

# Semi-Industrial Fluorination of $\beta$ -Keto Esters with $SF_4$ : Safety vs Efficacy

Serhii A. Trofymchuk<sup>a</sup>

Denys V. Kliukovskiy<sup>a</sup>

Sergey V. Semenov<sup>a</sup>


Andrii R. Khairulin<sup>a,b</sup>

Valerii O. Shevchenko<sup>a</sup>

Maksym Y. Bugera<sup>a,c</sup>

Karen V. Tarasenko<sup>a,c</sup>

Dmitriy M. Volochnyuk<sup>\*a,b,d</sup>

Sergey V. Ryabukhin<sup>\*a,d</sup> 

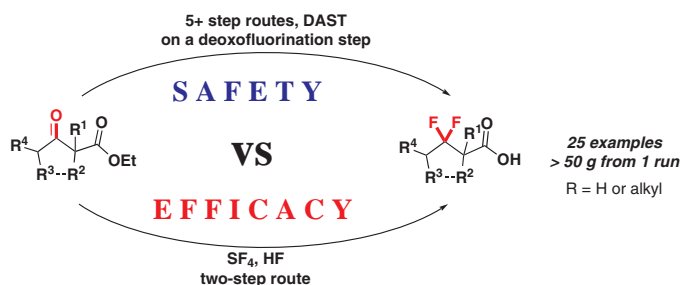
<sup>a</sup> Enamine Ltd., 78 Chervonotkatska Street, Kyiv 02094, Ukraine  
d.volochnyuk@gmail.com  
s.v.ryabukhin@gmail.com

<sup>b</sup> Institute of Organic Chemistry, National Academy of Sciences of Ukraine, 5 Murmanska Street, Kyiv 02660, Ukraine

<sup>c</sup> Institute of Bioorganic Chemistry and Petrochemistry, National Academy of Science of Ukraine, 1 Murmanska Street, Kyiv 02094, Ukraine

<sup>d</sup> Taras Shevchenko National University of Kyiv, 64 Volodymyrska Street, Kyiv 01601, Ukraine

Dedicated to 60th anniversary of Dr. Yuri Pustovit  
Published as part of the *ISySyCat2019 Special Issue*



Received: 28.10.2019

Accepted after revision: 20.12.2019

Published online: 20.01.2020

DOI: 10.1055/s-0037-1610744; Art ID: st-2019-b0588-l

**Abstract** The possibility of deoxofluorination of  $\beta$ -keto esters using  $SF_4$  was investigated. The scope and limitation of the reaction were determined. The efficient method for the synthesis of  $\beta,\beta$ -difluorocarboxylic acids was elaborated based on the reaction. The set of mentioned acids, being the perspective building blocks for medicinal chemistry, were synthesized on multigram scale. The safety of  $SF_4$  use was discussed. The described method does not improve upon the safety of using  $SF_4$ , but practical recommendations for working with the reagent are proposed. Despite the hazards of using toxic  $SF_4$ , a significant increase of efficacy in the synthesis of medicinal-chemistry-relevant building blocks, based on the reaction, in comparison with earlier described approaches is shown.

**Key words** organofluorine compounds, deoxofluorination, sulfur tetrafluoride,  $\beta$ -keto esters,  $\beta,\beta$ -difluorocarboxylic acids, building blocks

There are many efficient reagents for organic synthesis known from the classical textbooks, but by no means are all of them popular among chemists for real application in laboratory practice. Gaseous or volatile compounds which possess extremely high toxicity, like  $CH_2N_2$ , HCN,  $COCl_2$ , and MeNCO, are among the most characteristic examples. The Bhopal disaster, where approximately 200,000 people were exposed to MeNCO and around 20,000 died as a result, has clearly demonstrated such reagents as actually dangerous.<sup>1</sup> Lately some of the above-mentioned reagents are experi-

encing a renaissance due to achievements in flow technology. For example, during the last 10 years the safe flow method using  $CH_2N_2$ <sup>2</sup> and HCN<sup>3</sup> has been developed. Another, more common way of obtaining the same results, as in the case of using the dangerous reagents, is development of their less toxic, more convenient, and safe synthetic equivalents. Thus  $Me_3SiCHN_2$ ,<sup>4</sup>  $Me_3SiCN$ ,<sup>5</sup> triphosgene,<sup>6</sup> and  $MeN-HCO_2CH_2CF_3$ <sup>7</sup> were successfully introduced into organic synthesis. But despite the great achievements in modern reagent and technique developments, some synthetic transformations, which require extremely toxic and hazardous gaseous reagents are still remaining.  $SF_4$  is not so common reagent in comparison with the discussed above, but it is a key compound in organofluorine chemistry.<sup>8</sup> The compound is a colorless, highly reactive, and corrosive gas (bp  $-38^\circ C$ ), possessing extreme toxicity ( $LD_{50} = 19$  ppm (86 mg/m<sup>3</sup>, 4 h, rats<sup>9</sup>)). Also,  $SF_4$  causes burns on unprotected skin due to formation of HF and  $SO_2$  as a result of hydrolysis. Of course, such properties of  $SF_4$  significantly limited its application in synthesis, especially in regular laboratories. Nevertheless, unique properties of  $SF_4$  in substitution of carbonyl oxygen with two fluorine atoms are very attractive. This is making development of more safe and convenient  $SF_4$ -based analogues like DAST ( $Et_2NSF_3$ ) and XtalFluor-E ( $[Et_2N^+=SF_2]BF_4^-$ ) or other similar reactants like fluoroamine reagents (FAR) very important.<sup>10</sup> Such replacement of reagents is successful, but it does not always happen. Fluorination of carboxylic acids to  $CF_3$  derivatives is one of the

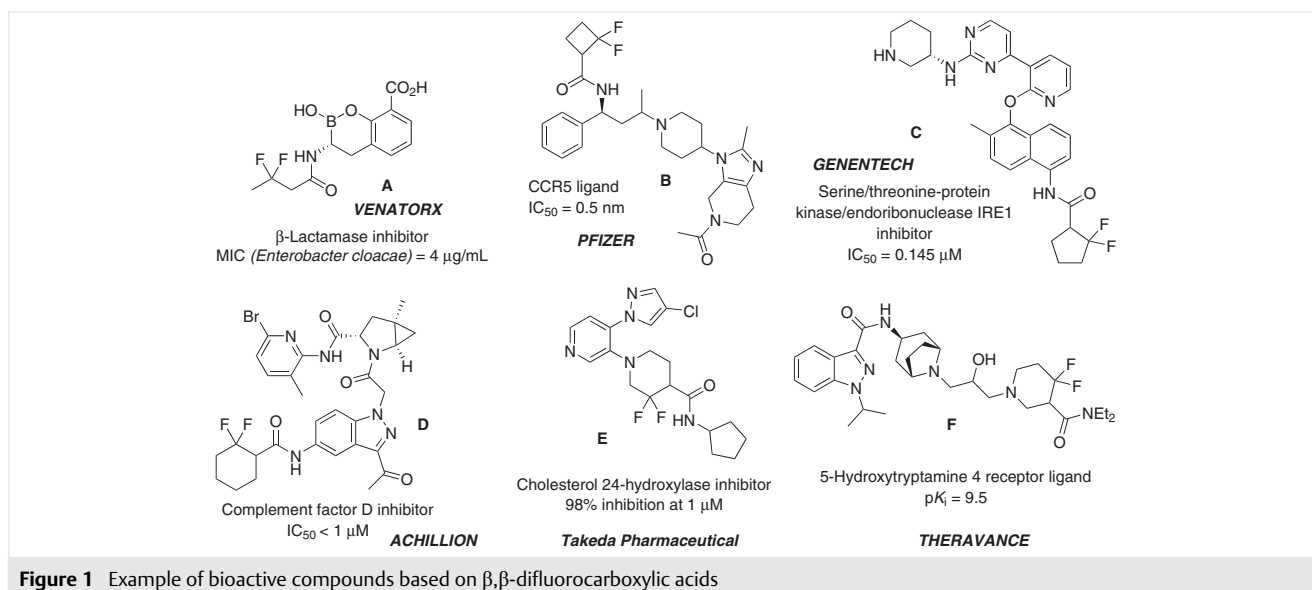
most known examples to the contrary. This process proceeds smoothly under SF<sub>4</sub> treatment, but in the case of DAST or XtalFluor-E the reaction stops at the fluoroanhydride formation step. There is only one successful example described – Fluolead (4-*tert*-Butyl-2,6-dimethylphenylsulfur trifluoride), which is used for fluorination of carboxylic acids to CF<sub>3</sub> derivatives instead of SF<sub>4</sub>.<sup>11</sup> However, Fluolead is a rather expensive reagent, therefore this approach does not find further application. In this work we describe another example of utilizing SF<sub>4</sub> as unique deoxofluorinative reagent, like cited above. As a part of our ongoing efforts on design and synthesis of advanced reagents for medicinal chemistry<sup>12</sup> and especially functionalized *gem*-difluoro derivatives<sup>13</sup>, we chose  $\beta$ -keto esters, the precursors for  $\beta,\beta$ -difluorocarboxylic acids, promising building blocks for medicinal chemistry, as substrates for the fluorination.

