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Catalytic activity of palladium complexes with stable diaminocarbenes containing five-, six- and seven-membered rings in the Suzuki—Miyaura reaction*

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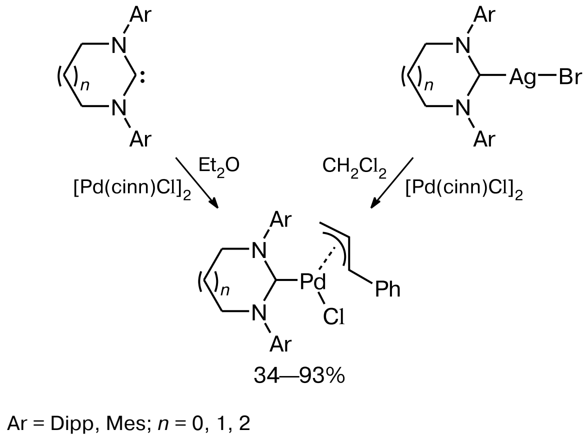
A comparative study of catalytic activity of palladium complexes with *N*-heterocyclic carbenes in the Suzuki—Miyaura reaction was conducted. The studies were carried out for the complexes containing carbenes with five-membered rings based on imidazole and imidazoline, and carbenes with expanded six- and seven-membered rings. The influence of the solvent nature, the base type, and the iodide ions on the catalytic activity of complexes was also examined.

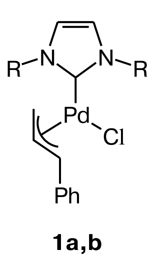
Key words: *N*-heterocyclic carbenes, palladium complexes, Suzuki—Miyaura reaction, cross-coupling.

Palladium complexes of *N*-heterocyclic carbenes are readily formed upon treatment of imidazolium salts with bases and palladium salts. Such complexes due to the strong electron-donating properties and steric loading of carbene ligand[1—4] exhibit high catalytic activity in the cross-coupling reactions, making it possible to accomplish reactions with low active aryl bromides and even aryl chlorides under relatively mild conditions.[5—9] However, amount of such complexes is limited and it seems important to synthesize new representatives of this family.[1,2]

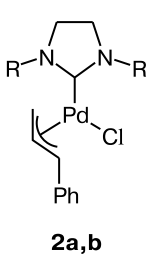
Earlier, we have obtained palladium complexes with sterically loaded six- and seven-membered *N*-heterocyclic carbenes as the ligands containing aryl groups with *ortho*-methyl and *ortho*-isopropyl substituents.[10] In the present work, we conducted comparative studies of catalytic activity of the synthesized earlier[5—9] palladium com-

Scheme 1

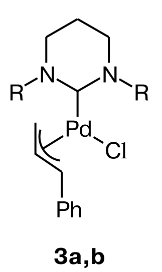




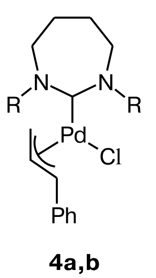
1a,b



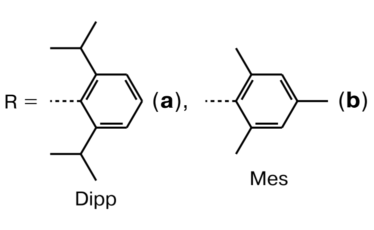
2a,b



3a,b



4a,b



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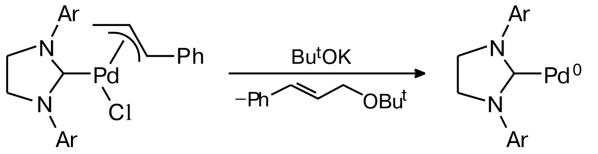
plexes **1a**,**b** and **2a**,**b** and obtained by us[10] complexes **3a**,**b** and **4a**,**b**.

These compounds were obtained from the free carbene by the reaction suggested earlier,[11] as well as by the transmetallation reaction of a silver carbene complex with dimeric cinamylpalladium chloride[10] (cinn stands for cinnamyl-1-phenylallyl, Scheme 1).

The Pd^{II} complexes obtained were converted to the Pd^0 complex upon treatment with bases,[1,12] which resulted in the formation of Pd^0 monoligand complexes (Scheme 2).

