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Novel Recyclable Pd/H-MOR Catalyst for Suzuki–Miyaura Coupling and Application in the Synthesis of Crizotinib

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Abstract: In this paper, we report an effective ultrasound method for the synthesis of Pd/H-MOR, which was used as a catalyst in the Suzuki–Miyaura coupling of aryl halides with phenylboronic acid. The structure and morphology of the as-prepared catalysts were fully characterized by X-ray diffraction (XRD), N2 sorption isotherms, scanning electron microscopy (SEM), and an inductively coupled plasma-atomic emission spectrometer (ICP-AES). The advantages of Pd/H-MOR in the coupling reaction are green solvents, high yields, absence of ligands, and recyclability. The catalysts were easily reused at least ten times without significant deterioration in catalytic activity. In addition, this protocol was used in the marketed anti-tumor drug crizotinib synthesis.

Keywords: heterogeneous catalyst; palladium catalysts; Suzuki coupling; ultrasound; crizotinib

1. Introduction

Zeolites are microporous materials consisting of a crystal structure with molecular sieving characteristics [1–3]. Zeolites have a wide range of applications when used as carriers to support metals for cross-coupling reactions, such as C-C coupling [4–7], C-N coupling [8–10], C-S coupling [11], and C-H activation [12]. Mordenite zeolite (MOR), which is composed of 12-membered ring (12-MR) channels with 8-MR channels (side pockets), is one of the most vital zeolites with many industrial applications in the catalytic processes of toluene disproportionation, hydro-isomerization, and the method of producing ethanol from non-grain feedstocks [13]. However, few pieces of literature have been published on the use of metals supported on MOR zeolite as catalysts for cross-coupling reactions. Ultrasound’s unique acoustic cavitation effect can provide transient high-temperature and high-pressure extreme reaction conditions and induce weak reducing agents, such as ethylene glycol or even water, to produce highly reactive free radicals so that the reduction reaction can be completed under milder conditions [14–16]. At the same time, the shear oscillation generated by ultrasonic waves can effectively reduce the agglomeration of metal nanoparticles [17,18]. Suzuki coupling reactions have been reported as an efficient and less toxic method to form Csp2–Csp3 bonds [19,20]. As a large number of natural products, polymers, and pharmaceuticals have biaryl segments, much effort has been spent on the development of practical conditions for performing Suzuki couplings [21]. A typical strategy in developing heterogeneous catalysts for Suzuki coupling is to deposit Pd species onto various solid supports. Nevertheless, the problems of high reaction temperature, long reaction time [16], and an environmentally friendly solvent [4] still exist.

In this study, the preparation, characterization, and application of Pd nanoparticles/H-MOR (Pd/H-MOR) by ultrasonic treatment are reported (Figure 1). Due to the high
active surface area, the contact between the reactants and the catalyst is significantly increased. Therefore, the advantages of Pd/H-MOR in the coupling reaction are green solvents, high yields, absence of ligands, and recyclability.

Figure 1. General procedure for the synthesis of Pd/H-MOR catalyst.

