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Green synthesis of 6-cyano-2,2-dimethyl-2-*H*-1-benzopyran and its subsequent enantioselective epoxidation

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ABSTRACT

The clean synthesis of 6-cyano-2,2-dimethyl-2-*H*-1-benzopyran epoxide starting from 3-methyl-2-butenal is reported using recyclable catalysts. $H_4PMo_{11}VO_{40}$ ($PMo_{11}V$) and $(PyH)_3HPMo_{11}VO_{40}$ (Py_3–$PMo_{11}V$) Keggin-type heteropolyacids were used to synthesize 6-cyano-2,2-dimethyl-2-*H*-1-benzopyran in two steps with 35% yield. This is an alternative procedure to the traditional methodology with pyridine or picoline as catalyst, where 6-cyano-2,2-dimethyl-2-*H*-1-benzopyran is obtained by condensation of 4-cyanophenol with 1,1-diethoxy-3-methyl-2-butene. The 6-cyano-2,2-dimethyl-2-*H*-1-benzopyran epoxide was obtained using Jacobsen-type catalysts, and *in situ* generated dimethyldioxirane (DMD) as oxidizing agent, that in comparison to *m*-CPBA/4-NMO and NaOCl/4-PPNO did not degrade the catalyst. In presence of 4-phenylpyridine *N*-oxide (4-PPNO) at 4 °C, enantioselectivities of 87% for 3S,4S-epoxide and 68% for 3R,4R-epoxide were obtained with the S,S- and R,R-Jacobsen catalysts, respectively. Overall yield was approximately 17% for 3S,4S-epoxide.

1. Introduction

As a result of their antidepressant, antihypertensive, and hypoglycemic activity, as well as other biological effects, the interest in the synthesis of 2-*H*-1-benzopyrans (chromenes) has increased in the last decades [1]. For example, the antihypertensive levcromakalim, an airways-selective potassium channel activator for asthma treatment [2], could be synthesized from 6-cyano-2,2-dimethyl-2-*H*-1-benzopyran (denoted here as 6-CN-2,2-DMB) through its chiral epoxide. The reported methods to obtain 6-CN-2,2-DMB have some drawbacks such as, low yields, long reaction times, and difficult work-up. Furthermore, the synthesis of benzopyran precursor is catalyzed by pyridine or pyrrolidine, which are toxic and cannot be recovered and reused [3]. Therefore, alternative methods for the green synthesis of 2*H*-1-benzopyrans are needed. In this context, heteropolyacids, which have been successfully evaluated and recovered for the sustainable synthesis of heterocycles such as, coumarins [4], flavones [5], chromones [6], and dihydropyrimidinones [7], may be good catalysts for the reaction.

The synthesis of chiral chromene epoxides has typically been carried out with the Jacobsen's catalytic system, based on chiral salen manganese(III) complexes under homogeneous reaction conditions [8]. Due to the intrinsic advantages of heterogeneous catalysis, *i.e.*, easy catalyst separation and recycling as well as product separation [9], some homogeneous chiral catalysts has been used in a two-phase system or they have been anchoring on a solid support. It is generally believed that the immobilization of chiral salen manganese(III) complexes onto solid supports could isolate the catalytically active intermediate species Mn(V)-oxo, which might greatly reduce the formation of inactive μ-oxo-Mn(IV) dimers and increase catalyst stability [10]. Unfortunately, in comparison with their homogeneous counterparts, the immobilized complexes often exhibit poor activity, leaching of the active species, or low accessibility to substrates [11]. These limitations seem to be well assessed by using a high ordered short hexagonal channel mesoporous support, modified with a long chain melamine–piperazine linker, which allows the immobilization of a type of dimeric chiral Mn(III) salen complex by covalent bonds [10]. As a second approach, the modification of the highly soluble

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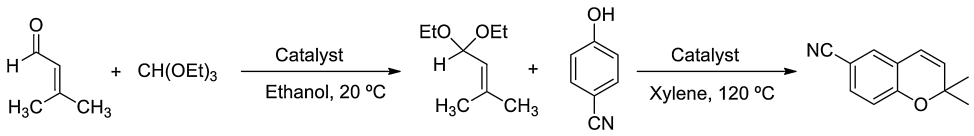

Fig. 1. Synthetic route of 6-CN-2,2-DMB.

Jacobsen's Mn(III) salen complex with trigol linker enables an easier work-up to recover and recycle the homogeneous catalyst by precipitation with a suitable solvent [11]. Although these approaches are appealing, the modification of the catalyst structure and/or the need of adding new reactants often result in a reduction of activity and selectivity.

