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Multicomponent Reactions

A Ugi Straightforward Access to Bis-β-lactam Derivatives

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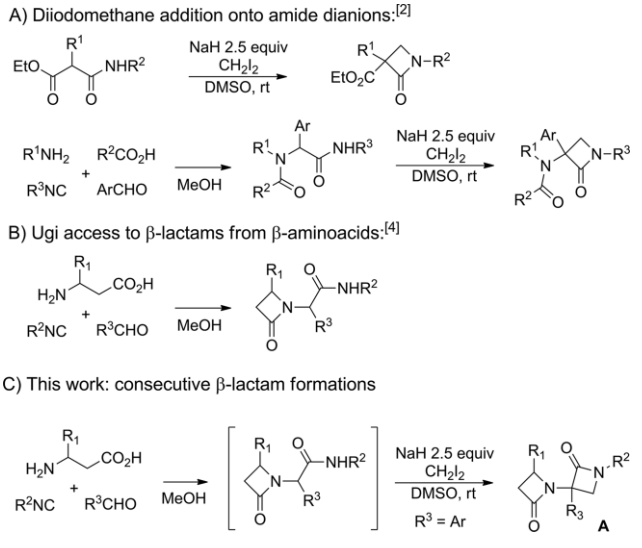
Abstract: THe Ugi reaction of β-amino acids with aromatic aldehydes affords β-lactams which may be used as starting materials in a second β-lactam formation following a base triggered diiodomethane addition. The sequence may be conducted in a one-pot fashion affording a straightforward access to bis-β-lactams.

Introduction

The chemistry of β-lactams has been largely been driven by their recognition as powerful drugs against bacterial infection.[1] The early apparition of resistance together with the disclosure of β-lactamase inhibitors have even increased the efforts devoted to these structures. We recently disclosed a very efficient access to the β-lactam core under diiodomethane addition onto diamide anions (Scheme 1).[2] We further demonstrated that this reaction could be easily performed on relatively acidic Ugi adducts obtained from aromatic aldehydes. In this case, the resulting β-lactams feature an amino substituent on the core β-lactam in agreement with the structure of most natural bioactive β-lactams.[3] This new approach towards this important family of heterocycles is not the first involving a Ugi reaction as the use of β-amino acids in the so called Ugi 4-center 3-component coupling is well recognized as an elegant access to β-lactams (U-4C-3C, Scheme 1).[4] In order to explore further the scope of our diiodomethane cyclocondensation and harness it to more sensitive substrates towards basic conditions, we decided to combine both approaches as a means to reach bis-β-lactams **A** in a straightforward manner (Scheme 1).

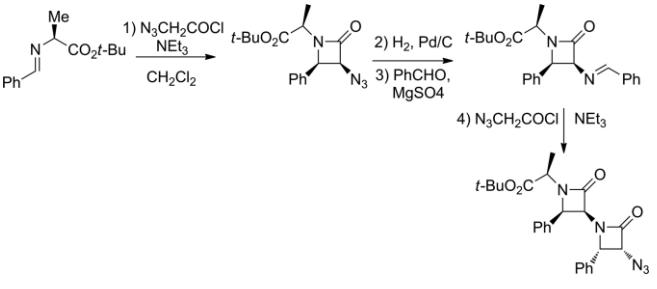


Scheme 1. Ugi reactions and β-lactams.

Results and Discussion

Bis-β-lactams **A** were first reported by Sharma et al. in 1980[5] and later studied by Ojima et al. as well as other groups.[6] The interest for these structures was associated with their potential biological activities together with their use as synthetic intermediates.

Disclosed preparations of bis-β-lactams involved [2+2] cycloadditions of imines with ketenes using a previously formed β-lactam bearing a ketene or an imine tether. In all these approaches, several steps are required to prepare the starting bactam with the functionality required for the final cycloaddition. An example from Ojima's work is displayed in Scheme 2.[6a]



Scheme 2. Ojima's procedure towards bis β-lactams A.

Most reported U-4C-3C couplings involve the use of β-amino acids with stoichiometric amount or slight excess of the two other reagents in methanol at room temperature. In some cases, water as solvent or cosolvent improves both kinetics and yields.[4d] With the aim of performing one-pot reactions at a

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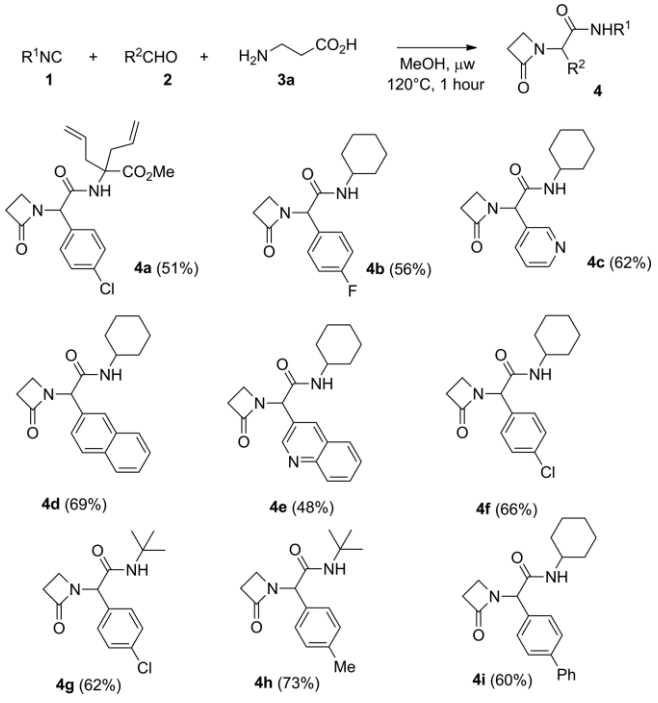
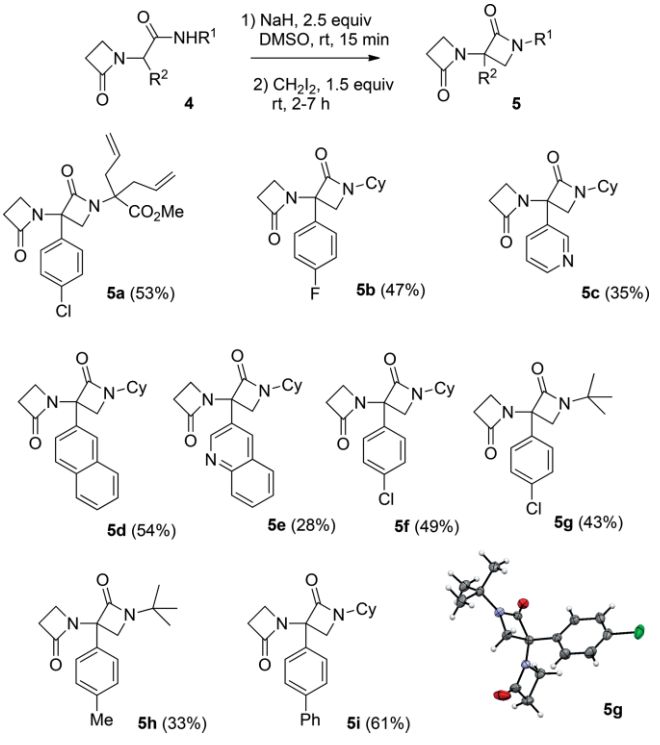
later stage of the study, we decided to focus on the conditions reported by Dömling et al. in 2015.[4g] Their use of microwave conditions allowed them to reach moderate to good yields of β-lactams under stoichiometric conditions and within one hour time. These conditions were selected to prepare a set of β-lactams **4** from isocyanides **1**, aldehydes **2** and β-amino acids **3** (Scheme 3). With this new family of Ugi β-lactams **4** in hand, we next examined the second β-lactam formation. These strained heterocycles are known to be rather sensitive toward base triggered ring-opening. In the case of our previous NaH-CH_2I_2 based β-lactam formation, the apparent stability of the latter was partly explained by the presence of bulky substituents on the cycle which could lower the nucleophilic attacks at the carbonyl lactam function. This is not the case with **4** and a potential ring opening of the β-lactam moiety of **4** was expected to be a threat for the success of the following step.



