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Microwave-Assisted Aqueous Carbon-Carbon Cross-Coupling Reactions of Aryl Chlorides Catalysed by Reduced Graphene Oxide Supported Palladium Nanoparticles

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The use of low cost and readily available aryl chlorides as the starting reactants in the palladium-catalyzed carbon-carbon cross-coupling reactions have drawn significant research focus. However, the previously reported heterogeneous palladium catalysts suffered from poor reactivity and harsh condition. Also, the valuable industrial products were rarely obtained in these catalytic systems until now. Herein, a simple and green in-situ assembly and reduction approach was developed for the fabrication of reduce graphene oxide supported palladium nanoparticles (Pd/rGO). Owing to the abundant surface functional groups. Pd NPs were uniformly dispersed on the sheets of rGO with an average size of around 2.0 nm. Interestingly, under microwave irradiation, Pd/rGO can efficiently promote Ullmann and Suzuki coupling reactions by using aryl chlorides as the reactants in aqueous media, which displayed even better catalytic performances than homogenous catalytic system. Notably, this mild reaction system can be demonstrated in the gram-scale synthesis of 4'methyl-2-biphenylcarbonitrile and 2-nitro-3',4',5'-trifluoro-1,1'-biphenyl, which are important pharmaceutical intermediates of Sartans and Fluxapyroxad, respectively. Based on material characterizations and the control experiments, this remarkable catalytic performance could be ascribed to its robust microwave absorption capability, efficient electron transfer and unique two-dimensional structure. Furthermore, it was easily recycled and used repetitively for at least six times without significant the loss of its

Introduction

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Cross-coupling reactions have become essential to industry and academia for the formation of C–C and C–X bonds, even for the construction of complex organic molecules¹⁻³. In this area, palladium-catalyzed carbon-carbon bond formations such as Ullmann⁴, Suzuki^{5, 6}, Negishi^{7, 8}, Stille⁹, Heck¹⁰, Sonogashira^{9, 11}, Tsuji-Trost reactions¹² are particularly appealing in modern organic synthesis. Although these reactions were discovered almost 50 years ago and now represent mature technology, they are typically conducted in homogeneous conditions by using inorganic palladium salts or organic palladium complexes^{1, 13}. Accordingly, the expensive price of palladium, the high toxicity of palladium residues, the use of organic toxic solvents and the tedious workup of the reaction process are not able to satisfy the increasing

activity. economic and environmental requirements. Accordingly, translating homogeneous catalysis to heterogeneous catalysis achieves considerable attention¹⁴⁻¹⁶. In recent years, various palladium species including Pd salt, Pd organometallic complex and Pd nanoparticles were immobilized on different solid supports such as metal oxide¹⁷, zeolite¹⁸, silica¹⁹, polymer²⁰, carbon^{16, 21} and metal-organic framework²², generating a large amount of heterogeneous palladium catalysts. Among different supports, carbon is believed as the excellent support for the immobilization of palladium active sites owing to chemical and thermal stability. To date, different allotropes of carbon including carbon black, carbon nanotube, carbon fibre, graphene, graphene oxide and C_{60} have been used as the support to prepare carbon-supported Pd catalysts^{23, 24}. They were able to promote several different carbon-carbon crosscoupling reactions such as Suzuki-Miyaura, Mizoroki-Heck and Sonogashira-Hagihara in organic solvents but also in aqueous media. However, there is still a significant amount of challenges to improve the scope of these reactions and make reactions more practical. First, most of these reported heterogeneous palladium catalysts displayed the inferior reactivity compared with homogenous catalysts. They often require the use of more reactive and expensive aryl iodides and bromides as the reactants²⁵. But, for low cost and readily available aryl chlorides, carbon-based Pd catalysts frequently need very long reaction time²⁶, high catalyst dosage¹³, harsh

reaction conditions¹ or different additives^{27, 28}. Also, in many

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⁺Electronic Supplementary Information (ESI) available: ICP results of different PdrGO catalyst; Reaction optimization of Ullmann and Suzuki reactions; TEM image of Pd/SiO₂; Microwave absorption ability tests of different samples; TEM and XPS results of the reused Pd-rGO-60 catalyst. This material is available free of charge via the Internet at http://pubs.acs.org. See DOI: 10.1039/x0xx00000x \$These authors contributed equally to this work.

