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L-Prolinamides Derived from Chiral and Achiral 1,2-Diamines as Useful Bifunctional Organocatalysts for Direct Diastereo- and Enantioselective Aldol Reaction

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Dedicated to Professor Josep Font on occasion of his 70th birthday

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Diastereomeric catalysts **5** and *epi*-**5**, which differ in the configuration of the stereocenter at the amino component, have been prepared from L-proline and (*S*)-N^2,N^2-dibenzyl-3-methylbutane-1,2-diamine or (*R*)-N^1,N^1-dibenzyl-3-methylbutane-1,2-diamine, respectively. Diastereomeric prolinamides **10** and *epi*-**10**, which are regioisomers of **5** and *epi*-**5**, respectively, were obtained from the same starting compounds. All of the catalysts promoted high diastereo- and enantioselectivity in the cross-aldol reaction between aromatic aldehydes and cyclohexanone using acetic acid as co-catalyst. A small match/mismatch effect over the stereoselection was observed, depending on the configuration of the stereocenters at the proline and diamine components. In general, the best results were obtained with catalyst **5**, which has the same configuration at both stereocenters. Under the same reaction conditions, prolinamide **20**, which was synthesized from L-proline and ethylene diamine, without stereocenters at the diamine component, behaved as an excellent enantioselective organocatalyst, giving the aldol products in very high diastereo- and enantioselectivity.

Introduction

The search for small molecules that are able to act as catalysts in enantioselective transformations has received extensive attention during the last ten years,[1] and direct aldol reactions between two different carbonyl compounds is probably one of the most studied processes.[2]

Proline was the first organocatalyst used for the aldol reaction of aldehydes and acetone,[3] but some problems associated with its solubility in organic solvents, and the possibility of tuning the reactivity of the catalyst by modifying the pK_a value of the hydrogen-donor unit led to the search for proline-modified structures acting as organocatalysts. These compounds are generally prolinamide derivatives that differ in the nature of the amine component attached to the carboxylic functionality of proline. In this regard, prolinamides derived from *trans*-1,2-diaminocyclohexane,[4] 1,2-diphenylethylenediamines,[5] cinchone derivatives,[6] 1,1′-binaphthyl-2,2′-diamine,[7] spirodiamines,[8] amino alcohols,[9] oxazoline derivatives,[10] amino indanes,[11] and di- and tripeptides,[12] have all been successfully used as organocatalysts in cross-aldol reactions. Very good results have been also obtained by using prolylsulfonamides, prolinethioamides,[13] modified or immobilized prolinamides,[14] and prolinamides derived from *o*-phenylene diamines.[15]

In general, the amine component of these prolinamides is chiral, and it has been observed that stereochemical control of the aldol reaction is affected by the configuration of the stereogenic elements in both the amine and proline components.[4a,5b,6,9a,10] It has also been described that bisprolinamides derived from achiral diamines catalyze the aldol reaction but with low *ee*.[5a]

These results led us to consider the preparation of bifunctional prolinamides derived from chiral diamines with only one stereocenter and to investigate their use as organocatalysts in direct aldol reactions. The idea was to obtain information on the influence of the stereocenter at the amine component, and its relative position with respect to the proline, on the diastereo- and enantioselectivity of the reaction. To this end, catalysts **5**, **10**, *epi*-**5**, and *epi*-**10** were prepared starting from diamines **1** and **11**, which were derived from L- or D-valine and L-proline. These prolinamides cover all the possible combinations of stereocenters and regioisomers in the catalysts. For instance, **5** and *epi*-**5**, or **10** and *epi*-**10**, derived from L-proline, differ in the configuration of the stereocenter at the amine component, whereas **5**

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and **10** or *epi*-**5** and *epi*-**10** are regioisomers that differ in the nitrogen atom where the L-proline moiety is attached. We have also prepared the enantiomer of *epi*-**10** starting from diamine **11** and D-proline. For comparative purposes, diamide **20** − with no stereocenter at the amine chain − was also synthesized from ethylenediamine and L-proline.

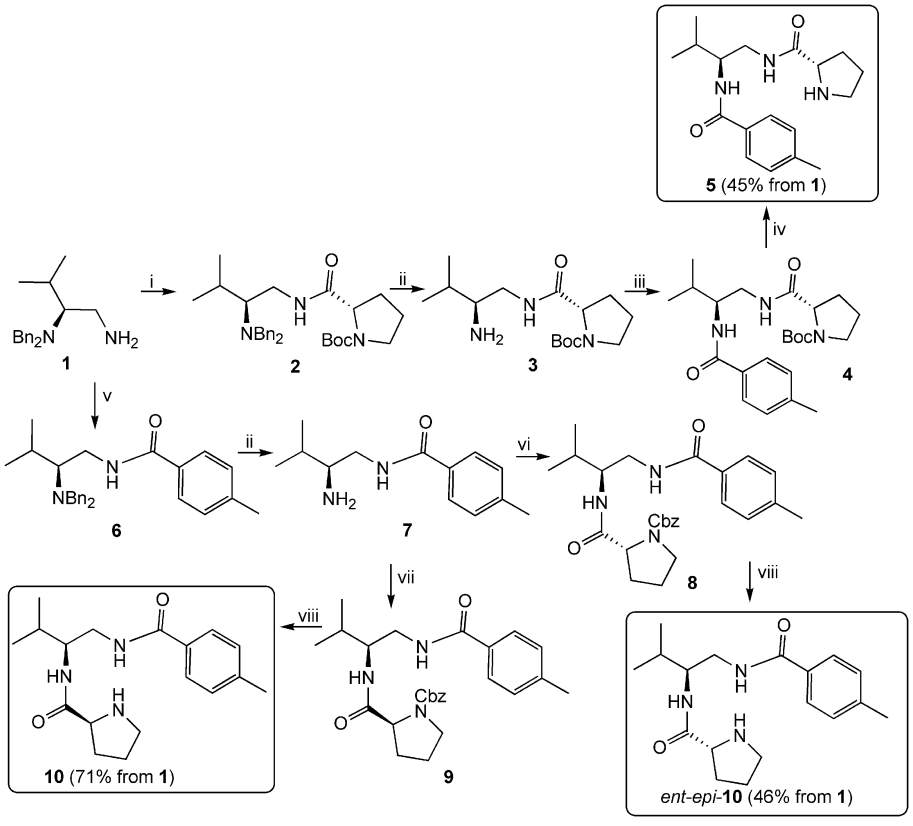
Results and Discussion

Diamides **5**, **10**, and *ent*-*epi*-**10** were prepared from (*S*)-N^2,N^2-dibenzyl-3-methylbutane-1,2-diamine (**1**)[16] in four steps, in moderate to good yields, as summarized in Scheme 1. The reaction of **1** with Boc-L-proline led to **2**, which was debenzylated by hydrogenolysis to **3**. Condensation of **3** with *p*-toluoyl chloride yielded **4**, which was transformed into **5** by hydrolysis of the Boc group. Reaction of **1** with *p*-toluoyl chloride gave **6**, which was transformed into **7** by debenzylation and subsequently converted into **10** by sequential condensation with Cbz-L-proline and deprotection by hydrogenolysis. Similarly, *ent*-*epi*-**10** was obtained following the same protocol starting from Cbz-D-proline as amino acid.

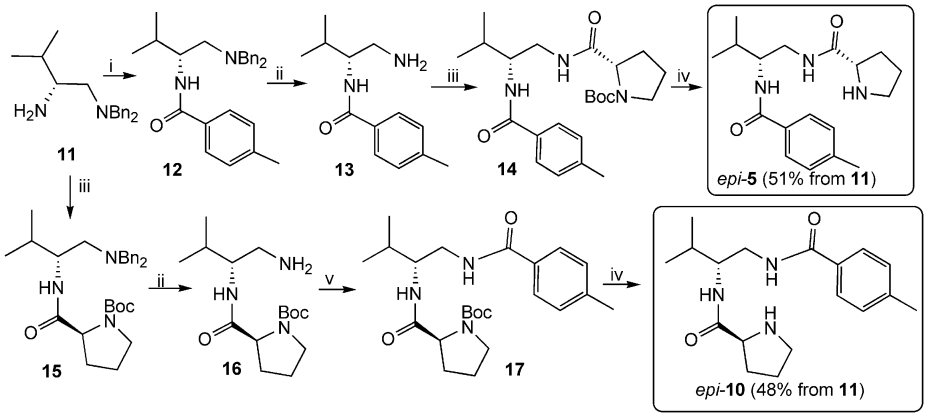
The synthesis of *epi*-**5** and *epi*-**10** started from (*R*)-N^1,N^1-dibenzyl-3-methylbutane-1,2-diamine (**11**)[16] and was also carried out in four steps (Scheme 2). The preparation of the two regioisomers only varied in the order of formation of the amides. *Epi*-**5** was obtained by reaction of **11** with *p*-toluoyl chloride and debenzylation to **13**, followed by condensation with Boc-L-proline and subsequent deprotection. *epi*-**10** was synthesized from **11** by condensation with Boc-L-proline and debenzylation to **17**, followed by reaction with *p*-toluoyl chloride and deprotection.

The catalytic activity of these prolinamides was evaluated in the direct enantioselective aldol reaction of 4-chlorobenzaldehyde and cyclohexanone (Scheme 3); the results are summarized in Table 1. In general, all the catalysts provided the *anti*-aldol product **21a** in good to excellent yields (77–98%) and very good enantio- (91:9 to 98:2) and diastereoselectivity (89:11 to 95:5 *anti*/*syn*).

