Published in final edited form as:

J Org Chem. 2018 November 16; 83(22): 13743–13753. doi:10.1021/acs.joc.8b02062.

Metal-Templated Assembly of Cyclopropane-Fused Diazepanones and Diazecanones via *exo-trig* Nucleophilic Cyclization of Cyclopropenes with Tethered Carbamates

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Abstract

A strain-release-driven, cation-templated nucleophilic 7- and 8-exotrig-cyclization of tethered Boc-protected amines to cyclopropenes is described. The featured reaction proceeds in diastereo- and regioselective fashion and allows for preparation of the corresponding 2,5-diazabicyclo[5.1.0]octan-6-ones and 2,6-diazabicyclo[6.1.0]nonan-7-ones as sole products in high yields. Preliminary studies on anticancer activities of these novel cyclopropane-fused medium heterocycles were performed.

Graphical Abstract

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The authors declare no competing financial interest.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b02062.

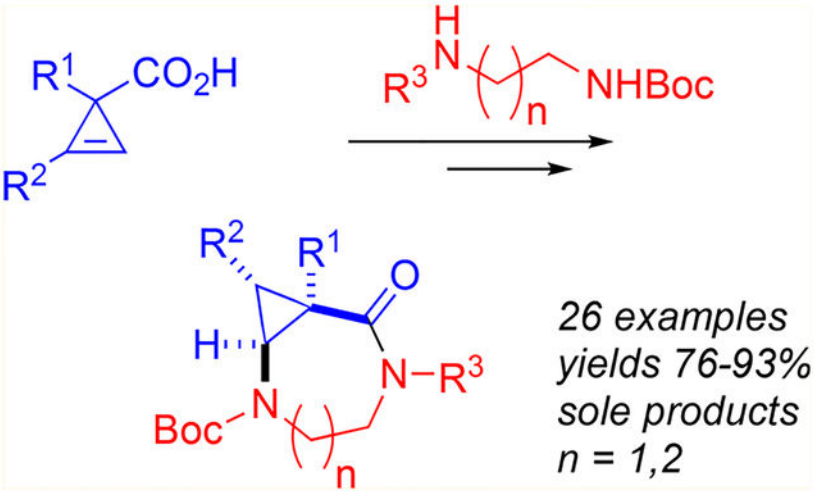
Spectral data (PDF)

Crystallographic information for 8ck (CIF)

Crystallographic information for 8ga (CIF)

Crystallographic information for 8ej (CIF)

Crystallographic information for 8da (CIF)



INTRODUCTION

The cyclopropene double bond is characterized by enhanced strain energy and much greater electrophilicity as compared to normal olefins. This feature allows for the utilization of strain-release driven addition of various nucleophilic entities across the C=C bond of cyclopropenes in design of bio-orthogonal transformations[1] or for the development of synthetic strategies toward novel cyclopropyl scaffolds.[2] Employment of carbon-,[3] nitrogen-,[4] oxygen-,[5] sulfur-,[6] or halogen-based[7] nucleophiles has been demonstrated in the intermolecular mode of the ring-retentive addition (Scheme 1, eq 1). The intramolecular version of this reaction involving nucleophilic species tethered to cyclopropenes and leading to the formation of fused bicyclic ring systems is much more challenging. Synthetic methodology employing 5-exo-trig nucleophilic attack by stabilized carbanions 3 allowing access to bicyclic lactams 4 (Scheme 1, eq 2) was recently developed in our group.[8] We also demonstrated several modes of potassium-templated cyclizations involving nucleophilic alkoxides 5 that afford medium sized cyclic ethers 6 (Scheme 1, eq 3).[9] During these studies, novel scaffolds were identified possessing promising biological activity,[9a] which justified further synthetic efforts, especially toward medium sized cyclic amines 8, that could mimic β- or γ-turns of polypeptides. Herein, we wish to disclose our initial progress toward this goal.

RESULTS AND DISCUSSION

At first glance, the planned cyclization involving amine-based nucleophilic entities seemed to be a reasonably straightforward extension of the work previously performed with alkoxides but, as usual, the devil was in the details. It should be pointed out that for successful base-assisted addition of the heteroatom-based entities across C=C bond of cyclopropenes, fine balance between nucleophilicity and acidity must be maintained.[4,5] Thus, the ring-retentive reaction of cyclopropenes with primary amines (9, X = NH_2, NHAlk) cannot be achieved because the nucleophilicity of these neutral amines is much lower that of alkoxides, and their acidity is not sufficient to produce much more reactive

anionic entities in the presence of typically employed weak bases. Increasing the strength of the base proved counterproductive because concurrent deprotonation of acidic C−H bonds of cyclopropene occurs, greatly diminishing its electrophilicity. At higher temperature, it was possible to force a thermally induced intramolecular nucleophilic attack in substrate 9, but the resulting donor−acceptor cyclopropane 10 tended toward facile ring-cleavage[10,11] and subsequent decomposition of cyclic imine 11 (Scheme 2).[12]

Arguably, the best solution to this problem would be the employment of an appropriate protecting group at the amine function, acidifying the N−H bond in the precursor and moderating the electron-donating character of the nitrogen atom in the cyclic product. Given the availability of the corresponding starting materials for this preliminary communication, we decided to concentrate on reactivity of Boc-protected amines 7. To this end, 1-phenylcycloprop-2-ene-1-carboxylic acid 12a was subjected to the acylation reaction with *tert*-butyl (2-aminoethyl)carbamate 13a. Without purification, the resulting amide 7aa was treated with powdered KOH to afford the desired 2,5-diazabicyclo[5.1.0]octan-6-one 8aa as the sole product in 86% overall yield (Scheme 3, entry1). This reaction proved to be pretty general for 7-exo-trig cyclization showing high tolerance for substituents at the amide nitrogen and at the C-1 of cyclopropene. It was shown that the starting amines could be protected not only by benzyl or substituted benzyl groups but also by alkyl (entries 4, 5, 9, 13−15, and 17) or 2-picolyl moieties (entry 6). The aryl group at quaternary center of cyclopropene (C-1) can bear alkoxy (12b) or halogen substituents (12c−f). All seven-membered bicyclic amides were obtained in very high yields as sole products (Scheme 3).

Similarly, acylation of cyclopropene-3-carboxylic acids **12a**, **e**, and **f** with N-benzylated derivatives of (3-aminopropyl)-carbamate **13h−j** afforded the corresponding tethered carbamates 7 in crude form (Scheme 4). After treatment with a base, the latter underwent smooth 8-exo-trig cyclization, leading to the formation of 2,6-diazabicyclo[6.1.0]nonan-7-ones 8ah, 8eh, 8ej, and 8fh (Scheme 4, entries 18−21). Next, we investigated if the diastereoselectivity of this reaction could be affected by the presence of additional stereogenic centers. First, we employed chiral cycloprop-2-enecarboxylic acids 12g and h (in racemic form, Scheme 5). They were converted into monocarbamates 13h and j uneventfully, and the following base-assisted cyclizations afforded tertiary amide species 7, possessing chiral cyclopropene units (Scheme 5). We were pleased to find that the reaction of these precursors proceeded regio- and diastereoselectively, affording in high yields seven-(**8ga**, **8ha**, and **8hb**) and eight-membered (8gh and 8hi) heterocycles as sole products with relative configurations (1S*,7S*,8R*) and (1S*,8S*,9R*), respectively (Scheme 5, entries 22−26). Overall, the addition of N−H moiety across C==C bond of cyclopropene proceeded in a formal *syn*-fashion. Next, reaction of tethered carbamate 7ck assembled by acylation of L-valine-derived chiral amine 13k with prochiral cycloprop-2-enecarboxylic acid 12c was evaluated (Scheme 6).

Cyclopropene moiety in 7ck possesses two diastereotopic sites for nucleophilic attack, but only one of them is involved in the reaction, giving rise to product 8ck with (1S,4S,7S)-configuration and bulky isopropyl group in the more favored bowsprit configuration (as shown by X-ray crystallography, see Figure 1). This stereochemical outcome is very similar

to the one recently reported for assembly of cyclopropane-fused oxazepanones (6, n = 1) via 7-exo-trig cyclizations of tethered chiral alkoxides.[9a]

As mentioned above, the obtained structures constitute very attractive biological probes as this unique heterocyclic scaffold just recently emerged on the chemical space map.[13] Accordingly, we performed a preliminary biological evaluation of a few representative compounds for anticancer activity using HeLa cell line (ATCC CCL-2) as a model for human cervical adenocarcinoma (Table 1) through the measurements of mitochondrial dehydrogenase activities using the MTT method.[14] Our preliminary tests revealed that some of obtained compounds possess strong anticancer activity, and the level of biological activity is very dependent on the character of R^1 and R^2 substituents in designed structures (Scheme 2). For example, the changing of R^2 from aryl or benzyl groups to alkyl group eliminates the antiproliferative activity of synthesized compounds 8 completely. The same effect was observed as a result of the replacement of H with Ph at the CH_2-group of the cyclopropane ring. At the same time, significant improvement of biological activity (almost threefold) was achieved after incorporation of Br in the meta-position of the aryl ring at C-1 (R^1 substituent). Thus, the obtained compounds **8ec** and **8ej** revealed great promise as novel anticancer scaffolds and will be the subject of further investigations.

CONCLUSION

In conclusion, a novel and highly efficient cyclization involving alkali-metal templated ring-retentive *exo-trig* nucleophilic attack of tethered amine moiety (activated by carbamate group) at the cyclopropene double bond was demonstrated. It was shown that this reaction proceeds in a highly regio- and diastereoselective fashion, which allows access to previously unknown cyclopropane-fused medium-sized nitrogen-based heterocycles as sole products. Utilization of chiral diamines derived from natural amino acids allows for expeditious access to enantiomerically pure molecules. Preliminary evaluation of the bioactivity of these previously unknown drug-like scaffolds was performed to reveal several structures with promising anticancer properties. Further synthetic studies utilizing a variety of different activating groups and building a library for further SAR-investigations are currently underway in our laboratories.

EXPERIMENTAL SECTION

General.

NMR spectra were recorded on a Bruker Avance DRX-500 (500 MHz) with a dual carbon/proton cryoprobe (CPDUL). ^{13}C NMR spectra were registered with broadband decoupling. The (+) and (−) designations represent positive and negative intensities of signals in ^{13}C DEPT-135 experiments. IR spectra were recorded on a ThermoFisher Nicolet iS 5 FT-IR Spectrometer. HRMS was carried out on LCT Premier (Micromass Technologies) instrument employing ESI TOF detection techniques. Glassware used in moisture-free syntheses was flame-dried in vacuum prior to use. Column chromatography was carried out on silica gel (Sorbent Technologies, 40−63 mm). Precoated silica gel plates (Sorbent Technologies Silica XG 200 mm) were used for TLC analyses. Anhydrous dichloro-methane was obtained by passing degassed commercially available HPLC-grade inhibitor-free solvent

consecutively through two columns filled with activated alumina and stored over molecular sieves under nitrogen. Water was purified by dual stage deionization followed by dual stage reverse osmosis. Anhydrous THF was obtained by refluxing commercially available solvent over calcium hydride followed by distillation in a stream of dry nitrogen. All other reagents and solvents were purchased from commercial vendors and used as received.

Biological Studies.

Cell culture: HeLa cells were cultured in DMEM supplemented with 10% FBS. To evaluate antiproliferative properties of the synthesized compounds, the cells were trypsinized and seeded 4×10^3 cells per well into 96-well microtiter plates. The cells were grown for 24 h before treatment.

MTT assay for HeLa: All compounds were dissolved in DMSO at a concentration of either 100 or 50 mM prior to cell treatment. The cells were treated at concentrations ranging from 0.004 to 100 μM and incubated for 48 h in 200 μL of media. Twenty microliters of MTT reagent in serum-free medium (5 mg/mL) was added to each well and incubated further for 2 h. Media was removed, and the resulting formazan crystals were resolubilized in 100 μL of DMSO. A490 was measured using a Thermomax Molecular Device plate reader. The experiments were performed in quadruplicate and repeated at least twice for each compound per cell line. Cells treated with 0.1% DMSO were used as a negative control, and phenyl arsine oxide (PAO) was used as a positive killing control.

Preparation of Starting Materials.

1-(4-Methoxyphenyl)-cycloprop-2-ene-1-carboxylic Acid (12b).—Typical procedure: Methyl (4-methoxyphenyl)acetate (6.86 g, 41.3 mmol, 1.00 equiv), and tosyl azide (9.0 g, 45.4 mmol, 1.1 equiv) were stirred in acetonitrile (150 mL) at 0 °C, and DBU (7.54 g, 49.5 mmol, 1.2 equiv) was added dropwise. Upon complete addition, the reaction was warmed to room temperature and stirred overnight. The solvent was then removed in vacuum, and the residue was partitioned between saturated ammonium chloride (100 mL) and methylene chloride (75 mL). The aqueous phase was then extracted with methylene chloride (3 × 30 mL). Combined organic phases were then washed with brine, dried with $MgSO_4$, filtered, and concentrated. The recovered material was then filtered through a short pad of silica gel (15 g) as solution in hexanes. The filtrate was concentrated in vacuum to obtain crude methyl 2-diazo-2-(4-methoxyphenyl)acetate as a red oil. This material was then mixed with trimethylsilylacetylene (2 mL) and added via a syringe pump over 18 h to a stirring and refluxing suspension of rhodium(II) acetate dimer (27.4 mg, 0.124 mmol, 0.3 mol %) in trimethylsilylacetylene (47 mL, 413 mmol, 10.0 equiv). The reaction was monitored by gas chromatography until complete consumption of the starting material was observed. Then, the reflux condenser was replaced with a distilling head, and most of the trimethylsilylacetylene was recovered by distillation at ambient pressure. The residual solvent was then removed under vacuum. The reaction mixture was then purified by short column chromatography, eluting with a mixture of hexane:EtOAc (10:1). Crude ethyl 1-(4-methoxyphenyl)-2-(trimethylsilyl)cycloprop-2-ene-1-carboxylate was obtained as a yellowish oil, which was stirred at 0 °C in a mixture of methanol and THF (1:1, 200 mL). An aqueous solution of sodium hydroxide (2 M, 200 mL) was added dropwise, and the

mixture was stirred for 18h. Organic solvents were then removed under vacuum, and the remaining aqueous solution was washed with dichloromethane (3 × 50 mL). The mixture was acidified to pH 2 with 2 M aqueous HCl and extracted with dichloromethane (3 × 50 mL). The combined organic phases were washed with brine, dried with $MgSO_4$, filtered, and concentrated. The obtained product was purified by column chromatography on silica gel eluting with a mixture of hexane:EtOAc (2:1). The title compound was obtained as an off-white crystalline solid (R_f 0.3, mp 115−116 °C). Overall yield 2.198 g (11.6 mmol, 28%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (s, 2H), 7.24−7.19 (m, 2H), 6.87−6.81 (m, 2H), 3.79 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 180.7, 158.5, 132.9, 129.5 (+, 2C), 113.8 (+, 2C), 107.6 (+, 2C),55.4 (+), 29.7. FT IR (NaCl, cm^{-1}): 3440 (br.), 1689, 1659, 1514, 1246, 1030, 773. HRMS (ESI-TOF) *m/z*: $[M - H]^-$ Calcd for $C_{11}H_9O_3$ 189.0552; Found 189.0551 (0.5 ppm).

