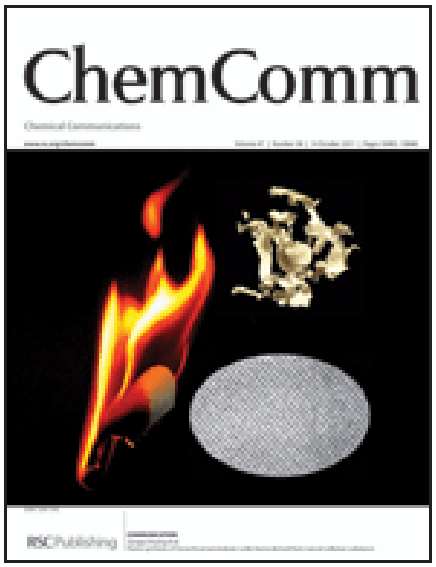

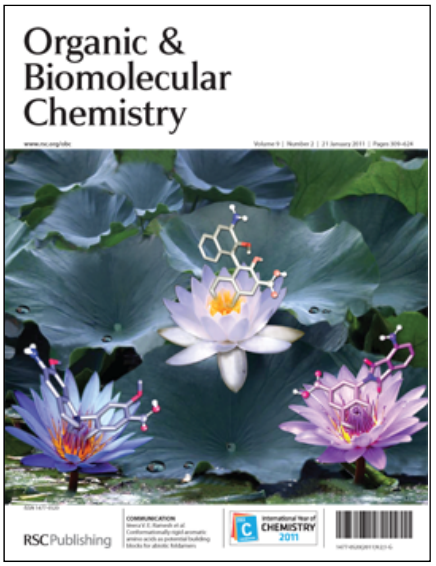

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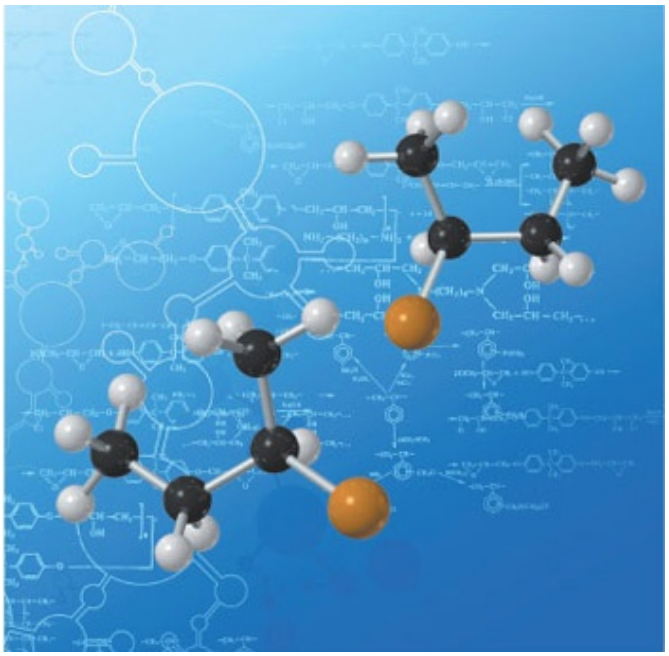

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PAPER

A tripeptide-like prolinamide-thiourea as an aldol reaction catalyst†‡

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A tripeptide-like prolinamide-thiourea catalyst with (*S*)-proline, (1*S*,2*S*)-diphenylethylenediamine and (*S*)-di-*tert*-butyl aspartate as building blocks provides the products of the reaction between ketones and aromatic aldehydes in high to quantitative yields and high stereoselectivities (up to 99 : 1 dr and 99% ee). Both the chiral centers of the diamine unit are essential, while the thiourea hydrogen originating from the amine and the amide hydrogen play a predominant role for the catalyst efficiency.

Introduction

The majority of organocatalysts developed up to now for asymmetric organic transformations[1] employ more than one functionality in the catalytic mechanism that acts through either covalent or non-covalent interactions.[2,3] The asymmetric aldol reaction is a powerful method for the construction of carbon–carbon bonds in an enantioselective fashion.[4,5] The most important improvement in the field of organocatalysed aldol reaction has been the development of catalysts combining the prolinamide unit with functionalities able to act as hydrogen bond donors. Representative examples of such prolinamides that efficiently catalyze asymmetric aldol reactions are shown in Fig. 1 (compounds **1–5**).[6–10]

Recently, we have presented catalyst **6** based on (*S*)-proline and (1*S*,2*S*)-diphenylethylenediamine, which provided the products of the reactions between ketones and aromatic aldehydes in high to quantitative yields and with high stereoselectivities.[11] Amide **6** bearing a thiourea group was designed based on the assumption that the pyrrolidine group would activate the nucleophile, while both the amide group and the thiourea functionality would activate the electrophile through hydrogen bonding.[11] However, there is no experimental evidence about which of the amide hydrogen or the thiourea hydrogens is really involved in the formation of hydrogen bonds. A study on the structural requirements of the prolinamide-thiourea was undertaken in order to achieve optimum reactivity.

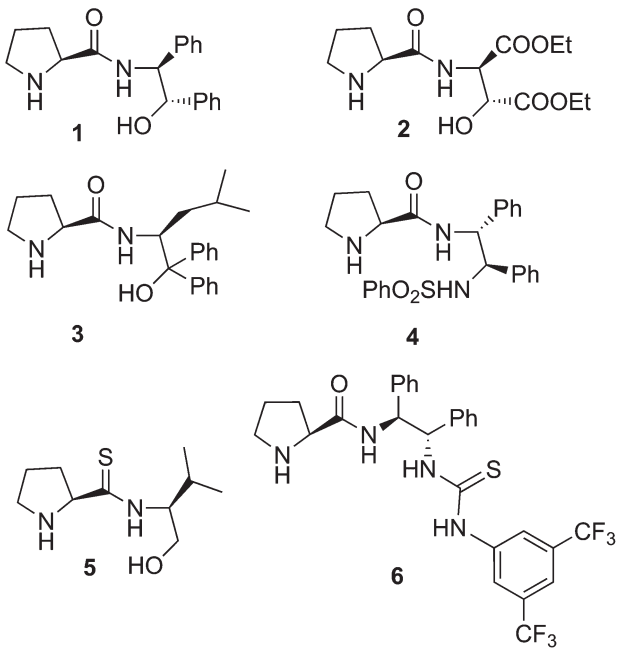

Fig. 1 Some known prolinamide catalysts.

