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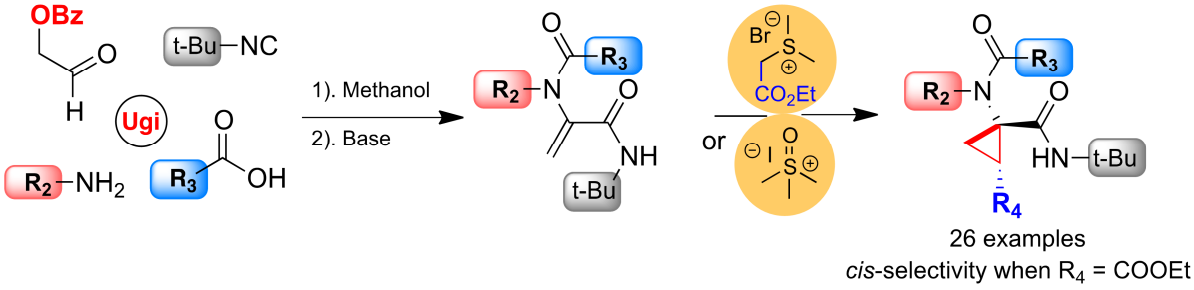

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Diversity-oriented synthesis of cyclopropyl peptides from Ugi-derived dehydroalanines

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ABSTRACT

A three-step synthesis of cyclopropyl peptides is reported. The protocol involves a consecutive Ugi-4CR/elimination reaction to prepare dehydroalanines followed by a Corey-Chaykovsky cyclopropanation reaction. Peptide-like molecules that resemble some pharmacologically active compounds with a variety of substituents in the cyclopropane ring were prepared. When (2-ethoxy-2-oxoethyl) dimethyl sulfonium ylide was used the reaction exclusively gives the cis-diastereoisomer cyclopropanes in good yields from readily prepared starting materials. A collection of 26 highly substituted cyclopropyl peptides were obtained.

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Cyclopropyl amino acids and peptides are important synthetic targets, some of which display significant pharmacological properties. Leading examples are eglumegad **1** (Figure 1) that offers significant potential for the treatment of anxiety disorders[1] and MK-0686 **2** that shows considerable promise for the treatment of chronic pain;[2] indeed, both molecules are currently in clinical trials. Additionally, belactosin A (**3**) is a natural product that shows significant antitumor effects and contains a cyclopropyl peptide framework.[3] Interestingly, the parent scaffold 1-aminocyclopropanecarboxylic acid (ACC) **4** possesses herbicidal activity and influences plant growth by itself.[4] Besides, ACC and their derivatives are the expected starting materials for the synthesis of a variety of biologically active cyclopropyl peptides through step-wise long peptide coupling reactions.[5] It is worth mentioning that the presence of the cyclopropyl ring into a peptide backbone could increase stability against metabolic degradation, as well as restriction of conformational flexibility.[6] Therefore, the development of practical methodologies for the rapid construction of libraries of peptide-like molecules containing a cyclopropane ring is highly desirable. In this context, approaches for the synthesis of cyclopropyl peptidomimetics involving dehydroalanine derivatives include the use of Corey-Chaykovsky cyclopropanation conditions, in which α,β-dehydrolactone adducts,[7] didehydroalanine methyl esters,[8] or Cbz-protected enones[9] are reacted with sulfur ylides.

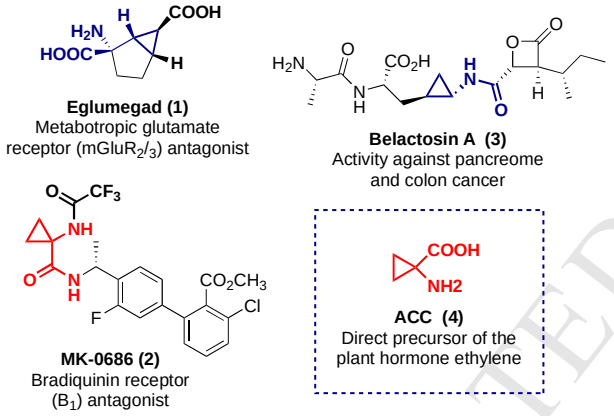


Figure 1. Biologically active cyclopropyl peptides.

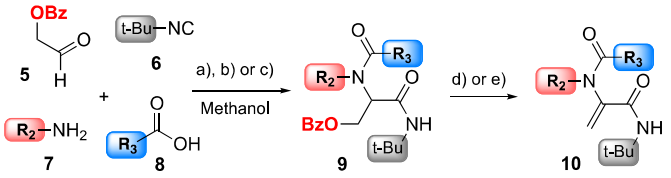
On the other hand, the 1,3-cycloaddition of diazo compounds to dehydroamino acid derivatives has also been used to synthesize cyclopropane amino acids. Diazomethane or diazoalkanes react with a dehydroamino acid derivative to furnish a pyrazoline, followed by extrusion of nitrogen gas which produces a cyclopropane. Chiral 1,4-oxazinones,[10] chiral azlactone,[11] chiral diketopiperazine,[12] dehydroamino acid acetonide,[13] and didehydroalanine methyl esters[8] have been used. However, diazo compounds exhibit high toxicity and are potentially explosive, which limits their utility.[14] Some reports have solved this problem by generating diazo compounds *in situ* from the corresponding tosylhydrazone salt.[15] Catalytic system involving tosylhydrazone salts, rhodium tetraacetate, and chiral sulfides to generate cyclopropanate α-amino acrylates has also been reported.[16] It is worth noting that in most of these methods the amide links are created through classic reagents and using time-consuming step-wise peptide coupling protocols.

The Ugi four component reaction (4-CR) is a process in which a dipeptide backbone is straightforwardly created using a single experimental setup, starting from an amine, a carboxylic acid, a carbonyl compound and an isonitrile.[17] Remarkably, when this reaction is combined with subsequent post-condensation reactions, libraries of chemically diverse peptide-like scaffolds can be rapidly assembled in a few reaction steps. Along this line, we have shown that diversely substituted dehydroalanines scaffolds could be accessed in a modular fashion through an Ugi-4CR followed by an elimination process, from readily accessible starting materials.[18] Based on this work, we envisioned that the application of a cyclopropanation reaction to these later Ugi-derived dehydroalanines might compile an attractive three-step protocol for the rapid construction of a library of cyclopropyl peptides. At the outset, it was clear that such a protocol might allow access to highly substituted cyclopropyl peptides, just by taking advantage of the three diversification vectors produced by the variation of the isonitrile, amine, and carboxylic acid in the original four-component set of the Ugi reaction (Table 1). Thus, in the present work, dehydroalanines obtained by an Ugi/elimination protocol were cyclopropanated using Corey-Chaykovsky conditions to construct a small cyclopropyl peptide library. This report is part of our ongoing work toward the development of novel applications of Ugi-derived dehydroalanines.[19]

Accordingly, our work commenced with the synthesis of a collection of differently substituted dehydroalanines using the previously reported Ugi-4C microwave-assisted reaction between the benzoyloxyacetaldehyde **5** with *tert*-butyl isonitrile **6** and various primary amines **7** and carboxylic acids **8**. Benzoyloxyacetaldehyde **5** was used as the aldehyde in the four-component input set in all Ugi reactions because the benzoyl group is essential to shape the dehydroalanine double bond in the elimination step. Due to its accessibility, we chose the *tert*-butyl isocyanide **6** for this study, although one cyclohexyl derivative was also utilized in the further cyclopropanation process (see Table 2, **11r**). As shown in Table 1, all the Ugi adducts were obtained in moderate to good yields, just by mixing the four components in methanol under microwave irradiation at 100 ºC for 2-3 h. As some decomposition of the product was observed in some experiments, selected examples were performed at 50 ºC, giving similar results, but with a cleaner profile (verified only by TLC). We also observed that the reaction can be carried out in refluxing methanol with similar yields, although over a longer reaction time (12 h).

With Ugi adducts **9a-q** in hand, the elimination process was implemented employing KOH as the base and tetrabutylammonium iodide (TBAI) as a phase transfer catalyst. Under these conditions, dehydroalanines **10a-q** were obtained in moderate to good yields (Table 1). In some cases, heating to 50 °C was required to accelerate the reaction (entries 3 and 5-17). As expected, using the (*S*)-(−)-α-methylbenzylamine as the amine input in the Ugi reaction (entry 8) gave an inseparable diastereomeric mixture of **9h** (1.7:1). However, this issue was inconsequential since one chiral center was further removed after the elimination process (**10h**), a reaction which unexpectedly gave only 11% yield. Similarly, a low yield of the dehydroalanine **10s** was observed in the elimination step when isopropylamine was used (**9s**, exp. 18). Furthermore, when bulkier *tert*-butylamine was used in the Ugi adduct **9t**, its total decomposition was observed under the elimination conditions and the dehydroalanine **10t** was not observed (Table 1, exp 19). These observations suggest that a bulky amine vector is deleterious to the efficiency of the elimination process (dehydroalanines **10h**, **10s**, **10t**).

Table 1. Synthesis of dehydroalanines.

