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Suzuki cross-coupling reaction catalyzed by sulfur-containing palladacycles: Formation of palladium active species

Danilo Zim [1], 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

Air-stable cyclopalladated compounds derived from the ortho-metalation of benzylic *tert*-butyl thioethers efficiently promote C–C coupling reactions and were studied mechanistically in the Suzuki reaction. The catalytic reaction was monitored by ^{19}F NMR and GC–MS and the decomposition of the S-palladacycle was studied under stoichiometric conditions, showing that these palladacycles serve as a reservoir of zerovalent palladium species. The formation of these species is initiated by attack of the arylboronic acid on the palladacycle resulting in the formation of an arylated palladacycle. Thereafter, this species undergoes a reductive elimination to form the active Pd(0) species. As a minor pathway, the Pd(0) species could also be generated in a pathway involving a reduction process that leads to the decomposition of the palladacycle to Pd(0) affording the ortho hydrogenated thioether. Poisoning studies and TEM analysis indicated the presence of palladium nanoparticles. Competitive experiments showed that electron-withdrawing substituents on the aryl halide and electron-donating substituents on the arylboronic acid facilitated the reaction. They also provide evidence that the soluble species formed from the oxidative addition, that are active for Heck and Suzuki reactions, are the same species.

1. Introduction

The palladium-catalyzed Suzuki cross-coupling reaction is one of the most efficient methods for the construction of C_{aryl}—C_{aryl} bonds and has found widespread use in organic synthesis [1–4]. Palladacycles, where the ligand is in a position to coordinate to the metal center through both a metalated carbon and a donor atom (P, N, S), are one of the most investigated classes of catalyst precursors in particular due to their facile synthesis, thermal stability and possibility of modulating their steric and electronic properties [5–8]. Our group have obtained sulfur-containing palladacycles from the ortho-metalation of benzylic alkyl thioethers [9] (Scheme 1) and have shown that they are excellent catalyst precursors for C–C coupling reactions such as Heck [10], Suzuki [11] and homocoupling [12] processes. The palladacycles were evaluated for the Suzuki coupling reaction of the relatively deactivated 4-bromotoluene with phenylboronic acid. All palladacycles depicted in Scheme 1 were active but the catalytic activity depended on the palladacycle structure. The most efficient catalyst precursors present one *tert*-butyl thioether moiety bonded to the palladium atom (**1**, **3**, **4**, and **5**). Lower activities were observed with a MeS (**2**) moiety or with two *t*-BuS groups (**6**) ligated to the palladium atom. Moreover, no discernible influence in activity was observed with a change from chloro (**1**) to acetate (**4**) bridges, from methyl to hydrogen (**3**) in the R^1 position, and from a phenyl (**1**) to a naphthyl group (**5**) in the palladacycle. Electron-rich and -poor aryl bromides as well as electron-poor aryl chlorides were efficiently coupled in the presence of **1** to provide the corresponding biaryl products in excellent isolated yields (>90%). Moreover, palladacycle **1** promotes the Suzuki coupling even at room temperature although longer reactions times are necessary with a wide variety of functional groups tolerated (nitro, acetyl, cyano, etc.). In this work we wish to report our results regarding the nature of the active species involved in the Suzuki reaction promoted by these palladacycles.

2. Experimental

2.1. General methods

All catalytic reactions were carried out under an argon atmosphere in oven-dried resealable Schlenk tubes. Chemical were purchased from commercial sources, and were used without further purification. Palladacycle **1** was obtained using procedure described earlier [9]. Elemental analyses were performed by the Analytical Central Service of IQ-UFRGS. NMR spectra

* Corresponding author. Tel.: +55 51 33086303; fax: +55 51 33087304.
E-mail addresses: danilo.zim@br.rhodia.com (D. Zim), adriano.monteiro@iufrgs.br (A.L. Monteiro).
[1] Present address: Rhodia Poliamida e Especialidades—CPP.

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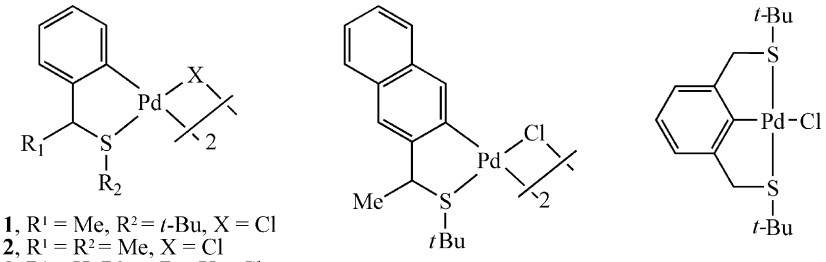
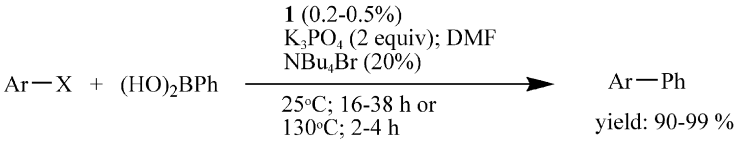


1, R¹ = Me, R² = *t*-Bu, X = Cl
2, R¹ = R² = Me, X = Cl
3, R¹ = H, R² = *t*-Bu, X = Cl
4, R¹ = Me, R² = *t*-Bu, X = OAc

5 **6**



X = Br or I, Ar = naphthyl or benzene substituted with Me, MeO, Ph, CF_3, Ac, CN, NO_2
X = Cl , Ar = benzene substituted with , Ac, CN, NO_2

Scheme 1. Palladacycles obtained from the ortho-metalation of benzylic alkyl thioethers and the Suzuki cross-coupling reaction.

were recorded on a Varian XL300 spectrometer. Infrared spectra were performed on a Bomem B-102 spectrometer. Mass spectra were obtained on a gas chromatograph/mass spectrometer (GC/MS) Shimadzu QP-5050 (EI, 70 eV). Gas chromatography (GC) analyses were performed on a Hewlett-Packard-5890 Gas Chromatograph with a flame ionization detector (FID) and 30 m capillary column with a dimethylpolysiloxane stationary phase.

