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FULL PAPER

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Use of an efficient polystyrene-supported cerium catalyst for one-pot multicomponent synthesis of spiro-piperidine derivatives and click reactions in green solvent

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One-pot multicomponent reactions are very demanding in synthetic organic chemistry. Here we report a new polystyrene-supported cerium catalyst (PS-Ce-amtp) obtained via an easy two-step procedure, which was thoroughly characterized using various techniques. PS-Ce-amtp catalyses the environmentally benign one-pot multicomponent synthesis of spiro-piperidine derivatives through the reaction of substituted aniline, cyclic active methylene compound and formaldehyde at room temperature. The catalyst also exhibits excellent catalytic activity in one-pot synthesis of 1,4-disubstituted 1,2,3-triazoles via click reaction between *in situ* generated azides (derived from anilines and amines) and terminal alkynes. The catalyst can be recovered easily after reaction and reused five times without significant loss in its catalytic activity. The advantageous features of this catalyst are atom economy, operational simplicity, short reaction times, easy handling and high recycling efficiency.

KEYWORDS

click reaction, eco-friendly catalysis, heterogeneous catalysis, multicomponent reaction, spiro-piperidine

1 | INTRODUCTION

Lanthanide salt-mediated Lewis acid-catalysed reactions have attracted tremendous interest over the years due to their low toxicity, ease of handling, low cost, stability and recoverability of reagents from aqueous work-up.[1–4] In particular, cerium chloride heptahydrate ($CeCl_3 \cdot 7H_2O$) has emerged as a potentially useful Lewis acid, which imparts high regio- and chemoselectivity in various organic transformations.[5,6] It is also a cheap, non-toxic and water-tolerant catalyst. Due to its unique catalytic properties, $CeCl_3 \cdot 7H_2O$ has been intensively studied as catalyst for a plethora of organic transformations such as hydrooxacyclization of unsaturated 3-hydroxy esters, Michael addition, dihydroxylation of unreactive olefins and Julia olefination of cyclopropyl carbinols.[7–10] However, the main limitation from economic and environmental points of view is the use in stoichiometric amounts and involvement in secondary reactions. The use of a core metal salt as a catalyst is associated with a major problem of recovery of the catalyst from the reaction medium making reaction work-up and product isolation tedious. To overcome this problem, researchers have made great efforts to find eco-friendly reusable heterogeneous

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catalysts based on organic, inorganic and organic–inorganic hybrid solid supports for various organic transformations.[11–16] Polystyrene is one of the most widely studied heterogeneous and polymeric supports due to its low cost, ready availability, environmental stability and hydrophobic nature which protects water-sensitive Lewis acids from hydrolysis by atmospheric moisture until suspended in an appropriate solvent where they can be used in a chemical reaction.[17–19] Heterogeneous polystyrene-supported acid catalysts have received much attention because of their non-toxicity, non-corrosiveness, ease of handling, recovery and reuse, thermal stability, mildness of reaction conditions, high selectivity and simple work-up procedure.[20]

Multicomponent reactions have received substantial consideration in organic synthesis due to their many advantages over conventional multistep synthesis.[21–29] Multicomponent reactions allow the creation of several bonds in a single operation and offer remarkable advantages like convergence, operational simplicity, facile automation, reduction in the number of work-up steps, and easy extraction and purification processes, and hence minimize waste generation, rendering such transformations green. One of the important reactions in the field of multicomponent synthesis is the formation of spiro-substituted piperidines.[30–34] Piperidine is a very common organic compound, being best known as a representative structural element within many pharmaceuticals, alkaloids, eudistomidines H and I,[35] tetraponerines[36] verbametrine[37] and verbamethine.[38] The piperidine structural motif is also present in numerous natural products such as piperine (present in black pepper), fire ant toxin solenopsin, the nicotine analogue anabasine of tree tobacco (Nicotiana glauca), lobeline of Indian tobacco and the toxic alkaloid coniine from poison hemlock. Various *N*-substituted piperidines are synthetic intermediates for spermidine-nitroimidazole drugs for the treatment of A549 lung carcinoma.[39] Due to significant biological activity and miscellaneous interesting physiological activities, spiro-substituted piperidines have received a great deal of attention in recent years.[40–44] The spiro-piperidine nucleus is frequently found in several plant alkaloids and animal toxins and widely used in the treatment of cocaine abuse, epileptic disorder and depression, in the prevention of various inflammatory diseases, immune diseases such as autoimmune diseases or allergic diseases, and HIV infection, and in 5-HT2B receptor antagonists.[40,41,45] Despite their great importance, to date there are only a few reports in the literature documenting the synthesis of these spiro-substituted compounds.[46–51] Although all these methods provide good yields, some of the reactions are conducted with a homogeneous catalyst, requiring high temperature and long time for completion, and often these reactions need to be performed in the presence of a relatively large amount of catalyst.

The development of environmentally benign and efficient catalytic reactions has been attracting growing interest over the years. Toxic organic solvents remain a scientific challenge to the chemical industry due to increasing environmental awareness. It is now widely accepted that their use is considered to be one of the major concerns in waste management in fine chemical industries and they pose serious health as well as environmental hazards. Among various solvent systems, water is frequently employed in organic transformations because it is a readily available, safe and environmentally friendly.[52–57] The use of water and water-miscible solvent systems has become one of the most exciting research endeavours in organic synthesis. Polyethylene glycol is also used as a green solvent with widespread industrial and medical applications.[58,59] They are inexpensive and significantly less hazardous than other organic solvents. They have good stability in both acidic and basic media and are suitable reaction media for various organic reactions.

Azide–alkyne cycloaddition reaction leads to the production of five-membered heterocycles containing nitrogen (1,2,3-triazoles).[60] Azide–alkyne cycloaddition reaction products have found much utility as photostabilizers, pharmaceutical agents, anti-HIV agents[61] and anti-allergic products,[62] in biological screening[63] and as antibacterial agents,[64] corrosion inhibitors, photographic materials and dyes. Cu(I/II)-catalysed 1,3-dipolar azide–alkyne cycloaddition is well known, which exhibits strong regioselectivity under mild reaction conditions in water as solvent and using little amount of catalyst and in the absence of any reducing agents or base.[65] The idea of 'click' chemistry was proposed by Sharpless and co-workers in 2001.[66] After the discovery of click chemistry, azide chemistry has been explored because reactions between alkynes and azides result in the regioselective production of 1,2,3-triazoles.[67] The Huisgen 1,3-dipolar cycloaddition reaction is considered as the most demanding click reaction. Additionally, azides are very harmful to use freely due to their toxic nature. These azides can be obtained from their related anilines or amines by diazotization followed by the displacement reaction between sodium azide and alkyl halide or by sodium azide addition. Hence a single-step azide–alkyne cycloaddition reaction between an alkyne and *in situ* produced azide from its related precursor is very attractive.