The tendency of salen manganese(III) catalysts to undergo oxidative degradation when sodium hypochlorite (NaOCl), *m*-chloroperbenzoic acid (*m*-CPBA), sodium periodate ($NaIO_4$), and iodobenzene (PhIO) are used as oxidants, limits the successful recycling of the immobilized catalyst [12]. Moreover, these oxidants are either expensive or result in undesirable by-products. A convenient and economical alternative could be the *in situ* generated dimethyldioxirane (DMD) as oxidant, by the addition of $KHSO_5$ and acetone, along with Jacobsen-type catalysts, which facilitate product isolation and catalyst recovery by lowering catalyst solubility during the epoxidation reaction of *cis*-ethyl cinnamate [13] and limonene [14]; the catalysts showed very good stability against oxidative degradation.

In this paper, a suitable synthesis of 6-cyano-2,2-dimethylbenzopyran (6-CN-2,2-DMB) and its subsequent enantioselective epoxidation is reported. The methodology includes three steps involving heteropolyacid and homogeneous Jacobsen catalysts: (i) 1,1-diethoxy-3-methyl-2-butene is prepared starting from 3-methyl-2-butenal using $PMo_{11}V$ heteropolyacid as catalyst, (ii) the isolated substrate is condensed with 4-cyanophenol in the presence of Py_3–$PMo_{11}V$ to obtain 6-CN-2,2-DMB (Fig. 1), and (iii) 6-CN-2,2-DMB is enantiomerically epoxidized using Jacobsen-type catalysts and *in situ* generated DMD as oxidizing agents (Fig. 2). Work-up to separate heteropolyacids is easily carried out, and the Jacobsen catalyst is precipitated in the reaction media containing the *in situ* DMD as oxidant.

2. Experimental

2.1. Materials and methods

All reactive grade solvents and reagents were purchased from Aldrich and Fluka, and were used without further purification. $H_3PMo_{12}O_{40}$ (PMo_{12}) and $H_4SiMo_{12}O_{40}$ ($SiMo_{12}$) catalysts are also commercial products. In the preparation of 6-CN-2,2-DMB, all yields are referred to the isolated products after purification. Products were characterized by ^1H NMR and ^{13}C NMR; the NMR spectra were recorded on 200 MHz and 50 MHz Varian equipment, and were measured in $CDCl_3$ relative to TMS (0.00 ppm). The organic phase was dried on anhydrous Na_2SO_4 and filtered for its analysis by GC using a Shimadzu 2014 instrument. Reactions were monitored by TLC. Melting points were measured in an open capillary using a Büchi melting point apparatus and were uncorrected.

The products of 6-CN-2,2-DMB epoxidation were analyzed by gas chromatography coupled with mass spectroscopy (GC–MS) in an Agilent 7890A–5975C chromatograph equipped with a chiral column (cyclodex-β, 30 m × 0.25 mm × 0.25 μm). The identification of (3S,4S)-6-CN-2,2-DMB oxide and (3R,4R)-6-CN-2,2-DMB oxide was carried out by using the S,S- or R,R-Jacobsen catalyst in dicloromethane with *m*-CPBA at 0 °C for 2 h and detected by GC–MS. The activity and enantioselectivity (ee) of the catalysts were evaluated by comparison of chromatographic peak areas.

2.2. Catalyst preparation

The heteropolyacid $H_4PMo_{11}VO_{40}$ ($PMo_{11}V$) was prepared by hydrothermal synthesis [15]. A stoichiometric mixture of 85 wt% phosphoric acid (0.98 g, 0.01 mol), vanadium pentoxide (0.91 g, 0.005 mol), and molybdenum trioxide (14.4 g, 0.11 mol) was prepared in distilled water (150 mL). The mixture was stirred for 3 h at 80 °C. After cooling down to 20 °C and removal of insoluble molybdates and vanadates, the heteropolyacid solution was evaporated and dried at 85 °C for 24 h, obtaining a deep orange solid.

The heteropolyacid $Py_3HPMo_{11}VO_{40}$ (Py_3–$PMo_{11}V$) (mixed proton–pyridinium salt, containing three pyridinium cations per heteropolyanion) was prepared as follows: firstly, an ethanolic solution of aniline (30 mmol) was added to an ethanolic solution of $PMo_{11}V$ (10 mmol), and the mixture was stirred at 75 °C for 1.5 h and concentrated; then, the precipitate was filtered, washed with more ethanol, and dried at 20 °C under vacuum; finally, the resulting orange fine powder was dissolved in water for recrystallization and further purification.

