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Efficient ball-mill procedure in the 'green' asymmetric aldol reaction organocatalyzed by (*S*)-proline-containing dipeptides in the presence of water

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ABSTRACT

The organocatalytic activity of (*S*)-proline-based dipeptides **1a**–**c** has been evaluated in the asymmetric aldol reaction between representative ketones with various aromatic aldehydes under solvent-free conditions in a ball mill. In particular, the methyl ester of (*S*)-proline-(*S*)-tryptophan, (*S*,*S*)-**1c**, proved to be an efficient organocatalyst, and the aldol reaction proceeded with good chemical yields and excellent diastereo- and enantioselectivity (up to 98:2 *anti*/*syn* dr and up to 98% ee), in the presence of water, and 5 mol % of benzoic acid as additive.

1. Introduction

Organocatalysis is essentially the acceleration of a chemical step by a non metal-containing relatively small organic molecule. This simple new concept has totally captured the attention of much of the organic chemistry community in the last decade.[1] For instance, the fact that organocatalysis prevents the use of a metal means that organocatalytic processes fulfill one of the guidelines of green chemistry, where the design of safe chemical process is a key concept.[2a] Furthermore, a relevant strategy followed by some researchers in the organocatalysis area to make it 'greener' involves the use of friendly reaction media, avoiding, for example, the use of toxic, volatile, and/or corrosive solvents.[2b,c] For example, the use of ionic liquids,[3] heterogeneous catalysts anchored on resins or inorganic solid supports,[4] water as a reaction media[5] or application of solvent-free processes[6] have all contributed to the development of more sustainable chemical processes.

In the field of organocatalysis, the asymmetric aldol reaction has been extensively studied in view of the fact that this reaction is one of the most powerful strategies for the formation of new C–C bonds; that is, facilitates the construction of larger molecules from smaller ones. Among the many reaction conditions that have been examined, an attractive advancement corresponds to asymmetric aldol reactions carried out under solvent-free conditions. For example, Nájera and co-workers have reported the use of L-prolinamides and L-prolinethioamides (5 mol %) as organocatalysts in solvent-free aldol reaction (2:1 ketone/aldehyde) with traditional magnetic stirring. The *anti*-aldol adducts were obtained in high yields and with excellent diastereo- and enantioselectivities (up to 99:1 dr, up to 98% ee).[7]

On the other hand, Bolm and Worch performed the enantioselective aldol reaction of cyclohexanone and aromatic aldehydes in solvent-free conditions (5:1 ketone/aldehyde), using L-prolyl-substituted sulfonimidamides as catalysts (10 mol %), observing moderate to very good yields and good to excellent stereoselectivities (up to 96:4 dr, up to 98% ee) after 2–4 days of stirring at 30 °C.[8] In related work, Bolm and co-workers reported the asymmetric aldol reaction under solvent-free conditions catalyzed by (*S*)-proline (10 mol %) in a ball mill, using nearly stoichiometric amounts of ketone and aldehyde (1.1:1). The *anti*-aldol products were obtained in high yields with up to 99% ee. In this study, Bolm and co-workers demonstrated that the efficiency of the process using High Speed Ball-Milling (HSBM) was superior relative to traditional magnetic stirring: reaction times were shorter and in general chemical yields, diastereo- and enantioselectivities were higher.[9] The above mentioned High Speed Ball-Milling technique has been increasingly used in synthetic organic chemistry to promote several solvent-free reactions. Reported applications include: Heck-type cross-couplings,[10] Knoevenagel condensation reactions,[11] Baylis–Hillman reactions,[12] Michael additions,[11] functionalization of fullerenes,[13] synthesis of nitrones,[14] synthesis of peptides,[15] and others.

Recently, as part of our continuing interest in HSBM,[15a] we examined the asymmetric aldol reaction between ketones and

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various aromatic aldehydes under solvent-free conditions in a ball mill using almost stoichiometric amounts of ketone and aldehyde (1.1:1). The reaction was catalyzed by the methyl ester of (*S*)-proline-(*S*)-phenylalanine, (*S*,*S*)-**1a** (7 mol %) and proceed efficiently affording the *anti*-aldol products in high yields and with good diastereo- and enantioselectivities (up to 91:9 dr, up to 95% ee).[16,17] We could demonstrate that dipeptide (*S*,*S*)-**1a** was more efficient organocatalyst in the asymmetric aldol reaction under solvent-free conditions, relative to the same reaction in solution. In addition we found that reaction times were shortened compared with the same reaction employing 10 mol % of amino acid (*S*)-proline, also in a ball mill under solvent-free conditions.[9] To explain the success of dipeptide (*S*,*S*)-**1a** as an organocatalyst under solvent-free conditions, we suggested that non-covalent π–π interactions between the aromatic rings of the catalyst and the substrate were maximized in the absence of solvent, which could be responsible for the high stereoselectivity in aldol product formation. With the aim of evaluating this hypothesis, we decided to prepare two additional (*S*)-proline-containing α,α-dipeptides, where the second amino acid presents a lipophilic residue, in order to compare their organocatalytic activity in the asymmetric aldol reaction of interest. Dipeptides (*S*,*S*)-**1b** and (*S*,*S*)-**1c**, derived from (*S*)-proline and (*S*)-phenylglycine or (*S*)-tryptophan, respectively (Fig. 1) were deemed most useful to test the mechanistic proposal.

