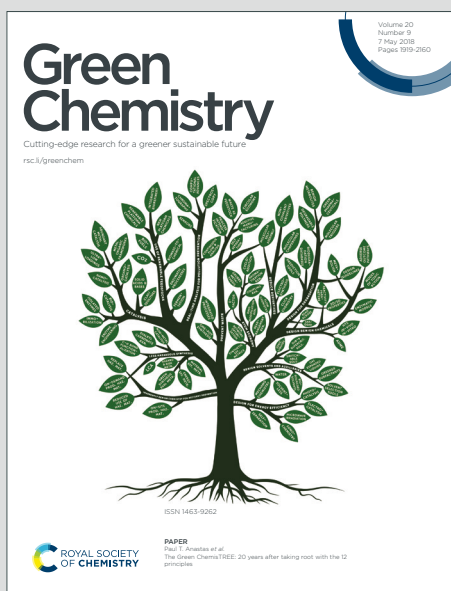


Green Chemistry

Cutting-edge research for a greener sustainable future

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: B. Saavedra, A. Meli, C. Rizzo, D. J. Ramón and F. D'Anna, *Green Chem.*, 2021, DOI: 10.1039/D1GC01647D.



This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the [Information for Authors](#).

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard [Terms & Conditions](#) and the [Ethical guidelines](#) still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.

ARTICLE

Natural Eutecto gels: Sustainable Catalytic Systems for C-C Bond Formation Reactions

Beatriz Saavedra,^a Alessandro Meli,^b Carla Rizzo,^b Diego J. Ramón*^a and Francesca D'Anna*^bReceived 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Natural eutecto gels were prepared combining properties of amino acids with the ones of deep eutectic solvents. Soft materials obtained were fully characterised determining the gel-sol transition temperatures and analysing mechanical and morphological features through rheological measurements and polarised optical microscopy. All eutecto gels were tested as catalytic reaction media for the enantioselective aldol reaction and, the best performing one was also used to carry out the Michael addition. In both cases, eutecto gels proved to have a great potential as sustainable reaction media, allowing to perform processes under mild conditions, obtaining excellent yields and, in some cases, also good enantiomeric excess. Catalytic soft materials can be reused up to five cycles keeping the stereochemical control of the reaction and using a recommended solvent by recent sustainable solvent guidelines.

Introduction

Carbon-carbon bond formation are a class of organic reactions that play a pivotal role in both academic and industrial organic chemistry. They allow the obtainment of complex organic molecules starting from simpler ones and, over the years, several efforts have been carried out to make them catalyst and additive free, environmentally friendly, economical and less sensitive to air. Furthermore, particular attention has been devoted to the possibility of separating products using operationally simple procedures, which also allow decreasing the environmental impact the whole process. This explains the surge in interest that, in the last few years, has promoted the employment of transition metal free protocols,¹ supported catalysts² and photochemical processes.³⁻⁵

Among different perspectives, also the possibility to perform these reactions in confined and highly organised media has recently gained attention. Consequently, the use of zeolites,^{6, 7} covalent organic frameworks,^{8, 9} and metal organic frameworks^{10, 11} has been promoted. The use of these systems opens the possibility to take advantage from both the heterogeneous nature of the catalytic site and its peculiar features of size and shape that can positively affect the outcome of the process. In this context, also supramolecular gels have been considered as suitable and environmentally friendly opportunities.¹²⁻¹⁶

Supramolecular gels are emerging materials originated by the self-assembling of small molecules (Low Molecular Weight Gelators, LMWGs) in dilute solution.^{17, 18} The structure of the gel is formed by non-covalent interactions (hydrogen bonding, van der Waals, π -interactions) established between the low molecular weight gelator and the solvent.¹⁹ Since these networks involve weak interactions, they can be readily transformed to a fluid by heating and are generally thermally reversible. Gels can be classified in different ways depending upon the type of gelator and the medium they encompass. Based on which solvent is hardened, gels are distinguished in hydrogels²⁰ and organogels,²¹ originated from solutions of water and organic solvents, respectively. A recent development in the field is represented by gels formed using ionic liquids (ionogels or ionic liquid gels)²²⁻²⁵ and even, deep eutectic solvents (eutecto gels).^{23, 26-30}

Thanks to their properties, supramolecular gels have been applied in different fields, like drug delivery systems,^{31, 32} sensors,³³⁻³⁵ and sorbent systems for the removal of different environmental pollutants.³⁶⁻³⁸ Among different applications, the use of these soft materials as reaction media has recently gained a raise in interest.¹²⁻¹⁴ This is mainly due to the porosity featuring supramolecular gel phases, that allows reactions to occur in a confined space. Performing reactions in supramolecular confined spaces offer different advantages, like microenvironment effects, the control of reagents conformation or the protection of unstable species. Furthermore, in supramolecular gels, catalytic behaviour derived from non-covalent interactions, could be used for the construction of multicomponent catalysts.³⁹ The above advantages can be further strengthened if the formation of the gelatinous network occurs in a sustainable solvent like water, ionic liquids or deep eutectic solvents (DEs).

In particular, DEs⁴⁰⁻⁴² are mixtures of two or more cheap and non-toxic components which are capable of forming a eutectic

^a Departamento de Química Orgánica and Instituto de Síntesis Orgánica (ISO), Facultad de Ciencias Universidad de Alicante, Apdo. 99, 03080 Alicante, Spain. Email: djramon@ua.es

^b Università degli Studi di Palermo, Dipartimento di Scienze Biologiche, Chimiche e Farmaceutiche, Viale delle Scienze, Ed. 17, 90128 Palermo, Italy. Email: francesca.danna@unipa.it

† Footnotes relating to the title and/or authors should appear here. Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

ARTICLE

Journal Name

mixture. Their unique properties such as easy preparation, low cost, low volatility, low or no toxicity and high biodegradability, highlight DESs promising application as sustainable solvents.

Although numerous types of molecules have been used to induce the gelation, amino acids are the simplest biological building blocks capable of forming discreet nanostructures by supramolecular self-assembly⁴³ and, in turn, they are well-known catalysts for some organic reactions like the aldol reaction.⁴⁴

The aldol reaction is one of the most renowned transformation in organic synthesis with several possibilities to control the stereochemical outcome of the process and using natural amino acids as organocatalysts, is the most sustainable protocol. However, as a drawback, most of these protocols imply the use of organic solvents⁴⁵ and only, few examples have reported the aldol transformation using DESs as solvents.⁴⁶⁻⁴⁹

Differently, the L-proline catalysed aldol reaction has been studied in hydrogel phases. This is mainly due to the fact that this reaction is a clear example of prebiotic chemistry and hydrogel phases resemble the cytoplasmatic environment of cells.⁵⁰⁻⁵² Furthermore, recently also data about the study of this reaction in ionogel phases have been reported.⁵³ In all above cases, significant improvements in yield and conversion values, with respect to the ones obtained in solution, have been reported.^{51, 53, 54} These results were ascribed to the close proximity of the catalytic functions on the gel surface and the increased basicity of the catalyst moiety used. However, in most cases, products were obtained in racemic mixtures or with low enantiomeric excesses, evidencing a scarce control of the stereochemical pathway.

