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ORIGINAL PAPER

TEMPO supported amine functionalized magnetic titania: a magnetically recyclable catalyst for the aerobic oxidative synthesis of heterocyclic compounds

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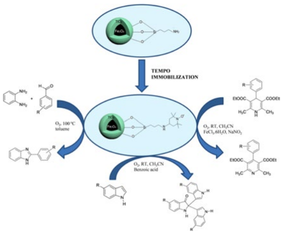
Abstract

The present protocol uncover a new strategy to synthesize highly efficient solid TEMPO based catalyst in which 4-oxo-TEMPO was covalently tethered to the surface of amine functionalized magnetic titania. The chemical nature and structure of the synthesized catalyst was authenticated by various techniques such as Fourier transform infrared spectroscopy, thermogravimetric analysis, X-ray powder diffraction, field emission gun scanning electron microscopy, high resolution transmission electron microscopy, energy dispersive X-ray spectroscopy, elemental analysis, and vibrating sample magnetometer. FT-IR confirmed the immobilization of titania, APTES, and TEMPO on the magnetic nanoparticles. Thermal behaviour of the catalyst was studied by TGA. Morphology of the catalyst was investigated by FEG-SEM and HR-TEM analysis. Furthermore, loading content of TEMPO on the catalyst was quantified by elemental analysis and found to be 0.61 mmol/g. Magnetic properties of the catalyst were investigated by VSM analysis. The catalytic performance of the synthesized catalyst has been investigated for the oxidative synthesis of benzimidazoles, oxidative aromatization of 1,4-dihydropyridines, and oxidative trimerization of indoles using molecular oxygen. In addition, the catalyst could be successfully recycled and reused up to five times without the prominent loss of catalytic activity.

Graphic abstract



Keywords TEMPO · Magnetic titania · Oxidative synthesis · *N*-Heterocycles · Molecular oxygen

Introduction

Selective oxidation of organic molecules is potentially an attractive transformation which provides the basis for streamlined conversion of simple precursors into fine chemicals and intermediates [1]. In particular, the oxidative synthesis of heterocyclic compounds has been intensively explored in the chemical industry. Among heterocycles, N-heterocycles are of extensive interest because these are pivotal building blocks in natural products and pharmaceuticals [2]. Various

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methods have been developed for carrying out the oxidative synthesis of N-containing heterocyclic compounds. However, most of these methods suffer from drawbacks such as drastic reaction conditions, low yields, and co-occurrence of several side reactions. In recent times, lot of work is being carried out for methodology improvement, especially in terms of waste product minimization and the use of renewable materials. In this context, molecular oxygen has emerged as one of the most favourable oxidants due to its remarkable advantages, including its abundance, safe use, low cost, and high atom economy. Many catalytic systems have been developed for catalysing the synthesis of heterocyclic compounds in the presence of molecular oxygen [3, 4] and one of the most impressive approaches involves the use of stable nitroxyl radicals.

Among the various persistent nitroxyl radicals, 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) is the most prominent free radical which is stabilized by both thermodynamic and kinetic effects [5]. TEMPO has attracted accumulative consideration not only because of its versatility and unique redox properties, but also due to its application in various strategic domains [6–9]. Although TEMPO based systems show high efficiency for various organic transformations, but its recovery from the reaction medium is inherently difficult due to its unique physicochemical properties which leads to industrial wastes and additional costs. Keeping in view the above mentioned limitations and increasing concerns about the environment, various organic or inorganic supports such as polymers [10–12], silica [13, 14], ionic liquids [15], graphene oxide [16], microporous organic nanotubes [17], C-60 [18], magnetic core–shell nanoparticles [19], and carbon-coated Co ferromagnetic nanoparticles [20] are being used to immobilize TEMPO. The most frequently used support is silica, but the problem associated with silica is its instability under basic conditions that leads to loss of active phase during chemical reactions [21]. Magnetic titania has attracted a considerable amount of attention as a new type of catalyst support because of its merits like magnetic property, easy modification, non-toxicity, good bio-compatibility, cost-effectiveness, and also its stability in different chemical environment. Also, the use of titania as support for the immobilization of TEMPO has been described only one time in literature [22]. Further enhancement of the multifunctional properties of the magnetic titania was done by (3-aminopropyl)triethoxysilane (APTES), which proved to be highly significant for the coupling of TEMPO to the surface of the magnetic titania.