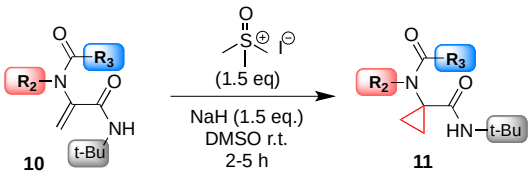


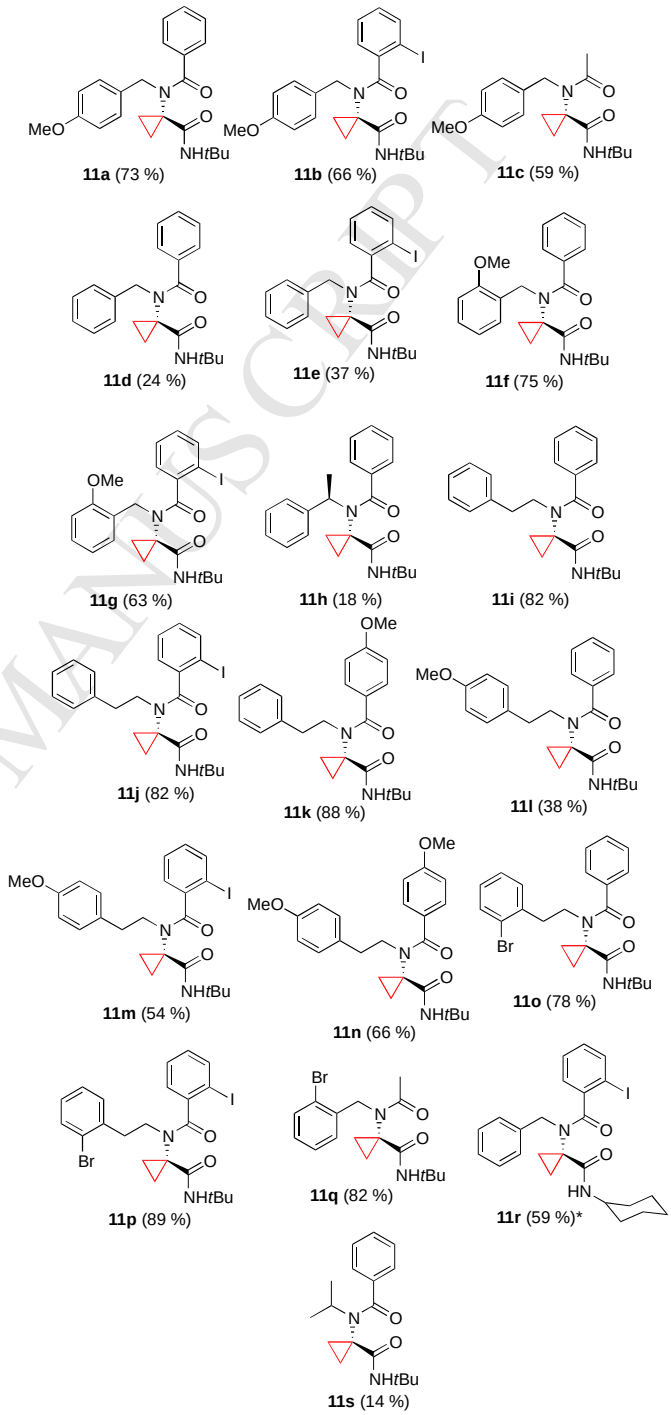
exp	R_2	R_3	Product yield (%)[f]	
1	4-MeO-Bn-	Ph-	**9a** (83)[a]	**10a** (73)[d]
2	4-MeO-Bn-	2-I-Ph-	**9b** (74)[a]	**10b** (60)[d]
3	4-MeO-Bn-	CH_3-	**9c** (56)[a]	**10c** (71)[e]
4	Bn-	Ph-	**9d** (32)[b]	**10d** (81)[d]
5	Bn-	2-I-Ph-	**9e** (49)[b]	**10e** (65)[e]
6	2-MeO-Bn-	Ph-	**9f** (63)[b]	**10f** (23)[e]
7	2-MeO-Bn-	2-I-Ph-	**9g** (69)[c]	**10g** (43)[e]
8		Ph-	**9h** (41)[c] (d.r. 1.7:1)	**10h** (11)[e]
9	Ph-CH_2-CH_2-	Ph-	**9i** (35)[c]	**10i** (67)[e]
10	Ph-CH_2-CH_2-	2-I-Ph-	**9j** (69)[c]	**10j** (87)[e]
11	Ph-CH_2-CH_2-	4-MeO-Ph-	**9k** (47)[c]	**10k** (67)[e]
12	4-MeO-Ph-CH_2-CH_2-	Ph-	**9l** (84)[c]	**10l** (74)[e]
13	4-MeO-Ph-CH_2-CH_2-	2-I-Ph-	**9m** (68)[c]	**10m** (80)[e]
14	4-MeO-Ph-$(CH_2)_2$-	4-MeO-Ph	**9n** (32)[c]	**10n** (53)[e]
15	2-Br-Ph-$(CH_2)_2$-	Ph-	**9o** (56)[c]	**10o** (78)[e]
16	2-Br-Ph-$(CH_2)_2$-	2-I-Ph-	**9p** (44)[c]	**10p** (84)[e]
17	2-Br-Bn-	CH_3-	**9q** (39)[c]	**10q** (68)[e]
18	*i*Pr-	Ph-	**9s** (72)[c]	**10s** (35)[d]
19	*t*Bu-	Ph-	**9t** (38)[e]	**10t** (0)[d]

Conditions: a) MeOH, 50 °C, MW. b) 100 °C, MW. c) reflux, MeOH. d) KOH, 50%, TBAI, C_6H_6:H_2O, 1:1, r.t., or e) 50 °C.

f) Isolated yield after column chromatography.

Table 2. Synthesis of unsubstitued cyclopropanes





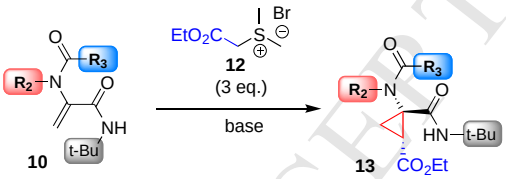
*See supporting information. Isolated yields after column chromatography.

The next task involved defining suitable conditions to carry out the cyclopropanation process. Fortunately, cyclopropane **11a** was easily obtained under Corey-Chaykovsky modified conditions applied to dehydroalanine **10a**.[20] Commercially available trimethylsulfoxonium iodide proved to be an efficient ylide source, and sodium hydride was used as the base; the reactions proceeded smoothly in anhydrous DMSO. Then we

prepared a series of cyclopropanes using dehydroalanines **10** (Table 2). In all cases, a slight excess of trimethylsulfoxonium iodide and sodium hydride were required to ensure the complete consumption of dehydroalanines **10**. Under these conditions, regular to good yields were obtained in general, except for the cyclopropanes **11h** and **11s** which were obtained in low yields, probably by the influence of the bulky amine moiety (*vide supra*). It is worth noting that cyclopropane **11r**, bearing a cyclohexyl moiety (from cyclohexylisocyanide, obtained previously by our group),[19a] was also obtained, demonstrating that dehydroalanines derived from a different isocyanide source can be cyclopropanated with good results.

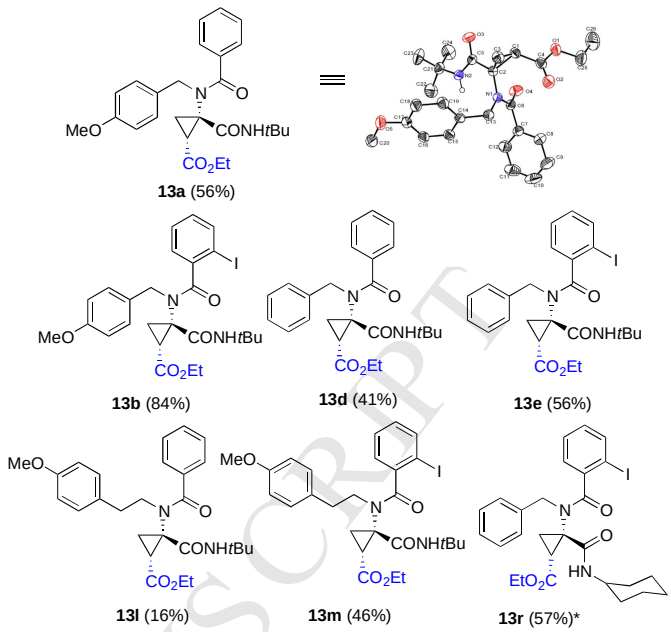
To extend the scope of the protocol, then we envisioned the variation of the ylide source to obtain three-substituted cyclopropanes. Thus, readily accessible (2-ethoxy-2-oxoethyl) dimethylsulfonium bromide **12** was tested as the ylide precursor and its sulfonium ylide was generated *in situ* under basic conditions from **12**. A short screening was carried out to optimize the process using dehydroalanine **10a** as a model substrate (Table 3). Under standard conditions, in which DMF was used as solvent, no conversion of dehydroalanine **10a** was observed (entries 1, 2). Likewise, solvents such as 1,2-DCE and chloroform (entries 3, 4) gave low yields. A slight increase in the yield was observed when a THF/chloroform mixture was used (entry 5), but the best yield was obtained using anhydrous THF and sodium hydride as the base (entry 7, 8). Potassium *tert*-butoxide gave poor results when used as the base in the same solvent (entry 6). Heating to reflux was necesary to shorten the reaction time and to improve the yield. Three equivalents of the sulfonium bromide and the base were required to reach complete consumption of starting material. Under these optimized conditions, cyclopropane **13a** was obtained in 56% yield (entry 8). Notably, exclusively *cis* diastereomer **13a** (with the *N*-benzylbenzamido group as reference)[21] was isolated after flash column chromatography and unambiguously characterized by single crystal X-Ray analysis (Table 4) and ^{1}H RMN spectroscopy.

Table 3. Optimization screening to obtain **13a**.



entry	solvent	base (eq.)	T (°C)	time (h)	yield (%)
1	DMF	NaH (3)	25	24	n.r
2	DMF	*t*BuOK (3)	25	48	n.r
3	1,2 DCE	DBU (2)	reflux	24	3
4	$CHCl_3$	DBU (1.5)	25	144	17
5	THF/$CHCl_3$ 1:1	NaH (2)	25	24	30
6	THF	*t*BuOK (3)	reflux	8	9
7	THF	NaH (3)	25	24	51
8	THF	NaH (3)	reflux	14	**56**

Table 4. Synthesis of substitued cyclopropanes.



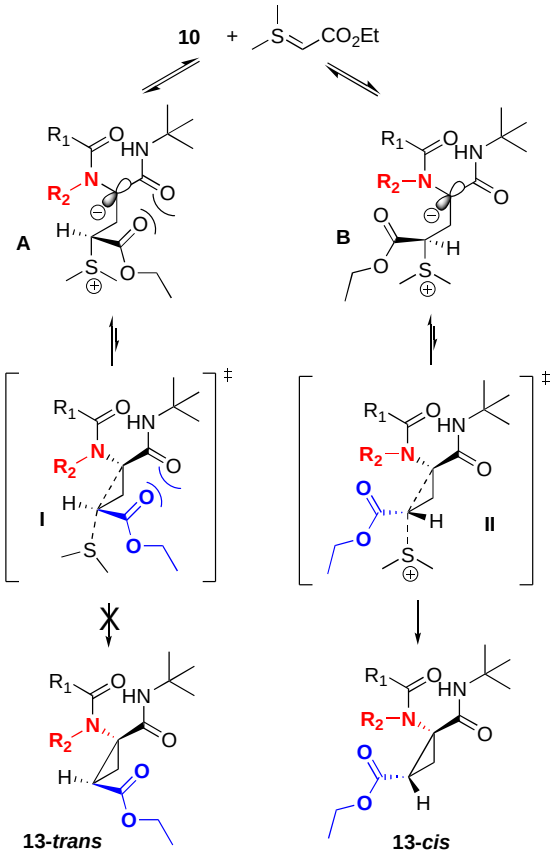
*See supporting information. Isolated yields after column chromatography.

Then, selected dehydroalanines **10** were submitted to the optimized conditions to obtain a series of seven three-substituted cyclopropyl peptides **13a-r** (Table 4). In general, moderate to good yields were obtained in the cyclopropanation process. It should be noted that higher temperatures and longer times were required to carry out cyclopropanation using sulfonium bromide **12** in comparison with cyclopropanation using trimethylsulfoxonium iodide. As expected, all further examples showed *cis* diastereoselectivity, as verified by the X-ray analysis of **13d**, **13e**, and **13m**.[22] Interestingly, dehydroalanines **10f, 10g**, **10h** and **10s** were unreactive under these conditions (see **11f, g, h, s** for reference). Apparently, the presence of a methyl or *o*-methoxy group near the double bond of the dehydroalanine moiety, exerts a certain steric hindrance for the ylide approximation, although this is only a speculation and the actual effect remains unknown.

Diastereoselectivity can be rationalized in the following way: the sulfonium ylide could react with dehydroalanine **10** in two orientations, generating the zwitterionic intermediates **A** or **B** (Scheme 1). Then, unfavorable dipole-dipole interaction between ester and amide carbonyl groups in transition state **I** of the cyclopropanation step might be expected to prevent the formation of th *trans*-diastereoisomer. Conversely, in the transition state **II** this interaction is avoided, and might be responsible for the exclusively observed *cis* diastereoselectivity. Interestingly, in the transition sate **II** the carbonyl group of the ester faces the amine moiety, an interaction that might be responsible for the failure of the cyclopropanation process in dehydroalanines **10f, g**, **h, s** which bear relatively bulkier residues as the R2 substituent.

