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Transition Metal-doped Heteropolyacid Catalysts for the Suitable Multicomponent Synthesis of Monastrol and Bioactive Related Compounds

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Abstract: Three transition metal-doped heteropolyacid catalysts ($H_4PMo_{11}VO_{40}$: PMoV, $FeHPMo_{11}VO_{40}$: FePMoV, and $CuH_2PMo_{11}VO_{40}$: CuPMoV) were prepared and characterized by Fourier transform infrared spectroscopy, ^{31}P nuclear magnetic resonance, and diffuse reflectance spectroscopy. The acid properties of the catalysts were determined by potentiometric titration with *n*-butylamine. A series of bioactive 3,4-dihydropyrimidin-2-(1H)-thiones/-ones (DHPMs) derivatives such as monastrol and piperastrol were synthesized by a one-pot procedure using the catalysts under solvent-free conditions. The proposed methodology required short reaction time (1 h) and a temperature of 80 °C to obtain DHPMs in very good yield and high selectivity. The incorporation of V, Fe and Cu in the primary or secondary structure of $H_3PMo_{12}O_{40}$ (PMo) improved the catalytic activity of the materials. A correlation between the yields of monastrol and the acid strength or the number of acid sites of the catalysts was observed, namely, FePMoV > CuPMoV > PMoV > PMo. The FePMoV catalyst was easily recycled and reused without appreciable loss of activity. The described synthetic method could be a simple, clean and environmentally friendly alternative for the preparation of bioactive substituted DHPMs.

Keywords: 3,4-Dihydropyrimidin-2-(1H)-thiones/-ones, Monastrol, Biginelli reaction, Transition metal-doped heteropolyacid catalysts, Solvent-free synthesis, Multicomponent reaction.

1. INTRODUCTION

In the field of Green Chemistry, the development of procedures to prepare molecular scaffolds by combining molecular diversity with eco-efficiency is an important challenge for synthetic organic chemistry. From the viewpoint of environmental care, the classical methods of performing organic synthesis are unsustainable, and multicomponent reactions (MCRs) provide an important solution since they generate less waste, have high atom economy and multiple-bond-forming efficiency.

As one of the known MCRs, Biginelli reaction has attracted much attention for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-thiones/-ones (DHPMs), due to their relevant biological activities and pharmacological uses [1,2].

In this regard, heteropolyacids (HPAs) and their derivatives represent one of the most important categories of solid catalysts to perform these reactions efficiently. HPAs are utilized due to their acid and redox properties, and represent an important family of materials used in heterogeneous catalysis [3-5].

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HPAs with Keggin structure, bulk or supported in materials of high surface area, are used in organic synthesis as catalysts for several 3,4-dihydropyrimidinones, quinazolinones, pyridines, xanthenones, azabicyclo [2.2.2] octan-5-ones, imidazoles, 1,4-dihydropyridines, and many others [6,7].

Moreover, in recent years, much attention has been paid to the synthesis of DHPMs due to their relevant biological activities, such as calcium channel inhibitors, anticancer, anti-inflammatory, antimicrobial and antioxidant agents [2,8,9].

The classical method for the synthesis of DHPMs is the Biginelli multicomponent synthesis between an aldehyde, a 1,3-dicarbonyl compound and urea or thiourea, in the presence of different acid–basic catalysts. A comprehensive review of the different catalysts used in this transformation was written by Suresh and Sandhu [10].

Furthermore, the incorporation of vanadium atom in the primary structure of molybdophosphoric acid (PMo) shows unique catalytic features for oxidations due to its bifunctional character, which arises because of the redox nature of vanadium and the oxidation/acidic character of the molybdophosphoric acid [11]. A diversity of reactions have been analyzed, including hydroxylation of benzene, oxidation of toluene, benzoin and methane, and the selective oxidation of sulfides using aqueous hydrogen peroxide [12-15]. Similarly, the incorporation of a transition metal such as

