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Microwave-promoted Suzuki–Miyaura cross-coupling of aryl halides with phenylboronic acid under aerobic conditions catalyzed by a new palladium complex with a thiosemicarbazone ligand

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Abstract—A new air- and moisture-stable palladium complex with salicylaldehyde *N*(4)-hexamethyleneiminylthiosemicarbazone has been synthesized. According to its crystal structure, the metal is bonded to 2 equiv monoanionic thiosemicarbazone moieties in a *N*,*S*-bidentate fashion, forming two five-membered chelate rings, while additional intramolecular bonds stabilize the structure. In contrast to other palladium complexes with thiosemicarbazones, this complex was inactive towards the Suzuki–Miyaura coupling under aerobic conditions, by conventional heating. On the other hand, microwave irradiation promoted the effective catalytic activity of the complex for the coupling of aryl bromides and chlorides with phenylboronic acid in DMF/H_2O, under aerobic conditions, with turnover numbers of up to 37,000.

Palladium-catalyzed carbon–carbon bond formation is a versatile tool in organic synthesis.[1] Suzuki–Miyaura coupling of aryl halides with organoboronic acids has been recognized as one of the most important palladium-catalyzed cross-coupling reactions,[1,2] and represents one of the most widely used processes for the synthesis of biaryls, which are important intermediates in organic synthesis and recurring features in natural products.[3] The development of new ligands for coupling reactions is currently topical, and a large number of phosphorus ligands[4] as well as phosphine-free ligands[5] for the Suzuki–Miyaura reaction under conventional heating have been reported. Since catalysis under phosphine-free conditions is a challenge of high importance, recently, for the first time, we used thiosemicarbazones as catalyst precursors for palladium-catalyzed coupling reactions.[6] These multidentate air- and moisture-stable ligands efficiently catalyzed the Mizoroki–Heck and the Suzuki–Miyaura reactions under aerobic conditions.

Microwave-promoted synthesis is currently an area of increasing interest, and the combination of transition-metal homogeneous catalysis and microwave irradiation is likely to have an impact on modern chemistry.[7,8] The first microwave-promoted Suzuki–Miyaura couplings were reported in 1996,[9] and since then a large number of investigations have focused on this subject.[10] We report here the synthesis and crystal structure of a palladium complex with salicylaldehyde *N*(4)-hexamethyleneiminylthiosemicarbazone, and the evaluation of this complex

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Keywords: Thiosemicarbazone; Suzuki–Miyaura cross-coupling; Microwave; Phosphine-free ligand; C–C bond formation; Homogeneous catalysis.

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in the Suzuki–Miyaura reaction of aryl halides with phenylboronic acid, in air with conventional heating or microwave activation.

The synthesis of the palladium complex **5** is outlined in Scheme 1.[11] Salicylaldehyde *N*(4)-hexamethyleneiminyl-thiosemicarbazone (H_2Sal4hexim) **4** was prepared by the reaction of salicylaldehyde **1** with *N*(4)-methyl-*N*(4)-phenylthiosemicarbazide **2**[12] and hexamethyleneimine **3**. Synthesis of the complex [Pd(HSal4hexim)$_2$] **5** was achieved by reacting K_2PdCl_4 with 2 equiv of the ligand **4** in H_2O/MeOH and in the pH range of 9.0–9.5. The microanalytical data were consistent with the formula $C_{28}H_{36}N_6O_2PdS_2$ and the structure [Pd(HSal4hexim)$_2$]. This formula is indicated also by the ESI MS spectrum of **5** ($M = 659$). The significant IR bands in **5** are close in energy to those found in other palladium complexes with thiosemicarbazones.[6] The band at 1613 cm^{-1} in the IR spectrum of **4** is assigned to C=N. In complex **5**, the co-ordination of the azomethine nitrogen to palladium is indicated by a shift to lower frequency (1603 cm^{-1}) of the C=N band compared to that of the free ligand. A band at 441 cm^{-1} in the far-IR spectrum of **5** is assignable to Pd–N stretching. Co-ordination via the thione sulfur is revealed by a shift of the C=S band (791 cm^{-1}) in the free ligand **4** to lower frequency (754 cm^{-1}) in complex **5**, and also by the presence of a band assignable to Pd–S at 388 cm^{-1}.

