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An Efficient and Recyclable Fluorous Palladium Catalyst for the Room-Temperature Suzuki Reaction

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Abstract A new fluorous nano-palladium catalyst was prepared and characterized. The catalytic activity of the catalyst has been evaluated for the Suzuki reaction of aryl halides and aryl boronic acids to afford the corresponding products in high yields. The reaction proceeded smoothly in the presence of 0.1 mol% catalyst in EtOH/H_2O at room temperature. In addition, the catalyst could be recovered by fluorous liquid–liquid separation and reused for three times without significant loss of activity.

Keywords Nano-palladium · Suzuki reaction · Co-solvent · Fluorous palladium catalyst

1 Introduction

The Suzuki reaction is one of the most versatile and utilized reactions for the formation of biaryl compounds [1–3]. In the past decade, the biaryl motif has received increased attention as a privileged structure by the agrochemical and pharmaceutical industries [4, 5]. The core of many types of natural products [6], advanced materials [7], polymers [8] and sensors [9] contain the biaryl moiety. Consequently, the development of new and efficient methods for the Suzuki reaction has attracted much interest.

A wide range of metal complexes have been used as catalysts in Suzuki coupling reactions, attention particularly being focused on palladium. Palladium catalysts with phosphines ligand [10], carbenes ligand [11], palladacycle [12] and other coordinates [13] have shown high activity and have improved the stability of the reactions with water or under air. However, problems such as expensive poisonous phosphine ligands and unrecyclability of the catalyst, which impacts cost and palladium contamination in the product, extremely limited their industrial applications. Thus, the development of efficient and recyclable catalysts that utilize cheap and phosphine-free ligands is a topic of enormous importance.

Recently, some phosphine-free ligands have been shown to have interesting applications, such as thioureas [14–16], imines [17], bispyridines [18], oxazolines [19], tetrazoles [20], and bisimidazoles [21]. These ligands are potentially advantageous for being chemically stable and economically inexpensive. Guo [22] reported amino acids can serve as excellent ligands for copper-catalyzed amidation of aryl iodides. Wang and co-workers [23] described a palladium anchored on proline-functionalized silica gel as catalyst to catalyze the Heck reaction. Therefore, simple amino acids and their derivatives as ligands for metal-catalyzed reactions attracted our attention.

In the last few years, fluorous chemistry has emerged as a powerful strategy for facilitating catalyst recovery [24–28]. Introducing a fluorous tag into the catalyst can make it easily recoverable by using simple fluorous liquid–liquid separation [29, 30]. Herein, we report a facile process to synthesize nano-palladium catalyst with a fluorous tag derived from proline. And the catalyst has been applied for the Suzuki reaction of aryl halides and aryl boronic acid at room

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temperature. Recyclability experiments of the fluorous nano-palladium catalyst were performed up to three runs without significant loss of activity under moist conditions.

2 Experimental

2.1 General Remarks

All of the reagents and solvents are commercially available and were used without further purification. IR spectra were recorded in KBr disks with a Bomem MB154S FT-IR spectrometer. Mass spectra were taken on an Agilent LC–MS 1100 series instrument in the electrospray ionization (positive ESI) mode. GC analyses were performed on an Agilent 7890A instrument. ^{1}H NMR and ^{13}C NMR were recorded on Bruker DRX 500 and tetramethylsilane (TMS) was used as a reference. Palladium content of the catalyst was measured by inductively coupled plasma (ICP) on PE5300DV analyzer. 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.

2.2 Preparation of the Catalyst

2.2.1 Preparation of Fluorous Pyrrolidine Imide

Under a dry N_2 atmosphere, to a stirred solution of Boc-proline (0.43 g, 2 mmol) and perflurooctane sulfluramide (0.99 g, 2 mmol) in 25 mL EtOAc, DMAP (4-dimethylaminopyridine, 0.58 g, 0.48 mmol) and EDCI (1-ethyl-3-(3-dimethylaminopropyl)carbodiimidehydrochloride, 0.57 g, 3 mmol) were added respectively. The reaction mixture was stirred at room temperature for 96 h. Then the mixture was washed with 30 mL 1 M aqueous HCl and 50 mL half-saturated brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give a colorless oil product. And the oil product was directly used in the next step without further purification. Deprotection Boc-group was performed by using 15 mL TFA (trifluoroacetic acid) for 2 h at 0 °C. After concentration, TFA salts were removed by triturating the residue with 30 mL MeOH saturated with ammonia (15 mL) to obtain the product. And the product was obtained as a white solid (0.62 g, 41%). mp 217–219 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 9.04 (s, 1H), 8.34 (s, 1H), 4.04–4.02 (t, 1H, J = 6.0 Hz), 3.20(s, 1H), 3.13–3.09 (m, 1H), 2.20–2.16 (m, 1H), 1.90–1.82 (m, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 172.82, 108-121 (m, CF_2, CF_3), 62.72, 45.84, 29.24, 23.53; MS (ESI) calcd for $C_{13}H_9F_{17}N_2O_3S$ $(M + Na)^+$ 619.25, found 619.22.