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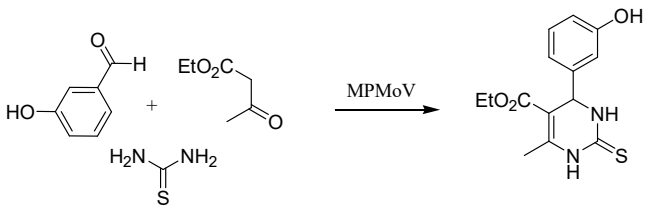
Cu or Fe improves the oxidative and acidity capacity of the catalyst, for example, in methacrolein oxidation to methacrylic acid, in 2,6-dimethylphenol conversion to 2,6-dimethyl-1,4-benzoquinone, dibenzothiophene oxidation, and glycerol acetylation [16-20]. However, there are few reports on the use of 11-molybdo-1-vanadophosphoric acid (PMoV) as the acid catalyst for organic transformations. PMoV catalysts were found to be very active for the acylation of alcohols with acetic anhydride under solvent-free conditions [21], and phenol mononitration using nitric acid and different solvents [22]. Recently, we reported a suitable method to prepare DHPMs using PMo doped with V and Bi in the primary structure of the heteropolyanion [23].

The aim of this work was to study the effect of adding transition metal counterions to 11-molybdo-1-vanadophosphoric acid on the catalytic activity of these materials for the Biginelli synthesis (a reaction catalyzed by the presence of an acid catalyst). We present a study of the multicomponent reaction between 3-hydroxybenzaldehyde, ethyl acetoacetate, and thiourea in the selective synthesis of monastrol (Scheme 1). We also studied the use of these recyclable solid catalysts in a simple, convenient, efficient, and ecofriendly process for the synthesis of related DHPMs suchs as bioactive piperastrol.



M = H, Fe, Cu

Scheme 1. Biginelli reaction for the multicomponent synthesis of monastrol using 3-hydroxybenzaldehyde, ethyl acetoacetate and thiourea.

2. MATERIALS AND METHOD

2.1. Catalyst preparation

Heteropolycompounds derived from doping $H_4PMo_{11}VO_{40}$ (PMoV) with transition metal cations, Fe^{3+} (FePMoV) or Cu^{2+} (CuPMoV), were prepared by a hydrothermal process according to Villabrille *et al.* [18].

2.2. Catalyst characterization

Bruker IFS 66 equipment, pellets in KBr and a measuring range of 400–1500 cm^{-1} were used to obtain the FT-IR spectra of the solid samples at room temperature.

FePMoV and CuPMoV solid samples were analyzed by ^{31}P MAS-NMR by means of Varian Mercury Plus 300 equipment with a sample holder 7 mm in diameter, a resonance frequency of 121.469 MHz, and a spinning rate of 5 kHz. The measurements were carried out at room temperature using 85% H_3PO_4 as external reference.

The UV–vis diffuse reflectance spectra of the samples were obtained by a Varian Super Scan 3 UV–vis spectrophotometer fitted with a diffuse reflectance chamber with its inner surface coated with $BaSO_4$. Once the solid samples were compacted in a Teflon sample holder to obtain a sample thickness of 2 mm, their spectra were recorded at 100 nm/min, in the range 200–600 nm, with a slit beam width of 2.3 nm. Spectral grade $BaSO_4$ was the reference material.

The total acidity of the solid samples was measured by potentiometric titration. The solid (0.05 g) was suspended in acetonitrile (Merck p.a.) and stirred for 3 h. Afterward, the suspension was titrated with 0.05 N *n*-butylamine (Carlo Erba) in acetonitrile, at a flow rate of 0.05 mL/min. The electrode potential variation was measured with an Instrumentalia S.R.L. digital pH meter using a double-junction electrode.

2.3 Representative procedure for the synthesis of monastrol

A mixture of ethyl acetoacetate (260 mg, 2 mmol), 3-hydroxybenzaldehyde (244 mg, 2 mmol), thiourea (228 mg, 3 mmol), and bulk HPA (1% mmol) was thoroughly mixed and then heated at 80 °C for 1 h (until the reaction was complete, checked by TLC). On cooling, the reaction mixture was washed with water (4 mL), and monastrol was filtered and dried under vacuum (50 °C). The crude product was recrystallized from methanol to give the pure product.

Recycling of the catalyst: the reaction was carried out as stated previously; then, the reaction mixture was refluxed with toluene (three times, 1.5 mL each). The catalyst (insoluble) was filtered, dried under vacuum (20 ºC) and reused.

