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Novel prolinamide–ureas as organocatalysts for the asymmetric aldol reaction

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ABSTRACT

Among the various versions of the aldol reaction, the enantioselective reaction between cyclic ketones and aldehydes constitutes a typical reaction model for the evaluation of novel organocatalysts. A multifunctional organocatalyst consisting of a prolinamide moiety, a *gem* diamine unit and a urea group was successfully employed in this asymmetric transformation. The products of the reaction between various ketones and aldehydes were obtained in high yields (up to 98%) with excellent diastereo- (up to >98:2 dr) and enantioselectivities (up to 99% ee).

1. Introduction

Among the various C–C bond forming reactions in modern asymmetric catalysis, aldol reaction possesses a pivotal role.[1] With the recognition of organocatalysis as the third branch of asymmetric catalysis, alongside the transition metal complexes catalysis and biocatalysis,[2,3] a significant increase in the number of the studies concerning aldol reactions has been realized. Proline and proline derivatives containing bioisosteric groups like sulfonamides and tetrazoles possess a prominent position among the organocatalysts utilized.[4] The five-membered secondary amine structure of the pyrrolidine ring enables the activation of carbonyl compounds through the formation of enamine intermediates, while incorporation of a chiral template provides extra interactions or a bulky environment leading to enhanced selectivity.

Since the pioneering work of List and co-workers,[5] the aldol reaction has been extensively studied. Nowadays, it is well accepted that organocatalysts combining the prolinamide unit with functionalities able to act as hydrogen bond donors are among the most successful classes of catalysts employed in the aldol reaction. Representative examples of such prolinamides that efficiently catalyze the aldol reactions are shown in Fig. 1 (compounds **1**–**5**).[6–10]

Taking into account the high catalytic activity of catalyst **5**,[10] and the assumption that the combination of a prolinamide with an urea moiety should provide similar modes of activation through hydrogen bonding as in catalyst **5**, we commenced a study on the catalytic activity presented by compounds that combine these two catalytic motives coupled with a chiral *gem* diamine derived from an amino acid (Fig. 2). In comparison to catalyst **5**, the novel family of catalysts lacks one of the chiral centres of the diamine backbone of catalyst **5**, while at the same time the prolinamide and the urea group are closer to each other.

2. Results and discussion

(*S*)-Benzyloxycarbonyl protected proline (**6**) was coupled with (*S*)-methyl phenylalaninate (**7a**), (*S*)-methyl phenylglycinate (**7b**) or (*R*)-methyl phenylglycinate (**7c**) using dicyclohexylcarbodiimide

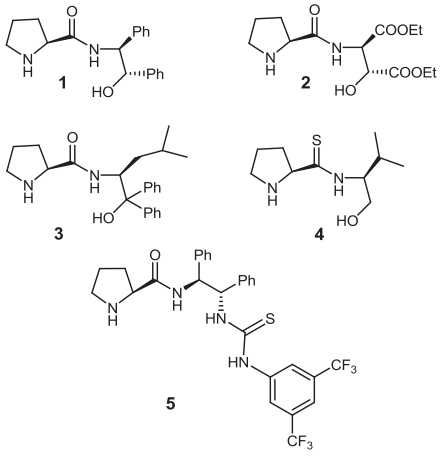

Fig. 1. Known prolinamide organocatalysts.

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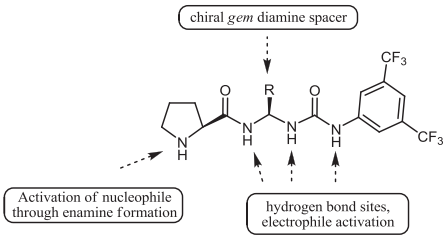
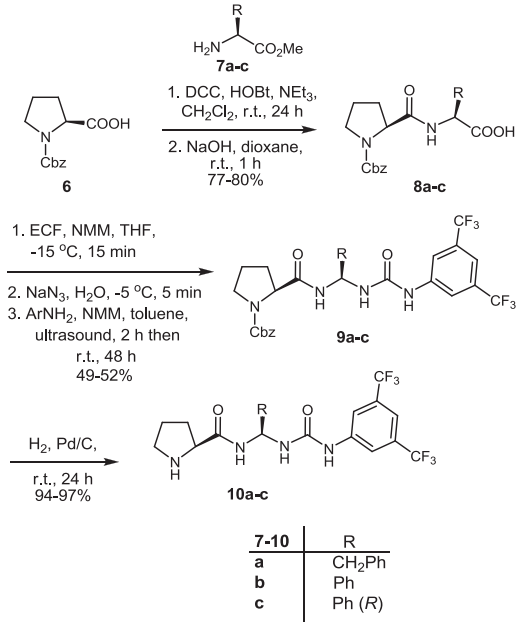


Fig. 2. Design of the organocatalysts used in this study.

(DCC) as a condensing agent in the presence of 1-hydroxybenzotriazole (HOBt). Saponification afforded the *N*-protected dipeptides **8a**–**c**. The crucial step in the synthesis of the catalyst is the formation of the isocyanate via a Curtius rearrangement[11] of the acyl azide derived from the reaction of the mixed anhydride of **8** with sodium azide. The Curtius rearrangement was accomplished by sonication[12,13] and the resultant isocyanate was converted into the urea derivative when it was treated with 3,5-bis(trifluoromethyl)aniline leading to the protected prolinamide–ureas **9a**–**c** with retention of stereochemistry.[14] Finally, deprotection via hydrogenation afforded organocatalysts **10a**–**c** (Scheme 1).



