we carried out the Suzuki-Miyaura reaction in air under ligand-free, only 72 % of the biaryl product was isolated (Table-2, Entry-6). These results indicate that electron-rich bulky ligands such as complex, **1**, shows high efficiency in the coupling reaction.

TABLE-2
EFFECT OF Pd-COMPLEX CONTAINING SUBSTITUTED 2,2'-DIPYRIDYL LIGANDS ON SUZUKI–MIYAURA REACTION

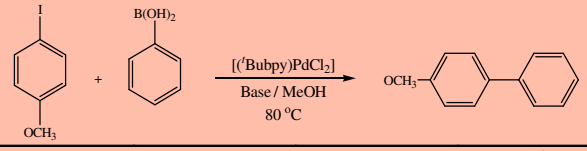


Entry	Pd-Catalyst	No.	Time (h)	Yield[b] (%)
1	[(^{t}Bubpy)$PdCl_2$]	1	16	97
2	[(MeObpy)$PdCl_2$]	2	16	90
3	[(bpy)$PdCl_2$]	3	16	86
4	[(Mebpy)$PdCl_2$]	4	16	66
5	$PdCl_2(PhCN)_2$	5	16	85
6	$PdCl_2$	6	16	72

[a]Conditions: Phenylboronic acid 1 equiv (50.0 mg, 0.41 mmol), 4-Iodoanisole 1 equiv (96.0 mg, 0.41 mmol), K_2CO_3 3 equiv (171 mg, 1.24 mmol), Pd-complexes 1 mol %, 80 °C, [b]Isolated yields

Effect of bases on the [(^{t}Bubpy)$PdCl_2$] catalyzed Suzuki-Miyaura reaction: With the preliminary results in mind, we carried out our studies to determine how bases influenced the coupling reaction. We studied the activities of series bases for the coupling. Of the bases tested, only $K_3PO_4{\cdot}3H_2O$ resulted in high coupling yield after 2 h and the corresponding coupling product was obtained in 98 % yield (Table-3, Entry-1) and K_2CO_3 gave slightly less yields 97 % but after 16 h, (Table-3, Entry-2). Other bases, including $C(CH_3)_3OK$, CH_3COONa, provided the product in moderate yield 81 % (Table-3, Entries-6, 7). Notably, NaOH, which is usually an effective base for Suzuki cross-couplings reaction, proved to be less active giving only 76 % (Table-3, Entry-5) and also piperidine was found equally effective (Table-3, Entry-8). However, when Et_3N was used for the reaction, under these conditions, poor yield was obtained (Table-3, Entry-9). The results are summarized in Table-3.

TABLE-3
EFFECT OF BASES ON THE [(^{t}Bubpy)$PdCl_2$] CATALYSED SUZUKI–MIYAURA REACTION[a]



Entry	Base	Time (h)	Yield[b] (%)
1	$K_3PO_4.3H_2O$	2	98
2	K_2CO_3	16	97
3	Na_2CO_3	16	95
4	KOH	16	94
5	NaOH	16	76
6	$C(CH_3)_3OK$	16	81
7	CH_3COONa	16	81
8	Piperidine	16	74
9	Et_3N	16	54

[a]Conditions: Phenylboronic acid 1 equiv (50.0 mg, 0.41 mmol), 4-Iodoanisole 1 equiv (96.0 mg, 0.41 mmol), Bases 3 equiv., [(^{t}Bubpy)$PdCl_2$] complex 1 mol % (2.00 mg, 4.50×10^{-3} mmol), 80 °C. [b]Isolated yield

[(^{t}Bubpy)$PdCl_2$] catalyzed Suzuki-Miyaura reaction of arylhalides with arylboronic acids under aerobic condition: From the optimized conditions, we observed that the coupling reaction was proceeding smoothly in the presence of MeOH as a solvent and 1 mol % of **1** as a catalyst with 3 equiv. of $K_3PO_4{\cdot}3H_2O$ as a base. As a result, we conducted our optimized condition with series of substituted arylhalides in the presence of phenylboronic acid or 4-methoxyphenylbo-ronic acid as sources of nucleophile. The results are summarized in Table-4.