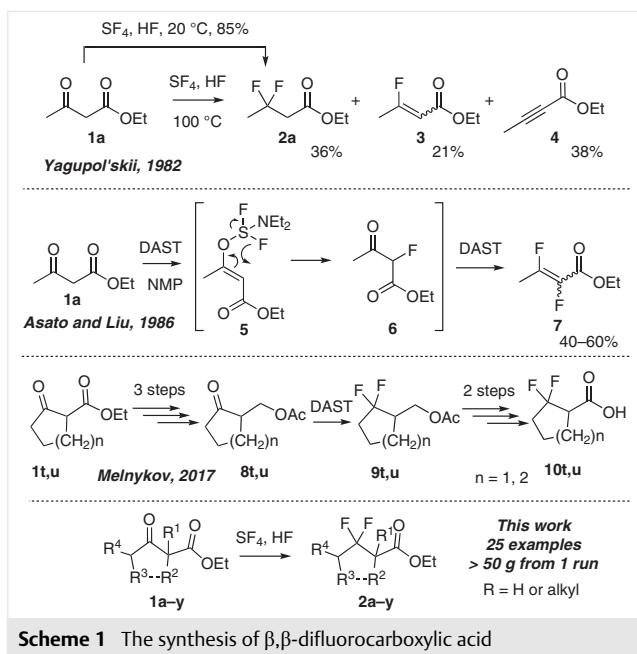
The products of deoxofluorination of  $\beta$ -keto esters are corresponding  $\beta,\beta$ -difluorocarboxylic acids, building blocks of high value to medicinal chemistry. Some recent representative examples **A–F** of such building blocks from medicinal chemistry programs related to different therapeutics areas are shown in Figure 1.<sup>14</sup> In spite of wide use of  $\beta,\beta$ -difluorocarboxylic acids as building blocks by big pharma and biotech companies, direct and efficient approaches to their synthesis are still unknown. The analysis of compounds presented in the literature reveals, that many of them are known, but available only from commercial sources without any information about synthetic routes and procedures.

The first attempts of deoxofluorination of  $\beta$ -keto esters were made in the early 1980s by L. M. Yagupol'skii and co-workers.<sup>15</sup> As were shown in these seminal researches, the reaction was accompanied by side dehydrofluorination processes, the impact of which could be decreased by reducing

the temperature (Scheme 1). Therefore, the reaction in HF media at room temperature could be considered as preparative.<sup>16</sup> Nevertheless, all attempts to replace SF<sub>4</sub> by DAST failed. Unexpectedly, in this reaction DAST, introducing an additional fluorine into the molecule, formally oxidizes the substrate.<sup>17</sup> In our previous investigations we also tried to optimize the reaction and replaced SF<sub>4</sub> with DAST-type reagents, but all our attempts failed as well. In consequence an alternative synthetic route was proposed.<sup>18</sup> The strategy was based on three-step transformation of the ester function into a nonacceptor CH<sub>2</sub>OAc group, which allowed DAST-based deoxofluorination. The further deacylation/oxidation led to desired  $\beta,\beta$ -difluorocarboxylic acids. In spite of successful realization of the strategy additional six-step sequence was needed, so the total yields were in 14–16% range. Such avoiding of SF<sub>4</sub> is justified for the small-scale synthesis but inefficient for the further scale-up. Therefore, we decided to test diverse deoxofluorination reactions of  $\beta$ -keto esters with hazardous SF<sub>4</sub> in autoclave conditions and scale them up to hundred grams.

Firstly, we tested the reaction of deoxofluorination by SF<sub>4</sub> with and without addition of HF at different temperatures and different ethylacetoacetate/SF<sub>4</sub> ratios using the simplest ethylacetoacetate (**1a**) as a model compound. It was found that in the absence of HF, the reaction proceeded nonselectively with predominant dehydrofluorination to the product **3** at 100 °C, as well as at 25 °C. The fraction of dehydrofluorination was dramatically decreased by addition of HF to the system, and at 25 °C a significant selectivity of formation of  $\beta,\beta$ -difluorocarboxylic ester **2a** was achieved (Scheme 1). Further optimization showed that the most favorable was the amount of HF of 0.8 mL per 1 g of ethylacetoacetate, the ratio of SF<sub>4</sub>/keto ester = 1.7:1, and the reaction time of 10 h. Using these conditions, we performed



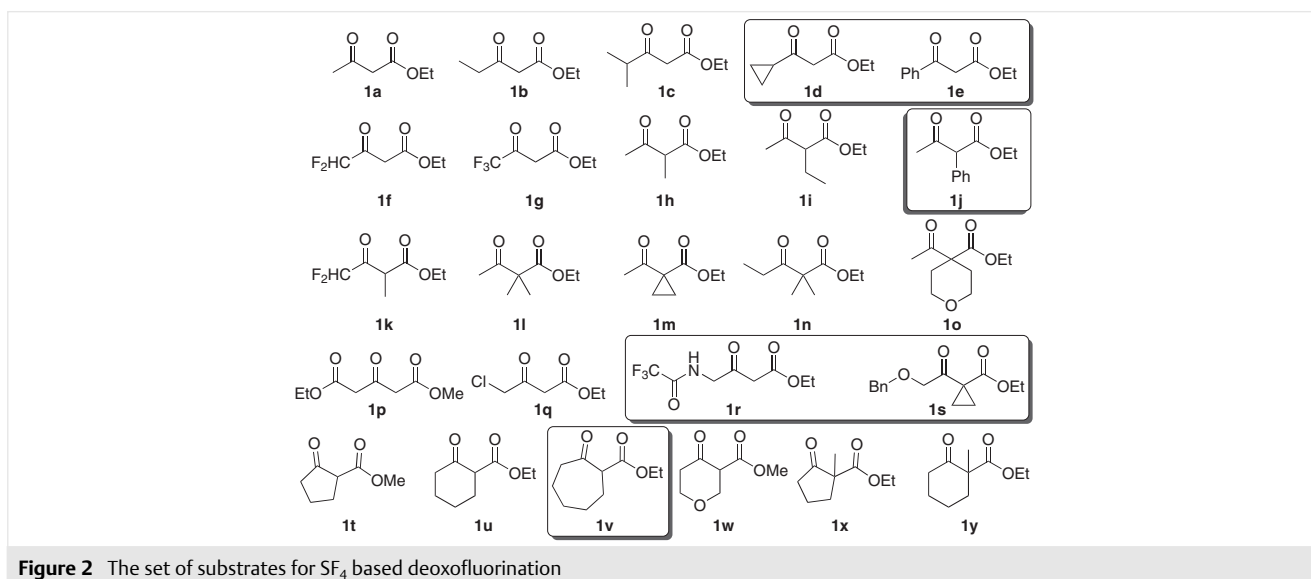


the reaction on 100 g scale of ethylacetoacetate in 1.2 L Hastelloy autoclave. The level of dehydrofluorination was less than 5% and as a result the desired  $\beta,\beta$ -difluorocarboxylic ester **2a** was isolated in preparative 70% yield.

For the investigation of scope and limitation of the developed protocol, a diverse set of substrates were chosen. Acetoacetic ester derivatives **1a–g**, their mono- and dialkyl-substituted analogues **1h–k** and **1l–o**, respectively, functionalized acetoacetic ester derivatives **1p–s** and cyclic  $\beta$ -keto esters **1t–y** were presented among them. The nonenolizable dialkylated derivatives **1h–k** were added to the set for checking the influence of possible enol formation as the

reaction occurs. Also, the set of functionalized acetoacetic esters **1p–s** were tested for the group-tolerance determination, and derivatives **1t–y** to examine the impact of conformational restriction (Figure 2).

