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Scientific paper

Synthesis of New Di- and Triamides as Potential Organocatalysts for Asymmetric Aldol Reaction in Water

Elif Keskin, Cigdem Yolacan and Feray Aydogan*

Department of Chemistry, Yildiz Technical University, Davutpasa Campus, 34010 Esenler, Istanbul, Turkey

** Corresponding author: E-mail: feray_aydogan@yahoo.com*
Tel: +90 212 383 42 15

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Abstract

New di- or triamide organocatalysts derived from (*L*)-proline were synthesized and successfully used in the direct asymmetric aldol reaction of aliphatic ketones and aromatic aldehydes in water at 0 °C in the presence of benzoic acid as co-catalyst. (*S*)-methyl-2-((*S*)-3-hydroxy-2-((*S*)-3-pyrrolidine-2-carboxamido)propanamido)-3-phenylpropanoate (**7c**) as organocatalyst showed best results under these reaction conditions, and good diastereoselectivities (up to 99%), enantioselectivities (up to 98%) and yields (up to 91%) were observed.

Keywords: Aldol reaction; organocatalysis; asymmetric synthesis; prolinamide

1. Introduction

The aldol reaction is an important tool in organic chemistry to synthesize attractive intermediates. This carbon-carbon bond formation reaction yields the β-hydroxyketones which are important precursors for pharmaceuticals and natural products. Especially, the asymmetric version of the reaction has been extensively studied and used for the synthesis of valuable intermediates, highly functionalized and complex molecules with important biological activities. The most considerable asymmetric method is the using of asymmetric organocatalysis which

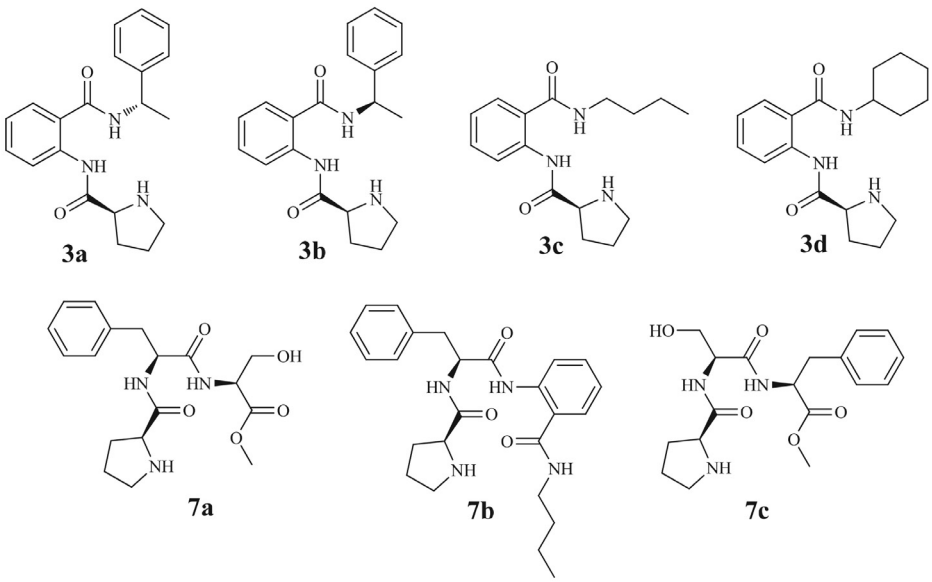


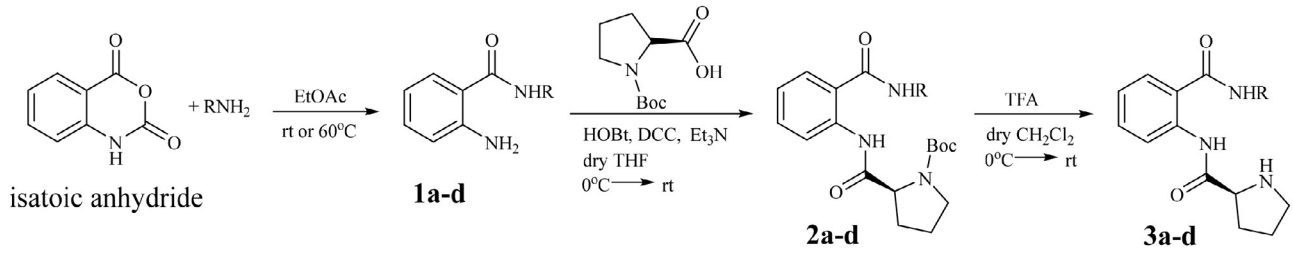
Figure 1. The structures of organocatalysts investigated in this study

are non-metal, small, easily synthesizable organic compounds with low toxicity and mostly natural products.[1–3] Among these natural organocatalysts, *L*-proline is the corner stone of natural amino acid organocatalysts and used successfully to catalyze various organic reactions.[4–7] But, this small organic compound has some drawbacks such as low solubility, low yields and low enantioselectivity with aromatic aldehydes as organocatalyst in asymmetric aldol condensation.[8] To overcome these drawbacks, some derivatives of proline had been succesfully synthesized and used in asymmetric aldol reaction and new modifications on proline are still under investigation.[9–24] Especially, proline based amides have been used succesfully for this reaction.[25–30] These derivatives have some advantages such as easy preperation, high stability and the presence of important functional groups. The catalytic effect of these catalysts based on secondary amine group on the pyrrolidine ring which form enamine to activate carbonyl group and the hyrogen bond donors which improve the activation of electrophile and selectivity. These advantages make them one of the most popular organocatalysts for organic synthesis and the design and investigation of new proline based amides as organocatalysts for various organic reactions is still under investigation by several research groups.[31,32]

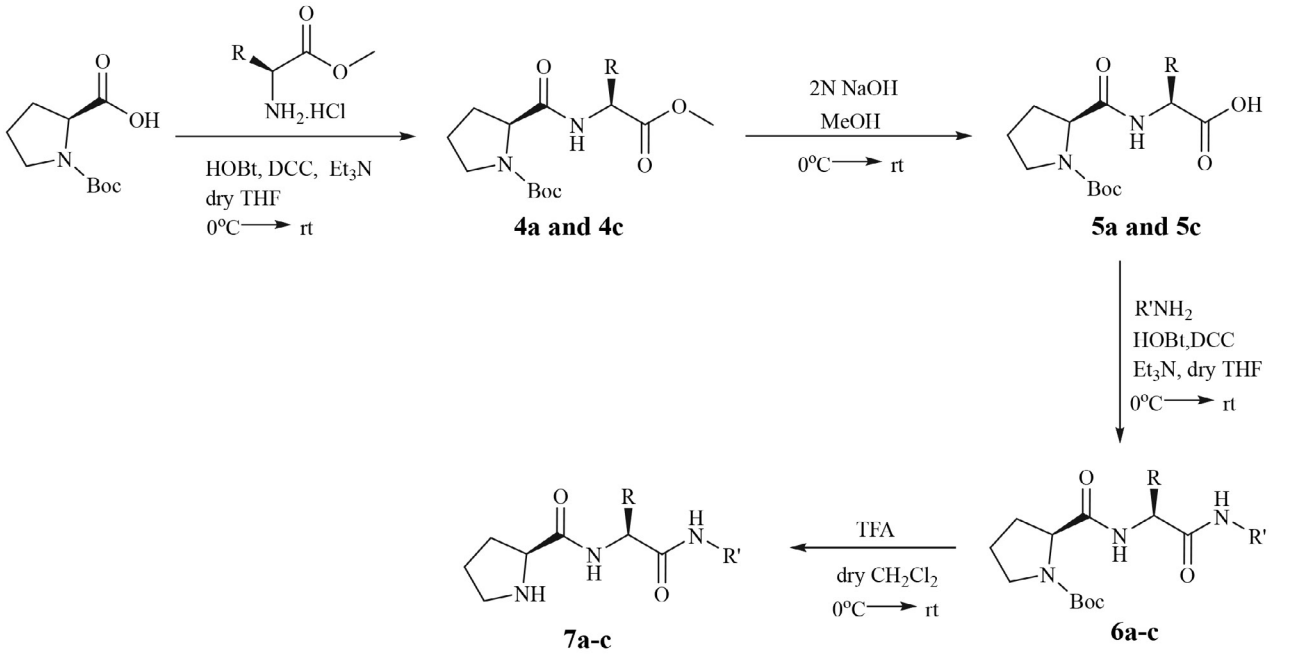
In our continuing research on the synthesis of chiral organocatalysts and their investigation in direct asymmetric aldol reaction, we have investigated the catalytic potential of some proline amide derivatives and also 1,2,3,4-tetrahydroisoquinoline and thiazolidine-4-carboxylic acid amide derivatives.[33–36] Now we herein report the synthesis of new proline based amides (**3a–d** and **7a–c**) (Figure 1) and their application in asymmetric direct aldol reaction.