After the optimal reaction conditions for monastrol synthesis were found, different aldehydes, methyl/ethyl acetoacetate, acetylacetone, dimedone, and urea/thiourea were employed for the synthesis of various DHPMs. All products were characterized by ^1H NMR and ^{13}C NMR spectra, which were recorded on a Bruker AVANCE-400 spectrometer (with TMS as an internal standard). Melting points were recorded on melting point apparatus (see complete characterization in the Supplementary Material).

3. RESULTS AND DISCUSSION

Heteropolycompounds, where one molybdenum atom of molybdophosphoric acid (PMo) was substituted by one vanadium atom (PMoV), were doped with Cu^{2+} (CuPMoV) or Fe^{3+} (FePMoV) and fully characterized in previous work [18]. The most relevant results are summarized in Table 1. The primary Keggin structure in the synthesized samples was confirmed. The changes observed indicate V inclusion in the primary structure of the anion. The characterizations suggest that Cu and Fe cations occupy positions in the secondary structure. Additionally, FePMoV and CuPMoV have stronger acid sites than PMoV.

Initially, the optimum reaction conditions were examined employing 3-hydroxybenzaldehyde, ethyl acetoacetate and thiourea as test reaction substrates, under solvent-free conditions at 80 °C for 1 h (Scheme 1).

Table **1.** Some relevant characteristics of synthesized catalysts.

Catalyst	δ/ppm	FT-IR ν_{as} /cm^{-1}				LMCT band/nm		MAS/mV
		P–Oa	Mo–Od	Mo–Ob–Mo	Mo–Oc–Mo			
PMo	-3.61	1064	964	871	784	270	390	586
PMoV	-3.20	1062 1081	960	866	776	285	474	978
CuMoV	-2.72	1062 1083	960	868	775	284	420	998
FeMoV	-3.19	1062 1080	960	873	780	285	450	1062

δ: chemical shift (^{31}P MAS-NMR), LMCT band: maximum of ligand-metal charge transfer band (UV-vis DRS), MAS: Maximum acid strength (potentiometric titration).

In a blank experiment, without the presence of catalyst, a poor yield (20%) of monastrol was detected (Table 2, entry 1). Then, the Keggin heteropolyacids PMo, PMoV, CuPMoV and FePMoV were checked under similar conditions (Table 2, entries 2-5). In the four experiments, good yields of monastrol between 84% and 99% were obtained, indicating that the presence of an acid catalyst is really necessary to improve the reaction yields. These experiments were performed under solvent-free conditions because the catalysts are soluble in polar media and for ecological consideration. In previous work, we found that the incorporation of V in the primary structure of PMo increases the number of acid sites. In this sense, a correlation between the yields and the number of acid sites was observed [18]. Here, the incorporation of Fe and Cu as counterion (secondary structure of HPAs) further increases the reaction yields.

Table **2.** Effect of different catalysts on monastrol synthesis.[a]

Entry	Catalyst	Yields (%)
1	None	20
2	PMo	84
3	PMoV	89
4	CuPMoV	93
5	FePMoV	99

a-Reaction conditions: 3-hydroxybenzaldehyde (2 mmol); ethyl acetoacetate (2 mmol); thiourea (3 mmol); catalyst (1 mmol %); solvent-free; temperature, 80 ºC; time, 1 h; stirring. The crude product was recrystallized.

Then, the catalytic activity of the most active catalyst (FePMoV) was tested for the multicomponent reaction between 3-hydroxybenzaldehyde, ethyl acetoacetate and thiourea under several reaction conditions, such as temperature, reaction time, amount of catalyst, substrate ratio and its reuse, in order to obtain the best reaction conditions (Table 3).

The influence of temperature on the production of monastrol is shown in Table 3, entries 1-4. Four experiments were performed (at 40, 60, 80 and 100 °C). The results show that at 40 ºC the reaction yield was very low (37%, Table 3, entry 1). A temperature increase led to a higher monastrol yield. For example, the yield of monastrol for a reaction time of 1 h at 60 °C was 82% (Table 3, entry 2), whereas at 80 °C the yield was 99% (Table 3, entry 3). Finally, at 100 °C the reaction yield was lower, 77%, (Table 3, entry 4) due to the several unidentified side products that were detected by TLC. The tested experimental reaction conditions were: 3-hydroxybenzaldehyde (2 mmol), ethyl acetoacetate (2 mmol), thiourea (3 mmol), catalyst (1 mmol %), 1 h stirring; under solvent-free conditions.