S,S-Jacobsen and R,R-Jacobsen catalysts were synthesized as previously reported [16]. 3-*tert*-Butyl-2-hydroxy benzaldehyde (3-TBHB) was allowed to react with (1S,2S)-(+)-1,2-diaminocyclohexane and (1R,2R)-(−)-1,2-diaminocyclohexane, respectively, in a 2:1 molar ratio. The obtained (S,S) and (R,R) ligands were complexed with tetra-hydrated manganese(III) acetate and an excess of LiCl to give S,S- and R,R-Jacobsen catalysts, respectively.

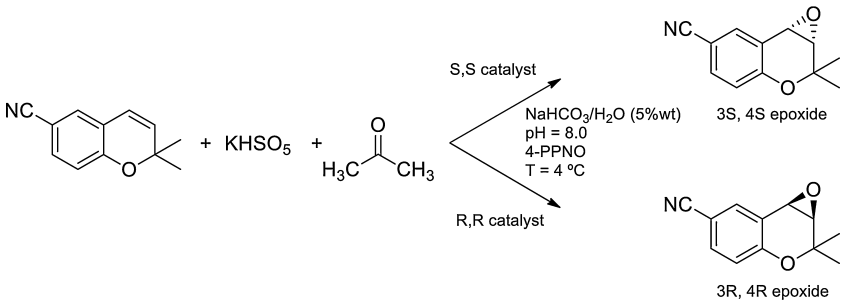

Fig. 2. Enantioselective epoxidation of 6-CN-2,2-DMB using Jacobsen catalyst (R,R and S,S optical configuration) and *in situ* generated DMD as oxidant.

2.3. Characterization methods

Complete characterization of the catalysts $PMo_{11}V$ and Py_3–$PMo_{11}V$ was reported in a previous work [17,18]. Here, we present some relevant analysis of the catalysts in order to verify their characteristics. $PMo_{11}V$ and Py_3–$PMo_{11}V$ were characterized with a Philips 505 scanning electron microscope (SEM) using an accelerating voltage of 15 eV solid. The catalysts were also analyzed by ^{31}P MAS NMR in Varian Mercury Plus 300 equipment; the measurements were carried out at room temperature using 85 wt% H_3PO_4 as external reference. The FTIR spectra at room temperature in the 400–4000 cm^{-1} range were obtained in a Thermo Nicolet IR200 equipment diluting the solid samples in KBR. The acidity of a suspension of the catalysts in acetonitrile was determined by means of potentiometric titration in a Metrohm 794 Basic Titrino apparatus with a double junction electrode using a solution of *n*-butylamine in acetonitrile (0.025 N); this methodology allows the evaluation of the total number of acid sites and their acid strength.

R,R- and S,S-Jacobsen catalysts were characterized as previously described [13]. FTIR spectra were recorded from KBR powder (1 wt%) using a Nicolet Avatar 330 FTIR spectrophotometer, and UV–vis spectra on a Lambda 4 PerkinElmer spectrophotometer with an integrating sphere using $BaSO_4$ as standard. TGA was performed on a TGA 2950 Thermal Analyzer at a heating rate of 5 K/min from 300 to 1073 K under flowing air (100 mL/min).

2.4. Catalytic experiments

2.4.1. Reaction analysis for optimizing the synthesis of 1,1-diethoxy-3-methyl-2-butene and 6-CN-2,2-DMB

1,1-Diethoxy-3-methyl-2-butene was obtained from triethyl orthoformate (1 mmol), 3-methyl-2-butenal (1 mmol), and absolute ethanol (0.3 mL) at 20 °C; 6-CN-2,2-DMB was synthesized with 1,1-diethoxy-3-methyl-2-butene (1.7 mmol), 4-cyanophenol (1.3 mmol), and xylene (2 mL). About 5 mg were collected from the reaction at fixed time intervals; the sample was diluted with 1 mL of acetone, filtered, and the filtrate was analyzed by GC (Shimadzu 2014, with a 30 m × 0.32 mm SPB-1 capillary column).

