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Ionic Liquid Gels: Supramolecular Reaction Media for the Alcoholysis of Anhydrides

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Abstract

The search of new enantioselective catalysts, able to promote synthetically useful organic reactions with high levels of asymmetric induction, should be associated with the attention to the suitable reaction medium able to achieve the best efficiency in chemical processes.

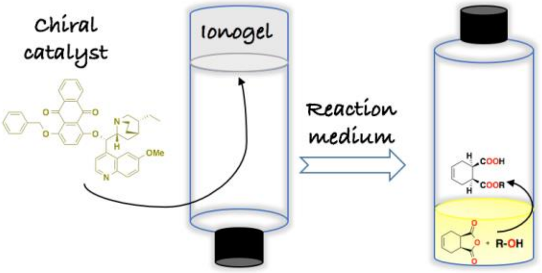
We have investigated the enantioselective desymmetrization of cyclic *meso*-anhydrides in non-conventional reaction media such as ionic liquids and supramolecular gels. With this aim, we examined several variables in the reacting system: the nature of ionic liquid used as the reaction medium, the gelation solvent, the structure of the anhydrides, the structure of alcohols, the chiral catalysts and the reaction conditions, *i.e.* temperature and time.

The different components of the system differently influence the reaction outcome and to understand the interactions existing among them, ^{1}H NMR investigation was carried out. In general, the non-conventional reaction media demonstrated better performance than conventional ones, applying only a small amount of solvent. Good results in terms of yield and enantiomeric excess have been obtained in ionic liquid gels that seem promising media in the

catalytic field. Furthermore, to the best of our knowledge, this is one of the first examples for the study of asymmetric alcoholysis of anhydrides in ionic liquid solution and gel phase.

Keywords: ionic liquid, ionic liquid gels, supramolecular gel, quinidine organocatalyst, asymmetric alcoholysis of cyclic anhydride.

TOC



Introduction

One of the challenges in modern organic synthesis is the preparation of complex chiral compounds in high yield and enantiomeric purity. Indeed, several enantioselective catalysts have been developed and applied to perform complex reactions to obtain natural products and biologically active substances.[1] Besides this main goal, in the last decades also the environmental sustainability of the chemical process became crucial. Indeed, according to the third and the fifth principles of Green Chemistry, the use of complex synthetic pathways has been discouraged, in favour of procedures that make use of minimal amounts of solvent or alternative reaction media.[2] In particular, ionic liquids (ILs) have conquered the definition of “green solvents” thanks to their low volatility and flammability.[3,4] They are formed by organic cations and inorganic or organic anions presenting melting temperature below 100 °C. Furthermore, in dependence on their structural features, cations and anions can be interconnected through weak interactions such as π–π stacking, hydrogen bonds and van der Waals interactions forming a supramolecular network that enables an additional level of control in some chemical processes.[5] Thus ILs, carrying out the double role of solvents and catalysts, have been widely applied not only for academic studies of several organic reactions but also,[6,7] and above all, in some industrial processes.[8,9]

Similarly, supramolecular interactions might favour the outcome of a given reaction[10] and it has been shown the advantage of using confined reaction media such as organo- and hydrogels.[11-13] Supramolecular gels are formed by a low molecular weight gelator interacting through non covalent bonds to form a self-assembled fibrillar network able to trap a solvent.[14,15] When the gelation solvent is an IL, the material can be defined as ionic liquid gel (ILG).[16,17] These materials are easily tuneable and can be applied for several purposes spanning from the energy field, where they have been used as conductive materials in electronic devices,[18,19] to the biological,[20,21] the antioxidant[22] and the environmental one.[23,24] Despite the large employment in catalysis of ionic liquid-silica gels comprising also metal nanoparticles,[25-27] the use of supramolecular ILGs in this area is quite new and promising. Indeed, a successful application of a Brønsted-acidic ILG leading to excellent yields in short reaction times has been reported for the synthesis of bis(indolyl)methanes.[26] As well as a series of basic ILGs have been applied to the hydrogen borrowing mediated dehydration of 1,3 propanediol, obtaining excellent conversions, selectivity and recyclability.[28] Furthermore, the fine tuning of the right combination of ILs or ILGs seems to explain also the different catalytic efficiency of the common organocatalyst L-proline, employed for the aldol reaction. In this study, the high degree of supramolecular organization induced by ILs and ILGs enhanced the activity and the asymmetric induction.[29]

Following this approach, we decided to examine if the use of ILs or ILGs could provide synthetically useful enantioselectivity levels in more organized media. Our main goal was the study of the solvent medium effect (IL or ILG) on the outcome of the desymmetrization of cyclic meso-anhydrides, assuming it could behave as a probe of molecular and supramolecular interactions. In this regard, it is worth noting that ILs are well established solvents for acylation reactions,[30,31] and that ILG supramolecular systems could conjugate advantages deriving from the presence of confined reaction media with a better extraction of the product from the gel phase. However, to the best of our knowledge, at the beginning of the present study no example of enantioselective opening of *meso*-anhydrides, in either of the two non-conventional reaction media, had been reported.

Indeed, the catalytic desymmetrization of cyclic meso-anhydrides has been widely studied for the purpose of elucidating its mechanism[32-34] and as a benchmark of new enantioselective catalysts.[35] After the pioneering work of the groups of Oda and Aitken with native *Cinchona* alkaloids,[36,37] and the subsequent optimization by Bolm and co-workers,[38,39] also chiral Lewis acids,[40] monomeric and dimeric alkaloid derivatives,[32,41,42] bifunctional compounds,[43-45] and chiral Brønsted acids[46] proved to be competent catalysts for this class of reactions. On the contrary, much less efforts were devoted to the reduction of the environmental impact of the process. Indeed, even if, some studies include enzymatic catalysis to obtain desymmetrization products, also in those conditions, long reaction times (5 days, 5 weeks) and conventional organic solvents are required.[47-49] In addition, despite the high efficiency reached, most of methodologies employ aqueous media with consequent hard product separation and purification. In a notable exception, Bolm and co-workers applied the ball milling technique to afford optically active dicarboxylic acid monoesters in good yields and in solvent free conditions. In this approach, they achieved a simplified product isolation thanks to the use of almost equimolar amounts of the starting materials and the quinidine organocatalyst.[50] In addition, immobilized variants of the most effective *Cinchona* alkaloid organocatalysts were developed and showed good recyclability in some cases.[51,52]

Hence, in the present work, the enantioselective desymmetrization of cyclic *meso*-anhydrides has been employed as model reaction and has been performed in ILs and ILGs. Several variables in the reacting system, such as the nature of IL or ILG, the gelation solvent, the structure of the anhydrides, the structure of alcohols, the chiral catalysts and the reaction conditions, have been examined. In addition, ^{1}H NMR analysis allowed investigating the interactions among the several components of the system.

