

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

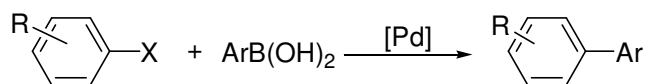
Abstract

In this chapter two novel bis(*o*-methoxyphenyl) phosphinoalkylsulfonate (P-O) ligands are applied in palladium-catalysed Suzuki-Miyaura cross-coupling reactions in neat water in conjunction with microwave heating. These ligands in combination with a palladium source yield efficient catalyst for the Suzuki-Miyaura reaction.

4.2.1. Introduction

The Suzuki-Miyaura coupling (**Scheme 1**) is one of the most useful methods for the formation of C-C bonds.¹ Due to the high solubility of arylboronic acids in water and the low toxicity of reagents and by-products as compared to other protocols,^{1,2} the Suzuki coupling is an ideal reaction to be performed in water. Over the last years, several reports have appeared describing Suzuki coupling reactions catalysed by water-soluble Pd systems.^{1a,3,4}

The fact that the ligands 2-{bis(o-methoxyphenyl)phosphino}ethanesulfonic acid (**a**) and 3-{bis(o-methoxyphenyl)phosphino}propanesulfonic acid (**b**) (section 4.1, **Figure 1**, pag. 171) are water-soluble and air stable, makes these ligands promising candidates to be use in the Suzuki-Miyaura cross-coupling reaction performed in non-deaerated water



X=I, Br, Cl

Scheme 1. Suzuki-Miyaura cross-coupling reaction

4.2.2. Results and Discussion

Catalytic Suzuki-Miyaura cross-coupling experiments

The properties of these new ligands **a** and **b** makes water the solvent of choice for the performance of the catalytic Suzuki-Miyaura cross-coupling reaction. To the best of our knowledge, no diaryl alkyl phosphine sulfonate anionic ligand has ever been employed in such reaction in neat water.

In **Table 1** are reported the results obtained for the Suzuki-Miyaura reaction between aryl bromides and aryl boronic acids in neat water and in open atmosphere.

Irrespective of the ligand employed, quantitative conversions were achieved when either 4-bromoacetophenone or bromobenzene were used for the catalytic cross-coupling reaction (entries 1-6), using only 0.05 mol% of palladium. On using the less reactive 4-bromoanisole, the catalytic conversions decrease slightly (entries 7-8) but they are still high.

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] a	Conversion ^b (%) [P-O] b
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 ₄	4-FC ₆ H ₄	>99	>99
6	C ₆ H ₄	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

^aConditions: 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). ^bConversion determined by GC and ¹H-NMR spectroscopy in CDCl₃

It is well known that microwave technology may be a successful technique for chemical syntheses.⁵ Since this technique may shorten the reaction times of catalytic Suzuki-Miyaura couplings, especially in water,⁶ some experiments with the present catalysts were performed in conjunction with microwave heating. The catalytic results of this study are summarised in **Table 2**. Under the catalytic conditions reported in **Table 2**, high conversions were obtained even in a very short time. When electron-poor aryl bromides were used as reagents,

conversions up to 96% were obtained in a reaction time of only 5 minutes (**Table 2**, entries 1-2 and entries 5-6) irrespective of the ligand used. Similar conversions were achieved with electron-rich aryl bromides prolonging the reaction time (10 min.) (**Table 2**, entries 3-4). As already shown (**Table 1**, entries 7-8), ligand **b**, containing a larger alkyl chain, is slightly more active than ligand **a** (**Table 2**, entries 3-4). This ligand effect is put in evidence in entry 6 that shows how high conversions can be obtained even with a very small amounts of Pd complex (0.025 mol%).

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.)	mol% Pd	R ¹	R ²	Conv.(%) ^b
1	a	5	0.05	4-AcC ₆ H ₄	1-naphthyl	87
2	a	5	0.05	4-AcC ₆ H ₄	F-C ₆ H ₄	96
3	a	10	0.05	4-MeOC ₆ H ₄	1-naphthyl	72
4	b	10	0.05	4-MeOC ₆ H ₄	1-naphthyl	86
5	b	5	0.05	4-AcC ₆ H ₄	Ph	90
6	b	5	0.025	4-AcC ₆ H ₄	Ph	90

^aConditions: microwave heating with cooling, cat. Pd(OAc)₂[P-O], L/Pd (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). ^bConversion determined by GC.

In the light of the results obtained with aryl bromides, ligands **a** and **b** 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]	mol% Pd	R ¹	R ²	Conv.(%) ^b
1	a	1.0	4-AcC ₆ H ₄	Ph	45
2	a	2.0	4-AcC ₆ H ₄	1-naphthyl	60
3	a	1.0	4-AcC ₆ H ₄	4-MeOC ₆ H ₄	45
4	b	0.2	4-AcC ₆ H ₄	Ph	30
5	b	0.2	4-AcC ₆ H ₄	2-formylphenyl	56

^aConditions: microwave heating with cooling, cat. Pd(OAc)₂/[P-O], L/Pd (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), L/Pd (1/1), K₂CO₃ (3 mmol). ^bConversion determined by GC.

