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Abstract	Organocatalysis is nowadays recognized as the third pillar of asymmetric synthesis, standing next to metal catalysis and enzymatic transformations. Proline has shown up as an ideal organocatalyst, being inexpensive and readily available. However, this amino acid has also manifested its limitations. Compared to the chemical modification of proline, the approach through adding small hydrogen-bond-donating cocatalysts to interact with proline is particularly attractive. Various additives have been investigated to date. This chapter discloses the use of guanidinium salts as additives for proline, investigated in the course of proline-catalyzed aldol reactions.	
Keywords (separated by '-')	Guanidinium salts - Organocatalysis - Proline - Supramolecular chemistry	

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Cooperative Guanidinium/Proline Organocatalytic Systems

Carmen Concellón and Vicente del Amo

Abstract Organocatalysis is nowadays recognized as the third pillar of asymmetric synthesis, standing next to metal catalysis and enzymatic transformations. Proline has shown up as an ideal organocatalyst, being inexpensive and readily available. However, this amino acid has also manifested its limitations. Compared to the chemical modification of proline, the approach through adding small hydrogen-bond-donating cocatalysts to interact with proline is particularly attractive. Various additives have been investigated to date. This chapter discloses the use of guanidinium salts as additives for proline, investigated in the course of proline-catalyzed aldol reactions.

Keywords Guanidinium salts · Organocatalysis · Proline · Supramolecular chemistry

Contents

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1 Brief Introduction to Organocatalysis and Its Limitations

During the last decades, the demand of enantiomerically pure synthetic products has grown exponentially. This request has made asymmetric catalysis the most active area of research in contemporary organic chemistry. Illustratively, 81 of the 200 blockbuster drugs by worldwide sales are enantiopure substances.

Traditional asymmetric catalysis relies on the use of transition metal complexes (organometallic chemistry), or enzymes (biocatalysis). However, recently, a third type of catalysts has appeared: the organocatalysts, with its associated discipline asymmetric organocatalysis. This consists in the use of catalytic or substoichiometric amounts of simple organic molecules to carry out highly enantioselective processes that take place in the absence of metallic elements. The use of organocatalysts shows a number of advantages over the utilization of transition metal complexes: lower toxicity, low environmental impact, and absence of metallic elements which present potential contaminants in final products, many of them synthesized for human or animal intake. Similarly, organocatalysts display advantages over the use of enzymes, which come at a significantly higher prize and scarce availability.

Projects dealing with organocatalysis can be framed inside Green Chemistry and Sustainable Chemistry schemes. The concept of Sustainable Chemistry (in many occasions synonymous with Green Chemistry) refers to actions aiming to improve the efficiency in the use of natural resources. Consequently, it comprises the design and implementation of new chemical processes and transformations operating in a more efficient, safer, and more environmentally friendly way. Having the intention of pursuing those goals, Sustainable Chemistry has been formulated in 12 universally accepted principles, put forward by Anastas and Warner [1, 2]. Organocatalytic processes satisfy several of them: high atomic efficiency, the use of reagents of low or nontoxicity, little generation of residues, and the use of reagents in catalytic amounts. Moreover, the E-factor values of these processes are remarkably low, which is of interest for industry. The E-factor quantifies how toxic/benign a particular chemical process is and is expressed as the ratio of generated waster per kilogram of product produced.

The use of small organic molecules as catalysts in chemical transformations can be tracked back as far as the nineteenth century, to the pioneering works of Emil Knoevenagel [3–6]. It wasn't however until the year 2000, with the findings of List, Lerner, and Barbas on the potential of proline as a catalyst for the intermolecular aldol reaction [7] and those of MacMillan [8], when the research in organocatalysis commenced as a separate and well-defined field. Since then, the interest of the scientific community over this discipline has been phenomenal. Nowadays, the number of publications and literature reviews dealing with different aspects of asymmetric organocatalysis is extraordinarily large. It is far from the objectives of this monograph to cover the multiple and colored possibilities of this field. Nonetheless, the following selected citations (literature reviews) can summarize the state of the art of the discipline [9–23].

Considering their low price and ready availability and based on the study of List [7], proline, or other natural amino acids, would be the first-choice organocatalysts. These naturally occurring compounds are cheap, are readily available in both enantiomeric forms, and can be used for a wide range of synthetic transformations. However, amino acids also present some major drawbacks as organocatalysts, namely, rather limited solubility and reactivity in nonpolar organic solvents, and parasitic side reactions that make using high catalyst loadings necessary to achieve acceptable conversions. To avoid these undesired issues, large efforts have been devoted to the careful design (assisted by molecular modeling) and synthesis of novel tailor-made catalysts. In this sense, the structures shown in Fig. 1, collected from the references cited above, represent some of the thousands of different catalysts that have recently been used in organocatalytic processes. Such processes make use of a classical approach to the phenomenon of catalysis, where a certain novel asymmetric organocatalyst is designed, synthesized, and applied to a particular transformation. The efficiency of the catalyst in question is evaluated in terms of chemical yield, diastereoselection, and/or enantioselection for the product obtained. If the results are unsatisfactory, a second-generation organocatalyst (typically based on the original motif) is redesigned and resynthesized, for being once again evaluated. This type of iterative approach is unattractive for industry, which cannot afford testing every single catalyst on a particular reaction, and also constrained by both economic and time limitations. It has to be noted that the preparation of structures like those represented in Fig. 1 is not trivial and normally encompasses considerable synthetic efforts. Moreover, before having found a good catalyst, many analogues of a proposed design are normally prepared and evaluated.

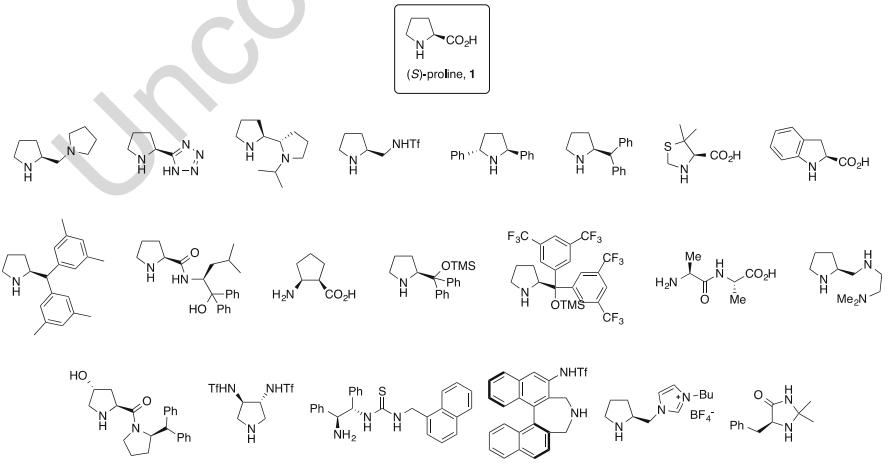


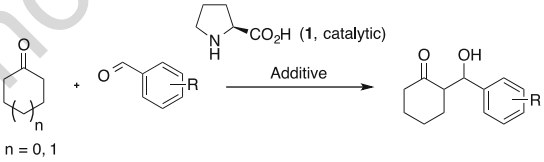
Fig. 1 Structure of (*S*)-proline (**1**) and examples of other structures used as organocatalysts

2 Additives Used for Proline in Organocatalyzed Reactions

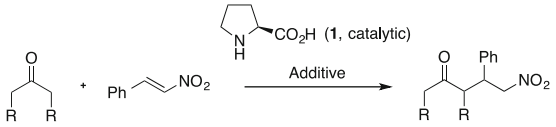
An alternative to the classical approach discussed above consists of adding simple, readily available additives to reactions containing known catalysts, ideally proline, whose behavior is thus reevaluated under the new reaction conditions. This late strategy is significantly beneficial in evading tedious chemical syntheses and would ultimately allow the construction of libraries of catalytic systems by simply changing the additives of choice. Moreover, the possibility of testing various additives in parallel with the aid of high-throughput screening methods is particularly appealing (for high-throughput screening methodologies of additives in organocatalyzed reactions, see [24–26]).

With the aim of avoiding the use of synthetically elaborated organocatalysts, various researches have recently embraced the look for rational additives capable of enhancing the reactivity and selectivity of off-the-bench catalysts, particularly (*S*)-proline, in different organic transformations. The classical proline-catalyzed cross-aldol reaction between cyclic ketones and aromatic aldehydes (Scheme 1) [7] and to a lesser extent the proline-catalyzed addition of ketones to β-nitro-styrene (Scheme 2) [27] have been adopted as paradigms for testing multiple additives.