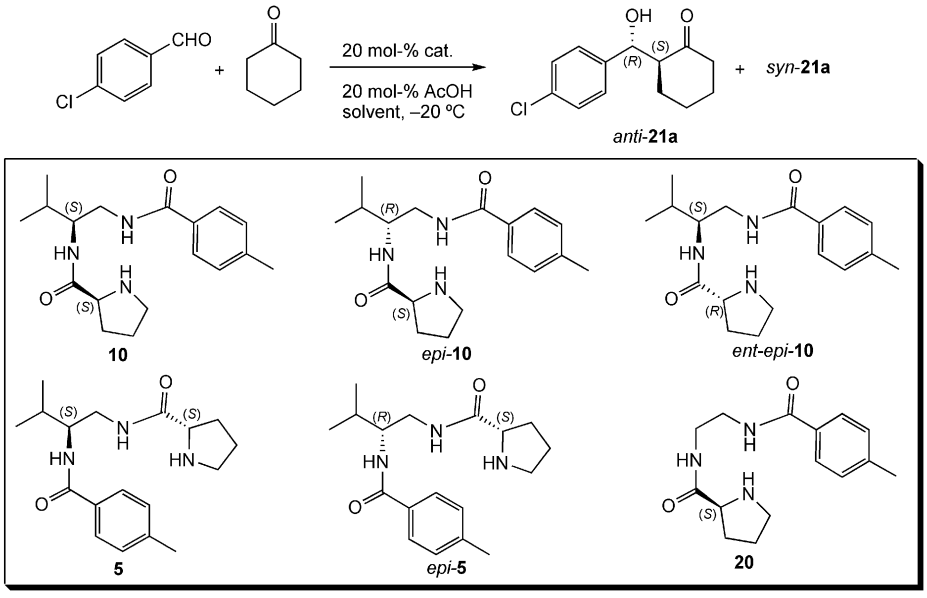
After preliminary screening to select appropriate experimental conditions, the reactions were carried out with 20 mol-% of catalyst **5** and 20 mol-% of acetic acid as cocatalyst, at –20 °C in 1:1 (v/v) mixtures of cyclohexanone and the corresponding solvent. The reaction could also be performed with only 5 mol-% of catalyst and cocatalyst with only a slight decrease in yield and the diastereo- and enantioselection (entry 4 in Table 1). It was found that tetrahydrofuran (THF) was a worse solvent than either chloroform or toluene in the reactions using prolinamide **5** as catalyst; the enantioselection was essentially maintained in the three solvents, but the diastereoselectivity decreased when THF was used (entries 1–3 in Table 1).



Scheme 1. *Reagents and conditions*: (i) Boc-L-proline, *N*,*N*′-dicyclohexylcarbodiimide (DCC), CH_2Cl_2, 0 °C to room temp. (ii) H_2, Pd-$(OH)_2$/C, MeOH. (iii) *p*-$CH_3C_6H_4COCl$, Et_3N, CH_2Cl_2, 0 °C to room temp. (iv) Trifluoroacetic acid (TFA), CH_2Cl_2, room temp. (v) *p*-$CH_3C_6H_4COCl$, CH_2Cl_2, 0 °C to room temp. (vi) Cbz-D-proline, DCC, CH_2Cl_2, 0 °C to room temp. (vii) Cbz-L-proline, DCC, CH_2Cl_2, 0 °C to room temp. (viii) H_2, Pd/C (10%), MeOH.



Scheme 2. *Reagents and conditions*: (i) *p*-$CH_3C_6H_4COCl$, CH_2Cl_2, 0 °C to room temp. (ii) H_2, $Pd(OH)_2/C$, MeOH. (iii) Boc-L-proline, DCC, CH_2Cl_2, 0 °C to room temp. (iv) TFA, CH_2Cl_2, room temp. (v) *p*-$CH_3C_6H_4COCl$, Et_3N, CH_2Cl_2, 0 °C to room temp.



Scheme 3. Direct aldol reaction catalyzed by **5**–**20**.

Table 1. Dependence of *er* and *ee* on the catalyst and the solvent.

Entry[a]	Catalyst	Solvent	*t* [h]	Yield[b]	*anti*/*syn*[c]	*er* (*anti*)[d]
1	**5**	$CHCl_3$	48	90	93:7	97:3
2	**5**	toluene	48	88	92:8	98:2
3	**5**	THF	24	98	90:10	96:4
4[e]	**5**	toluene	48	83	92:8	96:4
5	*epi*-**5**	$CHCl_3$	65	98	93:7	97:3
6	*epi*-**5**	toluene	48	96	94:6	97:3
7	**10**	$CHCl_3$	46	92	93:7	95:5
8	**10**	toluene	48	98	93:7	95:5
9	*epi*-**10**	$CHCl_3$	72	72	91:9	91:9
10	*epi*-**10**	toluene	48	87	90:10	94:6
11	*ent-epi*-**10**	toluene	48	97	93:7	92:8
12	**20**	$CHCl_3$	72	77	89:11	96:4
13	**20**	toluene	48	95	95:5	97:3

[a] *Reagents and conditions*: organocatalyst (0.1 mmol), AcOH (0.1 mmol), solvent/cyclohexanone (1:1, 2 mL), 20 min, –20 °C then aldehyde (0.5 mmol), 24–72 h. [b] Isolated yields. [c] Determined by ^1H NMR analysis of the crude product. [d] Determined by chiral HPLC (see conditions in the experimental section). [e] Reaction performed with 5 mol-% catalyst and 5 mol-% AcOH.

Small match/mismatch effects were observed by using epimeric catalysts **10** and *epi*-**10**, which differ in the configuration at the amine stereocenter. Catalyst **10**, which has the same configuration at the stereocenters of both components, gave better yield and diastereoselectivity than *epi*-**10**, although no difference was observed in the enantioselection when toluene was used as solvent (entries 8 and 10 in Table 1). In contrast, the yield and both the diastereo- and enantioselectivity decreased for *epi*-**10** when the reactions were carried out in chloroform (entries 7 and 9). As expected, *ent-epi*-**10** (entry 11) behaved in a similar way to *epi*-**10**, but led to the enantiomeric aldol (*ent-anti*-**21a**). These results showed that the stereochemistry of the final aldol product is determined by the proline component in the catalyst,[10,11c] and that amines with the same configuration as the proline constitutes a 'matched' component that results in an improved enantioselective organocatalyst.

Interestingly, no noticeable differences were observed in the reactions with **5** and *epi*-**5** as catalysts (entries 1 and 5

versus 2 and 6 in Table 1). These prolinamides, which are regioisomers of **10** and *epi*-**10**, respectively, essentially give the same mixtures of diastereo- and enantiomers, implying that the match/mismatch effects are not operative in these catalysts.

Intrigued by these facts, we prepared **20**, which does not contain a stereocenter at the amine component, and tested it as catalyst in the same reaction. Prolinamide **20** was prepared from ethylene diamine, in three steps, as outlined in Scheme 4. The diamine was transformed into **18** by treatment with *p*-toluoyl chloride, followed by condensation with Boc-L-proline to **19**. Deprotection of **19** with trifluoroacetic acid led to **20** in moderate total yield.

Fortunately, compound **20** also works as a catalyst in the aldol reaction under the same experimental conditions as described above (entries 12 and 13 in Table 1). In chloroform as a solvent, the reaction proceeds in 77% yield, with moderate diastereoselection (89:11 *anti*/*syn*) and excellent enantioselectivity (96:4). The process leads to the aldol product *anti*-**21a** with excellent yield, diastereo- and enantioselectivity when toluene was used as solvent.

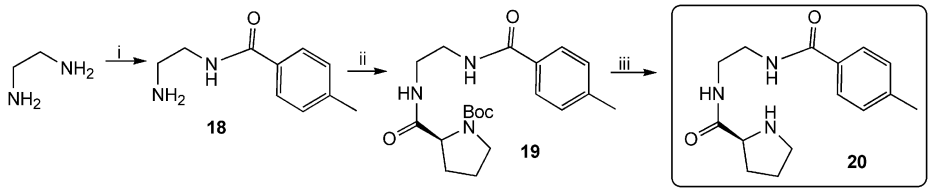
Using the described reaction conditions in toluene, a set of benzaldehydes with different electronic characteristics was treated with cyclohexanone by using **5**, its regioisomer **10**, and **20** as catalysts for comparative purposes, to study the generality of the cross-aldol reaction (Scheme 5).

The results, summarized in Table 2, show that *o*-, *m*-, and *p*-nitrobenzaldehydes (entries 4–10 in Table 2) or *p*-cyanobenzaldehyde (entries 11 and 12) are the most reactive, yielding the aldol products **21b–e** in excellent yields after 24 h at –20 °C. Whereas *p*-chlorobenzaldehyde required 48 h of reaction time to reach the same yields, benzaldehyde required 72 h to give the aldol product **21f** in moderate to good yields (entries 13–15). The less electrophilic *p*-methylbenzaldehyde is a poor substrate and gave the aldol product **21g** in moderate to good yields only after six or seven days of reaction (entries 16 and 17 in Table 2).

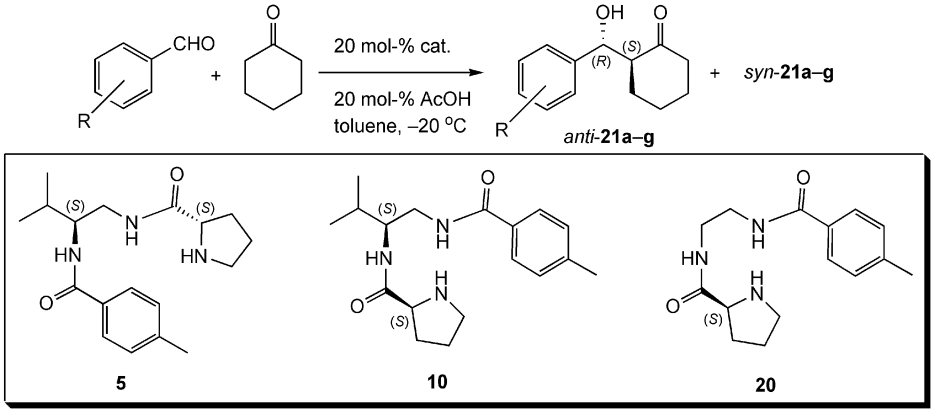
Table 2. Aldol reaction of cyclohexanone with aldehydes catalyzed by **5**, **10**, and **20**.

