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Gram-scale synthesis of amines bearing *gem*-difluorocyclopropane moiety

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Abstract. Synthesis of monocyclic, spirocyclic and fused bicyclic secondary amines bearing *gem*-difluorocyclopropane moiety *via* difluorocyclopropanation of unsaturated *N*-Boc derivatives using CF_3SiMe_3–NaI system is described. Relative order of the substrate reactivity is established. It is shown that for the reactive alkenes, the standard reaction conditions can be used, whereas for the substrates with low reactivity, slow addition of the Ruppert–Prakash reagent is necessary.

Keywords: Difluorocarbene; Cycloaddition; Cycloalkanes; Bicyclic compounds; Ruppert–Prakash reagent

Introduction

Organofluorine compounds and derivatives of small ring can be undoubtedly named among the hallmarks of modern drug discovery.[1–8] *Gem*-difluorocyclopropanes which combine these structural features are promising building blocks for medicinal chemistry.[9–11] In particular, they were used in design of experimental antineoplastic drug zosuquidar (**1**), which has reached Phase III clinical trials,[12] glutamate analogue **2** – selective mGluR2 agonist,[13] DDR1 inhibitor **3**,[14] potential insecticide **4**,[15] or fumagillol derivative **5** – a possible antiobesity agent (Figure 1).[16]

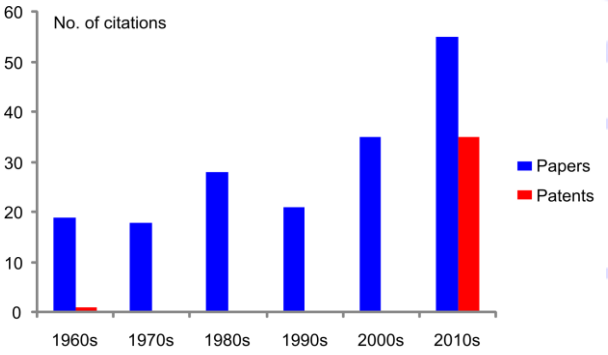


Figure 2. Distribution of papers and patents on difluorocyclopropanation of alkenes over the last 50 years.

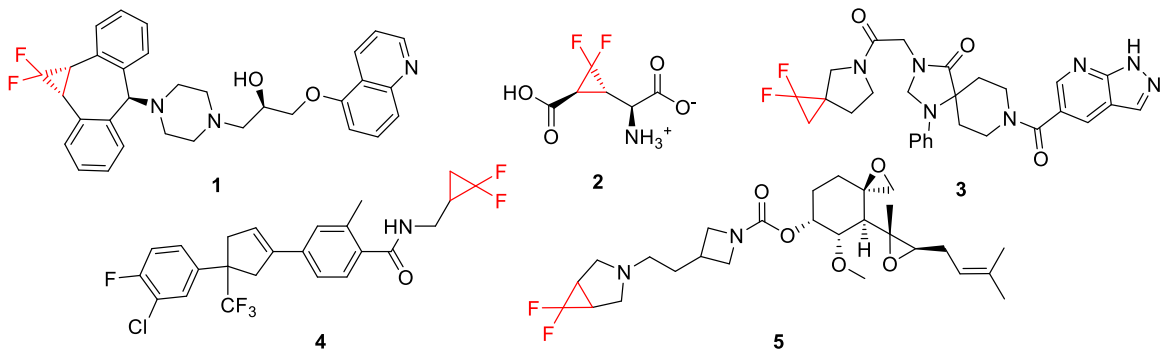


Figure 1. Biologically active *gem*-difluorocyclopropanes.

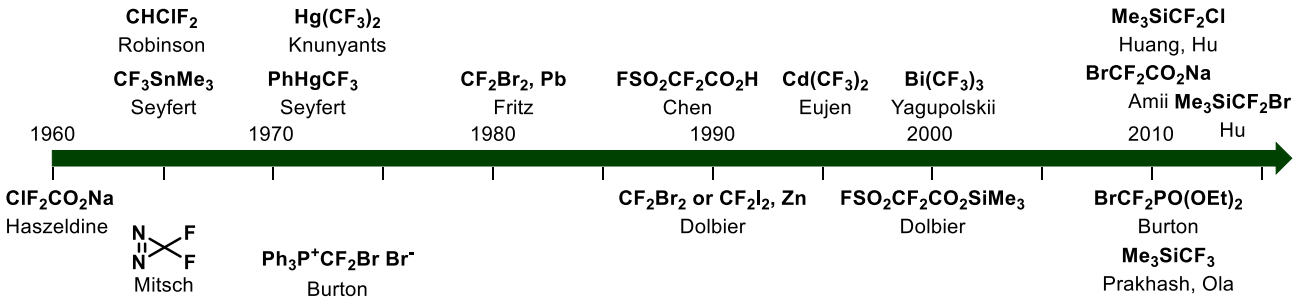


Figure 3. Discovery of alkene difluorocyclopropanation reagents.

A general approach to *gem*-difluorocyclopropanes relies on the reaction of alkenes with difluorocarbene source. Although the difluorocyclopropanation of alkenes has been known for more than 50 years, it represented mainly academic interest until recently (Figure 2).[17] In 2010s, this reaction has attracted attention of industrial chemists, which has been reflected in more than 30 recent patent applications. The main reason behind this is the fact that despite many reagents were known for the difluorocyclopropanation of alkenes prior 2010s (Figure 3),[18–35] most of them either showed low efficiency and limited substrate scope, or were toxic and hardly available.

As a part of our ongoing research on the synthesis of various fluorinated building blocks for medicinal chemistry,[36–41] we have become interested in mono- and bicyclic amines containing *gem*-difluorocyclopropane fragment. To our surprise, although the use of such amines was documented in patents,[14–16] their syntheses are quite rarely encountered in the literature. In particular, unstable bicyclic amines **6** were prepared *via* reaction of the corresponding enecarbamates with trimethylsilyl fluorosulfonyldifluoroacetate (TFDA) (Figure 4).[42] *cis*- and *trans*-4,5-Difluoromethanoproline derivatives **7a,b** were prepared by an analogous method using CF_2ClCO_2Na as the difluorocarbene source.[43] Recently, synthesis of *N*-Boc protected amines **8** was described *via* difluorocyclopropanation of the corresponding alkenes with Ruppert–Prakash reagent.[44]

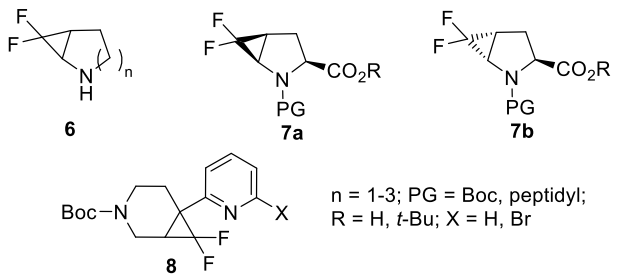


Figure 4. Literature examples of (*N*-protected) amines bearing *gem*-difluorocyclopropane moiety

In this work, we describe our study towards synthesis of monocyclic, fused bicyclic and spirocyclic amines bearing *gem*-difluorocyclopropane moiety starting from unsaturated amine derivatives and using the Ruppert–Prakash reagent (CF_3SiMe_3) – a readily available, non-toxic difluorocyclopropanation agent. It should be noted that since the first publication of Prakash, Olah and co-workers on the use of CF_3SiMe_3 for the difluorocyclopropanation of alkenes,[33] several papers appeared describing analogous transformations.[45–48] Nevertheless, none of them reported the use of unsaturated amine derivatives as the substrates (with a few exceptions: one described in a patent[49] and another mentioned above (compound **8**)[44]).

