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A highly efficient and recyclable fluorous palladium catalyst for Heck reactions in water

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Abstract A fluorous nano-palladium catalyst has been synthesized and characterized. The catalyst is highly active for the Heck reaction of aryl halides with substituted styrenes in water under air. The corresponding Heck products were obtained in high yields with good stereoselectivity (*E/Z* up to 98:2). In addition, the catalyst could be recovered by fluorous liquid–liquid separation and reused four times without significant loss of activity or stereoselectivity.

Introduction

The Heck reaction is one of the most powerful tools in organic synthesis for carbon–carbon bond formation, and it has found widespread applications in the stereoselective synthesis of various alkenes [1–4]. The reaction is normally carried out with a palladium phosphine catalyst in homogeneous solution. However, phosphine ligands have the disadvantages of being expensive, toxic, and air and moisture sensitive. Therefore, in recent years, much attention has been paid to developing phosphine-free ligands for the Heck reaction. Wang and co-workers [5] described a Heck reaction catalyst based on palladium anchored on proline-functionalized silica gel. Although the cross-coupling products were obtained in good to excellent yields under phosphine-free conditions, high catalyst loading and dimethylformamide were required in their experiments, which would restrict the industrial applications of this system. Polar aprotic solvents (DMF, NMP, DMA) still remain the preferred media for carrying out Heck reactions. However, these solvents are toxic and difficult to remove from the reaction mixture. Therefore, numerous efforts have been made to investigate this reaction in non-conventional reaction media [6], such as water [7], ionic liquids [8], and supercritical CO_2 [9].

Water, which is cheap, readily available, nontoxic, and nonflammable, has obvious advantages as a solvent in chemistry. Recently, Heck coupling reactions of water-soluble aryl iodides performed in water with palladium catalysts have been reported [10–13]. However, high catalyst loading (1–3 mol%) and high temperatures were required in most of these studies. Hence, the challenge of developing an efficient catalyst for Heck reactions with low catalyst loadings in water remains.

In the past decade, amino acids have been found to be excellent ligands for copper-catalyzed amidation of aryl iodides [14–16]. Although the amino acid ligand is easily removed after the reaction because of its high solubility in water, it is difficult to recycle the analogous palladium catalysts. Recently, fluorous chemistry has emerged as a powerful strategy for facilitating catalyst recovery [17–21]. Introducing a fluorous tag into the catalyst can make it easily recoverable through a simple fluorous liquid–liquid separation [22, 23]. Herein, we describe a facile process (Scheme 1) to synthesize a palladium catalyst with a fluorous ligand derived from proline [24]. This catalyst was applied in the Heck reaction of aryl halides with substituted styrenes with low catalyst loading (0.1 mol% Pd) in water under air. Recyclability experiments of the fluorous

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palladium catalyst were performed up to four runs without significant loss of activity.

Experimental

The catalyst was prepared and characterized as recently described [24]. All of the reagents and solvents were commercially available and were used without further purification. GC analyses were performed on an Agilent 7890A instrument. Palladium content was measured by inductively coupled plasma (ICP) on a PE5300DV instrument.

Typical procedure for Heck reactions

Under air, a glass tube was charged with aryl halide (1.0 mmol), substituted styrene (1.5 mmol), K_2CO_3 (2.0 mmol), tetra-*n*-butylammonium bromide (TBAB, 50 mol%), H_2O (2 mL) and catalyst (0.1 mol% Pd). The tube was sealed and the mixture was reacted at 100 °C for a certain period of time (monitored by GC). After the reaction was complete, the product was extracted with EtOAc. 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. All the products were known compounds and were identified by comparison with their physical and spectroscopic data with those of authentic samples.

Recycling of catalyst

A glass tube was charged with iodobenzene (1.0 mmol), styrene (1.5 mmol), TBAB (50 mol%), K_2CO_3 (2.0 mmol), H_2O (2 mL), and catalyst (0.1 mol% Pd) and then sealed. The reaction was performed at 100 °C for 12 h. After the reaction was complete, EtOAc (5 mL) and perfluorodecalin ($C_{10}F_{18}$, cis and trans-mixture, 5 mL) were added. The mixture was heated to 100 °C for 10 min and then cooled to room temperature. The fluorous phase was separated and concentrated to recover the catalyst for the next cycle. Perfluorodecalin was collected by distillation for reuse without further purification. The crude products were purified by flash chromatography with *n*-hexane/EtOAc as eluent.