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cases, the valuable industrial products were rarely obtained in these previously reported catalytic systems until now. Moreover, the preparation of carbon-supported palladium catalysts adopts the tedious procedures such as two-step impregnation-reduction^{29, 30} or post-grafting approach³¹.

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Microwave-assisted organic synthesis provides an efficient tool to accelerate carbon-carbon formation reactions³². But, carbon-supported palladium particle catalysts are rarely employed due to the potential arcing phenomena and hot spots that formed by microwave irradiation. Recently, Whittaker et al found that arcing is limited to large metal particles, which supports nanometre-sized particles can ensure safer reaction³³. Moreover, Vaccaro group revealed that hots spots are usually observed with low boiling solvents such as THF and CH₂Cl₂ in the presence of heterogeneous metal catalysts $^{\rm 34}\!.$ Accordingly, Pd/C catalyst was widely used in the microwave-assisted carbon-carbon cross-coupling reactions such as Suzuki-Miyaura Coupling, Mizoroki-Heck and Sonogashira^{5, 6, 9-11}. Nevertheless, the small pore size of Pd/C limited the reaction performance, especially for the reactants with large molecular size. Moreover, although it shortened the reaction time, the increase of reaction selectivity is still a difficulty. In recent years, reduced graphene oxide (rGO) represents an ideal support to form rGO-Pd nanoparticle composite, which possesses unique properties favourable for cross-coupling reactions due to large surface area, light weight, excellent stability and efficient electron mobility³⁵⁻³⁷. Noted that the previously reported results revealed that rGO/metal nanoparticles composites displayed the enhanced microwave absorption ability compared with other traditional materials³⁶. However, the combination of rGO supported Pd nanoparticles with microwave heat for chemical transformations is not fully explored until now. In this work, we synthesized rGO supported Pd nanoparticles composite by an in-situ assembly and reduction protocol. Owing to its unique two-dimensional structure and microwave absorption performance, it showed excellent catalytic performance for Ullmann and Suzuki reactions by using different aryl chlorides as the reactants in the aqueous solvent under microwave heating. For important pharmaceutical intermediates containing multiple substituents, such as 4'-methyl-2-biphenylcarbonitrile and 2-nitro-3', 4', 5'trifluoro-1, 1'-biphenyl, it also can obtain more than 90% yield in a gram-scale synthesis under the mild reaction conditions. Moreover, it can be recycled for six times without significant deactivation.

Experimental Section

Preparation of Graphene oxide.

Graphene oxide was synthesized by classical Hummers method. In the ice water bath, 1.0 g natural graphite powder and 1.0 g sodium nitrate were added into a 1.0 L three-necked flask, and then 40 mL of concentrated sulfuric acid was slowly introduced. After stirring for 2.0 h, 5.0 g potassium permanganate was slowly added and the mixture was allowed to stir at 35°C for another 6.0 h. Then, 100 mL 5.0 % sulfuric acid solution was slowly added and reacted for 2.0. htat 60°C and subsequently 10 g hydrogen per0x1de⁰.Was^{1/2}dded⁰8and stirred at 90°C for 1.0 h. After that, 1.0 L distilled water was added to continue the reaction for 1.0 h. Finally, the solid sample was obtained by centrifugation and washed with a 5.0% hydrochloric acid solution until the sulfate ion was completely washed, and then it was continued to wash by deionized water to be near neutral. And then it was dried at 80°C for 8.0 h and ground into a powder to obtain the final product.

Synthesize of Pd nanoparticles/reduced graphene oxide (Pd/rGO).

250 mg graphene oxide was dispersed into 100 mL sodium hydroxide aqueous solution and then 200 mL 0.10 mol/L sodium dodecyl sulfate solution was mixed. After ultrasonic for 1.0 h, 100 mg palladium acetate was added and stirred for 4.0 h at a certain temperature. After washing by ethanol and deionized water for three times and drying at 80°C for 12 h, a series of solid sample was obtained. These samples were denoted as Pd/rGO-30, Pd/rGO-60 and Pd/rGO-110, which were corresponded to the temperature at which the catalyst was prepared at 30°C, 60°C and 110°C, respectively.

