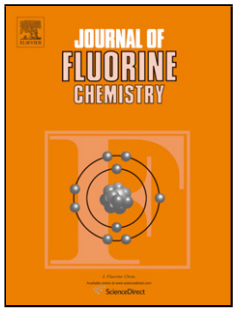

Title: Synthesis and studies on *gem*-fluorinated 2-azabicyclo[n.1.0]alkanes

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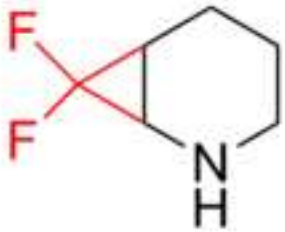
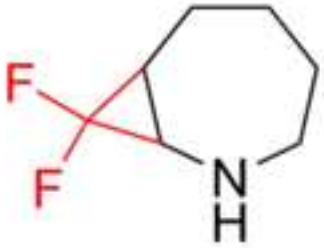
*Graphical Abstract - Pictogram

CF_2-pyrrolidine



CF_2-Piperidine



CF_2-Azepane

- Synthesis
- Stability
- Lypophilicity
- Clearence
- Basicity

The paper describes three novel amines – analogues of pyrrolidine, piperidine and azepane – in terms of their stability, integral properties and structure. The amines have their pK_a around neutral values, and the transition to the basic form triggers their quick fragmentation. In addition, we discuss the lipophilicity impact of the difluorocyclopropane moiety and structural features.

- the substances obtained via direct difluorocyclopropanation of corresponding ene-carbamates;
- deprotected substances possess different stability;
- fragmentation occurs by either intramolecular or intermolecular cyclopropane opening;
- the free amines undergo acid-base transition at neutral pH values;
- CF_2-fusion gives only minute impact on lipophilicity (slight increase).

Synthesis and studies on *gem*-fluorinated 2-azabicyclo[n.1.0]alkanes

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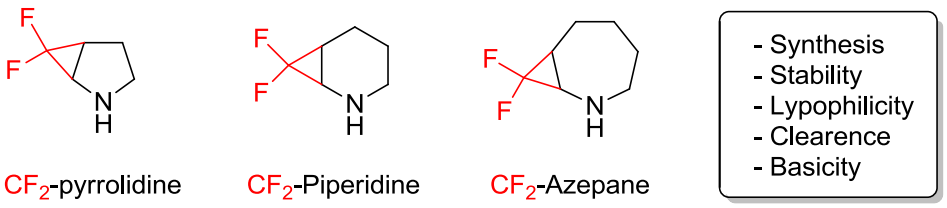
Abstract



Three novel amines all possessing *gem*-difluorocyclopropane, secondary amino group and a fused aliphatic cycle were synthesized by difluorocyclopropanation of N-Boc protected enamides. The compounds were stable when amino group was blocked by protonation or acylation, but otherwise underwent fragmentation already at the room temperature. Chemical structure, physico-chemical properties and fragmentation mechanisms of the fluorinated amines are studied in details.

Keywords

cyclic amine; cyclopropane; difluorocyclopropane; ^{19}F MNR; fragmentation

1. Introduction

Cyclic aliphatic amines **1** are important structural fragments in medicinal and combinatorial chemistry (Fig. 1) [1]. Through variations of the skeletons and ring substituents in such cyclic structures it is possible to modulate several important features of the parent moieties, such as electronic and conformational properties. Through these structural variations it is possible to realize a modulation in the pK_a values, or to fix certain conformational angles important for the molecular recognition and biomolecular affinity. Also, changes to corresponding amide bond properties are also important; particularly nitrogen pyramidalization and the conjugation energies and rotational barriers [2]. Considering biomedical applications, modifications to cyclic amine moieties should not lead to a significant increase in the molecular size and lipophilicity, i.e. the final compounds should fulfill Lipinski's rule of 5.

The high importance of the development of new small molecular fragments in drug design has been emphasized [3]. One of the more recent examples of this is design of 4-aryl-piperidines **2** with the cyclic fusion at the β,γ-site, with respect to the nitrogen, that enabled controlled modification of the molecular conformation [4].

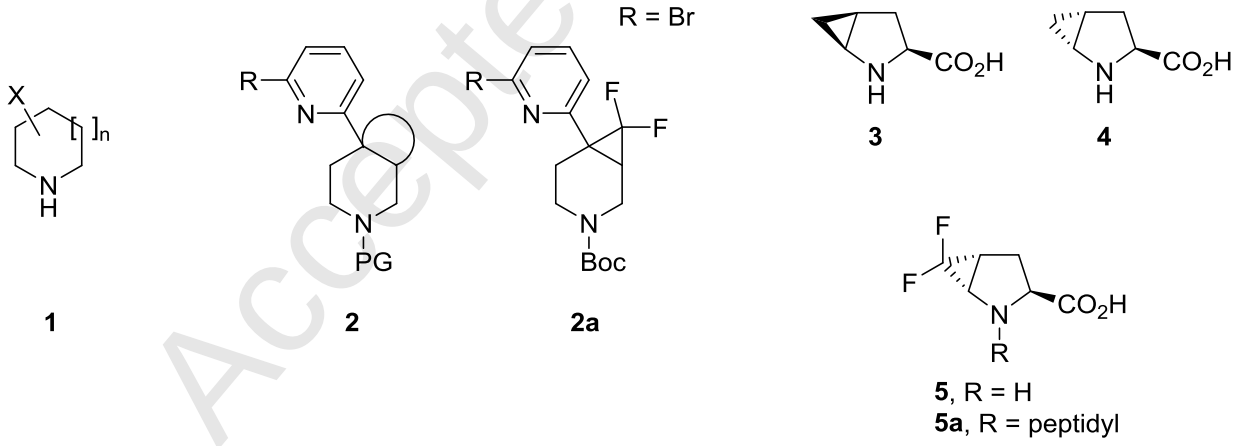


Fig.1. Cyclic aliphatic amines: **1** – general structure which allows variability in the ring size and substituents; **2** – recently reported 4-aryl-piperidines with systematic variations of the β,γ-fused ring for different conformational restriction; **3**, **4** – 4,5-methanoprolines; **5** – *gem*-difluoro-4,5-*trans*-methanoproline unstable as free amino acid (**5**), but stable in peptides (**5a**).

It is not only medicinal chemistry that requires availability of the cyclic amine scaffolds. Through the simple introduction of the carboxyl group, this transforms cyclic amines into amino acids, α-[5], β-[6],

γ- and so on. The former will make corresponding amine an analogue of proline (Pro), and depending on the ring size, an analogue of azetidin-2-carboxylic acid (Aze) or pipecolic acid (Pip). These analogues are powerful tools for modifications of the peptides and proteins towards site-specific polarity changes [7]. Furthermore, since the initial cyclic scaffolds bear a certain degree of conformational restriction, incorporation of further substituents into the ring system may enhance conformational populations, for example the proline puckers and amide bond rotamers in fluoroprolines [8]. Drawing analogies with proline, these chiral cyclic secondary amines are potential candidates for catalytical activity in asymmetric cascade reaction [9]. For example, 4,5-methanoprolines (**3**,**4**) have demonstrated good organocatalytic performance due to the strong conformational impact of the cyclopropane moiety [10].

The cyclopropane moiety has one of the strongest influences on the conformational properties of various substrates [11,12]. When fused to a cyclic amine [13] a cyclopropane ring may also significantly change electronic properties of the amino functions, especially when the fusion site is α,β-. The conventional methods for formation of a cyclopropane ring on a donor scaffold, such as Simmons-Smith reaction, cyclopropanation with diazomethane or organometalic reagents [14] often suffer from poor yields and often present significant safety issues. Interestingly, one of the easiest ways to construct a cyclopropane ring on a desired scaffold molecule is through difluorocyclopropanation (for instance, this was the case for **2a**). This requires generation of highly electrophilic difluorocarbene species, which then readily reacts with donor alkenes [15]. New methods for difluorocyclopropanation are being regularly developed, and new relatively mild methods with safe reagents become more and more available [16].

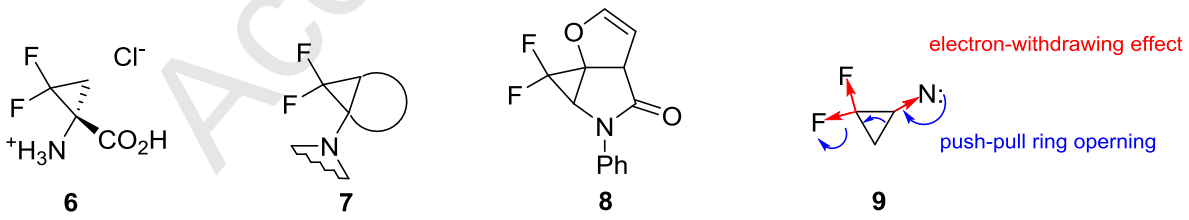
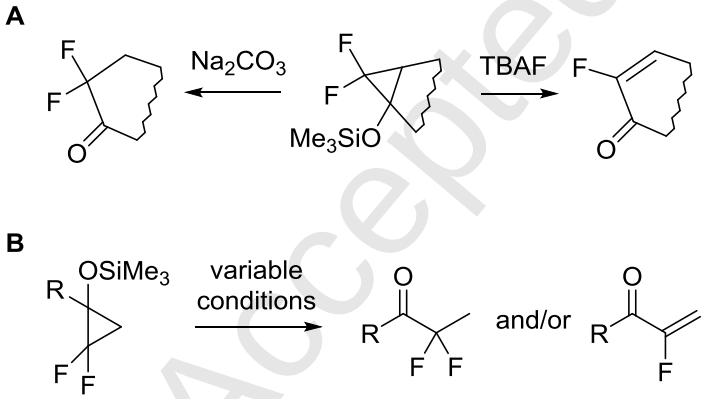


Fig. 2. Known amino-*gem*-difluorocyclopropanes **6**-**8**. **9** – electronic effects in amino-gem-difluorocyclopropanes.

Construction of difluorocyclopropanes with an amino functionality in close proximity may cause certain instabilities of the formed structures. For instance, from a number of published amino-difluorocyclopropanes **5**-**8** (Fig. 2) [17,18,19,20] conditions for a ring push-pull opening **9** are reported for

most of them. In particular, we recently reported the preparation of a novel amino acid – difluoromethanoproline (F_2MePro, **5**), analogue of the *trans*-4,5-methanoproline **4** [21]. The substance was stable when the amine functionality was protected (for instance, in peptides, **5a**), but as a free amino acid it rapidly decomposed at room temperature. One particularly interesting property of the F_2MePro residue is the dispersion of the ^{19}F NMR chemical shift: two inequivalent geminal fluorine atoms appeared extremely distant from one another in terms of the isotropic chemical shift (about 25 ppm difference). Thus, three anisotropic parameters can be extracted from corresponding solid state ^{19}F NMR spectra: two chemical shift anisotropy values for individual fluorine atoms and one strong (dipolar) coupling for orientation of the CF_2-fragment as whole. Therefore, F_2MePro was not only found to be an analogue of proline for conformational changes, but a very promising ^{19}F NMR probe as well [22].

