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Simple halogen-free synthesis of aryl cinnamates using Mo-Keggin heteropoly acids as catalyst*

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Abstract: A convenient chlorine-free procedure for the direct esterification of cinnamic acids with phenols is described. The method does not require stoichiometric activation of the carboxyl group with thionyl chloride or condensing reagents. The methodology is very simple, environmentally friendly, and high-yielding for both electron-releasing and -withdrawing substituted phenols. The Keggin heteropoly acids $H_3PMo_{12}O_{40}$ and $H_4SiMo_{12}O_{40}$ were employed as catalyst in simple bulk form. The effects of temperature, reaction time, and amount of the catalyst used on the ester yield were checked. Suitable conditions for the reaction include a 1:1 molar ratio of reactants and a 1 mmol % of catalyst to reactant ratio. Seventeen aryl cinnamates were obtained, yields ranged from 80 to 91 % for most of the esters. The catalyst was shown to be reusable for at least four times without any appreciable loss of its activity.

Keywords: acid catalysis; chlorine-free organic synthesis; cinnamates; direct esterification; Keggin heteropoly acids.

INTRODUCTION

Mild and effective esterification of carboxylic acids with alcohols is one of most important reactions in organic synthesis [1]. It has long been known that the process of esterification may be accelerated by the addition of a strong acid such as Brønsted acid [2]. The literature reported several methods for esterification using specific dehydrating reagents [3]. However, the classical esterifications have some disadvantages of the corrosiveness of strong acid, with accompanying side reactions such as carbonization and oxidation. For direct esterification of carboxylic acid under mild conditions, carboxyl group must be activated to more reactive species by using an activator [2].

Activation of the carboxyl group has been classily performed by means of the acyl chloride method, where the chlorine anion acts as electron-withdrawing moiety. These compounds are formed

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in classic organic synthesis techniques using phosphorous pentachloride or thionyl chloride as precursors [4]. This represents the main path for ester and amide synthesis.

In addition, halogen-free organic synthesis of organic chemistry is an area of recent study in green chemistry. Halogen-free conditions have been developed in a few cases, for example, the C–C bond formation in the Suzuki–Miyaura coupling [5] and Mizoroki–Heck-type reactions [6,7].

In this way, chlorine-free conditions in organic synthesis have been developed in various strategies replacing thionyl chloride (avoiding the acyl chloride preparation step); for example, acylation by means of Friedel–Craft reaction [8–12], synthesis of carbamates [13,14], cyclic carbonates [15,16], and urethanes [17].

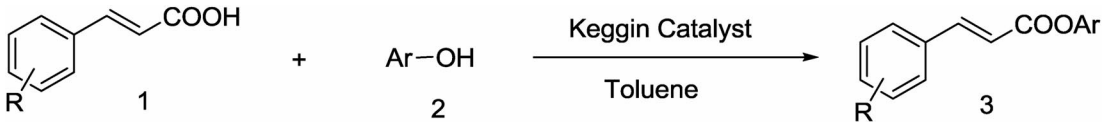
Cinnamates are important organic compounds owing to their application in a wide range of industrial products such as graphics, lubricants, plasticizers, flavors, perfumes, and cosmetics [18]. Cinnamates are also antioxidants and flavoring agents [19]. Particularly, aryl cinnamates have been used as intermediates for diverse heterocyclic compounds, such as chromones, pyrazoles, and furanones [20]. Some substituted aryl cinnamates are antifungal agents [19] and inhibitors of plant growth [20].

There are only a few procedures that have been used to prepare aryl cinnamates, including the most widely used method via cinnamoyl chloride [21], or using *N*,*N*'-dicyclohexylcarbodiimide (DCC) [22] or benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate (BOP) [18] as coupling agents to perform the direct reaction between cinnamic acid and a phenol, or between a phosphorane and a benzaldehyde [23]. However, these methods have drawbacks, such as the formation of the carcinogenic by-product hexamethylphosphoramide (HMPA) or, from the point of view of green chemistry, a low atom economy of chlorine (by using DCC or $SOCl_2$; besides, in the latter case heating at 350 °C is prescribed [21]).

