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Microwave accelerated Suzuki coupling of chloro-aryl phosphine-oxides: A method for introducing diversity into phosphine ligands

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Abstract

There is a demand for methodology that can rapidly produce families of catalysts for catalyst–structure–performance studies. The results reported here show microwave accelerated Suzuki coupling of a range of boronic acids with chloro-aryl phosphine-oxides can give high yields of arylated phosphine oxides. Chloro-aryl phosphine-oxide substrates have been found to be unreactive in previous studies, but in these examples, the combination of a highly active (but short lived) catalyst and instantaneous microwave heating at 140 °C allows the reactions to proceed. These cross-coupling reactions are being used as the basis for a rapid synthesis of phosphine ligands (readily available by microwave-assisted reduction of the phosphine oxides).

Keywords: Palladium; Cross-coupling; Microwave; Phosphine ligands; Diversity orientated synthesis

1. Introduction

Microwave heating has made a significant impact in medicinal chemistry laboratories, since it allows the rapid synthesis of structurally related families of compounds for drug structure-activity studies [1]. Palladium catalysed cross-coupling reactions between aryl bromides and nucleophiles using microwave heating have been heavily utilised. Reaction times are cut down from ∼1 day to 30 min or much less. Due to the subtlety and unpredictability of catalyst–structure–activity relationships in homogeneous catalysis, there is a similar demand for rapid syntheses of structurally related libraries of catalysts. There has been considerable worldwide research effort in this area [2], since rapid identification of effective catalysts is essential for their use in the pharmaceutical industry.

We were not aware of any reports in which microwave accelerated cross-coupling had been used as the key step to prepare families of phosphine ligands. We were intrigued by the very interesting reports of Xiao and co-workers who demonstrated that, under conventional heating, bromo-aryl phosphine-oxides will undergo palladium catalysed Suzuki, Heck, carbonylation and amination reactions to deliver new phosphine oxides (and subsequently phosphines) [3]. Unfortunately, we could not use the Xiao protocols directly as a general method for the rapid generation of phosphine libraries, since the use of a bromo-aryl functionality severely limits the types of phosphine structure that can be readily accessed. Suzuki coupling of chloro-aryl phosphine-oxides, on the other hand, could form the basis of a rapid method to make families of phosphines since they are stable to the manipulations needed to prepare a much larger range of mono- and di-phosphines (Grignard chemistry, Pd-catalysed P–C bond forming reactions, lithiation etc.). In this paper, we report the successful use of microwave-assisted Suzuki cross-coupling on chloro-aryl phosphine-oxides substrates, and an example demonstrating microwave-assisted P=O bond reduction to provide the corresponding phosphines.

2. Experimental

2.1. General information

All chemicals and solvents are standard laboratory grade, obtained from commercial sources and were used as received.

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Dry, degassed solvents were used for reactions unless otherwise indicated. Normal grade solvents were used for chromatography. Solvents were removed by rotary evaporation on a Heidolph labrota 4000. Flash column chromatography (eluents given in brackets) were performed using Davisil silica gel Fluorochem 60 Å, particle size 35–70 μm. All NMR spectra were recorded on Bruker Avance 300 instruments.

Microwave reactions were carried out in a Biotage® Initiator using 5 ml heavy-walled reactor vials equipped with an air tight seal. The temperature is measured by an infrared temperature probe that measures the temperature on the surface of the vial. The pressure is measured by direct reading of the deflection of the septa on the vial using a load cell behind the inner part of the cavity lid.

