

Synthesis of functionalized biaryls using iminophosphorane palladacycles as Suzuki catalysts

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Abstract: The Suzuki-Miyaura cross coupling reaction is a very powerful tool for making of C–C bonds from organic halides and organoboron compounds [1]. This reaction, for which palladacycles have shown great catalytic activity [2] is widely employed in academic laboratories as well as in pharmaceutical industries to synthesize organic compounds or drugs such as *Losartan* [3], an antihypertensive medicine.

Iminophosphoranes are organic compounds of general composition $R_3P=NR$ and can be used as in coordination and in organometallic chemistry [4]. The aim of this work is to study the catalytic activity of new palladium organometallic compounds derived from iminophosphorane ligands.

Keywords: Iminophosphorane, catalysis, Suzuki, palladacycle, organometallic

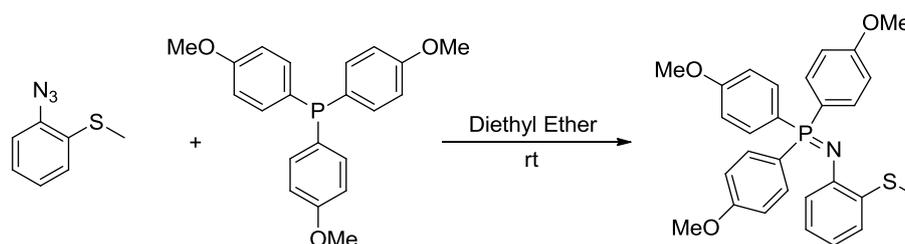
1. Introduction

Cross-coupling reactions have been widely used in organic synthesis as well as in the chemical industry. One of the most usual is the Suzuki catalysis, which allows formation of C–C bonds between two aryls by reaction of an organic halide and an organoboron compound. To perform the reaction a catalyst is needed, generally a palladium compound. In 1989, Hermann *et al.* showed that palladium cyclometallated compounds could behave as excellent catalysts for this reaction [2].

Iminophosphoranes are ligands in coordinated compounds as well as in cyclometallated compounds with many metals, especially Au [5], Pd [6] and Pt [7], which have luminescent and anti-cancer properties. For these reasons, we have considered important to approach the synthesis of new palladium (II) cyclometallated compounds derived from iminophosphoranes and to consider their properties as Suzuki catalysts.

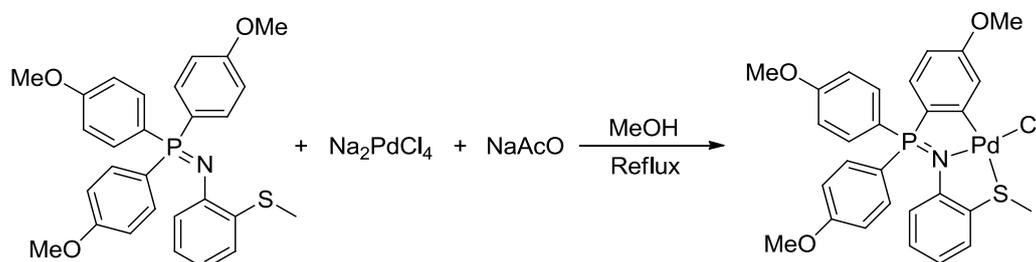
2. Methods

2-(methylthio)aniline iminophosphoranes may behave as tridentate ligands, which may be easily obtained by the Staudinger reaction as depicted in *Scheme 1*.



Scheme 1: Staudinger reaction

Compound **2** may be obtained by the reaction of a palladium salt with the iminophosphorane ligand (Scheme 2). The presence of a base is not necessary but facilitates the cyclometallation reaction and prevents de formation of the [N,S] coordination compound.



Scheme 2: Formation of the cyclometallated compound

Compound **2** is an air-stable bright yellow solid. The metal atom shows a square-planar geometry and has two covalent bonds with nitrogen and sulfur atoms and one σ bond with the carbon atom.

3. Results and discussion

3.1. Synthesis of 2-(methylthio)phenylazide

To a mixture of 2-(methylthio)aniline (1000 mg, 7.183 mmol), in water (1.5 cm³), ethyl acetate (7 cm³) and HCl 37% (1.5 cm³) was added dropwise sodium nitrite (843 mg, 12.211 mmol) in water under vigorous stirring at 0-5 °C. After 30 min aqueous NaN₃ (793 mg, 12.211 mmol) was added dropwise to the reaction mixture at 0-5 °C for 30 minutes. The mixture was extracted with ethyl acetate and washed with water. The organic layer was evaporated and a pale yellow powder was obtained. Yield 1021 mg (86%).

