DOI: 10.1002/ejoc.200600219

Asymmetric Direct Aldol Reaction Catalysed by L-Prolinethioamides

Dorota Gryko*[a] and Radosław Lipiński[a]

Keywords: Aldol reaction / Prolinethioamides / Asymmetric synthesis / Organocatalysis / Imidazolidinethione

L-Prolinethioamides have been found to be active catalysts for direct aldol reactions of acetone with aromatic aldehydes, affording aldol products in good yields and with good enantioselectivities. They were prepared from L-proline and simple aliphatic and aromatic amines in optically pure form and in good overall yields. Studies employing ten catalysts allowed us to unequivocally establish the basic principles governing the outcome of the L-prolinethioamide-catalysed aldol reaction. In particular, the catalyst prepared from L-proline and (*S*)-phenylethylamine catalysed the reaction of acetone with 4-cyanobenzaldehyde in 57% yield and 93% *ee* (100% *ee* at –78 °C). Most importantly, we found that steric interaction between the catalyst and a donor or an acceptor is crucial for the stereoselectivity of the aldol addition, while the unwanted formation of imidazolidinethione (from the catalyst and acetone or an aldehyde) was shown to decrease both the *ee* and the yield. The influence of the amine moiety (–CSNHR), different solvents and temperatures were studied, and we also found that there is a linear correlation between the optical purity of the catalyst and the *ee* of the aldol product, which supports the hypothesis that the reaction proceeds by the enamine–imine mechanism, involving only one molecule of the catalyst in the transition state. For the first time, the formation of 1,5-dihydroxypentan-3-one products (double addition products) was studied in detail. By precise optimisation we were able to show that the courses of the reactions of acetone with highly reactive aromatic aldehydes could be manipulated to give either the aldol products or 1,5-dihydroxypentan-3-one derivatives as the major product in moderate *ee*.

Introduction

Asymmetric reactions catalysed by simple organic molecules have attracted intense attention over the past few years and their contribution toward organic synthesis has become increasingly significant.[1–9] A wide variety of enantioselective transformations can be performed with only catalytic amounts of chiral promoter, providing highly economical access to optically active compounds. Over the past few years rapid progress has been made in the development of the organocatalysed aldol reaction,[6–11] starting from the pioneering observation by List et al.[12] that L-proline itself can catalyse the intermolecular aldol addition of acetone to 4-nitrobenzaldehyde, although only fair enantioselectivities were obtained. Though proline itself is a very attractive catalyst, its catalytic activity can be fine-tuned only by changing the reaction conditions. Since then, several proline-derived catalysts have been prepared,[13–27] in most cases with the carboxylic acid functionality having been modified. Unfortunately, none of them is a universal catalyst for aldol reactions of various ketones with all types of aldehydes. Recently, the use of L-prolineamides derived from L-proline and different amines[14] – including diamines[26,27] and amines with strongly electron-withdrawing groups[14c] – has appeared promising for catalyst design.

[a] Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland
Fax: +48-22-6326681
E-mail: dgryko@icho.edu.pl

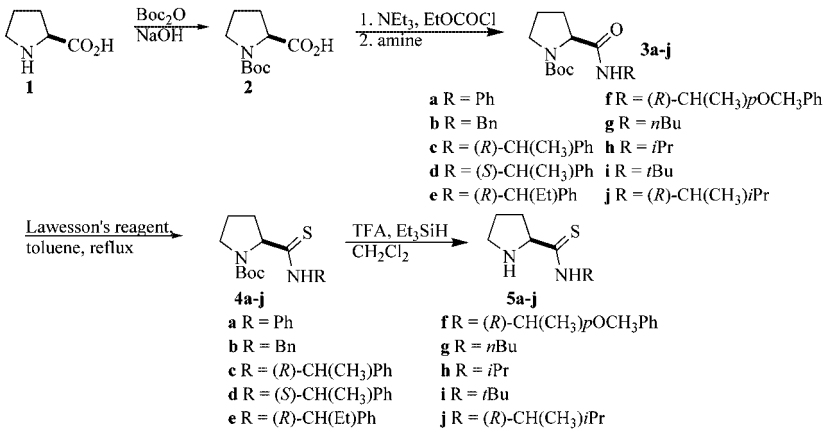
We have reported that the replacement of the amide group with the thioamide functionality has a beneficial effect on both the yield and the stereoselectivity of the aldol addition.[21] In that brief report we demonstrated that the increased reactivity was due to the higher acidity of the NH group (thioamide) relative to the amide NH functionality. Moreover, it was found that the stereochemical outcome and the chemical yields of the aldol additions were influenced not only by the acidity of the thioamide group but also by the steric interactions.

We now document a full, in-depth account on this topic, including (a) the correlation between the L-prolinethioamide structure and the enantioselectivity and the yield, (b) the synthetic scope of L-prolinethioamide catalysis in the aldol reaction, and (c) studies concerning the reaction mechanism. Moreover, the aldol reactions of some highly reactive aromatic aldehydes with acetone resulted predominately, depending on the reaction conditions, either in the corresponding aldol product or in a 1,5-dihydroxypentan-3-one compound.

Results and Discussion

Catalysts' Synthesis

All catalysts bearing thioamide functionalities were synthesised by the general strategy presented in Scheme 1, in overall yields ranging from 30 to 79%. The initial set of



Scheme 1. Synthesis of L-prolinethioamides.

thioamide catalysts was synthesised in four steps from L-proline and aniline, benzylamine and their simple analogous compounds. *N*-Boc-proline (**2**) was transformed into amides by the mixed anhydride method,[14b,21] and the following treatment with Lawesson's reagent gave the protected L-prolinethioamides (**4**).[28] In the last step, the Boc protecting group was removed under standard conditions to give catalysts **5a**–**d**.[29] The intriguing results obtained with these catalysts inclined us to synthesise a broader range of catalysts. The first class was made up of simple analogous compounds of **5c**, which had previously worked the best, and included derivatives synthesised from (*R*)-(α-ethylbenzyl)amine (**5e**) and (*R*)-[1-(4-methoxyphenyl)ethyl]-amine (**5f**). Because of the apparently fundamental role of steric hindrance in the performance of the thioamide catalysts, the second class of analogous compounds were derivatives **5g**–**j** of simple aliphatic amines. In our initial experiments we chose the reaction of 4-cyanobenzaldehyde (**6a**) with acetone as a model system, with four L-proline thioamides derived from aniline (**5a**), benzylamine (**5b**) and (*R*)- or (*S*)-(1-phenylethyl)amine (**5c** and **5d**, respectively) as catalysts. It has been shown that small changes in the catalyst structure can have a profound effect on the catalytic activity and we wanted to study this issue in greater detail. At this stage of our research, we decided not to change the α-amino acid part in our catalysts and so, in the light of the above findings, (*R*)-(α-ethylbenzyl)amine and (*R*)-[1-(4-methoxyphenyl)ethyl]amine were selected. By the previously described approach shown in Scheme 1, new optically pure L-prolinethioamides **5e** and **5f** were obtained in good yields. Furthermore, the optimised procedure also worked nicely when a series of aliphatic amines were allowed to react with L-proline to give amides **3**, which were subsequently transformed into the corresponding prolinethioamides **5g**–**j**. This class of compounds was synthesised in order to explain some issues concerning the influence of the second stereocenter present in the amine part, together with the formation of the imidazolidinethione, on the stereochemical course of the aldol addition.

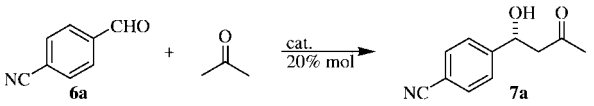
Asymmetric Aldol Reaction

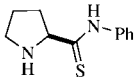
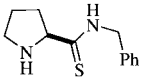
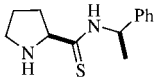
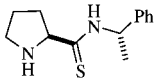
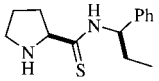
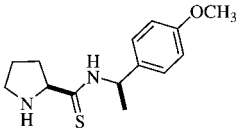
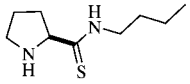
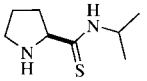
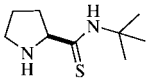
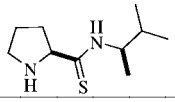
Novel catalysts **5e**–**j** were tested in the direct aldol addition between acetone and 4-cyanobenzaldehyde (**6a**). The initial reaction conditions (a large excess of acetone and 20 mol-% of the catalyst relative to the aldehyde) were the same as reported in our preliminary communication.[21] All reactions were carried out at +4 °C for 68 h, regardless of the catalyst activity. The results are summarized in Table 1.

As has previously been reported,[21] L-prolinethioamide **5a** was not used as a catalyst since all attempts to obtain it in an enantiomerically pure form failed. All remaining synthesised thioamides **5** catalysed the model aldol reaction of 4-cyanobenzaldehyde (**6a**) with acetone. *N*-Benzylamine derivative **5b** gave aldol product **7a** in only 20% yield and with low enantiomeric excess (Table 1, Entry 2). The main product formed in this reaction and detected by ^{1}H NMR (compound **8**; Scheme 2) was a result of cyclocondensation between acetone and the catalyst **5b**.

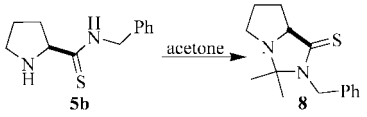
The two diastereoisomeric thioamides **5c** and **5d**, each containing a methyl group in the α-position, catalysed the addition of acetone to **6a** to give **7a** in good yields and with good *ee*s (Entries 3, 4). In the light of these intriguing results we synthesised the simple analogous compounds **5e**–**f**, all of which gave results comparable to those obtained with **5c**. The replacement of the methyl group (catalyst **5c**) with an ethyl group (catalyst **5e**) only slightly improved the *ee* of aldol product **7a** (Entry 5). The introduction of a methoxy substituent at the 4-position in the phenyl ring also had little influence, though the acidity of the N–H bond was changed (Entry 6). All the L-prolinethioamides with the (*R*) configuration in the amine part (**5c**, **5e**, **5f**; match pairs) gave a superior level of stereocontrol over compound **5d** with the (*S*) configuration (mismatch pair). Furthermore, we were intrigued by the question of whether the absence of the α-group in the amine part of the catalyst would necessarily result in cyclic product formation, thus preventing its good catalytic activity. *n*-Butylthioamide **5g** was consequently synthesised and used as the catalyst for the model

Table 1. Direct aldol addition of acetone to 4-cyanobenzaldehyde (**6a**) catalysed by L-prolinethioamides **5**.[a]



Entry	Catalyst		Temperature [°C]	Time [h]	Yield [%][b]	*ee* [%][c]
1		**5a**	r.t.	72	–	–
2		**5b**	+4	72	22	37
3		**5c**	r.t. +4 –18	24 72 96	67 **74** **57**	72 **86** **93**
4		**5d**	+4 –18 –78	68 68 10 days	76 83 **21**	68 77 **100**
5		**5e**	+4	68	71	89
6		**5f**	+4	68	76	83
7		**5g**	r.t.	68	36	62
8		**5h**	r.t. +4 –18	68 68 96	77 83 56	75 85 89
9		**5i**	r.t. +4	24 48	67 72	27 69
10		**5j**	+4	68	35	75

[a] Conditions: 1 mmol aldehyde, 2 mL acetone, 20 mol-% catalyst. [b] Isolated yields. [c] Determined by HPLC on a Daicel AS-H column.



Scheme 2. Cyclocondensation between catalyst **5b** and acetone.

reaction and afforded aldol product **7a** in only 36% yield and with 62% *ee* (Entry 7). Indeed, the presence of an α-group in thioproline derivatives had a profound effect both on the yield and on the enantioselectivity and ensured good catalytic activity in the L-prolinethioamides. The reaction of 4-cyanobenzaldehyde (**6a**) with acetone catalysed by thioamide **5h**, containing only one stereocenter (proline part), afforded the corresponding aldol product **7a** with fair yield and enantioselectivity (Entry 8), so we reasoned that a bulkier amino part such as the *t*Bu group should further improve the enantioselectivity of the reaction, but the thioamide **5i** gave a lower yield and a smaller *ee* (Entry 9). We can assume that the metal-free Zimmerman–Traxler-like transition state is destabilised by steric interactions due to the presence of the bulky *tert*-butyl group. Surprisingly, the use of catalyst **5j**, with the α-methyl group and an additional stereocenter, gave results similar to those obtained with **5g** (Entries 7 and 10).

Since the catalyst **5c** afforded good results (which could be further improved by lowering the reaction temperature) and is less expensive than analogue **5e**, L-prolinethioamide **5c** was chosen for further studies. Numerous data presented in the literature showed a significant influence of solvents on the stereoselectivity and yields of organocatalysed reactions.[13c,17,24,30–35] In this context a solvent screen was performed, and the results are summarised in Table 2. Regardless of the solvent used, the aldol reaction catalysed by **5c** afforded **7a** with much lower yields and enantioselectivities

than had been obtained from the reactions in acetone. The only exception was the reaction in the ionic liquid (BMIM[BF_4]), which gave optically pure **7a** but unfortunately in only 32% yield (Entry 11).

Table 2. Solvent screening.[a]

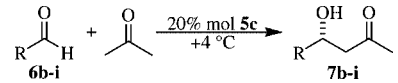
Entry	Solvent	Yield [%]	*ee* [%][c]
1	DMSO	–	
2	DMF	–	
3	NMP	–	
4	MeOH	23	n.d.
5	*i*PrOH/H_2O	76	23
6	CH_3CN	9	0
7	THF	37	35
8	dioxane	–	–
9	CH_2Cl_2	13	33
10	acetone/H_2O	70	68
11	BMIM[BF_4][b]	32	100

[a] Conditions: 1 mmol aldehyde, 0.8 mL acetone, 20 mol-% catalyst, 4 mL solvent, room temp., 68 h. [b] The reaction was carried out at +4 °C. [c] Determined by HPLC on a Daicel AS-H column.

