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Prolinamides Bearing Thiourea Groups as Catalysts for Asymmetric Aldol Reactions

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Organocatalysts based on α-amino acid amides (proline, valine, and threonine) and chiral diamines bearing thiourea groups were synthesized and their activities for aldol reactions were studied. The catalyst based on (*S*)-proline and (1*S*,2*S*)-diphenylethylenediamine proved to be an excellent catalyst, providing the products of reactions between ketones and aromatic aldehydes in high to quantitative yields and with high stereoselectivities (up to 98:2 *dr* and 99 % *ee*). The presence of an acid additive (4-nitrobenzoic acid) has a considerable impact on both yield and enantioselectivity.

Introduction

At the beginning of the 21st century, organocatalysis has emerged as a new and powerful methodology for the synthesis of enantiopure organic compounds.[1] The breakthrough of proline-catalyzed asymmetric direct aldol reactions reported by List, Lerner, and Barbas,[2] together with the pioneering work of Jacobsen on catalytic thioureas[3] and MacMillan on imidazolidinones,[4] opened new directions in asymmetric catalysis. The five-membered secondary amine structure of proline is considered a "privileged" structure capable of activating carbonyl compounds through the formation of enamine intermediates. A number of groups have thus successfully combined the proline scaffold with functionalities capable of acting as hydrogen-bond donors and have demonstrated the catalytic efficiency of prolinamides.[5–13] Compounds **1**–**6** (Figure 1) are representative examples of prolinamides that efficiently catalyze asymmetric aldol reactions.[6–11] In addition, primary amino acids and derivatives such as alanine amides or threonine and its derivatives have emerged as alternatives to proline catalysts.[14,15] In recognition of the pivotal role of extended hydrogen bonding networks in organocatalysis[16] and bearing in mind our recently reported primary amine-thioureas, which were successfully used in Michael reactions,[17] we thought of combining a thiourea group with a prolinamide unit. We thus describe here the synthesis of various α-amino acid amides based on chiral diamines bearing thiourea groups and the evaluation of their catalytic properties for aldol reactions.

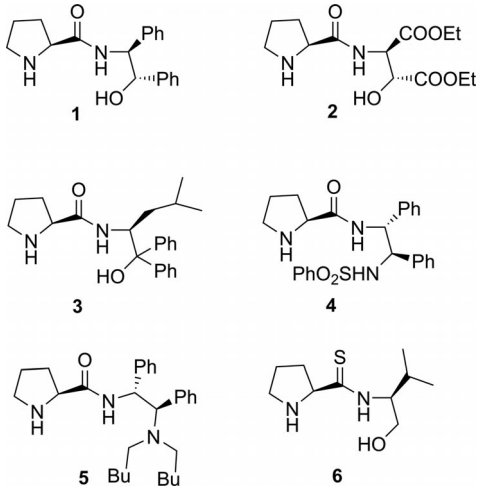

Figure 1. Some prolinamide catalysts.

Results and Discussion

According to the proposed catalytic mechanism for the known prolinamides **1**–**6**, both the amide hydrogen and either a hydroxy group or a sulfonamide hydrogen participate in simultaneous hydrogen bonding in the transition state. Our concept was to combine either a prolinamide unit or an α-amino acid moiety with a chiral unit bearing the thiourea group, because it is a well-known double hydrogen bond donor and chiral thioureas are known to be an important class of organocatalysts.[18] By this reasoning, as starting materials we used both the commercially available (1*S*,2*S*)- and (1*R*,2*R*)-diphenylethylenediamines, as well as various *N*-protected amino acids.

The straightforward synthesis of our new catalysts is depicted in Scheme 1. Boc-L-proline (**7a**), Boc-L-valine (**7b**), and Fmoc-L-threonine *O*-*tert*-butyl ether (**7c**) were each coupled with (1*S*,2*S*)-diphenylethylenediamine with use of

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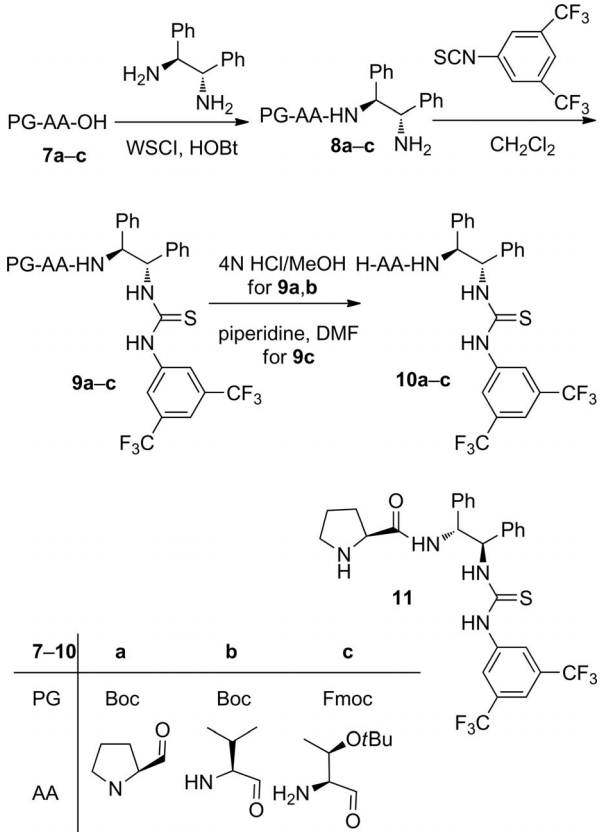
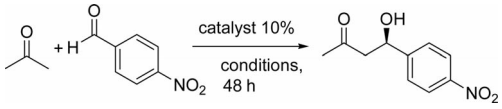
1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (WSCI) as a condensing agent in the presence of hydroxybenzotriazole (HOBt). The amides **8a**–**c** were then treated with the commercially available 3,5-bis(trifluoromethyl)phenyl isothiocyanate to give the thiourea derivatives **9a**–**c**. The Boc group was removed from **9a** and **9b** by treatment with HCl in methanol, whereas the Fmoc group was removed by treatment with piperidine in DMF. Alternative synthetic procedures to produce the desired organocatalysts were also explored, but none proved better (see the Supporting Information). To explain the role of the stereochemistry of the chiral diamine, the prolinamide **11**, based on (1*R*,2*R*)-diphenylethylenediamine, was also synthesized by similar procedures.



Scheme 1. Synthesis of the catalysts.

Asymmetric aldol reactions represent a powerful method for the construction of C–C bonds in an enantioselective fashion.[19,20] The reaction between acetone and 4-nitrobenzaldehyde is a standard model reaction for study of the efficacies of new organocatalysts. The catalytic activities of **10a**–**c** and **11** were first studied at various temperatures in toluene as a solvent (Table 1). A strong dependence of the catalytic activity on the temperature was observed. In all cases, the best enantioselectivities were achieved at –20 or –50 °C. The prolinamide catalyst **10a** (Entries 1 to 3, Table 1) was more efficient than the valinamide catalyst **10b** (Entries 4 to 6, Table 1) and the threoninamide catalyst **10c** (Entries 7 to 10, Table 1), indicating that a secondary amino group rather than a primary one is required for catalytic efficiency in the aldol reaction. On comparison of the prolinamide catalysts **10a** and **11** it is obvious that the *S* configuration of all three stereogenic centers leads to a matched effect. The effect of the solvent was then studied at –20 °C for the catalyst **10a**. However, none of the tested solvents proved better than toluene (Entries 13 to 18, Table 1).

