Suzuki-Miyaura Cross-Coupling Reaction Catalyzed by 4,4'-^tBu₂-2,2'-dipyridyl-palladium(II) Dichloride Complex in Aqueous Solvent Under Aerobic Condition

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4,4'-^tBu-2,2'-dipyridylpalladium(II) dichloride complex [^tBubpy)PdCl₂] 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 bonds¹⁻³. Among them, Suzuki-Miyaura cross-coupling reaction catalyzed by Pd-complexes is a powerful tool for biaryls and heterobiaryl synthesis⁴⁻⁸. This reaction can be the key step in the synthesis of pharmaceutical mediates or in natural products, ligands, polymer and in advanced materials⁹⁻¹¹.

It is known that the reaction of Suzuki-Miyaura is dependent on the type of ligands¹²⁻¹⁴. Bulky and electron-rich phosphine ligands have been used widely in palladium-catalyzed Suzuki-Miyaura coupling reactions and excellent results have been reported¹⁵⁻¹⁷. However, most of the phosphines ligands are sensitive to air and moisture, which causes a limit in their use¹⁸⁻²⁰. Therefore, number of phosphine-free ligands such as N-heterocyclic carbenes were employed²¹⁻²⁴. 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 handle²⁵⁻²⁹. One of the most interesting N-donor ligand is 4,4'-^tBu-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'-^tBu-2,2'-bipyridine palladium(II) dichloride complex, [^tBubpy)PdCl₂], **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 aryl iodides 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/H₂O and in the presence of stoichiometric amount of K₃PO₄·3H₂O 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: [^tBubpy)PdCl₂] 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 SiMe₄ *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 [(^tBupby)PdCl₂], [(MeObpy)PdCl₂], [(bpy)PdCl₂], [(Mebpy)PdCl₂] and [PdCl₂(PhCN)₂] were prepared according to literatures³⁴⁻³⁶.

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/iodide (1 equiv.), phenylboronic acid or 4-methoxyphenyl boronic acid (50 mg, 0.41 mmol), K₃PO₄·3H₂O (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 [(^tBupby)PdCl₂] 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 MgSO₄ 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-biphenyl³⁷: (73.1 mg, 0.40 mmol, 98 %), ¹H NMR (CDCl₃, 600 MHz) δ 7.80 (d, *J*_{H-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, OCH₃). ¹³C NMR (CDCl₃, 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⁺ (C₁₃H₁₂O), 169 [M-Me]⁺ (C₁₂H₉O). Anal. calcd. for C₁₃H₁₂O: 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-biphenyl³⁷: (67.3 mg, 0.34 mmol, 90 %), ¹H NMR (CDCl₃, 600 MHz) δ 7.73 (d, *J*_{H-H} = 8 Hz, 2H), 7.69 (d, *J*_{H-H} = 8 Hz, 2H), 7.59 (d, *J*_{H-H} = 7.2 Hz, 2H), 7.49 (t, *J*_{H-H} = 7.2 Hz, 2H), 7.43 (t, *J*_{H-H} = 7.2 Hz, 1H). ¹³C NMR (CDCl₃, 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⁺ (C₁₂H₉NO₂), 183 [M-O]⁺ (C₁₂H₉NO). Anal. calcd. for C₁₂H₉NO₂: 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 biphenyl³⁷: (60 mg, 0.26 mmol, 98 %), ¹H NMR (CDCl₃, 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). ¹³C NMR (CDCl₃, 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⁺ (C₁₃H₁₁NO₃), 198 [M-OMe]⁺ (C₁₃H₈NO). Anal. calcd. for C₁₃H₁₁NO₃: 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 biphenyl³⁸: (67.3 mg, 0.38 mmol, 99 %), ¹H NMR (CDCl₃, 600 MHz) δ 8.30 (d, *J*_{H-H} = 8.4 Hz, 2H), 7.74