In continuation of our interest in developing greener compatible processes,[68–72] in the work reported herein, we explored a novel and highly efficient synthetic one-pot reaction methodology for the synthesis of spiro-substituted piperidine compounds in three different green reaction media and at room temperature in the presence of a highly active polystyrene-supported cerium catalyst (PS-Ce-amtp). We also investigated a single-step method for the generation of five-membered 1,4-disubstituted heterocyclic 1,2,3-triazoles by the reaction between alkynes and *in situ* produced organic azides from related aromatic amines or anilines at room temperature catalysed by PS-Ce-amtp. The catalyst is not only readily prepared from cheap reagents, but also stable in air and can be easily recovered from a reaction mixture by simple filtration.

2 | EXPERIMENTAL

2.1 | Materials and Methods

Chloromethylated polystyrene (PS-Cl; 5.5 mmol Cl per gram of resin) was purchased from Sigma-Aldrich. Starting materials were commercially available or were synthesized by the reported procedures. All solvents and reagents were obtained from commercial sources and were used without further purification unless otherwise stated.

The Fourier transform infrared (FT-IR) spectra of samples were recorded from 400 to 4000 cm^{-1} with a PerkinElmer FT-IR 783 spectrophotometer. A Mettler Toledo TGA/SDTA 851 instrument was used for thermogravimetric analysis (TGA). The morphology of the functionalized polystyrene and complex was analysed using a scanning electron microscopy (SEM) instrument (Zeiss EVO40, UK) equipped with an energy-dispersive X-ray (EDX) analysis facility. Diffuse reflectance UV–visible spectra were obtained using a Shimadzu UV-2401PC double-beam spectrophotometer having an integrating sphere attachment for solid samples. The Ce content in the catalyst was estimated using atomic absorption spectrophotometry (AAS; Varian AA240). NMR spectra were obtained with a Bruker AMX-400 NMR spectrophotometer (400 MHz for ^{1}H NMR) using tetramethylsilane as internal standard.

2.2 | General Procedure for Synthesis of Spiro-substituted Piperidines

A mixture of aromatic amine (2 mmol), active cyclic methylene compound (4 mmol), formaldehyde (6 mmol, 37–41% aqueous solution) and catalyst (30 mg) in the solvent (15 ml) was stirred at room temperature for the required period of time. The appearance of a solid compound denoted the formation of products. After completion of the reaction (monitored by TLC), the reaction mixture was allowed to cool and extracted with a mixture of isopropyl alcohol and ethyl acetate (1:10). Solid products were obtained by further evaporation of this organic layer under reduced pressure. The catalyst in the remaining aqueous phase was filtered, washed with isopropanol–ethyl acetate (1:10) mixture, dried and reused for further catalytic cycles. Pure compounds were obtained by further recrystallization of crude products.

2.3 | General Procedure for Synthesis of 1,4-Disubstituted 1,2,3-Triazoles

In a 25 ml round-bottom flask, aromatic amine (1 mmol) was poured and kept in an ice bath at 0–5 °C. A solution of conc. H_2O–HCl (1:1, v/v) was poured in slowly and stirred for 5 min. Then sodium nitrite (1 mmol) was added to 1 ml of chilled water and poured dropwise into the solution. After mixing, NaN_3 (1.2 mmol) was poured into the solution and kept under magnetic stirring for 10 min. Then alkyne (1.2 mmol) and PS-Ce-amtp (20 mg) were added to the reaction mixture with continual stirring for 3 h at room temperature. The PS-Ce-amtp catalyst was separated by filtration and cleaned with water, ethanol and acetone. Extraction of other parts of the reaction mixture was performed with ethyl acetate. The aqueous part present in the mixture of the reaction was separated using Na_2SO_4 and the reaction mixture was added to a small amount of ethanol. After that, the separation of pure product was performed by crystallization to afford the resultant 1,4-disubstituted 1,2,3-triazoles.

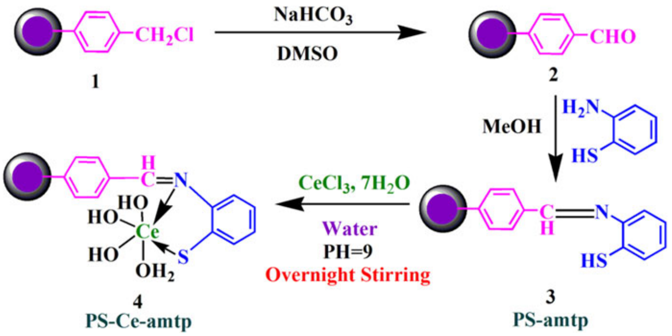
2.4 | Synthesis of Catalyst

2.4.1 | Synthesis of polymer-supported ligand

PS-Cl beads (**1**) were functionalized with aldehyde group according to a literature procedure.[73] To a suspension of the aldehyde-substituted polystyrene beads (**2**; 5.0 g) in methanol (20 ml), 2-aminothiophenol (2.0 g) was added, followed by stirring and refluxing for 20 h. After filtration and washing with absolute methanol, the polymeric ligand (**3**; PS-amtp) was obtained.

2.4.2 | Synthesis of PS-Ce-amtp catalyst

An amount of 1 g of $CeCl_3{\cdot}7H_2O$ was added to a suspension of PS-amtp (2 g) in 25 ml of water with continuous stirring. The pH of the solution was adjusted to *ca* 9.0 using 25% ammonia solution. The mixture was then continuously stirred overnight at room temperature and the resulting catalyst (**4**) was separated by filtration, washed with water and dried under vacuum at 60 °C (Scheme 1).



SCHEME 1 Synthesis of PS-Ce-amtp catalyst

3 | RESULTS AND DISCUSSION

3.1 | Characterization of Catalyst

The outline for the preparation of the polymer-supported cerium Schiff base complex, PS-Ce-amtp, is given in Scheme 1. Due to the insolubility of the complex in all common organic solvents, the characterization was limited to physicochemical properties, chemical analysis, SEM, transmission electron microscopy (TEM), TGA, and FT-IR and UV–visible spectral data.

SEM images of PS-Cl and the PS-Ce-amtp complex were recorded to understand the morphological changes occurring on the surface of the polymer matrix. In Figure 1 the SEM images of PS-Cl and the metal complex immobilized on modified polystyrene are shown. As expected, the pure polystyrene bead had a smooth and flat surface, while the anchored complex showed roughening of the top layer.

