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Synthesis of functionalized difluorocyclopropanes: unique building blocks for drug discovery

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Pavel K. Mykhailiuk[a,b]*

Abstract: Difluorocyclopropane-containing building blocks for drug discovery were synthesized from the functionalized alkenes and $TMSCF_3$/NaI. Novel fluorinated acids, amines, amino acids, alcohols, ketones and sulfonyl chlorides were obtained.

Introduction

The incorporation of fluorinated units into organic compounds can profoundly change their physico-chemical and biological properties. In particular, incorporation even of a single fluorine atom can significantly increase the bioavailability, metabolic stability and the lipophilicity of the corresponding bioactive molecules. Moreover, up to 20% of all modern marketed drugs and even 30% of all agrochemicals are fluorine-containing organic compounds.[1-3] Fluorine-substituted amino acids have also found another practical application – as ^{19}F-labels in structural and functional studies of peptides.[4,5,6]

Given the high popularity of cyclopropane motif in drugs, it is not surprising therefore that difluorocyclopropane-containing compounds also gained popularity in drug discovery in recent years (Figure 1).[7,8] They also proved to be valuable starting materials in organic synthesis.[9,10]

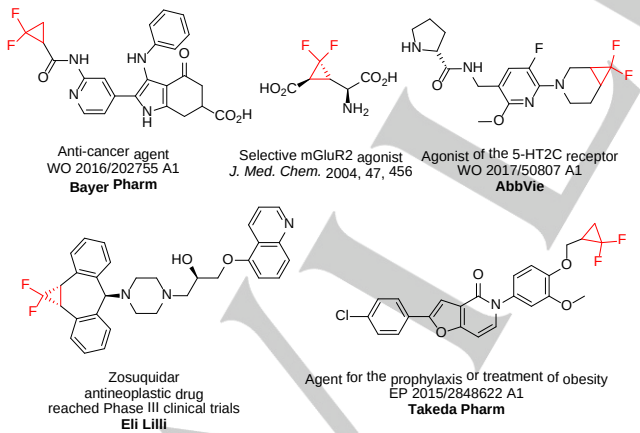

Figure 1. Bioactive compounds with a difluorocyclopropane motif.

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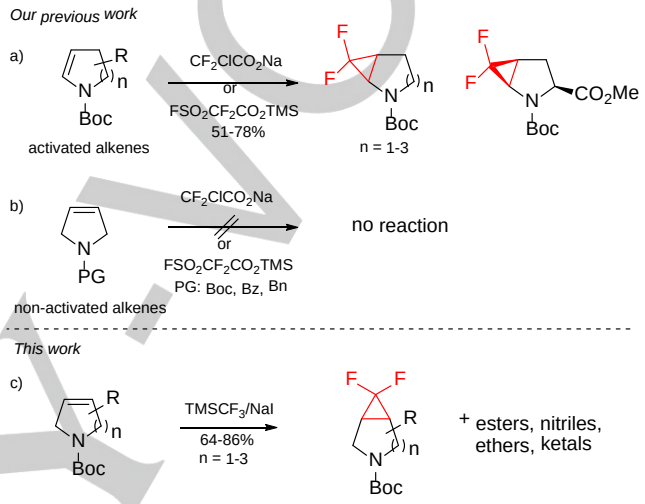
Supporting information for this article is available on the Internet



Scheme 1. Background and historical context of our research.

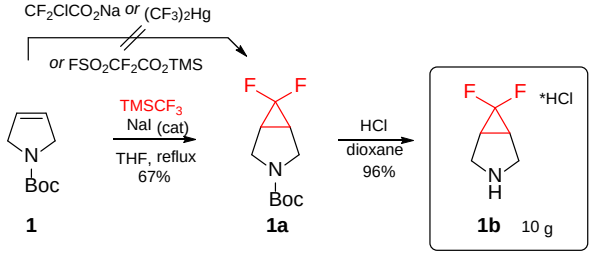
Diverse applications of fluorinated cyclopropanes promoted the development of general methods for their synthesis.[11-17] Recently, we performed the difluorocyclopropanation of cyclic *N*-Boc protected enamides - activated alkenes - with CF_2ClCO_2Na or *Dolbier* reagent ($FSO_2CF_2CO_2TMS$). We used these fluorinated amines as building blocks for drug discovery, and the fluorinated amino acids as ^{19}F-NMR labels for studying peptides (Scheme 1).[6] However, all previous attempts to perform this transformation on non-activated alkenes with the *N*-protected amino group, failed.

