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Pd complexes of iminophosphine ligands: A homogeneous molecular catalyst for Suzuki–Miyaura cross-coupling reactions under mild conditions

Sabrina M. Nobre, Adriano L. Monteiro*

Laboratory of Molecular Catalysis, Instituto de Química – UFRGS, Av. Bento Gonçalves, 9500 Porto Alegre 91501-970, CP 15003, RS, Brazil

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ABSTRACT

The complexes formed by combining $Pd(OAc)_2$ and iminophosphine ligands (PÑ) are active catalysts in Suzuki–Miyaura cross-coupling reactions under mild conditions. Aryl bromides and iodides, as well as benzyl chlorides give the corresponding coupled products in high yields at low temperatures (25–50 °C) using these catalysts. Iminophosphines containing the most sterically demanding groups attached to the N-imino moiety were the most effective ligands. New divalent Pd complexes of known iminophosphines were synthesised and their activity was compared with the in situ generated catalyst system. The complex resulting from the oxidative addition of 4-bromo anisole [Pd(4-$CH_3OC_6H_4$)Br(PÑ)] was more active than the in situ generated system. However, palladacycles containing the iminophosphine ligand (e.g., {[$C_6H_4CH(Me)_2$St-Bu]Pd(PÑ)}$^+PF_6^-$) were less active than the in situ generated catalyst due to the greater stability of the complexes that involve two bidentate ligands. Poisoning tests demonstrated that homogeneous mononuclear palladium species containing the iminophsophine ligand were responsible for the catalytic activity.

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1. Introduction

The palladium-catalyzed Suzuki–Miyaura cross-coupling reactions are one of the most efficient methods for the construction of C_{aryl}–C_{aryl} bonds and have found widespread use in organic synthesis [1–4]. Indeed, various efficient Pd catalyst precursors have been developed in recent years that allow aryl halides to be effectively coupled with aryl boronic acids under mild reaction conditions [5]. As part of our ongoing research addressing C–C bond formation by cross-coupling reactions, we studied palladacycles [6–8], ligandless Pd [9], and PPh_3–Pd mixtures [10–12] in order to obtain simple and efficient catalytic systems for Pd-catalyzed Suzuki–Miyaura reactions [13–21]. Among the several classes of phosphine ligand described in the literature for Pd-catalyzed Suzuki–Miyaura reactions, we became interested in iminophosphophine ligands. These are bidentate ligands with both hard and soft donor atoms and are expected to exhibit hemi-labile behavior when coordinated to palladium [22,23]. These ligands can easily be obtained from the reaction of o-(diphenylphosphine)benzaldeyde with an amine [24]. Additionally, we can modulate the steric and electronic properties of the N atom by choosing an appropriate amine. Thus, iminophosphine ligands in the context of Pd complexes are active catalysts for cross-coupling reactions (Suzuki–Miyaura [25,26], Heck [27–29], and Stille [30,31]), ethylene oligomerizations [32,33], hydroaminations [34], terminal alkyne arylations [35], and allylic alkylation reactions [36]. Scrivanti et al. have reported that η^2-(olefin)palladium(0) complexes containing iminophosphine ligands are highly efficient catalysts for the coupling of aryl bromides with boronic acids [25,26]. Their catalytic activity is strongly dependent on the reaction conditions and on the nature of the ligands, while the olefin plays an important role in stabilizing the catalyst [26]. In this paper, we wish to report (1) the synthesis and characterization of new divalent Pd iminophosphine complexes, (2) the optimization of an in situ generated catalyst system composed of $Pd(OAc)_2$ and an iminophosphine ligand for Suzuki–Miyaura reactions under mild conditions, and (3) a comparison of the catalytic activities of the in situ generated system with that of the new preformed complexes (Scheme 1). In addition we employed poisoning tests to evaluate the nature of the actual catalytic species.

2. Experimental

2.1. General methods

All catalytic reactions were carried out under an argon atmosphere in oven-dried resealable Schlenk tubes. Chemicals were purchased from commercial sources, and were used without

* Corresponding author. Tel.: +55 51 33086303; fax: +55 51 33087304.
E-mail address: adriano.monteiro@ufrgs.br (A.L. Monteiro).

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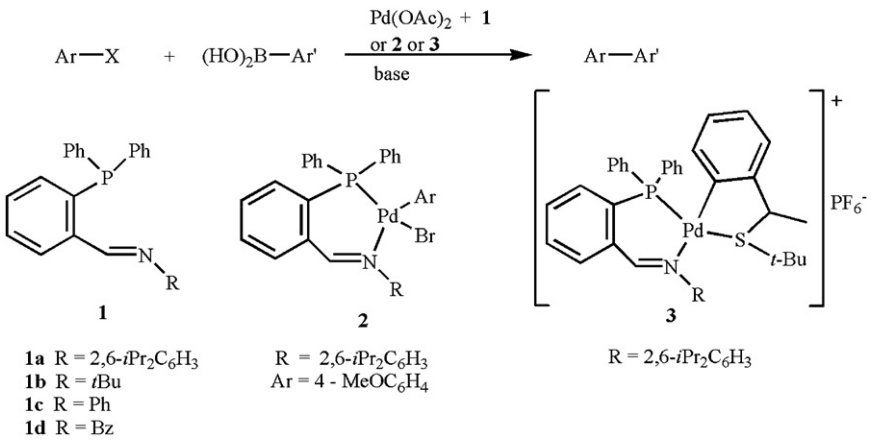


Scheme 1. Pd iminophosphine complexes as catalyst precursors for Suzuki–Miyaura cross-coupling reactions.

further purification. Palladacycle **4** [37] and iminophosphine ligands (see supporting information) were prepared as reported in the literature. NMR spectra were recorded on a Varian XL300 spectrometer. Infrared spectra were performed on a Bomem B-102 spectrometer. Mass spectra were obtained on a Shimadzu QP-5050 gas chromatograph/mass spectrometer (GC/MS) using EI methods (70 eV). Gas chromatography (GC) analyses were performed on a Hewlett-Packard 5890 Gas Chromatograph equipped with a flame ionization detector (FID) and a 30-m capillary column containing a dimethylpolysiloxane stationary phase. ESI mass spectra were obtained in positive ion mode on a Micromass QTof instrument in an ESI–QTOF configuration with a 7000 mass resolving power in the TOF mass analyzer. The following typical operating conditions were used with methanol solutions of the analyte: a 3 kV capillary voltage and a 10 V cone voltage. X-ray structure analyses were performed by the IQ-UFSM. Data from crystals were collected on a Bruker Kappa APEX-II CCD 3 kW sealed tube system. Diamond visual crystal structure information system, version 2.1 was used to generate the molecular representations.

