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Organocatalytic Synthesis of Benzazetidines by Trapping Hemiaminals with Protecting Groups

Riccardo Salvio,[a][b]* Simone Placidi,[a] Arianna Sinibaldi,[a] Antonio Di Sabato, [a] Dario C. Buscemi,[a] Andrea Rossi, [a]Achille Antenucci,[a]Andrei Malkov,[c] Marco Bella[a]*

[a] Dipartimento di Chimica Sapienza Università di Roma P.le Aldo Moro 5, 00185 Roma, Italy
[b] ISB-CNR Sezione Meccanismi di Reazione, Sapienza Università di Roma, Italy
[c] Department of Chemistry, Loughborough University, UK

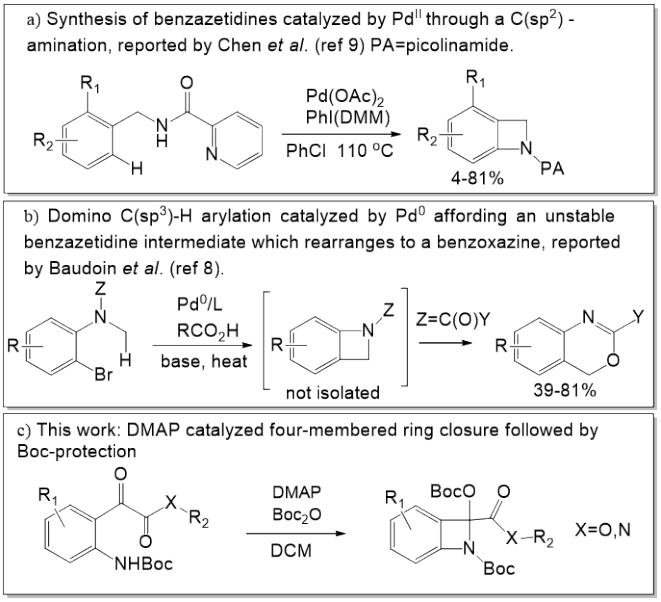
KEYWORDS: *hemiaminals •benzazetidine • ring strain • strained heterocycles*

ABSTRACT: Benzazetidines are highly strained and inherently unstable heterocycles. There are only few methodologies for assembling these compounds. Here, a protocol is presented to trap an elusive cyclic, 4-membered hemiaminal structure. This method affords several benzazetidine in moderate to good yields (up to 81%), it uses inexpensive materials and does not require catalysts based on transition metals. The high ring strain energy of these benzazetidine systems was estimated by DFT calculations to be about 32 kcal mol^{-1}. This synthesis can be applied also on gram scale with reaction yield essentially unchanged.

■INTRODUCTION

Hemiaminals are compounds generated by fast and reversible reaction of a carbonyl with an aromatic or aliphatic amine. They are intermediates in the formation of imines, usually highly unstable, and they have been rarely directly observed.[1-4] In a seminal report by Rebek *et al.*,[2] the trapping of this intermediate was accomplished in the cavity of a resorcinarene for a duration of time long enough (half-life about 30 minutes) to observe this species by NMR spectroscopy before it undergoes dehydration reaction. In another remarkable example, Fujita and coworkers reported the X-ray analysis of a short-lived hemiaminal entrapped within the pores of a porous coordination network.[3]

In the course of our recent research work on the development of new organocatalytic synthetic procedures,[5] we succeeded in reversibly trapping, with the aid of protecting groups, the hemiaminal function affording a benzazetidine scaffold. Benzazetidines are compounds containing a highly strained benzo-fused four-membered azetidine motif.[6-9] These small and strained *N*-heterocycles are potentially promising for applications in drug design and biomedical research.[7,10] However the synthesis of benzazetidine and their reactivity remain largely unexplored because of the scarcity of effective synthetic methodologies towards this class of compounds[6-9,11-13] which stems from their relative instability.[6,8,14] They also attract interest because, in the family of the fused four-membered *N*-heterocycles, the fused *β*-lactams account for the largest share of research efforts and, consequently, there is a lack of diversity among these compounds in the literature.



Scheme 1. Recent literature reports about the synthesis of the benzazetidine rings and comparison with the present work.

In 2016 Chen *et al.* reported the synthesis of benzazetidines by an intramolecular C(sp^2) amination accomplished with the use of Pd^{II} as catalyst (see Scheme 1a).[9] In this procedure, the use of phenyliodonium dimethylmalonate (PhI DMM) is crucial because the oxidation of Pd^{II} palladacycles with this reagent induces a kinetically controlled pathway to give the strained ring-closed compounds.

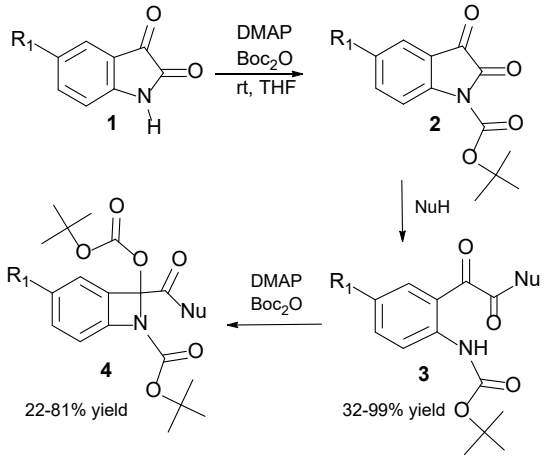
Recently, Baudoin and co-workers considered an alternative approach to benzazetidine from 2-bromo-*N*-methyl-anylides via an intramolecular C-(sp^3)-H arylation (Scheme 1b).[8] They attempted to synthesize this heterocycle by a method similar

to that reported for the synthesis of other strained four-membered rings such as *β*-lactams[15] and benzocyclobutenes.[16,17] However, they were unable to extend this methodology to the synthesis of benzazetidines, mainly because of the instability of this ring system under the high temperature conditions typically required in such reactions.[8] The four-membered heterocycles initially formed turned out to be unstable and underwent a ring expansion leading to 4*H*-3,1-benzoaxazines (Scheme 1b).

RESULTS AND DISCUSSION

In the present report, we disclose a novel approach to the synthesis of benzazetidines containing a diprotected hemiaminal fragment, which involves a base-catalyzed intramolecular nucleophilic cyclization of 2-(*N*-Boc-anilino)-α-ketoesters (amides), followed by the *in situ* protection of the hydroxyl group of thus generated labile cyclic hemiaminal species (Scheme 1c).

In this procedure, we used as starting materials the 1*H*-indole-2,3-dione (isatin, **1**) and its derivatives, which are inexpensive and available on a large-scale from commercial sources (see Scheme 2). Other features of this synthetic route also include the use of operationally simple procedures, mild reaction conditions, the employment of common and inexpensive reagents/catalysts. In contrast to the recently reported methods for the synthesis of benzazetidines, this protocol does not require the use of catalysts based on transition metals.[8,9]



Scheme 2. Synthetic pathway for the synthesis of benzazetidines described in the current work.

Isatins **1** from commercial source (Aldrich, 97-99%) can be turned in the corresponding *N*-Boc-protected derivatives **2** by reaction with di-*tert*-butyl dicarbonate (Boc_2O) in the presence of 4-dimethylaminopyridine (DMAP) with a procedure reported in the literature.[18] Upon this substitution we can obtain an inversion of the reactivity order of the carbonyl groups in the heterocyclic compound: in compound **2** the most reactive carbonyl toward a nucleophilic attack is the one in position 2, at variance with what is commonly observed in unprotected isatins.[19,20] For this reason, the *N*-Boc-protected isatins **2** can undergo the attack of oxygen or nitrogen nucleophiles (NuH), including methyl esters of amino acids, resulting in a ring opening to afford precursor **3**. The last and the most intriguing synthetic step consists in an intramolecular attack of the nitrogen atom onto the carbonyl group with the formation of the highly-strained di-Boc-protected hemiaminal **4**. This step can be classified as 4-exo-trig and it is predicted to be favored according to Baldwin's rules. [21,22]

In Table 1 are reported the conditions and the isolated yields of the ring opening reactions of Boc-protected isatins with different substituens on the aromatic ring with a variety of different nucleophiles to afford compounds **3**. In the table were reported the reaction conditions that resulted in the best isolated yields. The reactions were carried out using the nucleophile as solvent, as in the case of methanol and ethanol, or using the indicated solvent. The reactions with butylamine and amino acids protected as methyl esters, were carried out in a biphasic mixture of DCM: water as indicated in the Table and described in the Experimental Section. The yields are nearly quantitative in the case of entries 1 and 2, and good in a relevant number of cases.

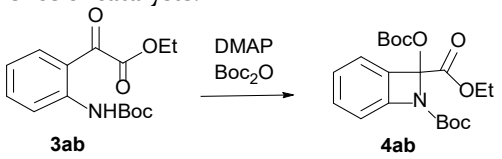
Table 1. Boc-protected isatin (2) ring opening with the listed nucleophiles to afford compounds 3.[a]

Entry[a]	R_1	NuH	Temp [°C]	Solvent	Yield % [b]	Product
1	H	MeOH	rt	MeOH	99	**3aa**
2	H	EtOH	rt	EtOH	99	**3ab**
3 [c]	H	hydroxyacetone	rt	DCM	85	**3ac**
4 [c]	H	Ethyl glycolate	4	DCM	81	**3ad**
5 [c]	H	2-chloroethanol	rt	DCM	78	**3ae**
6 [c]	H	2-iodoethanol	4	DCM	50	**3af**
7 [c]	H	2-propen-1-ol	rt	DCM	77	**3ag**
8 [c]	H	3-buten-2-ol	rt	DCM	32	**3ah**
9	H	butylamine	4	biphasic [d]	80	**3ai**
10	Cl	MeOH	rt	MeOH	58	**3ba**
11	Cl	EtOH	rt	EtOH	81	**3bb**
12 [c]	Cl	3-bromo propanol	rt	DCM	27	**3bj**
13 [c]	Cl	3-buten-2-ol	rt	DCM	59	**3bh**
14 [e]	Br	EtOH	rt	EtOH	45	**3cb**
15 [e]	Me	EtOH	rt	EtOH	57	**3db**
16 [e]	NO_2	EtOH	rt	EtOH	48	**3eb**
17	H	NH2-Glicine-OMe	rt	biphasic [d]	76	**3ak**
18	H	NH2L-phenylalanine-OMe	rt	biphasic [d]	86	**3al**
19	H	NH2-L-valine-OMe	rt	biphasic [d]	68	**3am**

[a] general procedure followed unless differently stated in the notes or in the Supporting Information: 100-200 mg of the Boc-protected isatin was dissolved in 3-5 mL of the indicated solvent thermostated at rt or 4 °C, 0.4 eq Et_3N. In the case NuH is not MeOH either EtOH, 1-3 equivalents of the nucleophile were added in a single addition unless otherwise stated (see note [c]). Reaction time: 1-5 h. See Experimental Section and Supporting Information for further details. [b] isolated yield; [c] the nucleophile addition was carried out in a portionwise manner. [d] the reaction was carried out in a 1:1 mixture of DCM and water (0.4 M of $NaHCO_3$). There was no evidence of the formation of the α-ketocarboxylic acid by nucleophilic attack of the hydroxide ion to compound **2**. [e] the protection of the isatin and the ring opening reaction were carried out by a *one pot* procedure because of the relative lability of the corresponding Boc-protected isatin. [f] the amino acids were employed as methyl esters.

