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The Combined Role of Asymmetric Counteranion-Directed Catalysis (ACDC) and Ionic Liquid Effect for the Enantioselective Biginelli Multicomponent Reaction

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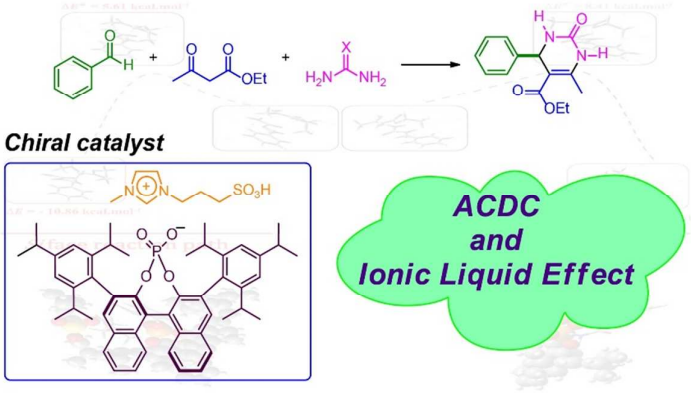


Abstract. The current manuscript describes new chiral task-specific ionic liquids bearing chiral anions as the catalysts for the enantioselective multicomponent Biginelli reaction. For the first time, the combined role of asymmetric counteranion-directed catalysis (ACDC) and ionic liquid effect (ILE) for the chiral induction in the Biginelli multicomponent reaction is demonstrated. The chiral induction arises from a supramolecular aggregate where the anion and the cation of the catalyst are alongside with a key cationic intermediate of the reaction. Each component of the new catalyst had a vital role for the chiral induction success. The mechanism of an asymmetric version of this multicomponent reaction is in addition demonstrated for the first time using electrospray (tandem) mass spectrometry – ESI-MS(/MS). The analyses indicated the reaction takes place preferentially and exclusively through the iminium mechanism. Unprecedented supramolecular aggregates were detected by ESI-MS and characterized by ESI-MS/MS. No intermediate of the other two possible reactions pathways could be detected. Theoretical

calculations shed light on the transition state of the transformation during the key step of the chiral induction and helped to elucidate the roles of the chiral anion (ACDC contribution) and of the imidazolium-containing non-chiral cation derivative (ILE contribution) in the molecular reaction process.

Key words. Catalysis, multicomponent reaction, ionic liquids, asymmetric counteranion-directed catalysis (ACDC), ESI-MS, mechanism, chiral induction, Biginelli, DFT, theoretical calculations.

Introduction

Asymmetric synthetic methodologies are vital to the development of several natural and non-natural bioactive compounds and have been used in several total syntheses.[1] There are however many achievements to be reached yet and several reactions still do not show satisfactory chiral induction control. Several recently published reviews[2-5] show insights and new catalytic methodologies to overcome drawbacks such as poor enantioselectivities. Among modern asymmetric catalytic approaches, asymmetric counteranion-directed catalysis (ACDC), is among the most promising strategies.[6-9] B. List defined ACDC as "*asymmetric counteranion-directed catalysis refers to the induction of enantioselectivity in a reaction proceeding through a cationic intermediate by means of ion pairing with a chiral, enantiomerically pure anion provided by the catalyst*".[10] Since the first years of this century,[10] attempts to make ACDC a feasible methodology and a more general concept are observed. Success in several reactions were reached by many groups using this relative new concept.[11-17]

Just like ACDC, ionic liquids (ILs) are a class of ionic fluids that emerged at the dawn of this century,[18-20] although we know these materials for more than a century. ILs are today also used in a plethora of industrial processes.[21] Chiral ILs (CILs) were reported[22] for the first time in 1999 and a representative chiral induction through ion-pairing effects were later described by Wasserscheid and coworkers.[23] CILs are currently used for asymmetric induction in catalysis,[24-26] but the ionic liquid effect (ILE), that is, their ability of ion-pairing and larger supramolecular aggregates formation,[27] is poorly explored. Because of the positive ILE, many reactions with charged intermediates had their yields and/or selectivities improved.[28-33] ILs are indeed capable of stabilizing reactive intermediates and transition states as argued by us[34] and

others.[35] Ion pairs formation is indeed a key feature for the success of many reactions conducted in the presence of IL-based structures.[36]

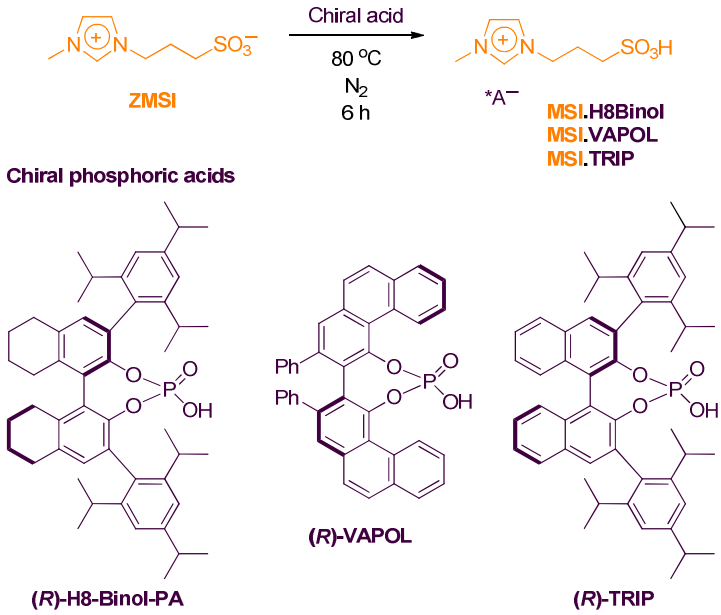
Multicomponent reactions (MCRs) are capable of addressing both diversity and complexity in organic synthesis in a single high atom economy chemical step.[37] MCRs have been for instance employed as the key step in the synthesis of natural products.[38] As reviewed,[39-41] the chiral induction in MCRs may be a hard task[42] and not always satisfactory selectivities are achieved during the reaction. Approaches such as chiral catalysts, asymmetric organocatalysis, chiral reagents and others are used to improve both diastereo- and enantioselectivities. Among MCRs, the Biginelli reaction[43] allows for the straight access of biologically active DHPM (3,4-dihydropyrimidin-2(1H)-one or -thione) derivatives.[44] For some, the Biginelli reaction is still considered the most important MCR.[45] In 2005, Zhu and coworkers[46] used a new chiral ytterbium catalyst for the first description of an enantioselective version of the Biginelli reaction. Phosphoric acids derivatives were later used with relative success.[47] Attempts to improve yields, selectivities and to shorten reaction times were also described[48-53] and revised.[54] Some major drawbacks are however still noted for this reaction. Low yields, long reaction times (typically 7 days), low ee, catalysts' synthesis with several synthetic steps, and others are still drawbacks of the enantioselective Biginelli MCR.