High-resolution TEM images of the PS-Ce-amtp material are shown in Figure 2 to understand the morphology and nanostructure of the polymer-supported Ce catalyst. As seen from these images, the Ce Schiff base complex

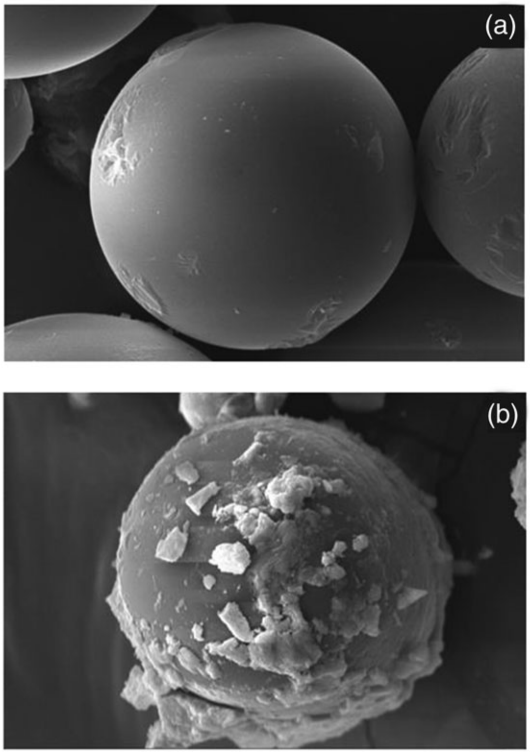


FIGURE 1 Field emission SEM images of (A) PS-Cl and (B) PS-Ce-amtp catalyst

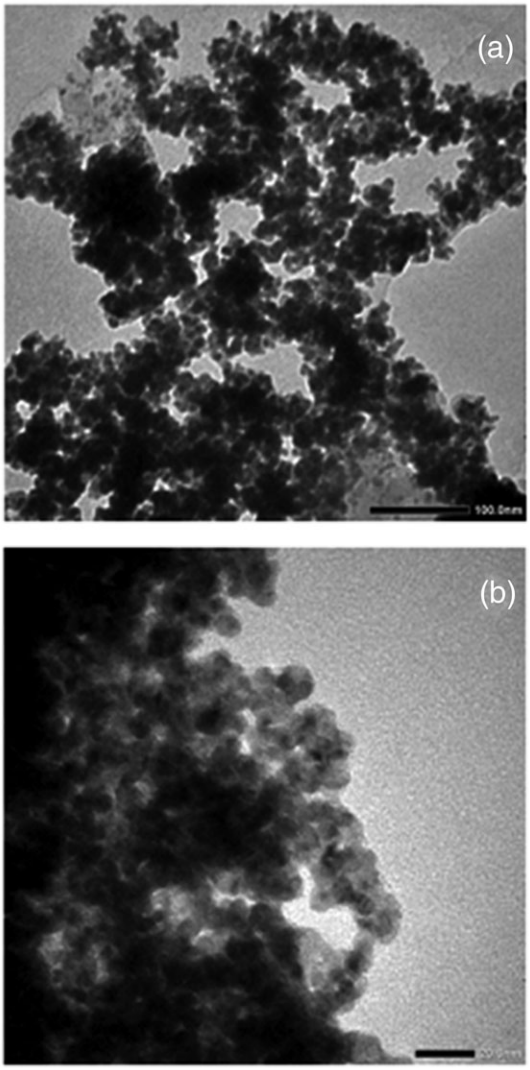


FIGURE 2 High-resolution TEM images of PS-Ce-amtp catalyst at (a) 100 nm and (b) 20 nm length scales

particles of size 8–10 nm are dispersed onto the polymer matrix throughout the specimens. Further, EDX analysis also confirmed the presence of Ce metal on the polymer matrix (Figure 3). From the EDX analysis it is seen that, in the metal complex, there is no chlorine atom. Since the immobilization of Ce(III) was performed in basic medium, the active metal species was Ce(III) in the form of $Ce(OH)_3$. AAS analysis suggested a loading of 4.65 wt% Ce in the PS-Ce-amtp material.

The mode of attachment of 2-aminothiophenol and metal onto the support was confirmed from FT-IR spectral bands (Figure 4). The sharp C—Cl peak (due to CH_2Cl groups) at 1264 cm^{-1}[76] in the spectrum of starting polymer material practically disappeared after introducing —CHO group in the polymer and a new peak was observed at 1702 cm^{-1} which indicated the C—O bond stretching vibration of the —CHO group. After ligand formation, there was a new peak at 1634 cm^{-1}, which indicated the formation of C—N bond in Schiff base moiety.[74] This band showed a decrease in intensity and shifted to lower wavenumber after complexation with metal. The thiophenolic (C—S) stretching frequency was observed in the region of 1287 cm^{-1} (of the ligand), which shifted to the lower frequency at 1268 cm^{-1} for the complex, indicating coordination of metal through the phenolic sulfur.[74,75] In the spectrum of the complex, bands at 281 and 554 cm^{-1} were assigned to νCe—S and νCe—N stretching frequencies, respectively.