Infrared spectra were recorded on a PerkinElmer Paragon 1000 Spectrum GX FT-IR system. Compounds were analysed as KBr disks. Mass spectra were recorded on a Waters Micromass GCT (Time of flight) fitted with lockspray for accurate mass (ESI) or GCT (CI) instruments. Only major peaks are reported and intensities are quoted as percentages of the base peaks. The ligands/precatalysts **5**–**7** are commercially available. The ligand and precatalyst **8** were prepared using a method previously developed by us [6]. Brief details are reproduced here for convenience. *N*-Methylpiperazine (0.48 g; 4.8 mmol) and triethylamine (0.48 g; 6.6 mmol) were placed in a schlenk tube equipped with a rubber septum under a dry nitrogen atmosphere. Dry diethyl ether (20 ml) was then added. The solution was cooled down to 0 °C and dicyclohexylchlorophosphine (1 g; 4.3 mmol) was added dropwise. The solution was then stirred at room temperature overnight, after which time phosphorus NMR demonstrated a quantitative conversion to the desired ligand ($^{31}P\{^1H\}$ NMR (121.5 MHz, C_6D_6) δ 76.12). If required, the ligand can be isolated by Schenk filtration and removal of volatiles and stored for long periods of time (many months) under a nitrogen atmosphere. To prepare air stable precatalyst, 8, 10 ml of the ligand solution were transferred to a Schlenk flask containing allylpalladium chloride dimer (0.2 g; 0.0014 mmol) and the resulting solution stirred for 3 h. The yellow precipitate that formed was filtered and washed with ether. ($^{31}P\{^1H\}$ NMR (121.5 MHz; $CDCl_3$) δ 96.87).

2.2. Example procedure for Suzuki coupling reactions

The triarylphosphine oxide (**1**) (0.15 g; 0.4 mmol), together with the precatalyst (2.5 mol%), $ArB(OH)_2$ (0.38 g; 3.1 mmol) and base (10 eq.) indicated in Table 1 were dissolved in the solvent (5 ml), placed in a microwave vial, and sealed under nitrogen before heating in the microwave. The conversion values shown in Table 1 were calculated using $^{31}P\{^1H\}$ NMR peak identities confirmed by spiking experiments, and relative responses (1:1:1:1) confirmed by comparing accurately measured authentic samples of starting material and products. (121.4 MHz; C_6D_6): (**2**) δ_P 29.7; (**3**) δ_P 29.8; (**4**) δ_P 29.9; starting material (**1**) δ_P 29.2.

The reaction was also run on 250 mg of starting material (5 mg × 50 mg) and the product (**2**) was isolated by column chromatography (elution mixture: ethyl acetate/hexane, from 30/70 to 90/10); (220 mg; 0.43 mmol; 67%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.29–7.42 (m, 9H, Ar*H*), 7.53–7.56 (m, 6H, Ar*H*), 7.62–7.56 (m, 12H, Ar*H*); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 127.6 (Ar*C*), 127.7 (Ar*C*), 127.8 (Ar*C*), 128.6 (Ar*C*), 129.4 (Ar*C*), 130.9 (Ar*C*), 132.3 (Ar*C*), 133.1 (d, $^2J_{C-P}$ 10.2 Hz, Ar*C*), 140.3 (Ar*C*), 145.2 (d, $^4J_{C-P}$ 2.6 Hz, Ar*C*); $^{31}P\{^1H\}$ NMR (121.5 MHz) δ 29.7; IR (KBr) ν_{max}: 1596 (m), 1544 (w), 1480 (m), 1443 (w), 1390 (m), 1264 (w), 1183 (s), 1117 (s), 1007 (m); LRMS (ES+) *m/z* 507.2 ($(M+H)^+$, 100%); HMRS (ES+): *m/z* calcd for $C_{36}H_{28}OP$: 507.1878, found: 507.1889.

Table 1
Screening of catalysts for cross-coupling reaction shown in Scheme 1[a]

Entry	Precatalyst	**1** (%)	**2** (%)	**3** (%)	**4** (%)
1	$Pd(OAc)_2$	100	0	0	0
2	**7**	15	49	15	21
3	**6**	0	0	92	8
4	**5**	0	>95	<5	0
5	**8**	0	>95[b]	0	0

[a] Reactions were conducted in MeCN with 10 equivalents of $PhB(OH)_2$ and CsF as base; 5 mol% catalyst at 140 °C in a Biotage Discover microwave oven for 30 min. Values refer to yield determined by ^{31}P NMR spectroscopy directly from reaction mixture. The relative NMR responses (1:1:1:1), and the relative positions of the peaks were assigned by spiking experiments.
[b] Product isolated in 67% yield after column chromatography.