2. Results and Discussion

The reaction of Boc-protected *L*-proline with aminobenzamide derivatives (**1a–d**) which were synthesized by the reaction of isatoic anhydride with some amines and subsequent deprotection of products (**2a–d**) gave new pro-



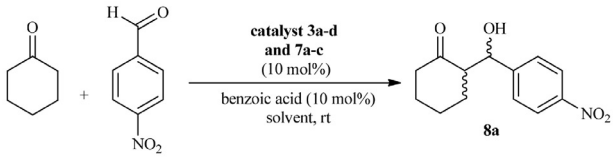
Scheme 1. The synthetic route for compounds **3a–d**.



Scheme 2. The synthetic route for compounds **7a–c.**

line based diamides (**3a–d**) (Scheme 1). Aminobenzamides (**1a–d**) were known in the literature[37,38] and the IR, ^{1}H NMR and MS data of the compounds **1a–d** were in accordance with those data. The characterization of unknown compounds **2a–d** and **3a–d** were performed from their spectral data.

Table 1. Catalytic activities of di- and tri-amides.



Catalyst (10 mol%)	Solvent	Reaction time (h)	dr[a] (syn/anti)	ee[a] (%) (anti)	Yield[b] (%)
3a	DCM	72	1/1.7	16.7	84.2
3a	H_2O	24	1/2.2	32.0	79.9
3a	none	48	1/1.5	32.4	77.7
3b	DCM	72	1/1.7	21.6	58.8
3b	H_2O	24	1/2.6	42.4	83.0
3c	DCM	72	1/2.3	24.7	58.4
3c	H_2O	72	1/1.8	34.5	75.7
3c	none	48	1/1.7	34.9	83.1
3d	DCM	72	1/2.1	28.8	80.6
3d	H_2O	24	1/1.9	45.9	95.8
3d	none	48	1/1.6	29.0	86.2
7a	DCM	72	1/2.7	47.9	86.9
7a	H_2O	24	1/3.9	65.5	70.3
7a	none	24	1/1.6	68.3	63.7
7b	DCM	72	1/3.5	50.7	76.0
7b	H_2O	24	1/2.5	32.0	91.0
7b	none	48	1/2.7	53.3	96.0
7c	DCM	72	1/3.9	78.5	52.0
7c	H_2O	48	1/9.3	90.6	89.4
7c	none	72	1/4.7	87.5	96.0
7c	H_2O/THF (2/1)	72	1/5.6	89.4	88.1

[a] Determined by chiral-phase HPLC analysis. [b] Combined yields of isolated diastereomers.

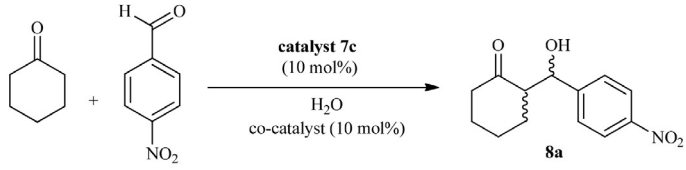
Compounds 7a–c were synthesized by a reaction sequence as amidation, hydrolysis, second amidation and deprotection reactions starting from Boc-protected proline and some amino acid esters and amine (Scheme 2). All new compounds were in accordance with their spectral data.

The reaction of *p*-nitrobenzaldehyde with cyclohexanone under diferent conditions was chosen as a model reaction to investigate the catalytic activities of amide compounds **3 a–d** and **7 a–c,** in direct asymmetric aldol reactions. First, the reaction was carried out with new amide compounds in water or dichloromethane (DCM), or without any solvent in the presence of benzoic acid (BA) as co-catalyst at room temperature. The results are shown in the Table 1. Compound **7c** showed the best catalytic activity with good diastereoselectivity (90%), enantioselectivity (91%) and yield (89%). The poor activities of **3 a–d** can be interpreted that the planar phenyl rings prevent the appropriate arrangement in the transition state due to the sterical effect and thus these compounds did not show good asymmetric induction. Compounds **7a** and **7b** also showed lower selectivities due to the steric effect of phenyl group. The best asymmetric induction was obtained with **7c**, which has less steric effect around proline NH and prolinamide NH. It is also thought that the OH group is effective in asymmetric induction through hydrogen bond formation.

Then, various co-catalysts containing 4-nitrobenzoic acid (4-NBA), (2*R*, 3*R*)-(+)-tartaric acid (2*R*, 3*R*-TA), acetic acid (AcOH) and benzoic acid (BA) were also tested at 0 °C and room temperature to determine the optimum conditions with the best organocatalyst **7c**. As it can be seen from the Table 2, the best results were obtained at 0 °C in the presence of BA as co-catalyst in water.

With these promising results, the substrates in the reaction were broadened with different aliphatic ketones and aromatic aldehydes in the presence of organocatalyst **7c** under the optimum conditions (Table 3). All aldol products are known in the literature, and their structures

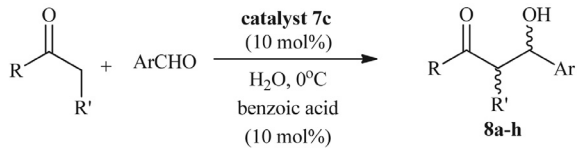
Table 2. Catalytic acitivity of organocatalyst **7c** under various conditions.



Catalyst (10 mol %)	Co-catayst (10 mol%)	Temperature time (h)	Reaction (syn/anti)	dr[a] (anti)	ee[a] (%) (%)	Yield[b]
7c	4-NBA	rt	72	1/4.5	90.1	79.6
7c	(2*R*-3*R*)-TA	rt	72	1/1.9	73.1	54.0
7c	AcOH	rt	48	1/5.6	92.2	77.6
7c	BA	rt	12	1/8.6	87.9	50.0
7c	BA	0 °C	72	1/12.7	95.4	91.3
7c (5% mol)	BA	0 °C	72	1/2.9	84.5	27.4
7c	4-NBA	0 °C	72	1/12.3	93.8	94.6

[a] Determined by chiral-phase HPLC analysis. [b] Combined yields of isolated diastereomers.

