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Short communication

Palladium catalyzed the Suzuki cross-coupling reaction using a fluorous NHC ligand

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ABSTRACT

The utilization of N-heterocyclic carbene palladium complex immobilized on fluorous silica gel through fluorous–fluorous interactions in the Suzuki cross-coupling reaction was described. The reactions were carried out under aerobic and phosphine-free conditions with moderate to excellent product yields. The catalyst was easily recovered and reused three times without significant loss of activity.

1. Introduction

The Suzuki reaction catalyzed by palladium is one of the most powerful routes for the formation of C(sp^2)–C(sp^2) bonds. This reaction has been used to make biaryl derivatives that are important intermediates in polymers, liquid crystals, pharmaceuticals, and herbicides [1–6]. From an industrial point of view, one of significant issues in the Suzuki reaction has focused on heterogeneous catalyst. Homogeneous catalysts have been of somewhat limited use, mainly because of the difficulty in separation from the reaction products that in turn may lead to economical/environmental problems especially in the case of expensive or toxic metal catalysts. Therefore, a heterogeneous catalyst for the Suzuki reaction is still needed for industrial applications.

Since Arduengo and co-workers isolated the first stable N-heterocyclic carbene, N-heterocyclic carbenes (NHCs) are widely used as ligands in inorganic and organometallic chemistry [7–14]. NHCs were first considered as simple phosphine mimics in organometallic chemistry [15]. However, increasing experimental data clearly showed that NHC–metal catalysts can surpass their phosphine-based counterparts in both activity and scope [16,17]. NHCs behave like typical σ-donor ligands in metal coordination chemistry. Moreover, NHCs have excellent air and moisture stability and have higher dissociation energy. Therefore, NHCs can enhance the reactivity and stability of palladium catalysts compared with phosphines [18–22]. Recently, several supported NHC–Pd catalysts by immobilization of the corresponding homogeneous complexes on Wang resin [23], Merrifield resin [24], polystyrene [25,26] have been developed to combine the advantages of both homogeneous and heterogeneous catalysts in a number of cross-coupling reactions. However, the polymer backbones in these catalysts are very expensive and most of them suffer from the drawback that many of their catalytic active sites are in the interior of the support. Therefore, it is often necessary to use a high loading of these palladium-based catalysts in a typical reaction.

Recently, Bannwarth and co-workers [27,28] have reported some immobilizing perfluoro-tagged palladium catalysts which were prepared via adsorption of palladium(II) complexes containing perfluorinated phosphine ligands on fluorous silica gel (FSG). These heterogeneous catalysts showed the advantages of their utilization (separation and recovery of perfluoro-tagged palladium) in the Suzuki cross-coupling reaction in comparison with fluorous biphasic catalysis approaches using expensive and environmentally persistent perfluorinated solvents. Vallribera and co-workers [29–31] have developed some new immobilized phosphine-free palladium systems in the alkynylation of aryl halides and the Heck reaction. Wang and co-workers reported the immobilized palladium nanoparticles on fluorous silica gel to catalyze the Suzuki reaction in water [32]. Although these systems are efficient in catalyzing these two C–C bond-forming reactions, the palladium catalysts were prepared in multiple steps, using

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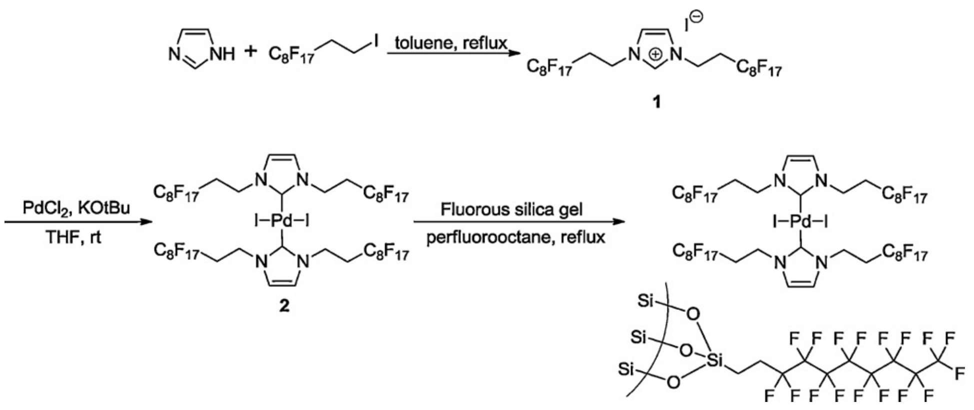