Results and Discussion

Primary screen for the difluorocyclopropanation reaction conditions started from the original protocol Prakash, Ola and co-workers (*i. e.* alkene (1 mol), $TMSCF_3$ (2.5 mol), NaI (0.2 mol), THF, 65 °C, 2 h)[33] using *N*-Boc-4-methylenepiperidone (**9a**) (described in the patent mentioned above[49]) and several allyl amine derivatives **9b–e** as the model substrates (Figure 5). It was found that in the case of **9a**, the product **10a** was obtained in 87% yield. Derivatives **9b,c** gave only trace amounts of the target products, whereas in the case of **9d,e**, no target compounds were detected at all.

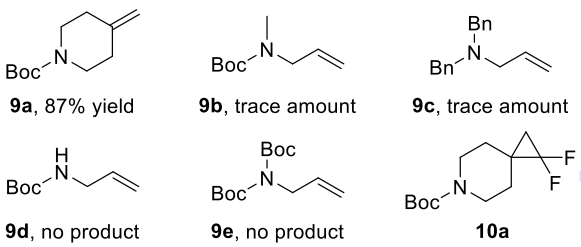


Figure 5. Substrates **9a–e** checked under the original conditions of Prakash, Olah and co-workers (alkene (1 mol), $TMSCF_3$ (2.5 mol), NaI (0.2 mol), THF, 65 °C, 2 h)[33]

Since the previous studies on the Ruppert–Prakash reagent showed significant solvent effect on the reaction outcome,[33,50] we have performed difluoro-

cyclopropanation of **9a** with $TMSCF_3$–NaI system in several solvents (Table 1). The literature results on C–H perfluoroalkylation of aromatic compounds with $TMSCF_3$[50] showed 1,2-dimethoxyethane to be the solvent of choice for the reaction. However, in the case of **9a**, the previous results of Prakash, Olah and co-workers were confirmed:[33] using THF gave the best conversion of the substrate to the target product. The solvent effect on the reaction outcome is not clear; it might be related to the differences in Na^+ solvatation, however, the detailed mechanism of the reaction (and hence the role of Na^+) is currently unknown.

Table 1. Difluorocyclopropanation of the substrate **9a** in various solvents

Solvent[a)]	Conversion, (%)	
	after 2 h	after 4 h
THF	>99	>99
1,4-Dioxane	0	N/A
t-BuOMe	0	N/A
MeCN	0	N/A
1,2-Dimethoxyethane	33	77

[a)] Conditions: **7a** (1 mol), $TMSCF_3$ (2.5 mol), NaI (0.2 mol), 65 °C.

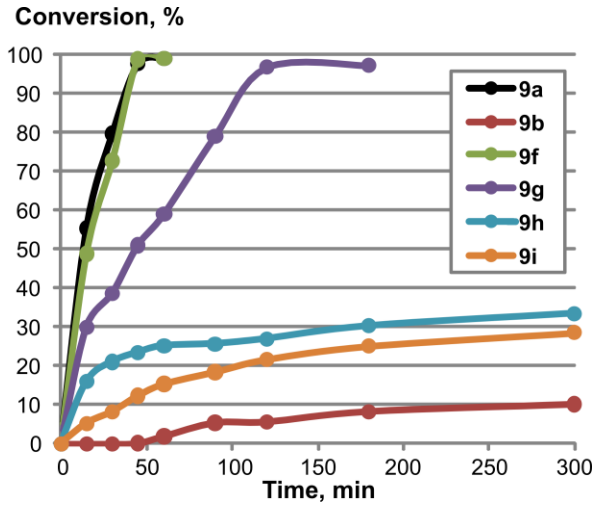


Figure 6. Conversion of the substrates **7a,b,f–i** as a function of the reaction time (conditions: alkene (1 mol), $TMSCF_3$ (2.5 mol), NaI (0.2 mol), THF, 65 °C)

In the next part of this work, we have aimed at optimization of the reaction time for the substrates **9a,b**, as well as for four additional unsaturated *N*-Boc derivatives **9f–i**. To achieve this, we have studied conversion of these substrates as a function of the reaction time under standard conditions (alkene (1 mol), $TMSCF_3$ (2.5 mol), NaI (0.2 mol), THF, 65 °C) (Figures 6 and 7). It was found that for the alkenes **9a** and **9f**, nearly complete conversion was observed after 1 h of the reaction. In the case of **9g**, the same situation was achieved after *ca.* 3 h. For the substrates **9b**, **9h** and **9i**, 10%, 34% and 29% conversion, respectively, was achieved after 5 h of the reaction, and these values did not improve further significantly even after 24 h.

We anticipate that upon action of NaI, partial decomposition of $TMSCF_3$ occurs, presumably *via* difluorocarbene or carbenoid intermediate. Such process becomes an important side reaction with less reactive substrates (like **9b**, **9h** and **9i**). This hypothesis is supported by recent positive results on the difluorocyclopropanation with $TMSCF_3$–NaI in continuous flow, published by Charette and co-workers.[45] Indeed, decomposition of the reagent can be alleviated under continuous flow conditions. Moreover, we have performed a control experiment without alkene ($TMSCF_3$ (0.4 M in THF), NaI (10 % mol), rt to reflux) (Figure 8). It was found that at these conditions, $TMSCF_3$ was transformed into a mixture containing mainly CF_2=CF_2 and Me_3SiF; formation of hexafluorocyclopropane was also observed (according to ^{19}F NMR data) (Scheme 1).[51–53] Notably, more than 90% decomposition of the reagent was observed after 1–1.5 h at reflux, and the ratio of CF_2=CF_2 and hexafluorocyclopropane in the resulting mixture was *ca.* 25:1.

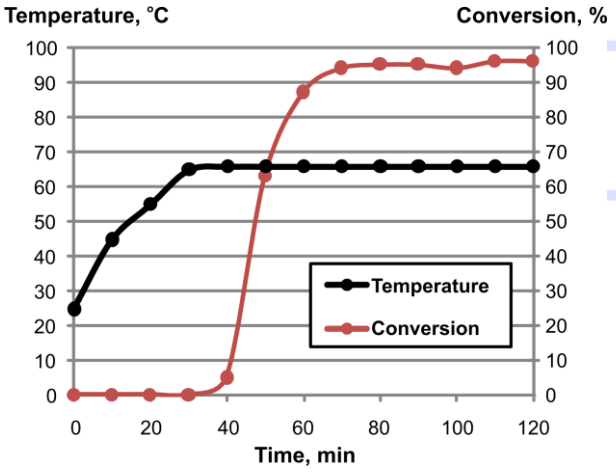


Figure 8. Decomposition of the Ruppert–Prakash reagent (conditions: $TMSCF_3$ (0.4 M in THF), NaI (10 % mol), rt to reflux)

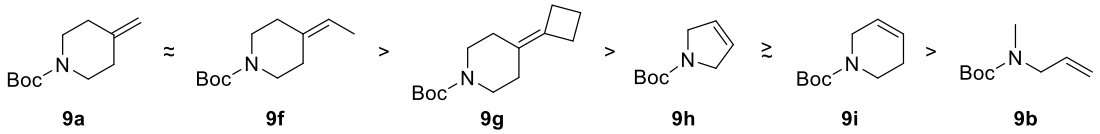
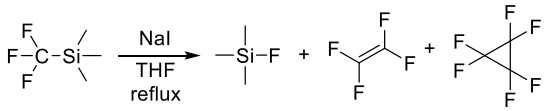


Figure 7. Relative reactivity of the substrates **9a,b,f–i** towards $TMSCF_3$–NaI system



Scheme 1. Reactions describing decomposition of the Ruppert–Prakash reagent.