2.2. Synthesis of palladacycle **9**

2.2.1. 1-(4′-Fluorophenyl)ethanol

To an ethanol (30 mL) solution of 4′-fluoroacetophenone (6.1 mL, 50 mmol) was added $NaBH_4$ (3.783 g, 100 mmol) and the mixture was stirred at room temperature for 1 h then warmed to 80 °C for 15 min. After the mixture was cooled to room temperature, the solvent was removed under reduced pressure and the mixture was diluted with ether (30 mL) and washed with water (3 × 10 mL), and then dried over $MgSO_4$. After filtration, the solvent was evaporated to give 1-(4′-fluorophenyl)ethanol as a colorless liquid (6.567 g, 95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.27 (m, 2H), 7.04–6.98 (m, 2H), 4.81 (q, J = 6.3 Hz, 1H), 2.90 (br, 1H), 1.43 (d, J = 6.3 Hz, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 162.3 (d, J = 243.4 Hz), 141.8 (d, J = 3 Hz), 127.4 (d, J = 7 Hz), 115.4 (d, J = 14 Hz), 69.8, 25.5. IR ν (cm^{-1}) 3362, 2975, 1605, 1509, 1222, 1157, 1085, 1014, 900, 836. GC–MS (EI, 70 eV) m/z (%) 140 (19, M), 125 (100), 97 (94), 96 (30), 95 (26), 77 (38), 51 (26), 43 (93).

2.2.2. 1-(1-tert-Butylsulfanylethyl)-4-fluorobenzene

A Schlenk flask was charged with 1-(4′-fluorophenyl)ethanol (2.800 g, 20 mmol), 2-methyl-2-propanethiol (2.25 mL, 20 mmol), ZnI_2 (2.394 g, 7.5 mmol), dichloromethane (80 mL), and the mixture was refluxed for 1 h. After cooling to room temperature, the mixture was washed with water (2 × 40 mL), and then dried over $MgSO_4$. After filtration, the solvent was evaporated and a Kugerloh distillation under reduced pressure (90 °C at 2 mmHg), afforded 1-(1-*tert*-butylsulfanylethyl)-4-fluorobenzene as an oil (1.49 g, 35%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.28 (m, 2H), 7.04–6.97 (m, 2H), 4.05 (q, J = 7.2 Hz, 1H), 1.55 (d, J = 7.2 Hz, 3H), 1.24 (s, 9H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 161.8 (d, J = 242.9 Hz), 142.6, 128.8 (d, J = 7.5 Hz), 115.5 (d, J = 22.6 Hz), 44.1, 42.0, 31.7, 25.7. GC–MS (EI, 70 eV) m/z (%) 212 (12, M^+), 123 (100, M^+-S*t*Bu), 103 (16), 101 (4), 103 (16), 77 (6), 59 (11), 57 (47).

2.2.3. Synthesis of palladacycle **9**

To a solution of palladium acetate (225 mg, 1 mmol) in acetic acid (30 mL) was added 1-(1-*tert*-butylsulfanylethyl)-4-fluorobenzene (234 mg, 1.1 mmol) at room temperature. The solution was stirred at 90 °C for 15 min. The brown solution thus obtained was evaporated to dryness and washed with hexanes (2 × 10 mL). The solid was dissolved in dichloromethane (50 mL), and the solution was filtered through a plug (5 cm) of alumina (grade I), and concentrated to ca. 1 mL. Addition of hexanes (50 mL) afforded a yellow solid, which was collected by filtration, washed with hexanes (2 × 10 mL), and dried under reduced pressure (151 mg, 40% yield based on Pd): Anal. Calcd for $C_{28}H_{38}F_2O_4S_2Pd_2$: C, 44.63%; H, 5.08%. Found: C, 44.44%; H, 4.98%. ^{1}H NMR (300 MHz, DMSO) δ 7.35 (br, d, J = 8.3 Hz, 1H), 6.94 (br, s, 1H), 6.71–6.69 (br, m, 1H), 4.31 (br, m, 1H), 3.34 (s, 3H), 1.58 (d, J = 7.2 Hz, 3H), 1.32 (s, 9H). IR (nujol) ν (cm^{-1}) 1574, 1458, 1443, 1397, 1252, 1229, 1186, 1159, 1112, 865, 811, 753.

