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Switching Diastereoselectivity in Proline-Catalyzed Aldol Reactions

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Supporting Information

ABSTRACT: The choice of the anion of an achiral TBD-derived guanidinium salt, used as cocatalyst for proline, allows reacting cycloketones with aromatic aldehydes and preparing either *anti*- or *syn*-aldol adducts with very high enantioselectivity. As a proof of principle, we show how the judicious choice of an additive allows individual access to all possible products, thus controlling the stereochemical outcome of the asymmetric aldol reaction. The origin of the *syn* diastereoselectivity unfolds from an unusual equilibrium process coupled to the enamine-based catalytic cycle standard for proline.

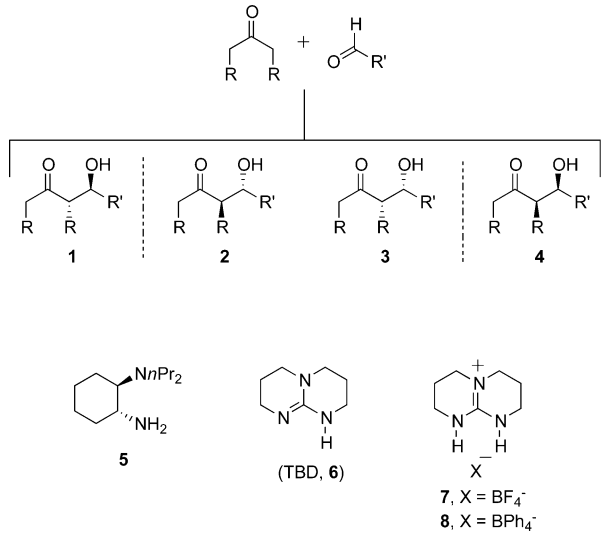
INTRODUCTION

Carboligation processes (C−C bond-forming reactions) are essential for assembling the backbone of complex organic molecules from small and simple building blocks. Among the dozens of possible reactions available to the organic chemist, the catalytic asymmetric aldol reaction constitutes one of the most powerful methodologies for the stereocontrolled formation of carbon−carbon bonds in the synthesis of enantiopure compounds.[1] Although impressive metal-based methodologies were known, the breakthrough discovery of the first proline-catalyzed intermolecular aldol reaction, due to List, Lerner and Barbas,[2] encouraged researchers to find out novel organocatalytic protocols for such transformations.[3]

Ordinarily a classical direct aldol reaction between a ketone and an aldehyde affords an aldol adduct bearing two additional stereogenic centers on its α- and β- position (Scheme 1). This fact offers the potential for stereodivergent product generation, as multiple stereoisomeric products can be derived from a common pair of synthetic precursors. Four products **1**−**4** can be drawn for the reaction sketched in Scheme 1. For every pair of ketone and aldehyde substrates, it would be ideal to have at hand a single chiral catalyst that would allow addressing individually the full matrix of products **1**−**4**. In principle, all mirror image products can be individually provided if both enantiomers of a chiral catalyst are available or can be chemically prepared.[4] Fulfilling this requirement is not always trivial (i.e., cinchona-based alkaloids, commonly used organocatalysts, do not present an accessible enantiomeric form). It is still more challenging controlling the relative stereochemical disposition[5] of aldol adducts (diastereoselectivity) using a single chiral catalyst. To our knowledge, only one recent example has appeared in the literature reporting a stereochemical switch in organocatalyzed aldol reactions, employing the synthetic chiral diamine **5**.[6]

Herein, we demonstrate the ability of different achiral triazabicyclo[4.4.0]dec-5-ene (TBD, **6**)-derived guanidinium salts (**7** and **8**) to modulate the reactivity of proline in direct aldol reactions between cyclic ketones and aromatic aldehydes, giving rise to diastereodivergent pathways. Considering that the (*S*) and (*R*) enantiomers of proline are both readily available, the choice of the proline configuration and the nature of the additive (**7** or **8**), allows access to individually to all possible products **1**−**4** represented in Scheme 1.

Scheme 1. General Scheme for a Direct Aldol Reaction between a Ketone and an Aldehyde: Structures of Organocatalyst 5, TBD 6, and Additives 7 and 8



RESULTS AND DISCUSSION

The ability of proline to catalyze aldol reactions, rendering *anti*-aldol adducts, is widely recognized. However, proline itself presents some major drawbacks: poor performance in direct aldol reactions with aromatic aldehydes, rather limited solubility and reactivity in nonpolar organic solvents, and potential parasitic side processes. In a previous contribution, we have shown that the addition of a catalytic amount of tetrafluor-