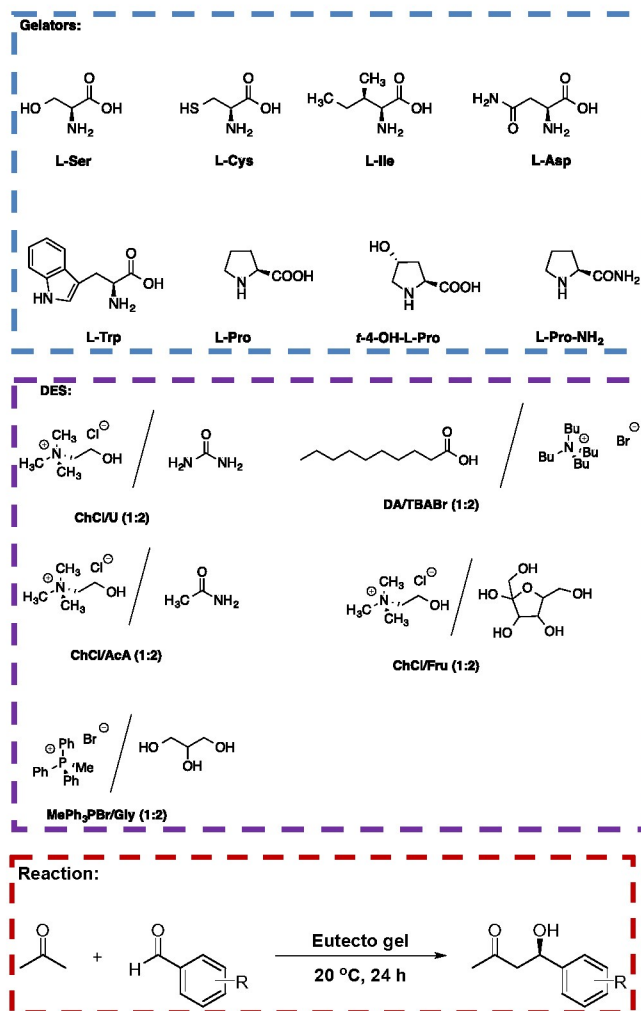
With the above information in mind, we explored the possibility to obtain catalytic gel phases for the aldol reaction, conjugating environmentally friendly aspects of DESs with the ones of some of the most widely used organocatalysts for such kind of reaction, *i.e.* the amino acids. The main objective of the present research was to obtain fully natural catalytic phases. Our idea was supported by results previously reported about the ability of natural amino acids to harden DESs and their efficiency to remove organic dyes from wastewater.^{30, 55}

To pursue our aim, L-Proline (L-Pro), L-serine (L-Ser), L-cysteine (L-Cys), L-isoleucine (L-Ile), L-asparagine (L-Asp) and L-tryptophan (L-Trp) were used as LMWGs. Furthermore, bearing in mind the high efficiency of some L-proline derivatives as organocatalysts, also L-prolinamide (L-Pro-NH₂) and *trans*-4-hydroxy-L-proline (*t*-4-OH-L-Pro) were tested. Their gelling ability was investigated using DESs differing for both the nature of hydrogen bond donor and hydrogen bond acceptor (Scheme 1).

Obtained eutecto gels were fully characterised by determining their gel-sol transition temperature (T_{gel}) and the ability to self-repair after the action of a mechanical stimulus. Furthermore, mechanical properties of eutecto gels were assessed by rheology investigation, whereas, morphological features were analysed by optical polarised microscopy (POM).

These soft materials were used to perform the benchmark reaction between acetone and *p*-nitrobenzaldehyde and the best performing eutecto gel was applied both in the study of

aldol and Michael reaction. Data obtained shed light on the potential of these new environmentally friendly reaction media. Indeed, they allow to carry out the reactions, under mild conditions, with good yield and, in some cases, also good enantiomeric excess. The obtained systems proved to be natural and cheap, in addition, products can be easily recovered using recommended organic solvents. The residual catalytic systems can be reused up to five cycles with good retention of the stereochemical control of the reaction.



Scheme 1. Structure of gelators, DESs and schematic representation of aldol reaction; a) picture of eutecto gel L-Pro/ChCl/U; b) picture of eutecto gel L-Pro/ChCl/U in contact with the reaction mixture.

Results and Discussion

Gelation tests and gel-sol transition temperatures. Gelation tests were performed in screw capped vials in which the suitable amount of solvent and gelator were weighted and heated at 80 °C, until a clear solution was obtained. The obtained solutions were left overnight at room temperature and after, gel phase formation was assessed by using the tube inversion test.⁵⁶ Results of gelation tests are reported in Table S1, whereas obtained eutecto gels together with T_{gel} , *i.e.* the temperature corresponding to gel-sol transition, are displayed in Table 1.

Table 1. Obtained eutecto gels ChCl/U (1:2) and corresponding T_{gel} values.

Gelator	Concentration (wt%) ^a	T_{gel} (°C) ^b
L-Pro	5.0	34
L-Pro	3.0	31
L-Pro-NH ₂	3.0	34
<i>t</i> -4-OH-L-Pro	3.0	34
L-Ser	3.0	31
L-Trp	3.0	35

^a Concentration: gelator mass/solvent and gelator mass; ^b T_{gel} are reproducible within 1 °C.

Analysis of data reported in Table 1 and S1 evidences that, with the exception of L-Ile, L-Asp and L-Cys, all the other tested gelators were able to harden ChCl/U (1:2) (from now on indicated as ChCl/U). In all cases, white opaque gels were obtained (Scheme 1a). Furthermore, in most cases gels were obtained at 3.0 wt%, but in the case of L-Trp soft material formation was already detected at 2.0 wt%. On the other hand, in the presence of L-Pro, stable gel phases were obtained both at 3.0 and 5.0 wt%.

T_{gel} values range from 31 up to 35 °C, showing only a marginal dependence on the gelator structure. In general, concentration being the same, the highest T_{gel} was obtained for L-Trp based eutecto gel, evidencing a certain relevance of π - π interactions in the building of the fibrillary supramolecular network. On the other hand, comparison among T_{gel} values collected for gel phases formed by L-Pro, L-Pro-NH₂ and *t*-4-OH-L-Pro allows assessing the positive role played by the functionalisation of both carboxyl group and aliphatic skeleton of the L-Pro, as accounted for by the increase in T_{gel} going from L-Pro to L-Pro-NH₂ and *t*-4-OH-L-Pro.

The comparison with T_{gel} values previously reported for eutecto gels obtained, using L-Pro and L-Trp as gelators in ChCl/PhAA (1:2) at 3 wt%, testifies the relevance of the solvent nature. Indeed, in both cases a significant decrease in T_{gel} was detected (T_{gel} : 38 and 43 °C for L-Trp and L-Pro gels in ChCl/PhAA (1:2), respectively),³⁰ indicating the positive effect deriving from the presence of an acid and aromatic HBD in the solvent.

With the only exception of L-Ser based eutecto gel, all soft materials proved to be thermoreversible. Furthermore, T_{gel} was also positively affected by gelator concentration as accounted for by the higher T_{gel} measured for L-Pro gel at 5 wt% with respect to the one obtained at 3 wt%.

All gel phases were also tested for their ability to respond to the action of external stimuli. In particular, taking in consideration

their possible application as reaction media, their thixotropic behaviour was analysed. To this aim, gel phases were magnetically stirred for 5 minutes at 1000 rpm. However, in all cases, disassembly of the soft materials was not observed, allowing to classify them as stable to the action of the stimulus.

Rheological investigation. Rheological response of eutecto gels was studied as function of strain and frequency applied to the gel on oscillatory mode. To this aim, all materials were prepared at 3 wt%. Only in the case of L-Pro, the gel mechanical features were also investigated at 5 wt%.

Both above investigations allowed to confirm the gel like nature of the materials as, at fixed frequency ($\gamma = 1$ rad/s), the classical intermediate behavior between a solid and a liquid was observed (Figure 1a). In particular, at low strain values, G' , indicating the elastic modulus was higher than G'' , that represents the loss modulus. In addition, at a fixed strain value ($\gamma = 0.025$ %), chosen within the linear viscoelastic region, G' was always higher than G'' (Figure 1b). Plots corresponding to rheological investigation for all the other eutecto gels are reported in Figure S1.

