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Carbohydrate derived thiosemicarbazone and semicarbazone palladium complexes: homogeneous catalyst for C–C cross coupling reactions

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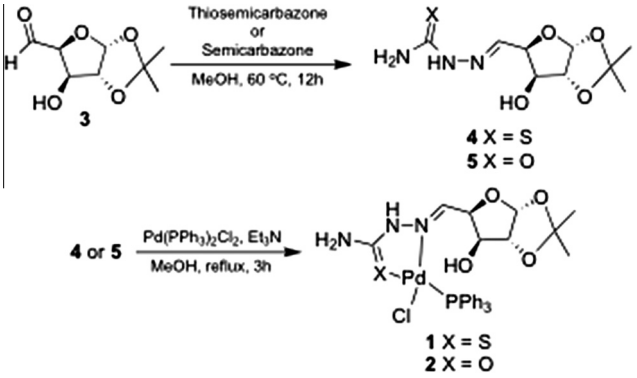
ABSTRACT

Palladium complexes of carbohydrate derived thiosemicarbazone and semicarbazone were used as catalysts for Suzuki and Sonogashira cross coupling reactions at ambient temperature. The catalysts were active after 5 cycles. Activation of 4-chlorotoluene has been achieved with 0.1% catalyst loading at ambient temperature with TON of 970 in 4 h.

Transition metal complexes of thiosemicarbazones and semicarbazones attract great interest for their biological applications as antimicrobial, antibacterial, and antitumor agents.[1] Possibilities of different binding modes of thiosemicarbazone and semicarbazone ligands open up scopes for interesting studies with transition metal complex formation.[2] Among them, palladium metals are of great importance owing to their famous catalytic activities for various C–C cross coupling reactions. For example, Suzuki–Miyaura cross coupling between aryl halide and aryl boronic acid is one of the most extensively used C–C bond formation reactions.[3] For obvious reasons aryl bromides and iodides undergo activation in a much faster rate than their chloride counterparts. However, since aryl chlorides are readily available and cheap, they can make the industrial application more economically viable. The use of aryl chlorides for Suzuki–Miyaura cross coupling reaction came only in late 90's[4] and only a few examples are in the literature till date.[5,6] Moreover, room temperature activation of aryl chlorides with low catalyst loading still remains a quest.

Herein we report two palladium(II) complexes with carbohydrate derived thiosemicarbazone and semicarbazone ligands. The known sugar aldehyde **3**[7] was treated with either thiosemicarbazide or semicarbazide in dry methanol at 60 °C to furnish the corresponding thiosemicarbazone (**4**) and semicarbazone (**5**) ligands respectively (Scheme 1).

Reaction of the ligands **4** and **5** with $Pd(PPh_3)_2Cl_2$ in refluxing methanol in the presence of Et_3N resulted in a color change from yellow to bright orange. The products thus formed were isolated by column chromatography using CH_2Cl_2/EtOAc (4:1) as eluent. The pure complexes **1** and **2** were characterized by mass and NMR spectroscopy which revealed the presence of a triphenyl phosphine and chlorine attached to the central palladium. The complexes **1** and **2** were crystallized from MeOH/CH_3CN (1:1)



Scheme 1. Synthesis of the palladium complexes **1** and **2**.

