Structural optimization of thiourea-based bifunctional organocatalysts for the highly enantioselective dynamic kinetic resolution of azlactones†

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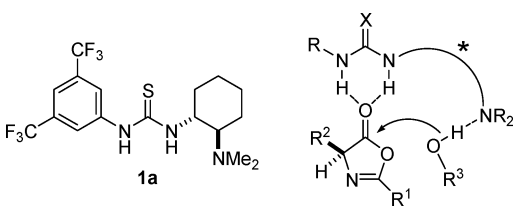
This article describes the synthesis of a library of structurally diverse bifunctional organocatalysts bearing both a quasi-Lewis acidic (thio)urea moiety and a Brønsted basic tertiary amine group. Sequential modification of the modular catalyst structure and subsequent screening of the compounds in the alcoholytic dynamic kinetic resolution (DKR) of azlactones revealed valuable structure–activity relationships. In particular, a "hit-structure" was identified which provides *e.g. N*-benzoyl-*tert*-leucine allyl ester in an excellent enantiomeric excess of 95%.

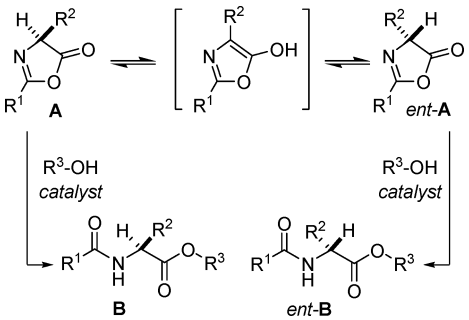
Introduction

The simultaneous activation of both nucleophilic and electrophilic substrates is a general concept of enzyme catalysis.[1] The synergistic cooperation of two functional groups in the active site helps to improve the reactivity as well as the stereodiscrimination. To achieve efficient double catalytic activation of the reaction partners, the two complementary functionalities have to be suitably positioned in a chiral environment.[2] This powerful concept has been successfully implemented by synthetic organic chemists for a variety of asymmetric transformations.[3] The Lewis basic part of the catalysts is often taken over by "organic" bases such as amines and phosphine oxides. On the other hand, transition metals were usually applied as Lewis acids for the activation of electrophilic substrates. One of the rare examples of purely organic quasi-Lewis acids is the (thio)urea moiety which is able to activate by forming hydrogen bonds with appropriate acceptors.[4] This property was utilized to develop efficient organocatalysts[5] which can activate carbonyl groups and related functionalities[6] for the attack of nucleophiles. Takemoto *et al.* combined a thiourea moiety with a tertiary amine in an effective bifunctional organocatalyst (**1a** in Scheme 1) for enantioselective Michael additions and the aza-Henry reaction.[7]



Scheme 1 Takemoto's catalyst **1a** and the bifunctional mode of activation for the DKR of azlactones (X = S, O).

We reasoned that compounds of this general structure could also be efficient catalysts for the asymmetric alcoholytic ring opening of azlactones and oxazinones.[8,9] The azlactone carbonyl can be activated by double hydrogen bonding from the quasi-Lewis acidic (thio)urea while the Brønsted basic tertiary amine can increase the nucleophilicity of the alcohol (Scheme 1). Because of the configurational lability of azlactones, asymmetric alcoholytic ring opening of these species leads to highly valuable protected α-amino acid derivatives *via* dynamic kinetic resolution (DKR) (Scheme 2).



Scheme 2 Basic principle of the DKR of azlactones.

In this article, we describe the synthesis of a library of bifunctional (thio)urea based organocatalysts and their screening in the DKR of azlactones.

Results and discussion

The goal of our initial experiments was to examine the catalytic activities of both Brønsted basic tertiary amine and quasi-Lewis acidic (thio)urea functionalities individually, as well as in combination. It is particularly noteworthy that the X-ray crystal structure of the urea catalyst **26b** revealed bifurcate intermolecular hydrogen bonding between the urea N–H groups and the urea oxygen atom of a neighbouring molecule of **26b** (Fig. 1). The urea moiety of **26b** is planar and there is no intramolecular H bond to the N atom of the tertiary amine. Thus, the H-bonding behaviour of **26b**, as revealed by its crystal structure, corresponds

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† Electronic supplementary information (ESI) available: General experimental details, syntheses of **1a–g** and **16–29**, ORTEP structures and crystallographic data of selected catalysts. See DOI: 10.1039/b607574f

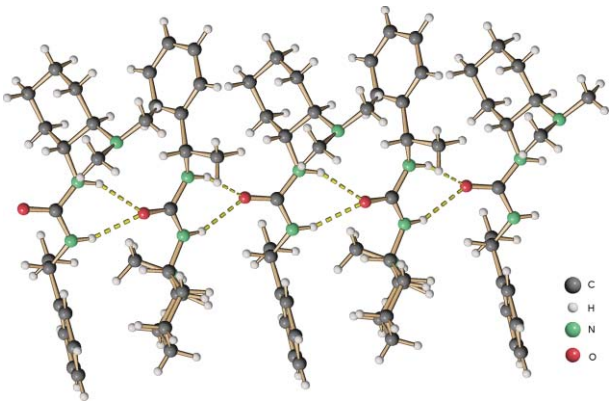


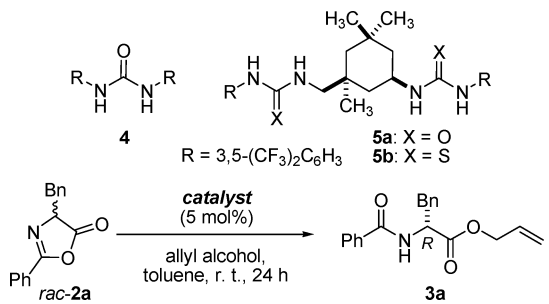
Fig. 1 Packing of **26b** in the crystal, intermolecular H bonding between neighbouring molecules of **26b**.

to the design features summarized in Scheme 1 for a bifunctional organocatalyst.

We first investigated the catalytic activity of NEt_3 for the ring opening of the benzyl substituted azlactone **2a** with allyl alcohol (Table 1, entry 1). Using 5 mol% of NEt_3 after a reaction time of 24 h, only 14% conversion was observed. Similarly, when the symmetric urea **4** was used as the catalyst, even lower conversion (4%) was achieved after 24 h (entry 2). However, when a combination of **4** and NEt_3 (5 mol% each) was applied, a significantly higher conversion of 50% was obtained after 24 h (entry 3). In the hope to achieve asymmetric induction, we tested the chiral (thio)ureas **5a,b** in combination with NEt_3. In these cases, similar levels of conversion were obtained as in the above case (entries 4 and 5). Although the achieved enantioselectivities were low, these experiments clearly proved the synergistic action of the achiral amine and the chiral (thio)ureas.

As the next step, we synthezised a library of bifunctional (thio)urea based organocatalysts. These compounds bearing both a (thio)urea and a tertiary amine moiety within the same molecule can be easily prepared by condensation of a chiral diamine and an iso(thio)cyanate.

Table 1 Screening of amine bases and bis-ureas

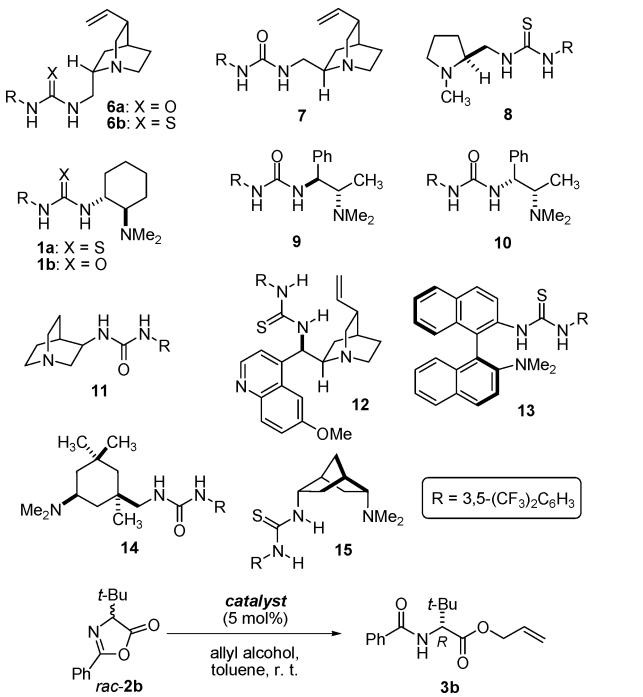


Entry	Catalyst	Conversion (%)[a]	ee (%)[a]
1	NEt_3	14	—
2	**4**	4	—
3	**4** + NEt_3	50	—
4	**5a** + NEt_3	50	<2
5	**5b** + NEt_3	33	5

[a] Conversion and ee were determined by chiral HPLC analysis.

During the process of structure optimization, we first screened the 3,5-bis(trifluoromethyl)phenyl ureas or thioureas derived from twelve structurally distinct diamines. In this sense, we synthesized ten compounds derived from 1,2-diamines **6–12** and three from 1,4-diamines **13–15** (Table 2). As shown in Table 2, all bifunctional (thio)ureas derived from 1,4-diamines were found to be completely inactive for the alcoholytic ring opening of the *tert*-butyl substituted azlactone **2b** (entries 12–14). In contrast, all the compounds containing 1,2-functionalities showed variable activities and enantioselectivities (entries 1–11). The catalysts with a quinuclidine backbone **6**, **7**, **11**, **12**, a proline derivative **8** and the ephedrine derived catalyst **10** afforded enantioselectivities below 60%. Significantly higher enantioselectivities were obtained using catalysts derived from pseudoephedrine **9** and *trans*-1,2-diamino cyclohexane **1** (entries 5–7). In the case of thiourea **1a** and urea **1b**, similar conversions and comparable enantioselectivities were

Table 2 Optimization of the diamine backbone



Entry	Catalyst	Time/h	Conversion (%)[a]	ee (%)[a]
1	**6a**	72	78	38[b]
2	**6b**	72	68	45[b]
3	**7**	72	71	33[b]
4	**8**	48	5	21[b]
5	**1a**	48	69	83
6	**1b**	48	67	87
7[c]	**1a**	48	16	91
8	**9**	48	6	78[b]
9	**10**	72	9	<2
10	**11**	24	8	7
11	**12**	48	27	55
12	**13**	24	<2	<2
13	**14**	24	<2	<2
14	**15**	24	<2	<2

[a] Conversion and ee were determined by chiral HPLC analysis. [b] (*S*)-Enantiomer was formed in excess. [c] Reaction was carried out at −20 °C.

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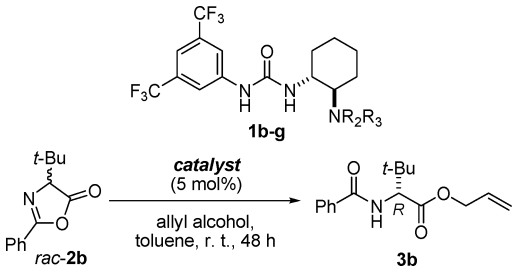
Table 3 Variation of the tertiary amine part



Entry	Catalyst	R_2	R_3	Conversion (%)[a]	ee (%)[a]
1	**1b**	Me	Me	67	87
2	**1c**	$-(CH_2)_4-$		75	75
3	**1d**	Et	Et	16	73
4	**1e**	Bn	Bn	<2	n.d.
5	**1f**	Me	Bn	<2	n.d.
6	**1g**	Allyl	Allyl	<2	n.d.

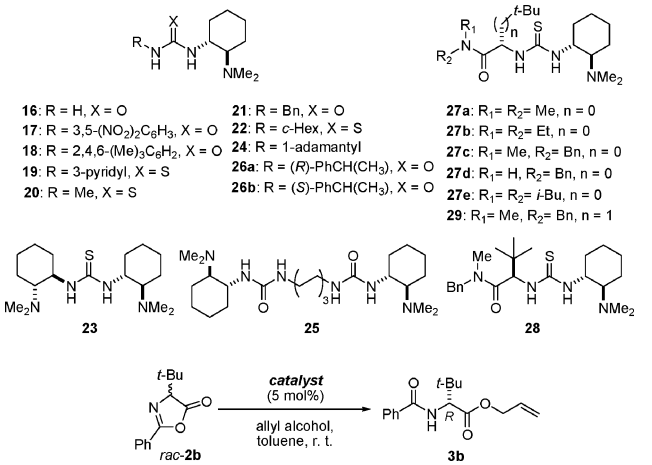
[a] Conversion and ee were determined by chiral HPLC analysis.

achieved at room temperature (entries 5 and 6). However, in the case of catalyst **1a**, by lowering the temperature to −20 °C, the enantioselectivity could be increased to 91% albeit at the expense of reaction rate (entry 7). For further optimization of the catalyst structure, *trans*-1,2-diamino cyclohexane was exclusively used as the diamine backbone.

