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Proline–threonine dipeptide as an organocatalyst for the direct asymmetric aldol reaction

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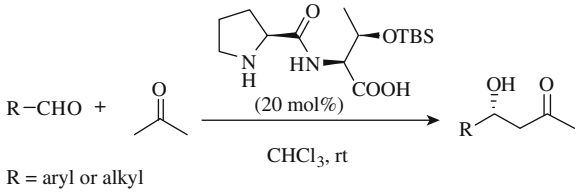
ABSTRACT

A new proline–threonine (H-Pro-Thr-OH) dipeptide has been demonstrated as an efficient organocatalyst for a direct asymmetric aldol reaction. It was found that this new peptide-based catalyst efficiently catalyzed the reaction between an aldehyde and acetone to provide β-hydroxy ketones in good yields with good enantioselectivities.

1. Introduction

L-Proline and several derivatives of this small amino acid have proven to be useful organocatalyst for metal-free aldol reactions.[1–3] For the proline-catalyzed reaction, the acidic proton of the carboxylic acid group is crucial for the stereoselectivity and reactivity. Based on transition state model studies most of the proline derivatives, for example, triazoles, tetrazoles, and sulfonamides, developed have been holding this acidic proton.[3] However, in simple L-prolinamide, the acidic nature of the –CONH proton is less, therefore it is ineffective catalyst for the aldol rection.[1c] To overcome this problem various prolinamide derivatives including di- and tri-peptides have been developed.[4] Particularly, prolinamides with a terminal hydroxyl group have received significant interest compared to other derivatives due to the improved hydrogen bond donor character of the hydroxyl group. However, prolinamide derivatives containing a free carboxyl group (C-terminal) are less explored for asymmetric direct aldol reactions.[5] Therefore, in continuation of our interest in organocatalysis,[3a,6] we became interested in a dipeptide prolinamide with a terminal carboxylic acid group catalyzed asymmetric aldol reaction. For this purpose, we chose a dipeptide derived from proline and threonine. We envisaged that the free –OH and –COOH groups on threonine after peptidation with proline would provide an additional push in the catalytic aldol process. Earlier attempts were made using a proline–threonine catalyst with free hydroxyl group while blocking the carboxylic acid as an ester for aldol reaction.[7] We were interested in preparing the dipeptide with silyl protection on the hydroxyl group while keeping free the –COOH group as in natural proline, thus deriving the dual advantages of selectivity and reactivity.[8] Hence, herein we report prolinamide with terminal carboxylic acid group (H-Pro-Thr-OH), derived from proline and threonine, catalyzed asymmetric direct aldol reaction of various aldehydes with acetone (Scheme 1).



Scheme 1. Direct asymmetric aldol reaction catalyzed by proline–threonine dipeptide (H-Pro-Thr-OH) **1**.

2. Results and discussion

The dipeptide catalyst **1** chosen for the asymmetric aldol reaction was synthesized in five steps starting from proline (Scheme 2). The coupling of Cbz-protected proline[9] **3** with threonine benzyl ester[8a] **4** was achieved under standard EDCI, HOBt coupling conditions. After obtaining the dipeptide **5**, the free hydroxyl group was protected as TBS ether **6** followed by hydrogenolysis to afford the required prolinamide-based dipeptide **1** with a terminal free carboxylic acid group.

Initially, the aldol reaction of 4-nitro benzaldehyde **7a** with acetone **8a** was investigated using the above dipeptide catalyst **1** (20 mol %) at room temperature. The reaction was complete in 1 h and provided the expected product **9a** in 70% yield with 75% ee (Table 1, entry 1). To check the effect of various solvents for better yield and selectivities, the same reaction was tested in different solvents and the results are summarized in Table 1. Among the

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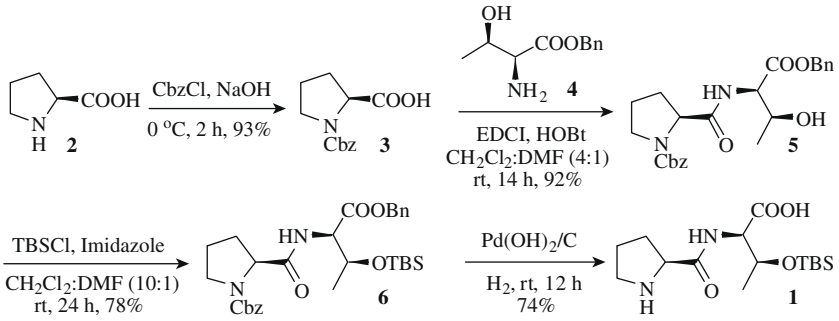
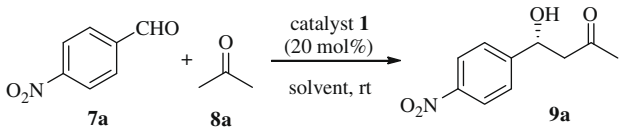