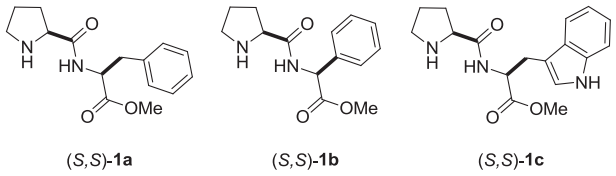
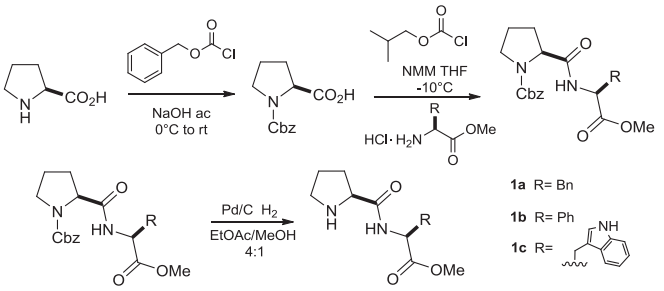


Fig. 1. Structure of dipeptides (*S*,*S*)-**1a**–**c**.

Dipeptide (*S*,*S*)-**1c** has been previously studied as catalyst in asymmetric aldol reactions. Szöllősi and co-workers reported the use of (*S*,*S*)-**1c** (10 mol %) in the aldol reaction between acetone and 2-ethylbutanal, in an excess of acetone (68:1). After 24 h of reaction, the expected (*R*)-β-hydroxyketone was obtained in moderate yield and 86% ee.[17o] Furthermore, the unprotected dipeptide (*S*)-NHPro-(*S*)-TrpOH (**1c**-OH) has been also evaluated as organocatalyst in aldol reactions and proved to be a privileged structure. In particular, List and Martin studied the asymmetric aldol reaction between acetone and 4-nitrobenzaldehyde in DMSO using 30 mol % of (**1c**-OH) and 18 h of reaction time. The expected aldol product was isolated in moderate yield and with 65% ee of the (*R*)-enantiomer.[17e] Furthermore, in 2007 Li and co-workers reported the use of dipeptide (**1c**-OH) in the aldol reaction of representative ketones with various aromatic, heteroaromatic, aliphatic, and unsaturated aldehydes in the presence of water. The desired aldol products were obtained in high yields (up to 94%) and good enantioselectivities (up to 97% ee).[17a] In addition, Li and co-workers examined dipeptide (**1c**-OH) in the asymmetric aldol reaction of different ketones and aldehydes in solid phase media (Al_2O_3), using 1,4-diazabicyclo[2.2.2]octane as additive, observing moderate to high reaction yields (35–95%), good diastereoselectivities (up to 99:1 dr) and excellent enantioselectivities (*anti*-aldol, 98% ee).[17d] Nevertheless, before the present work dipeptides (*S*,*S*)-**1b** and (*S*,*S*)-**1c** had not been studied as potential organocatalysts in aldol reactions under solvent-free reaction conditions.

2. Results and discussion

Methyl ester dipeptides (*S*,*S*)-**1a**, (*S*,*S*)-**1b** and (*S*,*S*)-**1c** (Fig. 1) were prepared by condensation of Cbz-*N*-protected (*S*)-proline with (*S*)-phenylalanine, (*S*)-phenylglycine and (*S*)-tryptophan methyl ester hydrochloride, followed by deprotection with hydrogen and palladium on carbon, according to the reported method for the preparation of dipeptide (*S*,*S*)-**1c** (Scheme 1).[17o]

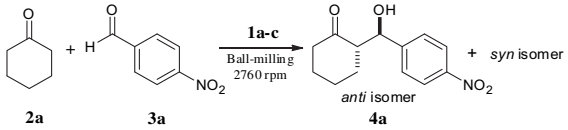


Scheme 1. Synthesis of dipeptides (*S*,*S*)-**1a**–**c**.

Initially, we examined the aldol reaction between cyclohexanone and 4-nitrobenzaldehyde in the presence of organocatalyst (*S*,*S*)-**1a**, (*S*,*S*)-**1b**, and (*S*,*S*)-**1c**. The reaction was carried out at −20 °C in a ball mill at 2760 rpm, using 7 mol % of catalyst (Table 1).