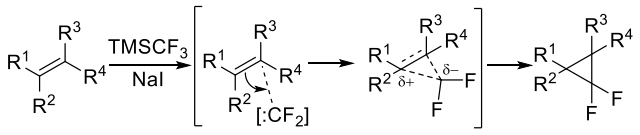
To diminish the negative effect of the reagent decomposition without using significant excess of $TMSCF_3$, we used slow addition technique for the substrates **9b**, **9h** and **9i**. Thus, $TMSCF_3$ was added slowly to a refluxing solution of the substrate and NaI in THF over the period of 6–8 h. Under these conditions, we could achieve nearly complete conversion for each of these substrates.

An important result obtained in this part of the study is the order of the substrate reactivity towards $TMSCF_3$–NaI system:

9a ≈ **9f** > **9g** > **9h** ≥ **9i** > **9b**

Apparently, *gem*-disubstituted alkenes (**9a**, **9f** and **9g**) show the best reactivity, and this part of the series correlates with steric effects observed in the substrate molecules. However, the rest of the series demonstrate an opposite correlation. In our opinion, a possible explanation might include (partially) non-synchronous formation of the two σ bonds by the difluorocarbene or carbenoid during cycloaddition (Scheme 2). The (partial) positive charge at one of the carbon atoms is stabilized best in the transition state formed from the *gem*-disubstituted substrates ("tertiary carbocationoid center"), whereas in the case of monosubstituted alkenes like **9b,** the poorest stabilization is observed.

It should be noted that to the best of our knowledge, the relative reactivity of various alkenes towards $TMSCF_3$–NaI system was not studied thoroughly to date, and the mechanism of this reaction remains unclear. Nevertheless, most of the examples described in the previous works included difluorocyclopropanation of aryl-substituted double bonds,[33,45–48] which supports the above hypothesis since the aryl groups can provide even better stabilization of the positive charge ("benzylic carbocationoid center"). Our results are also consistent with well-established electrophilic nature of singlet difluorocarbene, *i. e.* its preference to react with electron-rich alkenes.[54] A more thorough investigation of the reaction mechanism involving the $TMSCF_3$–NaI system is ongoing and will be published elsewhere.



Scheme 2. Possible explanation of the substrate reactivity order in the reaction with $TMSCF_3$–NaI system.

The procedures developed were used for the synthesis of monocyclic, spirocyclic and fused bicyclic *gem*-difluorocyclopropanes **10a,b,f–p** (Table 2). The products were obtained in 50–91 % yields after flash chromatography or distillation under reduced pressure. Finally, deprotection of **10** using ethereal HCl led to the formation of the title amines **11** (isolated as hydrochlorides in 85–94 % yields). The structures of hydrochlorides **11a**·HCl, **11j**·HCl and **11k**·HCl, as well as Boc derivative **10g** were confirmed using X-Ray single crystal diffraction studies (Figure 9).

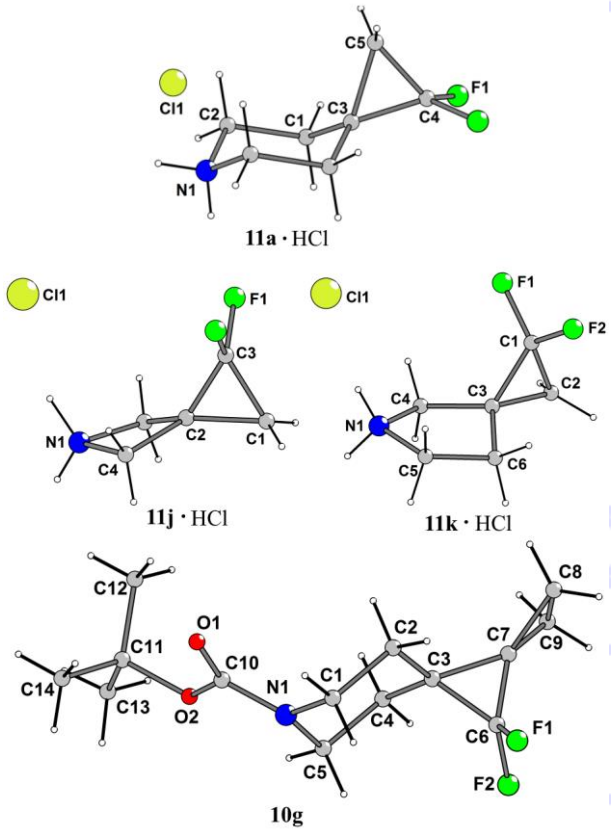
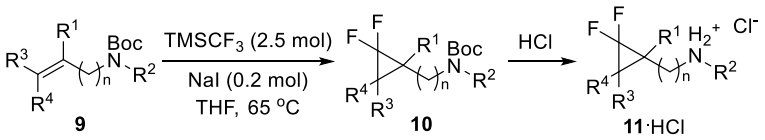


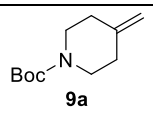
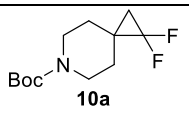
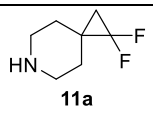
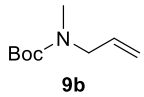
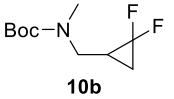
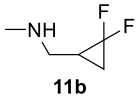
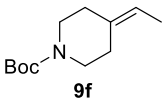
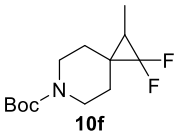
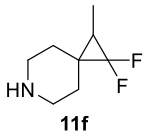
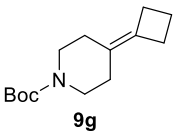
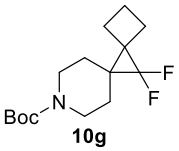
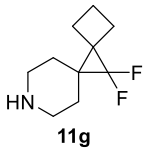
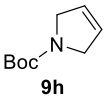
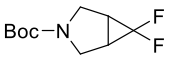
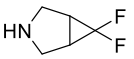
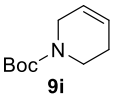
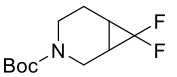
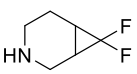
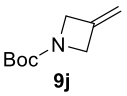
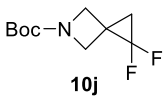
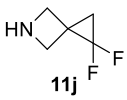
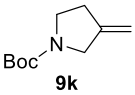
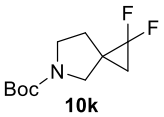
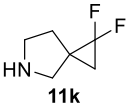
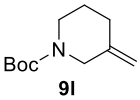
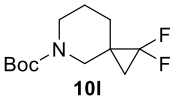
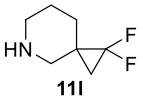
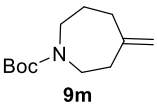
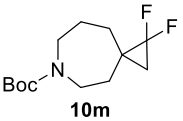
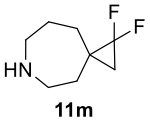
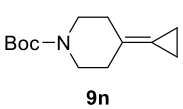
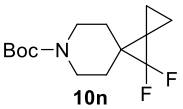
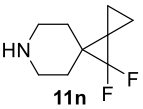
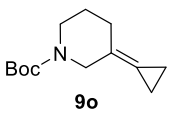
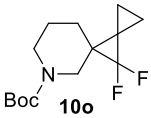
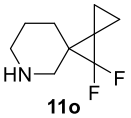
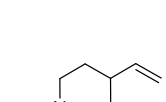
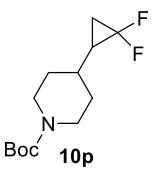
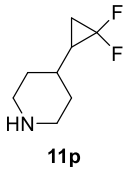
Figure 9. Molecular structure of **11a**·HCl, **11j**·HCl, **11k**·HCl and **10g**.

