



# In<sup>3+</sup> doped magnesium ferrite an efficient magnetic catalyst for the synthesis of functionalized quinazolinone and Henry reaction

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**Abstract.** Pristine and indium doped magnesium ferrite nanoparticles have been prepared by the sol-gel method. The phase formation has been confirmed from XRD (X-ray diffraction) whereas nanosize has been displayed through TEM (Transmission Electron Microscope) images. BET (Brunauer–Emmett–Teller) analysis showed an increase in surface area for the indium doped sample compared to pristine magnesium ferrite. The superparamagnetic nature of nanoparticles has been observed from *M–H* studies carried on VSM and these have been efficiently employed as a catalyst in organic transformation such as quinazolinone synthesis and Henry reaction. The indium doped magnesium ferrite catalyst has been found to be highly active and recyclable in nature. The high surface area and Lewis acidity govern their catalytic performance whereas magnetic nature makes the separation easier.

**Keywords.** Henry reaction; quinazolinone; magnesium ferrite; In doped nanoparticles.

## 1. Introduction

Heterogeneous catalysis has served as a blessing in the field of catalysis with its appealing properties like separation and recyclability, which turns out to be cost-effective too. Metal oxides have proved to be efficient heterogeneous catalysts over the years for several organic reactions such as oxidation, reductions, dehydrogenations, isomerisation, multi-component reactions (MCR's) and coupling reactions. In recent years among the metal oxides, nano ferrites have gained a lot of attention owing to the highlighting advantage of easy separation. Their nanosize and magnetic nature has made them a catalyst of choice for a plethora of applications. Several transition metal ferrites of the form  $AFe_2O_4$  (where  $A=Co, Cu, Ni, Fe$ ) have been explored for their catalytic activity,<sup>1</sup> in reactions such as aldol condensation, Prins condensation, Synthesis of  $\alpha$ -amino nitriles 1,8-dioxodecahydroacridines, synthesis of 1,4-dihydropyridines,<sup>2</sup>  $\beta,\gamma$ -unsaturated ketones and allylation to acid chlorides.<sup>3</sup>

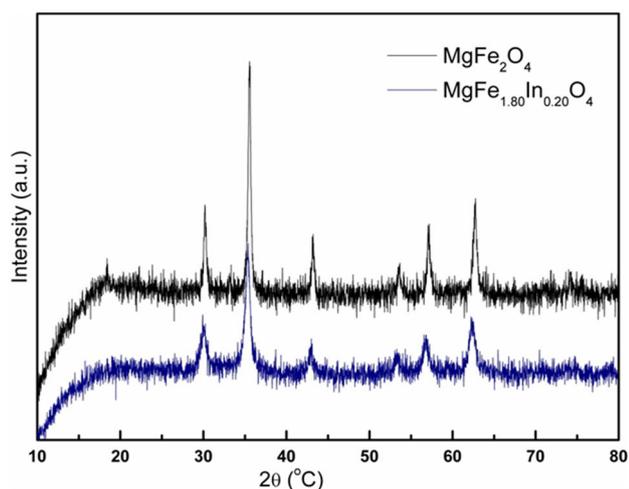
### 1.1 Magnesium Ferrite

$MgFe_2O_4$  is one of the important ferrite materials that have also found its applications in the catalytic field. The available reports include dehydrogenation of butenes,<sup>4</sup> ozonation of Acid Orange II,<sup>5</sup> synthesis of  $\alpha$ -hydroxy and  $\alpha$ -aminophosphonates,<sup>6</sup> 3,4-dihydropyrimidin-2(1H)-one/thione,<sup>7</sup> carbon removal,<sup>8</sup> etc.  $MgFe_2O_4$  is basically a spinel ferrite with attractive properties. It displays superparamagnetism when synthesized in nanosize.  $MgFe_2O_4$  doped with other metal ions such as transition metal or rare earths have been extensively studied for their variation in magnetic properties. In the present work, we have synthesized pristine and indium doped  $MgFe_2O_4$  nanoparticles and studied their catalytic activity for Henry reaction and in the synthesis of quinazolinones.

