Molecularly defined palladium(0) monophosphine complexes as catalysts for efficient cross-coupling of aryl chlorides and phenylboronic acid[1]

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Various 1,6-diene palladium(0) monophosphine complexes have been prepared from tmedaPd(CH_3)$_2$, PR_3, and the corresponding 1,6-diene. These molecularly defined Pd complexes catalyzed the Suzuki coupling of aryl chlorides with phenylboronic acid more efficiently than traditional Pd^{II}–PR_3 pre-catalysts.

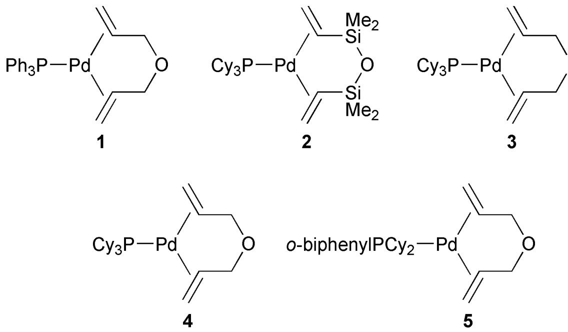
The cross-coupling reaction of aryl halides and arylboronic acids (Suzuki reaction) is the most versatile and important method for the synthesis of substituted biaryls.[2] This class of compounds constitute important building blocks for the synthesis of biologically active substances, *e.g.* pharmaceuticals such as the sartan family of drugs for high blood pressure and herbicides.[3] Additionally, biaryls have found application as chiral ligands[4] for catalysis and in materials science, *e.g.* liquid crystals.[5] Suzuki cross-coupling reactions of aryl bromides and iodides have been extensively studied in organic synthesis. Apart from further expanding the scope of this reaction, current interest focuses on the use of economically more attractive aryl chlorides as substrates for this reaction. Notable advances in the cross-coupling reactions of aryl chlorides[6] with arylboronic acids have been described recently by the groups of G. Fu,[7] S. Buchwald,[8] S. A. Guram,[9] S. Nolan,[10] and W. A. Herrmann[11] as well as by our group.[12] In general, important improvements in this area have been made possible by the use of *in situ* 'Pd'–L catalysts consisting of a Pd^{II} source and sterically hindered basic ligands such as dialkylarylphosphines, tri-*tert*-butylphosphine, adamantylphosphines or N-heterocyclic carbenes. It is generally agreed that these *in situ* catalysts are reduced under reaction conditions[13] to afford coordinatively unsaturated complexes such as 16e PdL_3, 14e PdL_2, and 12e PdL, which may constitute the 'real' catalysts. The importance of coordinatively unsaturated Pd^0 species as 'true catalysts' in various cross-coupling reactions has been demonstrated.[14]

In order to avoid side-reactions which may parallel the preformation of the 'real' catalyst and which often lead to loss of catalyst activity, it is desirable to use defined Pd monophosphine complexes as catalysts. To the best of our knowledge there is no report about the use of defined Pd^0 mono- or diphosphine complexes and only one report[11] applying a defined Pd^0 dicarbene species as catalyst in the Suzuki cross-coupling reaction. Recently, we introduced triphenylphosphine palladium(0) diallyl ether as a stable and active catalyst for telomerization of butadiene and methanol.[15] In this paper we describe the use of 1,6-diene stabilized Pd^0–PR_3 complexes as efficient catalysts for the Suzuki cross-coupling of aryl chlorides.

Based on the work of Pörschke[16] *et al.*, who developed a highly effective route for the synthesis of 1,6-diene Pd^0 complexes, we synthesized various monophosphine Pd^0 species as shown in Scheme 1. As phosphine ligands triphenylphosphine, tricyclohexylphosphine, and the so-called 'Buchwald-ligand' *o*-biphenyldicyclohexylphosphine were employed. In order to investigate the influence of the 1,6-diene part on the formation of the L–Pd^0 fragment we decided also to prepare the monotricyclohexylphosphine palladium complex with diallyl ether, diallyl amine and tetramethyldivinyl disiloxane. (Ph_3P)Pd($C_6H_{10}O$) **1**, (Cy_3P)Pd(dvds) **2**, (Cy_3P)Pd($C_6H_{10}NH$) **3**, (Cy_3P)Pd($C_6H_{10}O$) **4**, and (*o*-biphenyl)PCy_2)Pd($C_6H_{10}O$) **5** were obtained by suspending (tmeda)Pd(CH_3)$_2$[17] and PR_3 at −30 °C in the corresponding 1,6-diene. After gently warming the mixtures, elimination of ethane occurred and the desired products were isolated by filtration, washed with cold pentane and dried under vacuum.

A preliminary screening of optimal reaction conditions for the Suzuki coupling of an activated aryl chloride (2-chlorobenzonitrile) with phenylboronic acid in the presence of different palladium catalysts revealed that the coupling proceeds smoothly using THF as the solvent in the presence of a mixture of potassium triphosphate and potassium fluoride as base. In order to compare appropriately the efficiency of the different defined catalysts with each other and with *in situ* catalysts, we performed catalyst tests at low palladium concentration (0.05 mol% Pd). It is important to note that there are relatively few examples of Suzuki cross-couplings of aryl chlorides known that proceed at such low catalyst loading.[8c,18] As shown in Table 1 the cross-coupling reactions of a variety of aryl chlorides with phenylboronic acid proceed in the presence of 1,6-diene stabilized monophosphine in varying yields depending on the catalyst.