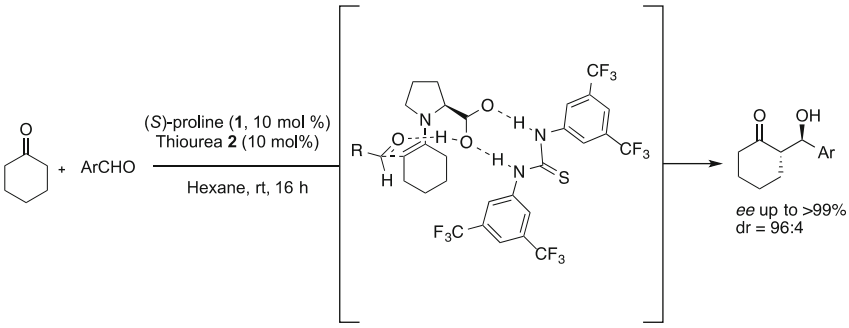
So far, it has been demonstrated how the addition of catalytic or substoichiometric amounts of inorganic Lewis acidic salts [28–35], Brønsted acids [36], water [37–40], chiral alcohols (BINOL or tartrates) [41, 42], achiral alcohols [43], ureas [44], thioureas [45–52], thiouronium salts [53], and imidazolium salts [54] increase the reactivity, efficiency, and selectivity of proline in cross-aldol reactions in comparison to the seminal report of List [7]. Additionally, ureas and thioureas have also been investigated to partner (*S*)-proline in the catalytic addition of ketones to β-nitro-styrene [49, 55, 56]. Although a full-bodied picture of the role played by these additives in the mechanisms of the reactions shown in Scheme 1 has not been disclosed, it seems clear that in nonpolar solvents, a network of hydrogen-bonding interactions between the carboxylate function of



Scheme 1 Proline-catalyzed cross-aldol reaction, commonly used as a model to evaluate different additives



Scheme 2 Proline-catalyzed addition of ketones to β-nitro-styrene, commonly used as a model to evaluate different additives



Scheme 3 Demir's (*S*)-proline/thiourea **2**-catalyzed aldol reaction between cyclohexanone and aromatic aldehydes. The proposed reaction intermediate is represented

proline, the corresponding additive, and the reaction substrates in the transition state is established. Based on this hypothesis, Demir and co-workers proposed a transition state characterized by the formation of a doubly hydrogen-bonded complex [Schreiner's thiourea **2** [57] · proline **1**], for the thiourea **2**/proline-catalyzed aldol reaction between cyclohexanone and aromatic aldehydes (Scheme 3) [45]. The establishment of such a complex would be ultimately responsible of the high selectivity observed for the process.

3 Guanidinium Salts as Additives for Proline in Organocatalyzed Reactions

3.1 Cross-Aldol Reaction Between Cyclic Ketones and Aromatic Aldehydes

Inspired by the aforementioned contributions [28–52, 54] and particularly by the work of Demir [45], back in 2010, our group started to explore the feasibility of using guanidinium salts as novel additives for proline in classical organocatalyzed reactions. In order to compare our results with those reported by other methodologies, we also adopted the direct cross-aldol reaction between cyclic ketones and aromatic aldehydes as a model (Scheme 1). We founded our work on the probed ability of guanidinium salts in binding carboxylic acids and carboxylates, amply documented in the literature [58–61]. Also, backing up this idea, ionic liquids based on guanidinium cores, although not used in a catalytic manner, were demonstrated to be superb solvents for proline-promoted aldol reactions [62].

Tetrasubstituted guanidinium cations can form H-bonds with appropriate partners. The conformation of the guanidinium motif, thus the directionality of the H-bonds, is ultimately determined by steric and stereoelectronic factors imposed by its substituents. Figure 2 shows the three possible conformations (named after

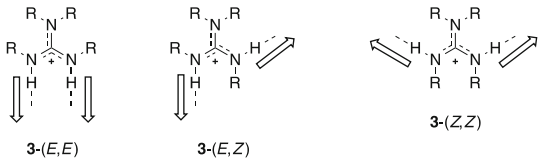


Fig. 2 Conformations of a general tetrasubstituted guanidinium cation **3**. *Bold arrows* indicate the direction in which H-bonds could be formed

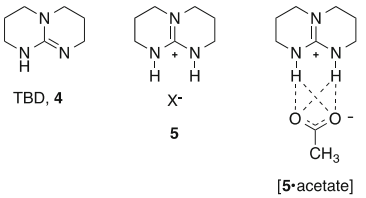


Fig. 3 Structure of guanidine TBD **4** (*left*), its corresponding guanidinium cation **5** (*center*), and the supramolecular complex [guanidinium · acetate] (*right*) with indication of its H-bond interactions

(*E*,*E*), (*E*,*Z*), and (*Z*,*Z*)) of a general tetrasubstituted guanidinium cation **3** and the directions amenable to H-bond formation.

In acyclic guanidinium salts, the three conformers represented in Fig. 2 can interconvert into each other by the successive rotation of C–N bonds. However, only the (*E*,*E*)-conformer is capable of forming well-defined complexes with carboxylates or other oxoanions. Bearing this in mind, we judiciously choose for our study guanidinium salts derived from the bicyclic guanidine TBD (triazabicyclo [4.4.0]dec-5-ene, **4**, Fig. 3), which are conformationally restricted and have a suitable geometry for hydrogen bonding.

TBD is readily available from commercial suppliers and is a reasonably inexpensive base,[1] intensively investigated as catalyst for various transformations [63–72]. This guanidine, in which the nitrogen atoms are embedded within a decaline core, shows high rigidity and conformational restriction. When TBD **4** is protonated, its corresponding guanidinium cation **5** (Fig. 3) presents a single (*E*,*E*)-conformation, with a pair of acidic hydrogen atoms preorganized according to a donor–donor (DD) pattern, which can form doubly H-bonded arrays with an appropriate acceptor–acceptor (AA) partner (i.e., a carboxylate anion) (Fig. 3). Such motifs are stabilized not only by primary and secondary H-bonding interactions but also through coulombic forces, as a consequence of the formation of an electroneutral ionic pair. This results in supramolecular complexes [guanidinium · carboxylate] typically displaying high association constants [73]

[1] 5g, 36 € (Sigma–Aldrich catalogue; April 2015).

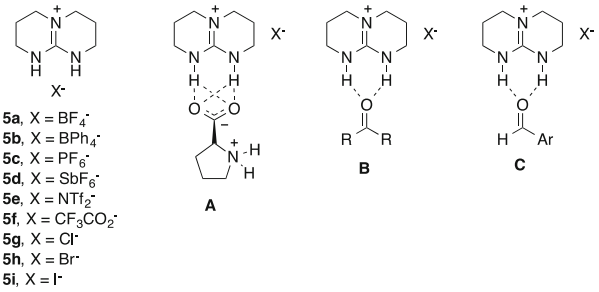


Fig. 4 TBD-derived guanidinium salts **5a–i** studied as additives for proline. Possible doubly H-bonded motifs formed by interaction of the TBD-derived guanidinium core with the carboxylate function of (*S*)-proline (model **A**), or the carbonyl moiety of a ketone (model **B**), or an aromatic aldehyde (model **C**)

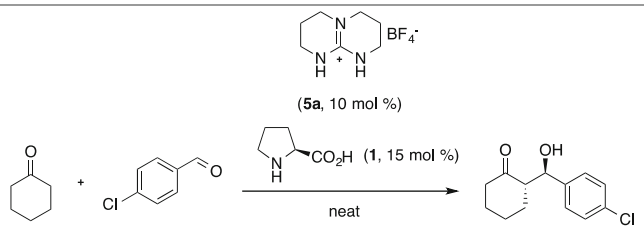
even in competitive polar media, which are generally larger than those measured for structurally related complexes [urea · carboxylate] or [thiourea · carboxylate].

We started off preparing a battery of guanidinium salts **5a–5g**, with anions featuring different geometries, bulkiness, and electronic properties (Fig. 4). Utilizing salts **5** as additives for proline in the direct cross-aldol reaction represented in Scheme 1, we postulated that the guanidinium cation of **5** could form doubly H-bonded motifs with the carboxylate function of proline (Fig. 4, model A), as well as with the carbonyl moieties of the ketone (Fig. 4, model B), and the aromatic aldehyde (Fig. 4, model C), thus enhancing their electrophilicity. Moreover, the participation of the anion counterpart X^- of salt **5** could be also presumed. In fact, our studies have demonstrated that the anion accompanying the guanidinium core of salt **5** was indeed crucial in the reaction outcome of the guanidinium salt/proline-catalyzed aldol reaction.