Table 1. Effect of temperature and solvent on the direct asymmetric aldol reaction between acetone and 4-nitrobenzaldehyde in the presence of catalysts **10a**–**c** and **11**.



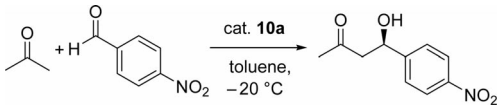
Entry	Catalyst	Solvent, temp. [°C]	Yield [%][a]	*ee* [%][b]
1	**10a**	toluene, room temp.	50[c]	42
2	**10a**	toluene, –20	90	83
3	**10a**	toluene, –50	66	90
4	**10b**	toluene, room temp.	76	55
5	**10b**	toluene, –20	60	77
6	**10b**	toluene, –50	21	73
7	**10c**	toluene, room temp.	48	57
8	**10c**	toluene, –20	33	86
9	**10c**	toluene, –50	20	83
10	**11**	toluene, room temp.	90	4
11	**11**	toluene, –20	95	34
12	**11**	toluene, –50	79	45
13	**10a**	neat, –20	73	24
14	**10a**	CH_2Cl_2, –20	74	69
15	**10a**	$CHCl_3$, –20	67	66
16	**10a**	THF, –20	81	40
17	**10a**	DMF, –20	22	60
18	**10a**	Et_2O, –20	37	41

[a] Isolated yield after column chromatography. [b] The *ee* was determined by HPLC with a Diacel Chiralpak AD-RH column. [c] Reaction time: 18 h.

With toluene as the optimum solvent and the reaction temperature set at –20 °C, a study on the effect of additives and the catalyst loading was undertaken (Table 2). As has been demonstrated, acid additives can influence the outcome of enamine-mediated reactions,[20] although only a few screening studies of acid co-catalysts are available in the literature.[10,11,21,22] Weak Brønsted acids such as acetic acid, benzoic acid, and mononitro-substituted benzoic acids gave excellent results (Entries 1–4, Table 2). It has previously been assumed that water can help the catalyst turnover by hydrolysis of the final product from the iminium intermediate, but in this case the addition of water has detrimental effects both on yield and on enantioselectivity (Entry 5 vs. Entry 1, Table 2). The best results were obtained when 4-nitrobenzoic acid was used: on reduction of the reaction time to 24 h the product was obtained in 95% yield and with 97% *ee* (Entry 3, Table 2). Although 2,4-dinitrobenzoic acid gave excellent enantioselectivity, the yield was not satisfactory (Entry 6, Table 2). Strong acids such as trifluoroacetic acid, toluenesulfonic acid, and camphorsulfonic acid did not catalyze the reaction (Entries 7–9, Table 2). A reduction in the catalyst loading to 5% afforded the product in high yield and enantioselectivity, whereas a

further decrease to 2% led to incomplete reagent consumption (Entries 10 and 11, Table 2). Reduction of the amount of ketone used led to a slight decrease in the yield with the same high level of enantioselectivity induction (Entry 12, Table 2). When the reaction was performed at room temperature, a quantitative yield was observed together with a slight decrease in the enantioselectivity (Entry 13, Table 2).

Table 2. Effect of additive and catalyst loading on the direct asymmetric aldol reaction between acetone and 4-nitrobenzaldehyde in the presence of the catalyst **10a**.

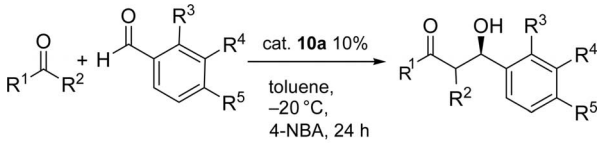


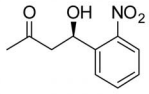
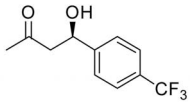
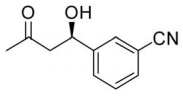
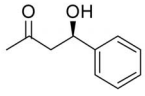
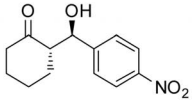
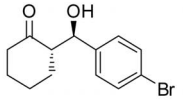
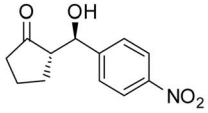
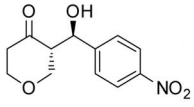
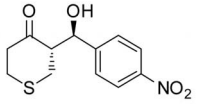
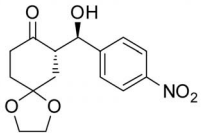
Entry	**10a** [%]	Additive	Time [h]	Yield [%][a]	*ee* [%][b]
1	10	AcOH	48	84	93
2	10	PhCOOH	24	95	95
3	10	4-NBA	24	95	97
4	10	2-NBA	48	84	97
5	10	AcOH, H_2O	48	58	77
6	10	2,4-DNBA	48	42	97
7	10	TFA	48	traces	–
8	10	TSA	48	traces	–
9	10	CSA	48	traces	–
10	5	4-NBA	48	90	97
11	2	4-NBA	48	58	97
12[c]	10	4-NBA	48	86	97
13[d]	10	4-NBA	24	98	87

[a] Isolated yield after column chromatography. [b] The *ee* was determined by HPLC with a Diacel Chiralpak AD-RH column. [c] 5 equiv. of ketone were used. [d] The reaction was performed at room temperature. TFA: trifluoroacetic acid. NBA: nitrobenzoic acid. DNBA: dinitrobenzoic acid. TSA: *p*-toluenesulfonic acid. CSA: (+)-camphorsulfonic acid.

The aldol reaction substrate scope for the new catalyst **10a** was studied and the results are summarized in Table 3. Electron-poor aldehydes such as 2-nitrobenzaldehyde, 4-trifluoromethylbenzaldehyde, and 3-cyanobenzaldehyde reacted easily with acetone, providing the products in high to quantitative yields (79–100%) and with high enantioselectivities (94–99%, Entries 1–3, Table 3). Benzaldehyde, however, produced the product only in moderate yield, although with high enantioselectivity (Entry 4, Table 3). When cyclohexanone or cyclopentanone were used as the donors and 4-nitrobenzaldehyde as the acceptor, the products were obtained both in quantitative yields and with excellent enantioselectivities (Entries 5 and 7, Table 3). In all cases the reactions occurred with high *anti* stereoselectivity. An unexpected reversal of the diastereoselectivity was observed in the case of cyclopentanone, in which the *syn* product was the predominant diastereomer. The product of the reaction between cyclohexanone and 4-bromobenzaldehyde was obtained in moderate yield and with slightly lower enantioselectivity (Entry 6, Table 3). A number of cyclic ketones reacted with 4-nitrobenzaldehyde to provide the products in varying yields (61–98%), with high diastereoselectivities (93:7 to 98:2)[23] and excellent enantioselectivities (98–99% *ee*, Entries 8–10, Table 3).

Table 3. Direct asymmetric aldol reactions between ketones and various aldehydes in the presence of the catalyst **10a**.



