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Synthesis of 3-substituted pyrrolidin-2-ones and 3-substituted piperidin-2-ones from esters

Lara Brunotte, Lars Beckmann, Marko Ljiljanic, and Till Opatz*

Department of Chemistry, Johannes Gutenberg University Mainz, Duesbergweg 10–14, 55128 Mainz, Germany
E-mail: opatz@uni-mainz.de

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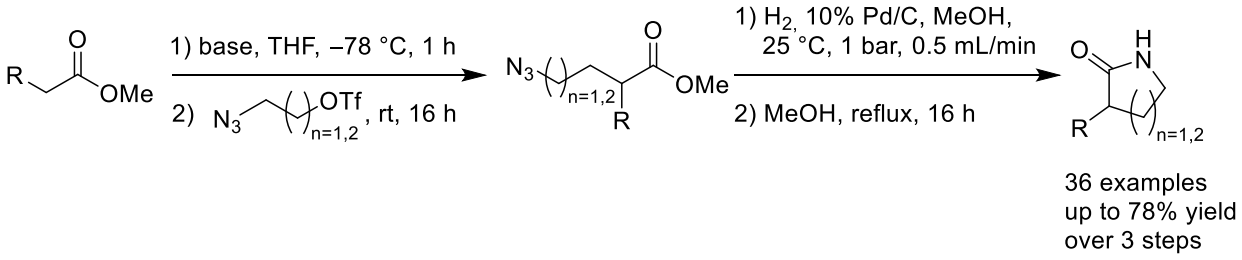
Abstract

δ-Lactams and γ-lactams present important structural moieties which are found in many pharmaceuticals, targeting a wide array of diseases.[1,2] Starting from commercially available esters, we developed a facile method for the synthesis of 3-substituted pyrrolidin-2-ones and piperidin-2-ones. To this end, the ester is α-alkylated with 2-azidoethyl trifluoromethanesulfonate or 2-azidopropyl trifluoromethanesulfonate, followed by azide reduction and ring closure. A continuous flow protocol was developed for the azide – amine transformation but a batch protocol is available as well.



Keywords: Ester α-alkylation, flow-reduction, lactam formation.

Introduction

Lactams, cyclic amides categorized by their ring size, are recognized as an important class of heterocycles.[2,3] Beyond their well-known therapeutic properties, the γ- and δ-lactam moiety is contained in a myriad of biologically significant compounds.[1,2] For example antibiotics,[1] antitumor agents,[4,5] and antidepressants,[6] HIV-1 integrase inhibitors,[7] and drugs for the treatment of type-II diabetes.[8] Additionally, these structures are essential intermediates in the synthesis of various natural products and pharmaceuticals,[1,2,9] driving the need of the development of innovative methods for the synthesis of these lactam structures.

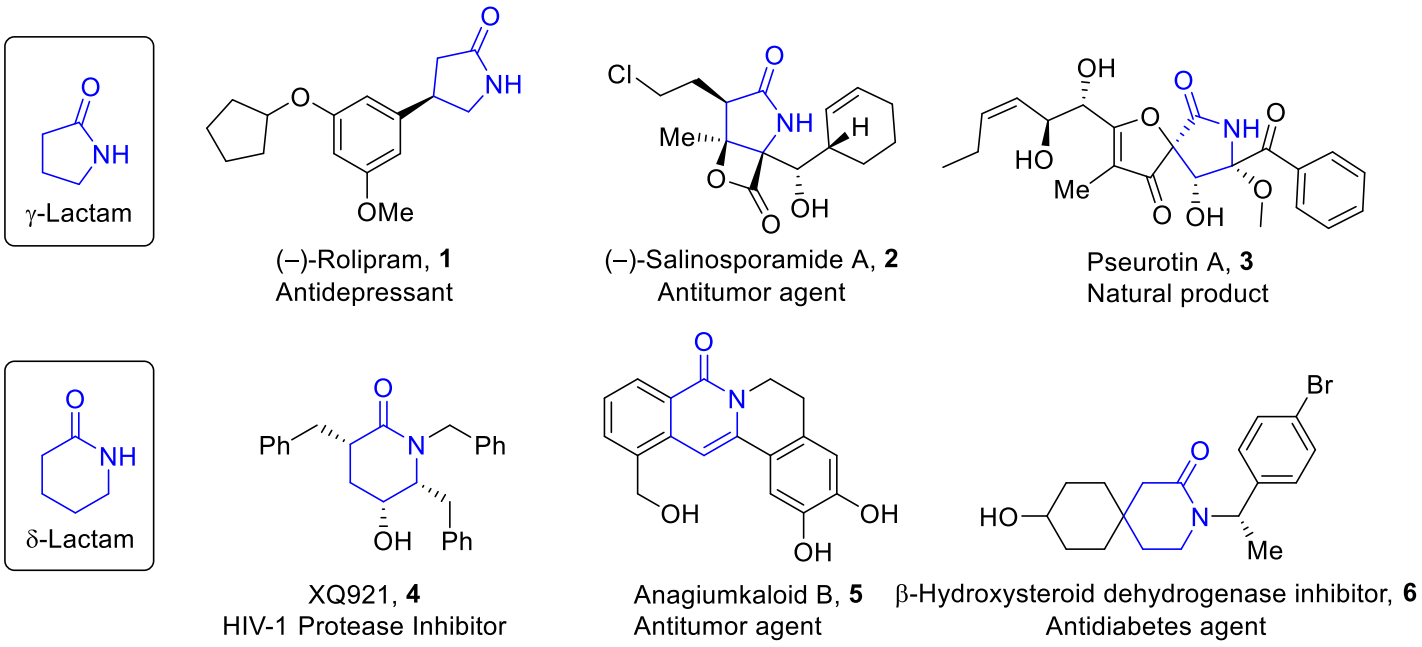
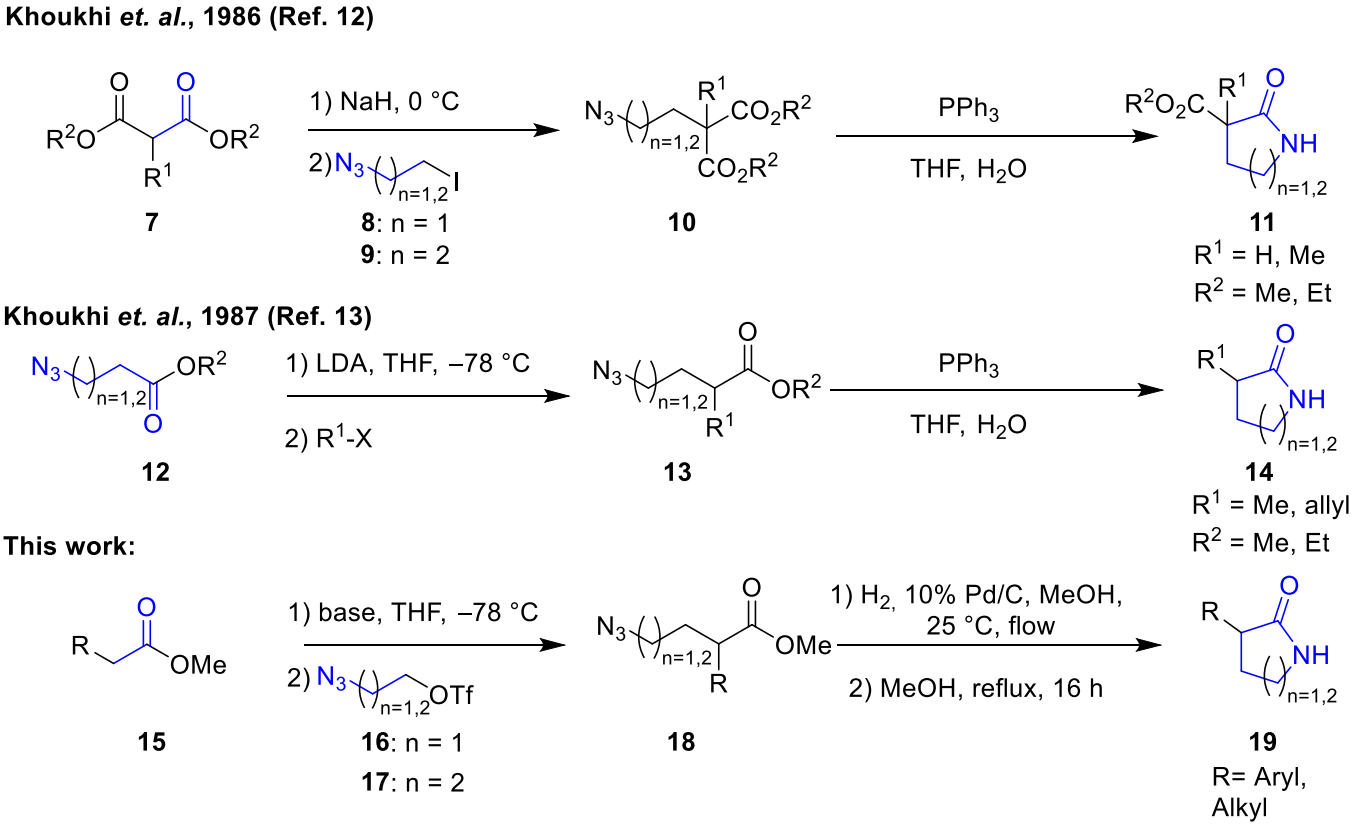


Figure 1. γ- and δ-lactam related APIs and natural products.

In recent years, numerous synthetic approaches have been reported for the synthesis of γ- and δ-lactams: One of the most common strategies is the cyclization by amide bond formation between a carboxylate group and an amine or amine precursor.[1] Lactam rings can also be synthesized by C–C bond formations,[1,3] in isocyanide-based multicomponent reactions[10] or different types of cycloadditions.[11]

As starting point of our investigations, we chose the work of Khoukhi *et al.*, they reported on a method for lactam synthesis, starting from malonic esters **7** and 1-azido-2-iodoethane **8** or 1-azido-3-iodopropane **9** as alkylating agents (Scheme 1). The latter were synthesized from the corresponding chloroalcohols in three steps.[12] Later, the same group reported on a different strategy where they directly used azidoesters **12**, which then underwent alkylation in α-position, albeit with only a limited scope being demonstrated.[13] The reduction of the azide, in both cases, was performed via a Staudinger reaction.