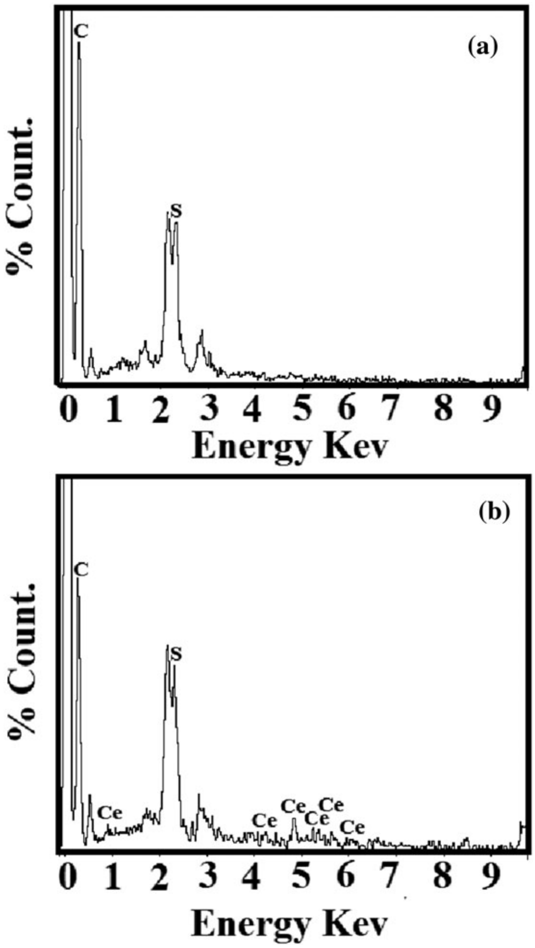


FIGURE 3 EDX spectra of (A) PS-amtp ligand and (B) PS-Ce-amtp catalyst

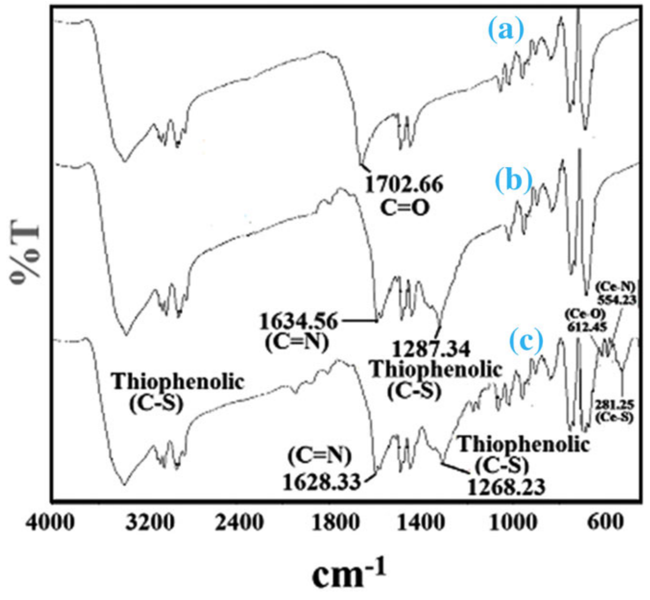


FIGURE 4 FT-IR spectra of (A) (P)-CHO, (B) PS-amtp and (C) PS-Ce-amtp catalyst

The thermal stability of the PS-amtp ligand and PS-Ce-amtp material was investigated using TGA at a heating rate of 10 °C min^{-1} in nitrogen atmosphere over a temperature range of 30–600 °C. It is seen that the thermal stability of the metal complex was slightly greater than that of the Schiff base ligand (Figure 5). The slight weight loss of the complex on heating below 200 °C might be attributed to the release of physically adsorbed water. The complex was stable up to 410 °C and further weight loss at a higher temperature (above 410 °C) was attributed to the decomposition of the complex. TGA suggested that the PS-Ce-amtp material degraded at considerably high temperature. The electronic spectrum of the PS-Ce-amtp material was recorded in diffuse reflectance spectrum mode using $BaSO_4$ disc as reference, as shown in Figure 6. The PS-Ce-amtp material showed a strong absorption at 350 nm, which could be attributed due to the presence of Ce(III).

3.2 | Catalytic Activity

3.2.1 | Activity of PS-Ce-amtp catalyst in synthesis of spiro-piperidine derivative

To explore appropriate reaction conditions is essential for the targeted synthesis. Initially, the three-component

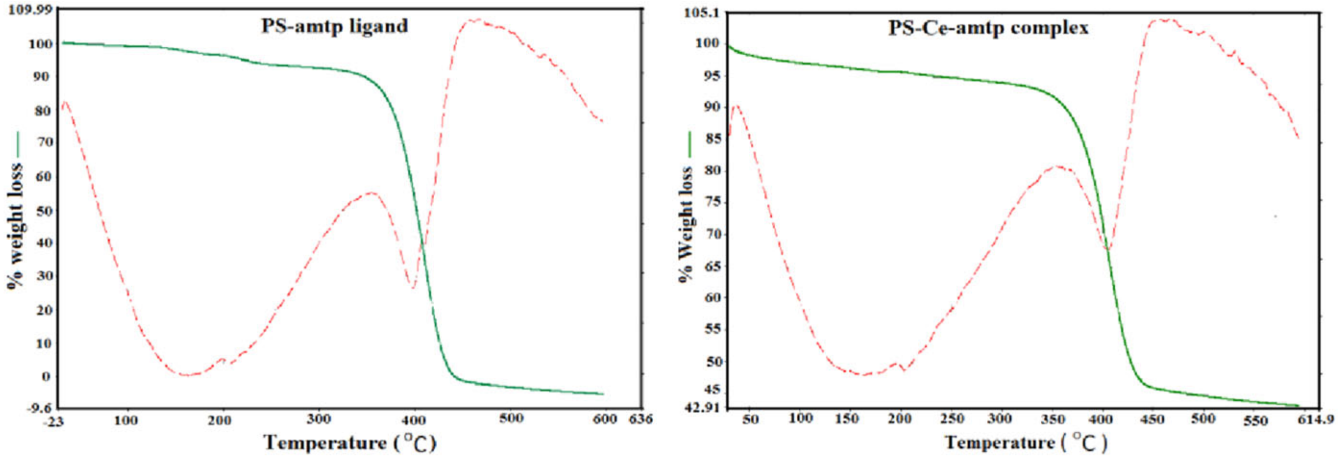


FIGURE 5 TGA weight loss plots for PS-amtp ligand and PS-Ce-amtp catalyst

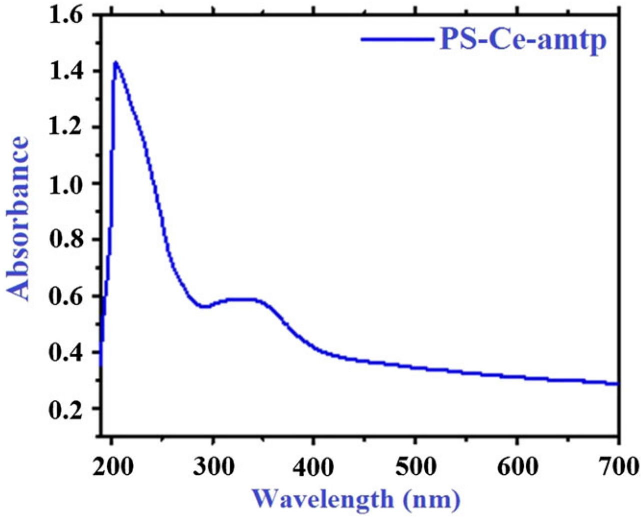
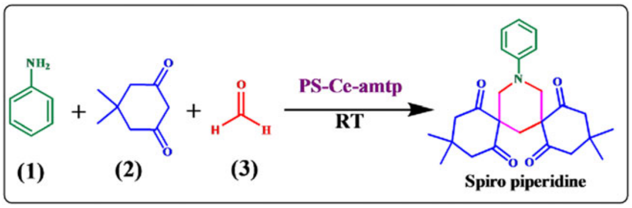


FIGURE 6 UV–visible spectrum of PS-Ce-amtp catalyst

condensation reaction of aniline (**1**), dimedone (**2**) and formaldehyde (**3**) was taken as a model reaction to establish the feasibility of the strategy and for optimizing the reaction conditions (Scheme 2). Here the maximum yield of the spiro-piperidine derivative was obtained when dimedone, aromatic amine and formaldehyde were taken in a ratio of 2:1:3.