1-(3-Chlorophenyl)cycloprop-2-ene-1-carboxylic Acid (12d).—This compound was obtained from methyl (3-chlorophenyl)acetate(5.65 g, 33.1 mmol) using the protocol described for the synthesis of 1-(4-methoxyphenyl)cycloprop-2-ene-1-carboxylic acid (*vide supra*). The title compound was obtained as an off-white crystalline solid (mp 84−86 °C). Yield 4.71 g (24.2 mmol, 73%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (td, J = 1.8, 0.6 Hz, 1H), 7.24−7.22 (m, 1H), 7.21 (t, J = 1.9 Hz, 1H), 7.20 (s, 2H), 7.19−7.17 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 180.9, 142.7, 134.1, 129.5 (+), 128.7 (+), 127.1 (+), 126.7 (+), 106.8 (+, 2C), 30.0. FT IR (NaCl, cm^{-1}): 3160 (br.), 1690, 1674, 1595, 1413, 1269, 1091, 984. HRMS (ESI-TOF) *m/z*: $[M - H]^-$ Calcd for $C_{10}H_6ClO_2$ 193.0056; Found 193.0057 (0.5 ppm).

1-(2,4-Dichlorophenyl)-2-phenylcycloprop-2-ene-1-carboxylic Acid (12h).—This compound was obtained using methyl (2,4-dichlorophenyl)acetate (2.11 g, 10.3 mmol) and a solution of ethynylbenzene (3.15 g, 30.9 mmol, 3.0 equiv) in 20 mL of CH_2Cl_2 according to the protocol described for the synthesis of 1-(4-methoxyphenyl)cycloprop-2-ene-1-carboxylic acid (vide supra). The title compound was obtained as a light-beige crystalline solid (mp 153−154 °C). Yield 1.79 g (5.87 mmol, 57%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73−7.68 (m, 2H), 7.50−7.42 (m, 3H), 7.37 (d, J = 2.1 Hz, 1H), 7.31 (s, 1H), 7.23 (d, J = 8.2 Hz, 1H), 7.11 (dd, J = 8.2, 2.1 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 180.0, 137.9, 135.9, 133.9, 131.1 (+), 130.6 (+), 130.1 (+, 2C), 129.5 (+), 129.2 (+, 2C), 127.3 (+), 125.2, 118.1, 101.3 (+), 32.8. FT IR (NaCl, cm^{-1}): 3381 (br.), 1685, 1471, 1260,1101, 821, 698. HRMS (ESI-TOF) *m/z*: $[M - H]^-$ Calcd for $C_{16}H_9Cl_2O_2$ 302.9980; Found 302.9982 (0.7 ppm).

tert-Butyl (S)-(2-(Benzylamino)-3-methylbutyl)carbamate (13k).—A 15 mL stainless steel autoclave vessel was charged with tert-butyl (S)-(2-amino-3-methylbutyl)carbamate[15] (300 mg, 1.48 mmol, 1.0 equiv), benzaldehyde (182 μL, 189 mg, 1.78 mmol, 1.2 equiv), 10 wt % palladium on carbon (78.9 mg, 0.074 mmol, 0.05 equiv), and methanol (3 mL). The mixture was stirred under hydrogen gas (1.5 atm) overnight. The catalyst was removed by vacuum filtration through Celite 545 nonacid-washed filter aid washing with methanol, and then the resulting mixture was evaporated. The product was isolated by column chromatography eluting with a chloroform:methanol mixture (40:1) as a

colorless oil (R_f 0.24), $[\alpha]_D^{20}$ +1.8° (c 1.50, $CHCl_3$). Yield: 239 mg (0.82 mmol, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−7.15 (m, 5H), 4.97 (br. s, 1H), 3.70 (s, 2H), 3.29−3.12 (m, 1H), 2.96 (dt, J = 12.9, 6.2 Hz, 1H), 2.36 (q, J = 6.2 Hz, 1H), 1.76 (nonet, J = 6.8 Hz, 1H), 1.38 (s, 9H), 0.86 (dd, J = 17.1,6.8 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.3, 140.6, 128.5 (+, 2C), 128.2 (+, 2C), 127.0 (+), 79.0, 62.1 (+), 51.5 (−), 40.5 (−),28.5 (+, 3C), 19.2 (+, 2C), 18.4 (+). FTIR (NaCl, cm^{-1}): 3350 (br.), 2963, 1699,1495, 1366, 1171738, 699. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{29}N_2O_2$ 293.2229, Found 293.2222 (2.4 ppm).

Synthesis of Medium-Sized Heterocycles.

tert-Butyl (1S*,7S*)-5-Benzyl-6-oxo-7-phenyl-2,5-diazabicyclo[5.1.0]octane-2-carboxylate (8aa).—Typical procedure: Flame-dried round-bottom flask was charged with 1-phenylcycloprop-2-ene-1-carboxylic acid (12a)[16] (200 mg, 1.25 mmol, 1.0 equiv), DMF (2 drops), and freshly distilled anhydrous dichloromethane (7 mL) under nitrogen atmosphere. Oxalyl chloride (400 μL, 592 mg, 4.68 mmol, 1.5 equiv) was then added dropwise, and the mixture was stirred at room temperature for 2 h. The solution was concentrated in a stream of nitrogen; then, the residue was subjected to a high vacuum, dissolved in anhydrous dichloromethane (2.0 mL), and added dropwise to a stirred solution of tert-butyl (2-(benzylamino)ethyl)carbamate (13a)[17] (375 mg, 1.5 mmol, 1.2 equiv) and triethylamine (1.3 mL, 948 mg, 9.36 mmol, 3.0 equiv) in anhydrous dichloromethane (3.0 mL). The reaction mixture was stirred at room temperature for 18 h and then partitioned between water (15 mL) and dichloromethane (20 mL). The aqueous phase was diluted with 5 mL of concentrated aqueous solution of ammonium chloride. The organic phase was then washed with saturated aq NH_4Cl (3 × 10 mL). The combined aqueous layers were back-extracted once with 10 mL of dichloro-methane, which was combined with other organic phases, washed with brine, dried with $MgSO_4$, filtered, and concentrated. The crude product tert-butyl (2-(N-benzyl-1-phenylcycloprop-2-ene-1-carboxamido)ethyl)carbamate (7aa) was filtered through a silica plug using EtOAc and then was concentrated and used at the cyclization step as-is without additional purification. An oven-dried 3 mL Wheaton vial was charged with powdered KOH (21.4 mg, 0.381 mmol) and anhydrous THF (800 μL). Crude carbamate 7aa (60 mg, 0.153 mmol) was added as a solution in anhydrous THF (400 μL). The mixture was vigorously stirred at 35 °C for 8 h; then, the reaction mixture was filtered through short plug of silica gel eluting with EtOAc, and the eluate was concentrated in vacuum. The titled product was isolated by column chromatography eluting with a hexanes:EtOAc mixture (3:1) as a colorless solid (R_f 0.30, mp 103−105 °C). Yield: 51.7 mg (0.132 mmol, 86%). ^{1}H NMR (500 MHz, C_6D_6) δ 7.19−7.14 (m, 3H), 7.14−7.06 (m, 5H), 7.08−7.00 (m, 2H),4.53 (br.s, 1H), 4.29 (br.s, 1H), 3.56 (br.s, 1H), 3.39 (td, J = 13.4, 4.0 Hz, 1H), 2.54−2.45 (m, 2H), 2.41 (dd, J = 12.8, 3.9 Hz, 1H), 1.97 (t, J = 5.6 Hz, 1H), 1.52 (t, J = 6.9 Hz, 1H), 1.42 (s, 9H). ^{13}C NMR (126 MHz, C_6D_6) δ 169.9, 156.5, 139.4, 138.4, 129.0 (+, 2C), 128.9 (+, 2C), 128.4 (+, 2C), 127.6 (+), 127.0 (+), 125.8 (+, 2C), 79.9,49.6 (−), 44.5 (−), 43.4 (−), 37.4 (+), 36.4, 28.4 (+, 3C), 26.5 (−). FTIR (NaCl, cm^{-1}): 2975, 2928, 1701, 1652, 1496, 1470, 1425, 1394, 1366, 1346, 1250, 1146, 1065, 1029, 987, 856, 811, 750, 698, 632, 606. HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for 415.1998; Found 415.2008 (2.4 ppm).

tert-Butyl(1S*,7S*)-5-(4-Methoxybenzyl)-6-oxo-7-phenyl-2,5-diazabicyclo[5.1.0]octane-2-carboxylate (8ab).—This compound was synthesized according to the typical procedure starting from 1-phenylcycloprop-2-ene-1-carboxylic acid (12a)[15] (200 mg, 1.25 mmol, 1.0 equiv) and tert-butyl (2-((4-methoxybenzyl)amino)ethyl)-carbamate (13b)[18] (420 mg, 1.5 mmol, 1.2 equiv). After extraction and filtration through a silica plug, crude *tert*-butyl (2-(N-(4-methoxybenzyl)-1-phenylcycloprop-2-ene-1-carboxamido)ethyl)-carbamate (7ab) was used at the cyclization step as-is without additional purification. To this end, amide 7ab (60 mg, 0.142 mmol) was treated with powdered KOH (19.9 mg, 0.355 mmol). The reaction mixture was vigorously stirred at 35 °C for 16 h. The product was isolated by column chromatography eluting with a hexanes:E-tOAc mixture (2:1) as a colorless solid (R_f 0.25, mp 134−136 °C). Yield: 51.7 mg (0.122 mmol, 86%). ^{1}H NMR (500 MHz, C_6D_6) δ7.21−7.17 (m, 2H), 7.11 (dd, J = 8.5, 6.9 Hz, 2H), 7.09−7.05 (m, 2H), 7.05−6.99 (m, 1H), 6.76−6.69 (m, 2H), 4.50 (br.s, 1H), 4.31 (br.s, 1H), 3.58 (br.s, 1H), 3.41 (td, J = 13.3, 4.1 Hz, 1H), 3.32 (s, 3H), 2.59−2.51 (m, 1H), 2.48 (dd, J = 7.1, 4.7 Hz, 1H), 2.43 (dd, J = 12.8, 3.9 Hz, 1H), 1.99 (t, J = 5.6 Hz, 1H), 1.53 (t, J = 6.8 Hz, 1H),1.42 (s, 9H). ^{13}C NMR (126 MHz, C_6D_6) δ 169.8, 159.8, 156.5, 139.5, 130.4, 129.8 (+, 2C), 129.0(+, 2C), 127.0 (+), 125.8 (+, 2C), 114.5 (+, 2C), 79.9, 54.8 (+), 49.1 (−), 44.6 (−), 43.3 (−), 37.5 (+),36.4, 28.4 (+, 3C), 26.4 (−). FTIR (NaCl, cm^{-1}): 2974, 2923, 1701, 1651, 1513, 1393, 1248, 1146, 1032, 808, 760. HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{25}H_{30}N_2O_4Na$ 445.2103; Found 445.2104(0.2 ppm).

tert-Butyl(1S*,7S*)-5-(4-Fluorobenzyl)-6-oxo-7-phenyl-2,5-diazabicyclo[5.1.0]octane-2-carboxylate (8ac).—This compound was synthesized according to the typical procedure starting from 1-phenylcycloprop-2-ene-1-carboxylic acid (12a)[15] (200 mg, 1.25 mmol, 1.0 equiv), and tert-butyl (2-((4-fluorobenzyl)amino)ethyl)-carbamate (13c)[19] (402 mg, 1.5 mmol, 1.2 equiv). After extraction and filtration through a silica plug, crude *tert*-butyl (2-(N-(4-fluorobenzyl)-1-phenylcycloprop-2-ene-1-carboxamido)ethyl)-carbamate (7ac) was used at the cyclization step as-is without additional purification. To this end, amide 7ac (60 mg, 0.146 mmol) was treated with powdered KOH (20.5 mg, 0.365 mmol). The reaction mixture was vigorously stirred at 35 °C for 16 h. The product was isolated by column chromatography eluting with a hexanes:E-tOAc mixture (2:1) as a colorless solid (R_f 0.26, mp 112−113 °C). Yield: 53.3 mg (0.13 mmol, 89%). ^{1}H NMR (500 MHz, C_6D_6) δ 7.14 (d, J = 7.4 Hz, 2H), 7.09 (dd, J = 8.5, 6.7 Hz, 2H), 7.05−7.00 (m, 1H), 6.93 (dd, J = 8.4, 5.5 Hz, 2H), 6.75 (t, J = 8.7 Hz, 2H), 4.34 (br.s, 1H), 4.20 (br.s, 1H), 3.51 (br.s, 1H), 3.37 (td, J = 13.2, 4.1 Hz, 1H), 2.47 (dd, J = 7.1, 4.6 Hz, 1H), 2.44−2.37 (m, 2H), 1.95 (t, J = 5.6 Hz, 1H), 1.50 (t, J = 6.9 Hz, 1H), 1.41 (s, 9H). ^{13}C NMR (126MHz, C_6D_6) δ 169.9, 162.8 (d, J = 245.3 Hz), 156.5, 139.2, 134.2 (d, J = 3.5 Hz), 130.1 (d, J = 8.1 Hz, + , 2C), 129.0 (+, 2C), 127.1 (+), 125.8 (+, 2C), 115.6 (d, J = 21.3 Hz, + , 2C), 80.0, 48.9 (−), 44.5 (−), 43.5 (−), 37.3 (+), 36.3, 28.4 (+, 3C), 26.4 (−). ^{19}F NMR (376MHz, $CDCl_3$) δ −114.6. FTIR (NaCl, cm^{-1}): 2976, 2929, 1701, 1650, 1509, 1365, 1346, 1222, 1146, 853, 765, 697. HRMS (ESITOF) *m/z*: [M + Na]$^+$ Calcd for $C_{24}H_{27}FN_2O_3Na$ 433.1903; Found 433.1910 (1.6 ppm).

