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Short Communication

Perfluoro-tagged nano-palladium catalyst immobilized on fluorous silica gel: Application in the Suzuki–Miyaura reaction

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ABSTRACT

The Suzuki–Miyaura reaction has been performed using a phosphine-free perfluoro-tagged palladium catalyst that is readily immobilized on fluorous silica gel through fluorous–fluorous interactions (Pd-**1**/FSG). The reactions are carried out under aerobic and phosphine-free conditions with excellent to quantitative product yields, and very low palladium content (<0.8 ppm) in the products was detected by ICP-AES. The catalyst can be recovered by simple filtration and reused several times without significant loss of activity.

1. Introduction

Palladium catalyzed Suzuki cross-coupling reactions have been increasingly employed for construction of unsymmetrical biaryl units which have a wide range of applications such as pharmaceutical, herbicides and natural products [1–6]. The explosive growth of studies in this area in the last decade is mainly due to low toxicity and high stability of organoboranes towards air and moisture. In addition, the handling and removal of boron-containing byproducts is easier when compared to other organometallic reagents, especially in a large scale synthesis [7]. However, palladium catalysts are expensive, and this may limit their applications in industry. Furthermore, their use might result in palladium contamination of the desired isolated products, a significant problem for the pharmaceutical industry, which has to meet strict specifications to limit the presence of heavy metal impurities in active substances [8]. To overcome these problems, immobilized palladium catalysts [9] provide a way to separate, recover, and reuse catalysts, thus reducing palladium contamination of the isolated products.

A number of studies have been devoted to immobilizing palladium on inert support materials, including activated carbon [10], silica gel [11,12], polymers containing covalently-bound ligands [13], metal oxides [14–17], ionic liquid [18], porous aluminosilicates and other inorganic materials, as well as microporous and mesoporous supports [19,20]. Although significant efforts have been achieved to develop heterogeneous palladium catalysts, such systems still suffer from high catalyst loadings and a lower efficiency compared to their analogues in the homogeneous phase. Moreover, phosphines remain the most employed ligands in these heterogeneous palladium catalysts. However, phosphine ligands are expensive, toxic and in large-scale applications the phosphines may be a more serious economical burden than even the metal itself [21].

Recently, palladium nanoparticles have been shown to be stabilized by entrapment in perfluoro-tagged, phosphine-free compounds [22–24]. Bannwarth et al. [25,26] have reported a successful example of immobilizing perfluoro-tagged palladium. Several catalysts were prepared by adsorption of palladium complexes containing perfluorinated phosphine ligands on fluorous silica gel (FSG) and showed the advantages of their utilization (separation and recovery of perfluoro-tagged palladium) in the Suzuki–Miyaura cross-coupling reaction in comparison with fluorous biphasic catalysis approaches using expensive and environmentally-persistent perfluorinated solvents. However, phosphines are often air-sensitive and some limits to their use in large-scale applications still remain. Vallribera et al. [27–29] have developed some new immobilized phosphine-free palladium systems in the alkynylation of aryl halides and the Heck reaction. Although these systems are efficient in catalyzing these two C–C bond-forming reactions, the palladium catalysts were prepared in multiple steps, using 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.

In our previous work, we have reported a facile process to synthesize a novel fluorous nano-palladium catalyst and its utilization in the

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Suzuki–Miyaura reaction at room temperature in ethanol/water mixture [30]. The catalyst was air and moisture-stable, and could be reused several times without a significant degradation in catalytic activity. However, using perfluorinated solvents when recycling the catalyst has prompted various concerns, the majority of which involve cost, fluorous solvent leaching, and environmental persistence [31]. In this context, we describe the synthesis of a novel heterogeneous cross-coupling catalyst by immobilization of a functionalized fluorous palladium complex on fluorous silica gel.

2. Experimental

2.1. General

All reagents and solvents were commercially available and used without any further purification. GC analyses were performed on an Agilent 7890A instrument. Palladium content was measured by inductively coupled plasma-atomic emission spectroscopy (ICP-AES) on a PE5300DV instrument. Transmission electron microscope (TEM) images were collected on a JEOL-2100 transmission electron microscope 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.

