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A Simple and Efficient Protocol for Proline-Catalysed Asymmetric Aldol Reaction

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Abstract: The proline-catalysed asymmetric aldol reaction is usually carried out in highly dipolar aprotic solvents (dimethylsulfoxide, dimethylformamide, acetonitrile) where proline presents an acceptable solubility. Protic solvents are generally characterized by poor stereocontrol (e.g., methanol) or poor reactivity (e.g., water). Here, we report that water/methanol mixtures are exceptionally simple and effective reaction media for the intermolecular organocatalytic aldol reaction using the simple proline as the catalyst.

Keywords: proline; organocatalysis; asymmetric aldol reaction; methanol/water mixtures; sustainability

1. Introduction

The asymmetric intermolecular aldol addition catalysed by (*S*)-proline, proposed by List and co-workers in 2000 [1], is the prototype of enamine-based organocatalysis [2,3]. Proline is the smallest air- and water-stable bifunctional catalyst; it is inexpensive, non-toxic, and available in both enantiomeric forms. It has been proven to catalyse enantioselective α-functionalizations of carbonyl compounds (aldol and Mannich reactions, Michael additions, α-halogenations, oxygenations, aminations, and so on), adopting reaction protocols that do not require inert atmosphere and anhydrous conditions and are carried out at room temperature [4,5].

The proline-catalysed aldol reaction [4,6–19] has been object of in-depth analyses after the first mechanistic rationale proposed by List and Houck [20], in particular, fundamental contributions have been given by Seebach [21], Armstrong and Blackmond [22,23], Sharma and Sunoj [24], Benaglia [25], and Gschwind [26,27]. However, proline scarce solubility in most organic solvents has limited its use in dimethylsulfoxide (DMSO), acetonitrile, or dimethylformamide (DMF). Moreover, proline often displays poor activity, requiring the use of high catalyst loadings and high reaction times, sometimes with unsatisfactory stereocontrol [1,28–36]. Because, in several cases, proline-catalysed aldol reactions are still underdeveloped, the last 15 years have witnessed an intense effort aimed at modifying the proline scaffold, following two directions: (1) the carboxylic group is replaced by a new hydrogen-bonding donor, such as a tetrazole, or by a sterically demanding group, such as the Hayashi–Jørgensen diarylmethanol and related compounds, as exhaustively reviewed by Trost [37]; and (2) the carboxylic group is retained and a supplementary substituent is bound to the proline scaffold. The new substituent, generally installed on the 4-OH group of 4-hydroxyproline, may play different roles: (*i*) it modifies the solubility profile of the parent amino acid, expanding the solvent choice to further classes [38]; and/or (*ii*) it enhances the catalyst activity and stereoselectivity, allowing a reduction of catalyst loading and reaction time; and/or (*iii*) it allows the catalyst immobilization on

a solid support [39–56], adopting a biphasic condition reaction protocol. Despite that high levels of reactivity and selectivity have been achieved with these modified prolines, most of the aforementioned proline derivatives require multi-step syntheses, dramatically increasing the catalyst cost, a severe limitation particularly when the catalyst cannot be efficiently recycled.

After having contributed to the synthesis of prolines, mostly modified with the incorporation of ionic tags on 4-position, and obtaining excellent results in terms of activity and stereoselectivity as well as catalyst recyclability [57–66], we decided to go back to the parent unmodified (*S*)-proline. We envisaged to improve the performance of this small, stable, inexpensive, non-toxic, and easily available organocatalyst exploring new experimental conditions.

The role of the solvent in determining the aldol reaction efficiency was also addressed by other authors. Invariably, the use of unmodified proline (without additives) forced to choose polar aprotic solvents to obtain acceptable yields and selectivities [1,11,13–15,28–36,44,45]. A peculiar case was represented by ionic liquids (ILs) [67–72], which allowed in a few cases to decrease the catalyst loading (up to 1 mol%) and, during the work-up, to confine proline in a separate phase, enabling a simple product isolation and the reuse of the catalytic system. In recent literature, attempts are reported where proline is used in acetone/$CHCl_3$ mixtures [73], in DMF at 4 °C (a condition that often requires several days) [74], in *tert*-butyl methyl ether (MTBE) [75], in deep eutectic solvents [76,77], or under solvent-free conditions, with [78–80] or without [81] the ball milling approach. However, many issues associated with the use of proline remain unsolved and polar aprotic solvents are characterized by several undesirable features (toxicity, high production cost, high environmental impact, difficult product recovery) [82–84].

The use of unmodified proline can be also combined with additives [85,86], such as water [85–87], acids [85,86,88], diols [89,90], amines [85,86], or thioureas [91–93]. In these cases, the additive can tune the solubility, the reactivity, and/or the stereoselectivity of native proline, making the asymmetric aldol process more efficient [18]. In one case, the addition of achiral guanidinium salts as additives allows to switch the diastereoselectivity as a function of the counterion, for example, tetrafluoroborate versus tetraphenylborate [94]. Nevertheless, the achieved performance is not optimal yet (long reaction times, stereocontrol strongly depending on the substrate) and some drawbacks are still present, such as high proline loadings and the cost of the not recovered chiral additive. Significant advances were accomplished employing metal salts as additives [95–106]. In particular, Reiser and co-workers developed a strategy based on cobalt(II)-proline complexes, which ensured excellent results in direct aldol reactions involving aromatic aldehydes [106]. However, several disadvantages lead the avoidance of the use of metals, especially at an industrial level (costs, toxicity, environmental impact, limited sources) [107–109].

In the present work, we aim to avoid the use of both polar aprotic solvents and additives (being sometimes expensive, mostly non-recoverable, and contaminants, used in non-generalizable procedures), in order to develop an efficient and sustainable organocatalyzed aldol condensation protocol, which can be interesting from a scale-up and an industrial point of view. In particular, our goals are as follows: (1) a reduction of the process costs, related to employed solvents and reagents, but also purification and waste disposal; and (2) an improved reactivity, especially for poorly reactive substrates. We planned to achieve these objectives by using the following: (*i*) the native proline, a small, stable, inexpensive, and non-toxic organocatalyst; and (*ii*) the minimum amount of a low-cost, non-toxic reaction solvent, enabling a good process efficiency and a simple and inexpensive final reaction work-up.

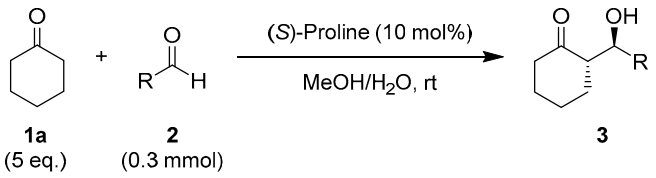
A number of research groups noticed that protic media were not suitable for aldol condensations promoted exclusively by native proline [15,29–33,87]. However, despite a plethora of studies focused on the use and the role of water (as solvent, co-solvent, or additive) [31,32,34,87,100–105,110,111], very few authors extended their investigations to alcohols [15,29,31,42,102,106], discouraged by the generally observed poor diastereo- and enantioselectivity. Only when proline was used in combination with metal salts as additives, the use of methanol as solvent [106] or co-solvent [102] afforded acceptable results.