In summary, a practical linear three-step synthesis of highly substituted cyclopropanes using the sequence Ugi-4CR/elimination/Corey-Chaykovsky reaction is reported. Using this strategy, a series of 1,1-two- substituted and 1,1,2-*cis*-three-substituted cyclopropanes were synthesized. The substitution pattern of the cyclopropanes could be diversely tuned in the multicomponent Ugi reaction and then in the Corey-Chaykovsky cyclopropanation process. Due to the important pharmacological properties of the peptidomimetic cyclopropanes, we believe that

this protocol might be useful for the synthesis of libraries of such scaffolds in medicinal chemistry programs.



Scheme 1. Rationalization of the *cis* selectivity

1. Experimental section

1.1 General methods.

Unless otherwise noted, all reagents were obtained commercially and used without further purification. ^{1}H and ^{13}C spectra were recorded on Jeol Eclipse-300 MHz, Bruker Avance III-400 MHz and Varian Unity Inova-500 MHz model spectrometers. Mass spectra were recorded on a Jeol JMS-700 spectrometer or on a Jeol JMS-T100LC spectrometer. Infrared spectra were obtained with a Bruker Tensor 27 FT-IR spectrometer. Optical rotation was measured on Perkin Elmer Model 343 polarimeter with sodium lamp. Column chromatography was performed with silica gel (200-300 mesh).

General procedures for the synthesis of Ugi adducts **9**.

For method A and method B: In a microwave tube under argon, 2-oxoethyl benzoate **5** (0.98 g, 6 mmol, 1.5 eq.) was dissolved in 14 mL of methanol. Then amine **7** (4 mmol, 1 eq.) was added and stirred for five minutes, and then carboxylic acid **8** (4 mmol, 1 eq.) was added. After five minutes, t-butyl isocyanide **6** (0.46 mL, 4 mmol, 1 eq.) was added and stirred for 5 minutes. The tube was sealed with a pressure cap and heated to 50 °C (Method A) or 100 °C (Method B) for 3 h, under microwave irradiation in a Biotage Initiator+ microwave reactor. After cooling to room temperature, the organic solvent was removed under vacuum to get a crude oil which was purified by flash chromatography eluting with a hexane/ethyl acetate solvent system.

For method C. In a round-bottom flask under argon atmosphere, 2-oxoethyl benzoate **5** (0.98 g, 6 mmol, 1.5 eq.) was dissolved in 14 mL of methanol. Then amine **7** (4 mmol, 1 eq.) was added and stirred to room temperature for fifteen minutes, and then carboxylic acid **8** (4 mmol, 1 eq.) was added. After stirring fifteen minutes, t-butyl isocyanide **6** (0.46 mL, 4 mmol, 1 eq.) was added and stirred for fifteen minutes. Heating to reflux was started and maintained for 12 h. After cooling to room temperature, the organic solvent was removed under vacuum to get a crude oil which was purified by flash column chromatography eluting with a hexane/ethyl acetate solvent system.

See supporting information for characterization details of the Ugi adducts.

General procedure for the synthesis of dehydroalanines **10**.

In a round-bottom flask under argon, the Ugi adduct **9** (1.35 mmol, 1 eq.) was taken in 11 mL of benzene, then tetrabutylammonium iodide (0.15 g, 0.4 mmol, 0.3 eq.) was added. Later, 11 mL of 50% aqueous KOH solution were added, and the mixture was stirred at room temperature (Method D) or with heating to 50 °C (Method E) until the starting material was consumed. Benzene was removed under vacuum, and the product was extracted with 10 mL of dichloromethane(3x10ml). The combined dichloromethane extracts were dried over sodium sulfate and concentrated under vacuum to furnish a brown oil. The residue was purified by flash column chromatography on silica gel eluting with hexane/ethyl acetate solvent system.

_N_-(3-(*tert*-butylamino)-3-oxoprop-1-en-2-yl)-_N_-(4-methoxybenzyl)benzamide (10a).

Ugi adduct **9a** (1.0 eq.) was reacted with KOH solution according to the general procedure *(Method D)* stirring for 3.5 hours. The resulting oil was purified by flash column chromatography eluting with a hexane/ethyl acetate (7:3) solvent system to provide **10a** as a light yellow solid (73%) Mp: 82-84 °C. ^{1}HNMR ($CDCl_3$, 400 MHz, 25 °C) δ = 1.03 (s, 9H), 3.79 (s, 3H), 4.90 (s, 2H), 5.24 (s, 2H), 5.88 (s, 1H), 6.87 (d, *J* = 8.7 Hz, 2H), 7.20-7.42 (m, 5H), 7.47-7.60 (m, 2H); ^{13}C NMR ($CDCl_3$,100 MHz) δ = 28.1, 51.1, 52.8, 55.3, 114.2, 128.0, 128.5, 129.3, 130.3, 130.5, 135.4, 145.0, 159.4, 162.8, 170.6; IR (Sol $CHCl_3$) 789, 1237, 1512, 1607, 1663, 3065 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{22}H_{27}N_2O_3$ $[M+H]^+$ 367.2021, found 367.2024.

_N_-(3-(*tert*-butylamino)-3-oxoprop-1-en-2-yl)-2-iodo-_N_-(4-methoxybenzyl)benzamide (10b).

Ugi adduct **9b** (1.0 eq.) was reacted with KOH solution according to the general procedure *(Method D)* stirring for 4 hours. The resulting oil was purified by flash column chromatography eluting with a hexane/ethyl acetate (7:3) solvent system to provide **10b** as a yellow solid (60%) Mp: 81-86 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ = 1.03 (s, 2H), 1.17 (s, 6H)*, 1.33 (s, 1H), 3.80 (s, 3H), 4.90 (s, 2H), 5.34 (s, 1H), 5.45 (s, 1H), 5.82 (s, 1H), 6.85- 6.90 (m, 2H), 7.22-7.77 (m, 5H), 7.74-7.76 (m, 1H) (*Rotamers can be observed at 25°C); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 28.0, 28.3, 51.1, 51.4, 51.6, 52.8, 55.3, 94.1, 114.1, 114.2, 121.5, 127.6, 127.9, 128.0, 128.4, 128.9, 129.3, 130.2, 130.4, 130.5, 130.8, 135.4, 139.3, 141.3, 142.6, 145.0, 159.4, 159.5, 162.5, 169.7; IR (Sol $CHCl_3$) 1626, 1664, 2968, 3269 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{22}H_{26}I_1N_2O_3$ $[M+H]^+$ 493.0988, found 493.0997.

***N*-*tert*-butyl-2-(*N*-(4-methoxybenzyl)acetamido)acrylamide (10c).**

Ugi adduct **9c** (1.0 eq.) was reacted with KOH solution according to the general procedure *(Method E)* stirring for 1.5 hours. The resulting oil was purified by flash column chromatography eluting with a hexane/ethyl acetate (65:35) solvent system to provide **10c** as a light orange solid (71%) Mp: 99-101 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ = 1.14 (s, 9H), 2.00 (s, 3H), 3.79 (s, 3H), 4.69 (s, 2H), 5.40 (s, 2H), 6.37 (s, 1H), 6.86 (d, *J* = 8.7 Hz, 2H), 7.28 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 22.2, 28.1, 51.1, 51.9, 55.2, 114.3, 122.4, 129.2, 130.6, 143.8, 159.5, 162.2, 170.3; IR (Sol $CHCl_3$) 1621, 1667, 2965, 3351 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{17}H_{25}N_2O_3$ $[M+H]^+$ 305.1865, found 305.1868.

***N*-benzyl-*N*-(3-(*tert*-butylamino)-3-oxoprop-1-en-2-yl)benzamide (10d).**

Ugi adduct **9d** (1.0 eq.) was reacted with KOH solution according to the general procedure *(Method D)* stirring for 24 hours. The resulting oil was purified by flash column chromatography eluting with a hexane/ethyl acetate (7:3) solvent system to provide **10d** as a colorless solid (81%) Mp: 55-59 °C. ^{1}H RMN ($CDCl_3$, 300 MHz, 25 °C) δ = 1.01 (s, 9H), 4.97 (s, 2H), 5.26 (s, 2H), 5.86 (br, 1H), 7.29-7.46 (m, 8H), 7.55-7.59 (m, 2H); ^{13}C RMN ($CDCl_3$, 75 MHz) δ = 28.1, 51.3, 53.6, 128.1, 128.2, 128.6, 128.9, 129.0, 130.8, 135.4, 137.3, 145.3, 162.9, 177.7. IR (Sol $CHCl_3$) 1613, 1664, 2974, 3353 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{21}H_{25}N_2O_2$ $[M+H]^+$ 337.1916, found 337.1917.

***N*-benzyl-*N*-(3-(*tert*-butylamino)-3-oxoprop-1-en-2-yl)-2-iodobenzamide (10e).**

Ugi adduct **9e** (1.0 eq.) was reacted with KOH solution according to the general procedure *(Method E)* stirring for 21 hours. The resulting oil was purified by flash column chromatography eluting with a hexane/ethyl acetate (7:3) solvent system to provide **10e** as a yellow solid (65 %) Mp: 104-107 °. ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ = 1.15 (s, 9H), 4.93 (s, 2H), 5.42 (s, 2H), 5.74 (s, 1H), 6.75-7.44 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 28.3, 51.4, 52.0, 94.2, 121.1, 127.6, 128.0, 128.0, 128.8, 129.3, 130.4, 136.8, 139.3, 141.2, 142.6, 162.6, 169.7; IR (Sol $CHCl_3$) 730, 1188,1619, 1664, 2970, 3332 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{21}H_{24}I_1N_2O_2$ $[M+H]^+$ 463.0882, found 463.0871.

***N*-(3-(*tert*-butylamino)-3-oxoprop-1-en-2-yl)-*N*-(2-methoxybenzyl)benzamide (10f).**

Ugi adduct **9f** (1.0 eq.) was reacted with KOH solution according to the general procedure *(Method E)* stirring for 55 hours. The resulting oil was purified by flash column chromatography eluting with a hexane/ethyl acetate (8:2) solvent system to provide **10f** as a light yellow solid (23 %) Mp: 95-98 °C. ^{1}HNMR ($CDCl_3$, 400 MHz, 25 °C) δ = 1.07 (s, 9H), 3.79 (s, 3H), 5.02 (s, 2H), 5.20 (s, 1H), 5.59 (s, 1H), 5.85 (s, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 6.96 (td, *J* = 7.5, 1.0 Hz, 1H), 7.24-7.41 (m, 4H), 7.48 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.53-7.60 (m, 2H); ^{13}C NMR($CDCl_3$, 100 MHz) δ = 28.1, 47.8, 51.0, 55.4, 110.6, 120.9, 125.0, 127.2, 128.0, 128.3, 129.1, 130.3, 130.5, 135.7, 144.7, 157.5, 162.8, 170.8; IR (Sol $CHCl_3$) 753, 1240, 1608, 1664, 2962, 3344 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{22}H_{27}N_2O_3$ $[M+H]^+$ 367.2021, found 367.2013.