The reaction did not proceed smoothly in the absence of the catalyst and only a trace amount of the product was formed, which could not be isolated. In search of a more efficient catalyst, a series of experiments was performed with the model reaction and the results are presented in Table 1. In the presence of strong acid like HCl, only a trace amount of the product was detected. This could be due to decomposition of the product in the presence of strong acid. Next, we carried out the reaction with various Lewis acids including different metal salts to compare the catalytic activity. Among the various homogeneous Lewis acids, it was found that $CeCl_3{\cdot}7H_2O$ was the most effective, and 71% conversion was obtained within 3 h at room temperature. Other homogeneous Lewis acids such as $FeCl_3$, $CuCl_2{\cdot}2H_2O$ and $AlCl_3$ gave low to moderate conversions. Compared to these homogeneous catalysts, heterogeneous acid catalysts afforded better isolated yields. Among them, PS-Ce-amtp showed excellent



SCHEME 2 Synthesis of spiro-piperidine derivative

TABLE 1 Effect of various catalysts on model reaction[a]

Entry	Catalyst	Time	Yield (%)[b]
1	HCl	3 h	8
2	$FeCl_3$	6 h	52
3	$CuCl_2{\cdot}2H_2O$	6 h	38
4	$AlCl_3$	6 h	67
5	$CeCl_3{\cdot}7H_2O$	3 h	71
6	PS-Cl	24 h	No product
7	PS-Al-amtp	3 h	72
8	PS-Ce-amtp	25 min	88
9	Silica-Ce-amtp	25 min	79
10	No catalyst	24 h	No product

[a] Reaction conditions: aniline (2 mmol), dimedone (4 mmol), formaldehyde (6 mmol), in water (15 ml) at room temperature. Reaction progress was monitored by TLC.

[b] Isolated yield.

catalytic activity under the present reaction conditions. The reaction did not proceed at all in the presence of the parent polymer, crosslinked PS-Cl, revealing that the support had almost no activity in the absence of Ce and Ce play the crucial role in this catalytic reaction. Also, PS-Ce-amtp was found to be a more effective catalyst than silica-Ce-amtp in terms of reaction time and yield of product under identical conditions. To determine the minimum optimum concentration of the PS-Ce-amtp catalyst, the model reaction was carried out with various amounts of catalyst and the results are presented in Figure 7. It is observed that the use of just 30 mg of PS-Ce-amtp is sufficient for the completion of the reaction in 25 min with 88% yield of the corresponding product in water medium at room temperature. With less than 30 mg of the catalyst, the reaction was incomplete and resulted in a low yield of product. On the other hand, an excessive amount of catalyst did not increase the yield significantly. Further studies showed that the reaction temperature has no such influence on the model reaction. On increasing the reaction temperature, no improvement in the yield was observed.

The choice of an appropriate reaction medium is of crucial importance for successful synthesis, so our next experiment focused on the selection of solvent. The results are summarized in Table 2. We screened various organic solvents such as dichloromethane (DCM), methanol, ethanol, acetonitrile and tetrahydrofuran (THF). All solvents gave low to moderate yield of product and the reaction required a long time for completion. Our literature investigation at this stage revealed that there are only very few reports on the synthesis of spiro-piperidine using a green reaction medium at room temperature. In most cases, the reaction time was long and moderate yield was obtained. Our main objective was to explore green synthesis conditions that can give higher yield of products in shorter time than the conventional reaction. To reduce the employment of ecologically suspect solvents we chose three different green solvents: polyethylene glycol (PEG), water–ethanol (1:1) and water. PEG is recognized as an attractive medium for many organic reactions. First, we conducted our model reaction in PEG. Because of the lower viscosity of PEG-200 than other PEGs (PEG-400 and PEG-600), it gave excellent product yields within 20 min. Next, we performed our model reaction in water–ethanol medium. The piperidine derivative was formed in a fairly high yield of 92% in 20 min. In our last set of experiments we used pure water as the solvent. To our delight, the results obtained were very satisfactory as the product in good yield (88%) was obtained in a short time period (25 min).

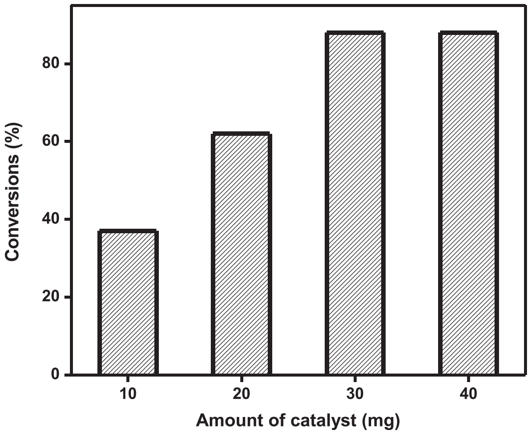


FIGURE 7 Effect of amount of PS-Ce-amtp catalyst on cyclocondensation reaction

TABLE 2 Effect of various solvents on model reaction[a]

Entry	Solvent	Time	Yield (%)[b]
1	DCM	2 h	65
2	Methanol	2 h	60
3	Ethanol	2 h	63
4	Acetonitrile	5 h	34
5	THF	5 h	28
6	PEG-200	20 min	97
7	PEG-400	20 min	80
8	PEG-600	20 min	38
9	Water–ethanol (1:1)	20 min	92
10	Water	25 min	88

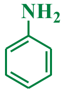
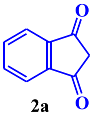
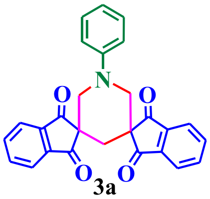
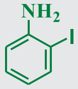
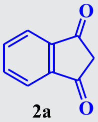
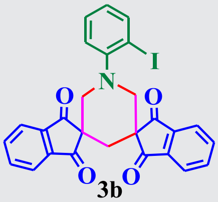
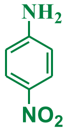
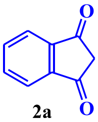
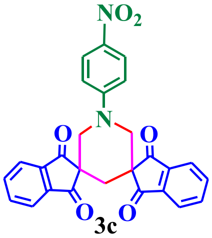
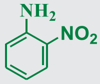
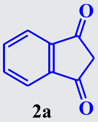
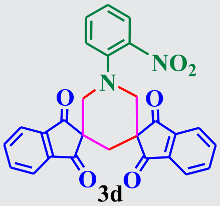
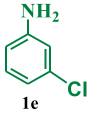
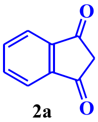
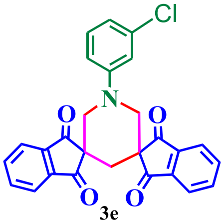
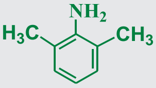
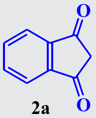
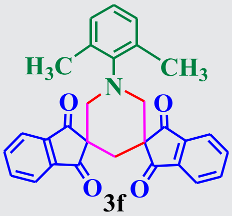
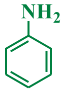
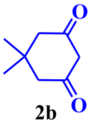
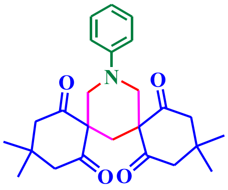
[a] Reaction conditions: aniline (2 mmol), dimedone (4 mmol), formaldehyde (6 mmol), PS-Ce-amtp catalyst (30 mg) at room temperature. Reaction progress was monitored by TLC.

