Short Communication

A novel system for the Suzuki cross-coupling reaction catalysed with light fluorous palladium–NHC complex

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ABSTRACT

A novel Pd–NHC catalyst containing fluorous tags was synthesized and characterized. The catalytic activity and stability of the catalyst has been evaluated for the Suzuki cross-coupling reaction of aryl halides and aryl boronic acids in the mixture solvent of C_6F_6 and EtOH to afford the corresponding products in excellent yields. In addition, the catalyst can be reused three times without obvious loss of catalytic activity. The structure of the catalyst was characterized by elemental analyses, FT-IR, ^{1}H NMR, ^{13}C NMR and ^{19}F NMR.

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1. Introduction

The palladium-catalyzed Suzuki cross-coupling reaction, involving cross-coupling of aryl halides with aryl boronic acids, has been shown as an powerful, attractive and convenient synthetic method for the construction of carbon–carbon bonds [1–4] and has been widely used for the synthesis of fine chemicals, pharmaceuticals and dyes [5,6].

In recent years, various efficient Pd catalyst precursors have been investigated [7–11]. In general, these reactions were carried out in the presence of a variety of phosphine based ligands [12–14]. Lately, N-heterocyclic carbenes (NHCs), as a substitute of phosphorus-containing ligands [15,16], have been introduced as potentially effective ligands for Suzuki cross-coupling reactions. Due to their strong σ-donating and low π-accepting abilities, the metal complexes of these carbenes showed high thermal stability and hydrolytic durability. Additional advantages of these ligands over the classic phosphines include easy preparation, variable structures and low toxicity. Therefore, these complexes have emerged as effective catalysts for a wide range of catalytic reactions. However, most of metal–NHC complexes were difficult to recycle when they worked as catalysts [17–19].

In the past decade, fluorous chemistry has attracted a great deal of attention for facilitating catalyst recovery [20–22]. Metal complexes with ligands containing fluorous tags exhibit special features, such as it can be used in fluorous biphase solvents to catalyze reactions and can be recovered from the reaction mixture by means of fluorous liquid–liquid separation [23,24]. But most of the fluorous catalysts are insoluble in most organic solvents, which limited their application in organic synthesis.

Recently, some palladium–NHC catalysts containing a fluorous tag have been reported with low catalytic activity in cross-coupling reactions [25,26]. Suzuki cross-coupling reactions have typically been performed under heterogeneous palladium catalysts where the palladium is fixed to a solid support in order to be recycled conveniently [27,28]. However, heterogeneous palladium catalysts have lower catalytic activity and selectivity compared to homogeneous catalysts. But homogeneous processes suffer from the problems concerning separation of products from reaction mixture, recycling of potentially expensive complexes and potential residual metals contamination in the product.

Based on an overall consideration of various factors, we sought for an adequate solution to the problem. In the last few years, we oriented our research on the study of heavy fluorous metal–NHC complex [29]. In continuation of our studies in developing new fluorous catalysts, we reported a novel system of the Suzuki cross-coupling reaction catalysed with light fluorous palladium–NHC complex. Compared with heavy fluorous catalysts, light fluorous catalysts can be recovered easily by using simple fluorous liquid–liquid separation, and also with better solubility in organic solvents. Herein, we prepared a new functionalized palladium–NHC complex containing a fluorous tag and its application in the Suzuki cross-coupling reaction in homogeneous system consisted of EtOH and C_6F_6. In this case, the catalyst can be readily recovered and reused for several times only with slightly decrease in its activity.
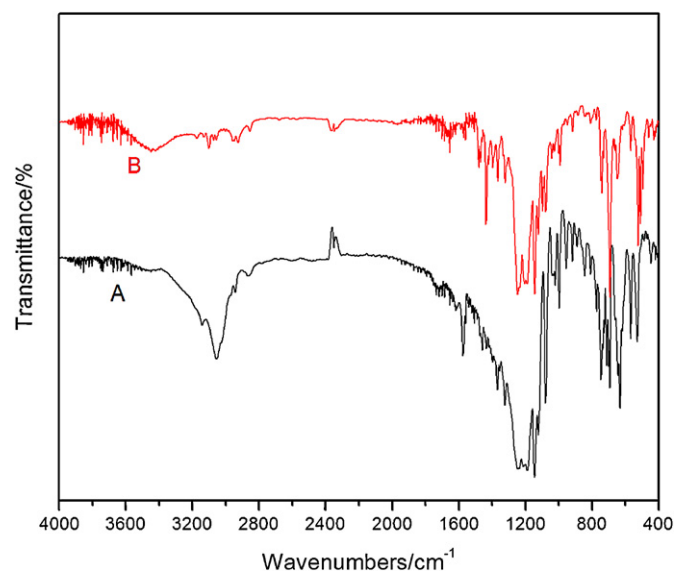
Fig. 1. IR spectra of 1,3-bis(polyfluoroalkyl)imidazolium salts (A) and fluoruos palladium–NHC catalyst (B).

