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Highly selective multifunctional nanohybrid catalysts for the one-pot synthesis of α,β-epoxy-chalcones

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ABSTRACT

An efficient one-pot heterogeneous process for producing chiral α,β-epoxy-chalcones from the corresponding aldehydes and ketones has been described. The nanohybrid materials based on poly-L-leucine immobilised into rehydrated hydrotalcites did not require any pre-activation and were easily recovered and recycled for four consecutive runs without losing their catalytic efficiency in terms of conversion, total selectivity towards the corresponding epoxy-chalcones and excellent enantioselectivity.

1. Introduction

Catalytic asymmetric synthesis is an important technique for the preparation of chiral epoxides in both academia and industry. These epoxides are versatile products that can easily undergo stereospecific ring-opening reactions to form multifunctional compounds. They are not only important chiral building blocks, but also key intermediates in the synthesis of more complex molecules with important bioactivity such as leukotriene, erythromycin, (+)-aurilol or brevetoxin B [1–3].

The main pathway to obtain the chiral epoxides consists in the epoxidation of olefins by either metal-catalysed reactions [2] or peptide-type reactions [4–6]. Even though metal-catalysed reactions gained much attention in the last years, they are not suitable to produce bioactive molecules due to some possible drawbacks: metal leaching, toxic effects of the metal used, etc. Thus, peptide-catalysed reactions represent a possible solution to these drawbacks.

In 1983 Colonna et al. introduced a triphasic catalytic system based on water–organic solvent–poly-amino acids which afforded optical active epoxides [7]. The long reaction time and the problems regarding the recovery of the catalyst were overcome by Roberts et al. who developed a biphasic system composed of an organic base and anhydrous urea-hydrogen peroxide and poly-amino acids on silica as catalyst [8].

To increase the yield of the epoxidation reaction, Geller et al. modified the triphasic protocol by adding tetrabutylammonium bromide (TBAB) as cocatalyst. Using this method and in the presence of poly-L-leucine, the reaction time was considerably decreased and the enantiomeric excess was improved [9].

Recently, our group developed a new catalyst based on poly-L-leucine immobilised into hydrotalcites able to catalyse the Juliá–Colonna epoxidation of *trans*-chalcone under triphasic conditions with good conversions and enantioselectivity [10].

Industry favours catalytic processes that require less workup and where intermediates are obtained *in situ*, avoiding unnecessary purification procedures. Various α,β-unsaturated ketones used in asymmetric epoxidation reactions require the preparation from the corresponding aldehydes and ketones, which can be troublesome according to the available procedures [11–13].

In the literature there are several homogeneous systems [14–17], but only two heterogeneous systems were able to carry out the Claisen–Schmidt condensation–asymmetric epoxidation reaction. Choudary et al. used nanomagnesium oxide (NAP-MgO), but the conversion and enantioselectivity obtained were moderate. Additionally, the catalytic system lost its activity by poisoning with the water formed during the condensation reaction [18]. Liu et al.

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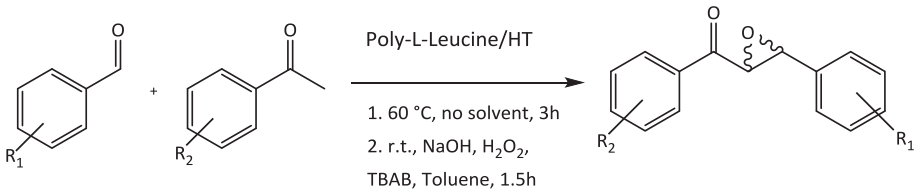


Scheme 1. One-pot synthesis of chiral epoxy-chalcones catalysed by immobilised poly-L-leucine (IPL).

carried out the first part of the reaction in homogeneous medium and added afterwards poly-L-leucine for the asymmetric epoxidation. Though they recycled the polymer, the system is not completely heterogeneous and the process requires longer reaction time [19].

Herein, we wish to report an efficient green one-pot way to synthesise chiral epoxy-chalcones from the corresponding aldehydes and ketones using poly-L-leucine immobilised into rehydrated hydrotalcites (Scheme 1).

2. Experimental

2.1. General

All chemicals and solvents were commercially available (Aldrich Chemical, Fluka) and used without further purification/drying unless otherwise mentioned.

XRD measurements were made using a Siemens D5000 diffractometer (Bragg–Brentano parafocusing geometry and vertical – goniometer) fitted with a curved graphite diffracted-beam monochromator and diffracted-beam Soller slits, a 0.06° receiving slit and scintillation counter as a detector. The angular 2θ diffraction range was between 1° and 70°. The sample was dusted onto a low background Si (510) sample holder. The data were collected with an angular step of 0.05° at 3 s per step and sample rotation. CuK radiation was obtained from a copper X-ray tube operated at 40 kV and 30 mA.

Thermogravimetric analyses coupled with MS and differential thermal analyses (TGA-MS/DTA) were performed on a SenSys Evo TG coupled with HiCube-Pfeiffer Vacuum system.

MALDI-TOF analyses were performed using a Voyager-DE STR MALDI mass spectrometer from Applied Biosystems equipped with a nitrogen laser using the following conditions: emission wavelength 337 nm, pulse duration 3 ns and 20 Hz repetition rate.

^{1}H NMR spectra were recorded on a Varian NMR System 400 spectrometer in $CDCl_3$. Chemical shifts (δ) are given in ppm and J values are given in Hz.