Scheme 3. U-4C-3C towards β-lactams **4**.

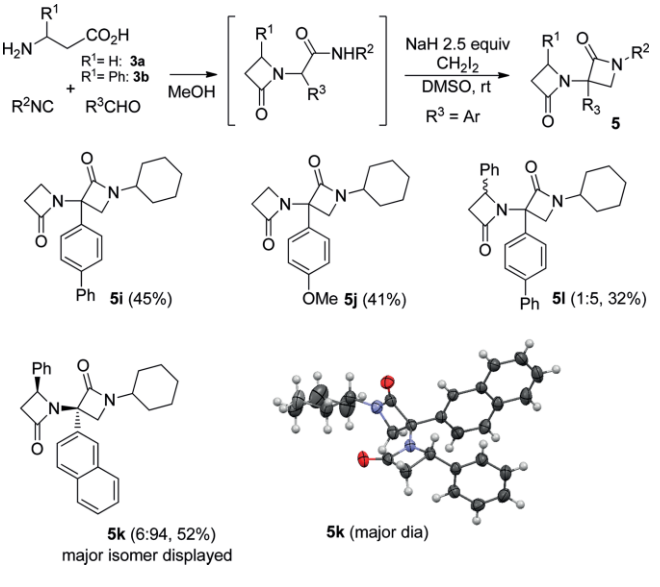
However when **4a** was treated with 2.5 equiv. of NaH in DMSO and let to react at r.t. for 3 hours (Scheme 4), we were pleased to observe the formation of **5a** in a moderate 53 % isolated yields. All lactams **4** behaved similarly affording the expected lactams **5** in moderate yields. Compared with our previous study working with less sensitive Ugi adducts, the reaction affords lower yields which can be mainly explained by the sensitivity of the β-lactams ring under these conditions. In agreement with these considerations, the lower yields observed with **5e** and **5h** were associated with the longer reaction time (6 and 7 hours respectively). The structure of the bis-lactam was confirmed by a single-crystal X-ray analysis of **5g**.[7]

In order to raise further the interest of the sequence, and having in mind a potential loss of material during the intermediate chromatography on rather acidic silica, we decided to examine the ability to achieve the preparation of **5** under a one-



Scheme 4. U-4C-3C towards β-lactams **4**.

pot sequence. Thus, after performing the Ugi reaction, the methanol was evaporated followed by DMSO addition and subsequent addition of sodium hydride and diiodomethane. Under these conditions the bis-lactam **5i** was directly obtained in a 45 % isolated yield (Scheme 5) which compares positively with the 60 % and 61 % isolated yield of the two steps with purification of the intermediate lactam **4i**.



Scheme 5. One-pot Ugi access to β-lactams **5**.

With this more efficient sequence in hand, we decided to examine the behavior of a substituted β-amino acid in relation with diastereoselectivity issues. Indeed, the interest of limiting

the first part of the study to the use of β-alanine **3a** was mainly associated with the lack of potential mixtures of diastereomers obtained in both steps of the sequence.

With substituted β-alanines, the Ugi reaction was expected to afford a very low diastereomeric excess as observed in previous studies using 3-phenyl-β-alanine **3b**.[8] This was indeed the case when **3b** and cyclohexyl isocyanide were added to 4-phenylbenzaldehyde or 3-naphthaldehyde. NMR of the crude mixtures revealed in both cases a ratio of diastereomers close to 1:1. Interestingly, the following deprotonation is expected to destroy part of these information leading to possible improvement of the overall selectivity after two steps. This was indeed the case with **5k** and **5l** (Scheme 5) as when the intermediate mixtures were treated under the basic conditions required for the second β-lactam formation, a strong improvement of the diastereoselectivity was observed with a 94:6 mixture in the case of naphthyl-substituted lactam **5k**. A single-crystal X-ray analysis of the major isomer of **5k**[9] suggests that a π stacking effect between the phenyl and the naphthyl rings might be at the origin of the control of the selectivity.

Antibacterial activity of the synthetic compounds were tested against *Escherichia coli* MC4100, *Staphylococcus aureus* subsp. *aureus* ATCC6538 and *Micrococcus luteus* ATCC9341 strain by soft-agar overlay technique. None of them was active on the Gram-negative bacterium *E. coli*. Some compounds showed weak activity toward *S. aureus* (**5i**, **5f**) or *M. luteus* (**5e**).

Conclusions

The present study demonstrates further the efficiency of Ugi reactions for the preparation of β-lactams as well as the robustness of the CH_2I_2 based β-lactam formation. Two consecutive β-lactam formation may be achieved in one pot conditions leading to a fast assembly of bis β-lactams. These methods based on Ugi reaction open access to these families of important heterocycles without the traditional use of [2+2] cycloaddition processes.[10] Further improvements could be probably brought in the first Ugi step of the sequence using water[4d] or, as recently disclosed, trifluoroethanol as solvent.[11] The observed activity of some compounds against Gram-positive bacteria, although poor, would set the starting point to further improvements such as the use of an *N*-benzyl removable group followed by deprotection and functionalization towards potentially more active monobactams.

Experimental Section

General Considerations: NMR spectra were recorded at 298 K using a Bruker AVANCE 400 spectrometer. ^{1}H NMR spectra were recorded at 400 MHz and residual solvent peaks were used as an internal reference ($CDCl_3$ δ = 7.26). Data are reported as follows: chemical shift in ppm, apparent multiplicity (s = singlet, d = doublet, dd = doublet of doublet, dt = doublet of triplet, t = triplet, m = multiplet or overlap of nonequivalent resonances), coupling constants, integration. ^{13}C NMR spectra were recorded at 100 MHz and residual solvent peaks were used as an internal reference ($CDCl_3$ δ = 77.16). Data are reported as follows: chemical shift in ppm, multiplicity deduced from DEPT experiments (CH_3, CH_2, CH, Cq), apparent multiplicity, coupling constants and integration where relevant. Analytical TLC was performed with Merck silica gel plates, pre-coated with silica gel 60 F254 (0.2 mm). Visualisation was effected by quenching of UV fluorescence (λ_{max} = 254 nm or 360 nm) and by staining with potassium permanganate or vanillin TLC stain solutions, followed by heating. Flash chromatography employed ASTM (70–230 mesh) silica gel. Reactions were conducted under a positive pressure of dry nitrogen. Anhydrous solvents were obtained from commercial sources. Commercially available chemicals were used without further purification. IR spectra were recorded on a Perkin Elmer FT 1600 Spectrometer with wavelengths in cm^{-1}. Melting points were measured on a Stuart SMP3 melting point apparatus and are uncorrected. High resolution mass spectra were recorded on a JEOL JMSGCmatell spectrometer. Monowave 300 produced by Anton Paar was used for the microwave conditions.