tert-Butyl(1S*,7S*)-5-Benzyl-7-(3-bromophenyl)-6-oxo-2,5-diazabicyclo[5.1.0]octane-2-carboxylate (8ea).—This compound was synthesized

according to the typical procedure starting from 1-(3-bromophenyl)cycloprop-2-ene-1-carboxylic acid (12e)[5a] (200 mg, 0.84 mmol, 1.0 equiv) and tert-butyl (2-(benzylamino)ethyl)-carbamate (13a)[16] (251 mg, 1 mmol, 1.2 equiv). After extraction and filtration through a silica plug, crude *tert*-butyl (2-(N-benzyl-1-(3-bromophenyl)cycloprop-2-ene-1-carboxamido)ethyl)carbamate (7ea) was used at the cyclization step as-is without additional purification. To this end, amide 7ea (60 mg, 0.127 mmol) was treated with powdered KOH (17.9 mg, 0.319 mmol). The reaction mixture was vigorously stirred at 35 °C for 8 h. The product was isolated by column chromatography eluting with a hexanes:EtOAc mixture (1:1) as a colorless solid (R_f 0.4, mp 151−152 °C). Yield: 54.6 mg (0.116 mmol, 91%). ^{1}H NMR (500 MHz, C_6D_6) δ 7.38 (t, J = 1.9 Hz, 1H),7.19−7.13 (m, 2H), 7.13−7.01 (m, 5H), 6.73 (t, J = 7.9 Hz, 1H),4.51 (br.s, 1H), 4.16 (br.s, 1H), 3.51 (br.s, 1H), 3.20 (td, J = 13.4, 4.1 Hz, 1H), 2.48−2.37 (m, 1H), 2.33 (dd, J = 12.9, 4.0 Hz, 1H), 2.29 (dd, J = 7.1, 4.7 Hz, 1H), 1.91 (t, J = 5.7 Hz, 1H), 1.41 (s, 9H), 1.39−1.35 (m, 1H). ^{13}C NMR (126 MHz, C_6D_6) δ 169.2, 156.3, 141.9, 138.2, 130.5 (+), 130.2 (+), 128.9 (+, 2C), 128.7 (+), 128.4 (+, 2C), 127.7 (+), 124.8 (+), 123.4, 80.0, 49.6 (−), 44.3 (−), 43.3 (−), 37.3 (+), 36.0, 28.4 (+, 3C), 26.6 (−). FTIR (NaCl, cm^{-1}): 2974, 2926, 1702, 1654, 1476, 1393, 1366, 1344, 1249, 1147, 1062, 994, 777, 754, 697. HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{24}H_{27}{}^{79}BrN_2O_3Na$ 493.1103; Found 493.1109 (1.2 ppm).

tert-Butyl(1S*,7S*)-7-(3-Bromophenyl)-5-(4-fluorobenzyl)-6-oxo-2,5-diazabicyclo[5.1.0]octane-2-carboxylate (8ec).—This compound was synthesized according to the typical procedure starting from 1-(3-bromophenyl)cycloprop-2-ene-1-carboxylic acid (12e)[5] (200 mg, 0.84 mmol, 1.0 equiv) and tert-butyl (2-((4-fluorobenzyl)-amino)ethyl)carbamate (13c)[18] (269 mg, 1 mmol, 1.2 equiv). After extraction and filtration through a silica plug, crude *tert*-butyl (2-(1-(3-bromophenyl)-N-(4-fluorobenzyl)cycloprop-2-ene-1-carboxamido)ethyl)carbamate (7ec) was used at the cyclization step as-is without additional purification. To this end, amide 7ec (60 mg, 0.123 mmol) was treated with powdered KOH (17.2 mg, 0.307 mmol). The reaction mixture was vigorously stirred at 35 °C for 8 h. The product was isolated by column chromatography eluting with a hexanes:EtOAc mixture (1:1) as a colorless solid (R_f 0.4, mp 156−157 °C). Yield: 54.1 mg (0.111 mmol, 90%). ^{1}H NMR (500 MHz, C_6D_6) δ 7.35 (t, J = 1.9 Hz, 1H), 7.19−7.13 (m, 1H), 7.01−6.96 (m, 1H), 6.92 (dd, J = 8.4, 5.5 Hz, 2H), 6.80−6.71 (m, 3H), 4.31 (br. s, 1H), 4.11 (br. s, 1H), 3.46 (br. s, 1H), 3.20 (ddd, J = 15.4, 13.4, 4.2 Hz, 1H), 2.42−2.31 (m, 2H), 2.29 (dd, J = 7.1, 4.7 Hz, 1H), 1.88 (dd, J = 6.7, 4.7 Hz, 1H), 1.40 (s, 9H), 1.43−1.34 (m, 1H). ^{13}C NMR (126 MHz, C_6D_6) δ 169.2, 162.8 (d, J = 246.0 Hz), 156.3, 141.8, 134.0 (d, J = 3.4 Hz), 130.5 (+), 130.3 (+), 130.1 (d, J = 8.1 Hz, + , 2C), 128.7 (+), 124.7 (+), 123.4, 115.7 (d, J = 21.3 Hz, + , 2C), 80.1,48.9 (−), 44.3 (−), 43.4 (−), 37.3 (+), 35.9, 28.4 (+, 3C), 26.5 (−).^{19}F NMR (376 MHz, C_6D_6) δ −114.8. FTIR (NaCl, cm^{-1}): 2977, 2931, 736, 693. HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{24}H_{26}{}^{79}BrFN_2O_3Na$ 511.1009; Found 511.1001 (1.6 ppm).

tert-Butyl(1S*,7S*)-5-(4-Methoxybenzyl)-7-(4-methoxyphenyl)-6-oxo-2,5-diazabicyclo[5.1.0]octane-2-carboxylate (8bb).—This compound was synthesized according to the typical procedure starting from 1-(4-methoxyphenyl)cycloprop-2-ene-1-carboxylic acid (12b) (200 mg, 1.05 mmol, 1.0 equiv) and tert-butyl (2-((4-

methoxybenzyl)amino)ethyl)carbamate (13b)[17] (354 mg, 1.26 mmol, 1.2 equiv). After extraction and filtration through a silica plug, crude *tert*-butyl (2-(N-(4-methoxybenzyl)-1-(4-methoxyphenyl)cycloprop-2-ene-1-carboxamido)ethyl)carbamate (7bb) was used at the cyclization step as-is without additional purification. To this end, amide 7bb (60 mg, 0.133 mmol) was treated with powdered KOH(18.6 mg, 0.332 mmol). The reaction mixture was vigorously stirred at 35 °C for 16 h. The product was isolated by column chromatography eluting with a hexanes:EtOAc mixture (1:1) as a colorless glass (R_f 0.43). Yield: 55.9 mg (0.123 mmol, 93%). ^{1}H NMR (500 MHz, C_6D_6) δ 7.19−7.16 (m, 2H), 7.07 (d, J = 8.5 Hz, 2H),6.78−6.70 (m, 4H), 4.57 (br.s, 1H), 4.26 (br.s, 1H), 3.63 (br.s, 1H),3.51 (td, J = 13.4, 3.9 Hz, 1H), 3.31 (s, 3H), 3.31 (s, 3H), 2.62−2.54 (m, 1H), 2.51−2.46 (m, 2H), 1.97 (t, J = 5.5 Hz, 1H), 1.51 (t, J = 6.8 Hz, 1H), 1.43 (s, 9H). ^{13}C NMR (126 MHz, C_6D_6) δ 170.1, 159.7, 159.3, 156.6, 131.3, 130.4, 129.7 (+, 2C), 127.3 (+, 2C), 114.7 (+, 2C), 114.5 (+, 2C), 79.8, 54.9 (+), 54.8 (+), 49.0 (−), 44.6 (−), 43.3 (−), 36.9 (+), 36.0, 28.5 (+, 3C), 26.1 (−). FTIR (NaCl, cm^{-1}): 2926, 1700, 1649, 1514, 1393, 1248, 1176, 1146, 1032, 829, 784. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{32}N_2O_5Na$ 475.2209; Found 475.2213 (0.8 ppm).

tert-Butyl (1S*,7S*)-5-Ethyl-6-oxo-7-phenyl-2,5-diazabicyclo- [5.1.0]octane-2-carboxylate (8ae).—This compound was synthesized according to the typical procedure starting from 1-phenylcycloprop-2-ene-1-carboxylic acid (12a)[15] (200 mg, 1.25 mmol, 1.0 equiv), and tert-butyl (2-(ethylamino)ethyl)carbamate (13e)[20] (282 mg, 1.5 mmol, 1.2 equiv). After extraction and filtration through a silica plug, crude *tert*-butyl (2-(N-ethyl-1-phenylcycloprop-2-ene-1-carboxamido)ethyl)carbamate (7ae) was used at the cyclization step as-is without additional purification. To this end, amide 7ae (60 mg, 0.182 mmol) was treated with powdered KOH (25.5 mg, 0.455 mmol). The reaction mixture was vigorously stirred at 35 °C for 8 h. The product was isolated by column chromatography eluting with a hexanes:EtOAc mixture (2:1) as a colorless glass (R_f 0.43). Yield: 51.1 mg (0.155 mmol, 85%). ^{1}H NMR (500 MHz, C_6D_6) δ 7.15−7.07 (m, 4H), 7.04−6.99 (m, 1H), 3.80 (br.t, J = 10.8 Hz, 1H), 3.42−3.28 (m, 2H), 3.01 (dq, J = 14.1, 7.1 Hz, 1H), 2.56−2.48 (m, 1H), 2.46 (dd, J = 7.1, 4.6 Hz, 1H), 2.30 (dd, J = 15.2, 4.6 Hz, 1H), 1.92 (t, J = 5.7 Hz, 1H), 1.48 (t, J = 6.9 Hz, 1H), 1.41 (s, 9H), 0.87 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, C_6D_6) δ 169.1, 156.6, 139.6, 128.9 (+, 2C), 126.9 (+), 125.7 (+, 2C), 79.9, 45.0 (−), 43.6 (−), 41.3 (−), 37.7 (+), 36.5, 28.5 (+, 3C), 26.3 (−), 13.5 (+). FTIR (NaCl, cm^{-1}): 2973, 2926, 1699, 1652, 1429, 1366, 1346, 1175, 1146, 1065, 757, 697, 614. HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{19}H_{26}N_2O_3Na$ 353.1841; Found 353.1836, (1.4 ppm).

tert-Butyl(1S*,7S*)-7-(3-Bromophenyl)-5-ethyl-6-oxo-2,5-diazabicyclo[5.1.0]octane-2-carboxylate (8ee).—This compound was synthesized according to the typical procedure starting from 1-(3-bromophenyl)cycloprop-2-ene-1-carboxylic acid (12e)[5] (200 mg, 0.84 mmol, 1.0 equiv) and tert-butyl (2-(ethylamino)ethyl)carbamate (13e)[19] (190 mg, 1.0 mmol, 1.2 equiv). After extraction and filtration through a silica plug, crude *tert*-butyl (2-(1-(3-bromophenyl)-N-ethylcycloprop-2-ene-1-carboxamido)ethyl)carbamate (7ee) was used at the cyclization step as-is without additional purification. To this end, amide 7ee (60 mg, 0.147 mmol) was treated with powdered KOH (20.6 mg, 0.367 mmol). The reaction mixture was vigorously stirred at 35 °C for 8 h. The product was isolated by column chromatography eluting with a

hexanes:EtOAc mixture (2:1) as a colorless glass (R_f 0.4). Yield: 52.2 mg (0.128 mmol, 87%). ^{1}H NMR (400 MHz, C_6D_6) δ 7.30 (t, J = 1.9 Hz, 1H), 7.16−7.11 (m, 1H),7.04 (d, J = 8.0 Hz, 1H), 6.70 (t, J = 7.9 Hz, 1H), 3.73 (br.s, 1H),3.36−3.20 (m, 1H), 3.16−3.07 (m, 1H), 2.86 (br.s, 1H), 2.40 (dd, J = 13.0, 4.0 Hz, 1H), 2.23 (dd, J = 7.2, 4.7 Hz, 1H), 2.15 (dd, J = 15.4,4.5 Hz, 1H), 1.85 (br.s, 1H), 1.39 (s, 9H), 1.42−1.33 (m, 1H), 0.80 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, C_6D_6) δ 168.5, 156.4, 142.1, 130.5 (+), 130.1 (+), 128.5 (+), 124.9 (+), 123.3, 80.1, 44.8 (−), 43.5 (−), 41.4 (−), 37.4 (+), 36.2, 28.4 (+, 3C), 26.3, 13.4 (+). FTIR (NaCl, cm^{-1}): 2973, 2928, 1701, 1652, 1477, 1394, 1366, 1344, 1249, 1147, 856, 778, 694. HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{19}H_{25}BrN_2O_3Na$ 431.0946; Found 431.0953, (1.6 ppm).

tert-Butyl(1S*,7S*)-5-Ethyl-7-(4-fluorophenyl)-6-oxo-2,5-diazabicyclo[5.1.0]octane-2-carboxylate (8ce).—This compound was synthesized according to the typical procedure starting from 1-(4-fluorophenyl)cycloprop-2-ene-1-carboxylic acid (12c)[5] (200 mg, 1.12 mmol, 1.0 equiv) and tert-butyl (2-(ethylamino)ethyl)carbamate (13e)[19] (256 mg, 1.35 mmol, 1.2 equiv). After extraction and filtration through a silica plug, crude *tert*-butyl (2-(N-ethyl-1-(4-fluorophenyl)cycloprop-2-ene-1-carboxamido)ethyl)carbamate (7ce) was used at the cyclization step as-is without additional purification. To this end, amide 7ce (60 mg, 0.172 mmol) was treated with powdered KOH (24.2 mg, 0.431 mmol). The reaction mixture was vigorously stirred at 35 °C for 8 h. The product was isolated by column chromatography eluting with a hexanes:EtOAc mixture (2:1) as a colorless solid (R_f 0.45, mp 146−148 °C). Yield: 52.2 mg (0.15 mmol, 87%). ^{1}H NMR (500 MHz, C_6D_6) δ 6.98−6.93 (m, 2H),6.78−6.71 (m, 2H), 3.87−3.72 (m, 1H), 3.34−3.25 (m, 2H), 2.98 (dq, J = 14.1, 7.1 Hz, 1H), 2.53 (dd, J = 13.0, 4.0 Hz, 1H), 2.35 (dd, J = 7.1, 4.6 Hz, 1H), 2.30 (dd, J = 15.3, 5.0 Hz, 1H), 1.85 (t, J = 5.6 Hz, 1H), 1.41 (s, 9H), 1.35 (t, J = 6.8 Hz, 1H), 0.84 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, C_6D_6) δ 169.0, 162.3 (d, J = 246.0 Hz), 156.6, 135.2 (d, J = 3.6 Hz), 127.5 (d, J = 8.1 Hz, + , 2C), 115.7 (d, J = 21.7 Hz, + , 2C), 80.0, 45.0 (−), 43.5 (−), 41.4 (−), 37.3 (+), 35.9, 28.5 (+, 3C), 26.1 (−), 13.5 (+). FTIR (NaCl, cm^{-1}): 2975, 2932, 1699, 1651, 1512, 1476, 1395, 1366, 1345, 1250, 1234, 1148, 1064, 834, 778. ^{19}F NMR (376 MHz, $CDCl_3$) δ −115.9. HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{19}H_{25}FN_2O_3Na$ 371.1747; Found 371.1756(2.4 ppm).

tert-Butyl(1S*,7S*)-7-(3-Bromophenyl)-5-isobutyl-6-oxo-2,5-diazabicyclo[5.1.0]octane-2-carboxylate (8ef).—This compound was synthesized according to the typical procedure starting from 1-(3-bromophenyl)cycloprop-2-ene-1-carboxylic acid (12e)[5] (200 mg, 0.84 mmol, 1.0 equiv) and tert-butyl (2-(isobutylamino)ethyl)-carbamate (13f)[21] (217 mg, 1.0 mmol, 1.2 equiv). After extraction and filtration through a silica plug, crude *tert*-butyl (2-(1-(3-bromophenyl)-N-isobutylcycloprop-2-ene-1-carboxamido)ethyl)-carbamate (7ef) was used at the cyclization step as-is without additional purification. To this end, amide 7ef (60 mg, 0.137 mmol) was treated with powdered KOH (19.2 mg, 0.342 mmol). The reaction mixture was vigorously stirred at 35 °C for 8 h. The product was isolated by column chromatography eluting with a hexanes:E-tOAc mixture (2:1) as a colorless solid (R_f 0.48, mp 122−123 °C).