The cyclization reaction of compound **3** to afford the four-membered benzo-fused system **4** is the crucial step of the preparation. This step is carried out in the presence of di-*tert*-butyl dicarbonate to trap the tetrahedral intermediate generated by the nucleophilic attack of the nitrogen onto the carbonyl group.

Table 2. Screening of the reaction conditions for the cyclization of compound 3ab to afford 4ab in presence of catalysts.[a]



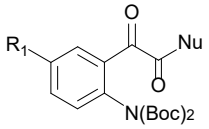
3ab **4ab**

Entry[a]	Cat	Boc_2O amount [eq]	T [°C]	Solvent	Yield % [b]	Time (h)
1	Et_3N	1-5	-20 - rt	[c]	nr [d]	-
2	DMAP	1.2	4	DCM	26	24
3	DMAP	3.1	4	DCM	62	4
4	DMAP	3.1	4	THF	39	15
5	DMAP	3.1	4	$CHCl_3$	<10	24
6	DMAP	5.0	4	DCM	38	24
7	DMAP	3.1	25	DCM	32	4
8	DMAP	3.1	-20	DCM	27	24

[a] The reaction was quenched when the TLC analysis revealed no reagent left or the reaction was not proceeding. The cyclic product 4 is easily detectable on TLC because is markedly fluorescent. Catalyst amount: 0.15 eq. Anhydrous conditions affect the reaction yield to a negligible extent. Further details are reported in the Supporting Information. No yield increase was observed using DMAP in combination with other organic bases such as quinine, triethylamine and DBU. [b] isolated yield [c] THF, DCM, chloroform and toluene were tested as solvents [d] no reaction: no product detected in 2 days.

A systematic screening of the reaction conditions was carried out using ethyl ester **3ab** as a model compound. The cyclization has been tested with a number of commonly used bases in organic preparations and organocatalysis: e.g. triethylamine, DBU, *Cinchona* alkaloids and their derivatives such as quinine (**I**), quinidine (**III**) and thiourea **II**[23] (see Chart in p. S53). None of them led to any detectable amount of product in the investigated solvents (note c to Table 2). On the other hand, 4-dimethylaminopyridine (DMAP) turned out to be an effective catalyst (Table 2, entries 2-8). Since other bases investigated did not promote formation of a relevant amount of cyclic product **4**, this may suggest that the formation of Boc-pyridinium[24] species, as acyl (*tert*-butoxycarbonyl) transfer agent, plays a crucial role in this process (nucleophilic catalysis). Furthermore, the reaction appears to be sensitive, in terms of isolated yields, to the experimental conditions such as temperature, quantity of Boc_2O, and the nature of the solvent. A possible reason of such a variance is a competitive side-reaction that leads to the formation of the *N*,*N*-di-Boc-protected compound **5**, which was isolated from most of the crude reaction mixtures by silica gel chromatography.

A number of tests, employing a Design of Experiment (DoE) approach,[25] were performed to explore the chemical space (see Experimental Section and p. S53 for further details). A representative selection of the experiments is shown in Table 2. The data indicate that the conditions in entry 3 appear to be the optimum for performing the hemiaminal trapping reaction. It was also noted that the use of anhydrous solvents had only a negligible effect on the yields and the reaction times.



5

The reaction scope was explored by employing several α-ketoesters/amides **3** prepared with different combinations of R_1 and NuH. These benzazetidines **4**, shown in Scheme 3, have been synthesized using the optimal conditions as per entry 3, Table 2, i.e. 15% mol DMAP, 3.1 eq Boc_2O and 4 °C in DCM.

The results indicate that the reaction has a reasonably wide scope. The yields are ranging from satisfactory to good; in only few occasions lower yields were observed. Scheme 3 also gives the reaction time in hours. The reactions were stopped upon disappearance of the reagent or whenever the product formation was not proceeding further.

Electron withdrawing substituents in the aromatic ring appear to accelerate the reaction rate, especially in the case of the nitro group. In the preparation of **4eb** from **3eb** the reaction was complete in less than one hour, in contrast with all the other preparative procedure that required longer reaction times. It is likely that the presence of the nitro group facilitates deprotonation of the NH-Boc to allow for an intramolecular attack onto the carbonyl to take place, which results in a shorter reaction time.

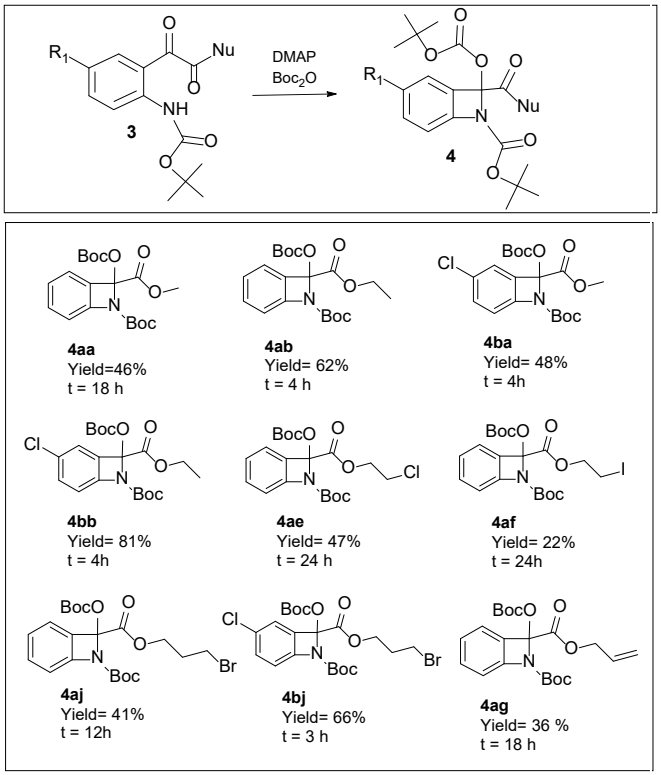
Compounds **4** were characterized by ^{1}H and ^{13}C-NMR and, for **4ab** and **4ac,** also by HMBC and HSQC 2D NMR spectroscopy, that allowed a complete assignment of signals (p. S25-6 and S28 in the SI). In the ^{13}C-NMR spectrum of compound **3ab** two signals at 190.3 ppm and 164.0 ppm are clearly visible. They can be assigned to the carbonyl carbon atoms of the ketone and ester function, respectively (p. S4 in the SI). In the ^{13}C-NMR spectrum of **4ab** only the carbonyl signal of the ester group was detected, at 167.8 ppm; the signal at 96.8 ppm can be justifiably attributed to the hemiaminal carbon atom (p. S24 in SI). The ^{1}H-NMR spectrum is also consistent with the structure **4ab** due to the presence of the signals assignable to the diastereotopic protons of the methylene group (p. S24).

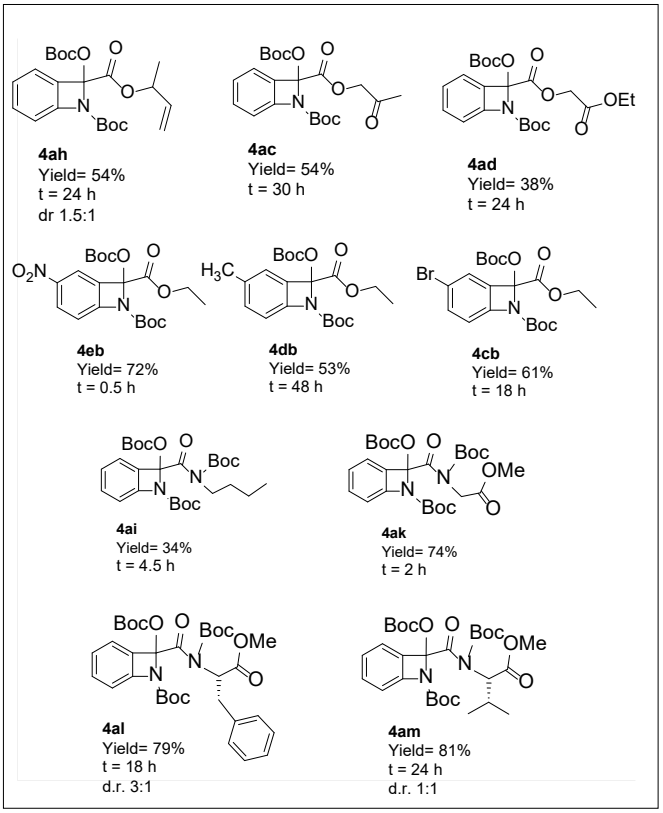
On the basis of spectroscopic evidence (see also IR spectra, p. S52), we can assign the structure of **4ab** and, by analogy, of the rest of compounds **4** synthesized in the present work, as consisting of the benzo-fused four-membered system. Formation of the alternative five-membered cycle, can be excluded, as this mode of cyclization was observed when different protecting groups in the place of the Boc were used (*vide infra*). On the basis of UV-Vis spectra, ^{15}N NMR and GIAO DFT calculations of ^{13}C chemical shifts we could also exclude the assignment of compounds **4** to a 6-membered acetal structure (see SI p. S63-66).

Purification of compounds **4** by chromatography can be critical because a slow degradation of **4** on the stationary phase (silica, neutral or basic alumina) is taking place during chromatography. For this reason, the purification has to be carried out in the shortest possible time. At the same time, compounds **4** are very stable if stored as oils or as solutions in methanol, DCM or ethyl acetate (no degradation was observed in 2 weeks).