Results and discussion

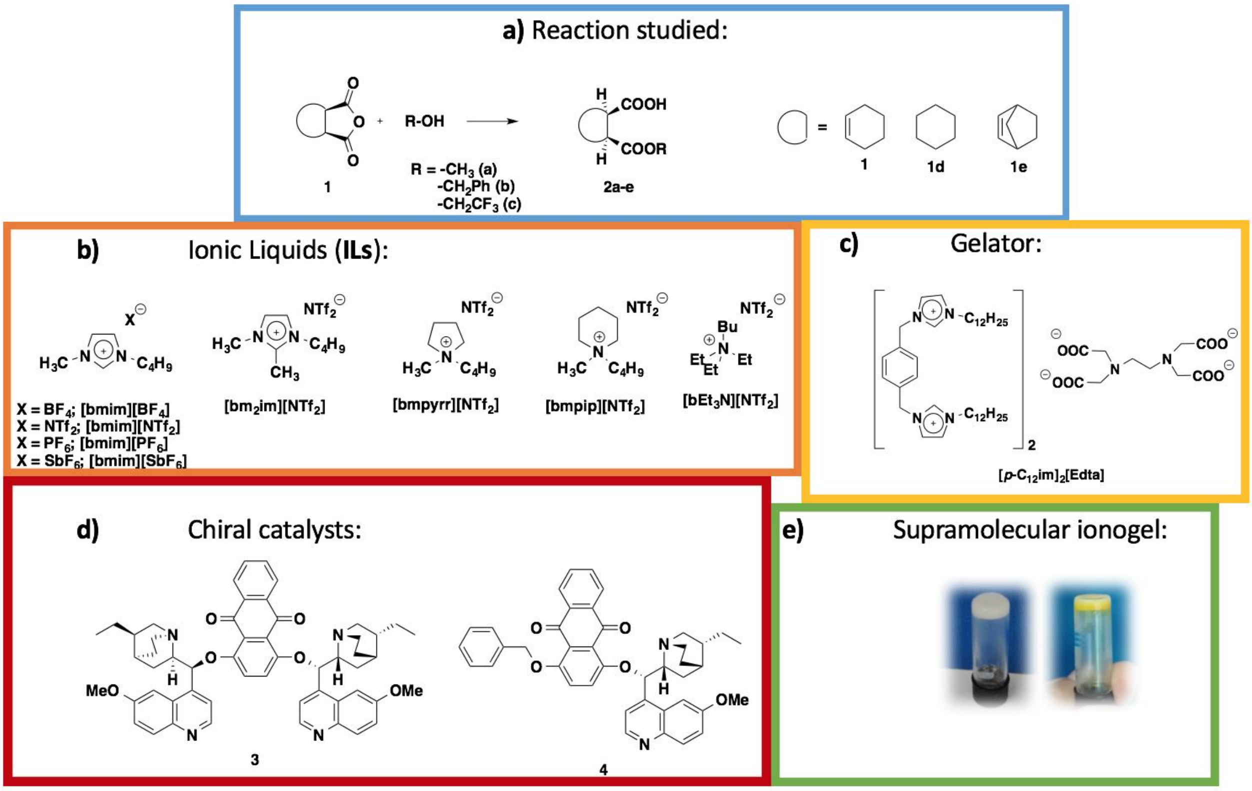
In order to tackle the goal stated above, we firstly focused the attention on the asymmetric alcoholysis of *cis*-1,2,3,6-tetrahydrophthalic anhydride (**1**) as a typical cyclic *meso*-substrate and precursor to the synthetically valuable chiral hemiesters **2a**-**2c** (Scheme 1a).[53-56]

Concerning the reaction medium, initially we analysed how the solvent affects the outcome of the process using some of the most common monocationic ILs (Scheme 1b). To introduce a further level of structural hierarchy in our reaction systems, next we examined the use of ILGs.

In this regard it is important to note that, besides the careful selection of the solvent, in order to obtain environmentally sustainable materials, also the choice of gelators should fall on easily synthesizable and whenever possible, eco-friendly compounds. Because dicationic organic salts can satisfy such requests,[57] di-3,3'-di-*n*-dodecyl-1,1'-(1,4-phenylenedimethylene)diimidazolium ethylenediaminetetraacetate, **[*p*-C$_{12}$im]$_2$[Edta]** (Scheme 1c), was chosen for the purpose. In fact, this gelator combines a cation with a proven gelling ability with a biocompatible anion and is able to form gels in a wide range of solvents, comprising both organic solvents and ILs.[58]

Reasoning that the IL solvent or gelator might provide electrophilic activation of the carbonyl substrate through hydrogen-bonding (*vide infra*), amongst the many effective organocatalysts for the reaction under exam, we selected the purely Lewis-basic dimeric hydroquinidine ether **3**[32,41] and its monomeric counterpart **4**[59] (Scheme 1d).

Because ILs may exert a catalytic effect in acylation reactions on their own, even when devoid of task-specific groups,[60,61] before addressing the issue of stereoselectivity, it became important to evaluate the behaviour of **1** in the neat IL or ILG phases. Therefore, the enantioselective alcoholysis runs were preceded by the study of the same reactions in either of the two types of non-conventional media, but in the absence of any added chiral organocatalyst.



Scheme 1. a) Model alcoholysis reactions; **b)** structures of ILs used as reaction media; **c)** structure of gelator used to form the supramolecular gels; **d)** structures of chiral catalysts; **e)** images of white opaque ILGs formed by **[*p*-C$_{12}$im]$_2$[Edta]** in [bmim][NTf$_2$] (left) and of the same gel after the reaction was performed using a chiral catalyst (right).

