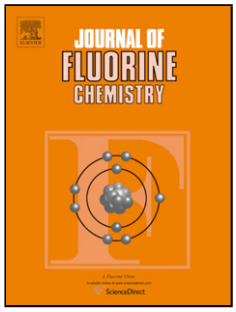

Title: Synthesis of 1-hetaryl-2,2-difluorocyclopropane-derived building blocks: the case of pyrazoles

Authors: Pavel S. Nosik, Sergey V. Ryabukhin, Mykola O. Pashko, Galyna P. Grabchuk, Oleksandr O. Grygorenko, Dmitriy M. Volochnyuk

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Synthesis of 1-hetaryl-2,2-difluorocyclopropane-derived building blocks: the case of pyrazoles

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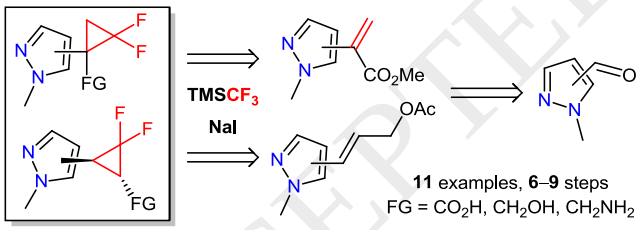
Graphical abstract



Highlights

- An approach to functionalized 1-pyrazolyl-2,2-difluorocyclopropanes was developed
- The method relied on difluorocyclopropanation with the $TMSCF_3$–NaI system as the key transformation
- 1,2-Disubstituted difluorocyclopropanes were prepared *via* the difluorocyclopropanation of 3-(pyrazolyl)allylacetates
- 1,1-Disubstituted difluorocyclopropanes could be obtained *via* the difluorocyclopropanation of 2-(pyrazolyl)acrylates
- Synthetic feasibility of major building block classes (amines, carboxylic acids) within the series was established

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ABSTRACT

An approach to 1-hetaryl-2,2-difluorocyclopropane building blocks compatible with the current criteria of lead-oriented synthesis was developed and implemented for the case of 3-, 4- and 5-subsituted pyrazole derivatives. The method implied 6–9 synthetic steps, including difluorocyclopropanation with the $TMSCF_3$–NaI system as the key transformation, and provided the title compounds on up to gram scale. The scope of the procedures towards substitution in the pyrazole ring and typical functional groups (*i.e.* COOH, NH_2, CH_2NH_2, CH_2OH) was established. The results obtained allowed formulation of preliminary guidelines for the synthetic feasibility of various functionalized 1-hetaryl-2,2-difluorocyclopropanes.

Keywords: Cycloalkanes, Organofluorine compounds, Nitrogen heterocycles, Lead-oriented synthesis, Ruppert–Prakash reagent

1. Introduction

In recent years, fluorinated fluorocyclopropanes have been outlined as a promising structural motif for drug discovery, agricultural chemistry and other areas [1–10]. In particular, *gem*-difluorocyclopropane moiety can be found in the structures of antineoplastic agentzosuquidar, which has reached Phase III clinical studies [11], glutamic acid analogue **1** – a selective metabotropic glutamate receptor mGluR2 agonist [12], γ-secretase inhibitor **2** (IC_{50} = 0.2 μM) [13], or sodium channel modulator **3** [14].

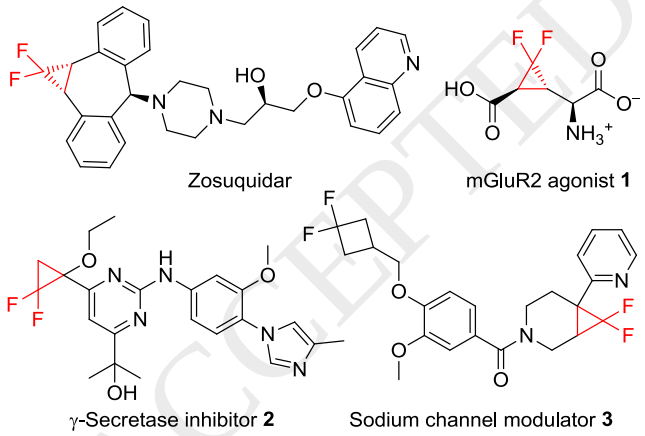
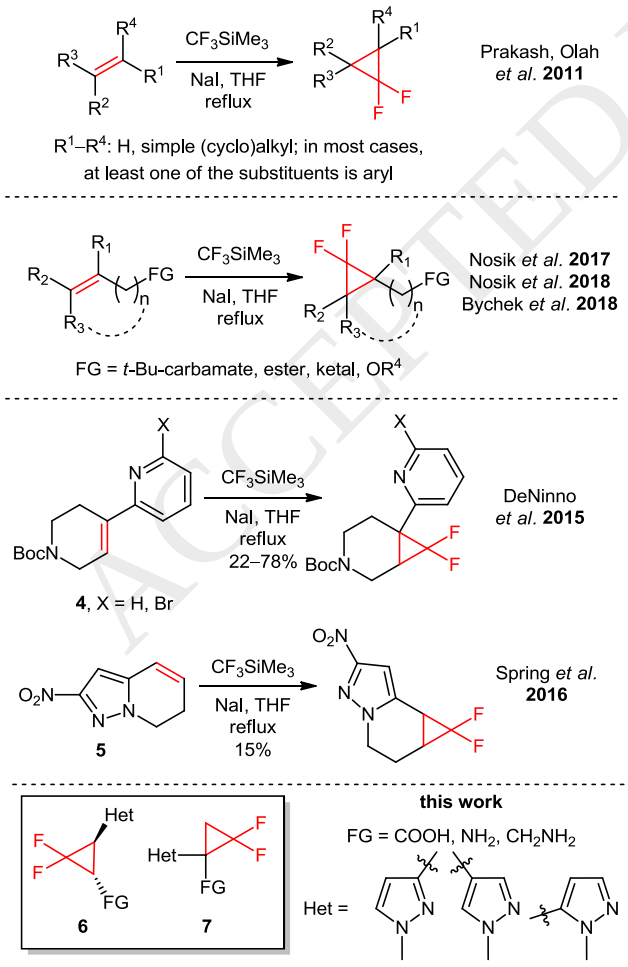


Figure 1. Some biologically active *gem*-difluorocyclopropanes

Numerous methods for the construction of *gem*-difluorocyclopropanes were published to date; typically, they rely on the difluorocyclopropanation of substrates bearing a double bond [2,15]. Nevertheless, the widespread use of these building blocks was hampered until recently since most of the above-mentioned methods had moderated efficiency and limited substrate scope, or involved the use of toxic and hardly available reagents. In 2011, Prakash, Olah and co-workers reported that the CF_3SiMe_3 – NaI system is an efficient reagent for the difluorocyclopropanation of sufficiently reactive alkenes *e.g.* styrenes [16] (Scheme 1). Later, several groups extended this procedure to various functionalized substrates, *i.e. N*-Boc derivatives, ethers, esters, nitriles, and ketals [15,17–22]. In

particular, we have described the "slow addition" protocol, which includes gradual introduction of the Ruppert – Prakash reagent (CF_3SiMe_3) into the reaction mixture. This modification allowed extending the scope of the method to less reactive substrates such as α,β-unsaturated esters [15,18].

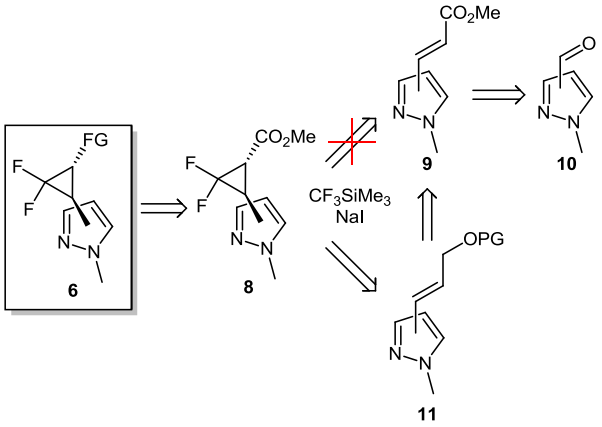
In this work, we have aimed at further extension of the CF_3SiMe_3 – NaI system applicability towards hetaryl-substituted alkenes bearing an additional functional group. *gem*-Difluorocyclopropanes thus obtained are promising synthetic intermediates which can be used to obtain low-molecular-weight, hydrophilic building blocks compatible with the concept of lead-oriented synthesis [23]. It should be noted that to date, only a few examples of similar transformations has been reported in the literature, involving pyridyl-substituted alkenes **4** [24] and a fused pyrazole derivative **5** [21]. It is also remarkable that other diflluorocyclopropanation reagents, *e.g.* $ClCF_2CO_2Na$ or methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (MFDA), demonstrated low to moderate efficiency in reaction with hetaryl-substituted double bonds [25,26]. Herein, we describe our synthetic efforts towards pyrazole derivatives of general formula **6** and **7** involving the use of the CF_3SiMe_3 – NaI system (Scheme 1). The choice of pyrazole as the model heterocycle relied on attractiveness of this moiety to medicinal and agricultural chemistry [27–29], as well as ability of isomeric pyrazolyl substituents to mimic π-acceptor, π-amphoteric, and π-donor heterocycles (in the case of 3-, 4-, and 5-isomers, respectively) [30,31]. Since the CF_3SiMe_3 – NaI system is not compatible with the free NH groups, the corresponding *N*-methyl-substituted pyrazole derivatives were used as the model substrates; the smallest alkyl substituent would allow maintaining low molecular weight of the building blocks obtained.