Table 3. Aldol reactions of different aldehydes and ketones catalyzed by **7c.**



Compound	Ketone	Aldehyde	Reaction time (h)	dr[a] (syn/anti)	ee[a] (%) (anti)	Yield[b] (%)
8a	Cyclohexanone	4-Nitrobenzaldehyde	72	1/12.7	95.4	91.3
8b	Cyclohexanone	2-Nitrobenzaldehyde	36	1/222.2	90.9	53.9
8c	Cyclohexanone	3-Nitrobenzaldehyde	72	1/39.5	93.4	66.5
8d	Cyclohexanone	4-Cyanobenzaldehyde	72	1/3.2	91.9	59.2
8e	Cyclohexanone	4-Bromobenzaldehyde	24	1/20.0	34.8	62.9
8f	Cyclohexanone	Trifluoromethylbenzaldehyde	24	1/19.6	94.0	64.5
8g	Cyclopentanone	4-Nitrobenzaldehyde	72	1/0.7	98.3[c]	73.4
8h	Acetone	4-Nitrobenzaldehyde	72	–	60.4	40.0

[a] Determined by chiral-phase HPLC analysis. [b] Combined yields of isolated diastereomers. [c] *syn* isomer.

are in agreement with the literature data.[39,40] The diastereomeric ratios and enantiomeric excesses were determined by chiral HPLC analysis of the products by using literature methods.[41–43]

3. Conclusion

In conclusion, we have designed and synthesized new di- or triamide organocatalysts derived from (*L*)-proline and successfully used in the direct asymmetric aldol reaction of aliphatic ketones and aromatic aldehydes in water. Among the catalysts investigated in this study, catalyst **7c** gave the best diastereoselectivities (up to 99%), enantioselectivities (up to 98%) and yields (up to 91%) when different aliphatic ketones and aromatic aldehydes with electron withdrawing groups were used. Furthermore, these catalysts showed their best catalytic activities in water which is also an important contribution to green chemistry requirements.

4. Experimental

General

All reagents were of commercial quality and reagent quality solvents were used without further purification. IR spectra were determined on a Perkin Elmer, Spectrum One FT-IR spectrometer and Bruker Tensor 27 spectrometer. NMR spectra were recorded on Bruker Avance III 500 MHz and Varian-INOVA 500 MHz NMR spectrometer. Chemical shifts δ are reported in ppm with TMS as internal standart and the solvents were $CDCl_3$ and CD_3OD. Column chromatography was conducted on silica gel 60 (40–63 μM). TLC was carried out on aluminum sheets precoated with silica gel $60F_{254}$ (Merck). GC-MS spectrum was recorded on Agilent 6890N-GC-System-5973 IMSD spectrometer. LC-MS (QTOF) spectra were obtained on Agilent G6530B model TOF/Q-TOF Mass Spectrometer. Optical rotations were measured with Bellingham Stanley ADP-410 Polarimeter. Chiral HPLC analyses were performed with Shimadzu HPLC (Daicel Chiralpak AD and AD-H columns) equipped with SPD-20A detector and isopropanol/hexane mixtures as the eluent. The protection of *L*-proline was carried out according to the literature procedure.[44] Spectroscopic data of this compound were in accordance with its structure.

General Procedure for the Synthesis of Aminobenzamid Derivatives (1a–d)

The corresponding amines (1.15 mmol) were added to isatoic anhydride (1.00 mmol), dissolved in ethyl acetate and stirred at room tempearature for 5 hours (for compound **1a** at 60 °C for 1.5 hours). The precipitates were filtered and the crude products were purified by crystallization or column chromatography.

General Procedure for Amidation Reactions

1-Hydroxy-1*H*-benzotriazole (HOBt, 1.00 mmol) was added to the stirred solution of Boc-protected acid (0.92 mmol) in dry THF. After 10 min stirring at 0 °C under nitrogen, dicyclohexylcarbodiimide (DCC) (1.00 mmol) was added. The mixture was stirred at 0 °C for 1 h, and the amine (1.02 mmol) was added. In the case of amino acid ester hydrochloride, to the suspension of amino acid ester hydrochloride in dry THF, triethylamine (0.5 mL) was added, and stirred at room temperature for 1 h. This solution was then added to the first mixture. The reaction mixture was then stirred at room temperature for 24 h, and the reaction monitored by TLC. The formed precipitate was removed by filtration, and filtrate evaporated under vacuum. The residue was dissolved in 50 mL of ethyl acetate, and resultant solution washed successively with

saturated aqueous solution of $NaHCO_3$ (30 mL × 3), 5% aqueous solution of $KHSO_4$ (30 mL × 3) and saturated aqueous solution of NaCl (30 mL × 3) and finally dried with anhydrous Na_2SO_4. After filtration, the mixture was evaporated under vacuum to give the crude products **2a–d, 4a, 4c** and **6a–c** which were purified by column chromatograpy on silica gel.

General Procedure for Hydrolysis to Synthesize 5a and 5c

To the solution of compounds **4a** and **4c** (1.00 mmol) in methanol (5 mL), 2 N aqueous NaOH was added at 0 °C to adjust to pH 11. The reaction mixture was stirred at 0 °C for 3 h, and at room temperature for 24 h, and then adjusted to pH 2 with aqueous solution of $KHSO_4$. The solution was evaporated under vacuum to remove methanol, and extracted with ethyl acetate (30 mL × 3). The combined organic layer was successively washed with brine (20 mL × 2) and dried with anhydrous Na_2SO_4. After filtration, the filtrate was evaporated to provide compounds **5a** and **5c** which was used without any further purification.

General Procedure for Deprotection and Synthesis of 3a–d and 7a–c

To the solution of *N*-Boc protected compounds **2a–d** and **6a–c** (1.00 mmol) in dry DCM (15 mL) at 0 °C, TFA (27.00 mmol) was added dropwise over 5 min with stirring. The reaction mixture was stirred at 0 °C for 1 h, and at room temperature for 2 h, then 2M K_2CO_3 was added to the reaction mixture to adjust basic pH. The organic phase was washed with water, dried over $MgSO_4$, filtered and evaporated to give the pure compounds **3a–d** and **7a–c**.

(*S*)-2-Amino-*N*-(1-phenylethyl)benzamide (1a)

White solid, yield 71 %, mp 132.4–133.2 °C, (mp 136–138 °C,[37]), $[\alpha]^{20}_D$ = −103.9 (c = 1.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.57 (d, *J* = 6.9 Hz, 3H, CH_3), 5.23–5.29 (m, 1H, C<u>H</u>CH_3), 6.29 (brs, 1H, NH), 5.49 (brs, 2H, NH_2), 6.61–6.66 (m, 2H, ArH), 7.17–7.20 (m, 1H, ArH), 7.25–7.28 (m, 1H, ArH), 7.31–7.38 (m, 5H, ArH) ppm; FTIR (ATR) ν 3418, 3299, 3083, 3057, 3029, 2984, 2971, 1618, 1531, 1493, 1447, 1156 cm^{-1}; GC-MS: *m/z* 240 (M^+), 136 ($C_7H_8N_2O$), 120 (C_7H_7NO-1), 105 (C_7H_6O-1), 92 (C_7H_8), 77 (C_6H_6-1).

(*R*)-2-Amino-*N*-(1-phenylethyl)benzamide (1b)

White solid, yield 95 %, mp 132.6–133.8 °C, $[\alpha]^{20}_D$ = + 82.0 (c = 1.00, $CHCl_3$), [30]. FTIR (ATR) ν 3417, 3298, 3084, 3057, 3028, 2984, 2927, 1618, 1531, 1493, 1447, 1346, 1156 cm^{-1}.

2-Amino-*N*-butylbenzamide (1c)

White solid, yield 95 %, mp 88.5–89.2 °C;[38] ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.93 (td, *J* = 7.3, 1.4 Hz, 3H, CH_3), 1.34–1.41 (m, 2H, CH_2), 1.52–1.58 (m, 2H, CH_2), 3.34–3.39 (m, 2H, CH_2), 5.34 (brs, 2H, NH_2), 6.20 (brs, 1H, NH), 6.59–6.62 (m, 1H, ArH), 6.65 (d, *J* = 8.2 Hz, 1H, ArH), 7.15–7.18 (m, 1H, ArH), 7.29 (d, *J* = 8.0 Hz, 1H, ArH) ppm; FTIR (ATR) ν 3421, 3303, 3076, 2958, 2931, 2872, 1633, 1531, 1488, 1448, 1367, 1155 cm^{-1}.