In 2011, *Prakash* reported that the combination CF_3TMS/NaI efficiently converted the non-activated alkenes into the *gem*-difluorocyclopropanes.[8] Most of the starting alkenes, however, contained no functional groups. Herein, we used this procedure to convert the functionalized non-activated alkenes - amines, esters, nitriles, ethers and ketals - into the functionalized difluorocyclopropanes: novel building blocks for drug discovery.[18]

Results and Discussion

Optimization. Our previous attempts to perform the difluorocyclopropanation of alkene **1** by reaction with CF_2ClCO_2Na, $(CF_3)_2Hg$ or $FSO_2CF_2CO_2TMS$/LiF failed (Scheme 2). However, following the procedure of *Prakash* - heating a solution of alkene **1**, $TMSCF_3$ (2.5 equiv), and NaI (0.2 equiv) in THF, - product **1a** was obtained in 67% yield. It is worth mentioning that for unclear reasons the reaction did not proceed

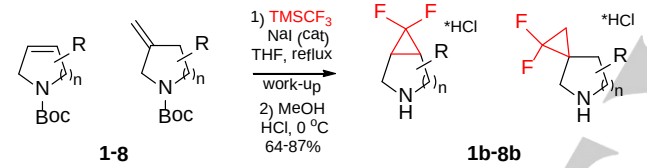
in acetonitrile or dioxane.[8] Cleavage of the *N*-Boc protecting group under the acidic conditions provided the target amine **1b**. The procedure was scalable, as we easily synthesized 10 g of amine **1b** in one run.

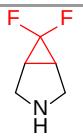
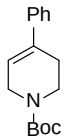
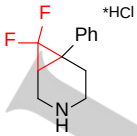
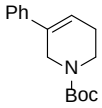
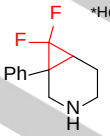
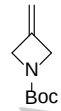
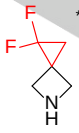
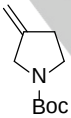
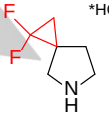
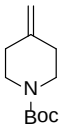
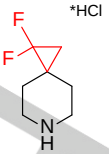
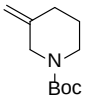
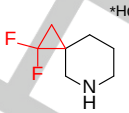
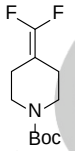
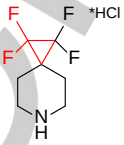


Scheme 2. Optimized synthesis of amine **1b**.

Reaction scope. Carbamates. We next explored the high potential of this procedure to synthesize other secondary fluorinated amines.[19] In fact, all carbamates **1**-**8** smoothly gave the corresponding difluorocyclopropanes **1a-8a** after the work-up (see SI). Acidic *N*-Boc deprotection resulted in the fused amines **1b**-**3b** and the spirocyclic amines **4b**-**8b** in 64-87% isolated yield over two steps (Table 1).

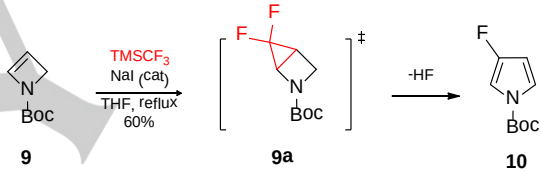
Table 1. Reaction scope. Carbamates.



	Alkene	Product	Yield (%)[a,b]
1		**1b** 	64
2		**2b** 	83
3		**3b** 	86
4		**4b** 	87
5		**5b** 	86
6		**6b** 	83
7		**7b** 	85
8		**8b** 	85

[a] Reaction conditions: (i) $TMSCF_3$ (2.5 equiv), NaI (0.5 equiv), alkene (1 equiv), THF, reflux for 4 h. (ii) alkene, 5M HCl, MeOH, rt, 12h. [b] Isolated yield over two steps.