Entry	Product	Yield [%][a]	*dr*[b]	*ee*[c] [%]
1		100	–	99
2[d]		100	–	94
3		79	–	99
4		48	–	97
5		100	97:3	99
6		62	97:3	88
7[d]		100	30:70	99[e]
8[d,f]		98	98:2	99
9[d,f]		61	93:7	98
10[d]		64[g]	94:6	98

[a] Isolated yield after column chromatography. [b] The diastereomeric ratio was determined by ^{1}H NMR spectroscopy and refers to the *anti*/*syn* ratio. [c] The *ee* was determined by chiral HPLC. [d] 10 equiv. of ketone were used. [e] 99% *ee* for *anti*, 92% *ee* for *syn*. [f] Reaction time 48 h. [g] 91% yield after 4 d.

It is clear that the combination of a prolinamide unit with the thiourea functionality might provide useful new organocatalysts. In the current study, the prolinamide **10a**,

bearing a thiourea-group-substituted (1*S*,2*S*)-diphenylethylenediamine moiety, proved to be an excellent catalyst for the direct aldol reaction. When proline or proline derivatives, such as 4-substituted prolines,[24] tetrazoles,[25] and sulfonamides,[25c,26] are used as catalysts, the catalytic mechanism includes enamine formation and an internal acid/hydrogen bond orienting the approach of the electrophile.[20] Prolinamides such as the catalysts **1** and **3**, which are regarded as the most active catalysts for direct aldol reactions, as well as a pyrrolidinyl-camphor-based organocatalyst,[27] are believed to act through a double hydrogen bonding activation mode. In the case of the new catalyst **10a**, it is likely that the amide group and the thiourea functionality form an extended hydrogen bonding network leading to high stereoselectivities. As illustrated in Figure 2 (model **I**), the pyrrolidine functionality activates the ketone through the formation of an enamine intermediate, whereas the aldehyde might be activated through the formation of a double hydrogen bond involving the amide hydrogen and one of the thiourea hydrogen atoms. The screening of the acid additives revealed that acids of medium acidity, such as benzoic or 4-nitrobenzoic acid, might enhance the enantioselectivity. These data indicate that the acid additive might play a key role in the catalytic mechanism. A possible activation mode involving the acid additive might be that shown in Figure 2 (model **II**).

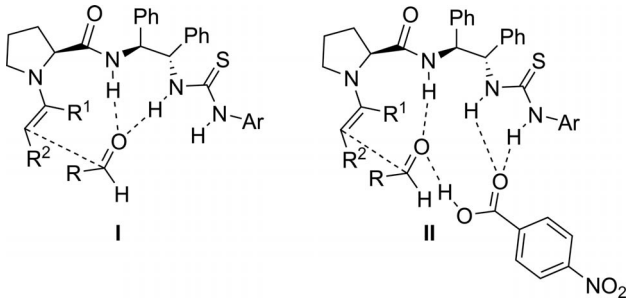


Figure 2. Proposed transition state model for the aldol reaction in the absence (**I**) and in the presence of the acid additive (**II**).

During the course of our studies, Wang et al. reported that prolinamides based on chiral diamines bearing thiourea groups catalyze Michael additions of α,α-disubstituted aldehydes to β-nitroalkenes.[28] They found that the catalyst based on (*S*)-proline and (1*R*,2*R*)-diphenylethylenediamine showed the best enantioselectivity (up to 96% *ee*), but the yields were moderate (47–71%). It has to be underlined that in that study the presence of an acid additive led to decreases both in yield and in enantioselectivity.[28] In addition, prolinamide-thiourea catalysts have been successfully used for α-amination of aldehydes.[29] Most recently, prolinamides derived either from a valine-based diamine or from 1,2-ethylenediamine,[30] as well as 4-acyloxy-L-prolines,[31] have been reported to be efficient catalysts for aldol reactions.

Conclusions

In conclusion, in this work four catalysts based on amino acid amides incorporating chiral diamines bearing thiourea groups were synthesized and their catalytic activities in aldol reactions were studied. Proline-based amides showed better catalytic activities than the amides of primary amino acids (valine or threonine). A screening of various acid additives revealed the great importance of their presence for improving both the yield and the enantioselectivity. The catalyst based on (*S*)-proline and (1*S*,2*S*)-diphenylethylenediamine, in the presence of 4-nitrobenzoic acid, proved to be an excellent catalyst, providing the products between ketones and aromatic aldehydes in high to quantitative yields and with high stereoselectivities (up to 98:2 *dr* and 99% *ee*).

Experimental Section

General Remarks: Chromatographic purification of products was accomplished by forced-flow 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 with phosphomolybdic acid, anisaldehyde, or ninhydrin stains. Melting points were determined with a Büchi 530 hot stage apparatus. Optical rotations were measured with a Perkin–Elmer 343 polarimeter. IR spectra were recorded with a Nicolet 6700 FT-IR spectrometer and are reported in cm^{-1}. ^1H and ^{13}C NMR spectra were recorded with a Varian Mercury instrument (200 MHz or 50 MHz) and are internally referenced to residual protio solvent signals ($CDCl_3$). Data for ^1H NMR are reported as follows: chemical shift (δ, ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet, br. s = broad singlet, br. m = broad multiplet), coupling constant, and assignment. Wherever rotamers exist, they are presented in brackets. Data for ^{13}C NMR are reported in terms of chemical shift (δ, ppm). Mass spectra were recorded with a Finnigan Surveyor MSQ Plus instrument, with only molecular ions and major peaks being reported, with intensities quoted as percentages of the base peak. Chiral High Performance Liquid Chromatography (HPLC) analyses were performed with an Agilent 1100 Series apparatus and Chiralpak® AD-RH, AD-H, or AS-H columns. The configurations of the aldol products were assigned by comparison with literature data.

General Procedure for the Synthesis of Compounds 8a–c: (1*S*,2*S*)-Diphenylethylenediamine (0.60 g, 2.82 mmol), Et_3N (0.44 mL, 3.10 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (WSCI) (0.59 g, 3.10 mmol), and hydroxybenzotriazole (HOBt, 0.43 g, 2.82 mmol) were added consecutively at 0 °C to a stirring solution of the *N*-protected amino acid (2.82 mmol) in dry dichloromethane (15 mL). The reaction mixture was left stirring at 0 °C for 1 h, and was then allowed to warm to room temperature and left stirring for 18 h. The solvent was evaporated under vacuum and the crude product was purified by flash column chromatography with elution with various $CHCl_3$/MeOH or CH_2Cl_2/MeOH mixtures.