[b] Isolated yield.

To further probe the potential of our methodology, the scope of the reaction was extended to a wider range of substituted aromatic amines using the PS-Ce-amtp catalyst under optimized reaction conditions (Table 3). The product yields were not significantly affected by the electronic nature of the substituent on the aromatic ring residue in the amine. Amines with both electron-donating and electron-withdrawing groups react efficiently to give spiro-piperidine adducts in good yield. The reaction of sterically hindered arylamine also proceeded smoothly affording the desired product in good yield. In addition, we also explored the reactivity of indane-1,3-dione (**2a**) for this transformation. From the results, it is clear that **2a** also showed excellent reactivity under the present reaction conditions.

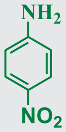
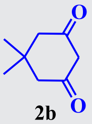
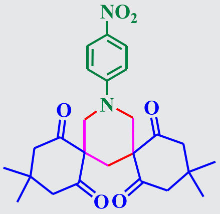
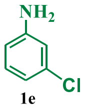
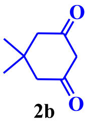
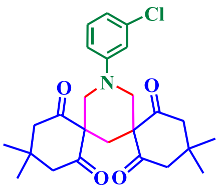
A possible reaction mechanism for the one-pot formation of the spiro-piperidine derivatives is shown in Scheme 3 on the basis of reported literature. The spiro-

TABLE 3 Synthesis of spiro-piperidine derivatives with various active methylene compounds and aromatic amines[a]

Entry	Aniline	Active methylene	Product	Time (min)	Yield (%)[b]
1	 **1a**	 **2a**	 **3a**	20 20 25	PEG: 97 WE: 93 W: 86
2	 **1b**	 **2a**	 **3b**	30 30 30	PEG: 92 WE: 84 W: 82
3	 **1c**	 **2a**	 **3c**	35 35 35	PEG: 91 WE: 80 W: 78
4	 **1d**	 **2a**	 **3d**	35 35 40	PEG: 88 WE: 86 W: 80
5	 **1e**	 **2a**	 **3e**	20 25 25	PEG: 96 WE: 91 W: 86
6	 **1f**	 **2a**	 **3f**	40 40 40	PEG: 84 WE: 77 W: 70
7	 **1a**	 **2b**	 **3g**	20 20 25	PEG: 97 WE: 92 W: 88

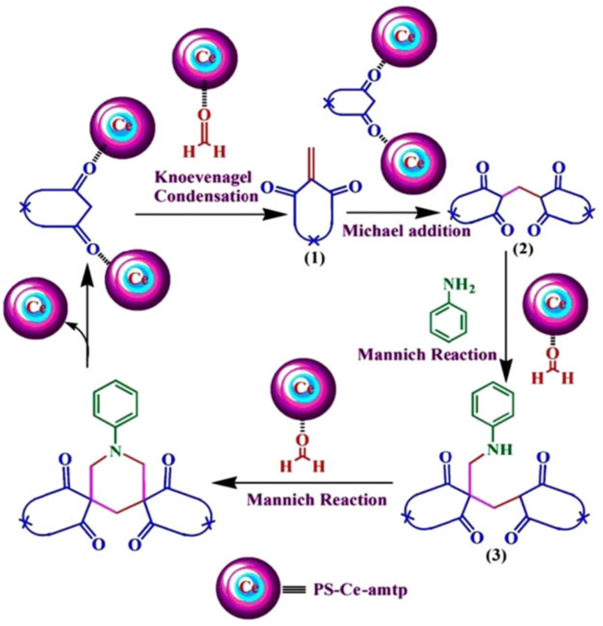
(Continues)

TABLE 3 (Continued)

Entry	Aniline	Active methylene	Product	Time (min)	Yield (%)[b]
8	 1c	 2b	 3h	35 35 35	PEG: 95 WE: 89 W: 85
9	 1e	 2b	 3i	25 25 25	PEG: 96 WE: 92 W: 87

[a]Reaction conditions: aniline (2 mmol), dimedone (4 mmol), formaldehyde (6 mmol), in water (15 ml) at room temperature. Reaction progress was monitored by TLC. Products were characterized by NMR spectral data. (PEG, polyethylene glycol; WE, water–ethanol (1:1); W, water).

[b]Isolated yield.



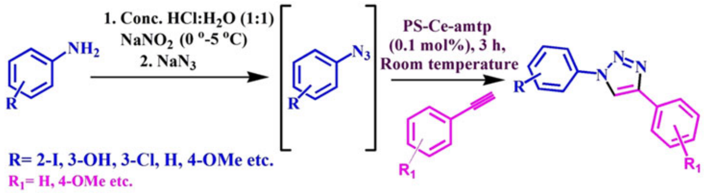
SCHEME 3 Proposed reaction mechanism of spiro-substituted piperidine ring formation

cyclization is proposed to proceed as a domino sequence of Knoevenagel, Michael and double Mannich reactions. First, the immobilized Ce catalyst activates both methylene compound and formaldehyde which leads to the formation of the standard active methylene–formaldehyde adduct (**2**) through Knoevenagel condensation followed by Michael addition. This undergoes two consecutive Mannich reactions with aniline to form the final spiro-piperidine product (**4**), freeing the catalyst for the subsequent cycle.

3.2.2 | Activity of PS-Ce-amtp catalyst for azide–alkyne one-pot click reaction

To explore the azide–alkyne one-pot click chemistry, we studied catalytic, high-yielding, environmentally benign and cheap reagents for click reaction and considered PS-Ce-amtp as a preference. When organic azide (produced from aromatic amine by the method of diazotization) and alkyne were reacted in the presence of PS-Ce-amtp in aqueous medium at room temperature, a five-membered heterocyclic 1,4-disubstituted 1,2,3-triazole was produced (Scheme 4).

As water is abundant in nature and is an environment-friendly and economical solvent, we initially tried to carry out the click reaction in water medium for the reaction between phenyl azide generated *in situ* from aniline and phenylacetylene using 20 mg of PS-Ce-amtp catalyst at room temperature. The reaction proceeded well resulting in the production of the corresponding five-membered heterocycle with 98% yield. We also performed this click reaction using $CeCl_3 \cdot 7H_2O$ and PS-Cl as catalyst. PS-Ce-amtp exhibited better activity than $CeCl_3 \cdot 7H_2O$ (78% yield obtained with the latter). PS-Cl did not exhibit any activity for this click reaction. Syntheses of spiro-substituted piperidines and 1,4-disubstituted 1,2,3-triazoles are metal-catalysed reactions. When PS-Cl, which is used as heterogeneous support, was used as catalyst, we could not observe any catalytic activity (Table 1, entry 6). Further, when homogeneous Ce salt was used as catalyst (Table 1, entry 5), conversion was much lower after longer reaction time. The immobilized polystyrene-supported cerium complex



SCHEME 4 Production of 1,4-disubstituted 1,2,3-triazoles from aromatic amines by two-step one-pot click reaction at room temperature in green solvent catalysed by PS-Ce-amtp

catalyst was found to be more active than the homogeneous metal salt. This could be attributed to the confinement effect where the immobilization of active sites over the support played crucial role in facilitating the reactions.

