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N-Difluorocyclopropyl-substituted pyrazoles: synthesis and reactivity

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Abstract: Difluorocyclopropanation of *N*-vinylazoles with the $CF3SiMe_3$ – NaI system was studied. It was found that *N*-vinylpyrazoles could be transformed into the corresponding *N*-difluorocyclopropyl-substituted derivatives. The method was efficient on a 100 g scale and could be applied for the preparation of various functionalized regioisomeric pyrazole derivatives bearing a *gem*-difluorocyclopropane moiety, *e.g.* amines, carboxylic acids, aldehydes, bromides, and boronic ester. It was found that *N*-difluorocyclopropylpyrazole moiety tolerated many common reagents including nitrating mixture, bromine, aqueous acids and alkali, $KMnO_4$, $LiBH_4$, and $Pd^{(0)}$ complexes; it was unstable towards $AlCl_3$, catalytic hydrogenation and lithiation conditions. The products obtained are advanced building blocks which of potential importance to medicinal and agrochemistry.

Introduction

Fluorinated cyclopropanes have become extraordinary structural motifs which attracted much attention in organic synthesis, drug discovery and agrochemistry over the last years.[1–10] In particular, highly potent compounds bearing a *gem*-difluorocyclopropyl substituent were disclosed in recent patents, *e.g.* as highly potent metabotropic glutamate receptor 2 (mGluR2) agonists **1**,[11] glycine transporter 1 (GlyT1) inhibitor **2**,[12] extracellular signal-regulated kinase 2 (ERK2) inhibitors **3**,[13] or macrocyclic factor XIa (FXIa) inhibitor **4**[14] (Figure 1).

While a number of papers describe synthetic approaches to the compounds having a *gem*-difluorocyclopropyl group attached to the carbon atom,[15–24] as well as their chemical transformations,[6,25–29] the corresponding *N*-substituted analogues are much less studied. Most of them referred to the parent *gem*-difluorocyclopropylamine (**5**) or its derivatives (Scheme 1);[26,30–33] it should be noted that similar aliphatic amines (*e.g.* **6**) were reported to have limited stability.[34] In a recent paper by Xiao and co-workers, a few *N*-difluorocyclopropyl-substituted indole, benzimidazole and benzotriazole derivatives of general formula **7** were synthesized by *N*-alkylation of the corresponding heterocyclic anions with tosylate **8**.[35] In the current work we describe an alternative approach to *N*-difluorocyclopropyl-substituted azo-

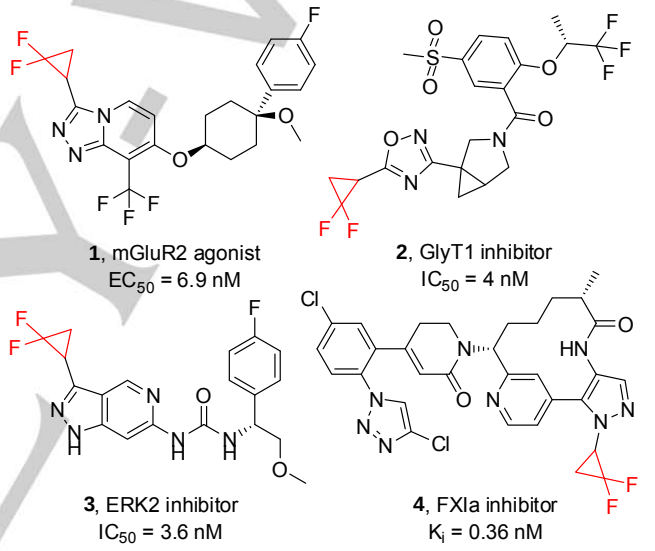
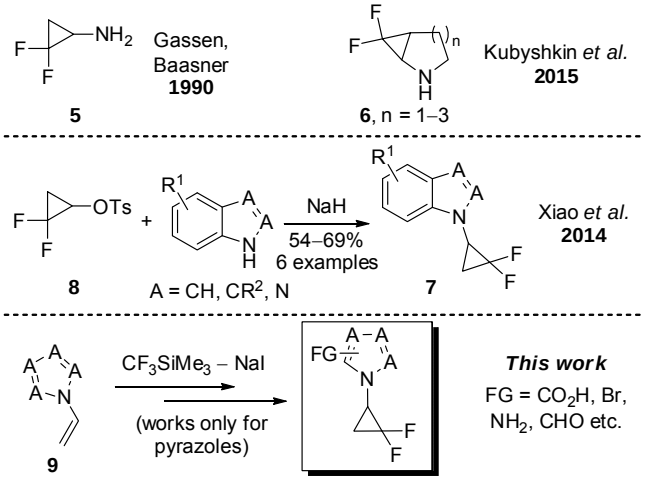


Figure 1. Biologically active heterocyclic compounds bearing a *gem*-difluorocyclopropyl substituent



Scheme 1. Synthesis of compounds bearing a *gem*-difluorocyclopropyl substituent at the nitrogen atom

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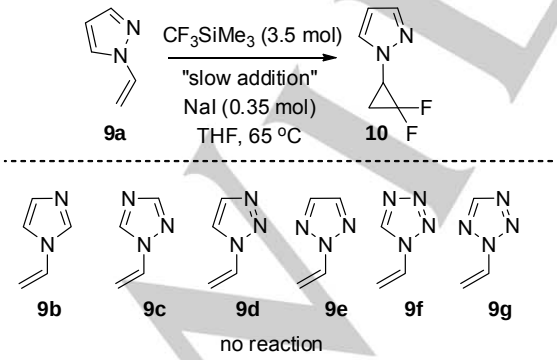
les, which is based on the difluorocyclopropanation of the corresponding *N*-vinylazoles **9** with the CF_3SiMe_3 – NaI system, which was initially developed by Hu, Prakash, Olah and co-workers in 2011,[15] and has been used by many other groups since then.[16–19,36–38] Although this method appeared to be suitable only for the pyrazole derivatives, a wide range of functionalized compounds could be obtained, which are valuable low-molecular-weight building blocks for drug discovery and agrochemistry. In addition to that, tolerance of the *N*-difluorocyclopropyl-substituted azole moiety towards the conditions of common organic reactions is studied herein.

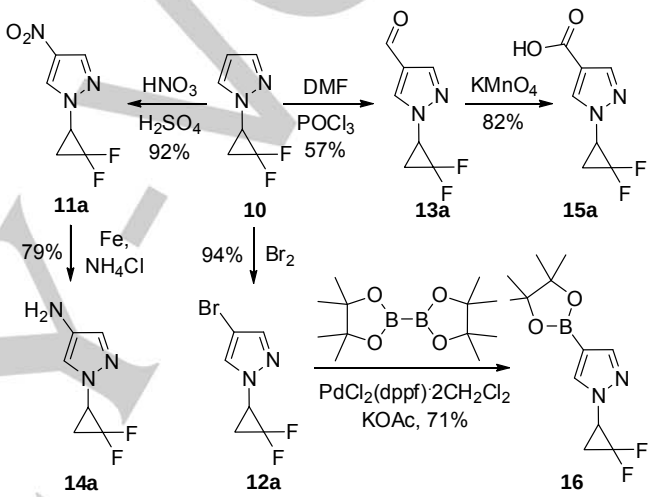
Results and Discussion

First of all, the conditions of Xiao and co-workers[35] (*i.e.* reaction of tosylate **8** with azole anion) were tested for the case of pyrazole. It was found that the method was unfruitful in this case. Therefore, we have prepared the parent *N*-vinylazoles **9a–g** using the known procedures[39,40] and evaluated them in the reaction with the CF_3SiMe_3 – NaI system. It was found that pyrazole derivative **9a** reacted smoothly when "slow addition" protocol was used (CF_3SiMe_3 (3.5 mol, added over 12–16 h), NaI (0.35 mol, reflux),[15,19] and the corresponding product **10** was obtained in 83% yield (Scheme 2). It should be noted that this transformation was performed at up to 128 g scale without considerable changes in the yield. In some cases, however, the reaction proceeded vigorously after addition of *ca.* 0.8–1.2 equivalents of CF_3SiMe_3; an induction period was observed. This is yet another fact showing that the reaction cannot be described simply as difluorocarbene cycloaddition;[18,20] in particular, some type of radical mechanism might be involved.
Unfortunately, other azole derivatives **9b–g** were unreactive towards the Ruppert–Prakash reagent with the use of either "one-batch" or "slow addition" protocol;[18,19] no conversion of **9b–g** was observed. Although the reason behind this result is unclear, it might be addressed either to the presence of a nucleophilic nitrogen atom (especially in the case of **9b**) or to electronic effects (for other representatives). Therefore, further study was focused on the preparation of various *N*-(difluorocyclopropyl)pyrazoles.