Results and discussion

In the present manuscript, our aim was to clarify the importance of the presence of: (a) a new chiral center in the amine of the thiourea, (b) the stereogenic centers of the diamine unit, (c) a thioamide instead of an amide bond, (d) an additional proline residue and (e) the hydrogen bond donors of the catalyst (amide hydrogen and hydrogen atoms of the thiourea group). At the beginning, the aromatic moiety of the thiourea was substituted by the chiral bulky unit of a *tert*-butyl ester of an α-amino acid (catalysts **7** and **8**, Fig. 2). The chiral bulky group is expected to help on placing the electrophile on the appropriate orientation, thus determining the face of the electrophile attack.

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‡ Electronic supplementary information (ESI) available: For detailed experimental procedures, NMR and HPLC data. See DOI: 10.1039/c2ob25693b

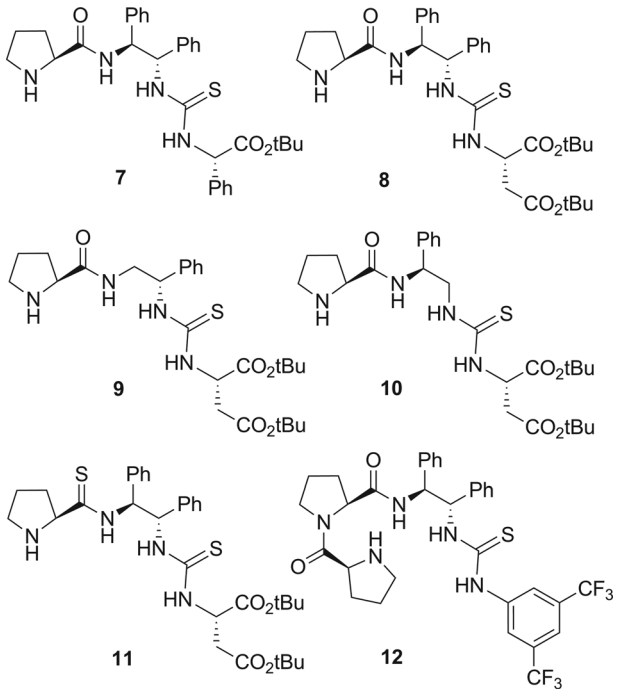


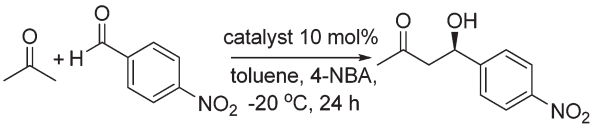
Fig. 2 Catalysts **7**–**12** employed in this study.

Simultaneously, it would efficiently block the back face of the transition intermediate. Starting from commercially available Fmoc-L-proline and utilizing either *tert*-butyl phenylglycinate or di-*tert*-butyl aspartate,[12] catalysts **7** and **8** were synthesized (for full experimental procedures for the synthesis of the catalysts utilized, see ESI‡).

The stereochemistry of the phenyl moieties on the chiral diamine backbone was postulated to play a crucial role on the conformation adopted by the catalyst. In an optimum scenario, these moieties should bring the thiourea moiety in close proximity to the area where the electrophile is placed in the transition intermediate. To assess the role of the chiral backbone of the diamine in the reactivity of the catalyst, compounds **9** and **10** were synthesized (Fig. 2). Since a number of catalysts exist in the literature bearing thioamide functionalitilies,[10,13] catalyst **11** was next synthesized employing Lawesson's reagent to introduce the sulfur of the thioamide (Fig. 2). Moreover, a number of peptide catalysts have emerged as efficient organocatalysts for organic transformations,[14] thus, the peptide-like catalyst **12** was prepared to be evaluated (Fig. 2).

The reaction of acetone with 4-nitrobenzaldehyde is a usual model reaction to study the efficacy of new organocatalysts. At the beginning, the catalytic activity of all catalysts that were synthesized was evaluated under our previous optimized reaction conditions utilizing toluene as a solvent at −20 °C for 24 hours (Table 1). From our previous studies, we had already showed that prolinamides bearing (1*S*,2*S*)-diphenylethylenediamine instead of (1*R*,2*R*)-diphenylethylenediamine, led to better results indicating that the conformation of the catalyst is extremely important for high catalytic activity (entry 1 *vs.* entry 2, Table 1).[11] The catalysts based on *tert*-butyl phenylglycinate (**7**) led to similar results, while the one based on di-*tert*-butyl aspartate provided the product in quantitative yield and excellent

Table 1 Direct asymmetric aldol reaction between acetone and 4-nitrobezaldehyde using various catalysts



Entry	Catalyst	Yield[a] (%)	ee[b] (%)
1	**6**[11]	95	97
2	**6** (*R*,*R*)[11]	70	82
3	**7**	96	96
4	**8**	100	99
5	**9**	97	58
6	**10**	70	4
7	**11**	100	97
8	**12**	53	5

[a] Isolated yield. [b] The enantiomeric excess (ee) was determined by chiral HPLC. 4-NBA: 4-nitrobenzoic acid.