Preparation of Pd nanoparticles/Silica (Pd/SiO₂).

As a control sample, Pd/SiO_2 was prepared by a similar protocol with Pd/rGO, except instead of rGO support as SiO_2 support.

Activity Test.

Ullmann reaction: In a typical run, 1.0 mmol chlorobenzene, 1.5 mmol sodium acetate, 0.50 mmol tetrabutylammonium bromide (TBAB), a certain amount of Pd/rGO, 1.0 mmol 1,3,5trimethylbenzene as the internal standard, 1.0 mL ethanol and 1.0 mL water were added into a 10 mL microwave reaction tube in Discover SP Microwave Synthesizer (CEM Discover SP) at a frequency of 2450 MHz with a maximum power of 300W. After the mixture was stirred under microwave irradiation at 100°C for 2.0 h, the solid catalyst was removed by filtration and then 2.0 mL ethyl acetate was added to the clear solution to extract the reaction products. The products were quantified using an Agilent 6410 Series Triple Quad LC/MS equipped with UV detector and Agilent C18 column (20 cm* ϕ 5 mm).

Suzuki reaction: 1.0 mmol chlorobenzene, 1.2 mmol phenylboronic acid, 0.50 mmol TBAB, 3.0 mmol potassium phosphate, 1.0 mmol 1, 3, 5-trimethylbenzene as internal standard, 1.0 mL ethanol and 1.0 mL water with a certain amount of Pd/rGO were added to a 10 mL microwave reaction tube in Discover SP Microwave Synthesizer (CEM Discover SP) at a frequency of 2450 MHz with a maximum power of 300W. The reaction was stirred at 100°C for 3.0 hours to complete the reaction. The products were quantified using a same method with Ullmann reactions.

Recyclability test: To test the recoverability of the Pd/rGO catalyst, the mixture was centrifuged after the completion of

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the reaction. To remove impurities which may be adsorbed by the catalyst, it was washed for three times with distilled water and ethanol, respectively. After drying at 80°C for 24 h, the mass of the recovered catalyst was weighed, and the loss due to the washing and transfer of the catalyst was calculated. The amounts of the corresponding reactants were used, and the recycling reactions were carried out under the same conditions. After each run of reactions, the content of Pd leached off in each reaction was analysed by ICP analysis.

Measurements and Characterization.

Fourier transform infrared (FTIR) spectra were obtained using a Nicolet Magna Model 550 infrared spectrometer. X-ray diffraction (XRD) patterns were acquired by a Rigaku D/Max-B diffractometer with Cu Ka radiation. High-resolution Transmission electron microscopy (TEM/HRTEM) images were obtained by a JEOL-2100 transmission electron microscope. Xray photoelectron spectroscopy (XPS) analysis was performed on a Perkin Elmer PHI 5000 ESCT System X-ray photoelectron spectrometer. Inductively coupled plasma spectroscopy (ICP) was analysed by Varian VISTA-MPX ICP-OES inductively plasma spectroscopy. The electromagnetic coupled parameters (complex permittivity and complex permeability) were measured via a coaxial line method at the frequency range of 1-18 GHz by an Agilent PNA-N5244A (E5071C) network analyser and the calculations involving complex numbers are performed by Fenghuo Technology Co., Ltd. via Matlab.

Calculation method of microwave absorb ability.

The dielectric loss and magnetic loss properties of the GO, Pd/rGO-60 and Pd/SiO_2 are respectively calculated by the equation (1) and equation (2). Calculation details of dielectric loss tangent and magnetic loss are the data in Figure 4 (a) and Figure S2 (a). The equations are described as follows:

$$\tan \delta_e = \frac{\varepsilon}{\varepsilon'}$$
(1)
$$\tan \delta_m = \frac{\mu''}{\mu'}$$
(2)

In order to obtain the attenuation constant $\boldsymbol{\alpha}\text{,}$ formula (3) can be used.