Scheme 1. Preparation of the fluorous NHC–Pd/FSG.

expensive starting materials and high palladium contamination in the products still limit their industrial applications. To address these concerns, the use of simple, low-cost, phosphine-free, recoverable and recyclable heterogeneous catalyst would provide obvious advantages in many synthetic applications.

We herein report an efficient fluorous heterogeneous NHC–Pd catalyst for the Suzuki cross-coupling reaction. In the presence of 0.1 mol% palladium catalyst, the reactions of aryl halides with arylboronic acids in DMF/water underwent efficiently to generate the corresponding products in good to excellent yields. Furthermore, the heterogeneous catalyst was recovered from the reaction mixture by a simple filtration and reused three times without significant loss of its activity.

2. Results and discussion

N-heterocyclics carbenes are easily accessible from imidazolium salts, which can in turn be prepared by alkylation of

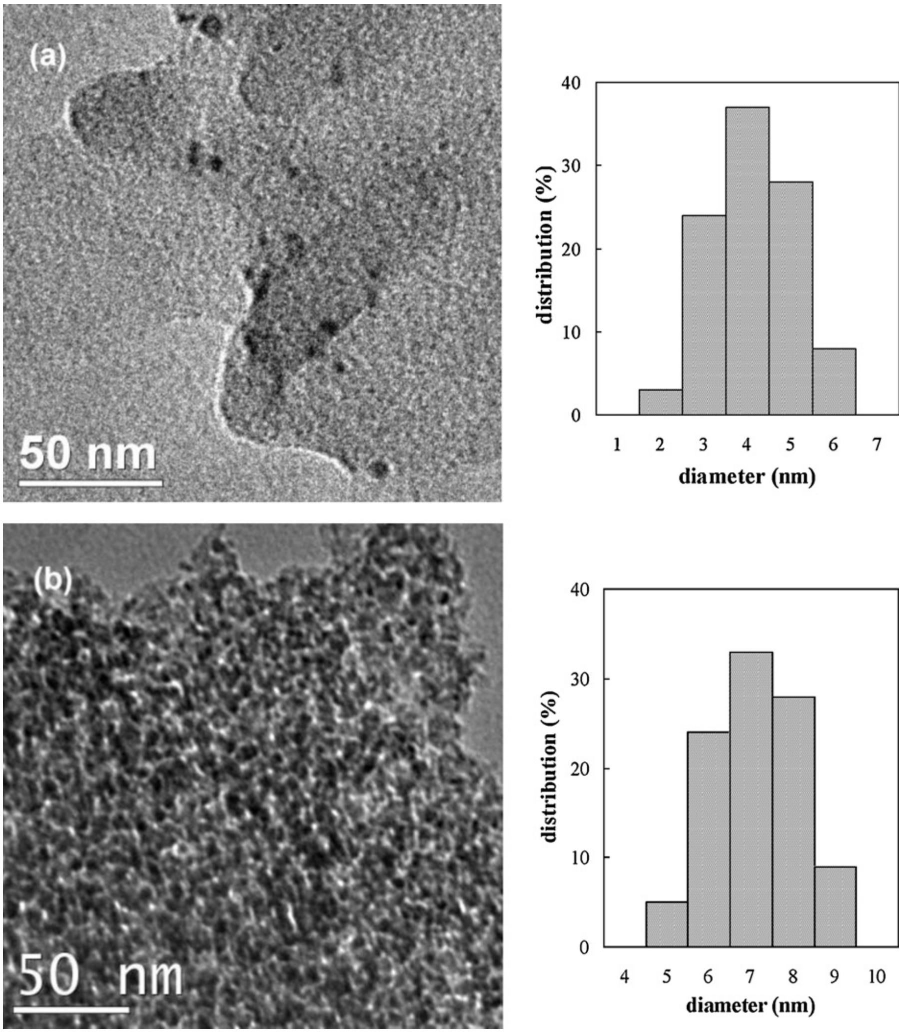
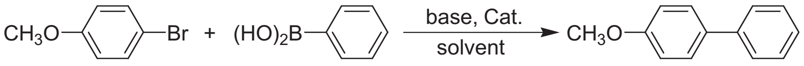