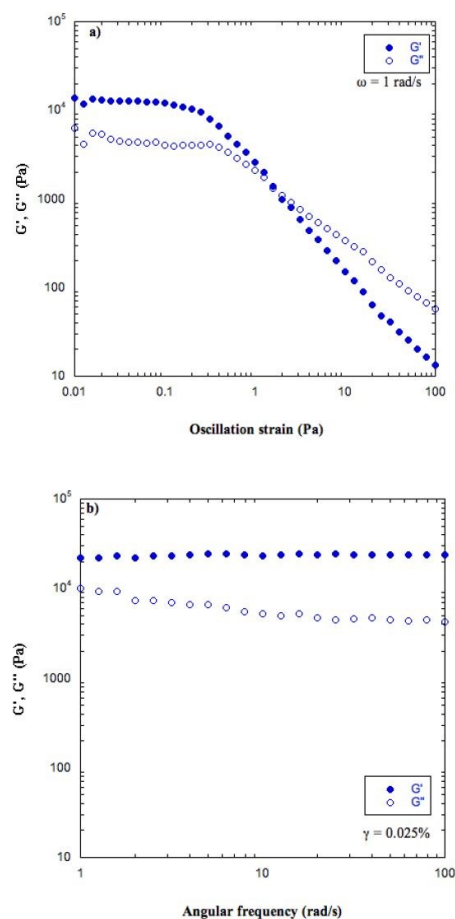


Figure 1. Rheological investigation of L-Pro in ChCl at 3 wt%: a) strain and b) frequency sweep.

ARTICLE

Journal Name

In the strain sweep measurements, G' and G'' inverted nearby a point named crossover point (γ), that indicated the stress to be applied for inducing gel breakdown.

All rheological parameters are reported in Table 2, together with $\tan \delta$, *i.e.* the ratio between G'' and G' , that allows assessing the stiffness of the gel and can give an idea of the colloidal forces held in the gel matrix.

Table 2. Rheological parameters at $\gamma = 0.025\%$ and $\omega = 1$ rad/s. G' and G'' , $\tan \delta = G''/G'$ and values of γ at $G' = G''$ for gels in ChCl/U investigated at 3 wt% of gelator at 25 °C. For rheological parameters, error limits are based on the average of three different measurements with different aliquots of gels.

Gelator	G' (Pa)	G'' (Pa)	$\tan \delta$	γ (%)
L-Pro (5%)	395000±78000	250000±35000	0.64±0.05	1.5±0.7
L-Pro (3%)	12500±4500	4500±500	0.35±0.03	0.8±0.2
L-Pro-NH ₂	22500±6500	14500±2200	0.65±0.09	0.8±0.1
<i>t</i> -4-OH-L-Pro	195000±99000	110000±42000	0.70±0.20	1±0.7
L-Ser	220000±85000	165000±79000	0.73±0.70	0.9±0.1
L-Trp	133000±14000	85000±40	0.60±0.07	0.6±0.3

Analysis of data obtained in Table 2 evidences that all soft materials are featured by the occurrence of strong colloidal forces, as accounted for by $\tan \delta$ values lower than 1. Furthermore, bearing in mind that stronger forces occur if lower $\tan \delta$ values are measured, results obtained allow identifying the L-Pro eutecto gel as the soft material showing the best mechanical performance. However, the increase in gelator concentration, going from 3 up to 5 wt%, weakens the occurring interactions.

The attempt to correlate mechanical response of gels to their gel-sol transition temperatures sheds light on the reverse relationship working between $\tan \delta$ and T_{gel} . Indeed, the eutecto gel showing the highest stiffness (L-Pro) exhibited the lowest T_{gel} .

The comparison with rheological parameters previously reported for L-Pro eutecto gel formed in ChCl/PhAA (1:2),^{23, 30} restates the role played by the DES nature. Indeed, the gel formed in the above solvent featured by a lower stiffness ($\tan \delta = 0.35$ for L-Pro/ChCl/U and 0.42 for L-Pro/ChCl/PhAA), with respect to the corresponding soft materials formed in ChCl/U. Also in this case, the gel exhibiting lower stiffness corresponds to a higher T_{gel} .

Morphological investigation. Morphological features of eutecto gels were analysed by using polarised optical microscopy (POM). Pictures corresponding to L-Pro/ChCl/U and L-Trp/ChCl/U are reported in Figure 2, whereas the ones corresponding to all the other eutecto gels are displayed in Figure S2.

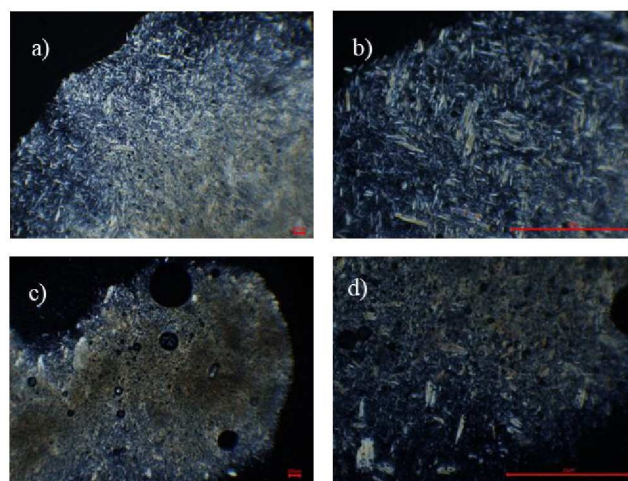


Figure 2. POM images for L-Pro/ChCl/U (a and b) and *t*-4-OH-L-Pro (c and d) eutecto gels at 3.0 wt% (scale bar: a and c, 100 μm; b and d, 10 μm).

Analysis of POM images indicate that morphology of the soft materials changes as a function of the gelator nature. In particular, L-Pro, of L-Pro-NH₂ and L-Trp gave a fibrous gelatinous network. Differently, in the case of *t*-4-OH-L-Pro and L-Ser a spherulitic network was evidenced.

Catalytic activity. To assess if our gel phases could be used as catalytic reaction media, we firstly tested the aldol reaction between acetone (**1a**) and *p*-nitrobenzaldehyde (**2a**) with different ChCl/U based eutecto gels (Table 3), at 20 °C and for 24 h.

The reagents were cast on the gel surface, which resisted to the contact for the reaction time (Scheme 1b). After 24 h, the reaction mixture was recovered by extraction with ethyl acetate and, verifying the integrity of the recovered gel phase by the tube inversion test.⁵⁶ The evolution of the reaction was studied under the optimal reaction conditions, observing that reactants/products seem to diffuse into the first layer of the eutectogel during the course of the reaction (see Supporting Information Figure S3). Additionally, stirring of reactants was studied (for the first 5 min or 24 h). When the eutectogel was stirred for the first 5 min of the reaction, the results were very similar in comparison with the model reaction (89% yield and 67% *ee* and 87% yield and 68% *ee*, respectively). However, when the eutectogel was stirred during a 24 h period, the gel structure was destroyed and the enantioselectivity of the reaction decreased (93% yield and 54% *ee*). We were also able to verify that no diffusion of the L-Pro occurred in the liquid phase on the top of the gel, as accounted for by the comparison between ¹H NMR spectrum of L-Pro and the one corresponding to the liquid phase after 24h (Figure S4).