3.2. Synthesis of the compound 1

To a solution of 2-(methylthio)phenylazide (300 mg, 1.816 mmol) in diethyl ether (15 cm³) was added tris(4-methoxyphenyl)phosphine (640 mg, 1.816 mmol) and stirred at room temperature for two hours. The solvent of the resulting solution was evaporated to dryness giving a yellow powder. Yield 752 mg (83.1 %). Anal. Calc. for C₂₈H₂₈NO₃PS: C, 68.7; H, 5.8; N, 2.7; S, 6.6. Found: C, 68.8; H, 5.9; N, 2.6; S, 6.5. ¹H NMR (CDCl₃): δ = 2.35 (s 3H, CH₃S) 3.74 (s 9H, CH₃O) 6.35 (m, 1H, H₄) 6.63 (m 2H, H₂, H₃) 6.87 (dd, 6H, ³J^{H₁-H} 8.7, ³J^{H₁-P} 1.9 Hz, *m*-Ar) 6.92 (m 1H, H₁) 7.66 (dd, 6H, ³J^{H₁-H} 8.7 ³J^{H₁-P} 11.5 Hz, *o*-Ar) ³¹P{¹H} NMR (CDCl₃): δ = -0.14 (s).

3.3. Synthesis of the compound 2

To a mixture of [Na₂PdCl₄] (75 mg, 0,255 mmol), NaOAc (19 mg, 0,255 mmol,) and compound 1 (125 mg, 0,255 mmol) was added methanol (10 cm³) and heated to 80 °C for 18 hours. The resulting solution was evaporated, the solid obtained was dissolved in dichloromethane and filtered through silica, after which the solvent was removed under vacuum and a yellow bright powder was obtained. Yield 116 mg (72.0 %). Anal. Calc. for C₂₈H₂₇ClNO₃PPdS: C, 53.3; H, 4.3; N, 2.2; S, 5.1. Found: C, 53.4; H, 4.5; N, 2.2; S, 5.0. ¹H NMR (CDCl₃): δ = 2.76 (s, 3H, CH₃S) 3.85 (s, 6H, CH₃O) 3.86 (s, 3H, CH₃O) 6.59 (m, 1H, H₇) 6.64 (d, 1H ³J^{H₁-H} 8.4 Hz, H₁) 6.71 (m, 2H, H₂, H₆) 6.86 (m, 1H, H₃) 7.01 (dd, 4H, ³J^{H₁-H} 8.7 ³J^{H₁-P} 2.1 Hz, *m*-Ar) 7.35 (d, 1H, ³J^{H₁-H} 7.7 Hz, H₄) 7.75 (dd, 5H, ³J^{H₁-H} 8.7 ³J^{H₁-P} 11.3 Hz, *o*-Ar, H₅), ³¹P{¹H} NMR (CDCl₃): δ = 44.63 (s).

3.4. Characterization

The compounds were characterized by ¹H and ³¹P{¹H} NMR spectroscopy.

The ^1H NMR shows the formation of the iminophosphorane **1**, the three phenyl rings bonded to phosphorus are chemically equivalent (Figure 1).