Scheme 1. Preparation of the fluorous palladium–NHC catalyst.

2. Results and discussion

The palladium–NHC catalyst was prepared according to Scheme 1. In order to ascertain fluorous NHC chelated with palladium, IR spectra were recorded separately at the different stage of preparation. As shown in Fig. 1, the C–H peaks between 2800 and 3200 cm^{-1} almost disappeared after introduction of [PdCl$_2$(PPh$_3$)]$_2$. Moreover, the peak at about 1140–1250 cm^{-1} was weakened, which attributed to the vibration of C–N. The catalyst was dissolved in C$_6$F$_6$, but not in H$_2$O and EtOH.

To evaluate the catalytic performance of palladium–NHC complex, a series of experiments have been performed with 4-bromoanisole and phenylboronic acid as model reaction to optimize the reaction conditions. As illustrated in Table 1, initial studies were performed by using different solvents in the presence of palladium–NHC catalyst. It was found that the single solvent such as H$_2$O, EtOH and THF gave low to moderate yields (Table 1, entries 1–3), and the fluorous biphase solvents also give the low yields (Table 1, entry 4). However, in EtOH/C$_6$F$_6$ (1:1 v/v), we obtained the desired product in 50% yield (Table 1, entry 7), as we found the reaction can goes in homogeneous way, in this case, the catalyst have higher catalytic activity and selectivity owing to its

better dispersion. Then, we chose EtOH/C$_6$F$_6$ (1:1 v/v) as the solvent for the Suzuki reaction.

Under same catalytic conditions, different bases were investigated in the experiments (Table 2). As can be seen in Table 2, potassium hydroxide gave the highest yield. Other inorganic bases such as K$_2$CO$_3$, K$_3$PO$_4$·3H$_2$O, NaOH and Cs$_2$CO$_3$, proved to be less effective for the cross-coupling of 4-bromoanisole with phenylboronic acid (Table 2, entries 1–4). Also, the organic base t-BuONa and Et$_3$N were studied but no satisfactory yields were obtained (Table 2, entries 6 and 7). KOH was found to be the most effective base for the reaction (Table 2, entry 5). Because KOH has properly alkaline in this system, and the size of cation K$^+$ also has benefit to promote the synthesis of ylide(Pd) efficiently to give high yields [30–32]. 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. Thus, we select KOH as base, EtOH/C$_6$F$_6$ (1:1 v/v) as solvent, and 0.1 mol% of catalyst as the best conditions for the Suzuki reaction.

After optimising the reaction conditions, we performed the Suzuki cross-coupling reaction of various aryl halides with aryl boronic acid, good yields of cross-coupling products were obtained and the results were summarized in Table 3. Both electron deficient and electron rich arylbromides afforded the corresponding biphenyls in good to excellent yields (Table 3, entries 1–8). The catalyst can tolerate a wide range of functional groups, such as –OMe, –Me, –NO$_2$, –CF$_3$, and –COMe. Also, the coupling reaction could be efficiently executed with aryl boronic acids containing electron-donating and electron-withdrawing groups (Table 3, entries 1, 9 and 10). And the coupling of aryl iodides with phenyl boronic acid gave excellent yields (Table 3, entries 11–14). We also performed the reaction with aryl chlorides in our system. However, only moderate yield was obtained in the coupling reaction (Table 3, entries 15–17).

