Accepted Manuscript

Combining prolinamides with 2-pyrrolidinone: Novel organocatalysts for the asymmetric aldol reaction

Ismini Vlasserou, Maria Sfetsa, Dimitrios-Triantafyllos Gerokonstantis, Christoforos G. Kokotos, Panagiota Moutevelis-Minakakis

PII: S0040-4020(18)30327-2

DOI: 10.1016/j.tet.2018.03.054

Reference: TET 29394

To appear in: *Tetrahedron*

Received Date: 18 January 2018

Revised Date: 19 March 2018

Accepted Date: 25 March 2018

Please cite this article as: Vlasserou I, Sfetsa M, Gerokonstantis D-T, Kokotos CG, Moutevelis-Minakakis P, Combining prolinamides with 2-pyrrolidinone: Novel organocatalysts for the asymmetric aldol reaction, *Tetrahedron* (2018), doi: 10.1016/j.tet.2018.03.054.

Graphical Abstract

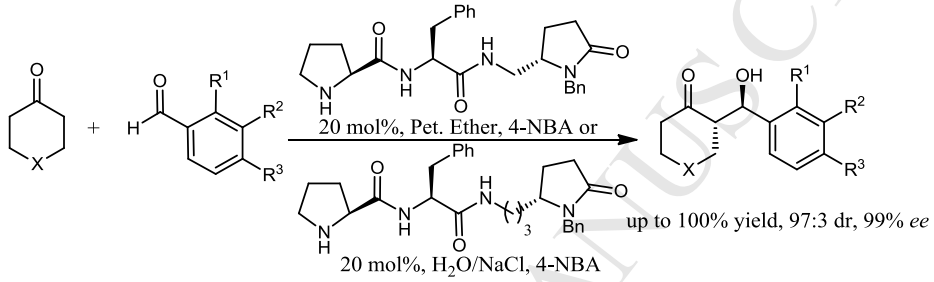
To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Combining Prolinamides with 2-Pyrrolidinone: Novel Organocatalysts for the Asymmetric Aldol Reaction

Leave this area blank for abstract info.

Ismini Vlasserou, Maria Sfetsa, Dimitrios-Triantafyllos Gerokonstantis, Christoforos G. Kokotos,* Panagiota Moutevelis-Minakakis*

Laboratory of Organic Chemistry, Department of Chemistry, University of Athens, Panepistimiopolis 15771, Athens, Greece.



Tetrahedron
journal homepage: www.elsevier.com

Combining Prolinamides with 2-Pyrrolidinone: Novel Organocatalysts for the Asymmetric Aldol Reaction

Ismini Vlasserou,[a] Maria Sfetsa,[a] Dimitrios-Triantafyllos Gerokonstantis,[a] Christoforos G. Kokotos*[a] and Panagiota Moutevelis-Minakakis*[a]

[a] *Laboratory of Organic Chemistry, Department of Chemistry, National and Kapodistrian University of Athens, Panepistimiopolis 15771, Athens, Greece*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Aldol reaction
Organocatalysis
Prolinamides
Water
Dipeptides

ABSTRACT

Peptides and especially prolinamides have been identified as excellent organocatalysts for the aldol reaction. The combination of prolinamides with derivatives bearing the 2-pyrrolidinone scaffold, deriving from pyroglutamic acid, led to the identification of novel organocatalysts for the intermolecular asymmetric aldol reaction. The new hybrids were tested both in organic and aqueous media. Among the compounds tested, **22** afforded the best results in petroleum ether, while **25** afforded the products in brine in high yields and selectivities. Then, various ketones and aldehydes were utilized and the products of the aldol reaction were obtained in high yields (up to 100%) with excellent diastereo- (up to 97:3 *dr*) and enantioselectivities (up to 99% *ee*).

1. Introduction

Since 2000, the year of its rebirth, asymmetric Organocatalysis, the use of small organic molecules as catalysts for the promotion of asymmetric organic transformations, has provided elegant solutions to previously under-developed reactions, complementary reactivities to transition-metal catalysis and biocatalysis and new ways of thinking and solving chemical problems.[1,2] It is often acknowledged that the work of List, Lerner and Barbas on the use of proline as the catalyst for the intermolecular aldol reaction[3] and the work by Macmillan on the use of imidazolidinones as catalysts for cycloadditions[4] had set the first stones on building the field of Organocatalysis, that nowadays is considered a common practice. The enantioselective aldol reaction is among the most commonly employed C-C bond forming reactions in modern asymmetric catalysis, and today is considered a test reaction for novel organocatalysts.[5] Since Organocatalysis' first days, it was evident that proline and proline derivatives have a prime role as catalysts in organocatalytic transformations.[6] Even today, research on the identification of novel organocatalysts is vibrant and it is well accepted that prolinamides containing functionalities able to act as hydrogen bond donors are the most successful class of organocatalysts. Representative examples are shown in Figure 1 (compounds **1**-**7**).[7] It is well accepted that the catalytic power of

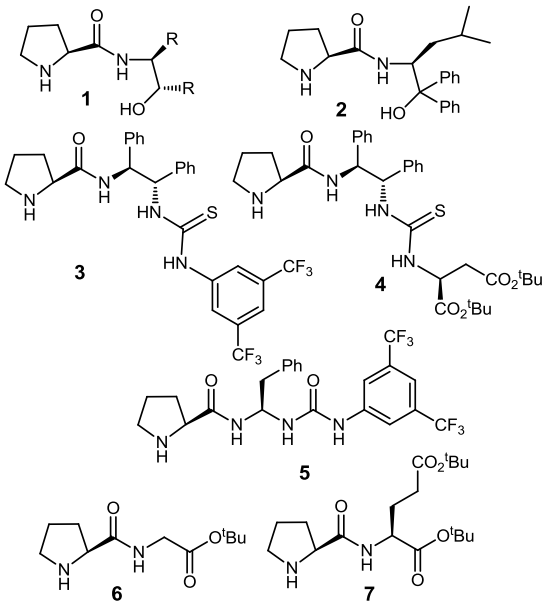


Figure 1. Known prolinamide organocatalysts.

these compounds derives from the secondary amine of the pyrrolidine ring, which can activate carbonyl compounds via

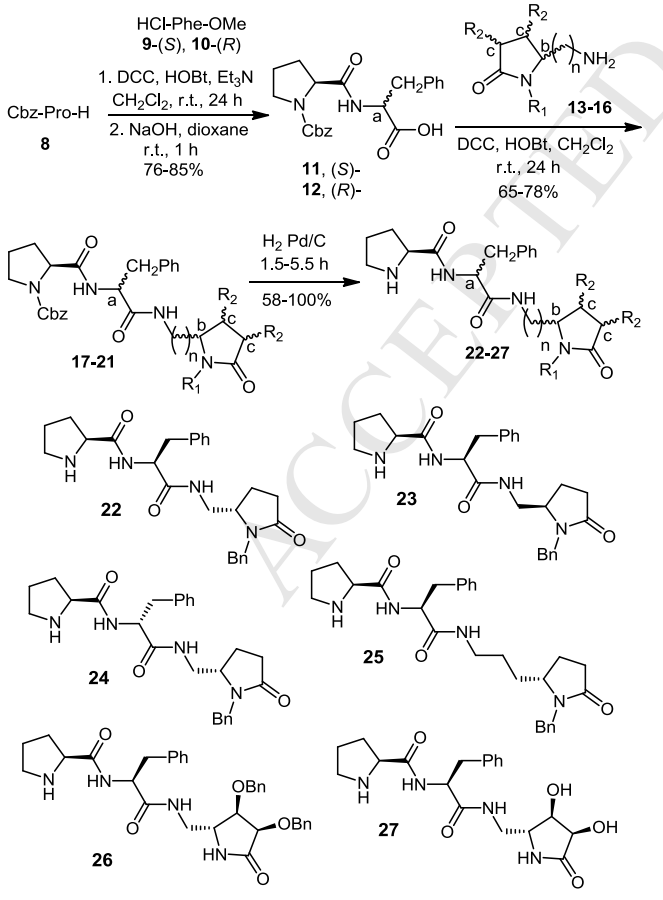
* Corresponding author. Tel.: +30-210-7274484; fax: +30-210-7274761;
e-mail: pminakak@chem.uoa.gr

enamine formation, while the additional hydrogen bonding interaction moieties on the molecules are responsible for the enhanced selectivities observed. For many years, peptides have been explored as potential organocatalysts,[8] unfortunately, low or moderate selectivities have been observed in most cases.[9,10] A very powerful step forward would be the use of water as the solvent, since it will coincide with the principles of Green Chemistry, since water is an abundant, safe and environmentally friendly medium to carry out reactions. Unfortunately, proline and most peptides fail to deliver high selectivities, until the pioneering work of Hayashi and Barbas on the aldol reaction.[11] Then, a number of amino acid derivatives[12] and proline derivatives[7e,13] have been successfully developed for aldol reactions being performed in aqueous media.

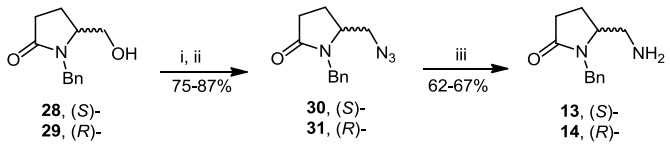
Recently, we have demonstrated that tripeptides of Pro-Phe with a *tert*-butyl ester from an amino acid are excellent organocatalysts for the aldol reaction,[14] while the use of dipeptides can also be succeesful.[7i,7j] We have also attempted to use carbon materials in combination with amines, in order to promote aldol reactions.[15] Having in mind our previous endeavours in Organocatalysis,[16] herein, we describe our efforts to combine the prolinamide efficiency with the 2-pyrrolidinone scaffold.

2. Results and Discussion

(*S*)-Benzyloxycarbonyl protected proline (**8**) was coupled with either (*S*)-methyl phenylalaninate (**9**) or (*R*)-methyl phenylalaninate (**10**) using dicyclohexylcarbodiimide (DCC) as the coupling reagent, in the presence of 1-hydroxybenzotriazole (HOBt).[17] Saponification afforded the, *N*-protected diastereomeric dipeptides, **11** and **12**, respectively. To the resulting dipeptides, a series of amines (**13-16**), derived from

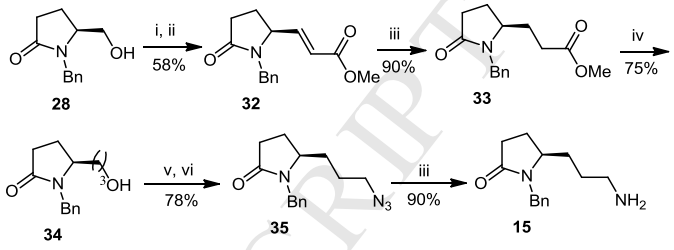


Scheme 1. Synthesis of the organocatalysts **22-27**.



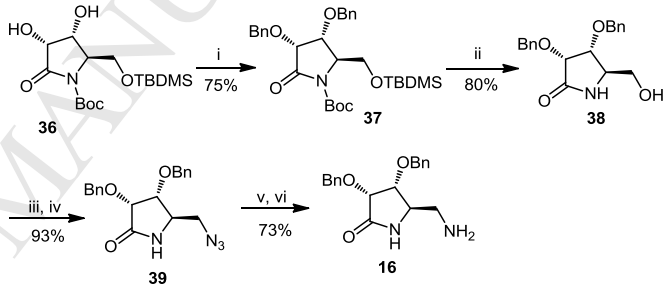
i: $MeSO_2Cl$, Et_3N in CH_2Cl_2; ii: NaN_3, in dry DMF at 55 °C; iii: H_2, Pd/C, r.t., 2-4 h.

Scheme 2. Synthesis of 2-pyrrolidinone amines **13** and **14**.



i: Moffatt oxidation: EDC.HCl, Pyridine, TFA drops in dry toluene, dry DMSO, under Ar. ii: PPh_3=$CHCOOCH_3$ in dry THF, 1 h reflux under Ar. iii: H_2, 10% Pd/C in MeOH, r.t.. iv: $LiBH_4$ in dry THF. v: $MeSO_2Cl$, Et_3N in CH_2Cl_2. vi: NaN_3, in dry DMF at 55 °C.

Scheme 3. Synthesis of 2-pyrrolidinone amine **15**.



i: Ag_2O, BnBr in CH_2Cl_2. ii: 4M HCl in dioxane. iii: $MeSO_2Cl$, Et_3N in CH_2Cl_2 iv: NaN_3, in dry DMF at 55 °C. v: PPh_3 in dry THF. vi: H_2O.

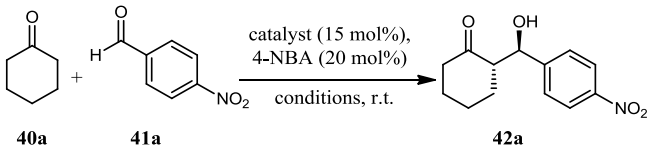
Scheme 4. Synthesis of 2-pyrrolidinone amine **16**.

either (*S*)- or (*R*)- pyroglutamic acid, were added under conventional peptide coupling conditions, affording the protected amides **17-21**. We have previously shown that no epimerization is occurring at this step.[14] Finally, deprotection via catalytic hydrogenation, afforded organocatalysts **22-27** (Scheme 1).

For the synthesis of 2-pyrrolidinone amines **13-16**, 2-pyroglutamic acid was employed (Schemes 2-4). Starting from alcohols **28**-(*S*) and **29**-(*R*),[18] a convenient method that avoids epimerization[19] was selected for the synthesis of the corresponding amines [**13**-(*S*) and **14**-(*R*)]. This synthetic approach combines mesyl ester activation, substitution from an azide and Staudiger reaction (Scheme 2). In order to study the efficiency of the additional hydrogen bonding, deriving from the 2-pyrrolidinone moiety, 2-pyrrolidinone amine **15**, having an extended alkyl chain between the 2-pyrrolidinone and the amine, was synthesized from **28** (Scheme 3). Wittig reaction was followed by hydrogenation and reduction in order to lead to alcohol **34**. Following the same route as before, alcohol **15** was obtained (Scheme 3). Finally, starting from **36**,[20] benzylation afforded compound **37**. Deprotection under acidic conditions led to alcohol **38**. As above, this was selectively transformed to amine **16**.

