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Asymmetric Aldol Reaction Organocatalyzed by (*S*)-Proline-Containing Dipeptides: Improved Stereoinduction under Solvent-Free Conditions

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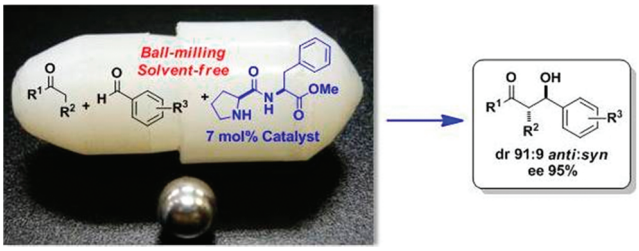
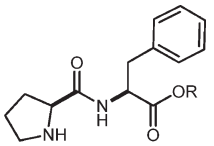


The organocatalytic activity of the methyl ester of (*S*)-proline-(*S*)-phenylalanine, (*S*,*S*)-**2**, in the asymmetric aldol reaction between cyclohexanone and acetone with various aromatic aldehydes under solvent-free conditions in a ball mill has been evaluated. α,α-Dipeptide (*S*,*S*)-**2** catalyzed the stereoselective formation of the expected aldol products, with higher diastereo- and enantioselectivity relative to similar reactions in solution, up to 91:9 *anti*:*syn* diastereomeric ratio and up to 95% enantiomeric excess.

The aldol reaction is one of the most powerful strategies in synthetic organic chemistry, since it allows for the formation of new C−C bonds, that is, facilitates the construction of larger molecules from smaller ones. The development of *enantioselective* versions of the aldol reaction was based for a long time on the use of preformed enolates, which added to prochiral carbonyl substrates with activation by metal-based chiral catalysts.[1] Nevertheless, the ability of (*S*)-proline to act as an organic catalyst in intramolecular asymmetric aldol reactions[2] has recently motivated the search of other chiral



1 R=H **2** R=Me

FIGURE 1. Structure of dipeptides (*S*,*S*)-**1** and (*S*,*S*)-**2**.

organic catalysts that might act as efficient organocatalysts.[3] Remarkable examples are (*S*)-proline-containing α-dipeptides[4a−e] and α-tripeptides,[4f−h] which have been shown to retain the catalytic properties of (*S*)-proline. In particular, dipeptide (*S*)-proline-(*S*)-phenylalanine [(*S*,*S*)-**1**, Figure 1] has been used to catalyze the enantioselective reaction of 4-nitrobenzaldehyde with acetone, using a DMSO-NMM-PEMG 5000 system; the aldol product was obtained in high yield and 73% ee.[4b] Furthermore, Li and co-workers reported the use of dipeptide (*S*,*S*)-**1** in the aldol reaction of 4-pyridinecarbaldehyde with cyclohexanone in water,[4a] and the *anti*-*β*-hydroxy carbonyl product was obtained in good yield and 73% ee. On the other hand, Sung et al. performed the enantioselective direct aldol reaction of cyclohexanone with 4-nitrobenzaldehyde and studied the effect of solvents, additives, and temperature.

The major *anti* diastereomeric product was obtained with 91% ee by using 30 mol % of catalyst (*S*,*S*)-**1**.[4c] In this context, Lei and co-workers examined dipeptide (*S*,*S*)-**1** in the asymmetric aldol reaction of 4-nitrobenzaldehyde with cyclohexanone in solid phase media (Al_2O_3), using 1,4-diazabicyclo[2.2.2]octane as additive, observing moderate yield and good diastereo- and enantioselectivity (*anti*-aldol, 86% ee). Nevertheless, this protocol required long reaction times (10−180 h).[4d]

With the exception of the work reported by Lei et al.,[4d] the above reactions were carried out with an organic solvent as a reaction medium. As part of our current interest in High Speed Ball-Milling (HSBM),[5] a sustainable mechanochemical technique, we decided to prepare the methyl ester of (*S*)-proline-(*S*)-phenylalanine [(*S*,*S*)-**2**, Figure 1] and evaluate its organocatalytic activity under solvent-free, "green" reactions conditions. There exists the precedent that (*S*)-proline (10 mol %) catalyzes the aldol reaction between acetone and 4-nitrobenzaldehyde under solvent-free conditions in a ball mill. This reaction required 19 h to take place, and an enantioselectivity of 56% ee was reported (entry 1 in Table 1).[6a]