Scheme 1. Difluorocyclopropanation of alkenes with the CF_3SiMe_3 – NaI system

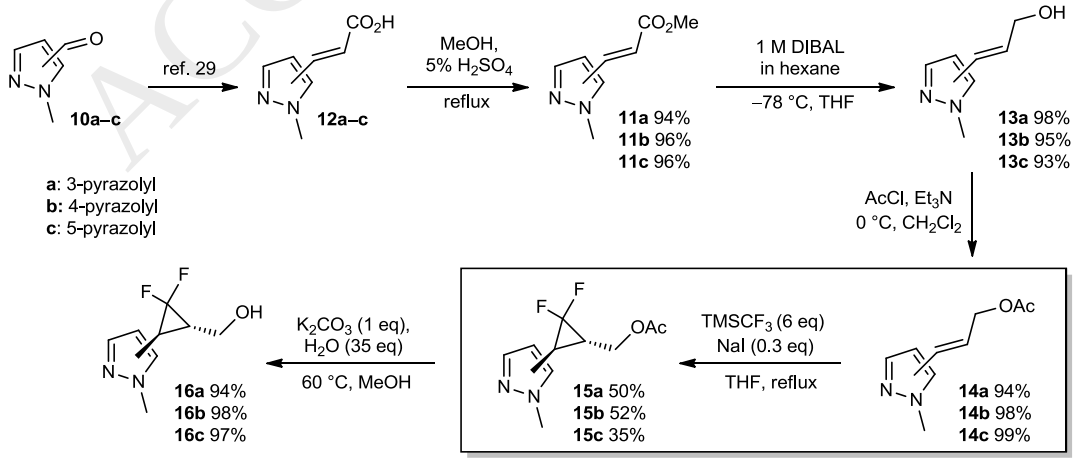
2. Results and discussion

First of all, the most obvious retrosynthetic approach to the chemotypes **6** was evaluated, which was based on α,β-unsaturated esters **8**, in turn being easily accessible from the corresponding aldehydes **10** [30] (Scheme 2). Unfortunately, the difluorocyclopropanation of **9** using either "slow addition" protocol [15,18] or flow approach [19] was unfruitful. Therefore, electronic deficiency of the double bond in the substrate was reduced by transforming the compounds of the type **9** into the corresponding protected alcohols **11**. According to the previous data [15], such modification should increase the alkene reactivity in the reaction with the CF_3TMS – NaI system.



Scheme 2. Retrosynthetic analysis of 1,2-disubstituted (2,2-difluorocyclopropyl)pyrazoles **6**

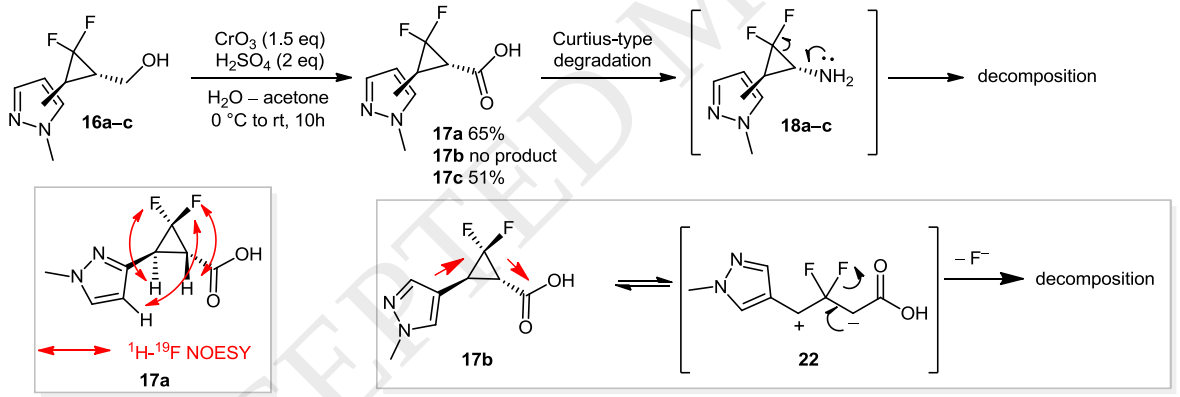
Therefore, synthesis of the target building blocks of the type **6** was performed using the reaction sequence shown in Scheme 3. In particular, aldehydes **10** were transformed into the corresponding carboxylic acids **12** (*E*-isomers) *via* the Knoevenagel condensation [30] and then – into esters **11** *via* the classical esterification. The reduction of esters **11** to the corresponding alcohols **13** was accomplished with DIBAL (–78 °C, THF) on a multigram scale, with *E* stereochemistry of the double bond being retained (93–98% yields). It should be noted that all our attempts to replace the DIBAL with cheaper $LiAlH_4$ were unsuccessful, since in the latter case, the reaction either proceeded unselectively, or the products of the C=C double bond reduction were formed.



Scheme 3. Retrosynthetic analysis of 1,2-disubstituted (2,2-difluorocyclopropyl)pyrazoles

Since the difluorocyclopropanation with the $TMSCF_3$ – NaI system is not compatible with the free hydroxyl group, the protection was required for the substrates **13**. Among numerous protective groups for the hydroxyl function, acetylation was selected due to atom-economy considerations and easiness of its introduction. The reaction was performed using AcCl in basic media, which gave compounds **14** in 94–99% yields. The key step of the reaction sequence, *i.e.* difluorocyclopropanation, was accomplished using the "slow addition" $TMSCF_3$ batch protocol [15,18] on *ca*. 5 g scale. The 3- and 4-pyrazolyl derivatives **14a** and **14b** gave the target products **15a** and **15b** in 50% and 52% yields, respectively, when a six-fold excess of $TMSCF_3$ was used. In the case of the 5-pyrazolyl derivative **14c**, the yield of the product **15c** under the same conditions was lower (up to 35%). This effect might be explained by steric hindrance provided by the neighbouring *N*-methyl group in the substrate **14c** in contrast to the compounds **14a** and **14b** – an effect observed by us for the similar objects earlier [30,31]. It should be noted that the yield of the target products **15** could be improved by repeating the difluorocyclopropanation step with the unreacted alkenes **14** recovered after the first run. In particular, we could achieve up to 63% conversion of **14a** into **15a** using this modification of the procedure.

It should be noted that the difluorocyclopropanation proceeded stereospecifically and led to the exclusive formation of *trans* isomers **15**, which was proven by ^{19}F NMR spectroscopic analysis of the reaction mixtures. The *trans* stereochemistry of the products was established by ^{1}H–^{19}F heteronuclear NOESY experiments with the compound **17a** obtained from **16a** (Scheme 4). In the case of other regioisomeric series, the stereochemistry was confirmed by similarity of the spectral patterns in their ^{1}H NMR spectra.



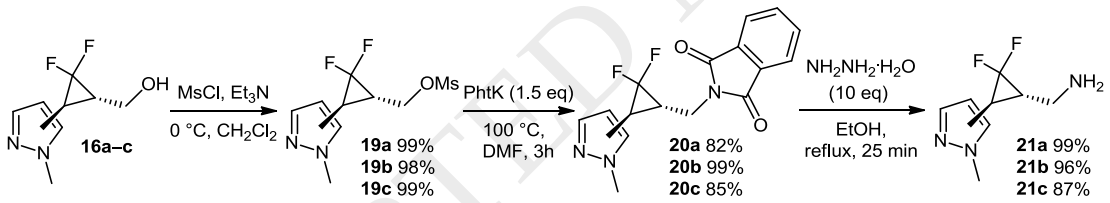
Scheme 4. Synthesis of carboxylic acids **17** and attempted preparation of amines **18**

Subsequent deprotection of the masked hydroxyl group in **15** was performed by K_2CO_3-mediated hydrolysis in MeOH to give alcohols **16** in 94–98% yields. In the subsequent step (*i.e.* oxidation to the carboxylic acids **17**), the nature of the pyrazole substitution appeared to be crucial for the reaction outcome. The common oxidation procedures implying the use of $KMnO_4$, CrO_3, and $RuCl_3$–$NaIO_4$ [32] were tested with the compound **16a**. The best results were obtained using the Jones reagent (CrO_3–H_2SO_4 in aqueous acetone), which gave the corresponding acid **17a** in 65% yield on a 3 g scale of the alcohol (Scheme 2). The other oxidation conditions resulted in decomposition of a considerable part of the product; the over-oxidized products *e.g.* (difluoromethyl)pyrazolylketones were detected in the crude product by LCMS.

In the case of less electron-deficient 5-pyrazolyl derivative **16c**, the CrO_3–H_2SO_4 procedure resulted in moderate yield of the corresponding acid **17c** to 51%; substantial formation of unidentified by-products was observed. Unfortunately, all our attempts to synthesize the acid **17b** by analogous procedure failed. In all experiments, only the decomposition products were detected by ^{19}F NMR analysis of the reaction mixtures. We assume that in the case of π-donor 4-pyrazolyl derivative **17b**, heterolytic cleavage of the three-membered ring occurred (which is characteristic for the donor-acceptor ("push-pull") cyclopropanes [33]), leading to the intermediate **22** and the products of its further decomposition (Scheme 4). It should be noted that analogous carboxylic acid lacking the fluorine atoms is stable under the aforementioned conditions [30]; the effect of the two fluorine atoms in the case of **17b** is unclear and needs further investigation.