Reactions in ILs

At the onset of this work, we tested the influence of solvent system, by comparing the results in ILs differing for both the cation and anion structure. The set of solvents selected included four 1-butyl-3-methylimidazolium-based ILs, namely **[bmim][BF$_4$]**, **[bmim][NTf$_2$]**, **[bmim][PF$_6$]** and **[bmim][SbF$_6$]**, bearing anions having different size, shape, hydrogen bonding accepting ability and hydrophobicity.

In the series of aromatic ILs, we also used **[bm$_2$im][NTf$_2$]** to evaluate the effect of the cation ability to give hydrogen bond. Finally, we employed five [NTf$_2^-$]-based ILs with the aim to assess the role played by the IL cation structure on the outcome of the reaction. So, together with **[bmim][NTf$_2$]** and **[bm$_2$im][NTf$_2$]**, we also used aliphatic ILs bearing cyclic or acyclic cations such as **[bmpyrr][NTf$_2$]**, **[bmpip][NTf$_2$]** and **[bEt$_3$N][NTf$_2$]**.

Initially, the reaction was carried out using the anhydride **1** at 4 °C, with methanol as the alcohol component. In agreement with the Green Chemistry principles, the minimal amount of solvent was employed as needed to dissolve the anhydride. Thanks to the high solubilisation ability of ILs, this was equal to 500 μL on a 0.1 mmol scale, *i.e.* between 20 and 30-fold less than usually reported in literature for the asymmetric process in conventional solvents.[32,33]

Then, the required volume of MeOH was added to start the reaction, in two series of experiments carried out with a large excess of alcohol with respect to the anhydride (200 μL, 48 equiv.) and with a lower amount (50 μL, 12 equiv.), respectively.

The reactions were monitored through TLC, observing in all cases no significant formation of products different from **2a**. The yield of the reaction was obtained at the fixed reaction time of 24 h, after recovery of the product by extraction with Et$_2$O and flash chromatography. The results obtained in the various runs are summarized in Table 1 together with the solvent polarity parameter, E^T_N, and the Kamlet-Taft solvatochromic descriptors α and β. As discussed in the following, the latter represent the ability of the medium to behave as a donor (α) or acceptor of hydrogen bonds (β), respectively.[62]

Table 1. Solvent parameters, amount of MeOH used, and yield of **2a** obtained for reactions carried out for 24 h, at 4 °C in ILs or in conventional organic solvents.

Entry	*Solvent*[a]	E^T_N [b]	α [b]	β[b]	*MeOH (μL)*	*Yield (%)*[e]
1	[bmim][BF_4]	0.670	0.627	0.376	200[c]	95
2					50[d]	44
3	[bmim][NTf_2]	0.644	0.617	0.243	200[c]	71
4					50[d]	15
5	[bm_2im][NTf_2]	0.542	0.381	0.239	200[c]	51
6					50[d]	37
7	[bmpyrr][NTf_2]	0.544	0.427	0.252	200[c]	51
8					50[d]	39
9	[bmpip][NTf_2]	0.528	0.433	0.338	200[c]	87
10	[bEt_3N][NTf_2]	-	-	0.303	200[c]	58
11	[bmim][PF_6]	0.669	0.634	0.207	200[c]	26
12	[bmim][SbF_6]	0.673	0.639	0.146	200[c]	10
13	1-Octanol	0.543	0.77	0.81	200[c]	<5
14	Diethyl ether	0.117	0.00	0.47	200[c]	36
15					50[d]	22

[a] Runs with 0.1 mmol of **1** and 500 μL of solvent; [b] Values from references[63,64] ; [c] (4.9 mmol, 48 equiv.); [d](1.2 mmol, 12 equiv.); [e] Isolated yield after flash chromatography; yield values were reproducible within 4% after triplicate runs.

In order to make a comparison with the use of ordinary solvents, the reaction was performed also in diethyl ether and 1-octanol. The former solvent is one of the most common media employed for the study of this process,[35,65] while the choice of the latter was prompted by its comparable polarity to the one of ILs and by the fact that the diimidazolium salt, **[*p*-C_{12}im]$_2$[Edta]**, is able to gel it.

With the only exception of **[bmim][PF_6]** and **[bmim][SbF_6]**, yields obtained using 200 μL of MeOH, in the absence of any added catalyst, result higher than the ones collected in conventional media (entries 1,3,5,7,9,10-12 *vs.* entries 13-14).

In general, data collected in the presence of a larger excess of MeOH, shed light on the effect of the IL structure on the outcome of the reaction. They clearly outline the relevance of the anion hydrogen bonding accepting ability, as accounted for by the decrease in yield values that perfectly recalls the one in β values (**[bmim][BF_4]** > **[bmim][NTf_2]** > **[bmim][PF_6]** > **[bmim][SbF_6]**; entries 1,3,11,12).

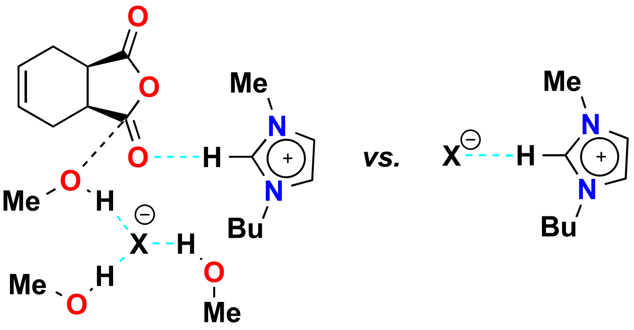
A less regular trend was obtained as a function of the cation structure. Indeed, for [NTf_2^-]-based ILs, we did not obtain a clear correlation between yield and α values. In general, yield in **2a** decreases on going from **[bmim][NTf_2]** to **[bm_2im][NTf_2]** (entries 3 and 5) and from **[bmpip][NTf_2]** to **[bEt_3N][NTf_2]** and **[bmpyrr][NTf_2]** (entries 9, 10 and 7), allowing to state a certain relevance of the cation ability to give hydrogen bond.

For some selected IL systems, namely **[bmim][BF_4]**, **[bmim][NTf_2]**, **[bm_2im][NTf_2]** and **[bmpyrr][NTf_2]** (entries 2,4,6,8), we also performed the reaction in the presence of 50 μL of MeOH, evidencing a less significant effect of the IL structure. However, also in this case, with the only exception of **[bmim][NTf_2]**, higher yields were obtained in ILs than in conventional solvents.