Unexpectedly, the corresponding reaction of *N*-Boc-protected azetidine **9** gave the monofluoro-substituted pyrrole **10** in 60% yield. The reaction might have proceeded via the ring-opening of the highly strained intermediate **9a** followed by an elimination of HF (Scheme 3).



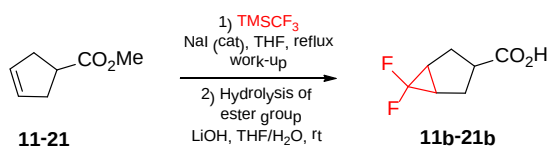
Scheme 3. Unexpected synthesis of pyrrole **10**.

Esters and nitriles. The reported conditions for the difluorocyclopropanation were relatively mild, and compatible with many functional groups: esters, nitriles, ethers and ketals (Table 2, Table 3).

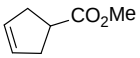
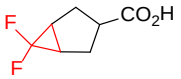
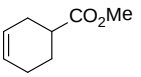
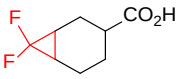
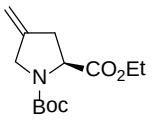
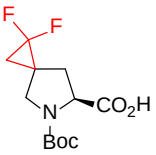
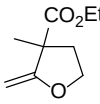
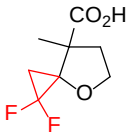
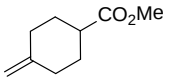
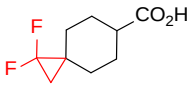
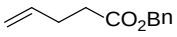
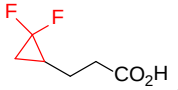
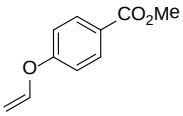
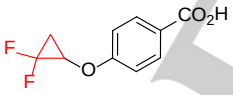
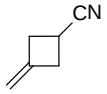
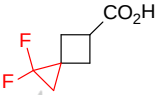
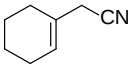
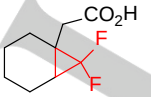
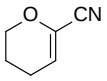
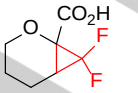
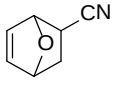
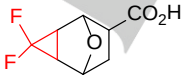
We studied the reaction of esters **11**-**17** and nitriles **18**-**21** with CF_3TMS/NaI (Table 2) to afford the corresponding difluorocyclopropanes. The trisubstituted amine **19** reacted slowly, and the conversion of the reaction reached only 10%. The final carboxylic acids **11b-21b** were synthesized by alkali hydrolysis of nitrile and ester groups in 10-89% combined yield.

Esters, ethers and ketals. Next, we performed the synthesis of alcohols **22b-26b** and ketones **27b**, **28b** with a difluorocyclopropanane moiety. We used an optimized above procedure: heating a mixture of alkene, CF_3TMS and NaI in acetonitrile at reflux for 12 h. After a standard work-up, the intermediate difluorocyclopropane-containing esters, ethers and ketals **11a**-**21a** – were obtained in good to high yields. The second step – hydrolysis of the functional groups – was performed under various conditions. In particular, phenol **22b** was obtained by cleaving the OMe-group in cyclopropane **22a** with BBr_3 at -35 ºC. Alcohols **23b**-**26b** were obtained by basic hydrolysis of the ester group in cyclopropanes **23a**-**26a**. Finally, ketones **27b** and **28b** were synthesized by an acidic cleavage of the ketal moiety in difluorocyclopropanes **27a** and **28a**, correspondingly.

Table 2. Reaction scope. Esters and nitriles.