2-Amino-*N*-cyclohexylbenzamide (1d)

White solid, yield 82 %, mp 156.9 °C;[38] ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.17–1.23 (m, 1H, CH_2), 1.35–1.40 (m, 4H, 2 × CH_2), 1.64–1.66 (m, 1H, CH_2), 1.76–1.79 (m, 2H, CH_2), 1.95–1.96 (m, 2H, CH_2), 3.86–3.93 (m, 1H, C<u>H</u>NH), 6.19 (brs, 2H, NH_2), 6.49–6.52 (m, 1H, ArH), 6.74 (d, *J* = 8.1 Hz, 1H, ArH), 7.11–7.14 (m, 1H, ArH), 7.25 (brs, 1H, NH), 7.48 (d, *J* = 7.8 Hz, 1H, ArH) ppm; FTIR (ATR) ν 3462, 3355, 3279, 3056, 2930, 2849, 1616, 1538, 1494, 1463, 1447, 1151 cm^{-1}.

(*S*)-*tert*-Butyl 2-(2-((*S*)-1-phenylethylcarbamoyl)phenylcarbamoyl)pyrrolidine-1-carboxylate (2a)

Colorless oil, yield 73.1 %, $[\alpha]^{20}_D$ = −88.00 (c = 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.36 and 1.53 (s, 9H, 3 × CH_3, rotamers), 1.59 (d, *J* = 6.9 Hz, 3H, CH_3), 1.77–1.80 (m, 2H, pro-γ), 2.02–2.08 (m, 1H, pro-β), 2.11–2.13 (m, 1H, pro-β), 3.46–3.51 (m, 1H, pro-δ), 3.61–3.66 (m, 1H, pro-δ), 4.22–4.25 and 4.38–4.41 (m, 1H, pro-α, rotamers), 5.27–5.32 (m, 1H, PhCH), 6.55 (brd, *J*=6.7 Hz, 1H, NH), 7.05–7.11 (m, 1H, ArH), 7.29–7.32 (m, 1H, ArH), 7.35–7.38 (m, 4H, ArH), 7.42–7.51 (m, 2H, ArH), 8.61–8.63 (m, 1H, ArH), 11.40 and 11.43 (brs, 1H, NH, rotamers) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.7 (CH_3), 23.7 (pro-γ), 28.2 (3xCH_3), 31.4 (pro-β), 46.6 (pro-δ), 49.2 (PhCH), 63.7 (pro-α), 80.1 ($C(CH_3)_3$), 120.8 ($C_{aro}H$), 121.1 ($C_{aro}H$), 122.9 ($C_{aro}H$), 126.1 ($C_{aro}H$), 126.4 ($C_{aro}H$), 127.5 ($C_{aro}H$), 128.7 ($C_{aro}H$), 132.6 (C_{aro}), 139.2 (C_{aro}), 142.9 (C_{aro}), 154.1 (C=O), 167.8 (C=O), 172.3 (C=O) ppm; LC-MS (ESI-QTOF) *m/z* $[M+H]^+$, found 438.2389. $C_{25}H_{31}N_3O_4$ requires 438.2393. FTIR (ATR) ν 3323, 3033, 2970, 2927, 1688, 1580, 1505, 1448, 1156 cm^{-1}.

(*S*)-*tert*-Butyl 2-(2-((*R*)-1-phenylethylcarbamoyl)phenylcarbamoyl)pyrrolidin-1-carboxylate (2b)

Pinkish solid, yield 27 %, mp 54.4 °C, $[\alpha]^{20}_D$ = −8.0 (c = 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.32 and 1.53 (s, 9H, 3 × CH_3, rotamers), 1.59 and 1.62 (d, *J* = 6.6 Hz, 3H, CH_3, rotamers), 1.86–1.91 (m, 1H, pro-γ), 1.93–2.02 (m, 1H, pro-γ), 2.08–2.16 and 2.21–2.29 (m, 2H, pro-β, rotamers), 3.41–3.47 and 3.51–3.56 (m, 1H, pro-δ, rotamers), 3.66–3.76 (m, 1H, pro-δ), 4.22–4.25 and 4.38–4.40 (dd, *J* = 8.5, 4.1 Hz, 1H, pro-α, rotamers), 5.27–5.33 (m, 1H, PhCH), 6.48 and 6.64 (brd, *J* = 7.5 Hz, 1H, NH, rotamers), 7.00–7.08 (m, 1H, ArH), 7.28–7.31 (m, 1H, ArH), 7.36–7.39 (m, 4H, ArH), 7.44–7.48 (m, 2H, ArH), 8.57–8.63 (m, 1H, ArH), 11.48 and 11.56 (brs, 1H, NH, rotamers) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.1 (CH_3), 21.6 (pro-γ), 28.2 (3 × CH_3), 31.4 (pro-β), 46.7 (pro-δ), 49.1 (Ph<u>C</u>H), 62.4 (pro-α), 80.0 ($C(CH_3)_3$), 120.0 ($C_{aro}H$), 121.0 ($C_{aro}H$), 122.8 ($C_{aro}H$), 126.3 ($C_{aro}H$), 126.6 ($C_{aro}H$), 127.5 ($C_{aro}H$), 128.7 ($C_{aro}H$), 132.4 (C_{aro}), 139.2 (C_{aro}),

142.7 (C_{aro}), 154.1 (C=O), 167.8 (C=O), 172.2 (C=O) ppm; LC-MS (ESI-QTOF): *m/z* $[M+H]^+$, found 438.2389. $C_{25}H_{31}N_3O_4$ requires 438.2393; FTIR (ATR): ν= 3313, 3065, 2974, 2931, 1676, 1642, 1585, 1444, 1386, 1158 cm^{-1}.

(*S*)-*tert*-Butyl 2-(2-(butylcarbamoyl)phenylcarbamoyl) pyrrolidine-1-carboxylate (2c)

Yellow oil, yield 85 %, $[\alpha]^{20}_D$ = −64.0 (c = 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.87 (brs, 3H, CH_3), 1.26 and 1.41 (s, 9H, 3 × CH_3, rotamers), 1.29–1.32 (m, 2H, CH_2), 1.49–1.51 (m, 2H, CH_2), 1.79–1.81 (m, 1H, pro-γ), 1.86–1.90 (m, 1H, pro-γ), 2.00–2.09 and 2.16–2.20 (m, 2H, pro-β), 3.26–3.31 (m, 1H, NCH_2), 3.32–3.36 (m, 1H, NCH_2), 3.41–3.46 (m, 1H, pro-δ), 3.59–3.65 (m, 1H, pro-δ), 4.13–4.16 and 4.28–4.30 (m, 1H, pro-α, rotamers), 6.68 and 6.72 (brs, 1H, NH, rotamers), 6.90–7.00 (m, 1H, ArH), 7.26–7.46 (m, 2H, ArH), 8.48 and 8.52 (brd, 1H, ArH, rotamers), 11.51 (brs, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.8 (CH_3), 20.1 (CH_2), 23.7 (CH_2), 28.2 (3 × CH_3), 30.5 (pro-γ), 31.5 (pro-β), 39.6 ($NHCH_2$), 46.7 (pro-δ), 62.4 (pro-α), 80.0 ($\underline{C}(CH_3)_3$), 120.8 ($C_{aro}H$), 120.9 ($C_{aro}H$), 122.8 ($C_{aro}H$), 126.7 ($C_{aro}H$), 132.2 (C_{aro}), 139.0 (C_{aro}), 154.1 (C=O), 168.6 (C=O), 172.2 (C=O) ppm; LC-MS (ESI-QTOF) *m/z* $[M+H]^+$, found 390.2388. $C_{21}H_{31}N_3O_4$ requires 390.2393; FTIR (ATR) ν 3351, 3067, 2957, 2931, 2873, 1679, 1644, 1585, 1516, 1477, 1446 cm^{-1}.