2.3. Decomposition of palladacycle **1** under stoichiometric conditions

A mixture of palladacycle **1** (50 mg, 0.15 mmol), phenylboronic acid (27.5 mg, 0.225 mmol), PPh_3 (39.3 mg, 0.15 mmol), undecane (8 mg, internal standard) and K_3PO_4 (63.6 mg, 0.3 mmol) in DMF (10 mL) was heated at 50 °C for 20 h, then heated at 80 °C for 3 h.GC–MS and GC analysis showed 1-(1-*tert*-butylsulfanylethyl)-2-phenylbenzene (**7**) as the main product (92%) and (1-*tert*-butylsulfanylethyl)benzene (**8**) as a by-product. The mixture was then allowed to cool to room temperature, taken up in ether (20 mL) and washed with aqueous NaOH (1 M, 3 × 10 mL) and brine (3 × 10 mL) and then dried over $MgSO_4$. 1-(1-*tert*-Butylsulfanylethyl)-2-phenylbenzene (**7**) was isolated

by chromatography (32 mg, 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66–7.16 (m, 9H), 4.17 (q, J = 6.65 Hz, 1H), 1.59 (d, J = 6.87 Hz, 3H), 1.01 (s, 9H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 143.8, 141.3, 139.7, 129.7, 129.4, 128.1, 127.9, 127.8, 127.1, 126.2, 37.8, 31.3, 29.7, 25.9. IR (nujol) ν (cm^{-1}) 3022, 3059, 2963, 2923, 2862, 1597, 1449, 1478, 1364, 1163, 1044, 1009, 762, 746, 701. GC–MS (IE, 70 eV) m/z (%): 270 (8, M^+), 182(12), 181(100), 179(11), 178(8), 166(18), 164(33), 152(6), 57(16).

The same procedure was used for the decomposition of palladacycle **1** under stoichiometric conditions in the absence of PPh_3. GC–MS and GC analysis after 20 h at 80 °C showed the *ortho*-phenyl thioether **7** as the main product (70%) and the thioether (1-*tert*-butylsulfanylethyl)benzene **8** as a by-product (17%) [9]. GC–MS (EI, 70 eV) m/z (%): 194 (7, M+), 106 (7), 105 (100), 79 (6), 77 (12), 59 (6), 57 (27), 51 (7).

2.4. Suzuki coupling reaction of 4-trifluoromethylbromobenzene with phenylboronic acid promoted by palladacycle **9**

Under argon, a resealable NMR tube was charged with palladacyle **9** (1.4 mg, 0.0037), K_3PO_4 (118 mg, 0.55 mmol), phenylboronic acid (54.1 mg, 0.44 mmol), 4-trifluoromethylbromobenzene (83.5 mg, 0.37 mmol) and DMF (5 mL). A capillary tube (D_2O/CF_3COOH) was placed into the tube that was introduced into the NMR spectrometer and the reaction was followed by ^{19}F NMR at 50 °C for 15 h. After 15 h the mixture was analyzed by GC and GC–MS showing a 25% yield of the 4-trifluormethylbiphenyl coupling product by comparison with the authentic sample. Otherwise, GC–MS and GC analysis showed 1-(1-*tert*-butylsulfanylethyl)-4-fluoro-2-phenylbenzene [**10**: 47% yield based on **9**; GC–MS (EI, 70 eV) m/z (%) 288(7, M+), 200(16), 199(100), 184(18), 183(42), 179(18), 57(29), 41(44), 39(17)] and 1-(1-*tert*-butylsulfanylethyl)-4-fluorobenzene (13% based on **9**). The reaction mixture was then transferred to a resealable Schlenk flask and stirred for 3 h at 130 °C, the conversion being improved to 70%.

2.5. Hg(0) poisoning studies

An oven-dried resealable Schlenk flask was charged with 4-bromonitrobenzene (1 mmol), phenylboronic acid (183 mg, 1.5 mmol), K_3PO_4 (424.5 mg, 2 mmol), 0.5 mol% palladacycle **1** (1.7 mg), DMF (5 mL) and 100 equiv of Hg(0) (relative to **1**). The reaction mixture was stirred at 30 °C but no conversion was observed after 20 h. A similar reaction without Hg furnished the coupling product in quantitative yield after 24 h.

An oven-dried resealable Schlenk flask was charged with K_3PO_4 (424.5 mg, 2 mmol), phenylboronic acid (183 mg, 1.5 mmol), 4-bromoacetophenone (199 mg, 1 mmol), palladacycle **1** (1.7 mg, 0.005 mmol) and DMF (6 mL), and the mixture was stirred at 30 °C for 3.5 h (20% conversion as judged by GC). Then 100 equiv of Hg(0) (relative to 1) were added and conversion was followed by GC over 24 h showing that the reaction stopped at 20% conversion. Under the same free conditions the coupling of 4-bromoacetophenone gave complete conversion to the coupling product after 24 h.

2.6. CS_2 poisoning studies

An oven-dried resealable Schlenk flask was charged with palladacycle **1** (1.7 mg, 0.005 mmol), K_3PO_4 (424.5 mg, 2 mmol), phenylboronic acid (183 mg, 1.5 mmol), 4-bromoacetophenone (199 mg, 1 mmol) and DMF (6 mL), and the mixture was stirred at 25 °C for 2 h (18–22% conversion). A solution of CS_2 in DMF was then added (0, 0.25, 0.375, 0.5, 1, 2 equiv. of CS_2). The mixture was stirred at the desired temperature (25, 50 and 80 °C) and the conversion was followed by GC over 3 days.

2.7. Transmission electron microscopy analysis

The morphology and the electron diffraction (ED) of the obtained particles were carried out on a JEOL JEM-2010 equipped with an energy-dispersive X-ray spectroscopy (EDS) system operating at accelerating voltage of 200 kV. The sample for TEM was performed by withdrawing samples of the Suzuki reaction of 4-bromoacetophenone with phenylboronic acid (0.5 mol% of 1, 2 h, 80 °C, 66% conversion) by simply depositing the solution on carbon-coated copper grids. The histograms of the nanoparticles size distribution, assuming spherical shape, were obtained from the measurement of about 500 particles and were reproduced in different regions of the Cu grid, found in an arbitrarily chosen area of enlarged micrographs.