2.2. Synthesis of complex [Pd(4-$CH_3OC_6H_4$)Br(PN̂)] (2)

A purple solution of $Pd_2(dba)_3$ (81.35 mg, 0.089 mmol) (dba = trans,trans-dibenzylideneacetone), P(o-tolyl)$_3$ (108.22 mg, 0.356 mmol), and 4-bromoanisole (84.15 mg, 0.45 mmol) in benzene (15 mL) was stirred at room temperature for 6 h. *N*-(2-(Diphenylphosphino)benzylidene)-2,6-diisopropylphenylamine (**1a**) was added and the solution was stirred at room temperature for an additional 16 h. After filtration through Celite™, the solvent was removed under reduced pressure. The residue was washed with ether (4× 20 mL) and dried under vacuum giving complex **2** as a yellow solid (87%). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.06 (s, 1H), 7.73–7.11 (m, 17H), 6.86 (d, *J* 8.4 Hz, 2H), 6.29 (d, *J* 8.4 Hz, 2H), 3.6 (s, 3H), 3.2 (sept, *J* 6.9 Hz, 2H), 1.45 (d, *J* 6.9 Hz, 6H), 0.98 (d, *J* 6.9 Hz, 6H), $(Me)_2$. ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 167.5, 156.3, 150.6, 140.6; 137.9, 137.8, 137.36, 134.8, 134.6, 134.3, 134.1, 133.7, 132.6, 131.4, 130.6, 129.9, 129.6, 129.5, 129.3, 129.2, 127.9, 127.4, 124.1, 123.9, 113.9, 68.6, 55.8, 29.5, 26.3, 25.3, 23.8. ^{31}P NMR (121 MHz, H_3PO_4): δ (ppm) 21.9. IR ν (cm^{-1}): 2955, 2925, 2854, 2360, 2341, 1615 (C=N), 1463, 1378, 1262, 1235.

2.3. Synthesis of complex {[$C_6H_4CH(Me)_2St$-Bu]Pd(PN̂)}$^+PF_6^-$ (3)

A Schlenk flask was charged with palladacycle (**4**) (39.5 mg, 0.1 mmol) and acetone (5 mL) and stirred at room temperature for 5 min. *N*-(2′-Diphenylphosphinobenzylidene)-2,6-diisopropylphenylamine **1a** (45 mg, 0.1 mmol) dissolved in acetone (5 mL) and KPF_6 (18.4 mg, 0.1 mmol) were added to the suspension, and the mixture was refluxed for 1 h. The solution was filtered though Celite™ and concentrated under reduced pressure. The resulting residue was washed with ether (3× 15 mL). After recrystallization from acetone–hexane (1:1) complex **3** was obtained as a yellow solid (63.4 mg, 70%). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.24 (s, 1H), 7.94–6.69 (m), 6.59 (t, *J* 7.5 Hz, 1H), 3.32 (t, *J* 7.5 Hz, 1H), 4.14–4.08 (m, 1H), 3.0 (sept, *J* 6.9 Hz, 1H), 2.84 (sept, *J* 6.9 Hz, 1H), 2.10 (d, *J* 6.9 Hz, 3H), 1.36 (d, *J* 6.9 Hz, 3H), 1.28 (d, *J* 6.9 Hz, 3H), 1.21 (d, *J* 6.9 Hz, 3H), 0.73 (s, 9H), 0.23 (d, *J* 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 170.9, 170.9, 158.8, 150.5, 150.1, 141.5, 141.3,140.3, 139.4, 139.2; 136.7, 135.7, 135.6, 135.7, 135.0, 134.5, 133.8, 132.5, 131.1, 130.9, 129.5, 129.1, 127.9, 127.5, 127.3, 127.2, 127.1, 126.9, 125.9, 125.4, 124.8, 124.7, 123.4, 53.0, 52.3, 31.5, 29.7, 29.6, 27.1, 26.8, 24.5, 23.9, 22.3. ^{31}P NMR (121 MHz, H_3PO_4): δ (ppm) 30.39 (s), −143 (sept, J_{P-F} 712 Hz). IR ν (cm^{-1}): 2956, 2924, 2854, 1615 (C=N), 1571, 1459, 1439, 1377, 1160, 1097. ESI(+) MS: {[$C_6H_4CH(Me)$ StBu]Pd(PN̂)}$^+$ (*m*/*z*): 748.2382 (calc'd = 748.2374).

2.4. Catalytic Suzuki–Miyaura cross-coupling reactions

In a typical experiment, an oven-dried resealable Schlenk flask was evacuated and back filled with argon then charged with $Pd(OAc)_2$ (0.01 mmol), iminophosphine **1a** (0.01 mmol), aryl halide (1 mmol), arylboronic acid (1.5 mmol), and dioxane (6 mL). The reaction was stirred at room temperature for 10 min, and then KOH (2 mmol) was added. The reaction mixture was stirred at the desired temperature for the chosen amount of time. After which the solution was then taken up in ether (30 mL), washed with aqueous NaOH (1 M, 2× 5 mL) and brine (2× 5 mL), and dried over $MgSO_4$. After purification by flash chromatography, the biphenyl product was characterized by ^{1}H and ^{13}C NMR, and GC–MS.