(*S*)-*tert*-Butyl 2-(2-(cyclohexylcarbamoyl)phenylcarbamoyl)pyrrolidine-1-carboxylate (2d)

Yellow solid, yield 86 %, mp 139.2–140.1 °C, $[\alpha]^{20}_D$ = −76.0 (c = 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.19–1.26 (m, 3H, CH_2), 1.35 and 1.50 (s, 9H, 3 × CH_3, rotamers), 1.41–1.43 (m, 2H, CH_2), 1.64–1.67 (m, 1H, CH_2), 1.74–1.76 (m, 2H, CH_2), 1.87–1.92 (m, 1H, CH_2), 1.96–1.98 (m, 3H, CH_2 ve pro-γ), 2.08–2.11 (m, 1H, pro-β), 2.16–2.19 (m, 1H, pro-β), 3.41–3.47 and 3.51–3.56 (m, 1H, pro-δ), 3.67–3.75 (m, 1H, pro-δ), 3.91–3.95 (m, 1H, NH$\underline{CH}$), 4.22–4.25 and 4.39–4.42 (m, 1H, pro-α, rotamers), 6.11 and 6.17 (brd, *J* = 7.3 Hz, 1H, NH), 7.02–7.09 (m, 1H, ArH), 7.39–7.47 (m, 2H, ArH), 8.61–8.63 (m, 1H, ArH), 11.47 (brs, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 23.8 (CH_2), 24.8 (CH_2), 25.5 (CH_2), 28.2 (3xCH_3), 30.5 (CH_2), 31.5 (pro-γ), 32.9 (CH_2), 33.0 (pro-β), 47.7 (N-CH), 48.5 (pro-δ), 62.5 (pro-α), 80.0 ($\underline{C}(CH_3)_3$), 121.1 ($C_{aro}H$), 121.3 ($C_{aro}H$), 122.8 ($C_{aro}H$), 126.4 ($C_{aro}H$), 132.4 (C_{aro}), 139.1(C_{aro}), 154.1 (C=O), 167.7 (C=O), 172.2 (C=O) ppm; LC-MS (ESI-QTOF) *m/z* $[M+H]^+$, found 416.2545. $C_{23}H_{33}N_3O_4$ requires 416.2549; FTIR (ATR) ν 3326, 3064, 2957, 2930, 2873, 1683, 1641, 1586, 1446, 1366, 1160 cm^{-1}.

(2*S*)-*N*-(2-((1*S*)-1-phenylethylcarbamoyl)phenyl)pyrrolidin-2-carboxamide (3a)

White solid, yield 57 %, mp 161.2–162.1 °C, $[\alpha]^{20}_D$ = −40.9 (c = 1.27, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.53 (d, *J* = 6.9 Hz, 3H, CH_3), 1.55–1.60 (m, 2H, pro-γ), 1.85–1.91 (m, 1H, pro-β), 1.99 (brs, 1H, NH), 2.04–2.11 (m, 1H, pro-β), 2.74–2.79 (m, 1H, pro-δ), 2.90–2.94 (m, 1H, pro-δ) , 3.76–3.79 (m, 1H, pro-α), 5.22–5.27 (m, 1H, PhCH), 6.33 (brd, *J* = 6.5 Hz, 1H, NH), 6.97–7.00 (m, 1H, ArH), 7.18–7.21 (m, 1H, ArH), 7.25–7.30 (m, 4H, ArH), 7.34–7.39 (m, 2H, ArH), 8.44–8.46 (d, *J*=8.2 Hz, 1H, ArH), 11.62 (brs, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.8 (CH_3), 26.1 (pro-γ), 31.1 (pro-β), 47.2 (pro-δ), 49.1 (Ph$\underline{C}$H), 61.5 (pro-α), 121.7 ($C_{aro}H$), 122.9 ($C_{aro}H$), 123.0 ($C_{aro}H$), 126.1 ($C_{aro}H$), 126.5 ($C_{aro}H$), 127.4 ($C_{aro}H$), 128.7 ($C_{aro}H$), 132.0 (C_{aro}), 138.2 (C_{aro}), 143.0 (C_{aro}), 167.6 (C=O), 174.8 (C=O) ppm; LC-MS (ESI-QTOF) *m/z* $[M+H]^+$, found 338.1866. $C_{20}H_{23}N_3O_2$ requires 338.1869; FTIR (ATR) ν 3292, 3063, 3031, 2975, 2933, 1673, 1640, 1597, 1514, 1447, 1374 cm^{-1}.

(2*S*)-*N*-(2-((*R*)-1–phenylethylcarbamoyl)phenyl)pyrrolidine-2-carboxamide (3b)

White solid, yield 77 %, mp 161–161.9 °C, $[\alpha]^{20}_D$ = −5.8 (c = 2.43, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.51 (d, *J* = 6.9 Hz, 3H, CH_3), 1.61–1.70 (m, 2H, pro-γ), 1.89–1.95 (m, 1H, pro-β), 2.03 (brs, 1H, NH), 2.06–2.12 (m, 1H, pro-β), 2.95–3.01 (m, 2H, pro-δ), 3.73–3.76 (m, 1H, pro-α), 5.21–5.27 (m, 1H, PhCH), 6.35 (brd, *J* = 7.6 Hz, 1H, NH), 6.95–6.98 (m, 1H, ArH), 7.19–7.23 (m, 1H, ArH), 7.27–7.36 (m, 6H, ArH), 8.43 (brd, *J*=8.2 Hz, 1H, ArH), 11.56 (brs, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.5 (CH_3), 26.1 (pro-γ), 31.1 (pro-β), 47.3 (pro-δ), 49.1 (PhCH), 61.5 (pro-α), 121.6 ($C_{aro}H$), 122.9 ($C_{aro}H$), 123.1 ($C_{aro}H$), 126.3 ($C_{aro}H$), 126.6 ($C_{aro}H$), 127.5 ($C_{aro}H$), 128.7 ($C_{aro}H$), 132.0 (C_{aro}), 138.1 (C_{aro}), 142.7 (C_{aro}), 167.7 (C=O), 174.8 (C=O) ppm; LC-MS (ESI-QTOF) *m/z* $[M+H]^+$, found 338.1863. $C_{20}H_{23}N_3O_2$ requires 338.1869; FTIR (ATR) ν 3332, 3283, 3059, 3027, 2969, 1656, 1633, 1597, 1429, 1343 cm^{-1}.

