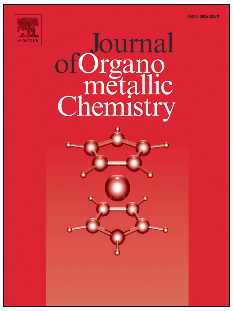

Polymer-anchored [Fe(III)Azo] complex: An efficient reusable catalyst for oxidative bromination and multi-components reaction for the synthesis of spiropiperidine derivatives

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Polymer-anchored [Fe(III)Azo] complex: An efficient reusable catalyst for oxidative bromination and multi-components reaction for the synthesis of spiropiperidine derivatives

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ABSTRACT: A heterogeneous catalyst was prepared by attaching Fe(III) into organically modified chloromethylated polytstyrene and characterized by AAS, IR, PXRD, TG-DTA, UV-Vis, and SEM studies. In presence of H_2O_2 and KBr as bromine source, the catalyst showed remarkably high conversion with para-selectivity towards the oxidative bromination reaction in acetic acid medium. The catalyst was also very active and highly efficient for the production of spiropiperidine derivatives through multi-component reaction in isopropyl alcohol at room temperature. The catalyst was not leached during the catalytic reactions, moreover, after five cycles the catalytic activity and selectivity of the catalyst were not decreased very significantly.

Keywords: Heterogeneous Catalyst, polymer support, oxidative bromination, spiropiperidine derivatives.

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1. Introduction

During several years, appreciable attention has been given to the improvement of the green environmental influences of the chemical process in the industry [1]. The heterogeneous catalysts can execute a pivotal role in the development of greener technologies. It is well accepted that heterogeneous catalysts can show high catalytic activity, can be separated very easily from the product mixture, stability and selectivity is higher in comparison to the unsupported metal catalysts [2] and the industrial needs of recyclability for steady operation can also be achieved here. A great attention has been given to the improvement of the heterogeneous catalyst because of these enormous advantages over the homogeneous catalyst [3]. Different types of supports have been used including organic resins [4] and polymers [5, 6] as well as inorganic carriers such as clays [7], silica [8], zeolites [9], and molecular sieves [10] to generate heterogeneous catalysts. In recent years, a great interest has been paid to the application of polymer-anchored metal catalysts for organic transformations [11], and the development of functionalized polymers supported catalytically active metal has produced a magnificent interest [12].

The bromination of organic substances is a significant reaction as the brominated products have been exclusively used as an important precursor for cross-coupling and substitution reactions which produced many pharmaceuticals, agricultural, and specialty chemicals [13]. Some brominated products are also very useful as pesticides, herbicides, flame retardants, and bioactive materials [13]. Numerous protocols for bromination reaction of organic compounds have been published previously [14]. In the classical method of direct bromination, elemental bromine is used and half of the bromine is consumed for the production of hydrogen bromide waste (eq. 1). Moreover, the elemental bromine is a health hazard material and a pollutant.

$$\mathbf{Ar\text{-}H + Br_2 \longrightarrow Ar\text{-}Br + HBr} \qquad (1)$$

Therefore, it will produce an economical and various environmental problems for large-scale synthesis. That's why development of environmental friendly bromination process has been focused on to avoid the use of elemental bromine [15]. Some reagents have been developed as a substitute for Br_2, such as N-bromosuccinimide, $[K^+18\text{-crown-}6]Br_3$, methylimidazolium tribromide, 1-butyl-3-methylpyridinium tribromide, $ZrBr_4$/diazene, 1-butyl-3 methylimidazolium tribromide, ethylene bis(N-methylimidazolium) ditribromide and 3-pentylpyridinium tribromide [16]. Some bromine containing reagent systems have also been used like: Br_2/Ag_2SO_4, $Br_2/SbF_3/HF$, Br_2/SO_2Cl_2/Zeolite, Br_2/ Zeolite, Br_2/H_2O_2, Br_2/H_2O_2/Layered Double Hydroxide-WO_4, Br_2/tetrabutylammonium peroxydisulphate, etc [17]. But those reagents are expensive, they have poor recovery and recycling performance and release large amounts of HBr waste on disposal. At some stage the synthesis of those reagents involves liquid bromine, as a result, increasing the cost of the end-product. Therefore, the catalytic oxidative bromination reaction has been still gaining a considerable importance to develop a more efficient and suitable method for the synthesis. Catalytic oxidative bromination is a process of generation of electrophilic bromine using different oxidants in presence of catalyst. From greener point of view environmentally benign oxidant H_2O_2 and O_2 are considered as best oxidants for oxidative bromination as only water is the waste product generated here [18].

Many metal complexes show catalytic activity towards oxidative bromination reaction along with other oxidation reactions [19]. However; these metal complexes usually used as a homogeneous catalyst and during the catalytic reaction they decomposes, as a result, it was very difficult to recover them from the reaction mixture. One of the important ways to solve this problem and make the catalyst heterogeneous is to immobilize the catalytically active metals onto organically modified polymer supports. The most widely used macromolecular support is Chloromethylated polystyrene [20]. The polystyrene supported materials offer advantageous characteristics of heterogeneous catalysis such as selectivity, recyclability, thermal stability, and their separation from the catalytic reaction mixture [21]. Though diverse materials have been explored as catalysts for oxidative bromination, polystyrene supported transition metal complexes have rarely been used [22]. Moreover, the application of polystyrene supported Fe(III) complex catalyst for oxidative bromination has been hardly studied [23].

Multicomponent reactions forming heterocyclic compounds are powerful tools in the drug discovery process. In a single method, they can provide the convenient synthesis of libraries of drug-related compounds [24]. The importance of multi-component reactions is simplicity, less costly, a high degree of variations, high atom economy, good yields, short reaction durations, high bond-forming efficiency [25], environmentally friendly methods, and ignorance of multiple steps with high-value purification processes [26].

Spiropiperidine derivatives conquer an important position in the field of heterocyclic chemistry as they are commonly found in numerous natural and synthetic products along with useful biopharmaceutical, physiopharmaceutical, and pharmaceutical activities. These derivatives are potent σ receptor ligands which can be utilized in the depression treatment, epileptic disorders, abuse of cocaine, and 5-HT$_{2B}$ receptor antagonists [27].

