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Article

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Cysteine isocyanide in multicomponent reaction: Synthesis of peptido-mimetic 1,3-azoles

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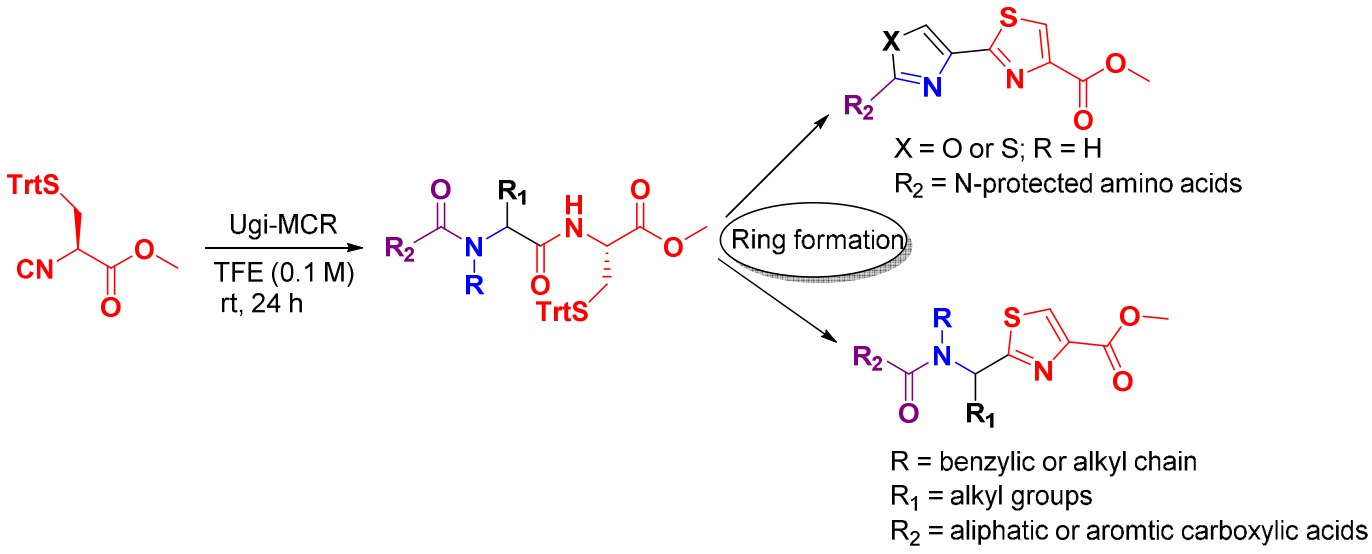
Abstract



An alternative approach towards the simple and robust synthesis of highly substituted peptidic thiazole derivatives by using Ugi-multicomponent reaction (U-MCR) is described. Thus, we introduced the enantiopure (R)-2-methyl-2-isocyano-3-(tritylthio)propanoate as novel class of isocyanide in MCR. This bifunctional isocyanide was found to undergo mild cyclodehydration to afford thiazole containing peptidomimetics in a short synthetic sequence. Several examples of bis-heterocyclic rings were also synthesized through the proper choice of the aldehyde component in the U-4CR. The method opens a wide range of applications towards the synthesis of non-ribosomal natural product and other bioactive compounds.

Introduction

Cysteine (Cys, C) possessing peptides and proteins have attracted widespread attention in medicinal chemistry as well as chemical biology.[1,2] It has been the most prominent target in protein chemical synthesis[3] and post-translational modifications.[4] One such modification involves the biosynthetic incorporation of thiazole onto the growing peptide through enzymatic cyclization (Figure 1).[5] The thiazole moiety has been commonly found in a variety of natural products with associated interesting biological activities.[6,7] Plantazolicin is a structurally impressive natural product containing multiple oxazole and thiazole moieties in which three and four heterocyclic rings are connected in a consecutive fashion.[8] A large number of synthetic drugs also comprises thiazole ring as active part in the molecule.[9] Due to the broad spectrum of pharmacological activities of 1,3-azoles numerous methods for their preparation have been described.[10] Commonly available synthetic methods mostly involve conventional peptide synthesis bearing Cys/Ser/Thr amides followed by cylcodehydration and oxidation.[11] However, the classical peptide synthesis is sequential, time consuming and costly. On the other hand, the Ugi multicomponent reaction (U-MCR) is an alternative approach for the synthesis of short peptide sequences.[12] It produces α-amino-amides from isocyanides which allows an easy and simple way for the synthesis of libraries of small molecules, peptides, peptidomimetics and macrocycles.[13] Additionally, post-condensation modification of isocyanide-based MCRs allow for a simple and fast entry to medicinal chemistry applications.[14,15]

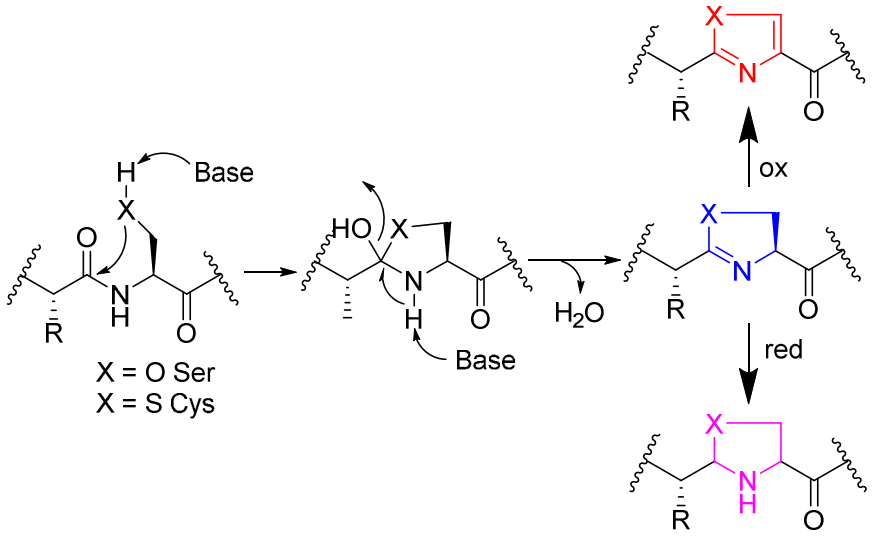


Figure 1. Biosynthesis of 1,3-azoles from Cys and Ser peptides

Focusing on the synthesis of thiazole derivatives through U-MCR, we have previously developed a one-pot thiazole synthesis through the Ugi reaction of thioacids and Schöllkopf isocyanide (Figure 2A, route 1).[16] The reaction was used in the total synthesis of tubulysin derivatives.[17] Similarly, the Kazmaier group employed a two-step synthesis involving U-MCR of thioacid and isocyanodimethylacetal and the resulting endothiopeptidic derivatives were cyclized to yield terminal thiazole peptide analogues (Figure 2A, route 2).[18]Although, the methods offer a variety of advantages but still they deserve improvement due to the limited availability of thioacids and the rather low yields due to the air sensitive nature of the thioacids. To overcome these issues, we were interested in an alternative MCR strategy for the synthesis of 1,3-azole derivatives. In this context, synthesis of isocyanide derived from cysteine amino acid would be an ideal choice. Moreover, dipeptide isocyanide bearing cysteine derivatives with an S-ethyl carbamate protecting group have been recently described for the synthesis of polyisocyanides.[19] In another report, (R)-methyl 3-(benzythio)-2-isocyanopropanoate was described for the synthesis of corresponding isoselenocyanate.[20] However, benzyl protection for thiol is not promising for many post-modifications on sulfur. Very recently, we have synthesized the stable and enantiomerically pure chiral isocyanide derived from S-trityl protected cysteine and employed it for the preparation of disulfide bridged macrocycles.[21] Herein we describe another important application of isocyanide **4** in U-MCR to access peptidic thiazole derivatives in short (Figure 2B).

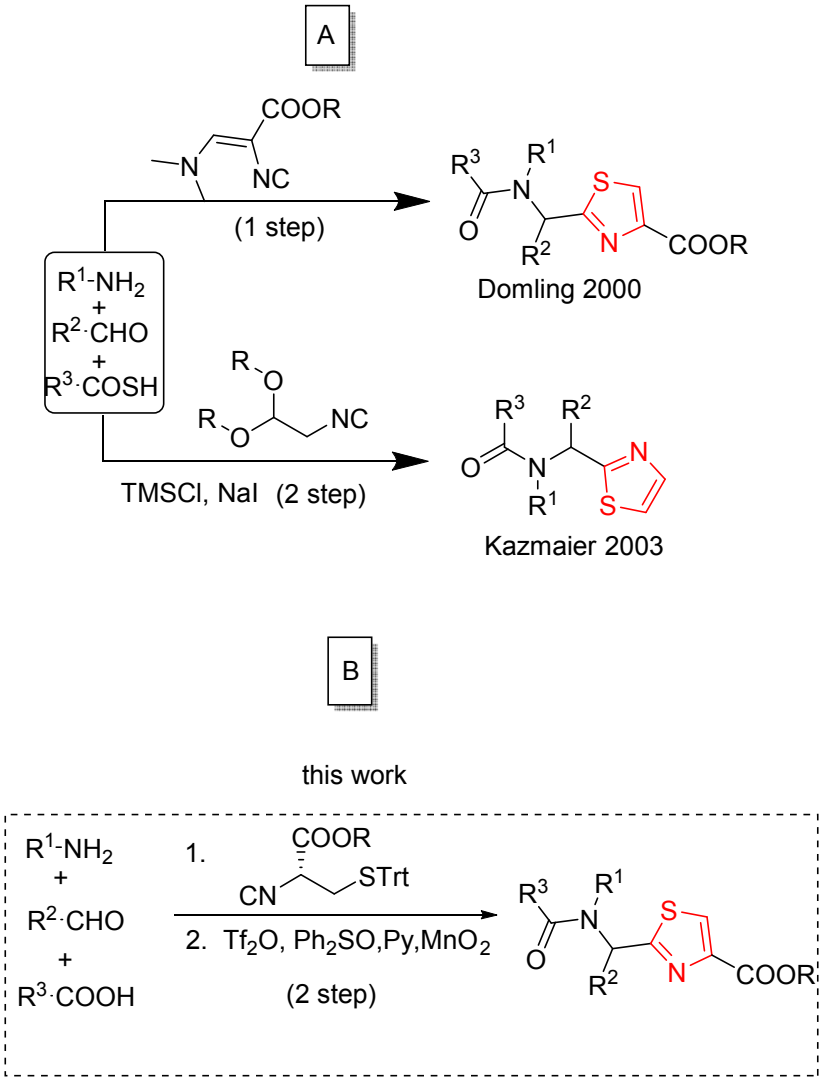
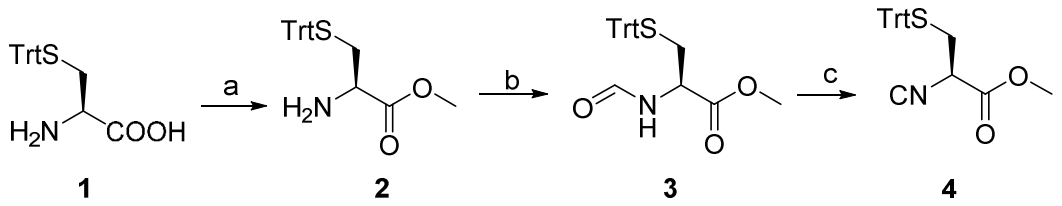