Aryl iodides easily underwent the reaction to give the desired products over than 97 % as a product (Table-4, Entries 1-5) and also with 2 mol % of the catalyst, the coupling of iodoaniline with phenylboronic acid reached completion within 4 h (Entry-5). However, the reaction of 1-iodo-3,5-*bis*(trifluoromethyl)benzene with 4-methoxyphenylboronic acid resulted in lower yields compared with other aryl iodides, giving only 94 % (Table-4, Entry-6). Low catalyst loading (0.1 mol %) was also examined for electronically donating substrates but low yield were observed after 12 h (Table-4, Entry-7). Good to excellent yields were obtained in the coupling of aryl bromides with phenylboronic acid or 4-methoxyphenylboronic acid and were also efficiently carried out with 1-2 mol % loading of the catalyst. The coupling reactions of electron-withdrawing substituents such as 4-bromobenzoate, 4-bromobenzaldehyde, 1-bromo-4-tri-flouromethylbenzene, 4-bromoacetophenone, 4-bromonitryl-benzene and 4-bromonitrobenzene gave excellent yields of functionalized biphenyls with a 1-2 mol % of the catalyst within 2 h (Table-4, Entries 8-20). Again, with low catalyst loading (0.1 mol %), the coupling of 4-bromo-nitrobenzene with phenylboronic acid gave only 86 % of the desired products after 16 h. But with 1 mol % of catalyst, the yield reached 90 % after 2 h, Table-4, (Table-4, Enteries-21 and 19). Unexpectedly, the coupling of 4-bromoanisole with phenylboronic acid could only achieve a comparable result after we extended the reaction time to 16 h (Table-4, Entry-20).

In addition, reactions of donating aryl bromides bearing a functional group such as hydroxyl or amino groups afforded

the coupling products in moderate to poor yields. For example, the reaction of 4-bromophenol with phenylboronic acid and 4-methoxyphenylboronic acid gave only 77 and 87 % respectively after we extended the time of the reaction with increasing the concentration of the catalyst (Table-4, Entries 22 and 23). But with the reaction of 4-bromaniline and 4-methoxyphenylboronic acid the conversion was only 36 % (Table-4, Entry-24). Furthermore, the reactions of 2-bromobenzaldehyde proceeded slower than 4-bromobenzal-dehyde and the reaction gave only 60 % of coupling product over a period of 4 h (Table-4, Entry-25) indicating that the steric hindrance plays some roles in the coupling reaction. The hindered substrates, 2- and 3-bromo anisole and also 2- and 3-bromotoluene, showed a poor reactivity (Table-4, Entry 26-29) explaining that our optimized condition is not suitable for the steric hindrance substituted aryl halide. In addition, no product was observed in the coupling of 4-chlorobenzaldehyde with phenylboronic acid within 16 h (Table-4, Entry-30).

Conclusion

In summary, a stable and efficient complex was applied for high yield Suzuki-Miyaura cross-coupling reaction of aryliodide and bromide with phenylboronic acid. 4,4'-^{t}Bu$_2$-2,2'-dipyridyl ligand showed high efficiency for the coupling and it was an attractive alternative to the phosphine ligands. The catalytic system showed high efficiency for the coupling of activated and deactivated *para*-aryl iodides and bromide with phenylboronic acid or methoxphenylboronic acid in aqueous solvent under aerobic conditions. But our condition is not suitable for arylchloride and also shows less reactivity for steric aryl halide.

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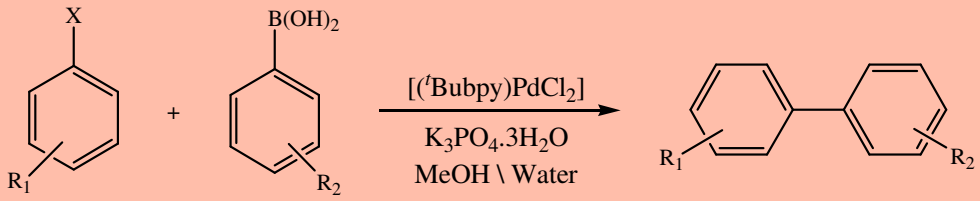
TABLE-4
[(^{t}Bubpy)PdCl$_2$] CATALYSED SUZUKI–MIYAURA REACTION OF ARYLHALIDES WITH ARYLBORONIC ACIDS