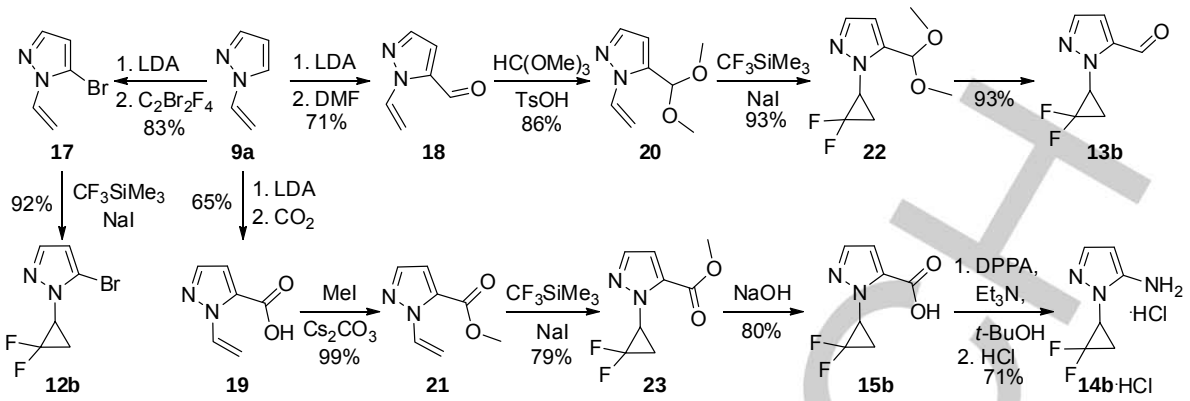
Scheme 2. Difluorocyclopropanation of parent *N*-vinylazoles

Initially, the product **10** was envisaged as the key intermediate for the preparation of the corresponding functionalized derivatives. Indeed, it was found that common electrophilic substitution reactions (*i.e.* nitration, bromination, and the Vilsmeier – Haack formylation) proceeded smoothly and gave the corresponding 1,4-disubstituted pyrazole derivatives **11a–13a** in 57–94% yields (Scheme 3). Further transformations of these products allowed for the preparation of some other important building blocks. In particular, amine **14a** was obtained in 79% yield by reduction of the nitro derivative **11a** with Fe – NH_4Cl in aq EtOH, whereas oxidation of aldehyde **13a** with $KMnO_4$ in 1,4-dioxane – H_2O gave the corresponding carboxylic acid **15a** (82% yield). It should be noted that catalytic hydrogenation of **11a** (H_2 (1 atm), Pd-C, rt) was unfruitful; a complex mixture of products was obtained, apparently due to instability of the difluorocyclopropane moiety at these conditions. Boronic ester **16** was prepared from the bromide **12a** by reaction with bis(pinacolato)diboron in the presence of $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ and KOAc in DMSO at 80 °C (71% yield).



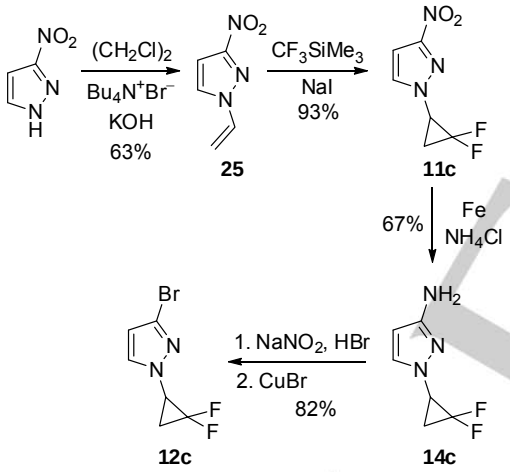
Scheme 3. Functionalization of *N*-(*gem*-difluorocyclopropyl)pyrazole (**10**)

Unfortunately, the compound **10** appeared to be unstable under the Friedel – Crafts acylation conditions (AcCl, $AlCl_3$, CH_2Cl_2, 0 °C); a complex mixture of products was obtained in this case. In addition to that, stability of **10** towards aqueous acids and alkali was studied. It was found that the compound remained intact upon heating with either 2 M or conc aq. HCl, as well as with 2 M aq NaOH at 100 °C for 1 h.
On the contrary, functionalization of the compound **10** at the position 5 of the pyrazole ring *via* lithiation was not fruitful; a complex mixture of unidentified products was formed instead, which clearly indicated instability of the *N*-*gem*-difluorocyclopropyl group towards the reaction conditions tested (*n*-BuLi, LiHMDS, LDA or *i*-PrMgCl·LiCl, THF, –78 °C; LiTMP, THF, –100°C). Therefore, we decided to introduce the corresponding functional groups into the starting material **9a** prior the difluorocyclopropanation step. In particular, bromide **17**, aldehyde **18**, and carboxylic acid **19** were obtained by lithiation of **9a** and subsequent trapping of the organolithium species with the corresponding electrophile (65–83% yield) (Scheme 4). Since the free aldehyde and carboxylic functions are not compatible with the difluorocyclopropanation conditions, the products **18** and **19** were transformed into the corresponding protected derivatives **20** (86% yield) and **21** (99% yield), respectively. Difluorocyclopropanation of **17**, **20** and **21** gave the correspon-



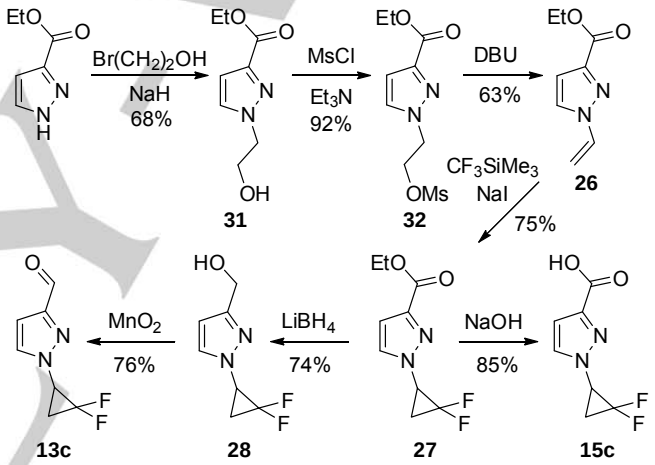
Scheme 4. Synthesis of 1,5-disubstituted *N*-(*gem*-difluorocyclopropyl)pyrazole derivatives

ding products **12b**, **22** and **23** (92%, 93% and 79% yield, respectively). The compounds **22** and **23** were transformed into the target building blocks **13b** and **15b** in 93% and 80% yield, respectively, upon deprotection. Finally, amine **14b** was obtained in 71% yield though a modified Curtius rearrangement via the corresponding *N*-Boc derivative **24**.

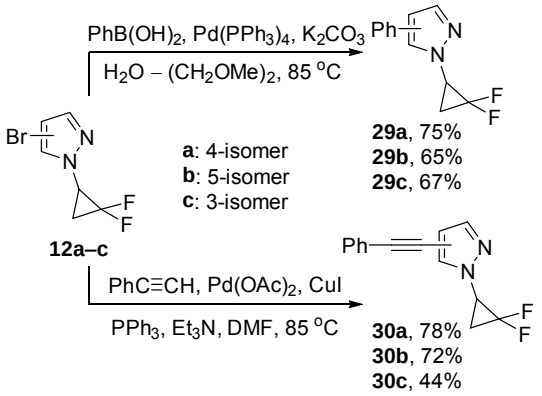


Scheme 5. Synthesis of 1,3-disubstituted *N*-(*gem*-difluorocyclopropyl)pyrazole derivatives **11c**, **12c** and **14c**

An approach to the remaining *N*-(*gem*-difluorocyclopropyl)pyrazole derivatives, *i.e.* 1,3-disubstituted isomers, relied on a synthesis of the corresponding *N*-vinylpyrazoles **25** and **26**. It should be noted that only compound **26** was described in the literature to date;[41] nevertheless, we have used our own methods for the preparation of both derivatives (Schemes 5 and 6). Difluorocyclopropanation of **25** and **26** occurred under standard conditions described above and gave the corresponding products **11c** and **27** in 93% and 75% yield, respectively. Transformations of the nitro derivative **11c** included reduction with Fe – NH_4Cl giving amine **14c** (67% yield), as well as subsequent diazotation of **14c** and Sandmeyer reaction leading to the formation of bromide **12c** (82% yield). Ester **27** was transformed into the corresponding carboxylic acid **15c** (85% yield) by alkaline hydrolysis; alternatively, it was reduced to alcohol **28** with $LiBH_4$ (74% yield), which in turn was oxidized to aldehyde **13c** with MnO_2 (76% yield).



Scheme 6. Synthesis of 1,3-disubstituted *N*-(*gem*-difluorocyclopropyl)pyrazole derivatives **13c** and **15c**



Scheme 7. Palladium-catalyzed couplings in the *N*-(*gem*-difluorocyclopropyl)pyrazole series

Since it is known from the literature *that gem*-difluorocyclopropanes are susceptible to palladium-catalyzed ring opening,[26] we

have studied common C–C and C–N coupling reactions with bromides **12a–c** (Scheme 7). It was found that the Suzuki – Miyaura and Sonogashira reactions were effective with **12a–c**, so that the corresponding products of C–C coupling **29a–c** and **30a–c** were obtained in 44–78% yield. Notably, the difluorocyclopropane ring tolerated the presence of palladium- and copper-containing species at 85 °C.