(*S*)-*N*-(2-(Butylcarbamoyl)phenyl)pyrrolidine-2-carboxamide (3c)

White solid, yield 83 %, mp 124.4–124.9 °C, $[\alpha]^{20}_D$ = −3.6 (c = 1.65, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.95 (t, *J* = 7.0 Hz, 3H, CH_3), 1.37–1.44 (m, 2H, CH_2), 1.56–1.62 (m, 2H, CH_2), 1.68–1.78 (m, 2H, pro-γ), 1.98–2.04 (m, 1H, pro-β), 2.14–2.20 (m, 1H, pro-β), 2.22 (brs, 1H, NH), 3.02–3.11 (m, 2H, pro-δ), 3.35–3.42 (m, 1H, NCH_2), 3.44–3.51 (m, 1H, NCH_2), 3.84–3.87 (m, 1H, pro-α), 6.38 (brs, 1H, NH), 7.02–7.05 (m, 1H, ArH), 7.40–7.43 (m, 2H, ArH), 8.53 (d, *J* = 8.5 Hz, 1H, ArH), 11.74 (brs, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.8 (CH_3), 20.1 (CH_2), 26.1 (CH_2), 31.1 (pro-γ), 31.6 (pro-β), 39.7 ($NHCH_2$), 47.3 (pro-δ), 61.6 (pro-α), 121.5 ($C_{aro}H$), 122.9 ($C_{aro}H$), 123.1 ($C_{aro}H$), 126.6 ($C_{aro}H$), 131.8 (C_{aro}), 138.1 (C_{aro}), 168.5 (C=O),174.9 (C=O) ppm; LC-MS (ESI-QTOF) *m/z* $[M+H]^+$, found 290.1868. $C_{16}H_{23}N_3O_2$ requires 290.1869; FTIR (ATR) ν 3353, 3162, 3086, 3063, 2960, 2930, 2872, 1665, 1632, 1595, 1577, 1441, 1321 cm^{-1}.

(*S*)-*N*-(2-(Cyclohexylcarbamoyl)phenyl)pyrrolidine-2-carboxamide (3d)

White solid, yield 83 %, mp 189.6–190.3 °C; $[\alpha]^{20}_D$ = −10.0 (c = 0.82, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.18–1.28 (m, 3H, CH_2), 1.38–1.45 (m, 2H, CH_2), 1.65–1.67 (m, 1H, CH_2), 1.71–1.78 (m, 4H, 2 × CH_2), 2.00–2.05 (m, 3H, 2 × pro-γ ve pro-β), 2.08 (brs, 1H, NH), 2.14–2.22 (m, 1H, pro-β), 3.01–3.12 (m, 2H, pro-δ), 3.85–3.88 (m, 1H, NCH), 3.93–3.99 (m, 1H, pro-α), 6.05 (brs, 1H, NH), 7.03–7.06 (m, 1H, ArH), 7.41 (d, *J* = 8.2 Hz, 2H, ArH), 8.54 (d, *J* = 8.1 Hz, 1H, ArH), 11.71 (brs, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 24.8 (2 × CH_2), 25.5 (CH_2), 26.2 (CH_2), 31.1 (pro-γ), 33.0 (CH_2), 33.1 (pro-β), 47.4 (NCH), 48.5 (pro-δ), 61.6 (pro-α), 121.5 ($C_{aro}H$), 122.9 ($C_{aro}H$), 123.4 ($C_{aro}H$), 126.6 ($C_{aro}H$), 131.8 (C_{aro}), 138.1 (C_{aro}), 167.7 (C=O), 174.9 (C=O) ppm; LC-MS (ESI-QTOF) *m/z* $[M+H]^+$, found 316.2020. $C_{18}H_{25}N_3O_2$ requires 316.2025; FTIR (ATR) ν 3462, 3355, 3279, 3056, 2930, 2849, 1616, 1588, 1538, 1463, 1447, 1371, 1187 cm^{-1}.

(*S*)-*tert*-Butyl 2-((*S*)-1-(methoxycarbonyl)-2-phenylethylcarbamoyl)pyrrolidine-1-carboxylate (4a)

Yellow oil, yield 73 %, $[\alpha]^{20}_D$ = −38.7 (c = 1.24, $CHCl_3$);[45] ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.42 (bs, 9H, $C(CH_3)_3$), 1.77–1.86 (m, 2H, pro-γ), 1.88–2.06 (m, 2H, pro-β), 2.90–3.03 (m, 1H, $PhCH_2$), 3.19 (dd, *J* = 14.0, 5.5 Hz, 1H, $PhCH_2$), 3.29–3.39 (m, 2H, pro-δ), 3.72 (s, 3H, OCH_3), 4.19–4.29 (m, 1H, pro-α), 4.85 (bs, 1H, Phe-CH), 7.09 (bd, *J* = 7.0 Hz, 2H, ArH), 7.22–7.25 (m, 3H, ArH) ppm; ^{13}C NMR (CD_3OD, 125 MHz) δ 24.3 (pro-γ), 28.5 (3 × CH_3), 32.2 (pro-β), 38.1 ($PhCH_2$), 47.8 (pro-δ), 52.7 (Phe-CH), 55.1 (OCH_3), 61.6 (pro-α), 81.5 ($OC(CH_3)_3$), 127.9 ($C_{aro}H$), 129.5 ($C_{aro}H$), 130.1 ($C_{aro}H$), 138.3 (C_{aro}), 173.3 (C=O), 175.1 (C=O), 175.8 (C=O) ppm; FTIR (ATR) ν 3277, 3079, 3028, 2976, 2877, 1738, 1689, 1660, 1552, 1445, 1389, 1365, 1210 cm^{-1}.

(*S*)-*tert*-Butyl 2-(((*S*)-3-hydroxy-1-methoxy-1-oxopropane-2-yl)carbamoyl)-pyrrolidine-1-carboxylate (4c)

Colorless oil, yield 94 %, $[\alpha]^{20}_D$ = +88.0 (c = 1.00, CH_3OH);[46] ^{1}H NMR (CD_3OD, 500 MHz) δ 1.45 and 1.48 (s, 9H, 3 × CH_3, rotamers), 1.88–1.92 (m, 1H, pro-γ), 1.94–1.98 (m, 1H, pro-γ), 2.00–2.05 (m, 1H, pro-β), 2.12–2.29 (m, 1H, pro-β), 3.33 (brs, 1H, OH), 3.40–3.45 (m, 1H, pro-δ), 3.51–3.55 (m, 1H, pro-δ), 3.74 (s, 3H, OCH_3), 3.79–3.85 (m, 1H, CH_2OH), 3.91–3.96 (m, 1H, CH_2OH), 4.27–4.30 (m, 1H, pro-α), 4.53–4.55 (m, 1H, C<u>H</u>CH_2OH) ppm; FTIR (ATR) ν 3293, 3082, 2975, 2881, 1743, 1662, 1533, 1470, 1454, 1205, 1160 cm^{-1}.

(*S*)-2-((*S*)-*tert*-Butyl 2-carbamoylpyrrolidine-1-carboxyloyl)-3-phenyl-propanoic acid (5a)

White solid, yield 96 %, mp 143–144 °C (mp 145–147 °C)[45,47]; $[\alpha]^{20}_D$ = −43.1 (c= 1.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.38 (s, 9H, $C(CH_3)_3$), 1.74–1.86 (m, 3H, pro-γ and pro-β), 2.06–2.09 (m, 1H, pro-β), 3.05–3.07 (m, 1H, CH_2Ph), 3.27–3.37 (m, 3H, CH_2Ph and pro-δ), 4.25–4.29 (m, 1H, pro-**α), 4.87 (bs, 1H,** Phe-CH), 7.14–7.16 (m, 2H, NH and ArH), 7.20–7.27 (m, 4H, ArH) ppm; FTIR (ATR) ν 3425, 3314, 3060, 3028, 2977, 2930, 2881, 1735, 1660, 1651, 1526, 1392, 1367, 1243, 1160 cm^{-1}.