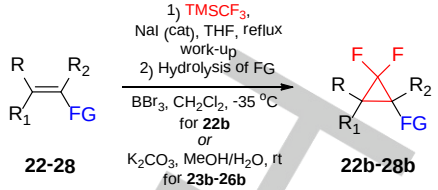


11-21 **11b-21b**

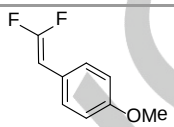
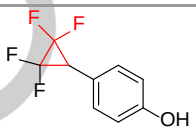
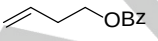
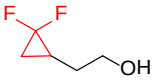
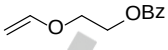
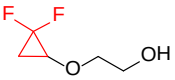
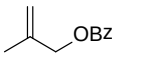
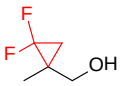
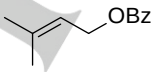
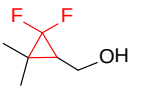
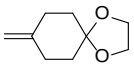
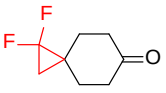
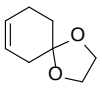
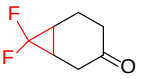
	Alkene	Product	Yield (%)[a,b,c]
11		**11b** 	89 (4:1)
12		**12b** 	87 (1:1)
13		**13b** 	88 (2:1)
14		**14b** 	82 (1:1)
15		**15b** 	87 (3:1)
16		**16b** 	56
17		**17b** 	86
18		**18b** 	75 (2:1)
19		**19b** 	10
20		**20b** 	72
21		**21b** 	12

[a] Reaction conditions: (i) $TMSCF_3$ (2.5 equiv), NaI (0.5 equiv), alkene (1 equiv), THF, reflux for 4 h. (ii) alkene (1 equiv), 1 M LiOH (2 equiv), THF, rt, 12h. [b] Isolated yield over two steps. [c] Diastereomeric ratio according to NMR.

Table 3. Reaction scope. Esters, ethers and ketals.

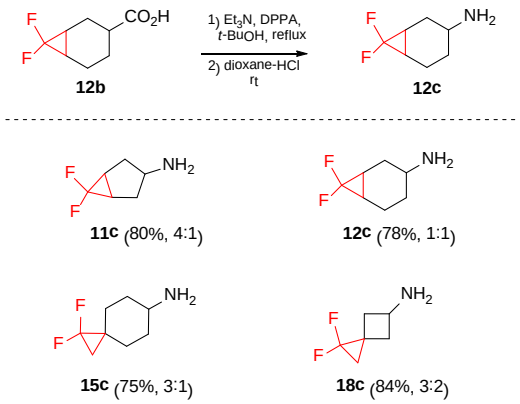


22-28 **22b-28b**

	Alkene	Product	Yield (%)[a,b]
22		**22b** 	35
23		**23b** 	48
24		**24b** 	55
25		**25b** 	76
26		**26b** 	75
27		**27b** 	73
28		**28b** 	88

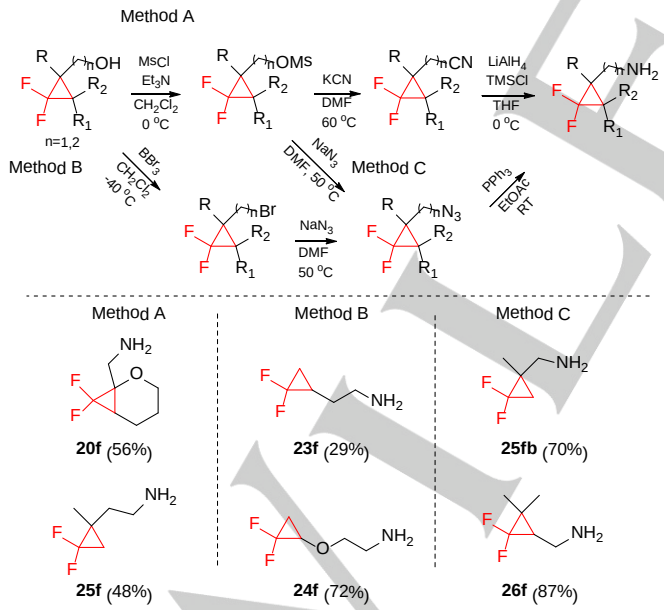
[a] Reaction conditions: (i) $TMSCF_3$ (2.5 equiv), NaI (0.5 equiv), alkene (1 equiv), THF, reflux for 4 h. (ii) Hydrolysis under different conditions. [b] Isolated yield over two steps.

Synthesis of building blocks. Having synthesized the difluorocyclopropyl-containing carboxylic acids (Table 2), we next converted some of them into the corresponding amines by *Curtius* reaction. In particular, compounds **11b**, **12b**, **15b** and **18b** were treated with diphenylphosphoryl azide (DPPA) in the presence of *tert*-butanol. Acidic cleavage of the *N*-Boc group in the intermediate carbamates afforded the target amines **11c**, **12c**, **15c** and **18c** as hydrochlorides in 78-84% combined yield (Scheme 4).