Results and discussion

In order to evaluate the catalytic activity of the fluorous palladium complex in Heck coupling reactions, we first investigated the reaction of iodobenzene and styrene in the presence of 0.1 mol% catalyst. The results are summarized in Table 1. Compared to the reaction performed in water, a good yield was obtained at 100 °C for 6 h in DMF (Table 1, entries 1 and 2). It has been reported that additives such as tetrabutylammonium bromide (TBAB) can give remarkable rate enhancements in the Heck reaction [25]. When the quantity of TBAB was increased to 50 mol%, the product was obtained in good yield (Table 1, entry 5). Prolonging the reaction time to 12 h, the product was obtained in 98% yield (Table 1, entry 6). The role of TBAB is thought to be that it facilitates solvation of the organic substrate in water.

Due to the sensitivity of Heck reactions to the base used, the effects of K_2CO_3, KOH, NaOH, Cs_2CO_3, K_3PO_4, and Et_3N were investigated (Table 1, entries 6–11). The highest yield was obtained with Et_3N; however, the product was obtained in lower stereoselectivity (Table 1, entry 11). Therefore, we chose K_2CO_3 as the base for our continuous reactions. In a control experiment, the fluorous palladium catalyst was replaced with the conventional catalytic precursor $Pd(OAc)_2$. In this case, lower yield and stereoselectivity were obtained under the same reaction conditions (Table 1, entry 12). These results indicate that the fluorous palladium complex is an efficient catalyst for the Heck reaction in water in the presence of 50 mol% TBAB.

With these favorable results in hand, we investigated the efficiency of the fluorous palladium catalyst with different substrates. As shown in Table 2, a range of aryl iodides and bromides was found to give the desired products in moderate to high yields with good stereoselectivity (the ratio of *E/Z* was up to 98:2). Aryl iodides bearing either electron-donating or electron-withdrawing substituents in the ortho and para positions afforded the corresponding products in good to excellent yields with good stereoselectivity (Table 2, entries 1–7). The ortho-substituted aryl iodides gave the products in lower yields because of steric effects. In addition, the coupling reaction could be efficiently carried out using aryl bromides with electron-withdrawing groups (Table 2, entries 9–11). However, aryl bromides

Scheme 1 Preparation of the fluorous palladium catalyst

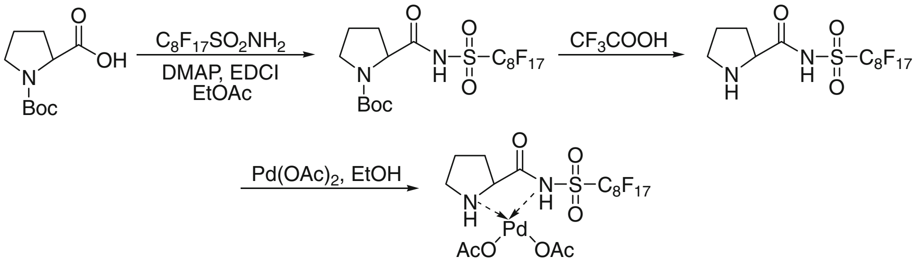
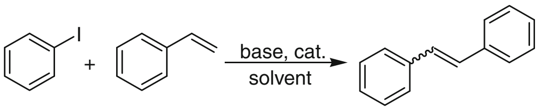


Table 1 Optimization of the Heck reaction conditions



Entry	Solvent	TBAB (mol %)	Temperature (°C)	Time (h)	Base	Yield[a] (%)	*E/Z*[b]
1	DMF	0	100	6	K_2CO_3	87	90:10
2	H_2O	0	100	6	K_2CO_3	43	93:7
3	H_2O	5	100	6	K_2CO_3	52	94:6
4	H_2O	20	100	6	K_2CO_3	69	94:6
5	H_2O	50	100	6	K_2CO_3	88	93:7
6	H_2O	50	100	12	K_2CO_3	98	93:7
7	H_2O	50	100	12	KOH	97	92:8
8	H_2O	50	100	12	NaOH	96	92:8
9	H_2O	50	100	12	Cs_2CO_3	91	92:8
10	H_2O	50	100	12	K_3PO_4	86	93:7
11	H_2O	50	100	12	Et_3N	99	91:9
12[c]	H_2O	50	100	12	K_2CO_3	79	88:12

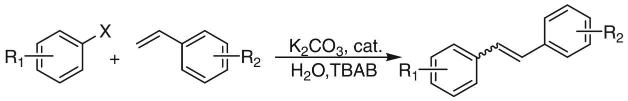
Reaction conditions Iodobenzene (1.0 mmol), styrene (1.5 mmol), TBAB, base (2.0 mmol), fluorous palladium catalyst (0.1 mol% Pd) in 2 mL solvent