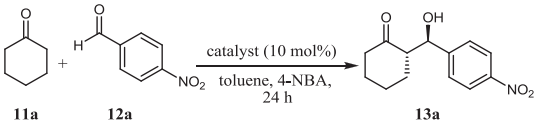
Scheme 1. Synthesis of the organocatalysts **10a**–**c**.

The synthesized organocatalysts were then evaluated in the aldol reaction between cyclohexanone (**11a**) and 4-nitrobenzaldehyde (**12a**) (Table 1). The reaction conditions that were used for the initial comparison of the three catalysts were the optimum reaction conditions for catalyst **5** (entry 8, Table 1),[10] since our expectations were to adopt similar activation modes. At low temperatures, all three organocatalysts afforded the product in good to excellent yields, high to excellent diastereoselectivities and high to excellent enantioselectivities (entries 1–3, Table 1).

Comparing organocatalysts **10a** with **10b**, it is obvious that the aromatic ring of the *gem* diamine spacer needs to be a carbon atom away from the stereogenic centre (phenylalanine instead of phenylglycine) in order to get faster reaction rates and thus higher yields, while in both cases the selectivities are excellent (entry 1 vs entry 2, Table 1). The combination of (*S*)-proline with (*R*)-phenylglycine led to lower yield and selectivities, when it was used instead of (*S*)-proline with (*S*)-phenylglycine, highlighting a clear mismatch effect (entry 2 vs entry 3, Table 1). When the reaction was carried out at 0 °C, all three catalysts afforded the product in high yields, however, the selectivities dropped (entries 3–6, Table 1). Finally, organocatalyst **10a** that afforded the best results, was also tested at room temperature (entry 7, Table 1). Unfortunately, the selectivity of the reaction dropped even more.

A survey on the reaction solvent and the acid additive was then undertaken (Table 2). Unfortunately, no other solvent or additive delivered better results (entries 1–6, Table 2). When the catalyst loading was reduced to 5 mol %, the reaction time had to be increased to afford similar results (entry 7, Table 2). Also, once the amount of ketone was reduced to 5 equiv, the reaction time had to be extended to obtain high yields and selectivities (entry 8, Table 2).

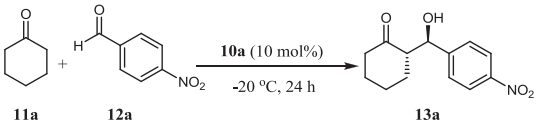
Table 1
Enantioselective aldol reaction of cyclohexanone with 4-nitrobenzaldehyde using catalysts **10a**–**c**



Entry	Catalyst	Temperature (°C)	Yield[a] (%)	dr[b]	ee[c] (%)
1	**10a**	−20	96	98:2	98
2[d]	**10b**	−20	72	99:1	96
3[d]	**10c**	−20	65	95:5	91
4	**10a**	0	94	91:9	95
5[d]	**10b**	0	91	92:8	94
6[d]	**10c**	0	85	85:15	83
7	**10a**	rt	97	83:17	85
8	**5**[10]	−20	100	97:3	99

[a] Yield of isolated product.
[b] The diastereomeric ratio (dr) was determined by ^{1}H NMR spectroscopy of the crude reaction mixture.
[c] The enantiomeric excess (ee) for the major isomer was determined by chiral HPLC.
[d] Reaction time 48 h. 4-NBA: 4-nitrobenzoic acid.

Table 2
Enantioselective aldol reaction of cyclohexanone with 4-nitrobenzaldehyde using catalyst **10a**

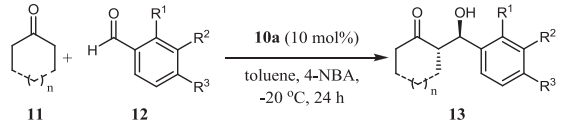


Entry	Conditions	Yield[a] (%)	dr[b]	ee[c] (%)
1	Toluene, 4-NBA	96	98:2	98
2	CH_2Cl_2, 4-NBA	74	97:3	79
3	THF, 4-NBA	86	97:3	52
4	Et_2O, 4-NBA	42	95:5	55
5	Toluene, AcOH	84	97:3	94
6	Toluene, PhCOOH	94	98:2	96
7[d]	Toluene, 4-NBA	88	98:2	98
8[e]	Toluene, 4-NBA	84	98:2	98

[a] Yield of isolated product.
[b] The diastereomeric ratio (dr) was determined by ^{1}H NMR spectroscopy of the crude reaction mixture.
[c] The enantiomeric excess (ee) for the major isomer was determined by chiral HPLC.
[d] Catalyst (5 mol%) was used, reaction time 48 h.
[e] Ratio of ketone to aldehyde 5:1, reaction time 48 h. 4-NBA: 4-nitrobenzoic acid, AcOH: acetic acid.