Scheme 4. Synthesis of amines via the *Curtius* rearrangement.

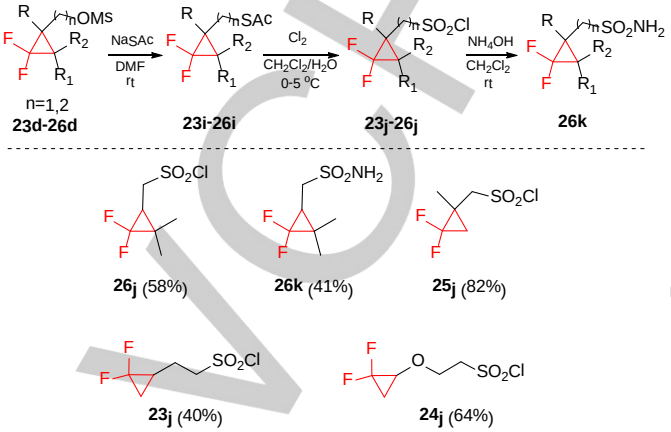
The high synthetic utility of the obtained difluorocyclopropane-containing alcohols (Table 3) was demonstrated by converting some of them into the primary amines (Scheme 5). We used three synthetic strategies (Scheme 5). Method A: the alcohols were converted into mesylates with MsCl, followed by an exchange of the leaving group with KCN in DMF at 60 ºC. The obtained nitriles were treated with *in situ* generated AlH_3 ($LiAlH_4$ + TMSCl) in THF to obtain the desired amines **20f** and **25f**. Method B: alternatively, we converted alcohols into the corresponding bromides with BBr_3. The bromides were next treated with NaN_3 (3 equiv) in DMF at 50 °C. The obtained azides were reduced with PPh_3 into the needed amines **23f** and **24f**. Method C: in this approach, the mesylates were first converted into the azides with NaN_3, followed by a reduction with PPh_3 into the target amines **25fb** and **26f**.



Scheme 5. Synthesis of difluorocyclopropane-containing amines from alcohols.

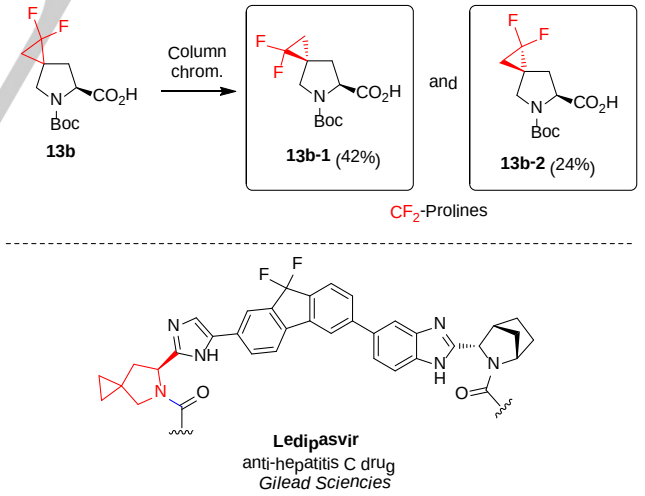
We next expanded our collection of building blocks into sulfonyl chlorides.[20] Reaction of mesylates **23d-26d** with sodium thioacetate in DMF at room temperature gave thioacetates **23i-26i**. Oxidation of **23i-26i** with gaseous chlorine yielded sulfonyl chlorides **23j-26j** in 40-82% overall yield (Scheme 6).

Representative synthesis of sulfonamide **26k** was performed by treating sulfonyl chloride **26j** with aq. ammonia at room temperature (Scheme 6).



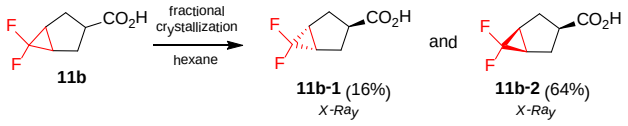
Scheme 6. Synthesis of sulfonyl chlorides and sulfonamides.