2. Results and Discussion

These as-prepared catalysts were characterized by X-ray diffraction (XRD), N\textsubscript{2} sorption isotherms, scanning electron microscopy (SEM), and an inductively coupled plasma-atomic emission spectrometer (ICP-AES). The XRD pattern in Figure 2A shows that Pd/H-MOR has a slightly weak diffraction peak intensity as compared to H-MOR, suggesting that the crystallinity of the zeolite is marginally reduced after the loading of metal. In addition, the diffraction peak at 2\textdegree \text{of} 40.22\textdegree proves the palladium nanoparticles decorated on zeolite [22]. The peaks at 2\textdegree of 90.88\textdegree, 19.78\textdegree, 25.86\textdegree, and 31.12\textdegree are attributed to the H-MOR support, confirming its structure without any changes [23]. The N\textsubscript{2} sorption isotherms of H-MOR and Pd/H-MOR are shown in Figure 2B, which prove that Pd/H-MOR is a micro/mesoporous catalyst. A steep increase at the relative pressure \(\frac{P}{P_0}<0.003\) signifies the presence of micropores, and the hysteresis loop at the pressure \(\frac{P}{P_0}\) of 0.4–1 indicates slit mesopores exist in Pd/H-MOR. Pd/H-MOR has a lower low-pressure adsorption capacity due to the loaded Pd nanoparticles. The textural parameters of the supports and catalysts in Table S1 show that Pd/H-MOR has a BET surface area of 412 cm\textsuperscript{2}/g and a microporous volume of 0.19 cm\textsuperscript{3}/g, lower than those of support (464 cm\textsuperscript{2}/g, 0.21 cm\textsuperscript{3}/g). This might be caused by the blockage of the MOR zeolite micropore channel. Figure 2C,D show the SEM images of Pd/H-MOR and H-MOR, respectively. Pd/H-MOR is an irregular grain particle with the size of 4-7 \(\mu\text{m}\). There is no obvious trace of Pd nanoparticle distribution on the surface of the catalyst, meaning Pd is present in the catalyst at the nanometer scale. The chemical composition of the Pd/H-MOR was determined by CP-AES, confirming that the content of Pd nanoparticles on the H-MOR is 3.17wt%, and the Si/Al ratio in the catalyst is around 11.3.
As shown in Table 1, Pd/H-MOR was used as the catalyst for the Suzuki cross-coupling reaction of phenylboronic acid 1a with 4-iodoanisole 2a. First of all, we tested the catalytic activity of Pd/H-MOR, which was an efficient heterogeneous palladium catalyst for the Suzuki coupling reaction (Table 1, entry 1). For a comparison with the homogeneous PdCl₂ catalyst, a slightly lower yield of 3a was obtained. The result means that Pd/H-MOR exhibits higher catalytic activity for the Suzuki coupling reaction (Table 1, entry 2). MOR and H-MOR were not able to catalyze the reaction (Table 1, entries 3, 4). Control experiments showed that the palladium catalyst was essential for this diphenyl formation reaction. Following from this, an effect of the base was observed and lower yields of 3a were obtained with NaHCO₃. In contrast, the application of other stronger bases, such as K₂CO₃, Na₂CO₃, and Cs₂CO₃, were more favorable in the formation of Suzuki product 3a (Table 1, entries 1, 5–8). The effect of the ratio of solvent was explored, and the results showed that the highest yield of the desired product 3a (95%) was obtained in H₂O:EtOH = 4:1 (Table 1, entries 1, 9–12). The effect of the temperature was then examined, and the result showed that 80 °C was the optimal temperature (Table 1, entries 12–15). Finally, the effect of time on the reaction was studied, and the results showed that the reaction could be completed in 0.5 h (Table 1, entries 12, 16, 17). The performance of Pd/H-MOR was also compared with that of some palladium heterogeneous catalysts reported in the literature. As shown in Table 2, the Pd/H-MOR exhibited a superior catalytic activity at a relatively mild temperature and green solvent, as well as a faster conversion.

**Table 1. Optimization of reaction conditions.**

| Entry | Catalyst  | Base    | Solvent | Temp. (°C) | Yield b (%) |
|-------|-----------|---------|---------|------------|-------------|
| 1     | Pd/H-MOR | K₂CO₃   | EtOH    | 80         | 92          |
| 2     | PdCl₂    | K₂CO₃   | EtOH    | 80         | 94 c        |
| 3     | MOR      | K₂CO₃   | EtOH    | 80         | NR          |