Figure 2. (a) Previous works on thiazole synthesis using Ugi multicomponent reaction and (b) this work

Results and discussion

We synthesized isocyanide **4** from readily available Cys(Trt)-OH **1** according to Scheme 1. The esterification of **1** with thionyl chloride yielded **2** in quantitative yield. The latter was subjected to formylation with methylformate to afford formyl protected Cys(Trt)-OMe **3** in 95% yield. Next, we examined the enantiopure preparation of isocyanide **4**. Commonly employed dehydrating conditions such as $POCl_3$/TEA, $POCl_3$/NMM, diphosgene/NMM at -78 °C resulted in considerable racemization and also affords low yields.[22,14b] Burgess reagent[23] and phosgene derivatives have been commonly employed

for the epimerization-free synthesis of amino acid isocyanides.[24] We carried out the dehydration of **3** in the presence of triphosgene (0.35 eq.) and NMM (2.0 eq.) at -78 °C for 3 h and in fact isocyanide **4** was obtained in 85% yield and high enantiopurity as shown by chiral HPLC (SI).[25] The synthesis of **4** has also been performed on a 30 g scale.



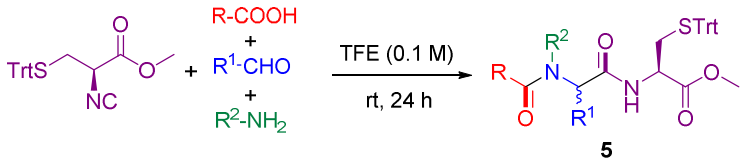
1 **2** **3** **4**

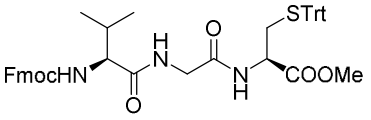
conditions: (a) $SOCl_2$, MeOH, reflux, 6h;(b) Methyl formate, reflux, 24 h;
(c) Triphosgene, NMM,-78 °C, 3 h

Scheme 1. Synthesis of chiral Cys(Trt)-isocyano methyl ester **4**

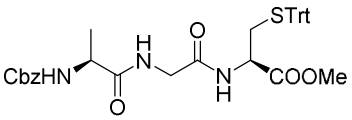
To demonstrate the usefulness of the novel isocyanide **4**, we tested its competency in peptide synthesis involving U-MCR. The most straightforward approach would involve ammonia as an amine component. However, the Ugi reaction using ammonia is often described as complex and low yielding, or no product formation is observed at all.[26] To overcome these issues, cleavable amine components or ammonium salts of carboxylic acid have been developed.[27] However, cleavable amine or aldehyde components require additional steps and racemization is possible.[28] In principle, ammonium salts of carboxylates could be ideal components in the U-MCR due to their general and simple preparation while maintaining a neutral pH during the Ugi reactions thus avoiding racemization during the peptide synthesis.[29] Therefore we have synthesized ammonium salt of carboxylates derived from *N*-protected amino acids (1.0 eq.) by the treatment of ammonium bicarbonate in a mixture of CH_3CN:H_2O. The ammonium salts were easy to isolate by filtration. In a general Ugi reaction the aldehyde component was added to the ammonium salt of carboxylate in trifluoroethanol (TFE, 0.1 M) at 0 °C. After 15 minutes isocyanide **4** was added and allowed to stir at r.t. for 24 h (Table 1). Aldehyde such as paraformaldehyde and isovaleraldehyde produced the Ugi adducts **5a-c** in moderate yields. Next, with the aim to access oxazoles, we focused on the incorporation of serine side chains into peptides using glycolaldehyde dimer (Table 1, entries **5d-f**).

Table 1. Synthesis of Ugi products **5** using isocyanide **4**

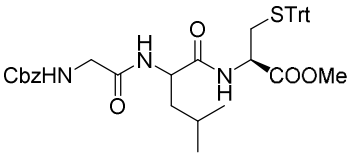




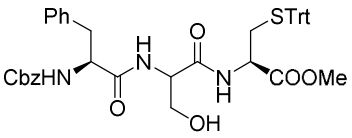
5a, 48%, ee 99%



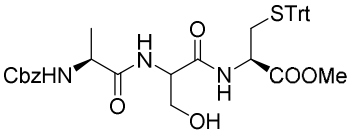
5b, 55%, ee 99%



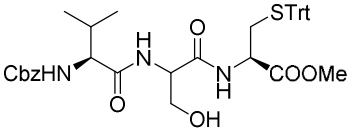
5c, 60%, dr 1:0.8



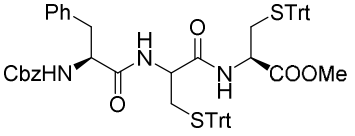
5d, 53%, dr 1:0.6



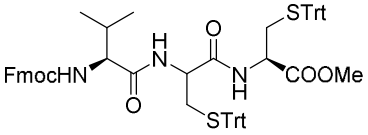
5e, 60%, dr 1:0.8)



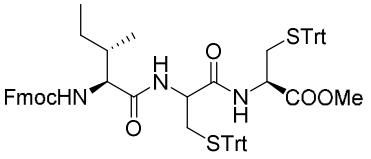
5f, 52%, dr 1:0.7



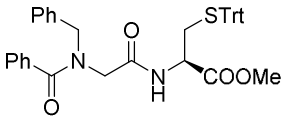
5g, 45%, dr 1:0.5



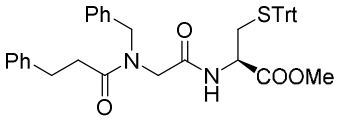
5h, 48%, dr 1:0.6



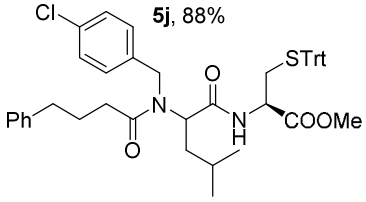
5i, 39%, dr 1:0.5



5j, 88%



5k, 91%



5l, 89%,dr 1:0.5

Isolated yields are given; diastereomeric ratios are given according to ^{1}H NMR analysis; enantiomeric excess determined by chiral SFC-HPLC

In these cases, the Ugi products were obtained in moderate yields without detection of any byproducts such as Passerini or Ugi-5C-3CR products as previously observed.[30] The synthesis of selenopeptidic derivatives through U-MCR reaction have been well described.[31] However, similar incorporation of sulfur is less common through U-MCR, for example, spiro derivatives of thiazolines were employed as components in U-MCR for the assembly of constrained analogues of peptides.[32] In an effort to introduce Cys moieties into glutathione derivatives, benzylthio aldehdyes and ketones were used in the Ugi reaction.[33] The benzyl protecting group for thiol, however, is not compatible for a straightforward post-modification strategy. The simple and scalable preparation of trityl protected mercaptoacetaldehyde as a component in U-4CR is therefore a viable alternative to other procedures.[34] Interestingly, trityl protected mercaptoacetaldehyde reacted with the ammonium salts of N-protected acids and isocyanide **4** at r.t. The reaction indeed worked well and the respective Ugi products were obtained in moderate yields (Table 1, entries **5g-i**). These examples demonstrate that sequential Cys(Trt) derivatives can be incorporated into the peptide backbone through the U-MCR. To demonstrate the general utility of the isocyanide **4** in the classical U-4CR, simple primary amines, acids and aldehydes were also employed. The resulting *N*-alkylated Ugi products were obtained in excellent yields (Table 1, entries **5j-l**). The diastereoselectivity of the Ugi products varied from 1:0.5 to 1:0.8. Compounds **5a** and **5b** were obtained as single crystals analysis confirmed their structures (Figure 3). As shown in table 1, the yields of Ugi products **5a-5i** are low when compare to the Ugi products **5j-5l**. The moderate yields for **5a-5i** is due to slow reactivity of the aldehydes with ammonium salt of carboxylates as evidenced by the LC-MS analysis of the crude reaction mixtures which showed only desired product and unreacted staring materials.