Most recently, our research group described two green procedure methods to prepare these compounds for the direct esterification of cinnamic acids with phenols or 2-(*N*-phthalimido)ethanol using Wells–Dawson and Preyssler heteropoly acids (HPAs) in bulk or silica-supported form [24,25].

On the other hand, there is an increasing interest in the area of heteropoly compound (HPC)-induced organic transformations. In view of their remarkable catalytic properties, HPCs are applied both in bulk or supported form, and homogeneous or heterogeneous catalysis is possible. The (HPCs) with Keggin structure are polynuclear complexes mainly constituted by molybdenum, tungsten, or vanadium as polyatoms (M), and phosphorus, silicon, or germanium as central atom or heteroatom (X). The Keggin structure is formed by a central tetrahedron XO4, surrounded by 12 octahedra MO6. They could be either multielectron oxidants or strong acids, with an acid strength higher than that of the classical acids [26]. Recently, our research group reported green catalytic acid and oxidation procedures using Keggin HPAs [27–31].

In connection with our research project on the ecofriendly organic synthesis related to selective pesticide, here we report the results obtained for the direct esterification between cinnamic acids (**1**) and phenols (**2**) (Scheme 1). Two commercial Keggin solid acid catalysts ($H_3PMo_{12}O_{40}$, PMo, and $H_4SiW_{12}O_{40}$, SiMo) were employed as ecofriendly, reusable catalysts in bulk form and using toluene as non-chlorine reaction solvent.



Scheme 1

EXPERIMENTAL

Catalysts

HPAs $H_3PMo_{12}O_{40}$ and $H_4SiMo_{12}O_{40}$ were purchased (Aldrich) and used without further purification. Both catalysts were dried in vacuum at room temperature (20 °C) overnight prior to use.

General procedures

All the reactions were monitored by thin layer chromatography (TLC) on precoated silica gel plates (254 mm). Flash column chromatography was performed with 230–400 mesh silica gel. All the yields were calculated from pure products. All the products were identified by comparison of physical data (mp, TLC, NMR) with those reported. Melting points of the compounds were determined in sealed capillary tubes and are uncorrected. ^{13}C NMR and ^{1}H NMR spectra were recorded at room temperature on Bruker AC-250 and Bruker Avance DPX-400 spectrometers using TMS as internal standard. Entries and target compounds have the same number.

General procedure for the synthesis of phenyl cinnamates

The esterification reaction was performed in a round-bottom flask, which was equipped with a condenser and immersed in an oil bath. A solution of cinnamic acid **1** (1 mmol) and phenol **2** (1 mmol) in toluene (4 mL) and the bulk HPA (10^{-2} mmol) were refluxed with stirring for the indicated time. In both cases, the catalyst was removed by filtration and washed twice with toluene (1 mL each). The organic solution was washed with cold 1 M NaOH (2 × 3 mL) and H_2O (2 × 3 mL) and then dried over anh. Na_2SO_4. Evaporation of the solvent under reduced pressure and silica flash column chromatography gave the pure cinnamate **3**.

Recycling of the catalyst

After reaction, the catalyst was filtered, washed thoroughly with toluene (2 × 3 mL), dried under vacuum, and reused for the esterification reaction, following the procedure described above.

RESULTS AND DISCUSSION

Optimization of catalytic tests

This work describes the application of a heterogeneous halogen-free system (toluene) for the direct esterification of cinnamates (without the use of thionyl chloride as activated carboxylic agent) with phenols in the presence of Keggin HPAs ($H_3PMo_{12}O_{40}$ and $H_4SiMo_{12}O_{40}$) as reusable catalyst. The phenylcinnamate (**3**) synthesis involving the esterification of cinnamic acids (**1**) and phenols (**2**) is illustrated in the reaction, Scheme 1.

Before attempting detailed catalytic work, a noncatalytic reaction between cinnamic acid (1 mmol), phenol (1 mmol), and toluene (4 mL) was examined, and it was observed that under the experimental conditions (110 °C, 4 h), no formation of phenylcinnamate was detected, indicating that from a practical point of view the reaction is not taking place in the absence of a catalyst.