After 4 h of milling, the dipeptides (*S*,*S*)-**1b** and (*S*,*S*)-**1c** afforded the aldol product in good yield, high diastereo- and enantioselectivity. In particular, with dipeptide (*S*,*S*)-**1c** as organocatalyst the aldol adduct was obtained with up to 84:16 *anti*/*syn* dr and 85% ee in favor of the (2*S*,1′*R*)-enantiomer (entry 3 in Table 1). The absolute configuration of the products was assigned by comparison with literature data.[5a,7c,9,17d]

Table 1
Direct asymmetric aldol reaction of 4-nitrobenzaldehyde with cyclohexanone catalyzed by (*S*,*S*)-dipeptides **1a**–**c**[a]



2a **3a** **4a**

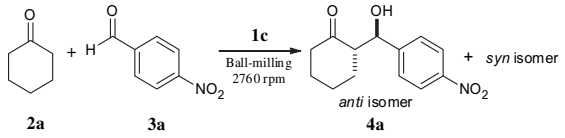
Entry	Cat.	Yield (%)[b]	dr (*anti*/*syn*)[c]	ee[d] (%)
1	**1a**	92	90:10	95[e]
2	**1b**	80	89:11	82
3	**1c**	86	86:14	85

[a] Reaction conditions: ketone **2a** (0.22 mmol), aldehyde **3a** (0.20 mmol), catalyst **1a**–**c** (7 mol %), −20 °C, 4.0 h.
[b] Isolated yield.
[c] Determined by ^{1}H NMR of the crude product.
[d] Determined by chiral HPLC.
[e] Ref. 16.

To improve the ee of the products obtained with (*S*,*S*)-**1c** as organocatalyst, we decided to evaluate the effect of water on the aldol reaction. Indeed, in aldol reaction catalyzed by proline residues embedded in a hydrophobic environment, water has demonstrated to play an important role in organocatalytic reactions inducing significant reaction rate acceleration and/or increasing the stereoselectivity.[5d,9,18]

Thus, the effect of different amounts of water in the model reaction of cyclohexanone and 4-nitrobenzaldehyde at −20 °C catalyzed by 7 mol % of dipeptide (*S*,*S*)-**1c** was examined (Table 2). The addition of 0.5 equiv of water to the reaction mixture did not result in an increase of the yield; however, a small improvement in the stereoselectivity of the product may be observed (entry 2 in Table 2). Higher conversion was observed when adding 1.1 equiv of water to the reaction mixture. Furthermore, the diastereo- and enantioselectivity were also superior (up to 91:9 dr, *anti*-aldol, 92% ee. Entry 3 in Table 2). Nevertheless, excess of water or the use of brine did not improve the yield nor the stereoinduction (entries 4 and 5 in Table 2). These results are consistent with the idea that in the presence of

Table 2
The effect of water on the direct aldol reaction of 4-nitrobenzaldehyde with cyclohexanone catalyzed by (*S*,*S*)-dipeptide **1c**[a]



2a **3a** **4a**

Entry	H_2O (equiv)	Yield (%)[b]	dr (*anti*/*syn*)[c]	ee[d] (%)
1	0.0	86	86:14	85
2	0.5	85	88:12	86
3	**1.1**	**90**	**91:9**	**92**
4	1.6	88	90:10	90
5	Brine[e]	85	89:11	90

Best results are highlighted in bold.
[a] Reaction conditions: ketone **2a** (0.22 mmol), aldehyde **3a** (0.20 mmol), catalyst **1c** (7 mol %), −20 °C, 4.0 h.
[b] Isolated yield.
[c] Determined by ^{1}H NMR of the crude product.
[d] Determined by chiral HPLC.
[e] Saturated brine (4.0 mg).

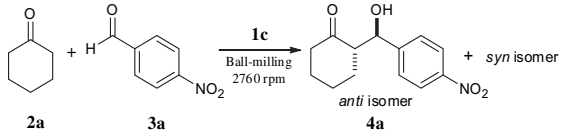
water, hydrophobic groups on the organocatalyst create a hydrophobic 'cavity' that facilitates the required proximity between the hydrophobic organocatalyst and the aromatic region of the aldehyde. On the other hand, the limited molar range of water, that is, beneficial is in line with the observed behavior of reactions catalyzed by enzymes, where variations in the amount of water present in the reaction medium influences drastically activity and stereoselectivity.[19]

The effect of acidic additives in the direct aldol reaction was then explored. It has been documented that the presence of Bronsted acids may affect the outcome of organocatalyzed process.[20]