Synthesis of 1a: Methyl 2-allyl-2-isocyanopent-4-enoate (**1a**):[12] To a solution of methyl α-isocyanoacetate (0.5 mL, 5.0 mmol, 1.0 equiv.) in MeCN (10 mL, 0.5 M) were added, K_2CO_3 (3.0 g, 22.0 mmol, 4.4 equiv.), triethylbenzylammonium chloride (57 mg, 5 mol-%) and allyl bromide (1.7 mL, 20.0 mmol, 4 equiv.). The reaction mixture was stirred at 72 °C for 6 hours. After completion, the reaction mixture was cooled to room temperature, quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with DCM (3 times). The combined organic layers were washed with brine (1 time), dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by column chromatography (PE/Et_2O = 95:5) to afford the compound **1a** (860 mg, 4.8 mmol, yield 96 %). Aspect: yellow solution. R_f: 0.26 (PE/Et_2O = 95:5). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.83–5.73 (m, 2H), 5.25–5.19 (m, 4H), 3.78 (s, 3H), 2.68–2.62 (dd, *J* = 13.9, 7.1 Hz, 2H), 2.57–2.52 (dd, *J* = 13.9, 7.1 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.4, 159.8, 129.9, 121.2, 67.7 (t, *J* = 7.0 Hz), 53.3, 42.6. HRMS: calculated for $C_{10}H_{13}NO_2$: 179.0946, found 178.0664. IR (thin film): $\tilde{\nu}$ = 3083, 2956, 2136, 1745, 1438, 1220, 1153, 993, 926, 663 cm^{-1}.

Synthesis of 4a to 4i

General Procedure A:[4g] To a dried microwave tube was added aldehyde **2** (1.0 mmol, 1 equiv.), MeOH (1.0 M, 1 mL) followed by β-amino acid **3** (1.0 mmol, 1 equiv.), and the isocyanide **1** (1.0 mmol, 1 equiv.). The tube was filled with nitrogen before heating under microwave condition to 120 °C, 100 W for 1 hour. After completion, the solvent was removed under reduced pressure and the crude mixture purified by column chromatography on silica gel to afford the desired **4a**– **4i**.

Methyl 2-Allyl-2-[2-(4-chlorophenyl)-2-(2-oxoazetidin-1-yl)acetamido]pent-4-enoate (4a): Following general procedure A, the synthesis was carried out with 4-chlorobenzaldehyde (141 mg, 1.0 mmol, 1 equiv.), β-alanine (89 mg, 1.0 mmol, 1 equiv.) and **1a** (179 mg, 1.0 mmol, 1 equiv.). The crude mixture was purified by column chromatography (PE/Et_2O = 60:40 to 40:60) to afford the compound **4a** (200 mg, 0.51 mmol, yield 51 %). Aspect: yellow solid, m.p. 86–88 °C. R_f: 0.26 (PE/Et_2O = 3:7) ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.35–7.28 (m, 4H), 6.75 (s, 1H), 5.59–5.38 (m, 2H), 5.36 (s, 1H), 5.08–4.98 (m, 4H), 3.73 (s, 3H), 3.56–3.53 (m, 1H), 3.14–3.11 (m, 1H), 3.10–3.05 (dd, *J* = 14.0, 7.2 Hz, 2H), 3.03–2.97 (m, 1H), 2.89–2.83 (m, 1H), 2.57–2.52 (dd, *J* = 14.0, 7.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 173.0, 167.8, 167.2, 134.8, 132.9, 131.8, 131.8, 129.9, 129.3, 119.7, 119.6, 64.4, 59.2, 53.0, 39.1, 39.0, 38.9, 36.5. HRMS: calculated for $C_{20}H_{23}ClN_2O_4$: 390.1346, not found, fragment: 195.0444. IR (thin film): $\tilde{\nu}$ = 3312, 3076, 2954, 1733, 1681, 1641, 1492, 1227, 922 cm^{-1}.

***N*-Cyclohexyl-2-(4-fluorophenyl)-2-(2-oxoazetidin-1-yl)acetamide (4b):** Following general procedure A, the synthesis was carried out with 4-fluorobenzaldehyde (0.11 mL, 1.0 mmol, 1 equiv.), β-alanine (89 mg, 1.0 mmol, 1 equiv.) and cyclohexyl isocyanide 95 % (0.13 mL, 1.0 mmol, 1 equiv.). The crude mixture was purified by column chromatography (PE/Et_2O, 60:40 to 20:80) to afford the compound **4b** (170 mg, 0.56 mmol, yield 56 %). Aspect: white solid, m.p. 105–108 °C. R_f: 0.19 (PE/Et_2O = 2:8). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36–7.32 (m, 2H), 7.08–7.03 (m, 2H), 6.24–6.23 (d, J = 7.0 Hz, 1H), 5.33 (s, 1H), 3.79–3.70 (m, 1H), 3.62–3.59 (m, 1H), 3.18–3.14 (m, 1H), 3.02–2.96 (m, 1H), 2.89–2.83 (m, 1H), 1.89–1.82 (m, 2H), 1.70–1.55 (m, 3H), 1.38–1.27 (m, 2H), 1.18–1.03 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.1, 167.6, 164.0–161.6 (d, J = 248.8 Hz), 130.9 (d, J = 3.3 Hz), 130.1–130.0 (d, J = 8.3 Hz), 116.2–116.0 (d, J = 21.6 Hz), 59.3, 48.8, 39.1, 36.3, 32.8, 32.8, 25.5, 24.8, 24.8. HRMS: calculated for $C_{17}H_{21}FN_2O_2$: 304.1587, not found, fragment: 178.0669. IR (thin film): $\tilde{\nu}$ = 3295, 3069, 2930, 2854, 1731, 1651, 1540, 1507, 1224, 731 cm^{-1}.

***N*-Cyclohexyl-2-(2-oxoazetidin-1-yl)-2-(pyridin-3-yl)acetamide (4c):** Following general procedure A, the synthesis was carried out with 3-pyridinecarboxaldehyde (0.09 mL, 1.0 mmol, 1 equiv.), β-alanine (89 mg, 1.0 mmol, 1 equiv.) and cyclohexyl isocyanide 95 % (0.13 mL, 1.0 mmol, 1 equiv.). The crude mixture was purified by column chromatography (PE/AcOEt = 40:60 to 0:100; DCM/MeOH = 95:5) to afford the compound **4c** (177 mg, 0.62 mmol, yield 62 %). Aspect: colorless oil. R_f: 0.36 (DCM/MeOH = 9.5:0.5). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.55–8.53 (dd, J = 4.8, 1.9 Hz, 1H), 8.52–8.51 (d, J = 1.9 Hz, 1H), 7.74–7.72 (dt, J = 7.9, 1.9 Hz, 1H), 7.31–7.27 (dd, J = 7.9, 4.8, 1H), 7.01–6.99 (d, J = 7.8 Hz, 1H), 5.44 (s, 1H), 3.74–3.67 (m, 1H), 3.67–3.63 (m, 1H), 3.22–3.18 (m, 1H), 3.00–2.94 (m, 1H), 2.88–2.83 (m, 1H), 1.85–1.78 (m, 2H), 1.68–1.53 (m, 3H), 1.32–1.25 (m, 2H), 1.13–1.04 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.0, 166.9, 149.7, 149.4, 135.7, 131.2, 123.9, 57.1, 48.8, 39.3, 36.4, 32.7, 32.7, 25.4, 24.8, 24.7. HRMS: calculated for $C_{16}H_{21}N_3O_2$: 287.1634, found 287.1644. IR (thin film): $\tilde{\nu}$ = 3301, 3055, 2931, 2855, 2246, 1736, 1659, 1542, 908, 726 cm^{-1}.