As expected from the presence of the Boc units, benzazetidines **4** are sensitive to the presence of acids. The two Boc units are not equivalent since one of them is a carbonate while the another is a carbamate. Their different reactivity can be exploited to selectively remove one of the protective group.

Scheme 3. Scope of the DMAP-catalyzed preparation of benzazetidines 4 from acyclic precursors 3. The reactions were performed employing the optimized conditions (see Table 2, entry 3). The reaction time in hours is reported below.

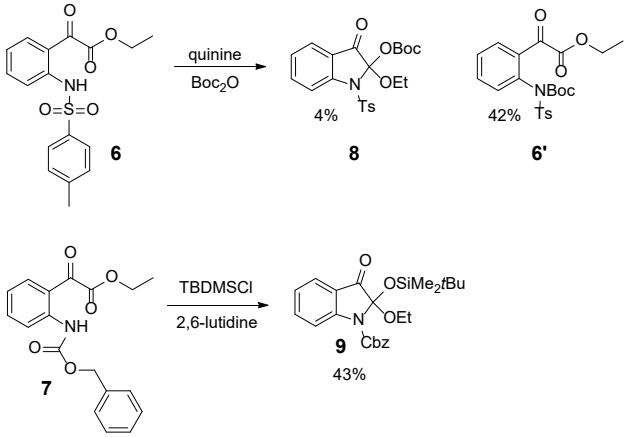




Small amount of $HClO_4$ in DCM (0.1 molar equivalents) rapidly cleave the carbonate converting the protected hemiaminal **4ab** into the corresponding acyclic precursor **3ab**. The other protecting unit can be removed with trifluoroacetic acid in DCM (1.1 eq, 2h) to afford the starting material isatins **1**.

In order to explore the possibility to obtain the benzazetidine scaffold with different protective motifs, precursors **6** and **7** were synthesized by reaction with *p*-toluenesulfonyl chloride and with benzyl chloroformate, respectively. Dicarbonyl compound **6** was treated with different combinations of bases and protective reagents, i.e. Boc_2O, acetic anhydride, acetyl chloride, benzoic anhydride, *t*-butyldimethylsilyl chloride. In none of the attempts any amount of bicyclic product has been detected, except for the case when Boc_2O was used in the presence of quinine (Scheme 4). This reagent/catalyst combination afforded the *N*-Boc protected derivative **6'**, as major product and, surprisingly, small quantities of five-membered cyclic product **8**, which could be isolated from the reaction mixture as a pure compound (4% yield, p. S48).

Chemical behaviour of the Cbz-protected derivative **7** was explored in a number of reactions. The reaction with Boc_2O and DMAP afforded only the *N*-Boc protected derivative with no detectable amount of bicyclic product, whereas the reaction in the presence of *t*-butyldimethylsilyl chloride (TBDMSCl) and 2,6-lutidine as a catalyst resulted in the formation of the five-membered heterocycle **9** in 43% yield (Scheme 4).



Scheme 4. Ring closing reactions of *N*-tosyl and *N*-Cbz protected aniline α-ketoesters.

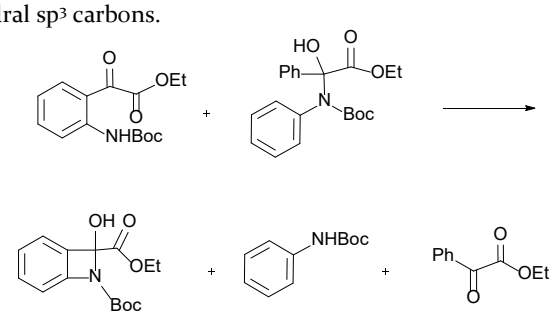
Compounds **8** and **9** were fully characterized by mass spectrometry and conventional and 2D NMR techniques (p. S48-51). The ^{13}C NMR spectra of **8** and **9** clearly indicate the presence of a carbonyl group at 193.2 and 194.1 ppm, respectively, that are consistent with the structures containing the five-membered ring and exclude the formation of the four-membered ring (in contrast, compounds **4** typically showed the signals of an ester in the area of 160-180 ppm).

To illustrate the robustness of our preparative procedure a gram-scale synthesis of compound **4ab** was carried out: starting from 1.80 g (5.18 mmol) of dicarbonyl compound **3ab** under the optimized conditions (Table 2, entry 3), **4ab** was obtained after chromatography in 57% yield.

In order to evaluate the ring strain of **4ab**, we carried out DFT calculation with the Gaussian 09 package[26] at b3lyp/6-31g(d,p)//b3lyp/6-31g(d,p)level of theory, (see Experimental Section and p. S55-60). The calculations consisted in the determination of the differences of energy, corrected for the zero-point vibrational energy, in a homodesmotic reaction[27] based on an intermolecular reaction taken as model (see Scheme 5).

An homodesmotic reaction in a real or hypothetical chemical reaction in which the type of chemical bonds broken in the reactant are the same as the type of bonds formed in the reaction product, taking in consideration also the states of hybridization of the atoms. This type of reaction is often used as a hypothetical in computational thermochemistry to increase the accuracy of the calculations.[27] The reaction in Scheme 5 can be taken as a measurement of the ring strain that is independent on the chemical transformation taking place in the cyclization.

The calculations indicated a strain energy for the four-membered ring of **4ab** as high as 32.7 kcal mol^{-1}. It is meaningful to compare this value with those of other analogous strained systems such as azetidine (23-27 kcal mol^{-1}) [28] and cyclobutane (26,5 kcal mol^{-1}) that are significantly lower than the value obtained in this calculations. This data overcomes even the value of strain energy of cyclopropane (27.5 kcal mol^{-1}),[22] probably because of the presence of two sp^2 carbon atoms in the ring of **4**, which generate a further destabilization of the cyclic species. This destabilization is probably attributable to the higher natural angle of 120° of this carbon atoms compared to tetrahedral sp^3 carbons.



Scheme 5. Homodesmotic reaction used to evaluate the ring strain energy of benzazetidine 4ab.

■CONCLUSIONS

In conclusion, we have developed a new method for trapping and isolating chemical compounds containing the labile hemiaminal functional group. This procedure affords Boc-protected heterocycles featuring a highly strained benzazetidine motif. We believe that the peculiarity of this reaction and the simplicity of the method, which employs cheap and commercially available starting materials /reagents/ catalysts, coupled with the scarcity of existing synthetic methodologies to prepare this type of heterocycles should render this procedure interesting for the scientific community. Furthermore, the presence of a stereocenter in these molecules opens up avenues for developing an asymmetric version of the reaction.

■EXPERIMENTAL SECTION

General informations. All analytical and technical grade solvents were used as received. All commercially available reagents and catalysts were used as received. *N*-Boc isatins **2a**, **2b**[18] and *N*-CBz isatin[18b] were prepared according to literature procedures. ^1H-NMR (400 MHz or 300 MHz) and ^{13}C-NMR {1H} (101 MHz or 75 MHz, $CDCl_3$) spectra were recorded on *Bruker* spectrometers 300 MHz or 400 MHz. The ^{15}N NMR spectrum was recorded with the *Bruker* 400 MHz. Chemical shifts are reported in ppm relative to the resonance of CDCl3 (δ= 7.26) for ^1H NMR and to the central peak of CDCl3 (δ= 77.3) for ^{13}C NMR{1H}. The multiplicity is abbreviated as follows: s (singlet), d (doublet), t (triplet), q (quartet), p (quintet), m (multiplet). The coupling constant J is given in Hz (Hertz). Flash chromatography (FC) was carried out using *Merck* silica gel 60 (230-400 mesh) employing mixtures of hexane/ethyl acetate or dichloromethane as eluants. High resolution mass spectrometry was performed on *Micromass* Q-Tof *micro* instrument.

Computational details. The DFT calculations were carried out using the Gaussian 09 D package.[26] The ring strain has been evaluated by the difference of the energies calculated for the molecules in the homodesmotic[27] reaction in Scheme 5.

The calculations were performed at the b3lyp/6-31g(d,p)//b3lyp/6-31g(d,p) level of theory. The optimization of the structures was carried out in cartesian coordinates. The calcfc option has been used in the optimization procedure, i.e. opt=(cartesian,calcfc). The polarized continuum model was used to take into account the solvent effect. The solvent parameters were set by using the following keyword and options: scrf = (pcm,solvent=dcm). The values were corrected for the zero-point-energy. The GIAO DFT calculations were carried out at b3lyp/6-31g(d,p)//b3lyp/6-311+(d,p) level of theory. The following option was used: scrf=(solvent=chloroform, pcm). The energies and the coordinates of the DFT calculations are reported in the Supporting Informations p. S55 and following.

Design of Experiments. The DoE was performed by applying a screening design to evaluate the main parameters and their influence on the reaction. The variables selected were: 1) equivalents of Boc_2O (continuous variable in the range 1.2-5 equiv); 2) amount of catalyst (a continuous variable in the range 5-25 mol%); 3) temperature (continuous variable in the range -20-25°C). The response we desired to optimize was the yield of compound **4ab**. The use of a screening design allowed the number of experiments to be reduced. To generate a design we used the custom design function in the software MODDE®. The design we generated required 15 experiments, the order of which was randomized (See SI, Table S1).

Procedures for the synthesis of compounds 3

Synthesis of 2-(*N*-Boc-anilino)-α-ketoesters 3aa-3ab, 3ba-3bh. 300 mg of the N-Boc-isatin (1.21 mmol, 1 equiv) were suspended in EtOH (3.5 mL, 60.7 mmol, 50 equiv) or MeOH (2.5 mL, 60.7 mmol, 50 equiv), then 67.5 µL of Et3N (0.486 mmol, 40 mol %) was added. The reaction mixture was stirred at room temperature for 30 min, then the solvent was evaporated at reduced pressure to afford the product as a yellow oil. The product was used without further purification.

*Methyl 2-(2-((Boc)amino)phenyl)-2-oxoacetate (**3aa**).* 334 mg (1.20 mmol), 99 % yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.37 (s, 1H), 8.52 (d, *J* = 8.5 Hz, 1H), 7.70 – 7.49 (m, 2H), 7.07 – 7.02 (m, 1H), 3.97 (s, 3H), 1.53 (s, 9H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 190.2, 164.5, 153.1, 144.1, 137.3, 133.9, 121.7, 119.6, 117.0, 81.6, 53.3, 28.6. HRMS (ESI): calcd for $C_{14}H_{17}NO_5Na$ $[M+Na]^+$ 302.1004; found 302.0992.