In particular, Pihko[21] and Gryko[22] have investigated the influence of acid additives on organocatalyzed aldol reactions and found that an appropriate proton donor can in fact enhance the acidity of the catalyst improving its activity. This was clearly demonstrated for pyrrolidine-based organocatalysts, where the reaction presumably proceeds via an enamine intermediate. In order to evaluate the effect of Bronsted acids, we carried out the reaction between cyclohexanone and 4-nitrobenzaldehyde at −20 °C, catalyzed by 7 mol % of dipeptide (*S*,*S*)-**1c** and in the presence of 1.1 equiv of water and 30 mol % of acetic acid. The reaction afforded the aldol adduct with better diastereoselectivity although the yield was low (compare entries 1 and 2 in Table 3). Then we evaluated the effect of benzoic acid as additive, using a range between 3 mol % and 30 mol % of $PhCO_2H$ (entries 3–7 in Table 3). The most efficient amount of acid was 5 mol %, which afforded the aldol product with high diastereo- and enantioselectivity (up to 92:8 dr, *anti*-aldol, 95% ee) in favor of the (2*S*,1′*R*)-enantiomer (entry 6 in Table 3). Finally, the reaction was performed using 20 mol % of $PhCO_2H$ in the absence of water in order to determine whether the increase in enantioinduction is due exclusively to the acid present. The observation that both the diastereo- and enantioselectivity of the product was lower than those found in the same reaction in the presence of water (compare entries 4 and 8 in Table 3) suggests that water does play a significant role in the observed improvements.

We also examined the effect of the amount of catalyst (*S*,*S*)-**1c**. This analysis revealed that best results are obtained when using 3 mol % of catalyst. The *anti*-product was obtained in 93% ee in favor of the (2*S*,1′*R*)-enantiomer (entry 3 in Table 4). Nevertheless, it is interesting that even with 1 mol % of the catalyst, the ee of the major *anti*-aldol product is remarkably high (up to 90% ee, entry 5 in Table 4).

Table 3
The effect of acidic additives on the direct aldol reaction of 4-nitrobenzaldehyde with cyclohexanone catalyzed by (*S*,*S*)-dipeptide **1c**[a]

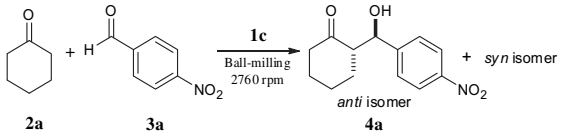


2a **3a** **4a**

Entry	Additive (mol %)	H_2O (equiv)	Yield (%)[b]	dr (*anti*/*syn*)[c]	ee[d] (%)
1	None	1.1	90	91:9	92
2	AcOH (30)	1.1	40	92:8	92
3	$PhCO_2H$ (30)	1.1	90	91:9	88
4	$PhCO_2H$ (20)	1.1	88	89:11	93
5	$PhCO_2H$ (10)	1.1	84	92:8	93
6	**$PhCO_2H$ (5)**	**1.1**	**82**	**92:8**	**95**
7	$PhCO_2H$ (3)	1.1	82	92:8	92
8	$PhCO_2H$ (20)	0.0	85	87:13	86

Best results are highlighted in bold.
[a] Reaction conditions: ketone **2a** (0.22 mmol), aldehyde **3a** (0.20 mmol), catalyst **1c** (7 mol %), −20 °C, 4.0 h.
[b] Isolated yield.
[c] Determined by ^{1}H NMR of the crude product.
[d] Determined by chiral HPLC.

Table 4
The effect of the amount of catalyst on the direct aldol reaction of 4-nitrobenzaldehyde with cyclohexanone catalyzed by (*S*,*S*)-dipeptide **1c**[a]



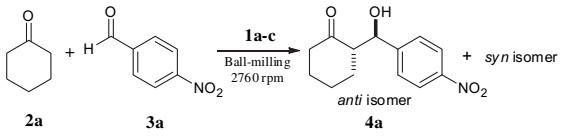
2a **3a** **4a**

Entry	**1c** (mol %)	Yield (%)[b]	dr (*anti*/*syn*)[c]	ee[d] (%)
1	14	94	90:10	91
2	7	90	91:9	92
3	5	80	91:9	92
4	**3**	**78**	**92:8**	**93**
5	1	68	91:9	90

Best results are highlighted in bold.
[a] Reaction conditions: ketone **2a** (0.22 mmol), aldehyde **3a** (0.20 mmol), catalyst **1c** (1–14 mol %), 1.1 equiv of water, −20 °C, 4.0 h.
[b] Isolated yield.
[c] Determined by ^{1}H NMR of the crude product.
[d] Determined by chiral HPLC.

Finally, dipeptides (*S*,*S*)-**1a**, (*S*,*S*)-**1b**, and (*S*,*S*)-**1c** were reexamined in the direct aldol reaction between cyclohexanone and 4-nitrobenzaldehyde under the optimized reaction conditions: 3 mol % of catalyst, 1.1 equiv of water, 5 mol % of benzoic acid, −20 °C at 2760 rpm in a ball mill (Table 5). Employing the optimized conditions, catalyst (*S*,*S*)-**1a** afforded the aldol product in 89% of yield and 94% ee, only slightly lower than our previously

Table 5
Direct asymmetric aldol reaction of 4-nitrobenzaldehyde with cyclohexanone catalyzed by (*S*,*S*)-dipeptides **1a**–**c** under optimum reaction conditions[a]



2a **3a** **4a**

Entry	Cat.	Yield (%)[b]	dr (*anti*/*syn*)[c]	ee[d] (%)
1	**1a**	89	93:7	94
2	**1b**	79	91:9	85
3	**1c**	**88**	**92:8**	**>98**

Best results are highlighted in bold.
[a] Reaction conditions: ketone **3a** (0.22 mmol), aldehyde **4a** (0.20 mmol), catalyst **1a**–**c** (3 mol %), −20 °C, 1.1 equiv H_2O, $PhCO_2H$ (5 mol %), 6.0 h.
[b] Isolated yield.
[c] Determined by ^{1}H NMR of the crude product.
[d] Determined by chiral HPLC.

