Pyrrolidine-Based Organocatalysts for Enantioselective Michael Addition of Cyclohexanone to *trans*-β-Nitrostyrene

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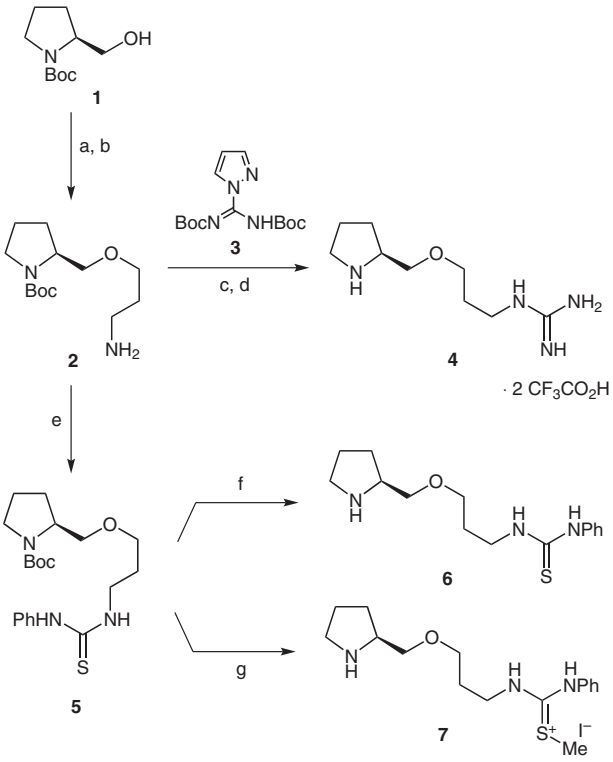
Abstract: A series of readily prepared bifunctional catalysts promote the Michael addition of cyclohexanone to *trans*-β-nitrostyrene with excellent asymmetric induction. The enantioselection (up to 97%) and diastereoselection (up to 95:5) is comparable to other pyrrolidine-thiourea organocatalysts recently reported, however, reaction times are often shorter.

Key words: addition reactions, asymmetric catalysis, Michael additions, bifunctional catalysis, nitroolefin

Enantioselective organocatalysis of the Michael addition of ketones to nitroalkenes[1,2] has been the focus of extensive recent effort, since synthetically valuable nitroalkane products bearing contiguous stereocentres are generated. Several chiral pyrrolidine-based catalysts have been developed and effective stereocontrol demonstrated via facial shielding of the expected enamine intermediate.[3] In particular, however, synergistic activation of both Michael donor and acceptor sites has been achieved with many elegant chiral diamine[4,5] and thiourea-amine[6,7] bifunctional catalyst systems. Bifunctional catalysis is believed to involve proline-catalysed formation of an enamine nucleophile[8] and activation of the nitroalkene via hydrogen bond formation with the thiourea motif,[9] and subsequent nitronate anion stabilisation in the same manner.

Although impressive progress towards improved stereoselectivity and substrate generality has been made, development of simple bifunctional systems of ready accessibility and improved catalytic activity remains of interest. Herein we wish to report the activity and stereocontrol exercised by L-proline-based organocatalysts, bearing tethered thiourea, thiouronium, or guanidinium functionality for dual catalysis of the conjugate addition of cyclohexanone to *trans*-β-nitrostyrene.

Candidate catalysts incorporating guanidinium **4**, thiourea **6**, or thiouronium **7** functionality, tethered to a proline-derived chiral pyrrolidine via an ether linkage, were readily prepared. Michael addition of *N*-Boc-L-prolinol (**1**) with acrylonitrile under phase-transfer conditions,[10] followed by nitrile reduction,[11] furnished **2**. Preparation of **4** was accomplished upon treatment of **2** with *N*,*N*′-bis-Boc-1-guanylpyrazole derivative **3**.[12] Coupling of primary amine **2** with phenyl isothiocyanate[13] was straightforward and subsequent N-deprotection furnished **6**, whilst thiourea methylation/N-deprotection steps gave **7** (Scheme 1).



Scheme 1 *Reagents and conditions*: (a) acrylonitrile, TBAI, aq 50% NaOH, toluene, r.t., 99% (**17**); (b) $NiCl_2$, $NaBH_4$, MeOH, r.t., 82% (**2**); (c) *N*,*N*′-bis-Boc-1-guanylpyrazole (**3**), THF, r.t., 31% (**18**); (d) 20% v/v TFA–CH_2Cl_2, r.t., 97% (**4**); (e) PhNCS, $CHCl_3$, MeOH, aq $NaHCO_3$, r.t., 82% (**5**); (f) 10% v/v TFA–CH_2Cl_2, r.t., then aq K_2CO_3, r.t., 98% (**6**); (g) MeI, acetone, r.t. 5 h, then 10% v/v TFA–CH_2Cl_2, r.t., then aq K_2CO_3, r.t., 88% (**7**).

We wished to investigate the nature and length of spacer separating the catalytic moieties and alternatively tethered organocatalysts **10a/b**, **12**, and **13** were also prepared.[14] Coupling of *N*-Boc-L-proline (**8**) with mono Cbz (benzyloxycarbonyl) protected diamines,[15] derived from 1,2-ethanediamine or 1,3-propanediamine, gave, after reduction, secondary amines **9a** and **9b**, respectively. Hydrogenolysis of **9a/b**, followed by coupling of each resulting bis-amine with 2 equivalents of PhNCS and removal of pyrrolidine *N*-Boc protection, gave bis-thioureas **10a/b**. *N*-Boc protection of **9a**, Cbz cleavage and coupling with PhNCS proved straightforward and **11** was obtained in good yield. Trifluoroacetic acid (TFA)-mediated *N*-Boc

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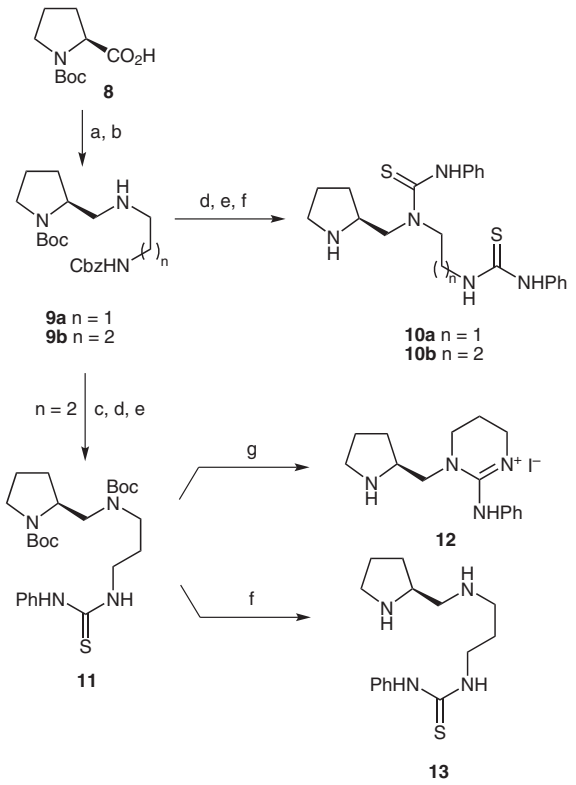
deprotection of **11** gave a thiourea functionalised chiral pyrrolidine **13** following basic workup. Further utility of **11** was also made; methylation to a thiouronium salt and global N-deprotection resulted in cyclisation upon basic workup and guanidinium **12** was isolated in excellent yield (Scheme 2).

