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Solvent-free asymmetric aldol reaction organocatalyzed by (*S*)-proline-containing thiodipeptides under ball-milling conditions

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ABSTRACT

An efficient, solvent-free ball-milling protocol for the asymmetric aldol reaction between cyclohexanone and cyclopentanone with various aromatic aldehydes using a novel series of (*S*)-proline-containing dipeptides and thiodipeptides **1a**–**f** as organocatalysts is reported. In general, (*S*)-proline-containing thiodipeptides proved to be better organocatalysts relative to their analogous amides. In particular, thiodipeptide (*S*,*S*)-**1d** catalyzed the stereoselective formation of the expected aldol products with excellent diastereo- and enantioselectivity (up to 98:2 *anti*/*syn* dr and up to 96% ee). This observation may be ascribed to the increased N–H acidity of the thioamide segment that leads to stronger H-bonding interaction with the aldehyde carbonyl at the transition state and thus higher stereoinduction. Furthermore, thiodipeptide **1f** proved to be an efficient organocatalyst for the aldol reaction of acetone with isatin and isatin derivatives (ee 56–86%).

1. Introduction

In the past decade, the success of (*S*)-proline and (*S*)-proline-derivatives as catalysts has promoted organocatalysis into a major, intensively active field in organic chemistry.[1] Among the outstanding attributes of organocatalytic processes is the fact that this strategy avoids the use of metals, implying that organocatalysis fulfills one of the guidelines of green chemistry, where the design of safer, less potentially toxic chemical processes is a key concept.[2] In this context, a powerful approach to 'Green Chemistry' seeks to avoid the use of solvents as a strategy to make the synthetic protocol 'greener'. For example, in asymmetric aldol reactions the use of solvents such as DMSO, DMF, NMP, toluene or $CHCl_3$ tends to become a thing of the past. Furthermore, the design of more energy-efficient processes such as those involving microwave heating, ultrasound irradiation or mechanochemical activation is becoming more common in recent years.[3] In particular, High Speed Ball-Milling (HSBM) is a sustainable mechanochemical technique, which is being increasingly used in synthetic organic chemistry to promote several synthetically useful reactions, under solvent-free conditions.[4] Reported applications of HSBM include: Heck-type cross-couplings,[5a] Knoevenagel condensation reactions,[5b] Baylis–Hillman reactions,[5c] Michael additions,[5b] functionalization of fullerenes,[5d] synthesis of nitrones,[5e] 1,3-dipolar cycloaddition,[5f] Sonogashira coupling,[5g] the Horner–Wadsworth–Emmons reaction,[5h] synthesis of peptides,[5i–j] and others.

Pioneers in the field of the organocatalytic aldol reaction under HSBM conditions, Bolm and co-workers reported the asymmetric aldol reaction under solvent-free conditions and catalyzed by (*S*)-proline (10 mol %) in a ball mill, employing a 1.1:1 ketone/aldehyde ratio to afford principally the *anti*-aldol products in high yields and with up to 99% ee.[6] 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 chemical yields and stereoselectivities were higher.[6] In this regard, Nájera and co-workers[7] have reported the use of (S_a)-binam-L-prolinamides (10 mol %) as organocatalysts in solvent-free aldol reactions between cyclohexanone and *p*-nitrobenzaldehyde (8:1 ratio) using a planetary ball mill. The *anti*-aldol adduct was obtained in high yield and with good diastereo- and enantioselectivity (up to 69:31 dr, up to 88% ee).[7] Recently, as part of our continuing interest in synthetic applications of HSBM,[5i,8a,b] we carried out the asymmetric aldol reaction between representative ketones and various aromatic aldehydes under solvent-free conditions in a ball mill, using essentially stoichiometric amounts of the starting 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 proceeded efficiently to afford mainly the *anti* diastereomeric aldol product in high yield and with good enantioselectivity (up to 91:9 dr, and

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up to 95% ee) (Fig. 1).[8a] We suggested that dipeptide **1a** is a more efficient organocatalyst in the solvent-free asymmetric aldol reaction relative to the same reaction in solution, probably because under solvent-free conditions non-covalent π–π interactions between the aromatic rings of the catalyst and the substrate are maximized, leading to a tighter transition state and thus higher stereoinduction.

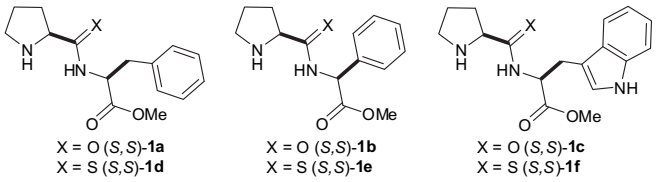


Fig. 1. Structure of (*S*,*S*)-dipeptides **1a**–**c** and (*S*,*S*)-thiodipeptides **1d**–**f** examined as potential organocatalysts under ball-milling conditions in this study.

In more recent work, we reported the asymmetric aldol reaction between ketones and various aromatic aldehydes under solvent-free conditions in a ball mill, with catalysis by (*S*)-proline-containing dipeptides (*S*,*S*)-**1b** and (*S*,*S*)-**1c** (Fig. 1), which were obtained by condensation with of (*S*)-proline with (*S*)-phenylglycine or (*S*)-tryptophan, respectively. It was observed that in the presence of an equimolar amount of water and a catalytic amount of benzoic acid, dipeptide (*S*,*S*)-proline-tryptophan–CO_2Me **1c** (3 mol %) is a particularly efficient catalyst. This result is in agreement with expectation that dipeptides of proline and a second hydrophobic residue are efficient catalysts in aldol reactions owing apparently to the formation of a hydrophobic core that maximizes the influence of non-bonding interactions in the stereoinducing transition state. We also suggested that molecules of water may be involved in the formation of hydrogen bonds with the carbonyl amide group in dipeptide (*S*,*S*)-**1c**. Such interaction would enhance the acidity of the N–H amide bond and provide stronger hydrogen bonding with the aldehyde substrate, fixing its orientation in the transition state and promoting higher stereoselectivity in the aldol process.[8b]