2.8. Typical experiment using Hammett parameters

2.8.1. Effect of the substituent on the aryl halide

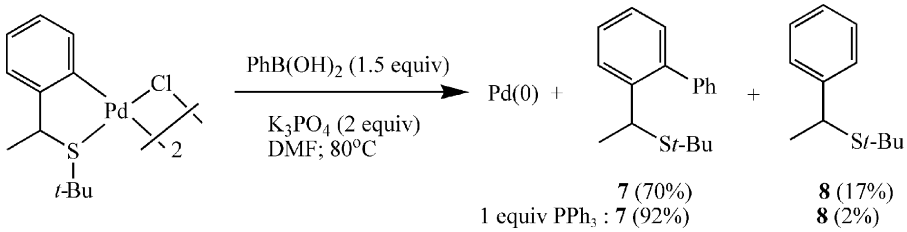
An oven-dried resealable Schlenk flask was evacuated and backfilled with argon and charged with K_3PO_4 (276 mg, 1.3 mmol), arylboronic acid (2 mmol), aryl halides (0.02 mmol of each one), palladacycle **1** (1 μmol), and DMF (1.5 mL). The reaction mixture was stirred at 80 °C and the reaction profile was monitored by CG.

2.8.2. Effect of the substituent on the arylboronic acid

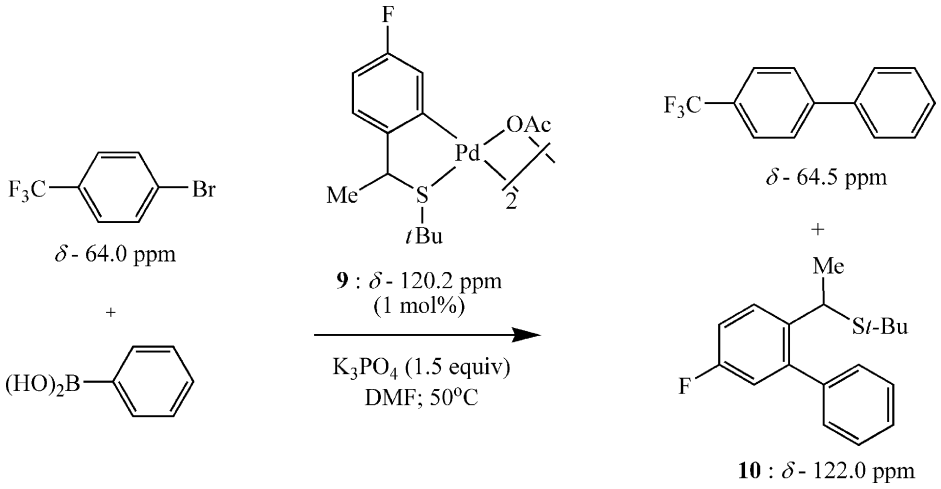
An oven-dried resealable Schlenk flask was evacuated and backfilled with argon and charged with K_3PO_4 (276 mg, 1.3 mmol), aryl halide (20 mmol), aryl boronic acids (0.25 mmol of each one), palladacycle **1** (1 μmol), and DMF (1.5 mL). The reaction mixture was stirred at 80 °C and the reaction profile was monitored by CG.

3. Results and discussion

Despite the importance of the Pd-catalyzed C–C coupling process, the nature of the true active species in most cases is not well-established. A comprehensive review of Pd-catalyzed Heck and Suzuki reactions with an eye toward identifying the nature of the actual active form of palladium was recently published and, it has been demonstrated that, regardless of the precatalyst used, a Pd(0)–Pd(II) cycle is involved [13]. In several reports on the use of known and new palladacycles as catalyst precursors for Heck coupling reactions, it has been stated that palladacycles serve as a reservoir of catalytically active Pd(0) which might be palladium nanoparticles or low-coordinated palladium zero species[6,7,13–15]. Bedford et al. have shown that under stoichiometric conditions phosphinite based palladacycles [16] and phosphine adducts of N- and S-based palladacycles [17,18] in the presence of arylboronic acid undergo a transmetalation/reductive elimination process to generate Pd(0) species and the orthoarylated ligand. This process was also observed for the reaction of a benzodiazepine-containing palladacycle with excess 3-tolylboronic acid [19]. We have since investigated whether a similar process occurs with sulphur-containing-palladacycles not only under stoichiometric conditions but also under catalytic conditions. Therefore, we first examined the reaction of **1** with phenylboronic acid in the presence of K_3PO_4 and DMF as solvent (Scheme 2). Even at room temperature, the formation of palladium black was observed within a few minutes. GC–MS and GC analysis after 20 h at 80 °C showed the *ortho*-phenyl thioether 1-(1-*tert*-butylsulfanylethyl)-2-phenylbenzene (**7**) as the main product (70%) and the thioether (1-*tert*-butylsulfanylethyl)benzene (**8**) as a by-product (17%). In order to see whether a phosphine ligand



