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Application of Palladium Single Atoms in C−C Coupling Reactions of Pharmaceutical Synthesis

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Abstract. Designing highly active and structurally well-defined catalysts while reducing the amount of catalyst has become a key issue in heterogeneous catalytic reactions. In this study, palladium single-atom catalysts were prepared for efficient catalysis in the Suzuki cross-coupling reaction of iodobenzene and phenylboronic acid, which was prepared by one-step high-temperature pyrolysis. The palladium single-atom catalysts have high activity as well as stability in Suzuki cross-coupling reactions and have great potential in catalyzing organic reactions.

Keywords: Pd single-atom catalysts (SACs); Suzuki reactions; C-C coupling; Heterogeneous catalysis

1. Introduction

In organic reactions, Suzuki cross-coupling of aryl halogenated hydrocarbons combined with aryl boronic compounds is one of the most effective methods for the formation of carbon-carbon bonds (C-C).[1, 2] As a result, it has found extensive use in the pharmaceutical, pesticide chemicals, and fine chemical synthesis industries. Palladium is the most commonly used catalyst for Suzuki cross-coupling reaction. This type of reaction is known for its mild reaction conditions, simple operation, and wide functional group tolerance.[3-5] The most commonly used palladium catalysts in Suzuki cross-coupling reactions are homogeneous palladium catalysts, which are characterized by high catalytic efficiency. However, it has the disadvantages of high price, high consumption and non-recyclability.[6-8]

As a result, heterogeneous palladium catalysts were explored. The palladium atoms anchored in different carriers such as carbon materials, metal oxides and zeolites, which have the advantages of high stability and easy separation.[9-11] In heterogeneous catalysts, theoretical and experimental results have shown that the smaller nanoparticles have better catalytic activity and selectivity, making it highly desirable to reduce the particles.[12, 13] The single-atom catalysts (SACs) are a new type of catalyst supported by metal atoms on the carrier anchored through B, N, O, S and other elements.[14] SACs are single-atom in nature and can utilize 100% of metal atoms as active sites.[15]

In this work, we developed highly atom-utilized palladium SACs by high-temperature sintering in a single step to form graphene-loaded palladium SACs, which was applied to the Suzuki cross-coupling reaction of aryl iodobenzene and aryl boronic acid.

2. Experimental section

Materials: We bought the Pristine graphene from Hunan Fenghua Materials Development Co., Ltd. All reagents are purchased from Macklin Biochemical Technology Co., Ltd. All reagents are up to 99% and can be used directly without further processing and purification.

Preparation and Characterization of Pd SACs/G : The graphene and palladium foil were placed in a porcelain ark, and raised to 900 ^{o}C at the rate of 5 $^{o}C/min$ in a tube furnace for 3 hours,

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and the Pd SACs/G was obtained by natural cooling. JEOL JEM was used for TEM analyses which resolution is 0.15 nm at 200kV. Acquired the AC-HAADF-STEM images through FEI Tian Cubed Themis G2 300.

3. Results and discussion

As shown in Fig. 1, the TEM and HAADF-STEM images indicated that the obtained single-atom catalyst was found to have no obvious particle state and uniformly distributed on the carrier, indicating that Pd SACs had been successfully prepared.