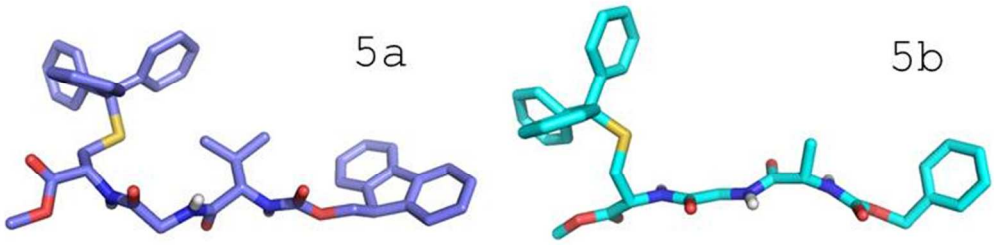
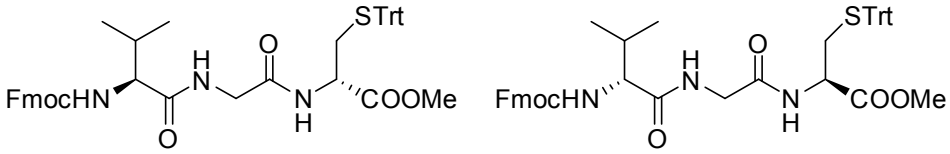


Figure 3. ORTEP pictures of Ugi products **5a** and **5b**

The retention of the optical purity of the isocyanide or the carboxylic acid was accessed by using model Ugi products **5m** and **5n** (Figure 4)**.** The excellent enantioselectivities observed in Ugi products **5a** and **5m** revealed that retention of chirality is maintained in the isocyanide part. An additional set of Ugi products **5a** and **5n** also showed that negligible epimerization was observed even at the N-protected amino acids. No racemization observed here, we speculate, is due to the neutral conditions in the Ugi reaction. This is also supported by the work of others.[28d]



5m[a] 51%, ee 99% **5n**[b] 45%, ee 97%

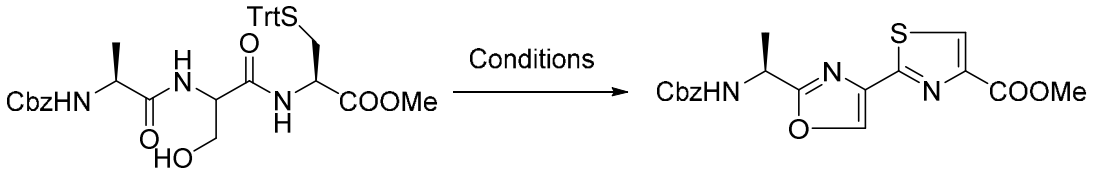
[a](D)-enantiomer of the isocyanide **4** is used in U-4CR; [b]Fmoc-(D)-Val-OH is used as acid component; isolated yields are given; enantiomeric excess determined by chiral SFC-HPLC

Figure 4 Racemization test for U-4CR

Having Cys(Trt) containing Ugi products at hand, we next elaborated the cyclodehydration towards thiazoles. We envisioned a cascade cyclization of Ser/Cys(Trt) or Cys(Trt)/Cys(Trt) amides fallowed by oxidation of resulting azolines to azoles in one-pot to avoid tedious isolations and purifications of intermediates. Activated MnO_2 has been commonly used oxidant for the conversion of azolines to azoles and it is highly compatible for many organic solvents. We speculated that direct treatment of MnO_2 after

the cyclodehydration could access to thiaozles in one-pot. Consequently, various known cyclodehydrating fallowed by MnO_2 oxidation procedures were examined by using **5d** as a model substrate (Table 2). Literature reported reagents such as $TiCl_4$ (Table 2, entries a,b),[35] diethylaminosulfur trifluoride (DAST) (Table 2, entries c, d)[36] and tosyl chloride (Ts-Cl) (Table 2, entries e,f)[37] were tested under various conditions from equimolar amounts to large excess.

Table 2. Optimization studies for the synthesis of **6d**[a]



5d **6d**

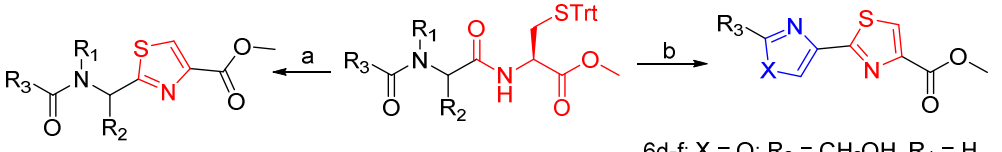
Entry	Reagent	Conditions	Time (h)	Yield of **6d** (%)
A	$TiCl_4$ (6 eq.)	0 °C to r.t.	48	10
B	$TiCl_4$ (6 eq.)	r.t.	48	-
C	DAST (5 eq.)	-78 °C to 0 °C	24	12
D	DAST (10 eq.)	-78 °C to 0 °C	24	15
E	Ts-Cl (10 eq.)	60 °C	24	-
F	Ts-Cl (20 eq.)	60 °C	48	-
G	Tf_2O/PPh_3O (3.0 eq./6 eq.)	-78 °C	8	18
H	Tf_2O/PPh_3O (3.0 eq./6 eq.)	-20 °C	8	28
I	Tf_2O/Ph_2SO/ Py (3.0 eq./6.0 eq./ 10.0 eq.)	-78 °C	5	62

[a]All reactions were conducted at 1.0 mmol scale; time refers to the formation of thiazoline. Activated MnO_2 (10 eq.) was added to the crude thiazoline flowed by refluxed at 80 ºC for 3 h in $CHCl_3$; isolated yields are given

All these reagents afforded complex product mixtures and often in low yields. Finally, we employed Tf_2O (3.0 eq.)/PPh_3O (6 eq.) at -78 °C (Table 2, entry g) and **6d** was obtained in 18% yield.[38] When the reaction was carried out at -20 °C (Table 2, entry h) resulted in

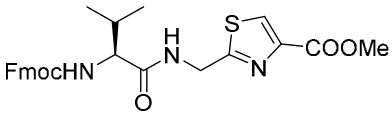
28% of **6d**. Further optimization by increasing the amount of reagents and time did not gave improved results. Encouragingly, changing the additive to Ph_2SO (6 eq.) and by using pyridine (10 eq.) as base in the presence of Tf_2O at -78 °C afforded 62% of **6d** after MnO_2 oxidation (Table 2, entry i).[39] As shown in table 3, the optimized conditions worked well for bis- as well as mono-cyclodehydration of Cys(Trt)-amides (Table 3, **6a-6l**).

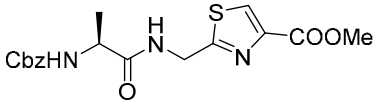
Table 3. List of thiazole derivatives synthesized.[a]

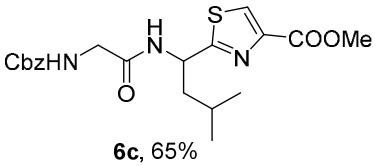


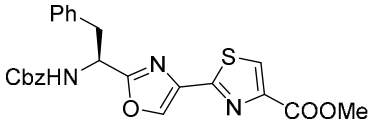
Conditions:

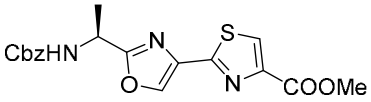
a = (1) Tf_2O (1.5 eq.), Ph_2SO (3.0 eq.),Py (10 eq.), -78 °C, 1h; (2) MnO_2 (10 eq.) $CHCl_3$ reflux, 3 h
b = Tf_2O (3.0 eq.), Ph_2SO (6.0eq.), Py (10 eq.), -78 °C 6 h; (2) MnO_2 (10 eq.) $CHCl_3$ reflux, 3 h

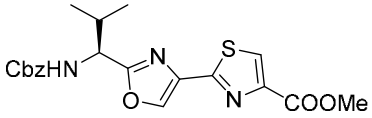

6a, 71%

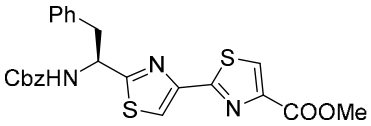

6b, 50%

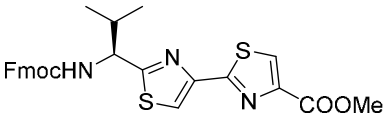

6c, 65%

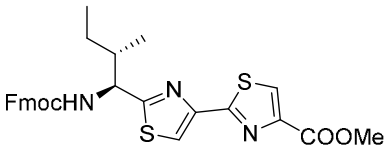

6d, 45%

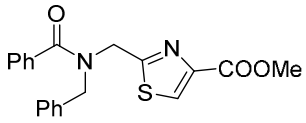

6e, 62%

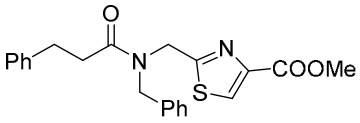

6f, 55%

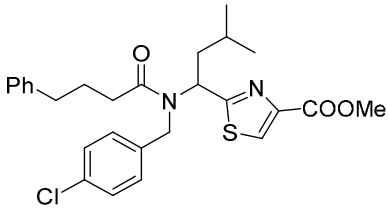

6g, 49%


6h, 64%


6i, 56%

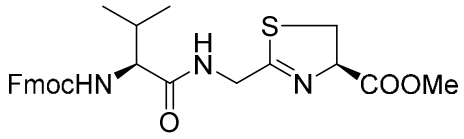

6j, 76%


6k, 73%

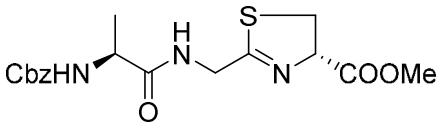

6l, 79%

[a]Isolated yields are given

In order to examine the racemization of the intermediate thiazolines, two peptide thiazolines **7a** and **7b** were isolated in moderate yield and were obtained in good enantioselectivity, indicating low epimerization (Figure 5).



7a 76%, ee: >98%



7b 65%, ee: >97%

Isolated yields are given; enatiomeric excess determined by chiral SFC-HPLC.

Figure 5. Thiazolines isolated for racemization test

Conclusions

In summary, we have introduced the cysteine-derived chiral isocyanide **4** as a versatile component for the short synthesis of thiazole and bis-oxazole/thiazole derivatives *via* Ugi-MCR and subsequent cyclodehydration strategy. We believe the methodology will prove for the formation of oxazole and thiazole fragments in natural product synthesis and their unnatural derivatives as well as in the synthesis of heterocyclic libraries to enrich screening decks, for example the European Lead Factory.[40] Additionally, the described novel isocyanide has wide synthetic applications in multicomponent reactions beyond thiazole formation, as we will communicate shortly.

Experimental Section

General methods

All N–protected amino acids, reagents and solvents were purchased from Sigma Aldrich. The enantiomers of the Cys(Trt)–OH were purchased from abcr GmbH company were used as received. All reaction mixtures were stirred magnetically and were monitored by thin–layer chromatography using silica gel precoated glass plates, which were visualized with UV light and then, developed using iodine. Flash chromatography was performed on a Teledyne ISCO

Combiflash R*f* , using RediSep R*f* Normal–phase Silica Flash Columns (Silica Gel 60 Å, 230 – 400 mesh). Cyclodehydration was carried under nitrogen atmosphere. Nuclear magnetic resonance spectra were recorded on a Bruker Avance 500 spectrometer {^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz)). Chemical shifts for ^{1}H NMR were reported as δ values and coupling constants were in hertz (Hz). ^{1}H and ^{13}C NMR values are given for major diastereomeric Ugi product. Mass spectra were measured on a Waters Investigator Supercritical Fluid Chromatograph with a 3100 MS Detector (ESI) using a solvent system of methanol and CO_2 on either a Viridis 2-ethyl pyridine column (4.6 × 250 mm, 5 μm particle size) or a Viridis silica gel column (4.6 × 250 mm, 5 μm particle size) and reported as (m/z). The specifications of chiral SFC-HPLC details are given on respective spectra. Optical rotations were measured using a 1 mL cell with a 10 mm path length on an P-2000 JASCO digital polarimeter.

