Catal Lett (2009) 129:363–366
DOI 10.1007/s10562-008-9778-9

Suzuki Cross-Coupling Reaction Catalyzed by the Palladium Complex Pd[*N*-MorphC(S)NP(O)(O*i*Pr)$_2$-*O*,*S*]$_2$

Damir A. Safin · Maria G. Babashkina ·
Axel Klein

Received: 4 September 2008 / Accepted: 11 November 2008 / Published online: 3 December 2008

Abstract Suzuki cross-coupling reaction between phenyl bromide and phenylboronic acid, catalyzed by the palladium complex Pd[*N*-MorphC(S)NP(O)(O*i*Pr)$_2$-1,5-*O*,*S*)]$_2$ in acetonitrile, toluene, THF or DMF has been investigated. Bases employed for the reaction were Na_2CO_3, K_2CO_3 or Cs_2CO_3. Varying largely the experimental conditions we found that excellent yields of the product were obtained using toluene and K_2CO_3 at 100 °C at the catalyst amount of 0.02 mmol.

Keywords Cross-coupling · Phenylboronic acid · Phenyl bromide · Suzuki-Miyaura reaction · *N*-Phosphorylthiourea · Palladium

1 Introduction

The Suzuki-Miyaura cross-coupling reaction catalyzed by palladium containing compounds has become very popular and one of the most efficient methods for the synthesis of bi-or polyaryl compounds by means of carbon-carbon bond formation [1–12]. The Suzuki reaction usually proceeds in the presence of a base and various bases as carbonates have been tried so far. The choice of solvent is also crucial to the reaction. Various bases and solvents have been tried; however, both the choice of base and solvent is still empirical.

Another important condition for palladium catalysts is the nature of the ligands. The key role of the ligand is to stabilize the palladium catalyst. Tertiary phosphine ligands were traditionally used together with catalyst precursors in Suzuki cross-coupling reactions. However, many of these ligands are air sensitive and therefore require special conditions. Moreover, this rather erratic approach does not allow insight into reaction mechanisms, since the reactive species remain uncertain. During the last decade, the application of various new ligands to improve efficiency and selectivity of this cross-coupling reaction has become very popular. Therefore, such compounds as *N*-heterocyclic carbines [13], Pd(OAc)$_2$ system in combination with various additional ligands [14], thiourea [15, 16], and many others were widely used.

Herein we present a new class of palladium catalyst system based on the *N*-phosphorylated thiourea Pd[*N*-MorphC(S)NP(O)(O*i*Pr)$_2$-1,5-*O*,*S*)]$_2$ (**PdL$_2$**), containing a tertiary nitrogen atom at the thiocarbonyl group (Fig. 1).

The palladium complex **PdL$_2$** was synthesized as previously described [17]. According to the NMR, IR and X-ray data it was established that the palladium atom is coordinated by two deprotonated ligands through the sulfur atoms of the thiocarbonyl groups and oxygen atoms of the phosphoryl groups both in the solid state and in solution.

Encouraged by our studies on palladium complexes with *N*-(thio)phosphoryl thioureas [17–22], we decided to investigate the catalytic properties of these complexes in the Suzuki cross-coupling reaction. Our first experiments were carried out using the denominated complex **PdL$_2$**, since this compound is very easy to be synthesized and was completely characterized including a structure determination by XRD [17].

As an obvious model reaction we have examined the formation of biphenyl from phenylboronic acid or phenyl

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D. A. Safin (✉) · M. G. Babashkina
A. M. Butlerov Chemistry Institute, Kazan State University,
Kremlevskaya St. 18, 420008 Kazan, Russian Federation
e-mail: damir.safin@ksu.ru

D. A. Safin · M. G. Babashkina · A. Klein
Institut für Anorganische Chemie, Universität zu Köln,
Greinstrasse 6, 50939 Cologne, Germany

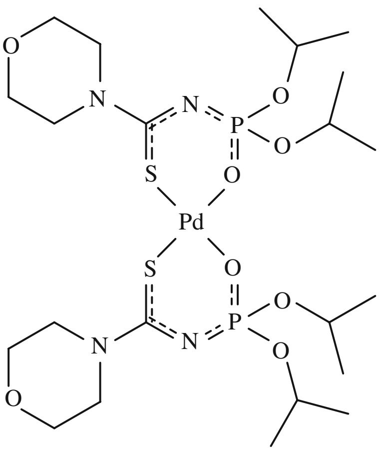


Fig. 1 Complex **PdL$_2$**

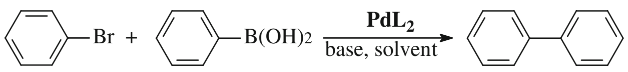
bromide separately in the presence of **PdL$_2$**, and using different reaction conditions. In all cases no homocoupling product was formed.

