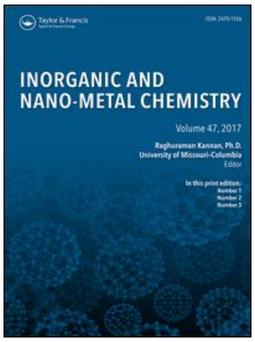

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One-step synthesis of magnetically recyclable palladium loaded magnesium ferrite nanoparticles: application in synthesis of anticancer drug PCI-32765

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ABSTRACT

Novel Palladium nanoparticles supported nano Magnesium ferrite catalyst (Pd/$MgFe_2O_4$) was synthesized by one-step ultrasound assisted coprecipitation. In-situ formed by-products assisted salt cage calcination approach was employed to control the particle size by minimizing the risk of nanoparticle aggregation during calcination. Palladium nanoparticles were grafted on the surface of nanocrystalline $MgFe_2O_4$ without using any reducing agents, capping agents and surface modifiers. The catalyst preparation method was having minimum process operations and can be used for synthesis of various potential nanocatalytic systems. The catalyst was extensively characterized by using various techniques SEM-EDS, TEM, FT-IR, XPS, XRD, VSM, BET, and ICP-AES. Pd/$MgFe_2O_4$ was magnetically separable and shown its potential utility for ligand less Suzuki-Miyaura coupling reaction using green solvent system Water and Ethanol. The nanocatalyst shows consistent activity and excellent reusability in the synthesis of Biaryls with excellent yields. In addition, the prepared catalytic nanoparticles were successfully applied in the synthesis of 5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine an intermediate for preparing the marketed anticancer drug PCI-32765 under the name IMBRUVICA® (Ibrutinib-BTK inhibitor).

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One-step synthesis; coprecipitation; salt cage assisted calcination; Pd-Magnesium ferrite; magnetic nanoparticles; Suzuki-Miyaura coupling

Introduction

Nanocatalysts are semi-heterogeneous catalysts which consists of hybrid advantages of both heterogeneous as well as homogenous catalysts. This is due to their structural and morphological properties, along with enhanced recovery and recyclability.[1] In the presence of magnetic field applied externally the magnetic nanocatalytic systems provide easy separation of the catalyst based on their intrinsic magnetic properties.[2] The catalyst activity depends on various characteristics such as particle size distribution, surface area, morphology and active phase dispersion on catalyst support phase. The combined physiochemical properties and electronic properties of the active phase and support material greatly influence the functionality of the catalyst.[3]

Nano magnetic ferrites are act as very good catalysts and also serve as excellent catalytic supports.[4] Ferrites have shown tremendous catalytic applications such as transfer hydrogenation, biodiesel synthesis, dye degradation, Nitrophenol reduction, and β-lactams synthesis.[5] Ferrites supported nano catalysts were highly stable, recyclable and magnetically retrievable after completion of reactions. Saire-Saire et al.[6] reported Au/$CoFe_2O_4$ for catalytic reduction of 4-nitrophenol and dimethylphenylsilane oxidation, Dutta et al.[7] developed $CoFe_2O_4$@SiO_2-SH-CuI, applied in the synthesis of oxidative amidation.

Ferrites can be prepared by various techniques, such as conventional coprecipitation, pyrolysis, solution combustion, freege drying.[8] Fino et al.[9] synthesized AB_2O_4 ($CoCr_2O_4$, $MnCr_2O_4$, $MgFe_2O_4$ and $CoFe_2O_4$ with high specific surface by solution combustion synthesis using metal nitrates and urea. Ultrasonic irradiation assisted co-precipitation was one of the important tool for synthesis ferrites and their composites.[10] Senapati et al.[11] prepared the $CoFe_2O_4$–Cr_2O_3–SiO_2 nanocomposite by using ultrasonic irradiation. Magnetic nanomaterial, magnesium ferrite is a soft spinel[12] and possess large number of surface hydroxyl groups and Lewis acidic Mg^{2+} sites of cubic spinel ferrite structure provides effective interaction with active phase and with the reactants. $MgFe_2O_4$ based catalysts shown considerable improvements in their catalytic functionality due to the physiochemical properties, surface interactions.[13] Magnetic nanomaterial $MgFe_2O_4$ and its composites offers applications in various fields such as biomedical applications, dye adsorption, mercury measurement, Pertechnetate ($^{99}TcO_4^{-}$) removal, photo catalysis, Hydrogen storage, Knoevenagel condensation, gas sensors, electro chemistry.[14] Magnesium ferrite supported catalysts and their nanocomposites are magnetically separable and shown their applications in diverse fields CO-oxidation, β-chloroacetates synthesis, vanillin production, Biomedical applications, antibacterial study.[15]

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Palladium is an industrially important active catalyst useful in the synthesis of pharmaceuticals, fine chemicals and agrochemicals.[16] Palladium supported on magnetic ferrite material is the most important heterogeneous catalyst as it offers high surface area and easy separation.[17] Rathi et al.[18] synthesized the Maghemite decorated with ultra-small palladium nanoparticles (γ-Fe_2O_3–Pd) by simple coprecipitation method. The incorporation of active catalytic species (Pd) during the synthesis of magnetic nanoparticles provides easy access in preparation.[19] The magnetic nano-palladium catalysts can be prepared by various chemical modifications includes functionalization and surface modification. However but most of the methods require several conversions steps and involve usage of several toxic chemicals.[20]

