Ionic Liquids, Supramolecular gels and Quinidine Organocatalysts: a new sustainable combination for the Asymmetric Alcoholysis of Cis-1,2,3,6-Tetrahydrophthalic Anhydride

Carla Rizzo,[†] Alessandro Mandoli,[§] Salvatore Marullo[†] and Francesca D'Anna.*[†]

[†] Dipartimento STEBICEF, Sez. Chimica, Università degli Studi di Palermo, Viale delle Scienze, Ed. 17, 90128 Palermo, Italy.

[§] Dipartimento di Chimica e Chimica Industriale, Università di Pisa, Via Giuseppe Moruzzi, n 13, 56124, Pisa, Italy.

Corresponding author E-mail: francesca.danna@unipa.it

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 environmental sustainability of the overall chemical process.

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

Even if the above parameters differently influence the reaction outcome, in all cases good yields were observed. In addition, the non-conventional reaction media demonstrated better performance than common organic solvents, applying only a small amount of solvent. Promising results in terms of yield and enantiomeric excess have been obtained in ionogel phase that seems

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

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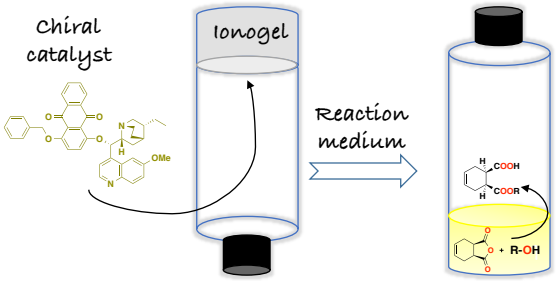


Keywords: ionic liquid, ionogel, supramolecular gel, quinidine organocatalyst, asymmetric alcoholysis of cyclic anhydride.

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 $\pi-\pi$ 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, and above all, in some industrial processes.[6-8]

Similarly, supramolecular interactions might favour the outcome of a given reaction[9] and it has been shown the advantage of using confined reaction media such as organo- and hydrogels.[10-12] 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.[13,14] When the gelation solvent is an IL, the material can be defined as ionogel.[15,16] These materials are easily tuneable and can be applied for several purposes spanning from the energetic field, where they have been used as conductive materials in electronic devices,[17,18] to the biological,[19,20] the antioxidant[21] and the environmental one.[22,23] In addition, a new class of alginate ionogels demonstrated high activity and promising recyclability in the Pd-catalyzed allylic substitution reaction.[24] However, ionogels and especially supramolecular ones have been scarcely tested so far in the catalytic field. Indeed, only recently a successful application of a Brønsted-acidic ionogel as heterogeneous catalyst for the synthesis of bis(indolyl)methanes has been reported.[25]

The catalytic desymmetrization of cyclic meso-anhydrides has been widely studied for the purpose of elucidating its mechanism[26-29] and as a benchmark of new enantioselective catalysts.[30-32] After the pioneering work of the groups of Oda and Aitken with native *Cinchona* alkaloids,[33,34] and the subsequent optimization by Bolm and co-workers,[35,36] also chiral Lewis acids,[37] monomeric and dimeric alkaloid derivatives,[38-40] bifunctional compounds,[41-51] and chiral Brønsted acids[52] 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. 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.[53] In addition, immobilized variants of the most effective *Cinchona* alkaloid organocatalysts were developed and showed good recyclability in some cases.[54-60]

In spite of these improvements, most of the examples where the reaction was used for preparing complex and biologically active chiral substances[31,32,61-66] adopted Bolm's optimized homogeneous conditions, or minor variations thereof.[46] Apart for the involvement of stoichiometric amounts of quinine or quinidine, this protocol suffers from the fact that optimal results are obtained at low temperature (typically, between -20°C and -55°C) and in diluted solutions made of environmentally hazardous solvents (*e.g.* 0.01-0.05 M in the substrate, in toluene or toluene-CCl_4). Some of these problems appear to be lifted with more recent procedures, especially those based on sulphonamide or thiourea bifunctional organocatalysts.[40,42-44,46-51,67,68]

For these reasons, we decided to examine if the use of ILs or ionogel could provide synthetically useful enantioselectivity levels under more environmentally benign conditions. In this regard, it is worth noting that ILs are well established solvents for acylation reactions,[69-75] and that ionogel 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 in the literature.

Results and discussion

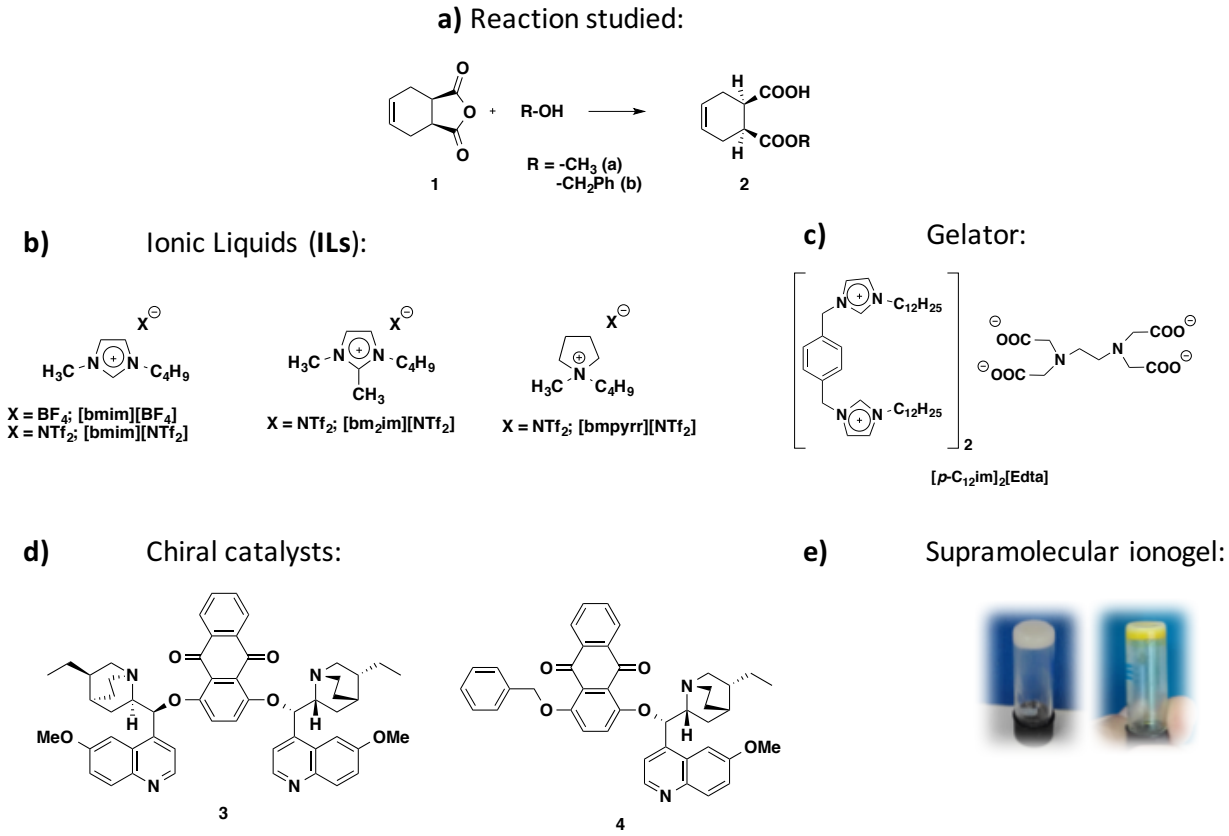
In order to tackle the goal stated above, we focused the attention on the asymmetric alcoholysis of *cis*-1,2,3,6-tetrahydrophthalic anhydride (**1**) as a typical cyclic *meso*-substrate and precursor to the synthetically valuable chiral hemiesters **2a** and **2b** (Scheme 1a).[51,63-66,68,76-78]