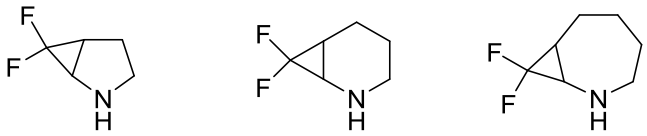
Instability of the difluorocyclopropane with the oxygen substituents has not been a big concern since several studies reported them to be stable [23]. Only very recently, a difluorocyclopropane ring-opening has been recognized as a synthetic method towards fluoroenones, or difluorohomologation (Scheme 1) [24,25].



Scheme 1. Synthetic methods based upon fragmentation of siloxydifluorocyclopropanes: **A.** reported by Kageshima *et* al. on cyclic scaffolds [24]; **B.** reported by Kosobokov *et* al. investigation towards difluorohomologation of ketons [25].

In this work, we designed, synthesized and studied novel 2-azabicyclo[n.1.0]alkanes **10-12** (Fig. 3). Due to the close positioning of the amino group to the difluorocyclopropane in a constrained bicyclic system we expected a significant mutual electronic and conformational influences. These properties will make **10-12** useful for various applications, both as amine moieties and as molecular skeletons for the

construction of functionalized molecules (e.g. amino acids). However, the first question to be answered was: how stable are these substrates and what are the factors affecting their stability? Can they be handled and which conditions are they able to tolerate?

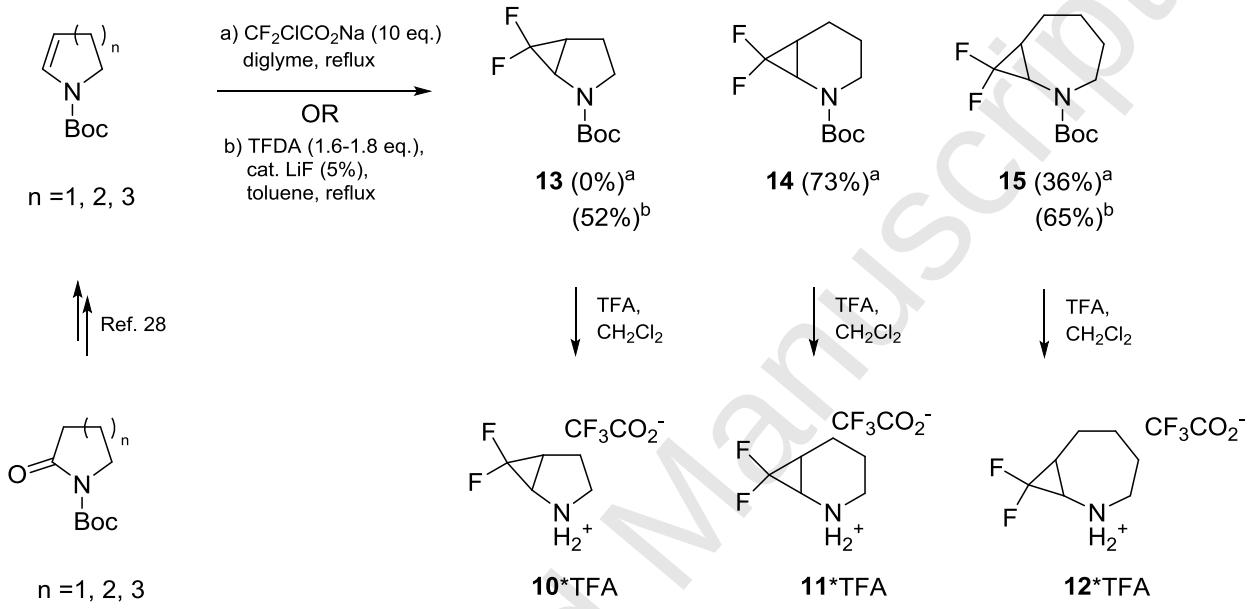


10 **11** **12**

Fig. 3. Amines **10**-**12** reported in this study.

2. Results and discussion

2.1. Synthesis



Scheme 2. Synthesis of the amines **10***TFA, **11***TFA, **12***TFA.[a]

[a] TFA = trifluoroacetic acid, TFDA = trimethylsilyl difluoro(fluorosylfonyl)acetate.

Highly energetic *gem*-difluorocyclopropanes are active towards chemical transformations [26,27]. Therefore, their synthesis requires a source of more reactive difluorocarbene species. We performed the preparation of the desired amines by difluorocyclopropanation of the corresponding N-Boc enamides, obtained in turn from the N-Boc lactams [28] (Scheme 2).

First we tried the oldest, and certainly one of the cheapest reagents - sodium chlorodifluoroacetate [29,30]. Despite the drastic reaction conditions (refluxing diglyme, large excess of the carbene precusor) we managed to obtain the N-Boc amines **14** and **15** in 73 and 36% yields, respectively (Scheme 2). Ten equivalents of the salt were enough to achieve the full conversion of the starting compounds [31]. The same synthesis on the 5-membered ene-carbamate **13** (N-Boc pyrroline) failed, yielding a complex mixture.

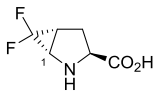
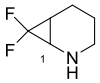
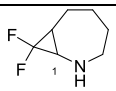
Subsequently we attempted the reaction with the Dolbier reagent - $FSO_2CF_2CO_2TMS$ (TFDA) [32]. In fact, the desired N-Boc amine **13** was obtained in 52% yield with TFDA. Also, with TFDA we improved the yield of product **15** to 64%.

As a short summary, we obtained the stable N-Boc amines **13-15** in gram scale. However, we noticed that (only) carbamate **13** changed its color to more intense upon storage during several months at the room temperature, and precipitated visible amounts of solid byproducts. We were also able to detect impurities by NMR, with the substrate showing complete decomposition after about a year and a half.

2.2. Stability

The N-Boc protection group in **13**-**15** was removed with trifluoroacetic acid (TFA) in dichloromethane in a conventional manner (Scheme 2). The resulting salts contained approximately 2 equivalents of TFA per amine **10**-**12**. Stability studies were conducted then by ^{1}H and ^{19}F NMR spectroscopy; this data is summarized in Table 1.

Table 1. Properties of substances **5** and **10**-**12**.

Compound	pK_a	δ(^{1}H) of CH-1, ppm[a]	Half-life			
			TFA salts			Free amines
			$CDCl_3$	D_2O	pH = 4.4[b]	$CDCl_3$ pH = 7.6[b]
 **5**	n.d.[c]	3.93	n.d.[c] *110±10 min*[d]	39±5 min	n.d.[c]	n.d.[c] *instant decomposition*[e]
 **10**	> 6.4	3.78	3±1 days	3±1 days	58±11 min	instant decomposition
 **11**	7.1±0.1	3.34	stable[f]	stable[f]	38±2 days	2±1 days 80±5 min
 **12**	6.7±0.1	3.48	stable[f]	stable[f]	72±6 days	6±2 days 120±10 min

[a] Measured in D_2O solution of the trifluoroacetates. [b] In sodium phosphate buffer. [c] Not determined. [d] The number found for the corresponding methyl ester (the free amino acid salt was found to be insoluble in chloroform). [e] The measurement was made in deuterium oxide and extrapolated on other conditions here. [f] Measurements were conducted for **5** ($CDCl_3$) and **15** (D_2O) months.

Several conclusions can be made from data in Table 1: 1) none of the amines was stable under all the conditions investigated; 2) the basic forms are less stable than the protonated ones; 3) their stability increases with the enlargement of the ring size. The drastic difference in stability occurred between **10** and **11**, when just one additional methylene in the ring led to a much more stable amine. Thus we proved that the intrinsic instability of the amino acid **5** was mainly caused by the instability of its bicyclic core. In general the stability row can be summarized as following: **5** < **10** << **11** < **12**.

We noticed that in aqueous phosphate buffers the salt and base forms of **11** and **12** exhibited somewhat different ^{19}F NMR chemical shifts and $^{2}J_{F\text{-}F}$ couplings displaying characteristic sigmoidal curves (Fig. 3). Thus direct pK_a determination was possible, and the corresponding values were found to be 7.1 and 6.7, for **11** and **12** respectively. In contrast, **10** only underwent a massive decomposition starting already from pH 6.2-6.4 without any deviation for values of chemical shift or ^{2}J. This was an indication that decomposition of **10** underwent instantaneously when transformed to the free base. If we consider the latter event to occur on the beginning of the sigmoidal transition, then the pK_a of **10** should not be lower than its homologs **11** and **12**. If we compare the observed pK_a values to common cyclic secondary amines such as piperidine (pK_a = 11.2) we find general reduction of the basicity by four orders of magnitude. Such a decrease is quite close to the predicted values [33]. Also, we demonstrated recently, that three β-fluorine atoms can reduce the basicity by up to six orders of magnitude [34], therefore two β-fluorines in **10**-**12** can be estimated to four orders difference within a linear approximation.

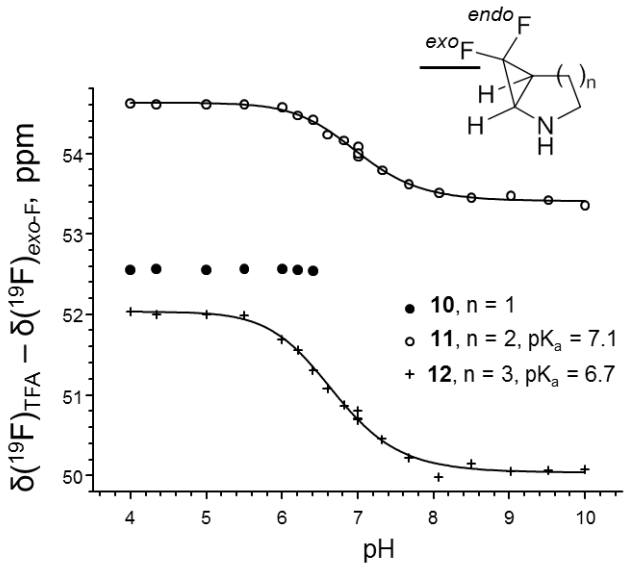


Figure 3. pH dependence of the *exo*-^{19}F resonance positions of **10**-**12**.[a]

[a] with respect to the TFA signal (-75 ppm); measured in aqueous phosphate buffers at 25°C.

Comparison of the ^{1}H NMR spectra for **10***TFA and **11***TFA revealed an interesting tendency, that all the resonances in the former case were shifted by 0.31-0.55 ppm downfield. The most critical position is CH-1, which is a prominent electrophilic center of the molecule, was shifted downfield by 0.44 ppm. Nevertheless, systematic comparison of the CH-1 chemical shift for the entire row (Table 1) did not correlate with the stabilities in a straightforward manner.