Scheme 2. Synthesis of proline–threonine dipeptide **1**.

solvents screened, $CHCl_3$ was found to be the best solvent, giving the product in 91% yield with 82% enantiomeric excess (Table 1, entry 9). Much improvement is not there in either the yield or the enantioselectivity when decreasing the reaction temperature to 0 °C (Table 1, entry 10). The enantioselectivity of this substrate in the case of known catalyst prolinamide with free terminal hydroxyl group (H-Pro-Thr-OMe) was 69%.[7] Encouraged by this result, we planned to expand the generality of this dipeptide catalyst with a free terminal acid group (H-Pro-Thr-OH) **1** using the reaction of various aldehydes with acetone.

Table 1
Effect of solvents



Entry	Solvent	Time (h)	Yield[a] (%)	ee[c] (%)
1	Acetone	1	70	75
2	DMSO	10	43	73
3	Dioxane	10.5	40	61
4	DMF	1.6	65	71
5	Water	10	35	31
6	Acetonitrile	5	35	69
7	Methanol	2	50	61
8	Dichloromethane	1.5	75	69
9	Chloroform	1.3	91	82
10[b]	Chloroform	12	86	85

[a] Isolated yields after column chromatography.
[b] Reactions performed at 0 °C.
[c] ee% calculated by using chiral HPLC.

Accordingly, the reaction of acetone **8a** (aldol donor) with a variety of aldehydes including aromatic and aliphatic ones was investigated using organocatalyst **1** under optimal conditions. The results are summarized in Table 2. All the reactions proceeded smoothly with 20 mol % of catalyst in good yields (72–91%) with high enantioselectivities regardless of the nature of the aldehyde.

3. Conclusions

In conclusion, we have developed a proline–threonine dipeptide catalyst with a free terminal acid group (H-Pro-Thr-OH) for the direct asymmetric aldol reaction of acetone with various aldehydes. The yields are typically good and the enantioselectivities are high in almost all the cases examined, including those with aromatic and aliphatic aldehydes. The synthetic utility of this dipeptide as an organocatalyst in organic synthesis will be explored to other reactions.

4. Experimental

4.1. General

All solvents and reagents were purified by standard techniques. Crude products were purified by column chromatography on silica gel of 60–120 mesh. IR spectra were recorded on a Thermo Nicolet Nexus 670 spectrometer. Optical rotations were obtained on Perkin Elmer digital polarimeter. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 solution on a Varian Gemini 200 and Brucker Avance 300. Chemical shifts were reported in parts per million (PPM) with respect to internal TMS. Coupling constants (J) are quoted in hertz. Mass spectra were obtained on an Agilent Technologies SHIMADZU GC/MS, 6510 Q-TOF LC/MS. HPLC was performed on SHIMADZU HPLC using chiral pak IA and eurocel IA columns with isopropyl alcohol and hexane as eluants.

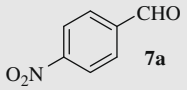
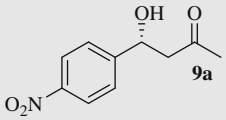
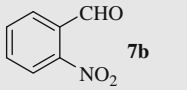
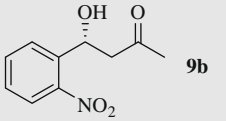
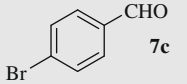
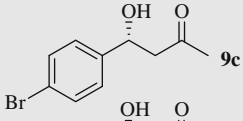
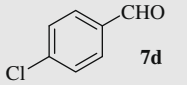
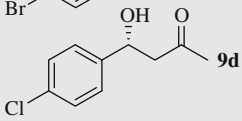
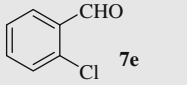
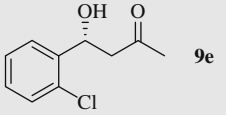
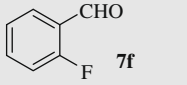
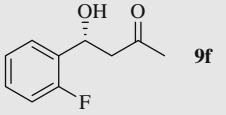
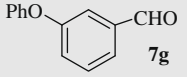
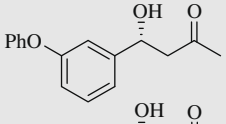
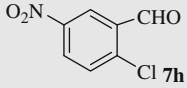
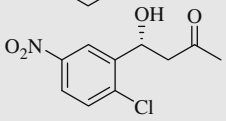
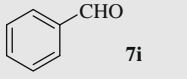
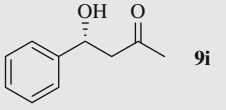
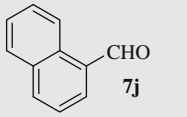
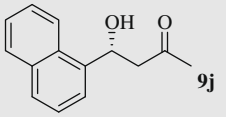
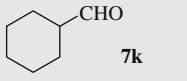
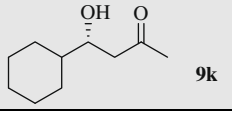
4.1.1. (*S*)-Benzyl 2-((2*R*,3*S*)-1-(benzyloxy)-3-hydroxy-1-oxobutan-2-ylcarbamoyl)pyrrolidine-1-carboxylate 5