Conclusion

Reaction of *N*-Boc protected unsaturated amines with CF_3SiMe_3 – NaI system, followed by deprotection is an efficient method for the synthesis of monocyclic, spirocyclic and fused bicyclic secondary amines bearing *gem*-difluorocyclopropane moiety. The optimal conditions for the difluorocyclopropanation include refluxing of the starting materials in THF as the solvent. At these conditions, a remarkable decomposition of the Ruppert–Prakash reagent occurs to give a mixture of gaseous by-products (mainly $CF_2{=}CF_2$ and Me_3SiF), which compete with the main reaction. While this side process is not a problem for the reactive substrates (possessing 1,1-disubstituted, tri- or tetrasubstituted double bond), in the case of mono- and 1,2-disubstituted alkenes, it prevents the

Table 2. Synthesis of amines **11** bearing *gem*-difluorocyclopropane fragment



#	Substrate **9**	Boc derivative **10**	Amine **11**[a)]	Method[b)]	Yield of **10** (%)	Yield of **11**·HCl (%)
1	 **9a**	 **10a**	 **11a**	A	91	94
2	 **9b**	 **10b**	 **11b**	B	50	95
3	 **9f**	 **10f**	 **11f**	A	88	92
4	 **9g**	 **10g**	 **11g**	A	82	93
5	 **9h**	 **10h**	 **11h**	B	81	91
6	 **9i**	 **10i**	 **11i**	B	87	96
7	 **9j**	 **10j**	 **11j**	A	64	85
8	 **9k**	 **10k**	 **11k**	A	81	90
9	 **9l**	 **10l**	 **11l**	A	75	89
10	 **9m**	 **10m**	 **11m**	A	88	91
11	 **9n**	 **10n**	 **11n**	A	88	92
12	 **9o**	 **10o**	 **11o**	A	81	85
13	 **9p**	 **10p**	 **11p**	B	76	96

[a)] Isolated as hydrochlorides. [b)] Method A: $TMSCF_3$ is added in one portion; Method B: slow addition of $TMSCF_3$

complete conversion, so that slow addition of CF_3SiMe_3 becomes necessary. The reactivity order of the substrates shows that the process is governed mainly by electronic and to lesser extent – by steric factors, which can be explained by partially non-synchronous transition state during addition of difluorocarbene (carbenoid) to the double bond.

The method includes only two operationally simple steps, relies on the readily available and non-toxic starting materials, gives 48–85% overall yields of the target products, have been used effectively on up to 40 gram scale and in our opinion, has potential for further scale-up. This makes secondary amines bearing *gem*-difluorocyclopropane moiety readily available to the chemical community, first of all for the use as building blocks for medicinal chemistry programs.

Experimental Section

The solvents were purified according to the standard procedures. Alkenes **9a–p** were prepared *via* Wittig olefination of the corresponding ketones using the methods reported in the literature. All other starting materials were purchased from commercial sources. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Varian Gemini 2000 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. 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 1100 LCMSD SL instrument (electrospray ionization (ESI)) or Agilent 7820A gas chromatograph system (electron impact ionization (EI), ionization energy – 70 eV)). Conversion measurements were performed using the same GCMS instrument (column: HP-5ms UI, 30 m×0.25 mm, 0.25 μm; carrier gas: helium at 1 mL/min; temperatures: injector – 250 °C, oven program – 50 °C initial temperature for 1 min, then ramp to 300 °C at 20 °C/min, then hold final temperature for 5 min; MSD transfer line – 280 °C, MSD source – 230 °C, MSD quad – 150 °C; injection parameters: split ratio 200:1, 0.5 μL injected; MS parameters: mass scan range – 35–550, ionization energy – 70eV).

*General procedure for the preparation of **10**:*

Method A:

Sodium iodide (5.30 g, 0.0354 mol) was added to a solution of alkene **9** (0.100 mol) in anhydrous THF (300 mL) under nitrogen atmosphere. Trimethyl-(trifluoromethyl)silane (48.9 g, 0.344 mol) was added, and the reaction mixture was heated at reflux overnight, at which time GCMS indicated complete conversion. The solid was filtered, and the solvent was evaporated. The crude product was dissolved in hexanes (100 mL), filtered through a pad of silica gel (100 g), and washed with hexanes (300 mL). The combined filtrates were evaporated to give the product **10**, which was used in the next step without further purification.

Method B:

Sodium iodide (0.540 g, 3.60 mmol) was added to a solution of alkene **9** (10.0 mmol) in anhydrous THF (20 mL) under nitrogen atmosphere and heated to reflux. Trimethyl(trifluoromethyl)silane (4.93 g, 34.7 mmol) was added dropwise over 6–8 h. The reaction mixture was heated overnight, at which time the conversion was detected by GCMS. If necessary, additional trimethyl(trifluoromethyl)silane (4.93 g, , 34.7 mmol) was added, and the reaction mixture was refluxed for additional 24 h. When the conversion was complete, the solvent was evaporated, and the crude product was distilled under reduced pressure.

*tert-Butyl 1,1-difluoro-6-azaspiro[2.5]octane-6-carboxylate (**10a**)*

Yield 66.7 g, 91% (Method A). Off-white crystalline powder. Mp 46–48 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.57 – 3.42 (m, 2H), 3.40 – 3.27 (m, 2H), 1.66 – 1.47 (m, 4H), 1.44 (s, *J* = 2.3 Hz, 9H), 1.08 (t, *J* = 8.3 Hz, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz,) δ 154.2, 115.4 (t, *J* = 288.1 Hz), 79.3, 42.8, 28.4, 28.1, 26.8 (t, *J* = 10.0 Hz), 21.0 (t, *J* = 10.1 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –140.6. MS (EI): m/z = 247 (M^+), 192 (M^+–*t*-Bu), 174 (M^+–*t*-BuO), 147 (M^+–Boc), 127 (M^+–Boc–HF). Anal. Calcd. for $C_{12}H_{19}F_2NO_2$: C, 58.29; H, 7.74; N, 5.66. Found: C, 58.49; H, 8.02; N, 5.30.

*tert-Butyl ((2,2-difluorocyclopropyl)methyl)(methyl)-carbamate (**10b**)*

The crude product obtained by Method B was dissolved in CH_2Cl_2 (100 mL) and treated with 5% aq $KMnO_4$ (100 mL). The mixture was stirred at rt overnight. The obtained solid was filtered, the phases were separated, and the organic layer was dried over Na_2SO_4, and evaporated in vacuo. Yield 1.05 g, 50%. Brownish oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.95 – 3.72 (m, 1H), 3.71 – 3.46 (m, 1H), 3.10 – 2.93 (m, 1H), 2.88 (s, 3H), 1.90 – 1.66 (m, 1H), 1.45 (s, 9H), 1.17 – 0.93 (m, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 154.7, 79.4, 45.8, 33.8, 28.1, 27.7, 21.1 (t, *J* = 8.0 Hz), 14.5 (t, *J* = 11.1 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –130.3 (dd, *J* = 157.9, 62.0 Hz), –143.3 (d, *J* = 158.6 Hz). MS (EI): m/z = 206 (M^+), 165 (M^+–*t*-Bu), 148

(M^+–*t*-BuO), 121 (M^+–Boc), 101 (M^+–Boc–HF). Anal. Calcd. for $C_{10}H_{17}F_2NO_2$: C, 54.29; H, 7.74; N, 6.33. Found: C, 54.30; H, 8.10; N, 6.66.