***N*-(3-(*tert*-butylamino)-3-oxoprop-1-en-2-yl)-2-iodo-*N*-(2-methoxybenzyl)benzamide (10g).**

Ugi adduct **9g** (1.0 eq.) was reacted with KOH solution according to the general procedure *(Method E)* stirring for 5.5 hours. The resulting oil was purified by flash column chromatography eluting with a hexane/ethyl acetate (7:3) solvent system to provide **10g** as a white solid (43 %) Mp: 108-110°C. ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ =1.17 (s, 9H), 3.81 (s, 3H), 5.05 (s, 2H), 5.49 (s, 1H), 5.59 (s, 1H), 5.87 (s, 1H), 6.83-7.02 (m, 3H), 7.20-7.32 (m, 3H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR($CDCl_3$, 100 MHz) δ = 28.3, 46.2, 51.2, 55.6, 94.1, 110.7, 121.0, 121.2, 124.6, 127.5, 128.0, 129.5, 130.3, 131.7, 139.4, 141.4, 142.5, 157.8, 162.4, 169.8; IR (Sol $CHCl_3$) 742, 1404, 1616, 1664, 2978, 3349 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{22}H_{26}I_1N_2O_3$ $[M+H]^+$ 493.0988, found 493.0998.

(*R*)-*N*-(3-(*tert*-butylamino)-3-oxoprop-1-en-2-yl)-*N*-(1-phenylethyl)benzamide (10h).

Ugi adduct **9h** (1.0 eq.) was reacted with KOH solution according to the general procedure *(Method E)* stirring for 2.5 hours. The resulting oil was purified by flash column chromatography eluting with a hexane/ethyl acetate (7:3) solvent system to provide **10h** as a yellow oil (11 %). $[\alpha]_D^{25}$ = -0.47 (c = 0.63, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ =0.99 (s, 9H), 1.67 (d, *J* = 7.1 Hz, 3H), 5.19 (br, 2H), 6.16 (br, 1H), 7.15-7.40 (m, 6H), 7.40-7.62 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ =27.9, 28.5, 51.0, 54.2, 126.8, 128.0, 128.2, 128.5, 128.7, 128.8, 129.6, 130.2, 133.2, 136.2, 163.0, 171.0; IR (Sol $CHCl_3$) 697, 1612, 1667, 2969, 3341 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{22}H_{27}N_2O_2$ $[M+H]^+$ 351.2072, found 351.2079.

***N*-(3-(*tert*-butylamino)-3-oxoprop-1-en-2-yl)-*N*-phenethylbenzamide (10i).**

Ugi adduct **9i** (1.0 eq.) was reacted with KOH solution according to the general procedure *(Method E)* stirring for 4 hours. The resulting oil was purified by flash column chromatography eluting with a hexane/ethyl acetate (7:3) solvent system to provide **10i** as a light yellow solid (67 %) Mp: 117-120°C. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ =1.16 (s, 4H)*, 1.39 (s, 5H), 2.94 (t, *J* = 6.9 Hz, 1H), 3.01-3.09 (m, 1H), 3.73 (td, *J* = 6.9, 5.9 Hz, 1H), 3.86-3.98 (m, 1H), 5.01 (s, 0.5H)*, 5.50 (s, 0.5H), 5.69 (d, *J* = 0.8 Hz, 0.5H)*, 6.13 (s, 0.5H), 6.81 (s, 0.5H), 7.19-7.57 (m, 9H), 7.69 (dd, *J* = 8.3, 1.4 Hz, 1H) (*Rotamers can be observed at 25°C); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 23.9, 28.2, 33.7, 35.7, 41.1, 51.2, 51.4, 51.5, 126.5, 126.7, 128.1, 128.3, 128.5, 128.6, 128.7, 128.8, 128.9, 130.5, 131.3, 134.6, 135.6, 138.7, 138.8, 145.3, 159.3, 163.1, 163.2, 167.4, 170.8; IR (Sol $CHCl_3$) 694, 1312, 1518, 1632, 2931, 2972, 3332 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{22}H_{27}N_2O_2$ $[M+H]^+$ 351.2072, found 351.2068.

***N*-(3-(*tert*-butylamino)-3-oxoprop-1-en-2-yl)-2-iodo-*N*-phenethylbenzamide (10j).**

Ugi adduct **9j** (1.0 eq.) was reacted with KOH solution according to the general procedure *(Method E)* stirring for 7 hours. The resulting oil was purified by flash column chromatography eluting with a hexane/ethyl acetate (7:3) solvent system to provide **10j** as a white solid (87 %) Mp: 117-119°C. ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ = 1.29 (s, 5H)*, 1.38 (s, 2H), 1.43 (s, 2H), 2.97 (t, *J* = 6.9 Hz, 0.5H), 3.09 (t, *J* = 7.8 Hz, 1H), 3.51 (s, 0.5H), 3.69-3.79 (m, 0.5H), 3.71- 3.77 (m, 0.5H), 3.91 (s, 1H), 5.41 (s, 0.5H), 5.56 (s, 1H), 5.73 (s, 0.5H), 6.75-7.47 (m, 8H), 7.81 (dd, *J* = 20.4, 7.9 Hz, 1H) (*Rotamers can be observed at 25°C); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 23.9, 28.2, 28.5, 28.7, 33.7, 35.4, 41.1, 49.7, 51.7, 92.4, 94.2, 126.5, 126.6, 127.4, 127.7, 128.1, 128.1, 128.3, 128.6, 128.7, 128.8, 129.0, 130.3, 130.7, 131.0, 138.4, 139.4, 139.8, 141.5, 143.0, 162.7, 169.9; IR (Sol $CHCl_3$) 499, 646, 696, 744, 1010, 1191, 1321, 1394, 1449, 1514, 1618, 1643, 1674, 2962, 3024, 3060, 3348 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{22}H_{26}I_1N_2O_2$ $[M+H]^+$ 477.1038, found 477.1035.

***N*-(3-(*tert*-butylamino)-3-oxoprop-1-en-2-yl)-4-methoxy-*N*-phenethylbenzamide (10k).**

Ugi adduct **9k** (1.0 eq.) was reacted with KOH solution according to the general procedure *(Method E)* stirring for 5 hours. The resulting oil was purified by flash column chromatography eluting with a hexane/ethyl acetate (7:3) solvent system to provide **10k** as a white solid (67 %) Mp: 142-145 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ = 1.17 (s, 6H), 1.38 (s, 3H)*, 2.93 (t, *J* = 6.9 Hz, 1H), 3.00-3.11 (m, 1H), 3.66-3.73 (m, 1H), 3.81 (s, 2H), 3.83 (s, 1H)*, 3.88-3.97 (m, 1H), 5.02 (s, 1H), 5.53 (s, 1H), 5.72 (d, *J* = 0.7 Hz, 1H), 6.83 (d, *J* = 9.0 Hz, 1H), 6.89 (d, *J* = 9.0 Hz, 1H), 7.21-7.37 (m, 5H), 7.52 (d, *J* = 9.0 Hz, 1H), 7.66 (d, *J* = 9.0 Hz, 1H) (*Rotamers can be observed at 25°C); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 23.9, 28.2, 28.3, 33.7, 35.8, 41.0, 51.2, 51.4, 51.6, 55.3, 113.3, 113.7, 115.9, 120.0, 126.5, 126.9, 127.8, 128.5, 128.6, 128.7, 128.8, 129.0, 130.4, 138.8, 139.0, 145.6, 159.3, 161.5, 162.1, 163.3, 166.9, 170.4; IR (Sol $CHCl_3$) 698, 1254, 1520, 1617, 2967, 3317 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{23}H_{29}N_2O_3$ $[M+H]^+$ 381.2178, found 381.2160.

***N*-(3-(*tert*-butylamino)-3-oxoprop-1-en-2-yl)-*N*-(4-methoxyphenethyl)benzamide (10l).**

Ugi adduct **9l** (1.0 eq.) was reacted with KOH solution according to the general procedure *(Method E)* stirring for 3.5 hours. The resulting oil was purified by flash column chromatography eluting with a hexane/ethyl acetate (7:3) solvent system to provide **10l** as a light yellow solid (74 %) Mp: 105-108°C. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ = 1.16 (s, 9H), 2.84-3.15 (m, 2H), 3.79 (s, 3H), 3.82-3.98 (m, 2H), 5.02 (s, 1H), 5.53 (s, 1H), 5.69 (d, *J* = 0.7 Hz, 1H), 6.85 (d, *J* = 8.7 Hz, 2H), 7.17 (d, *J* = 8.5 Hz, 2H), 7.36 (dd, *J* = 13.0, 7.1 Hz, 3H), 7.51 (dd, *J* = 8.1, 1.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 28.2, 28.5, 29.6, 32.7, 51.4, 51.6, 55.2, 114.0, 116.3, 126.8, 128.1, 128.3, 128.5, 129.7, 129.9, 130.4, 130.6, 131.3, 135.6, 145.2, 158.2, 163.2, 170.8; IR (Sol $CHCl_3$) = 702, 1240, 1612, 1664, 2966, 3337 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{23}H_{29}N_2O_3$ $[M+H]^+$ 381.2178, found 381.2167.

***N*-(3-(*tert*-butylamino)-3-oxoprop-1-en-2-yl)-2-iodo-*N*-(4-methoxyphenethyl)benzamide (10m).**

Ugi adduct **9m** (1.0 eq.) was reacted with KOH solution according to the general procedure *(Method E)* stirring for 3.5 hours. The resulting oil was purified by flash column chromatography eluting with a hexane/ethyl acetate (7:3) solvent system to provide **10m** as a light yellow solid (80 %) Mp: 162-164°C. ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ = 1.29 (s, 9H), 3.02 (t, *J* = 7.8 Hz, 2H), 3.79 (s, 3H), 3.87 (br, 2H), 5.42 (s, 1H), 5.59 (s, 1H), 5.75 (s, 1H), 6.63-6.92 (m, 3H), 7.10-7.33 (m, 4H), 7.72-7.82 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 28.5, 32.7, 49.9, 51.7, 55.2, 94.1, 114.0, 117.1, 120.1, 127.7, 129.6, 129.9, 130.3, 139.4, 141.5, 142.9, 158.3, 162.6, 169.9; IR (Sol $CHCl_3$) = 702, 1032, 1240,1335, 1612, 1664, 2924, 2966, 3337 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{23}H_{28}I_1N_2O_3$ $[M+H]^+$ 507.1144, found 507.1151.

***N*-(3-(*tert*-butylamino)-3-oxoprop-1-en-2-yl)-4-methoxy-*N*-(4-methoxyphenethyl)benzamide (10n).**

Ugi adduct **9n** (1.0 eq.) was reacted with KOH solution according to the general procedure *(Method E)* stirring for 5 hours. The resulting oil was purified by flash column chromatography eluting with a hexane/ethyl acetate (7:3) solvent system to provide **10n** as a white solid (53 %) Mp: 126-128°C. ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ = 1.17 (s, 4H), 1.38 (s, 5H)*, 2.86 (t, *J* = 6.9 Hz, 1H), 2.92-3.01 (m, 1H), 3.62-3.70 (m, 1H), 3.78-3.81 (m, 4H)*, 3.83 (s, 2H), 3.85-3.92 (m, 1H), 5.02 (s, 1H), 5.73 (d, *J* = 0.5 Hz, 1H), 6.05 (s, 1H), 6.72- 6.94 (m, 4H), 7.07-7.21 (m, 2H), 7.52 (d, *J* = 8.9 Hz, 1H), 7.66 (d, *J* = 8.9 Hz, 1H) (*Rotamers can be observed at 25°C); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 23.9, 28.2, 28.3, 32.8, 34.8, 41.2, 51.2, 51.3, 51.7, 55.2, 55.3, 113.3, 113.7, 114.0, 114.1, 115.9, 127.0, 127.8, 128.5, 129.7, 129.9, 130.4, 130.7, 130.9, 158.3, 159.3, 161.5, 162.1, 163.3, 166.9, 170.4; IR (Sol $CHCl_3$) = 83, 1031, 1245,1510, 1604, 1663, 2925, 2966, 3330 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{24}H_{31}N_2O_4$ $[M+H]^+$ 411.2283, found 411.2285.