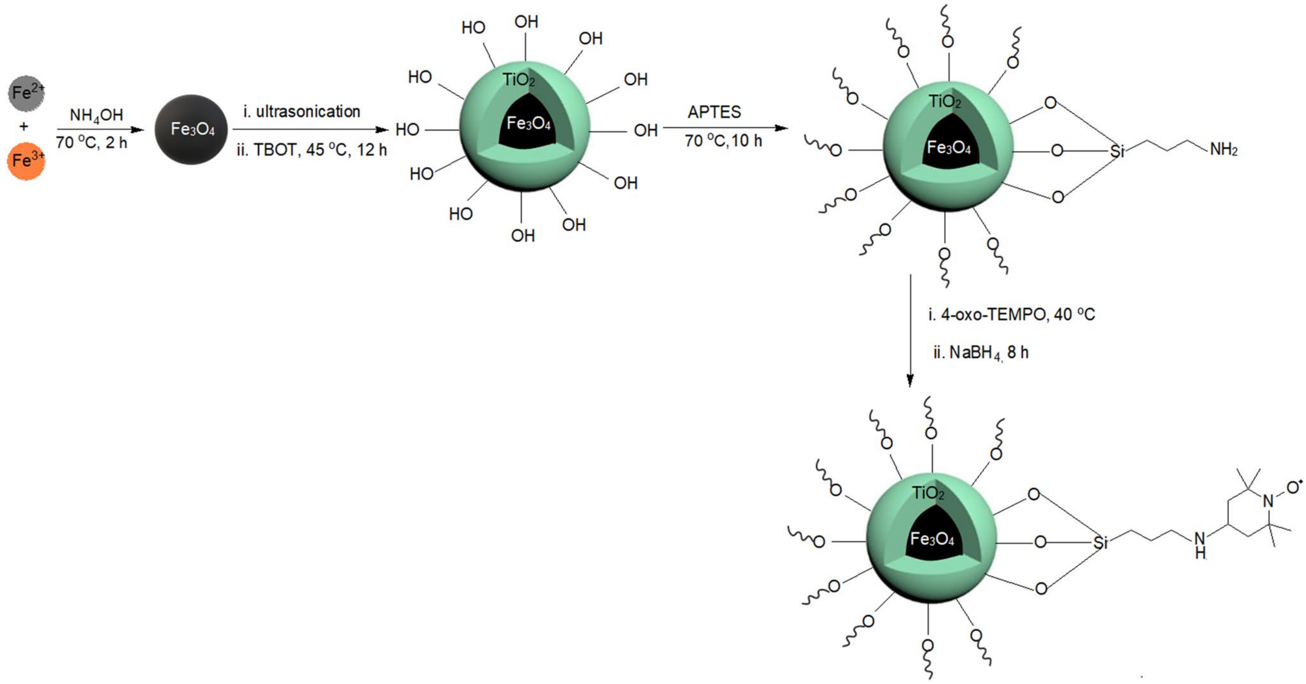
Various aerobic oxidation pathways have been reported in the literature for the oxidative synthesis of benzimidazoles using Co/SBA-15 nanocatalyst [23], CuI nanoparticles [24], $Fe(NO_3)_3$/TEMPO [25]; oxidative aromatization of 1,4-dihydropyridines catalysed by heterogeneous cobalt catalyst at 90 °C [26], Co-naphthenate in chloroform at 61 °C [27], activated carbon in acetic acid [28]; and oxidative trimerization of indoles making use of TEMPO/$CuCl_2$ and benzoic acid at 60 °C [29], TEMPO and benzoic acid at 65 °C [30]. However, most of these methods suffer from drawbacks such as use of transition metal catalyst, long reaction time, harsh reaction conditions, low yields, and tedious workup. Subsequently, the development of a convenient and an eco-friendly method for the synthesis of these N-heterocycles compounds would be highly enviable. Herein, stable radical based heterogeneous catalytic system has been developed, where TEMPO was supported onto amine functionalized magnetic titania and was fully characterized with different techniques such as Fourier transform infrared (FT-IR) spectroscopy, thermogravimetric analysis (TGA), X-ray powder diffraction (XRD), field emission gun scanning electron microscopy (FEG-SEM), high resolution transmission electron microscopy (HR-TEM), energy dispersive X-ray (EDX) spectroscopy, elemental analysis (CHN), and vibrating sample magnetometer (VSM). To the best of our knowledge, the catalytic activity of heterogeneous TEMPO for the oxidative synthesis of heterocycles has not been reported yet. This fact made us to study the activity of TEMPO based catalyst for carrying out the oxidative synthesis of benzimidazoles, oxidative aromatization of 1,4-dihydropyridines, and oxidative trimerization of indoles using O_2 as the green oxidant.

Results and discussion

Characterization of TEMPO@APTES–TiO_2–Fe_3O_4

In the present work, magnetically recoverable heterogeneous TEMPO based catalyst, TEMPO@APTES–TiO_2–Fe_3O_4 was successfully synthesized (Scheme 1). Initially, Fe_3O_4 nanoparticles were synthesized by the co-precipitation of aq. solution of $FeSO_4.7H_2O$ and $Fe_2(SO_4)_3$ and then titania was in situ coated onto the surface of Fe_3O_4, which helps in stabilizing magnetite nanoparticles from oxidation and provides the surface charges needed to prevent aggregation. The magnetic titania nanoparticles were then functionalized with APTES, which acted as an excellent inter-particle linker for the immobilization of TEMPO. The amino group present in APTES enables the magnetic titania material to be modified with TEMPO by interacting with the corresponding oxo group of TEMPO. The prepared catalyst was separated magnetically, washed successively with ethanol, and dried under vacuum. The TEMPO@APTES–TiO_2–Fe_3O_4 was characterized by various techniques like FT-IR, TGA, XRD, FEG-SEM, HR-TEM, EDX, CHN, and VSM.

The investigation about the presence of different functional groups in the catalyst was done with FT-IR spectroscopy (S1). It showed broad peak at 3468 cm^{-1}, which was attributed to the O–H stretching mode of the hydroxyl



groups present on the surface, whereas peak at 3404 cm^{-1} corresponds to N–H stretching vibrations [31]. The peak at 2926 cm^{-1} was assigned to the C–H stretching vibration of the propyl group present in APTES, which confirms the immobilization of APTES onto Fe_3O_4-TiO_2 [32]. The immobilization of TEMPO was confirmed by the peaks in the region 1400–1340 cm^{-1} corresponding to the bending modes of CH_3 group (1480 cm^{-1}) and stretching vibrations of N–O radical (1400–1340 cm^{-1}) [33–35]. The peak at 894 cm^{-1} was presumably due to the stretching vibrations of the Ti–O–Si bond [36], whereas the broad peak centred at 626 cm^{-1} is an envelope of stretching vibrations due to Ti–O of the TiO_2 and Fe–O of Fe_3O_4 nanoparticles. These results confirmed the immobilization of APTES and TEMPO onto magnetic titania. The thermal stability of TEMPO@APTES–TiO_2–Fe_3O_4 was determined by thermogravimetric analysis (TGA). The TGA graph of TEMPO@APTES–TiO_2–Fe_3O_4 (S2) showed an initial weight loss of 3.14% up to 100 ℃ due to the desorption of adsorbed water from the catalyst surface, while the weight loss from 100–300 ℃ may be due to the thermal crystal phase transformation from Fe_3O_4 to γ-Fe_2O_3 and also due to loss of some organic functionalities. Thus, from the TGA curve, it can be concluded that the catalyst is stable up to 100 ℃ and thus, it is safe to carry out the reactions up to 100 ℃.

The information about the phase purity was determined by X-ray diffraction patterns. XRD pattern of TEMPO@APTES–TiO_2–Fe_3O_4 (Fig. 1) exhibited diffraction patterns at $2\theta = 30.2°$, 35.4°, 42.3°, 57.3°, and 62.3°, which corresponds to (111), (220), (311), (440), and (511) planes of cubic phase of Fe_3O_4 lattice [37]. Further, peaks at $2\theta = 25.2°$, 48.1°, and 53.8° correspond to the (101), (200), and (105) planes of the cubic phase TiO_2 [38]. The sharp and strong peaks showed that the synthesized catalyst is crystalline in nature, which has been further confirmed by HR-TEM image. Thus, XRD spectra suggested the successful coating of titania onto Fe_3O_4 nano-particles.