The scope and the limitations of the organocatalyst **10a** were also tested (Table 3). A variety of substituted aromatic aldehydes could be utilized affording the products in good to excellent yields and high to excellent selectivities (entries 1–8, Table 3). Electron-withdrawing groups at any position of the aryl moiety led to excellent results, while the use of benzaldehyde or aromatic aldehydes *para*-substituted with halogens led to lower yields, albeit with excellent selectivities. Tetrahydropyran-4-one and tetrahydrothiopyran-4-one proved to be difficult substrates and required longer reaction times in order to deliver the products in high yields (entries 9 and 10, Table 3). Disubstituted cyclohexanone at the 4-position required prolonged reaction time to deliver a mediocre yield and lower diastereoselectivity (entry 11, Table 3). The desymmetrization of ketones is also possible utilizing organocatalyst **10a**, since 4-methylcyclohexanone delivered the product in high yield and with excellent selectivities (entry 12, Table 3). Cyclopentanone was also utilized with some success (entry 13, Table 3). Moreover, in order to broaden the scope of this methodology, we investigated the reaction of acetone with 4-nitrobenzaldehyde (entry 14, Table 3). Although a high yield was obtained, the enantioselectivity observed was not satisfactory. Comparing catalyst **10a** with parent catalyst **5**,[10] it is obvious that **10a** behaves similarly with **5** when cyclic ketones are used as the nucleophile. Unfortunately, when less bulky ketones are utilized, like acetone, **10a** leads to inferior results compared to **5**.[10]

Table 3
Enantioselective aldol reaction between ketones and aldehydes using catalyst **10a**



11 12 13

Entry	Ketone	Ar	Yield[a] (%)	dr[b]	ee[c] (%)
1		4-$NO_2C_6H_4$	96 (**13a**)	98:2	98
2		3-$NO_2C_6H_4$	87 (**13b**)	96:4	96
3[d]		2-$NO_2C_6H_4$	90 (**13c**)	>99:1	98
4[e]		4-$CF_3C_6H_4$	77 (**13d**)	>99:1	97
5[d]		3-CNC_6H_4	98 (**13e**)	>99:1	97
6[e]		C_6H_5	51 (**13f**)	>99:1	96
7[d]		4-FC_6H_4	47 (**13g**)	>99:1	97
8[d]		4-BrC_6H_4	30 (**13h**)	>99:1	95
9[f]		4-$NO_2C_6H_4$	90 (**13i**)	95:5	92
10[d]		4-$NO_2C_6H_4$	90 (**13j**)	92:8	97
11[d]		4-$NO_2C_6H_4$	42 (**13k**)	84:16	92
12		4-$NO_2C_6H_4$	90 (**13l**)	99:1	99
13		4-$NO_2C_6H_4$	97 (**13m**)	30:70	75[g]
14[e]		4-$NO_2C_6H_4$	91 (**13n**)	—	66

[a] Yield of isolated product.
[b] The diastereomeric ratio (dr) was determined by ^{1}H NMR spectroscopy of the crude reaction mixture.
[c] The enantiomeric excess (ee) for the major isomer was determined by chiral HPLC.
[d] Reaction time 72 h.
[e] Reaction time 48 h.
[f] Reaction time 120 h.
[g] Major isomer *syn*: 75% ee, minor isomer *anti*: 80% ee.

It is clear that an organocatalyst combining the prolinamide unit with a chiral diamine spacer derived from an α-amino acid and an aryl urea moiety provides the products of the aldol reaction between cyclic ketones and aromatic aldehydes in excellent yields and selectivities. Nowadays, it is well accepted that when proline derivatives are used as catalysts, the catalytic mechanism includes activation of the nucleophile via an enamine intermediate, while the approach of the electrophile is governed by an internal acid/hydrogen bonding. Similarly to catalyst **5**,[10] a plausible transition-state model is proposed in Fig. 3. The secondary amine of the pyrrolidine ring activates the ketone through the formation of an enamine intermediate. It is likely that the electrophile is activated through a multiple hydrogen bonding network comprised from the amide and the urea functionality (Fig. 3, **I**). An alternative pathway could be also envisaged where the acid co-catalyst participates in the transition state of the reaction (Fig. 3, **II**).

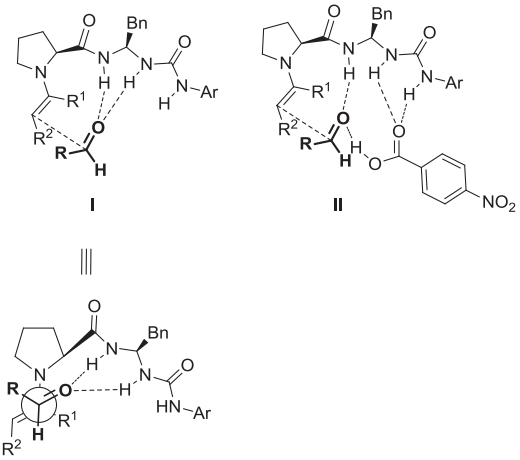


Fig. 3. Proposed transition-state models for the aldol reaction in the absence (**I**) and in the presence of the acid co-catalyst (**II**).

3. Conclusions

In conclusion, the synthesis and the evaluation of novel prolinamide compounds bearing an aryl urea moiety were carried out. When a chiral *gem* diamine spacer easily derived from the natural α-amino acid phenylalanine was used, the best results were obtained. This novel organocatalyst provided the products of the reaction between cyclic ketones with aromatic aldehydes in excellent yields and selectivities in the presence of 4-nitrobenzoic acid as the acid co-catalyst.

4. Experimental section

4.1. 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 aluminium 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 and are uncorrected. IR spectra were recorded on a Nicolet 6700 FT-IR spectrometer and are reported in terms of frequency of absorption (cm^{-1}). ^1H and ^{13}C NMR spectra were recorded on Varian Mercury (200 or 50 MHz) as noted, and are internally referenced to residual solvent signals ($CDCl_3$). Data for ^1H NMR spectroscopy are reported as follows: chemical shift (δ ppm), multiplicity (s=singlet, d=doublet, t=triplet, q=quadruplet, m=multiplet, bs=broad signal, bs m=broad signal multiplet), integration, coupling constant and assignment. Wherever rotamers exist, are presented in brackets. Diastereomeric ratios were determined by ^1H NMR spectroscopy (200 MHz). Data for ^{13}C NMR spectroscopy are reported in terms of chemical shift (δ ppm). 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. 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 and only when the diastereomeric ratio of the product was >99:1. The configuration of the products has been assigned by comparison to literature data. Data for known compounds match literature data.