$$\alpha = \frac{\sqrt{2}}{c} \pi f \bullet$$

$$\sqrt{(\mu_r^{"} \varepsilon_r^{"} - \mu_r^{'} \varepsilon_r^{'})} + \sqrt{(\mu_r^{"} \varepsilon_r^{"} - \mu_r^{'} \varepsilon_r^{'})^2 + (\mu_r^{'} \varepsilon_r^{"} + \mu_r^{"} \varepsilon_r^{'})^2}$$
(3)

The microwave absorb ability of different samples can be obtained by formula (4) and formula (5).

$$Z_{in} = \sqrt{\frac{\mu_r}{\varepsilon_r}} \tanh\left[j\left(\frac{2\pi}{c}\right)f d\sqrt{\mu_r \varepsilon_r}\right]$$
(4)

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Results and discussion

 $R(dB) = 20 \log \left| \frac{Z_{in} - 1}{Z_{in} + 1} \right|$



Scheme 1. Schematic illustration of the preparation of Ponanoparticles/reduced graphene oxide (Pd/rGO).

As shown in Scheme 1, Pd/rGO samples were prepared by an *in-situ* reduction approach using reduced graphene oxide as the support and palladium acetate as the precursor, respectively. We used sodium dodecyl sulfate to disperse rGO in the solution and after heating, it decomposed to 1dodecanol, which can reduce Pd(II) to Pd(0) by self-oxidizing to dodecanoic acid^{38, 39}. ICP measurement showed that the Pd content in the series of Pd/rGO samples was in the range of 0.05 mmol/g to 0.89 mmol/g, confirming the existence of palladium nanoparticles in these composites (Table S1).





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Powder X-ray diffraction (PXRD) pattern revealed that GO sample only displayed a typical amorphous peak and the same 1a). The new diffraction peaks at 40.12° and 46.56° were found in a series of Pd/rGO samples. Comparing with the standard patterns for pure Pd (JCPDS PDF #46-1043), the peak at 40.12° was assigned to the (111) crystal plane of Pd NPs, and the diffraction peak at 46.56° was considered to be the peak of the (200) crystal plane of Pd NPs⁴², confirming the formation of Pd/rGO composites. Meanwhile, in the catalyst synthesized at 110°C, the crystallinity of Pd NPs was significantly higher than that of the catalyst synthesized at 30°C and 60°C, which was due to the increased particle size of Pd NPs. FTIR spectrum of GO sample showed that it had a strong and broad absorption peak centred at 3421 cm⁻¹, which corresponded to the stretching vibration of the hydroxyl group (-OH) on the sheet (Figure 1b). Also, the peak at 1732 cm⁻¹ was the C=O stretching vibration at the carboxyl group, and the vibration absorption peaks at 1358, 1219, and 1049 cm⁻¹ were the stretching vibration of C-OH, C-O-C and C-O, respectively^{43,} ⁴⁴. After introducing palladium species on the GO, the C=O stretching vibration peak in the representative Pd/rGO-60 sample was disappeared, and the intensity of the C-OH vibration peak was weakened significantly, which indicated the oxygen-containing group in the GO is partially removed. Thus, Pd nanoparticles were probably bound to the sheets of rGO through the coordination between Pd species and surface oxygen-containing groups. Raman spectrum revealed that the intensity ratio of G peak and D peak of Pd/rGO-60 (1.07) was lower than that of graphene oxide (1.57), confirming the increased regularity degree of carbon framework after our insitu palladium loading process⁴⁵ (Figure 1c). This result further demonstrated that oxygen-containing groups was partially reduced in the preparation of Pd/rGO samples. Also, XPS spectrum of Pd/rGO-60 confirmed that all the palladium species existed as the zero metallic state, corresponding to the binding energy (BE) of 341.1 and 335.8 eV in the Pd 3d3/2 and 3d5/2 levels^{42, 46}, respectively (Figure 1d). On basis of these results, we can safely conclude that the successful incorporation of the Pd metallic species on the rGO sheets.