To explain the trends, it must be considered that MeOH could act in different ways on the reaction under exam: i) in a direct concentration-dependent manner, due to its role as the nucleophilic reagent; ii) through a dilution effect, expected to favour the product formation because of the reduced IL viscosity; iii) as a hydrogen bond donor, in assistance to the opening of the anhydride ring in the transition state (general acid catalysis); iv) by interference with the cation-anion hydrogen bond network in the IL structure, which might allow the IL cation to act as a general acid catalyst itself (Scheme 2).

While a clear-cut separation of all these effects is difficult, our results seem to rule out a dominant contribution by the second and the third phenomena. In particular, taking in consideration [bmim$^+$]-based ILs, the highest yields were obtained in a more viscous medium like **[bmim][BF$_4$]** (η= 233 cP) (entry 1).[66] Moreover, changes in yields observed as function of MeOH amount proved comparable in **[bmim][BF$_4$]** (entries 1-2) and in the least viscous solvent in the series, **[bmim][NTf$_2$]** (η=52 cP) (entries 3-4).[66] On the other hand, also the MeOH contribution as a direct hydrogen bond donor appears to play a secondary role, with respect to [bmim$^+$]-cation, as accounted for by the decrease in yields on going from **[bmim][NTf$_2$]** to **[bm$_2$im][NTf$_2$]** under MeOH-rich conditions (entries 3 and 5).

On the contrary, the data in Table 1 appear in agreement with the hypothesis that the protic solvent MeOH interferes to some extent with the cation-anion interaction, to increase the ability of the IL cation to assist the opening of the anhydride via hydrogen bond formation (Scheme 2).



Scheme 2. Schematic representation of the possible interaction between an imidazolium IL and the anhydride **1**.

The results in Table 1 indicate that the overall effect does not depend only on the amount of added MeOH. However, also the tightness of the ion pair in the neat IL and the propensity of the anionic fragment to be solvated by the alcohol component play a role. In this respect, it is not surprising that the IL with the tighter ion pair, **[bmim][BF$_4$]**, proved to be also the most responsive to the presence of a large excess of MeOH. Indeed, in addition to the coordinating catalytic effect of the [BF$_4^-$] anion increasing the nucleophilicity of MeOH, its stronger solvation by the alcohol could result in a [bmim$^+$] cation more available to interact with the anhydride. In this case, the IL seems to act as a bifunctional catalyst. A similar behavior has been previously detected performing kinetic study of base-induced elimination reaction and mononuclear rearrangement of heterocycles in IL solution.[67,68]

Conversely, in the presence of a smaller amount of MeOH, a tighter IL ion pair should be active, decreasing the catalytic effect.

To further support the above hypothesis, we took in consideration **[bmim][BF$_4$]** and **[bmim][NTf$_2$]** and recorded ^{1}H NMR spectra in the presence of increasing amounts of MeOH (50 and 200 μL; Figure S1-S2). In both cases a deshielding effect on the aromatic protons of imidazolium ion was observed and the above effect increased with cosolvent volume.

In general, chemical shift changes were more significant in the case of **[bmim][BF$_4$]** than in the presence of **[bmim][NTf$_2$]** (Figure S3), according to the higher structural order degree of the first IL deriving from the stronger and more extensive cation-anion interaction. The above result perfectly agrees with the one previously reported about the presence of different ion pairs in IL/cosolvent binary mixtures as a function of their composition. [67, 64]

However, when hydrogen bond donor ability is comparable (**[bmpyrr][NTf$_2$]** and **[bmpip][NTf$_2$]**), the increase in β value induces a concomitant increase in yield, evidencing a higher relevance of the solvent ability to accept than to give hydrogen bond.

All the above hypotheses could explain the larger yields obtained in ILs with respect to the use of a conventional solvent, like diethyl ether, under comparable conditions and even in the absence of any additional catalysts.

Reactions in gel phases

Once proved the ability of ILs to catalyse the reaction, we tested supramolecular ILGs as reaction media. As anticipated, the dicationic organic salt **[*p*-C_{12}im]$_2$[Edta]** is able to gel several solvents, among which **[bmim][BF_4]**, **[bmim][NTf_2]**, **[bmpyrr][NTf_2]** and 1-octanol.[58] Gels were prepared at a gelator concentration of 5 wt % with respect to the gelation solvent and, in order to avoid the disruption of gel phases, reactions were performed with 50 μL of MeOH.

The results obtained in gel phase and in the corresponding IL solution, without any catalysts, at 4 °C for 24 h are reported in Figure 1 (Table S2).

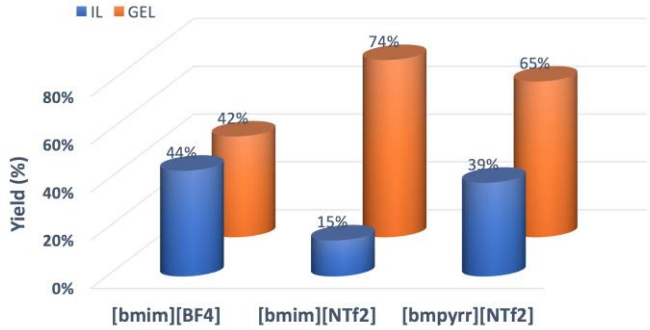


Figure 1. Yield of **2a** obtained in solution (purple) and in the gel phase (green), at 4 °C for 24 h (isolated yields after flash chromatography; yield values were reproducible within 4%, after triplicate runs).

Interestingly, in all of the examined ILGs the reaction presented comparable or even larger yields than in the corresponding IL solution. On the contrary, for the organogel prepared from 1-octanol no appreciable product formation was observed and, in addition, the organogel was partially destroyed after extraction with Et_2O. Therefore, at least for the reaction under study, ILGs are clearly preferable to organogels as they keep their gel state even after the separation of the product from the matrix.

Because the use of IL supramolecular gels increases the yield in two out of three cases, a positive but selective effect of the supramolecular network on the rate of the probe reaction is operating. In turn, this resulted in a change of the reactivity order *vs.* neat ILs, with product yields now decreasing as follows: **[bmim][NTf$_2$]** > **[bmpyrr][NTf$_2$]** > **[bmim][BF$_4$]** (the gelator being **[*p*-C$_{12}$im]$_2$[Edta]** in all cases).