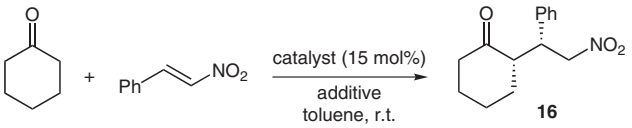


Scheme 2 *Reagents and conditions*: (a) benzyl (2-aminoethyl)carbamate (n = 1, HCl salt) or benzyl (3-aminopropyl)carbamate (n = 2, TFA salt), EDC, HOBt, *i*-Pr_2NEt, DMF–THF, 0 °C to r.t., 79% (**19**, n = 1), 71% (**20**, n = 2); (b) BH_3, THF, 0 °C to r.t., 69% (**9a**), 60% (**9b**); (c) $(Boc)_2O$, Et_3N, CH_2Cl_2, r.t., 69% (**25**); (d) Pd/C (10 mol%), H_2, MeOH, r.t., 96–ca. 100% (**21**, **23**, **26**); (e) PhNCS, $CHCl_3$, MeOH, aq $NaHCO_3$, r.t., 47–73% (**22**, **24**, **11**); (f) 10% v/v TFA–CH_2Cl_2, r.t., then aq K_2CO_3, r.t., 88% (**10a**), ca. 100% (**10b**), 85% (**13**); (g) MeI, acetone, r.t. 5 h, then 10% v/v TFA–CH_2Cl_2, r.t., then aq K_2CO_3, r.t., 98% (**12**).

As bis-secondary amine dual catalysis of the Michael addition between cyclic ketones and nitroalkenes has been described,[5c] we also prepared (*S*)-benzyl(pyrrolidin-2-ylmethyl)amine (**14**),[16] alongside (*S*)-2-(benzyloxymethyl)pyrrolidine (**15**),[17] in order to assess the influence of tethering amine/ether groups (Figure 1). Catalysis of the asymmetric Michael reaction of cyclohexanone with *trans*-β-nitrostyrene was now examined in the presence of added acetic acid and water[6c,7e] (Table 1).

Figure 1 Simple pyrrolidine organocatalysts

Table 1 Enantioselective Addition of Cyclohexanone to *trans*-β-Nitrostyrene[a]



Entry	Catalyst	Additive[b]	Time (h)	Conversion (%)[c]	dr (*syn*/*anti*)[d]	ee (%)[e] *syn*
1	**15**	–	720	23	91:9	94
2	**15**	AcOH–H_2O	720	10	91:9	93
3[f]	**4**	–	96	>90	92:8	71
4	**6**	–	24	>90	94:6	86
5	**6**	AcOH–H_2O	7	>90	94:6	78
6	**7**	–	24	>90	94:6	86
7	**7**	AcOH–H_2O	4	>90	94:6	80
8	**14**	–	120	>90	94:6	91
9	**14**	AcOH–H_2O	48	>90	95:5	90
10	**12**	AcOH–H_2O	12	>90	94:6	87
11	**13**	–	20	>90	91:9	87
12	**13**	AcOH–H_2O	7	>90	92:8	85
13	**10a**	–	120	>90	89:11	91
14	**10a**	AcOH–H_2O	9	>90	91:9	97
15	**10b**	–	144	>90	90:10	85
16	**10b**	AcOH–H_2O	4	>90	92:8	92

[a] The reaction was conducted with 0.5 mmol *trans*-β-nitrostyrene, 5.0 mmol cyclohexanone, and 15 mol% added catalyst in 0.75 mL toluene at r.t.
[b] Additive stoichiometry (entries 2, 5, 7, 9, 10, 12, 14, 16): 0.15 equiv AcOH and 1 equiv H_2O.
[c] Determined by HPLC analysis with naphthalene as internal standard. We chose to monitor the requisite reaction time for 90% conversion; unless this threshold had not been reached within 30 days, in which case the % conversion at that time is reported.
[d] Determined by reverse phase HPLC analysis of the diastereomeric mixture (MeCN–H_2O, 6:4).
[e] Determined by chiral HPLC analysis (Daicel Chiralpak AI, hexane–*i*-PrOH, 97:3).
[f] Carried out in the presence of 15 mol% added Et_3N.

Simple pyrrolidine **15** demonstrated good diastereo- and enantiocontrol of the Michael addition, however, conversion was low (Table 1, entries 1 and 2) and is indicative of the expected monofunctional activation of the cyclohexanone component only. Reaction time was improved in the presence of guanidinium-functionalised pyrrolidine **4**, however, to the detriment of enantioselectivity in comparison with **15** (entry 3). Ether tethered thiourea-pyrrolidine catalyst **6** demonstrated better activity and excellent diastereoselectivity both in the absence and presence of added acetic acid for catalysis of enamine formation,

although some loss of enantiocontrol was observed in the latter case (compare entries 4 and 5). Some enhancement of enantiocontrol was achieved with thiouronium-substituted catalyst **7**, the *syn*/*anti* diastereomeric ratio remained high and, pleasingly, significant rate enhancement was observed with complete reaction in just four hours with added acid (entry 7).

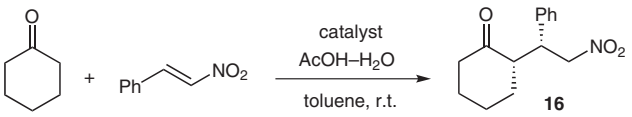
Simple diamine **14** promoted the Michael addition with excellent diastereo- and enantioselectivity, comparable to that reported by Pansare and Pandya for bis-secondary amine catalysis with *p*-TsOH as additive[5c] (entries 8 and 9). Diamine-thiourea catalyst **13** demonstrated rate enhancement, but without improved stereocontrol (entries 11 and 12). Bifunctional guanidinium **12** displayed similar activity to **13** (entry 10), and improved enantiocontrol in comparison with catalyst **4** in which guanidinium functionality is incorporated more remotely from the chiral pyrrolidine (compare entries 10 and 3). Alteration of the nature of the tether had a substantial effect; bis-thioureas **10a** and **10b** each displayed only moderate activity, resulting in long reaction times in toluene (entries 13 and 15) but a dramatic improvement in reaction time was observed in the presence of added acid, **10a** catalysing the Michael addition in nine hours (entry 14) and **10b** in only four hours (entry 16). Additionally, catalysis by bis-thiourea **10a** demonstrates excellent enantiocontrol (97% ee).

Reaction rates for catalysis by **7**, **10a/b**, and **13** are among the highest reported for this thiourea-promoted Michael addition,[18] and prompted us to examine catalyst loading and a reduction in the required amount of cyclohexanone. Known organocatalysts for the asymmetric Michael addition typically require catalyst loading of between 10–20 mol%, and are also usually performed with 10–20 equivalents of ketone. In several reported systems, reduced loading of catalyst and Michael donor results in substantial loss of yield and lower enantioselectivities.[19] We chose to use bis-thiourea **10b** and ether-linked catalysts **6** and **7** (Table 2).

Reduced cyclohexanone equivalents and catalyst loading appeared to be detrimental to both the reaction rate and the enantioselectivity, when the reaction was catalysed by bis-thiourea **10b** (Table 2, entries 1–3). Considering thiourea/uronium catalysts **6** and **7**, fewer equivalents of cyclohexanone resulted generally in slower Michael addition and also some loss of enantiocontrol, nonetheless it is pleasing that **7**, in particular, remains a highly effective catalyst; displaying high conversion, diastereo- and enantioselectivity with only a single equivalent of the Michael donor (entry 9). We were also successfully able to lower catalyst loading of **7** to 5 mol% without significant detriment to the enantiocontrol (entries 10–12).