Palladium particle size and distribution of different Pd/rGO samples can be obtained by TEM images. As shown in Figure 2, for all the samples, the apparent two-dimensional morphology of rGO can be observed while the presence of Pd nanoparticles on the basal plane of the materials was obvious. In the low preparation temperature (30°C, 60°C). homogeneously distributions of Pd nanoparticles with smaller size of ca. 2.0 nm on the rGO were founded (Figure 2a-b). But, in the high preparation temperature (110°C), the particle size of Pd NPs of Pd/rGO-110 was around 11 nm and their agglomerations were evident (Figure 2c). Also, for Pd/rGO-30, the distribution of Pd NPs was sparse on the sheet due to the low loading. Furthermore, HRTEM image of Pd/rGO-60 revealed that the lattice fringe width of Pd NPs was 0.224 nm, which corresponded to the Pd(111) crystal plane (Figure 2d)^{47,} ⁴⁸. On basis of the similar reported procedure¹², a plausible growth mechanism of Pd/rGO was presented. The surface

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Figure 2. TEM images and Pd nanoparticle size distributions of Pd/rGO-30 (a), Pd/rGO-60 (b), and Pd/rGO-110 (c) and HRTEM image of Pd/rGO-60 (d).

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hydroxyl groups can electrostatic absorb Pd(II) ions on the GO basal planes. Then, the reduction process of Pd(II) to Pd(0) was happened through the self-oxidation of the heating-generated 1-dodecanol to 1-dodecanonic acid.

 $\ensuremath{\text{Table 1. Catalytic performances of different Pd-based catalysts for Ullmann coupling reaction. <math display="inline">^a$



^a **Reaction conditions:** 1.0 mmol chlorobenzene, 0.50 mmol TBAB, 1.5 mmol CH₃COONa, 2.5 mmol KOH, 2.0 mL solvent (Vwater:VMeOH=1/1), 0.50 mol% Pd catalyst, 100°C (microwave heating); ^b heating by oil bath; ^c150°C.



Figure 3. (a) Reaction profiles with reaction time of Pd/rGO-60-catalyzed Ullmann reaction under microwave heating or oil bath heating, (b) Reaction profiles with reaction time of Ullmann reaction using Pd/rGO-60, Pd/SiO₂ and Pd(OAc)₂ catalyst under microwave heating, the solid point is the conversion rate and the hollow point is the yield.

initial investigation, homocoupling In our of chlorobenzene (Ullmann-type reaction) was chosen as a model reaction to explore the catalytic performances of our Pd/rGO samples in aqueous solvent under microwave heating. As shown in Table 1, all the Pd/rGO samples can promote chlorobenzene to biphenyl with a 0.50 mol% catalyst dosage (Entry 3-5). The control experiments by without catalyst or using rGO as the catalyst gave the negligible yields, confirming the palladium catalytic nature of the reaction (Table 1, Entry 1-2). Under the same conditions, both Pd/rGO-30 and Pd/rGO-110 exhibited the worse catalytic performances with the yields of 36.8% and 33.3%, respectively (Table 1, Entry 3, 5). Interestingly, Pd/rGO-60 displayed the good catalytic reactivity and the selectivity, delivering the highest yield of 69.5% (Table 1, Entry 4). The poor catalytic efficiency of Pd/rGO-30 was probably attributed to the low loading of Pd NPs, which caused the insufficient contact between the active site and the reactant (Table S1). Also, the inferior catalytic performance of Pd/rGO-110 was maybe ascribed to the large particle size of Pd NPs (Figure 2c), which resulted in the decreased accessibility of the active sites. Next, to explore the best utility of our Pd/rGO-60 catalyst, we investigated the effect of various parameters including temperature and type of base on the Pd/rGO-60 catalyzed Ullmann reactions (Table S2). Obviously, low reaction temperature offered the lower reaction conversion

and selectivity (Table S2, Entry 1-3). The optimal reaction temperature was 100°C. Meanwhile, $\square We^{10} f \partial \tilde{u} W \partial^{0} f h \partial \tilde{u} W^{0}$ that mixture of CH₃COONa and KOH was the most effective base among those tested (Table S2, Entry 4-9). After careful investigation, Pd/rGO-60 allowed a high conversion (97.2%) and selectivity (93.5%) by using CH₃COONa and KOH as the