Figure 1 shows the obtained results for the phenylcinnamate yield (**3a**) using the two different catalysts considered ($H_3PMo_{12}O_{40}$ and $H_4SiMo_{12}O_{40}$). The experimental conditions were: 1 % of catalyst, 1 mmol of cinnamic acid, 1 mmol of phenol, and 4 mL of toluene; reaction for 4 h at 110 °C. In these conditions, phenylcinnamate was obtained with a selectivity of 100 % for both catalysts. The yields were 83 and 72 %, respectively, $H_3PMo_{12}O_{40}$ resulting as the most active catalyst, in parallel with the decrease of their acidic strength [25].

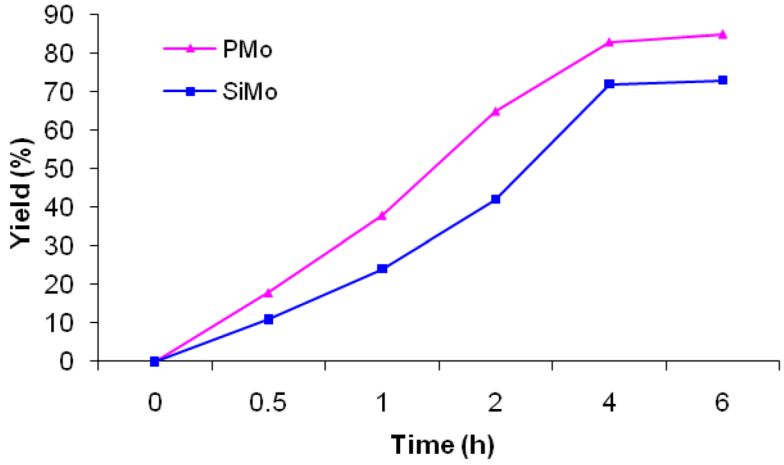


Fig. 1 Time reaction optimization for the synthesis of phenyl cinnamate using $H_3PMo_{12}O_{40}$ as catalyst. Reaction conditions: cinnamic acid (1 mmol), phenol (1 mmol), and $H_3PMo_{12}O_{40}$ (1 mol %); temperature: 110 °C, under toluene (4 mL).

Effect of reaction temperature and time on catalyst performance

The effect of temperature plays an important role in the catalytic synthesis of cinnamates. It was examined in the temperature range between 20 and 110 °C in toluene (4 mL) using $H_3PMo_{12}O_{40}$ as catalyst, and the results are illustrated in Fig. 2. The reaction is carried out using cinnamic acid (1 mmol), phenol (1 mmol), and catalyst (1 % mmol). Temperature increase leads to a higher cinnamic acid conversion. The conversion of 1,5-benzodiazepine for a reaction time of 6 h at 20 °C is only 5 %, whereas at 110 °C the conversion is 100 %. For the same time of 6 h, a conversion of only 62 % is observed when the temperature is raised from 20 to 45 °C. For this reason, 110 °C was employed as the ideal temperature to continue with the analysis of other reaction variables.

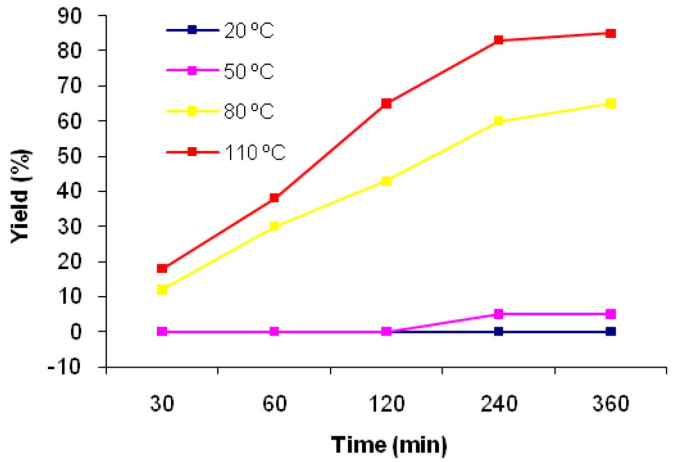


Fig. 2 Temperature optimization for the synthesis of phenyl cinnamate using $H_3PMo_{12}O_{40}$ as catalyst. Reaction conditions: cinnamic acid (1 mmol), phenol (1 mmol), and $H_3PMo_{12}O_{40}$ (1 mol %) at different temperatures under toluene (4 mL).