Recycling experiments have been investigated using 4-bromoanisole and phenylboronic acid as model substrates with

Table 1

Effect of solvents for the Suzuki cross-coupling reaction.[a]
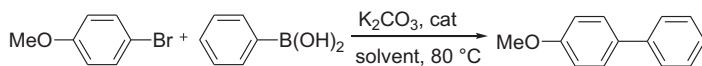
Entry	Solvent	Yield[b] (%)
1	H$_2$O	Trace
2	EtOH	32
3	THF	39
4	H$_2$O/C$_6$F$_6$(1:1 v/v)	18
5	Toluene/C$_6$F$_6$(1:1 v/v)	49
6	MeOH/C$_6$F$_6$(1:1 v/v)	44
7	DMF/C$_6$F$_6$(1:1 v/v)	Trace
8	EtOH/C$_6$F$_6$(1:1 v/v)	50
9	EtOH/C$_6$F$_6$(1:0.5 v/v)	39
10	EtOH/C$_6$F$_6$(0.5:1 v/v)	45
11	EtOH/H$_2$O/C$_6$F$_6$(0.5:0.5:1 v/v/v)	30

[a] Reaction conditions: 4-bromoanisole (1.0 mmol), phenylboronic acid (1.5 mmol), K$_2$CO$_3$ (2.0 mmol), catalyst (0.1 mol%) in 2 ml solvent at 80 °C for 3 h.
[b] Isolated yield.

Table 2
Effect of base and catalyst loadings for Suzuki cross-coupling reaction.[a]

MeO—⟨benzene⟩—Br + ⟨benzene⟩—B(OH)$_2$ $\xrightarrow[\text{EtOH/C}_6\text{F}_6,\ 80\ °C]{\text{base, cat}}$ MeO—⟨biphenyl⟩
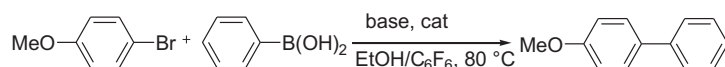
Entry	Catalyst loading (mol%)	Base	Yield[b] (%)
1	0.1	K_2CO_3	50
2	0.1	$K_3PO_4 \cdot 3H_2O$	67
3	0.1	NaOH	61
4	0.1	Cs_2CO_3	51
5	0.1	KOH	85
6	0.1	t-BuONa	52
7	0.1	Et_3N	39
8	0.05	KOH	63

[a] Reaction conditions: 4-bromoanisole (1.0 mmol), phenylboronic acid (1.5 mmol), base (2.0 mmol), 2 ml EtOH/C$_6$F$_6$ (1:1 v/v) at 80 °C for 3 h.
[b] Isolated yield.

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

R_1—⟨benzene⟩—X + R_2—⟨benzene⟩—B(OH)$_2$ $\xrightarrow[\text{EtOH/C}_6\text{F}_6,\ 80°C]{\text{KOH,cat}}$ R_1—⟨biphenyl⟩—R_2
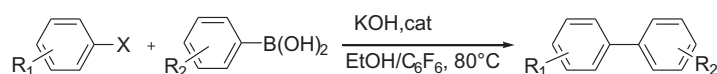
Entry	X	R_1	R_2	Yield[b] (%)
1	Br	H	H	83
2	Br	4-CH$_3$O	H	85
3	Br	4-CH$_3$	H	90
4	Br	4-NO$_2$	H	98
5	Br	2-NO$_2$	H	91
6	Br	4-CHO	H	95
7	Br	4-CF$_3$	H	86
8	Br	4-CH$_3$CO	H	93
9	Br	H	4-Cl	91
10	Br	H	4-CH$_3$	88
11	I	4-CH$_3$O	H	99
12	I	4-CH$_3$	H	98
13	I	4-NO$_2$	H	99
14	I	H	H	98
15	Cl	4-CH$_3$	H	21
16	Cl	4-NO$_2$	H	56
17	Cl	H	H	16

[a] Reaction conditions: aryl halide (1.0 mmol), aryl boronic acid (1.5 mmol), KOH (2.0 mmol), catalyst (0.1 mol%) in 2 ml EtOH/C$_6$F$_6$ (1:1 v/v) at 80 °C for 3 h.
[b] Isolated yield.