The generality of **5c** in catalysing direct aldol reactions of acetone with a variety of aromatic and aliphatic aldehydes was examined under optimal conditions: 20 mol-% of catalyst relative to the aldehyde, 0.5 M aldehyde in acetone, +4 °C, 68 h. The results are shown in Table 3.

For most of the aromatic aldehydes the *ee*s were higher than or similar to those obtained in reactions catalysed by L-proline. Unfortunately, prolinethioamide **5c** was not suitable for aldol additions with less reactive aromatic aldehydes or aliphatic aldehydes.

Table 3. Direct aldol reactions of acetone with arenecarbaldehydes **6b**–**i** in the presence of **5c**.



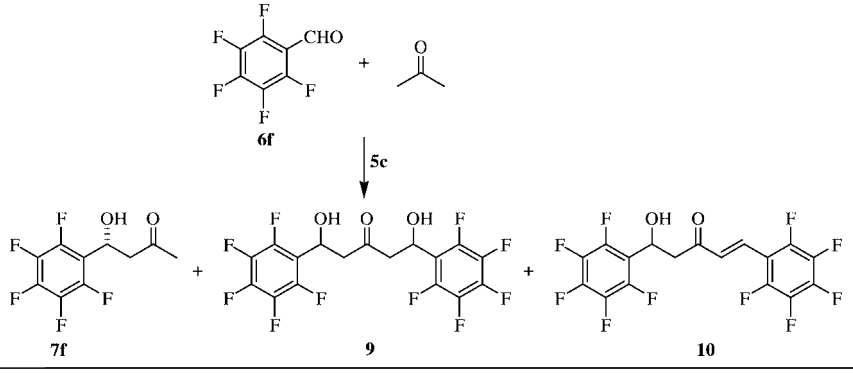
6b-i **7b-i**

Entry	R	Product	Yield [%][a]	*ee* [%][b]
1	4-$O_2NC_6H_4$	**7b**	62	84
			81[c]	94
2	2-ClC_6H_4	**7c**	70	73
3	4-ClC_6H_4	**7d**	61	87
4	2,6-$Cl_2C_6H_3$	**7e**	86	75
5	F_5C_6	**7f**	64[d]	84
6	4-FC_6H_4	**7g**	30	84
7	4-BrC_6H_4	**7h**	20	78
8	β-naphthyl	**7i**	60	82

[a] Isolated yields. [b] Determined by HPLC on a Daicel AS-H or AD-H column. [c] TFA·**5c** was used as the catalyst. [d] The 1,5-dihydroxypentan-3-one derivative was isolated as a side product.

During the course of these scope and limitation studies we found that the reaction of the highly reactive pentafluorobenzaldehyde (**6f**) with acetone afforded the desired aldol product **7f** accompanied by a double addition product **9** (i.e., the 1,5-dihydroxypentan-3-one derivative). These types of compounds had also been observed by Peng et al.[36] in pyrrolidine/*p*-nitrophenol-catalysed aldol reactions of highly reactive aromatic aldehydes with aliphatic ketones. Their highly functional catalyst allowed racemic aldol products to be obtained with very good yields and chemoselectivities and allowed the formation of unwanted products of

Table 4. Reaction of **6f** with acetone catalysed by L-prolinethioamide **5c**.



6f **7f** **9** **10**

Entry	Conc. of **6f** [M][a]	Catalyst **5c** [mol-%]	Temp. [°C]	Yield of **7f** [%][b]	*ee* of **7f** [%][c]	Yield of **9** [%][b]	Yield of **10** [%][b]
1	0.5	10	+4	23	nd	32	not isolated
2	0.5	5	+4	64	84	18	not isolated
3	0.5	5	–18	34	86	24	not isolated
4	0.5	20	–78	0	–	0	0
5	0.5	2.5	+4	77	96	22	6
6	0.5	1.25	+4	56	96	14	5
7	**0.25**	**5**	**+4**	**86**	**96**	**not isolated**	**10**
8	0.25	2.5	+4	77	96	22	6
9	**0.125**	**5**	**+4**	**67**	**98**	**12**	**8**
10	13.7	20	room temp.	31	81	40	12
11	**27**	**20**	**room temp.**	**14**	**92**	**44**	**10**

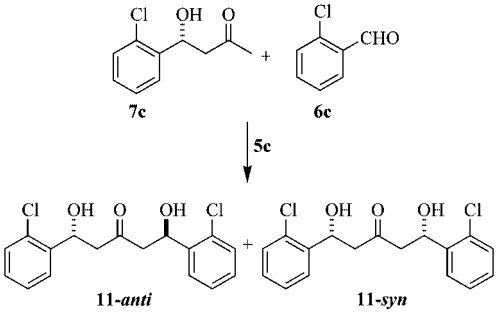
[a] Concentration of **6f** in acetone. [b] Isolated yields. [c] Determined by HPLC on a Daicel AS-H column.

type **9** to be suppressed. Moreover, a small amount of the 1,5-dihydroxypentan-3-one product derived from 4-nitrobenzaldehyde (**7b**) was isolated from the reaction catalysed by L-proline. To gain further insight into this issue we studied the reaction of **6f** with acetone in the presence of **5c** in greater detail; the results are summarised in Table 4.

A decrease in the catalyst loading caused an increase both in the yield and in the *ee* of **7f** (Table 4, Entries 1, 2, 5, 6). The best result – 86% yield of **7f** with 96% *ee* – was achieved when the concentration of the aldehyde was 0.25 M instead of 0.5 M, the catalyst loading 5 mol-%, and the reaction temperature +4 °C (Entry 7). Further dilution somewhat diminished the yield but the *ee* reached 98% (Entry 9). On the other hand, in order to obtain **9** as the main product (40% yield), 20 mol-% of **5c** had to be used and the [aldehyde]/[acetone] ratio had to be stoichiometric (2:1; Entry 11). Unfortunately, we were not able to determine the *syn*/*anti* ratio of the 1,5-dihydroxypentan-3-one product **9** regardless of the technique used. Treatment of 2-chlorobenzaldehyde (**6c**) with the stoichiometric amount of acetone at room temp. with catalysis by **5c** afforded a mixture (1:5) of 1,5-dihydroxypentan-3-one compounds **11** with an *anti* preference in 39% total yield. In this case the diastereomeric ratio was determined from the amounts of compounds isolated. The relative configuration of the major product *anti*-**11** was assigned by X-ray analysis (Figure 1). The *anti* product **11** was isolated in 94% *ee* but the single crystal measured by X-ray analysis was shown to be racemic, thus preventing the assignment of the absolute configuration.

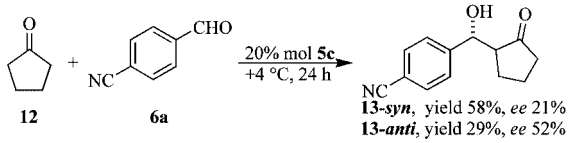
Accordingly, the aldol product **7c** (73% *ee*) was treated with 2-chlorobenzaldehyde (**6c**) in the presence of the catalyst **5c**, affording diols **11** with the same diastereomeric ratio as previously (Scheme 3). Since the remaining 2-hydroxy ketone **7c** was isolated in only 43% *ee*, partial kinetic resolution had taken place.

Finally, cyclopentanone (**12**) was explored as an aldol donor. The reaction of **12** with **6a** afforded products **13** in 87% yield (Scheme 4). The diastereomeric ratio according to ^{1}H NMR analysis was almost 2:1 with *syn* preference, while the reactions catalysed by L-proline led to *anti* preference (1:1.7). Unfortunately, the enantioselectivity was low. Wu et al.[33] have recently reported diastereoselective addition of cyclopentanone to an aldehyde through the use of



Scheme 3. Reaction of aldol product **7c** with aldehyde **6c**.

N′-benzyl-*N*′-prolylproline hydrazide (*syn*/*anti* = 75:25) and to the best of our knowledge this is the best *syn* diastereoselectivity for the reaction described.



Scheme 4. Reaction of cyclopentanone (**12**) with 4-cyanobenzaldehyde (**6a**).

Mechanistic Considerations

We assume that the direct, asymmetric aldol reaction catalysed by L-prolinethioamides **5** proceeds through the same mechanism as proposed for proline (Scheme 5).[12,37,38] In this mechanism, both a base and an acidic proton are required for effective catalysis. In our case the transferred proton originates from the thioamide group. The assumption is supported by the fact that L-proline-derived thioamides **5** gave better results than prolineamides itself, which implies that the thioamide group is able to form a stronger hydrogen bond with an aldehyde and, as a result, a tighter metal-free Zimmerman–Traxler-like transition state than the carboxylic acid functionality in L-proline.

Furthermore, we also investigated the relationship between the enantiomeric excess of the aldol product **7a** and the enantiomeric purity of L-prolinethioamide **5c**. Plotting the enantiomeric excess of **5c** against that of **7a** showed a

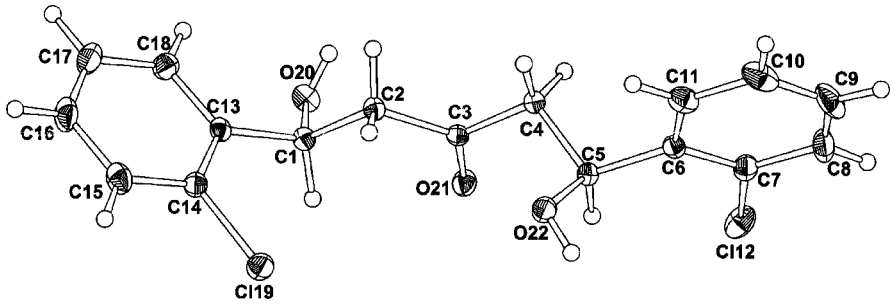
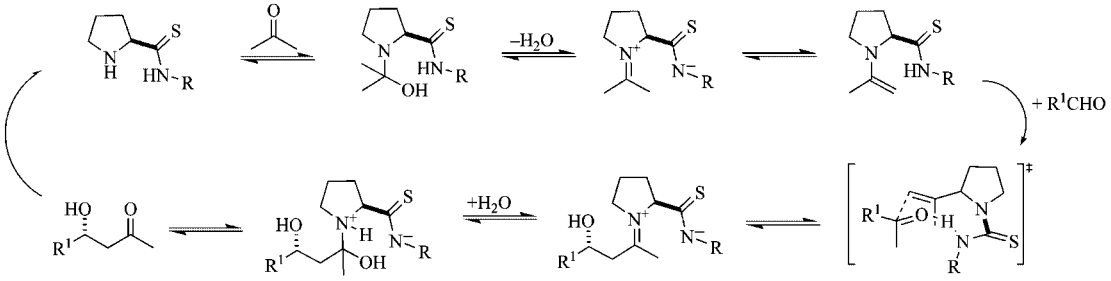


Figure 1. Crystal structure of *anti*-**11**.



Scheme 5. Proposed mechanism for aldol reactions catalysed by **5**.

linear correlation consistent with the involvement of only one molecule of the amino acid derivative **5c** in the asymmetric aldol reaction transition state (Figure 2).

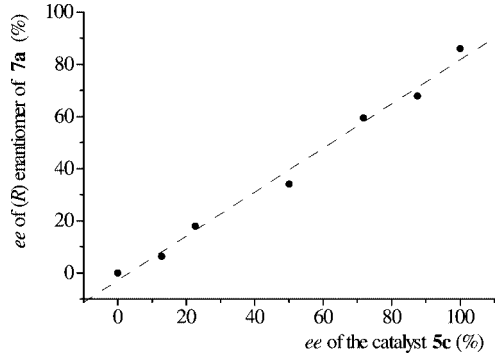
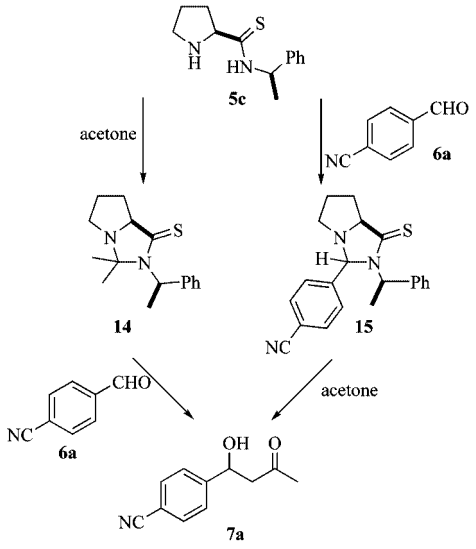


Figure 2. Linear effect in the aldol reaction of acetone with 4-cyanobenzaldehyde (**6a**).

As previously reported,[21] we believe that the level of stereocontrol is influenced by the formation of imidazolidinethiones of type **14** and **15**. By ^{1}H NMR spectroscopy we found that under standard reaction conditions, but in the absence of an aldehyde, thioamide **5c** would react with [D_6]-acetone to give analytically pure imidazolidinethione [D_6]-**14** within 80 min (Scheme 6).



Scheme 6. Reactions of **5c** with acetone and aldehyde **6a**.

Compound **14** was stable even in solution ($CDCl_3$) at room temperature for several days. When isolated imidazolidinethione **14** was treated with an equimolar amount of 4-cyanobenzaldehyde (**6a**) in acetone, the reaction afforded the aldol product **7a** in 43% yield and with 46% *ee* (Scheme 6). On the other hand, when **14** was used in a catalytic amount in the model reaction, both the yield and the selectivity increased (73%, 73% *ee*), reaching the same level of stereocontrol as in the reaction catalysed by thioamide derivative **5c**. Since the above reactions gave different results, we can assume that the free form of thioamide **5c** had to catalyse the aldol addition before the formation of **14**, which diminished both the yield and the enantioselectivity.