Entry	R	Cat.	*t* [h]	Yield[a]	Product	*anti*/*syn*[b,c]	*ee* (*anti*)[d,e]
1	*p*-Cl	**5**	48	88	**21a**	92:8	96
2	*p*-Cl	**10**	48	98	**21a**	93:7	90
3	*p*-Cl	**20**	48	95	**21a**	95:5 (96:4)	94 (94)
4	*o*-NO_2	**5**	24	93	**21b**	90:10	92
5	*o*-NO_2	**20**	24	98	**21b**	91:9 (99:1)	94 (96)
6	*m*-NO_2	**5**	28	95	**21c**	94:6	92
7	*m*-NO_2	**20**	22	95	**21c**	94:6 (96:4)	92 (94)
8	*p*-NO_2	**5**	21	95	**21d**	91:9	92
9	*p*-NO_2	**10**	24	96	**21d**	95:5	94
10	*p*-NO_2	**20**	21	93	**21d**	93:7 (96:4)	90 (92)
11	*p*-CN	**5**	24	98	**21e**	87:13	90
12	*p*-CN	**20**	24	98	**21e**	86:14 (95:5)	88 (94)
13	H	**5**	72	95	**21f**	93:7	92
14	H	**10**	71	81	**21f**	94:6	94
15	H	**20**	72	63	**21f**	92:8 (83:17)	92 (87)
16	*p*-Me	**5**	144	80	**21g**	91:9	92
17	*p*-Me	**20**	168	50	**21g**	91:9 (80:20)	92 (77)

[a] Isolated yield. [b] Determined by ^{1}H NMR analysis of the crude product. [c] Numbers in parenthesis correspond to the best *dr* previously described for the same reaction with different catalysts in organic solvents.[4a] [d] Determined by chiral HPLC analysis (see conditions in the experimental section). [e] Numbers in parenthesis correspond to the best *ee* previously described for the same reaction with different catalysts in organic solvents.[4a]



Scheme 4. *Reagents and conditions*: (i) *p*-$CH_3C_6H_4COCl$, MeOH, 0 °C, 60 s, 63%. (ii) Boc-L-proline, DCC, CH_2Cl_2, 0 °C to room temp., 87%. (iii) TFA, CH_2Cl_2, room temp., 80%.



Scheme 5. Direct aldol reaction of aldehydes with cyclohexanone catalyzed by **5**, **10**, and **20**.

The difference in reactivity did not affect the diastereoselectivity of the cross-aldol reaction, which was excellent for all the aldehydes except for *p*-cyanobenzaldehyde (entries 11 and 12). The enantioselectivity was maintained at excellent levels for all the studied reactions. Interestingly, no noticeable changes in either the diastereo- or enantioselection were observed in the reactions promoted by catalysts **5** and **10**, which were derived from a chiral diamine, and catalyst **20**, which was derived from achiral ethylene diamine.

Moreover, a comparison between the stereoselection obtained with **20** and the best previously described with a catalyst derived from (*R*,*R*)-1,2-cyclohexane diamine[4a] (see Table 2) showed that the diastereo- and enantioselection were quite similar for aldehydes with electron-withdrawing substituents (entries 3, 5, 7, and 9) and better for benzaldehyde and 4-methylbenzaldehyde (entries 15 and 17). In contrast, the stereodiscrimination was worse for the aldol reaction with 4-cyanobenzaldehyde (entry 11 in Table 2).

Conclusions

We have prepared six novel prolinamides, derived from 1,2-diamines, which act as organocatalysts in the enantioselective direct cross-aldol reaction of aromatic aldehydes with cyclohexanone. In all cases, the aldol products are obtained with good to excellent yields and stereoselectivities. Catalyst **10**, with the same configuration at the proline and amine components, led to better diastereo- and enantioselectivities than its epimers *epi*-**10** or *ent*-*epi*-**10**. This match/mismatch effect is less pronounced for catalysts **5** and *epi*-**5**. Based on these observations, prolinamide **20** was prepared from ethylene diamine and tested as an enantioselective catalyst in the same reaction. This compound, which is cheaper and easier to prepare than the prolinamides derived from chiral diamines, is a good organocatalyst for the enantioselective aldol reactions, leading to the final adducts with diastereo- and enantioselectivities as good, or better, than those previously described.

Experimental Section

General: ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$. Chemical shifts for protons are reported in ppm from tetramethylsilane, with the residual $CHCl_3$ resonance as internal reference. Chemical shifts for carbons are reported in ppm from tetramethylsilane and are referenced to the central carbon resonance of the solvent. Data are reported as follows: chemical shift, multiplicity (s for singlet, d for doublet, t for triplet, q for quartet, m for multiplet; br. broad), coupling constants in Hertz, and integration. Specific rotations were measured using a 5-mL cell with a 1-dm path length, and a sodium lamp, and concentration is given in g per 100 mL. Melting points were obtained with open capillary tubes. Flash chromatography was carried out using silica gel (230–240 mesh). Chemical yields refer to pure isolated substances. TLC analysis was performed with glass-backed plates coated with silica gel 60 containing an F_{254} indicator, and visualized by either UV irradiation or by staining with phosphomolybdic acid solution. Chiral HPLC analysis was performed with a Daicel Chiralcel OD Column (250 × 4.6 mm). UV absorbance was monitored at 220 nm or at 254 nm. Racemic samples were prepared by using racemic proline as the catalyst in DMF[17] or DMSO.[3c]

Organic compounds were used as received. Solvents were dried and stored over microwave-activated molecular sieves (4 Å).

(*S*)-*tert*-Butyl 2-[(*S*)-2-(Dibenzylamino)-3-methylbutylcarbamoyl]-pyrrolidine-1-carboxylate (2): *N*-Boc-L-Proline (740 mg, 3.44 mmol, 1.25 equiv.) and DCC (709 mg, 3.44 mmol, 1.5 equiv.) were dissolved in dichloromethane (25 mL) and cooled to 0 °C. The solution was stirred for 30 min, then a solution of **1** (776 mg, 2.75 mmol, 1 equiv.) in dichloromethane (25 mL) was added dropwise over 10 min. After the addition was complete, the mixture was warmed to r.t. and stirred for a further 10 h. After filtration and removal of solvent under reduced pressure, the residue was purified by flash column chromatography on silica gel (hexane/EtOAc, 4:1) to provide prolinamide **2** (1.16 g, 2.42 mmol, 88%) as a colorless oil; $[\alpha]_D^{23}$ = –56.4 (*c* = 1.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 330 K): δ = 0.95 (d, *J* = 6.8 Hz, 3 H), 1.03 (d, *J* = 6.8 Hz, 3 H), 1.43 (s, 9 H), 1.85 (m, 2 H), 2.03 (m, 2 H), 2.21 (br. s, 1 H), 2.45 (m, 1 H), 3.32 (m, 1 H), 3.42 (m, 2 H), 3.62 (m, 1 H), 3.70 (d, *J* = 13.6 Hz, 2 H), 3.76 (d, *J* = 13.6 Hz, 2 H), 4.22 (m, 1 H), 6.58 (br. s, 1 H), 7.20–7.35 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 330 K): δ = 19.8 (CH_3), 21.5 (CH_3), 24.2 (CH_2), 28.0 (CH), 28.3 (CH_3), 36.9 (CH_2), 47.0 (CH_2), 54.4 (CH_2), 60.8 (CH), 63.1 (CH), 80.1 (C), 126.7, 128.1, 128.9 (ArCH), 140.0 (ArC), 155.3 (NCO_2), 171.6 (CON) ppm. IR (film): $\tilde{\nu}$ = 3336, 2976, 1686, 1397, 1163, 1122, 749, 700 cm^{-1}. HRMS: calcd. for $C_{29}H_{41}N_3O_3Na^+$ 502.3046; found 502.3044.

(*S*)-*tert*-Butyl 2-[(*S*)-2-Amino-3-methylbutylcarbamoyl]pyrrolidine-1-carboxylate (3): To a solution of L-prolinamide **2** (1.07 g, 2.23 mmol) in MeOH (22 mL), was added $Pd(OH)_2$-C (320 mg) in one portion. The mixture was stirred under H_2 for 2 h and the catalyst was removed by filtration and washed with methanol. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel (EtOAc/methanol, 5:1) to give **3** (548 mg, 1.83 mmol, 82%) as a colorless oil. $[\alpha]_D^{23}$ = –28.0 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 330 K): δ = 0.95 (d, *J* = 7.0 Hz, 3 H), 0.97 (d, *J* = 6.6 Hz, 3 H), 1.46 (s, 9 H), 1.70 (m, 1 H), 1.95 (m, 4 H), 2.74 (br. s, 1 H), 3.05 (m, 1 H), 3.48 (m, 4 H), 3.58 (br. s, 2 H), 4.23 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 330 K): δ = 17.7 (CH_3), 19.1 (CH_3), 24.2 (CH_2), 28.4 (CH_3), 30.0 (CH_2), 32.1 (CH), 43.5 (CH_2), 47.1 (CH_2), 56.6 (CH), 60.8 (CH), 80.2 (C), 155.2 (NCO_2), 172.5 (CON) ppm. IR (film): $\tilde{\nu}$ = 3330, 2970, 1688, 1395, 1164, 1124, 772, 734 cm^{-1}. HRMS: calcd. for $C_{15}H_{29}N_3O_3$ + H^+ 300.2287; found 300.2281.

(*S*)-*tert*-Butyl 2-[(*S*)-3-Methyl-2-(4-methylbenzamido)butylcarbamoyl]pyrrolidine-1-carboxylate (4): A mixture of **3** (497 mg, 1.66 mmol) and triethylamine (0.28 mL, 2 mmol, 1.2 equiv.) in dichloromethane (8 mL) was cooled to 0 °C and *p*-toluoyl chloride (0.27 mL, 2 mmol, 1.2 equiv.) was added dropwise. After the addition was complete, the mixture was warmed to r.t. and stirred overnight. The resulting solution was quenched with aq. sat. ammonium chloride (8 mL) and the aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried with anhydrous $MgSO_4$ and the solvents were removed under vacuum. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc, 1:1) to give **4** (555 mg, 1.33 mmol, 80%) as a colorless solid; m.p. 120–121 °C (hexane/EtOAc); $[\alpha]_D^{23}$ = –74.3 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 330 K): δ = 0.99 (d, *J* = 6.6 Hz, 3 H), 1.00 (d, *J* = 7.0 Hz, 3 H), 1.38 (s, 9 H), 1.89 (m, 5 H), 2.36 (s, 3 H), 3.45 (m, 4 H), 4.03 (m, 1 H), 4.15 (m, 1 H), 6.54 (br. s, 1 H), 6.87 (br. s, 1 H), 7.19 (d, *J* = 7.9 Hz, 2 H),

7.67 (d, J = 7.9 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 300 K): δ = 18.6 (CH_3), 19.1 (CH_3), 21.2 (CH_3), 24.1 (CH_2), 28.4 (CH_3), 30.7 (CH), 41.7 (CH_2), 47.0 (CH_2), 56.1 (CHN), 60.6 (CHCO), 80.2 (C), 127.1, 129.1 (ArCH), 132.0, 141.6 (ArC), 155.1 (NCO_2), 167.7 (CON), 173.7 (CON) ppm. IR (KBr): $\tilde{\nu}$ = 3314, 2972, 1662, 1542, 1404, 1165, 752 cm^{-1}. HRMS: calcd. for $C_{23}H_{35}N_3O_4Na$ 440.2525; found 440.2522.