HPLC analyses were performed on a Shimadzu RID-10A (Refractive Index Detector) using CHIRALPACK IA column and heptane: ethanol 3:1 as mobile phase. Optical rotations were measured on a Perkin–Elmer 241 MC Polarimeter using Na-lamp and CH_2Cl_2 as solvent.

2.2. Synthesis of hydrotalcite materials (HTs)

Mg–Al HTs (molar ratio 2:1) were prepared by the co-precipitation method at room temperature and pH = 10. The appropriate amounts of $Mg(NO_3)_2{\cdot}6H_2O$ and $Al(NO_3)_3{\cdot}9H_2O$ were dissolved in 110 ml Milli-Q water and added dropwise into a vessel containing 150 ml of Milli-Q water. The pH was kept constant using 2 M NaOH solution. The suspension was stirred overnight at room temperature. The obtained solid was filtered and washed several times with water and dried under vacuum. The solids were calcined in air at 450 °C overnight to obtain the corresponding mixed oxides (HTc). HTr was obtained by the rehydration of HTc in inert atmosphere using decarbonated water and sonication for 30 min [10].

2.3. Synthesis of poly-L-leucine (PLL)

PLL was synthesised by the ring opening polymerisation method using trimethylamine as initiator, as previously reported [10]. The L-leucine-NCA (0.6 g) was dissolved in anhydrous 1,4-dioxane (11.4 ml) under Ar atmosphere and stirred at 60 °C. After 15 min the corresponding amount of trimethylamine (monomer/initiator ratio = 5) was added and the flask was closed with a freshly prepared $CaCl_2$ drying tube. The final mixture was left under stirring at 60 °C for 4 days. Milli-Q water was used as workup solvent and the mixture was stirred for another 2 h. The obtained solid was filtered and dried under vacuum. The polymer was characterised by MALDI-TOF spectroscopy.

2.4. Preparation of immobilised poly-L-leucine (IPL)

The poly-L-leucine synthesised using a monomer/initiator ratio of 5 at 60 °C was immobilised into Mg–Al HTr (molar ratio 2:1). In a typical procedure, 100 mg PLL was added over a mixture containing 300 mg HTr and 5 ml decarbonated water. The suspension was stirred for 1 h and subjected to ultrasound for another 30 min. The obtained material was washed with THF and dried at 40 °C under inert atmosphere. The nanohybrid materials were characterised by MALDI-TOF and XRD spectroscopy. The amount of PLL immobilised was determined by TGA analysis.

2.5. Standard conditions for the Claisen–Schmidt condensation

The Claisen–Schmidt condensation was performed in a 10 ml tube. The general procedure was as follows: acetophenone (0.19 mmol) and benzaldehyde (0.20 mmol) were added, along with the solvent – in some cases – over the catalyst (PLL, IPL, uncalcined HTs). The mixture was stirred for 3 h at different temperatures: 30 °C, 60 °C or 80 °C. The catalyst was recovered by centrifugation and washed several times with the solvent. The organic layer was dried over $MgSO_4$ and the solvent was removed by evaporation under reduced pressure. The products were identified by ^{1}H NMR.

2.6. Standard conditions for the one-pot Claisen–Schmidt condensation/Juliá–Colonna epoxidation reaction

The one-pot Claisen–Schmidt condensation/Juliá–Colonna epoxidation reaction was performed in a 10 ml tube. The corresponding ketones (0.19 mmol) and aldehydes (0.20 mmol) were added over IPL (100 wt% PLL with respect to ketone) and stirred for 3 h at 60 °C. In all the experiments the molar ratio ketone/aldehyde was 0.95. The reaction mixture was cooled at room temperature and TBAB (3.7 mg), H_2O_2 (169.7 μl), NaOH 2 M (245 μl) and 1 ml toluene were added. The reaction mixture was stirred at room temperature for another 1.5 h. The catalyst recovered by centrifugation was washed several times with toluene and water and reused without drying. The organic layer was dried over $MgSO_4$ and the solvent was removed by evaporation under reduced pressure. The products were identified by ^{1}H NMR. The ee% of the corresponding epoxide was determined by chiral HPLC. The

configuration of the major enantiomer was in each case determined by comparison with the literature data.

3. Results and discussion

3.1. Catalyst preparation and characterisation

Mg–Al HTs (molar ratio 2:1) were prepared by the co-precipitation method at pH 10. The obtained materials were calcined at 450 °C and rehydrated with decarbonated water under sonication, to increase the basic sites found between HT layers.

We have showed that the immobilisation of the PLL material into the HTr is favoured by the presence of the carboxylic group [10] in the bio-guest, whilst the N-terminal group of the polymer is important in the catalytic activity [5]. In this context, the polymer was synthesised by the ring-opening polymerisation of the L-leucine-NCA using trimethylamine as initiator, to afford the N- and C-terminals (Scheme 2).

The MALDI-TOF MS spectrum of the polymer (Fig. 1) shows a regular series of peaks, ranging from m/z 500 to 5000. The inset figure shows that the spectrum is a repetition of 3 peaks, corresponding peaks in two consecutive series being separated by 113 Da – representing the leucine residue. For example, the first peak at 1528 Da in the inset spectrum corresponds to a linear polymer containing 13 monomers adducted with potassium; the second peak at 1550 Da corresponds to a linear polymer of the same magnitude, deprotonated and adducted with sodium and potassium; the peak at 1599 Da is specific for a cyclic polymer of 13 monomers adducted with potassium and having an additional mass of two molecules of CO_2. The obtained polymer had a molecular weight of 2805.7 Da and a polydispersity of 1.38.

