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Amine Activation: N-Arylamino Acid Amide Synthesis from

Isothioureas and Amino Acids

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Abstract. *N*-arylamino acid amides have been synthesized via a novel method based on *N*-arylamine activation into isothioureas followed by reaction with amino acids under iron catalysis. The activated *N*-arylamines are easily prepared using a three-component reaction with commercial reagents, *tert*-butylisocyanide and *S*-phenyl benzenethiosulfonate. The protocol shows a broad functional group compatibility, with respect to side chain functionality of the amino acid (e.g. aliphatic and aromatic OH, (hetero)aromatic NH, amide NH, thioether), and the chiral amino acids do not undergo epimerization. The mechanism of the new amide synthesis has been studied.

Keywords: amine activation; amino acid; amide, iron catalysis; carbodiimide; steric hindrance

Introduction

The amide functionality is one of the most important units in organic chemistry. It is the basic structural unit of proteins, but is also widely present in various polymers (e.g. chitin, nylon), natural products (e.g. paclitaxel, penicillin), top-selling drugs (e.g. Atorvastatin, Valsartan, Sitagliptin) and agrochemicals (e.g. Boscalid, Fluxapyroxad) (Figure 1).^[1] It is present in more than 25% of all launched pharmaceuticals and 2/3 of the drug candidates.^[2] Moreover, it has been estimated that 16% of all reactions performed in pharma industry involve amide bond formation.^[3] Around 10 years ago, the ACS Green Chemistry Institute (GCI) Pharmaceutical roundtable identified amide synthesis as a key area of interest for the industry, and this has not changed since then.^[4]

Despite the significant number of methods which have been reported in the past decades, several limitations and challenges remain for amide synthesis such as: a) mild reaction conditions, avoiding epimerization of a stereocenter at the alpha methylene of the carboxylic acid; b) challenging amides e.g. featuring sterically hindered carboxylic acids and/or electron deficient (hetero)aromatic amines; c) versatile methods compatible with unprotected functional groups (e.g. NH₂ and OH groups); d) use of (at least) stoichiometric amounts of often toxic and hazardous coupling/activating reagents, and associated generation of the corresponding stoichiometric waste which is not always (easily) separable and usually not recoverable into the reagent. New synthetic approaches tackling one or more of these aspects are therefore highly sought after by organic chemists.



Figure 1. Examples of *N*-heteroarylamide containing active ingredients of agrochemicals and medicines.

Amide synthesis from a surrogate of an amine or carboxylic acid is an important area studied. Up to now, many innovative strategies have been reported which do not rely on an amine and carboxylic acid: aminocarbonylation of alkenes or alkynes,^[5] coupling of (activated) thioacids with amines or azides,^[6] various reactions of azides with *N*-tosyl aldimines or ketones,^[7] oxidation of in situ generated aminals from alcohols and amines,^[8] reaction of α -bromo nitroalkanes with amines and NIS,^[9] radical based coupling from α -keto acids with amines and aldehydes with *N*,*N*-disubstituted formamides^[10] and reaction of Grignard reagents with isocyanates or NCAS.^[11]

However, procedures starting from carboxylic acids and amines are still the most interesting due to the widespread availability of these building blocks. The acylation of amines with activated carboxylic acids (C->N direction), such as, acyl chloride, acyl imidazole, anhydride or activated ester (obtained by classical coupling reagents, such as carbodiimides, phosphonium salts, uronium/guanidinium reagents),^[12a] is still the most common route for amide synthesis. They generally allow mild reaction conditions and result in often good yields. Sometimes, the activated carboxylic acids are generated in an extra step and activation requires unstable, expensive and waste-intensive reagents. Recent advances in this field use acetylenes and a transition metal and ynamides to activate the carboxylic acid or Si-ligation with 9-silafluorenyl dichlorides.^[12b-d] Epimerization of sensitive α -chiral acids through the formation of oxazolone intermediates is difficult to suppress with carboxylic acid activation. Lewis acids catalysis involving boron species or metal salts is an interesting relatively new approach for amide synthesis, but the substrate scope is unfortunately still limited to standard amides.^[12e-g]

As an alternative approach, amine activation $(N \rightarrow C \text{ direction})$ has been developed. Its main advantage is that epimerization of α -chiral acids such as amino acids is expected to be easily avoided. But up to now only a few procedures have been reported based on this approach (Scheme 1). Amine activation as isocyanide (a),^[13] *N*-(imidazolylcarbonyl)amine (b),^[14] and iminophosphorane (*in situ* obtained from azides and phosphines) (c)^[15] have been developed.



Scheme 1. Amide synthesis based on amine activation.

Within our program on amide synthesis,^[16] we have recently reported isothiourea as a new class of activated amines suitable for *N*-(hetero)arylamide synthesis (Scheme 1, route d).^[17] The protocol uses an iron catalyst under mild reaction conditions and is especially suitable for the synthesis of very challenging *N*-heteroarylamides, from the point of view of sterics and electronics, which are not (or only in poor yield) accessible *via* classical coupling reagents. Realizing that *N*-activation strategies should avoid epimerization we herein report our findings on the use of sensitive side chain unprotected chiral amino acids using our recently disclosed method.^[16a] After all, *N*-heteroarylamino acid amide reaction products are important structural entities as exemplified by the amino acid based APIs Lidocaine, Tocainide, Mepivacaine, Prilocaine and Bentiromide (Figure 1).^[1] In this manuscript, we also study the reaction mechanism of our new amide synthesis based on fundamental studies with model compounds.

Results and Discussion

N-Protected α -amino acids **2** were evaluated under the standard conditions for amide synthesis disclosed in our communication (Fe(acac)₃(2.5 mol%), *i*-PrOH (2 mL), 83 °C, air, 24 h).^[16a] Reaction of amino acids L-**2** with the model activated aniline *N*-tert-butyl-*S*,*N*'-diphenylisothiourea (**1a**) gave the corresponding *N*-phenyl amino acid amides L-3 in moderate to excellent yield (57-97%) (Scheme 2). The reaction proved to be fully compatible with standard nitrogen protective groups for amino acids (Boc, Cbz and Fmoc). Acid labile Boc did not deprotect under these reaction conditions though a Lewis acid at a higher temperature is used. Remarkably, even very challenging amino acids, such as Boc-L-Gln-OH (L-**2g**), Boc-L-Thr-OH (L-**2i**), Boc-L-Tyr-OH (L-**2p**), Boc-L-Trp-OH (L-**2r**), and

Boc-L-His-OH (L-**2s**) featuring a nucleophilic group in the side chain could be used, without requiring any protection. Boc-L-Thr-OH (L-2i) was selected as model to test amide synthesis with other isothioureas. N'-Tert-butyl-S-phenyl-N'-(hetero)arylisothiourea featuring sterically hindered substituents (N-2,6-diisopropylphenyl, **1x**), strong electron-withdrawing substituents (N-4-methoxycarbonylphenyl, **1o**) and heteroaromatic cores (N-pyridin-3-yl, **1r**) afforded the threoninamides L-**3j**-L-**3l** in good yields. Similarly, D-amino acids D-**2** were successfully applied as exemplified for some selected representatives (Scheme 3). Importantly, no epimerization occurred with the L- and D-amino acids tested (Supporting Information).



Scheme 2. L-Amino acid (L-2) scope. Reaction conditions: isothiourea 1 (0.30 mmol), L-amino acid L-2 (0.36 mmol), Fe(acac)₃ (2.5 mol%), isopropanol (2 mL), 83 °C, air, 24 h. [a] 72 h. [b] Fe(acac)₃ (5 mol%). [c] Fe(acac)₃ (10 mol%). [d] 48 h.



Scheme 3. D-Amino acid scope. Reaction conditions: isothiourea 1 (0.30 mmol), D-amino acid D-2 (0.36 mmol), Fe(acac)₃ (2.5 mol%), isopropanol (2 mL), 83 °C, air, 24 h. [a] 72 h. [b] Fe(acac)₃ (5 mol%). [c] Fe(acac)₃ (10 mol%). [d] 48 h.

Unnatural amino acids as exemplified by Cbz-Aib-OH (2t), Boc- β -Ala-OH (2u), and Boc-Inp-OH (2v) also worked equally well (Scheme 4). Finally, we tested this protocol to transform the α -carboxylic acid group of a short peptide into an amide (Scheme 5). Rewardingly, **N-Boc-triglycine** (2w) readily reacted with *N*-aryl-*N*'-tert-butyl-*S*-phenylisothioureas (N-phenyl 1d, *N-t*-butylphenyl 1y, and *N*-4-bromophenyl **1m**) and the corresponding triglycinamides (**3aa-3ac**) were obtained in 79-87%. When more challenging tripeptides *N*-Boc-L-Pro-L-Val-L-Pro-OH (2x) and N-Boc-L-Trp-L-Gln-L-Ala-OH (2y) reacted with N-tert-butyl-S,N'-diphenylisothiourea (1a) under the standard condition, the desired tripeptides **3ad** and **3ae** were obtained in a very good yield.



Scheme 4. Unnatural amino acid scope. Reaction conditions: isothiourea 1 (0.30 mmol), amino acid 2 (0.36 mmol), Fe(acac)₃ (2.5 mol%), isopropanol (2 mL), 83 °C, air, 24 h.



Scheme 5. *N*-Boc-triglycine. Reaction conditions: isothiourea **1** (0.30 mmol), *N*-Boc-triglycine (**2w**) or *N*-Boc-L-Pro-L-Val-L-Pro-OH (**2x**) (0.36 mmol), Fe(acac)₃ (2.5 mol%), isopropanol (2 mL), 83 °C, air, 24 h. [a] isothiourea 1 (0.15 mmol), *N*-Boc-L-Trp-L-Gln-L-Ala-OH (**2y**) (0.18 mmol), 48 h.

In order to demonstrate the potential of the new methodology for amino-acid amide synthesis, we applied it for the synthesis of the antiarrythmic drug Tocainide (3x) (Scheme 6). This drug is sold as a racemate but the R-enantiomer is 4 times as potent as the S-enantiomer. Classically, 3x is made by acylation of 2,6-dimethylaniline with 2-bromopropanoyl bromide, followed by nucleophilic substitution of the remaining bromine atom with ammonia.^[18] Our approach starts from Boc-protected alanine (2c), of which both the and **D**-enantiomer readily commercially 1 are available. *N-tert*-Butyl-*N'*-2,6-dimethylphenyl-*S*-phenylisothiourea (**1v**) was easily prepared in very high yield from 2,6-dimethylaniline, S-phenyl benzenethiosulfonate and tert-butyl isocyanide.^[17] Reaction of 1v and D-2c in 2-butanol yielded (R)-N-Boc Tocainide in 93%. When the reaction was performed in isopropanol at 83 °C, 95% isolated yield was obtained but more Fe(acac)₃ catalyst (10 mol%) and a longer reaction time (72 h) were needed to achieve full conversion. Starting from L-2c the S enantiomer was easily obtained in a similar manner (91% yield). No epimerization occurred under the reaction conditions (Supporting Information). Boc deprotection of (R)-N-Boc Tocainide finally delivered (R)-Tocainide. An overall yield of 80% was obtained for the most active enantiomer, (R)-N-Boc Tocainide. Interestingly, the PhSSPh by-product formed from PhSH under the reaction conditions could be isolated in 81% yield. It can be transformed into S-phenyl benzenethiosulfonate reagent according to a literature procedure.^[19]



Scheme 6. Synthesis of *R*–Tocainide. [a] Reaction conditions: $Fe(acac)_3$ (10 mol%), isopropanol (2 mL), 83 °C, air, 72 h.

To gain insight in the reaction mechanism of our new amide synthesis and to identify possible reaction intermediates, a set of control experiments were performed (Scheme 7). *N*-phenylbenzamide The synthesis of (5a) was selected as model. When *N-tert*-butyl-N'-phenylurea (4) was treated with benzoic acid (5a) under the standard conditions no reaction occurred (Scheme 7, A). When N-benzoyl-N'-tert-butyl-N-phenylurea (7) was used as substrate, 6a was obtained in excellent yield (B). Reaction of *N-tert*-butyl-*N*'-phenylcarbodiimide (8) with 5a yielded a mixture of amide 6a and urea 4 in 85% and 8%, respectively (C). A similar result was obtained without Fe catalyst (C). When the same reaction was performed in the presence of the by-products formed during the amide synthesis [phenyldisulfide (D) and thiophenol (E)] similar results were obtained. These experiments indicate that N-acyl-N'-tert-butyl-N-(hetero)arylurea and *N-tert*-butyl-*N*'-(hetero)arylcarbodiimide serve as intermediates in the reaction mechanism. The Lewis acid acitity of the Fe(acac)₃-catalyst was confirmed by a reaction of *N-tert*-butyl-*S*, *N*[']-diphenylisothiourea (**1a**) with pivalic acid (**5e**) in the presence of Fe(acac)₂ which also affords N-phenylpivalamide (6e) in 84% yield (F and G).



Scheme 7. Control experiments to support the mechanism of the amide formation. Isolated yields. [a] ¹H NMR yield, using 1,3,5-trimethoxybenzene as internal standard.

On the basis of the above results, a reaction mechanism is proposed in Scheme 8 (left). Initially, the isothiourea-Fe complex **B** is formed. This complexation activates the substrate for elimination, yielding carbodiimide C. Reaction of **C** with carboxylic acid affords

O-acylisourea **D**, which undergoes an O \rightarrow N acyl migration (Mumm rearrangement)^[20] to form *N*-acyl-*N*-(hetero)aryl-*N'-tert*-butylurea **E**. Finally, E eliminates *tert*-butyl isocyanate yielding *N*-(hetero)arylamide. The avoidance of racemization in reactions with amino acids is in accordance with a very fast O \rightarrow N acyl migration, which protects the α -position of the carbonyl. The formation of urea side product F with electrophilic or more sterically hindered acyl groups can be explained by reaction of **D** with isopropanol (solvent). Alcoholysis of *O*-acylisourea can for those cases be suppressed by using a more sterically hindered alcohol (2-butanol) or a non-nucleophilic solvent (*o*-xylene) as we have disclosed in our communication.^[16a] It is actually remarkable that in the majority of reported examples alcoholysis with isopropanol does not compete with O \rightarrow N acyl migration and no **F** is formed, again pointing to very fast acyl transfer.