Entry	R^1	X	R^2	Pd (mol %)	Time (h)	Yield [b] %
1	4-MeO	I	MeO	1	2	100
2	4-COOH	I	H	1	2	99
3	4-MeO	I	H	1	2	98
4	3,5-CF_3	I	H	1	2	97[d]
5	4-NH_2	I	H	2	4	99
6	3,5-CF_3	I	OMe	1	2	94[d]
7	4-MeO	I	H	0.1	16	93
8	4-NH_2	Br	H	2	4	99[e]
9	4-COOMe	Br	MeO	1	2	99
10	4-CF_3	Br	H	1	2	99
11	4-CF_3	Br	OMe	1	2	99[e]
12	4-COMe	Br	H	1	2	99
13	4-CN	Br	H	1	2	98
14	4-CN	Br	H	2	2	99
15	4-CN	Br	MeO	1	2	98
16	4-CHO	Br	MeO	1	2	98
17	4-CHO	Br	H	1	2	91
18	4-NO_2	Br	MeO	1	2	98
19	4-NO_2	Br	H	1	2	90
20	4-OMe	Br	H	1	16	96
21	4-NO_2	Br	H	0.1	16	86
22	4-OH	Br	H	2	4	77[c,e]
23	4-OH	Br	MeO	2	4	87[c,e]
24	4-NH_2	Br	MeO	2	2	36[e]
25	2-CHO	Br	H	1	4	60[e]
26	4-OMe	2-Br	H	2	4	69[d]
27	4-OMe	3-Br	H	2	4	28[d]
28	4-CH_3	3-Br	H	1	4	51[d]
29	4-CH_3	2-Br	H	1	4	41[d]
30	4-CHO	Cl	H	2	16	0

[a]Conditions: Phenylboronic acid or methoxyphenylboronic acid 1 equiv (50.0 mg, 0.41 mmol; 0.0032 mmol), aryl halides 1 equiv., [(^{t}Bubpy)PdCl$_2$] complex 1 or 2 mol % (2.00 mg, 4.50×10^{-3} mmol or 4.00 mg, 8.98×10^{-3} mmol), $K_3PO_4.3H_2O$ 3 equiv., 80 ºC [b]Isolated yields [c]Phenylboronic acid 1.2 equiv (60.0 mg, 0.49 mmol) [d]Oil [e]Yield of biphenyl determined by GC