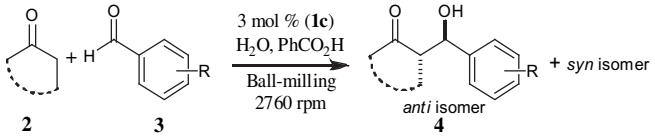
reported results.[16] Nevertheless the diastereoselectivity in favor of the *anti*-diastereomer was significantly improved under the new reaction conditions, affording the major *anti*-product in 93:7 dr, relative to the 90:10 dr that was previously reported (compare entries 1 in Tables 1 and 5). In the case of the methyl ester (*S*,*S*)-**1b**, the aldol adduct was also obtained with better diastereo- and enantioselectivity; however, the ee was only 85% (compare entries 2 in Tables 1 and 5). Best results were generated with dipeptide (*S*,*S*)-**1c** as catalyst, providing the aldol in 88% yield, a diastereomeric ratio of 92:8 in favor of the *anti*-product and with up to 98% ee of aldol (2*S*,1′*R*)-**4a**, which corresponds to the highest stereoselectivity so far reported for the preparation of aldol product **4a** under HSBM conditions.[9,16]

Following the thorough evaluation of the essential parameters, e.g., catalyst, amount of catalyst, equivalents of water and additives, we proceeded to employ (*S*)-proline-(*S*)-tryptophan methyl ester, (*S*,*S*)-**1c**, as organocatalyst in the direct asymmetric aldol reaction between cyclohexanone **2a** and cyclopentanone **2b** with several benzaldehyde derivatives containing different acceptor and donor substituents **3a**–**l**. The nitro, chloro, bromo, cyano, and trifluoromethyl substituents were chosen as electron-withdrawing groups, and the methoxy substituent as a representative electron-donating group. The collected data are summarized in Table 6. It can be appreciated that benzaldehydes substituted by electron-withdrawing groups are converted to the corresponding *anti*-aldol products in good yields (entries 1–10 in Table 6). The exception is aldol **4j** where the low yield can be explained by the large size of the *o*-trifluoromethyl group in the aldehyde substrate, which may sterically hinder the required approach of the reactive enamine to form the product. By contrast, the reaction of less reactive benzaldehyde with cyclohexanone afforded product **4k** in 71% yield (entry 11 in Table 6). In this context, the reaction of *p*-anisaldehyde with cyclohexanone afforded the aldol adduct **4l** in moderate yield (64%) (entry 12 in Table 6). Finally, the reaction of cyclopentanone with 4-nitrobenzaldehyde generated a 60:40 mixture of *syn*- and *anti*-isomers in good yield (73%) (entry 13 in Table 6).

Regarding the observed diastereoselectivity, the aldol reaction using 3 mol % of dipeptide (*S*,*S*)-**1c** as catalyst, exceeded in all cases the results previously obtained with 7 mol % of catalyst (*S*,*S*)-**1a**.[16] The diastereomeric ratio increased significantly and the major *anti*-isomer was obtained in a range of 92:8 to 98:2 (entries 1–12 in Table 6).

With respect to the observed enantioinduction, aldol reactions using 3 mol % of catalyst (*S*,*S*)-**1c** in the presence of water, showed an increase in the ee of the aldol products derived from nitro-containing benzaldehydes and cyclohexanone; 88–98% ee (entries 1–3 in Table 6), relative to the same reaction catalyzed by 7 mol % of (*S*,*S*)-**1a**. Also the ee in *anti*-aldol product **4m** was improved from 55% ee when using (*S*,*S*)-**1a**[16] to 80% ee when employing (*S*,*S*)-**1c** (this work). On the other hand, the aldol reaction of 4-cyanobenzaldehyde and 2-trifluoromethylbenzaldehyde with cyclohexanone afforded the aldol adducts in 87% and 90% ee, respectively (entries 9 and 10 in Table 6). The use of benzaldehyde derivatives containing chloro and bromo as electron-withdrawing groups with cyclohexanone generated the *anti*-aldol products with ees in the range of 80%–90% ee (entries 4–8 in Table 6), which is quite similar to that observed previously with (*S*,*S*)-**1a** as catalyst.[16] By contrast,