Table **3.** Effect of different reaction conditions on monastrol synthesis using FePMoV as catalyst.

Entry	Temp. (°C)	Time (h)	Catalyst amount (mg)	Molar Ratio B: A: T	Yields (%)
1	40	1	30	1:1:1.5	37
2	60	1	30	1:1:1.5	82
3	80	1	30	1:1:1.5	99
4	100	1	30	1:1:1.5	77
5	80	0.5	30	1:1:1.5	83
6	80	1.5	30	1:1:1.5	98
7	80	2	30	1:1:1.5	98
8	80	1	15	1:1:1.5	81
9	80	1	45	1:1:1.5	99
10	80	1	60	1:1:1.5	98
11	60	1	30	1:1:1	78
12	60	1	30	1.5:1:1	81
13	60	1	30	3:1:1	81
14	60	1	30	1:1.5:1	80
15	60	1	30	1:2:1	82
16	60	1	30	1:1:2	82
17	60	1	30	1:1:5	75
18	60	1	30	1:1:10	70
19[a]	80	1	30	1:1:1.5	98
20[b]	80	1	30	1:1:1.5	98
21[c]	80	1	30	1:1:1.5	97

B = Benzaldehyde, A = Ethyl acetoacetate, T = Thiourea
a-first, **b**-second, and **c**-third reuse.

The reaction time was also tested at the selected optimal temperature of 80 °C, using four different times of 0.5, 1, 1.5

and 2 h (Table 3, entries 3, 5-7). A good yield was obtained at 0.5 h of reaction (Table 3, entry 5, 83%), the optimal yields being reached at 1 h (Table 1, entry 3, 99%), without any variation at longer reaction times such as 2 h. (Table 1, entry 7, 98%).

Another key factor in these tests is the amount of FePMoV catalyst. The results achieved when different catalyst amounts were used under the previously defined optimal conditions are listed in Table 3, entries 3, 8-10. It can be seen that 1 mmol % of FePMoV gave very good yields (Table 3, entry 3, 99%) and no significant changes were observed when the catalyst amount was increased to 60 mg (Table 3, entry 10, 98%).

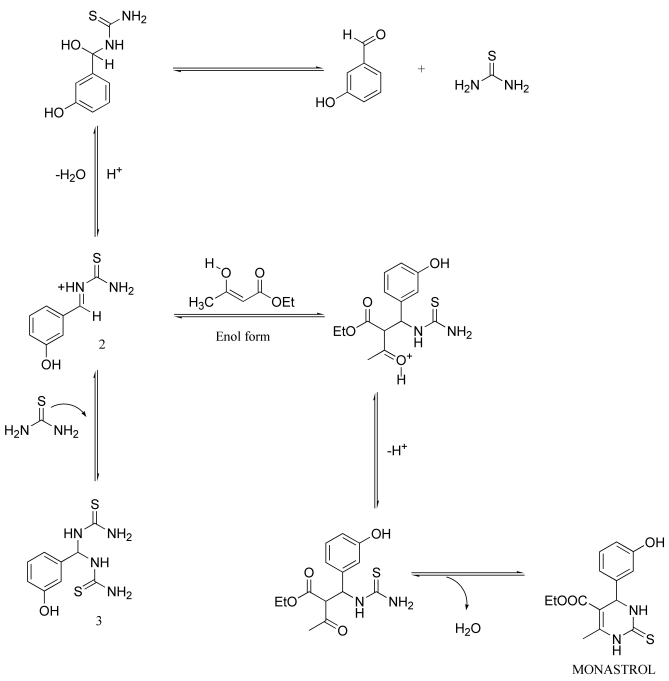
Then, we studied the effect of the molar ratio of reactants. This analysis is important to develop a plausible reaction mechanism. The results obtained when different amounts of the substrates where used at a defined temperature (60 °C) and time (1 h) are listed in Table 3, entries 2, 11-16. The yields were independent of an excess of 3-hydroxybenzaldehyde (Table 3, entries 11-13; 78%, 81% and 81%, respectively). Similarly, no effect was observed with an excess of ethyl acetoacetate (Table 3, entries 14 and 15; 80% and 82%, respectively). Finally, when excess of thiourea was used, the reaction yields evidently decreased (Table 3 entries 11, 16-18; 78%, 82%, 75% and 70%, respectively).

