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Suzuki–Miyaura cross-coupling reaction of aryl bromides and chlorides with phenylboronic acid under aerobic conditions catalyzed by palladium complexes with thiosemicarbazone ligands

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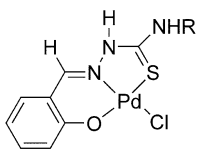
Abstract—For the first time, palladium complexes with salicylaldehyde thiosemicarbazones were applied as catalyst precursors to the Suzuki–Miyaura reaction. These air and moisture stable phosphine-free systems efficiently catalyze the cross-coupling of aryl bromides and chlorides (from electron rich to electron poor) with phenylboronic acid in DMF/H_2O at 100 °C for 24 h, using Na_2CO_3 as base, without addition of free ligand or any promoting additive, and under aerobic conditions no significant homo-coupling of phenylboronic acid to unsubstituted biphenyl was observed.

Palladium homogeneous catalysis is a versatile tool for carbon–carbon bond formation in organic synthesis.[1] The coupling of aryl halides with organoboronic acids, a procedure known as the Suzuki–Miyaura reaction, is one of the most important palladium-catalyzed cross-coupling reactions of both academic and industrial interest.[1–3] This reaction represents one of the most widely used processes for the synthesis of biaryls, which are important intermediates in organic synthesis and recurring functional groups in natural products.[4] Since phosphorus ligands are often water- and air-sensitive, catalysis under phosphine-free conditions is a challenge of high importance, and a number of phosphine-free ligands for the Suzuki–Miyaura reaction have been reported,[3j–p] some of which were successfully applied to this reaction under aerobic conditions.[3o,3p] In our attempts to evaluate phosphine-free systems in palladium catalysis, salicylaldehyde thiosemicarbazones were chosen for this purpose (see Fig. 1). These multidentate ligands with five potential co-ordination sites (three N, one O and one S) offer certain advantages, since it is known for transition–metal complexes, that an additional co-ordination site in the ligand as a stabilizing group during the course of a metal-mediated reaction can improve the catalytic efficiency of the complex.[5]

Recently, for the first time, we used thiosemicarbazones as catalyst precursors for palladium-catalyzed coupling reactions.[6] Palladium complex **1** [Pd(HSal4NHEt)Cl], the co-ordination mode of which was determined by spectroscopic and X-ray analysis, efficiently catalyzes the Heck reaction of aryl bromides with styrene, and for some substrates, even in air.[6] Within the present work, we also synthesized the analogous complex **2** [Pd(HSal4NH_2)Cl], in which, the terminal amino group



1: R = Et
2: R = H

Figure 1.

Keywords: Thiosemicarbazone; Phosphine-free ligand; Palladium complex; Suzuki–Miyaura cross-coupling; C–C bond formation; Homogeneous catalysis.
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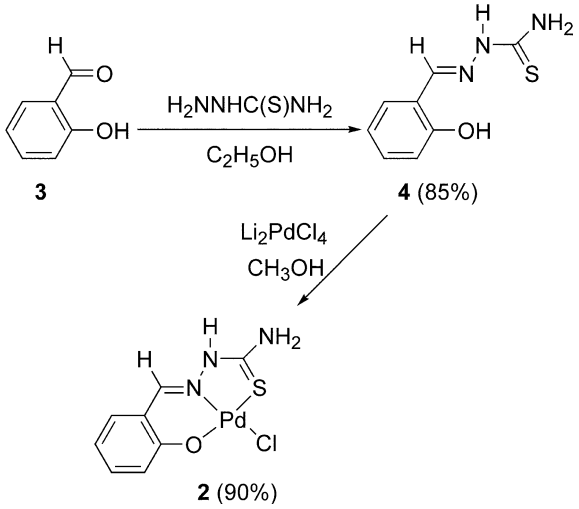
of the thiosemicarbazone is unsubstituted. Both complexes were applied to the Suzuki–Miyaura reaction of aryl bromides and chlorides with phenylboronic acid, under aerobic conditions. To our knowledge, this paper represents the first study concerning the evaluation of thiosemicarbazone ligands in the Suzuki–Miyaura reaction.