2.5. CS_2 poisoning studies

An oven-dried resealable Schlenk flask was charged with $Pd(OAc)_2$ (1.12 mg, 0.005 mmol), *N*-(2′-diphenylphosphinobenzylidene)-2,6-diisopropylphenylamine (0.005 mmol), KOH (56 mg, 1 mmol), phenylboronic acid (91.5 mg, 0.75 mmol), 4-bromoacetophenone (99.5 mg, 0.5 mmol), and dioxane (6 mL). The reaction mixture was stirred at 50 °C for 30 min (40% conversion). A solution of CS_2 in dioxane was then added (corresponding to 0, 0.5, 1.0, or 1.5 equiv. of CS_2). The mixture was stirred at 50 °C and further conversion was followed by GC over 3 days.

2.6. Hg(0) poisoning studies

An oven-dried resealable Schlenk flask was charged with $Pd(OAc)_2$ (1.12 mg, 0.005 mmol), *N*-(2′-diphenylphosphinobenzylidene)-2,6-diisopropylphenyl-amine (0.005 mmol) and dioxane (4 mL). The mixture was stirred at rt for 15 min. Then aryl bromide (0.5 mmol), phenylboronic acid (91.5 mg, 0.75 mmol), KOH (56 mg, 1 mmol), and dioxane (2 mL) were added. The reaction mixture was stirred at 50 °C for 30 min. Then Hg(0) (500 equiv. relative to $Pd(OAc)_2$) was added and the reaction mixture was stirred (900 rpm) at 50 °C for 41 h.

Aryl halide	Conversion at 30 min	Conversion at 41 h
4-Bromoacetophenone	40%	91%
4-Bromotoluene	22%	44%

2.7. Typical procedure for Maitlis's test

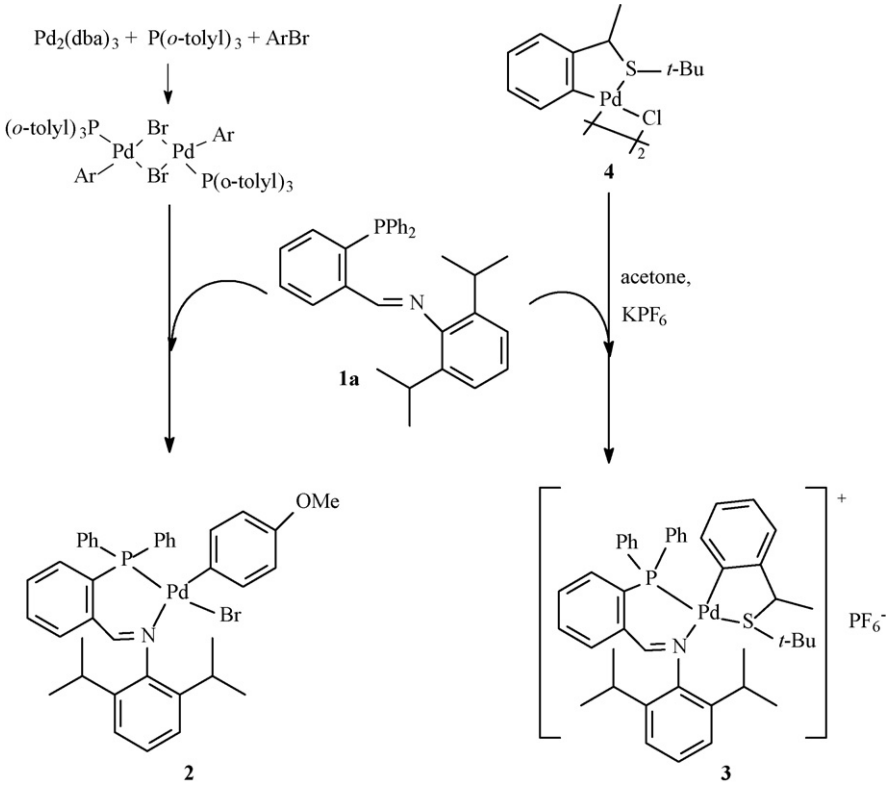
An oven-dried resealable Schlenk flask was charged with $Pd(OAc)_2$ (1.12 mg, 0.005 mmol), *N*-(2′-diphenylphosphinobenzylidene)-2,6-diisopropylphenyl-amine (0.005 mmol) and dioxane (4 mL). The mixture was stirred at rt for 15 min. Then 4-bromotoluene (0.5 mmol), phenylboronic acid (91.5 mg, 0.75 mmol), KOH (56 mg, 1 mmol), and dioxane (2 mL) were added. The reaction mixture was stirred at 50 °C for 30 min (25% conversion). Then, the reaction mixture was filtered through a sintered glass filter under argon and both the filtrate and the remaining cellulose were evaluated for the coupling reaction. KOH (56 mg, 1 mmol) was added to the filtrate and the reaction mixture was stirred at 50 °C for 16 h giving a 45% conversion. The cellulose was washed with dioxane (3× 5 mL) and transferred to an oven-dried resealable Schlenk flask along with aryl bromide (0.5 mmol), phenylboronic acid (91.5 mg, 0.75 mmol), KOH (56 mg, 1 mmol), and dioxane (6 mL). The reaction mixture was stirred at 50 °C for 16 h without any significative reaction (<1% coupling product formation).

3. Results and discussion

3.1. Synthesis and characterization of oxidative addition palladium complex **2** and palladacycle **3** containing an iminophosphine ligand

Complex **2** was obtained using the procedure described for the synthesis of [Pd(Ar)Br{(S)-BINAP}] complexes [38,39]. The complex resulting from a 1:4 mixture of $[Pd_2(dba)_3]$ and P(o-tolyl)$_3$ in benzene was reacted with an arylbromide to generate the corresponding bromide dimer $[Pd(\mu\text{-}Br)(C_6H_4OCH_3\text{-}4)\{P(o\text{-tolyl})_3\}]_2$ in situ. The addition of 2 equiv of *N*-(2-(diphenylphosphino)benzylidene)-2,6-diisopropylphenylamine (**1a**) gave complex **2** in 87% yield (Scheme 2). Cationic palladacycle **3** containing an iminophosphine ligand was prepared using the procedure described in the literature for the synthesis of similar complexes containing N-based palladacycles [40]. Therefore, treating the chloro-bridged sulfur-containing palladacycle **4** with the iminophosphine ligand **1a** in the presence of a stoichiometric amount of KPF_6 gave complex **3** in 70% yield.