(*S*)-*N*-[(*S*)-3-Methyl-2-(4-methylbenzamido)butyl]pyrrolidine-2-carboxamide (5): Compound **4** (501 mg, 1.2 mmol) was dissolved in a mixture of TFA/CH_2Cl_2 (1:4, 3 mL), and stirred at r.t. for 2 h. The mixture was basified with concentrated ammonia solution and extracted with dichloromethane (3 × 10 mL). After removal of the solvent under reduced pressure, the residue was purified by flash column chromatography on silica gel (EtOAc/MeOH, 5:1) to yield **5** (293 mg, 0.92 mmol, 77%) as a colorless solid; m.p. 161–162 °C (hexane/EtOAc); $[\alpha]_D^{23}$ = –52.1 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.97 (d, J = 6.9 Hz, 6 H), 1.62 (m, 2 H), 1.82 (m, 1 H), 1.89 (m, 1 H), 2.04 (m 1 H), 2.22 (br. s, 1 H), 2.34 (s, 3 H), 2.86 (m, 2 H), 3.22 (m, 1 H), 3.57 (m, 2 H), 4.04 (m, 1 H), 6.91 (d, J = 8.6 Hz, 1 H), 7.17 (d, J = 8.0 Hz, 2 H), 7.67 (d, J = 8.0 Hz, 2 H), 7.97 (br. s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.6 (CH_3), 18.8 (CH_3), 21.3 (CH_3), 25.9 (CH_2), 30.5 (CH_2), 30.7 (CH), 40.5 (CH_2), 47.0 (CH_2), 56.0 (CHN), 60.2 (CHCO), 126.9, 129.0 (ArCH), 131.6, 141.4 (ArC), 167.6 (CON), 176.7 (CON) ppm. IR (KBr): $\tilde{\nu}$ = 3305, 2964, 2869, 1658, 1630, 1548, 1434, 841, 679 cm^{-1}. HRMS: calcd. for $C_{18}H_{27}N_3O_2$ + H^+ 318.2182; found 318.2181.

(*S*)-*N*-[2-(Dibenzylamino)-3-methylbutyl]-4-methylbenzamide (6): To a cooled (0 °C) solution of **1** (847 mg, 3 mmol) in dichloromethane (12 mL) was slowly added *p*-toluoyl chloride (0.48 mL, 3.6 mmol, 1.2 equiv.). After the addition was complete, the mixture was warmed to r.t. and stirred overnight. The resulting solution was basified with 2 N ammonia (10 mL) and the aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed with water, dried with anhydrous $MgSO_4$ and the solvents were removed under vacuum. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc, 8:1) to give **6** (981 mg, 2.45 mmol, 82%) as a colorless oil; $[\alpha]_D^{23}$ = –64.6 (c = 1.6, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05 (d, J = 6.7 Hz, 3 H), 1.14 (d, J = 6.8 Hz, 3 H), 2.22 (m, 1 H), 2.44 (s, 3 H), 2.62 (m, 1 H), 3.27 (m, 1 H), 3.65 (d, J = 13.2 Hz, 2 H), 3.66 (m, 1 H), 3.89 (d, J = 13.2 Hz, 2 H), 6.52 (br. s, 1 H), 7.15–7.30 (m, 12 H), 7.49 (d, J = 8.0 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.0 (CH_3), 21.3 (CH_3), 22.7 (CH_3), 27.6 (CH), 37.9 (CH_2), 53.9 (CH_2), 62.3 (CH), 126.8, 127.0, 128.4, 128.9, 129.1 (ArCH), 131.8, 139.9, 141.3 (ArC), 167.0 (CON) ppm. IR (film): $\tilde{\nu}$ = 3343, 2957, 1644, 1494, 1454, 1286, 749, 700 cm^{-1}. HRMS: calcd. for $C_{27}H_{32}N_2ONa^+$ 423.2412; found 423.2407.

(*S*)-*N*-(2-Amino-3-methylbutyl)-4-methylbenzamide (7): Obtained by hydrogenation of **6** (933 mg, 2.33 mmol) with $Pd(OH)_2$-C in MeOH by using the procedure described for the preparation of **3**, and purified by flash column chromatography on silica gel (EtOAc/methanol, 5:1); yield 489 mg (2.22 mmol, 95%); colorless oil; $[\alpha]_D^{23}$ = +34.0 (c = 1.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (d, J = 6.8 Hz, 3 H), 0.95 (d, J = 6.8 Hz, 3 H), 1.65 (m, 1 H), 1.85 (br. s, 2 H), 2.37 (s, 3 H), 2.67 (m, 1 H), 3.06 (m, 1 H), 3.70 (ddd, J = 13.4, 6.6, 3.7 Hz, 1 H), 7.05 (br. s, 1 H), 7.20 (d, J = 8.1 Hz, 2 H), 7.70 (d, J = 8.1 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.5 (CH_3), 21.3 (CH_3), 29.8 (CH), 40.8 (CH_2), 57.9 (CH), 127.4, 128.9 (ArCH), 130.7, 141.9 (ArC), 168.2 (CON) ppm. IR (film): $\tilde{\nu}$ = 3311, 2959, 2873, 1636, 1545, 1306, 838, 752 cm^{-1}. HRMS: calcd. for $C_{13}H_{20}N_2O$ + H^+ 221.1654; found 221.1643.

(*R*)-Benzyl 2-[(*S*)-3-Methyl-1-(4-methylbenzamido)butan-2-ylcarbamoyl]pyrrolidine-1-carboxylate (8): Obtained by reaction of **7** (288 mg, 1.31 mmol) with Cbz-D-proline in the presence of DCC by the procedure described for the preparation of **2** and purified by flash column chromatography on silica gel (EtOAc/hexane, 1:1); yield 527 mg (1.17 mmol, 89%); colorless solid; m.p. 147–148 °C (hexane/EtOAc); $[\alpha]_D^{23}$ = +44.0 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 330 K): δ = 0.92 (d, J = 6.6 Hz, 3 H), 0.96 (d, J = 7.0 Hz, 3 H), 1.80 (m, 5 H), 2.34 (s, 3 H), 3.54 (m, 4 H), 3.91 (m, 1 H), 4.28 (dd, J = 8.3, 3.5 Hz, 1 H), 5.06 (m, 2 H), 6.60 (br. s, 1 H), 6.94 (br. s, 1 H), 7.16 (d, J = 8.0 Hz, 2 H), 7.30 (m, 5 H), 7.68 (d, J = 8.0 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 330 K): δ = 18.5 (CH_3), 19.5 (CH_3), 21.4 (CH_3), 24.4 (CH_2), 29.8 (CH_2), 30.7 (CH), 43.3 (CH_2), 47.4 (CH_2), 55.4 (CH), 61.3 (CH), 67.6 (CH_2), 127.3, 128.0, 128.3, 128.7, 129.2 (ArCH), 131.9, 136.7, 141.7 (ArC), 156.0 (NCO_2), 167.9 (CON), 173.4 (CON) ppm. IR (KBr): $\tilde{\nu}$ = 3282, 3133, 2962, 1702, 1648, 1549, 1419, 1360, 1126, 750, 740, 698 cm^{-1}. HRMS: calcd. for $C_{26}H_{33}N_3O_4Na^+$ 474.2369; found 474.2360.

(*S*)-Benzyl 2-[(S)-3-Methyl-1-(4-methylbenzamido)butan-2-ylcarbamoyl]pyrrolidine-1-carboxylate (9): Obtained by reaction of **7** (465 mg, 2.11 mmol) with Cbz-L-proline in the presence of DCC by the procedure described for the preparation of **2** and purified by flash column chromatography on silica gel (EtOAc/hexane, 2:1); yield 890 mg (1.97 mmol, 93%); colorless solid; m.p. 151–152 °C (hexane/EtOAc). $[\alpha]_D^{23}$ = –51.5 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 330 K): δ = 0.92 (d, J = 6.8 Hz, 3 H), 0.96 (d, J = 6.6 Hz, 3 H), 1.93 (m, 4 H), 2.20 (m, 1 H), 2.38 (s, 3 H), 3.35 (m, 1 H), 3.52 (m, 2 H), 3.64 (m, 1 H), 3.87 (m, 1 H), 4.32 (dd, J = 7.8, 3.2 Hz, 1 H), 5.06 (d, J = 12.3 Hz, 1 H), 5.15 (d, J = 12.3 Hz, 1 H), 6.50 (br. s, 1 H), 6.93 (br. s, 1 H), 7.20 (d, J = 8.1 Hz, 2 H), 7.30 (s, 5 H), 7.71 (d, J = 8.1 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.2 (CH_3), 19.3 (CH_3), 21.3 (CH_3), 28.6 (CH_2), 30.2 (CH), 33.9 (CH_2), 43.2 (CH_2), 47.0 (CH_2), 55.0 (CH), 60.8 (CH), 67.3 (CH_2), 127.1, 127.8, 128.1, 128.4, 129.0 (ArCH), 131.3, 136.2, 141.5 (ArC), 156.0 (NCO_2), 167.6 (CON), 172.8 (CON) ppm. IR (KBr): $\tilde{\nu}$ = 3299, 1715, 1662, 1636, 1543, 1423, 1355, 1120 cm^{-1}. HRMS: calcd. for $C_{26}H_{33}N_3O_4Na^+$ 474.2369; found 474.2354.