(1) Mahrwald, R., Ed. *Modern Aldol Additions*; Wiley-VCH: Weinheim, Germany, 2004.
(2) (a) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed.* **1971**, *10*, 496–497. (b) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615–1621.
(3) See, for example: (a) Torii, H.; Nakadai, M.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 1983–1986. (b) Zou, W.; Ibrahem, I.; Dziedzic, P.; Sundén, H.; Córdova, A. *Chem. Commun.* **2005**, 4946–4948. (c) Alza, E.; Cambeiro, X. C.; Jimeno, C.; Pericàs, M. A. *Org. Lett.* **2007**, *9*, 3717–3720. (d) Almaşi, D.; Alonso, D. A.; Nájera, C. *Adv. Synth. Catal.* **2008**, *350*, 2467–2472.
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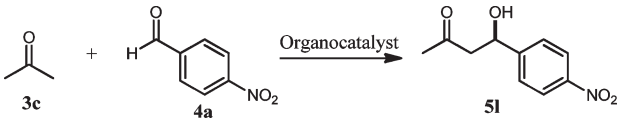
TABLE 1. Enantiomeric Excesses and Yields of Aldol Product 5*l* Observed in the Aldol Reaction of Acetone with 4-Nitrobenzaldehyde



entry	catalyst [mol %]	ref	equiv of **3c**	time [h]	yield [%]	ee (*R*) [%]
1	(*S*)-proline (10)[a]	6a	2.0	19	73	56
2	**2** (20)[b]	6b	>27	24−48	88	28
3	**2** (7)[a]	this work	2.0	4	82	69[c]

[a]Under ball-milling conditions. [b]The reaction was carried out in neat acetone with a concentration of 0.5 M of aldehyde. [c]Determined by chiral-phase HPLC.

On the other hand, the aldol reaction between acetone and 4-nitrobenzaldehyde was studied by Gong and co-workers,[6b] using the methyl ester of (*S*,*S*)-proline-phenylalanine, (*S*,*S*)-**2** (20 mol %), as catalyst in excess acetone, with a concentration of 0.5 M of 4-nitrobenzaldehyde. The aldol adduct was obtained with only 28% ee (entry 2 in Table 1).[6b]

In further work, Gong, et al. prepared a series of small peptides and evaluated them as catalysts for the asymmetric direct aldol reaction of hydroxyacetone with aldehydes in THF/H_2O. It turned out that the best catalysts were peptides with phenylalanine as lipophilic residue. In particular, dipeptide (*S*,*S*)-**2** afforded the expected aldol product, (*R*)-1,4-dihydroxy-4-(4-nitrophenyl)butan-2-one, in moderate yield and with 67% ee.[6c]

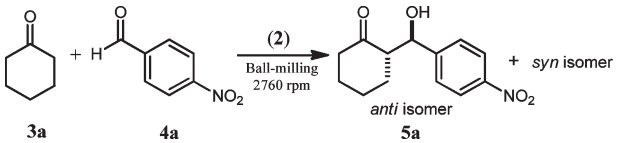
In view of this precedent, it was considered that dipeptide (*S*,*S*)-**2** could indeed act as organocatalyst under solvent-free conditions, employing equimolar amounts of aldehydes and ketones under HSBM techniques. Although high speed ball-milling has been applied in the area of synthetic organic chemistry to promote several solvent-free reactions,[7] only a few organocatalyzed asymmetric reactions have been explored under HSBM conditions. Thus, the present work is attractive in the search of alternatives to the traditional methodologies in solution phase.

