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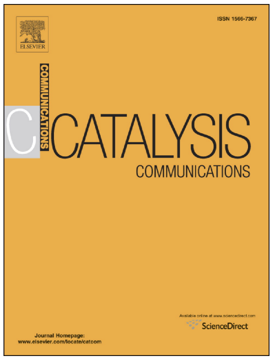

Imidazole-aryl coupling reaction via C-H bond activation catalyzed by palladium supported on modified magnetic reduced graphene oxide in alkaline deep eutectic solvent

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Imidazole-aryl coupling reaction via C−H bond activation catalyzed by palladium supported on modified magnetic reduced graphene oxide in alkaline deep eutectic solvent

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By employing reusable heterogeneous catalyst, modified magnetic reduced graphene oxide-supported palladium catalyst (MRGO@ DAP- AO-Pd^{II})), the regioselective C-5 arylation of imidazoles via C−H bond activation pathway for the preparation of C5-arylated imidazoles has been successfully achieved in alkaline deep eutectic solvent made of potassium carbonate and glycerol under aerobic conditions. Compared to previous procedures, significant improvements of this new protocol demonstrated by the high catalytic efficiency, easy recovery of catalyst, broad substrate scope and sustainable reaction condition using green solvent.

KEYWORDS: C-H arylation, imidazole, heterogeneous catalyst, magnetic reduced graphene oxide, palladium, deep eutectic solvent.

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1. Introduction

The palladium-catalyzed direct C-H arylation reactions of heteroarenes with aryl halides have become as the extremely powerful method for the synthesis of biaryl or aryl-heteroaryl products. Traditional cross coupling reactions require the preliminary synthesis of organometallic reagent that is time consuming and provide organometallic salt (MX) as the by-product[1].In the case of imidazole derivatives, 5-arylimidazoles are reported to be physiologically and pharmacologically active compounds[2]. Ohta and co-workers for the first time reported regioselectively C5-arylated imidazoles in the presence of $Pd(PPh_3)_4$, KOAc and DMA as catalyst, base and solvent, respectively[3]. Afterwards, Miura et al. described the reaction of arylhalids with azole compounds in the presence of $Pd(OAc)_2$ and PPh_3 in DMF using alkali metal carbonates(Cs_2CO_3 and K_2CO_3) as bases[4]. Subsequently, other groups have reported the direct C5-arylation of imidazoles using various palladium/ligand catalytic systems [5-8]. In 2009, a ligand-free procedure for the regioselective C5-arylation of imidazole derivatives with aryl bromides at low catalyst loading conditions was described by Doucet and co-worker[9]. Recently, examples of palladium NHC complex catalyzed C5-arylation of imidazoles via C–H bond activation have also been reported [10-15].

The major issue of Pd-catalyzed direct arylation in terms of green chemistry is related to the use of toxic solvents such as Dimethylformamide (DMF) and Dimethylacetamide (DMA)[16]. In recent years, several solvents such as water, polyethylene glycol, dialkyl carbonates, Biomass-derived solvents have replaced with toxic solvents for palladium-catalyzed aromatic C−H bond arylation[17-19]. The deep eutectic solvents (DESs) as an emergent class of solvents are attaining increasing interest due to their fascinating properties such as low cost of components, low toxicity, bio-degradability, simple and straightforward preparation and negligible vapor

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pressure[20]. Although DESs have been used as environmentally friendly solvents as well as catalysts in many chemical processes including Pd-catalyzed cross-coupling reactions[21, 22], application of DES in direct arylation reaction is in its childhood. Only, very recently, Farinola et al, in 2017, reported the first example of palladium- catalyzed C−H bond arylation reaction in DES[23].

In recent years, the use of heterogeneous catalysts in the field of C-H activation, especially C-H arylation reactions has received considerable attention[24]. The pioneering achievement was reported by Nakamura et al. in 1982 where commercially available Pd/C was introduced as a heterogeneous catalyst for arylation of isoxazole[25]. Also, Fairlamb et al. revealed that well-defined Pd nanoparticles (PdNPs) are rapidly formed and acted as an active catalytic species under working $Pd(OAc)_2$ catalyst in C-H bond functionalization reactions of heteroarenes[26].Following the early reports, many chemists developed more efficient methodologies via heterogeneous catalyst for Direct Csp^2_H and Csp^3_H arylation reactions[27, 28].Recently, a few recoverable palladium catalyst also have been reported for C-H arylation reaction of imidazoles[29, 30].