The synthesized organocatalysts were then evaluated in the aldol

Table 1. Enantioselective aldol reaction of cyclohexanone with 4-nitrobenzaldehyde using compounds **22-27** as catalysts.[a]



40a **41a** **42a**

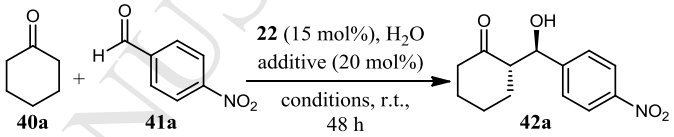
Entry	Catalyst	Conditions	Yield (%)[b]	dr[c]	ee (%)[d]
1	**22**	Pet. Ether, H_2O, 48 h	92	93:7	93
2	**22**	brine, 24 h	96	91:9	88
3	**23**	Pet. Ether, H_2O, 48 h	100	88:12	81
4	**23**	brine, 24 h	100	89:11	86
5	**24**	Pet. Ether, H_2O, 24 h	100	91:9	90
6	**24**	brine, 24 h	100	88:12	86
7	**25**	Pet. Ether, H_2O, 48 h	50	89:11	90
8	**25**	brine, 48 h	100	93:7	90
9	**26**	Pet. Ether, H_2O, 24 h	100	84:16	77
10	**26**	brine, 24 h	100	82:17	76
11	**27**	Pet. Ether, H_2O, 72 h	0	-	-
12	**27**	brine, 72 h	43	93:7	91

[a] Catalyst (0.014 mmol) in solvent (1.0 mL) (Pet. Ether with 1 drop of water or brine), additive (0.018 mmol), aldehyde (0.09 mmol) and cyclohexanone (0.90 mmol). [b] Yield determined by ^{1}H NMR. [c] The diastereomeric ratio (*dr*) *anti:syn* was determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [d] The enantiomeric excess (*ee*) for the *anti* diastereomer was determined by chiral HPLC. 4-NBA: 4-nitrobenzoic acid.

reaction between cyclohexanone and 4-nitrobenzaldehyde both in organic and aqueous medium (Table 1). Initially, peptide **22**, based on Pro-Phe and 2-pyrrolidinone was tested, leading to high yields in both reaction conditions (organic solvent of aqueous conditions) with good diastereoselectivity and enantioselectivity (entries 1 and 2, Table 1). Comparing the catalytic activity of **22** with the corresponding dipeptide Pro-Phe or H-Pro-Phe-^{t}Bu,[7i] there is a significant increase on the catalytic activity that can be attributed to the additional 2-pyrrolidinone ring. When the development of a chiral catalyst requires the presence of more than one chiral centers, matched and mis-matched effects might be present. A mis-matched effect between Pro-Phe and the chiral center of 2-pyrrolidinone was observed, when catalyst **23** was tested (entries 3 and 4, Table 1). This effect was observed in lesser extent, when the chiral center on the phenylalaline residue was altered in catalyst **24** (entries 5 and 6, Table 1). The distance on the linker between the Pro-Phe dipeptide backbone with 2-pyrrolidinone, (catalyst **25)** was then studied (entries 7 and 8, Table 1). In the latter case, high diastereoselectivity and enantioselectivity were observed. These results verify the hypothesis that if the catalyst has additional hydrogen bonding sites, it recognizes better the electrophile in the transition state leading to higher levels of stereocontrol. In an effort to study the substitution on the 2-pyrrolidinone moiety, catalysts **26** and **27** were tested (entries 9-12, Table 1). Unfortunately, in all cases lower yields and selectivities were obtained. As expected, catalyst **27** possesing multiple hydrogen bonding sites, worked in aqueous conditions, however, the conversion was low.

After identifying catalyst **25** as a potent catalyst in brine, we questioned whether we could find improved reaction conditions for catalyst **22** in organic medium, since it was the catalyst that provided the best enantioselectivity. Thus, a variety of solvents and reaction conditions were tested with catalyst **22** (Table 2). Initially, a number of organic solvents were utilized (entries 1-11, Table 2). It seems that a small quantity of water is beneficial for the catalysis, probably through facilitating the hydrolysis of the product from the catalyst. Petroleum ether proved to be the best solvent, along with diethyl ether and acetonitrile, leading to high yield and selectivities of the product. Lowering the reaction temperature, proved that petroleum ether afforded the best results

Table 2. Enantioselective aldol reaction of cyclohexanone with 4-nitrobenzaldehyde using catalyst **22**.[a]

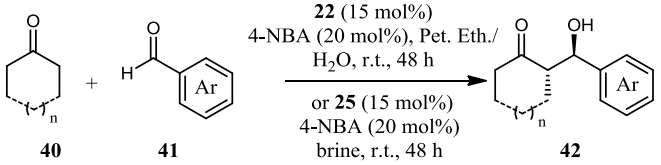


40a **41a** **42a**

Entry	Conditions	Yield (%)[b]	dr[c]	ee (%)[d]
1[e]	THF, 4-NBA	98	85:15	86
2	THF, 4-NBA	100	95:5	88
3	toluene, 4-NBA	93	90:10	92
4	AcOEt, 4-NBA	98	96:4	92
5	CH_2Cl_2, 4-NBA	84	82:18	91
6	Et_2O, 4-NBA	96	95:5	93
7[f]	brine, 4-NBA	96	91:9	88
8	MeCN, 4-NBA	86	93:7	94
9	MeOH, 4-NBA	55	88:12	84
10	Pet. Eth., 4-NBA	92	93:7	93
11	$CHCl_3$, 4-NBA	89	89:11	91
12[g]	brine, 4-NBA	95	84:16	85
13[g]	Et_2O, 4-NBA	88	97:3	94
14[e,g]	MeCN, 4-NBA	100	90:10	91
15[g]	Pet. Eth., 4-NBA	100	95:5	>99
16[h,g]	Pet. Eth., 4-NBA	0	-	-
17[i,g]	Pet. Eth., 4-NBA	0	-	-
18[j]	Pet. Eth., 4-NBA	62	88:12	89
19	Pet. Eth., AcOH	traces	-	-
20	Pet. Eth., PhCOOH	100	83:17	>99
21	Pet. Eth., TsOH	32	65:35	93
22	Pet. Eth., Z-Phe-OH	0	-	-
23	Pet. Eth., 4-FPO	51	70:30	96

[a] Catalyst (0.014 mmol) in solvent (1.0 mL), additive (0.018 mmol), H_2O (0.1 mL), aldehyde (0.09 mmol) and cyclohexanone (0.90 mmol). [b] Yield determined by ^{1}H NMR. [c] The diastereomeric ratio (*dr*) *anti:syn* was determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [d] The enantiomeric excess (*ee*) was determined by chiral HPLC. [e] No H_2O. [f] Reaction time 24 h. [g] 0 ^{o}C. [h] 10 mol% catalyst. [i] 10 mol% catalyst, 15 mol% 4-NBA. [j] 2 equiv. of cyclohexanone. 4-NBA: 4-nitrobenzoic acid. AcOH: acetic acid. TsOH: *p*-toluenesulfonic acid. 4-FPO: 4-fluorophenol.

Table 3. Enantioselective aldol reaction between ketones and aldehydes using catalyst **22** and **25**.[a]



40 **41** **42**

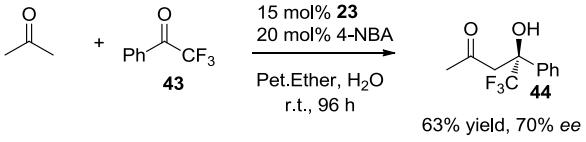
Entry	Ketone	Ar/ Conditions	Yield (%)[b]	dr[c]	ee (%)[d]
1		4-$NO_2C_6H_4$/A	92(**42a**)	93:7	93
2		4-$NO_2C_6H_4$/B	100(**42a**)	93:7	90
3		3-$NO_2C_6H_4$/A	100(**42b**)	81:19	89
4[e]		3-$NO_2C_6H_4$/B	97(**42b**)	93:7	92
5		2-$NO_2C_6H_4$/A	100(**42c**)	84:16	97
6[e]		2-$NO_2C_6H_4$/B	95(**42c**)	93:7	96
7[e]		3-CNC_6H_4/A	100(**42d**)	76:24	86
8[f]		3-CNC_6H_4/B	94(**42d**)	83:17	70
9[f]		4-$CF_3C_6H_4$/A	94(**42e**)	83:17	92
10[f]		4-$CF_3C_6H_4$/B	n.r.	-	-
11[f]		4-FC_6H_4/A	20(**42f**)	83:17	92
12[f]		4-FC_6H_4/B	89(**42f**)	88:12	92
13[e]		4-ClC_6H_4/A	90(**42g**)	95:5	70
14[g]		4-ClC_6H_4/B	92(**42g**)	88:12	90
15[e]		2-ClC_6H_4/A	89(**42h**)	82:18	74
16[e]		2-ClC_6H_4/B	100(**42h**)	79:21	88
17[f]		4-BrC_6H_4/A	85(**42i**)	97:3	88
18[g]		4-BrC_6H_4/B	100(**42i**)	77:23	86
19[f]		C_6H_5/A	69(**42j**)	97:3	83
20[g]		C_6H_5/B	71(**42j**)	86:14	99
21[h]		4-pyridinyl/A	100(**42k**)	94:6	76
22		4-pyridinyl /B	100(**42k**)	97:3	95
23[f]		4-$NO_2C_6H_4$/A	97(**42l**)	75:25	78
24[g]		4-$NO_2C_6H_4$/B	84(**42l**)	89:11	73
25[g]		4-$NO_2C_6H_4$/A	100(**42m**)	84:16	83
26[g]		4-$NO_2C_6H_4$/B	100(**42m**)	85:15	90
27[e]		4-$NO_2C_6H_4$/A	100(**42n**)	86:14	90
28[e]		4-$NO_2C_6H_4$/B	n.r.	-	-
29[f]		4-$NO_2C_6H_4$/A	92(**42o**)	71:29	37
30[e]		4-$NO_2C_6H_4$/B	100(**42o**)	78:22	90
31[e]		4-$NO_2C_6H_4$/A	100(**42p**)	40:60	76
32[e]		4-$NO_2C_6H_4$/B	100(**42p**)	32:68	36
33[h]		4-$NO_2C_6H_4$/A	58(**42q**)	-	89
34[e]		4-$NO_2C_6H_4$/B	n.r.	-	-

[a] Conditions **A**: **22** in Pet. Eth./H_2O Conditions **B**: **25** in brine. [b] Isolated yield. [c] The diastereomeric ratio (dr) *anti:syn* was determined by ^1H NMR spectroscopy of the crude reaction mixture. [d] The enantiomeric excess (*ee*) for the major isomer was determined by chiral HPLC. [e] Reaction time 72 h. [f] Reaction time 96 h. [g] Reaction time 120 h. [h] Reaction time 24 h.

(entries 12-15, Table 2). Among other reaction conditions, none proved better (entries 16-18, Table 2). Lowering the equivalents of ketone or the catalyst loading had a dentrimental effect on the reaction (entries 16-18, Table 2). Then, a variety of acid additives were employed, since it is known that these organocatalytic reactions are sometimes sensitive to acid counterparts and fine tuning is required (entries 19-23, Table 2). Only carboxylic acids that have similar pKa with 4-nitrobenzoic acid led to similar levels of reactivity (PhCOOH, entry 20, Table 2).

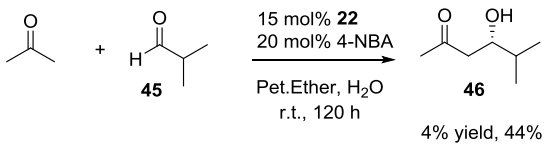
We then turned our attention in exploring the substrate scope of the enantioselective aldol reaction by employing either catalyst **22** in petroleum ether or catalyst **25** in aqueous environment (Table 3). A variety of substituted aromatic aldehydes can be employed with cyclohexanone leading to products from good to excellent yields and selectivities (entries 1-22, Table 3). Electron-withdrawing groups at any position of the aryl moiety led to good to excellent results, while the use of aromatic aldehydes substituted with halogens led from moderate to high yields and high to excellent selectivities. Benzaldehyde and heteroaromatic-substituted aldehydes proved more problematic (entries 19-22, Table 3). Tetrahydropyran-4-one and tetrahydrothiopyran-4-one required longer reaction time (entries 23-26, Table 3). Disubstituted cyclohexanone at the 4-position required prolonged reaction time, and only catalyst **22** delivered the product in good yield and high enantioselectivity (entries 27 and 28, Table 3). The desymmetrization of ketones is also possible,[6g,6i] since 4-methyl cyclohexanone delivered the product in high yield and with excellent selectivities in the case where catalyst **25** was employed (entries 29 vs 30, Table 3). Cyclopentanone was also utilized with some success, since very low diastereoselectivities were observed (entries 31 and 32, Table 3). Moreover, in order to broaden the scope of this methodology, we investigated the reaction of acetone with 4-nitrobenzaldehyde (entries 33 and 34, Table 3).

In an effort to further expand the possibilities of the catalytic acitivity, a very difficult aldol reaction between acetone and trifluoroacetophenone was tested (Scheme 5).[21] The desired

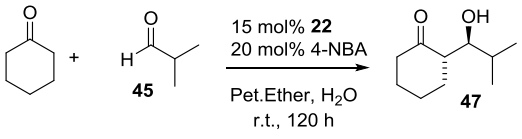


63% yield, 70% *ee*

Scheme 5. Expanding the catalytic activity of **23**.



4% yield, 44% *ee*



10% yield, >98:2 *dr*, 97% *ee*

Scheme 6. Study of the catalytic activity of **22** with aliphatic aldehydes.

product **44** was isolated in moderate yield with good enantioselectivity. In an effort to further expand the reaction, isobutyraldehyde (**45**) was employed. When **45** reacted with acetone, **46** was obtained in very low yield and enantioselectivity, while when reacted with cyclohexanone, **47** was obtained in low yield, but excellent diastereoselectivity and enantioselectivity (Scheme 6).

We then turned our attention in revocery and reuse of catalyst **22** for the reaction between cyclohexanone and 4-nitrobenzaldehyde. The catalyst was recovered succesfully (73%), and then its activity was studied in an additional catalytic cycle. The expected yield of the product remained high, unfortunately, the enantioselectivity dropped (yield 82%, *dr* 81:19, *ee* 72%).

A plausible transition-state model is proposed in Figure 2. The secondary amine of the pyrrolidine ring activates the ketone through the formation of an enamine intermediate. The electrophile is activated through a double hydrogen bonding network consisting of the two amide protons of the catalyst, while the bulkiness of the moiety of 2-pyrrolidinone ensures the single orientation of the aldehyde.