Intrigued by the few data available on the proline-mediated aldol condensation employing methanol, a prototypical green solvent [84,112] also in terms of LCA (life-cycle assessment) [113], we decided to explore in depth the impact of methanol on the asymmetric intermolecular aldol condensation promoted by unmodified (*S*)-proline. It should be stressed, however, that efficient organocatalyzed aldol condensations invariably require a large excess of a liquid donor ketone (5–10 equivalents) that must thus be considered as a part of the reaction solvent-system.

2. Results and Discussion

2.1. Optimization of the Reaction Protocol

As model reaction, we selected the (*S*)-proline–catalysed aldol condensation between cyclohexanone **1a** and aromatic aldehydes **2** (Scheme 1). At the outset, we confirmed the low performance of proline in terms of stereocontrol in pure methanol, but soon we realized that the simple use of a hydroalcoholic solution as the reaction medium was highly profitable. Here, we report a comparison among (*S*)-proline–catalysed reactions between cyclohexanone **1a** and four different aromatic aldehydes **2a**–**d**, carried out in methanol/water (2/1 V/V), pure water, and pure methanol, respectively, all other parameters being kept identical (Table 1). The 2/1 V/V methanol/water mixture composition ensures that the aldol reaction takes place under homogeneous conditions.



Scheme 1. The benchmark aldol reaction.

Table 1. Comparison of different protic reaction media [1].

R (2)	Solvent	t [h]	3 Conversion [%] [2]	*ee* [%] [3]	*anti*/*syn* [2]
4-NO_2Ph (**2a**)	MeOH/H_2O	19	>99	98	93:7
	H_2O	19	25	99	95:5
	MeOH	19	>99	76	59:41
4-CNPh (**2b**)	MeOH/H_2O	19	97	98	95:5
	H_2O	19	80	99	95:5
	MeOH	19	>99	87	82:18
4-ClPh (**2c**)	MeOH/H_2O	19	43	99	97:3
	H_2O	19	5	>99	nd
	MeOH	19	64	98	85:15
Ph (**2d**) [4]	MeOH/H_2O	30	58	97	88:12
	H_2O	30	20	>99	>99:1
	MeOH	30	64	83	72:28

[1] Reaction conditions: **1a** (5 equiv.), **2** (0.3 mmol), (*S*)-proline (10 mol%), rt, MeOH/H_2O (20 μL/10 μL, 2/1 V/V) or H_2O (10 μL), or MeOH (20 μL). [2] Determined by ^{1}H NMR on the crude mixture. [3] Determined by chiral stationary phase (CSP)-HPLC on the crude mixture. [4] Here, 20 mol% of (*S*)-proline was used. rt = room temperature, h = hours, nd = not determined.

The data collected in Table 1 demonstrate the crucial role of water; if in pure water conversions are the lowest, enantioselectivity reaches the highest values. On the other hand, pure methanol displays the highest reactivity and the poorest stereocontrol. The 2/1 V/V methanol/water solution is able to combine the pros of the two pure solvents, providing the same conversions of pure methanol and almost the same *ee*s and good *dr*s observed in pure water.

In Table 2, the results are reported when the 2/1 V/V methanol/water solution was applied to aldol reactions between cyclohexanone **1a** and other aromatic aldehydes **2e–i** (Table 2).

Table 2. MeOH/H_2O-based protocol applied to different aromatic aldehydes **2** [1].

R (2)	t [h]	3 Conversion [%] [2]	*ee* [%] [3]	*anti/syn* [2]
C_6F_5 (**2e**)	19	>99	97	>99:1
2-NO_2Ph (**2f**)	19	93	95	95:5
4-BrPh (**2g**)	19	41	99	98:2
2-naphthyl (**2h**)	24	37	93	91:9
4-MeOPh (**2i**) [4]	70	18	90	86:14

[1] Reaction conditions: **1a** (5 equiv.), **2** (0.3 mmol), (*S*)-proline (10 mol%), MeOH/H_2O (20 µL/10 µL), rt. [2] Determined by ^{1}H NMR on the crude mixture. [3] Determined by CSP-HPLC on the crude mixture. [4] Here, 20 mol% of (*S*)-proline was used.

With the most reactive electron-poor aldehydes (**2a**, **2b**, **2e**, and **2f**), high conversion and high stereocontrol were achieved in only 19 h. Moreover, these results are excellent if compared with those reported in the literature for analogous transformations promoted by unmodified (*S*)-proline and exploiting more complex protocols [114–117]. Unfortunately, the limitations of the proline-catalysed aldol reactions were not completely overcome. In fact, electron-rich aromatic aldehydes were confirmed to be less reactive, requiring longer reaction times. More in detail, for substrates **2g** and **2h**, the conversions reached after 19 and 24 h, respectively, were modest; nevertheless, it is worth mentioning that the enantio- and the diastereoselectivities were both higher than those reported so far by proline-based protocols [118,119]. As far as the electron-rich *p*-methoxy benzaldehyde **2i** is concerned, the only example with proline (20 mol%) in DMSO reported a low conversion (15%) and absence of diastereoselection [105]. The effect on product conversion was even poorer when a Lewis acid and water were added. Exploiting our MeOH/H_2O-based protocol, the product conversion remained poor (18%), but the reaction proceeded with good enantio- (90% *ee*) and diastereoselectivity (*anti/syn* = 86:14).

Once the performance of native proline in 2/1 V/V methanol/water solution had been examined, we explored the effect of a more methanol-rich aqueous mixture. In Table 3, aldol reactions of cyclohexanone **1a** and different aldehydes **2** in 2/1 V/V and 4/1 V/V solutions are compared.

Doubling the methanol volume (40 µL), the conversions significantly improved with all the tested aldehydes, while maintaining an excellent to remarkable level of enantiocontrol (Table 3). The most reactive substrates (**2a**, **2b**, **2e**, and **2f**) provided excellent conversions in only 4 h, demonstrating an unprecedented reactivity of proline. Moreover, interesting amounts of product were obtained exploiting these reaction conditions for less electrophilic aldehydes as well (**2c,2d**, **2g,2i**; Table 3). Concerning the diastereocontrol, a slight drop of the *anti/syn* ratio was observed with some aldehydes when the volume of methanol was increased. Conversely, for benzaldehyde **2d** and 2-naphthyl aldehyde **2h**, the diastereoselection lightly improved. In the case of benzaldehyde **2d**, the better performance could be the result of the reduced amount of catalyst (10 mol%), exploitable thanks to the higher proline reactivity reached with larger amounts of methanol. In the case of the most reactive 4-nitrobenzaldehyde **2a**, we solved the problem of diastereoselectivity drop by adding the methanol amount in two portions (one half after 2 h), completely restoring the diastereocontrol, while maintaining a high reaction rate. In general, a good diastereoselectivity level is retained with this protocol (4/1 V/V methanol/water) compared with the literature data [114–119]. At the same time, reaction rates are significantly enhanced. Therefore, these reaction conditions represent the best trade-off between reactivity and stereoselectivity. In Table 3, this optimized protocol was extended to some other aldehydes (**2j–m**), with good results compared with the literature data [120–123]. In particular, aliphatic aldehyde **2j**, known as poorly responsive in this kind of organocatalysed reaction, reached an interesting conversion (63%) and remarkably high stereochemical results (>99% *ee* and *anti/syn* > 99:1), superior to those reported by other authors for unmodified proline [120].