***tert*-Butyl (*S*)-2-[(1*S*,2*S*)-2-Amino-1,2-diphenylethylcarbamoyl]pyrrolidine-1-carboxylate (8a):** This compound was obtained from Boc-(*S*)-proline and (1*S*,2*S*)-diphenylethylenediamine. White solid, 0.52 g, 45% yield; m.p. 68–70 °C. $[\alpha]_D$ = –75.6 (*c* = 1.0, CH_2Cl_2).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.12–7.96 (br. m, 0.5 H, NHCO), 7.34–7.17 (m, 10.5 H, ArH and NHCO), 5.11 (dd, J = 8.3 and 4.2 Hz, 1 H, NCH), 4.38–4.26 (m, 2 H, 2× NCH), 3.42–3.26 (m, 2 H, NCH_2), 2.23–2.08 (s, 1 H, C*H*H), 1.88–1.62 (m, 5 H, 3× C*H*H and NH_2), 1.49 [s, 9 H, $C(CH_3)_3$] ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.7 (172.0) (NHCO), 155.8 (OCONH), 142.0 (Ar), 140.5 (Ar), 128.3 (Ar), 128.2 (Ar), 127.3 (Ar), 127.1 (Ar), 126.8 (Ar), 126.5 (Ar), 80.2 (80.1) [*C*$(CH_3)_3$], 60.0 (60.1) (NCH), 59.7 (59.8) (NCH), 58.7 (58.8) (NCH), 46.9 (NCH_2), 28.4 [C(*C*H_3)], 27.6 (27.9) (CH_2), 24.5 (24.3) (CH_2) ppm. IR (film): $\tilde{\nu}$ = 3310, 2974, 1693, 1400, 769, 701 cm^{-1}. MS (ES): *m*/*z* (%) = 410 (100) [M + H]$^+$. $C_{24}H_{31}N_3O_3$ (409.52): calcd. C 70.39, H 7.63, N 10.26; found C 70.10, H 7.84, N 10.17.

***tert*-Butyl (*S*)-1-[(1*S*,2*S*)-2-Amino-1,2-diphenylethylamino]-3-methyl-1-oxobutan-2-ylcarbamate (8b):** This compound was obtained from Boc-(*S*)-valine and (1*S*,2*S*)-diphenylethylenediamine. White solid, 0.96 g, 83% yield; m.p. 161–163 °C. $[\alpha]_D$ = –39.6 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.44–7.05 (m, 11 H, ArH and NH), 5.12 (dd, J = 8.2 and 3.0 Hz, 1 H, NCH), 5.18–4.95 (m, 1 H, NH), 4.44 (d, J = 3.0 Hz, 1 H, NCH), 3.86 (dd, J = 9.1 and 6.9 Hz, 1 H, NCH), 1.95–1.71 (m, 1 H, CH), 1.45 [s, 9 H, $C(CH_3)_3$], 1.40 (s, 2 H, NH_2), 0.68 (d, J = 6.8 Hz, 3 H, CH_3), 0.62 (d, J = 6.9 Hz, 3 H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.2 (NHCO), 155.9 (OCONH), 141.8 (Ar), 140.2 (Ar), 128.6 (Ar), 128.4 (Ar), 127.5 (Ar), 127.3 (Ar), 126.3 (Ar), 126.2 (Ar), 79.5 [*C*$(CH_3)_3$], 60.2 (NCH), 59.0 (NCH), 58.7 (NCH), 30.6 (CH), 28.3 [C(*C*H_3)], 19.1 (CH_3), 17.6 (CH_3) ppm. IR (film): $\tilde{\nu}$ = 3322, 2922, 1727, 1663, 1497, 760, 700 cm^{-1}. MS (ES): *m*/*z* (%) = 412 (100) [M + H]$^+$. $C_{24}H_{33}N_3O_3$ (411.54): calcd. C 70.04, H 8.08, N 10.21; found C 69.91, H 8.35, N 10.11.

(*9H*-Fluoren-9-yl)methyl (2*S*,3*R*)-1-[(1*S*,2*S*)-2-Amino-1,2-diphenylethylamino]-3-*tert*-butoxy-1-oxobutan-2-ylcarbamate (8c): This compound was obtained from Fmoc-(*S*)-threonine and (1*S*,2*S*)-diphenylethylenediamine. White solid, 1.22 g, 73% yield; m.p. 72–74 °C. $[\alpha]_D$ = –1.6 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.35 (d, J = 7.5 Hz, 1 H, NH), 7.76 (d, J = 7.4 Hz, 2 H, ArH), 7.60 (d, J = 7.3 Hz, 2 H, ArH), 7.54 (d, J = 7.4 Hz, 2 H, ArH), 7.44–7.23 (m, 12 H, ArH), 6.02 (d, J = 4.7 Hz, 1 H, NH), 5.20 (dd, J = 7.5 and 2.8 Hz, 1 H, NCH), 4.46–4.32 (m, 3 H, OCH and OCH_2), 4.32–4.11 (m, 3 H, 2× NCH and C*H*CH_2O), 1.43 [s, 11 H, $C(CH_3)_3$ and NH_2], 0.77 (d, J = 6.3 Hz, 3 H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 168.6 (NHCO), 155.9 (OCONH), 143.8 (Ar), 143.6 (Ar), 141.9 (Ar), 141.2 (Ar), 141.1 (Ar), 140.9 (Ar), 128.6 (Ar), 128.2 (Ar), 127.6 (Ar), 127.4 (Ar), 127.0 (Ar), 126.9 (Ar), 126.2 (Ar), 125.1 (Ar), 119.8 (Ar), 77.2 [*C*$(CH_3)_3$], 75.4 (OCH), 66.8 (OCH_2), 59.7 (NCH), 59.5 (NCH), 58.8 (NCH), 47.0 (OCH_2*C*H), 28.3 [C(*C*H_3)], 16.3 (CH_3) ppm. IR (film): $\tilde{\nu}$ = 3324, 2922, 1721, 1667, 1490, 757, 701 cm^{-1}. MS (ES): *m*/*z* (%) = 592 (100) [M + H]$^+$. $C_{37}H_{41}N_3O_4$ (591.74): calcd. C 75.10, H 6.98, N 7.10; found C 74.86, H 7.18, N 6.82.

General Procedure for the Synthesis of Compounds 9a–c: A solution of an isothiocyanate (0.18 g, 0.68 mmol) in dry dichloromethane (2 mL) was added to a stirring solution of an amine **8a–c** (0.68 mmol) in dry dichloromethane (6 mL). The reaction mixture was left stirring at room temperature for 18 h. The solvent was evaporated under vacuum and the crude product was purified by flash column chromatography with elution with various mixtures of petroleum ether (40–60 °C)/EtOAc.

***tert*-Butyl (*S*)-2-[(1*S*,2*S*)-2-{3-[3,5-Bis(trifluoromethyl)phenyl]thioureido}-1,2-diphenylethylcarbamoyl]pyrrolidine-1-carboxylate (9a):** White solid, 0.44 g, 95% yield; m.p. 106–108 °C. $[\alpha]_D$ = –41.7 (*c* = 1.0, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.31–9.08 (br. m, 1 H, NH), 8.35–7.82 (m, 3 H, 3× ArH), 7.67–7.59 (m, 1 H, ArH), 7.31–6.95 (m, 11 H, ArH, NH and NCH), 6.45–6.15 (br. s, 0.5 H, NH), 6.15–5.81 (br. s, 0.5 H, NH), 5.58–5.27 (m, 1 H, NCH), 4.39–4.08 (m, 1 H, NCH), 3.39–3.18 (m, 2 H, NCH_2), 2.41–1.60 (m, 4 H, 4× C*H*H), 1.26 [s, 9 H, $C(CH_3)_3$] ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 181.4 (181.3) (C=S), 174.1 (174.0) (NHCO), 155.6 (155.8) (OCONH), 140.2 (Ar), 137.9 (137.8) (Ar), 131.8 (q, J = 33.5 Hz, Ar), 128.8 (Ar), 128.4 (Ar), 128.1 (Ar), 128.0 (Ar), 127.8 (Ar), 127.7 (Ar), 127.4 (Ar), 123.9 (Ar), 123.1 (q, J = 272.8 Hz, CF_3), 118.3 (Ar), 80.8 [*C*$(CH_3)_3$], 60.6 (60.5) (NCH), 60.4 (60.5) (NCH), 59.5 (NCH), 47.2 (NCH_2), 29.7 (CH_2), 28.1 [C(*C*H_3)], 24.3 (CH_2) ppm. IR (film): $\tilde{\nu}$ = 3301, 2931, 1670, 1529, 1278, 1176, 1136, 769, 700 cm^{-1}. MS (ES): *m*/*z* (%) = 681 (100) [M + H]$^+$. $C_{33}H_{34}F_6N_4O_3S$ (680.70): calcd. C 58.23, H 5.03, N 8.23; found C 57.98, H 5.27, N 8.40.