Owing to the importance of the spiropiperidine compounds in medicinal field, unexpectedly, only a few procedures for the synthesis of these compounds are available in the literature [28]. However, the procedures mainly involve the use of homogeneous catalysts, long reaction time and toxic solvents. Therefore, development of an efficient and eco-friendly procedure which involves heterogeneous catalyst is highly expectable for the synthesis of spiropiperidine derivatives. For this purpose, here we developed an eco-friendly and cost-effective protocol in which spiropiperidine derivatives can be synthesized very easily within very short reaction time using a polymer supported heterogeneous metal catalyst.

In this paper, we report the preparation, characterization of a polymer-anchored iron(III) azo catalyst and the investigation of its catalytic activities for oxidative bromination and one pot multiple components reaction for the synthesis of spiropiperidine derivatives.

2. Experimental

2.1. Materials

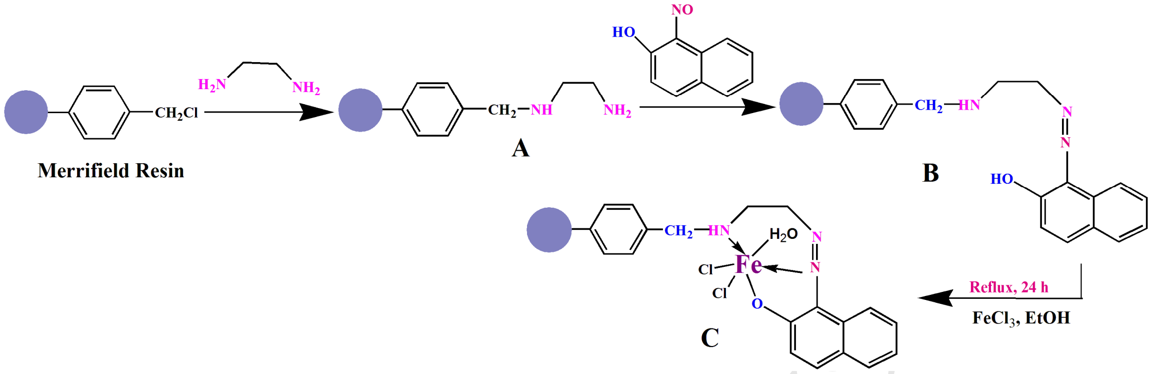
Chloromethylated polystyrene was purchased from Sigma-Aldrich Company (USA) and other chemicals were available from Merck (India). The reagents were used as received without any purification. Reagent grade solvents were dried and distilled prior to use.

2.2. Characterization techniques

Elemental analysis (C, H and N) was performed on Perkin-Elmer 2400 C elemental analyzer. FTIR spectra of the samples were carried out on a Perkin-Elmer FTIR 783 spectrophotometer using KBr pellets. Thermo gravimetric (TGA) analysis was done on Mettler Toledo TGA/SDTA 851 instrument. The morphology of samples was analyzed using a scanning electron microscope (SEM) (ZEISS EVO40, England) equipped with EDAX facility. NMR spectra were carried out using tetramethylsilane as internal standard on a Bruker AMX- 400 NMR spectrophotometer and UV-Vis spectra were done on Thermo Scientific (Model no. GENESYS 10S UV-VIS) spectrophotometer. AAS analysis for the loading of iron on polymer support was measured on Spectra- AA 240 (Agilent Technologies). The powder X-ray diffraction (PXRD) data were taken on a Bruker D8 Advance X-ray diffractometer using Cu-K_α radiation (λ = 1.5418 Å) operating at 40 kV and 40 mA. The XRD patterns were recorded in the 2θ range of 3-50 using a LynxEye detector (1D mode) with a step size of 0.02 and a dwell time of 1 s per step.

2.3. Preparation of the Catalyst

Synthesis of polymer-anchored iron(III)Azo (PS-[Fe(III)Azo]) complex is depicted in the following Scheme 1.



Scheme 1. Schematic presentation for the preparation of PS-[Fe(III)Azo] catalyst.

2.3.1. Preparation of polymer-anchored azo (PS-Azo) ligand (**B**)

PS-Azo ligand (**B**) was synthesized by two steps syntheses procedure. In the first step, in a 50 mL round-bottomed flask 1 g of chloromethylated polystyrene was dissolved in 10 mL dry THF. Then 0.7 mL ethylenediamine was added dropwise to this mixture and stirred it for 48 h at room temperature [29]. The obtained white solid bead **(A)** was filtered and washed thoroughly with deionized water and followed by methanol. The product was dried under vacuum.

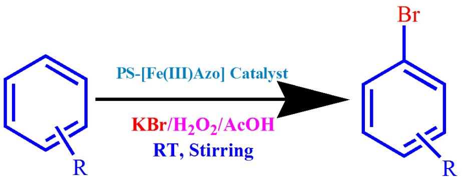
In the second step, 1 g of (**A**) was suspended in 50 mL methanol in a 250 mL round bottom flask. Then 50 mL methanolic solution of 1-nitroso-2-naphthol (1 g) was added dropwise to the suspension of (**A**). After that, the reaction mixture was refluxed for 24 h under stirring condition. The colour of the reaction mixture was changed from white to deep brown. The mixture was cooled to room temperature. Finally, PS-Azo Ligand (**B**) was obtained by filtering and washing thoroughly with methanol and drying it under vacuum.

2.3.2. Preparation of PS-[Fe(III)Azo] Catalyst (**C**)

In a 100 mL round bottom flask, 1 g of PS-Azo Ligand (**B**) was taken in 20 mL dry ethanol. Under constant stirring, 5 mL 1% (w/v) dry ethanolic solution of iron (III) chloride was added dropwise to the solution. Then the solution was refluxed for 24 h under stirring condition. The obtained complex was filtered and washed properly with methanol and then it was dried under vacuum.