Then we have examined **PdL$_2$** in the palladium catalyzed coupling reaction of phenyl bromide with phenylboronic acid (Table 1) all reactions and manipulations were run under air atmosphere. All the solvents were purified by conventional procedures and distilled prior to use. Phenyl bromide and phenylboronic acid were purchased from Aldrich Chemicals and used without further purification. Infrared spectra (Nujol) were recorded with a Specord M-80 spectrometer in the range 400–3600 cm^{-1}. NMR spectra were obtained on a Bruker Avance 300 MHz spectrometer. For column chromatography, 300–400 mesh silica gel was employed. Elemental analyses were performed on a CHNS HEKAtech EuroEA 3,000 analyzer.

PdL$_2$: m.p. 157–158 °C. ^{1}H NMR (CDCl$_3$): δ 1.33 (d, $^3J_{H,H} = 6.1$ Hz, 12H, CH$_3$), 1.34 (d, $^3J_{H,H} = 6.1$ Hz, 12H, CH$_3$), 3.62–3.97 (m, 16H, CH$_2$), 4.68 (d. sept, $^3J_{P,H} = 7.6$ Hz, $^3J_{H,H} = 6.1$ Hz, 4H, OCH). ^{31}P{^{1}H} NMR (CDCl$_3$): δ 9.9. IR: v 1005 (POC), 1,144 (COC), 1154 (P = O), 1,547 (SCN) cm^{-1}. Anal. Calc. for $C_{22}H_{44}N_4O_8P_2PdS_2$ (724.11): C, 36.44; H, 6.12; N, 7.73. Found: C, 36.49; H, 6.07; N, 7.68%.

General procedure for the Suzuki coupling reaction: Phenyl bromide (0.5 mmol), phenylboronic acid (0.75 mmol), base (1 or 0 mmol) and **PdL$_2$** (0.1 mmol) were mixed in the solvent (acetonitrile, toluene, THF or DMF; 5.0 mL), and the reaction mixture was stirred at room temperature or at 100 °C for 2 or 1 h, respectively, under aerobic conditions. The reaction was worked up by removing the solvent under reduced pressure, and purifying residue by chromatography on silica gel. Four solvents (acetonitrile, toluene, THF or DMF) and three different bases (Na_2CO_3, K_2CO_3 or Cs_2CO_3) were screened at room temperature and 100 °C. Toluene and K_2CO_3 turned out to be the best solvent and base combination at both temperatures (Table 1, entry 9). It was also established, that 9% yield of the product is observed in toluene at 100 °C without base addition (Table 1, entry 2).

Table 1 Suzuki cross-coupling reaction of phenyl bromide with phenyl boronic acid catalyzed by PdL$_2$[a]



Entry	Base	Solvent	Condition	Yield[b] (%)
1	No	Acetonitrile	RT, 2 h	No
			100 °C, 1 h	2
2	No	Toluene	RT, 2 h	6
			100 °C, 1 h	9
3	No	THF	RT, 2 h	No
			100 °C, 1 h	No
4	No	DMF	RT, 2 h	No
			100 °C, 1 h	3
5	Na_2CO_3	Acetonitrile	RT, 2 h	48
			100 °C, 1 h	57
6	K_2CO_3	Acetonitrile	RT, 2 h	64
			100 °C, 1 h	81
7	Cs_2CO_3	Acetonitrile	RT, 2 h	39
			100 °C, 1 h	51
8	Na_2CO_3	Toluene	RT, 2 h	76
			100 °C, 1 h	84
9	K_2CO_3	Toluene	RT, 2 h	100
			100 °C, 1 h	100
10	Cs_2CO_3	Toluene	RT, 2 h	69
			100 °C, 1 h	73
11	Na_2CO_3	THF	RT, 2 h	41
			100 °C, 1 h	55
12	K_2CO_3	THF	RT, 2 h	53
			100 °C, 1 h	72
13	Cs_2CO_3	THF	RT, 2 h	27
			100 °C, 1 h	46
14	Na_2CO_3	DMF	RT, 2 h	43
			100 °C, 1 h	61
15	K_2CO_3	DMF	RT, 2 h	60
			100 °C, 1 h	73
16	Cs_2CO_3	DMF	RT, 2 h	42
			100 °C, 1 h	53