The fact that the gel in **[bmim][NTf$_2$]** showed the best performance while that in **[bmim][BF$_4$]** the worst one, might look surprising at first. Nevertheless, one must consider that gels as reaction media are really different from solutions and that data obtained in the gel phase are influenced by soft-material properties such as rheology parameters, temperature of gel-sol transition (T_{gel}) or viscosity of the gelation solvent.

First of all, we have previously demonstrated that gelation solvent drastically influences supramolecular gel properties.[58] In particular, according to the rheological parameter (tan δ) that gives an idea of the stiffness of the gel (higher at lower tan δ values) and to the one that represents the level of stress needed to detect the flow of a material (stress %), it seems that the reaction is favoured in less strong gels (Table S3). Results are also supported by T_{gel} values, as the more thermally stable gel is **[*p*-C$_{12}$im]$_2$[Edta]** in **[bmim][BF$_4$]** in which we detected the lowest yield value. In addition, viscosity of gelation solvents well supports the above explanation as it increases in an opposite trend respect to yield obtained in gel phases **[bmim][NTf$_2$]** < **[bmpyrr][NTf$_2$]** < **[bmim][BF$_4$]** (Table S1).

The findings above suggest that results collected are mainly determined by the flexibility of the ILG network, and its ability to conform to reagents structural changes during the progress of the reaction.

Effect of alcohol structure and alkaloid catalyst

Encouraged by the results in ILs and in gel phases, we moved to explore the effect of adding an alkaloid organocatalyst or changing the structure of the alcohol (Table 2). With this aim, the best performing gel, **[*p*-C_{12}im]$_2$[Edta]** in **[bmim][NTf_2]**, and the corresponding IL solution were selected as the reaction media, while the mono quinidine derivative **4** (5 mol%) was employed as the basic catalyst. Besides methanol, benzyl alcohol (12 equiv. in both cases) was used as a more hindered nucleophile, bearing also an aromatic group.

Table 2. Yield of **2a** and **2b** in the reactions carried out for 24 h, at 4 °C in ILs and in gel phases.

Entry	*Reaction medium*[a]	*Catalyst (mol%)*	*Alcohol*	*Product*	*Yield (%)*[b]
1	IL	none	MeOH	**2a**	15
2		**4** (5)	MeOH	**2a**	47
3		none	BnOH	**2b**	18
4		**4** (5)	BnOH	**2b**	40
5	GEL	none	MeOH	**2a**	74
6		**4** (5)	MeOH	**2a**	61
7		none	BnOH	**2b**	43
8		**4** (5)	BnOH	**2b**	52

[a] Runs with 0.1 mmol of **1** and 50 μL (1.2 mmol, 12 equiv.) of MeOH or 130 μL (1.2 mmol, 12 equiv.) of BnOH, in 500 μL of **[bmim][NTf_2]** or 500 mg of gel formed by 5 wt % of **[*p*-C_{12}im]$_2$[Edta]** in **[bmim][NTf_2]**; [b] Isolated yield after flash chromatography; yield values were reproducible within 4%, after triplicate runs.

Irrespective of the actual conditions, yields obtained in gel phases were always larger than in IL solution, to further support the importance of confined reaction media for the reaction under exam.

Moreover, in the IL solution the addition of **4** as a basic catalyst significantly increased the yield with both alcohols, passing from 15% in the absence of catalyst to 47% in the presence of it, for reaction with MeOH (entries 1-2), and from 18% to 40%, for reaction with BnOH (entries 3-4).

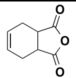
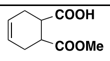
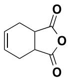
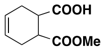
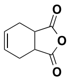
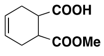
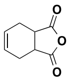
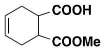
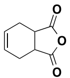
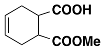
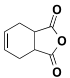
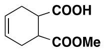
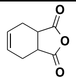
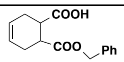
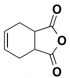
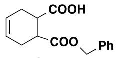
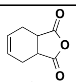
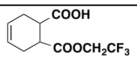
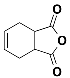
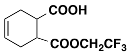
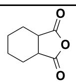
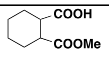
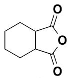
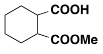
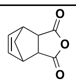
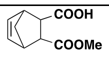
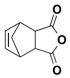
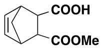
On the contrary, the catalytic effect of **4** was less efficient in gel phase, where we observed a moderate increase in yield for the reaction of BnOH (43% to 52%; entries 7-8) but, actually, a slight decrease with MeOH (74% to 61%; entries 5-6). Probably in solution the catalyst can easily fulfil its function, whereas in the gel phase further phenomena may come into play. Possibly, these are related to a modification of the gel structure by the alkaloid component and subsequent change of the diffusion rate of the alcohol into the (relatively hydrophobic) gel matrix.

The same discrepancy between ILs and gels is recorded when a different alcohol is used to perform the reaction. Indeed, the alcohol nature barely influenced the yields obtained in ILs (entries 1 and 3), while they drastically decreased in gel phases when benzyl alcohol instead of MeOH was used (entries 5 and 7). Probably, the higher steric hindrance of the phenyl group slows down the rate of reaction and this effect is more evident in the confined reaction media than in solution. A similar decrease in reactivity in presence of benzyl alcohol was also reported in conventional solvents.[69]

Enantioselectivity of the reaction

Rather disappointingly, in all of the experiments of Table 2 with the chiral organocatalysts **4** the hemiesters **2a** or **2b** were obtained in essentially racemic form. This was not totally unexpected, given the relatively fast reactions observed in ILs and, especially, gel phases devoid of any alkaloid catalyst. Although these findings witness of an important background, not-stereoselective process, the strong positive influence of temperature reduction on the enantioselectivity, often reported in the literature for the asymmetric methanolysis of **1** in conventional solvents,[35,65] prompted us to examine if an analogous approach could be useful for the problem at hand. With this idea in mind, the reaction of **1** and MeOH in **[bmim][NTf$_2$]**, or in the corresponding gel phase, was reexamined at the temperature of -30 °C (Table 3). The runs were carried out in the presence of either **4** (5 mol%) or the corresponding dimeric organocatalyst **3** (2.5 mol%), with a reaction time increased to 48 h to compensate for the reduced reaction rates.

Table 3. Yield and enantiomeric purity of hemiesters obtained in reactions carried out for 48 h, at -30 °C.