N-Benzyloxycarbonyl-protected proline **3** (2 g, 7.9 mmol) was dissolved in dry dichloromethane (10 mL), after which HOBt (1.28 g, 9.48 mmol) was added and the reaction mixture was stirred for 15 min. The solution was cooled to 0 °C and EDCI (3.02 g, 15.8 mmol) was added. To this solution was added a solution of benzyl ester of threonine **4** (2.55 g, 7.9 mmol) and DIEPA (7.9 mmol, 1.10 mL) dissolved in dry dichloromethane (10 mL) and the mixture was stirred overnight at room temperature. After completion of the reaction (monitored by TLC), water (20 mL) was added, and the two layers were separated. The organic layer was washed with aq ammonium chloride (10 mL) and sodium bicarbonate (15 mL) simultaneously, dried over sodium sulfate, and evaporated in vacuo. The crude product was purified by column chromatography (EtOAc/hexanes, 30:70) to yield the pure dipeptide **5** as a white solid (3.07 g, 92% yield). $[\alpha]_D^{25} = -53$ (c 1, $CHCl_3$); mp: 175–176 °C; IR (KBr): ν 3385, 3319, 2954, 1728, 1662 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 1.02 (dd, J = 37.7, 6.2 Hz, 3H), 1.68–1.88 (m, 1H), 2.06–2.16 (m, 3H), 3.43 (m, 2H), 4.14–4.24 (1H, m), 4.29–4.49 (m, 3H), 4.91–5.19 (m, 6H), 7.21–7.41 (m, 10H), 8.06 (t, J = 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.8, 172.5, 153.9, 153.8, 137.0, 136.9, 135.9, 128.3, 128.3, 128.2, 127.9, 127.7, 127.5, 127.4, 126.9, 66.3, 66.1, 65.9, 65.8, 65.9, 65.8, 65.7, 59.3, 58.8, 57.9, 57.8, 47.1, 46.5, 31.1, 29.8, 23.7, 29.8, 23.7, 22.8, 20.1, 20.0; ESIMS (m/z) 441 (M^+); HRMS calcd for $C_{24}H_{28}N_2O_6Na$ 463.1845, found 463.1841.

4.1.2. (*S*)-Benzyl 2-((2*R*,3*S*)-1-(benzyloxy)-3-(*tert*-butyldimethylsilyloxy)-1-oxobutan-2-ylcarbamoyl)pyrrolidine-1-carboxylate 6

To dipeptide **5** (100 mg, 0.23 mmol), dissolved in dry dichloromethane (2 mL), was added dry dimethyl formamide dropwise until the solution became clear. *tert*-Butyldimethylsilyl chloride

Table 2
Proline–threonine dipeptide **1** catalyzed aldol reaction of aldehydes with acetone

Entry	Aldehyde	Product	Time (h)	Yield[a] (%)	ee[c] (%)
1	 **7a**	 **9a**	1.5	91	82
2	 **7b**	 **9b**	2	85	71
3	 **7c**	 **9c**	3	88	71
4	 **7d**	 **9d**	2	88	77
5	 **7e**	 **9e**	2.5	86	57
6	 **7f**	 **9f**	10	78	80
7[b]	 **7g**	 **9g**	12	75	85
8	 **7h**	 **9h**	1	82	77
9	 **7i**	 **9i**	7	72	75
10	 **7j**	 **9j**	5	74	65
11	 **7k**	 **9k**	8	80	75

[a] Isolated yields after column chromatography.
[b] Reactions performed at 4 °C.
[c] ee% calculated by using chiral HPLC.