Compound **13b** was easily separated into the individual diastereomers **13b-1** and **13b-2** by the standard column chromatography on silicagel. The stereoconfiguration of the isolated compounds was determined by 2D-NMR experiments (SI). These novel fluorinated prolines have a potential for the applications as ^{19}F-labels in peptides studies[21] and building blocks for drug discovery.[22,23] For example, the corresponding none-fluorinated motif comprises to a structure of the anti-hepatitis C drug *Ledipasvir* (Scheme 7).



Scheme 7. Synthesis of fluorine-containing prolines **13b-1** and **13b-2**.

Acid **11b** was efficiently separated into the individual diastereomers **11b-1** and **11b-2** by fractional crystallization from hexane (Scheme 8). The structure of compounds was proven by an *X*-Ray analysis (Figure 2).[24]



Scheme 8. Synthesis of single diastereomers **11b-1** and **11b-2**.

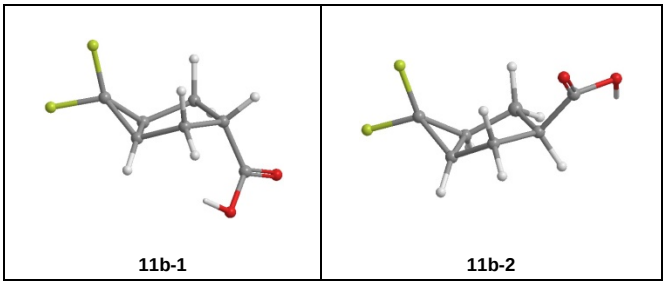
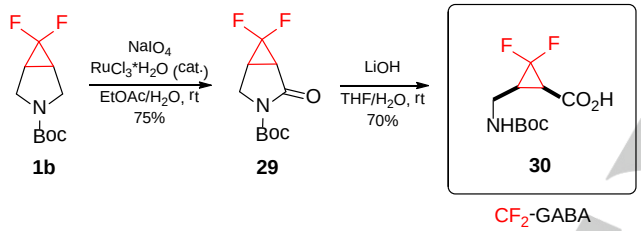


Figure 2. X-Ray crystal structure of acids **11b-1** and **11b-2**.

The C-H bond in the cyclic *N*-Boc-protected amine **1b** was oxidized using a modified procedure from a recent patent.[25] This reaction yielded *γ*-lactam **29**. Base-catalyzed hydrolysis of lactam **29** produced the *N*-Boc protected fluorinated GABA-analogue **30** in 53% overall yield (Scheme 9).



Scheme 9. Synthesis of GABA-analogue **30**.

Conclusions

We synthesized difluorocyclopropane-containing carboxylic acids, ketones, nitriles, alcohols, and amines from the functionalized alkenes and $TMSCF_3$/NaI. We believe that these novel fluorinated building blocks will find soon a wide application in drug discovery projects.

Experimental Section

1. General. All chemicals were provided by Enamine Ltd (www.enamine.net). Autoclaves were provided by UOSLab (en.uoslab.com). All solvents were treated according using standard methods. All reactions were monitored by thin-layer chromatography (TLC) and were visualized using UV light. Product purification was performed using silica gel column chromatography. TLC-characterization was performed with pre-coated silica gel GF254 (0.2 mm), while column chromatography characterization was performed with silica gel (100-200 mesh).^{1}H-NMR, ^{19}F-NMR, ^{13}C-NMR spectra were recorded with tetramethylsilane (TMS, δ = 0.00 ppm) as the internal standard. ^{1}H-NMR spectra were recorded at 400 or 500 MHz (Varian); ^{19}F-NMR spectra were recorded at 376 MHz (Varian), ^{13}C NMR spectra were recorded at 100 or 126 MHz (Varian). ^{1}H-NMR chemical shifts are reported downfield from $CDCl_3$ (δ = 7.26 ppm), D_2O (δ = 4.79 ppm) or DMSO-d_6 (δ = 2.50 ppm). ^{13}C-NMR chemical shifts for ^{13}C-NMR are reported relative to the central $CDCl_3$ (δ = 77.16 ppm) or DMSO-d_6 (δ = 39.52 ppm). Coupling constants are given in Hz. MS analysis was performed on an LCMS instrument with chemical ionization or GCMS with electrospray ionization.