4.2. General procedure for the synthesis of the catalysts

*4.2.1. (S)-2-[(S)-1-(Benzyloxycarbonyl)pyrrolidine-2-carboxamido]-3-phenylpropanoic acid (**8a**).* To a stirred solution of Cbz-proline (**6**) (1.20 g, 5.00 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C, 1-hydroxybenzotriazole (HOBt) (0.670 g, 5.00 mmol), (*S*)-methyl phenylalaninate hydrochloride (**7a**) (1.07 g, 5.00 mmol), Et_3N (0.700 mL, 5.00 mmol) and dicyclohexylcarbodiimide (DCC) (1.10 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 (30:70). White solid;[15] 1.90 g, 92% yield; R_f (pet. ether/EtOAc 7:3) 0.67; mp 66–68 °C; $[\alpha]_D$ −32.8 (*c* 1.0, CH_3OH) {lit.: $[\alpha]_D$ −35.4 (*c* 1.0, CH_3OH)[15b]}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.44–6.94 (10H, m, ArH), 6.35 (1H, br s, NH), 5.12 (2H, s, OCH_2), 4.83 (1H, dd, *J*=13.5, 6.7 Hz, NCH), 4.31 (1H, t, *J*=8.5 Hz, NCH), 3.68 (3H, s, OCH_3), 3.42–3.31 (2H, m, NCH_2), 3.21–3.05 (1H, m, PhC*H*H), 2.97(1H, dd, *J*=13.3, 6.9 Hz, PhCH*H*), 2.39–2.01 (1H, m, C*H*H), 1.99–1.65 (3H, m, 3×CH*H*); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.0, 170.5, 155.1, 135.9, 135.5, 128.6, 127.8, 127.3, 127.2, 127.1, 126.2, 66.4, 59.6, 52.6, 51.5, 46.1, 37.1, 27.6, 23.7.

To a stirred solution of the dipeptide (0.200 g, 0.48 mmol) in dioxane (1 mL), an aq solution of NaOH (2 N, 0.3 mL) was added. The reaction mixture was left stirring for 1 h at room temperature. The crude mixture was extracted with Et_2O (2×20 mL). The aqueous layer was acidified with aq HCl (2 N) until pH 2 and the crude product was extracted with EtOAc (2×30 mL). The combined organic layers were washed with H_2O (30 mL), dried and the solvent was removed under reduced pressure. The product **8a** was isolated as a white solid;[16] 0.162 g, 85% yield; R_f (*n*-butanol/AcOH/H_2O 4:1:1) 0.80; mp 124–126 °C; $[\alpha]_D$ −49.0 (*c* 2.5, $CHCl_3$) {lit.: $[\alpha]_D$ −49.0 (*c* 2.5, $CHCl_3$)}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.43–7.03 (10H, m, ArH), 6.48 (1H, br s, NH), 5.09 (2H, s, OCH_2), 4.82 (1H, dd, *J*=12.2, 6.5 Hz, NCH), 4.32–4.25 (1H, m, NCH), 3.41–3.11 (3H, m, PhC*H*H and NCH_2), 3.09–2.89 (1H, m, PhC*H*H), 2.37–2.05 (1H, m, C*H*H), 2.01–1.62 (3H, m, 3×CH*H*); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.8, 171.8, 156.0, 135.9, 135.7, 129.2, 128.3, 128.2, 128.0, 127.8, 126.8, 67.4, 60.2, 52.9, 46.7, 37.2, 28.2, 24.1.

*4.2.2. (S)-2-[(S)-1-(Benzyloxycarbonyl)pyrrolidine-2-carboxamido]-2-phenylacetic acid (**8b**).* Same procedure as above, but utilizing (*S*)-methyl phenylglycinate hydrochloride (**7b**) (1.00 g, 5.00 mmol). White solid; 1.529 g, 80% yield; R_f (*n*-butanol/AcOH/H_2O 4:1:1) 0.73; mp 194–195 °C; $[\alpha]_D$ +19.4 (*c* 1.0, CH_3OH); IR (KBr) 3313, 3062, 2960, 1732, 1662, 717, 695, 648 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) δ 8.70 (1H, br s, NH), 7.48–7.18 (10H, m, ArH), 5.39 (1H, br s, NCH), 5.11–5.01 (2H, m, OCH_2), 4.40 (1H, dd, *J*=8.3, 3.9 Hz, NCH), 3.63–3.43 (2H, m, NCH_2), 2.36–2.15 (1H, m, C*H*H), 2.11–1.82 (3H, m, 3×CH*H*); ^{13}C NMR (50 MHz, CD_3OD) δ 174.9, 173.5, 157.1, 137.7, 137.6, 129.8, 129.7, 129.5, 129.2, 128.9, 128.7, 68.2, 60.9, 58.2, 47.7, 32.5, 24.6; MS 381 (M−H^+, 100); HRMS exact mass calculated for $[M-H]^+$ ($C_{21}H_{21}N_2O_5$) requires *m*/*z* 381.4025, found *m*/*z* 381.4016.