Most importantly Green Chemistry states the need for environmentally benign and sustainable catalytic systems to save ecological aspects. There is still a need for developing simple, efficient methods to synthesize palladium nanocatalysts and their applicability in potential industrial processes. Herein we report an efficient and successful loading of palladium nanoparticles on magnetic ferrite during the synthesis itself. The catalyst was prepared by one-step ultrasound assisted co-precipitation method, and salt cage assisted calcination to minimize the risk of aggregation and controlled particle size.[21] The catalyst preparation was designed to improve the distribution of active catalytic phase over the catalyst support phase, by using the metal precursors directly and nanocrystal growth was controlled by using the with in-situ formed by-products aided calcination. This one-step co-precipitation method provides easy access for catalyst synthesis. It minimizes the addition of multiple reagents and number of steps which will save energy, time and reduces effluent. Proposed facile approach promises a wide range of applications and could be useful for preparation of various potential nano catalytic systems with good dispersion, controlled particle size. Magnesium and iron are very less toxic to humans and the environment. According to ICH-Q3D guidelines these metal impurities were having low inherent toxicity than class-3 elements,[22] $MgFe_2O_4$ based catalysts have advantages over more toxic Ni, Co based ferrites especially in pharmaceutical applications. Pd/$MgFe_2O_4$ nanocatalyst was applied for Suzuki cross coupling reactions and synthesis of an intermediate for preparing marketed anti-cancer drug PCI-32765, under the name of IMBRUVICA® via Suzuki coupling.[23]

Experimental

Materials and instruments

Iron(III)chloride ($FeCl_3$), Magnesium(II)chloride ($MgCl_2$) and Sodium Hydroxide were purchased from Fischer Scientific. Palladium chloride ($PdCl_2$) was purchased from Aldrich. Ethanol was purchased from Merck. All the chemicals were of analytical grade.

The prepared catalyst Pd/$MgFe_2O_4$ was characterized by various techniques such as SEM-EDS, TEM, ICP-AES, FT-IR, XPS, VSM, BET and XRD. Scanning Electron Microscopy with X-ray microanalysis was performed by SEM-EDS, JEOL JSM-7600F, at operating voltage range 0.1 to 30 kV. Transmission electron microscopy TEM-PHILIPS. CM 200, operating voltage range 20-200kV was used to examine the morphology, SAED pattern, and size of the nanoparticles. Powder X-ray diffraction pattern was examined by using XPert Pro (PANalytical) using Cu Kα radiation ($\lambda = 1.5406$ A°) with scanning rate 2 degree per minute to investigate the crystal structure and size of the nanoparticles. Inductively coupled plasma atomic emission spectroscopy ICP-AES-ARCOS 1.6 kW, 27.12 MHz was used to obtain the palladium content in samples. To record the NMR spectra of products NMR- VARIAN, USA, Mercury plus 300 MHz NMR Spectrometer, 5 mm Auto switchable probe with PFG was used. FT-IR spectra were obtained by using Agilantcary 300. The XPS analysis was carried out using X-ray Photoelectron Spectroscopy (XPS) with Auger Electron Spectroscopy (AES) Module Model: PHI 5000 Versa Prob II,FEI Inc. Surface area and Porosity analyzer (Gemini VII-2390t) was used to measure the BET surface area of the sample. The magnetic moment of the sample was analyzed with Lakeshore 7410S Vibrating Sample Magnetometer (VSM) 3.42 Tesla (Electromagnet) · Sensitivity: 10-7 emu, Low Temperature range 15-300 K.

Synthesis of palladium loaded magnesium ferrite (Pd/$MgFe_2O_4$) nanoparticles

Magnesium ferrite nanoparticles were loaded with palladium during their synthesis by ultrasound assisted co-precipitation method. In a 500 ml glass beaker containing 100 ml double distilled demineralized water, added $FeCl_3$(10 mmol), and $MgCl_2$ (5 mmol). The reaction mixture was placed in an ultrasonicator (Bio-technics, BTI-48, frequency 33 kHz, power 250 W) and added $PdCl_2$ 150 mg, sonicated for 10 min (clear solution observed). The reaction mixture pH was adjusted to 12 using 1 N aqueous NaOH solution (orange precipitate was observed). The reaction mixture was slowly evaporated to dryness at 120 °C. The obtained material was calcinated at 300 °C for about 4 h along with in-situ formed sodium chloride salts. Obtained cake was distributed in water, separated by centrifugation, washed with excess water, ethanol and then oven dried at 100 °C overnight under nitrogen atmosphere (flow rate 30 ml/min). The obtained catalyst was stored in a glass vial. The catalyst was reproduced by the above procedure. In this process, the salts obtained by adjustment of pH in the reaction mixture may surround the nanoparticles during calcination. Thus the nanocrystal growth was controlled. The catalyst obtained as a fine powder after calcination, further grinding was not required. The prepared Pd-Magnesium ferrite nanocatalyst was denoted as Pd/$MgFe_2O_4$.

Results and discussion

Synthesis and characterization of Pd/$MgFe_2O_4$

Magnesium ferrite was loaded with palladium by simple co-precipitation of metal precursors, represented as

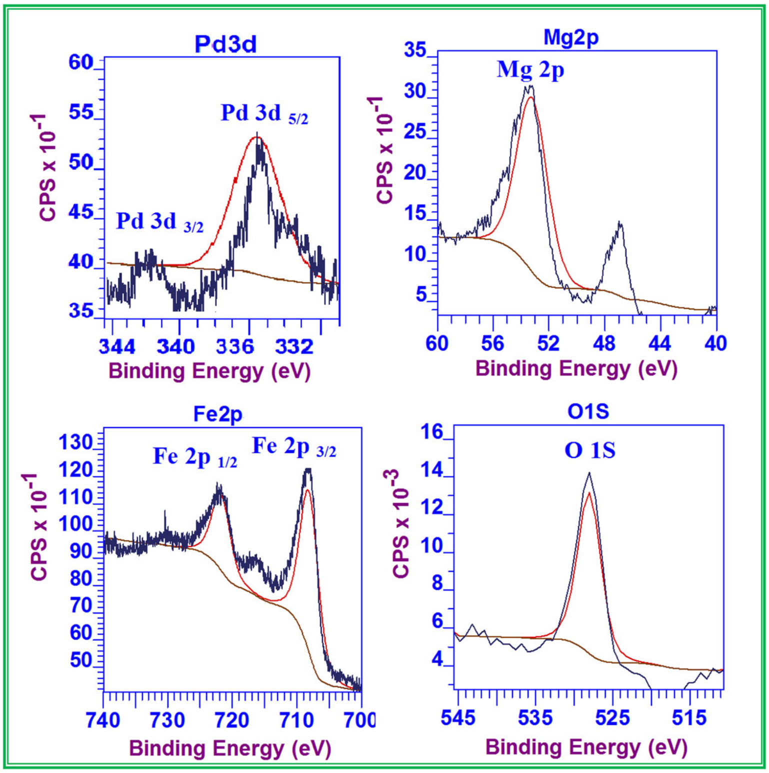


Figure 1. XPS spectra of Pd/$MgFe_2O_4$.