2D graphene, consists of Sp^2 hybridized carbon atom, possesses exceptional properties such as high chemical and mechanical stability, extremely large surface area and excellent dispersibility[31]. Several graphene-based catalysts already reported for C-H activation reaction by a few researchers[32]. Despite their tremendous catalytic performance, for the recycling of catalysts, traditional separation method such as filtration or centrifugation is required that is time- consuming. To address these issues, the introduction of Fe_3O_4 to graphene have proven to be an effective approach not only because this system provide high catalytic activity, but also improve separation capability using external magnet[33].

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Based on this introduction, herein, we developed an efficient protocol for C−H arylation reaction of imidazole with aryl bromide by introducing 2, 6-diaminopyridine (DAP) -Amidoxime (AO) palladium complex immobilized on the magnetic reduced graphene oxide (MRGO@DAP-AO-Pd^{ll}) as a highly efficient and reusable heterogeneous catalyst in K_2CO_3/Glycerol media.

2. Experimental

2.1. Typical Procedure for Direct C-5 Arylation of imidazole derivatives

1-methyl-1H-imidazole (2.0 mmol) or 1, 2- dimethyl-1H-imidazole (2.0 mmol), aryl halide (1.0 mmol), MRGO@ DAP-Pd^{ll} catalyst (25 mg, containing Pd 0.3 mol %) were weighed and placed in a reaction tube. DES (1ml) was added. The resulting heterogeneous reaction mixture was stirred at 130°C under aerobic conditions. The reaction was monitored by TLC. After the completion of reaction (17h), the mixture was cooled to room temperature and after water addition, the catalyst separated by magnetic. This mixture was extracted with EtOAc (3×30 mL), dried over Na_2SO_4 and evaporated under reduced pressure. Purification of crude product was carried out by column chromatography (hexane: ethyl acetate= 9:1)

3. Results and Discussion

3.1. Catalyst preparation

The detailed route of synthesis of MRGO@ DAP-AO-Pd^{ll} is depicted in Scheme 1. First, Fe_3O_4 nanoparticles were in situ synthesized on the surface of graphene oxide (GO) to form magnetic reduced graphene oxide (MRGO) by chemical co-precipitation method and adding hydrazine hydrate (80%)as reducing agent. MRGO was modified by reaction of MRGO with (3-chloropropyl) trimethoxysilane (CPTMS) followed by treatment with 2, 6 diaminopyridine (DAP) afforded MRGO@DAP. Further, MRGO@DAP-AO was synthesized by two steps.

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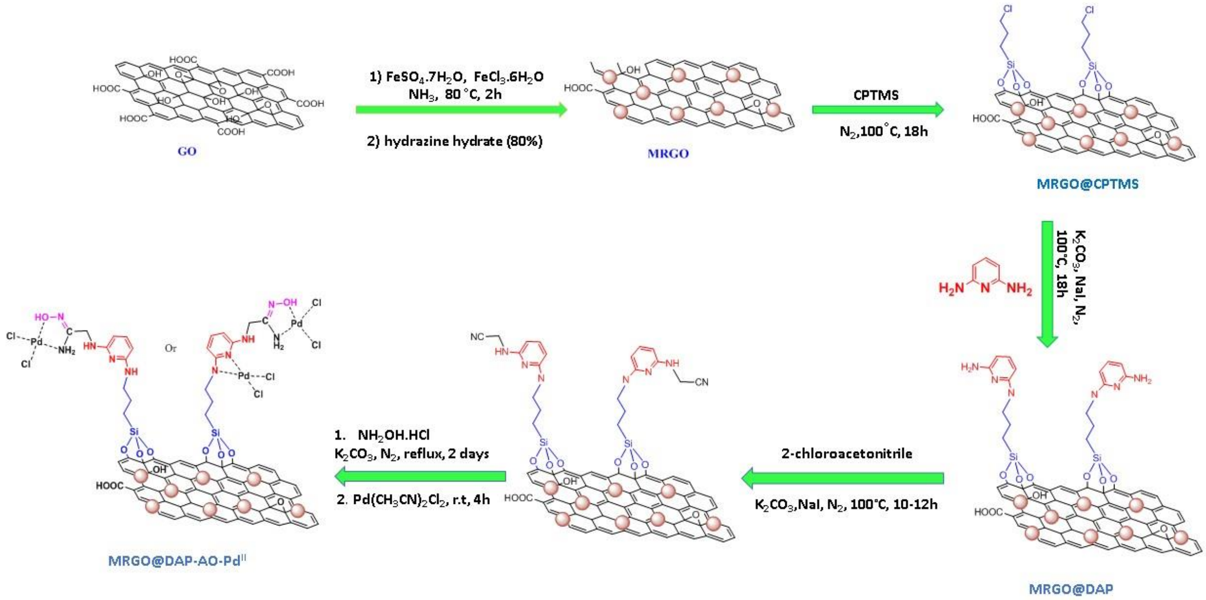
MRGO @DAP was functionalized using 2-chloroacetonitrile to get the cyanomethyl group. Then, conversion of nitrile group into amidoxime afforded MRGO@DAP-AO. Finally, the treatment of MRGO@DAP-AO with Pd $(CH_3CN)_2Cl_2$ gave a heterogeneous Pd-catalyst (MRGO@ DAP-AO-Pd^{II}).



