

New Homogeneous And Robust Catalyst for Heck and Suzuki Reactions

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Abstract

A novel and efficient palladium-based homogeneous catalyst was fabricated and used as a robust catalyst in Suzuki–Miyaura cross-coupling and Heck reactions. 2-Amino-N-(pyridin-2-ylmethyl)benzamide was introduced as a versatile ligand for palladium-catalyzed cross-coupling reactions. The desired active and stable homogeneous Pd catalyst was prepared via the coordination of Pd with 2-amino-N-(pyridin-2-ylmethyl)benzamide and fully characterized. The catalyst exhibited excellent activity in Suzuki–Miyaura cross-coupling and Heck reactions. The proposed protocol featured mild reaction conditions and efficiency using LiOH as base.

Keywords: Suzuki–Miyaura; Cross-coupling reaction; Heck reaction; 2-amino-N-(pyridin-2-ylmethyl)benzamide; Homogeneous Pd catalyst.

Introduction

Following the development of suitable methods for carbon-carbon bond formation, palladium catalyzed approaches have attracted organic chemist's attention in recent years. Among several known reactions, Suzuki and Heck cross coupling reactions have found a growing interest from the synthetic community in which an aryl boronic acid or alkene reacts with an unsaturated halide [1]. On the other hand, homogeneous catalyzed reactions are versatile methods for the synthesis of important molecules. However, there is a persistent problem with metal aggregation and precipitation leading to catalyst decomposition and considerable loss of catalytic activity [2]. Although, Pd catalysts are

known to aggregate easily and form Pd black, they have been useful catalytic systems in organic synthesis [3]. To overcome this intrinsic drawback of homogeneous Pd catalysis, several novel and modified ligands have been introduced for stabilizing the catalyst.

Recently, homogeneous Pd catalytic systems have been applied in a wide variety of chemical transformations such as asymmetric oxidation [4], aerobic oxidation of alcohols [5], several cross coupling reactions [6], carbonylation and carboxylation [7], hydrogenation especially asymmetric hydrogenation [8], and borylation [9] reactions. Although these methodologies have improved the Pd catalytic system, most of them suffer from different drawbacks in which the aggregation and easily formation of Pd black are

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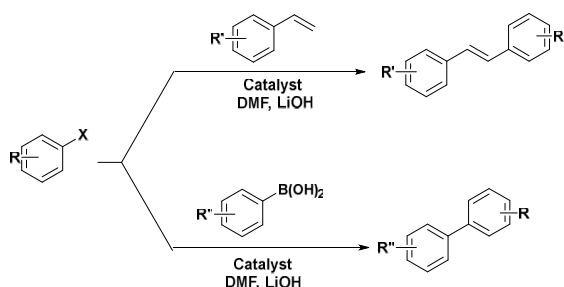
important problem [10]. There are three most popular approaches to successful catalytic reaction without the Pd black formation including sufficient oxygen partial pressure in oxidation reactions [11], low substrate to catalyst molar ratio [12], appropriate ligand design [13] and the third one is a proper way. Anthranilic amides were interestingly utilized for the synthesis of different biologically active materials [14]. Due to their ability in the coordination chemistry for the synthesis of a wide variety of transition metal complexes, we have designed desired catalyst using anthranilic amide derivate.

Herein, we report a new palladium-based homogeneous catalytic system using pyridine derivative of anthranilic amide as a nitrogen rich ligand. 2-Amino-*N*-(pyridin-2-ylmethyl)benzamide bearing large number of nitrogen atoms at appropriate site makes it a versatile candidate for coordinating to transition metals. Therefore, it encouraged us to use it as a ligand for the preparation of homogeneous palladium catalyst. To this purpose, we designed and synthesized 2-amino-*N*-(pyridin-2-ylmethyl)benzamide (L1) as a ligand for preparation 2-amino-*N*-(pyridin-2-ylmethyl) benzamide-palladium complex (denoted Pd (L1)). The main goal, involves high efficiency and stability in homogeneous Pd catalyzed Suzuki–Miyaura and Heck reactions along with the significant suppress of Pd black formation (Scheme 1).