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 ionogels.

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 eco-friendly compounds. Because dicationic organic salts can satisfy such a requests,[79] di-3,3'-di-*n*-dodecyl-1,1'-(1,4-phenylenedimethylene)diimidazolium ethylenediamine-tetraacetate, **[*p*-C_{12}im]$_2$[Edta]**, 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.[80]

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**[38,39] and its monomeric counterpart **4**[81] (Scheme 2d).

Because ILs may exert a catalytic effect in acylation reactions, even when devoid of task-specific groups,[82-85] before addressing the issue of stereoselectivity, it became important to evaluate the behaviour of **1** in the neat IL or ionogel 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 ionogel 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 the cation moiety of the solvent, by comparing the results in three different ILs containing a common bis-(trifluoromethanesulfonyl)imide counter-ion. The set of solvents selected for this aim included the aromatic IL 1-butyl-3-methyl-imidazolium *N*,*N*-bis-(trifluoromethanesulfonyl)imide (**[bmim][NTf_2]**), the aliphatic IL *N*-butyl-*N*-methyl-pyrrolidinium *N*,*N*-bis-(trifluoromethanesulfonyl)imide (**[bmpyrr][NTf_2]**), and 1-butyl-2,3-dimethyl-imidazolium *N*,*N*-bis-(trifluoromethanesulfonyl)imide

(**[bm$_2$im][NTf$_2$]**), an aromatic IL that, due to the absence of the proton on the 2-position of the imidazolium ring, is known to possess a lower hydrogen bond donor ability than the previous ones.[86] Moreover, we studied the effect of the IL anion by performing the reactions in 1-butyl-3-methyl-imidazolium tetrafluoroborate (**[bmim][BF$_4$]**), an imidazolium IL bearing a more coordinating fragment.

Initially, the model reaction of Scheme 1a was carried out 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 **1**. 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.[27,39]

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_2O 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, β, and π^* . As discussed in the following, the latter represent the ability of the medium to behave as a donor or acceptor of hydrogen bonds and to interact with solutes through dipolar effects, respectively.[87]

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.

Solvent[a]	E_N^T[b]	α[b]	β[b]	π^*[b]	*MeOH* (μL)	*Yield* (%)[e]
[bmim][BF_4]	0.670	0.627	0.376	1.047	200[c]	95
					50[d]	44
[bmim][NTf_2]	0.644	0.617	0.243	0.984	200[c]	71
					50[d]	15
[bm_2im][NTf_2]	0.542	0.381	0.239	1.010	200[c]	51
					50[d]	37
[bmpyrr][NTf_2]	0.544	0.427	0.252	0.954	200[c]	51
					50[d]	39
1-Octanol	0.543	0.77	0.81	0.400	200[c]	<5
Diethyl ether	0.117	0.00	0.47	0.270	200[c]	36
					50[d]	22

[a] Runs with 0.1 mmol of **1** and 500 μL of solvent; [b] Values from references[88 89 90]; [c] (4.9 mmol, 48 equiv.); [d](1.2 mmol, 12 equiv.); [e] Isolated yield after flash chromatography; yield values were reproducible within 4%.

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,[31,32] 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.

Yields obtained, using 200 μL of MeOH, decreased in dependence of reaction solvent in the following order: **[bmim][BF_4]** > **[bmim][NTf_2]** > **[bm_2im][NTf_2]** ≈ **[bmpyrr][NTf_2]** > diethyl ether > 1-octanol.

These results clearly show larger yields for the reactions in ILs with respect to those carried out in conventional reaction media, with the former ranging between 51% and 95% even in the absence of any added catalysts.

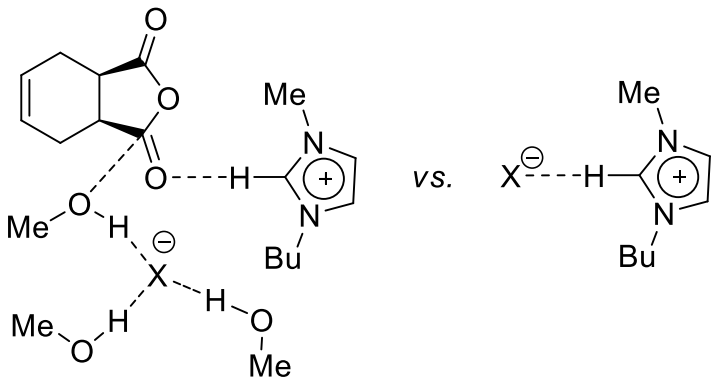
In general, higher yields were obtained using a larger excess of MeOH. Furthermore, lowering the amount of the alcohol to 50 μL led to a less significant effect of IL structure. Also in this case higher yields were obtained in IL than in conventional solvents, but with the only exception of **[bmim][NTf_2]**, now the results were rather independent on IL nature.