2. General procedure for synthesis of protected difluorocyclopropanes

$TMSCF_3$ (0.25 mol) and NaI (0.05 mol, 0.5 equiv) were added in one portion to a solution containing the appropriate alkene (0.10 mol, 1 equiv) in 200 mL of dry THF (freshly distilled from $LiAlH_4$). The mixture was refluxed for 4 h and monitored by TLC. If the reaction was incomplete after this time, additional $TMSCF_3$ (0.25 mol, 2.5 equiv) was added, and the mixture was heated for 4 h until the starting material was completely consumed. Upon completion of the reaction, the mixture was concentrated under reduced pressure in the following manner: the residue was dissolved in CH_2Cl_2, washed with water, a 0.1 M solution of sodium thiosulfate, brine, dried over Na_2SO_4, filtered, and the solvent was removed under reduced pressure to afford the desired product. In some cases the product required purification by column chromatography (gradient, hexane/MTBE) or distillation.

7,7-Difluoro-6-phenyl-3-azabicyclo[4.1.0]heptane hydrochloride (2b). Yield = 91% (19.1 g). The product is a beige powder, mp 233 ºC. **^{1}H NMR** (400 MHz, DMSO): δ 9.23 (br s, 2H), 7.50 (d, 2H, ^3J = 7.0 Hz, Ph), 7.39 (t, 2H, ^3J = 7.5 Hz, Ph), 7.33 (t, 1H, ^3J = 7.3 Hz, Ph), 3.78 - 7.72 (m, 1H), 3.17 - 3.09 (m, 2H), 2.71 - 2.65 (m, 1H), 2.46 - 2.38 (m, 2H), 2.15 - 2.07 (m, 1H). **^{19}F NMR** (376 MHz, DMSO-d_6): δ -129.6 (dd, $^2J_{FF}$ = 152.1 Hz, $^3J_{FH}$ = 13.5 Hz), -142.6 (d, $^2J_{FF}$ = 152.8 Hz). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 137.6, 128.6, 128.5, 127.7, 113.4 (t, $^1J_{CF}$ = 292.2 Hz, CF_2), 38.0 (d, J_{CF} = 5.1 Hz), 34.9, 29.2 (t, J_{CF} = 10.3 Hz, *C*Ph), 22.7, 19.7 (t, J_{CF} = 10.7 Hz, *C*CF_2). **MS** (APCI) *m/z* [M+H]$^+$ calculated for $C_{12}H_{14}F_2N$: 210.1; found: 210.1. Anal. calcd. for $C_{12}H_{14}ClF_2N$: C, 58.66; H, 5.74; N, 5.70. Found: C, 58.47; H, 5.85; N, 5.58.

3-(2,2-Difluorocyclopropyl)propanoic acid (16b). Yield = 60% (9.0 g) after recrystallization from hexanes. The product is a white solid, mp 36 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.81 (br s, 1H, OH), 2.52 - 2.48 (m, 2H, $CH_2C(O)$), 1.83 – 1.80 (m, 2H, CH_2), 1.65 – 1.57 (m, 1H, CH), 1.46 – 1.39 (m, 1H, C*H*HCF$_2$), 0.99 – 0.95 (m, 1H, CH*H*CF$_2$). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -128.9 (dt, $^2J_{FF}$ = 156.9 Hz, $^3J_{FH}$ = 12.6 Hz), -145.5 (dd, $^2J_{FF}$ = 156.9 Hz, $^3J_{FH}$ = 12.8 Hz). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 179.3 (C=O),, 114.1 (t, $^1J_{CF}$ = 291.8 Hz, CF_2), 33.1, 22.1 (d, J_{CF} = 4.5 Hz), 21.5 (t, $^2J_{CF}$ = 10.8 Hz, *C*CF_2), 16.0 (t, $^2J_{CF}$ = 11.0 Hz, CH_2CF_2). **MS** (APEI) *m/z* [M] calculated for $C_6H_8F_2O_2$: 150.1; found: 150.1. Anal. calcd. for $C_6H_8F_2O_2$: C, 48.00; H, 5.37. Found: C, 48.14; H, 5.20.