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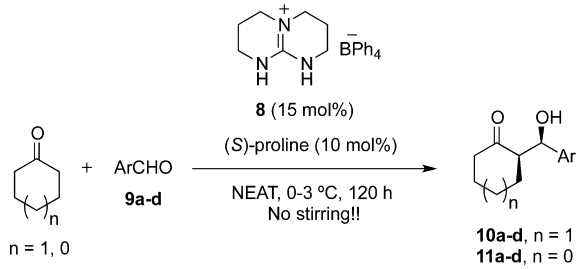
oborate TBD-derived guanidinium salt **7** accelerates the reaction rate, and increases the diastereo- and enantioselectivity of *anti*-aldols, in proline-catalyzed aldol reactions between cyclic ketones and aromatic aldehydes.[7] Additive **7** also allowed carrying out proline-catalyzed direct aldol reactions employing chloroacetone.[8] The nature of the anion in the guanidinium salts proved to be decisive in these studies. We observed an intriguing behavior for the tetraphenylborate salt **8**, which rendered *syn*-aldols when it was used as cocatalyst for proline. We aimed to explore further this feature, and the direct aldol reaction between cyclohexanone and 4-nitrobenzaldehyde, **9a**, cocatalyzed by (*S*)-proline and salt **8**, was studied as a model system. In accordance to our previously developed methodologies, we decided to work under solvent-free conditions, employing a moderate excess of ketone as reagent and reaction media. A screening of reaction temperatures (Supporting Information (SI), Table S1) and stoichiometries (SI, Table S2) unveiled an optimum protocol: when a suspension of 4-nitrobenzaldehyde **9a** (1.0 equiv), (*S*)-proline (10 mol %) and TBD-derived tetraphenylborate guanidinium salt **8** (15 mol %), in cyclohexanone (10.0 equiv), was allowed to react for 120 h at 0−3 °C, with no stirring,[9] the corresponding aldol adduct **10a** was rendered in full conversion, with moderate *syn*-diastereoselectivity (65:35 *syn*/*anti*) and excellent enantioselectivity (93% *ee*, for *syn*-**10a**) (Table 1, entry 1). The absolute stereochemical configuration of product *syn*-**10a** was assigned as (*R*,*R*) by comparison of the chiral HPLC trace of this compound with data previously reported in the literature.[6] Under the optimized conditions, other representative aldehydes **9b−d** were tested as substrates for this reaction (Table 1, entries 2−4). Products **10b−d** display a preferential *syn*-stereochemistry, peaking the *syn*/*anti* ratio at 75:25, and have an enantiomeric excess above 90% (for the *syn*-adducts). It has to be noted that only limited work has been done on the catalytic direct asymmetric aldol reaction of cyclohexanone with aldehydes to afford *syn* products. To expand the scope of our reaction, we also explored cyclopentanone as ketone donor. Without altering conditions, 4-nitrobenzaldehyde **9a** was reacted, isolating the expected cyclopentyl aldol **11a** in very high yield, with good diastereoselectivity (77:23 *syn* to *anti*) and excellent enantioselectivity (96% *ee*, for *syn*-**11a**). Again, aldehydes **9b−d** were tested as substrates (Table 1, entries 6−8). Their reactions proceeded smoothly, affording the aldol addcuts with high diastereo- and very high enantioselectivity, confirming the robustness of this transformation. The absolute stereochemistry of products *syn*-**11** was assigned unambiguously as (*R*,*R*) by comparison of the chiral HPLC chromatogram for compounds **11a** and **11c** with those previously reported in the literature.[10] The results of Table 1 are superior in terms of enantioselectivity, and of comparable diastereoselectivity, to the sole example describing an additive-mediated diastereoswitch in direct aldol reaction employing a synthetic organocatalyst.[6]

It is important to remark that, under rather closed reaction conditions, replacing additive **8** by the tetrafluoroborate guanidinium salt **7** in the experiments presented in Table 1 results in the preferential formation of the corresponding products *anti*-**10**, or *anti*-**11**, with very high enatiomeric excesses (see SI, Tables S3 and S4). It is relevant for cyclopentanone-derived products **11**, where the *syn* isomer is usually obtained in organocatalyzed aldol reactions. Moreover, when additives **7** or **8** do not participate in the proline-catalyzed aldol reaction, under our reaction conditions, adducts **10a−d** and **11a−d** are rendered with poor conversion and significantly low diastereoselectivity (SI, Tables S5 and S6).

Taking as example aldol **10c**, all four possible stereoisomers of this compound were accessed by our methodology picking out the appropriate combination of either (*R*)- or (*S*)-proline, and either guanidinium salt **7** or **8** (Figure 1, and SI). While proline exerts the enantiocontrol on the reaction, the guanidinium salt additive controls the diastereoselection of the process. It has to be emphasized that the chemistry of different organocatalysts in aldol reactions has been explored to extenuation, and that both *anti*- and *syn*-aldol products have been separately studied and prepared with much better results than those of Table 1 by choosing the right catalyst. It is far from our objective of presenting a synthetic work, a novel methodology for proline-catalyzed aldol reactions, but introducing a proof of principle: the judicious choice of an additive for the most widely known off-the-bench organocatalyst, proline, allows us to gain access to either stereoisomer of an aldol product.

Any mechanistic proposal for the reactions presented in Table 1 must account for the unusual *syn* diastereoselectivity observed for the resulting aldol adducts. To gain further insight into these processes, we decided to follow the evolution of the aldol reaction between cyclohexanone and 2-nitrobenzaldehyde **9c**, in the presence of (*S*)-proline and additive **8**, to render product **10c**, under our finest reaction conditions (Table 1, entry 3). Accordingly, a battery of reactions was set up in parallel containing each 0.2 mmol of aldehyde **9c**, and the indicated quantity of the other reagents. These reactions were strictly quenched, worked up and analyzed by ^{1}H NMR