*Ethyl 2-(2-((Boc)amino)phenyl)-2-oxoacetate (**3ab**).* 351 mg (1.20 mmol), 99 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.39 (s, 1H), 8.50 (d, *J* = 8.6 Hz, 1H), 7.70 – 7.45 (m, 2H), 7.03 (t, *J* = 7.6 Hz, 1H), 4.43 (q, *J* = 7.1 Hz, 2H), 1.51 (s, 9H), 1.39 (t, *J* = 7.1 Hz, 3H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 190.3, 164.0, 152.9, 143.9, 137.0, 133.7, 121.5, 119.4, 116.9, 81.4, 62.7, 28.5, 14.3. HRMS (ESI): calcd for $C_{15}H_{19}NO_5Na$ $[M+Na]^+$ 316.1161; found 316.1141.

*Methyl 2-(2-((Boc)amino)-5-clhorophenyl)-2-oxoacetate (**3ba**).* 193 mg (0.615 mmol), 58 % yield. FC performed with a mixture of Hexane/Ethyl Acetate as eluant in ratio 20:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.25 (s, 1H), 8.48 (d, J = 9.2 Hz, 1H), 7.59 (d, J = 2.5 Hz, 1H), 7.50 (dd, J = 9.2, 2.5 Hz, 1H), 3.97 (s, 3H), 1.50 (s, 9H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ 188.7, 163.6, 152.6, 142.4, 136.9, 132.6, 126.5, 121.0, 117.8, 81.8, 53.4, 28.4. HRMS (ESI): calcd for $C_{14}H_{16}ClNO_5Na$ $[M+Na]^+$ 336.0615; found 336.0638.

*Ethyl 2-(2-((Boc)amino)-5-chlorophenyl)-2-oxoacetate (**3bb**).* 281 mg (0.859 mmol), 81 % yield. FC performed with Dichloromethane as eluant. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.30 (s, 1H), 8.50 (d, J = 9.2 Hz, 1H), 7.63 (d, J = 2.5 Hz, 1H), 7.57 – 7.48 (m, 1H), 4.45 (q, J = 7.1 Hz, 2H), 1.51 (s, 9H), 1.41 (t, J = 7.1 Hz, 3H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 189.1, 163.3, 152.7, 142.5, 136.9, 132.7, 126.5, 121.1, 117.9, 81.8, 63.1, 28.5, 14.3. HRMS (ESI): calcd for $C_{15}H_{18}ClNO_5Na$ $[M+Na]^+$ 350.0771; found 350.0756.

Synthesis of 2-(*N*-Boc-anilino)-α-ketoesters 3ac-3aj, 3bj. To a solution of N-Boc-isatin (300 mg, 1.21 mmol, 1 equiv) and Et3N (67.5 µL, 0.486 mmol, 40 mol %) in dichloromethane (2 mL) was added the nucleophile (85-125 µL, 1.21 mmol, 1 equiv) in 5 portions of 17-25 µL (0.242 mmol, 0.2 equiv) each, every 30 min. The reaction mixture was stirred at room temperature for 12 more hours, then purified with flash silica chromatography using dichloromethane or mixtures of hexane and ethyl acetate as eluant. The products are obtained as sticky pale yellow oils.

*2-oxopropyl 2-(2-((Boc)amino)phenyl)-2-oxoacetate (**3ac**).* 330 mg (1.03 mmol), 85 % yield. FC performed with a mixture of Hexane/Ethyl Acetate as eluant in gradient from 10:1 to 5:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.35 (s, 1H), 8.52 (d, J = 8.6 Hz, 1H), 8.07 (dd, J = 8.0, 1.4 Hz, 1H), 7.71 – 7.52 (m, 1H), 7.19 – 7.03 (m, 1H), 4.95 (s, 2H), 2.26 (s, 3H), 1.53 (s, 9H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 199.8, 189.5, 163.1, 152.8, 143.9, 137.4, 134.6, 121.8, 119.2, 116.95, 81.4, 69.5, 28.5, 26.1. HRMS (ESI): calcd for $C_{16}H_{19}NO_6Na$ $[M+Na]^+$ 344.1110; found 344.1138.

*2-ethoxy-2-oxoethyl 2-(2-((Boc)amino)phenyl)-2-oxoacetate (**3ad**).* 344 mg (0.980 mmol), 81 % yield. FC performed with a mixture of Hexane/Ethyl Acetate as eluant in ratio 10:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.34 (s, 1H), 8.51 (d, J = 8.6 Hz, 1H), 7.99 (dd, J = 8.0, 1.4 Hz, 1H), 7.64 – 7.51 (m, 1H), 7.16 – 6.94 (m, 1H), 4.86 (s, 2H), 4.29 (q, J = 7.1 Hz, 2H), 1.52 (s, 9H), 1.32 (t, J = 7.2 Hz, 3H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 189.5, 167.1, 163.5, 153.0, 144.1, 137.5, 134.7, 121.9, 119.4, 117.1, 81.6, 62.4, 62.1, 28.7, 14.5. HRMS (ESI): calcd for $C_{14}H_{17}NO_5Na$ $[M-OCH_2COOEt+OCH_3+Na]^+$ 302.1004; found 302.0987

*2-chloroethyl 2-(2-((Boc)amino)phenyl)-2-oxoacetate (**3ae**).* 308 mg (0.944 mmol), 78 % yield. FC performed with Dichloromethane as eluant. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.35 (s, 1H), 8.50 (d, J = 8.4 Hz, 1H), 7.67 (dd, J = 8.0, 1.4 Hz, 1H), 7.65 – 7.56 (m, 1H), 7.09 – 7.01 (m, 1H), 4.67 – 4.60 (m, 2H), 3.83 – 3.77 (m, 2H), 1.51 (s, 9H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ 189.4, 163.4, 152.8, 144.0, 137.3, 133.8, 121.5, 119.3, 116.6, 81.4, 65.6, 41.3, 28.4. HRMS (ESI): calcd for $C_{14}H_{17}NO_5Na$ $[M-O(CH_2)_2Cl+OCH_3+Na]^+$ 302.1004; found 302.0982

*2-iodoethyl 2-(2-((Boc)amino)phenyl)-2-oxoacetate (**3af**).* 253 mg (0.605 mmol), 50 % yield. FC performed with a mixture of Hexane/Ethyl Acetate as eluant in ratio 10:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.33 (s, 1H), 8.50 (d, J = 8.6 Hz, 1H), 7.67 (dd, J = 8.0, 1.3 Hz, 1H), 7.63 – 7.55 (m, 1H), 7.08 – 7.00 (m, 1H), 4.62 (t, J = 6.8 Hz, 2H), 3.39 (t, J = 6.8 Hz, 2H), 1.51 (s, 9H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 189.3, 163.1, 152.7, 143.9, 137.2, 133.9, 121.5, 119.3, 116.6, 81.4, 66.3, 28.4, -1.1. HRMS (ESI): calcd for $C_{14}H_{17}NO_5Na$ $[M-O(CH_2)_2I+OCH_3+Na]^+$ 302.1004; found 302.0979.

*Allyl 2-(2-((Boc)amino)phenyl)-2-oxoacetate (**3ag**).* 284 mg (0.932 mmol), 77 % yield. FC performed with Dichloromethane as eluant. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.39 (s, 1H), 8.52 (d, J = 8.3 Hz, 1H), 7.73 – 7.46 (m, 2H), 7.16 – 6.87 (m, 1H), 6.00 (ddt, J = 16.3, 10.4, 5.9 Hz, 1H), 5.45 (ddd, J = 17.2, 2.6, 1.3 Hz, 1H), 5.35 (dd, J = 10.4, 1.1 Hz, 1H), 4.87 (dt, J = 5.9, 1.2 Hz, 2H), 1.52 (s, 9H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 190.0, 163.7, 153.0, 144.0, 137.2, 133.8, 130.9, 121.6, 120.5, 119.5, 116.9, 81.5, 67.0,

28.5. HRMS (ESI): calcd for $C_{14}H_{17}NO_5Na$ [M-$OCH_2CH=CH_2$+OCH_3+Na]$^+$ 302.1004; found 302.1009.

*But-3-en-2-yl 2-(2-((Boc)amino)phenyl)-2-oxoacetate (**3ah**).* 137 mg (0.387 mmol), 32 % yield. FC performed with a mixture of Hexane/Ethyl Acetate as eluant in gradient from 20:1 to 10:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.42 (s, 1H), 8.52 (d, *J* = 8.5 Hz, 1H), 7.64 – 7.57 (m, 2H), 7.13 – 6.97 (m, 1H), 5.92 (ddd, *J* = 17.0, 10.5, 6.3 Hz, 1H), 5.63 (p, *J* = 6.5 Hz, 1H), 5.39 (d, *J* = 17.2 Hz, 1H), 5.26 (d, *J* = 10.5 Hz, 1H), 1.52 (s, 9H), 1.47 (d, *J* = 6.5 Hz, 3H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ 190.7, 163.7, 153.3, 144.4, 137.5, 136.9, 134.1, 121.9, 119.8, 118.4, 117.3, 81.8, 74.5, 28.9, 20.6. HRMS (ESI): calcd for $C_{17}H_{21}NO_5Na$ [M+Na]$^+$ 342.1317; found 342.1303.

*3-bromopropyl 2-(2-((Boc)amino)phenyl)-2-oxoacetate (**3aj**).* 182 mg (0.472 mmol), 39 % yield. FC performed with a mixture of Hexane/Ethyl Acetate as eluant in ratio 60:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.37 (s, 1H), 8.53 (d, J = 8.5 Hz, 1H), 7.70 – 7.50 (m, 2H), 7.13 – 7.01 (m, 1H), 4.54 (t, J = 6.0 Hz, 2H), 3.49 (t, J = 6.4 Hz, 2H), 2.30 (q, J = 6.2 Hz, 2H), 1.53 (s, 9H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 189.9, 163.8, 152.9, 144.0, 137.3, 133.8, 121.6, 119.5, 116.8, 81.5, 64.1, 31.5, 29.1, 28.5. HRMS (ESI): calcd for $C_{16}H_{20}NO_5NaBr$ [M+Na]$^+$ 408.0423; found 408.0437.