To optimize the reaction conditions, a series of experiments altering catalyst amount, temperature and time for the click reaction were performed in aqueous medium. The experimental data are listed in Table 4. The best conversion was found utilizing 20 mg of PS-Ce-amtp at room temperature for 3 h (Table 4, entry 2). No yield was found in the absence of PS-Ce-amtp catalyst (Table 4, entry 7).

To examine the scope and limitation of the click reaction, a series of organic anilines and terminal alkynes with structurally diverse functional groups were studied and the results are presented in Table 5. In general, the method is extremely high yielding and clean. A series of various aromatic amines was investigated in the reaction with phenylacetylene. The results showed that aryl and benzyl azides formed *in situ* from substituted anilines and benzylamines reacted rapidly with phenylacetylene and the resultant five-membered heterocycles were obtained in elevated yield at room temperature within 3–4 h. The catalytic system was found to be very efficient regardless of the presence of electron-withdrawing (Cl, I, 2-NO_2) or electron-donating (4-OCH_3, 3-OH) substituents in the aromatic ring. All the *para*-, *meta*- and *ortho*-substituted aromatic amines reacted almost equally with the alkyne and gave comparable product yields (Table 5, entries 1–6), although *ortho*-substituted anilines required longer reaction time than the others. Substituted *p*-methoxyphenylacetylene was also employed to react with diversely substituted azides formed *in situ* from amines to form the corresponding 1,2,3-triazoles by this procedure. A good yield was also obtained with anilines having electron-donating and electron-withdrawing substituents (Table 5, entries 7–10).

The proposed mechanism for the PS-Ce-amtp-catalysed click reaction is shown in Scheme 5. PS-Ce-amtp generates μ-coordinated aggregate with the terminal alkyne, and subsequently by substitution of the terminal proton of the corresponding alkyne provides cerium acetylides (II). After that, the aromatic organic azide generates linkage with the terminal Ce composite, producing component III. Because of the nucleophilic nature of terminal nitrogen of the organic azide, a rearrangement generates metallacycles (IV), which first supports the C-4 position to attack. Subsequently, at carbon of C-5, the attack of unshared pairs of electrons on the nitrogen of N-1 generates in a novel metallacycle to provide component IV. Subsequently, in the last step, PS-Ce-amtp can depart from species V producing the 1,2,3-triazole.

To understand the efficiency of our catalytic system we compared the PS-Ce-amtp catalyst with some reported heterogeneous catalysts from the literature for the cyclo-condensation reaction[48,76] and one-pot click reaction.[77–80] In Table 6 is presented a comparison of

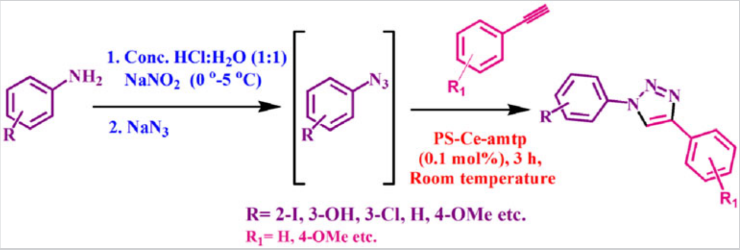
TABLE 4 Factors affecting the ‘click’ chemistry catalysed by PS-Ce-amtp[a]

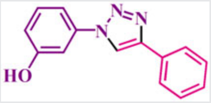
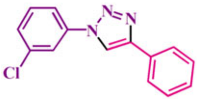
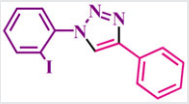
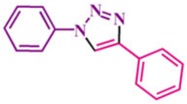
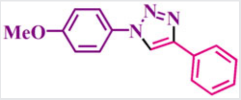
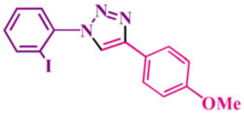
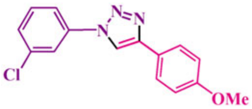
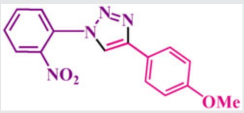
Entry	Catalyst amount (mg)	Time (h)	Temperature (°C)	Yield (%)[b]
1	20	4	70	98
2	**20**	**3**	**RT**	**98**
3	20	2	RT	96
4	15	3	RT	95
5	25	3	RT	98
6	25	2	RT	96
7	0	3	RT	No Yield

[a] Reaction conditions: phenylacetylene (1.2 mmol), aniline (1 mmol), water (10 ml).

[b] Isolated yield.

TABLE 5 Click reaction between various kinds of aromatic amine derivatives and phenylacetylene catalysed by PS-Ce-amtp[a]

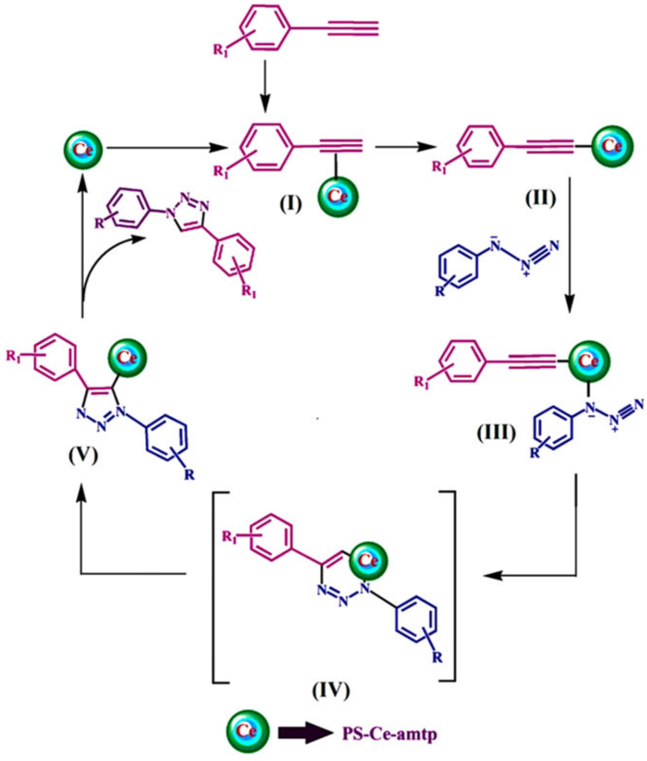


Entry	R	R_1	Product	Time	Yield (%)[b]
1	2-NO_2	H		4	94
2	3-OH	H		3	94
3	3-Cl	H		3	93
4	2-I	H		4	90
5	H	H		3	98
6	4-OMe	H		3	98
7	2-I	4-OMe		4	89
8	3-OH	4-OMe		3	92
9	3-Cl	4-OMe		3	92
10	2-NO_2	4-OMe		4	92

[a] Reaction conditions: phenylacetylene (1.2 mmol), aromatic amine (1 mmol), water (10 ml), 20 mg PS-Ce-amtp at room temperature. Products were characterized by NMR spectral data.