These substrates were tested in deoxofluorination reaction with  $\text{SF}_4/\text{HF}$  system according to the aforementioned optimized protocol for ethylacetoacetate (**1a**).<sup>19</sup> The procedure appeared to be suitable for most  $\beta$ -keto esters except for the substrates highlighted in boxes in Figure 2. Treatment of compounds **1d**, **1r**, and **1s** with  $\text{SF}_4/\text{HF}$  led to complex undefined mixture of products, the desired dehydrofluorinated compounds were not observed. The cyclopropane derivative **1d** probably decomposed via cyclopropylmethyl/cyclobutyl cation rearrangement, which we had observed during fluorinations earlier.<sup>20</sup> Decomposition of **1r** in the reaction conditions was unexpected due to our previous successful experience with DAST fluorination of TFA-protected amino ketones,<sup>18</sup> while decomposition of the substrate **1s** was anticipated. According to our previous expertise fluorination of compounds containing  $\text{PhCH}_2\text{O}$  fragment by  $\text{SF}_4$  led to debenzoylation with subsequent unselective decomposition. It should be noted that compound **1w**, bearing an ether fragment, also did not give the desired product in the  $\text{SF}_4/\text{HF}$  system. In this case the compound having  $m/z [M^+] = 286$  in GC-MS and  $m/z [M + 1] = 287$  in positive mode in APCI HPLC MS was observed as a major product, but we were not able to determine its structure based on these results as well as on NMR data. Nevertheless, the product **1w** was successfully deoxofluorinated by  $\text{SF}_4$  in the absence of HF at 60 °C in 61% preparative yield,<sup>21</sup> which was a rare exception to our procedure. The rate of dehydrofluorination in this case was less than 10%. Substrates **1e**, **1j**, and **1v** also reacted unselectively under the optimized conditions, but the corresponding deoxofluorinated products were registered at about 10%, making the proce-



ture nonpreparative. The results of deoxofluorination of  $\beta$ -keto esters **1** are summarized in Table 1. The preparative yields obtained using the above-mentioned substrate set are high (from 55–90%) and comparable for both enolizable

and nonenolizable keto esters. Considerable rate of dehydrofluorination was observed in the case of using substrates **1u** (up to 20%), **1c**, **1h** (up to 10%), and **1b**, **1i** (up to 5%).

**Table 1** Yields of Deoxofluorination of  $\beta$ -Keto Esters with Subsequent Hydrolysis to the Corresponding Carboxylic Acids

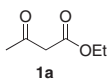
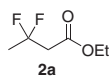
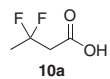
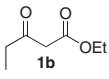
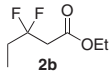
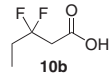
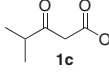
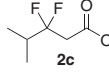
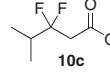
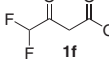
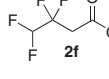
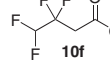
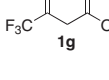
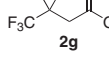
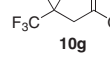
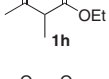
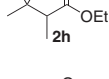
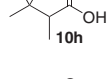
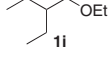
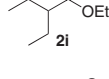
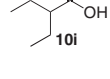
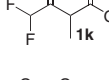
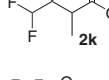
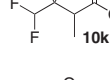
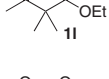
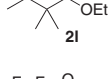
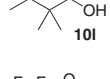
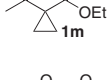
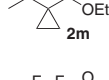
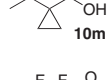
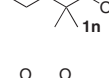
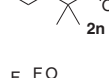
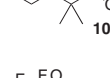
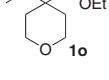
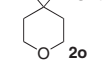
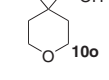
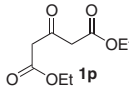
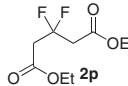
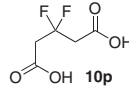
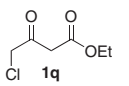
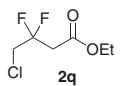
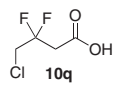
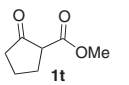
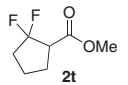
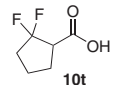
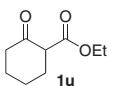
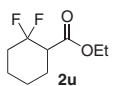
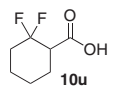
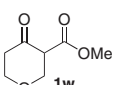
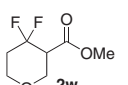
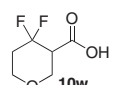
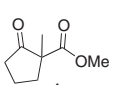
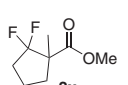
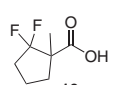
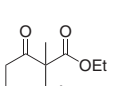
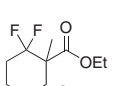
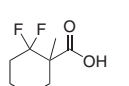
Entry	Substrate	Fluorination				Hydrolysis				
		Product	Scale (mol) <sup>a</sup>	Yield (%)	Protocol	Bp (°C/mmHg)	Product	Yield (%)	Protocol	Bp (°C/mmHg)
1			0.6	70	A1	126–127/760		78	A2	70–72/10
2			0.3	82	A1	44–46/20		83	A2	77–78/10
3			0.3	78	A1	67–69 / 20		84	A2	87–89/10
4			0.9	75	A1	57–59 / 20		69	A2	85–88/10
5			0.6	70	A1	35–37/20		74	A2	61–62/10
6			0.3	81	A1	61–62/20		80	A2	77–80/20
7			0.6	77	A1	77–72/20		80	A2	86–88/10
8			0.6	73	A1	50–52/20		70	A2	71–72/10
9			0.9	88	A1	65–66/20		82	B2	88–90/10
10			0.9	70	A1	55–56/20		69	B2	70–72/20
11			0.6	85	A1	75–76/20		88	B2	105–107/10
12			0.6	90	A1	58–59/0.3		88	B2	95–97/0.3 <sup>b</sup>

Table 1 (continued)

Entry	Fluorination		Scale (mol) <sup>a</sup>	Yield (%)	Protocol	Bp (°C/mmHg)	Hydrolysis		Protocol	Bp (°C/mmHg)
	Substrate	Product					Product	Yield (%)		
13			0.9	86	A1	46–47/0.3		67	A2	– <sup>c</sup>
14			0.6	48	A1 <sup>d</sup>	95/10		73	A2 <sup>d</sup>	– <sup>c</sup>
15			0.6	85	A1	52–53/20		87	A2	99–101/10 <sup>b</sup>
16			0.3	55	A1	56–57/20		84	A2	107–110/10 <sup>b</sup>
17			0.6	61	B1	64–67/10		79	A2	91–92/0.3 <sup>b</sup>
18			0.3	86	A1	67–68/20		90	B2	44–45/0.3 <sup>b</sup>
19			0.3	91	A1	88–82/20		85	B2	62–63/0.3 <sup>b</sup>

<sup>a</sup> Amount of starting  $\beta$ -keto ester.

<sup>b</sup> Crystallized after cooling, mp (**10o**) 90–91 °C; mp (**10t**) 68–69 °C; mp (**10u**) 74–75 °C; mp (**10w**) 78–79 °C; mp (**10x**) 72–73 °C; mp (**10y**) 77–78 °C.

<sup>c</sup> Solid compounds, crystallized from hexane, mp (**10p**) 162–163 °C; mp (**10q**) 58–59 °C.

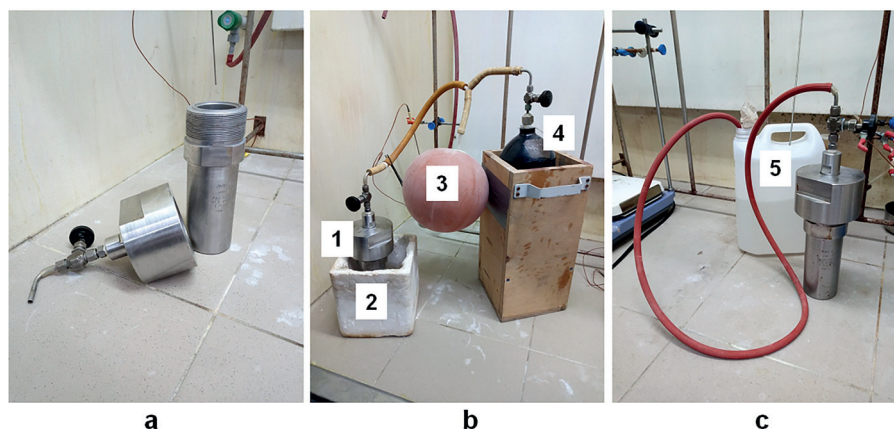
<sup>d</sup> 3 equivalents of SF<sub>4</sub> were used in step A1; 6 equivalents of HCl without formic acid were added in step A2.

The reaction was scaled up to 50–150 g (0.3–0.9 mol) of starting material from one synthetic run without changing the protocol. Such amounts required operating with significant quantity, up to 175 g, of SF<sub>4</sub> for one run. These operations were performed in the special well-ventilated laboratory with strictly limited staff access due to safety reasons. The staff always wear the personal-protection equipment including single-filter, full-face masks during operation in accordance with international safety regulations.<sup>22</sup> The damper technique applied for loading of SF<sub>4</sub> into the autoclave was shown in Figure 3. The standardized damper chambers were used, which contained 25±1 g of SF<sub>4</sub> at atmospheric pressure. The excess of SF<sub>4</sub>, along with the other gaseous byproducts, is vented from the autoclave through a KOH solution after the reaction is complete.