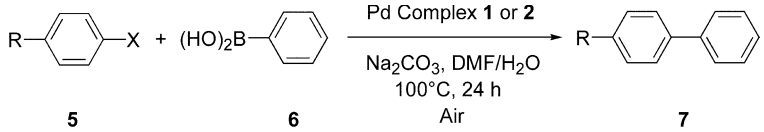
The synthetic sequence for the preparation of complex **2** was in accordance to that previously reported for the synthesis of **1**[6] (Scheme 1).[7] Salicylaldehyde thiosemicarbazone ($H_2Sal4NH_2$) **4**[8] was prepared by treatment of salicylaldehyde **3** with thiosemicarbazide in ethanol. The synthesis of complex **2** was achieved by reaction of ligand **4** with Li_2PdCl_4, prepared in situ from $PdCl_2$ and LiCl. The microanalytical data were consistent with the formula $C_8H_8ClN_3OPdS$, which indicates the structure [Pd(HSal4NH$_2$)Cl].

The co-ordination mode in complex **2** was determined by spectroscopic analysis, and it was found to be identical with that in complex **1**. The ligand is bound to palladium in a tridentate fashion via the azomethine nitrogen N(1), the sulfur atom and the phenoxy oxygen, forming one six- and one five-membered chelate ring. The significant IR bands in **2** are close in energy to those found in other palladium complexes with tridentate co-ordination.[6] The bands at 1617 and 1602 cm^{-1} in the IR spectrum of **4** were assigned to C=N. In complex **2**, the co-ordination of the azomethine nitrogen to palladium is indicated by the C=N band, which is shifted to lower frequency by 20 cm^{-1} compared to that of the free ligand. Additionally, the band at 454 cm^{-1} in the FAR-IR spectrum of **2** was assigned to Pd–N. Co-ordination via the thione sulfur is indicated by the shift of the C=S band (829 cm^{-1}) in the free ligand **4** to lower frequency in complex **2** (814 cm^{-1}), and also by the presence of a band assignable to Pd–S at 342 cm^{-1}. The phenolic oxygen, on loss of the OH proton occupies the third co-ordination site. A band at 383 cm^{-1} in the FAR-IR spectrum of **2** was assigned to Pd–O and the strong band at 312 cm^{-1} was attributed to Pd–Cl. In the ^{1}H NMR spectrum of **4**, the signal of the phenolic proton at 11.35 ppm was consistent with the presence of a hydrogen bonding isomer (OH–N). In the ^{1}H NMR spectrum of **2**, this signal was absent due to deprotonation and complex formation. In the ^{13}C NMR spectrum of complex **2**, deshielding of C–O and C–N(1) was observed, which should be related to the electrophilicity of palladium. A σ-charge donation from the *O* and *N* donor atoms to the palladium centre removes electron density from the ligand and produces this deshielding, which attenuates at positions remote from the metal. However π-back bonding from the palladium to the thione sulfur atom occurs causing an upfield shift of the C=S resonance.[9]



Scheme 1.

Complexes **1** and **2**, as a stock solution in DMF, were applied to the Suzuki–Miyaura reaction of phenylboronic acid with some representative aryl bromides and chlorides at 100 °C for 24 h, using Na_2CO_3 as base, without addition of free ligand or any promoting additive (Scheme 2, Table 1).[10] All reactions were performed in air. Addition of a small amount of water (close to one equivalent with respect to the substrates) to the reaction mixture enhances the activity of the catalyst (compare conversions in entries 3 and 4), and for that reason, catalysis was performed in the presence of water. It is worth noting that the catalysts seem to be air stable at 100 °C, and no palladium black was observed. It is also important to mention that homocoupling of phenylboronic acid to give unsubstituted biphenyl was negligible, as was obvious in GC and GC–MS analysis of the reaction mixtures resulting from the coupling of 4-substituted aryl halides. The reaction was first performed using a 1:1000 catalyst:aryl halide molar ratio. As expected, the catalytic activity depended on the halide, while electron-withdrawing groups on the aryl ring increased the reaction rate. For the deactivated 4-bromoanisole and the non-activated bromobenzene, the reaction proceeded with conversions ranging from 40% to 71%. For the activated 1-bromo-4-nitrobenzene and 4-bromobenzonitrile the conversions were usually about 80% or higher. For these substrates, the reaction was also performed with a 1:100,000 catalyst:aryl halide molar ratio, leading to TONs of up to 49,000, but with lower conversions. The use of aryl chlorides as substrates remains the goal in cross-coupling reactions due to their inexpensive cost and convenient availability,



Scheme 2.