REFERENCES

1. B.M. Trost, *Science*, **254**, 1471 (1991).
2. A. Suzuki, *J. Organomet. Chem*., **576**, 147 (1999).
3. J.-M. Lu, H. Ma, Sh.-Sh. Li, D. Ma and L.-X. Shao, *Tetrahedron*, **66**, 5185 (2010).
4. N. Miyaura, K. Yamada and A. Suzuki, *Tetrahedron Lett*., **20**, 3437 (1979).
5. N. Miyaura and A. Suzuki, *Chem. Rev*., **95**, 2457 (1995).
6. N. Miyaura, *J. Organomet. Chem*., **653**, 54 (2002).
7. F. Alonso, I.P. Beletskaya and M. Yus, *Tetrahedron*, **64**, 3047 (2008).
8. A. Suzuki, *Angew. Chem. Int. Ed*., **50**, 6722 (2011).
9. L. Pu, *Chem. Rev*., **98**, 2405 (1998).
10. A.F. Littke and G.C. Fu, *Angew. Chem. Int. Ed*., **41**, 4176 (2002).
11. B. Schlummer and U. Scholz, *Adv. Synth. Catal*., **346**, 1599 (2004).
12. N.G. Andersen and B.A. Keay, *Chem. Rev*., **101**, 997 (2001).
13. S.M. Nobre, S.I. Wolke, R.G. da Rosa and A.L. Monteiro, *Tetrahedron Lett*., **45**, 6527 (2004).
14. R. Martin and S.L. Buchwald, *Acc. Chem. Res*., **41**, 1461 (2008).
15. V.B.W. Bohm, C.W.K. Gstottmayr, T. Weskamp and W.A. Herrmann, *J. Organomet. Chem*., **595**, 186 (2000).
16. O. Navarro, R.A. Kelly III and S.P. Nolan, *J. Am. Chem. Soc*., **125**, 16194 (2003).
17. J. Zhou, X. Guo, C. Tu, X. Li and H. Sun, *J. Organomet. Chem*., **694**, 697 (2009).
18. W.A. Herrmann, *Angew. Chem. Int. Ed*., **41**, 1290 (2002).
19. J.-H. Li and W.-J. Liu, *Org. Lett*., **6**, 2809 (2004).
20. J.-H. Li, W.-J. Liu and Y.-X. Xie, *J. Org. Chem*., **70**, 5409 (2005).
21. V.P.W. Bohm, C.W. Gstottmayr, T. Weskamp and W.A. Herrmann, *J. Organomet. Chem*., **595**, 186 (2000).
22. B. Schlummer and U. Scholz, *Adv. Synth. Catal*., **346**, 1599 (2004).
23. J. Broggi, H. Clavier and S.P. Nolan, *Organometallics*, **27**, 5525 (2008).
24. X.-Q. Zhang, Y.-P. Qiu, B. Rao and M.-M. Luo, *Organometallics*, **28**, 3093 (2009).
25. C. Nájera, J. Gil-Moltó, S. Karlström and L.R. Falvello, *Org. Lett*., **5**, 1451 (2003).
26. J. Gil-Molto and C. Najera, *Eur. J. Org. Chem*., **2005**, 4073 (2005).
27. M. Joshaghani, E. Faramarzi, E. Rafiee, M. Daryanavard, J. Xiao and C. Baillie, *J. Mol. Catal. Chem*., **273**, 310 (2007).
28. M. Joshaghani, E. Faramarzi, E. Rafiee, M. Daryanavard, J. Xiao and C. Baillie, *J. Mol. Catal. Chem*., **259**, 35 (2006).
29. Z.-Z. Zhou, D.-S. Liu, D.-C. Shen, C. Tan, L.-Y. Luo, *Inorg. Chem. commun*., **14**, 659 (2011).
30. I.A. Mkhalid, J.H. Barnard, T.B. Marder, J.M. Murphy and J.F. Hartwig, *Chem. Rev*., **110**, 890 (2010).
31. J. Takagi, K. Sato, J.F. Hartwig, T. Ishiyama and N. Miyaura, *Tetrahedron Lett*., **43**, 5649 (2002).
32. S. Lin and X. Lu, *Org. Lett*., **12**, 2536 (2010).
33. W.-Y. Wu, S.-N. Chen and F.-Y. Tsai, *Tetrahedron Lett*., **47**, 9267 (2006).
34. N.D. Ball and M.S. Sanford, *J. Am. Chem. Soc*., **131**, 3796 (2009).
35. F. Ungváry, *J. Organomet. Chem*., **457**, 273 (1993).
36. J.R. Doyle, P.E. Slade, H.B. Jonassen and R.N. Rhoda, *Inorg. Synth*., **6**, 216 (1960).
37. C.-L. Deng, S.-M. Guo, Y.-X. Xie and J.-H. Li, *Eur. J. Org. Chem*., 1457 (2007).
38. L. Jiang, F. Shan, Z. Li and D. Zhao, *Molecules*, **17**, 12121 (2012).
39. S.E. Denmark and M.H. Ober, *Org. Lett*., **5**, 1357 (2003).
40. J.W. Lown, T.W. Maloney and G. Dallas, *Can. J. Chem*., **48**, 584 (1970).
41. Y. Monguchi, Y. Fujita, S. Hashimoto, M. Ina, T. Takahashi, R. Ito, K. Nozaki, T. Maegawa and H. Sajiki, *Tetrahedron*, **67**, 8628 (2011).
42. K. Ueura, T. Satoh and M. Miura, *Org. Lett*., **7**, 2229 (2005).
43. T. Maegawa, Y. Kitamura, S. Sako, T. Udzu, A. Sakurai, A. Tanaka, Y. Kobayashi, K. Endo, U. Bora, T. Kurita, A. Kozaki, Y. Monguchi and H. Sajiki, *Chem. Eur. J.*, **13**, 5937 (2007).
44. J.L. Bolliger and C.M. Frech, *Adv. Synth. Catal*., **352**, 1075 (2010).
45. P.D. Stevens, J. Fan, H.M.R. Gardimalla, M. Yen and Y. Gao, *Org. Lett*., **7**, 2085 (2005).