3.1.1 Studies on the Tetrafluoroborate Guanidinium Salt 5a (5, $\mathbf{X = BF_4^-}$)

From the compounds **5a–5i** represented in Fig. 4, the tetrafluoroborate guanidinium salt **5a** denoted being an outstanding additive for (*S*)-proline in the direct proline-catalyzed cross-aldol reaction [74]. Experimental conditions were optimized for the reaction occurring between cyclohexanone and 4-chlorobenzaldehyde **6a** to render the aldol adduct **7a** (Table 1). Looking for an inexpensive and green process, it was decided to avoid the use of any organic solvent apart from a moderate excess of cyclohexanone (tenfold excess), which acted as both reagent and reaction media. Organocatalyzed aldol reactions operating under solvent-free conditions are particularly interesting and therefore sought after (for recent examples of organocatalyzed aldol reactions carried out under solvent-free conditions, see [75–85]).

t1.1 **Table 1** Initial screening of conditions for the guanidinium salt **5a**/proline system in the formation of aldol **7a**



t1.2 **6a** **7a**

t1.3 Entry	Temp. (°C)	Time (h)	Conv. (%)[a]	*anti*:*syn*	*ee* (%)[b]
t1.4 1	20	48	99	76:24	82
t1.5 2	0	96	98	93:7	96
t1.6 3[c]	0–3	96	96	94:6	98
t1.7 4[c,d]	0–3	96	81	69:31	54

t1.8 Reaction conditions: cyclohexanone (10 equiv.), **6a** (1 equiv.), (*S*)-proline (**1**, 15 mol%), **5a** (10 mol%), and no solvent (neat); reaction mixture was stirred unless otherwise stated. Table figures represent an average of two experiments

[a]Conversion of aldehyde **6a** (limiting reagent) into aldol adduct **7a**

[b]Enantiomeric excess of the major (*anti*) diastereoisomer

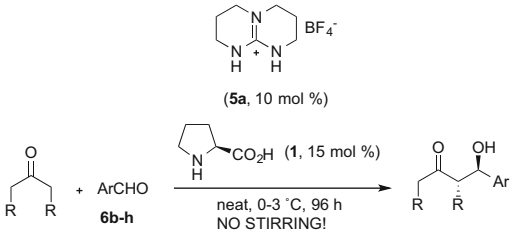
[c]The reaction mixture was left to stand inside a fridge (0–3°C) without stirring

[d]Guanidinium salt **5a** was not added

The best reaction conditions implied utilizing 15 mol% of proline **1** and 10 mol % of tetrafluoroborate guanidinium salt **5a**. The aldol reaction proceeded better at 0°C than at room temperature, although it required longer times (Table 1, entries 1 and 2). Interestingly, when a suspension of aldehyde **6a**, (*S*)-proline (15 mol%), and additive **5a** (10 mol%) in cyclohexanone was left to stand for 96 h inside a standard laboratory fridge (temperature ranging 0–3°C) without stirring or mechanical agitation, aldol **7a** was rendered in 96% conversion, with a relation of diastereoisomers 96:4 (*anti*/*syn*)peaking at 98% enantiomeric excess (Table 1, entry 3). Small differences were appreciated in terms of diastereo- and enantioselectivity of product **7a** when reaction mixtures were stirred at 0°C (Table 1, entry 2), or alternatively when they were left to stand inside the fridge at 0–3°C without any sort of agitation. However, the later protocol was favored, being significantly straightforward and avoiding the use of cryogenic baths for prolonged times. Moreover, there was no indication of any irreproducibility of results. Blank experiments, without the participation of additive **5a**, presented modest figures of chemical conversion, diastereo- and enantioselectivity of adduct **7a** (Table 1, entry 5), hence confirming the advantageous effect of the guanidinium salt under such rather mild reaction conditions.

The scope of this aldol protocol was established by reacting a collection of aldehydes **6b–h** bearing diverse functional groups and substitution patterns with cyclohexane, or other ketones, under the ideal reaction conditions presented in Table 1, entry 3. Table 2 gathers the results obtained. Aldols **7b–f**, derived from

Table 2 Scope of the (*S*)-proline/guanidinium salt **5a** co-catalyzed synthesis of aldols t2.1



t2.2

Entry	ArCHO	Product	Yield (%)[a]	*anti*:*syn*	*ee* (%)[b]
1[c]	**6b** 4-NO_2–C_6H_4	**7b**	92	92:8	99
2[c]	**6c** 4-CO_2Me–C_6H_4	**7c**	86	92:8	99
3[c]	**6d** 4-Br–C_6H_4	**7d**	94	97:3	99
4[c]	**6e** 2-OMe–C_6H_4	**7e**	87	95:5	98
5[c]	**6f** 3-Cl–C_6H_4	**7f**	94	96:4	98
6[c]	**6g** 2-furyl	**7g**	73	86:14	91
7[c]	**6h** 2-Thiophenyl	**7h**	70	93:7	90
8[d]	**6b** 4-NO_2–C_6H_4	**8b**	81	86:14:0:0	97
9[e]	**6b** 4-NO_2–C_6H_4	**9b**	84	74:26	98
10[f]	**6b** 4-NO_2–C_6H_4	**10b**	88	–	74

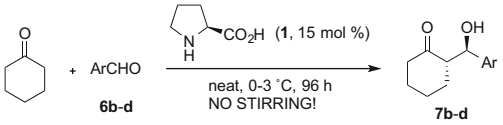
t2.3 t2.4 t2.5 t2.6 t2.7 t2.8 t2.9 t2.10 t2.11 t2.12 t2.13

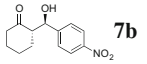
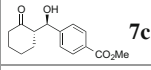
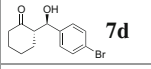
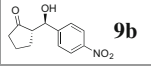
Reaction conditions: ketone (10 equiv.), aldehyde (1 equiv.), (*S*)-proline (**1**, 15 mol%), **5a** (10 mol%), and no solvent (neat); reaction mixture was left to stand inside a fridge (0–3°C) for 96 h without stirring t2.14

[a]Isolated yield of analytically pure products
[b]Enantiomeric excess of the major (*anti*) diastereoisomer
[c]Cyclohexanone was used as ketone
[d]4-Methylcyclohexanone was used as ketone
[e]Cyclopentanone was used as ketone
[f]Acetone was used as ketone

cyclohexanone (Table 2, entries 1–5), were isolated in good or very good yields, and with very high diastereo- and enantioselectivity. Particularly relevant are aldols **7g** and **7h**, prepared from 2-furfural and 2-thiophenecarboxaldehyde, respectively, which are challenging substrates for the direct aldol reaction (Table 2, entries 6 and 7). 4-Methylcyclohexanone was successfully desymmetrized by means of this methodology, affording aldol **8b** with high diastereo- and enantioselectivity, in a process where the absolute configuration of three stereogenic centers is fixed 217 218 219 220 221 222 223

t3.1 **Table 3** Direct aldol reaction without the addition of guanidinium salt **5a**

t3.2 

t3.3 Entry	ArCHO	Product	Conv.(%)[a]	*anti*:*syn*	*ee* (%)[b]
t3.4 1	**6b** 4-NO_2–C_6H_4	 **7b**	>99	85:15	n.d.[c]
t3.5 2	**6c** 4-CO_2Me–C_6H_4	 **7c**	56	76:24	95
t3.6 3	**6d** 4-Br–C_6H_4	 **7d**	26	69:31	94
t3.7 4[d]	**6b** 4-NO_2–C_6H_4	 **9b**	93	38:62	92

t3.8 Reaction conditions: ketone (10 equiv.), aldehyde (1 equiv.), (*S*)-proline (15 mol%), and no solvent (neat); reaction mixture was left to stand inside a fridge (0–3°C) for 96 h without stirring
[a]Conversion of aldehyde **6** (limiting reagent) into aldol adduct
[b]Enantiomeric excess of the major (*anti*) diastereoisomer
[c]Enantiomeric excess was not determined, hampered by impurities
[d]Cyclopentanone was used as ketone

(Table 2, entry 8). Reactions carried out with cyclopentanone or acetone were also successful.

To further confirm the positive effect of the tetrafluoroborate guanidinium salt **5a** on the course of the reactions outlined in Table 2, some were repeated under strictly analogous conditions using only (*S*)-proline as a single catalyst (Table 3). As it was anticipated, all aldol reactions performed without additive **5a** showed lower conversion as well as poorer diastereoisomeric ratios and enantiomeric excesses.