For the amines **10**-**12** we found several *J*-coupling constants which correlated with the stability - those were $^{2}J_{F\text{-}F}$, $^{1}J_{C\text{-}H}$ within the cyclopropane ring and N-CH_2 (Table 2). Curiously, couplings of this type have a strong Fermi contact term contribution [35,36,37]. The interpretation of the *J*-coupling tendencies is not a straightforward task. However, neither geminal $^{2}J_{F\text{-}F}$ nor cyclopropane $^{1}J_{C\text{-}H}$ exhibit sensitivity to hybridization state of the cyclopropane carbons [35,37]. Therefore we could assume those differences do not arise from the changes in cyclopropane hybridization state and geometry associated with it (see also chapter 'structure' below). We presume, such a systematic change of the *J*-values reveals a different electrophilic influence of the CH_2-chained (large) ring to the cyclopropane similar to what we emphasized for the chemical shifts above. Indeed, increasing numbers of the CH_2 may lead to a better electron donating compensation (acc to +I effect) to the electronically poor amino-difluorocyclopropane system **9**,

increasing its stability. This is why, we suspect, amino acid **5** (with an additional electron-withdrawing carboxyl-group) turned out to be less stable than its parent amine **10**.

Table 2. *J*-coupling values deviated along with the ring size variations in 10-12*TFA salts.[a]

amine*TFA	$^{2}J_{F\text{-}F}$, Hz	$^{1}J_{C\text{-}H\text{-}1}$, Hz	$^{1}J_{C\text{-}H\text{-}3}$, Hz	$^{1}J_{C\text{-}H\text{-}(4+n)}$, Hz
10, n = 1	177	195	150	177
11, n = 2	173	189	147	167
12, n = 3	171	187	145	167

[a] Measured in deuterium oxide solutions of the trifluoroacetates at 298 K.

However, such simple treatment does not explain the fact that the amines **10**-**12** are significantly unstable in the first place. For instance, other cyclic structures **7** reported by Nowak *et al*. [18] required high temperatures to undergo fragmentation. Among them the ones with the highest $^{2}J_{F\text{-}F}$ 152 Hz delivered lowest yields in the synthesis and also required lower temperature for their full decomposition (e.g. 1 h at 100 °C).Nevertheless, from the practical perspective we can propose to use the value $^{2}J_{F\text{-}F}$ as a simple criterion for predicting the instability of homologous difluorocyclopropanes: a higher *J* value would imply lower stability expectations.

2.3 Mechanism

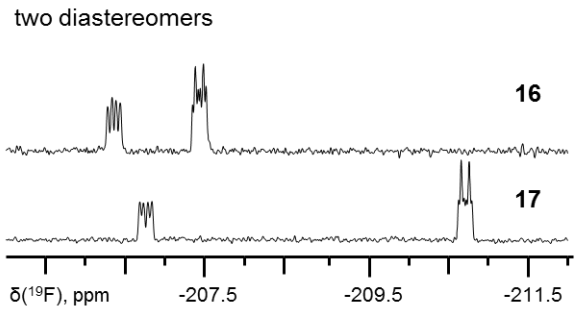
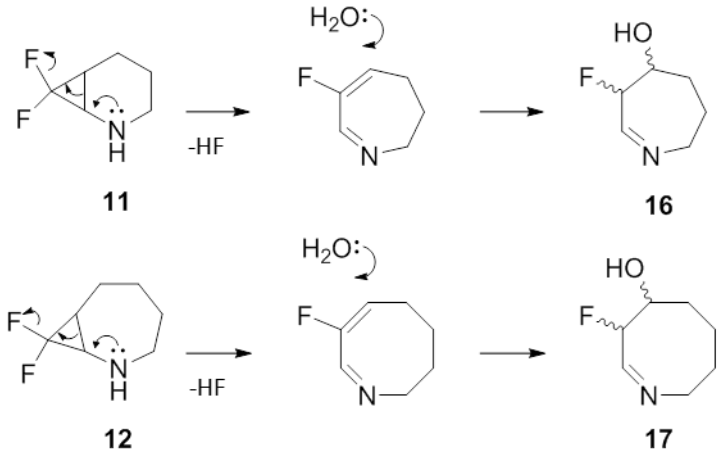


Figure 4. ^{19}F NMR spectra of the fragmentation of products **16** and **17**.[a]

[a] The two fluorine resonances correspond to the two diastereomers and the *J*-couplings originate from the neighboring ^{1}H nuclei (removed when ^{1}H decoupled). The spectra also contained the TFA singlet (at -75 ppm) and inorganic fluoride (at -120 ppm).

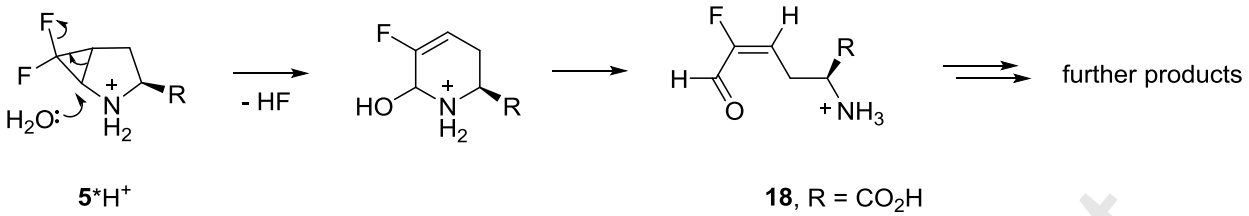
We were able to assign the major product of the decomposition of amines **11**, **12**. Overnight fragmentation of **11** and **12** under basic conditions (pH 7.6) led to formation of the substances **16** and **17** respectively. The assignment was based on the extensive NMR studies of the reaction mixtures (see SI). One particularly characteristic observation was the presence of two ^{19}F resonances at -207 – -211 ppm (Fig. 4). They corresponded to two diastereomeric forms of the cyclic azomethine products (different ^{1}H multiplicity). Mechanistically, their formation should include cyclopropane ring-opening followed by addition of a water molecule to the formed α-fluoro-α,β-unsaturated azomethines (Scheme 3). Though, substances **16** and **17** turned out to be the sole fluorine-containing products along with the inorganic fluoride (resonance at -120 ppm). Also both processes: the degradation of **11** and **12** and formation of **16** and **17** were found to be of the same 1st order kinetics and with the same $\tau_{½}$ of the reactions meaning that the cyclopropane ring-opening was the rate-limiting step of the fragmentation. We also found very similar ^{19}F NMR resonances in the final mixtures after three months fragmentation of **11** and **12** under acidic pH = 4.4.



Scheme 3. Fragmentation of the amines **11** and **12** in aqueous phosphate buffer.[a]

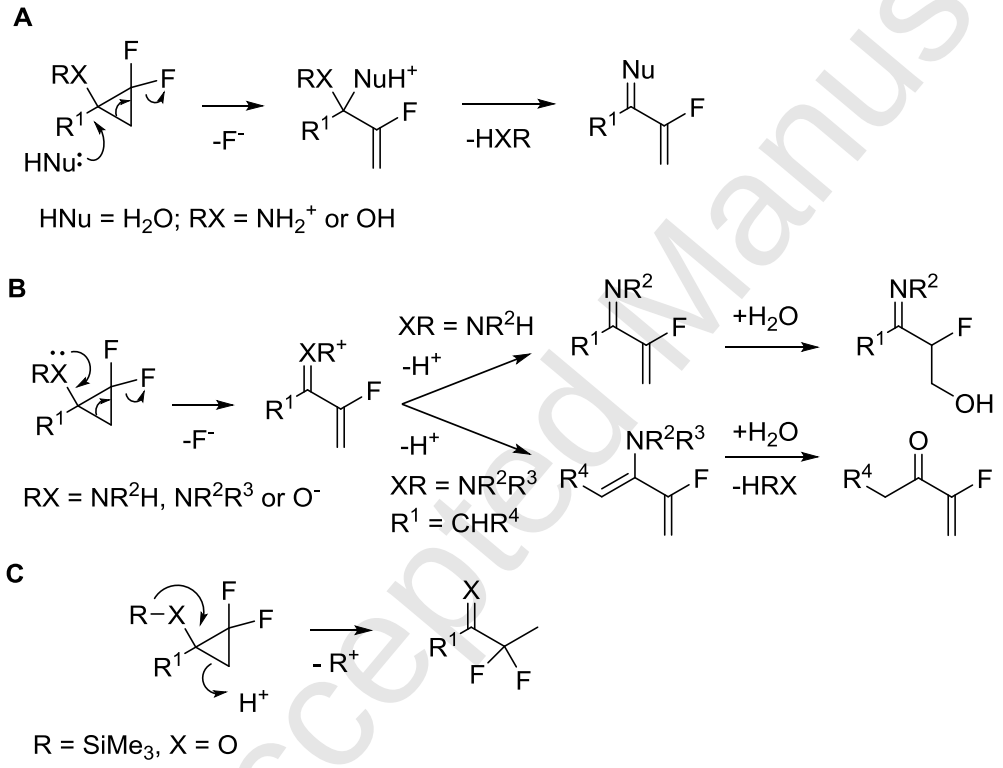
[a] as found by detection of **16** and **17** respectively; pH 7.6, 25 °C.

We reported already that decomposition of the amino acid **5***TFA proceeds via formation of the aldehyde **18**, which thereafter undergoes further degradation [21]. However, upon monitoring the decomposition of its parent amine **10***TFA (pH 4.4) we did not find any prominent dominant signals such as the azomethine or aldehyde type, but solely the formation of a complex mixture. We suspect that the kinetics of the reaction are unfavorable for the observation of the characteristic intermediates previously described. For instance, if similar aldehyde to **18** (with R = H) were to form, it would not be formed in a detectable amount in the mixture because its formation will be much slower ($\tau_{½}$ days *vs* minutes for **10** and **5** respectively). However, the fact that **10** decomposed already from the protonated form was evidence that it decomposed according to a mechanism different from amines **11** and **12**. For the rest of the decomposition processes, referred in the Table 1, the mixture was found to be complex, and without major distinguishable products. In particular, the degradation in chloroform was particularly complicated because the formation of a defined product according to the above mentioned mechanisms would require the presence of a water molecule (solvolysis).



Scheme 4. Fragnemtation of F_2MePro*TFA (**5***TFA) in deuterium oxide solution as reported in [21].[a]

[a] The starting substance degraded within the first 3 hours, whereas intermediate product was collecting in the mixture, reached maximal concentration after 3 hours of observation and then degraded completely within the next 20 hours of monitoring.