In order to explain these 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 cycle 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 the most viscous medium, **[bmim][BF_4]** (η= 233 cP).[91] Moreover, changes in yields observed as function of MeOH amount proved comparable in **[bmim][BF_4]** and in the least viscous solvent in the series, **[bmim][NTf_2]** (η=52 cP).[91] 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.

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**.

In order to gain a deeper understanding of the trends above, we attempted a QSAR analysis of the data summarized in Table 1. In general, no significant correlation could be found between the yield values and any single parameter of the corresponding reaction medium (*i.e.* E^T_N, α, β, or π^* in Table 1 and Figure S1). On a contrary, for all the solvents, except 1-octanol, a good agreement was obtained between the experimental yield values and those calculated by assuming a pseudo-first order kinetic equation and a linear relationship[87] between the logarithm of the apparent kinetic constant k_i' in the solvent *i* and the α_i and β_i parameters of the same medium (eq. 1):

$$\ln k_i' = a \cdot \alpha_i + b \cdot \beta_i + c \qquad \text{eq. 1}$$

In particular, when the analysis was performed using data collected in the presence of 200 μL of MeOH the non-linear regression model, with *a*, *b*, and *c* treated as adjustable coefficients (see SI for details) provided a good correspondence (R^2 = 0.974; Figure 1) between the predicted and the experimental yield values. In this case, the results of the fitting evidenced significant positive contributions deriving from both the solvent ability to give (*a* = 3.30 ± 0.35) and to accept hydrogen bond (*b* = 4.24 ± 0.84).

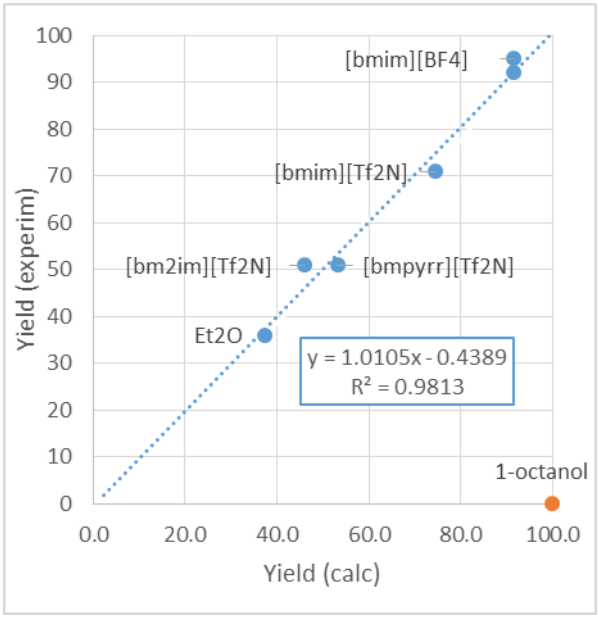


Figure 1: correlation between experimental and calculated yield values based on solvent parameters α and β, using 200 μL of MeOH.

Conversely, no clear correlation was found when taking in consideration the data obtained in the presence of a smaller amount of MeOH (Figure S3), thereby suggesting that under these conditions some other specific property of the medium is going to play an important role.

The results above 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.[92,93]

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

Taking in consideration [NTf_2]-based ILs, the reactivity trend perfectly matches the series of hydrogen bond donor ability (α) of ILs.[88] Indeed, the main influence seems due to the different nature of IL's cation, as the imidazolium ones show the best catalytic performance thanks to the presence of the most acidic protons. The further decrease of the α values, on going from **[bmim][NTf_2]** down to **[bm_2im][NTf_2]** and **[bmpyrr][NTf_2]**, corresponds to a concomitant decrease in reaction yield.

The hypotheses above 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 ionogels 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. 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 2 (Table S2).

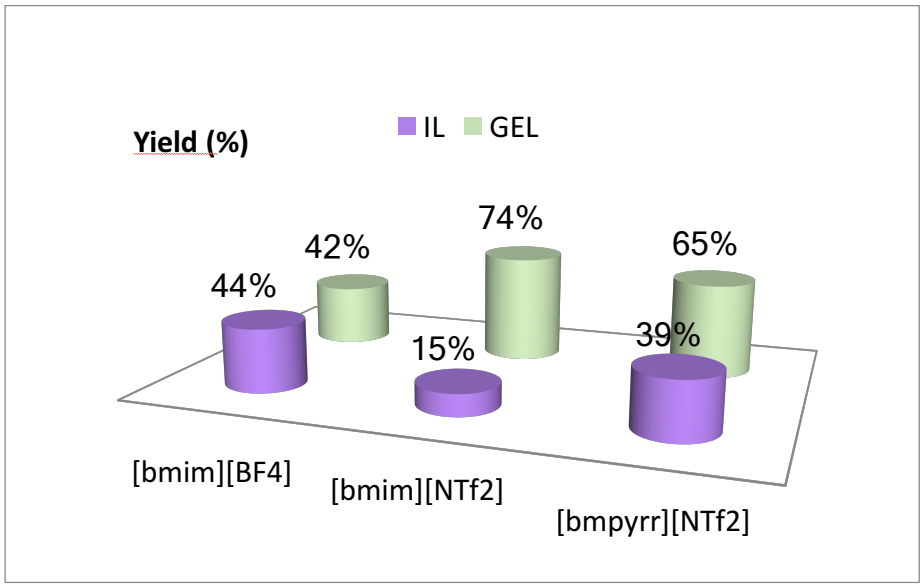


Figure 2: yield of **2a** obtained in solution (purple) and in the gel phase (green), at 4 °C for 24 h (isolated yields after flash chromatography; yield values were reproducible within 4%).

Interestingly, in all of the examined ionogels 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, ionogels 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.[80] 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, 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 ionogel 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.

Reaction medium[a]	*Catalyst (mol%)*	*Alcohol*	*Product*	*Yield (%)*[b]
IL	none	MeOH	**2a**	15
	4 (5)	MeOH	**2a**	47
	none	BnOH	**2b**	18
	4 (5)	BnOH	**2b**	40
GEL	none	MeOH	**2a**	74
	4 (5)	MeOH	**2a**	61
	none	BnOH	**2b**	43
	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%.