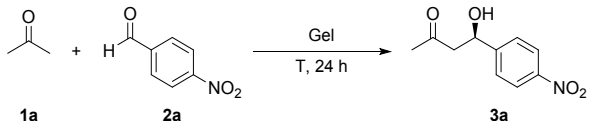
Results reported in Table 3 evidence how yields depend on the nature of the gelator. Indeed, it decreases along the following trend: L-Pro > L-Pro-NH₂ >> *t*-4-OH-L-Pro (entry 7, 4 and 3, respectively). In the presence of L-Ser and L-Trp, the reaction did not take place. To explain the above trend, we tried to have further insights on the gel structure, considering the best (L-Pro) and the worst (*t*-4-OH-L-Pro) catalytic system. In particular, we

measured the porosity of the gel network and recorded resonance light scattering (RLS) spectra of the gel phases (Figure S5). As previously reported, RLS intensity is related to the size of the aggregates featuring a self-assembled system⁵⁷ and this technique has been already used to study structural features of supramolecular gels.^{24, 25}

Compared eutectogels exhibited a similar porosity ($P = 86.9$ and 86.3% for L-Pro/ChCl/U and *t*-4-OH-L-Pro/ChCl/U, respectively; Table S2). However, they showed significant differences in the size of the aggregates, as $I_{\text{RLS}} = 24$ and 129 a.u. at $\lambda = 560$ nm for L-Pro/ChCl/U and *t*-4-OH-L-Pro/ChCl/U, respectively. The above results, recall differences observed in gel morphologies and shed light on the higher catalytic ability of the fibrous structure of the L-Pro based eutecto gel also featured by a higher stiffness (cfr $\tan\delta$ in Table 2).

Analysis of results obtained with L-Pro based catalysts sheds light on the performance of L-Pro/ChCl/U eutecto gel that, both at 3 and 5 wt%, allowed obtaining the product in 32 and 87% of yield, proving to be the best catalyst (entries 6-7). However, also with the best yield, only a modest enantiomeric excess (*ee*) was obtained (entry 7).

Table 3. Optimization of the aldol reaction between acetone (**1a**) and *p*-nitrobenzaldehyde (**2a**) in different ChCl/U based eutecto gels,^a together with data previously reported in literature.



Entry	Gelator	T(°C)	Yield (%) ^b	<i>ee</i> (%) ^c
1	L-Ser (3 wt%)	20	- ^d	-
2	L-Trp (5 wt%)	20	5	-
3	<i>t</i> -4-OH-L-Pro (3 wt%)	20	<5	50
4	L-Pro-NH ₂ (5 wt%)	20	50	20
5	L-Pro (2 wt%, aggregates)	20	20	69
6	L-Pro (3 wt%)	20	32	69
7	L-Pro (5 wt%)	20	87	68
8	L-Pro (8 wt%)	20	91 (98) ^e	62 (62) ^e
9	L-Pro (10 wt%)	20	92 (98) ^e	64 (64) ^e
10	L-Pro (5 wt%)	15	21	68
11	L-Pro (5 wt%)	4	7	56
12	L-Pro (5 wt%)	35	90	55
13	L-Pro-L-Val-C _n ⁵⁸		< 2	-
14	L-Pro (4.0 mol%) ⁵³		92	62

^a Reaction conditions: acetone (5 equiv.) and *p*-nitrobenzaldehyde (1 equiv.) at 20 °C during 24 h. ^b Yield calculated by ¹H NMR. ^c Enantioselectivities determined by chiral HPLC. ^d No reaction; ^e Reaction performed for 48 h.

Further increase of the L-Pro amount led to higher yields but slightly lower *ee* (compare entry 7 and entries 8-9). In addition, when the reaction time was increased up to 48 h, the yield suffered a further increase but the enantioselectivity was retained (entries 8-9). These results seem to indicate that no kinetic resolution/retro aldol reaction occurred. To improve the enantioselectivity, L-Pro/ChCl/U eutecto gel was tested at different temperatures ranging from 4 up to 35 °C (entries 10-12). Temperatures higher than 35 °C could not be used as a consequence of the gel melting. Analysis of data collected

demonstrates that changes in temperature did not positively affect the *ee*. Indeed, decreasing the temperature from 20 down to 4 °C, caused a significant decrease in both yield and *ee* (entries 7 and 10-11). On the other hand, the increase in temperature, from 20 up to 35 °C, induced a significant decrease in the *ee*, without significant changes in yield (entries 7 and 12).

Obviously, although both reaction temperatures stayed in the sustainable range defined by the Clark approach,⁵⁹ the lower one is more advisable also from an energetic point of view.

Results obtained in this work were compared with the ones previously reported, using L-Pro (30-40% mol) in ChCl/U solution.⁴⁸ We are aware that in the present case a higher L-Pro/aldehyde molar ratio was used (L-Pro/aldehyde molar ratio: 1.3 and 0.4 in the case of eutecto gel and solution, respectively). However, temperature and reaction time being equal, significant improvements both in term of yield and *ee* were obtained for the reaction performed in gel phase (yield: 87 and 32%; *ee*: 68 and 38% in gel phase and in solution, respectively). In our opinion, the better catalytic performance of eutecto gel, with respect to the catalyst in DES solution, cannot be ascribed only to the increased concentration of the catalyst. To verify this assertion, we performed reactions using L-Pro at 2 and 3 wt%. The first system, having a concentration lower than CGC, should be featured by the presence of gelatinous aggregates, whereas the latter one represents the gel phase at the CGC (entries 5-6). In the systems analysed (entries 5-7), the increase in L-Pro concentration induced a parallel increase in yield, without affecting *ee* value. A further increase in L-Pro caused a decrease in *ee* (entries 7-8), but it stayed unchanged increasing the L-Pro concentration up to 10 wt% (entries 8-9).

The obtained trend perfectly agrees with a previous report about the study of the Michael reaction in gel phase, showing that the increase in gelator concentration does not affect the *ee* value.⁶⁰ Probably, the obtained trend can be rather ascribed to the structural rigidification of the catalytic supramolecular aggregates⁵⁴ and to the confined and organised structure of the reaction environment, that favours the outcome of the reaction. A similar effect was previously detected studying the asymmetric alcoholysis of the anhydrides, catalysed by Cinchona alkaloids in ionic liquid gels.⁶¹

On the other hand, in gel phase, L-Pro based catalysts showed significant different reactivities with respect to the ones previously observed in ChCl/U solution.⁴⁸ Indeed, in DES solution (ChCl/Gly), no significant changes in yield were observed as a function of the catalyst nature, with a complete loss in *ee*, going from L-Pro to L-Pro-NH₂ or *t*-4-OH-L-Pro. Differently, in gel phase, changing the nature of the catalyst, a marked decrease in both yield and *ee* was observed. Probably, the presence of better hydrogen bond donor groups on the catalyst structure induces a rigidification of the gel network that exhibits worse catalytic performance.

The modest *ee* obtained in L-Pro eutecto gel indicates that the catalyst basicity did not significantly change as a consequence of the gel phase formation. Indeed, our result is different from the one previously reported about organogels formed by L-Pro

ARTICLE

based peptides whose increased basicity, induced by gelification, promoted the aldol racemisation.⁵⁴

To further verify this hypothesis, we prepared a L-Pro eutecto gel doped with bromothymol blue (BB; 0.00015 M) and compared the coloration of hot solution and gel phase obtained after 24 h (Figure 3). Cooling of the hot solution induced only a modest change in colour from green to light blue, indicating a modest increase in basicity that did not prove sufficient to induce the product racemisation.



Figure 3. Picture of L-Pro/ChCl/U/BB system as a function of temperature (temperature decreases from the left to right).

As above stated, the cross-aldol reaction between acetone and *p*-nitrobenzaldehyde has been widely investigated in supramolecular gels. In order to have a better evaluation of our results, data collected were compared with the ones previously reported by using organo- and ionic liquid gels based on L-Pro as gelator.

Our system proves to be better than the one obtained by using hydrogels based on L-Pro-L-Val-C_n hydrophobic peptides, that gave the product only traces (entry 13). This was ascribed to the low hydrophobicity of acetone in which was not able to accumulate itself in the hydrophobic pocket formed by gelator units, in order to favour the enamine intermediate formation.⁵⁸ Differently, our results are comparable to the ones recently obtained using L-Pro based ionic liquid gel as reaction media (entry 14).⁵³ However, in the present case a lower acetone/aldehyde molar ratio was used (5:1 and 10:1 in the case of eutecto gel and ionic liquid gel, respectively), raising the sustainability of our catalytic system.