Conclusions

Difluorocyclopropanation of *N*-vinylpyrazoles with subsequent modification of the products obtained is a convenient method for the regioselective synthesis of various functionalized *N*-(*gem*-difluorocyclopropyl)pyrazoles, including amines, carboxylic acids, aldehydes, bromides, and boronic derivative (Figure 2). The method is not fruitful for the preparation of other azole derivatives studied (*i.e.* imidazole and 1,2,4-triazole). The *N*-*gem*-difluorocyclopropyl moiety attached to the pyrazole ring tolerates a number of typical organic transformations including nitration, bromination, treatment with acids and alkali, mild oxidation and reduction, as well as Pd-catalyzed couplings; it is unstable towards action of metallation agents like *n*-BuLi or lithium amides, strong Lewis acids like $AlCl_3$, or catalytic hydrogenolysis (Table 1). The building blocks described in this work were obtained on up to 50 g scale. Therefore, they can be considered as readily available to scientific community and are promising reagents for drug discovery and agrochemistry, which are fully compatible with even the strictest compound selection criteria.[42,43]

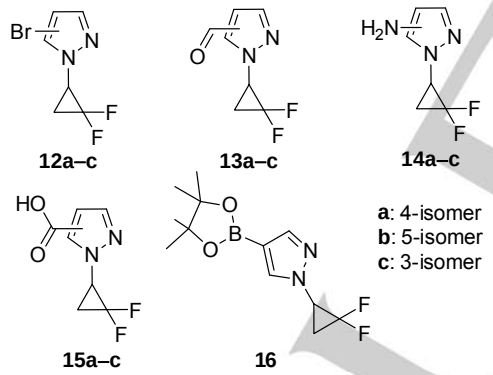


Figure 2. The key building blocks obtained in this work

Table 1. Tolerance of *N*-(*gem*-difluorocyclopropyl)pyrazoles to common organic reactions

Tolerate		Unstable towards
HNO_3 – H_2SO_4	2/12 M aq. HCl, 100 °C	*n*-BuLi, LiHMDS, LDA or *i*-PrMgCl·LiCl, THF, –78 °C
Br_2	2 M aq. NaOH, 100 °C	
DMF – $POCl_3$	$Pd(dppf)Cl_2$, B_2Pin_2, 80 °C[a]	LiTMP, THF, –100°C
$LiBH_4$	$Pd(PPh_3)_4$, 85 °C	H_2 (1 atm), Pd-C, rt
$KMnO_4$ or MnO_2	$Pd(OAc)_2$, PPh_3, CuI, 85 °C	$CH_3C(O)Cl$, $AlCl_3$

a) B_2Pin_2 – bis(pinacolato)diboron

Experimental Section

General. The solvents were purified according to the standard procedures.[44] All starting materials were purchased from commercial sources. Melting points were measured on MPA100 OptiMelt automated melting point system. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. ^1H and ^{13}C NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (at 499.9 MHz for Protons and 124.9 MHz for Carbon-13) and Varian Unity Plus 400 spectrometer (at 400.4 MHz for protons and 100.7 MHz for Carbon-13). Chemical shifts are reported in ppm downfield from TMS as an internal standard. Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, National Taras Shevchenko University of Kyiv. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (APCI), electrospray ionization (ESI)) and Agilent 5890 Series II 5972 GCMS instrument (electron impact ionization (EI)).

General procedure for the preparation of 10, 11c, 12b, 22, 23, and 27.
NaI (26.2 g, 0.175 mol) was added to a solution of the corresponding *N*-vinylpyrazole (0.500 mol) in THF (500 mL) under nitrogen atmosphere, and the mixture was heated to reflux. CF_3SiMe_3 (249 g, 1.75 mol) was added dropwise over 12–16 h at this temperature (CAUTION! In some cases, the reaction proceeded vigorously after addition of *ca.* 0.4–0.6 mol of CF_3SiMe_3). The reaction mixture was heated overnight, and the conversion was monitored by ^1H NMR and/or GCMS. After the completion of the reaction, the solvent was evaporated in *vacuo*, the residue was diluted with CH_2Cl_2 (500 mL), the precipitate was filtered off, and the combined filtrates were evaporated or subjected to distillation in *vacuo*.

1-(2,2-Difluorocyclopropyl)-1*H*-pyrazole (10). The compound was purified by distillation in *vacuo*. Yield 59.1 g (82%); yellowish liquid; bp 46–48 °C / 13 mmHg. ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 1.9 Hz, 1H), 7.48 (d, *J* = 2.4 Hz, 1H), 6.28 (t, *J* = 2.1 Hz, 1H), 4.06 (tdd, *J* = 9.6, 5.8, 2.3 Hz, 1H), 2.18 (ddt, *J* = 14.7, 9.6, 5.8 Hz, 1H), 2.11–1.99 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.4, 130.5, 109.3 (t, *J* = 286 Hz), 106.5, 38.7 (dd, *J* = 16.2, 9.8 Hz), 18.0 (t, *J* = 11.0 Hz). $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ –130.7 (d, *J* = 163 Hz), –143.3 (d, *J* = 163 Hz). GC/MS (EI): *m/z* = 144 $[M]^+$. Anal. Calcd. for $C_6H_6F_2N_2$: C, 50.00; H, 4.20; N, 19.44. Found: C, 49.78; H, 4.37; N, 19.26.

5-Bromo-1-(2,2-difluorocyclopropyl)-1*H*-pyrazole (12b). The compound was purified by distillation in *vacuo*. Yield 103 g (92%); yellowish oil; bp 71–73 °C / 13 mmHg. ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 1.9 Hz, 1H), 6.35 (d, *J* = 1.9 Hz, 1H), 3.94 (dddd, *J* = 10.3, 7.8, 5.8, 1.9 Hz, 1H), 2.51 – 2.39 (m, 1H), 2.12 (dtd, *J* = 12.4, 10.3, 7.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.9 (d, *J* = 0.7 Hz), 115.4, 109.6, 108.9 (dd, *J* = 287, 286 Hz), 37.9 (dd, *J* = 16.3, 9.9 Hz), 17.2 (t, *J* = 11.3 Hz). $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ –132.0 (d, *J* = 162 Hz), –144.0 (d, *J* = 162 Hz). GC/MS (EI): *m/z* = 222/224 $[M]^+$. Anal. Calcd. for $C_6H_5BrF_2N_2$: C, 32.31; H, 2.26; N, 12.56; Br, 35.83. Found: C, 32.69; H, 1.95; N, 12.89; Br, 35.59.

1-(2,2-Difluorocyclopropyl)-5-(dimethoxymethyl)-1*H*-pyrazole (22). Yield 101 g (93%); yellowish oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 1.8 Hz, 1H), 6.34 (d, *J* = 1.8 Hz, 1H), 5.52 (s, 1H), 4.01–4.07 (m, *J* = 10.0, 8.2, 5.9, 1.8 Hz, 1H), 3.37 (s, 3H), 3.28 (s, 3H), 2.48 (ddt, *J* = 14.4, 10.0, 5.9 Hz, 1H), 2.01 (ddd, *J* = 12.8, 10.0, 7.1 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.3, 138.7, 109.4 (dd, *J* = 288, 285 Hz), 107.3, 53.5, 52.3, 38.2 (dd, *J* = 15.7, 9.7 Hz), 16.6 (t, *J* = 11.1 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ –131.3 (dddd, *J* = 161, 12.8, 5.9, 1.8 Hz), –144.3 (ddd, *J* = 161, 14.4, 8.2 Hz). Anal. Calcd. for $C_9H_{12}F_2N_2O_2$: C, 49.54; H, 5.54; N, 12.84. Found: C, 49.42; H, 5.16; N, 12.86.

Methyl 1-(2,2-difluorocyclopropyl)-1*H*-pyrazole-5-carboxylate (23). Yield 79.9 g (79%); yellowish oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 2.0 Hz, 1H), 6.88 (d, *J* = 2.0 Hz, 1H), 4.40 (dddd, *J* = 10.4, 8.4, 5.9, 2.1

Hz, 1H), 3.91 (s, 3H), 2.46 (ddt, *J* = 13.9, 8.4, 5.9 Hz, 1H), 2.12 – 2.06 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.6, 138.9, 134.3, 112.2, 108.8 (dd, *J* = 288, 284 Hz), 52.1, 39.8 (dd, *J* = 15.8, 9.7 Hz), 16.9 (t, *J* = 11.2 Hz). ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ –132.0 (d, *J* = 163 Hz), –144.6 (d, *J* = 163 Hz). LC/MS (CI): *m/z* = 203 $[M+H]^+$. Anal. Calcd. for $C_9H_{12}F_2N_2O_2$: C, 49.54; H, 5.54; N, 12.84. Found: C, 49.50; H, 5.32; N, 12.64.

1-(2,2-Difluorocyclopropyl)-3-nitro-1*H*-pyrazole (11c). The compound was purified by flash chromatography on silica gel using hexanes – EtOAc (4:1) as eluent. Yield 67.1 g (71%); yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 2.7 Hz, 1H), 6.94 (d, *J* = 2.7 Hz, 1H), 4.22 (dddd, *J* = 10.9, 8.8, 5.5, 2.4 Hz, 1H), 2.40 – 2.31 (ddt, 14.4, 10.9, 5.5 Hz, 1H), 2.21 (dtd, *J* = 12.6, 8.8, 7.1 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.2, 133.7, 108.3 (dd, *J* = 289, 286 Hz), 103.6, 39.7 (dd, *J* = 16.4, 9.7 Hz), 17.9 (t, *J* = 11.2 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ –130.4 (dddd, *J* = 165, 12.6, 8.8, 5.5 Hz), –142.3 (dddd, *J* = 165, 14.4, 7.1, 2.4 Hz). LC/MS (CI): *m/z* = 190 $[M+H]^+$. Anal. Calcd. for $C_6H_5F_2N_3O_2$: C, 38.11; H, 2.66; N, 22.22. Found: C, 38.09; H, 2.95; N, 22.52.