We next turned our attention to the substitution pattern on the Brønsted basic tertiary amine part of the catalyst (Table 3). The exchange of the dimethylamino group for a pyrrolidine unit (**1c**) resulted in slightly higher conversion (75% compared to 67%) and a lower enantioselectivity of 75% compared to 87% with catalyst **1b** (entries 1 and 2). Increasing the steric demand of the *N*-substituents from methyl to ethyl resulted in drastically diminished conversion (67 to 16% after 48 h, entries 1 and 3). A similar but less pronounced trend was observed for the enantioselectivities, with a drop of ee from 87 to 73%. Further increase in steric bulk of the substituents completely eliminates the catalytic activity (entries 4–6). It is interesting to note that even the replacement of one methyl group on the tertiary amine by a benzyl group (**1f**) is sufficient to inactivate the catalyst (entry 5). These examples demonstrate that the catalytic activity is quite sensitive to the substituents on the tertiary amine nitrogen atom whereas the selectivity is almost unaffected by these substituents.

Having optimized the diamine part of the catalyst to *N*,*N*-dimethyl-1,2-diaminocyclohexane, we went on for further screening to find out the optimum substituent on the other (thio)urea nitrogen atom. At this stage of optimization, the best catalysts we found in terms of both activity and enantioselectivity were the bifunctional thiourea **1a** and urea **1b** containing the 3,5-bis(trifluoromethyl)phenyl moiety (see Table 2, entries 5–7). We reasoned that changing the steric and electronic properties of the substituent at this part of the molecule would substantially influence both the catalytic activity as well as the enantioselectivity. For this purpose, we synthesized several ureas and thioureas containing substituents with varying steric and electronic demand (Table 4). First, we replaced the 3,5-bis(trifluoromethyl)phenyl moiety of compound **1b** with only a hydrogen atom. To our

Table 4 Optimization of the (thio)urea *N*-substituents



Entry	Catalyst	Time/h	Conversion (%)[a]	ee (%)[a]
1[b]	**16**	24	7	58
2	**17**	48	66	86
3	**18**	48	9	84
4	**19**	48	12	82
5	**20**	66	35	78
6	**21**	48	13	81
7	**22**	48	47	87
8	**23**	48	33	88
9	**24**	48	32	87
10	**25**	48	30	80
11	**26a**	72	28	85
12	**26b**	24	18	88
13	**27a**	24	23	91
14	**27b**	48	26	90
15	**27c**	48	28	95
16	**27d**	48	38	92
17	**27e**	48	15	86
18	**28**	24	3	77
19	**29**	48	23	92

[a] Conversion and ee were determined by chiral HPLC analysis. [b] Phenylalanine-derived azlactone *rac*-**2a** was used as substrate.

surprise, even this simplest bifunctional urea derivative **16** proved to be moderately enantioselective in the ring opening of the phenylalanine-derived azlactone **2a** although the activity was low (entry 1). Because of its higher reactivity towards alcoholytic ring opening, the phenylalanine-derived azlactone was chosen in this particular case instead of azlactone **2b**. The exchange of the trifluoromethyl groups of catalyst **1b** with nitro groups gave the urea **17** which showed similar activity and enantioselectivity as **1b** (entry 2). In contrast, the urea **18** containing the electron rich and bulky mesityl substituent on the urea nitrogen atom showed considerably lower conversion (9%), whereas the enantioselectivity remained almost the same (entry 3). In line with this observation, the pyridine substituted thiourea **19** was found to have similar catalytic behaviour as the mesityl urea **18** with 12% conversion and 82% ee after 48 h (entries 3 and 4). In the next stage of the optimization, we examined a series of bifunctional organocatalysts bearing simple aliphatic substituents with increasing sterical demand (**20**–**22**, **24**). Methyl and benzyl substituted catalysts **20** and **21** provided similar enantioselectivities of 78 and 81% respectively but with lower conversions (entries 5 and 6). Cyclohexyl substitution

(thiourea **22**), on the other hand, increased both reactivity and enantoselectivity. After 48 h, the product **3b** was obtained in 87% ee and with a conversion of 47% (entry 7). Please note that the C_2-symmetric bifunctional thiourea **23** showed selectivity comparable to **22** (entry 8). Further enhancement of steric bulk by exchanging the cyclohexyl for a 1-adamantyl group (catalyst **24**) did not improve the selectivity but the conversion dropped from 47 to 32% (entries 7 and 9). The idea to enhance reactivity by incorporating two active centers in a single molecule yielded compound **25** (Table 4). Unfortunately, the reaction rate was not improved significantly when 5 mol% **25** was used as the catalyst in our test reaction (entry 10). However, the selectivity obtained was on the same level as with catalysts **20** and **21** (*vide supra*).

After studying the effect of various achiral substituents at the (thio)urea nitrogen atom, we set out to investigate the influence of an additional chiral centre at this part of the molecule. Incorporation of a 1-phenylethyl group furnished the two diastereomeric catalysts **26a–b**, neither of them showing enhanced selectivity (entries 11–12). We reasoned that inclusion of a bulkier group at the additional chiral centre might have a beneficial effect on the selectivity of the DKR. To prove this, we synthesized the L-*tert*-leucine amide-derived catalysts **27a–e** with different substituents at the amide nitrogen atom (Table 4). To our delight, enhancement in enantioselectivity, with a "jump" of ee values to the range >90% resulted with catalysts **27a–d** (entries 13–16). It was found that the substitution pattern of the amide controls both reactivity and enantioselectivity. Whereas *N*,*N*-dimethyl and *N*,*N*-diethyl amide catalysts **27a** and **27b** showed comparable selectivities of 90% and 91% ee, respectively, changing to *N*-methyl-*N*-benzyl substituents in **27c** significantly improved the selectivity (entries 13–15). After 48 h, the product ester **3b** was formed with 28% conversion and an excellent ee of 95% (entry 15). At this point, it is interesting to note that the "mismatched" diastereomeric catalyst **28**, derived from D-*tert*-leucine, provided significantly lower conversion and enantioselectivity (77% *vs.* 95%; entry 18). Replacement of the methyl group of the "matched" catalyst **27c** with a hydrogen atom (**27d**) increased the reaction rate (from 28 to 38% after 48 h) at the expense of enantioselectivity (95 *vs.* 92% ee; entries 15 and 16). That the optimum steric bulk of these substituents is essential for providing efficient catalytic performance is supported by the behaviour of the *N*,*N*-diisobutyl amide catalyst **27e**: both lower conversion (15%) and selectivity (86% ee) were obtained after 48 h (entry 17). In line with this argumentation, increasing the steric demand of the substituent at the additional chiral centre from *tert*-butyl to neopentyl in **29** did not provide any further enhancement (entry 19).

Conclusions

In summary, we have described the synthesis and screening of a library of (thio)urea-based bifunctional organocatalysts for the alcoholytic DKR of azlactones. Due to the modular structure of the compounds, it was possible to vary different parts of the catalyst structure independently. This allowed us to identify and optimize the parts of the catalyst structure which are crucial for both high reactivity and enantioselectivity. By this approach, the catalyst **27c** was found to be optimally selective in the DKR of *tert*-leucine derived azlactone **2b** with allyl alcohol.

Experimental

General

All reactions were carried out in oven-dried or flame-dried round bottomed flasks, and the reactions were conducted under a positive pressure of argon, unless otherwise stated. Stainless steel syringes or cannulae were used to transfer air- and/or moisture-sensitive liquids. Chromatographic separations were performed using silica gel 60 (230–400 mesh) from MN GmbH & Co. Commercial reagents were purchased from standard suppliers, and used as received. Solvents were distilled and dried prior to use following standard procedures.[10] Nuclear magnetic resonance (^{1}H and ^{13}C) spectra were recorded on Bruker AC250 (250 MHz), Bruker AC300 (300 MHz), Bruker DPX300 (300 MHz) or Bruker DRX500 (500 MHz) NMR spectrometers. Chemical shifts for protons and carbon atoms are reported in parts per million (ppm) downfield from tetramethylsilane and are referenced to residual protons in the NMR solvent ($CHCl_3$: δ 7.24) and carbon resonances of the solvent ($CDCl_3$: δ 77.0) respectively. Infrared (IR) spectra were recorded on a Perkin-Elmer 1600 Series FTIR or Perkin-Elmer Paragon 1000 FT-IR spectrometer with ATR technique. Data are reported as: wave number of absorption band (cm^{-1}), intensity of absorption band (vs = very strong, s = strong, m = medium, w = weak, br = broad, sh = sharp). Chiral HPLC analyses were performed using Agilent 1100 Series or Merck-Hitachi Lachrom HPLC instruments. Melting points were measured on a Büchi 535 Melting Point apparatus and are uncorrected. HRMS data were recorded on a Finnigan MAT 900S instrument (Δmu = 5). Optical rotations were measured using a 1 mL cell with a 1 dm path length on a Perkin-Elmer 343plus polarimeter at 20 °C.

Synthesis of azlactones

The azlactones were prepared by cyclodehydration of the corresponding racemic *N*-benzoyl amino acids with acetic anhydride according to the procedure by Goodman and Glaser.[11]

2-Phenyl-4-benzyloxazolone *rac*-2a. Compound *rac*-**2a** was prepared from *rac*-*N*-benzoylphenylalanine (1.00 g, 3.71 mmol) and isolated as a crystalline solid (730 mg, 78%). Mp 69–70 °C [lit.[12] 70–71 °C]. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 3.19 (dd, J = 6.7, 14.0 Hz; 1H), 3.38 (dd, J = 4.9, 13.9 Hz; 1H), 4.70 (dd, J = 4.9, 6.7 Hz; 1H), 7.18–7.28 (m; 5H), 7.42–7.48 (m; 2H), 7.52–7.58 (m; 1H), 7.90–7.94 (m; 2H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 37.3, 66.5, 125.7, 127.2, 127.8, 128.4, 128.7, 129.5, 132.7, 135.2, 161.7, 177.6. FT-IR (ATR):ν[cm^{-1}] = 1827 (s), 1814 (s), 1651 (s), 1450 (w), 1323 (w), 1296 (m), 1079 (m), 1048 (m), 943 (w), 902 (m), 756 (w), 659 (s).

2-Phenyl-4-*tert*-butyloxazolone *rac*-2b. Compound *rac*-**2b** was prepared from (*S*)-*N*-benzoyl-*tert*-leucine (1.00 g, 4.25 mmol) and isolated as a crystalline white solid (580 mg, 63%). Mp 69 °C [lit.[13] 73–74 °C]. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.14 (s; 9H), 4.08 (s; 1H), 7.46–7.60 (m; 3H), 8.00–8.04 (m; 2H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 26.2, 35.9, 74.1, 125.9, 127.9, 128.7, 132.6, 161.2, 177.0. FT-IR (ATR): ν[cm^{-1}] = 1814 (m), 1652 (s), 1603 (s), 1346 (m), 1143 (w), 1066 (w), 1019 (m), 923 (w), 888 (m), 782 (w), 702 (m), 586 (w).

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Synthesis of allyl esters

The allyl esters **3a–b** were prepared by reaction of the corresponding racemic *N*-benzoyl amino acids with thionyl chloride (1.15 eq.) in allyl alcohol as solvent.

2-Benzoylamino-3-phenylpropionic acid allyl ester 3a. Compound *rac*-**3a** was prepared from *rac*-*N*-benzoylphenylalanine (500 mg, 1.86 mmol, 1.00 eq.) and thionyl chloride (150 µL, 2.14 mmol, 1.15 eq.) in allyl alcohol (3.5 mL), and isolated as a white solid (482 mg, 84%). Mp 70 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 3.19–3.34 (m; 2H), 4.63–4.66 (m; 2H), 5.07–5.15 (m; 1H), 5.25–5.38 (m; 2H), 5.82–5.98 (m; 1H), 6.60 (d, J = 7.62 Hz; 1H), 7.12–7.52 (m; 8H), 7.70–7.75 (m; 2H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 37.9, 55.5, 66.2, 119.2, 127.0, 127.2, 128.6, 129.4, 131.3, 131.7, 133.9, 135.8, 166.8, 171.3. FT-IR (ATR): ν[cm^{-1}] = 3313 (w), 2926 (m), 1741 (s), 1642 (s), 1601 (m), 1579 (m), 1530 (s), 1487 (m), 1453 (w), 1180 (m), 1099 (m), 987 (w), 933 (w), 700 (m).

2-Benzoylamino-3,3-dimethylbutyric acid allyl ester 3b. Compound *rac*-**3b** was prepared from *rac*-*N*-benzoyl-*tert*-leucine (500 mg, 2.13 mmol, 1.00 eq.) and thionyl chloride (172 µL, 2.45 mmol, 1.15 eq.) in allyl alcohol (3.5 mL), and isolated as a colourless oil (270 mg, 46%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.05 (s; 9H), 4.62–4.66 (m; 2H), 4.72 (d, J = 9.4 Hz; 1H), 5.22–5.39 (m; 2H), 5.84–6.00 (m; 1H), 6.68 (d, J = 9.1 Hz; 1H), 7.39–7.54 (m; 3H), 7.77–7.81 (m; 2H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 26.7, 35.3, 60.2, 65.8, 119.2, 127.0, 128.6, 131.4, 131.7, 134.2, 167.1, 171.4. FT-IR (ATR): ν[cm^{-1}] = 3340 (w), 2962 (m), 1734 (s), 1647 (s), 1601 (w), 1579 (w), 1517 (s), 1485 (s), 1445 (w), 1400 (w), 1368 (m), 1335 (m), 1268 (w), 1211 (m), 1166 (m), 1091 (w), 1029 (w), 987 (m), 933 (w), 854 (w), 800 (w), 750 (w).

