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# Cerium Supported Chitosan as an Efficient and Recyclable Heterogeneous Catalyst for Sustainable Synthesis of Spiropiperidine Derivatives

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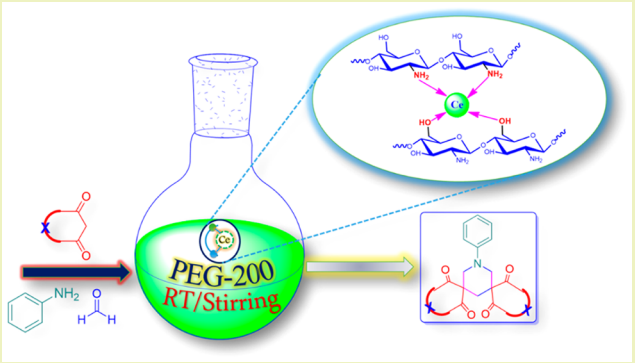
Supporting Information

**ABSTRACT:** A new Ce/chitosan catalyst has been prepared and used for the highly efficient synthesis of diverse range of spiropiperidine derivatives via multicomponent reaction of substituted anilines, formaldehyde and different cyclic active methylene compounds at room temperature in PEG-200. The catalyst could be reused for five consecutive cycles without appreciable loss in catalytic activity. The structure of the catalyst was determined by IR, XRD, EDX, TEM and ICP-AES techniques. The present green protocol has advantages such as novel products, energy sustainability, short reaction times, high yield of products, economic viability and recyclability of the catalyst.




**KEYWORDS:** *Heterogeneous, Multicomponent, Spiropiperidine, PEG-200, Green*

## INTRODUCTION

In the last decades, the use of lanthanides as Lewis acids in organic synthesis has increased enormously[1,2] and among them Ce salts, being the most abundant, have been extensively used in reduction, C−C, C−N and C−O bond formation reactions.[3] This extensive use of Ce salts is attributed to moderate to low toxicity, water tolerance, easy to handle, availability at moderate cost and suitability for use without purification. However, the main limitation from economic and environmental point of views is their use in stoichiometric amounts. Therefore, the development of heterogenized version of Ce salts remains a major objective of modern organic chemistry, and the simplest strategy to perform this task is by immobilization on a solid support. In recent years, biopolymers have gained lot of attention for their use as supporting materials.[4] Chitosan is a natural, abundant and low-cost polymer that exhibits interesting properties like nontoxicity, easy chemical modification due to presence of both amino and hydroxyl groups, inertness toward air and moisture, biocompatibility and biodegradability, and thus, make it a versatile supporting material.[5−8]

The piperidine ring unit forms the core of a large family of alkaloids and natural products with strong medicinal and interesting structural properties. The presence of piperidine motifs in drug molecules has generated a lot of interest in development of efficient protocols for the synthesis of these compounds.[9−14] Recently, spiro-substituted piperidines have received considerable attention due to their important pharmacological profiles like selective and potent $\sigma$ receptor ligands that can be used in the treatment of cocaine abuse, depression and epileptic disorders and 5-$HT_{2B}$ receptor antagonists.[15−20] Owing to the importance of these compounds in the field of medicine, unexpectedly, there are only few protocols available in the literature documenting the synthesis of these spiro compounds.[21−24] However, many shortcomings associated with these protocols include the use of homogeneous catalysts, toxic solvents, long reaction times and very limited substrate tolerance. Therefore, it is highly desirable to develop an efficient protocol for the synthesis of spiropiperidine adducts that is highly efficient, environmental friendly, tolerates a wide range of substrates and involves the reuse of the catalyst.

In the present work, taking advantage of the above-mentioned properties of chitosan, we have synthesized a new, effective, inexpensive and recyclable chitosan supported cerium catalyst and used it for the synthesis of novel spiropiperidine derivatives via multicomponent reaction of substituted anilines, formaldehyde and different active methylene compounds at room temperature using PEG-200 as a green solvent. It is worthy to mention that polyethylene glycols (PEGs) are inexpensive, nontoxic, nonvolatile and thermally stable compounds that serve as suitable media for environmentally sustainable organic transformations.[25] Their solubility in water leads to easy separation and recovery of products from the reaction medium.

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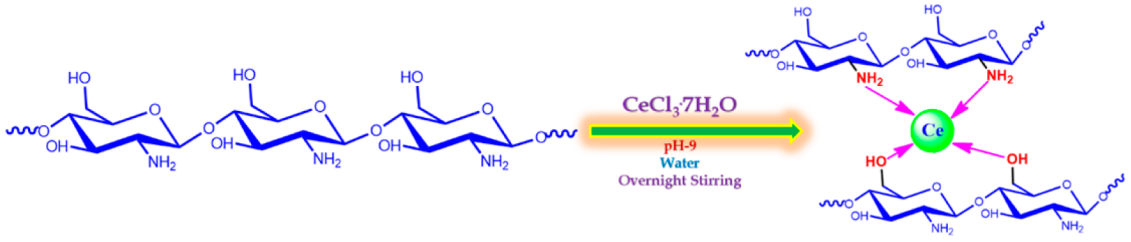
**Scheme 1. Schematic Representation of the Synthesis of the Catalyst**