Yield: 56.5 mg (0.129 mmol, 94%). ^{1}H NMR (500 MHz, C_6D_6) δ7.39 (t, J = 1.9 Hz, 1H), 7.18−7.15 (m, 1H), 7.06 (d, J = 7.9 Hz, 1H),6.76 (t, J = 7.9 Hz, 1H), 3.77 (br.t, J = 10.3 Hz, 1H), 3.33−3.20 (m, 2H), 2.65 (dd, J = 13.4, 8.2 Hz, 1H), 2.51−2.43 (m, 1H), 2.37−2.29 (m, 2H), 1.84 (t, J = 5.7 Hz, 1H), 1.67 (dh, J = 8.1, 6.7 Hz, 1H), 1.41 (s, 9H), 1.33 (t, J = 7.1 Hz, 1H), 0.75 (dd, J = 6.7, 1.1 Hz, 6H). ^{13}CNMR (126 MHz, C_6D_6) δ 169.1, 156.4, 142.1, 130.5 (+), 130.1 (+), 128.7 (+), 124.8 (+), 123.3, 80.1, 53.8 (−), 44.5 (−), 44.4 (−), 37.2 (+), 36.4, 28.4 (+, 3C), 28.0 (+), 26.6 (−), 20.3 (+), 20.1 (+). FTIR (NaCl, cm^{-1}): 2964, 2928, 2871, 1702, 1652, 1593, 1562, 1477, 1428, 1367, 1345, 1297, 1248, 1247, 1175, 1062, 856, 777, 693, 664. HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{21}H_{29}BrN_2O_3Na$ 459.1259; Found 459.1263 (0.9 ppm).

tert-Butyl(1S*,8S*)-8-(3-Bromophenyl)-6-(4-fluorobenzyl)-7-oxo-2,6-diazabicyclo[6.1.0]nonane-2-carboxylate (8ej).—This compound was synthesized according to the typical procedure starting from 1-(3-bromophenyl)cycloprop-2-ene-1-carboxylic acid (12e)[5] (200 mg, 0.84 mmol, 1.0 equiv) and tert-butyl (3-((4-fluorobenzyl)-amino)propyl)carbamate (13j)[22] (283 mg, 1 mmol, 1.2 equiv). After extraction and filtration through a silica plug, crude *tert*-butyl (3-(1-(3-bromophenyl)-N-(4-fluorobenzyl)cycloprop-2-ene-1-carboxamido)propyl)carbamate (7ej) was used at the cyclization step as-is without additional purification. To this end, amide 7ej (60 mg, 0.119 mmol) was treated with powdered KOH (16.7 mg, 0.298 mmol). The reaction mixture was vigorously stirred at 35 °C for 8 h. The product was isolated by column chromatography eluting with a hexanes:EtOAc mixture (3:1) as a colorless solid (R_f 0.27, mp 119−121 °C). Yield: 54.1 mg (0.107 mmol, 90%). ^{1}H NMR (500 MHz, C_6D_6) δ 7.32 (s, 1H), 7.11 (d, J = 7.1 Hz, 1H), 6.97 (dd, J = 8.1, 5.7Hz, 2H), 6.86 (d, J = 7.9 Hz, 1H), 6.79 (t, J = 8.6 Hz, 2H), 6.68 (t, J = 7.9 Hz, 1H), 5.01 (d, J = 14.6 Hz, 1H), 3.86 (d, J = 14.3 Hz, 1H),3.59 (d, J = 14.6 Hz, 1H), 3.28 (dd, J = 15.5, 11.2 Hz, 1H), 2.80−2.69 (m, 2H), 2.51 (dd, J = 15.5, 5.9 Hz, 1H), 2.41 (ddd, J = 14.6, 11.5, 3.2 Hz, 1H), 1.68−1.56 (m, 1H), 1.43 (s, 9H), 1.19 (dd, J = 8.5, 6.6 Hz, 1H), 0.92−0.82 (m, 1H). ^{13}C NMR (126 MHz, C_6D_6) δ 169.2, 162.8 (d, J = 245.3 Hz), 155.2, 143.3, 134.2 (d, J = 3.5 Hz), 130.5 (+), 130.3 (d, J = 8.1 Hz, + , 2C), 129.9 (+), 128.7 (+), 124.2 (+), 123.5, 115.7 (d, J = 21.1 Hz, + , 2C), 80.2, 50.3 (−), 48.7 (−), 46.6 (+), 46.2 (−), 37.0, 28.5 (+, 3C), 27.6 (−), 25.2 (−). FTIR (NaCl, cm^{-1}): 2973, 2925, 1692, 1639, 1593, 1562, 1509, 1477, 1414, 1383, 1367, 1256, 1221, 1154, 1107, 969, 858, 819, 769, 689. ^{19}F NMR (376 MHz, $CDCl_3$) δ −114.8. HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for C_{25} H_{28} $^{79}BrFN_2O_3Na$ 525.1165; Found 525.1165 (0.0 ppm).

tert-Butyl(1S*,7S*)-6-Oxo-7-phenyl-5-(pyridin-2-ylmethyl)-2,5-diazabicyclo[5.1.0]octane-2-carboxylate (8ag).—This compound was synthesized according to the typical procedure starting from 1-phenylcycloprop-2-ene-1-carboxylic acid (12a)[15] (200 mg, 1.25 mmol, 1.0 equiv) and tert-butyl (2-((pyridin-2-ylmethyl)amino)-ethyl)carbamate (13g)[23] (377 mg, 1.5 mmol, 1.2 equiv). After extraction and filtration through a silica plug, crude *tert*-butyl (2-(1-phenyl-N-(pyridin-2-ylmethyl)cycloprop-2-ene-1-carboxamido)-ethyl)carbamate (7af) was used at the cyclization step as-is without additional purification. To this end, amide 7af (60 mg, 0.152 mmol) was treated with powdered KOH (21.4 mg, 0.381 mmol). The reaction mixture was vigorously stirred at 35 °C for 8 h. The product was isolated by column chromatography eluting with a

hexanes:E-tOAc mixture (1:2) as a colorless glass (R_f 0.31). Yield: 48.6 mg(0.123 mmol, 81%). ^{1}H NMR (500 MHz, C_6D_6) δ 8.37 (d, J = 4.8 Hz, 1H), 7.16 (s, 4H), 7.12−6.98 (m, 3H), 6.66−6.59 (m, 1H), 4.65 (br.s, 2H), 3.65 (br.s, 1H), 3.51 (td, J = 14.8, 14.2, 3.8 Hz, 1H), 2.88 (dd, J = 15.2, 4.9 Hz, 1H), 2.47−2.38 (m, 2H), 1.94 (t, J = 5.6 Hz, 1H), 1.53 (t, J = 6.8 Hz, 1H), 1.39 (s, 9H). ^{13}C NMR (126 MHz, C_6D_6) δ 169.8, 158.4, 159.4, 149.3 (+), 139.4, 136.4 (+), 128.9 (+, 2C), 128.1, 126.9 (+), 125.8 (+, 2C), 122.8 (+), 122.3 (+), 79.8, 52.2 (−), 44.6 (−), 44.6 (−), 37.7 (+), 36.2, 28.4 (+, 3C), 26.3 (−). FTIR (NaCl, cm^{-1}): 2961, 2924, 2854, 1700, 1654, 1591, 1474, 1435, 1394, 1366, 1345, 1251, 1146, 1066, 756, 698, 610. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{23}H_{27}N_3O_3Na$ 416.195; Found 416.1958(1.9 ppm).

tert-Butyl (1S*,8S*)-6-Benzyl-7-oxo-8-phenyl-2,6-diazabicyclo- [6.1.0]nonane-2-carboxylate (8ah).—This compound was synthesized according to the typical procedure starting from 1-phenylcycloprop-2-ene-1-carboxylic acid (12a)[15] (200 mg, 1.25 mmol, 1.0 equiv) and tert-butyl (3-(benzylamino)propyl)carbamate (13h)[17] (396 mg, 1.5 mmol, 1.2 equiv). After extraction and filtration through a silica plug, crude *tert*-butyl (3-(N-benzyl-1-phenylcycloprop-2-ene-1-carboxamido)propyl)carbamate (7ah) was used at the cyclization step as-is without additional purification. To this end, amide 7ah (60 mg, 0.148 mmol) was treated with powdered KOH (20.7 mg, 0.369 mmol). The reaction mixture was vigorously stirred at 35 °C for 8 h. The product was isolated by column chromatography eluting with a hexanes:EtOAc mixture (2:1) as a colorless solid (R_f 0.21, mp 110−112 °C). Yield: 50.5 mg (0.124 mmol, 84%). ^{1}H NMR (500 MHz, C_6D_6) δ 7.18−7.16 (m, 4H), 7.13−6.98 (m, 6H), 5.19 (d, J = 14.7Hz, 1H), 3.89 (br.d, J = 14.6 Hz, 1H), 3.84 (d, J = 14.7 Hz, 1H), 3.54 (dd, J = 15.3, 11.5 Hz, 1H), 3.03 (dd, J = 8.8, 6.0 Hz, 1H), 2.80−2.75 (m, 1H), 2.65 (dd, J = 15.4, 5.6 Hz, 1H), 2.59 (ddd, J = 14.4, 11.3, 3.2 Hz, 1H), 1.76−1.65 (m, 1H), 1.46 (s, 9H), 1.33 (dd, J = 8.8, 6.7 Hz, 1H), 0.98−0.89 (m, 1H). ^{13}C NMR (126 MHz, C_6D_6) δ 170.0, 155.3, 140.9, 138.7, 129.0 (+, 2C), 128.8 (+, 2C), 128.6 (+, 2C), 127.5 (+), 126.7 (+), 125.9 (+, 2C), 80.0, 49.9 (−), 49.4 (−), 46.2 (+), 46.1 (−), 37.5, 28.5 (+, 3C), 27.6 (−), 24.8 (−). FTIR (NaCl, cm^{-1}): 2925, 2854, 1692, 1640, 1631, 1585, 1470, 1453, 1416, 1383, 1366, 1288, 1253, 1156, 1105, 1051, 939, 860, 788, 732, 699. HRMS (ESITOF) m/z: $[M + Na]^+$ Calcd for $C_{25}H_{30}N_2O_3Na$ 429.2154; Found 429.2164 (2.3 ppm).

tert-Butyl(1S*,8S*)-6-Benzyl-8-(2,4-dichlorophenyl)-7-oxo-2,6-diazabicyclo[6.1.0]nonane-2-carboxylate (8fh).—This compound was synthesized according to the typical procedure starting from 1-(2,4-dichlorophenyl)cycloprop-2-ene-1-carboxylic acid (12f)[24] (200mg, 0.87 mmol, 1.0 equiv) and tert-butyl (3-(benzylamino)propyl)-carbamate (13h)[17] (278 mg, 1.05 mmol, 1.2 equiv). After extraction and filtration through a silica plug, crude *tert*-butyl (3-(N-benzyl-1-(2,4-dichlorophenyl)cycloprop-2-ene-1-carboxamido)propyl)-carbamate (7fh) was used at the cyclization step as-is without additional purification. To this end, amide 7fh (60 mg, 0.126 mmol) was treated with powdered KOH (17.7 mg, 0.316 mmol). The reaction mixture was vigorously stirred at 35 °C for 8 h. The product was isolated by column chromatography eluting with a hexanes:E-tOAc mixture (2:1) as a colorless solid (R_f 0.24, mp 118−120 °C). ield: 51.5 mg (0.108 mmol, 86%). ^{1}H NMR (500 MHz, C_6D_6) δ7.48 (d, J = 8.5 Hz, 1H), 7.12 (d, J = 2.3 Hz, 1H), 7.04−6.93 (m, 5H), 6.84 (dd, J = 8.4, 2.2 Hz, 1H), 5.01 (d, J = 14.9

Hz, 1H), 4.11 (t, J = 13.6 Hz, 1H), 3.88−3.73 (m, 2H), 3.20−3.06 (m, 2H), 2.71−2.63 (m, 1H), 2.30 (t, J = 6.5 Hz, 1H), 1.47 (s, 9H), 1.39−1.31 (m, 1H),1.12 (dd, J = 8.9, 6.5 Hz, 1H), 0.99−0.85 (m, 1H). ^{13}C NMR (126MHz, C_6D_6) δ 169.7, 155.3, 138.4, 137.4, 135.2, 134.2 (+), 134.0, 130.4 (+), 128.8 (+, 2C), 128.2 (+, 2C), 127.5 (+), 127.5 (+), 80.2,49.9 (−), 45.2 (+), 44.7 (−), 44.0 (−), 35.7, 28.5 (+, 3C), 27.8 (−),21.3 (−). FTIR (NaCl, cm^{-1}): 2972, 2925, 2854, 1690, 1639, 1477, 1454, 1423, 1383, 1366, 1292, 1255, 1159, 1106, 1078, 1059, 968, 860, 750, 733, 699, 602. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{25}H_{28}Cl_2N_2O_3Na$ 497.1375; Found 497.1382 (1.4 ppm).