Figure 2. (A) XRD patterns of Pd/H-MOR (a) and H-MOR (b); (B) N₂ sorption isotherm of Pd/H-MOR (A) and H-MOR (B); SEM images (scale bar 10 μm) of Pd/H-MOR (C) and H-MOR (D).
The reaction conditions: phenylboronic acid, result-

| Number | R   | X     | Ar          | catalyst | Reaction conditions                  | Yield (%) | Ref. |
|--------|-----|-------|-------------|----------|--------------------------------------|-----------|------|
| 1      | H   | p-I   | C_{6}H_{4}-CH_{3} | Pd/H-MOR | H_{2}O:EtOH(4:1)/K_{2}CO_{3}/80 °C/0.5 h | 98        | This work |
| 2      | H   | p-I   | C_{6}H_{4-OCH_{3}} | Pd@mnc-S1 | MeOH/K_{2}CO_{3}/80 °C/0.5 h         | 93        | [4]   |
| 3      | H   | p-I   | C_{6}H_{4}-CH_{3} | Pd-OS    | EtOH/K_{2}CO_{3}/80 °C/0.5 h         | 93        | [24]  |
| 4      | H   | p-I   | Ph          | Z-Y-Pd NPs | H_{2}O:EtOH(1:1)/K_{2}CO_{3}/Reflux/1.5 h | 88        | [16]  |

Encouraged by the above results, the heterogeneous Suzuki coupling reactions of various aryl halides with phenylboronic acid were then examined under optimized reaction conditions. As shown in Table 3, Suzuki coupling products were obtained in moderate to excellent yields, showing that this catalytic system was compatible with various substrates. Phenylboronic acid 1a was used as the substrate to test the Suzuki coupling effects of different aryl iodides. The coupling reactions of phenylboronic acid with both electron-deficient and electron-rich substituted iodobenzenes using the catalyst proceeded in high yields (Table 3, entries 1–13). For a comparison with meta-substituted or ortho-substituted substrates, when para-substituted aryl halides, including electron-withdrawing and electron-donating groups, were used as a reactant, more than 95% yield was obtained. (Table 3, entries 2, 4–7, 10–13). These results showed that m-substituted substrates had little effect on the coupling reaction under optimized reaction conditions, and o-substituted substrates were only slightly affected. The scope of the reaction was then extended to less reactive aryl bromide and chloride derivatives. The catalyst also easily catalyzes the Suzuki coupling reaction of aryl bromides with phenylboronic acid, resulting in high yields (Table 3, entries 14–16). However, Pd/H-MOR did not exhibit an excellent catalytic performance when aryl chlorides were used as the substrate, even if the reaction times were extended to 8 hours (Table 3, entries 17–20). The coupling reactions using aryl boronic acids were also investigated, and the coupling products were obtained in good yields, while the electron-releasing groups in aryl boronic acid gave higher yields compared to substrates bearing electron-withdrawing groups (Table 3, entries 21–24). The Suzuki coupling reaction of heteroaryl bromide and phenylboronic acid was effective in
optimized reaction conditions, producing the corresponding products (Table 3, entries 25,26).

Table 3. Suzuki coupling between phenylboronic acid and aryl halides.

| Entry | R   | X       | Ar       | Yield b (%) |
|-------|-----|---------|----------|-------------|
| 1     | H   | p-I     | C₆H₄-OCH₃ | 95 (3a)     |
| 2     | H   | p-I     | C₆H₄-NH₂  | 95 (3b)     |
| 3     | H   | p-I     | C₆H₄-OH   | 96 (3c)     |
| 4     | H   | p-I     | C₆H₄-CHO  | 98 (3d)     |
| 5     | H   | p-I     | C₆H₄-NO₂  | 98 (3e)     |
| 6     | H   | p-I     | C₆H₄-CHO  | 97 (3f)     |
| 7     | H   | p-I     | C₆H₄-COCH₃ | 95 (3g)   |
| 8     | H   | p-I     | C₆H₄-Cl   | 95 (3h)     |
| 9     | H   | I       | Ph        | 95 (3i)     |
| 10    | H   | m-I     | C₆H₄-NO₂  | 94 (3j)     |
| 11    | H   | m-I     | C₆H₄-COCH₃ | 93 (3k)   |
| 12    | H   | o-I     | C₆H₄-NH₂  | 86 (3l)     |
| 13    | H   | o-I     | C₆H₄-CHO  | 84 (3m)     |
| 14    | H   | p-Br    | C₆H₄-CHO  | 79 (3d)     |
| 15    | H   | p-Br    | C₆H₄-CHO  | 92 (3f)     |
| 16    | H   | Br      | Ph        | 92 (3i)     |
| 17    | H   | p-Cl    | C₆H₄-NH₂  | 48 (3b)     |
| 18    | H   | p-Cl    | C₆H₄-CHO  | 50 (3f)     |
| 19    | H   | p-Cl    | C₆H₄-COCH₃ | 52 (3g)   |
| 20    | H   | p-Cl    | Ph        | 51 (3i)     |
| 21    | 4-CH₃O | p-I     | C₆H₄-OCH₃ | 96 (3n)     |
| 22    | 4-CH₃ | p-I     | C₆H₄-OCH₃ | 95 (3o)     |
| 23    | 4-F   | p-I     | C₆H₄-OCH₃ | 92 (3p)     |
| 24    | 3-NO₂ | p-I     | C₆H₄-OCH₃ | 86 (3q)     |
| 25    | H    | o-Br    | pyridine  | 83 (3r)     |
| 26    | H    | o-Br    | quinoline | 81 (3s)     |