Table 1. (*S*)-Proline/Guanidinium Salt 8 Cocatalyzed Synthesis of *syn*-Aldols Derived from Cyclohexanone or Cyclopentanone[a]



entry	ArCHO	product	conversion [%][b]	d.r.[c]	*ee* [%][d]
1	**9a** 4-NO_2−C_6H_4	**10a**	>99 (86)	65:35	93
2	**9b** 3-NO_2−C_6H_4	**10b**	>99 (87)	66:34	96
3	**9c** 2-NO_2−C_6H_4	**10c**	>99 (92)	75:25	98
4	**9d** 4-CN−C_6H_4	**10d**	>99 (98)	65:35	91
5	**9a** 4-NO_2−C_6H_4	**11a**	>99 (86)	77:23	96
6	**9b** 3-NO_2−C_6H_4	**11b**	>99 (89)	76:24	95
7	**9c** 2-NO_2−C_6H_4	**11c**	>99 (89)	89:11	94
8	**9d** 4-CN−C_6H_4	**11d**	>99 (88)	76:24	95

[a]Reaction conditions: ketone (2.0 mmol), ArCHO (0.2 mmol), (*S*)-proline (0.02 mmol), **8** (0.03 mmol), no solvent. The reaction mixture was left to stand for 120 h inside a fridge (0−3 °C) with no stirring. [b]Determined by ^{1}H NMR spectroscopy of the crude reaction mixtures. Isolated yield of analytically pure products **10**/**11** is given in brackets. [c]Diastereoisomeric ratio of *syn*- to *anti*-**10**/**11** determined by ^{1}H NMR spectroscopy of the crude reaction mixtures and identified by comparison with data previously described in the literature. [d]Enantiomeric excess of aldol adducts *syn*-**10**/**11** as determined by chiral HPLC on analytically pure samples.

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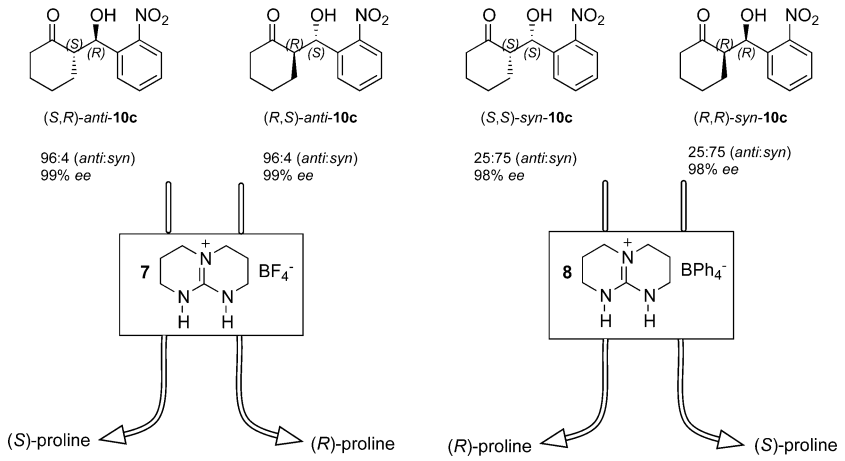

Figure 1. Combinations of either (*S*)- or (*R*)-proline, and additive **7** or **8**, employed for the preparation of all possible stereoisomers of product **10c**.

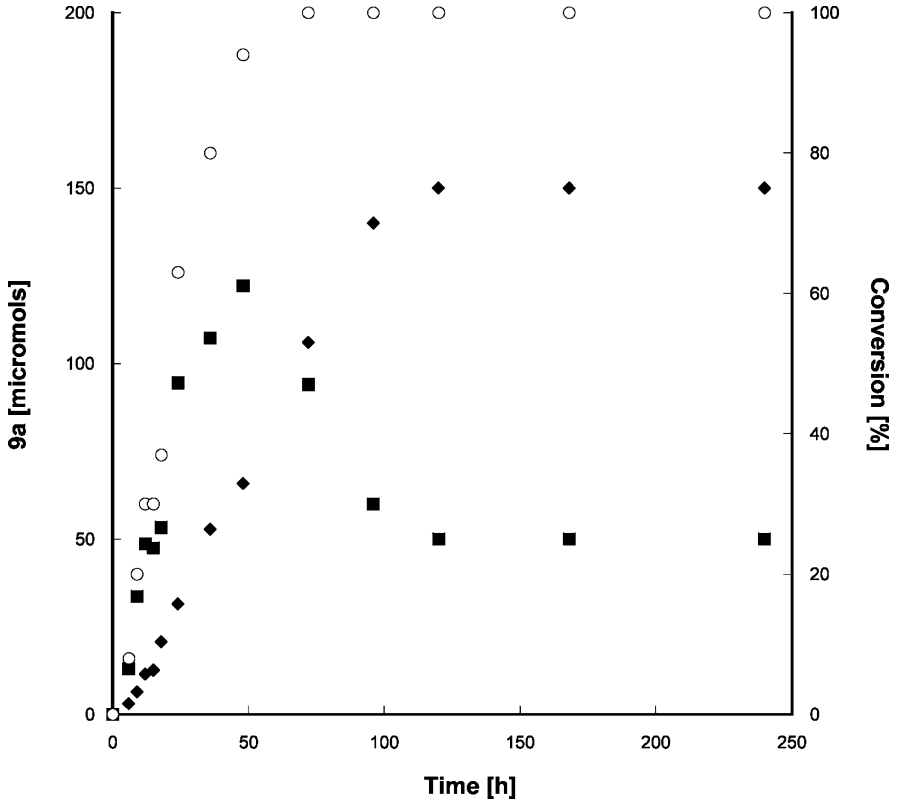

Figure 2. Concentration vs time profile for the formation of aldol adducts *syn*-**10c** and *anti*-**10c** from cyclohexanone and 2-nitrobenzaldehyde **9c**, and evolution of reaction conversion vs time. Every point is the average result of two individual reactions. All the experiments were carried out under the following reaction conditions: cyclohexanone (2.0 mmol), aldehyde **9c** (0.2 mmol), (*S*)-proline (0.02 mmol), **8** (0.03 mmol), no solvent. The reaction mixture was left to stand inside a fridge (0−3 °C) with no stirring. Aldol *syn*-**10c** is represented in micromoles (left axis, filled diamonds). Aldol *anti*-**10c** is represented in micromoles (left axis, filled squares). A maximum quantity of 200 micromoles can be reached by either aldol. Conversion is represented in percentage (right axis, open circles).