Materials and Methods

General

Commercially available reagents were used without further Purification. Melting points were measured onj Kofler hot stage apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on Bruker FT-400, 500, using TMS as an internal standard. IR spectra were obtained on a Shimadzu 470 spectrophotometer (KBr disks). MS were recorded on an Agilent Technology (HP) mass spectrometer operating at an ionization potential of 70 eV. Elemental analysis was performed on an Elementar Analysen system GmbH Vario



Scheme 1. Pd (L1) catalyzed Suzuki–Miyaura cross-coupling and Heck reactions.

ELCHNS mode.

General procedure for the Heck coupling reaction using Pd (L1) as catalyst

A mixture of aryl halide (1.0 mmol), alkene (1.0 mmol), LiOH (1.2 mmol) and catalytic amount of Pd (L1) (0.03 mmol) was taken in a round-bottom flask, stirred in DMF (3.0 ml) at 80 °C and the reaction progress was monitored by TLC. At the end of the reaction, the liquid was poured into distilled water (10 ml) and the product was extracted with ethyl acetate. The organic phase was dried over Na_2SO_4 . Then the combined organic phase was evaporated and the product was purified using column chromatography on silica gel using a mixture of n-hexane:ethyl acetate (5:1) as eluent.

General procedure for Suzuki reaction using Pd (L1) as catalyst

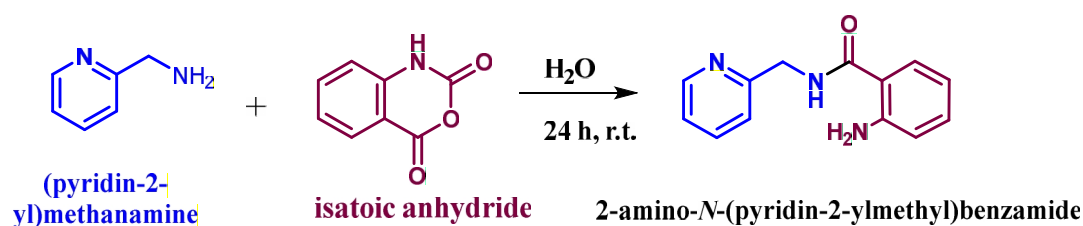
The mixture of aryl halide (1.0 mmol), aryl boronic acid (1.0 mmol), LiOH (1.2 mmol⁻) and the catalytic amount of Pd (L1) (0.03 mmol) was taken in a round-bottom flask and allowed to stirred in DMF (3.0 ml) at 80 °C and then, the progress of reaction was monitored by TLC. Then, the residual mixture was poured into distilled water (10 ml) and the product was extracted with ethyl acetate. The organic phase was washed with brine, dried over Na_2SO_4 , filtered, and then passed through celite. Next, the organic phase was evaporated and the residue was purified by column chromatography on silica gel using n-hexane:ethyl acetate (5:1) as eluent to give the corresponding product.

2-amino-*N*-(pyridin-2-ylmethyl)benzamide: mp 133–134 °C. IR (KBr): 3303, 3279, 1695, 1607, 1441, 1295, 1083, 756, 693 cm^{-1} . ^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ = 4.01 (m, 2H), 4.79 (s, 2H), 6.64–6.80 (m, 2H), 7.26–7.29 (m, 2H), 7.58 (d, J = 7.6 Hz, 1H), 7.70 (d, J = 7.8 Hz, 1H), 7.82 (t, J = 7.5 Hz, 1H), 8.64 (d, J = 8.2 Hz, 1H) 8.09 (m, 1H). ^{13}C NMR (125 MHz, $\text{DMSO}-d_6$): δ = 49.1, 116.4, 118.0, 118.9, 120.9, 124.1, 128.3, 133.0, 136.2, 148.4, 148.7, 156.2, 167.9.