*4.2.3. (S)-2-[(R)-1-(Benzyloxycarbonyl)pyrrolidine-2-carboxamido]-2-phenylacetic acid (**8c**).* Same procedure as above, but utilizing (*R*)-methyl phenylglycinate hydrochloride (**7c**) (1.00 g, 5.00 mmol). White solid; 1.472 g, 77% yield; R_f (*n*-butanol/AcOH/H_2O 4:1:1) 0.83; mp 185–186 °C; $[\alpha]_D$ −138.0 (*c* 1.0, CH_3OH); IR (KBr) 3379, 3063, 2953, 1733, 1666, 719, 697, 639 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) δ 7.51–7.21 (10H, m, ArH), 5.44 (1H, br s, NCH), 5.15–5.04 (2H, s, OCH_2), 4.42–4.31 (1H, m, NCH), 3.63–3.43 (2H, m, NCH_2), 2.39–2.13 (1H, m, C*H*H), 2.13–1.75 (3H, m, 3×CH*H*); ^{13}C NMR (50 MHz, CD_3OD) δ 174.6, 173.1, 156.4, 138.4, 137.8, 129.7, 129.5, 129.4, 129.2, 128.9, 128.5, 68.2, 61.2, 57.8, 47.6, 32.4, 24.5; MS 381 (M+H^+, 100); HRMS exact mass calculated for $[M-H]^+$ ($C_{21}H_{21}N_2O_5$) requires *m*/*z* 381.4025, found *m*/*z* 381.4014.

*4.2.4. (S)-Benzyl 2-{(R)-1-[3-(3,5-bis(trifluoromethyl)phenyl)ureiodo]-2-phenylethylcarbamoyl}pyrrolidine-1-carboxylate (**9a**).* To a stirred solution of dipeptide **8a** (0.476 g, 1.20 mmol) in dry THF (6 mL) at −15 °C, *N*-methylmorpholine (NMM) (0.145 mL, 1.32 mmol) and ethyl chloroformate (ECF) (0.126 mL, 1.32 mmol) were added. The reaction mixture was left stirring at −10 °C for 15 min. The reaction mixture was warmed to −5 °C and a solution of NaN_3 (0.195 g, 3 .00 mmol) in H_2O (2 mL) was added. The reaction mixture was left stirring for 5 min and then, the solvents were evaporated under reduced pressure. The crude material was dissolved in CH_2Cl_2 (20 mL) and washed with aq $NaHCO_3$ (5%, 20 mL), H_2O (20 mL), aq citric acid (10%, 20 mL), brine (20 mL), dried (Na_2SO_4) and the solvents were evaporated. The crude product was dissolved in dry toluene (6 mL) and *N*-methylmorpholine (NMM) (0.145 mL, 1.32 mmol) and 3,5-bis(trifluoromethyl)aniline (0.187 mL, 1.20 mmol) were added. The reaction mixture was put in an ultrasound bath for 2 h. Then, it was left to stir at room temperature for 48 h. After evaporation of the solvent, the crude product was purified using column chromatography eluting with pet. ether/EtOAc (10:90). White solid; 0.38 g, 52% yield; R_f (AcOEt/pet. ether 9:1) 0.69; mp 169–170 °C; $[\alpha]_D$ −22.6 (*c* 1.0, $CHCl_3$); IR (KBr) 3328, 1664, 1576, 1388, 1129, 880, 732, 699, 681 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.90 (2H, s, ArH), 7.42 (1H, s, ArH), 7.42–7.03 (12H, m, ArH and 2×NH), 6.61–6.20 (1H, br s, NH), 5.58–5.39 (1H, m, NCH), 5.18–4.87 (2H, m, OCH_2), 4.32–4.17 (1H, m, NCH), 3.62–2.81 (4H, m, NCH_2 and $PhCH_2$), 2.15–1.55 (4H, m, 4×CH*H*); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.7, 156.1, 154.8, 141.0, 135.8, 131.7 (q, *J*=33.0 Hz), 129.2, 128.9, 128.6, 128.5, 128.2, 127.8, 127.0, 123.3 (q, *J*=272.6 Hz), 118.4, 115.4, 67.5, 60.7, 58.7, 46.9, 40.0, 29.7, 24.1; ^{19}F NMR (188 MHz, $CDCl_3$) δ 9.47 (s); MS 623

(M+H$^+$, 100); HRMS exact mass calculated for [M+H]$^+$ ($C_{30}H_{29}F_6N_4O_4$) requires *m*/*z* 623.2088, found *m*/*z* 623.2068.

*4.2.5. (S)-Benzyl 2-{(R)-3-[3-(3,5-bis(trifluoromethyl)phenyl)ureiodo](phenyl)methylcarbamoyl}pyrrolidine-1-carboxylate (**9b**).* Same procedure as above, but utilizing **8b**; 0.37 g, 50% yield; R_f (AcOEt/pet. ether 7:3) 0.58; mp 190–191 °C; $[\alpha]_D$ −26.3 (*c* 1.0, DMF); IR (KBr) 3331, 2967, 2893, 1678, 1572, 1542, 1128, 879, 769, 735, 698 cm^{-1}; ^{1}H NMR (200 MHz, DMSO) *δ* 9.47 (1H, br s, NH), 8.86 (1H, s, NH), 8.04 (2H, s, ArH), 7.59 (1H, s, ArH), 7.46–7.11 (11H, m, ArH and NH), 6.59–6.41 (1H, m, NCH), 5.21–4.88 (2H, m, OCH_2), 4.37–4.19 (1H, m, NCH), 3.58–3.31 (2H, m, NCH_2), 2.31–2.03 (1H, m, C*H*H), 2.01–1.72 (3H, m, 3×CH*H*); ^{13}C NMR (50 MHz, DMSO) *δ* 171.7 (171.4), 153.6 (153.8), 153.5 (153.8), 142.0, 140.3, 136.7, 130.6 (q, *J*=32.2 Hz), 128.2, 128.1, 127.5, 127.3, 126.8, 125.8, 123.1 (q, *J*=265.1 Hz), 117.2, 113.9, 65.8, 59.8 (59.3), 57.9 (57.6), 47.0 (46.5), 31.9 (29.8), 23.0 (23.8); ^{19}F NMR (188 MHz, DMSO) *δ* 9.45 (s); MS 609 (M+H$^+$, 50); HRMS exact mass calculated for [M+H]$^+$ ($C_{29}H_{27}F_6N_4O_4$) requires *m*/*z* 609.1931, found *m*/*z* 609.1913.