2.2. Preparation of Pd-**1**/FSG

The phosphine-free perfluoro-tagged nano-palladium catalyst (Pd-**1**) was prepared according to our previously reported procedure [30]. 0.02 g of Pd-**1** was added to 15 mL perfluorooctane and the mixture was refluxed for 12 h. Then, 1 g of FSG (C8; 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: 0.25%. The size of the palladium particles was about 2.9 ± 0.7 nm, as determined by transmission electron microscopy.

2.3. Typical procedure for Suzuki–Miyaura reactions using 0.1 mol% Pd-**1**/FSG

A sealed tube was charged with aryl halide (1.0 mmol), arylboronic acid (1.5 mmol), K_2CO_3 (2.0 mmol), MeOH/H_2O (v/v = 1:0.5, 2 mL) and catalyst (0.1 mol% Pd), the mixture was stirred at 80 °C for 6 h under air atmosphere. After cooling 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.

2.4. Recycling of catalyst

A sealed tube was charged with 4-bromoanisole (1.0 mmol), phenylboronic acid (1.5 mmol), K_2CO_3 (2.0 mmol), MeOH/H_2O (v/v = 1:0.5, 2 mL) and catalyst (0.1 mol% Pd), the mixture was stirred at 80 °C for 6 h under aerobic conditions. Then the reaction mixture was cooled at room temperature, and filtered to obtain the solid immobilized palladium catalyst. The residual catalyst was washed with CH_2Cl_2 (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.

3. Results and discussion

The amount of palladium in the immobilized catalyst was found to be 0.25% based on ICP-AES analysis. Transmission electron microscopy (TEM) of the catalyst showed well-defined spherical particles dispersed in the silica matrix (Fig. 1a and 1b). The mean diameter of the nanoparticles was about 2.9 ± 0.7 nm. The particle size was diminished compared to the starting particles Pd-**1**. It was reported that palladium nanoparticles could be entrapped in heavily fluorinated compounds [32]. Poly(tetrafluoroethylene) (PTFE) has been reported as stabilizing agents of transition-metal nanoparticles as well as dendrimers fluorinated in the surface. Fluorous silica gel is similar to PTFE as a heavily fluorinated material, it is probably the inclusion of nanoparticulated palladium into the interstices of the nonfluorinated core of the dendrimer that caused the diminution of the particle size [33,34]. In addition, using perfluorooctane, which is a heavily fluorinated compound, as solvent in the preparation of the immobilized catalyst, might disperse the palladium particles well in the process and lead to diminution of the particle size.

The immobilized catalyst (Pd-**1**/FSG) was assessed for its activity in the Suzuki–Miyaura reaction initially by studying the coupling of 4-bromoanisole with phenylboronic acid to form 4-methoxybipheyl as the sole product. Various parameters including solvent, base and catalyst loading were screened to optimize the reaction conditions. Single solvents such as DMF, CH_3CN, EtOAc, THF, MeOH, and EtOH gave low to moderate yields ranging from 11 to 81% (Table 1, entries 1–6). However, when we adopted the organic/aqueous co-solvent, satisfactory results were obtained (Table 1, entries 7 and 8). The merit of the co-solvent is attributed to the good solubility of the organic reactants and the inorganic base. Then, we tested the influence of different volume ratios of MeOH/H_2O as a solvent under identical conditions. Evidently, the best volume ratio of MeOH/H_2O is 1:0.5 (Table 1, entry 9).

Next, an optimization of the base for the Suzuki–Miyaura reaction was performed using K_3PO_4, K_2CO_3, Na_2CO_3, $NaHCO_3$, NaOH, KOH, and Et_3N. K_2CO_3 was found to be the most effective base for the reaction. Slightly lower yields were obtained when using K_3PO_4 and Na_2CO_3 as the base (Table 2, entries 1 and 3). Then, different catalyst loadings between 0.05 and 1 mol% were investigated for the reaction. For the higher catalyst loading, the desired product was obtained in an almost quantitative yield (Table 2, entry 8). On the contrary, the yield of the reaction was lower with 0.05 mol% catalyst loading.