Typical procedure for the DKR of azlactones

To a solution of 8.33 µmol of the catalysts **6–30** (0.05 eq.) in 667 µl abs. toluene, 1.5 eq. of allyl alcohol were added. In the case of the monofunctional catalysts **4** and **5**, 8.33 µmol NEt_3 (0.05 eq.) were added. After addition of a solution containing 167 µmol of the azlactone *rac*-**2a–b** (1.00 eq.) in 1.00 ml abs. toluene, the homogeneous reaction mixture was stirred at ambient temperature. For analysis, 100 µl samples were withdrawn, diluted with 900 µl dichloromethane, and conversion and enantiomeric excess were determined immediately by HPLC (Daicel Chiralpak AD, *n*-hexane–2-propanol). Quantification was based on UV detection at λ = 230 nm and 210 nm, respectively. Conversion was determined by comparison with the peak areas of stock solutions of the azlactones and the corresponding *N*-benzoyl amino acid esters in dichloromethane. The absolute configurations of the product esters **3a–b** were determined by comparison with the esters synthesized from enantiomerically pure α-amino acids.

Synthesis of catalysts†

General procedure for the preparation of (thio)ureas: the iso(thio)cyanate (1.00 eq.) was added to a solution of the amine (1.00 eq.) in abs. THF, and the resulting mixture was stirred at room temperature under argon for 16 h. The reaction mixture was then concentrated *in vacuo* and the residue was purified by silica gel chromatography using CH_2Cl_2–CH_3OH–NEt_3 mixtures as the eluent.

1-{3,5-Bis(trifluoromethyl)phenyl}-3-{(1*R*,2*R*)-2-(dimethylamino)cyclohexyl}thiourea 1a. Compound **1a** was prepared from the corresponding amine (526 mg, 3.69 mmol, 1.00 eq.) and 3,5-bis(trifluoromethyl)phenyl isothiocyanate (670 µL, 3.69 mmol, 1.00 eq.), and isolated as a yellowish foam (1.28 g, 84%). Mp 111–113 °C. $[\alpha]_{589}$ = −30.9, $[\alpha]_{546}$ = −39.5, $[\alpha]_{405}$ = −166.2 (c = 1.035, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.07–1.36 (m; 4H, *H*-3), 1.69–1.91 (m; 3H), 2.26 (s; 6H), 2.41–2.55 (m; 2H, *H*-1), 3.88 (m; 1H), 7.58 (s; 1H), 7.83 (s; 2H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 21.9, 24.5, 24.8, 32.8, 40.1, 56.6, 67.4, 118.3, 123.0 (q, J = 271.05 Hz), 123.3, 132.5 (q, J = 33.15 Hz), 140.4, 178.7. FT-IR (CsI): ν[cm^{-1}] = 3225 (br w), 2944 (m), 2867 (w), 1544 (s), 1474 (m), 1386 (s), 1280 (s), 1181 (s), 1132 (s), 885 (m), 683 (m). HRMS (EI): calcd for [$C_{17}H_{21}F_6N_3S$] ([M]$^+$): 413.136, found: 413.138. Elemental analysis: anal. calcd. for $C_{17}H_{21}F_6N_3S$: C 49.39, H 5.12, N 10.16, found: C 49.19, H 5.15, N 10.12%.

1-{3,5-Bis(trifluoromethyl)phenyl}-3-{(1*R*,2*R*)-2-(dimethylamino)cyclohexyl}urea 1b. Compound **1b** was prepared from the corresponding amine (735 mg, 5.17 mmol, 1.00 eq.) and 3,5-bis(trifluoromethyl)phenyl isocyanate (939 µL, 5.17 mmol, 1.00 eq.), and isolated as an off-white crystalline solid (1.79 g, 87%). Mp 163–165 °C. $[\alpha]_{589}$ = −35.1, $[\alpha]_{546}$ = −41.5, $[\alpha]_{405}$ = −83.1, $[\alpha]_{365}$ = −106.8 (c = 1.00, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.09–1.35 (m; 4H), 1.67–1.89 (m; 3H), 2.20–2.25 (m; 1H), 2.26 (s; 6H), 2.34–2.38 (m; 1H), 3.47–3.55 (m; 1H), 5.76 (br s; 2H), 7.36 (s; 1H), 7.76 (s; 2H), 8.06 (br s; 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 21.4, 24.7, 25.0, 33.8, 40.1, 51.6, 67.4, 115.3, 118.5, 123.2 (q, J = 271.0 Hz), 131.9 (q, J = 32.97 Hz), 140.9, 155.6. FT-IR (CsI): ν[cm^{-1}] = 3320 (br), 2941 (m), 2866 (w), 2787 (w), 1853 (s), 1604 (s), 1574 (s), 1516 (m), 1474 (m), 1388 (s), 1342 (m), 1279 (s), 1235 (w), 1175 (s), 1132 (s), 1067 (w), 1045 (w), 942 (w), 884 (m), 849 (w), 704 (m), 685 (m), 664 (w). HRMS (EI): calcd for [$C_{17}H_{21}F_6N_3O$] ([M]+): 397.159, found: 397.159. Elemental analysis: anal. calcd for $C_{17}H_{21}F_6N_3O$: C 51.38, H 5.33, N 10.57, found: C 51.29, H 5.40, N 10.41%.

1-{3,5-Bis(trifluoromethyl)phenyl}-3-{(1*R*,2*R*)-2-(pyrrolidin-1-yl)cyclohexyl}urea 1c. Compound **1c** was prepared from the corresponding amine (325 mg, 1.93 mmol, 1.00 eq.) and 3,5-bis(trifluoromethyl)phenyl isocyanate (350 µL, 1.93 mmol, 1.00 eq.), and isolated as a yellowish foam (578 mg, 71%). Mp 98–100 °C. $[\alpha]_{589}$ = −18.7, $[\alpha]_{546}$ = −21.9, $[\alpha]_{405}$ = −37.7 (c = 1.00, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.07–1.36 (m; 4H), 1.62–1.86 (m; 7H), 2.25–2.29 (m; 1H), 2.44–2.48 (m; 1H), 2.62–2.71 (m; 4H), 3.50 (m; 1H), 5.87 (br s; 1H), 7.36 (s; 1H), 7.80 (s; 2H), 8.56 (br s; 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 23.1, 23.6, 24.3, 24.6, 33.1, 48.0, 53.3, 63.4, 115.2, 118.2, 123.0 (q, J = 271.1 Hz), 132.0 (q, J = 32.97 Hz), 141.1, 155.9. FT-IR (CsI): ν[cm^{-1}] = 3320 (br), 3112 (w), 2940 (m), 1863 (w), 1813 (w), 1663 (s), 1575 (s), 1508 (w), 1475 (m), 1390 (s), 1340 (w), 1278 (s), 1235 (w), 1182 (s), 1133 (s), 1040 (w), 941 (w), 881 (m), 848 (w), 704 (m), 682 (m). HRMS (ESI): calcd for [$C_{19}H_{24}F_6N_3O$] ([M + H]$^+$): 424.182, found: 424.183. Elemental analysis: anal. calcd for $C_{19}H_{23}F_6N_3O$: C 53.90, H 5.48, N 9.92, found: C 53.58, H 5.47, N 9.81%.

1-{3,5-Bis(trifluoromethyl)phenyl}-3-{(1*R*,2*R*)-2-(diethylamino)cyclohexyl}urea 1d. Compound **1d** was prepared from the corresponding amine (325 mmol, 1.91 mmol, 1.00 eq.) and

3,5-bis(trifluoromethyl)phenyl isocyanate (349 μL, 1.91 mmol, 1.00 eq.), isolated as a colourless crystalline solid (580 mg, 71%). Mp 195–197 °C. $[\alpha]_{589} = -58.1$, $[\alpha]_{546} = -68.7$, $[\alpha]_{405} = -134.5$, $[\alpha]_{365} = -174.0$, $[\alpha]_{334} = -226.1$ ($c = 1.01$, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 0.98$ (t, $J = 7.13$ Hz; 6H), 1.04–1.31 (m; 4H), 1.63–1.81 (m; 3H), 2.28–2.73 (m; 6H), 3.35–3.41 (m; 1H), 5.92 (br s; 1H), 7.42 (s; 1H), 7.86 (s; 2H). ^{13}C-NMR (75 MHz, $CDCl_3$): $\delta = 14.2$, 23.5, 24.5, 25.5, 33.4, 43.2, 51.9, 63.0, 115.5, 118.6, 123.2 (q, $J = 271.1$ Hz), 132.1 (q, $J = 32.97$ Hz), 141.0, 155.8. FT-IR (CsI): ν[cm^{-1}] = 3286 (s), 3099 (m), 2974 (m), 2937 (m), 2867 (w), 1667 (s), 1623 (w), 1581 (s), 1493 (s), 1476 (s), 1389 (s), 1338 (m), 1279 (s), 1238 (m), 1169 (s), 1140 (s), 1073 (w), 1000 (w), 957 (m), 882 (m), 734 (m). HRMS (ESI): calcd. for [$C_{19}H_{26}F_6N_3O$] ([M + H]$^+$): 426.198, found: 426.199. Elemental analysis: anal. calcd for $C_{19}H_{25}F_6N_3O$: C 53.64, H 5.92, N 9.88, found: C 53.56, H 5.93, N 9.85.

1-{3,5-Bis(trifluoromethyl)phenyl}-3-{(1*R*,2*R*)-2-(dibenzylamino)-cyclohexyl}urea 1e. Compound **1e** was prepared from the corresponding amine (160 mg, 632 μmol, 1.00 eq.) and 3,5-bis(trifluoromethyl)phenyl isocyanate (109 μL, 632 μmol, 1.00 eq.), and isolated as an off-white solid (270 mg, 83%). Mp 94 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 0.85$–0.96 (m; 1H), 1.13–1.28 (m; 2H), 1.35–1.48 (m; 1H), 1.62 (br d, $J = 11.8$ Hz; 1H), 1.85 (br d, $J = 10.4$ Hz; 1H), 2.12 (br d, $J = 11.1$ Hz; 1H), 2.30–2.38 (m; 2H), 3.41 (d, $J = 13.1$ Hz; 2H), 3.51–3.61 (m; 1H), 3.82 (d, $J = 13.3$ Hz; 2H), 5.08 (br s; 1H), 6.61 (br s; 1H), 7.22–7.27 (m; 10H), 7.51 (s; 1H), 7.81 (s; 2H). ^{13}C-NMR (75 MHz, $CDCl_3$): $\delta = 23.4$, 24.4, 25.4, 33.4, 51.4, 53.6, 61.6, 116.0, 118.8, 123.2 (q, $J = 273$ Hz), 127.4, 128.5, 129.0, 132.4 (q, $J = 33.6$ Hz), 139.8, 140.5, 154.9. FT-IR (ATR): ν[cm^{-1}] = 3329 (br, m), 3086 (w), 3026 (w), 2933 (m), 2859 (w), 1651 (s), 1565 (s), 1493 (m), 1470 (s), 1451 (m), 1378 (vs), 1274 (vs), 1173 (vs), 1129 (vs), 1036 (m), 1027 (m), 940 (m), 928 (m), 882 (s), 845 (m), 747 (m), 732 (m), 699 (s), 681 (vs).

1-{3,5-Bis(trifluoromethyl)phenyl}-3-{(1*R*,2*R*)-2-(*N*-benzyl-*N*-methylamino)cyclohexyl}urea 1f. Compound **1f** was prepared from the corresponding amine (421 mg, 1.93 mmol, 1.00 eq.) and 3,5-bis(trifluoromethyl)phenyl isocyanate (350 μL, 1.93 mmol, 1.00 eq.), and isolated as a colourless crystalline solid (980 mg, 87%). ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 0.99$–1.25 (m; 4H), 1.57–1.89 (m; 3H), 2.09 (s; 3H), 2.26–2.37 (m; 2H), 3.34 (d, $J = 13.1$ Hz; 1H), 3.40–3.47 (m; 1H), 3.61 (d, $J = 13.1$ Hz; 1H), 5.71 (br s; 1H), 7.15 (s; 5H), 7.38 (s; 1H), 7.68 (s; 2H), 8.18 (br s; 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): $\delta = 22.7$, 24.5, 25.2, 33.4, 36.3, 52.0, 57.9, 66.4, 115.5, 118.8, 123.2 (q, $J = 271.4$ Hz), 127.1, 128.3, 128.7, 132.1 (q, $J = 32.97$ Hz), 139.0, 140.9, 156.0. FT-IR (KBr): ν[cm^{-1}] = 3346 (br s), 3091 (w), 2939 (s), 2861 (m), 2800 (w), 1659 (s), 1624 (m), 1571 (s), 1497 (m), 1474 (s), 1454 (m), 1388 (s), 1278 (s), 1235 (m), 1182 (s), 1132 (s), 1063 (w), 1042 (w), 1026 (m), 958 (w), 940 (m), 882 (s), 849 (m), 734 (m), 701 (s). HRMS (EI): calcd for [$C_{23}H_{25}F_6N_3O$] ([M]$^+$): 473.190, found: 473.190.