Although our protocol and the one based on carbodiimide coupling reagents activating carboxylic acid (e.g. DCC) both involve an *O*-acylisourea intermediate they are mechanistically completely different (Scheme 8, right). In the latter case, *O*-acylisourea does not undergo $O \rightarrow N$ acyl migration, but reacts directly in an intermolecular reaction with amine or another molecule of carboxylic acid. Often a nucleophilic additive such as HOBt, HOAt or DMAP is added to form an "active ester", explicitly avoiding the migration. Moreover, the carbodiimide (intermediate) in our protocol results from the amine activation process, while it is a carboxylic acid activating reagent in the classical approach. This difference clearly reflects in the efficiency of both protocols (*vide infra*, Scheme 11).



Scheme 8. Reaction mechanism: carbodiimide as an intermediate (A) versus reagent (B).

Two different amides can in principle be formed in our protocol as the reaction mechanism involves $O \rightarrow N$ migration in the *O*-acylisourea intermediate **D**.^[20] In our reactions, however, only one amide was always selectively formed. The features of such migrations remain largely unstudied, as it is an undesired side reaction when using carbodiimide as coupling reagents (Scheme 8, right) (*vide infra*), diminishing the yield of the desired amide.^[21] Therefore, we studied the acyl migration on a series of isothiourea substrates in the reaction with benzoic acid under the same reaction conditions (Scheme 9). Isothioureas with an alkyl

and aryl group on nitrogen (9, 11) always gave the *N*-arylbenzamide irrespective of the sterics of the alkyl group (Scheme 9A-B). Even in 11, which features two *ortho* methyl's in the arene and an unbranched aliphatic chain, selective migration to the arylated nitrogen occurred. This supports the complete regio-selectivity obtained in our *N*-(hetero)arylamide synthesis featuring an alkyl and (hetero)aryl nitrogen substituent in the isothiourea substrate. This can be rationalized by protonation of the most basic nitrogen of the carbodiimide intermediate by carboxylic acid.

Next, substrates containing two *N*-alkyl groups were studied (**12**, **15** and **17**^[17]). Isothiourea **12**, containing a *tert*-butyl and an ethyl group, gave *N*-*tert*-butylbenzamide (**13**) as minor and *N*-ethylbenzamide (**14**) as major product (Scheme 9C). With an electron-withdrawing ester in the β -position (**15**), selectivity was lost and an almost equal amount of the two amides was obtained (Scheme 9D). When the electron-withdrawing character was further increased by building in three β -fluorine atoms (**17**), instead of an ester, almost exclusive formation of **13** was observed (Scheme 9E).



Scheme 9. Selectivity of amide formation in the reaction of N,N'-disubstituted-S-phenylisothiourea with carboxylic acids. Isolated yields. [a] ¹H NMR yield, using 1,3,5-trimethoxybenzene as internal standard.

Subsequently, the sterics of the acyl group were altered by changing the carboxylic acid in a reaction with **17**. More sterically hindered diphenylacetic acid (**5b**),

2,2-diphenylpropionic acid (**5c**) and triphenylacetic acid (**5d**) completely reversed the selectivity observed with benzoic acid (Scheme 9E) and gave the corresponding *N*-trifluorethylamide as major component (Scheme 9 **F-H**). From all these experiments we can conclude that in the absence of electronic effects, sterics always govern the acyl transfer but strong electron-withdrawing groups can overrule sterics in reactions with less bulky carboxylic acids. With two alkyl groups on the nitrogen atoms in the isothiourea simple nitrogenbasicity of the *in-situ* formed carbodiimide cannot explain the experimental observations.

Based on the regio-selectivity observed for the $O \rightarrow N$ acyl transfer in O-acylisourea, extension of the protocol towards challenging amides based on aliphatic amines seems to be limited by the steric properties of the carboxylic acid, and no generally applicable protocol could be identified (Scheme 9). Use of symmetrical isothiourea as activated amines would be a solution. However, as our previously developed three-component reaction for isothiourea synthesis does not tolerate the activation of aliphatic amines this would require a synthesis involving the corresponding carbodiimides.^[17] We therefore, envisioned that the use of symmetrical carbodiimides directly, which can be accessed from alkylamines, would be a potential strategy to overcome these limitations and therefore represents an interesting alternative amine activation.^[22] They can for instance be synthesized by reaction of an alkylamine and an alkylisocyanide using I2 as catalyst and cumene hydroperoxide as stoichiometric oxidant.^[22c] Pleasingly, when N,N'-dicyclohexyl- (23a), N,N'-diisopropyl- (23b), N,N'-di-*tert*-butyl- (23c) and N,N'-diadamantylcarbodiimide (23d) were reacted with 2,2,2-triphenylacetic acid (5d) the target sterically encumbered aliphatic amides were obtained in good yield (Scheme 10). The process starting from carbodiimide does not require an iron catalyst though a non-nucleophilic solvent, avoiding urea side product formation, and a higher reaction temperature are essential. This strategy can also be used for (hetero)aromatic amines exemplified for as the reaction of *N*,*N*[′]-(2,6-diisopropylphenyl)carbodiimide (**23e**) with **5d**.



Scheme 10. Synthesis of amides from carbodiimides and carboxylic acids. Reaction conditions: 23 (0.30 mmol), 5d (0.36 mmol), *o*-xylene (2 mL), 130 °C, air, 24 h.

When we attempted to synthesize amino acid amides with Boc-L-Thr-OH (L-2i) and Boc-L-His-OH (L-2s) featuring a nucleophilic group in the side chain or sterically hindered aliphatic amides 24 via classical reaction of amine and carboxylic acid with DCC no or only a low amount of the target amides was obtained (Scheme 11). The new amide synthesis

disclosed is therefore complementary with classical protocols. While both protocols will provide standard amides only the new protocol gives efficient access to the challenging representatives. Though the classical and new procedure both involve a carbodiimide, the efficiency difference reflects the different reaction mechanism (*vide supra*).



Scheme 11. Synthesis of examples of Scheme 2 and 10 using classical method from carboxylic acids and amines with DCC. [a] Method A. Reaction conditions: amino acid **2** (1.0 mmol), HOBt hydrate (1.1 mmol), DCC (1.1 mmol), aniline (1.1 mmol), anhydrous THF (5 mL), 25 °C, 24 h. [b] Method B. Reaction conditions: $R^{1}CO_{2}H$ **5** (1.05 mmol), DCC (1.08 mmol), DMAP (0.25 mmol), amine (1.0 mmol), CH₂Cl₂ (10 mL), 0-25 °C, 24 h.

Conclusion

A novel protocol for amino acid amide synthesis was developed based on rarely explored amine rather than carboxylic acid activation which does not require rigorously dried solvents or an inert atmosphere. (Hetero)arylamines are easily activated as bench stable N-tert-butyl-N'-(hetero)aryl-S-phenylisothiourea via a three-component reaction with commercially available reagents, tert-butylisocyanide and S-phenyl benzenethiosulfonate. N-(hetero)arylamino acid amides can be obtained in high selectivity and yield from these isothioureas via reaction with amino acids under iron catalysis, showing a broad functional group compatibility (e.g. aliphatic and aromatic OH, (hetero)aromatic NH, amide NH, thioether) without any racemization. The potential of the new methodology has been exemplified by the synthesis of the API Tocainide. Mechanistic studies revealed that the reaction involves a N-tert-butyl-N'-(hetero)arylcarbodiimide and is based on a selective $O \rightarrow N$ acyl transfer in the O-acyl-N-tert-butyl-N'-(hetero)arylisourea intermediate, formed via reaction of the carbodiimide with carboxylic acid. Such selective transfer cannot be achieved in the corresponding N,N'-dialkyl systems and therefore challenging aliphatic amides were in this case prepared from alternative activated amines, namely symmetrical carbodiimides. Although our protocol and the one based on classical carbodiimide coupling reagents (e.g. DCC) both involve an O-acylisourea intermediate they are mechanistically completely different, based on a different substrate, explaining the very poor results obtained for the latter approach in challenging amide synthesis.

Experimental Section

The general information of the equipment used to characterize the synthesized compounds can be found in the supporting information. The synthesis and characterization of compounds $1v^{[16a]}$, $6e^{[16a]}$ and $17^{[17]}$ has previously been described by us.

General procedure A for the synthesis of *N***-(hetero)arylamides:** A 10 mL pressure vial was charged with *N*-aryl-*N*´-*tert*-butyl-*S*-phenylisothiourea (**1**) (0.30 mmol), carboxylic acid (0.36 mmol), Fe(acac)₃ (2.7 mg, 2.5 mol%) and isopropanol (2.0 mL) or 2-butanol (2.0 mL). The vial was sealed and the reaction mixture was respectively stirred at 83 °C or 98 °C for 24 h under an air atmosphere. The mixture was cooled down to room temperature, concentrated under reduced pressure and dried under vacuum. The residue was purified by flash column chromatography on silica gel or recrystallized (compounds 3v-3x) to yield the corresponding *N*-(hetero)arylamide.

Benzyl [2-oxo-2-(phenylamino)ethyl]carbamate (3a)^[23]: Prepared from *N-tert*-butyl-*S*,*N'*-diphenylisothiourea (**1d**) (85 mg, 0.30 mmol, 1.0 equiv.) and Z-Gly-OH (**2a**) (75 mg, 0.36 mmol, 1.2 equiv.) according to the general procedure A. The residue was purified by column chromatography on silica gel with heptane/EtOAc = 1:1 as eluent. Benzyl [2-oxo-2-(phenylamino)ethyl]carbamate was obtained in 60% yield (51 mg). White solid, m.p.: 122-124 °C (lit.^[23]: 144-145 °C), ¹H NMR (400 MHz, DMSO-d₆): δ (ppm) 9.95 (s, 1H), 7.61 (d, *J* = 7.6 Hz, 2H), 7.53 (s, 1H), 7.38 (br s, 3H), 7.31 (t, *J* = 7.6 Hz, 4H), 7.05 (t, *J* = 7.2 Hz, 1H), 5.07 (s, 2H), 3.85 (d, *J* = 5.6 Hz, 2H); ¹³C NMR (101 MHz, DMSO-d₆): δ (ppm) 167.9, 156.6, 138.9, 137.0, 128.7, 128.3, 127.74, 127.67, 123.2, 119.1, 65.5, 44.1; HRMS (ESI): m/z [M+H]⁺ calcd for C₁₆H₁₇N₂O₃: 285.1239; found 285.1250.

(9H-Fluoren-9-yl)methyl [2-oxo-2-(phenylamino)ethyl]carbamate (3b) Prepared from N-tert-butyl-S,N'-diphenylisothiourea (1d) (85 mg, 0.30 mmol, 1.0 equiv.) and N-Fmoc-Gly-OH (2b) (107 mg, 0.36 mmol, 1.2 equiv.) according to the general procedure A. The residue was purified recrystalization with EtOAc/MeOH = 9:1. (9H-Fluoren-9-yl)methyl by [2-oxo-2-(phenylamino)ethyl]carbamate was obtained in 77% yield (86 mg). White solid, m.p.: 186-189 °C, ¹H NMR (400 MHz, DMSO-d₆): δ (ppm) 9.94 (s, 1H), 7.89 (d, J = 7.2 Hz, 2H), 7.74 (d, J = 7.2 Hz, 2H), 7.60 (d, J = 8.0 Hz, 3H), 7.40 (t, J = 7.2 Hz, 2H), 7.29-7.35 (m, 5H), 7.04 (t, J = 7.2 Hz, 1H), 4.32 (d, J = 7.2 Hz, 2H), 4.25 (t, J = 7.2 Hz, 1H), 3.82 (d, J = 6.0 Hz, 2H); ¹³C NMR (100 MHz, DMSO-d₆): δ (ppm) 167.9, 156.6, 143.8, 140.7, 138.9, 128.7, 127.6, 127.0, 125.2, 123.2, 120.0, 119.1, 65.7, 46.6, 44.0; HRMS (ESI): $m/z [M+H]^{+}$ calcd for $C_{23}H_{21}N_2O_3$: 373.1547; found 373.1557.

tert-Butyl (2*S*)-[1-oxo-1-(phenylamino)propan-2-yl]carbamate (L-3c) ^[24] Prepared from *N-tert*-butyl-*S*,*N*[']-diphenylisothiourea (1d) (85 mg, 0.30 mmol, 1.0 equiv.) and Boc-(L)-Ala-OH (L-2c) (68 mg, 0.36 mmol, 1.2 equiv.) according to the general procedure A. The residue was purified by column chromatography on silica gel with heptane/EtOAc = 2:1 as eluent. *tert*-Butyl (*S*)-[1-oxo-1-(phenylamino)propan-2-yl]carbamate was obtained in 96% yield (76 mg). White solid, m.p.: 142-144 °C, ¹H NMR (400 MHz, DMSO-d₆): δ (ppm) 9.87 (s, 1H), 7.61 (d, *J* = 7.6 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.04 (t, *J* = 7.6 Hz, 1H), 6.99 (s, 1H), 4.14 (quint, *J* = 7.2 Hz, 1H), 1.39 (s, 9H), 1.27 (d, *J* = 6.8 Hz, 3H); ¹³C NMR (101 MHz, DMSO-d₆): δ (ppm) 171.8, 155.2, 139.1, 128.6, 123.1, 119.1, 78.0, 50.4, 28.2, 18.0; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{21}N_2O_3$: 265.1547; found 265.1555.

tert-Butyl (2*R*)-[1-oxo-1-(phenylamino)propan-2-yl]carbamate (D-3c) ^[25]

Prepared from *N-tert*-butyl-*S*,*N*[']-diphenylisothiourea (**1d**) (85 mg, 0.30 mmol, 1.0 equiv.) and Boc-(D)-Ala-OH (**D-2c**) (68 mg, 0.36 mmol, 1.2 equiv.) according to the general procedure A. The residue was purified by column chromatography on silica gel with heptane/EtOAc = 2:1 as eluent. *tert*-Butyl (2*R*)-[1-oxo-1-(phenylamino)propan-2-yl]carbamate was obtained in 95% yield (75 mg). White solid, m.p.: 142-144 °C, ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.77 (s, 1H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.24 (t, *J* = 7.6 Hz, 2H), 7.05 (t, *J* = 7.2 Hz, 1H), 5.39 (d, *J* = 7.6 Hz, 1H), 4.41 (br s, 1H), 1.45 (s, 9H), 1.43 (s, 3H); ¹³C NMR (101 MHz, CDCl₃): δ (ppm) 171.2, 156.1, 137.8, 128.8, 124.1, 119.8, 80.4, 50.7, 28.3, 17.8; HRMS (ESI): m/z [M+H]⁺ calcd for C₁₄H₂₁N₂O₃: 265.1547; found 265.1557.