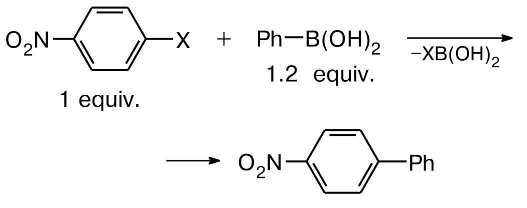
Scheme 2



Results and Discussion

The Suzuki—Miyaura reaction catalyzed by palladium carbene complex **1a** was studied on the model substrates: p-$NO_2C_6H_4X$ (X = I, Br, Cl) and $PhB(OH)_2$ (Scheme 3).[1,5,13]

Scheme 3



X = I, Br, Cl

Reagents and conditions: 1 mol.% of [Pd], 3 equiv. of K_2CO_3, 1,4-dioxane, 60—80 °C.

In the first step, compound **1a** was taken as an example to select reaction conditions optimal for the comparison of activity of other complexes. When we used 1 equiv. of *para*-iodonitrobenzene, 1,2 equiv. of phenylboric acid, 1 mol.% of the catalyst, and 3 equiv. of K_2CO_3 as the base in 1,4-dioxane at 60 °C, the reaction proceeded selectively, but slowly (4 h, 25%, Table 1, entry *1*).

Introduction of a two-fold excess of aryl iodide makes it possible to obtain the product of the cross-coupling reaction in almost quantitative yield already within 4 h (see Table 1, entry *3*). However, the use of similar excess of phenylboric acid appears to be less efficient: the yield of the product increases only to 67% (see Table 1, entry *4*).

Table 1. The Suzuki—Miyaura reaction of p-$NO_2C_6H_4I$ with $PhB(OH)_2$ catalyzed by **1a**[a]

Entry	Pd (mol.%)	T/°C	Time/h	C_{ArI}[b]	Y_{ArPh}[c]
				(%)	
1	1	60	4	27	25
2	3	60	4	63	60
3	1	60	4	96	96[d]
4	1	60	4	69	67[e]
5	1	80	0.5	14	11
6	1	80	1	82	80
7	1	80	1.5	86	85

[a] Reaction conditions: 1 equiv. of p-$NO_2C_6H_4I$, 1.2 equiv. of $PhB(OH)_2$, 1 mol.% of Pd cat., 3 equiv. of K_2CO_3, 1,4-dioxane.

[b] C_{ArI} is the conversion of ArI.

[c] Y_{ArPh} is the yield of ArPh.

[d] 2 equiv. of p-$NO_2C_6H_4I$.

[e] 2.4 equiv. of $PhB(OH)_2$.

A three-fold increase in the concentration of the catalyst also increases the product yield (see Table 1, entry *2*). However, elevation of temperature to 80 °C is the most efficient (see Table 1, entries *5*—*7*). This temperature regime was chosen as the optimal for the comparison of the catalytic properties of complexes. It is important to note that this reaction in all the cases requires an induction period (see Table 1, entries *1*—*7*). Apparently, this is due to the long-time formation of a true catalyst upon treatment with a weak base, potassium carbonate. No induction period is observed when a stronger base (Bu^{t}OK) is used.

A comparison of activity of known and new palladium carbene complexes (Table 2) showed that carbene complexes **1a**,**b** and **2a**,**b** only insignificantly differ in the activity under the selected conditions.

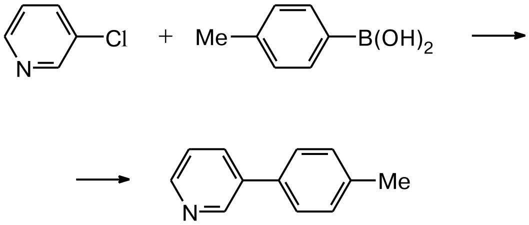
Table 2. The influence of the carbene ligand nature in the palladium complex on the activity in the Suzuki—Miyaura reaction*

Complex	Conversion ArI	Yield ArPh
	(%)	
1a	82	80
1b	91	89
2a	93	91
2b	87	83
3a	86	84
3b	49	45
4a	76	72
4b	69	65

* Reaction conditions: 1 equiv. of p-$NO_2C_6H_4I$, 1.2 equiv. of $PhB(OH)_2$, 1 mol.% of Pd, 3 equiv. of K_2CO_3, 1,4-dioxane, 80 °C, 1 h.