Based on our interest in the Biginelli reaction,[55,56] we envisaged the synthesis of a new CILs aiming at a combined effect of both ACDC and of ILE. The new catalysts were therefore designed bearing in mind two specific components i.e. a chiral anion and a Bronsted acid appended in the imidazolium cation. Herein, we wish to disclose our results and show there is indeed a combined role of these two main effects for the enantioselective version of the Biginelli MCR. The reaction mechanism was fully investigated by ESI(+)-MS(/MS) showing there is a preferable reaction pathway under

the catalytic condition developed. The detection of unprecedented supramolecular species allowed for DFT calculations to shed light on the possible transition states during the chiral induction step.

Results and Discussion

The designed chiral task-specific ILs were synthesized in quantitative yields by melting ZMSI (a known zwitterionic compound obtained by treating sultone with 1-methylimidazole) in the presence the respective chiral phosphoric acids (commercially available) in a sealed Schlenk tube under inert atmosphere (Scheme 1).



Scheme 1. Synthesis of the chiral task-specific ionic liquids used in this work. *A$^-$ refers to the chiral phosphate anion from the tested acids.

These catalysts were designed to have a Bronsted acid moiety appended to the imidazolium cation while the anion would be from a chiral phosphoric acid derivative.

Bronsted acid task-specific ILs acids display important physicochemical properties such as strong acid character, as already reviewed.[57] These salts are typically applied as catalysts in Bronsted acid catalyzed reactions.[58-60] Task-specific ILs are for long indeed known as efficient catalysts.[61] Enantiomerically pure phosphates and their derivatives are currently used with success to induce chirality in many different reactions being therefore a promising strategy toward chiral induction.[62-69] To the best of our knowledge, the combination of a chiral phosphates and task-specific ILs to afford new CILs has not been explored yet. The promising combination has in principle the advantage of a Bronsted acid catalysis in a chiral environment provided from the anion of the catalyst.

As will be discussed in due course, **MSI.TRIP** returned the best results in the enantioselective MCR investigated and, therefore, additional characterizations by MS analyses (positive and negative ion modes) were performed (Figure S1 in the Supporting Information file). After treating the neutral ZMSI structure (blind to MS analysis) with the chiral TRIP acid, it is noted the presence of an intense signal attributed to the MSI cation of *m/z* 205, which could be isolated in the gas phase and submitted to its structural MS/MS characterization. This feature pointed firmly to the protonation of the ZMSI in the presence of TRIP. The analysis was repeated but in the negative ion mode and a very intense signal of *m/z* 751 could be attributed to the chiral anion from the TRIP acid. It also indicated an efficient H transfer from the chiral phosphoric acid derivative to the ZMSI structure affording an intense anion signal.

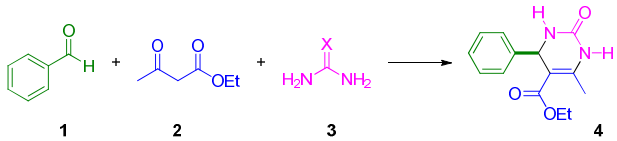
After the proper characterizations, the three chiral catalysts were initially tested in the model Biginelli reaction, that is, a reaction using urea, benzaldehyde and ethyl acetoacetate as the reagents. All reactions were carried out under solventless conditions using equimolar quantities of the reagents (0.2 mmol), at 30 °C and for 72 h. Initial

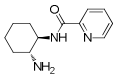
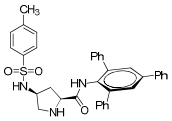
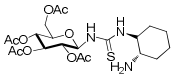
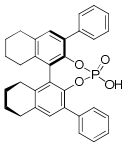
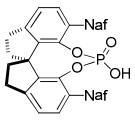
attempts using 1 and 5 mol% of the CILs catalysts gave reasonable yields (62-86%) except for **MSI.VAPOL** (99%). Switching the catalysts loadings to 10 mol% under standard reaction conditions, the desired Biginelli adduct could be obtained in almost quantitative yields (99%). **MSI.VAPOL** gave however unsuccessful enantiomeric excess (ee 12%). Switching the catalyst backbone to **MSI.H8Binol**, a great improvement in terms of enantioselectivity was observed (ee 70%). The extremely bulky **MSI.TRIP** finally gave a nearly perfect enantioselectivity control (ee 99%). The best reaction condition showed to be therefore 10 mol% of **MSI.TRIP** under solventless conditions at 30 °C.

In Table 1 it is summarized some chiral catalysts available in the literature, their reactions conditions and results in comparison with our best catalytic system. Some control experiments were also conducted using 10 mol% of a catalyst, 30 °C and 72 h of reaction aiming at depicting whether there is a combined role of the Bronsted acid cation of the catalyst and the chiral anion of **MSI.TRIP**. The reaction conducted with ZMSI under these conditions returned the Biginelli adduct in only 47% (racemic) after 72 hours of reaction. Using TRIP itself as the catalyst, the product was obtained in 41% of yield and 28% of ee. The sodium salt from TRIP was also tested and the DHPM was isolated in only 17% of yield and a nearly zero ee was observed. The result with the sodiated chiral catalyst is somehow expected since protonation (acidic medium) is required to further the Biginelli reaction. In addition, with no protonated (cationic) intermediate, the ion pair with the chiral anion will not constitute and, as a consequence, no chiral induction is expected. These results already indicated the importance of all components of the designed catalyst (**MSI.TRIP**) to the enantioselective Biginelli reaction and their roles will be discussed in due course. We are aware, however, that different chiral phosphoric acids may afford the desired DHPM with higher yields and

ee but under completely different conditions[50,52] (see Table 1). The use of TRIP as the chiral inductor for Biginelli condensations, as described elsewhere,[70] returned only moderated yields and ee, as it is observed in this work.