(*S*)-2-((*S*)-1-(*tert*-Butoxycarbonyl)pyrrolidine-2-carboxamido)-3-hydoxypropanoic Acid (5c)

White solid, yield 67 %, mp 139.4–140.1 °C; $[\alpha]^{20}_D$ = −106.0 (c = 1.00, CH_3OH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.30 (s, 9H, 3xCH_3), 1.66–1.75 (m, 2H, pro-γ), 1.90 (brs, 2H, pro-β), 3.24–3.37 (m, 2H, pro-δ), 3.71 (brs, 1H, CH_2OH), 3.88 (brs, 1H, CH_2OH), 4.17–4.23 (m, 2H, pro-α and <u>CH</u>CH_2OH), 7.12 (brs, 1H, OH), 7.53 and 7.69 (brs, 1H, NH, rotamers) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 24.3 (pro-γ), 28.4 (3 × CH_3), 30.8 (pro-β), 47.3 (pro-δ), 56.4 (pro-α), 60.2 (<u>C</u>HCH_2OH), 62.3 (CH_2OH), 80.4 ($C(CH_3)_3$), 155.2 (C=O), 173.0 (C=O), 177.8 (C=O) ppm; LC-MS (ESI-QTOF) *m/z* $[M+Na]^+$, found 325.1368. $C_{13}H_{22}N_2O_6$ requires 325.1376; FTIR (ATR) ν 3487, 3275, 3079, 2974, 2932, 1733, 1654, 1540, 1479, 1457, 1281, 1163 cm^{-1}.

(*S*)-*tert*-Butyl 2-(((*S*)-1-(((*S*)-3-hydroxy-1-methoxy-1-oxopropane-2-yl-amino)-1-oxo-3-phenylpropane-2-yl) carbamoyl)pyrrolidine-1-carboxylate (6a)

Colorless oil, yield 68 %, $[\alpha]^{20}_D$ = +26.0 (c = 1.00, CH_3OH);[48] ^{1}H NMR (CD_3OD, 500 MHz) δ 1.29 and 1.46 (s, 9H, 3 × CH_3, rotamers), 1.73–1.80 (m, 3H, 2 × pro-**γ and pro-β), 2.06**–2.16 (m, 1H, pro-β), 2.91–3.04 (m, 1H, $PhCH_2$), 3.19–3.21 (m, 1H, $PhCH_2$), 3.34–3.38 (m, 1H, pro-δ), 3.41 (brs, 1H, pro-δ), 3.73 (s, 3H, OCH_3), 3.77–3.81 (m, 1H, CH_2OH), 3.88–3.89 (m, 1H, CH_2OH), 4.16 (brs, 1H, pro-α), 4.52 (brs, 1H, Phe-CH), 4.73 (brs, 1H, C<u>H</u>CH_2OH), 7.19–7.22 (m, 1H, ArH), 7.26–7.29 (m, 4H, ArH) ppm; LC-MS (ESI-QTOF) *m/z* $[M+H]^+$, found 464.2397. $C_{23}H_{33}N_3O_7$ requires 464.2392; FTIR (ATR) ν 3294, 3065, 3004, 2971, 2953, 2882, 1741, 1650, 1523, 1454, 1523, 1392, 1215, 1160 cm^{-1}.

(*S*)-*tert*-Butyl 2-(((*S*)-1-(2-(butylcarbamoyl)phenylamino)-1-oxo-3-phenylpropane-2-yl)-carbamoylpyrrolidine-1-carboxylate (6b)

White solid, yield 52 %, mp 166.2–166.7 °C; $[\alpha]^{20}_D$ = +32.0 (c = 1.00, CH_3OH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.89 (t, *J* = 6.9 Hz, 3H, CH_3), 1.30–1.37 (m, 12H, 3 × CH_3 ve 3xbutyl-CH_2), 1.48–1.54 (m, 2H, 1 × butyl-CH_2 ve 1 × pro-β), 1.67–1.77 (m, 3H, pro-γ ve pro-β), 3.01 (brs, 1H, $PhCH_2$), 3.19–3.32 (m, 5H, $PhCH_2$, 2 × pro-δ, 2 × $NHCH_2$), 4.15 and 4.42 (brs, 1H, pro-α, rotamers), 4.76–4.80 (m, 1H, Phe-CH), 6.13 (brs, 1H, NH), 6.98–7.01 (m, 1H, ArH), 7.08–7.17 (m, 5H, ArH), 7.33–7.38 (m, 2H, ArH), 8.45 (d, *J*=8.4 Hz, 1H, ArH), 11.36 (brs, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.7 (CH_3), 19.1 (CH_2), 23.5 (CH_2), 27.3 (3xCH_3), 30.4 (pro-γ), 37.2 (pro-β), 38.7 (Phe-CH_2), 45.9 ($NHCH_2$), 54.1 (pro-δ), 58.7

(Phe-CH), 60.0 (pro-α), 79.3 ($C(CH_3)_3$), 120.4 ($C_{aro}H$), 122.0 ($C_{aro}H$), 125.4 ($C_{aro}H$), 125.5 ($C_{aro}H$), 125.7 ($C_{aro}H$), 127.3 ($C_{aro}H$), 128.3 ($C_{aro}H$), 131.2 (C_{aro}), 135.6 (C_{aro}), 137.7 (C_{aro}), 154.8 (C=O), 167.5 (C=O), 168.7 (C=O), 171.1 (C=O) ppm; LC-MS (ESI-QTOF) *m/z* $[M+H]^+$, found 537.3071. $C_{30}H_{40}N_4O_5$ requires 537.3071; FTIR (ATR) ν 3314, 3059, 2928, 2850, 1682, 1625, 1536, 1443, 1393, 1240, 1163 cm^{-1}.

(*S*)-*tert*-Butyl 2-(((*S*)-3-hydroxy-1-(((*S*)-1-methoxy-1-oxo-3-phenylpropane-2-yl)-amino-1-oxopropane-2-yl) carbamoyl)pyrrolidine-1-carboxylate (6c)

Colorless oil, yield 62 %, $[\alpha]^{20}_D$ = −28.0 (c = 1.00, CH_3OH); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.37 (s, 9H, 3xCH_3), 1.76–1.83 (m, 2H, pro-γ), 2.02 (brs, 2H, pro-β), 2.95–3.00 (m, 1H, $PhCH_2$), 3.06–3.10 (m, 1H, $PhCH_2$), 3.32 (brs, 1H, OH), 3.36–3.43 (m, 2H, pro-δ), 3.61 and 3.68 (s, 3H, OCH_3, rotamers), 3.83–3.86 (m, 2H, CH_2OH), 4.11–4.18 (m, 1H, pro-α), 4.37–4.40 (m, 1H, Phe-CH), 4.69–4.73 (m, 1H, C<u>H</u>CH_2OH), 7.06–7.08 (m, 2H, ArH), 7.12–7.15 (m, 1H, ArH), 7.18–7.22 (m, 2H, ArH), 7.28 (brd, *J* = 6.0 Hz, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 23.5 (pro-γ), 27.3 (3 × CH_3), 30.0 (pro-β), 36.6 ($PhCH_2$), 46.2 (pro-δ), 51.5 (OCH_3), 52.6 (pro-α), 53.6 (<u>C</u>HCH_2OH), 59.3 (Phe-CH), 61.6 (CH_2OH), 79.6 ($C(CH_3)_3$), 126.0 ($C_{aro}H$), 127.5 ($C_{aro}H$), 128.1($C_{aro}H$), 135.0 (C_{aro}), 154.5 (C=O), 169.8 (C=O), 170.8 (C=O),171.9 (C=O) ppm; LC-MS (ESI-QTOF) *m/z* $[M+H]^+$, found 464.2392. $C_{23}H_{33}N_3O_7$ requires 464.2397; FTIR (ATR) ν 3303, 3079, 2954, 2930, 1737, 1661, 1655, 1535, 1437, 1206, 1161 cm^{-1}.