Results and Discussion

To prepare the target Pd catalyst, Pd was coordinated to the 2-amino-*N*-(pyridin-2-ylmethyl)benzamide ligand using $\text{Pd}(\text{OAc})_2$ and L1 in dichloromethane as a solvent at room temperature. Then, NaBH_4 was added to the latter mixture as reducing agent. The obtained catalyst was characterized by UV-Vis spectroscopy.

The UV-Vis spectra of aqueous solutions of the



Scheme 2. Synthesis of 2-amino-N-(pyridin-2-ylmethyl)benzamide ligand (L1).

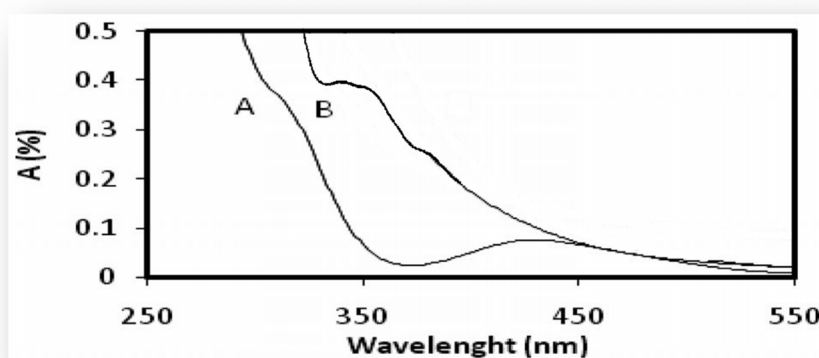


Figure 1. UV-Vis spectra of the palladium catalyst; (A) Pd(OAc)₂, (B) synthesized Pd catalyst.

synthesized Pd catalyst and Pd(OAc)₂ are shown in Figure 1. In the case of Pd(OAc)₂, the peak at around 450 nm shows the presence of PdII. However, in the spectra of aqueous solution of prepared catalyst, the disappearance of the peak around 450 nm confirms that PdII was reduced to the Pd0 species.

Catalyst activity in the Heck/Suzuki reactions

The activity of the synthesized catalyst was subsequently investigated in the Suzuki–Miyaura cross-coupling reaction as well as Heck reaction using less activated aryl halides (X = Cl, Br). Firstly, the evaluation and optimization of Pd (L1) was studied in

the Suzuki–Miyaura cross-coupling reaction between phenylboronic acid and bromo benzene as a model reaction. To this purpose, a series of bases including NaOH, K₂CO₃, Cs₂CO₃, LiOH and Et₃N and different amount of catalyst were tested (Table 1). Among different condition, LiOH (1.2 mmol), and Pd (L1) (0.03 mmol) as the optimal base and catalyst, respectively (Table 1, entry 3).

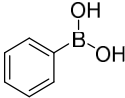

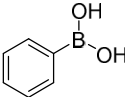

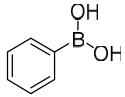

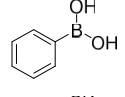

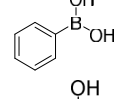

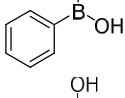

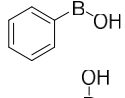

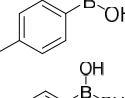

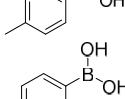

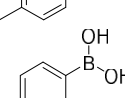

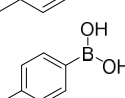

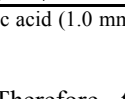

Based on the optimal conditions a mixture of phenylboronic acid: bromo benzene: Pd (L1) catalyst; LiOH = 1.0:1.0:0.03:1.2 mmol, respectively led to the best result. Also, performing the reaction in different solvents and temperatures revealed that DMF at 80 °C