***tert*-Butyl (*S*)-1-[(1*S*,2*S*)-2-{[3,5-Bis(trifluoromethyl)phenyl]thioureido}-1,2-diphenylethylamino]-3-methyl-1-oxobutan-2-ylcarbamate (9b):** White solid, 0.45 g, 97% yield; m.p. 191–193 °C. $[\alpha]_D$ = –3.8 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.23 (br. s, 0.4 H, NH), 8.92 (br. s, 0.6 H, NH), 8.11–7.76 (m, 3 H, 2× ArH and NH), 7.60 (s, 1 H, ArH), 7.28–7.01 (m, 11 H, ArH and NH), 6.73 (0.4, br. s, NH), 6.02 (br. s, 0.6 H, NH), 5.48–5.25 (m, 1 H, NCH), 5.28–4.87 (m, 1 H, NCH), 4.00 (dd, J = 8.0 and 5.8 Hz, 1 H, NCH), 2.21–1.98 (m, 1 H, CH), 1.33 [s, 9 H, $C(CH_3)_3$], 0.97–0.71 (m, 6 H, 2× CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 181.1 (181.0) (C=S), 173.2 (172.7) (NHCO), 156.1 (155.9) (OCONH), 139.9 (140.0) (Ar), 138.0 (138.1) (Ar), 137.7 (137.8) (Ar), 131.9 (q, J = 34.0 Hz, Ar), 128.6 (Ar), 128.5 (Ar), 128.1 (Ar), 127.9 (Ar), 127.7 (Ar), 127.6 (Ar), 123.7 (Ar), 123.0 (q, J = 272.8 Hz, CF_3), 118.4 (Ar), 80.4 [80.5, *C*$(CH_3)_3$], 63.0 (NCH), 60.3 (NCH), 59.6 (NCH), 30.3 (CH), 28.1 [C(*C*H_3)], 19.2 (CH_3), 17.3 (CH_3) ppm. IR (film): $\tilde{\nu}$ = 3266, 2962, 1686, 1656, 1529, 1279, 1177, 1137, 758, 700 cm^{-1}. MS (ES): *m*/*z* (%) = 683 (100) [M + H]$^+$. $C_{33}H_{36}F_6N_4O_3S$ (682.72): calcd. C 58.06, H 5.31, N 8.21; found C 57.79, H 5.55, N 8.31.

(*9H*-Fluoren-9-yl)methyl (2*S*,3*R*)-1-[(1*S*,2*S*)-2-{[3,5-Bis(trifluoromethyl)phenyl]thioureido}-1,2-diphenylethylamino]-3-*tert*-butoxy-1-oxobutan-2-ylcarbamate (9c): White solid, 0.57 g, 97% yield; m.p. 122–124 °C. $[\alpha]_D$ = +19.7 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.99 (br. s, 1 H, NH), 8.48 (br. s, 1 H, NH), 8.00 (s, 2 H, ArH), 7.89 (d, J = 8.7 Hz, 1 H, NH), 7.75 (dd, J = 7.4 and 3.0 Hz, 2 H, ArH), 7.61–7.53 (m, 2 H, ArH), 7.44–7.12 (m, 15 H, ArH), 6.22 (br. s, 1 H, NH), 5.78 (d, J = 6.6 Hz, 1 H, NCH), 5.45 (dd, J = 10.5 and 9.4 Hz, 1 H, NCH), 4.42–4.05 (m, 5 H, OCH, OCH_2, NCH and C*H*CH_2O), 1.19 (d, J = 6.3 Hz, 3 H, CH_3), 0.82 [s, 9 H, $C(CH_3)_3$] ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 181.6 (C=S), 172.2 (NHCO), 156.4 (OCONH), 144.3 (Ar), 142.8 (Ar), 141.3 (Ar), 141.2 (Ar), 140.3 (Ar), 138.3 (Ar), 137.7 (Ar), 131.7 (q, J = 33.4 Hz, Ar), 128.7 (Ar), 128.5 (Ar), 128.3 (Ar), 128.0 (Ar), 127.8 (Ar), 127.7 (Ar), 127.0 (Ar), 126.9 (Ar), 125.7 (Ar), 125.0 (Ar), 124.4 (Ar), 123.0 (q, J = 272.9 Hz, CF_3), 119.9 (Ar), 118.4 (Ar), 77.2 [*C*$(CH_3)_3$], 74.8 (OCH), 67.7 (OCH_2), 62.8 (NCH), 60.5 (NCH), 59.1 (NCH), 46.7 (OCH_2*C*H), 27.8 [C(*C*H_3)], 19.4 (CH_3) ppm. IR (film): $\tilde{\nu}$ = 3312, 2977, 1721, 1650, 1541, 1278, 1179, 1136, 757, 701 cm^{-1}. MS (ES): *m*/*z* (%) = 863 (100) [M + H]$^+$. $C_{46}H_{44}F_6N_4O_4S$ (862.93): calcd. C 64.03, H 5.14, N 6.49; found C 63.80, H 5.42, N 6.61.

General Procedure for the Synthesis of Compounds 10a, 10b, and 11: A solution of HCl/MeOH (6 N, 2.4 mL) was added to a stirring solution of an *N*-Boc-protected derivative **9** (0.29 mmol) in methanol (3 mL). The reaction mixture was left stirring at room temperature for 1 h. The pH of the mixture was adjusted to 8 with a solution of $NaHCO_3$ (10%). The resulting mixture was extracted

with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried with Na_2SO_4 and the solvent was evaporated to afford the desired product.