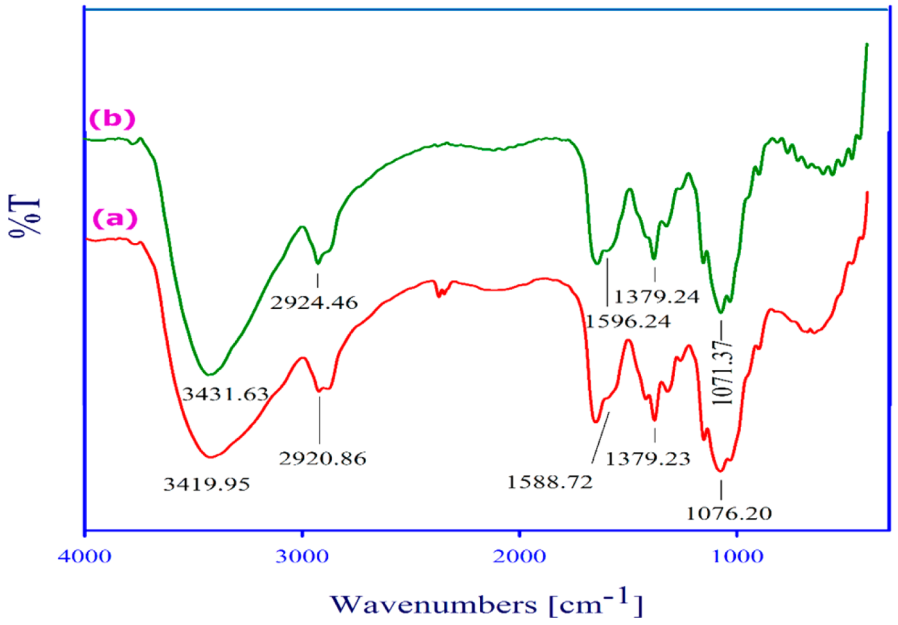




**Figure 1.** FT-IR spectral analysis (a) of chitosan and (b) of Ce immobilized chitosan.

## EXPERIMENTAL SECTION

**Synthesis of Ce–Chitosan Catalyst.** 1 g of $CeCl_3.7H_2O$ was added to the suspension of chitosan (80% deacetylated) (5 g) in 100 mL of water with continuous stirring. The pH of the solution was adjusted at 9 using 25% ammonia solution. The mixture was then continuously stirred overnight at room temperature and the resulting catalyst was separated by filtration and dried under vacuum at 60 °C (Scheme 1). The amount of Ce incorporated into chitosan was found to be 7.94% by ICP-AES analysis.

**General Procedure for the Synthesis of 3,5-Dispirosubstituted Piperidines (3a–e, 3k–o).** A mixture of amines **1a–e** (4 mmol), active methylene compounds **2a, 2c** (8 mmol), formaldehyde (12 mmol, 37–41% aqueous solution) and a catalytic amount of Ce/chitosan (0.8 g, 0.456 mmol of Ce) in PEG-200 (15 mL) was stirred at room temperature for the stipulated period of time (Table 3). The appearance of solid compound denoted the formation of products. After completion of the reaction (monitored by TLC), water (20 mL) was added in order to dissolve the PEG-200 and a mixture of isopropyl alcohol/ethyl acetate (1:10) was then added to extract the products. 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. The pure compounds were obtained by further recrystallization.

**General Procedure for the Synthesis of 3,5-Dispirosubstituted Piperidines (Coumarin Products) (3f–j).** A mixture of amines **1a–e** (4 mmol), 4-hydroxycoumarin **2b** (8 mmol), formaldehyde (12 mmol, 37–41% aqueous solution) and a catalytic amount of Ce/chitosan (0.8 g, 0.456 mmol of Ce) in PEG-200 (15 mL) was stirred at room temperature for the stipulated period of time (Table 3). The appearance of solid compound denoted the formation of products. After completion of the reaction (monitored by TLC), water was added and the mixture of catalyst and solid products was filtered. After filtration, DMSO (10 mL) was added to dissolve the products leaving behind the catalyst. The catalyst was filtered, washed with DMSO, isopropyl alcohol/ethyl acetate (1:10) mixture, dried and reused. The solvent containing products was left undisturbed in order to obtain pure compounds.

(According to the U.S. Food and Drug Administration (FDA) solvent classification based on their possible risk to human health, DMSO belongs to class 3, which is defined as solvents with low toxic potential and no health-based exposure limit is needed. It is one of the least toxic organic chemicals known, and hence is considered a green solvent. DMSO has also been shown to have applications in medicine. PEGs are components in many consumer products and have been approved by the U.S. Food and Drug Agency for internal consumption).[26,27]

## RESULTS AND DISCUSSION

Scheme 1 illustrates the synthesis of the catalyst from chitosan. The chitosan was suspended in water maintained at pH 9 by using ammonia solution, then further addition of $CeCl_3.7H_2O$ and overnight stirring at room temperature gave the desired catalyst.

The catalyst was characterized thoroughly by using FT-IR, powder X-ray diffraction (XRD), energy dispersive X-ray spectrometry (EDX), transmission electron microscopy (TEM) and ICP-AES techniques.