Nanohybrid materials based on PLL immobilised into rehydrated hydrotalcites were synthesised as previously mentioned [10]. The XRD patterns of all the synthesised materials presented d_{003} and d_{006} diffraction peaks corresponding to meixnerite structure (Fig. 2). Rehydrated hydrotalcite (HTr) displayed a main peak at 11.4 2θ corresponding to a d_{003} = 7.7 Å (Fig. 2b). The XRD spectra of IPL materials showed a new diffraction peak at 7.5 2θ indicating that the PLL was immobilised in the interlayer structure of the hydrotalcite (Fig. 2c) [20].

The thermal decomposition of the nanohybrid materials corresponds to the decomposition of both the immobilised polymer and the rehydrated hydrotalcite. The curve presented three characteristic weight loss: (i) between room temperature and 200 °C, with a maximum at 130 °C corresponding to the removal of surface-absorbed water, the presence of some residual THF after washing and interlayer water molecules; (ii) between 200 °C and 300 °C with a maximum at 246 °C corresponding to the loss of water absorbed in the PLL structure and (iii) from 300 °C to 785 °C with two maxima at 358 °C and 438 °C corresponding to the dihydroxylation of the HT and the decomposition of the PLL structure and the elimination of CO_2 remained from the HT structure (Figs. I and II in Supporting Information). The immobilisation ratio computed from thermogravimetric analysis varied, depending on the amount of polymer used. The typical amount of immobilised polymer was 0.1461 mg PLL/mg HT.

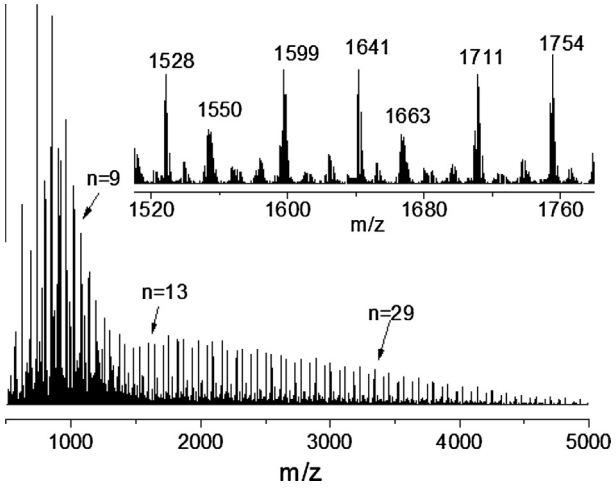


Fig. 1. MALDI-TOF spectrum of PLL. Insert: MALDI-TOF spectrum in the m/z range – 1500–1760.

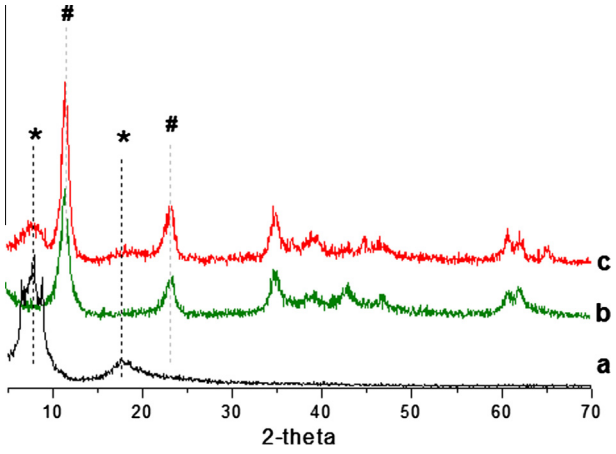
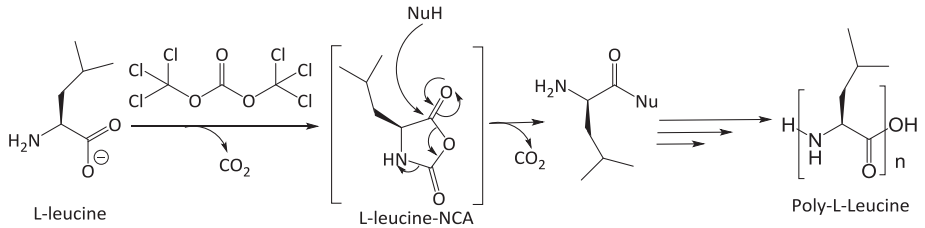


Fig. 2. XRD patterns of nanohybrid PLL/HTr materials: (a) PLL; (b) HTr and (c) IPL.* Basal peaks of (003) plane with immobilised PLL. # Basal peaks of (003) and (006) planes of the starting HTr material.

3.2. Claisen–Schmidt condensation

Claisen–Schmidt condensation is a common reaction catalysed by either an acidic or basic catalyst. Consequently, hydrotalcite materials have been intensively used in the aldol condensation of different aldehydes and ketones. Tichit et al. presented a kinetic study of chalcone synthesis involving calcined and rehydrated hydrotalcites. The later materials showed better activity due to the presence of the –OH groups at the edges of the HT layers



Scheme 2. Synthesis of PLL by ring-opening polymerisation of L-leucine-NCA.