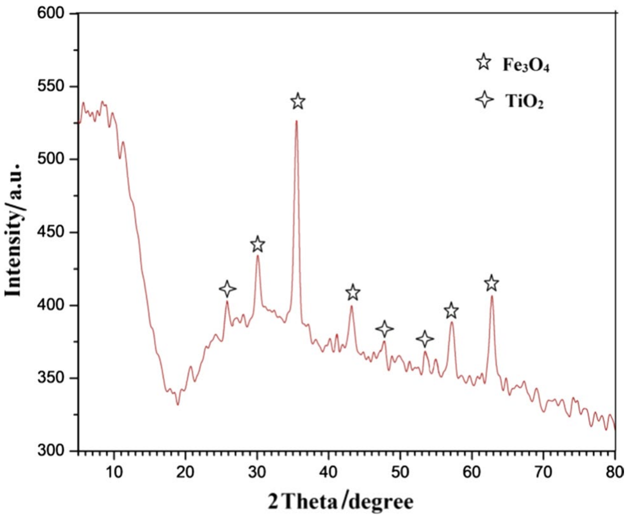


Fig. 1 XRD spectrum of TEMPO@APTES–TiO_2–Fe_3O_4

The shape and surface morphology of TEMPO@APTES–TiO_2–Fe_3O_4 was examined by scanning electron microscopy (Fig. 2). SEM images showed the formation of well-dispersed particles showing floccules like structure and most of the particles assumed quasi-spherical shape. On the other hand, the surface of the composite was non-smooth,

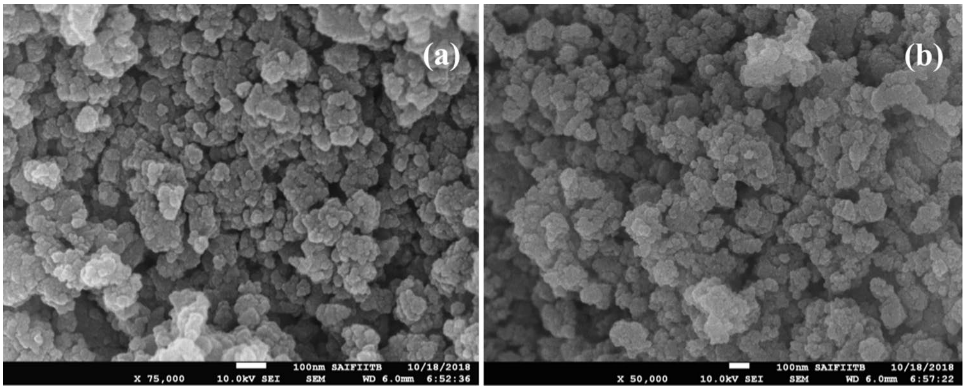


Fig. 2 FEG-SEM images of TEMPO@APTES–TiO_2–Fe_3O_4

which is responsible for increase in the surface area of the catalyst and, thus the increased catalytic efficiency.

The HR-TEM images were recorded to obtain the information about particle size and fine microstructure of TEMPO@APTES–TiO_2–Fe_3O_4. HR-TEM micrographs (Fig. 3) revealed that the catalyst has composite type nature. Moreover, it was also deciphered that APTES forms uniform covering over the Fe_3O_4–TiO_2 composite and thus, responsible for the better anchoring of TEMPO onto the support material. The black spots refer to the Fe_3O_4–TiO_2 composite, whereas light grey colour appeared around the Fe_3O_4–TiO_2 composite indicated its covering with APTES. Additionally, HR-TEM images showed the lattice fringes with an inter-planar spacing of approximately 0.485 nm corresponding to the (111) lattice plane of cubic Fe_3O_4 (Fig. 3c). The selected area diffraction pattern (SAED,