1-{3,5-Bis(trifluoromethyl)phenyl}-3-{(1*R*,2*R*)-2-(diallylamino)-cyclohexyl}urea 1g. Compound **1g** was prepared from the corresponding amine (170 mg, 875 μmol, 1.00 eq.) and 3,5-bis(trifluoromethyl)phenyl isocyanate (152 μL, 875 μmol, 1.00 eq.), and isolated as a colourless crystalline solid (200 mg, 51%). Mp 119 °C. $[\alpha]_{589} = -13.4$, $[\alpha]_{546} = -14.3$, $[\alpha]_{405} = -16.1$, ($c = 1.01$, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 1.02$–1.31 (m; 4H), 1.67 (br d, $J = 11.1$ Hz; 1H), 1.79–1.90 (m; 2H), 2.43–2.53 (m; 2H), 2.88 (dd, $J = 8.0$, 14.1 Hz; 2H), 3.27 (ddd, $J = 3.8$, 6.0, 10.6 Hz; 2H), 3.42 (tt, $J = 3.4$, 10.5 Hz; 1H), 5.11 (dd, $J = 13.6$, 14.5 Hz; 4H), 5.64 (br s; 1H), 5.66–5.78 (m; 2H), 7.25 (br s; 1H), 7.47 (s; 1H), 7.87 (s; 2H). ^{13}C-NMR (75 MHz, $CDCl_3$): $\delta = 23.3$, 24.5, 25.4, 33.3, 52.2, 52.3, 62.1, 115.8, 117.4, 118.8, 123.2 (q, $J = 273$ Hz), 132.2 (q, $J = 33.1$ Hz), 136.5, 140.7, 155.4. FT-IR (ATR): ν[cm^{-1}] = 3378 (w, br), 3083 (w), 2933 (m), 2859 (w), 2812 (w), 1653 (s), 1622 (m), 1569 (s), 1500 (s), 1472 (s), 1338 (m), 1275 (s), 1234 (s), 1172 (s), 1130 (s), 1037 (m), 998 (m), 945 (m), 920 (m), 881 (s), 847 (m), 732 (m), 702 (s), 681 (s). Elemental analysis: anal. calcd for $C_{21}H_{25}F_6N_3O$: C 56.12, H 5.61, N 9.35, found: C 55.71, H 5.50, N 9.16%.

***N*-[3,5-Bis(trifluoromethyl)phenyl]-*N*′-[(1*R*,3*S*)-3-{[({[3,5-bis-(trifluoromethyl)phenyl]amino}oxomethyl)amino]methyl}-3,5,5-trimethylcyclohexyl]urea 5a.** Compound **5a** was prepared from the corresponding diamine (272 μL, 1.47 mmol, 1.00 eq.) and 3,5-bis(trifluoromethyl)phenyl isocyanate (534 μL, 3.09 mmol, 2.00 eq.), and isolated as colourless crystals from $CHCl_3$–methanol (900 mg, 90%). Mp >230 °C. ^{1}H-NMR (300 MHz, DMSO-d_6): $\delta = 0.86$–1.12 (m; 12H), 1.13–1.26 (m; 1H), 1.53–1.67 (m; 2H), 2.80–3.00 (m; 2H), 3.74–3.91 (m; 1H), 6.33 (d; $J = 7.60$ Hz, 1H), 6.50–6.60 (m; 1H), 7.51 (s; 2H), 8.04 (s; 4H), 9.02 (s; 1H), 9.13 (s; 1H). ^{13}C-NMR (75 MHz, DMSO-d_6): $\delta = 23.1$, 27.4, 31.5, 34.9, 36.2, 41.4, 42.7, 45.7, 46.8, 52.7, 113.3, 113.4, 117.0, 117.1, 121.5, 125.1, 130.5 (q), 130.6 (q), 142.5, 154.0, 155.0. FT-IR (ATR, neat): ν[cm^{-1}] = 3339 (br w), 2955 (br w), 1652 (m), 1558 (m), 1427 (m), 1438 (w), 1385 (m), 1274 (s), 1230 (m), 1172 (m), 1127 (s), 1037 (w), 940 (w), 880 (m), 847 (w), 701, 681 (both m). HRMS (ESI): calcd for [$C_{28}H_{28}F_{12}N_4O_2Na$] ([M + Na]$^+$): 703.192, found: 703.192.

***N*-[3,5-Bis(trifluoromethyl)phenyl]-*N*′-[(1*R*,3*S*)-3-{[({[3,5-bis-(trifluoromethyl)phenyl]amino}thioxomethyl)amino]-methyl}-3,5,5-trimethylcyclohexyl]thiourea 5b.** Compound **5b** was prepared from the corresponding diamine (500 μL, 2.70 mmol, 1.00 eq.) and 3,5-bis(trifluoromethyl)phenyl isothiocyanate (991 μL, 5.43 mmol, 2.00 eq.), and isolated as colourless crystals from *n*-hexane–ethylacetate (1.73 g, 90%). Mp = 153 °C. $[\alpha]_{589} = +17.2$ ($c = 1.00$, $CHCl_3$). ^{1}H-NMR (300 MHz, DMSO-d_6): $\delta = 0.96$ (s; 3H), 1.02–1.21 (m; 9H), 1.24–1.36 (m; 1H), 1.65–1.85 (m; 2H), 3.28–3.51 (m; 2H), 4.47–4.67 (m; 1H), 7.66–7.75 (m; 2H), 8.09–8.19 (m; 2H), 8.21 (s; 2H), 8.29 (s; 2H), 9.85 (s; 1H), 10.07 (s; 1H). ^{13}C-NMR (75 MHz, DMSO-d_6): $\delta = 23.2$, 27.4, 31.6, 34.0, 34.7, 36.4, 40.6, 40.8, 44.3, 47.3, 57.3, 115.9, 121.4, 121.5, 121.9, 125.0, 130.2, 141.8, 179.3, 181.2. FT-IR (ATR, neat): ν[cm^{-1}] = 3240 (br w), 3049 (br w), 2957 (br w), 1621 (w), 1530 (s), 1469 (m), 1380 (s), 1274 (s), 1170 (s), 1130 (s), 1106 (s), 950 (m), 906 (m), 886 (m), 847 (w), 729 (s), 700 (s), 680 (s). HRMS (ESI): calcd for [$C_{28}H_{28}F_{12}N_4S_2Na$] ([M + Na]$^+$): 735.146, found: 735.147. Elemental analysis: anal. calcd for $C_{28}H_{28}F_{12}N_4S_2$: C 47.19, H 3.96, N 7.86, found: C 47.15, H 4.19, N 7.81%.

1-{3,5-Bis(trifluoromethyl)phenyl}-3-{(2*S*,5*R*)-5-vinyl-1-azabicyclo[2.2.2]oct-2-ylmethyl}urea 6a. Compound **6a** was prepared from the corresponding amine (166 mg, 1.00 mmol, 1.00 eq.) and 3,5-bis(trifluoromethyl)phenyl isocyanate (174 μL, 1.00 mmol, 1.00 eq.), and isolated as a colourless solid (237 mg, 60%). Mp = 78–81 °C. $[\alpha]_{589} = -1.4$, $[\alpha]_{546} = -2.2$, $[\alpha]_{405} = -2.8$ ($c = 1.03$,

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$CHCl_3$). ^{1}H-NMR (500 MHz, DMSO-d_6): $\delta = 0.72$–0.76 (m; 1H), 1.33, 1.51 (m; 2H), 1.65–1.69 (m; 1H), 2.13 (br s; 1H), 2.39 (br s; 1H), 2.43–2.82 (m; 2H), 2.79 (m; 1H), 2.88–3.13 (m; 2H), 2.98–3.20 (m; 2H), 4.85–4.93 (m; 2H), 5.75–5.82 (m; 1H), 6.17 (s; 1H), 7.37 (s; 1H), 7.90 (s; 2H), 9.35 (br s; 1H). ^{13}C-NMR (125 MHz, DMSO-d_6): $\delta = 25.7$, 27.1, 27.3, 40.4, 42.1, 45.7, 54.9, 55.1, 113.2, 114.2, 116.8, 120.1, 122.2, 124.4, 126.6, 130.3, 130.5, 130.8, 131.0, 142.1, 142.6, 154.6. FT-IR (ATR, neat): ν[cm^{-1}] = 3328 (br w), 3084 (w), 2937 (w), 2866 (w), 1664 (m), 1570 (m), 1472 (m), 1386 (m), 1275 (s), 1176 (m), 1127 (m), 989 (w), 942 (w), 913 (w), 879 (w), 702 (w), 681 (m). HRMS (ESI): calcd for [$C_{19}H_{22}F_6N_3O$] ([M + H]$^+$): 422.167, found: 422.167. Elemental analysis: anal. calcd for $C_{19}H_{21}F_6N_3O$: C 54.16, H 5.02, N 9.97, found: C 54.42, H 5.22, N 9.81%.

1-{3,5-Bis(trifluoromethyl)phenyl}-3-{(2*S*,5*R*)-5-vinyl-1-azabicyclo[2.2.2]oct-2-ylmethyl}thiourea 6b. Compound **6b** was prepared from the corresponding amine (948 mg, 2.25 mmol, 1.00 eq.) and 3,5-bis(trifluoromethyl)phenyl isothiocyanate (610 mg, 2.25 mmol, 1.00 eq.), and isolated as a colourless crystalline solid (912 mg, 93%). Mp 54–59 °C. $[\alpha]_{589} = -52.6$, $[\alpha]_{546} = -61.0$, $[\alpha]_{405} = -62.4$, $[\alpha]_{365} = +117.6$ ($c = 1.00$, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 0.97$–1.03 (m; 1H), 1.13–1.31 (m; 1H), 1.53–1.70 (m; 2H), 1.78–2.00 (m; 2H), 2.51–2.75 (m; 2H), 2.83–3.21 (m; 4H), 3.39–3.89 (m; 1H), 5.01–5.14 (m; 2H), 5.77–5.92 (m; 1H), 7.69 (s; 1H), 7.85–7.90 (m; 2H), 7.91 (s; 1H), 13.9 (s; 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): $\delta = 26.1$, 27.3, 27.5, 30.1, 40.4, 42.1, 47.7, 54.8, 115.1, 118.0, 122.6, 123.1 ($J = 272.9$ Hz), 132.3 (m, br), 140.8, 141.2, 179.8. FT-IR (ATR): ν[cm^{-1}] = 2941 (br), 1542 (w), 1472 (w), 1384 (m), 1276 (s), 1177 (m), 1132 (m), 883 (w), 700 (w), 682 (w). HRMS (EI): calcd for [$C_{19}H_{21}F_6N_3S$] ([M]+): 437.136, found: 437.136. Elemental analysis: anal. calcd for $C_{19}H_{22}F_6N_3S$: C 52.17, H 4.84, N 9.61, found: C 52.35, H 4.67, N 9.61%.

1-{3,5-Bis(trifluoromethyl)phenyl}-3-{(2*R*,5*R*)-5-vinyl-1-azabicyclo[2.2.2]oct-2-ylmethyl}urea 7. Compound **7** was prepared from the corresponding amine (166 mg, 1.00 mmol, 1.00 eq.) and 3,5-bis(trifluoromethyl)phenyl isocyanate (174 µL, 1.00 mmol, 1.00 eq.), and isolated as colourless solid (260 mg, 66%). Mp = 65 °C. $[\alpha]_{589} = +65.0$, $[\alpha]_{546} = +77.2$, $[\alpha]_{405} = +156.0$ ($c = 1.01$, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 1.25$–1.34 (m; 1H), 1.55–1.66 (m; 4H), 1.80 (br s; 1H), 2.32 (m; 1H), 2.75–3.05 (m; 6H), 3.27 (br s; 1H), 5.06 (dd, $J = 7.3$, 13.8 Hz; 2H), 5.76–5.89 (m; 1H), 6.63 (br s; 1H), 7.39 (s; 1H), 7.75 (s; 2H). ^{13}C-NMR (75 MHz, $CDCl_3$): $\delta = 25.3$, 26.1, 27.4, 39.3, 43.9, 46.2, 46.3, 48.6, 115.0, 115.3, 117.8, 118.0, 121.4, 125.0, 128.7, 131.3, 131.7, 132.1, 132.6, 139.2, 141.6, 155.6. FT-IR (ATR, neat): ν[cm^{-1}] = 3310 (br w), 3080 (w), 2940 (w), 2869 (w), 1665 (m), 1572 (m), 1473 (m), 1385 (s), 1275 (s), 1176 (s), 1127 (s), 943 (w), 912 (w), 879 (w), 702 (m), 681 (m). HRMS (ESI): calcd for [$C_{19}H_{22}F_6N_3O$] ([M + H]$^+$): 422.167, found: 422.167. Elemental analysis: anal. calcd for $C_{19}H_{21}F_6N_3O$: C 54.16, H 5.02, N 9.97, found: C 54.07, H 5.34, N 9.87%.