[21]. The same behaviour was observed by Corma et al. [22] and Figueras et al. [23] in the synthesis of flavones and condensation of benzaldehyde with acetone, respectively.

De Jong et al. [24] and Medina et al. [25] reported the synthesis of different more active HT materials prepared by sonication and rehydration, and demonstrated that the rehydration time strongly influenced the solid catalysts. Climent et al. demonstrated that the activity of rehydrated hydrotalcites in the Claisen–Schmidt condensation of acetophenone with aldehyde is dependent on the amount of water used in the rehydration process [26]. The role of the solvent in this reaction was also investigated confirming that solvents' acidity reduces the activity of the HTs by poisoning of the strong basic centres. One disadvantage of using HTs in the C–C bond-forming reactions is the acid–base character of the materials. Both the strong basic centres and the metals located on the surface are able to catalyse side reactions such as self-condensation of ketones or condensation between the reagent and the formed chalcone [27].

Interestingly, Córdova et al. showed that amino acids can catalyse not only the asymmetric aldol addition reaction, but also the aldol condensation reaction. The mechanism proposed can follow two pathways, depending on the amount of catalyst used: either the aldol pathway via the enamine intermediate or the Mannich one via the iminium ion [28].

Thus, this nanohybrid catalyst presents two potential active sites in the Claisen–Schmidt condensation reaction: the rehydrated hydrotalcite and the poly-amino acid. As hydrotalcites are already benchmarks of this reaction, we tested the PLL in the aldol condensation of benzaldehyde and acetophenone at 80 °C and water as solvent. The PLL inactivity in this reaction demonstrates that the last 3–4 monomers in the polymer structure – which are not involved in the hydrogen-bonding of the α-helical form of the polymer – are unable to form the desired iminium ion which would lead to chalcone formation (as Scheme 3 shows).

Consequently, we investigated the activity of the new material in the Claisen–Schmidt condensation of benzaldehyde and acetophenone. Under the conditions mentioned above, the main product of reaction was *trans*-chalcone with the formation of different side products: *cis*-chalcone and 1,3,5-triphenylpentane-1,5-dione (Scheme 4).

De Jong et al. previously showed that the Claisen–Schmidt condensation reaction catalysed by rehydrated HT proceeds through the extraction of a proton from the α-carbon atom of the ketone by the Brönsted basic sites of the catalysts, mainly the OH^- groups found at the edges of the laminar structure of the catalyst. In our preceding work we have demonstrated that the immobilisation of the poly-L-leucine proceeds via the interlayered hydroxyl groups and/or the OH^- anions located at the edges of the HTs [20]. Because in the IPL system the access to some of the OH^- groups is hindered by the presence of the polymer, the active basic sites involved in the catalytic process might be also located on the surface of the catalyst. This assumption was tested by using an uncalcined HT containing nitrates in the Claisen–Schmidt condensation reaction. The very low activity suggests the possible presence of active sites on the surface of the hydrotalcite.

Our results demonstrate that in the IPL material, the hydrotalcite is the only active catalyst in the Claisen–Schmidt condensation reaction.

3.2.1. Temperature effect

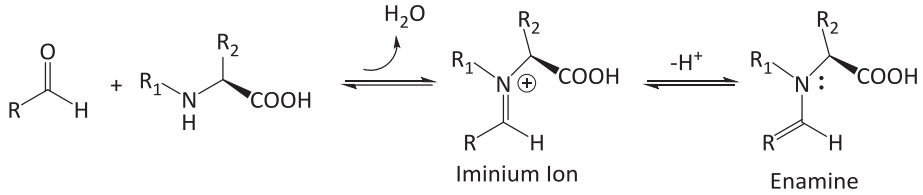
To better understand the catalytic process, we studied the effect of temperature upon the Claisen–Schmidt condensation reaction. Fig. 3 presents the results of the IPL-catalysed reaction between acetophenone and benzaldehyde at 30 °C, 60 °C and 80 °C.

When the reaction was carried out at 80 °C the conversion was 70% whilst the selectivity towards *trans*-chalcone (1a) was only of 49%. The other side products observed were *cis*-chalcone (1b) and the Michael addition product (2) between chalcone and acetophenone. Until now, the *cis*-isomer was obtained in the Claisen–Schmidt reaction only in the presence of the acidic zeolites [29]. Hence, hydrotalcites have dual functionality represented by the presence of the Brönsted basic sites and the Lewis acidic sites (Al^{3+}) found on the surface of the catalysts.

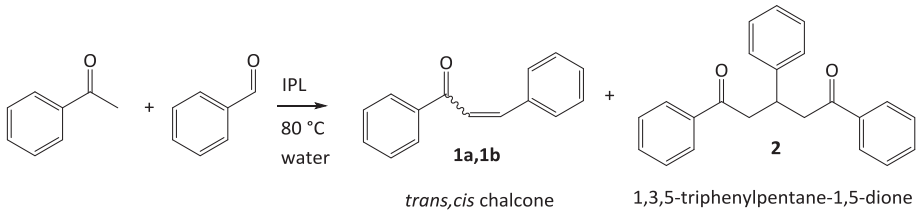
On the other hand, the presence of the Michael addition product (2) is explained by the reactivity of the enolate formed during the Claisen–Schmidt reaction. This enolate will interact with the aldehyde to form chalcone and will further interact with the obtained chalcone to form substance (2).