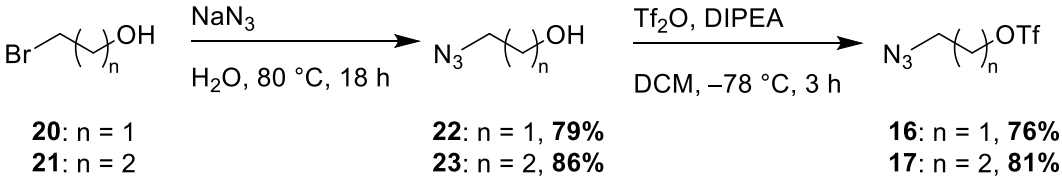
In comparison to Khoukhi *et al.*, we used 2-azidoethyl trifluoromethanesulfonate **16** or 3- azidopropyl trifluoromethanesulfonate **17** as alkylating agents, as they can be prepared in two steps. In contrast to the literature procedure, we focused on various methyl esters **15** as they, or their corresponding acids are abundantly and readily commercially available. A continuous flow protocol was developed using a flow hydrogenation reactor (H-Cube® Mini Plus) for efficient azide reduction. Ring closure to the desired product proceeded without the need of any further additives under heating (Scheme 1).



Scheme 1. Different methods to generate lactams from azido esters.

Results and Discussion

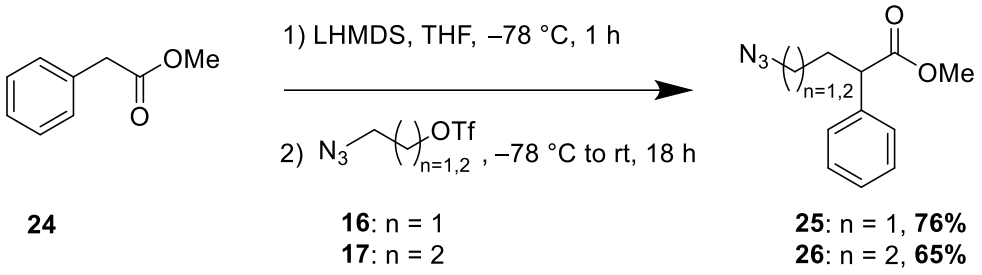
As a viable alkylating agent should carry a good leaving group to increase scope and efficiency along with a masked amine moiety and should be stable to allow for easy handling, we opted for ω-azido triflates. Azides as amine precursors are well established while being almost non-nucleophilic. Specifically, we synthesized 2-azidoethyl trifluoromethanesulfonate **16** and 2-azidopropyl trifluoromethanesulfonate **17** through a concise two-step process in good yields.[14–16] Notably, the synthesized compounds did not require further purification and are stable for several months when stored at −25 °C.



Scheme 2. Synthesis of 2-azidoethyl trifluoromethanesulfonate and 2-azidopropyl trifluoromethanesulfonate from the corresponding ω-bromo alcohols.

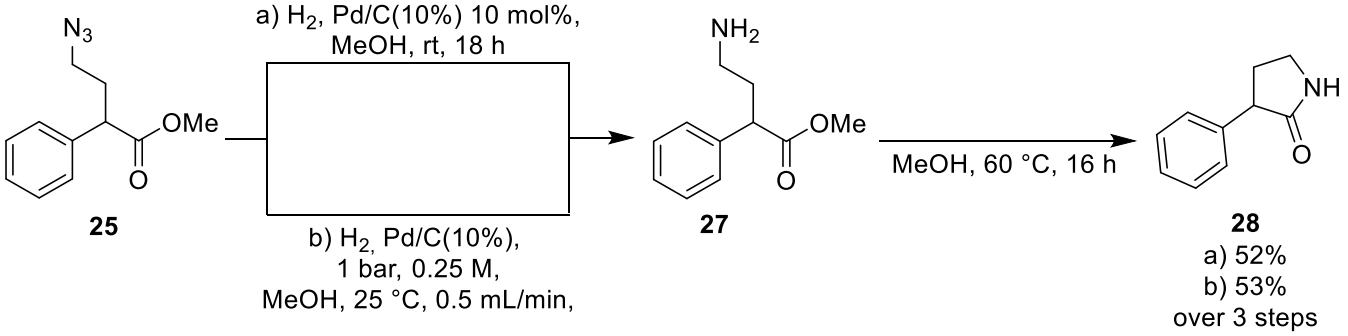
The alkylating agents **16** and **17** were tested in the reaction with methyl phenylacetate **24** under standard literature conditions (Scheme 3).[17,18] The procedure involved deprotonation with lithium hexamethyldisilazide (LHMDS) in THF at −78 °C under an inert atmosphere. GC/MS analysis indicated nearly full conversion of the

ester **24** to the corresponding azido esters **25** and **26**. However, a loss in yield during purification was observed. Consequently, we decided to proceed with the crude ω-azido esters to the next reaction step, which gratifyingly proved to be a feasible approach.



Scheme 3. Alkylation of methyl phenylacetate with 2-azidoethyltrifluoromethanesulfonate and 2- azidopropyl trifluoromethanesulfonate.

There are various options to reduce an azide to an amine and we selected the reduction with hydrogen in the presence of catalytic amounts of palladium on carbon to avoid the production of co-products and reagent waste, inevitably produced in Staudinger reactions and related procedures. Initially, we performed the reduction of the crude azido ester **25** using hydrogen in batch, followed by ring closure to synthesize 3-phenylpyrrolidin-2-one **28** from ester **24**. In addition, we developed a flow protocol for the reduction of the crude azido ester **25** using the H-Cube® Mini Plus, a flow hydrogenation reactor from ThalesNano. For this reduction, the crude azido ester **25** is dissolved in MeOH (0.25 M). The solution is mixed in the H-Cube® with electrochemically generated hydrogen and pumped through a cartridge containing Pd/C (10 wt-%) at a flow rate of 0.5 mL/min. TLC and LC-MS showed complete conversion to the corresponding amine **27** in both cases. Both the batch and flow reduction, followed by ring closure under heating, yielded similar results (Scheme 4).



Scheme 4. Reduction of methyl 4-azido-2-phenylbutanoate in a batch process and a flow process with subsequent ring closure (Yields are based on methyl phenylacetate).

We chose the flow reduction due to its advantages over the batch reduction: The flow reactor employed does not require external hydrogen source as it generates hydrogen by the electrolysis of water, which eliminates safety issues if performed on larger scale. Additionally, using the Pd/C (10 wt-%) cartridge in the flow process eliminates the need for catalyst removal and recycling. The cartridge can be re-used many times, during the entire project, only a single cartridge was used and no decrease of activity was observed. After the flow

reduction, the resulting amine, dissolved in MeOH, was directly heated to induce ring closure, without the need of any additives. Only the final product needs to be purified via column chromatography.

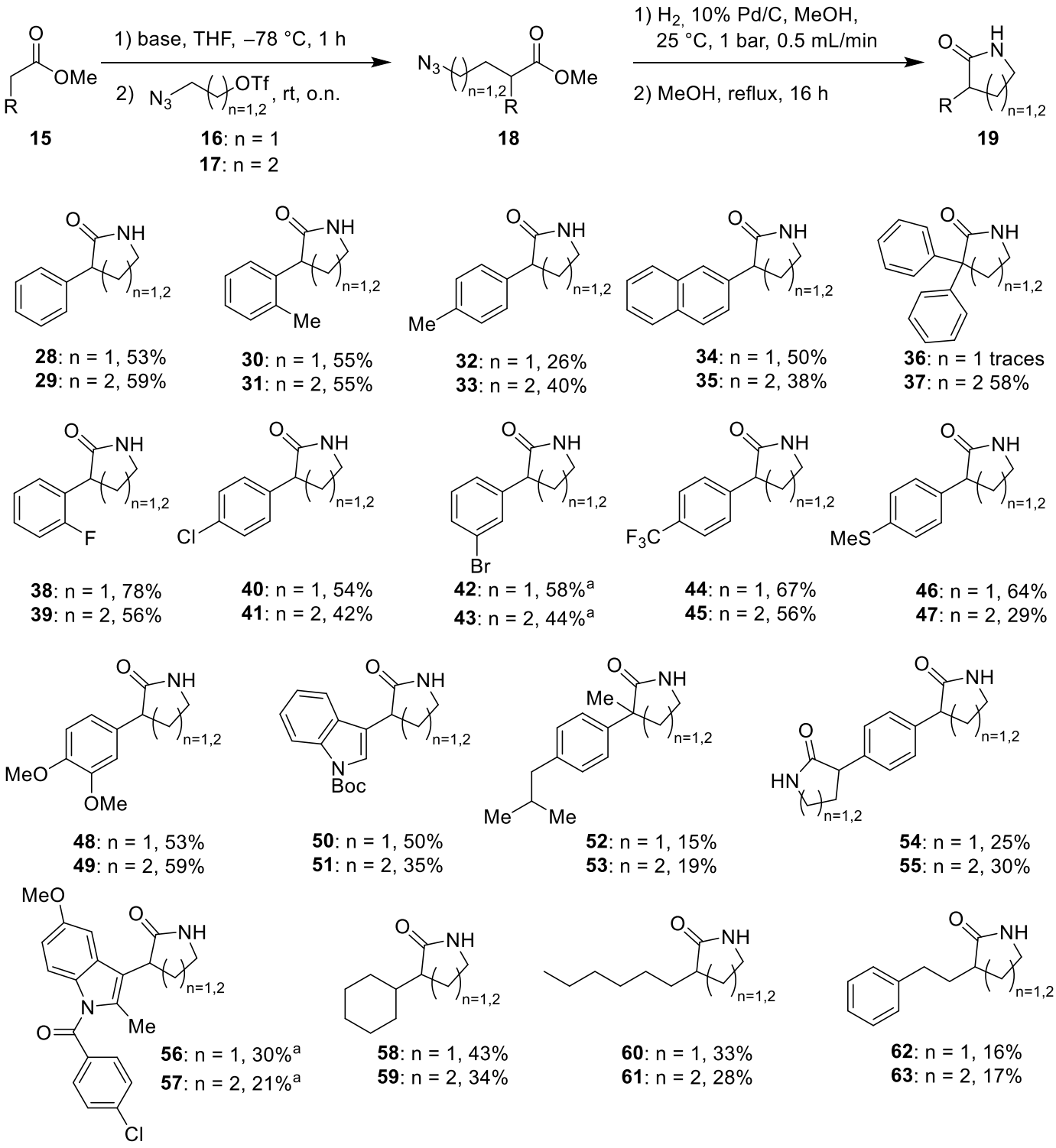
With this approach in hand, we proceeded to test our protocol in a broader scope of substrates (Scheme 5). The yields for lactams synthesized are reported over three steps. Starting from phenylacetic acid derivatives **15** yields up to 78% were achieved. Functional groups such as lighter halogens (**38**– **41**), methoxy groups (**48** and **49**), thioethers (**46** and **47**) and indoles (**50** and **51**) are tolerated remarkably well. It has to be noted however that the bromo-substituted aryl compounds underwent debromination upon hydrogenation and a Staudinger reaction had to be employed. This reaction directly yields the lactams **42** and **43**, due to the higher reaction temperature required for the reduction step. The use of triphenylphosphine led to the formation of stochiometric amounts of triphenylphosphine oxide, which needs to be removed. We also successfully synthesized two lactam rings on the same molecule, starting from dimethyl 2,2'-(1,4-phenylene)diacetate, this reaction gave the envisioned lactams **54** and **55** as diastereomeric mixtures. The diphenyl lactams **36** and **37** provided interesting results: the synthesis of the δ-lactam **37** proceeded successfully yielding the product in 58%. In contrast, the γ-lactam **36** was only formed in traces as judged by LCMS. In this case, the combination of the shorter alkyl chain and the sterically demanding α,α-diphenyl substitution hampers the ring closing and the open chain γ-amino acid ester is obtained instead according to LCMS.