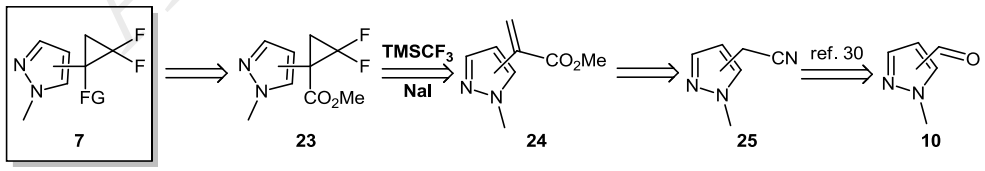
All our attempts to carry out the Curtius-type degradation (*e.g.* DPPA, toluene, *t*-BuOH) of the carboxylic acids **17a** and **17c** into the corresponding amines **18** were not successful. Despite the commercial availability and wide use of the parent 2,2-difluorocyclopropylamine as a hydrochloride in medicinal chemistry literature [34,35], this result is in agreement with the previously reported instability of such compounds [36]. The reason behind instability of the compounds **18** might be related to the push-pull-type cleavage of the cyclopropane ring with elimination of the fluorine anion (see Scheme 4).

Finally, the synthesis of homologous amines **21** was performed from alcohols **16** using a standard three-step reaction sequence (*i.e.* mesylation – phtalimide introduction – deprotection), which gave the target products in excellent preparative yields for all three regioisomers (Scheme 5).



Scheme 5. Synthesis of amines **21**

As in the case of 1,2-disubstituted difluorocyclopropanes **6**, our initial retrosynthetic approach to the building blocks of the type **7** was also based on the difluorocyclopropanation of the corresponding α,β-unsaturated esters **24** (Scheme 6). The compounds **24** might be obtained from the corresponding nitriles **25**, in turn prepared from the aldehydes **10** using a published method [31].

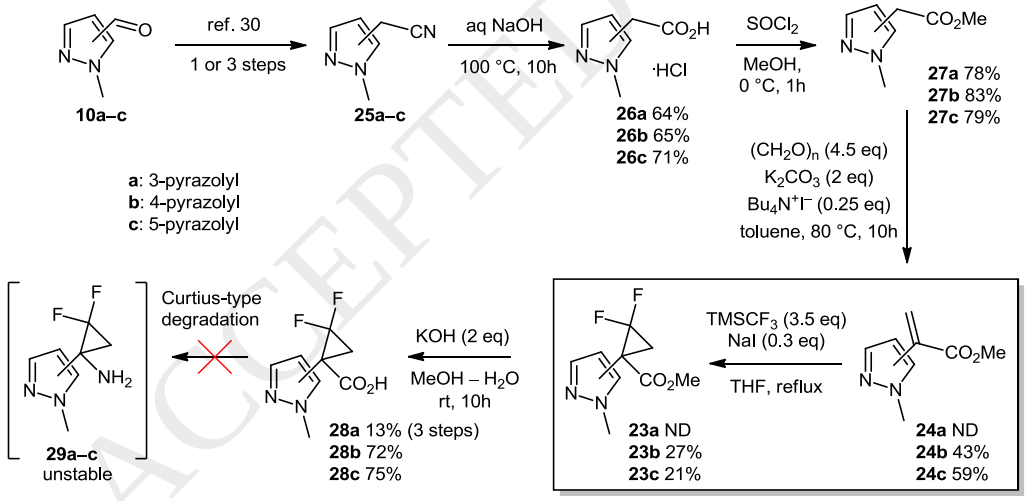


Scheme 6. Retrosynthetic analysis of 1,2-disubstituted (2,2-difluorocyclopropyl)pyrazoles **7**

Unlike the 1,2-disubstituted alkenes of the type **9**, the 1,1-disubstituted substrates **24** appeared to be amenable to the difluorocyclopropanation with the CF_3SiMe_3 – NaI system. This fact might be explained by more favorable combination of the electronic and steric

factors in the case of **24**. Therefore, the initial strategy for the preparation of the esters **23** was implemented as planned without substantial modification.

The detailed synthetic scheme of the synthesis of the building blocks of type **6** is shown in Scheme 7. In particular, the nitriles **25** were obtained from the aldehydes **10** and then hydrolyzed into the corresponding carboxylic acids **26**, which were isolated as hydrochlorides in moderate to good preparative yields (64–71%). Then, esterification with $SOCl_2$ in MeOH was used to obtain esters **27** (78–83% yields). The alkene moiety was introduced by the reaction of **27** with paraformaldehyde according to the procedure described in the literature for analogous arylacetic esters [37]. In the case of 4- and 5-pyrazolyl derivatives **27b** and **27c**, this method yielded the corresponding alkenes **24b** and **24c** in moderate preparative yields (43% and 59%, respectively) after chromatographic purification. The half-life time of alkenes **24b** and **24c** at rt was less than 12 h, but it was sufficient for their purification and further use in the next step. Their longer storage (even at low temperatures and under inert atmosphere) resulted in polymerization. In the case of 3-pyrazolyl derivative **27a**, the reaction accomplished with the formation of the unknown by-product (*m/z* = 279, GCMS, EI = 70 eV). All attempts to separate this by-product by either normal-phase chromatography or reverse-phase HPLC failed due to its very close retention time value to that of the target compound **24a** (see the SI). Other isolation techniques were also unfruitful since the half-life time of the alkene **24a** was less than 5 h. Nevertheless, the crude mixture containing **24a** could be subjected to the difluorocyclopropanation with the CF_3SiMe_3–NaI system affording the compound **23a** as a mixture with the aforementioned by-product, which remained intact. Separation of this mixture at this step also failed due to the close retention time values in the preparative HPLC method used (see the SI). Nevertheless, the subsequent alkaline hydrolysis of the mixture led to decomposition of the unknown by-product affording the pure carboxylic acid **28a** in 13% total yield after the simple liquid-liquid extraction.



Scheme 7. Synthesis of the building blocks of the type **7**

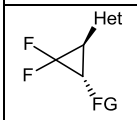
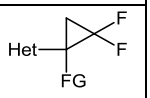
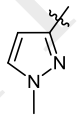
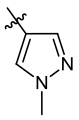
In the case of the pure alkenes **24b** and **24c**, the difluorocyclopropanation with the $TMSCF_3$–NaI system resulted in 27% and 21% yields of the compounds **23b** and **23c**, respectively, and was complicated by polymerization of the starting alkene. The polymerization process did not allow increasing the conversion by additional repeating of the procedure, as it was done in the case of compound **14**. Further hydrolysis of the ester **23b** and **23c** gave the corresponding target carboxylic acids **28b** and **28c** (72% and 75% yields, respectively).

As in a case of the carboxylic acids **17**, all our attempts to synthesize the amines **29** by Curtius-type degradation of **28** were unfruitful; only decomposition of the starting materials was observed.

3. Conclusions

The building blocks of the *trans*-1,2-disubstituted 1-pyrazolyl-2,2-difluorocyclopropane series can be obtained on a multigram scale starting from easily available *N*-alkylpyrazole-3-, -4-, and -5-carboxaldehydes and using difluorocyclopropanation with the CF_3SiMe_3 – NaI system as the key step. Analogous approach to the 1,1-disubstituted 1-pyrazolyl-2,2-difluorocyclopropane series appeared to be less efficient; only the corresponding carboxylic acids were prepared on a 100 mg scale. In total, 18 building blocks of the pyrazolyl-substituted difluorocyclopropane series were studied, and 11 of them appeared to be stable enough to be isolated and fully characterized. The building blocks obtained are compatible with criteria for the lead-oriented synthesis [23]; moreover, since the isomeric pyrazolyl substituents differ in their electronic properties, the electronic distribution can be varied significantly within the compounds libraries obtained, whilst the structural changes being kept minimal. The preliminary guidelines for the preparation of the building blocks of the type **6** and 7 are summarized in Table 1; we believe that these results can be extended to other 1-hetaryl-2,2-difluorocyclopropane-derived building blocks.

Table 1. Preliminary guidelines for the synthesis of 1-hetaryl-2,2-difluorocyclopropane-derived building blocks: the case of pyrazoles (legend: "+" – accessible on a multigram scale; "±" – can be prepared but problematic; "–" – cannot be obtained; "ND" – was not studied)

#	Het	FG	Building block type	
			 **6**	 **7**
1		COOH	+	±
2		CH_2OH, CH_2NH_2	+	ND
3		NH_2	–	–
4		COOH	–	±
5		CH_2OH, CH_2NH_2	+	ND
6		NH_2	–	–
7		COOH	+	±
8		CH_2OH, CH_2NH_2	+	ND
9		NH_2	–	–

4. Experimental

4.1. General

The solvents were purified according to the standard procedures [38]. All starting materials were purchased from commercial sources. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using silica gel as the stationary phase. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Varian Unity Plus 400 spectrometer (at 400 MHz for Protons, 101 MHz for Carbon-13, and 376 MHz for Fluorine-19). Tetramethylsilane (^{1}H, ^{13}C) or C_6F_6 (^{19}F) were used as internal standards. The 2D NMR experiments were made on Bruker 170 Avance 500 spectrometer. Elemental analyses were performed at the Laboratory of Organic Analysis, Institute of Organic Chemistry, National Academy of Sciences of Ukraine, their results were found to be in good agreement (±0.4%) with the calculated values. Mass spectra were recorded on an Agilent 1200 LCMSD SL instrument (chemical ionization (APCI), electrospray ionization (ESI)) or Agilent 7820A gas chromatograph system (electron impact ionization (EI), ionization energy – 70 eV)).