$Pd_xMgFe_2O_4$(palladium weight%, $x = 1$). The catalyst manufacturing process involves the utilization of in-situ formed sodium salts as a salt cage for nanoparticles. These Sodium chloride salts obtained by adjustment of pH in the reaction mixture were surrounding the palladium loaded Magnesium ferrite nanoparticles during calcination. Upon dispersion of calcinated cake in water, the surrounded sodium chloride salts were dissolved in water; Pd/$MgFe_2O_4$ was simply separated by application magnetic field. The catalyst obtained as fine powder, further grinding was not required. Thus, the nanocrystal growth was controlled by salt cage. Conventional Pd/MFe_2O_4($M = Co$, Ni, Zn) catalyst preparation methods required multiple process operations such as collecting the precipitate by centrifugation leaving sodium salts in mother liquors, loading of active catalytic phase, calcination and grinding the obtained calcinated cake. The Pd/$MgFe_2O_4$ catalyst preparation method was advantageous in terms of minimizing process operations, reducing the agglomerization risk, simplicity and industrially viability for large scale synthesis of nanocatalysts toward industrially important catalytic transformations. It provides high surface area, thereby the number of active sites was increased, and resulting in enhanced catalytic activity.

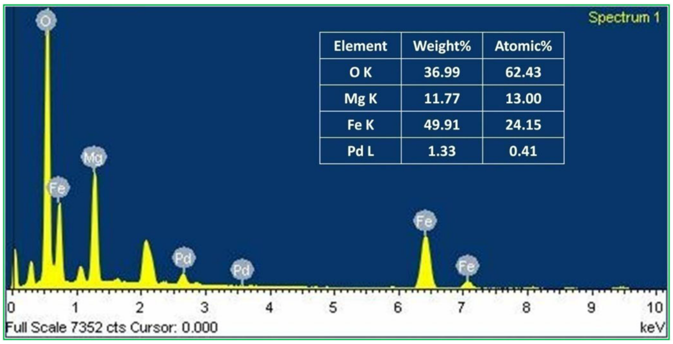
The active catalytic phase palladium was distributed by forming ultra fine nanoparticles <6nm upon the magnesium ferrite phase. The Palldium chloride ($PdCl_2$) was converted into palladium hydroxide ($Pd(OH)_2$) colloids and dispersed on the ferrite nanoparticles under basic conditions. The colloidal $Pd(OH)_2$ are further converted into PdO or Pd(0) nanoparticles in presence of aqueous NaOH at basic pH via reduction of Pd(II); and during workup with ethanol. The support phase magnesium ferrite was attributed by the corresponding elements XPS screening results of Fe 2p, Mg 2p and O 1S. The presence of XPS (Figure 1) characteristic peak at regions 335 eV and 342 eV for Pd(0) indicates that the majority amount of palladium was adsorbed on the surface of $MgFe_2O_4$ as palladium (0) nanoparticles.[17] The XPS peck position for $Pd(OH)_2$ and PdO were in the region 336.80 eV, so $Pd(OH)_2$ and/or PdO might be also present along with palladium nanoparticles. [19] The palladium content measured by XPS analysis was 1.24 wt%. And the palladium content measured by ICP-AES was 1.20 wt %.

The elemental analysis of Pd/$MgFe_2O_4$ was studied by SEM-EDS and shown in Figure 2. The elemental distribution of Pd/$MgFe_2O_4$ was Mg = 13.00%, Fe = 24.15%, O = 62.43%, and Pd = 0.41%. The atomic ratio of Fe to Mg obtained was 0.54. The palladium weight % obtained from EDS analysis was 1.33%.

XRD analysis (Figure 3) showed peaks at $2\theta = 29.79°$, 35.44°, 43.04°, 53.42°, 57.42°, 62.71° which represent the Braggs reflections from the (220), (311), (400), (422), (511), (440), respectively. The 'd' spacing values observed were 2.99, 2.53, 2.099, 1.714, 1.614 and 1.481. The crystalline data matches with the JCPDS Card No. (#89-4924). Palladium peaks were observed at 2θ values 40°, 46°. The data obtained from TEM, SAED pattern (Figures 4 and 5) were in agreement with XRD analysis. Based on the XRD patterns, the plane corresponding to the most intense peak 2θ value 35.44° was (311). The average crystallite domain sizes (D) of particles have been calculated from XRD peaks using Scherrer's equation: $D = \lambda/(\Delta W \, \mathrm{Cos}\theta)$, where λ is wavelength of X-ray, θ is the Bragg's diffraction angle in radians, and ΔW is the true half-peak width of the XRD lines. The average crystallite (grain) size was 6.4 nm obtained by XRD data, 8.5 nm from TEM analysis (particle size 5-18 nm). The grain size obtained from XRD analysis was lower than the particle size from TEM analysis.

Figure 5 shows that the Pd/$MgFe_2O_4$ nanoparticles are crystalline, having size below 20 nm with random distribution in 5-18nm range. The dispersion of palladium was confirmed by EDS element mapping analysis. Further the Pd nanoparticles (black dots, size $<$ 6 nm) are of lower size than nanocrystalline magnesium ferrite.