[a] Phenyl bromide (0.5 mmol), phenylboronic acid (0.75 mmol), base (1 mmol), **PdL$_2$** (0.1 mmol), solvent (5 mL)

[b] Isolated yield after column chromatography

Next, we investigated the relationship between reaction time and yield of the Suzuki cross-coupling reaction product at the following reaction conditions: phenyl bromide (0.05 mmol), phenylboronic acid (0.075 mmol), no base, **PdL$_2$** (0.1 mmol), toluene (5 mL) and $T = 100$ °C

(Fig. 2). It was established that the yield of the coupling product increases reaching the maximum at the reaction time of 8 h. The yield is 58–62%. It should be mentioned that, as shown in Fig. 2, there is no induction period for the catalyst. This suggests that the active catalyst (presumably Pd(0) species) is easily formed from **PdL$_2$** is the real catalytic species.

The catalytic activity of different amounts of **PdL$_2$** in toluene in the presence of K_2CO_3 (0.1 mmol) both at room temperature and 100 °C was also examined (Figs. 3, 4). As shown in Fig. 3 the yield of the product at room temperature increases slowly with increasing catalyst load till an amount of about 0.05 mmol. Then a sharp increase is observed with the final yield of 100% obtained with amounts ranging from 0.07 to 0.1 mmol. In contrast to this, at 100 °C the yield increases sharply and reaches the saturation at **PdL$_2$** amounts of about 0.02 mmol (Fig. 4), with almost complete conversion with catalyst amounts ranging from 0.04 to 0.1 mmol.

From preliminary studies on the complex stability of the related compounds Hg[RC(S)NP(X)(O*i*Pr)$_2$]$_2$ (X = O, S) for which the predominant decomposition reaction was found to be the formation of disulfide (*i*PrO)$_2$P(X)–N = C(R)–S–S–C(R) = N–P(X)(O*i*Pr)$_2$ and elementary Hg [23, 24], we assume that the complex stability of our system is also limited from a similar reaction. Thus, we suppose that the decomposition of **PdL$_2$** produces Pd(0) from an internal oxidation by the ligand anion **L**$^-$, with formation of the disulfide (*i*PrO)$_2$P(O)–N = C(*N*-Morph)–S–S–C(*N*-Morph) = N–P(O)(O*i*Pr)$_2$ (Scheme 1). Probably, Pd(0) is stabilized by the disulfide, which might act as ligand for Pd(0) through the sulfur atoms as well as the other function N or O in this complex molecule (Scheme 1). Thus, the catalyst is not recoverable.

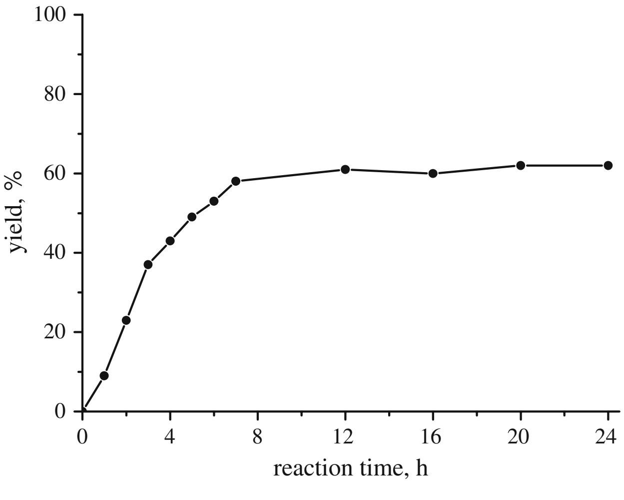


Fig. 2 Relationship between reaction time and yield of the Suzuki cross-coupling reaction product. Phenyl bromide (0.5 mmol), phenylboronic acid (0.75 mmol), no base, **PdL$_2$** (0.1 mmol), toluene (5 mL), $T = 100$ °C

