



Cyclopalladated complexes of 2-phenylaniline and their catalytic activity in Suzuki and Heck reactions under mild conditions

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ABSTRACT

A series of palladium complexes bearing monodentate and bidentate ligands were applied in the Suzuki reaction of aryl halides and the Heck reaction of styrene with phenylboronic acid. The complexes were found to be effective catalysts for these reactions affording the cross-coupled products in moderate to excellent yields.

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The palladium-catalyzed Suzuki cross-coupling is a very useful and convenient method, especially for the synthesis of various biaryl compounds^{1–6} that are found as important structural units in pharmaceuticals and natural products.^{7–10} The mild reaction conditions and the commercial availability of various boronic acids make this reaction preferable over other Pd-catalyzed cross-coupling reactions.^{1–3,11–16} Besides using aryl bromides, there is great interest in developing catalysts that use aryl chlorides in Suzuki reactions.^{1,17,18} Since the bond strengths of C–Cl and C–Br are stronger than C–I, the reactivity of aryl bromides and chlorides is reduced compared with the more active iodides. Thus, despite being cheaper, more available and practical, aryl bromides and chlorides often do not react efficiently.¹⁹ Furthermore, the Heck reaction and related chemistry has numerous applications in organic synthesis,^{20–25} polymers, dendrimers, fine chemicals and pharmaceutical intermediates.^{26–30} Many catalyst systems can be used to catalyze various frequently used cross-coupling reactions. In this regard, palladacycles have played an important role due to their versatility and non-toxicity. Besides phosphorus-containing complexes, a substantial amount of research has been undertaken on NC-based complexes. Cyclopalladated complexes with nitrogen donor atoms have been widely studied due to their novel and outstanding applications in a vast range of fields such as organic synthesis,³¹ insertion reactions,³² as anti-tumor drugs³³ and in catalysis.³⁴ The related benzylamine,³⁵ aryl urea,³⁶ sulfilimine³⁷ and benzodiazepine³⁸ based palladacycles have also shown good activity with aryl bromides in C–C coupling reactions.

We have reported the synthesis and characterization of thermal, oxygen and moisture stable palladium complexes containing a 2-phenylaniline cyclopalladated unit that conveniently formed six-membered NC palladacycles³⁹ (Fig. 1). Complex **4** was further studied by X-ray crystallography.³⁹ In this Letter, we report the application of the palladacycles in Suzuki and Heck reactions. During our research^{40,41} we have used aryl bromides and chlorides with phenylboronic acid in the Suzuki reactions and aryl bromides with styrene in the Heck reaction.

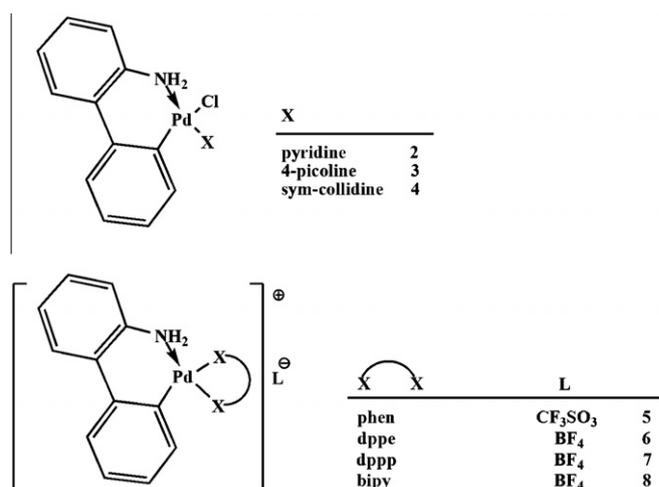
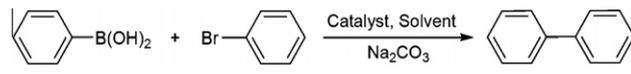


Figure 1. Palladium complexes used as pre-catalysts.

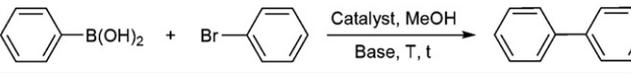
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Table 1
Effect of solvents on the Suzuki reaction of bromobenzene with phenylboronic acid^a


Entry	Catalyst	Solvent	Yield (%)
1	3	MeOH	100
2	3	THF	22
3	3	Acetone	27
4	3	Benzene	3
5	6	MeOH	38
6	6	THF	3
7	6	Acetone	11
8	6	Benzene	0

^a Reaction conditions: bromobenzene (0.5 mmol), phenylboronic acid (0.75 mmol), catalyst (0.01 mmol), Na₂CO₃ (1.5 mmol), solvent (6 mL), 1 h, 65 °C.