Methyl ester dipeptide (*S*,*S*)-**2** was prepared by condensation of Cbz-N-protected (*S*)-proline with phenylalanine methyl ester hydrochloride, followed by deprotection with hydrogen and palladium on carbon, according to the general method for the preparation of dipeptides.[8] Complete spectroscopic analysis of (*S*,*S*)-**2** is presented in the Supporting Information. We then proceeded to carry out the aldol reaction of acetone with 4-nitrobenzaldehyde under HSBM conditions in order to compare dipeptide (*S*,*S*)-**2** with (*S*)-proline as chiral organocatalysts, both under HSBM conditions. We also compared the efficiency of dipeptide (*S*,*S*)-**2** as organocatalyst in solvent-free conditions relative to traditional conditions in solution. The aldol reaction was carried out at −20 °C for 4 h in a ball mill at 2760 rpm, using 7 mol % of (*S*,*S*)-**2**. The expected product (*R*)-4-hydroxy-4-(4-nitrophenyl)butan-2-one (**5*l***) was obtained in 82% yield and with 69% ee (entry 3 in Table 1). It can be appreciated that under solvent-free methodology dipeptide (*S*,*S*)-**2** showed superior catalytic activity, both in terms of required reaction time and enantioselectivity, relative to (*S*)-proline as organocatalyst (cf. entries 1 and 3 in Table 1). Furthermore, dipeptide (*S*,*S*)-**2** was a more efficient organocatalyst under HSBM solvent-free conditions relative to traditional solution conditions (cf. entries 2 and 3 in Table 1).

(7) (a) Rodríguez, B.; Bruckmann, A.; Rantanen, T.; Bolm, C. *Adv. Synth. Catal.* **2007**, *349*, 2213–2233. (b) Bruckmann, A.; Krebs, A.; Bolm, C. *Green Chem.* **2008**, *10*, 1131–1141. (c) Walsh, P. J.; Li, H.; Anaya de Parrodi, C. *Chem. Rev.* **2007**, *107*, 2503–2545.

(8) See, for example: Szöllősi, G.; London, G.; Baláspiri, L.; Somlai, C.; Bartók, M. *Chirality* **2003**, *15*, S90–S96.

TABLE 2. Enantioselective Aldol Reaction between Cyclohexanone and 4-Nitrobenzaldehyde, Catalyzed by Dipeptide (*S*,*S*)-2 under Ball-Milling, Solvent-Free Conditions[a]



entry	cat. mol [%]	time [h]	temp [°C]	yield [%][b]	*anti*:*syn*[c]	ee [%][d]
1	22	4	30	96	67:33	33
2	22	4	−20	99	80:20	72
3	22	2	−20	86	83:17	84
4	22	1	−20	66	80:20	92
5	15	4	−20	90	78:22	93
6	**7**	**4**	**−20**	**92**	**90:10**	**95**
7	4	4	−20	56	91:9	90
8	1	4	−20	46	80:20	88

[a]Reaction conditions: ketone **3a** (0.22 mmol), aldehyde **4a** (0.20 mmol), dipeptide (*S*,*S*)-**2** (1−22 mol %). [b]Combined yield of the isolated diastereomers. [c]Determined by ^1H NMR spectroscopic analysis. [d]Determined by chiral-phase HPLC analysis of the *anti* isomer.

An examination of the effect the amount of catalyst, the reaction temperature, the time, and the frequency of milling on the reaction of cyclohexanone **3a** with 4-nitrobenzaldehyde **4a** (1.1:1 ratio of ketone and aldehyde) in the presence of catalyst (*S*,*S*)-**2** was undertaken. Initially, the amount of catalyst employed was 22 mol % and the reactants were ball milled at 2760 rpm. After 4 h at 30 °C the aldol product was obtained in high yield, in a diastereomeric ratio of 2:1 in favor of the *anti*-diastereomeric product; however, the observed ee_{anti} was low, 33% ee (entry 1 in Table 2). To increase the enantioselectivity of the reaction, it was decided to carry out the reaction at lower temperature. After 4 h at −20 °C the *anti* diastereomeric product was obtained with excellent yield (99%), and high diastereo- (80% ds) and enantioselectivity (72% ee, entry 2 in Table 2).

We then examined the reaction at shorter reaction times; this greatly favored the enantioselectivity, 84% ee and 92% ee after 2 and 1 h, respectively, although the isolated yields were lower (cf. entries 2−4 in Table 2).

In view of the satisfactory results obtained at low temperature, all subsequent tests were conducted at −20 °C, and now the effect of the amount of the catalyst **2** on the reaction was examined (cf. entries 5−8 in Table 2). The results reveal that best results are obtained when using 7 mol % of catalyst, the *anti*-product being obtained in 95% ee. Nevertheless, it is interesting that even with 1 mol % of the catalyst, the enantiomeric excess of the major *anti* aldol product is remarkably high (entry 8 in Table 2).