2.4. General procedure for the catalytic oxidative bromination reaction of organic compounds by PS-[Fe(III)Azo] catalyst

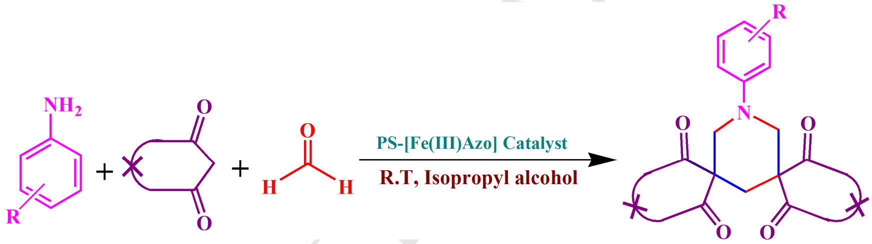
To a 50 mL two-necked round-bottomed flask 50 mg of catalyst, the substrate (5 mM) and KBr (2.2 mM) were taken in 5 mL acetic acid. Then 30% H_2O_2 (5 mM) was added dropwise to the reaction mixture and stirred at room temperature (Scheme 2). The progress of the reaction was monitored by thin layer chromatography (TLC). After completion of the reaction, 10 mL water was added to the reaction mixture. Then the catalyst was filtered and washed thoroughly with ether. To the filtrate, saturated sodium bicarbonate solution was added and the organic layer was extracted. Anhydrous sodium sulphate was used to dry the organic layer and solvent was evaporated under reduced pressure. The obtained products were analyzed by Varian 3400 gas chromatograph equipped with a 30 m CP-SIL8CB capillary column and a Flame Ionization Detector.



Scheme 2. Schematic presentation of PS-[Fe(III)Azo] catalysed oxidative bromination reaction.

2.5. General process for the preparation of spiropiperidine derivatives

In 50 mL round-bottomed flask, 2 mM of amines (1a-d), 4 mM of active methylene compounds (2a or 2b), 6 mM of 37% aqueous formaldehyde solution and 50 mg of PS-[Fe(III)Azo] catalyst were added to 15 mL isopropyl alcohol. The reaction mixture was stirred at room temperature for the specified period of time (Table 7). The precipitation of solid compound indicated the formation of products. After the stipulated time of completion of the reaction (monitored by TLC), 20 mL water was added to reaction mixture and 10 ml ethyl acetate was then added to extract the products. The solid products were obtained by the evaporation of organic layer under reduced pressure. Recrystallization of the solid products from ethanol solution gave pure compounds. The catalyst in the aqueous phase was filtered, washed thoroughly with the mixture of ether and methanol (1:10), dried and reused.



Scheme 3. General schematic presentation of synthesis of spiropiperidine derivatives.

3 Results and Discussion

3.1 Characterization of PS-[Fe(III)Azo] catalyst

The polymer-supported metal catalyst is generally insoluble in common organic solvents; so, its structural characterization was bounded to their chemical analysis, SEM, EDX, FTIR, PXRD, TGA, UV-Vis spectroscopic analysis and physicochemical properties. The elemental analysis data is given in Table 1. The metal loading on the catalyst was measured by atomic absorption spectroscopy (AAS).

Table 1

Chemical composition of Ps-Azo ligand and its iron(III) Catalyst.

Compound	Colour	C (%)	H (%)	N (%)	Cl (%)	Fe (%)
PS-Azo ligand	brown	84.13	7.24	4.14	1.20	-
PS-[Fe(III)Azo]Catalyst	dark brown	75.60	7.12	3.98	2.94	1.25 (1.24)[a] (1.17)[b] (0.72)[c]

[a] Reused catalyst after 1 cycle, [b]Reused catalyst after fourth cycle, [c]Reused catalyst after tenth cycle.

The loading of metal to the organically modified polymer support was confirmed by comparison of the FT-IR spectra (Fig. 1) of polymer-anchored ethylenediamine (PS-en), PS-Azo ligand and PS-[Fe(III)Azo] catalyst. Pure chloromethylated polystyrene shows an IR active absorption band at 1,261 cm^{-1} due to the C-Cl bond stretching frequency. This band is absent in the ligand as well as in the catalyst. The FTIR spectra of the PS-en **(A)** shows one band near 3410 $cm^{−1}$ for N–H stretching vibration of attached secondary amine. Due to N–H bending vibration of primary amine, PS-en **(A)** also gives a moderate peak at 1600 $cm^{−1}$. When **(A)** reacted with 1-nitroso-2-naphthol to form PS-Azo ligand **(B)** the peak at 1600 $cm^{−1}$ was disappeared. The band at 1510 $cm^{−1}$ of PS-Azo ligand **(B)** may be for the stretching vibrations of the azo group (N=N). This band is shifted to 1495 cm^{-1} in the PS-[Fe(III)Azo] catalyst (**C**) indicating coordination of the PS-Azo ligand to Fe through the azo N [30]. The peak observed at 2921 $cm^{−1}$ in all spectra may be due to C-H stretching vibration of ethylene group [31]. In case of PS-Azo ligand, a new band is appeared at 3205 $cm^{−1}$ due to OH stretching frequency, which is absent in the spectra of the catalyst that confirmed the coordination of the phenolic oxygen atom with Fe metal. In addition, a new absorption band is observed at 560 $cm^{−1}$ due to the formation of M–N bonds between metal ions and PS-Azo ligand [23]. The complexation of Fe(III) metal with PS-Azo ligand was further evidenced by the absorption band at 455 cm^{-1} due to the formation of the bond between metal and phenolic oxygen (M–O) [23].

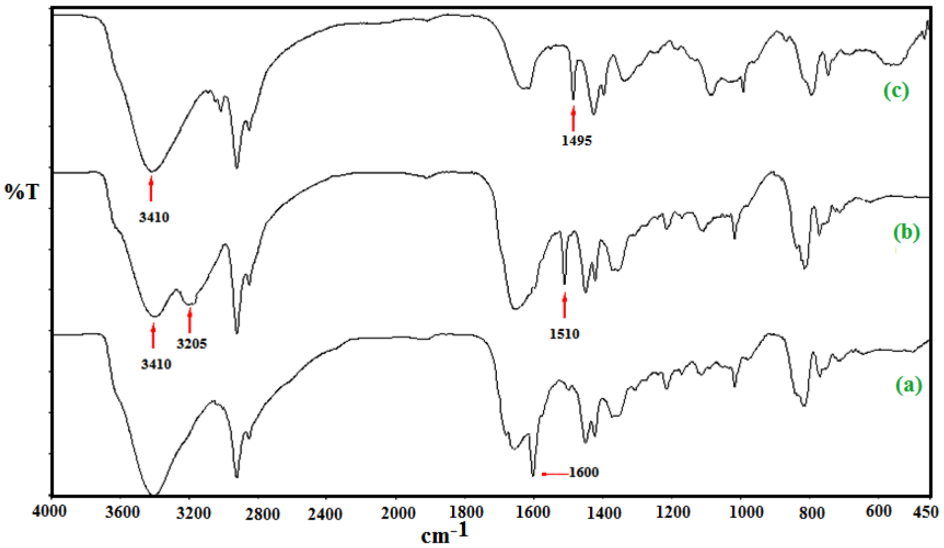


Fig. 1. FT-IR spectra of PS-en (a), PS-Azo ligand (b) and PS-[Fe(III Azo] Catalyst (c).