Table 1. Suzuki–Miyaura cross-coupling of aryl halides with phenylboronic acid catalyzed by palladium complexes **1** or **2**, in air

Entry	Catalyst	ArX (X; R)	ArX/Pd ratio	Conversion[a] (%)	TON
1	**1**	Br; OMe	1000	40	400
2	**2**	Br; OMe	1000	53	530
3	**1**	Br; H	1000	71	710
4[b]	**1**	Br; H	1000	51	510
5	**2**	Br; H	1000	71	710
6	**1**	Br; CN	1000	78	780
7	**2**	Br; CN	1000	88	880
8	**1**	Br; CN	100,000	13	13,000
9	**2**	Br; CN	100,000	39	39,000
10	**1**	Br; NO_2	1000	79	790
11	**2**	Br; NO_2	1000	83	830
12	**1**	Br; NO_2	100,000	31	31,000
13	**2**	Br; NO_2	100,000	49	49,000
14	**1**	Cl; H	1000	30	300
15	**2**	Cl; H	1000	26	260
16	**1**	Cl; NO_2	1000	36	360
17	**2**	Cl; NO_2	1000	37	370

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), 100 °C, 24 h.

[a] Conversion to coupled product, based on aryl halide (GC, decane as internal standard).

[b] H_2O was not added.

but unfortunately, the oxidative addition in these cases is difficult due to the comparatively high C–Cl bond strength. In spite of this difficulty, complexes **1** and **2** were applied to the cross-coupling of phenylboronic acid with chlorobenzene and 1-chloro-4-nitrobenzene, in air, under the above-mentioned conditions, yielding the corresponding biaryls with TONs of up to 370.

In conclusion, we have shown that easily accessible palladium complexes with salicylaldehyde thiosemicarbazone ligands can serve as efficient catalysts for the Suzuki–Miyaura cross-coupling of aryl bromides and chlorides with phenylboronic acid under mild reaction conditions. Although the activity is not as high as some other palladium systems, these phosphine-free catalysts offer the advantage of the successful coupling of aryl halides and the synthesis of biaryls under aerobic conditions. This first study of the application of thiosemicarbazones to the Suzuki–Miyaura reaction provides promising results. The development of chiral analogous air stable ligands for asymmetric catalysis is currently in progress.

Acknowledgements

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References and notes

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7. Analytical data. $H_2Sal4NH_2$ **4**: mp 210 °C. IR (KBr): ν 3320 (OH), 3173, 3133 (NH), 1617, 1602 (C=N), 829 cm^{-1} (C=S); ^1H NMR (DMSO-d_6): δ 11.35 (s, 1H), 9.85 (s, 1H), 8.37 (s, 1H), 8.07 (s, 1H), 7.89 (d, J = 8.4 Hz, 2H), 7.19 (t, J = 8.4 Hz, 1H), 6.85 (d, J = 7.3 Hz, 1H), 6.81 (t, J = 7.4 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ 177.7, 156.4, 139.8, 131.1, 126.6, 120.3, 118.3, 116.1. Anal. Calcd for $C_8H_9N_3OS$: C, 49.2; H, 4.6; N, 21.5; S, 16.4%. Found: C, 49.0; H, 4.8; N, 21.3; S, 16.3%. [Pd(HSal4NH_2)Cl] **2**: mp > 300 °C. IR (KBr): ν 3207, 3183 (NH), 1600, 1589 (C=N), 814 cm^{-1} (C=S); FAR-IR (PE): ν 454 (Pd–N),

383 (Pd–O), 342 (Pd–S), 312 (Pd–Cl); ^{1}H NMR (DMSO-d_6): δ 8.13 (s, 1H), 7.35 (d, J = 8.0 Hz, 2H), 7.28 (t, J = 8.7 Hz, 1H), 6.80 (d, J = 8.5 Hz, 1H), 6.57 (t, J = 7.9 Hz, 1H). ^{13}C NMR (DMSO-d_6): δ 174.6, 162.7, 147.4, 134.3, 134.2, 120.2, 116.6, 114.5. Anal. Calcd for $C_8H_8ClN_3OPdS$: C, 28.6; H, 2.4; Cl, 10.6; N, 12.5; Pd, 31.7; S, 9.5%. Found: C, 28.4; H, 2.4; Cl, 10.8; N, 12.3; Pd, 31.6; S, 9.7%.

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10. *General experimental procedure for the Suzuki–Miyaura coupling*: A round bottom flask equipped with a reflux condenser, was 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), a stock solution of complex **1** or **2** in DMF (1 or 0.01 mM, 1 mL, 0.001 or 0.00001 mmol, respectively), and decane (0.08 mL, 0.4 mmol) as internal standard. The mixture was stirred in a preheated 100 °C oil bath for 24 h, and then allowed to cool to room temperature. After 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. All the biaryls prepared are known compounds.[3g]