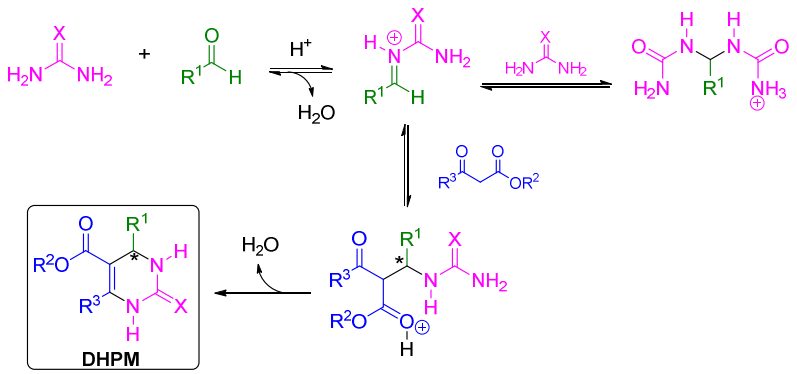
Table 1. Enantioselective model Biginelli reaction as carried out in the current work and as described by others.



Catalyst	Mol% Temp (°C) Time (h)	Solvent	Yield (%)	ee (%)	1:2:3 (mmol)	Notes	Ref.
	10 25 120	$CHCl_3$: Dioxane	15	99	0.20 0.60 0.60	The reaction required 10 mol% of HCl as cocatalyst. Large reagents excesses and low yields.	71
	10 25 96	THF: Dioxane	60	98	0.73 0.73 1.46	The reaction required 20 mol% of both $[Ph_3CNH_3^+CF_3CO_2^-]$ and $F_5C_6CO_2H$. *p*-MeOPhCHO instead of PhCHO.	51
	5 25 72	CH_2Cl_2	93	94	0.75 1.50 0.50	The reaction required 10 mol% of both $^tBuNH_2 \cdot TFA$ and Cl_3CCO_2H	72
	10 25 144	CH_2Cl_2	94	85	0.20 0.60 0.24	Iminium pre-formed and ethyl acetoacetate was added after two hours of reaction. Large reagents excesses.	50
	5 50 72	Xylene	92	94	0.10 0.30 0.12	Reaction under inert atmosphere and large reagents excesses. *p*-O_2NPhCHO instead of PhCHO.	52
MSI.TRIP	10 30 72	Solventless	99	99	0.20 0.20 0.20	No reagent excess, no cocatalyst, no solvent, no additive and no addition order are required.	This work

A few other reports[48,53,73-75] and some of Biginelli-like[76,77] reactions are also found in the literature, but in general, these works have similar results and experimental conditions as those cited in Table 1. The asymmetric version of the Biginelli reaction was reviewed elsewhere.[78] Depending on both the reaction condition and the nature of the reagents, the asymmetric version may require up to 240 h to carry out.[79]

Although all these works had brought great contributions to further the asymmetric version of this MCR, it is important to highlight that all cited works do not proceed experimentally as wished for MCRs. The aldehyde is mixed with urea alongside with the catalyst at the beginning of the reaction. Only after two hours (on average), the 1,3-dicarbonyl compound is added to the reaction mixture. The Biginelli reaction is known to be capable of taking place through at least three different mechanisms, that is, the iminium or the enamine or the Knoevenagel pathways. These three mechanism may be concurrent under typical Biginelli reaction conditions.[55] By mixing the aldehyde and urea in the absence of the third component, one may observe a clear attempt of both to induce the iminium ion formation (from the iminium mechanism – Scheme 2) and an attempt to avoid therefore the other two possible mechanisms. These procedures proved to be important to the chiral induction step after forming the iminium intermediate from the condensation of the aldehyde and the urea (Scheme 2). Although it is not the preference for any MCR at all, where all reagents should in principle be brought together (at the same time) in a one-pot version.



Scheme 2. Iminium mechanism of the Biginelli multicomponent reaction.

Using the catalyst developed in this work (**MSI.TRIP**), the idea of MCRs is fully preserved and all reagents are brought together at once and no further additions neither addition order are required. Solventless conditions are also a desirable feature, although not essential.[80] Beyond the chiral inductor, the enantioselective version of the Biginelli reaction typically requires the addition of an acid cocatalyst (typically a strong Bronsted acid) to befall (see Table 1). The dual function of **MSI.TRIP** i.e. the anion as the chiral inductor and the Bronsted acid at the imidazolium derivative allows its direct use in the reaction without requiring any cocatalyst.

Feng and coworkers[74] demonstrated that the addition of organic salts has a dramatic beneficial effect over the reaction displaying pronouncedly increased on the ee values in the presence of such salts. As perused in Table 1, most of the available works proceed through the addition of organic salts to improve the enantioselectivity of the Biginelli MCR. **MSI.TRIP** has therefore a third function and acts as an organic salt, as expected for ILs (organic salts in nature), thus merging in a single catalyst all features required to succeed the enantioselective version of the Biginelli reaction.

The best condition developed for the use of **MSI.TRIP** was tested for other substrates and results are summarized in Figure 1. The absolute stereochemistry could

be confirmed by comparing the **4c** $[\alpha]_D^{20}$ = - 37.5 (c 0.16, MeOH) with the current available literature[81] and only the (*R*) isomer is formed. The catalyst, beyond efficient, could also be recovered and reused. Most of the Biginelli adducts are known to be insoluble in ethanol and water. After the reaction, the catalyst could be recovered (typically above 95% of catalyst recover) and reused (see details in the Experimental Section). We also performed a reaction at 1 mmol scale of each reagent and similar results were obtained for the model reaction.