*4.2.6. (S)-Benzyl 2-{(S)-3-[3-(3,5-bis(trifluoromethyl)phenyl)ureiodo](phenyl)methylcarbamoyl}pyrrolidine-1-carboxylate (**9c**).* Same procedure as above, but utilizing **8c**; 0.36 g, 49% yield; R_f (AcOEt/pet. ether 7:3) 0.61; mp 189–190 °C; $[\alpha]_D$ −28.0 (*c*1.0, DMF); IR (KBr) 3329, 2961, 2891, 1678, 1571, 1541, 1127, 879, 768, 735, 697 cm^{-1}; ^{1}H NMR (200 MHz, DMSO) *δ* 9.55–9.45 (1H, m, NH), 8.94–8.77 (1H, m, NH), 8.03–8.00 (2H, m, ArH), 7.56 (1H, s, ArH), 7.38–7.07 (11H, m, ArH and NH), 6.56–6.41 (1H, m, NCH), 5.12–4.83 (2H, m, OCH_2), 4.32–4.18 (1H, m, NCH), 3.54–3.33 (2H, m, NCH_2), 2.21–2.03 (1H, m, C*H*H), 1.88–1.65 (3H, m, 3×CH*H*); ^{13}C NMR (50 MHz, DMSO) *δ* 171.5 (171.7), 153.7 (154.0), 153.6 (153.8), 142.0, 140.3, 136.7, 130.6 (q, *J*=32.5 Hz), 128.2, 127.6, 127.3, 126.8, 125.9, 125.7, 123.1 (q, *J*=265.1 Hz), 117.2, 113.9, 65.8, 59.8 (59.3), 57.9 (57.6), 47.0 (46.5), 31.0 (30.0), 23.0 (23.8); ^{19}F NMR (188 MHz, DMSO) *δ* 9.42 (s); MS 609 (M+H$^+$, 45); HRMS exact mass calculated for [M+H]$^+$ ($C_{29}H_{27}F_6N_4O_4$) requires *m*/*z* 609.1931, found *m*/*z* 609.1912.

*4.2.7. (S)-N-{(R)-1-[3-(3,5-Bis(trifluoromethyl)phenyl)ureiodo]-2-phenylethyl}pyrrolidine-1-carboxyamide (**10a**).* To a stirred solution of compound **9a** (0.195 g, 0.320 mmol) in dry THF (10 mL), 10% Pd/C (10 mol %) was added and the reaction mixture was left stirring at room temperature for 24 h under hydrogen atmosphere. After filtration through Celite, the solvent was evaporated to afford the desired product. White solid; 0.15 g, 96% yield; R_f (*n*-butanol/AcOH/H_2O 4:1:1) 0.58; mp 183–185 °C; $[\alpha]_D$ +24.1 (*c* 1.0, THF); IR (KBr) 3266, 1695, 1638, 1132, 879, 729, 701, 680 cm^{-1}; ^{1}H NMR (200 MHz, DMSO) *δ* 8.41 (1H, d, *J*=8.6 Hz, NH), 8.05 (2H, s, ArH), 7.57 (1H, s, ArH), 7.35–7.15 (6H, m, ArH and NH), 6.92 (1H, d, *J*=7.6 Hz, NH), 5.66–5.46 (1H, m, NCH), 3.46 (1H, dd, *J*=8.6, 4.2 Hz, NCH), 3.11–2.95 (2H, m, NCH_2), 2.88–2.73 (1H, m, PhC*H*H), 2.69–2.57 (1H, m, PhC*H*H), 1.93–1.72 (1H, m, C*H*H), 1.54–1.28 (4H, m, NH and 3×CH*H*); ^{13}C NMR (50 MHz, DMSO) *δ* 173.8, 153.6, 142.2, 137.2, 130.5 (q, *J*=32.5 Hz), 129.2, 128.1, 126.2, 123.3 (q, *J*=272.1 Hz), 117.3, 113.8, 59.9, 57.0, 46.5, 40.6, 30.2, 25.5; ^{19}F NMR (188 MHz, DMSO) *δ* 9.46 (s); MS 489 (M+H$^+$, 100); HRMS exact mass calculated for [M+H]$^+$ ($C_{22}H_{23}F_6N_4O_2$) requires *m*/*z* 489.1720, found *m*/*z* 489.1704.