We also evaluated the effect of the frequency of milling on the yield and ee of aldol product **5a**. When the reaction was carried out at higher frequency (3080 rpm) the aldol product was obtained in similar yield but in lower enantiomeric

excess (76% ee versus 95% ee), perhaps as a consequence of increased reactor temperature at higher milling speed.[6a]

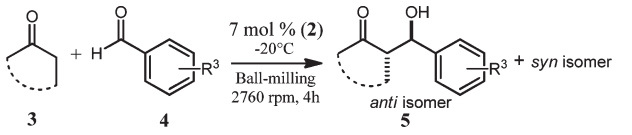
Under the optimum reaction conditions (entry 6 in Table 2), the application of (*S*)-proline-(*S*)-phenylalanine methyl ester, (*S*,*S*)-**2**, as organocatalyst in the direct asymmetric aldol reaction between cyclohexanone **3a** and cyclopentanone **3b** and several benzaldehyde derivatives containing different acceptor and donor substituents **4a**−**j** was further examined. The data are summarized in Table 3. The nitro, chloro, and bromo substituents were chosen as electron-withdrawing groups, and the methoxy substituent as a representative electron-donating group. It can be appreciated in Table 3 that benzaldehydes substituted by electron-withdrawing groups are converted to the corresponding *anti*-aldol products in higher yields and enantioselectivities, the latter in the 82−95% ee range (cf. entries 1−8 in Table 3). By contrast, the reaction of less reactive benzaldehyde with cyclohexanone afforded product **5i** in 70% yield and with 65% ee (entry 9 in Table 3). On the other hand, the aldol reaction of *p*-anisaldehyde with cyclohexanone afforded the aldol adduct **5j** in moderate yield (62%) and enantioselectivity, 57% ee (entry 10 in Table 3). Finally, the reaction of cyclopentanone with 4-nitrobenzaldehyde generated the *syn* aldol in major proportion with very low enantioselectivity, 3% ee, while the *anti* product **5k** was obtained with 55% ee (entry 11 in Table 3).

As proposed for other cases where catalysis by dipeptides[3a,9] and prolinamides is operative,[10] it is likely that dipeptide (*S*,*S*)-**2** catalyzes the aldol reaction via the transition state depicted in Figure 2. It is suggested that a hydrogen bond between amide group and the aldehyde is the essential controlling interaction. In solution, this interaction is apparently weakened by solvation and therefore enantioinduction is less effective.

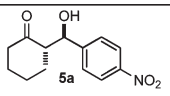
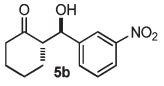
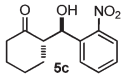
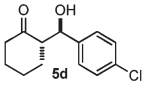
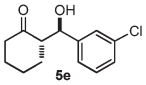
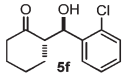
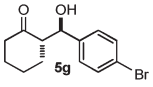
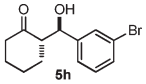
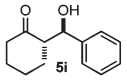
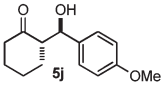
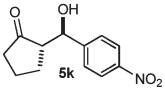
By contrast, under solvent free conditions there is no competition between the aldehyde and the solvent or additives for hydrogen bond formation and this interaction is maximized. On other hand, it has been reported that the stereoselectivity of aldol reactions carried out *in*, *on*, or *in the presence* of water can be improved by using catalyst with hydrophobic regions. Examples of such organocatalysts are tryptophan,[11] phenylalanine,[11] and short peptides such as Pro-(Phe)$_3$-OMe[6c] or NOBIN-prolinamide.[12]

In the case of tryptophan and NOBIN-prolinamide the authors propose the formation of a hydrophobic core that facilitates noncovalent $\pi-\pi$ interactions between aromatic rings of the catalyst and the substrate, which are probably responsible for the high estereoselectivity in aldol product formation. This interaction may also be relevant in the transition state for the aldol reaction of interest in the present work. Indeed, the absence of solvent reduces molecular motion and π-stacking interactions should be more effective[13] (Figure 2).