2.4.2. General procedure for the synthesis of 1,1-diethoxy-3-methyl-2-butene

$PMo_{11}V$ was used as catalyst in this preparation. Triethyl orthoformate (18 mmol), 3-methyl-2-butenal (18 mmol), and the catalyst ($PMo_{11}V$, 1 mmol%) were added to absolute ethanol (5 mL) at 20 °C. The progress of the reaction was monitored by thin layer chromatography (TLC) and gas chromatography (GC) analyses. After stirring for 1 h, the excess of ethanol was removed by evaporation, and the resulting mixture was treated with toluene (10 mL); finally, the catalyst was recovered by centrifugation and washing with toluene (5 mL). The organic phase was dried on anhydrous Na_2SO_4, filtered and concentrated to obtain the crude acetal. The acetal was isolated as a clear, colorless liquid by vacuum distillation (89% yield, 116–119 °C at 170 mm Hg, and 117.0–118.5 °C at 171–172 mm Hg).

2.4.3. General procedure for the synthesis of 6-CN-2,2-DMB

Py_3–$PMo_{11}V$ was used as catalyst for the preparation of 6-CN-2,2-DMB. 1,1-Diethoxy-3-methyl-2-butene (17 mmol), 4-cyanophenol (13 mmol), and the catalyst (Py_3–$PMo_{11}V$, 1 mmol%) were added to *p*-xylene (20 mL) as solvent at 20 °C. The progress of the reaction was monitored by TLC and GC analysis. The reaction mixture was heated and stirred at 120 °C. After 6 h, the reaction mixture was cooled down to room temperature. The clear, yellow solution was diluted with *p*-xylene (10 mL) and the catalyst was recovered by centrifugation, washed with *p*-xylene (5 mL), dried in vacuum, and reused. The organic phases were washed with HCl (1 M, 2 × 7 mL), NaOH (1 M, 2 × 7 mL), saturated solution of NaCl (10 mL), H_2O (10 mL), dried (anhydrous Na_2SO_4), and concentrated. The crude product was crystallized from hexanes. The crystals were recovered by filtration, washed with hexanes, and dried to give 35% yield, mp 46–47 °C, lit[1] 47 °C. ^1H NMR (200 MHz, $CDCl_3$) δ = 7.36 (dd, J = 8 Hz, J = 2 Hz, 1 H), 7.24 (*d*, J = 2 Hz, 1 H), 6.80 (*d*, J = 8 Hz, 1 H), 6.31 (*d*, J = 10 Hz, 1 H), 5.72 (*d*, J = 10 Hz, 1 H), and 1.46 (*s*, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 156.7, 133.3, 132.2, 130.2, 121.5, 120.6, 119.1, 117.2, 103.5, 77.8, and 28.2.

2.4.4. Enantioselective epoxidation of 6-CN-2,2-DMB

The enantioselective epoxidation of 6-CN-2,2-DMB was carried out following the procedure reported elsewhere [13,14]. Briefly, 20 mol% of S,S or R,R catalyst with 6-CN-2,2-DMB (0.0625 mmol) as substrate and 0.1875 mmol of $KHSO_5$ (Oxone® dissolved in 4 mL H_2O) as oxygen source were used. The catalyst and 6-CN-2,2-DMB were dissolved in acetone (4 mL), and the reaction was initiated by the stepwise addition of an aqueous $KHSO_5$ solution, whereas, the pH value of the reaction mixture was monitored and adjusted to 8.0–8.5 by slow addition of aqueous 5 wt% $NaHCO_3$ solution, under continuous stirring. After complete addition of the aqueous $KHSO_5$ solution, magnetic stirring was stopped and the obtained solid (catalyst and inorganic salts) was recovered by simple filtration, and it was washed with enough water. The obtained dark brown residue (recovered catalyst) was dissolved in 4 mL of acetone and reused in a further reaction. The liquid phase separated from the reaction system was extracted with CH_2Cl_2, the aqueous phase was discarded, and the organic phase was washed and dried with anhydrous sodium sulfate. The obtained mixture was concentrated under vacuum and the product was analyzed by GC–MS. The effect of 4-phenylpyridine *N*-oxide (4-PPNO, 0.0125 mmol) as additive, and the reaction temperature were also evaluated.