4.2. General procedure for the preparation of ***13***

Diisobutylaluminum hydride (108.3 mL, 108.3 mmol, 1 M in hexane) was added dropwise to a solution of ester **11** (6.07 g, 36.1 mmol) in dry THF (200 mL) under argon atmosphere upon stirring at -78 °C during 1 h. The resulting mixture was further stirred at -78°C for 3 h, then the reaction was quenched by careful addition of 10% aq NH_4Cl (30 mL) at 0 °C. The solid by-product was filtered off and washed with THF (3×50 mL). The filtrates were evaporated under reduced pressure to give the product **13**.

*4.2.1. (E)-3-(1-Methyl-1H-pyrazol-3-yl)prop-2-en-1-ol (**13a**).*

Yield 4.9 g (98%). Yellowish oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.23 (d, *J* = 2.0 Hz, 1H), 6.56 (d, *J* = 16.1 Hz, 1H), 6.30 (dt, *J* = 16.1, 5.6 Hz, 1H), 6.26 (d, *J* = 2.1 Hz, 1H), 4.22 (d, *J* = 5.5 Hz, 2H), 3.81 (s, 3H), 3.32 (s, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 150.1, 131.1, 130.4, 122.6, 102.8, 63.0, 38.7. MS (ESI): m/z = 139 ($[M+H]^+$), 109 ($[M–CH_2OH]^+$). Anal. Calcd. for $C_7H_{10}N_2O$: C, 60.85; H, 7.30; N, 20.28. Found: C, 60.98; H, 7.18; N, 20.64.

*4.2.2. (E)-3-(1-Methyl-1H-pyrazol-4-yl)prop-2-en-1-ol (**13b**).*

Yield 8.2 g (95%). Yellowish solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.44 (s, 1H), 7.26 (s, 1H), 6.33 (d, *J* = 15.9 Hz, 1H), 6.00 (dt, *J* = 15.9, 5.8 Hz, 1H), 4.15 (d, *J* = 5.8 Hz, 2H), 3.78 (s, 3H), 3.32 (brs, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 136.6, 127.3, 126.6, 120.2, 119.6, 62.7, 38.3. MS (ESI): m/z = 139 ($[M+H]^+$). Anal. Calcd. for $C_7H_{10}N_2O$: C, 60.85; H, 7.30; N, 20.28. Found: C, 60.80; H, 7.10; N, 20.26.

*4.2.3. (E)-3-(1-Methyl-1H-pyrazol-5-yl)prop-2-en-1-ol (**13c**).*

Yield 6.5 g (93%). Yellowish oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32 (s, 1H), 6.45 (d, *J* = 15.8 Hz, 1H), 6.28 (s, 1H), 6.30–6.22 (m, 1H), 4.27 (d, *J* = 3.6 Hz, 2H), 3.77 (s, 3H), 3.32 (brs, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 140.4, 138.3, 133.2, 116.2, 102.9, 62.5, 36.4. MS (ESI): m/z = 139 ($[M+H]^+$). Anal. Calcd. for $C_7H_{10}N_2O$: C, 60.85; H, 7.30; N, 20.28. Found: C, 61.11; H, 7.24; N, 20.62.

4.3. General procedure for the preparation of ***14***

Acetyl chloride (3.1 g, 39.1 mmol) was added dropwise to a solution of alcohol ***13*** (4.94 g, 35.5 mmol) and NEt_3 (5.92 mL, 42.6 mmol) in dry CH_2Cl_2 (100 mL) at 0°C over 30 min. The reaction mixture was stirred overnight at rt. The resulting mixture was washed with 10 % aq citric acid (100 mL). The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to give ***14.***

*4.3.1. (E)-3-(1-Methyl-1H-pyrazol-3-yl)allyl acetate (**14a**).*

Yield 6 g (94%). Yellowish oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.21 (d, *J* = 2.2 Hz, 1H), 6.57 (d, *J* = 16.0 Hz, 1H), 6.25 (d, *J* = 2.2 Hz, 1H), 6.19 (dt, *J* = 16.0, 6.3 Hz, 1H), 4.63 (d, *J* = 6.3 Hz, 2H), 3.79 (s, 3H), 2.01 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.7, 149.4, 131.1, 126.0, 124.0, 103.1, 64.7, 38.8, 20.9. MS (ESI): m/z = 181 ($[M+H]^+$), 121 ($[M–CH_3COO]^+$). Anal. Calcd. for $C_9H_{12}N_2O_2$: C, 59.99; H, 6.71; N, 15.55. Found: C, 59.84; H, 6.69; N, 15.68.

*4.3.2. (E)-3-(1-Methyl-1H-pyrazol-4-yl)allyl acetate (**14b**).*

Yield 10.5 g (98%). Yellowish oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.46 (s, 1H), 7.29 (s, 1H), 6.39 (d, *J* = 15.9 Hz, 1H), 5.92 (dt, *J* = 15.8, 6.7 Hz, 1H), 4.56 (d, *J* = 6.3 Hz, 2H), 3.78 (s, 3H), 1.99 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.8, 137.3, 128.1, 124.7, 121.0, 119.6, 65.3, 38.9, 20.9. MS (ESI): m/z = 181 ($[M+H]^+$), 121 ($[M–CH_3COO]^+$). Anal. Calcd. for $C_9H_{12}N_2O_2$: C, 59.99; H, 6.71; N, 15.55. Found: C, 60.37; H, 6.98; N, 15.74.

*4.3.3. (E)-3-(1-Methyl-1H-pyrazol-5-yl)allyl acetate (**14c**).*

Yield 7.8 g (99%). Orange oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34 (d, *J* = 1.3 Hz, 1H), 6.50 (d, *J* = 15.8 Hz, 1H), 6.32 (d, *J* = 1.6 Hz, 1H), 6.17 (dt, *J* = 15.8, 6.3 Hz, 1H), 4.67 (dd, *J* = 6.2, 1.1 Hz, 2H), 3.82 (s, 3H), 2.06 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.6, 139.5, 138.4, 126.8, 120.2, 103.5, 64.4, 36.6, 20.9. MS (ESI): m/z = 181 ($[M+H]^+$). Anal. Calcd. for $C_9H_{12}N_2O_2$: C, 59.99; H, 6.71; N, 15.55. Found: C, 60.20; H, 6.82; N, 15.60.

*4.4. General procedure for the preparation of **15***

Sodium iodide (1.65 g, 11.0 mmol) was added to a solution of alkene ***14*** (5.56 g, 30.5 mmol) in anhydrous THF (100 mL) under nitrogen atmosphere and heated to reflux. Trimethyl(trifluoromethyl)silane (15.2 g, 106.8 mmol, 3.5 eq) was added dropwise over 24 h. The reaction mixture was heated overnight; the conversion was detected by ^{1}H NMR. More trimethyl(trifluoromethyl)silane (15.2 g, 106.8 mmol, 3.5 eq) was added dropwise over 24 h and the reaction mixture was heated overnight. The solvent was evaporated, and the crude material was purified by column chromatography (EtOAc –hexane (1:2) as eluent) to give ***15.***

*4.4.1. (2,2-Difluoro-3-(1-methyl-1H-pyrazol-3-yl)cyclopropyl)methyl acetate (**15a**).*

Yield 3.5 g (50%). Orange oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.25 (s, 1H), 6.02 (s, 1H), 4.35 (dd, *J* = 11.9, 7.0 Hz, 1H), 4.11 (dd, *J* = 11.6, 8.6 Hz, 1H), 3.82 (s, 3H), 2.62 (q, *J* = 7.2 Hz, 1H), 2.34 – 2.22 (m, 1H), 2.04 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.8, 144.5, 131.0, 112.7 (t, *J* = 289.3 Hz), 104.1, 60.6, 38.8, 27.5 (t, *J* = 10.3 Hz), 26.0 (t, *J* = 11.6 Hz), 20.8. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –138.4. MS (ESI): m/z = 231 ($[M+H]^+$), 171 ($[M–CH_3CO–F]^+$. Anal. Calcd. for $C_{10}H_{12}F_2N_2O_2$: C, 52.17; H, 5.25; N, 12.17. Found: C, 51.91; H, 4.95; N, 12.56.