*tert-Butyl 1,1-difluoro-2-methyl-6-azaspiro[2.5]-octane-6-carboxylate (**10f**)*

Yield 60.6 g, 88% (Method A). Yellowish oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.58 – 3.43 (m, 2H), 3.14 (qd, *J* = 8.0, 5.0 Hz, 2H), 1.47 (m, 4H), 1.37 (s, 9H), 1.19 – 1.06 (m, 1H), 0.98 (dd, *J* = 6.5, 2.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 154.2, 116.2 (dd, *J* = 295.9, 289.2 Hz), 79.1, 42.8, 29.9, 27.9, 24.7 (t, *J* = 9.8 Hz), 23.4, 5.3 (d, *J* = 4.9 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –139.7 (dd, *J* = 153.7, 14.2 Hz), –151.4 (d, *J* = 153.7 Hz). MS (EI): m/z = 261 (M^+), 206 (M^+–*t*-Bu), 188 (M^+–*t*-BuO), 141 (M^+–Boc–HF). Anal. Calcd. for $C_{13}H_{21}F_2NO_2$: C, 59.75; H, 8.10; N, 5.36. Found: C, 59.91; H, 7.93; N, 5.18.

*tert-Butyl 11,11-difluoro-8-azadispiro[3.0.5^5.1^4]-undecane-8-carboxylate (**10g**)*

Yield 2.07 g, 82%. Yellowish oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.66 – 3.53 (m, 2H), 3.28 – 3.17 (m, 2H), 2.07 (s, 4H), 2.05 – 1.89 (m, 2H), 1.46 (s, 9H), 1.44 – 1.39 (m, 4H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 154.3, 114.9 (t, *J* = 294.3 Hz), 79.3, 42.9, 32.4 (t, *J* = 11.1 Hz), 28.2, 24.6, 20.1, 15.8. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –148.9. MS (EI): m/z = 287 (M^+), 231 (M^+–*t*-Bu), 214 (M^+–*t*-BuO), 166. Anal. Calcd. for $C_{15}H_{23}F_2NO_2$: C, 62.70; H, 8.07; N, 4.87. Found: C, 62.31; H, 8.10; N, 4.68.

*tert-Butyl 6,6-difluoro-3-azabicyclo[3.1.0]hexane-3-carboxylate (**10h**)*

The crude product obtained by Method B was distilled under reduced pressure (bp 75–78 °C / 1 mbar) to give **10h**. Yield 18.1 g, 81%. Yellowish solid. Mp 52–54 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.76 (dd, *J* = 32.4, 11.2 Hz, 2H), 3.65 – 3.51 (m, 2H), 2.23 (dd, *J* = 12.2, 5.1 Hz, 2H), 1.45 (s, 9H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 153.2, 112.9 (dd, *J* = 295.0, 276.9 Hz), 79.5, 45.1, 28.2, 26.0 (t, *J* = 12.0 Hz), 25.3 (t, *J* = 12.1 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –131.3 (dt, *J* = 162.0, 12.1 Hz), –157.6 (d, *J* = 162.0 Hz). MS (EI): m/z = 219 (M^+), 204 (M^+–CH_3), 164, 146 (M^+–*t*-BuO), 119 (M^+–Boc). Anal. Calcd. for $C_{10}H_{15}F_2NO_2$: C, 54.79; H, 6.90; N, 6.39. Found: C, 54.97; H, 6.89; N, 6.14.

*tert-Butyl 7,7-difluoro-3-azabicyclo[4.1.0]heptane-3-carboxylate (**10i**)*

The crude product obtained by Method B was distilled under reduced pressure (bp 85–93 °C / 1 mbar) to give **10i**. Yield 20.1 g, 87%. Yellowish oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.92 – 2.81 (m, 4H), 1.97 – 1.52 (m, 4H), 1.45 (s, 9H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 154.1, 113.6 (t, *J* = 285.9 Hz), 79.4, 39.4 (d, *J* = 95.6 Hz), 35.7 (d, *J* = 107.9 Hz), 28.2, 16.8, 15.7. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –128.0 (d, *J* = 158.5 Hz), –153.4 (dd, *J* = 158.4, 94.9 Hz). MS (EI): m/z = 233 (M^+), 218 (M^+–CH_3), 178 (M^+–*t*-Bu), 160 (M^+–*t*-BuO), 133 (M^+–Boc), 113 (M^+–Boc–HF). Anal. Calcd. for $C_{11}H_{17}F_2NO_2$: C, 56.64; H, 7.35; N, 6.00. Found: C, 56.69; H, 7.48; N, 5.71.

*tert-Butyl 1,1-difluoro-5-azaspiro[2.3]hexane-5-carboxylate (**10j**)*

Yield 45.3 g, 64% (Method A). Light brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.11 (d, *J* = 9.2 Hz, 2H), 3.96 (dt, *J* = 9.3, 2.3 Hz, 2H), 1.45 (s, 9H), 1.44 – 1.40 (m, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 155.4, 110.4 (t, *J* = 285.5 Hz), 79.7, 52.0, 33.6, 29.5, 28.1, 18.1, 0.9. ^{19}F NMR ($CDCl_3$, 376 MHz,) δ –140.4. MS (EI): m/z = 219 (M^+), 204 (M^+–CH_3), 164, 146 (M^+–*t*-BuO), 118, 103. Anal. Calcd. for $C_{10}H_{15}F_2NO_2$: C, 54.79; H, 6.90; N, 6.39. Found: C, 54.80; H, 6.69; N, 6.33.

*tert-Butyl 1,1-difluoro-5-azaspiro[2.4]heptane-5-carboxylate (**10k**)*

Yield 26.4 g, 81% (Method A). Light brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.64 – 3.22 (m, 4H), 2.12 – 2.02 (m, 1H), 1.97 – 1.84 (m, 1H), 1.44 (s, 9H), 1.32 (dd, *J* = 11.1, 6.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 153.7, 112.8 (t, *J* = 287.1 Hz), 79.2, 47.8 (d, *J* = 28.3 Hz), 45.5 (d, *J* = 35.1 Hz), 28.1, 18.6. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –138.7 (d, *J* = 152.6 Hz), –140.4 (d, *J* = 158.9 Hz). MS (EI): m/z = 233 (M^+), 178, 160 (M^+–*t*-BuO), 133 (M^+–Boc), 113 (M^+–Boc–HF). Anal. Calcd. for $C_{11}H_{17}F_2NO_2$: C, 56.64; H, 7.35; N, 6.00. Found: C, 56.78; H, 7.36; N, 5.63.

*tert-Butyl 1,1-difluoro-5-azaspiro[2.5]octane-5-carboxylate (**10l**)*

Yield 21.0 g, 75% (Method A). Light brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.59 – 3.15 (m, 4H), 1.73 – 1.61 (m, 1H), 1.61 – 1.44 (m, 3H), 1.38 (s, 9H), 1.25 – 1.02 (m, 1H), 1.03 – 0.89 (m, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 155.7, 115.0 (t, *J* = 287.6 Hz), 79.2, 46.1, 43.1, 27.9, 27.4 (t, *J* = 10.3 Hz), 27.1 (d, *J* = 4.7 Hz), 23.9, 20.4. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –140.1 (dd, *J* = 157.5, 12.7 Hz), –141.8 (d, *J* = 158.1 Hz). MS (EI): m/z = 247 (M^+), 191 (M^+–*t*-Bu), 174 (M^+–*t*-BuO), 147 (M^+–Boc), 127 (M^+–Boc–HF). Anal. Calcd. for $C_{12}H_{19}F_2NO_2$: C, 58.29; H, 7.74; N, 5.66. Found: C, 58.60; H, 7.91; N, 5.41.

*tert-Butyl 1,1-difluoro-6-azaspiro[2.6]nonane-6-carboxylate (**10m**)*

Yield 14.2 g, 88% (Method A). Light brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.61 – 3.17 (m, 4H), 1.88 – 1.55 (m, 6H), 1.46 (s, 9H), 1.10 – 0.95 (m, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 154.9, 115.9 (t, *J* = 287.7 Hz), 78.9, 46.5 (d, *J* = 75.4 Hz), 44.5 (d, *J* = 29.1 Hz), 31.4 (d, *J* = 50.7 Hz), 29.2, 28.5 (d, *J* = 21.2 Hz), 28.1, 24.8 (d, *J* = 9.9 Hz), 21.3 (dt, *J* = 40.0, 9.2 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –138.1 (dd, *J* = 152.4, 97.1 Hz), –139.7 (dd, *J* = 152.0, 115.5 Hz). MS (EI): m/z = 261 (M^+), 188 (M^+–*t*-BuO), 140 (M^+–Boc–HF). Anal. Calcd. for $C_{13}H_{21}F_2NO_2$: C, 59.75; H, 8.10; N, 5.36. Found: C, 59.45; H, 8.45; N, 5.37.