The complexes containing six- and seven-membered carbenes, except complex **3a**, posses a comparable, but lower activity. Complexes containing mesityl groups (**3b** and **4b**) are less active. At the same time, all the reactions are selective, and by the end of the reaction (2 h) the product yields become almost quantitative. Carbene complexes in this reaction can be arranged in the order of decreasing activity: **2a** ≥ **1b** > **2b** ~ **3a** > **1a** > **4a** > **4b** > **3b**. When water is used instead of 1,4-dioxane, the order of activity of these complexes considerably changes.[10] As it has been shown in our recent work[10] by a comparative testing of carbene complexes **2a**,**b**—**4a**,**b** under conditions given in Scheme 4, the catalytic activity depended the most strongly on the steric loading of substituents at the nitrogen atoms of the carbene ligand. The complexes containing diisopropylphenyl substituents (84% (**2a**), 86% (**3a**), 25% (**4a**)) exhibit higher activity than the complexes containing less bulky mesityl substituents (3% (**2b**), 33% (**3b**), 15% (**4b**)).

Scheme 4



Reagents and conditions: 0.5 mol.% of LPd(cinn)Cl, $NaHCO_3$, tetrabutylammonium tetrafluoroborate (TBAB), H_2O, reflux.

The size of the ring in carbene also plays a significant role in catalytic activity of complexes in the Suzuki reaction in water. A comparison of the catalytic activity of carbene homologs in the case of mesityl complexes (3% (**2b**), 33% (**3b**), 15% (**4b**)) and diisopropylphenyl complexes (84% (**2a**), 86% (**3a**), 25% (**4a**)) shows that the activity of complexes in the sequence of five-, six-, and seven-membered rings passes the maximum, with the six-membered carbene complexes being the most active.

It is seen from the results of our preceding work[10] that the order of activity of carbene complexes in the Suzuki—Miyaura reaction in water is changed as follows: **3a** ≥ **2a** >> **3b** > **4a** > **4b** >> **2b**. The highest activity is exhibited by the complexes containing bulky diisopropylphenyl substituents at the nitrogen atoms of the heterocyclic carbene ligand L.

The use of another solvent (water instead of 1,4-dioxane) and electrophilic component of the reaction (3-chloropyridine instead of *p*-iodonitrobenzene) leads to the increased differences in the catalytic activity of the complexes. The yields of the reaction products in water for *m*-PyCl vary within 3—86%, while in 1,4-dioxane the yields for *p*-NO_2PhI change from 45 to 91%.

The change of the solvent and electrophile considerably changed the orders of the catalytic activity of the systems under study. Thus, if in dioxane the five-membered complexes were the most active, the six-membered carbene complex **3a** synthesized by us appeared to be the most active in water. Besides, the order of comparative catalytic activity of complexes with carbenes with expanded rings underwent big changes:

1,4-Dioxane: **3a** > **4a** > **4b** > **3b**.

Water: **3a** >> **3b** > **4a** > **4b**.

We studied the differences in the reactivity of complexes varying the nature of the halogen in aryl halide. On going from complex **1b** to complex **3b**, in the case of ArI the yield of the product decreases from 89% to 45% (Table 3). These changes appear to be the most profound for the reactions with ArBr and ArCl, where the yield is dropped from 87 to 8% and from 27 to 3%, respectively.

We believe that the differences observed in the activity of catalysts **1b** and **3b** are due to the differences in the stability and reactivity of the reaction intermediates. One of the key steps in the catalytic cycle, which determines the rate of entire process, is the oxidative addition of aryl halide ArX to LPd^0, as well as stability and reactivity of the adduct $L(Ar)Pd^{II}X$ (Scheme 5).

The Suzuki—Miyaura reactions catalyzed by complex **1a** in the absence of Bu_4NI, with aryl iodide and aryl bromide proceed virtually quantitatively within 1.5 h (Table 4). Under similar conditions, the reaction with aryl chloride is only half complete. At the same time, after 30 min the process proceeded significantly further for aryl bromide and even for aryl chloride than for aryl iodide. This result is due to the formation of stable dimers from intermediates LPd(Ar)I (Scheme 5). Iodides LPd(Ar)I are known to form more stable dimers than the corresponding chloro and bromo derivatives.[14,15] The obtained dimer