2.2.2 Preparation of the Fluorous Nano-palladium Catalyst

In a round-bottom flask, fluorous pyrrolidine imide (120 mg, 0.2 mmol) was mixed with $Pd(OAc)_2$ (45 mg, 0.2 mmol) in anhydrous EtOH (2 mL). The mixture was stirred for 12 h under N_2 at room temperature. The mixture was filtered and the solid was washed with acetone and MeOH. The solid was dried under reduced pressure at room temperature for 6 h. The catalyst was obtained as a black solid (136 mg). The amount of palladium in the catalyst was found to be 12.6% based on ICP analysis.

2.2.3 Typical Procedure for Suzuki Reactions

Under air atmosphere, round-bottomed flask was charged with aryl halide (1.0 mmol), phenylboronic acid (1.5 mmol), K_2CO_3 (2.0 mmol), $EtOH/H_2O$ (v/v = 1:1, 2 mL) and catalyst (0.1 mol% Pd). The mixture was reacted at room temperature for a certain time (monitored by GC). After the reaction completed, water (3 mL) and EtOAc (5 mL) was added to the mixture. The organic phase was separated, dried over anhydrous Na_2SO_4, and evaporated. The crude products were purified by flash chromatography with n-hexane/EtOAc as eluent affording the corresponding products. All products were known compounds and were identified by comparison of their physical and spectra data with those of authentic samples.

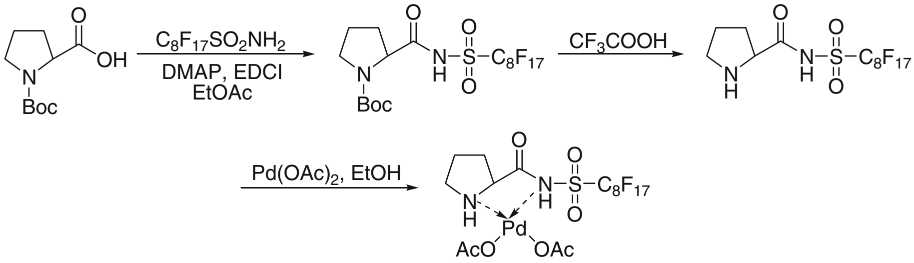
2.2.4 Recycling of Catalyst

A vial was charge with 4-bromoanisole (1.0 mmol), phenylboronic acid (1.5 mmol), K_2CO_3 (2.0 mmol), $EtOH/H_2O$ (v/v = 1:1, 2 mL) and catalyst (0.1 mol% Pd). The reaction was run at room temperature for 1 h. After the reaction completed, water (3 mL), EtOAc (5 mL) and perfluorodecalin ($C_{10}F_{18}$, cis and trans-mixture, 5 mL) were added. Then the mixture heated to 100 °C for 10 min. After the mixture was cooled to room temperature, the fluorous phase was separated and concentrated to afford the catalyst for the next cycle. And perfluorodecalin was collected for the next use without further purification. The yields of the reaction were determined by GC analysis.

3 Results and Discussion

The nano-palladium catalyst was prepared according to Scheme 1. In order to ascertain fluorous pyrrolidine imide chelated with palladium, IR spectra were recorded separately at the different stage of preparation. As shown in Fig. 1, the N–H peaks between 3000 and 3200 cm^{-1} almost disappeared after introduction of $Pd(OAc)_2$.

Scheme 1 Preparation of fluorous nano-palladium catalyst



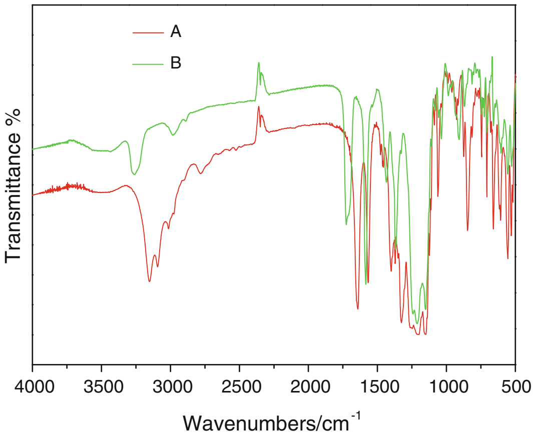


Fig. 1 IR spectra of fluorous pyrrolidine imide (*A*) and fluoruos nano-palladium catalyst (*B*)

Moreover, the peak at about 1400–1420 cm^{-1} was weakened, which attributed to the vibration of C–N. The TEM analysis of catalyst (Fig. 2) showed the formation of palladium nanoparticles with a diameter in the range 30–40 nm.