*tert-Butyl 10,10-difluoro-7-azadispiro[2.0.54.13]-decane-7-carboxylate (**10n**)*

Yield 6.14 g, 88% (Method A). Pale yellow crystalline powder. Mp 83-84 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.59 – 3.42 (m, 2H), 3.35 – 3.24 (m, 2H), 1.75 – 1.62 (m, 2H), 1.58 – 1.49 (m, 2H), 1.45 (s, 9H), 1.07 – 0.92 (m, 4H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 154.2, 116.7 (t, *J* = 293.4 Hz), 79.3, 42.9, 28.2, 27.8 (t, *J* = 10.2 Hz), 27.3, 22.9 (t, *J* = 9.7 Hz), 4.2. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –144.1. MS (EI): m/z = 200 (M^+–*t*-BuO), 172 (M^+–Boc), 145, 109. Anal. Calcd. for $C_{14}H_{21}F_2NO_2$: C, 61.52; H, 7.74; N, 5.12. Found: C, 61.35; H, 7.34; N, 5.44.

*tert-Butyl 10,10-difluoro-6-azadispiro[2.0.54.13]-decane-6-carboxylate (**10o**)*

Yield 0.668 g, 81% (Method A). Yellowish oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.58 – 3.19 (m, 4H), 1.82 – 1.71 (m, 1H), 1.65 – 1.52 (m, 3H), 1.42 (s, 9H), 1.09 – 0.88 (m, 4H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 153.9, 116.1 (t, *J* = 293.0 Hz), 79.2, 45.4, 43.0, 28.4 (s, *J* = 9.9 Hz), 28.0, 25.8, 23.9, 22.5 (t, *J* = 9.6 Hz), 4.4, 3.9. ^{19}F NMR ($CDCl_3$, 376 MHz) δ –143.5 (d, *J* = 152.0 Hz), –144.5 (d, *J* = 151.8 Hz). MS (EI): m/z = 217 (M^+–*t*-Bu), 197, 172 (M^+–Boc), 158. Anal. Calcd. for $C_{14}H_{21}F_2NO_2$: C, 61.52; H, 7.74; N, 5.12. Found: C, 61.41; H, 7.89; N, 5.08.

*tert-Butyl 4-(2,2-difluorocyclopropyl)piperidine-1-carboxylate (**10p**)*

The crude product obtained by Method B was distilled under reduced pressure (bp 104–107 °C / 0.1 mbar) to give **10p**. Yield 17.3 g, 76%. Yellowish oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.17 – 3.90 (m, 2H), 2.75 – 2.55 (2, 1H), 1.80 – 1.57 (m, 2H), 1.42 (s, 9H), 1.37 – 1.15 (m, 5H), 0.97 – 0.86 (m, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 154.3, 113.4 (dd, *J* = 346.1, 221.0 Hz), 79.0, 43.3, 34.7 (d, *J* = 2.8 Hz), 31.7, 30.3, 28.1, 27.2 (dd, *J* = 10.8, 9.8 Hz), 14.9 (t, *J* = 10.9 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ –128.1 (d, *J* = 157.3 Hz), –146.2 (dd, *J* = 157.3, 13.1 Hz). MS (EI): m/z = 261 (M^+), 204 (M^+–*t*-Bu), 188 (M^+–*t*-BuO), 160 (M^+–Boc), 140 (M^+–Boc–HF–H). Anal. Calcd. for $C_{13}H_{21}F_2NO_2$: C, 59.75; H, 8.10; N, 5.36. Found: C, 59.90; H, 8.15; N, 5.46.

Decomposition of CF_3SiMe_3 upon action of NaI:

$TMSCF_3$ (3.00 g, 0.0211 mol) and $PhCF_3$ (3.08 g, 0.0211 mol) were dissolved in THF (50 mL). NaI (0.315 g, 2.10 mmol) was added, and the mixture was heated at reflux with efficient condenser. The evaluated gases were trapped at –78 °C by a THF solution (25 mL) containing $PhCF_3$ (1.00 g, 6.85 mmol). The temperature of the reaction mixture was monitored, and ^{19}F NMR spectra were recorded for both THF solutions each 10 min and then used to build the graph shown in Figure 8.

*General procedure for the preparation of **11a–11o**:*

To a solution of **10** (45.0 mmol) in dry Et_2O (100 mL), 3.5 M HCl in Et_2O (100 mL) was added, and the reaction mixture was stirred overnight. The solid formed was filtered, washed with Et_2O (3×50 mL) and dried under reduced pressure.

*1,1-Difluoro-6-azaspiro[2.5]octane hydrochloride (**11a**·HCl)*

Yield 41.2 g, 94%. Pale yellow crystalline powder. Mp 199–203 °C (dec.). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.33 (br s, 1H), 9.23 (br s, 1H), 3.16 – 2.93 (m, 4H), 1.95 – 1.80 (m, 2H), 1.78 – 1.58 (m, 2H), 1.42 (t, *J* = 8.9 Hz, 2H). ^{13}C NMR (DMSO-d_6, 101 MHz) δ 116.1 (t, *J* = 287.2 Hz), 42.3, 25.0 (t, *J* = 10.5 Hz), 24.5, 20.7 (t, *J* = 9.8 Hz). ^{19}F NMR (DMSO-d_6, 376 MHz) δ –139.1 (t, *J* = 8.1 Hz). MS (EI): m/z = 147 (M^+), 127 (M^+–HF), 82. Anal. Calcd. for $C_7H_{12}ClF_2N$: C, 45.79; H, 6.59; N, 7.63; Cl, 19.31. Found: C, 46.03; H, 6.96; N, 7.71; Cl, 19.04.

*1-(2,2-difluorocyclopropyl)-N-methylmethanamine hydrochloride (**11b**·HCl)*

Yield 0.641 g, 95%. White solid. Mp 106-121 °C (dec.). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.50 (brs, 2H), 3.01 (d, *J* = 61.2 Hz, 2H), 2.51 (s, 3H), 2.10 (s, 1H), 1.69 (d, *J* = 42.2 Hz, 2H). ^{13}C NMR (DMSO-d_6, 101 MHz) δ 113.5 (t, *J* = 282.5 Hz), 44.6 (d, *J* = 4.7 Hz), 31.7, 17.9 (t, *J* = 11.4 Hz), 15.2 (t, *J* = 10.8 Hz). ^{19}F NMR (DMSO-d_6, 376 MHz) δ –128.3 (d, *J* = 155.9 Hz), –140.8 (dd, *J* = 156.0, 10.1 Hz). MS (EI): m/z = 121 (M^+), 99, 91. Anal. Calcd. for $C_5H_{10}ClF_2N$:

C, 38.11; H, 6.40; N, 8.89; Cl, 22.50. Found: C, 37.89; H, 6.14; N, 8.72; Cl, 22.58.