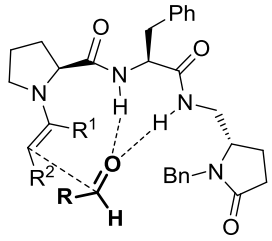


Figure 2. Proposed transition-state model for the aldol reaction.

In conclusion, the synthesis of peptides based on Pro-Phe and 2-pyrrolidinone moiety was carried out. Previously, we had shown that dipeptides tripeptides based on proline having at their *C*-terminus *tert*-butyl esters of amino acids provided excellent organocatalysts for the aldol reaction. In this study, we have shown that the addition of the 2-pyrrolidinone moiety affords catalysts that have a better catalytic behavior. Matched and mis-matched effects were observed. When catalyst **22** was utilized, the aldol products were obtained in good to excellent yields and selectivities in wet petroleum ether. When catalyst **25** was employed, the aldol product was obtained in similar high yields and selectivities but in brine. It is worth mentioning that both catalysts work at room temperature and both have distinct advantages compared to proline, since proline's low solubility in organic solvents and low selectivity obtained in aqueous media, can be bypassed with these two catalysts. The catalytic activity of these catalysts was demonstrated not only to aldol reaction between ketones and aromatic aldehydes, but also in aldol reactions of ketone with ketones.

3. Experimental section

3.1. General Information

Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of products was accomplished using column chromatography on Merck Kieselgel 60 F_{254} 230-400 mesh. Thin-layer chromatography (TLC) was performed on aluminum backed silica plates (0.2 mm, 60 F_{254}). Visualization of the developed chromatogram was performed by fluorescence quenching using ninhydrin stain. Melting points were determined on a Büchi 530 hot stage apparatus. ^{1}H, ^{19}F and ^{13}C NMR spectra were recorded on Varian Mercury 200 MHz and are internally referenced to residual solvent signals ($CDCl_3$, CD_3OD and DMSO-d_6). Data for ^{1}H NMR spectroscopy are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet, br s = broad signal), integration, coupling constant and assignment. Wherever rotamers exist, are presented in brankets. Diastereomeric ratios were determined by ^{1}H NMR spectroscopy (200 MHz). Data for ^{13}C NMR are reported in terms of chemical shift (δ ppm). Wherever rotamers exist, are cited in parenthesis. ^{19}F spectra were recorded on Varian Mercury (188 MHz) and are internally referenced to trifluoroacetic acid. Mass spectra were recorded on a Finnigan Surveyor MSQ Plus, with only molecular ions and major peaks being reported with intensities quoted as percentages of the base peak. HRMS spectra were recorded on Thermo® Orbitrap Velos spectrometer. High Performance Liquid Chromatography (HPLC) was used to determine enantiomeric excesses and was performed on an Agilent 1100 Series apparatus using Chiralpak® AD-H, OD-H and AS-H columns. Optical rotations were measured on a Perkin Elmer 343 polarimeter. The *syn*:*anti* ratio of the crude reaction mixture was assigned by comparison to literature data.[7h] The configuration of the products has been assigned by comparison to literature data.[7h] Data for known compounds match literature data. All new compounds were assigned by analogy.

3.2. General procedure for the synthesis of the catalysts

*Synthesis of amines **13-16***

*3.2.1. (S)-5-(Aminomethyl)-1-benzylpyrrolidin-2-one (**13**)*

To a stirred solution of alcohol **28**[18] (0.66 g, 3.22 mmol) in CH_2Cl_2 (3 mL) at 0 °C, Et_3N (0.67 mL, 4.83 mmol) and $MeSO_2Cl$ (0.38 mL, 4.83 mmol) were added. The reaction mixture was left stirring at 0 °C for 30 min, at room temperature for 30 min, and then, the solvent was evaporated under reduced pressure. The crude mixture was dissolved in AcOEt (10 mL) and washed with aq. H_2SO_4 (5%, 10 mL), H_2O (10 mL), aq. $NaHCO_3$ (5%, 10 mL) and brine (10 mL). After evaporation of the solvent, the crude methanosulfonic ester was dissolved in dry DMF (6 mL) and NaN_3 (0.63 g, 9.66 mmol) was added. The reaction mixture was left stirring at 55 °C overnight. After evaporation of the solvent, the residue was dissolved in H_2O (10 mL) and extracted with Et_2O (3 x 5 mL). The combined organic layers were washed with H_2O (3 x 10 mL) and the solvent was evaporated. Purification of the crude azide **30** was achieved using column chromatography eluting with pet.ether/EtOAc (40:60). Colorless oil, 645 mg, 87% yield; R_f (AcOEt/pet. ether 6:4) 0.40; $[\alpha]_D$ + 36.2 (c = 1.0, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.34-7.18 (5H, m, ArH), 4.88 (1H, d, *J* = 15.2 Hz, NC*H*HPh), 4.07 (1H, d, *J* = 15.2 Hz, NC*H*HPh), 3.59-3.49 (1H, m, NCH), 3.41(1H, dd, *J* = 12.8 and 4.4 Hz, C*H*HN_3), 3.27 (1H, dd, *J* = 12.8 and 3.6Hz, C*H*HN_3), 2.63-2.26 (2H, m, $COCH_2$), 2.12-1.97 (1H, m, C*H*H), 1.88-1.72 (1H, m, C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 175.2, 136.3, 128.7, 127.8, 127.6, 56.1, 52.9, 44.5, 29.7, 22.0. **MS (ESI)** *m/z* (%) 231 (100) ($[M+H]^+$).

To a stirred solution of azide **30** (0.41 g, 1.78 mmol) in MeOH (10 mL), 10% Pd/C (10 mol%) was added and the reaction mixture was left stirring at room temperature for 2.5 h under hydrogen atmosphere. After filtration through Celite, the solvent was evaporated to afford the crude product. Purification of the

desired amine **13** was achieved using column chromatography eluting with $CHCl_3$/MeOH (80:20). Colorless oil; 244 mg; 67% yield; R_f ($CHCl_3$/MeOH 8:2) 0.42; $[\alpha]_D$ + 25.7 (*c* = 1.0, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.29-7.26 (5H, m, ArH), 4.86 (1H, d, *J* = 15.0 Hz, C*H*HPh), 4.12 (1H, d, *J* = 15.0 Hz, CH*H*Ph), 3.53-3.47 (1H, m, NCH), 2.87 (1H, dd, *J* = 12.4 and 5.4 Hz, C*H*HNH$_2$), 2.74 (1H, dd, *J* = 12.4 and 1.8 Hz, CH*H*NH$_2$), 2.61-2.32 (2H, m, COCH$_2$), 2.17-1.83 (2H, m, CH$_2$), 1.54 (2H, br s, NH$_2$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 175.6, 136.6, 128.5, 127.7, 127.3, 58.8, 44.4, 42.9, 30.1, 21.3; **MS (ESI)** *m/z* (%) 205 (100) ([M+H]$^+$); HRMS exact mass calculated for [M+H]$^+$ ($C_{12}H_{17}N_2O$) requires m/z 205.1335, found m/z 205.1344.

*3.2.2. (R)-1-benzyl-5-(hydroxymethyl)pyrrolidin-2-one (**29**)*

Methyl (*R*)-pyroglutamate (4.50 g, 31.44 mmol) was dissolved in dry THF (30 mL), followed by the addition of benzylbromide (4.1 mL, 34.43 mmol). The reaction mixture was cooled at 0 °C and NaH (60% in paraffin oil, 1.89 g, 47.16 mmol) was added in portions. The stirring was continued for 30 min at 0 °C and 4 h at room temperature. The reaction was quenched by the addition of saturated solution of NH_4Cl (10 mL), the organic solvent was evaporated and the residue was dissolved in ethyl acetate (30 mL). The organic layer was washed with brine (30 mL) and the solvent was evaporated to afford the crude ester. Purification was achieved using column chromatography eluting with pet. ether/EtOAc (40:60). Colorless oil; 4.99 g; 68% yield; R_f (AcOEt/pet. ether 1:1) 0.30; $[\alpha]_D$ -2.2 (*c* = 0.9, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38-7.16 (5H, m, ArH), 4.99 (1H, d, *J* = 15.2 Hz, C*H*HPh), 4.02-3.94 (2H, m, CH*H*Ph & NCH), 3.64 (3H, s, OCH$_3$), 2.60-1.96 (4H, m, 2 x CH$_2$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 175.0, 172.2, 135.7, 128.7, 128.4, 127.7, 58.6, 52.3, 45.5, 29.5, 22.7.

In a two necked flask, $LiBH_4$ (0.26 g, 11.68 mmol) was suspended in dry THF (6 mL) under argon at room temperature. A solution of the above mentioned (*R*)-methyl 1-benzyl-5-oxopyrrolidine-2-carboxylate (2.72 g, 11.68 mmol) in dry THF (5 mL) was added dropwise. The reaction was completed within 1 h and it was quenched by the addition of a 20% solution of AcOH at 0 °C, until the production of the gas was ceased. The excess of acetic acid was neutralized by the addition of a small quantity of Na_2CO_3. The organic solvent was evaporated under reduced pressure and the residue was dissolved in EtOAc (30 mL). The organic phase was washed with brine (30 mL) and the solvent was evaporated to afford the desired alcohol **29** as a white solid; 1.75 g; 73% yield; mp 78-80 °C; R_f ($CHCl_3$/MeOH 9:1) 0.43; $[\alpha]_D$ -106.1 (*c* = 1.0, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$) *δ* 7.36-7.26 (5H, m, ArH), 5.00 (1H, d, *J* = 16.0 Hz, NC*H*HPh), 4.11 (1H, d, *J* = 16.0 Hz, NCH*H*Ph), 3.83-3.78 (1H, m, NC*H*), 3.52-3.49 (2H, m, C*H*$_2$OH), 2.65-2.28 (2H, m, COCH$_2$), 2.07-1.96 (2H, m, CH$_2$); ^{13}C NMR (50 MHz, $CDCl_3$) *δ* 176.3, 136.5, 128.7, 127.9, 127.5, 61.9, 58.6, 44.3, 30.6, 21.0. MS (ESI) *m/z* (%) 206 (100) ([M+H]$^+$).

*3.2.3. (R)-5-(Aminomethyl)-1-benzylpyrrolidin-2-one (**14**)*

Same procedure as above for the synthesis of the azide **30**, but utilizing alcohol **29** (0.66 g 3.22 mmol). The azide **31** was obtained as a colorless oil; 556 mg, 75% yield; R_f (AcOEt/pet. ether 6:4) 0.38; $[\alpha]_D$ -35.8 (*c* = 1.0, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$) *δ* 7.32.-7.18 (5H, m, ArH), 4.87 (1H, d, *J* = 16.0 Hz, C*H*HPh), 4.09 (1H, d, *J* = 16.0 Hz, CH*H*Ph), 3.57-3.48 (1H, m, NCH), 3.40 (1H, dd, *J* = 12.4 and 4.1 Hz, C*H*HN$_3$), 3.26 (1H, dd, *J* = 12.4 and 3.4 Hz, CH*H*N$_3$), 2.62-2.26 (m, 2H, COCH$_2$), 2.06-2.01 (m, 1H, C*H*H), 1.87-1.71 (m, 1H, CH*H*); ^{13}C NMR (50 MHz, $CDCl_3$) *δ* 175.1, 136.2, 128.6, 127.6, 127.5, 56.0, 52.8, 44.4, 29.6, 21.9; **MS (ESI)** *m/z* (%) 231 (100) ([M+H]$^+$).

The desired amine **14**, enantiomer of amine **13**, was obtained following the same procedure as above, but starting from azide **31** (0.41 g, 1.78 mmol) Colorless oil; 225 mg, 62% yield; R_f ($CHCl_3$/MeOH 8:2) 0.39; $[\alpha]_D$ -25.0 (*c* = 1.0, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$) *δ* 7.30-7.18 (5H, m, ArH), 4.80 (1H, d, *J* = 16.0 Hz, C*H*HPh), 4.07 (1H, d, *J* = 16.0 Hz, CH*H*Ph), 3.47-3.43 (1H, m, NCH), 2.87 (1H, dd, *J* = 12.1 and 5.5Hz, C*H*HNH$_2$), 2.74 (1H, dd, *J* = 12.1 and 1.6 Hz, CH*H*NH$_2$), 2.51-2.35 (2H, m, COCH$_2$), 2.12-1.80 (2H, m, CH$_2$), 1.52 (2H, br s, NH$_2$); ^{13}C NMR (50 MHz, $CDCl_3$) *δ* 175.4, 136.3, 128.3, 127.4, 127.1, 58.3, 44.1, 42.5, 29.9, 21.0; **MS (ESI)** *m/z* (%) 205 (100) ([M+H]$^+$); HRMS exact mass calculated for [M+H]$^+$ ($C_{12}H_{17}N_2O$) requires m/z 205.1335, found m/z 205.1342.

*3.2.4. Methyl (S, E)-3-(1-benzyl-5-oxopyrrolodin-2-yl)acrylate (**32**)*

To a stirred solution of alcohol **28** (0.60 g, 2.92 mmol) in a mixture of dry toluene and dry DMSO 2:1 (3.5 mL), EDC.HCl (1.46 g, 7.62 mmol) was added followed by the dropwise addition of dry pyridine (0.66 mL, 8.18 mmol) and TFA (90 μL, 1.17 mmol) under argon. After stirring at room temperature for 2 h the reaction was quenched by the addition of $CHCl_3$ (20 mL) and the solution was washed with brine (10 mL) and H_2O (10 mL). The solvent was evaporated and the resulting crude aldehyde was subjected to Wittig reaction without further purification. More specifically, it was dissolved in dry THF (5 mL), methyl (triphenylphosphoranylidene)acetate (0.97 g, 2.92 mmol) was added and the mixture was refluxed under argon for 1 h. The reaction was quenched by the addition of saturated solution of NH_4Cl (1 mL) and the solvent was evaporated. The residue, dissolved in Et_2O (30 mL), was successively washed with saturated solution of NH_4Cl (5 mL), brine (10 mL) and H_2O (10 mL). After evaporation of the solvent the crude alkene was purified using column chromatography eluting with AcOEt. Yellowish oil; 0.44 g, 58% yield; R_f (AcOEt) 0.50; $[\alpha]_D$ +25.4 (c = 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.29-7.13 (5H, m, ArH), 6.69 (1H, dd, *J* = 15.6 and 8.2 Hz, =CH), 5.83 (1H, d, *J* = 15.6 Hz, =CHCO), 5.02 (1H, d, *J* = 14.8 Hz, C*H*HPh), 4.04-3.94 (1H, m, NCH), 3.79-3.74 (4H, m, CH*H*Ph & OCH$_3$), 2.52-2.35 (2H, m, COCH$_2$), 2.24-2.13 (1H, m, C*H*H), 1.87-1.73 (1H, m, CH*H*); ^{13}C NMR (50 MHZ, $CDCl_3$) *δ* 174.9, 166.1, 146.3, 136.2, 128.8, 128.4, 127.8, 123.2, 58.0, 52.0, 44.7, 29.7, 24.7; MS (ESI) *m/z* (%) 260 (100) ([M+H]$^+$).