### 1.2 Henry reaction

The Henry reaction (nitro-aldol reaction) involves a base-catalyzed addition of nitroalkanes to carbonyl

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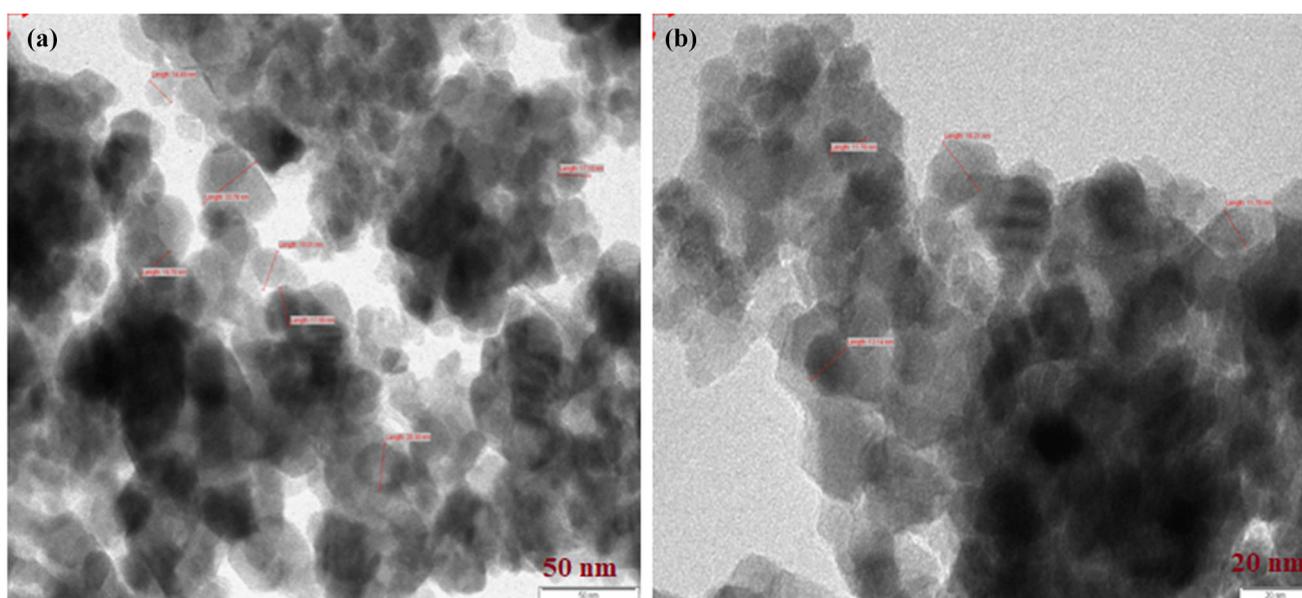
**Figure 1.** X-ray powder pattern of pristine  $\text{MgFe}_2\text{O}_4$  and  $\text{MgFe}_{1.80}\text{In}_{0.20}\text{O}_4$  nanoparticles.

compounds to generate  $\beta$ -nitro alcohols. This reaction, although discovered in 1895, still remains an important C-C bond forming reaction in organic chemistry

