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Unraveling the role of supramolecular additives in a proline-catalyzed reaction

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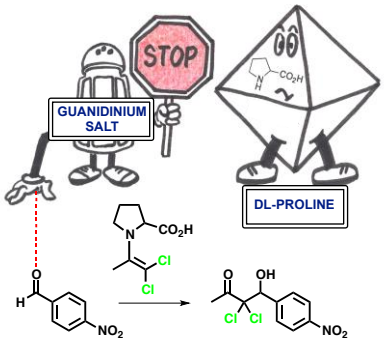


ABSTRACT

Various additives, typically based on molecules featuring H-bond donor motifs, have been essayed towards improving the catalytic properties of proline. However, their mode of action is not clear yet. Employing *in situ* ^{1}H and ^{19}F NMR DOSY experiments the role of a tetrafluoroborate guanidinium salt in a novel proline-catalyzed cross-aldol reaction between α,α-dichloroacetone and aromatic aldehydes has been fully disclosed.

INTRODUCTION

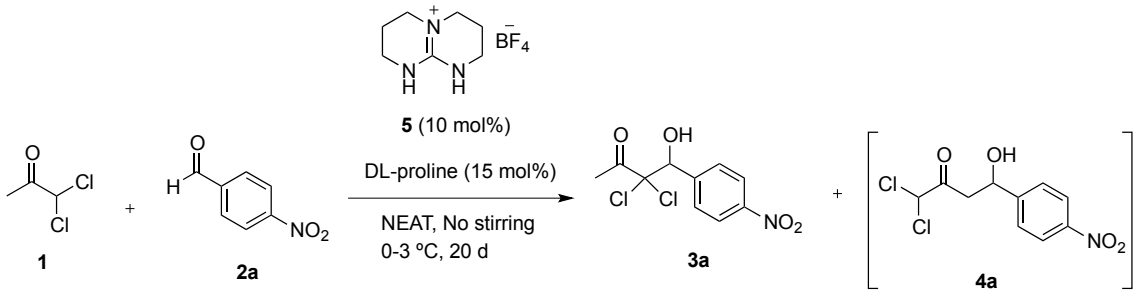
Proline stands among the most popular organocatalysts. This naturally occurring amino acid is cheap, readily available in both enantiomeric forms, or as racemate, and can be employed in a fair range of organic transformations.[1] In order to overcome the inherent limitations of proline (namely: poor solubility in organic solvents, low reactivity against some substrates, parasitic side reactions), our group has demonstrated how the addition of triazabicyclo[4.4.0]dec-5-ene (TBD)-derived guanidinium salts as additives can enhance the reactivity and selectivity of this off-the-bench catalyst in transformations such as the aldol reaction.[2] Also, the addition of such additives broadens the scope of proline. In this sense, we have previously reported the first proline-catalyzed asymmetric synthesis of chlorohydrins,[3] as well as the first enantioselective preparation of α□azido-β□hydroxy ketones,[4] both made feasible by the cooperation of a proline/guanidinium salt catalytic pair.

In this occasion we decided to explore the behaviour of our proline/guanidinium salt system in the intermolecular cross-aldol reaction between α□α□dichloroacetone **1** and aromatic aldehydes **2**, to render α□α□dichloro-β□hydroxy ketones **3**. This simple reaction has permitted us to study its mechanism in depth, thus to clarify the function played by the additive in the reaction outcome.

RESULTS AND DISCUSSION

4-Nitrobenzaldehyde **2a** was adopted as a model substrate (Table 1, heading). In accordance with our previous work we evaded the use of any organic solvent, apart from an excess of ketone **1**, which acts as both reagent and reaction medium.

Table 1. Proline/guanidinium salt **5** co-catalyzed synthesis of α□α□dichloro-β□hydroxy methyl ketone derivative **3a**.[a]



entry	conversion (%)[b]
1[c, d]	14
2[c]	97
3	>99 (91)
4[e]	13

[a] Reaction conditions: dichloroacetone **1** (2.0 mmol), 4-nitrobenzaldehyde **2a** (0.2 mmol), *rac*-DL-proline (15 mol%), **5** (10 mol%), no solvent. Reaction mixtures were left to stand 20 d inside a standard laboratory fridge (0–3 ˚C) with no stirring. [b] Determined by ^{1}H NMR spectroscopy of the crude reaction mixtures. Conversion of aldehyde **2a** (limiting reagent) into α□α□dichloro-β□hydroxy ketone **3a**, quantified against $CHBr_3$ (9 μL, 0.103 mmol) used as analytical internal standard. Isolated yield of analytical pure product is given in brackets. [c] Reaction stirred at 0 ˚C for 20 d. [d] Reaction carried out with L-(*S*)-proline (instead of DL-proline) and guanidinium salt **5**. [e] Reaction carried out without the addition of guanidinium salt **5**.

Initially, considering our previous experience with this type of catalytic system,[5-7] we suspended (*S*)-proline (15 mol%), TBD-derived tetrafluoroborate guanidinium salt **5** (10 mol%), and 4-nitrobenzaldehyde **2a**, in a moderate excess of α□α□dichloroacetone **1** (10 eq. respect to the aldehyde), and the resulting mixture was stirred at 0 °C for 20 days, rendering the corresponding α,α–dichloro-β–hydroxy methyl ketone **3a** in 14% conversion, amid unreactive aldehyde **2a** (54%) and by-products (Table 1, entry 1). The ketone **3a** obtained was racemic. To our surprise, when *rac*-DL-proline and salt **5** were used as catalysts under analogous reaction conditions product **3a** was afforded in 97% conversion (Table 1, entry 2). The formation of regioisomer **4a** was not observed. Considering the reaction time needed for completion,[5] we suspended aldehyde **2a**, DL-proline (15 mol%), and guanidinium salt **5** (10 mol%), in dichloroacetone **1**, in a close-capped tube, and it was left to stand for 20 d inside a standard laboratory fridge (temperature ranging 0–3 ˚C), without any sort of stirring or mechanical agitation. By this means, aldol **3a** was produced in >99% conversion, being isolated in analytically pure form in 91% yield (Table 1, entry 3). This rather straightforward and convenient protocol has been previously implemented by our group in other aldol reactions,[2-3] avoiding the use of cryogenic baths for long time.

When *rac*-DL-proline was used as the sole catalyst under the former set of conditions the reaction turned to be rather slow, only 13% of 4-nitrobenzadehyde **2a** being converted into ketone **3a** (Table 1, entry 4). It demonstrates the necessity of the guanidinium salt on the reaction course,

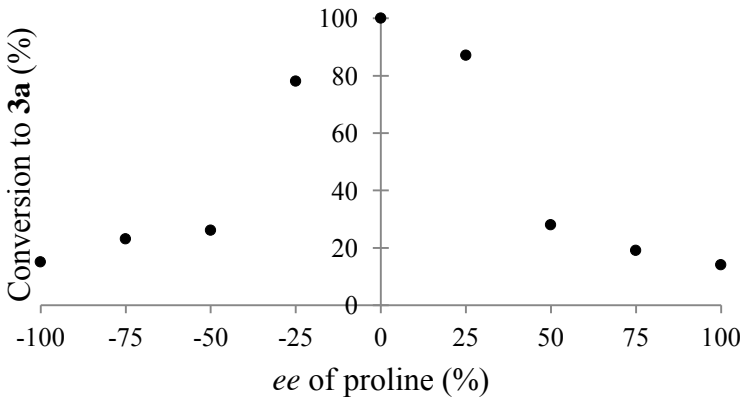
which makes possible a reaction that is not favourable with the single contribution of proline, as we have previously observed.[2-4]

Considering that neither α□α□dichloroacetone, **1**, nor aldehyde **2a** posses any stereochemical information, it is intriguing the fact that the cross-aldol reaction is slow with L-proline but it works neatly with the racemic amino acid (Table 1, entries 1 and 2). To our knowledge, there aren't other catalytic systems displaying a similar behavior and it is therefore a phenomenon worth exploring. Moreover, previous reports regarding the participation of other H-bond donor species (Brønsted acids,[6] water,[7] alcohols,[8] ureas,[9] thioureas,[10] thiouronium salts,[11] imidazolium salts,[12] secondary amines[13]) as additives in proline-promoted aldol reactions do not provide an insight on their mode of action. Filling up this gap would allow designing more effective cooperative catalyst/co-catalyst systems, which are not very much understood, particularly on asymmetric catalysis.[14] Accepting the challenge we decided to clarify the nature of the catalytic species involved in our cross-aldol transformation from the following studies: A) an examination of the catalytic activity of several systems composed of guanidinium salt **5** accompanied by prolines of varying stereopurity; B) a thorough comparative NMR analysis of both the racemic and the enantiopure catalyzed reaction mixtures by *in situ* NMR reaction monitoring, including ^{1}H and ^{19}F DOSY experiments.