Use of acyclic ketones in the Michael addition with *trans*-β-nitrostyrene was deleterious to catalyst performance in all cases. The use of acetone resulted in single addition products in an enantiomeric excess of only 5–30%, typically after 1–10 days. With butan-2-one, 5–30 days were required and mixed single addition products were produced with poor diastereoselectivity.[20]

Table 2 Enantioselective Addition of Cyclohexanone to *trans*-β-Nitrostyrene[a]



Entry	Catalyst (mol%)	Cyclohexanone (equiv)	Time (h)	Conversion (%)[b]	dr (*syn*/*anti*)[c]	ee (%)[d] *syn*
1	**10b** (15)	10	4	>90	92:8	92
2	**10b** (15)	1	504	>90	92:8	84
3	**10b** (5)	1	720	28	91:9	80
4	**6** (15)	10	11	>90	94:6	87
5	**6** (15)	5	24	>90	94:6	86
6	**6** (15)	1	336	>90	94:6	81
7	**7** (15)	10	5	>90	94:6	90
8	**7** (15)	5	8	>90	92:8	90
9	**7** (15)	1	30	>90	91:9	85
10	**7** (5)	10	24	>90	92:8	85
11	**7** (5)	5	48	>90	92:8	86
12	**7** (5)	1	120	>90	92:8	84

[a] The reaction was conducted with 0.5 mmol *trans*-β-nitrostyrene in 0.75 mL toluene at r.t. with 0.15 equiv AcOH and 1 equiv H_2O.
[b] Determined by HPLC analysis in comparison with naphthalene internal standard. We chose to monitor the requisite reaction time for 90% conversion; unless this threshold had not been reached within 30 days in which case the % conversion at that time is reported.
[c] Determined by reverse phase HPLC analysis of the diastereomeric mixture (MeCN–H_2O, 6:4).
[d] Determined by chiral HPLC analysis (Daicel Chiralpak AI, hexane-*i*-PrOH, 97:3).

The observed (2*S*,1*R*) absolute configuration of the major *syn* Michael adduct **16**[21] is consistent with a synclinical transition state for bifunctional catalysis[22] in which the hydrogen bond donor, thiourea, guanidinium or thiouronium, directs the nitrostyrene to attack the *re*-face of the enamine (Figure 2).

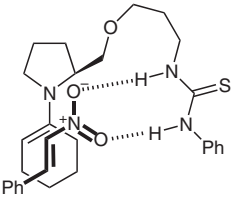


Figure 2 Proposed transition state for conjugate addition catalysis by thiourea-functionalised pyrrolidine **6**

In summary, we have developed a series of readily prepared catalysts, which promote the Michael addition of cyclohexanone to *trans*-β-nitrostyrene with excellent asymmetric induction. Reduced catalyst loading is tolerated for thiouronium-pyrrolidine organocatalyst **7** and development of related systems for catalysis of conjugate addition is underway, alongside further investigation of the mechanistic role of secondary amine and thiourea functionality within the tethering group of catalysts **13** and **10**. Combined short reaction time and high enantioinduction places **10a** amongst the most useful of amine-thiourea organocatalysts reported for this Michael addition.

Reagents and solvents were obtained from commercial suppliers and if necessary dried and distilled before use. THF was freshly distilled from sodium benzophenone ketal under argon. CH_2Cl_2 and Et_3N were freshly distilled from CaH_2. Petroleum ether (PE) used refers to the fraction boiling in the range 40–60 °C. Reactions requiring a dry atmosphere were conducted in oven dried glassware under N_2.

^1H and ^{13}C NMR spectra were recorded on Bruker 300 or 400 MHz spectrometers. ^1H chemical shifts are reported as values in parts per million, referenced to residual solvent. The following abbreviations are used to denote multiplicity and may be compounded: s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, qn = quintuplet, sext = sextet. Coupling constants, *J*, are measured in hertz (Hz). ^{13}C NMR spectra were proton decoupled and referenced to solvent. The number of adjacent protons was determined by DEPT experiments. IR spectra were recorded either as neat solids or as oils on a Thermo Nicolet 380 FT IR spectrometer fitted with an ATR accessory. Absorptions are given in wavenumbers (cm^{-1}) and the following abbreviations used to denote peak intensities: s = strong, m = medium, w = weak and/or br (broad). Low-resolution mass spectra were recorded on a Micromass platform single quadrupole mass spectrometer in MeOH or MeCN. Accurate mass spectra were recorded on a double focusing mass spectrometer. Melting points were determined in open capillary tubes using a Gallenkamp Electrothermal melting point apparatus and are uncorrected. HPLC chromatograms were recorded on a LaChrom D 7000 instrument using a Phenomenex 150 mm × 4.6 mm reverse phase column (flow rate 1 mL min^{-1}). Chiral HPLC was performed with a Chiralpak AI 250 mm × 4.6 mm column (flow rate 0.5 mL min^{-1}). Microanalysis was performed by MEDAC Ltd., Surrey, UK.

(*S*)-2-(3-Aminopropoxymethyl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (2)

N-Boc-L-Prolinol (**1**; 2.00 g, 9.94 mmol) was taken into a biphasic mixture of toluene (4 mL) and aq NaOH (40 mL of a 40% w/v aqueous solution). TBAI (260 mg, 0.703 mmol) and acrylonitrile (3.2 mL, 50.0 mmol) were added and the mixture stirred vigorously for 20 h. The phases were separated and the aqueous phase extracted with EtOAc (4 × 500 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification by column chromatography (SiO_2 eluted with 4:1 PE–EtOAc) gave (*S*)-2-(2-cyanoethoxymethyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (**17**) as a pale yellow oil (2.50 g, 99%). To a solution of **17** (200 mg, 0.786 mmol) in MeOH (6 mL) was added $NiCl_2$ (204 mg, 1.57 mmol) followed by H_2O (1 mL), the solution turned from colourless to pale green. $NaBH_4$ (179 mg, 4.70 mmol) was added portionwise, upon which the solution became black and effervescent. The mixture was stirred at room temperature for 3 h, MeOH (10 mL) was added and the mixture filtered through Celite and washed with MeOH (20 mL). H_2O (50 mL) was added to the pale green filtrate and this was extracted with CH_2Cl_2 (3 × 200 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification by column chromatography (SiO_2 eluted with 4:1 CH_2Cl_2–MeOH) gave the title compound **2** as an orange oil (167 mg, 82%); $[\alpha]_D^{29.5}$ +20.5 (*c* 1.00, $CHCl_3$).

IR (film): 3420 (w), 2970 (m), 2874 (m), 1689 (s), 1390 (m), 1167 (s), 1101 cm^{-1} (s).

^1H NMR (400 MHz, DMSO-d_6, 90 °C): δ = 3.81 (m, 1 H, C*H*CH_2), 3.52–3.42 (m, 3 H, CHCH*H′*O and CH_2O), 3.33 (dd, *J* = 9.5, 7.2 Hz, 1 H, CHC*H*H′O), 3.30 (m, 1 H, NCH*H′*), 3.20 (m, 1 H, NC*H*H′), 2.66 (t, *J* = 6.6 Hz, 2 H, C$H_2$$NH_2$), 2.20 (br s, 2 H, NH_2), 1.90–1.81 (m, 3 H, CH_2CH*H′*), 1.74 (m, 1 H, CHC*H*H′), 1.59 (qn, *J* = 6.6 Hz, 2 H, CH_2C$H_2$$CH_2$), 1.43 [s, 9 H, C($CH_3$)$_3$].