Effect of the amount of catalyst

The optimal reaction conditions (cinnamic acid, 1 mmol; phenol, 1 mmol; $H_3PMo_{12}O_{40}$, 1 %; temperature of 110 °C and a reaction time of 4 h) were used for the next experiment. Different amounts of $H_3PMo_{12}O_{40}$ catalyst were tested (0.01, 0.5, 1, and 5 %). The results show that 1 % is an optimal quantity of catalyst to obtain the best yields (see Fig. 3). When the experiment was carried out employing 5 % of $H_3PMo_{12}O_{40}$ catalyst, similar conversions were obtained.

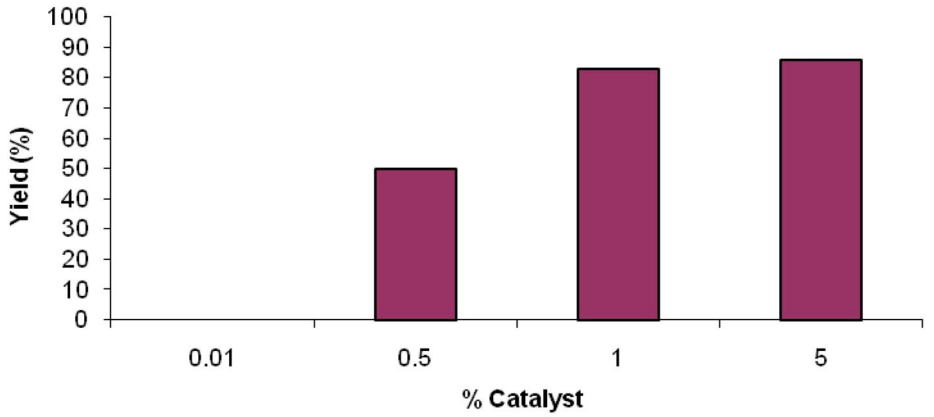


Fig. 3 Effect of catalyst concentration for the synthesis of phenyl cinnamate. Reaction conditions: cinnamic acid (1 mmol), phenol (1 mmol) and $H_3PMo_{12}O_{40}$, toluene, 4 mL, 110 °C, 4 h.

Reuse of the catalyst and solubilization test

The reuse of catalysts is central to their utility. In order to investigate the reusable properties of the catalysts, recycle experiments were tested and the results are shown in Fig. 4. After reaction, the catalysts were recycled by washing with toluene (2 × 2 mL), dried under vacuum at 20 °C for 24 h, and then reused. They were reused twice, and it was observed that there was a minor loss in catalyst weight during each recycle (total loss 5 %). For the $H_3PMo_{12}O_{40}$ catalyst, the isolated yields of phenylcinnamates were 83, 81, 80, and 80 %, which showed the good reusability of this catalyst (Fig. 4).