Table 6
Scope of the direct asymmetric aldol reaction of cyclic ketones with various aldehydes catalyzed by dipeptide **1c** under ball-milling conditions[a]



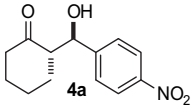
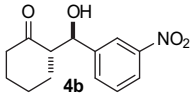
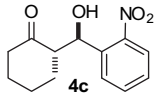
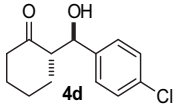
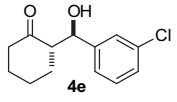
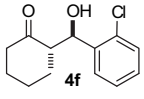
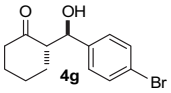
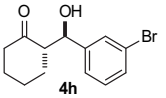
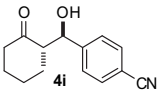
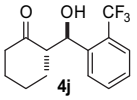
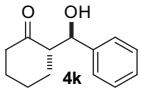
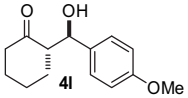
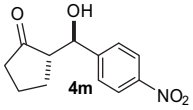
Entry	Product	Yield (%)[b]	dr (*anti*/*syn*)[c]	ee[d] (%)
1		89	92:8	>98
2		90	93:7	88
3		86	98:2	94
4		88	96:4	80
5		82	96:4	86
6		77	94:6	90

Table 6 (*continued*)

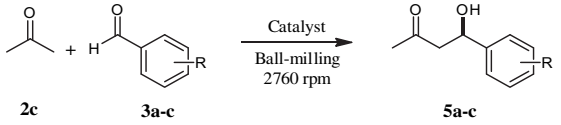
Entry	Product	Yield (%)[b]	dr (*anti*/*syn*)[c]	ee[d] (%)
7		80	94:6	88
8		84	94:6	83
9		81	94:6	87
10		62	96:4	90
11		71	95:5	86
12		64	96:4	55
13		73	40:60	80

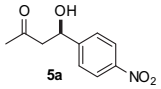
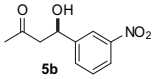
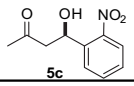
[a] Reaction conditions: ketone **2a** and **b** (0.22 mmol), aldehyde **3a**–**l** (0.20 mmol), catalyst **1c** (3 mol %), −20 °C, 1.1 equiv H_2O, $PhCO_2H$ (5 mol %), 6.0 h.
[b] Isolated yield.
[c] Determined by ^1H NMR of the crude product.
[d] Determined by chiral HPLC.

the reaction of less reactive benzaldehyde with cyclohexanone afforded product **4k** with 86% ee (entry 11 in Table 6). Finally the aldol reaction of *p*-anisaldehyde with cyclohexanone generated the aldol adduct **4l** in 55% ee (entry 12 in Table 6).

In our previous work, we also evaluated dipeptide (*S*,*S*)-**1a** as catalyst in the asymmetric aldol reaction between acetone and 4-nitrobenzaldehyde under HSBM conditions. It was found that organocatalyst (*S*,*S*)-**1a** performs better under solvent-free conditions, as compared with the same reaction in solution.[16] For this reason it was decided to examine the aldol reaction between acetone and nitrobenzaldehydes using dipeptide (*S*,*S*)-**1c** as catalyst in the presence of water, and using benzoic acid as additive. It can be appreciated in Table 7 that 3 mol % of (*S*,*S*)-**1c** afforded the corresponding aldol products in acceptable yields and with better enantioselectivities, relative to the same reaction catalyzed by 7 mol % of dipeptide (*S*,*S*)-**1a**.

Table 7
Relative catalytic activity of dipeptides (*S*,*S*)-**1a** and (*S*,*S*)-**1c** in asymmetric aldol reaction of acetone with nitrobenzaldehydes under ball-milling conditions[a]



Entry	Product	Catalyst	Yield (%)[b]	ee (%)[c]
1	 5a	(*S*,*S*)-**1a**	80	69[d]
		(*S*,*S*)-**1c**	65	58
2	 5b	(*S*,*S*)-**1a**	85	28
		(*S*,*S*)-**1c**	72	54
3	 5c	(*S*,*S*)-**1a**	75	67
		(*S*,*S*)-**1c**	68	69

Using **1c**: ketone **2c** (0.60 mmol), aldehyde **3a**–**c** (0.20 mmol), catalyst **1c** (3 mol %), −20 °C, 1.1 equiv H_2O, $PhCO_2H$ (5 mol %), 6 h.
[a] Reaction conditions using **1a**: ketone **2c** (0.40 mmol), aldehyde **3a**–**c** (0.20 mmol), catalyst **1a** (7 mol %), −20 °C, 4 h.
[b] Isolated yield.
[c] Determined by chiral HPLC.
[d] Ref. 16.