Scheme 1: A schematic illustration of the process for the preparation of the MRGO@ DAP-AO-Pd^{II}

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3.2. Catalyst characterization

The catalyst was fully characterized using various spectroscopic techniques. XRD patterns of catalyst are shown in Figure 1. In the three curves, the diffraction characteristic peaks at 2θ values of 10.85° and 30.69° can be attributed to the (001) and (002) planes of reduced GO, suggesting that GO has been reduced over the preparation process of MRGO. The weak diffraction peaks located at 2θ values of 35.33°, 41.53°, 50.67°, 63.67°, 67.85°, and 74.61° were assigned to the (220), (311), (400), (422), (511) and (440) planes of Fe_3O_4 lattice, respectively, which matched well with the standards of Fe_3O_4 (JCPDS 65–3107). Furthermore, no characteristic peaks for palladium chloride were observed in the XRD pattern of MRGO@DAP-AO-Pd^{II}, which may be due to the presence of well-dispersed small particles of the palladium species in the structure of the catalyst.

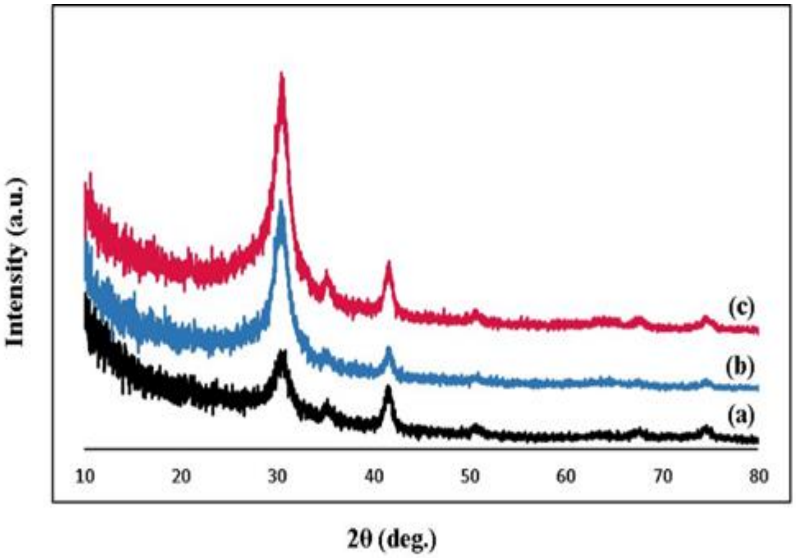

Figure 1: The X-ray diffraction patterns of (a) MRGO, (b) MRGO@DAP-AO and (c) MRGO@DAP-AO-Pd^{II}