(*S*)-*N*-[(*S*)-3-Methyl-1-(4-methylbenzamido)butan-2-yl]pyrrolidine-2-carboxamide (10): Compound **9** (841 mg, 1.86 mmol) was debenzylated by hydrogenation with Pd/C (10%) in MeOH and purified by flash column chromatography on silica gel (EtOAc/methanol, 5:1); yield 529 mg (1.67 mmol, 89%); colorless solid; m.p. 115–116 °C (hexane/EtOAc); $[\alpha]_D^{23}$ = –28.0 (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.97 (d, J = 6.8 Hz, 3 H), 0.98 (d, J = 6.8 Hz, 3 H), 1.68 (m, 2 H), 1.88 (m, 2 H), 2.12 (m, 1 H), 2.35 (s, 3 H), 2.65 (br. s, 1 H), 2.90 (dt, J = 10.2, 6.2 Hz, 1 H), 3.00 (dd, J = 10.2, 6.9 Hz, 1 H), 3.50 (m, 2 H), 3.70 (dd, J = 9.2, 5.1 Hz, 1 H), 3.88 (m, 1 H), 7.18 (d, J = 8.1 Hz, 2 H), 7.53 (br. s, 1 H), 7.69 (d, J = 8.1 Hz, 2 H), 8.00 (d, J = 8.8 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.0 (CH_3), 19.5 (CH_3), 21.3 (CH_3), 25.9 (CH_2), 30.2 (CH), 30.7 (CH_2), 44.4 (CH_2), 47.1 (CH_2), 54.0 (CH), 60.2 (CH), 126.9, 129.0 (ArCH), 131.2, 141.4 (ArC), 167.5 (CON), 176.7 (CON) ppm. IR (KBr): $\tilde{\nu}$ = 3291, 2957, 1636, 1551, 834, 670 cm^{-1}. HRMS: calcd. for $C_{18}H_{27}N_3O_2$ + H^+ 318.2182; found 318.2176.

(*R*)-*N*-[(*S*)-3-Methyl-1-(4-methylbenzamido)butan-2-ylcarbamoyl]-pyrrolidine-1-carboxylate (*ent-epi*-10): Compound **8** (497 mg, 1.1 mmol) was deprotected by hydrogenation with Pd/C (10%) in MeOH and purified by flash column chromatography on silica gel (EtOAc/methanol, 5:1); yield 210 mg (0.66 mmol, 60%); colorless solid; m.p. 140–141 °C (hexane/EtOAc); $[\alpha]_D^{23}$ = +75.6 (c = 1.0,

$CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.99 (d, J = 6.8 Hz, 3 H), 1.00 (d, J = 6.8 Hz, 3 H), 1.59 (m, 2 H), 1.71 (m, 1 H), 1.91 (m, 1 H), 2.07 (m, 1 H), 2.36 (s, 3 H), 2.89 (m, 1 H), 2.98 (m, 1 H), 3.10 (br. s, 1 H), 3.53 (m, 2 H), 3.83 (dd, J = 9.1, 5.5 Hz, 1 H), 3.91 (m, 1 H), 7.20 (d, J = 8.0 Hz, 2 H), 7.47 (br. s, 1 H), 7.71 (d, J = 8.2 Hz, 2 H), 8.00 (d, J = 8.7 Hz, 1 H) ppm. HRMS: calcd. for $C_{18}H_{27}N_3O_2$+ H^+ 318.2182; found 318.2175.

(*R*)-*N*-(1-Dibenzylamino)-3-(methylbutan-2-yl)-4-methylbenzamide (12): Prepared by reaction of diamine **11** (565 mg, 2.0 mmol) with *p*-toluoyl chloride by the procedure described for the preparation of **6** and purified by flash column chromatography on silica gel (EtOAc/hexane, 8:1); yield 697 mg (1.74 mmol, 87%); colorless solid; m.p. 154–156 °C (hexane/EtOAc); $[\alpha]_D^{23}$ = +5.3 (c = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.79 (d, J = 6.9 Hz, 3 H), 0.87 (d, J = 6.9 Hz, 3 H), 2.05 (m, 1 H), 2.45 (s, 3 H), 2.46 (m, 1 H), 2.54 (dd, J = 13.1, 5.7 Hz, 1 H), 3.43 (d, J = 13.3 Hz, 2 H), 3.75 (d, J = 13.3 Hz, 2 H), 4.28 (m, 1 H), 5.80 (d, J = 8.2 Hz, 1 H), 7.20–7.40 (m, 12 H), 7.63 (d, J = 8.2 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.4 (CH_3), 18.9 (CH_3), 21.4 (CH_3), 29.9 (CH), 51.7 (CH), 54.0 (CH_2), 58.5 (CH_2), 126.8, 126.9, 128.2, 129.0 (ArCH), 132.2, 139.3, 141.5 (ArC), 167.3 (CON) ppm. IR (KBr): $\tilde{\nu}$ = 3343, 3164, 1670, 1617, 1570, 1413, 1397, 840 cm^{-1}. HRMS: calcd. for $C_{27}H_{32}N_2O$ + H^+ 401.2593; found 401.2595.

(*R*)-*N*-(1-Amino-3-methylbutan-2-yl)-4-methylbenzamide (13): Compound **12** (561 mg, 1.4 mmol) was debenzylated by hydrogenation with $Pd(OH)_2$-C (10%) in MeOH by the procedure described for the preparation of **3** and purified by flash column chromatography on silica gel (EtOAc/methanol, 5:1); yield 293 mg (1.33 mmol, 95%); colorless solid; m.p. 173–174 °C (hexane/EtOAc); $[\alpha]_D^{23}$ = +13.1 (c = 0.8, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.94 (d, J = 6.8 Hz, 3 H), 0.95 (d, J = 6.7 Hz, 3 H), 1.88 (m, 1 H), 2.37 (s, 3 H), 2.90 (d, J = 5.7 Hz, 2 H), 3.19 (br. s, 2 H), 3.98 (m, 1 H), 6.78 (d, J = 9.0 Hz, 1 H), 7.19 (d, J = 8.1 Hz, 2 H), 7.72 (d, J = 8.1 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.6 (CH_3), 19.3 (CH_3), 21.2 (CH_3), 30.2 (CH), 42.3 (CH_2), 56.0 (CH), 127.1, 128.9 (ArCH), 131.4, 141.6 (ArC), 168.0 (CON) ppm. IR (KBr): $\tilde{\nu}$ = 3340, 2873, 1635, 1527, 1503, 834, 755 cm^{-1}. HRMS: calcd. for $C_{13}H_{20}N_2O$ + H^+ 221.1654; found 221.1648.

(*S*)-*tert*-Butyl 2-[(*R*)-3-Methyl-2-(4-methylbenzamido)butylcarbamoyl]pyrrolidine-1-carboxylate (14): Obtained by reaction of **13** (295 mg, 1.34 mmol) with Boc-L-proline in the presence of DCC by the procedure described for the preparation of **2** and purified by flash column chromatography on silica gel (EtOAc/hexane, 1:1); yield 459 mg (1.1 mmol, 82%); colorless oil; $[\alpha]_D^{23}$ = –39.3 (c = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 330 K): δ = 1.02 (d, J = 6.6 Hz, 3 H), 1.03 (d, J = 6.6 Hz, 3 H), 1.45 (s, 9 H), 1.69 (m, 2 H), 1.91 (m, 2 H), 2.07 (m, 1 H), 2.39 (s, 3 H), 3.30 (m, 3 H), 3.67 (m, 1 H), 4.07 (m, 1 H), 4.22 (dd, J = 8.8, 3.3 Hz, 1 H), 6.49 (br. s, 1 H), 6.83 (br. s, 1 H), 7.21 (d, J = 7.9 Hz, 2 H), 7.72 (d, J = 7.9 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.8 (CH_3), 19.4 (CH_3), 21.4 (CH_3), 24.2 (CH_2), 28.6 (CH_3), 29.8 (CH_2), 31.0 (CH), 41.5 (CH_2), 47.2 (CH_2), 56.2 (CH), 61.0 (CH), 80.6 (C), 127.3, 129.2 (ArCH), 132.1, 141.8 (ArC), 155.5 (CO_2tBu), 167.7 (CON), 173.8 (CON) ppm. IR (film): $\tilde{\nu}$ = 3318, 2972, 1661, 1538, 1505, 1392, 1364, 1164, 752, 733 cm^{-1}. HRMS: calcd. for $C_{23}H_{36}N_3O_4Na^+$ 440.2525; found 440.2518.

(*S*)-*N*-[(*R*)-3-Methyl-2-(4-methylbenzamido)butyl]pyrrolidine-2-carboxamide (*epi*-5): Prepared by reaction of **14** (434 mg, 1.04 mmol) with TFA in CH_2Cl_2 by the procedure described for the preparation of **5** and purified by flash column chromatography on silica gel (EtOAc/methanol, 5:1); yield 248 mg (0.78 mmol, 75%); colorless oil; $[\alpha]_D^{23}$ = –33.4 (c = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.00 (d, J = 7.0 Hz, 6 H), 1.46 (m, 2 H), 1.55 (m, 2 H), 1.90 (m, 2 H), 2.39 (s, 3 H), 2.78 (m, 1 H), 2.91 (m, 1 H), 3.17 (m, 1 H), 3.68 (m, 2 H), 4.09 (m, 1 H), 6.73 (d, J = 9.2 Hz, 1 H), 7.22 (d, J = 7.9 Hz, 2 H), 7.71 (d, J = 8.3 Hz, 2 H), 8.02 (br. s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.7 (CH_3), 19.1 (CH_3), 21.4 (CH_3), 25.9 (CH_2), 30.7 (CH_2), 31.1 (CH), 40.4 (CH_2), 47.1 (CH_2), 56.1 (CH), 60.4 (CH), 127.1, 129.1 (ArCH), 131.5, 141.6 (ArC), 167.6 (CON), 176.9 (CON) ppm. HRMS: calcd. for $C_{18}H_{27}N_3O_2$ + H^+ 318.2182; found 318.2157.

(*S*)-*tert*-Butyl 2-[(*R*)-1-(Dibenzylamino)-3-methylbutan-2-ylcarbamoyl]pyrrolidine-1-carboxylate (15): Obtained by reaction of **11** (904 mg, 3.2 mmol) with Boc-L-proline in the presence of DCC by the procedure described for the preparation of **2** and purified by flash column chromatography on silica gel (EtOAc/hexane, 4:1); yield 1.51 g (3.15 mmol, 98%); colorless oil; $[\alpha]_D^{23}$ = –35.8 (c = 1.3, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 330 K): δ = 0.69 (d, J = 7.0 Hz, 3 H), 0.86 (d, J = 7.0 Hz, 3 H), 1.46 (s, 9 H), 1.94 (m, 4 H), 2.30 (m, 1 H), 2.40 (dd, J = 13.2, 7.9 Hz, 1 H), 2.51 (dd, J = 13.2, 6.1 Hz, 1 H), 3.40 (m, 2 H), 3.61 (m, 4 H), 4.14 (m, 1 H), 4.30 (dd, J = 8.3, 2.8 Hz, 1 H), 6.22 (br. s, 1 H), 7.20–7.35 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 330 K): δ = 16.8 (CH_3), 19.6 (CH_3), 24.5 (CH_2), 28.7 (CH_3), 30.0 (CH), 47.5 (CH_2), 52.1 (CH), 55.5 (CH_2), 59.0 (CH_2), 61.3 (CH), 80.6 (C), 127.1, 128.4, 129.3 (ArCH), 139.6 (ArC), 155.7 (CO_2tBu), 172.1 (CON) ppm. IR (film): $\tilde{\nu}$ = 3327, 2961, 1698, 1393, 1164, 748, 700 cm^{-1}. HRMS: calcd. for $C_{29}H_{41}N_3O_3$ + H^+ 480.3226; found 480.3213.