To account for the stereochemical outcome of the current study, we propose a transition state similar to those that have been suggested in other cases where catalysis by dipeptides[17m] and prolinamides is operative (Fig. 2).[23] The increased diastereoselectivity observed in the aldol products obtained when using catalyst (*S*,*S*)-**1c** relative to that afforded by (*S*,*S*)-**1a** and (*S*,*S*)-**1b** may be the result of the large aromatic area present in the lipophilic residue of tryptophan, which is further reinforced by the creation of a hydrophobic environment with the use of water. Under these conditions, non-covalent π–π interactions between aromatic rings of the catalyst and the aldehydes are enhanced, and thus the hydrophobic organocatalyst and the aromatic region of the aldehyde may engage in a more rigid transition state that induces higher stereoselectivity.[24] In addition, present water molecules may be involved in the formation of hydrogen bonds with the carbonyl amide group in dipeptide (*S*,*S*)-**1c**. This interaction may enhance the acidity of the N–H amide bond and provide stronger hydrogen bond with the aldehyde substrate, which fixes it and promotes higher stereoselectivity in the process (Fig. 2).[5d,9,25,26]

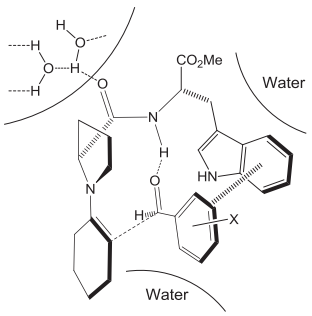


Fig. 2. Proposed transition state model of the aldol reaction catalyzed by (*S*,*S*)-**1c**.

3. Conclusion

In summary, (*S*)-proline-based dipeptides **1a**–**c** were prepared and evaluated as organocatalysts in the asymmetric aldol reaction under solvent-free condition in a ball mill. It was found that dipeptide (*S*,*S*)-proline-tryptophan-CO_2Me **1c** is the most efficient catalyst. This result is in agreement with expectation that dipeptides of proline and a second hydrophobic residue should be efficient catalysts in aldol reaction due to the possible formation of a hydrophobic core. The catalytic activity of (*S*,*S*)-**1c** was improved by the use of an equimolar amount of water and a catalytic amount of benzoic acid. In particular, it is shown that the aldol reaction proceeds efficiently affording the *anti*-aldol products in good yields with high diastereo- and enantioselectivities. It is worth mentioning that aldol products **4a**–**c**, **4m**, **4k**, and **5b** and **c** were obtained with higher stereoselectivity by the use of 3 mol % of dipeptide (*S*,*S*)-**1c**, relative to the same reaction employing 7 mol % of (*S*,*S*)-**1a**.[16] Furthermore, aldol products **4a**, **4d**, **4k**, and **5a** were obtained with higher enantioselectivity, relative to reactions employing 10 mol % of (*S*)-proline, also in a ball mill under solvent-free conditions.[9]

Further work seeking the optimization of the catalyst structure for asymmetric aldol reactions[27] under HSBM conditions is already in progress in our laboratory.

4. Experimental section

4.1. General remarks

^{1}H and ^{13}C NMR spectra were recorded on a 500 MHz spectrometer. Chemical shift (δ) are given in parts per million downfield from tetramethylsilane as an internal reference, coupling constants *J* are given in hertz. Molecular weights were determined by means of High-resolution mass spectrometry (HRMS). Infrared spectra (IR) were reported in reciprocal centimeters. ee was measured by chiral HPLC at room temperature using a Waters 600 E equipment fitted with a UV–vis Waters 2487 detector at 220 or 254 nm with Chiralpak AD-H and Chiralcel OD-H columns. Reactions carried out under ball-milling conditions were performed in a digital Amalgamator, fitted with a reactor (cylinder, 25 mm long and with a diameter 10 mm) containing one stainless steel ball of 5 mm diameter.

4.2. Preparation of methyl ester (*S*)-proline-containing dipeptides 1a–c

To a solution of *N*-Cbz-L-proline (3.0 g, 12.03 mmol) and NMM (1.45 mL, 13.19 mmol) in dry THF under nitrogen at −10 °C was added a solution of isobutyl chloroformate (1.75 mL, 13.41 mmol) in 5 mL of CH_2Cl_2 dropwise over 20 min. The resulting solution was stirred at −10 °C for 20 min before a solution of the corresponding α-amino ester hydrochlorides (2.6 g, 12.05 mmol for L-phenylalanine) and NMM (1.60 mL, 14.55 mmol) in dry CH_2Cl_2 was added dropwise over 20 min. After 2 h at −10 °C the mixture was allowed

to warm to room temperature and further stirred overnight. The mixture was concentrated and extracted with EtOAc. The organic phase was washed with satd 1 N HCl, satd $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatographic using CH_2Cl_2/MeOH (95:5 v/v) as eluent to afford the respective *N*(Cbz)-L-Pro-L-aa-CO_2Me dipeptide. To each of the solution of *N*(Cbz)-L-Pro-L-aa-CO_2Me dipeptide (500 mg) in 20 mL AcOEt/MeOH (4:1), 10% Pd/C (50 mg) was added, followed by stirring for 5 h under hydrogen balloon. The reaction mixture was filtered and washed with methanol, and the filtrate was concentrated. The crude product was purified by column chromatographic to afford the desired NH-L-Pro-L-aa-CO_2Me **1a**–**c** dipeptide.