2.3. Example procedure for Suzuki coupling on substrates *9a* and *9b*

To a microwave vial was added **9a** (0.1 g; 0.29 mmol), $PhB(OH)_2$ (0.2 g; 1.7 mmol), CsF (0.5 g; 3.4 mmol) and catalyst (**8**) (7 mg; 0.0014 mmol). The air was displaced with nitrogen and dry MeCN added (3 ml). The reaction was heated in a microwave for 30 min at 140 °C. This was repeated in further 5 vials, in order to obtain larger samples for characterisation. The reaction mixtures were then combined, water was added and the organic layer extracted with dichloromethane (3 ml × 50 ml), dried (Na_2SO_4) and concentrated. The product (**10a**) was isolated by column chromatography (elution mixture: ethyl acetate/hexane, from 30/70 to 90/10) (454 mg; 1.05 mmol; 62%) ^1H NMR (300 MHz, $CDCl_3$) δ 7.22–7.49 (m, 16H, Ar*H*), 7.63–7.69 (m, 4H, Ar*H*), 0.79 (d, $^1J_{H-H}$ 12.1 Hz, 2H, Ar*H*), 7.87 (s, 1H, Ar*H*); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 127.7 (Ar*C*), 128.4 (Ar*C*), 129.1 (d, $^2J_{C-P}$ 12.0 Hz, Ar*C*), 129.4 (Ar*C*), 129.9 (Ar*C*), 130.0 (Ar*C*), 132.2 (Ar*C*), 132.5 (Ar*C*), 132.6 (Ar*C*), 133.6 (Ar*C*), 140.4 (Ar*C*), 142.5 (d, $^1J_{C-P}$ 12.4 Hz, Ar*C*); $^{31}P\{^1H\}$ NMR (121.5 MHz) δ 30.57; IR (KBr) ν_{max}: 1591 (w), 1572 (w), 1498 (w), 1452 (w), 1412 (m), 1438 (m), 1190 (s), 1115 (s), 1135 (s), 1023 (w); LRMS (ES+) *m/z* 453.2 ($(M+Na)^+$, 100%); HMRS (ES+): *m/z* calcd for $C_{30}H_{23}ONaP$: 453.1384, found: 453.1384.

All the other products were prepared following the procedure described above, using the quantities of CsF and $ArB(OH)_2$ indicated in Scheme 2.

(**10b**) Reaction run on 200 mg of starting material (4 × 50), (234 mg; 0.48 mmol; 83%) ^1H NMR (300 MHz, $CDCl_3$) δ 3.64 (s, 6H, 2×OCH_3), 6.84–6.94 (m, 4H), 7.16–7.28 (m, 10H, Ar*H*), 7.35–7.79 (m, 7H, Ar*H*); ^{13}C NMR

(75.5 MHz, $CDCl_3$) δ 55.5 (O*C*H_3), 111.2 (Ar*C*), 120.9 (Ar*C*), 128.4 (d, $^2J_{C-P}$ 12.0 Hz, Ar*C*), 129.1 (Ar*C*), 129.5 (Ar*C*), 130.7 (Ar*C*), 130.9 (Ar*C*), 131.7 (Ar*C*), 131.8 (Ar*C*), 132.3 (d, $^2J_{C-P}$ 9.8 Hz, Ar*C*), 133.6 (Ar*C*), 134.2 (Ar*C*), 138.4 (d, $^1J_{C-P}$ 13.1 Hz, Ar*C*), 156.4 (Ar*C*); $^{31}P\{^1H\}$ NMR (121.5 MHz) δ 30.56; IR (KBr) ν_{max}: 1598 (w), 1493 (m), 1410 (m), 1278 (w), 1247 (w), 1247 (m), 1192 (s), 1117 (s), 1022 (m); LRMS (ES+) *m/z* 513.2 ($(M+Na)^+$, 100%); HMRS (ES+): *m/z* calcd for $C_{32}H_{27}O_3NaP$: 513.1596, found: 513.1394.