*3.2.5. (R)-1-Benzyl-5-(3-hydroxypropyl)pyrrolidin-2-one (**34**)*

To a stirred solution of alkene **32** (0.44 g, 1.70 mmol) in MeOH (5 mL), 10% Pd/C (10 mol%) was added and the reaction mixture was left stirring at room temperature, overnight. After filtration through Celite, the solvent was evaporated to afford the desired product as colorless oil.

To a two necked flask, $LiBH_4$ (56 mg, 2.57 mmol) was suspended in dry THF (8 mL) under argon at room temperature. A solution of compound **33** (0.40 g, 1.53 mmol) in dry THF (2 mL) was added dropwise and the reaction mixture was stirred for 10 h. The reaction was quenched by the addition of a 20% aq. solution of AcOH at 0 °C until gas production was ceased. The excess of acetic acid was neutralized by the addition of a small quantity of Na_2CO_3. The solvent was evaporated and the residue was dissolved in AcOEt (15 mL). The organic phase was washed

with brine (8 mL) and H_2O (8 mL) and the solvent was evaporated. The residue was purified with column chromatography eluting with AcOEt and the product was obtained as a yellowish oil, 268 mg, 75% yield; R_f (AcOEt) 0.22; $[\alpha]_D$ +38.6 (c = 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.34-7.19 (5H, m, ArH), 4.95 (1H, d, *J* = 15.2 Hz, NC*H*HPh), 3.95 (1H, d, *J* = 15.2 Hz, NCH*H*Ph), 3.71-3.36 (3H, m, CH_2OH & NCH), 2.54-1.99 (4H, m, 2 x CH_2), 1.76-1.36 (4H, m, 2 x CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 175.4, 136.7, 128.7, 128.0, 127.6, 62.3, 56.9, 44.2, 30.3, 29.1, 27.6, 23.9; **MS (ESI)** *m/z* (%) 234 (100) ($[M+H]^+$).

*3.2.6. (R)-5-(3-Aminopropyl)-1-benzylpyrrolidin-2-one (**15**)*

Same procedure as above utilizing alcohol **34**. Colorless oil; 130 mg, 90% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.29-7.16 (5H, m, ArH), 4.91 (1H, d, *J* = 15.2 Hz, NC*H*HPh), 3.93 (1H, d, *J* = 15.2 Hz, NCH*H*Ph), 3.50-3.39 (1H, m, NCH), 2.71 (2H, br s, NH_2), 2.48-2.41 (2H, m, CH_2NH$_2$) , 2.37-2.14 (2H, m, COCH_2), 2.10-1.96 (1H, m, C*H*H), 1.72-1.55 (2H, m, 2 x CH*H*), 1.41-1.21 (3H, m, 3 x CH*H*); ^{13}C NMR (50 MHz, $CDCl_3$) δ 175.2, 136.7, 128.7, 127.9, 127.5, 56.8, 49.5, 44.2, 30.5, 30.3, 24.6, 23.8; **MS (ESI)** *m/z* (%) 233.22 (35) ($[M+H]^+$); HRMS exact mass calculated for $[M+H]^+$ ($C_{14}H_{21}N_2O$) requires m/z 233.1648, found m/z 233.1654.

*3.2.7. tert-Butyl (2R,3R,4R)-3,4-bis(benzyloxy)-2-(((tert-butyldimethylsilyl)oxy)methyl)-5-oxopyrrolidine-1-carboxylate (**37**)*

To a stirred solution of alcohol **36**[20] (160 mg, 0.44 mmol) in CH_2Cl_2 (3 mL) freshly prepared Ag_2O[22] (0.27 g, 1.19 mmol) was added under argon, followed by the addition of benzylbromide (157 µL, 1.32 mmol) at 0 °C. The reaction mixture was left stirring at room temperature overnight. After filtration through Celite, the solvent was evaporated and the crude residue was purified using column chromatography eluting with pet.ether/AcOEt (70:30). Colorless oil, 179 mg, 75% yield; R_f (AcOEt/pet. ether 2:8) 0.40; $[\alpha]_D$ + 16.2 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.41-7.26 (10H, m, ArH), 5.01 (1H, d, *J* = 12.4 Hz, OC*H*HPh), 4.83 (1H, d, *J* = 12.4 Hz, OCH*H*Ph), 4.78 (1H, d, *J* = 12.0 Hz, OC*H*HPh), 4.65 (1H, d, *J* = 12.0 Hz, OCH*H*Ph), 4.41 (1H, d, *J* = 5.4 Hz, OCH), 4.10 (1H, m, OCH), 4.05 (1H, d, *J* = 5.4 Hz, NCH), 3.82 (1H, dd, *J* = 11.0 and 3.6 Hz, C*H*HOSi), 3.66 (1H, dd, *J* = 11.0 and 2.2 Hz, CH*H*OSi), 1.52 [9H, s, OC(CH_3)$_3$], 0.75 [9H, s, SiC(CH_3)$_3$], -0.09 (6H, s, 2 x CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.4, 150.1, 137.7, 137.5, 128.4, 127.7, 76.7, 75.0, 72.6, 62.4, 61.7, 28.0, 25.7, 18.1, -5.7; **MS (ESI)** *m/z* (%) 542 (100%) ($[M+H]^+$).

*3.2.8. (3R, 4R, 5R)-3,4-Bis(benzyloxy)-5-(hydroxymethyl)-pyrrolidin-2-one (**38**)*

To a stirred solution of compound **37** (520 mg, 0.96 mmol) in AcOEt (10 mL), a 4N solution of HCl in dioxane (2.5 mL, 10.0 mmol) was added at 0 °C and the reaction mixture was left stirring at room temperature for 2 h. After evaporation of the solvent, the product was precipitated by the addition of Et_2O/pet. ether. White gummy solid; 250 mg, 80% yield; R_f (AcOEt) 0.17; mp 53-56 °C; $[\alpha]_D$ + 114.0 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.37-7.26 (10H, m, ArH), 6.73 (1H, br s, NH), 4.86 (1H, d, *J* = 12.0 Hz, OC*H*HPh), 4.71 (1H, d, *J* = 12.0 Hz, OCH*H*Ph), 4.60 (1H, d, *J* = 11.4 Hz, OC*H*HPh), 4.49 (1H, d, *J* = 11.4 Hz, OCH*H*Ph), 4.10 (1H, d, *J* = 4.6 Hz, OCH), 3.95-3.92 (1H, m, OCH), 3.73-3.66 (2H, m, NCH & OC*H*H), 3.51-3.44 (1H, m, OCH*H*), 2.37 (1H, br s, OH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.6, 137.2, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 75.7, 75.4, 72.5, 71.9, 62.3, 59.8; **MS (ESI)** *m/z* (%) 328 (100%) ($[M+H]^+$).

*3.2.9. (3R, 4R, 5R)-5-(Aminomethyl)-3,4-bis(benzyloxy)pyrrolidin-2-one (**16**)*

Same procedure as above utilizing alcohol **38**. Colorless oil, 81 mg, 73% yield; R_f ($CHCl_3$/MeOH 80:20) 0.35; $[\alpha]_D$ + 21.8 (c = 0.9, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.43-7.26 (10H, m, ArH), 6.36 (1H, br s, NH), 4.92 (1H, d, *J* = 11.8 Hz, OC*H*HPh), 4.74 (1H, d, *J* = 11.8 Hz, OCH*H*Ph), 4.63 (1H, d, *J* = 11.6 Hz, OC*H*HPh), 4.46 (1H, d, *J* = 11.6 Hz, OCH*H*Ph), 4.04 (1H, d, *J* = 5.4 Hz, OCH), 3.81 (1H, t, *J* = 5.0 Hz, OCH), 3.74-3.67 (1H, m, NCH), 2.98 (1H, dd, *J* = 13.6 and 3.8 Hz, C*H*HNH$_2$), 2.59 (1H, dd, *J* = 13.2 and 7.2 Hz, CH*H*NH$_2$), 1.88 (2H, br s, NH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.9, 137.9, 137.2, 128.5, 128.2, 128.0, 127.8, 127.5, 127.3, 77.8, 74.7, 73.9, 72.5, 54.8, 42.9; **MS (ESI)** *m/z* (%) 327 (100%) ($[M+H]^+$); HRMS exact mass calculated for $[M+H]^+$ ($C_{26}H_{29}N_2O_3$) requires m/z 417.2173, found m/z 417.2180.

*Synthesis of catalysts **22-27***

*3.2.10. (S)-2-[(S)-1-(Benzyloxycarbonyl)pyrrolidine-2-carboxamido]-3-phenylpropanoic acid (**11**)*[7h]

*3.2.11. (R)-2-[(S)-1-(Benzyloxycarbonyl)pyrrolidine-2-carboxamido]-3-phenylpropanoic acid (**12**)*

To a stirred solution of Cbz-proline (**8**) (1.25 g, 5.00 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C, 1-hydroxybenzotriazole (HOBt) (676 mg, 5.00 mmol), (*R*)-methylphenylalaninate hydrochloride (**10**) (1.08 g, 5.00 mmol), Et_3N (0.700 mL, 5.00 mmol) and dicyclohexylcarbodiimide (DCC) (1.03 g, 5.00 mmol) were added consecutively. The reaction mixture was left stirring at 0 °C for 1 h and then warmed to room temperature and left stirring for 18 h. The solvents were evaporated under reduced pressure and the crude product was dissolved in EtOAc (30 mL). After filtration, the organic layer was washed with aq. H_2SO_4 (5%, 20 mL), H_2O (20 mL), aq. $NaHCO_3$ (5%, 20 mL) and brine (20 mL). After evaporation of the solvent, the crude ester was purified using column chromatography eluting with pet. ether/EtOAc (50:50). White solid; 1.95 g, 95% yield; R_f (pet. ether/EtOAc 1:1) 0.20; mp 69-72 °C; $[\alpha]_D$ -11.3 (*c* = 1.0, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38-7.02 (10H, m, ArH), 6.35 (1H, br s, NH), 5.21 (2H, s, OCH_2), 4.87-4.81 (1H, m, NCH), 4.41-4.35 (1H, m, NCH), 3.73 (3H, s, OCH_3), 3.50-3.41 (2H, m, NCH_2), 3.14-3.00 (2H, m, CH_2Ph), 2.24-2.06 (2H, m, CH_2), 1.93-1.77 (2H, m, CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.6, 171.3, 155.8, 136.3, 135.7, 129.2, 129.0, 128.0, 127.8, 127.0, 67.2, 60.6, 52.2, 46.9, 37.6, 31.0, 28.8, 24.3.

To a stirred solution of the protected dipeptide (0.20 g, 0.48 mmol) in dioxane (1 mL), an aq. solution of NaOH (2N, 3 mL) was added. The reaction mixture was left stirring for 1 h at room temperature. The crude mixture was extracted with Et_2O (2 x 20 mL). The aqueous layer was acidified with aq. HCl (2N) until pH 2 and the crude product was extracted with EtOAc (2 x 15 mL). The combined organic layers were washed with H_2O (30 mL), dried and the solvent was removed under reduced pressure. **12** was isolated as a white solid; 0.14 g, 76% yield; R_f (pet. ether/EtOAc 30:70) 0.05; mp 53-56 °C; $[\alpha]_D$ -76.7 (*c* = 2.5, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.40 (1H, br s, COOH), 7.26-7.01 (10H, m, ArH), 6.79 (1H, br s, NH), 5.08 (2H, s, OCH_2), 4.87-4.81 (1H, m, NCH), 4.33-4.31 (1H, m, NCH), 3.46-

3.36 (2H, m, NCH_2), 3.12-2.87 (m, 2H, CH_2Ph), 2.03-1.89 (2H, m, CH_2), 1.89-1.75 (2H, m, CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.7, 172.2, 155.8, 136.1, 135.9, 129.5, 128.6, 128.5, 128.2, 127.9, 127.0, 67.6, 60.4, 52.8, 47.0, 37.6, 29.8, 24.3; MS (ESI) *m/z* (%) 397 (100) ($[M+H]^+$).

*3.2.12. Benzyl (S)-2-(((S)-1-((((S)-1-benzyl-5-oxopyrrolidin-2-yl)methyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (**17**)*

To a stirred solution of dipeptide **11** (1.29 g, 3.26 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C, 1-hydroxybenzotriazole (HOBt) (0.44 g 3.26 mmol), compound **13** (0.67 g, 3.26 mmol) and dicyclohexyl carbodiimide (DCC) (0.72 g, 3.26 mmol) were added consecutively. The reaction mixture was left stirring at 0 °C for 1 h and then warmed to room temperature and left stirring for 18 h. The solvents were evaporated under reduced pressure and the crude product was dissolved in EtOAc (30 mL). After filtration, the organic layer was washed with aqueous aq. H_2SO_4 (5%, 20 mL), H_2O (20 mL), aq. $NaHCO_3$ (5%, 20 mL) and brine (20 mL). After evaporation of the solvent, the crude product was purified using column chromatography eluting with $CHCl_3$/MeOH (90:10). Colorless oil; 1.46 g, 77% yield; R_f ($CHCl_3$/MeOH 9:1) 0.50; $[\alpha]_D$ -48.7 (*c* = 0.9, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.34-7.07 (15H, m, ArH), 6.67 (1H, br s, NH), 6.45 (1H, br s, NH), 5.08-4.88 (3H, m, CH_2O & NCH), 4.63-4.54 (1H, m, NCH), 4.25-4.18 (1H, m, NCH), 4.06 (1H, d, *J* = 15.4 Hz, NC*H*HPh), 3.52-3.04 (7H, m, NCH*H*Ph, 2 x NCH_2 & CH_2), 2.46-2.25 (2H, m, CH_2), 2.07-1.67 (6H, m, 3 x CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 175.4, 171.5, 171.3, 156.0, 136.6, 136.0, 129.0, 128.7, 128.5, 128.5, 128.2, 127.9, 127.6, 127.5, 126.9, 67.4, 61.1, 56.2, 53.8, 47.1, 44.2, 40.5, 36.9, 29.9, 29.2, 24.3, 21.7; MS (ESI): m/z= 583 (100) ($M+H^+$).

