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Ionically tagged benzimidazole palladium(II) complex: preparation and catalytic application in cross-coupling reactions

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ABSTRACT

An imidazolium chloride tagged palladium(II) complex has been conveniently prepared and structurally analyzed. It is active toward cross-coupling of arylboronic acid with aryl halide and benzoyl chloride, giving moderate to high yield of the desired biaryls and aryl ketones, respectively. The present phosphine-free (N–N)Pd(II) complex could be efficiently recycled at least four times with minor decrease of activity in the aqueous Suzuki–Miyaura coupling reaction.

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Pd-catalyzed Suzuki–Miyaura cross-coupling of arylboronic acid with aryl halide provides a very important tool for the synthesis of unsymmetrical biaryls.¹ Aromatic ketone can also be effectively prepared by another cross-coupling of arylboronic acid with acid chloride,² and such method can avoid the disadvantages of other strategies such as the low region-selectivity of Friedel– Crafts acylation³ and handling the toxic carbon monoxide in the Pd-catalyzed carbonylation of arylboronic acid and aryl halide.⁴ Furthermore, separation and reuse of the expensive transition metal catalyst and commonly used excess phosphine ligand in the cross-coupling reactions is a particularly attractive feature from the viewpoint of the reduction of catalyst expense and the contamination to product.

Adding an ionic moiety such as imidazolium salt onto the neutral donor ligand to make the resultant metal complex more soluble in water or ionic salt is an ideal solution for immobilization and recycling of the expensive transition metal catalyst, and product could be conveniently extracted from catalyst system by using desirable aqueous or ionic liquid solvent system.⁵ Recently, a wide range of catalysts designed by this methodology have been successfully applied in the cross-coupling,⁶ olefin metathesis,⁷ oxidation,⁸ polymerization reaction⁹ and asymmetric catalysis.¹⁰

Herein, we report the preparation of a structurally defined imidazolium salt functionalized benzimidazole palladium(II) complex (**2**) and its catalytic applications in the C–C cross-coupling of arylboronic acid with aryl halide and acid chloride, respectively.

The route for the synthesis of the ionically tagged palladium catalyst (2) is illustrated in Scheme 1. Direct N-alkylation of commercially available 1,2-dimethyl imidazole with 2-chloromethyl-1-ethyl-benzenimidazole prepared according to our reported procedure afforded the desired methyl imidazolium chloride salt supported benzimidazole ligand (1) as a white solid in 87% yield.¹¹ Subsequently, the new Pd(II) complexes were obtained in 85% yield as yellow crystals from an aqueous methanolic solution of K₂[PdCl₄] with the ligand at room temperature. Formation of this ionically tagged ligand and its Pd(II) complex has been confirmed by ¹H NMR, ¹³C NMR and ESI-MS. For **2** there is an additional group resonance with a ratio of about 1:3.5 for the protons of the ligand's alkyl moieties in its ¹H NMR spectrum, this points to the presence of a secondary species in solution condition apart from the expected main *trans-trans*-Pd(II) complex, which is more stable because of the less steric hindrance between the two ligands. Single crystals suitable for X-ray crystallography of 2 were conveniently obtained by slow diffusion of Et₂O into its MeOH solution. X-ray diffraction analysis revealed an essentially square-planar Pd(II) coordination geometry with two cationic ligands trans to each other [Fig. 1, depository number: CCDC813731].

Pd-catalyzed Suzuki–Miyaura cross-coupling of aryl bromide or iodine with boronic acid is well documented.¹² However, the development of efficient phosphine-free¹³ and recyclable¹⁴ palladium catalyst system still remains to be developed further. Interestingly, we found that **2** was a highly active and recyclable catalyst toward the Suzuki–Miyaura cross-coupling reaction of aryl halides with arylboronic acid.



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Scheme 1. Synthesis of the Pd(II) complex (2) from imidazolium salt precursor (1).



Figure 1. Molecular structure of *trans-trans*-Pd(II) complex (2) showing 30% probability ellipsoids. Selected bond distances [Å] and angles [°]: Pd1-N1 2.015(3), Pd1-Cl1 2.297(8), N1-Pd1-N1A 180.0(2), N1-Pd1-Cl1 89.4(8), N1-Pd1-ClA 90.6(8), Cl1-Pd1-ClA 180.0.