It is important to mention that, as we have observed, all transformations implying the proline/guanidinium salt **5a** methodology are heterogenous, some (*S*)-proline remaining precipitated at the bottom of the reaction vessels along the reaction course. Literature reports have presented the behavior of proline as organocatalyst under heterogenous conditions ([86], and reference therein), and it is accepted that a saturated solution of the amino acid is equilibrated with a crystalline phase. Accordingly, we considered in our system the presence of some (*S*)-proline dissolved in cyclohexanone (or either of the other ketones employed), ultimately responsible of controlling the reaction course. Indeed, high-field ^{1}H NMR experiments have confirmed that the guanidinium salt **5a** significantly favors the dissolution of proline in acetone-d_6. Figure 5a shows the spectrum of guanidinium salt **5a** in acetone-d_6 at $C = 75$ mM, a concentration close to that featured in the experiments of Table 2. When equimolar amounts of (*S*)-proline were added to the former solution and the corresponding ^{1}H NMR spectrum was recorded, a deshielding of the resonances attributed to the N–H functions of

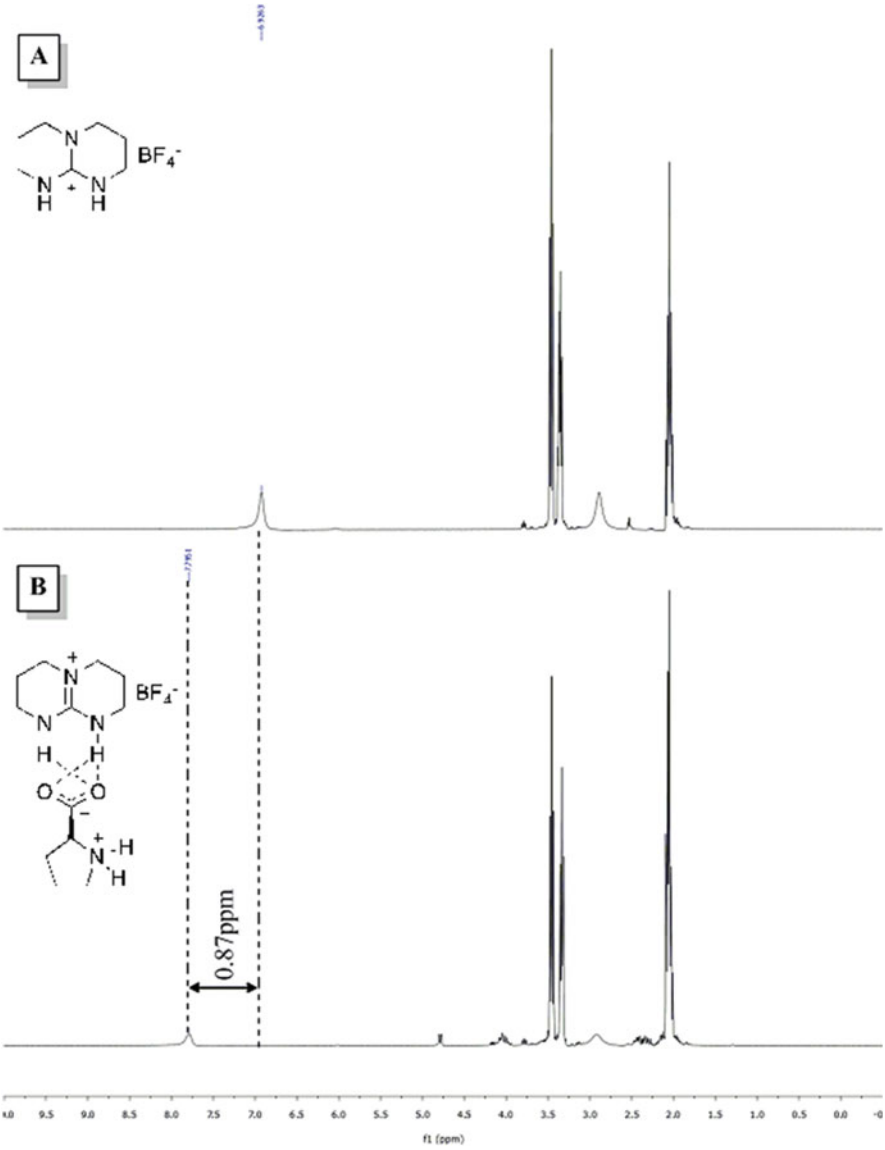
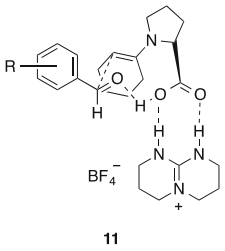


Fig. 5 (**a**) ^{1}H NMR spectrum (300 MHz, acetone-d_6) of guanidinium salt **5a** ($c = 75$ mM). (**b**) ^{1}H NMR spectrum (300 MHz, acetone-d_6) of guanidinium salt **5a** ($c = 75$ mM) and (*S*)-proline ($c = 75$ mM)

guanidinium salt **5a** was observed, together with resonances of the amino acid showing up (Fig. 5b). It is important to note that proline itself, in absence of the guanidinium salt, is completely insoluble in acetone-d_6. These data confirmed the



11

Fig. 6 Zimmerman–Traxler-type transition state **11** proposed to explain the observed stereochemistry of aldol **7** in the proline/tetrafluoroborate guanidinium salt **5a**-catalyzed aldol reaction

entity of the complex [proline · **5a**], which, in turn, served to validate the model A proposed in Fig. 4.

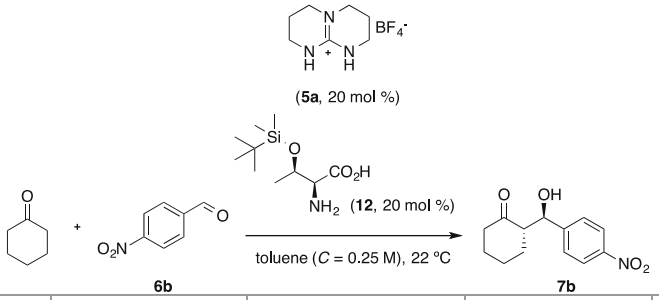
Granted the solubility of proline, the stereochemical outcome of the reaction was explained assuming that it operates through a Zimmerman–Traxler-type transition state. Similar reaction intermediates have been proposed by other authors. Therefore, the formation of a 1:1 complex between the guanidinium cation of additive **5a** and the solubilized proline would stabilize the chairlike transition state **11** (Fig. 6), which leads to the observed aldols and also accounts for their spatial configuration. Profound molecular mechanics calculations carried out by the group of Li and Cheng have recently given further support to the existence of the supramolecular complex [proline · guanidinium salt], both in the gas phase and in nonpolar solvents [87]. According to the authors, the calculated results predicted that the acidity of proline could be increased by no less than 9 pK_a units when it is assembled with the H-bond-donating guanidinium cation. Such an increment of acidity would rationalize the dramatically enhanced activity of proline in the presence of the additive. Notwithstanding with our mechanistic proposition and the suggestions of Li and Cheng, issues such as the role played by the tetrafluoroborate counterpart of salt **5a** in the reaction mechanism are yet unclear. In any case, further experiments carried out in our laboratory, discussed in Sect. 3.1.2, indicated that, as a matter of fact, the anion does play a central role.

Soon after the publication of this work, the group of Córdova studied the effect of adding guanidinium salt **5a**, or alternatively other additives, on the outcome of an aldol reaction between cyclohexanone and 4-nitrobenzaldehyde **6b** catalyzed by a *O*-silyl-protected threonine derivative **12** (Table 4) [88]. Reactions were carried out in toluene at room temperature. Under this set of conditions, it was evident that the concurrence of the additive did in fact not improve the performance of the primary amino acid catalyst.