Knowing that temperature favours the formation of side products in the Claisen–Schmidt condensation, we have carried out the reaction at 30 °C. Curiously, under these conditions, the aldol addition product is favoured (3) and no Michael adduct was obtained (Fig. 4).

Our present results demonstrate that the optimum temperature to carry out the Claisen–Schmidt condensation reaction catalysed



Scheme 3. Iminium and enamine ion formation in Claisen–Schmidt condensation catalysed by amino acids [28].



Scheme 4. Claisen–Schmidt condensation reaction between benzaldehyde and acetophenone. Reaction conditions: aldehyde and ketone in molar ratio of 0.95, 100 wt% PLL with respect to ketone, 1 ml water, 3 h, 80 °C.

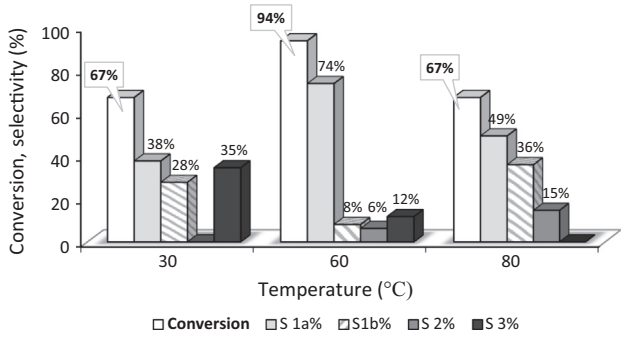
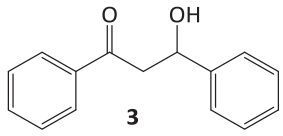


Fig. 3. Effect of temperature upon Claisen–Schmidt condensation. 1a – trans-chalcone; 1b – cis-chalcone; 2 – 1,3,5-triphenylpentane-1,5-dione; 3 – 3-hydroxy-1,3-diphenylpropan-1-one. Reaction conditions: 100 wt% PLL with respect to ketone, acetophenone and benzaldehyde 0.95 M ratio, 1 ml water, 3 h. Conversion and selectivity from ^{1}H NMR spectra of the crude material.



3-hydroxy-1,3-diphenylpropan-1-one

Fig. 4. The aldol addition product obtained in the Claisen–Schmidt condensation.

by the IPL is 60 °C. At this temperature total conversion was obtained with very good selectivity towards the *trans*-chalcone.

3.2.2. Solvent effect

It is widely acknowledged the importance of solvent effects on the chemical reactivity. Thus, we performed the Claisen–Schmidt condensation reaction in different solvents (toluene, ethanol, water) and without solvent (Fig. 5). The low conversion observed when ethanol (a non-aqueous protic solvent) was used can be explained through its acidic character which, during 3 h of reaction, could deactivate the strong basic sites of the hydrotalcite. The only detected product was *trans* – chalcone (1a). In the case of non-protic solvents (ex. toluene), the reaction proceeded with a better conversion than in the case of ethanol, with the formation of both *cis* and *trans*-chalcone.

When water was used as solvent, despite attaining a good conversion, the aldol addition product (3) was obtained, demonstrating that in an aqueous medium the formed chalcone can be hydrolysed.

Green chemistry implies the use of safer solvents or their elimination [30]. In this context, we have run Claisen–Schmidt condensation reaction under neat conditions. Literature reports that when this reaction was carried out without solvent, it either requires longer reaction times [31] and high reaction temperatures [32] or leads to very low conversions [33]. On the contrary, this new nanohybrid catalyst favours the aldol condensation reaction in the absence of solvent, affording total selectivity towards *trans*-chalcone and total conversion.

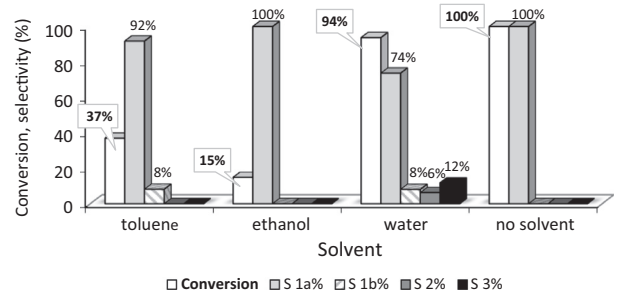


Fig. 5. Claisen–Schmidt condensation using different solvents: 1a – trans-chalcone; 1b – cis-chalcone; 2 – 1,3,5-triphenylpentane-1,5-dione; 3 – 3-hydroxy-1,3-diphenylpropan-1-one. Reaction conditions: 100 wt% PLL with respect to ketone, acetophenone and benzaldehyde 0.95 M ratio, 1 ml solvent, 3 h. Conversion and selectivity from ^{1}H NMR spectra of the crude material.

3.3. One-pot Claisen–Schmidt condensation/Juliá–Colonna epoxidation reaction

The results presented above demonstrate that the Claisen–Schmidt condensation reaction between acetophenone and benzaldehyde can be carried out at a lower temperature without solvent. To test the effectiveness of this nanohybrid catalyst, we studied its activity in the one-pot Claisen–Schmidt condensation/Juliá–Colonna epoxidation reaction. The protocol for α,β-epoxy ketone synthesis involves two steps: (i) formation of enone from the corresponding ketone and aldehyde catalysed by the HT part of the IPL and (ii) asymmetric epoxidation of enone with H_2O_2, catalysed by the immobilised poly-amino acid. To enhance the enantioselectivity, the length of the poly-L-leucine is of crucial importance, as Berkessel et al. showed [34]. Hence, we synthesised poly-L-leucine with a length between 30 and 45 monomers.

