Article

Synthesis of 5-(Fluoroalkyl)isoxazole Building Blocks by Regioselective Reactions of Functionalized Halogenoximes

Bohdan A. Chalyk, Kateryna V. Hrebeniuk, Yulia V. Fil, Konstantin S. Gavrilenko, Alexander B. Rozhenko, Bohdan V. Vashchenko, Oleksandr V. Borysov, Angelina V. Biitseva, Pavlo S. Lebed, Iulia Bakanovych, Yurii S. Moroz, and Oleksandr O. Grygorenko

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.9b02264 • Publication Date (Web): 18 Oct 2019

Synthesis of 5-(Fluoroalkyl)isoxazole Building Blocks by Regioselective Reactions of Functionalized Halogenoximes

Bohdan A. Chalyk,[†,‡] Kateryna V. Hrebeniuk,[†] Yulia V. Fil,[†] Dr. Konstantin S. Gavrilenko,[†,§] Dr. Alexander B. Rozhenko,[‡] Bohdan V. Vashchenko [†,§] Dr. Oleksandr V. Borysov,[†,‡] Dr. Angelina V. Biitseva,[†,§] Dr. Pavlo S. Lebed,[†,§] Iulia Bakanovych,[†,§] Dr. Yurii S. Moroz,[†,#] Dr. Oleksandr O. Grygorenko[†,§,]*

[†] Enamine Ltd. (www.enamine.net), Chervonotkatska Street 78, Kyiv 02094, Ukraine

[‡] Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Murmanska Street 5, Kyiv 02660, Ukraine

[§] Taras Shevchenko National University of Kyiv, Volodymyrska Street 60, Kyiv 01601, Ukraine

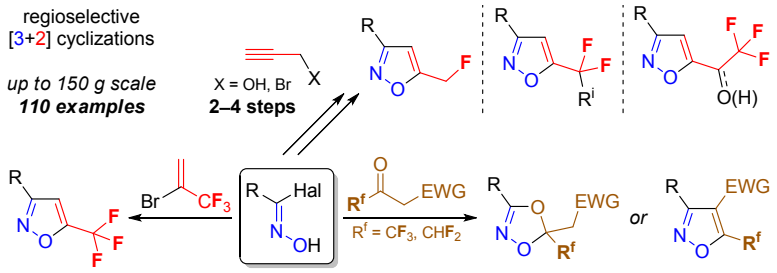
[#] Chemspace, Ilukstes iela 38-5, Riga, LV-1082, Latvia

gregor@univ.kiev.ua

RECEIVED DATE (to be automatically inserted after your manuscript is accepted if required according to the journal that you are submitting your paper to)

Abstract. A comprehensive study on the synthesis of 5-fluoroalkyl-substituted isoxazoles starting from functionalized halogenoximes is reported. One-pot metal-free [3+2] cycloaddition of CF_3-substituted alkenes and halogenoximes bearing ester, bromo, chloromethyl, and protected amino groups was developed for the preparation of 5-trifluoromethylisoxazoles. The target 3,5-disubstituted derivatives

were obtained in regioselective manner in good to excellent yield on up to 130 g scale. 5-Fluoromethyl- and 5-difluoromethylisoxazoles were synthesized by late-stage deoxofluorination of the corresponding 5-hydroxymethyl or 5-formyl derivatives, respectively, in turn prepared *via* metal-free cycloaddition of halogenoximes and propargylic alcohol. An alternative approach based on nucleophilic substitution in 5-bromomethyl derivatives was found to be more convenient for the preparation of 5-fluoromethylisoxazoles. Reaction of isoxazole-5-carbaldehydes with the Ruppert – Prakash reagent was used for the preparation of (β,β,β-trifluoro-α-hydroxyethyl)isoxazoles. Utility of described approaches was shown by multigram preparation of side-chain functionalized mono-, di- and trifluoro-methylisoxazoles, *e.g.* fluorinated analogues of ABT-418 and ESI-09.