*3.2.13. Benzyl (S)-2-(((S)-1-((((R)-1-benzyl-5-oxopyrrolidin-2-yl)methyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (**18**)*

Same procedure as above, utilizing dipeptide **11** and amine **14** (1 mmol). Eluent AcOEt/MeOH 90:10; Colorless oil; 0.41 g, 70% yield; R_f (AcOEt/MeOH 9:1) 0.45; $[\alpha]_D$ -65.8 (*c* = 1, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.32-7.00 (15H, m, ArH), 6.77 (1H, br s, NH), 6.73 (1H, br s, NH), 5.09-4.91 (3H, m, CH_2O & NCH), 4.66,-4.56 (1H, m, NCH), 4.22-4.16 (1H, m, NCH), 4.04 (1H, d, *J* = 14.2 Hz, NC*H*HPh), 3.48-3.06 (7H, m, NCHHPh, 2 x NCH_2 & CH_2), 2.47-2.22 (2H, m, CH_2), 2.10-1.67 (6H, m, 3 x CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 175.4, 171.5, 171.3, 156.0, 136.6, 136.0, 129.0, 128.7, 128.5, 128.5, 128.2, 127.9, 127.6, 127.5, 126.9, 67.4, 61.1, 56.2, 53.8, 47.1, 44.2, 40.5, 36.9, 29.9, 29.2, 24.3, 21.7; MS (ESI) *m/z* (%) 583 (100) ($[M+H]^+$).

*3.2.14. Benzyl (S)-2-(((R)-1-((((S)-1-benzyl-5-oxopyrrolidin-2-yl)methyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (**19**)*

Same procedure as above, utilizing dipeptide 12 and amine 13 (1.5 mmol). Eluent AcOEt; White solid; 0.63 g, 72% yield; R_f (EtOAc) 0.30; mp 161-163 °C; $[\alpha]_D$ -2.6 (*c* = 1.0, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.33-7.20 (15H, m, ArH), 6.77-6.73 (2H, m, 2 x NH), 5.04-4.95 (3H, m, CH_2O & NCH), 4.74-4.63 (1H, m, NCH), 4.09-3.97 (2H, m, NCH & NC*H*HPh), 3.94-3.05 (7H, m, NCHHPh, 2 x NCH_2 & CH_2), 2.42-2.23 (2H, m, CH_2), 1.99-1.74 (6H, m, 3 x CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) *δ* 175.6, 172.4, 171.7, 155.3, 137.1, 136.5, 136.2, 129.1, 128.7, 128.5, 128.5, 128.1, 127.7, 127.5, 127.4, 126.8, 67.0, 60.8, 56.5, 54.2, 46.9, 44.0, 40.1, 36.9, 30.1, 29.5, 24.6, 21.5; MS (ESI) *m/z* (%) 1165 (100) ($[2M+H]^+$).

*3.2.15. Benzyl (S)-2-(((S)-1-((3-((R)-1-benzyl-5-oxopyrrolidin-2-yl)propyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (**20**)*

Same procedure as above, utilizing dipeptide **11** and amine **15** (1.8 mmol). Eluent EtOAc/pet. ether 90:10; Colorless oil; 0.78 g, 65% yield; R_f (EtOAc/pet. ether 9:1) 0.55; $[\alpha]_D$ -42.0 (*c* = 1, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.96-7.08 (15H, m, ArH), 6.55-6.43 (2H, m, 2 x NH), 5.08-4.83 (3H, m, OCH_2 & NCH), 4.65-4.54 (1H, m, NCH), 4.22-4.16 (1H, m, NCH), 4.06 (1H, d, *J* = 15.0 Hz, NC*H*HPh), 3.94 (1H, d, *J* = 15.0 Hz, NCH*H*Ph), 3.53-2.98 (6H, m, 2 x NCH_2 & CH_2), 2.46-2.34 (2H, m, CH_2), 2.29-1.24 (10H, m, 5 x CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 175.3, 171.5, 170.6, 156.1, 136.8, 136.1, 129.2, 129.0, 128.7, 128.4, 128.1, 128.0, 127.8, 127.5, 127.1, 67.6, 61.3, 56.7, 53.8, 47.2, 44.2, 39.5, 37.2, 30.3, 30.1, 28.7, 24.4, 23.8, 12.9; MS (ESI) *m/z* (%) 611 (100) ($[M+H]^+$).

*3.2.16. Benzyl (S)-2-(((S)-1-((((2R,3R,4R)-3,4-bis(benzyloxy)-5-oxopyrrolidin-2-yl)methyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (**21**)*

Same procedure as above, utilizing dipeptide **11** and amine **16** (0.60 mmol). Eluent EtOAc/MeOH 90:10; Colorless oil; 0.33 g, 78% yield; R_f (EtOAc/MeOH 9:1) 0.32; $[\alpha]_D$ -5.9 (*c* = 1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35-7.08 (20H, m, ArH) , 6.89 (1H, br s, NH), 6.67-6.48 (2H, m, 2 x NH), 5.08 (1H, d, *J* = 12.2 Hz, OC*H*HPh), 4.93 (1H, d, *J* = 12.2 Hz, OCH*H*Ph), 4.80 (1H, d, *J* = 11.4 Hz, OC*H*HPh), 4.69 (1H, d, *J* = 11.4 Hz, OCH*H*Ph), 4.61-4.51 (3H, m, OCH_2 & OCH), 4.18 (1H, dd, *J* =8.2 and 4.0 Hz, OCH), 3.93-3.91 (1H, m, NCH), 3.74-3.72 (2H, m, 2 x NCH), 3.50-3.08 (6H, m, 2 x NCH_2 & CH_2), 2.04-1.57 (4H, m, 2 x CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.8, 171.4, 171.3, 156.4, 137.6, 137.5, 136.5, 135.8, 129.1, 128.8, 128.8, 128.6, 128.5, 128.4, 128.2, 128.1, 127.9, 127.8, 127.3, 127.2, 74.2, 72.1, 68.0, 61.5, 57.7, 53.8, 47.4, 41.3, 36.7, 34.1, 29.7, 25.7, 25.1; MS (ESI) *m/z* (%) 705 (100%) ($[M+H]^+$)

*3.2.17. (S)-N-((S)-1-((((S)-1-benzyl-5-oxopyrrolidin-2-yl)methyl)amino)-1-oxo-3-phenylpropan-2-yl)pyrrolidine-2-carboxamide (**22**)*

To a stirred solution of compound **17** (0.87 g, 1.50 mmol) in dry methanol (30 mL), 10% Pd/C (10 mol%) was added and the reaction mixture was left stirring at room temperature for 2.5 h under hydrogen atmosphere. After filtration through Celite, the solvent was evaporated to afford the desired product. Colorless oil; 0.55 g, 82% yield; R_f ($CHCl_3$/MeOH 7:3) 0.53; $[\alpha]_D$ -8.9 (*c* = 1, MeOH); ^{1}H NMR (200 MHz, DMSO) δ 8.91 (1H, br s, NH), 8.87 (1H, br s, NH), 8.37-7.23 (10H, m, ArH), 4.77 (1H, d, *J* = 15.4 Hz, NC*H*HPh), 4.59-4.48 (1H, m, NCH), 4.14-4.12 (1H, m, NCH), 4.04 (1H, d, *J* = 15.4 Hz, NCH*H*Ph), 3.35-3.15 (3H, m, NCH & NCH_2), 2.99-2.76 (2H, m, NCH_2), 2.33-2.15 (2H, m, CH_2), 1.94-1.00 (8H, m, 4 x CH_2); ^{13}C NMR (50 MHz, DMSO) δ 174.3, 172.7, 171.3, 137.4, 137.2, 129.2, 128.6, 128.0, 127.6, 127.2, 126.4, 59.7, 55.7, 53.3, 46.4, 43.3, 30.1, 29.4, 29.2, 25.2, 21.4, 16.9; MS 449 ($M+H^+$ 100); HRMS exact mass calculated

for $[M-H]^-$ ($C_{26}H_{31}N_4O_3$) requires *m/z* 447.2402, found *m/z* 447.2398.

*3.2.18. (S)-N-((S)-1-((((R)-1-benzyl-5-oxopyrrolidin-2-yl)methyl)amino)-1-oxo-3-phenylpropan-2-yl)pyrrolidine-2-carboxamide (**23**)*

Same procedure as above but utilizing **18** (0.84 mmol). Reaction time 2 h; white solid; 0.37 g, 99% yield; mp 118-120 ^oC; R*f* ($CHCl_3$/MeOH 7:3) 0.61; $[\alpha]_D$ -47.2 (*c* = 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 8.24 (1H, br s, NH), 8.20 (1H, br s, NH), 7.77-7.14 (10H, m, ArH), 4.92-4.84 (1H, d, *J* = 15.2 Hz, NC*H*HPh), 4.60-4.49 (1H, m, NCH), 4.03-3.95 (1H, d, *J* = 15.2 Hz, NCH*H*Ph), 3.80-3.73 (1H, m, NCH), 3.51-3.40 (1H, m, NCH), 3.23-2.71 (6H, m, 2 x NCH_2 & CH_2), 2.46-2.19 (2H, m, CH_2), 1.99-1.24 (6H, m, 3 x CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 175.8, 175.3, 172.1, 137.0, 136.5, 129.3, 128.9, 128.6, 128.0, 127.7, 126.9, 60.2, 56.8, 54.3, 47.1, 44.5, 40.1, 37.3, 30.6, 30.2, 25.7, 21.7; MS 449 ($M+H^+$ 100); HRMS exact mass calculated for $[M-H]^-$ ($C_{26}H_{31}N_4O_3$) requires *m/z* 447.2402, found *m/z* 447.2402.

*3.2.19. (S)-N-((R)-1-((((S)-1-benzyl-5-oxopyrrolidin-2-yl)methyl)amino)-1-oxo-3-phenylpropan-2-yl)pyrrolidine-2-carboxamide (**24**)*

Same procedure as above but utilizing **19** (0.78 mmol). Reaction time 1.5 h; white solid; 0.31 g, 90% yield; mp 116-119 ^oC; R*f* ($CHCl_3$/MeOH 7:3) 0.53; $[\alpha]_D$ -5.4 (*c* = 1.0, MeOH); ^1H NMR (200 MHz, $CDCl_3$) δ 8.28-8.24 (2H, br m, 2 x NH), 7.36-7.10 (10H, m, ArH), 4.90-4.83 (1H, d, *J* = 15.0 Hz NC*H*HPh), 4.59-4.48 (1H, m, NCH), 4.19-4.15 (1H, m, NCH), 4.04-3.96 (1H, d, *J* = 15.0 Hz, NCH*H*Ph, 3.84-3.77 (1H, m, NCH), 3.52-3.44 (2H, m, NCH_2), 3.38-2.86 (4H, m, NCH_2 & CH_2), 2.46-2.31 (2H, m, CH_2), 2.10-1.65 (6H, m, 3 x CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 175.6, 174.8, 171.9, 136.9, 136.4, 129.2, 128.8, 128.4, 127.9, 127.6, 126.8, 60.2, 56.5, 54.6, 47.0, 44.2, 40.1, 37.8, 30.6, 30.1, 25.8, 21.7; MS 449 ($M+H^+$ 100); HRMS exact mass calculated for $[M-H]^-$ ($C_{26}H_{31}N_4O_3$) requires *m/z* 447.2402, found *m/z* 447.2401.

*3.2.20. (S)-N-((S)-1-((3-((R)-1-benzyl-5-oxopyrrolidin-2-yl)propyl)amino)-1-oxo-3-phenylpropan-2-yl)pyrrolidine-2-carboxamide (**25**)*

Same procedure but utilizing compound **20** (0.25 mmol). Reaction time 3 h; colorless oil; 0.12 g, 100% yield; R*f* ($CHCl_3$/MeOH 7:3) 0.28; $[\alpha]_D$ -1.6 (*c* = 1.0, MeOH); ^1H NMR (200 MHz, $CDCl_3$) δ 8.52 (2H, br s, 2 x NH), 7.35-7.14 (10H, m, ArH), 4.97 (1H, m, NCH), 4.86 (1H, d, *J* = 15.4 Hz, NC*H*HPh), 4.63 (1H, m, NCH), 4.05 (1H, d, *J* = 15.4 Hz, NCH*H*Ph), 3.94 (1H, d, *J* = 15.0 Hz, NCH), 3.90-2.95 (7H, m, 2 x NCH_2, CH_2 & NH), 2.52-2.21 (4H, m, $COCH_2$ & CH_2), 2.12-1.98 (2H, m, CH_2), 1.80-1.23 (6H, m, 3 x CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 175.3, 170.2, 167.9, 136.7, 135.9, 129.9, 128.9, 128.7, 128.3, 127.9, 127.5, 56.7, 56.0, 44.7, 44.1, 39.7, 30.3, 29.9, 28.6, 24.4, 24.2, 23.8, 23.4, 12.8; MS 477 ($M+H^+$ 100); HRMS exact mass calculated for $[M+Na]^+$ ($C_{28}H_{36}N_4O_3Na$) requires *m/z* 499.2680, found *m/z* 499.2696.

*3.2.21. (S)-N-((S)-1-((((2R,3R,4R)-3,4-bis(benzyloxy)-5-oxopyrrolidin-2-yl)methyl)amino)-1-oxo-3-phenylpropan-2-yl)pyrrolidine-2-carboxamide (**26**)*

Same procedure but utilizing compound **21** (0.18 mmol). Reaction time 2 h; gummy solid; 59.6 mg, 58% yield; R*f* ($CHCl_3$/MeOH 8:2) 0.20; $[\alpha]_D$ +9.4 (*c* = 1.0, MeOH); ^1H NMR (200 MHz, $CDCl_3$) δ 8.19-8.15 (2H, m, 2 x NH), 7.90-7.82 (1H, m, NH), 7.31-7.13 (15H, m, ArH), 4.80 (1H, d, *J* = 11.6 Hz, OC*H*HPh), 4.64 (1H, d, *J* = 11.6 Hz, OCH*H*Ph), 4.51 (1H, d, *J* = 11.4 Hz, OC*H*HPh), 4.41 (1H, d, *J* = 11.4 Hz, OCH*H*Ph), 3.88 (1H, d, *J* = 5.0 Hz, OCH), 3.73-3.43 (4H, m, OCH & 3 x NCH), 3.09-2.77 (4H, m, 2 x NCH_2), 2.67- 2.44 (3H, m, NH & CH_2), 1.50-1.18 (4H, m, 2 x CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 176.1, 173.1, 172.2, 137.5, 137.4, 136.8, 129.3, 128.6, 128.6, 128.5, 128.4, 128.2, 128.2, 128.1, 127.0, 74.5, 72.1, 60.3, 57.6, 54.4, 47.1, 40.8, 37.5, 30.6, 25.9, 21.2, 14.3; MS 571 ($M+H^+$ 100); HRMS exact mass calculated for $[M-H]^-$ ($C_{33}H_{37}N_4O_5$) requires *m/z* 569.2769, found *m/z* 569.2754.