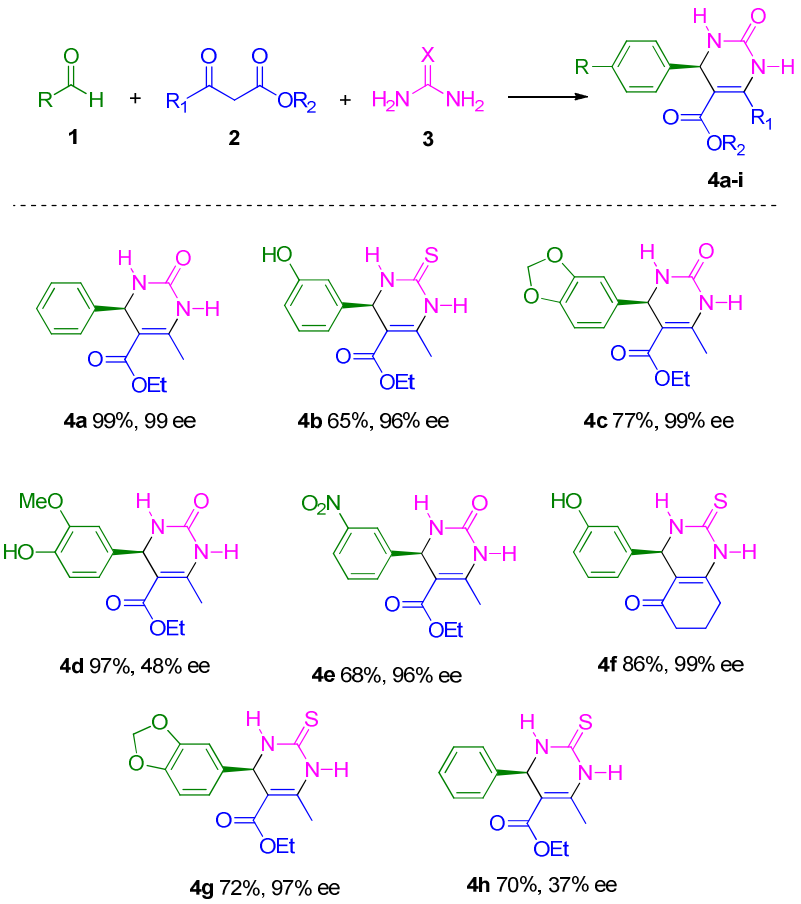


Figure 1. DHPMs from the enantioselective Biginelli reaction obtained using 0.20 mmol of the aldehyde, 0.20 mmol of the 1,3-dicarbonyl compound, 0.20 mmol of urea (or thiourea) and 10 mol% of **MSI.TRIP** at 30 °C for 72 h. Enantiomeric excess measured by enantiodiscriminating HPLC analyses.

All proposed mechanisms of the enantioselective version of the Biginelli MCR described so far are based on the iminium mechanism (Scheme 2) reexamined by Kappe.[82] It is known however that two other plausible mechanisms may concur and, to avoid them, the iminium intermediate had to be pre-formed in situ before the addition of the third component of the MCR. Although this is the typical operating mechanism, there are some works[44,83-85] showing the iminium mechanism is not always the preferred reaction pathway. The enantioselective mechanisms reported so far are in this context basically an assumption the transformation is going through the iminium pathway. Considering the iminium formation takes place in equilibrium, there is no warranty that the other two mechanisms will not compete with the iminium. Without any real proof of the preferred mechanism, the chiral step induction in the iminium intermediate is therefore highly questionable, although plausible. We are aware however the transition states associated with the chiral induction step are intimately dependent on the chiral inductor used.

Based on our experience in the investigation of MCRs mechanisms,[86-89] including the Biginelli reaction,[55,56] we decided to investigate the asymmetric version of the Biginelli MCR using electrospray (tandem) mass spectrometry – ESI-MS(/MS).[90-92] ESI proved to be an outstanding technique to an accurate investigation of several MCRs mechanisms.[93-97] We therefore prepared a solution of benzaldehyde, urea and ethyl acetoacetate (50 μM each) and mixed them in the presence of **MSI.TRIP** (5 μM). The solution was then injected and monitored online by MS and by its tandem MS/MS version.

As a result, only intermediates from the iminium mechanism could be detected (see Figure S2). These intermediates were previously characterized by us[98] and by

others.[94] The most interesting results were however the detection and characterization of unprecedent supramolecular aggregates of the iminium mechanism intermediates alongside with the chiral anion (and some with the cation as well) of the catalyst (Figure 2 and Figures S3-S4), which could be structurally characterized by ESI(+)-MS/MS.

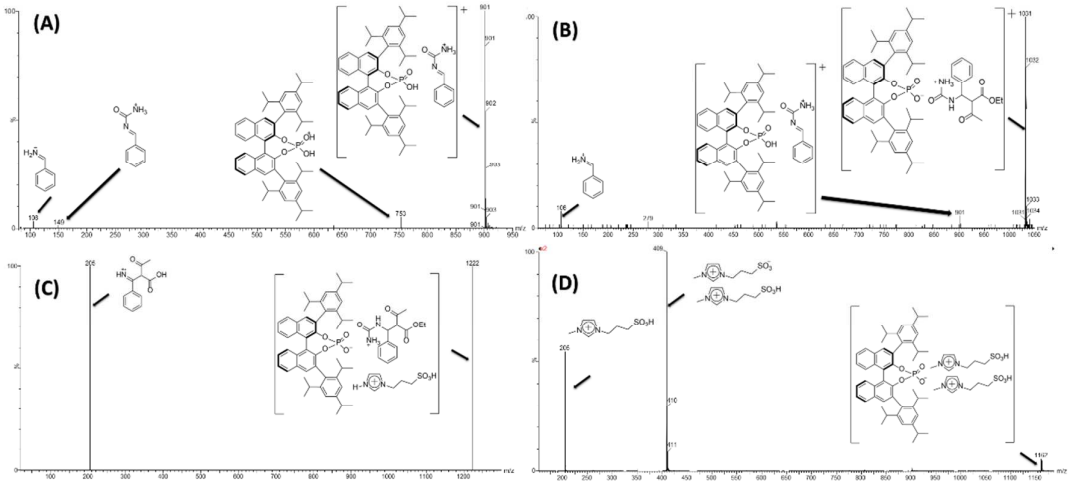


Figure 2. (A) ESI(+)-MS/MS of the iminium intermediate and the chiral moiety of the catalyst. (B) ESI(+)-MS/MS of the intermediate after 1,3-dicarnonyl addition to the iminium ion alongside with the chiral inductor. (C) ESI(+)-MS/MS of the supramolecular aggregate bearing an intermediate from the iminium mechanism, the chiral inductor and the imidazolium cation derivative. (D) ESI(+)-MS/MS of a supramolecular aggregate of the catalyst (type $[C_2A]^+$, C = cation and A = anion).