A) According to our plan we set up a series of experiments, under our finest set of conditions (Table 1, entry 3), reacting ketone **1** with 4-nitrobenzaldehyde **2a**, in the presence of guanidinium salt **5** (10 mol%) and

different enantio-enriched prolines (15 mol%).[15] From the obtained results, represented in Figure 1, it appears that there is a significant negative non-linear effect for this transformation.[16] The analysis of the data indicates a restriction for the enantiomeric excess of the proline used as catalyst: above a ±25% *ee* threshold for either (*S*)- or (*R*)-enriched proline the formation of product **3a** is severely damaged. It is worth noting that α,α–dichloro-β–hydroxy ketone **3a** produced from every experiment represented in Figure 1 is racemic and, surprisingly, ketone **3a** is rendered in quantitative conversion only when *rac*-DL-proline and the guanidinium salt **5** are employed.

Figure 1. Plot of conversion of 4-nitrobenzaldehyde, **2a**, into α□α□-dichloro-β□hydroxy methyl ketone **3a** (as determined by ^{1}H NMR of crude reaction mixtures), against the enantiomeric excess of the proline used as the catalyst. +100% *ee* implies enantiopure (*S*)-(+)-proline, while –100% *ee* indicates enantiopure (*R*)-(–)-proline. Plotted points are the average of two individual experiments. In all cases guanidinium salt **5** was used as co-catalyst.



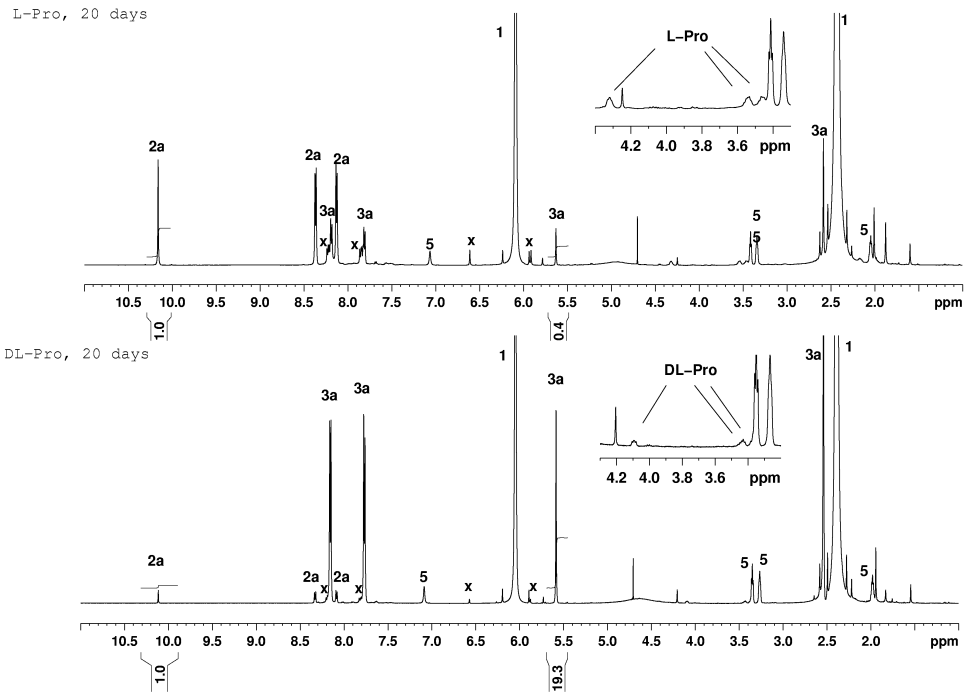
The groups of Agami and Kagan have observed non-linear effects in intramolecular proline-catalyzed cross-aldol/Robinson annulation reactions towards the preparation of Wieland-Miescher ketones.[17] The authors experienced a non-linear relationship between the enantiomeric purity of (*S*)-

proline and the enantiomeric excess measured on the annulation product, being always smaller for the later. Such observations were explained assuming the participation of more than one proline unit in the key transition state. According to the authors it features an intramolecular H-bond contact in a proline-enamine-type intermediate that is protonated from a second proline unit.

B) In order to gain further insight into our system we decided to study the course of the cross-aldol reaction between α,α-dichloroacetone, **1**, and 4-nitrobenzaldehyde, **2a**, by high-field NMR spectroscopy. Accordingly, samples featuring ketone **1** (4.0 mmol), aldehyde **2a** (0.4 mmol), tetrafluoroborate guanidinium salt **5** (0.04 mmol), and either L-(*S*)-proline or DL-proline (0.06 mmol) were set up in close-capped test tubes and placed inside a standard laboratory fridge at 0–3 ºC, with no stirring. After 10 days these mixtures were homogeneous to the naked eye. Their content was filtered through cotton wool and then transferred into NMR probes containing a coaxial capillary tube filled up with deuterium oxide. To our delight, despite having an excess of a non-deuterated medium (α,α-dichloroacetone, **1**), meaningful 600 MHz ^{1}H NMR spectra could be registered for these samples. The spectra confirmed differences in the composition of both reaction mixtures. The conversion of 4-nitrobenzaldehyde **2a** into product **3a** was higher for the reaction containing DL-proline as the organocatalyst: the ratio between unreacted aldehyde **2a** and β-hydroxyketone **3a** was 28:72 in the reaction catalyzed by DL-proline, whereas this ratio was inverted in the L-(*S*)-proline-catalyzed reaction (72:28) (see Figure SI_1 in the Supporting Information (SI) file). Moreover, in the later case does also appear a significant amount of a reaction by-product.[18] When ^{1}H NMR

spectra were registered again after 20 d (Figure 2) it could be observed how the sample containing DL-proline had reacted almost to completion (**2a**:**3a**, 5:95), whereas the one containing the chiral amino acid catalyst didn't progress.

Figure 2. ^{1}H NMR spectra (600 MHz, 298 K) of samples containing α,α-dichloroacetone (4.0 mmol), 4-nitrobenzaldehyde (0.4 mmol), tetrafluoroborate guanidinium salt **5** (0.04 mmol), and either L-(*S*)-proline or DL-proline (0.06 mmol), registered after 20 d. Samples contain a coaxial capillary tube filled up with D_2O. Resonances attributable to dichloroacetone **1**, aldehyde **2a**, aldol adduct **3a**, guanidinium salt **5**, and proline are indicated in the spectra. **X** indicates a reaction by-product (reference 18). Expansions with the resonances of proline are included.



A close look at the spectra represented in Figure 2 reveals other subtle differences: the chemical shifts of the resonances assigned to the hydrogen atom borne on the stereogenic centre of proline are different in each reaction mixture, with deshieldings of 0.2 ppm registered for the sample that contains L-(*S*)-proline. This discrepancy, although small, is significant considering that the

organocatalyst (L-(*S*)-proline, or *rac*-DL-proline) and the guanidinium salt **5** are present in the same quantity in both of the analyzed samples.

Taking into account these findings we considered carrying out ^{1}H and ^{19}F DOSY NMR experiments on the DL-proline and L-(*S*)-proline-catalyzed mixtures to evaluate the existence of molecular aggregates participating in the catalytic process that could account for the observed differences. Diffusion Ordered Spectroscopy (DOSY)[19] is a useful NMR technique that permits estimating the size of a molecule in solution from its diffusion coefficient. It has been successfully applied in the identification and study of H-bond contacts,[20] and the detection of dimers and other aggregation states.[21] The measured diffusion coefficient of the molecule in the NMR sample is a translational property which the Stokes–Einstein equation relates to the hydrodynamic radius of the molecule in solution.[22] If two different size molecules are present in the measuring solution, an inverse relationship between the ratio of their diffusion coefficients and their hydrodynamic radii ($D_a/D_b = r_{Hb}/r_{Ha}$) can be established. Moreover, considering that the two molecules have a spherical shape, this relation can be extended to a volume ratio between them,[23] ($(D_a/D_b) = (V_b/V_a)^{1/3}$), and even a molecular weight can be also estimated ($D_a/D_b = (MW_b/MW_a)^{1/3}$).

In order to evaluate the nature of the catalytic species present in our reaction mixtures we considered carrying out ^{1}H and ^{19}F DOSY experiments in two NMR samples containing the tetrafuloroborate guanidimium salt **5** and either DL-proline (Sample 1 (**S1**)) or L-(*S*)-proline (**S2**) dissolved in α□α-

dichloroacetone **1**, in the same proportion featured in the experiments of Table 1, entry 3, and those used for recording the ^{1}H NMR spectra shown in Figure 2 (α,α-dichloroacetone (4.0 mmol), tetrafluoroborate guanidinium salt **5** (0.04 mmol), and proline (0.06 mmol)). We also considered using NBu_4BF_4 as a reference compound to study the possible influence of the NH moieties present in the guanidinium cation on the diffusing behavior of proline. Accordingly, a second pair of NMR samples was also prepared in the conditions mentioned above but replacing the guanidinium salt **5** by NBu_4BF_4 (samples **S3** and **S4**). Finally, two standard solutions were prepared containing either tetrafluoroborate guanidinium salt **5** (0.04 mmol), or NBu_4BF_4 (0.04 mmol), in $\alpha\square\alpha$-dichloroacetone (4.0 mmol) (**S5** and **S6**, respectively). In contrast to the guanidinium cation of **5** NBu_4^+ does not posses NH moieties and, as a consequence, cannot establish H-bond contacts either with BF_4^- or proline, so will be present in solution as a discrete monomeric unit. Thus, calculating the radius of NBu_4^+ by DOSY and correlating it with that reported in the literature will allow judging the righteousness of our NMR measurements.