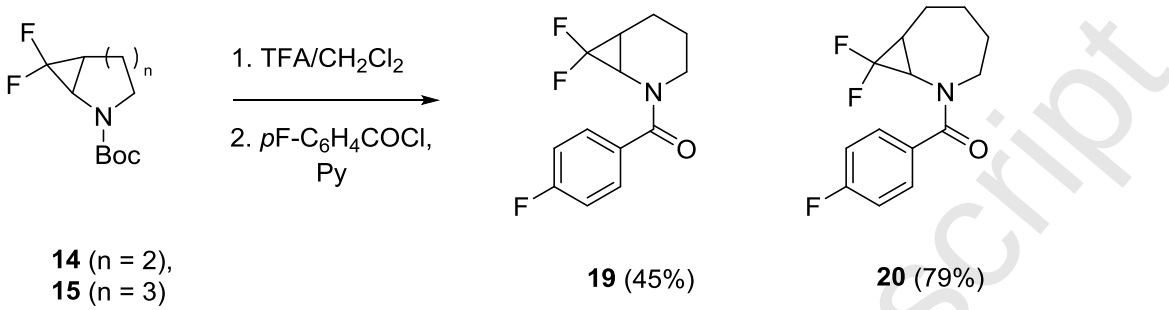


Scheme 5. Fragmentation mechanisms for amino- and oxy-difluorocyclopropanes.

According to our findings and the literature data [18,19,20,24,25] of amino- and oxy-difluorocyclopropanes, we can summarize their fragmentation mechanisms as depicted on Scheme 5. Noteworthy, all of them involve the cleavage of the same C-C bond in cyclopropane on the initial step. Mechanism A is an intermolecular nucleophilic attack (solvolysis) which occurs with the most electron deficient species (like **5** or **10**) and can proceed easily when amino-group is protonated. Mechanism B is an intramolecular nucleophilic attack. This is the only mechanism possible for the amines **11** and **12** and

also the mechanism for the pyrolysis of **7**. In addition, this occurs when RX is a silyloxyl-substituent, in particular when removing a silyl-protecting group (TBAF / THF, -78 °C) releases a highly nucleophilic negatively charged O^- which thereafter attacks the cyclopropane ring [24]. Mechanism C has only been described for X = O, and it produces useful α,α-difluoroketones. therefore, this mechanism was the target for the development of corresponding synthetic routes [24,25]. In particular in [25] it was the sole fragmentation pathway when the initial cyclopropanated compound was treated with a strong acid in a poorly nucleophilic medium (HCl / dioxane; HBr / acetic acid). It should be also noted, that only in the case when X = N, the two mechanisms A and B can be discriminated based upon the observation of the degradation products. Whereas when X = O, the two mechanisms produce the same α,β-unsaturated ketone species.

2.4. Derivatives



14 (n = 2),
15 (n = 3)

19 (45%)

20 (79%)

Scheme 6. Synthesis of amides **19**, **20**.

In order to demonstrate the practical potential of the synthesized amines **10**-**12**, we performed their acylation by 4-fluorobenzoylchloride in pyridine (Scheme 6). The derivatives **19** and **20** were prepared in 45% and 79% yields respectively, whereas amine **10** decomposed upon N-deprotection (0% yield). The reaction yields correlated well with the previously observed stability order: **10** << **11** ≤ **12**.

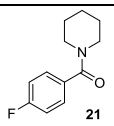
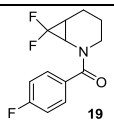
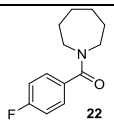
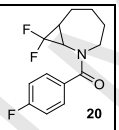
The solid acylated compounds **19**, **20** (similar to N-Boc derivatives **14**, **15**) were stored at room temperature without any detectable decomposition. Apparently the nitrogen lone pair was sufficiently locked within either the amide or carbamate conjugated system, so that the intramolecular opening was effectively impossible.

2.5. Integral properties

For the stable substances **19** and **20**, we measured the parameters important for medicinal chemistry – water solubility, lipophilicity, metabolic stability – and compared the data to those of the parent N-substituted piperidine (**19**) and azepane (**20**) (Table 3). In fact, the difluorocyclopropane slightly increased the lipophilicity of both of the substances, but unexpectedly decreased the metabolic stability (usually F-atom increases it), while keeping the water solubility almost constant. However, slide increase in the lipophilicity may indeed reduce their metabolical stability [38].

It is also worth mentioning, that the difluorocyclopropane ring increased the melting point of the compounds, probably by reducing ("freezing") their conformational plasticity.

Table 3. Integral properties of the N-4-fluorobenzoyl secondary amines.

	 21	 19	 22	 20
Solubility, μM[a]	181±14	169±4	168±6	179±6
log$D_{7.2}$[b]	2.2±0.3	3.0±0.3	2.6±0.6	2.7±0.3
CL_{int}, μl•mg^{-1}•min^{-1}[c]	42	82	50	76
Melting point, °C	62-63	108-109	oil	68-69

[a] In 10 mM potassium K-phosphate buffer (pH = 7.4) with 140 mM inorganic chloride. [b] Distribution between n-octanol and the same buffer. [c] In mouse hepatic microsomes

An impact of a cyclopropane fusion on the net lipophilicity was expected to be small. Incorporation of fluorine at a certain position in place of hydrogens has a dual influence. On the one hand, fluorine substitution would increase the polarity, hence hydrophilicity, and on the other hand, increasing the

molecular volume would increase lipophilicity [39,40]. The data we reported here on solubility and distribution coefficient of amides **19**-**22** allow us to conclude, that the net influence of a difluorocyclopropane fusion was rather modest. Previously, we reported on the gramicidin S analog with the difluoromethanoproline **5** in place of one proline in the structure [22]. We found that the RP-HPLC retention time (which is a very characteristic parameter for amphipathic peptides such as gramicidin S [41]) was only slightly higher for the analog if compared to the wild type structure. Resultingly, the microbiological activity values obtained for the analog were close to that of the gramicidin S wild type. This observation supports our conclusion, that fusion with a difluorocyclopropane would generally increase lipophilicity, albeit only slightly.

2.6. Structure

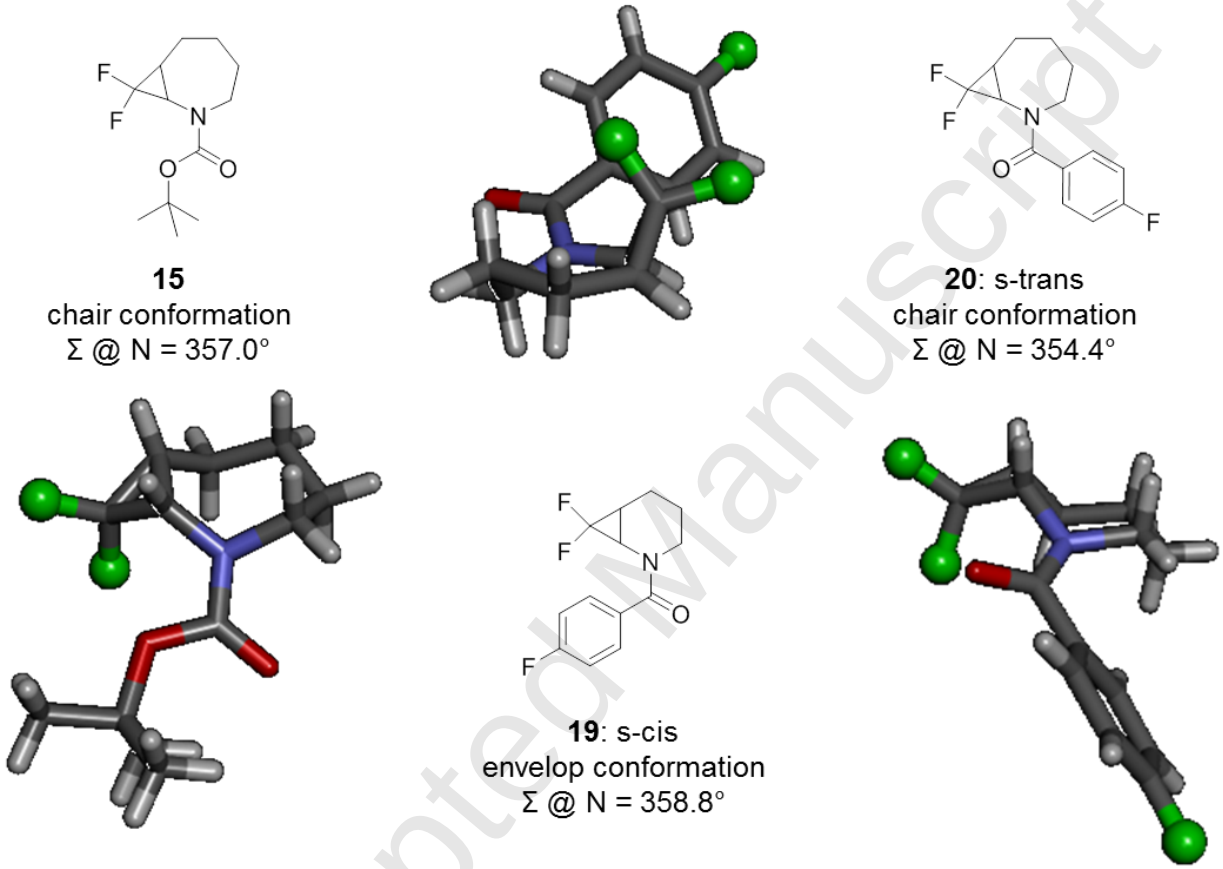


Figure 5. X-ray crystal structures of the compounds **15**, **19** and **20**.[a]

[a] The sums of the nitrogen valency angles and the ring conformations are denoted.

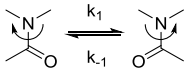
Several compounds (**15**, **19** and **20**) produced high quality crystals that could be analyzed by X-ray diffraction [42]. The corresponding structures are shown on Fig. 5. In general, the structures were consistent with what has been already known for difluorocyclopropanes [26]. Namely, the incorporation of two geminal fluorine atoms in the cyclopropane unit led to shortening of the F_2C-CH bonds (1.46-1.47 Å) and stretching of the remaining CH-CH bond (1.54-1.55 Å). The latter C-C bond is the weakest one and it is exactly the one that breaks in the fragmentation of corresponding amines. The F-C-F valency angle

was also significantly shortened to about 108.3°, whereas in the parent cyclopropane H-C-H angle is expected to be 115° [43].

Interestingly, the conformation of the large rings was found to be the same as if it was one carbon atom shorter i.e. an envelope for the 6-membered ring in **19** and chair for the 7-membered ring in **15** and **20**. Significant repulsion between the cyclopropane and the substituents at the carbonyl species led to observable degree of nitrogen pyramidalization. Finally, the phenyl ring in **19** and **20** was found to be pushed out of carbonyl plane significantly (by ~ 40°) regardless on the rotational state of the carbonyl (s-*cis* in **19** or s-*trans* in **20**).