tert-Butyl(1S*,8S*)-6-Benzyl-8-(3-bromophenyl)-7-oxo-2,6-diazabicyclo[6.1.0]nonane-2-carboxylate (8eh).—This compound was synthesized according to the typical procedure starting from 1-(3-bromophenyl)cycloprop-2-ene-1-carboxylic acid (12e)[5] (200 mg, 0.84 mmol, 1.0 equiv) and tert-butyl (3-(benzylamino)propyl)-carbamate (13h)[17] (267 mg, 1 mmol, 1.2 equiv). After extraction and filtration through a silica plug, crude *tert*-butyl (3-(N-benzyl-1-(3-bromophenyl)cycloprop-2-ene-1-carboxamido)propyl)carbamate (7eh) was used at the cyclization step as-is without additional purification. To this end, amide 7eh (60 mg, 0.124 mmol) was treated with powdered KOH (17.3 mg, 0.308 mmol). The reaction mixture was vigorously stirred at 35 °C for 8 h. The product was isolated by column chromatography eluting with a hexanes:EtOAc mixture (2:1) as a colorless solid (R_f 0.24, mp 121−123 °C). Yield: 49.8 mg (0.103 mmol, 83%). ^{1}H NMR (500 MHz, C_6D_6) δ 7.39 (s, 1H), 7.16−7.11 (m, 5H), 7.06 (t, J = 6.7 Hz, 1H), 6.94 (d, J = 7.9 Hz, 1H), 6.71 (t, J = 7.9 Hz, 1H), 5.19 (d, J = 14.7 Hz, 1H), 3.87 (br.d, J = 14.3 Hz, 1H),3.73 (d, J = 14.7 Hz, 1H), 3.32 (dd, J = 15.5, 11.1 Hz, 1H), 2.80 (dd, J = 8.3, 6.3 Hz, 1H), 2.75 (t, J = 6.3 Hz, 1H), 2.61 (dd, J = 15.2, 5.7 Hz, 1H), 2.43 (ddd, J = 14.4, 11.6, 3.0 Hz, 1H), 1.73−1.61 (m, 1H), 1.45 (s, 9H), 1.21 (dd, J = 8.6, 6.7 Hz, 1H), 0.92−0.84 (m, 1H). ^{13}C NMR (126 MHz, C_6D_6) δ 169.2, 155.2, 143.4, 138.4, 130.5 (+), 129.9 (+), 128.9 (+, 2C), 128.7 (+), 128.6 (+, 2C), 127.6 (+), 124.3 (+), 123.4,80.2, 50.2 (−), 49.4 (−), 46.6 (+), 46.1 (−), 37.1, 28.5 (+, 3C), 27.5 (−), 25.3 (−). FTIR (NaCl, cm^{-1}): 2972, 2925, 1691, 1639, 1593, 1561, 1476, 1454, 1418, 1383, 1366, 1282, 1256, 1158, 1106, 1078, 968, 860, 768, 752, 700. HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for C H 7925 29 BrN_2O_3Na 507.1259; Found 507.1255 (0.8 ppm).

tert-Butyl (1S*,7S*)-5-Methyl-6-oxo-7-phenyl-2,5-diazabicyclo- [5.1.0]octane-2-carboxylate (8ad).—This compound was synthesized according to the typical procedure starting from 1-phenylcycloprop-2-ene-1-carboxylic acid (12a)[15] (200 mg, 1.25 mmol, 1.0 equiv) and tert-butyl (2-(methylamino)ethyl)carbamate (13d)[25](261 mg, 1.5 mmol, 1.2 equiv). After extraction and filtration through a silica plug, crude *tert*-butyl (2-(N-methyl-1-phenylcycloprop-2-ene-1-carboxamido)ethyl)carbamate (7ad) was used at the cyclization step as-is without additional purification. To this end, amide 7ad (60 mg, 0.19 mmol) was treated with powdered KOH (26.6 mg, 0.474 mmol). The reaction mixture was vigorously stirred at 35 °C for 8 h. The product was isolated by column chromatography eluting with a hexanes:EtOAc mixture (2:1) as a colorless solid (R_f 0.42, mp 188−189 °C). Yield: 54.6 mg (0.173 mmol, 91%). ^{1}H NMR (500 MHz, C_6D_6) δ 7.15−7.06 (m, 4H), 7.03 (dd, J = 8.1, 6.0 Hz, 1H), 3.79 (br.t, J = 11.4 Hz, 1H), 3.43 (ddd, J = 15.5, 13.7, 3.7 Hz, 1H), 2.58 (s, 3H), 2.52−2.43 (m, 2H), 2.17 (dd, J = 15.4, 4.7 Hz, 1H), 1.87 (t, J = 5.3 Hz, 1H), 1.46 (t, J = 6.7

Hz, 1H), 1.41 (s, 9H). ^{13}C NMR (126 MHz, C_6D_6) δ 169.5, 156.7, 139.5, 128.9 (+, 2C), 127.0 (+), 125.9 (+, 2C),80.0, 45.5 (−), 43.6 (−), 37.3 (+), 36.4, 33.3 (+), 28.5 (+, 3C), 26.3 (−). FTIR (NaCl, cm^{-1}): 2974, 2928, 1698, 1655, 1479, 1432, 1396, 1357, 1345, 1251, 1175, 1146, 1067, 856, 775, 758, 698, 615. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{24}N_2O_3Na$ 339.1685; Found 339.1696 (3.2 ppm).

tert-Butyl(1S*,7S*)-7-(3-Bromophenyl)-5-methyl-6-oxo-2,5-diazabicyclo[5.1.0]octane-2-carboxylate (8ed).—This compound was synthesized according to the typical procedure starting from 1-(3-bromophenyl)cycloprop-2-ene-1-carboxylic acid (12e)[5] (200 mg, 0.84 mmol, 1.0 equiv) and tert-butyl (2-(methylamino)ethyl)-carbamate (13d)[24] (175 mg, 1 mmol, 1.2 equiv). After extraction and filtration through a silica plug, crude *tert*-butyl (2-(1-(3-bromophenyl)-N-methylcycloprop-2-ene-1-carboxamido)ethyl)-carbamate (7ed) was used at the cyclization step as-is without additional purification. To this end, amide 7ed (60 mg, 0.152 mmol) was treated with powdered KOH (21.3 mg, 0.38 mmol). The reaction mixture was vigorously stirred at 35 °C for 8 h. The product was isolated by column chromatography eluting with a hexanes:EtOAc mixture (1:1) as a colorless solid (R_f 0.39, mp 115−117 °C). Yield:54.1 mg (0.137 mmol, 90%). ^{1}H NMR (500 MHz, C_6D_6) δ 7.36−7.31 (m, 1H), 7.19−7.15 (m, 1H), 7.06 (d, J = 7.9 Hz, 1H), 6.75 (t, J = 7.9 Hz, 1H), 3.72 (br.t, J = 10.6 Hz, 1H), 3.34−3.23 (m, 1H), 2.52 (s, 3H), 2.42 (dd, J = 13.1, 3.8 Hz, 1H), 2.33−2.28 (m, 1H), 2.13 (dd, J = 15.3, 4.4 Hz, 1H), 1.80 (t, J = 5.6 Hz, 1H), 1.40 (s, 9H), 1.31 (t, J = 7.0 Hz, 1H). ^{13}C NMR (126 MHz, C_6D_6) δ 168.9, 156.6, 142.0, 130.5 (+), 130.2 (+), 128.6 (+), 125.1 (+), 123.3, 80.1, 45.4 (−), 43.5 (−), 37.0 (+), 36.1, 33.3 (+), 28.4 (+, 3C), 26.4 (−). FTIR (NaCl, cm^{-1}): 2974, 2928, 1699, 1657, 1593, 1563, 1478, 1394, 1356, 1342, 1250, 1174, 1147, 1082, 1054, 856, 778, 695, 664. HRMS (ESITOF) *m/z*: $[M + Na]^+$ Calcd for C H 7918 23 BrN_2O_3Na 417.0790; Found 417.0786 (1.0 ppm).

tert-Butyl(1S*,7S*)-7-(2,4-Dichlorophenyl)-5-methyl-6-oxo-2,5-diazabicyclo[5.1.0]octane-2-carboxylate (8fd).—This compound was synthesized according to the typical procedure starting from 1-(2,4-dichlorophenyl)cycloprop-2-ene-1-carboxylic acid[23] (12f) (200 mg, 0.87 mmol, 1.0 equiv) and tert-butyl (2-(methylamino)ethyl)-carbamate (13d)[24] (183 mg, 1.05 mmol, 1.2 equiv). After extraction and filtration through a silica plug, crude *tert*-butyl (2-(1-(2,4-dichlorophenyl)-N-methylcycloprop-2-ene-1-carboxamido)ethyl)-carbamate (7ed) was used at the cyclization step as-is without additional purification. To this end, amide 7ed (60 mg, 0.156 mmol) was treated with powdered KOH (21.8 mg, 0.389 mmol). The reaction mixture was vigorously stirred at 35 °C for 8 h. The product was isolated by column chromatography eluting with a hexanes:E-tOAc mixture (1:1) as a colorless solid (R_f 0.42, mp 180−181 °C). Yield: 52.2 mg (0.136 mmol, 87%). ^{1}H NMR (500 MHz, C_6D_6) δ7.48 (d, J = 8.5 Hz, 1H), 7.12 (d, J = 2.0 Hz, 1H), 6.85 (dd, J = 8.5,2.0 Hz, 1H), 4.16−4.06 (m, 1H), 3.82 (br.t, J = 11.7 Hz, 1H), 2.99−2.95 (m, 1H), 2.78−2.72 (m, 1H), 2.48 (s, 3H), 2.27 (dd, J = 15.4,4.4 Hz, 1H), 1.73 (br.s, 1H), 1.40 (s, 9H), 1.27 (br.s, 1H). ^{13}C NMR (126 MHz, C_6D_6) δ 168.7, 156.6, 135.3, 134.8, 134.4 (+), 134.0, 130.7 (+), 127.4 (+), 80.1, 45.3 (−), 43.8 (−), 36.0 (+), 35.6, 34.2 (+), 28.4 (+, 3C), 26.3 (−). FTIR (NaCl, cm^{-1}): 2974, 2929, 1700, 1656, 1474, 1428, 1380,

1366, 1277, 1253, 1174, 1145, 1107, 1079, 858, 829, 781. HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{18}H_{22}Cl_2N_2O_3Na$ 407.0905; Found 407.0921 (3.9 ppm).

tert-Butyl(1S*,7S*)-5-Benzyl-7-(2,4-dichlorophenyl)-6-oxo-2,5-diazabicyclo[5.1.0]octane-2-carboxylate (8fa).—This compound was synthesized according to the typical procedure starting from 1-(2,4-dichlorophenyl)cycloprop-2-ene-1-carboxylic acid[23] (12f) (200mg, 0.87 mmol, 1.0 equiv) and tert-butyl (2-(benzylamino)ethyl)-carbamate (13a)[16] (262 mg, 1.05 mmol, 1.2 equiv). After extraction and filtration through a silica plug, crude *tert*-butyl (2-(N-benzyl-1-(2,4-dichlorophenyl)cycloprop-2-ene-1-carboxamido)ethyl)carbamate (7fa) was used at the cyclization step as-is without additional purification. To this end, amide 7fa (60 mg, 0.13 mmol) was treated with powdered KOH (18.2 mg, 0.324 mmol). The reaction mixture was vigorously stirred at 35 °C for 8 h. The product was isolated by column chromatography eluting with a hexanes:EtOAc mixture (3:1) as a colorless solid (R_f 0.33, mp 92−93 °C). Yield: 50.9 mg (0.11 mmol, 85%). ^{1}H NMR (500 MHz, C_6D_6) δ 7.53 (d, J = 8.4 Hz, 1H), 7.12 (d, J = 2.3 Hz, 1H), 7.06−6.97 (m, 5H), 6.86 (dd, J = 8.5, 2.3 Hz, 1H), 4.34 (br.s, 1H), 4.28 (br.s, 1H), 4.09 (td, J = 13.2, 3.7 Hz, 1H), 3.61 (br.s, 1H), 2.99 (dd, J = 7.2, 4.4 Hz, 1H), 2.72−2.64 (m, 1H), 2.61−2.53 (m, 1H), 1.84 (t, J = 5.4 Hz, 1H), 1.41 (s, 9H),1.38−1.34 (m, 1H). ^{13}C NMR (126 MHz, C_6D_6) δ 169.2, 156.4, 138.0, 135.3, 134.8, 134.5 (+), 134.1, 130.8 (+), 128.9 (+, 2C), 128.2 (+, 2C), 127.7 (+), 127.5 (+), 80.0, 50.4 (−), 44.5 (−), 43.2 (−),36.3 (+), 35.7, 28.4 (+, 3C), 26.4 (−). FTIR (NaCl, cm^{-1}): 2973, 2927, 1701, 1653, 1585, 1473, 1419, 1392, 1366, 1346, 1253, 1168, 1145, 1107, 1078, 1046, 992, 858, 820, 784, 734, 700. HRMS (ESITOF) m/z: [M + Na]$^+$ Calcd for $C_{24}H_{26}Cl_2N_2O_3Na$ 483.1218; Found 483.1214 (0.8ppm).

tert-Butyl(1S*,7S*)-5-Benzyl-7-(4-methoxyphenyl)-6-oxo-2,5-diazabicyclo[5.1.0]octane-2-carboxylate (8ba).—This compound was synthesized according to the typical procedure starting from 1-(4-methoxyphenyl)cycloprop-2-ene-1-carboxylic acid (12b) (200 mg, 1.05 mmol, 1.0 equiv) and tert-butyl (2-(benzylamino)ethyl)-carbamate (13a)[16] (316 mg, 1.26 mmol, 1.2 equiv). After extraction and filtration through a silica plug, crude *tert*-butyl (2-(N-benzyl-1-(4-methoxyphenyl)cycloprop-2-ene-1-carboxamido)ethyl)carbamate (7ba) was used at the cyclization step as-is without additional purification. To this end, amide 7ba (60 mg, 0.142 mmol) was treated with powdered KOH (19.9 mg, 0.355 mmol). The reaction mixture was vigorously stirred at 35 °C for 8 h. The product was isolated by column chromatography eluting with a hexanes:EtOAc mixture (3:1) as a colorless solid (R_f 0.26, mp 103−105 °C). Yield: 51.5 mg (0.122 mmol, 86%). ^{1}H NMR (500 MHz, C_6D_6) δ 7.15−7.07 (m, 6H),7.07−7.02 (m, 1H), 6.77−6.73 (m, 2H), 4.60 (br.s, 1H), 4.25 (br.s, 1H), 3.61 (br.s, 1H), 3.51 (td, J = 14.4, 2.2 Hz, 1H), 3.33 (s, 3H), 2.58−2.41 (m, 3H), 1.96 (t, J = 5.4 Hz, 1H), 1.50 (t, J = 6.4 Hz, 1H),1.43 (s, 9H). ^{13}C NMR (126 MHz, C_6D_6) δ 170.2, 159.3, 156.6, 138.5, 131.2, 128.9 (+, 2C), 128.3 (+, 2C), 127.6 (+), 127.2 (+, 2C), 114.7 (+, 2C), 79.8, 55.0 (+), 49.5 (−), 44.6 (−), 43.4 (−), 36.8 (+),35.9, 28.5 (+, 3C), 26.1 (−). FTIR (NaCl, cm^{-1}): 2974, 2928, 1700, 1651, 1515, 1496, 1428, 1393, 1366, 1346, 1250, 1179, 1146, 1065, 1030, 829, 777, 731, 701. HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{25}H_{30}N_2O_4Na$ 445.2103; Found 445.2098 (1.1 ppm).