*1,1-Difluoro-2-methyl-6-azaspiro[2.5]octane hydrochloride (**11f**·HCl)*

Yield 29.2 g, 92%. White solid. Mp 171–174 °C (dec.). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.26 (br s, 2H), 3.20 – 2.88 (m, 4H), 1.93 – 1.63 (m, 4H), 1.63 – 1.43 (m, 1H), 1.06 (dd, *J* = 6.5, 2.6 Hz, 3H). ^{13}C NMR (101 DMSO-d_6, 101 MHz) δ 116.6 (dd, *J* = 295.5, 288.1 Hz), 42.4 (d, *J* = 4.4 Hz), 26.2 (t, *J* = 10.1 Hz), 26.0 (d, *J* = 5.3 Hz), 24.6 (t, *J* = 9.6 Hz), 19.8 (d, *J* = 4.9 Hz), 5.6 (d, *J* = 4.7 Hz). ^{19}F NMR (DMSO-d_6, 376 MHz) δ –138.0 (dd, *J* = 152.5, 14.8 Hz), –149.5 (d, *J* = 152.5 Hz). MS (EI): m/z = 161 (M^+), 141 (M^+–HF), 126. Anal. Calcd. for $C_8H_{14}ClF_2N$: C, 48.61; H, 7.14; N, 7.09; Cl, 17.94. Found: C, 48.94; H, 6.77; N, 6.75; Cl, 18.15.

*11,11-Difluoro-8-azadispiro[3.0.5^5.1^4]undecane hydrochloride (**11g**·HCl)*

Yield 1.27 g, 93%. White solid. Mp 228–232 °C (dec.). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.16 – 2.97 (m, 4H), 2.23 – 2.09 (m, 2H), 2.05 – 1.94 (m, 4H), 1.71 – 1.61 (m, 2H), 1.61 – 1.51 (m, 2H), NH_2 are exchanged with HDO. ^{13}C NMR (DMSO-d_6, 101 MHz) δ 115.0 (t, *J* = 294.9 Hz), 42.2, 32.4 (t, *J* = 10.7 Hz), 26.2 (t, *J* = 9.1 Hz), 20.9, 19.6, 15.2. ^{19}F NMR (DMSO-d_6, 376 MHz) δ –147.2. MS (EI): m/z = 187 (M^+), 167, 139. Anal. Calcd. for $C_{10}H_{16}ClF_2N$: C, 53.69; H, 7.21; N, 6.26; Cl, 15.85. Found: C, 53.89; H, 7.33; N, 6.63; Cl, 15.50.

*6,6-Difluoro-3-azabicyclo[3.1.0]hexane hydrochloride (**11h**·HCl)*

Yield 11.6 g, 91%. White solid. Mp 183–185 °C (dec.). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.94 (br s, 2H), 3.58 (d, *J* = 12.4 Hz, 2H), 3.42 (d, *J* = 12.4 Hz, 2H), 2.80 (d, *J* = 11.3 Hz, 2H). ^{13}C NMR (DMSO-d_6, 101 MHz) δ 113.2 (dd, *J* = 292.3, 281.5 Hz), 44.7, 26.4 (t, *J* = 12.1 Hz). ^{19}F NMR (DMSO-d_6, 376 MHz) δ –128.3 (d, *J* = 160.1 Hz), –149.3 (d, *J* = 160.1 Hz). MS (EI): m/z = 119 (M^+), 98, 90. Anal. Calcd. for $C_5H_8ClF_2N$: C, 38.60; H, 5.18; N, 9.00; Cl, 22.79. Found: C, 38.91; H, 5.19; N, 9.30; Cl, 22.40.

*7,7-Difluoro-3-azabicyclo[4.1.0]heptane hydrochloride (**11i**·HCl)*

Yield 13.9 g, 96%. White solid. Mp 98–102 °C (dec.). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.27 (br s, 1H), 3.61 – 3.46 (m, 1H), 3.07 – 2.93 (m, 1H), 2.93 – 2.81 (m, 1H), 2.22 – 1.95 (m, 3H), 1.91 – 1.78 (m, 1H). ^{13}C NMR (DMSO-d_6, 101 MHz) δ 113.9 (dd, *J* = 286.3, 284.2 Hz), 37.9, 34.3, 14.8 (t, *J* = 11.4 Hz), 13.5 (dd, *J* = 13.1, 10.2 Hz), 12.9. ^{19}F NMR (DMSO-d_6, 376 MHz) δ –127.9 (d, *J* = 156.1 Hz), –148.1 (d, *J* = 156.2 Hz). MS (EI): m/z = 133 (M^+), 113 (M^+–HF–H), 85. Anal. Calcd. for $C_6H_{10}ClF_2N$: C, 42.49; H, 5.94; N, 8.26; Cl, 20.90. Found: C, 42.75; H, 5.77; N, 8.65; Cl, 20.91.

*1,1-Difluoro-5-azaspiro[2.3]hexane hydrochloride (**11j**·HCl)*

Yield 26.1 g, 85%. Light brown crystalline powder. Mp 143–146 °C (dec.). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.66 (br s, 2H), 4.29 – 4.06 (m, 2H), 4.06 – 3.89 (m, 2H), 1.81 (t, *J* = 9.4 Hz, 2H). ^{13}C NMR (DMSO-d_6, 101 MHz) δ 110.7 (t, *J* = 286.3 Hz), 47.0, 23.7, 17.3 (t, *J* = 9.9 Hz). ^{19}F NMR (DMSO-d_6, 376 MHz) δ –138.6. MS (EI): m/z = 119 (M^+), 98 (M^+–HF–H), 90. Anal. Calcd. for $C_5H_8ClF_2N$: C, 38.60; H, 5.18; N, 9.00; Cl, 22.79. Found: C, 38.74; H, 5.11; N, 9.10; Cl, 23.16.

*1,1-Difluoro-5-azaspiro[2.4]heptane hydrochloride (**11k**·HCl)*

Yield 19.6 g, 90%. Brownish crystalline powder. Mp 130–133 °C (dec.). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.71 (br s, 2H), 3.49 – 3.12 (m, 4H), 2.25 – 1.88 (m, 1H), 1.91 – 1.45 (m, 1H). ^{13}C NMR (DMSO-d_6, 101 MHz) δ 113.1 (t, *J* = 287.1 Hz), 45.9 (d, *J* = 5.7 Hz), 45.1, 28.8 (t, *J* = 9.8 Hz), 27.3, 18.7 (t, *J* = 10.0 Hz). ^{19}F NMR (DMSO-d_6, 376 MHz) δ –136.5 (dd, *J* = 377.8, 160.5 Hz). MS (EI): m/z = 133 (M^+), 82, 68. Anal. Calcd. for $C_6H_{10}ClF_2N$: C, 42.49; H, 5.94; N, 8.26; Cl, 20.90. Found: C, 42.53; H, 5.73; N, 8.39; Cl, 20.56.

*1,1-Difluoro-5-azaspiro[2.5]octane hydrochloride (**11l**·HCl)*

Yield 18.6 g, 89%. Light brown crystalline powder. Mp 143-151 °C (dec.). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.30 (br s, 2H), 3.22 – 2.90 (m, 4H), 1.87 – 1.66 (m, 3H), 1.66 – 1.52 (m, 2H), 1.52 – 1.37 (m, 1H). ^{13}C NMR (DMSO-d_6, 101 MHz) δ 115.1 (t, *J* = 286.8 Hz), 44.0 (d, *J* = 6.6 Hz), 43.0, 24.7 (dd, *J* = 22.9, 7.0 Hz), 20.9. ^{19}F NMR (DMSO-d_6, 376 MHz) δ –137.3 (d, *J* = 169.5 Hz), –139.8 (d, *J* = 167.8 Hz). MS (EI): m/z = 147 (M^+), 126 (M^+–HF–H), 96, 82. Anal. Calcd. for $C_7H_{12}ClF_2N$: C, 45.79; H, 6.59; N, 7.63; Cl, 19.31. Found: C, 45.86; H, 6.96; N, 8.03; Cl, 19.10.