Figure 2A shows the iminium intermediate from the urea addition in the aldehyde associated with the chiral anion of the **MSI.TRIP** catalyst. Figure 2B shows the MS/MS characterization of the supramolecular aggregate bearing the reaction intermediate after the addition of the 1,3-dicarbonyl compound to the key iminium ion in the presence of the chiral anion. The presence of the imidazolium derivative, the chiral anion and one intermediate from the iminium mechanism in Figure 2C is, in fact, an unprecedented supramolecular structure pointing firmly to a positive ILE and

ACDC, that is, ion-pairing effects, formation of larger supramolecular ionic structures and the possibility of chiral induction. Figure 2D shows the supramolecular structure composed of two cations (MSI cation) associated with one chiral anion (TRIP anion derivative) in a $[C_2A]^+$ type.[99] No intermediate form the enamine neither from the Knoevenagel mechanism were detected in the experiments.

To ensure no intermediate of the Biginelli reaction mechanism neither those supramolecular aggregates had escaped detection, we decided to monitor the reaction using a charge-tagged aldehyde derivative instead of benzaldehyde. This elegant strategy of using charge-tagged reagents[100-102] was developed to facilitate the detection and characterization of transient intermediates, intermediates with low abundance in the ESI-MS spectrum, intermediates with fast kinetics of formation and/or consumption, and for neutral intermediates (blind to MS), which detection would not be possible without the charge tag appended in the reagent(s).

The experiments using the charge-tagged aldehyde returned interesting results (Figure 3 and Figures S5-S6) and, once more, only intermediates from the iminium mechanism could be detected. The lack of detection of intermediates from the Knoevenagel neither from the enamine reaction pathways using a charge-tagged reagent is a strong evidence of the clear preference for the iminium mechanism under the catalytic conditions developed herein. Aldehyde activation in the presence of imidazolium-based ILs was proposed by Dupont, Eberlin and co-workers.[103] Later, we observed this effect also for esters and carboxylic acids.[104] This feature may be contributing towards the iminium formation and favoring this reaction pathway.

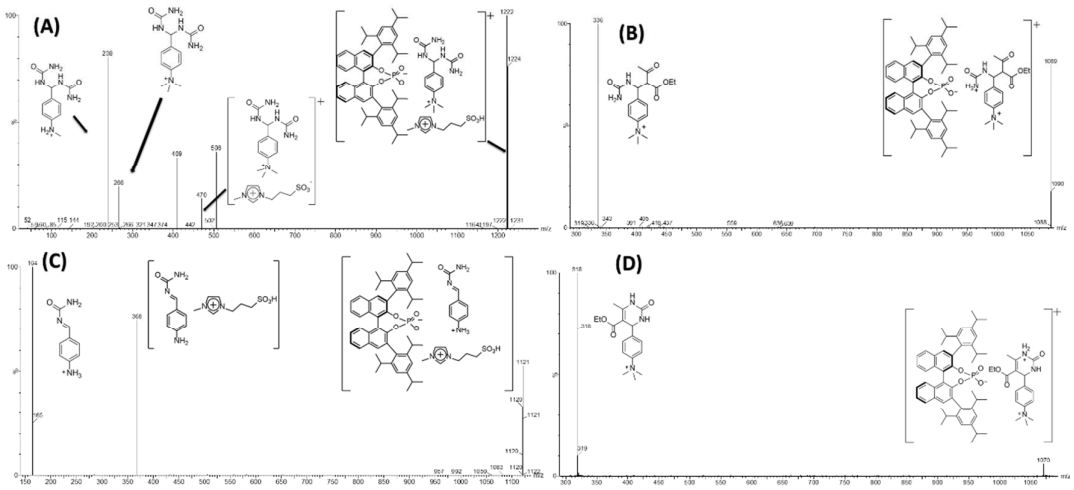


Figure 3. (A) ESI(+)-MS/MS of the supramolecular structure bearing the bisureide intermediate associated with the cation and anion of the catalyst. (B) ESI(+)-MS/MS of the intermediate after 1,3-dicarnonyl addition to the iminium ion and the chiral inductor. (C) ESI(+)-MS/MS the supramolecular aggregate of the key iminium intermediate associated with the chiral inductor and the imidazolium cation derivative. (D) ESI(+)-MS/MS of the Biginelli adduct associated with the chiral anion.

Supramolecular aggregates (C_2A type - see Figure 3) detection and characterization (MS/MS) bearing both the imidazolium derivative and the anion of the catalyst plus the key intermediates of the iminium mechanism is a clear evidence of the combined role of ILE (over the stabilization of the formed charged intermediates in the reaction) and ACDC (due to the presence of the chiral anion).

Based on the evidences of the MS experiments described, DFT calculations were performed to depict plausible transition states (TSs) to explain the chiral induction step in the iminium intermediate upon 1,3-dicarbonyl compound addition. We considered for the calculations a supramolecular structure containing the iminium intermediate, the chiral anion and the imidazolium derivative of the catalyst (as seen, for instance, in

Figure 3C) to evaluate the possible TSs (Figure 4). The structure had its geometry fully optimized.