Figure 6 represents the EDS elemental mapping of Fe, Mg, O and Pd. The TEM image analysis (Figure 5) and SEM-EDS elemental dot mapping (Figure 6) clearly representing the palladium active phase was well distributed along with the catalyst support (nano magnesium ferrite). The histogram (Figure 7) reveals that the magnesium ferrite nanoparticles size ranging from 5 nm to 18 nm with an average size of 8.5 nm. The palladium nanoparticles are having lower particle size than Magnesium ferrite nanocrystal. The FT-IR spectrum shown in Figure 8, indicates the presence of OH groups (3450 cm^{-1}) on the surface of magnesium ferrite, and 576 cm^{-1} and 434 cm^{-1} bands indicates tetrahedral and octahedral intrinsic stretching vibrations of Fe-O.[24]



Element	Weight%	Atomic%
O K	36.99	62.43
Mg K	11.77	13.00
Fe K	49.91	24.15
Pd L	1.33	0.41

Figure 2. SEM-EDS of Pd/$MgFe_2O_4$.

The magnetic properties of the nanocrystalline Pd/$MgFe_2O_4$ were measured as a function of the field and temperature. Figure 9 shows the magnetization curves of the Pd/$MgFe_2O_4$ nanoparticles. The saturation magnetization (M_s) obtained was 19.65 emu/g. The magnetization slightly decreased in comparison with bulk sample due to weak bonding of magnetic spins at the surface of nanocrystalline $MgFe_2O_4$.

The nitrogen adsorption–desorption isotherms of Pd/$MgFe_2O_4$ NPs were studied using Brunauer-Emmett-Teller (BET) method at temperature 77.35 K (Figure 10). The BET surface area for Pd/$MgFe_2O_4$ was found to be 31.28 m^2 g^{-1}. The higher surface area of $MgFe_2O_4$ NPs can be attributed to the decrease in size of the crystallite. The average pore diameter of Pd/$MgFe_2O_4$ was calculated by using Barret-Joyner-Halenda (BJH) method and found to be 3.04 nm. The average pore diameters obtained from ferrite NPs are due to the intra-granular pore formed within the metal oxides.

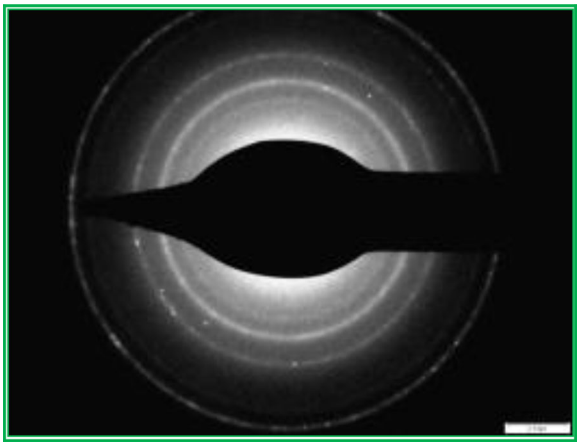


Figure 4. TEM-SAED pattern of Pd/$MgFe_2O_4$.

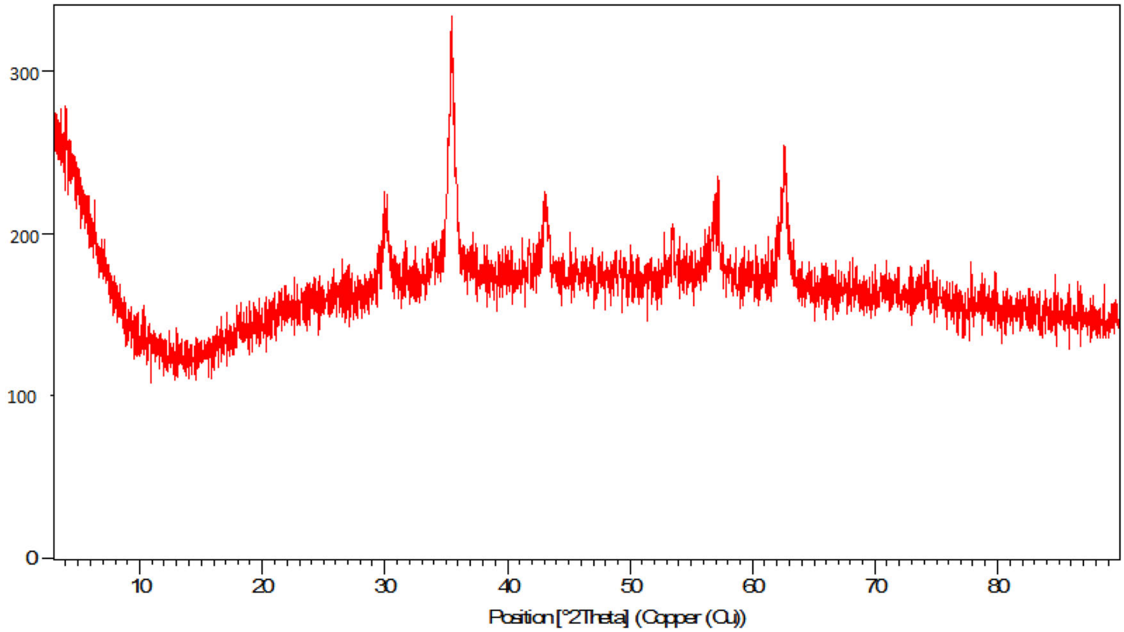


Figure 3. XRD pattern of Pd/$MgFe_2O_4$.

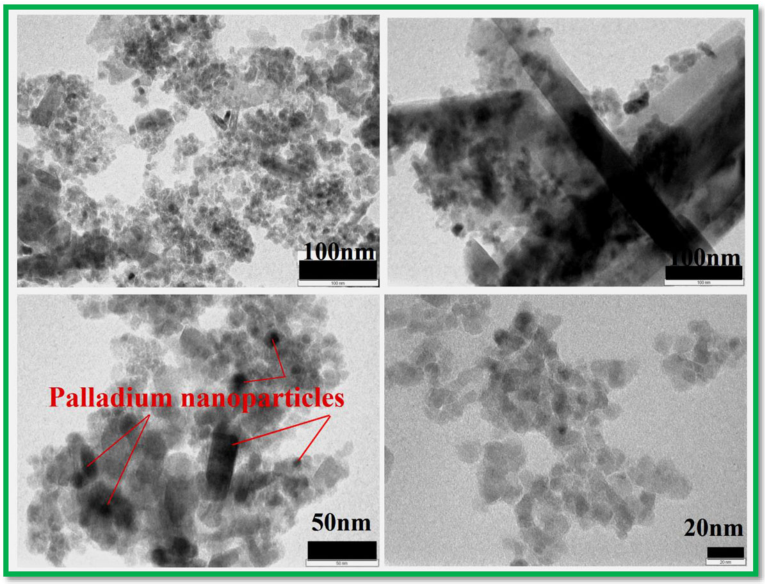


Figure 5. TEM-Imaging of $Pd/MgFe_2O_4$ at different magnifications.