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, and from 18% to 40%, for reaction with BnOH.

On the contrary, the catalytic effect of **4** was smoothed in gel phase, where we observed a moderate increase in yield for the reaction of BnOH (43% to 52%) but, actually, a slight decrease with MeOH (74% to 61%). 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, while they drastically decreased in gel phases when benzyl alcohol instead of MeOH was used. 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.[47]

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,[31,32] 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 **2a** obtained in reactions carried out for 48 h at -30 °C .

Reaction medium[a]	*Catalyst (mol%)*	*Yield (%)*[b]	*ee (%)*[c]
IL	**4** (5)	38	22
	3 (2.5)	88	24
GEL	**4** (5)	78	81
	3 (2.5)	92	9
Diethyl ether	**4** (5)	53	83
	3 (2.5)	20	48

[a] Runs with 0.1 mmol of **1**, 50 μL (1.2 mmol, 12 equiv.) of MeOH, 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%; [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[94] and

in hydrogels, where the chirality was induced by chiral nanomaterials,[95] but never in ionogels. Taking into account the observations at the beginning of this section, the findings above confirmed the possibility to shut-down the not-stereoselective background process by cooling, which in turn allowed the reaction to be largely funnelled through the alkaloid-mediated enantioselective route.

Examination of Table 3 reveals further aspects, some of which could be hardly anticipated on the basis of literature findings and the results discussed in the previous sections. In particular, 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, but the reverse is true in diethyl ether. Also the dramatic fall in *ee* observed on switching from **4** to **3** in the gel medium and in the conventional organic solvent 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,[27] 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*.[38]

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,[46] 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**.[27,30,96] 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 and totally

unanticipated 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.

Conclusions

ILs and supramolecular ionogels allowed to perform the enantioselective desymmetrization of the cyclic anhydride **1** with 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 ionogel phase.

All the reaction variables examined in this study appear to influence the reaction outcome, but in most cases good to excellent yields were observed. In general, the more organized was the system the higher was the reactivity that, in fact, 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 ionogel matrix, thus underlining the importance of supramolecular interactions for the stereoselective outcome of the process.

Overall, the findings of this study encourage the application of supramolecular ionogels in the hitherto scarcely explored catalytic field. Ionogels can represent an evolution of ILs as new

reaction media and, like ILs, may prove helpful for diminishing the environmental impact of synthetic organic processes. In this respect, the attainment of good yield and enantioselectivity values for the methanolysis of **1** in a concentrated ionogel phase represents a first step towards this goal.

Experimental section

[*p*-C_{12}im][Edta]$_2$[80] and the quinidine derivatives **4**[81] and **3**[97] were synthesized as previously reported.

cis-1,2,3,6-tetrahydrophthalic anhydride, dry methanol, 1-octanol, benzyl alcohol, diethyl ether were analytical reagents purchased from commercial sources and used as received.

ILs such as [bmim][BF_4], [bmim][NTf_2] and [bmpyrr][NTf_2] were purchased from commercial sources and used as received, while [bm_2im][NTf_2] was prepared and purified according to the reported procedures.[98] All ILs were dried on high vacuum and stored in desiccator.

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, dry methanol was added to the mixture -50 μL (1.2 mmol, 12 equiv.) or 200 μL (4.9 mmol, 48 equiv.). When required, also 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 isopropyl alcohol (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.

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 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.

Supporting Information. Tables of ILs and gels properties, QSAR demonstration, graphs of fitting models based on solvent parameters

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References

(1) E. N. Jacobsen; A. Pfaltz; H.Yamamoto: *Comprehensive Asymmetric Catalysis*; Springer: New York, 1999; Vol. I-III.

(2) Anastas, P.; Eghbali, N. Green Chemistry: Principles and Practice. *Chem. Soc. Rev.* **2010**, *39*, 301-312.

(3) Rogers, R. D.; Seddon, K. R. Ionic Liquids--Solvents of the Future? *Science* **2003**, *302*, 792.

(4) Vekariya, R. L. A review of ionic liquids: Applications towards catalytic organic transformations. *J. Mol. Liq.* **2017**, *227*, 44-60.

(5) Dupont, J. On the solid, liquid and solution structural organization of imidazolium ionic liquids. *J. Braz. Chem. Soc.* **2004**, *15*, 341-350.

(6) D'Anna, F.; Marullo, S.; Vitale, P.; Rizzo, C.; Lo Meo, P.; Noto, R. Ionic liquid binary mixtures: Promising reaction media for carbohydrate conversion into 5-hydroxymethylfurfural. *Applied Catalysis A: General* **2014**, *482*, 287-293.

(7) Plechkova, N. V.; Seddon, K. R. Applications of ionic liquids in the chemical industry. *Chem. Soc. Rev.* **2008**, *37*, 123-150.

(8) Rizzo, C.; D'Anna, F.; Noto, R. Functionalised diimidazolium salts: the anion effect on the catalytic ability. *RSC Adv.* **2016**, *6*, 58477-58484.

(9) Raynal, M.; Ballester, P.; Vidal-Ferran, A.; van Leeuwen, P. W. N. M. Supramolecular catalysis. Part 1: non-covalent interactions as a tool for building and modifying homogeneous catalysts. *Chem. Soc. Rev.* **2014**, *43*, 1660-1733.

(10) Araújo, M.; Muñoz Capdevila, I.; Díaz-Oltra, S.; Escuder, B. Tandem Catalysis of an Aldol-'Click' Reaction System within a Molecular Hydrogel. *Molecules* **2016**, *21*.

(11) Escuder, B.; Rodriguez-Llansola, F.; Miravet, J. F. Supramolecular gels as active media for organic reactions and catalysis. *New J. Chem.* **2010**, *34*, 1044-1054.

(12) Fang, W.; Zhang, Y.; Wu, J.; Liu, C.; Zhu, H.; Tu, T. Recent Advances in Supramolecular Gels and Catalysis. *Chemistry – An Asian Journal* **2018**, *13*, 712-729.

(13) Sangeetha, N. M.; Maitra, U. Supramolecular gels: Functions and uses. *Chem. Soc. Rev.* **2005**, *34*, 821-836.

(14) Terech, P.; Weiss, R. G. Low Molecular Mass Gelators of Organic Liquids and the Properties of Their Gels. *Chem. Rev. (Washington, DC, U. S.)* **1997**, *97*, 3133-3160.