With these good results at hand, we optimized the Suzuki reaction conditions. Initially, the reaction between 4-bromoanisole and phenylboronic acid was chosen as a model reaction. Various parameters including solvent, base and catalyst loading were screened to optimize the reaction conditions. The single solvent such as DMF, CH_3CN, EtOAc, CH_2Cl_2, MeOH, EtOH and H_2O gave low to moderate yields ranging from 11 to 82% (Table 1, entries 1–7). However, when we adopted the organic/water co-solvent, satisfactory results were obtained (Table 1, entries 9–10). 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 EtOH/H_2O as a solvent at room temperature. And yields of 89–98% were obtained in 1 h. Evidently, the best volume ratio of EtOH/H_2O is 1:1. Compared to the fluorous nano-palladium catalyst, lower yield was obtained when $Pd(OAc)_2$ used as catalyst (Table 1, entry 11).

Next, we examined the effect of bases for the room temperature Suzuki reaction in EtOH/H_2O. Some bases including K_3PO_4, K_2CO_3, Na_2CO_3, NaOAc, $NaHCO_3$, Et_3N, NaOH and KOH were all investigated (Table 2, entries 1–8). K_2CO_3 was found to be the most effective base for the reaction. Slightly lower yields were obtained when K_3PO_4 and Na_2CO_3 were used as base (Table 2, entries 1, 3). Also, the organic base Et_3N was studied but not satisfactory yield was obtained (Table 2, entry 6). Then, different catalyst loadings were tested for the reaction. As the results shown in Table 2, 0.1 mol% of catalyst was sufficient to catalyze the reaction successfully (entries 2, 9, 10). Thus, we select K_2CO_3 as base, EtOH/H_2O (v/v = 1:1) as solvent, and 0.1 mol% of catalyst which are the best conditions for the Suzuki reaction.

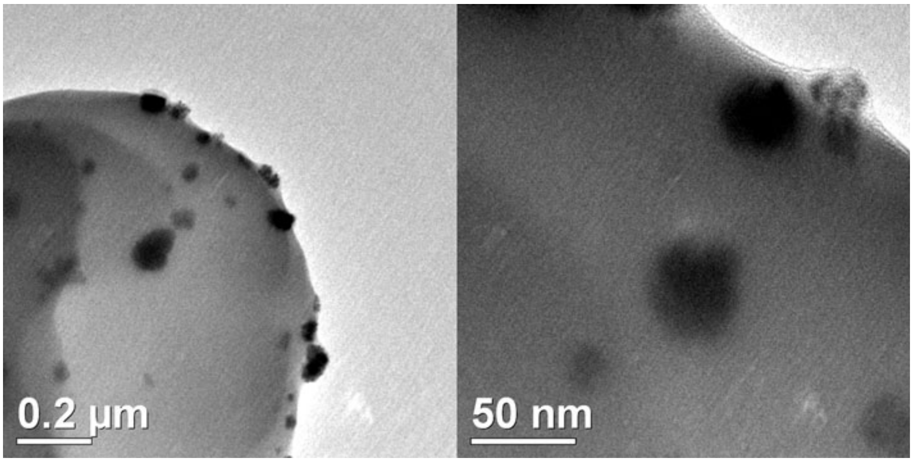
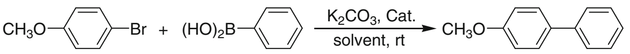


Fig. 2 TEM micrographs of palladium nanoparticles

Table 1 Effect of solvent and catalyst on the room-temperature Suzuki reaction[a]



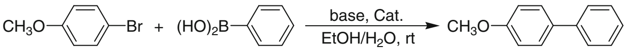
Entry	Solvent	Time (h)	Yield[c] (%)
1	DMF	3	11
2	CH_3CN	3	21
3	EtOAc	3	36
4	CH_2Cl_2	3	33
5	MeOH	3	68
6	EtOH	3	82
7	H_2O	12	23
8	$EtOH/H_2O$ (v/v = 1:0.5)	1	89
9	$EtOH/H_2O$ (v/v = 1:1)	1	98
10	$EtOH/H_2O$ (v/v = 0.5:1)	1	94
11[b]	$EtOH/H_2O$ (v/v = 1:1)	1	76