The corresponding rotational properties of the carbamates (**13**-**15**) and amides (**19**-**20**) were determined in the chloroform solution by EXSY NMR (Table 4). The rotational constants and corresponding activation energies displayed several interesting properties. First, the amides were rotating more freely than the carbamates, whereas for non-cyclopropanated species exactly the opposite would normally be expected. This fact can be explained by considering the structure; we observed significant repulsion of the phenyl-ring from the aliphatic ring, which might destabilize the ground structure of the amide. For the carbamate species such a repulsion would not play a large role. Second, amide **20** and carbamate **15** with a 7-membered large rings were rotating more freely than corresponding species with the 6-membered large ring, **19** and **14** (7-8 kJ/mol difference in the activation energies). This was surprising due to the fact that the amides of piperidine or morpholine are normally more freely rotating than corresponding azepane or pyrrolidine derivatives [44]. Here again the heterocyclic rings exhibit properties as if they were one carbon atom shorter, in a similar fashion as was seen in the structural overview previously.

Table 4. Amide rotamers rotational parameters for the N-Boc and N-4-fluorobenzoyl derivatives.[a]



$k_1/k_{-1} = K$

Compound	K[b]	k_1, s^{-1} [c]	E_a (k_1), kJ/mol[d]	k_{-1}, s^{-1} [c]
13	1.60±0.15	36.7±0.5	64	22.2±1.3
14	4.70±0.11	5.5±0.3	69	1.2±0.05
15	7.65±0.15	190	60	24
19	2.89±0.06	33.0±1.6	64	11.1±0.4
20	3.0±0.3	350	58	120

[a] the major rotamer was not determined due to the fast transition; [b] determined by integration of the ^{1}H and ^{19}F NMR spectra (chloroform, 25 °C); [c] measured by either EXSY or coalescence; [d] derived from the large rotation rate k_1 according to the Eyring equation.

3. Conclusions

We have reported the synthesis and characterization of a series of novel bicyclic fluorinated amines **10**-**12**. The critical parameter of the substances was their stability, which increased with the enlargement of the heterocyclic ring from 5- to 7-membered as **10** < **11** < **12**. The most unstable substance **10** decomposed as protonated salt, whereas this was only possible if **11** and **12** were present as the free bases, and thus followed different degradation mechanism. Though, the substances were stable as amides or carbamates. Given their appropriate ADMET profile (lipophilicity, water solubility, metabolic stability), we believe these compounds will become useful, in particular, in drug discovery as promising building blocks.

4. Experimental

4.1. General information

All chemicals were obtained from common sources. Diglyme was distilled under sodium/benzophenone/argon, toluene was distilled under phosphorus pentoxide/air. The initial *N*-Boc 2-pyrroline, 2,3-dehydropyrrolidine and 2,3-dehydroazepane were obtained by the convenient literature protocol starting from pyrrolidone, valerolactame and caprolactame respectively [28]. For bulk chromatographic separation silica gel 230-400 mesh of CC grade (Sudambe chemicals) was used.

^{1}H and $^{13}C\{^{1}H\}$ spectra were recorded on Bruker Avance 400, Bruker Avance DRX 500 and Bruker Avance III 500 devices and referenced to TMS using deuterium lock signal as the internal standard. ^{19}F NMR spectra were recorded on Varian UNITY Plus 400 and Bruker Avance III 500 spectrometers and referenced to Freon-11. Mass spectra were recorded on Finnigan MAT90 device using EI ionization (70 eV). IR spectra were taken at Bruker Alpha spectrometer with a diamond ATR module. CHN-analysis was done on varioMICRO cube analyzer. Thin layer chromatography was done on ALUGRAM® Xtra SIL G/UV.

The NMR chemical shifts are given in ppm in the δ scale. The IR bands are in cm^{-1}.

4.2. Difluorocyclopropanation

4.2.1. *Tert*-butyl 6,6-difluoro-2-azabicyclo[3.1.0]hexane-2-carboxylate (**13**)

Anhydrous toluene (150 ml), N-Boc 2-pyrroline (1.5 g; 8.9 mmol) and anhydrous lithium fluoride (23 mg; 0.88 mmol) were mixed under argon, and the mixture was heated to reflux. After 30 min TFDA (3.88 g; 15.5 mmol) in toluene solution (10 ml mixture volume) was added by 1 ml portions to the reaction mixture over 140 min, while reflux was continued. The reaction mixture was refluxed for additional 5 h. The solvent was removed under reduced pressure and resulting crude material was purified on a silica

gel column using hexane – ethyl acetate 2:1 mixture as an eluent (R_f = 0.4). 1.01 g of the product was obtained as orange oil (yield 52 %).

^{1}H NMR ($CDCl_3$, 500 MHz), Boc-rotamers (ratio 3:2): 3.86 and 3.71 (br m, 1H, N-CH) 3.68 (br m, 1H, N-C<u>H</u>H), 3.28 and 3.15 (two br m, 1H, N-CH<u>H</u>), 2.19 (m, 3H, CH-CH_2), 1.45 (s, 9H, CH_3). ^{13}C NMR ($CDCl_3$, 126 MHz), Boc-rotamers: 154.3 (s, C=O), 111.9 (dd, *J* = 293 and 302 Hz, CF_2), 80.0 (s, CMe_3), 46.6 (br s, major) and 46.0 (br s, minor, N-CH_2), 41.4 (dd, *J* = 11 and 15 Hz, N-CH), 27.9 (s, CH_3), 26.7 (m, major) and 25.3 (m, minor, CH), 22.9 (s, minor) and 22.2 (s, major, CH_2). ^{19}F NMR ($CDCl_3$, 376 MHz), Boc-rotamers: -128.9 (dd, $J_{F\text{-}F}$ = 161, $J_{F\text{-}H}$ = 11 Hz, major) and -129.3 (dm, $J_{F\text{-}F}$ = 160 Hz, minor, *exo*-F), -153.9 (d, $J_{F\text{-}F}$ = 160 Hz, minor) and -154.4 (d, $J_{F\text{-}F}$ = 161 Hz, major, *endo*-F). IR: 3076, 2974, 1683. Mass-spectrum (m/z): 200, 164 [M-^{t}Bu+1]. CHN (found/calc.): 54.40/54.79 C, 6.86/6.90 H, 6.42/6.39 N.

4.2.2. *Tert*-butyl 7,7-difluoro-2-azabicyclo[4.1.0]heptane-2-carboxylate (**14**)

Solution of N-Boc 2,3-dehydropyrrolidine (1.5 g, 8.1 mmol) in anhydrous diglyme (100 ml) under argon was heated to reflux in an oil bath (175-180°C in bath). Suspension of ClF_2CCO_2Na (12.5g, 82 mmol) in anhydrous diglyme (40 ml) was added to the reaction mixture over 25 min upon stirring. After 10 min the bath was removed and the mixture was allowed to cool down to ambient temperature. The solvent was removed under reduced pressure and resulting crude material was purified on a silica gel column using hexane – diethyl ether 2:1 mixture as an eluent (Rf = 0.5). 1.39 g of the product was obtained as a pale yellow oil (yield 73 %).

^{1}H NMR ($CDCl_3$, 400 MHz), Boc-rotamers (ratio 4:1): 3.78 (dt, *J* = 13 and 4 Hz, major) and 3.54 (dt, *J* = 13 and 5 Hz, minor, 1H, N-C<u>H</u>H), 3.22 (dd, *J* = 8 and 11 Hz) and 3.12 (ddd, *J* = 2, 8 and 10 Hz, major, 1H, N-CH), 2.67 (tm, *J* = 11 Hz, minor) and 2.48 (ddt, *J* = 11, 13 and 2 Hz, major, 1H, N-CH<u>H</u>), 1.81-1.62 (m, 3H, C<u>H</u>-CH_2-C<u>H_2</u>-CH_2-N), 1.54-1.37 (m, 2H, CH-C<u>H_2</u>), 1.41 (s, 9H). ^{13}C NMR ($CDCl_3$, 101 MHz), Boc-rotamers: 156.0 (s, C=O), 111.2 (dd, *J* = 286 and 290 Hz, CF_2), 80.3 (s, minor) and 80.2 (s, major, CMe_3), 41.2 (s, minor) and 39.6 (d, *J* = 2 Hz, major, N-CH_2), 33.1 (dd, *J* = 10 and 16 Hz, N-CH),

28.3 (s, minor) and 28.2 (s, major, CH_3), 22.0 (m, minor) and 21.8 (t, J = 2 Hz, major, $\underline{C}H_2$-CH_2-N), 19.9 (t, J = 11 Hz, major) and 19.6 (m, minor, CH), 14.8 (s, major) and 14.7 (s, minor, CH-$\underline{C}H_2$). ^{19}F NMR ($CDCl_3$, 376 MHz), Boc-rotamers: -131.5 (ddd, $J_{F\text{-}F}$ = 163, $J_{F\text{-}H}$ = 12 and 8 Hz, minor) and -132.0 (ddd, $J_{F\text{-}F}$ = 163, $J_{F\text{-}H}$ = 13 and 8 Hz, major, *exo*-F), -153.7 (d, $J_{F\text{-}F}$ = 163 Hz, major) and -154.4 (d, $J_{F\text{-}F}$ = 163 Hz, minor, *endo*-F). IR: 2976, 2940, 2870, 1699. Mass-spectrum (m/z): 134 $[M]^+$, 114. CHN (found/calc.): 56.40/56.64 C, 7.12/7.35 H, 5.91/6.00 N.

4.2.3. *Tert*-butyl 8,8-difluoro-2-azabicyclo[5.1.0]octane-2-carboxylate (**15**)

Anhydrous toluene (150 ml), N-Boc 2,3-dehydroazepane (2.56 g, 13.0 mmol) and lithium fluoride (17 mg, 0.65 mmol) were mixed under argon, and the mixture was heated to reflux. After 30 min TFDA (5.18 g, 20.7 mmol) in toluene solution (10 ml mixture volume) was added to the stirred refluxed mixture by 1 ml portions over 100 min. The mixture was refluxed for additional 4 h. The solvent was removed under reduced pressure and the residue was purified on a silica gel column using hexane – ethyl acetate 4:1 mixture as an eluent (R_f = 0.35). 2.07 g of the product was obtained as colorless oil, which then crystallized as white crystals (yield 64 %).

2,3-dehydroazepane (1.5 g; 7.6 mmol) was dissolved in anhydrous diglyme (75 ml) under argon atmosphere, and the mixture was heated to reflux by an oil bath (175-180°C in bath). Suspension of ClF_2CCO_2Na (11.6 g, 76 mmol) in anhydrous diglyme (40 ml) was added to the reaction mixture over 1 h upon stirring. After 15 min the bath was removed and the mixture was allowed to cool down to ambient temperature. The solvent was removed under reduced pressure and the residue was purified on a silica gel column using hexane – diethyl ether 9:1 mixture as an eluent (R_f = 0.3). 0.68 g of the product was obtained as a yellow oil (yield 36 %).