(44.41 mg, 0.29 mmol) and imidazole (31.3 mg, 0.46 mmol) were then added simultaneously at 0 °C. The solution was stirred for 24 h at room temperature. After completion of the reaction (monitored by TLC), water (2 mL) was added, the two layers were separated, and the aqueous layer was extracted twice with dichloromethane (2 × 3 mL). The combined organic layers were dried over sodium sulfate, concentrated, and the crude product was purified by column chromatography (EtOAc/hexanes: 10/90) to give the product as colorless viscous oil (98 mg, 78%). $[\alpha]_D^{25} = -30.4$ (*c* 1, $CHCl_3$); IR (neat): *ν* 2953, 1747, 1691 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): *δ* −0.09 to 0.03 (m, 3H), 0.08 (s, 9H), 1.02 (dd, *J* = 37.9, 6.0 Hz, 3H), 1.72–2.17 (m, 4H), 3.40 (m, 2H), 4.27–4.58 (m, 3H), 4.90–5.17 (m, 4H), 7.26–7.41 (s, 10H), 7.73–7.85 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 172.6, 172.1, 169.9, 154.1, 153.8, 153.6, 136.8, 135.4, 128.3, 128.0, 127.9, 127.6, 127.4, 127.3, 126.9, 68.1, 66.1, 65.9, 65.8, 65.6, 59.3, 58.7, 57.5, 57.5, 47.0, 46.4, 31.0, 29.4, 25.4, 23.7, 22.7, 20.1, 19.9, 17.5, −4.5, −5.4; ESIMS: (*m*/*z*) 555 (M^+); HRMS calcd for $C_{30}H_{42}N_2O_6SiNa$ 577.2709, found 577.2721.

4.1.3. (2*R*,3*S*)-3-(*tert*-Butyldimethylsilyloxy)-2-(*S*)-pyrrolidine-2-carboxamido)butanoic acid 1

The TBS-protected peptide **6** (500 mg, 0.90 mmol) was dissolved in methanol (5 mL), after which 20% $Pd(OH)_2/C$ (50 mg) was added and the reaction mixture was stirred for 24 h at room temperature under a hydrogen atmosphere. The reaction mass

was filtered through Celite, washed with methanol (2 × 3 mL), and evaporated in vacuo. The crude product was recrystallized from ether to obtain the dipeptide organocatalyst **1** (74% yield, 218 mg); $[\alpha]_D^{25} = -21.1$ (*c* 0.5, MeOH); mp: 227–228 °C; IR (KBr, thinfilm): *v* 3430, 3271, 2933, 1679, 1586, 1389 cm^{-1}; ^1H NMR (CD_3OD, 300 MHz): δ 0.07 (s, 6H), 0.74 (s, 9H), 1.01 (d, *J* = 6.2 Hz, 3H), 1.79–1.96 (m, 2H), 1.94–2.07 (m, 1H), 2.30–2.24 (m, 1H), 3.07–3.24 (m, 3H), 4.07–4.11 (d, *J* = 2.2 Hz, 1H), 4.18–4.24 (dd, *J* = 8.4, 6.4 Hz, 1H), 4.32–4.40 (m, 1H). ^{13}C NMR (CD_3OD, 75 MHz): δ 175.7, 175.5, 170.7, 70.7, 61.7, 61.2, 47.5, 31.1, 26.4, 26.2, 25.3, 22.0, 19.0, −3.56, −4.37, −4.47, −5.69; ESIMS: (*m*/*z*) 331 (M^+); HRMS calcd for 331.2053 $C_{15}H_{31}N_2O_4SiNa$, found 331.2068.

4.1.4. Representative procedure for the aldol reaction

To a stirred solution of catalyst **1** (20 mol %) in chloroform (2 mL), was added acetone (4 mmol) and then stirred for 15 min. After this time, aldehyde (1 mmol) was added and stirring was continued for a given time (Table 2) at room temperature. After completion of the reaction, (monitored by TLC), water was added and extracted with dichloromethane (2 × 5 mL). The combined organic layers were dried over sodium sulfate and evaporated in vacuo. The crude product was purified by silicagel column chromatography to afford the pure product.

4.1.4.1. (*R*)-4-(2-Fluorophenyl)-4-hydroxybutan-2-one 9f. Colorless oil, $[\alpha]_D^{25} = +65.9$ (*c* 1, $CHCl_3$); IR (neat): *v* 3417, 2923, 1636, 769 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.19 (s, 3H), 2.83–2.89 (m, 2H), 3.69 (d, *J* = 3.7 Hz, 1H), 5.39–5.46 (m, 1H), 6.96–7.04 (1H, m), 7.12–7.18 (m, 1H), 7.21–7.29 (m, 1H), 7.49–7.56 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 30.4, 50.3, 63.9, 114.8, 115.1, 124.2, 127.1, 127.2, 128.7, 128.8, 129.5, 129.7, 157.5, 160.7, 208.9; ESIMS: (*m*/*z*) 205 ($M+Na^+$); HRMS calcd for 182.0743 $C_{10}H_{11}FO_2$, found 182.0740. Enantiomeric excess: 80%, determined by HPLC analysis using chiral pak 250 × 4.6μ, column (isopropanol/hexanes 05:95), UV , 210 nm, flow rate 1.0 ml/min, , major isomer t_R 7.39 min, t_R minor isomer 8.23; IR, ^1H, ^{13}C NMR and mass spectral data of the known products **9a** and **9b**,[6c] **9c** to **9e**,[4f] **9g**,[10] **9h**,[6c] **9i** to **9k**[4f] were identical with the reported data.

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