enantioselectivity (99% ee) (entries 3 and 4, Table 1). The steric hindrance provided by the side chain bulky *tert*-butyl ester of aspartic acid could be the reason for the slight increase on the enantioselectivity. The bulkiness provides additional blocking of the back face and also control the face of the attack of the electrophile by pushing the aryl moiety away from it. In order to shed light on whether the chiral backbone of the diphenylethylene diamine played any role in the catalytic activity, catalysts **9** and **10** were evaluated. As shown in entries 5 and 6 of Table 1, a phenyl group on both chiral centers is required otherwise the enantioselectivity is considerably lower. It seems that both phenyl groups are necessary to the current chirality in order for the catalyst to adopt the appropriate conformation for high catalytic activity. When one of the chiral centers and the phenyl moiety is missing a different conformation is adopted which leads to diminished catalytic activity. The use of thioamide **11** led to similar results as those obtained with catalyst **8** (entry 7, Table 1). Thus, subtle changes in the hydrogen bonding power of the prolinamide unit provide alterations in the catalytic activity, showing that this amide bond is most likely taking part in influencing the outcome of the reaction. Peptide-like catalyst **12** led to far inferior results, thus leading to the conclusion that adding a prolyl unit in the catalyst does not lead to the appropriate conformation for high reactivity being adopted (entry 8, Table 1). We assume that moving the pyrrolidine nitrogen and the hydrogen bonding sites of the catalyst further apart (changing the optimum distance), as well as the lack of the α-amide in relation to the free pyrrolidine nitrogen are the key reasons for this deterioration in both reactivity and selectivity.

From Table 1, it is quite obvious that the prolinamide unit and the (1*S*,2*S*)-diphenylethylenediamine chiral moiety, as well as the thiourea moiety are required for high catalytic activity. Moreover, when the aromatic moiety on the thiourea is replaced by a bulky chiral group such as di-*tert*-butyl aspartate, better results are obtained. To elucidate the role of each of the potential hydrogen bonding sites, derivative **13**, where the amide bond was replaced by an ester bond, and derivative **14**, where the thiourea hydrogen originating from the diamine residue was

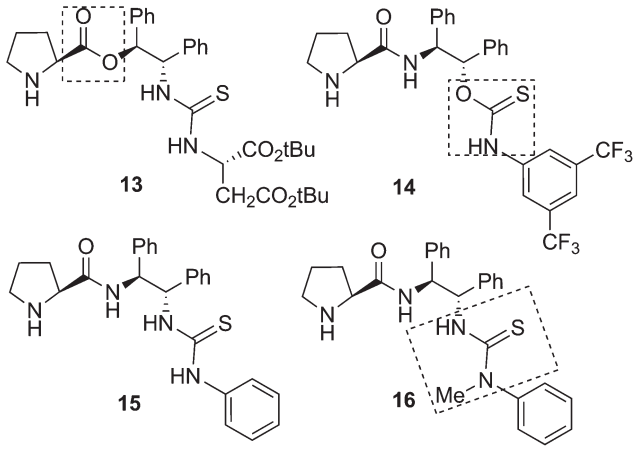
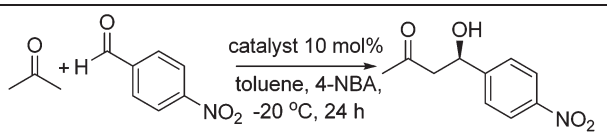


Fig. 3 New catalysts **13–16** to probe the necessity of each hydrogen bond.

Table 2 Direct asymmetric aldol reaction between acetone and 4-nitrobezaldehyde using various catalysts



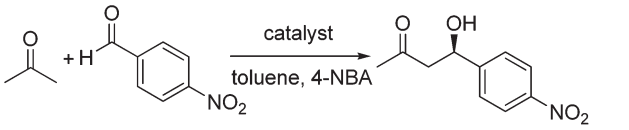
Entry	Catalyst	Yield[a] (%)	ee[b] (%)
1	**6**	95	97
2	**8**	100	99
3[c]	**13**	92	48
4[c]	**14**	79	70
5[c]	**15**	100	98
6[c]	**16**	98	29

[a] Isolated yield. [b] The enantiomeric excess (ee) was determined by chiral HPLC. [c] Reaction time: 48. 4-NBA: 4-nitrobenzoic acid.

replaced by an oxygen atom, were synthesized (Fig. 3, for the synthesis see the ESI‡). In addition, derivatives **15** and **16** were also synthesized. The results of the catalytic activity of these derivatives are summarized in Table 2. Derivative **13** provided the product in high yield and moderate ee (entry 3 *vs.* entry 2, Table 2) clearly demonstrating the involvement of the amide hydrogen in the transition state. When the aromatic part of the thiourea is just a phenyl group, the catalytic results are similar to those observed with catalyst **6** (entry 5 *vs.* entry 1, Table 2). However, a dramatic loss of the enantioselectivity was observed, when the NH of the thiourea was replaced by NMe (entry 6 *vs.* entries 1 and 5, Table 2). The low ee (29%) highlights the importance of that NH for the outcome of the reaction. Finally, the replacement of the NH by O in derivative **14**, led to mediocre enantioselectivity (entry 4 *vs*. entry 1, Table 2). Taken together, the importance of the hydrogen bond donors of the catalyst follows the order: thiourea hydrogen originating from the amine > amide hydrogen > thiourea hydrogen originating from the diamine.

We then turned our attention to the direct comparison of the new catalyst **8** with catalyst **6** (Table 3). Although the catalyst

Table 3 Comparison of catalysts **6** and **8** on the direct asymmetric aldol reaction between acetone and 4-nitrobenzaldehyde[a]



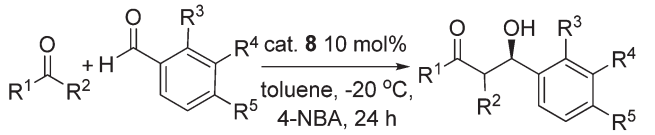
Entry	Catalyst, loading (mol%)	Time (h)	Temp. (°C)	Yield[a] (%)	ee[b] (%)
1	**8**, 10	24	r.t.	100	63
2	**6**, 10	24	r.t.	98	87
3	**8**, 10	24	0	96	93
4	**6**, 10	24	0	94	94
5	**8**, 10	24	−20	100	99
6	**6**, 10	24	−20	95	97
7	**8**, 5	48	−20	98	98
8	**6**, 5	48	−20	90	97
9	**8**, 2	48	−20	63	98
10	**6**, 2	48	−20	58	97
11	**8**, 5	48	−40	77	99
12	**6**, 5	48	−40	46	98