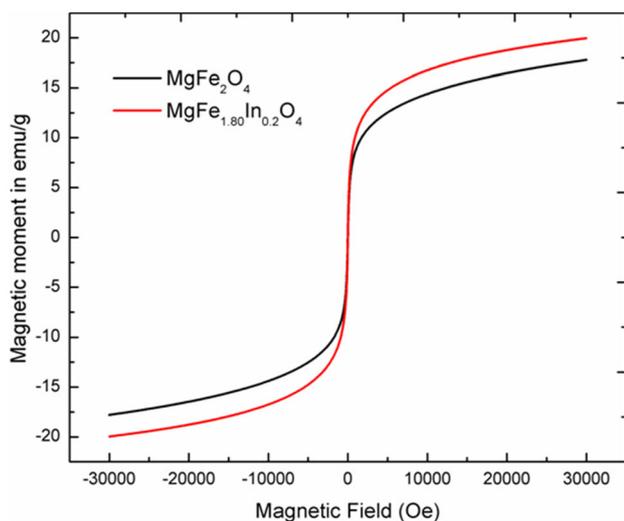
mainly because the product of this reaction serves as precursors for important building blocks such as nitroalkenes, 1,2-amino alcohols,  $\alpha$ -hydroxy acids, 1,2-diamines, 2-nitrocarbonyls,<sup>9,10</sup> etc. Several catalysts such as alkali metal hydroxides, alkaline earth oxides, carbonates, bicarbonates, alkoxides, alkaline earth hydroxides, guanidine derivatives, organo-phosphorous derivatives, Lewis acids or electrophilic activators, and quaternary ammonium salts have been used for the nitro-aldol reaction.<sup>11</sup> However, any base-catalyzed nitro-aldol reactions are associated with various competitive reactions such as aldol condensation, Cannizzaro reaction, Tishchenko reaction, and Nef-type reaction. In addition, the base-catalyzed elimination of water can lead to the formation of nitroolefin, which polymerizes readily.<sup>12</sup> To combat these problems, a number of heterogeneous catalysts have been developed in recent years which include rhodium complex, KG-60- $\text{NEt}_2$ , 2:1 Mg:Al hydrotalcite, phosphine, proazaphosphatranes, and ionic liquids but they are also associated with drawbacks like a mixture of

**Table 1.** Crystallite size and lattice parameters calculated for  $\text{MgFe}_{2-x}\text{In}_x\text{O}_4$ .

Compositions	Crystallite size ( $\text{\AA}$ )	Lattice constant (a=b=c) $\text{\AA}$	Lattice volume ( $\text{\AA}^3$ )
$\text{MgFe}_2\text{O}_4$	240.1	8.36	585.3
$\text{MgFe}_{1.80}\text{In}_{0.20}\text{O}_4$	114.5	8.41	595.5



**Figure 2.** TEM image of (a)  $\text{MgFe}_2\text{O}_4$  and (b)  $\text{MgFe}_{1.80}\text{In}_{0.20}\text{O}_4$  nanoparticles.



**Figure 3.** Plot of Magnetic moment v/s Magnetic field for  $\text{MgFe}_2\text{O}_4$  and  $\text{MgFe}_{1.80}\text{In}_{0.20}\text{O}_4$ .

products, low yields or high cost.<sup>13</sup> Since our synthesised indium doped ferrite is acidic in nature, we envisaged that this could be effectively employed as a catalyst in the nitroaldol reaction.

### 1.3 Quinazolinone synthesis

Quinazolinones are significant heterocyclic scaffolds present in many natural products and important synthetic drugs. Numerous quinazolinone derivatives exhibit a wide range of biological activities which include analgesic, anaesthetic, antibacterial, anti-cancer, anticonvulsant, antihypertensive, anti-inflammatory, antimalarial, antiparasitic, antiviral, diuretic, muscle relaxant, and sedative properties.<sup>14</sup> Various important drugs like proquazone, methaqualone, gefitinib, ertonib and actinomycin consist of the quinazolinone nucleus.<sup>15</sup>

Consequently a plethora of methods for the synthesis of 2, 3-dihydroquinazolinones exist from various starting materials and catalysts.<sup>16</sup> However, some of the methods have limitations such as drastic reaction conditions, use of hazardous organic solvents, low

yields, etc. Thus the development of more convenient routes for the synthesis of these compounds has always been important. In view of the same it is planned to explore the utility of our nanocatalysts in a direct three-component condensation of isatoic anhydride, aromatic aldehyde and ammonium acetate under microwave irradiation.

The magnetic separation, high surface area and Lewis acidity are the highlighting features of this catalyst that motivated the current research.