Complexes **2** and **3** were characterized by standard spectroscopic techniques and the complexes' structures were determined in the solid state by X-ray diffraction analysis. The ^{31}P NMR spectra of complexes **2** and **3** displayed singlets at δ 22.4 ppm and δ 30.4 ppm, respectively, which confirmed the coordination of the phosphine ligand to the palladium center (free ligand **1a** δ −15.1 ppm) [40,41]. Cationic complex **3** also displayed the typical septuplet resonance in the ^{31}P NMR spectra due to the PF_6^- anion. IR analysis showed the ν (C=N) band of the free ligand **1a** at 1625 cm^{-1}, whereas this absorption was shifted to 1615 cm^{-1} in both complexes due to the coordination of the imino group's nitrogen to the palladium center [26,41]. ESI MS analysis of a methanol



Scheme 2. Synthesis of complexes **2** and **3**.

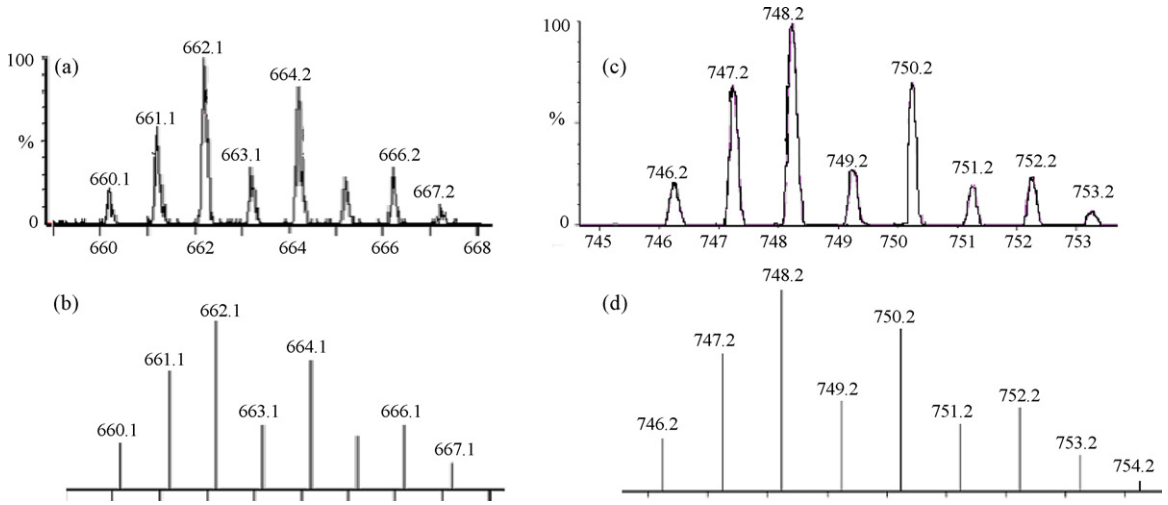


Fig. 1. (a) ESI mass spectrum (positive mode) showing the experimental isotopic distribution pattern of **2** in methanol. (b) Simulated isotopic distribution pattern of $[Pd(C_6H_4OCH_3\text{-}4)(2\text{-}(PPh_2)C_6H_4\text{-}1\text{-}CH{=}NC_6H_3\text{-}iPr_2\text{-}2,6)]^+$. (c) ESI mass spectrum (positive mode) showing the experimental isotopic distribution pattern of **3** in methanol. (d) Simulated isotopic distribution pattern of **3**.

solution of complex **2** showed a main peak at $m/z = 662.2$, which presented the isotopic patterns corresponding to loss of a bromine atom to form for the cationic complex $[M-Br]^+$ (Fig. 1a and b). Complex **3** is cationic and therefore the ESI MS analysis on positive mode showed the cationic complex's molecular ion at $m/z = 748.2$ with the expected isotopic pattern (Fig. 1c and d).

Single crystals of complexes **2** and **3** suitable for X-ray analysis were obtained by slow evaporation of chloroform solutions. In both complexes the planar arrangement around the palladium atom is slightly distorted (Figs. 2 and 3; Table 1). These palladium complexes may exist as two geometrical isomers, but ^{31}P NMR analysis indicates the presence of only one isomer in solution. X-ray structural analysis showed the ligand arrangement with the aryl ligand trans to the imino group in both complexes, as already observed for related complexes in the solid state and in solution [22,27,40,42–44]. All the bonds and the bond angles involving the Pd atom lie within the normal range, except the larger deviation of the P1-Pd-S angle (167.38(3)°) in complex **3** [22,27,40,42,43]. This angular deviation is attributed to the steric effect of the 2,6-diisopropylphenyl group and the StBu moiety.

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3.2. Suzuki–Miyaura cross-coupling reaction: optimization of an in situ generated catalyst system formed from $Pd(OAc)_2$ and iminophosphine ligands

Scrivanti et al. reported that the success of Suzuki–Miyaura reactions involving η^2-(olefin)palladium(0)iminophosphine complexes as catalysts is strongly dependent on the reaction conditions and on the nature of the ligands. Under optimized conditions, the reactions were carried out in aromatic solvents in the presence of K_2CO_3 at 90–110 °C [26]. We decided to investigate the performance of the catalyst system formed in situ from $Pd(OAc)_2$ and an iminophosphine ligand in the absence of an olefin ligand and