Ethyl 1-(2,2-difluorocyclopropyl)-1*H*-pyrazole-3-carboxylate (27). Yield 81.1 g (75%); yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 2.4 Hz, 1H), 6.78 (d, *J* = 2.4 Hz, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 4.13 (dddd, *J* = 9.7, 6.9, 6.1, 2.3 Hz, 1H), 2.24 (ddt, *J* = 14.7, 9.7, 5.7 Hz, 1H), 2.09 (dtd, *J* = 12.2, 9.8, 6.1 Hz, 1H), 1.34 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.8, 144.8, 132.0, 109.4, 108.8 (dd, *J* = 288, 286 Hz), 61.1, 39.3 (dd, *J* = 16.3, 9.7 Hz), 18.2 (t, *J* = 11.0 Hz), 14.3. ^{19}F NMR (470 MHz, $CDCl_3$) δ –130.3 (dddd, *J* = 164, 12.2, 9.8, 5.7 Hz), –142.3 (ddd, *J* = 164, 14.7, 6.9 Hz). LC/MS (CI): *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, 50.39; H, 4.43; N, 12.65.

1-(2,2-Difluorocyclopropyl)-4-nitro-1*H*-pyrazole (11a). HNO_3 (20 mL) was added to a solution of **10** (10.0 g, 69.4 mmol) in H_2SO_4 (96%, 150 mL) at 0 °C. The reaction mixture was stirred at 70 °C for 3 h, then cooled to rt and poured into ice, and extracted with CH_2Cl_2 (3×100 mL). The combined organic layers were dried over Na_2SO_4 and evaporated in *vacuo*. Yield 12.1 g (92%); yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (s, 1H), 8.11 (s, 1H), 4.18 (dddd, *J* = 12.5, 9.8, 5.8, 2.4 Hz, 1H), 2.33 – 2.27 (m, 1H), 2.21 (dtd, *J* = 12.5, 9.8, 6.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.4, 136.3, 129.9, 108.2 (dd, *J* = 287, 286 Hz), 39.5 (dd, *J* = 16.7, 9.6, Hz) 18.0 (t, *J* = 11.1 Hz). ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –130.8 (d, *J* = 165 Hz), –142.7 (d, *J* = 165 Hz). LC/MS (CI): *m/z* = 190 $[M+H]^+$. Anal. Calcd. for $C_6H_5F_2N_3O_2$: C, 38.11; H, 2.66; N, 22.22. Found: C, 38.27; H, 2.72; N, 22.15.

4-Bromo-1-(2,2-difluorocyclopropyl)-1*H*-pyrazole (12a). A stirred solution of **10** (10.0 g, 69.4 mmol) in CH_2Cl_2 (100 mL) was cooled to 10 °C under argon atmosphere. Br_2 (16.6 g, 0.104 mol) was added over 10 min (NOTE: the temperature should not exceed 28 °C) and the resulting mixture was stirred at 25 °C for 1.5 h. Then, the solution was quenched with small portions of 10% aq Na_2SO_3 (50 mL) over 10 min, (NOTE: the temperature should not exceed 25 °C). The organic layer was separated, washed with brine (50 mL), dried over Na_2SO_4 and evaporated in *vacuo*. Yield 14.5 g (94%); brown oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.49 (s, 1H), 4.06 (dtd, *J* = 9.5, 6.6, 2.2 Hz, 1H), 2.19 (ddt, *J* = 14.2, 9.5, 5.6 Hz, 1H), 2.06 (dtd, *J* = 12.3, 9.9, 6.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.5, 130.2, 108.4 (dd, *J* = 288, 286 Hz), 93.6, 38.5 (dd, *J* = 16.2, 9.7 Hz), 17.3 (t, *J* = 11.1 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ –130.3 (dddd, *J* = 163, 12.3, 9.2, 5.6 Hz), –142.7 (dddd, *J* = 163, 14.2, 6.6, 2.2 Hz). GC/MS (EI): *m/z* = 222/224 $[M]^+$. Anal. Calcd. for $C_6H_5BrF_2N_2$: C, 32.31; H, 2.26; N, 12.56; Br, 35.83. Found: C, 32.44; H, 1.87; N, 12.26; Br, 35.44.

1-(2,2-Difluorocyclopropyl)-1*H*-pyrazole-4-carbaldehyde (13a). $POCl_3$ (162 mL, 266 g, 1,74 mol) was added dropwise to DMF (750 mL) at rt, the resulting mixture was stirred for 0.5 h, and pyrazole **10** (50.0 g, 0.347 mol) in DMF (500 mL) was added. The reaction mixture was stirred at 110 °C overnight, and most of DMF were evaporated in *vacuo* and the residue was poured into ice. Then aq $NaHCO_3$ was added to pH = 7–8, and the mixture was extracted $CHCl_3$ (4×250 mL). The combined organic layers were dried over Na_2SO_4 and evaporated in *vacuo*. The compound was purified by distillation in *vacuo*. Yield 34.0 g (57%); colorless liquid; bp 64–66 °C / 0.26 mmHg ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.88 (s, 1H), 8.05 (s, 1H), 8.01 (s, 1H), 4.22 – 4.11 (m, 1H), 2.28 – 2.14 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.7, 141.1, 134.3, 124.9, 108.6 (dd, *J* = 288, 286 Hz), 39.0 (dd, *J* = 16.3, 9.9 Hz), 18.1 (t, *J* = 11.1 Hz). ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –130.6 (d, *J* = 164 Hz), –142.7 (d, *J* = 164 Hz). GC/MS (EI): *m/z* = 172 $[M]^+$. Anal. Calcd. for $C_7H_6F_2N_2O$: C, 48.84; H, 3.51; N, 16.27. Found: C, 49.00; H, 3.53; N, 15.97.

General procedure for the preparation of 14a and 14c.

To a solution of nitropyrazole **11a** or **11c** (68.5 g, 0.362 mol) in EtOH (700 mL), aqueous solution of NH_4Cl (193 g, 3.62 mol) and Fe powder (80.4 g, 1.44 mol) were added. The reaction mixture was refluxed overnight, then cooled to rt, filtered through silica gel (500 g) and washed with EtOH (100 mL). The solvent was evaporated in *vacuo*, the residue was diluted with H_2O (500 mL) and extracted with CH_2Cl_2 (3×200 mL). The combined organic layers were dried over Na_2SO_4 and evaporated in *vacuo*.

1-(2,2-Difluorocyclopropyl)-1*H*-pyrazol-4-amine (14a). The compound was purified by column chromatography on silica gel using $CHCl_3$ – MeOH (30:1) as eluent. Yield 45.5 g (79%); violet powder; mp 54–56 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (s, 1H), 7.09 (s, 1H), 3.97 (tdd, *J* = 10.1, 5.8, 2.3 Hz, 1H), 2.82 (br s, 2H), 2.17 (ddt, *J* = 14.6, 9.4, 5.8 Hz, 1H), 2.01 (dtd, *J* = 12.8, 10.1, 6.2 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 132.6, 129.7, 118.9, 109.4 (t, *J* = 287 Hz), 38.9 (dd, *J* = 16.1, 9.7 Hz), 17.6 (t, *J* = 10.9 Hz). ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –130.9 (d, *J* = 162 Hz), –143.9 (d, *J* = 162 Hz). LC/MS (CI): *m/z* = 160 $[M+H]^+$. Anal. Calcd. for $C_6H_7F_2N_3$: C, 45.28; H, 4.43; N, 26.41. Found: C, 45.27; H, 4.56; N, 26.73.

1-(2,2-Difluorocyclopropyl)-1*H*-pyrazol-3-amine (14c). The compound was purified by flash chromatography on silica gel using $CHCl_3$ – MeOH (24:1) as eluent. Yield 38.6 g (67%); brown liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 2.4 Hz, 1H), 5.64 (d, *J* = 2.4 Hz, 1H), 3.97 – 3.83 (m, 1H), 3.54 (s, 2H), 2.08 – 1.92 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.1, 132.0, 109.7 (t, *J* = 286 Hz), 94.4, 38.2 (dd, *J* = 16.1, 9.6 Hz), 18.1 (t, *J* = 10.8 Hz). ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –130.5 (d, *J* = 162 Hz), –143.1 (d, *J* = 162 Hz). LC/MS (CI): *m/z* = 160 $[M+H]^+$. Anal. Calcd. for $C_6H_7F_2N_3$: C, 45.28; H, 4.43; N, 26.41. Found: C, 45.19; H, 4.78; N, 26.19.

1-(2,2-Difluorocyclopropyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (16). Bromide **12a** (1.20 g, 5.38 mmol), bis(pinacolato)diboron (1.65 g, 6.49 mmol) and KOAc (1.81 g, 18.4 mmol) were dissolved in DMSO (20 mL) under nitrogen atmosphere, and $PdCl_2(dppf)_2.CH_2Cl_2$ (220 mg, 0.269 mmol) was added. The resulting mixture was stirred under argon atmosphere at 80 °C overnight. Then the reaction mixture was cooled to rt, filtered through a Celite pad and washed with EtOAc (3×25 mL). The filtrate was washed with H_2O (2×50 mL) and brine (50 mL), the organic layer was dried over Na_2SO_4 and evaporated in *vacuo*. The crude compound was purified by flash chromatography on silica gel using hexanes – EtOAc (3:2) as eluent. Yield 1.03 g (71%); yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.79 (s, 1H), 4.09 (tdd, *J* = 10.0, 9.8, 2.2 Hz, 1H), 2.17 (ddt, *J* = 14.3, 9.6, 5.4 Hz, 1H), 2.07 (dtd, *J* = 13.7, 9.8, 6.3 Hz, 1H), 1.30 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.2, 137.4, 109.1 (t, *J* = 287 Hz), 83.4, 38.6 (dd, *J* = 16.2, 9.7 Hz), 24.8, 24.7, 17.9 (t, *J* = 11.0 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ –130.3 (dddd, *J* = 163, 13.7, 10.0, 5.4 Hz), –142.6 (ddd, *J* = 163, 14.3, 6.3 Hz). LC/MS (CI): *m/z* = 189 $[M–(HO(CH_3)_2C)_2+H]^+$, 271 $[M+H]^+$. Anal. Calcd. for $C_{12}H_{17}BF_2N_2O_2$: C, 53.36; H, 6.34; N, 10.37. Found: C, 53.52; H, 6.29; N, 10.74.