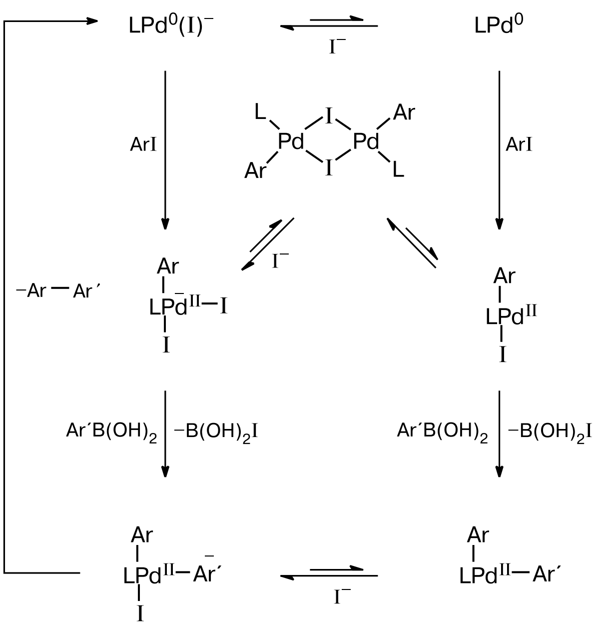
Table 3. The Suzuki—Miyaura reaction of *p*-$NO_2C_6H_4X$ (X = I, Br, Cl) with $PhB(OH)_2$ catalyzed with complexes **1b** and **3b**[a]

X in ArX	Yield of ArPh (%)	
	Complex **1b**	Complex **3b**
I	89	45
Br	87	8[b]
Cl	27[b]	3[b]

[a] Reaction conditions: 1 equiv. of ArI, 1.2 equiv. of $PhB(OH)_2$, 3 equiv. of K_2CO_3, 1 mol.% of Pd, 1,4-dioxane; 60 °C and 4 h for X = Br, Cl; 80 °C and 1 h for X = I.

[b] The yield of the side product Ph_2 was 1—7%.

Scheme 5



$[LPd(Ar)I]_2$ can be involved in the reaction with arylboronic acid after dissociation to form a monomer.

The addition of some iodide ions considerably changes the picture due to the formation of the anionic complexes LPd^0I^- and the monomeric complex $Ar(L)PdI^-{}_2$. The reactivities of ArBr and ArCl significantly decrease.

It was shown earlier that the Suzuki—Miyaura reaction catalyzed by palladium carbene complexes is the most efficient when carried out in isopropanol in the presence of strong bases.[4,16] We conducted a series of experiments under similar conditions (Table 5).

Table 4. The influence of Bu_4NI on the Suzuki—Miyaura reaction of p-$NO_2C_6H_4X$ (X = I, Br, Cl) with $PhB(OH)_2$ catalyzed with complex **1a**[a]

Time /h	X in ArX	In the absence of Bu_4NI		In the presence of Bu_4NI[b]	
		C_{ArX}[c]	Y_{ArPh}[d]	C_{ArX}	Y_{ArPh}
0.5	I	14	11	18	14
	Br	60	59	20	17
	Cl	42	34[e]	8	2
1.5	I	86	85	95	93
	Br	92	89	27	24
	Cl	50	48[e]	10	3

[a] Reaction conditions: 1 equiv. of ArI, 1.2 equiv. of $PhB(OH)_2$, 1 mol.% of Pd, 3 equiv. of K_2CO_3, 1,4-dioxane, 80 °C, 30 min.
[b] Added 0.2 equiv. relative to ArX.
[c] Conversion of ArX (%).
[d] Yield of ArPh (%).
[e] The yield of the side product Ph_2 was 6%.

Table 5. The Suzuki—Miyaura reaction of p-$NO_2C_6H_4X$ (X = I, Br, Cl) with $PhB(OH)_2$ catalyzed by complex **1a** in the presence of Bu^tOK[a]

X in ArX	After 1 h		After 24 h	
	C_{ArX}[b]	Y_{ArPh}[c]	C_{ArX}	Y_{ArPh}
I	13	11	95	92
Br	16	14	94	94
Cl	7	5	87	82