Cross-coupling of deactivated 1-bromo-4-methylbenzene (**3a**) with phenylboronic acid was selected as a model reaction to screen the reaction conditions of the catalyst, and the results are shown in Table 1. Because of the good water solubility of complex **2**, pure water was initially used as a solvent resulting in a 68% isolated yield of the desired biaryl (**5a**) at room temperature within 12 h in the presence of K_2CO_3 as a base (entry 1), and yield could only be improved to 72% by extending the reaction time to 24 h (entry 2), which probably indicates the reaction duration is not a decisive factor to achieve a higher yield of the product. Tetrabutyl ammonium bromide (TBAB) has been approved to be a useful phase

Table 1

Screening experiments for the Suzuki–Miyaura cross-coupling reaction catalyzed by $\boldsymbol{2}^a$

-						
	Entry	Solvent	Base	T (°C)	<i>t</i> (h)	Yield ^b (%)
	1	H ₂ O	K ₂ CO ₃	25	12	68
	2	H_2O	K ₂ CO ₃	25	24	72
	3	TBAB/H ₂ O	K ₂ CO ₃	25	12	89
	4	TBAB/H ₂ O	K ₂ CO ₃	60	12	97
	5	TBAB/H ₂ O	NEt ₃	60	12	77
	6	TBAB/H ₂ O	NaOAc	60	12	23
	7	TBAB/H ₂ O	DMAP	60	12	19

^a Reaction condition: phenylboronic acid (0.6 mmol), 1-bromo-4-methylbenzene (0.5 mmol), TBAB (1.0 g), H₂O (1.0-1.5 mL), base (0.8 mmol), catalyst **2** (1.0 mol %). ^b Isolated yield a free column charmed terrarphy.

^b Isolated yield after column chromatography.

transfer catalyst and stabilizer to improve activity of the metal catalyst in the aqueous catalytic system.¹⁵ Consequently, the yield was promoted from 68% to 89% by addition of certain amount of TBAB (entry 3), raising the temperature to 60 °C gave the excellent yield of 97% (entry 4). Then the aqueous TBAB/H₂O mixture and 60 °C were selected as the optimized solvent system and reaction temperature, respectively. Lower yield (77%) was obtained in the presence of organic base such as triethyl amine (NEt₃) (entry 5), NaOAc and 4-dimethylamiopryidine (DMAP) even gave quite low yield of the product (entries 6 and 7).

With the optimized reaction condition in hand, we next extended scope of the present protocol to the cross-coupling of other aryl halides with the substituted phenylboronic acid (Table 2). Phenyl bromides with an electronic withdrawing group (EWG) (**3b-3f**) could couple efficiently with general high isolated yields (>90%) of the desired product (5b-5f) (entries 1-5). Coupling of biphenyl bromide with phenylboronic acid also proceeded smoothly giving an 88% yield of 5g (entry 6). The deactivated 1-bromo-4-methylbenzene (3a) worked well toward the phenylboronic acid with a EWG (4b and 4c) (entries 7 and 8). 4-Nitrophenyl bromide could react with boronic acid having either a EWG or electronic donating group (EDG), resulting in the corresponding substituted biaryls (5j-5l) in 92-98% yield (entries 9–11). The catalyst was also effective toward the coupling of activated arvl bromide with 2- or 3-methyl substituted phenylboronic acid with excellent yield of the desired products (5m-5o, entries 12-14). Interestingly, the present water soluble catalyst also worked well toward the coupling of aryl chloride giving a 70% yield of 5a (entry 15).

The reusability of expensive metal catalyst is very important from the viewpoints of economy and the reduction of catalyst contamination to the product. Suzuki–Miyaura coupling of deactivated **3a** with phenylboronic acid was selected to test the recyclability of **2**, because of its air stability and insolubility with less polar organic solvent such as ether, the catalyst (H₂O–TBAB phase containing catalyst) could be easily separated from the product phase (nonpolar organic solvent phase) by extraction three times with diethyl ether, subsequently the catalyst phase can be directly reused in the next run with fresh addition of base, and it was found that the present phosphine-free ionic Pd(II) complex showed high stability and could be used at least five times with the fifth run giving a 86% isolated yield of the desired 4-methylbiphenyl (**5a**) (for more details about reuse experiment, see Supplementary data).