A recent report by Silva and coworkers [24] clearly shows that the most appropriate reaction mechanism between benzaldehyde, ethyl acetoacetate and urea is the iminium mechanism. Our observations for the synthesis of monastrol are in agreement with the iminium mechanism (Scheme 2), mainly because an excess of thiourea would displace the equilibrium from 2 to 3.

The formation of intermediate 3 in the Biginelli reaction was reported by us in previous work [23]. We confirmed the formation of the bis-ureide compound in the reaction between benzaldehyde and N-methyl urea by means of ^{1}H NMR and ^{13}C NMR spectroscopic analyses of the reaction product.

Based on these results, the plausible reaction mechanism for the catalytic reaction, using HPAs as catalyst, is similar to the mechanism postulated by Kappe [25]. The initial step of the mechanism suggests the formation of an N-acyliminium ion **2** (by condensation of one molecule of urea and another one of benzaldehyde), which subsequently reacts with the β-ketoester. The intermediate formed undergoes cyclization and subsequent dehydration, finally giving the DHPM (Scheme 2).

We also investigated the reuse of the catalyst. For this purpose, after completion of the reaction, toluene was added to the solid reaction mixture. All the reaction products are very soluble in hot toluene, but the catalyst is insoluble. So it could be separated by simple filtration. The reaction mixture was refluxed with toluene (3 x 1.5 mL), and the catalyst was filtered and dried under vacuum (20 ºC). FePMoV was reused, and the product yields for the first, second and third reuse were 98%, 98% and 97%, respectively (Table 3, entries 19-20).



Scheme 2. Plausible mechanism of monastrol formation.

The scope of this procedure is illustrated by various examples using different aldehydes, methyl/ethyl acetoacetate, acetylacetone, dimedone, and urea/thiourea, and the results are summarized in Table 4. Based on the results of optimization experiments for the reaction conditions, the reactions were carried out in the presence of FePMoV catalyst (1 mmol %) at 80 ºC under solvent-free conditions, and the corresponding DHPMs were obtained in excellent yields (Table 4). The workup and catalyst recovery are simple, and all reactions have very high selectivity toward the corresponding products. The TLC analysis showed only trace amounts of by-products. After completion of the reaction (monitored by TLC, eluent: EtOAc:*n*-hexane mixtures), the catalyst was separated from the reaction mixture for extracting the product in hot toluene. After evaporation of the solvent, the crude product was easily isolated in almost pure state. Further purification was performed by recrystallization from alcohols. The extraction solvent can be recovered by simple distillation and reused. The products were characterized by ^{1}H NMR and ^{13}C NMR spectroscopy. The characterization details of compounds are shown in the Supplementary Material.

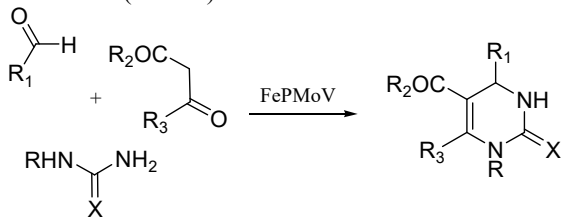
Finally, in order to quantify how much 'greener' the methodology is, yields (Y%), the atom economy (AE), and process mass intensity (PMI) were calculated for each reaction product (see Supplementary Material), and the results are listed in Table 4. The high AE value (> 85%) indicates that this reaction is theoretically greener. This is confirmed by the low PMI values, especially when aromatic aldehydes were used (< 1.5). It is noteworthy that this procedure is very simple to prepare relevant bioactive compounds: monastrol and piperastrol.

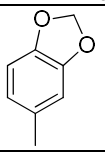
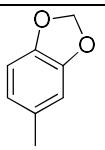
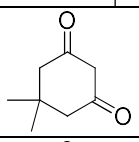
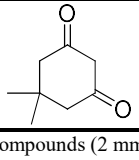
In addition, the new catalyst could potentially be applied to other reactions such as Hantzsch pyridine synthesis and selective oxidation of 2,6-dimethylphenol to 2,6-dimethyl-1,4,-benzoquinone, due to its acid and redox properties.