All obtained  $\beta,\beta$ -difluoroesters **2** were subjected to subsequent hydrolysis into the corresponding acids. Taking into account unsustainability of enolizable  $\beta,\beta$ -difluoroesters to fluorine anion elimination,<sup>23</sup> the acidic condi-

tions<sup>24</sup> were chosen for hydrolysis. In the case of nonenolizable  $\beta,\beta$ -difluoroesters **2e,f** and **2l–o** more convenient alkali hydrolysis was applied.<sup>25</sup> The corresponding acids were obtained in good preparative yields under both conditions (Table 1).

The next milestone of the investigation was the elaboration of an efficient method for the synthesis of Medicinal chemistry relevant difluorinated cyclic amino acid derivatives type **11** starting from readily available compounds type **12** (Scheme 2). Earlier, this methodology was applied only for the 3,3-difluoroproline derivative **11c**. Recently, the preparative deoxofluorination of the corresponding precursor, where PG = Cbz and R = *t*-Bu, was described using DAST as a reagent.<sup>26</sup> The approaches to derivatives of amino acids **11b** and **11c** were also described based on another methodology. The 3,3-difluoroisoneipicotic acid derivatives were obtained via multistep synthesis starting from ethyl bromodifluoroacetate as CF<sub>2</sub> moiety source.<sup>27</sup> In the case of 4,4-difluoro- $\beta$ -proline the core was assembled

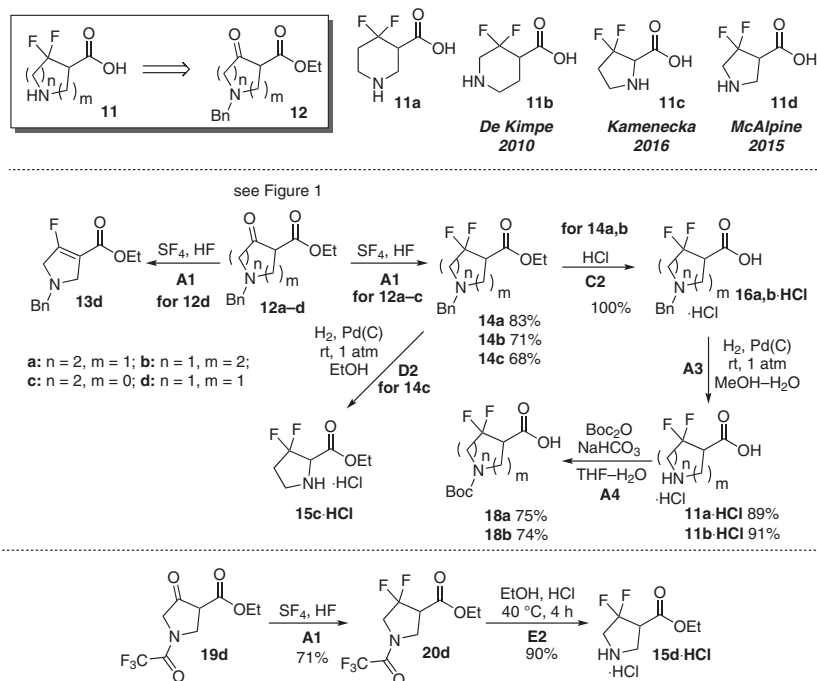


**Figure 3** Equipment for SF<sub>4</sub>-based difluorination. (a) Opened Hastelloy autoclave 1200 mL; (b) loading of SF<sub>4</sub> to vacuum autoclave from the balloon through damper chamber; (c) releasing of the excess of SF<sub>4</sub> and gaseous byproducts into KOH solution. 1 – vacuumed autoclave loaded with substrate and anhydrous HF; 2 – tank with liquid nitrogen; 3 – damper chamber filled with SF<sub>4</sub>; 4 – balloon with SF<sub>4</sub>; 5 – canister with 15% aqueous solution of KOH.

by [3+2] cycloaddition of azomethine ylide with benzyl 3,3-difluoroacrylate.<sup>28</sup>

At first, we chose the N<sub>Bn</sub>-protected compounds **12a–d** as potential substrates for deoxofluorination. These compounds were examined in a standard protocol with SF<sub>4</sub> in HF. Among them substrates **12a–c** gave the corresponding difluoro derivatives **11a–c** in good preparative yields (from 68–83% on 0.6 mol scale of starting materials). But compound **12d** unexpectedly gave dehydrofluorinated compound **13d** as the major product under the reaction conditions according to <sup>19</sup>F NMR and <sup>1</sup>H NMR analysis of the reac-

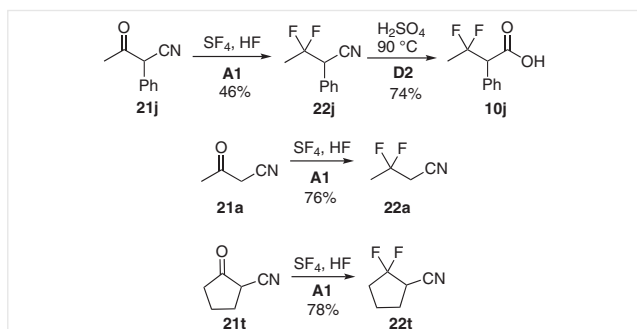
tion mixture and the crude product (Scheme 2). Unfortunately, all attempts to isolate the reactive compound **13d** in a pure state failed. The deprotected fluorinated amino acids **14** could be quantitatively hydrolyzed in acidic conditions<sup>29</sup> to the corresponding acids **16** as hydrochloric salts. It was illustrated by the synthesis of Bn-protected amino acids **16a,b**. Amino acids **11a,b** were formed by catalytic hydrogenation of Bn-protected derivatives **16a,b** at room temperature and 1 atm hydrogen pressure over Pd on carbon in MeOH–H<sub>2</sub>O media<sup>30</sup> as hydrochloric salts. These compounds were easily transformed into Boc-



**Scheme 2** The synthesis of *gem*-difluorinated cyclic amino acid derivatives

protected derivatives **18a,b**<sup>31</sup> that are more convenient for utilizing as building blocks in parallel synthesis in comparison with Bn-protected derivatives. The orthogonal benzyl deprotection from the compound type **14** could be also accomplished by catalytic hydrogenation.<sup>32</sup> It was demonstrated by synthesis of the amino ester **15c**. In the case of 4,4-difluoro- $\beta$ -proline derivatives replacement of Bn protection group with TFA in substrate **19d** changed the behavior of deoxofluorination. The standard SF<sub>4</sub>/HF protocol gave the desired difluoro derivative **20d** in 71% preparative yield on 80 g scale of the used starting material. TFA deprotection by classical nucleophilic methodologies with such reagents as NH<sub>2</sub>NH<sub>2</sub>, NH<sub>2</sub>OH, or NaOMe is incompatible with enolizable  $\beta,\beta$ -difluoroesters. Therefore, an alternative mild acidic deprotection method was applied. It was found that ethanolic solution of anhydrous HCl, generated by addition of acetyl chloride into EtOH,<sup>33</sup> selectively cleaved TFA amide, leaving the ester function intact.<sup>34</sup> In the case of compound **20d** the method led to amino ester **15d** in 90% yield as hydrochloride (Scheme 2).

A preparative solution for substrate **1j** and its analogues was found. The ester group in these compounds could be exchanged to a nitrile. Deoxofluorination of keto nitriles **21a**, **21j**, and **21t** proceeded smoothly in SF<sub>4</sub>/HF system according to protocol A1 at room temperature (Scheme 3). The desired  $\beta,\beta$ -difluoronitriles **22a**, **22j**, and **22t** were formed in moderate to good yields (46–78%) on 0.15–0.3 mol scale. The possibility of hydrolysis of such nitriles was demonstrated on the intermediate **22j**. The acid **10j** was obtained through acidic hydrolysis of nitrile **22j** by H<sub>2</sub>SO<sub>4</sub> at 90 °C<sup>35</sup> in 74% yield.



**Scheme 3** Deoxofluorination of  $\beta$ -keto nitriles by SF<sub>4</sub> in HF

Finally, the reaction of deoxofluorination of  $\beta$ -keto esters and  $\beta$ -keto nitriles by SF<sub>4</sub> in anhydrous HF media was investigated. The scope and limitation of the reaction were determined. Substrates having steric hindrance at the keto group, bearing ArCH<sub>2</sub>O-, -NHTFA, and fragments capable of cationic-like rearrangements, are out of the scope of the procedure. The reaction was scaled up to 0.9 mol of starting material using 1200 mL Hastelloy autoclave. Work with such quantity of SF<sub>4</sub> required a special technique and equipment, which was also demonstrated. The promising build-

ing blocks for medicinal chemistry,  $\beta$ -difluorinated acids, were produced by hydrolysis of the appropriate esters on 100 g scale. Despite the serious difficulties of using toxic, hazardous SF<sub>4</sub> towards special lab space, equipment, personal protection, and staff skills, the elaborated methods are substantially more efficient in comparison with multi-step sequences based on less hazardous fluorine sources. Moreover, the proposed protocol can be easily introduced into the production cycle at industrial facilities that use SF<sub>4</sub>.