The L-Pro-based eutecto gel was also tested for its recyclability, which is considered to be a crucial point for the sustainability of many industrial processes. For this purpose, after the completion of the reaction, the product obtained was extracted with a small amount of a VOC solvent deriving from renewable sources (2- MeTHF).⁶² The remaining solvent in gel phase was evaporated and the gel material was reused by adding fresh reagents. This allowed us to recycle the eutecto gel for five consecutive cycles, maintaining enantioselectivity constant (Figure 4), although a decrease in yield was observed after the third cycle.

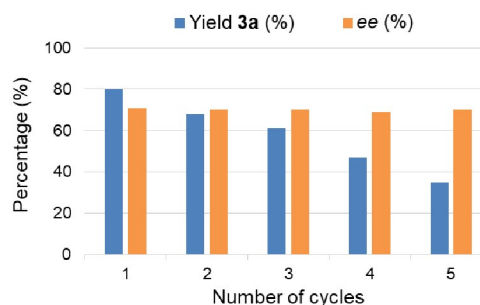


Figure 4. Recyclability of L-Pro/ChCl/U eutecto gel in aldol reaction between acetone and *p*-nitrobenzaldehyde, at 20 °C and for 24 h.

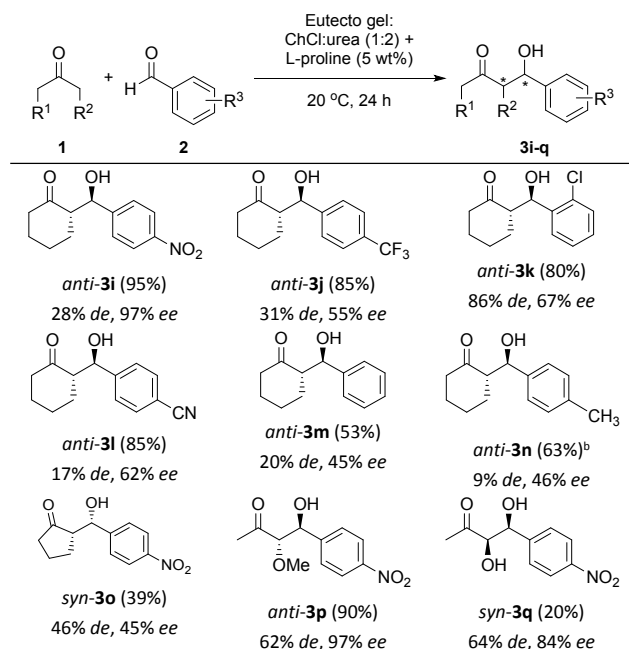
With the optimum reaction conditions established (Table 3, entry 7), the substrate scope was studied (Table 4). Different aryl aldehydes were used, to test both the electronic effect of the substituent and the relevance of its position on the aromatic ring. In general, electron withdrawing groups favoured the outcome of the reaction (cfr entries 1, 4-5 and 8). Among the groups tested, the cyano and nitro group allowed obtaining better results both in terms of yield and *ee* (entries 1 and 4). In the latter case, the outcome of the reaction was not affected by the substituent position (entries 1-3). The above results are similar to the ones previously obtained studying the same reaction in D-glucose (D/L)/malic acid (1:1) solution.⁴⁸ In gel phase, the high yield obtained in the presence of the unsubstituted aldehyde is quite characteristic (entry 7).

Table 4. Aldol reaction between acetone and aldehydes in L-Pro/ChCl/U eutecto gel.^a

Entry	R	Product	Yield (%) ^b	<i>ee</i> (%) ^c
1	4-NO ₂	3a	87	68
2	3-NO ₂	3b	93	70
3	2-NO ₂	3c	95	72
4	4-CN	3d	94	72
5	4-CF ₃	3e	97	46
6	2-Cl	3f	98	61
7	H	3g	93	53
8	4-CH ₃	3h	22 (80 ^d)	59 (65 ^d)

^a Reaction conditions: acetone (5 equiv.) and aldehyde (1 equiv.) at 20 °C during 24 h. ^b Yield calculated by ¹H NMR. ^c Enantioselectivities determined by chiral HPLC. ^d Reaction time: 5 days.

The versatility of this transformation was also evaluated using different ketones (Table 5). When cyclohexanone was used as nucleophile, yields ranged from 53 (**3m**) up to 95% (**3i**) as a function of the aldehydes. In all cases, the main achieved diastereoisomer had *anti* configuration, but with low diastereoselectivity (20-30%). The only exception to the above trend was represented by 2-chlorobenzaldehyde that gave 86% *de*. As for the *ee*, it ranged from 45% (**3m**) up to 97% (**3i**).

Table 5. Aldol reaction between ketones and aldehydes in L-Proline based eutecto gel.^a

^a Reaction conditions: ketone (5 equiv.) and aldehyde (1 equiv.) at 20 °C during 24 h. Yield calculated by ¹H NMR (yield%, *anti:syn*). Enantioselectivities determined by chiral HPLC; ^b Reaction performed for 4 days.

On the other hand, aldehyde being the same (*p*-nitrobenzaldehyde), different behaviours were detected as a function of different ketones. Indeed, *anti* diastereoisomers were mainly obtained in the presence of cyclohexanone (**3i**) and methoxypropanone (**3p**). Differently, cyclopentanone (**3o**) and hydroxypropanone (**3q**) gave *syn* diastereoisomers as the prevalent ones. The highest *de* values were observed by using the propanone derivatives (*de*: 62 and 64 % for **3p** and **3q**, respectively). In particular, methoxypropanone was the ketone that warranted the highest *ee*. Among investigated ketones, this was the most structurally flexible. On the other hand, on the grounds of rheological parameters, the L-Pro eutecto gel shows a certain rigidity, as accounted for by the high *G'* value measured. Probably, in the formation of the enamine intermediate, essential to have a control of the stereochemical pathway, a more flexible substrate better conforms to the rigid and interconnected fibrous network. This result is different from the one previously obtained for the alcoholysis of the anhydrides.⁶¹ Indeed, in that case, as a consequence of the high rigidity of the substrates, better catalytic performance was obtained in the presence of more flexible gelatinous network able to reorganise around the reactive intermediate.

Table 6. Yield, *de* and *ee* values for the aldol reaction between cyclohexanone and *p*-nitrobenzaldehyde in gel phase.

Entry	Solvent	Gelator	Yield (%)	<i>de</i> (%)	<i>ee</i> (%)	Reference
1	ChCl/U	L-Pro	95	28	97	This work
2	Toluene	L-Pro-L-Val-C ₁₂	99	75	12	⁵⁴
3	ACN ^a	(L-Pro-L-Val) ₂ C ₁₂	20	-	80	⁵¹
4	Phosphate buffer	L-Pro-peptide	99	86	88	⁶³

^aThe reaction was performed at -20 °C for 25 h.

The reaction between cyclohexanone and *p*-nitrobenzaldehyde has been previously performed in organo- and hydrogels based on L-Pro peptides. Then, to better understand the potential of the present catalytic system, we compared our results with the ones previously collected in literature (Table 6).

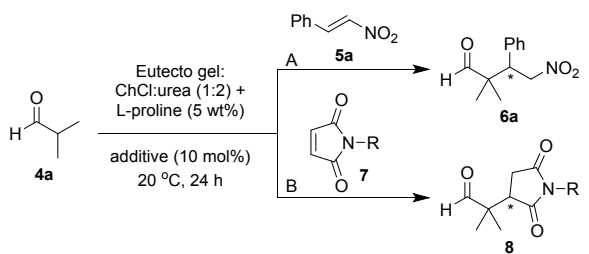
In general, the main advantage of the L-Pro eutecto gel stays in the possibility to perform the reaction using a lower ketone/aldehyde molar ratio (10:1) was used.