*3.2.22. (S)-N-((S)-1-((((2R,3R,4R)-3,4-dihydroxy-5-oxopyrrolidin-2-yl)methyl)amino)-1-oxo-3-phenylpropan-2-yl)pyrrolidine-2-carboxamide (**27**)*

Same procedure but utilizing compound 21 (0.22 mmol). Reaction time 5.5 h; gummy solid; 84.2 mg, 98% yield; R*f* (EtOAc/MeOH 9:1) 0.45; $[\alpha]_D$ +22.2 (*c* = 0.9, MeOH); ^1H NMR (200 MHz, DMSO-d_6 & CD_3OD) δ 8.13-8.09 (2H, m, 2 x NH), 7.64-6.91 (5H, m, ArH), 6.32 (1H, br s, NH), 5.27-4.99 (2H, m, 2 x OCH), 4.35-4.27 (1H, m, NCH), 4.07-3.76 (2H, m, 2 x NCH, 3.21-2.77 (6H, m, 2 x NCH_2 & CH_2), 2.66-1.38 (6H, 2 x OH & 2 x CH_2), 0.94 (1H, br s, NH); ^{13}C NMR (50 MHz, DMSO-d_6 & CD_3OD) δ 168.4, 164.4, 160.2, 128.6, 120.7, 120.1, 118.5, 62.1, 61.6, 51.7, 51.5, 47.7, 37.9, 32.4, 28.9, 21.4, 15.6; MS 391 ($M+H^+$ 100); HRMS exact mass calculated for $[M-H]^-$ ($C_{19}H_{25}N_4O_5$) requires *m/z* 389.1830, found *m/z* 389.1948.

4. General procedure for the aldol reaction

Conditions A: To a round-bottom flask, **22** (10 mg, 0.021 mmol), 4-NBA (4.7 mg, 0.028 mmol) and aldehyde (0.14 mmol) were added. After the addition of Petroleum ether (1 mL) and H_2O (0.1 mL), ketone (1.40 mmol) was added and the reaction mixture was stirred for 24-120 h at room temperature. The solvent was evaporated and the crude product was purified using flash column chromatography eluting with the appropriate mixture of petroleum ether (40-60 ^oC)/ethyl acetate to afford the desired product. Conditions B: To a round-bottom flask, **25** (10 mg, 0.021 mmol), 4-NBA (4.7 mg, 0.028 mmol) and aldehyde (0.14 mmol) were added. After the addition of brine (1 mL), ketone (1.40 mmol) was added and the reaction mixture was stirred for 24-120 h at room temperature. The solvent was evaporated and the crude product was purified using flash column chromatography eluting with the appropriate mixture of petroleum ether (40-60 ^oC)/ethyl acetate to afford the desired product.

*4.1. (S)-2-[(R)-Hydroxy-(4-nitrophenyl)methyl]-cyclohexanone (**42a**, Table 3, entry 1)*[14]

Colorless oil, 32 mg, 92% yield; R_f (AcOEt:Pet. Ether 3:7) 0.56; ^1H NMR (200 MHz, $CDCl_3$) *anti* δ 8.20 (2H, d, *J* = 8.8 Hz, ArH), 7.51 (2H, d, *J* = 8.8 Hz, ArH), 4.87 (1H, d, *J* = 8.4 Hz, OCH), 4.09 (1H, br s, OH), 2.64-2.26 (3H, m, COCH & 2 x C*H*H), 2.17-1.29 (6H, m, 6 x C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 214.6, 148.4, 127.9, 127.8, 123.4, 73.8, 57.0, 42.5, 30.6, 27.5, 24.5; HPLC analysis: Diacel Chiralpak AD-H, hexane:^{i}PrOH 90:10, flow rate 1.0 mL/min, retention time: 33.07 (minor) and 44.02 (major), 93% *ee*.

*4.2 (S)-2-[(R)-Hydroxy-(3-nitrophenyl)methyl]-cyclohexanone (**42b**, Table 3, entry 4)*[14]

Colourless oil, 34 mg, 97% yield; R_f (AcOEt:Pet. Ether 3:7) 0.48; ^{1}H NMR (200 MHz, $CDCl_3$) *anti* δ 8.23-8.14 (2H, m, ArH), 7.67 (1H, d, *J* = 7.3 Hz, ArH), 7.55 (1H, d, *J* = 7.6 Hz, ArH), 4.90 (1H, d, *J* = 8.4 Hz, OCH), 4.11 (1H, br s, OH), 2.68-2.31 (3H, m, COCH & 2 x C*H*H), 2.17-1.32 (6H, m, 6 x C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 214.6, 148.2, 143.1, 133.1, 129.2, 122.7, 121.9, 74.0, 57.0, 42.6, 30.6, 27.6, 24.6; HPLC analysis: Diacel Chiralpak AD-H, hexane:^{i}PrOH 95:5, flow rate 1.0 mL/min, retention time: 53.41 (major) and 69.16 (minor), 92% *ee*.

*4.3. (S)-2-[(R)-Hydroxy-(2-nitrophenyl)methyl]-cyclohexanone (**42c**, Table 3, entry 5)*[14]

Yellow solid, 35 mg, 100% yield; R_f (AcOEt:Pet. Ether 3:7) 0.46; ^{1}H NMR (200 MHz, $CDCl_3$) *anti* δ 7.91-7.72 (2H, m, ArH), 7.63 (1H, t, *J* = 6.5 Hz, ArH), 7.42 (1H, t, *J* = 6.6 Hz, ArH), 5.43 (1H, d, *J* = 7.1 Hz, OCH), 4.16 (1H, br s, OH), 2.85-2.61 (1H, m, COCH), 2.55-2.08 (2H, m, 2 x C*H*H), 1.90-1.52 (6H, m, 6 x C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 214.9, 136.5, 133.0, 128.9, 128.3, 124.0, 69.7, 57.2, 42.8, 31.1, 27.7, 24.9; HPLC analysis: Diacel Chiralpak AD-H, hexane:^{i}PrOH 95:5, flow rate 0.8 mL/min, retention time: 60.85 (major) and 65.23 (minor), 97% *ee*.

*4.4. (R)-3-[Hydroxy-(2-(S)-oxocyclohexyl)methyl]-benzonitrile (**42d**, Table 3, entry 7)*[14]

White solid, 32 mg, 100% yield; mp 66-68 °C; R_f (AcOEt:Pet. Ether 3:7) 0.42; ^{1}H NMR (200 MHz, $CDCl_3$) *anti* δ 7.68-7.38 (4H, m, ArH), 4.81 (1H, d, *J* = 8.5 Hz, OCH), 4.01 (1H, br s, OH), 2.65-2.03 (4H, m, COCH & 3 x C*H*H), 1.87-1.22 (5H, m, 5 x C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 214.6, 142.6, 131.5, 130.6, 129.1, 118.7, 112.4, 73.9, 57.1, 42.6, 30.6, 27.6, 24.6; HPLC analysis: Diacel Chiralpak AD-H, hexane:^{i}PrOH 95:5, flow rate 1.0 mL/min, retention time: 46.07 (minor) and 68.80 (major), 87% *ee*.

*4.5. (S)-2-[(R)-Hydroxy-(4-(trifluoromethyl)phenyl)methyl]-cyclohexanone (**42e**, Table 3, entry 9)*[14]

White solid, 36 mg, 94% yield; mp 73-75 °C; R_f (AcOEt:Pet. Ether 3:7) 0.48; ^{1}H NMR (200 MHz, $CDCl_3$) *anti* δ 7.61 (2H, d, *J* = 8.2 Hz, ArH), 7.44 (2H, d, *J* = 8.2 Hz, ArH), 4.84 (1H, d, *J* = 8.6 Hz, OCH), 4.03 (1H, br s, OH), 2.69-2.02 (4H, m, COCH & 3 x C*H*H), 1.90-1.39 (5H, m, 5 x C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 215.1, 144.9, 129.6 (q, *J* = 31.2 Hz), 127.3, 125.3 (q, *J* = 8.1 Hz), 123.9 (q, *J* = 271.4 Hz), 74.2, 57.2, 42.6, 30.7, 27.6, 24.7; ^{19}F NMR (188 MHz, $CDCl_3$) δ -7.50 (s); HPLC analysis: Diacel Chiralpak AD-H, hexane:^{i}PrOH 90:10, flow rate 0.5 mL/min, retention time: 27.39 (minor) and 33.61 (major), 92% *ee*.

*4.6. (S)-2-[(R)-Hydroxy-(4-(fluorophenyl)methyl]-cyclohexanone (**42f**, Table 3, entry 12)*[14]

White solid, 28 mg, 89% yield; mp 66-68 °C; R_f (AcOEt:Pet. Ether 3:7) 0.52; ^{1}H NMR (200 MHz, $CDCl_3$) *anti* δ 7.33-7.27 (2H, m, ArH), 7.03 (2H, t, *J* = 8.7 Hz, ArH), 4.77 (1H, d, *J* = 8.4 Hz, OCH), 4.03 (1H, br s, OH), 2.65-2.31 (3H, m, COCH & 2 x C*H*H), 2.08-1.22 (6H, m, 6 x C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 215.4, 162.3 (d, *J* = 246.2 Hz), 136.6, 128.5 (d, *J* = 5.1 Hz), 115.2 (d, *J* = 20.0 Hz), 74.1, 57.4, 42.6, 30.7, 27.7, 24.6; ^{19}F NMR (188 MHz, $CDCl_3$) δ -59.49 (m); HPLC analysis: Diacel Chiralpak AD-H, hexane:^{i}PrOH 90:10, flow rate 0.5 mL/min, retention time: 36.72 (minor) and 40.35 (major), 92% *ee*.

*4.7. (S)-2-[(R)-Hydroxy-(4-(chlorophenyl)methyl]-cyclohexanone (**42g**, Table 3, entry 14)*[7i]

White solid, 31 mg, 92% yield; mp 96-98 °C; R_f (AcOEt:Pet. Ether 3:7) 0.38; ^{1}H NMR (200 MHz, $CDCl_3$) *anti* δ 7.32 (2H, d, *J* = 8.5 Hz, ArH), 7.24 (2H, d, *J* = 8.5 Hz, ArH), 4.76 (1H, d, *J* = 8.7 Hz, OCH), 3.98 (1H, br s, OH), 2.63-2.28 (3H, m, COCH & 2 x CHH), 2.19-2.01 (1H, m, C*H*H), 1.88-1.42 (5H, m, 5 x C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 215.3, 139.5, 133.6, 128.5, 128.4, 74.2, 57.4, 42.7, 30.7, 27.7, 24.7; HPLC analysis: Diacel Chiralpak OD-H, hexane:^{i}PrOH 95:5, flow rate 1.0 mL/min, retention time: 19.34 (major) and 31.10 (minor), 90% *ee*.

*4.8. (S)-2-[(R)-Hydroxy-(2-(chlorophenyl)methyl]-cyclohexanone (**42h**, Table 3, entry 16)*[7i]

Pale yellow solid, 33 mg, 100% yield; mp 60-62 °C; R_f (AcOEt:Pet. Ether 3:7) 0.42; ^{1}H NMR (200 MHz, $CDCl_3$) *anti* δ 7.54 (1H, dd, *J* = 7.8 and 1.9 Hz, ArH), 7.36-7.16 (3H, m, ArH), 5.34 (1H, d, *J* = 8.2 Hz, OCH), 3.86 (1H, br s, OH), 2.77-2.61 (1H, m, COCH), 2.54-2.22 (2H, m, COCHH), 2.17-2.02 (1H, m, C*H*H), 1.86-1.42 (5H, m, 5 x C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 215.3, 139.1, 132.9, 129.2, 128.7, 128.3, 127.3, 70.5, 57.6, 42.7, 30.4, 27.8, 24.9; HPLC analysis: Diacel Chiralpak OD-H, hexane:^{i}PrOH 95:5, flow rate 1.0 mL/min, retention time: 14.29 (major) and 18.86 (minor), 88% *ee*.

*4.9. (S)-2-[(R)-Hydroxy-(4-(bromophenyl)methyl]-cyclohexanone (**42i**, Table 3, entry 17)*[7i]

White solid, 34 mg, 85% yield; mp 89-91 °C; R_f (AcOEt:Pet. Ether 3:7) 0.42; ^{1}H NMR (200 MHz, $CDCl_3$) *anti* δ 7.47 (2H, d, *J* = 8.5 Hz, ArH), 7.20 (2H, d, *J* = 8.5 Hz, ArH), 4.75 (1H, d, *J* = 8.6 Hz, OCH), 3.94 (1H, br s, OH), 2.61-2.13 (3H, m, COCH & 2 x C*H*H), 2.11-2.01 (1H, m, C*H*H), 1.88-1.24 (5H, m, 5 x C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 215.2, 140.0, 131.5, 128.7, 121.7, 74.2, 57.3, 42.6, 30.7, 27.7, 24.7; HPLC analysis: Diacel Chiralpak AD-H, hexane:^{i}PrOH 90:10, flow rate 0.5 mL/min, retention time: 41.79 (minor) and 49.33 (major), 88% *ee*.

*4.10. (S)-2-[(R)-Hydroxy-(phenyl)methyl]-cyclohexanone (**42j**, Table 3, entry 20)*[14]

Colourless oil, 58 mg, 71% yield; R_f (AcOEt:Pet. Ether 7:3) 0.42; ^{1}H NMR (200 MHz, $CDCl_3$) *anti* δ 7.51-7.21 (5H, m, ArH), 4.78 (1H, d, *J* = 8.8 Hz, OCH), 3.84 (1H, br s, OH), 2.70-2.31 (3H, m, COCH & CHH), 2.15-1.24 (6H, m, 6 x C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 215.5, 140.8, 128.3, 127.8, 125.7, 74.7, 57.4, 42.6, 30.8, 27.8, 24.7; HPLC analysis: Diacel Chiralpak OD-H, hexane:^{i}PrOH 90:10, flow rate 0.5 mL/min, retention time: 22.91 (major) and 32.08 (minor), 99% *ee*.