Table 2 and Table 3 summarize the diffusion coefficients measured by ^{1}H and ^{19}F DOSY and the hydrodynamic radii of the detected species in solution for the surveyed NMR samples, calculated by the Stokes–Einstein equation.

Table 2. Data from ^{1}H and ^{19}F-DOSY NMR experiments performed on samples **S3**, **S4**, **S6**.[a]

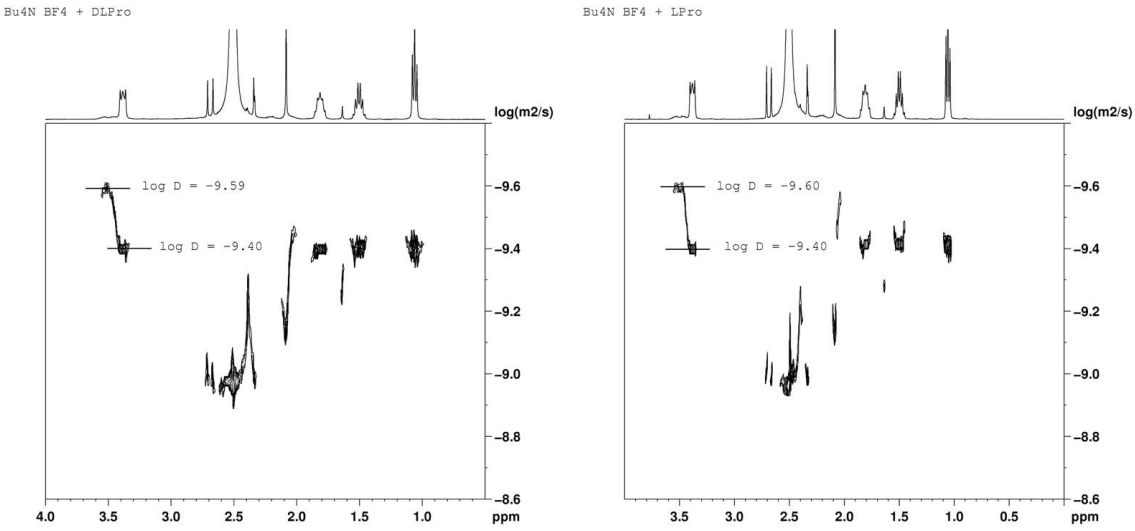
	Sample **S3**[b] (DL-proline + NBu_4BF_4)			Sample **S4**[c] (L-proline + NBu_4BF_4)			Sample **S6**[d] (NBu_4BF_4)		
	log D (m^2/s)	D (10^{-10} m^2/s)	r_H (Å)	log D (m^2/s)	D (10^{-10} m^2/s)	r_H (Å)	log D (m^2/s)	D (10^{-10} m^2/s)	r_H (Å)
NBu_4^+	–9.40	3.98	4.69	–9.40	3.98	4.69	–9.40	3.98	4.69
BF_4^-	–9.29	5.13	3.64	–9.30	5.01	3.73	–9.27	5.37	3.48
Proline	–9.59	2.57	7.27	–9.60	2.51	7.44	-	-	-
Solvent[e]	–9.00	-	-	–9.00	-	-	–9.00	-	-

[a] General conditions: DOSY experiments were carried out on a 400 MHz spectrometer, at 298 K, under the conditions specified in the Experimental Section. NMR samples contain a coaxial capillary tube filled up with D_2O. Viscosity of α,α-dichloroacetone **1** was experimentally determined as η = 1.168 cp, employing an Ostwald viscosimeter (see SI for details). DOSY is measured in a logarithmic scale. The accuracy of the measurement is ±0.01 unit. [b] Sample 3 (**S3**): prepared from NBu_4BF_4 (0.04 mmol) and DL-proline (0.06 mmol) in freshly distilled α,α-dichloroacetone **1** (4.0 mmol). [c] Sample 4 (**S4**): prepared from NBu_4BF_4 (0.04 mmol) and L-(*S*)-proline (0.06 mmol) in freshly distilled α,α-dichloroacetone **1** (4.0 mmol). [d] Sample 6 (**S6**): prepared from NBu_4BF_4 (0.04 mmol) in freshly distilled α,α-dichloroacetone **1** (4.0 mmol). [e] The diffusion coefficient of the solvent is similar in the three experiments, ensuring that the viscosity of the media does not change.

Figure 3 reproduces the ^{1}H DOSY plots registered for samples **S3** (left) and **S4** (right). The NMR signals in the chemical shift dimension are resolved in the indirect dimension according to their diffusion coefficient, which results in well-defined traces for each of the diffusing species. In the two spectra of Figure 3, it can be observed that the amino acid diffuses much slower than the NBu_4^+ cation of the salt, in agreement with proline species being larger than the NBu_4^+ cation. The diffusion coefficient values measured for DL-proline and L-(*S*)-proline accounts for species in solution whose hydrodynamic radius are 7.27 Å and 7.44 Å, respectively. These values are much larger than the radii calculated from their X-ray structures ($r_{X\text{-}ray}$ (DL-proline) = 3.187 Å, and $r_{X\text{-}ray}$ (L-proline) = 3.218 Å),[24] and therefore than the value expected for a discrete monomeric proline unit in solution. These findings support the hypothesis of DL- and L-(*S*)-proline exhibiting a high degree of molecular self-aggregation within the α□α-dichloroacetone solution. The aggregation number can be derived from the reference compound NBu_4BF_4. In this sense, the ^{1}H and ^{19}F DOSY data collected for the lone NBu_4BF_4 salt in solution (Table 2, **S6**) agree with the cation NBu_4^+ and the anion BF_4^- diffusing separately. Furthermore, the hydrodynamic radius calculated from ^{19}F DOSY for the BF_4^- anion (r_H = 3.48 Å) is in agreement with the radius calculated for this anion (3.43 Å) from published X-ray diffraction data for the structurally related salt NPr_4BF_4.[25] The analysis of the DOSY spectra of samples **S3**, **S4** and **S6** also shows that the diffusion coefficient of the ammonium cation (NBu_4^+) is not influenced by the presence of DL-proline or L-(*S*)-proline, presenting in the three cases the same value: log D_{NBu4} = –9.40 m^2/s (Table 2). Thus, an interaction of NBu_4^+ with the amino acid

aggregate can be discarded. As a result, the cation NBu_4^+ can be established as a valid reference probe to estimate the size of the proline clusters.

Figure 3. ^{1}H NMR DOSY spectra (400 MHz, 298 K) registered on samples containing NBu_4BF_4 (0.04 mmol), DL-proline (0.06 mmol), in α,α-dichloroacetone (4.0 mmol) (left, **S3** in Table 2); and NBu_4BF_4 (0.04 mmol), L-(*S*)-proline (0.06 mmol), in α,α-dichloroacetone (4.0 mmol) (right, **S4** in Table 2). The samples contain a coaxial capillary tube filled up with D_2O. DOSY is measured in a logarithmic scale. The accuracy of the measurement is ±0.01 unit.



The relationship $(D_{NBu4}/D_{DL\text{-}pro})^3 = (MW_{DL\text{-}pro}/MW_{NBu4})$ allows estimating a molecular weight for the DL-proline aggregate (Table 2, **S3**) of about $MW_{DL\text{-}pro} = 242.46 \times (3.98/2.57)^3 = 900.51$ g/mol, which is nearly 8-fold the molecular weight of one proline unit (900.51 / 115.13 = 7.82). When the same calculation is carried out for the solution featuring L-(*S*)-proline (Table 2, **S4**), the ratio $(D_{NBu4} / D_{L\text{-}pro})^3$ estimates a molecular weight $MW_{L\text{-}pro} = 242.46 \times (3.98/2.51)^3 = 966.65$ g/mol. This number is also in agreement with an aggregation of 8 proline units (966.65 / 115.13 = 8.40). As a consequence, these results suggest that proline exists in the α□α-dichloroacetone solution as a self-associated octamer in samples prepared from either the racemic or the enantiopure amino acid.