We studied the one-pot reaction with a Claisen–Schmidt condensation of benzaldehyde and acetophenone at 60 °C under neat conditions, followed by the addition of the phase-transfer cocatalyst (TBAB), H_2O_2, NaOH and solvent. The IPL catalyst was reused for 4 consecutive runs, to study its stability and selectivity (Table 1). The material proved to be very sable and efficient in terms of selectivity and enantioselectivity (both of which remained constant in all the 4 runs).

To identify whether the hydrotalcite-part of the IPL plays a role in the second part of the reaction we have carried out four control experiments, using the same conditions as previously mentioned (results presented in Table 2). The first two experiments consisted in carrying out the epoxidation reaction with and without rehydrated hydrotalcite (Table 2, entries 1 and 2) and in both cases total conversion was obtained. Knowing that rehydrated hydrotalcites possess basic properties, we have run the epoxidation reaction without the presence of NaOH using HT_{rus} and IPL (Table 2, entry 3 and 4). In the former case a conversion of 5% was obtain whilst in the latter one no epoxide was observed. This information suggests than any basic centre found in the HT_{rus} capable to deprotonate the hydrogen peroxide is deactivated when the polymer is immobilised. All these findings demonstrate that in the second part of the one-pot reaction only the poly-L-leucine is responsible for the asymmetric induction and the HT_{rus} is not active.

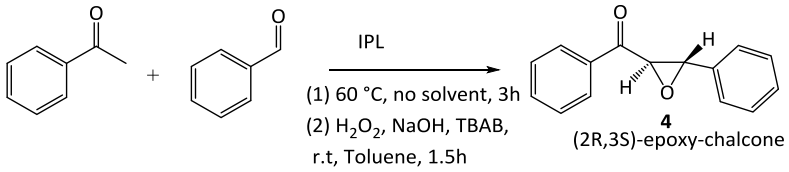
As mentioned in the section dedicated to the Claisen–Schmidt condensation, there are several side products that might appear, depending on the basicity of the environment, excess of reactants and the solvent used. A key point in recycling the catalyst for the one-pot reaction is washing the material after each run, to eliminate the following: (i) any unreacted NaOH, (ii) any unreacted reagent and (iii) traces of the obtained product, which may lead to side products in the next run.

The TGA pattern of the catalyst after 4 consecutive runs resembles to that of the catalyst before reaction and no difference in weight loss is observed, ruling out the possible leaching of the catalyst (Fig. III in Supporting Information).

3.4. One-pot Claisen–Schmidt condensation/Juliá–Colonna epoxidation reaction – scope of reaction

To confirm the activity of this new nanohybrid system, we studied the one-pot reaction using acetophenone/benzaldehyde with

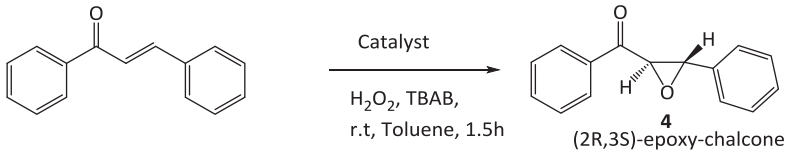
Table 1
One-pot Claisen–Schmidt condensation/Juliá–Colonna epoxidation of acetophenone and benzaldehyde.



Run[a]	Conversion[b] (%)	Selectivity[b] (%)	Yield (%)	ee[c] (%)
1	>99	>99	>98	91
2	>99	>99	>98	89
3	>99	>99	>98	88
4	>99	>99	>98	87

[a] Reaction conditions: acetophenone and benzaldehyde in molar ratio of 0.95 were added over the catalyst (100 wt% PLL with respect to the ketone), stirred 3 h at 60 °C; 3.7 mg TBAB, 1 ml toluene, 245 μl NaOH, 169.7 μl H_2O_2 were added and the reaction was further stirred for 1.5 h at room temperature.
[b] Conversion and selectivity were computed from ^{1}H NMR spectra of the crude material.
[c] ee was computed from HPLC spectra.

Table 2
Control experiments for the epoxidation reaction.



Experiment[a]	Catalyst	NaOH (μl)	Conversion[b] (%)
1	–	245	>99
2	HT_{rus} (120 mg)	245	>99
3	HT_{rus} (120 mg)	–	5
4	IPL (100 wt% PL)	–	–

[a] Reaction conditions: 10 mg chalcone, 3.7 mg TBAB, 1 ml toluene, 169.7 μl H_2O_2 were added and the reaction was stirred for 1.5 h at room temperature.
[b] Conversion was computed from ^{1}H NMR spectra of the crude material.

different aldehydes/ketones bearing electron donating or electron withdrawing groups in 4 consecutive runs (Tables 3 and 4).

Strong electronic withdrawing groups (EWG) on benzaldehyde led to the highest conversion and selectivity in all the 4 consecutive runs (Table 3, entries 1 and 2). The presence of the EWG makes the carbonyl carbon more electron deficient, thus being more vulnerable to the nucleophilic attack in the Claisen–Schmidt part of the reaction. The steric effect of the nitro group (present in the *ortho* or *para* position) is observed in the stereochemistry of the epoxide. When the nitro group is found in *ortho* position the (*2S, 3R*)-epoxy-chalcone was obtained with a very good enantioselectivity. On the other hand, when a weak EWG was in *para* position the selectivity towards the epoxide decreased slowly (variation which is in the error limit of the equipment) during the 4 runs, even though the conversion was constant (Table 3, entry 3).