Fig. 1. (a) TEM image and particle size distribution histogram of the fluorous NHC–Pd/FSG. (b) TEM image and particle size distribution histogram of the catalyst after 3 runs.

Table 1
Optimization study for the Suzuki reaction of 4-bromoanisole with phenylboronic acid.[a]



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Entry	Solvent	TBAB (mol%)	Base	Time (h)	Yield[b] (%)
1	H_2O	0	K_2CO_3	2	39
2	H_2O	50	K_2CO_3	2	48
3	H_2O	50	K_3PO_4	2	70
4	H_2O	100	K_3PO_4	2	62
5	H_2O	50	K_3PO_4	6	78
6	EtOH/H_2O (v/v = 1:0.5)	0	K_2CO_3	2	12
7	DMF/H_2O (v/v = 1:1)	0	K_2CO_3	2	78
8	DMF/H_2O (v/v = 1:0.5)	0	K_2CO_3	2	50
9	DMF/H_2O (v/v = 0.5:1)	0	K_2CO_3	2	39
10	DMF/H_2O (v/v = 1:1)	0	Cs_2CO_3	2	81
11	DMF/H_2O (v/v = 1:1)	0	K_3PO_4	2	99
12	DMF	0	K_3PO_4	2	74
13	DMF/H_2O (v/v = 1:1)	0	K_3PO_4	0.5	99
14[c]	DMF/H_2O (v/v = 1:1)	0	K_3PO_4	0.5	89

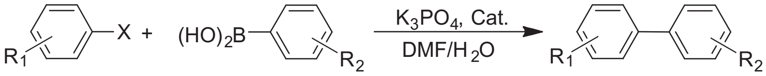
[a] Reaction conditions: 4-bromoanisole (1.0 mmol), phenylboronic acid (1.5 mmol), base (2.0 mmol), catalyst (0.1 mol%) in 2 mL solvent at 100 °C in air.
[b] Isolated yield.
[c] 0.05 mol% catalyst loading.

imidazoles [33]. The N,N′-difluoroalkyl-substituted imidazolium salt **1** was prepared by alkylation of imidazole with 1H,1H,2H,2H-perfluorodecyl iodide in toluene in one pot (Scheme 1). The product was obtained by filtration and washed with solvents without further purification in moderate yield (43%).

N-heterocyclic carbene metal complex can be prepared by ligand substitution reactions using free carbenes, which are accessible via deprotonation of the corresponding imidazolium salts in THF with KO-*t*-Bu at room temperature. The fluorous NHC–Pd complex was isolated as gray solid. The immobilization of the catalyst was according to the usual procedure, which heating the fluorous NHC–Pd complex in perfluorooctane at 100 °C for 12 h, then added FSG (C_8; 35–70 μm) and stirred the mixture at the same temperature for 2 h. The fluorous solvent was vaporized to obtain the immobilized catalyst as gray solid. The TEM image was shown in Fig. 1a. It was obvious that the palladium nanoparticles were successfully dispersed in the fluorous silica gel with an average size of 3–5 nm [34,35]. Due to the low palladium loading on the fluorous silica gel, there are no obvious peaks in XRD analysis.