Table 3. Optimization of the MeOH/H_2O-based protocol [1].

R (2)	MeOH/H_2O [μL/μL]	t [h]	3 Conversion [%] [2]	*ee* [%] [3]	*anti/syn* [2]
4-NO_2Ph (**2a**)	20/10	4	**3aa**, 47	97	94:6
	40/10	4	**3aa**, 82	98	92:8
	20 + 20 [4]/10	4	**3aa**, 84	97	94:6
4-CNPh (**2b**)	20/10	4	**3ab**, 65	97	95:5
	40/10	4	**3ab**, 77	95	94:6
4-ClPh (**2c**)	20/10	19	**3ac**, 43	99	97:3
	40/10	19	**3ac**, 64	98	95:5
Ph (**2d**)	20/10 [5]	30	**3ad**, 58	97	88:12
	40/10	30	**3ad**, 75	96	90:10
C_6F_5 (**2e**)	20/10	4	**3ae**, 63	97	>99:1
	40/10	4	**3ae**, 67	96	>99:1
2-NO_2Ph (**2f**)	20/10	4	**3af**, 34	97	98:2
	40/10	4	**3af**, 59	97	97:3
4-BrPh (**2g**)	20/10	19	**3ag**, 41	99	98:2
	40/10	19	**3ag**, 88	96	94:6
2-naphthyl (**2h**)	20/10	24	**3ah**, 37	93	91:9
	40/10	24	**3ah**, 72	93	92:8
4-MeOPh (**2i**) [5]	20/10	68	**3ai**, 18	90	86:14
	40/10	68	**3ai**, 43	89	80:20
i-Pr (**2j**) [5]	40/10	72	**3aj**, 63	>99	>99:1
4-CF_3Ph (**2k**)	40/10	4	**3ak**, 78	97	97:3
2-thiophenyl (**2l**) [5]	40/10	48	**3al**, 65	88	84:16
4-CH_3Ph (**2m**)	40/10	40	**3am**, 64	94	87:13

[1] Reaction conditions: **1a** (5 equiv.), **2** (0.3 mmol), (*S*)-proline (10 mol%), rt. [2] Determined by ^{1}H NMR on the crude mixture. [3] Determined by CSP-HPLC on the crude mixture. [4] Here, 20 μL of MeOH was added after 2 h. [5] Here, 20 mol% of (*S*)-proline was used.

The next step of our investigation was directed to the ketone partner **1** of the asymmetric aldol condensation. In proline-catalysed aldol reactions, a typical drawback is represented by the excess of ketone over the limiting aldehyde generally required to achieve good yields. To increase the sustainability of the process, we planned to lower the ketone excess (Table 4).

Some aldehydes characterized by high or medium reactivity were selected for this study, in which the ketone amount was reduced to 2 equivalents. With almost all the tested substrates, high conversions and excellent *ee* values were again obtained. Although longer reaction times were required, the reaction rates remained worthy of note, especially when compared with the performance of other protocols in similar conditions. The main drawback of this procedure was a slight decrease of diastereoselectivity, an effect that is not immediately obvious. Benaglia, using the reaction progress kinetic analysis (RPKA) approach [25], a technique that allowed Blackmond et al. to define the kinetic rate law of proline-catalysed aldol reactions [23], proved the reversibility of the aldol reaction. Lowering the ketone excess leads to the following: (*i*) longer reaction times to preserve the same level of product conversion; and (*ii*) a less efficient opposition to the retroaldol reaction, which is a slow process within the time scale of our reactions. Both factors promote equilibrium on a little extent, likely accounting for the slightly decreased diastereocontrol observed when reduced amounts of cyclohexanone **1a** were used (Table 4). In conclusion, the high efficiency achieved by MeOH/H_2O/(*S*)-proline-based protocol

allows to reduce the ketone excess, involving (*i*) slight adverse effects on aldol reaction performance; and (*ii*) benefits, such as lower costs and easier work up and product purification.

Table 4. Effects of cyclohexanone **1a** amount in the MeOH/H_2O/(*S*)-proline-based protocol [1].

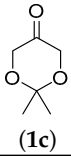
R (2)	1a [eq.]	t [h]	3 Conversion [%] [2]	*ee* [%] [3]	*anti/syn* [2]
4-NO_2Ph (**2a**)	5	4	82	98	92:8
	5	4	84 [4]	97	94:6
	2	19	99	95	92:8
	1.05	19	92	97	90:10
4-CNPh (**2b**)	5	4	77	95	94:6
	2	24	98	91	90:10
C_6F_5 (**2e**)	5	4	67	97	>99:1
	2	24	>99	92	>99:1
2-NO_2Ph (**2f**)	5	4	59	97	97:3
	2	24	92	93	94:6
4-BrPh (**2g**)	5	19	88	96	94:6
	2	24	97	91	90:10
4-CF_3Ph (**2k**)	5	4	78	97	97:3
	3	20	96	96	95:5
	2	24	93	94	93:7

[1] Reaction conditions: **2** (0.3 mmol), (*S*)-proline (10 mol%), MeOH/H_2O (40 µL/10 µL), rt. [2] Determined by ^{1}H NMR on the crude mixture. [3] Determined by CSP-HPLC on the crude mixture. [4] Here, 20 µL of MeOH was added after 2 h.

2.2. Application of the Protocol to Other Ketones

Afterwards, we focused on the application of the developed catalytic protocol to two different donor ketones **1b,1c** (Table 5). Considering the excellent performance (stereoselectivity and reaction rate) achieved employing the MeOH/H_2O/(*S*)-proline protocol in the presence of 5 equivalents of **1a**, we decided for convenience to apply these conditions to the ketones investigation.

Table 5. MeOH/H_2O/(*S*)-proline-based protocol applied to ketones **1b,c** [1].

