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Active palladium catalyst supported by bulky diimine ligand catalyzed Suzuki–Miyaura coupling reaction in water under phosphanefree and low catalyst loading conditions[†]

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A new catalytic system based on palladium and bulky diimine ligand for Suzuki-Miyaura coupling reaction of aryl iodides, bromides and chlorides in neat water is described. The desired biphenyl products were obtained in high to excellent yields for aryl iodides and bromides in the presence of low catalyst loading. Air-stable catalyst has been recycled for the reaction of iodobenzene with phenylboronic acid for five consecutive runs. Copyright © 2014 John Wiley & Sons, Ltd.

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Keywords: Suzuki; palladium; bulky diimine; supported; water

Introduction

Palladium-catalyzed cross-coupling reactions have become a key and powerful tool in organic synthesis for the formation of carbon-carbon bonds.^[1,2] Among the different types of palladium-catalyzed reaction, the Suzuki-Miyaura reaction, which is the reaction between aryl halides and arylboronic acids, represents possibly the most important and widely used one.[3-7] Over recent years, the Suzuki-Miyaura reaction has had an important impact on industry and academic laboratories in the synthesis, for example, of pharmaceuticals, fine chemicals and polymers, and the total synthesis of natural products.^[1-7] Palladium-catalyzed carbon-carbon and carbon-heteroatom bond formation reactions have been traditionally performed using palladium catalysts in the presence of various phosphane ligands.^[8-18] These ligands suffer from issues such as difficulty of synthesis, and poor thermal and air stability. Moreover, most phosphane ligands are expensive, not easily available, unrecoverable, and also toxic, giving rise to particular environmental and economic concerns, especially when large-scale operations are under consideration. To avoid these drawbacks, there is a growing interest in using phosphane-free and eco-friendly ligands such as diazabutadienes,^[19] oximes,^[20-24] Nheterocyclic carbenes^[25-30] and amine-bridged (bis)phenol ligands^[31] in the presence of palladium pre-catalysts.

Previous findings reveal that the bulky electron-rich ligands show high activity in different palladium-catalyzed coupling reactions by stabilizing Pd(0) intermediates and avoiding precipitation of the metal in homogeneous catalysis.^[32] The electron richness imparted to the palladium by the ligand assists the cleavage of the Ar-X bond in the oxidative addition step, while the steric bulk of the ligand promotes reductive elimination of the desired coupling product.

Today, environmental consciousness encourages the chemical community to search for more environmentally sustainable chemical processes for chemical syntheses. For this purpose, the use of new heterogeneous recyclable catalysts and of less toxic materials as solvents and reagents are two important challenging subjects. The use of water as a cheap and safe solvent instead of expensive, flammable and toxic organic solvents reduces environmental damage caused by organic solvents.^[33] Thus in recent years there has been growing interest in the development of the Suzuki–Miyaura coupling reaction in water.^[34]

Experimental

General

¹H NMR spectra were recorded at 250 and 400 MHz and ¹³C NMR spectra were recorded at 62.9 and 100 MHz in CDCl₃ using tetramethylsilane (TMS) as internal standard. Organic solvents were purified by known procedures and stored over molecular sieves (4 Å). All reagents used in this study were purchased from Aldrich and Merck Chemical and used without further purification.

Catalyst Synthesis

Primary ligand (Scheme 1, compound 1)

Ligands and catalysts were synthesized following a procedure reported in the literature,^[35] which will briefly be explained in the following paragraphs.

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- [†] This paper is dedicated to Professor Nasser Iranpoor on the occasion of his 60th birthday.
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4,4'-((4-methoxyphenyl)methylene)bis(2,6-dimethylaniline) was prepared by reacting 2,6-dimethylaniline with *p*-methoxybenzaldehyde. 2,6-Dimethylaniline was heated to 130 °C under an inert atmosphere to which *p*-methoxybenzaldehyde dissolved in concentrated HCl and THF were added over a period of 1 h. The reaction mixture was refluxed for 24 h. After cooling to room temperature, it was basified with aqueous NaOH and extracted with CHCl₃. The combined organic layers were washed with water and brine, respectively. The solution was dried over MgSO₄ and pentane was added to precipitate the product, which was then purified through recrystallization twice in CHCl₃ using pentane to obtain the product as a pure creamy white crystalline powder.