*4.4.2. (2,2-Difluoro-3-(1-methyl-1H-pyrazol-4-yl)cyclopropyl)methyl acetate (**15b**).*

Yield 7.0 g (52%). Orange oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34 (s, 1H), 7.23 (s, 1H), 4.29 (dddd, *J* = 12.0, 7.7, 2.4, 1.1 Hz, 1H), 4.15 (ddd, *J* = 12.0, 7.7, 1.8 Hz, 1H), 3.84 (s, 3H), 2.44 (dd, *J* = 14.1, 7.1 Hz, 1H), 2.07 (s, 3H), 1.95 (dq, *J* = 13.4, 7.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.3, 138.0, 128.1, 113.1, 112.9 (dd, *J* = 298.7, 278.3 Hz), 60.4 (d, *J* = 5.8 Hz), 38.7, 29.3 (t, *J* = 10.2 Hz),

22.8 (t, *J* = 10.2 Hz), 20.6. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –137.2 (dd, *J* = 158.0, 13.6 Hz), –139.0 (dd, *J* = 158.0, 14.2 Hz). MS (ESI): m/z = 231 ($[M+H]^+$), 181, 171 ($[M–CH_3CO–F]^+$), 151. Anal. Calcd. for $C_{10}H_{12}F_2N_2O_2$: C, 52.17; H, 5.25; N, 12.17. Found: C, 52.05; H, 4.89; N, 12.51.

*4.4.3. (2,2-Difluoro-3-(1-methyl-1H-pyrazol-5-yl)cyclopropyl)methyl acetate (**15c**).*

Yield 4.0 g (35%). Yellowish oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 (d, *J* = 1.8 Hz, 1H), 6.11 (s, 1H), 4.32 (d, *J* = 7.8 Hz, 2H), 3.89 (s, 3H), 2.54 (dd, *J* = 13.3, 7.1 Hz, 1H), 2.20 (dq, *J* = 13.4, 7.4 Hz, 1H), 2.11 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.7, 138.5, 134.5, 112.2 (t, *J* = 289 Hz), 105.4, 60.3 (d, *J* = 5.0 Hz), 36.7, 29.1, 23.2, 20.9. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –135.9 (dd, *J* = 159.0, 13.2 Hz), –137.8 (dd, *J* = 159.2, 13.0 Hz). MS (ESI): m/z = 231 ($[M+H]^+$), 181, 171 ($[M–CH_3CO–F]^+$). Anal. Calcd. for $C_{10}H_{12}F_2N_2O_2$: C, 52.17; H, 5.25; N, 12.17. Found: C, 51.84; H, 5.17; N, 12.04.

*4.5. General procedure for the preparation of **16***

A solution of K_2CO_3 (1.8 g, 13 mmol) in H_2O (8 mL) was added to solution of acetate ***15*** (3.0 g, 13 mmol) in MeOH (240 mL, 0.05 M) and the mixture was heated at 60 °C overnight. The complete conversion was confirmed by TLC. The reaction mixture was concentrated under reduced pressure and quenched with CH_2Cl_2 (30 mL). The organic layer was filtered through a pad of Na_2SO_4 and evaporated. The resulted sample was purified by column chromatography (EtOAc –hexane (1:1) as eluent) to give ***16.***

*4.5.1. (2,2-Difluoro-3-(1-methyl-1H-pyrazol-3-yl)cyclopropyl)methanol (**16a**).*

Yield 2.4 g (98%). Yellowish oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.27 (d, *J* = 2.2 Hz, 1H), 6.07 (dd, *J* = 2.3, 1.3 Hz, 1H), 3.89 – 3.78 (m, 2H), 3.83 (s, 3H), 3.65 (brs, 1H), 2.60 (dd, *J* = 13.7, 7.4 Hz, 1H), 2.21 (dq, *J* = 13.9, 7.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 144.7, 130.6, 113.0 (t, *J* = 288.3 Hz), 103.9, 58.6 (d, *J* = 5.3 Hz), 38.5, 31.1 (t, *J* = 9.5 Hz), 25.3 (t, *J* = 9.5 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –137.5 (dd, *J* = 158.2, 14.1 Hz), –139.3 (dd, *J* = 158.2, 13.9 Hz). MS (ESI): m/z = 189 ($[M+H]^+$), 171 ($[M-HF]^+$, 151. Anal. Calcd. for $C_8H_{10}F_2N_2O$: C, 51.06; H, 5.36; N, 14.89. Found: C, 51.31; H, 5.03; N, 14.52.

*4.5.2. (2,2-Difluoro-3-(1-methyl-1H-pyrazol-4-yl)cyclopropyl)methanol (**16b**).*

Yield 5.6 g (98%). Orange oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.31 (s, 1H), 7.22 (s, 1H), 3.86 – 3.74 (m, 2H), 3.82 (s, 3H), 3.64 (brs, 1H), 2.36 (dd, *J* = 14.2, 7.2 Hz, 1H), 1.86 (dq, *J* = 14.3, 7.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 137.9, 128.3, 113.8, 113.5 (dd, *J* = 300.8, 276.0 Hz), 58.7 (d, *J* = 5.8 Hz), 38.6, 32.6, 22.1. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –136.7 (dd, *J* = 157.2, 13.9 Hz), –139.8 (dd, *J* = 157.2, 14.2 Hz). MS (ESI): m/z = 189 ($[M+H]^+$), 139 ($[M–HF–CH_2OH]^+$). Anal. Calcd. for $C_8H_{10}F_2N_2O$: C, 51.06; H, 5.36; N, 14.89. Found: C, 51.24; H, 5.57; N, 15.29.

*4.5.3. (2,2-Difluoro-3-(1-methyl-1H-pyrazol-5-yl)cyclopropyl)methanol (**16c**).*

Yield 1.9 g (97%). Orange oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34 (d, *J* = 1.9 Hz, 1H), 6.08 (s, 1H), 3.90 (ddd, *J* = 12.0, 7.1, 1.5 Hz, 1H), 3.82 (s, 3H), 3.83 – 3.76 (m, 1H), 2.43 (dd, *J* = 13.2, 7.2 Hz, 1H), 2.07 (dq, *J* = 14.2, 7.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 137.7, 135.1, 112.3 (t, *J* = 287.7 Hz), 104.8, 57.7 (d, *J* = 5.0 Hz), 36.0, 31.8, 21.9 (dd, *J* = 13.2, 10.6 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –135.2 (dd, *J* = 158.0, 13.9 Hz), –138.6 (dd, *J* = 158.0, 13.2 Hz). MS (ESI): m/z = 189 ($[M+H]^+$), 139 ($[M–HF–CH_2OH]^+$). Anal. Calcd. for $C_8H_{10}F_2N_2O$: C, 51.06; H, 5.36; N, 14.89. Found: C, 51.04; H, 5.08; N, 14.78.

*4.6. General procedure for the preparation of **17***

Sulfuric acid (3.12 g, 95–98%) was added to a solution of chromium trioxide (2.39 g, 23.9 mmol) in water (5.4 mL) at 0 °C, and the mixture was stirred for 30 min. This mixture was added to a solution of alcohol ***16*** (2.98 g, 15.9 mmol) in acetone (30 mL) at 0 °C, and the resulting mixture was stirred overnight at rt. The organic layer was decanted and evaporated. The crude product was purified by column chromatography (EtOAc –hexane – HCOOH (40:40:1) as eluent) to give pure acid ***17***.

*4.6.1. 2,2-Difluoro-3-(1-methyl-1H-pyrazol-3-yl)cyclopropane-1-carboxylic acid (**17a**).*

Yield 1.4 g (65%). Yellowish solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.93 (brs, 1H), 7.32 (d, *J* = 2.2 Hz, 1H), 6.17 (s, 1H), 3.90 (s, 3H), 3.52 (ddd, *J* = 12.9, 7.6, 2.5 Hz, 1H), 2.74 (dd, *J* = 13.5, 7.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 169.1, 142.7, 131.1 (d, *J* = 30.2 Hz), 110.2 (dd, *J* = 293.3, 286.9 Hz), 104.6 (d, *J* = 1.7 Hz), 38.6, 32.2 (t, *J* = 11.2 Hz), 27.3 (dd, *J* = 12.7, 8.4 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –133.9 (dd, *J* = 152.4, 13.4 Hz), –135.7 (dd, *J* = 152.5, 12.9 Hz). MS (ESI): m/z = 203 ($[M+H]^+$), 185 ($[M–H_2O]^+$), 157 ($[M–COOH]^+$). Anal. Calcd. for $C_8H_8F_2N_2O_2$: C, 47.53; H, 3.99; N, 13.86. Found: C, 47.72; H, 4.07; N, 13.83.

*4.6.2. 2,2-Difluoro-3-(1-methyl-1H-pyrazol-5-yl)cyclopropane-1-carboxylic acid (**17c**).*

Yield 1 g (51%). Yellowish solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.35 (s, 1H), 6.23 (s, 1H), 3.81 (s, 3H), 3.54 (dd, *J* = 12.1, 7.9 Hz, 1H), 3.09 (dd, *J* = 14.3, 7.7 Hz, 1H). ^{13}C NMR (DMSO-d_6, 101 MHz) δ 166.7, 138.1, 133.7, 111.0 (t, *J* = 299.9, 287.0 Hz), 105.7, 36.9, 32.2 (t, *J* = 10.0 Hz), 23.9. ^{19}F NMR (DMSO-d_6, 376 MHz) δ –132.7 (d, *J* = 147.9 Hz), –134.5 (d, *J* = 147.9 Hz). MS (ESI): m/z = 203 ($[M+H]^+$). Anal. Calcd. for $C_8H_8F_2N_2O_2$: C, 47.53; H, 3.99; N, 13.86. Found: C, 47.22; H, 3.63; N, 13.71.