[b] Isolated yield.

catalytic data for our PS-Ce-amtp catalytic system with those published in the literature. As is evident from Table 6, the PS-Ce-amtp catalyst showed higher catalytic activity compared to previously published data. Reactions were carried out at room temperature, reaction times of minutes were necessary and, most significantly, these reactions were carried out in aqueous medium with the PS-Ce-amtp catalyst.



SCHEME 5 Proposed pathway for click reaction catalysed by PS-Ce-amtp

3.3 | Catalyst Recycling

One of the major thrusts of our present work was to find high recycling efficiency of the catalyst and this is obviously imperative in the context of financial viability and sustainable development. The catalyst recycling experiment was carried out using the model reaction of dimedone, formaldehyde and aniline and the one-pot click reaction of aniline with phenylacetylene under the optimized reaction conditions. After the first run, the catalyst was recovered by extracting the mixture with (1:10) isopropyl alcohol–ethyl acetate followed by filtration. The catalyst then washed with ethyl acetate under reduced pressure and dried. The catalyst was recovered almost quantitatively and tested in up to five more reaction cycles (Figure 8). It was found that, after five cycles, the catalyst still had a high activity and gave the desired product in good yield.

3.4 | Leaching Study

Catalyst lifetime and leaching of active metal species into solution are important issues to be considered when a

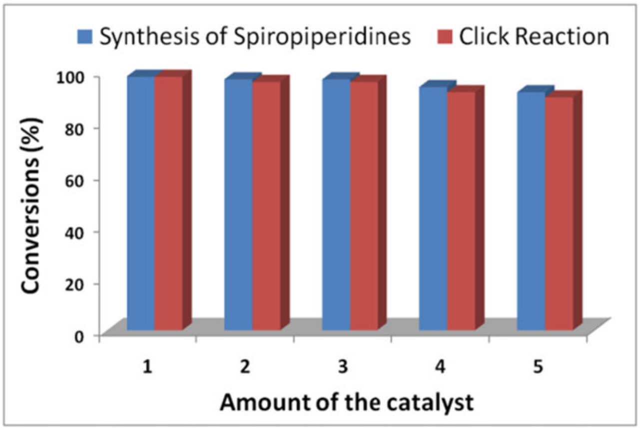


FIGURE 8 Recycling efficiency of PS-Ce-amtp catalyst for multicomponent and click reactions

TABLE 6 Comparison of catalytic activity of present catalyst in synthesis of spiro-piperidine derivatives and click reactions with that of other reported catalyst systems

Catalyst	Reaction conditions	Yield (%)	Ref.
Synthesis of spiro-piperidine derivatives			
STA	Aniline (1 mmol), dimedone (2 mmol), formaldehyde (3 mmol), water, RT, 6 h	74	[50]
Cu/SiO$_2$	4-Chloroaniline (1 mmol), dimedone (2 mmol), formaldehyde (3 mmol), DCM, RT, 10 h	81	[78]
PS-Ce-amtp	Aniline (2 mmol), dimedone (4 mmol), formaldehyde (6 mmol), water, RT, 25 min	88	Present study
Click reaction			
Silver(I) acetate complex	Phenylacetylene, benzyl azide, caprylic acid, PhMe, 48 h, RT	95	[79]
Ag$_2$CO$_3$	Phenylacetylene, NMP, ethyl 2-isocyanoacetate, 80 °C	89	[80]
Cu(MeCN)$_4$PF$_4$ and silver acetylide	Pyridine, azide, 24 h, RT	75	[81]
Silver acetate complex	Phenyl acetylene, benzyl azide, caprylic acid, PhMe, 90 °C	79	[82]
PS-Ce-amtp	Aniline (1 mmol), phenylacetylene (1.2 mmol), RT, 3 h	98	Present study

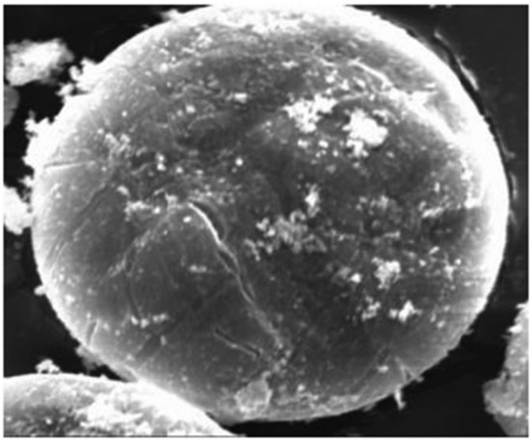


FIGURE 9 SEM image of the recycled PS-Ce-amtp catalyst after five cycles

heterogeneous catalyst is employed for large-scale industrial operation. Our present PS-Ce-amtp catalyst is very stable in air and moisture. In order to determine the absolute amount of metal species dissolved in solution caused by leaching, AAS analysis was performed. The AAS analysis of the reaction mixture revealed that at the end of the first run only 0.06 wt% of Ce metal was lost into the solution, indicative that Ce is tightly bound to the support. It is seen that after five recycling experiments less than 0.2 wt% of Ce metal was leached into the solution. This leaching level was negligible which was also confirmed by the excellent recoverability and reusability of this heterogeneous catalyst. The morphology of the catalyst obtained after five recycles observed using SEM (Figure 9) also does not show any significant changes, indicating that the structural integrity of the catalyst is maintained throughout the recycling process.

4 | CONCLUSIONS

We have synthesized a polymer-supported Ce catalyst which catalyses efficiently the synthesis of spiro-piperidine derivatives and five-membered heterocyclic 1,2,3-triazoles through one-pot multicomponent reactions. All the reactions were conducted in a green solvent medium which is less expensive and less toxic than organic solvents. Moreover, both the synthesis of the catalyst and the catalysed reactions are simple and cost-effective and offer several advantages such as shorter reaction time, simple experimental work-up procedure and easy recovery of the catalyst, suggesting high sustainability of these reactions over this supported Ce catalyst. These advantages could make the system highly promising from the synthetic and environmental points of view.

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