Table 2
Effect of catalyst, base, temperature and time on the Suzuki reaction of bromobenzene with phenylboronic acid^a


Entry	Catalyst	Base	Temp/time	Yield (%)
1	3	K ₂ CO ₃	65 °C/1 h	100
2	3	K ₃ PO ₄ ·3H ₂ O	65 °C/1 h	99
3	3	Na ₂ CO ₃	65 °C/30 min	86
4	3	Na ₂ CO ₃	rt/1 h	100
5	2	Na ₂ CO ₃	rt/1 h	100
6	4	Na ₂ CO ₃	rt/1 h	100
7	5	Na ₂ CO ₃	rt/1 h	36
8	6	Na ₂ CO ₃	rt/1 h	12
9	7	Na ₂ CO ₃	rt/1 h	76
10	8	Na ₂ CO ₃	rt/1 h	55

^a Reaction conditions: bromobenzene (0.5 mmol), phenylboronic acid (0.75 mmol), catalyst (0.01 mmol), base (1.5 mmol), MeOH (6 mL).

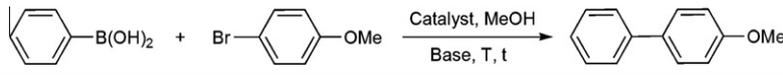
The reaction conditions such as the solvent and base, reaction temperature and time were optimized. Initially, the effectiveness of different solvents such as MeOH, THF, acetone and benzene were tested with palladacycles **3** and **6** in the Suzuki reaction.⁴² The coupling of bromobenzene with phenylboronic acid in the presence of 0.01 mmol of **3** or **6**, 1.5 mmol of Na₂CO₃ as the base and a reaction time of one hour and temperature of 65 °C were chosen as initial conditions to optimize the reaction (Table 1).

MeOH proved to be the best solvent and this may be due to the better solubility of the reagents and easier reduction of Pd(II) to

Pd(0), and hence a facile entry to the catalytic cycle. The reaction did not proceed in benzene. After optimizing the solvent, the reaction was run with two different substrates, 4-bromoanisole and 2-bromobenzaldehyde, in order to optimize the base (Tables 3 and 4). Among the bases employed, K₂CO₃, K₃PO₄·3H₂O and Na₂CO₃, Na₂CO₃ (Table 2) and K₃PO₄·3H₂O (Tables 3 and 4) were found to be the best. The third factor to be optimized was the reaction time. A shorter reaction time had a positive effect on the reaction of 4-bromoanisole with phenylboronic acid (Table 3, entry 3) which may be due to the prevention of homocoupling. In contrast, two reactions were negatively affected by this change and the catalytic activity decreased (Tables 2 and 4, entry 3). Decreasing the temperature of the reactions, led to different catalytic activity. As the temperature was lowered, there was no decrease in the reaction yield for the reaction of bromobenzene with phenylboronic acid (Table 2, entry 4). Moreover, utilizing Na₂CO₃ instead of K₂CO₃ showed no effect on the reaction, as the anion, CO₃²⁻, which contributes to the catalytic cycle, is the same. The catalytic activity in two other reactions (Tables 3 and 4, entry 4) was reduced, however. The optimized conditions for the reaction of bromobenzene with phenylboronic acid were Na₂CO₃ as base, MeOH as solvent, 1 h as the reaction time, and room temperature. The study was pursued to test catalysts **2**, **4**–**8** using these conditions which resulted in diverse yields. The catalysts with monodentate ligands (**2**–**4**) were the best in all reactions and exhibited better catalytic reactivity than complexes with bidentate ligands (**5**–**8**). Also, the catalytic activity of **6** was lower than that of **7** in all the reactions in this work. This may be due to the fact that Pd(II) in palladacycles with five-membered rings is difficult to reduce to Pd(0). The best conditions for the reactions of 4-bromoanisole and 2-bromobenzaldehyde with phenylboronic acid were the same as those for the reaction of bromobenzene with phenylboronic acid, except for differences in the reaction times, which are shown in Tables 3 and 4.

Using the optimized reaction conditions, complex **4** was applied to a representative range of aryl chlorides (Table 5). The activated electron-deficient substrate, 4-chlorobenzaldehyde coupled with phenylboronic acid to give a relatively high yield of product (entry 1). Unexpectedly, the reaction of 4-nitrochlorobenzene failed to give a high yield (entry 2). Chlorobenzene was also coupled with phenylboronic acid to afford a high yield of biphenyl (entry 3). The deactivated electron-rich aryl chlorides, 4-chlorotoluene and 4-chloroaniline were poor substrates (entries 4 and 5). It can be inferred that the electronic effects of the substituents on the aryl chlorides had significant influence on the reaction and electron-withdrawing substituents were more appropriate for the coupling.