3. Results and discussion

3.1. Catalyst characterization

The synthesis and full characterization of the $PMo_{11}V$ and Py_3–$PMo_{11}V$ catalysts were reported in a previous work [17,18]. The SEM–EDAX analysis of heteropolyacid catalysts shows a homogeneous distribution of V, Mo, and P according to the expected percent atomic ratios. ^{31}P MAS NMR results of $PMo_{11}V$ show only a wide dissymmetric line at −3.20 ppm, which has been related with the substitution of one Mo^{6+} atom by one V^{5+} atom in the Keggin structure [15]. The FTIR spectrum of PMoV shows the main bands at 1061 cm^{-1} with a shoulder at 1081 (P–Oa), 960 (Mo–Od), 866 (Mo–Ob–Mo), and 776 (Mo–Oc–Mo) cm^{-1} [15]. The FTIR spectra of pyridinium salt (Py_3–$PMo_{11}V$) showed four peaks assigned to a heteropolyacid Keggin structure and a shift of the characteristic bands for pyridinium ion from 1440 cm^{-1} and 1380 cm^{-1} to 1533 cm^{-1} and 1483 cm^{-1}, respectively, in good agreement with previous reports [19]. This behavior indicates that the pyridine acts as counter-cation and it does not modify the Keggin units. X-ray diffraction patterns for $PMo_{11}V$ and Py_3–$PMo_{11}V$ are similar to those of Keggin commercial PMo structure, showing seven main diffraction peaks at 8.1°, 8.9°, 9.3°, 27.8°, 28.8°, and 28.2° corresponding to a triclinic symmetry [20,21]. In regards to the acidic properties, the heteropolyacid is a Brönsted acid, and PMoV displays very strong acid sites at 20 °C with a maximum acid strength corresponding to an initial electrode potential of 978 mV, higher than that obtained for the V-free sample (600 mV) [15]. When PMoV is transformed into the Py_3–PMo catalyst, the number of sites and their acid strength decrease (initial electrode potential = 365 mV).

Chiral salen ligand and Mn(III) salen complexes were identified according to previously reported characterization methods [13,14].

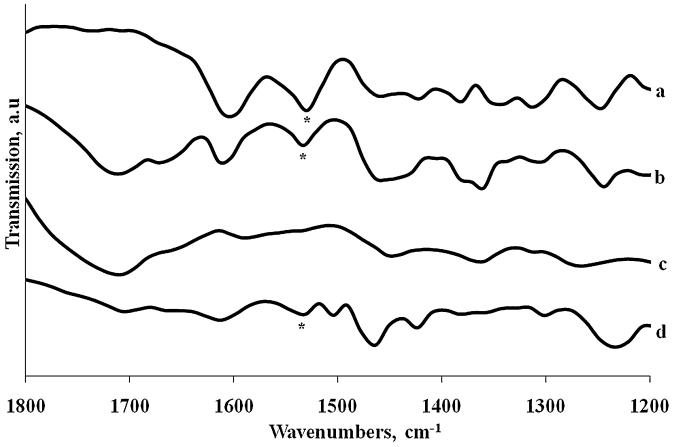

Fig. 3. FTIR spectra of the fresh S,S-Jacobsen catalyst and used once with different oxidizing agents. (a) fresh catalyst, (b) DMD, (c) *m*-CPBA/4-NMO, and (d) NaOCl/4-PPNO.

The main feature of the FTIR spectra of the chiral salen ligands is the intense band at 1640 cm^{-1}, assigned to C=N stretching vibrations (see Fig. 3) [14]. The coordination of the chiral salen ligand to the manganese atom is indicated by a band typical of metallosalen complexes at *ca.* 1530 cm^{-1} (see Fig. 3) [14]. Two characteristic bands of the C=N absorption at 450 and 510 nm in the DR UV–vis spectra of the complexes also indicate the binding of manganese to the chiral salen ligand [14].

3.2. Catalytic activity

3.2.1. Synthesis of 1,1-diethoxy-3-methyl-2-butene

This section describes the preparation of 1,1-diethoxy-3-methyl-2-butene in the presence of Keggin heteropolyacids (PMo_{12}, $SiMo_{12}$, and $PMo_{11}V$), as reusable catalyst, in a homogeneous system. 1,1-diethoxy-3-methyl-2-butene synthesis involving the reaction of 3-methyl-2-butenal with triethyl orthoformate is illustrated in Fig. 1. The possible presence of non-catalytic effects was assessed by studying the reaction in absence of catalyst, and no appreciable formation of 1,1-diethoxy-3-methyl-2-butene was detected (5%, Table 1, entry 1).

The yields of 1,1-diethoxy-3-methyl-2-butene of 70, 68, and 89% (selectivity 100%), were obtained with the three catalysts (PMo_{12}, PW_{12}, and $PMo_{11}V$, respectively, entries 2–4 of Table 1). These results show that the incorporation of V into the structure of PMo notably increases the catalytic activity. In a previous work, we found that $PMo_{11}V$ displays a number of acidic sites larger than PMo_{12} support [22].