tert-Butyl(1S*,7S*)-5-Benzyl-7-(3-chlorophenyl)-6-oxo-2,5-diazabicyclo[5.1.0]octane-2-carboxylate (8da).—This compound was synthesized according to the typical procedure starting from 1-(3-chlorophenyl)cycloprop-2-ene-1-carboxylic acid (12d) (200 mg, 1.03 mmol, 1.0 equiv) and tert-butyl (2-(benzylamino)ethyl)-carbamate (13a)[16] (309 mg, 1.23 mmol, 1.2 equiv). After extraction and filtration through a silica plug, crude *tert*-butyl (2-(N-benzyl-1-(3-chlorophenyl)cycloprop-2-ene-1-carboxamido)ethyl)carbamate (7da) was used at the cyclization step as-is without additional purification. To this end, amide 7da (60 mg, 0.141 mmol) was treated with powdered KOH (19.7 mg, 0.351 mmol). The reaction mixture was vigorously stirred at 35 °C for 8 h. The product was isolated by column chromatography eluting with a hexanes:EtOAc mixture (1:1) as a colorless solid (R_f 0.4, mp 100−102 °C). Yield: 52.9 mg (0.124 mmol, 88%). ^{1}H NMR (500 MHz, C_6D_6) δ 7.21 (s, 1H), 7.1−7.1 (m, 4H), 7.05 (t, J = 6.4 Hz, 1H), 7.02−6.98 (m, 2H), 6.81 (t, J = 7.9 Hz, 1H), 4.50 (br.s, 1H), 4.19 (br.s, 1H), 3.51 (br.s, 1H), 3.22 (td, J = 13.3, 4.1 Hz, 1H), 2.44 (dd, J = 15.5, 5.0 Hz, 1H), 2.35 (dd, J = 12.9,4.0 Hz, 1H), 2.31 (dd, J = 7.2, 4.7 Hz, 1H), 1.92 (t, J = 5.7 Hz, 1H),1.41 (sk, 9H), 1.39−1.29 (m, 1H). ^{13}C NMR (126 MHz, C_6D_6) δ 169.2, 156.3, 141.7, 138.2, 135.2, 130.2 (+), 128.9 (+, 2C), 128.4 (+, 2C), 127.7 (+), 127.2 (+), 125.8 (+), 124.3 (+), 80.0, 49.6 (−), 44.3 (−), 43.4 (−), 37.4 (+), 36.1, 28.4 (+, 3C), 26.6 (−). FTIR (NaCl, cm^{-1}): 2974, 2926, 2855, 1699, 1651, 1593, 1510, 1478, 1392, 1366, 1344, 1248, 1223, 1148, 1065, 993, 852, 815, 777, 736. HRMS (ESITOF) m/z: $[M + Na]^+$ Calcd for $C_{24}H_{27}ClN_2O_3Na$ 449.1608; Found 449.1618, (1.0 ppm).

tert-Butyl(1S*,7S*,8R*)-5-Benzyl-6-oxo-7,8-diphenyl-2,5-diazabicyclo[5.1.0]octane-2-carboxylate (8ga).—This compound was synthesized according to the typical procedure starting from 1,2-diphenylcycloprop-2-ene-1-carboxylic acid (12g)[26] (150 mg, 0.63 mmol, 1.0 equiv) and tert-butyl (2-(benzylamino)ethyl)carbamate (13a)[16] (191 mg, 0.76 mmol, 1.2 equiv). After extraction and filtration through a silica plug, crude *tert*-butyl (2-(N-benzyl-1,2-diphenylcycloprop-2-ene-1-carboxamido)ethyl)carbamate (7ga) was used at the cyclization step as-is without additional purification. To this end, amide 7ga (50 mg, 0.107 mmol) was treated with powdered KOH (15 mg, 0.267 mmol). The reaction mixture was vigorously stirred at 50 °C for 16 h. The product was isolated by column chromatography eluting with a hexanes:EtOAc mixture (2:1) as a colorless solid (R_f 0.43, mp 183−184 °C). Yield: 45.6 mg (0.097 mmol, 91%). ^{1}H NMR (500 MHz, C_6D_6) δ 7.31 (d, J = 7.6 Hz, 2H),7.20 (br. s, 2H), 7.10−6.98 (m, 5H), 6.96 (t, J = 7.6 Hz, 4H), 6.87 (t, J = 7.3 Hz, 2H), 4.51 (br. s, 1H), 4.25 (br. s, 1H), 3.80−3.56 (m, 2H), 3.37 (d, J = 4.7 Hz, 1H), 3.22 (d, J = 4.7 Hz, 1H), 2.62 (d, J = 9.2 Hz, 1H), 2.49 (d, J = 10.6 Hz, 1H), 1.34 (s, 9H). ^{13}C NMR (126 MHz, C_6D_6) δ 170.3, 156.9, 138.2, 136.1, 134.7, 129.4 (+, 2C), 128.8 (+, 2C), 128.8 (+, 2C), 128.6 (+, 2C), 128.4 (+, 2C), 128.0 (+, 2C), 127.6 (+), 127.4 (+), 126.6 (+), 80.2, 49.8 (−), 44.6 (−), 44.6, 43.1 (−), 40.9 (+), 39.1 (+), 28.5 (+, 3C). FTIR (NaCl, cm^{-1}): 2976, 2926, 2868, 1701, 1647, 1496, 1469, 1423, 1363, 1252, 1170, 1142, 777, 735, 698. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{30}H_{32}N_2O_3Na$ 491.2311; Found 491.2318 (1.4 ppm).

tert-Butyl(1S*,8S*,9R*)-6-Benzyl-7-oxo-8,9-diphenyl-2,6-diazabicyclo[6.1.0]nonane-2-carboxylate (8gh).—This compound was synthesized according to the typical procedure starting from 1,2-diphenylcycloprop-2-ene-1-carboxylic

acid (12g)[25] (150 mg, 0.63 mmol, 1.0 equiv) and tert-butyl (3-(benzylamino)propyl)carbamate (13h)[17] (202 mg, 0.76 mmol, 1.2 equiv). After extraction and filtration through a silica plug, crude *tert*-butyl (3-(N-benzyl-1,2-diphenylcycloprop-2-ene-1-carboxamido)propyl)carbamate (7gh) was used at the cyclization step as-is without additional purification. To this end, amide 7gh (50 mg, 0.104 mmol) was treated with powdered KOH (14.5 mg, 0.258 mmol). The reaction mixture was vigorously stirred at 50 °C for 16 h. The product was isolated by column chromatography eluting with a hexanes:EtOAc mixture (2:1) as a colorless solid (R_f 0.4, mp 98−99 °C). Yield: 43.9 mg (0.091 mmol, 88%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42−7.17 (m, 15H),5.39 (d, J = 15.0 Hz, 1H), 4.20 (d, J = 15.0 Hz, 1H), 4.22 (br. s, 1H),4.09 (dd, J = 15.3, 11.5 Hz, 1H), 4.05 (br. s, 1H), 3.78 (d, J = 6.5 Hz, 1H), 3.54 (ddd, J = 14.2, 9.7, 3.2 Hz, 1H), 3.19 (ddd, J = 15.4, 5.3, 2.3 Hz, 1H), 2.08−1.97 (m, 1H), 1.89−1.78 (m, 1H), 1.60 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.1, 156.2, 137.5, 135.8, 135.2, 128.8 (+, 2C), 128.6 (+, 2C), 128.4 (+, 4C), 127.9 (+, 4C), 127.4 (+), 127.2 (+), 126.3 (+), 80.9, 49.4 (−, 2C), 47.7 (+), 45.7 (−), 45.4,36.8 (+), 28.6 (+, 3C), 28.3 (−). FTIR (NaCl, cm^{-1}): 2976, 2928, 1694, 1634, 1477, 1417, 1365, 1294, 1258, 1155, 1078, 735, 698. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{31}H_{34}N_2O_3Na$ 505.2467; Found 505.2472 (1.0 ppm).

tert-Butyl(1S*,7S*,8R*)-5-Benzyl-7-(2,4-dichlorophenyl)-6-oxo-8-phenyl-2,5-diazabicyclo[5.1.0]octane-2-carboxylate (8ha).—This compound was synthesized according to the typical procedure starting from 1-(2,4-dichlorophenyl)-2-phenylcycloprop-2-ene-1-carboxylic acid (12h) (150 mg, 0.49 mmol, 1.0 equiv) and tert-butyl (2-(benzylamino)ethyl)carbamate (13a)[16] (148 mg, 0.59 mmol, 1.2 equiv). After extraction and filtration through a silica plug, crude *tert*-butyl (2-(N-benzyl-1-(2,4-dichlorophenyl)-2-phenylcycloprop-2-ene-1-carboxamido)ethyl)carbamate (7ha) was used at the cyclization step as-is without additional purification. To this end, amide 7ha (50 mg, 0.093 mmol) was treated with powdered KOH (13 mg, 0.232 mmol). The reaction mixture was vigorously stirred at 50 °C for 16 h. The product was isolated by column chromatography eluting with a hexanes:EtOAc mixture (4:1) as a colorless glass (R_f 0.33). Yield: 38.5 mg (0.072 mmol, 77%). ^{1}H NMR (500 MHz, C_6D_6) δ 7.71 (d, J = 8.5 Hz, 1H), 7.03 (d, J = 9.7 Hz, 6H), 6.97−6.89 (m, 4H), 6.89−6.79 (m, 1H), 6.71−6.55 (m, 1H), 4.48−4.27 (m, 3H), 3.93 (d, J = 4.8 Hz, 1H), 3.78 (br. s, 1H), 3.20 (br. s, 1H), 2.85−2.80 (m, 1H), 2.64 (dd, J = 15.6, 5.3 Hz, 1H), 1.28 (s, 9H). ^{13}C NMR (126 MHz, C_6D_6) δ 169.8, 156.6, 137.8, 136.6 (+), 136.3, 134.6, 134.2, 130.6, 130.4 (+), 128.9 (+, 2C), 128.6 (+, 2C), 128.2 (+, 2C), 128.2 (+, 2C), 127.7 (+), 127.6 (+), 126.8 (+), 80.2, 50.5 (−), 44.3 (−), 44.3, 43.0 (−),42.2 (+), 41.1 (+), 28.4 (+, 3C). FTIR (NaCl, cm^{-1}): 2974, 2926, 2864, 1701, 1649, 1473, 1386, 1365, 1250, 1142, 812, 736, 696. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{30}H_{30}Cl_2N_2O_3Na$ 559.1531; Found 559.1539 (1.4 ppm).

tert-Butyl(1S*,7S*,8R*)-7-(2,4-Dichlorophenyl)-5-(4-methoxybenzyl)-6-oxo-8-phenyl-2,5-diazabicyclo[5.1.0]octane-2-carboxy-late (8hb).—This compound was synthesized according to the typical procedure starting from 1-(2,4-dichlorophenyl)-2-phenylcycloprop-2-ene-1-carboxylic acid (12h) (150 mg, 0.49 mmol, 1.0 equiv) and tert-butyl (2-((4-methoxybenzyl)amino)ethyl)carbamate (13b)[17] (165mg, 0.59 mmol, 1.2 equiv). After extraction and filtration through a silica plug, crude *tert*-butyl (2-(1-(2,4-

dichlorophenyl)-N-(4-methoxybenzyl)-2-phenylcycloprop-2-ene-1-carboxamido)ethyl)carbamate (7hb) was used at the cyclization step as-is without additional purification. To this end, amide 7hb (50 mg, 0.088 mmol) was treated with powdered KOH (12.4 mg, 0.221 mmol). The reaction mixture was vigorously stirred at 50 °C for 16 h. The product was isolated by column chromatography eluting with a hexanes:EtOAc mixture (5:1) as a colorless glass (R_f 0.33). Yield: 40.5 mg (0.071 mmol, 81%). ^{1}H NMR (500 MHz, C_6D_6) δ 7.73 (d, J = 8.6 Hz, 1H), 7.02 (d, J = 2.2 Hz, 1H), 7.00 (d, J = 8.3 Hz, 2H), 6.96−6.90 (m, 4H), 6.85 (ddd, J = 8.5, 5.7, 2.3 Hz, 1H), 6.68 (d, J = 8.6 Hz, 2H), 6.64 (dd, J = 8.6, 2.3 Hz, 1H), 4.36 (ddd, J = 15.4, 13.2, 4.4 Hz, 1H), 4.36 (br. s, 2H), 3.93 (d, J = 4.7 Hz, 1H), 3.79 (s, 1H), 3.27 (s, 3H), 3.21 (br. s, 1H), 2.85 (dd, J = 13.1, 4.2 Hz, 1H), 2.70 (dd, J = 15.6, 5.2 Hz, 1H), 1.28 (s, 9H). ^{13}C NMR (126 MHz, C_6D_6) δ 169.7, 159.8, 156.6, 136.6 (+), 136.3, 134.6, 134.2, 130.7, 130.4 (+), 129.8, 129.6 (+, 2C), 128.4 (+, 2C), 128.2 (+, 2C), 127.6 (+), 126.8 (+), 114.6 (+, 2C), 80.2, 54.8 (+), 50.0 (−), 44.4 (−), 44.4, 42.8 (−), 42.2 (+), 41.1 (+), 28.4 (+, 3C). FTIR (NaCl, cm^{-1}): 2974, 2928, 1701, 1647, 1512, 1474, 1364, 1248, 2242, 1035, 810, 769, 736, 696. HRMS (ESI-TOF) *m/z*: [M +Na]$^+$ Calcd for $C_{31}H_{32}Cl_2N_2O_4Na$ 589.1637; Found 589.1639 (0.3 ppm).