3.1.2 Studies on the Tetraphenylborate Guanidinium Salt 5b (5, X = BPh_4^-)

In the reactions shown in Table 2, *syn*-aldols were preferentially formed when the TBD-derived tetraphenylborate guanidinium salt **5b** replaced the tetrafluoroborate salt **5a** as cocatalyst for proline. This intriguing observation was further examined in our laboratory [89]. The aldol reaction between cyclohexanone and

Table 4 *O*-Silylated threonine **12**/guanidinium salt **5a** co-catalyzed aldol reaction t4.1



t4.2

Entry	Time (h)	Conv. (%)[a]	*anti*:*syn*	*ee* (%)[b]	t4.3
1	27	82 (76)	92:8	98	t4.4
2[c]	24	77 (64)	91:9	99	t4.5

Reaction conditions: cyclohexanone (10 equiv.), **6b** (1 equiv.), threonine derivative **12** (20 mol%), **5a** (20 mol%), in toluene ($c = 0.25$ M), 22°C t4.6

[a]Conversion of aldehyde **6b** (limiting reagent) into adduct **7b** in crude reaction mixtures. Isolated yield of analytically pure products is given in brackets

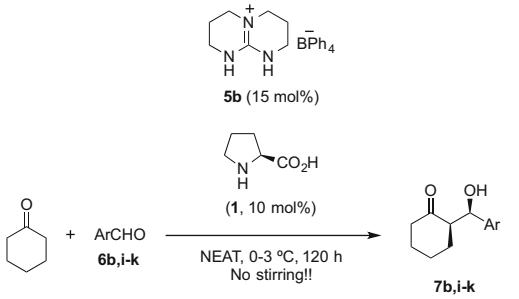
[b]Enantiomeric excess of major (*anti*) diastereoisomer

[c]Guanidinium salt **5a** was not added

4-nitrobenzaldehyde, **6b**, was adopted as a model to gain proper experimental conditions that maximized the amount of *syn*-adduct produced. It was found that when a suspension of 4-nitrobenzaldehyde **6b** (1.0 equiv.), (*S*)-proline (**1**, 10 mol %), and TBD-derived tetraphenylborate guanidinium salt **5b** (15 mol%) in cyclohexanone (10.0 equiv.) was allowed to react for 120 h at 0–3°C inside a fridge without stirring, the corresponding aldol adduct **7b** was rendered in full conversion, with moderate *syn*-diastereoselectivity (35:65 *anti*/*syn*) and excellent enantioselectivity (93% *ee*, for *syn*-**7b**) (Table 5, entry 1). The stereochemistry of the product *syn*-**7b** was assigned as (*R*,*R*) by comparison with literature values. Other aromatic aldehydes **6i–j** decorated with nitro substituents and 4-cyanobenzaldenyde **6k** were examined as substrates for this reaction (Table 1, entries 2–4). Products **7i–k** also displayed a preferential *syn*-stereochemistry, peaking the *anti*/*syn* ratio at 25:75, and had enantiomeric excesses above 90%. It has to be highlighted that limited work had been done on the catalytic direct asymmetric aldol reaction aiming to render *syn*-adducts [90–92].

When the additive **5b** did not participate in the proline-catalyzed aldol reaction, adducts **7b**, **i–k** were rendered with poor conversion and significantly low diastereoselectivity, the *anti*-configured products being favored (Table 6, entries 1–4). In addition, the small amount of *syn*-adducts produced in the absence of guanidinium salt **5b** featured the absolute configuration (*S*,*S*), opposite to the examples shown in Table 5. These observations demonstrated how the participation of the guanidinium salt controls the stereopreference of the aldol reaction (for a general review on the stereocontrol of asymmetric reactions, including organocatalyzed transformations, see [93]). To our knowledge, only Yang and

Table 5 (*S*)-Proline/guanidinium salt **5b** co-catalyzed synthesis of *syn*-aldols derived from cyclohexanone



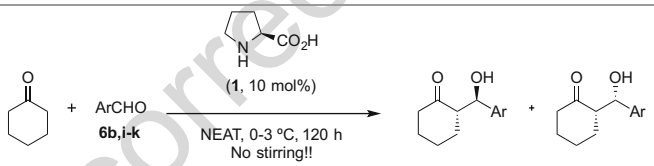
Entry	ArCHO	Conv. (%)[a]	*anti*:*syn*	*ee* (%)[b]
1	**6b** 4-NO_2–C_6H_4	>99 (86)	35:65	93
2	**6i** 3-NO_2–C_6H_4	>99 (87)	34:66	96
3	**6j** 2-NO_2–C_6H_4	>99 (92)	25:75	98
4	**6k** 4-CN–C_6H_4	>99 (98)	35:65	91

Reaction conditions: cyclohexanone (10 equiv.), aldehyde (1 equiv.), (*S*)-proline (**1**, 10 mol%), guanidinium salt **5b** (15 mol%), and no solvent. The reaction mixture was left to stand inside a fridge (0–3°C) for 120 h without stirring

[a]Conversion of aldehyde **6** (limiting reagent) into aldol **7**. Isolated yield of analytically pure products is given in brackets

[b]Enantiomeric excess of aldol adduct *syn*-**7**

Table 6 Direct aldol reaction between cyclohexanone and aromatic aldehydes **6b**,**i–k** catalyzed by (*S*)-proline, without the participation of tetraphenylborate guanidinium salts **5b**



Entry	ArCHO	Conv. (%)[a]	*anti*:*syn*	*ee* (%)[b]
1	4-NO_2–C_6H_4**6b**	68	66:34	92 (95)
2	3-NO_2–C_6H_4**6i**	51	72:28	96 (89)
3	2-NO_2–C_6H_4**6j**	76	90:10	99 (80)
4	4-CN–C_6H_4**6k**	79	67:33	95 (94)

Reaction conditions: cyclohexanone (10 equiv.), aldehyde (1 equiv.), (*S*)-proline (**1**, 10 mol%), and no solvent; reaction mixtures left to stand inside a fridge (0–3°C) for 120 h without stirring or mechanical agitation

[a]Conversion of aldehyde **6** (limiting reagent) into aldol **7**

[b]Enantiomeric excess of aldol adduct *anti*-**7**. The enantiomeric excess of adduct *syn*-**7** is given in brackets (a preferred (*S*,*S*) absolute configuration is observed for these later compounds, in opposition to the (*R*,*R*) configuration of the adducts rendered according to the conditions of Table 5)

co-workers have presented another organocatalytic system of this kind, where the diastereoselectivity of aldol reactions is determined by the participation of different additives [94].

Taking as an example aldol **7j** decorated with a nitro group in position 2 of the aromatic ring and making use of the methodologies represented in Tables 2 and 5, all four possible spatial configurations of this compound could be accessed with excellent enantioselectivity by choosing the appropriate combination of either (*S*)- or (*R*)-proline and either guanidinium salts **5a** or **5b** (Fig. 7). Moreover, considering that the *anti*- and *syn*-diastereoisomers of product **7j** were readily separated by standard flash chromatography on silica gel, these four products could be isolated in analytically pure form with high yield. Proline exerted the enantiocontrol on the reaction, whereas the guanidinium salt additive controlled the diastereoselection. It is worth noting that the paradigmatic organocatalyzed aldol reaction represented in Scheme 1 has been explored in depth, almost to extenuation, and consequently both *anti*- and *syn*-products have been studied and prepared independently. It was far from our interest to present a novel methodology for the proline-catalyzed aldol reaction but rather to demonstrate, as a proof of principle, how the judicious choice of an additive for the most widely known off-the-bench organocatalyst, proline, allows to gain access to either stereoisomer of a particular aldol product.

^{1}H NMR kinetic studies, DFT calculations, and further experiments were carried out in order to give an explanation for the unexpected *syn*-selectivity recorded in the case of using the tetraphenylborate guanidinium salt **5b**. In light of these experiments, the reaction mechanism shown in Fig. 8 was proposed.

Thus, on the one hand, *anti*-conformers would be afforded according to a Zimmerman–Traxler-type transition state **13** (similar to intermediate **11**

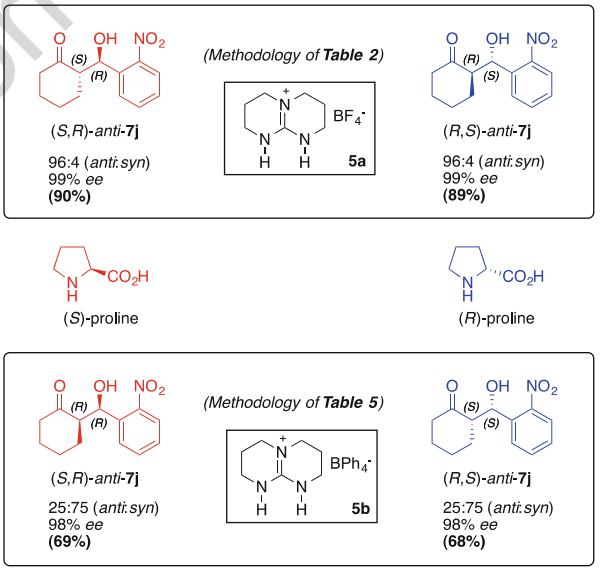


Fig. 7 Combinations of either (*S*)- or (*R*)-proline and guanidinium salt **5a** or **5b**, employed for the preparation of all possible spatial configurations of aldol product **7j** according to the methodologies shown in Tables 2 and 5. Isolated yield for each of the four stereoisomers in analytically pure form is given in *brackets*