(15) Le Bideau, J.; Viau, L.; Vioux, A. Ionogels, ionic liquid based hybrid materials. *Chem. Soc. Rev.* **2011**, *40*, 907-925.

(16) Marr, P. C.; Marr, A. C. Ionic liquid gel materials: applications in green and sustainable chemistry. *Green Chem.* **2016**, *18*, 105-128.

(17) Sasada, Y.; Ichinoi, R.; Oyaizu, K.; Nishide, H. Supramolecular Organic Radical Gels Formed with 2,2,6,6-Tetramethylpiperidin-1-oxyl-Substituted Cyclohexanediamines: A Very Efficient Charge-Transporting and -Storable Soft Material. *Chem. Mater.* **2017**, *29*, 5942-5947.

(18) Yu, Q.; Wu, Y.; Li, D.; Cai, M.; Zhou, F.; Liu, W. Supramolecular ionogel lubricants with imidazolium-based ionic liquids bearing the urea group as gelator. *J. Colloid Interface Sci.* **2017**, *487*, 130-140.

(19) Rizzo, C.; Arrigo, R.; Dintcheva Nadka, T.; Gallo, G.; Giannici, F.; Noto, R.; Sutera, A.; Vitale, P.; D'Anna, F. Supramolecular Hydro- and Ionogels: A Study of Their Properties and Antibacterial Activity. *Chem. Eur. J.* **2017**, *23*, 16297-16311.

(20) Tang, B.; Schneiderman, D. K.; Zare Bidoky, F.; Frisbie, C. D.; Lodge, T. P. Printable, Degradable, and Biocompatible Ion Gels from a Renewable ABA Triblock Polyester and a Low Toxicity Ionic Liquid. *ACS Macro Letters* **2017**, *6*, 1083-1088.

(21) Rizzo, C.; Arcudi, F.; Đorđević, L.; Dintcheva, N. T.; Noto, R.; D'Anna, F.; Prato, M. Nitrogen-Doped Carbon Nanodots-Ionogels: Preparation, Characterization, and Radical Scavenging Activity. *ACS Nano* **2018**, *12*, 1296-1305.

(22) Marullo, S.; Rizzo, C.; Dintcheva, N. T.; Giannici, F.; D'Anna, F. Ionic liquids gels: Soft materials for environmental remediation. *J. Colloid Interface Sci.* **2018**, *517*, 182-193.

(23) Xia, L.; Cui, Q.; Suo, X.; Li, Y.; Cui, X.; Yang, Q.; Xu, J.; Yang, Y.; Xing, H. Efficient, Selective, and Reversible SO2 Capture with Highly Crosslinked Ionic Microgels via a Selective Swelling Mechanism. *Adv. Funct. Mater.* **2018**, *28*, 1704292.

(24) Vittoz, P.-F.; El Siblani, H.; Bruma, A.; Rigaud, B.; Sauvage, X.; Fernandez, C.; Vicente, A.; Barrier, N.; Malo, S.; Levillain, J.; Gaumont, A.-C.; Dez, I. Insight in the Alginate Pd-Ionogels—Application to the Tsuji–Trost Reaction. *ACS Sustainable Chemistry & Engineering* **2018**, *6*, 5192-5197.

(25) Tran Phuong, H.; Nguyen Xuan-Trang, T.; Chau Duy-Khiem, N. A Brønsted-Acidic Ionic Liquid Gel as an Efficient and Recyclable Heterogeneous Catalyst for the Synthesis of Bis(indolyl)methanes under Solvent-Free Sonication. *Asian Journal of Organic Chemistry* **2017**, *7*, 232-239.

(26) Dedeoglu, B.; Catak, S.; Houk, K. N.; Aviyente, V. A Theoretical Study of the Mechanism of the Desymmetrization of Cyclic meso-Anhydrides by Chiral Amino Alcohols. *ChemCatChem* **2010**, *2*, 1122-1129.

(27) Balzano, F.; Jumde Ravindra, P.; Mandoli, A.; Masi, S.; Pini, D.; Uccello-Barretta, G. Mono- and bis-quinidine organocatalysts in the asymmetric methanolysis of cis-1,2,3,6-tetrahydrophthalic anhydride: A conformational and mechanistic NMR study. *Chirality* **2011**, *23*, 784-795.

(28) Yang, H.; Wong, M. W. Oxyanion Hole Stabilization by C–H···O Interaction in a Transition State—A Three-Point Interaction Model for Cinchona Alkaloid-Catalyzed Asymmetric Methanolysis of meso-Cyclic Anhydrides. *J. Am. Chem. Soc.* **2013**, *135*, 5808-5818.

(29) Blise, K.; Cvitkovic, M. W.; Gibbs, N. J.; Roberts, S. F.; Whitaker, R. M.; Hofmeister, G. E.; Kohen, D. A Theoretical Mechanistic Study of the Asymmetric Desymmetrization of a Cyclic meso-Anhydride by a Bifunctional Quinine Sulfonamide Organocatalyst. *J. Org. Chem.* **2017**, *82*, 1347-1355.

(30) Spivey, A. C.; Andrews, B. I. Catalysis of the asymmetric desymmetrization of cyclic anhydrides by nucleophilic ring-opening with alcohols. *Angew. Chem., Int. Ed.* **2001**, *40*, 3131-3134.

(31) Chen, Y.; McDaid, P.; Deng, L. Asymmetric Alcoholysis of Cyclic Anhydrides. *Chem. Rev. (Washington, DC, U. S.)* **2003**, *103*, 2965-2984.

(32) Atodiresei, I.; Schiffers, I.; Bolm, C. Stereoselective Anhydride Openings. *Chem. Rev. (Washington, DC, U. S.)* **2007**, *107*, 5683-5712.

(33) Hiratake, J.; Inagaki, M.; Yamamoto, Y.; Oda, J. *J. Chem. Soc., Perkin Trans.* **1987**, 1053-1058.

(34) Aitken, R. A.; Gopal, J. *Tetrahedron: Asymmetry* **1990**, *1*, 517-520.

(35) Bolm, C.; Gerlach, A.; Dinter, C. L. Simple and highly enantioselective nonenzymic ring opening of cyclic prochiral anhydrides. *Synlett* **1999**, 195-196.