tert-Butyl-(2*S*)-[3-methyl-1-oxo-1-(phenylamino)butan-2-yl]carbamate (L-3d)^[26] Prepared from *N-tert*-butyl-*S*,*N*'-diphenylisothiourea (1d) (85 mg, 0.30 mmol, 1.0 equiv.), Boc-(L)-Val-OH (L-2d) (78 mg, 0.36 mmol, 1.2 equiv.) and Fe(acac)₃ (2.65 mg, 2.5 mol%) according to the general procedure A. The residue was purified by column chromatography on silica gel with heptane/EtOAc = 1:1 as eluent. *tert*-Butyl (2*S*)-[3-methyl-1-oxo-1-(phenylamino)butan-2-yl]carbamate was obtained in 95% yield (83 mg). White solid, m.p.: 120-121 °C (lit.^[26]: 120-122 °C), ¹H NMR (400 MHz, CDCl₃): δ (ppm) 9.00 (s, 1H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.19 (t, *J* = 7.6 Hz, 2H), 7.03 (t, *J* = 7.6 Hz, 1H), 5.74 (d, *J* = 8.4 Hz, 1H), 4.23 (s, 1H), 2.21 (t, *J* = 6.8 Hz, 1H), 1.44 (s, 9H), 1.06 (d, *J* = 7.2 Hz, 3H), 1.05 (d, *J* = 7.2 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃): δ (ppm) 171.0, 156.5, 137.8, 128.7, 124.0, 120.0, 80.0, 61.0, 31.0, 28.3, 19.3; HRMS (ESI): m/z [M+Na]⁺ calcd for C₁₆H₂₄N₂O₃Na: 315.1685; found 315.1681.

tert-Butyl-(2*R*)-(3-methyl-1-oxo-1-(phenylamino)butan-2-yl)carbamate (p-3d)^[26] Prepared from *N*-*tert*-butyl-*S*,*N*[′]-diphenylisothiourea (1d) (85 mg, 0.30 mmol, 1.0 equiv.), Boc-(D)-Val-OH (p-2d) (78 mg, 0.36 mmol, 1.2 equiv.) according to the general procedure A. The residue was purified by column chromatography on silica gel with heptane/EtOAc = 1:1 as eluent. *tert*-Butyl-(2*R*)-(3-methyl-1-oxo-1-(phenylamino)butan-2-yl)carbamate was obtained in 90% yield (88 mg). White solid, m.p.: 120-121 °C (lit.^[26]: 120-122 °C), ¹H NMR (400 MHz, CDCl₃): δ (ppm) 9.28 (br s, 1H), 7.47 (d, *J* = 7.6 Hz, 2H), 7.12 (br s, 2H), 6.99-6.97 (m, 1H), 5.97 (d, *J* = 8.4 Hz, 1H), 4.28 (br s, 1H), 2.18-2.16 (m, 1H), 1.40 (s, 9H), 1.05 (d, *J* = 6.4 Hz, 6H); ¹³C NMR (101 MHz, CDCl₃): δ (ppm) 171.2, 156.5, 137.8, 128.5, 123.9, 120.0, 79.7, 61.0, 31.1, 28.2, 19.2; HRMS (ESI): m/z [M+Na]⁺ calcd for C₁₆H₂₄N₂O₃Na: 315.1685; found 315.1681.

tert-Butyl [(*25,35*)-3-methyl-1-oxo-1-(phenylamino)pentan-2-yl]carbamate (L-3e)^[25] Prepared from *N-tert*-butyl-*S*,*N*′-diphenylisothiourea (1d) (85 mg, 0.30 mmol, 1.0 equiv.) and Boc-(L)-Ile-OH (L-2e) (83 mg, 0.36 mmol, 1.2 equiv.) according to the general procedure A. The residue was purified by column chromatography on silica gel with heptane/EtOAc = 1:1 as eluent. *tert*-Butyl [(*25,35*)-3-methyl-1-oxo-1-(phenylamino)pentan-2-yl]carbamate was obtained in 96% yield (88 mg). White solid, m.p.: 161-163 °C (lit. ^[25]: 124-125 °C), ¹H NMR (400 MHz, CDCl₃): δ (ppm) 9.17 (s, 1H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.17 (t, *J* = 7.6 Hz, 2H), 7.02 (t, *J* = 7.6 Hz, 1H), 5.82 (s, 1H), 4.29 (s, 1H), 1.96 (d, *J* = 5.6 Hz, 1H), 1.69 (br s, 1H), 1.43 (s, 9H), 1.23-1.29 (m, 1H), 1.04 (d, *J* = 6.8 Hz, 3H), 0.93 (t, *J* = 7.6 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃): δ (ppm) 171.3, 156.5, 137.9, 128.6, 123.9, 120.0, 79.8, 60.0, 37.2, 28.3, 25.0, 15.4, 10.8; HRMS (ESI): m/z [M+H]⁺ calcd for C₁₇H₂₇N₂O₃: 307.2022; found 307.2020. *tert*-Butyl (2*S*)-2-(phenylcarbamoyl)pyrrolidine-1-carboxylate (L-3f)^[27] Prepared from *N-tert*-butyl-*S*,*N*[']-diphenylisothiourea (1d) (85 mg, 0.30 mmol, 1.0 equiv.) and Boc-(L)-Pro-OH (L-2f) (77 mg, 0.36 mmol, 1.2 equiv.) according to the general procedure A. The residue was purified by column chromatography on silica gel with heptane/EtOAc = 1:1 as eluent. *tert*-Butyl (*S*)-2-(phenylcarbamoyl)pyrrolidine-1-carboxylate was obtained in 97% yield (84 mg). Brown solid, m.p.: 186-188 °C (lit. ^[27]: 187-188 °C), ¹H NMR (400 MHz, CDCl₃): δ (ppm) 9.49 (br s, 1H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.25 (m, 2H), 7.03 (m, 1H), 4.47 (m, 1H), 3.48 (m, 2H), 2.44 (m, 1H), 1.91-1.99 (m, 3H), 1.49 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ (ppm) 170.1, 156.4, 138.0, 128.9, 123.9, 119.7, 80.8, 60.4, 47.2, 28.4, 27.3, 24.1; HRMS (ESI): m/z [M+H]⁺ calcd for C₁₆H₂₃N₂O₃: 291.1703; found 291.1715.

tert-Butyl (2*R*)-2-(phenylcarbamoyl)pyrrolidine-1-carboxylate (D-3f) Prepared from *N*-*tert*-butyl-*S*,*N*[']-diphenylisothiourea (1d) (85 mg, 0.30 mmol, 1.0 equiv.) and Boc-(D)-Pro-OH (D-2f) (77 mg, 0.36 mmol, 1.2 equiv.) according to the general procedure A. The residue was purified by column chromatography on silica gel with heptane/EtOAc = 1:1 as eluent. *tert*-Butyl (2*R*)-2-(phenylcarbamoyl)pyrrolidine-1-carboxylate was obtained in 90% yield (78 mg). White solid, m.p.: 186-188 °C, ¹H NMR (400 MHz, CDCl₃): δ (ppm) 9.43 (br s, 1H), 7.51 (d, *J* = 7.6 Hz, 2H), 7.31 (t, *J* = 7.6 Hz, 2H), 7.08 (t, *J* = 6.4 Hz, 1H), 4.45 (br s, 1H), 3.44 (br s, 2H), 2.54 (br s, 1H), 1.91 (br s, 2H), 1.58 (br s, 1H), 1.49 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ (ppm) 167.7, 132.4, 130.8, 128.8, 123.7, 119.6, 80.8, 68.1, 47.1, 28.3, 23.7, 22.9; HRMS (ESI): m/z [M+H]⁺ calcd for C₁₆H₂₃N₂O₃: 291.1703; found 291.1710.

tert-Butyl (2S)-[5-amino-1,5-dioxo-1-(phenylamino)pentan-2-yl]carbamate (L-3g) Prepared from N-tert-butyl-S,N'-diphenylisothiourea (1d) (85 mg, 0.30 mmol, 1.0 equiv.), Boc-(L)-Gln-OH (L-2g) (89 mg, 0.36 mmol, 1.2 equiv.) and Fe(acac)₃ (5.3 mg, 5 mol%) according to the general procedure A with 72 hours reaction time. The residue was purified by column chromatography on silica gel with heptane/EtOAc 1:3 as eluent. tert-Butyl = (25)-[5-amino-1,5-dioxo-1-(phenylamino)pentan-2-yl]carbamate was obtained in 83% yield (80 mg). White solid, m.p.: 174-176 °C, ¹H NMR (400 MHz, DMSO-d₆): δ (ppm) 9.91 (s, 1H), 7.59 (d, J = 7.6 Hz, 2H), 7.30 (t, J = 7.6 Hz, 3H), 7.04 (t, J = 7.2 Hz, 1H), 6.98 (d, J = 6.8 Hz, 1H), 6.75 (br s, 1H), 4.04 (m, 1H), 2.15-2.16 (m, 2H), 1.79-1.90 (m, 2H), 1.38 (s, 9H); ¹³C NMR (101 MHz, DMSO-d₆): δ (ppm) 174.2, 171.4, 155.9, 139.4, 129.2, 123.8, 119.8, 78.6, 55.3, 32.0, 29.0, 28.7; HRMS (ESI): $m/z [M+H]^{+}$ calcd for $C_{16}H_{24}N_{3}O_{4}$: 322.1761; found 322.1765.

tert-Butyl (2R)-[5-amino-1,5-dioxo-1-(phenylamino)pentan-2-yl]carbamate (D-3g) Prepared from N-tert-butyl-S,N'-diphenylisothiourea (1d) (85 mg, 0.30 mmol, 1.0 equiv.), Boc-(D)-Gln-OH (D-2g) (89 mg, 0.36 mmol, 1.2 equiv.) and Fe(acac)₃ (5.3 mg, 5 mol%) according to the general procedure A with 72 hours reaction time. The residue was purified by column chromatography on silica gel with heptane/EtOAc = 1:3 as eluent. *tert*-Butyl (2R)-[5-amino-1,5-dioxo-1-(phenylamino)pentan-2-yl]carbamate was obtained in 83% yield (80 mg). White solid, m.p.: 174-176 °C, ¹H NMR (400 MHz, DMSO-d₆): δ (ppm) 9.92 (s, 1H), 7.60 (d, J = 7.6 Hz, 2H), 7.31 (t, J = 7.6 Hz, 3H), 7.05 (t, J = 7.2 Hz, 1H), 7.00 (d, J = 7.2 Hz, 1H), 6.75 (s, 1H), 4.05 (m, 1H), 2.13-2.19 (m, 2H), 1.79-1.90 (m, 1H), 1.88-1.94 (m, 1H), 1.39 (s, 9H); ¹³C NMR (101 MHz, DMSO-d₆): δ (ppm) 173.4, 171.0, 155.4, 139.0, 128.7, 123.2, 119.2, 78.1, 55.9, 31.6, 28.2, 27.6; HRMS (ESI): $m/z [M+H]^+$ calcd for $C_{16}H_{24}N_3O_4$: 322.1761; found 322.1768.

Dibenzyl-(2S)-[6-oxo-6-(phenylamino)hexane-1,5-diyl]dicarbamate (L-3h) Prepared from *N-tert*-butyl-*S*,*N*[']-diphenylisothiourea (**1d**) (85 mg, 0.30 mmol, 1.0 equiv.) and Z-(L)-Lys(Z)-OH

(**L**-**2h**) (149 mg, 0.36 mmol, 1.2 equiv.) according to the general procedure A. The residue was purified by column chromatography on silica gel with heptane/EtOAc = 1:2 as eluent. Dibenzyl-(2*S*)-[6-oxo-6-(phenylamino)hexane-1,5-diyl]dicarbamate was obtained in 74% yield (109 mg). White solid, m.p.:126-128 °C, ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.78 (br s, 1H), 7.52 (d, *J* = 7.6 Hz, 2H), 7.31-7.33 (m, 9H), 7.27 (d, *J* = 7.2 Hz, 2H), 7.24 (s, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 6.02 (d, *J* = 6.4 Hz, 1H), 5.08-5.11 (m, 5H), 4.40 (br s, 1H), 3.16 (d, *J* = 5.2 Hz, 2H), 1.93-1.90 (m, 1H), 1.77-1.72 (m, 1H), 1.51-1.43 (m, 2H); ¹³C NMR (101 MHz, CDCl₃): δ (ppm) 170.5, 156.7, 137.6, 136.5, 136.0, 128.8, 128.4, 128.37, 128.1, 127.9, 127.87, 127.83, 124.3, 120.0, 67.1, 66.5, 55.4, 40.2, 31.8, 29.2, 22.3; HRMS (ESI): m/z [M+H]⁺ calcd for C₁₈H₃₂N₃O₅: 490.2336; found 490.2344.