Table 1
Synthesis of 1,1-diethoxy-3-methyl-2-butene.[a]

Entry	Catalyst	Catalyst (mmol%)	Time (h)	Yield (%)
1	None	–	3	5
2	PMo_{12}	1	1	70
3	PW_{12}	1	1	68
4	$PMo_{11}V$	1	1	89
5	$PMo_{11}V$	0.1	1	48
6	$PMo_{11}V$	0.5	1	75
7	$PMo_{11}V$	2	1	90
8	$PMo_{11}V$	1	0.5	77
9	$PMo_{11}V$	1	2	88
10	$PMo_{11}V$	1	1	88
11	$PMo_{11}V$	1	1	88
12	$PMo_{11}V$	1	1	87
13[b]	$PMo_{11}V$	1	1	89

[a] Reaction conditions: triethyl orthoformate (1 mmol), 3-methyl-2-butenal (1 mmol), absolute ethanol (0.3 mL), and 20 °C. Entries 10–12 correspond to the first, second, and third catalyst reuse.
[b] Scaled until 10-fold.

The most active catalyst ($PMo_{11}V$) was used in the next experiments. Table 1, entries 4–7, displays the effect of the amount of catalyst on the yield of 1,1-diethoxy-3-methyl-2-butene in the reaction. The reaction yield increased from 48% to 89% when the amount of $PMo_{11}V$ increased from 0.1 to 1 mmol% (Table 1, entries 4 and 5); a further increase in the amount of $PMo_{11}V$ caused a very slight increase in 1,1-diethoxy-3-methyl-2-butene yield (90%, Table 1, entry 7). Thus, 1 mmol% of $PMo_{11}V$ is an appropriate amount in this reaction.

The effect of reaction time on 1,1-diethoxy-3-methyl-2-butene yield using $PMo_{12}V$ as catalyst, under the same reaction conditions, is shown in Table 1, entries 4, 7, and 8. It can be observed that the yield increased with the reaction time up to 1 h and then leveled off.

The possibility of recycling the $PMo_{11}V$ was examined and no appreciable loss of catalytic activity was observed after four cycles (Table 1, entries 4, 10–12); product yields varied from 89% to 87%.

It is well known that the reaction of an aldehyde with two alcohol molecules in the presence of an acid catalyst results in the formation of an acetal. Alternatively, an orthoester could be used instead as a source of the alcohol; in fact, the orthoesters can be considered as the 'acetals of esters' or the triesters of the unknown 'orthoacids'—the hydrates of carboxylic acids. The orthoesters are hydrolyzed by water to ester and two alcohol molecules, in the presence of an acid catalyst; in our case, triethylortoformate would be hydrolyzed by the Brönsted sites of the $PMo_{11}V$ heteropolyacid. Then, the aldehyde (in our case, 3-methyl-2-butenal), would react with ethanol to form the corresponding acetal; this reaction is also catalyzed by the Brönsted acid sites of the heteropolyacids. A plausible mechanism is attached as supplementary material. The results show that the incorporation of V into the structure of PMo notably increases the acidity and catalytic activity. In a preview work, using potentiometric titration, we found that $PMo_{11}V$ presents a greater number of acidic sites than PMo_{12} [22].

3.2.2. Synthesis of 6-cyano-2,2-dimethyl-benzopyran (6-CN-2,2-DMB)

The 6-CN-2,2-DMB synthesis involving in the reaction of 1,1-diethoxy-3-methyl-2-butene with 4-cyanophenol is illustrated in Fig. 1. Traditionally, this reaction has been catalyzed by pyridine or picoline in homogeneous medium [23]. Initially, the non-catalytic reaction between 1,1-diethoxy-3-methyl-2-butene and 4-cyanophenol was examined, and it was not observed in the formation of 6-CN-2,2-DMB (Table 2, entry 1). Similarly, using PMo_{12} and $PMo_{11}V$, under the same reaction conditions, the reaction does not take place (Table 2, entries 2 and 3). However, the use of Py_3–$PMo_{11}V$ led to a 35% yield of product under the same reaction conditions (Table 2, entry 5). This finding could be related to the mechanism originally proposed by North et al. [1], who indicated that both acid and basic catalysts with an appropriate pH are necessary to carry out this reaction [1]. In our case, we propose that small amounts of non-protonated pyridine and free heteropolyacid on the catalyst surface can replace the function of basic and acid catalysts reported in a homogeneous medium (see Fig. 4). Therefore, it can be concluded that the synthesized catalyst Py_3–PMoV possesses bifunctional properties.