Complex **1** ($PPh_3Pd(C_6H_{10}O)$) was shown to be inactive towards all the substrates, although at higher concentrations (0.5 mol% Pd) with the activated 2-chlorobenzonitrile a limited cross-coupling reaction could be observed (32%). 1,6-Diene palladium(0) complexes with the more basic ligand tricyclohexylphosphine **2**–**4** show good conversion with 2-chlorobenzonitrile, chlorobenzene and 4-chlorotoluene (67–96%). Best results were achieved with the 1,6-diene complex containing 'Buchwald's ligand' [**5** (*o*-biphenyl)$PCy_2Pd(C_6H_{10}O)$]. With only 0.05 mol% of this catalyst good to excellent yields of biaryls were obtained from activated (2-chlorobenzonitrile: 97%), non-activated (4-chlorotoluene: 82%; chlorobenzene: 87%) and deactivated (4-chloroanisole: 72%) aryl chlorides. The general trend of catalyst activity is in good agreement with previously reported investigations on the corresponding *in situ* systems. However, there are some notable features of the new catalysts: 1. 1,6-Diene palladium(0) monophosphine complexes are significantly more reactive than mixtures of Pd(OAc)$_2$ or $Pd_2(dba)_3$ and phosphines (Table 2). Hence, the obtained



Scheme 1 1,6-Diene complexes of palladium(0).

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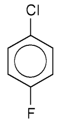
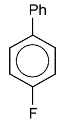
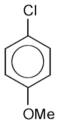
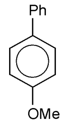
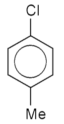
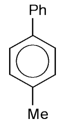
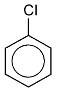
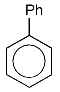
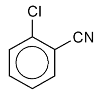
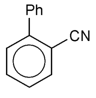
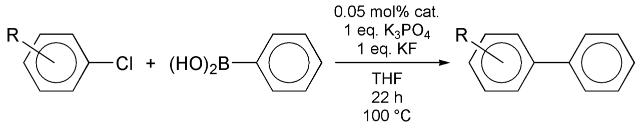
Table 1 Reactions of aryl chlorides with phenylboronic acid in the presence of various Pd^0 complexes^a

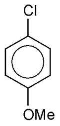
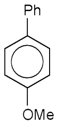
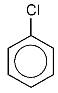
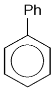
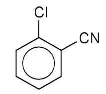
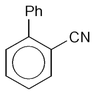
Entry	Substrate	Product	Catalyst	Yield (%)^b	TON
1			2	15	300
2			3	34	680
3			4	34	680
4			**5**	**67**	**1340**
5			2	28	560
6			3	48	960
7			4	56	1120
8			**5**	**72**	**1440**
9			2	23	460
10			3	54	1080
11			4	67	1340
12			**5**	**82**	**1640**
13			2	29	580
14			3	45	900
15			4	79	1580
16			**5**	**87**	**1740**
17			2	96	1920
18			3	95	1900
19			4	96	1920
20			**5**	**97**	**1940**

[a] 3.0 mmol aryl chloride, 4 mmol phenylboronic acid, 3 mmol potassium triphosphate, 3 mmol potassium fluoride, 0.05 mol% catalyst, 8 ml THF, 100 °C, 22 h. [b] Determined by GC with hexadecane as internal standard.



Scheme 2 Suzuki cross-coupling reactions of aryl chlorides with phenylboronic acid.

Table 2 Reactions of aryl chlorides with phenylboronic acid in the presence of various Pd^0 catalysts^a

Entry	Substrate	Product	Catalyst	Yield (%)^b	TON
1			A	5	100
2			B	8	160
3			C	28	560
4			**4**	**56**	**1120**
5			A	8	160
5			B	11	220
7			C	28	560
8			**4**	**79**	**1580**
9			A	91	1820
10			B	91	1820
11			C	95	1900
12			**4**	**96**	**1920**

[a] 3.0 mmol aryl chloride, 4 mmol phenylboronic acid, 3 mmol potassium triphosphate, 3 mmol potassium fluoride, 0.05 mol% catalyst, 8 ml THF, 100 °C, 22 h. [b] Determined by GC with hexadecane as internal standard. A: $\mathrm{Pd_2(dba)_3}$–$\mathrm{PCy_3}$ 1 : 1. B: $\mathrm{Pd(OAc)_2}$–$\mathrm{PCy_3}$ 1 : 1. C: $\mathrm{Pd(OAc)_2}$–$\mathrm{PCy_3}$ 1 : 2.

catalyst turnover numbers are amongst the highest yet reported for the Suzuki reaction of non-activated aryl chlorides. 2. The catalyst properties are mainly determined by the phosphine ligand as shown by an increase of product yields in the series: (*o*-biphenyl)$\mathrm{PCy_2Pd(C_6H_{10}O)}$ **5** > $\mathrm{(Cy_3P)Pd(C_6H_{10}O)}$ **4** ≫ $\mathrm{(Ph_3P)Pd(C_6H_{10}O)}$ **1**. 3. The effectiveness of the studied complexes **2–4** is directly related to their ability to liberate the diene part and to generate the corresponding 12e [L–Pd^0] species. Previously, it has been shown that an increasing acceptor strength of the 1,6-diene moiety results in an increasing stability of the 1,6-diene complex.[16] In agreement with these studies we observe an decrease in reactivity in the order **4** > **3** > **2**.

In summary, we have shown that 1,6-diene palladium(0) monophosphine complexes are extremely efficient catalysts for Suzuki cross-coupling reactions of various aryl chlorides. By variations of both the diene and the phosphine part of the complex the catalytic properties of the complexes can be tuned. It is clearly shown that these defined monophosphine catalysts are superior to generally applied mixtures of Pd-pre-catalysts and phosphines. Thus, this class of catalysts offers promising features for a number of other important palladium-catalyzed coupling reactions.

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