Dibenzyl-(2*R***)-[6-oxo-6-(phenylamino)hexane-1,5-diyl]dicarbamate (D-3h)** Prepared from *N-tert*-butyl-*S*,*N*[′]-diphenylisothiourea (**1d**) (85 mg, 0.30 mmol, 1.0 equiv.) and Z-(D)-Lys(Z)-OH (**D-2h**) (149 mg, 0.36 mmol, 1.2 equiv.) according to the general procedure A. The residue was purified by column chromatography on silica gel with heptane/EtOAc = 1:2 as eluent. Dibenzyl-(2*R*)-[6-oxo-6-(phenylamino)hexane-1,5-diyl]dicarbamate was obtained in 76% yield (110 mg). White solid, m.p.:126-128 °C, ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.75 (br s, 1H), 7.46 (d, *J* = 7.5 Hz, 2H), 7.27-7.19-7.26 (m, 12H), 7.04 (t, *J* = 7.2 Hz, 1H), 5.99 (d, *J* = 6.5 Hz, 1H), 5.08-5.03 (m, 5H), 4.35 (br s, 1H), 3.10 (br s, 2H), 1.88-1.86 (m, 1H), 1.73-1.69 (m, 1H), 1.45-1.38 (m, 4H), ¹³C NMR (101 MHz, CDCl₃): δ (ppm) 170.5, 156.7, 137.6, 136.5, 136.0, 128.8, 128.4, 128.4, 128.1, 128.0, 127.9, 127.9, 124.3, 120.0, 67.1, 66.6, 55.4, 40.2, 31.8, 29.2, 22.3; HRMS (ESI): m/z [M+H]⁺ calcd for C₁₈H₃₂N₃O₅: 490.2336; found 490.2344.

tert-Butyl [(25,3R)-3-hydroxy-1-oxo-1-(phenylamino)butan-2-yl]carbamate (L-3i) Prepared from N-tert-butyl-S,N'-diphenylisothiourea (1d) (85 mg, 0.30 mmol, 1.0 equiv.), Boc-(L)-Thr-OH (L-2i) (79 mg, 0.36 mmol, 1.2 equiv.) and Fe(acac)₃ (5.3 mg, 5 mol%) according to the general procedure A with 72 hours reaction time. The residue was purified by column chromatography tert-Butyl on silica gel with heptane/EtOAc 1:1 as eluent. = [(2S,3R)-3-hydroxy-1-oxo-1-(phenylamino)butan-2-yl]carbamate was obtained in 88% yield (78 mg). White solid, m.p.: 101-103 °C, ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.87 (s, 1H), 7.49 (d, J = 8.0 Hz, 2H), 7.29 (t, J = 8.0 Hz, 2H), 7.10 (t, J = 7.6 Hz, 1H), 5.85 (d, J = 7.6 Hz, 1H), 4.42 (q, J = 5.6 Hz, 1H), 4.28 (d, J = 6.4 Hz, 1H), 3.96 (s, 1H), 1.48 (s, 9H), 1.24 (d, J = 6.4 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃): δ (ppm) 169.6, 156.8, 137.3, 128.8, 124.5, 120.2, 80.6, 67.0, 59.0, 28.2, 18.2; HRMS (ESI): m/z [M+H]⁺ calcd for C₁₅H₂₃N₂O₄: 295.1652; found 295.1663.

tert-Butyl {(2*S*, 3*R*)-1-[(2,6-diisopropylphenyl)amino]-3-hydroxy-1-oxobutan-2-yl}carbamate (L-3j) Prepared from *N*-*tert*-butyl-*N*'-(2,6-diisopropylphenyl)-*S*-phenylisothiourea (1x) (133 mg, 0.30 mmol, 1.0 equiv.), Boc-(L)-Thr-OH (L-2i) (79 mg, 0.36 mmol, 1.2 equiv.) and Fe(acac)₃ (5.3 mg, 5 mol%) according to the general procedure A with 72 hours reaction time. The residue was purified by column chromatography on silica gel with heptane/EtOAc = 1:1 as eluent. *tert*-Butyl {(2*S*, 3*R*)-1-[(2,6-diisopropylphenyl) amino]-3-hydroxy-1-oxobutan-2-yl}carbamate was obtained in 82% yield (93 mg). White solid, m.p.: 156-158 °C, ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.97 (s, 1H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.16 (d, *J* = 7.6 Hz, 2H), 5.67 (d, *J* = 7.6 Hz, 1H), 4.48 (d, *J* = 6.4 Hz, 1H), 4.22 (d, *J* = 7.6 Hz, 1H), 3.03 (sep, *J* = 6.8 Hz, 2H), 1.49 (s, 9H), 1.27 (d, *J* = 6.4 Hz, 3H), 1.19 (d, *J* = 7.6 Hz, 6H), 1.17 (d, *J* = 7.6 Hz, 6H); ¹³C NMR (101 MHz, CDCl₃): δ (ppm) 171.7, 157.0, 146.0, 130.4, 128.5, 123.4, 80.6, 66.4, 57.7, 28.7, 28.3, 23.7, 23.4, 18.5; HRMS (ESI): m/z [M+H]⁺ calcd for C₂₁H₃₅N₂O₄: 379.2591; found 379.2599.

Methyl 4-{(2*S*,3*R*)-2-[(*tert*-butoxycarbonyl)amino]-3-hydroxybutanamido}benzoate (L-3k) Prepared from *N-tert*-butyl-*N*'-(4-methoxycarbonyl phenyl)-*S*-phenylisothiourea (**1o**) (103 mg, 0.30 mmol, 1.0 equiv.) and Boc-(L)-Thr-OH (L-2i) (79 mg, 0.36 mmol, 1.2 equiv.) with 72 hours reaction time according to the general procedure A. The residue was purified by column chromatography on silica gel with heptane/EtOAc = 1:1 as eluent. Methyl 4-{(2*S*,3*R*)-2-[(*tert*-butoxycarbonyl)amino]-3-hydroxy butanamido}benzoate was obtained in 57% yield (60 mg). White solid, m.p.: 135-137 °C, ¹H NMR (400 MHz, CDCl₃): δ (ppm) 9.08 (s, 1H), 7.93 (d, *J* = 8.8 Hz, 2H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.78 (d, *J* = 7.6 Hz, 1H), 4.42 (d, *J* = 4.4 Hz, 1H), 4.25 (d, *J* = 5.2 Hz, 1H), 3.87 (s, 3H), 2.02 (s, 1H), 1.45 (s, 9H), 1.23 (d, *J* = 2.4 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃): δ (ppm) 171.2, 170.0, 166.5, 141.6, 130.7, 125.8, 119.1, 80.9, 66.7, 60.4, 51.9, 28.2, 14.1; HRMS (ESI): m/z [M+H]⁺ calcd for C₁₇H₂₅N₂O₆: 353.1707; found 353.1728.

tert-Butyl [(2*S*,3*R*)-3-hydroxy-1-oxo-1-(pyridin-3-ylamino)butan-2-yl]carbamate (ι-3l) Prepared from *N-tert*-butyl-*N*'-(3-pyridinyl)-*S*-phenylisothiourea (1r) (86 mg, 0.30 mmol, 1.0 equiv.), Boc-(L)-Thr-OH (**L**-2i) (79 mg, 0.36 mmol, 1.2 equiv.) and Fe(acac)₃ (5.3 mg, 5 mol%) according to the general procedure A with 72 hours reaction time. The residue was purified by column chromatography on silica gel with heptane/EtOAc = 1:1 as eluent. *tert*-Butyl [(2*S*,3*R*)-3-hydroxy-1-oxo-1-(pyridin-3-ylamino)butan-2-yl]carbamate was obtained in 77% yield (68 mg). White solid, m.p.: 127-129 °C, ¹H NMR (400 MHz, CDCl₃): δ (ppm) 9.08 (s, 1H), 8.60 (s, 1H), 8.29 (d, *J* = 4.0 Hz, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.21 (dd, *J* = 8.0, 4.8 Hz, 1H), 5.82 (d, *J* = 7.6 Hz, 1H), 4.47-4.45 (m, 2H), 4.28 (d, *J* = 6.0 Hz, 1H), 1.47 (s, 9H), 1.24 (d, *J* = 6.4 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃): δ (ppm) 170.3, 156.8, 145.0, 141.1, 134.5, 127.3, 123.7, 80.9, 66.7, 59.2, 28.3, 18.5; HRMS (ESI): m/z [M+H]⁺ calcd for C₁₄H₂₂N₃O₄: 296.1605; found 296.1608.

tert-Butyl (2*R*)-[3-(benzylsulfanyl)-1-oxo-1-(phenylamino)propan-2-yl]carbamate (ι-3m) Prepared from *N-tert*-butyl-*S*,*N*[′]-diphenylisothiourea (1d) (85 mg, 0.30 mmol, 1.0 equiv.), Boc-(L)-Cys(Bn)-OH (ι-2m) (112 mg, 0.36 mmol, 1.2 equiv.) and Fe(acac)₃ (10.6 mg, 10 mol%) according to the general procedure A with 72 hours reaction time. The residue was purified by column chromatography on silica gel with heptane/EtOAc = 1:1 as eluent. *tert*-Butyl (2*R*)-[3-(benzylsulfanyl)-1-oxo-1-(phenylamino)propan-2-yl]carbamate was obtained in 91% yield (105 mg). White solid, m.p.: 94-96 °C, ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.18 (br s, 1H), 7.53 (d, *J* = 7.9 Hz, 2H), 7.36-7.23 (m, 7H), 7.11 (t, *J* = 7.3 Hz, 1H), 5.33 (d, *J* = 6.4 Hz, 1H), 4.34 (d, *J* = 5.8 Hz, 1H), 3.83-3.69 (m, 2H), 2.99-2.80 (m, 2H), 1.1.47 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ (ppm) 168.8, 155.7, 137.9, 137.4, 129.0, 128.7, 127.3, 124.6, 120.0, 80.8, 54.6, 36.7, 33.4, 28.3; HRMS (ESI): m/z [M+H]⁺ calcd for C₂₁H₂₇N₂O₃S: 387.1737; found 387.1744.

tert-Butyl (2S)-[3-(benzylsulfanyl)-1-oxo-1-(phenylamino)propan-2-yl]carbamate (D-3m) Prepared from *N-tert*-butyl-*S*,*N*[']-diphenylisothiourea (1d) (85 mg, 0.30 mmol, 1.0 equiv.), Boc-(D)-Cys(Bn)-OH (D-2m) (112 mg, 0.36 mmol, 1.2 equiv.) and Fe(acac)₃ (10.6 mg, 10 mol%) according to the general procedure A with 48 hours reaction time. The residue was purified by an automated flash chromatography system using heptane/EtOAc (from 100% heptane to 25% EtOAc, 25 mL/min) as eluent. *tert*-Butyl (2S)-[3-(benzylsulfanyl)-1-oxo-1-(phenylamino) propan-2-yl]carbamate was obtained in 95% yield (111 mg). White solid, m.p.: 106-107 °C, ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.23 (br s, 1H), 7.49 (d, *J* = 7.8 Hz, 2H), 7.34-7.23 (m, 7H), 7.11 (t, *J* = 7.4 Hz, 1H), 5.37 (d, *J* = 7.1 Hz, 1H), 4.34 (d, *J* = 5.5 Hz, 1H), 3.81-3.73 (m, 2H), 2.98-2.81 (m, 2H), 1.47 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ (ppm) 168.8, 155.7, 137.9, 137.4, 129.0, 128.7, 127.3, 124.6, 120.0, 80.8, 54.6, 36.7, 33.5, 28.3; HRMS (ESI): $m/z [M+H]^+$ calcd for $C_{21}H_{27}N_2O_3S$: 387.1737; found 387.1743.

tert-Butyl (2*S*)-[4-(methylsulfanyl)-1-oxo-1-(phenylamino)butan-2-yl]carbamate (L-3n)^[28] Prepared from *N*-*t*-butyl-*S*,*N*[']-diphenylisothiourea (1d) (85 mg, 0.30 mmol, 1.0 equiv.) and Boc-(L)-Met-OH (L-2n) (90 mg, 0.36 mmol, 1.2 equiv.) according to the general procedure A with 72 hours reaction time. The residue was purified by column chromatography on silica gel with heptane/EtOAc = 1:1 as eluent. *tert*-Butyl (2*S*)-[4-(methylsulfanyl)-1-oxo-1-(phenylamino)butan-2-yl]carbamate was obtained in 89% yield (87 mg). White solid, m.p.: 103-105 °C, ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.99 (s, 1H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.23 (s, 2H), 7.07 (d, *J* = 7.2 Hz, 1H), 5.81 (s, 1H), 4.56 (s, 1H), 2.64 (t, *J* = 7.2 Hz, 2H), 2.22-2.15 (m, 1H), 2.10 (s, 3H), 2.08-2.03 (m, 1H), 1.44 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ (ppm) 170.6, 156.2, 137.7, 128.7, 124.2, 119.9, 80.3, 54.2, 31.8, 30.2, 28.2, 15.2; HRMS (ESI): m/z [M+H]⁺ calcd for C₁₆H₂₅N₂O₃S: 325.1586; found 325.1598.

(2R)-[4-(methylsulfanyl)-1-oxo-1-(phenylamino)butan-2-yl]carbamate *tert*-Butyl (D-3n) Prepared from N-tert-butyl-S,N'-diphenylisothiourea (1d) (85 mg, 0.30 mmol, 1.0 equiv.), and Boc-(D)-Met-OH (D-2n) (90 mg, 0.36 mmol, 1.2 equiv.) according to the general procedure A with 72 hours reaction time. The residue was purified by column chromatography on silica gel with heptane/EtOAc 1:1 = as eluent. tert-Butyl (2R)-[4-(methylsulfanyl)-1-oxo-1-(phenylamino)butan-2-yl]carbamate was obtained in 85% yield (83 mg). White solid, m.p.: 103-105 °C, ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.99 (s, 1H), 7.50 (d, J = 8.0 Hz, 2H), 7.23 (s, 2H), 7.07 (d, J = 7.2 Hz, 1H), 5.81 (s, 1H), 4.56 (s, 1H), 2.64 (t, J = 7.2 Hz, 2H), 2.22-2.15 (m, 1H), 2.10 (s, 3H), 2.08-2.03 (m, 1H), 1.44 (s, 9H); 13 C NMR (101 MHz, CDCl₃): δ (ppm) 170.5, 156.2, 137.6, 128.8, 124.2, 119.9, 80.4, 54.2, 31.7, 30.2, 28.3, 15.2; HRMS (ESI): m/z $[M+H]^{+}$ calcd for C₁₆H₂₅N₂O₃S: 325.1586; found 325.1590.

N-tert-butoxycarbonyl)-*N*-phenyl-L-phenylalaninamide (L-30)^[29] Prepared from *N-tert*-butyl-*S*,*N*[']-diphenylisothiourea (**1a**) (85 mg, 0.30 mmol, 1.0 equiv.) and Boc-(L)-Phe-OH (L-20) (95 mg, 0.36 mmol, 1.2 equiv.) according to the general procedure A. The residue was purified by column chromatography on silica gel with heptane/EtOAc = 1:1 as eluent. *N*₀202*tert*-butoxycarbonyl)-*N*-phenyl-L-phenylalaninamide was obtained in 94% yield (96 mg). White solid, m.p.: 138-139 °C (lit.^[29] 138-139 °C), ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.75 (s, 1H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.28-7.25 (m, 5H), 7.22 (t, *J* = 7.6 Hz, 2H), 7.07 (t, *J* = 7.2 Hz, 1H), 5.75 (d, *J* = 8.0 Hz, 1H), 4.73 (br s, 1H), 3.21 (dd, *J* = 13.6, 6.4 Hz, 1H), 3.10 (dd, *J* = 13.6, 8.4 Hz, 1H), 1.41 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ (ppm) 170.4, 156.1, 137.5, 136.7, 129.2, 128.7, 128.5, 126.7, 124.1, 120.0 80.2, 56.7, 38.8, 28.2; HRMS (ESI): m/z [M+Na]⁺ calcd for C₂₀H₂₄N₂O₃Na: 363.1685; found 363.1680.