Table 1. Effect of different bases on the catalytic efficiency of Pd (L1) in the reaction of phenylboronic acid and bromobenzene.^a

| Entry | Base | Time (h) | Yield (%) |
|-------|---------------------------------|----------|-----------|
| 1 | - | 48 | - |
| 2 | NaOH | 12 | 64 |
| 3 | K ₂ CO ₃ | 12 | 18 |
| 4 | Cs ₂ CO ₃ | 12 | 27 |
| 5 | LiOH | 2 | 91 |
| 6 | LiOH | 1 | 76 |
| 7 | Et ₃ N | 12 | 45 |

^a Reaction conditions: phenylboronic acid (1.0 mmol), bromobenzene (1.0 mmol), Pd (L1) (0.03 mmol), base (1.2 mmol) in DMF.

Table 2. Studying the efficiency of Pd (L1) catalyst in Suzuki–Miyaura cross-coupling reaction.a

| Entry | Aryl boronic acid | Aryl halide | Time (h) | Yield (%) ^[b] |
|-------|---|---|----------|--------------------------|
| 1 |  |  | 2 | 91 |
| 2 |  |  | 1 | 96 |
| 3 |  |  | 4 | 83 |
| 4 |  |  | 4 | 88 |
| 5 |  |  | 2 | 93 |
| 6 |  |  | 1.5 | 90 |
| 7 |  |  | 3 | 89 |
| 8 |  |  | 1 | 94 |
| 9 |  |  | 2 | 90 |
| 10 |  |  | 2.5 | 85 |
| 11 |  |  | 1.5 | 92 |
| 12 |  |  | 2 | 89 |

^a Reaction conditions: phenylboronic acid (1.0 mmol), aryl halide (1.0 mmol), Pd catalyst (0.03 mmol), base (1.2 mmol) in DMF; [b] Yields of the isolated products.



















offered the best condition. Therefore, the optimized conditions was applied to wide variety of substrates to form the corresponding cross-coupled products. As shown in Table 2, high efficiency of the Pd (L1) catalyst provided very good to excellent yields for the reaction of different halo arenes and boronic acids containing various electron-donating and electron-withdrawing substituents.

To investigate further efficiency of Pd (L1) catalyst, it was used in the Heck reaction. To this purpose, the reaction of phenyl bromide and styrene was treated as the model reaction. Various bases (KOAc, NaOH,

K₂CO₃, Et₃N and LiOH) were screened. However, using LiOH and DMF as base and solvent, respectively. The optimal conditions were found as ratio of 1.0:1.0:0.03:1.5 mmol for bromo benzene: styrene: Pd (L1) catalyst: LiOH, respectively, in DMF as solvent at 80 °C. As the results given in Table 3, Pd (L1) shows great performance in the reaction of phenyl bromide and styrene derivatives to give the corresponding stilbenes.

In this study, we introduced a novel and efficient Pd-containing 2-amino-*N*-(pyridin-2-ylmethyl) benzamide catalyst for Suzuki–Miyaura and Heck reactions under mild conditions.

Table 3. Studying the efficiency of Pd (L1) catalyst in Heck reaction.^a

| Entry | Aryl boronic acid | Aryl halide | Time (h) | Yield (%) ^[b] |
|-------|---|---|----------|--------------------------|
| 1 |  |  | 2 | 93 |
| 2 |  |  | 1 | 95 |
| 3 |  |  | 3.5 | 89 |
| 4 |  |  | 3.5 | 91 |
| 5 |  |  | 2.5 | 90 |
| 6 |  |  | 2 | 92 |
| 7 |  |  | 1.5 | 94 |
| 8 |  |  | 1.5 | 93 |
| 9 |  |  | 2 | 95 |

^a Reaction conditions: alkylhalide (1.0 mmol), styrene (1.0 mmol), Pd catalyst (0.03 mmol), base (1.5 mmol) in DMF; [b] Yield of the isolated products.

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