(1)	R (2)	t [h]	3, Conversion [%] [2]	*ee* [%] [3]	*anti/syn* [2]
 (**1b**)	4-NO_2Ph (**2a**)	4	**3ba**, >99	94	61:39
	4-NO_2Ph (**2a**)	19 [4]	**3ba**, 91	94	78:22
	4-BrPh (**2g**)	19	**3bg**, 64	93	75:25
	Ph (**2d**)	30	**3bd**, 70	93	73:27
 (**1c**)	4-BrPh (**2g**)	24	**3cg**, 90	86	78:22
	Ph (**2d**)	48	**3cd**, 82	86	77:23

[1] Reaction conditions: **2** (0.3 mmol), **1** (5 eq.), (*S*)-proline (10 mol%), MeOH/H_2O (40 µL/10 µL), rt. [2] Determined by ^{1}H NMR on the crude mixture. [3] Determined by CSP-HPLC on the crude mixture. [4] Reaction carried out at 0 °C.

At first, we tested cyclopentanone **1b** with highly reactive 4-nitrobenzaldehyde **2a**, observing a particularly high reaction rate, with the transformation being complete in only 4 hours. This result is unprecedented in the presence of unmodified proline or most of its derivatives [124–127], confirming once again the high reactivity achievable employing the MeOH/H_2O protocol. The corresponding product **3ba** was obtained with excellent *ee*, but low diastereoselectivity. This behaviour was expected because poorly diastereoselective aldol reactions catalyzed by proline or its derivatives were regularly

reported for cyclopentanone **1b** [87,124–127]. To improve the diastereoselctivity, we lowered the reaction temperature to 0 °C and we obtained a good 78:22 *anti/syn* ratio, maintaining a high conversion in a reasonable time.

Considering the excellent performance achievable with MeOH/H_2O/(*S*)-proline-based protocol, we were particularly interested in the results obtainable with less reactive aldehydes. In fact, 4-Br benzaldehyde **2g** and benzaldehyde **2d** provided the corresponding products (**3bg** and **3bd**, respectively) with good conversions and diastereoselectivities, and, noteworthy, with the best enantioselectivities ever achieved employing unmodified proline as catalyst [128].

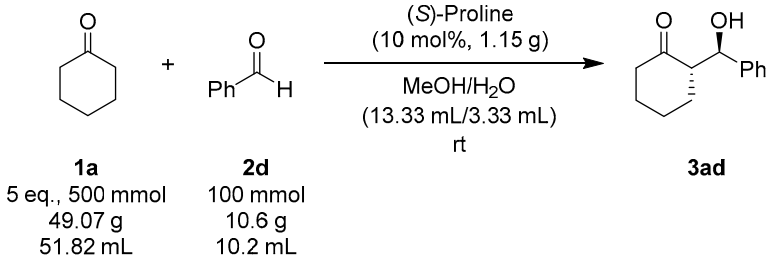
As further confirmation, 2,2-dimethyl-1,3-dioxan-5-one **1c** (Table 5) also displayed good reactivity and stereoselectivity when reacted with less reactive aldehydes **2g** and **2d**. In particular, our results represent the first examples of organocatalyzed aldol condensation between 2,2-dimethyl-1, 3-dioxan-5-one **1c** and 4-Br benzaldehyde **2g** or benzaldehyde **2d**, promoted by only 10 mol% of proline [129–133].

At last, we applied our protocol to acetone **1d** as simple aliphatic ketone (Table S3, Section 2, Supplementary Materials). Although with 4-NO_2 benzaldehyde **2a**, we obtained an unprecedented high reaction rate if compared with the published corresponding transformations, the enantioselectivity was poor, as commonly reported for the proline-catalysed aldol additions involving these substrates.

2.3. Large-Scale Application of the Protocol

Our aim is the development of an efficient and sustainable organocatalyzed aldol condensation protocol, which can be interesting from a scale-up perspective. Therefore, as a first step, we confirmed the excellent performance of the MeOH/H_2O/(*S*)-proline-based protocol by carrying out the aldol condensation between moderately reactive benzaldehyde **2d** and cyclohexanone **1a** on a 10 mmol scale (gram scale). The desired product **3ad** was isolated in 78% yield and with high stereocontrol (90:10 *dr*, 95% *ee*), fully confirming the data obtained on small scale (Table 3).

The next step was the accomplishment of the same reaction on a 100 mmol scale of the limiting reagent benzaldehyde **2d** (Scheme 2) in order to study some aspects in more detail.



Scheme 2. Process scale-up on 100 mmol of limiting aldehyde **2d**.

At first, we investigated the impact of the aldehyde addition rate on the reaction outcome (Table 6). With benzaldehyde **2d** not being very reactive, good conversions were recorded only after 23 h and we did not observe a significant difference depending on the addition rate of benzaldehyde (Table 6).

Then, we monitored product conversion and stereoselectivity for a longer reaction time (Table 6), to establish if a high conversion could be achieved without a significant loss in stereocontrol exploiting our reaction conditions. Indeed, as previously mentioned, aldol reaction is reversible and longer reaction times could make the retroaldol process competitive, providing a decreased diastereomeric ratio. Actually, we observed a slow increase of the product conversion, achieving 85% after 2 days, without a significant erosion of *anti/syn* ratio (in comparison with small scale-reactions, a slightly lower *dr* was recorded, which remained constant for the first 48 h). We confirmed that even the enantiomeric excess of the product remained at high levels (94% *ee* after 47 h).

Table 6. Process scale-up study [1].

Aldehyde Addition Rate	t [h]	Conversion [%] [2]	*anti/syn* [2]	*ee* [%] [3]
45 min	23	72	86:14	96
	28	78	87:13	-
	47	83	85:15	94
6 h	23	71	87:13	-
	28	80	85:15	-
	47	85	84:16	-

[1] Reaction conditions: **2d** (100 mmol), **1a** (500 mmol), (*S*)-proline (10 mol%), MeOH/H_2O (13.33 mL/3.33 mL), rt. Total volume = 79 mL. [2] Determined by ^{1}H NMR on the crude mixture. [3] Determined by CSP-HPLC on the crude mixture.

The results reported in Table 6 clearly show that the best reaction outcome is obtained at a reaction time representing the best balance between product conversion and stereocontrol. To further explore this effect, we compared the data obtained with different moderately or poorly reactive aldehydes (Table 7).

Table 7. Study of the reaction outcome as a function of the reaction time [1].

R (2)	t [h]	Conversion [%] [2]	*anti/syn* [2]
Ph (**2d**)	24	75	86:14
	46	81	84:16
	71	85	79:21
	94	85	71:29
4-CH_3Ph (**2m**)	23	53	90:10
	45	65	87:13
	71	74	84:16
	138	75	79:21
4-MeOPh (**2i**) [3]	68	43	80:20
	115	49	72:28
	164	52	66:34

[1] Reaction conditions: **2** (50 mmol), **1a** (5 eq.), (*S*)-proline (10 mol%), MeOH/H_2O (6.67 mL/1.67 mL), rt. [2] Determined by ^{1}H NMR on the crude mixture. [3] Here, 20 mol% of (*S*)-proline was used.