***N*-Cyclohexyl-2-(naphthalen-2-yl)-2-(2-oxoazetidin-1-yl)acetamide (4d):** Following general procedure A, the synthesis was carried out with 2-naphthaldehyde (156 mg, 1.0 mmol, 1 equiv.), β-alanine (89 mg, 1.0 mmol, 1 equiv.) and cyclohexyl isocyanide 95 % (0.13 mL, 1.0 mmol, 1 equiv.). The crude mixture was purified by column chromatography (PE/Et_2O = 60:40 to 0:100) to afford the compound **4d** (231 mg, 0.69 mmol, yield 69 %). Aspect: yellow solid, m.p. 146–150 °C. R_f: 0.4 (Et_2O). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.81–7.76 (m, 4H), 7.47–7.43 (m, 3H), 6.79–6.77 (d, J = 7.9 Hz, 1H), 5.67 (s, 1H), 3.79–3.72 (m, 1H), 3.71–3.67 (m, 1H), 3.16–3.13 (m, 1H), 2.97–2.91 (m, 1H), 2.81–2.75 (m, 1H), 1.85–1.81 (m, 2H), 1.64–1.50 (m, 3H), 1.31–1.22 (m, 2H), 1.11–1.03 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.1, 167.8, 133.3, 133.1, 132.4, 129.0, 128.2, 127.8, 127.6, 126.7, 126.7, 125.6, 59.8, 48.7, 39.1, 36.4, 32.8, 25.5, 24.8, 24.8. HRMS: calculated for $C_{21}H_{24}N_2O_2$: 336.1838, found 336.1830. IR (thin film): $\tilde{\nu}$ = 3296, 3056, 2927, 2853, 1731, 1651, 1543, 1247, 753, 732 cm^{-1}.

***N*-Cyclohexyl-2-(2-oxoazetidin-1-yl)-2-(quinolin-3-yl)acetamide (4e):** Following general procedure A, the synthesis was carried out with 3-quinolinecarboxaldehyde (157 mg, 1.0 mmol, 1 equiv.), β-alanine (89 mg, 1.0 mmol, 1 equiv.) and cyclohexyl isocyanide 95 % (0.13 mL, 1.0 mmol, 1 equiv.). The crude mixture was purified by column chromatography (PE/AcOEt = 60:40 to 0:100) to afford the compound **4e** (163 mg, 0.48 mmol, yield 48 %). Aspect: yellow oil. R_f: 0.2 (PE/EA = 2:8) ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.84–8.83 (d, J = 2.3 Hz, 1H), 8.19 (d, J = 2.3 Hz, 1H), 8.09–8.07 (d, J = 8.5 Hz, 1H), 7.82–7.80 (dd, J = 8.5, 0.8 Hz, 1H), 7.75–7.71 (m, 1H), 7.59–7.55 (m, 1H), 6.79–6.77 (d, J = 7.9 Hz, 1H), 5.60 (s, 1H), 3.83–3.74 (m, 1H), 3.72–3.68 (m, 1H), 3.22–3.19 (m, 1H), 3.04–2.99 (m, 1H), 2.91–2.85 (m, 1H), 1.92–1.85 (m, 2H), 1.69–1.62 (m, 2H), 1.59–1.54 (m, 1H), 1.37–1.27 (m, 2H), 1.18–1.05 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.1, 167.0, 150.3, 147.9, 135.5, 130.3, 129.3, 128.2, 128.1, 127.7, 127.4, 57.6, 49.0, 39.3, 36.5, 32.9, 32.8, 25.5, 24.8, 24.8. HRMS: calculated for $C_{20}H_{23}N_3O_2$: 337.1790, found 337.1801, 212,0946. IR (thin film): $\tilde{\nu}$ = 3293, 3054, 2929, 2853, 1732, 1656, 1538, 1248, 753, 731 cm^{-1}.

2-(4-Chlorophenyl)-*N*-cyclohexyl-2-(2-oxoazetidin-1-yl)acetamide (4f): Following general procedure A, the synthesis was carried out with 4-chlorobenzaldehyde (141 mg, 1.0 mmol, 1 equiv.), β-alanine (89 mg, 1.0 mmol, 1 equiv.) and cyclohexyl isocyanide 95 % (0.13 mL, 1.0 mmol, 1 equiv.). The crude mixture was purified by column chromatography (PE/Et_2O = 60:40 to 10:90) to afford the compound **4f** (211 mg, 0.66 mmol, yield 66 %). Aspect: yellow solid, m.p. 127–130 °C. R_f: 0.42 (Et_2O). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.35–7.28 (m, 4H), 6.36–6.34 (d, J = 7.6 Hz, 1H), 5.34 (s, 1H), 3.77–3.69 (m, 1H), 3.63–3.60 (m, 1H), 3.19–3.15 (m, 1H), 3.01–2.95 (m, 1H), 2.89–2.83 (m, 1H), 1.86–1.82 (m, 2H), 1.70–1.63 (m, 2H), 1.59–1.56 (m, 1H), 1.37–1.26 (m, 2H), 1.17–1.06 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.1, 167.4, 134.7, 133.5, 129.6, 129.3, 59.3, 48.8, 39.2, 36.4, 32.8, 25.5, 24.8, 24.7. HRMS: calculated for $C_{17}H_{21}ClN_2O_2$: 331.1532, not found, fragment: 194.0376. IR (thin film): $\tilde{\nu}$ = 3296, 3064, 2929, 2853, 1732, 1656, 1538, 1490, 1249, 1091, 802 cm^{-1}.

***N*-(*tert*-Butyl)-2-(4-chlorophenyl)-2-(2-oxoazetidin-1-yl)acetamide (4g):** Following general procedure A, the synthesis was carried out with 4-chlorobenzaldehyde (141 mg, 1.0 mmol, 1 equiv.), β-alanine (89 mg, 1.0 mmol, 1 equiv.) and *tert*-butyl isocyanide (0.11 mL, 1.0 mmol, 1 equiv.). The crude mixture was purified by column chromatography (PE/Et_2O = 60:40 to 40:60) to afford the compound **4g** (181 mg, 0.62 mmol, yield 62 %). Aspect: yellow oil. R_f: 0.37 (PE/Et_2O = 2:8). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.33–7.28 (m, 4H), 6.57 (s, 1H), 5.45 (s, 1H), 3.68–3.65 (m, 1H), 3.15–3.14 (m, 1H), 2.97–2.92 (m, 1H), 2.82–2.78 (m, 1H), 1.29 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.9, 167.7, 134.4, 133.8, 129.5, 129.2, 58.7, 51.7, 39.1, 36.2, 28.5. HRMS: calculated for $C_{15}H_{19}ClN_2O_2$: 294.1135, not found, fragment: 194.0372. IR (thin film): $\tilde{\nu}$ = 3322, 3056, 2969, 1732, 1677, 732 cm^{-1}.

***N*-(*tert*-Butyl)-2-(2-oxoazetidin-1-yl)-2-(*p*-tolyl)acetamide (4h):** Following general procedure A, the synthesis was carried out with 4-methylbenzaldehyde (0.12 mL, 1.0 mmol, 1 equiv.), β-alanine (89 mg, 1.0 mmol, 1 equiv.) and *tert*-butyl isocyanide (0.11 mL, 1.0 mmol, 1 equiv.). The crude mixture was purified by column chromatography (PE/Et_2O = 60:40 to 30:70) to afford the compound **4h** (200 mg, 0.73 mmol, yield 73 %). Aspect: white solid, m.p. 140–144 °C. R_f: 0.18 (PE/Et_2O = 4:6). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.22–7.20 (d, J = 8.1 Hz, 2H), 7.15–7.13 (d, J = 8.1 Hz, 2H), 6.21 (s, 1H), 5.35 (s, 1H), 3.64–3.61 (m, 1H), 3.09–3.06 (m, 1H), 2.94–2.89 (m, 1H), 2.78–2.72 (m, 1H), 2.31 (s, 3H), 1.28 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.3, 167.8, 138.3, 132.1, 129.7, 128.1, 59.2, 51.6, 38.8, 36.1, 28.6, 21.2. HRMS: calculated for $C_{16}H_{22}N_2O_2$: 287.1634, not found, fragment: 174.0914. IR (thin film): $\tilde{\nu}$ = 3321, 2966, 2922, 1731, 1678, 1666, 1541, 1361, 1245, 1223, 577 cm^{-1}.