(*S*)-Methyl 3-hydroxy-2-((*S*)-3-phenyl-2-((*S*)-pyrrolidine-2-carboxamido)propanamidopropanoate (7a)

White solid, yield 85 %, mp 52 °C; $[\alpha]^{20}_D$ = +120.0 (c = 1.00, CH_3OH); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.42–1.48 (m, 1H, pro-**γ), 1.57**–1.64 (m, 2H, pro-γ and pro-β), 1.97–2.04 (m, 1H, pro-β), 2.73–2.77 (m, 1H, $PhCH_2$), 2.90–2.95 (m, 1H, $PhCH_2$), 2.96–3.01 (m, 1H, pro-δ), 3.22 (dd, *J*=5.5, 14.0 Hz, 1H, pro-δ), 3.58 (brs, 2H, pro-α and OH), 3.73 (s, 3H, OCH_3), 3.83–3.93 (m, 2H, <u>CH</u>$_2$OH), 4.58–4.61 (m, 1H, Phe-CH), 4.70 (brs, 1H, C<u>H</u>CH_2OH), 7.18–7.25 (m, 5H, ArH), 7.61 (d, *J* = 7.5 Hz, 1H, NH), 8.30 (brs, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.8 (pro-γ), 30.5 (pro-β), 37.9 ($PhCH_2$), 47.0 (pro-δ), 52.6 (OCH_3), 54.1 (pro-α), 54.9 (<u>C</u>HCH_2OH), 60.1 (Phe-CH), 62.4 (CH_2OH), 126.9 ($C_{aro}H$), 128.4 (C_{aro} H), 129.3 (C_{aro} H), 136.5 (C_{aro}), 170.8 (C=O), 171.3 (C=O), 175.8 (C=O) ppm; LC-MS (ESI-QTOF) *m/z* $[M+H]^+$, found 364.1869. $C_{18}H_{25}N_3O_5$ requires 364.1872; FTIR (ATR) ν 3272, 3100, 2963, 1660, 1559, 1442, 1299, 1189, 1132 cm^{-1}.

(*S*)-*N*-((*S*)-1-(2-(Butylcarbamoyl)phenylamino-1-oxo-3-phenylpropane-2-yl)pyrrolidine-2-carboxamide (7b)

White solid, yield 72 %, mp 117–118 °C; $[\alpha]^{20}_D$ = −96.0 (c = 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.95 (t, *J* = 7.5 Hz, 3H, CH_3), 1.35–1.42 (m, 2H, butyl-CH_2), 1.44–1.50 (m, 1H, pro-γ), 1.53–1.59 (m, 2H, butyl-CH_2), 1.61–1.67 (m, 2H, pro-γ ve pro-β), 2.02–2.06 (m, 1H, pro-β), 2.80–2.84 (m, 1H, $PhCH_2$), 2.90–2.95 (m, 1H, $PhCH_2$), 3.07–3.11 (m, 1H, pro-δ), 3.28–3.37 (m, 3H, 2 × butyl-CH_2, pro-δ), 3.79–3.82 (m, 1H, pro-α), 4.83–4.87 (m, 1H, Phe-CH), 6.33 (brt, 1H, NH), 7.04–7.07 (m, 1H, ArH), 7.18–7.21 (m, 3H, ArH), 7.25–7.28 (m, 3H, ArH), 7.41–7.44 (m, 2H, ArH), 8.24 (d, *J* = 9.0 Hz, 1H, NH), 8.60 (d, *J* = 8.5 Hz, 1H, NH), 11.52 (brs, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.7 (CH_3), 20.2 (CH_2), 25.7 (CH_2), 30.2 (pro-γ), 31.4 (pro-β), 37.8 (Phe-CH_2), 39.6 ($NHCH_2$), 46.8 (pro-δ), 54.4 (Phe-CH), 60.4 (pro-α), 121.0 ($C_{aro}H$), 121.2 ($C_{aro}H$), 123.0 ($C_{aro}H$), 126.4 ($C_{aro}H$), 126.8 ($C_{aro}H$), 128.4 ($C_{aro}H$), 129.3 ($C_{aro}H$), 132.4 (C_{aro}), 136.9 (C_{aro}), 139.8 (C_{aro}), 168.7 (C=O), 170.1 (C=O), 175.6 (C=O) ppm; LC-MS (ESI-QTOF) *m/z* $[M+H]^+$, found 437.2638. $C_{25}H_{32}N_4O_3$ requires 437.2553; FTIR (ATR) ν 3335, 3244, 3061, 3025, 2955, 2930, 1688, 1661, 1624, 1588, 1490, 1435, 1282, 1185 cm^{-1}.

(*S*)-Metyl 2-((*S*)-3-hydroxy-2-((*S*)-3-pyrrolidine-2-carboxamido)propanamido)-3-phenylpropanoate (7c)

Colorless oil, yield 90 %, $[\alpha]^{20}_D$ = +6.0 (c = 1.00, CH_3OH); ^1H NMR (CD_3OD, 500 MHz) δ 1.86–1.95 (m, 3H, 2 × pro-γ and pro-β), 2.24–2.31 (m, 1H, pro-β), 3.01–3.05 (m, 1H, $PhCH_2$), 3.12–3.20 (m, 3H, $PhCH_2$ and 2 × pro-δ), 3.66 (m, 2H, CH_2OH), 3.70 (s, 3H, OCH_3), 4.01–4.04 (m, 1H, pro-α), 4.47–4.49 (m, 1H, Phe-CH), 4.71–4.74 (m, 1H, C<u>H</u>CH_2OH), 7.20–7.31 (m, 5H, ArH) ppm; ^{13}C NMR (CD_3OD, 125 MHz) δ 26.1 (pro-γ), 31.5 (pro-β), 38.4 ($PhCH_2$), 47.7 (pro-δ), 52.7 (OCH_3), 55.2 (pro-α), 56.4 (<u>C</u>HCH_2OH), 61.4 (Phe-CH), 63.1 (CH_2OH), 128.0 ($C_{aro}H$), 129.5 ($C_{aro}H$), 130.3 ($C_{aro}H$), 137.8 (C_{aro}), 171.8 (C=O), 173.2 (C=O), 174.2 (C=O) ppm; LC-MS (ESI-QTOF) *m/z* $[M+H]^+$, found 364.1868. $C_{18}H_{25}N_3O_5$ requires 364.1872; FTIR (ATR) ν 3340, 2958, 2848, 1666, 1554, 1450, 1191, 1136 cm^{-1}.

General procedure for aldol reaction catalyzed by organocatalyst 7c

The catalyst **7c** (0.10 mmol) and benzoic acid (0.10 mmol) were stirred in water at 0 °C for 10 min. Then, aldehyde (1.00 mmol) and ketone (10.00 mmol) were added, and the reaction mixture was stirred at 0 °C until the reaction completed. After the evaporation of water, the crude products were purified by column chromatography, eluted by EtOAc/hexane mixture. The enantioselectivity was determined by chiral HPLC with a Chiralpak AD and AD-H columns (UV detection set at 254 nm, *i*-PrOH/hexane as eluent).

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Povzetek

Prispevek poroča o sintezi novih di- in triamidnih organokatalizatorjih, pridobljenih iz (L)-prolina, in njihovi uspešni uporabi v neposredni asimetrični aldolni kondenzaciji alifatskih ketonov in aromatskih aldehidov v vodi pri 0 °C v prisotnosti benzojske kisline kot ko-katalizatorja. (S)-metil-2-((S)-3-hidroksi-2-((S)-3-pirolidin-2-karboksamido)propanamido)-3-fenilpropanoat (7c) je kot organokatalizator pri teh reakcijskih pogojih pokazal najboljše rezultate z dobro diastereoselektivnostjo (do 99 %), enantioselektivnostjo (do 98 %) in izkoristkom reakcij (do 91 %).