*4.2.8. (S)-N-{(R)-1-[3-(3,5-Bis(trifluoromethyl)phenyl)ureiodo]-2-phenylmethyl}pyrrolidine-1-carboxyamide (**10b**).* Same procedure as above, but utilizing **9b**. White solid; 0.14 g, 94% yield; R_f (*n*-butanol/AcOH/H_2O 4:1:1) 0.43; mp 170–171 °C; $[\alpha]_D$ −18.9 (*c* 1.0, CH_3OH); IR (KBr) 3280, 3097, 1683, 1626, 1583, 1129, 883, 751, 696, 681 cm^{-1}; ^{1}H NMR (200 MHz, CD_3OD) *δ* 8.02 (2H, s, ArH), 7.52 (1H, s, ArH), 7.52–7.19 (5H, m, ArH), 6.59 (1H, s, NCH), 3.83–3.65 (1H, m, NCH), 3.08–2.85 (2H, m, NCH_2), 2.27–2.03 (1H, m, C*H*H), 1.97–1.57 (3H, m, 3×CH*H*); ^{13}C NMR (50 MHz, CD_3OD) *δ* 176.4, 156.1, 143.1, 140.8, 133.2 (q, *J*=33.2 Hz), 129.8, 129.3, 127.1, 124.6 (q, *J*=250.2 Hz), 119.3, 116.0, 61.7, 60.3, 48.0, 32.1, 27.0; ^{19}F NMR (188 MHz, CD_3OD) *δ* 9.45 (s); MS 475 (M+H$^+$, 100); HRMS exact mass calculated for [M+H]$^+$ ($C_{21}H_{21}F_6N_4O_2$) requires *m*/*z* 475.1563, found *m*/*z* 475.1546.

*4.2.9. (S)-N-{(S)-1-[3-(3,5-Bis(trifluoromethyl)phenyl)ureiodo]-2-phenylmethyl}pyrrolidine-1-carboxyamide (**10c**).* Same procedure as above, but utilizing **9c**; 0.15 g, 97% yield; R_f (*n*-butanol/AcOH/H_2O 4:1:1) 0.38; mp 177–178 °C; $[\alpha]_D$ −10.0 (*c* 1.0, CH_3OH); IR (KBr) 3280, 3095, 1679, 1655, 1582, 1130, 844, 751, 696, 681 cm^{-1}; ^{1}H NMR (200 MHz, CD_3OD) *δ* 8.01 (2H, s, ArH), 7.51 (1H, s, ArH), 7.51–7.24 (5H, m, ArH), 6.65 (1H, s, NCH), 3.81–3.75 (1H, m, NCH), 3.14–2.89 (2H, m, NCH_2), 2.29–2.06 (1H, m, C*H*H), 1.92–1.67 (3H, m, 3×CH*H*); ^{13}C NMR (50 MHz, CD_3OD) *δ* 174.1, 154.9, 141.9, 139.4, 131.9 (q, *J*=32.3 Hz), 128.9, 128.1, 125.9, 123.5 (q, *J*=249.8 Hz), 117.9, 114.7, 60.3, 59.1, 46.7, 30.8, 25.5; ^{19}F NMR (188 MHz, CD_3OD) *δ* 9.45 (s); MS 475 (M+H$^+$, 100); HRMS exact mass calculated for [M+H]$^+$ ($C_{21}H_{21}F_6N_4O_2$) requires *m*/*z* 475.1563, found *m*/*z* 475.1547.

4.3. General procedure for the aldol reaction

To a stirred solution of catalyst (0.014 mmol) in toluene (1.0 mL), 4-nitrobenzoic acid (2.3 mg, 0.014 mmol) was added. The reaction mixture was cooled to −20 °C. The aldehyde (0.140 mmol) was added, followed by the ketone (1.40 mmol). The reaction mixture was left stirring at −20 °C for 24–120 h. The solvent was evaporated and the crude product was purified using column chromatography eluting with the appropriate mixture of petroleum ether (40–60 °C)/EtOAc to afford the desired product.

*4.3.1. (S)-2-[(R)-Hydroxy-(4-nitrophenyl)methyl]-cyclohexanone (**13a**, Table 3, entry 1).*[10] Colourless oil, 34 mg, 96% yield; R_f (AcOEt/pet. ether 4:6) 0.10; ^{1}H 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 and CHH), 2.17–1.29 (6H, m, 6×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: 25.15 min (minor) and 33.10 min (major), 98% ee.

*4.3.2. (S)-2-[(R)-Hydroxy-(3-nitrophenyl)methyl]-cyclohexanone (**13b**, Table 3, entry 2).*[17] Colourless oil, 31 mg, 87% yield; R_f (AcOEt/pet. ether 4:6) 0.20; ^{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 and CHH), 2.17–1.32 (6H, m, 6×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 92:8, flow rate 1.0 mL/min, retention time: 25.15 min (major) and 31.99 min (minor), 96% ee.

*4.3.3. (S)-2-[(R)-Hydroxy-(2-nitrophenyl)methyl]-cyclohexanone (**13c**, Table 3, entry 3).*[17] Yellow solid, 31 mg, 90% yield; R_f (AcOEt/pet. ether 3:7) 0.25; $[\alpha]_D$ +16.6 (*c* 1.5, $CHCl_3$); ^{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), 2.85–2.01 (3H, m, COCH, CHH), 1.90–1.52 (6H, m, 6×C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$) *δ* 214.9, 136.5, 133.0, 128.9, 128.3, 128.2, 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: 40.77 min (major) and 42.92 min (minor), 98% ee.

*4.3.4. (S)-2-[(R)-Hydroxy-(4-(trifluoromethyl)phenyl)methyl]-cyclohexanone (**13d**, Table 3, entry 4).*[18] White solid, 29 mg, 77% yield; R_f (AcOEt/pet. ether 4:6) 0.48; $[\alpha]_D$ +2.0 (*c* 0.5, $CHCl_3$); ^{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 and 3×C*H*H), 1.90–1.39 (5H, m, 5×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 3.89 (s); HPLC analysis: Diacel Chiralpak AD-H, hexane/^{i}PrOH 90:10, flow rate 0.5 mL/min, retention time: 22.16 min (minor) and 27.63 min (major), 97% ee.