(**10c**) Reaction run on 400 mg of starting material (4 × 100), (444 mg; 0.90 mmol; 79%) ^1H NMR (300 MHz, $CDCl_3$) δ 3.73 (s, 6H, 2xOC*H*$_3$), 6.87 (d, $^1J_{H-H}$ 8.6 Hz, 4H, Ar*H*), 7.36–7.48 (m, 10H, Ar*H*), 7.63–7.72 (m, 6H, Ar*H*), 7.79 (s, 1H, Ar*H*); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 55.4 (O*C*H_3), 114.4 (Ar*C*), 128.4 (Ar*C*), 128.5 (Ar*C*), 128.7 (Ar*C*), 132.1 (Ar*C*), 132.2 (Ar*C*), 132.6 (Ar*C*), 133.1 (d, $^1J_{C-P}$ 26.6 Hz, Ar*C*), 134.3 (Ar*C*), 141.6 (d, $^1J_{C-P}$ 12.6 Hz, Ar*C*), 159.6 (Ar*C*); $^{31}P\{^1H\}$ NMR (121.5 MHz) δ 30.85; IR (KBr) ν_{max}: 1608 (m), 1513 (s), 1437 (m), 1288 (w), 1254 (s), 1181 (s), 1117 (m), 1118 (m), 1029 (w); LRMS (ES+) *m/z* 513.2 ($(M+Na)^+$, 100%); HMRS (ES+): *m/z* calcd for $C_{32}H_{27}O_3NaP$: 513.1596, found: 513.1600.

(**10d**) Reaction run on 300 mg of starting material (6 × 50 mg), (400 mg; 0.65 mmol; 75%) ^1H NMR (300 MHz, $CDCl_3$) δ 6.95–7.07 (m, 10H, Ar*H*), 7.25–7.30 (m, 4H, Ar*H*), 7.38–7.51 (m, 10H, Ar*H*), 6.64–7.83 (m, 7H, Ar*H*); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 118.0 (d, $^2J_{C-P}$ 13.5 Hz, Ar*C*), 122.6 (Ar*C*), 127.5 (Ar*C*), 127.6 (Ar*C*), 127.7 (Ar*C*), 127.8 (Ar*C*), 127.9 (Ar*C*), 128.8 (Ar*C*), 130.5 (Ar*C*), 131.0 (Ar*C*), 131.1 (Ar*C*), 132.0 (d, $^2J_{C-P}$ 8.7 Hz, Ar*C*), 133.4 (Ar*C*), 133.8 (Ar*C*), 140.4 (d, $^1J_{C-P}$ 12.6 Hz, Ar*C*), 155.7 (Ar*C*), 156.5 (Ar*C*); $^{31}P\{^1H\}$ NMR (121.5 MHz) δ 30.74; IR (KBr) ν_{max} (cm^{-1}): 1588 (m), 1508 (m), 1488 (s), 1437 (w), 1238 (s), 1195 (w), 1119 (w); LRMS (ES+) *m/z* 637.3 ($(M+Na)^+$, 100%); HMRS (ES+): *m/z* calcd for $C_{42}H_{32}O_3P$: 615.2089, found: 615.2092.

(**10e**) Reaction run on 200 mg of starting material (4 × 50 mg), (179 mg; 0.51 mmol; 79%). ^1H NMR (300 MHz, $CDCl_3$) δ 6.96–7.91 (m, 19H, Ar*H*); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 127.23 (Ar*C*), 127.9 (Ar*C*), 128.6 (d, $^2J_{C-P}$ 12.1 Hz, Ar*C*), 128.8 (Ar*C*), 128.9 (Ar*C*), 130.6 (Ar*C*), 130.7 (d, $^3J_{C-P}$ 2.9 Hz, Ar*C*), 130.8 (d, $^2J_{C-P}$ 10.13 Hz, Ar*C*), 131.8 (Ar*C*), 132.1 (Ar*C*), 132.2 (Ar*C*), 133.2 (Ar*C*), 133.9 (Ar*C*), 140.0 (Ar*C*), 141.6 (d, $^1J_{C-P}$ 11.9 Hz, Ar*C*); $^{31}P\{^1H\}$ NMR (121.5 MHz) δ 30.46; IR (KBr) ν_{max}: 1471 (w), 1438 (m), 1398 (w), 1185 (s), 1120 (s); LRMS (ES+) *m/z* 377.1 ($(M+Na)^+$, 100%); HMRS (ES+): *m/z* calcd for $C_{24}H_{19}ONaP$: 377.1071, found: 377.1067.