FT-IR spectra (Figure 1a) of pure chitosan showed a broad band for OH and NH stretching of amine groups centered at 3419 $cm^{-1}$. The presence of band at 1588 $cm^{-1}$ confirms the



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presence of the $NH_2$ groups. The absorption bands present at 1076 and 1379 $cm^{-1}$ correspond to the stretching vibrations of C−OH and C−N groups, respectively. The band centered at 2920 $cm^{-1}$ is attributed to the C−H stretching mode of methylene groups.[28] The FT-IR spectra of Ce immobilized chitosan (Figure 1b) shows different fingerprint region to that of pure chitosan owing to formation of Ce−N and Ce−O coordinate bonds in the low-frequency region (600−500 $cm^{-1}$).[29,30] Moreover, decrease in the intensity of −NH band at 1596 $cm^{-1}$, may be due to the complexation of cerium with $-NH_2$ groups. Similarly, shifting of the OH-bending band at 1071 $cm^{-1}$ is accounted for the interaction of cerium species with the OH groups of chitosan.[5,6]

The XRD patterns of the catalyst (Figure 2a) and chitosan (Figure 2b) were similar. The complexation of cerium with chitosan through coordinate bonds coupled with its low content and small size may be the reason for the absence of peaks pertaining to cerium in the XRD of the catalyst. However, the presence of Ce in the catalyst was confirmed by EDX analysis (Figure 3). The EDX spectrum does not show presence of Cl; therefore, the active species, immobilized on the support, is Ce(III) in the form of $Ce(OH)_3$. ICP-AES analysis was performed in order to obtain the actual amount of Ce in the catalyst. The analysis showed the weight percentage of cerium to be 7.94%, which corresponded to the loading amount of 0.57 mmol/gram of catalyst. TEM images (Figure 4a,b) of the catalyst showed a very well dispersion of Ce nanoparticles (dark spots) in the form of $Ce(OH)_3$, with a particle diameter of 3−8 nm, on the surface of chitosan.

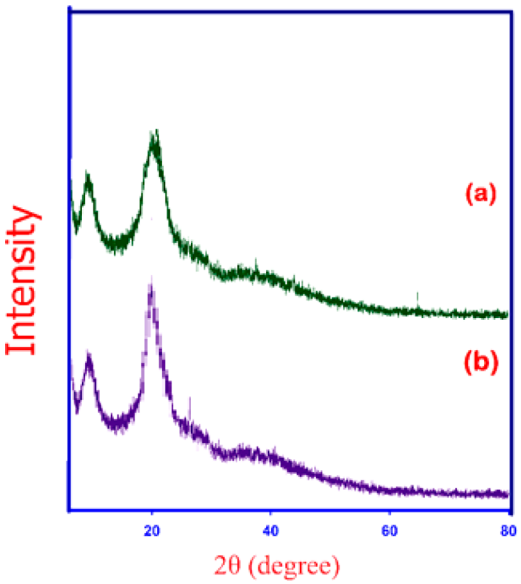


**Figure 2.** XRD analysis (a) Ce immobilized chitosan and (b) of chitosan.

## OPTIMIZATION OF REACTION CONDITIONS

To make sure that catalytic activity originated from Ce sites bound to chitosan, various control experiments were carried out at room temperature in PEG-200 using indane-1,3-dione (2 mmol), formaldehyde (3 mmol) and aniline (1 mmol) as model substrates. Reaction in the absence of any catalyst could not lead to any product formation, whereas using chitosan (10 mol %) as a catalyst gave unsatisfactory results. We then tried the reaction using $CeCl_3{\cdot}7H_2O$ (10 mol %) as a catalyst, and it was observed that the reaction proceeded with good results giving product yield of 74% in 2.5 h. This clearly proves that the catalytic activity originated from Ce sites, but the homogeneous nature of $CeCl_3{\cdot}7H_2O$ made recyclability of the catalyst cumbersome. When the reaction was performed with Ce/chitosan (200 mg, 0.114 mmol of Ce) as a catalyst, a remarkable increase in its catalytic activity was observed affording the product with high yield (92%) in a shorter time period. Then our study focused on the development of the optimal reaction conditions for this transformation, which included solvent screening and influence of the catalyst amount. The reaction between indane-1,3-dione (2 mmol), formaldehyde (3 mmol) and aniline (1 mmol) under various conditions was used as a model reaction for all experiments. First, the effect of different solvents on the model reaction was investigated at room temperature using 200 mg of the catalyst. Various solvents like water, methanol, ethanol, isopropyl alcohol, PEG-200, PEG-400 and PEG-600 were screened to test the efficiency of our catalyst, and the results are summarized in Table 1. The reaction in water could not proceed to completion, methanol as a solvent could not produce satisfactory results, using ethanol and isopropyl alcohol