Additionally, we could show that our method is suitable for late-stage modification of pharmaceutical compounds like ibuprofen and indomethacin. This gave lactams **52**, **53**, **56** and **57**. However, the indomethacin derivates **56** and **57** required the Staudinger reduction as decomposition was observed during flow hydrogenation.

Gratifyingly, we could transfer this workflow to aliphatic esters by switching the base to freshly prepared lithium diisopropylamide (LDA) as the base in the alkylation step. The yields for alkyl lactams **58 – 63** are however generally lower compared to the aryl substituted counterparts.

Upscaling of the reaction to ten times standard size only needed slight modifications to the procedure (increasing the flow rate to 1.0 mL/min and doubling the cartridge size). The overall yield of the 3-phenylpiperidin-2-one decreased from 59% to 35%, which can likely be counteracted by further optimization.

The use of higher homologues of the ω-azido triflates is not feasible, as these compounds readily decompose during workup.



[a] Staudinger reduction: PPh_3 (1.1 eq.), THF/H_2O (10/1), 60 °C, 16 h.

Scheme 5. Substrates for the three-step synthesis of γ- and δ-lactams.

Conclusions

In summary, we have developed a three-step synthesis of γ- and δ-lactams starting from commercially available esters showing good functional group tolerance in combination with purification only in the last step. The synthesis sequence consists of an aromatic or aliphatic ester with 2-azidoethyl trifluoromethanesulfonate **16** and 3-azidopropyl trifluoromethanesulfonate **17**, followed by a continuous flow protocol on the H-Cube® Mini Plus for efficient azide reduction. The amine closes the ring to the desired product without the need for any additives.

Experimental Section

General. Unless stated otherwise, all solvents and reagents were obtained from commercial suppliers and used without prior purification. MeOH for esterifications was purchased from commercial suppliers as extra dry solvent stored over 3 Å molecular sieves and used without additional purification. Anhydrous THF and DCM was used from an SPS5 solvent purification system (MBRAUN). All air or moisture sensitive reactions were performed under an inert atmosphere of nitrogen in glassware that was oven dried using standard Schlenk techniques.
Preparative column chromatography was performed using an *Isolera One* (Biotage) using either cyclohexane and ethyl acetate (35–70 µm, Acros Organics normal phase) or water and acetonitrile (C-18 modified silica, reverse phase). Thin-layer chromatography (TLC) was carried out on silica plates (TLC Silica 60 F_{254}, Merck KGaA). Visualization of the compounds was accomplished by illumination with UV light of the developed plates and by staining with Seebach's reagent. NMR spectra were recorded on a Bruker Avance-III HD (^{1}H NMR: 300 MHz, ^{13}C NMR: 75.5 MHz) or a Bruker Avance-II (^{1}H NMR: 400 MHz, ^{13}C NMR: 100.6 MHz) spectrometer. Chemical shifts are referenced to residual solvent signals ($CDCl_3$: 7.26 ppm and 77.16 ppm or MeOD-d_4: 3.31 ppm and 49.0 ppm for ^{1}H NMR and ^{13}C NMR) and reported in parts per million (ppm) relative to tetramethylsilane (TMS). Electron spray ionization (ESI) mass spectra were recorded on a 1200-series HPLC- system (Agilent-Technologies) with binary pump and integrated diode array detector coupled to an *Agilent Infinity Lab 6100 Series* LCMSD (G6125B). High resolution mass spectra were recorded on an *Agilent G6545A Q-Tof* with ESI source coupled with an *Agilent 1260 Infinity II HPLC system*. GC-MS was performed using an *Agilent 8890 GC* gas chromatograph coupled to a *5977 GC/MS* detector and an FID (flame ionization detector). As the stationary phase, an *Agilent Technologies HP 5MS UI* GC column (30 m × 0.25 mm × 0.25 µm) and helium as a carrier gas were used. IR spectra were recorded on a Tensor 27 spectrometer with a diamond ATR unit from Bruker. The measured spectra were analyzed using the Opus 7.2 software from Bruker. In the following, only the ten most intense bands are given together with characteristic bands. Melting ranges were determined in open glass capillaries on a melting point measuring device type MP30 from Mettler Toledo.

General procedure 1. Esterification of carboxylic acids
To a 50 mL round-bottom flask containing the corresponding carboxylic acid MeOH was added and a catalytic amount of conc. H_2SO_4. The reaction mixture was stirred overnight under reflux. The solvent was removed under reduced pressure and the crude material was dissolved in diethyl ether and washed with brine. The ether phase was dried over Na_2SO_4 and the solvent was removed in vacuum to give the methyl ester.
All methyl esters used are known compounds and therefore not reported separately here.

General procedure 2. Synthesis of azido alcohols

The bromo alcohol (1.00 eq.) was dissolved in water (20 mL) and sodium azide (3.00 eq.) was added. The reaction mixture was heated to 80 °C for 18 h. The mixture was cooled to room temperature and extracted with ether (3 × 20 mL). The organic layers were dried over Na_2SO_4, filtered and the concentrated in vacuum to give the crude azido alcohols. The azido alcohols were used in the next reactions without further purification. Attention: products are highly volatile.[14]

2-Azidoethan-1-ol (22). Synthesized from 2-bromo ethanol (**20**, 3.00 g, 24.0 mmol, 1.00 eq.) according to the general procedure 2. Yield: 79%; colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$)**:** δ(ppm) = 3.77 (dd, *J* = 10.3, 5.4 Hz, 2H), 3.44 (t, *J* = 4.8 Hz, 2H), 1.98 (t, *J* = 5.8 Hz, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$)**:** δ(ppm) = 61.6, 53.6. IR (ATR)**:** $\tilde{\nu}$ (cm^{-1}) = 3366, 2935, 2881, 2093, 1441, 1347, 1285, 1061, 876, 497. The spectroscopic data are in accordance with literature.[14]

3-Azidopropan-1-ol (23). Synthesized from 3-bromo propan-1-ol (**21**, 3.00 g, 21.7 mmol, 1.00 eq.) according to the general procedure 2. Yield: 86%; colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$)**:** δ(ppm) = 3.75 (t, *J* = 6.0 Hz, 2H), 3.45 (t, *J* = 6.6 Hz, 2H), 1.88 – 1.78 (m, 2H), 1.73 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$)**:** δ(ppm) = 60.0, 48.6, 31.5. IR (ATR)**:** $\tilde{\nu}$ (cm^{-1}) = 3332, 2945, 2881, 2089, 1454, 1344, 1258, 1045, 956, 557. The spectroscopic data are in accordance with literature.[15]

General procedure 3. Synthesis of azido triflates

The azido alcohol (1.00 eq.) was dissolved in dry DCM (20 mL). The solution was cooled to −78 °C and DIPEA (1.10 eq.) was added. Trifluoromethanesulfonic anhydride (1.05 eq.) was added slowly over a period of 10 to 15 min. The reaction mixture was stirred for 3 h at −78 °C. The reaction was stopped by the addition of sat. $NaHCO_3$ solution. The organic layer was separated and washed with $NaHCO_3$ (2 × 20 mL) and 1 M HCl (3 × 30 mL), dried over Na_2SO_4, filtered and the concentrated in vacuum to give the raw azido triflates. The azido triflates were used in the next reactions without further purification.

2-Azidoethyl trifluoromethanesulfonate (16). Synthesized from 2-azidoethan-1-ol (**22**, 1.60 g, 18.4 mmol, 1.00 eq.) according to the general procedure 3. Yield: 76%, brown liquid. ^{1}H NMR (300 MHz, $CDCl_3$)**:** δ(ppm) = 4.60 (t, *J* = 5.0 Hz, 2H), 3.68 (t, *J* =4.9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$)**:** δ(ppm) = 120.8, 116.6 ,74.2, 49.7. HR-MS (ESI^+)**:** Not detectable. IR (ATR)**:** $\tilde{\nu}$ (cm^{-1}) = 2982, 2112, 1411, 1244, 1200, 1140, 971, 919, 787, 609. The spectroscopic data are in accordance with literature.[16]

3-Azidopropyl trifluoromethanesulfonate (17). Synthesized from 3-azidopropan-1-ol (**23**, 1.60 g, 18.4 mmol, 1.00 eq.) according to the general procedure 3. Yield: 81%. brown liquid, ^{1}H NMR (300 MHz, $CDCl_3$)**:** δ(ppm) = 4.63 (t, *J* = 6.0 Hz, 2H), 3.52 (t, *J* = 6.4 Hz, 2H), 2.12 – 2.02 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$)**:** δ(ppm) = 120.9, 116.6, 73.9, 46.9, 29.0. HR-MS (ESI^+)**:** Not detectable. IR (ATR)**:** $\tilde{\nu}$ (cm^{-1}) = 2946, 2100, 1625, 1411, 1243, 1199, 1141, 1027, 928, 610.