(*S*)-1-[3,5-Bis(trifluoromethyl)phenyl]-3-[(1-methylpyrrolidin-2-yl)methyl]thiourea 8. Compound **8** was prepared from the corresponding amine (264 mg, 2.31 mmol, 1.00 eq.) and 3,5-bis(trifluoromethyl)phenyl isothiocyanate (464 µL, 2.54 mmol, 1.10 eq.), and isolated as a brownish solid (82.0 mg, 12%). Mp = 71 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 1.55$–2.11 (m; 3H), 2.13–2.84 (m; 3H), 2.60 (s; 3H), 2.90–3.34 (m; 2H), 3.52–3.73 (m; 1H), 7.56 (s; 1H), 7.98 (s; 2H). The signals of the NH-protons could not be detected. ^{13}C-NMR (75 MHz, DMSO-d_6): $\delta = 21.8$, 24.2, 26.6, 30.1, 40.1, 40.8, 47.2, 55.9, 56.9, 64.7, 66.0, 116.8, 120.9, 121.9, 124.5, 130.9, 131.5, 141.7, 182.9. FT-IR (ATR, neat): ν[cm^{-1}] = 3239 (w), 2945 (w), 2872 (w), 2790 (w), 1609 (w), 1508 (w), 1471 (m), 1383 (s), 1274 (s), 1171 (s), 1128 (s), 1107 (m), 1056 (w), 1006 (w), 952 (w), 882 (m), 847 (w), 719 (w), 699 (m), 681 (m). HRMS (ESI): calcd for [$C_{15}H_{17}F_6N_3S$] ([M + H]$^+$): 389.113, found: 389.113.

1-{3,5-Bis(trifluoromethyl)phenyl}-3-{(2*S*)-dimethylamino-(1*S*)-phenylpropyl}urea 9. Compound **9** was prepared from the corresponding amine (190 mg, 1.07 mmol, 1.00 eq.) and 3,5-bis(trifluoromethyl)phenyl isocyanate (186 µL, 1.07 mmol, 100 eq.), and isolated as a colourless solid (280 mg, 62%). Mp 214 °C. $[\alpha]_{589} = +15.4$, $[\alpha]_{546} = +18.8$, $[\alpha]_{405} = +48.1$, $[\alpha]_{365} = +74.6$ ($c = 0.83$, $CHCl_3$). ^{1}H-NMR (500 MHz, CD_2Cl_2): $\delta = 0.80$ (d, $J = 6.5$ Hz; 3H), 2.31 (s; 6H), 2.77–2.81 (m; 1H), 4.29 (d, $J = 10.3$ Hz; 1H), 6.91 (br s; 1H), 7.30 (t, $J = 6.8$ Hz; 1H), 7.36–7.41 (m; 4H), 7.46 (s; 1H), 7.59 (s; 1H), 7.82 (s; 2H). ^{13}C-NMR (125 MHz, CD_2Cl_2): $\delta = 7.1$, 39.7, 59.0, 63.8, 115.4, 118.2, 123.6 (q, $J = 271$ Hz), 127.7, 127.8, 128.8, 131.9 (q, $J = 32.7$ Hz), 141.4, 142.1, 155.2. FT-IR (ATR): ν[cm^{-1}] = 3307 (m, br), 3110 (w, br), 2934 (m), 2863 (w), 2828 (w), 2786 (w), 1660 (s), 1620 (w), 1570 (s), 1504 (m), 1472 (s), 1386 (s), 1274 (vs), 1233 (m), 1176 (s), 1128 (vs), 1067 (m), 1042 (m), 1028 (m), 939 (w), 878 (m), 848 (w), 702 (m), 681 (s). Elemental analysis: anal. calcd for $C_{20}H_{21}F_6N_3O$: C 55.43, H 4.88, N 9.70, found: C 55.02, H 4.81, N 9.68%.

1-{3,5-Bis(trifluoromethyl)phenyl}-3-{(2*S*)-dimethylamino-(1*R*)-phenylpropyl}urea 10. Compound **10** was prepared from the corresponding amine (140 mg, 785 µmol, 1.00 eq.) and 3,5-bis(trifluoromethyl)phenyl isocyanate (136 µL, 785 µmol, 1.00 eq.), and isolated as a colourless solid (90 mg, 26%). Mp 186 °C. ^{1}H-NMR (300 MHz, acetone-d_6): $\delta = 1.99$ (d, $J = 6.4$ Hz; 3H), 2.22 (s; 6H), 2.82–2.91 (m; 1H), 5.02–5.07 (m; 1H), 6.67 (br s; 1H), 7.18–7.24 (m; 1H), 7.28–7.38 (m; 4H), 7.50 (s; 1H), 8.12 (s; 2H), 8.88 (s; 1H). ^{13}C-NMR (75 MHz, acetone-d_6): $\delta = 11.3$, 43.3, 57.5, 65.2, 115.7, 119.2, 125.5 (q, $J = 271$ Hz), 127.3, 128.5, 129.8, 133.3 (q, $J = 32.7$ Hz), 144.2, 144.6, 156.1. FT-IR (ATR): ν[cm^{-1}] = 3327 (w, br), 3101 (w), 2831 (w), 2782 (w), 1654 (m), 1576 (m), 1499 (w), 1473 (w), 1386 (s), 1276 (s), 1170 (m), 1137 (s), 950 (w), 880 (w), 705 (m), 681 (m). Elemental analysis: anal. calcd for $C_{20}H_{21}F_6N_3O$: C 55.43, H 4.88, N 9.70, found: C 55.30, H 4.84, N 9.50%.

1-{3,5-Bis(trifluoromethyl)phenyl}-3-(quinuclidin-3-yl)urea 11. Compound **11** was prepared from the corresponding amine (160 mg, 1.27 mmol, 1.00 eq.) and 3,5-bis(trifluoromethyl)phenyl isocyanate (220 µL, 1.27 mmol, 1.00 eq.), and isolated as a colourless, hygroscopic solid (60 mg, 15%). ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 1.45$–1.55 (m; 1H), 1.65–1.73 (m; 2H), 2.03 (m; 2H), 2.69–2.88 (m; 4H), 2.95–3.03 (m; 1H), 3.31–3.39 (m; 1H), 3.95 (br s; 1H), 5.90 (br s; 1H), 7.35 (s; 1H), 7.92, (s; 2H), 9.31 (br s; 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): $\delta = 19.3$, 24.6, 25.5, 46.2, 47.0, 52.8, 55.6, 114.5, 117.6, 123.3 (q, $J = 270$ MHz), 131.7 (q, $J = 32.5$), 141.6, 155.5. HRMS (EI): calcd for [$C_{16}H_{18}F_6N_3O$] ([M + H]$^+$): 382.135, found: 382.135.

1-[3,5-Bis(trifluoromethyl)phenyl]-3-[(*R*)-(6-methoxyquinolin-4-yl)-(8-vinylquinuclidin-2-yl)methyl]thiourea 12. Compound **12** was prepared from the corresponding amine (50 mg, 155 μmol, 1.00 eq.) and 3,5-bis(trifluoromethyl)phenyl isothiocyanate (31 μL, 170 μmol, 1.10 eq.), and isolated as a pale yellow solid (56 mg, 61%). Mp = 150 °C (decomposition). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.90–1.06 (m; 1H), 1.17–1.35 (m; 1H), 1.43–1.74 (m; 3H), 2.27–2.41 (m; 1H), 2.71–3.32 (m; 5H), 3.96 (s; 3H), 5.11–5.25 (m; 2H), 5.77–5.99 (m; 2H), 7.08–7.19 (m; 1H), 7.35 (dd; J = 9.06, 2.49 Hz, 1H), 7.64 (s(br); 1H), 7.67 (s; 1H), 7.85 (s; 2H), 7.95 (d; J = 9.06 Hz, 1H), 8.46–8.58 (m; 1H). The signals of the NH-protons could not be detected. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 25.0, 26.0, 27.1, 38.6, 47.1, 48.6, 55.7, 61.4, 101.7, 115.4, 118.7, 118.8, 121.1, 122.4, 123.6, 124.8, 128.4, 131.6, 132.5 (q; CF_3), 139.5, 144.7, 145.7, 147.3, 158.2, 181.4. FT-IR (ATR, neat): ν[cm^{-1}] = 3234, 2937, 2872 (all w), 1620, 1507, 1472, 1381 (all m), 1275 (s), 1226 (w), 1175 (s), 1130 (s), 1106 (m), 1029, 957, 908, 883, 849, 824, 728 (all w), 680 (m). HRMS (ESI): calcd for [$C_{29}H_{29}F_6N_4OS$] ([M + H]$^+$): 595.197, found: 595.197.

1-{3,5-Bis(trifluoromethyl)phenyl}-3-[1-{2-(dimethylamino)naphthalen-1-yl}naphthalen-2-yl]thiourea 13. Compound **13** was synthesized following the literature procedure.[9d]

1-[3,5-Bis(trifluoromethyl)phenyl]-3-{[(1*S*,5*R*)-5-(dimethylamino)-1,3,3-trimethylcylohexyl]methyl}urea 14. Compound **14** was prepared from the corresponding amine (26 mg, 131 μmol, 1.00 eq.) and 3,5-bis(trifluoromethyl)phenyl isocyanate (23 μL, 131 μmol, 1.00 eq.), and isolated as a colourless solid (according to ^{1}H-NMR, the product contains ~20% unidentified impurities). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.81–1.48 (m; 15H); 1.65–1.93 (m; 2H), 2.15 (s; 1H), 2.72 (s; 6H), 3.18–3.34 (m; 1H), 6.84–6.94 (m; 1H), 7.34 (s; 1H), 7.97 (s; 2H), 9.31 (s; 1H). FT-IR (ATR, neat): ν[cm^{-1}] = 3290 (w), 2959 (w), 2678 (w), 1697 (m), 1566, 1555, 1473, 1387 (all m), 1275, 1172, 1126 (all s), 1032, 999, 946, 878, 844, 800 (all w), 732 (m), 702 (m), 680 (s). HRMS (ESI): calcd for [$C_{21}H_{30}F_6N_3O$] ([M + H]$^+$): 454.229, found: 454.230.

1-{3,5-Bis(trifluoromethyl)phenyl}-3-{(1*S*,2*S*,4*S*,5*S*)-5-(dimethylamino)bicyclo[2.2.1]hept-2-yl}thiourea 15. Compound **15** was isolated as a pale yellow solid (52%).† Mp 54 °C. $[\alpha]_{589}$ = −40.9, $[\alpha]_{546}$ = −49.0, $[\alpha]_{405}$ = −90.1 (c = 0.88, $CHCl_3$). ^{1}H-NMR (300 MHz, CD_3OD): δ = 1.24–1.28 (m; 1H), 1.45–1.60 (m; 1H), 1.56 (s; 2H), 1.65–1.74 (m; 1H), 1.88–1.98 (m; 1H), 2.21 (s; 6H), 2.29 (s; 1H), 2.33 (s; 1H), 2.65 (s; 1H), 4.59 (br s; 1H), 7.62 (s; 1H), 8.11 (s; 2H). The signals of the NH-protons could not be detected. ^{13}C-NMR (75 MHz, CD_3OD): δ = 28.0, 29.2, 38.5, 41.4, 41.8, 45.1, 57.4, 70.4, 117.7, 123.7, 124.8, 132.7, 143.2, 182.7. FT-IR (CsI): ν[cm^{-1}] = 3519 (s), 3288 (s), 3195 (m), 1590 (s), 1474 (w), 1387 (m), 1350 (m), 1280 (m), 1181 (m), 1135 (m), 887 (w), 682 (m). HRMS (ESI): calcd for [$C_{18}H_{22}F_6N_3S$] ([M + H$^+$]): 426.144, found: 426.143. Elemental analysis: anal. calcd for $C_{18}H_{21}F_6N_3S\cdot1/2H_2O$: C 49.76, H 5.10, N 9.67, found: C 49.50, H 5.32, N 9.45%.

1-{(1*R*,2*R*)-2-(Dimethylamino)cyclohexyl}urea 16. Compound **16** was prepared from the corresponding amine (140 mg, 1.23 mmol, 1.00 eq.), KOCN (99.8 mg, 1.23 mmol, 1.00 eq.) and acetic acid (73.6 mg, 1.23 mmol, 1.00 eq.), and isolated as a colourless semisolid (120 mg, 53%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.25–1.33 (m; 4H), 1.74–1.91 (m; 2H), 1.97–2.12 (m; 2H), 2.78 (s; 6H), 3.00–3.20 (m; 1H), 3.78–3.79 (m; 1H), 5.57 (br s; 1H), 7.60 (br s; 2H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 23.0, 24.3, 24.4, 33.7, 39.1, 49.4, 66.6, 159.0. HRMS (ESI): calcd for [$C_9H_{19}N_3O$] ([M + H]$^+$): 185.153, found: 185.153.