Conversions up to 60 % were achieved using ligand **a** (Table 3, entry 2) with 2 mol% of Pd complex, while for ligand **b** conversions up to 56 % were obtained with 0.2 mol% of Pd complex (entry 5).

4.2.3. Conclusions

Both ligands **a** and **b** have been successfully used in conjunction with Pd(OAc)₂ in the Suzuki-Miyaura cross-coupling reaction of aryl bromides as well as aryl chlorides in neat and non-deaerated water under either, conventional and microwave heating.

4.2.4. Experimental Section

General Considerations

Deuterated solvents (dichloromethane-d₂ or chloroform-d₁) were used as purchased from Sigma-Aldrich. Commercial reagents were used as supplied, unless otherwise stated. ¹H-NMR spectra (chemical shifts relative to residual solvent), were recorded on a Varian Mercury VX 400 MHz or Varian Gemini 300

MHz spectrometer. Gas chromatography analyses were run on a Hewlett-Packard HP 5890A instrument equipped with a Hewlett-Packard HP 366 series II integrator, using an HP-5(25 m x 0.25 mm d. i.). Microwave experiments were performed in a CEM microwave Discover model.

Catalysis

In a 25 mL round bottom flask was added ligand **a** or **b** (0.05 mol%) to a solution of K_2CO_3 (3 mmol) in 3 mL of non-deaerated water. This mixture was allowed to stir for 5 minutes. Afterwards were added successively aryl bromide (1.5 mmol), arylboronic acid (1.72 mmol) and $Pd(OAc)_2$ (0.05 mol%). After stirring the solution at 80 °C for 2 h, the reaction was quenched by cooling it by means of an ice-bath. In those reactions where microwave heating was employed, the water solution was heated to 150 °C for 5 or 10 minutes, followed by quenching the reaction with an ice-bath. The organic product was extracted with CH_2Cl_2 (3 x 15 mL) and the organic extracts were dried over magnesium sulfate, followed by concentration of the solution to dryness. The catalytic conversion, which is reported as average value of two analyses, was estimated by GC or 1H -NMR spectroscopy.

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4.2.5. References

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- ¹ a) F. Churruca, R. SanMartin, B. Inés, I. Tellitu, and E. Domínguez, *Adv. Synth. Catal.*, **2006**, *348*, 1836; b) T.E. Barder, S.D. Walker, J. R.Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.*, **2005**, *127*, 4685; c) A. Suzuki, *Chem. Commun.*, **2005**, 4759; d) R. Franzén, Y. Xu, *Can. J. Chem.*, **2005**, *83*, 266; e) .S. Kotha, K. Lahiri, D. Kashinath, *Tetrahedron*, **2002**, *58*, 9633
- ² Boronic Acids: *Preparation and Applications in Organic Synthesis and Medicine*, (Ed.: D. G. Hall), VCH, Weinheim, **2005**.
- ³ a) K. W. Anderson, S. L. Buchwald, *Angew. Chem. Int. Ed.*, **2005**, *44*, 6173; b) L. R. Moore and K. H. Shaughnessy, *Org. Lett.*, **2004**, *6*, 225; c) E. C. Western, J. R. Daft, E. M. Johnson, P.M. Gannett, K. H. Shaughnessy, *J. Org. Chem.*, **2003**, *68*, 6767; d) C. Dupuis, K. Adiey, L. Charruault, V. Michelet, M. Savignac, J.-P.Genêt, *Tetrahedron Lett.*, **2001**, *42*, 6523.
- ⁴ a) Jin-Heng Li, Xi-Chao Hu, Yun Liang, Ye-Xiang Xie, *Tetrahedron*, **2006**, *62*, 31; b) D. Schönfelder, O. Nuyken, R. Weberskirch, *J. Organomet. Chem.*, **2005**, *690*, 4648; c) L. Liu, Y. Zhang, Y. J. Wang, *Org. Chem.*, **2005**, *70*, 6122; d) E. Paetzold, G. Oehme, *J. Mol. Catal. A*, **2000**, *152*, 69.
- ⁵ a) C. O. Kappe, *Angew. Chem. Int. Ed.*, **2004**, *43*, 6250; b) *Microwave-Assisted Organic Synthesis*, ed. P. Lidström and J. P. Tierney, Blackwell, Oxford, **2004**; b) *Microwave Synthesis: Chemistry at the Speed of Light*, CEM Publishing, Matthews, NC, **2002**; c) P. Lidström, J. P. Tierney, B. Wathey and J. Westman, *Tetrahedron*, **2001**, *57*, 9225; d) S. Caddick, *Tetrahedron*, **1995**, *51*, 10403.
- ⁶ Microwave-assisted Suzuki-Miyaura coupling, for example: N.E. Leadbeater, *Chem. Commun.*, **2005**, 2881