N-tert-butoxycarbonyl)-*N*-phenyl-D-phenylalaninamide (D-30)^[29] Prepared from *N-tert*-butyl-*S*,*N*[']-diphenylisothiourea (**1a**) (85 mg, 0.30 mmol, 1.0 equiv.) and Boc-(D)-Phe-OH (D-20) (95 mg, 0.36 mmol, 1.2 equiv.) according to the general procedure A. The residue was purified by column chromatography on silica gel with heptane/EtOAc = 1:1 as eluent. $N_{\mathbb{P}}$ Detert-butoxycarbonyl)-*N*-phenyl-D-phenylalaninamide was obtained in 95% yield (97 mg). White solid, m.p.: 138-139 °C (lit.^[29] 138-139 °C), ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.63 (br s, 1H), 7.35 (d, *J* = 7.8 Hz, 2H), 7.22-7.16 (m, 7H), 7.02 (t, *J* = 7.1 Hz, 1H), 5.66 (d, *J* = 7.4 Hz, 1H), 4.67 (br s, 1H), 3.19-3.14 (m, 1H), 3.08-3.03 (m, 1H), 1.37 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ (ppm)

170.2, 156.0, 137.5, 136.8, 129.3.9, 128.7, 128.5, 126.8, 124.2, 120.1, 80.3, 56.7, 38.7, 28.2; HRMS (ESI): $m/z \ [M+Na]^+ \ calcd \ for \ C_{20}H_{24}N_2O_3Na: 363.1685; \ found \ 363.1681.$

N-tert-Butoxycarbonyl)-*N*-phenyl-L-tyrosinam (L-3p)^[30] Prepared from *N-tert*-butyl-*S*,*N'*-diphenylisothiourea (1a) (85 mg, 0.30 mmol, 1.0 equiv.), Boc-(L)-Tyr-OH (L-2p) (101 mg, 0.36 mmol, 1.2 equiv.) and Fe(acac)₃ (5.3 mg, 5 mol%) according to the general procedure A with 72 hours reaction time. The residue was purified by column chromatography on silica gel with heptane/EtOAc = 1:3 as eluent. *N-tert*-butoxycarbonyl)-*N*-phenyl-L-tyrosinam was obtained in 96% yield (103 mg). White solid, m.p.: 117-120 °C, ¹H NMR (400 MHz, CDCl₃): *δ* (ppm) 8.15 (br s, 1H), 7.38 (d, *J* = 7.6 Hz, 2H), 7.25 (t, *J* = 7.6 Hz, 2H), 7.06 (d, *J* = 8.0 Hz, 2H), 6.76 (br s, 1H), 6.74 (d, *J* = 8.4 Hz, 2H), 5.41 (br s, 1H), 4.46 (br s, 1H), 3.04 (t, *J* = 7.2 Hz, 2H), 1.43 (s, 9H); ¹³C-NMR (101 MHz, CDCl₃): *δ* (ppm) 170.0, 156.0, 155.1, 137.2, 130.4, 128.9, 128.1, 124.6, 120.2, 115.7, 60.5, 37.7, 28.3, 14.2; HRMS (ESI): m/z [M+H]⁺ calcd for C₂₀H₂₅N₂O₄: 357.1809; found 357.1816.

N-tert-Butoxycarbonyl)-*N*-phenyl-D-tyrosinam (D-3p)^[30] Prepared from *N-tert*-butyl-*S*,*N'*-diphenylisothiourea (1a) (85 mg, 0.30 mmol, 1.0 equiv.), Boc-(D)-Tyr-OH (D-2p) (101 mg, 0.36 mmol, 1.2 equiv.) and Fe(acac)₃ (5.3 mg, 5 mol%) according to the general procedure A with 72 hours reaction time. The residue was purified by column chromatography on silica gel with heptane/EtOAc = 1:3 as eluent. *N-tert*-butoxycarbonyl)-*N*-phenyl-D-tyrosinam was obtained in 94% yield (101 mg). White solid, m.p.: 117-120 °C, ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.45 (br s, 1H), 7.41 (br s, 1H), 7.35 (d, *J* = 7.6 Hz, 2H), 7.22-7.12 (m, 2H), 7.02 (d, *J* = 8.0 Hz, 3H), 6.72 (d, *J* = 8.2 Hz, 2H), 5.56 (br s, 1H), 4.51 (br s, 1H), 3.07-2.94 (m, 2H), 1.39 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ (ppm) 170.2, 156.0, 155.2, 137.2, 130.4 128.8, 124.6, 120.3, 115.7, 80.8, 59.1, 41.9, 37.8, 28.3; HRMS (ESI): m/z [M+H]⁺ calcd for C₂₀H₂₅N₂O₄: 357.1809; found 357.1816.

tert-Butyl-(1*S*)-(2-oxo-1-phenyl-2-(phenylamino)ethyl)carbamate (L-3q)^[31a] Prepared from *N*-*tert*-butyl-*S*,*N*[']-diphenylisothiourea (1d) (85 mg, 0.30 mmol, 1.0 equiv.), Boc-(L)-Phg-OH (L-2q) (90 mg, 0.36 mmol, 1.2 equiv.) according to the general procedure A. The residue was purified by column chromatography on silica gel with heptane/EtOAc = 1:1 as eluent. *tert*-Butyl-(1*S*)-(2-oxo-1-phenyl-2-(phenylamino)ethyl)carbamate was obtained in 90% yield (88 mg). White solid, m.p.: 116-119 °C, ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.68 (br s, 1H), 7.50 (d, *J* = 6.3 Hz, 2H), 7.41 (d, *J* = 7.8 Hz, 2H), 7.36-7.27 (m, 3H), 7.18 (t, *J* = 7.5 Hz, 2H), 7.02 (t, *J* = 7.0 Hz, 1H), 6.06 (d, *J* = 4.8 Hz, 1H), 5.57 (br s, 1H), 1.43 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ (ppm) 169.0, 155.7, 137.6, 137.4, 128.9, 128.7, 128.4, 127.3, 124.2, 119.9, 80.5, 59.2, 28.3; HRMS (ESI): m/z [M+H]⁺ calcd for C₁₉H₂₃N₂O₃: 327.1703; found 327.1712.

tert-Butyl-(1*R*)-(2-oxo-1-phenyl-2-(phenylamino)ethyl)carbamate (D-3q)^[31b] Prepared from *N*-*tert*-butyl-*S*,*N*'-diphenylisothiourea (1d) (85 mg, 0.30 mmol, 1.0 equiv.), Boc-(D)-Phg-OH (D-2q) (90 mg, 0.36 mmol, 1.2 equiv.) according to the general procedure A. The residue was purified by column chromatography on silica gel with heptane/EtOAc = 1:1 as eluent. *tert*-Butyl-(1*R*)-(2-oxo-1-phenyl-2-(phenylamino)ethyl)carbamate was obtained in 91% yield (89 mg). White solid, m.p.: 116-119 °C (lit.^[31b]: 120-121 °C), ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.64 (br s, 1H), 7.48 (d, *J* = 6.4 Hz, 2H), 7.39 (d, *J* = 7.9 Hz, 2H), 7.34-7.26 (m, 3H), 7.15 (t, *J* = 7.5 Hz, 2H), 6.99 (t, *J* = 7.1 Hz, 1H), 6.04 (d, *J* = 4.5 Hz, 1H), 5.54 (br s, 1H), 1.41 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ (ppm) 168.9, 155.7, 137.6, 137.4, 128.9, 128.7, 128.4, 127.3, 124.3, 119.9, 80.5, 59.1, 28.3; HRMS (ESI): m/z [M+H]⁺ calcd for C₁₉H₂₃N₂O₃: 327.1703; found 327.1712.

N-tert-Butoxycarbonyl)-*N*-phenyl-L-tryptophanamide (L-3r)^[32] Prepared from *N-tert*-butyl-*S*,*N*'-diphenylisothiourea (1a) (85 mg, 0.30 mmol, 1.0 equiv.) and Boc-(L)-Trp-OH (L-2r) (109 mg, 0.36 mmol, 1.2 equiv.) according to the general procedure A with 72 hours reaction time. The residue was purified by column chromatography on silica gel with heptane/EtOAc = 1:1 to 1:2 as eluent. *N-tert*-Butoxycarbonyl)-*N*-phenyl-L-tryptophanamide was obtained in 92% yield (105 mg). White solid, m.p.: 151-153 °C (lit.^[32]: 48-49°C), ¹H NMR (400 MHz, DMSO-d₆): δ (ppm) 10.81 (s, 1H), 10.01 (s, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.62 (d, *J* = 7.6 Hz, 2H), 7.32 (dd, *J* = 14.8, 7.6 Hz, 3H), 7.19 (s, 1H), 7.04 (dd, *J* = 14.4, 7.6 Hz, 2H), 6.99 (t, *J* = 7.6 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 4.42 (d, *J* = 5.6 Hz, 1H), 3.16 (dd, *J* = 14.4, 5.2 Hz, 1H), 3.03 (dd, *J* = 14.4, 5.2 Hz, 1H), 1.35 (s, 9H); ¹³C NMR (101 MHz, DMSO-d₆): δ (ppm) 171.1, 155.3, 139.0, 136.0, 128.6, 127.3, 123.8, 123.3, 120.9, 119.4, 118.6, 118.2, 111.3, 109.9, 78.1, 55.8, 28.2, 27.8; HRMS (ESI): m/z [M+H]⁺ calcd for C₂₂H₂₆N₃O₃: 380.1974; found 380.1982.

N-tert-Butoxycarbonyl)-*N*-phenyl-D-tryptophanamide (D-3r)^[33] Prepared from *N-tert*-butyl-*S*,*N*'-diphenylisothiourea (**1a**) (85 mg, 0.30 mmol, 1.0 equiv.) and Boc-(D)-Trp-OH (D-2r) (109 mg, 0.36 mmol, 1.2 equiv.) according to the general procedure A with 72 hours reaction time. The residue was purified by column chromatography on silica gel with heptane/EtOAc = 1:1 to 1:2 as eluent. *N-tert*-Butoxycarbonyl)-*N*-phenyl-D-tryptophanamide was obtained in 93% yield (106 mg). White solid, m.p.: 151-153 °C, ¹H NMR (400 MHz, DMSO-d₆): *δ* (ppm) 10.80 (s, 1H), 10.01 (s, 1H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.61 (d, *J* = 7.6 Hz, 2H), 7.32 (dd, *J* = 15.6, 8.0 Hz, 3H), 7.18 (s, 1H), 7.06 (dd, *J* = 14.4, 7.2 Hz, 2H), 6.98 (t, *J* = 7.6 Hz, 1H), 6.90 (d, *J* = 7.6 Hz, 1H), 4.42 (d, *J* = 5.2 Hz, 1H), 3.16 (dd, *J* = 14.4, 4.4 Hz, 1H), 3.03 (dd, *J* = 14.4, 4.4 Hz, 1H), 1.34 (s, 9H); ¹³C NMR (101 MHz, DMSO-d₆): *δ* (ppm) 171.2, 155.4, 139.0, 136.1, 128.7, 127.3, 123.9, 123.3, 120.9, 119.4, 118.7, 118.2, 111.3, 110.0, 78.1, 55.8, 28.2, 27.8; HRMS (ESI): m/z [M+H]⁺ calcd for C₂₂H₂6N₃O₃: 380.1974; found 380.1980.

N-tert-Butoxycarbonyl)-*N*-phenyl-L-histidinamide (L-3s)^[34] Prepared from *N-t*-butyl-*S*,*N*[′]-diphenylisothiourea (1d) (85 mg, 0.30 mmol, 1.0 equiv.), Boc-(L)-His-OH (L-2s) (92 mg, 0.36 mmol, 1.2 equiv.) and Fe(acac)₃ (10.6 mg, 10 mol%) according to the general procedure A with 72 hours reaction time. The residue was purified by column chromatography on silica gel with EtOAc as eluent. *N-tert*-Butoxycarbonyl)-*N*-phenyl-L-histidinamide was obtained in 88% yield (88 mg). White solid, m.p.: 118-120 °C, ¹H NMR (400 MHz, CDCl₃): δ (ppm) 9.54 (br s, 1H), 9.00 (br s, 1H), 7.52 (s, 1H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.26 (t, *J* = 8.0 Hz, 2H), 7.07 (t, *J* = 7.6 Hz, 1H), 6.77 (s, 1H), 6.15 (br s, 1H), 4.61 (br s, 1H), 3.10 (d, *J* = 5.2 Hz, 2H), 1.42 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ (ppm) 171.2, 170.5, 156.0, 137.7, 134.8, 128.8, 124.4, 120.2, 80.4, 60.4, 29.8, 29.2, 28.3; HRMS (ESI): m/z [M+H]⁺ calcd for C₁₇H₂₃N₄O₃: 331.1765; found 331.1767.

N-tert-Butoxycarbonyl)-*N*-phenyl-D-histidinamide (D-3s) Prepared from *N-tert*-butyl-*S*,*N*[']-diphenylisothiourea (**1a**) (85 mg, 0.30 mmol, 1.0 equiv.), Boc-(D)-His-OH (D-2s) (92 mg, 0.36 mmol, 1.2 equiv.) and Fe(acac)₃ (10.6 mg, 10 mol%) according to the general procedure A with 72 hours reaction time. The residue was purified by column chromatography on silica gel with EtOAc as eluent. *N-tert*-Butoxycarbonyl)-*N*-phenyl-D-histidinamide was obtained in 88% yield (87.6 mg). White solid, m.p.: 118-120 °C, ¹H NMR (400 MHz, CDCl₃): δ (ppm) 10.44 (br s, 1H), 9.46 (br s, 1H), 7.59 (s, 1H), 7.48 (d, *J* = 7.6 Hz, 2H), 7.26 (t, *J* = 8.0 Hz, 2H), 7.07 (t, *J* = 7.6 Hz, 1H), 6.78 (s, 1H), 6.08 (br s, 1H), 4.60 (br s, 1H), 3.10 (d, *J* = 6.0 Hz, 2H), 1.40 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ (ppm) 176.5, 170.4, 156.0, 137.7, 134.6, 128.9, 124.4, 120.2, 80.4, 53.8, 29.7, 29.2, 28.2; HRMS (ESI): m/z [M+H]⁺ calcd for C₁₇H₂₃N₄O₃: 331.1765; found 331.1767.