*4.7. General procedure for the preparation of **19***

Methanesulfonyl chloride (0.34 g, 3.0 mmol) was added dropwise to a solution of alcohol ***16*** (0.51 g, 2.7 mmol) and NEt_3 (0.55 g, 5.4 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C over 30 min. The reaction mixture was stirred overnight at rt. The organic layer was washed with 10 % aq citric acid (10 mL), dried over Na_2SO_4 and evaporated under reduced pressure to give ***19***.

*4.7.1. (2,2-Difluoro-3-(1-methyl-1H-pyrazol-3-yl)cyclopropyl)methyl methanesulfonate (**19a**).*

Yield 1.4 g (99%). Yellowish oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30 (d, *J* = 2.2 Hz, 1H), 6.10 (d, *J* = 2.2 Hz, 1H), 4.55 – 4.46 (m, 1H), 4.35 (ddd, *J* = 11.4, 8.4, 1.4 Hz, 1H), 3.85 (s, 3H), 3.06 (s, 3H), 2.74 (ddd, *J* = 12.5, 7.2, 2.0 Hz, 1H), 2.51 – 2.40 (m, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 143.1, 130.7, 111.8 (t, *J* = 288.8 Hz), 104.1, 65.6 (d, *J* = 5.7 Hz), 38.7, 37.8, 27.1 (t, *J* = 10.6 Hz), 26.2 (t, *J* = 10.6 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –138.5 (dd, *J* = 159.4, 12.3 Hz), –139.1 (dd, *J* = 159.4, 11.2 Hz). MS (ESI): m/z = 267 ($[M+H]^+$), 171($[M–CH_3SO_2–F]^+$, 151. Anal. Calcd. for $C_9H_{12}F_2N_2O_3S$: C, 40.60; H, 4.54; N, 10.52; S, 12.04. Found: C, 40.77; H, 4.48; N, 10.36; S, 12.17.

*4.7.2. (2,2-Difluoro-3-(1-methyl-1H-pyrazol-4-yl)cyclopropyl)methyl methanesulfonate (**19b**).*

Yield 1.4 g (99%). Red oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35 (s, 1H), 7.27 (s, 1H), 4.45 – 4.30 (m, 2H), 3.83 (s, 3H), 3.03 (s, 3H), 2.56 (dd, *J* = 14.3, 7.0 Hz, 1H), 2.04 (dq, *J* = 12.7, 7.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 137.9, 128.4, 112.5 (t, *J* = 288.7 Hz),

112.3, 65.7 (d, *J* = 5.9 Hz), 38.8, 37.6, 29.3 (t, *J* = 10.5 Hz), 23.3 (dd, *J* = 12.7, 10.7 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –136.8 (dd, *J* = 159.2, 12.5 Hz), –138.3 (dd, *J* = 159.3, 14.2 Hz). MS (ESI): m/z = 267 ($[M+H]^+$), 171 ($[M–CH_3SO_2–F]^+$), 151. Anal. Calcd. for $C_9H_{12}F_2N_2O_3S$: C, 40.60; H, 4.54; N, 10.52; S, 12.04. Found: C, 40.95; H, 4.74; N, 10.77; S, 11.74.

*4.7.3. (2,2-Difluoro-3-(1-methyl-1H-pyrazol-5-yl)cyclopropyl)methyl methanesulfonate (**19c**).*

Yield 1.4 g (99%). Reddish oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 (s, 1H), 6.15 (s, 1H), 4.53 (dd, *J* = 11.0, 7.5 Hz, 1H), 4.43 – 4.36 (m, 1H), 3.90 (s, 3H), 3.08 (s, 3H), 2.68 (dd, *J* = 13.4, 7.0 Hz, 1H), 2.30 (dq, *J* = 15.0, 7.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 137.9, 133.2, 111.2 (t, *J* = 287.7 Hz), 104.9, 64.5 (d, *J* = 4.9 Hz), 37.4, 36.2, 28.5 (t, *J* = 10.3 Hz), 23.0 (dd, *J* = 13.2, 10.5 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –135.0 (d, *J* = 160.3 Hz), –136.6 (d, *J* = 160.3 Hz). MS (ESI): m/z = 267 ($[M+H]^+$). Anal. Calcd. for $C_9H_{12}F_2N_2O_3S$: C, 40.60; H, 4.54; N, 10.52; S, 12.04. Found: C, 40.92; H, 4.24; N, 10.53; S, 12.29.

*4.8. General procedure for the preparation of **20***

Potassium phthalimide (0.65 g, 3.5 mmol) was added to a solution of mesylate ***19*** (0.61 g, 2.3 mmol) in DMF (10 mL) at rt. The reaction mixture was stirred vigorously at 100 °C for 3 h. The completion of the reaction was controlled by the disappearance of the mesylate in TLC. The resulting mixture was cooled to rt. The combined organic layers were washed with H_2O (3×50 mL), brine (2×30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. A crude product was purified by column chromatography (EtOAc –hexane (1:1) as eluent) afforded pure ***20***.

*4.8.1. 2-((2,2-Difluoro-3-(1-methyl-1H-pyrazol-3-yl)cyclopropyl)methyl)-isoindoline-1,3-dione (**20a**).*

Yield 0.60 g (82%). White solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.87 – 7.80 (m, 2H), 7.74 – 7.67 (m, 2H), 7.23 (d, *J* = 2.2 Hz, 1H), 6.00 (d, *J* = 2.1 Hz, 1H), 4.01 (dd, *J* = 14.7, 7.0 Hz, 1H), 3.91 (ddt, *J* = 14.5, 8.1, 1.5 Hz, 1H), 3.80 (s, 3H), 2.78 (ddd, *J* = 11.8, 7.4, 2.6 Hz, 1H), 2.50 – 2.38 (m, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 167.3, 144.1, 133.6, 131.5, 130.4, 123.0, 112.5 (t, *J* = 289.5 Hz), 103.7, 38.6, 34.7 (d, *J* = 4.9 Hz), 27.4 (t, *J* = 10.1 Hz), 26.7 (t, *J* = 11.4 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –138.5 (dd, *J* = 157.6, 11.5 Hz), –139.0 (dd, *J* = 157.6, 11.5 Hz). MS (ESI): m/z = 318 ($[M+H]^+$). Anal. Calcd. for $C_{16}H_{13}F_2N_3O_2$: C, 60.57; H, 4.13; N, 13.24. Found: C, 60.78; H, 4.00; N, 13.18.

*4.8.2. 2-((2,2-Difluoro-3-(1-methyl-1H-pyrazol-4-yl)cyclopropyl)methyl)-isoindoline-1,3-dione (**20b**).*

Yield 1.1 g (91%). White solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.89 – 7.81 (m, 2H), 7.76 – 7.69 (m, 2H), 7.27 (s, 1H), 7.18 (s, 1H), 4.04 (dd, *J* = 14.6, 6.1 Hz, 1H), 3.85 – 3.76 (m, 1H), 3.80 (s, 3H), 2.59 (dd, *J* = 14.1, 7.2 Hz, 1H), 2.09 – 1.97 (m, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 167.4, 137.9, 133.7, 131.4, 128.0, 123.0, 113.3, 113.1 (t, *J* = 289.5 Hz), 38.7, 34.9 (d, *J* = 5.5 Hz), 29.4 (t, *J* = 9.9 Hz), 23.7 (t, *J* = 11.6 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –137.0 (dd, *J* = 157.9, 13.7 Hz), –138.6 (dd, *J* = 157.9, 14.1 Hz). MS (ESI): m/z = 318 ($[M+H]^+$), 171. Anal. Calcd. for $C_{16}H_{13}F_2N_3O_2$: C, 60.57; H, 4.13; N, 13.24. Found: C, 60.37; H, 3.94; N, 12.95.

*4.8.3. 2-((2,2-Difluoro-3-(1-methyl-1H-pyrazol-5-yl)cyclopropyl)methyl)-isoindoline-1,3-dione (**20c**).*

Yield 1 g (85%). White solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.84 (dd, *J* = 5.1, 3.1 Hz, 2H), 7.72 (dd, *J* = 5.2, 3.0 Hz, 2H), 7.30 (s, 1H), 5.96 (s, 1H), 4.09 (dd, *J* = 14.6, 5.6 Hz, 1H), 3.84 (dd, *J* = 14.5, 9.3 Hz, 1H), 3.76 (s, 3H), 2.66 (dd, *J* = 13.0, 7.2 Hz, 1H), 2.27 (td, *J* = 13.5, 6.9 Hz, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 168.0, 138.3, 134.8, 134.4, 131.8, 123.6, 112.2 (t, *J* = 291.6 Hz), 104.9, 36.5, 34.6

(d, *J* = 5.2 Hz), 29.0 (t, *J* = 9.9 Hz), 23.8. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –135.7 (d, *J* = 158.8 Hz), –137.2 (d, *J* = 158.8 Hz). MS (ESI): m/z = 318 ($[M+H]^+$). Anal. Calcd. for $C_{16}H_{13}F_2N_3O_2$: C, 60.57; H, 4.13; N, 13.24. Found: C, 60.79; H, 4.28; N, 13.29.

