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Magnetically recyclable  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>–HAP nanoparticles for the cycloaddition reaction of alkynes, halides and azides in aqueous media<sup>†</sup>

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A simple and novel  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> supported on hydroxyapatite (HAP) heterogeneous catalytic system is described that is useful in the synthesis of disubstituted 1,2,3-triazoles from terminal alkynes and *in situ* generated organic azide in aqueous media; this green methodology emerges as this new catalyst for the one-pot synthesis of 1,2,3-triazoles can be used in water without the addition of any reagent/base. The catalyst can be successfully recycled five times without significant loss of activity. It is important to note that 100% regioselectivity was observed for the cycloaddition reaction.

Over the past few decades iron-based catalysts and reagents have been found to be effective and promising alternatives to expensive transition metal catalysts, the major attributes being their inexpensive and sustainable nature, their relative nontoxicity and environmentally benign characteristics.<sup>1</sup> A simple magnetically driven separation of the catalyst from the reaction mixture makes the catalyst reusability easier than filtration or centrifugation and this accounts for the development of a plethora of synthetic methods employing such magnetically recovered catalysts.<sup>2</sup> Onepot synthetic operations using heterogeneous acid/base catalysts have attracted the attention of organic chemists because of their synthetic utility and ease of operation that includes easy isolation of product and recovery and recyclability of the catalysts.<sup>3</sup>

Triazoles are an important class of heterocyclic compounds and have a wide range of biological activities such as antiallergenic,<sup>4</sup> anti-infective agents,<sup>5</sup> anti-HIV,<sup>6</sup> and anti-bacterial.<sup>7</sup> Consequently, many newer synthetic methodologies have been advanced for the generation of triazoles using various catalysts<sup>8</sup> including some greener protocols.<sup>9</sup> Among the various methods for the regioselective synthesis of triazoles, the most commonly employed metals are copper<sup>10</sup> and ruthenium.<sup>11</sup> After the discovery of click chemistry, these reactions have recorded tremendous growth in organic synthesis and drug discovery.<sup>12</sup> The development of novel transition metal catalysts and environmentally benign catalytic protocols for the cycloaddition of alkynes to *in situ* generated azides in aqueous media is still an active area of research.

Nano-catalysis has become an active area of research, as these materials exhibit better catalytic activity due to the enhanced surface area towards organic reactions;<sup>13</sup> copper-supported magnetic nanoparticles have been investigated for the synthesis of disubstituted 1,2,3-triazoles.<sup>14</sup>

In a continuation of our efforts towards the design of magnetic nanocatalysts and their sustainable synthetic applications,<sup>15–17</sup> we herein present for the first time,  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> supported on hydroxyapatite (HAP) as a hitherto unknown novel catalyst for the cycloaddition reactions culminating in the synthesis of 1,2,3triazoles and their derivatives in water. Notably, no ligands, base or extra additives/reagents are needed for the reaction (Scheme 1). To the best of our knowledge this is the first report of a copper-free iron-based nanoparticle catalyst used in the cycloaddition reaction for the synthesis of triazoles.



Scheme 1  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>-HAP catalyzed cycloaddition reaction of alkynes and *in situ* generated azides in water.

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Fig. 1 FT-IR spectrum of the  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>-HAP catalyst.

## **Result and discussion**

The iron nanoparticles supported on hydroxyapatite ( $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>–HAP) were prepared by a simple co-precipitation method and characterized using various techniques such as XRD, FT-IR, SEM, TEM, TGA, ICP-AES, EDAX and BET surface area (ESI<sup>†</sup>).

The characteristic absorption bands due to the bending vibration mode of O-P-O surface phosphate groups in the hydroxyapatite shell were observed at 570 and 602 cm<sup>-1</sup> which were overlapping with the Fe-O stretching bands. Also, the stretching of the P-O bond appeared at 1041 cm<sup>-1</sup>, overlapping with the S-O stretching peak (Fig. 1).

The TEM images (10–35 nm) of the freshly prepared catalyst and the catalyst recovered after the fifth cycle are depicted in Fig. 2 indicating no change in the morphology of the  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>-HAP nanocatalyst occurred.