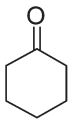
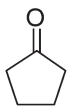
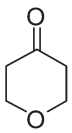
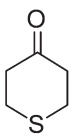
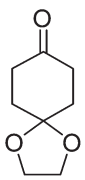
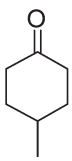
[a] Isolated yield. [b] The enantiomeric excess (ee) was determined by chiral HPLC.

based on aspartic acid leads to quantitative yield at room temperature, the enantioselectivity is quite low compared with the results obtained with catalyst **6** (entry 1 *vs.* entry 2, Table 3). However, when the temperature is decreased to 0 °C, both catalysts behave similarly (entry 3 *vs.* entry 4, Table 3). Decreasing the temperature even more and going to optimum catalyst conditions, the results are reversed and now catalyst **8** based on aspartic acid leads to quantitative yield and almost complete stereocontrol, outperforming catalyst **6** (entry 5 *vs.* entry 6, Table 3). Thus, it is obvious that the enantioselectivity induced by catalyst **8** is highly dependent on temperature, while in the case of catalyst **6**, there is a dependence but not to the same extent. When the catalyst loading was decreased down to 5 mol%, catalyst **8** continued to provide the desired product in almost quantitative yield and excellent enantioselectivity, while catalyst **6** led to inferior results (entry 7 *vs.* entry 8, Table 3). In both cases, prolonged reaction time was needed. Trying to identify the limits of both catalysts, the catalyst loading was dropped to 2 mol%. Still the catalyst based on aspartic acid was slightly better (entry 9 *vs.* entry 10, Table 3). Finally, when the reaction was performed at −40 °C, catalyst **8** outperformed catalyst **6** (entry 11 *vs.* entry 12, Table 3).

Having established catalyst **8** as the optimum catalyst, the scope and limitations were sought and the results are shown in Table 4. The reaction of acetone with aromatic aldehydes bearing electron-withdrawing groups led to excellent yields (82–100%) and high enantioselectivities (96–99%) (entries 1–4, Table 4). However, benzaldehyde produced the product in moderate yield, although in high enantioselectivity (entry 5, Table 4). Cyclic ketones such as cyclohexanone are well tolerated as well (entries 6–10, Table 4). When electron-withdrawing groups existed on the aromatic ring, the products were obtained in excellent yields, high diastereoselectivity and enantioselectivity. While the use of 4-bromobenzaldehyde or benzaldehyde led to diminished yields but the diastereocontrol and enantiocontrol

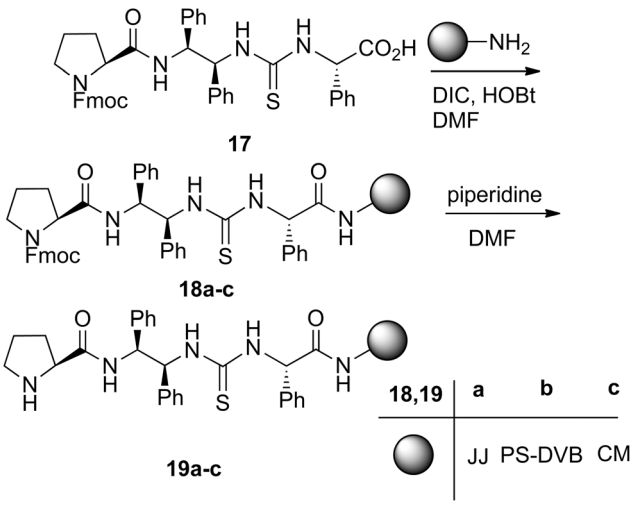
Table 4 Direct asymmetric aldol reaction between ketones and various aldehydes using catalyst **8**



Entry	Ketone	Ar	Yield[a] (%)	dr[b]	ee[c] (%)
1		4-$NO_2C_6H_4$	100	—	99
2		2-$NO_2C_6H_4$	100	—	96
3		4-$CF_3C_6H_4$	100	—	99
4		3-CNC_6H_4	82	—	99
5[d]		C_6H_5	40	—	90
6		4-$NO_2C_6H_4$	100	95 : 5	99
7[d]		3-$NO_2C_6H_4$	95	93 : 7	97
8[d]		2-$NO_2C_6H_4$	92	94 : 6	98
9[d]		C_6H_5	57	>97 : 3	96
10[d]		4-BrC_6H_4	49	97 : 3	96
11		4-$NO_2C_6H_4$	100	35 : 65	99[e]
12[d]		4-$NO_2C_6H_4$	98	96 : 4	97
13[d]		–$NO_2C_6H_4$	86	99 : 1	93
14[d]		4-$NO_2C_6H_4$	66	96 : 4	92
15		4-$NO_2C_6H_4$	99	93 : 7	99

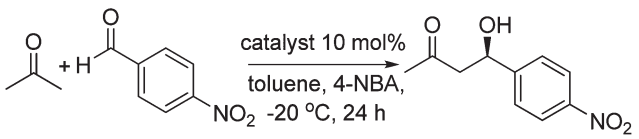
[a] Isolated yield. [b] The diastereomeric ratio (dr) was determined by ^{1}H NMR spectroscopy and refers to the *anti* : *syn* ratio. [c] The enantiomeric excess (ee) was determined by chiral HPLC. [d] The reaction time was 48. [e] 86% ee for the *anti*, 99% ee for *syn*.

remained high. When cyclopentanone was utilized, a reverse in the diastereocontrol was observed. In most cases, the reaction occurred with high *anti* stereoselectivity, however, in the case of cyclopentanone, the *syn* product was the predominant diastereomer (entry 11, Table 4). A number of cyclic ketones reacted with 4-nitrobenzaldehyde providing the products in varying yields (66–99%), high diastereoselectivities (96 : 4 to 99 : 1)[15] and excellent enantioselectivities (92–99% ee) (entries 12–14, Table 4). Finally, the desymmetrization of 4-substituted cyclohexanones was found to be possible. When 4-methyl cyclohexanone was utilized, quantitative yield was obtained along with high stereo- and enantiocontrol (entry 15, Table 4).



