

New alkyl derivatives phosphine sulfonate (P–O) ligands. Catalytic activity in Pd-catalysed Suzuki–Miyaura reactions in water†‡

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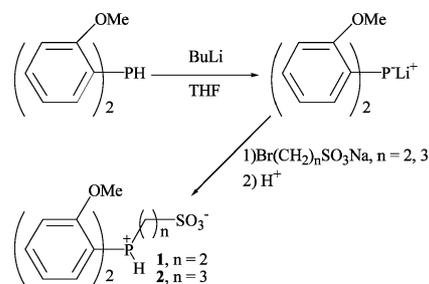
Two novel bis(*o*-methoxyphenyl) phosphinoalkylsulfonate (P–O) ligands have been prepared through a new and sustainable synthetic route; they are air stable as well as water soluble and have been applied in Pd-catalysed Suzuki–Miyaura cross-coupling reactions in neat water in conjunction with microwave heating.

Chelating anionic P–O ligands constitute a class of ligands that have been studied much less than their diphosphine counterparts. Oligomerization and polymerization reactions are efficiently catalysed by metal complexes with anionic P–O ligands.¹ The palladium catalysed copolymerisation of carbon monoxide and ethene gives perfectly alternating polyketones with diphosphine ligands while non-alternating polyketones with P–O ligands are obtained.²

We present here the synthesis of two novel diaryl alkyl phosphine sulfonate ligands through a new and clean synthetic protocol. This kind of ligand, containing an alkyl backbone, can be modified both in the length of the aliphatic chain and in the nature of the substituents on the aryl moieties. Synthetic routes for related phenyl derivatives reported in the literature involve the use of ammonia as solvent³ or sulfones as reactants.⁴ Indeed, all attempts to synthesise phosphinoalkylsulfonate ligands without either ammonia or sulfones were unsuccessful.⁵

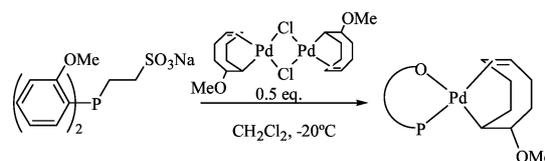
Ligands **1** and **2** were synthesised by the reaction of butyllithium with bis(*o*-methoxy)phenylphosphine in THF,⁶ followed by reaction of the lithium salt with the appropriate bromoalkylsulfonate derivative as shown in Scheme 1. The ligands were isolated as zwitterions in 54% and 43% yield, respectively. Both ligands are water soluble and air stable.

Evidence for the presence of a P–H bond in either ligand was confirmed by low temperature ³¹P NMR spectroscopy, showing the characteristic ¹J_{PH} coupling constants of 545 Hz for ligand **1** and 533 Hz for ligand **2**.



Scheme 1 Synthesis of ligands **1** and **2**.

The palladium(II) complex **1a** with ligand **1** was synthesised by adding [Pd₂(μ-Cl)₂{η⁻¹,η⁻²-C₈H₁₂OMe₂}₂]⁷ to a solution of ligand **1** as its sodium salt in CH₂Cl₂ (Scheme 2).



Scheme 2 Synthesis of Pd(II) complex **1a**.

The structure of **1a** was determined by X-ray crystallography.† An ORTEP drawing of the complex is shown in Fig. 1. The complex exhibits a distorted square-planar geometry. The phosphine sulfonate ligand coordinates to palladium in a bidentate fashion.

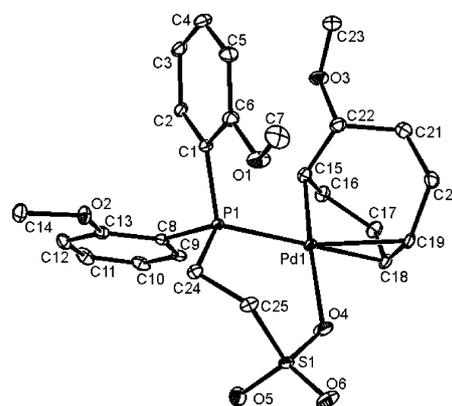


Fig. 1 ORTEP drawing of complex **1a**. Hydrogen atoms are omitted for clarity. Thermal ellipsoids are shown at the 30% probability level.

Very few examples of metal complexes containing a direct M–O–SO₂ bond are reported in the literature due to the poor ligating properties of the sulfonate group. The Pd(1)–O(4) bond length

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‡ Electronic supplementary information (ESI) available: Synthetic procedures and characterization for **1**, **2** and **1a**; X-ray data for **1a**. See DOI: 10.1039/b707590c

Table 1 Palladium catalysed S–M cross-coupling of aryl bromides R¹–Br and boronic acids R²–B(OH)₂^a

Entry	R ¹	R ²	Conversion ^b (%) [P–O] 1	Conversion ^b (%) [P–O] 2
1	4-AcC ₆ H ₄	Ph	>99	>99
2	4-AcC ₆ H ₄	1-naphthyl	>99	>99
3	4-AcC ₆ H ₄	4-FC ₆ H ₄	>99	>99
4	4-AcC ₆ H ₄	4-MeOC ₆ H ₄	>99	>99
5	C ₆ H ₅	4-FC ₆ H ₄	>99	>99
6	C ₆ H ₅	4-MeOC ₆ H ₄	>99	>99
7	4-MeOC ₆ H ₄	4-FC ₆ H ₄	60	71
8	4-MeOC ₆ H ₄	4-MeOC ₆ H ₄	90	90

^a Conditions; 0.05 mol% Pd(OAc)₂, T = 80 °C, t = 2 h, Solvent H₂O (3 ml), R¹–Br (1.5 mmol), R²–B(OH)₂ (1.72 mmol), L : Pd (1 : 1), K₂CO₃ (3 mmol).