***N*-(2-bromophenethyl)-*N*-(3-(*tert*-butylamino)-3-oxoprop-1-en-2-yl)benzamide (10o).**

Ugi adduct **9o** (1.0 eq.) was reacted with KOH solution according to the general procedure *(Method E)* stirring for 5 hours. The resulting oil was purified by flash column chromatography eluting with a hexane/ethyl acetate (7:3) solvent system to provide **10o** as a colorless solid (78 %) Mp: 127-130 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ = 1.20 (s, 9H), 3.10-3.36 (m, 2H), 3.81-4.04 (m, 2H), 5.02 (s, 1H), 5.55 (s, 1H), 5.51 (s, 1H), 7.10 (td, *J* = 7.8, 1.8 Hz, 1H), 7.18-7.45 (m, 5H), 7.54 (dd, *J* = 6.9, 1.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 28.4, 34.2, 49.6, 51.5, 115.8, 124.6, 127.7, 128.1, 128.3, 130.5, 131.4, 132.8, 135.6, 138.2, 145.5, 163.4, 171.0; IR (Sol $CHCl_3$) = 664, 719, 761, 1520, 1623, 1639, 1923, 2956, 3332 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{22}H_{26}{}^{79}Br_1N_2O_2$ $[M+H]^+$ 429.1177, found 429.1180.

***N*-(2-bromophenethyl)-*N*-(3-(*tert*-butylamino)-3-oxoprop-1-en-2-yl)-2-iodobenzamide (10p).**

Ugi adduct **9p** (1.0 eq.) was reacted with KOH solution according to the general procedure *(Method E)* stirring for 5.5 hours. The resulting oil was purified by flash column chromatography eluting with a hexane/ethyl acetate (8:2) solvent system to provide **10p** as a light yellow solid (84 %) Mp: 158-160 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ = 1.30 (s, 5H)*, 1.38 (s, 1H), 1.44 (s, 3H), 2.92-3.25 (m, 2H), 3.47-3.99 (m, 2H), 5.25-5.76 (m, 2H), 5.89-6.19 (m, 1H), 6.98-7.63 (m, 7H), 7.70-7.89 (m, 1H) (*Rotamers can be observed at 25°C); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 28.2, 28.6, 28.7, 34.1, 35.1, 35.6, 39.7, 47.8, 50.2, 51.7, 94.2, 116.3, 119.3, 124.6, 127.7, 127.9, 128.1, 128.1, 128.4, 130.4, 130.6, 131.0, 131.1, 131.5, 132.8, 132.9, 133.0, 137.8, 139.0, 139.4, 139.9, 141.4, 143.2, 162.8, 170.0; IR (Sol $CHCl_3$) = 665, 735, 920, 1323, 1405, 1527, 1627, 1662, 2868, 2961, 3332 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{22}H_{25}{}^{79}Br_1I_1N_2O_2$ $[M+H]^+$ 555.0144, found 555.0141.

2-(*N*-(2-bromobenzyl)acetamido)-*N*-*tert*-butylacrylamide (10q).

Ugi adduct **9q** (1.0 eq.) was reacted with KOH solution according to the general procedure *(Method E)* stirring for 5 hours. The resulting oil was purified by flash column chromatography eluting with a hexane/ethyl acetate (6:4) solvent system to provide **10q** as yellow solid (68 %) Mp: 70-73 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ = 1.19 (s, 9H), 2.06 (s, 3H), 4.94 (s, 2H), 5.47 (s, 1H), 5.68 (s, 1H), 6.37 (s, 1H), 7.18 (td, *J* = 7.7, 1.8 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.39-7.46 (m, 1H), 7.56 (dd, *J* = 7.9, 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 22.3, 28.3, 51.5, 100.0, 122.7, 124.7, 128.1, 129.8, 132.2, 133.1, 136.0, 143.5, 162.2, 170.8; IR (Sol $CHCl_3$) = 746, 1206, 1231, 1391, 1535, 1627, 1664, 2924, 2970, 3306 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{16}H_{22}{}^{79}Br_1N_2O_2$ $[M+H]^+$ 353.0864, found 353.0853.

***N*-benzyl-*N*-(3-(cyclohexylamino)-3-oxoprop-1-en-2-yl)-2-iodobenzamide (10r).**

This compound was prepared according to the method reported by Miranda.[2] Spectral data matched well with previously reported.

***N*-(3-(*tert*-butylamino)-3-oxoprop-1-en-2-yl)-*N*-isopropylbenzamide (10s).** Purified by flash column chromatography eluting with a hexane/ethyl acetate (7:3) solvent system to provide **10s** as pale yellow solid (35%), M.p. 63-66 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ = 1.28-1.31 (m, 15H), 4.63-4.67 (m, 1H), 5.27 (s, 1H), 5.84 (br, 1H), 6.06 (s, 1H), 7.28-7.36 (m, 3H), 7.45-7.48 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 20.4, 28.4, 49.7, 51.4, 99.9, 121.5, 127.8, 128.0, 129.9, 136.5, 141.9, 163.6, 171.0; IR (thin film) 713, 792, 1128, 1245, 1365, 1453, 1527, 1618, 1670, 2929, 2971, 3333, 3436 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{17}H_{25}N_2O_2$ $[M+H]^+$ 289.19160, found 289.19156.

General procedure for the synthesis of cyclopropanes **11** *with trimethylsulfoxonium iodide.*

In a round-bottom flask under argon, dehydroalanine **10** (0.15 mmol, 1 eq.) was taken in 3 mL of dry DMSO. Then trimethylsulfoxonium iodide (52 mg, 0.23 mmol, 1.5 eq.) and NaH 60% (9 mg, 0.23 mmol, 1.5 eq.) were added and the reaction mixture was stirred at room temperature until the starting material was consumed. The reaction was quenched with 5 mL of water and extracted with 5 mL of ethyl acetate for three times; the combined organic extracts were dried over sodium sulfate and concentrated under vacuum to furnish a brown oil. This material was purified by flash column chromatography on silica gel eluting with hexane/ethyl acetate solvent system.

***N*-(1-(*tert*-butylcarbamoyl)cyclopropyl)-*N*-(4-methoxybenzyl)benzamide (11a).**

Dehydroalanine **10a** (1 eq.) was reacted with trimethyl sulfoxonium iodide and NaH 60 % according to the general procedure, stirring for 2 hours. The resulting oil was purified by flash column chromatography eluting with a hexane/ethyl acetate (6:4) solvent system to provide **11a** as a yellow oil (73 %). ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ = 1.42 (s, 9H), 1.70-2.48 (m, 2H), 2.97-3.65 (m, 2H), 3.79 (s, 3H), 3.89-4.27 (m, 1H), 4.35 – 4.69 (m, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 7.07-7.75 (m, 7H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 22.9, 27.4, 42.7, 54.0, 55.3, 59.6, 114.1, 127.0, 128.4, 129.0, 129.7, 136.1, 159.0, 171.3, 171.9; IR (Sol $CHCl_3$) = 720, 1038, 1248, 1399, 1516, 1630, 1656, 2931, 2964, 3322 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{23}H_{29}N_2O_3$ $[M+H]^+$ 381.2178, found 381.2166.

***N*-(1-(*tert*-butylcarbamoyl)cyclopropyl)-2-iodo-*N*-(4-methoxybenzyl)benzamide (11b).**

Dehydroalanine **10b** (1 eq.) was reacted with trimethyl sulfoxonium iodide and NaH 60 % according to the general procedure, stirring for 2 hours. The resulting oil was purified by flash column chromatography eluting with a hexane/ethyl acetate (6:4) solvent system to provide **11b** as a yellow oil (66 %). ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ = 1.26 (s, 1H), 1.35 (s, 2H), 1.42 (s, 6H)*, 1.81-2.48 (m, 2H), 3.02-3.37 (m, 1H), 3.50-3.70 (m, 1H), 3.79 (d, 3H)*, 3.86-4.68 (m, 3H), 6.76-6.92 (m, 2H), 6.99-7.91 (m, 6H) (*Rotamers can be observed at 25°C); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 14.1, 21.0, 22.3, 22.9, 23.5, 27.3, 27.4, 29.6, 41.6, 42.9, 46.1, 54.0, 54.4, 54.7, 55.2, 59.2, 59.6, 60.3, 61.7, 92.1, 92.5, 113.7, 114.0, 126.9, 127.7, 127.9, 128.2, 128.4, 128.4, 128.8, 129.1, 129.3, 129.7, 130.1, 130.1, 130.4, 139.0, 141.7, 142.3, 158.7, 159.1, 170.2, 170.8, 172.0; IR (Sol $CHCl_3$) = 727, 1244, 1638, 1685, 2240, 2927, 2960, 3056 cm^{-1}. HRMS (ESI+) *m/z* calcd for $C_{23}H_{28}I_1N_2O_3$ $[M+H]^+$ 507.1144, found 507.1146.

***N*-*tert*-butyl-1-(*N*-(4-methoxybenzyl)acetamido)cyclopropanecarboxamide (11c).**

Dehydroalanine **10c** (1 eq.) was reacted with trimethylsulfoxonium iodide and NaH 60% according to the general procedure, stirring for 2 hours. The resulting oil was purified by flash column chromatography eluting with ethyl acetate solvent to provide **11c** as a clear oil (59 %). ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ = 1.39 (s, 9H), 1.88-2.10 (m, 2H), 2.12 (s, 3H), 3.21-3.30 (m, 1H), 3.45 (td, *J* = 9.4, 2.8 Hz, 1H), 3.81 (s, 3H), 4.53 (q, *J* = 17.0 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 7.19 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 22.2, 23.2, 27.4, 42.3, 52.0, 54.4, 55.3, 59.4, 113.8, 127.7, 129.2, 159.0, 171.3, 171.6; IR (Sol $CHCl_3$) = 728, 1030, 1243, 1289, 1407, 1644, 1685, 2965, 3461 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{18}H_{27}N_2O_3$ $[M+H]^+$ 319.2021, found 319.2011.

***N*-benzyl-*N*-(1-(*tert*-butylcarbamoyl)cyclopropyl)benzamide (11d).**

Dehydroalanine **10d** (1 eq.) was reacted with trimethylsulfoxonium iodide and NaH 60% according to the general procedure, stirring for 5 hours. The resulting oil was purified by flash column chromatography eluting with a hexane/ethyl acetate (8:2→7:3) solvent system to provide **11d** as a cloudy oil (24 %). ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ = 1.42 (s, 9H), 2.05-2.17 (m, 2H), 3.08-3.69 (m, 2H), 3.91-4.22 (m, 1H), 4.47-4.83 (m, 2H), 7.28 -7.59 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 22.9, 27.4, 42.7, 54.6, 59.8, 127.0, 127.5, 128.4, 128.8, 129.8, 136.0, 137.3, 171.2, 172.2; IR (Sol $CHCl_3$) = 697, 732, 1287, 1400, 1646, 1684, 2922, 2970, 3057 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{22}H_{27}N_2O_2$ $[M+H]^+$ 351.2072, found 351.2070.