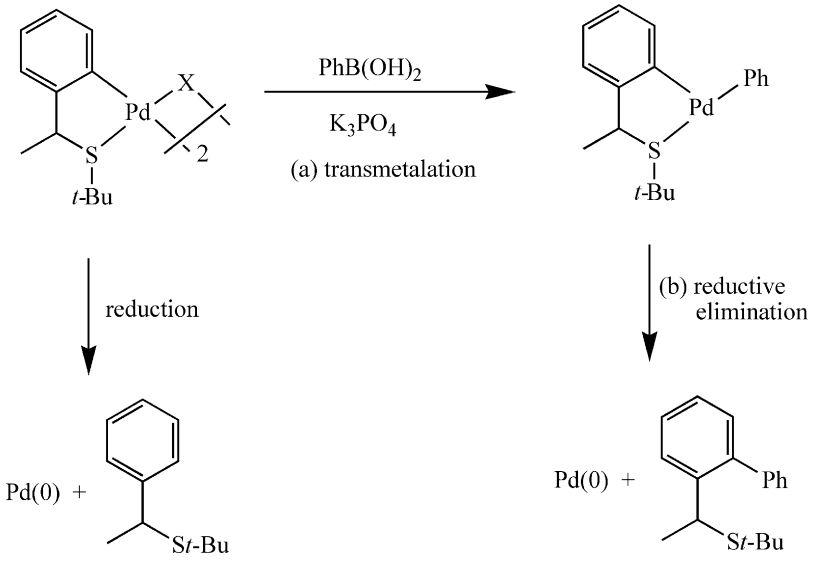
Scheme 2. Decomposition of palladacycle **1** under stoichiometric conditions.



Scheme 3. Suzuki coupling reaction monitored by ^{19}F NMR and GC–MS.

suppresses or decreases the formation of this by-product the same reaction was carried out in the presence of triphenylphosphine. The yield of **7** was improved to 92% and **8** was still formed but in a lower yield (2%).

As proposed for phosphine adduct palladacycles [16–18], the generation of Pd(0) species from the palladacycle **1** may be explained by a process involving a nucleophilic attack of the boronate species at the metal center followed by a reductive elimination. However, we cannot exclude that the Pd(0) species can be also generated in a pathway involving a reduction process to generate the organic thioether **8**. Similar reduced organic products have been observed in the stoichiometric studies of the Pd-catalyzed Stille [20], amination [20] and cycloamidation [21] reactions. For instance, the stoichiometric reaction of



Scheme 4. Postulated mechanism for the formation of active Pd(0) catalysts from the palladacycle **1**.

Herrmann's palladacycle with Me_3SnPh gave the *ortho*-arylated P(*o*-Tol)$_2$(C_6H_4-*o*-CH_2Ph) (73%) and the reduced P(*o*-Tol)$_3$ (14%) [20]. The thioethers **7** and **8** formed under stoichiometric conditions were also observed under catalytic conditions. Thus the coupling reaction of 4-bromotoluene with phenylboronic acid catalyzed by 2 mol% of **1** at 80 °C was followed by GC and GC–MS analysis. The thioethers **7** and **8** were formed in 50 and 15% yields based on **1**, respectively.

In order to gain more evidence for the palladacycle activation under catalytic conditions, we have synthesized a new palladacycle containing a fluorine substituent on the aromatic ring and followed its reactivity by ^{19}F NMR. The preparation of the sulfur-containing palladacycle **9** was accomplished using a similar procedure described earlier [9]. Thus, the reaction of 1-(1-*tert*-butylsulfanylethyl)-4-fluorobenzene with palladium acetate in acetic acid at 90 °C affords the dimeric acetato-bridged palladacycle **9** in moderate yield (45%). This air- and water-stable orange compound has the same activity for the Suzuki coupling reaction of aryl halides as the other sulfur-containing palladacycles.

The coupling of 4-trifluormethylbromobenzene with phenylboronic acid promoted by palladacycle **9** was monitored by ^{19}F NMR (Scheme 3) [22]. The 4-trifluormethylbiphenyl coupling product was detected within the first half hour (δ −64.9 ppm). During this time the signal for the palladacycle became broader and after 1 h a new broad signal appeared at −122.0 ppm. As the resonance for **9** decreased, the resonance at −122.0 ppm increased and the signal for the palladacycle **9** disappeared after 4.5 h. The only change in the ^{19}F NMR spectra after this time was in the relative intensity of the coupling product trifluormethylbiphenyl. After 15 h the mixture was analyzed by GC showing a 25% yield of the 4-trifluormethylbiphenyl coupling product. Otherwise, GC–MS and GC analysis showed the *ortho*-phenyl thioether **10** formed from the coupling reaction between palladacycle **9** and phenylboronic acid (47% yield based on **9**). Again a reduced product, the *tert*-butyl 1-(4′-fluorophenyl)ethyl sulphide, corresponding to the starting ligand, and analogous to the thioether **8**, was observed by GC–MS, but due to the small concentration (13% based on **9**) it was not detected by ^{19}F NMR (δ −119.5 ppm). When the reaction mixture was then transferred to a resealable Schlenk flask and stirred for 3 h at 130 °C, the conversion was improved to 70%, showing that the catalytically active species retained activity after the palladacycle was completely consumed. These results clearly indicate that in our system palladacycles also serve as a reservoir of catalytic species. On the basis of this spectroscopic information above, we propose an activation mechanism that is initiated by the attack of the arylboronic acid on palladium resulting in the formation of the aryl palladacycle that undergoes a reductive elimination to form the active Pd(0) species (Scheme 4, path A). However, we cannot exclude that the Pd(0) species could also be generated in a pathway involving a reduction process that regenerates the organic ligand (Scheme 4, path B).