^{1}H NMR ($CDCl_3$, 500 MHz): 3.95 (d, J = 13 Hz, 1H, N-C$\underline{H}$H), 2.93 (dd, J = 10 and 13 Hz, 1H, N-CH), 2.79 (t, J = 12 Hz, 1H, N-CH$\underline{H}$), 1.99 (m, 1H, C$\underline{H}$H), 1.80-1.64 (m, 3H, C$\underline{H}$H, C$\underline{H}$H and CH), 1.54-1.36 (m, 3H, CH$\underline{H}$, CH$\underline{H}$ and CH$\underline{H}$), 1.42 (s, 9H). ^{13}C NMR ($CDCl_3$, 126 MHz): 155.9 (s, C=O), 111.4 (t, J

= 287 Hz, CF_2), 79.7 (s, CMe_3), 49.1 (s, N-CH_2), 39.5 (dd, *J* = 15 and 8 Hz, N-CH), 30.1 (s, CH_2), 27.6 (s, CH_3), 26.9 (d, *J* = 2 Hz, CH_2), 26.4 (t, *J* = 8 Hz, CH), 21.6 (d, *J* = 5 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz), Boc-rotamers (ratio 8:1): -127.7 (dm, J_{F-F} = 163 Hz, minor) and -128.5 (dm, J_{F-F} = 160 Hz, J_{F-H} = 11 Hz, major, *exo*-F), -149.9 (d, J_{F-F} = 160 Hz, major) and -150.6 (d, J_{F-F} = 163 Hz, minor, *endo*-F). IR: 2978, 2933, 2868, 1702. Mass-spectrum (m/z): 248 $[M]^+$, 192 $[M-^tBu]^+$, 178. CHN (found/calc.): 58.55/58.29 C, 7.87/7.74 H, 5.55/5.66 N. The substance crystallized spontaneously, further these crystals were used for the X-ray analysis. T_m = 32 °C.

4.3. Deprotection and free amines

4.3.1. 6,6-Difluoro-2-azoniabicyclo[3.1.0]hexane fluoroacetate (**10***TFA)

To **13** (162 mg; 0.74 mmol) dichloromethane (2 ml) and trifluoroacetic acid (0.5 ml) were added upon stirring. After 1 h the volatilities were blown off by argon current over 40 min. The product was obtained as red oil. The substance contained variable amounts of TFA in complex and was first assigned as difluoroacetate (based upon ^{19}F NMR integrals and the weight). Therefore it was not possible to obtain the exact yield and the latter was assumed as being quantitative.

^{1}H NMR (D_2O, 500 MHz): 3.78 (t, *J* = 9 Hz, 1H, N-CH), 3.49 (m, 1H, N-C<u>H</u>H), 3.10 (m, 1H, N-CH<u>H</u>), 2.65 (m, 1H, CH), 2.32 (m, 2H, CH_2). ^{13}C NMR (D_2O, 126 MHz): 162.2 (q, *J* = 37 Hz, C=O), 115.7 (q, *J* = 293 Hz, CF_3), 109.9 (dd, *J* = 283 and 296 Hz, CF_2), 45.6 (d, *J* = 11 Hz, N-CH_2), 39.5 (dd, *J* = 11 and 18 Hz, N-CH), 27.5 (t, *J* = 11 Hz, CH), 23.1 (s, CH_2). ^{19}F NMR (D_2O, 376 MHz): -74.2 (s, CF_3), -126.8 (dt, J_{F-F} = 178 Hz, J_{F-H} = 11 Hz, 1F, *exo*-F), -147.3 (d, J_{F-F} = 178 Hz, 1F, *endo*-F). Half-life time in chloroform 3 days.

4.3.2. 7,7-Difluoro-2-azoniabicyclo[4.1.0]heptane fluoroacetate (**11***TFA)

Was obtained in analogous procedure as yellow oil starting from **14**.

^{1}H NMR (D_2O, 500 MHz): 3.34 (t, *J* = 10 Hz, 1H, N-CH), 3.03 (m, 1H, N-C<u>H</u>H), 2.84 (t, *J* = 11 Hz, 1H, N-CH<u>H</u>), 2.14 (m, 1H, CH), 1.87 (m, 2H, CH_2-C<u>H</u>$_2$-CH_2), 1.64 (m, 1H, C<u>H</u>H-CH), 1.51 (m, 1H, CH<u>H</u>-CH). ^{13}C NMR (D_2O, 126 MHz): 162.8 (q, *J* = 36 Hz, C=O), 116.2 (q, *J* = 291 Hz, CF_3), 109.9 (dd, *J* = 284 and 292 Hz, CF_2), 40.8 (s, N-CH_2), 29.7 (dd, *J* = 9 and 16 Hz, N-CH), 17.7 (t, *J* = 11 Hz, CH), 16.7 (dd, *J* = 2 and 3 Hz, CH_2), 12.1 (d, *J* = 2 Hz, CH_2). ^{13}C NMR ($CDCl_3$, 101 MHz): 161.2 (q, *J* = 36 Hz, C=O), 115.0 (q, *J* = 290 Hz, CF_3), 108.7 (dd, *J* = 285 and 295 Hz, CF_2), 41.7 (s, N-CH_2), 30.3 (dd, *J* = 9 and 16 Hz, N-CH), 17.9 (t, *J* = 11 Hz, CH), 17.2 (s, CH_2), 12.7 (s, CH_2). ^{19}F NMR (D_2O, 376 MHz): -73.7 (s, CF_3), -128.3 (dt, $J_{F\text{-}F}$ = 174 Hz, $J_{F\text{-}H}$ = 12 Hz, 1F, *exo*-F), -146.8 (d, $J_{F\text{-}F}$ = 173 Hz, 1F, *endo*-F). IR: 3300-2150 broad, 1779, 1662, 1617. Mass-spectrum (m/z): 134 [M^+].

4.3.3. 8,8-Difluoro-2-azabicyclo[5.1.0]octane difluoroacetate (**12***TFA)

Was obtained in analogous procedure as white oil starting from **15**.

^{1}H NMR (D_2O, 500 MHz): 3.48 (d, *J* = 13 Hz, 1H, N-C<u>H</u>H), 3.44 (t, *J* = 10 Hz, 1H, N-CH), 3.10 (t, *J* = 13 Hz, 1H, N-CH<u>H</u>), 2.18 (m, 1H, CH), 2.13 (m, 1H), 1.86 (m, 1H), 1.79 (m, 1H), 1.54 (qt, *J* = 12 and 3 Hz, 1H), 1.42 (q, *J* = 13 Hz, 1H), 1.32 (q, *J* = 13 Hz, 1H). ^{13}C NMR ($CDCl_3$, 126 MHz): 161.0 (q, *J* = 39 Hz, C=O), 115.2 (q, *J* = 288 Hz, CF_3), 109.4 (dd, *J* = 286 and 298 Hz, CF_2), 50.8 (s, N-CH_2), 38.7 (dd, *J* = 10 and 15 Hz, N-CH), 27.3 (s, CH_2), 26.6 (s, CH_2), 26.1 (t, *J* = 11 Hz, CH), 21.2 (d, *J* = 4 Hz, CH_2). ^{13}C NMR (D_2O, 126 MHz): 162.3 (q, *J* = 36 Hz, C=O), 115.9 (q, *J* = 291 Hz, CF_3), 110.6 (dd, *J* = 284 and 297 Hz, CF_2), 50.7 (s, N-CH_2), 38.8 (dd, *J* = 9 and 15 Hz, N-CH), 27.3 (s, CH_2), 26.2 (d, *J* = 3 Hz, CH_2), 26.1 (t, *J* = 11 Hz, CH), 21.4 (d, *J* = 5 Hz, CH_2). ^{19}F NMR (D_2O, 376 MHz): -73.7 (s, CF_3), -125.7 (dt, $J_{F\text{-}F}$ = 171 Hz, $J_{F\text{-}H}$ = 12 Hz, 1F, *exo*-F), -147.2 (d, $J_{F\text{-}F}$ = 171 Hz, *endo*-F). IR: 3300-2200 broad, 1779, 1663, 1617. Mass-spectrum (m/z): 147 [$M]^+$, 132, 118, 96.

4.3.4. Procedure towards free amines

Analytical samples of the amines **10**-**12** were prepared as following: a Boc-amine **13**,**14** or **15** (100-105 mg) was dissolved in dichloromethane (2 ml), TFA (0.5 ml) was added and the solution stand at the room temperature (20°C) for 50 min. The volatilities were blown off by argon current for the next 30 min and the residue was diluted with 2 ml of 10% potassium carbonate. The aqueous layer was extracted with deuterochloroform (1x1 ml), resulting organic fraction was dried over sodium sulfate and thereafter transferred into an NMR tube for measurements. The amine **10** exhibited absence of the expected main product, as it has already decomposed before NMR measurements could be conducted.

4.3.5. 7,7-Difluoro-2-azabicyclo[4.1.0]heptane (**11**)

^{1}H NMR ($CDCl_3$, 500 MHz): 2.83 (td, *J* = 2 and 11 Hz, 1H), 2.77 (dt, *J* = 3 and 13 Hz, 1H), 2.37 (m, 1H), 1.92 (m, 1H), 1.80 (m, 1H), 1.55 (m, 1H), 1.46 (m, 1H), 1.28 (m, 1H), 2.0-1.3 (br s, 1H. NH).^{13}C NMR ($CDCl_3$, 126 MHz): 113.3 (t, *J* = 287 Hz, CF_2), 40.8 (s, N-CH_2), 32.8 (t, *J* = 12 Hz, N-CH), 21.7 (s, CH_2), 17.8 (t, *J* = 12 Hz, CH), 14.3 (s, CH_2). ^{19}F NMR ($CDCl_3$, 471 MHz): -128.2 (dt, J_{F-F} = 159 Hz, J_{F-H} = 12 Hz, 1F, *exo*-F), -151.5 (d, J_{F-F} = 160 Hz, 1F, *endo*-F). Half-life time in chloroform 2 days.

4.3.6. 8,8-Difluoro-2-azabicyclo[5.1.0]octane (**12**)

^{1}H NMR ($CDCl_3$, 500 MHz): 3.09 (d, *J* = 13 Hz, 1H), 2.87 (m, 1H), 2.66 (m, 1H), 1.97 (m, 1H), 1.88 (m, 1H), 1.81 (m, 1H), 1.62 (m, 2H), 1.8-1.5 (br s, 1H, NH), 1.43 (m, 2H). ^{13}C NMR ($CDCl_3$, 126 MHz): 114.2 (t, *J* = 290 Hz, CF_2), 50.0 (s, N-CH_2), 42.1 (dd, *J* = 10 and 14 Hz, N-CH), 34.2 (s, CH_2), 28.7 (d, *J* = 2 Hz, CH_2), 28.4 (t, *J* = 9 Hz, CH), 21.9 (d, *J* = 4 Hz, CH_2). ^{19}F NMR ($CDCl_3$, 376 MHz): -125.5 (dt, J_{F-F} = 156 Hz, J_{F-H} = 14 Hz, 1F, *exo*-F), -152.9 (d, J_{F-F} = 156 Hz, 1F, *endo*-F). Half-life time in chloroform 6 days.

