

Highly Active Heterogeneous Palladium Catalyst for the Suzuki Reaction of Heteroaryl Chlorides

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The field of supported transition metal complex catalysts is attracting widespread interest at the present time.¹ The objective of this study is to combine the advantages of homogeneous catalysts with the great ease of separation in large-scale synthesis afforded by heterogeneous catalysts. The most satisfactory method of supporting transition metal complexes involves the formation of a chemical bond between the surface of a solid support and a ligand group in the metal complex.² In this way, transition metal complexes can be attached to the surface of organic and inorganic solids and used as heterogeneous catalysts. Recently we have shown that magnetic particle-supported β -ketoiminatophosphanyl Pd complex **1** acts as an efficient catalyst for the Suzuki coupling reaction of aryl chlorides.³

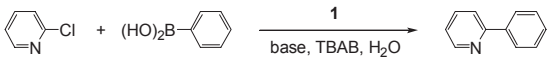
The Suzuki reaction between aryl halides and arylboronic acids is one of the most useful methods for the preparation of biaryls, which are important compounds as precursors to pharmaceuticals, ligands, and polymers.⁴ Although many heterogeneous catalysts have been developed for this process in recent years, a long-standing limitation in the couplings arises from the inability to effectively couple readily accessible and cheap aryl chlorides.⁵ Moreover, the couplings of heteroaryl chlorides are more difficult because the competitive binding between the substrates and the metal center may result in the formation of catalytically inactive complexes.⁶ In spite of considerable research effort, there is only few efficient method for the heterogeneous couplings of heteroaryl chlorides.⁷ Therefore, the development of efficient heterogeneous catalysts for the Suzuki couplings of heteroaryl chlorides would be highly desired. Herein, we report the Suzuki reaction of heteroaryl chlorides using supported Pd catalyst **1**.

In the initial studies, we tested the Suzuki coupling of 2-chloropyridine with phenylboronic acid in the presence of 0.5 mol % of **1** and 2 equiv of K_2CO_3 (Table 1). Water was used as a solvent for environmental benefit, even though the activity was increased in organic solvents. Tetrabutylammonium bro-

midate (TBAB) as a phase transfer agent was added to enhance the reactivity in water. The reaction proceeded to completion at 60 °C within 4 h (entry 1). Good conversions was observed even at 40 - 50 °C but it was necessary to use longer reaction time (entries 2 and 3). It is interesting that the reactions in water gave good results under mild conditions. The effects of base and catalyst loading were also surveyed. The use of K_3PO_4 , Na_2CO_3 , and Cs_2CO_3 instead of K_2CO_3 as a base gave inferior results under the same conditions (entries 4-6). When the extent of catalyst loading was increased to 1 mol %, only a minor improvement of rate was observed (entry 7). However, decreasing the catalyst loading to 0.2 mol % caused a significant drop in the rate (entry 8).

Using the optimized conditions, we next investigated the scope and generality of this process (Table 2). The coupling of 3- and 4-chloropyridine with phenylboronic acid gave the corresponding products in excellent yields, respectively (entries 1 and 2). 2-Chloropyridine underwent the coupling with different arylboronic acids (entries 3-5). It should be noted that deactivated 2-chloro-3-methylpyridine proceeded very well (entry 6). The catalyst also displayed high activity in the coupling of heteroaryl chlorides such as 2-chloropyrimidine, 2-chloroquinoline, 1-chloroisoquinoline and 2-chloroimidazole (entries 7-10). Importantly, unprotected aminochloropyridines were found to be suitable coupling substrates (entries 11 and 12). It is known that the coupling of basic heteroaryl chlorides bearing unprotected amino groups can be severely retarded by an affinity of the

Table 1. Suzuki coupling of 2-chloropyridine with phenylboronic acid^a

					
Entry	1 (mol %)	base	temp (°C)	time (h)	yield (%) ^b
1	0.5	K_2CO_3	60	5	95
2	0.5	K_2CO_3	50	8	91
3	0.5	K_2CO_3	40	12	83
4	0.5	K_3PO_4	60	5	90
5	0.5	Na_2CO_3	60	5	73
6	0.5	Cs_2CO_3	60	5	52
7	1.0	K_2CO_3	60	5	97
8	0.2	K_2CO_3	60	10	83

^aReaction conditions: 2-chloropyridine (1.0 mmol), phenylboronic acid (1.2 mmol), base (2.0 mmol), H_2O (2 mL), TBAB (0.5 mmol), and catalytic amount of **1** (0.21 mmol/g). ^bIsolated yield.