(*S*)-*tert*-Butyl 2-[(*R*)-1-Amino-3-methylbutan-2-ylcarbamoyl]pyrrolidine-1-carboxylate (16): Obtained by hydrogenation of **15** (1.48 g, 3.04 mmol) with $Pd(OH)_2$-C in MeOH by the procedure described for the preparation of **3** and purified by flash column chromatography on silica gel (EtOAc/methanol, 5:1); yield 820 mg (2.74 mmol, 90%); colorless solid; m.p. 103–104 °C; $[\alpha]_D^{23}$ = –35.3 (c = 1.0, $CHCl_3$). ^1H NMR (300 MHz, CD_3OD, 330 K): δ = 0.97 (d, J = 6.6 Hz, 3 H), 0.99 (d, J = 6.6 Hz, 3 H), 1.46 (s, 9 H), 1.92 (m, 4 H), 2.24 (m, 1 H), 2.96 (dd, J = 13.2, 11.0 Hz, 1 H), 3.24 (dd, J = 13.2, 3.1 Hz, 1 H), 3.48 (m, 2 H), 3.94 (m, 1 H), 4.20 (dd, J = 7.9, 5.3 Hz, 1 H), 4.30 (br. s, 1 H) ppm. ^{13}C NMR (75 MHz, CD_3OD, 330 K): δ = 18.8 (CH_3), 19.7 (CH_3), 25.5 (CH_2), 29.0 (CH_3), 31.6 (CH_2), 31.7 (CH), 43.9 (CH_2), 48.6 (CH_2), 54.6 (CH), 61.9 (CH), 82.0 (C), 156.9 (CO_2tBu), 176.5 (CON) ppm. IR (KBr): $\tilde{\nu}$ = 3448, 3220, 2975, 1670, 1420, 1394, 1164, 924, 733 cm^{-1}. HRMS: calcd. for $C_{15}H_{29}N_3O_3$ + H^+ 300.2287; found 300.2284.

(*S*)-*tert*-Butyl 2-[(*R*)-3-Methyl-1-(4-methylbenzamido)butan-2-ylcarbamoyl]pyrrolidine-1-carboxylate (17): Prepared by reaction of compound **16** (748 mg, 2.5 mmol) with *p*-toluoyl chloride in the presence of Et_3N by the procedure described for the preparation of **4** and purified by flash column chromatography on silica gel (EtOAc/hexane, 3:2); yield 741 mg (1.78 mmol, 71%); colorless solid; m.p. 96–97 °C (from hexane/EtOAc); $[\alpha]_D^{23}$ = –72.4 (c = 1.4, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.98 (d, J = 6.6 Hz, 3 H), 1.01 (d, J = 6.6 Hz, 3 H), 1.42 (s, 9 H), 1.72 (m, 2 H), 1.90 (m, 2 H), 2.11 (m, 1 H), 2.35 (s, 3 H), 3.33 (m, 2 H), 3.54 (m, 2 H), 3.91 (m, 1 H), 4.24 (dd, J = 8.3, 3.1 Hz, 1 H), 6.69 (br. s, 1 H), 6.98 (br. s, 1 H), 7.16 (d, J = 7.9 Hz, 2 H), 7.68 (d, J = 7.9 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.1 (CH_3), 19.3 (CH_3), 21.1 (CH_3), 24.1 (CH_2), 28.3 (CH_3), 29.2 (CH_2), 30.4 (CH), 43.3 (CH_2), 47.1 (CH_2), 55.0 (CH), 60.8 (CH), 80.4 (C), 127.1, 129.0 (ArCH), 131.8, 141.4 (ArC), 155.4 (CO_2tBu), 167.5 (CON), 173.6 (CON) ppm. IR (KBr): $\tilde{\nu}$ = 3311, 2960, 1699, 1651, 1543, 1393, 1162, 756 cm^{-1}.

(*S*)-*N*-[(*R*)-3-Methyl-1-(4-methylbenzamido)butan-2-yl]pyrrolidine-2-carboxamide (*epi*-10): Prepared by reaction of **17** (710 mg,

1.7 mmol) with TFA in CH_2Cl_2 by the procedure described for the preparation of **5** and purified by recrystallization from hexane/EtOAc; yield 410 mg (1.29 mmol, 76%); colorless solid; m.p. 141–142 °C; $[a]_D^{23}$ = –78.3 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (d, *J* = 6.6 Hz, 3 H), 1.02 (d, *J* = 6.6 Hz, 3 H), 1.56 (m, 2 H), 1.71 (m, 1 H), 1.93 (m, 1 H), 2.05 (m, 1 H), 2.38 (s, 3 H), 2.85 (m, 1 H), 2.96 (m, 1 H), 3.53 (m, 2 H), 3.76 (dd, *J* = 9.2, 5.3 Hz, 1 H), 3.91 (m, 1 H), 7.21 (d, *J* = 7.9 Hz, 2 H), 7.43 (br. s, 1 H), 7.74 (d, *J* = 7.9 Hz, 2 H), 7.97 (d, *J* = 8.8 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.5 (CH_3), 19.6 (CH_3), 21.5 (CH_3), 26.1 (CH_2), 30.4 (CH), 31.0 (CH_2), 44.6 (CH_2), 47.2 (CH_2), 54.0 (CH), 60.6 (CH), 127.1, 129.2 (ArCH), 131.3, 141.6 (ArC), 167.5 (CON), 177.3 (CON) ppm. IR (KBr): $\tilde{\nu}$ = 3361, 3275, 2959, 1647, 1559, 1526, 1140, 1102, 717, 670 cm^{-1}. HRMS: calcd. for $C_{18}H_{27}N_3O_2 + H^+$ 318.2182; found 318.2176.

***N*-(2-Aminoethyl)-4-methylbenzamide (18):** Ethylenediamine (1.6 mL, 24 mmol, 1.2 equiv.) was added in one portion to a vigorously stirred solution of the *p*-toluoyl chloride (2.6 mL, 20 mmol) in methanol (100 mL) in an ice-water bath. Stirring was continued for 60 s, then the reaction was quenched with 10% NaOH (10 mL). The heterogeneous mixture was stirred at r.t. for 5 min and the methanol was removed under vacuum. The resulting aqueous phase was diluted with water and extracted with chloroform (3 × 25 mL). The combined organic layers were washed with water, dried with anhydrous $MgSO_4$ and the solvents were removed under vacuum. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2/methanol, 3:2). to give **18** (2.24 g, 12.6 mmol, 63%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.33 (s, 5 H), 2.87 (m, 2 H), 3.45 (m, 2 H), 7.15 (d, *J* = 8.3 Hz, 2 H), 7.25 (br. s, 1 H), 7.68 (d, *J* = 8.3 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5 (CH_3), 41.3 (CH_2), 42.2 (CH_2), 127.1, 129.2 (ArCH), 131.7, 141.9 (ArC), 168.0 (CON) ppm. IR (KBr): $\tilde{\nu}$ = 3293, 2924, 1636, 1544, 1505, 1305, 838, 752 cm^{-1}. HRMS: calcd. for $C_{10}H_{14}N_2ONa^+$ 201.1004; found 201.0996.

(*S*)-*tert*-Butyl 2-[2-(4-Methylbenzamido)ethylcarbamoyl]pyrrolidine-1-carboxylate (19): Obtained by reaction of **18** (1.03 g, 5.8 mmol) with Boc-L-proline (1.50 g, 6.96 mmol, 1.25 equiv.) in the presence of DCC (1.43 g, 6.96 mmol, 1.25 equiv.) by the procedure described for the preparation of **2** and purified by flash column chromatography on silica gel (EtOAc); yield 1.89 g (5.05 mmol, 87%); colorless oil; $[a]_D^{23}$ = –21.9 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 330 K): δ = 1.39 (s, 9 H), 1.83 (m, 2 H), 2.00 (m, 2 H), 2.34 (s, 3 H), 3.50 (m, 6 H), 4.17 (m, 1 H), 6.97 (br. s, 1 H), 7.16 (d, *J* = 7.9 Hz, 2 H), 7.23 (br. s, 1 H), 7.70 (d, *J* = 7.9 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 300 K): δ = 21.4 (CH_3), 24.4 (CH_2), 28.5 (CH_3), 29.9 (CH_2), 39.9 (CH_2), 41.0 (CH_2), 47.3 (CH_2), 61.0 (CH), 127.3, 129.2 (ArCH), 131.8, 141.7 (ArC), 155.3 (NCO_2), 168.0 (CON), 174.2 (CON) ppm. IR (KBr): $\tilde{\nu}$ = 3313, 2976, 1651, 1538, 1393, 1162, 1123, 753.1 cm^{-1}. HRMS: calcd. for $C_{20}H_{29}N_3O_4Na^+$ 398.2056; found 398.2054.

(*S*)-*N*-[2-(4-Methylbenzamido)ethyl]pyrrolidine-2-carboxamide (20): Obtained by reaction of **19** (1.31 g, 3.5 mmol) with TFA/CH_2Cl_2 (1:4) by the procedure described for the preparation of **5** and purified by flash column chromatography on silica gel (EtOAc/methanol, 5:1); yield 0.77 g (2.8 mmol, 80%); colorless solid; m.p. 142–143 °C (EtOAc); $[a]_D^{23}$ = –65.4 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.64 (m, 2 H), 1.81 (m, 1 H), 2.09 (m, 2 H), 2.36 (s, 3 H), 2.86 (dt, *J* = 10.1, 6.1 Hz, 1 H), 2.97 (dt, *J* = 10.1, 6.6 Hz, 1 H), 3.52 (m, 4 H), 3.72 (dd, *J* = 9.2, 5.3 Hz, 1 H), 7.20 (d, *J* = 8.2 Hz, 2 H), 7.57 (br. s, 1 H), 7.72 (d, *J* = 8.2 Hz, 2 H), 8.13 (br. s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.4 (CH_3), 26.1 (CH_2), 30.8 (CH_2), 38.7 (CH_2), 41.7 (CH_2), 47.2 (CH_2), 60.4 (CH), 127.1, 129.1 (ArCH), 131.3, 141.6 (ArC), 167.7 (CON), 177.5 (CON) ppm. IR (KBr): $\tilde{\nu}$ = 3328, 3290, 2939, 1637, 1540, 1216, 835 cm^{-1}. HRMS: calcd. for $C_{15}H_{21}N_3O_2 + H^+$ 276.1712; found 276.1702.