*3-bromopropyl 2-(2-((Boc)amino)-5-chlorophenyl)-2-oxoacetate (**3bj**).* 120 mg (0.286 mmol), 27 % yield. FC performed with a mixture of Hexane/Ethyl Acetate as eluant in gradient from 60:1 to 40:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.27 (s, 1H), 8.51 (d, J = 9.2 Hz, 1H), 7.63 (d, J = 2.4 Hz, 1H), 7.53 (dd, J = 9.2, 2.4 Hz, 1H), 4.55 (t, J = 6.0 Hz, 2H), 3.50 (t, J = 6.3 Hz, 2H), 2.31 (p, J = 6.2 Hz, 2H), 1.51 (s, 9H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 188.6, 163.0, 152.7, 142.5, 137.0, 132.6, 126.6, 121.1, 117.8, 81.9, 64.4, 31.4, 28.9, 28.5. HRMS (ESI): calcd for $C_{15}H_{20}ClNO_6Na$ [M-$O(CH_2)_3Br$+$(OCH_3)_2$+H+Na]$^+$ 368.0877; found 368.0858.

*But-3-en-2-yl 2-(2-((Boc)amino)-5-chlorophenyl)-2-oxoacetate **(3bh).*** 113 mg (0.319 mmol), 59 % yield. FC performed with a mixture of Hexane/Ethyl Acetate as eluent in gradient from 40:1 to 10:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.33 (s, 1H), 8.51 (d, *J* = 9.2 Hz, 1H), 7.63 (d, *J* = 2.4 Hz, 1H), 7.53 (dd, *J* = 9.2, 2.5 Hz, 1H), 5.93 (ddd, *J* = 17.0, 10.5, 6.4 Hz, 1H), 5.64 (p, *J* = 6.5 Hz, 1H), 5.35 (dd, *J* = 35.8, 13.8 Hz, 2H), 1.52 (s, 9H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ 189.0, 162.6, 152.7, 142.5, 136.8, 136.3, 132.7, 126.4, 121.0, 118.3, 117.9, 81.7, 74.4, 28.4, 20.1. HRMS (ESI): calcd for $C_{15}H_{20}NO_6NaCl$ [M-$OCH(CH_3)CH=CH_2$+$(OCH_3)_2$+H+Na]$^+$ 368.0877; found 368.0855.

Synthesis of 2-(*N*-Boc-anilino)-α-ketoesters 3cb-3eb. 200 mg of 5-substituted isatin (1.24 mmol, 1 equiv) and 61 mg DMAP (0.497 mmol, 40 mol %) were suspended in 20 mL of THF at 0 °C (ice bath), then 325 mg of Boc2O (1.49 mmol, 1.2 equiv) was added. The reaction was stirred at 0°C for 30 min and then at room temperature until the disappear of the isatin on TLC plate (eluant hexane/ethyl acetate 2:1). After that, 3.6 mL of EtOH (62.1 mmol, 50 equiv) and 69.1 µL of Et3N (0.497 mmol, 40 mol %) were added and the mixture was stirred at room temperature for 30 min. Solvents were evaporated at reduced pressure and the crude was purified with flash silica chromatography using as eluant a mixture of hexane/ethyl acetate (30:1) to afford the products as yellow oils.

*Ethyl 2-(2-((Boc)amino)-5-bromophenyl)-2-oxoacetate (**3cb**).* 158 mg (0.420 mmol), 45 % yield. FC performed with a mixture of Hexane/Ethyl Acetate as eluant in gradient from 80:1 to 50:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.32 (s, 1H), 8.46 (d, J = 9.2 Hz, 1H), 7.78 (d, J = 2.3 Hz, 1H), 7.67 (dd, J = 9.2, 2.3 Hz, 1H), 4.46 (q, J = 7.2 Hz, 2H), 1.52 (s, 9H), 1.43 (t, J = 7.2 Hz, 3H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 189.1, 163.3, 152.7, 143.0, 139.7, 135.7, 121.3, 118.4, 113.6, 81.9, 63.1, 28.5, 14.4. HRMS (ESI): calcd for $C_{15}H_{20}BrNO_6Na$ [M-OCH_2CH_3+$(OCH_3)_2$+H+Na]$^+$ 412.0372; found 412.0346.

*Ethyl 2-(2-((Boc)amino)-5-methylphenyl)-2-oxoacetate (**3db**).* 217 mg (0.707 mmol), 57 % yield. FC performed with a mixture of Hexane/Ethyl Acetate as eluant in ratio 10:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.29 (s, 1H), 8.40 (d, J = 8.9 Hz, 1H), 7.42 - 7.40 (m, 2H), 4.46 (q, J = 7.1 Hz, 2H), 2.32 (s, 3H), 1.52 (s, 9H), 1.42 (t, J = 7.1 Hz, 3H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 190.4, 164.2, 153.1, 141.7, 138.1, 133.6, 131.0, 119.5, 116.9, 81.3, 62.7, 28.6, 20.8, 14.4. HRMS (ESI): calcd for $C_{16}H_{21}NO_5Na$ [M+Na]$^+$ 330.1317; found 330.1329.

*Ethyl 2-(2-((Boc)amino)-5-nitrophenyl)-2-oxoacetate (**3eb**).* 169 mg (0.499 mmol), 48 % yield. FC performed with a mixture of Hexane/Ethyl Acetate as eluant in ratio 10:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.71 (s, 1H), 8.75 (d, J = 9.5 Hz, 1H), 8.67 (d, J = 2.6 Hz, 1H), 8.42 (dd, J = 9.5, 2.6 Hz, 1H), 4.52 (q, J = 7.1 Hz, 2H), 1.55 (s, 9H), 1.46 (t, J = 7.1 Hz, 3H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ 188.9, 162.7, 152.2, 148.9, 141.0, 131.3, 129.7, 119.7, 116.1, 83.1, 63.6, 28.4, 14.4. HRMS (ESI): calcd for $C_{15}H_{20}N_2O_8Na$ [M-OCH_2CH_3+$(OCH_3)_2$+H+Na]$^+$ 379.1117; found 379.1096.

Synthesis of 2-(*N*-Boc-anilino)-α-ketoamides 3ai-3am. To a stirred solution of the N-Boc isatin (300 mg, 1.21 mmol, 1 equiv) in 10 mL dichloromethane was added a mixture of the amino acid (372/639 mg, 2.96 mmol, 2.45 equiv) and saturated sodium hydrogen carbonate solution (3 mL) in 7 mL water at 5°C. The reaction mixture was warmed to room temperature and stirred for 24 h. The organic layer was diluted with 20 mL of dichloromethane and extracted with 15 mL of aqueous hydrochloric acid 0.5 M and 20 mL water. The organic extract was dried over anhydrous Na2SO4, filtered and concentrated under vacuum. The crude product was purified by gravity column chromatography over silica with dichloromethane to give the product as a yellow oil.

*Boc (2-(2-(butylamino)-2-oxoacetyl)phenyl)carbamate (**3ai**).* 310 mg (0.968 mmol), 80 % yield. FC performed with Dichloromethane as eluant. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.27 (s, 1H), 8.40 (d, *J* = 8.6 Hz, 1H), 8.33 (d, *J* = 8.1 Hz, 1H), 7.53 (t, *J* = 7.9 Hz, 1H), 7.01 (t, *J* = 7.7 Hz, 1H), 3.37 (dd, *J* = 13.3, 6.8 Hz, 2H), 1.58 (m, 2H), 1.51 (s, 9H), 1.38 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ 192.4, 163.7, 153.4, 143.9, 137.0, 135.1, 121.8, 119.7, 118.8, 81.6, 40.0, 32.0, 28.9, 20.7, 14.4. HRMS (ESI): calcd for $C_{17}H_{24}N_2O_4Na$ [M+Na]$^+$ 343.1634; found 343.1652.

*Methyl (2-(2-((Boc)amino)phenyl)-2-oxoacetyl)glycinate (**3ak**).* 310 mg (0.921 mmol), 76 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.20 (s, 1H), 8.31 (d, J = 8.6 Hz, 1H), 8.12 (d, J = 8.1 Hz, 1H), 7.66 (t, J = 5.6 Hz, 1H), 7.45 (t, J = 8.0 Hz, 1H), 6.92 (t, J = 7.7 Hz, 1H), 4.05 (d, J = 5.7 Hz, 2H), 3.66 (s, 3H), 1.44 (s, 9H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 191.2, 169.6, 163.9, 152.7, 143.2, 136.5, 134.4, 121.3, 119.0, 117.8, 81.1, 52.5, 41.1, 28.3. HRMS (ESI): calcd for $C_{16}H_{20}N_2O_6K$ [M+K]$^+$ 375.0958; found 375.0979.

*Methyl (2-(2-((Boc)amino)phenyl)-2-oxoacetyl)-L-phenylalalinate (**3al**).* 445 mg (1.05 mmol), 86 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.28 (s, 1H), 8.41 (d, J = 8.6 Hz, 1H), 8.03 (d, J = 8.1 Hz, 1H), 7.51 (t, J = 7.9 Hz, 1H), 7.38 – 7.23 (m, 4H), 7.16 (d, J = 6.9 Hz, 2H), 6.94 (t, J = 7.7 Hz, 1H), 5.05 – 4.88 (m, 1H), 3.73 (s, 3H), 3.25 (dd, J = 14.0, 5.4 Hz, 1H), 3.11 (dd, J = 13.9, 7.1 Hz, 1H), 1.52 (s, 9H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 191.2, 171.4, 163.2,

153.0, 143.6, 136.8, 135.8, 134.7, 129.6, 129.1, 127.6, 121.4, 119.3, 118.0, 81.3, 53.6, 52.9, 38.2, 28.6. HRMS (ESI): calcd for $C_{23}H_{26}N_2O_6Na$ $[M+Na]^+$ 449.1689; found 449.1699.

*Methyl (2-(2-((Boc)amino)phenyl)-2-oxoacetyl)-L-valinate (**3am**).* 310 mg (0.820 mmol), 68 % yield. ^1H NMR (400 MHz, $CDCl_3$) δ 10.65 (s, 1H), 8.72 (d, *J* = 8.6 Hz, 1H), 8.54 (d, *J* = 8.1 Hz, 1H), 7.84 (t, *J* = 7.9 Hz, 1H), 7.74 (d, *J* = 8.9 Hz, 1H), 7.29 (t, *J* = 7.6 Hz, 1H), 4.93 (dd, *J* = 8.9, 4.9 Hz, 1H), 4.08 (s, 3H), 2.78 – 2.35 (m, 1H), 1.84 (s, 9H), 1.30 (dd, *J* = 16.6, 6.8 Hz, 6H). $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 190.8, 171.3, 163.0, 152.5, 143.1, 136.3, 134.2, 121.0, 118.8, 117.6, 80.8, 57.2, 52.2, 31.2, 28.1, 18.9, 17.6. HRMS (ESI): calcd for $C_{19}H_{26}N_2O_6Na$ $[M+Na]^+$ 401.1689; found 401.1674.