(**10f**) Reaction run on 100 mg of starting material (2 × 50 mg), (104 mg; 0.27 mmol; 85%). ^1H NMR (300 MHz, $CDCl_3$) δ 3.63 (s, 3H, OC*H*$_3$), 6.84–6.94 (m, 2H, Ar*H*), 7.18–7.26 (m, 2H, Ar*H*), 7.34–7.48 (m, 7H, Ar*H*), 7.56–7.67 (m, 6H, Ar*H*), 7.73–7.77 (m, 1H, Ar*H*); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 55.8 (O*C*H_3), 111.6 (Ar*C*), 121.4 (Ar*C*), 128.6 (Ar*C*), 128.9 (d, $^2J_{C-P}$ 12.2 Hz, Ar*C*), 129.6 (Ar*C*), 130.9 (d, $^2J_{C-P}$ 9.6 Hz, Ar*C*), 131.2 (Ar*C*), 131.6 (d, $^2J_{C-P}$ 13.5 Hz, Ar*C*), 132.3 (d, $^3J_{C-P}$ 2.5 Hz, Ar*C*), 132.6 (d, $^2J_{C-P}$ 9.9 Hz, Ar*C*), 133.0 (Ar*C*), 133.4 (d, $^3J_{C-P}$ 2.6 Hz, Ar*C*), 133.6 (Ar*C*), 133.8 (Ar*C*), 139.0 (d, $^1J_{C-P}$ 12.7 Hz, Ar*C*), 156.7 (Ar*C*); ^{31}P NMR $\{^1H\}$(121.5 MHz) δ 30.54; IR ($CDCl_3$) ν_{max} (cm^{-1}): 1898 (w), 1820 (w), 1601 (w), 1497 (m), 1465 (m), 1437 (s), 1398 (m), 1261 (m), 1239 (m), 1182 (s), 1119 (s), 1058 (w), 1027 (m); LRMS (ES+) *m/z* 407.1 ($(M+Na)^+$, 100%); HMRS (ES+): *m/z* calcd for $C_{25}H_{21}O_2NaP$: 407.1177, found: 407.1170.

(**10g**) Reaction run on 300 mg (3 × 100 mg), (214 mg; 0.56 mmol; 58%). ^1H NMR (300 MHz, $CDCl_3$) δ 3.70 (s, 3H, OC*H*$_3$), 6.83 (d, $^1J_{H-H}$ 8.7 Hz, 2H, Ar*H*), 7.33–7.45 (m, 10H, Ar*H*), 7.58–7.64 (m, 5H, Ar*H*), 7.84 (d, $^1J_{H-H}$ 12.5 Hz, 1H, Ar*H*); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 55.7 (O*C*H_3), 114.7 (Ar*C*), 128.7 (Ar*C*), 129.0 (d, $^2J_{C-P}$ 12.1 Hz, Ar*C*), 129.3 (d, $^2J_{C-P}$ 12.8 Hz, Ar*C*), 130.5 (Ar*C*), 130.6 (Ar*C*), 130.7 (Ar*C*), 132.2 (Ar*C*), 132.4 (Ar*C*), 132.6 (Ar*C*), 132.8 (Ar*C*), 133.9 (d, $^1J_{C-P}$ 37.9 Hz, Ar*C*), 141.5 (d, $^1J_{C-P}$ 11.98 Hz, Ar*C*), 160.0 (Ar*C*); $^{31}P\{^1H\}$ NMR (121.5 MHz) δ 30.53; IR (KBr) ν_{max}: 1602 (s), 1570 (w), 1513 (w), 1412 (m), 1339 (s), 1310 (s), 1245 (s), 1171 (s), 1108 (w), 1025 (m); LRMS (ES+) *m/z* 407.1 ($(M+Na)^+$, 100%); HMRS (ES+): *m/z* calcd for $C_{25}H_{21}O_2NaP$: 407.1177, found: 407.1172.