(36) Bolm, C.; Schiffers, I.; Dinter, C. L.; Gerlach, A. Practical and Highly Enantioselective Ring Opening of Cyclic Meso-Anhydrides Mediated by Cinchona Alkaloids. *J. Org. Chem.* **2000**, *65*, 6984-6991.

(37) Seebach, D.; Jaeschke, G.; Wang, Y. M. Highly enantioselective opening of cyclic meso-anhydrides to isopropyl hemiesters with diisopropoxytitanium TADDOLates. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2395-2396.

(38) Chen, Y.; Tian, S.-K.; Deng, L. A Highly Enantioselective Catalytic Desymmetrization of Cyclic Anhydrides with Modified Cinchona Alkaloids. *J. Am. Chem. Soc.* **2000**, *122*, 9542-9543.

(39) Li, H.; Liu, X.; Wu, F.; Tang, L.; Deng, L. Elucidation of the active conformation of cinchona alkaloid catalyst and chemical mechanism of alcoholysis of meso anhydrides. *Proceedings of the National Academy of Sciences* **2010**, *107*, 20625.

(40) Peschiulli, A.; Gun'ko, Y.; Connon, S. J. Highly enantioselective desymmetrization of meso anhydrides by a bifunctional thiourea-based organocatalyst at low catalyst loadings and room temperature. *J. Org. Chem.* **2008**, *73*, 2454-2457.

(41) Uozumi, Y.; Yasoshima, K.; Miyachi, T.; Nagai, S.-i. Enantioselective desymmetrization of meso-cyclic anhydrides catalyzed by hexahydro-1H-pyrrolo[1,2-c]imidazolones. *Tetrahedron Lett.* **2001**, *42*, 411-414.

(42) Rho, H. S.; Oh, S. H.; Lee, J. W.; Lee, J. Y.; Chin, J.; Song, C. E. Bifunctional organocatalyst for methanolytic desymmetrization of cyclic anhydrides: increasing enantioselectivity by catalyst dilution. *Chem. Commun.* **2008**, 1208-1210.

(43) Oh, S. H.; Rho, H. S.; Lee, J. W.; Lee, J. E.; Youk, S. H.; Chin, J.; Song, C. E. A Highly reactive and enantioselective bifunctional organocatalyst for the methanolytic desymmetrization of cyclic anhydrides: prevention of catalyst aggregation. *Angew. Chem., Int. Ed.* **2008**, *47*, 7872-7875.

(44) Wang, S. X.; Chen, F. E. A Novel Cost-Effective Thiourea Bifunctional Organocatalyst for Highly Enantioselective Alcoholysis of meso-Cyclic Anhydrides: Enhanced Enantioselectivity by Configuration Inversion. *Adv. Synth. Catal.* **2009**, *351*, 547-552.

(45) Wakchaure, V. N.; List, B. A New Structural Motif for Bifunctional Bronsted Acid/Base Organocatalysis. *Angew. Chem., Int. Ed.* **2010**, *49*, 4136-4139, S4136/4131-S4136/4147.

(46) Schmitt, E.; Schiffers, I.; Bolm, C. Highly enantioselective desymmetrizations of meso-anhydrides. *Tetrahedron* **2010**, *66*, 6349-6357.

(47) Manzano, R.; Andrés, J. M.; Muruzábal, M.-D.; Pedrosa, R. Synthesis of both Enantiomers of Hemiesters by Enantioselective Methanolysis of Meso Cyclic Anhydrides Catalyzed by α-Amino Acid-Derived Chiral Thioureas. *J. Org. Chem.* **2010**, *75*, 5417-5420.

(48) Yang, H.-J.; Xiong, F.-J.; Li, J.; Chen, F.-E. A family of novel bifunctional organocatalysts: Highly enantioselective alcoholysis of meso cyclic anhydrides and its application for synthesis of the key intermediate of P2X7 receptor antagonists. *Chin. Chem. Lett.* **2013**, *24*, 553-558.

(49) Yan, L. J.; Wang, H. F.; Chen, W. X.; Tao, Y.; Jin, K. J.; Chen, F. E. Development of Bifunctional Thiourea Organocatalysts Derived from a Chloramphenicol Base Scaffold and their

Use in the Enantioselective Alcoholysis of meso Cyclic Anhydrides. *ChemCatChem* **2016**, *8*, 2249-2253.

(50) Sano, S.; Kamura, M.; Nakamura, A.; Kitaike, S.; Nakao, M. Asymmetric synthesis of cis-4a,5,8,8a-tetrahydrophthalazin-1(2H)-one derivatives based on organocatalytic alcoholysis of cyclic dicarboxylic anhydride. *Heterocycles* **2016**, *93*, 391-398.

(51) Wang, H.; Yan, L.; Wu, Y.; Lu, Y.; Chen, F. Asymmetric Synthesis of Vitamin D3 Analogues: Organocatalytic Desymmetrization Approach toward the A-Ring Precursor of Calcifediol. *Org. Lett.* **2015**, *17*, 5452-5455.

(52) Yamada, K.-i.; Oonishi, A.; Kuroda, Y.; Harada, S.; Kiyama, H.; Yamaoka, Y.; Takasu, K. Desymmetrization of acid anhydride with asymmetric esterification catalyzed by chiral phosphoric acid. *Tetrahedron Lett.* **2016**, *57*, 4098-4100.

(53) Rantanen, T.; Schiffers, I.; Bolm, C. Solvent-Free Asymmetric Anhydride Opening in a Ball Mill. *Org. Process Res. Dev.* **2007**, *11*, 592-597.

(54) Bigi, F.; Carloni, S.; Maggi, R.; Mazzacani, A.; Sartori, G.; Tanzi, G. Homogeneous versus heterogeneous approach to the catalytic desymmetrisation of meso-anhydrides promoted by cinchona alkaloids. *J. Mol. Catal. A: Chem.* **2002**, *182-183*, 533-539.

(55) Woltinger, J.; Krimmer, H.-P.; Drauz, K. The potential of membrane reactors in the asymmetric opening of meso-anhydrides. *Tetrahedron Lett.* **2002**, *43*, 8531-8533.

(56) Kim, H. S.; Song, Y.-M.; Choi, J. S.; Yang, J. W.; Han, H. Heterogeneous organocatalysis for the asymmetric desymmetrization of meso-cyclic anhydrides using silica gel-supported bis-cinchona alkaloids. *Tetrahedron* **2004**, *60*, 12051-12057.