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The Raman spectra displays four main vibrational modes (Figure 2). The characteristic peaks at 1350 and 1590 cm^{-1} can be assigned as D and G bands respectively and two broad peaks positioned at 2695 and 2933 cm^{-1} are related to the 2D and D+G bands. The intensity ratio of D and G band, I_D /I_G, highly influences the structural transformation and expressing the sp^3/sp^2 carbon ratio in carbonaceous materials. The I_D/I_G ratio of the MRGO nanocomposites (1.09) showed remarkable increase over that of GO (0.97). This is due to the removal of oxygen functional groups and the decrease of the sp^2 in-plane domain induced by the introduction of defects and disorder of the sp^2 domain upon the reduction of the exfoliated GO. Additionally, the Raman spectrum of MRGO composite displays signals at 200–700 cm^{-1}, which are related to the Fe_3O_4 NPs. After the functionalization of MRGO, the I_D/I_G of MRGO-DAP-AO increased from 1.09 to 1.14 that it can be related to the augmentation of the sp^3 hybridization carbons from the grafting DAP-AO on MRGO (figure 2-c). Finally, I_D/I_G of MRGO@DAP-AO-Pd^{II} decreases to 1.02, indicating the palladium ions filled in defective regions of the MRGO@DAP-AO surface (Figure 2-d).

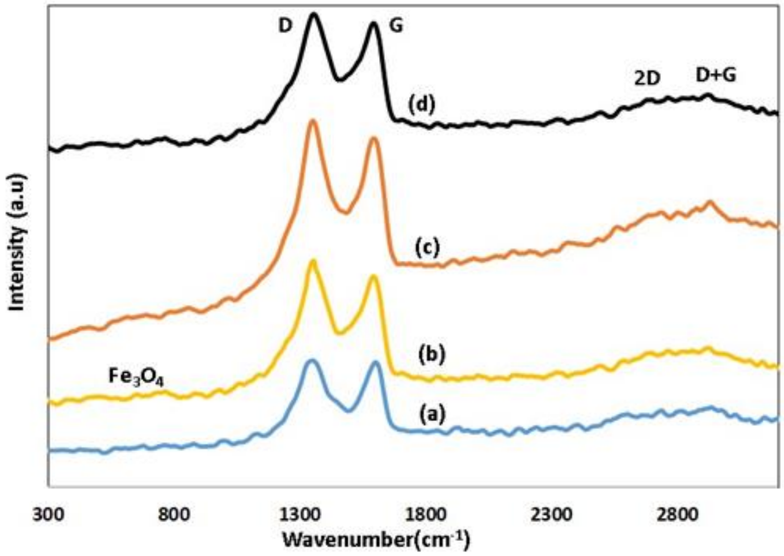

Figure 2: Raman spectra of (a) GO, (b) MRGO, (c)MRGO@DAP-AO and (d) MRGO@DAP-AO-Pd^{II} nanohybrids

The SEM images of the catalysts are shown in Figure S1 (a-d). The magnetite nanoparticles have appeared in bunches on the curled and thin wrinkled sheets of graphene, having a uniform distribution on the surface of RGO. The SEM images of MRGO@DAP-AO and MRGO@DAP-AO-Pd^{II} show that they remain as the nanosheet-like structures. Energy-dispersive X-ray (EDX) analysis was performed to confirm the presence of the expected elements in the structure of MRGO@DAP-AO-Pd^{II}, namely carbon, iron, silicon, oxygen, nitrogen and palladium with wt% of 31.13, 20.53, 0.1, 40.60, 6.58 and 1.06, respectively (Figure S1 e). Additionally, the density and distribution of the numbered elements were evaluated by quantitative energy dispersive X-ray spectroscopy (EDS) mapping(Figure S2).

The TEM images clearly display that Fe_3O_4 nanoparticles as spherical particles with an average size of 10–20 nm are uniformly dispersed on the wrinkled surfaces of RGO and no aggregated or free particles are detected (Figure 3). Probably, the homogeneous distribution of the palladium complex on the surface of modified MRGO is owing to the existence of the electrostatic interaction between palladium ions and functional groups of the modified MRGO.