Concerning the stereoselectivity, in this study, we focused our attention on diastereoselectivity variation, which is much more impaired by retroaldol reaction (see Supplementary Materials for a study on enantioselectivity variation). The data collected in Table 7 demonstrate that the aldol transformation reaches a position, after which the product conversion no longer grows, while the *dr* continues to drop. The time required to achieve this situation depends on the aldehyde reactivity. On the other hand, the rate of retroaldol process is less affected by the aldehyde nature; therefore, the retroaldol effects are less troublesome for reactive aldehydes (high conversion in short time with high *dr*) and more marked for poorly reactive aldehydes (long time required to reach acceptable conversion with low *dr*). This study proves that, in the asymmetric aldol process promoted by proline, the reaction time providing the best performance (balance between conversion and stereoselectivity) strongly depends on the substrate; therefore, a careful investigation should be done before tackling a large-scale application.

A further point that we evaluated to increase the sustainability of our large-scale protocol was the reduction of the ketone excess. For this purpose, we applied the MeOH/H_2O/(*S*)-proline-based protocol to moderately reactive benzaldehyde **2d** (50 mmol) in the presence of only 2 equivalents of cyclohexanone **1a**, monitoring the results over the time. After 71 h, we achieved the highest product conversion (83%) with an excellent 89:11 *dr*. Prolonging the reaction time (98 h) only led to a drop in *dr* (84:16). These findings suggest that, exploiting our protocol, a large excess of ketone (5 equivalents)

only enhances the initial reaction rate, but it is not necessary for the achievement of an excellent final performance.

2.4. Work-Up Investigations

As the last point, we investigated some different work-up approaches, in order to (*i*) compare the results (also in terms of sustainability), and (*ii*) establish if part of the organocatalyst could be easily recovered. The first 100 mmol-scale aldol condensation (Table 6, 45 min long aldehyde addition) was stopped after 49 h and the reaction mixture (total volume = 79 mL) was divided in six portions, treated as described in Table 8.

Table 8. Process work-up study [1].

Method	Conditions	Final Volume (mL)	Crude Analysis [2]
A	Reaction mixture = 18 mL (22.8 mmol) filtered on a silica-pad, mobile phase = EtOAc	242	Conv. = 87% *dr* = 84:16
B	Reaction mixture = 18 mL (22.8 mmol) diluted with EtOAc, quenched with aqueous NH_4Cl, extracted with EtOAc, dried with Na_2SO_4 (washed with EtOAc)	90	Conv. = 86% *dr* = 83:17
C	Reaction mixture = 10 mL (12.6 mmol) diluted with EtOAc and placed at −15 °C for 36 h. 1° vacuum filtration. At −15 °C for 36 h. 2° vacuum filtration. Solution dried with Na_2SO_4 (washed with EtOAc)	46	Conv. = 89% *dr* = 84:16 Proline recovery: 113.3 mg (78%)
D	Reaction mixture = 10 mL (12.6 mmol) diluted with Et_2O and placed at −15 °C for 36 h. 1° vacuum filtration. At −15 °C for 36 h. 2° vacuum filtration. Solution dried with Na_2SO_4 (washed with Et_2O)	52	Conv. = 90% *dr* = 85:15 Proline recovery: 124.8 mg (86%)
E	Reaction mixture = 10 mL (12.6 mmol) diluted with DCM and placed at −15 °C for 36 h. Two liquid phases obtained, dried with Na_2SO_4 (washed with DCM)	36	Conv. = 88% *dr* = 85:15
F	Reaction mixture = 10 mL (12.6 mmol) diluted with *n*-hexane and placed at −15 °C for 36 h. Two liquid phases obtained, dried with Na_2SO_4 (washed with *n*-hexane)	43	Conv. = 89% *dr* = 86:14

[1] Aldol condensation carried out on 100 mmol of **2d,** reaction conditions described in Scheme 2, reaction stopped after 49 h, reaction mixture (total volume = 79 mL) divided in six portions and treated with six different work-up methods. [2] Determined by ^{1}H NMR on the crude mixture. EtOAc = ethyl acetate, Et_2O = diethyl ether, DCM = dichloromethane.

The first portion of reaction mixture (18 mL, 22.8 mmol) was filtered through a short pad of silica to remove water and proline (method **A**, Table 8). EtOAc was used as mobile phase to elute product **3ad** (along with residual reagents **1a** and **2d**). Despite the significant polarity of EtOAc, a large amount of solvent was required to recover all the product and an undesirable high volume of organic solvent (242 mL) had to be evaporated under reduced pressure.

The second portion of reaction mixture (18 mL, 22.8 mmol) was subjected to a typical aqueous work-up to remove water and proline (method **B**, Table 8). NH_4Cl (2 equivalents with respect to proline, solved in 20 mL of H_2O) was employed to quench proline, the two phases were separated, and the aqueous phase was extracted two additional times with EtOAc, until complete recovery of the product (checked by thin-layer chromatography). The solution was dried with Na_2SO_4, which restrained a significant amount of aldol product **3ad**, so that it was necessary to wash it three times with EtOAc. A considerable volume of organic solvent (90 mL) had to be evaporated.

At this point, we tried to develop a work-up method that allowed us in a simple way not only to remove the catalyst, but also to recover it, at least partially. Exploiting the very low amount of protic

polar solvents used in our MeOH/H_2O/(*S*)-proline-based protocol, we envisaged that the addition of a small portion of organic solvent could make the reaction environment sufficiently lipophilic to trigger the catalyst precipitation. Four different organic solvents were tested: EtOAc (method **C**, Table 8), Et_2O (method **D**), dichloromethane (method **E**), and *n*-hexane (method **F**). The minimum amount of solvent able to provide an opalescent solution was added to each portion (10 mL, 12.6 mmol) and the mixtures were stored at −15 °C for 36 h. In the portions treated with EtOAc and Et_2O (methods **C** and **D**, respectively), a white precipitate, corresponding to proline, was clearly observed; therefore, it was filtered under vacuum and washed with a small amount of cold solvent. The filtered solutions were stored at −15 °C for further 36 h and a second portion of catalyst was recovered in both cases. Afterwards, the mixtures were dried with Na_2SO_4, which was required to be washed three times with organic solvent. In these two cases (methods **C** and **D**), a considerable amount of organic solvent also had to be evaporated (46 and 52 mL, respectively). In the portions treated with DCM and *n*-hexane (methods **E** and **F**, respectively), two liquid phases were observed and we decided to directly use Na_2SO_4 to remove the small water-based phase. Na_2SO_4 was washed with solvent until complete recovery of the product (three times for DCM, four times for *n*-hexane). In these two cases (methods **E** and **F**), the lowest amounts of organic solvent were employed (36 and 43 mL, respectively).