4.4. Acylated substances

4.4.1. (7,7-Difluoro-2-azabicyclo[4.1.0]hept-2-yl)(4-fluorophenyl)methanone (**19**)

The *N*-Boc amine **14** (0.23 g; 0.98 mmol) was dissolved in dichloromethane (4 ml) and TFA (1 ml) was added, resulting mixture stand at the room temperature for the next 40 min. Volatilities were blown off by argon current in 10 min. *p*-Fluorobenzoyl chloride (0.24 g; 1.5 mmol) in anhydrous pyridine (5 ml) was added quickly. Resulting reaction mixture was stirred for the next 15 h at the room temperature. Water (30 ml) was added, and the mixture was extracted with dichloromethane (2x80 ml). The organic fractions were washed with 13 % hydrochloric acid (2x50 ml), saturated sodium carbonate solution (2x50 ml), 13 % hydrochloric acid (1x50 ml), water (1x50 ml), dried over sodium sulfate, filtered and concentrated in vacuum. The crude product was purified by silica gel chromatography using hexane – ethyl acetate 2:1 mixture as an eluent (R_f = 0.35). 0.11 g of the product was obtained as white crystals (yield 44 %).

^{1}H NMR ($CDCl_3$, 500 MHz), amide rotamers (ratio 3:1): 7.53 (t, *J* = 6Hz, major) and 7.46 (br m, minor, 2H, *orto*-H), 7.13 (t, *J* = 9 Hz, 2H, *meta*-H), 4.31 (d, *J* = 13 Hz, major), 3.58 (m, minor, 1H, N-C<u>H</u>H), 3.67 (m, minor), 3.15 (t, *J* = 8 Hz, major, N-CH), 2.91 (t, *J* = 11 Hz, minor), 2.73 (t, *J* = 12 Hz, major, 1H, N-CH<u>H</u>), 2.06-1.58 (group of m, 5H, CH-CH_2-CH_2). ^{13}C NMR ($CDCl_3$, 126 MHz), amide rotamers: 172.1 (s, C=O), 163.6 (d, *J* = 250 Hz, CF), 132.0 (s, <u>C</u>-C=O), 129.5 (d, *J* = 8 Hz, <u>C</u>H-C-C=O), 115.5 (d, *J* = 22 Hz, <u>C</u>H-CF), 110.6 (dd, *J* = 287 and 293 Hz, CF_2), 44.8 (s, minor) and 39.5 (s, major, N-CH_2), 35.8 (dd, *J* = 9 and 16 Hz, major) and 33.4 (m, minor, N-CH), 21.2 (s, CH_2), 20.2 (t, *J* = 11 Hz, CH), 15.0 (s, CH_2). ^{19}F NMR ($CDCl_3$, 471 MHz), amide rotamers (ratio 3:1): -109.85 (m, major) and -109.93 (br m, minor, 1F, CF), -129.9 (dm, J_{F-F} = 166 Hz, minor), -130.9 (dm, J_{F-F} = 166 Hz, major, 1F, *exo*-F), -150.5 (d, J_{F-F} = 166 Hz, major), -152.2 (d, J_{F-F} = 166 Hz, minor, 1F, *endo*-F). IR: 3052, 2926, 1619, 1600, 1592, 1513. Mass-spectrum (m/z): 256 $[M+1]^+$, 214. CHN (found/calc.): 61.53/61.17 C, 5.02/4.74 H, 5.33/5.49 N. The crystals for the X-ray analysis were obtained by crystallization from dichloromethane. T_m = 108 °C.

4.4.2. (8,8-Difluoro-2-azabicyclo[5.1.0]oct-2-yl)(4-fluorophenyl)methanone (**20**)

Was obtained in analogous procedure to **19**. Chromatographic purification was not necessary. 0.25 g of the product was obtained starting from **15** (0.29 g; 1.17 mmol) as yellowish crystals (yield 79 %).

^{1}H NMR ($CDCl_3$, 500 MHz): 7.57 (dd, *J* = 5.5 and 8.2 Hz, 2H), 7.08 (t, *J* = 8.5 Hz, 2H), 4.33 (br, 1H, N-CHH), 3.39 (br, 1H, N-CH), 3.00 (t, *J* = 13 Hz, 1H, N-CHH), 2.09 (br, 1H, CH-CHH), 1.89 (m, 2H, N-CH_2-CH_2-CHH and N-CH_2-CHH), 1.82 (m, 1H, CH), 1.72 (m, 1H, N-CH_2-CH_2-CHH), 1.51 (br, 2H, N-CH_2-CHH and CH-CHH). ^{13}C NMR ($CDCl_3$, 126 MHz): 163.4 (d, *J* = 250 Hz, CF), 131.5 (s, C-C=O), 129.8 (d, *J* = 9 Hz, CH-C-C=O), 114.5 (d, *J* = 22 Hz, CH-CF), 111.1 (t, *J* = 288 Hz, CF_2), 50.8 (br, N-CH_2), 41.9 (br, N-CH), 30.1 (br, CH-CH_2-CH_2), 27.4 (br, CH), 26.9 (s, N-CH_2-CH_2), 21.9 (d, *J* = 5 Hz, CH-CH_2). ^{19}F NMR ($CDCl_3$, 376 MHz), amide-rotamers (ratio 3:1): -110.1 (s, 1F, CF), -125.8 (major, d, *J* ~ 156 Hz) and -128.2 (minor, br, 1F, *exo*-F), -145.1 (major, br d, *J* ~ 162 Hz) and -151.5 (minor, br, 1F, *endo*-F). IR: 3069, 2940, 2866, 1708, 1646, 1601, 1510 . Mass-spectrum (m/z): 270 $[M+1]^+$. CHN: 62.67/62.45 C, 5.35/5.24 H, 4.98/5.20 N. The substance crystals obtained from the synthesis were suitable for X-ray structure analysis. T_m = 68 °C.

4.4.3. (4-Fluorophenyl)(piperidin-1-yl)methanone (**21**)

Piperidine (0.5 g; 5.9 mmol) was diluted in the mixture of pyridine (5 ml) with *p*-fluorobenzoyl chloride (0.98 g; 6.2 mmol). Resulting mixture was stirred at the room temperature for 12 h, then concentrated in vacuum. Water (5 ml) was added and the mixture was extracted with dichloromethane (2x10 ml). The combined organic extracts were washed with hydrochloric acid (2M, 1x5 ml), water (1x5 ml) and saturated sodium hydrogencarbonate solution (1x5 ml), dried over sodium sulfate and concentrated under reduced pressure to give 0.85 g of **16** (70 % yield) as white solid.

NMR data for the obtained substance was consistent with the literature [45].

^{1}H NMR ($CDCl_3$, 500 MHz): 7.39 (m, 2H), 7.06 (t, *J* = 8.5 Hz, 2H), 3.68 (br s, 2H), 3.34 (br s, 2H), 1.69-1.48 (br m, 6H). ^{13}C NMR ($CDCl_3$, 126 MHz): 169.0 (s, C=O), 162.8 (d, *J* = 249 Hz, CF), 132.1 (d, *J* = 4 Hz, C-C=O), 128.7 (d, *J* = 8 Hz, CH-C-C=O), 115.0 (d, *J* = 22 Hz, CH-CF), 48.4 (br s), 42.9 (br s),

26.1 and 25.2 (br s), 24.1 (s). ^{19}F NMR ($CDCl_3$, 376 MHz): -111.5 (m, 1F, CF). IR: 2950, 2930, 2855, 1634, 1602, 1504. Mass-spectrum (m/z): 208 [M+1]. CHN: 69.71/69.55 C, 7.08/6.81 H, 6.70/6.76 N. T_m = 63 °C.

4.4.4. Azepan-4-yl(4-fluorophenyl)methanone (**22**)

Was synthesized in analogous procedure to **21** starting from azepane (0.5 g; 5.1 mmol). 0.71 g of **22** (64 % yield) was obtained as yellowish oil.

^{1}H NMR ($CDCl_3$, 400 MHz): 7.35 (m, 2H), 7.04 (t, *J* = 8.6 Hz, 2H), 3.63 (m, 2H), 3.34 (m, 2H), 1.84-1.53 (m, 8H). ^{13}C NMR ($CDCl_3$, 126 MHz): 170.3 (s, C=O), 162.6 (d, *J* = 249 Hz, CF), 133.0 (d, *J* = 4 Hz, C-C=O), 128.3 (d, *J* = 8 Hz, CH-C-C=O), 115.0 (d, *J* = 22 Hz, CH-CF), 49.4 (s), 46.0 (s), 29.1 (s), 27.4 (s), 26.8 (s), 26.0 (s). ^{19}F NMR ($CDCl_3$, 376 MHz): -111.9 (m, 1F, CF). IR: 2928, 2856, 1628, 1604, 1509. Mass-spectrum (m/z): 222 [M+1]. CHN: 70.74/70.56 C, 7.03/7.29 H, 6.22/6.33 N.

Supporting Information

Experimental procedures, substance characterization details, copies of the NMR spectra, details on rotation rates determination, decomposition kinetics, fragmentation products NMR analysis and ADME parameters.

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References

1 a) M. E. Welsch, S. A. Snyder, B. R. Stockwell, Curr. Opin. Chem. Biol. 14 (2010) 347-361. DOI: 10.1016/j.cbpa.2010.02.018; b) M. Hartenfeller, M. Eberle, P. Meier, C. Nieto-Oberhuber, K.-H. Altmann, G. Schneider, E. Jacoby, S. Renner, J. Chem. Inf. Model. 52 (2012) 1167-1178. DOI: 10.1021/ci200618n.

2 E. Kleinpeter, J. Mol. Struct. 380 (1996) 139-156. DOI: 10.1016/0022-2860(95)09188-2.

3 T. Fink, J.-L. Reymond, J. Chen. Inf. Model. 47 (2007) 342-353. DOI: 10.1021/ci600423u.

4 J. Zhou, E. L. Campbell-Conroy, A. Silina, J. Uy, F. Pierre, D. J. Hurley, N. Hilgraf, B. A. Frieman, M. P. DeNinno, J. Org. Chem. 80 (2015), 70-79. DOI: 10.1021/jo501967m.

5 Either naturally occurring: a) A. b. Mauger, J. Nat. Prod. 59 (1996) 1205-1211. DOI: 10.1021/np9603479; b) T. M. H. Bach, H. Tagaki, Appl. Microbiol. Biotechnol. 97 (2013) 6623-6634. DOI: 10.1007/s00253-013-5022-7; or synthetic: c) M. I. Calaza, C. Cativiela, Eur. J. Org. Chem. (2008) 3427-3448. DOI: 10.1002/ejoc.200800225; d) A. N. Tkachenko, D. S. Radchenko, P. K. Mykhailiuk, O. O. Grygorenko, I. V. Komarov, Org. Lett. 11 (2009), 5674-5676. DOI: 10.1021/ol902381w; e) V. S. Kubyshkin, P. K. Mykhailiuk, A. S. Ulrich, I. V. Komarov, Synthesis (2009) 3327-3331. DOI: 10.1055/s-0029-1216963.