1-(2,2-Difluorocyclopropyl)-1*H*-pyrazole-4-carboxylic acid (15a). Aldehyde **13a** (19.8 g. 0.115 mol) was dissolved in 1,4-dioxane (75 mL)

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and a solution $KMnO_4$ (20 g. 0.126 mol, 1.1 eq.) in H_2O (15 mL) was added. The resulting mixture was stirred ar rt for 5 h, then filtered and evaporated in *vacuo*. The residue was diluted with H_2O (100 mL) and acidified with 10% aq citric acid to pH 3–4. The precipitate was filtered, washed with H_2O (2×30 mL) and dried in *vacuo*. Yield 17.7 g (82%); white solid; mp 150–152 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.12 (s, 1H), 8.05 (s, 1H), 7.99 (s, 1H), 4.17 – 4.10 (m, 1H), 2.27 – 2.18 (m, 1H), 2.16 – 2.06 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$ + DMSO-d_6) δ 164.1, 141.7, 134.1, 116.4, 108.9 (dd, *J* = 288, 286 Hz), 39.0 (dd, *J* = 16.2, 9.7 Hz), 17.5 (t, *J* = 11.1 Hz). ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –130.7 (d, *J* = 165 Hz), –142.9 (d, *J* = 165 Hz). LC/MS (CI): *m/z* = 189 $[M+H]^+$. Anal. Calcd. for $C_7H_6F_2N_2O_2$: C, 44.69; H, 3.21; N, 14.89. Found: C, 44.49; H, 2.83; N, 14.75.

5-Bromo-1-vinyl-1*H*-pyrazole (17). Diisopropylamine (8.10 g, 80.0 mmol) was dissolved in THF (70 mL) and 2.5 M solution of *n*-BuLi in hexanes (29.2 mL, 73.0 mmol) was added dropwise. The resulting solution was stirred for 20 min at –15 °C, then cooled to –40 °C, and a solution of *N*-vinylpyrazole **9a** (5.00 g, 53.1 mmol) in THF (10 mL) was added dropwise. The resulting mixture was stirred at –30 °C for 30 min, then cooled to –78 °C, and 1,2-dibromo-1,1,2,2-tetrafluoroethane (23.4 g, 9.01 mmol) was added dropwise. The mixture was stirred at –78 °C for 30 min, then warmed up to 0 °C. H_2O (100 mL) was added dropwise, and the mixture was stirred at rt for 5 min, and then diluted with EtOAc (100 mL). The organic phase was separated, and the aqueous phase was extracted with EtOAc (2×70 mL). The combined organic layers were washed with 10% aq citric acid (100 mL), dried over Na_2SO_4 and evaporated in *vacuo*. The crude compound was purified by flash chromatography on silica gel using hexanes – EtOAc (14:1) as eluent. Yield 7.63 g (83%); yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 1.8 Hz, 1H), 7.15 (dd, *J* = 15.3, 8.8 Hz, 1H), 6.36 (d, *J* = 1.8 Hz, 1H), 5.81 (d, *J* = 15.3 Hz, 1H), 4.95 (d, *J* = 8.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.7, 129.1, 112.9, 109.6, 102.9. GC/MS (EI): *m/z* = 172/174 $[M]^+$. Anal. Calcd. for $C_5H_5BrN_2$: C, 34.71; H, 2.91; N, 16.19; Br, 46.18. Found: C, 35.09; H, 2.82; N, 15.96; Br, 46.50.

1-Vinyl-1*H*-pyrazole-5-carboxylic acid (19). *N*-vinylpyrazole (100 g 1.06 mol) was dissolved in THF (1800 mL). 2.5 M *n*-BuLi in hexanes (468 mL, 1.17 mol) was added dropwise, and the solution was stirred at 0 °C for 30 min. Then, dry CO_2 (440 g. 10.0 mol) was added in portions at –78 °C, the mixture was stirred for 30 min and warmed up to 0 °C. Then, H_2O (600 mL) was added dropwise, most of THF was evaporated in *vacuo*, and the residue was extracted with CH_2Cl_2 (300 mL) and acidified with 10% aq citric acid to pH 3–4. The precipitate was filtered and washed with H_2O (2×100 mL). Yield 95.2 g (65%); yellowish powder; mp 135–137 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.71 (s, 1H), 7.99 (dd, *J* = 15.4, 8.8 Hz, 1H), 7.73 (d, *J* = 1.9 Hz, 1H), 6.95 (d, *J* = 1.9 Hz, 1H), 5.75 (d, *J* = 15.4 Hz, 1H), 5.01 (d, *J* = 8.8 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 160.9, 140.4, 133.1, 131.8, 113.1, 103.3. LC/MS (CI): *m/z* = 139 $[M+H]^+$. Anal. Calcd. for $C_6H_6N_2O_2$: C, 52.17; H, 4.38; N, 20.28. Found: C, 51.93; H, 4.66; N, 20.36.

Methyl 1-vinyl-1*H*-pyrazole-5-carboxylate (21). Cs_2CO_3 (196 g, 0.602 mol) was added to a solution of the acid **19** (83.2 g, 0.602 mol) in MeCN (850 mL) at rt. The solution was stirred for 30 min at rt and MeI (37.5 mL, 85.4 g, 0.602 mol, 1 eq.) was added dropwise andthe resulting mixture was stirred at rt overnight. Then, most of MeCN was evaporated in *vacuo*, the residue was crystallized from CH_2Cl_2 (500 mL) and the precipitate was filtered off. The mother liquor was dried over Na_2SO_4 and evaporated in *vacuo*. Yield 90.1 g (99%); yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 9.5, 8.6 Hz, 1H), 7.60 (d, *J* = 0.8 Hz, 1H), 6.91 (d, *J* = 2.0 Hz, 1H), 5.90 (d, *J* = 15.4 Hz, 1H), 5.00 (d, *J* = 8.8 Hz, 1H), 3.90 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.9, 139.6, 131.5, 131.3, 112.6, 103.6, 52.1. LC/MS (CI): *m/z* = 153 $[M+H]^+$. Anal. Calcd. for $C_7H_8N_2O_2$: C, 55.26; H, 5.30; N, 18.41. Found: C, 55.49; H, 4.96; N, 18.50.

General procedure for the preparation of 15b and 15c.

Ester **23** or **27** (80.0 g. 0.396 mol) was dissolved in EtOH (800 mL), and a solution of NaOH (23.8 g. 0.594 mol) in H_2O (50 mL) was added. The mixture was stirred at rt overnight, and most of EtOH was evaporated in *vacuo*. The residue was diluted with H_2O (500 mL) and the mixture was washed with CH_2Cl_2 (3×100 mL). The aqueous phase was acidified with 10% aq citric acid to pH 2–3, extracted with with EtOAc (3×250 mL). The combined organic layers were dried over Na_2SO_4 and evaporated in *vacuo*.

1-(2,2-Difluorocyclopropyl)-1*H*-pyrazole-5-carboxylic acid (15b). Yield 59.2 g (80%); yellowish crystals; mp 127–129 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (br s, 1H), 7.59 (d, *J* = 2.1 Hz, 1H), 7.04 (d, *J* = 2.1 Hz, 1H), 4.50 – 4.38 (m, 1H), 2.55 – 2.45 (m, 1H), 2.18 – 2.08 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.5, 139.2, 133.8, 113.7, 108.7 (dd, *J* = 288, 284 Hz), 39.9 (dd, *J* = 16.1, 9.7 Hz), 17.1 (t, *J* = 11.0 Hz). ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –132.5 (d, *J* = 164 Hz), –144.8 (d, *J* = 164 Hz). LC/MS (CI): *m/z* = 189 $[M+H]^+$. Anal. Calcd. for $C_7H_6F_2N_2O_2$: C, 44.69; H, 3.21; N, 14.89. Found: C, 44.71; H, 3.45; N, 15.25.

1-(2,2-Difluorocyclopropyl)-1*H*-pyrazole-3-carboxylic acid (15c). Yield 62.9 g (85%); beige powder; mp 113–115 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.19 (s, 1H), 7.56 (d, *J* = 2.4 Hz, 1H), 6.89 (d, *J* = 2.5 Hz, 1H), 4.24 – 4.08 (m, 1H), 2.41 – 2.25 (m, 1H), 2.20 – 2.09 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.3, 143.7, 132.5, 110.1, 108.7 (dd, *J* = 288, 287 Hz), 39.4 (dd, *J* = 16.3, 9.8 Hz), 18.2 (t, *J* = 11.1 Hz). ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –130.8 (d, *J* = 164 Hz), –142.7 (d, *J* = 164 Hz). LC/MS (CI): *m/z* = 189 $[M+H]^+$. Anal. Calcd. for $C_7H_6F_2N_2O_2$: C, 44.69; H, 3.21; N, 14.89. Found: C, 44.52; H, 3.53; N, 14.87.