Benzyl [2-methyl-1-oxo-1-(phenylamino)propan-2-yl]carbamate (3t)^[35] Prepared from *N-tert*-butyl-*S*,*N*'-diphenylisothiourea (**1a**) (85 mg, 0.30 mmol, 1.0 equiv.) and Z-2-methylalanine (**2t**) (85 mg, 0.36 mmol, 1.2 equiv.) according to the general procedure A. The residue was purified by column chromatography on silica gel with heptane/EtOAc = 1:2 as eluent. Benzyl [2-methyl-1-oxo-1-(phenylamino)propan-2-yl]carbamate was obtained in 91% yield (85 mg). White solid, m.p.: 162-164 °C (lit. ^[35]: 142-144 °C), ¹H-NMR (400 MHz, DMSO-d₆): δ (ppm) 9.41 (s, 1H), 7.60 (d, *J* = 7.6 Hz, 2H), 7.34-7.39 (m, 4H), 7.29 (t, *J* = 7.6 Hz, 3H), 7.03 (t, *J* = 7.2 Hz, 1H), 5.02 (s, 2H), 1.44 (s, 6H); ¹³C NMR (101 MHz, DMSO-d₆): δ (ppm) 172.9, 154.8, 139.2, 137.0, 128.3, 128.2, 127.6, 127.5, 123.0, 120.0, 65.2, 56.6, 25.0; HRMS (ESI): m/z [M+H]⁺ calcd for C₁₈H₂₁N₂O₃: 313.1547; found 313.1553.

tert-Butyl [3-oxo-3-(phenylamino)propyl]carbamate (3u)^[35] Prepared from *N*-*t*-butyl-*S*,*N*[']-diphenylisothiourea (1a) (85 mg, 0.30 mmol, 1.0 equiv.) and Boc-β-Ala-OH (2u) (68 mg, 0.36 mmol, 1.2 equiv.) according to the general procedure A. The residue was purified by column chromatography on silica gel with heptane/EtOAc = 1:1 as eluent. *tert*-Butyl [3-oxo-3-(phenylamino)propyl] carbamate was obtained in 92% yield (73 mg). White solid, m.p.: 164-166 °C (lit. ^[35]: 162-164°C), ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.97 (br s, 1H), 7.55 (d, *J* = 7.2 Hz, 2H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.12 (t, *J* = 7.2 Hz, 1H), 5.24 (br s, 1H), 3.50 (d, *J* = 4.4 Hz, 2H), 2.61 (s, 2H), 1.45 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ (ppm) 169.7, 156.6, 137.9, 128.9, 124.3, 119.9, 79.6, 37.6, 36.6, 28.4; HRMS (ESI): m/z [M+H]⁺ calcd for C₁₄H₂₁N₂O₃: 265.1552; found 265.1546.

tert-Butyl 4-(phenylcarbamoyl)piperidine-1-carboxylate (3v)^[36] Prepared from *N-tert*-butyl-*S*,*N'*-diphenylisothiourea (1a) (85 mg, 0.30 mmol, 1.0 equiv.) and Boc-Inp-OH (2v) (83 mg, 0.36 mmol, 1.2 equiv.) according to the general procedure A. The residue was purified by column chromatography on silica gel with heptane/EtOAc = 1:1 as eluent. *tert*-Butyl 4-(phenylcarbamoyl)piperidine-1-carboxylate was obtained in 99% yield (90 mg). White solid, m.p.: 156-158 °C (lit. ^[36]: 155-158 °C), ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.33 (d, *J* = 6.4 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 2H), 7.27 (t, *J* = 7.6 Hz, 2H), 7.07 (t, *J* = 7.6 Hz, 1H), 4.13 (d, *J* = 11.6 Hz, 2H), 2.70 (m, 2H), 2.36-2.43 (m, 1H), 1.82 (d, *J* = 2.4 Hz, 1H), 1.80 (s, 1H), 1.69-1.76 (dt, *J* = 12.0, 4.0 Hz, 2H), 1.46 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ (ppm) 173.2, 154.6, 137.9, 128.7, 124.1, 120.1, 79.7, 43.7, 42.9, 28.4, 28.3; HRMS (ESI): m/z [M+H]⁺ calcd for C₁₇H₂₅N₂O₃: 305.1865; found: 305.1864.

N-tert-Butoxycarbonyl)glycylglycyl-N-phenylglycinamide Prepared from (3aa) *N-tert*-butyl-*S*,*N*[']-diphenylisothiourea (**1a**) (85 mg, 0.30 mmol, 1.0 equiv.) and Boc-Gly-Gly-OH (2w) (104 mg, 0.36 mmol, 1.2 equiv.) according to the general procedure A. The residue purified by recrystalization with MeOH. was N-tert-Butoxycarbonyl)glycylglycyl-N-phenylglycinamide was obtained in 83% yield (91 mg). White solid, m.p.: 193-195 °C, ¹H NMR (400 MHz, DMSO-d₆): δ (ppm) 9.78 (s, 1H), 8.16-8.23 (m, 2H), 7.61 (d, J = 7.6 Hz, 2H), 7.30 (t, J = 8.0 Hz, 2H), 6.99-7.07 (m, 2H), 3.89 (d, J = 6.0 Hz, 2H), 3.77 (d, J = 5.6 Hz, 2H), 3.61 (d, J = 6.0 Hz, 2H), 1.38 (s, 9H); ¹³C NMR (101 MHz, DMSO-d₆): δ (ppm) 170.1, 169.2, 167.5, 155.8, 138.7, 128.6, 123.3, 119.2, 78.1, 42.2, 40.1, 39.9, 28.1; HRMS (ESI): $m/z [M+H]^{+}$ calcd for $C_{17}H_{25}N_4O_5$: 365.1825;

 N_{\square} - \square *tert*-Butoxycarbonyl)-*N*-phenyl-D-histidinamide (3ab) Prepared from *N*-*t*-butyl-*N*'-(4-(*t*-butyl)phenyl)-*S*-phenylisothiourea (1y) (102 mg, 0.30 mmol, 1.0 equiv.), Boc-Gly-Gly-Gly-OH (2w) (104 mg, 0.36 mmol, 1.2 equiv.) and Fe(acac)₃ (2.65 mg, 2.5 mol%) according to the general procedure A. The residue was purified by recrystalization with MeOH.

N-tert-Butoxycarbonyl)-*N*-phenyl-D-histidinamide was obtained in 87% yield (110 mg). White solid, m.p.: 202-204 °C, ¹H NMR (400 MHz, DMSO-d₆): δ (ppm) 9.83 (s, 1H), 8.31 (s, 1H), 8.26 (s, 1H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.01 (s, 1H), 3.88 (d, *J* = 5.2 Hz, 2H), 3.76 (d, *J* = 4.4 Hz, 2H), 3.63 (d, *J* = 4.8 Hz, 2H), 1.37 (s, 9H), 1.25 (s, 9H); ¹³C NMR (101 MHz, DMSO-d₆): δ (ppm) 170.2, 169.2, 167.3, 155.8, 145.5, 136.2, 125.1, 119.0, 78.1, 43.4, 42.6, 42.3, 33.9, 31.1, 28.1; HRMS (ESI): m/z [M+H]⁺ calcd for C₂₁H₃₃N₄O₅: 421.2445; found: 421.2449.

N-tert-Butoxycarbonyl)glycylglycyl-N-(4-bromophenyl)glycinamide (3ac) Prepared from N-tert-butyl-N'-(4-bromophenyl)-S-phenylisothiourea (1m) (109 mg, 0.30 mmol, 1.0 equiv.) and Boc-Gly-Gly-Gly-OH (2w) (104 mg, 0.36 mmol, 1.2 equiv.) according to the general procedure A. The residue was purified by recrystalization with MeOH. *N-tert*-Butoxycarbonyl)glycylglycyl-*N*-(4-bromophenyl)glycinamide was obtained in 79% yield (105 mg). White solid, m.p.: 239-241 °C, ¹H NMR (400 MHz, DMSO-d₆): δ (ppm) 10.14 (s, 1H), 8.33 (s, 1H), 8.26 (s, 1H), 7.65 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H), 7.01 (s, 1H), 3.90 (d, J = 5.2 Hz, 2H), 3.77 (d, J = 5.2 Hz, 2H), 3.63 (d, J = 5.2 Hz, 2H), 1.36 (s, 9H); ¹³C NMR (101 MHz, DMSO-d₆): δ (ppm) 170.2, 169.3, 167.8, 155.8, 138.2, 131.4, 121.4, 114.8, 78.1, 43.3, 42.7, 42.2, 28.1; HRMS (ESI): m/z $[M+H]^+$ calcd for C₁₇H₂₄BrN₄O₅: 443.0925; found: 443.0924.

tert-Butyl

2-((3-methyl-1-oxo-1-(2-(phenylcarbamoyl)pyrrolidin-1-yl)butan-2-yl)carbamoyl)pyrrolidine-1-c arboxylate (3ad) Prepared from N-tert-butyl-S,N'-diphenylisothiourea (1a) (85 mg, 0.30 mmol, 1.0 equiv.), N-Boc-L-pro-L-val-L-pro-OH (2x) (148 mg, 0.36 mmol, 1.2 equiv.) according to the general procedure A. The residue was purified by column chromatography on silica gel with heptane/EtOAc = 1:3 as eluent. *tert*-Butyl 2-((3-methyl-1-oxo-1-(2-(phenylcarbamoyl)pyrrolidin-1-yl)butan-2-yl)carbamoyl)pyrrolidine-1-car boxylate was obtained in 69% yield (101 mg). White solid, m.p.: 80-82 °C, ¹H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.47 (br s , 1H), 7.66 (br, s, 1H), 7.47 (d, J = 8.0 Hz, 2H), 7.25 (t, J = 6.8 Hz, 2H), 7.03 (t, J = 6.8 Hz, 1H), 4.78 (d, J = 6.4 Hz, 1H), 4.55 (s, 1H), 4.37 (s, 1H), 3.81 (q, J = 8.0 Hz, 1H), 3.63 (s, 1H), 3.46 (s, 1H), 3.37 (s, 1H), 2.49 (s, 1H), 2.29 (s, 1H), 2.17 (s, br, 2H), 2.03-2.08 (m, 2H), 1.90 (s, br, 3H), 1.47 (s, 9H), 0.93 (d, J = 6.4 Hz, 3H), 0.89 (d, J = 6.8 Hz, 3H); ¹³CNMR (101 MHz, CDCl₃): δ (ppm) 172.4, 172.2, 169.0, 138.2, 128.7, 123.8, 119.6, 80.3, 60.6, 59.6, 55.7, 47.7, 46.9, 31.3, 28.3, 26.4, 25.1, 19.2, 17.6; HRMS (ESI): m/z [M+H]⁺ calcd for C₂₆H₃₉N₄O₅: 487.2915; found 487.2919.

N-(tert-butoxycarbonyl)-L-tryptophyl-L-glutaminyl-N-phenyl-L-alaninamide (3ae) Prepared from N-tert-butyl-S,N'-diphenylisothiourea (1a) (42.4 mg, 0.15 mmol, 1.0 equiv.), N-Boc-L-Trp-L-Gln-L-Ala-OH (2y) (90 mg, 0.18 mmol, 1.2 equiv.) according to the general procedure A with 48 hours reaction time. The residue was purified twice by an automated flash chromatography system using a C_{18} -silica cartridge and H_2O/CH_3CN (from 100% H_2O to 40% CH₃CN 40 minutes, 25 mL/min) in as eluent. N-(tert-butoxycarbonyl)-L-tryptophyl-L-glutaminyl-N-phenyl-L-alaninamide was obtained in 77% yield (66 mg). White solid, m.p.: 206-207 °C, ¹H NMR (400 MHz, DMSO-d₆, 80 °C): δ (ppm) 10.57 (br s, 1H), 9.60 (br s, 1H), 8.21 (s, 1H), 7.88 (t, J = 7.7 Hz, 2H), 7.61-7.56 (m, 2H), 7.32-7.27 (m, 3H), 7.13 (s, 1H), 7.13-6.99 (br s, 2H), 6.97 (t, J = 7.7 Hz, 2H), 6.43 (br s, 1H), 4.46-4.26 (m, 4H), 2.18-2.15 (t, J = 7.5 Hz, 1H), 2.04-1.83 (m, 1H), 3.37 (s, 1H), 2.49 (s, 1H), 2.29 (s, 1H), 2.17 (s, br, 2H), 2.03-2.08 (m, 2H), 1.35-1.33 (m, 12H); 13 C NMR (101 MHz, DMSO-d₆, 80°C): δ (ppm) 173.5, 171.7, 170.5, 170.5, 154.8, 138.5, 135.9, 128.1, 123.0, 120.4, 119.3, 117.9, 117.8, 110.8, 109.9, 78.7, 78.0, 55.3, 52.2, 48.8, 31.0, 27.7, 27.5, 17.5; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{30}H_{39}N_6O_6$: 579.2926; found 579.2925.

tert-Butyl-(2*R*)-(1-((2,6-dimethylphenyl)amino)-1-oxopropan-2-yl)carbamate (D-3w) <u>Method 1:</u> Prepared from *N-tert*-butyl-*N*'-(2,6-dimethylphenyl)-*S*-phenylisothiourea (1v) (94 mg, 0.30 mmol, 1.0 equiv.) and Boc-(D)-Ala-OH (D-2c) (68 mg, 0.36 mmol, 1.2 equiv.) according to the general procedure A in 2-butanol at 98 °C. The residue was purified by column chromatography on silica gel with heptane/EtOAc = 1:1 as eluent. *tert*-Butyl-(2*R*)-(1-((2,6-dimethylphenyl)amino)-1-oxopropan-2-yl)carbamate was obtained in 93% yield (81 mg).

<u>Method 2:</u> Prepared from *N-tert*-butyl-*N*'-(2,6-dimethylphenyl)-*S*-phenylisothiourea (**1v**) (94 mg, 0.3 mmol, 1.0 equiv.), Boc-(D)-Ala-OH ((D)-**2c**) (68 mg, 0.36 mmol, 1.2 equiv.) and Fe(acac)₃ (11 mg, 10 mol%) according to the general procedure A in isopropanol at 83 °C for 72 hours. The residue was purified by column chromatography on silica gel with heptane/EtOAc = 1:1 as eluent. *tert*-Butyl-(2*R*)-(1-((2,6-dimethylphenyl)amino)-1-oxopropan-2-yl)carbamate was obtained in 95% yield (83 mg). Yellow solid, m.p.: 129-131 °C, ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.88 (br s, 1H), 6.98-7.04 (m, 3H), 5.38 (d, *J* = 6.4 Hz, 1H), 4.38 (br s, 1H), 2.14 (s, 6H), 1.43-1.45 (m, 12H); ¹³C NMR (101 MHz, CDCl₃): δ (ppm) 171.5, 155.7, 135.3, 133.4, 127.9, 127.0, 79.9, 50.2, 28.2, 18.3, 18.0; HRMS (ESI): m/z [M+H]⁺ calcd for C₁₆H₂₅N₂O₃: 292.1787; found 293.1876.

tert-Butyl-(2*S*)-(1-((2,6-dimethylphenyl)amino)-1-oxopropan-2-yl)carbamate (L-3w) Prepared from *N*-*tert*-butyl-*N*'-(2,6-dimethylphenyl)-*S*-phenylisothiourea (1v) (94 mg, 0.30 mmol, 1.0 equiv.) and Boc-(L)-Ala-OH (L-2c) (68 mg, 0.36 mmol, 1.2 equiv.) according to the general procedure A in 2-butanol at 98 °C. The residue was purified by column chromatography on silica gel with heptane/EtOAc = 1:1 as eluent. *tert*-Butyl-(2*S*)-(1-((2,6-dimethylphenyl)amino)-1-oxopropan-2-yl)carbamate was obtained in 91% yield (80 mg). Yellow solid, m.p.: 129-131 °C, ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.88 (br s, 1H), 6.98-7.04 (m, 3H), 5.38 (d, *J* = 6.4 Hz, 1H), 4.38 (br s, 1H), 2.14 (s, 6H), 1.43-1.45 (m, 12H); ¹³C NMR (101 MHz, CDCl₃): δ (ppm) 171.5, 155.7, 135.3, 133.4, 127.9, 127.0, 79.9, 50.2, 28.2, 18.3, 18.0; HRMS (ESI): m/z [M+H]⁺ calcd for C₁₆H₂₅N₂O₃: 292.1787; found 293.1876.