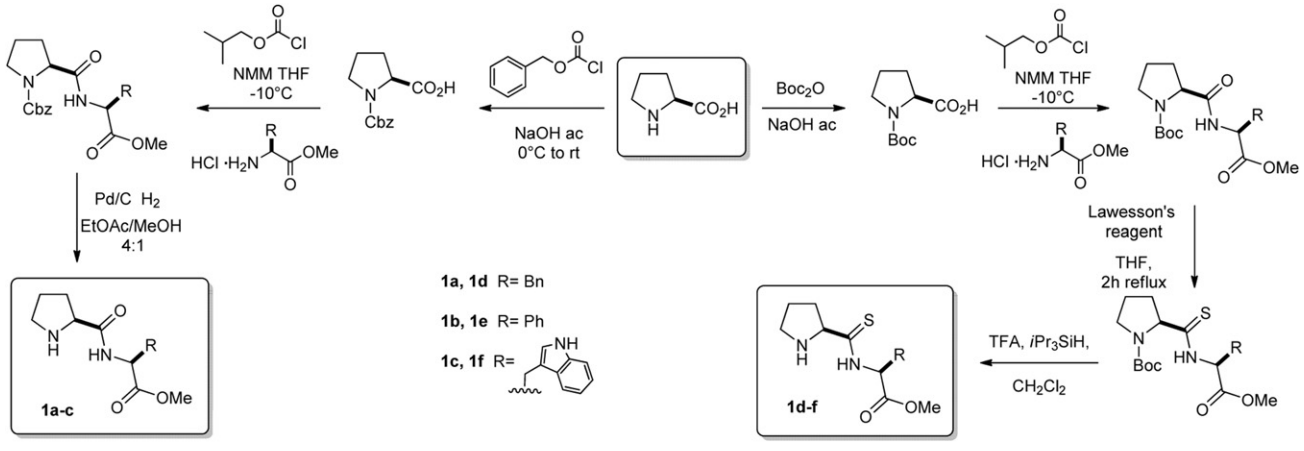
One way to increase the strength of the proposed H-bonding interaction would be through the replacement of the amide group with the thioamide functionality in proline derivatives, as consequence of the higher acidity of the N–H function present in a thioamide relative to the N–H group present in the analogous amide segment.[9] In this regard, Gryko and co-workers recently reported the use of L-proline-containing thioamides as organocatalysts (5–20 mol %) in aldol reactions between representative ketones and various aromatic aldehydes in high yields (up to 97%), and with high diastereo- and enantioselectivity (up to 95:5 dr and 98% ee).[10] Furthermore, Nájera and co-workers compared the organocatalytic activity of (*S*)-prolinamides and (*S*)-prolinethioamides in the aldol reaction of aliphatic ketones (2 equiv) with aromatic aldehydes, demonstrating that (*S*)-prolinethioamides are superior catalysts relative to (*S*)-prolinamides, affording the *anti*-aldol adducts in higher yields and with excellent diastereo- and enantioselectivities (up to 98:2 dr, and up to 98% ee).[11] More recently, Li and co-workers confirmed the superior catalytic activity of (*S*)-prolinethioamides relative to the analogous (*S*)-prolinamides in the direct asymmetric aldol reaction of acetone (5 equiv) with various aromatic aldehydes. In aqueous media, the reaction catalyzed by (*S*)-proline-containing thioamides (0.1–0.2 mol %) in the presence of $PhCO_2H$ (2 mol %) afforded the aldol adducts in excellent enantioselectivities and yields (up to 99% ee in 98% yield).[12a] Finally, in 2009 Li and co-workers prepared several organocatalysts derived from (*S*)-proline, such as dipeptide (*S*)-Pro-(*S*)-Val–CO_2Me, and its thio analog (*S*)-Pro(C=S)-(*S*)-Val–CO_2Me.

The evaluation of both catalysts in the enantioselective direct aldol reaction between acetone and 4-nitrobenzaldehyde in DMSO solution and in the presence of 10 mol % of benzoic acid as additive revealed that the (*S*,*S*)-thiodipeptide afforded the aldol product in better yield and higher enantioselectivity (72% yield, 85% ee) relative to the same reaction using the (*S*,*S*)-dipeptide (59% yield, 35% ee).[12b]

Nevertheless, no evaluation of (*S*,*S*)-proline-containing thiodipeptides as potential organocatalysts in aldol reactions *under solvent-free reaction conditions* has been reported in the literature. For this reason we decided to synthesize the three novel (*S*,*S*)-prolinethiodipeptides **1d**–**f** (Fig. 1), and compare their organocatalytic activity in the asymmetric aldol reaction with that exhibited by the analogous **1a**–**c**.

2. Results and discussion

(*S*)-Proline-containing dipeptides and thiodipeptides (*S*,*S*)-**1a**–**f** were synthesized by condensation of Cbz- or Boc-*N*-protected (*S*)-proline with (*S*)-phenylalanine, (*S*)-phenylglycine, or (*S*)-tryptophan methyl ester hydrochloride. The dipeptides **1a**–**c** were obtained by deprotection of Cbz-*N*-protected dipeptides with hydrogen and palladium on carbon. On the other hand, Boc-*N*-protected dipeptides were treated with Lawesson's reagent, followed by deprotection of the amine function with trifluoroacetic acid to afford the desired thiodipeptides **1d**–**f** (Scheme 1).



Scheme 1. Synthesis of organocatalysts (*S*,*S*)-**1a**–**f**.