spectroscopy and chiral HPLC after particular times.[11] Deconvolution of the appropriate resonances allowed calculating and plotting the amount of adducts *syn*-**10c** and *anti*-**10c** featured in this process against time, as well as the reaction conversion (Figure 2).

Analyzing Figure 2, it can be concluded that at the start of the reaction, adduct *anti*-**10c** is formed at a faster rate compared to *syn*-**10c**. This observation is to be expected from the admitted role of (*S*)-proline acting as organocatalyst in aldol reactions selective for *anti* addcuts. Product *anti*-**10c** is gradually converted with time into aldol *syn*-**10c**, which after around 70 h it is already the major product featured in the reaction media. At ≈120 h the reaction reaches equilibrium, the population of adducts *syn*- and *anti*-**10c** reflecting the diastereoselectivity indicated in Table 1, entry 3. Importantly, the enantiomeric excesses of aldols *anti*-**10c** (99% *ee*, (*S*,*R*) configuration) and *syn*-**10c** (98% *ee*, (*R*,*R*) configuration) are constant for every experiment represented in Figure 2, independently of reaction conversion values. Intrigued by these results, we decided to evaluate the relative stability of the

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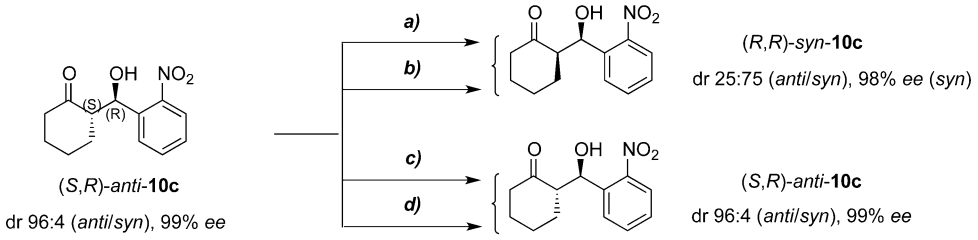
Scheme 2. Experiments on Aldol Adduct (*S,R*)-*anti*-10c to Gain Insight into the Mechanism of the Proline/Guanidinium Salt 8 Catalyzed Synthesis of *syn*-Aldols[a]



a): cyclohexanone (10 equiv), (*S*)-proline (10 mol%), **8** (15 mol%)

b): cyclopentanone (10 equiv), (*S*)-proline (10 mol%), **8** (15 mol%)

c): cyclohexanone (10 equiv), (*S*)-proline (10 mol%)

d): cyclohexanone (10 equiv), **8** (15 mol%)

[a]All the experiments were set up employing 0.2 mmol of aldol (*S,R*)-*anti*-**10c** as starting material. All the reaction mixtures were left to stand for 10 days inside a fridge (0−3 °C) with no stirring or mechanical agitation.

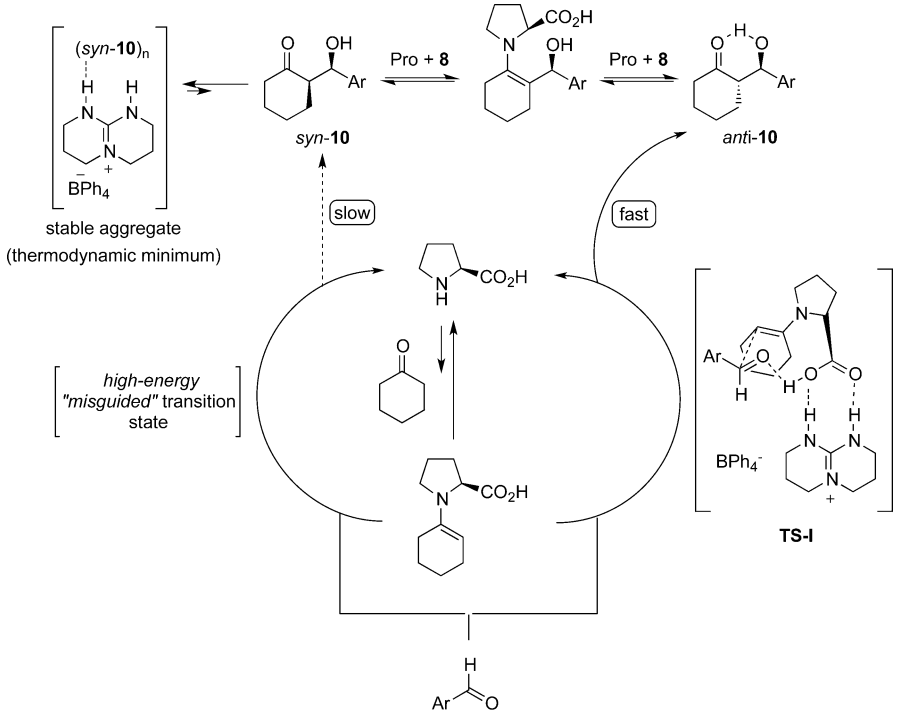


Figure 3. Mechanistic proposal for the (*S*)-proline/guanidinium salt **8** cocatalyzed direct aldol reaction between cyclohexanone and aromatic aldehydes.

reaction products. The geometries of the *anti* and *syn* pair of adducts **10c** and **11a−c** were fully optimized at the B3LYP/6-31G* level of theory. To our wonder, these calculations showed that the *anti* adducts are always more stable than their corresponding *syn* partners (see SI).