***tert*-Butyl (1-(2,2-difluorocyclopropyl)-1*H*-pyrazol-5-yl)carbamate (24)**. The compound existed as *ca.* 5:1 mixture of rotamers. Et_3N (17.5 g, 0.173 mol) was added to a solution of carboxylic acid **15b** (19.2 g, 0.102 mol) in toluene (200 mL) at rt. DPPA (42.1 g, 0.153 mol) and *t*-BuOH (60.5 g, 0.816 mol) were added and the mixture was refluxed overnight. The solvent was evaporated in *vacuo*, and the residue was dissolved in EtOAc (500 mL). The organic phase was washed with 10% aq citric acid (150 mL), saturated aq. $NaHCO_3$ (150 mL), and brine, (150 mL), dried over Na_2SO_4, and evaporated in *vacuo*. The crude compound was purified by column chromatography on silica gel using hexanes – EtOAc (4:1) as eluent. Yield 19.6 g (74%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 2.0 Hz, 1H), 6.45 (s, 1H), 6.20 (s, 1H), 3.95 – 3.83 (m, 1H), 2.41 – 2.32 (m, 1H), 2.15 – 2.06 (m, 1H), 1.52 (s, 7.5H) and 1.43 (s, 1.5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.3, 139.7, 137.9, 109.6 (dd, *J* = 286, 284 Hz), 99.8, 82.0, 36.1 (dd, *J* = 16.1, 9.8 Hz), 28.1 and 26.9, 17.3 (t, *J* = 10.9 Hz). ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ –130.6 (d, *J* = 160 Hz), –142.8 (d, *J* = 160 Hz). LC/MS (CI): *m/z* = 260 $[M+H]^+$. Anal. Calcd. for $C_{11}H_{15}F_2N_3O_2$: C, 50.96; H, 5.83; N, 16.21. Found: C, 50.78; H, 5.70; N, 16.49.

1-(2,2-Difluorocyclopropyl)-1*H*-pyrazol-5-amine hydrochloride (14b). 3.5 M HCl in 1,4-dioxane (100 mL) was added to a solution of *N*-Boc-amine **24** (45.0 mmol) in Et_2O (100 mL), and the reaction mixture was stirred overnight at rt. The precipitate was filtered, washed with Et_2O (3×50 mL) and dried in *vacuo*. Yield 8.71 g (99%); beige solid; mp 140–142 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.78 (d, *J* = 2.8 Hz, 1H), 6.29 (s, 3H), 5.67 (d, *J* = 2.8 Hz, 1H), 4.27 (dddd, *J* = 10.4, 8.5, 6.1, 2.8 Hz, 1H), 2.49 – 2.32 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 151.6 (d, *J* = 34.4 Hz), 137.4, 110.4 (dd, *J* = 288, 283 Hz), 91.22, 34.45 (dd, *J* = 16.6, 9.2 Hz), 17.76 (t, *J* = 10.6 Hz). ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ –130.5 (d, *J* = 159 Hz), –142.1 (d, *J* = 159 Hz). LC/MS (CI): *m/z* = 160 $[M\text{-}HCl+H]^+$. Anal. Calcd. for $C_6H_8ClF_2N_3$: C, 36.84; H, 4.12; N, 21.48; Cl, 18.12. Found: C, 37.13; H, 4.27; N, 21.63; Cl, 17.89.

1-Vinyl-1*H*-pyrazole-5-carbaldehyde (18). Diisopropylamine (116 g, 1.14 mol) was dissolved in THF (1000 mL), and 2.5 M *n*-BuLi in hexanes (414 mL, 1.04 mol) was added dropwise. The resulting solution was stirred for 20 min at –15 °C, then cooled to –30 °C, and a solution of *N*-vinylpyrazole **9a** (71.4 g, 0.757 mol) in THF (150 mL) was added

dropwise. The resulting mixture was stirred at –30 °C for 30 min, and then cooled to –78 °C. DMF (111 g, 1.52 mol) was added dropwise, and the mixture was stirred at –78 °C for 30 min. Then, the mixture was warmed up to 0 °C, H_2O (700 mL) was added dropwise. The mixture stirred for 15 min at rt, and diluted with EtOAc (500 mL). The organic phase was separated, and the aqueous phase was extracted with EtOAc (2×500 mL). The combined organic layers were washed with aq citric acid (10%, 750 mL), dried over Na_2SO_4 and evaporated in *vacuo*. The crude compound was purified by distillation in *vacuo*. Yield 66.6 g (72%); yellowish oil; bp 77–79 °C / 13 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.86 (s, 1H), 7.89 (dd, *J* = 15.4, 8.7 Hz, 1H), 7.63 (d, *J* = 2.2 Hz, 1H), 6.94 (d, *J* = 1.9 Hz, 1H), 5.89 (d, *J* = 15.4 Hz, 1H), 5.01 (d, *J* = 8.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.6, 140.3, 137.9, 131.4, 116.6, 104.4. GC/MS (EI): *m/z* = 122 $[M]^+$. Anal. Calcd. for $C_6H_6N_2O$: C, 59.01; H, 4.95; N, 22.94. Found: C, 59.36; H, 5.20; N, 23.14.

5-(Dimethoxymethyl)-1-vinyl-1*H*-pyrazole (20). Aldehyde **18** (64.9 g, 0.513 mol) was dissolved in MeOH (900 mL), and trimethyl orthoformate (65.3 g, 0.616 mol) and *p*-toluenesulfonic acid monohydrate (5.44 g, 2.86 mmol) were added to the solution. The reaction mixture was stirred at rt for 20 h. Then, H_2O (500 mL) and 10% aq $NaHCO_3$ were added to pH 9–10, and most of MeOH was evaporated in *vacuo*. The resulting mixture was extracted with CH_2Cl_2 (3×300 mL), dried over Na_2SO_4, and evaporated in *vacuo*. The crude compound was purified by distillation in *vacuo*. Yield 74.2 g (86%); yellowish oil; bp 70–72 °C / 0.27 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 2.2 Hz, 1H), 7.17 (dd, *J* = 9.6, 8.9 Hz, 1H), 6.35 (d, *J* = 1.7 Hz, 1H), 5.71 (d, *J* = 15.3 Hz, 1H), 5.47 (s, 1H), 4.81 (d, *J* = 8.8 Hz, 1H), 3.26 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.8, 138.7, 130.4, 107.8, 101.4, 97.1, 52.8. GC/MS (EI): *m/z* = 168 $[M]^+$. Anal. Calcd. for $C_8H_{12}N_2O_2$: C, 57.13; H, 7.19; N, 16.66. Found: C, 57.44; H, 7.59; N, 17.03.

1-(2,2-Difluorocyclopropyl)-1*H*-pyrazole-5-carbaldehyde (13b). Acetal **22** (57.0 g. 0.261 mol) was dissolved in THF (285 mL), and 1 M aq HCl (285 mL) was added. The reaction mixture was stirred at rt overnight. Then most of THF was evaporated in *vacuo*, the residue was diluted with H_2O (200 mL) and neutralized with 10% $NaHCO_3$ to pH = 7. The mixture was extracted with CH_2Cl_2 (3×200 mL), dried over Na_2SO_4 and evaporated in *vacuo*. The crude compound was purified by distillation in *vacuo*. Yield 41.8 g (93%); yellowish liquid; bp 77–79 °C / 0.27 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.93 (s, 1H), 7.60 (d, *J* = 2.0 Hz, 1H), 6.96 (d, *J* = 2.0 Hz, 1H), 4.47 (tdd, *J* = 10.1, 6.8, 2.0 Hz, 1H), 2.53 – 2.44 (m, 1H), 2.12 (dtd, *J* = 12.3, 10.1, 6.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.2, 140.7, 139.5, 115.2, 108.7 (dd, *J* = 289, 285 Hz), 39.6 (dd, *J* = 15.9, 9.7 Hz), 16.7 (t, *J* = 11.1 Hz). ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –132.0 (d, *J* = 163 Hz), –145.1 (d, *J* = 163 Hz). GC/MS (EI): *m/z* = 172 $[M]^+$. Anal. Calcd. for $C_7H_6F_2N_2O$: C, 48.84; H, 3.51; N, 16.27. Found: C, 49.19; H, 3.55; N, 15.87.

3-Nitro-1-vinyl-1*H*-pyrazole (25). To a solution of 3-nitropyrazole (88.5 g, 0.783 mol) in $(CH_2Cl)_2$ (1200 mL), $Bu_4N^+Br^-$ (12.6 g, 39.1 mmol) was added, followed by a solution of KOH (350 g, 6.24 mol) in H_2O (600 mL). The reaction mixture was refluxed overnight, then cooled to rt, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2×300 mL), the combined organic layers were washed with 10% aq citric acid (300 mL), dried over Na_2SO_4 and evaporated in *vacuo*. The crude compound was purified by column chromatography on silica gel using hexanes – EtOAc (gradient 8:1 to 4:1) as eluent. Yield 68.6 g (63%); yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 2.6 Hz, 1H), 7.08 (dd, *J* = 15.6, 8.8 Hz, 1H), 7.00 (d, *J* = 2.7 Hz, 1H), 5.80 (dd, *J* = 15.7, 2.1 Hz, 1H), 5.18 (dd, *J* = 8.8, 2.2 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.6, 132.5, 129.7, 105.3, , 103.9. LC/MS (CI): *m/z* = 140 $[M+H]^+$. Anal. Calcd. for $C_5H_5N_3O_2$: C, 43.17; H, 3.62; N, 30.21. Found: C, 43.31; H, 3.85; N, 29.90.