1-(3,5-Dinitrophenyl)-3-{(1*R*,2*R*)-2-(dimethylamino)cyclohexyl}-urea 17. Compound **17** was prepared from the corresponding amine (295 mg, 2.07 mmol, 1.00 eq.) and 3,5-dinitrophenyl isocyanate (433 mg, 2.07 mmol, 1.00 eq.), and isolated as a yellow foam (584 mg, 80%). Mp 97–99 °C. $[\alpha]_{589}$ = −40.3, $[\alpha]_{546}$ = −48.4 (c = 1.00, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.13–1.28 (m; 4H), 1.66–1.89 (m; 3H), 2.28 (s; 6H), 2.31–2.35 (m; 2H), 3.47–3.50 (m; 1H), 5.87 (br s; 1H), 8.44–8.46 (m; 1H), 8.53–8.54 (m; 2H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 21.6, 24.6, 24.9, 33.6, 40.1, 51.9, 67.2, 110.9, 117.8, 142.5, 148.6, 155.4. FT-IR (CsI): ν[cm^{-1}] = 3330 (br), 3113 (w), 2940 (m), 2865 (w), 1780 (w), 1677 (s), 1601 (s), 1547 (s), 1475 (m), 1346 (s), 1261 (m), 1225 (m), 1068 (m), 1044 (w), 894 (m), 829 (w), 731 (s). HRMS (ESI): calcd for [$C_{15}H_{22}N_5O_5$] ([M + H]$^+$): 352.162, found: 352.162. Elemental analysis: anal. calcd for $C_{15}H_{21}N_5O_5$: C 51.28, H 6.02, N 19.93, found: C 51.20, H 6.32, N 19.55%.

1-{(1*R*,2*R*)-2-(Dimethylamino)cyclohexyl}-3-mesitylurea 18. Compound **18** was prepared from the corresponding amine (373 mg, 2.62 mmol, 1.00 eq.) and mesitylisocyanate (422 mg, 2.62 mmol, 1.00 eq.), and isolated as a colourless crystalline solid (513 mg, 65%). Mp 168–169 °C. $[\alpha]_{589}$ = −43.1, $[\alpha]_{546}$ = −50.9, $[\alpha]_{405}$ = −103.9, $[\alpha]_{365}$ = −136.1 (c = 1.02, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.89–1.32 (m; 4H), 1.55–1.74 (m; 3H), 1.99–2.02 (m; 1H), 2.08 (s; 6H), 2.22 (s; 6H), 2.25 (s; 3H), 2.30–2.38 (m; 1H), 3.33–3.43 (m; 1H), 4.97 (br s; 1H), 5.91 (br s; 1H), 6.87 (s; 2H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 18.0, 20.9, 21.6, 24.7, 25.3, 33.8, 39.8, 51.5, 66.5, 129.0, 131.8, 137.0, 157.6. FT-IR (CsI): ν[cm^{-1}] = 3343 (m), 2937 (m), 2859 (w), 1638 (s), 1559 (s), 1458 (w), 1316 (w), 1264 (w), 1051 (w), 846 (m), 707 (w). HRMS (ESI): calcd for [$C_{18}H_{29}N_3NaO$] ([M + Na]$^+$): 326.221, found: 326.221. Elemental analysis: anal. calcd for $C_{18}H_{29}N_3O$: C 71.25, H 9.63, N 13.85, found: C 70.87, H 9.60, N 13.75%.

1-{(1*R*,2*R*)-2-(Dimethylamino)cyclohexyl}-3-(pyridine-3-yl)thiourea 19. Compound **19** was prepared from the corresponding amine (300 mg, 2.11 mmol, 1.00 eq.) and 3-pyridylisothiocyanate (235 μL, 2.11 mmol, 1.00 eq.), and isolated as a yellow foam (415 mg, 71%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.14–1.27 (m; 5H), 1.65–1.92 (m; 3H), 2.31 (m; 1H), 2.45 (s; 6H), 2.86–2.92 (m; 1H), 4.26 (br s; 1H), 6.14 (br s; 1H), 7.13–7.17 (m; 1H), 7.94–7.96 (m; 1H), 8.23–8.24 (m; 1H), 8.53 (s; 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 22.6, 24.2, 24.3, 32.4, 39.9, 54.5, 67.0, 123.0, 131.0, 136.0, 144.7, 145.3, 181.5. FT-IR (ATR): ν[cm^{-1}] = 3234 (br), 3027 (br), 2931 (s), 2857 (sh), 2783 (w), 1538 (s), 1481 (m), 1425 (m), 1316 (s), 1229 (m), 1185 (w), 1160 (sh), 1096 (m), 1062 (w), 1043 (w), 1025 (w), 991 (sh), 954 (w), 938 (w), 910 (w), 883 (m), 851 (w), 804 (s), 725 (m). HRMS (EI): calcd for [$C_{14}H_{23}N_4S$] ([M + H]$^+$): 279.164, found: 279.165.

1-{(1*R*,2*R*)-2-(Dimethylamino)cyclohexyl}-3-methylthiourea 20. Compound **20** was prepared from the corresponding amine (103 mg, 725 mmol, 1.00 eq.) and methylisothiocyanate (50 μL, 725 mmol, 1.00 eq.), and isolated as an off-white amorphous solid (100 mg, 64% yield). Mp 101 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.05–1.39 (m; 4H), 1.68–1.96 (m; 3H), 2.33 (s; 6H), 2.40–2.61

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(m; 2H), 2.96 (d, $J = 4.5$ Hz; 3H), 3.91 (m; 1H), 6.70 (s; 1H), 7.10 (s; 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): $\delta = 21.8$, 24.5, 24.9, 30.9, 33.1, 40.0, 55.5, 66.9, 182.8. FT-IR (ATR): ν[cm^{-1}] = 3259 (m), 2930 (s), 2855 (m), 1548 (s), 1447 (m), 1352 (m), 1269 (m), 1237 (w), 1208 (w), 1184 (w), 1089 (w), 1040 (m), 883 (w), 717 (m), 644 (w). HRMS (EI): calcd for [$C_{10}H_{21}N_3S$] ([M]+): 216.153, found: 216.153.

1-{(1*R*,2*R*)-2-(Dimethylamino)cyclohexyl}-3-benzylurea 21. Compound **21** was prepared from the corresponding amine (47.8 mg, 336 mmol, 1.00 eq.) and benzylisocyanate (50 μL, 336 mmol, 1.00 eq.), and isolated as an off-white amorphous solid (49 mg, 53%). Mp 135–140 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta =$ 1.02–1.23 (m; 4H), 1.60–1.82 (m; 3H), 2.19 (s; 6H), 2.26–2.34 (m; 2H), 3.33–3.41 (m; 1H), 4.23–4.36 (m; 2H), 5.47 (t, $J = 5.3$ Hz; 1H), 5.65 (d, $J = 3.9$ Hz; 1H), 7.17–7.33 (m; 5H). ^{13}C-NMR (75 MHz, $CDCl_3$): $\delta = 21.7$, 24.5, 25.0, 33.8, 39.7, 51.3, 52.8, 66.8, 126.9, 127.3, 128.4, 139.6, 158.9. FT-IR (ATR): ν[cm^{-1}] = 2929 (br), 1616 (s), 1571 (s), 1491 (m), 1454 (m), 1319 (w), 1261 (w), 1237 (w), 1070 (w), 1045 (w), 745 (w), 698 (m), 637 (w). HRMS (EI): calcd for [$C_{16}H_{25}N_3O$] ([M]+): 275.200, found: 275.200.

1-{(1*R*,2*R*)-2-Dimethylaminocyclohexyl}-3-cyclohexylthiourea 22. Compound **22** was prepared from the corresponding amine (390 mg, 2.74 mmol, 1.00 eq.) and cyclohexylisothiocyanate (375 μL, 2.74 mmol, 1.00 eq.), and isolated as a colourless foam (600 mg, 77%). Mp 59–60 °C. $[\alpha]_{589} = +23.4$, $[\alpha]_{546} = +27.9$, $[\alpha]_{405} = +45.0$, $[\alpha]_{365} = +29.3$ ($c = 1.01$, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 1.01$–1.41 (m; 9H), 1.54–1.83 (m; 6H), 1.91–2.01 (m; 2H), 2.21 (s; 6H), 2.28–2.43 (m; 2H), 3.50–3.55 (m; 1H), 3.73 (br s; 1H), 6.28 (s; 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): $\delta = 22.1$, 24.4, 24.7, 24.8, 24.9, 25.4, 32.8, 32.9, 33.1, 40.2, 52.8, 56.1, 67.3, 181.1. FT-IR (ATR): ν[cm^{-1}] = 3259 (br), 3050 (w), 2926 (s), 2852 (s), 2783 (m), 1539 (s), 1473 (w), 1448 (m), 1360 (m), 1321 (m), 1271 (w), 1254 (m), 1239 (w), 1207 (w), 1187 (w), 1152 (w), 1081 (w), 1061 (w), 1040 (w), 978 (w), 946 (w), 889 (w), 872 (w), 847 (w), 734 (m). HRMS (EI): calcd for [$C_{15}H_{29}N_3S$] ([M]$^+$): 283.208, found: 283.209. Elemental analysis: anal. calcd for $C_{15}H_{29}N_3S$: C 63.55, H 10.31, N 14.82, found: C 63.26, H 10.22, N 14.75%.

1,3-Bis{(1*R*,2*R*)-2-(dimethylamino)cyclohexyl}thiourea 23. Compound **23** was isolated as an off-white foam (330 mg, 60%).† ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 0.99$–1.33 (m; 8H), 1.61–1.84 (m; 6H), 2.21 (s; 12H), 2.33–2.41 (m; 4H), 3.60–3.69 (m; 2H), 7.17 (br s; 2H). ^{13}C-NMR (75 MHz, $CDCl_3$): $\delta = 21.9$, 24.5, 25.0, 33.0, 39.1, 55.7, 66.7, 182.6. FT-IR (KBr): ν[cm^{-1}] = 3265 (br), 2931 (s), 2857 (s), 2783 (m), 1540 (s), 1457 (m), 1362 (m), 1323 (m), 1270 (m), 1240 (w), 1187 (w), 1165 (w), 1085 (w), 1038 (m), 957 (w), 871 (m), 739 (m). HRMS (EI): calcd for [$C_{17}H_{34}N_4S$] ([M]$^+$): 326.250, found: 326.251.

1-Adamantan-1-yl-3-{(1*R*,2*R*)-2-dimethylaminocyclohexyl}thiourea 24. Compound **24** was prepared from the corresponding amine (300 mg, 2.11 mmol, 1.00 eq.) and 1-adamantylisothiocyanate (408 mg, 2.11 mmol, 1.00 eq.), and isolated as a colourless amorphous solid (550 mg, 78%). Mp 78–79 °C. $[\alpha]_{589} = -69.0$, $[\alpha]_{546} = -81.8$, $[\alpha]_{405} = -158.6$, $[\alpha]_{365} = -194.8$ ($c = 1.00$, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 0.93$–1.35 (m; 4H), 1.55–1.66 (m; 7H), 1.80–1.82 (m; 2H), 1.94 (s; 6H), 2.05 (s; 3H), 2.17 (s; 6H), 2.31–2.38 (m; 1H), 2.93–2.97 (m; 1H), 3.45–3.55 (m; 1H), 6.09 (br s; 1H), 6.61 (br s; 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): $\delta = 21.4$, 24.3, 25.3, 29.3, 32.6, 36.0, 39.6, 41.8, 53.4, 56.8, 67.2, 180.8. FT-IR (ATR): ν[cm^{-1}] = 3273 (br), 2904 (s), 2849 (sh), 2784 (m), 1521 (s), 1473 (w), 1450 (m), 1399 (w), 1370 (w), 1356 (sh), 1340 (w), 1306 (m), 1294 (m), 1250 (w), 1228 (w), 1203 (m), 1186 (w), 1149 (w), 1114 (w), 1088 (m), 1060 (m), 1039 (m), 979 (w), 957 (w), 914 (m), 872 (w), 836 (sh), 730 (s). HRMS (EI): calcd for [$C_{19}H_{34}N_3S$] ([M + H]$^+$): 336.247, found: 336.247. Elemental analysis: anal. calcd for $C_{19}H_{33}N_3S$: C 68.01, H 9.91, N 12.52, found: C 67.65, H 9.78, N 12.58%.

1,6-Di-{3-(1*R*,2*R*)-2-dimethylaminocyclohexyl}ureado hexane 25. Compound **25** was prepared from the corresponding amine (300 mg, 2.11 mmol, 2.27 eq.) and 1,6-diisocyanatohexane (156 mg, 0.93 mmol, 1.00 eq.), and isolated as a colourless foam (330 mg, 79%). ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 0.92$–1.78 (m; 24H), 2.15 (s; 12H), 2.26–2.30 (m; 2H), 3.02–3.08 (m; 4H), 3.27–3.37 (m; 2H), 4.96–4.98 (m; 2H), 5.35–5.36 (m; 2H). ^{13}C-NMR (75 MHz, $CDCl_3$): $\delta = 21.4$, 24.6, 25.2, 26.3, 29.8, 34.0, 39.9, 40.1, 51.3, 66.7. FT-IR (ATR): ν[cm^{-1}] = 3315 (br), 2926 (s), 2854 (sh), 2774 (m), 1632 (s), 1562 (s), 1453 (w), 1314 (w), 1262 (m), 1238 (m), 1188 (w), 1084 (w), 1043 (m), 871 (sh), 848 (w), 729 (m). HRMS (EI): calcd for [$C_{24}H_{49}N_6O_2$] ([M + H]$^+$): 453.392, found: 453.391.