***N*-benzyl-*N*-(1-(*tert*-butylcarbamoyl)cyclopropyl)-2-iodobenzamide (11e).**

Dehydroalanine **10e** (1 eq.) was reacted with trimethylsulfoxonium iodide and NaH 60% according to the general procedure, stirring for 2 hour. The resulting oil was purified by flash column chromatography eluting with a hexane/ethyl acetate (6:4) solvent system to provide **11e** as a yellow solid (37 %) Mp: 47-50 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, 25 °C) δ = 1.35 (s, 2H), 1.42 (s, 7H)*, 1.80-2.45 (m, 2H), 3.05-3.64 (m, 2H), 3.87-4.54 (m, 2H), 6.98-7.10 (m, 1H), 7.18-7.59 (m, 7H), 7.77-7.86 (m, 1H) (*Rotamers can be observed at 25°C); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 22.4, 23.7, 27.4, 27.5, 41.7, 42.9, 46.9, 54.6, 59.5, 61.8, 92.2, 92.5, 127.0, 127.7, 127.8, 127.9, 128.2, 128.4, 128.5, 128.7, 129.0, 130.2, 130.2, 139.1, 151.7, 170.8; IR (Sol $CHCl_3$) = 697, 1290, 1407, 1640, 1686, 2922, 2956 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{22}H_{26}I_1N_2O_2$ $[M+H]^+$ 477.1038, found 477.1033.

***N*-(1-(*tert*-butylcarbamoyl)cyclopropyl)-*N*-(2-methoxybenzyl)benzamide (11f).**

Dehydroalanine **10f** (1 eq.) was reacted with trimethylsulfoxonium iodide and NaH 60% according to the general procedure, stirring for 2 hour. The resulting oil was purified by flash column chromatography eluting with a hexane/ethyl acetate (6:4) solvent system to provide **11f** as a pale yellow solid (75 %) Mp: 124-126°C. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ = 1.42 (s, 9H), 1.86-2.17 (m, 2H), 3.22-3.57 (m, 2H), 3.72 (s, 3H), 4.61 (q, *J* = 16.6 Hz, 2H), 6.79-7.01 (m, 2H), 7.24-7.62 (m, 7H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 14.3, 21.1, 22.7, 27.5, 42.8, 50.7, 54.4, 55.1, 60.0, 60.4, 110.1, 120.7, 125.4, 127.3, 128.2, 128.8, 128.9, 129.8, 136.4, 157.4, 171.4, 172.4; IR (Sol $CHCl_3$) = 723, 1235, 1398, 1633, 1686, 2933, 2967 cm^{-1};

HRMS (ESI+) *m/z* calcd for $C_{23}H_{29}N_2O_3$ $[M+H]^+$ 381.2178, found 381.2195.

***N*-(1-(*tert*-butylcarbamoyl)cyclopropyl)-2-iodo-*N*-(2-methoxybenzyl)benzamide (11g).**

Dehydroalanine **10g** (1 eq.) was reacted with trimethylsulfoxonium iodide and NaH 60% according to the general procedure, stirring for 3.5 hours. The resulting oil was purified by flash column chromatography eluting with a hexane/ethyl acetate (65:35) solvent system to provide **11g** as a white solid (63 %) Mp: 143-147 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ = 1.33 (s, 3H), 1.42 (s, 6H)*, 2.13 (s, 0H), 1.82-2.20 (m, 2H), 3.05-3.64 (m, 2H), 3.73 (s, 2H)*, 3.84 (s, 1H), 3.97-4.52 (m, 3H), 6.76-7.10 (m, 3H), 7.20-7.43 (m, 3H), 7.59-7.89 (m, 2H) (*Rotamers can be observed at 25°C); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 22.5, 23.3, 27.3, 29.6, 41.2, 41.6, 42.9, 49.1, 54.3, 54.5, 55.0, 59.8, 61.7, 92.1, 92.8, 109.8, 120.4, 120.6, 124.2, 126.2, 127.6, 127.8, 127.9, 128.4, 128.6, 128.7, 129.1, 130.0, 138.9, 141.6, 142.4, 156.2, 156.9, 170.4, 170.8, 172.0; IR (Sol $CHCl_3$) = 751, 1239, 1399, 1644, 1681, 2926, 2961 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{23}H_{28}I_1N_2O_3$ $[M+H]^+$ 507.1144, found 507.1148.

(*R*)-*N*-(1-(*tert*-butylcarbamoyl)cyclopropyl)-*N*-(1-phenylethyl)benzamide (11h).

Dehydroalanine **10h** (1 eq) was reacted with trimethylsulfoxonium iodide and NaH 60% according to the general procedure, stirring for 2 hours. The resulting oil was purified by flash column chromatography eluting with a hexane/ethyl acetate (7:3) solvent system to provide **11h** as a clear oil (18 %). $[\alpha]_D^{25}$ = +93.86 (c = 0.57, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ = 1.39 (s, 9H), 1.42-1.61 (m, 1H), 1.69 (d, *J* = 6.9 Hz, 3H), 1.97-2.18 (m, 1H), 3.20 (td, *J* = 8.9, 6.1 Hz, 1H), 3.56 (td, *J* = 10.0, 9.2, 6.2 Hz, 2H), 5.05 (q, *J* = 6.7 Hz, 1H), 7.22-7.44 (m, 8H), 7.50-7.57 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 17.7, 22.8, 27.4, 43.0, 54.4, 56.3, 56.9, 126.4, 127.3, 127.4, 127.8, 128.7, 129.4, 136.9, 171.5; IR (Sol $CHCl_3$) = 698, 728, 1289, 1427, 1632, 1688, 2238, 2927, 2973, 3059 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{23}H_{29}N_2O_2$ $[M+H]^+$ 365.2229, found 365.2232.

***N*-(1-(*tert*-butylcarbamoyl)cyclopropyl)-*N*-phenethylbenzamide (11i).**

Dehydroalanine **10i** (1 eq.) was reacted with trimethylsulfoxonium iodide and NaH 60% according to the general procedure, stirring for 2 hours. The resulting oil was purified by flash column chromatography eluting with a hexane/ethyl acetate (6:4) solvent system to provide **11i** as a yellow oil (82 %). ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ = 1.37-1.44 (m, 9H)*, 1.69-2.25 (m, 2H), 2.82-3.65 (m, 6H), 4.27-4.41 (m, 1H), 6.91 (br, 1H), 7.20-7.51 (m, 9H) (*Rotamers can be observed at 25°C); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 23.1, 23.3, 27.3, 34.3, 36.3, 41.4, 42.8, 46.2, 52.4, 54.5, 60.1, 62.0, 126.2, 126.4, 127.1, 128.4, 128.6, 128.9, 129.3, 129.4, 136.4, 137.9, 139.9, 170.6, 171.1, 171.7, 172.5; IR (Sol $CHCl_3$) = 699, 1290, 1406, 1632, 1686, 2970, 3473 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{23}H_{29}N_2O_2$ $[M+H]^+$ 365.2229, found 365.2212.

***N*-(1-(*tert*-butylcarbamoyl)cyclopropyl)-2-iodo-*N*-phenethylbenzamide (11j).**

Dehydroalanine **10j** (1 eq.) was reacted with trimethylsulfoxonium iodide and NaH 60% according to the general procedure, stirring for 2 hours. The resulting oil was purified by flash column chromatography eluting with a hexane/ethyl acetate (6:4) solvent system to provide **11j** as a brown oil (82 %). ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ = 1.36 (s, 3H), 1.45 (s, 6H)*, 2.24-3.47 (m, 6H), 3.62-3.78 (m, 1H), 3.96-4.18 (m, 1H), 5.28 (s, 1H), 6.78-7.49 (m, 8H), 7.77-7.88 (m, 1H) (*Rotamers can be observed at 25°C); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 14.2, 22.1, 23.2, 23.5, 24.0, 27.3, 27.4, 29.6, 34.0, 34.4, 36.0, 36.3, 41.3, 41.7, 42.7, 43.3, 45.8, 47.0, 50.3, 53.3, 53.4, 54.5, 54.7, 58.3, 60.3, 61.0, 61.5, 62.4, 92.2, 92.4, 92.8, 93.2, 126.2, 126.3, 126.4, 126.5, 127.6, 127.9, 128.1, 128.2, 128.4, 128.5, 128.6, 128.9, 129.0, 130.1, 138.0, 138.2, 138.9, 139.0, 139.1, 139.6, 139.7, 140.1, 141.7, 142.0, 142.4, 169.3, 170.0, 170.3, 170.8, 171.2, 171.5; IR (Sol $CHCl_3$) = 699, 746, 1290, 1408, 1636, 1685, 2923, 2959, 3439 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{23}H_{28}IN_2O_2$ $[M+H]^+$ 491.1195, found 491.1202.

***N*-(1-(*tert*-butylcarbamoyl)cyclopropyl)-4-methoxy-*N*-phenethylbenzamide (11k).**

Dehydroalanine **10k** (1 eq.) was reacted with trimethylsulfoxonium iodide and NaH 60% according to the general procedure, stirring for 2 hours. The resulting oil was purified by flash column chromatography eluting with a hexane/ethyl acetate (7:3) solvent system to provide **11k** as a white oil (88 %). ^{1}H NMR ($CDCl_3$, 400 MHz, 50 °C) δ = 1.27 (s, 1H), 1.41 (s, 9H), 1.63-2.11 (m, 2H), 2.91-3.66 (m, 5H), 3.82 (s, 3H), 4.36 (br, 1H), 6.89 (d, *J* = 8.8 Hz, 2H), 7.07-7.47 (m, 7H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 23.3, 27.4, 29.7, 34.4, 36.3, 41.6, 42.9, 46.4, 52.7, 54.6, 55.3, 60.3, 62.2, 113.7, 126.3, 128.5, 128.7, 128.8, 160.6, 171.1, 172.0; IR (Sol $CHCl_3$) = 700, 838, 1249, 1631, 1679, 2924, 2965 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{24}H_{31}N_2O_3$ $[M+H]^+$ 395.2334, found 395.2320.

***N*-(1-(*tert*-butylcarbamoyl)cyclopropyl)-*N*-(4-methoxyphenethyl)benzamide (11l).**

Dehydroalanine **10l** (1 eq.) was reacted with trimethylsulfoxonium iodide and NaH 60% according to the general procedure, stirring for 2 hours. The resulting oil was purified by flash column chromatography eluting with a hexane/ethyl acetate (6:4) solvent system to provide **11l** as a white oil (38 %). ^{1}H NMR ($CDCl_3$, 400 MHz, 50 °C) δ = 1.41 (s, 9H), 1.89-2.20 (m, 2H), 2.77-3.57 (m, 6H), 3.75 (s, 3H), 4.32 (br, 1H), 6.79-7.41 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 23.2, 23.3, 27.3, 29.6, 33.4, 35.4, 41.4, 42.8, 46.4, 52.6, 54.5, 55.2, 60.1, 62.1, 113.8, 126.5, 127.1, 128.3, 128.4, 129.3, 129.5, 129.9, 132.0, 136.5, 158.1, 170.6, 171.2, 171.8, 172.5; IR (Sol $CHCl_3$) = 702, 1030, 1244, 1632, 1686, 2925, 2958, 3475 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{24}H_{31}N_2O_3$ $[M+H]^+$ 395.2334, found 395.2350.

