Suzuki Coupling Catalyzed by Ligand-Free Palladium(II) Species at Room Temperature and by Exposure to Air

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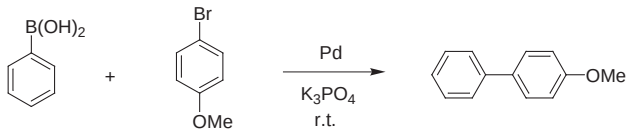
Abstract: Ligand-free palladium acetate and palladium chloride have been evaluated as catalysts in the Suzuki cross-coupling of aryl boronic acid with aryl and vinyl bromide in ethanol at room temperature and with exposure to air. The substrates with a wide variety of functional groups, including base-sensitive ones are tolerated.

Key words: Suzuki coupling, palladium, catalysis

The palladium-catalyzed cross coupling of aryl halides with organoboron reagents has become one of the most useful methods for the formation of C–C bonds, especially in the construction of materials with conjugated units.[1] The original and general procedure involve the use of palladium–phosphine complexes as catalysts and performing the reactions at high temperature and in oxygen-free system to avoid the side reaction.[2] In recent years, the development of efficient catalysts for Suzuki coupling of sterically demanding substrates has received much attention. However, much attention has not been paid to find a process to conduct this reaction under mild conditions, in particular, to run the reaction in air in the presence of readily available and comparably cheaper palladium species. Wallow and Novak have shown that phosphine ligand limits the catalytic efficiency of palladium.[2] 'Ligandless' palladium species give fast coupling reactions,[3] and the phosphine-related side reactions can be suppressed.[4] Badone et al. and Bussolari et al. have independently reported that $Pd(OAc)_2$ in combination with Bu_4NBr can catalyze Suzuki coupling[5] in water to provide the products in good yields. Bletter et al. have found that microwaves are beneficial to the $Pd(OAc)_2$-catalyzed Suzuki couping.[6] Dupont and coworkers have observed that $PdCl_2(SEt_2)_2$ and $Pd(OAc)_2$ can catalyze the coupling in DMF even at room temperature, but the reaction is much slower than that is performed at high temperature.[7] Our interest is to develop a much milder condition for Suzuki coupling using readily available palladium compounds as catalysts. In this paper we wish to report our preliminary results that $Pd(OAc)_2$ and $PdCl_2$ catalyze Suzuki coupling at room temperature and by *exposure to air*.

For initial studies we examined the coupling of 4-bromoanisole (**2a**) with phenyl boronic acid (**1a**) in the presence of 2% palladium acetate using K_3PO_4 as base at room temperature to find the optimal conditions. The results are recorded in Table 1, which show that the solvents used have dramatic effects on the reaction rate. In nonpolar or polar aprotic solvents such as toluene, THF, and acetone, the reaction provides an incomplete conversion of lower than 20%. The polar aprotic solvent DME leads to a higher conversion of 49% (entry 2). A considerable improvement of the conversion is obtained when the reaction is carried out in protic solvents, for example, in H_2O or ethanol (entries 4, 6, and 7). Ethanol represents the optimal reaction media for this system (entries 6 and 7). The addition of a catalytic amount of phase-transfer catalyst (PTC) is beneficial to the reaction (entries 8 and 9). However, stoichiometric amount of PTC is required when the similar conversion was carried out in water.[5b] Interestingly, $PdCl_2$ can also serve as an efficient catalyst for this reaction with 84% conversion rate.

Table 1 Effects of Solvent on Cross-Coupling of **1a** and **2a** Catalyzed by Ligandless Palladium[a]



1a **2a** **3a**

Entry	Pd Catalyst	Solvent	Additive	Time (h)	Conv. (%)[b]
1	$Pd(OAc)_2$	THF	none	2	10
2	$Pd(OAc)_2$	DME	none	2	49
3	$Pd(OAc)_2$	acetone	none	2	2
4	$Pd(OAc)_2$	H_2O	none	2	54
5	$Pd(OAc)_2$	toluene	none	2	18
6	$Pd(OAc)_2$	EtOH	none	2	74
7	$PdCl_2$	EtOH	none	2	76
8	$Pd(OAc)_2$	EtOH	Bu_4NBr (5 mol%)	2	82
9	$PdCl_2$	EtOH	Bu_4NBr (5 mol%)	2	84

[a] All couplings were carried out at r.t. in the presence of 1.2 equiv of $PhB(OH)_2$, 2% equiv of Pd, and 2 equiv of K_3PO_4.
[b] The percentage of conversion was detected by GC.