Entry	*Reaction medium*[a]	*Catalyst (mol%)*	*Anhydride*	*Alcohol*	*Product*	*Yield (%)*[b]	*ee (%)*[c]
1	IL	**4** (5)	 1	MeOH	 2a	38	22
2		**3** (2.5)	 1	MeOH	 2a	88	24
3	GEL	**4** (5)	 1	MeOH	 2a	78	81
4		**3** (2.5)	 1	MeOH	 2a	92	9
5	Diethyl ether	**4** (5)	 1	MeOH	 2a	53	83
6		**3** (2.5)	 1	MeOH	 2a	20	48
7	IL	**4** (5)	 1	BnOH	 2b	36	14
8	GEL	**4** (5)	 1	BnOH	 2b	93	3
9	IL	**4** (5)	 1	CF_3CH_2OH	 2c	21	79
10	GEL	**4** (5)	 1	CF_3CH_2OH	 2c	38	80
11	IL	**4** (5)	 1d	MeOH	 2d	39	16
12	GEL	**4** (5)	 1d	MeOH	 2d	38	12
13	IL	**4** (5)	 1e	MeOH	 2e	99	36
14	GEL	**4** (5)	 1e	MeOH	 2e	99	61

[a] Runs with 0.1 mmol of anhydride, 1.2 mmol (12 equiv.) of alcohol, and 500 μL of Et_2O or **[bmim][NTf$_2$]** or 500 mg of gel formed by 5 wt % **[*p*-C$_{12}$im]$_2$[Edta]** in **[bmim][NTf$_2$]**; [b] Isolated yield after flash chromatography, yields were reproducible within 4%, after triplicate runs; [c] Determined *via* chiral HPLC.

Much to our delight, under these conditions fair to very good yields and measurable enantiomeric excess (*ee*) values were obtained in every run. The result is especially intriguing when the gel matrix is the reaction medium, because good enantioselectivity has been previously obtained in hydrogels formed through self-assembly of an organocatalyst attached to gelator molecules[70] and in hydrogels, where the chirality was induced by chiral nanomaterials,[71] but rarely in ILGs. Taking into account the observations at the beginning of this section, the findings above confirmed the possibility to shut-down the non-stereoselective background process by cooling, which in turn allowed the reaction to be largely funnelled through the alkaloid-mediated enantioselective route. While the increased yields in the gel system with respect to pure IL conform to data in Figure 1 and Table 2, the influence of catalyst structure on the reaction progress and its enantioselectivity is far less obvious. For instance, in spite of the same concentration of alkaloid units, the dimeric organocatalyst **3** shows a significantly larger activity than the monomeric derivative **4** in the IL and in the gel (Table 3, entries 1-2 and 3-4), but the reverse is true in diethyl ether (entries 5-6). Also the dramatic fall in *ee* observed on switching from **4** to **3** in the gel medium (entries 3-4) and in the conventional organic solvent (entries 5-6) has no literature precedent. On the contrary, in an investigation of alkaloid organocatalysts with a phthalazine core, monomeric and dimeric derivatives displayed similar activity and asymmetric induction extent in toluene,[33] whereas, the use of **3** under the reported literature conditions (7 mol% alkaloid catalysts, 0.01 M concentration of **1** in diethyl ether) provides **2a** with 98% *ee*.[41]

The observation of a large enantioselectivity drop when the methanolysis promoted by **3** is performed in concentrated solutions, is similar to the findings with other chiral organocatalysts,[72] and is possibly related to the unsettled problem of how the reaction can proceed catalytically in **3** and with high asymmetric induction, even by forming the acidic hemiester product **2a**.[33,73,74] In any case, it is remarkable that such a negative concentration effect seems to afflict the dimeric organocatalyst **3** and not the monomeric analogue **4**, both in the conventional solvent and in the supramolecular gel-phase system. In this respect, it seems likely that the peculiar behaviour of **4** was a key factor in reaching the main goal of the present investigation, *i.e.* the attainment of synthetically useful asymmetric induction and yield levels in a concentrated reaction medium devoid of volatile solvents. On the other hand, comparison with the results obtained in pure IL confirms that the supramolecular structure of the gel phase was a second, essential factor for the accomplishment of the same task. Indeed, the ILGs could act as a sort of hydrophobic cage-like nanoreactor, in which only the right configuration of reagents, induced by effect of shape and size selectivity could favour the transition state achievement.[75] On the other hand, we have previously observed effects of supramolecular activation in organic catalysis, studying the base-induced elimination reaction of the tribromo-bis(phenyl-substituted)ethanes[68] or performing the mononuclear rearrangement of heterocycles.[67,76]

The asymmetric alcoholysis, using the anhydride **1** and the monomeric catalyst **4**, was also performed using BnOH and trifluoroethanol (TFE), to assess the effect deriving from a different alcohol structure.

Analysis of collected data shows that in IL solution yields increase in the order: **TFE** < **BnOH** ~ **MeOH** (entries 9, 7, 1); while in gel phase the following trend is observed: **TFE** < **MeOH** < **BnOH** (10, 3, 8). In both cases, the lower reactivity of **TFE** perfectly matches its lower nucleophlicity; nonetheless, in either medium this did not prevent the attainment of *ee* values comparable to those observed with MeOH under best gel conditions (entries 9 and 10 *vs.* entry 3).

Differently from data collected at 4 °C, at a lower temperature, the steric hindrance of the benzyl group does not adversely affect the activity of the catalyst.

Finally, to have information about the substrate influence, the reaction was also carried out using 1,2-cyclohexanedicarboxylic anhydride (**1d**) and *cis*-5-norbornene-*endo*-2,3-dicarboxylic anhydride (**1e**). Overall, yields in the order: **1d** < **1** < **1e** (entries 11, 1, 13 and 12, 3, 14 for ILs and gels), which appears to mirror the decrease in conformational flexibility of the substrate. Interestingly, the same factor also affects the stereoselectivity in IL solution, as accounted for by the fact that the highest *ee* value in this medium was obtained in the reaction of anhydride **1e**. Moreover, according to results collected in the case of **1**, it significantly increases on going from IL to gel phase.