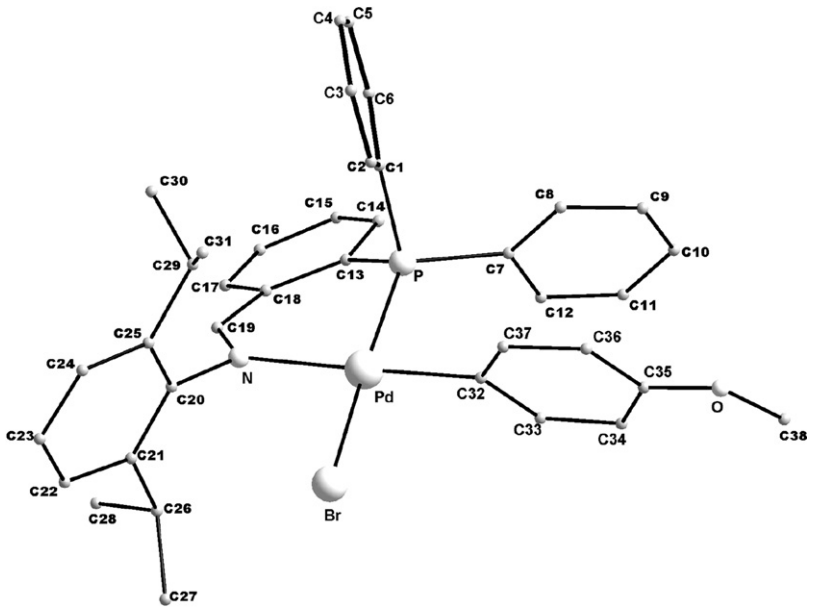


Fig. 2. Image of complex **2**. All hydrogen atoms are omitted for clarity.

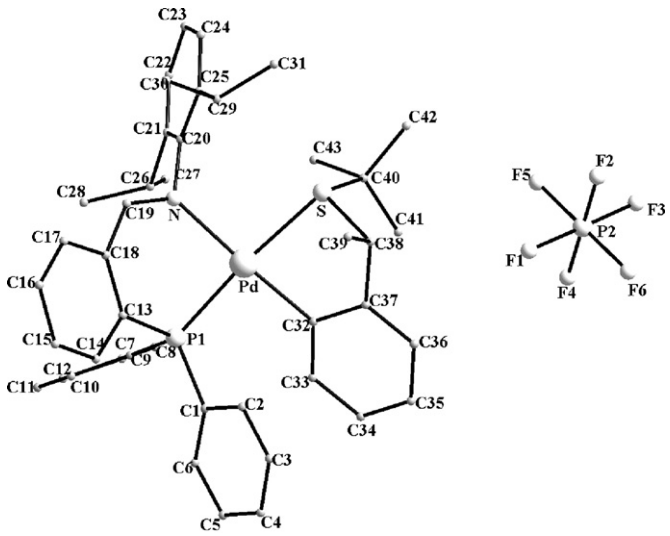


Fig. 3. Image of complex **3**. All hydrogen atoms are omitted for clarity.

Table 1
Selected bond lengths (Å) and angles (°) for complexes **2** and **3**.

	Lengths		Angles	
2	Pd-C_{32}	2.028(6)	C_{32}-Pd-P	88.08(17)
	Pd-N	2.188(5)	N-Pd-P	90.83(13)
	Pd-P	2.238(16)	N-Pd-Br	92.87(13)
	Pd-Br	2.485(8)	C_{32}-Pd-N	178.5(2)
			C_{32}-Pd-Br	88.18(16)
			P-Pd-Br	175.28(5)
3	Pd-C_{32}	2.023(3)	C_{32}-Pd-P	92.61(8)
	Pd-N	2.154(2)	N-Pd-P	89.48(6)
	Pd-P1	2.274(8)	C_{32}-Pd-S	82.66 (8)
	Pd-S	2.365(8)	N-Pd-S	94.21 (6)
			C_{32}-Pd-N	174.32(10)
			P1-Pd-S	167.38(3)

at milder reaction temperatures (Table 2). For the initial screening, we compared iminophosphine **1b** with the most common and inexpensive phosphine ligand, PPh_3, using dioxane as the solvent and CS_2CO_3 as a base (Table 2). Both ligands gave complete conversion after 2 h at 130 °C (Table 2, entries 1 and 2). At milder temperatures (50 °C) the iminophosphine ligand **1b** gave complete conversion whereas PPh_3 gave only 44% conversion under the same conditions (Table 2, entries 3 and 4). Using either ligand **1b** or PPh_3 no activity was observed at room temperature (Table 2, entries 5 and 6). It is interesting to note that when we replaced the tert-butyl group on the imino moiety with a 2,6-diisopropylphenyl group (ligand **1a**), we did observe some activity at room temperature (18% conversion, Table 2, entry 7). As already observed for Suzuki–Miyaura couplings using $Pd(OAc)_2/PPh_3$ as a catalyst precursor, KOH was the base of choice (Table 2, entries 8–14). Dioxane gave the best results among the solvents examined (Table 2, entries 14–19). It has been proposed that the transmetalation step in these reactions proceeds through the intermediacy of a complex containing an O-bonded boron anion when K_2CO_3 is used as the base in toluene [26]. Although we cannot exclude the possibility of a similar intermediate under our conditions (KOH and dioxane), a transmetalation step involving an organoborate $ArB(OH)_3^-$ is more likely to be operative in the presence of KOH [45–47].

After determining the optimal base and solvent, we used these conditions to evaluate the effect of the ligand (Table 3, entries 1–4). All of the iminophosphine ligands tested gave superior results as compared with PPh_3. As evident from Table 2 (entries 6 and 7) and Table 3 (entries 1–5), iminophosphine **1a**, which contains the most hindered group attached to the N-imino group, was the most effective ligand. The opposite effect was noted with η^2-(olefin)palladium(0)iminophosphine complexes. Higher reaction rates were observed when the substituent on the N-imino group was an aromatic group of low steric hindrance [26]. The apparent contradiction can be rationalized by considering the stability of the actual catalytic species proposed by Scrivanti et al. In both cases, coordinatively unsaturated and highly active (iminophosphine)Pd(0) complexes would be formed in the reductive elimination step, and this complex's oxidative addition of an aryl bromide would represent the start of a new catalytic cycle (Scheme 3). The presence of this coordinatively unsaturated species leads to the formation of metallic palladium particles. However, the coordination of an olefin to the (iminophosphine)Pd(0) complex prevents this decomposition pathway, and the coordination of the olefin to the palladium center is favored by less bulky substituents on the N-imino group [26,48]. In our case, no olefin ligand is present and the only way to prevent (or minimize) the decomposition pathway is to protect the palladium

Table 2
Effect of the different parameters on the Pd-catalyzed Suzuki–Miyaura cross-coupling reaction between 4-bromotoluene and phenylboronic acid[a].