In all the reactions of aryl bromides and chlorides, particularly when complexes **2**–**4** were applied, the suspension color turned

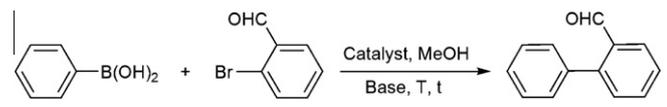
Table 3
Effect of base, catalyst, temperature and time on the Suzuki reaction of 4-bromoanisole with phenylboronic acid^a


Entry	Catalyst	Base	Temp/time	Yield (%)
1	3	K ₂ CO ₃	65 °C/1 h	89
2	3	K ₃ PO ₄ ·3H ₂ O	65 °C/1 h	90
3	3	K ₃ PO ₄ ·3H ₂ O	65 °C/30 min	92
4	3	K ₃ PO ₄ ·3H ₂ O	rt/30 min	85
5	2	K ₃ PO ₄ ·3H ₂ O	65 °C/30 min	89
6	4	K ₃ PO ₄ ·3H ₂ O	65 °C/30 min	98
7	5	K ₃ PO ₄ ·3H ₂ O	65 °C/30 min	31
8	6	K ₃ PO ₄ ·3H ₂ O	65 °C/30 min	20
9	7	K ₃ PO ₄ ·3H ₂ O	65 °C/30 min	71
10	8	K ₃ PO ₄ ·3H ₂ O	65 °C/30 min	35

^a Reaction conditions: 4-bromoanisole (0.5 mmol), phenylboronic acid (0.75 mmol), catalyst (0.01 mmol), base (1.5 mmol), MeOH (6 mL).

Table 4

Effect of base, catalyst, temperature and time on the Suzuki reaction of 2-bromobenzaldehyde with phenylboronic acid^a



Entry	Catalyst	Base	Temp/time	Yield (%)
1	3	K ₂ CO ₃	65 °C/1 h	97
2	3	K ₃ PO ₄ ·3H ₂ O	65 °C/1 h	99
3	3	K ₃ PO ₄ ·3H ₂ O	65 °C/30 min	97
4	3	K ₃ PO ₄ ·3H ₂ O	rt/1 h	89
5	2	K ₃ PO ₄ ·3H ₂ O	65 °C/1 h	96
6	4	K ₃ PO ₄ ·3H ₂ O	65 °C/1 h	88
7	5	K ₃ PO ₄ ·3H ₂ O	65 °C/1 h	33
8	6	K ₃ PO ₄ ·3H ₂ O	65 °C/1 h	24
9	7	K ₃ PO ₄ ·3H ₂ O	65 °C/1 h	40
10	8	K ₃ PO ₄ ·3H ₂ O	65 °C/1 h	54

^a Reaction conditions: 2-bromobenzaldehyde (0.5 mmol), phenylboronic acid (0.75 mmol), catalyst (0.01 mmol), base (1.5 mmol), MeOH (6 mL).

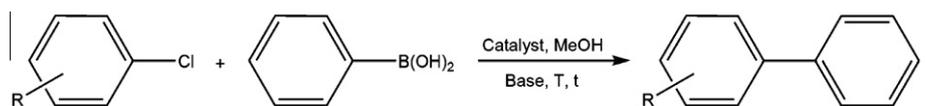
black at the beginning of the reactions. Thus, it can be inferred that the reaction mechanism starts with a pre-dissociation and/or reduction step in which the Pd(II) source is converted into the more active and coordinatively unsaturated Pd(0) catalyst.⁴³ This is followed by oxidative addition of the aryl halide which is often the rate determining step in cross-coupling catalytic cycles.⁴⁴ The high C–Cl bond strength compared with C–Br disfavors oxidative addition and makes the coupling of such substrates far more challenging.⁴⁵ The catalytic cycle is completed by transmetalation, aryl group transfers from boron to palladium, and a final reduction–elimination to release the product. Therefore, the relative contribution of steric and electronic effects is very important, particularly for less reactive aryl halides.^{46–48}

In comparison with PdCl₂, complex **4** showed higher catalytic activity in the reactions of bromo- and chlorobenzene with phenylboronic acid (Table 5, entries 6 and 7). The rate of coupling for each of these reactions was lower than that when complex **4** was used (Table 2, entry 6 and Table 5, entry 3).