To have mechanistic insights on the reaction, and to have information about the interaction of substrate and catalyst with the components of IL or gel phase, we tried to follow by ^{1}H NMR the methanolysis of **1**, in the presence of the dimeric catalyst **3**. Unfortunately, in both media, the signals of substrate and catalyst were difficult to spot, due to their broadening and merging with the overwhelming resonances from the surrounding matrix. To overcome this problem, we prepared a $CDCl_3$ solution of **[bmim][NTf$_2$]**, containing the other reactants at the suitable molar ratio (see Experimental Section), and monitored the reaction progress by ^{1}H NMR. The measurements showed a gradual decrease of the signal of the olefinic protons of the anhydride **1** (5.93 ppm) and a concomitant increase of that due to the olefinic protons of the hemiester **2a** (5.63 ppm, see Figure S4), thereby confirming the formation of the target product also under $CDCl_3$-diluted conditions.

With the above information in mind, we searched next for any anhydride-IL, catalyst-IL and catalyst-MeOH interactions in the same IL-$CDCl_3$ medium (Figure S5, S6 and S7). Interestingly, the addition of the anhydride to **[bmim][NTf$_2$]** solution induces a shielding effect on H2 of the imidazolium ion ($\Delta\delta$ = 0.05 ppm; Figure S5), which can provide some supporting evidence to the hypothesis about the ability of the IL cation to assist the opening of the anhydride via hydrogen bond formation (see above).

Moreover, the addition of MeOH to the solution containing catalyst **3** induces a shielding effect of the proton in the *ortho*-position to the nitrogen of the quinidine unit (8.65 ppm, Figure S7). Such a shielding effect increases as a function of the MeOH amount ($\Delta\delta$ = 0.05 and 0.12 ppm in the presence of 50 μL and 200 μL of MeOH, respectively) and could be a clear indication of interaction between the catalyst and the nucleophile.

On the contrary, attempts to identify substrate-catalyst and product-catalyst interactions, also using 2D NMR investigation, did not give useful information. On this ground, we suppose that the reaction proceeds through a general base catalysed mechanism, in which the IL anion-MeOH and catalyst-MeOH interactions induce an increase in the alcohol nucleophilicity and thus promote the progress of the non-stereoselective and stereoselective reaction, respectively. In addition, the good *ee* values recorded, above all in the gel phase, can be considered as the result of the action of the "asymmetric environment" that becomes gradually more important in a condensed phase, like the gel one, which significantly slows down both diffusion and conformational exchanges rates. This latter hypothesis could also explain why the best results in terms of activity, as well as enantioselectivity, were detected in the presence of the more flexible monomeric catalyst **4** that to a higher extent should be affected by the action of the condensed phase.

Conclusions

ILs and supramolecular ILGs allowed to perform the enantioselective desymmetrization of the cyclic anhydride **1** achieving good yields and, in the case of the gel medium, with good enantiomeric excess. This is one of the first examples for the study of the selected reaction in IL solution and to the best of our knowledge, it is the only one performed in a supramolecular ILG phase.

All the reaction variables examined in this study appear to influence the reaction outcome. In general, the reactivity increased on going from organic solvents, to ILs and, eventually, to gels. The reaction seems driven by the hydrogen bond donor or accepting ability in ILs, while in the gel phase it is favoured by a more flexible network. Interestingly, opposite trends, in dependence of the IL nature, were observed if the reaction was carried out in IL solution or in the corresponding gel phase.

The highest yield and *ee* values were achieved in the confined medium of ILG matrix, thus underlining the importance of supramolecular interactions for the stereoselective outcome of the process. In particular, the organized structure of the gel phase, acting as a cage-like nanoreactor, plays a pivotal role in determining performance of the chiral catalysts both in terms of activity and stereoselectivity.

Overall, the findings of this study encourage the application of supramolecular ILGs in the catalytic field. ILGs can represent an evolution of ILs as new reaction media and, like ILs, can improve the efficiency of synthetic organic processes.

Experimental section

[*p*-C_{12}im][Edta]$_2$[58] and the quinidine derivatives **4**[59] and **3**[77] were synthesized as previously reported.

cis-1,2,3,6-tetrahydrophthalic anhydride (**1**), 1,2-cyclohexanedicarboxylic anhydride (**1d**), *cis*-5-Norbornene-*endo*-2,3-dicarboxylic anhydride (**1e**), dry methanol, 1-octanol, benzyl alcohol, trifluoroethanol, diethyl ether were analytical reagents purchased from commercial sources and used as received.

ILs such as [bmim][BF_4], [bmim][PF_6], [bmim][NTf_2], [bmpip][NTf_2] and [bmpyrr][NTf_2] were purchased from commercial sources and used as received, while [bm_2im][NTf_2], [bmim][SbF_6], [bEt_3N][NTf_2] were prepared and purified according to the reported procedures.[78] All ILs were dried on high vacuum and stored in desiccator.

Temperature control: reaction temperature was ensured using a Thermo Haake EK45 immersion cooler with an open bath circulator, equipped with a water/ethylene glycol mixture bath.

Reaction time was determined after disappearance of the substrate on TLC plate.

Reaction conditions in IL solutions

In a 4 mL screw-capped vial, the anhydride (16 mg, 0.1 mmol) was dissolved in 500 μL of the selected IL. After the obtainment of a clear solution, the proper alcohol was added to the mixture - 50 μL (1.2 mmol, 12 equiv.) or 200 μL (4.9 mmol, 48 equiv.) in case of MeOH. When required, also 5 or 2.5 mol % of organocatalyst were added to the reaction mixture, that was stirred for 24 h, at 4 °C or for 48 h, at -30 °C.

Then, the product was extracted from IL phase with diethyl ether monitoring through TLC the disappearance of the product in diethyl ether solution. The diethyl ether was subsequently removed with a rotary evaporator, and the reaction yield was determined after the purification of the crude product by flash chromatography (SiO_2, petroleum ether: AcOEt = 3:1). A viscous oil that solidified on standing was obtained.

After dissolution in isopropanol (IPA, 1 mL), the enantiomeric composition of the sample was determined by HPLC analysis (210 nm, Chiralpack AS-H, flow of 0.5 mL/min, eluent formed by n-hexane: isopropanol = 70: 30 and 0.1% trifluoroacetic acid): t_{minor} = 8.7 min; t_{major} = 9.4 min, for hemiester **2a**.