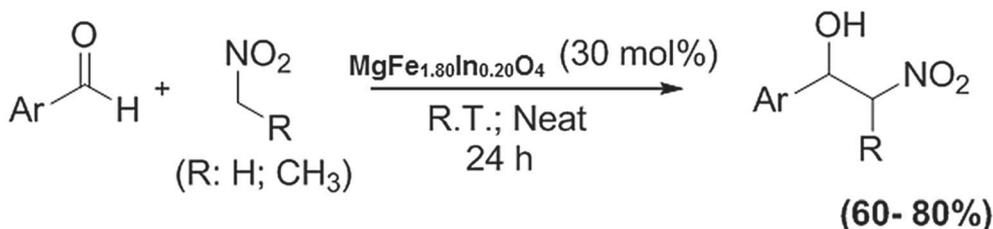
## 2. Experimental

### 2.1 Preparation of the catalyst

Pristine  $\text{MgFe}_2\text{O}_4$  and  $\text{MgFe}_{1.80}\text{In}_{0.20}\text{O}_4$  nanoparticles were synthesized by sol-gel method using citric acid as a fuel. The metal nitrate to citric acid ratio was maintained to 1:3. All the chemicals used were of high purity. The synthetic procedure is as follows: the calculated amount of indium oxide ( $\text{In}_2\text{O}_3$ ) was brought into the solution by dissolving in nitric acid (pure A.R Grade). To this stoichiometric amounts of magnesium nitrate [ $\text{Mg}(\text{NO}_3)_2$ ] and iron nitrate [ $\text{Fe}(\text{NO}_3)_3$ ] were added. The mixture was stirred for 15 min followed by the addition of citric acid. Further heating with continuous stirring resulted in gel formation. The obtained gel was dried at 200 °C for 10 h, which was further ground and calcined at 600 °C for 6 h in an open-air furnace. The detailed procedure is given elsewhere.<sup>17</sup> The resulting nanoparticles were characterised using IR, XRD, SEM and TEM. These nanoparticles were used as a catalyst for the synthesis of quinazolinones and Henry reaction.

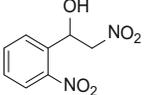
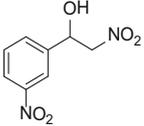
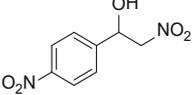
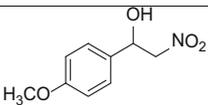
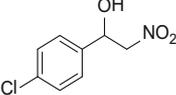
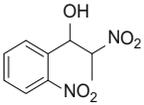
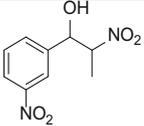
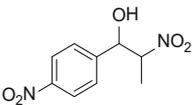
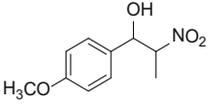
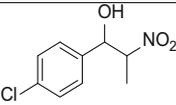
### 2.2 General procedure for Henry reaction catalysed by prepared nanocatalyst

In a typical synthesis the aldehyde (1 mmol) and the nitro alkane (5 mL) which also acts as a solvent, were added to the round-bottomed flask containing a



**Scheme 1.** Henry reaction on various substituted aromatic aldehydes with nitromethane and nitroethane.

**Table 2.** Henry reactions of various substituted aromatic aldehydes with nitromethane and nitroethane using MgFe<sub>1.80</sub>In<sub>0.20</sub>O<sub>4</sub> catalyst.

Sr. No.	Aldehyde (Ar-CHO)	R	Product	Yield (%)
1	<i>o</i> -nitrobenzaldehyde	H		72
2	<i>m</i> -nitrobenzaldehyde	H		70
3	<i>p</i> -nitrobenzaldehyde	H		75
4	<i>p</i> -anisaldehyde	H		60
5	<i>p</i> -chlorobenzaldehyde	H		62
6	<i>o</i> -nitrobenzaldehyde	CH <sub>3</sub>		77
7	<i>m</i> -nitrobenzaldehyde	CH <sub>3</sub>		78
8	<i>p</i> -nitrobenzaldehyde	CH <sub>3</sub>		80
9	<i>p</i> -anisaldehyde	CH <sub>3</sub>		61*
10	<i>p</i> -chlorobenzaldehyde	CH <sub>3</sub>		64*

Reaction conditions: aldehyde (1 mmol), nitro alkane (5 mL) and 30 mol% MgFe<sub>1.80</sub>In<sub>0.20</sub>O<sub>4</sub> catalyst stirred for 24 h.\*Thick yellow oil. The reaction was also studied in a microwave but no satisfying results were obtained.

weighed amount of the catalyst and the mixture was stirred for 24 h. Progress of the reaction was monitored using thin-layer chromatography (TLC) (ethyl acetate/pet ether 10:90). The catalyst was then separated with the help of a magnet/filtration. The reaction mixture was then extracted in ether (20 mL) and the product was purified by column chromatography using ethyl acetate and pet ether (10:90). The compound was then dried and characterised by its spectroscopic data.