*4.3.5. (R)-3-[Hydroxy-(2-(S)-oxocyclohexyl)methyl]-benzonitrile (**13e**, Table 3, entry 5).*[19] Yellow solid, 32 mg, 98% yield; R_f (AcOEt/pet. ether 3:7) 0.17; $[\alpha]_D$ +20.2 (*c* 1.1, $CHCl_3$); ^{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 and 3×C*H*H), 1.87–1.22 (5H, m, 5×C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 214.6, 142.6, 131.5, 130.6, 129.1, 129.0, 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: 28.15 min (minor) and 42.58 min (major), 97% ee.

*4.3.6. (S)-2-[(R)-Hydroxy-(phenyl)methyl]-cyclohexanone (**13f**, Table 3, entry 6).*[18] Colourless oil, 15 mg, 51% yield; R_f (AcOEt/pet. ether 4:6) 0.42; $[\alpha]_D$ +23.1 (*c* 1.0, $CHCl_3$); ^{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 and CHH), 2.15–1.24 (6H, m, 6×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: 17.73 min (major) and 24.49 min (minor), 96% ee.

*4.3.7. (S)-2-[(R)-Hydroxy-(4-(fluorophenyl)methyl)]-cyclohexanone (**13g**, Table 3, entry 7).*[20] White solid, 17 mg, 47% yield; R_f (AcOEt/pet. ether 4:6) 0.16; $[\alpha]_D$ +22.5 (*c* 0.9, $CHCl_3$); ^{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 and CHH), 2.08–1.22 (6H, m, 6×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 −48.12 (s); HPLC analysis: Diacel Chiralpak AD-H, hexane/^{i}PrOH 90:10, flow rate 0.5 mL/min, retention time: 26.65 min (minor) and 29.59 min (major), 97% ee.

*4.3.8. (S)-2-[(R)-Hydroxy-(4-(bromophenyl)methyl)]-cyclohexanone (**13h**, Table 3, entry 8).*[10] White solid, 12 mg, 30% yield; R_f (AcOEt/pet. ether 3:7) 0.24; $[\alpha]_D$ +18.3 (*c* 0.5, $CHCl_3$); ^{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 and CHH), 2.11–2.01 (1H, m, C*H*H), 1.88–1.24 (5H, m, 5×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: 29.89 min (minor) and 34.91 min (major), 95% ee.

*4.3.9. (S)-3-[(R)-Hydroxy-[4-(nitrophenyl)methyl]dihydro-2H-pyran-4(3H)-one (**13i**, Table 3, entry 9).*[10] Pale yellow solid, 32 mg, 90% yield; 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×OC*H*H and OH), 3.44 (1H, dd, *J*=11.4, 9.8 Hz, OC*H*H), 3.02–2.41 (3H, m, 3×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: 20.34 min (minor) and 23.74 min (major), 92% ee.

*4.3.10. (S)-3-[(R)-Hydroxy-[4-(nitrophenyl)methyl]dihydro-2H-thiopyran-4(3H)-one (**13j**, Table 3, entry 10).*[10] Yellow solid, 34 mg, 90% yield; R_f (AcOEt/pet. ether 3:7) 0.13; ^{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 and CHH), 2.87–2.70 (2H, m, 2×C*H*H), 2.68–2.42 (2H, m, 2×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: 51.85 min (minor) and 73.77 min (major), 97% ee.

*4.3.11. (S)-7-[(R)-Hydroxy-4-(nitrophenyl)methyl]-1,4-dioxospiro [4.5]decan-8-one (**13k**, Table 3, entry 11).*[10] White solid, 18 mg, 42% yield; R_f (AcOEt/pet. ether 3:7) 0.06; ^{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×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×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: 10.16 min (*syn* minor) and 15.08 min (*syn* major), 11.96 min (*anti* minor) and 18.97 min (*anti* major), 92% ee.

*4.3.12. (2S,4R)-2-[(R)-Hydroxy-(4-(nitrophenyl)methyl)]-4-methylcyclohexanone (**13l**, Table 3, entry 12).*[21] Yellow solid, 33 mg, 90% yield; R_f (AcOEt/pet. ether 3:7) 0.15; $[\alpha]_D$ −6.8 (*c* 1.0, $CHCl_3$); ^{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 and CHH), 2.15–1.29 (5H, m, 4×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 AD-H, hexane/ ^{i}PrOH 90:10, flow rate 1.0 mL/min, retention time: 28.87 min (major) and 31.22 min (minor), 99% ee.

*4.3.13. (S)-2-[(R)-Hydroxy-(4-(nitrophenyl)methyl)]-cyclopentanone (**13m**, Table 3, entry 13).*[10] Pale yellow oil, 32 mg, 97% 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 and CHH), 2.15–1.83 (2H, m, 2×C*H*H), 1.78–1.55 (2H, m, 2×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: 26.51 min (*syn* major) and 37.88 min (*syn* minor), 48.25 min (*anti* minor) and 50.49 min (*anti* major), *syn* isomer 75% ee, *anti* isomer 80% ee.

*4.3.14. (R)-4-Hydroxy-4-(4-nitrophenyl)-butan-2-one (**13n**, Table 3, entry 14).*[10] Colourless oil, 27 mg, 91% yield; R_f (AcOEt/pet. ether 4:6) 0.14; $[\alpha]_D$ +36.9 (*c* 1.4, $CHCl_3$); ^{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 AD-RH, MeCN/H_2O 30:70, flow rate 0.5 mL/min, retention time: 20.25 min (major) and 25.14 min (minor), 66% ee.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.08.023.

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