(57) Song, Y.-M.; Choi, J. S.; Yang, J. W.; Han, H. Silica gel-supported bis-cinchona alkaloid: a chiral catalyst for the heterogeneous asymmetric desymmetrization of meso-cyclic anhydrides. *Tetrahedron Lett.* **2004**, *45*, 3301-3304.

(58) Youk, S. H.; Oh, S. H.; Rho, H. S.; Lee, J. E.; Lee, J. W.; Song, C. E. A polymer-supported Cinchona-based bifunctional sulfonamidecatalyst: a highly enantioselective, recyclable heterogeneous organocatalyst. *Chem. Commun.* **2009**, 2220-2222.

(59) Gleeson, O.; Davies, G.-L.; Peschiulli, A.; Tekoriute, R.; Gun'ko, Y. K.; Connon, S. J. The immobilisation of chiral organocatalysts on magnetic nanoparticles: the support particle cannot always be considered inert. *Org. Biomol. Chem.* **2011**, *9*, 7929-7940.

(60) Jumde, R. P.; Di Pietro, A.; Manariti, A.; Mandoli, A. New Polymer-Supported Mono- and Bis-Cinchona Alkaloid Derivatives: Synthesis and Use in Asymmetric Organocatalyzed Reactions. *Chem. - Asian J.* **2015**, *10*, 397-404.

(61) Xiong, F.; Xiong, F. J.; Chen, W. X.; Jia, H. Q.; Chen, F. E. Highly Enantioselective Methanolysis of Meso-Cyclic Anhydride Mediated by Bifunctional Thiourea Cinchona Alkaloid Derivatives: Access to Asymmetric Total Synthesis of (+)-Biotin. *J. Heterocycl. Chem.* **2013**, *50*, 1078-1082.

(62) Huang, J.; Xiong, F.; Chen, F.-E. Total synthesis of (+)-biotin via a quinine-mediated asymmetric alcoholysis of meso-cyclic anhydride strategy. *Tetrahedron: Asymmetry* **2008**, *19*, 1436-1443.

(63) Henderson, A. R.; Stec, J.; Owen, D. R.; Whitby, R. J. The first total synthesis of (+)-mucosin. *Chem. Commun.* **2012**, *48*, 3409-3411.

(64) Bernardi, A.; Arosio, D.; Dellavecchia, D.; Micheli, F. Improved synthesis of both enantiomers of trans-cyclohex-4-ene-1,2-dicarboxylic acid. *Tetrahedron: Asymmetry* **1999**, *10*, 3403-3407.

(65) Doknic, D.; Abramo, M.; Sutkeviciute, I.; Reinhardt, A.; Guzzi, C.; Schlegel Mark, K.; Potenza, D.; Nieto Pedro, M.; Fieschi, F.; Seeberger Peter, H.; Bernardi, A. Synthesis and

Characterization of Linker-Armed Fucose-Based Glycomimetics. *Eur. J. Org. Chem.* **2013**, *2013*, 5303-5314.

(66) Campbell, C. L.; Hassler, C.; Ko, S. S.; Voss, M. E.; Guaciaro, M. A.; Carter, P. H.; Cherney, R. J. Enantioselective Synthesis of Benzyl (1S,2R,4R)-4-(tert-Butoxycarbonylamino)-2-(hydroxymethyl)cyclohexylcarbamate Using an Iodolactamization As the Key Step. *J. Org. Chem.* **2009**, *74*, 6368-6370.

(67) Gleeson, O.; Tekoriute, R.; Gun'ko, Y. K.; Connon, S. J. The first magnetic nanoparticle-supported chiral DMAP analogue: highly enantioselective acylation and excellent recyclability. *Chemistry* **2009**, *15*, 5669-5673.

(68) Gerfaud, T.; Xie, C.; Neuville, L.; Zhu, J. Protecting-Group-Free Total Synthesis of (E)- and (Z)-Alstoscholarine. *Angew. Chem., Int. Ed.* **2011**, *50*, 3954-3957.

(69) Fidale, L. C.; Possidonio, S.; El Seoud, O. A. Application of 1-Allyl-3-(1-butyl)imidazolium Chloride in the Synthesis of Cellulose Esters: Properties of the Ionic Liquid, and Comparison with Other Solvents. *Macromol. Biosci.* **2009**, *9*, 813-821.

(70) Jiang, D.; Wang, Y. Y.; Dai, L. Y. Esterification of alcohols with acetic anhydride in Bronsted acidic ionic liquids at room temperature. *React. Kinet. Catal. Lett.* **2008**, *93*, 257-263.

(71) Koehler, S.; Liebert, T.; Schoebitz, M.; Schaller, J.; Meister, F.; Guenther, W.; Heinze, T. Interactions of ionic liquids with polysaccharides 1. Unexpected acetylation of cellulose with 1-ethyl-3-methylimidazolium acetate. *Macromol. Rapid Commun.* **2007**, *28*, 2311-2317.

(72) Lafuente, L.; Diaz, G.; Bravo, R.; Ponzinibbio, A. Efficient and Selective N-, S- and O-Acetylation in TEAA Ionic Liquid as Green Solvent. Applications in Synthetic Carbohydrate Chemistry. *Lett. Org. Chem.* **2016**, *13*, 195-200.

(73) Lehmann, A.; Volkert, B. Preparing esters from high-amylose starch using ionic liquids as catalysts. *Carbohydr. Polym.* **2011**, *83*, 1529-1533.

(74) Liu, Y.; Liu, L.; Lu, Y.; Cai, Y.-Q. An imidazolium tosylate salt as efficient and recyclable catalyst for acetylation in an ionic liquid. *Monatsh. Chem.* **2008**, *139*, 633-638.

(75) Misuk, V.; Breuch, D.; Loewe, H. Paramagnetic ionic liquids as "liquid fixed-bed" catalysts in flow application. *Chem. Eng. J. (Amsterdam, Neth.)* **2011**, *173*, 536-540.

(76) Yun, S. Y.; Zheng, J. C.; Lee, D. Concise Synthesis of the Tricyclic Core of Platencin. *Angew. Chem., Int. Ed.* **2008**, *47*, 6201-6203.