Methyl S–trityl–L–cysteinate, 2

This compound was synthesized according to the procedure of Graham *et al*. and the analytical data were compared.[41]

To a stirred solution of S–trityl–L–cysteine (1.0 g, 2.76 mmol) in 50 mL of methanol at 0 ˚C was added thionyl chloride (1.50 mL, 0.206 mmol) in a dropwise fashion. The solution was allowed to warm up to r.t. and then refluxed at 80 °C for 5 h. The solvent was removed under reduced pressure and the crude product was extracted with ethyl acetate and washed with saturated sodium bicarbonate for several times. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated to give ester **2** as a pale yellow gum.

yield = 85% (0.865 g), yellow gum, R_f 0.41 (PE/EtOAc, 1:1), $[\alpha]_D^{20}$ = +31.5 (*C*1, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 – 7.14 (m, 15H), 6.73– 6.78 (br, m, 2H), 3.62 (s, 3H), 3.20 (m, 1H), 2.58 (dd, *J* = 12.4, 4.9 Hz, 1H), 2.47 (dd, *J* = 12.5, 7.7 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 174.1, 144.4, 129.7, 129.5, 128.0, 127.9, 127.7, 126.8, 126.7, 66.8, 53.7, 52.1, 36.8.

MS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{23}H_{23}NO_2SNa$ 400.13; Found 400.10.

Methyl N–formyl–S–trityl–L–cysteinate, 3

Amine **2** (1.0 g, 2.65 mmol) was dissolved in methyl formate (10 mL, solvent) and the solution was allowed to reflux at 60 °C until TLC showed complete consumption of the starting material (usually 24 h). The solvent was evaporated and the product was purified through column chromatography to yield formyl ester **3** as a white solid.

yield = 95% (1.03 g), white solid, mp: 132–133 °C, R_f 0.50 (PE/EtOAc, 1:1), $[\alpha]_D^{20}$ = +19.1 (*C*1, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.50 – 7.11 (m, 15H), 6.14 (d, *J* = 8.1 Hz, 1H), 4.64 (dt, *J* = 8.2, 5.2 Hz, 1H), 3.68 (s, 3H), 2.77 (dd, *J* = 12.7, 5.8 Hz, 1H), 2.69 (dd, *J* = 12.9, 6.5 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 160.4, 144.1, 129.4, 128.0, 128.0, 126.9, 126.8, 67.0, 52.6, 49.7, 33.5.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{24}NO_3S$ 406.1471; Found 406.1477.

Methyl (R)–2–isocyano–3–(tritylthio)propanoate, 4

To a solution of *N*–formyl Cys(Trt)–methyl ester **3** (30.0 g, 74.0 mmol) in CH_2Cl_2 (150.0 mL) at –78 °C, N–methylmorpholine (2.0 eq. 16.5 mL) was added. After 5 min triphosgene (7.6 g, 0.35 eq.) in CH_2Cl_2 (50.0 mL) was added dropwise and the reaction mixture was stirred for 3h at –78 ^{o} C (TLC analysis). Saturated $NaHCO_3$ solution (10 mL) was added at same temperature and allowed to warm to r.t. The reaction mixture was extracted with CH_2Cl_2, the organic extracts were separated, dried over anhydrous Na_2SO_4, filtered, and concentrated. The solution was

diluted with diethyl ether (10 mL) and stored at –15 °C for 5 h which resulted pure solid of isocyanide **4** which was collected by filtration.

yield = 85% (24.3 g), white solid, mp: 96 –97 °C, R_f 0.42 (EtOAc/ PE, 10:90), $[\alpha]_D^{20}$ = +32.8 (*C*1, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 – 7.06 (m, 15H), 3.70 (s, 3H), 3.34 (dd, *J* = 7.7, 5.8, Hz, 1H), 2.89 – 2.63 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.6, 160.9, 143.9, 129.4, 129.2, 128.2, 128.0, 128.0, 127.9, 127.1, 67.5, 55.3, 53.4, 34.2.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{22}NO_2S$ 388.1365; Found 388.1363.

Methyl S–trityl–R–cysteinate, 2b

This compound was synthesized according to general procedure for the preparation of **2** by using S–trityl–R–cysteine **1b** (1.0 g, 2.76 mmol)

yield = 80% (0.830 g), yellow gum; R_f 0.41 (PE/EtOAc, 1:1), $[\alpha]_D^{20}$ = -31.1 (*C*1, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 – 7.18 (m, 15H), 6.72 – 6.75 (br, m, 2H) 3.61 (s, 3H), 3.24 (dd, *J* = 7.9, 4.8 Hz, 1H), 2.56 (dd, *J* = 12.5, 4.7 Hz, 1H), 2.48 (dd, *J* = 12.5, 7.8 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 174.2, 144.5, 130.1, 129.6, 128.3, 128.0, 66.9, 53.8, 52.2, 36.9.

MS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{23}H_{23}NO_2SNa$ 400.13; Found 400.04.

Methyl N–formyl–S–trityl–R–cysteinate, 3b

This compound was synthesized according to general procedure for the preparation of **3** by using methyl S–trityl–R–cysteinate, **2b** (1.0 g, 2.65 mmol)

yield = 78 % (0.837 mg), white solid, mp: 135–137 °C, R_f 0.50 (PE/EtOAc, 1:1), $[\alpha]_D^{20}$ = -18.8 (*C*1, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.52 – 7.12 (m, 15H), 6.15 (d, *J* = 12.6 Hz, 1H), 4.69 (dt, *J* = 8.1, 5.2 Hz, 1H), 3.65 (s, 3H), 2.82 (dd, *J* = 12.7, 5.8 Hz, 1H), 2.67 (dd, *J* = 12.7, 4.7 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 160.6, 144.3, 129.6, 129.5, 128.2, 128.1, 127.1, 67.0, 52.8, 49.8, 33.7.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{24}NO_3S$ 406.1477; Found 406.1477.

Methyl (S)–2–isocyano–3–(tritylthio)propanoate, 4b

This compound was synthesized according to general procedure for the preparation of **4** by using methyl N–formyl–S–trityl–R–cysteinate, **3b** (2.0 g, 5.0 mmol)

yield = 76% (20.9 g), white solid, mp: 101 –103 °C, R_f 0.42 (EtOAc/ PE, 10:90), $[\alpha]_D^{20}$ = -32.9 (*C*1, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 – 7.26 (m, 15H), 3.71 (s, 3H), 3.36 (dd, *J* = 7.9, 5.8 Hz, 1H), 2.89 – 2.60 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.6, 160.9, 143.9, 130.7, 129.5, 128.3, 128.0, 128.0, 127.7, 127.3, 127.2, 127.1, 67.6, 55.4, 53.4, 34.2.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{22}NO_2S$ 388.1365; Found 388.1363.

Trityl thioacetic acid

This compound was synthesized according to the procedure of Tam *et al*. and the analytical data were compared.[42]

To a mixture of mercaptoacetic acid (3.48 mL, 50.0 mmol) and triphenylmethanol (13.0 g, 50.0 mmol) in 50 mL of chloroform was added trifluoroacetic acid (10 mL) in 5 min. After stirring at r.t. for 1 h, the volatiles were removed *in vacuo*. The crude product was purified by recrystallization (CH_2Cl_2/Hexane; 1/2) to give trityl thioacetic acid.

yield = 98% (16.3 g), white solid, mp: 159–161 °C, R_f 0.38 (EtOAc/ PE/ AcOH, 30:70:1.0),

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 – 7.15 (m, 15H), 3.06 (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 175.5, 143.9, 129.5, 128.1, 127.9, 127.0, 67.3, 34.5.

MS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{18}O_2SNa$ 357.09; Found 357.21.

N–methoxy–N–methyl–2–(tritylthio)acetamide

To a solution of acid (20.0 mmol), PyBOP (1.1 equiv.) and TEA (2.5 equiv.) in CH_2Cl_2 (50 mL) was added *N,O*–dimethylhydroxylamine hydrochloride (1.2 equiv.) and the solution was allowed to stir at r.t. overnight. The solution was then diluted with excess CH_2Cl_2 and washed consecutively with 1 M HCl solution (3 x 10 mL), saturated aq. $NaHCO_3$ (3 x 10 mL), and water (1 x 10 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel to afford the desired Weinreb amide.

yield = 95% (7.1 g), white solid, mp: 125–127 °C, R_f 0.32 (EtOAc/ PE, 30:70)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 – 7.44 (m, 7H), 7.32–7.31 (m, 8H), 3.49 (s, 3H), 3.14 (s, 3H), 3.11 (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.0, 144.3, 129.6, 128.0, 127.8, 126.8, 66.9, 61.4, 33.7.

MS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{23}H_{23}NO_2SNa$ 400.13; Found 400.25.

2–(tritylthio)acetaldehyde

A stirred solution of Weinreb amide (10.0 mmol) in dry THF (50 mL) was cooled to 0 °C. Lithium aluminium hydride (LAH, 11.0 mmol) was added in portions and after 30 minutes 0.2 M $KHSO_4$ (30 mL) was added. The organic compounds were extracted with diethyl ether (3x 30 mL). The combined organic phases were washed with 1 M HCl (3x 10 mL), brine (3x 10 mL) and dried ($MgSO_4$). The solvent was evaporated under reduced pressure and the crude colorless oil was used immediately in the Ugi reaction (analysis was done only by TLC).

yield = 88% (2.7 g), pale yellow oil, R_f 0.25 (EtOAc/ PE, 10:90)

Preparation of Ammonium salt of carboxylate

Ammonium bicarbonate (1.3 mmol) was added to a solution of N-protected amino acid (1.0 mmol) in acetonitrile (10.0 mL) followed by dropwise addition of water (1.0 mL) with rapid stirring. The ammonium salt of carboxylate was precipitated out in 5 min. The stirring is continued for another 5 min and the precipitate was filtered, dried and used for Ugi reaction.