The catalytic activity of the palladacycles was also studied in the Heck reaction⁴⁹ of the aryl bromides with styrene. The catalytic activity of **2**, **3**, and **4** with the optimal conditions obtained from the Suzuki reaction of aryl bromides with phenylboronic acid were examined in the Heck reaction of bromobenzene, 4-bromoanisole, and 2-bromobenzaldehyde with styrene. The results are summarized in Table 6.

Table 5

Use of the optimized conditions for the Suzuki reaction of aryl chlorides with phenylboronic acid^a



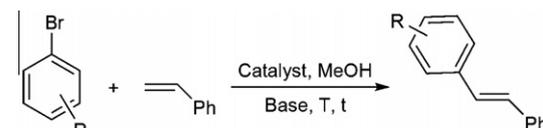
Entry	R	Catalyst	Base	Temp/time	Yield (%)
1	<i>p</i> -CHO	4	K ₃ PO ₄ ·3H ₂ O	65 °C/1 h	77
2	<i>p</i> -NO ₂	4	K ₃ PO ₄ ·3H ₂ O	65 °C/1 h	35
3	H	4	Na ₂ CO ₃	rt/1 h	74
4	<i>p</i> -Me	4	K ₃ PO ₄ ·3H ₂ O	65 °C/30 min	17
5	<i>p</i> -NH ₂	4	K ₃ PO ₄ ·3H ₂ O	65 °C/30 min	13
6	H	PdCl ₂	Na ₂ CO ₃	rt/1 h	20
7 ^b	H	PdCl ₂	Na ₂ CO ₃	rt/1 h	42

^a Reaction conditions: aryl chloride (0.5 mmol), phenylboronic acid (0.75 mmol), catalyst (0.01 mmol), base (1.5 mmol), MeOH (6 mL).

^b Bromobenzene was used as the aryl halide.

Table 6

The catalytic activity in the Heck reaction of aryl bromides with styrene using the optimized Suzuki reaction conditions^a

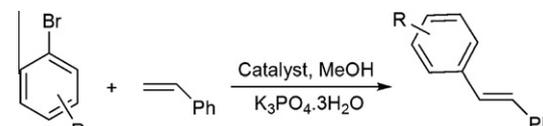


Entry	R	Catalyst	Base	Temp/time	Yield (%)
1	<i>o</i> -CHO	2	K ₃ PO ₄ ·3H ₂ O	65 °C/1 h	2
2	H	3	Na ₂ CO ₃	rt/1 h	0
3	<i>p</i> -OMe	4	K ₃ PO ₄ ·3H ₂ O	65 °C/30 min	37

^a Reaction conditions: aryl bromide (0.5 mmol), styrene (0.75 mmol), catalyst (0.01 mmol), base (1.5 mmol), MeOH (6 mL).

Table 7

Optimization of the Heck reaction of aryl bromides with styrene^a



Entry	Catalyst	R = H ^b (%)	R = <i>p</i> -OMe (%)	R = <i>o</i> -CHO (%)
1	2	7	40	2
2	3	10	27	0
3	4	22	29	3
4	5	2	23	0
5	6	34	45	0
6	7	34	0	0
7	8	0	0	0

^a Reaction conditions: aryl bromides (0.5 mmol), styrene (0.75 mmol), catalyst (0.01 mmol), K₃PO₄·3H₂O (1.5 mmol), MeOH (6 mL), 3 h, 65 °C.

^b Na₂CO₃ (1.5 mmol) was used as the base.

The catalytic activity of **2** (Table 6, entry 1) was negligible and only a trace amount of product was obtained. In the reaction of bromobenzene with styrene using catalyst **3** (Table 6, entry 2), no reaction occurred at room temperature. In addition, there was low catalytic activity in the reaction of 4-bromoanisole with styrene using catalyst **4** (Table 6, entry 3). As these conditions were not efficient for the Heck reaction of aryl bromides, different conditions were employed. The time for all the reactions and the temperature for the reaction of bromobenzene with styrene (Table 6,

entry 2) were both increased. Even after changing the reaction time to 3 h, some reactions showed no catalytic activity. In other reactions, low to moderate yields were obtained. Moreover, the lower yields of the reaction 2-bromobenzaldehyde with styrene can be ascribed to the steric effect of the –CHO group. The results are summarized up in Table 7.

In conclusion, we have developed a new combination of palladacycles with 2-phenylaniline, monodentate and bidentate ligands, which proved to be efficient for the Suzuki reactions of various aryl bromides and chlorides with phenylboronic acid. However, these palladacycles did not work as efficiently in the Heck reaction.

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