4. CONCLUSION

In this communication, we report the use of Mo, V, Fe and Cu Keggin structure where Mo is partially replaced by V (PMoV) in molybdophosphoric acid (PMo), and Fe and Cu cations occupy positions in the secondary structure (FePMoV, CuPMoV). In addition, the activities of these catalysts were evaluated in the solvent-free multicomponent synthesis of monastrol and related compounds corresponding to families of DHPMs.

Table **4.** Synthesis of 1,3-dihydropyrimidinones (thiones).[a]



Entry	Reagent					Product	Yield (%)	AE (%)	PMI
	R^1	R^2	R^3	X	NR				
1	Ph	OCH_2CH_3	CH_3	O	H	**4a**	97	87.8	1.35
2	4-CH_3-Ph	OCH_2CH_3	CH_3	O	H	**4b**	97	88.4	1.34
3	2-Cl-Ph	OCH_2CH_3	CH_3	O	H	**4c**	90	89.1	1.42
4	4-Cl-Ph	OCH_2CH_3	CH_3	O	H	**4d**	94	89.1	1.36
5	2-OH-Ph	OCH_2CH_3	CH_3	O	H	**4e**	92	88.5	1.41
6	3-OH-Ph	OCH_2CH_3	CH_3	O	H	**4f**	97	88.5	1.33
7	4-OH-Ph	OCH_2CH_3	CH_3	O	H	**4g**	91	88.5	1.42
8	4-NO_2-Ph	OCH_2CH_3	CH_3	O	H	**4h**	88	89.4	1.42
9	4-SCH_3-Ph	OCH_2CH_3	CH_3	O	H	**4i**	96	89.5	1.32
10	4-OH-3-OCH_3-Ph	OCH_2CH_3	CH_3	O	H	**4j**	92	89.5	1.37
11		OCH_2CH_3	CH_3	O	H	**4k**	90	89.4	1.41
12	CH=CH-Ph	OCH_2CH_3	CH_3	O	H	**4l**	81	89.2	1.21
13	1-Naph	OCH_2CH_3	CH_3	O	H	**4m**	93	89.6	1.36
14	Ethyl	OCH_2CH_3	CH_3	O	H	**4n**	40	85.5	3.46
15	*n*-Propyl	OCH_2CH_3	CH_3	O	H	**4o**	44	86.3	3.09
16	Ph	OCH_3	CH_3	O	H	**4p**	98	87.2	1.36
17	4-Cl-Ph	OCH_3	CH_3	O	H	**4q**	91	88.6	1.42
18	Ph	CH_3	CH_3	O	H	**4r**	88	86.5	1.54
19	4-Cl-Ph	CH_3	CH_3	O	H	**4s**	90	88.0	1.45
20	Ph	OCH_2CH_3	CH_3	S	H	**4t**	92	88.5	1.44
21 Monastrol	3-OH-Ph	OCH_2CH_3	CH_3	S	H	**4u**	99	89.0	1.32
22 Piperastrol		OCH_2CH_3	CH_3	S	H	**4v**	95	89.9	1.23
23	4-Cl-Ph			O	CH_3	**4w**	91	89.7	1.40
24	4-CH_3-Ph			O	CH_3	**4x**	92	89.2	1.41

a-Reaction conditions: Aldehyde (2 mmol); 1,3-dicarbonyl compounds (2 mmol); urea or thiourea (3 mmol); catalyst (1 mmol %); solvent-free; temperature, 80 ºC; time, 1 h; stirring. The crude product was recrystallized.

The incorporation of V in the primary structure of the heteropolyanion, and Fe and Cu in the secondary structure increases the catalytic activity. For monastrol synthesis, a correlation between the yields and the number of acid sites and acid strength was observed. The reactivity order was: PMoVFe > PMoVCu > PMoV > PMo. In this reaction, the catalyst can be recycled without loss of the catalytic activity.

The reaction experiments were performed in the absence of solvent, at 80 ºC, for 1 h. Under these conditions and using the most active catalyst (PMoVFe), 22 examples were obtained with very good yields (88%-99%) and high selectivity. The catalyst was easily recycled and reused without appreciable loss of its catalytic activity. The synthetic method presented is a simple, clean and environmentally friendly alternative for obtaining substituted DHPMs from aromatic aldehydes.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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SUPPLEMENTARY MATERIAL

Supplementary Material contains characterization details of compounds 4a-x and the definition of AE and PMI.

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