N-(2,6-dimethylphenyl)-D-alaninamide (D-3x)^[37] A 50 mL round-bottom flask was charged with tert-Butyl-(2R)-(1-((2,6-dimethylphenyl)amino)-1-oxopropan-2-yl)carbamate (p-3w) (292 mg, 1.0 mmol, 1.0 equiv.), and EtOAc (5 mL). Then hydrochloric acid in dioxane (4 M, 2 mL) was added dropwise to the mixture. The reaction mixture was stirred at 25 °C for 24 hours. The solvent was removed under reduced pressure, and EtOAc (30 mL) was added. The organic phase was washed three times with NaOH (10% in H_2O , 20 mL) and dried over anhydrous MgSO₄ and subsequently concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with heptane/EtOAc = 1:3 as eluent. N-(2,6-Dimethylphenyl)-D-alaninamide was obtained in 89% yield (171 mg). White solid, m.p.: 246-266 °C (lit.^[37]: 242-246 °C), ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.88 (br s, 1H), 6.96-6.99 (m, 3H), 3.74 (q, J = 6.4 Hz, 1H), 3.20 (br s, 2H), 2.14 (s, 6H), 1.41 (d, J = 6.8 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃): δ (ppm) 173.6, 134.9, 133.7, 127.9, 126.8, 50.8, 21.4, 18.2; HRMS (ESI): m/z [M+H]⁺ calcd for C₁₁H₁₇N₂O: 193.1263; found 193.1339.

N-(*tert*-Butylcarbamoyl)-*N*-phenylbenzamide (7) A 100 mL round-bottom flask was charged with *N*-*tert*-butyl-*N*'-phenylurea (4) (576 mg, 3.0 mmol, 1.0 equiv.) and pyridine (3.0 mL). The reaction mixture was cooled to 0 °C and stirred for 30 minutes. Then, benzoyl chloride (504 mg,

3.6 mmol, 1.2 equiv.) was dropwise added to the above reaction mixture under 0 °C. The mixture was stirred for 1 h at 0 °C. The mixture was extracted with EtOAc (30 mL) and washed with HCl (1 M, 20 mL) for three times. The organic phase was dried with anhydrous MgSO₄. The filtrate was concentrated and dried under vacuum. The residue was purified by column chromatography on silica gel heptane/EtOAc = 1:1 as eluent. *N*-(*tert*-Butylcarbamoyl)-*N*-phenylbenzamide was obtained in 74% yield (657 mg).

White solid, m.p.: 82-84 °C, ¹H NMR (400 MHz, CDCl₃): δ (ppm) 9.10 (s, 1H), 7.10-7.24 (m, 10H), 1.45 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ (ppm) 173.7, 152.8, 139.0, 136.3, 130.1, 130.0, 128.5, 128.4, 127.8, 127.7, 51.4, 28.8; HRMS (ESI): m/z [M+H]⁺ calcd for C₁₈H₂₁N₂O₂: 297.1598; found 297.1603.

N-Pentyl-N'-(2,6-dimethylphenyl)-S-phenylisothiourea (9) Prepared from 2,6-dimethylaniline (206 mg, 1.7 mmol, 1.7 equiv.), S-phenyl benzenethiosulfonate (250 mg, 1.0 mmol, 1.0 equiv.) and 1-isocyanopentane (242.5 mg, 2.5 mmol, 2.5 equiv.) according to our previous reported procedure.^[17] The residue was purified by column chromatography on silica with Heptane/EtOAc 100:1 10:1 gel = to as eluent. N-Pentyl-N'-(2,6-dimethylphenyl)-S-phenylisothiourea was obtained in 99% yield (323 mg). White solid, m.p.: 72-74 °C, ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.56 (d, J = 7.2 Hz, 2H), 7.40-7.45 (m, 3H), 7.07 (d, J = 7.2 Hz, 2H), 6.93 (t, J = 7.2 Hz, 1H), 4.02 (s, 1H), 3.40 (q, J = 6.4 Hz, 2H), 2.26 (s, 6H), 1.54 (t, J = 7.2 Hz, 2H), 1.30-1.34 (m, 2H), 1.21-1.28 (m, 2H), 0.91 (t, J = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 149.5, 147.1, 135.9, 129.7, 129.6, 129.59, 127.6, 122.7, 43.0, 28.9, 28.8, 22.3, 18.3, 13.9 (1C missed). HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{20}H_{27}N_2S$: 327.1889; found: 327.1887.

N-(2,6-Dimethylphenyl)benzamide (10)^[38]

<u>Method 1:</u> Prepared from N-2,6-dimethylphenyl-N'-pentyl-S-phenylisothiourea (**9**) (85 mg, 0.30 mmol, 1.0 equiv.), and benzoic acid (**5a**) (44 mg, 0.36 mmol, 1.2 equiv.) in *o*-xylene at 130 °C for 24 hours according to the general procedure A. The residue was purified by column chromatography on silica gel with Heptane/EtOAc = 3:1 as eluent. N-(2,6-dimethylphenyl)benzamide (**10**) was obtained in 91% yield (61 mg).

<u>Method</u> 2: Prepared from *N*-(2,4,4-trimethylpent-2-yl)-*N*'-(2,6-dimethylphenyl)-*S*-phenyl isothiourea (**11**) (110 mg, 0.3 mmol, 1.0 equiv.) and benzoic acid (**5a**) (44 mg, 0.36 mmol, 1.2 equiv.) in *o*-xylene at 130 °C for 24 hours according to the general procedure A. The residue was purified by column chromatography on silica gel with Heptane/EtOAc = 3:1 as eluent. *N*-(2,6-dimethylphenyl)benzamide (**10**) was obtained in 93% yield (63 mg). Yellow solid, m.p.: 154-156 °C (lit.^[38]: 157-158 °C), ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.91 (d, *J* = 7.2 Hz, 2H), 7.77 (s, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.10-7.16 (m, 3H), 2.28 (s, 6H); ¹³C NMR (101 MHz, CDCl₃): δ (ppm) 165.9, 135.6, 134.4, 134.0, 131.6, 128.6, 128.1, 127.3, 127.2, 18.3; HRMS (ESI): m/z [M+H]⁺ calcd for C₁₅H₁₅NO: 226.1226; found 226.1224.

N-(2,4,4-Trimethylpentan-2-yl)-*N*'-(2,6-dimethylphenyl)-*S*-phenylisothiourea (11) Prepared from 2,6-dimethylaniline (206 mg, 1.7 mmol, 1.7 equiv.), *S*-phenyl benzenethiosulfonate (250 mg, 1.0 mmol, 1.0 equiv.) and 2-isocyano-2,4,4-trimethylpentane (348 mg, 2.5 mmol, 2.5 equiv.) according to our previous reported procedure.^[17] The residue was purified by column chromatography on silica gel with Heptane/EtOAc = 100:1 to 10:1 as eluent. *N*-(2,4,4-Trimethylpentan-2-yl)-*N*'-(2,6-dimethylphenyl)-*S*-phenylisothiourea was obtained in 65% yield (239 mg). Yellow solid, m.p.: 65-68 °C, ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.46 (d, *J* = 7.2 Hz,

2H), 7.34 (br t, 3H), 7.01 (d, J = 7.6 Hz, 2H), 6.88 (d, J = 7.2 Hz, 1H), 3.84 (s, 1H), 2.25 (s, 6H), 1.79 (s, 2H), 1.38 (s, 6H), 0.89 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ (ppm) 147.6, 146.0, 136.1, 130.1, 129.6, 129.5, 129.2, 127.6, 122.4, 53.7, 50.7, 31.3, 30.9, 28.8, 18.6; HRMS (ESI): m/z [M+H]⁺ calcd for C₂₃H₃₃N₂S: 369.2359; found: 369.2361.

N-(*tert*-Butyl)-*N*'-(*ethyl*)-*S*-phenylisothiourea (12) To a suspension of *N*-*tert*-butyl-*N*-ethyl carbodiimide (129 mg, 1.0 mmol, 1.0 equiv.) in DCM (10 mL, dry) was added benzenethiol (121 mg, 1.1 mmol, 1.1 equiv.) at room temperature under Ar atmosphere. The reaction mixture was stirred for 12 hours at room temperature. The mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with Heptane/EtOAc = 10:1 as eluent. *N*-(*tert*-Butyl)-*N*'-ethyl -*S*-phenylisothiourea was obtained in 90% yield (212 mg). Colorless oil, ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.43 (d, *J* = 6.8 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.28 (d, *J* = 6.8 Hz,1H), 3.68 (s, 1H), 3.41 (q, *J* = 7.2 Hz, 2H), 1.24 (s, 9H), 1.15 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 143.5, 133.1, 132.3, 129.3, 127.9, 52.4, 45.9, 28.6, 16.8; HRMS (ESI): m/z [M+H]⁺ calcd for C₁₃H₂₁N₂S: 237.1420; found: 237.1422.

N-(*tert*-Butyl)benzamide (13)^[39]

<u>Method 1:</u> Prepared from *N-tert*-butyl-*N*'-ethyl-*S*-phenylisothiourea (**12**) (85 mg, 0.30 mmol, 1.0 equiv.) and benzoic acid (**5a**) (44 mg, 0.36 mmol, 1.2 equiv.) in *o*-xylene at 130 °C for 24 hours according to the general procedure A. The residue was purified by column chromatography on silica gel with Heptane/EtOAc = 3:1 to 1:1 as eluent. *N-(tert*-Butyl)benzamide (**13**) was obtained in 14% yield (7 mg) together with *N*-ethylbenzamide (**14**).

<u>Method 2:</u> Prepared from *N-tert*-butyl-*N*'-ethylglycinyl-*S*-phenylisothiourea (**15**) (88 mg, 0.30 mmol, 1.0 equiv.) and benzoic acid (**5a**) (43.9 mg, 0.36 mmol, 1.2 equiv.) in *o*-xylene at 130 $^{\circ}$ C according to the general procedure A. The residue was purified by column chromatography on silica gel with Heptane/EtOAc = 3:1 to 1:1 as eluent. *N-(tert*-butyl)benzamide (**13**) was obtained in 33% yield (17.5 mg) together with *N*-ethyl benzoylglycinate (**16**).

<u>Method 3:</u> Prepared from *N*-tert-butyl-*N'*-2,2,2-trifluoroethyl-*S*-phenylisothiourea (**17**) (87 mg, 0.30 mmol, 1.0 equiv.) and benzoic acid (**5a**) (44 mg, 0.36 mmol, 1.2 equiv.) in *o*-xylene at 130 °C for 24 hours according to the general procedure A. The residue was purified by column chromatography on silica gel with Heptane/EtOAc = 3:1 to 1:1 as eluent. *N*-(*tert*-Butyl)benzamide (**13**) was obtained in 82% yield (44 mg). White solid, m.p.: 136-138 °C (lit. ^[39]: 136 °C), ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.72 (d, *J* = 7.2 Hz, 2H), 7.45 (t, *J* = 7.2 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 2H), 6.03 (br s, 1H), 1.47 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ (ppm) 166.8, 135.9, 130.9, 128.3, 126.6, 51.5, 28.8; HRMS (ESI): m/z [M+H]⁺ calcd for C₁₁H₁₆NO: 178.1232; found: 178.1235.

N-Ethylbenzamide (14)^[40]

This compound was obtained in 84% yield (38 mg) together with *N*-(*tert*-butyl)benzamide (**13**) when *N*-*tert*-butyl-*N*'-ethyl-*S*-phenylisothiourea (**12**) was used as reactant.

White solid, m.p.: 64-66 °C (lit. ^[40]: 60 °C), ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.78 (d, J = 7.2 Hz, 2H), 7.47 (t, J = 7.2 Hz, 1H), 7.40 (t, J = 7.6 Hz, 2H), 6.45 (br s, 1H), 3.45-3.52 (m, 2H), 1.24 (t, J = 7.2 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃): δ (ppm) 167.5, 134.8, 131.2, 128.4, 126.8, 34.8, 14.8; HRMS (ESI): m/z [M+H]⁺ calcd for C₉H₁₂NO: 150.0913; found 150.0915.

N-(*tert*-Butyl)-*N*'-(ethyl glycinyl)-*S*-phenylisothiourea (15) To a suspension of ethyl 2-azidoacetate (129 mg, 1.0 mmol, 1.0 equiv.) in DCM (10 mL, dry) was added triphenylphosphine (262 mg, 1.0 mmol, 1.0 equiv.) at room temperature under Ar atmosphere. The reaction mixture was stirred for 2 hours at room temperature. Then *tert*-butyl isocyanate (99

mg, 1.0 mmol, 1.0 equiv.) was added to the above mixture at 0 °C. Subsequently, benzenethiol (121 mg, 1.1 mmol, 1.0 equiv.) was added. The reaction mixture was stirred at room temperature for 12 hours. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with Heptane/EtOAc = 100:1 to 10:1 as eluent. *N*-(*tert*-Butyl)-*N*'-(ethylglycinyl)-*S*-phenylisothiourea was obtained in 61% yield (179 mg). Colorless oil, ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.43 (d, *J* = 6.8 Hz, 2H), 7.35 (d, *J* = 7.6 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 2H), 4.24 (s, 2H), 4.17 (q, *J* = 7.2 Hz, 2H), 4.02 (s, 1H), 1.29 (s, 9H), 1.27 (t, *J* = 7.2 Hz, 3H); ¹³C-NMR (100 MHz, CDCl₃): δ (ppm) 171.8, 135.3, 132.8, 131.7, 129.5, 128.2, 60.4, 52.9, 28.8, 28.5, 14.2; HRMS (ESI): m/z [M+H]⁺ calcd for C₁₅H₂₃N₂O₂S: 295.1475; found: 295.1470.

