First Reusable Ligand-Free Palladium Catalyzed C-P Bond Formation of Aryl Halides With Trialkylphosphites in Neat Water

Nasser Iranpoor*, Habib Firouzabadi*, Khashayar Rajabi Moghadam and Somayeh Motavalli

Iranpoor@susc.ac.ir, Firouzabdi@susc.ac.ir

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1. General considerations:

1.1 Reagents:
All the palladium catalysts have purity greater than 97% and arylhalides were reagent grade. All reagents and solvents were obtained from commercial suppliers and used without further purification.

1.2 Analytical methods:
$^1$H and $^{13}$C spectra were recorded on a Brucker Avance DPX-250 spectrometer and $^{31}$P NMR (on a Brucker UltraShield-400 spectrometer) using tetramethylsilane (TMS) as internal standard in pure deuterated solvents. The reaction monitoring was carried out on silica gel analytical sheets or by GC analysis using a 1m length column packed with DC-200 stationary phase. Column chromatography was carried out on column of silica gel.

2 Palladium-catalyzed coupling of aryl halides with P(OEt)$_3$ and P(OPr$_i$)$_3$:

![Chemical reaction diagram]

R: H, NO$_2$, CN, OCH$_3$, CH$_3$, CF$_3$, Br, Cl, OH, NH$_2$, Ph  
R': Et, i-Pr, Ph  
X: Cl, Br, I

2.1 General Procedure for phosphonation of aryl halides with trialkylphosphites using PdCl$_2$ as catalyst in neat water:

A mixture of PdCl$_2$ (0.004 g, 0.022 mmol, 4.4 mol%), aryl halide (0.5 mmol), trialkylphosphite (2.0 mmol), $n$-Pr$_3$N (1.0 mmol, 0.18 mL), TBAB (0.5 mmol, 0.166 g.), in water (1.5 mL) was heated at 100 °C. After completion of the reaction monitored by GC or TLC analysis, the reaction mixture was cooled to room temperature. The organic compounds were extracted with ethyl acetate ($3 \times 10$ mL) from the aqueous layer and dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated in vacuum. The crude organic mixture was then purified by silica gel column chromatography using petroleum ether/ethyl acetate 4:1 as eluent to obtain the desired product (Table 1).
2.1 Characterization of the products:

**Diethyl-phenyl-posphonate** $^{1,2,3,6}$: (3a) [CAS No. 1754-49-0] oil, yield: 99%; 1H NMR (250 MHz, CDCl$_3$/TMS): $\delta$ (ppm) = 1.22 (t, $J = 7.0$ Hz, 6H), 3.99-4.10 (m, 2H), 7.38-7.48 (m, 2H); 13C NMR (CDCl$_3$, 62.5 MHz) $\delta$ 132.35, 131.69, 128.58, 128.34, 62.16, 16.37; $^{31}$P NMR (CDCl$_3$, 162 MHz): $\delta$(ppm) 18.35; HRMS: m/z 241.1

**diethyl (4-methoxyphenyl)phosphonate** $^{1,2,6}$: (3b) [CAS No. 3762-33-2] oil yield 90% 1H NMR (250 MHz, CDCl$_3$/TMS): $\delta$ (ppm) =1.18-1.23 (t, $J = 7.1$ Hz, 6H), 3.7-4.06 (m, 4H), 6.83-6.89 (m 2H), 7.59-7.68(m, 2H); 13C NMR (CDCl$_3$, 62.5 MHz) $\delta$ 159.5, 129.4, 120.6, 113.8, 58.0, 55.0, 16.8; $^{31}$P NMR(CDCl$_3$, 162 MHz) $\delta$ 18.4; HRMS: m/z 244.1

**diethyl p-tolylphosphonate** $^{1,2,3,6}$ (3c) [CAS No. 3762-25-2] oil yield 83% 1H NMR (250 MHz, CDCl$_3$/TMS): $\delta$ (ppm) =1.18 (t, $J = 6.9$ Hz, 6H), 2.27(s), 3.93-4.01 (m, 4H), 7.12-7.16(m, 2H), 7.53-7.61(m, 2H); 13C NMR (CDCl$_3$, 62.5 MHz) $\delta$ 143.4, 137.4, 133.0, 127.4, 64.0, 21.8, 16.4; $^{31}$P NMR(CDCl$_3$, 162 MHz) $\delta$ 18.8 HRMS: m/z 228.1