Using ^{1}H NMR techniques, List's group[39] was able to detect the oxazolidinone formation from proline and acetone and to estimate the equilibrium constant. The influence of the oxazolidinone on the course of the aldol reaction was not explained. Furthermore, they also demonstrated that, in the proline-catalysed reaction of isobutyraldehyde with acetone in [D_6]DMSO, the proline was initially quantitatively engaged in the formation of the oxazolidinone (analogous to **15**), and that the formation of this compound diminished the rate but allowed for turnover. In our case, we did not observe the cyclic compound **15** under the standard reaction conditions (^{1}H NMR), but the imidazolidinethione **15** was formed when 4-cyanobenzaldehyde (**6a**) was allowed to react with catalyst **5c** in CH_2Cl_2. It was not stable enough for purification and was therefore used as obtained in the reaction with acetone. After 3 d at room temperature, the reaction had afforded **7a** in 38% yield and with 43% *ee*.

Our results contrast with the findings of Blackmond's group,[40] who showed that the formation of oxazolidinone-type compounds in the α-aminoxylation reaction enhanced the rate of the process since they were better catalysts of the studied reaction than proline itself. In our studies of the aldol reaction catalysed by thioamide **5c**, the unwanted formation of imidazolidinethiones derived both from acetone – **14** – and the aldehyde – **15** – diminished the yield and the enantioselectivity.

Furthermore, the progress of the reaction of a catalyst with [D_6]acetone was monitored by ^{1}H NMR and it was observed that the catalyst **5c** converted into the corresponding imidazolidinethione of type **14** within 80 min whereas its diastereoisomer **5d** and **5h** required only approximately 25 min (Figure 3). Since it had been shown that the forma-

tion of the unwanted cyclic product diminished the yield and the enantioselectivity of the aldol reaction catalysed by thioamides **5**, we suggest that the slower the unwanted imidazolidinethione formation between the catalyst and acetone, the higher the stereoselectivity in the aldol addition. To corroborate this assumption, ^{1}H NMR studies were conducted with **5f**; this catalyst gave similar results to **5c**. Indeed, the reaction of **5f** with [D$_6$]acetone took longer than that with **5d** (approximately 2 h). Similar conclusions were drawn by Arvidsson and Hartikka for the reaction catalysed by the tetrazole catalyst.[13c] They confirmed by ^{1}H NMR that the catalyst did not engage in parasitic bicyclic oxazolidinone formation from an aldehyde and the catalyst. Consequently, more catalyst is available for the formation of the enamine intermediate, thus increasing the reactivity of the catalyst in relation to L-proline, which forms this type of compound immediately.

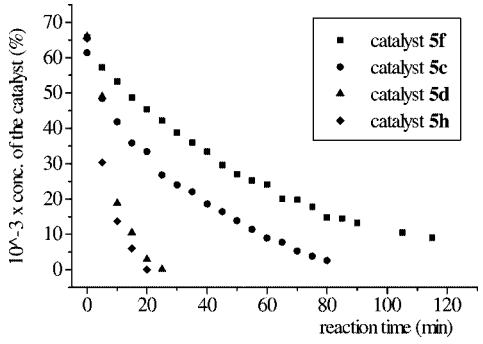


Figure 3. Graph showing the conversion of catalysts into imidazolidinethiones of type **14** as a function of time.

Conclusions

In summary, we present L-proline-derived thioamides **5**, prepared from L-proline and chiral and achiral amines, as very efficient catalysts for direct aldol additions. Both the yields and the enantioselectivities were low for *tert*-butyl-, *n*-butyl- and benzylamine. The replacement of the *N*-benzyl substituent by the analogous (*R*)-1-phenylethyl, (*R*)-α-ethylbenzyl and (*R*)-1-(4-methoxyphenyl)ethyl moieties on the amine part changes the outcomes of the reactions, while the introduction of various alkylamines with two α-substituents in the amine part also produced good reactivity and selectivity. Moreover, we have tried in this paper to explain the influence of the formation of the imidazolidinethiones **14** and **15** on the course of the model aldol reaction of acetone with the aldehyde **6a**. It was shown that the unwanted formation of imidazolidinethione-type compounds **14** and **15** diminished both the yield and the *ee*, and that the slower the unwanted imidazolidinethione formation between the catalyst and acetone, the higher the stereoselectivity in the aldol addition.

Our investigations confirmed that the organocatalysed reactions often depend on essential hydrogen-bond stabilization of the transition state, since the thioamides, with more acidic N–H protons than those in the corresponding amides, are more effective catalysts. The reaction catalysed by thioamides **5** showed a linear effect, supporting the involvement of the imine–enamine mechanism and the transition state proposed by Houk and List,[37–39] involving only one molecule of the catalyst. Perhaps of greater significance for the future is the fact that a new type of L-proline derivatives can be added to the repertoire of organocatalysts, thus inspiring chemists towards further developments in this field.

Experimental Section

General: All chemicals were used as received unless otherwise noted. Reagent-grade solvents (CH_2Cl_2, hexane) were distilled prior to use. All reported ^{1}H NMR spectra were collected either with a Bruker spectrometer at 500 (^{1}H NMR) or 125 (^{13}C NMR) MHz or with a Varian Gemini spectrometer at 200 (^{1}H NMR) and 50 (^{13}C NMR) MHz. Chemical shifts are reported as δ values relative to TMS, defined as δ = 0.00 ppm (^{1}H NMR) or δ = 0.0 ppm (^{13}C NMR). IR spectra were obtained with a Perkin–Elmer 1640 FTIR unit. Mass spectra were obtained with an AMD-604 Intectra instrument by EI or with a Mariner PerSeptive Biosystem instrument by the ESI technique. Chromatography was performed on silica gel (Kieselgel 60, 200–400 mesh). Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. The *ee* values were determined by HPLC on Daicel OD-H, AS-H or AD-H columns and the configuration was assigned as (*R*) by comparison of the retention time with the reported values.

General Procedure for the Preparation of L-Proline-Derived Amides: *N*-Boc-L-proline (**2**, 10.0 mmol, 2.15 g) was dissolved in dry THF (40 mL) and treated with triethylamine (10.0 mmol, 1.39 mL). The reaction mixture was cooled to 0 °C and ethyl chloroformate (10.0 mmol, 1.23 mL) was then added dropwise over 15 min. After the mixture had been stirred for another 30 min, an amine (10.0 mmol) was added over 15 min. The resulting solution was stirred at 0 °C for 1 h and at room temperature for another 16 h and was then heated at reflux for 3 h. After it had cooled, it was filtered through a Celite pad and the solvents were evaporated. Column chromatography on silica gel (hexane/AcOEt) gave the desired amides.

***tert*-Butyl 2-(Benzylcarbamoyl)pyrrolidine-1-carboxylate (3b):** Yield: 78% (2.37 g, 7.80 mmol). White crystals; m.p. 121–122 °C (from Et_2O/hexane). $[\alpha]_D^{20}$ = –80.8 (*c* = 1.03, CH_2Cl_2), ref.[41] –80.2 (*c* = 0.6, $CHCl_3$). ^{1}H NMR (500 MHz, [D$_6$]DMSO, 353 K): δ = 8.08 (br s, 1 H, CON*H*), 7.30–7.18 (m, 5 H, Ph), 4.33 (dd, *J* = 6.2 Hz, *J* = 15.1 Hz, 1 H, CH_aH$_b$Ph), 4.23 (dd, *J* = 5.8 Hz, *J* = 15.1 Hz, 1 H, CH$_a$$H_b$Ph), 4.12 (m, 1 H, C*H*), 3.44–3.36 (m, 1 H, CH_aH$_b$N), 3.35–3.28 (m, 1 H, CH$_a$$H_b$N), 2.11 (m, 1 H, C$H_aH_b$), 1.90–1.72 (m, 3 H, CH$_a$$H_b$, C$H_2$), 1.35 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO, 353 K): δ = 171.9, 153.2, 139.2, 127.7, 126.8, 126.2, 95.2, 78.2, 59.6, 46.2, 41.8, 27.7 ppm. IR (KBr): $\tilde{\nu}$ = 3316, 2978, 2872, 1685, 1656, 1531, 1396, 1370, 1169, 1159 1129, 1016, 974, 725, 694 cm^{-1}. HR ESI-MS: *m*/*z* calcd. for [$C_{17}H_{24}N_2O_3Na^+$] 327.1679; found 327.1695. $C_{17}H_{24}N_2O_3$ (304.07): calcd. C 67.08, H 7.95, N 9.20; found C 67.24, H 7.95, N 9.33.

***tert*-Butyl (2*S*)-2-{[(1*R*)-1-Phenylethyl]carbamoyl}pyrrolidine-1-carboxylate (3c):** Yield: 89% (1.21 g, 3.81 mmol). White crystals; m.p. 84–85 °C (from Et_2O/hexane). $[\alpha]_D^{20}$ = –70.6 (*c* = 1.04, CH_2Cl_2). ^{1}H NMR (500 MHz, [D$_6$]DMSO, 353 K): δ = 7.89 (d, 1 H, CON*H*), 7.34–7.30 (m, 2 H, Ph), 7.29–7.24 (m, 2 H, Ph), 7.21–7.16 (m, 1 H,

Ph), 4.92 (quint, 1 H, C*H*Ph), 4.12 (d, 1 H, C*H*CO), 3.41–3.35 (m, 1 H, CH_aH_bN), 3.29 (dt, J_d = 10.2 Hz, J_t = 7.0 Hz, 1 H, CH$_a$$H_b$N), 2.08 (br s, 1 H, C$H_aH_b$), 1.89–1.70 (m, 3 H, CH$_a$$H_b$, C$H_2$), 1.37 (d, 3 H, C$H_3$), 1.29 (br s, 9 H, *t*Bu) ppm. ^{13}C NMR (125 MHz, [D$_6$]-DMSO, 353 K): δ = 170.9, 153.2, 144.0, 127.6, 126.1, 125.7, 95.2, 78.1, 59.4, 47.4, 46.2, 27.7, 23.0, 21.6 ppm. IR (KBr): $\tilde{\nu}$ = 3302, 3061, 2977, 2880, 1669, 1539, 1456, 1416, 1364, 1239, 1166, 1127, 700 cm^{-1}. HR ESI-MS: *m*/*z* calcd. for [$C_{18}H_{26}N_2O_3Na^+$] 341.1836; found 341.1825. $C_{18}H_{26}N_2O_3$ (318.18): calcd. C 67.90, H 8.23, N 8.80; found C 68.02, H 7.94, N 8.89.

***tert*-Butyl (2*S*)-2-{[(1*S*)-1-Phenylethyl]carbamoyl}pyrrolidine-1-carboxylate (3d):** Yield: 89% (2.89 g, 9.09 mmol). White crystals; m.p. 97–99 °C (from Et$_2$O/hexane). $[\alpha]_D^{20}$ = –106.5 (*c* = 1.01, CH_2Cl_2), ref.[41] –109.8 (*c* = 1.3, $CHCl_3$). ^{1}H NMR (500 MHz, [D$_6$]DMSO, 353 K): δ = 7.92 (d, *J* = 6.0 Hz, 1 H, CON*H*), 7.31–7.26 (m, 4 H, Ph), 7.20 (m, 1 H, Ph), 4.94 (q, *J* = 7.2 Hz, 1 H, C*H*Ph), 4.12 (dd, *J* = 3.0 Hz, *J* = 8.3 Hz, 1 H, C*H*CO), 3.40–3.35 (m, 1 H, CH_aH_bN), 3.30–3.25 (m, 1 H, CH$_a$$H_b$N), 2.15–2.06 (m, 1 H, C$H_aH_b$), 1.90–1.70 (m, 3 H, CH$_a$$H_b$, C$H_2$), 1.38 (s, 3 H, C$H_3$), 1.37 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO, 353 K): δ = 170.9, 153.2, 144.2, 127.7, 126.1, 125.5, 95.2, 78.1, 59.4, 47.2, 46.2, 30.3, 27.7, 23.0, 21.6 ppm. IR (KBr): $\tilde{\nu}$ = 3301, 2973, 1697, 1650, 1547, 1398, 1391, 1365, 1246, 1167, 1120, 761, 702, 536 cm^{-1}. HR ESI-MS: *m*/*z* calcd. for [$C_{18}H_{26}N_2O_3Na^+$] 341.1836; found 341.1847. $C_{18}H_{26}N_2O_3$ (318.18): calcd. C 67.90, H 8.23, N 8.80; found C 67.65, H 8.16, N 8.76.

***tert*-Butyl (2*S*)-2-{[(1*R*)-1-Phenylpropyl]carbamoyl}pyrrolidine-1-carboxylate (3e):** Yield: 70% (4.30 g, 12.1 mmol). White crystals; m.p. 101–103 °C (from AcOEt/hexane). $[\alpha]_D^{20}$ = –44.5 (*c* = 0.95, CH_2Cl_2). ^{1}H NMR (500 MHz, [D$_6$]DMSO, 353 K): δ = 7.85 (d, *J* = 6.9 Hz, 1 H, CON*H*), 7.35–7.25 (m, 4 H, Ph), 7.20–7.16 (m, 1 H, Ph), 4.70 (dd, *J* = 7.6 Hz, *J* = 15.5 Hz, 1 H, C*H*Ph), 4.14 (d, *J* = 6.4 Hz, 1 H, C*H*CO), 3.40–3.30 (m, 1 H, CH_aH_bN), 3.30–3.25 (m, 1 H, CH$_a$$H_b$N), 2.10–2.0 (br s, 1 H, CH_aH_b), 1.85–1.70 (m, 5 H, CH$_a$$H_b$, 2 × C$H_2$), 1.25 (br s, 9 H, *t*Bu), 0.85 (t, *J* = 7.3 Hz, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO, 353 K): δ = 171.3, 153.3, 143.1, 127.6, 126.2, 126.1, 95.2, 78.1, 59.4, 53.7, 46.2, 28.5, 27.7, 23.0, 10.4 ppm. IR (KBr): $\tilde{\nu}$ = 3295, 2974, 2931, 2876, 1700, 1670, 1656, 1554, 1454, 1398, 1257, 1163, 1122, 1089, 886, 770, 699 cm^{-1}. HR ESI-MS: *m*/*z* calcd. for [$C_{19}H_{28}N_2O_3Na^+$] 355.1992; found 355.2007. $C_{19}H_{28}N_2O_3$ (332.20): calcd. C 68.65, H 8.49, N 8.43; found C 68.65, H 8.66, N 8.26.