Further experiments were designed and implemented to shed light on the unanticipated equilibrium process that converts aldol *anti*-**10c** into *syn*-**10c** (Scheme 2). A suspension of preformed pure aldol *anti*-**10c** (0.2 mmol, d.r. 96:4 *anti/syn*, 99% *ee*), (*S*)-proline (0.02 mmol), tetraphenylborate guanidinium salt **8** (0.03 mmol), in cyclohexanone (2.0 mmol) was allowed to react for 10 days, at 0−3 °C, with no agitation or stirring (Scheme 2, reaction *a*). Aldol (*R,R*)-*syn*-**10c** was rendered as sole reaction product displaying a d.r. 25:75 (*anti/syn*) and 98% *ee*, a similar figure as that represented in Table 1, entry 3. A comparable reaction outcome was experienced when preformed aldol *anti*-**10c** (d.r. 96:4 *anti/syn*, 99% *ee*), was treated with (*S*)-proline and additive **8** in the presence of cyclopentanone under similar reaction conditions (Scheme 2, reaction *b*). Aldols incorporating a cyclopentyl moiety were not observed in this later experiment, thus ruling out an aldol/retro-aldol process responsible for equilibrating species *anti*-**10c** and *syn*-**10c**.[12] Moreover, the experiments *c* and *d* from Scheme 2 confirm that neither the autonomous action of proline, nor the action of additive **8**, suffices for switching the stereochemistry of aldol **10c**.

On the basis of the experimental observations, presented in Figure 1 and Scheme 2, we adventure the following mechanistic

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scheme (Figure 3). On the one hand, as proposed by other authors, the formation of *anti*-aldols could be explained considering a Zimmerman−Traxler-type transition state.[13] Therefore, we speculate that the establishment of a 1:1 complex between the guanidinium cation of additive **8** and the corresponding enamine, formed from the cyclic ketone and (*S*)-proline, would stabilize the chairlike transition state **TS-I** that leads to *anti* products. As we have previously studied,[7] *anti* aldols formed in this way present a very high diastereoselectivity and enantiomerical purity. On the other hand, *syn* aldols would be slowly formed, in minimal quantity, through a high-energy "misguided" transition state. While the *anti* aldols seems to be more stable in the gas phase, according to the calculations (SI, Figures S1, S2), the *syn* isomers possess lower free energy under our reaction conditions. The data provided in Figure 2 and Scheme 2 (experiment *a*) give a strong support for this interpretation. As the possibility of a direct aldol/retro-aldol sequence can be discarded (Scheme 2, reaction *b*), the channel that connects both diastereoisomers most probably consists of a common proline−enamine intermediate, followed by hydrolysis. If this is the case, the high enantiopurity of the isolated products **10** and **11** reflects the stereochemical integrity of the C3 (C−OH) stereocenter. Anyhow, to give a clarification for the equilibrium process, it remains to be established why *syn* diastereoisomers could be more stable products under the reaction conditions applied. The B3LYP76-31G* optimized geometries of adducts (SI, Figures S1 and S2) show how the *anti* compounds, particularly *anti*-**10c**, are stabilized by strong intramolecular hydrogen bonds accounting for 6.3−12.5 kJ/mol. Under the specified reaction conditions the rather weak intramolecular interactions calculated for the *syn* compounds are replaced with stronger intermolecular hydrogen bonds. Keeping in mind the key effect played by the counteranions of our additives, it can be reasoned that replacing the tightly bound tetrafluoroborate anion with the large tetraphenylborate allows the bicyclic guanidinium core of salt **8** to participate in the hydrogen bonded networks with the *syn*-aldols. Also, it can be added that although all of the reactions in which additive **8** participates are homogeneous to the naked eye, we can not rule out the appearance of crystalline aggregates that would take *syn* adducts away from the reaction media, hence favoring their formation.[14] While the mechanism illustrated in Figure 3 is only a suggestion, it gives a full account for the experimental observations presented in Figure 2 and Scheme 2.

It is fair noting that the *syn* diastereoselectivity observed for aldols **10**, or **11**, originated from an equilibrium as that showed in Figure 2, could not be predicted taking into account the nature of the catalysts used and the substrates involved. It is however the consideration of the whole complex network resulting from the simultaneous coexistence of *anti*-aldols, *syn*-aldols, (*S*)-proline, guanidinium and guanidine species, aromatic aldehyde, cyclic ketone, enamines, all featured in the reaction media to some extent, their interactions (including supramolecular interactions[15]) and competition, their different solubility, solvation, etc., that makes it possible to figure out a processes of the like. We believe that this kind of approach, a systems chemistry strategy,[16] the study of the properties emerged from collections/systems of compounds (i.e., catalytic systems), can be of great benefit for areas such as organocatalysis.