Reaction conditions in gel phases

Supramolecular gels of 5 wt % of gelator, **[*p*-C_{12}im]$_2$[Edta]**, were prepared in a screw-capped vial of 4 mL in a total amount of 500 mg of the desired IL. The mixture was heated at 90 °C in an oil bath until a clear solution was obtained. Then the vial was stored at 4 °C overnight to give rise to gel phase formation.

The suitable amount of alcohol, catalyst and the anhydride, previously grounded, were cast on the top of gel phase and the vial was stored at 4 or -30 °C for the reaction time. Then, the reaction product was extracted from gel phase with diethyl ether monitoring through TLC the disappearance of the product in diethyl ether solution. Finally, even for reactions in gel phase, the same procedure described above was followed to obtain yield and enantiomeric excess.

NMR measurements

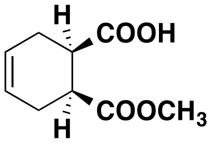
^{1}H and ^{13}C NMR spectra were recorded on a 300 MHz spectrometer. Chemical shifts were reported relative to $SiMe_4$.

Typical samples for NMR measurements in pure ILs were prepared using 500 mg of IL and adding 50 μL or 200 μL of MeOH, DMSO[d_6] was used as internal standard and 64 scans were required to record spectra.

To detect the NMR signals of all species involved in the reaction, kinetic measurements were carried out in $CDCl_3$ mimicking the real reaction media. In particular, 0.1 mmol of anhydride were dissolved in 750 μL of $CDCl_3$, adding 50 mg of IL, 2.5 mol % of catalyst and 50 μL of MeOH. NMR spectra of IL in presence of anhydride and of catalyst in presence of MeOH in $CDCl_3$ were studied using the same amounts of reagents used for the kinetic experiment. All measurements required at least 64 scans.

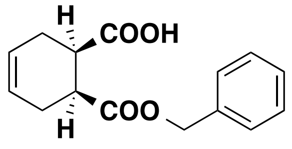
Products characterization

Hemiesters obtained are known compounds and have been previously reported and characterized.[32,69]



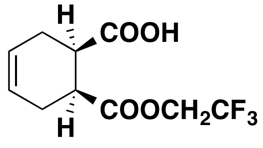
2a

^{1}H NMR, CDCl$_3$ δ (ppm): 2.42 (m, 2H), 2.57 (m, 2H), 3.10 (m, 2H), 3.72 (s, 3H), 5.70 (bs, 2H). ^{13}C[^{1}H]NMR, CDCl$_3$ δ (ppm): 25.5, 25.7, 39.5, 39.6, 51.9, 125.1, 125.2, 173.7, 179.4. HPLC analysis (210 nm, Chiralpack AS-H, flow of 0.5 mL/min, eluent formed by n-hexane: isopropanol = 70: 30 and 0.1% trifluoroacetic acid): t_{minor} = 8.7 min; t_{major} = 9.4 min.



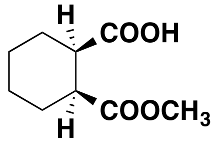
2b

^{1}H NMR, CDCl$_3$ δ (ppm): 2.40 (m, 2H), 2.60 (m, 2H), 3.11 (m, 2H), 5.15 (dd, J_1= 15 Hz J_2= 12 Hz, 2H), 5.69 (bs, 2H), 7.33 (m, 5H). ^{13}C[^{1}H]NMR, CDCl$_3$ δ (ppm): 25.6, 25.8, 39.4, 39.5, 66.4, 125.1, 125.2, 128.0, 128.1, 128.5, 135.8, 173.1, 178.9. HPLC analysis (210 nm, Chiralpack AS-H, flow of 0.3 mL/min, eluent formed by n-hexane: isopropanol = 80: 20 and 0.1% trifluoroacetic acid): t_{minor} = 20 min; t_{major} = 22 min.



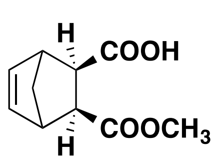
2c

^{1}H NMR, CDCl$_3$ δ (ppm): 2.41 (m, 2H), 2.60 (m, 2H), 3.13 (m, 2H), 4.47 (m, 2H), 5.70 (bs, 2H). ^{13}C[^{1}H]NMR, CDCl$_3$ δ (ppm): 25.4, 30.2, 39.2, 39.3, 60.3, 60.8, 124.7, 125.0, 165.9, 171.6. HPLC analysis (210 nm, Chiralpack AS-H, flow of 0.3 mL/min, eluent formed by n-hexane: isopropanol = 80: 20 and 0.1% trifluoroacetic acid): t_{minor} = 14.5 min; t_{major} = 15.5 min.



2d

^{1}H NMR, CDCl$_3$ δ (ppm): 1.44 (m, 4 H); 1.76 (m, 2H), 2.02 (m, 2H), 2.85 (m, 2H), 3.68 (s, 3H). ^{13}C[^{1}H]NMR, CDCl$_3$ δ (ppm): 23.6, 23.8, 25.9, 26.3, 42.4, 42.5, 51.7, 174.1, 179.9. HPLC analysis (210 nm, Chiralpack AD-H, flow of 0.5 mL/min, eluent formed by n-hexane: isopropanol = 80: 20 and 0.1% trifluoroacetic acid): t_{minor} = 10.6 min; t_{major} = 11.5 min.



2e

^{1}H NMR, CDCl$_3$ δ (ppm): 1.33 (d, J_1 = 9 Hz, 1H); 1.48 (d, J_1 = 9 Hz, 1H), 3.18 (d, J_1 = 9 Hz, 2H), 3.31 (dd, J_1 = 9 Hz, J_2 = 3 Hz, 2H), 3.60 (s, 3H), 6.26 (m, 2H). ^{13}C[^{1}H]NMR, Acetone-d6 δ (ppm): 45.9, 46.4, 47.5, 47.6, 48.1, 50.4, 117.9, 122.2, 133.9, 135.3. HPLC analysis (210 nm, Chiralpack AD-H, flow of 0.3 mL/min, eluent formed by n-hexane: isopropanol = 80: 20 and 0.1% trifluoroacetic acid): t_{minor} = 19.2 min; t_{major} = 21.4 min.

Supporting Information. Tables of ILs and gels properties, ^{1}H NMR spectra for mechanistic studies, hemiester spectra for product characterization and HPLC data.

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