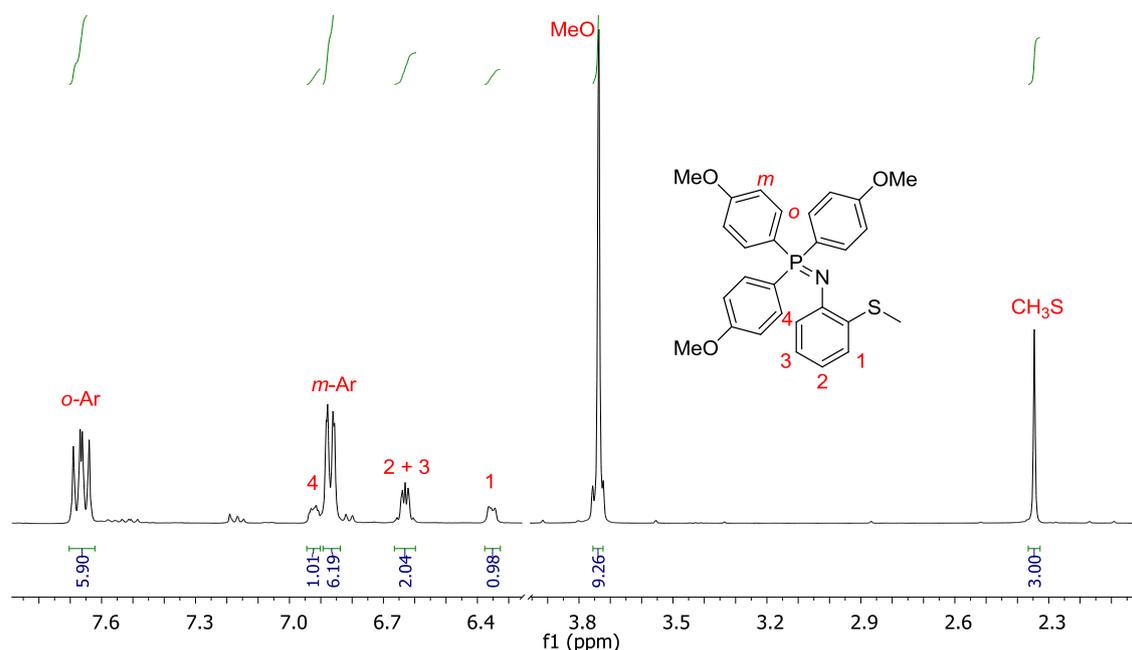


Figure 1. ^1H NMR spectrum for **1**

In compound **2**, only two of the three phenyl rings bonded to the phosphorus atom are chemically equivalent, the other ring shows different signals after metallation by palladium (Figure 2).

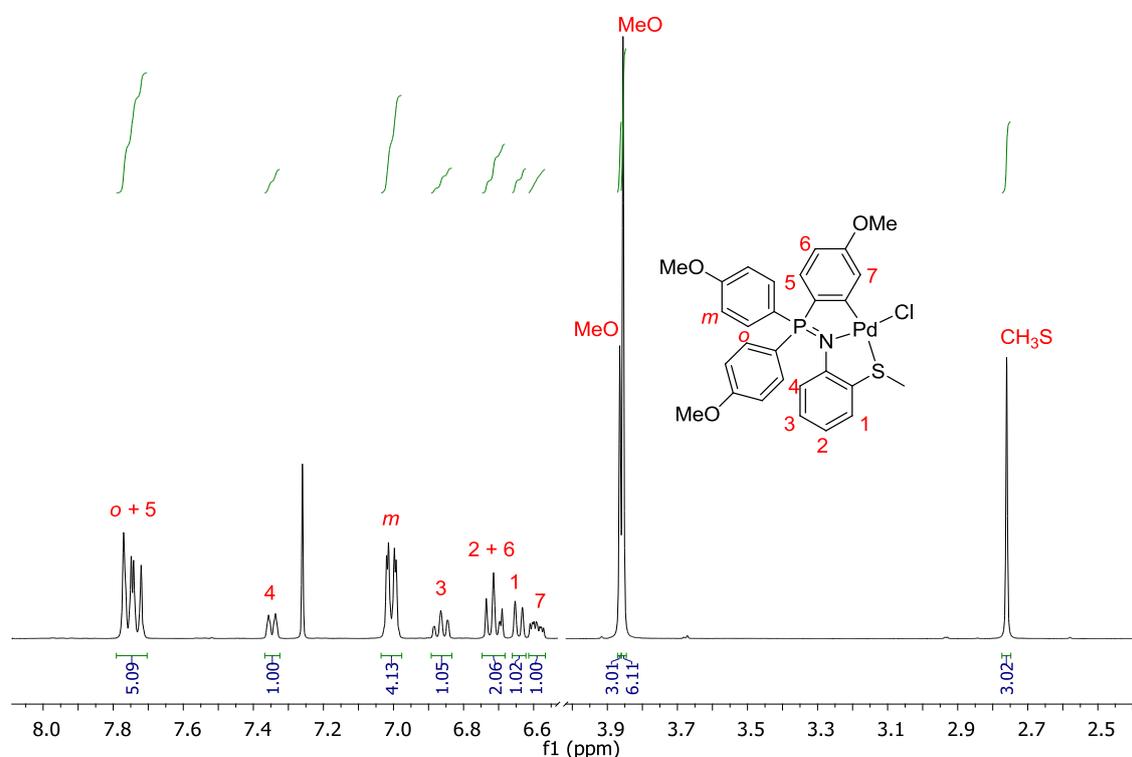


Figure 2. ^1H NMR spectrum for **2**

Comparison of the $^{31}\text{P}\{^1\text{H}\}$ spectra of compounds **1** and **2** clearly shows a shift of the signal assigned to the phosphorus nucleus (Figure 3).