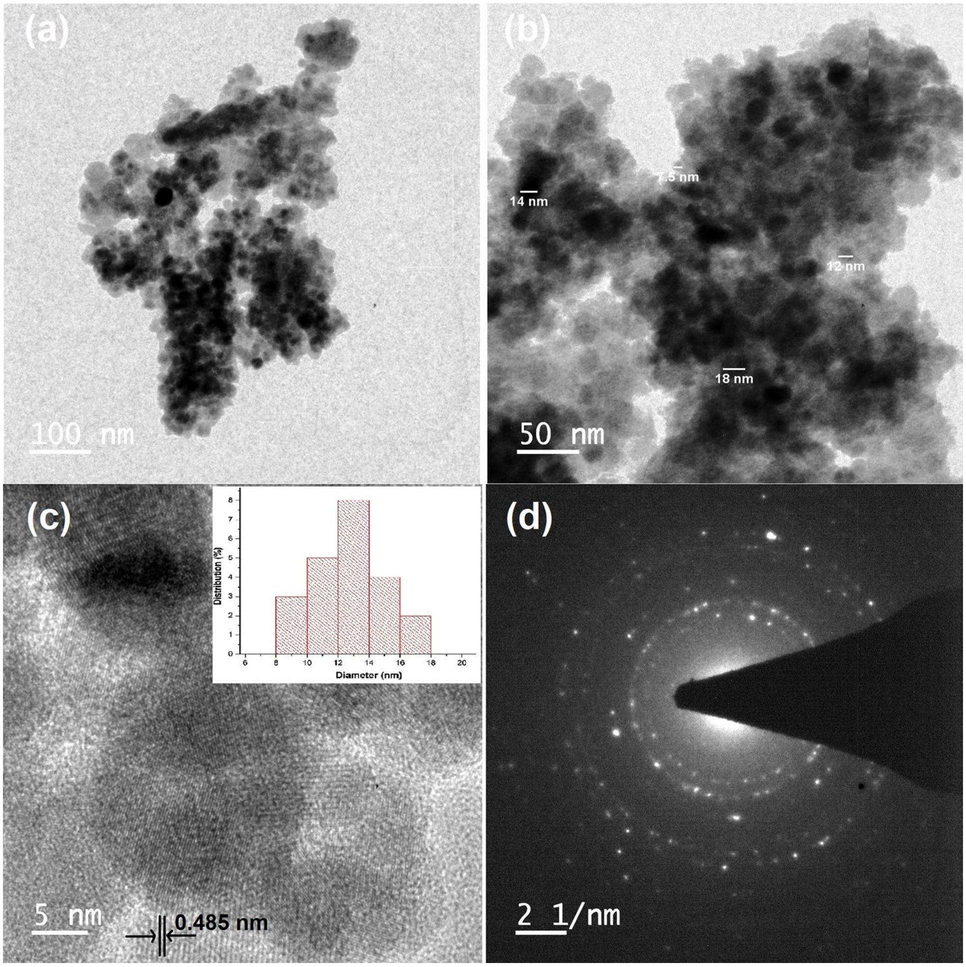


Fig. 3 HR-TEM images and particle size histogram of TEMPO@APTES–TiO_2–Fe_3O_4

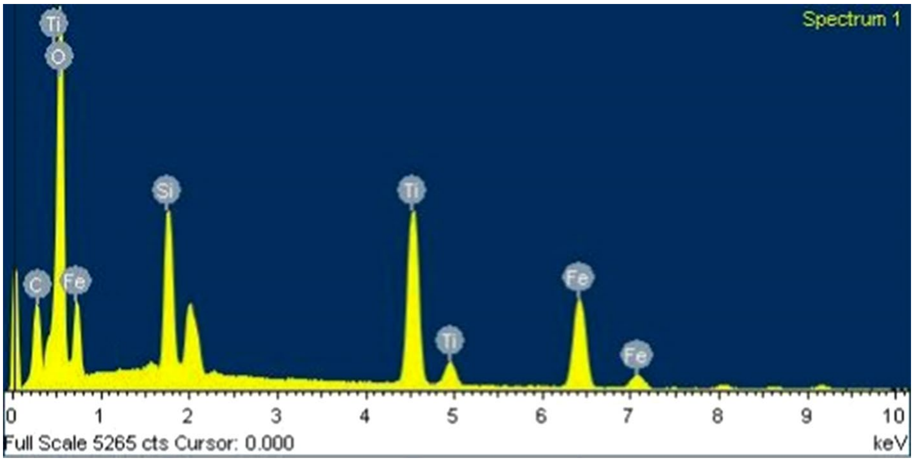


Fig. 4 EDX spectrum of TEMPO@APTES–TiO_2–Fe_3O_4

Table 1 Elemental analysis and TEMPO loading

Entry	Sample	*N*/wt%	TEMPO loading / mmol g^{-1}
1	APTES–TiO_2–Fe_3O_4	1.150	–
2	TEMPO@APTES–TiO_2–Fe_3O_4	2.054	0.61

Fig. 3d) showed small spots forming concentric rings, thereby confirming the polycrystalline nature of the catalyst. The average particle size of the composite was 12–14 nm as depicted by the histogram.

The elemental composition of TEMPO@APTES–TiO_2–Fe_3O_4 as well as its chemical purity was analysed by using energy dispersive X-ray spectroscopy (EDX). The EDX spectrum of TEMPO@APTES–TiO_2–Fe_3O_4 (Fig. 4) confirms the presence of C, Ti, O, Si, and Fe elements.

To determine the loading of TEMPO on the catalyst, elemental analysis has been undertaken which showed that the catalyst (TEMPO@APTES–TiO_2–Fe_3O_4) has an appreciably higher nitrogen content than APTES–TiO_2–Fe_3O_4 (Table 1). The loading of TEMPO on the catalyst is estimated to be 0.61 mmol/g. Thus, CHN study showed the evidence for the successful grafting of APTES and TEMPO over the Fe_3O_4–TiO_2 support.

The magnetic properties of the synthesized and reused catalysts (after 5th run) were investigated by using vibrating sample magnetometry (VSM) at room temperature. VSM curves of fresh and reused TEMPO@APTES–TiO_2–Fe_3O_4 are shown in Fig. 5. The magnetization curve unveils the value of saturation magnetization (Ms) of ~ 20.49 emu/g for the fresh and ~ 16.69 emu/g for the reused solid TEMPO. There is small decrease in the saturation value of reused catalyst, but still the catalyst show fast response to the external magnet and can be readily separated magnetically. The coating of TiO_2 onto Fe_3O_4 NPs protects them from oxidation, reinforces the magnetic stability and enables it to disperse rapidly when the magnetic field is removed. As seen from Fig. 5, the curves intersect the origin which means that the catalyst exhibit superparamagnetic behaviour [39].

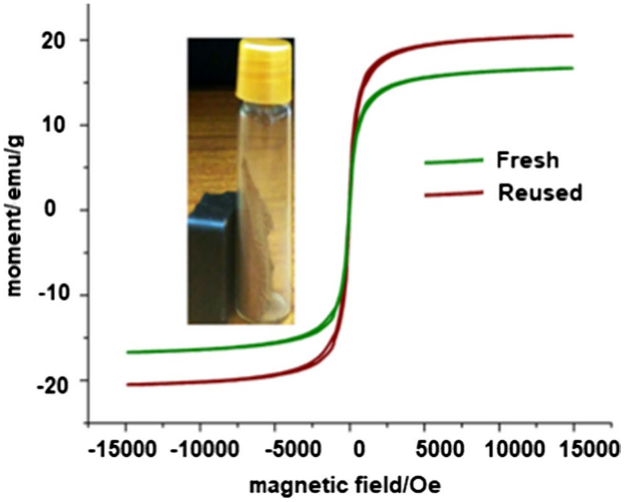


Fig. 5 Room temperature magnetization curves of TEMPO@APTES–TiO_2–Fe_3O_4 (fresh and reused)

Catalytic activity of TEMPO@APTES–TiO_2–Fe_3O_4 for the synthesis of 2-substituted benzimidazoles

Considering the immense biological significance of 2-substituted benzimidazoles, our main focus was to develop a simple and greener approach for their synthesis using TEMPO@APTES–TiO_2–Fe_3O_4. To optimize the reaction conditions for the synthesis of 2-substituted benzimidazoles, the reaction between *o*-phenylenediamine (1 mmol) and 4-methoxybenzaldehyde (1 mmol) was selected as the model reaction. To optimize the appropriate catalyst amount, the model reaction was performed by varying the catalyst amount to 0.05 g, 0.1 g, 0.15 g, and 0.2 g, and the best results were obtained with 0.1 g of the catalyst. Further decrease in the amount of the catalyst from 0.1 g to 0.05 g led to decrease in yield of the product (entry 2, Table 2) and also with increasing the catalyst amount did not increase the yield considerably (entries 4, 5, Table 2). To compare the catalytic activity of solid TEMPO with its precursors, the model reaction was performed using 0.1 g of precursors of the developed catalyst while keeping the other conditions unaltered. Unfortunately, the yields obtained with the precursors were not satisfactory (entries 6–8, Table 2). To select the best solvent, the model reaction was carried out in different solvents such as ethanol, toluene, and acetonitrile, wherein the reaction in ethanol gave low yield (entries 1, 2, Table 3). Further, the yield has been improved in acetonitrile (entries 3, 4, Table 3), but the best results were obtained in toluene (entry 6, Table 3). Also, among oxidants i.e., air and O_2, the good results in terms of time, yield, and selectivity were obtained with O_2. Thus, toluene was selected as the optimized solvent and O_2 as the oxidant to carry out the oxidative synthesis of 2-substituted benzimidazoles. With optimal conditions in hand, the scope of the catalytic system was explored for the reaction between *o*-phenylenediamine and diversely substituted aldehydes (Table 4). The reactions were equally facile with both electron-donating and electron-withdrawing groups present in aldehyde.