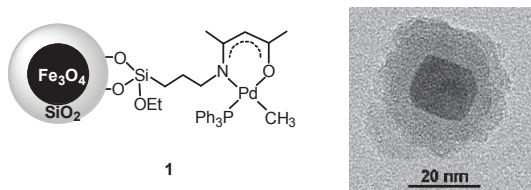
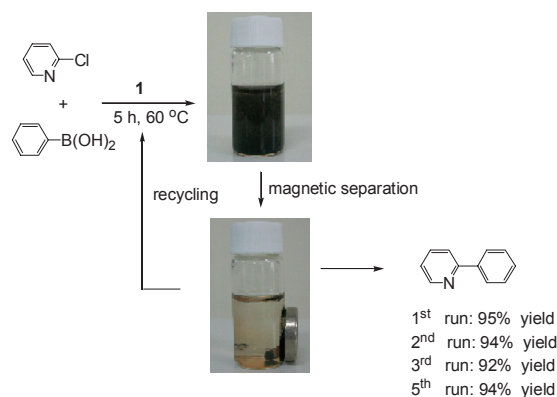


Figure 1. Structure and TEM image of Pd complex **1**.

Table 2. Suzuki coupling of heteroaryl chlorides with arylboronic acids^a

$\text{Heteroaryl-Cl} + (\text{HO})_2\text{B-} \begin{array}{c} \text{---} \text{R} \end{array} \xrightarrow[\text{H}_2\text{O, 60 } ^\circ\text{C}]{\text{1 (0.5 mol \%), K}_2\text{CO}_3, \text{TBAB}} \text{Heteroaryl-} \begin{array}{c} \text{---} \text{R} \end{array}$				
Entry	Heteroaryl-Cl	Aryl-B(OH) ₂	Time (h)	Yield (%) ^b
1			5	85
2			5	91
3			5	92
4			5	86
5			8	91
6			10	85
7			5	92
8			8	91
9			8	90
10			8	92
11 ^c			10	86
12 ^c			10	87
13			10	81
14			12	80
15			5	92
16			5	90
17			8	91
18			8	88
19			8	84
20			8	83
21			8	81

^aReaction conditions: heteroaryl chloride (1.0 mmol), arylboronic acid (1.2 mmol), TBAB (0.5 mmol), H₂O (2 mL), **1** (0.5 mol %, 0.21 mmol/g), and 50 °C. ^bIsolated yields. ^cReaction temperature: 80 °C.

**Figure 2.** Magnetic separation and recycling of **1** in the Suzuki coupling of 2-chloropyridine with phenylboronic acid.

amino group to the Pd center of the catalyst.⁸ Moreover, satisfactory results were obtained in the coupling with 3-pyridinylboronic acid known as a less reactive reagent (entries 13 and 14). The reaction is impressive when the scope of this catalytic system was further extended to the couplings of 2- and 3-chlorothiophene. The reaction afforded the corresponding products in good yields. (entries 15–19). These results came as a surprise since sulfur-containing heteroaryl chlorides in the coupling reaction are also challenging substrates due to the strong affinity of the sulfur to the Pd. This catalytic system also allowed the coupling with 3-pyridinylboronic acid (entries 20 and 21). Overall, our catalyst showed unprecedented activity for the mild Suzuki coupling reaction of heteroaryl chlorides in water.

The separation of heterogeneous catalysts is generally performed by filtration with reduced efficiency. In our catalyst system, because of the superparamagnetic nature of the Fe₃O₄ support, it can be separated by using external magnets with high efficiency. The recycling of **1** was attempted in the coupling of 2-chloropyridine with phenylboronic acid (Figure 2).⁹ The reusability of heterogeneous catalysts is very important for its practical applications. It was shown that the Fe₃O₄ nanoparticle catalyst could be reused at least five times without significant loss of catalytic activity.

In summary, Fe₃O₄-supported β-ketoiminatophosphanyl Pd complex **1** showed excellent catalytic activity for the Suzuki coupling reaction in water. This heterogeneous catalyst could be reused without a significant loss in the catalytic activity. Moreover, recovery of the catalyst by an external permanent magnet was very facile and efficient.

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9. Chloropyridine (114 mg, 1.0 mmol), phenylboronic acid (146 mg, 1.2 mmol), K₂CO₃ (276 mg, 2.0 mmol), TBAB (161 mg, 0.5 mmol), dodecane (10 mg, internal standard) and catalyst **1** (24 mg, 0.5 mol %, 0.21 mmol/g) were mixed in H₂O (2 mL). The mixture was stirred at 60 °C in an air atmosphere. After magnetic separation of the catalyst, the reaction mixture was extracted twice with diethyl ether. The organic layer was dried over MgSO₄ and the solvent was evaporated under reduced pressure. The crude was analysed by GC/GC-MS. The product was purified by short-column chromatography on silica gel. In the recycling experiment, the separated catalyst was successively reused for the next reaction without any treatment.