The self-association of amino acids is documented in literature and has been studied mainly through mass spectrometry techniques.[26] Self-association in octameric clusters is well-established for serine,[26a] while L-(*S*)-proline octamers have been previously detected through coldspray ionization mass spectrometry.[26b] To our knowledge, proline clusters had not been previously identified by NMR spectroscopy so this work complements the existing techniques and allows studying the association phenomenon in solution.

Next we carried out the diffusion study on NMR samples containing the tetrafluoroborate guanidinium salt **5**, featured in our full catalytic system (Table 3, samples **S1**, **S2** and **S5**).

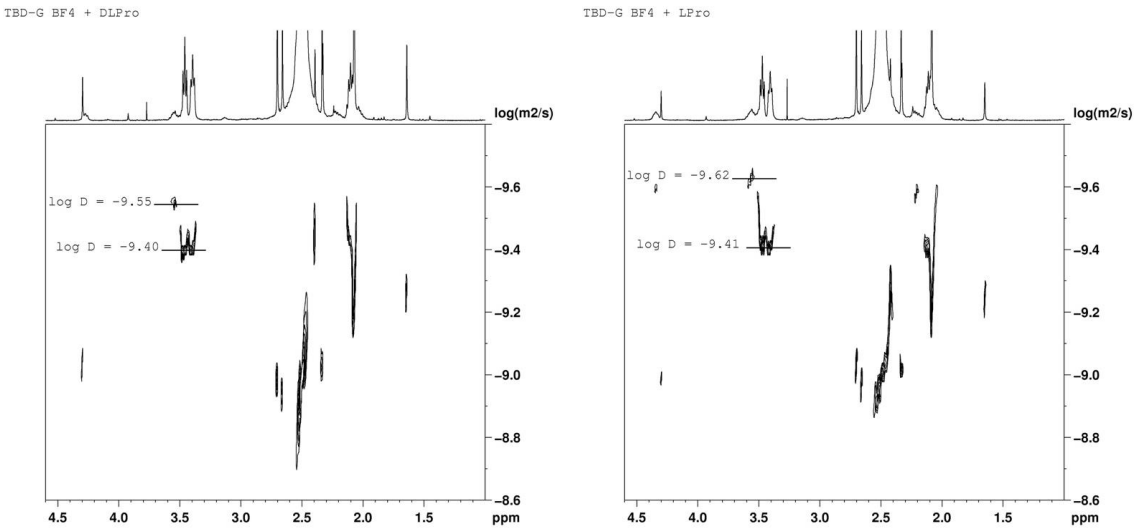
Table 3. Data from ^{1}H and ^{19}F-DOSY NMR experiments performed on samples **S1**, **S2**, **S5**.[a]

	Sample **S1**[b] (DL-proline + guanidinium salt **5**)			Sample **S2**[c] (L-proline + guanidinium salt **5**)			Sample **S5**[d] (guanidinium salt **5**)		
	log D (m^2/s)	D (10^{-10} m^2/s)	r_H (Å)	log D (m^2/s)	D (10^{-10} m^2/s)	r_H (Å)	log D (m^2/s)	D (10^{-10} m^2/s)	r_H (Å)
Guanidinium$^+$	–9.40	3.98	4.69	–9.41	3.89	4.80	–9.31	4.89	3.81
Guanidinium$^+$ NH	–9.04	9.12	-	–9.19	6.46	-	–9.29	5.13	3.64
BF_4^-	–9.30	5.01	3.73	–9.36	4.36	4.28	–9.28	5.25	3.56
Proline	–9.55	2.82	6.63	–9.62	2.40	7.79	-	-	-
Solvent[e]	–9.00	-	-	–9.00	-	-	–9.00	-	-

[a] General conditions: DOSY experiments were carried out on a 400 MHz spectrometer, at 298 K, under the conditions specified in the Experimental Section. NMR samples contain a coaxial capillary tube filled up with D_2O. Viscosity of α,α-dichloroacetone **1** was experimentally determined as η = 1.168 cp, employing an Ostwald viscosimeter (see SI for details). DOSY is measured in a logarithmic scale. The accuracy of the measurement is ±0.01 unit. [b] Sample 1 (**S1**): prepared from tetrafluoroborate guanidinium salt **5** (0.04 mmol) and DL-proline (0.06 mmol) in freshly distilled α,α-dichloroacetone **1** (4.0 mmol). [c] Sample 2 (**S2**): prepared from tetrafluoroborate guanidinium salt **5** (0.04 mmol) and L-(*S*)-proline (0.06 mmol) in freshly distilled α,α-dichloroacetone **1** (4.0 mmol). [d] Sample 5 (**S5**): prepared from tetrafluoroborate guanidinium salt **5** (0.04 mmol) in freshly distilled α,α-dichloroacetone **1** (4.0 mmol). [e] The diffusion coefficient of the solvent is similar in the three experiments, ensuring that the viscosity of the media does not change. Accordingly, the observed differences between samples **S1**, **S2** and **S5** is a consequence of intermolecular interactions.

Figure 4 shows ^{1}H DOSY plots corresponding to samples **S1** (left; consisting of α,α-dichloroacetone (4.0 mmol), tetrafluoroborate guanidinium salt **5** (0.04 mmol), DL-proline (0.06 mmol)) and **S2** (right; α,α-dichloroacetone (4.0 mmol), tetrafluoroborate guanidinium salt **5** (0.04 mmol), and L-(*S*)-proline (0.06 mmol)). Inspection of the DOSY spectra reveals that DL-proline and L-(*S*)-proline remain aggregated. However, in this occasion the measured diffusion coefficients for the homochiral and the heterochiral aggregates are significantly different. It is also worth remarking that the guanidinium cation displays unalike diffusion coefficients in the presence of DL-proline (sample **S1**) or in the sample containing L-(*S*)-proline (sample **S2**). Moreover, these later values are smaller in comparison to the one measured on sample **S5**, where there is no amino acid. This finding is in agreement with a size increment of the guanidinium ion as a consequence of the establishment of H-bond interactions with the proline aggregates, presumably from the acidic NH moieties featured in the guanidinium core. It also gives an account on the different size of the homochiral and heterochiral proline aggregates, discussed above, which is a direct consequence of their association with the guanidinium cation rather than a variation in the number of aggregated proline monomers. It is worth recalling that, as it was discussed before, the NBu_4^+ cation of the salt NBu_4BF_4 presents the same diffusion coefficient in samples **S3**, **S4**, and **S6**, which indicates the lack of interactions between this cation and the amino acid clusters.

Figure 4. ^{1}H NMR DOSY spectra (400 MHz, 298 K) registered on samples containing tetrafluoroborate guanidinium salt **5** (0.04 mmol), DL-proline (0.06 mmol), in α,α-dichloroacetone (4.0 mmol) (left, **S1** in Table 3); and tetrafluoroborate guanidinium salt **5** (0.04 mmol), L-(*S*)-proline (0.06 mmol), in α,α-dichloroacetone (4.0 mmol) (right, **S2** in Table 3). The samples contain a coaxial capillary tube filled up with D_2O. DOSY is measured in a logarithmic scale. The accuracy of the measurement is ±0.01 unit.



Additionally, more differences can be appreciated between the two NMR samples under study (Table 3, samples **S1** and **S2**) concerning the behavior in solution of the BF_4^- anion that accompanies the guanidinium core in salt **5**, and the NH groups of the later:

a) The BF_4^- anion displays different diffusion coefficient in either of the examined samples **S1**, **S2**, or **S5**. Particularly, the values obtained from **S1** and **S2** are significantly dissimilar. Comparing the number measured from sample **S5**, where there is no amino acid, with the values obtained from **S1** and **S2** (Table 3) it can be concluded that the presence of the L-(*S*)-proline aggregate promotes a stronger diminution in the diffusion coefficient of BF_4^- than the presence of the DL-proline aggregate does. These findings are in agreement with the BF_4^- anion being also engaged in the interactions that the guanidinium

core establishes with the proline aggregates in the cases where they exist, as a consequence of anion-cation interactions. Moreover, it is important to signal out that the participation of the BF_4^- anion in this interaction is larger with the homochiral aggregate than with the heterochiral cluster, as it is reflected by the unlike enlargement of the hydrodynamic radii of BF_4^- measured by the ^{19}F NMR DOSY experiments on sample **S1** (Table 3, $r_H(BF_4^-)$ = 3.73 Å), and sample **S2** (Table 3, $r_H(BF_4^-)$ = 4.28 Å), when compared to sample **S5** ($r_H(BF_4^-)$ = 3.56 Å).

b) The resonances corresponding to the NH motifs of the guanidinium salt **5** present different chemical shift (δ_{NH} = 7.87 ppm for sample **S1**, □and δ_{NH} = 7.37 for sample **S2**) and display different diffusions coefficient depending on whether it accompanies the DL- or the L-(*S*)-proline aggregate (Table 3, samples **S1** and **S2**). It supports a more labile character of the NH groups in the presence of DL-proline than in the presence of L-(*S*)-proline.