Catalyst testing for oxidative aromatization of 1, 4-dihydropyridines

For the oxidative aromatization of 1,4-dihydropyridines, the reaction conditions were optimized using diethyl 4-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate as the test substrate at room temperature and results revealed that oxidative aromatization of

Table 2 Optimization of the reaction conditions for the oxidative synthesis of N-containing heterocyclic compounds using molecular oxygen

Entry	Catalyst	Amount/g	Benzimidazoles[a]		Pyridines[b]		Indolin-3-one[c]	
			Time/h	Yield/%[d]	Time/h	Yield/%[d]	Time/h	Yield/%[d]
1	No catalyst	–	12	NR	7	NR	24	NR
2	TEMPO@APTES–TiO_2–Fe_3O_4	0.05	5	80	3.5	80	19	70
3	**TEMPO@APTES–TiO_2–Fe_3O_4**	**0.1**	**5**	**92**	**3.5**	**94**	**19**	**85**
4	TEMPO@APTES–TiO_2–Fe_3O_4	0.15	5	93	3.5	95	19	86
5	TEMPO@APTES–TiO_2–Fe_3O_4	0.2	5	93	3.5	95	19	86
6	Fe_3O_4	0.1	12	10[e]	7	Traces	24	Traces
7	Fe_3O_4–TiO_2	0.1	12	15[e]	7	15[e]	24	15[e]
8	Fe_3O_4–TiO_2–APTES	0.1	12	25[e]	7	20[e]	24	25[e]

Reaction conditions: [a]0.13 g 4-methoxybenzaldehyde (1 mmol), 0.10 g *o*-phenylenediamine (1 mmol) at 100 °C in 5 cm^3 toluene under O_2 atmosphere. [b]0.359 g diethyl 4-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1 mmol), 0.013 g $FeCl_3 \cdot 6H_2O$ (0.05 mmol), 0.0034 g $NaNO_2$ (0.05 mmol), 5 cm^3 acetonitrile under O_2 atmosphere at room temperature. [c]0.117 g Indole (1 mmol), 0.06 g benzoic acid (0.5 mmol), 5 cm^3 acetonitrile under O_2 atmosphere at room temperature. [d]Isolated yield. [e]Column chromatography yield

Table 3 Effect of solvent and oxidant on the TEMPO@APTES–TiO_2–Fe_3O_4 catalysed oxidative synthesis of N-containing heterocyclic compounds

Entry	Solvent	Oxidant	Benzimidazoles[a]		Pyridines[b]		Indolin-3-one[c]	
			Time/h	Yield/%[d]	Time/h	Yield%[d]	Time/h	Yield/%[d]
1	Ethanol	Air	5	30	3.5	25	19	30
2	Ethanol	O_2	5	39	3.5	35	19	40
3	Acetonitrile	Air	5	70	3.5	85	19	78
4	Acetonitrile	**O_2**	5	77	**3.5**	**94**	**19**	**85**
5	Toluene	Air	5	82	3.5	65	19	60
6	Toluene	**O_2**	**5**	**92**	3.5	70	19	69

Reaction conditions: [a]0.13 g 4-methoxybenzaldehyde (1 mmol), 0.10 g *o*-phenylenediamine (1 mmol), and 0.1 g TEMPO@APTES–TiO_2–Fe_3O_4 (0.06 mmol TEMPO) at 100 °C in 5 cm^3 toluene under O_2 atmosphere. [b]0.359 g diethyl 4-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1 mmol), 0.013 g $FeCl_3 \cdot 6H_2O$ (0.05 mmol), 0.0034 g $NaNO_2$ (0.05 mmol), 0.1 g TEMPO@APTES–TiO_2–Fe_3O_4 (0.06 mmol TEMPO), and O_2 atmosphere in 5 cm^3 acetonitrile at room temperature. [c]0.117 g Indole (1 mmol), 0.06 g benzoic acid (0.5 mmol), 0.1 g TEMPO@Fe_3O_4–TiO_2–APTES (0.06 mmol TEMPO), and O_2 atmosphere in 5 cm^3 acetonitrile at room temperature. [d]Isolated yield

1,4-dihydropyridines using 0.1 g of catalyst with O_2 as an oxidant in acetonitrile gave 75% yield in 5 h. However, it has been reported in the literature that the combination of TEMPO with some metallic and non-metallic elements results in increased catalytic activity [40, 41]. In this context, we attempted to improve the yield and reduce the time of the oxidative aromatization by using catalytic amount of ferric chloride and sodium nitrite. It was found that the yield of the corresponding product was increased to 94% in 3.5 h (entry 3, Table 2). This indicates that $FeCl_3{\cdot}6H_2O$ and $NaNO_2$ plays an important role in promoting the catalytic activity of TEMPO for the aromatization of 1,4-DHPs. To demonstrate the generality of the developed protocol, various 1,4-dihydropyridines substituted with electron-releasing and electron-withdrawing groups were subjected to oxidation under the optimized conditions and excellent results were obtained (Table 5). The presence of electron-withdrawing or electron-donating substituents on the 1,4-DHP did not affect the course of the reaction.

Catalyst testing for the oxidative trimerization of indoles

The excellent catalytic activity of catalyst for the oxidative synthesis of 2-substituted benzimidazoles and oxidative aromatization of 1,4-dihydropyridines motivated us to extend the application of the developed catalyst for the oxidative trimerization of indoles to give 2,2-disubstituted indolin-3-ones. Initially, oxidative trimerization of indole was selected as the model reaction to select the optimum reaction conditions. The reaction was performed using various precursors of the catalyst as well as different amounts of the catalyst and the results revealed that 0.1 g of catalyst under O_2 atmosphere gave 12% yield in 24 h. After carrying out different experiments and also from the literature data [30], it has been found that benzoic acid is critical for the success of trimerization reaction. It was found that the yield of the trimerization product was increased to 85% in 19 h using 0.5 mmol of benzoic acid (entry 3, Table 2). We further screened various solvents such as ethanol, toluene, and acetonitrile under oxygen and air atmosphere. The results revealed that the conversion was not good in ethanol and toluene, however acetonitrile under oxygen atmosphere gave high yield of the desired product. After optimization of the reaction conditions, the scope and generality of the developed protocol was studied with respect to 5-substituted indoles and the products were obtained in good yield (Table 6).