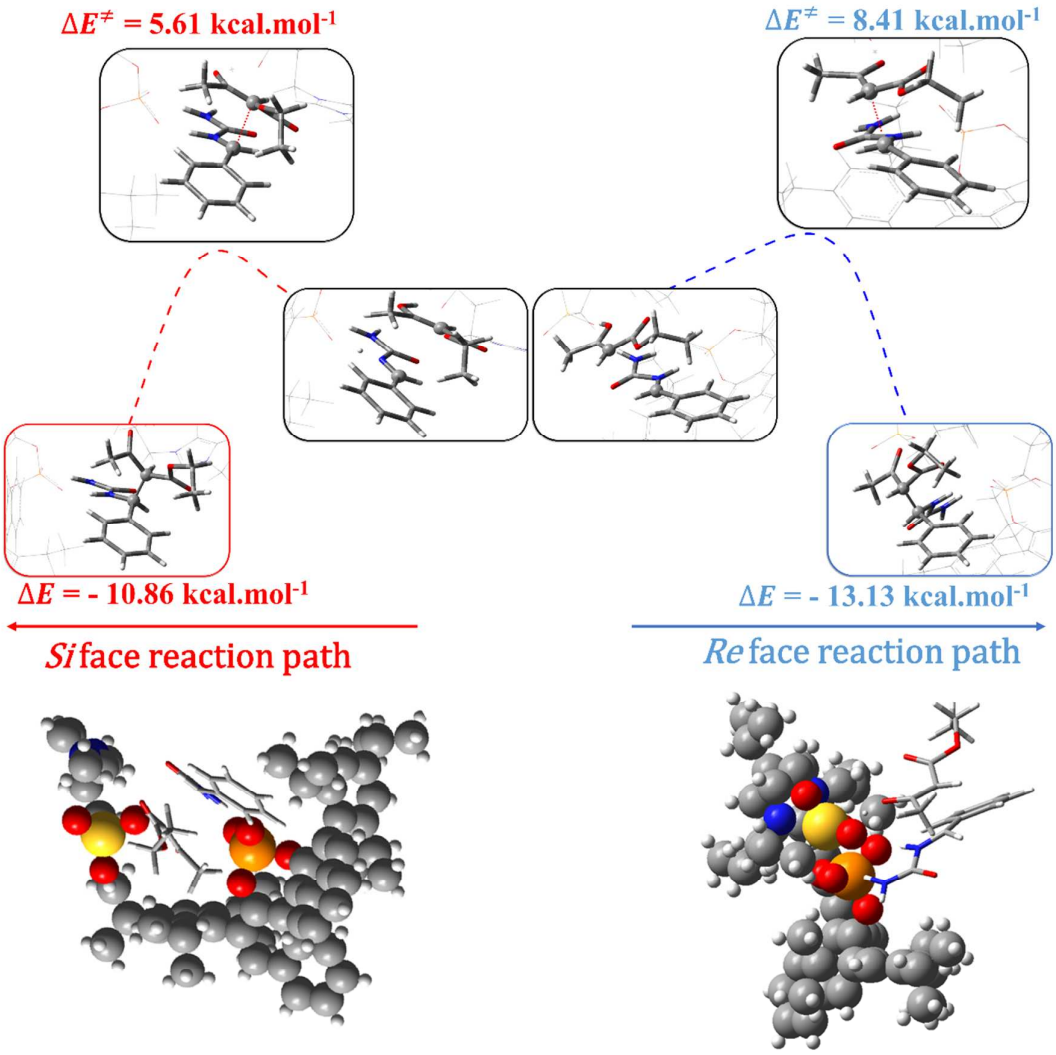


Figure 4. Plausible transition states for the enantioselective Biginelli reaction catalyzed by **MSI.TRIP** calculated at HF/3-21G//wB97XD/6-311G(d) level of theory. The addition to the iminium intermediate was considered the key step of the chiral induction. (Top) Potential energies curves with specific stationary points. (Bottom) Van der Waals representations of the transition states.

In the TS showing the addition of the ethyl acetoacetate in the *Re* face (less favored) it is noted the free approximation of both the iminium intermediate and of the other reagent in an open arrangement. In the TS favoring the *Si* face however a cage-like arrangement is noted. In this case, the imidazolium derivative is capable of locking the iminium intermediate alongside with the 1,3-dicarbonyl compound one side while the chiral anion locks the other side. As depicted from Figure 4, the chiral anion is blocking the *Re* face of the C=O bond of the iminium intermediate and allowing for the addition of the other reagent exclusively by the *Si* face. Although the energy difference noted when comparing both possible TSs were not so large, the attack on the *Si* face was clearly favored, as experimentally determined (99% ee). To better understand this result and the energetic involved, TSs relative populations could also be predicted at different temperatures from electronic energy differences (Figure 5) based on the Boltzmann distribution analysis using the Boltzmann factor to estimate the ee (see the experimental section for details).