Recapitulating, from our NMR study, it has been solidly proved that the tetrafluoroborate guanidinium salt **5** interacts with octameric proline aggregates through both the cation and the anion, being this interaction established in larger extension with the homochiral L-(*S*)-proline self-aggregate than with the heterochiral cluster resulting of the association of DL-amino acid units. The addition of salt **5** is crucial for our cross-aldol reaction to take place, as it has been manifested from the discussion of Table 1 (entries 3 and 4). Previously,[2a] we had envisioned the guanidinium salt playing a role in enhancing the electrophilicity of aromatic aldehydes in cross-aldol reactions through the formation of H-bond arrays with their carbonyl function. Our recent findings back up this hypothesis: the more intense the interaction of guanidinium salt **5** (cation

+ anion) with the L-(*S*)-proline aggregate, the more hampered it is for activating the aldehyde. On the contrary, a weaker interaction of **5** with the heterochiral cluster results in a guanidinium cation more accessible for participating in other H-bonding recognition events.

Pursuing this thesis, the effect of the catalytic system on the aldehyde **2a** was evaluated by ^{1}H and ^{19}F DOSY experiments carried out on NMR samples containing the full set of reagents: DL-proline, or alternatively L-(*S*)-proline, guanidinium salt **5**, 4-nitrobenzaldehyde **2a**, dissolved in α,α-dichloroacetone under the optimized reaction conditions (see DOSY spectra in Figures SI_16-23, and Table SI_1 in the SI file). As it was expected, the corresponding ^{19}F and ^{1}H DOSY spectra showed differences in the diffusing behavior of the cation and the anion of the guanidinium salt **5** in each of the NMR samples. While the diffusion coefficient of the BF_4^- anion matches the value of its cationic fragment in the L-(*S*)-proline catalyzed reaction (log D_{BF4} = –9.50 m^2/s, and log $D_{guanidinium}$ = –9.50 m^2/s), anion and cation display different values for the DL-proline-catalyzed process (log D_{BF4} = –9.46 m^2/s; and log $D_{guanidinium}$ = –9.54 m^2/s). In agreement with the former discussion, this experimental observation points out that the guanidinium cation fragment of salt **5** is more available to establish H-bonds contacts with the aldehyde in the presence of the heterochiral proline aggregate that in the company of the homochiral assembly. Complementarily, the changes in the hydrodynamic radii as a consequence of H-bonding interactions with the aldehyde were estimated through comparison of relative diffusion coefficients, as it has been previously described in in the literature,[20b] choosing the solvent as the reference compound. This procedure avoids

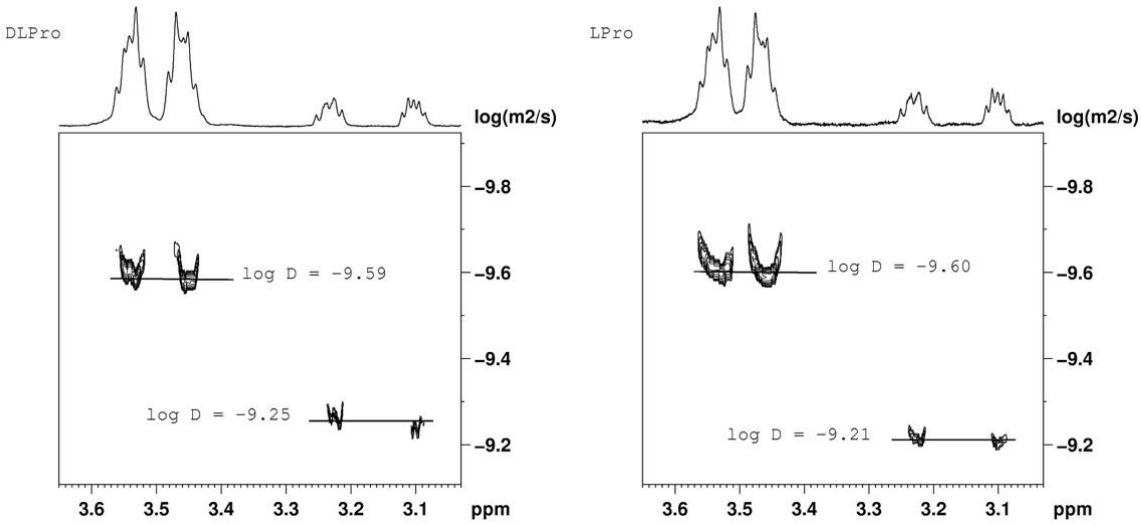
misleading results derived from alterations in the viscosity of the medium, which would be reflected in the diffusion coefficients measured.

For both the DL- and L-(*S*)-proline catalytic systems, the ratio $D_{guanidinium}$ / $D_{solvent}$ was compared before and after the addition of 4-nitrobenzaldehyde **2a**, so that an increase of the hydrodynamic radius of the guanidinium salt $r_{H(guanidinium)}$ attributable to H-bonding with the aldehyde was obtained. The experiments reveal that a size increment for the guanidinium cation of salt **5** is noticed in the case of the DL-proline catalyzed reaction mixture, with a size increment of a 10% ((Δr_H (DL) = 1.10). On the contrary, this effect is not observed for the L-(*S*)-proline-catalyzed mixture (Δr_H (L) = 1.00) (see Table SI_2 in the SI file). Again, these results support a more effective coordination of 4-nitrobenzaldehyde **2a** with the guanidinium core of salt **5** in the presence of the heterochiral amino acid aggregate than in the presence of the homochiral cluster.

In the end, we decided to study the behavior of proline itself in α,α-dichloroacetone. For that means, we prepared two NMR samples containing the amino acid in the same concentration present in the reaction mixtures: 0.06 mmol of DL-proline (sample **S7**), or L-(*S*)-proline (sample **S8**), in 4.0 mmol of freshly distilled α,α-dichloroacetone **1**. Interestingly, apart from the expected NMR signals corresponding to the proline aggregates, a second minor set of signals was observed, in a similar ratio, for both sample **S7** and **S8** (Figure 5). For those resonances, their chemical shift and line shape permit their assignment to protons belonging also to a proline molecule. The ^{1}H DOSY

spectra revealed very different diffusion coefficients for the major and the minor set of signals (log D_{major} = –9.59 m^2/s, log D_{minor} = –9.25 m^2/s in sample **S7**; and log D_{major} = –9.60 m^2/s, log D_{minor} = –9.21 m^2/s in sample **S8**).

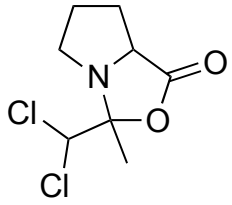
Figure 5. ^1H NMR DOSY spectra (400 MHz, 298 K) registered on sample **S7** (left, DL-proline (0.06 mmol), in freshly distilled α,α-dichloroacetone (4.0 mmol)) and on sample **S8** (right, L-proline (0.06 mmol), in freshly distilled α,α-dichloroacetone (4.0 mmol)). Both samples contain a coaxial capillary tube filled up with D_2O. DOSY is measured in a logarithmic scale. The accuracy of the measurement is ±0.01 unit.



In order to elucidate the structure of this compound, an NMR study including ^1H–^1H and ^1H–^{13}C correlations, and selective NOE experiments, was performed on both samples **S7** and **S8** (Figures SI_24 to SI_36 in the SI file). Analysis of the spectra led us to identify the minor component of these samples as the oxazolidinone **6** represented in Figure 6, existing as mixture of diastereoisomers.[27] Also, the value of its diffusion coefficients in the ^1H DOSY experiment led us to calculate the hydrodynamic radii of **6** (r_H = 3.3 Å, measured from sample **S7**), which is close to the radii calculated for DL- and L-(*S*)-proline

from X-ray diffraction experiments.[24] Hence, specie **6** can be assessed as a monomeric unit in solution. On the contrary most of the amino acid participates in the aggregated form already discussed. The formation of **6** can be explained by a nucleophilic attack of a proline unit, detached from the self-aggregated cluster, on the α□α-dichloroketone used as solvent with the extrusion of a molecule of water.

Figure 6. Structure of oxazolidinone **6** (mixture of diastereoisomers) identified *in situ* from samples **S7** and **S8** by ^{1}H NMR spectrosopy.