R = *N*-Boc-amino acid-derived moiety, CO_2Et, CH_2Cl, CH_2OH, Br, Ar

Introduction

Isoxazole ring has been recognized as an essential heterocyclic scaffold for organic synthesis and medicinal chemistry.[1–3] In particular, nearly two dozens of pharmaceuticals containing 3- or 5-methylisoxazole motif were approved by FDA to date, and many more have reached various phases of clinical studies (*e.g.* β-lactam antibiotics,[4,5] sulfonamide antibacterials,[6] antidepressants,[7] antirheumatic drugs,[8], anti-inflammatory,[9] antiviral,[10] or hypoglycemic[11] agents, fungicides[12] and other classes)[13,14] (Figure 1). Introducing fluorine atoms into alkyl substituents is one of the most powerful design tools in drug discovery. Such modification often improves physicochemical characteristics and pharmacokinetic properties of the compounds.[15,16]

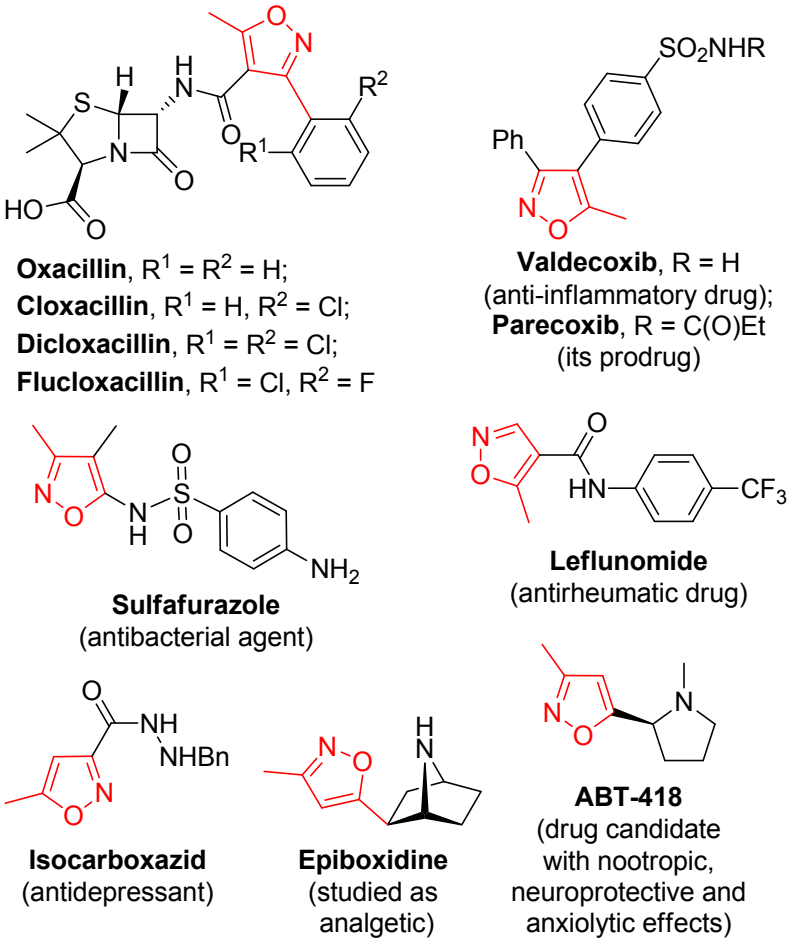
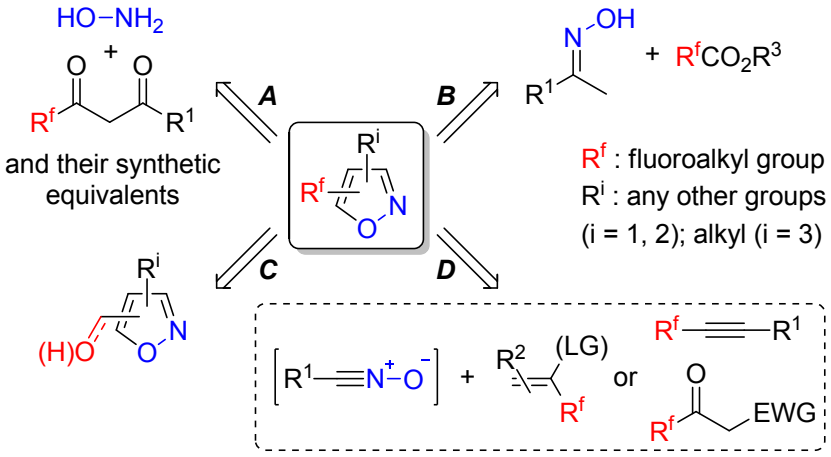


Figure 1. Some biologically active compounds bearing a 3- or 5-methylisoxazole moiety.