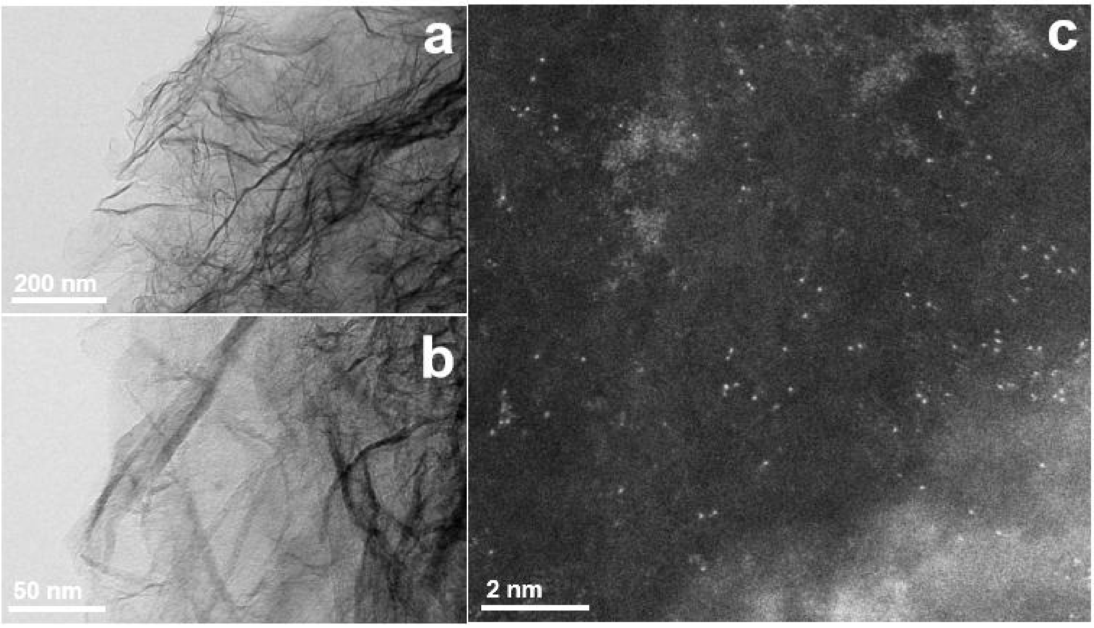
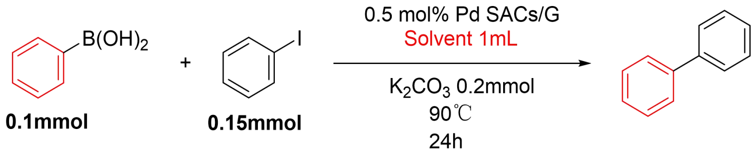


Fig. 1. The TEM images (a-b) and HAADF-STEM image (c) of Pd SACs/G.

Suzuki cross-coupling reactions. In order to investigate the activity of Pd SACs/G in Suzuki cross-coupling, optimization of the reaction conditions was required, and a detailed screening of solvents, bases, temperatures and reaction time was carried out. The coupling reaction of iodobenzene with phenylboronic acid was chosen as a model reaction. As shown in Table 1, the yield was low at 27.3% when water was used as the reaction solvent. When methanol and ethanol alone were used as solvents, the yields were moderate at 41% and 55.7%, respectively. Very notably, the yield soared to 90% when the solvent was a mixture of ethanol and water. When organic solvents such as cyclohexane and benzene were used as reaction solvents, the yields were very low which showed only 8% and 13%. Especially when DMF was used as solvent, the yield was negligible. Therefore, the optimized solvent EtOH:H_2O=1:1=1mL in the reaction conditions of iodobenzene and phenylboronic acid.

Table 1. Solvents screening for the optimisation of the Suzuki coupling.

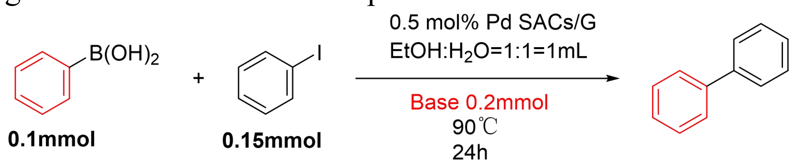


Entry	Solvent	Yeild%
1	H_2O	27.3
2	MeOH	41
3	EtOH	55.7
4	EtOH:H_2O=1:1	90
5	DMF	Trace
6	Cyclohexane	8
7	Benzene	13

[a] Reaction conditions: a mixture of 0.1 mmol of Phenylboric acid, 0.15 mmol iodobenzene, 0.5 mol% Pd SACs/G, 0.2 mmol K_2CO_3, and 1 mL of solvent at 90 °C for 24 hours; [b] all yields were obtained by isolated.

The optimal base conditions also the important factor for Suzuki coupling. As shown in Table 2, the highest yield of 90% was achieved when K_2CO_3 was used as the base. When Cs_2CO_3 , Na_2CO_3 , K_3PO_4 and $KHCO_3$ were used as the bases, the yields were moderate with 44.5%, 60%, 48.5 and 52%, respectively. When KOH and NaOH, two relatively strong bases, were used as reaction conditions, the yields were lower, only 18.3% and 15.7%. Therefore, in the reaction conditions of iodobenzene and phenylboronic acid, the yield was optimal when K_2CO_3 was used as the base required for the reaction.