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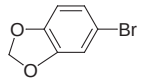
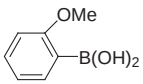
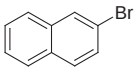
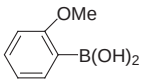
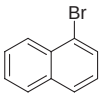
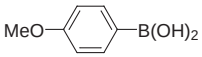
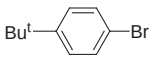
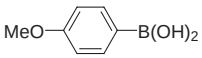
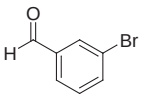
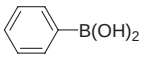
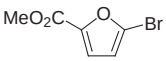
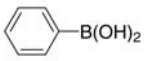
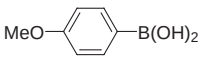
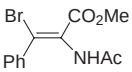
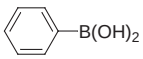
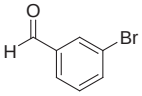
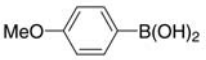
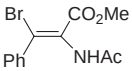
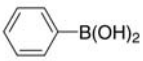
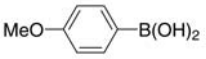
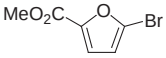
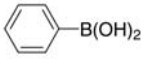
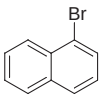
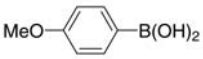
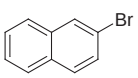
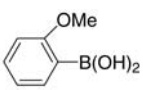
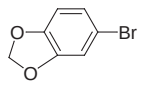
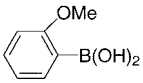
To evaluate the scope and limitation of this procedure, the reactions of a wide variety of aryl bromides with aryl boronic acids are examined in the presence of catalytic amounts of palladium acetate and palladium chloride under optimal conditions (Table 2). In most cases, the reactions work well to provide the corresponding products in acceptable and high yields. This process generally offers lower yield starting from aryl bromides containing electron-donating groups, for example the coupling of **2b** with **1b** always gives much lower yield than the reaction of **2c**

Table 2 Ligandless Palladium-Catalyzed Suzuki Cross-Coupling of Aryl Bromides and Arylboronic Acids[a]

Entry	ArX		Boronic Acid		Pd Catalyst	Time (h)	Yield (%)[b]
1		**2b**		**1b**	$PdCl_2$	12	50
2		**2c**		**1b**	$PdCl_2$	12	94
3		**2d**		**1e**	$PdCl_2$	12	71
4		**2e**		**1e**	$PdCl_2$	6	81
5[c]		**2f**		**1a**	$PdCl_2$	2	91
6[c]		**2g**		**1a**	$PdCl_2$	0.5	99
7		**2h**		**1e**	$PdCl_2$	5	26
8[c]		**2i**		**1a**	$PdCl_2$	12	41
9		**2f**		**1e**	$Pd(OAc)_2$	2	98
10[c]		**2i**		**1a**	$Pd(OAc)_2$	8	78
11		**2h**		**1e**	$Pd(OAc)_2$	3	92
12[c]		**2g**		**1a**	$Pd(OAc)_2$	1	96
13		**2d**		**1e**	$Pd(OAc)_2$	10	67
14		**2c**		**1b**	$Pd(OAc)_2$	3	98
15		**2b**		**1b**	$Pd(OAc)_2$	10	67

[a] All couplings were carried out at r.t. in the presence of 1.2 equiv of $PhB(OH)_2$, 2% equiv of Pd, and 2 equiv of K_3PO_4.
[b] Isolated yield.
[c] 2 Equiv of K_2CO_3 as base was used.

with **1b**, catalyzed by both $PdCl_2$ (entries 1 and 2) and $Pd(OAc)_2$ (entries 14 and 15). Although $PdCl_2$ shows similar catalytic activity as $Pd(OAc)_2$, $PdCl_2$ is much more readily available and easier to handle. In the presence of $Pd(OAc)_2$, the dehydroamino ester **2i** reacts with **1a** to smoothly furnish methyl 2-acetylamino-3,3′-diphenylacrylate in 78% yield (entry 10). Thus, this method provides an easy way to prepare the tetrasubstituted dehydroamino esters.

In summary, we have found that ligand-free palladium acetate and palladium chloride can catalyze Suzuki cross coupling of aryl boronic acid with aryl and vinyl bromide in ethanol *at room temperature and with exposure to air*. The substrates with a wide variety of functional groups, including base-sensitive ones are tolerated.

All reagents and solvents were purchased from Across and used directly. ^{1}H NMR spectra were recorded on a Bruker AMX-300 instrument.