General Procedure for Ugi 4CR. Preparation of Ugi products 5

Aldehyde component (1.3 mmol, 1.3 eq.) was added to a solution of ammonium salt of carboxylate (1.2 eq.) in trifluoroethanol (10 mL) at 0 °C. After stirring for 30 min, isocyanide **4** (387 mg, 1.0 mmol, 1.0 eq.) was added. Small amount of THF (1.0 mL) was added to get a homogeneous solution. The mixture was allowed to stir r.t. for 24 h, the solution was diluted with CH_2Cl_2 (30 mL) and washed with 1 N $KHSO_4$ and sat. $NaHCO_3$ solution. The organic layer was dried over Na_2SO_4 and the solvent was evaporated in vacuo. The crude product was purified by flash column chromatography to afford Ugi products.

"1N $KHSO_4$ solution necessary to decolorize the reaction mixture from dark yellow color to pale yellow and also helps to separate the CH_2Cl_2 layer from the aqueous layer".

Spectroscopic data for compounds 5a–l

Methyl *N*–(((9H–fluoren–9–yl)methoxy)carbonyl)–*L*–valylglycyl–*S*–trityl–*L*–cysteinate, 5a

yield = 48% (0.360 g), white solid, mp: 132–133 °C, R_f 0.32 (EtOAc/ PE, 50:50), $[\alpha]_D^{25}$ = +21.5 (*C*1, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 – 7.19 (m, 23H), 6.52 (br, s, 1H), 6.36 (d, *J* = 8.3 Hz, 1H), 5.38 (br, s, 1H), 4.58 – 4.50 (m, 1H), 4.43 (d, *J* = 7.5 Hz, 2H), 4.23 (t, *J* = 12.5 Hz, 1H), 4.04

(dd, *J* = 7.8, 15.6 Hz, 1H), 3.95 (s, 2H), 3.71 (s, 3H), 2.75 (dd, *J* = 12.1, 9.2 Hz, 1H), 2.69 (dd, *J* = 12.6, 6.3 Hz, 1H), 2.23 – 2.20 (m, 1H), 0.99 (d, *J* = 8.6 Hz, 3H), 0.88 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.0, 171.0, 170.1, 155.8, 144.0, 142.1, 140.7, 129.3, 127.8, 127.5, 126.9, 126.7, 124.9, 119.8, 66.9, 60.8, 56.5, 51.1, 47.0, 42.5, 33.3, 26.2, 18.9, 18.1.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{45}H_{46}N_3O_6S$ 756.3101; Found 756.3100.

Methyl *N*–((benzyloxy)carbonyl)–*L*–alanylglycyl–*S*–trityl–*L*–cysteinate, 5b

yield = 55% (0.351 g), white solid, mp: 115–116 °C, R_f 0.41 (EtOAc/ PE, 50:50), $[\alpha]_D^{25}$ = +62.5 (*C*1, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 – 7.18 (m, 20H), 6.73 (br, s, 1H), 6.44 (br, s, 1H), 5.30 (d, *J* = 7.2 Hz, 1H), 5.15 (s, 2H), 4.51 (ddd, *J* = 7.9, 6.3, 4.7 Hz, 1H), 4.34 – 4.22 (m, 1H), 3.98 (s, 2H), 3.71 (s, 3H), 2.75 (dd, *J* = 12.7, 6.3 Hz, 1H), 2.65 (dd, *J* = 12.6, 4.7 Hz, 1H), 1.40 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.5, 170.7, 168.9, 155.3, 144.2, 136.0, 129.5, 128.6, 128.3, 128.2, 128.1, 127.0, 67.2, 64.1, 52.7, 51.3, 42.8, 28.3, 18.4.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{36}H_{38}N_3O_6S$ 640.2475; Found 640.2472.

Methyl *N*–((benzyloxy)carbonyl)glycylleucyl–*S*–trityl–*L*–cysteinate, 5c

yield = 60% (0.400 g), gummy solid, R_f 0.45 (EtOAc/ PE, 50:50), $[\alpha]_D^{25}$ = +139.1 (*C*1, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$) (major diastereomer) δ 7.48 – 7.17 (m, 20H), 6.55 (d, *J* = 8.5 Hz, 1H), 5.95 (d, *J* = 7.9 Hz, 1H), 5.42 (br, s, 1H), 5.13 (s, 2H), 4.64 (dt, *J* = 7.9, 5.2 Hz, 1H), 4.49 – 4.47 (m, 1H), 3.74 (s, 3H), 3.70 (s, 2H), 2.69 – 2.60 (m, 2H), 1.82 – 1.75 (m, 2H), 1.53 – 1.49 (m, 1H), 0.93 (d, *J* = 7.9, Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) (major diastereomer) δ 171.5, 171.0, 168.9, 156.6, 144.3, 144.2, 136.1, 129.5, 128.6, 128.2, 128.1, 128.1, 128.1, 128.0, 128.0, 127.0, 127.0, 126.9, 126.9, 67.3, 67.0, 57.4, 57.1, 51.1, 44.6, 40.9, 29.1, 24.5, 23.1, 22.2.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{39}H_{44}N_3O_6S$ 682.2945; Found 682.2945.

Methyl *N*–((benzyloxy)carbonyl)–*L*–phenylalanylseryl–*S*–trityl–*L*–cysteinate, 5d

yield = 53% (0.39 g), white solid, mp: 129–132 °C, R_f 0.32 (EtOAc/ PE, 70:30), $[\alpha]_D^{25}$ = +179.5 (*C*1, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) (major diastereomer) δ 7.44 – 7.37 (m, 6H), 7.36 – 7.12 (m, 19H), 7.10 (d, *J* = 6.6 Hz, 1H), 6.98 – 6.92 (m, br, 1H), 5.59 (d, *J* = 7.7 Hz, 1H), 5.03 (s, 2H), 4.51 – 4.31 (m, 3H), 3.90 – 3.80 (br, m, 1H), 3.68 (s, 3H), 3.67 – 3.59 (m, 1H), 3.45 – 3.30 (m, 2H), 3.15 – 2.95 (m, 2H), 2.70 – 2.60 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) (major diastereomer) δ 171.6, 170.8, 169.9, 156.2, 144.5, 136.9, 136.2, 129.5, 129.3, 129.2, 128.7, 128.5, 128.2, 128.1, 128.0, 127.1, 127.0, 126.9, 67.7, 67.1, 62.7, 56.2, 54.0, 52.8, 51.8, 38.5, 33.1.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{43}H_{44}N_3O_7S$ 746.2894; Found 746.2897.

Methyl *N*–((benzyloxy)carbonyl)–*L*–alanylseryl–*S*–trityl–*L*–cysteinate, 5e

yield = 60% (0.41 g), white solid, mp: 141–144 °C, R_f 0.35 (EtOAc/ PE, 70:30), $[\alpha]_D^{25}$ = +75.6 (*C*1, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) (major diastereomer) δ 7.43 – 7.14 (m, 20H), 7.11 (d, *J* = 7.8 Hz, 1H), 6.78 (d, *J* = 7.8 Hz, 1H), 5.68 (d, *J* = 6.8 Hz, 1H), 5.13 (s, 2H), 5.05 (d, *J* = 11.8 Hz, 1H), 4.51 – 4.36 (m, 1H), 4.30 – 4.23 (m, 1H), 4.06 (Br, s, 1H), 3.69 (s, 3H), 3.35 (dd, *J* = 8.3, 5.6 Hz, 2H), 2.75 – 2.70 (m, 1H), 2.65 – 2.61 (m, 1H), 1.40 (d, *J* = 3.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) (major diastereomer) δ 170.8, 170.7, 156.2, 144.2, 136.2, 129.5, 128.5, 128.1, 128.0, 127.1, 126.8, 67.0, 62.4, 56.3, 54.5, 54.4, 52.6, 50.7, 26.3, 18.1.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{37}H_{40}N_3O_7S$ 670.2581; Found 670.2581.

Methyl *N*–((benzyloxy)carbonyl)–*L*–valylseryl–*S*–trityl–*L*–cysteinate, 5f

yield = 52% (0.36 g), white solid, mp: 125–127 °C, R_f 0.41 (EtOAc/ PE, 70:30), $[\alpha]_D^{25}$ = +155.5 (*C*1, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) (major diastereomer) δ 7.49 – 7.18 (m, 20H), 6.81 (d, *J* = 7.8 Hz, 1H), 6.78 (d, *J* = 8.8 Hz, 1H), 5.46 (d, *J* = 8.2 Hz, 1H), 5.16 (s, 2H), 4.74 – 4.63 (m, 1H), 4.49 – 4.33 (m, 2H), 4.23 – 4.16 (m, 1H), 4.15 – 3.88 (m, 1H), 3.71 (s, 3H),3.24 (br, m, 1H), 2.87 – 2.76 (m, 1H), 2.68–2.57 (m, 1H), 2.16 – 2.03 (m, 1H), 0.92 (d, *J* = 11.8, Hz, 3H), 0.85 (d, *J* = 6.8, Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) (major diastereomer) δ 174.6, 173.5, 170.4, 156.7, 144.2, 136.8, 129.5, 128.5, 128.1, 128.0, 127.8, 126.9, 68.1, 66.4, 64.2, 60.4, 56.8, 53.7, 51.7, 33.0, 27.3, 19.7, 17.9.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{39}H_{44}N_3O_7S$ 698.2894; Found 698.2894.

Methyl *N*–(*N*–(((benzyloxy)carbonyl)–*L*–phenylalanyl)–*S*–tritylcysteinyl)–*S*–trityl–L–cysteinate, 5g

yield = 45% (0.45 g), yellow gum, R_f 0.38 (EtOAc/ PE, 30:70), $[\alpha]_D^{25}$ = +155.9 (*C*1, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) (major diastereomer) δ 7.50 – 7.07 (m, 41H), 6.42 (d, *J* = 18.2 Hz, 1H), 6.18 (d, *J* = 6.4 Hz, 1H), 5.04 (s, 2H), 4.38 (dt, *J* = 7.5, 5.6 Hz, 1H), 4.20 (dd, *J* = 7.1, 2.7 Hz, 1H), 4.10 – 4.03 (m, 1H), 3.65 (s, 3H), 3.15 – 2.98 (m, 2H), 2.67 – 2.62 (m, 2H), 2.59 – 2.25 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) (major diastereomer) δ 172.4, 170.5, 155.7, 145.3, 144.2, 136.8, 136.4, 129.6, 129.5, 129.3, 128.9, 128.7, 128.5, 128.3, 128.2, 128.1, 128.0, 126.9, 126.8, 69.0, 67.0, 66.3, 65.8, 53.1, 52.0, 50.6, 38.3, 34.8, 28.7.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{62}H_{58}N_3O_6S_2$ 1004.3761; Found 1004.3761.