CONCLUSIONS

To conclude, we have succeeded in using proline as a single chiral catalyst to control the stereochemical outcome of the asymmetric direct aldol reaction between cyclohexanone, or cyclopentanone, and aromatic aldehydes. The choice of the anion of an achiral TBD-derived guanidinium salt, used as cocatalyst for proline, allows preparation of either *anti*- or *syn*-aldol adducts with very high enantioselectivity. The origin of the *syn* diastereoselectivity unfolds from an unusual equilibrium process coupled to the enamine-based catalytic cycle standard for proline. This paper shows, as a proof of principle, how the right choice of an additive for proline allows a diastereoswitch in the aldol reaction. We are currently exploring different additives and reactions that allow proline, or other natural amino acids, for reversible diastereoswithcing.

EXPERIMENTAL SECTION

General Remarks. All commercially available reagents and solvents were used without further purification unless otherwise stated. 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 $60F_{254}$ 0.2 mm plates, and compounds were visualized by UV fluorescence or 5% phosphomolybdic acid in methanol. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 300 MHz spectrometer, using deuterated solvents, and were referenced internally to the residual solvent peak (δ_H = 7.26 ppm, δ_C = 77.36 ppm) signal. Coupling constants (*J*-values) are given in hertzs (Hz). The DEPT 135 technique was used to assign methylene (CH_2) signals. Chemical shifts are reported as follows: value (number of protons, description of absorption, coupling constant(s) where applicable). NMR spectra assignation was aided by comparison with literature values for similar compounds. Chiral HPLC analyses were performed according to the conditions specified in the Supporting Information.

Standard Procedure for the Synthesis of *anti*-Aldols 10a−d or 11a−d (SP1). Tetrafluoroborate guanidinium salt **7**[7] (4.5 mg, 0.02 mmol), (*S*)-proline (3.5 mg, 0.03 mmol) and solid aldehyde **9a−d** (0.2 mmol) were weighed together inside a screw-capped test tube. Either cyclohexanone (196 mg, 0.21 mL, 2.0 mmol) or cyclopentanone (168 mg, 0.18 mL, 2.0 mmol) was added to the mixture, and the resulting suspension, placed on a test tubes grid, was allowed to stay for 120 h inside a standard fridge (temperature fixed at 0−3 °C) without agitation of 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 eliminated under reduced pressure. Crude reaction mixtures were filtered through a plug of silica gel to afford pure aldols *anti*-**10a−d** (cyclohexanone) or *anti*-**11a−d** (cyclopentanone).

Standard Procedure for the Synthesis of *syn*-Aldols 10a−d or 11a−d (SP2). Tetraphenylborate guanidinium salt **8**[17] (13.8 mg, 0.03 mmol), (*S*)-proline (2.3 mg, 0.02 mmol) and solid aldehyde **9a−d** (0.2 mmol) were weighed together inside a screw-capped test tube. The mixture of solids was finely grinded and homogenized before either cyclohexanone (196 mg, 0.21 mL, 2.0 mmol) or cyclopentanone (168 mg, 0.18 mL, 2.0 mmol) was added, and the resulting suspension, placed on a test tubes grid, was allowed to stay for 120 h inside a standard fridge (temperature fixed at 0−3 °C) without agitation of 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 eliminated under reduced pressure. Crude reaction mixtures were purified by flash chromatography, when required, to afford pure aldols *syn*-**10a−d** (cyclohexanone) or *syn*-**11a−d** (cyclopentanone).

(*S*)-2-((*R*)-Hydroxy(4-nitrophenyl)methyl)cyclohexan-1-one (*anti*-10a).[7] Prepared according to **SP1**. Obtained as a yellow solid, 46 mg, 92% isolated yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.21−8.18 (2H, m), 7.52−7.47 (2H, m), 4.89 (1H, dd, *J* = 8.4, 3.1 Hz), 4.07 (1H, d, *J* = 3.1 Hz), 2.63−2.30 (3H, m), 2.15−2.07 (1H, m), 1.85−1.52

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(4H, m), 1.45−1.30 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 215.0 (C═O), 148.7, 147.9, 128.2 (2 x ArCH), 123.9 (2 x ArCH), 74.3, 57.5, 43.0, 31.1, 28.0, 25.0.

(*R*)-2-((*R*)-Hydroxy(4-nitrophenyl)methyl)cyclohexan-1-one (*syn*-10a).[6,18] Prepared according to **SP2**. Obtained as a yellow solid, 42 mg, 86% isolated yield. Purified by flash chromatography (Hex/EtOAc, 3:1): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.21−8.18 (2H, m), 7.52−7.47 (2H, m), 5.48 (1H, s), 3.20 (1H, d, J = 3.1 Hz), 2.66−2.59 (1H, m), 2.52−2.33 (2H, m), 2.16−2.06 (1H, m), 1.89−1.80 (1H, m), 1.76−1.48 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 214.4 (C═O), 149.4, 147.4, 126.2 (2 x ArCH), 123.8 (2 x ArCH), 70.4, 57.1, 43.0, 28.2, 26.2, 25.1.