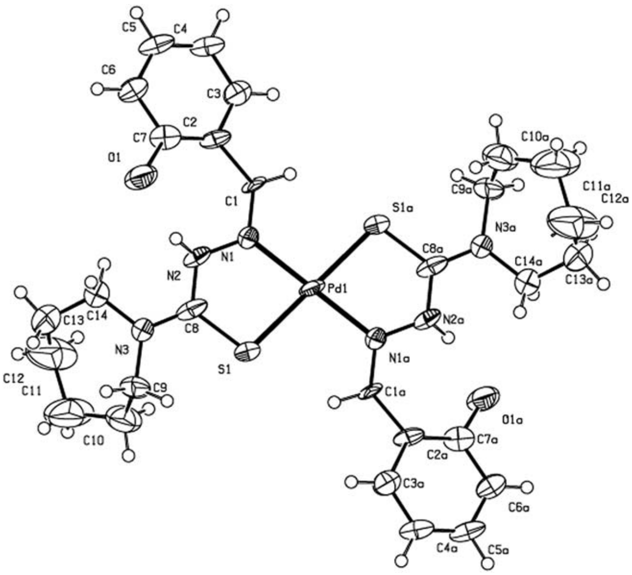
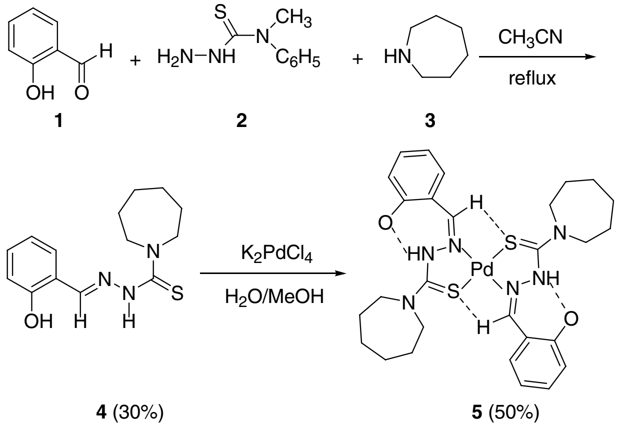


Figure 1. ORTEP drawing of palladium complex **5**.

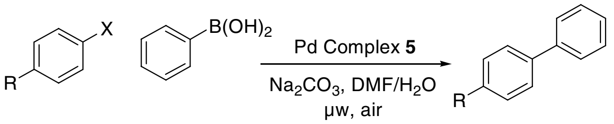
Recrystallization of complex **5** from a minimum volume of DMF yielded orange plates suitable for single crystal X-ray analysis. The atom numbering scheme and molecular structure with thermal ellipsoids is shown in Figure 1.[13] The palladium(II) atom is in a square planar environment surrounded by two *trans* sulfur and two *trans* nitrogen atoms. The monoanionic ligands HSal4hexim are equivalent and are co-ordinated to palladium in a bidentate fashion via the azomethine nitrogen N(1) and the sulfur atom, forming two five-membered chelate rings. The structure determination shows that the co-ordinated ligands exist in the thione form. The negative charge of the monoanionic ligand is delocalized over the thiosemicarbazone moiety as we can see from the bond distances on the thiosemicarbazone moiety. The C–S distance of 1.741(15) Å is intermediate between those of single and double bonds (1.82 and 1.56 Å, respectively), showing the partial double bond character. The N–N bond distance of 1.375(18) Å is shorter than 1.44 Å, accepted as typical for a single N–N bond, in accordance with similar thiosemicarbazones.[14] The imine N(1)–C(1) distance of 1.327(15) Å and both thioamide C–N distances (N(2)–C(8), 1.324(19) Å; N(3)–C(8), 1.34(2) Å) indicate an increased single bond character, in accordance with a molecule protonated on N(2). There is an intramolecular hydrogen bond between the protonated N(2) and the deprotonated O(1) [N–H···O, 2.591 Å, 141°] and another intramolecular bond between the formyl hydrogen atom and the co-ordinated sulfur atom [C(1)–H···S, 3.246(16) Å, 133°].



Scheme 1.

Initial catalytic studies with the complex **5** were performed on the Suzuki–Miyaura coupling of bromobenzene with phenylboronic acid with conventional heating, in air. The coupling was achieved at 100 °C for 24 h by a 1:1000 catalyst/bromobenzene molar ratio, using a variety of bases (Na_2CO_3, K_2CO_3, KO^{t}Bu) and solvents (toluene, DMSO, acetone, dioxane) in the presence or absence of water. Although, no palladium black was observed, unfortunately, all attempts led to very discouraging results, as the work-up procedure gave the starting materials and no coupling product. These results are in contrast with our catalytic studies under aerobic conditions by using other palladium complexes with thiosemicarbazone ligands.[6] An explanation may lie in the structure of **5**: the metal is bonded to two thiosemicarbazone moieties by the presence of four intramolecular bonds (N(2)–H···O, C(1)–H···S), and perhaps, this results in an inhibition of the addition of the aryl halide to the metal during the catalytic cycle.