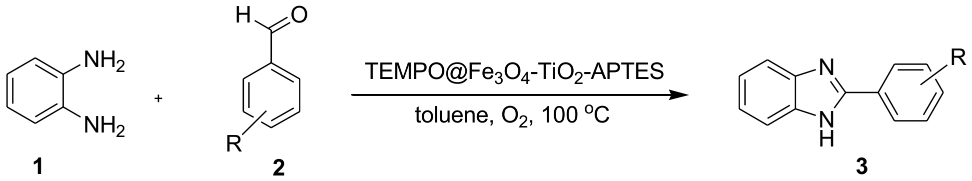
Proposed mechanism

A plausible mechanism for the synthesis of 2-substituted benzimidazoles is proposed in Scheme 2a. In the 1st step, loss of water take place leading to the formation of 2-aminobenzoimine [**A**]. TEMPO present in the catalyst then interacts with **A** and initiate the reaction by a hydrogen abstraction from the N–H bond of the amine moiety to produce radical [**B**] and TEMPOH, which was further reoxidized to TEMPO radical by oxygen. The radical [**B**] so formed then undergoes intramolecular cyclization to form corresponding aminyl radical [**C**]. The driving force for the aromatization allows the second hydrogen abstraction between **C** and TEMPO to yield benzimidazole and TEMPOH, which undergoes reoxidation to TEMPO radical by oxygen. A plausible mechanism for the oxidative aromatization of Hantzsch 1,4-dihydropyridines is proposed in Scheme 2b, which is a sequential cascade of double-cycle redox reaction. In the 1st step, one electron oxidation of TEMPO by Fe^{3+} produces a highly electrophilic *N*-oxoammonium species [**A**] which convert 1,4-DHP to its corresponding pyridine and itself gets reduced. The reduced derivative of TEMPO [**B**] then undergoes oxidation to TEMPO [**A**] by NO_2^-, which itself get reduced to NO and then NO undergoes reoxidation to NO_2^- by O_2 or in other words, NO_2^- is formed via rapid oxidation of NO with O_2. A plausible mechanism for the synthesis of 2,2-disubstituted indolin-3-ones is proposed in Scheme 2c. In the 1st step, TEMPO present in the catalyst in the presence of molecular oxygen interacts with the indolenine tautomer **A**, leading to the formation of C3 located indole hydroperoxide **B**, which after loss of water lead to indol-3-one (**C**). Then the rapid nucleophilic addition of second indole molecule on the C=N bond of this highly reactive species **C** in the presence of benzoic acid gave dimer **D**, which was further oxidized by O_2, resulting in the formation of dimer **E**. Again nucleophilic addition of third indole molecule to dimer **E** take place in the presence of benzoic acid leading, finally to trimerization of indole.

Recyclability

To confirm the reusability of the catalyst, different experiments were carried out in case of **3c** (Table 4), **5a** (Table 5), and **7a** (Table 6) using TEMPO@APTES–TiO_2–Fe_3O_4 under the optimum reaction condition. After completion of the reaction, catalyst was separated via magnet, washed with deionized water (2 × 20 cm^3) and ethanol (2 × 15 cm^3) and dried under vacuum. Then a fresh reaction was carried out with the used catalyst. A very small decrease in the catalytic activity of the synthesized catalyst was observed up to 5 runs for each reaction and hence the catalyst could be used at least five times without any change in activity (Fig. 6).

Table 4 TEMPO@APTES–TiO_2–Fe_3O_4 catalysed synthesis of 2-substituted benzimidazoles



Entry	R	Product	Time/h	Yield/%	TON	Melting point/℃	
						Measured	Literature
1	H	**3a**	6	89[a]	14	292–294	292–293 [43]
2	4-Me	**3b**	5.5	90[a]	14	267–269	268–270 [44]
3	4-OMe	**3c**	5	92[a]	14	224–226	225–226 [44]
4	4-Br	**3d**	5.5	90[a]	14	298–299	299–300 [43]
5	4-Cl	**3e**	5.5	90[a]	14	293–294	292–294 [43]
6	2-Cl	**3f**	6	89[a]	14	232–233	233–234 [43]
7	3-OMe	**3g**	6	90[a]	14	206–208	204–206 [44]
8	2-NO_2	**3h**	6.5	88[b]	13	262–264	264–266 [44]
9	3-NO_2	**3i**	6.5	89[b]	14	206–208	206–207 [43]
10	4-NO_2	**3j**	6	90[a]	14	310–312	312–314 [44]

Reaction conditions: aldehyde (1 mmol), 0.10 g *o*-phenylenediamine (1 mmol), and 0.1 g TEMPO@APTES–TiO_2–Fe_3O_4 (0.06 mmol TEMPO) at 100 °C in 5 cm^3 toluene under O_2 atmosphere

[a] Isolated yield

[b] Column chromatography yield

Conclusion

We have developed a novel non-toxic, low-cost, and stable radical based catalyst with good activity via immobilization of TEMPO onto the surface of the amine functionalized magnetic titania. The introduction of amino functionalized silanes onto the surface of magnetic titania improve the adhesion between the radical and the titania. The resultant heterogeneous catalyst has been explored for the very first time for catalysing the oxidative synthesis of heterocyclic compounds. All the reactions were performed under oxygen atmosphere, which is suitable from a green and sustainable chemistry point of view. The easy recovery, together with the intrinsic stability of the support material, allows the catalyst to be recycled five times without any discernible loss in its activity.

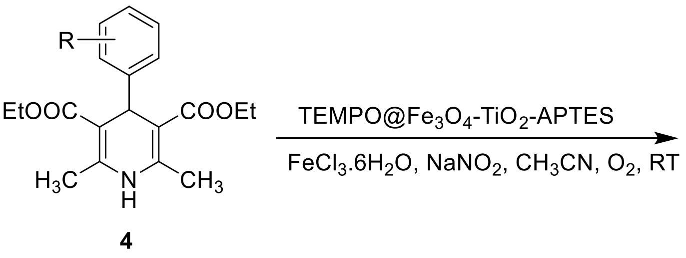
Experimental

All of the chemical materials used were purchased from Aldrich or Merck Chemical Company. To determine the thermal stability of the synthesized catalyst, thermogravimetric analysis (TGA) was recorded on a PerkinElmer, Diamond TG/differential thermal analysis (DTA) with a heating rate of 10 °C min^{-1}. X-ray diffraction (XRD) was recorded in the 2θ range of 10–80° on a Bruker AXSD8 ADVANCE X-ray diffractometer using Cu Kα radiations. Scanning electron microscopy (SEM) images were recorded using a FEG SEM JSM7600F scanning electron microscope and high-resolution transmission electron microscopy (HRTEM) images were recorded using a FEG, Tecnai G2, F30 transmission electron microscope. Energy-dispersive X-ray analysis (EDX) analysis was carried out using Oxford X-Max Model JSM-7600F and the extent of magnetism (magnetic moment) of the synthesized catalyst was measured using a vibrating sample magnetometer (VSM) bearing Model: 7410 series, Lakeshore at room temperature from -10,000 to + 15,000 Oe.