Synthesis of benzoazetidines 4aa-5db. 100 mg of 3 (0.34 mmol, 1 equiv) were dissolved in 1.2 mL of dichloromethane. The solution was cooled down to 4 °C. After 10 minutes 230 mg of Boc_2O (1.06 mmol, 3.1 equiv) were added and the solution was stirred for 30 minutes at the same temperature. After that time 6 mg of DMAP (0.051 mmol, 15 mol %) were added and the mixture was stirred for 1-48 h. The crude was purified with flash silica chromatography using as eluant a mixture of hexane/ethyl acetate (30:1 to 5:1).

*7-(tert-butyl) 8-methyl 8-((tert-butoxycarbonyl)oxy)-7-azabicyclo[4.2.0]octa-1,3,5-triene-7,8-dicarboxylate (**4aa**).* Performed on 84 mg of **3aa**. 52 mg (0.137 mmol), 46 % yield. FC performed with a mixture of Petroleum Ether/Ethyl Acetate as eluant in gradient from 20:1 to 5:1. ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8.1 Hz, 1H), 7.42 (ddd, J = 9.4, 5.8, 1.9 Hz, 2H), 7.19 (td, J = 7.6, 0.9 Hz, 1H), 3.69 (s, 3H), 1.64 (s, 9H), 1.34 (s, 9H). $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 167.1, 149.9, 148.8, 140.0, 131.4, 124.7, 124.2, 123.2, 115.6, 96.3, 84.7, 84.1, 52.4, 28.1, 27.4. HRMS (ESI): calcd for $C_{19}H_{25}NO_7Na$ $[M+Na]^+$ 402.1529; found 402.1528.

*7-(tert-butyl) 8-ethyl 8-((tert-butoxycarbonyl)oxy)-7-azabicyclo[4.2.0]octa-1,3,5-triene-7,8-dicarboxylate (**4ab**).* Performed on 77 mg of **3ab**. 63 mg (0.160 mmol), 61 % yield. FC performed with a mixture of Hexane/Ethyl Acetate as eluant in gradient from 40:1 to 5:1. ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8.2 Hz, 1H), 7.46 – 7.36 (m, 2H), 7.19 (td, J = 7.6, 0.9 Hz, 1H), 4.14 – 4.00 (m, 2H), 1.64 (s, 9H), 1.33 (s, 9H), 1.21 (t, J = 7.1 Hz, 3H). $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 167.8, 150.3, 149.2, 140.3, 131.6, 125.0, 124.9, 123.6, 115.9, 96.8, 85.0, 84.4, 61.0, 28.4, 27.8, 15.5. HRMS (ESI): calcd for $C_{20}H_{27}NO_7Na$ $[M+Na]^+$ 416.1685; found 416.1666.

*7-(tert-butyl) 8-(2-oxopropyl) 8-((tert-butoxycarbonyl)oxy)-7-azabicyclo[4.2.0]octa-1,3,5-triene-7,8-dicarboxylate (**4ac**).* Performed on 100 mg of **3ac**. 71 mg (0.168 mmol), 54 % yield. FC performed with a mixture of Hexane/Diethyl Ether as eluant in gradient from 20:1 to 1:1. ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8.2 Hz, 1H), 7.50 – 7.40 (m, 2H), 7.21 (td, J = 7.6, 0.8 Hz, 1H), 4.74 (d, J = 17.1 Hz, 1H), 4.59 (d, J = 17.1 Hz, 1H), 2.16 (s, 3H), 1.63 (s, 9H), 1.34 (s, 9H). $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 204.6, 167.9, 150.0, 149.1, 140.6, 132.2, 125.5, 124.3, 123.8, 116.1, 96.0, 85.4, 85.1, 69.7, 28.5, 27.9, 26.9. HRMS (ESI): calcd for $C_{21}H_{27}NO_8Na$ $[M+Na]^+$ 444.1634; found 444.1625.

*7-(tert-butyl) 8-(2-ethoxy-2-oxoethyl) 8-((tert-butoxycarbonyl)oxy)-7-azabicyclo[4.2.0]octa-1,3,5-triene-7,8-dicarboxylate (**4ad**).* Performed on 59 mg of **3ad**. 29 mg (0.0643 mmol), 38 % yield. FC performed with a mixture of Petroleum Ether/Ethyl Acetate as eluant in gradient from 20:1 to 1:1. ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8.2 Hz, 1H), 7.52 – 7.46 (m, 1H), 7.45 – 7.39 (m, 1H), 7.22 – 7.18 (m, 1H), 4.82 (d, J = 16.3 Hz, 1H), 4.55 (d, J = 16.3 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 1.63 (s, 9H), 1.34 (s, 9H), 1.24 (d, J = 7.2 Hz, 3H). $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 169.1, 167.6, 149.9, 149.0, 140.5, 132.0, 125.3, 124.2, 123.7, 115.9, 95.8, 85.0, 84.8, 62.2, 61.4, 28.4, 27.8, 14.4. HRMS (ESI): calcd for $C_{22}H_{29}NO_9Na$ $[M+Na]^+$ 474.1740; found 474.1719.

*7-(tert-butyl) 8-(2-chloroethyl) 8-((tert-butoxycarbonyl)oxy)-7-azabicyclo[4.2.0]octa-1,3,5-triene-7,8-dicarboxylate (**4ae**).* Performed on 100 mg of **3ae**. 61 mg (0.143 mmol), 47 % yield. FC performed with a mixture of Petroleum Ether/Diethyl Ether as eluant in gradient from 30:1 to 25:1. ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8.2 Hz, 1H), 7.46-7.40 (m, 2H), 7.20 (td, J = 7.6, 0.9 Hz, 1H), 4.31 (td, J = 6.1, 1.5 Hz, 2H), 3.63 (td, J = 6.2, 0.8 Hz, 2H), 1.64 (s, 9H), 1.34 (s, 9H). $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 167.3, 149.6, 148.7, 140.0, 131.6, 124.9, 124.1, 123.3, 115.6, 96.0, 84.8, 84.4, 64.5, 42.3, 28.1, 27.4. HRMS (ESI): calcd for $C_{20}H_{26}NO_7NaCl$ $[M+Na]^+$ 450.1295; found 450.1286.

*7-(tert-butyl) 8-(2-iodoethyl) 8-((tert-butoxycarbonyl)oxy)-7-azabicyclo[4.2.0]octa-1,3,5-triene-7,8-dicarboxylate (**4af**).* Performed on 18 mg of **3af**. 5 mg (0.00945 mmol), 22 % yield. FC performed with a mixture of Hexane/Diethyl Ether as eluant in gradient from 20:1 to 10:1. ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8.1 Hz, 1H), 7.50 – 7.38 (m, 2H), 7.21 (t, J = 7.1 Hz, 1H), 4.30 (td, J = 7.1, 1.2 Hz, 2H), 3.24 (t, J = 7.2 Hz, 2H), 1.64 (s, 9H), 1.34 (s, 9H). $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 167.7, 150.0, 149.1, 140.3, 131.9, 125.2, 125.1, 123.6, 115.9, 96.2, 85.2, 84.8, 65.5, 28.4, 27.8, 1.8. HRMS (ESI): calcd for $C_{20}H_{26}NO_7KI$ $[M+K]^+$ 558.0391; found 558.0364.

*8-allyl 7-(tert-butyl) 8-((tert-butoxycarbonyl)oxy)-7-azabicyclo[4.2.0]octa-1,3,5-triene-7,8-dicarboxylate (**4ag**).* Performed on 100 mg of **3ag**. 47 mg (0.112 mmol), 36 % yield. FC performed with a mixture of Petroleum Ether/Ethyl Acetate as eluant in gradient from 20:1 to 8:1. ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.2 Hz, 1H), 7.45 (d, J = 7.4 Hz, 1H), 7.41 (dd, J = 11.3, 4.5 Hz, 1H), 5.90 (ddt, J = 22.8, 10.9, 5.7 Hz, 1H), 5.28 (dd, J = 17.2, 1.2 Hz, 1H), 5.16 (d, J = 10.4 Hz, 1H), 4.71 – 4.46 (m, 2H), 1.64 (s, 9H), 1.34 (s, 9H). $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 167.7, 150.2, 149.2, 140.3, 133.6, 131.7, 125.1, 124.8, 123.6, 118.1, 115.9, 96.5, 85.0, 84.5, 66.1, 28.4, 27.8. HRMS (ESI): calcd for $C_{21}H_{27}NO_7Na$ $[M+Na]^+$ 428.1685; found 428.1665.

*8-(but-3-en-2-yl) 7-(tert-butyl) 8-((tert-butoxycarbonyl)oxy)-7-azabicyclo[4.2.0]octa-1,3,5-triene-7,8-dicarboxylate (**4ah**).* Performed on 64 mg of **3ah**. 46 mg (0.110 mmol), 54 % yield. FC performed with a mixture of Petroleum Ether/Ethyl Acetate as eluant in gradient from 20:1 to 7:1. ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, J = 8.1, 2.7 Hz, 1H), 7.49 – 7.35 (m, 2H), 7.18 (td, J = 7.6, 0.9 Hz, 1H), 5.94 – 5.76 (m, 1H), 5.24 – 4.95 (m, 3H), 1.64 (s, 9H), 1.33 (s, 9H), 1.26 (d, J = 6.4 Hz, 3H). $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 168.5, 150.3, 149.2, 140.3, 139.6, 131.6, 125.1, 123.7, 123.3, 115.8, 114.9, 96.6, 84.9, 84.2, 72.5, 28.4, 27.8, 21.7. HRMS (ESI): calcd for $C_{22}H_{29}NO_7Na$ $[M+Na]^+$ 442.1842; found 442.1824.