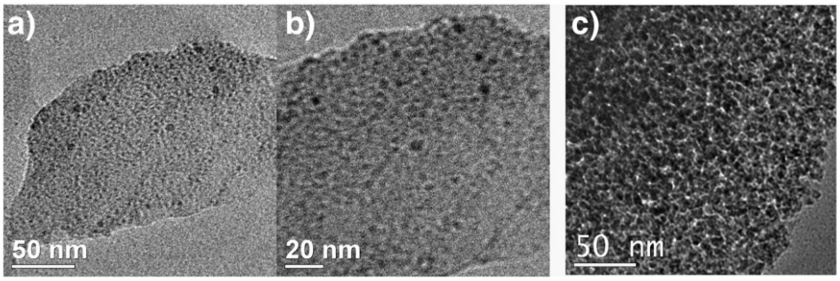
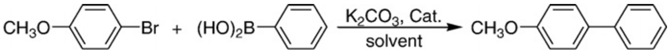


Fig. 1. TEM images of the immobilized catalyst. (a) and (b) TEM images of Pd-**1**/FSG. (c) TEM image of Pd-**1**/FSG after fifth cycle for the Suzuki–Miyaura reaction.

Table 1
Effect of solvents for the Suzuki–Miyaura reaction.[a]



Entry	Solvent	Time (h)	Yield[b] (%)
1	DMF	6	43
2	CH_3CN	6	11
3	EtOAc	6	31
4	THF	6	26
5	MeOH	6	81
6	EtOH	6	68
7	EtOH/H_2O (v/v = 1:1)	6	83
8	MeOH/H_2O (v/v = 1:1)	6	89
9	MeOH/H_2O (v/v = 1:0.5)	6	97
10	MeOH/H_2O (v/v = 0.5:1)	6	74
11	H_2O	6	13

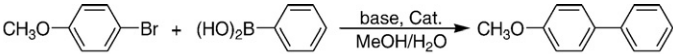
[a] Reaction conditions: 4-bromoanisole (1.0 mmol), phenylboronic acid (1.5 mmol), K_2CO_3 (2.0 mmol), catalyst (0.1 mol%) in 2 mL solvent at 80 °C.
[b] Isolated yield.

Therefore, it was decided to use K_2CO_3 as the base, MeOH/H_2O in volume ratio of 1:0.5 as solvent, and 0.1 mol% catalyst as the optimal conditions in further studies. It should be noted that the absence of phosphines in the system not only reduces process costs but also eliminates side reactions that may occur between the phosphines and phenylboronic acid [35].

To survey the generality of the catalytic protocol, we investigated the reaction using various aryl halides coupled with arylboronic acids under the optimized conditions. As shown in Table 3, aryl bromides containing both electron-donating and electron-withdrawing groups in the para position afforded the corresponding products in excellent yields. The ortho-substituted aryl bromides gave the products lower yields because of steric effects (Table 3, compare entry 2 with entry 3, entry 4 with entry 5). Also, the coupling reaction could be efficiently carried out using arylboronic acids bearing either electron-rich or electron-poor substituted groups (Table 3, entries 10–13). Next, we examined aryl iodides for the Suzuki reaction. And excellent yields of the corresponding products were obtained under the optimized conditions (Table 3, entries 14–16). In addition, we also investigated whether aryl chlorides were active for the Suzuki–Miyaura reaction under the same conditions. In this case, the corresponding products were obtained in poor yields except for 4-nitrochlorobenzene afforded the product in a moderate yield (Table 3, entry 18).