2-([1,1′-Biphenyl]-4-yl)-*N*-cyclohexyl-2-(2-oxoazetidin-1-yl)acetamide (4i): Following general procedure A, the synthesis was carried out with 4-biphenylaldehyde (182 mg, 1.0 mmol, 1 equiv.), β-alanine (89 mg, 1.0 mmol, 1 equiv.) and cyclohexyl isocyanide 95 % (0.13 mL, 1.0 mmol, 1 equiv.). The crude mixture was purified by column chromatography (PE/Et_2O = 40:60 to 3:7) to afford the compound **4i** (219 mg, 0.60 mmol, yield 60 %). Aspect: yellow oil. R_f: 0.2 (PE/Et_2O = 4:6). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.60–7.56 (t, J =

7.9 Hz, 4H), 7.46–7.42 (t, *J* = 7.8 Hz, 4H), 7.38–7.34 (m, 1H), 6.36–6.34 (d, *J* = 7.8 Hz, 1H), 5.45 (s, 1H), 3.82–3.75 (m, 1H), 3.69–3.66 (m, 1H), 3.24–3.21 (m, 1H), 3.03–2.98 (m, 1H), 2.90–2.85 (m, 1H), 1.92–1.89 (m, 2H), 1.70–1.65 (m, 2H), 1.60–1.56 (m, 1H), 1.38–1.29 (m, 2H), 1.18–1.10 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.1, 167.8, 141.5, 140.4, 134.0, 129.0, 128.6, 127.8, 127.7, 127.2, 59.6, 48.8, 39.1, 36.4, 32.8, 25.5, 24.8, 24.8.

Synthesis of 5a to 5i

General Procedure B, following the literature report:[2]The Ugi product **4** (1 equiv.) was disolved in a solution of anhydrous DMSO (0.5 M) under nitrogen. Then, NaH (2.5 equiv.) was added and a emulsion was observed until complete dissolution of the base. After 15 min, CH_2I_2 (1.5 equiv.) was added. The reaction mixture was stirred vigorously at room temperature for some hours under nitrogen. After completion, the organic layers were extracted with DCM (three times). The combined organic layers were washed with brine (two times), dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by column chromatography (× 10 silica mass) to afford **5a**–**5i**.

Methyl 2-Allyl-2-[3′-(4-chlorophenyl)-2,2′-dioxo-(1,3′-biazetidin)-1′-yl]pent-4-enoate (5a): Following general procedure B, the synthesis was carried out with **4a** (182 mg, 0.47 mmol, 1 equiv.), NaH (46 mg, 1.2 mmol, 2.5 equiv.) and CH_2I_2 (0.06 mL, 0.7 mmol, 1.5 equiv.). The reaction mixture was stirred vigorously at room temperature for three hours under nitrogen. The crude mixture was purified by column chromatography (DCM/Et_2O = 100:0 to 90:10) to afford the compound **5a** (101 mg, 0.25 mmol, yield 53 %). Aspect orange oil. R_f: 0.18 (DCM). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.41–7.35 (m, 4H), 5.79–5.64 (m, 2H), 5.18–5.09 (m, 4H), 4.57–4.55 (d, *J* = 5.9 Hz, 1H), 3.73 (s, 3H), 3.70–3.69 (d, *J* = 5.9 Hz, 1H), 3.38–3.34 (m, 1H), 3.17–3.13 (m, 1H), 3.01–2.95 (m, 1H), 2.93–2.88 (m, 1H), 2.87–2.70 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.0, 167.1, 164.5, 134.8, 134.1, 131.5, 131.4, 129.3, 128.3, 120.2, 120.2, 70.3, 66.0, 53.3, 52.7, 39.2, 39.0, 38.8, 36.7. HRMS: calculated for $C_{21}H_{23}ClN_2O_4$: 402.1346, not found, fragment: 207.0450. IR (thin film): $\tilde{\nu}$ = 3078, 2954, 2923, 1737, 1370, 1219 cm^{-1}.

1′-Cyclohexyl-3′-(4-fluorophenyl)-[1,3′-biazetidine]-2,2′-dione (5b): Following general procedure B, the synthesis was carried out with **4b** (141 mg, 0.46 mmol, 1 equiv.), NaH (48 mg, 1.2 mmol, 2.5 equiv.) and CH_2I_2 (0.06 mL, 0.7 mmol, 1.5 equiv.). The reaction mixture was stirred vigorously at room temperature for five hours under nitrogen. The crude mixture was purified by column chromatography (PE/Et_2O = 80:20 to 40:60) to afford the compound **5b** (68 mg, 0.21 mmol, yield 47 %). Aspect: yellow oil. R_f: 0.13 (PE/Et_2O = 4:6). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45–7.42 (m, 2H), 7.08–7.04 (m, 2H), 4.42–4.41 (d, *J* = 5.6 Hz, 1H), 3.63–3.56 (m, 1H), 3.46–3.44 (d, *J* = 5.6 Hz, 1H), 3.31–3.28 (m, 1H), 3.08–3.05 (m, 1H), 2.98–2.92 (m, 1H), 2.88–2.82 (m, 1H), 1.95–1.92 (m, 1H), 1.83–1.70 (m, 3H), 1.62–1.57 (m, 1H), 1.41–1.22 (m, 4H), 1.16–1.06 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.1, 164.1, 164.0–161.5 (d, *J* = 248.2 Hz), 131.6–131.5 (d, *J* = 3.3 Hz), 128.9–128.8 (d, *J* = 8.3 Hz), 116.1–115.9 (d, *J* = 21.7 Hz), 70.2, 51.4, 49.8, 38.6, 36.6, 30.5, 30.5, 25.2, 24.7. HRMS: calculated for $C_{18}H_{21}FN_2O_2$: 316.1587, not found, fragment: 191.0747. IR (thin film): $\tilde{\nu}$ = 2931, 2855, 1737, 1602, 1509, 1403, 1365, 1224 cm^{-1}.