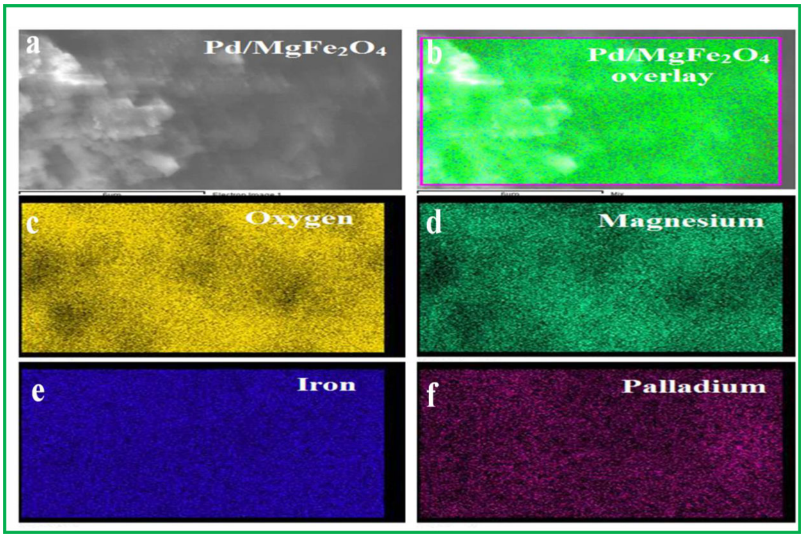


Figure 6. SEM-EDS, Elemental mapping a) SEM, b) $Pd/MgFe_2O_4$, c) Oxygen, d) Magnesium, e) Iron, f) Palladium.

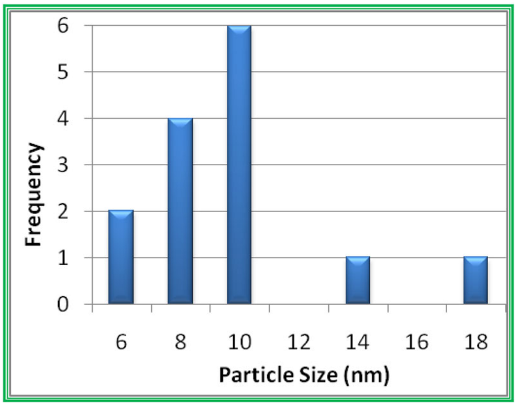


Figure 7. Particle size distribution of $Pd/MgFe_2O_4$.

The reduced particle size of the $Pd/MgFe_2O_4$ nanocatalyst results increased active surface area. The number of active catalytic active sites was increased and resulting in leads to enhanced catalytic efficiency. The effective distribution of palladium nanoparticles and hydroxyl groups of $MgFe_2O_4$ provides an effective interaction of active catalytic species with catalyst support and with reactant molecules. So the catalyst efficiency in Suzuki coupling reaction was improved and the products were obtained with excellent yield.

Catalytic activity of $Pd/MgFe_2O_4$

The catalytic activity of nano $Pd/MgFe_2O_4$ has been evaluated against the Suzuki coupling reaction (Scheme 1). Reaction of Iodobenzene with phenylboronicacid was treated as a model reaction to verify various reaction parameters. 0.50 mmol of Iodobenzene was treated with 0.75 mmol phenylboronicacid in the presence of $Pd/MgFe_2O_4$ (0.2 mol% of Pd), K_2CO_3 (1.00 mmol) as base in 4 ml of ethanol: water (1:1) solvent system at 80 °C. Experiments were performed

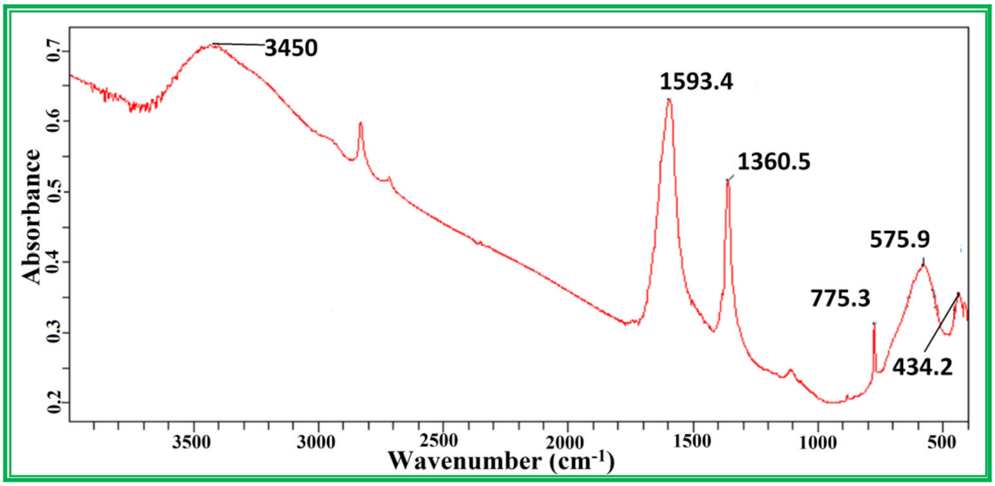


Figure 8. Infrared spectrum of Pd/$MgFe_2O_4$.