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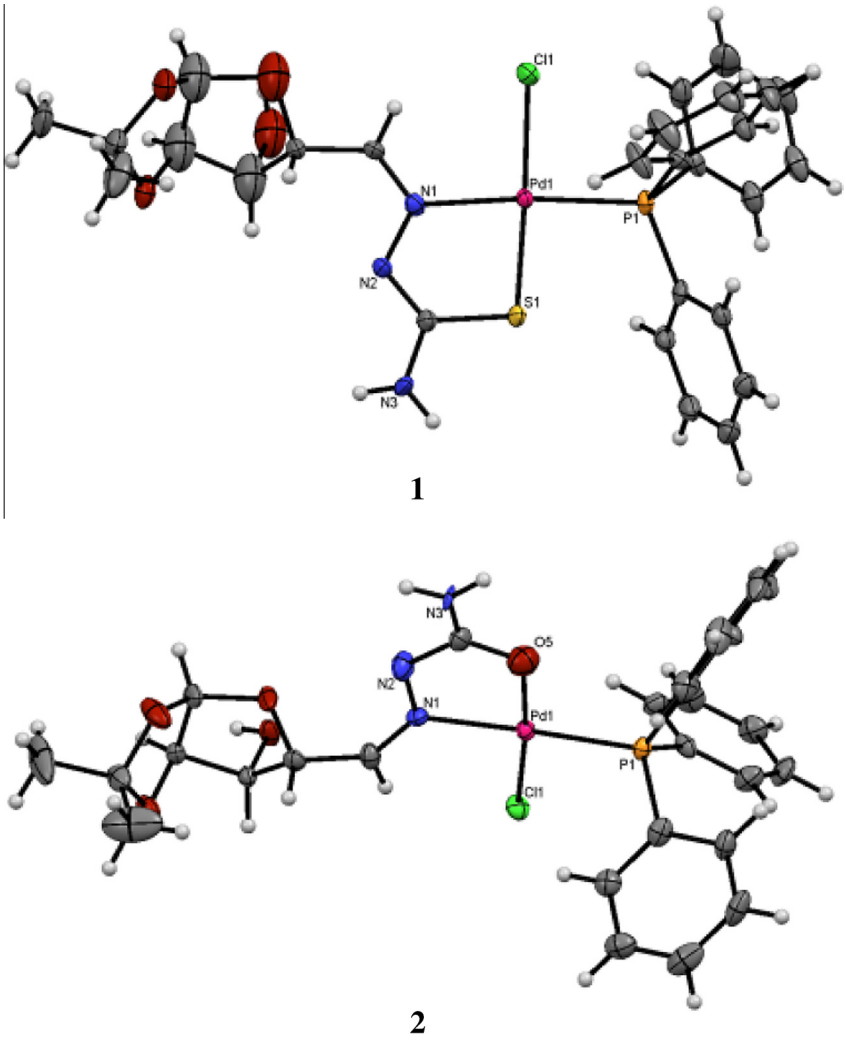


Figure 1. ORTEP diagram of complexes **1** and **2** with 50% probability of the thermal ellipsoids.[a]CCDC numbers for the crystals **1** and **2** are 904793 and 904792, respectively.

and CH_2Cl_2/CH_3CN (1:1) respectively. The single crystal X-ray diffraction clearly showed the attachment of the thiosemicarbazone moiety to the central palladium through S1 and N1 in complex **1**. Other two sites of the central palladium are occupied by a PPh_3 and a Cl. Similarly, in the semicarbazone complex **2**, the semicarbazone moiety of the ligand is attached through N1 and O5. The geometry around palladium was square planar in both complexes **1** and **2** (Fig. 1).

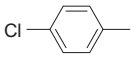
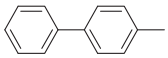
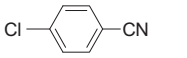
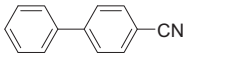
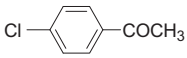
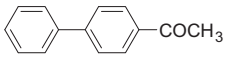
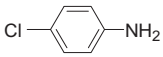
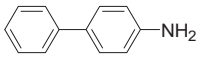
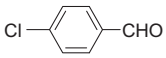
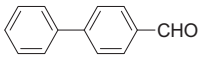
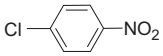
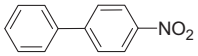
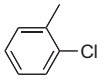
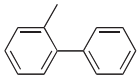
Catalytic efficiency of the iso-structural thiosemicarbazone and semicarbazone-palladium catalysts was investigated by using them for Suzuki–Miyaura C–C cross coupling reaction between aryl boronic acids and aryl halides to form biaryl compounds. Since activation of aryl chlorides at ambient temperature is our prime target, phenyl boronic acid was reacted with 4-chlorotoluene in the presence of complex **1** (0.2 mol %) using K_2CO_3 as base at 25 °C. To our satisfaction the reaction was complete within 1 h to form the corresponding biaryl derivative in 98% yield. In a similar reaction with complex **2** resulted in the formation of the biaryl derivative in 98% yield with 0.2% catalyst loading revealing comparable catalytic efficiency. Other aryl chlorides having different substituents at *p*-position resulted in the formation of biaryls in near quantitative yields upon coupling phenyl boronic acid at ambient temperature[8] (Table 1).