The active Pd(0) species generated from the sulphur-containing palladacycle could be a soluble palladium complex or colloidal species. Several techniques have been used to assess the homogeneity or heterogeneity of catalyst system [13,23]. For instance, Hg poisoning tests have been used to analyze the possibilities for Heck coupling reactions involving palladacycle species [24–28]. We have performed poisoning experiments for the Suzuki reaction. In the first reaction, we used 4-bromonitrobenzene, phenylboronic acid, K_3PO_4, 0.5 mol% palladacycle **1**, and 100 equiv of Hg(0) (relative to **1**). The reaction mixture was stirred at 30 °C but no conversion was observed after 20 h. A similar reaction without Hg furnished the coupling product in quantitative yield. Under the same Hg-free conditions the coupling of 4-bromoacethophenone gave also complete conversion to the coupling product. However, when Hg was added before complete conversion (∼20%), the reaction terminated. Although a positive response to a mercury poisoning test alone cannot be taken as a confirmation of the presence of heterogeneous catalytically active palladium species in this reaction, it is reliable evidence for a catalytic cycle involving a Pd(0) intermediate.

Quantitative poisoning experiments with CS_2 have been employed to determine the number of active metal atoms and provide evidence of the nature of the catalyst (homogeneous or heterogeneous) [29]. This method was used to evaluate the turnover number for a palladium-containing perovskite catalyst system in the Suzuki reaction [30]. We performed the CS_2 poisoning experiment for the coupling of 4-bromoacetophenone with phenylboronic acid (1 mol% **1**, 2 equivs K_3PO_4, DMF). In order to

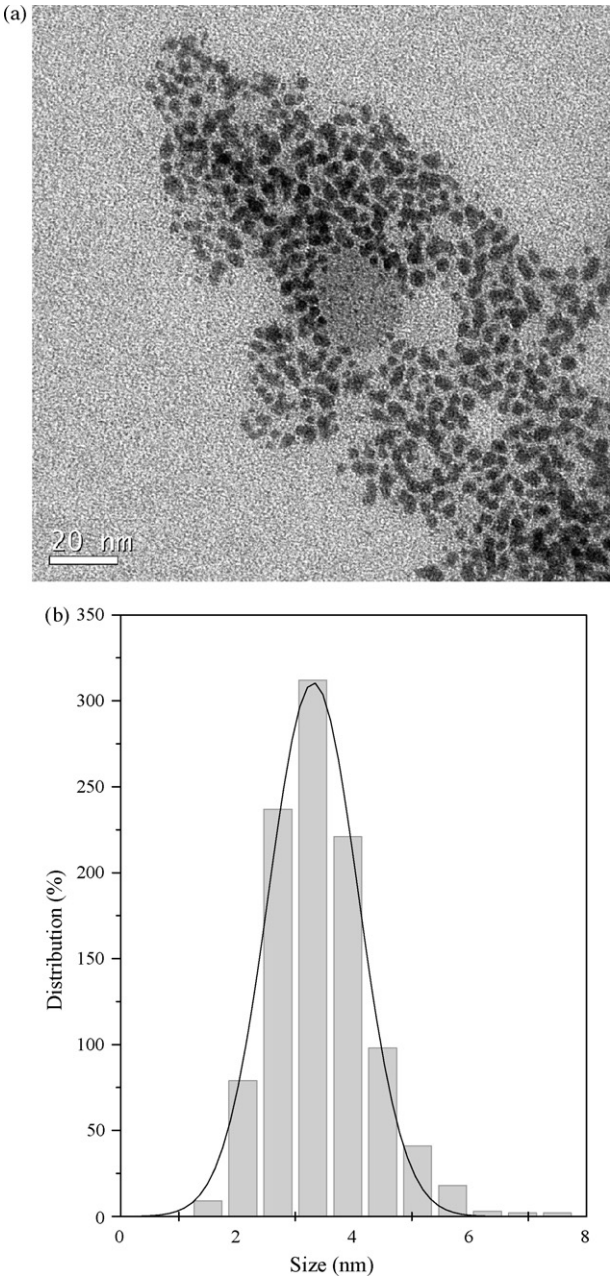


Fig. 1. (a) Transmission electron microscopy images of a typical sample of palladium nanoparticles formed during Suzuki reaction using **1** as catalyst precursor. (b) Histogram illustrating the particle size distribution (512 particles count) that can be reasonably well fitted by a Gaussian curve; the mean diameter of the Pd (0) particles was estimated to be around 3.3 nm ± 0.8.

prevent ligand dissociation the experiments were carried out a low temperature (25 °C). Under these conditions a 20% conversion was achieved after 2 h. For each experiment CS_2 in DMF was added (0, 0.25, 0.375, 0.5, 1, and 2 equiv. of CS_2) and the reactions were analyzed by GC over 3 days. It was found that 0.375 equiv of CS_2 were necessary for completely terminating the reaction, indicating that only part of the palladium added is active as a catalyst. Similar behavior was found for the Heck reaction with PCP pincer palladium complexes [28]. One limitation of the use of small molecule poison for establishing the stoichiometry is the fact that many catalyst are thought to slowly release active palladium which can deactivate with time, making the total active species count dynamic. We performed the same CS_2 poisoning experiment in a higher conversion (40%) and temperature (50 °C) and the result was the same (0.375 equiv of CS_2). More CS_2 (0.5 equiv) was necessary for stopping the reaction at higher temperatures (80 °C) and conversions (70%). However, at this temperature the active site counting using CS_2 may be overestimated since CS_2 does not bind irreversibly at higher temperatures (>50 °C). Other limitations of the use of small molecule poison for establishing the stoichiometry in this case is that we may have a mixture of nanoparticle and soluble active palladium species, and also for molecular species with labile solvent ligands more poison molecules may be needed. Nevertheless, the poison necessary for stopping the reaction is neither characteristic of a complete molecular system (≥1 equiv) nor comparable with heterogeneous catalyts («1.0 equiv.) [23], suggesting problably the presence of both palladium nanoparticles and molecular palladium species.