(*S*)-*N*-[(1*S*,2*S*)-2-{3-[3,5-Bis(trifluoromethyl)phenyl]thioureido}-1,2-diphenylethyl]pyrrolidine-2-carboxamide (10a): White solid, 167 mg, 99% yield; m.p. 151–153 °C. $[\alpha]_D$ = +17.8 (*c* = 1.0, CH_3OH). ^1H NMR (200 MHz, $CDCl_3$): δ = 10.08–9.95 (br. m, 1 H, NH), 8.92–8.81 (m, 2 H, 2× NH), 8.04 (s, 2 H, ArH), 7.60 (s, 1 H, ArH), 7.35–7.01 (m, 11 H, ArH and NH), 6.37–6.17 (m, 1 H, NCH), 5.41 (t, *J* = 9.4 Hz, 1 H, NCH), 3.81–3.58 (m, 1 H, NCH), 2.98–2.61 (m, 2 H, NCH_2), 2.05–1.81 (m, 1 H, C*H*H), 1.79–1.45 (m, 3 H, 3× C*H*H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 181.6 (C=S), 176.1 (NHCO), 140.9 (Ar), 137.9 (Ar), 137.8 (Ar), 131.6 (q, *J* = 33.2 Hz, Ar), 128.8 (Ar), 128.5 (Ar), 128.2 (Ar), 127.9 (Ar), 127.6 (Ar), 127.4 (Ar), 123.5 (Ar), 123.1 (q, *J* = 272.7 Hz, CF_3), 118.0 (Ar), 62.6 (NCH), 60.5 (NCH), 59.5 (NCH), 46.8 (NCH_2), 30.4 (CH_2), 25.5 (CH_2) ppm. IR (film): $\tilde{\nu}$ = 3303, 2921, 1732, 1636, 1527, 1276, 1178, 1135, 759, 698 cm^{-1}. MS (ES): *m*/*z* (%) = 581 (100) $[M + H]^+$. $C_{28}H_{26}F_6N_4OS$ (580.59): calcd. C 57.92, H 4.51, N 9.65; found C 57.61, H 4.75, N 9.48.

(*S*)-2-Amino-*N*-[(1*S*,2*S*)-2-{3-[3,5-bis(trifluoromethyl)phenyl]thioureido}-1,2-diphenylethyl]-3-methylbutanamide (10b): White solid, 164 mg, 97% yield; m.p. 99–101 °C. $[\alpha]_D$ = +16.2 (*c* = 1.0, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 9.76 (br. s, 1 H, NH), 8.94–8.76 (m, 1 H, NH), 8.37 (d, *J* = 8.8 Hz, 1 H, NH), 7.99 (s, 2 H, ArH), 7.61 (s, 1 H, ArH), 7.34–7.08 (m, 10 H, ArH), 6.42–6.32 (m, 1 H, NCH), 5.54 (t, *J* = 9.8 Hz, 1 H, NCH), 3.37–3.22 (m, 1 H, NCH), 2.28–1.98 (m, 3 H, CH and NH_2), 0.95–0.82 (m, 6 H, 2× CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 181.6 (C=S), 175.5 (NHCO), 140.6 (Ar), 138.2 (Ar), 135.2 (Ar), 131.7 (q, *J* = 33.5 Hz, Ar), 128.8 (Ar), 128.5 (Ar), 128.2 (Ar), 127.9 (Ar), 127.6 (Ar), 127.3 (Ar), 123.9 (Ar), 123.1 (q, *J* = 272.9 Hz, CF_3), 118.2 (Ar), 62.3 (NCH), 60.1 (NCH), 59.8 (NCH), 31.3 (CH), 19.4 (CH_3), 15.6 (CH_3) ppm. IR (film): $\tilde{\nu}$ = 3261, 2921, 1729, 1665, 1547, 1278, 1179, 1136, 760, 700 cm^{-1}. MS (ES): *m*/*z* (%) = 583 (100) $[M + H]^+$. $C_{28}H_{28}F_6N_4OS$ (582.60): calcd. C 57.72, H 4.84, N 9.62; found C 57.45, H 5.02, N 9.71.

(*S*)-*N*-[(1*R*,2*R*)-2-{3-[3,5-Bis(trifluoromethyl)phenyl]thioureido}-1,2-diphenylethyl]pyrrolidine-2-carboxamide (11): White solid, 167 mg, 99% yield; m.p. 173–174 °C. $[\alpha]_D$ = –78.5 (*c* = 1.0, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 8.98 (d, *J* = 9.9 Hz, 1 H, NH), 8.53 (d, *J* = 9.1 Hz, 1 H, NH), 8.10 (s, 2 H, ArH), 7.59 (s, 1 H, ArH), 7.32–7.08 (m, 12 H, ArH and 2× NH), 6.46 (t, *J* = 9.8 Hz, 1 H, NCH), 5.46 (t, *J* = 9.8 Hz, 1 H, NCH), 3.70 (dd, *J* = 8.1 and 5.1 Hz, 1 H, NCH), 3.28–2.87 (m, 2 H, NCH_2), 2.11–1.52 (m, 4 H, 4× C*H*H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 181.5 (C=S), 176.4 (NHCO), 141.0 (Ar), 138.1 (Ar), 137.8 (Ar), 131.6 (q, *J* = 33.5 Hz, Ar), 129.0 (Ar), 128.7 (Ar), 128.6 (Ar), 128.5 (Ar), 127.9 (Ar), 127.7 (Ar), 123.1 (q, *J* = 272.9 Hz, CF_3), 122.9 (Ar), 117.6 (Ar), 61.7 (NCH), 60.4 (NCH), 58.6 (NCH), 47.2 (NCH_2), 31.1 (CH_2), 26.0 (CH_2) ppm. IR (film): $\tilde{\nu}$ = 3264, 2921, 1734, 1638, 1528, 1275, 1176, 1132, 758, 700 cm^{-1}. MS (ES): *m*/*z* (%) = 581 (100) $[M + H]^+$. $C_{28}H_{26}F_6N_4OS$ (580.59): calcd. C 57.92, H 4.51, N 9.65; found C 57.67, H 4.69, N 9.53.

General Procedure for the Synthesis of Compound 10c: A solution of piperidine in DMF (50%, 2 mL) was added to a stirring solution of the *N*-Fmoc-protected derivative **9c** (0.14 g, 0.16 mmol) in DMF (1 mL). The reaction mixture was left stirring at room temperature for 1 h. After completion of the reaction, the solvents were removed in vacuo. The resulting crude was dried with P_2O_5 and purified by flash column chromatography with elution initially with petroleum ether/EtOAc (40:60), followed by CH_2Cl_2/CH_3OH (70:30).

(2*S*,3*R*)-2-Amino-*N*-[(1*S*,2*S*)-2-{[3,5-bis(trifluoromethyl)phenyl]thioureido}-1,2-diphenylethylamino]-3-*tert*-butoxybutanamide (10c): White solid, 100 mg, 98% yield; m.p. 63–65 °C. $[\alpha]_D$ = –9.8 (*c* = 0.5, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 8.60 (br. d, *J* = 8.5 Hz, 1 H, NH), 7.95 (br. s, 1 H, NH), 7.61 (s, 1 H, NH), 7.41–6.99 (m, 13 H, ArH), 6.11–5.87 (m, 1 H, OCH), 5.35 (t, *J* = 9.2 Hz, 1 H, NCH), 3.99–3.71 (m, 1 H, NCH), 3.36–3.18 (m, 1 H, NCH), 1.12 (d, *J* = 5.8 Hz, 3 H, CH_3), 0.99 [s, 9 H, $C(CH_3)_3$] ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 181.3 (C=S), 175.1 (NHCO), 140.4 (Ar), 138.6 (Ar), 138.0 (Ar), 131.8 (q, *J* = 33.2 Hz, Ar), 128.9 (Ar), 128.7 (Ar), 128.3 (Ar), 128.2 (Ar), 127.8 (Ar), 127.6 (Ar), 124.3 (Ar), 123.1 (q, *J* = 273.0 Hz, CF_3), 118.4 (Ar), 77.2 [*C*(CH_3)$_3$], 74.4 (OCH), 67.6 (NCH), 59.8 (NCH), 59.4 (NCH), 28.2 [C(*C*H_3)], 19.3 (CH_3) ppm. IR (film): $\tilde{\nu}$ = 3310, 2950, 1725, 1650, 1536, 1278, 1178, 1134, 759, 700 cm^{-1}. MS (ES): *m*/*z* (%) = 641 (100) $[M + H]^+$. $C_{31}H_{34}F_6N_4O_2S$ (640.68): calcd. C 58.11, H 5.35, N 8.74; found C 57.83, H 5.51, N 8.58.