(**10h**) Reaction run on 100 mg of starting material (2 × 50 mg), (139 mg; 0.31 mmol; 98%). ^1H NMR (300 MHz, $CDCl_3$) δ 6.95–7.07 (m, 5H, Ar*H*), 7.24–7.30 (m, 2H, Ar*H*), 7.36–7.50 (10H, Ar*H*), 7.59–7.66 (m, 5H, Ar*H*), 7.86 (d, $^1J_{H-H}$ 12.6 Hz, 1H, Ar*H*); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 117.9 (Ar*C*), 118.1 (Ar*C*), 122.5 (Ar*C*), 127.5 (d, $^3J_{C-P}$ 2.3 Hz, Ar*C*), 127.6 (Ar*C*), 127.9 (d, $^2J_{C-P}$ 12.7 Hz, Ar*C*), 128.8 (Ar*C*), 129.2 (Ar*C*), 129.3 (Ar*C*), 129.5 (Ar*C*), 129.6 (Ar*C*), 131.0 (Ar*C*), 131.1 (Ar*C*), 130.7 (Ar*C*), 131.4 (Ar*C*), 132.1 (Ar*C*), 132.8 (Ar*C*), 133.8 (Ar*C*), 139.8 (d, $^1J_{C-P}$ 11.9 Hz, Ar*C*), 155.7 (Ar*C*), 156.4 (Ar*C*); $^{31}P\{^1H\}$ NMR (121.5 MHz) δ 30.50; IR (KBr) ν_{max}: 1589 (w), 1509 (w), 1489 (m), 1436 (w), 1239 (m), 1193 (w), 1118 (m); LRMS (ES+) *m/z* 447.2 ($(M+H)^+$, 100%); HMRS (ES+): *m/z* calcd for $C_{30}H_{23}O_2NaP$: 469.1333, found: 469.1320.

2.4. Procedure of microwave-assisted reduction of (*10c*)

Phosphine oxide (**10c**) (65 mg; 0.13 mmol) was placed in a microwave vial and sealed under an inert atmosphere and dry MeCN added, followed by dry Et_3N (131.5 mg; 1.3 mmol) and $HSiCl_3$ (88 mg; 0.65 mmol). The reaction was heated in a microwave at 145 °C for 10 min. MeCN was removed under reduced pressure and the crude residue was dissolved in dry DCM and passed through a short pad of silica under nitrogen. The solvent was removed under reduced pressure and the NMR sample was prepared using dried and degassed $CDCl_3$ (51 mg; 0.11 mmol; 83%).

(**11**) ^1H NMR (300 MHz, $CDCl_3$) δ 3.75 (s, 6H, 2×OC*H*$_3$), 6.85–6.88 (m, 4H, Ar*H*), 7.25–7.41 (m, 15H, Ar*H*), 7.61 (t, 1H, Ar*H*); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 55.4 (O*C*H_3), 114.25 (Ar*C*), 125.7 (Ar*C*), 128.6 (d, $^2J_{C-P}$ 6.9 Hz, Ar*C*), 130.3 (Ar*C*), 130.5 (Ar*C*), 133.3 (Ar*C*), 133.7 (Ar*C*), 133.9 (Ar*C*), 137.0 (d, $^1J_{C-P}$ 10.1 Hz, Ar*C*), 138.2 (d, $^1J_{C-P}$ 10.7 Hz, Ar*C*), 141.3 (d, $^1J_{C-P}$ 7.6 Hz; Ar*C*), 159.3 (Ar*C*); $^{31}P\{^1H\}$ NMR (121.5 MHz) δ 3.23; LRMS (CI+) *m/z* 475.17 $(M+H)^+$; HMRS (CI+): *m/z* calcd for $C_{32}H_{28}O_2P$: 475.1815, found: 475.1827.

3. Results and discussion

It is well known that aryl chlorides are significantly more reluctant cross-coupling partners and it is only recently that a few rapid microwave-assisted aryl chloride cross-couplings have been developed [4]. Xiao has previously noted that chloro-aryl phosphine-oxides do not participate in Suzuki cross-coupling under conventional conditions [3b]. In our hands, the best result for cross-coupling of tris(4-chlorophenyl)phosphine oxide under conventional conditions made use of $[Pd(OAc)_2]$/**5** and gave only a 43% isolated yield of the mono-arylated product, **4** after 48 h in refluxing toluene. No diarylated or triarylated products were detected.