tert-Butyl(1S*,8S*,9R*)-8-(2,4-Dichlorophenyl)-6-(4-methoxybenzyl)-7-oxo-9-phenyl-2,6-diazabicyclo[6.1.0]nonane-2-carboxy-late (8hi).—This compound was synthesized according to the typical procedure starting from 1-(2,4-dichlorophenyl)-2-phenylcycloprop-2-ene-1-carboxylic acid (12h) (150 mg, 0.49 mmol, 1.0 equiv) and tert-butyl (3-((4-methoxybenzyl)amino)propyl)carbamate (13i)[17] (173mg, 0.59 mmol, 1.2 equiv). After extraction and filtration through a silica plug, crude tert-butyl (3-(1-(2,4-dichlorophenyl)-N-(4-methoxybenzyl)-2-phenylcycloprop-2-ene-1-carboxamido)propyl)carbamate (7hi) was used at the cyclization step as-is without additional purification. To this end, amide 7hi (50 mg, 0.086 mmol) was treated with powdered KOH (12.1 mg, 0.216 mmol). The reaction mixture was vigorously stirred at 50 °C for 16 h. The product was isolated by column chromatography eluting with a hexanes:EtOAc mixture (5:1) as a colorless glass (R_f 0.25). Yield: 37.9 mg (0.065 mmol, 76%). ^{1}H NMR (500 MHz, C_6D_6) δ 7.46 (d, J = 8.4 Hz, 1H), 7.11 (d, J = 7.7 Hz, 2H), 7.04 (d, J = 1.7 Hz, 1H), 7.00−6.93 (m, 4H), 6.88 (t, J = 7.3 Hz, 1H), 6.64 (d, J = 8.5 Hz, 2H), 6.65−6.63 (m, 1H), 5.02 (d, J = 14.6 Hz, 1H), 4.61 (br. s, 1H), 4.21 (t, J = 13.3 Hz, 2H), 3.91 (br. s, 1H), 3.83 (d, J = 14.6 Hz, 1H), 3.47 (br. s, 1H), 3.35 (br. s, 1H), 3.24 (s, 3H), 2.77 (dt, J = 15.2, 3.1 Hz, 1H), 1.70−1.27 (m, 2H), 1.44 (s, 9H). ^{13}C NMR (126 MHz, C_6D_6) δ 170.1, 159.7, 155.6, 136.3, 135.4 (+), 134.0, 132.6, 130.6 (+), 130.2, 129.6 (+, 2C), 128.4 (+, 2C), 128.4 (+, 2C), 127.2 (+), 126.9 (+), 114.4 (+, 2C), 80.3, 54.8 (+),49.5 (−), 49.1 (+), 45.0, 44.8 (−, 2C), 37.2 (+), 28.5 (−), 28.5 (+, 3C). FTIR (NaCl, cm^{-1}): 2974, 2928, 1695, 1636, 1512, 1471, 1413, 1365, 1246, 1153, 1105, 1033, 158, 808, 767, 696. HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{32}H_{34}Cl_2N_2O_4Na$ 603.1793; Found 603.1793 (0.0 ppm).

tert-Butyl(1S,4S,7S)-5-Benzyl-7-(4-fluorophenyl)-4-isopropyl-6-oxo-2,5-diazabicyclo[5.1.0]octane-2-carboxylate (8ck).—This compound was synthesized according to the typical procedure from 1-(4-fluorophenyl)cycloprop-2-ene-1-carboxylic acid (12c) (100 mg, 0.56 mmol, 1.0 equiv) and *tert*-butyl (S)-(2-(benzylamino)-3-methylbutyl)carbamate (13k) (197 mg, 0.67 mmol, 1.2 equiv). After extraction and filtration

through a silica plug, crude *tert*-butyl (S)-(2-(N-benzyl-1-(4-fluorophenyl)cycloprop-2-ene-1-carboxamido)-3-methylbutyl)carbamate (7ck) was used at the cyclization step as-is without additional purification. To this end, amide 7ck (50 mg, 0.11 mmol) was treated with powdered KOH (15.5 mg, 0.276 mmol). The reaction mixture was vigorously stirred at 50 °C for 16 h. The product was isolated by column chromatography eluting with a hexanes:EtOAc mixture (5:1) as a colorless solid (R_f 0.33, mp 155−157 °C), $[\alpha]^{20}_D$ +97.8° (c 0.90, $CHCl_3$). Yield: 44.6 mg (0.099 mmol, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.21 (m, 5H), 7.14−7.06 (m, 2H), 7.05−6.97 (m, 2H), 5.44 (br. d, J = 15.1 Hz, 1H), 3.99 (br. d, J = 15.2 Hz, 1H), 3.54 (ddd, J = 12.6, 10.3, 3.9 Hz, 1H), 3.01 (br. s, 1H), 2.86 (dd, J = 12.6, 3.9 Hz, 1H), 2.60 (dd, J = 7.1, 4.6 Hz, 1H),2.20−2.05 (m, 1H), 1.91 (dd, J = 7.0, 4.6 Hz, 1H), 1.79 (t, J = 7.1 Hz, 1H), 1.69 (s, 1H), 1.42 (s, 9H), 0.88 (dd, J = 10.1, 6.4 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.1, 161.8 (d, J = 245.8 Hz), 156.4, 138.4, 134.0 (d, J = 3.1 Hz), 128.7 (+, 2C), 127.9 (+), 127.4 (+, 2C), 126.2 (d, J = 8.1 Hz, + , 2C), 115.7 (d, J = 21.5 Hz, + , 2C), 80.5, 61.1 (+), 46.9 (−), 44.3 (−), 39.0 (+), 35.2, 28.3 (+, 3C), 27.4 (−), 21.9 (+, 2C), 19.9 (+). ^{19}F NMR (376 MHz, $CDCl_3$) δ − 115.7. FTIR (NaCl, cm^{-1}): 2973, 2929, 1701, 1649, 1513, 1368, 1147, 832, 730. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{27}H_{33}FN_2O_3Na$ 475.2373; Found 475.2375 (0.4 ppm).

3-(N-Benzyl-1-phenylcycloprop-2-ene-1-carboxamido)propan-1-aminium Chloride (9).—Gaseous hydrogen chloride was bubbled through a solution of crude (3-(N-benzyl-1-phenylcycloprop-2-ene-1-carboxamido)propyl)carbamate (7ah) (589 mg, 1.45 mmol) in dichloromethane (25 mL) while stirring at rt. The reaction was allowed to proceed until TLC analysis indicated consumption of the starting carbamate (45 min). Volatiles were removed under reduced pressure. The resultant solid was triturated with diethyl ether and collected via vacuum filtration to afford the title compound as a white crystalline material (390 mg, 1.14 mmol, 79%); mp 89.1 °C (dec.); NMR spectra indicate the presence of two rotamers (ratio of 1.4:1): ^{1}H NMR (500 MHz, DMSO-d_6) δ [7.93 (s) and 7.89 (s) and 7.62(s), ∑5H], [7.38−7.17 (m) and 7.12−7.05 (m) and 7.01−6.98 (m), ∑10H], [4.54 (s) and 4.52 (s), ∑2H], [3.26 (t, J = 7.9 Hz) and 3.21 (t, J = 7.2 Hz), ∑2H], [2.71 (q, J = 6.6 Hz) and 2.54 (q, J = 6.4 Hz), ∑2H], [1.78 (p, J = 7.4 Hz) and 1.72−1.64 (m), ∑2H]; FT IR (NaCl, cm^{-1}): 3122, 3084, 2817, 2788, 2712, 1590, 1531, 1441, 1430, 1367, 1242, 738, 709, 696, 662, 537; HRMS (ESI-TOF) m/z: $[M]^+$ Calcd for $C_{20}H_{23}N_2O$ 307.1810; Found 307.1827 (5.5 ppm).

Supplementary Material

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ACKNOWLEDGMENTS

Financial support from Russian Science Foundation (Grant 18-13-00238) is gratefully acknowledged. Support for NMR instruments used in this project was provided by NIH Shared Instrumentation Grant S10RR024664 and NSF Major Research Instrumentation Grant 0329648.

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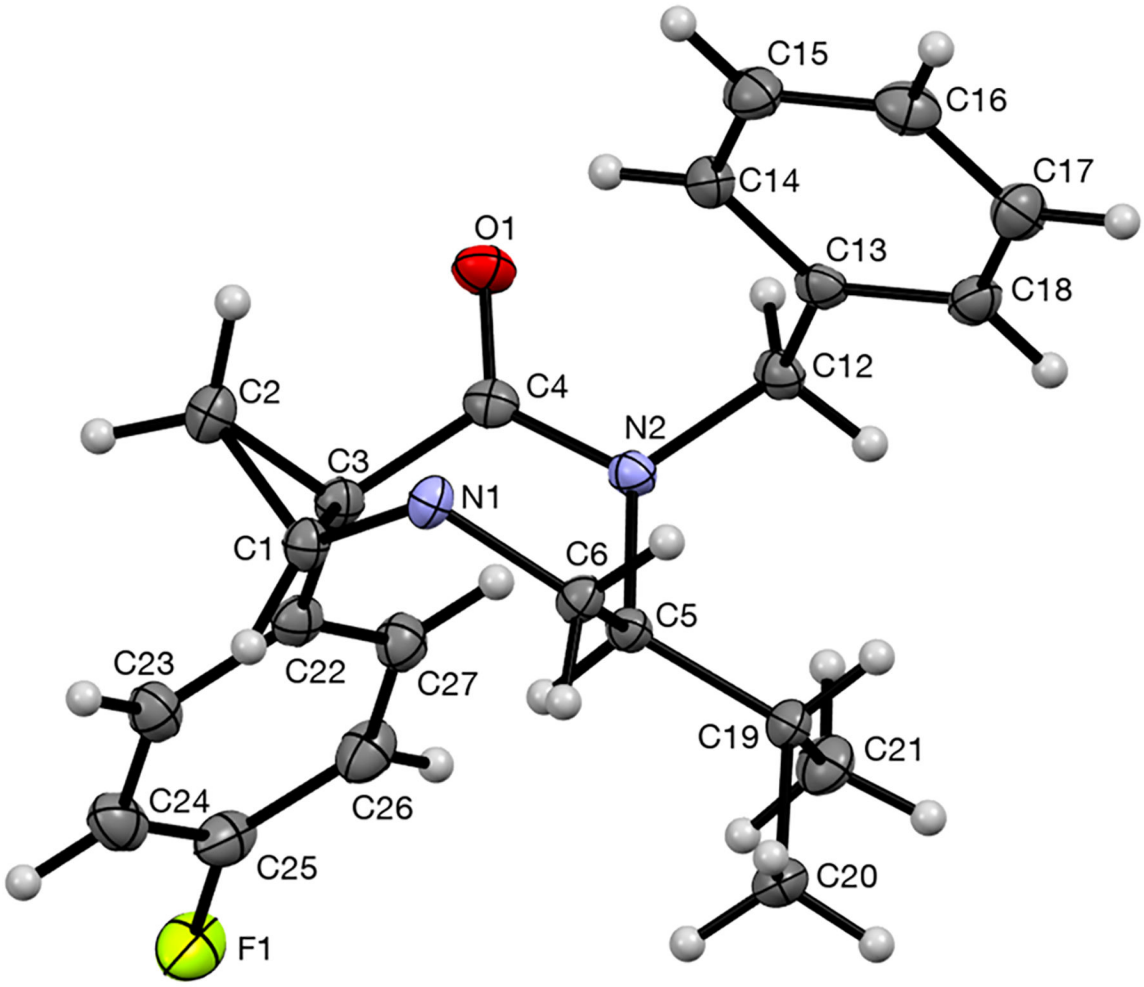
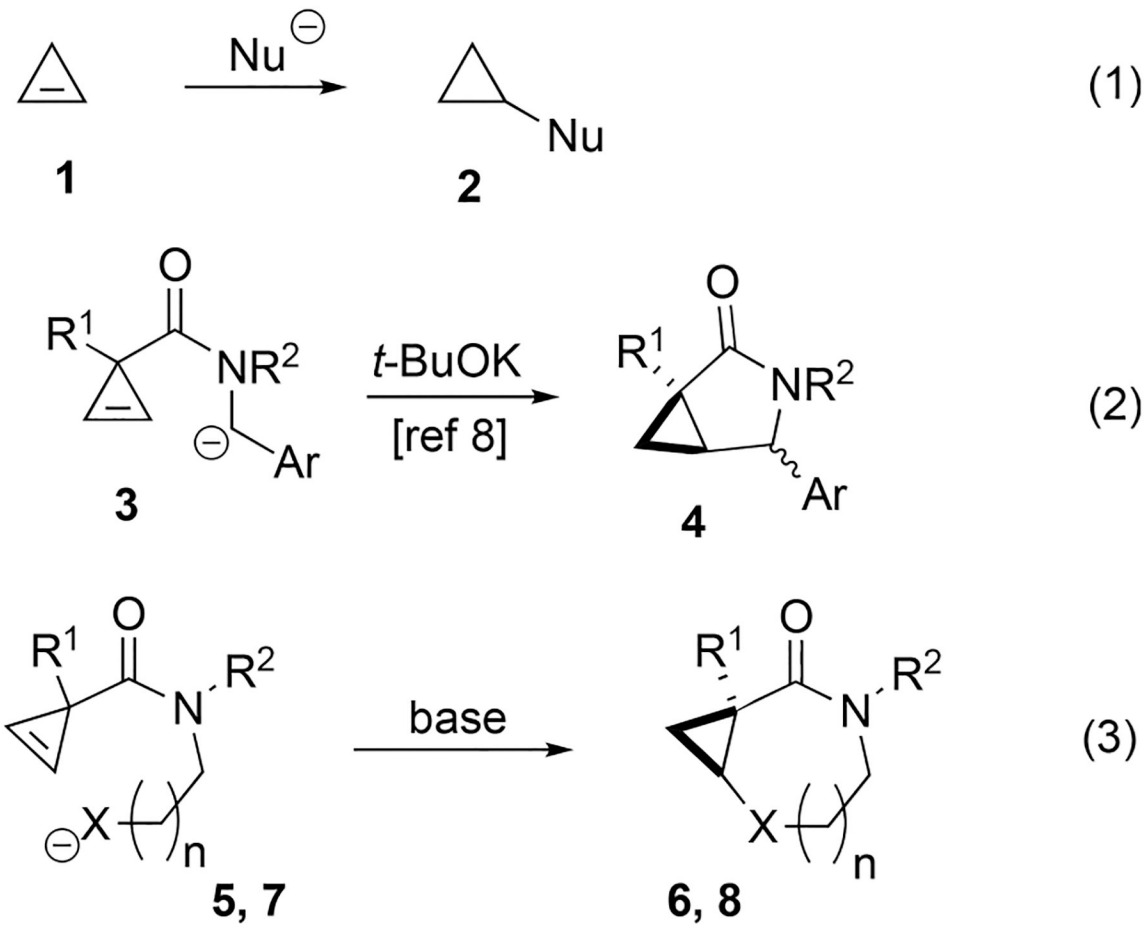
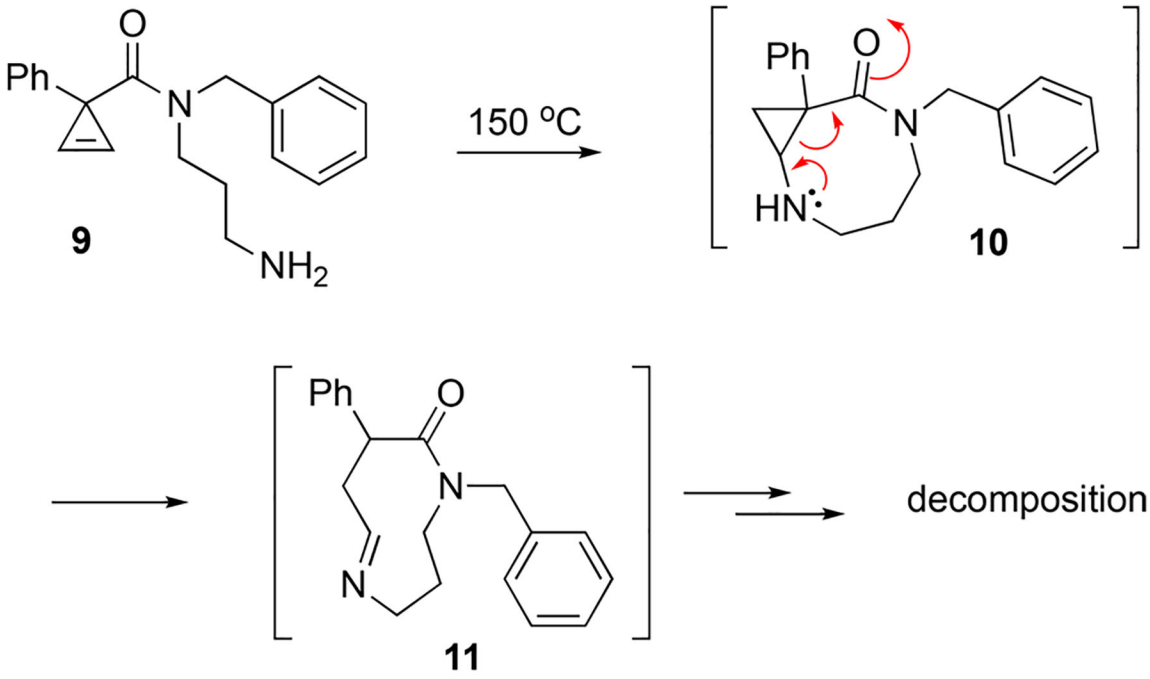


Figure 1.