Synthesis of ligand (N,N'-(acenaphthylene-1,2-diylidene)bis(4-((4-amino-3,5-dimethylphenyl)(4-methoxyphenyl)methyl)-2,6-dimethylaniline)) (Scheme 1, compound **2**)

To a methanol solution of 4,4'-((4-methoxyphenyl)methylene) bis(2,6-dimethylaniline), acenaphthenequinone (AQN) in 2:1 ratio and a catalytic amount of formic acid were added. The reaction mixture was stirred overnight at 50 °C. After the reaction, methanol was removed under vacuum with a rotary evaporator and the resulting product was purified via column

chromatography (ethyl acetate-hexane, silica gel). The solvent was evaporated to obtain the product, which was then dried at $50 \,^{\circ}$ C under vacuum.

Palladium complex synthesis (scheme 1, compound 4)

The Pd-diimine catalyst used in this study, [(ArN-C(AQN)-(AQN)C-NAr)Pd(CH₃)(N-CMe)]SbF₆ (Ar-4,4'-((4-methoxyphenyl)methylene)bis(2,6dimethylaniline)), was synthesized following a similar procedure reported in the literature,^[36] which will briefly be explained in the following. Under an inert atmosphere, (COD) PdClMe and diimine ligand were dissolved in a 1:1 ratio in diethyl ether. The reaction was run for 24 h at room temperature. The air-stable orange precipitate formed was recovered by filtration, washed with 3 × 25 ml diethyl ether and dried under vacuum. For synthesizing the final catalyst, AgSbF₆ was added to the acetonitrile solution of [(ArN-C(AQN) - (AQN)C-NAr)Pd(CH₃) (CI) in a 1:1 ratio at room temperature, resulting in immediate precipitation of AgCl. This mixture was allowed to stir overnight. AgCl was removed via filtration and the solvent was evaporated.

General Experimental Procedure for the Suzuki-Miyaura Reaction

Palladium catalyst (0.8 mol%, 10 mg), aryl halide (1 mmol), arylboronic acid (1.5 mmol), potassium carbonate (1.5 mmol) and distilled water (2 ml) were added to a 5 ml flask. The mixture was stirred for an appropriate reaction time at 100 °C and the progress of the reaction was monitored by GC. After completion of the reaction, the aqueous layer was extracted with ethyl acetate or hexane (5 × 1 ml). Further

purification of the product was achieved by flash chromatography using hexane–EtOAc to give the desired biphenyl compound.

Results and Discussion

Recently, different bidendate α -diimine ligands coordinated to nickel were used as an active catalyst in ethylene polymerization.^[35] Condensations of bulky ortho-substituted anilines bearing remote push-pull substituents with acenaphthenequinone, in the presence of nickel pre-catalysts, give nickel catalyst precursors for which the polymerization activity varied with substituents on the catalyst. In the present work, we report the synthesis of the palladium complex 4 catalyst (Fig. 1) and its performance in the Suzuki-Miyaura coupling reaction of structurally different aryl halides under low loading of catalyst in water as an eco-friendly medium. Catalyst synthesis steps were characterized by ¹H NMR, mass, TGA and FT-IR analysis (see supporting information). TGA of compound 4 showed three steps of weight losses. The first weight loss occurred between 25 and 100 °C, with an observed weight loss of 3.3% corresponding to the loss of acetonitrile ligand. The second and third weight losses



Figure 1. Synthesis steps of palladium catalyst.

occurred between 100 and 275 °C and between 275 and 375 °C and may be related to the loss of methyl and 1,2-dihydroacenaphthylene.