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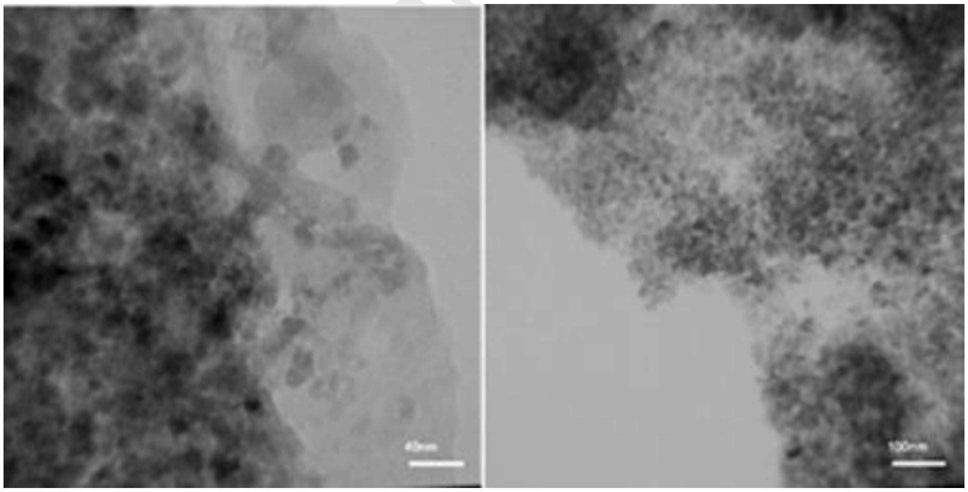

Figure 3: TEM images of MRGO@DAP-AO-Pd^{II}

Thermogravimetric analysis (TGA) were shown in Figure S3. In the three curves, the weight loss below 200 °C is due to the loss of physically adsorbed water. The main weight loss from 200 °C to 630 °C is attributed to the thermal decomposition of the organic moieties including oxygen-containing functional groups, carbon, and the complex. According to the TGA, the weight percentage of palladium is estimated to be about 6.29 wt%. Moreover, inductively coupled plasma (ICP) analysis was used to determine the exact loading of Pd in the structure of the catalyst and it was evaluated to be 0.14 mmol g^{-1}.

The magnetic measurement was carried out at room temperature. As shown in Figure S4, the saturation magnetization (Ms) value for MRGO@DAP-AO-Pd^{ll} is 18.26 emu•g^{-1}, demonstrating the catalyst is paramagnetic.

3.3. Catalyst activity in C-H arylation reaction

Direct C-H arylation reaction of 1,2 -dimethyl-1H-imidazole with 4-bromobenzaldehyde was chosen as the model reaction (Table S1). For the optimization studies, initially, we chose DMA as the solvent, KOAc as the base and MRGO@DAP-AO-Pd^{ll} (containing 0.3 mol % Pd) as the catalyst at 130℃ for 17h. The desired product of regioselective arylation at the C-5 position (3a) was isolated in 78% yields (entry 1). By Switching of the base to K_2CO_3, yield of the product was increased (86 % yield) (entry 2). In the case of the optimization of solvent, since the DMA was not desirable solvent in terms of "green chemistry", we decided to survey the effect of greener solvents for this coupling using different DESs. Several types of choline based deep eutectic solvents such as choline chloride/urea (1:2), choline chloride/ethylene glycol (1:2), choline chloride/glycerol (1:2) were prepared and their efficiency was tested (entry 3-5) resulting in 51%, 56% and 59% yields of the product, respectively (entry4 and 5). We also focus on the different ratios molar of potassium carbonate and potassium acetate to glycerol as basic DESs[34]. Three different DES ratios by varying glycerol molar ratio at a fixed amount of salt (1:5, 1:7, 1:10) were prepared and their effect on yield of the model reaction was explored (entry

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6-11). A superior yield obtained when K_2CO_3/ glycerol(1:5) was used (entry 9). When the palladium loading was reduced to 0.15 and 0.05 mol %, great loss of efficiency (45 % and 20 % yields, respectively) was encountered (entry 12 and 13). Loading of 0.3 or 0.5mol% of catalyst resulted in good yields. poor selectivity was obtained when the amount of catalyst loading increased up to 1mol% due to the increasing of biphenyl as a by-product (25% yield) (entry 14 and 15). Thus, among the different amount of catalyst screened, a loading of 0.3 mol % was the best choice. Moreover, screening of reaction temperature was performed. Among further lowering of temperature to 110ºC and 90 °C, poor results were obtained with 52 % and 45 % yields, respectively (entry 16 and 17)., in the absence of catalyst, no product was generated, even after 24 h (entry 18). Finally, the activity of the magnetite reduced graphen oxide (solid support) was evaluated as the unique catalyst, only trace amount of product was obtained that resulting of inactivity of the support (entry 19).