Methyl *N*–(*N*–((((9*H*–fluoren–9–yl)methoxy)carbonyl)–*L*–valyl)–*S*–tritylcysteinyl)–*S*–trityl–*L*–cysteinate, 5h

yield = 48% (0.50 g), pale yellow solid, m.p: 113 –116 °C, R_f 0.44 (EtOAc/ PE, 30:70), $[\alpha]_D^{25}$ = -89.3 (*C*1, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) (major diastereomer) δ 7.95 – 7.00 (m, 38H), 6.72 (d, *J* = 7.6 Hz, 1H), 6.33 (d, *J* = 7.5 Hz, 1H), 5.59 (d, *J* = 8.5 Hz, 1H), 4.58 – 4.44 (m, 1H), 4.43 (t, *J* = 6.8 Hz, 1H), 4.25 – 4.19 (m, 1H), 4.17 – 4.08 (m, 3H), 3.62 (s, 3H), 2.77 – 2.68 (m, 1H), 2.66 – 2.55 (m, 3H), 2.54 – 2.48 (m, 1H), 0.89 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 12.2 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) (major diastereomer) δ 171.2, 170.1, 169.3, 156.3, 144.5, 144.2, 143.9, 141.2, 129.5, 129.4, 129.3, 128.1, 128.0, 127.9, 127.6, 127.0, 126.9, 126.7, 125.1, 119.9, 67.8, 66.9, 66.6, 60.3, 60.2, 59.8, 51.4, 47.0, 33.7, 33.3, 31.3, 19.2, 17.7.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{65}H_{62}N_3O_6S_2$ 1044.4074; Found 1044.4075.

Methyl *N*–(*N*–((((9*H*–fluoren–9–yl)methoxy)carbonyl)–*L*–isoleucyl)–*S*–tritylcysteinyl)–*S*–trityl–*L*–cysteinate, 5i

yield = 39% (0.41 g), yellow gum, R_f 0.41 (EtOAc/ PE, 30:70), $[\alpha]_D^{25}$ = +166.9 (*C*1, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) (major diastereomer) δ 7.87 – 7.08 (m, 39H), 6.35 (d, *J* = 7.7 Hz, 1H), 6.17 (d, *J* = 9.4 Hz, 1H), 4.48 – 4.40 (m, 1H), 4.39 – 4.33 (m, 2H), 4.25 (t, *J* = 6.9 Hz, 1H), 4.18 – 4.10 (m, 1H), 4.08 – 3.96 (m, 1H), 3.62 (s, 3H), 2.70 – 2.65 (m, 2H), 2.64 – 2.53 (m, 2H), 1.81 – 1.73 (m, 1H), 1.50 – 1.33 (m, 2H), 0.96 (d, *J* = 12.4 Hz, 3H), 0.88 (t, *J* = 6.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) (major diastereomer) δ 170.1, 170.0, 169.2, 156.0, 144.2, 143.7, 141.3, 129.5, 129.5, 128.1, 128.0, 127.7, 127.1, 126.9, 125.1, 120.0, 67.2, 66.7, 59.7, 52.5, 51.5, 47.1, 37.0, 33.6, 24.7, 15.5, 11.4.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{66}H_{64}N_3O_6S_2$ 1058.4231; Found 1058.4233.

Methyl *N*–(*N*–benzoyl–*N*–benzylglycyl)–*S*–trityl–*L*–cysteinateCompound, 5J

yield = 88% (0.55 g), white solid, mp: 97 – 98 °C, R_f 0.52 (EtOAc/ PE, 30:70).

^{1}H NMR (500 MHz, $CDCl_3$) (major rotamer) δ 7.81 – 7.20 (m, 25H), 5.82 (br, s, 1H), 4.96 – 4.90 (m, 1H), 4.73 (s, 2H)), 4.16 (s, 2H), 3.68 (s, 3H), 2.88 – 2.79 (m, 1H), 2.77 – 2.50 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) (major rotamer) δ 170.5, 170.1, 169.1, 144.7, 136.4, 130.6, 129.9, 127.7, 126.8, 126.5, 126.1, 125.7, 67.3, 59.8, 57.1, 52.5, 51.2, 30.3, 29.4.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{39}H_{37}N_2O_4S$ 629.2468; Found 629.2467.

Methyl *N*–(*N*–benzyl–*N*–(3–phenylpropanoyl)glycyl)–*S*–trityl–*L*–cysteinate, 5k

yield = 91% (0.59 g), white solid, mp: 74–75 °C, R_f 0.35 (EtOAc/ PE, 30:70).

^{1}H NMR (500 MHz, $CDCl_3$) (major rotamer) δ 7.51 – 7.11 (m, 25H), 6.81 (d, J = 8.8 Hz, 1H), 4.66 (s, 2H), 4.59 – 4.50 (m, 1H), 4.11 (s, 2H), 3.69 (s, 3H), 3.22 – 3.88 (m, 2H), 2.68 (t, J = 12.8 Hz, 2H), 2.57 (t, J = 18.6 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) (major rotamer) δ 171.1, 170.5, 168.4, 144.2, 140.9, 135.6, 129.7, 129.5, 129.4, 129.0, 128.8, 128.5, 128.1, 127.9, 126.9, 126.2, 66.8, 52.6, 51.9, 51.2, 49.4, 34.9, 33.3, 31.2.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{41}H_{41}N_2O_4S$ 657.2781; Found 657.2784.

Methyl *N*–(*N*–(4–chlorobenzyl)–*N*–(4–phenylbutanoyl)leucyl)–*S*–trityl–*L*–cysteinate, 5l

yield = 89% (0.67 g), yellow gum, R_f 0.46 (EtOAc/ PE, 30:70), $[\alpha]_D^{25}$ = +79.4 (*C*1, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) (major diastereomer) δ 7.51 – 6.83 (m, 25H), 5.24 – 5.21 (m, 1H), 4.48 (s, 2H), 4.30 – 4.25 (m, 1H), 3.69 (s, 3H), 2.80 – 2.74 (m, 2H), 2.69 – 2.50 (m, 2H), 2.20 – 2.14 (m, 2H), 1.98 – 1.85 (m, 3H), 1.55 – 1.48 (m, 1H), 0.92 (d, *J* = 9.6 Hz, 3H), 0.87 (d, *J* = 12.8 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) (major diastereomer) δ 175.5, 170.8, 170.4, 144.2, 141.2, 136.2, 132.9, 129.5, 128.5, 128.4, 128.0, 127.8, 127.2, 126.8, 126.0, 66.9, 55.4, 52.5, 51.2, 47.8, 36.8, 35.0, 32.9, 26.6, 26.5, 25.1, 22.4, 22.3.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{46}H_{50}ClN_2O_4S$ 761.3174; Found 761.3171.

Methyl *N*-(((9*H*-fluoren-9-yl)methoxy)carbonyl)-L-valylglycyl-S-trityl-D-cysteinate, 5m

yield = 51% (0.57 g), yellow gum, R_f 0.32 (EtOAc/ PE, 50:50), $[\alpha]_D^{25}$ = -22.0 (*C*1, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (dd, *J* = 7.7, 3.3 Hz, 2H), 7.59 (dd, *J* = 13.4, 7.5 Hz, 2H), 7.46 – 7.35 (m, 5H), 7.35 – 7.02 (m, 14H), 6.48 (d, *J* = 8.6 Hz, 1H), 6.30 (d, *J* = 16.0 Hz, 1H), 5.42 (d, *J* = 12.2 Hz, 1H), 4.52 (d, *J* = 6.4 Hz, 2H), 4.41 (dd, *J* = 10.6, 7.4 Hz, 1H), 4.31 (d, *J* = 10.6, 1H), 4.18 (dt, *J* = 15.8, 7.1 Hz, 1H), 4.09 (br, s, 2H), 3.62 (s, 3H), 2.73 (dd, *J* = 12.6, 6.6 Hz, 1H), 2.65 (dd, *J* = 12.6, 4.9 Hz, 1H), 2.20 – 2.11 (m, 1H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.89 (d, *J* = 12.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.2, 170.6, 168.6, 156.7, 144.2, 143.9, 143.8, 141.3, 129.5, 128.2, 127.8, 127.7, 127.1, 126.9, 125.2, 120.0, 119.9, 67.2, 67.0, 60.5, 52.6, 51.5, 47.1, 42.8, 33.6, 31.1, 19.3, 18.0.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{45}H_{51}N_3O_6S$ 756.3101; Found 756.3100.

Methyl *N*-(((9*H*-fluoren-9-yl)methoxy)carbonyl)-D-valylglycyl-S-trityl-L-cysteinate, 5n

yield = 45% (0.49 g), yellow gum, R_f 0.33 (EtOAc/ PE, 50:50), $[\alpha]_D^{25}$ = -36.4 (*C*1, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.7 Hz, 2H), 7.59 (d, *J* = 13.5 Hz, 2H), 7.47 – 7.37 (m, 10H), 7.28 – 7.17 (m, 9H), 6.88 (d, *J* = 7.8 Hz, 1H), 6.55 (d, *J* = 14.2 Hz, 1H), 5.72 (d, *J* = 8.5 Hz, 1H), 4.51 (d, *J* = 6.4 Hz, 2H), 4.34 (dd, *J* = 10.7, 6.9 Hz, 1H), 4.30 (t, *J* = 7.1 Hz, 1H), 4.17 – 4.11 (m, 1H), 4.00 (br, s, 2H), 3.65 (s, 3H), 2.76 (dd, *J* = 12.5, 6.8 Hz, 1H), 2.67 (dd, *J* = 9.5, 3.2 Hz, 1H), 2.17 – 2.10 (m, 1H), 0.96 (d, *J* = 13.9, 3H), 0.88 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.0, 170.5, 168.5, 156.6, 144.2, 143.8, 141.2, 129.5, 128.5, 128.2, 127.7, 127.1, 126.9, 126.6, 125.1, 120.0, 67.1, 66.8, 60.5, 52.7, 51.5, 47.2, 42.8, 33.5, 31.0, 19.3, 17.9.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{45}H_{52}N_3O_6S$ 756.3101; Found 756.3100.