3-Bromo-1-(2,2-difluorocyclopropyl)-1*H*-pyrazole (12c). A solution of $NaNO_2$ (8.67 g, 126 mmol) in H_2O (10 mL) was added dropwise to a solution of amine **14c** (10.0 g; 62.8 mmol) in 40% aq HBr (40 mL) at 0 °C, the reaction mixture was warmed up to 30 °C and stirred for 1 h. Then CuBr (4.50 g; 31.4 mmol) was added in portions at 0 °C. After the completion of intensive gas evolution, the reaction mixture was warmed up to 35 °C and stirred for 40 min. H_2O (120 mL) was added, and the resulting mixture was washed with CH_2Cl_2 (3×50 mL), combined organic layers were washed with 10% aq Na_2CO_3 (50 mL), dried over Na_2SO_4, filtered through silica gel and evaporated in *vacuo*. Yield 11.5 g (82%); yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 2.6 Hz, 1H), 6.30 (d, *J* = 2.4 Hz, 1H), 4.04 (tdd, *J* = 9.7, 5.8, 2.5 Hz, 1H), 2.19 (ddt, *J* = 14.4, 9.7, 5.8 Hz, 1H), 2.12 – 2.04 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.8, 126.8, 109.6, 109.0 (t, *J* = 287 Hz), 38.9 (dd, *J* = 16.4, 9.7 Hz), 18.1 (t, *J* = 11.0 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ –130.7 (d, *J* = 164 Hz), –142.8 (d, *J* = 164 Hz). LC/MS (CI): *m/z* = 223/225 $[M+H]^+$. Anal. Calcd. for $C_6H_5BrF_2N_2$: C, 32.31; H, 2.26; N, 12.56; Br, 35.83. Found: C, 31.92; H, 2.15; N, 12.22; Br, 35.66.

Ethyl 1-(2-hydroxyethyl)-1*H*-pyrazole-3-carboxylate (31). NaH (60%, 18.8 g, 0.470 mol) was suspended in THF (900 mL) at 0 °C and ethyl-1*H*-pyrazole-3-carboxylate (60.0 g; 0.428 mol) was added in portions at 0 °C. After addition, the reaction mixture was warmed up to 35 °C and stirred for 1.5 h, then cooled to 5 °C, and 2-bromoethanol (62.2 g; 0.514 mol) was added at 5 - 10 °C. The mixture was stirred overnight at 38 °C, then cooled to 5 °C, and H_2O (450 mL) was added dropwise. Most of THF was evaporated in *vacuo*, and the residue was washed with CH_2Cl_2 (3×450 mL). The combined organic layers were washed with H_2O (300 mL), dried over Na_2SO_4 and evaporated in *vacuo*. The residue was purified by flash chromatography on silica gel using $CHCl_3$ – MeOH (40:1) as eluent. Yield 53.6 g (68%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, *J* = 2.2 Hz, 1H), 6.78 (d, *J* = 2.2 Hz, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 4.31 (t, *J* = 5.1 Hz, 2H), 4.02 (t, *J* = 5.1 Hz, 2H), 2.71 (s, 1H), 1.38 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.3, 143.9, 131.7, 108.8, 61.3, 60.9, 54.9, 14.3. LC/MS (CI): *m/z* = 185 $[M+H]^+$. Anal. Calcd. for $C_8H_{12}N_2O_3$: C, 52.17; H, 6.57; N, 15.21. Found: C, 52.40; H, 6.85; N, 14.86.

Ethyl 1-(2-((methylsulfonyl)oxy)ethyl)-1*H*-pyrazole-3-carboxylate (32). MsCl (24.6 g, 0.215 mol) was added to a solution of alcohol **31** (36.0 g, 0.195 mol) in CH_2Cl_2 (250 mL) at rt. The reaction mixture was cooled to 5 °C and Et_3N (32.8 mL, 0.235 mol) was added at 5 °C. After addition, the mixture was stirred at rt overnight, then washed with 10% aq citric acid (150 mL), dried over Na_2SO_4 and evaporated in *vacuo*. The residue was diluted with hexanes - EtOAc (10:1, v/v, 200 mL) and the precipitate was filtered. Yield 47.1 g (92%); yellowish solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, *J* = 2.3 Hz, 1H), 6.81 (d, *J* = 2.3 Hz, 1H), 4.61 (t, *J* = 4.5 Hz, 2H), 4.52 (t, *J* = 4.9 Hz, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 2.88 (s, 3H), 1.38 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.0, 144.8, 132.1, 109.2, 67.5, 61.1, 51.8, 37.4, 14.4. LC/MS (CI): *m/z* = 263 $[M+H]^+$. Anal. Calcd. for $C_9H_{14}N_2O_5S$: C, 41.22; H, 5.38; N, 10.68; S, 12.22. Found: C, 41.26; H, 5.72; N, 10.98; S, 12.44.

Ethyl 1-vinyl-1*H*-pyrazole-3-carboxylate (26). DBU (178 g, 1.29 mol) was added to a solution of mesylate **32** (169 g, 0.644 mol) in THF (1500 mL), and the mixture was heated 48 h. Then, the reaction mixture was cooled to rt and most of THF was evaporated in *vacuo*. The residue was dissolved in CH_2Cl_2 (1000 mL), the solution was washed with 10% aq citric acid (2×600 mL), dried over Na_2SO_4 and evaporated in *vacuo*. The crude compound was purified by column chromatography on silica gel using hexanes – EtOAc (8:1 to 4:1) as eluent. Yield 67.4 g (63%). For phisical and spectral data, see ref.[41]

(1-(2,2-Difluorocyclopropyl)-1*H*-pyrazol-3-yl)methanol (28). The crude compound was purified by flash chromatography on silica gel using hexanes – EtOAc (4:1) as eluent. A suspension of ester **28** (43.0 g; 0.199 mol) and $LiBH_4$ (6.53 g; 0.300 mol) in THF (1300 mL) was refluxed overnight. Then, the reaction mixture was cooled to 0 °C and quenched with 1N aq HCl to pH = 6. The resulting mixture was diluted with EtOAc (3×500 mL) and washed with saturated aq $NaHCO_3$ (2×400 mL), the combined organic layers were dried over Na_2SO_4 and evaporated in *vacuo*. Yield 25.8 g (74%); yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ

7.42 (d, *J* = 2.4 Hz, 1H), 6.26 (d, *J* = 2.4 Hz, 1H), 4.64 (s, 2H), 4.01 (tdd, *J* = 9.7, 5.8, 2.3 Hz, 1H), 2.62 (s, 1H), 2.17 – 2.08 (m, 1H), 2.03 (ddt, *J* = 12.6, 9.7, 5.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.8, 129.2, 106.7 (dd, *J* = 287, 286 Hz), 102.5, 56.2, 35.9 (dd, *J* = 16.0, 9.6 Hz), 15.5 (t, *J* = 11.0 Hz). ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –130.7 (d, *J* = 163 Hz), –143.0 (d, *J* = 163 Hz). LC/MS (CI): *m/z* = 157 $[M\text{-}F+H]^+$. Anal. Calcd. for $C_7H_8F_2N_2O$: C, 48.28; H, 4.63; N, 16.09. Found: C, 48.21; H, 4.62; N, 15.93.

1-(2,2-Difluorocyclopropyl)-1*H*-pyrazole-3-carbaldehyde (13c). MnO_2 (50.0 g, 0.575 mol) was added to a solution of alcohol **28** (10.0 g, 57.4 mmol) in EtOAc (200 mL) and reaction mixture was refluxed overnight. Then, the mixture was cooled to rt, filtered through silica gel (50 mL) and evaporated in *vacuo*. The crude compound was purified by column chromatography on silica gel using hexanes – EtOAc (6:1) as eluent. Yield 7.51 g (76%); yellowish crystals; mp 127–129 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.97 (s, 1H), 7.58 (d, *J* = 2.3 Hz, 1H), 6.85 (d, *J* = 1.6 Hz, 1H), 4.20 (dddd, *J* = 10.5, 8.2, 5.9, 2.1 Hz, 1H), 2.35 (ddt, *J* = 15.1, 8.2, 5.9 Hz, 1H), 2.22 – 2.16 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.1, 152.0, 132.7, 108.6 (dd, *J* = 288, 286 Hz), 106.5, 39.3 (dd, *J* = 16.1, 9.9 Hz), 17.8 (t, *J* = 11.2 Hz). ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –130.8 (d, *J* = 164 Hz), –143.3 (d, *J* = 164 Hz). LC/MS (CI): *m/z* = 173 $[M+H]^+$. Anal. Calcd. for $C_7H_6F_2N_2O$: C, 48.84; H, 3.51; N, 16.27. Found: C, 48.69; H, 3.58; N, 16.01.

General procedure for the preparation of 29a–c.

The corresponding bromide **12** (250 mg, 1.12 mmol), phenylboronic acid (164 mg, 1.35 mmol) and K_2CO_3 (387 mg, 2.80 mmol) were dissolved in $(CH_2OMe)_2$ - H_2O (3:1, v/v, 12 mL) under argon atmosphere at rt. The resulting solution was heated at 40 °C for 20 min, and $Pd(PPh_3)_4$ (64.7 mg, 56.0 μmol) was added under argon flow. The reaction mixture was stirred at 85 °C overnight, then cooled to rt and diluted with EtOAc (25 mL) and H_2O (10 mL). The organic layer was separated, filtered through silica gel and washed with EtOAc (25 mL). The mother liquor was dried over Na_2SO_4 and evaporated in *vacuo*. The compound was purified by column chromatography on silica gel using hexanes – EtOAc (6:1) as eluent.