With the optimized reaction conditions in hand, we next investigated the scope of established protocol by applying an array of imidazoles and (hetero) aryl halides (Table 1). In all the reactions, the C5-monoarylated imidazole was formed regioselectively, as C5 is more reactive than C4 position in imidazoles[35]. Higher yields of the corresponding products were obtained in the reaction of 1, 2-dimethylimidazole with different para-substituted electron deficient aryl bromides such as 4-bromobenzaldehyde, methyl 4-bromobenzoate, and 1-bromo-4-fluorobenzene (3a, 3b, 3c). Only 20% of arylation product was obtained when aryl chloride such as 4-chlorobenzaldehyde was choose as coupling candidate. Since aryl bromides bearing electron donating groups such as 4-bromoanisole and 1-bromo-4-methylbenzene stabilize Ar-X bond, only moderate yields of 64−75 % were obtained (3d, 3e). Sterically hindered 1-naphthyl bromide afforded the desired coupled product in compatible and satisfactory yield of 75 % (3g).

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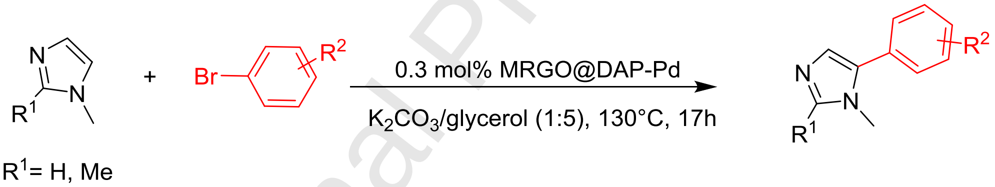
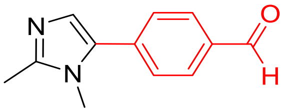
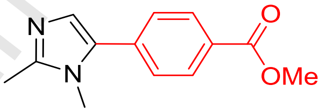
Markedly, good yield was obtained with 2-bromopyridine as a heteroaryl bromide (3j). As expected, the more hindered ortho-substituted aryl bromides such as 2-bromoanisole and 2-bromoaniline gave low yields of 45 and 48%, respectively (3h, 3i). Morevere, we reacted another substituted imidazole, 1-methyl-1H-imidazole as the coupling partners, with various aryl (hetero) halides in the same conditions. Since both the positions 2 and 5 of this challenging substrates can be arylated, using our procedure, the 5-arylated imidazoles were obtained regioselectivity in 57–89 % yields and only trace amounts of C2-position was detected (4a-4f). Finally, we examined the reaction using free (NH)-1H-imidazole with 4-bromoanisole. In the optimized reaction conditions, the corresponding *N*-aryl product was obtained as the major product.

Table 1 : reaction scope[a]

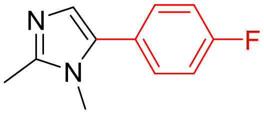




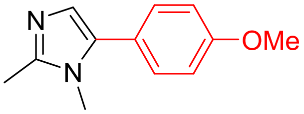
3a: 95 % (20%) [b]



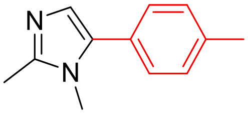
3b: 80%



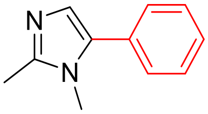
3c: 70%



3d: 64%



3e: 75%



3f: 65%

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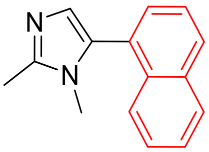
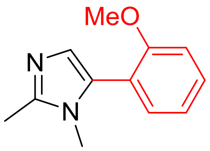
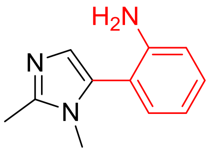


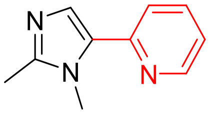
3g: 75%



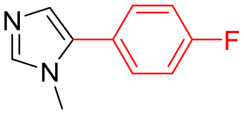
3h: 45%



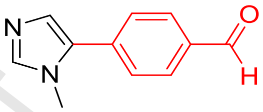
3i: 48%



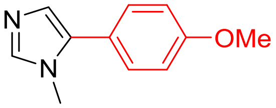
3j: 68%



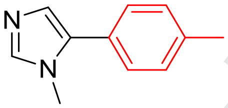
4a: 85%



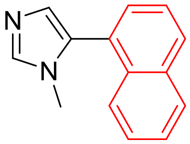
4b: 89%



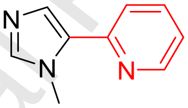
4c: 57%



4d: 68%



4e: 79%



4f: 58%

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[a] Conditions: imidazoles (2 mmol), aryl bromide (1.0 mmol), catalyst (25 mg, containing 0.3 mol %Pd), K_2CO_3/glycerol (1mL), 130℃, 17h in aerobic atmosphere. [b] when 4-chlorobenzaldehyde was used as the substrate (isolated yield in parenthes)