The metal loading in the catalyst was measured by AAS which suggested 1.25% (w/w) of Fe present in the immobilized metal catalyst.

Fig. 2 showing the powder XRD pattern of PS-Azo ligand and PS-[Fe(III)Azo] catalyst. Both ligand and catalyst exhibit a broad band at the range of 2θ (10-30) which clearly indicates the amorphous nature of ligand as well as the catalyst [32]. Thus there was no nano-crystalline material of iron is formed after the introduction of metal onto the ligand.

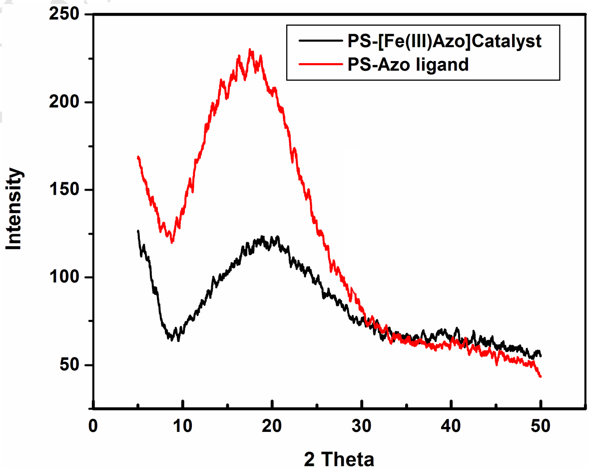


Fig. 2. PXRD of PS-Azo ligand and PS-[Fe(III)Azo] catalyst.

The field emission scanning electron micrographs of PS-Azo ligand (**a**) and its iron complex (**b**) are shown in Fig. 3. There is a clear change observed in the morphological pattern of the PS-Azo ligand after insertion of iron metal by the SEM image which confirms the loading of metal on the functionalized polymer surface. EDX analysis of PS-[Fe(III)Azo] catalyst further confirms the loading of iron on organically modified polymer support (Fig. 4).

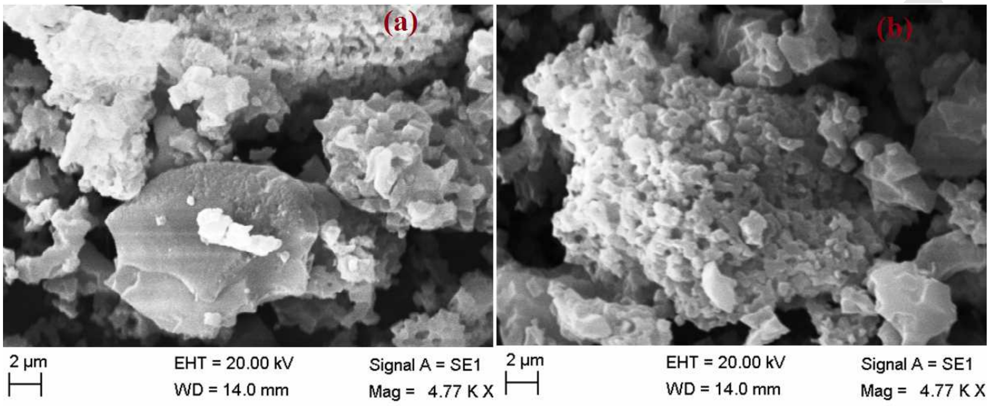


Fig. 3. FE SEM image of PS-Azo ligand (a) and PS-[Fe(III)Azo] catalyst (b).

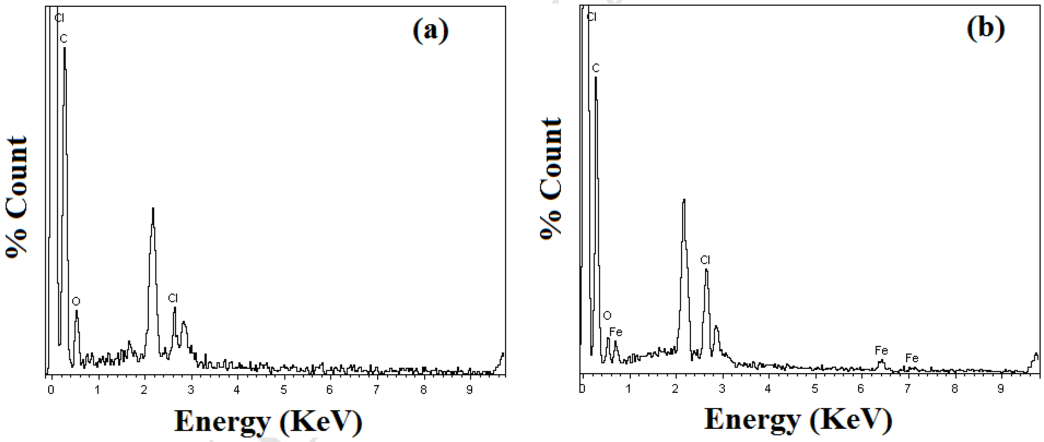


Fig. 4. EDX images of PS-Azo ligand (**a**) and PS- [Fe(III)Azo] Catalyst (**b**).

UV-Vis spectrum (Fig. S1) of the PS-Azo ligand and PS-[Fe(III)Azo] catalyst were taken after ultra-sonicating the samples in MeOH medium. The PS-Azo ligand in MeOH shows two intense band at 225 and 293 nm due to n-π* and π-π* transitions respectively [23]. These bands shifted at 213 and 281 nm respectively in PS-[Fe(III)Azo] catalyst. A very weak new band has appeared near at 400-410 nm in the spectra of the catalyst. This band is for the spin forbidden d-d transition of the Fe complex [33]. The shifting of bands and appearing in new band for d-d transition clearly indicates the formation of the iron complex with the PS-Azo ligand.