The reaction conditions: boronic acids 1 (1.3 mmol), aryl halides 2 (1 mmol), Pd/H-MOR (10 mg), and K₂CO₃ (2 mmol) in 10 mL solvent (H₂O:EtOH = 4:1) were reacted for 0.5 h under air. Isolated yield. 8 h.

To further showcase the abilities of the catalyst system on the synthetic utility for medicinal purposes, we turned our attention to the preparation of crizotinib, which is a tyrosine kinase inhibitor used to treat anaplastic lymphoma kinase-positive lung cancer (Scheme 1) [25]. The synthetic method was used as the catalyst for the Suzuki cross-coupling reaction of aryl bromide 4 with pinacol boronate 5. This transformation was accomplished with excellent results in the presence of the Pd/H-MOR catalyst and K₂CO₃ in water and ethanol at 80 °C for 6 h. Then, the intermediate was treated with 4 M HCl in 1,4-dioxane/CH₂Cl₂, and the crizotinib API was isolated in a 90% yield with 97% purity and < 10 ppm Pd.
Scheme 1. Application of the catalyst in the synthesis of crizotinib.

A significant practical application of a heterogeneous catalysis is to be able to recycle the catalyst from the reaction mixture and reuse it for subsequent reactions. Thus, the ability to recycle the Pd/H-MOR catalyst was studied for the reaction of phenylboronic acid 1 with 4-idoanisole 2a. After the completion of the reaction, the catalyst was separated by centrifugation after each round and reused in the next catalyst reaction. As shown in Figure 3, with increasing recycle times, the catalytic activities of Pd/H-MOR catalysts were decreased slightly. The yield of the first run was 95%, and after the tenth run, its yield fell to 90%, which indicated the steadiness of the Pd/H-MOR catalyst.

Figure 3. Recycling of Pd/H-MOR in the Suzuki coupling.

3. Experimental Materials

The starting materials were commercially available and, except for the solvents, were used without further purification. H-MOR zeolite was provided by Nankai University Catalyst Co., Ltd (Tianjin, China). Palladium (II) chloride (PdCl₂, 59.5%) was provided by J&K Scientific Ltd (Shanghai, China). Ethanol was provided by Anhui Ante Food Co., Ltd (Suzhou, Anhui, China). Potassium hydroxide was provided by Sinopharm Chemical Reagent Co., Ltd (Shanghai, China). Other materials were of an analytical grade and used as received.