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3.4. Recyclability test

The recyclability of our heterogeneous catalyst was tested in the C-H bond arylation of 4-bromobenzaldehyde with 1, 2-dimethylimidazole under the optimized reaction conditions. After the first run of the arylation, the reaction mixture diluted with H_2O, the catalyst was removed by external magnetic field, washed with water and ethanol respectively, dried at ambient temperature and reused for the next run. We observed the recovered MRGO@DAP-AO-Pd^{II} was still adequately active catalyst after 7 runs and moderate deactivation of the catalyst has been noticed with the yield of 85% (figure 4a). However, we observed a drastic decrease of yield in the 8 run (only 20% yield). ICP-MS analysis indicated that about 9.4 % of palladium on catalyst leached into the reaction solution after the seven cycles. By studying TEM images of the recovered catalyst, no significant morphology change on MRGO@ DAP-AO-Pd^{II} was observed. Therefore, the loss of catalytic activity could be attributed to leaching of palladium after seven runs (Figure 4 b).

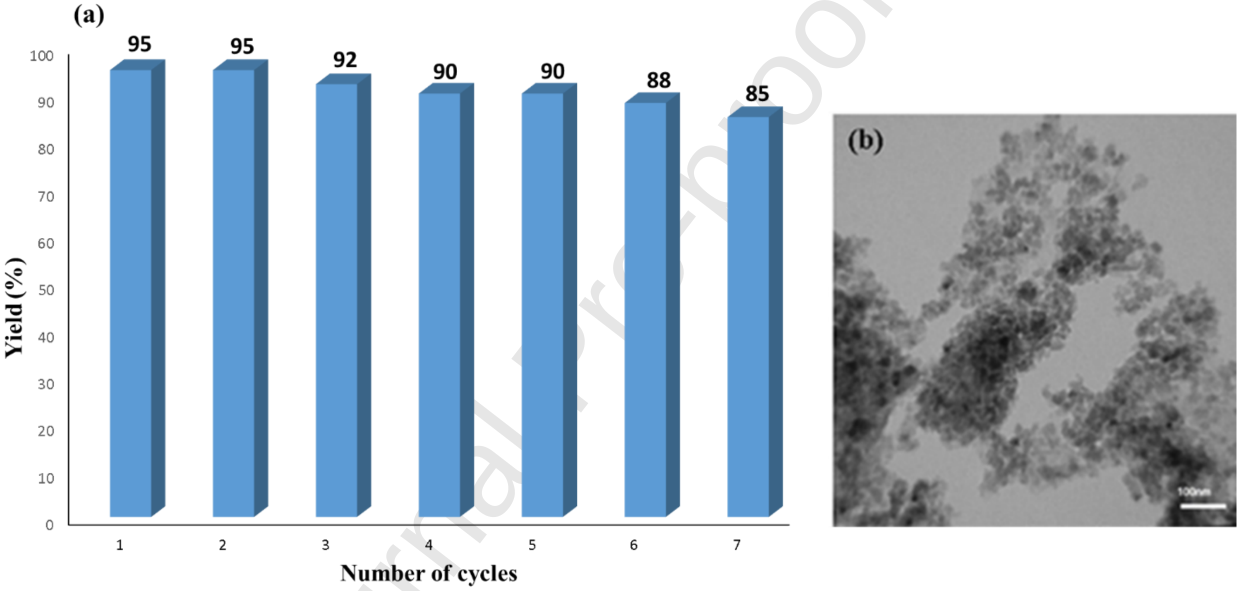

Figure 4: (a) The recyclability of MRGO@ DAP-AO-Pd^{II} catalyst in the C-H bond arylation between 1, 2-dimethylimidazole and 4-bromobenzaldehyde

(b) A representative TEM image of MRGO@DAP-AO-Pd^{II} catalyst after 7 runs.