Scheme 1 Synthesis of catalysts **19a–c**.

Table 5 Direct asymmetric aldol reaction between acetone and 4-nitrobezaldehyde using various catalysts



Entry	Catalyst	Yield[a] (%)	ee[b] (%)
1	**19a**	31	70
2[c]	**19a**	64	15
3[c,d]	**19a**	61	34
4	**19b**	35	68
5[c]	**19b**	54	38
6	**19c**	42	69
7[c]	**19c**	71	41

[a] Isolated yield. [b] The enantiomeric excess (ee) was determined by chiral HPLC. [c] The reaction took place at room temperature. [d] 50 mol% catalyst was employed. 4-NBA: 4-nitrobenzoic acid.

Solid-supported catalysts present a number of advantages.[16] Organocatalysts have been successfully employed in the synthesis of solid-supported systems that present distinct catalytic activities.[17] Thus, we envisaged the incorporation of our catalyst on a number of commercially available resins (Scheme 1). In this study, JandaJel (JJ), polystyrene-divinylbenzene (PS-DVB) and CM (ChemMatrix) resins were employed, coupled with intermediate **17** and deprotection of the Fmoc group furnished the desired solid-supported organocatalysts **19a–c**. Unfortunately, when the catalyst was anchored on the solid support, the catalytic activity dropped significantly (entries 1–7, Table 5). Utilising the JandaJel (JJ) resin, low yield and diminished enantioselectivity were observed, while performing the reaction at room temperature or using higher catalyst loading did not improve the catalytic activity (entries 1–3, Table 5). The PS-DVB resin had similar reactivity both at low temperature and room temperature (entries 4 and 5, Table 5). Finally, the use of CM resin led to slightly improved yield but the enantioselectivity

still remained mediocre (entry 6, Table 5). When the reaction was performed at room temperature, the yield was increased in the expense of the enantioselectivity (entry 7, Table 5).

From the above studies, we come to the conclusion that an efficient prolinamide-thiourea may have optimized activity for the aldol reaction when it contains: (a) the (*S*)-prolinamide unit, (b) the (1*S*,2*S*)-diphenylethylenediamine unit and (c) the thiourea functionality involving the amino group of a chiral bulky amino acid (preferably di-*tert*-butyl aspartate). It has to be noted that we have reported that a primary amine thiourea consisting of (1*S*,2*S*)-diphenylethylenediamine and (*S*)-di-*tert*-butyl aspartate is a very efficient catalyst for the Michael reaction.[12a] It is apparent that by adding just one proline residue, we may convert this catalyst to a new catalyst efficient for the enantioselective aldol reaction.

Conclusions

In conclusion, in this work we present our studies to understand the structural features that a prolinamide-thiourea has to include in order to catalyze the enantioselective aldol reaction. It has been proven that both the chiral centers of the diamine unit are essential, while the thiourea hydrogen originating from the amine and the amide hydrogen play a predominant role in the hydrogen bonding. These studies led to the tripeptide-like catalyst **8** which effectively catalyzes this reaction. An application of this improved organocatalyst has already been shown[18] and its use in other asymmetric organic transformations is under way.

Experimental section

General information

Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of products was accomplished using forced-flow chromatography on Merck Kieselgel 60 F_{254} 230–400 mesh. Thin-layer chromatography (TLC) was performed on aluminum backed silica plates (0.2 m, 60 F_{254}). Visualization of the developed chromatogram was performed by fluorescence quenching using phosphomolybdic acid, anisaldehyde or ninhydrin stains. Melting points were determined on a Buchi 530 hot stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on Varian Mercury (200 MHz or 50 MHz) and are internally referenced to residual protio solvent signals ($CDCl_3$). Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet, bs = broad signal, bs m = broad signal multiplet), coupling constant and assignment. Wherever rotamers exist, are presented in brankets. Data for ^{13}C NMR are reported in terms of chemical shift (δ ppm). Mass spectra were recorded on a Finnigan Surveyor MSQ Plus, with only molecular ions and major peaks being reported with intensities quoted as percentages of the base peak. High performance liquid chromatography (HPLC) was used to determine enantiomeric excesses and was performed on a Agilent 1100 Series apparatus using Chiralpak® AD-H, OD-H, AS-H and AD-RH columns. The configuration of the products has been assigned by comparison to literature data. Optical rotations were measured on a Perkin Elmer 343 polarimeter. Catalysts **6**, **6** (*R*,*R*), **7** and **8** have been synthesized following our previous protocols.[11] For detailed synthetic procedures for the synthesis of the catalysts utilized in this study, see the ESI.‡

(*S*)-*tert*-Butyl 2-{3-[(1*S*,2*S*)-1,2-diphenyl-2-[(*S*)-pyrrolidine-2-carboxamido]ethyl]thioureido}-2-phenylacetate (7). Light yellow solid; 0.11 g, 99% yield; mp 79–81 °C; $[\alpha]_D$ = +24.7 (c = 1.0, CH_3OH); ^{1}H NMR (200 MHz, CD_3OD) δ 7.47–6.98 (15H, m, ArH), 6.03–5.86 (2H, m, 2 × NCH), 5.19 (1H, d, J = 10.6 Hz, NCH), 3.79–3.21 (1H, m, NCH), 2.99–2.60 (2H, m, NCH_2), 1.95–1.43 (4H, m, 4 × C*H*H),1.30 [9H, s, $C(CH_3)_3$]; ^{13}C NMR (50 MHz, CD_3OD) δ 184.2 (184.0) (C═S), 176.2 (176.6) (CO), 171.4 (171.7) (CO), 140.2 (Ar), 139.8 (Ar), 138.0 (Ar), 129.7 (Ar), 129.6 (Ar), 129.4 (Ar), 129.2 (Ar), 128.8 (Ar), 128.7 (Ar), 128.6 (Ar), 128.5 (Ar), 83.2 (82.8) [$C(CH_3)_3$], 63.6 (NCH), 62.7 (NCH), 61.4 (NCH), 60.1 (NCH), 46.6 (NCH_2), 31.6 (CH_2), 27.9 (28.1) [$C(CH_3)_3$], 26.5 (CH_2); MS (ESI) 559 (M + H^+, 100%); HRMS exact mass calculated for [M + H]$^+$ ($C_{32}H_{39}O_3N_4S$) requires m/z 559.2737, found m/z 559.2733.