4.2.1. (S,S)-Proline-phenylalanine methyl ester, ***1a****.* R_f=0.35 [silica gel, DCM/MeOH 95:5], $[\alpha]_D^{22}$ −4.7 (*c* 1.0, CH_3Cl), (FT-IR/ATR cm^{-1}) ν_{max} 3324, 2951, 1740, 1667. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (1H, br d, *J*=8.3 Hz), 7.29–7.18 (3H, m), 7.13–7.08 (2H, m), 4.83 (1H, m), 3.71 (3H, s), 3.67 (1H, m), 3.16 (1H, dd, *J*=5.6, 13.9 Hz), 3.02 (1H, dd, *J*=7.3, 13.9 Hz), 2.91 (1H, m), 2.72 (1H, m), 2.24 (1H, br s), 2.03 (1H, m), 1.72 (1H, m), 1.64–1.45 (2H, m) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.9, 172.0, 136.1, 129.2, 128.3, 126.9, 60.2, 52.4, 52.2, 47.1, 38.0, 30.6, 26.0 ppm. HR-ESI-TOF: calculated for $C_{15}H_{21}N_2O_3$ $[M+H]^+$: 277.1546; found: 277.1551 (1.5 ppm error).

4.2.2. (S,S)-Proline-phenylglycine methyl ester ***1b****.* R_f=0.32 [silica gel, DCM/MeOH 95:5], $[\alpha]_D^{22}$ −13.0 (*c* 1.0, CH_3Cl), (FT-IR/ATR cm^{-1}) ν_{max} 3327, 2952, 1742, 1661. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (1H, br d, *J*=5.5 Hz), 7.37–7.27 (5H, m), 5.56 (1H, d, *J*=8.0 Hz), 3.75 (1H, m), 3.70 (3H, s), 2.95 (2H, m), 2.16 (1H, br s) 2.09 (1H, m), 2.02–1.84 (1H, m), 1.80–1.64 (2H, m) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.8, 171.5, 137.0, 129.0, 128.5, 127.3, 60.7, 56.1, 52.6, 47.4, 30.7, 26.2 ppm. HR-ESI-TOF: calculated for $C_{14}H_{19}N_2O_3$ $[M+H]^+$: 263.1390; found: 263.1393 (1.1 ppm error).

4.2.3. (S,S)-Proline-tryptophan methyl ester ***1c****.* R_f=0.30 [silica gel, DCM/MeOH 95:5], $[\alpha]_D^{22}$ +2.2 (*c* 2.1, CH_3Cl), (FT-IR/ATR cm^{-1}) ν_{max} 3297, 2951, 1737, 1650. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.57 (1H, br s), 7.99 (1H, br s), 7.50 (1H, d, *J*=8.1 Hz), 7.36 (1H, d, *J*=8.1 Hz), 7.09 (2H, t, *J*=7.7 Hz), 7.00 (1H, t, *J*=7.6 Hz), 4.68 (1H, q, *J*=6.7 Hz), 3.64 (3H, s), 3.56 (1H, dd, *J*=8.6, 9.1 Hz), 3.21 (2H, dq, *J*=5.8, 14.6 Hz), 2.82 (1H, m), 2.64 (1H, m), 1.90 (1H, m), 1.66 (1H, m), 1.51 (2H, m) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ 174.5, 172.3, 136.2, 127.3, 123.8, 121.1, 118.5, 118.1, 111.5, 109.0, 60.0, 52.3, 52.0, 46.7, 30.4, 27.2, 25.9 ppm. HR-ESI-TOF: calculated for $C_{17}H_{22}N_3O_3$ $[M+H]^+$: 316.1655 found: 316.1659 (1.0 ppm error).

4.3. Typical procedure for the intermolecular aldol reaction; ball-mill method

A mixture of catalyst **1c** (3 mol %), ketone **2** (0.22 mmol), aldehyde **3** (0.2 mmol), water (0.22 mmol), and benzoic acid (5 mol %) was vigorously milled for 4.0–6.0 h at 2760 rpm at −20 °C in a digital Mixer/Amalgamator fitted with a reactor made of Nylamid (cylinder, 25 mm long and with a diameter 10 mm) containing one stainless steel ball with a 5 mm diameter. The crude reaction mixture was purified by flash chromatography (silica gel, hexane/EtOAc: 10:1–3:1) to afford the expected *syn*/*anti* aldol mixture.

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Supplementary data

Supplementary data associated with this article (copies of NMR spectra and HPLC chromatograms) are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.06.042.

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