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Catalytic performance of the present catalyst was compared with previously reported catalysts in C-H arylation reaction between 1, 2 dimethylimidazole and 4-bromobenzaldehyde (table S2). As seen in Table S2, Although all of the listed catalysts can produce the desired C-5-arylated imidazole in good to excellent yield, it is clearly seen that newly synthesized MRGO@DAP-AO-Pd^{II} as a heterogeneous catalyst is noticeably comparable with the homogeneous Palladium catalytic system in term of high yield of the desired product, facile magnetic recoverability, low catalyst loading and using eco-friendly solvent.

4. Conclusion

In conclusion, we have successfully applied environmentally safe conditions for direct regioselective C−H arylation reactions between imidazoles and aryl bromides in a deep eutectic solvent, k$_2$CO$_3$/glycerol (1:5) mixture, via magnetically separable and recyclable MRGO@DAP-AO-Pd^{ll} as a heterogeneous catalyst. Our finding suggest that replacement of reprotoxic solvent (DMA) by DESs affords a readily accessible, inexpensive and green reaction medium. MRGO@DAP-AO-Pd^{ll} showed good catalytic efficiency for arylation reaction of imidazoles with several electron-deficient and electron -rich aryl bromides under these conditions. Catalyst recycled at least 7 times without significant decreasing yield of reaction. Hot filtration and Hg (0) poisoning test demonstrate that catalyst has heterogeneous character.

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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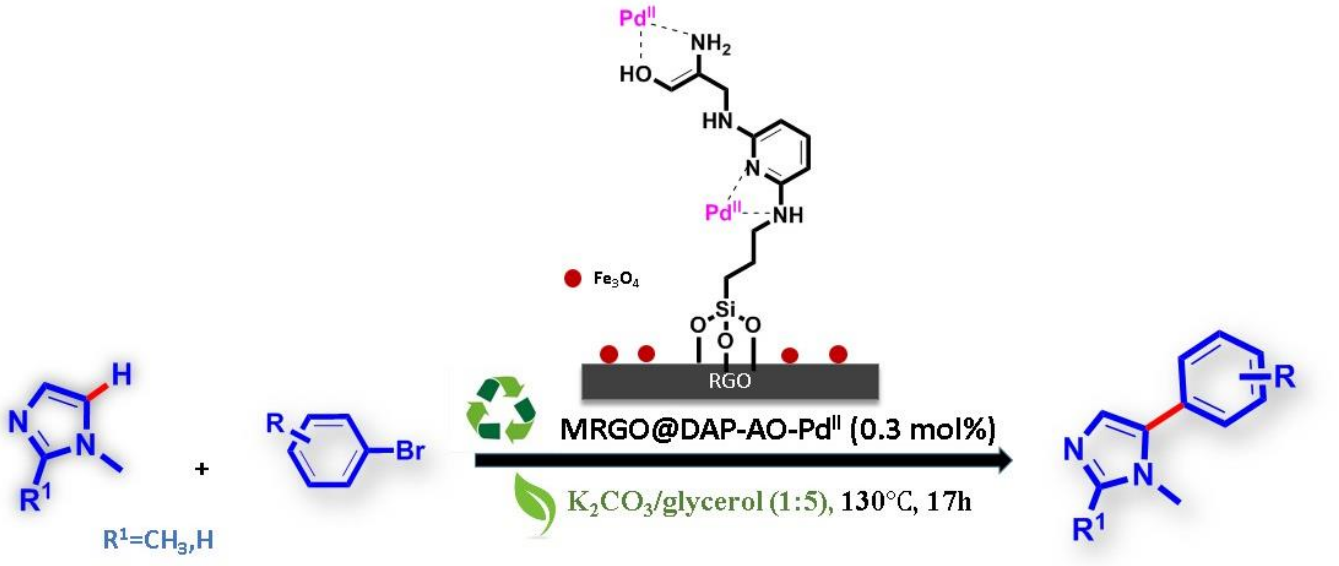
Graphical Abstract



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Highlights

- Palladium supported on modified magnetic reduced graphene oxide (MRGO-DAP-AO-Pd^{II}) was well synthesized.
- The catalyst was exhibited high activity in C-H arylation reaction of imidazoles with arylbromides.
- Alkaline deep eutectic solvent (K_2CO_3/glycerol) was applied as green solvent.
- The catalyst was simply recycled and reused successfully at least for seven runs.

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