1′-Cyclohexyl-3′-(pyridin-3-yl)-[1,3′-biazetidine]-2,2′-dione (5c): Following general procedure B, the synthesis was carried out with **4c** (255 mg, 0.9 mmol, 1 equiv.), NaH (88 mg, 2.2 mmol, 2.5 equiv.) and CH_2I_2 (0.11 mL, 1.3 mmol, 1.5 equiv.). The reaction mixture was stirred vigorously at room temperature for six hours under nitrogen. The crude mixture was purified by column chromatography (PE/Et_2O = 20:80 to 0:100; EP/EA = 50:50 to 30:70) to afford the compound **5c** (94 mg, 0.31 mmol, yield 35 %). Aspect: yellow oil. R_f: 0.23 (PE/EA = 5:5). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.68 (s, 1H), 8.60–8.59 (m, 1H), 7.81–7.79 (d, *J* = 7.9 Hz, 1H), 7.34–7.31 (m, 1H), 4.42–4.41 (d, *J* = 5.6 Hz, 1H), 3.64–3.56 (m, 1H), 3.51–3.50 (d, *J* = 5.6 Hz, 1H), 3.36–3.33 (m, 1H), 3.14–3.12 (m, 1H), 3.01–2.88 (m, 2H), 1.95–1.92 (d, *J* = 12 Hz, 1H), 1.84–1.74 (m, 3H), 1.62–1.58 (d, *J* = 12 Hz, 1H), 1.42–1.22 (m, 4H), 1.16–1.06 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.2, 163.3, 150.1, 148.3, 134.7, 131.6, 123.8, 69.1, 51.6, 49.6, 38.8, 36.8, 30.6, 30.5, 25.2, 24.7. HRMS: calculated for $C_{17}H_{21}N_3O_2$: 299.1634, not found, fragment: 174.0782. IR (thin film): $\tilde{\nu}$ = 3330, 2929, 2854, 1736, 1668, 1365, 711 cm^{-1}.

1′-Cyclohexyl-3′-(naphthalen-2-yl)-[1,3′-biazetidine]-2,2′-dione (5d): Following general procedure B, the synthesis was carried out with **4d** (209 mg, 0.6 mmol, 1 equiv.), NaH (62 mg, 1.6 mmol, 2.5 equiv.) and CH_2I_2 (0.08 mL, 0.9 mmol, 1.5 equiv.). The reaction mixture was stirred vigorously at room temperature for three and a half hours under nitrogen. The crude mixture was purified by column chromatography (PE/Et_2O = 70:30 to 40:60) to afford the compound **5d** (112 mg, 0.32 mmol, yield 54 %). Aspect: yellow solid, m.p. 90 °C. R_f: 0.25 (PE/Et_2O = 8:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.01–8.00 (d, *J* = 1.6 Hz, 1H), 7.90–7.83 (m, 3H), 7.52–7.50 (m, 3H), 4.58–4.57 (d, *J* = 5.6 Hz, 1H), 3.70–3.63 (m, 1H), 3.57–3.56 (d, *J* = 5.6 Hz, 1H), 3.36–3.33 (m, 1H), 3.10–3.06 (m, 1H), 3.01–2.95 (m, 1H), 2.92–2.86 (m, 1H), 2.01–1.97 (m, 1H), 1.86–1.72 (m, 3H), 1.63–1.60 (m, 1H), 1.46–1.27 (m, 4H), 1.18–1.10 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.3, 164.4, 133.2, 133.1, 133.0, 129.2, 128.4, 127.8, 126.8, 126.8, 126.1, 124.5, 71.1, 51.3, 49.6, 38.7, 36.6, 30.6, 30.5, 25.3, 24.8. HRMS: calculated for $C_{22}H_{24}N_2O_2$: 348.1838, not found, fragment: 223.0997. IR (thin film): $\tilde{\nu}$ = 3337, 3055, 2927, 2853, 1735, 1363, 748 cm^{-1}.

1′-Cyclohexyl-3′-(quinolin-3-yl)-[1,3′-biazetidine]-2,2′-dione (5e): Following general procedure B, the synthesis was carried out with **4e** (186 mg, 0.6 mmol, 1 equiv.), NaH (56 mg, 1.4 mmol, 2.5 equiv.) and CH_2I_2 (0.07 mL, 0.8 mmol, 1.5 equiv.). The reaction mixture was stirred vigorously at room temperature for six hours under nitrogen. The crude mixture was purified by column chromatography (PE/Et_2O = 40:60 to 0:100; PE/AcOEt = 40:60) to afford the compound **5e** (53 mg, 0.15 mmol, yield 28 %). Aspect: orange oil. R_f: 0.12 (Et_2O). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.96–8.95 (d, *J* = 2.3 Hz, 1H), 8.34–8.33 (d, *J* = 2.3 Hz, 1H), 8.13–8.11 (d, *J* = 8.2 Hz, 1H), 7.87–7.84 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.78–7.73 (m, 1H), 7.61–7.57 (m, 1H), 4.58–4.57 (d, *J* = 5.8 Hz, 1H), 3.69–3.63 (m, 1H), 3.62–3.60 (d, *J* = 5.8 Hz, 1H), 3.39–3.36 (m, 1H), 3.15–3.12 (m, 1H), 3.04–2.98 (m, 1H), 2.96–2.90 (m, 1H), 2.01–1.97 (m, 1H), 1.85–1.72 (m, 3H), 1.65–1.60 (m, 1H), 1.38–1.27 (m, 4H), 1.19–1.11 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.2, 163.6, 149.4, 148.0 134.3, 130.4, 129.4, 128.6, 128.3 127.6, 127.4, 69.3, 51.6, 49.5, 38.9, 36.9, 30.6, 30.6, 25.2, 24.8. HRMS: calculated for $C_{21}H_{23}N_3O_2$: 349.1790, not found, fragment: 224.0951. IR (thin film): $\tilde{\nu}$ = 2931, 2854, 1742, 1671, 1370, 754 cm^{-1}.

3′-(4-Chlorophenyl)-1′-cyclohexyl-[1,3′-biazetidine]-2,2′-dione (5f): Following general procedure B, the synthesis was carried out with **4f** (100 mg, 0.3 mmol, 1 equiv.), NaH (31 mg, 1.8 mmol, 2.5 equiv.) and CH_2I_2 (0.04 mL, 0.45 mmol, 1.5 equiv.). The reaction mixture was stirred vigorously at room temperature for four hours under nitrogen. The crude mixture was purified by column chromatography (PE/Et_2O = 50:50 to 40:60) to afford the compound **5f** (49 mg, 0.15 mmol, yield 49 %). Aspect: yellow oil. R_f: 0.24 (PE/Et_2O = 4:6). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.40–7.34 (m, 4H), 4.42–4.41 (d, *J* = 5.6 Hz, 1H), 3.62–3.55 (m, 1H), 3.45–3.44 (d, *J* = 5.6 Hz, 1H), 3.32–3.29 (m, 1H), 3.09–3.06 (m, 1H), 2.99–2.93 (m, 1H), 2.89–2.83 (m, 1H), 1.94–1.91 (m, 1H), 1.82–1.73 (m, 3H), 1.61–1.58 (m, 1H),

1.34–1.22 (m, 4H), 1.15–1.09 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.2, 163.9, 134.8, 134.2, 129.3, 128.4, 70.3, 51.4, 49.7, 38.7, 36.6, 30.6, 30.5, 25.2, 24.7. HRMS: calculated for $C_{17}H_{21}ClN_2O_2$: 332.1292, not found, fragment: 207.0454. IR (thin film): $\tilde{\nu}$ = 3316, 2929, 2854, 1737, 1666, 1491, 1401, 1364, 1091, 1013 cm^{-1}.