General procedure 4. α-Alkylation

The ester (0.50 mmol, 1.00 eq.) was dissolved in 1 mL dry THF and cooled to −78 °C. LHMDS (1 M in THF, 0.55 mmol, 1.10 eq.) was added slowly and the mixture was stirred for one hour. The azido triflate (**16** or **17**) (0.60 mmol, 1.20 eq.) was dissolved in THF (0.30 mL) and added to the reaction mixture. The mixture was stirred for an additional 10 min at −78 °C, after which it was allowed to reach rt and was stirred overnight (16 h). The reaction was stopped by the addition of sat. $NaHCO_3$ solution (5 mL), the aqueous phase was extracted with DCM (3 × 15 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to give the crude azido esters.

Methyl 4-azido-2-phenylbutanoate (25). Following procedure 4: Synthesized from methyl phenylacetate **24** and azido triflate **16** and isolated by reversed phase flash chromatography (10% MeCN in water to 90% MeCN in water) for characterization. Yield: 76%, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$)**:** δ(ppm) = 7.40 – 7.23 (m, 5H),

3.73 (t, *J* = 7.7 Hz, 1H), 3.67 (s, 3H), 3.38 – 3.12 (m, 2H), 2.44 – 2.26 (m, 1H), 2.12 – 1.94 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$)**:** *δ*(ppm) = 173.8, 137.9, 129.0, 128.1, 127.8, 52.4, 49.3, 48.4, 32.5. HR-MS (ESI$^+$)**:** *m/z* (%) = $[M+Na]^+$, calculated: 242.0900, found: 242.0891. IR (ATR)**:** ṽ (cm^{-1}) = 2952, 2098, 1734, 1455, 1436, 1268, 1164, 736, 700, 511.

Methyl 5-azido-2-phenylpentanoate (26). Following procedure 4: Synthesized from methyl phenylacetate **24** and azido triflate **17** and isolated by reversed phase flash chromatography (10% MeCN in water to 90% MeCN in water) for characterization. Yield: 65%, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$)**:** *δ*(ppm) = 7.38 – 7.23 (m, 5H), 3.66 (s, 3H), 3.56 (t, *J* = 7.7 Hz, 1H), 3.33 – 3.20 (m, 2H), 2.23 – 2.07 (m, 1H), 1.94 – 1.79 (m, 1H), 1.66 – 1.43 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$)**:** *δ*(ppm) = 174.2, 138.7, 128.9, 128.0, 127.6, 52.2, 51.2, 51.2, 30.7, 27.0. HR-MS (ESI$^+$)**:** *m/z* (%) = $[M+Na]^+$, calculated: 256.1056, found: 256.1052. IR (ATR)**:** ṽ (cm^{-1}) = 2952, 2870, 2095, 1733, 1453, 1434, 1252, 1159, 734, 699.

Geeral procedure 5a. H-Cube® reduction and ring closure

The crude azido esters (0.50 mmol, 1.00 eq.) were dissolved in MeOH (20.0 mL). The solution was pumped through an H-Cube® with a capture with 10%Pd/C. The Parameters of the H-Cube® were set to 0.5 mL/min, 25 °C and 1 bar. The corresponding amine was collected in a flask and then heated to 60 °C overnight (16 h). The solvent was removed under reduced pressure and the lactam was isolated by reversed phase flash chromatography (10% MeCN in water to 90% MeCN in water).

General procedure 5b: Staudinger reduction and ring closure

The crude azido esters (0.50 mmol, 1.00 eq.) were dissolved in a mixture of THF (5.00 mL) and water (0.5 mL). Then PPh_3 (0.14 g, 0.55 mmol, 1.10 eq.) was added and the reaction mixture was heated to 60 °C overnight (16 h). After evaporation, the residue was dissolved in ethyl acetate (EtOAc, 10.0 mL) and diluted with 1 M HCl (20 mL). The aqueous layer was extracted with EtOAc (10 mL), neutralized with sat. $NaHCO_3$ solution and extracted again with EtOAc (2 × 10 mL). The combined organic layers were washed with brine and dried over Na_2SO_4, filtered and the concentrated in vacuum to give the crude lactam. The lactam was isolated by reversed phase flash chromatography (10% MeCN in water to 90% MeCN in water).

3-Phenylpyrrolidin-2-one (28). Following procedure **4** and **5a**. Synthesized starting from methyl 2-phenylacetate **24** and azido triflate **16**. Yield: 53%, colorless solid. mp: 84.1 – 88.1 °C; Lit: 84 – 85 °C.[19] ^{1}H NMR (300 MHz, $CDCl_3$)**:** *δ*(ppm) = 7.66 (s, 1H, NH), 7.40 – 7.22 (m, 5H), 3.62 (t, *J* = 9.1 Hz, 1H), 3.52 – 3.33 (m, 2H), 2.57 (dddd, *J* = 12.9, 9.1, 6.9, 3.9 Hz, 1H), 2.29 – 2.14 (m, 1H).^{13}C NMR (75 MHz, $CDCl_3$)**:** *δ*(ppm) = 179.3, 139.5, 128.9, 128.1, 127.2, 47.8, 40.8, 30.8. HR-MS (ESI$^+$)**:** *m/z* (%) = $[M+K]^+$, calculated: 200.0472, found: 200.0471. IR (ATR)**:** ṽ (cm^{-1}) = 3201, 3088, 2885, 1693, 1603, 1495, 1454, 1377, 1281, 1251. The spectroscopic data are in accordance with literature.[19]

3-Phenylpiperidin-2-one (29). Following procedure **4** and **5a**. Synthesized starting from methyl 2-phenylacetate **24** and azido triflate **17**. Yield: 59%, colorless solid. mp: 169.4 – 171.1 °C; Lit: 166 – 168 °C.[19] ^{1}H NMR (300 MHz, $CDCl_3$)**:** *δ*(ppm) = 7.38 – 7.17 (m, 5H), 6.88 (s, 1H, NH), 3.64 (dd, *J* = 8.2, 6.1 Hz, 1H), 3.49 – 3.33 (m, 2H), 2.26 – 2.11 (m, 1H), 2.02 – 1.68 (m, 2H).^{13}C NMR (75 MHz, $CDCl_3$)**:** *δ*(ppm) = 173.5, 141.4, 128.6, 128.4, 126.8, 48.4, 42.7, 30.7, 20.8. HR-MS (ESI$^+$)**:** *m/z* (%) = $[M+H]^+$, calculated: 176.1070, found: 176.1071. IR (ATR)**:** ṽ (cm^{-1}) = 3192, 3065, 2938, 1652, 1488, 1449, 1414, 1356, 1317, 1297. The spectroscopic data are in accordance with literature.[19]

3-(*o*-Tolyl)pyrrolidin-2-one (30). Following procedure **4** and **5a**. Synthesized starting from methyl 2-(*o*-tolyl)acetate and azido triflate **16**. Yield: 55%, colorless solid. mp: 118.4 – 126.8 °C. ^{1}H NMR (300 MHz, $CDCl_3$)**:** *δ*(ppm) = 7.26 (s, 1H, NH), 7.22 – 7.14 (m, 4H), 3.85 (t, *J* = 9.1 Hz, 1H), 3.50 – 3.37 (m, 2H), 2.59 (dddd, *J* = 12.8, 9.2, 6.4, 4.6 Hz, 1H), 2.37 (s, 3H), 2.18 – 2.02 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$)**:** *δ*(ppm) = 179.6, 138.1, 136.6,

130.7, 127.4, 127.1, 126.7, 44.7, 40.7, 30.3, 19.8. HR-MS (ESI$^+$)**:** *m/z* (%) = [M+Na]$^+$, calculated: 198.0889, found: 198.0886. IR (ATR)**:** ṽ (cm^{-1}) = 3245, 2946, 2869, 1695, 14923, 1459, 1280, 1110, 753, 725.

3-(*o*-Tolyl)piperidin-2-one (31). Following procedure **4** and **5a**. Synthesized starting from methyl 2-(*o*-tolyl)acetate and azido triflate **17**. Yield: 55%, colorless solid. mp: 133.0 – 148.2 °C. ^{1}H NMR (300 MHz, $CDCl_3$)**:** *δ*(ppm) = 7.19 – 7.12 (m, 5H, H_{Ar}, NH), 3.84 – 3.77 (m, 1H), 3.49 – 3.33 (m, 2H), 2.35 (s, 3H), 2.19 – 2.05 (m, 1H), 1.96 – 1.70 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$)**:** *δ*(ppm) = 173.8, 139.9, 135.9, 130.8, 128.4, 126.9, 126.3, 45.6, 42.8, 29.2, 21.0, 19.6. HR-MS (ESI$^+$)**:** *m/z* (%) = [M+Na]$^+$, calculated: 212.1046, found: 212.1045. IR (ATR)**:** ṽ (cm^{-1}) = 3197, 2938, 1653, 1489, 1460, 1412, 1351, 1316, 754, 725.

3-(*p*-Tolyl)pyrrolidin-2-one (32). Following procedure **4** and **5a**. Synthesized starting from methyl 2-(*p*-tolyl)acetate and azido triflate **16**. Yield: 26%, colorless solid. mp: 137.6 – 140.4 °C. ^{1}H NMR (300 MHz, $CDCl_3$)**:** *δ*(ppm) = 7.33 (s, 1H, NH), 7.17 (s, 4H), 3.58 (t, *J* = 9.1 Hz, 1H), 3.50 – 3.35 (m, 2H), 2.57 (dddd, *J* = 12.9, 8.9, 7.0, 3.8 Hz, 1H), 2.33 (s, 3H), 2.29 – 2.15 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$)**:** *δ*(ppm) = 179.5, 136.8, 136.5, 129.6, 128.0, 47.4, 40.8, 30.8, 21.2. HR-MS (ESI$^+$)**:** *m/z* (%) = [M+Na]$^+$, calculated: 198.0889, found: 198.0882. IR (ATR)**:** ṽ (cm^{-1}) = 3204, 3093, 2946, 1692, 1516, 1375, 1280, 1060, 802, 544.

3-(*p*-Tolyl)piperidin-2-one (33). Following procedure **4** and **5a**. Synthesized starting from methyl 2-(*p*-tolyl)acetate and azido triflate **17**. Yield: 40%, colorless solid. mp: 171.2 – 174.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$)**:** *δ*(ppm) = 7.19 (s, 1H, NH), 7.13 (s, 4H), 3.59 (dd, *J* = 8.3, 6.1 Hz, 1H), 3.41 – 3.34 (m, 2H), 2.32 (s, 3H), 2.15 (dddd, *J* = 13.3, 10.3, 7.0, 3.3 Hz, 1H), 2.00 – 1.81 (m, 2H), 1.81 – 1.63 (m, 1H). ^{13}C NMR (300 MHz, $CDCl_3$)**:** *δ*(ppm) = 173.6, 138.4, 136.3, 129.3, 128.2, 48.0, 42.7, 30.7, 21.1, 20.8. HR-MS (ESI$^+$)**:** *m/z* (%) = [M+H]$^+$, calculated: 190.1226, found: 190.1218. IR (ATR)**:** ṽ (cm^{-1}) = 3185, 3050, 2932, 1655, 1491, 1421, 1325, 1113, 809, 548.