Thermo gravimetric analysis of PS-Azo ligand and PS-[Fe(III)Azo] catalyst (Fig. 5) were performed in open atmosphere in between temperature range from 30 ºC to 600 ºC with 10 ºC min^{-1} heating rate. The higher thermal stability of the PS-[Fe(III)Azo] catalyst compares to PS-Azo ligand clearly evidences the loading of iron metal to the polymer surface. Both the metal catalyst and ligand were thermally stable up to ca. 400 ºC; beyond the temperature, they decomposed.

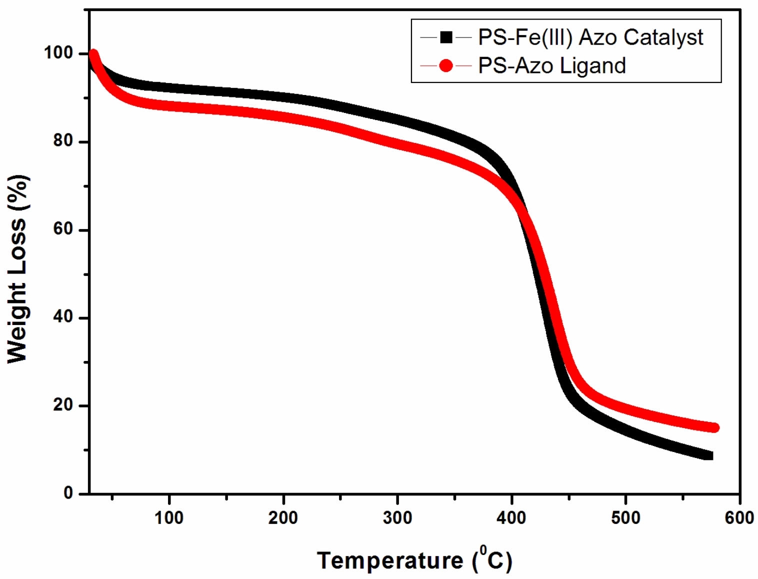
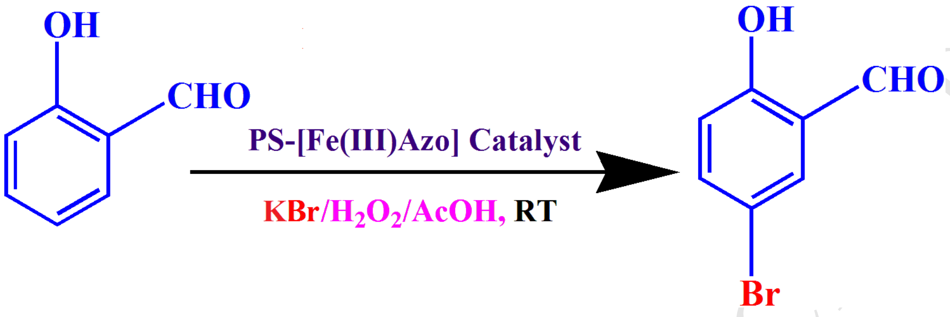


Fig. 5. TGA curves for PS-Azo Ligand and PS-[Fe(III)Azo] catalyst.

3.2 Catalytic Activity

3.2.1 Catalytic oxidative bromination reaction of organic compounds

The catalytic activity of PS-[Fe(III)Azo] catalyst was tested for oxidative bromination reaction of different organic compounds under mild conditions. The effects of different salts were investigated for this reaction taking salicylaldehyde as a model substrate. The polymer-catalyst PS-[Fe(III)Azo] was used with oxidant H_2O_2 and metal bromide (like NaBr, KBr and LiBr) as a bromine source for the bromination reaction (Table 2). Potassium bromide was seemed to be the most powerful bromine source among the three bromide salts and its application gave the mono-selective product. The regioselective product was not obtained by the use of sodium bromide and lithium bromide was less efficient than Potassium bromide.



Scheme 4. PS-[Fe(III)Azo] catalyzed oxidative bromination of salicyaldehyde.

Table 2

Effect of various bromide salts on the bromination reaction of salicylaldehyde using PS-[Fe(III)Azo] catalyst[a].

Entry	Bromide salt	% of conversion[b]	Product selectivity[b, c]
1	Sodium bomide	75	5-Bromo-2-hydroxy benzaldehyde (60) + 3, 5-dibromo-2-hydroxy benzaldehyde (40)
2	Lithium bromide	92	5-Bromo-2-hydroxy benzaldehyde (100)
3	Potassium bromide	100	5-Bromo-2-hydroxy benzaldehyde (100)

[a]Conditions: Salicylaldehyde (5 mM); Metal bromide (2.2 mM); glacial AcOH (5 mL); H_2O_2 (2.2 mM); 50 mg catalyst; room temperature. [b]Conversion and selectivity were checked by GC.

The effect of temperature was also monitored for the same bromination reaction. But there is no influence of temperature on the transformation of salicylaldehyde. The conversion of salicylaldehyde with raise in temperature remains almost same. Different solvents like hexane, carbon tetrachloride, ethanol, acetonitrile, acetic acid, chloroform, and methanol were used to study the solvent effects on the catalytic bromination reaction of salicylaldehyde. Among the different solvents, acetic acid worked as the best solvent. The function of hydrogen peroxide (H_2O_2) as an oxidant was established by conducting a blank test where no production of bromo derivative was found.

The oxidative bromination of various organic compounds was extensively carried out maintaining the reaction conditions as optimized for salicylaldehyde (Table 3). Selective mono-brominated products were obtained from the bromination reaction of substrates with the activated aromatic ring. Phenol, resorcinol and anisole gave the para-selective product with the excellent high conversion. But in case of the deactivated aromatic substrate, like nitrobenzene, did not show any conversion under the similar reaction conditions. Under same reaction conditions, benzene showed a low conversion after long reaction times. 2-Substituted organic compounds were selectively converted to 4-bromo derivatives and vice versa.