Entry	Ligand	Solvent	Base	Temp (°C)	Time (h)	Conv (%)	Yield (%)[b]
1	PPh_3	Dioxane	CS_2CO_3	130	2	100	100
2	**1b**	Dioxane	CS_2CO_3	130	2	100	100
3	PPh_3	Dioxane	CS_2CO_3	50	2	44	38
4	**1b**	Dioxane	CS_2CO_3	50	2	96	95
5	PPh_3	Dioxane	CS_2CO_3	25	3	–	–
6	**1b**	Dioxane	CS_2CO_3	25	3	–	–
7	**1a**	Dioxane	CS_2CO_3	25	3	18	16
8	**1b**	Dioxane	CS_2CO_3	50	1	46	30
9	**1b**	Dioxane	CSF	50	1	30	29
10	**1b**	Dioxane	K_3PO_4	50	1	22	20
11	**1b**	Dioxane	K_3PO_4	50	1	22	20
12	**1b**	Dioxane	K_2CO_3	50	1	36	21
13	**1b**	Dioxane	NaOAc	50	1	13	10
14	**1b**	Dioxane	KOH	50	1	99	99
15	**1b**	DMA	KOH	50	1	74	50
16	**1b**	DMF	KOH	50	1	72	44
17	**1b**	EtOH	KOH	50	1	69	42
18	**1b**	MeOH/THF	KOH	50	1	65	36
18	**1b**	MeCN	KOH	50	1	23	7
19	**1b**	PhMe	KOH	50	1	72	14

[a] Reaction conditions: 4-bromotoluene (0.5 mmol), phenylboronic acid (0.75 mmol), base (1 mmol), $Pd(OAc)_2$ (1 mol%), **1a** or **1b** (1 mol%), PPh_3 (2 mol%), solvent (4 mL).
[b] Yields determined by GC.

Table 3
Effect of the ligand on Pd-catalyzed Suzuki–Miyaura cross-coupling reactions between 4-bromotoluene and phenylboronic acid[a].

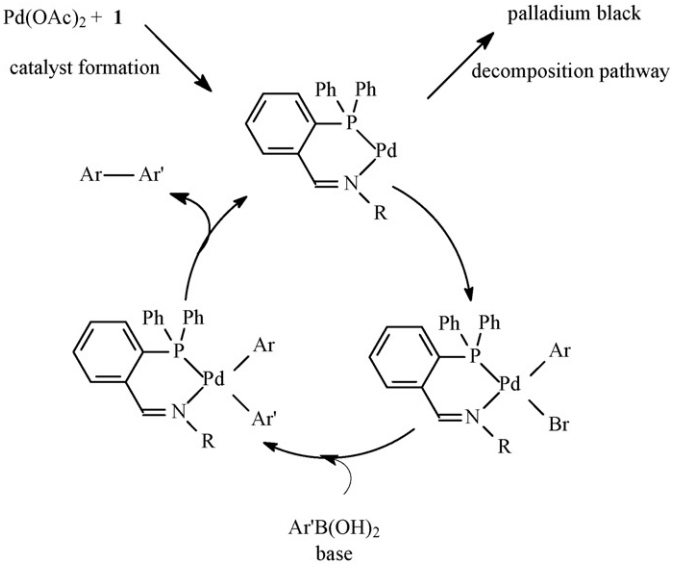
Entry	ArBr	Ligand	Pd (mol%)	Temp (°C)	Time (h)	Conv (%)	Yield (%)[b]
1	4-$MeOC_6H_4Br$	**1a**	1	50	1	100	100
2	4-$MeOC_6H_4Br$	**1b**	1	50	1	99	99
3	4-$MeOC_6H_4Br$	**1c**	1	50	1	91	87
4	4-$MeOC_6H_4Br$	PPh_3	1	50	1	66	53
5	4-AcC_6H_4Br	**1a**	1	25	16	100	100
6	4-AcC_6H_4Br	**1a**	0.1	25	16	10	10
7	4-AcC_6H_4Br	**1a**	0.2	50	16	100	100
8	4-AcC_6H_4Br	**1a**	0.1	50	16	82	80
9	4-AcC_6H_4Br	**1a**	0.02	50	16	19	17

[a] Reaction conditions: aryl halide (0.5 mmol), phenylboronic acid (0.75 mmol), KOH(1 mmol), $Pd(OAc)_2$:ligand = 1:1, dioxane (4 mL).
[b] Yields determined by GC.

coordination sites by using iminophosphines with hindered substituents.

After establishing the best solvent, base, and ligand for the reaction, we investigated the palladium loading required for low temperature reactions (Table 3, entries 6–10). Activated aryl bromides, such as 4-bromoacetophenone, can be coupled at room temperature by using 1 mol% Pd (Table 3, entry 5). When the temperature was increased to 50 °C a loading of 0.2 mol% Pd was sufficient to achieve complete conversion of the activated substrate 4-bromoacetophenone (Table 3, entry 5). Under the same conditions a loading of 1 mol% Pd was necessary to achieve complete conversion of the deactivated substrate 4-bromoanisole (Table 3, entry 1). It is important to note that TONs of up to 80,000 were obtained at higher temperatures (110 °C) using η^2-(olefin)palladium(0)iminophosphine complexes as catalyst precursors [26].