General Procedure for Enantioselective Aldol Reaction: The catalyst (0.1 mmol) and AcOH (0.1 mmol) were stirred in solvent/cyclohexanone (1:1, 2 mL) for 20 min at –20 °C. The corresponding aldehyde (0.5 mmol) was added and the mixture was stirred for 24–72 h. The reaction mixture give pure aldol adduct after flash column chromatography on silica gel.

The diastereoselectivity was determined by ^{1}H NMR analysis of the crude aldol product after short column chromatography purification to remove the cyclohexanone and the catalyst. The enantiomeric excess was determined by chiral HPLC analysis using a Daicel Chiralpak OD column with a mixture of hexane/2-propanol as eluting solvents. The absolute stereochemistry was determined by comparison with the literature data.

2-[(4-Chlorophenyl)hydroxymethyl]cyclohexanone (21a):[10,18,19] Yield 88%; ratio *anti*/*syn* = 92:8. *anti*-Diastereomer (2*S*,1′*R*). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26–2.11 (m, 6 H), 2.31–2.49 (m, 2 H), 2.52–2.59 (m, 1 H), 3.61 (s, 1 H), 4.76 (d, *J* = 8.4 Hz, 1 H), 7.25 (d, *J* = 8.4 Hz, 2 H), 7.31 (d, *J* = 8.8 Hz, 2 H) ppm. HPLC analysis Chiracel OD (hexane/*i*PrOH = 95:5; 1.0 mL/min; 220 nm; 20 °C) t_R = 14.3 min (major) and t_R = 21.6 min (minor); *er* = 98:2; $[a]_D$ = +23.7 (*c* = 1.1, $CHCl_3$). *syn*-Diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.49–2.09 (m, 6 H), 2.32–2.46 (m, 2 H), 2.53–2.57 (m, 1 H), 2.92 (br. s, 1 H), 5.34 (d, *J* = 2.0 Hz, 1 H), 7.23 (d, *J* = 8.4 Hz, 2 H), 7.30 (d, *J* = 8.4 Hz, 2 H) ppm.

2-[Hydroxy(2-nitrophenyl)methyl]cyclohexanone (21b):[12b,19,20] Yield 98%; ratio *anti*/*syn* = 91:9. *anti*-Diastereomer (2*S*,1′*R*): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.57–1.88 (m, 6 H), 2.07–2.13 (m, 1 H), 2.33–2.49 (m, 2 H), 2.74–2.78 (m, 1 H), 5.45 (d, *J* = 7.0 Hz, 1 H), 7.44 (t, *J* = 7.5 Hz, 1 H), 7.76 (t, *J* = 7.5 Hz, 1 H), 7.77 (d, *J* = 8.1 Hz, 1 H), 7.85 (d, *J* = 8.1 Hz, 1 H) ppm. HPLC analysis Chiracel OD (hexane/*i*PrOH = 95:5; 1.0 mL/min; 220 nm; 20 °C) t_R = 17.8 min (major) and t_R = 21.8 min (minor); *er* = 97:3; $[a]_D$ = +36.7 (*c* = 1.3, $CHCl_3$). *syn*-Diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.50–1.89 (m, 6 H), 2.08–2.14 (m, 1 H), 2.41–2.47 (m, 2 H), 2.85–2.92 (m, 1 H), 5.96 (d, *J* = 2.2 Hz, 1 H), 7.43 (t, *J* = 7.5 Hz, 1 H), 7.65 (t, *J* = 7.5 Hz, 1 H), 7.84 (d, *J* = 7.9 Hz, 1 H), 8.01 (d, *J* = 7.9 Hz, 1 H) ppm.

2-[Hydroxy(3-nitrophenyl)methyl]cyclohexanone (21c):[12b,19,20] Yield 95%; ratio *anti*/*syn* = 94:6. *anti*-Diastereomer (2*S*,1′*R*): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30–1.85 (m, 6 H), 2.32–2.43 (m, 1 H), 2.48–2.53 (m, 1 H), 2.58–2.67 (m, 1 H), 4.13 (br. s, 1 H), 4.90 (d, *J* = 9.0 Hz, 1 H), 7.53 (t, *J* = 7.9 Hz, 1 H), 7.67 (d, *J* = 7.5 Hz, 1 H), 8.16 (d, *J* = 7.9 Hz, 1 H), 8.21 (d, *J* = 1.7 Hz, 1 H) ppm. HPLC analysis Chiracel OD (hexane/*i*PrOH = 95:5; 1.5 mL/min; 220 nm; 20 °C) t_R = 15.8 min (major) and t_R = 21.9 min (minor); *er* = 96:4; $[a]_D$ = +30.6 (*c* = 0.9, $CHCl_3$). *syn*-Diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.50–1.90 (m, 6 H), 2.39–2.52 (m, 2 H), 2.62–2.69 (m, 1 H), 3.23 (br. s, 1 H), 5.48 (s, 1 H), 7.52 (t, *J* = 7.9 Hz, 1 H), 7.67 (t, *J* = 7.5 Hz, 1 H), 8.12 (d, *J* = 8.3 Hz, 1 H), 8.19 (s, 1 H) ppm.

2-[Hydroxy(4-nitrophenyl)methyl]cyclohexanone (21d):[12b,18,19] Yield 95%; ratio *anti*/*syn* = 91:9. *anti*-Diastereomer (2*S*,1′*R*): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22–1.84 (m, 6 H), 2.30–2.41 (m, 1 H), 2.46–2.63 (m, 2 H), 4.11 (d, *J* = 3.0 Hz, 1 H), 4.89 (dd, *J* = 8.3, 2.9 Hz, 1 H), 7.50 (d, *J* = 8.6 Hz, 2 H), 8.19 (d, *J* = 8.6 Hz, 2 H) ppm. HPLC analysis Chiracel OD (hexane/*i*PrOH = 95:5; 1.0 mL/min; 220 nm; 20 °C) t_R = 31.5 min (major) and t_R =

46.3 min (minor); *er* = 97:3; $[\alpha]_D$ = +10.9 (*c* = 0.5, $CHCl_3$). *syn*-Diastereomer: ^{1}H NMR ($CDCl_3$): δ = 1.52–2.12 (m, 6 H), 2.33–2.50 (m, 2 H), 2.57–2.61 (m, 1 H), 3.20 (br. s, 1 H), 5.43 (s, 1 H), 7.43 (d, *J* = 8.0 Hz, 2 H), 7.63 (d, *J* = 8.3 Hz, 2 H) ppm.

2-[(4-Cyanophenyl)hydroxymethyl]cyclohexanone (21e):[18–20] Yield 98%; ratio *anti*/*syn* = 87:13. *anti*-Diastereomer (2*S*,1′*R*): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35–2.14 (m, 6 H), 2.30–2.50 (m, 2 H), 2.53–2.61 (m, 1 H), 4.07 (br. s, 1 H), 4.83 (d, *J* = 8.8 Hz, 1 H), 7.45 (d, *J* = 8.3 Hz, 2 H), 7.65 (d, *J* = 8.3 Hz, 2 H) ppm. HPLC analysis Chiracel OD (hexane/*i*PrOH = 95:5; 1.0 mL/min; 220 nm; 20 °C) t_R = 31.5 min (major) and t_R = 46.3 min (minor); *er* = 95:5; $[\alpha]_D$ = +17.7 (*c* = 0.9, $CHCl_3$). *syn*-Diastereomer: ^{1}H NMR ($CDCl_3$): δ = 1.52–2.12 (m, 6 H), 2.33–2.50 (m, 2 H), 2.57–2.61 (m, 1 H), 3.20 (br. s, 1 H), 5.43 (s, 1 H), 7.43 (d, *J* = 8.0 Hz, 2 H), 7.63 (d, *J* = 8.3 Hz, 2 H) ppm.

2-[Hydroxy(phenyl)methyl]cyclohexanone (21f):[12b,18,19] Yield 81%; ratio *anti*/*syn* = 94:6. *anti*-Diastereomer (2*S*,1′*R*): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27–2.13 (m, 6 H), 2.31–2.52 (m, 2 H), 2.55–2.67 (m, 1 H), 3.99 (br. s, 1 H), 4.79 (d, *J* = 8.8 Hz, 1 H), 7.29–7.40 (m, 5 H) ppm. HPLC analysis Chiracel OD (hexane/*i*PrOH = 90:10; 1.0 mL/min; 220 nm; 20 °C) t_R = 9.6 min (major) and t_R = 13.0 min (minor); *er* = 97:3; $[\alpha]_D$ = +21.8 (*c* = 0.7, $CHCl_3$). *syn*-Diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.48–2.12 (m, 6 H), 2.33–2.48 (m, 2 H), 2.50–2.64 (m, 1 H), 3.05 (br. s, 1 H), 5.41 (s, 1 H), 7.25–7.41 (m, 5 H) ppm.

2-[Hydroxy(4-methylphenyl)methyl]cyclohexanone (21g):[19,20] Yield 80%; ratio *anti*/*syn* = 91:9. *anti*-Diastereomer (2*S*,1′*R*): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.51–1.80 (m, 5 H), 2.05–2.11 (m, 1 H), 2.34 (s, 3 H), 2.41–2.50 (m, 2 H), 2.57–2.64 (m, 1 H), 3.94 (br. s, 1 H), 4.76 (d, *J* = 8.8 Hz, 1 H), 7.16 (d, *J* = 8.3 Hz, 2 H), 7.21 (d, *J* = 8.3 Hz, 2 H) ppm. HPLC analysis Chiracel OD (hexane/*i*PrOH = 95:5; 1.0 mL/min; 220 nm; 20 °C) t_R = 12.2 min (major) and t_R = 16.2 min (minor); *er* = 96:4; $[\alpha]_D$ = +22.3 (*c* = 0.7, $CHCl_3$). *syn*-Diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.48–1.88 (m, 5 H), 2.05–2.12 (m, 1 H), 2.35 (s, 3 H), 2.38–2.48 (m, 2 H), 2.55–2.62 (m, 1 H), 2.99 (br. s, 1 H), 5.36 (s, 1 H), 7.15 (d, *J* = 8.3 Hz, 2 H), 7.20 (d, *J* = 8.3 Hz, 2 H) ppm.