Synthesis of TEMPO@Fe_3O_4–TiO_2–APTES

For the synthesis of TEMPO@Fe_3O_4–TiO_2–APTES, 1 g Fe_3O_4 prepared by co-precipitation method [42] was suspended in 40 cm^3 EtOH followed by the addition of 5 cm^3 of ammonia solution and sonication up to 1 h. The solution was then transferred to round bottom flask (100 cm^3), followed by addition of 4 cm^3 titanium butoxide in 30 cm^3 ethanol, which was then stirred at 45 °C for 12 h. The resultant Fe_3O_4–TiO_2 colloid was separated with magnet and washed repeatedly with distilled water (3 × 20 cm^3)

Table 5 TEMPO@APTES–TiO_2–Fe_3O_4 catalysed oxidative aromatization of 1,4-DHPs



Entry	R	Product	Time/h	Yield/%[a]	TON	Melting point/℃	
						Measured	Literature
1	4-OMe	**5a**	3.5	94	14	57–58	55–57 [45]
2	4-Me	**5b**	3	92	14	73–74	72–73 [46]
3	4-Br	**5c**	3	92	14	–	–
4	4-Cl	**5d**	4	90	14	65–66	63–65 [45]
5	H	**5e**	3	90	14	63–64	62–64 [45]
6	2-OMe	**5f**	3.5	89	14	56–58	55–57 [47]
7	2-NO_2	**5g**	4	85	13	72–73	73–75 [48]
8	3- NO_2	**5h**	4.5	88	14	61–62	61–63 [45]
9	4- NO_2	**5i**	4	88	14	115–116	114–116 [45]

Reaction conditions: 1,4-dihydropyridine (1 mmol), 0.013 g $FeCl_3{\cdot}6H_2O$ (0.05 mmol), 0.0034 g $NaNO_2$ (0.05 mmol), and 0.1 g TEMPO@APTES–TiO_2–Fe_3O_4 (0.06 mmol TEMPO) in 5 cm^3 acetonitrile at room temperature under O_2 atmosphere

[a] Isolated yield

Table 6 TEMPO@APTES–TiO_2–Fe_3O_4 catalysed oxidative trimerization of indole

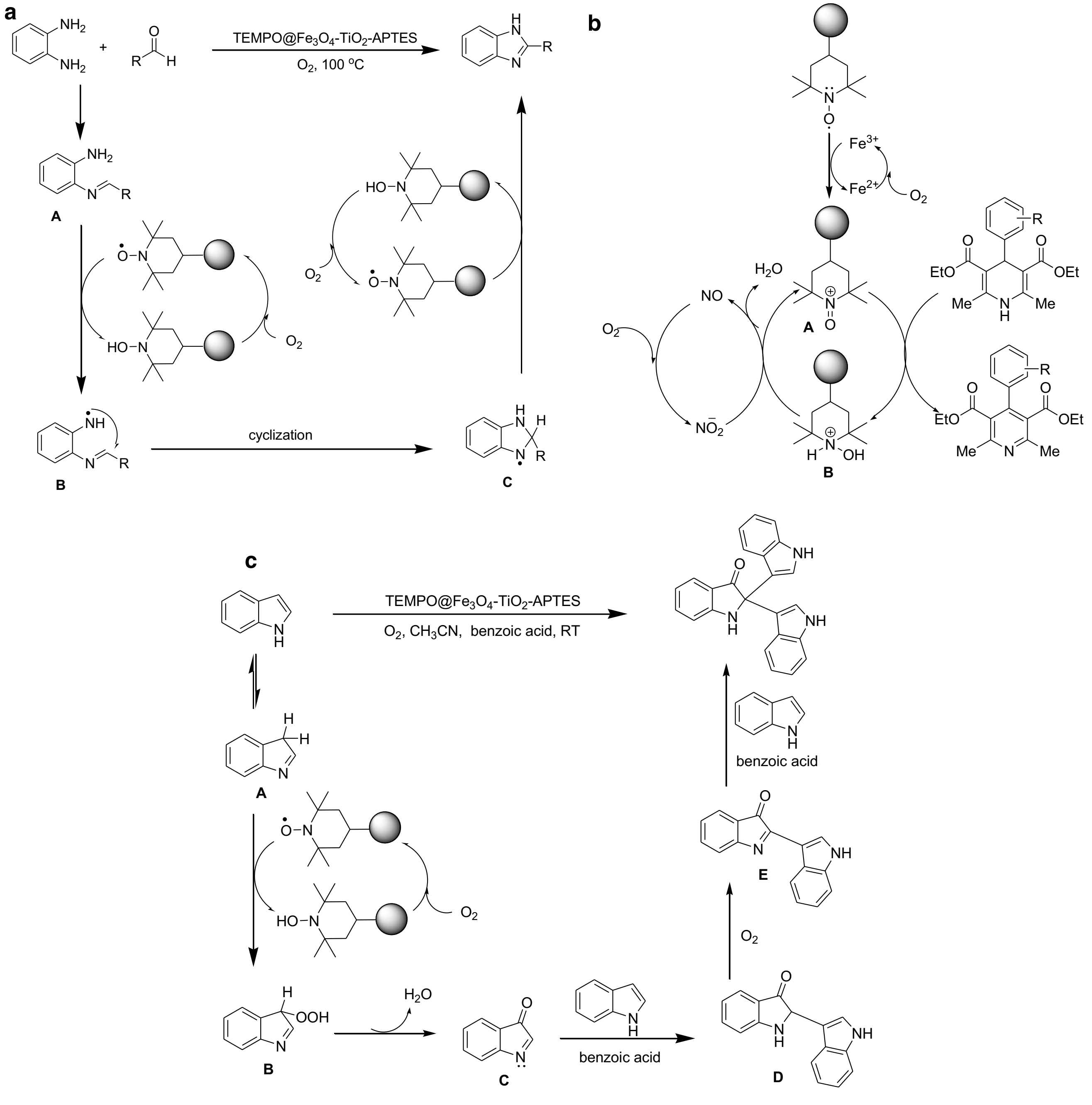
Entry	R	Product	Time/h	Yield/%	TON	Melting point/℃	
						Measured	Literature
1	H	**7a**	19	85[a]	13	242–244	243–245 [30]
2	NO_2	**7b**	25	70[a]	11	215–217	214–216 [29]
3	OMe	**7c**	22	76[a]	12	224–226	226–228 [30]
4	Br	**7d**	20	79[b]	12	247–249	247–249 [30]