^{13}C NMR (75 MHz, DMSO-d_6): δ = 153.4 (C), 78.2 (C), 71.0 (CH_2), 68.6 (CH_2), 56.0 (CH), 46.1 (CH_2), 38.7 (CH_2), 33.4 (CH_2), 28.0 (CH_3), 23.1 (CH_2), 22.3 (CH_2).

MS (ES+): *m*/*z* (%) = 259 (100, $[M + H]^+$).

HRMS (ES+): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{27}N_2O_3$: 259.2016; found: 259.2021.

2-(3-{[(*S*)-Pyrrolidin-2-yl]methoxy}propyl)guanidininium Trifluoroacetate (4)

To a solution of amine **2** (200 mg, 0.774 mmol) in THF (1 mL) was added pyrazole **3**[12] (240 mg, 0.774 mmol) and the mixture stirred at r.t. for 8 h before concentration in vacuo. Purification by column chromatography (SiO_2 eluted with 97:3 CH_2Cl_2–MeOH) gave (*S*)-2-(*tert*-butoxycarbonylimino-3-guanidinopropoxymethyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (**18**) as a colourless oil (120 mg, 31%). *tert*-Butyl ester **18** (48 mg, 0.0959 mmol) was treated with TFA (5 mL of a 20% v/v solution in CH_2Cl_2) and stirred at r.t. for 4 h before concentration in vacuo. Excess TFA was removed as the toluene azeotrope in vacuo. The title compound **4** was isolated as a cloudy white oil without further purification (40 mg, 97%); $[\alpha]_D^{31}$ +7.2 (*c* 0.90, $CHCl_3$).

IR (film): 3374 (w), 3202 (w), 2964 (w), 1642 (s), 1589 (s), 1477 (m), 1397 (m), 1241 (s), 1142 cm^{-1} (s).

^1H NMR (400 MHz, CD_3OD): δ = 7.78 (br s, 1 H, NH), 6.45 (br s, 1 H, NH), 3.79 (ddd, *J* = 15.8, 7.9, 3.6 Hz, 1 H, C*H*CH_2), 3.67 (dd, *J* = 10.6, 3.6 Hz, 1 H, CHCH*H′*O), 3.54–3.44 (m, 3 H, C*H*H′OCH_2), 3.22–3.19 (m, 4 H, 2 NCH_2), 2.09 (ddd, *J* = 15.8, 7.8, 4.8 Hz, 1 H, CHCH*H′*CH_2), 2.00–1.89 (m, 2 H, CH_2C$H_2$$CH_2$), 1.77 (qn, *J* = 6.7 Hz, 2 H, CH_2C$H_2$$CH_2$), 1.68 (ddd, *J* = 16.3, 12.4, 7.9 Hz, 1 H, CHC*H*H′CH_2).

^{13}C NMR (100 MHz, CD_3OD): δ = 158.8 (C), 70.6 (CH_2), 69.3 (CH_2), 60.8 (CH), 46.7 (CH_2), 39.4 (CH_2), 29.8 (CH_2), 27.4 (CH_2), 24.8 (CH_2).

MS (ES+): *m*/*z* (%) = 239 (100, $[M + K]^+$).

(*S*)-2-[3-(3-Phenylthioureido)propoxymethyl]pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (5)

Amine **2** (800 mg, 3.10 mmol) and PHNCS (370 μL, 3.10 mmol) were taken into a biphasic mixture of $CHCl_3$ (95 mL), MeOH (30 mL) and aq sat. $NaHCO_3$ (30 mL). The reaction mixture was stirred vigorously at r.t. for 18 h before separation of the organic phase and washing with H_2O (2 × 100 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL), the combined organic phases were dried ($MgSO_4$), and concentrated in vacuo. Purification by column chromatography (SiO_2 eluted with 95:5 CH_2Cl_2–MeOH) gave the title compound **5** as a white foam (1.00 g, 82%); $[\alpha]_D^{30.5}$ +15.5 (*c* 1.00, $CHCl_3$).

IR (neat): 3312 (w), 2975 (w), 1675 (m), 1398 (m), 1168 (m), 1108 (m), 726 cm^{-1} (s).

^{1}H NMR (400 MHz, DMSO-d_6, 90 °C): δ = 9.14 (br s, 1 H, NH), 7.44 (dd, *J* = 8.3, 1.1 Hz, 2 H, 2CC*H*CH), 7.31 (tt, *J* = 7.3, 1.9 Hz, 2 H, 2CHC*H*CH), 7.10 (tt, *J* = 7.3, 1.1 Hz, 1 H, CHC*H*CH), 3.81 (m, 1 H, C*H*CH$_2$), 3.56 (q, *J* = 6.8 Hz, 2 H, C*H*$_2$NH), 3.59–3.49 (m, 3 H, CHC*H*H′O and CH$_2$O), 3.33 (dd, *J* = 9.6, 7.2 Hz, 1 H, CHC*H*H′O), 3.29 (m, 1 H, NCH*H*′CH$_2$), 3.22 (m, 1 H, NC*H*H′CH$_2$), 1.91–1.78 (m, 5 H, CHCH*H*′ and 2 CH$_2$C*H*$_2$CH$_2$), 1.75 (m, 1 H, CHC*H*H′), 1.42 [s, 9 H, C(CH$_3$)$_3$].

^{13}C NMR (75 MHz, DMSO-d_6): δ = 180.4 (C), 153.5 (C), 139.2 (C), 128.6 (CH), 124.0 (CH), 123.1 (CH), 78.3 (C), 71.1 (CH$_2$), 68.5 (CH$_2$), 55.9 (CH), 46.2 (CH$_2$), 41.5 (CH$_2$), 28.7 (CH$_2$), 28.1 (CH$_3$), 23.2 (CH$_2$), 22.3 (CH$_2$).

MS (ES+): *m*/*z* (%) = 416 (100, [M + Na]$^+$).

HRMS (ES+): *m*/*z* [M + Na] $^+$ calcd for $C_{20}H_{31}N_3O_3S$ + Na: 416.1978; found: 416.1969.

1-Phenyl-3-{3-[(*S*)-1-pyrrolidin-2-ylmethoxy]propyl}thiourea (6)

Thiourea **5** (412 mg, 1.05 mmol) was treated with TFA (10 mL of a 20% v/v solution in CH_2Cl_2) and the mixture stirred at r.t. for 2 h before concentration in vacuo. The resulting ammonium salt was taken into CH_2Cl_2 (15 mL), treated with aq sat. K_2CO_3 (1 mL) and stirred vigorously at r.t. for 30 min. The phases were separated and the aqueous phase extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo to give the title compound **6** as a colourless oil (302 mg, 98%); $[\alpha]_D^{21}$ +6.2 (*c* 1.00, $CHCl_3$).

IR (film): 2974 (w), 2875 (w), 1684 (s), 1392 (s), 1102 (s), 732 cm^{-1} (s).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.28 (m, 5 H, 4 CH and NH), 7.18 (tt, *J* = 6.7, 1.9 Hz, 1 H, CHC*H*CH), 3.80–3.65 (m, 2 H, CH$_2$O), 3.54 (q, *J* = 5.6 Hz, 2 H, NHC*H*$_2$), 3.38 (dd, *J* = 9.5, 3.9 Hz, 1 H, CHCH*H*′O), 3.25 (dd, *J* = 9.5, 7.9 Hz, 1 H, CHC*H*H′O), 3.15 (m, 1 H, C*H*CH$_2$), 2.96–2.80 (m, 2 H, NHC*H*$_2$), 1.86 (qn, *J* = 5.7 Hz, 2 H, CH$_2$C*H*$_2$CH$_2$), 1.78–1.60 (m, 3 H, CHH*H*′C*H*$_2$), 1.30 (m, 1 H, CHC*H*H′).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 180.9 (C), 137.8 (C), 129.5 (CH), 126.1 (CH), 124.8 (CH), 73.5 (CH$_2$), 70.2 (CH$_2$), 58.1 (CH), 46.3 (CH$_2$), 44.1 (CH$_2$), 28.4 (CH$_2$), 27.7 (CH$_2$), 25.2 (CH$_2$).