It is not surprising therefore that synthesis of fluoroalkyl-substituted isoxazoles have attracted significant interest. A classical approach to the synthesis of these compounds relies on the heterocyclization reaction of fluorinated 1,3-bis-electrophiles and hydroxylamine (Scheme 1, **A**).[17–23] Similar method involves condensation of enolizable oximes with trifluoroacetates (Scheme 1, **B**).[24] In addition to that, deoxofluorination of the oxygen-containing isoxazoles, *e.g.* alcohols or aldehydes, was described (Scheme 1, **C**).[25,26] An alternative approach includes [3+2] cycloaddition[27–32] of fluoroalkyl-substituted alkenes,[33–35] alkynes[35–37] or enolizable ketones[38–40] and generated *in situ* nitrile oxides (Scheme 1, **D**). To the best of our knowledge, many examples of aforementioned [3+2] cycloadditions were not regioselective under reported conditions.[41–45] In other cases, when 5-(fluoroalkyl)isoxazoles were the desired product, the observed regioselectivity led to target compounds only as minor product.[35,37,46] Moreover, limited substrate scope was typically demonstrated, often including only aryl-substituted nitrile oxides.

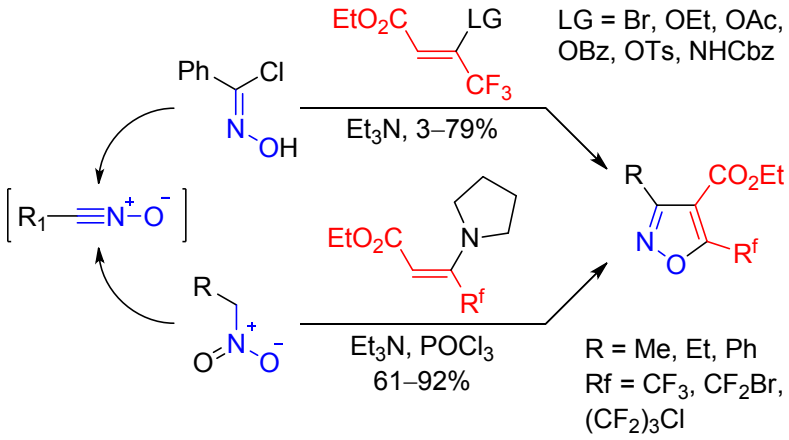


Scheme 1. Known approaches to fluoroalkyl-substituted isoxazoles

In line with our continuous efforts to synthesize fluorinated oxazoles,[47–50] in this work we report a comprehensive study on the regioselective synthesis of various 5-(fluoroalkyl)isoxazoles *via* the [3+2] cycloaddition approach involving halogenoximes as the nitrile oxide source, focusing mainly on the preparation of functionalized substrates (*e.g.* bearing a protected amino group). In addition to that, we

have aimed at expanding of chemical space covered by fluorinated isoxazoles with a series of small-molecule building blocks accessible on multigram scale.

Our previous experience with [3+2] cycloadditions showed that regioselectivity of the reaction can be controlled by using alkenes bearing a leaving group (*e.g.* bromo or dialkylamino substituents) as the starting materials.[51] To date, only a few examples of similar reactions with trifluoromethyl-substituted substrates were described in the literature, being limited to simple alkyl- or benzonitrile oxides and α,β-unsaturated esters (Scheme 2).[33,34,52]