In addition, if the total active species is dynamic, the ratio release of active molecular palladium/deactivation remains constant under the conditions studied as proposed by de Vries for the Heck reaction [31]. Indeed, transmission electron microscopy analysis of aliquots taken from the Suzuki coupling between 4-bromoacethophenone and phenylboronic acid under the same conditions as those used for the CS_2 poisoning experiment (0.5 mol% of **1**, DMF, 80 °C, 66% conversion) confirmed the presence of palladium nanoparticles 3 nm in average size (Fig. 1). Several methods of synthesis of palladium nanoparticles and their application for the C—C bond formation have been reported [32–34]. Otherwise generation of palladium nanoparticles during the catalytic coupling reaction was also detected or proposed [35]. For instance, Pd nanoparticles were observed during Heck coupling reaction using oxime palladacycles as catalyst [8]. Whether the nanoparticles are preformed or generated in situ the evidence suggests that the Pd species leached from the nanoparticles surface are the true catalysts [35–37]. The mechanism proposed for the Heck reaction [13,14,38] involving Pd atom escape from the palladium nanoparticles by a oxidative addition generating discrete Pd(II) species in solution was also proposed to the Suzuki reaction [39]. Alternatively, the Pd(II) complexes can be formed by oxidative addition to Pd(0) atoms that have already leached into solution [37]. Based on our results and the considerations above we propose that sulfur containing palladacycles decompose to Pd(0), and an equilibrium between palladium nanoparticles and the actual active species (Pd(0) atoms or Pd(II) ions) exists during the catalytic reaction.

In order to gain some insight into the oxidative addition and transmetallation steps we studied the reaction of different aryl halides and arylboronic acids catalyzed by palladacycle **1**. A plot of the relative reactivity of substituted aryl bromides (Fig. 2a) and aryl iodides (Fig. 2b) against the σ Hammett parameter gave a value of $\rho = 2.34$ and 0.65 for the coupling with phenylboronic acid, respectively. However a different effect was observed for the substituents on the arylboronic acids. Approximately the same linear correlation was observed for the competitive reaction of bromobenzene ($\rho = -0.68$, Fig. 2c) and iodobenzene ($\rho = -0.68$, Fig. 2d) with substituted arylboronic acids.

Dupont et al. have proposed a kinetic model for a competitive Heck reaction involving two differently substituted aryl halides where the reaction starts with the two aryl halides competing for the same catalytically active palladium zero species for the formation of the respective oxidative addition products and the catalytic cycle proceeds with their corresponding rate constants [24]. This