Entry	Catalyst	Time (min)	Conversion (%)	Yield (%)
1	Blank	60	Trace	Trace
2	GO	60	Trace	Trace
3	Pd/rGO-30	60	41.4	36.8
4	Pd/rGO-60	60	72.3	69.5
5	Pd/rGO-110	60	35.9	33.3
6	Pd/rGO-60	120	97.2	93.5
7 ^b	Pd/rGO-60	120	10.2	5.4
8 ^c	Pd/rGO-60	120	53.4	49.6
9	Pd(OAc) ₂	120	52.4	49.2
10	Pd/SiO ₂	120	32.6	27.5

base, water/ethanol solvent and TBAB as the dispersant under microwave radiation for 2.0 h (Table 1, Entry 6). Noted that Pd/rGO-60 showed the negligible activity at 100°C for 2.0 h by using oil bath heating (Table 1, Entry 7). Even at 150°C for 2.0 h, it only gave the conversion of 53.4% and the yield of 49.6% (Table 1, Entry 8). Furthermore, we found that homogeneous catalyst Pd(OAc)₂ also delivered the lower efficiency with the yield of 49.2% for 2.0 h under microwave heating (Table 1, Entry 9). By extending the reaction time to 20 h under oil bath heating, it still exhibited the inferior catalytic performance (Table S2, Entry 10). The profiles of catalytic performances with the reaction time (Figure 3a) revealed that the conversion of Pd/rGO-60 can reach 93.5% after 2.0 h under microwave heating. In comparison, its catalytic activity by using oil bath heating was only 5.4%. After 20 h, the reaction conversion in the oil bath reached almost 100%. But the yield was only 85.6%, which revealed microwave heating also enhanced the reaction selectivity. Next, in order to compare the effect of the microwave absorbing ability of different carriers on the catalytic activity, we used the similar preparation method to obtain Pd/SiO₂ catalyst as the control sample. TEM revealed

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that the particle size of Pd NPs in the Pd/SiO_2 catalyst was similar as that of Pd/rGO-60 (Figure S1). However, the catalytic activity of Pd/SiO₂ catalyst was much lower than Pd/rGO-60 under the same reaction conditions, which demonstrated the unique effect of rGO support.

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In order to study the correlations between the microwave absorption property of the supports and their catalyst performances, the relative complex permittivity and complex permeability of different samples were measured using a vector network analyser and the calculation method of microwave absorb ability for different samples was shown in Experimental Section. For the real part (energy storage capacity, ε') and imaginary part (energy consumption capacity, ϵ'') of the complex dielectric constant, the complex dielectric constant of Pd/rGO-60 was higher than that of Pd/SiO₂ catalyst (Figure 4a), which was due to the highest electrical conductivity of rGO. The complex permeability μ' and μ'' are consistent for all samples (Figure S2a). The dielectric loss tangent function and magnetic loss function were used to evaluate the dielectric and magnetic losses of Pd/rGO-60 and Pd/SiO₂. As show in Figure 4b, Pd/rGO-60 had the largest dielectric loss ability, and all the samples had no difference in magnetic loss (Figure S2b). The above phenomenon obviously indicated that Pd/rGO-60 had the best microwave absorption ability. Meanwhile, the attenuation constant was an important parameter for microwave attenuation. Calculation results showed that Pd/rGO-60 had the largest attenuation constant, indicating that electromagnetic waves were more likely to

dissipate inside Pd/rGO-60 (Figure 4c). Pd/rGO₁₆O₂₅₀₆CGERP reflection loss graph (Figure 4d) further shows PRACORS has efficient microwave absorption performance. The minimum reflection loss (RL_{min}) of Pd/rGO-60 is -51.8 dB (7.4 GHz) and the thickness of the absorber is 3.6 mm. On basis of these results, we can safely conclude that Pd/rGO can effectively absorb microwave radiation. Specially, the microwaves are



Figure 4. Frequency dependence of real part and imaginary part of permittivity (a), dielectric loss tangent (b), attenuation constant (c) of GO, Pd/rGO-60 and Pd/SiO₂ samples, and reflection loss characteristic of Pd/rGO-60 with varying the absorber thickness (d).

absorbed by rGO support and next rGO converted the energy to the surface of Pd NPs, leading to the increased local high temperature. This heating effect resulted in the enhanced catalytic reactivity of the Pd/rGO-60 catalyst.