Coupling reactions involving several aryl halides and a variety of arylboronic acids were examined under the optimized conditions (Table 4). Aryl bromides and iodides containing *para* electron-withdrawing and electron-donating groups reacted to furnish the corresponding biaryl products in high yields (81–98% yield, Table 4, entries 1–4). A challenging issue in Suzuki–Miyaura coupling reactions is the difficulty of coupling sterically hindered substrates [5]. By increasing the temperature to 80 °C, a good yield of the biphenyl product could be obtained even with two ortho substituents on the aryl halide (Table 4, entries 5 and 6). Moderate yield and reactivity were observed with the aryl bromide containing two ortho substituents (Table 4, entries 5 and 6), but a tri-ortho-substituted biaryl was obtained in 89% yield (Table 4, entry 6). The reaction is more sensitive to steric hinderance from ortho substituents on the aryl boronic acid (Table 4, compare entries 5 and 7). Thus, the coupling reaction of 4-bromoacetophenone with 2,4,6-trimethylphenylboronic acid gave only 13% of the desired coupling product along with a 67% yield of the reduced product acetophenone (Table 4, entry 7). These results clearly indicate that in the classical Suzuki–Miyaura coupling mechanism the transmetalation step is much more sensitive to steric effects than the oxidative addition step. The catalytic system is also efficient for the coupling of benzyl chlorides and diarylmethanes were obtained in high yields (Table 4, entries 8–9). Even without a specific optimization for the benzyl chlorides coupling reaction, the results obtained using 1 mol% of Pd loading are similar to those described in the literature [15,49–53].



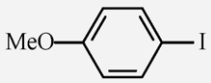
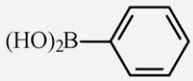
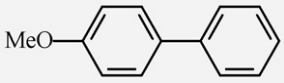
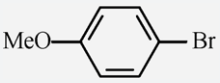
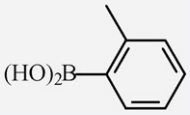
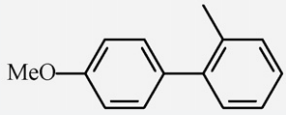
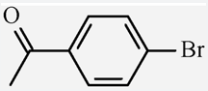
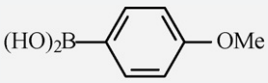
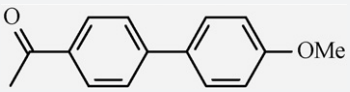
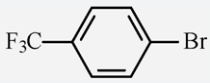
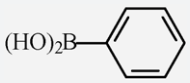
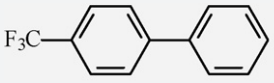
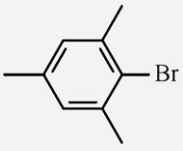
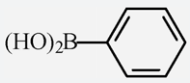
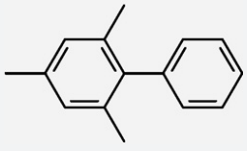
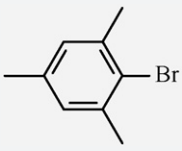
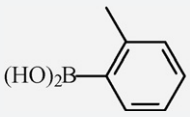
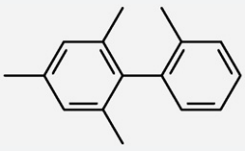
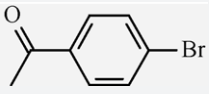
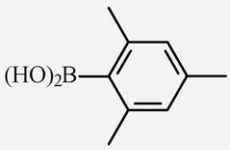
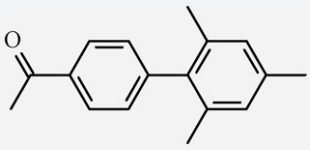
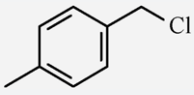
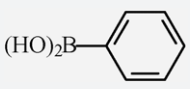
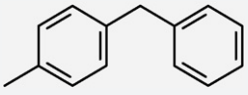
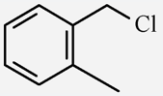
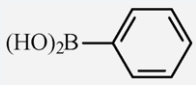
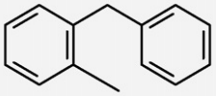
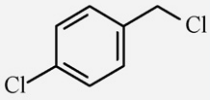
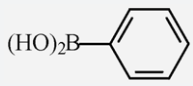
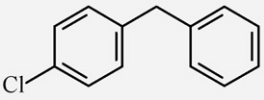
Scheme 3. Simplified catalytic cycle for Suzuki–Miyaura cross-coupling reactions.

3.3. Suzuki–Miyaura cross-coupling reaction: comparison of the preformed complexes 2 and 3 with the in situ generated catalyst, and poisoning tests

We have performed a comparison between the catalytic activity of the in situ generated system and the new preformed complexes **2** and **3**. At room temperature the activity of the catalyst generated in situ by combining $Pd(OAc)_2$ and 1 equiv. of iminophosphine **1a** is less than that of complex **2** (Table 5, entries 1 and 2). This result was expected since complex **2** is an intermediate in the catalytic cycle (Scheme 3), while coordination of the ligand and reduction of the Pd(II) species to a Pd(0) species are required to form the catalytically active species from the mixture of $Pd(OAc)_2$ + **1a**. Complete conversion was obtained after 2 h both for the mixture of $Pd(OAc)_2$ + **1a** and for complex **2** at 50 °C (Table 5, entries 4 and 5). Surprisingly, complex **3** was almost inactive at room temperature (Table 5, entry 3), and even at 50 °C the conversion was not complete after 2 h (Table 5, entries 6 and 7). These results indicate that the coordination of two bidentate ligands to the Pd center gives a very stable complex, which is therefore a less active catalyst. On the other hand, no significative differences were observed in the product coupling yield by premixing $Pd(OAc)_2$ and **1a** in dioxane prior to adding base, boronic acid and aryl halide (Table 5, entries 4 and 5).

Discerning between homogenous and heterogeneous Pd catalyst systems is not a trivial task [54,55]. For Suzuki–Miyaura reactions in the presence of the sulfur-containing palladacycle **4**, the addition of Hg immediately suppressed the catalytic activity. Quantitative poisoning experiments with CS_2 indicated that 0.375 equiv. of CS_2 were necessary to completely terminate the reaction, indicating that only part of the palladium added to the reaction is active as a catalyst [56]. Although we were not able to determine the nature of the ligand-free palladium catalyst (homogenous or heterogeneous), TEM analysis indicated the presence of palladium nanoparticles. While the addition of Hg to Heck reactions catalyzed by iminosphosphine–Pd(0) complexes at

Table 4
Pd-catalyzed Suzuki–Miyaura cross-coupling reaction between substituted haloarenes and phenylboronic acids using **1a** as ligand[a].