1-{(1*R*,2*R*)-2-(Dimethylamino)cyclohexyl}-3-{(*R*)-1-phenylethyl}-urea 26a. Compound **26a** was prepared from the corresponding amine (315 mg, 2.21 mmol, 1.00 eq.) and (*R*)-1-phenylethyl isocyanate (310 μL, 2.21 mmol, 1.00 eq.), and isolated as a colourless crystalline solid (445 mg, 70%). Mp 137 °C. $[\alpha]_{589} = -33.3$, $[\alpha]_{546} = -38.6$, $[\alpha]_{405} = -66.5$, $[\alpha]_{365} = -77.0$, $[\alpha]_{334} = -82.1$ ($c = 1.015$, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 0.88$–1.30 (m; 4H), 1.37 (d, $J = 6.82$ Hz; 3H), 1.54–1.71 (m; 3H), 1.91 (s; 6H), 2.03–2.11 (m; 1H), 2.37–2.43 (m; 1H), 3.11–3.19 (m; 1H), 4.64 (dq, $J = 6.53$, 6.82 Hz; 1H), 5.11 (d, $J = 6.53$ Hz; 1H), 5.35 (br s; 1H), 7.16–7.25 (m; 1H), 7.28 (d, $J = 4.41$ Hz; 4H). ^{13}C-NMR (75 MHz, $CDCl_3$): $\delta = 21.1$, 23.8, 24.5, 25.2, 33.5, 39.4, 50.5, 51.7, 66.5, 125.8, 127.0, 128.5, 144.6, 158.8. FT-IR (KBr): ν[cm^{-1}] = 3359 (s), 3298 (s), 3060 (w), 2970 (m), 2933 (s), 2858 (s), 2820 (m), 2778 (m), 1670 (w), 1622 (s), 1570 (s), 1449 (m), 1375 (w), 1321 (w), 1262 (m), 1239 (m), 1190 (w), 1095 (m), 1027 (w), 872 (m), 764 (m), 706 (s). HRMS (ESI): calcd for [$C_{17}H_{28}N_3O$] ([M + H]$^+$): 290.223, found: 290.223. Elemental analysis: anal. calcd for $C_{17}H_{27}N_3O$: C 70.55, H 9.40, N 14.52, found: C 70.05, H 9.22, N 14.45%.

1-{(1*R*,2*R*)-2-(Dimethylamino)cyclohexyl}-3-{(*S*)-1-phenylethyl}-urea 26b. Compound **26b** was prepared from the corresponding amine (225 mg, 1.58 mmol, 1.00 eq.) and (*S*)-1-phenylethyl isocyanate (223 μL, 1.58 mmol, 1.00 eq.), and isolated as a colourless crystalline solid (345 mg, 75%). Mp 146 °C. $[\alpha]_{589} = -57.2$, $[\alpha]_{546} = -67.7$, $[\alpha]_{405} = -137.1$, $[\alpha]_{365} = -179.5$, $[\alpha]_{334} = -230.2$ ($c = 1.00$, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta =$ 0.88–1.29 (m; 4H), 1.42 (d, $J = 6.93$ Hz; 3H), 1.56–1.77 (m; 3H), 2.09–2.14 (m, 1H), 2.16 (s; 6H), 2.36–2.42 (m; 1H), 3.19–3.28 (m; 1H), 4.79 (dq, $J = 6.93$, 6.85 Hz; 1H), 4.98 (br s; 1H), 5.18 (br s; 1H), 7.17–7.31 (m; 5H). ^{13}C-NMR (75 MHz, $CDCl_3$): $\delta = 21.4$, 23.1, 24.5, 25.2, 33.6, 39.9, 50.0, 51.9, 66.8, 126.0, 127.0, 128.5, 144.6, 158.4. FT-IR (KBr): ν[cm^{-1}] = 3335 (s), 3302 (s), 2976 (m), 2921 (s), 2859 (m), 2821 (m), 2777 (m), 1674 (w), 1622 (s), 1559 (s), 1456 (m), 1372 (w), 1330 (m), 1255 (m), 1235 (m), 1208 (m), 1106 (m), 1074 (m), 1052 (w), 1020 (m), 873 (w), 830 (w),

745 (w), 703 (s). HRMS (ESI): calcd for $[C_{17}H_{27}N_3NaO]$ ([M + Na]$^+$): 312.205, found: 312.206. Elemental analysis: anal. calcd for $C_{17}H_{27}N_3O$: C 70.55, H 9.40, N 14.52, found: C 70.32, H 9.34, N 14.47%.

1-{(*S*)-1-(Dimethylcarbamoyl)-2,2-dimethylpropyl}-3-{(1*R*,2*R*)-2-(dimethylamino)cyclohexyl}thiourea 27a. Compound **27a** was prepared from the corresponding isothiocyanate (337 mg, 1.68 mmol, 1.00 eq.) and the (1*R*,2*R*)-*N*,*N*-dimethyl-1,2-diaminocyclohexane (275 mg, 1.93 mmol, 1.15 eq.), and isolated as a colourless foam (350 mg, 61%). Mp 146 °C. $[\alpha]_{589} = +7.3$, $[\alpha]_{546} = +8.9$, $[\alpha]_{405} = +10.6$, $[\alpha]_{365} = -2.9$ ($c = 0.71$, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 0.93$ (s; 9H), 1.02–1.12 (m; 4H), 1.58–1.76 (m; 3H), 2.13 (s; 6H), 2.21–2.29 (m; 2H), 2.85 (s; 3H), 3.15 (s; 3H), 3.50 (m; 1H), 5.50 (d, $J = 8.97$ Hz; 1H), 6.66 (br s; 1H), 7.03 (d, $J = 8.97$ Hz; 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): $\delta = 21.9$, 24.5, 24.9, 26.6, 32.9, 35.4, 35.9, 38.4, 40.1, 55.4, 59.9, 66.5, 171.9, 182.3. FT-IR (ATR): ν[cm^{-1}] = 3307 (br), 2928 (s), 2857 (sh), 2781 (w), 1624 (s), 1536 (s), 1477 (w), 1416 (w), 1396 (m), 1364 (m), 1319 (w), 1253 (w), 1238 (w), 1188 (w), 1139 (m), 1118 (w), 1083 (m), 1062 (w), 1036 (m), 947 (m), 914 (m), 872 (sh), 825 (w), 730 (s). HRMS (ESI): calcd for $[C_{17}H_{35}N_4OS]$ ([M + H]$^+$): 343.253, found: 343.253. Elemental analysis: anal. calcd for $C_{17}H_{34}N_4OS$: C 59.61, H 10.00, N 16.36, found: C 59.20, H 9.88, N 16.19.

1-{(*S*)-1-(Diethylcarbamoyl)-2,2-dimethylpropyl}-3-{(1*R*,2*R*)-2-(dimethylamino)cyclohexyl}thiourea 27b. Compound **27b** was prepared from the corresponding isothiocyanate (440 mg, 1.93 mmol, 1.00 eq.) and (1*R*,2*R*)-*N*,*N*-dimethyl-1,2-diaminocyclohexane (313 mg, 2.20 mmol, 1.14 eq.), and isolated as a colourless foam (515 mg, 72%). Mp 120–121 °C. $[\alpha]_{589} = -46.4$, $[\alpha]_{546} = -55.9$, $[\alpha]_{405} = -135.9$, $[\alpha]_{365} = -209.7$ ($c = 1.01$, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 0.94$ (s; 9H), 1.02 (t, $J = 7.13$ Hz; 3H), 1.09–1.12 (m; 4H), 1.20 (t, $J = 7.13$ Hz; 3H), 1.58–1.78 (m; 3H), 2.14 (s; 6H), 2.25–2.33 (m; 2H), 2.91–3.03 (m; 1H), 3.25–3.34 (m; 1H), 3.45–3.49 (m; 1H), 3.54–3.67 (m; 2H), 5.44 (d, $J = 8.96$ Hz; 1H), 6.60 (br s; 1H), 6.95 (d, $J = 8.96$ Hz; 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): $\delta = 12.7$, 14.5, 21.8, 24.5, 24.8, 26.7, 32.9, 36.1, 39.8, 40.0, 42.7, 55.2, 59.7, 66.5, 170.6, 182.2. FT-IR (ATR): ν[cm^{-1}] = 3320 (br), 2934 (s), 2861 (m), 2788 (w), 1622 (s), 1540 (s), 1458 (s), 1364 (s), 1321 (m), 1265 (m), 1216 (w), 1187 (w), 1138 (w), 1084 (w), 1035 (w), 949 (m), 873 (m), 840 (m), 787 (w), 747 (m). HRMS (ESI): calcd for $[C_{19}H_{39}N_4OS]$ ([M + H]$^+$): 371.284, found: 371.284. Elemental analysis: anal. calcd for $C_{19}H_{38}N_4OS$: C 61.58, H 10.34, N 15.12, found: C 61.28, H 10.30, N 15.01%.

1-{(*S*)-1-(*N*-Benzyl-*N*-methylcarbamoyl)-2,2-dimethylpropyl}-3-{(1*R*,2*R*)-2-(dimethylamino)cyclohexyl}thiourea 27c. Compound **27c** was prepared from the corresponding isothiocyanate (430 mg, 1.56 mmol, 1.00 eq.) and the (1*R*,2*R*)-*N*,*N*-dimethyl-1,2-diaminocyclohexane (260 mg, 1.83 mmol, 1.17 eq.), and isolated as a colourless foam (483 mg, 74%). Mp 58–59 °C. $[\alpha]_{589} = -17.5$, $[\alpha]_{546} = -21.8$, $[\alpha]_{405} = -60.2$, $[\alpha]_{365} = -99.2$ ($c = 1.01$, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): $\delta = 1.06$ (s; 9H), 1.18–1.32 (m; 4H), 1.69–1.87 (m; 3H), 2.28 (s; 6H), 2.36–2.42 (m; 1H), 2.56–2.58 (m; 1H), 3.19 (s; 3H), 3.84 (m; 1H), 4.50 (d, $J = 14.6$ Hz; 1H), 4.69 (d, $J = 14.6$ Hz; 1H), 5.48 (d, $J = 8.5$ Hz; 1H), 7.11 (br s; 1H), 7.20 (br d, $J = 8.5$ Hz; 1H), 7.22–7.34 (m; 5H). ^{13}C-NMR (125 MHz, $CDCl_3$): $\delta = 21.8$, 24.5, 24.8, 26.8, 32.9, 35.7, 36.0, 39.9, 51.2, 55.2, 60.3, 66.5, 127.2, 127.9, 128.4, 136.8, 172.5, 182.5. FT-IR (ATR): ν[cm^{-1}] = 3308 (br), 3060 (w), 2930 (s), 2857 (m), 2782 (w), 1626 (s), 1535 (s), 1494 (w), 1477 (w), 1450 (m), 1413 (m), 1364 (m), 1320 (m), 1267 (w), 1237 (w), 1186 (w), 1081 (m), 1030 (w), 950 (w), 873 (w), 733 (m), 701 (s). HRMS (ESI): calcd for $[C_{23}H_{39}N_4OS]$ ([M + H]$^+$): 419.285, found: 419.284. Elemental analysis: anal. calcd for $C_{23}H_{38}N_4OS$: C 65.99, H 9.15, N 13.38, found: C 65.60, H 9.15, N 13.15%.

1-{(*S*)-1-(Benzylcarbamoyl)-2,2-dimethylpropyl}-3-{(1*R*,2*R*)-2-(dimethylamino)cyclohexyl}thiourea 27d. Compound **27d** was prepared from the corresponding isothiocyanate (430 mg, 1.64 mmol, 1.00 eq.) and (1*R*,2*R*)-*N*,*N*-dimethyl-1,2-diaminocyclohexane (275 mg, 1.93 mmol, 1.18 eq.), and isolated as an off-white foam (490 mg, 74%). Mp 89–91 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 1.00$ (s; 9H), 1.09–1.85 (m; 4H), 1.61–1.76 (m; 3H), 2.16 (s; 6H), 2.22–2.24 (m; 1H), 2.54 (m; 1H), 3.98 (m; 1H), 4.20 (dd, $J = 5.38$, 14.88 Hz; 1H), 4.42 (dd, $J = 6.10$, 14.88 Hz; 1H), 4.70 (m; 1H), 4.86 (br m; 1H), 7.17–7.24 (m; 7H). ^{13}C-NMR (75 MHz, $CDCl_3$): $\delta = 22.0$, 24.5, 24.6, 27.0, 32.9, 34.4, 39.8, 43.1, 54.9, 66.5, 127.0, 127.6, 128.3, 138.1, 171.3, 182.2. FT-IR (ATR): ν[cm^{-1}] = 3264 (br), 3061 (m), 2933 (s), 2862 (m), 2793 (w), 1644 (s), 1537 (s), 1474 (w), 1452 (m), 1399 (w), 1359 (m), 1309 (m), 1232 (w), 1182 (w), 1088 (m), 1028 (sh), 991 (w), 949 (w), 909 (m), 873 (sh), 851 (w), 824 (w), 728 (s). HRMS (ESI): calcd for $[C_{22}H_{37}N_4OS]$ ([M + H]$^+$): 405.269, found: 405.269.