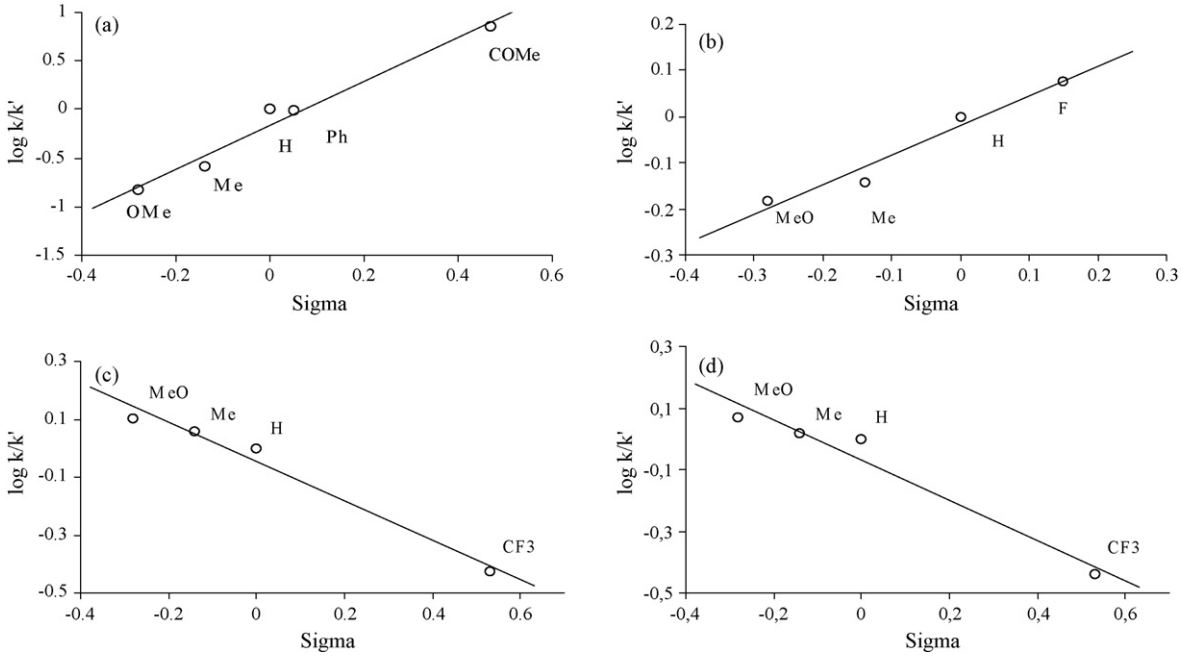


Fig. 2. Hammett correlation for the Suzuk reaction at 80 °C in DMF promoted by palladacycle **1**: (a) effects of substituents on aryl bromides ($\rho = 2.3$; $R = 0.93$); (b) effects of substituents on aryl iodides ($\rho = 0.65$; $R = 0.96$); (c) effects of substituents on aryl boronic acids ($\rho = -0.68$; $R = 0.98$); (d) effects of substituents on aryl boronic acids ($\rho = -0.65$; $R = 0.96$).

kinetic model has shown that, whatever the rate limiting step, in a competitive Heck reaction the changes in the relative reactivity involving different aryl halides is strictly bound to the changes in the rate constant for the oxidative addition step. Experimentally, they performed a Hammett correlation for the Heck competitive reaction between bromoarenes and *n*-butylacrylate and, found that the four different palladacycles evaluated gave the same ρ value (2.4–2.5), indicating that the same active species are formed in the oxidative addition step. Interestingly, we have found a very close ρ value (2.3 for Ar–Br, Fig. 2a) for the Suzuki reaction promoted by palladacycle **1**. $PdCl_2(SEt_2)_2$ is the simplest sulfur-containing palladium complex that mediate the Suzuki cross-coupling reaction of aryl bromides at room temperature [40]. We have studied the reactivity of different aryl bromides for the Suzuki coupling promoted by this simple sulfur-containing Pd divalent complex. A plot of the relative reactivity of substituted aryl bromides against the σ Hammett parameter also gave a linear correlation with the same value of ρ (2.3). These results provide evidence that palladacycle **1** and $PdCl_2(SEt_2)_2$ form the same active species in the oxidative addition step in Suzuki reactions and that these species are equivalent to those for the Heck reaction promoted by palladacycles. The soluble Pd(II) intermediate can be formed by oxidative addition, either on the nanoparticle surface or through reaction with Pd(0) atoms that have already leached into solution. The positive slope shows that the rate of the oxidative addition increases with the presence of electron-withdrawing substituents on the aryl halide and that consequently the transition state for the oxidative addition is stabilized for groups that remove electronic density from the C_{ipso} of the aryl bromide. Since the halogen–carbon bond is weaker for the aryl iodides, the influence of the substituents is less pronounced and a ρ value of 0.7 was obtained (Fig. 2b); this value is lower than those obtained for the same palladacycle for the Heck reaction ($\rho = 1.8$) [24].

Compared to the oxidative addition and reductive elimination steps, little is known about the transmetalation process [41,42]. Miyaura et al. have isolated and characterized the cationic intermediate $[Pd(Ph)(dppe)(PPh_3)](BF_4)$ by transmetalation reaction of $[Pd(dppe)(PhCN)_2](BF_4)_2$ and $PhB(OH)_2$ in the presence of PPh_3 [41]. The reaction of a series of para-substituted arylboronic acids with this intermediate showed a slightly negative ρ value (-0.54), demonstrating an electronic effect that was accelerated by the electron-donating substituents. It is worthwhile mentioning that we have observed a very similar effect of substituents for arylboronic acids under catalytic conditions for both bromobenzene ($\rho = -0.68$) and iodobenzene ($\rho = -0.65$). Similar correlations were obtained for the Suzuki cross-coupling of arylboronic acids with vinyl bromide ($\rho = -1.26$) [43] and with (*E*)-bromostilbene ($\rho = -0.71$) [44] using $Pd(OAc)_2/PPh_3$ as catalyst precursor. As proposed for oxidative addition, in this case also the changes in the relative reactivity involving different arylboronic acids are strictly related to the changes in the rate constant for the elementary step involving the boron species (transmetalation). The negative slope indicates that the rate of the reaction increases with the presence of electron-donating substituents on the arylboronic acid and this behaviour could be explained by the fact that electron-donating groups enhance the nucleophilicity of the C_{ipso} of the arylboronic acid or arylboronate anion for arylation of an aryl-Pd-Br complex.

4. Conclusion

In summary, we have demonstrated that sulfur-containing palladacycles served as a reservoir of zerovalent palladium species. The formation of these species is initiated by attack of the arylboronic acid on the palladacycle resulting in the formation of an arylated palladacycle. This undergoes a reductive elimination to form the active Pd(0) species. As a minor process, the Pd(0) species can be generated in a pathway involving a reduction process that leads to the decomposition of the palladacycle to Pd(0) affording the ortho hydrogenated thioether. Poisoning studies and transmission electron microscopy analysis results indicated the presence of small palladium nanoparticles that release the soluble actual catalytic active Pd species. Competitive experiments showed that electron-withdrawing substituents on the aryl halide and electron-donating substituents on the arylboronic acid facilitate the reaction. They also provide evidence that sulfur-containing palladacycle and $PdCl_2(SEt_2)_2$ form the same active species in the oxidative addition step in Suzuki reactions and that these species are equivalent to those for the Heck reaction using the same palladacycle. The soluble Pd(II) intermediate can be formed by oxidative addition, either on the nanoparticle surface or through reaction with Pd(0) atoms that have already leached into solution.

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