Ligand-free Suzuki–Miyaura reaction catalysed by Pd/C at room temperature

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Ligand-free Suzuki–Miyaura coupling reaction has been developed which utilises a commercially available 10% Pd/C (2.6 mol% Pd) in 2-propanol-H_2O (1/1) and Na_3PO_4 at room temperature. The reaction is mild and generates excellent yields of the coupled products (90–100%). The catalyst is heterogeneous and ligand-free, and the product isolation is simple.

Keywords: Suzuki–Miyaura reaction, Pd/C, ligand-free, cross-coupling

The palladium-catalysed Suzuki–Miyaura coupling reaction, involving the cross-coupling of aryl halides with arylboronic acids, is one of the most powerful and convenient synthetic methods for the preparation of biaryl compounds.[1] The reaction has been applied to many areas,[2] including natural product synthesis.[3] The reaction is normally promoted by a palladium catalyst, a ligand that binds to the palladium center to stabilise the catalyst during the reaction process, and a base that captures the boronic acid moiety. Triarylphosphine/Pd complexes are commonly used as catalysts for the reaction. In order to develop active and efficient catalysts, advances have been made by modifying traditional ligands. Recently electron-rich, bulky phosphines[4] and phosphine oxides[5] have been reported to be effective ligands. Moreover, a number of important developments with phosphine-free ligands, such as C-based heterocyclic carbenes,[6] C,N-based 2-aryl-2-oxazolines,[7] aryloximes,[8] arylimines,[9] and N,N-based diazabutadienes[10] have been reported. These non-phosphine ligands have overcome problems of catalyst sensitivity to air and environmental concerns. However, most of these new ligands are not commercially available and some are difficult to synthesise and of those which are commercially available, many are very expensive. The reaction usually proceeds in the presence of a homogeneous palladium catalyst which makes recycling the metal tedious if not impossible and might result in a high palladium contamination of the product. A method to overcome these difficulties would be the use of a heterogeneous palladium catalyst such as a solid-supported metal. The most readily available form of supported catalyst is palladium on carbon which is widely used in heterogeneous hydrogenation processes. This paper reports results that commercially available 10% Pd/C which can be recycled, catalyse Suzuki–Miyaura coupling reaction without a ligand at room temperature.

Initial studies were concerned with the coupling of 4-bromoanisole (**1a**) and phenyl boronic acid (**2a**) in the presence of 10%Pd/C using Na_3PO_4 as base at room temperature to find the optimal conditions. The results are recorded in Table 1. These show that the solvents used have dramatic effects on the yield of coupled product. In aprotic solvent such as acetonitrile, the reaction provided a very low yield of the coupled product (entry 8). A considerable improvement of the yield was obtained when the reaction was carried out in protic solvents. Compared with alcohols, mixtures with water gave higher yields of the coupled products (entry 3 *vs* entry 2, entry 5 *vs* entry 4, and entry 7 *vs* entry 6). 2-Propanol/water (1/1) was the optimal reaction solvent for this system (entry 7). The yield of the coupled product was 97% even using 2.6mol % Pd for 8 hours.

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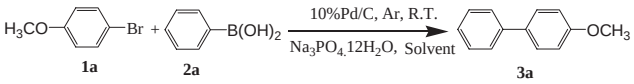
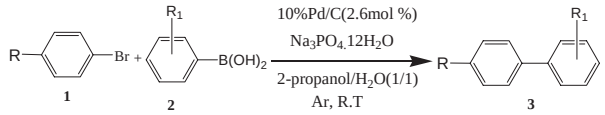
Table 1 Effects of solvent on the Suzuki-Miyaura cross-coupling of **1a** and **2a** catalysed by 10%Pd/C at room temperature[a]



Entry	Solvent	Yield/%[b]
1	Water	20
2	Methanol	47
3	Methanol/water (1/1)	91
4	Ethanol	58
5	Ethanol/water (1/1)	94
6	2-Propanol	44
7	2-Propanol/water (1/1)	98 (97[c])
8	Acetonitrile	3

[a]All couplings were carried out in the presence of 0.5mmol *p*-bromoanisole, 1.1 equiv of phenylboronic acid, 2.5 equiv of $Na_3PO_4.12H_2O$, 3.5% equiv of Pd , 2ml solvent under argon at room temperature for 24 hours. [b] Isolated yield. [c] 2.6% equiv of Pd for 8 hours.