By comparing the results obtained with the tested work-up methods, we can infer the following: (1) no work-up approach adversely affects reaction conversion and diastereoselectivity, in fact all the crude mixtures showed comparable good results (Table 8). (2) The least suitable and sustainable method to remove water and proline seems to be the silica-pad (method **A**), owing to the large amount of solvent required to recover all the desired product; (3) when two organic and aqueous phases are formed (methods **B**, **E** and **F**), the simplest and cheapest work-up appears the dilution with a very small amount of DCM, cooling, and directly drying with Na_2SO_4 (method **E**). This approach is practicable only thanks to the very low amount of protic polar solvents used in our MeOH/H_2O/(*S*)-proline-based protocol. (4) Among the tested work-up approaches, the most convenient are those allowing an easy recovery of a large part of the organocatalyst (methods **C** and **D**). In particular, method **D** employing Et_2O reached 86% of proline recovery using an acceptable volume of organic solvent. Moreover, this result is obtainable on the basis of very low amount of protic polar solvents used in our protocol.

Although the tested work-up methods are not optimized and, therefore, can be further improved, they give a clear indication of the advantages that our protocol can offer.

3. Materials and Methods

3.1. General Information

^1H and ^{13}C NMR spectra were recorded on Inova 400 NMR instrument (Agilent, Santa Clara, CA, United States) with a 5 mm probe. Chemical shifts (δ) are reported in ppm, relative to the residual peaks of deuterated solvent signals.

HPLC-MS analyses were performed on an Agilent Technologies HP1100 instrument (Agilent, Santa Clara, CA, United States) coupled with an Agilent Technologies MSD1100 single-quadrupole mass spectrometer (Agilent, Santa Clara, CA, United States). A Phenomenex Gemini C18, 3 µm (100 × 3 mm) column was employed for the chromatographic separation: mobile phase H_2O/CH_3CN, gradient from 30% to 80% of CH_3CN in 8 min, 80% of CH_3CN until 22 min, and then up to 90% of CH_3CN in 2 min; flow rate 0.4 mL min^{-1} (Phenomenex, Torrance, CA, United States).

Chiral stationary phase (CSP)-HPLC analyses were performed on an Agilent Technologies Series 1200 instrument (Agilent, Santa Clara, CA, United States) using Daicel®chiral columns and *n*-hexane/2-propanol (*n*-Hex/IPA) mixtures (Daicel, Osaka, Japan).

Optical rotation measurements were performed on a polarimeter Schmidt+Haensch UniPol L1000 (Schmidt + Haensch GmbH & Co, Berlin, Germany).

Flash chromatography purifications were carried out using Merck silica gel 60 (230–400 mesh particle size). Thin layer chromatography was performed on Merck 60 F254 plates (Merck, Darmstadt, Germany).

Commercial reagents were used as received without additional purification, with exception of liquid aldehydes, which were distilled and stored under nitrogen atmosphere to avoid the formation of the corresponding acids. Dry methanol (Sure/Seal™ bottle) was used to ensure a reproducible water content.

The diastereomeric and enantiomeric compositions were checked on the crude products against the corresponding racemic products, obtained under the same reaction conditions using racemic proline.

3.2. Synthetic Procedures.

3.2.1. General Procedure for the Small-Scale Aldol Condensation Between Aldehydes **2** and Ketones **1**

The aldol reaction was carried out in a 2 mL vial. In a typical reaction, the vial was charged at room temperature with the reactants in the following order: (*S*)-proline (0.03 mmol), methanol (40 μL), water (10 μL), the selected ketone **1** (1.5 mmol), and the selected aldehyde **2** (0.3 mmol). The flask was capped with a stopper and sealed. Then, the reaction mixture was stirred at room temperature for the desired time. The conversion was monitored by TLC (Merck, Darmstadt, Germany) and ^{1}H-NMR (a small portion was taken, diluted, and immediately analyzed) (Agilent, Santa Clara, CA, United States). Then, the mixture was filtered on a short pad of silica with ethyl acetate and concentrated under reduced pressure.

The product conversion with respect to the limiting aldehyde and the diastereomeric ratio were determined by ^{1}H-NMR in $CDCl_3$ on the crude mixture. The enantiomeric excess was determined by chiral stationary phase (CSP)-HPLC (Agilent, Santa Clara, CA, United States) on the crude mixture.

The study of the solvent role (Tables 1–3), the study of the effects of ketone amount (Table 4), and the protocol application to other ketones (Table 5) were carried out following this general procedure.

3.2.2. Procedure for the Aldol Condensation Between Benzaldehyde **2d** and Cyclohexanone **1a** on 10 mmol Scale

The aldol reaction was conducted in a 25 mL flask. The flask was charged with (*S*)-proline (115 mg, 1 mmol), methanol (1.33 mL), water (330 μL), and cyclohexanone **1a** (5.18 mL, 50 mmol) and the mixture was allowed to stir for 10 min at room temperature. Then, the mixture was cooled at 0 °C and benzaldehyde **2d** (1.02 mL, 10 mmol) was slowly added by means of a syringe. The flask was capped with a stopper and sealed. The reaction mixture was stirred at room temperature for 30 h. Then, the mixture was filtered on a pad of silica with ethyl acetate and concentrated under reduced pressure. The conversion (85%) with respect to the limiting aldehyde and the diastereomeric ratio (90:10) were determined by ^{1}H-NMR in $CDCl_3$ on the crude mixture. The obtained residue was purified by column chromatography (ethyl acetate/cyclohexane = 2:8 as the eluent) to afford the product **3ad** in 78% yield. The enantiomeric excess (95% *ee*) was determined by CSP-HPLC on the pure product.

3.2.3. Procedure for the Aldol Condensation between Benzaldehyde **2d** and Cyclohexanone **1a** on 100 mmol Scale (Table 6)

The aldol reaction was conducted in a 250 mL flask. The flask was charged with (*S*)-proline (1.15 g, 10 mmol), methanol (13.33 mL), water (3.33 mL), and cyclohexanone **1a** (51.8 mL, 500 mmol) and the mixture was allowed to stir for 15 min at room temperature. Then, the mixture was cooled at 0 °C and benzaldehyde **2d** (10.2 mL, 100 mmol) was slowly added by means of (*i*) addition funnel (addition rate = 45 min), or (*ii*) syringe for slow addition (addition rate = 6 h). Then, the flask was capped with a stopper and sealed. The reaction mixture was stirred at room temperature. The reaction performance was monitored over time (a small portion was taken, diluted, and immediately analyzed); the product conversion with respect to the limiting aldehyde and the diastereomeric ratio were determined by

^{1}H-NMR in $CDCl_3$ on the crude mixture, and the enantiomeric excess was determined by CSP-HPLC on the crude mixture. After 49 h, the first reaction (addition rate = 45 min) was stopped, the reaction mixture (total volume = 79 mL) was divided in six portions, and they were treated as described in Table 8 (see below for details).