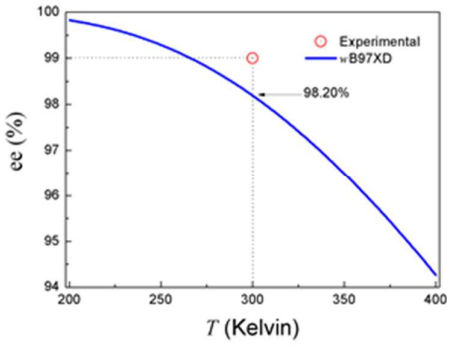
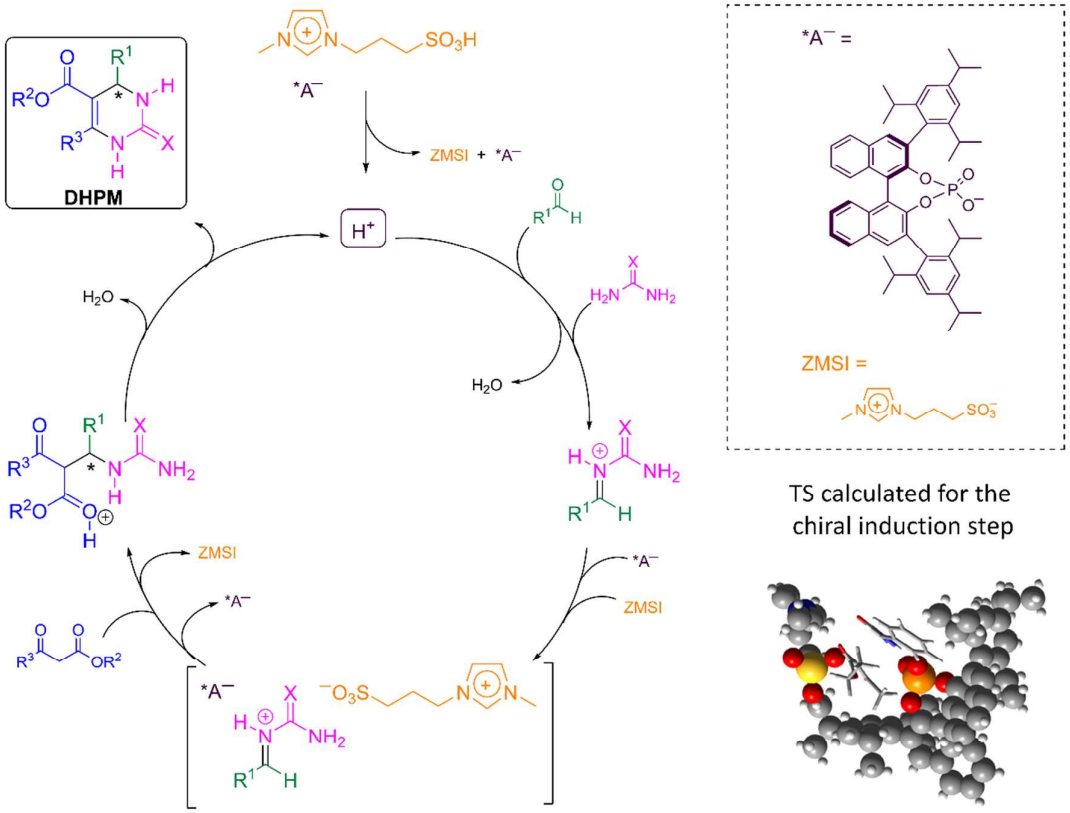


Figure 5. TS relative populations (Boltzmann distribution) from electronic energy differences using the Boltzmann factor to estimate the ee.

The method returned a theoretical ee of 98.20% while the experimental result had an ee of 99% therefore confirming the accuracy of the employed theoretical

methodology to explain the plausible TS and the preferential *Si* face attack. Considering the MS results revealed unprecedented larger supramolecular structures with at least two chiral anions (Figures S3 and S6), it is expected a larger and more organized TS but the size and complexity of these supramolecular structures considering more anions and cations would not allow for such a high level of theory calculation.

Based on the results described herein, a catalytic cycle could be proposed (Scheme 3) to explain the enantioselective Biginelli MCR using **MSI.TRIP**.



Scheme 3. Catalytic cycle of the enantioselective Biginelli reaction catalyzed by **MSI.TRIP**. Note the proposition is based on the iminium mechanism and the favored calculated TS is shown.

In the proposed catalytic cycle, the aldehyde is protonated and the urea addition takes place affording the key iminium intermediate. The chiral anion and the ZMSI (imidazolium derivative) coordinates and the supramolecular chiral structure prone to the 1,3-dicarbonyl addition is formed likely the calculated cage-like structure (Figure 4, bottom and left). After, the Biginelli adduct is formed by cyclization and the acid hydrogen is restored during the release of the ZMSI, the chiral anion and water.

In summary, a new chiral Bronsted IL was successfully synthesized and applied as the catalyst for the enantioselective version of the Biginelli reaction. The chiral IL tested as the catalyst had three important roles acting as the acid hydrogen source, as the chiral inductor and as an organic salt (like an additive). The mechanism analysis by ESI-MS(/MS) allowed the detection and characterization of unprecedented chiral supramolecular structures pointing to the presence of the chiral anion and the imidazolium derivative in the structure. These results are strong evidences of the combined role of ILE and ACDC. The iminium mechanism is highly favored in the developed conditions and no intermediate of the other two mechanisms could be detected. Theoretical calculations based on the detected unprecedent supramolecular aggregated from MS results, shed light on the possible TS favoring the *Si* face attack by the 1,3-dicarbonyl reagent during the key step for the chiral induction in the model reaction analyzed. DFT results also pointed to the importance of the chiral anion and of the imidazolium derivative in the chiral induction step to proceed through a cage-like structure, thus once more pointing firmly to the combined role of ILE and ACDC. The results described herein indeed open up a new avenue of opportunities for the exploration of CILs allowing a unique combination of ILE and ACDC to be further exploited.

Experimental Section

General. ESI-MS and ESI-MS/MS measurements were performed in the positive ion mode (*m/z* 50-2000 range) on a HDMS instrument. This instrument has a hybrid quadrupole/ion mobility/orthogonal acceleration time-of-flight (oa-TOF) geometry and was used in the TOF V+ mode. All samples were dissolved in methanol to form 50 μM solutions and were directly infused into the ESI source at a flow rate of 10 μL/min after 5 minutes at 80 °C. ESI source conditions were as follows: capillary voltage 3.0 kV, sample cone 20 V, extraction cone 3 V. NMR spectra were recorded on a 7.05 T instrument using a 5-mm internal diameter probe operating at 600 MHz for ^{1}H and at 150 MHz for ^{13}C. Chemical shifts were expressed in parts per million (ppm) and referenced by the signals of the residual hydrogen atoms of the deuterated solvent, as indicated in the legends. Melting point were recorded using a sealed capillary tube.

Synthesis of the chiral catalysts. The new catalysts were prepared by treating the zwitterionic MSI (1 mmol, 204 mg) with the respective phosphoric acids derivatives, that is, (R)-H8-Binol-PA (1 mmol, 760 mg), or (R)-VAPOL (1 mmol, 600 mg) or (R)-TRIP (1 mmol, 752 mg). The mixtures were stirred for 6 h under inert atmosphere at 80 °C affording the respective catalysts in quantitative yields. **MSI.H8Binol** (965 mg), **MSI.VAPOL** (805 mg) and **MSI.TRIP** (957 mg).