General Procedure for the Aldol Reaction: 4-Nitrobenzoic acid (2.5 mg, 0.0138 mmol) was added to a stirring solution of the catalyst **10a** (8 mg, 0.0138 mmol) in toluene (1.1 mL). The aldehyde (0.138 mmol) was added at –20 °C, followed by the ketone (3.70 mmol). The reaction mixture was left stirring at –20 °C until the reaction was complete (by TLC). The solvent was evaporated and the crude product was purified by flash column chromatography with elution with various mixtures of petroleum ether (40–60 °C)/EtOAc to afford the desired product.

(*R*)-4-Hydroxy-4-(4-nitrophenyl)butan-2-one:[26d] Table 1, Entry 1. 27 mg, 95% yield. ^1H NMR (200 MHz, $CDCl_3$): δ = 8.20 (d, *J* = 7.0 Hz, 2 H, ArH), 7.52 (d, *J* = 7.0 Hz, 2 H, ArH), 5.25 (m, 1 H, OCH), 3.56 (br. s, 1 H, OH), 3.01–2.71 (m, 2 H, CHHCO), 2.21 (s, 3 H, CH_3CO) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 208.6 (C=O), 149.9 (Ar), 147.4 (Ar), 126.4 (Ar), 123.8 (Ar), 68.9 (OCH), 51.5 (CH_2), 30.7 (CH_3) ppm. HPLC analysis: Diacel Chiralpak AD-RH, MeCN/H_2O 20:80, flow rate 0.5 mL min^{-1}, retention time: 35.45 (major) and 46.45 (minor).

(*R*)-4-Hydroxy-4-(2-nitrophenyl)butan-2-one:[32] Table 3, Entry 1. 29 mg, 100% yield. ^1H NMR (200 MHz, $CDCl_3$): δ = 8.05–7.85 (m, 2 H, ArH), 7.72–7.61 (m, 1 H, ArH), 7.49–7.38 (m, 1 H, ArH), 5.68 (d, *J* = 9.3 Hz, 1 H, OCH), 3.76 (br. s, 1 H, OH), 3.15 (d, *J* = 17.8 Hz, 1 H, CHHCO), 2.73 (dd, *J* = 17.8 and 9.3 Hz, 1 H, CHHCO), 2.25 (s, 3 H, CH_3CO) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 208.7 (C=O), 148.1 (Ar), 144.6 (Ar), 131.8 (Ar), 129.4 (Ar), 122.5 (Ar), 120. 6 (Ar), 68.6 (OCH), 51.4 (CH_2), 30.7 (CH_3) ppm. HPLC analysis: Diacel Chiralpak AS-H, hexane/*i*PrOH 80:20, flow rate 0.8 mL min^{-1}, retention time: 15.41 (major) and 22.94 (minor).

(*R*)-4-Hydroxy-4-[4-(trifluoromethyl)phenyl]butan-2-one:[33] Table 3, Entry 2. 32 mg, 100% yield. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.62–7.52 (m, 2 H, ArH), 7.48–7.38 (m, 2 H, ArH), 5.17 (t, *J* = 5.9 Hz, 1 H, OCH), 3.62 (br. s, 1 H, OH), 2.85–2.77 (m, 2 H, CHHCO), 2.17 (s, 3 H, CH_3CO) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 208.8 (C=O), 146.6 (Ar), 129.6 (q, *J* = 31.0 Hz, Ar), 125.8 (Ar), 125.3 (Ar), 123.9 (q, *J* = 271.0 Hz, Ar), 69.0 (OCH), 51.6 (CH_2), 30.6 (CH_3) ppm. HPLC analysis: Diacel Chiralpak AS-H, hexane/*i*PrOH 80:20, flow rate 0.5 mL min^{-1}, retention time: 11.17 (major) and 12.88 (minor).

(*R*)-3-(1-Hydroxy-3-oxobutyl)benzonitrile: Table 3, Entry 3. Pale yellow oil, 21 mg, 79% yield. $[\alpha]_D$ = +51.9 (*c* = 1.0, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 7.74–7.68 (m, 1 H, ArH), 7.65–7.54 (m, 2 H, ArH), 7.52–7.40 (m, 1 H, ArH), 5.19 (t, *J* = 6.4 Hz, 1 H, OCH), 3.61 (br. s, 1 H, OH), 2.84 (d, *J* = 6.4 Hz, 2 H, CHHCO), 2.22 (s, 3 H, CH_3CO) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 208.5

(C=O), 144.3 (Ar), 131.1 (Ar), 130.1 (Ar), 129.2 (Ar), 129.1 (Ar), 118.6 (CN), 112.3 (Ar), 68.6 (OCH), 51.5 (CH_2), 30.6 (CH_3) ppm. MS (ES): *m/z* (%) = 188 (33) $[M - H]^+$, 170 (100) $[M - H_2O]^+$. $C_{11}H_{11}NO_2$ (189.21): calcd. C 69.83, H 5.86, N 7.40; found C 69.58, H 6.10, N 7.20. HPLC analysis: Diacel Chiralpak AD-RH, MeCN/H_2O 40:60, flow rate 1.0 mL min^{-1}, retention time: 7.58 (major) and 9.04 (minor).

(*R*)-4-Hydroxy-4-phenylbutan-2-one:[33] Table 3, Entry 4. 11 mg, 48% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.37–7.21 (m, 5 H, ArH), 5.21–5.07 (m, 1 H, OCH), 3.27 (br. s, 1 H, OH), 2.88–2.77 (m, 2 H, CHHCO), 2.15 (s, 3 H, CH_3CO) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 209.0 (C=O), 142.5 (Ar), 128.3 (Ar), 127.6 (Ar), 125.5 (Ar), 69.6 (OCH), 51.9 (CH_2), 30.6 (CH_3) ppm. HPLC analysis: Diacel Chiralpak AS-H, hexane/*i*PrOH 90:10, flow rate 0.8 mL min^{-1}, retention time: 14.58 (major) and 17.15 (minor).

(*S*)-2-[(*R*)-Hydroxy-(4-nitrophenyl)methyl]cyclohexanone:[34] Table 3, Entry 5. 34 mg, 100% yield. ^{1}H NMR (200 MHz, $CDCl_3$): *anti* δ = 8.20 (d, *J* = 8.8 Hz, 2 H, ArH), 7.51 (d, *J* = 8.8 Hz, 2 H, ArH), 4.87 (d, *J* = 8.4 Hz, 1 H, OCH), 4.09 (br. s, 1 H, OH), 2.64–2.26 (m, 3 H, CH and CHH), 2.17–1.29 (m, 6 H, 6× C*H*H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 214.6 (C=O), 148.4 (Ar), 127.9 (Ar), 127.8 (Ar), 123.4 (Ar), 73.8 (OCH), 57.0 (CH), 42.5 (CH_2), 30.6 (CH_2), 27.5 (CH_2), 24.5 (CH_2) ppm. HPLC analysis: Diacel Chiralpak AS-H, hexane/*i*PrOH 80:20, flow rate 0.5 mL min^{-1}, retention time: 26.75 (minor) and 34.89 (major).