In terms of yield, our result is comparable to the ones obtained using organo- or hydrogels (cfr entries 1, 2 and 4). In our case, the aldol was obtained with lower *de*, but with significantly better *ee*, above all if organogels are considered (cfr entries 1-3). Furthermore, in all cases previously reported, the possibility to recycle the gel phase was not considered.

The L-Pro/ChCl/U eutecto gel was also tested as catalyst for the enantioselective Michael reaction. In this case, the isobutyraldehyde (**4a**) was employed as nucleophile in the reaction with *trans*- β -nitrostyrene or different maleimides as electrophiles (Table 7).

The reaction proceeded only in the presence of additives and, data reported in the Table evidence the effect exerted by the additive nature on the outcome of the reaction. Indeed, using *trans*- β -nitrostyrene as electrophile, the reaction proceeded with excellent yields, only in the presence of bases (entries 2-6). With the only exception of pyridine (entry 6), in all the other cases quantitative yields were obtained with low *ee*. Also in this case, the attempt to improve the *ee*, by decreasing the temperature was unsuccessful (entries 4 and 10), as a significant decrease in yield was detected, without significant improvement in the stereochemical pathway of the reaction.

In the presence of acidic additives (entries 7-9), *ee* stayed almost constant whereas a significant drop in yield was detected.

Table 7. Michael reactions performed in L-Pro/ChCl/U based eutecto gel.^a


Entry	Alkene	Additive	Yield (%) ^b	<i>ee</i> (%) ^c
1	<i>trans</i> - β -nitrostyrene	-	8	-
2	<i>trans</i> - β -nitrostyrene	DMAP	>99	23
3	<i>trans</i> - β -nitrostyrene	DABCO	>99	19
4	<i>trans</i> - β -nitrostyrene	Imidazole	>99	20
5	<i>trans</i> - β -nitrostyrene	DBU	>99	16
6	<i>trans</i> - β -nitrostyrene	Pyridine	53	24
7	<i>trans</i> - β -nitrostyrene	Benzoic acid	44	24
8	<i>trans</i> - β -nitrostyrene	<i>p</i> -Nitrobenzoic acid	36	27
9	<i>trans</i> - β -nitrostyrene	Adipic acid	27	25
10	<i>trans</i> - β -nitrostyrene	Imidazole	43 ^d	9
11	<i>N</i> -phenylmaleimide	-	4	-
12	<i>N</i> -phenylmaleimide	Pyridine	10	-
13	<i>N</i> -phenylmaleimide	2,6-Lutidine	3	-
14	<i>N</i> -phenylmaleimide	<i>p</i> -Nitrobenzoic acid	<1	-
15	Maleimide	Imidazole	11	-

^a Reaction conditions A: *trans*- β -nitrostyrene (0.2 mmol) and aldehyde (0.8 mmol) at 20 °C during 24 h; Reaction conditions B: **7** (0.2 mmol) and aldehyde (0.4 mmol) at 20 °C during 24 h. ^b Yield calculated by ¹H NMR. ^c Enantioselectivities determined by chiral HPLC. ^d Reaction performed at -10 °C.

It is worth mentioning that *ee* values collected in our case are perfectly in line with the ones previously reported in literature, studying the Michael reaction between cyclohexanone and *trans*- β -nitrostyrene in the organogel formed by L-Pro-L-Val peptide in a toluene/hexane mixture (90:10).⁶⁰ According to a previous report, the low enantioselectivity can be ascribed to the occurrence of two concomitant mechanisms. The first one foresees the enamine intermediate formation and the second one, occurring through a base catalysis that induces the formation of enolate intermediate. The occurrence of this latter pathway could be a consequence of the change in the L-Pro basicity induced by gelation process (see above) and this being the case, this factor proves to be more relevant in the case of the Michael than aldol reaction.

The reaction was also performed in the presence of cyclohexanone that gave 73% of yield with low

enantioselectivities (96% *de*, *syn* 29%, *ee*). Unfortunately, changing the nature of the maleimide gave only traces in product (entries 11-15). Also in this case, the obtained trend can be ascribed to the higher structural organisation and rigidity of the maleimides, which with more difficulty can reach the catalytic site to promote the reaction.

Conclusions

Natural eutecto gels have been developed combining properties of amino acids with properties of deep eutectic solvents. Among tested solvents, amino acids used were able to gel ChCl/U (1:2) and soft materials obtained were characterised to determine their thermal stability, rheological properties and morphological features.

Eutecto gels were used as catalytic systems to promote C-C bond reaction formation like the enantioselective aldol reaction, taking advantage of the dual role of amino acids that acted both as gelators and catalysts. Among tested materials, the L-Pro/ChCl/U eutecto gel was the one exhibiting the best catalytic performance. In particular, it was able to catalyse the cross-aldol reaction between acetone and *p*-nitrobenzaldehyde with excellent yield and good *ee*. The obtained results are better than the ones previously reported in literature for the study of the same reaction in organo- or hydrogels.

Data collected demonstrate that the rigidification of the aggregates in the hydrogen bond rich gelatinous network of the eutecto gel allows to preserve a certain stereochemical control of the reaction, notwithstanding the increase in catalyst basicity induced by the gelation process. This latter factor became more relevant as far as the Michael reaction was taken in consideration. Indeed, in this case, beside the quantitative yield in product, low *ee* were collected.

Interestingly, for both tested reactions, catalytic performance of the eutecto gel proved to be affected by the structural organisation of the substrate. Indeed, in both cases, the substrate scope evidenced that better results in terms of yield, *de* and *ee* (aldol reaction) were obtained with more flexible substrate. This can be ascribed to their ability to conform to the rigid gelatinous network, better interacting with the catalytic active site.

From the environmental point of view, the tested catalytic systems present different advantages. Firstly, they were prepared using natural, cheap and renewable components. As catalytic systems, they were used employing lower reagents loading with respect to similar systems so far reported in literature. The procedure respects most of the purposes of the Green Chemistry, since it is simple, clean and safe. Furthermore, products can be recovered with a green solvent and, the eutecto gel can be reused five consecutive times maintaining the enantioselectivity in each cycle. On the grounds of all above results, we are confident in stating that eutecto gels represent new materials to carry out enantioselective organic reaction in a totally eco-friendly manner.

Experimental section

General procedure for the preparation of DESs. A mixture of hydrogen-bond donor and hydrogen-bond acceptor, with the previously specified molar ratio, was added in a round bottom flask. The mixture was stirred for 30 minutes at 80 °C obtaining the corresponding DES.

General procedure for eutecto gel preparation. Gels were prepared by weighting into a screw-capped sample vial (diameter 1 cm) the suitable amounts of gelator and DES. The sample vial was heated in an oil bath at 80 °C until a clear solution was obtained (30 minutes). Then, the vial was rapidly cooled at 4 °C and then left to stand at room temperature for one night.

Determination of T_{gel} . Gel-sol transition temperature, T_{gel} , was determined through the falling drop method. The vial, filled with the gel, was immersed and turned upside down in a water bath, and the bath temperature was gradually increased, with a rate of 2 °C min⁻¹. The temperature at which the first drop of the gel fell was recorded as T_{gel} and these values were reproducible within 1 °C.

Whenever possible, T_{gel} was also confirmed by the lead-ball method. In this case, a lead-ball (weighing 46.23 mg and with 2 mm of diameter) was placed on top of the gel, and the vial was immersed in a water bath. The bath temperature was gradually increased (2 °C min⁻¹) until the gel melted and the lead-ball reached the bottom of the vial.

