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Organocatalytic activity of α,α-dipeptide derivatives of (*S*)-proline in the asymmetric aldol reaction in absence of solvent. Evidence for non-covalent π–π interactions in the transition state

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ABSTRACT

The trend in the magnitude of stereoselectivities observed in the asymmetric aldol reaction between cyclohexanone and aromatic aldehydes with varying electron densities, catalyzed by dipeptidic organocatalyst (*S*,*S*)-**1d**, which contains an aromatic naphthyl substituent in the acyclic amino acid residue, is in line with expectation based on π–π stacking interactions between the aromatic ring on the organocatalyst and the aromatic aldehydes. Such non-covalent interactions are apparently enhanced under solvent-free mechanochemical activation in a ball mill.

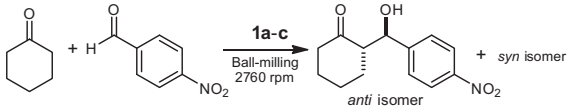
Introduction

The area of organocatalysis has grown exponentially since the realization that small organic molecules can catalyze organic reactions with efficiency comparable to that exhibited by enzymes.[1] In particular, proline and proline derivatives have been widely studied as chiral organocatalysts in asymmetric organic transformations.[2] Application of these organocatalysts in asymmetric aldol reactions is of great importance both in academics and in the pharmaceutical industry.[3] Several research groups have recently reported the successful application of dipeptide and tripeptide derivatives containing the proline residue as chiral organocatalysts in asymmetric reactions.[4]

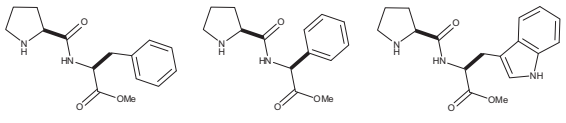
In this context, we recently examined the aldol reaction between representative ketones and various aromatic aldehydes in the presence of organocatalysts (*S*,*S*)-**1a**–**c**.[5] The reaction was carried out at −20 °C in a ball mill at 2760 rpm, in the presence of 1.1 equiv H_2O, and $PhCO_2H$ (5 mol %) as additive. After 6 h of milling, all six catalysts **1a**–**c** afforded the aldol product in good yields, high *anti* diastereoselectivity and high enantioselectivity (Table 1).

Best results were generated with dipeptide (*S*,*S*)-**1c** as catalyst, providing the aldol product in 88% yield, a diastereomeric ratio

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



Cat.



(*S*,*S*)-**1a** (*S*,*S*)-**1b** (*S*,*S*)-**1c**

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**

[a] Reaction conditions: cyclohexanone (**2**, 0.22 mmol), 4-nitrobenzaldehyde (**3**, 0.20 mmol), catalyst **1a**–**c** (3 mol %), −20 °C, 1.1 equiv H_2O, $PhCO_2H$ (5 mol %), 6.0 h. Best values are highlighted in bold.
[b] Isolated yield.
[c] Determined by ^1H NMR of the crude product.
[d] Determined by chiral HPLC.

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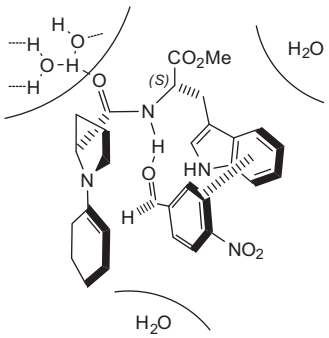
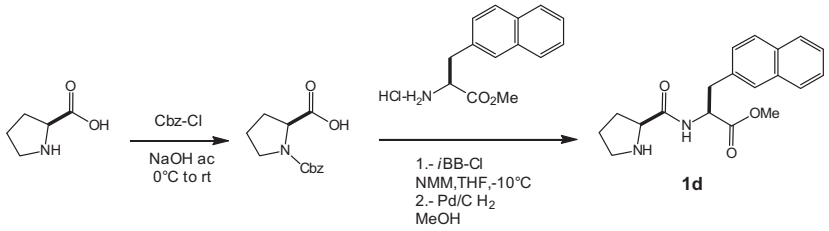


Figure 1. Proposed transition state model of the aldol reaction catalyzed by (*S*,*S*)-**1c**.

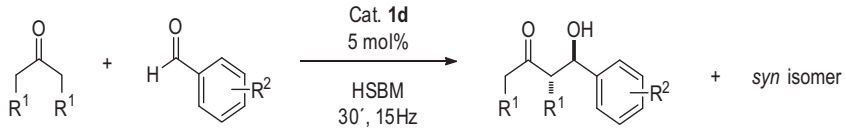
of 92:8 in favor of the *anti* isomer and higher than 98% ee of aldol (2*S*,1′*R*)-**4**.

To account for the observed stereoselectivity, the transition state presented in Figure 1 was suggested, which takes into account previously advanced mechanistic proposals where catalysis by dipeptides and prolinamides is operative.[6] In particular, the pyrrolidine functionality in (*S*,*S*)-**1c** activates the ketone through the formation of a chiral enamine intermediate, while the aldehyde is activated through the formation of a strong hydrogen bond involving the amide N–H hydrogen atom.[7] In addition, it was proposed that a non-covalent π–π interaction between aromatic rings of the catalyst and the aldehydes probably gives rise to a rigid transition state that induces higher stereoselectivity in the aldol reaction.[8]

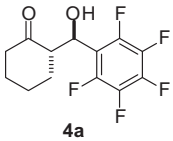
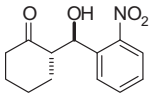
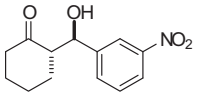
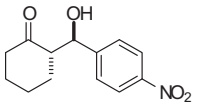


Scheme 1. Synthesis of organocatalyst (*S*,*S*)-**1d**.

Table 2
Efficiency of organocatalyst (*S*,*S*)-**1d** in the asymmetric aldol reaction of cyclohexanone as representative ketone with aromatic aldehydes of different electron densities[a]



2 **3** **4**

Entry	Product	Yield[b] (%)	dr (*anti*/*syn*)[c]	er[d] (%)
1	 **4a**	**99**	**99:1**	**99:1**
2	 **4b**	94	96:4	95:5
3	 **4c**	98	95:5	89:11
4	 **4d**	98	98:2	95:5

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