1-{(*S*)-1-(Diisobutylcarbamoyl)-2,2-dimethylpropyl}-3-{(1*R*,2*R*)-2-(dimethylamino)cyclohexyl}thiourea 27e. Compound **27e** was prepared from the corresponding isothiocyanate (598 mg, 2.10 mmol, 1.00 eq.) and the (1*R*,2*R*)-*N*,*N*-dimethyl-1,2-diaminocyclohexane (320 mg, 2.25 mmol, 1.07 eq.), and isolated as a colourless foam (600 mg, 67%). Mp 59–61 °C. $[\alpha]_{589} = -34.9$, $[\alpha]_{546} = -42.6$, $[\alpha]_{405} = -107.3$, $[\alpha]_{365} = -174.3$ ($c = 1.03$, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 0.80$–0.88 (m; 12H), 0.97 (s; 9H), 1.03–1.24 (m; 4H), 1.59–1.79 (m; 3H), 1.85–2.05 (m; 2H), 2.13 (s; 6H), 2.19–2.35 (m; 2H), 2.58–2.65 (m; 1H), 3.05–3.12 (m; 1H), 3.37–3.65 (m; 3H), 5.53 (br s; 1H), 6.43 (s; 1H), 6.92 (d, $J = 8.6$ Hz; 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): $\delta = 19.3$, 20.2, 20.4, 20.5, 21.7, 24.5, 25.0, 26.5, 26.9, 27.9, 32.9, 36.9, 39.9, 53.5, 55.3, 56.2, 59.8, 66.6, 172.2, 182.1. FT-IR (ATR): ν[cm^{-1}] = 3315 (br), 3054 (br), 2954 (s), 2928 (s), 2865 (m), 2825 (w), 2782 (w), 1617 (s), 1527 (s), 1465 (s), 1445 (s), 1385 (m), 1363 (s), 1338 (w), 1320 (w), 1301 (w), 1268 (w), 1238 (m), 1207 (m), 1188 (w), 1140 (m), 1119 (w), 1096 (m), 1085 (m), 1062 (w), 1035 (m), 946 (sh), 900 (w), 872 (sh), 848 (w), 821 (m), 753 (sh). HRMS (EI): calcd for $[C_{23}H_{46}N_4OS]$ ([M]$^+$): 426.339, found: 426.339. Elemental analysis: anal. calcd for $C_{23}H_{46}N_4OS$: C 64.74, H 10.87, N 13.13, found: C 64.34, H 10.84, N 13.09%.

1-{(*R*)-1-(*N*-Benzyl-*N*-methylcarbamoyl)-2,2-dimethyl propyl}-3-{(1*R*,2*R*)-2-(dimethylamino)cyclohexyl}thiourea 28. Compound **28** was prepared from the corresponding isothiocyanate (552 mg, 2.00 mmol, 1.00 eq.) and the (1*R*,2*R*)-*N*,*N*-dimethyl-1,2-diaminocyclohexane (310 mg, 2.18 mmol, 1.09 eq.), and isolated as a colourless foam (530 mg, 64%). Mp 64–65 °C. $[\alpha]_{589} = +47.7$, $[\alpha]_{546} = +58.9$, $[\alpha]_{405} = +149.1$, $[\alpha]_{365} = +216.7$ ($c = 1.00$, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 1.02$ (s; 9H), 1.09–1.26 (m; 4H), 1.64–1.85 (m; 3H), 2.19–2.31 (m; 2H), 2.24 (s; 6H), 3.17 (s; 3H),

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3.48 (br s; 1H), 4.36 (d, J = 14.6 Hz; 1H), 4.76 (d, J = 14.6 Hz; 1H), 5.60 (d, J = 9.3 Hz; 1H), 6.45 (br s; 1H), 7.19–7.34 (m; 5H), 8.28 (br s; 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 23.3, 24.5, 24.9, 26.8, 33.0, 36.1, 36.2, 40.8, 51.1, 56.7, 60.8, 67.5, 127.3, 128.0, 128.5, 136.9, 172.1, 183.3. FT-IR (ATR): ν[cm^{-1}] = 3324 (br), 3059 (w), 3027 (w), 2929 (s), 2857 (m), 2823 (w), 2782 (m), 1620 (s), 1530 (s), 1494 (w), 1477 (w), 1448 (m), 1413 (m), 1363 (m), 1319 (m), 1268 (m), 1253 (w), 1234 (m), 1207 (w), 1189 (w), 1153 (w), 1108 (w), 1082 (m), 1028 (w), 947 (m), 910 (m), 873 (sh), 849 (w), 822 (w), 730 (s). HRMS (ESI): calcd for [$C_{23}H_{39}N_4OS$] ([M + H]$^+$): 419.285, found: 419.284. Elemental analysis: anal. calcd for $C_{23}H_{38}N_4OS$: C 65.99, H 9.15, N 13.38, found: C 65.55, H 9.08, N 13.38%.

1-{(*S*)-1-(*N*-benzyl-*N*-methylcarbamoyl)-3,3-dimethylbutyl}-3-{(1*R*,2*R*)-2-(dimethylamino)cyclohexyl}thiourea 29. Compound **29** was prepared from the corresponding isothiocyanate (747 mg, 2.57 mmol, 1.00 eq.) and (1*R*,2*R*)-*N*,*N*-dimethyl-1,2-diaminocyclohexane (400 mg, 2.81 mmol, 1.09 eq.), and isolated as a colourless foam (832 mg, 75%). Mp 67–68 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.82, 0.99 (2s; 9H), 1.06–1.27 (m; 5H), 1.53–1.77 (m; 5H), 2.24, 2.26 (2s; 6H), 2.34–2.41 (m; 2H), 2.92, 3.11 (2s; 3H), 3.64–3.71 (br s; 1H), 4.42 (d, J = 14.84 Hz; 0.7H), 4.60 (d, J = 16.50 Hz; 0.3H), 4.68 (d, J = 14.84 Hz; 0.7H), 5.06 (d, J = 16.50 Hz; 0.3H), 5.63–5.68 (m; 1H), 6.66 (br s; 1H), 7.18–7.35 (m; 5H), 7.91 (br s; 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 22.0, 22.3, 24.5, 24.8, 29.7, 30.0, 30.7, 30.9, 33.2, 34.4, 35.0, 40.2, 46.2, 46.8, 51.3, 52.4, 53.5, 55.1, 55.3, 67.0, 127.1, 127.4, 127.6, 127.7, 128.6, 128.7, 136.5, 136.7, 174.2, 181.7, 182.0. FT-IR (ATR): ν[cm^{-1}] = 3318 (br s), 2931 (s), 2858 (m), 2823 (w), 2779 (m), 1629 (s), 1543 (s), 1494 (w), 1475 (w), 1450 (m), 1419 (w), 1362 (m), 1318 (w), 1270 (w), 1253 (w), 1206 (w), 1150 (w), 1084 (m), 1038 (w), 945 (w), 911 (m), 875 (w), 851 (w), 730 (s). HRMS (EI): calcd for [$C_{24}H_{41}N_4OS$] ([M + H]$^+$): 433.300, found: 433.300.

X-Ray crystallography data‡

1-{3,5-Bis(trifluoromethyl)phenyl}-3-{(1*R*,2*R*)-2-(*N*-benzyl-*N*-methylamino)cyclohexyl}urea 1f. $C_{23}H_{25}F_6N_3O{\cdot}CH_3HCOHCH_3$, M = 533.55, monoclinic, a = 14.2234(7), b = 8.9069(5), c = 21.5226(13) Å, β = 90.890(0)°, U = 2726.3(3) Å^3, T = 100(2) K, space group $P21$, Z = 4, μ = 0.110 mm^{-1}, 13 589 reflections measured, 6269 unique (R_{int} = 0.105). The final $R1$ and w$R2$ were 0.075 and 0.111 ($I>2\sigma(I)$).

1-{3,5-Bis(trifluoromethyl)phenyl}-3-{(1*R*,2*R*)-2-(diallylamino)-cyclohexyl}urea 1g. $C_{21}H_{25}F_6N_3O$, M = 449.44, triclinic, a = 9.3840(10), b = 9.9690(10), c = 12.6230(10) Å, α = 81.560(10), β = 89.690(10), γ = 71.130(10)°, U = 1104.19(18) Å^3, T = 293(2) K, space group $P1$, Z = 2, μ = 0.119 mm^{-1}, 6801 reflections measured, 4749 unique (R_{int} = 0.043). The final $R1$ and w$R2$ were 0.067 and 0.149 ($I>2\sigma(I)$).

***N*-[3,5-Bis(trifluoromethyl)phenyl]-*N*′-[(1*R*,3*S*)-3-{[({[3,5-bis-(trifluoromethyl)phenyl]amino}oxomethyl)amino]methyl}-3,5,5-trimethylcyclohexyl]urea 5a.** $C_{28}H_{28}F_{12}N_4O_2{\cdot}CH_3OH$, M = 712.59, orthorhombic, a = 10.0545(8), b = 15.0943(13), c = 21.3967 Å, U = 3247.3(4) Å^3, T = 100(2) K, space group $P212121$, Z = 4, μ = 0.141 mm^{-1}, 11 456 reflections measured, 3913 unique (R_{int} = 0.073). The final $R1$ and w$R2$ were 0.048 and 0.091 ($I>2\sigma(I)$).

1-{3,5-Bis(trifluoromethyl)phenyl}-3-{(2*S*)-dimethylamino-(1*S*)-phenylpropyl}urea 9. $C_{20}H_{21}F_6N_3O$, M = 433.40, monoclinic, a = 10.5778(9), b = 18.5187(16), c = 11.1532(13) Å, β = 100.72(1)°, U = 2146.6(4) Å^3, T = 293(2) K, space group $P21$, Z = 4, μ = 0.120 mm^{-1}, 12 334 reflections measured, 4834 unique (R_{int} = 0.097). The final $R1$ and w$R2$ were 0.063 and 0.116 ($I>2\sigma(I)$).

1-(3,5-Dinitrophenyl)-3-{(1*R*,2*R*)-2-(dimethylamino)cyclohexyl}-urea 17. $C_{31}H_{48}N_{10}O_{12}$, M = 752.79, monoclinic, a = 8.1767(6), b = 22.874(2), c = 10.1933(6) Å, β = 108.158(3)°, U = 1811.5(2) Å^3, T = 100(2), space group $P21$, Z = 2, μ = 0.107 mm^{-1}, 7412 reflections measured, 4031 unique (R_{int} = 0.038). The final $R1$ and w$R2$ were 0.059 and 0.157 ($I>2\sigma(I)$).

1-{(1*R*,2*R*)-2-(Dimethylamino)cyclohexyl}-3-mesitylurea 18. $C_{18}H_{29}N_3O$, M = 303.44, orthorhombic, a = 11.8168(3), b = 16.6626(6), c = 18.2008(5) Å, U = 3583.71(19) Å^3, T = 100(2) K, space group $P212121$, Z = 8, μ = 0.071 mm^{-1}, 18 006 reflections measured, 4342 unique (R_{int} = 0.093). The final $R1$ and w$R2$ were 0.052 and 0.084 ($I>2\sigma(I)$).

1-{(1*R*,2*R*)-2-(Dimethylamino)cyclohexyl}-3-methylthiourea 20. $C_{10}H_{21}N_3S$, M = 215.36, orthorhombic, a = 11.5762(4), b = 12.7340(4), c = 16.3923(6) Å, U = 2416.41(14) Å^3, T = 100(2) K, space group $P212121$, Z = 8, μ = 0.238 mm^{-1}, 13 703 reflections measured, 5270 unique (R_{int} = 0.038). The final $R1$ and w$R2$ were 0.035 and 0.066 ($I>2\sigma(I)$).

1-{(1*R*,2*R*)-2-(Dimethylamino)cyclohexyl}-3-{(*R*)-1-phenylethyl}-urea 26a. $C_{17}H_{27}N_3O$, M = 289.42, monoclinic, a = 8.7335(2), b = 22.1650(6), c = 9.9252(3) Å, β = 101.774(1)°, U = 1880.88(9) Å^3, T = 100(2) K, space group $P21$, Z = 4, μ = 0.065 mm^{-1}, 9471 reflections measured, 3892 unique (R_{int} = 0.043). The final $R1$ and w$R2$ were 0.039 and 0.082 ($I>2\sigma(I)$).

1-{(1*R*,2*R*)-2-(Dimethylamino)cyclohexyl}-3-{(*S*)-1-phenylethyl}-urea 26b. $C_{17}H_{27}N_3O$, M = 289.42, orthorhombic, a = 9.1661(4), b = 11.3191(6), c = 15.5757(8) Å, U = 1616.01(14) Å^3, T = 293(2) K, space group $P212121$, Z = 4, μ = 0.075, 7841 reflections measured, 2021 unique (R_{int} = 0.044). The final $R1$ and w$R2$ were 0.034 and 0.068 ($I>2\sigma(I)$).

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