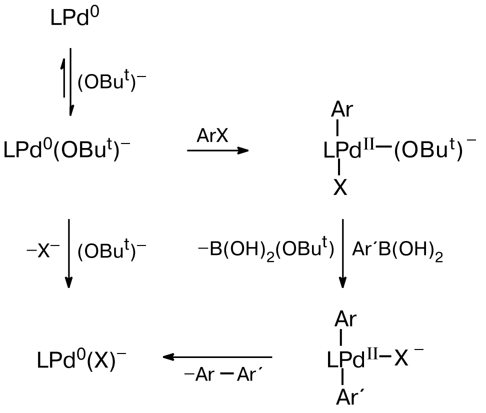
[a] Reaction conditions: 1 equiv. of ArI, 1.2 equiv. of $PhB(OH)_2$, 1 mol.% of Pd, 1.5 equiv. of Bu^tOK, Pr^iOH, 20 °C.
[b] Conversion of ArX (%).
[c] Yield of ArPh (%).

In the case of aryl bromide and aryl iodide, the product yields close to quantitative are reached within 24 h at 20 °C. The yield for aryl chloride is slightly lower, but also high. The data on conversions and product yields for 1 h show that aryl bromide enters the reaction more actively than aryl iodide. However, the difference in activity of bromide and iodide is not that large as for the system 1,4-dioxane—K_2CO_3 (see Table 4).

The higher total rate of the Suzuki reaction in isopropanol in the presence of Bu^tOK at room temperature is explained by the considerably higher rate of the formation of the catalyst LPd^0 from complex LPd(cinn)Cl upon treatment with Bu^tOK (see Scheme 2).

It cannot be excluded that the high activity of the catalyst in the presence of Bu^tOK is explained by the higher reactivity of intermediates $LPd^0(OBu^t)^-$ and $LPd^{II}(Ar)(X)(OBu^t)^-$ in the steps of oxidative addition and transmetallation, respectively (Scheme 6). As a result, an increase in the medium polarity and the base strength accelerates the catalytic process.[14,17—19]

Scheme 6



In conclusion, palladium carbene complexes catalyze the Suzuki—Miyaura reaction of aryl halides under different conditions (1,4-dioxane—K_2CO_3, isopropanol—Bu^tOK, water—$NaHCO_3$). The order of comparative catalytic activity of five-, six-, and seven-membered carbene complexes under study changes depending on the chosen reaction conditions. The rate of the reaction is strongly influenced not only by the choice of catalyst, base, solvent, and temperature, but also by the presence of additional ions in the reaction mixture. Thus, it was shown that the presence of the I^- ion in the reaction mixture autocatalytically accelerates the cross-coupling of aryl iodides, but inhibits the coupling of aryl bromides and aryl chlorides. The Suzuki reaction studied under different conditions showed that the conditions crucially influence a possibility of efficient cross-coupling of aryl chlorides.

Experimental

All the aryl halides used in the work, phenylboric acid, solvents, and standards for the GLC calibration were purchased from Lancaster and Aldrich and used without additional purification.

The reaction products were analyzed by GLC on a Kristalyuks 4000 M chromatograph with a flame-ionizing detector, a CrompackCP-Sil 8 CB column, 25 m, 32 mm, 0.25 μm # CP7452, and programmed temperature from 120 °C to 300 °C (25 deg min^{-1}). The injector and detector temperature was 310 °C.

All the compounds were isolated in the pure form by column chromatography (silica gel, eluents hexane—ethyl acetate, hexane—dichloromethane).

Reactions (general procedure). The compounds p-$NO_2C_6H_4X$ (0.075 mmol), $PhB(OH)_2$ (0.09 mmol), the base K_2CO_3 (0.22 mmol) or Bu^tOK (0.11 mmol), 1,4-dioxane or isopropanol (0.3 mL) were placed in a glass test-tube (5 mL) with a magnetic stirrer in air. Then, the catalyst was added by syringe as a solution (0.1 mL) containing a proper amount of the palladium complex. The test-tube with the reaction mixture was placed into an oil bath heated to a desired temperature with the accuracy of ±(1—2) °C. The moment when the test-tube was immersed into the bath was considered as the beginning of the reaction. The reaction was carried out with vigorous stirring by a magnetic stirrer. After the reaction came to an end, the test-tube with the reaction mixture was removed from the bath, the mixture was diluted with saturated aqueous NaCl (2 mL), followed by addition of the internal standard $C_{16}H_{34}$ (5—7 μL) and extraction with dichloromethane (3×2 mL). The extract was dried with anhydrous Na_2SO_4 and analyzed by GLC.

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