3-(Naphthalen-2-yl)pyrrolidin-2-one (34). Following procedure **4** and **5a**. Synthesized starting from methyl 2-(naphthalen-2-yl)acetate and azido triflate **16**. Yield: 50%, colorless solid. mp: 147.9 – 151.8 °C. ^{1}H NMR (300 MHz, $CDCl_3$)**:** *δ*(ppm) = 7.89 – 7.73 (m, 4H), 7.59 (s, 1H, NH), 7.52 – 7.35 (m, 3H), 3.80 (t, *J* = 9.1 Hz, 1H), 3.55 – 3.38 (m, 2H), 2.70 – 2.56 (m, 1H), 2.42 – 2.24 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$)**:** *δ*(ppm) = 179.3, 136.9, 133.6, 132.7, 128.7, 127.8, 127.7, 127.0, 126.2, 126.0, 125.83, 48.0, 40.9, 30.7. HR-MS (ESI$^+$)**:** *m/z* (%) = [M+H]$^+$, calculated: 212.1070, found: 212.1068. IR (ATR)**:** ṽ (cm^{-1}) = 3220, 3053, 2981, 2883, 1690, 1365, 1279, 816, 746, 477.

3-(Naphthalen-2-yl)piperidin-2-one (35). Following procedure **4** and **5a**. Synthesized starting from methyl 2-(naphthalen-2-yl)acetate and azido triflate **17**. Yield: 38%, colorless solid. mp: 169.1 – 174.9 °C. ^{1}H NMR (300 MHz, $CDCl_3$)**:** *δ*(ppm) = 7.87 – 7.66 (m, 4H), 7.52 – 7.31 (m, 3H), 7.24 (s, 1H, NH), 3.80 (dd, *J* = 8.5, 6.1 Hz, 1H), 3.48 – 3.35 (m, 2H), 2.28 – 2.16 (m, 1H), 2.09 – 1.97 (m, 1H), 1.97 – 1.65 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$)**:** *δ*(ppm) = 173.4, 138.8, 133.6, 132.5, 128.4, 127.8, 127.7, 127.1, 126.6, 126.1, 125.7, 48.6, 42.8, 30.6, 20.9. HR-MS (ESI$^+$)**:** *m/z* (%) = [M+H]$^+$, calculated: 226.1226, found: 226.1221. IR (ATR)**:** ṽ (cm^{-1}) = 3198, 3051, 2935, 2869, 1655, 1490, 1352, 816, 726, 479.

3,3-Diphenylpiperidin-2-one (37). Following procedure **4** and **5a**. Synthesized starting from methyl 2,2-diphenylacetate and azido triflate **17**. Yield: 58%, colorless solid. mp: 176.6 – 184.9 °C; Lit: 189.5 – 191 °C.[19] ^{1}H NMR (300 MHz, $CDCl_3$)**:** *δ*(ppm) = 7.36 – 7.26 (m, 10H), 7.14 (s, 1H, NH), 3.34 (td, *J* = 6.4, 2.2 Hz, 2H), 2.65 – 2.54 (m, 2H), 1.82 – 1.67 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$)**:** *δ*(ppm) = 174.3, 144.0, 128.6, 128.0, 126.6, 56.8, 42.5, 34.8, 18.9. HR-MS (ESI$^+$)**:** *m/z* (%) = [M+H]$^+$, calculated: 252.1383, found: 252.1375. IR (ATR)**:** ṽ (cm^{-1}) = 3195, 3060, 2965, 2868, 1656, 1492, 1214, 698, 556. The spectroscopic data are in accordance with literature.[19]

3-(2-Fluorophenyl)pyrrolidin-2-one (38). Following procedure **4** and **5a**. Synthesized starting from methyl 2-(2-fluorophenyl)acetate and azido triflate **16**. Yield: 78%, colorless solid. mp: 105.8 – 109.4 °C. ^{1}H NMR: ($CDCl_3$, 300 MHz): *δ*(ppm) = 7.63 (s, 1H, NH), 7.32 – 7.21 (m, 2H), 7.13 (td, *J* = 7.5, 1.3 Hz, 1H), 7.10 – 7.03 (m, 1H), 3.89 (t, *J* = 9.5 Hz, 1H), 3.52 – 3.37 (m, 2H), 2.65 – 2.52 (m, 1H), 2.29 – 2.11 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$)**:** *δ*(ppm)

= 178.5, 161.2 (d, *J* = 246.2 Hz), 130.0 (d, *J* = 4.1 Hz), 128.9 (*J* = 8.5 Hz), 126.7 (d, *J* = 14.6 Hz), 124.5 (d, *J* = 3.6 Hz), 115.7 (d, J = 21.7 Hz), 42.3, 40.8, 30.0. ^{19}F NMR (282 MHz, $CDCl_3$): *δ*(ppm) = -117.69 (m,1F). HR-MS (ESI$^+$)**:** *m/z* (%) = $[M+H]^+$, calculated: 180.0819, found: 180.0820. IR (ATR): ṽ (cm^{-1}): 3227, 2888, 1694, 1492, 1455, 1376, 1281, 1230, 816, 756.

3-(2-Fluorophenyl)piperidin-2-one (39). Following procedure **4** and **5a**. Synthesized starting from methyl 2-(2-fluorophenyl)acetate and azido triflate **17**. Yield: 63%, colorless solid. mp: 176.8 – 182.2 °C. ^{1}H NMR: ($CDCl_3$, 300 MHz): *δ*(ppm) = 7.30 (s, 1H, NH), 7.26 – 7.17 (m, 2H), 7.13 – 6.99 (m, 2H), 3.79 (dd, *J* = 9.2, 6.2 Hz, 1H), 3.46 – 3.30 (m, 2H), 2.19 – 2.06 (m, 1H), 2.00 – 1.73 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$)**:** *δ*(ppm) = 172.6, 160.8 (d, *J* = 245.9 Hz), 130.4 (d, *J*= 4.4 Hz), 128.7 (d, *J* = 15 Hz), 128.6 (d, *J* = 8.3 Hz), 124.2 (d, *J* = 3.6 Hz), 115.7 (d, *J* = 21.7 Hz), 43.2, 42.6, 29.3, 21.5. ^{19}F NMR (282 MHz, $CDCl_3$): *δ*(ppm) = -117.57 (m,1F). HR-MS (ESI$^+$)**:** *m/z* (%) = $[M+Na]^+$, calculated: 216.0795, found: 216.0790. IR (ATR): ṽ (cm^{-1}): 3189, 3073, 2945, 1656, 1491, 1323, 1222, 1110, 858, 756.

3-(4-Chlorophenyl)pyrrolidin-2-one (40). Following procedure **4** and **5a**. Synthesized starting from methyl 2-(4-chlorophenyl)acetate and azido triflate **16**. Yield: 54%, colorless solid. mp: 119.8 – 126.0 °C; Lit: 124.5 – 125.5 °C.[20] ^{1}H NMR (300 MHz, $CDCl_3$)**:** *δ*(ppm) = 7.71 (s, 1H, NH), 7.31 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.5 Hz, 2H), 3.59 (t, *J* = 9.2 Hz, 1H), 3.48 – 3.34 (m, 2H), 2.56 (dddd, *J* = 12.8, 9.0, 6.6, 3.9 Hz, 1H), 2.25 – 2.09 (m, 1H).^{13}C NMR (75 MHz, $CDCl_3$)**:** *δ*(ppm) = 178.9, 137.9, 132.97, 129.5, 128.9, 47.2, 40.7, 30.6. HR-MS (ESI$^+$)**:** *m/z* (%) = $[M+H]^+$, calculated: 196.0524, found: 196.0523. IR(ATR)**:** ṽ (cm^{-1}) = 3236, 2880, 1693, 1492, 1281, 1091, 1059, 1015, 822, 730. The spectroscopic data are in accordance with literature.[20]

3-(4-Chlorophenyl)piperidin-2-one (41). Following procedure **4** and **5a**. Synthesized starting from methyl 2-(4-chlorophenyl)acetate and azido triflate **17**. Yield: 42%, colorless solid. mp: 151.2 – 154.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$)**:** *δ*(ppm) = 7.29 (d, *J* = 8.5 Hz, 2H), 7.17 (d, *J* = 8.5 Hz, 2H), 6.78 (s, 1H, NH), 3.60 (dd, *J* = 8.7, 5.9 Hz, 1H), 3.46 – 3.34 (m, 2H), 2.21 – 2.12 (m, 1H), 1.95 – 1.84 (m, 2H), 1.83 – 1.74 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$)**:** *δ*(ppm) = 172.9, 139.8, 132.7, 129.8, 128.8, 47.9, 42.8, 30.5, 21.0. HR-MS (ESI$^+$)**:** *m/z* (%) = $[M+H]^+$, calculated: 210.0680, found: 210.0680. IR (ATR)**:** ṽ (cm^{-1}) = 3186, 3067, 2938, 1653, 1492, 1421, 1360, 1322, 1091, 818.

3-(3-Bromophenyl)pyrrolidin-2-one (42). Following procedure **4** and **5b**. Synthesized starting from methyl 2-(3-bromophenyl)acetate and azido triflate **16**. Yield: 58%, light yellow solid. mp: 124.8 – 127.3 °C. ^{1}H NMR (300 MHz, $CDCl_3$): *δ*(ppm) = 7.60 – 7.53 (m, 2H), 7.35 – 7.24 (m, 2H), 7.12 (ddd, *J* = 8.0, 6.6, 2.4 Hz, 1H), 4.13 (t, *J* = 9.4 Hz, 1H), 3.51 – 3.37 (m, 2H), 2.75 – 2.61 (m, 1H), 2.14 – 1.95 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$)**:** *δ*(ppm) = 178.6, 139.2, 133.1, 129.3, 128.7, 128.1, 125.1, 47.9, 40.6, 30.4. HR-MS (ESI$^+$)**:** *m/z* (%) = $[M+H]^+$, calculated: 240.0019, found: 240.0009. IR(ATR)**:** ṽ (cm^{-1}) = 3234, 1692, 1473, 1437, 1279, 1022, 752, 559.