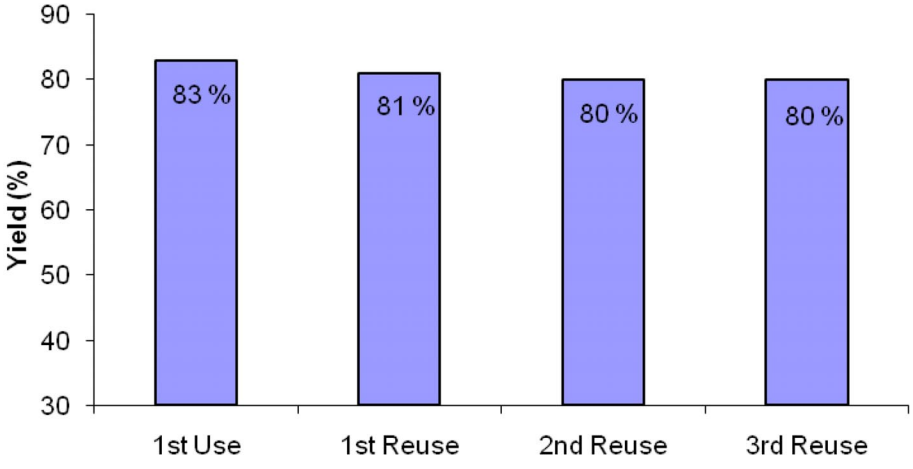


Fig. 4 Catalyst reuse. Reaction conditions: cinnamic acid (1 mmol), phenol (1 mmol) and $H_3PMo_{12}O_{40}$, toluene, 4 mL, 110 °C, 4 h.

In order to evaluate the possible catalyst solubilization, an additional test was performed. The $H_3PMo_{12}O_{40}$ (1 mmol) sample was refluxed in toluene (4 mL) for 6 h, filtered and dried in vacuum until constant weight. The activity of the so-treated catalyst was the same as that of the fresh catalyst. The refluxed toluene was used as solvent for attempting the reaction without adding the catalyst. After 6 h of reaction the phenylcinnamates were not obtained. Figure 5 show the Fourier transform-infrared (FT-IR) spectra of pure and reused $H_3PMo_{12}O_{40}$. There are no changes in the HPA structure.

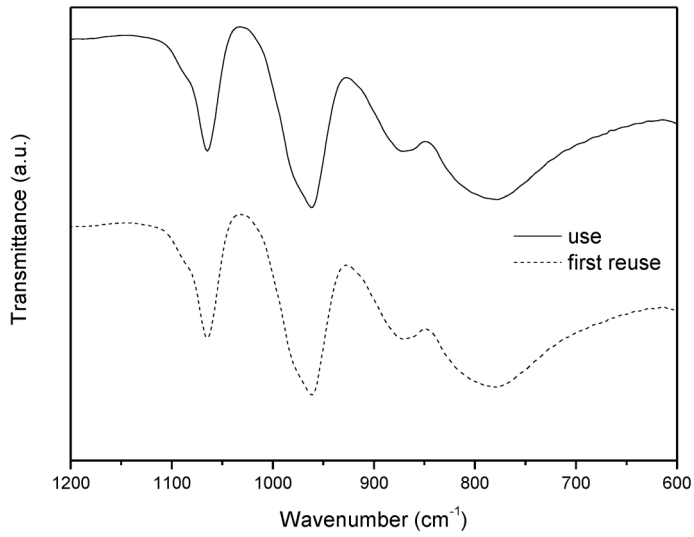
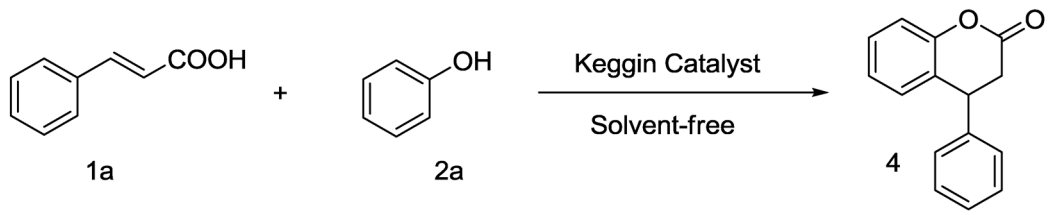


Fig. 5 FT-IR spectra of $H_3PMo_{12}O_{40}$.

Effect of the solvent volume

In this case, the solvent volume is a key aspect, because 5 % of subproduct 4-phenyl-3,4-dihydrocoumarin (**4**) was observed when a low volume (1 mL) was used. In fact, this is the main selective product from the same substrates in the case of solvent-free reaction conditions [22] (Scheme 2).



Scheme 2

Plausible reaction mechanism

As a result of the assays performed and reported in this research, in Fig. 6 we propose a catalytic cycle for the esterification of cinnamic acids with phenols using PWMo as catalyst. The cycle begins with the protonation of the carboxylic oxygen of the cinnamic acid caused by the HPA; this interaction generates a carbocation in the carboxylic carbon atom that is later attacked by a phenol molecule acting as nucleophile. The instability of the generated ion promotes the proton transfer and consequent water molecule elimination, generating a new cation that finally deprotonates, giving the aryl cinnamate and recovering the catalyst. In the same manner, in Fig. 7 we propose a catalytic cycle for 4-phenyl-3,4-dihydrocoumarin formation.