3.2.4. General Procedure for the Study of Reaction Outcome as a Function of Reaction Time (Table 7)

The aldol reaction was conducted in a 100 mL flask. The flask was charged with (*S*)-proline (575 mg, 5 mmol), methanol (6.67 mL), water (1.67 mL), and cyclohexanone **1a** (25.9 mL, 250 mmol) and the mixture was allowed to stir for 15 min at room temperature. Then, the mixture was cooled at 0 °C and the desired aldehyde **2** (50 mmol) was slowly added by means of an addition funnel. Then, the flask was capped with a stopper and sealed. The reaction mixture was stirred at room temperature. The reaction performance was monitored over time (a small portion was taken, diluted, and immediately analyzed); the product conversion with respect to the limiting aldehyde and the diastereomeric ratio were determined by ^{1}H-NMR in $CDCl_3$ on the crude mixture, and the enantiomeric excess was determined by CSP-HPLC on the crude mixture. At the reported time (Table 7), the mixture was filtered on a pad of silica with ethyl acetate and concentrated under reduced pressure. The obtained residue was purified by column chromatography (ethyl acetate/cyclohexane = 2:8 as the eluent) to afford the pure product (**3ad**: 76% yield, **3am**: 67% yield, **3ai**: 43% yield).

3.2.5. Procedure for the Aldol Condensation between Benzaldehyde **2d** (50 mmol) and Cyclohexanone **1a** (2 equivalents, 100 mmol)

The aldol reaction was conducted in a 100 mL flask. The flask was charged with (*S*)-proline (575 mg, 5 mmol), methanol (6.67 mL), water (1.67 mL), and cyclohexanone **1a** (10.36 mL, 100 mmol) and the mixture was allowed to stir for 15 min at room temperature. Then, the mixture was cooled at 0 °C and benzaldehyde **2d** (5.1 mL, 50 mmol) was slowly added by means of an addition funnel. Then, the flask was capped with a stopper and sealed. The reaction mixture was stirred at room temperature. The reaction performance was monitored over time (a small portion was taken, diluted, and immediately analyzed); the product conversion with respect to the limiting aldehyde and the diastereomeric ratio were determined by ^{1}H-NMR in $CDCl_3$ on the crude mixture, and the enantiomeric excess was determined by CSP-HPLC on the crude mixture. After 99 h, the reaction was stopped and it was filtered on a pad of silica with ethyl acetate and concentrated under reduced pressure. The obtained residue was purified by column chromatography (ethyl acetate/cyclohexane = 2:8 as the eluent) to afford the product **3ad** in 76% yield. The enantiomeric excess (91% *ee*) was determined by CSP-HPLC on the pure product.

3.3. Work-Up Procedures

3.3.1. Procedure for Filtration on a Silica-Pad (Method **A**, Table 8)

A portion (18 mL corresponding to 22.8 mmol) of the first reaction (addition rate = 45 min) carried out on 100 mmol of limiting aldehyde **2d** (see Section 3.2.3) was filtered on a silica-pad: 1.5 cm height, 9.6 cm diameter, gooch porosity = 4 (10–16 μm), mobile phase = EtOAc. In the last EtOAc portions (25 mL each), the presence of product was checked by TLC. The filtered reaction mixture (total volume = 242 mL) was concentrated under reduced pressure. The product conversion (87%) with respect to the limiting aldehyde and the diastereomeric ratio (84:16 = *anti*:/*syn*) were determined by ^{1}H-NMR in $CDCl_3$ on the obtained residue.

3.3.2. Procedure for Aqueous Work-Up Employing NH_4Cl (Method **B**, Table 8)

A portion (18 mL corresponding to 22.8 mmol) of the first reaction (addition rate = 45 min) carried out on 100 mmol of limiting aldehyde **2d** (see Section 3.2.3) was diluted with EtOAc (5 mL) and treated with an aqueous solution of NH_4Cl (242 mg, 2 equivalents with respect to proline, in 20 mL of H_2O).

The two layers were separated and the aqueous phase was further extracted with EtOAc (2 x 20 mL, the complete product extraction was checked by TLC). The collected solution was dried with Na_2SO_4 (1.15 g), and then it was filtered and washed with EtOAc (3 x 9 mL, the complete product recovery was checked by TLC). The filtered reaction mixture (total volume = 90 mL) was concentrated under reduced pressure. The product conversion (86%) with respect to the limiting aldehyde and the diastereomeric ratio (83:17 = *anti*/*syn*) were determined by ^{1}H-NMR in $CDCl_3$ on the obtained residue.

3.3.3. Procedure for Dilution with EtOAc and Cooling (Method **C**, Table 8).

A portion (10 mL corresponding to 12.6 mmol) of the first reaction (addition rate = 45 min) carried out on 100 mmol of limiting aldehyde **2d** (see Section 3.2.3) was diluted with EtOAc (4 mL) and placed at −15 °C for 36 h. A white precipitate was formed, was filtered under vacuum, and washed with cold EtOAc (2 × 4 mL). Here, 86.2 mg of white solid was recovered. The obtained solution was placed at −15 °C for further 36 h. A second portion of white solid was filtered under vacuum and washed with cold EtOAc (2 × 3 mL). Here, 27.1 mg of white solid was recovered. The collected solution was dried with Na_2SO_4 (650 mg), and then it was filtered and washed with EtOAc (3 × 6 mL, the complete product recovery was checked by TLC). The filtered reaction mixture (total volume = 46 mL) was concentrated under reduced pressure. The product conversion (89%) with respect to the limiting aldehyde and the diastereomeric ratio (84:16 = *anti*/*syn*) were determined by ^{1}H-NMR in $CDCl_3$ on the obtained residue. Total recovered proline = 113.3 mg (78%). The nature of the white solid was confirmed by ^{1}H-NMR spectroscopy (see Supplementary Materials) and optical rotation measurement ($[\alpha]_D^{25} = -84$; c = 0.135, water) in comparison with the commercial compound ($[\alpha]_D^{25} = -86$; c = 0.133, water).

3.3.4. Procedure for Dilution with Et_2O and Cooling (Method **D**, Table 8).

A portion (10 mL corresponding to 12.6 mmol) of the first reaction (addition rate = 45 min) carried out on 100 mmol of limiting aldehyde **2d** (see Section 3.2.3) was diluted with Et_2O (4 mL) and placed at −15 °C for 36 h. A white precipitate was formed, it was filtered under vacuum and washed with cold Et_2O (2 × 4 mL). Here, 109.4 mg of white solid was recovered. The obtained solution was placed at −15 °C for further 36 h. A second portion of white solid was filtered under vacuum and washed with cold Et_2O (2 × 3 mL). Here, 15.4 mg of white solid was recovered. The collected solution was dried with Na_2SO_4 (650 mg), and then it was filtered and washed with Et_2O (3 × 8 mL, the complete product recovery was checked by TLC). The filtered reaction mixture (total volume = 52 mL) was concentrated under reduced pressure. The product conversion (90%) with respect to the limiting aldehyde and the diastereomeric ratio (85:15 = *anti*/*syn*) were determined by ^{1}H-NMR in $CDCl_3$ on the obtained residue. Total recovered proline = 124.8 mg (86%). The nature of the white solid was confirmed by ^{1}H-NMR spectroscopy (see Supplementary Materials) and optical rotation measurement ($[\alpha]_D^{25} = -80$; c = 0.131, water) in comparison with the commercial compound ($[\alpha]_D^{25} = -86$; c = 0.133, water).