(77) Houpis, I. N.; Molina, A.; Reamer, R. A.; Lynch, J. E.; Volante, R. P.; Reider, P. J. Towards the synthesis of HIV-protease inhibitors. Synthesis optically pure 3-carboxyl-decahydroisoquinolines. *Tetrahedron Lett.* **1993**, *34*, 2593-2596.

(78) Onogi, S.; Higashibayashi, S.; Sakurai, H. Microwave-assisted synthesis of methyl (1S,2R,4S,5S)-7-aza-5-hydroxybicyclo[2.2.1]heptane-2-carboxylate through unexpected stereoselective substitution reaction. *Tetrahedron Lett.* **2012**, *53*, 3710-3712.

(79) D'Anna, F.; Noto, R. Di- and Tricationic Organic Salts: An Overview of Their Properties and Applications. *Eur. J. Org. Chem.* **2014**, *2014*, 4201-4223.

(80) Rizzo, C.; D'Anna, F.; Noto, R.; Zhang, M.; Weiss, R. G. Insights into the Formation and Structures of Molecular Gels by Diimidazolium Salt Gelators in Ionic Liquids or “Normal” Solvents. *Chem. Eur. J.* **2016**, *22*, 11269-11282.

(81) Uccello Barretta, G.; Mandoli, A.; Balzano, F.; Aiello, F.; De Nicola, B.; Del Grande, A. Monomeric and Dimeric 9-O Anthraquinone and Phenanthryl Derivatives of Cinchona Alkaloids as Chiral Solvating Agents for the NMR Enantiodiscrimination of Chiral Hemiesters. *Chirality* **2015**, *27*, 693-699.

(82) Duan, Z.; Gu, Y.; Deng, Y. Neutral ionic liquid [BMIm]BF4 promoted highly selective esterification of tertiary alcohols by acetic anhydride. *J. Mol. Catal. A: Chem.* **2006**, *246*, 70-75.

(83) Chakraborti, A. K.; Roy, S. R. On Catalysis by Ionic Liquids. *J. Am. Chem. Soc.* **2009**, *131*, 6902-6903.

(84) Sarkar, A.; Roy, S. R.; Parikh, N.; Chakraborti, A. K. Nonsolvent Application of Ionic Liquids: Organo-Catalysis by 1-Alkyl-3-methylimidazolium Cation Based Room-Temperature Ionic Liquids for Chemoselective N-tert-Butyloxycarbonylation of Amines and the Influence of the C-2 Hydrogen on Catalytic Efficiency. *J. Org. Chem.* **2011**, *76*, 7132-7140.

(85) Tao, Y.; Dong, R.; Pavlidis, I. V.; Chen, B.; Tan, T. Using imidazolium-based ionic liquids as dual solvent-catalysts for sustainable synthesis of vitamin esters: inspiration from bio- and organo-catalysis. *Green Chem.* **2016**, *18*, 1240-1248.

(86) Handy, S. T.; Okello, M. The 2-Position of Imidazolium Ionic Liquids: Substitution and Exchange. *J. Org. Chem.* **2005**, *70*, 1915-1918.

(87) Quina Frank, H.; Bastos Erick, L.: Fundamental Aspects of Quantitative Structure-Reactivity Relationships. In *Encyclopedia of Physical Organic Chemistry*; 1st ed.; Wang, Z., Wille, U., Juaristi, E., Eds.; Major Reference Works; Wiley, 2017.

(88) Crowhurst, L.; Mawdsley, P. R.; Perez-Arlandis, J. M.; Salter, P. A.; Welton, T. Solvent-solute interactions in ionic liquids. *Phys. Chem. Chem. Phys.* **2003**, *5*, 2790-2794.

(89) Reichardt, C.: *Solvents and Solvent Effects in Organic Chemistry*; Second Edition ed.; VCH: Weinheim, Germany, 1988.

(90) Sancho, M. I.; Almandoz, M. C.; Blanco, S. E.; Castro, E. A. Spectroscopic Study of Solvent Effects on the Electronic Absorption Spectra of Flavone and 7-Hydroxyflavone in Neat and Binary Solvent Mixtures. *International Journal of Molecular Sciences* **2011**, *12*.

(91) Huddleston, J. G.; Visser, A. E.; Reichert, W. M.; Willauer, H. D.; Broker, G. A.; Rogers, R. D. Characterization and comparison of hydrophilic and hydrophobic room temperature ionic liquids incorporating the imidazolium cation. *Green Chem.* **2001**, *3*, 156-164.

(92) D'Anna, F.; Frenna, V.; Noto, R.; Pace, V.; Spinelli, D. Room Temperature Ionic Liquids Structure and its Effect on the Mononuclear Rearrangement of Heterocycles: An Approach Using Thermodynamic Parameters. *J. Org. Chem.* **2006**, *71*, 9637-9642.

(93) D'Anna, F.; Frenna, V.; Pace, V.; Noto, R. Effect of ionic liquid organizing ability and amine structure on the rate and mechanism of base induced elimination of 1,1,1-tribromo-2,2-bis(phenyl-substituted)ethanes. *Tetrahedron* **2006**, *62*, 1690-1698.

(94) Rodriguez-Llansola, F.; Miravet, J. F.; Escuder, B. A supramolecular hydrogel as a reusable heterogeneous catalyst for the direct aldol reaction. *Chem. Commun.* **2009**, 7303-7305.

(95) Jiang, J.; Meng, Y.; Zhang, L.; Liu, M. Self-Assembled Single-Walled Metal-Helical Nanotube (M-HN): Creation of Efficient Supramolecular Catalysts for Asymmetric Reaction. *J. Am. Chem. Soc.* **2016**, *138*, 15629-15635.

(96) Ivsic, T.; Hamersak, Z. Inversion of enantioselectivity in quinine-mediated desymmetrization of glutaric meso-anhydrides. *Tetrahedron: Asymmetry* **2009**, *20*, 1095-1098.

(97) Becker, H.; Sharpless, K. B. A New Ligand Class for the Asymmetric Dihydroxylation of Olefins. *Angewandte Chemie International Edition in English* **1996**, *35*, 448-451.

(98) D'Anna, F.; Marca, S. L.; Noto, R. Kemp Elimination: A Probe Reaction To Study Ionic Liquids Properties. *J. Org. Chem.* **2008**, *73*, 3397-3403.