MS (ES+): *m*/*z* (%) = 294 (100, [M + H] $^+$).

HRMS (ES+): *m*/*z* [M]$^+$ calcd for $C_{15}H_{24}N_3OS$: 294.1635; found: 294.1640.

Anal. Calcd for $C_{15}H_{23}N_3OS$: C, 61.40; H, 7.90; N, 14.31; S, 10.93. Found: C, 61.21; H, 7.23; N, 14.53; S, 10.50.

Methyl(1-phenylamino-1-{3-[(*S*)-1-pyrrolidin-2-ylmethoxy]propylamino}methylidene)sulfonium Iodide (7)

To a solution of thiourea **5** (682 mg, 1.73 mmol) in acetone (10 mL) was added MeI (1.08 mL, 17.3 mmol) and the reaction mixture stirred at r.t. for 5 h before concentration in vacuo to give a thiouronium iodide as a yellow foam (926 mg, ca. 100%). A solution of this thiouronium iodide (439 mg, 0.82 mmol) was treated with TFA (10 mL of a 20% v/v solution in CH_2Cl_2) and stirred at r.t. for 3 h before concentration in vacuo. The resulting ammonium salt was taken into CH_2Cl_2 (10 mL), treated with aq sat. K_2CO_3 (1 mL), and stirred vigorously at r.t. for 30 min. The phases were separated and the aqueous phase extracted with CH_2Cl_2 (5 × 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo to give the title compound **7** as a pale yellow oil (314 mg, 88%); $[\alpha]_D^{21}$ +6.3 (*c* 1.00, $CHCl_3$).

IR (film): 3315 (w), 3051 (w), 2870 (w), 1581 (s), 1484 (m), 1118 (s), 696 cm^{-1} (s).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27 (t, *J* = 7.3 Hz, 2 H, 2 CHC*H*CH), 7.02 (tt, *J* = 7.4, 1.2 Hz, 1 H, CHC*H*CH), 6.90 (dd, *J* = 8.3, 1.2 Hz, 2 H, 2CC*H*CH), 3.81 (ddd, *J* = 15.1, 7.6, 3.8 Hz, 1 H, C*H*CH$_2$), 3.68 (dd, *J* = 10.2, 3.8 Hz, 1 H, CHCH*H*′O), 3.63–3.55 (m, 3 H, CH$_2$O and CHC*H*H′O), 3.49 (dt, *J* = 6.4, 4.1 Hz, 2 H, NHC*H*$_2$), 3.23 (t, *J* = 7.2 Hz, 2 H, NHC*H*$_2$), 2.28 (s, 3 H, CH$_3$), 2.12–1.84 (m, 5 H, CH*H*′C*H*$_2$ and CH$_2$C*H*$_2$CH$_2$), 1.75 (m, 1 H, CHC*H*H′).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.6 (C), 149.1 (C), 129.1 (CH), 123.2 (CH), 122.8 (CH), 69.7 (CH$_2$), 69.1 (CH$_2$), 59.1 (CH), 45.7 (CH$_2$), 40.6 (CH$_2$), 29.4 (CH$_2$), 27.0 (CH$_2$), 24.2 (CH$_2$), 14.2 (CH$_3$).

MS (ES+): *m*/*z* (%) = 308 (100, [M]$^+$).

HRMS (ES+): *m*/*z* [M]$^+$ calcd for $C_{16}H_{26}N_3OS$: 308.1791; found: 308.1789.

Anal. Calcd for $C_{16}H_{26}IN_3OS$: C, 44.14; H, 6.02; N, 9.65; S, 7.36. Found: C, 44.60; H, 6.31; N, 9.30; S, 7.18.

(*S*)-2-[(2-Benzyloxycarbonylaminoethylamino)methyl]pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (9a)

A solution of *N*-Boc-L-proline (**8**; 4.85 g, 22.5 mmol) in DMF–THF (220 mL of a 1:1 v/v solution) was cooled to 0 °C before the addition of 2-benzyloxycarbonylaminoethylammonium chloride[15] (4.81 g, 24.8 mmol), HOBt (4.57 g, 33.8 mmol), EDC (4.76 g, 24.8 mmol) and *i*-Pr$_2$NEt (19.6 mL, 113 mmol). The reaction mixture was warmed to r.t. and stirred for 17 h before concentration in vacuo. The resulting oil was taken into CH_2Cl_2 (200 mL) and washed with aq 1 M $KHSO_4$ (3 × 150 mL), aq sat. $NaHCO_3$ (2 × 150 mL) and brine (150 mL). The organic phase was separated and dried ($MgSO_4$) before concentration in vacuo. Crystallisation (EtOAc–hexane) gave (*S*)-2-(3-benzyloxycarbonylaminoethylcarbamoyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (**19**), as an off-white crystalline solid (6.92 g, 79%). A solution of amide **19** (7.29 g, 18.6 mmol) in THF (22 mL) was cooled to –5 °C and BH_3·THF complex (37.2 mL of a 1 M solution, 37.2 mmol) was added dropwise over 10 min. The mixture was stirred between –5 and 0 °C for 2 h, then warmed to r.t., and stirred for 7 days. The mixture was then cooled to –5 °C and cold H_2O (40 mL) added dropwise over 30 min. The mixture was extracted with EtOAc (3 × 250 mL) and the combined EtOAc layers were washed with brine (100 mL), aq sat. $NaHCO_3$ (100 mL), and H_2O (2 × 100 mL) before drying ($MgSO_4$) and concentration in vacuo. Purification by column chromatography (SiO_2 eluted with 4:1 CH_2Cl_2–MeOH) gave the title compound **9a** as a colourless oil (4.87 g, 69%); $[\alpha]_D^{31}$ –24.9 (*c* 1.00, $CHCl_3$).

IR (film): 3326 (w), 2973 (w), 2880 (w), 1675 (s), 1533 (m), 1392 (s), 1247 cm^{-1} (m).

^{1}H NMR (400 MHz, DMSO-d_6, 80 °C): δ = 7.37–7.34 (m, 4 H, 4 CH), 7.28 (m, 1 H, CHC*H*CH), 6.71 (br s, 1 H, NH), 5.03 (s, 2 H, C*H*$_2$Ph), 3.71 (ddd, *J* = 10.8, 7.0, 3.6 Hz, 1 H, C*H*CH$_2$), 3.26 (m, 1 H, NCH*H*′), 3.17 (m, 1 H, NC*H*H′), 3.15–3.09 (m, 3 H, N*H*C*H*$_2$), 2.70 (dd, *J* = 11.8, 4.1 Hz, 1 H, CHCH*H*′), 2.64 (dt, *J* = 6.6, 1.3 Hz, 2 H, NHC*H*$_2$), 2.50 (dd, *J* = 11.9, 7.9 Hz, 1 H, CHC*H*H′), 1.87–1.67 (m, 4 H, 2 CH$_2$), 1.40 [s, 9 H, C(CH$_3$)$_3$].