Indeed the catalytic efficiency of both **1** and **2** is found to be excellent for the activation of aryl chlorides at ambient temperature. However, since the catalysts are soluble in the reaction media, it is impossible to recover them to check the retention of catalytic activity. Thus, the only way remaining to postulate their activity is to run several catalytic cycles in one-pot. In a model reaction of 4-chlorotoluene with phenyl boronic acid using 0.2 mol % of catalyst **1**, we added fresh batch of substrates in every 2 h interval after confirming the consumption of the aryl halide by ^{1}H NMR. After 5 such cycles, the desired biaryl compound was isolated in 94% yield which demonstrates that the catalyst remains live after the catalytic cycle.

To judge the catalytic efficiency further, 4-chlotoluene was reacted with phenyl boronic acid with 0.1 mol % of catalyst **1**. The reaction was complete in 4 h and the desired biaryl was obtained in 97% yield showing that the catalyst is almost equally active in 0.1 mol % loading. Lowering of the catalyst loading to 0.05 mol % resulted in a very slow reaction and after 24 h the desired product was obtained in 60% yield only. The results of the reactions with lowered catalyst loading are summarized in Table 2 with calculated TON values.

The success of the Suzuki–Miyaura cross coupling reactions using catalysts **1** and **2** prompted us to investigate their potential

Table 1
Suzuki–Miyaura C–C cross coupling reactions of aryl chlorides and phenyl boronic acid at ambient temperature[a]

No.	Substrate	Catalyst	Product	Time (min)	Yield[b] (%)
1		**1**		60	98[9]
2		**2**		60	98
			6		
3		**1**		50	98[10]
4		**2**		50	97
			7		
5		**1**		45	97[10]
6		**2**		45	98
			8		
7		**1**		90	97[11]
8		**2**		90	96
			9		
9		**1**		30	97[10]
10		**2**		30	97
			10		
11		**1**		30	98[11]
12		**2**		30	97
			11		
13		**1**		60	76[12]
14		**2**		60	75
			12		

[a] Conditions: aryl chloride (1 mmol), phenyl boronic acid (1.2 mmol), K_2CO_3 (2 mmol), and catalyst (0.2 mol %) in 5 mL EtOH at 25 °C.
[b] Yield after chromatographic purification.

Table 2
Suzuki–Miyaura C–C cross coupling reactions of 4-chlorotoluene and phenyl boronic acid with different catalyst loadings at ambient temperature[a]

No.	Catalyst loading (mol %)	Time (h)	Yield[b] (%)	TON
1	0.2	1	98	490
2	0.1	4	97	970
3	0.05	24	60	1200

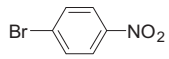
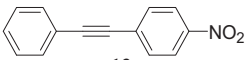
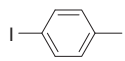
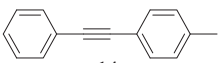
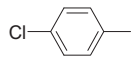
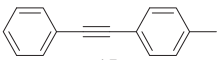
[a] Conditions: 4-chlorotoluene (1 mmol), phenyl boronic acid (1.2 mmol), K_2CO_3 (2 mmol), and catalyst (as mentioned) in 5 mL EtOH at 25 °C.
[b] Yield after chromatographic purification.

to catalyze Sonogashira coupling reactions (Table 3).[13] Different aryl halides were reacted with phenyl acetylene in the presence of catalyst **1** or **2** with CuI and Et_3N. Reactions with aryl bromides and iodides were complete in 12 h at 80 °C resulted in the formation of the desired product in moderate yield. However, the aryl chlorides were found to be lethargic and only after 24 h, the desired products were obtained in comparative yields. Both catalyst **1** and **2** were found to be of equal efficiency and effective at 0.5 mol % of catalyst loading.[14]