(*S*)-2-((*R*)-Hydroxy(3-nitrophenyl)methyl)cyclohexan-1-one (*anti*-10b).[18] Prepared according to **SP1**. Obtained as a yellow solid, 49 mg, 98% isolated yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.20−8.11 (2H, m), 7.67−7.64 (1H, m), 7.53−7.48 (1H, m), 4.88 (1H, d, J = 8.4 Hz), 4.13 (1H, s), 2.66−2.29 (3H, m), 2.14−2.06 (1H, m), 1.85−1.53 (4H, m), 1.44−1.31 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 215.1 (C═O), 148.5, 143.6, 133.5, 129.6, 123.1, 122.3, 74.3, 57.4, 42.9, 31.0, 27.9, 24.9.

(*R*)-2-((*R*)-Hydroxy(3-nitrophenyl)methyl)cyclohexan-1-one (*syn*-10b).[6,18] Prepared according to **SP2**. Obtained as a yellow solid, 43 mg, 87% isolated yield. Purified by flash chromatography (Hexane/EtOAc, 3:1): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.18−8.10 (2H, m), 7.67−7.65 (1H, m), 7.54−7.49 (1H, m), 5.48 (1H, s), 3.20 (1H, s), 2.68−2.62 (1H, m), 2.51−2.34 (2H, m), 2.16−2.04 (1H, m), 1.88−1.49 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 214.5 (C═O), 148.6, 144.1, 132.3, 129.5, 122.4, 121.9, 70.2, 57.0, 42.9, 28.2, 26.2, 25.1.

(*S*)-2-((*R*)-Hydroxy(2-nitrophenyl)methyl)cyclohexan-1-one (*anti*-10c).[18] Prepared according to **SP1**. Obtained as a yellow solid, 49 mg, 98% isolated yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.84−7.74 (2H, m), 7.65−7.59 (1H, m), 7.44−7.39 (1H, m), 5.43 (1H, d, J = 7.1 Hz), 3.84 (1H, s), 2.79−2.71 (1H, m), 2.47−2.27 (2H, m), 2.12−2.04 (1H, m), 1.89−1.54 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 215.2 (C═O), 149.0, 136.9, 133.4, 129.3, 128.7, 124.4, 70.0, 57.6, 43.1, 31.4, 28.1, 25.3.

(*R*)-2-((*R*)-Hydroxy(2-nitrophenyl)methyl)cyclohexan-1-one (*syn*-10c).[6,18] Prepared according to **SP2**. Obtained as a yellow solid, 45 mg, 92% isolated yield. Purified by flash chromatography (Hex/EtOAc, 3:1): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.01−7.98 (1H, m), 7.84−7.81 (1H, m), 7.67−7.61 (1H, m), 7.45−7.39 (1H, m), 5.95 (1H, s), 3.29 (1H, d, J = 3.2 Hz), 2.91−2.84 (1H, m), 2.47−2.35 (2H, m), 2.14−2.04 (1H, m), 1.89−1.49 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 214.4 (C═O), 147.4, 137.3, 133.5, 129.9, 128.2, 125.0, 67.0, 55.1, 42.9, 28.3, 26.8, 25.1.

(*S*)-2-((*R*)-Hydroxy(4-cyanophenyl)methyl)cyclohexan-1-one (*anti*-10d).[18] Prepared according to **SP1**. Obtained as a white solid, 45 mg, 98% isolated yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.64−7.61 (2H, m), 7.44−7.41 (2H, m), 4.82 (1H, d, J = 8.4 Hz), 4.06 (1H, s), 2.60−2.29 (3H, m), 2.13−2.05 (1H, m), 1.86−1.51 (4H, m), 1.40−1.23 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 215.1 (C═O), 146.7, 132.4, 128.1, 119.0, 111.9, 74.5, 57.4, 42.9, 31.0, 27.9, 25.0.

(*R*)-2-((*R*)-Hydroxy(4-cyanophenyl)methyl)cyclohexan-1-one (*syn*-10d).[6,18] Prepared according to **SP2**. Obtained as a white solid, 45 mg, 98% isolated yield. Purified by flash chromatography (Hexane/EtOAc, 3:1): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.64−7.61 (2H, m), 7.43−7.40 (2H, m), 5.42 (1H, s), 3.17 (1H, s), 2.63−2.53 (1H, m), 2.51−2.32 (2H, m), 2.16−2.03 (1H, m), 1.88−1.80 (1H, m), 1.74−1.48 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 214.5 (C═O), 147.3, 132.3 (2 x ArCH), 126.8 (2 x ArCH), 119.2, 111.1, 70.5, 57.1, 42.9, 28.2, 26.2, 25.1.

(*S*)-2-((*R*)-Hydroxy(4-nitrophenyl)methyl)cyclopentan-1-one (*anti*-11a).[18] Prepared according to **SP1**. Obtained as a yellow solid, 39 mg, 84% isolated yield. Purified by flash chromatography (Hex/CH_2Cl_2, 1:10): ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 8.21 (2H, d, J = 8.8 Hz), 7.54 (2H, d, J = 8.7 Hz), 4.84 (1H, d, J = 9.1 Hz), 4.75 (1H, s), 2.52−2.17 (3H, m), 2.07−1.97 (1H, m), 1.79−1.51 (3H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 222.5 (C═O), 149.0, 148.0, 127.7 (2 x ArCH), 124.1 (2 x ArCH), 74.8, 55.4, 39.0, 27.2, 20.7.