## Acknowledgment

The authors thank Prof. Andrey A. Tolmachev for his encouragement and support, Dr. Halyna Buvailo for her help with manuscript preparation, and UOSLab (www.en.uoslab.com) for providing and customizing high-pressure reactors. The work was supported by Enamine Ltd.

## Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0037-1610744>.

## References and Notes

- (1) Varma, R.; Varma, D. R. *Bull. Sci. Technol. Soc.* **2005**, *25*, 37.
- (2) Mastronardi, F.; Gutmann, B.; Kappe, C. O. *Org. Lett.* **2013**, *15*, 5590.
- (3) Köckinger, M.; Hone, C. A.; Kappe, C. O. *Org. Lett.* **2019**, *21*, 5326.
- (4) Shioiri, T.; Aoyama, T.; Snowden, T.; Lee, D.; Gupta, S. *Trimethylsilyldiazomethane*. In *Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons: Chichester, **2019**, doi 10.1002/047084289X.rt298.pub3.
- (5) Groutas, W. C.; Jin, Z.; Zhang, H. *Cyanotrimethylsilane*. In *Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons: Chichester, **2011**, doi 10.1002/047084289X.rc276.pub2.
- (6) Roestamadj, J.; Mobashery, S.; Banerjee, A.; Saputra, M. A.; Malone, J. A.; Cleveland, A. H.; Van Houten, J. P.; Kartika, R. *Bis(trichloromethyl) Carbonate*. In *Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons: Chichester, **2018**, doi 10.1002/047084289X.rb200.pub3.
- (7) (a) Bogolubsky, A. V.; Ryabukhin, S. V.; Pipko, S. E.; Lukin, O. V.; Shivan'yuk, A. N.; Mykytenko, D. M.; Tolmachev, A. A. *Tetrahedron* **2011**, *67*, 3619. (b) Bogolubsky, A. V.; Moroz, Y. S.; Savych, O.; Pipko, S. E.; Konovets, A. I.; Platonov, M. O.; Vasylenko, O. V.; Hurmach, V. V.; Grygorenko, O. O. *ACS Comb. Sci.* **2018**, *20*, 35. (c) Bogolubsky, A. V.; Moroz, Y. S.; Mykhailiuk, P. K.; Granat, D. S.; Pipko, S. E.; Konovets, A. I.; Doroschuk, R.; Tolmachev, A. A. *ACS Comb. Sci.* **2014**, *16*, 303. (d) Bogolubsky, A. V.; Moroz, Y. S.; Mykhailiuk, P. K.; Dmytriv, Y. V.; Pipko, S. E.; Babichenko, L. N.; Konovets, A. I.; Tolmachev, A. A. *RSC Adv.* **2015**, *5*, 1063.
- (8) (a) Richardson, P. *Expert Opin. Drug Discov.* **2016**, *11*, 983. (b) Wang, C.-L. *J. Org. React.* **1985**, *319*, 34; doi: 10.1002/0471264180.or034.02.
- (9) Clayton, J. W. *J. Occup. Med.* **1962**, *4*, 262.
- (10) (a) Ni, C.; Hu, M.; Hu, J. *Chem. Rev.* **2015**, *115*, 765. (b) Petrov, V. A.; Swearingen, S.; Hong, W.; Petersen, W. C. *J. Fluor. Chem.* **2001**, *109*, 25. (c) Grieco, L. M.; Halliday, G. A.; Junk, C. P.; Lustig, S. R.; Marshall, W. J.; Petrov, V. A. *J. Fluor. Chem.* **2011**, *132*, 1198.