[a] Isolated yield

[b] The ratio of *E/Z* was determined by GC analysis of the crude product

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

Table 2 Heck reactions of aryl halides and substituted styrenes



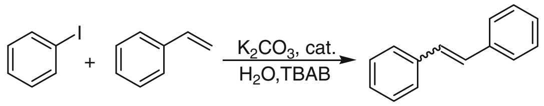
Entry	X	R_1	R_2	Time (h)	Yield[a] (%)	*E/Z*[b]
1	I	H	H	12	98	93:7
2	I	4-CH_3	H	12	99	93:7
3	I	3-CH_3	H	12	91	93:7
4	I	2-CH_3	H	12	89	94:6
5	I	4-NO_2	H	12	90	92:8
6	I	3-NO_2	H	12	83	91:9
7	I	2-NO_2	H	12	80	91:9
8	Br	H	H	24	73	96:4
9	Br	4-NO_2	H	24	89	98:2
10	Br	4-CF_3	H	24	93	98:2
11	Br	3-CF_3	H	24	90	97:3
12	Br	4-CH_3	H	24	69	90:10
13	Br	4-CH_3O	H	24	63	96:4
14	Cl	H	H	24	13	92:8
15	Cl	4-NO_2	H	24	45	94:6
16	Cl	4-CH_3	H	24	29	93:7
17	I	H	4-CH_3	12	96	93:7
18	I	H	2-CH_3	12	90	92:8
19	I	H	4-Cl	12	97	94:6
20	I	H	2-Cl	12	92	93:7

Reaction conditions Aryl halide (1.0 mmol), substituted styrene (1.5 mmol), TBAB (50 mol %), K_2CO_3 (2.0 mmol), catalyst (0.1 mol% Pd) in 2 mL H_2O

[a] Isolated yield

[b] The ratio of *E/Z* was determined by GC analysis of the crude product

Table 3 Recycling of the fluorous catalyst in the Heck reaction



Cycle	Time (h)	Yield[a] (%)	E/Z[b]
1	12	98	93:7
2	12	96	93:7
3	12	93	92:8
4	12	90	92:8

Reaction conditions Iodobenzene (1.0 mmol), styrene (1.5 mmol), TBAB (50 mol %), K_2CO_3 (2.0 mmol), fluorous palladium catalyst in 2 mL H_2O

[a] Isolated yield

[b] The ratio of *E/Z* was determined by GC analysis of the crude product

containing electron-donating groups were less active and the corresponding products were obtained in moderate yields (Table 2, entries 12 and 13). Next, we examined whether aryl chlorides were active for the Heck reaction under the same conditions. In this case, the corresponding products were obtained in poor yields except for a moderate yield obtained with 4-nitrochlorobenzene (Table 2, entry 15). Substituted styrenes were investigated with iodobenzene (Table 2, entries 17–20) and the desired products were obtained in high yields with good stereoselectivity.

Catalyst recovery and reuse are important issues in Heck coupling reactions. Easy separation and recycling make the catalyst useful for industrial applications. Therefore, the recovery and reusability of the catalyst were investigated using iodobenzene with styrene as model substrates. The fluorous palladium catalyst could be easily recovered by fluorous liquid–liquid separation. As expected, the catalyst showed good reusability with only slight decreases in its activity and stereoselectivity (Table 3). The slight decrease in the yield may be due to the small amount of catalyst lost by manipulation. The coupling products were purified by silica column chromatography, after which only very low palladium contents (<1.8 ppm) were detected in the samples. This low Pd level satisfies the specifications required by the pharmaceutical industry regarding the final purity of the products (Pd < 2 ppm).

Conclusion

In summary, we have prepared a new fluorous nanopalladium catalyst and successfully applied it for the Heck reaction in water. The catalyst shows high catalytic activity for the reaction of aryl halides and substituted styrenes with low catalyst loading, and the corresponding products were obtained in moderate to excellent yields with good stereoselectivity toward trans-stilbenes (with *E/Z* ratio of up to 98:2). Water as a solvent is more eco-friendly than DMF that is mostly used in Heck reactions. Moreover, the catalyst could be easily recovered by fluorous liquid–liquid separation and reused for four times without significant loss of activity or stereoselectivity. The excellent performance of the catalyst in water under air and its easy preparation and reusability make it a useful alternative to other palladium catalysts.

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