0.1 mol% catalyst loading at 80 °C. After the reaction completed, the reaction mixture was cooled to room temperature, then concentrated to get the mixture of products and catalyst, which was washed with H$_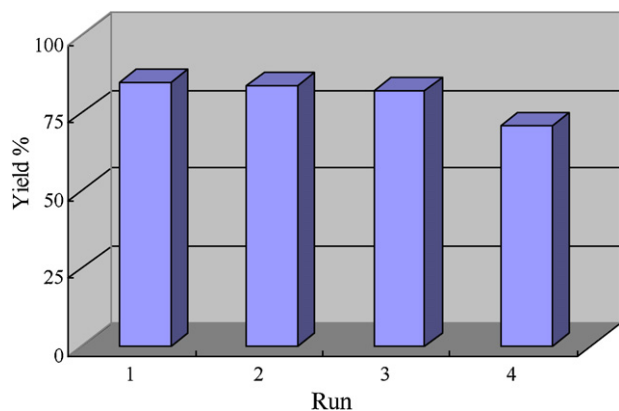2$O and EtOH, the residue was the recycled catalyst and was dried under vacuum for the next cycle. And the solvent collected, which include perfluorobenzene and EtOH, could be reused without further purification. Fig. 2 shows the results obtained after three reuse cycles, and the yields are 85, 84, 82 and 71% and the purity of the recycled catalyst are 94, 93, 91 and 90% respectively to run 1, run 2, run 3 and run 4; as it can be seen, there was no significant loss of catalytic activity after three cycles. The slight decrease of the yield may be due to the small amount of catalyst lost during manipulation.

Fig. 2. Recycling experiments.

3. Conclusions

In conclusion, we have successfully prepared a new light fluorous palladium–NHC catalyst which was performed as an efficient catalyst for the Suzuki cross-coupling reaction. Short reaction times, high yields, easy purification and recyclability are main characteristic of the process which can be used to generate a diverse range of biphenyls in excellent yields. Further studies on the reaction mechanism with this catalytic system and further applications are currently under investigation.

4. Experimental

4.1. General remarks

All chemicals were reagent grade and used as purchased. IR spectra were recorded in KBr disks with a Bomem MB154S FT-IR spectrometer. GC analyses were performed on an Agilent 7890A instrument. Elemental analyses were performed on a Vario EL III recorder. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker DRX 500 and tetramethylsilane (TMS) was used as a reference. ^{19}F NMR spectra was recorded on Bruker DRX 500 using CCl$_3$F as the internal standard. All the products are known compounds and were identified by comparing of their physical and spectra data with those reported in the literature.

4.2. Preparation of 1,3-bis(polyfluoroalkyl)imidazolium salts

The preparation of polyfluoroalkylated imidazolium salts was based on the reaction of imidazole with polyfluoroalkyl halide. Imidazole (0.34 g, 5 mmol) and 1H,1H,2H,2H-perfluorooctyl iodide (5.22 g, 11 mmol) were dissolved in 5 ml toluene. The mixture was stirred at 110 °C for 24 h. After being cooled to room temperature, organic phase was washed with water (2 ml × 20 ml). Combined organic phases were dried with anhydrous magnesium sulfate, solvents were removed by rotary vacuum evaporator. Then the crude product was dissolved in EtOAc (20 ml) and precipitated with 10-fold excess of hexane (200 ml).The precipitate was separated and dried in vacuum. And the product was obtained as a white solid (2.27 g, 51%).