*1,1-Difluoro-6-azaspiro[2.6]nonane hydrochloride (**11m**·HCl)*

Yield 10.2 g, 91%. White solid. Mp 113-121 °C (dec.). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.41 (br s, 2H), 3.21 – 2.99 (m, 4H), 2.08 – 1.94 (m, 1H), 1.94 – 1.73 (m, 4H), 1.73 – 1.51 (m, 1H), 1.47 – 1.19 (m, 2H). ^{13}C NMR (DMSO-d_6, 101 MHz) δ 116.1 (t, J = 292.4 Hz), 43.4, 43.0, 26.1 (t, J = 292.6 Hz), 23.7, 23.3 (t, J = 9.5 Hz), 20.6, 5.3, 4.4. ^{19}F NMR (DMSO-d_6, 376 MHz) δ –136.9. MS (EI): m/z = 161 (M^+), 140 (M^+–HF–H), 96, 56. Anal. Calcd. for $C_8H_{14}ClF_2N$: C, 48.61; H, 7.14; N, 7.09; Cl, 17.94. Found: C, 48.78; H, 7.08; N, 7.47; Cl, 18.07.

*10,10-Difluoro-7-azadispiro[2.0.54.13]decane hydrochloride (**11n**·HCl)*

Yield 4.36 g, 92%. White solid. Mp 245-252 °C (dec.). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.18 (br s, 2H), 3.14 – 3.04 (m, 2H), 3.04 – 2.91 (m, 2H), 1.99 – 1.85 (m, 2H), 1.80 – 1.63 (m, 2H), 1.27 – 1.17 (m, 2H), 1.08 – 0.99 (m, 2H). ^{13}C NMR (DMSO-d_6, 101 MHz) δ 117.0 (t, J = 293.3 Hz), 42.0, 25.9 (t, J = 10.6 Hz), 23.7, 23.3 (t, J = 9.3 Hz), 4.4. ^{19}F NMR (DMSO-d_6, 376 MHz) δ –142.0. MS (EI): m/z = 173 (M^+), 158, 145, 109. Anal. Calcd. for $C_9H_{14}ClF_2N$: C, 51.56; H, 6.73; N, 6.68; Cl, 16.91. Found: C, 51.84; H, 6.44; N, 6.63; Cl, 17.20.

*10,10-Difluoro-6-azadispiro[2.0.5^4.1^3]decane hydrochloride (**11o**·HCl)*

Yield 0.334 g, 85%. Light brown crystalline powder. Mp 157–160 °C (dec.). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.38 (br s, 1H), 9.20 (br s, 1H), 3.25 – 3.08 (m, 1H), 3.08 – 2.78 (m, 3H), 1.86 – 1.65 (m, 3H), 1.61 – 1.45 (m, 2H), 1.16 – 0.94 (m, 3H). ^{13}C NMR (DMSO-d_6, 101 MHz) δ 116.1 (t, J = 292.4 Hz), 43.4, 43.0, 26.0 (dd, J = 11.5, 10.0 Hz), 23.7, 23.3 (t, J = 9.5 Hz), 20.6, 5.3, 4.4. ^{19}F NMR (DMSO-d_6, 376 MHz) δ –139.9 (dd, J = 151.7, 7.7 Hz), –142.2 (dd, J = 151.7, 8.3 Hz). MS (EI): m/z = 173 (M^+), 158, 144, 82. Anal. Calcd. for $C_9H_{14}ClF_2N$: C, 51.56; H, 6.73; N, 6.68; Cl, 16.91. Found: C, 51.23; H, 6.92; N, 7.05; Cl, 17.02.

*4-(2,2-Difluorocyclopropyl)piperidine hydrochloride (**11p**·HCl)*

Yield 12.3 g, 96%. White solid. Mp 216–218 °C (dec.). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.36 (br s, 1H), 9.17 (br s, 1H), 3.20 (t, J = 12.0 Hz, 2H), 2.89 – 2.71 (m, 2H), 1.79 (t, J = 14.8 Hz, 2H), 1.69 – 1.30 (m, 5H), 1.24 – 1.02 (m, 1H). ^{13}C NMR (DMSO-d_6, 101 MHz) δ 114.9 (t, J = 282.8 Hz), 42.7, 42.4, 31.9 (d, J = 2.8 Hz), 28.2, 26.9, 26.5 (t, J = 10.0 Hz), 14.8 (t, J = 10.4 Hz). ^{19}F NMR (DMSO-d_6, 376 MHz) δ –125.8 (d, J = 153.6 Hz), –143.5 (dd, J = 153.6, 13.1 Hz). MS (EI): m/z = 161 (M^+), 132, 96, 68, 56. Anal. Calcd. for $C_8H_{14}ClF_2N$: C, 48.61; H, 7.14; N, 7.09; Cl, 17.94. Found: C, 48.41; H, 7.28; N, 7.33; Cl, 17.61.

X-Ray structure determination

Single crystals were obtained by slow evaporation of the solutions in MeCN (**11a**·HCl, **11j**·HCl and **11k**·HCl) or hexanes (**10g**). All crystallographic measurements for **11a**·HCl, **11k**·HCl and **10g** were performed at 173 K, for **11j**·HCl – at 123 K on a Bruker Smart Apex II diffractometer operating in the ω scans mode. The intensity data were collected with graphite-monochromated Mo-K_α radiation (λ = 0.71078 Å).

Table 3. Crystal data, data collection and structure refinement details for **10g**, **11j**·HCl, **11a**·HCl and **11k**·HCl

Parameter	**10g**	**11j**·HCl	**11a**·HCl	**11k**·HCl
Formula	$C_{14}H_{21}F_2NO_2$	$C_5H_8ClF_2N$	$C_7H_{12}ClF_2N$	$C_6H_{10}ClF_2N$
M	273.32	155.57	183.63	279.31
Crystal system	Monoclinic	Monoclinic	Orthorhombic	Orthorhombic
Space group, Z	$P2_1/c$, 4	Cm, 2	Cmca, 8	$P2_12_12_1$, 4
a, Å	13.723(3)	10.332(4)	9.783(4)	5.3683(10)
b, Å	10.149(2)	7.205(4)	7.335(3)	10.4694(19)
c, Å	10.666(2)	5.670(3)	24.443(12)	13.742(3)
β, º	105.924(8)	121.987(9)	90	90
V, Å^3	1428.5(5)	358.0(3)	1754.0(13)	772.3(3)
Dc, g·cm^{-1}	1.271	1.443	1.391	1.459
μ(Mo-K$_\alpha$), *mm^{-1}*	0.101	0.482	0.405	0.454
θ_{max}, º	26.48	28.39	28.38	28.28
Measured/unique reflections	13924/2953	2020/ 913	9037/1162	4797/1739
R_{int}	0.0535	0.0236	0.0622	0.0352
Parameters refined	172	68	68	92
$R_1[I > 2\sigma(I)]$	0.045	0.0233	0.0383	0.037
wR_2 (all data)	0.1269	0.0517	0.0873	0.081
Goof on F^2	1.054	1.066	0.989	1.07
Max, min peak, Å^{-3}	0.26/–0.22	0.26/–0.20	0.41/–0.19	0.24/–0.25

The data were corrected for Lorentz-polarization effects and for the effects of absorption (numerical for **11j**·HCl, **11k**·HCl and multi-scans method for **11k**·HCl**, 10g**). The structures were solved by direct methods and refined by the full-matrix least-squares technique in the anisotropic approximation for non-hydrogen atoms using the Bruker SHELXTL program package.[55] All CH hydrogen atoms were placed at calculated positions and refined as 'riding' model. Crystal data, data collection and structure refinement details are summarized in Table 3. CCDC-1556358, CCDC-1556359, CCDC-1556360, and CCDC-1556361 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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FULL PAPER

Gram-scale synthesis of amines bearing *gem*-difluorocyclopropane moiety

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