MSI.TRIP. 1-methyl-3-(3-sulfopropyl)-1H-imidazol-3-ium (R)-3,3′-Bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl phosphate. ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 0.68 (d, *J* = 5.87 Hz, 7H), 0.89 (d, *J* = 6.60 Hz, 7H), 0.99 (dd, J = 15H), 1.22 (d, *J* = 6.97Hz, 15H), 2.52 (qui, *J* = 6.60 Hz, 2H), 2.60 (qui, *J* = 6.60 Hz, 2H), 2.83 (qui, *J* = 6.97 Hz, 2H), 6.94 (d, *J* = 7.61 Hz, 5H), 7.31 (m, 5H), 7.49 (dt, *J* = 1.83, 6.24 Hz, 2H), 7.80 (s, 2H), 7.87 (d, *J* = 8.07Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm 18.1, 22.7,

23.3, 23.9, 24.1, 25.0, 26.3, 30.7, 30.9, 34.3, 120.2, 121.1, 122.08, 122.09, 125.6, 126.2, 127.4, 128.1, 131.0, 131.5, 132.2, 132.21, 132.5, 132.6, 145.8, 145.9, 147.5, 148.1, 148.4. HRMS (ESI-TOF) *m/z*: In the positive ion mode $[M]^+$ Calcd for $C_7H_{13}NO_3S$ 205.0647; Found 205.0644. In the negative ion mode $[M]^-$ Calcd for $C_{50}H_{56}O_4P$ 751.3916; Found 751.3934.

MSI.H8Binol. 1-methyl-3-(3-sulfopropyl)-1H-imidazol-3-ium (R)-3,3'-diphenyl-1,1'-H8-binaphthyl-2,2'-diyl phosphate. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.92-0.89 (m, 10 H), 1.06-1.04 (m, 7 H), 1.10-1.09 (m, 7 H), 1.23-1.20 (m, 14 H), 1.89-1.81 (m, 8 H), 2.28-2.26 (m, 2 H), 2.32-2.29 (m, 2 H), 2.60-2.58 (m, 3 H), 2.67-2.64 (m, 3 H), 2.85-2.78 (m, 10 H), 6.93-6.92 (m, 6 H), 6.97 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 147.9, 147.8, 147.2, 144.0, 136.5, 133.9, 132.6, 131.8, 129.3, 126.8, 120.9, 120.0, 58.5, 34.2, 31.0, 30.6, 29.3, 27.8, 26.6, 24.9, 24.1, 23.9, 23.4, 23.9, 23.4, 22.9, 22.8, 18.3. HRMS (ESI-TOF) *m/z*: In the positive ion mode $[M]^+$ Calcd for $C_7H_{13}NO_3S$ 205.0647; Found 205.0648. In the negative ion mode $[M]^-$ Calcd for $C_{50}H_{64}O_4P$ 759.4542; Found 759.4547.

MSI.VAPOL. 1-methyl-3-(3-sulfopropyl)-1H-imidazol-3-ium (R)-2,2μ-Diphenyl-3,3μ-biphenanthryl-4,4μ-diyl phosphate. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.90-0.82 (m, 2 H), 1.25-1.19 (m, 2 H), 1.69-1.66 (m, 2H), 6.50 (d, 4 H, J = 7 Hz), 6.92 (t, 4 H, J = 7 Hz), 7.10-7.07 (m, 3 H), 7.48-7.47 (m, 5 H), 7.59-7.57 (m, 3 H), 7.68-7.67 (m, 3 H), 7.78-7.75 (m, 5 H). ^{13}C NMR (125 MHz, $CDCl_3$) 141.3, 139.8, 134.6, 133.3, 129.6, 129.1, 127.7, 127.1, 126.9, 126.7, 121.8, 47.0, 46.7, 39.7. HRMS (ESI-TOF) *m/z*: In the positive ion mode $[M]^+$ Calcd for $C_7H_{13}NO_3S$ 205.0647; Found 205.0645. In the negative ion mode $[M]^-$ Calcd for $C_{40}H_{24}O_4P$ 599.1412; Found 599.1419.

General procedure for the enantioselective Biginelli reaction and catalyst recover. A Schlenk tube containing 0.2 mmol of aldehyde, 0.2 mmol of the 1,3-dicarbonyl compound, 0.2 mmol of urea (or thiourea), 10 mol% of the **MSI.TRIP** (9.5 mg) was allowed to react at 30 °C for 72 h. All Biginelli adducts were purified by chromatographic column using ethyl acetate and hexanes mixtures. Most of the Biginelli adduct are not soluble in ethanol neither water. For these compounds (e.g. 4a), ethanol was used to wash and recover the catalyst from the reaction mixture. The procedure allows the catalyst to be recovered in up to 95% and reused without any notable loss in yields and enantioselectivity. Biginelli adduct could also be crystallized from hot ethanol, a known well-stablished procedure used to purify these compounds.[105] In this work, however, we purified them by chromatographic column because yields were on average 15-25% lower when purified by the crystallization procedure.

Computational procedures. The electronic structure calculation performed in this work were carried within compound model chemistry HF/3-21G//*w*B97XD/6-311G(d) using Gaussian 09 program suite.[106] *w*B97XD is a long-range corrected hybrid density functional with empirical dispersion correction with satisfactory accuracy for thermochemistry, kinetics and noncovalent interactions.[107] In spirit of the computational protocol applied in the available literature,[108,109] minimum energy reaction paths were located using the relaxed scan procedure, since the conventional synchronous transit-guided quasi-Newton QST2 method was unable locating the transition state. To elucidate the relative energy of the reaction, relaxed potential energy surface (PES) scans were performed by driving the C-C bond (0.02 A over 10 steps) starting from from 1.5A value up to 3.3A. The relaxed scan presented a loose and flat transition state supporting the weakness of the conventional QST2 procedure.

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Supporting Information

Catalyst analyses, ESI-MS/MS, chiral HPLC traces and NMR spectra related with this manuscript. Energies and Cartesian coordinates for all calculated structures These materials are available free of charge via the internet at http://pubs.acs.org.

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