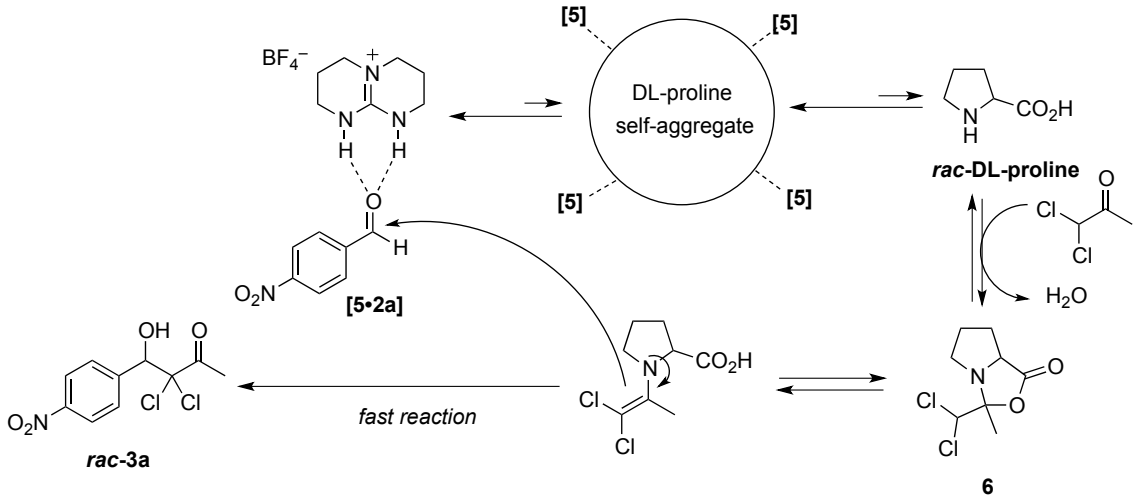


6

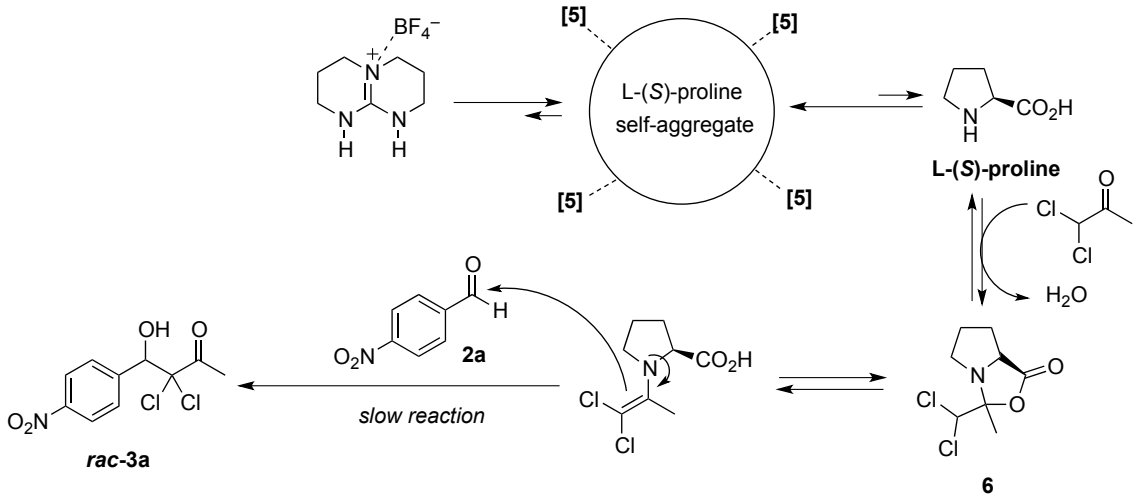
Although the oxazolidinone **6** was detected in the NMR samples containing the full set of reagents, although it could not be studied by DOSY. We believe it is implied in the mechanism of our reaction (Figure 7), as it is widely accepted for proline-catalyzed aldolizations.[28] Tentatively, oxazolidinone **6** is in equilibrium with the enamine specie **7**, which is the nucleophile that attacks 4-nitrobenzaldehyde **2a**, somehow activated through H-bond contacts by the guanidinium cation of salt **5**, **[2a•5]**,[29] promoted by the presence of the DL-amino acid self-aggregate (Figure 7A).

Figure 7. Mechanistic proposal for the formation of α,α-dichloro-β-hydroxyketone **3a** from 4-nitrobenzaldehyde **2a** and α,α-dichloroacetone in the presence of DL-proline self-aggregate (**A**, top), or L-(*S*)-proline self-aggregate (**B**, bottom).

A)



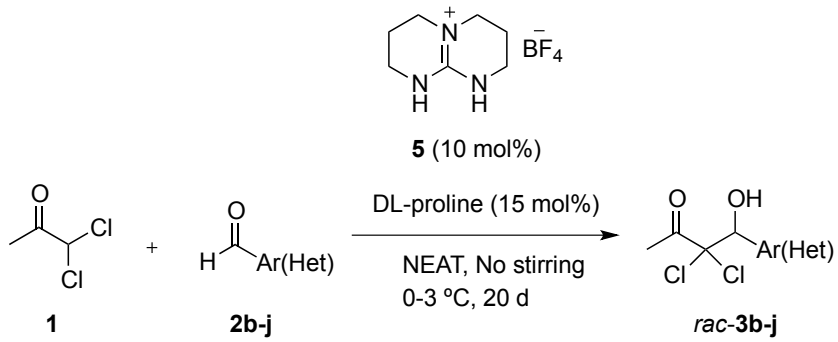
B)



To verify that the performance of our cooperative proline/guanidinium salt catalytic system was not exclusive of 4-nitrobenzaldehyde **2a** being selected as an electrophile, a set of aromatic aldehydes **2b-i**, displaying different functional groups and substitution patterns, were reacted with ketone **1** under our finest reaction conditions (Table 4, entries 1-7). The reactions were satisfactory employing the racemic amino acid, but inefficient when they were attempted with the L-(*S*)-proline system. As it is outlined in Table 4 the corresponding α□α□dichloro-β□hydroxy methyl ketones could be isolated in good yield.

Moreover, 3-pyridylcarboxaldehyde, **2j**, a challenging substrate for the aldol reaction, proved to be appropriate for our protocol (Table 4, entry 8).

Table 4. DL-Proline/guanidinium salt **5** co-catalyzed synthesis of α□α□dichloro-β□hydroxy methyl ketones **3**.[a]



entry	Ar–CHO	conversion (%)[b]
1	**2b**, 3-NO_2-C_6H_4	96 (76)
2	**2c**, 2-NO_2-C_6H_4	87[c]
3	**2d**, 2,4-diNO_2-C_6H_3	89 (80)
4	**2e**, 4-CN-C_6H_4	91 (82)
5	**2f**, 4-CO_2Me-C_6H_4	78 (61)
6	**2g**, 4-F-C_6H_4	99 (66)
7	**2h**, 4-Cl-C_6H_4	99 (69)
8	**2i**, 4-Br-C_6H_4	65 (64)
9	**2j**, 3-pyridyl	90 (73)

[a] Reaction conditions: dichloroacetone **1** (2.0 mmol), ArCHO (0.2 mmol), DL-proline (0.03 mmol, 15 mol%), **5** (0.02 mmol, 10 mol%), no solvent. Reaction mixtures were left to stand 20 d inside a standard laboratory fridge (0–3 ˚C) with no stirring. [b] Determined by ^{1}H NMR spectroscopy of the crude reaction mixtures. Conversion of aldehydes **2** (limiting reagent) into α□α□dichloro-β□hydroxy ketones **3**, quantified against $CHBr_3$ (9 μL, 0.103 mmol) used as analytical internal standard. Isolated yield of analytical pure product is given in brackets. [c] Product **3c** can not be fully separated from unreacted 2-nitrobenzaldehyde.

CONCLUSIONS

Summing up, a cooperative DL-proline/TBD-derived tetrafluoroborate guanidinium salt pair catalyzes the cross-aldol reaction between α□α□dichloroacetone and aromatic aldehydes, rendering the corresponding α□α□dichloro-β□hydroxy ketones in excellent yield. Surprisingly, the system consisting of L-(*S*)-proline and the guanidinium salt is unsuccessful. Accordingly, the catalytic activities of these two closely related but distantly effective systems has been studied by ^{1}H and ^{19}F DOSY NMR, a non-invasive technique that allows gaining insight into the behavior of different species in solution and the interactions that can establish one with another. By these means, the self-organization of proline in octameric aggregates has been detected in solution for the first time. Homochiral aggregates derived from L-(*S*)-proline and heterochiral aggregates formed from DL-proline have a dissimilar nature, supported by differences in terms of diffusion coefficients and hydrodynamic radii. Their unlikeness has critical consequences on the observed catalytic performance. Particularly, the presence of the homochiral amino acid cluster induces larger ionic interactions between the TBD-derived guanidinium cation and its accompanying BF_4^- anion, and also interactions of the cation and the anion with the cluster. On the contrary, the heterochiral cluster causes a less engaged guanidinim unit. As a consequence, the effectiveness of the guanidinium core to activate the aldehyde through H–bonding contacts from its NH moieties is maximized in the presence of the DL-proline aggregate. These later interactions are ultimately responsible for the catalytic activities observed for the racemic and the chiral system.