The EDAX spectrum of the  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>–HAP nanocatalyst shows the presence of Fe from the  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>, and Ca and P from the HAP (Fig. 3).

The XRD spectrum of the  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>-HAP is depicted in Fig. 4 which shows the crystalline nature of the nanocatalyst. The observed diffraction peaks agree with those of the tetragonal structure of  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>.

Nitrogen adsorption–desorption isotherms are depicted in Fig. 5 and reveal that the adsorption–desorption process is not reversible. The surface area, calculated using the BET method, revealed a value of 103 m<sup>2</sup> g<sup>-1</sup> for  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>–HAP.

To examine the catalytic activity of  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>–HAP, we began our investigation with the optimization of the reaction parameters. The reaction of phenyl acetylene, sodium azide and benzyl bromide in the presence of  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>–HAP in an aqueous medium was chosen as a model reaction.

The hydroxyapatite acts as a base and removes the acetylenic proton to form a Fe–HAP acetylide complex.<sup>18</sup> The Fe–HAP acetylide complex undergoes cycloaddition with an *in situ* formed azide to form a triazole. To probe the active species involved in the reaction, we carried out the reaction of diphenyl acetylene with benzyl bromide and sodium azide, but the reaction did not proceed, indicating the involvement of the acetylenic hydrogen in the mechanism of the reaction.

The various reaction parameters such as the influence of catalyst loading, time and temperature were investigated for the







Fig. 2 TEM images of the  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>-HAP nanocatalyst: (a) "fresh" catalyst and (b) "recovered" catalyst after the fifth run.

cycloaddition reaction. It was observed that an increase in the catalyst loading (Fe mol%) from 1 mol% to 5 mol%, resulted an increase in the yield of 1-benzyl-4-phenyl-1*H*-1.2.3-triazole up to 94% (Table 1, entries 2–4). The yield of the triazole reaction remained unchanged beyond 5 mol% (Table 1, entry 5). To check the influence of temperature on the yield of the triazole product, we carried out our model reaction at varying temperatures in the



Fig. 3 EDAX spectrum of the  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>-HAP catalyst.





Fig. 4 XRD pattern of the  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>-HAP catalyst.

range of 30 °C to 120 °C (Table 1, entries 6–9), showing that at 100 °C, the yield of the product was maximised to 94% (Table 1, entry 5). A further increase in temperature had no profound effect on the yield of the reaction.

It is important to note that reactions on only HAP did not take place; this clearly indicates that the role of  $Fe_2O_3$  is important in catalysing the reaction. Notably, for the model reaction 100% regioselectivity was observed.

With these optimized reaction conditions, the scope of the reaction was probed with an array of alkynes, aliphatic as well as aromatic halides and sodium azide (Table 2). Various aromatic and aliphatic halides and alkynes afforded moderate to good yields under these reaction conditions in an aqueous medium. Trace amounts of the triazole product were observed by GC-MS, when the reaction was carried out with hexyl and heptyl halides with phenyl acetylene, which can be attributed to a steric hindrance of the reaction centre by the alkane chain (entries not mentioned in Table 2).

Both aliphatic as well as aromatic halides gave moderate to good yields of the corresponding triazole derivatives (Table 2); usually aliphatic halides are known to be less reactive then aromatic ones.



Fig. 5 Nitrogen adsorption-desorption isotherm plot of the γ-Fe<sub>2</sub>O<sub>3</sub>-HAP catalyst.

 $\label{eq:table_$ 

	+ NaN <sub>3</sub> + [	Br F	e₂O₃-HAP I₂O, 100 °C	
Entry	Fe (mol%)	Time (h)	Temp. (°C)	Yield <sup><math>b</math></sup> (%)
Effect of	f catalyst loadir	ıg		
1	0	24	100	0
2	1	5	100	40
3	2	5	100	82
4	5	5	100	94
5	10	5	100	94
Effect of	ftemperature			
6	5	5	30	0
7	5	5	60	54
8	5	5	80	82
9	5	5	120	94
Effect of	f time			
10	5	1	100	35
11	5	3	100	72

 $^a$  Reactions were performed with phenyl acetylene (1 mmol), benzyl halide (1 mmol) and sodium azide (1.2 mmol) in 5 mL water.  $^b$  GC Yield

The reusability of the catalyst for the cycloaddition reaction of phenyl acetylene, sodium azide and benzyl bromide, was subsequently investigated (Fig. 6). It is noteworthy that the catalyst was successfully reused for five cycles, without any significant loss in activity (the  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>–HAP was separated by an external magnet).