(*S*)-Di-*tert*-butyl 2-{3-[(1*S*,2*S*)-1,2-diphenyl-2-[(*S*)-pyrrolidine-2-carboxamido]-ethyl]thioureido}succinate (8). White solid; 0.11 g, 99% yield; mp 89–91 °C; $[\alpha]_D$ = +35.3 (c = 0.88, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.56 (1H, d, J = 8.6 Hz, NH), 8.05–7.87 (1H, br m, NH), 7.46–7.01 (10H, m, ArH), 6.92–6.66 (1H, br m, NH), 5.98–5.65 (1H, m, NCH), 5.33–5.06 (2H, m, 2 × NCH), 3.97–3.68 (1H, m, NCH), 3.09–2.76 (4H, m, CH_2CO_2tBu, NCH_2), 2.19–2.03 (1H, m, C*H*H), 1.87–1.55 (4H, m, 3 × C*H*H, NH), 1.43 [9H, s, $C(CH_3)_3$], 1.36 [9H, s, $C(CH_3)_3$]; ^{13}C NMR (50 MHz, $CDCl_3$) δ 182.6 (C═S), 170.4 (CO), 170.1 (CO), 169.9 (CO), 138.7 (Ar), 138.6 (Ar), 128.5 (Ar), 128.3 (Ar), 128.0 (Ar), 127.7 (Ar), 127.5 (Ar), 127.4 (Ar), 82.2 [$C(CH_3)_3$], 81.4 [$C(CH_3)_3$], 64.2 (NCH), 60.3 (NCH), 58.8 (NCH), 54.0 (NCH), 47.1 (NCH_2), 37.8 (CH_2CO_2tBu), 30.5 (CH_2), 28.0 [$C(CH_3)$], 27.9 [$C(CH_3)$], 25.8 (CH_2); MS (ESI) 597 (M + H^+, 100%); HRMS exact mass calculated for [M + H]$^+$ ($C_{32}H_{45}O_5N_4S$) requires m/z 597.3105, found m/z 597.3100.

(*S*)-Di-*tert*-butyl 2-{3-[(*S*)-1-phenyl-2-[(*S*)-pyrrolidine-2-carboxamido]ethyl]thioureido}succinate (9). Light yellow solid; 0.16 g, 92% yield; mp 52–54 °C; $[\alpha]_D$ = −8.6 (c = 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.27–7.99 (2H, m, 2 × NH), 7.43–7.08 (6H, m, ArH, NH), 5.29–5.09 (1H, m, NCH), 4.29–4.11 (1H, m, NCH), 3.93–3.34 (3H, m, NCH, 2 × NC*H*H), 3.00–2.72 (4H, m, CH_2CO_2tBu, NCH_2), 2.11–1.51 (5H, m, 4 × C*H*H, NH), 1.33 [9H, s, $C(CH_3)_3$], 1.30 [9H, s, $C(CH_3)_3$]; ^{13}C NMR (50 MHz, $CDCl_3$) δ 182.7 (C═S), 175.3 (CO), 170.1 (CO), 169.9 (CO), 139.1 (Ar), 128.3 (Ar), 127.3 (Ar), 126.5 (Ar), 81.7 [$C(CH_3)_3$], 80.9 [$C(CH_3)_3$], 60.0 (NCH), 58.2 (NCH), 57.9 (NCH), 53.8 (NCH_2), 46.7 (NCH_2), 37.6 (CH_2CO_2tBu), 30.3 (CH_2), 27.8 [$C(CH_3)_3$], 27.7 [$C(CH_3)_3$], 25.4 (CH_2); MS (ESI) 521 (M + H^+, 100%); HRMS exact mass calculated for [M + H]$^+$ ($C_{26}H_{41}O_5N_4S$) requires m/z 521.2792, found m/z 521.2783.

(*S*)-Di-*tert*-butyl 2-{3-[(*S*)-2-phenyl-2-[(*S*)-pyrrolidine-2-carboxamido]ethyl]thioureido}succinate (10). Yellow solid; 0.12 g,

97% yield; mp 73–75 °C; $[\alpha]_D$ = +19.4 (*c* = 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 8.46–8.18 (1H, m, NH), 7.69–7.13 (7H, m, ArH, 2 × NH), 5.66–5.34 (1H, m, NCH), 4.49–3.58 (4H, m, NCH_2, 2 × NCH), 3.23–2.52 (4H, m, CH_2CO_2tBu, NCH_2), 2.29–1.57 (5H, m, 4 × C*H*H, NH), 1.40 [18H, s, 2 × C$(CH_3)_3$]; ^{13}C NMR (50 MHz, $CDCl_3$) δ 183.6 (C═S), 175.2 (CO), 173.6 (CO), 169.2 (CO), 138.5 (Ar), 128.8 (Ar), 127.8 (Ar), 126.3 (Ar), 82.4 [*C*$(CH_3)_3$], 82.2 [*C*$(CH_3)_3$], 60.4 (NCH), 55.6 (NCH), 51.2 (NCH), 51.0 (NCH_2), 46.9 (NCH_2), 36.2 (CH_2CO_2tBu), 30.3 (CH_2), 27.9 [C(*C*$H_3)_3$], 27.9 [C(*C*$H_3)_3$], 25.9 (CH_2); MS (ESI) 521 (M + H^+, 100%); HRMS exact mass calculated for $[M + H]^+$ ($C_{26}H_{41}O_5N_4S$) requires *m*/*z* 521.2792, found *m*/*z* 521.2782.