Table 2. Screening of different bases for the optimization of the Suzuki cross-coupling



Entry	Base	Yeild%
1	Cs_2CO_3	44.5
2	Na_2CO_3	60
3	KOH	18.3
4	NaOH	15.7
5	K_2CO_3	90
6	Na_2SO_4	37
7	K_3PO_4	48.5
8	$KHCO_3$	52

[a] Reaction conditions: a mixture of 0.1 mmol of Phenylboric acid, 0.15 mmol iodobenzene, 0.5 mol% Pd SACs/G, 0.2 mmol of bases, and 1 mL of EtOH:H_2O=1:1 at 90 °C for 24 hours. [b] all yields were obtained by isolated

After screening the optimum solvent and base, we tried to screen the optimum temperature and time of the reaction, firstly, after 24 hours of reaction at room temperature (25 °C), the yield was almost nothing, which indicated that Suzuki cross-coupling reaction is difficult to occur at low temperature; immediately after that, we tried the reaction at 50 °C and 70 °C, and the yields were 36.2% and 59%, respectively. So, the reaction temperature of 90 °C was determined as the optimum temperature. On this basis, we continued the optimization of the reaction time, and the yields were not obvious when the reaction was 3 hours and 6 hours; when the reaction time reached 12 hours, the yield was 35%; when the reaction lasted for 18 hours, the yield reached 77.2%, and the highest yield was 90% when the reaction was 24 hours.

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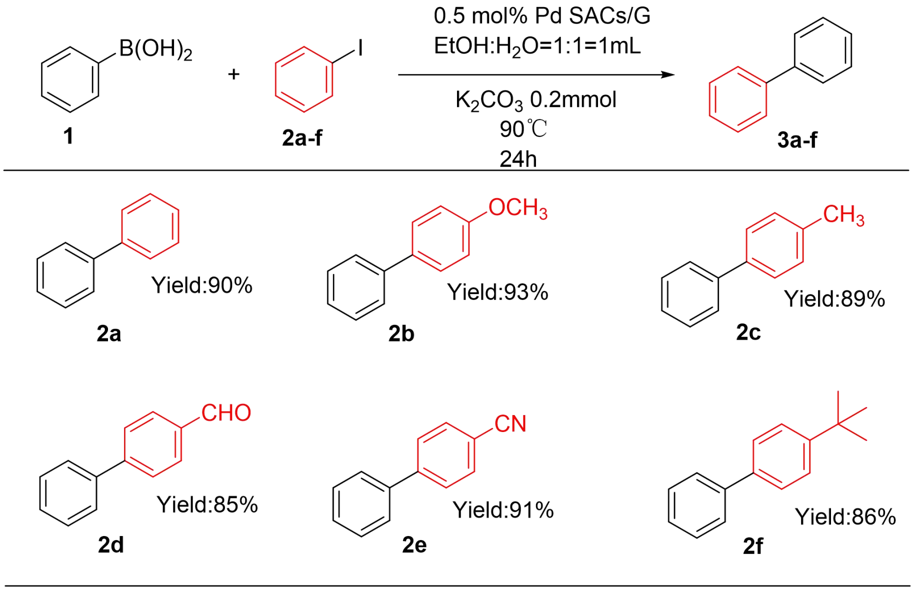
In order to verify the substrate broadness of our prepared Pd SACs/G for Suzuki cross-coupling reaction, the reaction was carried out under optimized optimal conditions using mainly iodoaromatic hydrocarbons and phenylboronic acids as reaction substrates. As shown in the Table 3, in terms of functional group tolerance, the Pd SACs/G catalysts performed well and were suitable for the cross-coupling of substrates with different functional groups. For example, the yield of 4-methoxybiphenyl reached 93%, 4-methylbiphenyl reached 89%, 4-cyanobiphenyl was 91%, 4-tert-butylbiphenyl was 86%, and 4-formylbiphenyl was 85%. That is to say, our prepared single-atom catalysts have a wide range of substrate tolerance in the Suzuki cross-coupling reaction, and have excellent catalytic effects for both electron-donating and electron-pulling groups.

Table 3. Pd SACs/G-Catalyzed Coupling of Suzuki cross-coupling reaction.[a]



[a] Reaction conditions: 0.1 mmol Phenylboronic acid, 0.15 mmol Aryl iodobenzene,0.5 mol% Pd SACs/G, EtOH:H_2O=1:1=1mL, 0.2 mmol K_2CO_3, it reacts uner 90 ºC for 24 hours. Isolated yield.

4. Summary

In briefly, we successfully prepared high-efficiency palladium single-atom catalysts by high-temperature pyrolysis. No particle aggregation was found in transmission electron microscope image characterization, and Pd atoms were uniformly dispersed in HAADF-STEM image characterization. The Pd SACs/G was applied to the Suzuki cross-coupling reaction of aryl iodobenzene and phenylboric acid, and showed high catalytic activity and excellent substrate tolerance. It provides an efficient heterogeneous palladium catalyst which is called single-atom catalyst and further advances palladium catalyst in Suzuki cross-coupling reaction.

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