(*R*)-2-((*R*)-Hydroxy(4-nitrophenyl)methyl)cyclopentan-1-one (*syn*-11a).[18] Prepared according to **SP2**. Obtained as a yellow solid, 40 mg, 86% isolated yield. Purified by flash chromatography (Hex/EtOAc, 3:1): ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 8.22−8.18 (2H, m), 7.54−7.50 (2H, m), 5.42 (1H, d, J = 2.9 Hz), 2.66 (1H, s), 2.51−1.65 (7H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 219.8 (C═O), 150.4, 147.5, 126.7 (2 x ArCH), 124.0 (2 x ArCH), 70.8, 56.4, 39.3, 22.8, 20.7.

(*S*)-2-((*R*)-Hydroxy(3-nitrophenyl)methyl)cyclopentan-1-one (*anti*-11b).[18] Prepared according to **SP1**. Obtained as a yellow solid, 36 mg, 77% isolated yield. Purified by flash chromatography (Hex/CH_2Cl_2, 1:10): ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 8.25−8.15 (2H, m), 7.72−7.66 (1H, m), 7.56−7.51 (1H, m), 4.83 (1H, d, J = 9.3 Hz), 2.54−2.17 (3H, m), 2.08−1.98 (1H, m), 1.78−1.50 (3H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 222.7 (C═O), 148.7, 144.0, 133.0, 129.8, 123.7, 122.0, 74.8, 55.4, 39.0, 27.3, 20.7.

(*R*)-2-((*R*)-Hydroxy(3-nitrophenyl)methyl)cyclopentan-1-one (*syn*-11b).[18] Prepared according to **SP2**. Obtained as a yellow solid, 42 mg, 89% yield. Purified by flash chromatography (Hex/EtOAc, 3:1): ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 8.22−8.10 (2H, m), 7.70−7.66 (1H, m), 7.54−7.49 (1H, m), 5.41 (1H, d, J = 2.2 Hz), 2.52−1.93 (5H, m), 1.79−1.65 (2H, m); ^{13} C NMR ($CDCl_3$, 75 MHz) δ = 220.0 (C═O), 148.6, 145.3, 132.0, 129.7, 122.6, 120.9, 70.6, 56.4, 39.3, 22.7, 20.7.

(*S*)-2-((*R*)-Hydroxy(2-nitrophenyl)methyl)cyclopentan-1-one (*anti*-11c).[19] Prepared according to **SP1**. Obtained as a yellow solid, 38 mg, 80% isolated yield. Purified by flash chromatography (Hex/CH_2Cl_2, 1:10): ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.84−7.78 (2H, m), 7.67−7.62 (1H, m), 7.46−7.41 (1H, m), 5.44 (1H, d, J = 8.6 Hz), 4.47 (1H, s), 2.57−2.23 (3H, m), 2.10−1.97 (1H, m), 1.80−1.65 (3H, m); ^{13} C NMR ($CDCl_3$, 75 MHz) δ = 222.4 (C═O), 148.8, 136.6, 133.5, 129.3, 128.9, 124.4, 69.4, 55.8, 39.0, 26.9, 20.8.

(*R*)-2-((*R*)-Hydroxy(2-nitrophenyl)methyl)cyclopentan-1-one (*syn*-11c).[19] Prepared according to **SP2**. Obtained as a yellow solid, 42 mg, 89% isolated yield. Purified by flash chromatography (Hex/EtOAc, 3:1): ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.96 (1H, dd, J = 8.2, 1.2 Hz), 7.88 (1H, dd, J = 7.9, 1.2 Hz), 7.67−7.62 (1H, m), 7.45−7.39 (1H, m), 5.89 (1H, d, J = 2.9 Hz), 2.74−1.65 (7H, m); ^{13} C NMR ($CDCl_3$, 75 MHz) δ = 219.2 (C═O), 147.2, 138.9, 133.7, 128.9, 128.3, 124.8, 66.9, 55.1, 38.9, 23.2, 20.5.

(*S*)-2-((*R*)-Hydroxy(4-cyanophenyl)methyl)cyclopentan-1-one (*anti*-11d).[18] Prepared according to **SP1**. Obtained as a white solid, 32 mg, 35% isolated yield. Purified by flash chromatography (Hex/CH_2Cl_2, 1:10): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.65 (2H, d, J = 8.3 Hz), 7.47 (2H, d, J = 8.2 Hz), 4.78 (1H, d, J = 9.2 Hz), 2.51−2.18 (3H, m), 2.06−1.96 (1H, m), 1.81−1.51 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 222.6 (C═O), 147.0, 132.7 (2 x ArCH), 127.6 (2 x ArCH), 119.0, 112.2, 75.0, 55.4, 39.0, 27.2, 20.7.

(*R*)-2-((*R*)-Hydroxy(4-cyanophenyl)methyl)cyclopentan-1-one (*syn*-11d).[18] Prepared according to **SP2**. Obtained as a white solid, 38 mg, 88% isolated yield. Purified by flash chromatography (Hex/EtOAc, 3:1): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.64−7.61 (2H, m), 7.47−7.41 (2H, m), 5.35 (1H, d, J = 2.7 Hz), 2.73 (1H, s), 2.48−1.88 (5H, m), 1.77−1.65 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 219.9 (C═O), 148.5, 132.5 (2 x ArCH), 126.6 (2 x ArCH), 119.1, 111.4, 70.9, 56.3, 39.2, 22.7, 20.7.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Supporting tables and figures. Copies of ^{1}H and ^{13}C NMR spectra and HPLC plots for compounds **10a−d** and **11a−d**. Conformational study of compounds **10c** and **11a−c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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