After gel melting, the solution was left to rest to check the reformation and the thermoreversibility of the gel.

Thixotropy tests. The eutecto gels were subjected to a mechanical stimulus that involved the stirring of the gel phase at 1000 rpm for 5 min, using a stirring bar (length 8 mm, height 3 mm). Then, the ensuing materials were kept to rest overnight and, afterwards, gels were considered thixotropic if they were self-supporting with the tube inversion test.

Rheological measurements. Rheological measurements of eutecto gels were performed on ARES G2 (TA Instruments) strain-controlled rheometer using an oscillatory mode and a plate-plate geometry tool (PP 25-2). The sample, previously formed on a blister, was cast between the shearing plates of the rheometer.

Strain and frequency sweeps were recorded three times on three different aliquots of gels at 3 or 5 wt% of gelator. Measurements were carried out after determining the linear viscoelastic region (LVR) of gels. In particular, strain sweeps were recorded at a fixed angular frequency of 1 rad s⁻¹ and frequency sweeps at a fixed strain of 0.025%. All measurements were performed at 25 °C.

Polarized Optical Microscopy investigation. Morphological investigation was carried out on polarized optical microscope, Optika B-353 PL, equipped with crossed polarizers, and an Optika camera interfaced to a computer with Optika Pro View Software. Eutecto gels at 3 wt% of the gelator were cast between two glasses to record the POM images.

Porosity measurements. Porosity of eutectogels was determined according to the reported procedure,⁶⁴ using HPLC-grade hexane as solvent. Hexane was cast on gels for 24 h.

Knowing the initial weight of the empty vial (W_1), the weight of the vial and the gel before (W_{dry}) and after (W_2) adding hexane and the final weight of the vial and gel after removing the hexane ($W_3 = W_{wet}$), it was possible to determine porosity (P), using the following equations:

$$V_g = 4 - \left(\frac{W_2 - W_1 - W_{dry}}{\rho_h} \right) \quad (1)$$

$$V_p = \left(\frac{W_2 - W_1 - W_{dry}}{\rho_h} \right) \quad (2)$$

$$P = \left(\frac{V_p}{V_p + V_g} \right) \times 100 \quad (3)$$

where ρ_h is density of hexane, V_p and V_g (mL) represent the volume of gel and of the hexane in the pores, respectively. 4 mL is the total volume occupied by gel and hexane.

RLS Measurements. RLS measurements were carried out at 288 K on a spectro-fluorophotometer (JASCO FP-777W) using a synchronous scanning mode in which the emission and excitation monochromators were preset to identical wavelengths. The RLS spectrum was recorded from 300 to 600 nm with both the excitation and emission slit widths set at 1.5 nm. Samples for a typical measurement were prepared injecting in a quartz cuvette (light path 0.2 cm) the limpid hot solution of gelator. The solution was rapidly cooled at 4 °C and then left to stand at room temperature for one night. The gel phase obtained at the end of the measurement was stable after the tube inversion test.

General procedure for the aldol reaction. Aldehyde (0.165 mmol, 1 equiv.) and ketone (0.825 mmol, 5 equiv.) were added in 500 mg of the corresponding gel in a vial. The reaction mixture was kept at 20 °C during 24 h. Then, the mixture was extracted with EtOAc (3 x 1 mL). The resulting organic phase was dried over MgSO₄ and the solvent was removed under reduced pressure. The resulting crude was purified by preparative TLC or column chromatography.

General procedure for the Michael reaction. Electrophile (0.2 mmol) and freshly distilled isobutyraldehyde (reaction A: 0.8 mmol or reaction B: 0.4 mmol) were added in 500 mg of the corresponding gel in a vessel. The reaction mixture was kept at 20 °C during 24 h. Then, the mixture was extracted with EtOAc (3 x 1 mL). The resulting organic phase was dried over MgSO₄ and the solvent was removed under reduced pressure. The resulting crude was purified by preparative TLC or column chromatography.

General procedure for the recycling experiments. The reaction was performed according to the general procedure. Once the reaction was completed, the formed product was extracted with a small amount of a renewable VOC solvent (2- MeTHF, 3 x 1 mL), the remaining solvent was evaporated and finally, the gel material was charged again with fresh reagents, repeating the process.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by the University of Alicante (VIGROB-316FI) and the Spanish Ministerio de Economía, Industria y Competitividad (PGC2018-096616-B-100). BS thanks Generalitat Valenciana (ACIF/2017/211) for her fellowship. We thank University of Palermo (FFR 2020) for financial support. C. R. thanks Elsevier and Società Chimica Italiana (*Reaxys-SCI Small Research Grants 2019/2020*; Project title: *Supracages*) for financial support.