6 a) V. S. Yarmolchuk, P. K. Mykhailiuk, I. V. Komarov, Tetrahedron Lett. 52 (2011) 1300-1302. DOI: 10.1016/j.tetlet.2011.01.070; b) A. V. Tymtsunik, Y. M. Ivon, I. V. Komarov, O. O. Grygorenko, Tetrahedron. Lett. 55 (2014) 3312-3315. DOI: 10.1016/j.tetlet.2014.04.038.

7 D. Dietz, V. Kubyshkin, N. Budisa, ChemBioChem 16 (2015) 403-406. DOI: 10.1002/cbic.201402654.

8 M. D. Shoulders, R. T. Raines, Annu. Rev. Biochem. 78 (2009) 928-958. DOI: 10.1146/annurev.biochem.77.032207.120833.

9 a) X. Yu, W. Wang, Org. Biomol. Chem. 6 (2008) 2037-2046. DOI: 10.1039/B800245M; b) C-Y. Ho, Y.-C. Chen, M.-K. Wong, D. Yang, J. Org. Chem. 70 (2005) 898-906. DOI: 10.1021/jo048378t.

10 a) S. Hanessian, Z. Shao, J. S. Warrier, Org. Lett. 8 (2006), 4787-4790. DOI: 10.1021/ol0618407; b) P. H.-Y. Cheong, K. N. Houk, J. S. Warrier, S. Hanessian, Adv. Synth. Catal. 346 (2004) 1111-1115. DOI: 10.1002/adsc.200404127; c) H. Yu, M. Liu, S. Hang, Tetrahedron 70 (2014) 8380-8384. DOI: 10.1016/j.tet.2014.08.069.

11 For example, see: a) M. Watanabe, T. Kobayashi, T. Hirokawa, A. Yoshida, Y. Ito, S. Yamada, N. Orimoto, Y. Yamasaki, M. Arisawa, S. Shuto, Org. Biomol. Chem. 10 (2012) 736-745. DOI: 10.1039/C1OB06496G; b) A. Reichelt, S. F. Martin, Acc. Chem. Res. 39 (2006) 433-442. DOI: 10.1021/ar030255s; c) H. Zhang, W. Tückmantel, J. B. Eaton, P.-w. Yen, L.-F. Yu, K. M. Bajjuri, A. Fedolak, D. Wang, A. Ghavami, B. Caldarone, N. E. Paterson, D. A. Lowe, D. Brunner, R. J. Lukas, A. P. Kozikowski, J. Med. Chem. 55 (2012) 717-724. DOI: 10.1021/jm201157c.

12 S. F. Martin, Pure Appl. Chem. 79 (2007) 193-200. DOI: 10.1351/pac200779020193.

13 G.-D. Tebben, K. Rauch, C. Stratmann, C. M. Williams, A. de Meijere, Org. Lett. 5 (2003) 483-485. DOI: 10.1021/ol027352q.

14 H. Lebel, J.-F. Marcoux, C. Molinaro, A. B. Charette, Chem. Rev. 103 (2003) 977-1050. DOI: 10.1021/cr010007e.

15 C. Ni, J. Hu, Synthesis (2014) 842-863. DOI: 10.1055/s-0033-1340856.

16 For recent ones, see: a) L. Li, F. Wang, C. Ni, J. Hu, Angew. Chem. 125 (2013) 12616-12620. DOI: 10.1002/ange.201306703; b)D.M. Gill, N. McLay, M. J. Waring, C. T. Wilkinson, J. B. Sweeney, Synlett (2014), 1756-1758. DOI: 10.1055/s-0033-1341155.

17 a) M. Kirihara, T. Takuwa, M. Kawasaki, H. Kakuda, S.-i. Hirokami, H. Takahata, Chem. Lett. 28 (1999) 405-406. DOI: 10.1246/cl.1999.405; b) M. Kirihara, M. Kawasaki, T. Takuwa, H. Kakuda, T. Wakikawa, Y. Takeuchi, K. L. Kirk, Tetrahedron: Asymmetry 14 (2003) 1753-1761. DOI: 10.1016/S0957-4166(03)00350-1.

18 I. Nowak, J. F. Cannon, M. J. Robins, Org. Lett. 6 (2004) 4767-4770. DOI: 10.1021/ol047943b.

19 I. V. Voznyi, M. S. Novikov, A. F. Khlebnikov, Synlett (2005) 1006-1008. DOI: 10.1055/s-2005-864820.

20 X.-C. Hang, Q.-Y. Chen, J.-C. Xiao, J. Org. Chem. 73 (2008) 8598-8600. DOI: 10.1021/jo801610t.

21 V. S. Kubyshkin, P. K. Mykhailiuk, S. Afonin, A. S. Ulrich, I. V. Komarov, Org. Lett. 14 (2012) 5254-5257. DOI: 10.1021/ol302412a.

22 V. S. Kubyshkin, P. K. Mykhailiuk, S. Afonin, S. L. Grage, I. V. Komarov, A. S. Ulrich, J. Fluorine Chem. 152 (2013) 136-143. DOI: 10.1016/j.jfluchem.2013.03.002.

23 a) I. Nowak, M. J. Robinson, J. Org. Chem. 72 (2007) 3319-3325; b) I. Nowak, J. F. Cannon, M. J. Robins, J. Org. Chem. 72 (2007) 532-537. DOI: 10.1021/jo061965p.

24 Y. Kageshima, C. Suzuki, K. Oshiro, H. Amii, Synlett (2015) 63-66. DOI: 10.1055/s-0034-1379599.

25 M. D. Kosobokov, V. V. Levin, M. I. Struchkova, A. D. Dilman, Org. Lett. 17 (2015) 760-763. DOI: 10.1021/acs.orglett.5b00097.

26 a) T. Taguchi, M. Okada, J. Fluorine Chem. 105 (2000) 279-283. DOI: 10.1016/S0022-1139(99)00272-9; b) W. R. Dolbier, Jr., M. A. Battiste, Chem. Rev. 103 (2003) 1071-1098. DOI: 10.1021/cr010023b.

27 M. Fedoryńsky, Chem. Rev. 103 (2003) 1099-1132. DOI: 10.1021/cr0100087.

28 J. Yu, V. Truc, P. Riebel, E. Hierl, B. Mudruk, Tetrahedron Lett. 46 (2005) 4011-4013. DOI: 10.1016/j.tetlet.2005.04.030.

29 J. M. Birchall, G. E. Cross, R. N. Haszeldine, Proc. Chem. Soc. (1960) 81. DOI: 10.1039/PS9600000037.

30 For typical procedures see a) P. Crabbe, A. Cervantes, A. Cruz, E. Galeazzi, J. Iriarte, E. Velarde, J. Am. Chem. Soc. 95 (1973) 6655-6665. DOI: 10.1021/ja00801a022; b) Y. Kobayashi, T. Taguchi, M. Mamada, H. Shimizu, H. Murohashi, Chem. Pharm. Bull. 27 (1979) 3123-3129. DOI: 10.1248/cpb.27.3123; For the use of F_3CCO_2Na decomposition for difluorocyclopropanation see c) Y. Chang, C. Cai, Chem. Lett. 34 (2005) 1440-1441. DOI: 10.1246/cl.2005.1440.

31 For example, dipeptide scaffolds required more difluorocarbene (25 eq.) for full conversion of the starting material. See Ref. 21, 22.

32 a) F. Tian, V. Kruger, O. Bautista, J.-X. Duan, A.-R. Li, W. R. Dolbier, , Jr. Q.-Y. Chen, Org. Lett. 2 (2000) 563-564. DOI: 10.1021/ol0055622; b) W. R. Dolbier, Jr., F. Tian, J.-X. Duan, A.-R. Li, S. Ait-Mohand, O. Bautista, S. Buathong, J. M. Baker, J. Crawford, P. Anselme, X. H. Cai, A. Modzelewska, H. Koroniak, M. A. Battiste, Q.-Y. Chen, J. Fluorine Chem. 125 (2004) 459-469. DOI: 10.1016/j.jfluchem.2003.12.002.

33 For **11** and **12** pK_a values predicted in MarinSketch 5.12 (ChemAxon Ltd.): 6.5 and 6.8 respectively.

34 A. V. Shcherbatiuk, O. S. Shishlyk, D. V. Yarmoliuk, O. V. Shishkin, S. V. Shishkina, V. S. Starova, O. A. Zaporozhets, S. Zozulya, R. Moriev, O. Kravchuk, O. Manoilenko, A. A. Tolmachev, P. K. Mykhailiuk, Tetrahedron 69 (2013) 3796-3804. DOI: 10.1016/j.tet.2013.03.067.

35 Á. C. Neto, F. P. dos Santos, R. H. Contreras, R. Rittner, C. F. Tormena, J. Phys. Chem. A 112 (2008) 11956-11959. DOI: 10.1021/jp8069805.

36 V. Barone, P. F. Provasi, J. E. Peralta, J. P. Snyder, S. P. A. Sauer, R. H. Countreras, J. Phys. Chem. A 107 (2003) 4748-4754. DOI: 10.1021/jp0300851.

37 K. Hirao, H. Nakatsuji, H. Kato, J. Am. Chem. Soc. 95 (1973) 31-41. DOI: 10.1021/ja00782a006.

38 D. A. Smith, B. C. Jones, D. K. Walker, Med. Res. Rev. 16 (1996) 243-266.

39 Q. A. Huchet, B. Kuhn, B. Wagner, H. Fischer, M. Kansy, D. Zimmerli, E. M. Carreira, K. Müller, J. Fluorine Chem. 152 (2013) 119-128. DOI: 10.1016/j.jfluchem.2013.02.023.

40 S. Purcer, P. R. Moore, S. Swallow, V. Gouverneur, Chem. Soc. Rev. 37 (2008) 320-330. DOI: 10.1039/B610213C.

41 L. H. Kondejewski, M. Jelokhani-Niaraki, S. W. Farmer, B. Lix, C. M. Kay, B. D. Sykes, R. E. W. Hancock, R. S. Hodges, J. Biol. Chem. 274 (1999) 13181-13192. DOI: 10.1074/jbc.274.19.13181.

42 Deposited as: **15** - CCDC1011966; **19** – CCDC1011965; **20** – CCDC1011967. These data can be obtained free of charge from the Cambridge crystallographic data center via www.ccdc.cam.ac.uk/data_request/cif.

43 As it is in the N-Boc methanoprolines **3**, **4**: S. Hanessian, U. Reinhold, G. Gentile, Angew. Chem. 109 (1997) 1953-1956. DOI: 10.1002/ange.19971091721.

44 For N-4-methylbenzoyl pyrrolidine and piperidine the barriers were reported as 63.7 and 59.2 kJ/mol respectively: E. Buhleier, W. Wehner, F. Vögtle, Chem. Ber. 112 (1979) 559-566. DOI: 10.1002/cber.19791120219.

45 M. Zhu, K.-i. Fujita, R. Yamaguchi, J. Org. Chem. 77 (2012) 9102-9109. DOI: 10.1021/jo301553v.