3-(3-Bromophenyl)piperidin-2-one (43). Following procedure **4** and **5b**. Synthesized starting from methyl 2-(3-bromophenyl)acetate and azido triflate **17**. Yield: 44%, light yellow solid. mp: 174.3 – 176.8 °C. ^{1}H NMR (300 MHz, $CDCl_3$): *δ*(ppm) = 7.55 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.32 – 7.20 (m, 2H), 7.10 (ddd, *J* = 8.0, 6.9, 2.1 Hz, 1H), 6.88 (s, 1H), 4.03 (dd, *J* = 8.7, 6.0 Hz, 1H), 3.51 – 3.34 (m, 2H), 2.25 – 2.08 (m, 1H), 2.01 – 1.71 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$)**:** *δ*(ppm) = 172.7, 140.8, 133.2, 130.2, 128.2, 127.7, 124.4, 48.5, 42.7, 28.9, 21.2. HR-MS (ESI$^+$)**:** *m/z* (%) = $[M+Na]^+$, calculated: 275.9994, found: 275.9993. IR(ATR)**:** ṽ (cm^{-1}) = 3207, 2939, 1658, 1489, 1470, 1354, 1320, 1197, 1023, 751.

3-[4-(Trifluoromethyl)phenyl]pyrrolidin-2-one (44). Following procedure **4** and **5a**. Synthesized starting from methyl 2-[4-(trifluoromethyl)phenyl]acetate and azido triflate **16**. Yield: 67%, colorless solid. mp: 125.9 – 128.9 °C. ^{1}H NMR: ($CDCl_3$, 300 MHz): *δ*(ppm) = 7.70 (s, 1H, NH), 7.61 (d, *J* = 8.1 Hz, 2H), 7.40 (d, *J* = 8.0 Hz, 2H), 3.69 (t, *J* = 9.3 Hz, 1H), 3.52 – 3.34 (m, 2H), 2.60 (dddd, *J* = 12.9, 9.0, 6.4, 3.9 Hz, 1H), 2.31 – 2.14 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$)**:** *δ*(ppm) = 178.6, 143.5, 129.5 (q, *J* = 32.5 Hz), 128.6, 125.8 (q, *J* = 3.8 Hz), 125.1 (q, *J* = 272.0 Hz), 47.7, 40.8, 30.6. ^{19}F NMR (282 MHz, $CDCl_3$): *δ*(ppm) = -62.49 (s, 3F). HR-MS (ESI$^+$)**:** *m/z* (%) = $[M+H]^+$,

calculated: 230.0787, found: 230.0785. IR (ATR): ṽ (cm^{-1}): 3237, 1692, 1619, 1420, 1324, 1281, 1162, 1112, 1067, 945.

3-[4-(Trifluoromethyl)phenyl]piperidin-2-one (45). Following procedure **4** and **5a**. Synthesized starting from methyl 2-[4-(trifluoromethyl)phenyl]acetate and azido triflate **17**. Yield: 56%, colorless solid. mp: 126.2 – 129.1 °C. ^{1}H NMR: ($CDCl_3$, 300 MHz): *δ*(ppm) = 7.58 (d, *J* = 8.1 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.24 (s, 1H, NH), 3.68 (t, *J* = 6.0 Hz, 1H), 3.46 – 3.33 (m, 2H), 2.26 – 2.11 (m, 1H), 1.97 – 1.73 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$)**:** *δ*(ppm) = 172.7, 145.4, 129.6 (q, *J* = 34.7 Hz), 128.9, 125.6 (q, *J* = 269.3 Hz), 125.6 (q, *J* = 3.8 Hz), 48.4, 42.7, 30.5, 21.0. ^{19}F NMR (282 MHz, $CDCl_3$): *δ*(ppm) = -62.55 (s, 3F).HR-MS (ESI^+)**:** *m/z* (%) = $[M+H]^+$, calculated: 244.0944, found: 244.0945. IR (ATR): ṽ (cm^{-1}): 3217, 2944, 1662, 1491, 1323, 1162, 1113, 1067, 988, 832.

3-[4-(Methylthio)phenyl]pyrrolidin-2-one (46). Following procedure **4** and **5a**. Synthesized starting from methyl 2-[4-(methylthio)phenyl]acetate and azido triflate **16**. Yield: 64%, light yellow solid. mp: 144.5 – 147.8 °C. ^{1}H NMR: ($CDCl_3$, 300 MHz): *δ*(ppm) = 7.50 (s, 1H, NH), 7.32 – 7.16 (m, 4H), 3.60 (t, *J* = 9.2 Hz, 1H), 3.50 – 3.37 (m, 2H), 2.64 – 2.52 (m, 1H), 2.48 (s, 3H), 2.30 – 2.13 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): *δ*(ppm) = 179.2, 137.2, 136.4, 128.6, 127.4, 47.3, 40.7, 30.7, 16.2. HR-MS (ESI^+)**:** *m/z* (%) = $[M+H]^+$, calculated: 208.0791, found: 208.0785. IR (ATR): ṽ (cm^{-1}): 3212, 3092, 1678, 1493, 1438, 1375, 1278, 1094, 801, 560.

3-[4-(Methylthio)phenyl]piperidin-2-one (47). Following procedure **4** and **5a**. Synthesized starting from methyl 2-[4-(methylthio)phenyl]acetate and azido triflate **17**. Yield: 29%, light yellow solid. mp: 188.9 – 194.8 °C. ^{1}H NMR: ($CDCl_3$, 300 MHz): *δ*(ppm) = 7.22 (d, *J* = 8.5 Hz, 2H), 7.15 (d, *J* = 8.3 Hz, 2H), 6.78 (s, 1H, NH), 3.59 (dd, *J* = 8.4, 5.9 Hz, 1H), 3.45 – 3.36 (m, 2H), 2.46 (s, 3H), 2.24 – 2.10 (m, 1H), 1.97 – 1.73 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): *δ*(ppm) 173.3, 138.2, 136.8, 128.9, 127.2, 47.9, 42.8, 30.5, 20.9, 16.2. HR-MS (ESI^+)**:** *m/z* (%) = $[M+H]^+$, calculated: 222.0947, found: 222.0939. IR (ATR): ṽ (cm^{-1}): 3186, 3069, 2946, 1667, 1599, 1494, 1417, 1089, 811, 514.

3-(3,4-Dimethoxyphenyl)pyrrolidin-2-one (48). Following procedure **4** and **5a**. Synthesized starting from methyl 2-(3,4-dimethoxyphenyl)acetate and azido triflate **16**. Yield 58%, colorless solid. mp: 144.9 – 149.6 °C. ^{1}H NMR (300 MHz, $CDCl_3$)**:** *δ*(ppm) = 7.26 (s, 1H, NH), 6.89 – 6.73 (m, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 3.56 (t, *J* = 9.2 Hz, 1H), 3.50 – 3.34 (m, 2H), 2.57 (dddd, *J* = 12.7, 9.0, 6.8, 3.6 Hz, 1H), 2.30 – 2.14 (m, 1H). ^{13}C NMR (300 MHz, $CDCl_3$)**:** *δ*(ppm) = 179.2, 149.2, 148.3, 131.9, 120.2, 111.6, 111.3, 56.1, 56.0, 47.3, 40.7, 30.9. HR-MS (ESI^+)**:** *m/z* (%) = $[M+H]^+$, calculated: 222.1125, found: 222.1122. IR (ATR)**:** ṽ (cm^{-1}) = 3234, 2931, 1691, 1515, 1462, 1253, 1231, 1142, 1025, 728.

3-(3,4-Dimethoxyphenyl)piperidin-2-one (49). Following procedure **4** and **5a**. Synthesized starting from methyl 2-(3,4-dimethoxyphenyl)acetate and azido triflate **17**. Yield: 30%, colorless solid. mp: 126.3 – 130.4 °C. ^{1}H NMR (300 MHz, $CDCl_3$)**:** *δ*(ppm) = 7.14 (s, 1H, NH), 6.85 – 6.70 (m, 3H), 3.85 (s, 3H), 3.83 (s, 3H), 3.54 (dd, *J* = 8.5, 6.0 Hz, 1H), 3.44 – 3.29 (m, 2H), 2.14 (ddt, *J* = 15.3, 8.8, 4.0 Hz, 1H), 1.99 – 1.79 (m, 1H), 1.80 – 1.65 (m, 2H). ^{13}C NMR (300 MHz, $CDCl_3$)**:** *δ*(ppm) = 173.6, 148.9, 147.9, 133.8, 120.4, 111.7, 111.3, 55.9, 55.9, 47.97, 42.7, 30.6, 20.9. HR-MS (ESI^+)**:** *m/z* (%) = $[M+H]^+$, calculated: 236.1281, found: 236.1281. IR (ATR)**:** ṽ (cm^{-1}) = 3209, 2938, 2252, 1657, 1514, 1247, 1226, 1141, 1025, 726.

***tert*-Butyl 3-(2-oxopyrrolidin-3-yl)-1*H*-indole-1-carboxylate (50).** Following procedure **4** and **5a**. Synthesized starting from methyl tert-butyl 3-(2-methoxy-2-oxoethyl)-1*H*-indole-1-carboxylate and azido triflate **16**. Yield: 50%, brown oil. ^{1}H NMR: ($CDCl_3$, 300 MHz): *δ*(ppm) = 8.15 (d, *J* = 8.3 Hz, 1H), 7.59 – 7.51 (m, 2H), 7.36 – 7.28 (m, 1H), 7.26 – 7.20 (m, 1H), 3.85 (t, *J* = 9.2 Hz, 1H), 3.55 – 3.42 (m, 2H), 2.70 – 2.53 (m, 1H), 2.41 – 2.24 (m, 1H), 1.65 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): *δ*(ppm) = 178.4, 149.7, 136.0, 129.5, 124.6, 123.6, 122.7, 119.3, 118.2, 115.6, 83.7, 40.8, 39.1, 29.1, 28.3. HR-MS (ESI^+)**:** *m/z* (%) = $[M+H]^+$, calculated: 301.1547, found: 301.1538. IR (ATR): ṽ (cm^{-1}): 3225, 2979, 1729, 1695, 1476, 1369, 1275, 1219, 1043, 744.