[a] *Reaction conditions*: 4-bromoanisole (1.0 mmol), phenylboronic acid (1.5 mmol), K_2CO_3 (2.0 mmol), catalyst (0.1 mol% Pd) in 2 mL solvent at room temperature

[b] $Pd(OAc)_2$ used as catalyst

[c] Isolated yield

Table 2 Effect of base and catalyst loading on the room-temperature Suzuki reaction[a]

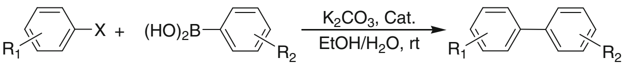


Entry	Catalyst loading (mol %)	Base	Time (h)	Yield[b] (%)
1	0.1	K_3PO_4	1	95
2	0.1	K_2CO_3	1	98
3	0.1	Na_2CO_3	1	92
4	0.1	NaOAc	1	23
5	0.1	$NaHCO_3$	1	45
6	0.1	Et_3N	1	41
7	0.1	NaOH	1	56
8	0.1	KOH	1	77
9	1	K_2CO_3	1	99
10	0.05	K_2CO_3	1	83

[a] *Reaction conditions*: 4-bromoanisole (1.0 mmol), phenylboronic acid (1.5 mmol), base (2.0 mmol), catalyst in 2 mL $EtOH/H_2O$ (v/v = 1:1) at room temperature

[b] Isolated yield

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



Entry	X	R_1	R_2	Time (h)	Yield[b] (%)
1	Br	H	H	1	99
2	Br	4-CH_3O	H	1	98
3	Br	2-CH_3O	H	3	87
4	Br	4-NO_2	H	5	92
5	Br	2-NO_2	H	5	85
6	Br	4-CF_3	H	2	99
7	Br	2-CF_3	H	2	98
8	Br	4-CH_3CO	H	1	96
9	Br	4-CHO	H	1	99
10	Br	H	4-Cl	2	99
11	Br	H	4-CF_3	2	96
12	Br	H	4-CH_3O	2	94
13	Br	H	4-CH_3	2	95
14	I	H	H	1	99
15	I	4-NO_2	H	1	98
16	I	4-CH_3	H	3	88
17	Cl	H	H	3	16
18	Cl	4-NO_2	H	3	43
19	Cl	4-CH_3	H	3	23

[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 $EtOH/H_2O$ (v/v = 1:1) at room temperature

[b] Isolated yield

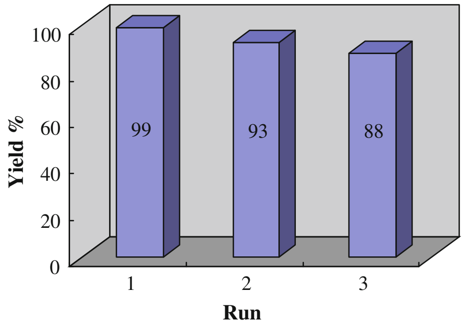


Fig. 3 Recycling experiments

To survey the generality of the catalytic protocol, we investigated the reaction using a variety of aryl halides coupled with aryl boronic acids under the optimized condition. As shown in Table 3, aryl bromides bearing either electron-donating or electron-withdrawing substituents in the ortho and para positions afforded the corresponding products in good to excellent yields. Also, the coupling reaction could be efficiently executed of aryl boronic acids with electron-donating and electron-withdrawing groups (Table 3, entries 10–13). Then, we examined aryl iodides for the Suzuki reaction. And excellent yields of the corresponding products were obtained under the optimized condition. We also investigated the reactivity of aryl chlorides with phenylboronic acid in our system. However, only moderate yield was obtained in the coupling reaction (Table 3, entry 18). Recycling experiments were investigated with 0.1 mol% catalyst loading at room temperature. The catalyst can be recovered by fluorous liquid–liquid separation and reused for three times without significant loss of activity (Fig. 3). The slight decrease of the yield may be due to the small amount of catalyst lost by manipulation. The coupling products were obtained by purification on silica column chromatography, only very low palladium amount (<2.0 ppm) was detected.

4 Conclusions

In summary, we have successfully prepared a new fluorous nano-palladium catalyst which was performed as an efficient catalyst for the Suzuki reaction at room temperature. The catalyst has showed highly catalytic activity for the reaction affording a diverse range of biphenyls in excellent yields. And EtOH/H_2O as solvent is more eco-friendly than DMF, which was mostly used as solvent in Suzuki reactions. Furthermore, the catalyst could be easily recovered by fluorous liquid–liquid separation and reused for three times without significant loss of activity. The simple procedure for catalyst preparation, easy recovery and reusability of the catalyst are expected to contribute its utilization for the development of benign chemical process and products. To increase the recyclability of the catalyst is continuous in our further work.

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