Last but not the least, the presence of a weak electron donating group (EDG) in *para* position deactivates the benzaldehyde – effect observed on both conversion and enantiomeric excess of the final epoxide (Table 3, entry 4).

As expected, the substituted acetophenones were far less reactive than the corresponding aldehydes. In this case, the ketones bearing weak EWD and the EDG found in *para* position favoured the Claisen–Schmidt condensation/Juliá–Colonna epoxidation reaction, generating very good conversion, selectivity and good enantiomeric excess (Table 4, entries 3 and 4).

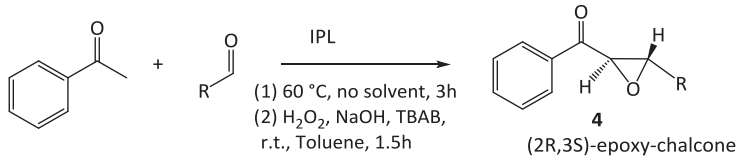
The *ortho*-nitro acetophenone was less reactive than the *para*-nitro acetophenone (Table 4, entries 1 and 2). The low ee% obtained in this case is directly related to the steric effect created by the nitro group in *ortho* position during the epoxidation reaction.

3.5. Mechanism of the Claisen–Schmidt condensation/Juliá–Colonna epoxidation reaction

The proposed mechanism of Claisen–Schmidt condensation/Juliá–Colonna epoxidation reaction catalysed by the nanohybrid material proceeds at the Brönsted basic sites near the edges of the hydrotalcite part of the IPL catalyst (Fig. 6A) and/or the basic sites located at the surface of the HTr. The OH^- groups remove the alpha hydrogen from the aromatic ketone, producing the corresponding enolate ion which will further attack the carbonyl carbon of the aldehyde molecule. Depending on the basicity of the catalyst and on the functional groups attached to the aromatic ring, the aldol product formed undergoes dehydration producing the *cis* and *trans* α,β-unsaturated ketone. The very reactive enolate ion can further give a Michael addition reaction with the freshly formed chalcone. All the side products can be avoided if no solvent is used in the first part of the one-pot reaction.

In the next step, chalcone interacts with the immobilised polymer to give the corresponding chiral epoxide. The last 4 terminal amino groups of the α-helical structure of the immobilised polymer create an oxyanion hole which facilitates the bonding of the hydroperoxide anion with the already formed chalcone [34]. The specific pattern in which they interact dictates the stereochemistry of the final epoxide. Even though the kinetic models present in the literature [5,6,35,36] have postulated that the epoxide formation

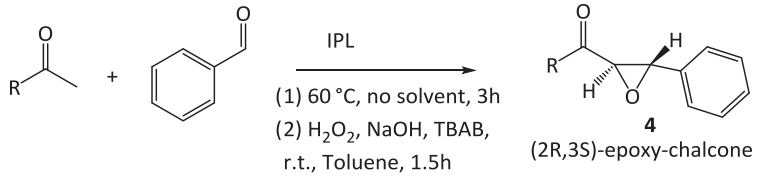
Table 3
One-pot Claisen–Schmidt condensation/Juliá–Colonna epoxidation of acetophenone and different benzaldehydes.



Entry	R	Run[a]	Conversion[b] (%)	Selectivity[b] (%)	Yield (%)	ee[c] (%)
1	o-NO_2-C_6H_4	1	98	98	96	91[d]
		2	96	98	94	84[d]
		3	94	98	92	79[d]
		4	94	98	92	79[d]
2	p-NO_2-C_6H_4	1	95	99	94	94
		2	98	99	97	92
		3	98	99	97	90
		4	97	99	96	86
3	p-Cl-C_6H_4	1	97	95	92	94
		2	97	94	91	95
		3	98	92	90	96
		4	97	93	90	91
4	p-CH_3-C_6H_4	1	87	94	82	87
		2	84	92	77	82
		3	82	92	75	77
		4	85	95	81	72

[a] Reaction conditions: acetophenone and corresponding aldehyde in molar ratio of 0.95 were added over the catalyst (100 wt% PLL with respect to the ketone), stirred 3 h at 60 °C; 3.7 mg TBAB, 1 ml toluene, 245 μl NaOH, 169.7 μl H_2O_2 were added and the reaction was further stirred for 1.5 h at room temperature.
[b] Conversion and selectivity were computed from ^{1}H NMR spectra of the crude material.
[c] ee was computed from HPLC spectra.
[d] The (2S,3R) is the major enantiomer.

Table 4
One-pot Claisen–Schmidt condensation/Juliá–Colonna epoxidation of benzaldehyde with different acetophenones.