Procedure for entries a-f in Table 2

A solution of Ugi product **5d** (1.0 mmol), in 10 mL of CH_2Cl_2 was maintained at the temperature indicated in the table. After 5 min, the corresponding reagents were added slowly. The reaction mixture was allowed to stir until the starting material was completely consumed (TLC analysis,). The solution was quenched with saturated $NaHCO_3$ and the solution was extracted with CH_2Cl_2 (2 X 10 mL) and the organic layer was separated, dried over $MgSO_4$, filtered and evaporated. The crude product in $CHCl_3$ (10 mL) was treated with activated MnO_2 (10 mmol) and the reaction mixture was refluxed for 3h at 80 °C. The crude reaction mixture was analyzed with SFC-MS.

Procedure for entries g-i in Table 2

A solution of PPh_3O or Ph_2SO (6.0 mmol) in 10 mL of CH_2Cl_2 was cooled to –78 °C, triflic anhydride (3.0 mmol) was added dropwise and stirred at same temperature for 30 min. Pyridine (6.0 mmol) was added to the reaction mixture. A solution of Cys(Trt) amide (1.0 mmol) in 5 mL of CH_2Cl_2 was added and stirred at the indicated temperature in the table. After complete

consumption of the reactant (TLC analysis) the reaction mixture was warmed to r.t. and quenched with saturated solution of $NaHCO_3$. The solution was extracted with CH_2Cl_2 (2 X 10 mL) and the organic layer was separated, dried over $MgSO_4$, filtered and evaporated. The crude product in $CHCl_3$ (10 mL) was treated with activated MnO_2 (10 mmol) and the reaction mixture was refluxed for 3h at 80 °C. The reaction mixture was cooled to r.t. and filtered through a pad of Cellite®. After evaporation of the solvent, the residue was purified by flash chromatography (silica gel, PE/EtOAc) and gave the corresponding azoles.

General Procedure for the optimized synthesis of 1,3 azoles 6a–c and 6j–l

A solution of diphenyl sulfoxide (3.0 mmol) in 10 mL of CH_2Cl_2 cooled to –78 °C, triflic anhydride (1.5 mmol) was added dropwise and stirred at the same temperature for 30 minutes and pyridine (3.0 mmol) was added to the reaction mixture. A solution of Cys(Trt) amide (1.0 mmol) in 5 mL of CH_2Cl_2 was added and stirred for 5h at –78 °C. After complete consumption of the reactant (TLC analysis) the reaction mixture was warmed to r.t. and quenched with saturated solution of $NaHCO_3$. The solution was extracted with CH_2Cl_2 (2 X 10 mL) and the organic layer was separated, dried over $MgSO_4$, filtered and evaporated. The crude product in $CHCl_3$ (10 mL) was treated with activated MnO_2 (10 mmol) and the reaction mixture was refluxed for 3h at 80 °C. The reaction mixture was cool to r.t. and filtered through a pad of Cellite®. After evaporation of the solvent, the residue was purified by flash chromatography (Silica gel, PE/EtOAc) and gave the corresponding azoles.

General Procedure for the synthesis of 6d–i

A solution of diphenyl sulfoxide (6.0 mmol) in 15 mL of CH_2Cl_2 cooled to –78 °C, triflic anhydride (3.5 mmol) was added dropwise and stirred at same temperature for 30 min. Pyridine (6.0 mmol) was added to the reaction mixture. A solution of Cys(Trt) amide (1.0 mmol) in 5 mL

of CH_2Cl_2 was added dropwise and the reaction mixture was stirred for 6 h at –78 °C. After completion of the reaction (TLC analysis) a saturated solution of $NaHCO_3$ was added and extracted with CH_2Cl_2 (2 X 10 mL). The organic layer was separated, dried over $MgSO_4$, filtered and evaporated. The crude product in $CHCl_3$ (10 mL) was treated with activated MnO_2 (10.0 mmol) and the reaction mixture was refluxed for 3h at 80 °C. The reaction mixture was cool to r.t. and filtered through a pad of Cellite®. After evaporation of the solvent, the residue was purified by flash chromatography (Silica gel, PE/EtOAc) and gave the corresponding azoles.

Methyl (*S*)–2–((2–((((9*H*–fluoren–9–yl)methoxy)carbonyl)amino)–3–methylbutanamido)methyl)thiazole–4–carboxylate, 6a

yield = 71% (0.35 g), white solid, mp: 98 – 99 °C, R_f 0.51 (EtOAc/ PE, 40:60), $[\alpha]_D^{25}$ = +7.2 (*C*1, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.78 –7.11 (m, 8H), 5.80 (d, *J* = 12.6 Hz, 1H), 5.72 (d, *J* = 6.0 Hz, 1H), 4.42 (d, *J* = 8.6 Hz, 2H), 4.23 (t, *J* = 12.4, 1H), 4.20 – 4.14 (m, 1H), 4.00 (br, s, 2H), 3.77 (s, 3H), 2.61 – 2.49 (m, 1H), 0.99 (d, *J* = 12.1 Hz, 3H), 0.96 (d, *J* = 3.8 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.5, 164.1, 160.2, 156.4, 143.9, 143.7, 141.3, 127.8, 127.1, 126.3, 125.1, 124.3, 123.7, 120.0, 67.1, 65.4, 51.8, 47.2, 37.4, 31.0, 19.1, 17.5.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{28}N_3O_5S$ 494.1744; Found 494.1747.

Methyl (*S*)–2–((2–(((benzyloxy)carbonyl)amino)propanamido)methyl)thiazole–4–carboxylate, 6b

yield = 80% (0.30 g), white solid, mp: 75 – 76 °C, R_f 0.51 (EtOAc/ PE, 40:60), $[\alpha]_D^{25}$ = +15.5 (*C*1, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.48–7.15 (m, 5H), 6.28 (d, *J* = 12.2 Hz, 1H), 5.81 (d, *J* = 6.8 Hz, 1H), 5.12 (s, 2H), 4.31 (dd, *J* = 3.4, 12.8 Hz, 1H), 4.15 (d, *J* = 8.1 Hz, 2H), 3.78 (s, 3H), 1.40 (d, *J* = 9.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.0, 163.7, 160.6, 156.5, 144.2, 136.1, 129.5, 128.5, 128.2, 128.1, 128.0, 126.9, 67.1, 54.1, 52.7, 43.1, 18.4.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{20}N_3O_5S$ 378.1118; found 378.1118.

Methyl 2–(1–(2–(((benzyloxy)carbonyl)amino)acetamido)–3–methylbutyl)thiazole–4–carboxylate, 6c

yield = 65% (0.27 g), yellow solid, mp: 69–71 °C, R_f 0.43 (EtOAc/ PE, 50:50).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.31 –7.49 (m, 5H), 6.73 (d, *J* = 3.5 Hz, 1H), 6.08 (d, *J* = 5.6 Hz, 1H), 5.15 (s, 2H), 4.10–4.18 (m, 1H), 3.81 (d, *J* = 7.6 Hz, 2H), 3.68 (s, 3H), 1.72 (dt, *J* = 11.6, 5.4, 1.3 Hz, 2H), 1.11–1.25 (m, 1H), 0.92 (d, *J* = 11.4 Hz, 3H), 0.86 (d, *J* = 5.7 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.0, 169.3, 160.8, 155.6, 148.6, 136.4, 130.6, 128.1, 127.9, 127.6, 127.0, 126.6, 66.3, 52.5, 50.0, 43.1, 40.4, 24.3, 22.7, 21.1.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{26}N_3O_5S$ 420.1587; Found 420.1583.

Methyl (*S*)–2–(2–(1–(((benzyloxy)carbonyl)amino)–2–phenylethyl)oxazol–4–yl)thiazole–4–carboxylate, 6d

yield = 45% (0.20 g), white solid, mp: 111–112 °C, R_f 0.33 (EtOAc/ PE, 60:40), $[\alpha]_D^{25}$ = +13.7 (*C*1, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.99 (s, 1H), 7.61–7.32 (m, 1H), 6.91 (br, s, 1H), 5.28 (s, 2H), 5.11–5.03 (m, 1H), 3.79 (s, 3H), 2.65 (dd, *J* = 15.1, 8.6 Hz, 1H), 2.48 (dd, *J* = 22.4, 6.5 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2, 167.9, 167.5, 156.9, 145.7, 140.6, 136.0, 135.7, 129.5, 129.4, 128.7, 128.6, 128.5, 128.3, 128.3, 128.2, 128.0, 127.7, 127.2, 123.8, 121.5, 67.8, 54.8, 50.5, 38.6.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{22}N_3O_5S$ 464.1274; Found 464.1272.

Methyl (*S*)–2–(2–(1–(((benzyloxy)carbonyl)amino)ethyl)oxazol–4–yl)thiazole–4–carboxylate, 6e

yield = 62% (0.24 g), white solid, mp: 85 – 86 °C, R_f 0.33 (EtOAc/ PE, 60:40), $[\alpha]_D^{25}$ = +24.6 (*C*1, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.70 (s, 1H), 7.32– 7.28 (m, 5H), 6.48 (d, *J* = 5.8 Hz, 1H), 5.18 (s, 2H), 4.50–4.46 (m, 1H), 3.80 (s, 3H), 1.48 (d, *J* = 12.6 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 164.6, 160.8, 159.0, 155.8, 144.9, 141.1, 136.0, 128.6, 128.3, 128.2, 128.0, 122.3, 120.7, 67.6, 53.2, 49.5, 18.4.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{18}N_3O_5S$ 388.0961; Found 388.0965.

Methyl (*S*)–2–(2–(1–(((benzyloxy)carbonyl)amino)–2–methylpropyl)oxazol–4–yl)thiazole–4–carboxylate, 6f

yield = 55% (0.22 g), white solid, mp: 69–70 °C, R_f 0.33 (EtOAc/ PE, 60:40), $[\alpha]_D^{25}$ = +32.5 (*C*1, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.79 (s, 1H), 7.51–7.20 (m, 5H), 6.23 (br, s, 1H), 5.15 (s, 2H), 4.48 (dd, *J* = 12.8, 6.5 Hz, 1H), 3.78 (s, 3H), 2.30 – 2.28 (m, 1H), 1.12 (d, *J* = 12.5 Hz, 3H), 0.98 (d, *J* = 5.6 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 161.6, 160.7, 159.5, 153.8, 144.8, 140.6, 136.2, 128.6, 128.5, 128.4, 128.2, 128.1, 127.9, 127.1, 123.8, 122.9, 67.2, 63.8, 50.8, 31.1, 19.1, 19.0, 17.4.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{22}N_3O_5S$ 416.1274; Found 416.1272.