***tert*-Butyl 3-(2-oxopiperidin-3-yl)-1*H*-indole-1-carboxylate (51).** Following procedure **4** and **5a**. Synthesized starting from methyl tert-butyl 3-(2-methoxy-2-oxoethyl)-1*H*-indole-1-carboxylate and azido triflate **17**. Yield: 35%, brown oil. ^{1}H NMR: ($CDCl_3$, 300 MHz): δ(ppm) = 8.14 (d, *J* = 8.2 Hz, 1H), 7.53 – 7.43 (m, 2H), 7.34 – 7.27 (m, 1H), 7.25 – 7.18 (m, 1H), 7.05 (s, 1H), 3.85 (dd, *J* = 8.6, 6.2 Hz, 1H), 3.49 – 3.34 (m, 2H), 2.23 – 2.00 (m, 2H), 2.00 – 1.74 (m, 2H), 1.65 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ(ppm) = 172.7, 149.7, 135.8, 129.4, 124.5, 123.7, 122.5, 120.1, 119.3, 115.5, 83.6, 42.7, 39.7, 28.4, 28.3, 21.2. HR-MS (ESI$^+$)**:** *m/z* (%) = $[M+H]^+$, calculated: 315.1703, found: 315.1695. IR (ATR): ṽ (cm^{-1}): 2977, 2940, 2869, 1728, 1661, 1452, 1369, 1250, 1156, 1090.

3-(4-Isobutylphenyl)-3-methylpyrrolidin-2-one (52). Following procedure **4** and **5a**. Synthesized starting from methyl 2-(4-isobutylphenyl)propanoate and azido triflate **16**. Yield: 15%, colorless solid. mp: 89.2 – 95.5 °C. ^{1}H NMR: ($CDCl_3$, 300 MHz): δ(ppm) = 7.35 – 7.29 (m, 2H), 7.13 – 7.08 (m, 2H), 6.63 (s, 1H, NH), 3.42 – 3.26 (m, 2H), 2.57 – 2.46 (m, 1H), 2.44 (d, *J* = 7.2 Hz, 2H), 2.29 – 2.16 (m, 1H), 1.92 – 1.76 (m, 1H), 1.55 (s, 3H), 0.90 (s, 3H), 0.88 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ(ppm) = 181.7, 140.6, 140.3, 129.4, 125.9, 47.6, 45.1, 39.2, 38.1, 30.3, 24.7, 22.5. HR-MS (ESI$^+$)**:** *m/z* (%) = $[M+H]^+$, calculated: 232.1696, found: 232.1690. IR (ATR): ṽ (cm^{-1}): 3214, 2953, 2868, 1692, 1511, 1461, 1382, 1278, 1094, 794.

3-(4-Isobutylphenyl)-3-methylpiperidin-2-one (53). Following procedure **4** and **5a**. Synthesized starting from methyl 2-(4-isobutylphenyl)propanoate and azido triflate **17**. Yield: 19%, colorless solid, mp: 84.2 – 89.1 °C. ^{1}H NMR: ($CDCl_3$, 300 MHz): δ(ppm) = 7.24 (d, *J* = 8.3 Hz, 2H), 7.08 (d, *J* = 8.3 Hz, 2H), 6.43 (s, 1H, NH), 3.37 – 3.29 (m, 2H), 2.43 (d, *J* = 7.1 Hz, 2H), 2.24 – 2.14 (m, 1H), 1.94 – 1.76 (m, 2H), 1.72 – 1.61 (m, 2H), 1.57 (s, 3H), 0.90 (s, 3H), 0.88 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ(ppm) = 176.7, 142.5, 139.8, 129.2, 126.0, 47.2, 45.0, 42.9, 36.8, 30.3, 27.2, 22.5, 19.1. HR-MS (ESI$^+$)**:** *m/z* (%) = $[M+H]^+$, calculated: 246.1852, found: 246.1842. IR (ATR): ṽ (cm^{-1}): 3205, 2951, 2867, 1659, 1509, 1492, 1349, 1278, 843, 802.

3,3'-(1,4-Phenylene)bis(pyrrolidin-2-one)(Diastereomeric mixture) (54). Following procedure **4** and **5a**. Synthesized starting from dimethyl 2,2'-(1,4-phenylene)diacetate and azido triflate **16**. Yield: 25%, colorless oily substance. ^{1}H NMR: (MeOD-d_4, 300 MHz): δ(ppm) = 7.37 – 7.29 (m, 1H), 7.21 – 7.15 (m, 3H), 3.68 (td, *J* = 8.9, 1.6 Hz, 2H), 3.52 – 3.42 (m, 4H), 2.68 – 2.55 (m, 2H), 2.27 – 2.11 (m, 2H).^{13}C NMR (75 MHz, MeOD-d_4): δ(ppm) = 181.0, 141.7, 130.0, 129.3, 129.2, 127.9, 127.8, 49.2, 41.7, 32.1, 32.0. HR-MS (ESI$^+$)**:** *m/z* (%) = $[M+H]^+$, calculated: 245.1285, found: 245.1282. IR (ATR): ṽ (cm^{-1}): 2951, 2884, 2405, 1679, 1488, 1455, 1410, 1288, 1186, 706.

3,3'-(1,4-Phenylene)bis(piperidin-2-one)(Diastereomeric mixture) (55). Following procedure **4** and **5a**. Synthesized starting from dimethyl 2,2'-(1,4-phenylene)diacetate and azido triflate **17**. Yield: 30%, colorless oily substance. ^{1}H NMR: (MeOD-d_4, 300 MHz): δ(ppm) = 7.33 – 7.23 (m, 1H), 7.20 – 7.07 (m, 3H), 3.69 – 3.59 (m, 4H), 3.38 (t, *J* = 5.6 Hz, 2H), 2.27 – 2.05 (m, 2H), 2.01 – 1.62 (m, 6H). ^{13}C NMR (75 MHz, MeOD-d_4): δ(ppm) = 175.4, 143.2, 130.5, 129.9, 129.7, 128.7, 128.2, 127.76, 52.4, 43.3, 41.7, 31.8, 31.7, 21.4. HR-MS (ESI$^+$)**:** *m/z* (%) = $[M+H]^+$, calculated: 273.1598, found: 273.1590. IR (ATR): ṽ (cm^{-1}): 2946, 2864, 2366, 1734, 1637, 1487, 1487, 1438, 1355, 1262.

3-[1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]pyrrolidin-2-one (56). Following procedure **4** and **5b**. Synthesized starting from methyl 2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acetate and azido triflate **16**. Yield: 30%, colorless solid. mp: 184.9 – 188.5 °C. ^{1}H NMR: ($CDCl_3$, 300 MHz): δ(ppm) = 7.73 – 7.65 (m, 2H), 7.51 – 7.41 (m, 2H), 7.21 (s, 1H, NH), 6.88 (d, *J* = 2.5 Hz, 1H), 6.85 (d, *J* = 9.1 Hz, 1H), 6.65 (dd, *J* = 9.1, 2.5 Hz, 1H), 3.87 (t, *J* = 9.6 Hz, 1H), 3.79 (s, 3H), 3.64 – 3.44 (m, 2H), 2.59 – 2.42 (m, 1H), 2.39 (s, 3H), 2.36 – 2.30 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ(ppm) = 178.4, 168.4, 155.8, 139.4, 136.2, 134.0, 131.4, 131.4, 129.3, 129.2, 116.6, 115.2, 110.9, 102.4, 55.8, 40.8, 38.7, 28.4, 13.5. HR-MS (ESI$^+$)**:** *m/z* (%) = $[M+H]^+$, calculated: 383.1157, found: 383.1152. IR (ATR): ṽ (cm^{-1}): 3224, 1931, 1686, 1590, 1476, 1399, 1322, 908, 755, 730.

3-[1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]piperidin-2-one (57). Following procedure **4** and **5b**. Synthesized starting from methyl 2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acetate and

azido triflate **17**. Yield: 21%, brown oil. ^{1}H NMR: ($CDCl_3$, 300 MHz): δ(ppm) = 7.71 – 7.63 (m, 2H), 7.48 – 7.41 (m, 2H), 6.89 (s, 1H), 6.87 – 6.79 (m, 2H), 6.63 (dd, *J* = 9.0, 2.5 Hz, 1H), 3.78 (s, 3H), 3.76 – 3.67 (m, 1H), 3.58 – 3.40 (m, 2H), 2.35 (s, 3H), 2.15 – 1.85 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ(ppm) = 172.6, 168.4, 155.8, 139.3, 135.3, 134.2, 131.3, 129.6, 129.2, 119.0, 115.2, 110.6, 102.5, 55.85, 43.1, 39.3, 28.6, 22.7, 13.7. HR-MS (ESI$^+$)**:** *m/z* (%) = $[M+H]^+$, calculated: 397.1313, found: 397.1306. IR (ATR): ṽ (cm^{-1}): 3206, 1660, 1590, 1475, 1399, 1260, 1149, 949, 752, 727.

3-Cyclohexylpyrrolidin-2-one (58). Following procedure **4** (Usage of freshly prepared LDA instead of LHMDS) and **5a**. Synthesized starting from methyl 2-cyclohexylacetate and azido triflate **16**. Yield:43%, colorless solid. mp: 88.9 – 93.9 °C. ^{1}H NMR: ($CDCl_3$, 300 MHz): δ(ppm) = 6.90 (s, 1H, NH), 3.27 (dd, *J* = 8.0, 6.0 Hz, 2H), 2.29 (td, *J* = 8.8, 4.4 Hz, 1H), 2.17 – 1.99 (m, 1H), 2.00 – 1.85 (m, 1H), 1.85 – 1.50 (m, 6H), 1.36 – 1.17 (m, 2H), 1.17 – 0.98 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ(ppm) 180.5, 46.4, 40.9, 38.1, 31.4, 28.0, 26.6, 26.4, 26.3, 23.1. HR-MS (ESI$^+$)**:** *m/z* (%) = $[M+H]^+$, calculated: 168.1383, found: 168.1374. IR (ATR): ṽ (cm^{-1}): 3217, 2920, 2850, 1688, 1492, 1448, 1377, 1313, 1283, 1061.