**diethyl (4-nitrophenyl)phosphonate** $^{1}$ (3d) [CAS No. 3762-25-2, 1754-42-3] oil yield 85% 1H NMR (250 MHz, CDCl$_3$/TMS): $\delta$ (ppm) =1.22 (t, $J = 7.1$ Hz, 3H), 3.77-3.89 (m, 4H), 7.50–7.54 (m, 2H), 8.16-8.20 (m, 2H); 13C NMR (CDCl$_3$, 62.5 MHz) $\delta$ 149.60, 134.55, 129.26, 123.38, 57.81-58.00 (d, J = 2.2 Hz), 16.88-16.80 (d, J = 0.8 Hz), $^{31}$P NMR(CDCl$_3$, 162 MHz) $\delta$ 14.91; HRMS: m/z 259.1

**diethyl (4-cyanophenyl)phosphonate** $^{1,6}$ (3e) [CAS No. 28255-72-3] oil yield 65% 1H NMR (250 MHz, CDCl$_3$/TMS): $\delta$ (ppm) =1.19-1.25 (t, $J = 7.0$ Hz, 6H), 3.80-3.86 (m,
diethyl (4-(trifluoromethyl)phenyl)phosphonate\(^6\) (3f) [CAS No. 99578-68-4] oil yield 83\% \(^1\)H NMR (250 MHz, CDCl\(_3\)/TMS): \(\delta\) (ppm) =1.24 (t, \(J = 6.9\) Hz, 6H), 3.96-4.09 (m, 4H), 7.40–7.46 (m, 2H), 7.54-7.63 (m, 2H); \(^{13}\)C NMR (CDCl\(_3\), 62.5 MHz) \(\delta\) 140.1, 135.4, 131.2, 118.2, 114.5, 66.5, 16.5; \(^{31}\)P NMR(CDCl\(_3\), 162 MHz) \(\delta\) 18.5; HRMS: \(m/z\) 239.1

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\text{diethyl o-tolylphosphonate}\(^6\) (3g) [CAS No. 62778-16-9] oil yield 67\% \(^1\)H NMR (250 MHz, CDCl\(_3\)/TMS): \(\delta\) (ppm) =1.19 (t, \(J = 6.75\) Hz, 6H), 2.45 (s), 3.96-4.02 (m, 4H), 7.11-7.31 (m, 2H), 7.77-7.85 (m, 2H); \(^{13}\)C NMR (CDCl\(_3\), 62.5 MHz) \(\delta\) 141.7, 133.9, 132.4, 131.2, 131.0, 125.4, 61.9, 19.7, 16.2; \(^{31}\)P NMR(CDCl\(_3\), 162 MHz) \(\delta\) 18.0; HRMS: \(m/z\) 228.1

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\text{diethyl naphthalen-1-ylphosphonate}\(^1,\(^2,\(^6\) (3h) [CAS No. 25944-75-6] oil yield 99\% \(^1\)H NMR (250 MHz, CDCl\(_3\)/TMS): \(\delta\) (ppm) =1.13(t, \(J = 6.8\) Hz, 6H), 3.78-3.88 (m, 4H), 7.11-7.31 (m, 2H), 7.02-8.23 (m, 9H); \(^{13}\)C NMR (CDCl\(_3\), 62.5 MHz) \(\delta\) 133.7,131.4, 127.3, 126.3, 59.1, 16.7; \(^{31}\)P NMR(CDCl\(_3\), 162 MHz) \(\delta\) 19.1; HRMS: \(m/z\) 264.1

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\text{diethyl [1,1'-biphenyl]-4-ylphosphonate}\(^2,\(^6\) (3i) oil yield 99\% \(^1\)H NMR (250 MHz, CDCl\(_3\)/TMS): \(\delta\) (ppm) =1.30-1.36 (t, \(J = 7.1\) Hz, 6H), 4.08-4.17 (m, 4H), 7.42-7.91 (m, 9H); \(^{13}\)C NMR (CDCl\(_3\), 62.5 MHz) \(\delta\) 145.1, 141.1, 132.3, 128.8, 127.2, 118.2, 111.8 , 59.1, 16.2; \(^{31}\)P NMR(CDCl\(_3\), 162 MHz) \(\delta\) 17.8; HRMS: \(m/z\) 290.1