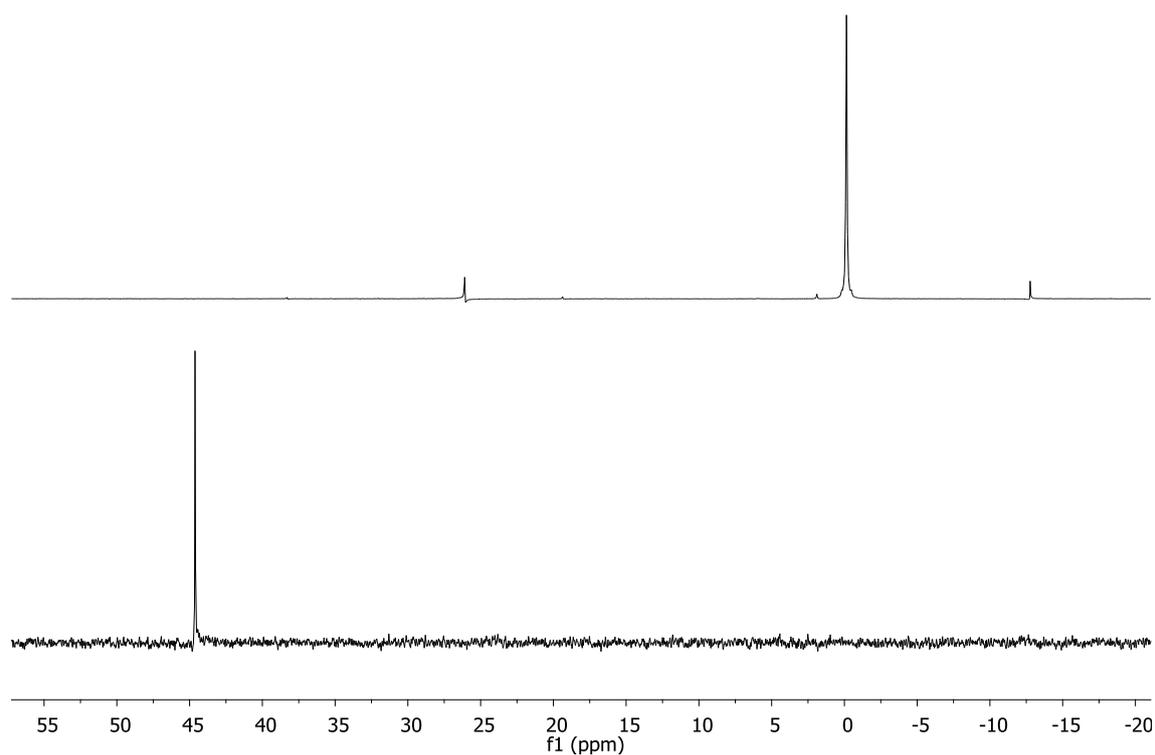


Figure 3. $^{31}\text{P}\{^1\text{H}\}$ spectrum for 1 (above) and 2 (bottom)

Crystals of compound 2 were obtained by slow evaporation from a chloroform solution. The X-ray diffraction study confirms the formation of the cyclometallated compound as is shown in Figure 4.