Supporting Information (see also the footnote on the first page of this article): Synthesis of diamines **1** and **11**, experimental procedures, spectroscopic data for new compounds and intermediates, HPLC separation conditions and retention times for compounds **21a**–**g**.

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[1] For special issues that summarize the interest in organocatalysts, see: a) *Adv. Synth. Catal.* **2004**, *346*, issues 9–10; b) *Acc. Chem. Res.* **2004**, *37*, issue 8; c) *Chem. Rev.* **2007**, *107*, issue 12; d) *Chimia* **2007**, *61*, issue 5.

[2] For recent reviews, see: a) C. Palomo, M. Oiarbide, J. M. García, *Chem. Soc. Rev.* **2004**, *33*, 65; b) *Modern Aldol Reactions* (Ed.: R. Mahrwald), Wiley-VCH, Weinheim, Germany, **2004**, 2 volumes; c) B. List, *Chem. Commun.* **2006**, 819; d) R. M. Figueiredo, M. Christmann, *Eur. J. Org. Chem.* **2007**, 2575; e) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471; f) H. Pellissier, *Tetrahedron* **2007**, *63*, 9267; g) G. Guillena, C. Nájera, D. J. Ramón, *Tetrahedron: Asymmetry* **2007**, *18*, 2249; h) H. Kotsuki, H. Ikishima, A. Okuyama, *Heterocycles* **2008**, *75*, 493; i) J. Mlynarski, J. Paradowska, *Chem. Soc. Rev.* **2008**, *37*, 1502; j) M. Raj, V. K. Singh, *Chem. Commun.* **2009**, 6687; k) M. Gruttadauria, F. Giacalone, R. Noto, *Adv. Synth. Catal.* **2009**, *351*, 33.

[3] a) B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395; b) W. Notz, B. List, *J. Am. Chem. Soc.* **2000**, *122*, 7386; c) K. Sakthievel, W. Notz, T. Bui, C. F. Barbas III, *J. Am. Chem. Soc.* **2001**, *123*, 5260; d) H. Torii, M. Nakadai, K. Ishihara, S. Saito, H. Yamamoto, *Angew. Chem. Int. Ed.* **2004**, *43*, 1983.

[4] a) J.-R. Chen, H. H. Lu, X. Y. Li, L. Cheng, J. Wan, W. J. Xiao, *Org. Lett.* **2005**, *7*, 4543; b) J.-R. Chen, X.-Y. Li, X.-N. Xing, W.-J. Xiao, *J. Org. Chem.* **2006**, *71*, 8198; c) J.-R. Chen, X. P. Liu, X. Y. Zhu, L. Li, Y. F. Qiao, J. M. Zang, W. J. Xiao, *Tetrahedron* **2007**, *63*, 10437; d) W. P. Huang, J. R. Chen, X. Y. Li, Y. J. Cao, W. J. Xiao, *Can. J. Chem.* **2007**, *85*, 208.

[5] a) S. Samanta, J. Liu, R. Dodda, C.-G. Zao, *Org. Lett.* **2005**, *7*, 5321; b) F. Wang, Y. Xiong, X. Liu, X. Feng, *Adv. Synth. Catal.* **2007**, *349*, 2665; c) S. Gandhi, V. K. Singh, *J. Org. Chem.* **2008**, *73*, 9411; d) Y.-N. Jia, F.-C. Wu, X. Ma, G.-J. Zhu, C.-S. Da, *Tetrahedron Lett.* **2009**, *50*, 3059.

[6] a) J.-R. Chen, X.-L. An, X.-Y. Zhu, X.-F. Wang, W. J. Xiao, *J. Org. Chem.* **2008**, *73*, 6006; b) J. Zhao, A. Chen, Q. Liu, *Chin. J. Chem.* **2009**, *27*, 930.

[7] a) S. Guizzetti, M. Benaglia, L. Pignataro, A. Puglisi, *Tetrahedron: Asymmetry* **2006**, *17*, 2754; b) G. Guillena, M. Hita, C. Nájera, *Tetrahedron: Asymmetry* **2006**, *17*, 1493; c) S. Guizzetti, M. Benaglia, L. Raimondi, G. Celentano, *Org. Lett.* **2007**, *9*, 1247; d) G. Guillena, M. Hita, C. Nájera, S. F. Viózquez, *Tetrahedron: Asymmetry* **2007**, *18*, 2300; e) G. Guillena, C. Nájera, S. F. Viózquez, *Synlett* **2008**, 3031; f) G. Guillena, M. C. Hita, C. Nájera, S. F. Vióquez, *J. Org. Chem.* **2008**, *73*, 5933.

[8] M. Jiang, S.-F. Zhu, Y. Yang, L.-Z. Gong, X.-G. Zhou, Q.-L. Zhou, *Tetrahedron: Asymmetry* **2006**, *17*, 384.

[9] a) Z. Tang, F. Jiang, L.-T. Yu, X. Cui, L.-Z. Gong, A.-Q. Mi, Y.-Z. Jiang, Y.-D. Wu, *J. Am. Chem. Soc.* **2003**, *125*, 5262; b) Z. Tang, Z.-H. Yang, L.-F. Cun, L.-Z. Gong, A.-Q. Mi, Y.-Z. Jiang, *Org. Lett.* **2004**, *6*, 2285; c) H.-M. Guo, L.-F. Cun, L.-Z. Gong, A.-Q. Mi, Y.-Z. Jiang, *Chem. Commun.* **2005**, 1450; d) Z. Tang, Z.-H. Yang, X.-H. Chen, L.-F. Cun, A.-Q. Mi, Y.-Z. Jiang, L.-Z. Gong, *J. Am. Chem. Soc.* **2005**, *127*, 9285; e) Y.-Q. Fu, Z.-C. Li, L.-N. Ding, J.-C. Tao, S.-H. Zhang, M.-S. Tang, *Tetrahedron: Asymmetry* **2006**, *17*, 3351; f) C. Wang, Y. Jiang, X.-X. Zhang, Y. Huang, B.-G. Li, G.-L. Zhang, *Tetrahedron Lett.* **2007**, *48*, 4281; g) J.-P. Zhao, L. He, J. Jiang, Z. Tang, L.-F. Cun, L.-Z. Gong, *Tetrahedron Lett.* **2008**, *49*, 3372; h) M. R. Vishnumaya, V. K. Singh, *J. Org. Chem.* **2009**, *74*, 4289.

[10] S. Doherty, J. G. Knight, A. McRae, R. W. Harrington, W. Clegg, *Eur. J. Org. Chem.* **2008**, 1759.

[11] a) D. Almasi, D. A. Alonso, E. Gómez-Bengoa, Y. Nagel, C. Nájera, *Eur. J. Org. Chem.* **2007**, 2328; b) D. Almasi, D. A. Alonso, C. Nájera, *Adv. Synth. Catal.* **2008**, *350*, 2467; c) D. Almasi, D. A. Alonso, A.-N. Balaguer, C. Nájera, *Adv. Synth. Catal.* **2009**, *351*, 1123.

[12] a) P. Krattiger, R. Kovasy, J. D. Revell, S. Ivan, H. Wennemers, *Org. Lett.* **2005**, *7*, 1101; b) P. Dziezic, W. Zou, J. Háfren, A. Córdova, *Org. Biomol. Chem.* **2006**, *4*, 38; c) M. Lei, L. Shi, G. Li, S. Chen, W. Fang, Z. Ge, T. Cheng, R. Li, *Tetrahedron* **2007**, *63*, 7892; d) H. Wennemers, *Chimia* **2007**, *61*, 276; e) J. D. Revell, H. Wennemers, *Tetrahedron* **2007**, *63*, 8420; f) F. Chen, S. Huang, H. Zhang, F. Liu, Y. Peng, *Tetrahedron* **2008**, *64*, 9585.

[13] a) Y. Wu, Y. Zhang, M. Yu, G. Zhao, S. Wang, *Org. Lett.* **2006**, *8*, 4417; b) D. Gryko, W. J. Saletra, *Org. Biomol. Chem.* **2007**, *5*, 2148; c) H. Zu, H. Xie, H. Li, J. Wang, W. Wang, *Org. Lett.* **2008**, *10*, 1211; d) S.-P. Zhang, X.-K. Fu, S.-D. Fu, J.-F. Pan, *Catal. Commun.* **2009**, 401; e) S.-D. Fu, X.-K. Fu, S.-P. Zhang,

X.-C. Zou, X.-J. Wu, *Tetrahedron: Asymmetry* **2009**, *20*, 2390.

[14] a) K. Akagawa, S. Sakamoto, K. Kudo, *Tetrahedron Lett.* **2005**, *46*, 8185; b) M. Gruttadauria, F. Giacalone, A. M. Marculescu, R. Noto, *Adv. Synth. Catal.* **2008**, *350*, 1397; c) Y. Wu, Y. Zhang, M. Yu, G. Zhao, S. Wang, *Org. Lett.* **2006**, *8*, 4417; d) D. E. Siyutkin, A. S. Kucherenko, S. G. Zlotin, *Tetrahedron* **2010**, *66*, 513.

[15] a) Z.-H. Tzeng, H.-Y. Chen, R. J. Reddy, C. T. Huang, K. Chen, *Tetrahedron* **2009**, *65*, 2879; b) S. Saha, J. N. Moorthy, *Tetrahedron Lett.* **2010**, *51*, 912.

[16] Diamines **1** and **11** were prepared from commercially available L-valinamide or Boc-D-valine (see the Supporting Information).

[17] P. M. Phiko, K. M. Laurikainen, A. Usano, A. I. Nyberg, J. A. Kaavi, *Tetrahedron* **2006**, *62*, 317.

[18] V. Maya, M. Raj, V. K. Singh, *Org. Lett.* **2007**, *9*, 2593.

[19] S.-P. Zhang, X.-K. Fu, S.-D. Fu, *Tetrahedron Lett.* **2009**, *50*, 1173.

[20] Y. Wu, Y. Zhang, M. Yu, G. Zhao, S. Wang, *Org. Lett.* **2006**, *8*, 4417.

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