*4.9. General procedure for the preparation of **21***

Phthalimide derivative ***20*** (0.412 g, 1.30 mmol) was heated in EtOH (10 mL) to reflux. Hydrazine monohydrate (0.651 g, 13.0 mmol) was added dropwise at reflux over 10 min. The resulting mixture was further stirred for 15 min at reflux leading to formation of a colorless solid product. The colorless suspension was allowed to cool down to rt and poured into a mixture of CH_2Cl_2 (10 mL) and H_2O (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine (2×10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give ***21***.

*4.9.1. (2,2-Difluoro-3-(1-methyl-1H-pyrazol-3-yl)cyclopropyl)methanamine (**21a**).*

Yield 0.24 g (99%). Yellowish oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.24 (d, *J* = 2.2 Hz, 1H), 6.02 (dd, *J* = 2.1, 1.3 Hz, 1H), 3.81 (s, 3H), 3.03 – 2.95 (m, 1H), 2.87 (ddd, *J* = 13.6, 8.0, 1.3 Hz, 1H), 2.48 (dd, *J* = 13.7, 7.4 Hz, 1H), 2.04 (qd, *J* = 7.9, 1.1 Hz, 1H), 1.68 (brs, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 144.9, 130.5, 113.5 (t, *J* = 288.9 Hz), 103.6, 39.4 (d, *J* = 5.5 Hz), 38.5, 31.9 (dd, *J* = 10.0, 8.7 Hz), 25.9 (dd, *J* = 12.0, 10.7 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –137.7 (dt, *J* = 156.8, 16.3 Hz), –140.2 (dt, *J* = 156.8, 16.3 Hz). MS (ESI): m/z = 188 ($[M+H]^+$), 171($[M–NH_3]^+$), 151. Anal. Calcd. for $C_8H_{11}F_2N_3$: C, 51.33; H, 5.92; N, 22.45. Found: C, 51.21; H, 5.64; N, 22.73.

*4.9.2. (2,2-Difluoro-3-(1-methyl-1H-pyrazol-4-yl)cyclopropyl)methanamine (**21b**).*

Yield 0.45 g (96%). Yellowish oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29 (s, 1H), 7.17 (s, 1H), 3.78 (s, 3H), 2.94 (ddd, *J* = 13.5, 6.7, 3.0 Hz, 1H), 2.83 (dd, *J* = 13.5, 7.9 Hz, 1H), 2.23 (dd, *J* = 14.3, 7.2 Hz, 1H), 1.67 (dq, *J* = 14.5, 7.2 Hz, 1H), 1.48 (brs, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 137.9, 128.0, 114.0 (t, *J* = 288.3 Hz), 113.9, 39.5 (d, *J* = 5.6 Hz), 38.6, 33.6, 22.6. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –136.4 (dd, *J* = 156.3, 14.4 Hz), –140.6 (dd, *J* = 156.1, 14.3 Hz). MS (ESI): m/z = 188 ($[M+H]^+$), 171($[M–NH_3]^+$), 151. Anal. Calcd. for $C_8H_{11}F_2N_3$: C, 51.33; H, 5.92; N, 22.45. Found: C, 51.61; H, 5.64; N, 22.80.

*4.9.3. (2,2-Difluoro-3-(1-methyl-1H-pyrazol-5-yl)cyclopropyl)methanamine (**21c**).*

Yield 0.26 g (87%). Yellowish oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.31 (d, *J* = 1.7 Hz, 1H), 6.01 (s, 1H), 3.80 (s, 3H), 2.99 (ddd, *J* = 13.5, 6.7, 2.8 Hz, 1H), 2.92 (dd, *J* = 13.5, 7.9 Hz, 1H), 2.31 (dd, *J* = 13.1, 7.2 Hz, 1H), 1.91 (dq, *J* = 14.7, 7.3 Hz, 1H), 1.41 (brs, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 138.2, 135.4, 113.1 (t, *J* = 290.5 Hz), 105.0, 39.3 (d, *J* = 5.1 Hz), 36.5, 32.7 (dd, *J* = 10.5, 8.3 Hz), 22.6 (dd, *J* = 12.8, 10.9 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –134.7 (d, *J* = 156.9 Hz), –139.2 (d, *J* = 156.9 Hz). MS (ESI): m/z = 188 ($[M+H]^+$), 168($[M–HF]^+$). Anal. Calcd. for $C_8H_{11}F_2N_3$: C, 51.33; H, 5.92; N, 22.45. Found: C, 51.70; H, 5.53; N, 22.39.

*4.10. General procedure for the preparation of **23***

Sodium iodide (1.27 g, 8.5 mmol) was added to a solution of alkene ***24*** (4.01 g) in anhydrous THF (60 mL) under nitrogen atmosphere and heated to reflux. Trimethyl(trifluoromethyl)silane (12 g, 84.8 mmol) was added dropwise during 24 h. The reaction

mixture was heated overnight; the conversion was detected by ^{1}H NMR. The solvent was evaporated, and the crude material was purified by column chromatography (EtOAc –hexane (1:1) as eluent) to give ***23.***

*4.10.1. Methyl 2,2-difluoro-1-(1-methyl-1H-pyrazol-3-yl)cyclopropane-1-carboxylate (**23a**).*

Used in the next step without purification. Yield 2.50 g. Yellowish oil. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –131.4 (d, *J* = 146.8 Hz), –135.7 (d, *J* = 146.8 Hz). MS (EI): m/z = 216 (M^+), 185 (M^+–CH_3–F), 155.

*4.10.2. Methyl 2,2-difluoro-1-(1-methyl-1H-pyrazol-4-yl)cyclopropane-1-carboxylate (**23b**).*

Yield 1.5 g (27%). Yellowish oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.44 (d, *J* = 2.5 Hz, 2H), 3.88 (s, 3H), 3.74 (s, 3H), 2.60 (ddd, *J* = 13.2, 7.9, 6.0 Hz, 1H), 1.82 (ddd, *J* = 11.7, 7.9, 5.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 167.0, 138.9, 130.2, 112.4, 110.8 (t, *J* = 292.9 Hz), 52.6, 38.6, 30.9 (t, *J* = 11.5 Hz), 22.1 (dd, *J* = 9.9, 8.9 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –130.8 (d, *J* = 147.2 Hz), –135.8 (d, *J* = 147.2 Hz). MS (ESI): m/z = 217 ($[M+H]^+$), 167. Anal. Calcd. for $C_9H_{10}F_2N_2O_2$: C, 50.00; H, 4.66; N, 12.96. Found: C, 50.37; H, 4.52; N, 13.09.

*4.10.3. Methyl 2,2-difluoro-1-(1-methyl-1H-pyrazol-5-yl)cyclopropane-1-carboxylate (**23c**).*

Yield 1.1 g (21%). Yellowish oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36 (s, 1H), 6.16 (s, 1H), 3.80 (s, 3H), 3.68 (s, 3H), 2.71 (dt, *J* = 12.1, 7.4 Hz, 1H), 1.94 (ddd, *J* = 12.4, 7.7, 4.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 165.9, 138.4, 134.3, 110.9 (dd, *J* = 292.0, 287.9 Hz), 107.5, 53.4, 36.9, 31.1 (dd, *J* = 12.4, 10.9 Hz), 23.3 (dd, *J* = 10.3, 8.7 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –128.9 (d, *J* = 147.8 Hz), –135.7 (d, *J* = 147.8 Hz). MS (ESI): m/z = 217 ($[M+H]^+$). Anal. Calcd. for $C_9H_{10}F_2N_2O_2$: C, 50.00; H, 4.66; N, 12.96. Found: C, 50.37; H, 4.9; N, 13.26.

*4.11. General procedure for the preparation of **24***

Paraformaldehyde (6.6 g, 0.22 mol), TBAI (4.88 g, 0.013 mol) and K_2CO_3 (12.2 g, 0.088 mol) were added to a solution of ester ***27*** (7.50 g, 0.049 mol) in toluene (115 mL). The reaction mixture was stirred overnight at 80 °C, then filtered, and the solvent was evaporated. The residue was dissolved in CH_2Cl_2 (150 mL) and washed with distilled water (100 mL) and brine (100 mL). The solution was dried over Na_2SO_4, and CH_2Cl_2 was evaporated. The crude product was purified by column chromatography (EtOAc –hexane (1:1) as eluent).

*4.11.1. Methyl 2-(1-methyl-1H-pyrazol-3-yl)acrylate (**24a**).*

Used in the next step immediately after preparation. Yield 4.0 g. Yellowish oil. MS (ESI): m/z = 168 ($[M+H]^+$).

*4.11.2. Methyl 2-(1-methyl-1H-pyrazol-4-yl)acrylate (**24b**).*

Yield 4.6 g (43%). Yellowish oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.71 (s, 1H), 7.64 (s, 1H), 6.11 (s, 1H), 5.89 (s, 1H), 3.84 (s, 3H), 3.78 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 166.2, 137.2, 131.0, 129.1, 121.5, 117.0, 51.6, 38.4. MS (ESI): m/z = 167 ($[M+H]^+$). Anal. Calcd. for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.86; H, 6.44; N, 16.75.