Reaction conditions: indole (1 mmol), 0.06 g benzoic acid (0.5 mmol), and 0.1 g TEMPO@APTES–TiO_2–Fe_3O_4 (0.06 mmol TEMPO) in 5 cm^3 acetonitrile at room temperature under O_2 atmosphere

[a] Isolated yield

[b] Column chromatography yield

Scheme 2



and ethanol (2×10 cm^3) and dried in an oven at 70 °C for 8 h. 1 g Fe_3O_4–TiO_2 and 20 cm^3 anhydrous toluene were taken in a round bottom flask (100 cm^3) followed by the addition of APTES (10 mmol). The resulting mixture was then stirred at 70 °C for 10 h to allow completion of silanization reaction. The Fe_3O_4–TiO_2–APTES so prepared was separated with magnet, washed with toluene (3×10 cm^3) followed by ethanol (2×10 cm^3) and dried in an oven at 70 °C. For the anchoring of TEMPO onto Fe_3O_4–TiO_2–APTES, 2 g Fe_3O_4–TiO_2–APTES, 4-oxo-TEMPO (1.5 mmol), and 20 cm^3 ethanol were added in a round bottom flask (100 cm^3) and the resulting mixture was stirred at 40 °C for 12 h. After that, 5 cm^3 aqueous solution of $NaBH_4$ (2 mmol) was added to the above reaction mixture during 6 h and the stirring was continued for another 2 h. Finally, the catalyst so prepared was separated with an external magnet, washed successively with ethanol (2×10 cm^3), and dried in an oven at 40 °C for 8 h.

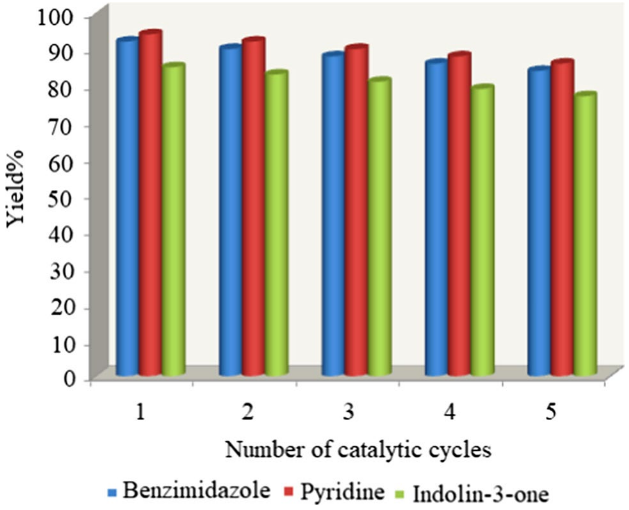


Fig. 6 Recyclability of TEMPO@APTES–TiO_2–Fe_3O_4

General procedure for the oxidative synthesis of 2-substituted benzimidazoles using TEMPO@APTES–TiO_2–Fe_3O_4 in the presence of molecular oxygen

To a mixture of *o*-phenylenediamine (1 mmol), aromatic aldehyde (1 mmol), and 0.1 g TEMPO@APTES–TiO_2–Fe_3O_4 in a round bottom flask (25 cm^3), 5 cm^3 toluene was added and the reaction mixture was stirred at 100 °C under an oxygen atmosphere. When the starting materials were completely consumed as determined by TLC, the reaction mixture was diluted with 20 cm^3 ethyl acetate and the catalyst was separated with external magnet. The catalyst obtained was washed with ethyl acetate (3 × 5 cm^3), dried in an oven and then used in the next reaction. The organic layer was washed with water (3 × 20 cm^3) and dried over anhyd. Na_2SO_4. The crude product obtained after removal of the solvent under reduced pressure was further purified either by crystallization or by passing through column of silica gel using ethyl acetate and petroleum ether as eluting solvents. 2-substituted benzimidazoles **3a**–**3j** were synthesized in high yields.

General procedure for the TEMPO@APTES–TiO_2–Fe_3O_4 catalysed oxidative aromatization of Hantzsch 1,4-dihydropyridines in the presence of molecular oxygen

1,4-DHP (1 mmol), 0.013 g $FeCl_3·6H_2O$ (0.05 mmol), 0.0034 g $NaNO_2$ (0.05 mmol), 0.1 g TEMPO@APTES–TiO_2–Fe_3O_4, and 5 cm^3 acetonitrile were taken in a round bottom flask (50 cm^3) and the reaction mixture was stirred at room temperature with an oxygen balloon until the reaction was completed as monitored by TLC. After completion, the reaction mixture was diluted with 20 cm^3 ethyl acetate and the catalyst was separated with external magnet, washed with ethyl acetate (2 × 5 cm^3), dried in an oven, and then used in the next reaction. The organic layer was washed with water (3 × 20 cm^3) and dried over anhyd. Na_2SO_4. The crude product obtained after removal of the solvent under reduced pressure was purified by crystallization.

General procedure for the synthesis of 2,2-disubstituted indolin-3-ones using TEMPO@APTES–TiO_2–Fe_3O_4 as catalyst under O_2 atmosphere

To a mixture of indole (1 mmol), 0.06 g benzoic acid (0.5 mmol), and 0.1 g TEMPO@APTES–TiO_2–Fe_3O_4 in a round bottom flask (25 cm^3), 5 cm^3 acetonitrile was added and the reaction mixture was stirred at room temperature with an oxygen balloon for the appropriate time. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with 20 cm^3 ethyl acetate and the catalyst was separated with external magnet, washed with ethyl acetate, dried in an oven, and then used in the next reaction. The organic layer was washed with water (3 × 20 cm^3) and dried over anhyd. Na_2SO_4. The crude product obtained was purified either by crystallization or by passing through column of silica gel (EtOAc-pet. ether).

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