### 2.3 General procedure for the synthesis of 2,3-dihydroquinazolinones-4(1H)-one using prepared nanocatalyst

Aldehyde (1 mmol), isatoic anhydride (1 mmol), ammonium acetate (1 mmol) and catalyst (10 mol %) were taken in a 25 mL conical flask and subjected to microwave irradiation for 5 min. Progress of the reaction was monitored by TLC at a time interval of 1 min. On completion, the reaction mixture was dissolved in 15 mL hot ethanol, and the catalyst was separated using a magnet. The decanted solution was reduced to approximately 5 mL, cooled at 0 °C and filtered to obtain the crystalline product.

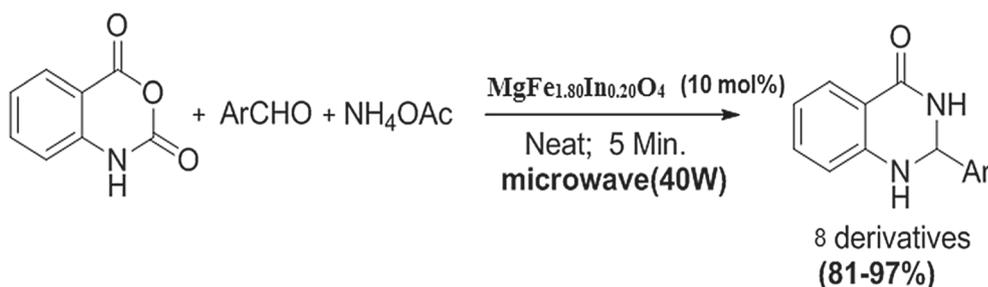
### 2.4 Characterisation techniques

The phase identification of the catalyst by X-ray diffraction (XRD) using a RIGAKU MINIFLEX diffractometer with Cu-K $\alpha$  radiation, in steps of 0.02°. The characteristic metal oxide band vibration for spinels was obtained in infrared spectra recorded on SHIMADZU IR -PRESTIGE-21. Particle size and morphology were determined using PHILIPS CM 200 transmission electron microscope (TEM), operating at an accelerating voltage of 200 kV. The surface area of the prepared catalyst was measured by multipoint BET on Quanta chrome Nova-1000 instrument. The <sup>1</sup>H NMR spectra of a few organic compounds are recorded using 400 MHz on Bruker machine. TMS was used as an internal standard and CDCl<sub>3</sub> and DMSO as solvents depending on the solubility of compounds.

## 3. Results and Discussion

### 3.1 XRD

The phase identification of the catalyst by X-ray diffraction (XRD) was carried out using a RIGAKU



**Scheme 2.** Synthesis of 2,3 dihydroquinazolinones-4(1H)-one.

MINIFLEX diffractometer with Cu-K $\alpha$  radiation, in steps of 0.02°. X-ray powder pattern displayed in Figure 1 showed the formation of pure single-phase compounds. All peaks were indexed to the cubic structure of spinel ferrite and matched with the JCPDS File No.01-089-3084. The broadening of peaks suggested the smaller size of the particles. The lattice parameter and the crystallite size calculated by Scherrer formula are shown in Table 1. The crystallite size for the doped sample is lowered whereas the lattice parameter is found to increase on doping.

### 3.2 Infrared and TEM analysis

The infrared spectra also showed the presence of Fe-O bands corresponding to the octahedral and tetrahedral stretching, thus confirming the spinel ferrite structure. (Figure S1 in Supplementary Information). Figure 2 displays the TEM image of MgFe<sub>2</sub>O<sub>4</sub> and MgFe<sub>1.80</sub>In<sub>0.20</sub>O<sub>4</sub> catalysts, where spherical nature is clearly seen with few agglomerates owing to magnetic property of the compound. The average particle size of the pristine compound is around 30 nm whereas for the doped it is around 15 nm. The lowering of particle size greatly affects the surface area of the catalyst and it is well exploited in the reactions further.