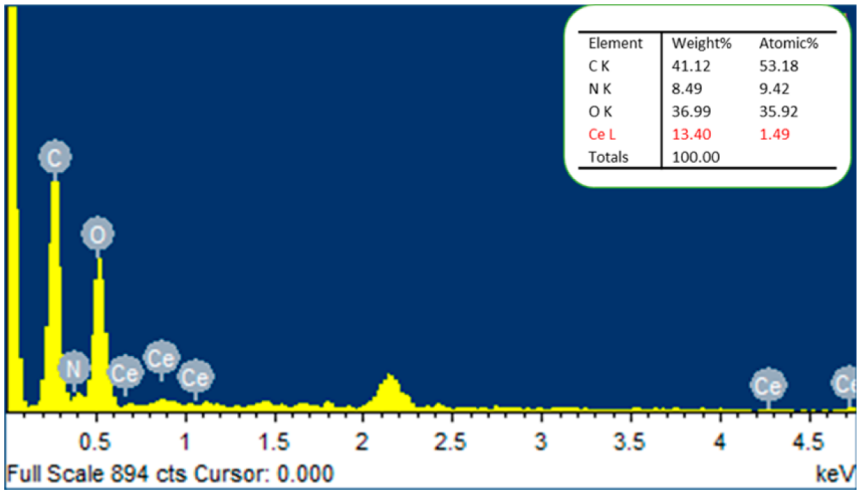


**Figure 3.** EDX spectra of Ce immobilized chitosan catalyst showing the presence of Ce in addition to C, N and O.


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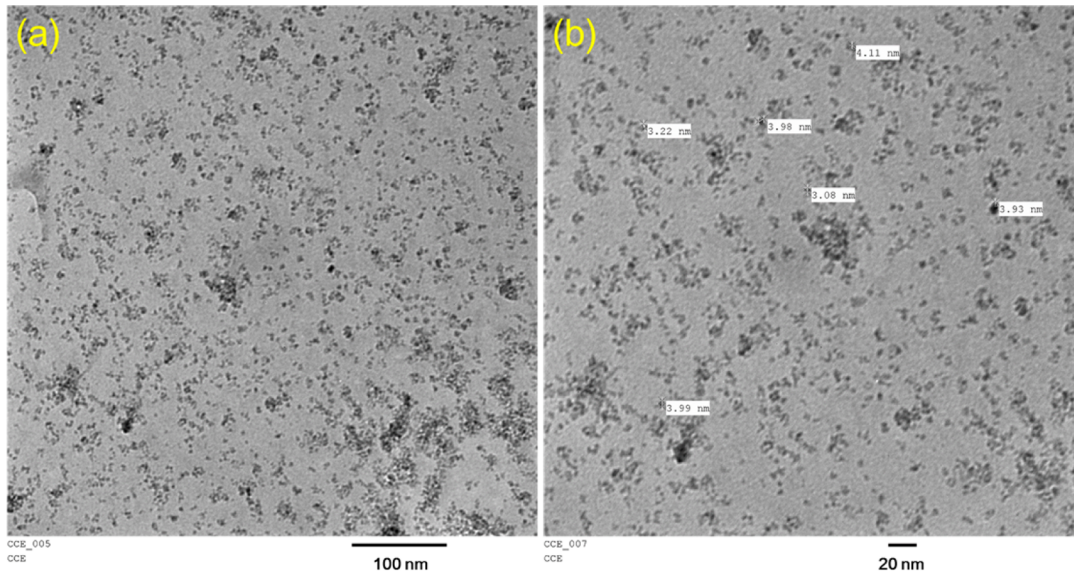
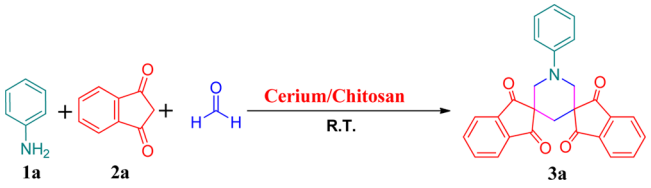



**Figure 4.** TEM images (a and b) of the synthesized catalyst at different magnifications.

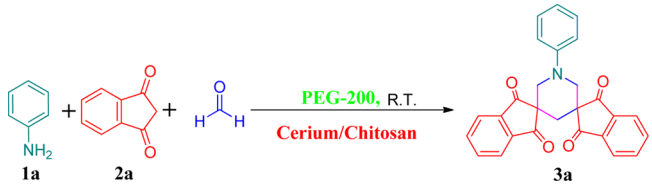
**Table 1. Effect of Different Solvents on the Reaction**




| entry | solvent (5 mL) | time[a] (min) | yield (%)[b,c] | TOF[d] |
|---|---|---|---|---|
| 1 | water | 60 | no reaction | |
| 2 | methanol | 53 | 68 | 6.77 |
| 3 | ethanol | 48 | 78 | 8.55 |
| 4 | isopropyl alcohol | 45 | 81 | 9.47 |
| 5 | PEG-200 | 35 | 92 | 13.91 |
| 6 | PEG-400 | 42 | 85 | 10.67 |
| 7 | PEG-600 | 65 | 45 | 3.66 |

[a]Reaction of aniline (**1a**) (1 mmol), indane-1,3-dione (**2a**) (2 mmol) and formaldehyde (3 mmol) under different conditions at room temperature. Reaction progress monitored by TLC. [b]Isolated yield. [c]200 mg (0.114 mmol of Ce) of the catalyst was used. [d]TOF = TON/reaction time (h); TON = no. of moles of the starting materials being converted per mole of active site of the catalyst.

**Table 2. Effect of Different Catalyst Loading on the Reaction**




| entry | catalyst loading (mg) | time (min)[a] | yield (%)[b] |
|---|---|---|---|
| 1 | 50 | 85 | 70 |
| 2 | 100 | 65 | 81 |
| 3 | 150 | 45 | 87 |
| 4 | 200 | 35 | 92 |
| 5 | 250 | 35 | 92 |

[a]Reaction of aniline (**1a**) (1 mmol), indane-1,3-dione (**2a**) (2 mmol) and formaldehyde (3 mmol) in PEG-200 (5 mL) at room temperature. Reaction progress monitored by TLC. [b]Isolated yield.

as solvents gave average results with moderate product yield. Then we turned our attention toward green solvents like PEGs and the results obtained were very satisfactory (Table 1, entries 5−7). Among different PEGs, PEG-200 was found to be most efficient with excellent product yield in 35 min. The high viscosity of PEG-600 at room temperature may be the reason for its poor performance. The results clearly indicated the superiority of PEG-200 over other solvents.

To find the optimized amount of catalyst, the reaction was carried out by varying the amount of the catalyst on the model reaction (Table 2). It was observed that the conversion of spiropiperidine derivative increased linearly with the increase in the amount of catalyst from 50 to 200 mg and became steady with further increase to 250 mg. Therefore, it was found that 200 mg of the catalyst is sufficient to give the desired products in excellent yields.

## CATALYTIC REACTION

After optimization of reaction conditions, the substrate scope of the Ce/chitosan catalyzed synthesis of spiropiperidine derivatives was examined (Scheme 2). The results showed that the reaction tolerated amines with both electron donating and electron withdrawing groups efficiently. The reactions with alicyclic amine also gave a very good result. Furthermore, the scope of different cyclic active methylene compounds was also investigated. The reaction also efficiently tolerated indane-1,3-dione, 4-hydroxycoumarin and dimedone as substrates, giving products in excellent yields (Table 3). It is pertinent to mention that all the protocols available to date have only used dimedone as the substrate for this reaction and now, for the first time, we have successfully extended it to other cyclic active methylene compounds also. The above results demonstrate the scope and generality of this novel protocol for the synthesis of spiropiperidine derivatives in view of the fact that a range of structurally varied cyclic active methylene substrates and amines can be used. In order to further show the efficiency of our protocol, a comparison with all available reported protocols in the literature was done (Table 4). The data showed the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**Scheme 2. General Scheme for the Formation of Spiropiperidine Derivatives**

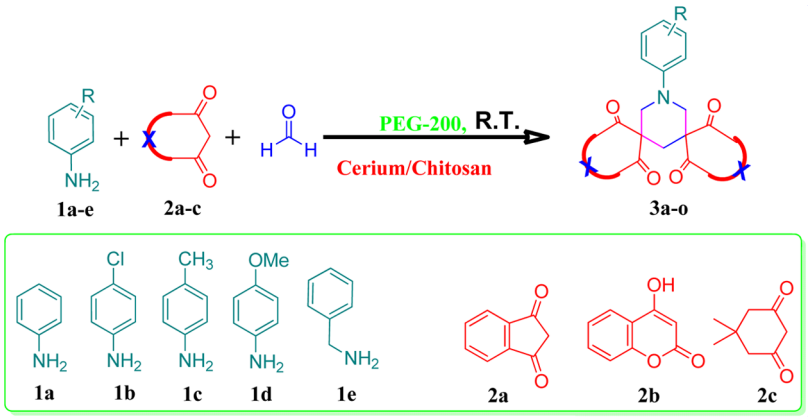


**Table 3. Scope of Different Active Methylene Compounds and Amines for the Synthesis of Spiropiperidine Derivatives**

| Entry | 1a-e | 2a-c | Products | Time (min) [a] | Yield (%) [b] | TOF[d] |
|---|---|---|---|---|---|---|
| 1 | 1a | 2a | 3a | 35 | 92 | 13.91 |
| 2 | 1b | 2a | 3b | 41 | 85 | 10.95 |
| 3 | 1c | 2a | 3c | 35 | 89 | 13.46 |
| 4 | 1d | 2a | 3d | 38 | 85 | 11.84 |
| 5 | 1e | 2a | 3e | 33 | 87 | 13.87 |
| 6 | 1a | 2b | 3f | 45 | 83 | 9.70 |
| 7 | 1b | 2b | 3g | 48 | 81 | 8.88 |
| 8 | 1c | 2b | 3h | 42 | 87 | 10.90 |
| 9 | 1d | 2b | 3i | 47 | 85 | 9.56 |
| 10 | 1e | 2b | 3j | 40 | 89 | 11.82 |
| 11[c] | 1a | 2c | 3k | 38 | 94 | 13.09 |
| 12[c] | 1b | 2c | 3l | 41 | 93 | 12.00 |
| 13[c] | 1c | 2c | 3m | 35 | 96 | 14.51 |
| 14[c] | 1d | 2c | 3n | 40 | 91 | 12.09 |
| 15 | 1e | 2c | 3o | 32 | 92 | 15.22 |

[a]Reaction progress monitored by TLC. [b]Isolated yield. [c]Compounds characterized by their melting points and comparing them with authentic samples.[21−24] [d]TOF = TON/reaction time (h); TON = no. of moles of the starting materials being converted per mole of active site of the catalyst.

superior efficiency, environment compatibility and practical applicability of our protocol in comparison to reported procedures.

## REACTION MECHANISM

A plausible mechanism for the synthesis of spiropiperidine derivative (**3a**) is outlined in Scheme 3. The spirocyclization seems to proceed via Knoevenagel, Michael and double Mannich reactions.[21−24] First, the cerium immobilized catalyst activates both indane-1,3-dione (**2a**) and formaldehyde for Knoevenagel condensation reaction to give intermediate (**4**). The intermediate (**4**) then undergoes Michael addition by another activated molecule of indane-1,3-dione (**2a**) across the double bond to generate **5**. Another intermediate (**6**) is formed via Mannich reaction involving intermediate **5**, formaldehyde and aniline **1a**. The intermediate **6** undergoes another Mannich


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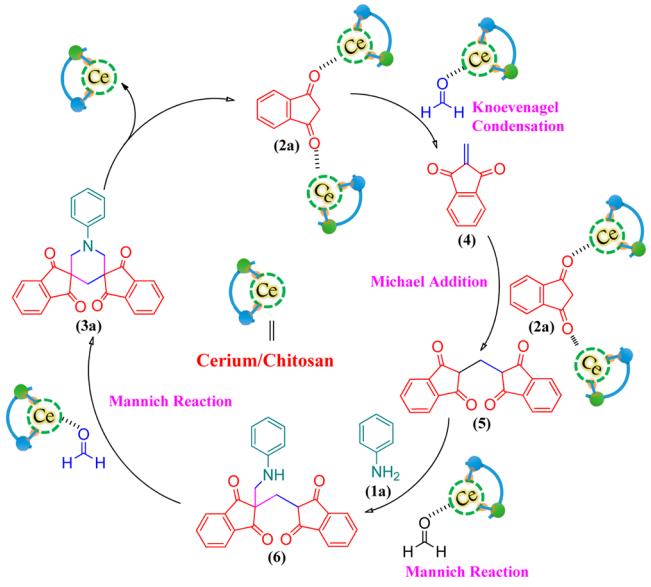
**Table 4. Comparison of the Efficiency of Ce/Chitosan Catalyst with Reported Procedures[a]**

| entry | catalyst | condition | solvent | yield (%) | time | TOF | ref. |
|---|---|---|---|---|---|---|---|
| 1 | Ce/chitosan | R. T. | PEG-200 | 96 | 35 min | 14.51 | present work |
| 2 | STA | R. T. | DCM | 92 | 4 h | 2.3 | 21 |
| 3 | $FeCl_3$ | R. T. | DCM | 88 | 6 h | 2.9 | 22 |
| 4 | $Fe_3O_4$ | 80 °C | solvent-free | 89 | 3 h | 5.93 | 23 |
| 5 | | reflux (5 min)/ overnight/R. T. | ethanol | 84 | 12 h | | 24 |

[a]Comparison based on the reaction of dimedone (**2c**), formaldehyde and *p*-toluidine (**1c**) under different reaction conditions.

**Scheme 3. Proposed Reaction Mechanism**




reaction with formaldehyde to form final product **3a**, freeing the catalyst for subsequent cycles.

**Leaching Study of Ce/Chitosan Catalyst.** The leaching of the catalyst before and after five catalytic cycles was studied by ICP-AES analysis. The analysis revealed that the Ce concentration before (7.94 wt % Ce) and after recycling experiments (7.90 wt % Ce) was fairly in agreement (within the experimental error). This denotes that Ce is tightly bound to the support and no leaching of the catalyst occurs upon its reuse. To establish the heterogeneity of the catalyst, the ICP-AES analysis of the filtrate after extracting the product and filtering the catalyst, was carried out and the result revealed the absence of Ce in the filtrate. This confirms that Ce is not leached during the course of reaction. The TEM images of the catalyst after five cycles (Figure 5) did not show any significant changes in the morphology of the catalyst, which indicates that the integrity of the catalyst is maintained throughout the recycling studies. The above studies thus confirm that the structure of the catalyst is stable and cerium is tightly bound to the support, which in turn facilitates efficient recycling.

**Catalyst Recycling.** The catalyst recycling experiment was done using the model reaction of indane-1,3-dione, formaldehyde, aniline and 200 mg of the catalyst in PEG-200 at room temperature. After completion of the reaction, water was added to the reaction mixture in order to dissolve PEG-200, a 1:10 mixture of isopropyl alcohol and ethyl acetate was then added to extract the product. The remaining catalyst in aqueous layer was filtered, washed with isopropyl alcohol/ethyl acetate (1:10) and reused. It was found that the catalyst maintained good activity for a minimum of five cycles (Figure 6). The TEM images of the catalyst after five cycles (Figure 5) showed

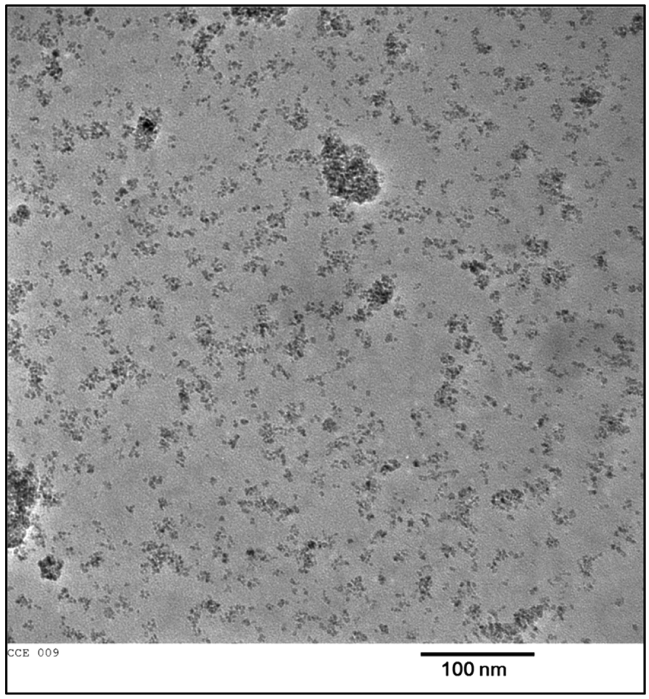



**Figure 5.** TEM image of the recycled catalyst after five cycles.

that the structure of the catalyst does not alter during the course of study.

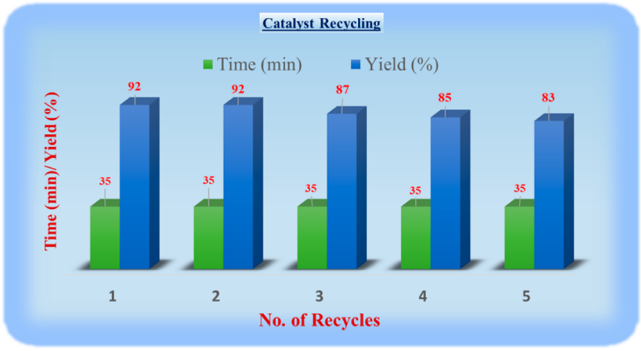



**Figure 6.** Recycling data of Ce/chitosan catalyst.

## CONCLUSION

In summary, a new, simple, efficient and environmentally benign method for the synthesis of spiropiperidine derivatives by the use of efficient and heterogeneous Ce/chitosan catalyst at room temperature has been described. Low catalyst loading, clean reaction profiles, the use of one pot and multicomponent procedure, reusability of the catalyst and operational simplicity are the important features of this methodology.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## ■ ASSOCIATED CONTENT

### Supporting Information

Description of the general experimental remarks, details of characterization data of the novel products and melting point comparison of compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acssuschemeng.5b00223.

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### Notes

The authors declare no competing financial interest.

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## ■ REFERENCES


(1) Molander, G. A. Application of lanthanide reagents in organic synthesis. *Chem. Rev.* **1992**, *92*, 29−68.

(2) Mikami, K.; Terada, M.; Matsuzawa, H. Asymmetric" catalysis by lanthanide complexes. *Angew. Chem., Int. Ed.* **2002**, *41*, 3554−3571.

(3) Bartoli, G.; Marcantoni, E.; Marcolini, M.; Sambri, L. Applications of $CeCl_3$ as an environmental friendly promoter in organic chemistry. *Chem. Rev.* **2010**, *110*, 6104−6143.

(4) Leadbeater, N. E.; Marco, M. Preparation of polymer-supported ligands and metal complexes for use in catalysis. *Chem. Rev.* **2002**, *102*, 3217−3274.

(5) Shen, C.; Xu, J.; Yu, W.; Zhang, P. A highly active and easily recoverable chitosan@copper catalyst for the C−S coupling and its application in the synthesis of zolimidine. *Green Chem.* **2014**, *16*, 3007−3012.

(6) Varma, A. J.; Deshpande, S. V.; Kennedy, J. F. Metal complexation by chitosan and its derivatives: a review. *Carbohydr. Polym.* **2004**, *55*, 77−93.

(7) Baig, R. B. N.; Vaddula, B. R.; Gonzalez, M. A.; Varma, R. S. *N*-Allylation of amines with allyl acetates using chitosan-immobilized palladium. *RSC Adv.* **2014**, *4*, 9103−9106.

(8) Baig, R. B. N.; Varma, R. S. Copper on chitosan: a recyclable heterogeneous catalyst for azide−alkyne cycloaddition reactions in water. *Green Chem.* **2013**, *15*, 1839−1843.

(9) Viegas, C., Jr.; Bolzani, V.; da, S.; Furlan, M.; Barreiro, E. J.; Young, M. C. M.; Tomazela, D.; Eberlin, M. N. Further Bioactive Piperidine Alkaloids from the Flowers and Green Fruits of Cassia spectabilis. *J. Nat. Prod.* **2004**, *67*, 908−910.

(10) Dewick, P. M.; *Medicinal Natural Products: A Biosynthetic Approach*, 2nd ed.; Wiley: New York, 2002. p 307.

(11) Petit, S.; Nallet, J. P.; Guillard, M.; Dreux, J.; Chermat, R.; Poncelet, M.; Bulach, C.; Simon, P.; Fontaine, C.; Barthelmebs, M.; Imbs, J. L. Synthesis and psychotropic activity of 3,4-diarylpiperidines. Structure-activity relationship and antihypertensive activity. *Eur. J. Med. Chem.* **1991**, *26*, 19−32.

(12) Ho, B.; Crider, A. M.; Stables, J. P. Synthesis and structure−activity relationships of potential anticonvulsants based on 2-piperidinecarboxylic acid and related pharmacophores. *Eur. J. Med. Chem.* **2001**, *36*, 265−286.

(13) Kuramoto, M.; Tong, C.; Yamada, K.; Chiba, T.; Hayashi, Y.; Uemura, D. Halichlorine, an inhibitor of VCAM-1 induction from the marine sponge Halichondria okadai Kadata. *Tetrahedron Lett.* **1996**, *37*, 3867−3870.