Entry	R	Run[a]	Conversion[b] (%)	Selectivity[b] (%)	Yield (%)	ee[c] (%)
1	o-NO_2-C_6H_4	1	82	75	62	63
		2	80	72	58	63
		3	76	65	49	62
		4	70	67	47	60
2	p-NO_2-C_6H_4	1	97	99	96	89
		2	91	95	87	81
		3	82	84	69	78
		4	85	82	70	75
3	p-Cl-C_6H_4	1	99	97	96	91
		2	99	97	96	89
		3	99	98	97	81
		4	99	98	97	71
4	p-CH_3-C_6H_4	1	94	97	91	80
		2	92	96	88	79
		3	90	98	88	79
		4	91	99	90	74

[a] Reaction conditions: acetophenone and corresponding aldehyde in molar ratio of 0.95 were added over the catalyst (100 wt% PLL with respect to the ketone), stirred 3 h at 60 °C; 3.7 mg TBAB, 1 ml toluene, 245 μl NaOH, 169.7 μl H_2O_2 were added and the reaction was further stirred for 1.5 h at room temperature.
[b] Conversion and selectivity were computed from ^{1}H NMR spectra of the crude material.
[c] ee was computed from HPLC spectra.

proceeds through two possible pathways (Fig. 6B) we have recently observed that the favoured one is pathway I, where hydroperoxide anion interacts with the polymer and only afterwards with chalcone, leading to the formation of the PLL:HOO^-:chalcone complex (unpublished work). These experiments were done using Quartz Crystal Microbalance with Dissipation (QCM-D), a sensitive mass sensor which measures a mass per unit area by monitoring the frequency shift of the crystal sensor. A change in frequency is induced

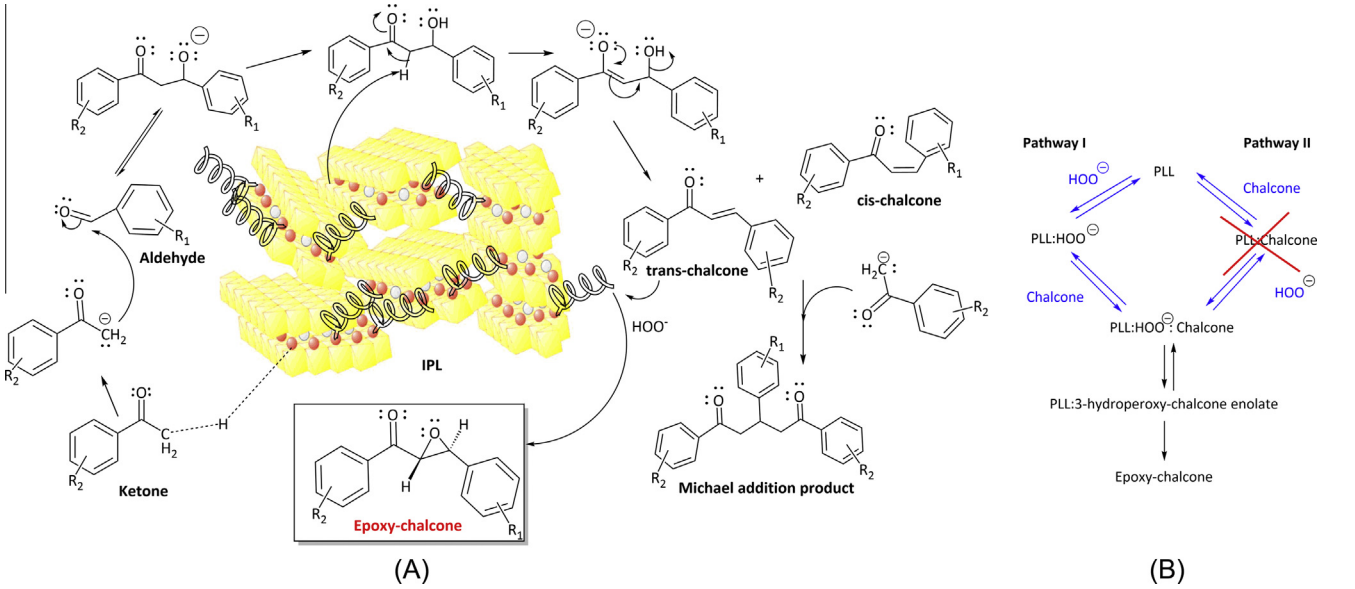


Fig. 6. A – General mechanism of the one-pot Claisen–Schmidt condensation/Juliá–Colonna epoxidation reaction catalysed by IPL; B – proposed kinetic pathways for the Juliá–Colonna epoxidation.

by molecular deposition on the sensor surface. QCM-D is now well-established to study biomolecular interactions or binding events at the solid–liquid interface with detection limits at around nanograms per cm^2 [37] and can be used to distinguish between different mechanisms by monitoring the enzymatic activity [38].

4. Conclusions

Nowadays, research is focused on developing catalytic processes that require less workup and where intermediates are obtained *in situ*, avoiding unnecessary purification procedures. We have managed to successfully develop a convenient and efficient one-pot process for production of chiral α,β-epoxy-chalcones starting from the corresponding acetophenones and benzaldehydes, catalysed by poly-L-leucine immobilised into rehydrated hydrotalcite.

The removal of the solvent in the Claisen–Schmidt condensation part not only creates a greener process, but eludes the presence of side products.

The catalyst has been continuously reused without any further pre-activation and recycled for 4 consecutive runs without losing its activity in terms of selectivity towards the epoxide, enantioselectivity and conversion. Moreover, the unique properties of this catalytic system were observed when *ortho* nitro substituted benzaldehyde was used leading to the formation of the (2S,3R)-isomer. The present work demonstrates the viability and sustainability of this nanohybrid catalytic system in the synthesis of chiral epoxides.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jcat.2015.11.020.

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