***tert*-Butyl (2*S*)-2-{[(1*R*)-1-(4-Methoxyphenyl)ethyl]carbamoyl}pyrrolidine-1-carboxylate (3f):** Yield 87% (7.03 g, 20.2 mmol). White crystals; m.p. 116–117 °C (from AcOEt/hexane). $[\alpha]_D^{20}$ = –43.5 (*c* = 0.98, CH_2Cl_2). ^{1}H NMR (500 MHz, [D$_6$]DMSO, 353 K): δ = 7.68 (d, *J* = 5.3 Hz, 1 H, CON*H*), 7.23 (m, 2 H, Ar), 6.84 (m, 2 H, Ar), 4.88(m, 1 H, C*H*Ar), 4.10 (dd, *J* = 2.8 Hz, *J* = 8.6 Hz, 1 H, C*H*CO), 3.72 (s, 3 H, OCH_3), 3.40–3.35 (m, 1 H, CH_aH_bN), 3.35–3.25 (m, 1 H, CH$_a$$H_b$N), 2.07 (m, 1 H, C$H_aH_b$), 1.85–1.70 (m, 3 H CH$_a$$H_b$, C$H_2$), 1.35 (d, *J* = 7.0 Hz, 3 H, CH_3), 1.31 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO, 353 K): δ = 170.7, 157.8, 153.2, 136.0, 126.7, 113.2, 78.0, 59.3, 54.7, 46.7, 46.1, 27.6, 22.9, 21.4 ppm. IR (KBr): $\tilde{\nu}$ = 3324, 2977, 2952, 1670, 1541, 1514, 1415, 1250, 1186, 1165, 1132, 1037, 1025, 835, 771 cm^{-1}. HR ESI-MS: *m*/*z* calcd. for [$C_{19}H_{28}N_2O_4Na^+$] 371.1941; found 371.1928. $C_{19}H_{28}N_2O_4$ (348.19): calcd. C 65.52, H 8.05, N 8.05; found C 65.49, H 8.12, N 7.97.

***tert*-Butyl (2*S*)-2-(Butylcarbamoyl)pyrrolidine-1-carboxylate (3g):** Yield: 84% (2.62 g, 9.70 mmol). White solid; m.p. 56–58 °C. $[\alpha]_D^{20}$ = –88.8 (*c* = 0.98, CH_2Cl_2). ^{1}H NMR (500 MHz, [D$_6$]DMSO, 353 K): δ = 7.41 (br s, 1 H, CON*H*), 4.03 (dd, *J* = 3.4 Hz, *J* = 8.4 Hz, 1 H, C*H*CO), 3.40–3.35 (m, 1 H, CH_aH_bN), 3.30–3.25 (m, 1 H, CH$_a$$H_b$N), 3.10–3.00 (m, 2 H, C$H_2$N), 2.10–2.00 (m, 1 H, C$H_aH_b$), 1.90–1.70 (m, 3 H, CH$_a$$H_b$, C$H_2$), 1.45–1.35 (m, 2 H, C$H_2$), 1.36 (s, 9 H, *t*Bu), 1.30–1.25 (m, 2 H, CH_2), 0.87 (t, *J* = 7.3 Hz, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO, 353 K): δ = 171.6, 153.2, 95.1, 78.0, 59.5, 46.1, 37.8, 30.9, 27.7, 22.9, 19.0, 13.0 ppm. IR (KBr): $\tilde{\nu}$ = 3289, 3248, 3089, 2975, 2932, 2875, 16.90, 1651, 1567, 1404, 1363, 1256, 1245, 1173, 1117, 987, 909, 770 cm^{-1}. HR ESI-MS: *m*/*z* calcd. for [$C_{14}H_{26}N_2O_3Na^+$] 341.1836; found 341.1847. $C_{18}H_{26}N_2O_3$ (318.18): calcd. C 62.19, H 9.69, N 10.36; found C 62.24, H 9.77, N 10.50.

***tert*-Butyl (2*S*)-2-(Isopropylcarbamoyl)pyrrolidine-1-carboxylate (3h):** Yield: 80% (2.05 g, 8.01 mmol). White crystals; m.p. 128–129 °C (from Et$_2$O/hexane). $[\alpha]_D^{20}$ = –98.1 (*c* = 1.3, CH_2Cl_2). ^{1}H NMR (500 MHz, [D$_6$]DMSO, 353 K): δ = 7.16 (br s, 1 H, CON*H*), 4.01 (dd, *J* = 4.0 Hz, *J* = 8.5 Hz, 1 H, C*H*CO), 3.84 (m, 1 H, C*Hi*Pr), 3.40–3.30 (m, 1 H, CH_aH_bN), 3.30–3.20 (m, 1 H, CH_aH_bN), 2.10–2.00 (m, 1 H, CH_aH_b), 1.90–1.70 (m, 3 H, CH$_a$$H_b$, C$H_2$), 1.37 (s, 9 H, *t*Bu), 1.06 (t-like, *J* = 6.7 Hz, 6 H, 2 × CH_3, *i*Pr) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO, 353 K): δ = 170.7, 153.1, 90.1, 77.9, 59.4, 46.1, 29.1, 27.6, 22.8, 21.7 ppm. IR (KBr): $\tilde{\nu}$ = 3287, 2970, 2880, 1700, 1650, 1556, 1396, 1364, 1254, 1163, 1118, 922, 772 cm^{-1}. HR ESI-MS: *m*/*z* calcd. for [$C_{13}H_{24}N_2O_3Na^+$] 279.1679; found 279.1686. $C_{13}H_{24}N_2O_3$ (256.16): calcd. C 60.91, H 9.44, N 10.93; found C 60.83, H 9.29, N 10.85.

***tert*-Butyl (2*S*)-2-(*tert*-Butylcarbamoyl)pyrrolidine-1-carboxylate (3i):** Yield: 76% (3.82 g, 14.15 mmol). White crystals; m.p. 115–116 °C (from AcOEt). $[\alpha]_D^{20}$ = –109.8 (*c* = 1.05, CH_2Cl_2). ^{1}H NMR (500 MHz, [D$_6$]DMSO, 353 K): δ = 6.87 (br s, 1 H, CON*H*), 4.01 (dd, *J* = 3.5 Hz, *J* = 8.4 Hz, 1 H, C*H*), 3.35–3.25 (m, 2 H, CH_2N), 2.10–2.00 (m, 1 H, CH_aH_b), 1.85–1.70 (m, 3 H, CH$_a$$H_b$, C$H_2$), 1.38 (s, 9 H, *t*Bu, Boc), 1.26 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO, 353 K): δ = 171.0, 153.2, 95.1, 77.9, 59.6, 49.4, 46.1, 30.0, 28.1, 27.6, 22.8 ppm. IR (KBr): $\tilde{\nu}$ = 3314, 2973, 2934, 2878, 1694, 1661, 1548, 1461, 1403, 1362, 1262, 1250, 1163, 1119, 984, 862, 770, 662 cm^{-1}. HR ESI-MS: *m*/*z* calcd. for [$C_{14}H_{26}N_2O_3Na^+$] 293.1836; found 293.1831. $C_{14}H_{26}N_2O_3$ (270.18): calcd. C 62.19, H 9.69, N 10.36; found C 62.12, H 9.69, N 10.36.

***tert*-Butyl (2*S*)-2-{[(1*R*)-1,2-Dimethylpropyl]carbamoyl}pyrrolidine-1-carboxylate (3j):** Yield: 62% (3.29 g, 11.59 mmol). White crystals; m.p. 103–104 °C (from AcOEt/hexane). $[\alpha]_D^{20}$ = –122.2 (*c* = 0.98, CH_2Cl_2). ^{1}H NMR (500 MHz, [D$_6$]DMSO, 353 K): δ = 7.11 (br d, *J* = 7.3 Hz, 1 H), 4.08 (dd, *J* = 3.0 Hz, *J* = 8.5 Hz, 1 H, C*H*CON), 3.59 (dq, J_q = 6.7 Hz, J_d = 8.6 Hz 1 H, C*H*CH$_3$), 3.40–3.34 (m, 1 H, CH_aH_bN), 3.33–3.27 (m, 1 H, CH$_a$$H_b$N), 2.05 (m, 1 H, C$H_aH_b$), 1.85–1.71 (m, 3 H, C$H_2$ + CH$_a$$H_b$), 1.65 (m, 1 H, C*Hi*Pr), 1.37 (s, 9 H, *t*Bu), 0.99 (d, *J* = 6.8 Hz, 3 H, CH_3), 0.84 (d, *J* = 6.8 Hz, 6 H, 2 × CH_3, *i*Pr) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO, 353 K): δ = 171.3, 153.3, 143.1, 127.6, 126.2, 126.1, 95.2, 78.1, 59.4, 53.7, 46.2, 28.5, 27.7, 23.0, 10.4 ppm. IR (KBr): $\tilde{\nu}$ = 3321, 2978, 2965, 1670, 1545, 1421, 1365, 1237, 1169, 1126, 1089, 979, 772, 552 cm^{-1}. HR ESI-MS: *m*/*z* calcd. for [$C_{15}H_{28}N_2O_3Na^+$] 307.1992; found 307.2005. $C_{15}H_{28}N_2O_3$ (284.20): calcd. C 63.38, H 9.86, N 9.86; found C 63.48, H 9.96, N 9.78.

General Procedure for the Preparation of Thioamides: An amide **3** (3.47 mmol) and Lawesson's reagent (1.74 mmol) in dry toluene (40 mL) were heated at reflux until the amide **3** was consumed (TLC, usually 2–3 h). The reaction mixture was cooled and was then concentrated to dryness. Column chromatography on silica gel gave pure thioamides **4**.

***tert*-Butyl (2*S*)-2-(Phenylthiocarbamoyl)pyrrolidine-1-carboxylate (4a):** Column chromatography on silica (CH_2Cl_2 and then hexane/

acetone gradually from 7:3 to 5:5) gave a white solid. Yield: 61% (2.47 g, 8.07 mmol). White crystals; m.p. 175–177 °C (from AcOEt/hexane). *ee* = 26%. ^{1}H NMR (500 MHz, [D$_6$]DMSO, 353 K): δ = 11.14 (brs, 1 H, CSN*H*), 7.60 (d, *J* = 7.9 Hz, 2 H, Ph), 7.38 (m, 2 H, Ph), 7.22 (t, *J* = 7.4 Hz, 1 H, Ph), 4.69 (dd, *J* = 4.2 Hz, *J* = 8.5 Hz, 1 H, C*H*CS), 3.60–3.50 (m, 1 H, CH_aH$_b$N), 3.50–3.40 (m, 1 H, CH$_a$$H_b$N), 2.30–2.20 (m, 1 H, C$_3$$H_aH_b$), 2.00 (m, 2 H, C$_4$$H_2$), 1.80 (m, 1 H, C$_3H_a$$H_b$), 1.36 (9 H, *t*Bu) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO, 353 K): δ = 204.7, 152.9, 139.1, 127.8, 125.5, 123.2, 78.2, 67.3, 46.6, 33.1, 27.8, 22.8 ppm. IR (KBr): $\tilde{\nu}$ = 3277, 3210, 3053, 3038, 2975, 2874, 1657, 1558, 1498, 1411, 1367, 1321, 1163, 1129, 921, 761, 699 cm^{-1}. HR ESI-MS: *m*/*z* calcd. for [$C_{16}H_{22}N_2O_2SNa^+$] 329.1294; found 329.1309. $C_{16}H_{22}N_2O_2S$ (306.13): calcd. C 62.72, H 7.24, N 9.14, S 10.74; found: C 62.50, H 7.23, N 8.99, S 10.49.

***tert*-Butyl (2*S*)-2-(Benzylthiocarbamoyl)pyrrolidine-1-carboxylate (4b):** Column chromatography on silica (hexane/CH_2Cl_2 gradually from 8:2 to 2:8 and then hexane/AcOEt, 6:4) gave a white solid. Yield: 73% (1.52 g, 4.75 mmol). White crystals; m.p. 152–153 °C (from AcOEt/hexane). $[\alpha]_D^{20}$ = –149.1 (*c* = 0.98, CH_2Cl_2). ^{1}H NMR (500 MHz, [D$_6$]DMSO, 353 K): δ = 9.96 (brs, 1 H, CSN*H*), 7.35–7.25 (m, 4 H, Ph), 7.25–7.20 (m, 1 H, Ph), 4.92 (dAB/2, *J* = 6.3 Hz, *J* = 14.8 Hz, 1 H, CH_aH$_b$Ph), 4.71(dAB/2, *J* = 5.5 Hz, *J* = 14.8 Hz, 1 H, CH$_a$$H_b$Ph), 4.60 (dd, *J* = 3.6 Hz, *J* = 8.7 Hz, 1 H, C*H*CS), 3.50–3.45 [m, 1 H, C(5)H_aH$_b$N], 3.38 [dt, *J* = 6.9 Hz, *J* = 10.2 Hz, 1 H, C(5)H$_a$$H_b$N], 2.30–2.20 (m, 1 H, C$H_2$), 1.95–1.85 (m, 2 H, C$H_2$), 1.80–1.70 (m, 1 H, C$H_2$), 1.34 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO, 353 K): δ = 204.2, 152.6, 136.5, 127.1, 126.6, 126.0, 77.8, 66.3, 47.1, 46.1, 32.5, 27.2, 22.2 ppm. IR (KBr): $\tilde{\nu}$ = 3224, 3063, 3003, 2975, 2879, 1656, 1558, 1450, 1418, 1323, 1165, 1127, 971, 734, 697 cm^{-1}. HR ESI-MS: *m*/*z* calcd. for [$C_{17}H_{24}N_2O_2SNa^+$] 343.1451; found 343.1465. $C_{17}H_{24}N_2O_2S$ (320.15): calcd. C 63.72, H 7.55, N 8.99, S 10.01; found C 63.53, H 7.58, N 8.79, S 10.26.