^{13}C NMR (75 MHz, DMSO-d_6): δ = 155.9 (C), 153.3 (C), 136.9 (C), 128.3 (CH), 128.1 (CH), 127.7 (CH), 77.8 (C), 64.8 (CH$_2$), 56.4 (CH), 51.1 (CH$_2$), 48.6 (CH$_2$), 45.9 (CH$_2$), 40.3 (CH$_2$), 28.4 (CH$_2$), 27.8 (CH$_3$), 22.9 (CH$_2$).

MS (ES+): *m*/*z* (%) = 378 (100, [M + H]$^+$).

HRMS (ES+): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{32}N_3O_4$: 378.2387; found: 378.2381.

(*S*)-2-[(3-Benzyloxycarbonylaminopropylamino)methyl]pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (9b)

A solution of *N*-Boc-L-proline (**8**; 0.95 g, 4.43 mmol) in DMF–THF (60 mL of a 1:1 v/v solution) was cooled to 0 °C before addition of 3-benzyloxycarbonylaminopropylammonium trifluoroacetate[15] (1.57 g, 4.87 mmol), HOBt (898 mg, 6.65 mmol), EDC (934 mg, 4.87 mmol), and *i*-Pr_2NEt (3.39 mL, 19.5 mmol). The reaction mixture was warmed to r.t. and stirred for 17 h before concentration in vacuo. The resulting oil was taken into CH_2Cl_2 (50 mL) and washed with aq 1 M $KHSO_4$ (2 × 30 mL), aq sat. $NaHCO_3$ (2 × 30 mL), and brine (30 mL). The organic phase was separated and dried ($MgSO_4$) before concentration in vacuo. Crystallisation (EtOAc–hexane) gave (*S*)-2-(3-benzyloxycarbonylaminopropylcarbamoyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (**20**) as an off-white crystalline solid (1.28 g, 71%). A solution of amide **20** (3.67 g, 9.05 mmol) in THF (11 mL) was cooled to –5 °C and BH_3·THF complex (18.1 mL of a 1 M solution, 18.1 mmol) was added dropwise over 10 min. The mixture was stirred between –5 and 0 °C for 2 h, then warmed to r.t., and stirred for a further 7 days. The mixture was then cooled to –5 °C and cold H_2O (40 mL) added dropwise over 20 min. The mixture was extracted with EtOAc (200 mL), the EtOAc layer washed with aq sat. $NaHCO_3$ (200 mL) and brine (200 mL) before drying ($MgSO_4$) and concentration in vacuo. Purification by column chromatography (SiO_2 eluted with 9:1 CH_2Cl_2–MeOH) gave the title compound **9b** as a colourless oil (2.13 g, 60%); $[\alpha]_D^{30}$ –25.6 (*c* 1.00, $CHCl_3$).

IR (film): 3305 (w), 2973 (w), 1678 (s), 1530 (w), 1392 (s), 1165 (m), 749 cm^{-1} (s).

^1H NMR (400 MHz, DMSO-d_6, 80 °C): δ = 7.38–7.29 (m, 5 H, 5 CH), 6.96 (br s, 1 H, NH), 5.04 (s, 2 H, CH_2Ph), 3.89 (m, 1 H, C*H*CH_2), 3.32 (m, 1 H, NCH*H*′), 3.24 (m, 1 H, NC*H*H′), 3.10 (q, *J* = 6.7 Hz, 2 H, NHCH_2), 3.05 (br s, 1 H, NH), 2.85 (dd, *J* = 12.2, 4.9 Hz, 1 H, CHCH*H*′N), 2.75 (t, *J* = 7.1 Hz, 2 H, NHCH_2), 2.70 (dd, *J* = 12.2, 7.3 Hz, 1 H, CHC*H*H′N), 1.92 (m, 1 H, CHC*H*H′), 1.86–1.79 (m, 3 H, CH*H*′CH_2), 1.70 (qn, *J* = 7.2 Hz, 2 H, $CH_2CH_2CH_2$), 1.43 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.9 (CH_2), 25.7 (CH_2), 28.6 (CH_3), 29.7 (CH_2), 40.7 (CH_2), 46.8 (CH_2), 48.6 (CH_2), 53.1 (CH_2), 56.9 (CH), 66.7 (CH_2), 79.7 (C), 128.1 (CH), 128.2 (CH), 128.6 (CH), 136.8 (C), 156.7 (C), 158.3 (C).

MS (ES+): *m*/*z* (%) = 392 (100, $[M + H]^+$).

HRMS (ES+): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{34}N_3O_4$: 392.2544, found: 392.2536.

(*S*)-2-{3-Phenyl-1-[2-(3-phenylthioureido)ethyl]thioureidomethyl}pyrrolidine (10a)

A solution of carbamate **9a** (573 mg, 1.52 mmol) in MeOH (30 mL) was treated with 10% Pd/C (162 mg, 1.52 mmol) and stirred under H_2 (1 atm) at r.t. for 5 h before filtration through Celite. The filtrate was concentrated in vacuo to give (*S*)-2-[(2-aminoethylamino)methyl]pyrrolidine-1-carboxylic acid *tert*-butyl ester (**21**) as a colourless oil (364 mg, 98%). Diamine **21** (324 mg, 1.33 mmol) was taken into a biphasic solution of $CHCl_3$ (65 mL), MeOH (20 mL), and aq sat. $NaHCO_3$ (20 mL) and treated with phenyl isothiocyanate (398 mL, 3.33 mmol). The reaction mixture was stirred vigorously at r.t. for 3 days before separation of the organic phase and washing it with H_2O (2 × 50 mL). The combined aqueous phases were extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic phases dried ($MgSO_4$) and concentrated in vacuo. Purification by column chromatography (SiO_2 eluted with 3:1 PE–EtOAc) gave (*S*)-2-{3-phenyl-1-[2-(3-phenylthioureido)ethyl]thioureidomethyl}pyrrolidine-1-carboxylic acid *tert*-butyl ester (**22**) as a white foam (462 mg, 68%). Carbamate **22** (355 mg, 0.691 mmol) was treated with TFA (10 mL of a 20% v/v solution in CH_2Cl_2) and stirred at r.t. for 3 h before concentration in vacuo The resulting oil was taken into CH_2Cl_2 (10 mL), treated with aq sat. K_2CO_3 (1 mL) and stirred vigorously for 30 min. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (5 × 20 mL). The combined organic phase was dried ($MgSO_4$) and concentrated in vacuo to give to give the title compound **10a** as a white foam (251 mg, 88%); $[\alpha]_D^{27}$ –64.0 (*c* 1.00, $CHCl_3$).

IR (neat): 3243 (w), 2926 (w), 1538 (s), 1496 (s), 1347 (s), 1311 (s), 1255 (s) 695 cm^{-1} (s).

^1H NMR (400 MHz, DMSO-d_6): δ = 9.71 (br s, 1 H, NH), 8.06 (br s, 1 H, NH), 7.41–7.34 (m, 4 H, 4 CCH), 7.33 (t, *J* = 7.7 Hz, 2 H, CHC*H*CH), 7.28 (t, *J* = 7.6 Hz, 2 H, CHC*H*CH), 7.13 (t, *J* = 7.3 Hz, 1 H, CHC*H*CH), 7.05 (t, *J* = 7.3 Hz, 1 H, CHC*H*CH), 4.42–3.59 (m, 6 H, CH_2NCH_2 and NHCH_2), 3.41 (m, 1 H, C*H*CH_2), 3.00 (m, 1 H, NHC*H*H′CH_2), 2.75 (m, 1 H, NHCH*H*′CH_2), 1.92 (m, 1 H, CH_2C*H*H′), 1.79 (m, 1 H, CH_2CH*H*′), 1.61 (dt, *J* = 15.8, 7.9 Hz, 1 H, CHC*H*H′), 1.40 (dt, *J* = 14.6, 7.5 Hz, 1 H, CHCH*H*′).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 182.6 (C), 180.7 (C), 141.5 (C), 138.9 (C), 128.6 (CH), 128.0 (CH), 124.4 (CH), 123.5 (CH), 123.3 (CH), 123.2 (CH), 57.8 (CH), 56.3 (CH_2), 50.3 (CH_2), 45.2 (CH_2), 41.3 (CH_2), 28.8 (CH_2), 26.1 (CH_2).