*Tert-butyl 8-((tert-butoxycarbonyl)(butyl)carbamoyl)-8-((tert-butoxycarbonyl)oxy)-7-azabicyclo[4.2.0]octa-1,3,5-triene-7,8-dicarboxylate (**4ai**).* Performed on 118 mg of **3ai**. 53 mg (0.124 mmol), 34 % yield. FC performed with a mixture of Hexane/Ethyl Acetate as eluant in gradient from 40:1 to 15:1. ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 8.2 Hz, 1H), 7.68 (d, J = 7.4 Hz, 1H), 7.55 (m, 1H), 7.12 (t, J = 7.5 Hz, 1H), 3.68 – 3.62 (m, 2H), 1.69 (m, 2H), 1.59 (s, 9H), 1.45 – 1.35 (m, 2H), 1.32 (s, 9H), 1.09 (s, 9H), 0.97 (t, J = 7.3 Hz, 3H). $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$) δ 151.4, 150.5, 148.7, 136.4, 123.4, 123.4, 123.2, 116.0, 93.1,

84.4, 83.4, 82.3, 77.5, 45.9, 32.3, 28.7, 28.0, 27.7, 20.3, 14.2.HRMS (ESI): calcd for $C_{27}H_{40}N_2O_8Na$ $[M+Na]^+$ 543.2682; found 543.2689.

*8-(3-bromopropyl) 7-(tert-butyl) 8-((tert-butoxycarbonyl)oxy)-7-azabicicyclo[4.2.0]octa-1,3,5-triene-7,8-dicarboxylate (**4aj**).* Performed on 60 mg of **3aj**. 31 mg (0.0638 mmol), 41 % yield. FC performed with a mixture of Petroleum Ether/Ethyl Acetate as eluant in gradient from 20:1 to 10:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 8.1 Hz, 1H), 7.44-7.43 (m, 2H), 7.20 (t, J = 7.5 Hz, 1H), 4.13 (td, J = 5.9, 1.3 Hz, 2H), 3.44 (t, J = 6.8 Hz, 2H), 2.18 – 2.10 (m, 2H), 1.63 (d, J = 6.4 Hz, 9H), 1.34 (s, 9H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 167.7, 150.1, 149.1, 140.3, 131.8, 125.1, 124.6, 123.6, 115.9, 96.6, 85.1, 84.5, 62.9, 33.2, 30.0, 28.4, 27.8. HRMS (ESI): calcd for $C_{21}H_{28}NO_7NaBr$ $[M+Na]^+$ 508.0947; found 508.0934.

*7-(tert-butyl) 8-methyl 8-((tert-butoxycarbonyl)oxy)-3-chloro-7-azabicicyclo[4.2.0]octa-1,3,5-triene-7,8-dicarboxylate (**4ba**).* Performed on 156 mg of **3ba**. 97 mg (0.255 mmol), 48 % yield. FC performed with a mixture of Hexane/Ethyl Acetate as eluant in ratio 20:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.80 (m, 1H), 7.47 – 7.30 (m, 2H), 3.69 (s, 3H), 1.63 (s, 9H), 1.37 (s, 9H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 166.8, 150.3, 149.0, 138.8, 131.6, 130.6, 126.3, 123.8, 117.3, 96.1, 85.4, 84.8, 52.8, 28.4, 27.8. HRMS (ESI): calcd for $C_{19}H_{24}NO_7NaCl$ $[M+Na]^+$ 436.1139; found 436.1122.

*7-(tert-butyl) 8-ethyl 8-((tert-butoxycarbonyl)oxy)-3-chloro-7-azabicicyclo[4.2.0]octa-1,3,5-triene-7,8-dicarboxylate (**4bb**).* Performed on 108 mg of 3bb. 114 mg (0.267 mmol), 81 % yield. FC performed with a mixture of Petroleum Ether/Ethyl Acetate as eluant in gradient from 60:1 to 20:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.7 Hz, 1H), 7.48 – 7.30 (m, 2H), 4.16 – 3.96 (m, 2H), 1.63 (s, 9H), 1.36 (s, 9H), 1.22 (t, *J* = 7.0 Hz, 3H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ 167.1, 150.3, 149.0, 138.7, 131.5, 130.6, 126.7, 123.8, 117.3, 96.2, 85.3, 84.7, 61.2, 28.4, 27.8, 15.4. HRMS (ESI): calcd for $C_{20}H_{26}NO_7NaCl$ $[M+Na]^+$ 450.1295; found 450.1289.

*8-(3-bromopropyl) 7-(tert-butyl) 8-((tert-butoxycarbonyl)oxy)-3-chloro-7-azabicicyclo[4.2.0]octa-1,3,5-triene-7,8-dicarboxylate (**4bj**).* Performed on 77 mg of 3bj. 63 mg (0.121 mmol), 66 % yield. FC performed with a mixture of Petroleum Ether/Ethyl Acetate as eluant in gradient from 60:1 to 20:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.6 Hz, 1H), 7.41-7.37 (m, 2H), 4.14 (t, *J* = 6.0 Hz, 2H), 3.45 (t, *J* = 6.7 Hz, 2H), 2.14 (p, *J* = 6.3 Hz, 2H), 1.63 (s, 9H), 1.37 (s, 9H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 166.7, 149.9, 148.6, 138.4, 131.3, 130.3, 126.0, 125.5, 123.5, 116.9, 95.6, 85.1, 84.6, 62.7, 32.8, 29.5, 28.0, 27.5. HRMS (ESI): calcd for $C_{21}H_{27}NO_7NaClBr$ $[M+Na]^+$ 542.0557; found 542.0531.

*7-(tert-butyl) 8-ethyl 3-bromo-8-((tert-butoxycarbonyl)oxy)-7-azabicicyclo[4.2.0]octa-1,3,5-triene-7,8-dicarboxylate (**4cb**).* Performed on 50 mg of 3cb. 39 mg (0.0820 mmol), 61 % yield. FC performed with a mixture of Hexane/Ethyl Acetate as eluant in gradient from 60:1 to 20:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.6 Hz, 1H), 7.57 – 7.50 (m, 2H), 4.10 – 4.02 (m, 2H), 1.63 (s, 9H), 1.37 (s, 9H), 1.22 (t, *J* = 7.1 Hz, 3H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 167.0, 150.3, 149.0, 139.3134.4, 127.0, 126.6, 118.0, 117.6, 96.2, 85.4, 84.7, 61.2, 28.4, 27.8, 15.4. HRMS (ESI): calcd for $C_{20}H_{26}NO_7NaBr$ $[M+Na]^+$ 494.0790; found 494.0788.

*7-(tert-butyl) 8-ethyl 8-((tert-butoxycarbonyl)oxy)-3-methyl-7-azabicicyclo[4.2.0]octa-1,3,5-triene-7,8-dicarboxylate (**4db**).* Performed on 108 mg of 3db. 69 mg (0.170 mmol), 53 % yield. FC performed with a mixture of Hexane/Ethyl Acetate as eluant in gradient from 50:1 to 10:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.3 Hz, 1H), 7.24 - 7.23 (m, 1H), 7.20 - 7.18 (m, 1H), 4.13 – 3.99 (m, 2H), 2.34 (s, 3H), 1.62 (s, 9H), 1.33 (s, 9H), 1.21 (t, *J* = 7.1 Hz, 3H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 167.9, 150.2, 149.2, 137.8, 134.8, 132.1, 124.9, 124.0, 115.7, 97.0, 84.8, 84.3, 61.0, 28.4, 27.8, 21.3, 15.5. HRMS (ESI): calcd for $C_{21}H_{29}NO_7Na$ $[M+Na]^+$ 430.1842; found 430.1818.

*7-(tert-butyl) 8-ethyl 8-((tert-butoxycarbonyl)oxy)-3-nitro-7-azabicicyclo[4.2.0]octa-1,3,5-triene-7,8-dicarboxylate (**4eb**).* Performed on 64 mg of 3eb. 60 mg (0.137 mmol), 72 % yield. FC performed with a mixture of Hexane/Ethyl Acetate as eluant in gradient from 50:1 to 15:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 – 8.30 (m, 2H), 8.09 (dd, *J* = 8.9, 0.5 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 1.65 (s, 9H), 1.38 (s, 9H), 1.23 (t, *J* = 7.1 Hz, 3H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 166.7, 150.6, 148.7, 145.3, 145.0, 127.6, 126.4, 119.3, 116.2, 95.6, 86.2, 85.1, 61.5, 28.4, 27.8, 15.4. HRMS (ESI): calcd for $C_{20}H_{26}N_2O_9Na$ $[M+Na]^+$ 461.1536; found 461.1519.

*Tert-butyl 8-((tert-butoxycarbonyl)(2-methoxy-2-oxoethyl)carbamoyl)-8-((tert-butoxycarbonyl)oxy)-7-azabicicyclo[4.2.0]octa-1,3,5-triene-7,8-dicarboxylate (**4ak**).* Performed on 110 mg of **3ak**. 130 mg (0.243 mmol), 74 % yield. FC performed with a mixture of Hexane/Ethyl Acetate as eluant in gradient from 30:1 to 5:1. ^{1}H NMR (400 MHz, CDCl3) δ 7.86 (d, J = 8.2 Hz, 1H), 7.73 (d, J = 7.4 Hz, 1H), 7.38 (td, J = 8.1, 1.3 Hz, 1H), 7.16 (t, J = 7.5 Hz, 1H), 4.46 (d, J = 17.9 Hz, 2H), 3.77 (s, 3H), 1.61 (s, 9H), 1.26 (s, 9H), 1.11 (s, 9H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 170.9, 169.6, 152.5, 149.0, 148.0, 141.8, 131.0, 125.2, 124.6, 124.2, 114.9, 85.1, 84.5, 84.1, 82.8, 52.0, 46.0, 28.0, 27.6, 27.3. HRMS (ESI): calcd for $C_{26}H_{36}N_2O_{10}K$ $[M+K]^+$ 575.2007; found 575.1999.