Based on ICP-AES analysis, the Fe content in the catalyst was found to be 1.093 mmol  $g^{-1}$  before the reaction and 1.091 mmol  $g^{-1}$ , after the reaction, revealing that present reaction takes place heterogeneously with negligible leaching of Fe. Standard leaching experiments were conducted as reported earlier in the literature.<sup>19</sup> The model reaction was conducted for 20 min at 100 °C, then the hot reaction mixture was separated from the catalyst. The reaction mixture was then heated for 24 h, but no enhancement in the yield of the product was observed even after 24 h, and no Fe could be detected in the filtered solution by ICP-AES analysis. This result clearly verified that the reaction proceeded heterogeneously and no homogeneous catalyst was involved during the course of the reaction.

To measure the "greenness" of the  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>–HAP catalyzed cycloaddition reaction, we calculated the E-factor for the various iron catalyzed cycloaddition reactions. The comparison of  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>–HAP with different iron-based catalysts is depicted in Table 3. It was observed that the heterogeneous catalyst ( $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>–HAP) showed excellent relative performance compared to homogeneous iron catalysts presumably because of the large surface area which could promote the reaction.

## Experimental

NMR spectra were recorded on a Varian Mercury Plus NMR spectrometer (<sup>1</sup>H NMR at 300 MHz and <sup>13</sup>C NMR at 75 MHz) in pure deuterated solvents. IR spectra were recorded using a Perkin

## Table 2 Application of the optimized reaction protocol to various substrates<sup>ab</sup>

Entry	Halide	Alkyne	Triazole	Time (h)	Isolated yield (%)
1	Br		N=N	5	87
2	CI		N=N	5	86
3	CI			5	85
4	CI			5	90
5	CI			5	85
6	F		F N N	5	87
7	Br		N=N N	6	79
8	CI		N=N	6	78
9	Second Se		N=N N	6	80
10			N=N N	6	80
11	Br		N=N	6	76

### Table 2 (Continued)

Communication

Entry	Halide	Alkyne	Triazole	Time (h)	Isolated yield (%)
12	Br			5	81
13	CI			5	83
14	O= ↓ OEt			5	84
15	<b>├</b> ─Br			5	72
16	Br			7	81
17	CI			7	84
18	CI			7	81
19	CI			7	85
20	CI			7	84
21	F CI			7	89
22	Br			7	80



#### Table 2 (Continued)

Entry	Halide	Alkyne	Triazole	Time (h)	Isolated yield (%)
23	Br	$\rightarrow =$	N°NN N°NN	12	69
24	Br		N×N N×N	8	81
25	O= ←Br OEt			8	85
26	CI			8	80
27	CI			8	79
28	F Cl			8	80
29	F CI			8	82
30	Br			9	80
31	Br			9	84
32	Br			9	89

#### Table 2 (Continued)



<sup>*a*</sup> Reactions were performed with phenyl acetylene (1 mmol), halide (1 mmol) and sodium azide (1.2 mmol) in 5 mL water, catalyst (0.05 g, 5 mol% Fe) 100  $^{\circ}$ C. <sup>*b*</sup> The identity of the products was confirmed by IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR and GC-MS.