Suzuki Cross-Coupling; General Procedure

A round bottom flask was charged with a solution of $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), the appropriate boronic acid (0.6 mmol), the appropriate aryl bromide (0.5 mmol), $K_3PO_4{\cdot}3H_2O$ (266 mg, 1.0 mmol), Bu_4NBr (8.3 mg, 0.025 mmol) in EtOH (2 mL). The reaction mixture was stirred at r.t. until the aryl bromide was completely consumed (monitored by TLC). Then the mixture was diluted with EtOAc (5 mL). The organic layer was washed with aq 1 M NaOH (5 mL), and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried ($MgSO_4$). After removal of the solvent, the residue was purified by column chromatography on silica gel to give the corresponding pure products.

5-(2-Methoxyphenyl)-1,3-benzodioxole (Table 2, entries 1, 15)

Colorless oil.

IR (KBr): 3066, 3002, 2935, 2834, 2778, 1600, 1505, 1460, 1426, 1338, 1245, 1181, 1103, 1038, 936, 867, 813, 753, 634, 549 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.84 (s, 3 H), 6.00(s, 2 H) 6.87–7.32 (m, 7 H).

MS (EI): *m*/*z* = 229 (100), 183 (40), 155 (20).

Anal. Calcd for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.94; H, 5.34.

2-(2- Methoxyphenyl)naphthalene (Table 2, entries 2, 14)

Mp 43–44 °C (Lit.[8a] mp 43–44.5 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.86 (s, 3 H), 7.01–7.99 (m, 11 H).

1-(4-Methoxyphenyl)naphthalene (Table 2, entries 3, 13)

Mp 117–119 °C (Lit.[8b] mp 116–116.5 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.92 (s, 3 H), 7.04–7.94 (m, 11 H).

4′-(*tert*-Butyl)[1,1′-biphenyl]-4-yl Methyl Ether (Table 2, entry 4)

Mp 143–144 °C.

IR (KBr): 2957, 1601, 1498, 1461, 1392, 1288, 1249, 1210, 1184, 1037, 822, 527 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37 (s, 9 H), 3.85 (s, 3 H), 6.9–7.5 (m, 8 H).

MS (EI): *m*/*z* = 240 (49), 225 (100), 197 (10), 99 (10), 41 (12).

Anal. Calcd for $C_{17}H_{20}O$: C, 84.96; H, 8.39. Found: C, 84.96; H, 8.25.

4′-Methoxy[1,1′-biphenyl]-3-carbaldehyde (Table 2, entry 9)

Mp 60–61 °C.

IR (KBr): 2935, 2838, 1689, 1605, 1515, 1476, 1442, 1391, 1290, 1248, 1184, 1161, 1028, 899, 836, 794, 688, 653, 574 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–8.03 (m, 9 H), 10.00 (s, 1 H).

MS (EI): *m*/*z* = 212 (100), 197 (21), 169 (34), 139 (26), 115 (25), 40 (25), 29 (34).

Anal. Calcd for $C_{14}H_{12}O_2$: C, 79.22; H, 5.70. Found: C, 78.92; H, 5.50.

Methyl 5-Phenylfuran-2-carboxylate (Table 2, entries 6, 12)

Yellow oil.[8c]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.92 (s, 3 H), 6.74 (d, 1 H, *J* = 3.6 Hz), 7.25 (d, 1 H, *J* = 3.6 Hz), 7.41–7.81 (m, 5 H).

2-(4-Methoxyphenyl)thiophene (Table 2, entries 7, 11)

Mp 110–112 °C (Lit.[8d] mp 107–109 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.85 (s, 3 H), 6.91 (d, 2 H, *J* = 8.9 Hz), 7.05–7.24 (m, 3 H), 7.54 (d, 2 H, *J* = 8.9 Hz).

Methyl 2-Acetylamino-3,3′-diphenylacrylate (Table 2, entries 8, 10)

Mp 195–197 °C.

IR (KBr): 3244, 3021, 2945, 1724, 1656, 1608, 1573, 1522, 1487, 1439, 1370, 1336, 1293, 1261, 1205, 1150, 1021, 775, 746, 702, 602, 523 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.03 (s, 3 H), 3.55 (s, 3 H), 7.1–7.4 (m, 10 H).

MS (EI): *m*/*z* = 295 (20), 267 (38), 254 (11), 253 (65), 194 (25), 193 (100), 188 (22), 165 (63), 43 (96).

Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.27; H,5.69; N, 4.94.

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