***N*-(1-(*tert*-butylcarbamoyl)cyclopropyl)-2-iodo-*N*-(4-methoxyphenethyl)benzamide (11m)**

Dehydroalanine **10m** (1 eq.) was reacted with trimethylsulfoxonium iodide and NaH 60% according to the general procedure, stirring for 3 hours. The resulting oil was purified by flash column chromatography eluting with a hexane/ethyl acetate (6:4) solvent system to provide **11m** as a yellow oil (54 %). ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ = 1.36 (s, 3H), 1.46 (s, 6H)*, 1.88-2.62 (m, 2H), 2.72-3.67 (m, 5H), 3.74 (s, 2H)*, 3.79 (s, 1H), 3.95-4.18 (m, 1H), 5.29 (s, 1H), 6.71-6.89 (m, 3H), 7.04-7.49 (m, 4H), 7.77-7.89 (m, 1H) (*Rotamers can be observed at 25°C); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 22.1, 23.2, 23.5, 24.0, 27.3, 27.4, 29.6, 33.1, 33.5, 35.0, 35.4, 41.3, 41.6, 42.7, 43.3, 46.0, 47.2, 50.5, 53.4, 54.5, 54.6, 55.2, 58.2, 60.9, 61.5, 62.4, 92.2, 92.3, 113.8, 113.9, 126.5, 127.6, 127.8, 128.0, 128.2, 128.4, 128.5, 129.6, 129.8, 130.0, 130.1, 131.6, 132.1, 138.8, 138.9, 139.1, 139.7, 141.7, 142.4, 158.0, 158.1, 170.0, 170.3, 170.8, 171.2, 171.4; IR (Sol $CHCl_3$) = 746, 1031, 1243, 1636, 1686, 2930, 2960, 3474 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{24}H_{30}IN_2O_3$ $[M+H]^+$ 521.1301, found 521.1298.

***N*-(1-(*tert*-butylcarbamoyl)cyclopropyl)-4-methoxy-*N*-(4-methoxyphenethyl)benzamide (11n).**

Dehydroalanine **10n** (1 eq.) was reacted with trimethylsulfoxonium iodide and NaH 60% according to the general procedure, stirring for 2.5 hours. The resulting oil was purified by flash column chromatography eluting with a hexane/ethyl acetate (7:3) solvent system to provide **11n** as a clear oil (66 %). ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ = 1.41 (s, 9H), 1.57-2.22 (m, 3H), 2.81-3.64 (m, 6H), 3.77 (s, 3H), 3.83 (s, 3H), 6.79-7.41 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 23.3, 27.4, 29.7, 54.6, 55.2, 55.3, 113.7, 113.9, 128.7, 129.7, 158.2, 160.6, 171.2, 172.0.; IR (Sol $CHCl_3$) = 837, 1028, 1244, 1608, 1686, 2924, 3484 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{25}H_{33}N_2O_4$ $[M+H]^+$ 425.2440, found 425.2441.

***N*-(2-bromophenethyl)-*N*-(1-(*tert*-butylcarbamoyl)cyclopropyl)benzamide (11o).**

Dehydroalanine **10o** (1 eq.) was reacted with trimethylsulfoxonium iodide and NaH 60% according to the general procedure, stirring for 4 hours. The resulting oil was purified by flash column chromatography eluting with a hexane/ethyl acetate (6:4) solvent system to provide **11o** as a clear oil (78 %). ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ = 1.41 (s, 4H), 1.50 (s, 5H)*, 1.86-2.04 (m, 1H), 2.37 (dd, *J* = 17.0, 7.8 Hz, 1H), 2.99-3.82 (m, 6H), 4.45 (s, 1H), 6.97-7.60 (m, 9H) (*Rotamers can be observed at 25°C); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 21.0, 23.2, 23.4, 27.4, 28.7, 29.7, 34.6, 36.6, 41.5, 42.9, 44.1, 50.4, 54.6, 54.7, 60.1, 62.2, 124.4, 126.6, 127.2, 127.7, 128.2, 128.3, 128.4, 128.5, 129.4, 129.6, 131.0, 131.8, 132.7, 132.8, 136.4, 136.5, 137.4, 139.2, 170.5, 171.2, 171.9, 172.8; HRMS (ESI+) *m/z* calcd for $C_{23}H_{28}{}^{79}Br_1N_2O_2$ $[M+H]^+$ 443.1334, found 443.1320.

***N*-(2-bromophenethyl)-*N*-(1-(*tert*-butylcarbamoyl)cyclopropyl)-2-iodobenzamide (11p).**

Dehydroalanine **10p** (1 eq.) was reacted with trimethylsulfoxonium iodide and NaH 60% according to the general procedure, stirring for 5 hours. The resulting oil was purified by flash column chromatography eluting with a hexane/ethyl acetate (6:4) solvent system to provide **11p** as a brown oil (89 %). ^{1}H NMR ($CDCl_3$, 400 MHz, 50 °C) δ = 1.27 (s, 1H), 1.36 (s, 3H), 1.46 (s, 5H)*, 2.14-2.39 (m, 2H), 2.94 – 3.87 (m, 6H), 6.99-7.54 (m, 7H), 7.78-7.84 (m, 1H) (*Rotamers can be observed even at 50°C); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 14.0, 14.1, 21.0, 22.1, 22.6, 23.1, 23.3, 24.0, 27.3, 27.4, 28.8, 29.6, 31.8, 34.3, 34.7, 36.3, 36.5, 41.2, 41.6, 42.5, 43.3, 43.8, 44.7, 48.0, 51.1, 54.5, 54.7, 58.2, 60.3, 60.9, 61.5, 62.5, 70.5, 92.1, 92.5, 124.2, 124.3, 127.6, 127.8, 127.8, 128.1, 128.2, 128.5, 130.1, 131.2, 131.6, 132.5, 132.7, 137.3, 137.8, 138.8, 138.9, 139.2, 139.8, 141.6, 142.3, 170.1, 170.2, 170.7, 171.6; IR (Sol $CHCl_3$) 748,1016, 1290, 1408, 1637, 1685, 2922, 2958, 3459 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{23}H_{27}{}^{79}Br_1I_1N_2O_2$ $[M+H]^+$ 569.0300, found 569.0308.

1-(*N*-(2-bromobenzyl)acetamido)-*N*-*tert*-butylcyclopropanecarboxamide (11q).

Dehydroalanine **10q** (1 eq.) was reacted with trimethylsulfoxonium iodide and NaH 60% according to the general procedure, stirring for 5 hours. The resulting oil was purified by flash column chromatography eluting with ethyl acetate to provide **11q** as a yellow oil (82 %). ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ = 1.11 (s, 2H), 1.40 (s, 7H)*, 1.95 (d, *J* = 62.2 Hz, 0H), 1.76- 2.03 (m, 2H), 2.07 (s, 2H)*, 2.23-2.29 (m, 1H), 3.25-3.53 (m, 1H), 4.41-4.73 (m, 2H), 7.16-7.58 (m , 4H) (*Rotamers can be observed at 25°C); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 18.0, 21.9, 23.1, 27.4, 28.2, 29.6, 41.7, 42.3, 49.5, 51.2, 53.0, 54.4, 59.8, 61.1, 122.3, 127.5, 127.9, 128.0, 128.1, 128.3, 128.5, 129.0, 129.5, 130.7, 132.4, 132.9, 133.0, 136.1, 171.2, 171.5; IR (Sol $CHCl_3$) 750, 1023, 1291, 1403, 1648, 1686, 2922, 2963, 3489 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{17}H_{24}{}^{79}Br_1N_2O_2$ $[M+H]^+$ 367.1021, found 367.1014.

***N*-benzyl-*N*-(1-(cyclohexylcarbamoyl)cyclopropyl)-2-iodobenzamide (11r).**

Dehydroalanine **10r** (1.0 eq.) was reacted with trimethylsulfoxonium iodide and NaH 60% according to the general procedure, stirring for 2 hours. The resulting oil was purified by flash column chromatography eluting with a hexane/ethyl acetate (6:4) solvent system to provide **11r** as a yellow solid (59 %) Mp: 105-108 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ = 1.07-1.42 (m, 5H), 1.56-1.91 (m, 5H), 2.15-2.49 (m, 2H), 2.96-3.52 (m, 2H), 3.88-4.47 (m, 3H), 7.00-7.57 (m, 8H), 7.79-7.89 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 22.3, 23.5, 24.8, 24.8, 24.9, 25.0, 25.1, 28.9, 29.6, 29.7, 38.8, 39.9, 46.4, 50.9, 53.9, 58.4, 60.6, 91.7, 92.0, 126.6, 127.1, 127.2, 127.3, 127.8, 127.9, 128.1, 128.1, 128.3, 129.7, 135.6, 137.8, 138.5, 138.6, 141.1, 141.7, 168.9, 169.4, 170.2, 171.6; IR (Sol $CHCl_3$) 748, 1432, 1645, 1687, 2854, 2931, 3060 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{24}H_{28}I_1N_2O_2$ $[M+H]^+$ 503.1195, found 503.1198.

***N*-(1-(*tert*-butylcarbamoyl)cyclopropyl)-*N*-isopropylbenzamide (11s).** Purified by flash column chromatography eluting with a hexane/ethyl acetate (7:3) solvent system to provide **11s** as white solid (14%), M.p. 145-151 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ = 1.42-1.58 (m, 19H), 3.99 (q, *J*= 6 Hz, 1H), 6.70 (br, 1H), 7.37-7.46 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 20.9, 22.2, 28.7, 29.7, 51.4, 54.1, 100.0, 126.7, 128.2, 129.9, 171.5; IR (thin film) 675, 694, 1133, 1364, 1395, 1525, 1621, 1656, 2923, 2976, 3326 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{18}H_{27}N_2O_2$ $[M+H]^+$ 303.20725, found 303.20745.

General procedure for the synthesis of cyclopropanes **13** *with sulfonium bromide* **12**.

In a round-bottom flask under argon, dehydroalanine **10** (0.28 mmol, 1 eq.) was taken in 5 mL of dry THF. Then sulfonium bromide **12** (0.19 g, 0.84 mmol, 3 eq.) and NaH 60% (34 mg, 0.84 mmol, 3 eq.) were added and the reaction mixture was stirred at room temperature for 10 min and then refluxed until dehydroalanine was consumed. The reaction was quenched with 5 mL of water and extracted with 5 mL of CH_2Cl_2 for three times; the combined dichloromethane extracts were dried over sodium sulfate and concentrated under vacuum. This material was purified by column chromatography on silica gel eluting with hexane/ethyl acetate solvent system.

Ethyl 2-(*tert*-butylcarbamoyl)-2-(*N*-(4-methoxybenzyl)benzamido)cyclopropanecarboxylate (13a).