Using tris(4-chlorophenyl)phosphine oxide as a model substrate, a catalyst screen was carried out under microwave heating conditions with product conversion analysed by $^{31}P\{^1H\}$ NMR spectroscopy [5]. Precatalysts **5**–**8** were selected since they are readily available and have all shown activity in cross-coupling of deactivated aryl chlorides [4i,6,7,8].

Selected reactions are shown in Table 1 (Fig. 1). The main findings are that the use of the [Pd(dcymepip)(allyl)Cl] (**8**) and Buchwald catalyst system **5** enabled the first effective cross-coupling of chloro-aryl phosphine-oxides, producing triarylated product **2** in good yield. Both these catalysts are significantly more active than the palladacycle-based catalyst **7** or $[Pd(OAc)_2]$ alone, which was ineffective. This is a relatively rare example of a reaction that will only work if microwave heating is employed, at least using the catalysts screened to date.

Catalyst **8** was subsequently selected for further synthetic studies. After optimisation, it was pleasing to find that this protocol could be used to couple a range of boronic acids with 3-chlorophenyl(diphenyl)phosphine oxide and the potentially more challenging double coupling of 3,5-dichlorophenyl(diphenyl)phosphine oxide in high yield (Scheme 2).

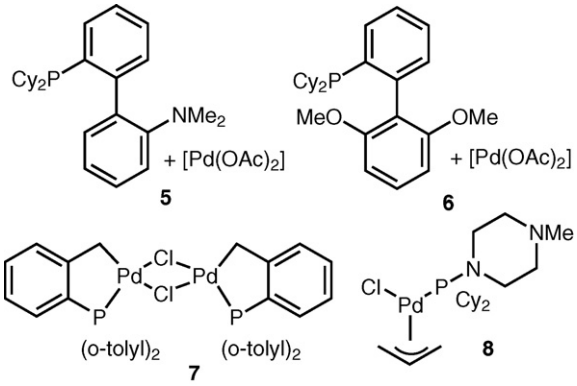
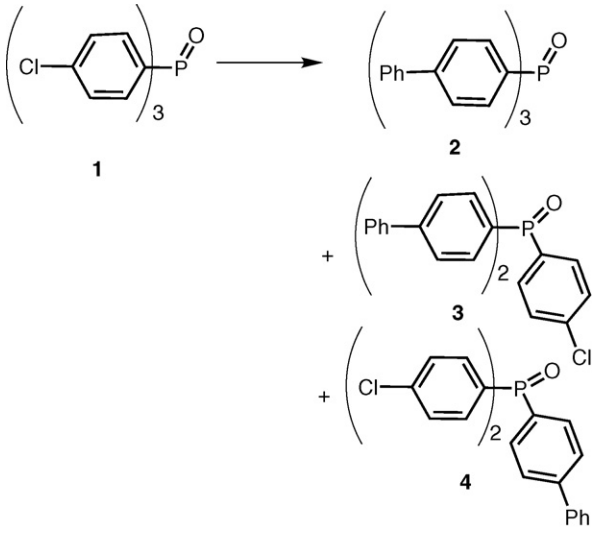


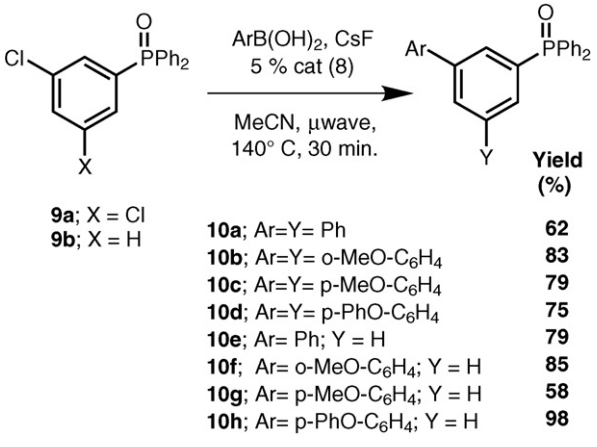
Fig. 1. Catalysts used in cross-coupling reactions.