1′-(*tert*-Butyl)-3′-(4-chlorophenyl)-[1,3′-biazetidine]-2,2′-dione (5g): Following general procedure B, the synthesis was carried out with **4g** (330 mg, 1.1 mmol, 1 equiv.), NaH (108 mg, 2.7 mmol, 2.5 equiv.) and CH_2I_2 (0.14 mL, 1.7 mmol, 1.5 equiv.). The reaction mixture was stirred vigorously at room temperature for four and a half hours under nitrogen. The crude mixture was purified by column chromatography (PE/Et_2O = 90:10 to 50:50) to afford the compound **5g** (144 mg, 0.47 mmol, yield 43 %). Aspect: orange crystals, m.p. 87–88 °C. R_f: 0.18 (PE/Et_2O = 4:6). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.42–7.34 (m, 4H), 4.41–4.39 (d, J = 5.7 Hz, 1H), 3.42–3.41 (d, J = 5.7 Hz, 1H), 3.34–3.30 (m, 1H), 3.09–3.06 (m, 1H), 3.00–2.94 (m, 1H), 2.89–2.84 (m, 1H), 1.34 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.2, 163.5, 134.8, 134.4, 129.3, 128.4, 69.5, 53.8, 49.4, 38.7, 36.7, 27.6. HRMS: calculated for $C_{16}H_{19}ClN_2O_2$: 306.1135, not found, fragment: 207.0446. IR (thin film): $\tilde{\nu}$ = 2971, 2905, 1737, 1680, 1492, 1365, 1092, 1013 cm^{-1}.

1′-(*tert*-Butyl)-3′-(*p*-tolyl)-[1,3′-biazetidine]-2,2′-dione (5h): Following a modified version of general procedure B, the synthesis was carried out with **4h** (160 mg, 0.6 mmol, 1 equiv.), NaH (90 mg, 2.3 mmol, 3.75 equiv.) and CH_2I_2 (0.11 mL, 1.4 mmol, 2.25 equiv.). The reaction mixture was stirred vigorously at room temperature for seven hours under nitrogen. The crude mixture was purified by column chromatography (PE/Et_2O = 70:30 to 40:60) to afford the compound **5h** (55 mg, 0.19 mmol, yield 33 %). Aspect: yellow solid, m.p. 110 °C. R_f: 0.38 (PE/Et_2O = 3:7). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36–7.34 (d, J = 8.2 Hz, 2H), 7.21–7.19 (d, J = 8.2 Hz, 2H), 4.44–4.43 (d, J = 5.5 Hz, 1H), 3.44–3.43 (d, J = 5.5 Hz, 1H), 3.33–3.29 (m, 1H), 3.09–3.05 (m, 1H), 2.99–2.93 (m, 1H), 2.88–2.83 (m, 1H), 2.35 (s, 3H), 1.35 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.3, 164.2, 138.7, 132.9, 129.7, 126.9, 69.9, 53.7, 49.5, 38.6, 36.5, 27.7, 21.3. HRMS: calculated for $C_{17}H_{22}N_2O_2$: 286.1681, not found, fragment: 187.0992. IR (thin film): $\tilde{\nu}$ = 2969, 2924, 1737, 1365 cm^{-1}.

3′-([1,1′-Biphenyl]-4-yl)-1′-cyclohexyl-[1,3′-biazetidine]-2,2′-dione (5i): Following general procedure B, the synthesis was carried out with **4i** (192 mg, 0.53 mmol, 1 equiv.), NaH (90 mg, 1.3 mmol, 2.5 equiv.) and CH_2I_2 (0.065 mL, 0.8 mmol, 1.5 equiv.). The reaction mixture was stirred vigorously at room temperature for five hours under nitrogen. The crude mixture was purified by column chromatography (DCM/Et_2O = 95:5) to afford the compound **5i** (120 mg, 0.32 mmol, yield 61 %). Aspect: orange oil. R_f: 0.25 (DCM/Et_2O = 9:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.63–7.52 (m, 6H), 7.45–7.42 (m, 2H), 7.37–7.33 (m, 1H), 4.50–4.48 (d, J = 5.6 Hz, 1H), 3.68–3.61 (m, 1H), 3.55–3.53 (d, J =5.6 Hz, 1H), 3.38–3.34 (m, 1H), 3.17–3.13 (m, 1H), 3.01–2.95 (m, 1H), 2.93–2.87 (m, 1H), 2.00–1.96 (m, 1H), 1.88–1.85 (m, 1H), 1.81–1.72 (m, 2H), 1.64–1.60 (m, 1H), 1.49–1.25 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.2, 164.3, 141.6, 140.3, 134.5, 128.9, 127.7, 127.7, 127.3, 127.1, 70.7, 51.3, 49.8, 38.7, 36.6, 30.6, 30.5, 25.2, 24.8. HRMS: calculated for $C_{24}H_{26}N_2O_2$: 374.1994, not found, fragment: 249.1149. IR (thin film): $\tilde{\nu}$ = 3478, 3030, 2929, 2853, 1736, 1666, 1486, 1400, 1363, 1262, 1006, 761, 729 cm^{-1}.

One Pot Synthesis of 5i to 5l

General Procedure C: To a dried microwave tube was added aldehyde **2** (1.0 mmol, 1 equiv.), β-amino acid **3** (1.0 mmol, 1 equiv.), isocyanide **1** (1.0 mmol, 1 equiv.) and MeOH (1.0 M, 1 mL). The tube was filled with nitrogen before heating under microwave condition to 120 °C, 100 W for 1 hour. After completion, the solvent was removed under reduced pressure, and the obtained oil was disolved in a solution of anhydrous DMSO (0.5 M) under nitrogen. Then, NaH (2.5 equiv.) was added and a emulsion was observed until complete dissolution of the base. After 15 min, CH_2I_2 (1.5 equiv.) was added. The reaction mixture was stirred vigorously at room temperature for five hours under nitrogen. The organic layers were extracted with DCM (three times). The combined organic layers were washed with brine (two times), dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by column chromatography (× 10 silica mass) to afford **5i**–**5l**.

3′-([1,1′-Biphenyl]-4-yl)-1′-cyclohexyl-[1,3′-biazetidine]-2,2′-dione (5i): Following general procedure C, the synthesis was carried out with 4-biphenylaldehyde (182 mg, 1.0 mmol, 1 equiv.), β-alanine (89 mg, 1.0 mmol, 1 equiv.) and cyclohexyl isocyanide 95 % (0.13 mL, 1.0 mmol, 1 equiv.). The crude mixture was purified by column chromatography (PE/Et_2O = 70:30 to 50:50) to afford the compound **5i** (169 mg, 0.45 mmol, yield 45 %). Aspect: orange oil. R_f: 0.18 (PE/Et_2O = 4:6). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.63–7.52 (m, 6H), 7.45–7.42 (m, 2H), 7.37–7.33 (m, 1H), 4.50–4.48 (d, J = 5.6 Hz, 1H), 3.68–3.61 (m, 1H), 3.55–3.53 (d, J =5.6 Hz, 1H), 3.38–3.34 (m, 1H), 3.17–3.13 (m, 1H), 3.01–2.95 (m, 1H), 2.93–2.87 (m, 1H), 2.00–1.96 (m, 1H), 1.88–1.85 (m, 1H), 1.81–1.72 (m, 2H), 1.64–1.60 (m, 1H), 1.49–1.25 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.2, 164.3, 141.6, 140.3, 134.5, 128.9, 127.7, 127.7, 127.3, 127.1, 70.7, 51.3, 49.8, 38.7, 36.6, 30.6, 30.5, 25.2, 24.8. HRMS: calculated for $C_{24}H_{26}N_2O_2$: 374.1994, not found, fragment: 249.1149. IR (thin film): $\tilde{\nu}$ = 3478, 3030, 2929, 2853, 1736, 1666, 1486, 1400, 1363, 1262, 1006, 761, 729 cm^{-1}.