- (11) Umemoto, T.; Singh, R. P.; Xu, Y.; Saito, N. *J. Am. Chem. Soc.* **2010**, *132*, 18199.
- (12) (a) Subota, A. I.; Lutsenko, A. O. Vashchenko B. V.; Volochnyuk, D. M.; Levchenko, V.; Dmytriv, Y. V.; Rusanov, E. B.; Gorlova, A. O.; Ryabukhin, S. V.; Grygorenko, O. O. *Eur. J. Org. Chem.* **2019**, *22*, 3636. (b) Melnykov, K. P.; Artemenko, A. N.; Ivanenko, B. O.; Sokolenko, Y. M.; Nosik, P. S.; Ostapchuk, E. N.; Grygorenko, O. O.; Volochnyuk, D. M.; Ryabukhin, S. V. *ACS Omega* **2019**, *4*, 7498. (c) Adamovskiy, M. I.; Ryabukhin, S. V.; Sibgatulin, D. A.; Rusanov, E. B.; Grygorenko, O. O. *Org. Lett.* **2017**, *19*, 130. (d) Subota, A. I.; Grygorenko, O. O.; Valter, Y. B.; Tairov, M. A.; Artamonov, O. S.; Volochnyuk, D. M.; Ryabukhin, S. V. *Synlett* **2015**, *26*, 408.
- (13) (a) Nosik, P. S.; Poturai, A. S.; Pashko, M. O.; Melnykov, K. P.; Ryabukhin, S. V.; Volochnyuk, D. M.; Grygorenko, O. O. *Eur. J. Org. Chem.* **2019**, *27*, 4311. (b) Chernykh, A. V.; Melnykov, K. P.; Tolmacheva, N. A.; Kondratov, I. S.; Radchenko, D. S.; Daniliuc, C. G.; Volochnyuk, D. M.; Ryabukhin, S. V.; Kuchkovska, Y. O.; Grygorenko, O. O. *J. Org. Chem.* **2019**, *84*, 8487. (c) Melnykov, K. P.; Granat, D. S.; Volochnyuk, D. M.; Ryabukhin, S. V.; Grygorenko, O. O. *Synthesis* **2018**, *50*, 4949. (d) Nosik, P. S.; Ryabukhin, S. V.; Grygorenko, O. O.; Volochnyuk, D. M. *Adv. Synth. Catal.* **2018**, *360*, 4104. (e) Nosik, P. S.; Ryabukhin, S. V.; Grygorenko, O. O.; Volochnyuk, D. M. *Adv. Synth. Catal.* **2017**, *359*, 3126.
- (14) (a) Barber, C. G.; Blakemore, D. C. WO 200766201, **2007**. (b) Long, D.; Marquess, D.; Choi, S.; Fatheree, P. R.; Gendron, R.; Goldblum, A.; Turner, D. S. WO 200669125, **2006**. (c) Koike, T.; Kajita, Y.; Yoshikawa, M.; Ikeda, S.; Kimura, E.; Hasui, T.; Nishi, T.; Fukuda, H. EP 2933247, **2015**. (d) Braun, M.-G.; Gibbons, P.; Lee, W.; Ly, C.; Rudolph, J.; Schwarz, J.; Ashkenazi, A.; Fu, L.; Lai, T.; Wang, F.; Beveridge, R.; Zhao, L. WO 2018166528, **2018**. (e) Wiles, J. A.; Phadke, A. S.; Deshpande, M.; Agarwal, A.; Chen, D.; Gadachanda, V. R.; Hashimoto, A.; Pais, G.; Wang, Q.; Wang, X.; Barrish, J. C.; Greenlee, W.; Eastman, K. J. WO 2018160891, **2018**. (f) Burns, C. J.; Pevear, D. C.; Trout, R. E. L.; Jackson, R. W.; Hamrick, J.; Zulli, A. L.; Mesaros, E. F.; Boyd, S. A. WO 2017100537, **2017**.
- (15) (a) Bloschchitsa, F. A.; Burmakov, A. I.; Kunshenko, B. V.; Alekseeva, L. A.; Bel'ferman, A. L.; Pazderskii, Y. A.; Yagupol'skii, L. M. *J. Org. Chem. USSR (Engl. Transl.)* **1981**, *17*, 1260. (b) Bloschchitsa, F. A.; Burmakov, A. I.; Kunshenko, B. V.; Alekseeva, L. A.; Yagupol'skii, L. M. *J. Org. Chem. USSR (Engl. Transl.)* **1982**, *18*, 679.
- (16) Buss, C. W.; Coe, P. L.; Tatlow, J. C. *J. Fluor. Chem.* **1986**, *34*, 83.
- (17) Asato, A. E.; Liu, R. S. H. *Tetrahedron Lett.* **1986**, *27*, 3337.
- (18) Melnykov, K. P.; Nosik, P. S.; Kurpil, B. B.; Sibgatulin, D. A.; Volochnyuk, D. M.; Ryabukhin, S. V.; Grygorenko, O. O. *J. Fluor. Chem.* **2017**, *199*, 60.
- (19) **Deoxofluorination Protocol A1**  
The keto ester **1** (1 mol) was placed in a Hastelloy autoclave (1200 mL) and cooled with liquid nitrogen. Anhydrous hydrogen fluoride (1 mL per 0.01 mol of the keto ester) was added. The autoclave was evacuated and SF<sub>4</sub> (about 1.7 equiv) was condensed into it. The autoclave was warmed up to room temperature and was stirred on a magnetic stirrer overnight. Gaseous products were released, the solution was removed from the autoclave and poured onto ice, the oil obtained was extracted with MTBE, the extracts were combined and washed with aqueous solution of Na<sub>2</sub>CO<sub>3</sub>, dried, evaporated and distilled. In the case of obtaining an admixture of monofluoroalkene during the fluorination (substrates **1a-c, h, i, u**), the crude product was dissolved in dichloromethane/water mixture before purification (100 g of product per 1 L of dichloromethane and water), and KMnO<sub>4</sub> was added in portions under stirring until the boiling was ceased and the raspberry color was stabilized for 1 h (usually 0.3–0.7 g of potassium permanganate per 1 g of the mixture). Excess of potassium permanganate was quenched with Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>, the precipitate was filtered and washed with dichloromethane. The organic phase was separated, dried, and distilled. The bp and yields for products **2** are given in Table 1. Bp (**14a**) = 105–108°C/0.3 mmHg. Bp (**14c**) = 65–67°C/0.3 mmHg. The compound **14b** was purified by recrystallization from hexane mp 64 °C; bp (**22a**) 49–51 °C/20 mmHg; bp (**22j**) 55–59 °C/0.3 mmHg; bp (**22t**) 69–71 °C/20 mmHg.
- Representative Examples**  
**Ethyl 1-Benzyl-4,4-difluoropiperidine-3-carboxylate (14a)**  
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.52–7.04 (m, 5 H), 4.16 (qd, J = 7.1, 4.2 Hz, 2 H), 3.76–3.35 (m, 2 H), 2.96 (tt, J = 12.0, 5.6 Hz, 1 H), 2.86–2.61 (m, 3 H), 2.50 (t, J = 9.6 Hz, 1 H), 2.39–2.23 (m, 1 H), 2.09–1.90 (m, 1 H), 1.22 (t, J = 7.2 Hz, 3 H). <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>): δ = 168.2, 138.0, 128.7, 128.3, 127.3, 120.51 (t, J = 246.3 Hz), 61.7, 61.0, 52.3, 49.8 (t, J = 5.3 Hz), 48.6 (t, J = 21.9 Hz), 33.3 (t, J = 22.2 Hz), 14.0. <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>): δ = –97.3 (d, J = 239.1 Hz). LC–MS (positive mode): m/z = 284 [M + H]<sup>+</sup>.
- 3,3-Difluorobutanenitrile (22a)**  
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 2.95 (t, J = 11.0 Hz, 2 H), 1.78 (t, J = 18.5, 3 H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): δ = 119.4 (t, J = 243.8 Hz), 113.6 (t, J = 4.8 Hz), 28.3 (t, J = 40.2 Hz), 22.9 (t, J = 25.1 Hz). <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>): δ = –88.7.
- (20) (a) Chernykh, A. V.; Tkachenko, A. N.; Feskov, I. O.; Daniliuc, C. G.; Tolmachova, N. A.; Volochnyuk, D. M.; Radchenko, D. S. *Synlett* **2016**, *27*, 1824. (b) Chernykh, A. V.; Feskov, I. O.; Chernykh, A. V.; Daniliuc, C. G.; Tolmachova, N. A.; Volochnyuk, D. M.; Radchenko, D. S. *Tetrahedron* **2016**, *72*, 1036.
- (21) **Deoxofluorination Protocol B1**  
The keto ester **1** (1 equiv) was placed in a Hastelloy autoclave (1200 mL), cooled with liquid nitrogen, vacuumed, and SF<sub>4</sub> was condensed into it (about 1.7 equiv). The autoclave was warmed up to room temperature and stirred at 60 °C on a magnetic stirrer for 48 h. Gaseous products were released, the solution was poured from the autoclave onto ice, and the oil formed was extracted with MTBE. The extracts were washed with aqueous solution of Na<sub>2</sub>CO<sub>3</sub> and dried. The residue was evaporated and purified with potassium permanganate (as in protocol A) and distilled. The bp and yields of products **2** are given in Table 1.
- Representative Examples**  
**Ethyl 3,3-Difluorobutanoate (2a)**  
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 4.20 (qd, J = 7.2, 3.4 Hz, 2 H), 2.92 (td, J = 14.1, 3.3 Hz, 2 H), 1.78 (td, J = 18.8, 3.3 Hz, 3 H), 1.29 (td, J = 7.2, 3.3 Hz, 3 H). <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>): δ = –87.0
- Ethyl 4-Chloro-3,3-difluorobutanoate (2q)**  
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 4.18 (q, J = 7.1 Hz, 2 H), 3.93 (t, J = 12.7 Hz, 2 H), 3.09 (t, J = 14.2 Hz, 2 H), 1.26 (t, J = 7.1 Hz, 3 H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): δ = 166.4 (t, J = 8.4 Hz), 119.5 (t, J = 244.4 Hz), 61.5, 43.6 (t, J = 33.4 Hz), 38.9 (t, J = 27.6 Hz), 14.0. <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>): δ = –97.9. EIMS (70eV): m/z (%) = 186 [M – H]<sup>+</sup> (1), 161 (15), 159 (49), 143 (30), 141 (100), 113 (24), 99 (14), 94 (15), 77 (17), 64 (15), 77 (17), 64 (150), 59 (11), 45 (14), 42 (12)
- Ethyl 2,2-Difluorocyclohexanecarboxylate (2u)**  
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 4.17 (qd, J = 7.2, 2.7 Hz, 2 H), 2.81 (dq, J = 19.3, 6.9 Hz, 1 H), 2.30–2.11 (m, 1 H), 1.89 (q, J = 6.9, 6.5 Hz, 2 H), 1.83–1.53 (m, 4 H), 1.46–1.30 (m, 1 H), 1.25 (t, J = 7.1 Hz, 3 H). <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>): δ = 169.8 (d, J = 6.1 Hz), 121.7 (dd, J = 246.9, 244.6 Hz), 60.9, 48.8 (t, J = 23.0 Hz), 33.2 (t,