***tert*-Butyl (2*S*)-2-{[(1*R*)-1-Phenylethyl]thiocarbamoyl}pyrrolidine-1-carboxylate (4c):** Column chromatography on silica (hexane/CH_2Cl_2 gradually from 8:2 to 2:8 and then hexane/acetone, 6:4) gave a white solid. Yield: 72% (2.17 g, 6.44 mmol). White crystals, m.p. 134–135 °C (from AcOEt/hexane). $[\alpha]_D^{20}$ = –31.1 (*c* = 1.1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 9.20 (brs, 0.5 H, CSN*H*), 7.94 (brs, 0.5 H, CSN*H*), 7.35 (m, 2 H, Ph), 7.28 (m, 3 H, Ph), 5.77 (brs, 1 H, C*H*Ph), 4.69 (dd, *J* = 3.2 Hz, *J* = 8.2 Hz, 1 H, C*H*CS), 3.46 (brs, 1 H, CH_aH$_b$N), 3.38 (m, 1 H, CH$_a$$H_b$N), 2.27 (brs, 2 H, C$H_2$), 1.83 (m, 2 H, C$H_2$), 1.58 (d, *J* = 6.9 Hz, 3 H, CH_3), 1.45 (s, 9 H, *t*Bu) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 201.9, 152.0, 142.0, 128.8, 127.7, 126.2, 80.9, 49.0, 47.6, 28.3, 23.8, 21.0 ppm. IR (KBr): $\tilde{\nu}$ = 3205, 3032, 2980, 2880, 1672, 1656, 1548, 1453, 1424, 1369, 1360, 1320, 1303, 1170, 1133, 763, 699 cm^{-1}. HR ESI-MS: *m*/*z* calcd. [$C_{18}H_{26}N_2O_2SNa^+$] 357.1607; found 357.1625. $C_{18}H_{26}N_2O_2S$ (334.16): calcd. C 64.64, H 7.84, N 8.38, S 9.59; found: C 64.58, H 7.78, N 8.22, S 9.53.

***tert*-Butyl (2*S*)-2-{[(1*S*)-1-Phenylethyl]thiocarbamoyl}pyrrolidine-1-carboxylate (4d):** Column chromatography on silica (hexane/CH_2Cl_2 gradually from 8:2 to 4:6 and then hexane/AcOEt gradually from 8:2 to 7:3) gave a white solid. Yield: 97% (2.12 g, 6.35 mmol). White crystals; m.p. 105–107 °C (from Et_2O/hexane). $[\alpha]_D^{20}$ = –221.8 (*c* = 1.1, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.92 (brs, 0.5 H, CSN*H*), 7.93 (brs, 0.5 H, CSN*H*), 7.36–7.32 (m, 4 H, Ph), 7.29–7.26 (m, 1 H, Ph), 5.79 (brs, 1 H, C*H*Ph), 4.68 (dd, *J* = 3.8 Hz, *J* = 8.2 Hz, 1 H, C*H*CS), 3.50 (brs, 1 H, CH_aH$_b$N), 3.44 (m, 1 H, CH$_a$$H_b$N), 2.34 (brs, 2 H, C$H_2$), 1.86 (m, 2 H, C$H_2$), 1.57 (d, *J* = 6.9 Hz, 3 H, CH_3), 1.33 (brs, 9 H, *t*Bu) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 202.0, 152.0, 141.2, 128.7, 127.7, 126.4, 126.2, 80.9, 53.6, 47.7, 47.6, 28.3, 28.1, 23.7, 23.6, 20.0 ppm. IR (KBr): $\tilde{\nu}$ = 3223, 3032, 2975, 1670, 1538, 1452, 1421, 1355, 1166, 1158, 1130, 876, 767, 755, 697 cm^{-1}. HR ESI-MS: *m*/*z* calcd. for [$C_{18}H_{26}N_2O_2SNa^+$] 357.1607; found 357.1619. $C_{18}H_{26}N_2O_2S$ (334.16): calcd. C 64.64, H 7.84, N 8.38, S 9.59; found C 64.71, H 7.80, N 8.35, S 9.63.

***tert*-Butyl (2*S*)-2-{[(1*R*)-1-Phenylpropyl]thiocarbamoyl}pyrrolidine-1-carboxylate (4e):** Column chromatography on silica (hexane/CH_2Cl_2 gradually from 8:2 to 6.5:4.5 and then hexane/AcOEt gradually from 7:3 to 6:4) gave a white solid. Yield: 89% (2.34 g, 6.72 mmol). White crystals; m.p. 114–118 °C (from AcOEt/hexane). $[\alpha]_D^{20}$ = –54.5 (*c* = 1.2, CH_2Cl_2). ^{1}H NMR (500 MHz, [D$_6$]DMSO, 353 K): δ = 9.81 (brs, 1 H, CSN*H*), 7.36 (m, 2 H, Ph), 7.28 (m, 2 H, Ph), 7.22 (m, 1 H, Ph), 5.51 (m, 1 H, C*H*Ph), 4.58 (dd, *J* = 3.7 Hz, *J* = 8.7 Hz, 1 H, C*H*CS), 3.50 (m, 1 H, CH_aH$_b$N), 3.36 (dt, J_t = 7.1 Hz, J_d = 10.1 Hz, 1 H, CH$_a$$H_b$N), 2.26–2.18 (m, 1 H, C$H_aH_b$), 1.95–1.80 (m, 4 H, 2 × CH_2), 1.78–1.70 (m, 1 H, CH$_a$$H_b$), 1.26 (brs, 9 H, *t*Bu), 0.88 (t, *J* = 7.4 Hz, 3 H, CH_3, Et) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO, 353 K): δ = 204.4, 153.1, 141.1, 127.7, 127.6, 126.6, 126.5, 95.2, 78.2, 66.4, 59.4, 46.7, 27.7, 27.5, 10.3 ppm. IR (KBr): $\tilde{\nu}$ = 3220, 3042, 2967, 2932, 2874, 1661, 1546, 1419, 1363, 1357, 1322, 1255, 1165, 1129, 1098, 974, 917, 891, 764, 699 cm^{-1}. HR ESI-MS: *m*/*z* calcd. for [$C_{19}H_{28}N_2O_2SNa^+$] 371.1780; found 371.1764. $C_{19}H_{28}N_2O_2S$ (348.18): calcd. C 65.48, H 8.10, N 8.04, S 9.20; found C 65.22, H 7.96, N 8.03, S 9.17.

***tert*-Butyl (2*S*)-2-{[(1*R*)-1-(4-Methoxyphenyl)ethyl]thiocarbamoyl}-pyrrolidine-1-carboxylate (4f):** Column chromatography on silica (hexane/CH_2Cl_2 gradually from 8:2 to 5:5 and then hexane/AcOEt gradually from 8:2 to 7:3) gave a white solid. Yield: 70% (2.90 g, 7.97 mmol). White crystals; m.p. 134–135 °C (from AcOEt/hexane). $[\alpha]_D^{20}$ = +24.3 (*c* = 0.98, CH_2Cl_2). ^{1}H NMR (500 MHz, [D$_6$]DMSO, 353 K): δ = 9.65 (brs, 1 H, CSN*H*), 7.29 (m, 2 H, Ar), 6.86 (m, 2 H, Ar), 5.67 (m, 1 H, C*H*Ar), 4.54 (dd, *J* = 3.8 Hz, *J* = 8.7 Hz, 1 H, C*H*CS), 3.73 (s, 3 H, OCH_3), 3.50–3.40 (m, 1 H, CH_aH$_b$N), 3.37 (dt, J_t = 7.1 Hz, J_d = 10.1 Hz, 1 H, CH$_a$$H_b$N), 2.20 (m, 1 H, C$_3$$H_aH_b$), 1.95–1.80 (m, 2 H, C$_4$$H_2$), 1.80–1.70 (m, 1 H, C$_3H_a$$H_b$), 1.46 (d, *J* = 6.9 Hz, 3 H, CH_3) 1.30 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO, 353 K): δ = 203.1, 158.1, 153.0, 133.9, 127.2, 113.3, 95.1, 78.1, 66.3, 54.7, 52.3, 46.6, 27.6, 22.6, 19.6 ppm. IR (KBr): $\tilde{\nu}$ = 3205, 3029, 2974, 2933, 1669, 1660, 1542, 1515, 1417, 1361, 1293, 1253, 1179, 1130, 1094, 1030, 876, 833, 757 cm^{-1}. HR ESI-MS: *m*/*z* calcd. for [$C_{19}H_{28}N_2O_3SNa^+$] 387.17129; found 387.1732. $C_{19}H_{28}N_2O_3S$ (364.17): calcd. C 62.69, H 7.71, N 7.92, S 8.90; found C 62.61, H 7.74, N 7.69, S 8.80.

***tert*-Butyl (2*S*)-2-(Butylthiocarbamoyl)pyrrolidine-1-carboxylate (4g):** Column chromatography on silica (hexane/CH_2Cl_2 gradually from 8:2 to 5:5 and then hexane/AcOEt gradually from 7:3 to 6:4) gave a white solid. Yield: 86% (2.15 g, 7.52 mmol). White crystals; m.p. 78–79 °C (from AcOEt/hexane). $[\alpha]_D^{20}$ = –125.3 (*c* = 1.1, CH_2Cl_2). ^{1}H NMR (500 MHz, [D$_6$]DMSO, 353 K): δ = 9.47 (brs, 1 H, CSN*H*), 4.50 (dd, *J* = 3.6 Hz, *J* = 8.6 Hz, 1 H, C*H*), 3.60 (m, 1 H, CH_aH$_b$N), 3.51–3.40 (m, 2 H, CH$_a$$H_bN, CH_aH_b$), 3.40–3.30 (m, 1 H, CH$_a$$H_b$), 2.30–2.10 (m, 1 H, C$H_aH_b$), 1.90–1.80 (m, 2 H, C$H_2$), 1.80–1.70 (m, 1 H, CH$_a$$H_b$), 1.56 (q, *J* = 7.3 Hz, 2 H, CH_2), 1.35 (s, 9 H, *t*Bu), 1.40–1.30 (m, 2 H, CH_2), 0.89 (t, *J* = 7.3 Hz, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO, 353 K): δ = 203.8, 153.0, 95.1, 78.2, 66.6, 46.6, 44.1, 33.0, 28.9, 27.7, 22.7, 19.1, 13.0 ppm. IR (KBr): $\tilde{\nu}$ = 3242, 3027, 2980, 2966, 2933, 2874, 1667, 1554, 1416, 1365, 1299, 1170, 1121, 870, 771 cm^{-1}. HR ESI-MS: *m*/*z* calcd. for [$C_{14}H_{26}N_2O_2SNa^+$] 309.1607; found 309.1608. $C_{14}H_{26}N_2O_2S$ (286.16): calcd. C 58.65, H 9.15, N 9.78, S 11.19; found C 58.47, H 9.16, N 9.61, S 11.26.

***tert*-Butyl (2*S*)-2-(Isopropylthiocarbamoyl)pyrrolidine-1-carboxylate (4h):** Column chromatography on silica (hexane/CH_2Cl_2 gradually from 1:1 to 4:6 and then hexane/AcOEt gradually from 8:2 to 6:4) gave a white solid. Yield: 94% (1.56 g, 5.74 mmol). White crystals. m.p. 158–159 °C (from AcOEt). $[\alpha]_D^{20}$ = –132.8 (*c* = 1.0, CH_2Cl_2). ^{1}H NMR (500 MHz, [D$_6$]DMSO, 353 K): δ = 9.22 (br s, 1 H, CSN*H*), 4.55 (m, 1 H, C*H*, *i*Pr), 4.46 (dd, *J* = 4.2 Hz, *J* = 8.6 Hz, 1 H, C*H*CS), 3.48 (ddd, *J* = 5.5 Hz, *J* = 7.6 Hz, *J* = 10.2 Hz, 1 H, CH_aH$_b$N), 3.37 (dt, J_d = 7.0 Hz, J_t = 10.2 Hz, 1 H, CH$_a$$H_b$N), 2.18 (m, 1 H, C$H_aH_b$), 1.95–1.85 (m, 1 H, CH$_a$$H_b$), 1.85–1.80 (m, 1 H, C$H_aH_b$), 1.75–1.70 (m, 1 H, CH$_a$$H_b$), 1.36 (s, 9 H, *t*Bu), 1.17 (t-like, *J* = 6.7 Hz, 6 H, 2×CH_3, *i*Pr) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO, 353 K): δ = 202.6, 153.0, 95.1, 78.1, 66.3, 46.5, 45.8, 32.9, 27.7, 22.6, 20.1, 20.0 ppm. IR (KBr): $\tilde{\nu}$ = 3247, 3058, 2970, 2934, 2874, 1674, 1549, 1453, 1419, 1387, 1364, 1325, 1165, 1126, 923, 871, 765, 755, 688 cm^{-1}. HR ESI-MS: *m*/*z* calcd. for [$C_{13}H_{24}N_2O_2SNa^+$] 295.1451; found 295.1436. $C_{13}H_{24}N_2O_2S$ (272.15): calcd. C 57.32, H 8.88, N 10.28, S 11.77; found C 57.39, H 8.82, N 10.10, S 11.90.