Table 2 10%Pd/C catalysed Suzuki-Miyaura cross-coupling of aryl bromides and arylboronic acids[a]



Entry	R	R_1	Product No.	Reaction time/h	Yield/%[b]
1	OCH_3	H	**3a**	8	97
2	$COCH_3$	H	**3b**	6	96
3	NO_2	H	**3c**	2	97
4	CHO	H	**3d**	6	100
5	$COCH_3$	4-OCH_3	**3e**	2	100
6	CHO	4-OCH_3	**3f**	2	99
7	NO_2	4-OCH_3	**3g**	1	97
8	OCH_3	4-OCH_3	**3h**	3	91
9	OCH_3	2-OCH_3	**3i**	5	100
10	CHO	2-OCH_3	**3j**	5	100
11	$COCH_3$	2-OCH_3	**3k**	3	96
12	NO_2	2-OCH_3	**3l**	4	90
13	NO_2	4-$COCH_3$	**3m**	20	97
14	$COCH_3$	4-$COCH_3$	**3n**	21	96
15	$COOC_2H_5$	H	**3o**	3	98

[a]All couplings were carried out in the presence of 0.5 mmol aryl bromides, 1.1 equiv of arylboronic acids, 2.5 equiv of $Na_3PO_4.12H_2O$, 2.6% equiv of Pd , 1 ml water and 1 ml 2-propanol with Ar at room temperature for given times. [b]Isolated yield.

To evaluate the scope and limitation of this procedure, the reactions of a wide variety of aryl bromides with aryl boronic acids were examined in the presence of 10%Pd/C under optimal conditions (Table 2). Aryl bromides with either electron-withdrawing or electron-donating substituents coupled readily

with aryl boronic acids in excellent yields (90–100%). A substrate with a base-sensitive group was also tolerated (entry 15).

A striking advantage of heterogeneous Pd/C catalysts is that they are easily separated from the reaction products by simple filtration. The Suzuki–Miyaura reaction is usually used in the last steps of a convergent synthesis of bioactive compounds. That it is difficult to remove both the residual metal and ligands of homogeneous catalysts usually presents a significant practical problem. Extra chromatographic, precipitation, or extraction steps are often required.[11] However, it was reported[12] that there is less than 1.0 ppm Pd in the reaction mixture after filtration Pd/C through 0.45 mm filter. Because the catalyst is heterogeneous and ligand-free, the product isolation is simplified and potential side reactions between aryl groups of the phosphines and boronic acid are eliminated.[13]

In summary, a ligand-free Suzuki-Miyaura coupling reaction has been developed which utilises a commercially available Pd/C in 2-propanol-H_2O (1/1) and Na_3PO_4 at room temperature. The reaction is mild and generates excellent yields of the coupled products. A substrate with a base-sensitive group was tolerated. The catalyst is heterogeneous, ligand-free and can be recycled using a simple filtration. The product isolation is simple.

Experimental

All reagents and solvents were obtained from commercial suppliers and used without further purification. Thin-layer chromatography (TLC) performed on glass-backed silica gel 60 F_{254}, 0.2 mm plates (Merck), and compounds were visualised under UV light (254nm). Melting points were determined on a Yanagimoto melting point apparatus and were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL EX-400 (400 MHz). Low- and high-resolution mass spectra were taken on a JEOL JMS-SX 102A machine.

Suzuki-Miyaura cross-coupling; general procedure

A glass tube was charged with the appropriate aryl bromide (0.5 mmol), the appropriate aryl boronic acid (0.55 mmol), $Na_3PO_4.12H_2O$ (476 mg, 1.25 mmol), 10%Pd/C (14 mg, 0.0132 mmol), water (1 ml) and 2-propanol (1 ml). After three vacuum/argon cycles to remove air from the reaction tube, the reaction mixture was stirred at room temperature under argon for the given reaction time. Then the mixture was diluted with 10ml H_2O and 10 ml ether or CH_2Cl_2, and filtered using a membrane filter (Advantec Dismic-13HP, 0.45 μm). The organic phase was separated, and the aqueous layer was extracted with ether or CH_2Cl_2 (2 × 10 ml). The combined organic layers were washed with water (10 ml) and dried over $MgSO_4$. The solvent was removed by evaporation *in vacuo*. The residue was purified by flash silica gel column chromatography, if necessary.

4-Methoxybiphenyl **(3a)**: Colourless solid. m.p. 87–88°C (lit.[14a] m.p. 86–87°C). ^{1}H NMR ($CDCl_3$): δ=3.85(s, 3H), 6.98(d, *J*=8.8Hz, 2H), 7.30 (t, *J*=7.3Hz, 1H), 7.41 (t, *J*=7.3Hz, *J*=7.8Hz, 2H), 7.54 (t, *J*=8.8Hz, *J*=7.8Hz, 4H). MS (EI): *m/z*=184 (base peak), 169, 141, 115, 84, 66.

4-Acetylbiphenyl **(3b)**: White solid. m.p. 118–120°C (lit.[14b] m.p. 119–120°C). ^{1}H NMR ($CDCl_3$): δ=2.64(s, 3H), 7.41(d, *J*=7.3Hz, 1H), 7.47(t, *J*=7.3Hz, *J*=7.8Hz, 2H), 7.62(d, *J*=7.8Hz, 2H), 7.68 (d, *J*=8.3Hz, 2H), 8.03(d, *J*=8.3Hz, 2H). MS (EI): *m/z*=196, 181 (base peak), 152, 151.