The effect of reaction temperature was studied with the most active catalyst (Py_3–$PMo_{11}V$), Table 2, entries 4, 6, and 7. It was found that, at temperature of 120 °C, the reaction significantly takes place.

The possibility of recycling the catalyst was also examined and no appreciable loss of catalytic activity was observed after four cycles (Table 2, entries 5, 9–11); product yield varied between 38 and 36%.

Table 2
Preparation of 6-CN-2,2-DMB.[a]

Entry	Catalyst	Catalyst (mmol%)	Temp. (°C)	Time (h)	Conv. (%)	Selectivity (%)	Yield (%)
1	None	–	120	12	–	–	–
2	PMo_{12}	1	120	12	–	–	–
3	$PMo_{11}V$	1	120	12	–	–	–
4	Py_3–$PMo_{11}V$	1	120	12	37	90	33
5	Py_3–$PMo_{11}V$	1	120	6	38	92	35
6	Py_3–$PMo_{11}V$	1	100	12	5	100	5
7	Py_3–$PMo_{11}V$	1	80	12	–	–	–
8	Py_3–$PMo_{11}V$	2	120	6	34	94	32
9	Py_3–$PMo_{11}V$	1	120	6	37	92	34
10	Py_3–$PMo_{11}V$	1	120	6	36	94	34
11	Py_3–$PMo_{11}V$	1	120	6	36	94	34
12[b]	Py_3–$PMo_{11}V$	1	120	6	38	92	35

[a] Reaction conditions: 1,1-Diethoxy-3-methyl-2-butene (1.7 mmol), 4-cyanophenol (1.3 mmol), xylene (2 mL), and 120 °C. Entries 9–11 correspond to the first, second, and third catalyst reuse.
[b] Scaled until 10-fold.

In order to assess the possible catalyst solubilization, additional tests were performed. The Py_3–$PMo_{11}V$ sample (*ca.* 20 mg) was stirred in xylene (2 mL) for 12 h, filtered, and dried in vacuum till constant weight. No mass loss was detected. Moreover, the refluxed xylene was used as solvent for attempting the reaction without adding the catalyst. After 6 h, formation of 6-CN-2,2-DMB was not detected and the starting material was almost quantitatively recovered.

3.2.3. *Enantioselective epoxidation of 6-CN-2,2-DMB*

The S,S and R,R complexes were used as catalysts in the enantioselective epoxidation of 6-CN-2,2-DMB at room temperature. Dimethyldioxirane, formed from the reaction between acetone and $KHSO_5$ (oxygen source) in a slightly basic medium, that acted as oxidizing agent. The enantioselective epoxidation reaction is outlined in Fig. 2, whereas, the catalytic results are summarized in Table 3. In terms of high conversion and selectivity, a $KHSO_5$/6-CN-2,2-DMB molar ratio of six was appropriate. Complete conversion and 70% of selectivity were obtained in absence of the catalyst, but no enantioselectivity was achieved (Table 3, entry 1). On the other hand, the presence of S,S-Jacobsen as catalyst resulted in an ee of 35% (Table 3, entry 2), indicating that the catalyst promotes the chiral induction between its catalytically active form and the substrate. Also, 4-PPNO has a pronounced effect on the enantioselectivity (Table 3, entry 3). It is known that in a biphasic reaction pyridine derivatives play a dual role: (a) stabilizing the oxo-Mn(V) and (b) transporting the oxidant into the organic phase [24]. As the reduction in temperature resulted into an increase in chiral induction (Table 3, entry 4), further experiments were performed with 4-PPNO at a reaction temperature of 4 °C, Table 3, entries 5 and 6. When S,S-Jacobsen was used as catalyst, the enantioselectivity (87% for 3S,4S-epoxide) was better than that obtained using the R,R catalyst (68% for 3R,4R-epoxide). These results are equivalent to those obtained by using Jacobsen-type catalysts with NaOCl/4-PPNO as oxidant [25]. However, in our methodology, the catalyst could be recovered and recycled after its precipitation during the reaction. The catalyst can be conveniently recovered by filtration, washed with water, and then, dissolved in acetone to be reused. In fact, the recovered S,S catalyst was used twice under similar reaction conditions, Table 3, entry 7; the slight decrease in enantioselectivity (from 87% to 80%) was attributed to the physical loss of catalyst rather than to its oxidative degradation; this was evidenced by conducting epoxidation experiments using NaOCl/4-PPNO and *m*-CPBA/NMO as oxidation systems. In general, the reaction with *m*-CPBA/NMO as oxidant proceeded much faster than with NaOCl/4-PPNO and gave higher ee values (75% against 38%). However, in both cases, the initially dark brown catalyst was partially decolorized after the reaction. Catalyst decolorization was much more severe with *m*-CPBA/NMO than with NaOCl/4-PPNO. Therefore, as confirmed by FTIR analysis (aromatic region) of the reused catalyst, the catalyst was deactivated in the presence of these oxidation systems. In fact, comparison of the FTIR spectrum of the recovered catalyst by vacuum distillation at 180 °C after reaction with *m*-CPBA/NMO and NaOCl/4-PPNO as oxidizing agents, with that of the catalyst used with *in situ* generated DMD as oxidant, revealed that the main bands assigned to the Mn(III) salen complexes (1530 cm^{-1}) do not appear in the spectrum of the catalyst used with *m*-CPBA/NMO (Fig. 3). The reported catalytic system is attractive because, it allows the use of an alternative oxygen source under smooth conditions, thus,