In order to evaluate the catalytic activity of the immobilized fluorous NHC–Pd catalyst in Suzuki coupling reactions, we first investigated the reaction between 4-bromoanisole and phenylboronic acid in the presence of 0.1 mol% Pd catalyst. To begin our study, we examined various parameters to optimize reaction conditions. Water is cheap, readily available, nontoxic, and nonflammable, which offers practical advantages over organic solvents. Using water as solvent the yield was given in 39% (Table 1, entry 1). It has been reported that additives such as

Table 2
Suzuki cross-coupling reactions of aryl halides with arylboronic acids.[a]



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Entry	X	R_1	R_2	Time (h)	Yield[b] (%)
1	Br	H	H	0.5	98
2	Br	4-CH_3O	H	0.5	98
3	Br	2-CH_3O	H	0.5	94
4	Br	4-NO_2	H	0.5	99
5	Br	2-NO_2	H	0.5	95
6	Br	4-CF_3	H	0.5	99
7	Br	3-CF_3	H	0.5	99
8	Br	4-CH_3CO	H	0.5	96
9	Br	4-CHO	H	0.5	97
10	I	H	H	0.5	99
11	I	4-NO_2	H	0.5	99
12	I	2-NO_2	H	0.5	99
13	I	4-CH_3	H	0.5	98
14	I	2-CH_3	H	0.5	96
15	Br	4-CH_3O	4-Cl	0.5	98
16	Br	4-CH_3O	4-CF_3	0.5	97
17	Br	4-CH_3O	4-CH_3O	0.5	95
18	Br	4-CH_3O	4-CH_3	0.5	92
19	Cl	H	H	1	35
20	Cl	4-NO_2	H	1	43
21	Cl	4-CH_3	H	1	18

[a] Reaction conditions: aryl halide (1.0 mmol), arylboronic acid (1.5 mmol), K_3PO_4 (2 mmol), catalyst (0.1 mol% Pd) in 2 mL DMF/H_2O (v/v = 1:1) at 100 °C in air.
[b] Isolated yield.

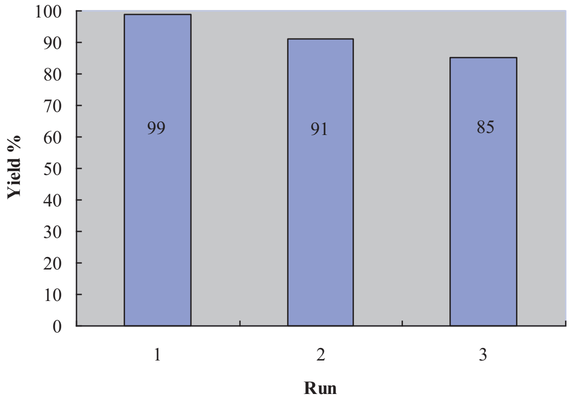

Fig. 2. Recycling experiments of the catalyst.

tetrabutylammonium bromide (TBAB) can enhance the reaction rate in the coupling reactions. However, only a little increase in yield when using 50 mol% TBAB (Table 1, entry 2). Then, we chose K_3PO_4 as a base in the Suzuki reaction and a good yield was obtained (Table 1, entry 3). Increase in the amount of TBAB and prolongation of the reaction time did not result in the satisfactory level of the corresponding product yield (Table 1, entries 4 and 5). It was known that organic/aqueous co-solvent has the merit of good solubility of the organic reactants and the inorganic base. Compared with EtOH/H_2O, a higher yield was obtained in DMF/H_2O (Table 1, entries 6 and 8). Next, we examined the effect of the volume ratio of DMF/H_2O and the base on the product yield (Table 1, entries 7–11). As shown in Table 1, the best volume ratio of DMF/H_2O is 1:1, and the highest yield was obtained when using K_3PO_4 as base in 0.5 h. When the catalyst loading was decreased to 0.05 mol%, a slightly low yield (89%) was observed (Table 1, entry 14).