ORTEP drawings of 8ck (CCDC #1854746) showing atom numbering schemes and 50% probability ellipsoids. Boc-group at N1 is removed for clarity. Also, see Supporting Information for X-ray data of compounds 8da (CCDC #1854743), 8ga (CCDC #1854744), and 8ej (CCDC #1854745).

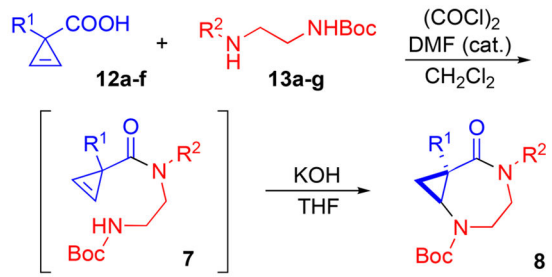


Scheme 1.
Nucleophilic Additions to Cyclopropenes



Scheme 2.

Decomposition of the Product of Intramolecular Nucleophilic Addition of Primary Amine to Cyclopropene



12a: R^1 = Ph;
12b: R^1 = 4-$MeOC_6H_4$;
12c: R^1 = 4-FC_6H_4;
12d: R^1 = 3-ClC_6H_4;
12e: R^1 = 3-BrC_6H_4;
12f: R^1 = 2,4-$Cl_2C_6H_3$.

13a: R^2 = $PhCH_2$;
13b: R^2 = 4-$MeOC_6H_4CH_2$;
13c: R^2 = 4-$FC_6H_4CH_2$;
13d: R^2 = Me;
13e: R^2 = Et;
13f: R^2 = *i*-Bu;
13g: R^2 = 2-$PyCH_2$.

(1) **7aa, 8aa**: R^1 = Ph, R^2 = $PhCH_2$, 86%;
(2) **7ab, 8ab**: R^1 = Ph, R^2 = 4-$MeOC_6H_4CH_2$, 86%;
(3) **7ac, 8ac**: R^1 = Ph, R^2 = 4-$FC_6H_4CH_2$, 89%;
(4) **7ad, 8ad**: R^1 = Ph, R^2 = Me, 91%;
(5) **7ae, 8ae**: R^1 = Ph, R^2 = Et, 85%;
(6) **7ag, 8ag**: R^1 = Ph, R^2 = 2-$PyCH_2$, 81%;

(7) **7ba, 8ba**: R^1 = 4-$MeOC_6H_4$, R^2 = $PhCH_2$, 86%;
(8) **7bb, 8bb**: R^1 = 4-$MeOC_6H_4$, R^2 = 4-$MeOC_6H_4CH_2$, 93%;

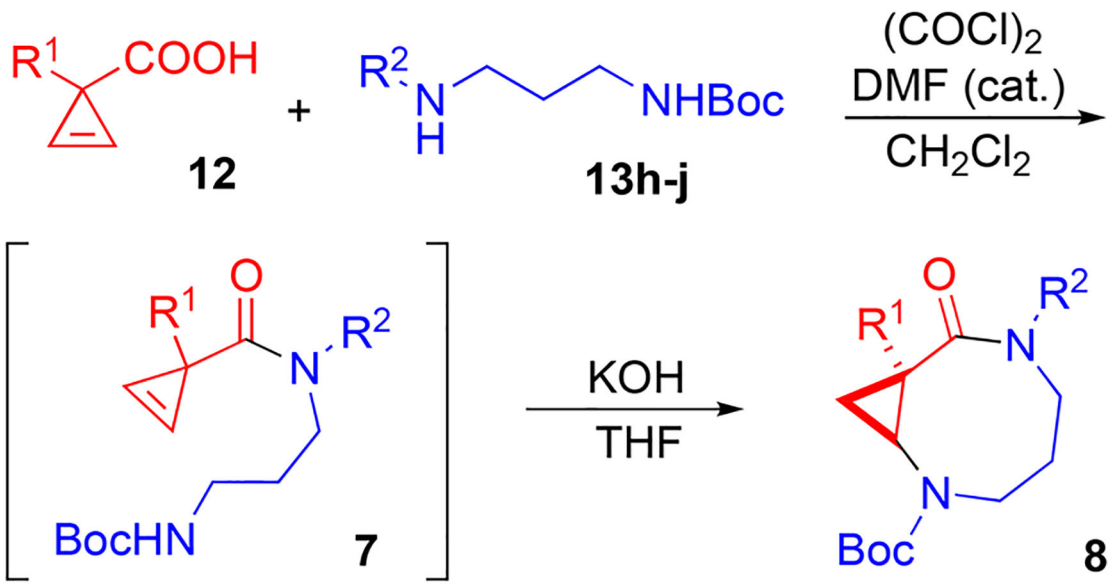
(9) **7ce, 8ce**: R^1 = 4-FC_6H_4, R^2 = Et, 87%;

(10) **7da, 8da**: R^1 = 3-ClC_6H_4, R^2 = $PhCH_2$, 93%;

(11) **7ea, 8ea**: R^1 = 3-BrC_6H_4, R^2 = $PhCH_2$, 91%;
(12) **7ec, 8ec**: R^1 = 3-BrC_6H_4, R^2 = 4-$FC_6H_4CH_2$, 90%;
(13) **7ed, 8ed**: R^1 = 3-BrC_6H_4, R^2 = Me, 90%;
(14) **7ee, 8ee**: R^1 = 3-BrC_6H_4, R^2 = Et, 87%;
(15) **7ef, 8ef**: R^1 = 3-BrC_6H_4, R^2 = *i*-Bu, 94%;

(16) **7fa, 8fa**: R^1 = 2,4-$Cl_2C_6H_3$, R^2 = $PhCH_2$, 85%;
(17) **7fd, 8fd**: R^1 = 2,4-$Cl_2C_6H_3$, R^2 = Me, 87%.

Scheme 3.
7-exo-trig Cyclization of Tethered Carbamates

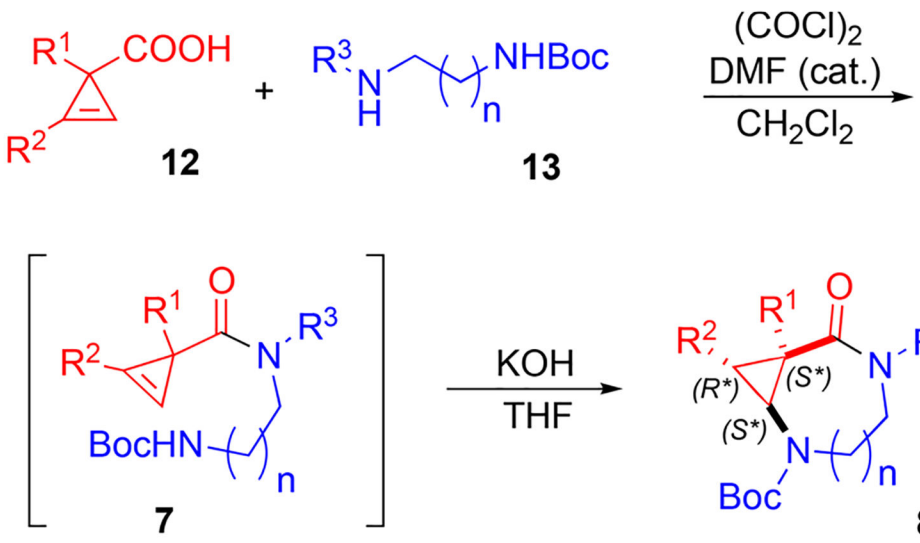


12a: R^1 = Ph;
12e: R^1 = 3-BrC_6H_4;
12f: R^1 = 2,4-$Cl_2C_6H_3$.

13h: R^2 = $PhCH_2$;
13j: R^2 = 4-$FC_6H_4CH_2$.

(18) **7ah, 8ah**: R^1 = Ph, R^2 = $PhCH_2$, 84%;
(19) **7eh, 8eh**: R^1 = 3-BrC_6H_4, R^2 = $PhCH_2$, 83%;
(20) **7ej, 8ej**: R^1 = 3-BrC_6H_4, R^2 = 4-$FC_6H_4CH_2$, 90%;
(21) **7fh, 8fh**: R^1 = 2,4-$Cl_2C_6H_3$, R^2 = $PhCH_2$, 85%.

Scheme 4.
8-exo-trig Cyclization of Tethered Carbamates

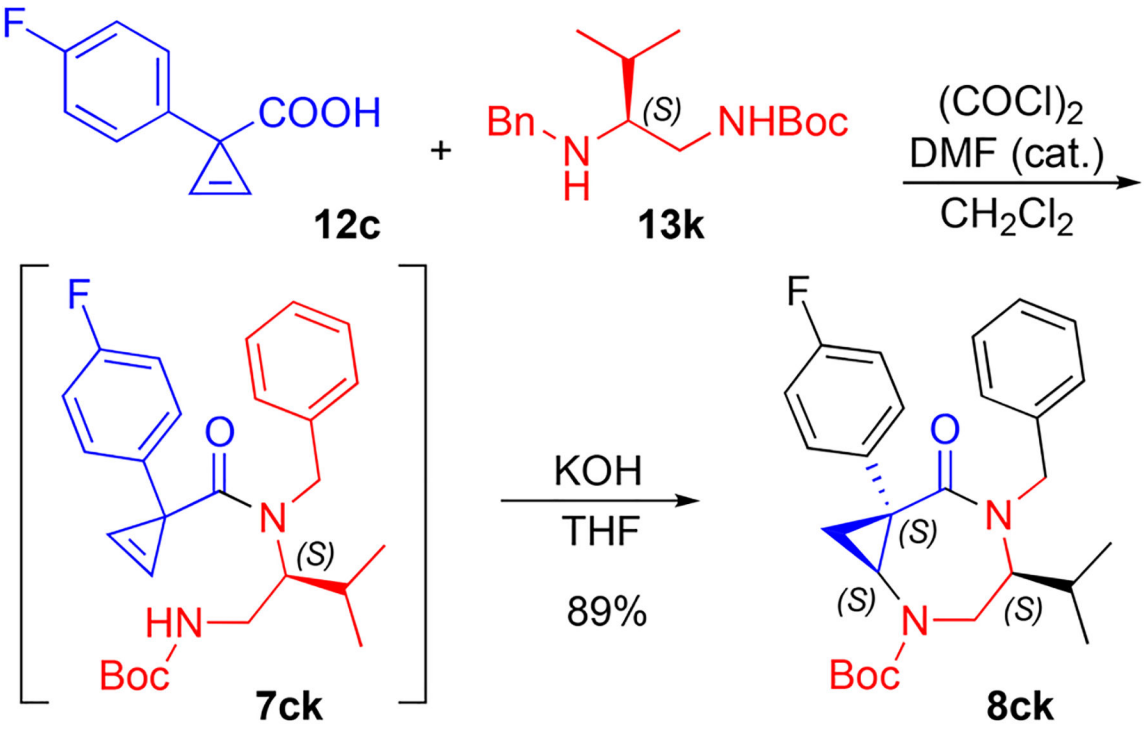


12g: $R^1 = R^2 = Ph$;
12h: $R^1 = Ph$, $R^2 = 2,4\text{-}Cl_2C_6H_3$.

13a: $R^3 = PhCH_2$, n = 1;
13b: $R^3 = 4\text{-}MeOC_6H_4CH_2$; n = 1;
13h: $R^3 = PhCH_2$, n = 2;
13i: $R^3 = 4\text{-}MeOC_6H_4CH_2$; n = 2.

(22) **7ga, 8ga**: $R^1 = R^2 = Ph$, $R^3 = PhCH_2$, n = 1, 91%;
(23) **7gh, 8gh**: $R^1 = R^2 = Ph$, $R^3 = PhCH_2$, n = 2, 88%;
(24) **7ha, 8ha**: $R^1 = 2,4\text{-}Cl_2C_6H_3$, $R^2 = Ph$, $R^3 = PhCH_2$, n = 1, 77%;
(25) **7hb, 8hb**: $R^1 = 2,4\text{-}Cl_2C_6H_3$, $R^2 = Ph$, $R^3 = 4\text{-}MeOC_6H_4CH_2$, n = 1, 81%;
(26) **7hi, 8hi**: $R^1 = 2,4\text{-}Cl_2C_6H_3$, $R^2 = Ph$, $R^3 = 4\text{-}MeOC_6H_4CH_2$, n = 2, 76%.

Scheme 5.
Regio- and Stereoselective Cyclization of Chiral Cyclopropenes with Achiral Tethered Carbamates



Scheme 6.

Stereoselective Cyclization of Prochiral Cyclopropenes with Chiral Enantiomerically Pure Carbamates

Table 1.

Biological Activities of 2,5-Diazabicyclo[5.1.0]octan-6-ones and 2,6-Diazabicyclo[6.1.0]nonan-7-ones[a]

compound	IC50, μM, HeLa	compound	IC50, μM, HeLa
8ac	78.0 ± 1.8	**8ah**	66.2 ± 4.3
8ad	>100	**8eh**	39.0 ± 1.0
8ag	>100	**8ej**	23.7 ± 0.6
8ce	>100	**8fh**	78.1 ± 1.8
8ec	17.4 ± 0.9	**8ga**	>100

[a]Concentration required to reduce the viability of cells by 50% after a 48 h treatment with the indicated compounds relative to a DMSO control ± SD from two independent experiments, each performed in four replicates, as determined by the MTT assay.