(d, *J*_{H-H} = 8.4 Hz, 2H), 7.62 (d, *J*_{H-H} = 7.2 Hz, 2H), 7.49 (t, *J*_{H-H} = 7.2 Hz, 2H), 7.45 (t, *J*_{H-H} = 7.2 Hz, 1H). ¹³C NMR (CDCl₃, 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⁺ (C₁₃H₉N), 153 [M-CN]⁺ (C₁₂H₉). Anal. calcd. for C₁₃H₉N: 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 biphenyl³⁹: (62.6 mg, 0.30 mmol, 98 %), ¹H NMR (CDCl₃, 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, OCH₃). ¹³C NMR (CDCl₃, 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 (C₁₄H₁₁NO), 195 [M-N]⁺ (C₁₄H₁₁O). Anal. calcd. for C₁₄H₁₁NO: 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 biphenyl³⁸: (74 mg, 0.38 mmol, 99 %), ¹H NMR (CDCl₃, 400 MHz) δ 8 (d, *J*_{H-H} = 8.4 Hz, 2H), 7.69 (d, *J*_{H-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, CH₃). ¹³C NMR (CDCl₃, 150 MHz) δ 196.50 (CO), 146, 140.08, 136.06, 129.15, 129.11, 128.43, 127.47, 127.43, 26.86, (CH₃). GC-MS (70 Ev) *m/z* (relt.): 196 M⁺ (C₁₄H₁₂O), 182 [M-CH₃]⁺ (C₁₃H₁₀O). Anal. calcd. for C₁₄H₁₂O: C 85.68; H 6.16. Found: C 85.55; H 6.13. m.p. (119-120 °C).

4-Phenyl benzaldehyde⁴⁰: (60 mg, 0.33 mmol, 98 %), ¹H NMR (CDCl₃, 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). ¹³C NMR (CDCl₃, 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⁺ (C₁₃H₁₀O), 153 [M-CHO]⁺ (C₁₂H₉). Anal. calcd. for C₁₃H₁₀O: C 85.69; H 5.53. Found C 85.57; H 5.50. m.p. (85-86 °C).

4-(4'-Methoxyphenyl)benzaldehyde⁴¹: (60 mg, 0.28 mmol, 98 %), ¹H NMR (CDCl₃, 600 MHz) δ 10.03 (s, 1H), 7.00-7.02 (m, 2H), 7.92-7.94 (m, 2H), 7.2 (d, *J*_{H-H} = 7.8 Hz, 2H), 7.58-7.61 (m, 2H), 3.87 (s, 3H, OCH₃). ¹³C NMR (CDCl₃, 150 MHz) δ 191.97 (CO), 160.08, 146.79, 134.63, 132.04, 130.34, 128.51, 127.06, 114.45, 55.40 (OCH₃). GC-MS (70 ev) *m/z* (relt.): 212 M⁺ (C₁₄H₁₂O₂), 181 [M-OCH₃]⁺ (C₁₃H₉O). Anal. calcd. for C₁₄H₁₂O₂: C 79.22; H 5.70. Found: C 79.07; H 5.66. m.p. (103-104 °C).

4-Trifluoromethyl biphenyl⁴²: (73.6 mg, 0.33 mmol, 99 %), ¹H NMR (CDCl₃, 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). ¹³C NMR (CDCl₃, 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⁺ (C₁₃H₉F₃), 201 [M-H₂F]⁺ (C₁₃H₇F₃). Anal. calcd. for C₁₃H₉F₃: C 70.27; H 4.08. Found: C 70.12; H 4.03. m.p. (69-70 °C).

4-Trifluoromethyl-4'-methoxy biphenyl³⁹: (60.4 mg, 0.24 mmol, 99 %), ¹H NMR (CDCl₃, 400 MHz) δ 7.64-7.67 (m, 4H), 7.53-7.56 (m, 2H), 7.99-0.027 (m, 2H), 3.86 (s, 3H, OCH₃). ¹³C NMR (CDCl₃, 150 MHz) δ 158.82, 143.27, 131.17, 127.32, 125.84, 124.65, 124.63, 113.40, 54.36 (OCH₃). GC-MS (70 ev) *m/z* (relt.): 252 M⁺ (C₁₄H₁₁F₃O), 237 [M-Me]⁺ (C₁₃H₈F₃O). Anal. calcd. for C₁₄H₁₁F₃O: 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 %), ¹H NMR (CDCl₃, 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). ¹³C NMR (CDCl₃, 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⁺ (C₁₄H₈F₆), 271 [Me-M]⁺ (C₁₄H₈F₅). Anal. calcd. for C₁₄H₈F₆: C 57.94; H 2.78. Found: C 57.77; H 2.74.