***tert*-Butyl (2*S*)-2-(*tert*-Butylthiocarbamoyl)pyrrolidine-1-carboxylate (4i):** Column chromatography on silica (hexane/CH_2Cl_2 gradually from 8:2 to 4:6) gave a white solid. Yield: 63% (1.32 g, 4.63 mmol). White crystals. m.p. 166–167 °C (from AcOEt/hexane). $[\alpha]_D^{20}$ = –128.5 (*c* = 1.30, CH_2Cl_2). ^{1}H NMR (500 MHz, [D$_6$]DMSO, 353 K): δ = 8.61 (br s, 1 H, CSN*H*), 4.45 (dd, *J* = 4.2 Hz, *J* = 8.6 Hz, 1 H, C*H*), 3.50–3.40 (m, 1 H, CH_aH$_b$N), 3.40–3.30 (m, 1 H, CH$_a$$H_b$N), 2.16 (m, 1 H, C$H_aH_b$), 1.91 (m, 2 H, C$H_2$), 1.76–1.68 (m, 1 H, CH$_a$$H_b$), 1.48 (s, 9 H, *t*Bu), 1.37 (s, 9 H, *t*Bu, Boc) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO, 353 K): δ = 203.2, 153.1, 95.1, 78.2, 67.3, 54.1, 46.6, 32.8, 27.7, 26.9, 22.6 ppm. IR (KBr): $\tilde{\nu}$ = 3276, 3062, 2980, 2968, 2875, 1675, 1550, 1416, 1363, 1325, 1216, 1165, 1119, 920, 768 cm^{-1}. HR ESI-MS: *m*/*z* calcd. for [$C_{14}H_{26}N_2O_2SNa^+$] 309.16079; found 309.1622. $C_{14}H_{26}N_2O_2S$ (286.16): calcd. C 58.7, H 9.15, N 9.78, S 11.20; found C 58.67, H 8.92, N 9.90, S 11.11.

***tert*-Butyl (2*S*)-2-{[(1*R*)-1,2-Dimethylpropyl]thiocarbamoyl}pyrrolidine-1-carboxylate (4j):** Column chromatography on silica (hexane/CH_2Cl_2 gradually from 8:2 to 4:6 and then hexane/AcOEt gradually from 8:2 to 7:3) gave a white solid. Yield: 80% (1.69 g, 5.63 mmol). White crystals; m.p. 124–125 °C (from AcOEt/hexane). $[\alpha]_D^{20}$ = –125.1 (*c* = 1.03, CH_2Cl_2). ^{1}H NMR (500 MHz, [D$_6$]DMSO, 353 K): δ = 9.49 (d, *J* = 5.7 Hz, 1 H, CSN*H*), 4.51 (dd, *J* = 3.2 Hz, *J* = 8.6 Hz, 1 H, C*H*CS), 4.32 (br s, 1 H, C*H*CH$_3$), 3.49 (m, 1 H, CH_aH$_b$N), 3.33 (m, 1 H, CH$_a$$H_b$N), 2.23 (br s, 1 H, C$H_aH_b$), 1.86 (m, 2 H, CH$_a$$H_b$ + C*H*i*Pr), 1.74 (br s, 2 H, CH_2), 1.33 (s, 9 H, *t*Bu), 1.06 (bd, *J* = 5.2 Hz, 2 H, CH_2), 0.88 (d, *J* = 6.8 Hz, 3 H, CH_3, *i*Pr), 0.86 (d, *J* = 6.8 Hz, 3 H, CH_3*i*Pr) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO, 363 K): δ = 203.3, 153.2, 95.4, 78.3, 66.7, 55.8, 47.0, 33.9, 31.4, 28.0, 22.7, 19.5, 18.4, 15.5 ppm. IR (KBr): $\tilde{\nu}$ = 3262, 3055, 2969, 2933, 2870, 1675, 1546, 1453, 1416, 1364, 1323, 1249, 1161, 1121, 1105, 953, 921, 763, 687 cm^{-1}. HR ESI-MS: *m*/*z* calcd. for [$C_{15}H_{28}N_2O_2SNa^+$] 323.17637; found 323.1772. $C_{15}H_{28}N_2O_2S$ (300.18): calcd. C 60.00, H 9.33, N 9.33, S 10.67; found C 59.87, H 9.37, N 9.32, S 10.43.

General Procedure for the Removal of the *N*-Boc-Amino Group: *N*-Boc-thioamide **4** (1.4 mmol) was dissolved in dry CH_2Cl_2 (2.8 mL) and was treated with TFA (18.2 mmol, 1.40 mL) and then with Et_3SiH (3.30 mmol, 0.55 mL). After 3 h, the solvent and volatile compounds were removed. The remaining oil was treated with Et_2O and in most cases a white solid precipitated and was filtered off (sometimes addition of hexane was necessary). The precipitate was dissolved in $CHCl_3$, washed with saturated $NaHCO_3$ and dried with $NaSO_4$. After the removal of the solvent, catalyst **5** was obtained as a colourless oil, which often solidified as noted.

(2*S*)-*N*-Phenylpyrrolidine-2-carbothioamide (5a): Yield: 98% (160 mg, 0.79 mmol), *ee* = 26%. Solid; m.p. 56–57 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 11.75 (br s, 1 H, CSN*H*), 7.94 (m, 2 H, Ph), 7.40 (m, 2 H, Ph), 7.3–7.2 (m, 1 H, Ph), 4.28 (dd, *J* = 5.6 Hz, *J* = 9.1 Hz, 1 H, C*H*CS), 3.15 (dt, J_t = 6.8 Hz, J_d = 10.1 Hz, 1 H, CH_aH$_b$N), 3.05 (dt, J_t = 6.2 Hz, J_d = 10.1 Hz, 1 H, CH$_a$$H_b$N), 2.46 [ddt, J_t = 7.3 Hz, J_d = 9.0 Hz, J_d = 13.3 Hz 1 H, C(3)H_aH$_b$], 2.12 [m, 2 H, C(3)H$_a$$H_b$, N*H*], 1.75 [m, 2 H, C(4)H_2] ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 203.0, 138.4, 128.8, 126.3, 122.2, 69.6, 47.5, 34.8, 26.2 ppm. IR (KBr): $\tilde{\nu}$ = 3445, 3295, 2970, 2937, 2863, 1673, 1589, 1519, 1442, 1417, 1368, 1279, 1165, 1110, 1076, 907, 764, 744, 729, 690 cm^{-1}. HR ESI-MS: *m*/*z* calcd. for [$C_{11}H_{15}N_2S^+$] 207.095; found 207.0943. $C_{11}H_{14}N_2S$ (184.09): calcd. C 64.04, H 6.84, N 13.58, S 15.54; found: C 63.81, H 6.80, N 13.31, S 15.35.

(2*S*)-*N*-Benzylpyrrolidine-2-carbothioamide (5b): Yield: 92% (350 mg, 1.59 mmol). Solid; m.p. 45–46 °C. $[\alpha]_D^{20}$ = –107.2 (*c* = 0.99, CH_2Cl_2). ^{1}H NMR (500 MH, $CDCl_3$): δ = 10.08 (s, 1 H, CSN*H*), 7.4–7.3 (m, 5 H, Ph), 4.86 (d, *J* = 5.1 Hz, 2 H, CH_2Ph), 4.25 (dd, *J* = 5.5 Hz, *J* = 9.1 Hz, 1 H, C*H*CS), 3.05 (dt, J_t = 6.8 Hz, J_d = 10.0 Hz, 1 H, CH_aH$_b$N), 2.88 (dt, J_t = 6.2 Hz, J_d = 10.0 Hz, 1 H, CH$_a$$H_b$N), 2.45–2.35 [m, 1 H, C(3)H_aH$_b$], 2.06 [m, 1 H, C(3)H$_a$$H_b$], 1.91 (s, 1 H, N*H*), 1.69 [m, 2 H, C(4)H_2] ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 205.2, 136.6, 128.8, 127.9, 127.8, 68.1, 48.6, 47.4, 34.5, 26.0 ppm. IR (KBr): $\tilde{\nu}$ = 3302, 3162, 2961, 2941, 2915, 2870, 1525, 1495, 1453, 1382, 1343, 1312, 1287, 1177, 1069, 962, 892, 758, 734, 695 cm^{-1}. HR ESI-MS: *m*/*z* calcd. for [$C_{12}H_{17}N_2S^+$] 221.1107; found 221.1097. $C_{12}H_{16}N_2S$ (220.11): calcd. C 65.41, H 7.32, N 12.71, S 14.55; found: C 65.41, H 7.32, N 12.73, S 14.52.

(2*S*)-*N*-[(1*R*)-1-Phenylethyl]pyrrolidine-2-carbothioamide (5c): Yield: 94% (385 g, 1.65 mmol). White solid; m.p. 39–40 °C. $[\alpha]_D^{20}$ = +57.51 (*c* = 1.05, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.12 (br s, 1 H, CSN*H*), 7.35 (m, 2 H, Ph), 7.28 (m, 3 H, Ph), 5.72 (m, 1 H, C*H*Ph), 4.22 (dd, *J* = 5.5 Hz, *J* = 9.0 Hz, 1 H, C*H*CS), 3.05 (dt, J_d = 10.0 Hz, J_t = 6.8 Hz, 1 H, CH_aH$_b$N), 2.89 (dt, *J* = 10.0 Hz, *J* = 6.2 Hz, 1 H, CH$_a$$H_b$N), 2.36 [m, 1 H, C(3)$H_aH_b$], 1.99 [m, 1 H, C(3)$H_aH_b$], 1.90 (br s, 1 H, N*H*), 1.68 [m, 1 H, C(4)H_aH$_b$], 1.62 [m, 1 H, C(4)H$_a$$H_b$], 1.59 (d, *J* = 6.9 Hz, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 203.7, 144.0, 128.7, 127.4, 126.1, 68.2, 52.8, 47.4, 34.4, 26.0, 20.6 ppm. IR (KBr): $\tilde{\nu}$ = 3174, 2970, 2929, 2869, 1510, 1453, 1379, 1277, 1073, 757, 698 cm^{-1}. HR EI-MS: *m*/*z* calcd. for [$C_{13}H_{18}N_2S$] 234.11907; found 234.12003. $C_{13}H_{18}N_2S$ (234.12): calcd. C 66.62, H 7.74, N 11.95, S 13.68; found C 66.49, H 7.84, N 12.02, S 13.95.

(2*S*)-*N*-[(1*S*)-1-Phenylethyl]pyrrolidine-2-carbothioamide (5d): Yield: 95% (669 mg, 2.86 mmol). Solid; m.p. 43–44 °C. $[\alpha]_D^{20}$ = –300.1 (*c* = 1.05, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.11 (br s, 1 H, CSN*H*), 7.36–7.26 (m, 5 H, Ph), 5.73 (m, 1 H, C*H*Ph), 4.19 (dd, *J* = 5.6 Hz, *J* = 9.0 Hz, 1 H, C*H*CS), 3.07 (dt, J_d = 10.1 Hz, J_t = 6.9 Hz, 1 H, CH_aH$_b$N), 2.96 (dt, J_d = 10.1 Hz, J_t = 6.2 Hz, 1 H, CH$_a$$H_b$N), 2.45–2.30 [m, 1 H, C(3)H_aH$_b$], 2.18 (br s, 1 H, N*H*), 2.05–1.95 [m, 1 H, C(3)H$_a$$H_b$], 1.75–1.65 [m, 2 H, C(4)H_2], 1.57 (d, *J* = 6.9 Hz, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 203.5, 141.7, 128.8, 127.6, 126.5, 68.1, 53.1, 47.4, 34.5, 26.0, 20.5 ppm. IR (film): $\tilde{\nu}$ = 3176, 2971, 2940, 2869, 1509, 1451, 1378, 1278, 1176, 1073, 758, 698 cm^{-1}. HR ESI-MS: *m*/*z* calcd. for [$C_{13}H_{19}N_2S^+$] 235.1263; found 235.1260. $C_{13}H_{18}N_2S$ (234.12): calcd. C 66.62, H 7.74, N 11.95, S 13.68; found. C 66.52, H 8.03, N 11.80, S 13.46.

(2*S*)-*N*-[(1*R*)-1-Phenylpropyl]pyrrolidine-2-carbothioamide (5e): Yield: 81% (1.08 g, 4.35 mmol). White solid, m.p. 46–48 °C. $[\alpha]_D^{20}$

= +48.6 (c = 1.09, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.19 (brs, 1 H, CSN*H*), 7.35–7.30 (m, 2 H, Ph), 7.30–7.20 (m, 3 H, Ph), 5.49 (dd, J = 7.2 Hz, J = 15.6 Hz, 1 H, C*H*Ph), 4.23 (dd, J = 5.5 Hz, J = 9.0 Hz, 1 H, C*H*CS), 3.07 (dt, J_t = 6.8 Hz, J_d = 10.0 Hz, 1 H, CH_aH$_b$N), 2.92 (dt, J_t = 6.2 Hz, J_d = 10.0 Hz, 1 H, CH$_a$$H_b$N), 2.33 (ddt, J_t = 7.3 Hz, J_d = 9.0 Hz, J_d = 13.0 Hz, 1 H, CH_aH$_b$), 2.05–1.95 (m, 2 H, CH_2), 1.95–1.85 (m, 2 H, CH$_a$$H_b$, N*H*), 1.67 (m, 1 H, C$H_aH_b$), 1.58 (m, 1 H, CH$_a$$H_b$), 0.91 (t, J = 7.4 Hz, 3 H, CH_3, Et) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 204.0, 140.8, 128.6, 127.3, 126.6, 68.3, 58.9, 47.4, 34.4, 28.5, 26.0, 10.5 ppm. IR (KBr): $\tilde{\nu}$ = 3327, 3131, 2972, 2940, 2923, 2855, 1516, 1380, 1364, 1311, 1290, 1260, 1099, 1058, 903, 893, 870, 796, 765, 703 cm^{-1}. HR ESI-MS: m/z calcd. for [$C_{14}H_{21}N_2S^+$] 249.1420; found 249.1408. $C_{14}H_{20}N_2S$ (248.14): calcd. C 67.74, H 8.06, N 11.29, S 12.91; found C 67.84, H 8.19, N 11.30, S 13.05.