Notes and references

- A. Batra and K. N. Singh, *Eur. J. Org. Chem.*, 2020, **2020**, 6676-6703.
- L. Rahimi, Y. Mansoori, A. Nuri, B. Koohi-Zargar and D. Esquivel, *Appl. Organomet. Chem.*, 2021, **35**, e6078.
- S. Baš, Y. Yamashita and S. Kobayashi, *ACS Catal.*, 2020, **10**, 10546-10550.
- S. Feng, X. Xie, W. Zhang, L. Liu, Z. Zhong, D. Xu and X. She, *Org. Lett.*, 2016, **18**, 3846-3849.
- M. Hayakawa, H. Shirota, S. Hirayama, R. Yamada, T. Aoyama and A. Ouchi, *Journal of Photochemistry and Photobiology A: Chemistry*, 2021, **413**, 113263.
- F. Lin and Y.-H. Chin, *J. Catal.*, 2014, **311**, 244-256.
- Z. Wei, Y.-Y. Chen, J. Li, W. Guo, S. Wang, M. Dong, Z. Qin, J. Wang, H. Jiao and W. Fan, *J. Phys. Chem. C*, 2016, **120**, 6075-6087.
- D. Zhang, G. Wang, C. Chen, T. Joshi, X.-K. Chen, A. M. Evans, M. Matsumoto, W. R. Dichtel, H. Li, M. F. Crommie and J.-L. Brédas, *Chem. Mater.*, 2020, **32**, 10688-10696.
- J. Qiu, H. Wang, Y. Zhao, P. Guan, Z. Li, H. Zhang, H. Gao, S. Zhang and J. Wang, *Green Chem.*, 2020, **22**, 2605-2612.
- K. D. Nguyen, S. Ehrling, I. Senkovska, V. Bon and S. Kaskel, *J. Catal.*, 2020, **386**, 106-116.
- H. Tian, S. Liu, Z. Zhang, T. Dang, Y. Lu and S. Liu, *ACS Sustainable Chemistry & Engineering*, 2021, **9**, 4660-4667.
- D. Díaz Díaz, D. Kühbeck and R. J. Koopmans, *Chem. Soc. Rev.*, 2011, **40**, 427-448.
- W. Fang, Y. Zhang, J. Wu, C. Liu, H. Zhu and T. Tu, *Chemistry – An Asian Journal*, 2018, **13**, 712-729.
- B. Maiti, A. Abramov, R. Pérez-Ruiz and D. Díaz Díaz, *Acc. Chem. Res.*, 2019, **52**, 1865-1876.
- C. Rizzo, S. Marullo, F. Billeci and F. D'Anna, *Eur. J. Org. Chem.*, 2021, **2021**, 3148-3169.
- D. B. D. Kühbeck, B.; Schön, E.-M.; Cativiela, C.; Gotor-Fernández, V.; Díaz Díaz, D., *Beilstein J. Org. Chem.*, DOI: 10.3762/bjoc.9.123, 8.
- B. O. Okesola and D. K. Smith, *Chem. Soc. Rev.*, 2016, **45**, 4226-4251.
- E. R. Draper and D. J. Adams, *Chem.*, 2017, **3**, 390-410.
- D. B. Amabilino, D. K. Smith and J. W. Steed, *Chem. Soc. Rev.*, 2017, **46**, 2404-2420.
- S. Roy and A. Banerjee, *Soft Matter*, 2011, **7**, 5300-5308.
- P. Bairi, B. Roy, P. Routh, K. Sen and A. K. Nandi, *Soft Matter*, 2012, **8**, 7436-7445.
- P. C. Marr and A. C. Marr, *Green Chem.*, 2016, **18**, 105-128.
- S. Marullo, C. Rizzo, N. T. Dintcheva, F. Giannici and F. D'Anna, *J. Colloid Interface Sci.*, 2018, **517**, 182-193.
- F. D'Anna, C. Rizzo, P. Vitale, G. Lazzara and R. Noto, *Soft Matter*, 2014, **10**, 9281-9292.
- C. Rizzo, F. D'Anna, R. Noto, M. Zhang and R. G. Weiss, *Chem. Eur. J.*, 2016, **22**, 11269-11282.
- B. Joos, T. Vranken, W. Marchal, M. Safari, M. K. Van Bael and A. T. Hardy, *Chem. Mater.*, 2018, **30**, 655-662.
- F. Delbecq, P. Delfosse, G. Laboueix, C. Paré and T. Kawai, *Colloids Surf., A*, 2019, **567**, 55-62.
- C. N. Prieto Kullmer, D. Ta, C. Y. Chen, C. J. Cieker, O. Annunziata and S. V. Dzyuba, *ACS Omega*, 2019, **4**, 9400-9406.
- J. Ruiz-Olles, P. Slavik, N. K. Whitelaw and D. K. Smith, *Angew. Chem. Int. Ed.*, 2019, **131**, 4217-4222.
- S. Marullo, A. Meli, N. T. Dintcheva, G. Infurna, C. Rizzo and F. D'Anna, *ChemPlusChem*, 2020, **85**, 301-311.
- N. Falcone, T. Shao, N. M. O. Andoy, R. Rashid, R. M. A. Sullan, X. Sun and H.-B. Kraatz, *Biomaterials Science*, 2020, **8**, 5601-5614.
- L. C. Tomé and D. Mecerreyes, *J. Phys. Chem. B*, 2020, **124**, 8465-8478.
- X. Cao, A. Gao, J.-t. Hou and T. Yi, *Coord. Chem. Rev.*, 2021, **434**, 213792.
- S. Panja, A. Panja and K. Ghosh, *Materials Chemistry Frontiers*, 2021, **5**, 584-602.
- C. Wang, Q. Han, P. Liu, G. Zhang, L. Song, X. Zou and Y. Fu, *ACS Sensors*, 2021, **6**, 252-258.
- F. Billeci, F. D'Anna, H. Q. N. Gunaratne, N. V. Plechkova and K. R. Seddon, *Green Chem.*, 2018, **20**, 4260-4276.
- C. Rizzo, S. Marullo, P. R. Campodonico, I. Pibiri, N. T. Dintcheva, R. Noto, D. Millan and F. D'Anna, *ACS Sustainable Chemistry and Engineering*, 2018, **6**, 12453-12462.
- C. Rizzo, J. L. Andrews, J. W. Steed and F. D'Anna, *J. Colloid Interface Sci.*, 2019, **548**, 184-196.
- B. Escuder, F. Rodríguez-Llansola and J. F. Miravet, *New J. Chem.*, 2010, **34**, 1044-1054.
- E. L. Smith, A. P. Abbott and K. S. Ryder, *Chem. Rev. (Washington, DC, U. S.)*, 2014, **114**, 11060-11082.
- D. A. Alonso, A. Baeza, R. Chinchilla, G. Guillena, I. M. Pastor and D. J. Ramón, *Eur. J. Org. Chem.*, 2016, DOI: 10.1002/ejoc.201501197, 612-632.
- D. J. Ramón and G. Guillena, *Deep Eutectic Solvents: Synthesis, Properties, and Applications*, Wiley-VCH: Weinheim, 2019.
- P. Chakraborty and E. Gazit, *ChemNanoMat*, 2018, **4**, 730-740.
- B. List, R. A. Lerner and C. F. Barbas, *J. Am. Chem. Soc.*, 2000, **122**, 2395-2396.
- J. Liu and L. Wang, *Synthesis*, 2017, **49**, 960-972.
- D. Brenna, E. Massolo, A. Puglisi, S. Rossi, G. Celentano, M. Benaglia and V. Capriati, *Beilstein J. Org. Chem.*, 2016, **12**, 2620-2626.
- N. Fanjul-Mosteirín, C. Concellón and V. del Amo, *Org. Lett.*, 2016, **18**, 4266-4269.
- R. Martínez, L. Berbegal, G. Guillena and D. J. Ramón, *Green Chem.*, 2016, **18**, 1724-1730.
- D. A. Alonso, S.-J. Burlingham, R. Chinchilla, G. Guillena, D. J. Ramón and M. Tiecco, *Eur. J. Org. Chem.*, 2021, DOI: <https://doi.org/10.1002/ejoc.202100385>.

Journal Name

ARTICLE

50. K. Hawkins, A. K. Patterson, P. A. Clarke and D. K. Smith, *J. Am. Chem. Soc.*, 2020, **142**, 4379-4389.
51. F. Rodríguez-Llansola, B. Escuder and J. F. Miravet, *Org. Biomol. Chem.*, 2009, **7**, 3091-3094.
52. N. Singh, K. Zhang, C. A. Angulo-Pachón, E. Mendes, J. H. van Esch and B. Escuder, *Chem. Science*, 2016, **7**, 5568-5572.
53. R. Porcar, M. I. Burguete, P. Lozano, E. Garcia-Verdugo and S. V. Luis, *ACS Sustainable Chemistry & Engineering*, 2016, **4**, 6062-6071.
54. F. Rodríguez-Llansola, J. F. Miravet and B. Escuder, *Chem. Commun.*, 2009, DOI: 10.1039/B916250J, 7303-7305.
55. S. Marullo, A. Meli, F. Giannici and F. D'Anna, *ACS Sustainable Chemistry & Engineering*, 2018, **6**, 12598-12602.
56. X. Huang, S. R. Raghavan, P. Terech and R. G. Weiss, *J. Am. Chem. Soc.*, 2006, **128**, 15341-15352.
57. R. Pasternack and P. Collings, *Science*, 1995, **269**, 935-939.
58. C. Berdugo, J. F. Miravet and B. Escuder, *Chem. Commun.*, 2013, **49**, 10608-10610.
59. C. R. McElroy, A. Constantinou, L. C. Jones, L. Summerton and J. H. Clark, *Green Chem.*, 2015, **17**, 3111-3121.
60. F. Rodríguez-Llansola, J. F. Miravet and B. Escuder, *Chem. Eur. J.*, 2010, **16**, 8480-8486.
61. C. Rizzo, A. Mandoli, S. Marullo and F. D'Anna, *J. Org. Chem.*, 2019, **84**, 6356-6365.
62. D. Prat, O. Pardigon, H.-W. Flemming, S. Letestu, V. Ducandas, P. Isnard, E. Guntrum, T. Senac, S. Ruisseau, P. Cruciani and P. Hosek, *Org. Process Res. Dev.*, 2013, **17**, 1517-1525.
63. M. Tena-Solsona, J. Nanda, S. Díaz-Oltra, A. Chotera, G. Ashkenasy and B. Escuder, *Chem. Eur. J.*, 2016, **22**, 6687-6694.
64. Y. Zu, Y. Zhang, X. Zhao, C. Shan, S. Zu, K. Wang, Y. Li and Y. Ge, *Int. J. Biol. Macromol.*, 2012, **50**, 82-87.