MS (ES+): *m*/*z* (%) = 414 (100, $[M + H]^+$).

HRMS (ES+): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{28}N_5S_2$: 414.1781; found: 414.1785.

Anal. Calcd for $C_{21}H_{27}N_5S_2$: C, 60.98; H, 6.58; N, 16.92; S, 15.52. Found: C, 60.37; H, 6.56; N, 16.89; S, 15.99.

(*S*)-2-{3-Phenyl-1-[2-(3-phenylthioureido)propyl]thioureidomethyl}pyrrolidine (10b)

A solution of carbamate **9b** (539 mg, 1.38 mmol) in MeOH (30 mL) was treated with 10% Pd/C (147 mg, 1.4 mmol) and stirred under H_2 (1 atm) at r.t. for 18 h before filtration through Celite. The filtrate was concentrated in vacuo to give diamine (*S*)-2-[(3-aminopropylamino)methyl]pyrrolidine-1-carboxylic acid *tert*-butyl ester (**23**) as a pale yellow oil (343 mg, 96%). Diamine **23** (300 mg, 1.17 mmol) was taken into a biphasic solution of $CHCl_3$ (65 mL), MeOH (20 mL), and aq sat. $NaHCO_3$ (20 mL) and treated with phenyl isothiocyanate (349 mL, 2.91 mmol). The reaction mixture was stirred vigorously at r.t. for 3 days before separation of the organic phase and washing with H_2O (2 × 50 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic phases dried ($MgSO_4$) and concentrated in vacuo. Purification by column chromatography (SiO_2 eluted with 3:1 PE–EtOAc) gave (*S*)-2-{3-phenyl-1-[2-(3-phenylthioureido)propyl]thioureidomethyl}pyrrolidine-1-carboxylic acid *tert*-butyl ester (**24**) as a white foam (290 mg, 47%). Carbamate **24** (201 mg, 0.381 mmol) was treated with TFA (10 mL of a 20% v/v solution in CH_2Cl_2) and stirred at r.t. for 3 h before concentration in vacuo The resulting oil was taken into CH_2Cl_2 (10 mL), treated with aq sat. K_2CO_3 (1 mL) and stirred vigorously for 30 min. The phases were separated and the aqueous phase extracted with CH_2Cl_2 (5 × 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo to give the title compound **10b** as a white foam (163 mg, ca. 100%); $[\alpha]_D^{27}$ –55.9 (*c* 1.00, $CHCl_3$).

IR (neat): 3247 (w), 2926 (w), 1538 (s), 1496 (s), 1347 (s), 1311 (s), 1255 (s), 695 cm^{-1} (s).

^1H NMR (300 MHz, $CDCl_3$): δ = 12.48 (br s, 1 H, NH), 7.76 (br s, 1 H, NH), 7.51 (br s, 1 H, NH), 7.21–7.18 (m, 9 H, 9 CH), 7.07 (tt, *J* = 7.0, 1.6 Hz, 1 H, CHC*H*CH), 4.00 (dd, *J* = 13.8, 6.8 Hz, 1 H, CHCH*H*′N), 3.82 (q, *J* = 6.5 Hz, 2 H, CH_2NH), 3.72–3.63 (m, 3 H, CH_2N and C*H*CH_2), 3.25 (d, *J* = 13.6 Hz, 1 H, CHC*H*H′N), 3.09 (m, 1 H, NHC*H*H′CH_2), 2.84 (ddd, *J* = 11.0, 8.5, 6.2 Hz, 1 H, NHCH*H*′CH_2), 2.09–1.97 (m, 3 H, CH_2C*H*H′ and $CH_2CH_2CH_2$), 1.89 (m, 1 H, CH_2CH*H*′), 1.70 (ddd, *J* = 19.9, 15.9, 7.4 Hz, 1 H, CHC*H*H′), 1.42 (dt, *J* = 14.0, 7.3 Hz, 1 H, CHCH*H*′).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 184.3 (C), 180.4 (C), 141.3 (C), 136.2 (C), 130.1 (CH), 128.5 (CH), 127.2 (CH), 125.3 (CH), 124.1 (CH), 123.4 (CH), 58.4 (CH), 56.4 (CH_2), 49.4 (CH_2), 46.3 (CH_2), 42.2 (CH_2), 29.7 (CH_2), 27.1 (CH_2), 26.7 (CH_2).

MS (ES+): *m/z* (%) = 428 (100, $[M + H]^+$).

HRMS (ES+): *m/z* $[M + H]^+$ calcd for $C_{22}H_{30}N_5S_2$: 428.1937; found: 428.1937.

Anal. Calcd for $C_{22}H_{29}N_5S_2$: C, 61.79; H, 6.84; N, 16.37; S, 15.00. Found: C, 61.87; H, 6.46; N, 16.18; S, 15.15.

(*S*)-2-({*tert*-Butoxycarbonyl-[2-(3-phenylthioureido)propyl]amino}methyl)pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (11)

A solution of amine **9b** (1.68 g, 4.29 mmol) in CH_2Cl_2 (200 mL) was treated with di-*tert*-butyl dicarbonate (1.03 g, 4.72 mmol) and Et_3N (658 mL, 4.72 mmol) and then stirred at r.t. for 18 h before washing with aq sat. K_2CO_3 (3 × 40 mL), drying ($MgSO_4$), and concentration in vacuo. Purification by column chromatography (SiO_2 eluted with CH_2Cl_2) gave (*S*)-2-{[(2-benzyloxycarbonylaminopropyl)-*tert*-butoxycarbonylamino]methyl}pyrrolidine-1-carboxylic acid *tert*-butyl ester (**25**) as a colourless oil (1.45 g, 69%). A solution of the bis-carbamate **25** (1.39 g, 2.82 mmol) in MeOH (40 mL) was treated with 10% Pd/C (301 mg, 2.82 mmol) and stirred under H_2 (1 atm) at r.t. for 18 h before filtration through Celite. The filtrate was concentrated in vacuo to give (*S*)-2-{[(2-aminopropyl)-*tert*-butoxycarbonylamino]methyl}pyrrolidine-1-carboxylic acid *tert*-butyl ester (**26**), as a colourless oil (1.01 g, ca. 100%). Amine **26** (500 mg, 1.39 mmol) was taken into a biphasic mixture of $CHCl_3$ (85 mL), MeOH (25 mL), and aq sat. $NaHCO_3$ (25 mL) and treated with phenyl isothiocyanate (167 mL, 1.39 mmol). The reaction mixture was stirred vigorously at r.t. for 36 h before separation of the organic phase and washing it with H_2O (2 × 55 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 55 mL), the combined organic phases were dried ($MgSO_4$), and concentrated in vacuo. Purification by column chromatography (SiO_2 eluted with 3:1 PE–EtOAc) gave the title compound **11** as a pale yellow oil (500 mg, 73%); $[\alpha]_D^{31}$ –21.6 (*c* 1.00, $CHCl_3$).