1-(2,2-Difluorocyclopropyl)-4-phenyl-1*H*-pyrazole (29a). The compound was purified by column chromatography on silica gel using hexanes – EtOAc (6:1) as eluent. Yield 185 mg (75%); white solid; mp 68–70 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.73 (s, 1H), 7.48 – 7.44 (m, 2H), 7.38 – 7.33 (m, 2H), 7.28 – 7.20 (m, 1H), 4.11 – 4.03 (m, 1H), 2.27 – 2.21 (m, 1H), 2.13 – 2.06 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.0, 131.9, 128.9, 127.3, 126.8, 125.7, 124.0, 109.2 (t, *J* = 287 Hz), 38.9 (dd, *J* = 16.2, 9.7 Hz), 18.0 (t, *J* = 11.0 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ –124.5 – –132.9 (m), –142.6 (ddd, *J* = 163, 14.5, 6.2 Hz). LC/MS (CI): *m/z* = 221 $[M+H]^+$. Anal. Calcd. for $C_{12}H_{10}F_2N_2$: C, 65.45; H, 4.58; N, 12.72. Found: C, 65.58; H, 4.80; N, 12.86.

1-(2,2-Difluorocyclopropyl)-5-phenyl-1*H*-pyrazole (29b). The compound was purified by column chromatography on silica gel using hexanes – EtOAc (6:1) as eluent. Yield 160 mg (65%); yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 1.8 Hz, 1H), 7.53 – 7.50 (m, 2H), 7.50 – 7.47 (m, 2H), 7.46 – 7.42 (m, 1H), 6.41 (d, *J* = 1.8 Hz, 1H), 4.03 (tdd, *J* = 9.6, 6.9, 2.1 Hz, 1H), 2.47 (ddt, *J* = 14.4, 9.6, 5.8 Hz, 1H), 2.02 (dtd, *J* = 13.1, 9.6, 6.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.2, 139.4, 129.8, 128.8, 128.8, 128.4, 110.0 (dd, *J* = 288, 286 Hz), 107.0, 38.5 (dd, *J* = 15.7, 9.8 Hz), 17.0 (t, *J* = 11.1 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ –131.5 (ddt, *J* = 161, 13.1, 6.9 Hz), –143.8 (ddd, *J* = 161, 14.4, 6.9 Hz). LC/MS (CI): *m/z* = 221 $[M+H]^+$. Anal. Calcd. for $C_{12}H_{10}F_2N_2$: C, 65.45; H, 4.58; N, 12.72. Found: C, 65.53; H, 4.28; N, 12.64.

1-(2,2-Difluorocyclopropyl)-3-phenyl-1*H*-pyrazole (29c). The compound was purified by column chromatography on silica gel using hexanes – EtOAc (6:1) as eluent. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.79 (m, 1H), 7.78 (s, 1H), 7.51 (d, *J* = 2.4 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.30 (t, *J* = 7.3 Hz, 1H), 6.58 (d, *J* = 2.5 Hz, 1H), 4.12 (tdd, *J* = 10.1, 6.3, 2.4 Hz, 1H), 2.25 (ddt, *J* = 14.5, 10.1, 5.6 Hz, 1H), 2.11 (dtd, *J* = 12.9, 9.8, 6.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.5, 133.0, 131.9, 128.64, 128.0, 125.8, 109.4 (t, *J* = 289 Hz), 103.8, 38.9 (dd, *J* = 16.1, 9.7 Hz), 18.20 (t, *J* = 10.9 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ –130.0 (dddd, *J* = 163, 12.9, 9.8, 5.6 Hz), –142.4 (ddd, *J* = 163, 14.5, 6.3 Hz). LC/MS (CI): *m/z* = 221 $[M+H]^+$. Anal. Calcd. for $C_{12}H_{10}F_2N_2$: C, 65.45; H, 4.58; N, 12.72. Found: C, 65.73; H, 4.89; N, 12.73.

General procedure for the preparation of 30a–c.

The corresponding bromide **12** (250 mg, 1.12 mmol) was dissolved in DMF (2 mL), Et_3N (339 mg, 0.468 mL, 3.36 mmol) and phenylacetylene (172 mg, 0.185 mL, 1.68 mmol) were added under argon atmoshere. Then, $Pd(OAc)_2$ (7.63 mg, 34.0 μmol), PPh_3 (17.6 mg, 67.0 μmol) and CuI (21.3 mg, 112 μmol) were added in argon flow. The resulting mixture was stirred at 85 °C overnight, then cooled to rt and diluted with EtOAc (25 mL) and H_2O (10 mL). Organic layer was separated, dried over Na_2SO_4 and evaporated in *vacuo*.

1-(2,2-Difluorocyclopropyl)-4-(phenylethynyl)-1*H*-pyrazole (30a). The compound was purified by column chromatography on silica gel using hexanes – EtOAc (9:1) as eluent. Yield 210 mg (78%); yellowish solid; mp 61–63 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.68 (s, 1H), 7.49 – 7.45 (m, 2H), 7.34 – 7.29 (m, 3H), 4.12 – 4.04 (m, 1H), 2.26 – 2.16 (m, 1H), 2.14 – 2.03 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.8, 133.1, 131.4, 128.4, 128.2, 123.2, 108.9 (t, *J* = 287 Hz), 104.5, 90.5, 79.8, 38.8 (dd, *J* = 16.2, 9.7 Hz), 17.9 (t, *J* = 11.1 Hz). ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –130.7 (d, *J* = 163 Hz), –143.1 (d, *J* = 163 Hz). LC/MS (CI): *m/z* = 245 $[M+H]^+$. Anal. Calcd. for $C_{14}H_{10}F_2N_2$: C, 68.85; H, 4.13; N, 11.47. Found: C, 68.77; H, 3.98; N, 11.26.

1-(2,2-Difluorocyclopropyl)-5-(phenylethynyl)-1*H*-pyrazole (30b). The compound was purified by column chromatography on silica gel using hexanes – EtOAc (9:1) as eluent. Yield 195 mg (72%); yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 6.7, 3.0 Hz, 2H), 7.51 (d, *J* = 1.8 Hz, 1H), 7.38 – 7.34 (m, 3H), 6.52 (d, *J* = 1.9 Hz, 1H), 4.17 – 4.06 (m, 1H), 2.49 – 2.40 (m, 1H), 2.18 – 2.07 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.6, 131.53, 129.2, 128.5, 127.5, 121.9, 110.8, 109.2 (t, *J* = 287 Hz), 97.5, 38.0 (dd, *J* = 16.2, 9.7 Hz), 17.2 (t, *J* = 11.2 Hz). ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –131.6 (d, *J* = 162 Hz), –143.5 (d, *J* = 162 Hz). Anal. Calcd. for $C_{14}H_{10}F_2N_2$: C, 68.85; H, 4.13; N, 11.47. Found: C, 68.86; H, 3.75; N, 11.52.

1-(2,2-Difluorocyclopropyl)-3-(phenylethynyl)-1*H*-pyrazole (30c). The compound was purified by column chromatography on silica gel using hexanes – EtOAc (9:1) as eluent. Yield 120 mg (44%); white solid; mp 75–77 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 2H), 7.48 (s, 1H), 7.35 – 7.28 (m, 3H), 6.48 (s, 1H), 4.15 – 3.98 (m, 1H), 2.31 – 2.21 (m, 1H), 2.13 – 2.04 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.0, 131.7, 131.3, 128.6, 128.3, 122.6, 110.5, 109.0 (t, *J* = 287 Hz), 90.1, 81.6, 38.96 (dd, *J* = 16.3, 9.7 Hz), 18.0 (t, *J* = 10.9 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ –130.2 (ddd, *J* = 163, 14.4, 7.0 Hz), –142.5 (ddd, *J* = 163, 14.2, 6.4 Hz). LC/MS (CI): *m/z* = 245 $[M+H]^+$. Anal. Calcd. for $C_{14}H_{10}F_2N_2$: C, 68.85; H, 4.13; N, 11.47. Found: C, 68.65; H, 4.31; N, 11.25.

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Keywords: organofluorine compounds • cycloalkanes • Ruppert – Prakash reagent • azoles • building blocks

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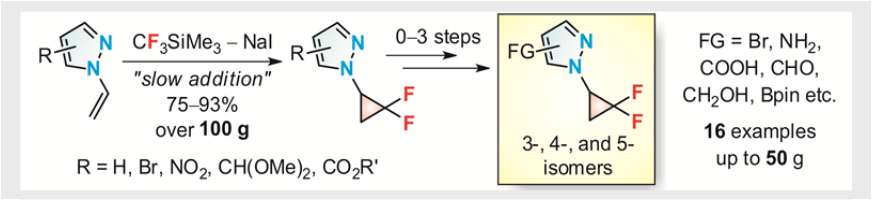

N-Difluorocyclopropyl-substituted pyrazoles were prepared on a multigram scale by reaction of *N*-vinylpyrazoles and CF_3SiMe_3 – NaI system. Tolerance of the *N*-difluorocyclopropylpyrazole moiety towards many typical organic transformations (*i.e.* electrophilic substitution, oxidation, reduction was demonstrated.

Fluorinated Cyclopropanes

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N-Difluorocyclopropyl-substituted pyrazoles: synthesis and reactivity