Methyl (*S*)–2'–(1–(((benzyloxy)carbonyl)amino)–2–phenylethyl)–[2,4'–bithiazole]–4–carboxylate, 6g

yield = 49% (0.23 g), pale yellow gum, R_f 0.33 (EtOAc/ PE, 60:40), $[\alpha]_D^{25}$ = +14.8 (*C*1, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.98 (s, 1H), 7.51 – 7.10 (m, 10H), 5.61 (d, *J* = 8.4 Hz, 1H), 5.11 (s, 2H), 4.80–4.71 (m, 1H), 3.75 (s, 3H), 3.25 (dd, *J* = 9.8, 2.5 Hz, 1H), 3.18 (dd, *J* = 22.4, 18.1 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.3, 163.7, 162.0, 156.3, 146.4, 145.3, 140.0, 136.1, 129.9, 129.7, 129.2, 128.5, 128.3, 128.1, 128.0, 127.0, 126.5, 120.5, 112.7, 67.6, 58.8, 50.6, 37.8.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{22}N_3O_4S_2$ 480.1046; Found 480.1046.

Methyl (*S*)–2'–(1–((((9*H*–fluoren–9–yl)methoxy)carbonyl)amino)–2–methylpropyl)–[2,4'–bithiazole]–4–carboxylate, 6h

yield = 64% (0.33 g), white solid, mp: 107 –108 °C, R_f 0.25 (EtOAc/ PE, 50:50), $[\alpha]_D^{25}$ = +22.6 (*C*1, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.79 (s, 1H), 7.63 – 7.10 (m, 8H), 6.18 (br, s, 1H), 4.49 (d, *J* = 4.5 Hz, 2H), 4.48 –4.30 (m, 1H), 4.23 (t, *J* = 11.4 Hz, 1H), 3.80 (s, 3H), 2.32 – 2.24 (m, 1H), 1.01 (d, *J* = 8.9 Hz, 3H), 0.98 (d, *J* = 15.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.8, 163.7, 160.8, 156.4, 149.2, 145.8, 143.9, 143.7, 141.3, 129.7, 127.8, 127.1, 126.1, 125.5, 125.1, 122.8, 120.0, 120.0, 117.0, 67.2, 63.8, 52.5, 47.2, 31.1, 19.1, 17.5.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{27}H_{26}N_3O_4S_2$ 520.1359; Found 520.1358.

Methyl 2'–((1*S*,2*S*)–1–((((9*H*–fluoren–9–yl)methoxy)carbonyl)amino)–2–methylbutyl)–[2,4'–bithiazole]–4–carboxylate, 6i

yield = 56% (0.29 g), white solid, mp: 114 – 115 °C, R_f 0.30 (EtOAc/ PE, 50:50), $[\alpha]_D^{25}$ = +7.9 (*C*1, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.76 (s, 1H), 7.63 – 7.02 (m, 8H), 6.28 (d, *J* = 9.4 Hz, 1H), 4.49 (d, *J* = 13.5 Hz, 2H), 4.46 – 4.38 (m, 1H), 4.26 (t, *J* = 11.1 Hz, 1H), 3.79 (s, 3H), 1.61–1.49 (m, 1H), 1.25 (dt, *J* = 22.1, 18.5, 11.6 Hz, 2H), 1.01 – 0.91 (m, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2, 163.7, 160.8, 155.8, 149.8, 148.5, 143.8, 143.7, 141.3, 135.5, 129.4, 128.7, 127.8, 127.3, 127.1, 125.1, 125.0, 123.7, 120.0, 114.5, 67.1, 54.6, 50.5, 47.1, 37.7, 22.9, 14.9, 11.9.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{28}H_{28}N_3O_4S_2$ 534.1515; Found 534.1512.

Methyl 2–((*N*–benzylbenzamido)methyl)thiazole–4–carboxylate, 6j

yield = 76% (0.27 g), white solid, mp: 101–102 °C, R_f 0.38 (EtOAc/ PE, 50:50).

^{1}H NMR at 38 ˚C (500 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.58 – 7.07 (m, 10H), 4.98 (s, 2H), 4.59 (s, 2H), 3.90 (s, 3H).

^{13}C NMR ^{1}H NMR at 38 ˚C (126 MHz, $CDCl_3$) δ 172.2, 167.4, 161.4, 145.9, 135.7, 134.9, 130.2, 129.4, 129.3, 128.9, 128.7, 128.6, 128.5, 128.0, 127.8, 127.6, 126.9, 52.9, 52.4, 46.6.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{19}N_2O_3S$ 367.1110; Found 367.1115.

Methyl 2–((*N*–benzyl–3–phenylpropanamido)methyl)thiazole–4–carboxylate, 6k

yield = 73% (0.28 g), white solid, mp: 89–91 °C, R_f 0.41 (EtOAc/ PE, 50:50).

^{1}H NMR (500 MHz, $CDCl_3$) (major rotamer) δ 8.25 (s, 1H), 7.74 – 7.05 (m, 10H), 4.85 (s, 2H), 4.53 (s, 2H), 3.81 (s, 3H), 3.11 (t, *J* = 8.9 Hz, 2H), 2.74 (t, *J* = 16.8 Hz, 2H).

^{1}H NMR (500 MHz, $CDCl_3$) (minor rotamer) δ 8.21 (s, 0.2 H), 7.74 – 7.05 (m, 3 H), 4.74 (s, 0.7H), 4.61 (0.5 H), 3.83 (s, 0.8 H), 3.15 –3.13 (m, 0.4 H), 2.76–2.74 (m, 0.5H).

^{13}C NMR (126 MHz, $CDCl_3$) (major rotamer) δ 31.4, 34.7, 47.4, 51.2, 52.4, 126.2, 127.5, 127.8, 127.9, 128.4, 128.8, 129.3, 135.6, 140.1,145.5, 147.4, 161.4, 168.5, 173.3.

^{13}C NMR (126 MHz, $CDCl_3$) (minor rotamer) δ 31.2, 35.0, 48.6, 49.4, 52.5, 126.1, 126.8, 127.5, 128.5, 129.3, 136.4, 140.7, 147.5, 161.5, 169.5, 172.5.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{23}N_2O_3S$ 395.1423; Found 395.1424.

Methyl 2–(1–(*N*–(4–chlorobenzyl)–4–phenylbutanamido)–3–methylbutyl)thiazole–4–carboxylate, 6l

yield = 79% (0.39 g), white solid, mp: 121 – 122 °C, R_f 0.52 (EtOAc/ PE, 50:50).

^{1}H NMR (500 MHz, $CDCl_3$) (maior rotamer) δ 8.10 (s, 1H), 7.45 – 6.78 (m, 10H), 5.97 (t, *J* = 7.7 Hz, 1H), 4.53 (s, 2H), 3.92 (s, 3H), 2.62 (t, *J* = 7.5 Hz, 2H), 2.26 (t, *J* = 14.8 Hz, 2H), 2.16 – 1.99 (m, 2H), 1.93 – 1.85 (m, 2H), 1.55–1.51 (m, 1H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) (major rotamer) δ 174.0, 169.9, 161.7, 146.1, 141.4, 137.2, 132.9, 129.5, 128.8, 128.5, 128.4, 128.3, 128.1, 127.4, 127.0, 57.6, 52.5, 48.1, 45.8, 40.4, 35.2, 33.1, 26.6, 24.5, 22.4, 22.1.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{27}H_{32}ClN_2O_3S$ 499.1816; Found 499.1817.

Methyl (S)-2-(((S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3methyl butanamido) methyl)-4,5-dihydrothiazole-4-carboxylate, 7a

yield = 82% (0.31g), yellow gum, R_f 0.25 (EtOAc/ PE, 60:40), $[\alpha]_D^{25}$ = -98.9 (*C*1, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 – 7.11 (m, 8H), 7.03 – 6.90 (m, 1H), 5.57 (d, *J* = 8.4 Hz, 1H), 4.84 (dt, *J* = 8.2, 4.4 Hz, 1H), 4.49 – 4.33 (m, 2H), 4.27 – 4.14 (m, 1H), 4.10 – 3.92 (m, 2H), 3.72 (s, 3H), 2.95 (dd, *J* = 9.1, 4.5 Hz, 2H), 2.25 – 2.07 (m, 1H), 0.94 (dt, *J* = 26.7, 6.8 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 178.1, 176.2, 170.1, 156.6, 143.8, 141.3, 127.8, 127.1, 125.1, 120.0, 74.7, 67.1, 60.7, 52.8, 47.3, 43.5, 35.5, 29.6, 19.3, 18.1.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{30}N_3O_5S$ 496.1900; Found 496.1904.

methyl (R)-2-(((S)-2-(((benzyloxy)carbonyl)amino)propanamido)methyl)-4,5-dihydrothiazole-4-carboxylate, 7b

yield = 82% (0.24 g), yellow gum, R_f 0.28 (EtOAc/ PE, 60:40), $[\alpha]_D^{25}$ = + 9.8 (*C*1, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.18 (m, 5H), 5.91 (d, *J* = 7.2 Hz, 1H), 5.17 (s, 2H), 5.06 (d, *J* = 11.7 Hz, 1H), 4.85 (dt, *J* = 7.8, 4.7 Hz, 1H), 4.32 (d, *J* = 6.8 Hz, 2H), 3.73 (s, 3H), 3.01 – 2.90 (m, 2H), 1.39 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 177.0, 176.7, 170.0, 154.1, 136.0, 129.4, 128.5, 128.4, 128.2, 128.1, 74.3, 67.0, 54.0, 51.4, 43.0, 33.5, 18.8, 18.3.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{22}N_3O_5S$ 380.1274; Found 380.1271.

ASSOCIATED CONTENT

Supporting Information

^{1}H-NMR, ^{13}C-NMR spectra, HRMS, SFC-HPLC chromatogram (PDF) and X-ray crystal details of **5a** and **5b** (cif) are available free of charge on the ACS publication websites

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