In order to find optimized reaction conditions for the Suzuki–Miyaura coupling reaction, less reactive 4-bromoanisole was selected as a model compound and its coupling reaction with phenylboronic acid was studied under different reaction conditions. Our initial investigation focused on the effect of various solvents and using different bases (Table 1).

The results indicated that in the presence of catalyst, using water as a solvent and K_2CO_3 as a base, the best reaction yield was obtained under heterogeneous conditions. However, to ensure that the temperature was optimal, the reaction was performed at different reaction temperatures (Table 2).

Using the optimized reaction conditions, we attempted to apply the catalyst to Suzuki–Miyaura coupling reactions of structurally different aryl halides with arylboronic acids (Table 3).

The results of Table 3 indicated that, using this protocol, the reaction of aryl iodides proceeded smoothly to produce the desired biphenyl compounds in high to excellent yields (entries 1–4). Also, the reaction of aryl bromides with arylboronic acids proceeded well and afforded the corresponding biphenyl products in high to excellent yields (entries 5–15). Reactions of 5-bromopyrimidine and 3-bromothiophene as heterocyclic aryl bromides with phenylboronic acid performed well and afforded the desired products in 94% and 89% isolated yields, respectively. In addition, we studied reaction of 4-chlorotoluene, 4-chloronitrobenzene and 4-chlorobenzonitril under optimized reaction conditions. The desired biphenyls were isolated in 48%, 58% and 65% isolated yields, respectively, after 24 h.

Since the palladium precursors are expensive and also there are typically strict guidelines to limit the levels of palladium impurity in the drug product, separation of the palladium catalyst is highly attractive from economic and environmental viewpoints. Finally, we studied the recycling of the catalyst for the reaction of

Table 1. Effect of different solvents and bases			
Cat. (0.8 mol%) Br K ₂ CO ₃ , H ₂ O (2 mL) + Ph-B(OH) ₂ 100 °C, 15 h OMe OMe			
Entry	Solvent	Base	Yield (%)
1	DMF	Et ₃ N	22
2	DMF	КОН	40
3	DMF	K ₂ CO ₃	46
4	Toluene	Et₃N	34
5	Toluene	K ₂ CO ₃	72
6	H ₂ O	Et₃N	25
7	H ₂ O	КОН	76
8	H ₂ O	K ₂ CO ₃	88
9	H ₂ O	DBU	29
10	Dioxane	Et₃N	54
11	Dioxane	КОН	42
12	Dioxane	K ₂ CO ₃	43
13	DMF-H ₂ O	Et ₃ N	62
14	DMF-H ₂ O	K ₂ CO ₃	70

Table 2. Effect of different reaction temperatures on the reaction of 4-bromoanisole and phenylboronic acid in the presence of catalyst using K_2CO_3 as a base in water within 15 h





iodobenzene (5 mmol) with phenylboronic acid (7.5 mmol). For this purpose, the heterogeneous solid catalyst was separated by centrifugation from the reaction mixture and was charged into another batch of the reaction for five runs (Table 4).

Finally, in order to gain information about the active catalytic species at 100 °C, we studied the hot filtration test for the reaction of 4-bromoanisole and phenylboronic acid. The reaction mixture was filtered after 2 h at the reaction temperature (49% GC yield after 2 h) and allowed the filtrate to react. GC analysis



of the reaction after 15 h showed 57% yield. Also, leaching of the catalyst into the reaction mixture after 15 h was determined by atomic absorption spectroscopy to be <1.5%. We may conclude that the catalyst had a predominantly heterogeneous nature under the reaction conditions.

Conclusion

In this article we studied the catalytic activity of bulky diimine palladium complex in Suzuki–Miyaura coupling reactions of structurally different aryl halides in water. In the presence of low catalyst loading, aryl iodides and bromides reacted efficiently and gave the desired biphenyl products in high to excellent yields. Reactions of less reactive aryl chlorides were sluggish and biphenyl products were obtained in moderates yields. The heterogeneous catalyst has been easily separated and recycled for five runs with decreasing activity.

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