Under the optimized conditions, we then evaluated the efficiency of the immobilized fluorous NHC–Pd catalyst with different substrates. As shown in Table 2, aryl bromides bearing either electron-donating or electron-withdrawing substitutents in the ortho and para positions, afforded the corresponding biphenyls in excellent yields. The trifluoromethyl substituted aryl bromides were more activated than bromobenzene in terms of yields (Table 2, entries 6 and 7). Next, we examined aryl iodides for the Suzuki reaction. And excellent yields of the corresponding products were obtained under the optimized conditions. In addition, the coupling reaction of 4-bromoanisole could be efficiently carried out using various substituted arylboronic acids (Table 2, entries 15–18). We also examined whether aryl chlorides were active for the Suzuki reaction in our system. In this case, the corresponding products were obtained in poor yields except for a moderate yield obtained with 4-nitrochlorobenzene after 1 h reaction (Table 2, entry 20).

Catalyst recovery and reuse are important issues that determine the applicability of a heterogeneous catalyst. The immobilized fluorous NHC–Pd catalyst can be recovered by simple filtration and reused several times without significant loss of activity (Fig. 2). The slight decrease of the yield may be due to the size of palladium nanoparticles increased to about 5–8 nm and the aggregation of palladium nanoparticles (Fig. 1b). The coupling crude products obtained by extraction were detected with low palladium contents (<3 ppm). This Pd level was a little higher than the specifications required by the pharmaceutical industry regarding the final purity of the products ($Pd < 2$ ppm). This might be the fluorous–fluorous interactions were not strong enough to highly stabilized the NHC–Pd complex on the fluorous silica gel, so that it caused the Pd leaching in the reaction and contaminated the Suzuki products.

3. Conclusions

In summary, we have prepared and characterized a novel immobilized fluorous NHC–Pd catalyst and successfully applied it for the Suzuki reaction. The catalyst showed high catalytic activity for the reaction of aryl halides and arylboronic acid in DMF/H_2O (v:v = 1:1). And the corresponding coupling products were obtained in moderate to excellent yields. Moreover, the catalyst could be easily recovered by filtration and reused three times without significant loss of activity. The simple procedure for catalyst preparation, easy recovery and reusability of the catalyst is expected to contribute to its utilization for the development of benign chemical process.

4. Experimental

4.1. General

All the reagents were commercially available and used without any further purification. The solvents were dried before use. IR spectra were recorded in KBr disks with a Bomem MB154S FT-IR spectrometer. ^1H NMR and ^{13}C NMR were recorded on Bruker DRX 500 and tetramethylsilane (TMS) was used as a reference. Palladium content was measured by inductively coupled plasma-atomic emission spectroscopy (ICP-AES) on a PE5300DV instrument. The XRD spectra were recorded on a Bruker D8 ADVANCE X-ray diffraction spectrometer at 40 kV, 40 mA. Transmission electron microscope (TEM) images were collected on a JEOL-2100 transmission electron microscopy at 200 kV and the images were recorded digitally with a Gatan 794 charge-coupled device (CCD) camera. The TEM measurements were made by sonication of the nanoparticulate material in perfluorodecalin for several minutes, then one drop of the finely divided suspension was placed on a specially produced structureless carbon support film having a thickness of 4–6 nm and dried before observation.