### 3.3 BET surface area analysis

The surface area of the prepared catalyst was measured by multipoint BET on Quanta chrome Nova-1000 instrument. First, the sample was degassed for 12 h followed by nitrogen adsorption/desorption studies. The surface area obtained by multipoint analysis for the pristine sample (MgFe<sub>2</sub>O<sub>4</sub>) is 26.01 m<sup>2</sup>/g whereas for MgFe<sub>1.80</sub>In<sub>0.20</sub>O<sub>4</sub> it is 40.78 m<sup>2</sup>/g. The pore volume also followed the same trend where the obtained value for MgFe<sub>2</sub>O<sub>4</sub> is 0.06761 cc/g and for MgFe<sub>1.80</sub>In<sub>0.20</sub>O<sub>4</sub> is 0.11861 cc/g. An

increase in surface area for the doped sample could be attributed to the lowered crystallite and particle size as shown in Table 1. The BET isotherms for the MgFe<sub>2</sub>O<sub>4</sub> and MgFe<sub>1.80</sub>In<sub>0.20</sub>O<sub>4</sub> are displayed in Figures S2 and S3 (Supplementary Information). The increased surface area serves as an advantage for its catalytic behavior. In<sup>3+</sup> doping might have also introduced some more defects which can further aid in the catalytic activity.

### 3.4 Magnetic studies

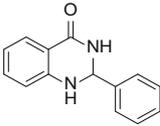
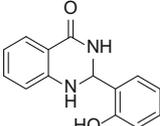
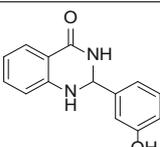
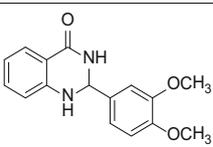
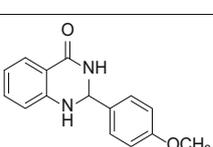
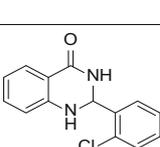
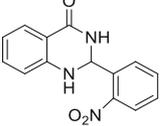
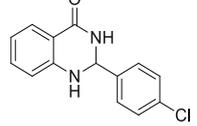
The Magnetic properties of MgFe<sub>2</sub>O<sub>4</sub> and MgFe<sub>1.80</sub>In<sub>0.20</sub>O<sub>4</sub> catalysts studied at room temperature were carried out on Vibrating Sample Magnetometer (VSM). Figure 3 displays the *MH* curves for both compounds. The catalysts exhibit super-paramagnetic nature. Indium doping decreases the saturation magnetization which is attributed to the octahedral occupancy of In<sup>3+</sup> ions. There is also a slight reduction in the coercivity (*H<sub>c</sub>*) on doping making the material a perfect super-paramagnetic in nature. The magnetic properties are well used in catalytic reactions to easily separate the catalyst.

### 3.5 Catalysis

After characterization, the nanoparticles were tested for their catalytic activity. Henry reaction and quinazolinone synthesis are the two reactions studied using the prepared catalyst.

**3.5a Henry reaction:** The Henry reaction was studied first where the initial optimisation was carried out using p-NO<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>-CHO and NO<sub>2</sub>Me as the standard reaction. Both pristine as well as In doped MgFe<sub>2</sub>O<sub>4</sub> were screened for their catalytic performance. The blank reaction gave no product, indium doped MgFe<sub>2</sub>O<sub>4</sub> gave comparatively better yield (75%) than the pristine sample (70%). Further

**Table 3.** Synthesis of derivatives of quinazolinones using MgFe<sub>1.80</sub>In<sub>0.20</sub>O<sub>4</sub> catalyst.