(2*S*)-*N*-[(1*R*)-1-(4-Methoxyphenyl)ethyl]pyrrolidine-2-carbothioamide (5f): Yield 67% (208 mg, 0.79 mmol). White solid, m.p. 42–43 °C. $[a]_D^{20}$ = +128.8 (c = 0.98, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.04 (brs, 1 H, CSN*H*), 7.24 (m, 2 H, Ar), 6.88 (m, 2 H, Ar), 5.67 (m, 1 H, C*H*Ar), 4.20 (dd, J = 5.5 Hz, J = 9.0 Hz, 1 H, C*H*CS), 3.80 (s, 3 H, OCH_3), 3.04 (dt, J_t = 6.8 Hz, J_d = 10.1 Hz, 1 H, CH_aH$_b$N), 2.87 (dt, J_t = 6.2 Hz, J_d = 10.0 Hz, 1 H, CH$_a$$H_b$N), 2.35 [ddt, J_t = 7.3 Hz, J_d = 9.0 Hz, J_d = 13.1 Hz, 1 H, C(3)H_aH$_b$], 1.98 [m, 1 H, C(3)H$_a$$H_b$], 1.88 (brs, 1 H, N*H*), 1.70–1.65 [m, 1 H, C(4)H_aH$_b$], 1.65–1.57 [m, 1 H, C(4)H$_a$$H_b$], 1.56 (d, J = 6.9 Hz, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 203.3, 158.9, 134.0, 127.3, 114.0, 68.1, 55.2, 52.3, 47.4, 34.4, 26.0, 20.3 ppm. IR (KBr): $\tilde{\nu}$ = 3305, 3176, 2966, 2933, 2869, 1611, 1512, 1455, 1377, 1286, 1248, 1179, 1101, 1031, 832, 763 cm^{-1}. HR ESI-MS: m/z calcd. for [$C_{14}H_{21}N_2OS^+$] 265.13691; found 265.1357. $C_{14}H_{20}N_2OS$ (264.14): calcd. C 63.64, H 7.58, N 10.61, S 12.12; found C 63.67, H 7.59, N 10.45, S 11.99.

(2*S*)-*N*-Butylpyrrolidine-2-carbothioamide (5g): Yield: 98% (472 mg, 2.51 mmol), 95% purity. $[a]_D^{20}$ = –129.8 (c = 1.00, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.86 (brs, 1 H, CSN*H*), 4.19 (dd, J = 5.6 Hz, J = 9.0 Hz, 1 H, C*H*CS), 3.65 (m, 2 H, NCH_2, Bu), 3.08 (dt, J_t = 6.8 Hz, J_d = 10.0 Hz, 1 H, CH_aH$_b$N), 2.94 (dt, J_t = 6.2 Hz, J_d = 10.0 Hz, 1 H, CH$_a$$H_b$N), 2.37 [m, 1 H, C(3)$H_aH_b$], 2.22 (brs, 1 H, N*H*), 2.00 [m, 1 H, C(3)H$_a$$H_b$], 1.70–1.60 (m, 4 H, 2×CH_2), 1.39 (m, 2 H, CH_2), 0.96 (t, J = 7.4 Hz, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 204.3, 67.9, 47.3, 44.3, 34.3, 30.0, 25.9, 20.1, 13.6 ppm. IR (KBr): $\tilde{\nu}$ = 3296, 3190, 2959, 2932, 2871, 1528, 1461, 1385, 1287, 1107, 1066, 894, 751, 736 cm^{-1}. HR ESI-MS: m/z calcd. for [$C_9H_{19}N_2S^+$] 187.12635; found 187.1269.

(2*S*)-*N*-Isopropylpyrrolidine-2-carbothioamide (5h): Yield: 93% (587 mg, 3.41 mmol). $[a]_D^{20}$ = –108.5 (c = 1.03, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.65 (brs, 1 H, CSN*H*), 4.61 (m, 1 H, C*Hi*Pr), 4.16 (dd, J = 5.7 Hz, J = 9.0 Hz, 1 H, C*H*CS), 3.07 (dt, J_t = 6.8 Hz, J_d = 10.0 Hz, 1 H, CH_aH$_b$N), 2.93 (dt, J_t = 6.2 Hz, J_d = 10.0 Hz, 1 H, CH$_a$$H_b$N), 2.38 [m, 1 H, C(3)$H_aH_b$], 2.03 (brs, 1 H, N*H*), 1.99 [m, 1 H, C(3)H$_a$$H_b$], 1.68 [m, 2 H, C(4)$H_2$], 1.26 (d, J = 6.6 Hz, 3 H, CH_3, *i*Pr), 1.25 (d, J = 6.6 Hz, 3 H, CH_3, *i*Pr) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 204.3, 67.9, 47.3, 44.3, 34.3, 30.0, 25.9, 20.1, 13.6 ppm. IR (film): $\tilde{\nu}$ = 3300, 3182, 2968, 2938, 2870, 1518, 1459, 1389, 1374, 1284, 1168, 1068, 739 cm^{-1}. HR EI-MS: m/z calcd. for [$C_8H_{16}N_2S^+$] 172.1034; found 172.1039. $C_8H_{16}N_2S$ (172.10): calcd. C 55.77, H 9.36, N 16.26, S 18.61; found C 55.55, H 9.36, N 16.13, S 18.38.

(2*S*)-*N*-(*tert*-Butyl)pyrrolidine-2-carbothioamide (5i): Yield: 96% (250 mg, 1.34 mmol). White solid, m.p. 34–35 °C. $[a]_D^{20}$ = –185.3 (c = 1.25, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.82 (brs, 1 H, CSN*H*), 4.08 (dd, J = 5.8 Hz, J = 8.9 Hz, 1 H, C*H*), 3.08 (dt, J_t = 6.8 Hz, J_d = 10.0 Hz, 1 H, CH_aH$_b$N), 2.95 (dt, J_t = 6.2 Hz, J_d = 10.0 Hz, 1 H, CH$_a$$H_b$N), 2.38 [m, 1 H, C(3)$H_aH_b$], 2.19 (brs, 1 H, N*H*), 1.96 [m, 1 H, C(3)H$_a$$H_b$], 1.68 [m, 2 H, C(4)$H_2$], 1.55 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 202.8, 69.5, 54.2, 47.4, 34.6, 27.6, 26.0 ppm. IR (KBr): $\tilde{\nu}$ = 3304, 3092, 2965, 2878, 1532, 1402, 1380, 1364, 1290, 1217, 1113, 1069, 901, 833, 799, 773 cm^{-1}. HR ESI-MS: m/z calcd. for [$C_9H_{19}N_2S^+$] 187.12635; found 187.1255. $C_9H_{18}N_2S$ (186.13): calcd. C 58.02, H 9.74, N 15.04, S 17.21; found C 58.21, H 9.58, N 14.99, S 17.19.

(2*S*)-*N*-[(1*R*)-1,2-Dimethylpropyl]pyrrolidine-2-carbothioamide (5j): Yield: 89% (148 mg, 0.74 mmol). Oil. $[a]_D^{20}$ = –146.6 (c = 1.14, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.84 (brs, 1 H, CSN*H*), 4.40 (m, 1 H, C*H*CH$_3$), 4.18 (dd, J = 5.3 Hz, J = 9.1 Hz, 1 H, C*H*CS), 3.09 (dt, J_t = 6.9 Hz, J_d = 10.0 Hz, 1 H, CH_aH$_b$N), 2.94 (dt, J_t = 6.1 Hz, J_d = 10.1 Hz, 1 H, CH$_a$$H_b$N), 2.40–2.30 [m, 1 H, C(3)H_aH$_b$], 2.04 [m, 1 H, C(3)H$_a$$H_b$], 1.94 (brs, 1 H, N*H*), 1.90 [m, 1 H, C(4)H_aH$_b$], 1.72 [m, 1 H, C(4)H$_a$$H_b$], 1.64 (m, 1 H, C*H*, *i*Pr), 1.17 (d, J = 6.7 Hz, 3 H, CH_3), 0.92 (t-like, J = 7.0 Hz, 6 H, 2×CH_3, *i*Pr) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 203.3, 68.2, 54.4, 47.4, 34.5, 32.4, 25.9, 18.5, 18.4, 15.8 ppm. IR (film): $\tilde{\nu}$ = 3301, 3178, 2963, 2937, 2871, 1518, 1458, 1382, 1279, 1108, 1071, 1048, 896, 767, 746 cm^{-1}. HR ESI-MS: m/z calcd. for [$C_{10}H_{21}N_2S^+$] 201.1420; found 201.1429. $C_{10}H_{20}N_2S$ (200.14): calcd. C 59.95, H 10.06, N 13.98, S 16.01; found C 60.02, H 10.06, N 13.85, S 15.92.

(7a*S*)-2-Benzyl-3,3-dimethylhexahydro-1*H*-pyrrolo[1,2-*c*]imidazole-1-thione (8): Yield: 99% (209 mg, 0.80 mmol). White solid; m.p. 78–81 °C. $[a]_D^{20}$ = –76.0 (c = 0.99, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42–7.24 (m, 5 H, Ph), 5.28 (AB/2, J = 15.1 Hz, 1 H, CH_aH$_b$Ph), 4.61 (AB/2, J = 15.1 Hz, 1 H, CH$_a$$H_b$Ph), 4.28 (m, 1 H, C*H*CS), 2.83 (dd, J = 6.5 Hz, J = 8.4 Hz, 1 H, CH_aH$_b$N), 2.50–2.40 [m, 2 H, C(3)H_2], 2.34 (ddd, J = 5.7 Hz, J = 8.6 Hz, J = 11.8 Hz, 1 H, CH$_a$$H_b$N), 1.90–1.70 [m, 2 H, C(4)H_2], 1.34 (s, 3 H, CH_3), 1.30 (s, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 204.1, 136.8, 128.6, 127.6, 127.4, 87.1, 74.6, 48.5, 48.1, 29.3, 26.8 25.0, 22.4 ppm. HR ESI-MS m/z calcd. for [$C_{15}H_{21}N_2S^+$] 261.142; found 261.1432.

(7a*S*)-3,3-Dimethyl-2-[(1*R*)-1-phenylethyl]hexahydro-1*H*-pyrrolo-[1,2-*c*]imidazole-1-thione (14): Yield: 99% (329 mg, 1.20 mmol). White solid; m.p. 83–87 °C. $[a]_D^{20}$ = +314.5 (c = 0.98, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.30 (m, 4 H, Ph), 7.28–7.24 (m, 1 H, Ph), 6.61 (m, 1 H, C*H*Ph), 4.26 (dd, J = 9.5 Hz, J = 4.4 Hz, 1 H, C*H*CS), 2.68 (t-like, J = 7.5 Hz, 1 H, CH_aH$_b$N), 2.55–2.45 [m, 1 H, C(3)H_aH$_b$], 2.45–2.35 [m, 1 H, C(3)H$_a$$H_b$], 2.09 (ddd, J = 12.1 Hz, J = 8.4 Hz, J = 5.9 Hz, 1 H, CH$_a$$H_b$N), 1.87–1.82 [m, 1 H, C(4)H_aH$_b$], 1.79 (d, J = 7.4 Hz, 3 H, CHCH_3), 1.77–1.70 [m, 1 H, C(4)H$_a$$H_b$], 1.54 (s, 3 H, C$H_3$), 1.02 (brs, 3 H, C$H_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 204.4, 140.5, 128.7, 128.4, 127.5, 126.5, 126.3, 88.4, 74.1, 53.0, 48.2, 47.3, 34.4, 30.9, 29.8, 25.9, 24.7, 22.7, 20.6, 16.2 ppm. HR ESI-MS: m/z calcd. for [$C_{16}H_{23}N_2S^+$] 275.1576; found 275.1581. $C_{16}H_{22}N_2S$ (274.16): calcd. C 70.03, H 8.08, N 10.21, S 11.69, found C 69.90 H 7.91, N 10.38, S 11.83.

4-{(7a*S*)-2-[(1*R*)-1-phenylethyl]-1-thioxohexahydro-1*H*-pyrrolo-[1,2-*c*]imidazol-3-yl}benzonitrile (15): Yellowish solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.40–7.10 (m, 7 H, Ar), 6.89 (d, J = 7.6 Hz, 2 H, Ar), 6.40 (q, J = 7.2 Hz, 1 H, C*H*CH$_3$), 5.93 (d, J = 1.6 Hz, 1 H, C*H*NN), 4.29 (m, 1 H, C*H*CS), 2.51–2.25 (m, 4 H, CH_2N, CH_2), 1.83–1.62 (m, 2 H, CH_2), 1.55 (d, J = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 207.2, 140.1, 138.4, 131.7, 130.4, 128.6, 128.1, 127.7, 113.1, 84.7, 77.8, 55.4, 49.0, 31.1, 25.7, 15.2 ppm. ESI-MS: m/z = 348 [M$^+$ + H].