1′-Cyclohexyl-3′-(4-methoxyphenyl)-[1,3′-biazetidine]-2,2′-dione (5j): Following a modified version of general procedure C, the synthesis was carried out with *p*-anisaldehyde (0.12 mL, 1.0 mmol, 1 equiv.), β-alanine (89 mg, 1.0 mmol, 1 equiv.) and cyclohexyl isocyanide 95 % (0.13 mL, 1.0 mmol, 1 equiv.). After the addition of NaH and CH_2I_2, the reaction mixture was stirred vigorously at 50 °C for three hours under nitrogen. The crude mixture was purified by column chromatography (PE/Et_2O = 80:20 to 20:80) to afford the compound **5j** (134 mg, 0.41 mmol, yield 41 %). Aspect: orange oil. R_f: 0.31 (PE/Et_2O = 2:8). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39–7.35 (m, 2H), 6.91–6.87 (m, 2H), 4.42–4.41 (d, J = 5.5 Hz, 1H), 3.78 (s, 3H), 3.63–3.55 (m, 1H), 3.45–3.44 (d, J = 5.5 Hz, 1H), 3.28–3.24 (m, 1H), 3.06–3.03 (m, 1H), 2.95–2.89 (m, 1H), 2.86–2.80 (m, 1H), 1.96–1.92 (m, 1H), 1.82–1.70 (m, 3H), 1.60–1.57 (m, 1H), 1.44–1.22 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.1, 164.6, 159.8, 128.3, 127.7, 114.3, 70.4, 55.4, 51.2, 49.8, 38.5, 36.4, 30.5, 30.5, 25.3, 24.8. HRMS: calculated for $C_{19}H_{24}N_2O_3$: 328.1787, not found, fragment: 203.0940. IR (thin film): $\tilde{\nu}$ = 2923, 2853, 1737, 1680, 1513, 1365, 1247, 1179 cm^{-1}.

1′-Cyclohexyl-3′-(naphthalen-2-yl)-4-phenyl-[1,3′-biazetidine]-2,2′-dione (5k): Following a modified version of general procedure C, the synthesis was carried out with 2-naphthaldehyde (156 mg, 1.0 mmol, 1 equiv.), DL-3-Amino-3-phenylpropionic acid (165 mg, 1.0 mmol, 1 equiv.) and cyclohexyl isocyanide 95 % (0.13 mL, 1.0 mmol, 1 equiv.). After the addition of NaH and CH_2I_2, the reaction mixture was stirred vigorously at 50 °C for three hours under nitrogen. The crude mixture was purified by column chromatography (PE/Et_2O = 90:10 to 0:100) to afford the compound **5k** (220 mg, 0.52 mmol, yield 52 %). Mixture of diastereomers: *dr* 94:6. Aspect: orange solid, m.p. 135–137 °C. R_f: 0.34 (PE/Et_2O = 3:7). ^{1}H NMR (400 MHz, $CDCl_3$) δ = (C-H$^{major\ isomer}$) 7.77–7.59 (m, 4H), 7.51–7.44 (m, 2H), 7.30–7.27 (m, 1H), 7.05–6.98 (m, 3H), 6.92–6.90 (m, 2H), 4.54–4.53 (dd, J = 5.5, 2.5 Hz, 1H), 4.38–4.37 (d, J = 5.3 Hz, 1H), 3.71–3.64 (m, 1H), 3.70–3.69 (d, J = 5.3 Hz, 1H), 3.44–3.39 (dd, J = 15.1,

5.5 Hz, 1H), 2.91–2.87 (dd, *J* = 15.1, 2.5 Hz, 1H), 2.09–2.06 (m, 1H), 1.84–1.63 (m, 5H), 1.37–1.29 (m, 3H), 1.20–1.11 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = ($C^{major\ isomer}$) 167.4, 164.6, 138.5, 133.0, 132.7, 131.6, 128.3, 128.2, 128.1, 128.1 127.5, 127.4, 126.7, 126.6, 126.3, 125.4, 70.9, 55.2, 51.4, 50.4, 46.0, 30.5, 30.5, 25.4, 24.8, 24.8. HRMS: calculated for $C_{28}H_{28}N_2O_2$: 424.2151, not found, fragment: 299.1306. IR (thin film): $\tilde{\nu}$ = 3319, 3057, 2929, 2854, 1732, 1661, 1362, 1346, 745, 697 cm^{-1}.

3′-([1,1′-Biphenyl]-4-yl)-1′-cyclohexyl-4-phenyl-[1,3′-biazetidine]-2,2′-dione (5l): Following a modified version of general procedure C, the synthesis was carried out with 4-biphenylaldehyde (182 mg, 1.0 mmol, 1 equiv.), DL-3-Amino-3-phenylpropionic acid (165 mg, 1.0 mmol, 1 equiv.) and cyclohexyl isocyanide 95 % (0.13 mL, 1.0 mmol, 1 equiv.). After the addition of NaH and CH_2I_2, the reaction mixture was stirred vigorously at 50 °C for three hours under nitrogen. The crude mixture was purified by column chromatography (PE/Et_2O = 98:2 to 30:70) to afford the compound **5l** (145 mg, 0.32 mmol, yield 32 %). Mixture of diastereomers: *dr* 0.85:0.15. Aspect: yellow solid, m.p. 60–65 °C. R_f: 0.25 (PE/Et_2O = 4:6). ^{1}H NMR (400 MHz, $CDCl_3$) δ = ($C\text{-}H^{major\ isomer}$) 7.41–7.33 (m, 4H), 7.29–7.26 (m, 1H), 7.22–7.15 (m, 4H), 7.09–7.00 (m, 3H), 6.88–6.87 (d, *J* = 7.7 Hz, 2H), 4.45–4.44 (m, 1H), 4.26–4.24 (d, *J* = 4.8 Hz, 1H), 3.57–3.52 (m, 1H), 3.55–3.54 (d, *J* = 4.8 Hz, 1H), 3.32–3.27 (dd, *J* = 15.0, 5.4 Hz, 1H), 2.79–2.75 (d, *J* = 15.0 Hz, 1H), 1.97–1.94 (m, 1H), 1.73–1.63 (m, 3H), 1.55–1.52 (m, 1H), 1.29–1.14 (m, 4H), 1.09–1.04 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = ($C^{major\ isomer}$) 167.4, 164.7, 141.4, 140.6, 138.7, 133.1, 128.9, 128.4, 128.4, 128.0, 127.6, 127.1, 126.9, 126.8, 70.6, 55.1, 51.4, 50.2, 45.9, 30.5, 30.4, 25.4, 24.8. HRMS: calculated for $C_{30}H_{30}N_2O_2$: 450.2307, not found, fragment: 325.1458. IR (thin film): $\tilde{\nu}$ = 3285, 3058, 3030, 2928, 2853, 1739, 1658, 1364, 1343, 762, 730, 695 cm^{-1}.

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Keywords: β-Lactams · Ugi reaction · Amide dianions · Multicomponent reactions · Diiodomethane

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[7] CCDC 1900062 (for **5g**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[8] For poorly selective U-4C-3C using 3-aryl β-alanines see: ref (4d), (4h). For a diastereoselective β-lactam formation using chiral isocyanides in U-4C-3C see: T. M. Vishwanatha, N. Narendra, V. V. Sureshbabu, *Tetrahedron Lett.* **2011**, *52*, 5620–5624.

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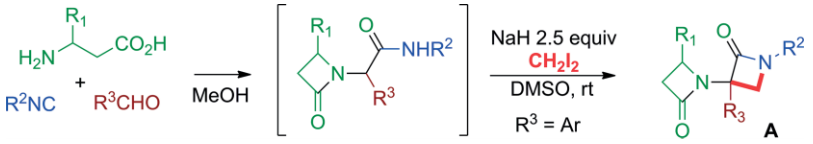

Ugi reactions at the cutting edge of β-lactams synthesis: consecutive cyclizations towards bis-β-lactam derivatives from β-amino acids derivatives

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