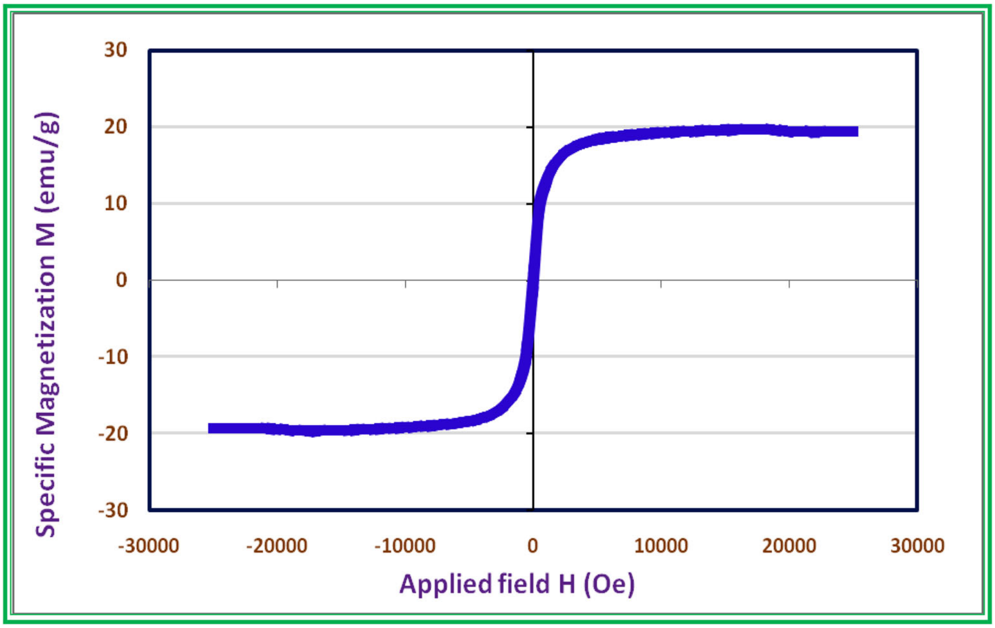


Figure 9. Hysteresis curve of nanocrystalline Pd/$MgFe_2O_4$ measured at 300 K.

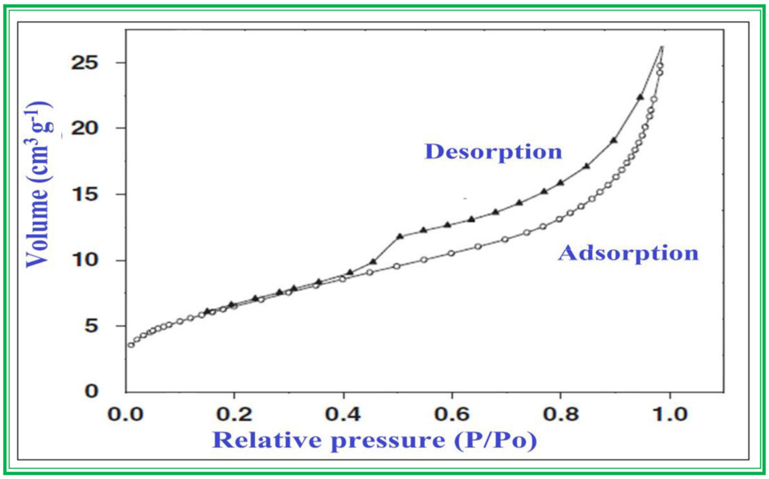
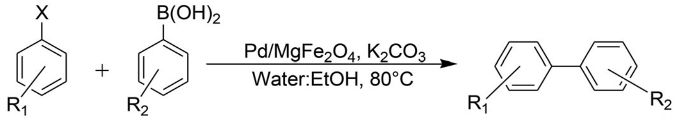


Figure 10. N_2 adsorption-desorption isotherm of Pd/$MgFe_2O_4$ sample obtained at 77 K.



Scheme 1. Suzuki coupling reaction of Aryl Halides and Arylboronicacids.

Table 1. Optimization of reaction conditions for Suzuki coupling[a] with Iodobenzene and Phenylboronicacid.

Solvent	Base	Catalyst (mol %)	Temp. (°C)	Time (h)	Yield[b] (%)
DMF	K_2CO_3	0.2	80	4	84
Ethanol	K_2CO_3	0.2	80	12	86
Water	K_2CO_3	0.2	80	20	64
Toluene	K_2CO_3	0.2	100	8	69
Ethanol/Water	K_2CO_3	0.2	80	2	99
Ethanol/Water	TEA	0.2	80	2	92
Ethanol/Water	KOAc	0.2	80	8	88
Ethanol/Water	Na_2CO_3	0.2	80	2	94
Ethanol/Water	Cs_2CO_3	0.2	80	4	93
Ethanol/Water	K_2CO_3	0.5	80	1	96
Ethanol/Water	K_2CO_3	0.1	80	8	94
Ethanol/Water	K_2CO_3	0.2	RT	30	58
Ethanol/Water	K_2CO_3	0.2	50	15	86
Ethanol/Water	K_2CO_3	–	80	24	No reaction

[a] Reaction conditions: 0.5 mmol of Iodobenzene, 0.75 mmol of Phenylboronicacid and 1.0 mmol of base, nano $Pd/MgFe_2O_4$ catalyst, ethanol 2 ml and water 2 ml, Temperature RT-80 °C.

[b] isolated yield by column chromatography

Table 2. Suzuki cross coupling reactions[a] of Aryl halides and Aryl boronic acids by using $Pd/MgFe_2O_4$.

Aryl halide (R_1)	Aryl boronic acid (R_2)	X	Time (h)	Yield (%)[b]
H	H	I	2	99
H	H	Br	4	96
H	H	Cl	24	81
3-NO_2	4-Me	I	1.5	93
3-NO_2	3-NO_2	I	2	91
4-Cl	4-OMe	I	3.5	93
4-COMe	4-OMe	I	2.5	96
4-OMe	4-COMe	I	3	94
3-NO_2	4-Et	I	2	95
4-NO_2	4-OMe	I	1.5	97
H	4-OMe	I	2	98
4-OMe	H	I	2	94
Thienyl	4-Me	I	6	96
Thienyl	4-Me	Br	9	92
4-OMe	Thienyl	I	7	87
Thienyl	4-OMe	I	5	96
Naphthyl	4-OMe	I	4	98

[a] Reaction conditions: 0.5 mmol of Aryl Halide, 0.75 mmol of Aryl boronic acid and 1.0 mmol of K_2CO_3, 0.2 mol% nano $Pd/MgFe_2O_4$ catalyst, ethanol 2 ml and water 2 ml, 80 °C.