With this knowledge we are currently engaged in the study of other supramolecular and catalytic systems capable of being tuned by the incorporation of other additives decorated with H-bond donor or acceptor units. Results will be reported in due course.

EXPERIMENTAL SECTION

General

α,α-Dichloroacetone was freshly distilled under reduced pressure and stored, prevented from light, under nitrogen atmosphere. Aldehydes that are liquids at room temperature (4-fluorobenzaldehyde, 3-pyridyne carboxaldehyde) were distilled under reduced pressure prior to use. Other commercially available reagents and solvents were used without further purification. Guanidinium salt **5** was prepared following the methodology previously described by our group.[2a] Flash chromatography of reaction products was carried out using Silica 60A, particle size 230–400 μm. Analytical thin layer chromatography (TLC) was performed on DC-Alufolien Kieselgel 60F254 0.2 mm plates, and compounds were visualized by UV fluorescence or with a solution of $KMnO_4/K_2CO_3$ in water.

Experimental conditions for NMR experiments

NMR spectra were recorded on a Bruker AV 600 spectrometer operating at 600.15 (^{1}H), 150.91 MHz (^{13}C), using a 5 mm TXI-^{1}H/D-^{13}C/^{15}N probe with a z-gradient coil, or on a Bruker AV 400 spectrometer operating at 400.13 (^{1}H), 376.45 (^{19}F) and 100.61 MHz (^{13}C), using a 5 mm TBO ^{1}H/X-BB/^{31}P/D direct probe with a z-gradient coil, or on a Bruker AV 300 spectrometer operating at 300.13 (^{1}H), and 75.47 MHz (^{13}C), equipped with a 5 mm QNP ^{1}H-^{13}C/^{19}F/^{31}P/D

probe. After the desired time, mixtures were filtered through cotton wool and transferred into 5 mm Wilmad precision NMR tubes. Then, a capillary tube capped with a 5/2.5 mm capillary adapter (New Era), filled up with deuterium oxide for lock acquisition, was introduced inside the NMR sample.

All the experiments were acquired and processed with the TOPSPIN 2.1 Bruker NMR software. The ^{1}H and ^{19}F-DOSY experiments were performed on the AV400 spectrometer. For the 1H nucleus, a 90 degree pulse of 10.50 us for an attenuation level of –2 dB was used. The ^{19}F nucleus was tuned to a basic transmitter frequency of 376.45 MHz through the ^{1}H channel of the probe and detected through the X-BB preamplifier module. To the X-BB channel a D-stop filter and a ^{13}Cstop/^{31}Ppass filter were added. For these conditions the 90 degree pulse was calibrated to 10.76 us for an attenuation level of 0 dB. The gradient unit of the spectrometer produce magnetic field pulsed gradients in the z-axis of 53.5 G/cm. The gradient strength was calibrated using a D_2O sample to obtain a diffusion coefficient of 1.90 x $10^{-9}m^2/s$ for HDO. During the DOSY experiments, the temperature was set to 298 K and maintained with an air flow of 535 l/h. The experiments were acquired with the bipolar longitudinal eddy current delay pulse program (*ledbpgps2s*) in Bruker software. ^{1}H and ^{19}F DOSY experiments were acquired without spinning of the sample, since no convection effects were detected and no differences were observed when spinning was applied,[30] because of the presence of the coaxial capillary tube.[31] The diffusion time (D20) and the gradient duration (P30) were previously optimized with the *ledbpgp2s1d* sequence to get a 1-5% of residual signal with the maximum strength, while observing a progressive decay of the signal intensities. For a typical ^{1}H or ^{19}F- DOSY experiment P30 = was 0.9–1.2 ms and

D20 = 200–300 ms. An eddy current delay (Te) of 5 ms and a spoil gradient (P19) of 0.8 ms were used. The pulse gradients were increased from 5 to 95% of the maximum strength in a linear ramp through 16 steps of 16K data points (for ^{19}F-DOSY) or 24K data points (for ^{1}H-DOSY). For the ^{1}H DOSY experiments the number of scans were 8–16 and a relaxation delay D1 = 1s was used; for the ^{19}F-DOSY the number of scans were 16–32 and a relaxation delay D1 = 2s was used. The direct dimension was zero-filled to 32K, fourier transformed and phase corrected. The diffusion dimension was processed with the standard Bruker dosy algorithm. The diffusion coefficients were measured in a logarithmic scale and the accuracy of the reported values is ±0.01 in that scale.

Standard procedure for the synthesis of α,α-dichloro-β-hydroxy methyl ketones 3a-j (SP1). Tetrafluoroborate guanidinium salt **5** (4.5 mg, 0.02 mmol), *rac*-DL-proline (3.5 mg, 0.03 mmol) and aldehyde **2a-j** (0.2 mmol) were weighed together inside a screw-capped test tube. Freshly distilled α,α-dichloroacetone (254 mg, 0.19 mL, 2.0 mmol) was added to the mixture, and the resulting suspension, placed on a test tubes grid, was allowed to stay 20 d inside a standard laboratory fridge (temperature fixed at 0–3 ºC) without agitation or mechanical stirring. The mixture was then quenched with NH_4Cl (aq. sat.) and extracted with DCM (2 × 15 mL), and the organic liquors were dried ($MgSO_4$). Solvents and excess of ketone were evacuated under reduced pressure. Crude reaction mixtures were filtered through a plug of silica gel, eluting with an EtOAc/hexane mixture, to afford analytically pure aldols **3a-j**.

3,3-Dichloro-4-hydroxy-4-(4-nitrophenyl)butan-2-one (3a).

Prepared according to **SP1**. Purified by flash chromatography (hexane/EtOAc, 4:1). Obtained as a pale-yellow solid, 51 mg, 91% isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.23 (2H, d, *J* = 8.8 Hz, ArC*H*), 7.74 (2H, d, *J* = 8.8 Hz, ArC*H*), 5.50 (1H, s, C*H*), 3.68 (1H, broad s, O*H*), 2.60 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.5 (*C*(O)), 148.5 (Ar*C*), 142.9 (Ar*C*), 130.6 (Ar*C*H), 123.0 (Ar*C*H), 87.9 (*C*Cl_2), 76.3 (*C*HOH), 24.6 (*C*H_3); MS (ESI$^+$): *m/z* (%) = 300 (100) [*M* + Na]$^+$; HRMS (ESI$^+$): *m/z* calcd. for [$C_{10}H_9Cl_2NO_4$ + Na]$^+$ 299.9801, found 299.9800.

3,3-Dichloro-4-hydroxy-4-(3-nitrophenyl)butan-2-one (3b).

Prepared according to **SP1**. Purified by flash chromatography (Hexane/EtOAc, 4:1). Obtained as a pale-yellow solid, 42 mg, 76% isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.44 (1H, s, Ar*H*), 8.24 (1H, dd, *J* = 8.2, 2.1 Hz, Ar*H*), 7.89 (1H, d, *J* = 7.7 Hz, Ar*H*), 7.56 (1H, t, *J* = 8.2 Hz Hz, Ar*H*), 5.50 (1H, s, C*H*), 3.68 (1H, broad s, O*H*), 2.61 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.6 (*C*(O)), 148.0 (Ar*C*), 138.1 (Ar*C*), 135.7 (Ar*C*H), 128.9 (Ar*C*H), 124.7 (Ar*C*H), 124.2 (Ar*C*H), 88.0 (*C*Cl_2), 76.3 (*C*HOH), 24.6 (*C*H_3); MS (ESI$^+$): *m/z* (%) = 300 (100) [*M* + Na]$^+$; HRMS (ESI$^+$): *m/z* calcd. for [$C_{10}H_9Cl_2NO_4$ + Na]$^+$ 299.9801, found 299.9800.

3,3-Dichloro-4-hydroxy-4-(2-nitrophenyl)butan-2-one (3c).

Prepared according to **SP1**. Purified by flash chromatography (Hexane/EtOAc, 4:1). Obtained as a pale-yellow solid, 45 mg, 80% isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.05 (1H, dd, *J* = 7.9, 1.4 Hz, Ar*H*), 7.89 (1H, dd, *J* = 8.2, 1.4 Hz, Ar*H*), 7.68 (1H, td, *J* = 7.7, 1.4 Hz, Ar*H*), 7.54 (1H, td, *J* = 7.7, 1.4 Hz, Ar*H*), 6.59 (1H, s, C*H*), 3.65 (1H, broad s, O*H*), 2.58 (3H, s, CH_3); ^{13}C NMR (75 MHz, CDCl3): δ = 197.9 (*C*(O)), 132.3 (Ar*C*H), 131.2 (Ar*C*H), 130.1 (Ar*C*), 129.6

(Ar*C*H), 124.5 (Ar*C*H), 124.1 (Ar*C*), 88.1 (*C*Cl_2), 69.4 (*C*HOH), 23.9 (*C*H_3); MS (ESI$^+$): *m/z* (%) = 300 (100) [*M* + Na]$^+$; HRMS (ESI$^+$): *m/z* calcd. for [$C_{10}H_9Cl_2NO_4$ + Na]$^+$ 299.9801, found 299.9800.