3.3.5. Procedure for Dilution with DCM and Cooling (Method **E**, Table 8)

A portion (10 mL corresponding to 12.6 mmol) of the first reaction (addition rate = 45 min) carried out on 100 mmol of limiting aldehyde **2d** (see Section 3.2.3) was diluted with DCM (5 mL) and placed at −15 °C for 36 h. Two liquid phases were formed. The mixture was directly dried with Na_2SO_4 (650 mg), and then it was filtered and washed with DCM (3 × 7 mL, the complete product recovery was checked by TLC). The filtered reaction mixture (total volume = 36 mL) was concentrated under reduced pressure. The product conversion (88%) with respect to the limiting aldehyde and the diastereomeric ratio (85:15 = *anti*/*syn*) were determined by ^{1}H-NMR in $CDCl_3$ on the obtained residue.

3.3.6. Procedure for Dilution with n-Hexane and Cooling (Method **F**, Table 8)

A portion (10 mL corresponding to 12.6 mmol) of the first reaction (addition rate = 45 min) carried out on 100 mmol of limiting aldehyde **2d** (see Section 3.2.3) was diluted with *n*-hexane (5 mL) and placed at −15 °C for 36 h. Two liquid phases were formed. The mixture was directly dried with

Na_2SO_4 (650 mg), and then it was filtered and washed with *n*-hexane (4 × 7 mL, the complete product recovery was checked by TLC). The filtered reaction mixture (total volume = 43 mL) was concentrated under reduced pressure. The product conversion (89%) with respect to the limiting aldehyde and the diastereomeric ratio (86:14 = *anti*:*syn*) were determined by ^{1}H-NMR in $CDCl_3$ on the obtained residue.

3.4. Products Characterization.

All the synthesized products were known compounds and the obtained data were in agreement with the published ones:

[134] for products **3aa**, **3ab**, **3ac**, **3ad**, **3af**, **3ag**, and **3ah**;
[135] for products **3ae**, **3ai**, **3ak**, and **3ba**;
[106] for product **3aj**;
[136] for product **3bd**;
[137] for product **3cd**;
[138] for products **3al** and **3am**;
[139] for product **3bg**;
[129] for product **3cg**.

As an example, the complete characterization of the most studied aldol product **3ad** (*anti* isomer) is reported in the Supplementary Materials. CSP-HPLC separation conditions and chromatograms of all the aldol products **3** are reported in the Supplementary Materials.

4. Conclusions

Since 2000, the time the first seminal publication by List, Lerner, and Barbas III on the intermolecular asymmetric aldol reaction catalyzed by proline appeared, a countless number of papers focused on enamine organocatalysis with the aim to solve a few critical issues inherent in the use of proline. Summarizing, high catalyst loading, long reaction times, solvent limitations owing to proline solubility, variable stereocontrol mainly dependent on the donor-acceptor aldol partners, difficult and/or expensive product isolation, and catalyst recovery characterize the proline-catalysed aldol protocol. On the other hand, advantages have been previously underlined such as low cost, no toxicity, no need for anhydrous solvents or controlled atmosphere, and process practicality.

Over these two decades, the greatest efforts have been dedicated to the design and synthesis of new catalysts, mostly sharing with proline the chiral pyrrolidine scaffold. These derivatives allow to enlarge the platform of solvent candidates, up to enabling the possibility of catalyst recycling. Reaction kinetics improve with shorter reaction times and lower catalyst loadings. If these improvements are beyond doubt, the costs coupled to their preparation are clearly a limiting factor. On the other hand, it is known that a number of common solvents have been questioned in recent years as their hazardous properties have come to light, for example, the environmental, safety, and health issues associated to the use of DCM, toluene, DMSO, and others.

The work presented here shows that very good results can be simply achieved using methanol/water mixtures as reaction medium. When only water is used, these reactions take place in a typical heterogeneous conditions (emulsions), where the interphase water has as many as about a quarter of the O–H bonds not being involved in hydrogen bonding. According to Jung and Marcus [140], the interactions of these unbound hydroxyl groups with organic reactants and, more importantly, with the transition states, lower the activation energies, enabling rate and yield enhancements. Faster reactions occur in pure methanol because of the homogeneous conditions, which allow all the amount of proline used to participate to catalysis, but this superior reactivity is characterized by a lower stereocontrol. Recent papers evidenced, by DFT calculations, the positive effects of co-additives such as water or methanol in stabilizing the transition states of the aldol reaction, with methanol displaying the larger effects [24,141–143]. These protic additives could directly participate in the reaction mechanism, acting as an active proton transfer relay between the proline carboxylic acid group and the incoming aldehyde. The amount and the nature of the protic

additive could significantly change the reactivity and stereoselectivity of this transformation, as transition states with one, two, and even three molecules of the additive have been located and described.

If both methanol and water as pure solvents give largely unsatisfactory results that discouraged further investigations, we demonstrated that methanol/water mixtures provide the high reaction rates (good yields in short reaction times) typical of methanol and the high stereocontrol typical of water. The efficient, simple, and cost-effective reaction protocol proposed, easily scaled up here up to the 100 mmol scale, as well as the safe handling of the methanol/water mixture, positively impact the overall efficiency and sustainability of this proline-catalysed aldol protocol. However, we have to observe that, also following this procedure, the recurring dependence of relative reaction rates and stereochemical outcome on the nature of the donor-acceptor pair has not been overcome. Thus, cyclohexanone is the best donor in terms of reactivity and stereocontrol, while cyclopentanone works faster, but with a much lower stereocontrol. Electron-rich aromatic aldehydes are the slowest reaction acceptors, requiring long reaction times, while electron-poor aldehydes are the best. Nevertheless, given that the usual relative behavior of ketones and aldehydes is confirmed, the aldol protocol in methanol/water can be considered a useful contribution, enabling the achievement of performance never obtained before (also for less reactive compounds), employing the smallest and cheapest organocatalytic species, proline.

Supplementary Materials: The following are available online at http://www.mdpi.com/2073-4344/10/6/649/s1, Table S1: Enantioselectivity variation as a function of reaction time; Figure S1: ^{1}H-NMR spectrum of commercial proline; Figure S2: ^{1}H-NMR spectrum of recovered proline employing work-up method C (Table 8); Figure S3: ^{1}H-NMR spectrum of recovered proline employing work-up method D (Table 8), CSP-HPLC separation conditions and chromatograms of aldols **3** (racemic and enantio-enriched), full characterization of *anti* aldol product **3ad** (CSP-HPLC chromatogram of enantio-enriched product, ^{1}H-NMR spectrum, ^{13}C-NMR spectrum, HPLC-MS chromatograms, ESI-MS spectrum).

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