(*S*)-Di-*tert*-butyl 2-{3-[(1*S*,2*S*)-1,2-diphenyl-2-[(*S*)-pyrrolidine-2-carbothioamido]-ethyl]thioureido}succinate (11). White solid; 0.04 g, 98% yield; mp 82–84 °C; $[\alpha]_D$ = +21.4 (*c* = 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 10.86 (1H, br s, NHC═S), 7.73–7.07 (12H, m, ArH, 2 × NH), 6.89–6.38 (1H, m, NCH), 6.21–5.84 (1H, m, NCH), 5.25–4.93 (1H, m, NCH), 4.32–4.01 (1H, m, NCH), 3.28–2.67 (4H, m, CH_2CO_2tBu, NCH_2), 2.47–1.65 (5H, m, 4 × C*H*H, NH), 1.43 [9H, s, C$(CH_3)_3$], 1.39 [9H, s, C$(CH_3)_3$]; ^{13}C NMR (50 MHz, $CDCl_3$) δ 205.7 (C═S), 181.5 (NHC═SNH), 170.2 (CO), 169.8 (CO), 137.9 (Ar), 136.9 (Ar), 128.7 (Ar), 128.5 (Ar), 128.1 (Ar), 127.8 (Ar), 82.5 [*C*$(CH_3)_3$], 81.9 [*C*$(CH_3)_3$], 67.9 (NCH), 63.2 (NCH), 62.8 (NCH), 54.1 (NCH), 47.2 (NCH_2), 38.0 (CH_2CO_2tBu), 29.7 (CH_2), 28.0 [C(*C*$H_3)_3$], 27.9 [C(*C*$H_3)_3$], 25.8 (CH_2); MS (ESI) 623 (M + H^+, 100%); HRMS exact mass calculated for $[M + H]^+$ ($C_{32}H_{45}O_4N_4S_2$) requires *m*/*z* 613.2877, found *m*/*z* 613.2874.

(*S*)-N-((1S,2S)-2-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)-1,2-diphenylethyl)-1-((*S*)-pyrrolidine-2-carbonyl)pyrrolidine-2-carboxamide (12). Light yellow solid; 0.07 g, 100% yield; mp 149–151 °C; $[\alpha]_D$ = −45.1 (*c* = 1.0, CH_3OH); ^1H NMR (200 MHz, CD_3OD) δ 8.24–8.13 (2H, m, 2 × ArH), 7.66–7.59 (1H, m, ArH), 7.36–7.08 (10H, m, ArH), 6.16 (1H, d, *J* = 9.6 Hz, NCH), 5.40 (1H, d, *J* = 9.6 Hz, NCH), 4.56–4.41 (1H, m, NCH), 4.00–3.84 (1H, m, NCH), 3.65–3.44 (2H, m, NCH_2), 3.14–2.63 (2H, m, NCH_2), 2.33–1.53 (8H, m, 8 × C*H*H); ^{13}C NMR (50 MHz, CD_3OD) δ 182.6 (C═S), 174.1 (173.9) (CO), 172.9 (172.8) (CO), 143.0 (Ar), 140.0 (Ar), 139.7 (Ar), 132.7 (q, *J* = 33.1 Hz, Ar), 129.6 (Ar), 129.5 (Ar), 129.1 (Ar), 128.9 (Ar), 128.7 (Ar), 128.6 (Ar), 124.7 (q, *J* = 272.3 Hz, CF_3), 123.5 (Ar), 117.9 (Ar), 63.9 (NCH), 61.7 (NCH), 60.0 (NCH), 59.8 (NCH), 48.2 (NCH_2), 48.0 (NCH_2), 30.7 (CH_2), 30.4 (CH_2), 26.7 (CH_2), 25.8 (CH_2); MS (ESI) 678 (M + H^+, 100%); HRMS exact mass calculated for $[M + H]^+$ ($C_{33}H_{34}F_6O_2N_5S$) requires *m*/*z* 678.2332, found *m*/*z* 678.2322.

(*S*)-Di-*tert*-butyl 2-(3-((1*S*,2*S*)-1,2-diphenyl-2-((*S*)-pyrrolidine-2-carbonyloxy) ethyl)thioureido)succinate (13). White solid; 0.07 g, 95% yield; mp 60–62 °C; $[\alpha]_D$ = +16.4 (*c* = 1.0, $CHCl_3$); IR (film) 3347, 2916, 2848, 1732, 1556, 1219, 1152, 772 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.43–6.88 (12H, m, ArH, 2 × NH), 6.19–6.01 (1H, m, NCH), 5.26–5.04 (1H, m, OCH), 3.88–3.68 (1H, m, NCH), 3.18–2.74 (5H, m, CH_2CO, NCH_2 and NCH), 2.25–2.01 (1H, m, C*H*H), 1.99–1.57 (4H, m, 3 × C*H*H and NH), 1.40 [9H, s, C$(CH_3)_3$], 1.35 [9H, s, C$(CH_3)_3$]; ^{13}C NMR (50 MHz, $CDCl_3$) δ 182.2 (C═S), 174.8 (174.5) (CO), 170.6 (CO), 170.0 (169.7) (CO), 137.6 (Ar), 136.4 (Ar), 128.3 (Ar), 128.2 (Ar), 127.7 (Ar), 127.4 (Ar), 127.2 (Ar), 126.9 (Ar), 82.2 [*C*$(CH_3)_3$], 81.2 [*C*$(CH_3)_3$], 78.1 (77.2) (OCH), 62.3 (NCH), 59.7 (NCH), 54.2 (NCH), 46.7 (NCH_2), 37.6 (CH_2CO), 30.0 (CH_2), 28.0 [C(*C*$H_3)_3$], 27.8 [C(*C*$H_3)_3$], 25.2 (CH_2); MS (ESI) 598 (M + H^+, 100%); HRMS exact mass calculated for $[M + H]^+$ ($C_{32}H_{44}O_6N_3S$) requires *m*/*z* 598.2945, found *m*/*z* 598.2927.