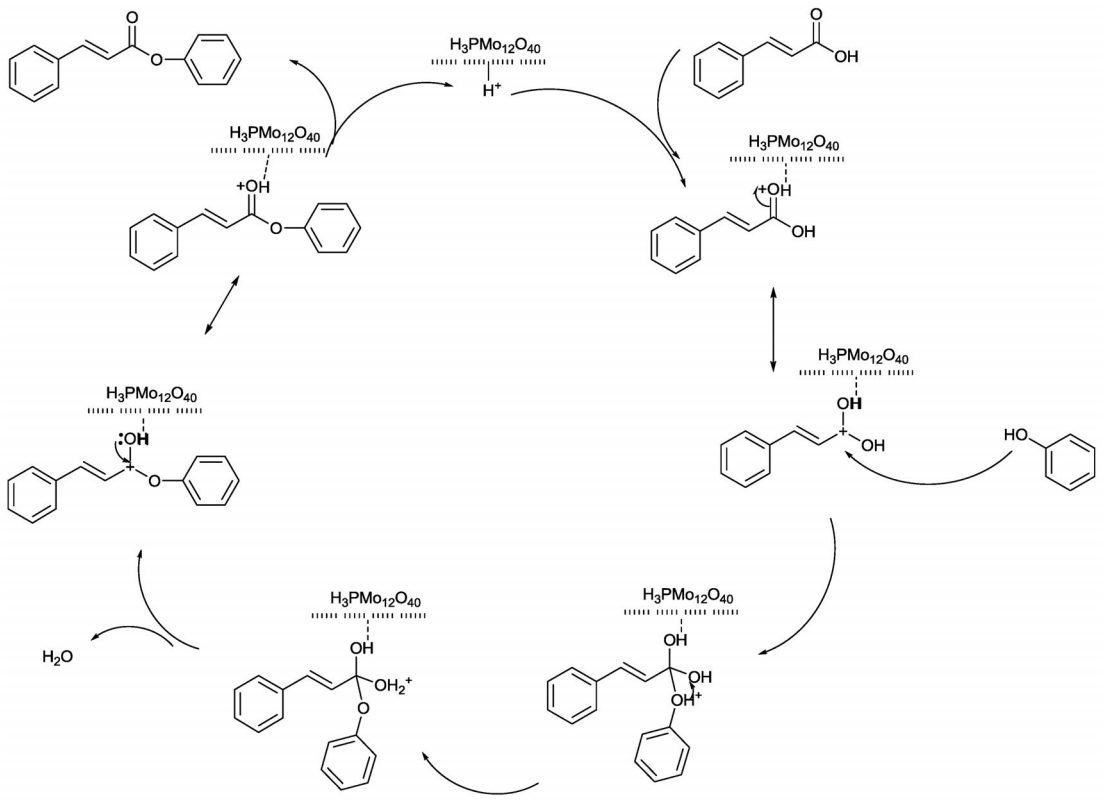


Fig. 6 Proposed catalytic cycle for the aryl cinnamate Keggin ($H_3PMo_{12}O_{40}$) acid-mediated esterification.