3-Cyclohexylpiperidin-2-one (59). Following procedure **4** (Usage of freshly prepared LDA instead of LHMDS) and **5a**. Synthesized starting from methyl 2-cyclohexylacetate and azido triflate **17**. Yield: 34%, colorless solid. mp: 112.5 – 117.9 °C; Lit: 95 °C.[21] ^{1}H NMR: ($CDCl_3$, 300 MHz): δ(ppm) = 6.47 (s, 1H, NH), 3.33 – 3.15 (m, 2H), 2.27 – 2.05 (m, 2H), 1.91 – 1.46 (m, 9H), 1.41 – 0.97 (m, 5H).^{13}C NMR (75 MHz, $CDCl_3$): δ(ppm) = 174.7, 46.7, 42.5, 38.7, 31.0, 28.2, 26.9, 26.6, 26.5, 22.4, 22.0. HR-MS (ESI$^+$)**:** *m/z* (%) = $[M+H]^+$, calculated: 182.1539, found: 182.1537. IR (ATR): ṽ (cm^{-1}): 3200, 2922, 2850, 1649, 1492, 1448, 1415, 1269, 1201, 844. The spectroscopic data are in accordance with literature.[21]

3-Octylpyrrolidin-2-one (60). Following procedure **4** (Usage of freshly prepared LDA instead of LHMDS) and **5a**. Synthesized starting from methyl decanoate and azido triflate **16**. Yield: 33%, colorless solid. mp: 76.2 – 80.9 °C; Lit: 80 – 81 °C.[22] ^{1}H NMR: ($CDCl_3$, 300 MHz): δ(ppm) = 6.47 (s, 1H, NH), 3.35 – 3.25 (m, 2H), 2.38 – 2.19 (m, 2H), 1.91 – 1.67 (m, 2H), 1.35 – 1.22 (m, 13H), 0.86 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ(ppm) = 181.1, 41.1, 40.5, 32.0, 31.0, 29.7, 29.6, 29.4, 27.6, 27.4, 22.8, 14.2. HR-MS (ESI$^+$)**:** *m/z* (%) = $[M+H]^+$, calculated: 198.1852, found: 198.1849. IR (ATR): ṽ (cm^{-1}): 3203, 3092, 2918, 1851, 1693, 1586, 1379, 1264, 1109, 776. The spectroscopic data are in accordance with literature.[23]

3-Octylpiperidin-2-one (61). Following procedure 4 (Usage of freshly prepared LDA instead of LHMDS) and **5a**. Synthesized starting from methyl decanoate and azido triflate **17**. Yield: 28%, colorless solid. mp: 64.6 – 68.1 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ(ppm) = 6.36 (s, 1H, NH), 3.32 – 3.20 (m, 2H), 2.31 – 2.15 (m, 1H), 1.99 – 1.75 (m, 3H), 1.76 – 1.59 (m, 1H), 1.56 – 1.38 (m, 2H), 1.34 – 1.18 (m, 12H), 0.86 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ(ppm) = 175.5, 42.5, 41.1, 32.0, 31.6, 29.8, 29.6, 29.4, 27.1, 26.1, 22.8, 21.4, 14.2. HR-MS (ESI$^+$)**:** *m/z* (%) = $[M+H]^+$, calculated: 212.2009, found: 212.2002. IR (ATR): ṽ (cm^{-1}): 2922, 2853, 2015, 1671, 1646, 1544, 1492, 1333, 1206, 1113.

3-Phenethylpyrrolidin-2-one (62). Following procedure **4** (Usage of freshly prepared LDA instead of LHMDS) and **5a**. Synthesized starting from methyl 4-phenylbutanoate and azido triflate **16**. Yield: 16%, colorless solid. mp: 78.2 – 81.9 °C. ^{1}H NMR: ($CDCl_3$, 300 MHz): δ(ppm) 7.31 – 7.15 (m, 5H), 6.42 (s, 1H, NH), 3.41 – 3.26 (m, 2H), 2.85 – 2.61 (m, 2H), 2.42 – 2.09 (m, 4H), 1.86 – 1.75 (m, 1H), 1.74 – 1.59 (m, 1H).^{13}C NMR (75 MHz, $CDCl_3$): δ(ppm) = 180.6, 141.6, 128.6, 128.5, 126.1, 40.5, 40.3, 33.6, 32.7, 27.8. HR-MS (ESI$^+$)**:** *m/z* (%) = $[M+H]^+$, calculated: 190.1226, found: 190.1221. IR (ATR): ṽ (cm^{-1}): 3220, 2939, 2861, 1690, 1602, 1494, 1454, 1276, 749, 700.

3-Phenethylpiperidin-2-one (63). Following procedure **4** (Usage of freshly prepared LDA instead of LHMDS) and **5a**. Synthesized starting from methyl 4-phenylbutanoate and azido triflate **17**. Yield: 17%, colorless solid. mp: 95.2 – 99.5 °C; Lit: 99 – 100 °C.[24] ^{1}H NMR: ($CDCl_3$, 300 MHz): δ(ppm) = 7.32 – 7.13 (m, 5H), 6.28 (s, 1H, NH), 3.36 – 3.24 (m, 2H), 2.83 – 2.59 (m, 2H), 2.38 – 2.21 (m, 2H), 2.09 – 1.94 (m, 1H), 1.94 – 1.82 (m, 1H), 1.82 – 1.66 (m,

2H), 1.66 – 1.50 (m, 1H). ^{13}C NMR HSQC, HMBC (75 MHz, $CDCl_3$): δ(ppm) = 175.1, 142.0, 128.6, 128.5, 126.0, 42.5, 40.5, 33.4, 33.3, 26.4, 21.5. HR-MS (ESI$^+$)**:** *m/z* (%) = $[M+H]^+$, calculated: 204.1383, found: 204.1377. IR (ATR): $\tilde{\nu}$ (cm^{-1}): 3196, 3026, 2946, 2860, 1648, 1494, 1453, 1303, 751, 700. The spectroscopic data are in accordance with literature.[24]

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Supplementary Material

Copies of ^{1}H and ^{13}C NMR spectra of the synthesized compounds are given in the Supplementary Material file associated with this manuscript.

References

1. Caruano, J.; Muccioli, G. G.; Robiette, R. *Org. Biomol. Chem.* **2016**, *14*, 10134. https://doi.org/10.1039/c6ob01349j
2. Albrecht, A.; Albrecht, Ł.; Janecki, T. *Eur. J. Org. Chem.* **2011**, 2747. https://doi.org/10.1002/ejoc.201001486
3. Ye, L. W.; Shu, C.; Gagosz, F. *Org. Biomol. Chem*. **2014**, *12*, 1833. https://doi.org/10.1039/c3ob42181c
4. Fenical, W.; Jensen, P. R.; Palladino, M. A.; Lam, K. S.; Lloyd, G. K.; Potts, B. C. *Bioorg. Med. Chem.* **2009**, *17*, 2175. https://doi.org/10.1016/j.bmc.2008.10.075
5. Pailee, P.; Prachyawarakorn, V.; Mahidol, C.; Ruchirawat, S.; Kittakoop, P. *Eur. J. Org. Chem.* **2011**, *2011*, 3809. https://doi.org/10.1002/ejoc.201100423
6. Zhu, J.; Mix, E.; Winblad, B. *CNS Drug Rev*. **2001**, *7*, 387. https://doi.org/10.1111/j.1527-3458.2001.tb00206.x
7. De Lucca, G. V. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 501. https://doi.org/10.1016/S0960-894X(97)00007-3
8. C.H. Boehringer Sohn AG & Co. KG. Polynucleotides Having Promoter Activity. Patent **2011**.
9. Wenke, J.; Anke, H.; Sterner, O. *Biosci. Biotechnol. Biochem.* **1993**, *57*, 961. https://doi.org/10.1271/bbb.57.961
10. Pharande, S. G. *Synthesis* **2021**, *53*, 418. https://doi.org/10.1055/s-0040-1706297
11. Hassan, I. S.; Ta, A. N.; Danneman, M. W.; Semakul, N.; Burns, M.; Basch, C. H.; Dippon, V. N.; McNaughton, B. R.; Rovis, T. *J. Am. Chem. Soc.* **2019**, *141*, 4815.

https://doi.org/10.1021/jacs.9b01596
12. Khoukhi, M.; Vaultier, M.; Carrié, R. *Tetrahedron Lett.* **1986**, *27*, 1031. https://doi.org/10.1016/S0040-4039(86)80040-5
13. Khoukhi, N.; Vaultier, M.; Carrié, R. *Tetrahedron* **1987**, *43*, 1811. https://doi.org/10.1016/S0040-4020(01)81492-7
14. De Ruysscher, D.; Pang, L.; Mattelaer, C.-A.; Nautiyal, M.; De Graef, S.; Rozenski, J.; Strelkov, S. V.; Lescrinier, E.; Weeks, S. D.; Van Aerschot, A. *Bioorg. Med. Chem.* **2020**, *28*, 115580. https://doi.org/10.1016/j.bmc.2020.115580
15. Wolf, N.; Kersting, L.; Herok, C.; Mihm, C.; Seibel, J. *J. Org. Chem.* **2020**, *85*, 9751. https://doi.org/10.1021/acs.joc.0c01084
16. Barosi, A.; Berisha, A.; Mangeney, C.; Pinson, J.; Dhimane, H.; Dalko, P. I. *Mater. Adv.* **2021**, *2*, 2358. https://doi.org/10.1039/d1ma00022e
17. Bashore, C. G.; Samardjiev, I. J.; Bordner, J.; Coe, J. W. *J. Am. Chem. Soc.* **2003**, *125*, 3268. https://doi.org/10.1021/ja028152c
18. Calmès, M.; Escale, F.; Martinez, J. *Tetrahedron: Asymmetry* **2002**, *13*, 293. https://doi.org/10.1016/S0957-4166(02)00075-7
19. Michael, J. P.; De Koning, C. B.; Van der Westhuyzen, C. W.; Fernandes, M. A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2055. https://doi.org/10.1039/b103560f
20. Wall, G. M.; Baker, J. K. *J. Med. Chem.* **1989**, *32*, 1340. https://doi.org/10.1021/jm00126a033
21. Dressel, M.; Aechtner, T.; Bach, T. *Synthesis* **2006**, 2206. https://doi.org/10.1055/s-2006-942412
22. Nikishin, G. I.; Mustafaev, R. I. *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)* **1964**, *13*, 1745. https://doi.org/10.1007/BF00849441
23. Wu, X.; Qu, J.; Chen, Y. *J. Am. Chem. Soc.* **2020**, *142*, 15654. https://doi.org/10.1021/jacs.0c07126
24. Padwa, A.; Beall, L. S.; Heidelbaugh, T. M.; Liu, B.; Sheehan, S. M. *J. Org. Chem.* **2000**, *65*, 2684. https://doi.org/10.1021/jo991742h