^b Conversion determined by GC and NMR spectroscopy.

Table 2 Palladium catalysed S–M cross-coupling of aryl bromides R¹–Br and boronic acids R²–B(OH)₂ promoted by microwave heating^a

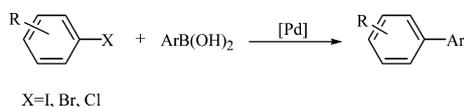
Entry	[P–O]	t/min	Pd (mol%)	R ¹	R ²	Conv. (%) ^b
1	1	5	0.05	4-AcC ₆ H ₄	1-naphthyl	87
2	1	5	0.05	4-AcC ₆ H ₄	F-C ₆ H ₄	96
3	1	10	0.05	4-MeOC ₆ H ₄	1-naphthyl	72
4	2	10	0.05	4-MeOC ₆ H ₄	1-naphthyl	86
5	2	5	0.05	4-AcC ₆ H ₄	Ph	90
6	2	5	0.025	4-AcC ₆ H ₄	Ph	90

^a Conditions: microwave heating with cooling, cat. Pd(OAc)₂/[P–O], Pd : L (1 : 1), T = 150 °C, (300 W), Solvent H₂O (3 ml), R¹–Br (1.5 mmol), R²–B(OH)₂ (1.72 mmol), K₂CO₃ (3 mmol). ^b Conversion determined by GC.

is 2.161(2) Å, which is comparable to the analogous distance in known palladium structures containing a {O₂S–O[–]} group.^{2b,8}

Due to their solubility in water and their stability to oxygen, ligands **1** and **2** can be used in aqueous catalysis.

The Suzuki–Miyaura coupling reaction (Scheme 3) is one of the most useful methods for the formation of C–C bonds.⁹ Due to the high solubility of arylboronic acids in water and the low toxicity of reagents and by-products as compared to other protocols,^{9,10} the Suzuki coupling is an ideal reaction to be performed in water. Over the last few years, several reports have appeared describing Suzuki coupling reactions catalysed by water-soluble Pd systems.^{9a,11,12}

**Scheme 3** Suzuki–Miyaura cross-coupling reaction.

We present here the application of compounds **1** and **2** as catalyst precursors for the Suzuki–Miyaura cross-coupling reaction. To the best of our knowledge, no diaryl alkyl phosphine sulfonate anionic ligand has ever been employed in such a reaction in neat water.

In Table 1 we report the results obtained for the Suzuki–Miyaura reaction between aryl bromides and aryl boronic acids in neat water and open to the air.

Excellent conversions were achieved under these conditions when either 4-bromoacetophenone or bromobenzene was used for the cross-coupling reaction (entries 1–6), using only 0.05 mol% of palladium. Good conversions were obtained with 4-bromoanisole (entries 7–8).

It is well known that microwave technology may be a successful technique for chemical synthesis.¹³ Since this technique may shorten the reaction times of Suzuki–Miyaura couplings,

especially in water,¹⁴ some experiments with the present catalysts were performed in conjunction with microwave heating.

Table 2 summarizes the results obtained when the Suzuki–Miyaura reaction with aryl bromides was promoted in neat water by microwave heating. Under these conditions, high conversions were obtained even in a very short time. When electron-poor aryl bromides were used conversions up to 96% were obtained in only 5 min (entries 1–2 and entries 5–6) using either ligand. With electron-rich aryl bromides, longer times (10 min) were required to achieve similar conversions (entries 3–4). As already shown (Table 1, entries 7–8), ligand **2**, containing a larger alkyl chain, is slightly more active than ligand **1** (entries 3–4). Further evidence for this ligand effect is provided by entry 6 that shows how a good conversion can be obtained even with very small amounts of Pd complex (0.025 mol%).

In the light of the results obtained with aryl bromides, ligands **1** and **2** were tested with the much less reactive and less expensive 4-chloroacetophenone substrate. The results obtained are shown in Table 3.

Table 3 Palladium catalysed S–M cross-coupling of aryl chlorides R¹–Cl and boronic acids R²–B(OH)₂ promoted by microwave heating^a

Entry	[P–O]	Pd (mol%)	R ¹	R ²	Conv. (%) ^b
1	1	1.0	4-AcC ₆ H ₄	Ph	45
2	1	2.0	4-AcC ₆ H ₄	1-naphthyl	60
3	1	1.0	4-AcC ₆ H ₄	4-MeOC ₆ H ₄	45
4	2	0.2	4-AcC ₆ H ₄	Ph	30
5	2	0.2	4-AcC ₆ H ₄	2-formylphenyl	56

^a Conditions: microwave heating with cooling, cat. Pd(OAc)₂/[P–O], Pd/L (1/1), T = 150 °C, (300 W), Solvent H₂O (3 ml), t = 10 min, R¹–Cl (1.5 mmol), R²–B(OH)₂ (1.72 mmol), K₂CO₃ (3 mmol). ^b Conversion determined by GC.

Conversions of up to 60% were achieved using ligand **1** with 2 mol% of Pd complex (entry 2), while for ligand **2** conversions up to 56% were obtained with 0.2 mol% of Pd complex (entry 5).

In conclusion, two new diaryl alkyl phosphine sulfonate ligands have been synthesized as zwitterions. The structure of complex **1a** confirms the coordination of the phosphine sulfonate ligand in a bidentate fashion. Both ligands **1** and **2** have been successfully used in the palladium-catalysed Suzuki–Miyaura cross-coupling reaction of aryl bromides as well as aryl chlorides in neat and non-deaerated water.

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