[b] Isolated yield by column chromatography

to optimize the reaction parameters such as catalyst loading, solvent, base and temperature.

The investigated experimental results explored the optimized reaction conditions were found in Ethanol: Water solvent media with 0.2 mol% of Pd ($Pd/MgFe_2O_4$) at 80 °C temperature in the presence of K_2CO_3 as a base for about 2 h (Table 1).

The scope of the reaction was studied with various substituents (electron withdrawing and electron releasing nature) on both Aryl halides and Arylboronicacids (Table 2). The obtained yields are good to excellent with various Aryl, Heteroaryl Halides and Boronicacids depending on the nature of substituent due to electronic effects.

Figure 11. Magnetic separation of $Pd/MgFe_2O_4$ from the reaction mixture.

In economical and environmental point of view, the recovery and reuse of catalyst are most important. The catalytic activity and magnetic separation of nano $Pd/MgFe_2O_4$ were investigated at present reaction conditions. The magnetic property of $Pd/MgFe_2O_4$ provides an efficient magnetic separation from the reaction mixture as shown in Figure 11. The recyclability of $Pd/MgFe_2O_4$ catalyst for coupling reaction of Iodobenzene with Phenylboronicacid is shown in Figure 12. After completion of the reaction, the reaction mixture was cooled to ambient temperature and the catalyst was separated by an external magnet. The recovered catalyst was washed with excess EtOH, dried in vacuum oven at 100 °C and reused for next cycle. The catalyst reusability was tested up to five cycles without significant loss of its activity. The isolated yields were decreased slightly after the fifth cycle due to Pd leaching, which was confirmed by ICP-AES analysis. After five cycles, the leaching of Pd was 0.1% wt was observed.

Reusability of $Pd/MgFe_2O_4$ catalyst

The heterogeneous nature of the catalyst was examined by hot filtration test. The supported catalyst was filtered off after 30 min of the reaction time and the filtrate was allowed to react further for the required time under the same reaction conditions. The results indicate that after this hot filtration, further reaction did not proceed. The catalyst was heterogeneous, there is no leaching of Pd during the reaction. The results were supported by ICP-AES analysis. The leaching of Pd was not observed up to 5 cycles. Further, after five cycles the catalyst was analyzed by SEM image shown in Figure 10 (Supplementary information). It clearly showed that the catalyst was highly stable and reusable.

Comparison of catalytic activity for Suzuki coupling reaction

The catalytic activity of $Pd/MgFe_2O_4$ in the preparation of biphenyl using Iodobenzene and Phenylboronicacid was compared with various palladium nanocatalysts reported in literature. The $Pd/MgFe_2O_4$ nanocatalyst showed remarkable

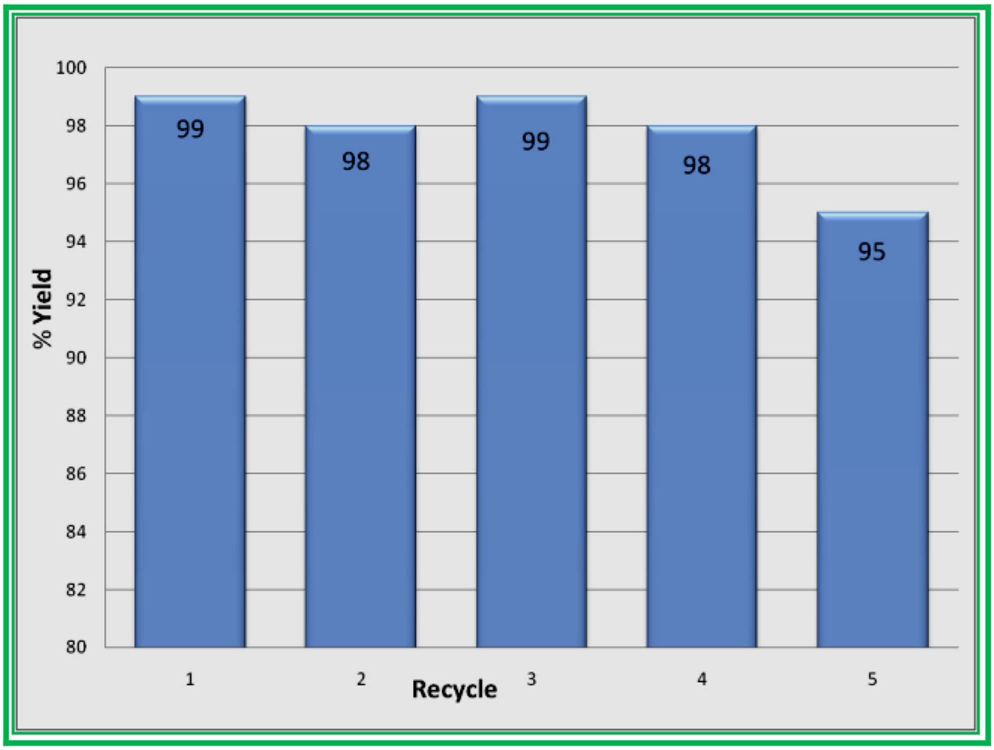


Figure 12. Recyclability of $Pd/MgFe_2O_4$ with Iodobenzene and Phenylboronicacid cross coupling reaction.

Table 3. Comparison of various $MgFe_2O_4$ catalyst preparation methods.