4-Phenyl benzoic acid⁴³: (74.7 mg, 0.38 mmol, 99 %), ¹H NMR (CDCl₃, 400 MHz) δ 8.18 (d, *J*_{H-H} = 8.4 Hz, 2H), 7.70 (d, *J*_{H-H} = 8.4 Hz, 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). ¹³C NMR (CDCl₃, 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⁺ (C₁₃H₁₀O₂), 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 %), ¹H NMR (CDCl₃, 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, OCH₃), 1.44 (s, 3H, CH₃). ¹³C NMR (CDCl₃, 150 MHz) δ 167 (CO), 160.90, 140.91, 130.22, 129.40, 128.90, 128.47, 127.30, 114.60, 56.00 (OCH₃), 50.40 (C OCH₃). GC-MS (70 ev) *m/z* (relt.) 242 M⁺ (C₁₅H₁₄O₃), 227 [M-Me]⁺ (C₁₄H₁₃O₃). Anal. calcd. For C₁₄H₁₂O₃: 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 %), ¹H NMR (CDCl₃, 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). ¹³C NMR (CDCl₃, 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 (OCH₃). GC-MS (70 ev) *m/z* (relt.): 228 M⁺ (C₁₄H₁₂O₃), 211 [M-OH]⁺ (C₁₄H₁₁O₂). Anal. calcd. for C₁₄H₁₂O₃: C 73.67; H 5.30. Found: C 73.55; H 5.24. m.p. (114-115 °C).

2-Methoxy biphenyl⁴⁴: (52.3 mg, 0.28 mmol, 70 %), ¹H NMR (CDCl₃, 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, OCH₃). ¹³C NMR (CDCl₃, 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⁺ (C₁₃H₁₂O), 169 [M-Me]⁺ (C₁₂H₉). Anal. calcd. for C₁₃H₁₂O: C 84.75; H 6.57. Found: C 84.57; H 6.55.

3-Methoxyl biphenyl⁴⁵: (21.0 mg, 0.11 mmol, 28 %), ¹H NMR (CDCl₃, 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, OCH₃). ¹³C NMR (CDCl₃, 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 (OCH₃). GC-MS (70 ev) *m/z* (relt.): 184 M⁺ (C₁₃H₁₂O), 169 [M-Me]⁺ (C₁₂H₉). Anal. calcd. for C₁₃H₁₂O: C 84.75; H 6.57. Found: C 84.66; H 6.53.

2-Methyl biphenyl³⁸: (38.3 mg, 0.23 mmol, 51 %), ¹H NMR (CDCl₃, 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, CH₃). ¹³C NMR (CDCl₃, 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 (CH₃). GC-MS (70 ev) *m/z* (relt.): 168 M⁺ (C₁₃H₁₂), 153 [M-CH₃]⁺ (C₁₃H₁₂). Anal. calcd. for C₁₃H₁₂: C 92.81; H 7.19. Found: C 92.79; H 7.14.

3-Methyl biphenyl³⁸: 30.6 mg, 0.18 mmol, 41 %), ¹H NMR (CDCl₃, 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, CH₃). ¹³C NMR (CDCl₃, 150 MHz) δ 143.1, 141.2 141.40, 136.56, 129, 127.90, 127.12, 119.70, 113.40, 112.90, 21.20 (CH₃). GC-MS (70 ev) *m/z* (relt.): 168 M⁺ (C₁₃H₁₂), 153 [M-CH₃]⁺ (C₁₃H₁₂). Anal. calcd. for C₁₃H₁₂: C 92.81; H 7.19. Found: C 92.66; H 7.16.