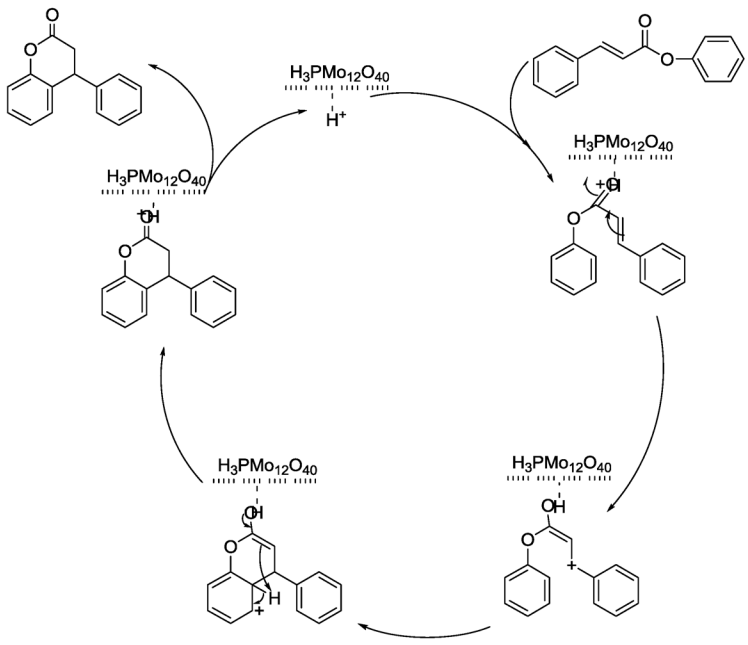


Fig. 7 Proposed catalytic cycle for secondary product formation (4-phenyl-dihydrocoumarin).

Preparation of substituted phenylcinnamates

To explore the general validity of the process previously described, a series of phenylcinnamate derivatives were prepared under the optimal conditions. The reactivity of different cinnamic acids and phenols was tested under the same conditions. Results of the obtained yields are listed in Table 1. The results showed that, in general, the reactions were clean and products were isolated by liquid column chromatography in pure form without further purification (^{1}H and ^{13}C NMR). The reaction is very selective, and no competitive side reactions were observed by gas chromatography (GC). The electronic nature of the substituents seems to have no great effects on the reaction yield.

Table 1 Synthesis of different phenyl cinnamates using $H_3PMo_{12}O_{40}$ as catalyst[a].

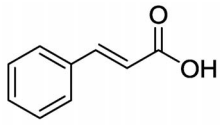
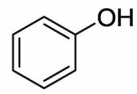
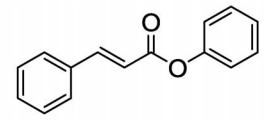
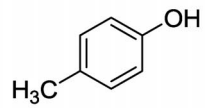
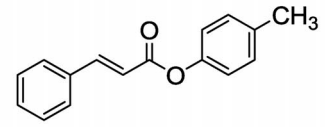
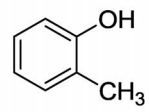
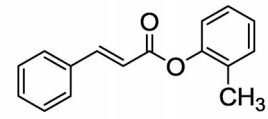
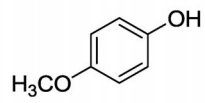
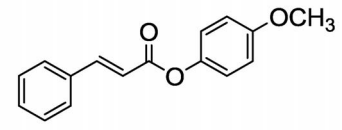
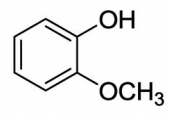
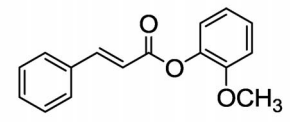
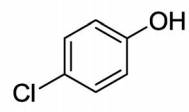
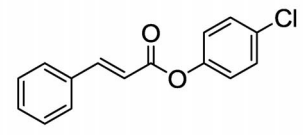
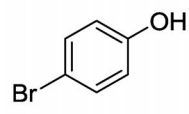
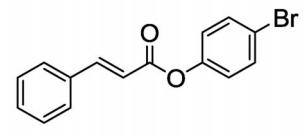
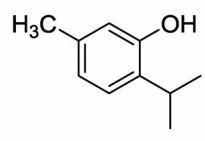
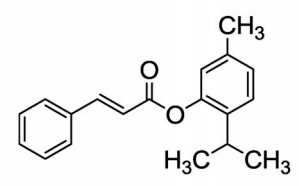
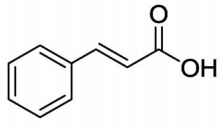
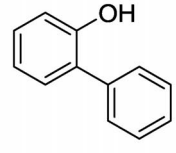
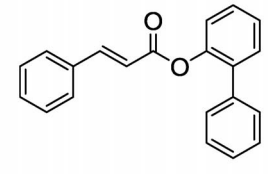
Entry	Cinnamic acid	Phenol	Product	Yields (%)
1				83
2				87
3				82
4				83
5				81
6				83
7				80
8				79
9				82