*4.11.3. Methyl 2-(1-methyl-1H-pyrazol-5-yl)acrylate (**24c**).*

Yield 4.8 g (59%). Yellowish oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45 (d, *J* = 1.9 Hz, 1H), 6.64 (d, *J* = 1.3 Hz, 1H), 6.25 (d, *J* = 1.9 Hz, 1H), 5.94 (d, *J* = 1.3 Hz, 1H), 3.82 (s, 3H), 3.76 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 164.9, 137.9, 137.7, 131.5, 130.7, 107.1, 52.3, 37.1. MS (ESI): m/z = 167 ($[M+H]^+$), 107. Anal. Calcd. for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.60; H, 5.97; N, 17.04.

4.12. General procedure for the preparation of ***26***

Nitrile ***25*** (21,5 g, 0.1775 mol) was added to a solution of NaOH (71.0 g, 1.775 mol) in distilled water (640 mL). The reaction mixture was stirred overnight at reflux. The mixture was allowed to cool to rt, washed with CH_2Cl_2 (300 mL), and aq HCl was added to acidify to pH = 1. The water from the solution was evaporated and triturated with *i*-PrOH (300 mL). The solid was filtered off, and the filtrate was evaporated in vacuo to give acid ***26.***

*4.12.1. 2-(1-Methyl-1H-pyrazol-3-yl)acetic acid hydrochloride (**26a**).*

Yield 20.0 g (64%). Yellowish solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.15 (brs, 2H), 7.66 (s, 1H), 6.18 (s, 1H), 3.78 (s, 3H), 3.51 (s, 2H). ^{13}C NMR (DMSO-d_6, 101 MHz) δ 171.8, 144.6, 131.8, 108.5, 38.1, 33.7. MS (ESI): m/z = 141 ($[M+H]^+$). Anal. Calcd. for $C_6H_9ClN_2O_2$: C, 40.81; H, 5.14; N, 15.86; Cl, 20.08. Found: C, 41.04; H, 5.28; N, 16.13; Cl, 20.16.

*4.12.2. 2-(1-Methyl-1H-pyrazol-5-yl)acetic acid hydrochloride (**26c**).*

Yield 8.1 g (71%). White solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.78 (brs, 2H), 7.29 (s, 1H), 6.12 (s, 1H), 3.77 (s, 3H), 3.63 (s, 2H). ^{13}C NMR (DMSO-d_6, 101 MHz) δ 170.8, 137.2, 135.9, 106.0, 36.1, 31.1. MS (ESI): m/z = 141 ($[M+H]^+$), 95. Anal. Calcd. for $C_6H_9ClN_2O_2$: C, 40.81; H, 5.14; N, 15.86; Cl, 20.08. Found: C, 41.04; H, 5.32; N, 15.52; Cl, 20.30.

4.13. General procedure for the preparation of ***27***

Thionyl chloride (20.2 g, 12.3 mL, 0.170 mol) was added dropwise to a solution of acid ***26*** (20.0 g, 0.113 mol) in dry methanol (200 mL) at 0 °C over 1 h. The reaction mixture was stirred overnight at rt. The methanol was evaporated, the solid residue was dissolved in water (300 mL) and washed with CH_2Cl_2 (150 mL). The layers were separated, and NaOH was added to the aqueous layer to pH = 12–14, with further extraction with CH_2Cl_2 (3×200 mL). The organic layers were mixed, dried over Na_2SO_4 and CH_2Cl_2 was evaporated to give ester ***27***.

*4.13.1. Methyl 2-(1-methyl-1H-pyrazol-3-yl)acetate (**27a**).*

Yield 13.5 g (78%). Yellowish oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.20 (s, 1H), 6.09 (s, 1H), 3.75 (s, 3H), 3.60 (s, 3H), 3.58 (s, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.8, 144.5, 130.5, 104.9, 51.4, 38.1, 33.5. MS (EI): m/z = 154 (M^+), 95 (M^+–$COOCH_3$). Anal. Calcd. for $C_7H_{10}N_2O_2$: C, 54.54; H, 6.54; N, 18.17. Found: C, 54.43; H, 6.65; N, 18.06.

*4.13.2. Methyl 2-(1-methyl-1H-pyrazol-4-yl)acetate (**27b**).*

Yield 18.2 g (83%).^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30 (s, 1H), 7.27 (s, 1H), 3.77 (s, 3H), 3.61 (s, 3H), 3.41 (s, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 171.4, 138.6, 128.9, 112.7, 51.6, 38.6, 29.7. MS (ESI): m/z = 155 ($[M+H]^+$). Anal. Calcd. for $C_7H_{10}N_2O_2$: C, 54.54; H, 6.54; N, 18.17. Found: C, 54.63; H, 6.33; N, 18.56.

*4.13.3. Methyl 2-(1-methyl-1H-pyrazol-5-yl)acetate (**27c**).*

Yield 5.6 g (79%). Yellowish oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.33 (d, *J* = 1.7 Hz, 1H), 6.10 (d, *J* = 1.4 Hz, 1H), 3.75 (s, 3H), 3.65 (s, 3H), 3.62 (s, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 168.8, 137.7, 134.1, 106.1, 52.1, 36.2, 31.3. MS (ESI): m/z = 155 ($[M+H]^+$). Anal. Calcd. for $C_7H_{10}N_2O_2$: C, 54.54; H, 6.54; N, 18.17. Found: C, 54.61; H, 6.76; N, 18.03.

*4.14. General procedure for the preparation of **28***

A solution of KOH (0.17 g, 4.2mmol) in water (1 mL) was added to solution of ester ***23*** (0.46 g) in methanol (5 mL). The reaction mixture was stirred overnight at rt, evaporated and the solid residue was dissolved in water (7 mL). The solution was washed with CH_2Cl_2 (2×5 mL) and acidified with citric acid to pH = 3. The obtained solution was extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure to give ***28***.

*4.14.1. 2,2-Difluoro-1-(1-methyl-1H-pyrazol-3-yl)cyclopropane-1-carboxylic acid (**28a**).*

Yield 0.55 g (43%). Yellowish solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 13.26 (brs, 1H), 7.64 (d, *J* = 1.7 Hz, 1H), 6.35 (d, *J* = 1.8 Hz, 1H), 3.79 (s, 3H), 2.47 – 2.38 (m, 1H), 2.31 (dt, *J* = 13.5, 6.8 Hz, 1H). ^{13}C NMR (DMSO-d_6, 101 MHz) δ 167.4, 142.5, 131.6, 111.9 (t, *J* = 287.2 Hz), 106.6, 38.5, 34.1 (t, *J* = 11.0 Hz), 20.3 (t, *J* = 9.2 Hz). ^{19}F NMR (DMSO-d_6, 376 MHz) δ –131.1 (d, *J* = 144.5 Hz), –134.2 (d, *J* = 144.4 Hz). MS (ESI): m/z = 203 ($[M+H]^+$), 185 ($[M–OH]^+$). Anal. Calcd. for $C_8H_8F_2N_2O_2$: C, 47.53; H, 3.99; N, 13.86. Found: C, 47.21; H, 3.98; N, 13.64.

*4.14.2. 2,2-Difluoro-1-(1-methyl-1H-pyrazol-4-yl)cyclopropane-1-carboxylic acid (**28b**).*

Yield 0.67 g (72%). Yellowish solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 13.02 (brs, 1H), 7.74 (s, 1H), 7.42 (s, 1H), 3.80 (s, 3H), 2.42 (dd, *J* = 13.5, 7.1 Hz, 1H), 2.13 (ddd, *J* = 12.9, 8.1, 5.0 Hz, 1H). ^{13}C NMR (DMSO-d_6, 101 MHz) δ 167.9, 138.8, 131.0, 112.3 (t, *J* = 289.4 Hz), 112.3, 38.5, 31.4 (t, *J* = 11.0 Hz), 21.2 (t, *J* = 8.8 Hz). ^{19}F NMR (DMSO-d_6, 376 MHz) δ –131.1 (d, *J* = 144.0 Hz), –134.8 (d, *J* = 143.9 Hz). MS (ESI): m/z = 203 ($[M+H]^+$), 153. Anal. Calcd. for $C_8H_8F_2N_2O_2$: C, 47.53; H, 3.99; N, 13.86. Found: C, 47.33; H, 3.59; N, 14.10.

*4.14.3. 2,2-Difluoro-1-(1-methyl-1H-pyrazol-5-yl)cyclopropane-1-carboxylic acid (**28c**).*

Yield 0.70 g (75%). Yellowish solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.36 (s, 1H), 6.28 (s, 1H), 3.77 (s, 3H), 2.68 (dt, *J* = 12.5, 7.8 Hz, 1H), 2.31 (ddd, *J* = 13.1, 8.1, 5.5 Hz, 1H). ^{13}C NMR (DMSO-d_6, 101 MHz) δ 166.6, 137.5, 134.6, 111.9 (dd, *J* = 290.9, 285.1 Hz), 107.2, 36.5, 30.9 (t, *J* = 11.4 Hz), 22.7 (t, *J* = 9.1 Hz). ^{19}F NMR (DMSO-d_6, 376 MHz) δ –127.9 (d, *J* = 145.5 Hz), –134.9 (d, *J* = 145.4 Hz). MS (ESI): m/z = 203 ($[M+H]^+$), 155. Anal. Calcd. for $C_8H_8F_2N_2O_2$: C, 47.53; H, 3.99; N, 13.86. Found: C, 47.31; H, 3.59; N, 13.60.

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