Table 2. Reaction scope of Pd/rGO-60 catalyzed Ullmann coupling reactions. ^a							
	R CI -	Pd/rGO-60 H ₂ O/MeOH	R	R			
Entry	Reactant	Conversion (%)	Yield (%)	TON ^c	TOF ^c		
1		96.6	93.0	186.0	93.0		
2	но-СІ	99.0	95.0	190.0	95.0		
3	MeO	92.1	88.5	177.0	88.5		
4	↓−ci	46.3	41.2	82.4	41.2		
5 ^b	CI-CI	92.4	88.3	176.6	44.2		

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^a Reaction conditions: 1.0 mmol aryl chlorides, 0.50 mmol TBAB, 1.5 mmol CH₃COONa, 2.5 mmol KOH, 2.0 mL solvent (Vwater:VMeOH=1/1), 0.50 mol% Pd catalyst, View Article Onlige 100°C (microwave heating), 2.0 h; ^b DMF as solvent, 4.0 h. ^c Turnover number: moles of product per mole of Pd. Turnover frequency: moles of product per moles of pe

To verify the substrate universality of Pd/rGO-60, different aryl chlorides with various substituted groups were tested. As shown in Table 2, under the same conditions, both electronwithdrawing and electron-donating groups in the para- and meta-position didn't harm to the outcome of Pd/rGO-60. For the replacement of chlorobenzene by the ortho position with large steric hindrance, the good yield was also obtained by extending the reaction time to 4.0 h and changing ethanol to DMF. These results confirmed that Pd/rGO-60 had the good substrate tolerance in Ullmann coupling reaction.

Table 3. Catalytic performances of Pd/rGO-60 catalyzed Suzuki cross-coupling reactions. ^a						
		OH B-OH -	Pd/rGO-60	R		
Entry	Reactant	Conversion (%)	Yield (%)	TON ^c	TOF ^c	
1	⟨	>99	94.8	189.6	63.2	
2	an a	94.5	91.2	182.4	60.8	
3	a 2018 (1997) and you with the second second	>99	94.2	188.4	62.8	
4		74.2	68.8	137.6	45.9	
5 ^b		95.2	90.4	180.4	36.1	
6	galar an an tagan an a	64.2	59.6	119.2	39.8	
7 ^b	Detain an an the grant and a set of a second sec	80.4	78.5	157.0	31.4	
8		75.2	70.2	140.4	46.8	
9 ^b		92.4	88.3	176.6	35.3	

^a **Reaction conditions:** aryl chloride (1.0 mmol), phenylboronic acid (1.2 mmol), TBAB (0.50 mmol), K₃PO₄ (3.0 mmol), 0.50 mol% Pd/rGO-60, 100°C (microwave heating), 2.0 mL (V_{water}-V_{MeOH}=1/1), 3.0 h; ^b 5.0 h. ^c Turnover number: moles of product per mole of Pd. Turnover frequency: moles of product per mole of Pd per hour.

Furthermore, we tested the reactivity of Pd/rGO-60 in the Suzuki-Miyaura cross-coupling reaction, which is very popular in the synthesis of pharmaceutical intermediates and fine chemicals. By using chlorobenzene with phenylboronic acid as the reactant, the excellent yield (94.8%) of biphenyl was achieved. For substituted chlorobenzene, an electron-rich group such as a methyl group, a hydroxyl group or a cyano group in the para-position, the yields still can reach to at least 90% (Table 3, Entry 1-5). Even with the use of methoxy and 2-chlorotoluene with a large steric hindrance, the good yield of

78.5% and 88.3% was obtained by extending reaction time to 5.0 h, respectively (Table 3, Entry 6-9).