The conditions used here are clearly a highly suitable procedure for cross-coupling some of the most sluggish aryl chloride substrates, as judged by comparing the results shown in Table 1 and Scheme 2 with the failure of Buchwald's remarkably active (and other) catalysts under conventional heating. There has been some debate as to the origin of the microwave effect on Suzuki coupling reactions. The reactions reported here do not seem possible with conventional heating. In our view, the microwave effect is connected to the reaction vessel reaching an unusually high temperature in <5 s, allowing the reaction to proceed rapidly before the relatively short lived Pd-mono-phosphine catalyst decomposes.

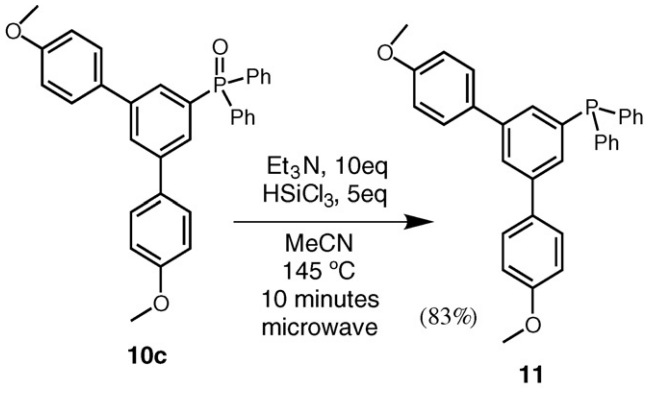
Due to the subtlety of ligand effects in asymmetric catalysis, it would be desirable to rapidly prepare chiral ligands with novel P-aryl substituents from a readily available precursor and this was the initial ambition in this project. However, the synthesis of bis(3,5-dichlorophenyl)chloro-phosphine always resulted in some difficulty to remove impurities that made conversion into the desired chiral di(3,5-dichlorophenyl) substituted phosphines problematic. However, there may be other



Scheme 1. Reaction used for optimisation of the procedure.



Scheme 2. Microwave accelerated cross-coupling of chloro-aryl phosphine-oxides: variation of aryl chloride and boronic acid. For coupling of **9a**, 6 equivalents of $Ar(B(OH)_2)$ and 12 equivalents of CsF were used. For **9b**, 3 equivalents of $ArB(OH)_2$/6 equivalents CsF were applied. Yields are for isolated pure compounds after chromatography: conversions are considerably higher, and often approach 100% (phosphine oxides do not elute well on silica).



Scheme 3. Microwave accelerated reduction of one of the phosphine oxides.

diphosphine systems that lend themselves to using this protocol.

In order to demonstrate that the procedure can produce phosphines, the reduction of one of the oxides was investigated. Using the simple mono-phosphine oxide **10c**, we investigated the reduction from the crude reaction mixture after the Suzuki coupling. However, this one-pot reaction did not proceed, presumably due to some incompatibility of the $SiCl_3H$ reducing agent with the boron waste in the Suzuki reaction. However, the reduction does take place on purified phosphine oxides, and moreover, P=O reduction at 145 °C in MeCN using microwave heating allows this reduction to take place in much shorter times than are typically employed using conventional heating [9]. Phosphine oxide **10c** was reduced to phosphine **11** in 83% yield using a microwave accelerated P=O reduction. (Scheme 3). The faster reaction time is merely due to the ability to heat MeCN beyond its boiling point.

4. Conclusions

We have shown that a series of substrates that were thought to be unreactive in Suzuki cross-coupling can indeed be coupled in high yield using microwave heating and an appropriate catalyst. In addition, we also report here an example of a microwave accelerated P=O reduction to complete the process. The overall process uses two microwave accelerated reactions that each take 30 min or less to potentially produce a range of ligands from readily available chloro-aryl phosphine oxide precursors. The methodology should be quite advantageous in the synthesis of a collection of simple 3,5-diarylphenyl substituted phosphines. More structurally complex multidentate phosphine libraries will require a convenient synthesis of the chloro-aryl precursors in order to offer significant advantages over standard methods.

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