Entry	ArX	Ar′B(OH)$_2$	Temp (°C)	Coupling product (%)
1			50	 98
2			50	 93
3			30	 98
4			30	 81
5			80	 93
6			80	 89[b]
7			80	 13[c]
8			80	 85
9			80	 92
10			80	 87

[a] Reaction conditions: aryl or benzyl halide (1 mmol), arylboronic acid (1.5 mmol), KOH (2 mmol), Pd(Oac)$_2$ (1 mol%), **1a** (1 mol%), dioxane (4 mL), 16 h (reaction times are unoptimized).
[b] Yield determined by GC (89% conversion).
[c] A 67% yield of hydrodebrominated product (acetophenone) was isolated.

Table 5
Comparison of the reactivity of the catalyst formed from $Pd(OAc)_2$ + **1a** to complexes **2** and **3** in the Pd-catalyzed Suzuki–Miyaura cross-coupling reaction between 4-bromotoluene and phenylboronic acid[a].

Entry	Catalyst	Temp (°C)	Time (h)	Conv (%)	Yield (%)[b]
1	$Pd(Oac)_2$ + **1a**	25	2	37	36
2	**2**	25	2	85	83
3	**3**	25	2	2	2
4	$Pd(OAc)_2$ + **1a**	50	0.5	38	37
			2	100	100
5	$Pd(OAc)_2$ + **1a**[b]	50	0.5	40	38
			2	100	100
6	**2**	50	2	100	100
7	**3**	50	2	96	96

[a] Reaction conditions: 4-bromotoluene (0.5 mmol), phenylboronic acid (0.75 mmol), KOH (1 mmol), $Pd(OAc)_2$ and **1a**, **2**, or **3** (1 mol%), dioxane (4 mL), 2 h.
[b] Yields determined by GC. $Pd(OAc)_2$ and **1a** were premixed in dioxane and stirred at room temperature for 15 min prior to adding the substrates.

140 °C completely stopped the reactions, the addition of PPh_3 (0.05 or 0.1 equiv.) or of thiophenol (0.05 or 0.1 equiv.) had no effect [28]. For the $Pd(OAc)_2$ + **1a** mixture and complexes **2** and **3** we used Hg and CS_2 poisoning tests in order to determine if the actual catalyst was the molecular iminophosphine Pd complex or ligand-free colloidal palladium nanoparticles or clusters. We performed the Hg poisoning experiment in a coupling reaction between 4-bromoacetophenone and phenylboronic acid (1 mol% Pd, 2 equiv. KOH, dioxane, 50 °C). Under these conditions 40% conversion was achieved after 30 min, and then Hg (200 equiv.) was added. In all cases the reaction did not stop (~ 90% conversion), indicating that monometallic species (PdL) are the true active species rather than Pd nanoparticles or clusters particles [54,55,57]. It is important to mention that the ligand identity had a significant effect on catalyst efficiency (Table 2). We also used the Hg poisoning test in a coupling reaction between a deactivated aryl halide (4-bromotoluene) and phenylboronic acid. The reaction mixture was stirred at 50 °C for 30 min (22% conversion). Then Hg (0) (500 equiv. relative to $Pd(OAc)_2$) was added and the reaction mixture was stirred at 50 °C for 41 h affording 44% conversion. These results can be rationalized assuming that molecular palladium species containing the iminophosphine ligand are responsible for the catalytic activity. Hg(0) does not quench the reaction because these Pd(0) species are protected by the ligand. The fact that Hg(0) did not stop the reaction immediately but causes incomplete conversion can be explained by the ligand dissociation. The "naked' molecular palladium species formed will react with Hg(0) [55] decreasing the catalytic species concentration until complete deactivation. Therefore, we cannot exclude the possibility that phosphine-free complex or colloid are also active species for the catalytic reaction.

Quantitative poisoning experiments with CS_2 have been employed to determine the number of catalytically active metal atoms and provide evidence as to the nature of the catalyst (homogeneous or heterogeneous) [58,59]. We performed CS_2 poisoning experiments in coupling reactions between 4-bromoacetophenone and phenylboronic acid using the same conditions that were used in the Hg test. Under these conditions 40% conversion was achieved after 30 min. At which point, different amounts of CS_2 in dioxane were added (0, 0.5, 1, or 1.5 equiv. of CS_2) to different trials, and the reactions were analyzed by GC over 3 days. It was found that 1.5 equiv. of CS_2 were necessary to completely terminate the reaction, which also indicates that the catalyst is of a molecular nature [55].

Maitlis's filtration experiments were performed and the catalytic activity of the resulting solution measured [59,60]. The coupling reaction between 4-bromotoluene and phenylboronic acid reaction after a 25 % conversion and filtering the reaction through a sintered glass filter containg cellulose to remove the metal particles. We have found that the filtrate was catalytically active (56% conversion) and the no coupling product was obtained using the Pd rettained in the cellulose. These results also support the presence of a soluble catalyst (homogeneous catalysis).

4. Conclusions

In conclusion, the catalyst formed in situ by mixing $Pd(OAc)_2$ and an iminophosphine ligand is active in the Suzuki–Miyaura cross-coupling reaction. Aryl bromides, iodides, and benzyl chlorides give the corresponding coupling products in high yields at low temperatures (25–50 °C). Only hindered substrates required higher temperatures (80 °C). The iminophosphines that contain the most hindered groups attached to the N-imino group were the most effective ligands, probably due to the steric effect of the iminophosphine that prevents the catalyst's decomposition to inactive palladium black. New divalent Pd complexes containing iminophosphine ligands were obtained and compared with the in situ generated system. The relative activity of the catalysts was $[Pd(4\text{-}CH_3OC_6H_4)Br(P\hat{N})] > Pd(OAc)_2 + P\hat{N} > \{[C_6H_4CH(Me)_2St\text{-}Bu]Pd(P\hat{N})\}^+PF_6^-$. The decreased activity of the palladacycle containing the iminophosphine ligand can be correlated to the stabilization of the complex caused by having two bidentate ligands. Poisoning tests indicate that homogeneous molecular palladium species containing the iminophosphine ligand are responsible for the catalytic activity, or, to be more cautious, that it is at least a strongly contributing reaction pathway.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.molcata.2009.08.003.

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