Another interesting application of **2** was the cross-coupling of arylboronic acid with acid chloride to yield aryl ketones, which are extensively used in pharmaceuticals fragrance and agrochemicals.^{2a,16} Firstly, reaction of phenylboronic acid with benzoyl chloride was chosen to optimize reaction conditions (Table 3). Typical reaction was carried out in the presence of 1.0 mol % Pd(II) catalyst (**2**) at room temperature with water as solvent. Unfortunately, benzophenone (**7a**) was obtained as a main product only in 43% yield with carboxylic anhydride (17%) as the only by-product, which led to the low yield of the desired **7a** (entry 1). In 2008, Xin reported

Table 2

Pd(II) complex catalyzed Suzuki-Miyaura cross-coupling of aryl halides with arylboronic acids in aqueous TBAB solution^a

$$R^{2} \xrightarrow{} X = CI,Br \xrightarrow{} R^{1} \xrightarrow{} B(OH)_{2} \xrightarrow{1.0 \text{ mol } \% 2} \xrightarrow{R^{2}} \xrightarrow{} R^{1}$$

Entry	R ²	R ¹	Product	Yield ^b (%)
1	CF ₃ , 3b	H, 4a	CF ₃ 5b	98
2	CN, 3c	Н, 4а		98
3	NO ₂ , 3d	H, 4a	Sd	89
4	F, 3e	Н, 4 а	F 5e	96
5	Cl, 3f	Н, 4а		90
6	Ph, 3g	H, 4a	⟨Ph 5g	88
7	CH₃, 3a	4-F, 4b	F-CH ₃ 5h	81
8	CH ₃ , 3a	4-CF ₃ , 4c	F ₃ C-CH ₃ 5i	79
9	NO ₂ , 3d	4-F, 4b	F	98
10	NO ₂ , 3d	4-CF ₃ , 4c		97
11	NO ₂ , 3d	3-CH ₃ , 4d	H ₃ C 51	92
12	F, 3e	3-CH ₃ , 4d	H ₃ C 5m	90
13	F, 3e	2-CH ₃ , 4e	CH ₃ 5n	93
14	CN, 3c	2-CH ₃ , 4e		93
15 ^c	CH ₃ , X = Cl, 3h	H, 4a	<u>С</u> -Сн ₃ 5а	70

^a Reaction condition: aryl halide **3** (0.5 mmol), arylboronic acid **4** (0.6 mmol), TBAB (1.0 g), H₂O (1.0–1.5 mL), K₂CO₃ (0.8 mmol), 12 h.

^b Isolated yield after column chromatography.

^c Temperature is 80 °C.

 Table 3

 Screening experiment for the cross-coupling reaction of benzoyl chloride with phenylboronic acid^a

Entry	Solvent	T (°C)	<i>t</i> (h)	Yield ^b (%)
1	H ₂ O	25	12	43
2	Acetone + H ₂ O	25	4	62
3	Acetone + H ₂ O	25	12	65
4	Acetone + H ₂ O	60	4	70
5	Acetone + H ₂ O	60	12	85

 a Reaction condition: phenylboronic (1.2 mmol), benzoyl chloride (1.0 mmol), acetone (1.5 mL), H₂O (1.5 mL), Na₂CO₃ (1.6 mmol).

^b Isolated yield after column chromatography.

that reaction of arylboronic acid with carboxylic anhydride to afford ketone can be promoted in good to excellent yield by using a mixture of acetone/ H_2O (the best rate is 1:1) as solvent.¹⁷ In order to convert the carboxylic anhydride by-product in our catalytic system to ketone, coupling reaction was performed in acetone/ H_2O aqueous mixture and a surprising promotion of yield to 62% was observed in 4 h at room temperature (entry 2), and there was no by-product (carboxylic anhydride) detected any more from GC– MS analysis. Raising temperature to 60 °C can increase the catalytic activity further, and an optimized yield of 85% could be achieved by extending the reaction time to 12 h (entries 4 and 5).