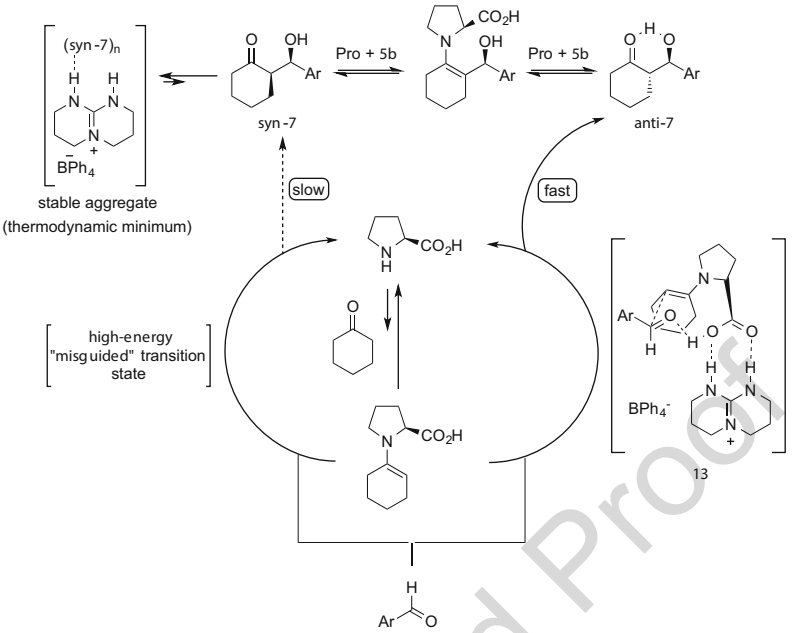


Fig. 8 Reaction mechanism proposed for the aldol reaction between cyclohexanone and aromatic aldehydes catalyzed by the system proline **1**/tetraphenylborate guanidinium salt **5b**

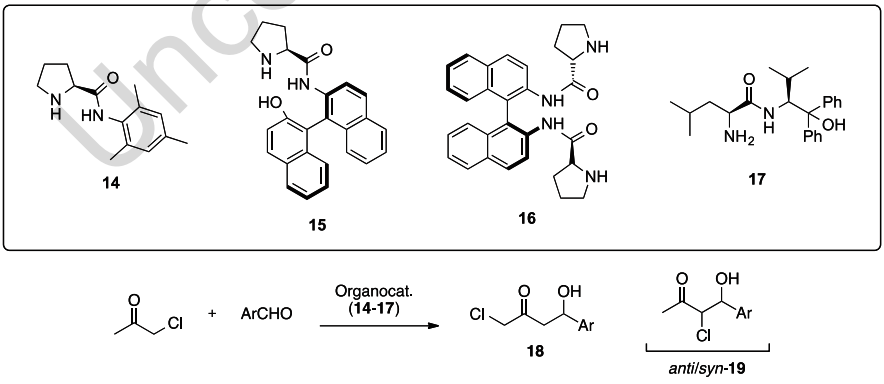
represented in Fig. 6), stabilized by the establishment of a 1:1 complex between the guanidinium cation of additive **5b** and proline. This sort of intermediate was previously postulated by others and by us to justify the high selectivity observed for *anti* products. On the other hand, *syn*-aldols would be formed slowly and in small quantity through a high-energy "misguided" transition state. While the *anti*-aldols seem to be far more stable in the gas phase (according to DFT calculations), *syn* isomers possess lower free energies under our experimental setup, being isolated as the major reaction products. Ruling out an aldol/retro-aldol sequence, the channel that connects both diastereoisomers was proposed to consist of a common proline–enamine intermediate, followed by its subsequent hydrolysis. This hypothesis served to explain the high enantiomeric excess observed for both *anti*- and *syn*-diastereoisomers. Nonetheless, it remains to be clarified why *syn*-diastereoisomers could be more stable products under the reactions conditions applied. The geometries of various adducts, optimized at the B3LYP6-31G* level of theory, showed how the *anti* adducts are stabilized by strong intramolecular hydrogen bonds, between the oxygen atom of the ketone carbonyl group and the O–*H* in β-position, accounting for 6.3–12.5 kJ/mol. The weak intramolecular interactions calculated for the *syn* compounds were suggested to be compensated with stronger intermolecular hydrogen bonds. Thus, considering the central effect played by the counter anions of our TBD-derived additives, it was reasoned that replacing the small and tightly bound tetrafluoroborate anion featured in **5a** with the bulkier

tetraphenylborate of salt **5b** allows the bicyclic guanidinium core of **5b** to take part in large hydrogen-bonding networks with the *syn*-aldols. A mechanism like that depicted in Fig. 8 offers a full account for all the experimental observations regarding this proline/guanidinium salt **5b** system.

3.2 *Cross-Aldol Reaction Between Chloroacetone and Aromatic Aldehydes*

The stereoselective construction of carbon stereocenters bearing halogenated substituents is a challenging synthetic task, particularly if organocatalytic methodologies are to be employed [95]. For instance, a collection of organocatalysts **14** [96], **15** [97], **16** [98, 99], and **17** [100] had been surveyed on the direct aldol reaction of chloroacetone and aromatic aldehydes, to render chlorohydrins **18** and **19** (Scheme 4). Catalysts **14**–**17** have to be prepared by cumbersome sequences implying various synthetic operations and manipulations. Moreover, structures such as **15** or **16** are based on expensive chiral building blocks such as (*S*)-NOBIM ((*S*)-2-amino-2′-hydroxy-1,1′-binaphthyl) and (*S*)-BINAM ((*S*)-2,2′-diamino-1,1′-binaphthyl), respectively.

2-Chloro-3-hydroxy ketone **19**, with two contiguous stereocenters, one of them halogenated, has attracted more interest than their regioisomeric analogue **18**. However, the available methodologies which employ organocatalysts **14**–**17** only achieved modest regioselectivities **18**:**19** and diastereoselectivities (ratio *anti*/*syn* for compounds **19**), except in the case of a few selected examples. Looking for an alternative solution to this problem, we decided to study our proline/guanidinium salt system on the reaction sketched in Scheme 4 [101]. Compared to the chemical modification of proline or the de novo synthesis of other organocatalysts, an

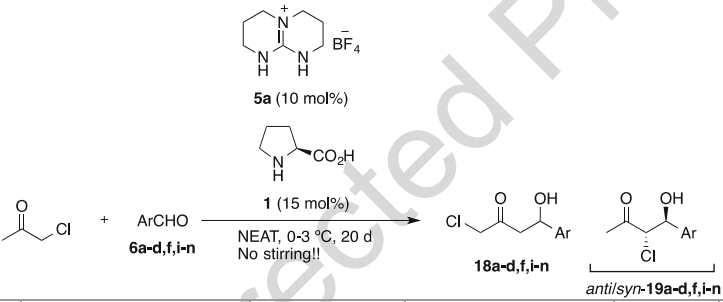


Scheme 4 Organocatalysts **14**–**17** previously employed for the direct aldol reaction between chloroacetone and aromatic aldehydes to afford α-chloro-β-hydroxy ketones (chlorohydrins) **18** and **19**

approach employing hydrogen-bond-donating cocatalysts (guanidinium salts) to interact with proline and form a supramolecular catalyst complex is very attractive. Satisfyingly, under optimal reaction conditions, when a suspension of (*S*)-proline (**1**, 15 mol%), tetrafluoroborate guanidinium salt **5a** (10 mol%), and 4-nitrobenzaldehyde **6b** in chloroacetone (again, it was opted to work in the absence of organic solvent) was left to stand inside a standard laboratory fridge (0–3°C) for 20 days without any sort of stirring or mechanical agitation, a mixture of chlorohydrins **18b + 19b** was produced with good regio- (96:4, **19b**:**18b**), diastereo- (*anti*:*syn*-**19b** 91:9), and enantioselectivity (98% *ee* for *anti*-**19b**) (Table 7, entry 1). Attempts to reduce the reaction time resulted in a severe decrease in selectivity for the reaction product **19b**.