*Tert-butyl 8-((tert-butoxycarbonyl)((S)-1-methoxy-1-oxo-3-phenylpropan-2-yl)carbamoyl)-8-((tert-butoxycarbonyl)oxy)-7-azabicicyclo[4.2.0]octa-1,3,5-triene-7-carboxylate (**4al**).* Performed on 38 mg of **3al**. 35 mg (0.0558 mmol), 79 % yield. FC performed with a mixture of Hexane/Ethyl Acetate as eluant in gradient from 40:1 to 5:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 8.2 Hz, 1H), 7.54 (d, J = 7.3 Hz, 2H), 7.49 – 7.32 (m, 3H), 7.25 – 7.16 (m, 2H), 7.13 (t, J = 7.4 Hz, 1H), 4.83 (dd, J = 8.8, 2.9 Hz, 1H), 3.74 – 3.65 (m, 1H), 3.63 (s, 3H), 3.21 (dd, J = 13.7, 2.9 Hz, 1H), 1.63 (s, J = 2.2 Hz, 9H), 1.33 (s, 9H), 1.24 (s, 9H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 171.5, 169.2, 152.1, 149.1, 147.9, 141.8, 139.5, 139.4, 134.6, 130.9, 130.0, 128.1, 126.1, 124.2, 123.7, 114.9, 86.1, 84.3, 84.0, 83.0, 59.7, 52.0, 38.9, 28.1, 27.7, 27.3. Tabulation referred to the major diastereoisomer. HRMS (ESI): calcd for $C_{33}H_{42}N_2O_{10}K$ $[M+K]^+$ 665.2477; found 665.2472.

*Tert-butyl 8-((tert-butoxycarbonyl)((S)-1-methoxy-1-3-methyl-1-oxobutan-2-yl)carbamoyl)-8-((tert-butoxycarbonyl)oxy)-7-azabicicyclo[4.2.0]octa-1,3,5-triene-7-carboxylate (**4am**).* Performed on 90 mg of **3am**. 111 mg (0.192 mmol), 81 % yield. FC performed with a mixture of Hexane/Ethyl Acetate as eluant in gradient from 30:1 to 5:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 8.2 Hz, 1H), 7.56 (dd, J = 7.6, 0.8 Hz, 1H), 7.39 (td, J = 8.1, 1.3 Hz, 1H), 7.14 (td, J = 7.6, 0.7 Hz, 1H), 4.32 (d, J = 8.0 Hz, 1H), 3.65 (s, 3H), 2.66 – 2.55 (m, 1H), 1.62 (s, 9H), 1.27 (s, 9H), 1.21 (s, 9H), 1.17 – 1.11 (m, 6H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ

172.1, 169.0, 152.3, 149.7, 148.3, 142.2, 131.2, 124.5, 124.3, 124.1, 115.4, 85.6, 84.7, 84.1, 83.0, 62.5, 52.0, 30.0, 28.5, 28.1, 27.7, 22.5, 19.9. HRMS (ESI): calcd for $C_{29}H_{42}N_2O_{10}Na$ $[M+Na]^+$ 601.2737; found 601.2748.

Ethyl 2-(2,2-((diBoc)amino)-5-methylphenyl)-2-oxoacetate ***(5db).*** 46 mg (0.113 mmol), 35 % yield. FC performed with a mixture of Hexane/Ethyl Acetate as eluant in gradient from 50:1 to 10:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 1.7 Hz, 1H), 7.39 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.10 (d, *J* = 8.1 Hz, 1H), 4.39 (q, *J* = 7.2 Hz, 2H), 2.40 (s, 3H), 1.39 (m, 3H), 1.36 (s, 18H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 186.9, 164.3, 150.8, 138.4, 137.1, 135.1, 131.5, 131.3, 130.1, 83.5, 62.9, 28.0, 21.3, 14.3. HRMS (ESI): calcd for $C_{21}H_{29}NO_7Na$ $[M+Na]^+$ 430.1842; found 430.1855.

Synthetic procedures for compounds 6-9.

Ethyl 2-(2-((4-methylphenyl)sulfonamido)phenyl)-2-oxoacetate ***(6).*** 1 g of isatin (6.8 mmol, 1 equiv) was dissolved in 14 mL of dichloromethane and the solution was cooled to 0 °C with ice bath. Then 1.94 mg of p-Toluenesulfonyl chloride (10.2 mmol, 1.5 equiv) were added to the solution and subsequently 2.84 mL of Et_3N (20.4 mmol, 3 equiv) were added dropwise. The solution was stirred at room temperature. After 2 h, 30 mL of ethanol (0.51 mol, 75 equiv) were added and the mixture was stirred for 12 h. The crude product was purified with flash silica chromatography using a mixture of petroleum ether/ethyl acetate (10:1 to 1:1), affording 6 as an ocher solid. 1.30 g (3.74 mmol), 55 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.75 (s, 1H), 7.77 (d, J = 8.2 Hz, 2H), 7.72 (d, J = 8.5 Hz, 1H), 7.64 – 7.60 (m, 1H), 7.53 (dd, J = 8.2, 7.7 Hz, 1H), 7.25 (m, 2H), 7.08 (t, J = 7.7 Hz, 1H), 4.43 (q, J = 7.1 Hz, 2H), 2.37 (s, 3H), 1.40 (t, J = 7.1 Hz, 3H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$) δ 190.3, 163.4, 144.7, 142.1, 137.0, 136.5, 134.2, 130.2, 127.7, 123.0, 118.9, 117.9, 63.1, 21.9, 14.4. HRMS (ESI): calcd for $C_{17}H_{17}NO_5NaS$ $[M+Na]^+$ 370.0725; found 370.0723.

Ethyl 2-(2-(((benzyloxy)carbonyl)amino)phenyl)-2-oxoacetate ***(7).*** 1.768 g of N-CBz-isatin (6.29 mmol, 1 equiv) were suspended in EtOH (18 mL, 314,5 mmol, 50 equiv) then 0.334 mL of Et_3N (2.51 mmol, 40 mol %) was added. The reaction was stirred at room temperature for 24 h, then the crude product was adsorbed on silica and purified with flash silica chromatography using a mixture of hexane and ethyl acetate as eluant (10:1 to 5:1), affording 7 as a yellow oil. 605 mg (1.85 mmol), 29 % yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.68 (s, 1H), 8.56 (d, J = 8.5 Hz, 1H), 7.73 – 7.57 (m, 2H), 7.48 – 7.31 (m, 5H), 7.10 (dd, J = 11.8, 4.3 Hz, 1H), 5.24 (s, 2H), 4.46 (q, J = 7.2 Hz, 2H), 1.42 (t, J = 7.1 Hz, 3H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ 190.4, 163.9, 153.6, 143.3, 137.2, 136.1, 133.8, 128.9, 128.6, 128.5, 122.1, 119.5, 117.1, 67.5, 62.8, 14.4. HRMS (ESI): calcd for $C_{18}H_{17}NO_5Na$ $[M+Na]^+$ 350.1004; found 350.0994.

Tert-butyl (2-ethoxy-3-oxo-1-tosylindolin-2-yl)carbonate ***(8).*** 100 mg of 6 (0.28 mmol, 1 equiv) were dissolved in 0.90 mL of dichloromethane. After 10 minutes 189 mg of Boc_2O (0.87 mmol, 3.1 equiv) and 91 mg of quinine (0.28 mmol, 1 equiv) were added and the mixture was stirred at room temperature for 4 days. The crude was purified with flash silica chromatography using as eluant a mixture of petroleum ether and ethyl acetate (10:1 to 8:1). 6 mg (0.0134 mmol), 5 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 8.4 Hz, 2H), 7.77 (d, J = 8.5 Hz, 1H), 7.63 (dd, J = 7.6, 0.8 Hz, 1H), 7.58 (ddd, J = 8.7, 7.4, 1.5 Hz, 1H), 7.22 (d, J = 8.1 Hz, 2H), 7.09 (td, J = 7.5, 0.7 Hz, 1H), 3.88 (q, J = 7.1 Hz, 2H), 2.37 (s, 3H), 1.38 (s, 9H), 1.20 (t, J = 7.1 Hz, 3H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ 193.2, 149.8, 144.1, 137.8, 136.9, 129.8, 129.1, 128.5, 124.9, 123.4, 120.0, 114.9, 106.8, 79.6, 60.0, 29.9, 21.5, 14.8. HRMS (ESI): calcd for $C_{17}H_{17}NO_5NaS$ $[M-(CH_3)_3COC=O+H+Na]^+$ 370.0725; found 370.0708.

Benzyl 2-((tert-butyldimethylsilyl)oxy)-2-ethoxy-3-oxoindoline-1-carboxylate ***(9).*** 84 mg of 7 (0.257 mmol, 1 equiv) and 129 mg of TBDMSOTf (t-butildimethylsilyl trifluoromethanesulphonate, 0.488 mmol, 1.9 equiv) were loaded in a two-neck round flask under a flow of argon, then dissolved in 2.17 mL of anhydrous dichloromethane. After this 66 µL of 2,6-dimethylpyridine (0.565 mmol, 2.2 equiv) were added and the reaction stirred at room temperature for 18 h. The crude was then diluted with 10 mL of Et_2O, washed with brine (3 x 10 mL) and the aqueous layers extracted with Et_2O (3 x 15 mL). The organic fractions were reunited, dried over Na_2SO_4, evaporated at reduced pressure and purified with flash silica chromatography using as eluant a mixture of hexane and ethyl acetate (20:1 to 8:1). 49 mg (0.111 mmol), 43 % yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, J = 8.4 Hz, 1H), 7.71 – 7.60 (m, 2H), 7.47 (dd, J = 7.7, 1.4 Hz, 2H), 7.37 (ddd, J = 12.7, 5.5, 3.4 Hz, 3H), 7.14 (t, J = 7.5 Hz, 1H), 5.53 (d, J = 12.4 Hz, 1H), 5.16 (d, J = 12.3 Hz, 1H), 3.53 – 3.44 (m, 2H), 1.10 (t, J = 7.0 Hz, 3H), 0.83 (s, 9H), 0.13 (s, 3H), 0.10 (s, 3H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ 194.5, 152.2, 151.4, 138.5, 136.2, 134.4, 128.8, 128.6, 124.7, 123.7, 120.1, 116.8, 103.2, 67.6, 60.2, 25.8, 18.4, 15.2, -2.9, -3.3. HRMS (ESI): calcd for $C_{24}H_{31}NO_5NaSi$ $[M+Na]^+$ 464.1869; found 464.1866.

■ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. 1D and 2D-NMR spectra (^{1}H and ^{13}C). IR spectra. Details about the DOE. Coordinates and Energies of the DFT calculations.

■AUTHOR INFORMATION

Corresponding Author

*E-mail: riccardo.salvio@uniroma1.it, marco.bella@uniroma1.it.

ORCID

Riccardo Salvio: 0000-0003-0398-8408
Marco Bella: 0000-0003-2223-6025

Notes The authors declare no competing financial interest.

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