To further understand the scope and limitations of this catalytic system for cross-coupling reaction, we have investigated the cou-

Table 4

Coupling reaction of acid chlorides with arylboronic acids^a



Entry	\mathbb{R}^1	R ³	Product	Yield ^b (%)
1	Н	Н		85
2	4-F	Н	F The second sec	98
3	4-CF ₃	Н	F ₃ C 7c	70
4	3-CH₃	Н		82
5	2-CH ₃	Н		73
6	Н	Me	CH ₃ 7f	51
7	4-F	Me	Р С. С. Н ₃ 7g	45
8	4-CF ₃	Me	F ₃ C CH ₃ 7h	63
9	3-CH₃	Me		90
10	2-CH ₃	Me		47
11	Н	Cl	C ¹ 7k	68
12	4-F	Cl	F Cl 7l	51
13	4-CF ₃	Cl	F ₃ C Cl 7m	55

Table 4 (a)	
	mmea



^a Reaction condition: acid chloride **6** (1.0 mmol), arylboronic acid **4** (1.2 mmol), H_2O (1.5 mL), acetone (1.5 mL), Na_2CO_3 (1.6 mmol), 12 h.

^b Isolated yield after column chromatography.

pling of representative acid chlorides and arylboronic acids under the optimized reaction conditions (Table 4).¹⁸ As shown in Table 4, the reaction of benzoyl chloride with arylboronic acids bearing electron-withdrawing (-F, -CF₃) and electron-donating (-CH₂) groups proceeded the corresponding ketones (7b-7e) in good to high isolated yield, which indicated that the effect of substituent of arylboronic acids on the catalytic activity is not obvious. In order to gain more information about the effect of substituents on another coupling partner (benzoyl chloride), p-toluoyl chloride and 4-chlorobenzoyl chloride were selected to react with a range of arylboronic acids. As seen in Table 4 (entries 6-15), it was observed that either 4-chlorobenzoyl chloride or p-toluoyl chloride could couple smoothly with arylboronic acids, resulting in the corresponding substituted aryl ketones (7f-7o) in 45-90% yield.¹⁹ A sterically hindered 2-methylphenylboronic acid could also react with acid chlorides giving 47-86% vield of the desired products (entries 5, 10, and 15). As found in other catalyst systems for the cross coupling of acid chloride and boronic acid, the present ionically tagged Pd(II) complex did not show obvious substituent effect on its catalytic performance.^{2c}

In summary, we have prepared a structurally defined Pd(II) complex which demonstrated efficient activities toward the cross-couplings of aryl halides with representative phenylboronic acids under aqueous catalytic system. This imidazolium salt supported (N–N)Pd(II) complex could be conveniently recycled up to four times keeping high reactivity under aerobic conditions. Its utility can be extended to another cross-coupling of arylboronic acids with acid chlorides affording moderate to good yields of the desired aryl ketones. Investigations on preparation of active and stably recyclable catalyst in matching aqueous solvent system are ongoing in our lab.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.05.079.

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- 18. General procedure for cross-coupling reaction of boronic acid with benzoyl chloride: The catalyst (3.8 mg, 1.0 mol %), Na_2CO_3 (170 mg, 1.6 mmol), H_2O (1.5 mL) and acetone (1.5 mL) were added into a 25 mL schlenk flask, then the reactor was stirred at room temperature for several minutes to dissolve the catalyst and base homogenously. Subsequently, benzoyl chloride (1.0 mmol) and boronic acid (1.2 mmol) were introduced. Then the flask was immersed in an oil bath preheated at 60 °C for 12 h. After the reaction was completed, the mixture was extracted with diethyl ether, and the combined organic layer was dried over anhydrous Na_2SO_4 and was subsequently purified by flash chromatography using silica gel (petroleum ether/ethyl acetate = 20:1) yielding the desired products.
- NMR data for selected product: m-tolyl-p-tolyl-methanone (**7i**) (Table 3, entry 9): ¹H NMR(CDCl₃, 400 MHz): δ 7.71–7.69 (d, J = 7.70 Hz, 2H), 7.59 (s, 1H), 7.55–7.53 (d, J = 7.54 Hz, 1H), 7.37–7.30 (m, 2H), 7.26–7.24 (d, J = 7.25 Hz, 2H), 2.41 (s, 3H), 2.39 (s, 3H); ¹³C NMR(CDCl₃, 100 MHz): δ 195.6, 142.1, 137.0, 136.9, 134.0, 131.9, 129.3, 129.2, 127.9, 127.0, 126.1, 20.6, 20.3.