Catalyst	Preparation method	Application	Ref.
$Pd/MgFe_2O_4$	One-step synthesis 1. $Pd/MgFe_2O_4$ synthesis by Co-precipitation,	Suzuki coupling	Present work
Au/ $MgFe_2O_4$	Two-step synthesis 1. $MgFe_2O_4$ synthesis by Sol-gel, 2. Colloidal deposition of synthesized Au nanoparticles	CO-oxidation	[15(a)]
$Pt/MgFe_2O_4$	Two-step synthesis 1. $MgFe_2O_4$ synthesis by solid-state method, 2. Colloidal deposition of synthesized Pt nanoparticles.	CO-oxidation	[15(b)]
Au /MgO/$MgFe_2O_4$	Three-step synthesis 1. $MgFe_2O_4$ synthesis by Co-precipitation, 2. MgO/$MgFe_2O_4$ synthesis by impregnation, 3. Colloidal deposition of synthesized Au nanoparticles.	Benzyl alcohols oxidation	[15(c)]

activity with 99% yield with 0.2 mol% palladium loadings (TON-495, TOF-247.5 h^{-1}) toward ligand less Suzuki coupling reaction utilizing greener solvent mixture Water: Ethanol. Moreover, the catalyst preparation procedure is one-step co-precipitation, salt cage assisted calcination. $Pd/MgFe_2O_4$ was one of the efficient catalysts among the reported un-functionalized and functionalized catalysts.

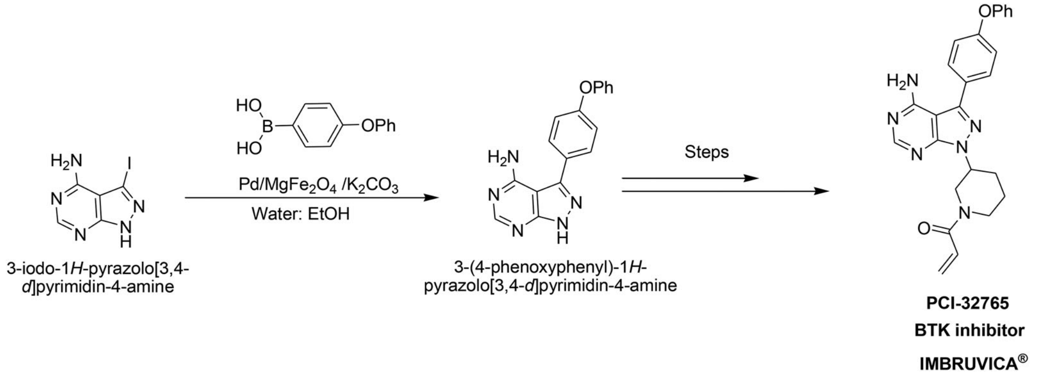
Comparison of catalyst preparation methods

The proposed catalyst preparation was compared with reported methods; magnesium ferrite supported metal catalysts and shown in Table 3. Generally, multi-step synthesis and numerous operations were involved in the preparation of catalysts. The present work is a one-step coprecipitation and in-situ formed by-products act as a masking agent during calcination. This methodology is superior, does not involves additives, templating agent and surface modifiers. Proposed method is more efficient compared to other reported methods, requires minimum number of operations and minimal instrumentation.

Application of $Pd/MgFe_2O_4$ nanocatalyst in synthesis of PCI-32765

The prepared $Pd/MgFe_2O_4$ nanocatalyst was applied for the synthesis of 5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine an intermediate in preparation of the marketed drug PCI-32765 under the name IMBRUVICA® (Ibrutinib -BTK inhibitor). Our group successfully prepared the drug PCI-32765 by a new synthetic approach.[25] The molecule is biologically active and can be used as an anticancer drug to treat B cell cancers like mantle cell lymphoma, chronic lymphocytic leukemia, and Waldenström's macroglobulinemia, a form of non-Hodgkin's lymphoma by binding the Bruton's tyrosine kinase(BTK) protein of B cells.

The synthetic intermediate 5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyriMidin-4-ylamine can be easily prepared from commercially available 3-Iodo-1H-pyrazolo[3,4-d]pyrimidin-



Scheme 2. Synthesis of PCI-32765.

4-amine and 4-phenoxybenzeneboronicacid by Suzuki coupling reaction (Scheme 2). The active molecule PCI-32765 can be synthesized by reacting obtained product with 1-(tert-butoxycarbonyl) piperidin-3-yl methanesulfonate,[26] simultaneous deprotection and amide formation with Acrylic acid. The magnetically recoverable Pd/MgFe$_2$O$_4$ is an efficient catalyst in the synthesis of intermediate for preparing PCI-32765 drug and, the obtained product was having negligible content of trace metals <2ppm.

Conclusions

In conclusion, we have prepared a new, palladium nanoparticles loaded magnesium ferrite nanocatalyst (Pd/MgFe$_2$O$_4$) was synthesized by one-step co-precipitation using ultrasound; in-situ formed by-products assisted salt cage calcination method. The catalyst was well characterized by using SEM-EDS, TEM, FT-IR, XPS, XRD, VSM, BET, and ICP-AES. The synthesized Pd/MgFe$_2$O$_4$ was magnetically separable (Saturation magnetization Ms = 19.85 emu/g), having particle size (TEM) 5 nm to 18 nm and posses specific surface area 31.28 m^2 g^{-1}. The active phase palladium was effectively dispersed and Pd/MgFe$_2$O$_4$ particle size was controlled by minimizing aggregation risk during calcination. The palladium nanoparticles preparation was carried out without using additional reducing agents such as Hydrazine, Sodium borohydride, Hydrogen. This one-step preparation method was simple, efficient and having very less number of process operations, can be used for several potential nanocatalysts. The catalyst preparation process was useful for preparing several potential nano catalytic systems having numerous industrial applications. The active catalyst efficaciously catalyzed the Suzuki coupling reaction without using toxic Phosphine ligands. The Pd/MgFe$_2$O$_4$ catalyst is reusable up to 5 cycles with superior catalytic activity. The magnetic nature of the catalyst provides the ease of separation from the reaction mixture in the presence of an applied external magnetic field, which eliminates the need of catalyst filtration after completion of the reaction. Furthermore, easy isolation of the crude products, negligible metal contamination and reusability of the catalyst can have a huge green impact and industrial interest. The proposed nano Pd/MgFe$_2$O$_4$ catalyst was successfully applied in the synthesis of 5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine, an important intermediate for preparing the marketed drug PCI-32765.

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