(*S*)-2-[(*R*)-(4-Bromophenyl)-hydroxymethyl]cyclohexanone:[35] Table 3, Entry 6. 24 mg, 62% yield. ^{1}H NMR (200 MHz, $CDCl_3$, *anti*): δ = 7.46 (d, *J* = 8.4 Hz, 2 H, ArH), 7.19 (d, *J* = 8.4 Hz, 2 H, ArH), 4.74 (d, *J* = 8.7 Hz, 1 H, OCH), 3.98 (br. s, 1 H, OH), 2.61–2.11 (m, 3 H, CH and CHH), 2.13–2.07 (m, 1 H, C*H*H), 1.81–1.43 (m, 5 H, 5× C*H*H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 215.2 (C=O), 140.0 (Ar), 131.5 (Ar), 128.7 (Ar), 121.7 (Ar), 74.2 (OCH), 57.3 (CH), 42.7 (CH_2), 30.7 (CH_2), 27.7 (CH_2), 24.7 (CH_2) ppm. HPLC analysis: Diacel Chiralpak AD-H, hexane/*i*PrOH 90:10, flow rate 0.5 mL min^{-1}, retention time: 28.70 (minor) and 33.59 (major).

(*S*)-2-[(*R*)-Hydroxy-(4-nitrophenyl)methyl]cyclopentanone:[34] Table 3, Entry 7. 33 mg, 100% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.20 (d, *J* = 8.8 Hz, 2 H, ArH), 7.15 (d, *J* = 8.8 Hz, 2 H, ArH), 5.41 (s, 1 H, OCH *syn*), 4.83 (d, *J* = 9.2 Hz, 1 H, OCH *anti*), 4.76 (br. s, 1 H, OH *anti*), 2.69 (br. s, 1 H, OH *syn*), 2.52–2.18 (m, 3 H, CH and CHH), 2.15–1.83 (m, 2 H, 2× C*H*H), 1.78–1.55 (m, 2 H, 2× C*H*H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 214.6 (C=O), 213.4 (C=O), 149.2 (Ar), 147.9 (Ar), 147.4 (Ar), 147.3 (Ar), 127.2 (Ar), 126.5 (Ar), 123.0 (Ar), 122.9 (Ar), 73.5 (OCH), 69.8 (OCH), 57.0 (CH), 56.3 (CH), 42.5 (CH_2), 30.2 (CH_2), 27.7 (CH_2), 25.5 (CH_2), 24.6 (CH_2), 24.3 (CH_2) ppm. HPLC analysis: Diacel Chiralpak AD-H, hexane/*i*PrOH 95:5, flow rate 1 mL min^{-1}, retention time: 27.50 (*syn* major) and 38.01 (*syn* minor), 47.94 (*anti* minor) and 49.63 (*anti* major).

(*S*)-3-[(*R*)-Hydroxy-(4-nitrophenyl)methyl]dihydro-2*H*-pyran-4(3*H*)-one:[34] Table 3, Entry 8. 34 mg, 98% yield. ^{1}H NMR (200 MHz, $CDCl_3$, *anti*): δ = 8.21 (d, *J* = 8.8 Hz, 2 H, ArH), 7.50 (d, *J* = 8.8 Hz, 2 H, ArH), 4.97 (d, *J* = 8.2 Hz, 1 H, OCH), 4.28–4.09 (m, 1 H, OC*H*H), 3.90–3.64 (m, 3 H, 2× OC*H*H and OH), 3.44 (dd, *J* = 11.4 and 9.8 Hz, 1 H, OC*H*H), 3.02–2.41 (m, 3 H, 3× C*H*H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 209.2 (C=O), 147.7 (Ar), 147.4 (Ar), 127.4 (Ar), 123.8 (Ar), 71.2 (OCH), 69.7 (OCH_2), 68.2 (OCH_2), 57.5 (CH), 42.7 (CH_2) ppm. HPLC analysis: Diacel Chiralpak AD-H, hexane/*i*PrOH 80:20, flow rate 1 mL min^{-1}, retention time: 21.17 (minor) and 25.00 (major).

(*S*)-3-[(*R*)-Hydroxy-(4-nitrophenyl)methyl]dihydro-2*H*-thiopyran-4(3*H*)-one:[34] Table 3, Entry 9. 23 mg, 61% yield. ^{1}H NMR (200 MHz, $CDCl_3$, *anti*): δ = 8.21 (d, *J* = 8.3 Hz, 2 H, ArH), 7.53 (d, *J* = 8.3 Hz, 2 H, ArH), 5.04 (d, *J* = 7.9 Hz, 1 H, OCH), 3.65 (br. s, 1 H, OH), 3.13–2.91 (m, 3 H, CH and CHH), 2.87–2.70 (m, 2 H, 2× C*H*H), 2.68–2.42 (m, 2 H, 2× C*H*H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 211.2 (C=O), 147.7 (Ar), 147.6 (Ar), 127.7 (Ar), 123.8 (Ar), 73.1 (OCH), 59.4 (CH), 44.7 (CH_2), 32.8 (CH_2), 30.7 (CH_2) ppm. HPLC analysis: Diacel Chiralpak AD-H, hexane/*i*PrOH 90:10, flow rate 1 mL min^{-1}, retention time: 54.77 (minor) and 75.12 (major).

(*S*)-7-[(*R*)-Hydroxy-(4-nitrophenyl)methyl]-1,4-dioxospiro[4.5]decan-8-one:[36] Table 3, Entry 10. 27 mg, 64% yield. ^{1}H NMR (200 MHz, $CDCl_3$, *anti*): δ = 8.20 (d, *J* = 8.8 Hz, 2 H, ArH), 7.49 (d, *J* = 8.8 Hz, 2 H, ArH), 4.83 (d, *J* = 7.5 Hz, 1 H, OCH), 4.04 (br. s, 1 H, OH), 3.98–3.68 (m, 4 H, 4× OC*H*H), 2.91–2.74 (m, 1 H, CH), 2.66–2.54 (m, 1 H, C*H*H), 2.51–2.42 (m, 1 H, C*H*H), 2.07–1.55 (m, 3 H, 3× C*H*H), 1.54–1.44 (m, 1 H, C*H*H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 213.1 (C=O), 147.9 (Ar), 127.8 (Ar), 126.5 (Ar), 123.6 (Ar), 106.7 [*C*$(OCH_2)_2$], 73.8 (OCH), 64.6 (OCH_2), 64.5 (OCH_2), 52.9 (CH), 38.8 (CH_2), 37.8 (CH_2), 34.3 (CH_2) ppm. HPLC analysis: Diacel Chiralpak AS-H, hexane/*i*PrOH 70:30, flow rate 1 mL min^{-1}, retention time: 10.11 (minor) and 14.95 (major).

Supporting Information (see footnote on the first page of this article): Experimental details, NMR spectra and HPLC data.

Acknowledgments

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