The reaction was then performed with microwave irradiation by mixing bromobenzene, a stock solution of complex **5** (Pd/PhBr ratio of 1:1000) in DMF, phenylboronic acid and Na_2CO_3 as base (Scheme 2, Table 1).[15] All reactions were performed without exclusion of air.



Scheme 2.

Table 1. Microwave-promoted Suzuki–Miyaura cross-coupling of aryl halides with phenylboronic acid catalyzed by palladium complex **5**, in air

Entry	ArX (X; R)	ArX/Pd ratio	T (°C)	Time (min)	GC Yield (%)	TON[a]
1	Br; H	1000	100	60	74	740
2[b]	Br; H	1000	100	60	24	240
3	Br; H	1000	130	60	85	850
4	Br; H	1000	150	45	70	700
5[b]	Br; H	1000	150	45	36	360
6	Br; H	1000	157	15	56	560
7	Br; NO_2	100,000	100	60	37	37,000
8	Cl; NO_2	100,000	155	60	25	25,000

Reaction conditions: ArX (1.0 mmol), $PhB(OH)_2$ (1.5 mmol), Na_2CO_3 (2.0 mmol), H_2O (1.7 mmol), Pd complex in DMF (1 mM or 0.01 mM, 1 mL).

[a] TON: turnover number (fraction of product × substrate/catalyst ratio).

[b] H_2O was not added.

Addition of a small amount of water (close to 1 equiv with respect to the substrates) to the reaction mixture enhanced the activity of the catalyst (compare yields in entries 1–2 and 4–5), and for that reason, most experiments were performed in the presence of water.[8f,16] The coupling proceeded in a good yield (74%) at 100 °C within 60 min (entry 1). For the activated 1-bromo-4-nitrobenzene, the coupling was performed at 100 °C with a 1:100,000 catalyst:aryl halide molar ratio, leading to a TON of 37,000, while no unsubstituted biphenyl was detected in GC and GC–MS analysis of the reaction mixture, indicating the absence of homo coupling of phenylboronic acid (entry 7). The corresponding aryl chloride led to a TON of 25,000 at 155 °C (entry 8). The reaction of bromobenzene with phenylboronic acid was performed again with conventional heating, in DMF as solvent without exclusion of air, using identical conditions (amounts of materials, temperature, reaction time) as those described in entries 1, 3, 4, 6 of Table 1. However, no coupling product was detected by GC or GC–MS analysis of the reaction mixture. Also, no coupling product was observed even after 24 h at 100 °C with conventional heating. This observation clearly underlines, under these conditions, the intervention of important non-purely thermal specific MW effects. They are evidently connected to the involvement of highly polar species and intermediates.[8a]

In summary, we have synthesized and characterized an easily accessible palladium complex with salicylaldehyde *N*(4)-hexamethyleneiminylthiosemicarbazone. According to its crystal structure, deprotonation from the alcohol function takes place, and 2 equiv monoanionic thiosemicarbazone moities are co-ordinated to palladium in a bidentate fashion via the azomethine nitrogen and the sulfur atom, forming two five-membered chelate rings. An intramolecular hydrogen bond between the protonated nitrogen and the phenoxy oxygen, and another intramolecular bond between the formyl hydrogen atom and the co-ordinated sulfur atom stabilize the structure. In contrast to other palladium complexes with thiosemicarbazone ligands, recently reported by us,[6] the present complex was inactive towards Suzuki–Miyaura coupling under aerobic conditions, by using conventional heating. On the other hand, a microwave irradiation promoted the effective catalytic activity of the complex for this coupling, under strictly similar conditions with those used under conventional heating. These results lead us to propose that specific microwave effects rather than thermal effects are responsible for the acceleration of this reaction.[8a] The microwave-promoted cross-coupling reaction by palladium complexes with thiosemicarbazones provides a convenient approach compared to existing methods that require an inert atmosphere due to the air-sensitive nature of other catalysts.