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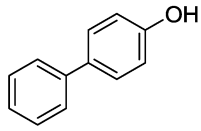
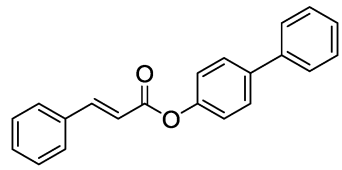
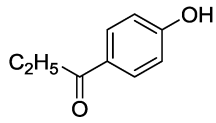
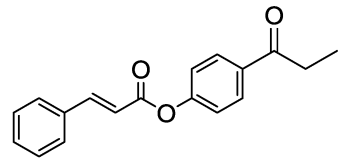
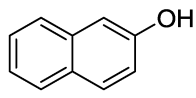
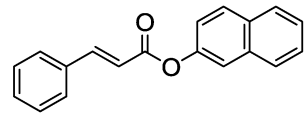
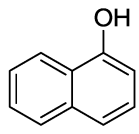
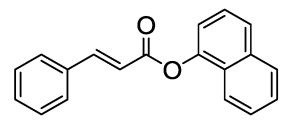
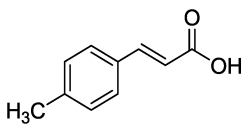
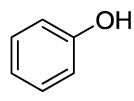
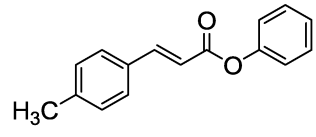
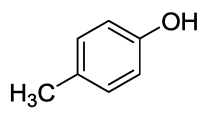
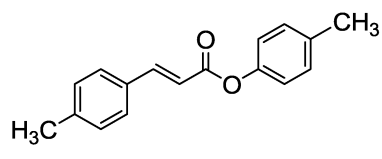
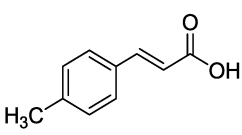
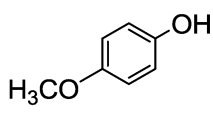
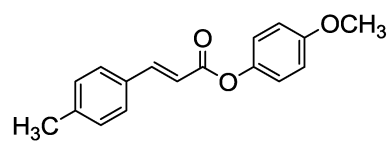
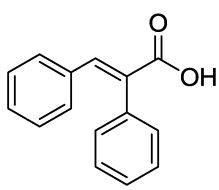
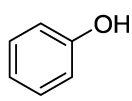
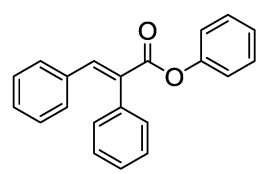
Table 1 (*Continued*).

Entry	Cinnamic acid	Phenol	Product	Yields (%)
10				87
11				80
12				83
13				85
14				82
15				88
16				89
17				85

[a]Experimental condition: cinnamic acids (1 mmol), phenols (1 mmol), $H_3PMo_{12}O_{40}$ (1 mol %), 110 °C, toluene, 4 h, stirring.

CONCLUSIONS

The described procedure for the direct esterification of substituted cinnamic acids in halogen-free condition (without thionyl chloride) using commercial Keggin HPAs ($H_3PMo_{12}O_{40}$ and $H_4SiMo_{12}O_{40}$) results in a clean and useful alternative for the preparation of aryl cinnamates. The advantages of this methodology are operative simplicity, use of a reusable and noncorrosive solid acid catalyst, soft reaction conditions, and excellent yields. The use of a solid acid catalyst instead of the usual soluble acid catalyst (sulfuric, hydrochloric, etc.) contributes to a reduction in waste generation by allowing an easy separation and recovery without any loss of its catalytic activity. No metal chloride such as $AlCl_3$ was used as catalyst, no acid chloride was used as acylating agent, and no solvent chloride was used as reaction medium. Therefore, this reaction system could be a model of a halogen-free esterification process.

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SUPPLEMENTARY INFORMATION

Melting point and NMR spectra of representatives cinnamates are available online (doi:10.1351/PAC-CON-11-06-05).

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