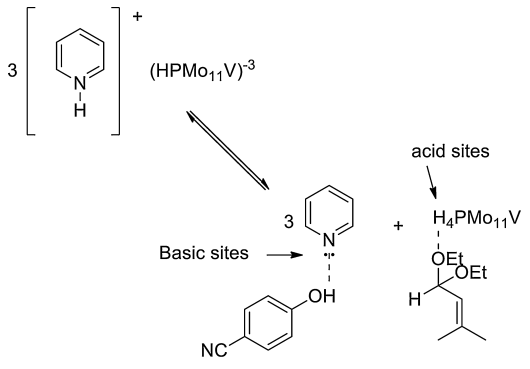

Fig. 4. Possible substrate activation by Py_3–PMoV catalyst.

Table 3
Enantioselective epoxidation of 6-CN-2,2-DMB.[a]

Entry	Conversion (%)	Selectivity (%)	ee (%)
1[b]	100	70	0
2	100	60	35[h]
3[c]	96	65	6[h]
4[d]	100	62	7[h]
5[e]	97	60	8[h]
6[f]	100	60	68[i]
7[g]	100	62	80[h]
8[j]	95	60	85

[a] Reaction conditions: 6-CN-2,2-DMB (0.0625 mmol), $KHSO_5$ (0.375 mmol), acetone (4 mL), S,S-Jacobsen (0.016 mmol), water (4 mL), and room temperature.
[b] Without catalyst.
[c] 4-PPNO (0.0125 mmol).
[d] 4 °C.
[e] 4-PPNO (0.0125 mmol) and 4 °C.
[f] R,R-Jacobsen instead of S,S-Jacobsen, using the same condition as in "e".
[g] Second reuse of S,S-Jacobsen under similar conditions to "e".
[h] Optical configuration 3S,4S.
[i] Optical configuration 3R,4R.
[j] Scaled until 2-fold.

avoiding catalyst oxidative degradation that results from utilizing strong oxidizing agents. Furthermore, the easy recovery of the catalyst from the reaction medium and their recycling is another strong advantage of this catalytic process. Finally, some of the catalytic reactions was carried out using large-scale amounts (see entries 13, 12, and 8 in Tables 1, 2, and 3, respectively); these results show that the activity of the catalytic systems did not change significantly, which demonstrates the potential application in industry of entire process.

4. Conclusions

A new clean route, based on recyclable heteropolyacids as catalysts, was developed as an alternative for the preparation of 6-cyano-2,2-dimethyl-2*H*-1-benzopyran. This compound was obtained by condensation of 4-cyanophenol with 1,1-diethoxy-3-methyl-2-butene over $H_4PMo_{11}VO_{40}$, that was active after partial substitution of protons by pyridine. The enantioselective epoxidation of benzopyran was carried out with Jacobsen-type catalysts with different optical configuration (R,R and S,S), and *in situ* generated DMD as oxidizing agent. The best chiral induction (ee = 87%) was obtained (97% conversion and 60% epoxide selectivity) with S,S-Jacobsen catalyst using 4-phenylpyridine *N*-oxide as axial base, at low temperature (4 °C). The Jacobsen-type catalysts were recovered and recycled without appreciable loss of their initial catalytic activity when the oxidizing agent was DMD, in contrast to the case of using NaOCl and *m*-CPBA.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.molcata.2014.11.027.

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