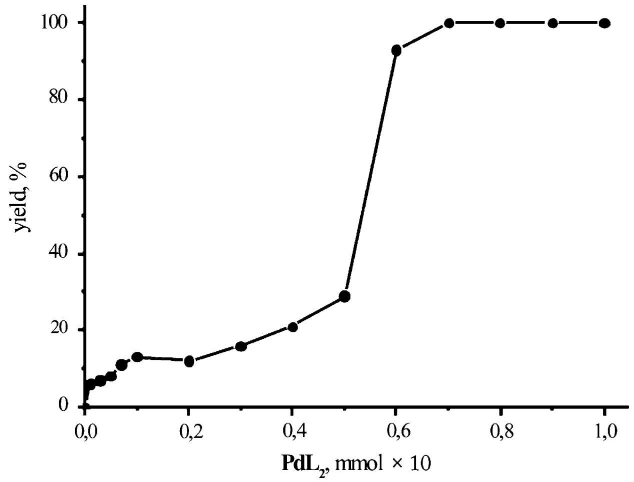


Fig. 3 Relationship between catalyst amount and yield of the Suzuki cross-coupling reaction product. Phenyl bromide (0.5 mmol), phenylboronic acid (0.75 mmol), K_2CO_3 (1 mmol), toluene (5 mL), T = RT

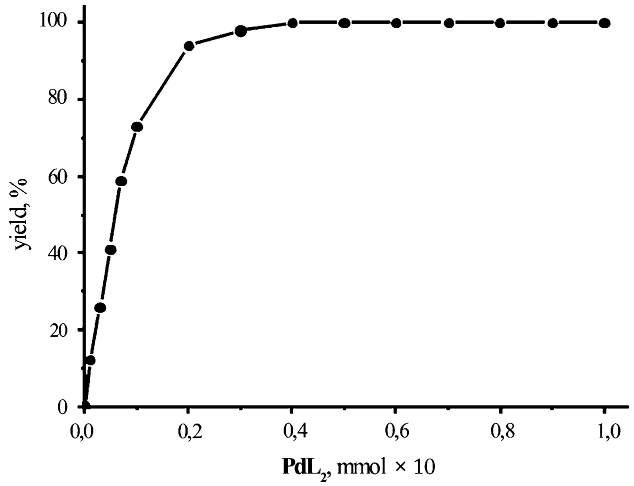
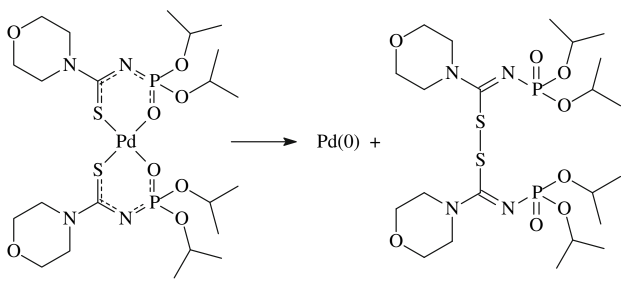


Fig. 4 Relationship between catalyst amount and yield of Suzuki cross-coupling reaction product. Phenyl bromide (0.5 mmol), phenylboronic acid (0.75 mmol), K_2CO_3 (1 mmol), toluene (5 mL), $T = 100$ °C



Scheme 1

In summary, the obtained results represent the successful application of the new air- and moisture stable palladium catalyst system Pd[*N*-MorphC(S)NP(O)(O*i*Pr)$_2$-1,5-*O*,*S*)]$_2$

based on a *N*-phosphorylated thiourea ligand, in the palladium catalyzed Suzuki cross-coupling reaction of phenyl bromide with phenylboronic acid under aerobic conditions. The coupling reaction was investigated in different solvents (acetonitrile, toluene, THF, DMF) and various bases were used (Na_2CO_3, K_2CO_3, Cs_2CO_3).

It was established that using toluene and K_2CO_3 at 100 °C shows excellent yields of the product at the catalyst amount of 0.02 mmol. Under the same reaction conditions at room temperature shows good to excellent yields at 0.06 mmol of **PdL$_2$** were observed. In the absence of base the coupling reaction product was obtained in yields of nearly 60%.

Further evaluation of the complex **PdL$_2$** in the palladium catalyzed Suzuki cross-coupling reaction using other aryl halides, and the modification of the catalyst, with the aim of smaller amounts of required catalyst and higher catalyst stability are currently underway. Additionally we seek to prove the assumption that the active Pd(0) catalyst is stabilized by the disulfide molecule, generated during catalyst formation from the precursor complex **PdL$_2$.**

Acknowledgments This work was supported by the joint program of CRDF and the Russian Ministry of Education and Science (BRHE 2008 Y5-C-07-09); Russian Science Support Foundation. DAS and MGB thank DAAD for the scholarships (Forschungsstipendien 2008/2009).

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