4-Nitrobiphenyl **(3c)**: Pale yellow solid. m.p. 113–114°C (lit.[14a] m.p. 112–113°C). ^{1}H NMR ($CDCl_3$): δ=7.43-7.52(m, 3H), 7.64(dd, *J*=8.3Hz, *J*=1.5Hz, 2H), 7.74(dd, *J*=6.8Hz, *J*=2.0Hz, 2H), 8.30(dd, *J*=6.8Hz, *J*=2.0Hz, 2H). MS (EI): *m/z*=199 (base peak), 169, 153, 152, 141.

Biphenyl-4-carbaldehyde **(3d)**: Colourless solid. m.p. 60–61°C (lit.[14a] m.p. 58–59°C). ^{1}H NMR ($CDCl_3$): δ=7.41(t, *J*=7.3Hz, 1H), 7.48(t, *J*=7.8Hz, *J*=6.8Hz, 2H), 7.64(dd, *J*=6.8Hz, *J*=1.5Hz, 2H), 7.74(d, *J*=8.3Hz, 2H), 7.94(d, *J*=8.8Hz, 2H), 10.05(s, 1H). MS (EI): *m/z*=182(base peak), 181(base peak), 153, 152.

4-Acetyl-4'-methoxybiphenyl **(3e)**: Colourless solid. m.p. 155–156°C (lit.[14c] m.p. 152–153°C). ^{1}H NMR ($CDCl_3$): δ=2.63 (s, 3H), 3.87(s, 3H), 7.00 (d, *J*=6.8Hz, *J*=2.0Hz, 2H), 7.58 (dd, *J*=6.8Hz, *J*=2.0Hz, 2H), 7.65 (dd, *J*=6.8Hz, *J*=2.0Hz, 2H), 8.01 (dd, *J*=6.8Hz, *J*=2.0Hz, 2H). MS (EI): *m/z*=226, 211(base peak), 183, 168, 152, 139.

4'-Methoxybiphenyl-4-carbaldehyde **(3f)**: White solid. m.p. 104–105°C. ^{1}H NMR($CDCl_3$): δ=3.86(s, 3H), 7.00(dd, *J*=7.8Hz, *J*=2.0Hz, 2H), 7.59(dd, *J*=7.8Hz, *J*=2.0Hz, 2H), 7.71(d, *J*=8.3Hz, 2H), 7.92 (dd, *J*=8.3Hz, *J*=2.0Hz, 2H), 10.03(s, 1H). ^{13}C NMR($CDCl_3$): δ=55.4, 114.5, 127.1, 128.5, 130.3, 132.1, 134.7, 146.8, 160.1, 191.9. HRMS (FAB) calcd for $C_{14}H_{13}O_2$ [M^++1] 213.0916, found 213.0908. MS (EI): *m/z*=212 (base peak), 211, 197, 169, 141, 139, 115.

4-Methoxy-4'-nitrobiphenyl **(3g):** Yellow solid. m.p. 107–108°C (lit.[14a] m.p. 107–109°C). ^{1}H NMR($CDCl_3$): δ=3.87(s, 3H), 7.02 (d, *J*=8.8Hz, 2H), 7.58(dd, *J*=6.8Hz, *J*=2.0Hz, 2H), 7.68(dd, *J*=6.8Hz, *J*=2.0Hz, 2H), 8.25(dd, *J*=6.8Hz, *J*=2.0Hz, 2H). MS (EI): *m/z*=229 (base peak), 214, 199, 183, 168, 139.

4,4'-Dimethoxybiphenyl **(3h)**: Colourless solid. m.p. 174–175°C (lit.[14d] m.p. 174–176°C). ^{1}H NMR ($CDCl_3$): δ=3.84(s, 6H), 6.95 (d, *J*=8.8Hz, 4H), 7.47(d, *J*=8.8Hz, 4H). MS (EI): *m/z*=214 (base peak), 199, 171, 156, 139, 128.

2,4'-Dimethoxybiphenyl **(3i)**: White solid. m.p. 72–74°C (lit.[14c] m.p. 69–70°C). ^{1}H NMR ($CDCl_3$): δ=3.80(s, 3H), 3.84(s, 3H), 6.94–7.03(m, 4H), 7.29(t, *J*=7.3Hz, *J*=7.8Hz, 2H), 7.47(d, *J*=8.8Hz, 2H). ^{13}C NMR($CDCl_3$): δ=55.3, 55.5, 111.2, 113.5, 120.8, 128.2, 130.4, 130.6, 130.7, 130.9, 156.5, 158.7. HRMS (FAB) calcd for $C_{14}H_{15}O_2$ [M^++1] 215.1072, found 215.1055. MS (EI): *m/z*=214(base peak), 199, 184, 171, 168, 156, 139, 128.