Table 3

PS-[Fe(III)Azo] catalysed oxidative bromination reaction of different organic substrates[a].

Entry	Substrate	% of Conversion [b] (time in h)	Product selectivity[b] (%)	TON[c]/TOF[d]
1[d]	Salicylaldehyde	100, 99, 98, 96, 93, 89, 80, 71, 62, 54, 40 (3.0)	5-Bromo-2-hydroxy benzaldehyde (100)	(447/149)[e], (444/148)[f], (310/103)[g]
2	Phenol	100 (2)	4-Bromophenol (100)	448/224
3	4-Aminophenol	88 (3)	2-Bromo-4-aminophenol (100)	393/131
4	Resorcinol	90 (3)	4-Bromo-1,3-dihydroxybenzene (100)	402/134
5	4-Nitrophenol	78 (6)	2-Bromo-4-nitrophenol (100)	348/58
6	2-Nitrophenol	65 (6)	4-Bromo-2-nitrophenol (100)	288/48
7	Anisole	100 (2.5)	4-Bromoanisole (100)	445/178
8	Aniline	98 (3)	4-Bromoaniline (97) 2-Bromoaniline (3)	438/146
9	4-Nitroaniline	88 (3)	2-Bromo-4-nitroaniline (100)	393/131
10	Benzene	14 (6.0)	Bromobenzene (100)	60/10
11	Nitrobenzene	-	-	

[a]Conditions: substrate (5 mM); KBr (2.2 mM); glacial AcOH (5 mL); 30% aq H_2O_2 (2.2 mM), catalyst (50 mg), room temperature. [b]Conversion and selectivity were determined by GC. [d]Catalytic runs to test recyclability. [c]TON (turn over number) = moles of substrate converted/moles of active sites of catalyst, [d]TOF (turn over frequency) = TON/time (in h); [e]TON/TOF calculated after first cycle based on AAS data of fresh catalyst; [f] TON/TOF calculated after fifth cycle based on AAS data of reused catalyst after fourth cycle; [g] TON/TOF calculated after fifth cycle based on AAS data of reused catalyst after tenth cycle.

Table 4

Comparison of the catalytic activity of PS-[Fe(III)Azo] catalyst with other reported systems towards oxidative bromination.

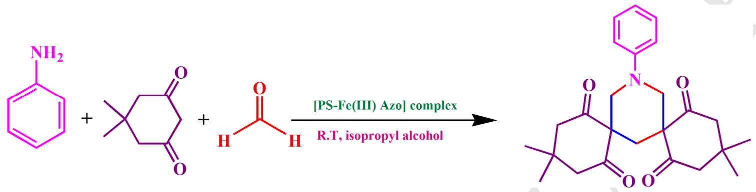
Sl. No	Catalyst	Substrate	% conversion	Product Selectivity (%)	TOF	Reference
1	PS-[Fe(III)teta]	Aniline	96.0	4-bromoaniline (85.0) 2-bromoaniline (15.0)	118	23
2	PS-[Fe(III)teta]	Anisole	94.0	4-bromoanisole (100.0)	96	23
3	Fe(opbmzl)$_2$-Y	Aniline	84.4	4-bromoaniline (95.6) 2-bromoaniline (4.4)	77	34
4	Fe(opbmzl)$_2$-Y	Anisole	72.0	4-bromoanisole (100.0)	-	35
5	PS-[Fe(III)Azo]	Aniline	98.0	4-Bromoaniline (97.0) 2-Bromoaniline (3.0)	146	This work
6	PS-[Fe(III)Azo]	Anisole	100.0	4-bromoanisole (100.0)	178	This work

3.2.2 Catalytic synthesis of spiropiperidine derivatives by PS-[Fe(III)Azo] catalyst

At room temperature, different control reactions were carried out in isopropyl alcohol using dimedone, formaldehyde and aniline as model substrates to ensure that Fe sites bound to PS-Azo ligand create the catalytic activity. In absence of any catalyst no product was obtained, whereas using PS-Azo ligand (10 M %) as a catalyst gave disappointing results. Then the reaction was performed by using $FeCl_3 \cdot 6H_2O$ (10 M %) as a catalyst, a good result with product yield of 64% after 3 h was observed. This result confirmed that the Fe sites are responsible for the catalytic activity, but $FeCl_3 \cdot 6H_2O$ act as a homogeneous catalyst under this reaction conditions, as a result, the recyclability of the catalyst becomes complicated. Then the reaction was carried out in presence of PS-[Fe(III)Azo] catalyst (50 mg), an incredible yield of 95% product in a short range of time period was obtained. Effects of different solvents and the catalyst loading were monitored to optimize the reaction conditions. The reaction between dimedone (4 mM), formaldehyde (6 mM) and aniline (2 mM) under different reaction conditions was used as a model reaction for all experiments. At room temperature, the effects of different solvents like H_2O, MeOH, EtOH, isopropyl alcohol, PEG-600, PEG-400 and PEG-200 on the model reaction were explored using 50 mg of the catalyst (Table 5). The best result was obtained when isopropyl alcohol was used as a solvent compared to others.

Table 5

Solvents effect on the model reaction.



Entry	Solvent	Time^a (min)	% of Yield^{b,c}
1.	methanol	60	90
2.	isopropyl alcohol	30	95
3.	PEG-400	60	74
4.	PEG-600	60	72
5.	PEG-200	60	77
6.	ethanol	60	92
7.	Water	60	trace

^{a}Reaction of aniline (2 mM), demidone (4 mM and formaldehyde (6 mM), room temperature. Progress of reaction was monitored by thin layer chromatography. ^{b}Isolated yield. ^{c}catalyst amount 50 mg.

Table 6

Effects of the different amount of catalyst on the model the reaction.