(*S*)-2-[(1*S*,2*S*)-2-3,5-Bis(trifluoromethyl)phenylcarbamothioyloxy]-1,2-diphenylethylcarbamoyl) pyrrolidinium 2,2,2-trifluoroacetate (14). White solid; 0.11 g, 91% yield; mp 97–99 °C; $[\alpha]_D$ = −9.3 (*c* = 1.0, $CHCl_3$); IR (film) 3238, 2917, 2849, 1735, 1672, 1563, 1379, 1218, 1180, 1136, 772 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) δ 8.18–8.01 (2H, m, ArH), 7.74–6.96 (13H, m, 11 × ArH, 2 × NH), 6.32 (0.6H, d, *J* = 12 Hz, OCH), 6.14 (0.4H, dd, *J* = 7.2 Hz and 4.0 Hz, OCH), 4.58–4.46 (0.5H, m, NCH), 4.44–4.26 (0.5H, m, NCH), 4.21–3.98 (1H, m, NCH), 3.31–3.06 (2H, m, NCH_2), 2.57–1.63 (6H, m, 4 × C*H*H, 2 × NH); ^{13}C NMR (50 MHz, CD_3OD) δ 188.5 (C═S), 168.4 (q, *J* = 15.9 Hz, $CF_3CO_2^-$) 168.7 (168.2) (CO), 142.8 (143.5) (Ar), 142.2 (142.5) (Ar), 141.7 (141.8) (Ar), 133.2 (q, *J* = 33.2 Hz, Ar), 130.2 (Ar), 129.6 (Ar), 129.2 (Ar), 129.1 (Ar), 128.1(Ar), 127.4 (Ar), 124.5 (q, *J* = 272.1 Hz, CF_3), 119.8 (Ar), 117.4 (Ar), 114.9 (q, *J* = 243.9 Hz, CF_3), 76.9 (80.7) (OCH), 60.7 (m, NCH), 57.9 (58.6) (m, NCH), 47.2 (m, NCH_2), 30.6 (m, CH_2), 24.5 (m, CH_2); MS (ESI) 582 (M + H^+, 100%); HRMS exact mass calculated for $[M + H]^+$ ($C_{28}H_{26}F_6O_2N_3S$) requires *m*/*z* 582.1644, found *m*/*z* 582.1626.

(*S*)-*N*-((1*S*,2*S*)-1,2-Diphenyl-2-(3-phenylthioureido) ethyl) pyrrolidine-2-carboxamide (15). White solid; 0.05 g, 100% yield; mp 85–88 °C; $[\alpha]_D$ = −25.8 (*c* = 1.0, $CHCl_3$); IR (film) 3303, 2916, 2849, 1735, 1665, 1540, 1465, 1218, 772 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.04 (1H, s, NH), 8.63 (1H, d, *J* = 9.4 Hz, NH), 7.86 (1H, d, *J* = 8.8 Hz, ArH), 7.56–6.15 (15H, m, 14 × ArH and NH), 6.07 (1H, t, *J* = 9.0 Hz, NCH), 5.29 (1H, t, *J* = 9.8 Hz, NCH), 3.67 (1H, dd, *J* = 4.2 Hz, *J* = 6.2 Hz, NCH), 3.15–2.63 (3H, m, NCH_2, NH), 2.16–1.35 (4H, m, 4 × C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 180.8 (C═S), 175.0 (CO), 137.9 (Ar), 137.4 (Ar), 129.1 (Ar), 128.4 (Ar), 128.2 (Ar), 127.5 (Ar), 127.4 (Ar), 127.3 (Ar), 125.9 (Ar), 124.3 (Ar), 63.3 (NCH), 60.2 (NCH), 58.8 (NCH), 46.6 (NCH_2), 29.9 (CH_2), 25.4 (CH_2); MS (ESI) 445 (M + H^+, 100%); HRMS exact mass calculated for $[M + H]^+$ ($C_{26}H_{29}ON_4S$) requires *m*/*z* 445.2057, found *m*/*z* 445.2038.

(*S*)-*N*-((1*S*,2*S*)-2-(3-Methyl-3-phenylthioureido)-1,2-diphenylethyl)pyrrolidine-2-carboxamide (16). White solid; 0.06 g, 100% yield; mp 55–57 °C; $[\alpha]_D$ = −112.5 (*c* = 1.0, $CHCl_3$); IR (film) 3248, 2916, 2848, 1735, 1651, 1515, 1465, 1218, 772 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.38 (1H, d, *J* = 9.0 Hz, NH), 7.62–7.39 (3H, m, ArH), 7.38–6.89 (9H, m, ArH), 6.88–6.69 (3H, m, ArH), 6.48 (1H, d, *J* = 8.0 Hz, NH), 5.87 (1H, t, *J* = 8.8 Hz, NCH), 4.99 (1H, t, *J* = 9.2 Hz, NCH), 3.83–3.35 (4H, m, NCH_3, NCH), 3.02–2.57 (3H, m, NCH_2, NH), 2.16–1.91 (1H, m, C*H*H), 1.79–1.38 (3H, m, 3 × C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 181.5 (C═S), 174.8 (CO), 142.6 (Ar), 138.7 (Ar), 138.2 (Ar), 130.4 (Ar), 128.5 (Ar), 128.3 (Ar),

128.2 (Ar), 128.0 (Ar), 127.4 (Ar), 127.3 (Ar), 126.9 (Ar), 64.3 (NCH), 60.3 (NCH), 58.0 (NCH), 47.0 (NCH_2), 43.2 (NCH_3), 30.3 (CH_2), 25.8 (CH_2); MS (ESI) 459 ($M + H^+$, 100%); HRMS exact mass calculated for $[M + H]^+$ ($C_{27}H_{31}ON_4S$) requires *m*/*z* 459.2213, found *m*/*z* 459.2196.

General procedure for the aldol reaction

To a stirring solution of catalyst **8** (8 g, 0.014 mol) in toluene (1.0 mL), 4-nitrobenzoic acid (2.5 g, 0.014 mol) was added. Aldehyde (0.14 mol) followed by ketone (1.40 mol) were added at −20 °C. The reaction mixture was left stirring at −20 °C until the reaction was complete (by TLC). The solvent was evaporated and the crude product was purified using flash column chromatography eluting with various mixtures of petroleum ether (40–60 °C): EtOAc. All characterization data for the aldol products are in accordance with literature. For full experimental data of the aldol products, see the ESI.‡

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