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11. *H_2Sal4hexim* **4**: Salicylaldehyde **(1)** (0.53 mL, 5 mmol), *N*(4)-methyl-*N*(4)-phenylthiosemicarbazide **(2)**[12] (0.905 g, 5 mmol) and hexamethyleneimine **(3)** (0.56 mL, 5 mmol) in MeCN (5 mL) were stirred under reflux for 15 min, and then the reaction mixture was allowed to settle in the refrigerator overnight. A bright yellow powder was isolated by filtration, washed with cold MeCN and dried in vacuo under silica gel at 40–50 °C for 4 h, yielding **4** (0.417 g, 30%), mp 155 °C. IR (KBr): ν 3315, 1613 (C=N), 955 (N–N), 791 cm^{-1} (C=S); ^{1}H NMR ($CDCl_3$): δ 12.10 (s, 1H), 8.54 (s, 1H), 7.34 (d, $J = 7.4$ Hz, 1H), 7.29 (s, 1H), 6.88 (t, $J = 7.5$ Hz, 2H), 3.88 (br s, 4H), 1.75 (s, 4H), 1.50 (s, 4H). Anal. Calcd for $C_{14}H_{19}N_3OS$: C, 60.6; H, 6.9; N, 15.2; S, 11.6. Found: C, 60.3; H, 6.7; N, 15.3; S, 11.7. *[Pd(HSal4hexim)$_2$]* **5**: H_2Sal4hexim **4** (0.191 g, 0.69 mmol) in methanol (5 mL) was added to a solution of K_2PdCl_4 (0.108 g, 0.33 mmol) in distilled water (4 mL), and the pH of the solution was adjusted to 9.0–9.5 by the addition of 1 N NH_4OH. The reaction mixture was stirred for 24 h at room temperature at constant pH, and then was allowed to settle in the refrigerator for 1 day. An orange powder was filtered off, washed with cold methanol and ether, dried in vacuo over silica gel, and then was redried at 70 °C in vacuo over P_4O_{10} for 2 h, yielding **5** (0.109 g, 50%), mp 261 °C. IR (KBr): ν 3448, 1603 (C=N), 754 cm^{-1} (C=S); far-IR (PE): ν 441 (Pd–N), 388 cm^{-1} (Pd–S); ^{1}H NMR ($CDCl_3$): δ 7.62 (s, 1H), 7.35 (t, $J = 7.4$ Hz, 1H), 7.16 (t, $J = 7.6$ Hz, 1H), 6.83–6.89 (m, 2H), 3.91 (br s, 4H), 1.75 (s, 4H), 1.50 (s, 4H); ESI MS: *m*/*z* 659 (M). Anal. Calcd for $C_{28}H_{36}N_6O_2PdS_2$: C, 51.0; H, 5.5; N, 12.7; Pd, 16.1; S, 9.7. Found: C, 51.2; H, 5.6; N, 12.2; Pd, 16.0; S, 9.6.
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13. Crystallographic data for the structure of **5** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 297691. Crystal data for **5**: intensity data were collected on a Rigaku AFC6S diffractometer with graphite monochromated Mo-Kα radiation ($\lambda = 0.71069$ Å) at 296 K, using the $\omega - 2\theta$ technique to a maximum 2θ of 55°. $C_{28}H_{36}N_6O_2PdS_2$, $M = 659.2$, Monoclinic, Space group $P21/n$ (No. 14), $a = 14.043(5)$ Å, $b = 5.622(6)$ Å, $c = 18.054(5)$ Å, $\alpha = 90.02(4)°$, $\beta = 91.73(3)°$, $\gamma = 89.95(5)°$, $V = 1424.6(15)$ Å^3, $Z = 4$, $d_{\text{calcd}} = 1.537\ \text{g/cm}^3$, 3425 reflections measured, 3293 reflections $[I > 2\sigma(I)]$ were used in all calculations, $R = 0.0737$, $R_w = 0.2670$. All hydrogen atoms were located in their calculated positions (C–H 0.93–0.97 Å) and refined using a riding model, except hydrogen atom N(2)H which were located by difference maps and refined isotropically.
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15. *General experimental procedure for the microwave-promoted Suzuki–Miyaura coupling:* All reactions were carried out with a CEM Discover LabMate 300W single mode Microwave instrument. Reaction vessels were special glass tubes with self-sealing septa fitted with needle pressure sensors. Temperature control and measurements were carried out via an infrared temperature feedback system positioned below the reaction vessel and magnetic stirring was provided to assure complete mixing of the reactants. The 10 mL reaction vessels were charged in air with aryl halide (1.0 mmol), phenylboronic acid (0.183 g, 1.5 mmol), Na_2CO_3 (0.212 g, 2.0 mmol), distilled water (30 μL, 1.7 mmol), and a stock solution of complex **5** in DMF (1 or 0.01 mM, 1 mL, 0.001 or 0.00001 mmol, respectively). The reaction vessel was submitted for the appropriate time to microwave irradiation in the cavity,

where power was self-adjusted to maintain the preselected temperature. After the reaction, the mixture was cooled rapidly to room temperature and worked up by addition of water and extraction with dichloromethane. The organic phase was washed with brine, dried over Na_2SO_4, filtered, passed through Celite and analyzed by GC and GC–MS.

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