*4.11. (S)-2-[(R)-Hydroxy-(pyridine-4-yl)methyl]-cyclohexanone (**42k**, Table 3, entry 22)*[7i]

White solid, 29 mg, 100% yield; mp 107-109 °C; R_f (AcOEt:Pet. Ether 4:6) 0.23; ^{1}H NMR (200 MHz, $CDCl_3$) *anti* δ 8.58-8.52 (2H, m, ArH), 7.27-7.21 (2H, m, ArH), 4.78 (1H, d, *J* = 8.1 Hz, OCH), 3.19 (1H, br s, OH), 2.67-2.25 (3H, m, COCH & CHH), 2.18-2.01 (1H, m, C*H*H), 1.87-1.35 (5H, m, 5 x C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 214.5, 150.1, 149.7, 122.1, 73.3, 57.0, 42.6, 30.8, 27.7, 24.7; HPLC analysis: Diacel Chiralpak AD-H, hexane:^{i}PrOH 92:8, flow rate 1.0 mL/min, retention time: 35.88 (minor) and 47.63 (major), 95% *ee*.

*4.12. (S)-3-[(R)-Hydroxy-[4-(nitrophenyl)methyl]dihydro-2H-pyran-4(3H)-one (**42l**, Table 3, entry 23)*[14]

Pale yellow solid, 34 mg, 97% yield; mp 116-118 °C; R_f (AcOEt:Pet. Ether 4:6) 0.16; ^{1}H NMR (200 MHz, $CDCl_3$) *anti* δ 8.21 (2H, d, *J* = 8.8 Hz, ArH), 7.50 (2H, d, *J* = 8.8 Hz, ArH), 4.97 (1H, d, *J* = 8.2 Hz, OCH), 4.28-4.09 (1H, m, OC*H*H), 3.90-3.64 (3H, m, 2 x OC*H*H & OH), 3.44 (1H, dd, *J* = 11.4 and 9.8 Hz, OC*H*H), 3.02-2.41 (3H, m, 3 x C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 209.2, 147.7, 147.4, 127.4, 123.8, 71.2, 69.7, 68.2, 57.5, 42.7; HPLC analysis: Diacel Chiralpak AD-H, hexane:^{i}PrOH 80:20, flow rate 1.0 mL/min, retention time: 23.53 (minor) and 33.52 (major), 78% *ee*.

4.13. *(S)-3-[(R)-Hydroxy-[4-(nitrophenyl)methyl]dihydro-2H-thiopyran-4(3H)-one (**42m**, Table 3, entry 26)*[14]

Yellow solid, 37 mg, 100% yield; mp 137-139 °C; R_f (AcOEt:Pet. Ether 3:7) 0.39; ^{1}H NMR (200 MHz, $CDCl_3$) *anti* δ 8.23 (2H, d, *J* = 8.3 Hz, ArH), 7.53 (2H, d, *J* = 8.3 Hz, ArH), 5.04 (1H, d, *J* = 7.9 Hz, OCH), 3.63 (1H, br s, OH), 3.07-2.91 (3H, m, COCH & CHH), 2.87-2.70 (2H, m, 2 x C*H*H), 2.68-2.42 (2H, m, 2 x C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 211.2, 147.7, 147.6, 127.7, 123.8, 73.1, 59.4, 44.7, 32.8, 30.7; HPLC analysis: Diacel Chiralpak AD-H, hexane:^{i}PrOH 90:10, flow rate 1.0 mL/min, retention time: 89.93 (minor) and 108.34 (major), 90% *ee*.

4.14. *(S)-7-[(R)-Hydroxy-4-(nitrophenyl)methyl]-1,4-dioxospiro[4.5]decan-8-one (**42n**, Table 3, entry 27)*[14]

White solid, 43 mg, 100% yield; mp 89-91 °C; R_f (AcOEt:Pet. Ether 3:7) 0.20; ^{1}H NMR (200 MHz, $CDCl_3$) *anti* δ 8.21 (2H, d, *J* = 8.8 Hz, ArH), 7.49 (2H, d, *J* = 8.8 Hz, ArH), 4.92 (1H, d, *J* = 7.5 Hz, OCH), 4.04 (1H, br s, OH), 3.98-3.68 (4H, m, 4 x OC*H*H), 2.91-2.74 (1H, m, COCH), 2.66-2.54 (1H, m, C*H*H), 2.51-2.42 (1H, m, C*H*H), 2.07-1.55 (3H, m, 3 x C*H*H), 1.54-1.44 (1H, m, C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 213.1, 147.9, 127.8, 126.5, 123.6, 106.6, 73.8, 64.8, 64.5, 52.9, 38.8, 37.8, 34.3; HPLC analysis: Diacel Chiralpak AS-H, hexane:^{i}PrOH 70:30, flow rate 1.0 mL/min, retention time: 17.08 (minor) and 26.70 (major), 90% *ee*.

4.15. *(2S,4R)-2-[(R)-Hydroxy-(4-(nitrophenyl)methyl]-4-methylcyclohexanone (**42o**, Table 3, entry 30)*[14]

Pale yellow solid, 37 mg, 100% yield; mp 99-101 °C; R_f (AcOEt:Pet. Ether 4:6) 0.22; ^{1}H NMR (200 MHz, $CDCl_3$) *anti* δ 8.22 (2H, d, *J* = 8.8 Hz, ArH), 7.51 (2H, d, *J* = 8.8 Hz, ArH), 4.92 (1H, d, *J* = 8.6 Hz, OCH), 3.99-3.87 (1H, br s, OH), 2.81-2.29 (3H, m, COCH & CHH), 2.15-1.29 (5H, m, 4 x C*H*H & CH); 1.07 (3H, d, *J* = 7.1 Hz, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 214.8, 148.4, 147.5, 127.8, 123.7, 73.9, 52.9, 38.3, 36.1, 33.0, 26.5, 18.2; HPLC analysis: Diacel Chiralpak OD-H, hexane:^{i}PrOH 95:5, flow rate 1.0 mL/min, retention time: 46.34 (minor) and 54.23 (major), 90% *ee*.

4.16. *(S)-2-[(R)-Hydroxy-(4-(nitrophenyl)methyl]-cyclopentanone (**42p**, Table 3, entry 31)*[14]

Colourless oil, 33 mg, 100% yield; R_f (AcOEt:Pet. Ether 4:6) 0.23; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.21 (2H, d, *J* = 8.8 Hz, ArH), 7.52 (2H, d, *J* = 8.8 Hz, ArH), 5.42 (1H, s, OCH *syn*), 4.84 (1H, d, *J* = 9.2 Hz, OCH *anti*), 4.76 (1H, br s, OH *anti*), 2.69 (1H, br s, OH *syn*), 2.52-2.18 (3H, m, COCH & CHH), 2.15-1.83 (2H, m, 2 x C*H*H), 1.78-1.55 (2H, m, 2 x C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 214.6, 213.4, 149.2, 147.9, 147.4, 147.3, 127.2, 126.5, 123.0, 122.9, 73.5, 69.8, 57.0, 56.3, 42.5, 30.2, 27.7, 25.5, 24.6, 24.3; HPLC analysis: Diacel Chiralpak AD-H, hexane:^{i}PrOH 95:5, flow rate 1.0 mL/min, retention time: 40.32 (*syn* major) and 57.11 (*syn* minor), 72.75 (*anti* minor) and 76.19 (*anti* major), 90% *ee*.

4.17. *(S)-4-Hydroxy-4-(4-nitrophenyl)-butan-2-one (**42q**, Table 3, entry 33)*[14]

Colourless oil, 17 mg, 58 % yield; R_f (AcOEt:Pet. Ether 4:6) 0.14; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.20 (2H, d, *J* = 7.0 Hz, ArH), 7.52 (2H, d, *J* = 7.0 Hz, ArH), 5.25 (1H, m, OCH), 3.56 (1H, br s, OH), 3.01-2.71 (2H, m, CHHCO), 2.21 (3H, s, CH_3CO); ^{13}C NMR (50 MHz, $CDCl_3$) δ 208.6, 149.9, 147.4, 126.4, 123.8, 68.9, 51.5, 30.7; HPLC analysis: Diacel Chiralpak AS-H, hexane:^{i}PrOH 85:15, flow rate 1.0 mL/min, retention time: 28.59 (minor) and 35.28 (major), 89% *ee*.

5.0. General procedure for the aldol reaction for the synthesis of 44

*(R)-5,5,5-trifluoro-4-hydroxy-4-phenylpentan-2-one (**44**)*[21]

To a round-bottom flask, **23** (10 mg, 0.021 mmol), 4-NBA (4.7 mg, 0.028 mmol) and 2,2,2-trifluoroacetophenone (24 mg, 0.14 mmol) were added. After the addition of Petroleum ether (1 mL) and H_2O (0.1 mL), acetone (1 mL) was added and the reaction mixture was stirred for 96 h at room temperature. The solvent was evaporated and the crude product was purified using flash column chromatography eluting with the appropriate mixture of petroleum ether (40-60 °C)/ethyl acetate to afford the desired product.[21] Colorless oil, 21 mg, 63% yield; R_f (AcOEt:Pet. Ether 3:7) 0.56; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.62-7.52 (2H, m), 7.46-7.34 (3H, m), 5.46 (1H, br s), 3.39 (1H, d, *J* = 17.2 Hz), 3.21 (1H, d, *J* = 17.2 Hz), 2.22 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 209.1, 137.3, 128.7, 128.4, 126.0, 124.4 (q, *J* = 284.9 Hz), 75.9 (q, *J* = 29.1 Hz), 44.8, 31.8; ^{19}F NMR (188 MHz, $CDCl_3$) δ -13.97 (s); HPLC analysis: Diacel Chiralpak AS-H, hexane:iPrOH 95:5, flow rate 0.7 mL/min, retention time: 12.34 (minor) and 17.06 (major), 70% *ee*.

*5.1 (S)-4-Hydroxy-5-methylhexan-2-one (**46**)*[23]

To a round-bottom flask, **22** (13.4 mg, 0.03 mmol), 4-NBA (6.9 mg, 0.04 mmol) and isobutyraldehyde (15 mg, 0.21 mmol) were added. After the addition of Petroleum ether (3 mL) and H_2O (0.1 mL), acetone (1 mL) was added and the reaction mixture was stirred for 120 h at room temperature. The solvent was evaporated and the crude product was purified using flash column chromatography eluting with petroleum ether (40-60 °C)/ethyl acetate (70:30). Colourless oil, 1.1 mg, 4%, yield; R_f (AcOEt:Pet. Ether 3:7) 0.66; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.87-3.77 (1H, m, OCH), 2.93 (1H, br s, OH), 2.57–2.53 (2H, m, $COCH_2$), 2.21 (3H, s, CH_3), 1.77–1.60 (1H, m, CH), 1.00–0.80 (6H, m, 2 x CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 210.4, 72.2, 46.9, 33.0, 30.9, 18.4; HPLC analysis: Diacel Chiralpak AD-H, hexane:^{i}PrOH 98:2, flow rate 0.5 mL/min, retention time: 26.06 (minor) and 31.64 (major), 44% *ee*.

*5.2 (S)-2-((R)-1-Hydroxy-2-methylpropyl)cyclohexanone (**47**)*[24]

To a round-bottom flask, **22** (13.4 mg, 0.03 mmol), 4-NBA (6.9 mg, 0.04 mmol) and isobutyraldehyde (15 mg, 0.21 mmol) were added. After the addition of Petroleum ether (3 mL) and H_2O (0.1 mL), cyclohexanone (206 mg, 2.10 mmol) was added and the reaction mixture was stirred for 120 h at room temperature. The solvent was evaporated and the crude product was purified using flash column chromatography eluting with petroleum ether (40-60 °C)/ethyl acetate (50:50) Oil, 3.6 mg, 10%, yield, R_f (AcOEt:Pet. Ether 1:1) 0.70; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.52 (1H, m, OCH), 3.27 (1H, d, *J* = 4.8 Hz, COC*H*H), 2.42-2.34 (3H, m, 3 x COC*H*H), 2.35-2.25 (2H, m, 2 x C*H*H), 2.04-1.62 (5H, m, 5 x C*H*H), 0.98 (3H, d, *J* = 6.8 Hz, CH_3), 0.88 (3H, d, *J* = 6.8 Hz, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 216.1, 75.6, 53.7, 42.9, 30.6,

29.2, 27.8, 25.0, 20.1, 15.2; HPLC analysis: Diacel Chiralpak AD-H, hexane:^{i}PrOH 97:3, flow rate 0.5 mL/min, retention time: 25.08 (minor) and 37.71 (major), 97% *ee*.

For the recovery of catalyst **22**, after completion of the reaction, the petroleum ether was evapotated and the residue, dissolved in $CHCl_3$ and acidified with 2N HCl (1 mL). The aqueous layer was evaporated in high vacuum and the evaporation was repeated twice, after the addition of toluene (2 x 1 mL). After drying, catalyst **22** was isolated as the hydrochloride salt and identified by ^{1}H , ^{13}C NMR , measurement of optical activity and MS; yield 73% (7.4 mg). The recovered catalyst, was further subjected in an identical second catalytic reaction after the addition of the appropriate Et_3N (2 μL, 0.015 mmol). The desired compound **42a** was finally isolated in 82 % yield; *dr* 81:19 and *ee* 72%.

6 Acknowledgments

C. G. K. gratefully acknowledges the Operational Program "Education and Lifelong Learning" for financial support through the NSRF program "ΕΝΙΣΧΥΣΗ ΜΕΤΑΔΙΔΑΚΤΟΡΩΝ ΕΡΕΥΝΗΤΩΝ" (PE 2431)" co-financed by ESF and the Greek State. P. M. M. acknowledges Dr K. Georgikopoulou for the synthesis of compound **34** and G. Michas (MSc.) for the synthesis of compounds **37** and **38**. Dr M. Kokotou is acknowledged for acquiring HRMS data.