Reusability is an important feature that determines the applicability of a heterogeneous catalyst. The coupling reaction of 4-bromoanisole with phenylboronic acid was chosen as the model reaction. As shown in Fig. 2, the immobilized fluorous palladium catalyst can be recovered and reused in further reactions without a significant loss of activity. Although the catalytic activity gradually diminished, a yield of over 80% was still achieved in the fifth cycle. The recovered catalyst was also examined by TEM after the fifth cycle and it was observed that the size of palladium nanoparticles increased to about 5 nm and the particle already has aggregation, which proved a decrease in its activity after several cycles (Fig. 1c). Moreover, very low palladium content (<0.8 ppm) was detected by ICP-AES in the obtained products. This result is much better than the catalyst system reported by Vallribera and co-workers [28]. It should be pointed out that this low Pd level satisfies specifications required by the pharmaceutical industry regarding the final purity of the products (Pd<2.0 ppm).

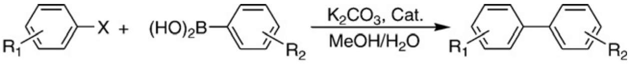
Table 2
Effect of bases and catalyst loadings for the Suzuki–Miyaura reaction.[a]



Entry	Catalyst loading (mol%)	Base	Time (h)	Yield[b] (%)
1	0.1	K_3PO_4	6	95
2	0.1	K_2CO_3	6	97
3	0.1	Na_2CO_3	6	90
4	0.1	$NaHCO_3$	6	46
5	0.1	NaOH	6	58
6	0.1	KOH	6	72
7	0.1	Et_3N	6	43
8	1	K_2CO_3	6	>99
9	0.05	K_2CO_3	6	86

[a] Reaction conditions: 4-bromoanisole (1.0 mmol), phenylboronic acid (1.5 mmol), base (2.0 mmol), catalyst in 2 mL MeOH/H_2O (v/v = 1:0.5) at 80 °C.
[b] Isolated yield.

Table 3
Suzuki cross-coupling reactions of aryl halides with arylboronic acids.[a]



Entry	X	R_1	R_2	Time (h)	Yield[b] (%)
1	Br	H	H	6	99
2	Br	4-CH_3O	H	6	97
3	Br	2-CH_3O	H	6	89
4	Br	4-NO_2	H	6	96
5	Br	2-NO_2	H	6	85
6	Br	4-CF_3	H	6	99
7	Br	3-CF_3	H	6	98
8	Br	4-CH_3CO	H	6	96
9	Br	4-CHO	H	6	98
10	Br	4-CH_3O	4-Cl	6	98
11	Br	4-CH_3O	4-CF_3	6	97
12	Br	4-CH_3O	4-CH_3O	6	>99
13	Br	4-CH_3O	4-CH_3	6	92
14	I	H	H	6	98
15	I	4-NO_2	H	6	97
16	I	4-CH_3	H	6	95
17	Cl	H	H	6	21
18	Cl	4-NO_2	H	6	45
19	Cl	4-CH_3	H	6	7

[a] Reaction conditions: aryl halide (1.0 mmol), arylboronic acid (1.5 mmol), K_2CO_3 (2 mmol), catalyst (0.1 mol% Pd) in 2 mL MeOH/H_2O (v/v = 1:0.5) at 80 °C.
[b] Isolated yield.

4. Conclusions

In summary, we have successfully prepared a novel perfluoro-tagged nano-palladium catalyst immobilized on fluorous silica gel (Pd-**1**/FSG). The immobilized catalyst exhibits high activity towards the Suzuki–Miyaura cross-coupling reaction without any added phosphine ligands under aerobic conditions. Low palladium contamination in the products was detected by ICP-AES, which meets the level required by the pharmaceutical industry. And the catalyst can be recovered by simple filtration and reused after washing without a significant degradation in activity.

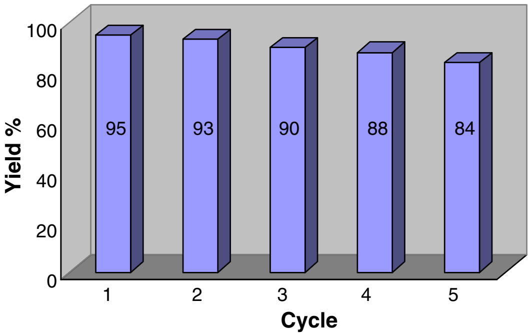


Fig. 2. Reusability of the immobilized fluorous palladium catalyst for the Suzuki reaction.

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