TABLE 3. Scope of Direct Asymmetric Aldol Reaction of Cyclic Ketones (3a,b) with Various Aldehydes Catalyzed by Dipeptide (*S*,*S*)-2 under Ball-Milling Conditions[a]



3 4 5

Entry	Product	Yield [%] [b]	*anti*:*syn* [c]	*ee*[%] [d]
1	 5a	92	90:10	95
2	 5b	94	88:12	85
3	 5c	88	89:11	90
4	 5d	90	89:11	82
5	 5e	87	90:10	89
6	 5f	80	91:9	90
7	 5g	81	88:12	88
8	 5h	83	91:9	88
9	 5i	70	88:12	65
10	 5j	62	84:16	57
11	 5k	70	31:69	55

[a]Reaction conditions: ketone **3** (0.22 mmol), aldehyde **4** (0.20 mmol). [b]Combined yield of the isolated diastereomers. [c]Determined by ^{1}H NMR spectroscopic analysis. [d]Determined by chiral HPLC analysis of the *anti* isomer.

In summary, we have demostrated that dipeptide (*S*,*S*)-**2** is a more efficient organocatalyst in the asymmetric aldol reaction under solvent-free conditions, relative to reaction in solution. This is a significant result and suggests that noncovalent interactions which are enhanced in the absence of solvents are crucial for the course of the reaction. In particular, it is shown that ball milling activates the aldol reaction between cyclohexanone and various aromatic aldehydes. The reaction proceeds efficiently affording the *anti* aldol

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(10) Fuentes de Arriba, A. L.; Simón, L.; Raposo, C.; Alcázar, V.; Sanz, F.; Muñiz, M. F.; Morán, J. R. *Org. Biomol. Chem.* **2010**, *8*, 2979–2985.
(11) Jiang, Z.; Liang, Z.; Wu, X.; Lu, Y. *Chem. Commun.* **2006**, 2801–2803.
(12) Wang, C.; Jiang, Y.; Zhang, X.-X.; Huang, Y.; Li, B.-G.; Zhang, G.-L. *Tetrahedron Lett.* **2007**, *48*, 4281–4285.
(13) For discussions on hydrophobic interactions and π-stacking, see for example: (a) Otto, S.; Engberts, J. B. F. N. *Org. Biomol. Chem.* **2003**, *1*, 2809–2820. (b) Gruttadauria, M.; Giacalone, F.; Noto, R. *Adv. Synth. Catal.* **2009**, *351*, 33–57. (c) Jones, B. G.; Chapman, B. J. *Synthesis* **1995**, 475–497. (d) Saha, S.; Moorthy, J. N. *Tetrahedron Lett.* **2010**, *51*, 912–916.

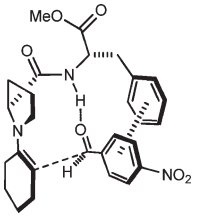

FIGURE 2. Proposed transition state model of the aldol reaction catalyzed by (*S*,*S*)-**2**.

products with good diastereo- and enantioselectivities. In addition, aldol products **5a**, **5d**, **5i**, and **5*l*** were obtained in shorter reaction times and with higher stereoselectivity by using 7 mol % of dipeptide (*S*,*S*)-**2** relative to conditions employing 10% mol of amino acid (*S*)-proline, also in a ball mill under solvent-free conditions.[6a,14]

Research toward the examination of other dipeptides with potential organocatalytic activity in asymmetric, organocatalyzed reactions is already in progress in our laboratory.

(14) The work described herein refers to experiments carried out at the milligram scale; nevertheless, the performance of catalyst (*S*,*S*)-**2** should be preserved at greater scales, e.g. grams scale, when using ball mills of the proper size. See ref 6a.

Experimental Section

General Procedure for the Intermolecular Aldol Reaction Catalyzed by (*S*,*S*)-2, in a Ball Mill. A mixture of the catalyst (*S*,*S*)-**2** (7 mol %), cyclohexanone (20.56 mg, 0.22 mmol), and 4-nitrobenzaldehyde (30.2 mg, 0.2 mmol) was vigorously milled for 4 h at 2760 rpm at −20 °C in a digital Mixer/Amalgamator used with a reactor made of Nylamid (cylinder, 25 mm long and with a diameter of 10 mm) containing one stainless steel ball with a 5 mm diameter. Then the mixture was dissolved in AcOEt and extracted. The organic phase was dried over $MgSO_4$, then concentrated to give the crude reaction mixture that was purified by flash chromatography (silica gel, hexane/EtOAc: 10:1−3:1) to afford aldol mixture (*syn*-*anti*). The ee values were determined by HPLC on a chiral column.

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Supporting Information Available: Experimental procedures, copies of NMR spectra, and HPLC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.