RESULTS AND DISCUSSION

Effect of solvents on the [(^tBubpy)PdCl₂] 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 K₂CO₃ (3 equiv.) as a base with different solvents at 80 °C 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 [(^tBubpy)PdCl₂]
CATALYZED SUZUKI-MIYAUURA 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

^aConditions: Phenylboronic acid 1 equiv (50.0 mg, 0.41 mmol), 4-iodoanisole 1 equiv (96.0 mg, 0.41 mmol), K₂CO₃ 3 equiv (171 mg, 1.24 mmol), Catalyst (^tBubpy)PdCl₂ 1 mol % (2.00 mg, 4.50 × 10⁻³ mmol), 80 °C, ^bIsolated 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'-MeO₂-2,2'-dipyridyl-palladium(II) dichloride complex, [(MeObpy)PdCl₂] (**2**), 2,2'-dipyridyl-palladium(II) dichloride complex [(bpy)PdCl₂] (**3**) and 4,4'-Me₂-2,2'-

dipyridyl-palladium(II) dichloride complex [(Mebpy)PdCl₂] (**4**), on the coupling of 4-iodoanisole with phenylboronic acid in the presence of 1 mol % of catalyst and K₂CO₃ 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'-*t*Bu₂-2,2'-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'-MeO₂-2,2'-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'-Me₂-2,2'-dipyridyl also showed less activity for the reaction, the yield of biaryl product was only 66 % (Table-2, Entry-4). Nevertheless, when PdCl₂(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-MIYAUURA 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

^aConditions: Phenylboronic acid 1 equiv (50.0 mg, 0.41 mmol), 4-Iodoanisole 1 equiv (96.0 mg, 0.41 mmol), K₂CO₃ 3 equiv (171 mg, 1.24 mmol), Pd-complexes 1 mol %, 80 °C, ^bIsolated yields

Effect of bases on the [(^tBubpy)PdCl₂] 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 K₃PO₄·3H₂O resulted in high coupling yield after 2 h and the corresponding coupling product was obtained in 98 % yield (Table-3, Entry-1) and K₂CO₃ gave slightly less yields 97 % but after 16 h, (Table-3, Entry-2). Other bases, including C(CH₃)₃OK, CH₃COONa, 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 Et₃N 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 [(^tBubpy)PdCl₂] CATALYSED SUZUKI-MIYAUURA REACTION^a

Entry	Base	Time (h)	Yield ^b (%)
1	K ₃ PO ₄ ·3H ₂ O	2	98
2	K ₂ CO ₃	16	97
3	Na ₂ CO ₃	16	95
4	KOH	16	94
5	NaOH	16	76
6	C(CH ₃) ₃ OK	16	81
7	CH ₃ COONa	16	81
8	Piperidine	16	74
9	Et ₃ N	16	54

^aConditions: Phenylboronic acid 1 equiv (50.0 mg, 0.41 mmol), 4-Iodoanisole 1 equiv (96.0 mg, 0.41 mmol), Bases 3 equiv., [(^tBubpy)PdCl₂] complex 1 mol % (2.00 mg, 4.50 × 10⁻³ mmol), 80 °C. ^bIsolated yield

[(^tBubpy)PdCl₂] 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 K₃PO₄·3H₂O as a base. As a result, we conducted our optimized condition with series of substituted arylhalides in the presence of phenylboronic acid or 4-methoxyphenylboronic 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-trifluoromethylbenzene, 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-bromonitrobenzene 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, Entries-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-bromobenzaldehyde 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 aryl iodide and bromide with phenylboronic acid. 4,4'-^tBu₂-2,2'-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 methoxyphenylboronic acid in aqueous solvent under aerobic conditions. But our condition is not suitable for aryl chloride and also shows less reactivity for steric aryl halide.

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TABLE-4
[^tBubpy]PdCl₂] CATALYSED SUZUKI-MIYAUURA 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

^aConditions: Phenylboronic acid or methoxyphenylboronic acid 1 equiv (50.0 mg, 0.41 mmol; 0.0032 mmol), aryl halides 1 equiv., [^tBubpy]PdCl₂] complex 1 or 2 mol % (2.00 mg, 4.50 × 10⁻³ mmol or 4.00 mg, 8.98 × 10⁻³ mmol), K₃PO₄·3H₂O 3 equiv., 80 °C ^bIsolated yields ^cPhenylboronic acid 1.2 equiv (60.0 mg, 0.49 mmol) ^dOil ^eYield of biphenyl determined by GC

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