Dehydroalanine **10a** (1 eq.) was reacted with sulfonium bromide **12** and NaH 60 % according to the general procedure, refluxing for 14 hours. The resulting mixture was purified by flash column chromatography eluting with a hexane/ethyl acetate (8:2) solvent system to provide **13a** as a colorless solid (51 %) Mp: 112-117°C. ^{1}H NMR ($CDCl_3$, 500 MHz, 25 °C) δ = 1.09 (s, 9H), 1.21 (t, J= 7 Hz, 3H), 1.79 (dd, J= 7 Hz, 1H), 2.14 (dd, *J* = 5 Hz, 1H), 2.68 (dd, *J* = 7 Hz, 1H), 3.75 (s, 3H), 4.1 (c, J= 7 Hz, 2H), 4.43 (dd, *J* = 15 Hz, 2H), 6.34 (br, 1H), 6.9 (dd, J= 8.5 Hz, 4H), 7.45 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 14.1, 19.5, 28.2, 30.7, 48.0, 50.7, 53.7, 55.2, 61.1, 114.3, 126.8, 127.9, 128.6, 129.8, 130.2, 136.3, 159.5, 167.1, 170.5, 173.8; IR (Sol $CHCl_3$) 1240.6, 1658, 2922, 2963, 3429 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{26}H_{33}N_2O_5$ $[M+H]^+$ 453.2389, found 453.2402.

Ethyl 2-(*tert*-butylcarbamoyl)-2-(2-iodo-*N*-(4-methoxybenzyl)benzamido)cyclopropanecarboxylate (13b).

Dehydroalanine **10b** (1 eq.) was reacted with sulfonium bromide **12** and NaH 60 % according to the general procedure, refluxing for 8 hours. The resulting mixture was purified by flash column chromatography eluting with a hexane/ethyl acetate (8:2) solvent system to provide **13b** as a colorless solid (84 %) Mp: 148-153°C. ^{1}H NMR ($CDCl_3$, 500 MHz, 25 °C) δ = 1.15 (s, 9H), 1.23 (t, *J* = 7 Hz, 3H), 1.77 (dd, *J* = 5 Hz, 1H), 2.14 (dd, *J* = 5 Hz, 1H), 2.7 (dd, *J* = 7 Hz, 1H), 3.77 (s, 3H), 4.12 (m, 2H), 4.28 (dd, *J* = 14.5 Hz, 2H), 6.5 (br, 1H), 6.78- 7.89 (m, 8H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 14.0, 20.2, 28.2, 28.6, 30.8, 51.6, 54.2, 55.3, 61.2, 114.1, 126.8, 128.4, 128.6, 130.2, 130.6, 131.3, 139.4, 141.7, 159.6, 166.8, 170.9, 172.7; IR (Sol $CHCl_3$) 1247, 1653, 2854, 2924, 3416 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{26}H_{32}I_1N_2O_5$ $[M+H]^+$ 579.1355, found 579.1360.

Ethyl 2-(*N*-benzylbenzamido)-2-(*tert*-butylcarbamoyl)cyclopropanecarboxylate (13d).

Dehydroalanine **10d** (1 eq.) was reacted with sulfonium bromide **12** and NaH 60 % according to the general procedure, refluxing for 6 hours. The resulting mixture was purified by flash column chromatography eluting with a hexane/ethyl acetate (8:2) solvent system to provide **13d** as colorless solid (41 %) Mp: 150-153°C. ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ = 1.08 (s, 9H), 1.21 (t, *J* = 7.2 Hz, 3H), 1.80 (dd, *J* = 5 Hz, 1H), 2.14 (dd, *J* = 5 Hz), 2.68 (dd, *J* = 7 Hz, 1H), 4.11 (m, 2H), 4.49 (dd, *J* = 14.8 Hz, 2H), 6.39 (br, 1H), 7.09-7.46 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 14.1, 19.5, 28.2, 30.7, 48.1, 50.8, 54.4, 61.2, 126.8, 128.3, 128.7, 128.9, 129.0, 129.8, 135.8, 136.2, 167.0, 170.5, 174.0; IR (Sol $CHCl_3$) 447, 698, 1154, 1180, 1206, 1237, 1387, 1518, 1652, 1715, 2976, 3059, 3440 cm^{-1} ; HRMS (ESI+) *m/z* calcd for $C_{25}H_{31}N_2O_4$ $[M+H]^+$ 423.2283, found 423.2281.

Ethyl 2-(*N*-benzyl-2-iodobenzamido)-2-(*tert*-butylcarbamoyl)cyclopropanecarboxylate (13e).

Dehydroalanine **10e** (1 eq.) was reacted with sulfonium bromide **12** and NaH 60 % according to the general procedure, refluxing for 24 hours. The resulting mixture was purified by flash column chromatography eluting with a hexane/ethyl acetate (8:2) solvent system to provide **13e** as colorless solid (56 %) Mp: 169-173°C. ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ = 1.14 (s, 9H), 1.23 (t, *J* = 7 Hz, 3H), 1.79 (dd, *J* = 4.8 Hz, 1H), 2.13 (dd, *J* = 4.8 Hz, 1H), 2.71 (dd, *J* = 6.8 Hz, 1H), 4.13 (m, 2H), 4.34 (dd, J= 15 Hz, 2H), 6.54 (br, 1H), 7.11-7.89 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 14.1, 20.2, 28.6, 30.9, 47.4, 51.6, 54.9, 61.2, 93.3, 126.8, 128.4, 128.7, 128.7, 130.0, 130.7, 134.7, 139.4, 141.6, 166.8, 170.9, 172.8; IR (Sol $CHCl_3$) 460, 698, 744, 1157, 1182, 1203, 1233, 1383, 1653, 1708, 2924, 2968, 3061, 3418 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{25}H_{30}I_1N_2O_4$ $[M+H]^+$ 549.1250, found 549.1252.

Ethyl 2-(*tert*-butylcarbamoyl)-2-(*N*-(4-methoxyphenethyl)benzamido)cyclopropanecarboxylate (13l).

Dehydroalanine **10l** (1 eq.) was reacted with sulfonium bromide **12** and NaH 60 % according to the general procedure, refluxing for 24 hours. The resulting mixture was purified by flash column chromatography eluting with a hexane/ethyl acetate (85:15) solvent system to provide **13l** as colorless oil (16 %). ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ = 1.22 (t, *J* = 7.1 Hz, 3H), 1.36 (s, 9H), 1.66 (dd, *J* = 6.8, 5.2 Hz, 1H), 2.22 (dd, *J* = 9.0, 5.2 Hz, 1H), 2.60 (dd, *J* = 9.0, 6.9 Hz, 1H), 2.64-2.69 (m, 1H), 2.90 (ddd, *J* = 13.6, 10.7, 4.7 Hz, 1H), 3.32 (ddd, *J* = 14.5, 10.5, 4.8 Hz, 1H), 3.64-3.73 (m, 1H), 3.75 (s, 3H), 4.09 (dtt, *J* = 10.8, 7.3, 3.7 Hz, 2H), 6.74 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 7.17 (s, 1H), 7.32-7.47 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 14.0, 18.0, 28.5, 30.2, 34.2, 48.2, 51.2, 52.6, 55.2, 61.2, 113.9, 126.5, 128.5, 129.4, 129.6, 129.8, 135.9, 158.3, 168.2, 170.0, 174.6; IR (Sol $CHCl_3$) 700, 1180, 1244, 1512, 1629, 1674, 1722, 2963, 3290 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{27}H_{35}N_2O_5$ $[M+H]^+$ 467.2546, found 467.2551.

Ethyl 2-(*tert*-butylcarbamoyl)-2-(2-iodo-*N*-(4-methoxyphenethyl)benzamido)cyclopropanecarboxylate (13m).

Dehydroalanine **10m** (1 eq.) was reacted with sulfonium bromide **12** and NaH 60 % according to the general procedure, refluxing for 20 hours. The resulting mixture was purified by flash column chromatography eluting with a hexane/ethyl acetate (8:2) solvent system to provide **13m** as colorless solid (46 %) Mp: 138-142 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ = 1.26 (t, *J* = 7.1 Hz, 3H), 1.42 (s, 9H), 1.68 (dd, *J* = 6.9, 5.0 Hz, 1H), 2.27 (dd, *J* = 9.0, 5.0 Hz, 1H), 2.68 (dd, *J* = 9.0, 7.0 Hz, 1H), 2.96 (dd, *J* = 9.4, 7.8 Hz, 2H), 3.10-3.24 (m, 1H), 3.40 (ddd, *J* = 13.9, 9.7, 7.9 Hz, 1H), 3.74 (s, 3H), 4.05-4.22 (m, 2H), 6.77 (d, *J* = 8.7 Hz, 2H), 6.92 (d, *J* = 8.7 Hz, 2H), 7.10 (ddd, *J* = 8.0, 6.2, 3.0 Hz, 1H), 7.22 (br, 1H), 7.34-7.41 (m, 2H), 7.85 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR (CDCl3, 100 MHz) δ = 14.1, 18.4, 29.0, 30.5, 34.4, 47.3, 52.0, 52.9, 55.2, 61.2, 92.1, 114.0, 128.1, 128.6, 129.5, 129.7, 130.6, 138.8, 142.1, 158.3, 167.8, 170.3, 173.3; IR (Sol $CHCl_3$) 763, 1025, 1211, 1243, 1511, 1634, 1669, 1714, 2967, 3310 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{27}H_{34}I_1N_2O_5$ $[M+H]^+$ 593.1512, found 593.1521.

Ethyl 2-(*N*-benzyl-2-iodobenzamido)-2-(cyclohexylcarbamoyl)cyclopropanecarboxylate (13r).

Dehydroalanine **10r** (1 eq.) was reacted with sulfonium bromide **12** and NaH 60 % according to the general procedure, refluxing for 24 hours. The resulting mixture was purified by flash column chromatography eluting with a hexane/ethyl acetate (7:3) solvent system to provide **13s** as a white solid (57 %) Mp: 100-102°C. ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ = 0.78 (m, 1H), 1.05 (m, 3H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.6 (m, 5H), 1.82 (dd, *J* = 5.0 Hz, 1H), 1.92 (m, 1H), 2.13 (dd, *J* = 5.0 Hz, 1H), 2.77 (dd, *J* = 7 Hz, 1H), 3.51 (m, 1H), 4.12 (m, 2H), 4.34 (dd, *J* = 14.8 Hz, 2H), 6.55 (d, *J* = 7.6 Hz, 1H), 7.11-7.89 (m, 9H); ^{13}C NMR (CDCl3, 100 MHz) δ = 14.1, 20.6, 25.1, 25.1, 25.6, 31.1, 33.0, 33.2, 46.9, 49.6, 54.9, 61.2, 93.2, 128.3, 128.4, 128.5, 128.7, 130.0, 130.7, 134.6, 139.3, 141.7, 166.9, 171.0, 172.8; IR (Sol $CHCl_3$) 694, 745, 1158, 1182, 1235, 1383, 1652, 1714, 2852, 2923, 3423 cm^{-1}; HRMS (FAB+) *m/z* calcd for $C_{27}H_{32}I_1N_2O_4$ $[M+H]^+$ 575.1407, found 575.1409.

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22. Full crystallographic data for compounds 13a, 13d, 13e and 13m were submitted as CIF files with the Cambridge Crystallographic Data Center, CCDC Nos. 1513702, 1513703, 1513704 and 1513705

Supplementary data

Full analytical data for all new compounds. This material is available free of charge via the Internet at