2-(2,2-Difluorocyclopropyl)ethane-1-sulfonyl chloride (23j). Yield = 90% (18.4 g). The product is a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.82 – 3.73 (m, 2H, CH_2S), 2.25 – 2.18 (m, 2H), 1.75 – 1.55 (m, 2H, CH, C*H*HCF$_2$), 1.13 – 1.08 (m, 1H, CH*H*CF). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -129.4 (d, $^2J_{FF}$ = 160.9 Hz), -145.1 (d, $^2J_{FF}$ = 159.2 Hz). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 113.1 (dd, $^1J_{CF}$ = 282.1 Hz, $^1J_{CF}$ = 282.1 Hz, CF_2), 64.0 (d, J_{CF} = 2.0 Hz, CH_2S), 22.5 (d, J_{CF} = 5.1 Hz, CH_2C), 19.8 (t, $^2J_{CF}$ = 11.1 Hz, CH), 16.4 (t, $^2J_{CF}$ = 11.1 Hz, CH_2CF_2). **MS** (APEI) *m/z* [M] calculated for $C_5H_7ClF_2O_2S$: 204.0; found: 204.0. Anal. calcd. for $C_5H_7ClF_2O_2S$: C, 29.35; H, 3.45; S, 15.67. Found: C, 29.51; H, 3.24; S, 15.83.

3-(((*tert*-Butoxycarbonyl)amino)methyl)-2,2-difluorocyclopropane-1-carboxylic acid (30). The crude product was dissolved in THF (20 mL) and an aqueous solution of 1 M LiOH (0.2 g, 0.0075 mol, 2 equiv) was added. The resulting solution was stirred overnight. The mixture was partially concentrated under reduced pressure, and washed several times with CH_2Cl_2. The aqueous layer was acidified with a saturated solution of

$NaHSO_4$ and extracted with CH_2Cl_2. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was solidified in hexanes to give the final product as a white powder, mp 117 °C, (1.3 g, 70%). **^{1}H NMR** (400 MHz, DMSO-d_6): δ 12.85 (br s, 1H, OH), 7.07 (br s, 1H, NH), 3.47 – 3.33 (m, 2H, CH_2), 2.65 (t, ^3J = 11.6 Hz, 1H, CH), 2.28 (s, 1H, CH), 1.39 (br s, 9H, *t*-Bu). **^{19}F NMR** (376 MHz, DMSO-d_6): δ -122.1 (d, 1F, $^2J_{FF}$ = 153.6 Hz), -148.9 (d, $^2J_{FF}$ = 153.7 Hz). **^{13}C NMR** (126 MHz, DMSO-d_6): δ 166.6 (COOH), 155.5 (C=O), 112.3 (t, $^1J_{CF}$ = 286.7 Hz, CF_2), 77.9 (C, *t*-Bu), 32.7 – 32.6 (m), 28.2 (3×CH_3), 27.3 – 26.7 (m). **MS** Anal. calcd. for $C_{10}H_{15}F_2NO_4$: C, 47.81; H, 6.02; N, 5.58. Found: C, 47.61; H, 6.27; N, 5.44.

Acknowledgements

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Keywords: fluorine • difluorocyclopropane • CF_3TMS • amines • cycloaddition

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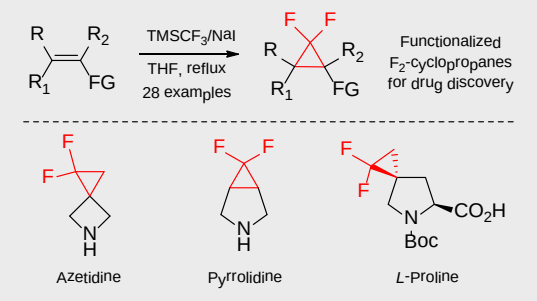

Fluorinated heterocycles*

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Synthesis of functionalized difluorocyclopropanes: unique building blocks for drug discovery

Difluorocyclopropane-containing building blocks for drug discovery were synthesized from the functionalized alkenes and $TMSCF_3$/NaI. Novel fluorinated acids, amines, amino acids, alcohols, ketones and sulfonyl chlorides were obtained.