3,3-Dichloro-4-hydroxy-4-(2,4-dinitrophenyl)butan-2-one (3d).

Prepared according to **SP1**. Purified by flash chromatography (Hexane/EtOAc, 3:1). Obtained as a yellow solid, 52 mg, 80% isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.76 (1H, d, *J* = 2.3 Hz, ArC*H*), 8.51 (1H, dd, *J* = 8.7, 2.4 Hz, ArC*H*), 8.31 (1H, d, *J* = 8.7 Hz, ArC*H*), 6.66 (1H, s, C*H*OH), 3.80 (1H, broad s, O*H*), 2.59 (3H, s, C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.5 (*C*(O)), 149.7 (Ar*C*), 148.2 (Ar*C*), 137.0 (Ar*C*), 133.5 (Ar*C*H), 126.6 (Ar*C*H), 119.9 (Ar*C*H), 87.3 (*C*Cl_2), 69.5 (*C*H), 24.1 (*C*H_3); MS (ESI+): *m/z* (%) = 345 (100) [*M* + Na]$^+$; HRMS (ESI$^+$): *m/z* calcd. for [$C_{10}H_8Cl_2N_2O_6$ + Na]$^+$ 344.9652, found 344.9650.

3,3-Dichloro-4-hydroxy-4-(4-cyanophenyl)butan-2-one (3e).

Prepared according to **SP1**. Purified by flash chromatography (Hexane/EtOAc, 4:1). Obtained as a white solid, 42 mg, 82% isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69–7.67 (4H, m, Ar*H*), 5.44 (1H, s, C*H*), 3.58 (1H, broad s, O*H*), 2.60 (3H, s, C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.6 (*C*(O)), 141.1 (Ar*C*), 131.7 (Ar*C*H), 130.4 (Ar*C*H), 118.9 (Ar*C*), 113.1 (*C*N), 88.0 (*C*Cl_2), 76.6 (*C*HOH), 24.6 (*C*H_3); MS (ESI$^+$): *m/z* (%) = 280 (100) [*M* + Na]$^+$; HRMS (ESI$^+$): *m/z* calcd. for [$C_{11}H_9Cl_2NO_2$ + Na]$^+$ 279.9903, found 279.9903.

3,3-Dichloro-4-hydroxy-4-(4-methoxycarbonylphenyl)butan-2-one (3f).

Prepared according to **SP1**. Purified by flash chromatography (Hexane/EtOAc, 4:1). Obtained as a white solid, 36 mg, 61% isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.03 (2H, d, *J* = 8.3 Hz, ArC*H*), 7.62 (2H, d, *J* = 8.3 Hz, ArC*H*), 5.43 (1H, s, C*H*), 3.91 (3H, s, CO_2C*H*$_3$), 3.62 (1H, broad s, CHO*H*), 2.57 (3H, s,

C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.6 (*C*(O)), 167.1 (*C*$O_2$$CH_3$), 140.9 (Ar*C*), 130.9 (Ar*C*), 129.6 (Ar*C*H), 129.1 (Ar*C*H), 88.6 (*C*Cl_2), 76.9 (*C*HOH), 52.5 (CO_2*C*H_3), 24.8 (*C*H_3); MS (ESI$^+$): *m/z* (%) = 313 (100) [*M* + Na]$^+$; HRMS (ESI$^+$): *m/z* calcd. for [$C_{12}H_{12}Cl_2O_4$ + Na]$^+$ 313.0005, found 313.0004.

3,3-Dichloro-4-hydroxy-4-(4-fluorophenyl)butan-2-one (3g).

Prepared according to **SP1**. Purified by flash chromatography (Hexane/EtOAc, 4:1). Obtained as a white solid, 33 mg, 66% isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55–7.50 (2H, m, ArC*H*), 7.07 (2H, t, *J* = 8.6 Hz, ArC*H*), 5.38 (1H, s, C*H*), 2.58 (3H, s, C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.9 (*C*(O)), 163.4 (1C, d, *J* = 247.4 Hz, *C*F), 131.8 (2C, d, *J* = 3.2 Hz, Ar*C*), 131.3 (2C, d, *J* = 8.3 Hz, Ar*C*H), 115.0 (2C, d, *J* = 21.4 Hz, Ar*C*H), 88.8 (*C*Cl_2), 76.8 (*C*HOH), 24.9 (*C*H_3); ^{19}F NMR (282 MHz, $CDCl_3$): δ = –112.9; MS (ESI$^+$): *m/z* (%) = 273 (15) [*M* + Na]$^+$; HRMS (ESI$^+$): *m/z* calcd. for [$C_{10}H_9Cl_2FO_2$ + Na]$^+$ 272.9856, found 272.9855.

3,3-Dichloro-4-hydroxy-4-(4-chlorophenyl)butan-2-one (3h).

Prepared according to **SP1**. Purified by flash chromatography (Hexane/EtOAc, 4:1). Obtained as a white solid, 37 mg, 69% isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48 (2H, d, *J* = 8.6 Hz, ArC*H*), 7.35 (2H, d, *J* = 8.6 Hz, ArC*H*), 5.37 (1H, s, C*H*), 3.49 (1H, broad s, CHO*H*), 2.58 (3H, s, C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.7 (*C*(O)), 135.2 (Ar*C*), 134.5 (Ar*C*), 130.9 (Ar*C*H), 128.2 (Ar*C*H), 88.9 (*C*Cl_2), 76.8 (*C*HOH), 24.9 (*C*H_3); MS (ESI$^+$): *m/z* (%) = 289 (100) [*M* + Na]$^+$; HRMS (ESI$^+$): *m/z* calcd. for [$C_{10}H_9Cl_3O_2$ + Na]$^+$ 288.9560, found 288.9560.

3,3-Dichloro-4-hydroxy-4-(4-bromophenyl)butan-2-one (3i).

Prepared according to **SP1**. Purified by flash chromatography (Hexane/EtOAc, 4:1). Obtained as a white solid, 40 mg, 64% isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.51 (2H, d, *J* = 8.4 Hz, ArC*H*), 7.41 (2H, d, *J* = 8.4 Hz, ArC*H*), 5.35 (1H, s, C*H*), 3.42 (1H, broad s, O*H*), 2.58 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.8 (*C*(O)), 135.0 (Ar*C*), 131.2 (2 x Ar*C*H), 123.5 (Ar*C*), 88.7 (*C*Cl_2), 76.8 (*C*H), 24.8 (*C*H_3); MS (ESI$^+$): *m/z* (%) = 335 (100) [*M* + Na]$^+$; HRMS (ESI$^+$): *m/z* calcd. for [$C_{10}H_9Cl_2BrO_2$ + Na]$^+$ 334.9055, found 334.9031.

3,3-Dichloro-4-hydroxy-4-(3-pyridyl)butan-2-one (3j).

Prepared according to **SP1**. Purified by flash chromatography (Hexane/EtOAc, 1:1). Obtained as a white solid, 34 mg, 73% isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.71 (1H, s, Ar*H*), 8.58 (1H, s, Ar*H*), 7.98 (1H, d, *J* = 8.1 Hz, Ar*H*), 7.36 (1H, dd, *J* = 8.0, 4.0 Hz, Ar*H*), 5.45 (1H, s, C*H*OH), 4.19 (1H, broad s, O*H*), 2.60 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.4 (*C*(O)), 150.1 (Ar*C*H), 149.7 (Ar*C*H), 137.7 (Ar*C*H), 132.7 (Ar*C*), 123.4 (Ar*C*H), 88.6 (*C*Cl2), 75.3 (*C*HOH), 24.9 (*C*H_3); MS (ESI$^+$): *m/z* (%) = 234 (60) [*M* + H]$^+$; HRMS (ESI$^+$): *m/z* calcd. for [C9H9Cl2NO2 + H]+ 234.0083, found 234.0081.

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SUPPORTING INFORMATION

The Supporting Information (SI) file contains: (a) Full ^{1}H and ^{19}F DOSY NMR spectra of samples **S1**–**S6**; (b) ^{1}H and ^{19}F DOSY NMR spectra of samples containing the catalytic system DL-proline/guanidinium salt and L-(*S*)-proline/guanidinium salt, and a Table summarizing the diffusion coefficients and hydrodynamic radii of all the species involved; (c) DOSY NMR experiments comparing the diffusion coefficient of guanidinium salt **5**, in the presence of DL- or L-proline, before and after the addition of 4-nitrobenzaldehyde **2a**; (d) Characterization of oxazolidinone **6** by *in situ* NMR experiments on samples **S7** and **S8**; (e) Copies of ^{1}H and ^{13}C NMR spectra for compounds **3a-j**.

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