Ethyl *N*-benzoylglycinate (16)^[41]

This compound was obtained in 45% yield (28 mg) together with *N*-(*tert*-butyl)benzamide (**13**) when *N*-*tert*-butyl-*N*'-(ethylglycinyl)-*S*-phenylisothiourea (**15**) was used as reagent. White solid, m.p.: 61-63 °C (lit. ^[41]: 61 °C), ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.82 (d, *J* = 7.2 Hz, 2H), 7.49 (d, *J* = 7.2 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 6.83 (br s, 1H), 4.25 (t, *J* = 7.2 Hz, 2H), 4.23 (s, 2H), 1.30 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃): δ (ppm) 170.1, 167.5, 133.7, 131.7, 128.5, 127.0, 61.6, 41.8, 14.1; HRMS (ESI): m/z [M+H]⁺ calcd for C₁₁H₁₄NO₃: 208.0974; found 208.0968.

N-(*tert*-Butyl)-2,2-diphenylacetamide (18)^[42]

Prepared from N-tert-butyl-N'-(2,2,2-trifluoroethyl)-S-phenylisothiourea (17) (87 mg, 0.30 mmol, 1.0 equiv.) and 2,2-diphenylacetic acid (5b) (76 mg, 0.36 mmol, 1.2 equiv.) in o-xylene at 130 °C according to the general procedure A. The residue was purified by column chromatography on silica gel with Heptane/EtOAc = 3:1 to 1:1 as eluent. 2,2-N-(tert-butyl)-2,2-diphenylacetamide (18) was obtained in 12% yield (10 mg) together with 2,2-diphenyl-N-(2,2,2-trifluoroethyl)acetamide (19). White solid, m.p.: 200-203 °C (lit.^[42]: 201-202 °C), ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.31 (t, J = 7.2 Hz, 4H), 7.26 (d, J = 7.2 Hz, 4H), 7.24 (t, J = 7.2 Hz, 2H), 5.39 (br s, 1H), 4.81 (s, 1H), 1.32 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ (ppm) 171.0, 139.9, 128.8, 128.7, 127.1, 59.9, 51.5, 28.7; HRMS (ESI): m/z [M+H]⁺ calcd for C₁₈H₂₂NO: 268.1701; found 268.1707.

2,2-Diphenyl-N-(2,2,2-trifluoroethyl)acetamide (19)

compound was obtained in 63% yield (55 This mg) together with N-(tert-butyl)-2,2-diphenylacetamide (18). White solid, m.p.: 144-147 °C, ¹H NMR (400 MHz, $CDCl_3$: δ (ppm) 7.33 (t, J = 7.6 Hz, 4H), 7.27 (d, J = 6.8 Hz, 2H), 7.22 (d, J = 7.6 Hz, 4H), 6.11 (br s, 1H), 4.95 (s, 1H), 3.85 (dq, J = 9.6, 3.2 Hz, 2H); ¹³C NMR (101 MHz, CDCl₃): δ (ppm) 172.3, 138.7, 128.9, 128.8, 127.5, 124.0 (q, J_{C-F} = 278.6 Hz), 58.8, 40.8 (q, J_{C-F} = 34.6 Hz); ¹⁹F-NMR (376 MHz, CDCl₃): δ (ppm) -72.371; HRMS (ESI): m/z [M+H]⁺ calcd for C₁₆H₁₅NOF₃: 294.1106; found 294.1108.

2,2-Diphenyl-N-(2,2,2-trifluoroethyl)propanamide (21)

Prepared from *N*-*tert*-butyl-*N*'-(2,2,2-trifluoroethyl)-*S*-phenylisothiourea (**17**) (87 mg, 0.30 mmol, 1.0 equiv.) and 2,2-diphenylpropanoic acid (**5c**) (81 mg, 0.36 mmol, 1.2 equiv.) in *o*-xylene at 130 °C according to the general procedure A. The residue was purified by column chromatography on silica gel with Heptane/EtOAc = 3:1 to 1:1 as eluent. 2,2-Diphenyl-*N*-(2,2,2-trifluoroethyl)propanamide (**21**) was obtained in 71% yield (65 mg) together with *N*-(*tert*-butyl)-2,2-diphenylpropanamide (**20**).

White solid, m.p.: 101-103 °C, ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.33 (t, J = 7.2 Hz, 4H), 7.28 (d, J = 6.8 Hz, 2H), 7.23 (d, J = 7.2 Hz, 4H), 5.73 (br s, 1H), 3.89 (dq, J = 9.2, 6.8 Hz, 2H), 2.00 (s, 3H); ¹³C NMR (101 MHz, CDCl₃): δ (ppm) 175.4, 144.1, 128.6, 128.0, 127.2, 124.0 (q, J_{C-F} = 278.7 Hz), 57.1, 40.9 (q, J_{C-F} = 34.6 Hz), 27.1; ¹⁹F-NMR (376 MHz, CDCl₃): δ (ppm) -72.371; HRMS (ESI): m/z [M+H]⁺ calcd for C₁₇H₁₇NOF₃: 308.1262; found 308.1272.

2,2,2-Triphenyl-N-(2,2,2-trifluoroethyl)acetamide (22)

Prepared from N-tert-butyl-N'-(2,2,2-trifluoroethyl)-S-phenylisothiourea (17) (87 mg, 0.30 mmol, 1.0 equiv.) and 2,2,2-triphenylacetic acid (5d) (104 mg, 0.36 mmol, 1.2 equiv.) in o-xylene at 130 °C according to the general procedure A. The residue was purified by column chromatography on silica gel with Heptane/EtOAc = 3:1 to 1:1 as eluent. 2,2,2-Triphenyl-N-(2,2,2-trifluoroethyl)acetamide (22) was obtained in 83% yield (92 mg). White solid, m.p.: 157-159 °C, ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.30 (d, J = 7.2 Hz, 3H), 7.27 (d, J = 7.6 Hz, 6H), 7.25 (t, J = 8.0 Hz, 6H), 6.04 (br s, 1H), 3.93 (dq, J = 9.2, 6.8 Hz, 2H); ¹³C NMR (101 MHz, CDCl₃): δ (ppm) 173.6, 142.7, 130.4, 128.1, 127.3, 124.0 (q, J_{CF} = 278.8 Hz), 67.8, 41.0 (q, J_{CF} = 34.6 Hz); HRMS (ESI): m/z [M+H]⁺ calcd for C₂₂H₁₉NOF₃: 370.1419; found 370.1414.

General procedure B for the synthesis of *N***-alkylamides:** A 10 mL pressure vial was charged with N,N'-dialkyldicarbodiimide (23) (0.30 mmol, 1.0 equiv.), 2,2,2-triphenylacetic acid (5d) (0.36 mmol, 1.2 equiv.) and *o*-xylene (2.0 mL). The vial was sealed and the reaction mixture was stirred at 130 °C for 24 h under air atmosphere. The mixture was cooled down to room temperature, concentrated under reduced pressure and dried under vacuum. The residue was purified by flash column chromatography on silica gel to yield the corresponding *N*-alkylamide.

N-Cyclohexyl-2,2,2-triphenylacetamide (24a)^[43]

Prepared from 1,3-dicyclohexylcarbodiimide (**23a**) (62 mg, 0.30 mmol, 1.0 equiv.) according to general procedure B. The residue was purified by column chromatography on silica gel with Heptane/EtOAc = 3:1 to 1:1 as eluent. *N*-Cyclohexyl-2,2,2-triphenylacetamide (**24a**) was obtained in 68% yield (75 mg). White solid, m.p.: 116-119 °C (lit.: ^[43] 144-145 °C), ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.26 (m, 15H), 5.62 (d, *J* = 4.0 Hz, 1H), 3.92 (t, *J* = 4.0 Hz, 1H), 1.85 (d, *J* = 9.2 Hz, 2H), 1.53 (d, *J* = 5.2 Hz, 2H), 1.33 (q, *J* = 10.8 Hz, 2H), 1.13 (t, *J* = 10.8 Hz, 2H), 1.05 (hex, *J* = 10.8 Hz, 2H); ¹³C NMR (101 MHz, CDCl₃): δ (ppm) 172.0, 143.5, 130.4, 127.7, 126.8, 67.5, 48.5, 32.5, 25.4, 24.4; HRMS (ESI): m/z [M+H]⁺ calcd for C₂₆H₂₈NO: 370.2171; found 370.2181.

N-IsopropyI-2,2,2-triphenylacetamide (24b) Prepared from *N,N'*-diisopropylcarbodiimide (**23b**) (38 mg, 0.30 mmol, 1.0 equiv.) according to general procedure B. The residue was purified by column chromatography on silica gel with Heptane/EtOAc = 3:1 to 1:1 as eluent. *N*-IsopropyI-2,2,2-triphenylacetamide (**24b**) was obtained in 73% yield (72 mg). White solid, m.p.: 113-116 °C, ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.26 (m, 15H), 5.52 (s, 1H), 4.18 (hex, *J* = 6.8 Hz, 1H), 1.07 (d, *J* = 6.8 Hz, 6H); ¹³C-NMR (101 MHz, CDCl₃): δ (ppm) 172.0, 143.5, 130.5, 127.8, 126.8, 67.5, 42.0, 22.3; HRMS (ESI): m/z [M+H]⁺ calcd for C₂₃H₂₄NO: 330.1858; found 330.1859.

N-(*tert*-Butyl)-2,2,2-triphenylacetamide (24c)^[44] Prepared from di-*tert*-butylcarbodiimide (23c) (46 mg, 0.30 mmol, 1.0 equiv.) according to general procedure B. The residue was purified by column chromatography on silica gel with Heptane/EtOAc = 3:1 to 1:1 as eluent. *N*-(*tert*-Butyl)-2,2,2-triphenylacetamide (24c) was obtained in 71% yield (73 mg). White solid, m.p.: 106-109 °C (lit.^[44]: 125.8–127.1 °C), ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.26 (m, 15H), 5.51 (s, 1H), 1.29 (s, 9H); ¹³C NMR (101 MHz, CDCl₃): δ (ppm) 172.0, 143.7, 130.5, 127.7, 126.8, 68.1, 51.6, 28.4; HRMS (ESI): m/z [M+H]⁺ calcd for C₂₄H₂₆NO: 344.2014; found 344.2002.

N-(Adamantan-1-yl)-2,2,2-triphenylacetamide (24d)^[45] Prepared from di-(1-adamantanyl)carbodiimide (23d) (93 mg, 0.30 mmol, 1.0 equiv) according to general procedure B. The residue was purified by column chromatography on silica gel with Heptane/EtOAc = 3:1 to 1:1 as eluent. *N*-(Adamantan-1-yl)-2,2,2-triphenylacetamide (24d) was obtained in 62% yield (78 mg). White solid, m.p.: 221-224 °C, ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.24-7.27 (m, 15H), 5.38 (s, 1H), 2.03 (br, s, 3H) 1.95 (s, 6H), 1.64 (s, 6H); ¹³C NMR (101 MHz, CDCl₃): δ (ppm) 171.8, 143.7, 130.5, 127.7, 126.7, 68.1, 41.2, 36.3, 29.3; HRMS (ESI): m/z [M+H]⁺ calcd for C₃₀H₃₂NO: 422.2484; found 422.2495.

N-(2,6-Diisopropylphenyl)-2,2,2-triphenylacetamide (24e) Prepared from bis(2,6-diisopropylphenyl)carbodiimide (23e) (109 mg, 0.30 mmol, 1.0 equiv.) according to general procedure B. The residue was purified by column chromatography on silica gel with Heptane/EtOAc = 3:1 to 1:1 as eluent. *N*-(2,6-Diisopropylphenyl)-2,2,2-triphenylacetamide (24e) was obtained in 72% yield (97 mg). White solid, m.p.: 97-100 °C, ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.50 (d, *J* = 7.6 Hz, 6H), 7.31 (t, *J* = 7.2 Hz, 6H), 7.25 (d, *J* = 7.2 Hz, 3H), 7.21 (d, *J* = 8.4 Hz, 1H), 7.16 (s, 1H), 7.11 (d, *J* = 7.6 Hz, 2H), 2.87 (hept, *J* = 6.8 Hz, 2H), 1.09 (d, *J* = 6.8 Hz, 12H); ¹³C NMR (101 MHz, CDCl₃): δ (ppm) 171.8, 145.9, 143.4, 131.2, 130.4, 128.0, 127.0, 123.3, 68.6, 28.4, 23.6 (1c missing); HRMS (ESI): m/z [M+H]⁺ calcd for C₃₂H₃₄NO: 448.2640; found 448.2640.

General procedures for amide synthesis via DCC coupling:

<u>Method 1 (for compounds L-3j, L-3l, L-3s):</u>^[46] A solution of carboxylic acid **2** (1.0 mmol, 1.0 equiv.) and 1-hydroxybenzotriazole hydrate (1.1 mmol, 1.1 equiv.) in THF (5 mL, anhydrous) was cooled to 0 °C. Subsequently, a solution of 1,3-dicyclohexylcarbodiimide (1.1 mmol, 1.1 equiv.) (DCC) in THF (1 mL, anhydrous) was added. After 20 minutes an amine (1.1 mmol, 1.1 equiv.) was added to the reaction mixture. After stirring the mixture at room temperature overnight, THF was evaporated and the residue was taken up in EtOAc (40 mL) and cooled in the refrigerator. Then *N*,*N*'-dicyclohexylurea (DCU) was filtered off, the filtrate washed with saturated Na₂CO₃ (3 x 10 mL), HCl (1 N, 3 x 10 mL), brine (3 x 10 mL) and dried over MgSO₄. The solvent was evaporated to give the crude product which was purified by flash column chromatography on silica gel.

<u>Method 2 (for compounds **24a-24e**):^[47] A 25 mL round bottomed flask was charged with 2,2,2-triphenylacetic acid (**5d**, 1.05 mmol, 1.05 equiv.) and DCM (5 mL) and cooled to 0 °C, then 1,3-dicyclohexylcarbodiimide (DCC, 1.08 mmol, 1.08 equiv.) and 4-dimethylaminopyridine (DMAP, 0.25 mmol, 25 mol%) were dissolved in DCM (5 mL) and added dropwise to the above mixture. The reaction mixture was subsequently stirred at 0 °C for 30 minutes, then an amine (1.0 mmol, 1.0 equiv.) was added and the reaction mixture was stirred for 24 h at room temperature. The mixture was filtered through filter paper, the solid was thoroughly washed with EtOAc, and the combined filtrates concentrated and dried *in vacuo*. The residue was purified by flash column chromatography on silica gel.</u>

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