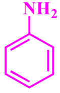
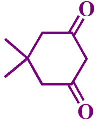
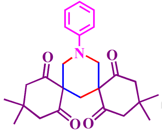
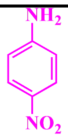
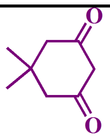
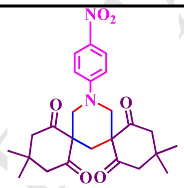
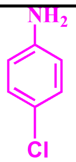
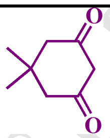
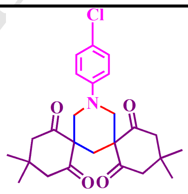
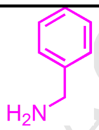
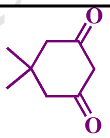
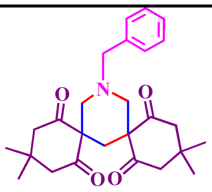
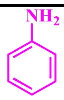
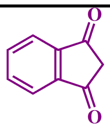
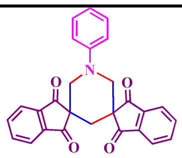
Entry	Amount of catalyst (mg)	Reaction time (min)^a	% of yield^b
1.	20	90	73
2.	30	60	85
3.	40	30	90
4.	50	30	95
5.	60	30	95

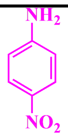
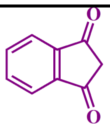
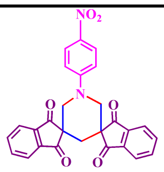
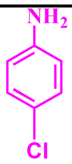
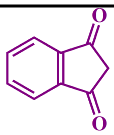
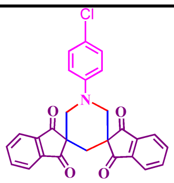
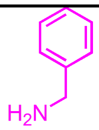
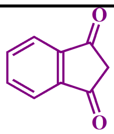
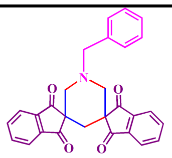
^{a}Reaction of aniline (2 mM), indane-1,3-dione (4 mM) and HCHO (6 mM) in isopropyl alcohol (10 mL) at room temperature. Progress of the reaction was monitored by TLC. ^{b}Isolated yield.

Under the optimized conditions, various spiropiperidine derivatives were synthesized and the results are summarized in Table 7. The result of Table 7 clearly indicates that the catalyst is very efficient for the synthesis of spiropiperidine derivatives. For further confirmation of the catalytic efficacy of the catalyst a comparison with the reported catalysts is shown in Table 8.

Table 7

Synthesis of different spiropiperidine derivatives using amines, active methylene compounds and formaldehyde in presence of PS-[Fe(III)Azo] Catalyst[a].

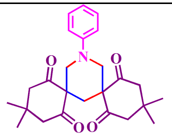
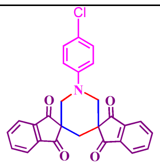
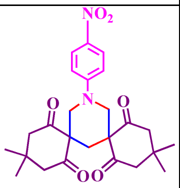
Entry	Amines (1a-1d)	Active methylene compounds (2a-2b)	Products[b] (3a-3h)	Time (min)[c]	Yield (%)[d]	TOF[e]
1.	 1a	 2a	 3a	30	95	340
2.	 1b	 2a	 3b	30	85	304
3.	 1c	 2a	 3c	30	90	322
4.	 1d	 2a	 3d	30	88	314
5.	 1a	 2b	 3e	30	92	328

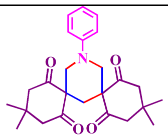
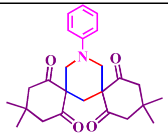
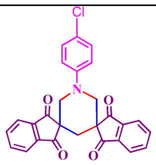
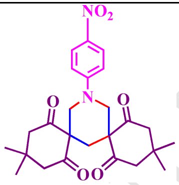
6.	 1b	 2b	 3f	30	83	296
7.	 1c	 2b	 3g	30	89	318
8.	 1d	 2b	 3h	30	88	314

[a]Reaction of amine (2 mM), dikitone (4 mM) and HCHO (6 mM), catalyst (50mg) in isopropyl alcohol (10 mL) at room temperature. [b]Compounds characterized by ^{1}H NMR spectra. [c]Reaction progress monitored by TLC. [d]Isolated yield. [e]TOF (turn over frequency) = no. of moles of the starting materials being converted per mole of active site of the catalyst /time (in h).

Table 8

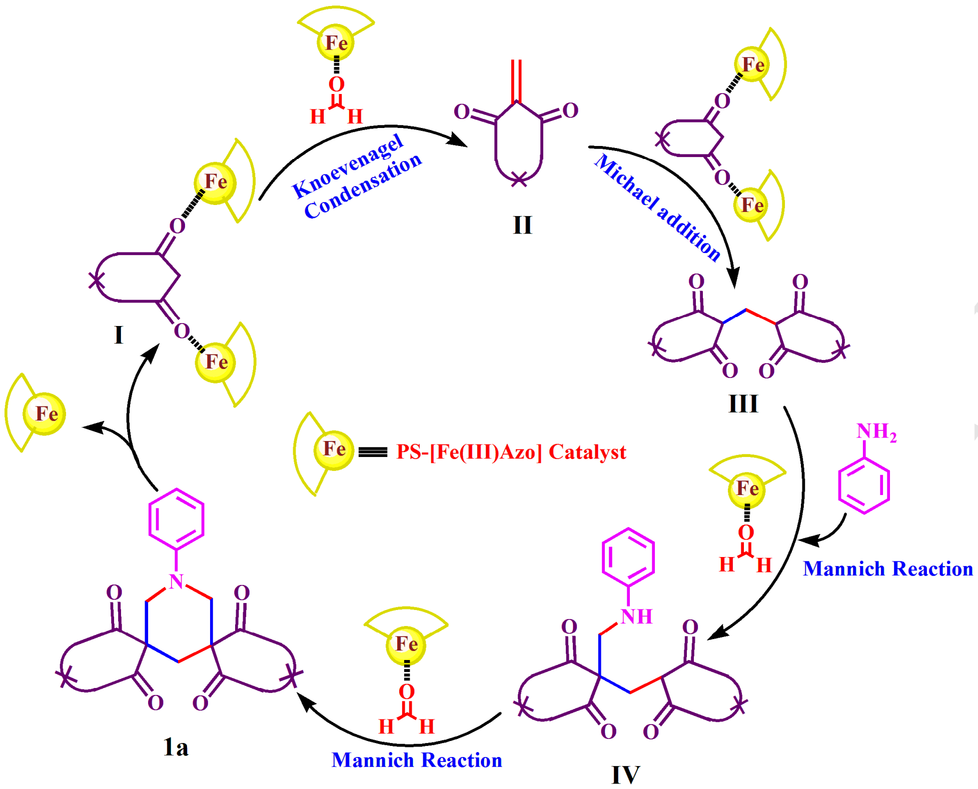
Catalytic efficacy of PS-[Fe(III)Azo] catalyst for the synthesis of spiropiperidine derivatives with other reported protocols.