7 References and notes

1. For books, see: a) Berkessel, A.; Groger, H. *Asymmetric Organocatalysis - From Biomimetic Concepts to Powerful Methods for Asymmetric Synthesis*, Wiley-VCH: Weinheim, 2005; b) Dalko, P. I. *Enantioselective Organocatalysis Reactions and Experimental Procedure*, Wiley-VCH: Weinheim, 2007; c) Dalko, P. I. *Comprehensive Enantioselective Organocatalysis*, Wiley-VCH: Weinheim, 2013; d) Rios Torres, R. *Stereoselective Organocatalysis*, Wiley: Weinheim, 2013.
2. For selected reviews, see: a) Gruttadauria, M.; Giacalone, F.; Noto, R *Adv. Synth. Catal.* **2009**, *351*, 33-57; b) Raj, M.; Singh, V. K. *Chem. Commun.* **2009**, 6687-6703; c) Pihko, P. M.; Majander, I.; Erkkila, A. *Top. Curr. Chem.* **2010**, *291*, 29-75; d) Moyano, A.; Rios, R. *Chem. Rev.* **2011**, *111*, 4703-4832; e) Giacalone, F.; Gruttadauria, M.; Agrigento, P.; Noto, R. *Chem. Soc. Rev.* **2012**, *41*, 2406-2447; f) Aleman, J.; Cabrera, S. *Chem. Soc. Rev.* **2013**, *42*, 774-793; g) Scheffler, U.; Mahrwald, R. *Chem. Eur. J.* **2013**, *19*, 14346-14396; h) Tsakos, M.; Kokotos, C. G. *Tetrahedron* **2013**, *69*, 10199-10222; i) Volla, C. M. R.; Atodiresei, I.; Rueping, M. *Chem. Rev.* **2014**, *114*, 2390-2431; j) Bhowmick, S.; Mondal, A.; Ghosh, A.; Bhowmick, K. C. *Tetrahedron:Asymmetry* **2015**, *26*, 1215-1244; k) Jimeno, C. *Org. Biomol. Chem.* **2016**, *14*, 6147-6164; l) Liu, J.; Wang, L. *Synthesis* **2017**, *49*, 960-972.
3. List, B.; Lerner, R. A.; Barbas III, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395-2396.
4. Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243-4244.
5. For recent reviews on the aldol reaction, see: a) Trost, B. M.; Brindle, C. S. *Chem. Soc. Rev.* **2010**, *39*, 1600-1632; b) Heravi, M. M.; Asadi, S. *Tetrahedron: Asymmetry* **2012**, *23*, 1431-1465; c) Mlynarski, J.; Bas, S. *Chem. Soc. Rev.* **2014**, *43*, 577-587.
6. For selected papers, see: a) Sakthivel, K.; Notz, W.; Bui, T.; Barbas III, C. F. *J. Am. Chem. Soc.* **2001**, *123*, 5260–5267; b) Torii, H.; Nakadai, M.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2004**, *43*, 1983-1986; c) Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 84-96; d) Berkessel, A.; Koch, B.; Lex, J. *Adv. Synth. Catal.* **2004**, *346*, 1141-1146; e) Bellis, E.; Vasilatou, K.; Kokotos, G. *Synthesis* **2005**, 2407-2413; f) Bellis, E.; Kokotos, G. *Tetrahedron* **2005**, *61*, 8669-8676; g) Companyo, X.; Valero, G.; Crovetto, L.; Moyano, A.; Rios, R. *Chem. Eur. J.* **2009**, *15*, 6564-6568; h) Tsandi, E.; Kokotos, C. G.; Kousidou, S.; Ragoussis, V.; Kokotos, G. *Tetrahedron* **2009**, *65*, 1444-1449; i) El-Hamdouni, N.; Companyo, X.; Rios, R.; Moyano, A. *Chem. Eur. J.* **2010**, *16*, 1142-1148.
7. For selected examples, see: a) Tang, Z.; Jiang, F.; Yu, L. T.; Cui, X.; Gong, L. Z.; Mi, A. Q.; Jiang, Y. Z. *J. Am. Chem. Soc.* **2003**, *125*, 5262-5263; b) Tang, Z.; Jiang, F.; Cui, X.; Gong, L. Z.; Mi, A. Q.; Jiang, Y. Z.; Wu, Y. D. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5755-5760; c) Tang, Z.; Yang, Z. H.; Chen, X. H.; Cun, L. F.; Mi, A. Q.; Jiang, Y. Z.; Gong, L. Z. *J. Am. Chem. Soc.* **2005**, *127*, 9285-9289; d) Gandgi, S.; Singh, V. K. *J. Org. Chem.* **2008**, *73*, 9411-9416; e) Wang, B.; Chen, G.-H.; Liu, L.-Y.; Chang, W.-X.; Li, J. *Adv. Synth. Cat.* **2009**, *351*, 2441-2448; f) Fotaras, S.; Kokotos, C. G.; Tsandi, E.; Kokotos, G. *Eur. J. Org. Chem.*, **2011**, 1310-1317; g) Fotaras, S.; Kokotos, C. G.; Kokotos, G. *Org. Biomol. Chem.* **2012**, *10*, 5613-5619; h) Revelou, P.; Kokotos, C. G.; Moutevelis-Minakakis, P. *Tetrahedron* **2012**, *68*, 8732-8738; i) Triandafillidi, I.; Bisticha, A.; Voutyritsa, E.; Galiatsatou, G.; Kokotos, C. G. *Tetrahedron* **2015**, *71*, 932-940; j) Bisticha, A.; Triandafillidi, I.; Kokotos, C. G. *Tetrahedron: Asymmetry* **2015**, *26*, 102-108.
8. For reviews, see: a) Colby Davie, E. A.; Mennen, S. M.; Xu, Y.; Miller, S. J. *Chem. Rev.* **2007**, *107*, 5759-5812; b) Wennemers, H. *Chem. Commun.* **2011**, *47*, 12036-12041.
9. For selected examples of organocatalytic transformations utilizing peptides not containing proline, see: a) Tsogoeva, S. B.; Wei, S. *Tetrahedron: Asymmetry* **2005**, *16*, 1947-1951; b) Zou, W.; Ibrahem, I.; Dziedzic, P.; Sunden, H.; Cordova, A. *Chem. Commun.* **2005**, 4946-4948; c) Dziedzic, P.; Zou, W.; Hafren, J.; Cordova, A. *Chem. Commun.* **2006**, *4*, 38-40; d) Cordova, A.; Zou, W.; Dziedzic, P.; Ibrahem, I.; Reyes, E.; Xu, Y. *Chem. Eur. J.* **2006**, *12*, 5383-5397
10. For selected examples of organocatalytic transformations utilizing proline-based peptides, see: a) Martin, H. J.; List, B. *Synlett* **2003**, 1901-1902; b) Kofoed, J.; Nielsen, J.; Reymond, J.-L. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2445-2447.; c) Tang, Z.; Tang, Z.-H.; Cun, L.-F.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z. *Org. Lett.* **2004**, *6*, 2285-2287; d) Shi, L.-X.; Sun, Q.; Ge, Z. M.; Zhu, Y.-Q.; Cheng, T.-M.; Li, R.-T. *Synlett* **2004**, 2215-2217; e) Krattiger, P.; Kovasy, R.; Revell, J. D.; Ivan, S.; Wennemers, H. *Org. Lett.* **2005**, *7*, 1101-1103; f) Lei, M.; Shi, L.; Li, G.; Chen, S.; Fang, W.; Ge, Z.; Cheng, T.; Li, R. *Tetrahedron* **2007**, *63*, 7892-7898; g) Revell, J. D.; Wennemers, H. *Adv. Synth. Catal.* **2008**, *350*, 1046-1052; h) Chen, Y.-H.; Sung, P.-H.; Sung, K. *Amino Acids* **2010**, *38*, 839-845
11. a) Hayashi, Y.; Sumiya, T.; Takahashi, J.; Gotoh, H.; Urushima, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2006**, *45*, 958-961; b) Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas III, C. F. *J. Am. Chem. Soc.* **2006**, *128*, 734-735.
12. For tryptophane-catalyzed aldol reaction, see: a) Jiang, Z.; Liang, Z.; Wu, X.; Lu, Y. *Chem. Commun.* **2006**, 2801-203; b) Amedjkouh, M. *Tetrahedron: Asymmetry* **2007**, *18*, 390-395; for threonine-catalyzed aldol reaction, see: c) Wu, X.; Jiang, Z.; Shen, H.-M.; Lu, Y. *Adv. Synth. Cat.* **2007**, *349*, 812-816; for serine-catalyzed aldol reaction, see: d) Teo, Y.-C. *Tetrahedron: Asymmetry* **2007**, *18*, 1155-1158; e) Wu, C.; Fu, X.; Li, S. *Tetrahedron* **2011**, *67*, 4283-4290; for chitosan-catalyzed aldol reaction, see: f) Gioia, C.; Ricci, A.; Bernardi, L.; Bourahla, K.; Tanchoux, N.; Robitzer, M.; Quignard, F. *Eur. J. Org. Chem.* **2013**, 588-594; for leucine-catalyzed aldol reaction, see: g) Burroughs, L.; Vale, M. E.; Gilks, J. A. R.; Forintos, H.; Hayes, C. J.; Clarke, P. A. *Chem. Commun.* **2010**, *46*, 4776-4778; h) Burroughs, L.; Clarke, P. A.; Forintos, H.; Gilks, J. A. R.; Hayes, C. J.; Vale, M. E.; Wade, W.; Zbytniewski, M. *Org. Biomol. Chem.* **2012**, *10*, 1565-1570.
13. a) Guillena, G.; Hita, M. C.; Najera, C. *Tetrahedron: Asymmetry* **2006**, *17*, 1493-1497; b) Wu, Y.; Zhang, Y.; Yu, M.; Zhao, G.; Wang, S. *Org. Lett.* **2006**, *8*, 4417-4420; c) Font, D.; Jimeno, C.; Pericas, M. A. *Org. Lett.* **2006**, *8*, 4653-4656; d) Guizzetti, S.; Benaglia, M.; Raimondi, L.; Celentano, G. *Org. Lett.* **2007**, *9*, 1247-1250; e) Maya, V.; Raj. M.; Singh, V. K. *Org. Lett.* **2007**, *9*, 2593-2595; f) Wang, C.; Jiang, Y.; Zhang, X.-X.; Huang, Y.; Li, B.-G.; Zhang, G.-L. *Tetrahedron Lett.* **2007**, *48*, 4281-4285; g) Aratake, S.; Itoh, T.; Okano, T.; Nagae, N.; Sumiya, T.; Shoji, M.; Hayashi, Y. *Chem. Eur. J.* **2007**, *13*, 10246-10256; h) Zu, L.; Xie, H.; Li, H.; Wang, J.; Wang, W. *Org. Lett.* **2008**, *10*, 1211-1214; i) Zhao, J.-F.; He, L.; Jiang, J.; Tang, Z.; Cun, L.-F.; Gong, L.-Z. *Tetrahedron Lett.* **2008**, *49*, 3372-3375; j) Mase, N.; Noshiro, N.; Mokuya, A.; Takabe, K. *Adv. Synth. Cat.* **2009**, *351*, 2791-2796;

k) Zhang, S.-P.; Fu, X.-K.; Fu, S.-D. *Tetrahedron Lett.* **2009**, *50*, 1173-1176; l) Giacalone, F.; Gruttadauria, M.; Agrigento, P.; Lo Meo, P.; Noto, R. *Eur. J. Org. Chem.* **2010**, 5696-5704; m) Wang, B.; Liu, X.-W.; Liu, L.-Y.; Chang, W.-X.; Li, J. *Eur. J. Org. Chem.* **2010**, 5951-5954; n) Tang, G.; Hu, X.; Altenbach, H. J. *Tetrahedron Lett.* **2011**, *52*, 7034-7037; o) Lipshutz, B. H.; Ghorai, S. *Org. Lett.* **2012**, *14*, 422-425; p) Kochetkov, S. V.; Kucherenko, A. S.; Kryshtal, G. V.; Zhdankina, G. M.; Zlotin, S. G. *Eur. J. Org. Chem.* **2012**, 7129-7134.

14. Psarra, A.; Kokotos, C. G.; Moutevelis-Minakakis, P. *Tetrahedron* **2014**, *70*, 608-615.
15. a) Chronopoulos, D. D.; Tsakos, M.; Karousis, N.; Kokotos, C. G.; Tagmatarchis, N. *Mat. Lett.* **2014**, *137*, 343-346; b) Chronopoulos, D. D.; Kokotos, C. G.; Karousis, N.; Kokotos, G.; Tagmatarchis, N. *Nanoscale* **2015**, *7*, 2750-2757; c) Chronopoulos, D. D.; Kokotos, C. G.; Tsakos, M.; Karousis, N.; Kokotos, G.; Tagmatarchis, N. *Mat. Lett.* **2015**, *157*, 212-214.
16. a) Tsakos, M.; Elsegood, M. R. J.; Kokotos, C. G. *Chem. Commun.***2013**, *49*, 2219-2221; b) Limnios, D.; Kokotos, C. G. *RSC Adv.* **2013**, *3*, 4496-4499; c) Theodorou, A.; Papadopoulos, G. N.; Kokotos, C. G. *Tetrahedron* **2013**, *69*, 5438-5443; d) Kokotos, C. G. *Org. Lett.* **2013**, *15*, 2406-2409.
17. The main pathway for racemization in peptide coupling is azlactone formation. It is known in literature that proline does not give racemization in peptide coupling; for a book, see: Doonan, S. *Peptides and Proteins*, Royal Chemical Society: Cambridge, 2002, p 37-38.
18. Brɐpa-Valle, L. J.; Sαnchez, C. R.; Cruz-Almanza, R. *Tetrahedron: Asymmetry* **1996**, *7*, 1019-1026.
19. Kokotos, G.; Constantinou, V. *J. Chem. Research* **1992**, *391*, 3117-3132.
20. Qiu, X. L.; Qing, F. L. *J. Org. Chem.* **2005**, *70*, 3826-3837.
21. Kokotos, C. G. *J. Org. Chem.* **2012**, *77*, 1131-1135.
22. Tanabe, M.; Peters, R. *Org. Synth.* **1990**, *7*, 386-392.
23. Subba Reddy, B. V.; Bhavani, K.; Raju, A.; Yadav, J. S. *Tetrahedron: Asymmetry* **2011**, *22*, 881-886.
24. Karmakar, A.; Maji, T.; Wittmann, S.; Reiser, O. *Chem. Eur. J.* **2011**, *17*, 11024-11029.