3.1. Characterization

X-ray diffraction (XRD) measurements were performed at room temperature by using a Rigaku Ultimate VI X-ray diffractometer (40 kV, 40 mA) (Tokyo, Japan) using CuKα (λ = 1.5406 Å). The N₂ sorption isotherms at the temperature of liquid nitrogen were measured using Micromeritics ASAP 2020 (Norcross, GA, USA). The Pd loading of the sample was determined by an inductively coupled plasma-atomic emission spectrometer (ICP-AES) with a Perkin-Elmer 3300DV emission spectrometer (Norwalk, CA, USA). Scanning electron microscopy (SEM) experiments were performed on a Hitachi SU-1510 electron microscope.
microscope (Tokyo, Japan). $^1$H and $^{13}$C NMR spectra were measured with a Bruker Advance 400 spectrometer (New York, NY, USA) by using CDCl$_3$ or DMSO-$d_6$ as solvents and TMS as the internal standard.

3.2. **Preparation of Pd/H-MOR Catalyst**

We added 0.5 g of H-MOR zeolite to 50 mL of ethanol in a 100 mL round-bottom flask. This mixture was infiltrated and dispersed by an ultrasonic bath for 30 min. After this period of ultrasonic treatment, PdCl$_2$ (0.075 g) was added to the solution and dispersed by ultrasonic for 20 min. Then, KOH (0.048 g with 10 mL H$_2$O) was added to this solution by a constant pressure dropping funnel for 10 min. This mixture was dispersed by an ultrasonic bath for 1 h. After ultrasonic treatment, the product was centrifuged, washed, and kept constant at 100 °C overnight.

3.3. **General Procedure for the Suzuki Coupling Reactions**

 Aryl halides (1 mmol), aryl boronic acid (1.3 mmol), K$_2$CO$_3$ (2 mmol), Pd/H-MOR (10 mg), 8 mL H$_2$O, and 2 mL ethanol were placed in a reaction flask and stirred at 80 °C under air. After the reaction was complete, it was cooled to room temperature. The mixture was then extracted with ethyl acetate, dried, filtered, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel, using pure petroleum to afford the product.

3.4. **General Procedure for Catalyst Recovery**

 The 4-iodoanisole (2.5 mmol), phenylboronic acid (3.25 mmol), K$_2$CO$_3$ (5 mmol), and Pd/H-MOR (50 mg) were mixed in H$_2$O and ethanol (25 mL, 4:1). The mixture was stirred at 80 °C under air. After the reaction was complete, the catalyst was centrifugated, washed, vacuum dried, and used in the next run. The ingredients involved in the cyclic reaction are based on the Pd/H-MOR obtained by separation and are fed in proportion.

4. **Conclusions**

In summary, a simple and green sonochemical method was applied to palladium nanoparticles deposited on MOR zeolite with ultrasonic treatment. Pd/H-MOR (3.17 wt% of Pd) was an efficient heterogeneous catalyst for Suzuki coupling of aryl halides and phenylboronic acid. Reaction conditions, including the base, temperature, time, catalyst type, solvent ratio, and substrate scope, were optimized. Furthermore, the catalyst was recycled and reused up to 10 times. This work introduces the advantages of green solvents, short reaction times, high yields, absence of ligands, and reusability of the catalyst. Moreover, this catalyst easily synthesized the marketed drug crizotinib (anti-tumor). This work expands the application’s scope of inorganic material MOR as the catalyst carrier as well as promoting the development of green chemistry.

**Supplementary Materials:** The following are available online at www.mdpi.com/article/10.3390/catal11110121/s1, Table S1: Textural parameters of the synthesized sample. $^1$H and $^{13}$C NMR patterns of products.

**Author Contributions:** Conceptualization, C.S. and J.J.; investigation, E.Z. and L.Z.; supervision, K.Z. and H.X.; writing—original draft, E.Z. All authors have read and agreed to the published version of the manuscript.

**Funding:** Financial support from Zhejiang Provincial Natural Science Foundation of China (No. LGF19B060002, LY17B020005) and the National Natural Science Foundation of China (No.21302171). This work is also supported by the Zhejiang Shuren University Basic Scientific Research Special Funds (2020XZ011).

**Acknowledgments:** Many thanks to all co-authors, and Huimin Luan from Zhejiang University for catalyst characterization. And love from my family.

**Conflicts of Interest:** The authors declare no conflicts of interest.