- $J = 23.0$  Hz), 26.5 (t,  $J = 3.3$  Hz), 22.3–22.2, 22.2, 14.1.  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ ):  $\delta = -94.6$  (d,  $J = 240.3$  Hz). EIMS (70eV):  $m/z$  (%) = 192 [ $\text{M}]^+$  (2), 172 (21), 147 (59), 145 (13), 100 (42), 99 (100), 98 (14), 97 (11), 85 (20), 80 (41), 77 (26), 72 (16), 55 (22).
- (22) (a) Pohanish, R. P. In *Sittig's Handbook of Toxic and Hazardous Chemicals and Carcinogens*, 6th ed; Pohanish, R. P., Ed.; Elsevier: Oxford, **2012**, 2472. (b) US Environmental Protection Agency (November 30, 1987). Chemical Hazard Information Profile: Sulfur Tetrafluoride. Washington, DC: Chemical Emergency Preparedness Program. (c) New Jersey Department of Health and Senior Services (February 2000). Hazardous Substances Fact Sheet: Sulfur Tetrafluoride. Trenton, NJ, USA.
- (23) (a) Wu, Y.; Zhang, B.; Zheng, Y.; Wang, Y.; Lei, X. *RSC Adv.* **2018**, *8*, 16019. (b) Huang, W.-Y.; Liu, Y.-S.; Lu, L. *J. Fluor. Chem.* **1994**, *66*, 263.
- (24) **Hydrolysis Protocol A2**  
A mixture of the ester **2** (1 equiv), formic acid (4 equiv), and 20% hydrochloric acid (3 equiv of HCl) was stirred at 100 °C with 10 cm Vigreux column for 2 days. The reaction mixture was saturated with NaCl, and the product was extracted with dichloromethane (for the substance **2p**, the precipitated product was filtered off and washed with cold water). The extracts were dried, evaporated, and distilled. The bp and yields of products **10** are given in Table 1.
- Representative Examples**  
**3,3-Difluorobutanoic Acid (10a)**  
 $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 9.70$  (br, 1 H), 2.97 (t,  $J = 13.9$  Hz, 2 H), 1.77 (t,  $J = 18.7$  Hz, 3 H).  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ ):  $\delta = 173.2$  (t,  $J = 7.8$  Hz), 120.7 (t,  $J = 239.9$  Hz), 42.9 (t,  $J = 29.3$  Hz), 23.2 (t,  $J = 26.4$  Hz).  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ ):  $\delta = -87.2$ . EIMS (70eV):  $m/z$  (%) = 122 (1), 107 (12), 104 (21), 89 (41), 76 (12), 65 (100), 64 (11), 63 (10), 60 (62), 59 (23), 45 (44), 43 (14), 42 (23), 40 (12), 39 (10).
- 2,2-Difluorocyclopentanecarboxylic Acid (10t)**  
 $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 11.20$  (br, 1 H), 3.00–3.20 (m, 1 H), 2.40–2.00 (m, 4 H), 2.00–1.80 (m, 1 H), 1.80–1.60 (m, 1 H).  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta = 175.8$ , 130.6 (t,  $J = 266.6$  Hz), 51.4 (t,  $J = 24.1$  Hz), 35.4 (t,  $J = 23.6$  Hz), 26.3, 20.6.  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ ):  $\delta = -92.6$  (d,  $J = 229.7$  Hz),  $-100.8$  (d,  $J = 229.7$  Hz). EIMS (70eV):  $m/z$  (%) = 150 [ $\text{M}]^+$  (1), 130 (7), 115 (11), 110 (13), 109 (17), 91 (10), 82 (14), 77 (21), 73 (100), 66 (13), 65 (11), 59 (11), 55 (33), 51 (14), 45 (15), 41 (20), 39 (20).
- (25) **Hydrolysis Protocol B2**  
A mixture of the ester **2** (1 equiv) and sodium hydroxide (1.5 equiv) in 50% aqueous ethanol (2 L per 1 mol) was boiled until the reaction was completed (from 1 night to 3 days). The reaction mixture was evaporated, acidified with hydrochloric acid, and the product was extracted with dichloromethane. The extracts were combined, dried, evaporated, and distilled. The bp and yields of products **10** are given in Table 1.
- Representative Examples**  
**3,3-Difluoro-2,2-dimethylbutanoic Acid (10l)**  
 $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 11.51$  (br, 1 H), 1.71 (t,  $J = 19.2$  Hz, 3 H), 1.35 (s, 6 H).  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ ):  $\delta = 179.8$ , 123.9 (t,  $J = 246.1$  Hz), 49.7 (t,  $J = 24.7$  Hz), 20.3 (t,  $J = 27.7$  Hz), 20.0 (t,  $J = 4.2$  Hz).  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ ):  $\delta = -98.1$ . EIMS (70eV):  $m/z$  (%) = 154 [ $\text{M} + 2\text{H}]^+$  (1), 145 (1), 88 [ $\text{M} - \text{CF}_2\text{CH}_3]^+$  (94), 87 (25), 73 (100), 70 (31), 65 (49), 59 (17), 45 (16), 42 (11), 41 (23), 39 (15).
- 1-(1,1-Difluoroethyl)cyclopropanecarboxylic Acid (10m)**  
 $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 11.07$  (s, 1 H), 1.88 (t,  $J = 18.7$  Hz, 3 H), 1.41–1.32 (m, 2 H), 1.35–1.26 (m, 2 H).  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ ):  $\delta = 177.6$ , 120.8 (t,  $J = 240.4$  Hz), 28.9 (t,  $J = 29.4$  Hz), 22.9 (t,  $J = 28.3$  Hz), 13.8 (t,  $J = 3.5$  Hz).  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ ):  $\delta = -94.7$ . LC-MS (negative mode):  $m/z = 149$  [ $\text{M} - \text{H}]^-$ .
- (26) Doebelin, C.; He, Y.; Kamenecka, T. M. *Tetrahedron Lett.* **2016**, *57*, 5658.
- (27) Surmont, R.; Verniest, G.; Thuring, J. W.; Macdonald, G.; Deroose, F.; De Kimpe, N. *J. Org. Chem.* **2010**, *75*, 929.
- (28) McAlpine, I.; Tran-Dubé, M.; Wang, F.; Scales, S.; Matthews, J.; Collins, M. R.; Nair, S. K.; Nguyen, M.; Bian, J.; Alsina, L. M.; Sun, J.; Zhong, J.; Warmus, J. S.; O'Neill, B. T. *J. Org. Chem.* **2015**, *80*, 7266.
- (29) **Hydrolysis Protocol C2**  
A mixture of the ester **14**, acetic acid (2 mL per 1 g of ether) and 20% hydrochloric acid (2 mL per 1 g of ether) was stirred overnight at 110 °C with 10 cm Vigreux column. The resulting mixture was evaporated. The solid residue was washed with MTBE to obtain hydrochloride of the acid **16**; mp (**16a-HCl**) 199 °C (with decomposition); mp (**16b-HCl**) 200 °C (with decomposition).
- Representative Examples**  
**1-Benzyl-4,4-difluoropiperidine-3-carboxylic Acid Hydrochloride (16a-HCl)**  
 $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta = 13.47$  (s, 1 H), 12.13 (s, 1 H), 7.64 (dd,  $J = 6.7$ , 2.9 Hz, 2 H), 7.51–7.40 (m, 3 H), 4.41 (s, 2 H), 3.88–3.66 (m, 1 H), 3.54 (d,  $J = 12.8$  Hz, 1 H), 3.37 (s, 1 H), 3.28 (t,  $J = 12.7$  Hz, 1 H), 3.16 (t,  $J = 12.4$  Hz, 1 H), 2.72–2.52 (m, 1 H), 2.39 (t,  $J = 14.8$  Hz, 1 H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta = 167.3$ , 131.8, 130.2, 130.0, 129.3, 119.5 (t,  $J = 247.6$  Hz), 58.8, 49.4, 48.0, 45.2, 31.2.  $^{19}\text{F}$  NMR (376 MHz,  $\text{DMSO}-d_6$ ):  $\delta = -98.9$  (d,  $J = 237.1$  Hz),  $-110.0$  (d,  $J = 237.1$  Hz). LC-MS (negative mode):  $m/z = 254$  [ $\text{M} - \text{HCl} - \text{H}]^-$ .
- 1-Benzyl-3,3-difluoropiperidine-4-carboxylic Acid Hydrochloride (16b-HCl)**  
 $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta = 11.81$  (br, 2 H), 7.63 (s, 2 H), 7.53–7.36 (m, 3 H), 4.55–4.17 (m, 2 H), 3.74–2.94 (m, 5 H), 2.18 (s, 2 H).  $^{13}\text{C}$  NMR (151 MHz,  $\text{DMSO}-d_6$ ):  $\delta = 169.0$ , 132.2, 130.1, 129.4, 129.2, 118.4 (t,  $J = 246.2$  Hz), 59.4, 53.1, 49.6, 45.0, 22.4.  $^{19}\text{F}$  NMR (376 MHz,  $\text{DMSO}-d_6$ ):  $\delta = -100.9$  (d,  $J = 243.0$  Hz),  $-106.3$  (d,  $J = 255.7$  Hz). LC-MS (positive mode):  $m/z = 256$  [ $\text{M} - \text{HCl} + \text{H}]^+$ .
- (30) **Debenzylation Protocol A3**  
10% Pd on carbon (0.1 g for 1 g of **16**) was added to the solution of a compound **16** in MeOH– $\text{H}_2\text{O}$  (2:1, 10 mL of mixture for 1 g of **16**), and the mixture was hydrogenated at room temperature and atmospheric pressure until the reaction was completed (check by NMR). The catalyst was filtered off, and the filtrate was evaporated dry. The crude product was washed by MTBE–acetone mixture affording the desired compounds **11**, which were then treated by a saturated solution of HCl in dioxane and isolated in pure form as hydrochloride; mp (**11a-HCl**) 185 °C; mp (**11b-HCl**) 188 °C.
- Representative Examples**  
**4,4-Difluoropiperidine-3-carboxylic Acid Hydrochloride (11a-HCl)**  
 $^1\text{H}$  NMR (400 MHz,  $\text{D}_2\text{O}$ ):  $\delta = 3.56$ –3.18 (m, 5 H), 2.48–2.12 (m, 2 H); NH, OH not observed due to exchange.  $^{13}\text{C}$  NMR (151 MHz,  $\text{D}_2\text{O}$ ):  $\delta = 170.2$ , 118.2 (t,  $J = 247.6$  Hz), 45.4 (t,  $J = 23.8$  Hz), 42.7, 41.0, 29.7 (t,  $J = 25.3$  Hz).  $^{19}\text{F}$  NMR (376 MHz,  $\text{D}_2\text{O}$ ):  $\delta = -98.9$  (d,  $J = 244.7$  Hz),  $-106.7$  (d,  $J = 247.6$  Hz). LC-MS (positive mode):  $m/z = 166$  [ $\text{M} - \text{HCl} + \text{H}]^+$ .
- 3,3-Difluoropiperidine-4-carboxylic Acid Hydrochloride (11b-HCl)**  
 $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta = 10.56$  (br, 3 H), 3.64 (dt,  $J =$

17.1, 9.3 Hz, 1 H), 3.47 (dd,  $J = 27.4, 12.9$  Hz, 1 H), 3.38–3.22 (m, 1 H), 3.18 (d,  $J = 12.6$  Hz, 1 H), 3.01 (t,  $J = 12.1$  Hz, 1 H), 2.12 (d,  $J = 14.9$  Hz, 1 H), 1.99 (q,  $J = 12.4, 11.9$  Hz, 1 H).  $^{13}\text{C}$  NMR (126 MHz, DMSO- $d_6$ ):  $\delta = 169.4, 118.3$  (t,  $J = 247.4$  Hz), 46.2 (dd,  $J = 36.1, 28.6$  Hz), 45.2 (t,  $J = 21.1$  Hz), 41.0, 22.9 (d,  $J = 5.2$  Hz).  $^{19}\text{F}$  NMR (376 MHz, DMSO- $d_6$ ):  $\delta = -101.4$  (d,  $J = 251.5$  Hz),  $-108.0$  (d,  $J = 251.9$  Hz). LC-MS (positive mode):  $m/z = 166$  [M - HCl + H] $^+$ .