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On basis of these excellent results, we tried to use Pd/rGO-60 to catalyse the practical useful reactants. As shown in Figure 5, we selected 4'-methyl-2-biphenylcarbonitrile and 2-nitro-3',4',5'-trifluoro-1,1'-biphenyl as the target product, which are the important intermediates of the drugs of Sartans and Fluxapyroxad, respectively. After optimizing the reaction conditions (Table S3), Pd/rGO-60 can deliver 93.8% yield of 4'methyl-2-biphenylcarbonitrile under microwave heating for 3.0 h. Compared with the catalytic activity of the previously reported homogeneous catalysts including Pd₂(dba)₃⁴⁹, oximederived palladacycles⁵⁰, Pd(OAc)₂⁵¹, Pd-KITPHOS-10⁵² and heterogeneous catalysts such as PEG-PdL⁵³, Pd@NPad2⁵⁴, Pd@PAN-Ad⁵⁵, the reaction conditions is quite mild and the reaction time is shortest (Scheme 2). For more complicated 2nitro-3', 4', 5'-trifluoro-1, 1'-biphenyl, the optimal reactivity was also obtained by carefully investigating the reaction conditions, the final yield can reach to 89.7% (Table S4). To the best of our knowledge, this is the first report of a heterogeneous catalyzed system for this important substance. Interestingly, even in the gram-scale synthesis, the yield of 85.1% can be obtained. These results fully demonstrated the potential application of Pd/rGO-60 for the practical application in the preparation of valuable molecules with complex structures. Interestingly, even in the gram-scale synthesis, the yield of 85.1% can be obtained. These results fully demonstrated the potential application of Pd/rGO-60 for the practical application in the fabrication of valuable molecules with complex structures.



Figure 5. (a) Pd/rGO-60 catalyzed synthesis of the intermediate of Sartans by Suzuki reaction of 2-bromobenzonitrile and 4-tolueneboronic acid; (b) Pd/rGO-60 catalyzed synthesis of the intermediate of Fluxapyroxad by Suzuki reaction of 2-nitrochlorobenzene and 3,4,5-trifluorophenylboronic acid. Reaction conditions were in Table S3 and Table S4.



To verify the reusability of Pd/rGO-60 catalyst othe recyclability test was carried out in Ullmannin teaction by Using chlorobenzene as the reactant. As shown in Figure 6, it displayed almost constant activity and selectivity even after being used repetitively for 6 times. The hot filtration test was performed to confirm the heterogeneity of the catalyst. After reacting for 1.0 h, Pd/rGO-60 was filtered and the reaction was allowed to proceed under the same reaction conditions. But, we found that no coupling product of biphenyl was obtained even after allowing the reaction with for the longer reaction time (6.0 h). Moreover, the liquid phase of the reaction mixture was collected after each reaction to test if palladium was leaching from the solid catalyst during reaction. ICP-AES analysis confirmed that an extremely low amount of Pd (less than 1.0 ppm) was found in the filtrate. These results indicated that the current reaction was heterogeneous in nature, which was maybe attributed to the strong bonding between rGO and Pd NPs. Furthermore, XPS spectrum of the reused Pd/rGO-60 catalyst (Figure S3) revealed that the zero-valence state of Pd NPs didn't changed after six cycles. TEM image (Figure S4) of the reused Pd/rGO-60 showed no significant change in the two-dimensional morphology and only a small amount of palladium nanoparticles tended to agglomerate, which may explain the extremely slight decrease in reactivity of the



Scheme 2. Catalytic performance comparison of different catalytic system for Suzuki reaction of 2-bromobenzonitrile and 4-tolueneboronic acid.

recycled Pd/rGO-60 catalyst after six repetitions.

Conclusions

In summary, palladium nanoparticles were introduced on the sheets of reduced graphene oxide by a facile *in-situ* reduction

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approach. The obtained Pd/rGO composite possessed the typical two-dimensional plane structure and uniformly dispersed Pd nanoparticles. With the assistance of microwave heating, it can efficiently activate various aryl chlorides to the desired biphenyl products with very high conversion and selectivity as well as durability for aqueous Ullmann and Suzuki cross-coupling reactions. Noted that it also realized the gramscale synthesis of key intermediates of important Sartans and Fluxapyroxad medicines, showing a good potential in the future industrial application. Further exploration of the development of magnetite/rGO composite supported Pd nanoparticles with easy separation and enhanced recyclability^{56, 57} is being pursued in our laboratory.

Conflicts of interest

There are no conflicts to declare.

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Microwave-assisted reduced graphene oxide supported palladium nanoparticles can efficiently promote aqueous Ullmann and Suzuki coupling reactions of aryl chlorides