A representative collection of aromatic aldehydes was reacted under analogous conditions (Table 7, entries 2–11). With no exception, all reactions proceeded smoothly with good conversion and high regio-, diastereo-, and enantioselectivity

Table 7 (*S*)-Proline/guanidinium salt **5a** co-catalyzed synthesis of chlorohydrins **19a–d,f,i–n**



Entry	ArCHO	Conv. (%)[a]	Regioselectivity[b]	dr[c]	*ee* (%)[d]
1	**6b** 4-NO_2–C_6H_4	99	96:4	91:9	98
2	**6i** 3-NO_2–C_6H_4	97	96:4	92:8	97
3	**6j** 2-NO_2–C_6H_4	98	>99:1	93:7	97
4	**6c** 4-CO_2Me–C_6H_4	96	99:1	91:9	97
5	**6k** 4-CN–C_6H_4	>99	96:4	90:10	98
6[e]	**6l** 3-F–C_6H_4	95	92:8	94:6	94
7	**6a** 4-Cl–C_6H_4	79	95:5	94:6	95
8	**6f** 3-Cl–C_6H_4	98	96:4	93:7	96
9	**6d** 4-Br–C_6H_4	77	97:3	93:7	93
10	**6m** 2-Br–C_6H_4	90	>99:1	90:10	92
11	**6n** C_6H_5	99	98:2	93:7	94

Reaction conditions: chloroacetone (10 equiv.), aldehyde (1 equiv.), (*S*)-proline (**1**, 15 mol%), guanidinium salt **5a** (10 mol%), and no solvent. The reaction mixture was left to stand inside a fridge (0–3°C) for 20 days without stirring

[a]Conversion of aldehyde **6** (limiting reagent) into chlorohydrins **18 + 19**

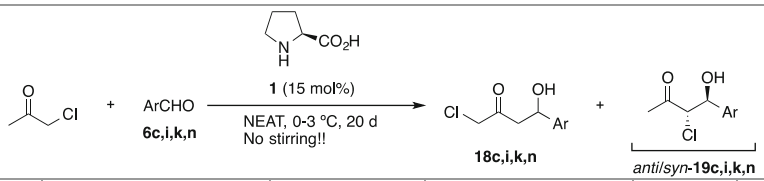
[b]Ratio **19** (*anti*- + *syn*-):**18**

[c]Diastereoisomeric ratio *anti*- to *syn*-**19**

[d]Enantiomeric excess of compounds *anti*-**19**

[e]The reaction was stopped after 14 days

Table 8 Proline-catalyzed aldol reaction between chloroacetone and aromatic aldehydes, in the absence of guanidinium salt **5a** t8.1



t8.2

Entry	ArCHO	Conv. (%)[a]	Regioselectivity[b]	dr[c]	*ee* (%)[d]	
1	**6c** 4-CO_2Me–C_6H_4	98	93:7	85:15	95	t8.4
2	**6k** 4-CN–C_6H_4	99	85:15	83:17	96	t8.5
3	**6n** C_6H_5	99	94:6	84:16	92	t8.6
4	**6i** 3-NO_2–C_6H_4	99	80:20	78:22	97	t8.7

t8.3

Reaction conditions: chloroacetone (10 equiv.), aldehyde (1 equiv.), (*S*)-proline (**1**, 15 mol%), and no solvent. The reaction mixture was left to stand inside a fridge (0–3°C) for 20 days without stirring t8.8

[a]Conversion of aldehyde **6** (limiting reagent) into chlorohydrins **18** + **19**

[b]Ratio **19** (*anti*- + *syn*-):**18**

[c]Diastereoisomeric ratio *anti*- to *syn*-**19**

[d]Enantiomeric excess of compounds *anti*-**19**

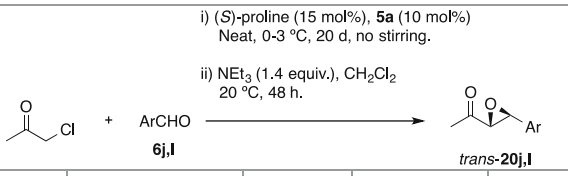
for the desired products **19**, independent of the nature of the substituents of the aldehyde. This observation highlights the robustness and reproducibility of this organocatalytic methodology. Moreover, blank experiments performed without guanidinium salt **5a** showed significantly poorer regio- and diastereoisomeric ratios for chlorohydrins **19**, as well as poorer enantiomeric excesses, hence corroborating the virtues of TBD-derived guanidinium salts as additives for proline in the aldol reaction (Table 8).

Product **19**, which probed to be unstable during chromatography and when stored for prolonged times, was readily transformed into the corresponding chiral α,β-epoxy ketones *trans*-**20** according to a procedure described in the literature [98]. Interestingly, conditions were found that permitted preparing such epoxides in a one-pot procedure straight from chloroacetone and aromatic aldehydes (Table 9).

3.3 Cross-Aldol Reaction Between α-Azidoacetone and Aromatic Aldehydes

Densely functionalized α-azido-β-hydroxy ketone **21** is substances of considerable synthetic value which can be readily transformed into a broad variety of useful building blocks [102]. Access to compound **21** can be gained by a base-promoted aldol reaction of an α-azidoketone **22** and a non-enolizable aldehyde **23** (Scheme 5). There are many reports in the literature describing this type of approach [103–106], rendering the adduct **21** in optimum chemical yield, but featuring undesired

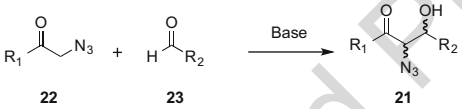
Table 9 One-pot synthesis of representative *trans*-α,β-epoxy ketones **20j,l** from chloroacetone and aromatic aldehydes



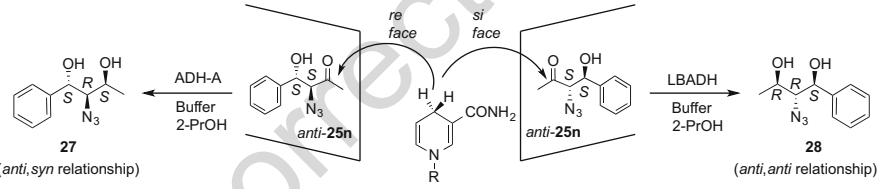
Entry	ArCHO	Product	Yield (%)[a]	*ee* (%)
1	**6j** 2-NO_2–C_6H_4	**20j**	55	85
2	**6l** 3-F–C_6H_4	**20l**	33	79

Reaction conditions: chloroacetone (10 equiv.), aldehyde (1 equiv.), (*S*)-proline (**1**, 15 mol%), guanidinium salt **5a** (10 mol%), and no solvent. The reaction mixture was left to stand inside a fridge (0–3°C) for 20 days without stirring, then allowed to warm to r.t., and stirred for 48 h with NEt_3 (1.4 equiv.) and CH_2Cl_2 ($c = 0.4$ M)

[a]Isolated yield of analytically pure product



Scheme 5 Classical synthetic scheme for the preparation of α-azido-β-hydroxy ketones **21**

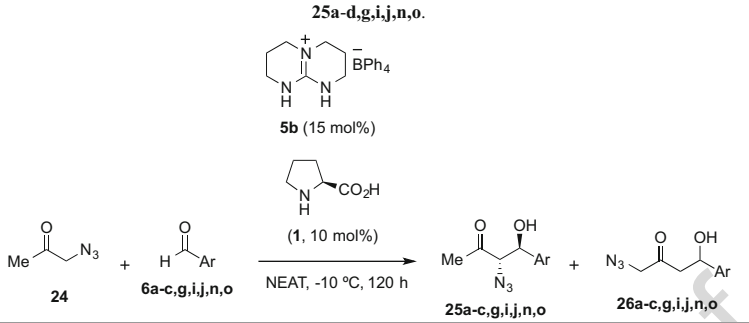


Scheme 6 Stereodivergent reduction of *anti*-**25n** with ADH-A ((*S*)-selective enzyme) affording diol **27** and LBADH ((*R*)-selective enzyme) giving access to diol **28**. In the middle, the structure of the nicotinamide cofactor present in both ADHs is drawn

mixtures of diastereoisomers. However, there were no previous works describing the synthesis of synthon **21** in a diastereo- or enantioselective manner.