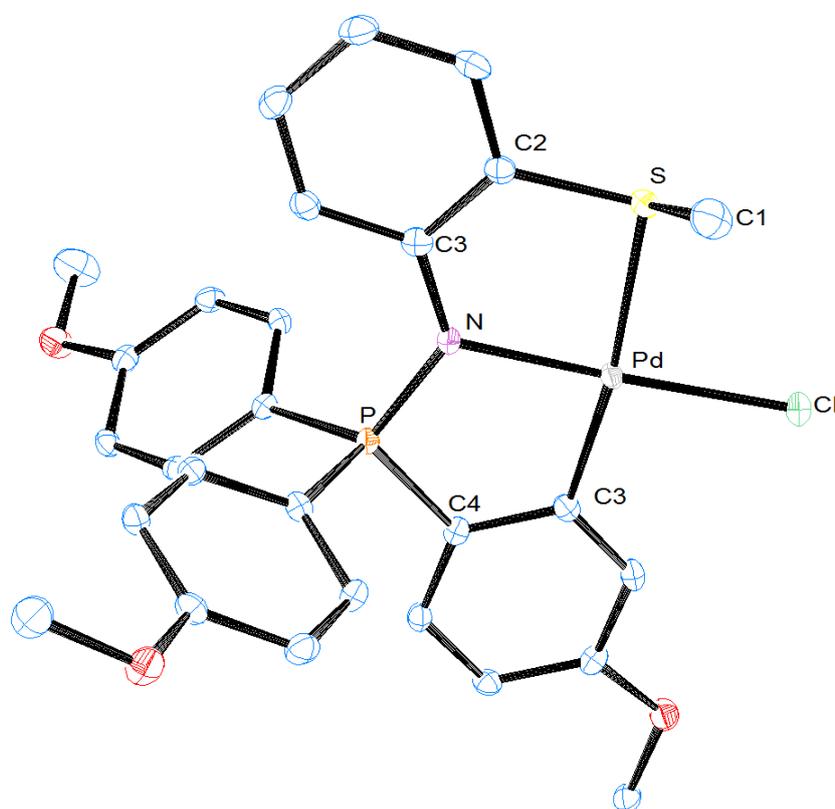


Figure 4. Structure of 2, hydrogen atoms are omitted

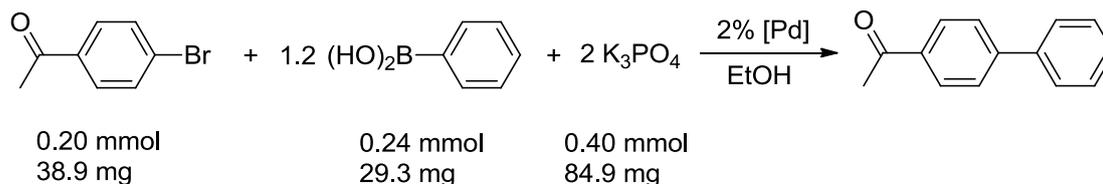
Crystal data is shown in Table 1.

Empirical formula	$C_{28}H_{27}ClNO_3PPdS$
Molecular weight	630.39
Temperature	100.0(1) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	P2(1)2(1)2(1)
Unit cell dimensions	a = 12.223(5) Å α = 90.000(5)° b = 13.996(5) Å β = 90.000(5)° c = 15.093(5) Å γ = 90.000(5)°
Volume	2582.0(16) Å ³
Z	4
Calculated density	1.622 Mg/m ³
Absorption coefficient	0.997 mm ⁻¹
F(000)	1280
Crystal size	0.42 x 0.36 x 0.20 mm
θ range for data collection	1.98-30.50°
Index ranges	-17 ≤ h ≤ 17, -19 ≤ k ≤ 18, -21 ≤ l ≤ 19
Reflections collected/independent	59539 / 7893 [R _{int} = 0.0586]
Data/restraints/parameters	7893 / 0 / 325
Goodness-of-fit on F ²	1.032
Final R indices [I > 2σ(I)]	R ₁ = 0.0287, wR ₂ = 0.0583
R indices (all data)	R ₁ = 0.0322, wR ₂ = 0.0594

Table 1. Crystal data

3.5. Catalysis

The cross-coupling reaction between 4-bromoacetophenone and phenylboronic acid was studied using a 2% M compound **2** as catalyst. The reaction was carried out in ethanol, using an excess of K₃PO₄ as base (Scheme 3).



Scheme 3. Catalysis reaction

The yield of the reaction was measured by ¹H NMR spectroscopy (Table 2).

Temperature/ °C	Time/ h	Yield/ %
	1	51
50	4	91
	6	100
80	1	100

Table 2: Catalysis results

4. Conclusions

A new palladacycle derived from an iminophosphorane ligand has been synthesized and characterized. This compound shows good catalytic activity in the Suzuki-Miyaura reaction even at relatively low temperatures.

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Conflicts of Interest: the authors declare no conflict of interest.

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