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\text{diethyl (4-bromophenyl)phosphonate (3j) [CAS No. 20677-12-7] oil yield 99\% \(^1\)H NMR (250 MHz, CDCl\(_3\)/TMS): \(\delta\) (ppm) =1.19-1.22 (t, \(J = 0.06\) Hz, 6H), 3.97-4.02 (m, 4H), 7.49-7.59 (m, 4H); \(^{13}\)C NMR (CDCl\(_3\), 62.5 MHz) \(\delta\) 137.0, 133.1, 128.8, 126.0, 58.9, 16.8; \(^{31}\)P NMR(CDCl\(_3\), 162 MHz) \(\delta\) 18.2 HRMS: \(m/z\) 292.1

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**diethyl (4-chlorophenyl)phosphonate**\(^1\)(3k) [CAS No. 39225-17-7] oil yield 99% \(^1\)H NMR (250 MHz, CDCl\(_3\)/TMS): δ (ppm) =1.22(t, 6H), 3.95-4.04 (m, 4H), 7.33-7.38 (m, 2H), 7.61-7.69 (m, 2H); \(^{13}\)C NMR (CDCl\(_3\), 62.5 MHz) δ 138.5, 134.5, 129.2, 123.3, 58.0, 16.8; \(^{31}\)P NMR(CDCl\(_3\), 162 MHz) δ 18.1; HRMS: m/z 248.0

**diethyl (2-methyl-4-nitrophenyl)phosphonate** (3l) oil yield 85% \(^1\)H NMR (250 MHz, CDCl\(_3\)/TMS): δ (ppm) =1.17-1.20 (t, J= 7.0, 6H), 2.45(s, 3H), 3.96-4.02 (m, 4H), 7.29-7.32 (m, 1H); 7.77-7.88 (m, 2H); \(^{13}\)C NMR (CDCl\(_3\), 62.5 MHz) δ 153.4, 147.8, 135.6, 132.4, 126.6, 120.6, 61.0, 21.5, 16.9; \(^{31}\)P NMR(CDCl\(_3\), 162 MHz) δ 17.9; HRMS: m/z 273.1

**diethyl (4-hydroxyphenyl)phosphonate**\(^1\) (3m) [CAS No. 28255-39-2] oil yield 90%; \(^1\)H NMR (250 MHz, CDCl\(_3\)/TMS): δ (ppm) =1.26-1.27 (t, J= 7.0, 6H), 4.01-4.14(m, 4H), 6.92-7.62 (m, 4H); 9.42-9.44(1H); \(^{13}\)C NMR (CDCl\(_3\), 62.5 MHz) δ 158.9, 138.6, 128.1, 127.9, 115.5, 68.6, 16.7; \(^{31}\)P NMR(CDCl\(_3\), 162 MHz) δ 18.1; HRMS: m/z 230.1

**diethyl (4-aminophenyl)phosphonate**\(^1\) (3n) [CAS No. 42822-57-1] oil yield 90% \(^1\)H NMR (250 MHz, CDCl\(_3\)/TMS): δ (ppm) =1.19-1.24 (t, J= 6.9 6H), 3.93-4.08 (m, 4H), 6.64-6.66 (m, 2H); 7.44-7.53 (m, 4H); \(^{13}\)C NMR (CDCl\(_3\), 62.5 MHz) δ 150.5, 133.5, 121.1, 114.3, 61.7, 16.8; \(^{31}\)P NMR(CDCl\(_3\), 162 MHz) δ 18.2; HRMS: m/z 229.1