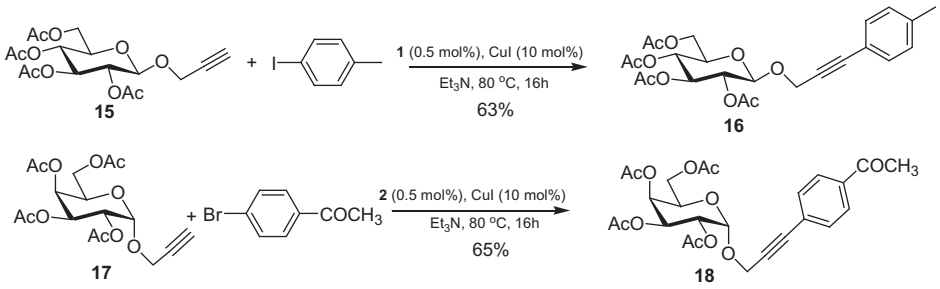
Encouraged by successful Sonogashira coupling of phenyl acetylene with aryl halides, we tried to couple propargyl glycosides with aryl halides. Indeed the propargyl derivatives[16] undergo coupling with the aryl halides to form the corresponding glycoconjugates in moderate yields (Scheme 2).

In conclusion, we have developed two palladium catalysts with carbohydrate derived thiosemicarbazone and semicarbazone ligands and fully characterized them with NMR, mass, and single crystal X-ray crystallography. The catalysts are found to be efficient for both Suzuki–Miyaura and Sonogashira coupling reactions. The catalysts are capable of activating aryl chlorides in Suzuki–Miyaura coupling reaction at ambient temperature at a low catalyst loading of 0.05 mol %. The catalysts remain active even after 5 consecutive cycles. In addition to the aromatic alkynes, aliphatic terminal alkynes of propargyl glycosides were successfully coupled with aryl halides in Sonogashira coupling reaction.

Table 3
Sonogashira coupling reactions of aryl halides and phenyl acetylene using catalysts **1** and **2**[a]

No.	Substrate	Catalyst	Product	Time (h)	Yield[b] (%)
1		**1**		16	66[15]
2		**2**		16	65
			13		
3		**1**		16	64[15]
4		**2**		16	65
			14		
5		**1**		24	67
6		**2**		24	65
			15		

[a] Conditions: aryl halide (1 mmol), phenyl acetylene (1.5 mmol), catalyst **1** or **2** (0.5 mmol %), CuI (10 mol %), and Et_3N (5 mL) at 80 °C.
[b] Yield after chromatographic purification.



Scheme 2. Sonogashira coupling reaction with propargyl glycosides.

Acknowledgments

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8. General procedure for Suzuki–Miyaura coupling reactions: To a solution of catalyst **1** or **2** (0.2 mol %) in EtOH (3 mL) were added phenylboronic acid (146 mg, 1.2 mmol), aryl halide (1 mmol) and K_2CO_3 (276 mg, 2.0 mmol) and the mixture was allowed to stir at ambient temperature for minutes as described in Table 1. After completion of the reaction, water (15 mL) was added and the organic materials were extracted with CH_2Cl_2. The organic layer was washed with water, dried over anhydrous Na_2SO_4 and filtered. Solvent was removed under vacuum and the residue was purified by flash chromatography using *n*-hexane–EtOAc to afford pure biaryl compound.
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14. General procedure for Sonogashira coupling: A mixture of aryl halide (1 mmol), CuI (9 mg, 10 mol %) and catalyst **1** or **2** (0.5 mol %) phenylacetylene (82.2 L, 1.5 mmol) in Et_3N (5 mL) reaction mixture was stirred at 80 °C for hours as mentioned in Table 2. After completion of the reaction, Et_3N was evaporated. The organic materials were extracted with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4 and filtered. Solvent was removed under vacuum and the residue was purified by flash chromatography using *n*-hexane–EtOAc to afford pure compounds.
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