(31) **Boc-Protection Protocol A4**

The Boc $_2$ O (1.2 equiv) was added to the stirred mixture of compound **11** (1 equiv), NaHCO $_3$  (3.5 equiv) in THF-H $_2$ O (1:1, 10 mL of mixture for 1 g of **11**). The resulting suspension was stirred at room temperature overnight. The THF was distilled at rotor evaporator (20 mmHg, 40 °C). The suspension formed was filtered, and the mother liquor was extracted with MTBE. The water phase was acidified with citric acid, the product was extracted with EtOAc. The combined extracts were dried with Na $_2$ SO $_4$  and evaporated to give the desired Boc-protected product **18**; mp (**18a**) 185 °C; mp (**18b**) 188 °C.

**Representative Examples**

**4,4-Difluoropiperidine-3-carboxylic Acid Hydrochloride (11a-HCl)**

**1-(tert-butoxycarbonyl)-4,4-difluoropiperidine-3-carboxylic acid (18a)**

$^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta = 12.95$  (s, 1 H), 3.86–3.41 (m, 4 H), 3.05–2.90 (m, 1 H), 2.36–2.17 (m, 1 H), 1.91 (q,  $J = 9.8, 6.1$  Hz, 1 H), 1.39 (s, 9 H).  $^{13}\text{C}$  NMR (126 MHz, DMSO- $d_6$ ):  $\delta = 169.5, 153.8, 125.5$ – $117.2$  (m), 79.9, 47.6, 44.0, 43.2, 32.1, 28.3.  $^{19}\text{F}$  NMR (376 MHz, DMSO- $d_6$ ):  $\delta = 95.9$  (dm,  $J = 238.8$  Hz),  $-100.1$  (dm,  $J = 242.1$  Hz),  $-103.3$  (dm,  $J = 245.8$  Hz). LCMS, negative mode,  $m/z: 264$  [M-H] $^-$ .

**1-(tert-butoxycarbonyl)-3,3-difluoropiperidine-4-carboxylic acid (18b)**

$^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta = 12.86$  (s, 1 H), 4.02 (s, 1 H), 3.77 (d,  $J = 13.8$  Hz, 1 H), 3.45–3.37 (m, 1 H), 3.18–2.98 (m, 2 H), 1.89 (dt,  $J = 13.6, 4.1$  Hz, 1 H), 1.80–1.66 (m, 1 H), 1.40 (s, 9 H).  $^{13}\text{C}$  NMR (126 MHz, chloroform- $d$ ):  $\delta = 170.2$  (d,  $J = 2.4$  Hz), 154.2, 119.1 (t,  $J = 249.7$  Hz), 80.1, 49.2, 48.2, 46.8 (t,  $J = 21.5$  Hz), 28.4, 25.7.  $^{19}\text{F}$  NMR (376 MHz, DMSO- $d_6$ ):  $\delta = -103.3$  (dd,  $J = 239.2, 172.0$  Hz),  $-112.5$  (dd,  $J = 239.6, 101.1$  Hz). LCMS, negative mode,  $m/z: 264$  [M-H] $^-$ .

(32) **Debenzylation Protocol D2**

10% Pd on carbon (0.1 g for 1 g of **14c**) was added to the solution of compound **14c** (as hydrochloride) in EtOH (10 mL for 1 g of **14c**), and the mixture was hydrogenated at room temperature and atmospheric pressure until the consumption of hydrogen ceased. The catalyst was filtered off, and the filtrate was evaporated and dried. The crude product was washed by MTBE affording the desired compound **15c**. Then crude compound **15c**

was treated by a saturated solution of HCl in dioxane and isolated in pure form as hydrochloride; mp (**15c-HCl**) 95 °C.

**Representative Example**

**Ethyl 3,3-Difluoropyrrolidine-2-carboxylate Hydrochloride (15c-HCl)**

$^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta = 10.76$  (s, 2 H), 4.94 (dd,  $J = 17.4, 9.2$  Hz, 1 H), 4.44–4.19 (m, 2 H), 3.55–3.36 (m, 2 H), 2.78–2.52 (m, 2 H), 1.25 (t,  $J = 7.1$  Hz, 3 H).  $^{13}\text{C}$  NMR (126 MHz, DMSO- $d_6$ ):  $\delta = 163.3$  (d,  $J = 2.7$  Hz), 126.9 (dd,  $J = 257.5, 250.4$  Hz), 63.4, 62.7 (dd,  $J = 33.1, 28.7$  Hz), 42.3 (d,  $J = 5.8$  Hz), 33.4 (t,  $J = 24.1$  Hz), 14.3.  $^{19}\text{F}$  NMR (376 MHz, DMSO- $d_6$ ):  $\delta = -98.3$  (d,  $J = 234.8$  Hz),  $-100.7$  (d,  $J = 234.8$  Hz). LC-MS (positive mode):  $m/z = 180$  [M - HCl + H] $^+$ .

(33) Bogolubsky, A. V.; Ryabukhin, S. V.; Stetsenko, S. V.; Chupryna, A. A.; Volochnyuk, D. M.; Tolmachev, A. A. *J. Comb. Chem.* **2007**, *9*, 661.

(34) **TFA-Deprotection Protocol E2**

A solution of **20d** (1 equiv) in 1 M HCl in EtOH (prepared from AcCl (4 equiv) and EtOH) was stirred at 40 °C for 4 h. The solution was evaporated dry, and the crude product was washed by MTBE affording the desired compound **15d**. Then crude compound **15d** was treated by a saturated solution of HCl in dioxane and isolated in pure form as hydrochloride; mp (**15d-HCl**) 116 °C.

**Representative Example**

**Ethyl 4,4-Difluoro-pyrrolidine-3-carboxylate Hydrochloride (15d-HCl)**

$^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta = 10.40$  (s, 2 H), 4.28–4.11 (m, 2 H), 4.00–3.83 (m, 1 H), 3.84–3.66 (m, 3 H), 3.55 (dd,  $J = 12.1, 10.1$  Hz, 1 H), 1.22 (t,  $J = 7.1$  Hz, 3 H).  $^{13}\text{C}$  NMR (151 MHz, DMSO- $d_6$ ):  $\delta = 165.6, 126.2$  (t,  $J = 253.2$  Hz), 62.2, 50.4 (t,  $J = 32.5$  Hz), 49.0 (t,  $J = 22.8$  Hz), 44.8, 14.4.  $^{19}\text{F}$  NMR (376 MHz, DMSO- $d_6$ ):  $\delta = -102.3$ . LC-MS (positive mode):  $m/z = 180$  [M - HCl + H] $^+$ .

(35) **Hydrolysis Protocol F2**

A mixture of nitrile **22j** (1 mol) and conc sulfuric acid (3 mL per 1 g of nitrile) was heated to 90 °C and stirred for 1 h, diluted with water (10 mL per 1 g of nitrile), and boiled overnight. After cooling, the product was extracted with dichloromethane, the extracts were dried, evaporated, and distilled; bp (**10j**) 91–92 °C/0.3 mmHg.

**Representative Example**

**3,3-Difluoro-2-phenylbutanoic Acid (10j)**

$^1\text{H}$  NMR (400 MHz, CDCl $_3$ ):  $\delta = 10.56$  (br, 1 H), 7.43 (dd,  $J = 6.7, 3.0$  Hz, 2 H), 7.37 (d,  $J = 3.6$  Hz, 3 H), 4.15 (t,  $J = 12.2$  Hz, 1 H), 1.65 (t,  $J = 19.0$  Hz, 3 H).  $^{13}\text{C}$  NMR (151 MHz, CDCl $_3$ ):  $\delta = 174.5$  (d,  $J = 7.0$  Hz), 131.4 (t,  $J = 3.5$  Hz), 129.5, 128.8, 128.7, 122.04 (t,  $J = 244.6$  Hz), 58.4 (t,  $J = 26.9$  Hz), 21.6 (t,  $J = 26.3$  Hz).  $^{19}\text{F}$  NMR (376 MHz, CDCl $_3$ ):  $\delta = -89.7$  (d,  $J = 248.0$  Hz),  $-92.4$  (d,  $J = 248.0$  Hz). LCMS (negative mode):  $m/z = 199$  [M - H] $^-$ .