IR (film): 3271 (w), 2974 (w), 2926 (w), 1675 (s), 1536 (m), 1158 (s), 728 cm^{-1} (s).

^{1}H NMR (400 MHz, DMSO-d_6, 80 °C): δ = 9.33 (br s, 1 H, NH), 7.61 (br s, 1 H, NH), 7.45 (dd, *J* = 8.7, 1.3 Hz, 2 H, 2 CH), 7.30 (td, *J* = 7.5, 2.0 Hz, 2 H, 2 CH), 7.09 (tt, *J* = 7.5, 1.1 Hz, 1 H, CHC*H*CH), 3.94 (m, 1 H, C*H*CH_2), 3.50 (q, *J* = 7.1 Hz, 2 H, CH_2NH), 3.30–3.25 (m, 4 H, 2 NCH_2), 3.23 (dd, *J* = 14.5, 7.2 Hz, 2 H, CHCH_2N), 1.88–1.75 (m, 6 H, 3 CH_2), 1.43 [s, 9 H, $C(CH_3)_3$], 1.42 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.4 (C), 159.4 (C), 156.5 (C), 136.4 (C), 129.8 (CH), 126.6 (CH), 125.3 (CH), 80.5 (C), 80.2 (C), 55.6 (CH), 47.7 (CH_2), 46.2 (CH_2), 42.6 (CH_2), 41.6 (CH_2), 29.7 (CH_2), 28.6 (CH_3), 28.3 (CH_3), 23.4 (CH_2), 22.5 (CH_2).

MS (ES+): *m/z* (%) = 515 (100, $[M + Na]^+$).

HRMS (ES+): *m/z* $[M + Na]^+$ calcd for $C_{25}H_{40}N_4O_4S$ + Na: 515.2662; found: 515.2658.

2-Phenylamino-3-(*S*)-1-pyrrolidin-2-ylmethyl-3,4,5,6-tetrahydropyrimidinium Iodide (12)

To a solution of thiourea **11** (389 mg, 0.793 mmol) in acetone (5 mL) was added MeI (494 μL, 7.93 mmol) and the reaction mixture stirred at r.t. for 5 h before concentration in vacuo to give a thiouronium iodide as a yellow foam (503 mg, ca. 100%). A solution of this thiouronium iodide (340 mg, 0.537 mmol) was treated with TFA (10 mL of a 20% v/v solution in CH_2Cl_2) and stirred at r.t. for 4 h before concentration in vacuo. The resulting ammonium salt was taken into CH_2Cl_2 (10 mL), treated with aq sat. K_2CO_3 (1 mL) and stirred vigorously for 30 min. The phases were separated and the aqueous phase extracted with CH_2Cl_2 (5 × 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo to give the title compound **12** as a colourless oil (205 mg, 98%); $[\alpha]_D^{21}$ +6.0 (*c* 1.00, $CHCl_3$).

IR (film): 3432 (w), 2963 (w), 1579 (m), 1199 (m), 1125 (m), 752 cm^{-1} (s).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (br s, 2 H, 2 NH), 7.29 (t, *J* = 7.6 Hz, 2 H, 2CHC*H*CH), 7.08 (tt, *J* = 7.4, 1.0 Hz, 1 H, CHC*H*CH), 6.99 (dd, *J* = 8.5, 1.1 Hz, 2 H, 2CC*H*CH), 4.01 (apparent dq, *J* = 7.6, 2.0 Hz, 1 H, C*H*CH_2), 3.78 (dd, *J* = 15.1, 9.5 Hz, 1 H, CHCH*H*′N), 3.66 (m, 1 H, NHCH*H*′), 3.35–3.20 (m, 5 H, 2 NCH_2 and CHC*H*H′N), 2.88 (td, *J* = 11.0, 7.1 Hz, 1 H, NHC*H*H′), 2.09–2.00 (m, 2 H, $CH_2CH_2CH_2$), 1.97 (m, 1 H, CHH*H*′), 1.95–1.87 (m, 2 H, $CH_2CH_2CH_2$), 1.49 (td, *J* = 12.8, 7.7 Hz, 1 H, CHC*H*H′).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.1 (C), 141.1 (C), 130.0 (CH), 124.8 (CH), 124.0 (CH), 58.2 (CH), 55.4 (CH_2), 48.2 (CH_2), 44.9 (CH_2), 39.4 (CH_2), 28.5 (CH_2), 26.2 (CH_2), 21.9 (CH_2).

MS (ES+): *m/z* (%) = 293 (100, $[M + H]^+$).

HRMS (ES+): *m/z* $[M]^+$ calcd for $C_{15}H_{23}N_4$: 259.1917; found: 259.1920.

Anal. Calcd for $C_{15}H_{23}IN_4$: C, 46.64; H, 6.00; N, 14.50. Found: C, 46.95; H, 6.32; N, 14.84.

1-Phenyl-3-(3-{[(*S*)-1-pyrrolidin-2-ylmethyl]amino}propyl)thiourea (13)

Carbamate **11** (371 mg, 0.753 mmol) was treated with TFA (10 mL of a 20% v/v solution in CH_2Cl_2) and stirred at r.t. for 3 h before concentration in vacuo. The residual ammonium salt was taken into CH_2Cl_2 (10 mL) and treated with aq sat. K_2CO_3 (1 mL), and stirred vigorously at r.t. for 30 min. The phases were separated and the aqueous phase extracted with CH_2Cl_2 (5 × 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo to give the title compound **13** as a pale yellow oil (186 mg, 85%); $[\alpha]_D^{28.5}$ –6.8 (*c* 0.90, $CHCl_3$).

IR (film): 2956 (w), 1668 (m), 1200 (m), 1132 (m), 722 cm^{-1} (s).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.87 (br s, 1 H, NH), 7.38–7.29 (m, 4 H, 4 CH), 7.16 (t, *J* = 7.0 Hz, 1 H, CHC*H*CH), 5.20 (br s, 2 H, 2 NH), 3.77–3.66 (m, 2 H, CH_2NH), 3.30 (m, 1 H, C*H*CH_2), 3.05–3.00 (m, 2 H, NHCH_2), 2.75–2.63 (m, 3 H, CHCH*H*′NH and NHCH_2), 2.55 (dd, *J* = 12.6, 9.7 Hz, 1 H, CHC*H*H′NH), 1.90–1.79 (m, 3 H, CH*H*′CH_2), 1.71 (qn, *J* = 6.0 Hz, 2 H, $CH_2CH_2CH_2$), 1.42 (m, 1 H, CHC*H*H′).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 181.0 (C), 138.4 (C), 129.3 (CH), 125.8 (CH), 124.8 (CH), 58.6 (CH), 51.9 (CH_2), 47.3 (CH_2), 45.4 (CH_2), 43.7 (CH_2), 28.8 (CH_2), 28.4 (CH_2), 24.7 (CH_2).

MS (ES+): *m/z* (%) = 293 (100, $[M + H]^+$).

Anal. Calcd for $C_{15}H_{24}N_4S$: C, 61.61; H, 8.27; N, 19.15; S, 10.97. Found: C, 61.91; H, 8.06; N, 19.41; S, 10.68.

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(21) Configuration of (*S*)-2-[(*R*)-2-nitro-1-phenylethyl]cyclohexanone (**16**) was determined by literature comparison of HPLC elution order, see ref. 7e; and optical rotation; $[\alpha]_D$ –26.7 (*c* = 1.0, $CHCl_3$, 24 °C), see ref. 22.

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