4.2. Preparation of 1,3-bis(1H,1H,2H,2H-perfluorodecyl)imidazolium iodide

A sealed tube was charged with imidazole (0.35 g, 5 mmol), 1H,1H,2H,2H-perfluorodecyl iodide (8.61 g, 15 mmol) and 10 mL toluene. The mixture was heated at 110 °C overnight. After being cooled to room temperature, the imidazolium salt was filtered, washed with 5 mL EtOAc, 5 mL H_2O, and dried at 50 °C to give 2.3 g product (43%, white solid). ^1H NMR (acetone-d_6): δ 3.20 (m, 4H), 4.96 (t, 4H, $J = 7.0$ Hz), 8.10 (s, 2H), 9.77 (s, 1H). ^{13}C NMR (acetone-d_6): δ 32.8, 44.1, 108–122 (m), 125.1, 139.6. MS (ESI), *m*/*z* (%): 961 $[M-I^-]^+$ (100), IR (KBr) ν 3414, 3142, 3057, 1580, 1334, 1203, 1149, 659 cm^{-1}. Anal. Calc. for $C_{23}H_{11}N_2F_{34}I$ (1088.20): C, 25.39; H, 1.02; N, 2.57. Found: C, 25.72; H, 1.13; N, 2.49.

4.3. Preparation of bis[1,3-bis(1H,1H,2H,2H-perfluorodecyl)imidazol-2-ylidene]di-iodopalladium(II)

In an oven-dried Schlenk flask, the imidazolium salt **1** (0.272 g, 0.25 mmol), $PdCl_2$ (0.022 g, 0.125 mmol), KO-*t*-Bu (0.028 g, 0.25 mmol) and THF (5 mL) were added. The resulting suspension was stirred at room temperature for 24 h under an inert atmosphere. Then the solution was filtered and the solid was washed with 5 mL EtOAc, 5 mL H_2O respectively, and dried under vacuum at 50 °C for 6 h to obtain the fluorous NHC–Pd complex as gray powder (0.269 g, 94%). ^1H NMR (acetone-d_6): δ 3.19 (m, 8H), 4.95 (t, 8H, $J = 7.0$ Hz), 8.09 (s, 4H). IR (KBr) ν 3468, 3103, 1657, 1565, 1534, 1498, 1471, 1412, 1242, 1205, 1149 cm^{-1}. Anal. Calc. for $C_{46}H_{22}N_4F_{68}I_2Pd$ (2282.81): C, 24.20; H, 0.97; N, 2.45. Found: C, 24.64; H, 1.05; N, 2.38.

4.4. Preparation of the fluorous NHC–Pd/FSG

0.02 g fluorous NHC–Pd was added to 15 mL perfluorooctane and the mixture was heated at 100 °C for 12 h. Then, 1.0 g FSG (C_8; 35–70 μm) was added and the mixture was stirred at the same temperature for 2 h. After this time, the solvent was evaporated under vacuum to obtain the immobilized catalyst. Palladium content was found to be 0.1% based on ICP analysis. The size of the palladium particles was about 3–5 nm, as determined by transmission electron microscopy.

4.5. General procedures for Suzuki–Miyaura reactions using 0.1 mol% NHC–Pd/FSG

A sealed tube was charged with aryl halide (1.0 mmol), arylboronic acid (1.5 mmol), K_3PO_4 (2.0 mmol), DMF/H_2O (v/v = 1:1, 2 mL) and catalyst (0.1 mol% Pd), the mixture was stirred at 100 °C for a certain time under air atmosphere. After being cooled to room temperature, the mixture was diluted with CH_2Cl_2 and filtered. The organic phase was separated and dried over Na_2SO_4. The solvent was removed under vacuum and the residual was purified by column chromatography on silica gel with EtOAc/petroleum ether as eluent. All the products were known compounds and were identified by comparison of their physical and spectroscopic data with those of authentic samples.

4.6. Recycling of catalyst

A sealed tube was charged with 4-bromoanisole (1.0 mmol), phenylboronic acid (1.5 mmol), K_3PO_4 (2.0 mmol), DMF/H_2O (v/v = 1:1, 2 mL) and catalyst (0.1 mol% Pd), the mixture was stirred at 100 °C for 0.5 h under aerobic conditions. Then the reaction mixture was cooled to room temperature, and filtered to obtain the solid palladium catalyst. The residual catalyst was washed with EtOAc (3 × 5 mL) and H_2O (3 × 5 mL) and then dried under vacuum at 50 °C for 2 h. After this, it could be used for the next run.

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