2'-Methoxybiphenyl-4-carbaldehyde **(3j)**: Pale yellow solid. m.p. 54–55°C. ^{1}H NMR($CDCl_3$): δ=3.83(s, 3H), 7.01(d, *J*=7.8Hz, 1H), 7.05 (t, *J*=7.8Hz, *J*=7.3Hz, 1H), 7.33–7.39(m, 2H), 7.70(d, *J*=8.3Hz, 2H), 7.91(d, *J*=8.3, 2H), 10.04(s, 1H). ^{13}C NMR($CDCl_3$): δ=55.5, 111.4, 121.0, 129.3, 129.4, 129.7, 130.2, 130.7, 134.8, 145.0, 156.4, 192.1. HRMS (FAB) calcd for $C_{14}H_{13}O_2$ [M^++1] 213.0915, found 213.0903. MS (EI): *m/z*=212(base peak), 211, 183, 168, 152, 139, 115.

4-Acetyl-2'-methoxybiphenyl **(3k)**: White solid. m.p. 108–109°C. ^{1}H NMR($CDCl_3$): δ=2.63(s, 3H), 3.82(s, 3H), 7.00(d, *J*=8.8Hz, 1H), 7.04(t, *J*=7.8, *J*=7.3Hz, 1H), 7.32–7.38(m, 2H), 7.63(d, *J*=8.8Hz, 2H), 8.00(d, *J*=8.8Hz, 2H). ^{13}C NMR($CDCl_3$): δ=26.6, 55.5, 111.3, 120.9, 128.0, 129.4, 129.4, 129.7, 130.7, 135.5, 143.5, 156.4, 197.8. HRMS (EI) calcd for $C_{15}H_{14}O_2$ [M^+] 226.0994, found 226.0988. MS (EI): *m/z* =226, 211(base peak), 168, 152, 139, 106.

2-Methoxy-4'-nitrobiphenyl **(3l)**: Pale yellow solid. m.p. 61–63°C (lit.[14e] m.p. 62–64°C). ^{1}H NMR($CDCl_3$): δ=3.84(s, 3H), 7.02 (d, *J*=8.3Hz, 1H), 7.07(t, *J*=7.3Hz, 1H), 7.32(dd, *J*=1.5Hz, *J*=7.8Hz, 1H), 7.40(t, *J*=7.8Hz, 1H), 7.69(d, *J*=8.8Hz, 2H), 8.25(d, *J*=8.8Hz, 2H). ^{13}C NMR($CDCl_3$): δ=55.5, 111.4, 121.1, 123.2, 128.3, 130.2, 130.3, 130.6, 145.4, 146.6, 156.4. HRMS (EI) calcd for $C_{13}H_{11}NO_3$ [M^+] 229.0739, found 229.0731. MS (EI): *m/z*=229 (base peak), 168, 139.

4-Acetyl-4'-nitrobiphenyl **(3m)**: Pale yellow solid. m.p. 151–152°C. ^{1}H NMR($CDCl_3$): δ=2.67(s, 3H), 7.73(d, *J*=8.8Hz, 2H), 7.78(d, *J*=8.8Hz, 2H), 8.09(d, *J*=8.8Hz, 2H), 8.33(d, *J*=8.8Hz, 2H). ^{13}C NMR($CDCl_3$): δ=26.7, 124.2, 127.6, 128.1, 129.1, 137.1, 143.1, 146.2, 147.6, 197.4. HRMS (EI) calcd for $C_{14}H_{11}NO_3$ [M^+] 241.0739, found 241.0730. MS (EI): *m/z*=241, 226(base peak), 180, 168, 152, 126.

4,4'-Diacetylbiphenyl **(3n)**: White solid. m.p. 193–195°C. (lit.[14d] m.p. 190–193°C). ^{1}H NMR($CDCl_3$): δ=2.65(s, 6H), 7.72(d, *J*=8.8Hz, 4H), 8.06(d, *J*=8.8Hz, 4H). MS (EI): *m/z*=238, 223(base peak), 180, 165, 152.

4-(Ethoxycarbonyl) biphenyl **(3o)**: White solid. m.p. 49–50°C. (lit.[14f] m.p. 48–49°C). ^{1}H NMR($CDCl_3$): δ=1.41(t, *J*=7.2Hz, 3H), 4.40 (q, *J*=7.2Hz, 2H), 7.37–7.48(m, 3H), 7.61–7.66(m, 4H), 8.11(dd, *J*=1.6Hz, *J*=6.8Hz, 2H). MS (EI): *m/z*=226, 198, 181 (base peak), 152.

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