Elmer FT-IR spectrum 100 spectrophotometer. Mass spectra were determined using a Shimadzu GCMS QP 2010 instrument. GC of all compounds were obtained on a Thermo Scientific GC [capillary column, 30 m  $\times$  60 mm, ID-BP1 0.25 UM]. Melting points were determined in capillary tubes using digital melting point apparatus. Elemental analysis was done on a Harieusrapid analyser. Column chromatography of some compounds was



Fig. 6 Reusability of the  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>-HAP catalyst (reactions were performed with phenyl acetylene (1 mmol), benzyl bromide (1 mmol) and sodium azide (1.2 mmol) in 5 ml water, catalyst (0.05 g, 5 mol% of Fe), 100 °C.

carried out using silica gel with 60–120 mesh size. The chemicals required were purchased from Sigma Aldrich and were used as received. Wide angle XRD patterns of the catalyst were obtained on a Rigaku, Japan, miniflex X-ray diffractometer with a monochromatic Cu-K $\alpha$  beam ( $\lambda = 0.154$  nm). The diffractometer was operated at 30 kV and 15 mA using a scanning step of 2 in two theta and a dwell time of 1 s was used.

#### General procedure for the cycloaddition reaction

In a 10 ml round bottom flask fitted with a magnetic stirrer, the catalyst (0.05 g), phenyl acetylene (1 mmol), sodium azide (1.2 mmol) and benzyl bromide (1 mmol) were stirred in water (5 ml) at 100 °C for 5 h. The reaction progress was monitored by TLC and the catalyst was recovered using an external magnet. The reaction mixture was quenched and the product was extracted with ethyl acetate. The organic layer was then separated out using a separating funnel. The separated layer was washed with water and dried over sodium sulfate. The ethyl acetate solvent was removed using a rotary evaporator, which left the pure desired product. The recovered catalyst was reused for further runs without removing the catalyst from the flask. All of the prepared compounds were confirmed by GC-MS, IR,  $^{1}$ H and  $^{13}$ C NMR.

#### Catalyst recycling procedure

An important aspect for heterogeneous catalysis is the reusability of the catalyst. To achieve this goal, the reaction of phenyl acetylene, benzyl bromide and sodium azide was chosen to test the catalyst reusability. After completion of reaction, the  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>-

Table 3	The	comparison	of	different iron	containing	catalysts	for	the	formation	of	triazole in	aqueous	media <sup>a</sup>	

Catalyst (mol% of Fe)	Time (h)	Temp (K)	GC yield (%)	E-Factor	Catalyst reusability
FeSO <sub>4</sub> (10)	12	373	18	381.95	No
$FeCl_3 \cdot 6H_2O(5)$	12	373	15	572.42	No
$FeCl_3 \cdot 6H_2O(10)$	12	398	22	295.11	No
$NH_4(FeSO_4)_2 \cdot 12H_2O(10)$	12	298	35	122.97	No
$\gamma$ -Fe <sub>2</sub> O <sub>3</sub> /HAP (5)	5	373	94	13.63	Yes

<sup>*a*</sup> Reactions were performed with phenyl acetylene (1 mmol), halide (1 mmol) and sodium azide (1.2 mmol) in 5 mL water, catalyst (0.05 g, 5 mol% Fe), 100 °C.

HAP was separated using an external magnet and the reaction mixture was extracted in ethyl acetate. The organic layer was separated and passed through anhydrous sodium sulphate. After separating the product, fresh aliquots of phenyl acetylene (1 mmol), benzyl bromide (1 mmol) and sodium azide (1.2 mmol) were added to the reaction flask for the next cycle of the reaction. It was observed that the catalyst showed excellent activity for the cycloaddition reaction even after the fifth cycle in aqueous media.

## Conclusions

In summary,  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>-HAP nanoparticles have been developed as a heterogeneous catalyst for the cycloaddition reaction of alkynes and in situ formed organic azides in aqueous media. The use of an iron-based heterogeneous catalyst instead of a more commonly used copper or ruthenium catalyst renders the reported methodology comparatively more economical, experimentally simple, and, therefore, appealing for industrial use. Moreover, the presented protocol has several advantages: (1) the catalyst can be reused in up to five consecutive cycles without loss of catalytic activity, (2) recovery of the catalyst can be accomplished easily using a simple external magnet, (3) the starting materials are readily available and are inexpensive, (4) the catalyst preparation is simple and facile, (5) the present protocol is applicable to a combination of substrates such as aromatic and aliphatic alkynes, and halides containing aromatic and aliphatic groups. Further studies are on going to understand the mechanism of the reaction and other applications of the catalyst in various organic transformations.

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