Sr. No.	Aldehyde (Ar-CHO)	Product	Recrystallized yield (%)
1	Benzaldehyde		93
2	Salicylaldehyde		93
3	<i>m</i> -hydroxybenzaldehyde		87
4	Veratraldehyde		96
5	<i>p</i> -anisaldehyde		86
6	<i>o</i> -chlorobenzaldehyde		92
7	<i>p</i> -( <i>N,N</i> -dimethylamino) benzaldehyde		80
8	<i>o</i> -nitrobenzaldehyde		95
9	<i>p</i> -Chloro benzaldehyde		94

<sup>a</sup> All individuals coming within 1 m to inspect experimental setup and, in parentheses, all individuals that made attempts

<sup>b</sup> Proportion successful

efforts were made to screen the amount of catalyst required for the reaction. An increase in the yield of the product was obtained from 57% (with 10 mol%

catalyst) to 75% where 30 mol % of the catalyst was used; however further increase in the catalyst did not show any significant change in the yield

Several derivatives were prepared using 30 mol% of the catalyst using the following conditions given in Scheme 1. The results are tabulated in Table 2 given below:

The catalyst worked efficiently at room temperature giving products in fairly good yield. The compounds were initially characterized based on their melting points and IR values corresponding to hydroxyl and nitro group as mentioned in supplementary file. The <sup>1</sup>H NMR of some of the compounds was also recorded. All the data is discussed in the supplementary file (TS<sub>1</sub>).

The catalyst was recycled 3 times with negligible loss in activity. The results are shown in table TS<sub>2</sub> in the supplementary file.

**3.5b Synthesis of 2,3 dihydroquinazolinones-4(1H)-one:** For our initial studies, a model reaction of *p*-Cl-benzaldehyde isotopic anhydride and ammonium acetate in 1:1:1 ratio and 10 mol% catalyst under solvent-free conditions was carried out under microwave irradiation. MgFe<sub>2</sub>O<sub>4</sub> and MgFe<sub>1.80</sub>In<sub>0.20</sub>O<sub>4</sub> were the two catalysts screened for this reaction under microwave where former gave the yield of 90% whereas latter gave 94% yield. So MgFe<sub>1.80</sub>In<sub>0.20</sub>O<sub>4</sub> was chosen as the catalyst. Further optimization of the amount of catalyst was done during which it was observed that the 5 mol % of the catalyst gave 86% yield, best results were obtained with 10 mol % of the In doped catalyst (94%). Further increase in the catalyst did not show any significant change in the yield. Very poor yield was obtained when the reaction was conducted without any catalyst (Scheme 2).

Next, the applicability of this protocol was established by using various substituted aldehydes as shown in Table 3. Good yields of the quinazolinone derivatives were obtained with aldehydes having both electron-withdrawing as well as donating groups. The method also worked well with heteroaromatic aldehydes.

The compounds were recrystallised using ethanol. The Infrared values corresponding to carbonyl, amine and nitro are obtained. The NMR of some of the compounds was also recorded. All the data is discussed in the supplementary file (TS<sub>3</sub>).

Recyclability of the catalyst was also studied for up to 3 cycles. An initial 10% decrease in the yield was observed during the first cycle while the remaining

two cycles gave fairly constant yield. The results of the recyclability studies are given in Table TS<sub>4</sub> in supplementary Information. A decrease in the yield could be attributed to the difficulty in recovering the catalyst to 100% efficiency owing to its fine particle size.

#### 4. Conclusions

We could successfully carry out Henry reaction and synthesis of quinazolinones using In doped Mg Ferrite nanoparticles. The Lewis acidity inherited by the ferrites plays a vital role in their catalytic activity. The increase in activity for the doped sample could be attributed to the slight distortion in the structure leading to an increase in porosity and also the increase in the surface area owing to a decrease in particle size. The superparamagnetic nature was also enhanced on doping. Magnetic separation and easy handling are the highlights of the catalyst. Simple procedure for the preparation, recyclability of the catalyst and easy availability of raw materials makes the process economical. This method may find its potential in exploring the process at higher scales which needs to be studied. The catalyst can also be considered in future for studying several other organic transformations.

#### Supplementary Information (SI)

Supplementary information includes Infrared spectra of Catalysts (Figure S1), BET Isotherms of catalysts (Figure S2 and S3), IR, physical constants of products of Henry reaction (TS<sub>1</sub>) and quinazolinone synthesis (TS<sub>3</sub>), NMR data along with spectra (Figures S4 to S9 for Henry reaction and S10 to S14 for quinazolinone synthesis) and plausible mechanisms for the catalytic reactions (MS<sub>1</sub> and MS<sub>2</sub>). Supplementary information is available at [www.ias.ac.in/chemsci](http://www.ias.ac.in/chemsci).

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