Considering the efficiency of the proline/guanidinium salt organocatalytic system, it was investigated in reactions like that illustrated in Scheme 6 [107]. Azidoacetone (**24**, 1-azidopropan-2-one) was readily prepared from chloroacetone and sodium azide. In correspondence with our previous work, it was decided to evade the use of any organic solvent apart from a moderate excess of the ketone **24** acting as both reagent and reaction medium. The reaction was carefully optimized by modifying the stoichiometry of the reagents, temperature, and reaction time. Various TBD-derived guanidinium salt **5** were also examined. Eventually, when a suspension of (*S*)-proline (**1**, 10 mol%), tetraphenylborate

Table 10 (*S*)-Proline/guanidinium salt **5b** co-catalyzed synthesis of α-azido-β-hydroxy ketones **25a–d,g,i,j,n,o** t10.1



t10.2

Entry	ArCHO	Conv. (%)[a]	dr[b]	*ee* (%)[c]	
1	**6b** 4-NO_2–C_6H_4	>99 (90)	90:10	94	t10.4
2	**6i** 3-NO_2–C_6H_4	>99 (91)	90:10	95	t10.5
3	**6j** 2-NO_2–C_6H_4	99 (88)	90:10	97	t10.6
4	**6n** C_6H_5	>99 (84)	90:10	95	t10.7
5	**6a** 4-Cl–C_6H_4	98 (85)	90:10	94	t10.8
6	**6d** 4-Br–C_6H_4	98 (84)	89:11	95	t10.9
7	**6c** 4-CO_2Me–C_6H_4	99 (83)	88:12	95	t10.10
8	**6g** 2–furyl	>99 (78)	85:15	93	t10.11
9	**6o** 2–pyridyl	>99 (80)	87:13	88	t10.12
10[d]	**6b** 4-NO_2–C_6H_4	12	82:18	n.d.	t10.13

Reaction conditions: azidoacetone **24** (10 equiv.), aldehyde (1 equiv.), (*S*)-proline (**1**, 10 mol%), guanidinium salt **5b** (15 mol%), and no solvent (neat). The reaction mixtures were stirred for 120 h at −10°C t10.14

[a]Conversion of aldehyde **6** (limiting reagent) into α-azido-β-hydroxy ketone **25** (*anti*-+*syn*-). Chemical yield of analytically pure products *anti*-**25** is given in brackets

[b]Diastereoisomeric ratio *anti*- to *syn*-**25**

[c]Enantiomeric excess of analytically pure compounds *anti*-**25**

[d]Reaction carried out without the addition of guanidinium salt **5b**. The enantiomeric excess of the product **5b** was not determined as a consequence of the low conversion

guanidinium salt **5b** (15 mol%), and 4-nitrobenzaldehyde **6b** was stirred in azidoacetone **24** (10 equiv. relative to the aldehyde) for 120 h at −10°C, the α-azido-β-hydroxy ketone **25b** was produced in quantitative conversion with good diastereo- (*anti*-**25b**:*syn*-**25b**, 90:10) and enantioselectivity (97% *ee* for *anti*-**25b**, Table 10, entry 1). The corresponding regioisomer **26** was not detected.

A set of aldehydes **6a**,**c**,**d**,**g**,**i**,**j**,**n**,**o**, decorated with different functional groups and substitution patterns, were reacted with azidoacetone under the best set of reaction conditions (Table 10, entries 2–7). All of these reactions proceeded with good conversion and high *anti*-diastereoselectivity and enantioselectivity (around 97% *ee* in all cases), independent of the nature of the aldehyde employed. Also, heteroaromatic aldehydes such as 2-furylcarboxaldehyde **6g** and 2-pyridylcarboxaldehyde **6o** proved to be appropriate substrates for this reaction, the corresponding products **25g** and **25o** displaying good selectivity figures

(Table 10, entries 8 and 9). The tolerance of the reaction for heteroaromatic aldehydes, challenging substrates in aldol-type C–C bond-forming reactions, confirms the reproducibility and robustness of this transformation. All adducts *anti*-**25a**–**d**,**i**,**j**,**n**,**o** could be easily isolated by standard chromatographic techniques, affording analytically pure products in high yield and high *ee*. The presence of the corresponding regioisomers **26a**–**d**,**g**,**i**,**j**,**n**,**o** was not observed in any of these transformations. A blank experiment performed without additive **5b** (Table 10, entry 10) resulted in a significantly lower conversion as well as poorer diastereomeric ratio for the reaction product. Other reactions performed without additive **5b** were rather messy, rendering complex mixtures of unidentifiable products from which it was not possible to determine conversion values to aldol **25**. This demonstrates the positive effect of the guanidinium salt on the reaction course, which does not only improve the performance of the proline catalyst but even enables a transformation that is not favorable with the exclusive use of the amino acid itself. Alternatively, the sole presence of guanidinium salt **5b** was insufficient to catalyze the aldol reaction between aldehyde **6** and azidoacetone **24** to any extent.

Product **25** had not been described previously, and determining their absolute spatial configuration was a difficult exercise. After several unfruitful attempts, this was finally accomplished by the bioreduction of the ketone moiety of diastereopure α-azido-β-hydroxy ketone **25n**, used as a representative model, employing two stereocomplementary alcohol dehydrogenase enzymes (ADHs), one from *Rhodococcus ruber* (ADH-A) [108] and another from *Lactobacillus brevis* (LBADH) [109]. These enzymes have shown excellent stereoselectivities toward the reduction of α-azido ketones [110] with opposite stereopreference: ADH-A affords the corresponding (*S*)-alcohols, while LBADH gives the corresponding (*R*)-configured antipodes. So, when α-azido-β-hydroxy ketone **25n** was treated with either ADH-A or LBADH enzymes, the corresponding 2-azido-1,3-diol **27** or **28** was afforded, respectively (Scheme 6). Since the absolute configuration of the new alcohol function formed was fully predictable as a consequence of the enzyme's inherent selectivity, measuring the coupling constants between the protons at positions C2 (C*H*–N_3) and C3 (CH_3C*H*–OH) in diols **27** ($^3J_{syn}$) and **28** ($^3J_{anti}$) allowed the unambiguous assignation of the absolute stereochemical configuration of the preceding aldol adduct as *anti*-(3*S*,4*S*)-**25n**. The rest of the α-azido-β-hydroxy methyl ketones rendered from the organocatalyzed process were characterized by analogy.

4 Conclusions and Outlook

In summary, the assembly of supramolecular catalysts constructed from proline and H-bond-donating molecules has been revealed as an interesting alternative to the chemical modification of the amino acid unit. Typically, this simple and economic approach has made use of alcohols, ureas, thioureas, and other small organic molecules. Recently, conformationally restricted guanidinium salts derived from

TDB have emerged as outstanding additives for proline in organocatalyzed aldol reactions. Thus, a straightforward, green, efficient, and highly selective protocol has been developed for the direct aldol reaction between aromatic aldehydes and various ketones (cyclohexanone, cyclopentanone, or acetone) making use of a cooperative proline/guanidinium salt catalytic system. These processes operate under rather mild reaction conditions: without organic solvent, in closed-cap tubes standing inside a standard laboratory fridge, and without agitation or mechanical stirring. The participation of the guanidinium salt, forming a 1:1 supramolecular complex [guanidinium cation · proline] in the transition state, has been demonstrated to greatly enhance the reactivity and selectivity of the amino acid itself in a classical transformation such as the aldol reaction.

Besides, it has been put forward how the choice of the anion accompanying the guanidinium core of the TBD-derived salts used as cocatalysts for proline can give rise to stereodivergent pathways in the cross-aldol reaction, allowing the preparation of either *anti*- or *syn*-aldols from cyclohexanone and aromatic aldehydes. The origin of the *syn*-diastereoselectivity has been studied mechanistically and was shown to originate from an unusual equilibrium process coupled to the enamine-based catalytic cycle standard for proline. The outcome of the *syn*-selectivity reactions could not be predicted or foreseen considering the nature of the organocatalyst used (proline) and the substrates involved. It unfolds from the consideration of the whole complex network resulting from the simultaneous coexistence of *anti*-aldols, *syn*-aldols, (*S*)-proline, guanidinium and guanidine species, aromatic aldehydes, cyclohexanone, and enamines, all of which featured in the reaction media to some extent, as well as their interactions (including supramolecular contacts) and competition, their different solubility, solvation, etc. In the opinion of these authors, the study of collections/systems of compounds (i.e., catalytic systems) being considered as a whole, i.e., a System Chemistry approximation (for general comprehensive reviews on System Chemistry, see [111–115]), can lead to interesting discoveries in areas such as organocatalysis.

Relevantly, the addition of guanidinium salts does not only improve the classical aldol reaction but can also break the boundaries of proline as a catalyst. By these means, α-chloro-β-hydroxy ketones have been prepared with high enantioselectivity, employing for the first time catalytic amounts of (*S*)-proline, aided by the participation of a TBD-derived tetrafluoroborate guanidinium salt. Similarly, a cooperative proline/tetraphenylborate guanidinium salt has given rise to the pioneering synthesis of α-azido-β-hydroxy ketones. These families of compounds could be readily transformed into synthetically useful chiral α,β-epoxy ketones or different isomers of 2-azido-1,3-diols.

The construction and study of supramolecular catalytic systems involving guanidinium salts are yet in its infancy. So far, to our knowledge, only five reports have appeared in the literature about this topic [74, 88, 89, 101, 107]. Granted the success of the TBD-derived guanidinium salts, we anticipate other species of the like will be capable of displaying similar or better properties as additives for proline or other natural amino acids. The possibility of replacing the anion of these salts, possibly leading to different reactivities, is particularly appealing. Therefore, in

principle, carefully designed systems could be engineered to catalyze novel transformations, even other than aldol-type reactions. Surely, the years to come will show further examples of the potential of such systems.

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