Entry	Catalysts	Conditions	solvents	Products	Yield (%)	Time	reference
1	STA	R. T.	DCM		93	4 h	35(a)
2	Fe_3O_4	80 °C	solvent-free		73	5 h	35(b)
3		reflux (5 min)/ overnight/R. T.	ethanol		62	12 h	35(d)

4	Ce/chitosan	R. T.	PEG-200		94	38 min	36
5	PS-[Fe(III)Azo]	R. T.	isopropyl alcohol		95	30 min	This work
6	PS-[Fe(III)Azo]	R. T.	isopropyl alcohol		89	30 min	This work
7	PS-[Fe(III)Azo]	R. T.	isopropyl alcohol		85	30 min	This work

3.2.3. Reaction Mechanism

The probable mechanism of the synthesis of spiropiperidine derivatives is depicted in Scheme 5. The derivatives are seemed to derive through Knoevenagel condensation, Michael addition and double Mannich reactions [35]. In the very first step, PS-[Fe(III)Azo] catalyst activates formaldehyde and dimedone via Knoevenagel condensation to produce intermediate **(II)**. Then Michael addition occurs to the intermediate **(II)** by another mole of activated iron-dimedone intermediate **(I)** through the double bond to form intermediate **(III)**. In the next step, the Mannich reaction between intermediate **(III)**, aniline and activated iron-formaldehyde gives intermediate **(IV)**. Finally, intermediate **(IV)** and activated iron-formaldehyde take part in another Mannich reaction to generate final product **1a**, releasing PS-[Fe(III)Azo] catalyst for successive cycles.



Scheme 5. Proposed reaction mechanism for the syntheses of spiropiperidine derivatives.

4. Tests for Heterogeneity

After catalytic reaction, the leaching of iron from PS-[Fe(III)Azo] catalyst was assured through IR, UV-Vis, AAS analysis of the utilized catalyst and the product mixtures. The analysis did not show any considerable loss of iron loading compares to the unused catalyst. We got similar results from IR spectrums of the reused and fresh catalyst. AAS of used catalyst after first cycle (Table 1) showed the metal loading remains almost same in the fresh and reused catalyst but AAS data of reused catalyst after fourth cycle showed some small decrease (~ 6.4 %) in metal loading of the catalyst. AAS analysis of product mixtures confirmed the absence of iron in the product mixture. After catalytic reaction, a UV-Vis spectrum of product mixture was taken but no characteristics absorption peak of catalyst was observed. All these analyses clearly confirm that there was very low leaching of iron takes place during the course of each recycling reaction. All the above mention observations definitely support the heterogeneous nature of PS-[Fe(III)Azo] catalyst.

5. Recycling of Catalyst

The recycling experiment of the catalyst was carried out using the model reaction of salicyaldehyde (5 mM); KBr (2.2 mM); glacial AcOH (5 mL); 30% aq H_2O_2 (2.2 mM), catalyst (50 mg) at room temperature. After completion of the reaction, 20 mL H_2O was added to the final reaction mixture and 10 ml ethyl acetate was then also added to extract the products. The solid product was obtained by evaporating the organic layer under reduced pressure. The catalyst was filtered from the remaining aqueous phase, washed thoroughly with ether and methanol (1:10) mixture, dried and reused. Even after five cycles, the catalyst shows its good catalytic efficiency (Fig. 6). The catalytic conversion by the catalyst becomes almost half after ten cycle. After eleven cycle we got only 40% conversion of salicyaldehyde. AAS data showed that the catalyst contains 0.72% of iron after tenth cycle. So the metal loading decreases nearly 43% after tenth cycle and the TON decreased from 447 to 310. The leaching of metal from support and catalysis poison is responsible for this decrease of catalytic efficiency.

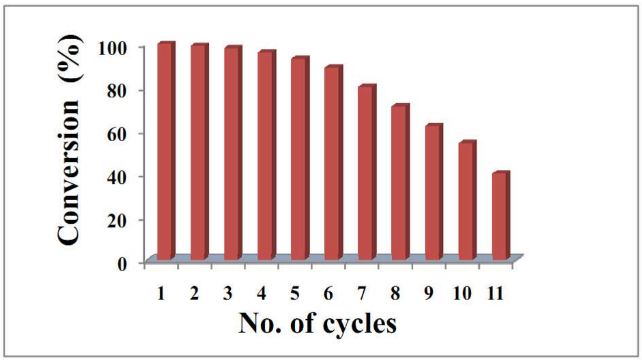


Fig. 6. Chart showing the recyclability of the PS-[Fe(III)Azo] Catalyst.

5. Conclusion

An organically modified polymer-anchored [Fe(III)Azo] catalyst was synthesized and characterized properly. The catalyst showed magnificent catalytic activity towards oxidative bromination reaction of different organic substrates. This bromination protocol offers simple reaction conditions of commercially available reagents and product yield is excellent without generation of hydrogen bromide waste product. It is a green alternative method in compare to the hazardous method of classical bromination and thus carrying an opportunity of easy production to a variety of bromo-derivatives.

The catalyst was also very effective in one pot three components synthesis of spiropiperidine derivatives. An environmentally benign simple and efficient method for the preparation of spiropiperidine derivatives by the efficient PS-[Fe(III)Azo] heterogeneous catalyst at room temperature has been reported here. The catalyst was recyclable and stable under the reaction conditions. The reusability of this catalyst is high (i.e. five times) without the significant decrease in its activity.

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Research Highlights

- A polymer supported catalyst, PS-[Fe(III)Azo] has been synthesized and characterized .
- The oxidative bromination of organic substrates was carried out by PS-[Fe(III)Azo].
- The catalyst showed excellent activities towards oxidative bromination of organic substrates under mild reaction conditions.
- The catalyst was also useful for the syntheses of spiropiperidine derivatives.
- The catalyst is reusable upto five times without diminishing of its activity.