**diethyl (E,Z)-styrylphosphonate**\(^6\) (3o) oil yield 90% \(^1\)H NMR (250 MHz, CDCl\(_3\)/TMS): δ (ppm) =1.26-1.33(t, J= 8.9, 6H), 4.02-4.11 (m, 4H), 6.13-6.28 (m, 2H), 7.25-7.46 (m, 5H); \(^{13}\)C NMR (CDCl\(_3\), 62.5 MHz) δ 148.7, 132.7, 130.2, 129.0 128.5, 127.6, 126.2, 112.1, 61.8, 16.2; \(^{31}\)P NMR(CDCl\(_3\), 162 MHz) δ 17.4; HRMS: m/z 228.1
diisopropyl phenylphosphonate\textsuperscript{1,3,4} (3p) [CAS No. 7237-16-3] oil yield 90\% \textsuperscript{1}H NMR (250 MHz, CDCl\textsubscript{3}/TMS): $\delta$ (ppm) =1.17-1.34(m, 12H), 4.53-4.71 (m, 2H), 7.39-7.46 (m, 2H), 7.73-7.82 (m, 2H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 62.5 MHz) $\delta$ 133.6, 124.1, 70.2, 24.0; \textsuperscript{31}P NMR(CDCl\textsubscript{3}, 162 MHz) $\delta$ 16.0; HRMS: $m/z$ 242.1

diisopropyl (4-methoxyphenyl)phosphonate\textsuperscript{2} (3q) oil yield 90\% \textsuperscript{1}H NMR (250 MHz, CDCl\textsubscript{3}/TMS): $\delta$ (ppm) =1.09-1.26 (m, 12H), 3.72 (s, 3H), 4.50-4.58 (m, 2H), 6.81-6.86 (m, 2H) 7.59-7.68 (m, 2H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 62.5 MHz) $\delta$ 162.5, 133.6, 122.3, 113.8, 70.4, 55.1, 23.7; \textsuperscript{31}P NMR(CDCl\textsubscript{3}, 162 MHz) $\delta$ 15.9 HRMS: $m/z$ 272.1

diisopropyl (4-nitrophenyl)phosphonate\textsuperscript{3} (3r) oil yield 90\% \textsuperscript{1}H NMR (250 MHz, CDCl\textsubscript{3}/TMS): $\delta$ (ppm) =1.20-1.37(m, 12H), 4.54-4.61 (m, 2H), 7.93-8.23 (m, 4H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 62.5 MHz) $\delta$ 149.3, 139.4, 133.8, 121.2, 70.3, 25.8; \textsuperscript{31}P NMR(CDCl\textsubscript{3}, 162 MHz) $\delta$ 16.5; HRMS: $m/z$ 287.1

diisopropyl (E,Z)-styrylphosphonate\textsuperscript{4} (3s) oil yield 90\% \textsuperscript{1}H NMR (250 MHz, CDCl\textsubscript{3}/TMS): $\delta$ (ppm) =1.22-1.30(m, 12H), 4.60-4.68 (m, 2H), 6.11-6.25 (m, 1H), 7.21-7.44(m, 6H), 7.50(s, 1H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 62.5 MHz) $\delta$ 148.0, 134.7, 130.0, 128.7, 127.6, 116.8, 70.6, 23.0; \textsuperscript{31}P NMR(CDCl\textsubscript{3}, 162 MHz) $\delta$ 19.5; HRMS: $m/z$ 256.1

diphenyl phenylphosphonate (3t) [CAS No. 3049-24-9] oil yield 90\% \textsuperscript{1}H NMR (250 MHz, CDCl\textsubscript{3}/TMS): $\delta$ (ppm) =6.88-6.93(m, 2H), 7.18-7.33 (m, 8H), 7.48-7.63 (m, 6H), 7.99-8.08(m, 2H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 62.5 MHz) $\delta$ 150.2, 133.6, 132.3, 129.4, 129.0, 128.7, 125.5, 119.8; \textsuperscript{31}P NMR(CDCl\textsubscript{3}, 162 MHz) $\delta$ 12.6; HRMS: $m/z$ 310.1
2.2 Synthesis of Diethyl-phenyl-posphonate in large scale:

Iodobenzene (0.1 mol, 11.1mL), PdCl$_2$ (0.05 g, 0.22 mmol), triethylphosphite (0.4 mol, 67.2 mL), $n$-Pr$_3$N (0.2 mol, 37.7 mL) and TBAB (0.1 mol, 32.23 g.), in water (150 mL) was heated at 100 °C. After completion, the reaction mixture was cooled to room temperature and extracted with ethyl acetate from the aqueous layer, and dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated in vacuum. The crude organic mixture was then purified by silica gel column chromatography using petroleum ether/ethyl acetate 4:1 to obtain the desired product. (Yield 78%)
2.3 Copies of 1H, 13C, and 13P NMR spectra
diethyl (2-methyl-4-nitrophenyl) phosphonate
3 References: