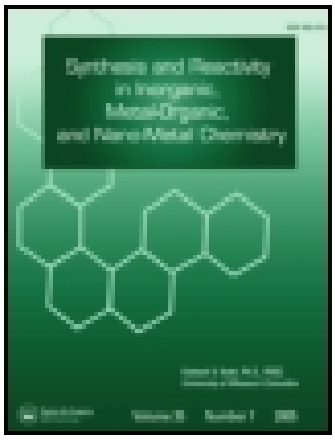

Synthesis and Reactivity in Inorganic, Metal-Organic, and Nano-Metal Chemistry

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# Synthesis of (S)-(-)-Propranolol by using $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ Nanocatalyst as Green, Eco-Friendly, Reusable and Recyclable Catalyst

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# Synthesis of (*S*)-(-)-Propranolol

# by using $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ Nanocatalyst as Green, Eco-Friendly, Reusable and Recyclable Catalyst

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**Abstract:** $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ nanoparticles catalyst appear to be a new and efficient solid acid catalyst for an economical, and environmentally benign synthesis of (*S*)-(-)-Propranolol. $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ nanocatalyst are used as a new, recyclable and reusable. Synthesis of (*S*)-(-)-Propranolol is carried out in two steps with usual reagents. Heteropolyacid, (+)-tartaric acid catalyzed enantioselective synthesis of (*S*)-(-)-propranolol via kinetic resolution of key intermediate α-naphthyl glycidyl ether with high optical and chemical yield. With this synthesis, we have two products in the first reaction and it is not necessary to purify the crude oil. This by-product is removed in the second step by extraction and yield is satisfactory. Nanocatalyst of $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ catalyzed the synthesis of propranolol in high yields and good selectivity.

**Keywords:** Cesium heteropolytungstate, nanoparticles, (*S*)-(-)-Propranolol, Catalyst, Heteropolyacid, recyclable, reusable

## INTRODUCTION

Propranolol is a *β*-blocker and antihypertensive drug, which suffers from the first-pass elimination resulting in decreased bioavalibility of oral doses compared to intravenous injections. Propranolol is used in the treatment of angina and hypertension. By antagonizing the $\beta_2$ -receptor, propranolol should pose serious problems to asthmatic patients. β-Blockers of the 3-(aryloxy)-1-(alkylamino)-2-propanol type, *e.g.* propranolol **4**, are one such class of drugs where the activity resides mainly in the *S* isomers.[1,2] Stereochemistry is one of the most important factors in synthesis of drugs molecules. chirality is emerging as a key issue in pharmaceutical research.[3] Prodrugs may protect a drug from first-pass effects. One of the major metabolites is the *O*-glucuronide. For example, the activity of (*S*)-(-)-propranolol is almost 98 times higher than that of its *R* enantiomer. Therefore, (*R*)-**4** is known to act as a contraceptive drug. Methods reported for the synthesis of (*S*)-propranolol involved the use of enzymes for resolution of intermediate,[4] asymmetric epoxidation of allyl alcohol,[5] from sorbitol,[6] asymmetric hydrogenation using chiral metal complex of the intermediate,[7] and also by employing polymer supported reagent.[8] Heteropolyacids (HPAs) are good catalysts for both acid and oxidationreactions. Heteropolyacids (HPAs) have been extensively studied as acid and oxidation catalysts for many reactions and found industrial application in several processes.[9] HPAs are promising solid acids to replace environmentally harmful liquid acid catalysts such as $H_2SO_4$.[9] HPAs use for fine chemical industries with green processes. As stereochemistry in a drug molecule governs its biological activity,[10] chirality is emerging as a key issue in pharmaceutical research.[11] Heteropolyacids (HPAs), presently being used in several industrial processes, are important for the so-called clean technologies since many of the environmental pollution and corrosion problems of the traditional technologies are avoided. Heteropolyacids (HPAs) catalyze a wide variety of reactions in homogeneous liquid phase offering strong options for more efficient and cleaner processing compared to conventional mineral acids.[12] There are, however, some specific features in the HPA catalysis. First, being stronger acids, HPAs have significantly higher catalytic activity than mineral acids. In organic media, the molar catalytic activity of heteropoly acid is usually 100–1000 times higher than that of $H_2SO_4$.[13] Heteropolyacids (HPAs) have long been known as catalysts for condensation reactions, e.g., the condensation of

acetone to mesityl oxide and alkylbenzenes.[14] It has been shown that HPA is an efficient catalyst for condensations in the syntheses of vitamins E, $K_1$ and C.[15] Heteropolyacids (HPAs) are early transition metal oxygen anion clusters that exhibit a wide range of molecular sizes, compositions, and architectures.[16] Generally, tungsten heteropoly acids are the catalysts of choice because of their stronger acidity, higher thermal stability, and lower oxidation potential compared to molybdenum heteropolyacids. Usually, if the reaction rate is controlled by the catalyst acid strength, heteropolyacids shows the highest catalytic activity. The HPAs-based catalysts, with the strong Brønsted and Lewis acid nature, have many advantages over the other catalysts.[17]For example, Keggin-type HPAs are wellknown[18] which among them $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ (CsPW) with a high specific surface acidity has been applied as an effective acid catalyst.[19]

The major goal is the development of nanocatalyst application ($Cs_{2.5}H_{0.5}PW_{12}O_{40}$ nanocatalyst) in organic synthesis. We now report the application of $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ nanocatalyst, with exclusive properties surpassing the Keggin heteropolyacids, for highly selective in order to synthesize (*S*)-(-)-Propranolol.

**Results and Discussion**

We use from $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ nanocatalyst as a catalyst in synthesis of propranolol report herein a method for efficient synthesis of (*S)*-isomer of propranolol via $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ nanocatalyst /(+)-tartaric acid-catalyzed with a intermediate α-naphthyl glycidyl ether **3 (Scheme 1)**.

**Scheme 1.**

At least two products are obtained in the first step reaction, however, it is not necessary to purify the crude oil. The by-product results from nucleophilic attack of potassium salt of naphthol to the formed epoxide. This by-product is removed in the second step by ether extraction. The yield is satisfactory. Spectrometric data analysis is recommended. With condensation of α-naphtol **1** together epichlorohydrin **2** in presence of KOH in methanol solvent at room temperature for 7 h was created α-naphtyl glycidyl ether **3** with good yield 97%, ( Scheme 1). Treatment of this ether

with excess of isopropylamine for 24 h reflux, gives (+,-)-propranolol **4** with a good yield (93%). Using of $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ nanocatalyst and (+)-tartaric acid allowed to stirred with α-naphthyl-glycidyl ether for 15 min in methanol solvent, followed by addition of isopropylamine to the same reaction gave (*S*)-propranolol in good optical purity and chemical yield. The enantiomeric excess was calculated by correlation of optical rotation [α] with literature values $[\alpha]_D$ = -10.2.[20] Mole ratios of epoxide: epoxide, heteropolyacid (HPAs) catalyst and (+)-tartaric acid was effected on chemical and optical yields. The best mole ratio is 1: 0.5: 1 with 77% isolated yield of crude product which showed 90% ee of (*S*)-enantiomer. The best catalyst was $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ nanocatalyst, with high yield%. We have obtained that (*S*)-propranolol with high purity (68% ee) can be provide only in two steps and without any purification or resolution of intermediate. We suggested a preliminarily chiral complex, which kinetically favored for (*S*)-enantiomer responsible for this optical purity. Finally we can concluded that enantioselective ring opening by using $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ nanocatalyst and (+)-tartaric acid is an efficient short route, with simple work up and high enantiomeric excess for synthesis of (*S*)-(-)-Propranolol. By using different forms of heteropolyacids catalysts, the observed selectivity. The results of the kinetic resolution ring opening of epoxide were listed in (Table 1).

**Table 1.**

a) Mole ratio corresponding to epoxide **3**: heteropolyacid catalyst: (+)-tartaric acid.

b) Isolated yield. c) Calculated by correlation of optical rotation [α] (C = 1.0, EtOH) with comparison of literature values, $[\alpha]_D$ = -10.2 (C = 1.02, EtOH).[21]



The result shows that $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ nanocatalyst has higher activity and performance in (*S*)-(-)-Propranolol reactions compared with the other heteropolyacids such as Keggin as well as normal method using $H_2SO_4$ (Table 1). Compared with Keggin and $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ nanocatalyst, is more active and show higher selectivity and minimizing side reactions. The results of the synthesis of (*S*)-(-)-Propranolol with condensation of α-naphthol **2** with epichlorohydrin **3** using $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ nanocatalyst as catalysts at reflux conditions are shown in (Table 1). The experiment was carried out for the first time by an inexpensive,

recyclable $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ nanocatalyst. The results show that $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ nanocatalyst has higher activity and performance in (*S*)-(-)-Propranolol reactions compared to $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ nanocatalyst, Keggin type under the same-conditions. The best yield of (*S*)-(-)-Propranolol (97%) with good selectivity was attained with $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ nanocatalyst at almost 24 h of reaction at reflux conditions (Table 1. entry 6). Keggin ($H_3[PW_{12}O_{40}]$, $H_4[SiW_{12}O_{40}]$, $H_3[PMo_{12}O_{40}]$, $H_4[SiMo_{12}O_{40}]$) heteropolyacid has also lower activity than $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ nanocatalyst. They lead to order 95, 93, 91, 86.5% (*S*)-(-)-Propranolol with good selectivity after 24 h of reaction at reflux conditions (Table 1. entry 6).



**Effect of the catalyst type:**

Initially, we compared the catalytic performance of $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ nanoparticles catalyst, Keggin, $H_3[PW_{12}O_{40}]$, $H_4[SiW_{12}O_{40}]$, $H_3[PMo_{12}O_{40}]$, $H_4[SiMo_{12}O_{40}]$ in the synthesis of (*S*)-(-)-Propranolol. The results are shown in Table 1. The yield of product decreases in the following order:

$Cs_{2.5}H_{0.5}PW_{12}O_{40}$ nanoparticles catalyst> $H_3[PW_{12}O_{40}]$> $H_4[SiW_{12}O_{40}]$> $H_3[PMo_{12}O_{40}]$> $H_4[SiMo_{12}O_{40}]$. As could be seen 12-tungstophosphoric acid, $H_3[PW_{12}O_{40}]$, Keggin type of heteropolyacid, is more effective than the other heteropoly anions and in the presence of this catalyst the highest yields of products are obtained. The interesting feature of this poly anion compared the other heteropolyacids is its hydrolytic stability (pH 0-12), which is very important in catalytic processes.

It is clear from these reactions that the efficiency of $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ nanocatalyst is higher than these of Keggin heteropolyacids. The reason is due to higher surface area available. Also, as a matter of fact, if the particle size of nanomaterial decreases, the relative number of surface atoms will be increased and thus the catalyst activity will be enhanced.

**Synthesis and characterization of nano-catalyst CsPW :**

The catalytic properties of HPAs are modified by using of some large cations like $Cs^+$ as counter-cation.[22-24] This modification is done via lowering of the solubility of catalyst which overcomes the separation problems in catalysis processes. In this work, we used ultrasound irradiation in synthesis of CsPW to achieve a unique catalyst in nano-scale.

**Study on structure and morphology of nano-catalyst CsPW:**

The IR spectrum of nano-powder shows the characteristic bands of $[PW_{12}O_{40}]^{3-}$ anion at 800 $cm^{-1}$ (W-$O_c$-W), 890 $cm^{-1}$ (W-$O_b$-W), 985 $cm^{-1}$ (W-$O_d$) and 1080 $cm^{-1}$ (P-$O_a$). The $O_a$, $O_b$, $O_c$ and $O_d$ atoms are the oxygen atoms which bonded to P and W, the corner-shared oxygen atoms of $WO_6$ octahedra, the edge-shared oxygen atoms of $WO_6$ octahedra and the terminal oxygen atoms, respectively. SEM images indicate that the particles are fairly spherical. The existence of cesium, tungsten and oxygen in CsPW was confirmed by SEM-EDX analysis (Figure. 1).

**Insert Here Fig. 1.**

The XRD pattern of nanoparticles CsPW was recorded in the range of 5 to 50$^o$ for 2Θ (Figure. 2).

**Insert Here Fig. 2.**

The average particles size (D) was calculated by using the Debye-Scherrer equation,[25] $D = 0.89l\lambda / (\beta\cos\Theta)$, where l is the wavelength of the radiation, β is the full-width at half-maximum and Θ is the diffraction angle. The thermal stability of nano-catalyst CsPW was studied by its TGA from 39 to 600 $^oC$ (Figure. 3).

**Insert Here Fig. 3.**

**EXPERIMENTAL**

**Chemicals and apparatus**

All solvents were purchased from commercial sources.

**Instruments**

The IR spectra were recorded on a Shimadzu model impact 400D FT-IR spectrophotometer

using KBr pellets. $^{1}H$ NMR were recorded on a Bruker AC-300F 400 MHz spectrometer in $CDCl_3$ using tetramethylsilane (TMS) as an internal standard with $^{1}H$ resonant frequency of 400 MHz. Optical rotation values were considered on Bellingham Stanly polarimeter. The resultant milky suspension was centrifuged and the solid was dried at 323 K. A multiwave ultrasonic generator (Misonix Sonicator 4000 (S-4000), equipped with a generator, converter, converter cable, a 1/2-inch replaceable tip horn, operating frequency at 20 kHz with a maximum power output of 600 W) was used for the ultrasound irradiation.

**Preparation of heteropolyacid catalyst**

Keggin type HPAs were acquired from commercial sources. Synthesis and characterization of nano-catalyst CsPW Acidic cesium salt of 12-tungstophosphoric acid was prepared by stoichiometric ratio according to published method.[18] A 0.0125M aqueous solution of $Cs_2CO_3$ (20 mL) was added dropwise (rate of about l mL.min$^{-1}$) to a 0.01M aqueous solution of $H_3PW_{12}O_{40}.nH_2O$ (20 mL) at room temperature, under ultrasound irradiation for 30 min in a beaker. The wave amplitude in this experiment was 40 and ultrasonic energy dissipated was set at 2.92 W, through the calorimetric method.[26] The structure and morphology of nanoparticles $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ have been studied by scanning electron microscope (SEM), a Leo 1450 VP with accelerate voltage 35 kV and resolution 2.5 nm. The energy dispersive X-ray spectroscopic (EDX) was measured with an Oxford 7353. XRD patterns were recorded on a Bruker, D8 Advance using Ni-filtered, Cu Ka radiation (l = 1.5406 A˚ ). The BET surface area was determined via nitrogen adsorption at 77 K using Quantachrome Corporation. The sample was outgassed at 140 8C for 10 h before the measurement. Thermo gravimetric analysis (TGA) was performed under air with a Shimadzu TGA-50 system at a heating rate of 10 $^{o}$C.min$^{-1}$.

**Synthesis of epoxide (Glycidyl-α-Naphthyl Ether (3)):**

Transfer 7.2 g (0.05 mol) of 1-naphthol, 5 g KOH to a round-bottom flask and add ethanol/$H_2O$ (9:1), the mixture was stirred for 30 min at room temperature. After dissolution, add dropwise 12 mL (0.15 moles) epichlorhydrin slowly in 45 min and stirring was continued at room temperature for 7 h. The reaction is left under magnetic stirring at room temperature for 45 min. TLC is carried out in an eluent system (hexane/ethyl acetate 9:1) to monitor the end of the reaction. The reaction was finished with $H_2O$ (50 mL) and extracted with chloroform (2×75 mL). The combined organic layers were washed with water (5×100 mL) and sodium hydroxide solution (2×30 mL), and dried over sodium sulfate. Remove ethanol by vacuum evaporator and to give the glycidyl-α-naphthyl ether **3** in 96% yield. Extract aqueous phase with ethyl ether. The ethyl ether extract is dried with anhydrous sodium sulfate. Filter and remove solvent to obtain the crude brown oil.

bp = 201-203°C (lit[21] 203-205°C]. $^1$H-NMR (400 MHz, $CDCl_3$, $\delta$/ppm): 2.5-2.9 (m, 2H), 3.3 (m, 1H), 3.8-4.3 (m, 2H) 6.4-6.8 (m. 1H), 6.9-7.7 (m,5H), 7.9-8.2 (m, 1H). $^{13}$C-NMR (400 MHz, DMSO-$d_6$, $\delta$/ppm): 154.2, 134.5, 134.7, 127.7, 126.5, 126.1, 125.5, 123.6, 120.4, 107.4, 69.9, 49.8, 22.4. IR (Neat, $cm^{-1}$): 3050, 2980, 1580, 1540, 1500, 1460, 1390, 1340, 1310, 1270, 1240, 1180, 1100, 1080, 1020, 960, 870, 790, 770, 750, 700, 670, 640, 570. Anal. Calcd for $C_{13}H_{12}O_2$: C 77.95, H 6.06%; Found C 77.90, H 5.97%; HRMS (EI) Calcd. for $C_{13}H_{12}O_2$ $[M]^+$, 200.1001, Found 200.1008;

**Synthesis of (±)-Propranolol (4):**

Transfer 0.2 g (1.0 mmol) of the solution of glycidyl-α-naphthyl ether **3** (2.0 g, 10 mmol) in excess 20 mL isopropylamine (235 mmol; 2.78 g) and water (1 mL) and nanoparticles

$Cs_{2.5}H_{0.5}PW_{12}O_{40}$ catalyst was stirred and to reflux for 24 h. Removal of solvent yielded crude (±)-propranolol (2.38 g, 92%), which could be purified by recrystalization in hexane.

mp= 95°C (lit.[28] 96°C), $^1$H-NMR (400 MHz, $CDCl_3$, $\delta$/ppm): 1.2 (d, 6H), 2.4-3.1 (m, 4H), 6.8-8.3 (m, 7H). $^{13}$C-NMR (400 MHz, DMSO-$d_6$, $\delta$/ppm): 154.3, 134.6, 134.4, 127.5, 126.6, 126.2,123.6, 70.8, 69.8, 49.6, 49.1, 23.8. IR (Neat, $cm^{-1}$): 3450, 3200, 3050, 2980, 1630, 1590,

1580, 1500, 1460, 1400, 1340, 1320, 1270, 1240, 1180, 1160, 1100, 1070, 1020, 960, 870, 790, 770, 760, 640, 620, 570, 520. Anal. Calcd for $C_{16}H_{21}NO_2$: C 74.11, H 8.15, N 5.41%; Found C 74.06, H 8.11, N 5.48%; HRMS (EI) Calcd. for $C_{16}H_{21}NO_2$ $[M]^+$, 259.2004, Found 259.2009;

**Synthesis of *(S)*-(-)-Propranolol (4):**

A solution of glycidyl-α-naphthyl ether **3** (8 mmol, 1.6 g), L-(+)-tartaric acid (8 mmol, 1.2 g) and nanoparticles $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ catalyst (0.03 g) in (20 mL) ethanol was stirred for 15 min. The isopropylamine (16 mmol, 1.2 mL) was added and stirred and to reflux for 24 h. The reaction mixture was cooled and filtered. The solid was washed with dichloromethane and then treated with aqueous 10% sodium hydroxide solution (10 mL), and extracted with dichloromethane (2×50 mL). The combined organic layer was washed with water (5×50 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure to give crude product (1.59 g, 77% yield), that showed 90% ee for (*S*)-(-)-Propranolol. mp = 72°C [α] = -9.08 (C = 1.0, EtOH), $[\alpha]_D$ = -10.2 (C = 1.02 EtOH).[28]

**Reusability of the catalyst**

The catalyst was recovered after the reaction and reused as a catalyst in the synthesis of (*S*)-(-)-Propranolol. Several times recoveries had only slightly decreased the catalytic activity, pointing to the stability and retention capability of this useful polyanion. At the end of the reaction, the catalyst was filtered, washed with diethyl ether, dried at 130 $^oC$ for 1 h, and reused in another reaction. The recycled catalystwas used for three reactions without observation of appreciable lost in its catalytic activities. In Table **2**, the comparison of efficiency of nanoparticles $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ catalyst in the synthesis of **4** after five times is reported. As it is shown in Table **5** the first, second, third, fourth and fifth reaction using recovered nanoparticles $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ catalyst afforded similar yield to those obtained in these runs. The reusability of the catalyst was also investigated. At the end of the reaction, the catalyst was recovered by a simple filtration. The recycled catalyst was washed with water and subjected to a second run of the reaction process.

**Table 2**.

## CONCLUSIONS

In conclusion, we have reported a new catalytic method for the synthesis of propranolol using nanoparticles $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ catalyst as efficient, reusable and eco-friendly heterogeneous inorganic catalysts. The advantages of this method are reusability of catalysts, easy work-up procedure and high yields. The propranolol synthesis is carried out in two steps with usual reagents. However, the results show that nanoparticles $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ catalyst shows the highest yield. Compared with mineral acids, such as $H_2SO_4$, nanoparticles $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ catalyst is more active and shows a higher selectivity, and minimizing side reactions. Important features of this polyanion are high thermal and hydrolytic stability throughout a wide pH range. Eco-friendly, recyclable, and easily prepared nanoparticles $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ catalyst is an efficient solid acid catalyst for highly selective synthesis of (*S*)-(-)-Propranolol. In the nanoparticles $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ catalyst in both heterogeneous conditions can easily be recovered and reused without loss of structure and activity. The CsPW catalyst was prepared ultrasonically in the nano-scale and used as a heterogeneous catalyst for the synthesis of (*S*)-(-)-Propranolol. The results of the kinetic resolution ring opening of epoxide were showed in Table1. Mole ratios of epoxide: nanoparticles $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ catalyst (Heteropolyacids): (+)-tartaric acid was affected on chemical and optical yields.



 

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**Schemes and Figures captions**

**Scheme 1.** Synthesis of (*S*)-(-)-Propranolol in the presence of $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ nanocatalyst

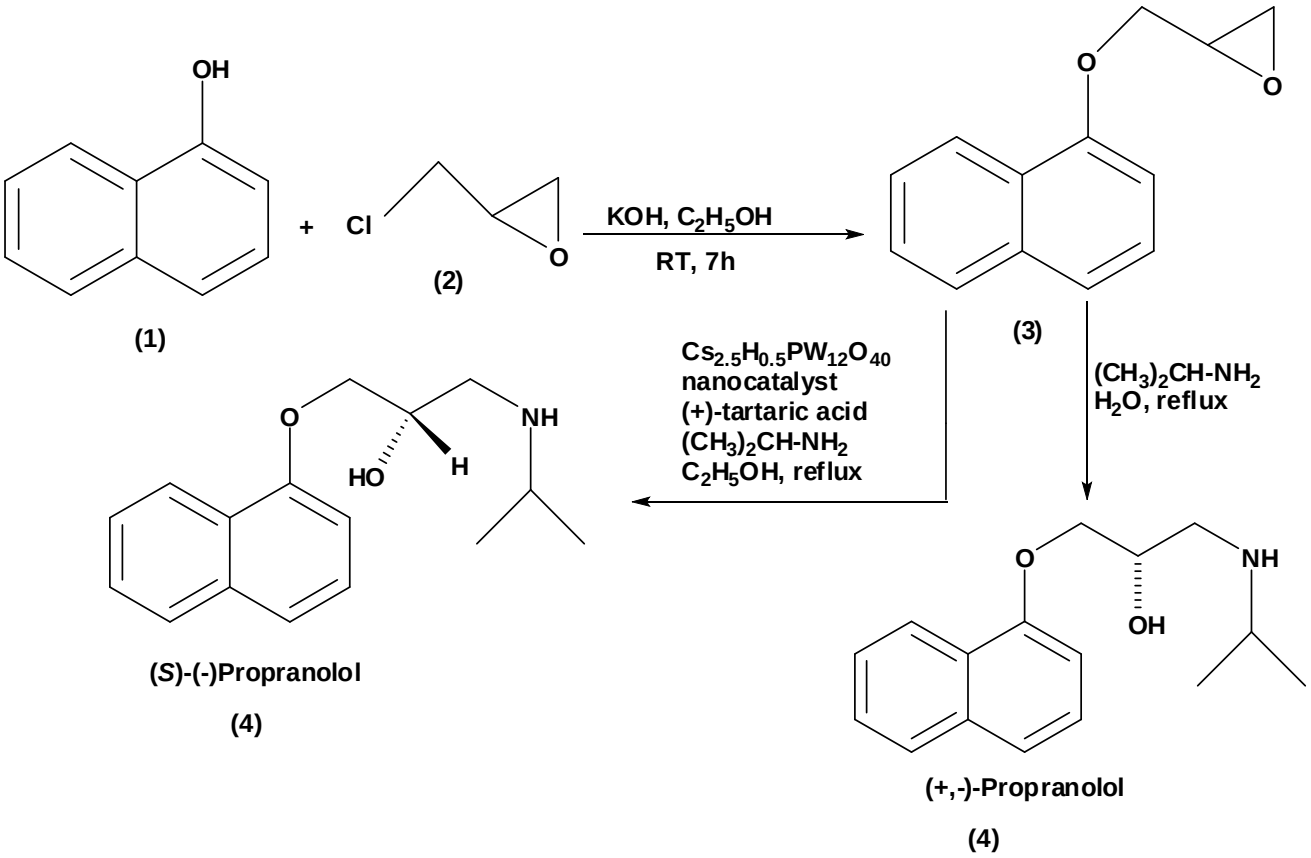
**Fig. 1.** SEM-EDX images of nanoparticles $Cs_{2.5}H_{0.5}PW_{12}O_{40}$.

**Fig. 2.** XRD pattern of nanoparticles $Cs_{2.5}H_{0.5}PW_{12}O_{40}$.

**Fig. 3.** Shows the TGA profile for nanoparticles $Cs_{2.5}H_{0.5}PW_{12}O_{40}$.






**Scheme 1.** Synthesis of (*S*)-(-)-Propranolol in the presence of $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ nanocatalyst

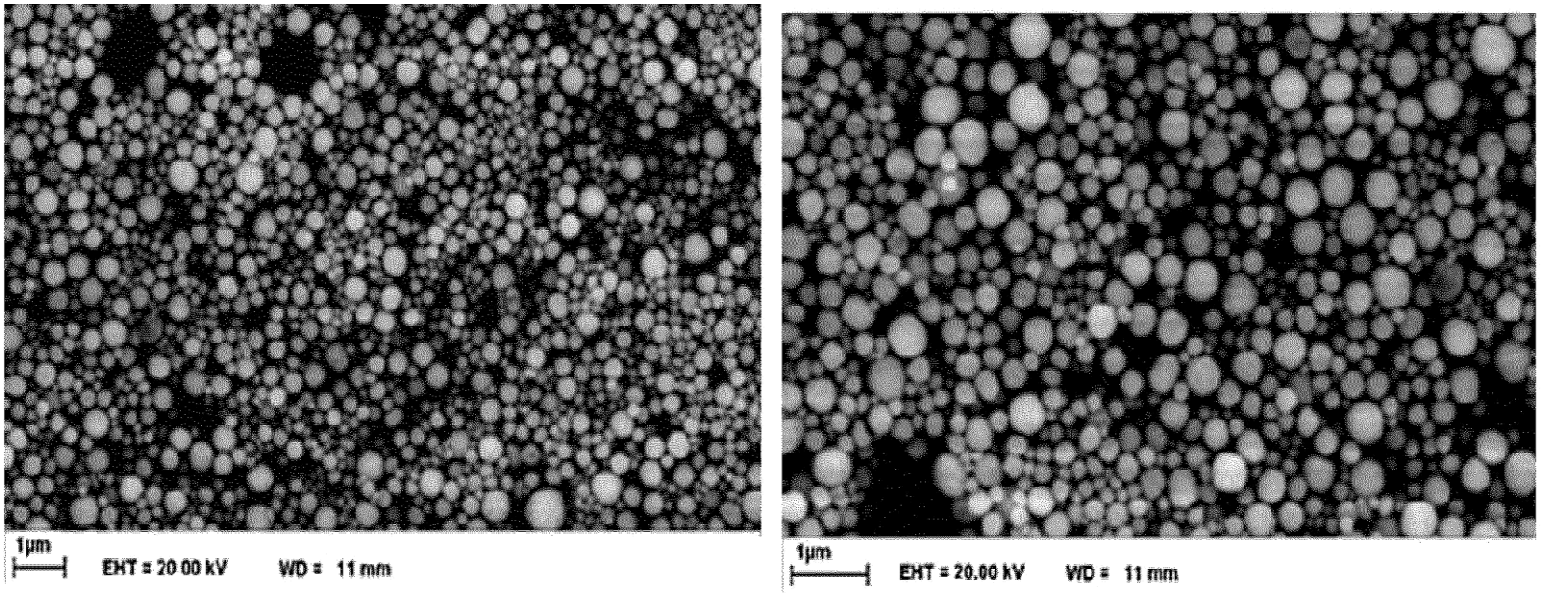



**Fig. 1.** SEM-EDX images of nanoparticles $Cs_{2.5}H_{0.5}PW_{12}O_{40}$.

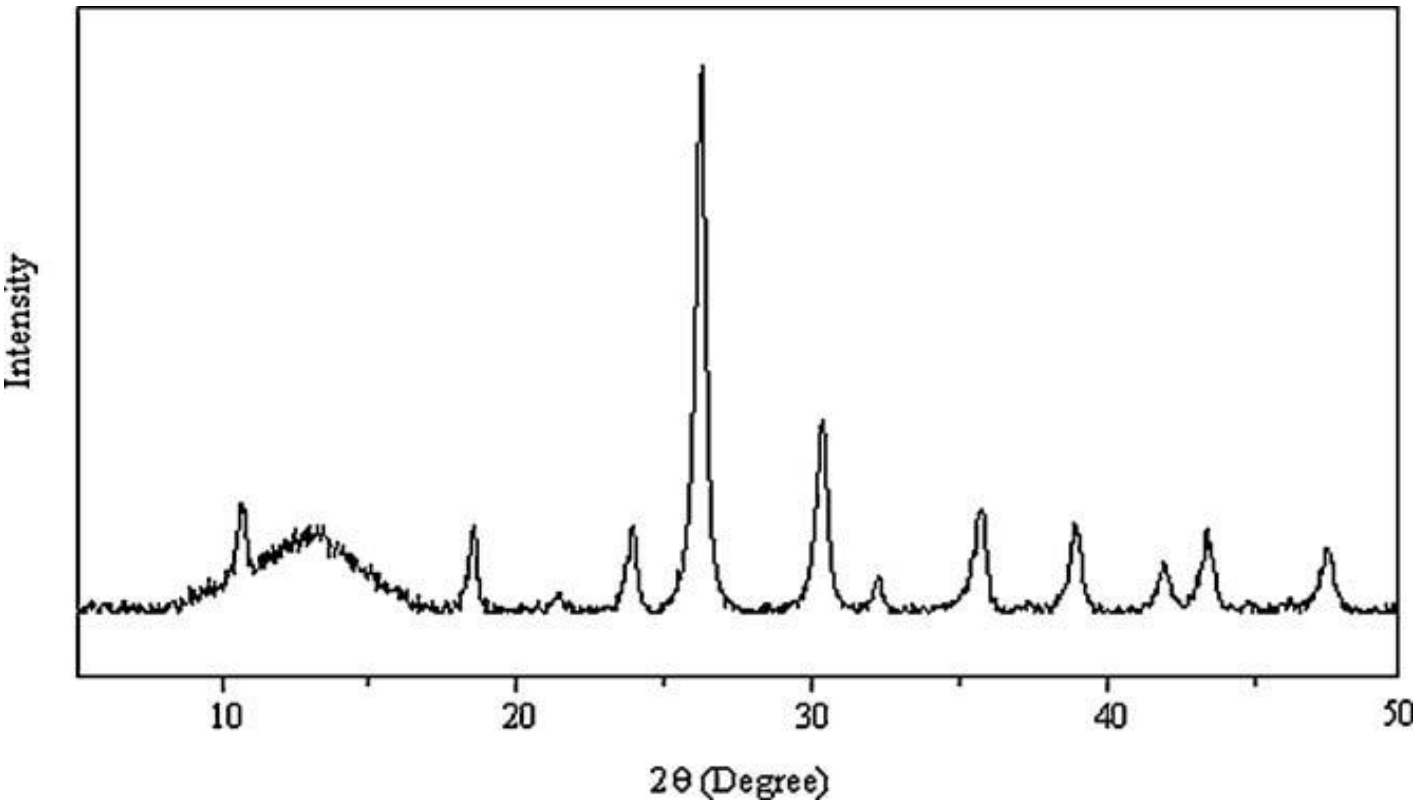



**Fig. 2.** XRD pattern of nanoparticles $Cs_{2.5}H_{0.5}PW_{12}O_{40}$.

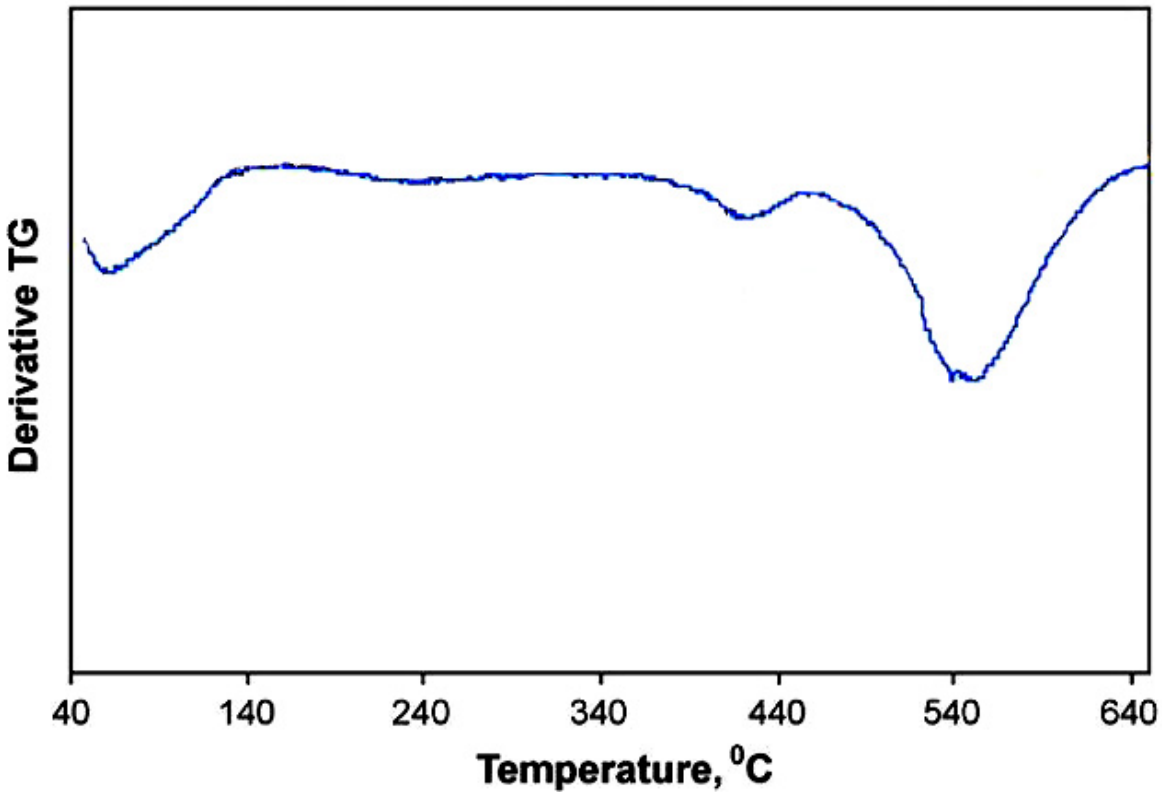



**Fig. 3.** Shows the TGA profile for nanoparticles $Cs_{2.5}H_{0.5}PW_{12}O_{40}$.

**Table 1.** Enantioselective synthesis of (*S*)-(-)-Propranolol via kinetic resolution of racemic epoxide **3** catalyzed by $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ nanocatalyst, various heteropolyacids catalysts and (+)-tartaric acid at reflux conditions

| Entry | Mole ratio[a] | [b] Yield % $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ nanoparticles | [b] Yield % $H_3[PW_{12}O_{40}]$ | [b] Yield % $H_4[SiW_{12}O_{40}]$ | [b] Yield % $H_3[PMo_{12}O_{40}]$ | [b] Yield % $H_4[SiMo_{12}O_{40}]$ | [b]Yield% ($H_2SO_4$) | ee%[c] |
|---|---|---|---|---|---|---|---|---|
| **1** | 1: 1: 1 | 95 | 93 | 90 | 88 | 82.5 | 80 | 17 |
| **2** | 1: 0: 0 | 92 | 91 | 86 | 84 | 81 | 77 | 0 |
| **3** | 1: 0.5: 0.5 | 81 | 78 | 77 | 76 | 75.5 | 70 | 38 |
| **4** | 1: 0.5: 1 | 77 | 76 | 74 | 71.5 | 67 | 59 | 90 |
| **5** | 1: 0: 1 | 94 | 91 | 89 | 87.5 | 84.5 | 78 | 18 |
| **6** | 1: 0.08: 0.08 | 97 | 95 | 93 | 91 | 86.5 | 83 | 68 |
| **7** | 1: 0.5: 2 | 68 | 67 | 64 | 62.5 | 59 | 45 | 71 |
| **8** | 1: 0.5: 0.16 | 82 | 81 | 78.5 | 75 | 70.5 | 76 | 36 |

a) Mole ratio corresponding to epoxide **3**: heteropolyacid catalyst: (+)-tartaric acid.

b) Isolated yield. c) Calculated by correlation of optical rotation [α] (C = 1.0, EtOH) with comparison of literature values, $[\alpha]_D$ = -10.2 (C = 1.02, EtOH).[21]

**Table 2**. Reuse of the nanoparticles $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ catalyst for synthesis of (*S*)-(-)-Propranolol**.**

| **Entry** | **Run** | **[a]Yield (%)** |
|---|---|---|
| 1 | 1 | 97 |
| 2 | 2 | 96 |
| 3 | 3 | 95.5 |
| 4 | 4 | 94 |
| 5 | 5 | 94 |

[a] *Isolated Yields*