^{1}H NMR (500 MHz, DMSO-d$_6$), δ: 2.97–3.05 (m, 4H), 4.61 (t, 4H, J = 12.5 Hz), 7.95 (s, 2H), 9.42 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d$_6$), δ: 29.4, 41.0, 106–122 (m), 133.9, 136.9. ^{19}F NMR (470 MHz, Acetone-d$_6$), δ: −80.9 (bs, 6F), −114.3 (bs, 4F), −122.0 (bs, 4F), −123.0 (bs, 4F), −123.5 (bs, 4F), −126.3 (bs, 4F). Anal. Calc. for C$_{19}$H$_{11}$N$_2$F$_{26}$I: C: 25.69, H: 1.25, N: 3.15; Found C: 25.76, H: 1.35, N:3.18%.

4.3. Preparation of the fluorous palladium–NHC catalyst

Under a dry N$_2$ atmosphere, to a stirred solution of the salt (0.45 g, 0.5 mmol) and sodium hydride (0.17 g, 0.75 mmol) in THF (10 ml). The reaction mixture was heated under reflux for 4 h. After cooling to room temperature, the volatiles were removed. The residue was charged with [PdCl$_2$(PPh$_3$)]$_2$ (0.22 g, 0.25 mmol) and toluene (5 ml). The mixture was stirred at 110 °C for 4 h under N$_2$, then cooled to room temperature and hexane (10 ml) was added. The resulting precipitate was filtered off and recrystallized from CH$_2$Cl$_2$/Et$_2$O. And the product was obtained as a yellow solid (0.29 g, 48%).

^{1}H NMR (500 MHz, CDCl$_3$), δ: 2.97–3.03 (m, 4H), 4.67 (t, 4H, J = 17 Hz), 7.07 (s, 2H), 7.40–7.44 (m, 9H) 7.67–7.70 (m, 6H). ^{13}C NMR (125 MHz, CDCl$_3$), δ: 30.3, 42.6, 121.6, 126.6–131.2 (m), 134.1.

^{19}F NMR (470 MHz, CDCl$_3$), δ: −80.7 (bs, 6F), −113.6 (bs, 4F), −121.7 (bs, 4F), −122.7 (bs, 4F), −123.3 (bs, 4F), −126.0 (bs, 4F). Anal. Calc. for C$_{37}$H$_{25}$N$_2$F$_{26}$Cl$_2$PPd: C: 37.02, H: 2.08, N: 2.33; Found C: 37.11, H: 2.15, N: 2.40%.

4.4. Typical procedure for Suzuki reactions

Under air atmosphere, round-bottomed flask was charged with aryl halide (1.0 mmol), phenylboronic acid (1.5 mmol), KOH (2.0 mmol), EtOH/C$_6$F$_6$ (1:1 v/v, 2 ml) and catalyst (0.1 mol%).

The mixture was reacted at 80 °C for a certain time (monitored by GC). After the reaction completed, the reaction mixture was cooled to room temperature, then concentrated to get the mixture of products and catalyst, which was washed with H$_2$O (2 ml × 10 ml) and EtOH (2 × 10 ml), the residue is the catalyst recycled. And the EtOH washings were dried over anhydrous Na$_2$SO$_4$, and evaporated to obtain the crude products. After that 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.

4.5. Recycling of catalyst

A round-bottomed flask was charged with 4-bromoanisole (1.0 mmol), phenylboronic acid (1.5 mmol), KOH (2.0 mmol), EtOH/C$_6$F$_6$ (1:1 v/v, 2 ml) and catalyst (0.1 mol%). The mixture was reacted at 80 °C for 3 h. After the reaction completed, the reaction mixture was cooled to room temperature, then concentrated to get the mixture of products and catalyst, which was washed with H$_2$O (2 ml × 10 ml) and EtOH (2 × 10 ml), the residue was the recycled catalyst and was dried under vacuum for the next cycle. And the solvent collected, which include C$_6$F$_6$ and EtOH, could be reused without further purification.

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