General Procedure for the Aldol Reaction Catalysed by L-Proline-thioamides 5: An aldehyde **6** (1 mmol) was added at 0 °C to a solu-

tion of thioamide **5** (0.2 mmol) in acetone (2 mL). The resulting solution was stirred at +4 °C for 68 h. After this time, the solution was quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate (3×). The combined organic layers were dried with $NaSO_4$ and filtered, and the solvents were evaporated in vacuo. Purification by column chromatography (hexane/AcOEt) gave aldol product **7**.

General Procedure for the Synthesis of 1,5-Dihydroxypentan-3-one Derivatives: An aldehyde **6** (1 mmol) was added at 0 °C to a solution of thioamide **5** (0.2 mmol) in acetone (37 μL). The resulting solution was stirred at room temp. for 1 h. After this time, the solution was quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate (3×). The combined organic layers were dried with $NaSO_4$ and filtered, and the solvents were evaporated in vacuo. Purification by column chromatography (hexane/AcOEt) gave the 1,5-dihydroxypentan-3-one derivatives as a fourth band.

1,5-Dihydroxy-1,5-bis(perfluorophenyl)pentan-3-one Mixture (9-*anti*/9-*syn*): Yield: 44% (100 mg, 0.22 mmol). White crystals; m.p. 142–144 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.42 (dt, J_t = 5.3 Hz, J_d = 7.8 Hz, 2 H, C*H*), 3.93 (d, J = 5.1 Hz, 2 H, O*H*), 3.22 (dd, J = 8.0 Hz, J = 17.3 Hz, 2 H, CH_aH_b), 2.97 (dd, J = 5.7 Hz, J = 17.3 Hz, 2 H, CH$_a$*H*$_b$) ppm. ^{13}C NMR (50 MHz, [D$_6$]acetone): δ = 206.5, 146.0, 144.1, 141.9, 139.9, 138. 6, 136.7, 62.2, 50.3 ppm. IR (KBr): $\tilde{\nu}$ = 3512, 1702, 1529, 1506, 1395, 1130, 1092, 994, 948 cm^{-1}. $C_{17}H_8F_{10}O_3$ (450.25): calcd. C 45.35, H 1.79, F 42.20; found C 45.41, H 1.62, F 41.99.

***anti*-1,5-Bis(2-chlorophenyl)-1,5-dihydroxypentan-3-one (11-*anti*):** Yield: 33% (50 mg, 0.15 mmol). White crystals; m.p. 129–131 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.62 (dd, J = 1.7 Hz, J = 7.7 Hz, Ar), 7.35–7.25 (m, 4 H, Ar), 7.22 (td, J_d = 1.7 Hz, J_t = 7.6 Hz, 2 H, Ar), 5.56 (dt, J_t = 2.9 Hz, J_d = 9.6 Hz, 2 H, C*H*), 3.34 (d, J = 3.5 Hz, 2 H, O*H*), 2.97 (dd, J = 2.4 Hz, J = 17.1 Hz, 2 H, CH_aH_b), 2.77 (dd, J = 9.6 Hz, J = 17.1 Hz, 2 H, CH$_a$*H*$_b$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 210.8, 139.9, 131.2, 129.4, 128.7, 127.3, 127.0, 66.6, 49.9 ppm. IR (KBr): $\tilde{\nu}$ = 3459, 1698, 1474, 1402, 1370, 1200, 1084, 1036, 895, 750 cm^{-1}. HR ESI-MS: *m*/*z* calcd. for [$C_{17}H_{16}O_3Cl_2Na^+$] 361.03687; found 361.0386. $C_{17}H_{16}Cl_2O_3$ (338.05): calcd. C 60.19, H 4.75, Cl 20.90; found C 60.16, H 4.79, Cl 21.04. *ee* = 94%, determined by HPLC (Daicel Chiralpak AS-H, *i*PrOH/hexane, 10:90), λ = 207 nm, flow rate 1 mL·min^{-1}, minor isomer t_R = 17.0 min, major isomer t_R = 18.6 min.

***syn*-1,5-Bis(2-chlorophenyl)-1,5-dihydroxypentan-3-one (11-*syn*):** Yield: 6% (10 mg, 0.03 mmol). White crystals; m.p. 113–114 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.62 (dd, J = 1.7 Hz, J = 7.7 Hz, 2 H, Ar), 7.35–7.25 (m, 4 H, Ar), 7.22 (td, J_d = 1.7 Hz, J_t = 7.7 Hz, 2 H, Ar), 5.58 (dt, J_t = 2.8 Hz, J_d = 9.7 Hz, 2 H, C*H*), 3.26 (d, J = 3.5 Hz, 2 H, O*H*), 3.02 (dd, J = 2.4 Hz, J = 17.2 Hz, 2 H, CH_aH_b), 2.74 (dd, J = 9.7 Hz, J = 17.2 Hz, 2 H, CH$_a$*H*$_b$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 210.9, 139.9, 131.2, 129.4, 128.7, 127.3, 127.1, 66.8, 50.0 ppm. IR (KBr): $\tilde{\nu}$ = 3553, 3329, 3271, 1697, 1474, 1437, 1403, 1388, 1369, 1195, 1080, 1032, 895, 755, 700 cm^{-1}. HR ESI-MS: *m*/*z* calcd. for [$C_{17}H_{16}O_3Cl_2Na^+$] 361.03687; found 361.0362. $C_{17}H_{16}Cl_2O_3$ (338.05): calcd. C 60.19, H 4.75, Cl 20.90; found C 60.26, H 4.69, Cl 21.21.

Crystallographic Data for the X-ray Structure of *anti*-11: All crystal measurements were performed with a KM4CCD κ-axis diffractometer with use of graphite-monochromated Mo-K_α radiation. The crystal was positioned 62 mm from the CCD camera. 2400 frames were measured at 0.5° intervals with a counting time of 10 s. The data were corrected for Lorentz and polarisation effects. Empirical correction for absorption was applied.[42] Data reduction and analysis were carried out with the Oxford Diffraction programs.[43] The structure was solved by direct methods[44] and refined by use of SHELXL.[45] The refinement was based on F^2 for all reflections except those with very negative F^2. Weighted R factors wR and all goodness-of-fit S values are based on F^2. Conventional R factors are based on F with F set to zero for negative F^2. The $F_o^2 > 2\sigma(F_o^2)$ criterion was used only for calculating R factors and is not relevant to the choice of reflections for the refinement. The R factors based on F^2 are about twice as large as those based on F. All hydrogen atoms were located geometrically and their positions and temperature factors were refined. Scattering factors were taken from Tables 6.1.1.4 and 4.2.4.2.[46] CCDC-600255 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgments

The X-ray measurements were undertaken in the Crystallographic Unit of the Physical Chemistry Laboratory at the Chemistry Department of the University of Warsaw.

[1] A. Berkessel, H. Groger, *Asymmetric Organocatalysis*, VCH, Weinheim, **2005**.
[2] P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175.
[3] U. Kazmaier, *Angew. Chem. Int. Ed.* **2005**, *44*, 2186–2188.
[4] B. List, *Acc. Chem. Res.* **2004**, *37*, 548–557.
[5] B. List, *Synlett* **2001**, 1675–1684.
[6] S. Saito, H. Yamamoto, *Acc. Chem. Res.* **2004**, *37*, 570–579.
[7] W. Notz, F. Tanaka, C. F. Barbas, *Acc. Chem. Res.* **2004**, *37*, 580–591.
[8] B. List, *Tetrahedron* **2002**, *58*, 5572–5590.
[9] B. List, *Chem. Commun.* **2006**, 819–824.
[10] B. List, in: *Modern Aldol Reactions*, vol. 1 (Ed.: R. Marhwald), VCH, Weinheim, **2004**, pp. 161–200.
[11] A. B. Northrup, D. W. MacMillan, *Science* **2004**, *305*, 1752–1754.
[12] B. List, R. A. Lerner, C. F. Barbas, *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396.
[13] a) A. Hartikka, P. I. Arvidsson, *Tetrahedron: Asymmetry* **2004**, *15*, 1831–1834; b) H. Torii, M. Nakadai, K. Ishihara, S. Saito, H. Yamamoto, *Angew. Chem. Int. Ed.* **2004**, *43*, 1983–1986; c) A. Hartikka, P. I. Arvidsson, *Eur. J. Org. Chem.* **2005**, 4287–4295.
[14] 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*, 5262–5263; b) Z. Tang, F. Jiang, X. Cui, L.-Z. Gong, A.-Q. Mi, Y.-Z. Jiang, Y.-D. Wu, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5755–5760; c) 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*, 9285–9289.
[15] S. Saito, M. Nakadai, H. Yamamoto, *Synlett* **2001**, 1245–1248.
[16] Y. Hayashi, J. Yamaguchi, K. Hibino, T. Sumiya, T. Urushima, M. Shoji, D. Hashizume, H. Koshino, *Adv. Synth. Catal.* **2004**, *346*, 1435–1439.
[17] A. Berkessel, B. Koch, J. Lex, *Adv. Synth. Catal.* **2004**, *346*, 1141–1146.
[18] E. Bellis, K. Vasilatou, G. Kokotos, *Synthesis* **2005**, 2407–2413.
[19] W. Zou, I. Ibrahem, P. Dziedzic, H. Sundén, A. Córdova, *Chem. Commun.* **2005**, 4946–4948.
[20] A. J. A. Cobb, D. M. Shaw, D. A. Longbottom, J. B. Gold, S. V. Ley, *Org. Biomol. Chem.* **2005**, *3*, 84–96.
[21] D. Gryko, R. Lipiński, *Adv. Synth. Catal.* **2005**, *347*, 1948–1952.
[22] T. Kano, J. Takai, O. Tokuda, K. Maruoka, *Angew. Chem. Int. Ed.* **2005**, *44*, 3055–3057.

[23] E. Bellis, G. Kokotos, *Tetrahedron* **2005**, *61*, 8669–8676.
[24] C. Cheng, J. Sun, C. Wang, Y. Zhang, S. Wei, F. Jiang, Y. Wu, *Chem. Commun.* **2006**, 215–217.
[25] N. Mase, Y. Nakai, N. Ohara, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2006**, *128*, 734–735.
[26] S. Samanta, J. Liu, R. Dodda, C.-G. Zhao, *Org. Lett.* **2005**, *7*, 5321–5323.
[27] J.-R. Chen, H.-H. Lu, X.-Y. Li, L. Cheng, J. Wan, W.-J. Xiao, *Org. Lett.* **2005**, *7*, 4543–4545.
[28] S. Scheibe, B. S. Pedersen, S. O. Lawesson, *Bull. Soc. Chim. Belg.* **1978**, *87*, 229–238.
[29] A. Mehta, R. Jaouhari, T. J. Benson, K. T. Douglas, *Tetrahedron Lett.* **1992**, *33*, 5441–5444.
[30] A. J. A. Cobb, D. M. Shaw, S. V. Ley, *Synlett* **2004**, 558–559.
[31] Y. Hayashi, T. Sumiya, J. Takahashi, H. Gotoh, T. Urushima, M. Shoji, *Angew. Chem. Int. Ed.* **2006**, *45*, 958–961.
[32] P. Kotrusz, I. Kmentová, B. Gotov, Š. Toma, E. Solčániová, *Chem. Commun.* **2002**, 2510–2511.
[33] Ch. Cheng, J. Sun, Ch. Wang, Y. Zhang, S. Wei, F. Jiang, Y. Wu, *Chem. Commun.* **2006**, 215–217.
[34] A. Córdova, W. Notz, C. F. Barbas, *Chem. Commun.* **2002**, 3024–3025.
[35] F. Tanaka, R. Thayumanavan, N. Mase, C. F. Barbas, *Tetrahedron Lett.* **2004**, *45*, 325–328.
[36] Ch. Ji, Y. Peng, Ch. Huang, N. Wang, Y. Jiang, *Synlett* **2005**, 986–988.
[37] L. Hoang, S. Bahmanyar, K. N. Houk, B. List, *J. Am. Chem. Soc.* **2003**, *125*, 16–17.
[38] S. Bahmanyar, K. N. Houk, *J. Am. Chem. Soc.* **2001**, *123*, 11273–11283.
[39] B. List, L. Hoang, H. J. Martin, *Proc. Natl. Acad. Sci.* **2004**, *101*, 5839–5842.
[40] a) H. Iwamura, S. P. Mathew, D. G. Blackmond, *J. Am. Chem. Soc.* **2004**, *126*, 11770–11771; b) H. Iwamura, D. H. Wells, S. P. Mathew, M. Klaussmann, A. Armstrong, D. G. Blackmond, *J. Am. Chem. Soc.* **2004**, *126*, 16312–16313.
[41] S. K. Davidsen, P. D. May, J. S. Summers, *J. Org. Chem.* **1991**, *56*, 5482–5485.
[42] CrysAlis RED, Oxford Diffraction Ltd., Version 1.171.28cycle2 beta (release 25-10-2005 CrysAlis171.NET) (compiled Oct 25 2005, 08:50:05). Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.
[43] CrysAlis CCD, Oxford Diffraction Ltd., Version 1.171.28cycle2 beta; CrysAlis RED, Oxford Diffraction Ltd., Version 1.171.28cycle2 beta.
[44] G. M. Sheldrick, *Acta Crystallogr., Sect. A* **1990**, *46*, 467–473.
[45] G. M. Sheldrick, *SHELXL93, Program for the Refinement of Crystal Structures*, University of Göttingen, Germany.
[46] *International Tables for Crystallography* (Ed.: A. J. C. Wilson), Kluwer, Dordrecht, **1992**, vol. V.

Received: March 13, 2006
Published Online: June 29, 2006