(14) Chou, T.; Kuramoto, M.; Otani, Y.; Shikano, M.; Yazawa, K.; Uemura, D. Pinnaic acid and tauropinnaic acid: two novel fatty acids composing a 6- azaspiro[4.5]decane unit from the okinawan bivalve *Pinna muricata*. *Tetrahedron Lett.* **1996**, *37*, 3871−3874.

(15) Bienayme, H.; Chene, L.; Grisoni, S.; Grondin, A.; Kaloun, El-B.; Poigny, S.; Rahali, H.; Tam, E. New spiro-piperidines as 5-$HT_{2B}$ receptor antagonists. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4830−4833.

(16) Maier, C. A.; Wunsch, B. Novel spiropiperidines as highly potent and subtype selective $\sigma$-receptor ligands. Part 1. *J. Med. Chem.* **2002**, *45*, 438−448.

(17) Feliu, L.; Martinez, J.; Amblard, M. Synthesis of an 8-Benzyl-4-(p-substituted-benzyl)-1,4,8-triazaspiro[4.5]decan-2-one library on SynPhase TMLanterns. *QSAR Comb. Sci.* **2004**, *23*, 56−60.

(18) Kouznetsov, V. V.; Diaz, B. P.; Sanabria, C. M. M.; Vargas, L. Y. M.; Poveda, J. C.; Stashenko, E. E.; Bahsas, A.; Amaro-Luis, J. Synthesis and transformations of new spiro-4-piperidines. Acetyl migration in 1-acetyl-1-benzyl-4-methyl-3,4-dihydrospiro [(1h)-quinoline-2,4-piperidines] under debenzylation conditions. *Lett. Org. Chem.* **2005**, *2*, 29−32.

(19) Watson, P. S.; Jiang, B.; Scott, B. A Diastereoselective Synthesis of 2,4-Disubstituted Piperidines: Scaffolds for Drug Discovery. *Org. Lett.* **2000**, *2*, 3679−3681.

(20) Quaglia, W.; Gianella, M.; Piergentili, A.; Pigini, M.; Brasili, L.; Di Toro, R.; Rossetti, L.; Spampinato, S.; Melchiorre, C. 1′-Benzyl-3,4-dihydrospiro[2H-1- benzothiopyran-2,4′-piperidine] (Spipethiane), a Potent and Highly Selective $\sigma$1 Ligand. *J. Med. Chem.* **1998**, *41*, 1557−1560.

(21) Atar, A. B.; Jeong, Y. T. Silica supported tungstic acid (STA): an efficient catalyst for the synthesis of bis-spiro piperidine derivatives under milder condition. *Tetrahedron Lett.* **2013**, *54*, 1302−1306.

(22) Mukhopadhyay, C.; Rana, S.; Butcher, R. J. $FeCl_3$ catalysed two consecutive aminomethylation at the $\alpha$-position of the $\beta$-dicarbonyl compounds: an easy access to hexahydropyrimidines and its spiro analogues. *Tetrahedron Lett.* **2011**, *52*, 4153−4157.

(23) Janati, F.; Heravi, M. M.; Mirshokraie, A. Superparamagnetic iron oxide as an efficient catalyst for the one-pot, solvent-free synthesis of 5,5-disubstituted hexahydropyrimidines and their spiro analogues. *J. Chem.* **2013**, *2013*, 1.

(24) Kozlov, N. G.; Kadutskii, A. P. A novel three-component reaction of anilines, formaldehyde and dimedone: simple synthesis of spirosubstituted piperidines. *Tetrahedron Lett.* **2008**, *49*, 4560−4562.

(25) Chen, J.; Spear, S. K.; Huddleston, J. G.; Rogers, R. D. Polyethylene glycol and solutions of polyethylene glycol as green reaction media. *Green Chem.* **2005**, *7*, 64−82.

(26) Martí, M.; Molina, L.; Alemán, C.; Armelin, E. Novel epoxy coating based on DMSO as a green solvent, reducing drastically the volatile organic compound content and using conducting polymers as a nontoxic anticorrosive pigment. *ACS Sustainable Chem. Eng.* **2013**, *1*, 1609−1618.

(27) Kerton, F. M. *Alternative Solvents for Green Chemistry*; RSC Green Chemistry Book Series; Royal Society of Chemistry: London, 2009.

(28) Sudheesh, N.; Sharma, S. K.; Shukla, R. S. Chitosan as an eco-friendly solid base catalyst for the solvent-free synthesis of jasminaldehyde. *J. Mol. Catal. A: Chem.* **2010**, *321*, 77−82.

(29) Primo, A.; Quignard, F. Chitosan as efficient porous support for dispersion of highly active gold nanoparticles: design of hybrid catalyst for carbon−carbon bond formation. *Chem. Commun.* **2010**, *46*, 5593−5595.

(30) Kramareva, N. V.; Stakheev, A. Y.; Tkachenko, O. P.; Klementiev, K. V.; Grunert, W.; Finashina, E. D.; Kustov, L. M. Heterogenized palladium chitosan complexes as potential catalysts in oxidation reactions: study of the structure. *J. Mol. Catal. A: Chem.* **2004**, *209*, 97−106.




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