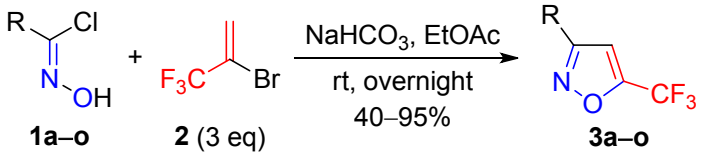


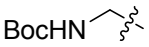
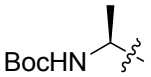
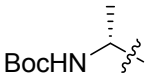
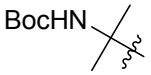
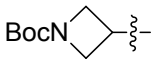
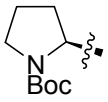
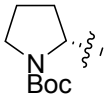
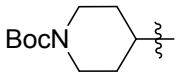
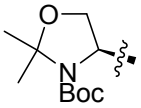
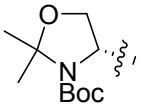
Scheme 2. Known syntheses of 5-(fluoroalkyl)isoxazoles by [3+2] cycloaddition of nitrile oxides and α,β-unsaturated esters

Results and discussion

Synthesis of 5-(trifluoromethyl)isoxazoles. In addition to that, reaction of chloroxime **1a** and 2-bromo-3,3,3-trifluoroprop-1-ene (**2**) in the presence of Et_3N in Et_2O was disclosed in a patent.[53] In our hands, the latter transformation was not successful under the conditions reported (the corresponding furoxan was obtained as the major product); nevertheless, reaction of **1a** and **2** occurred in the presence of $NaHCO_3$ in EtOAc as the solvent (Table 1, Entry 1). Using three-fold excess of **2** was necessary to achieve the complete conversion; with smaller amounts of **2**, significant nitrile oxide dimerization was

Table 1. Synthesis of 5-(trifluoromethyl)isoxazoles **3a–o**



Entry	Chloroxime	R	Product	Yield, %[a]
1	**1a**	CO_2Et	**3a**	69
2	**1b**	Ph	**3b**	44
3	**1c**	4-$MeOC_6H_4$	**3c**	74
4	**1d**	4-FC_6H_4	**3d**	73
5	**1e**	2-thienyl	**3e**	40
6	**1f**		**3f**	89 (73[b])
7	**1g**		**3g**	72
8	**1h**		**3h**	76
9	**1i**		**3i**	85
10	**1j**		**3j**	42 (81[c])
11	**1k**		**3k**	94
12	**1l**		**3l**	95
13	**1m**		**3m**	57
14	**1n**		**3n**	40
15	**1o**		**3o**	42

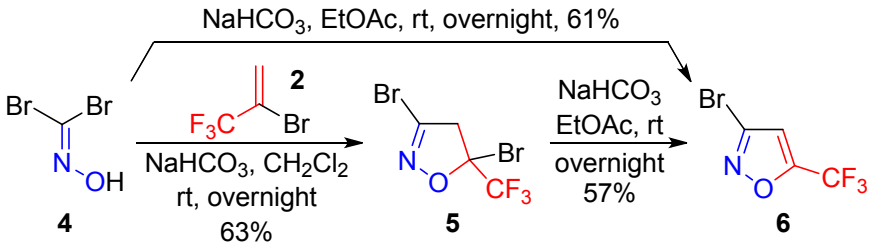
[a] Yields of isolated products [b] At 160-g scale of **1f**, 2.5-fold excess of **2** was used, which resulted in slightly diminished yield of the product [c] The reaction was performed in EtOAc – THF (1:1, v/v) due to limited solubility of **1j** in EtOAc

observed. On the contrary, using higher excess of **2** did not improve the yield of the product. The target compound **3a** was isolated in 69% yield on up to 100 g scale after distillation *in vacuo*.

It should be noted that alkene **2** can be considered as the synthetic equivalent of 3,3,3-trifluoroprop-1-yne, which is hardly accesssible and inconvenient to handle due to its low boiling point (–48…–47 °C).

Taking into account the literature examples of [3+2] cycloadditions of benzonitrile oxide shown in Scheme 2,[33,34,52] we have checked the developed procedure with aryl chloroximes **1b–e** (Table 1, Entries 2–5). The title products **3b–e** were obtained as single regioisomers in 40–74% yield after distillation in *vacuo* (**3b**) or chromatographic purification (**3c–e**). The method was also extended to amino acid-derived chloroximes **1f–o**, prepared using a protocol reported by our group previously.[54] Reaction of **1f–o** and **2** under the conditions described above led to the formation of 5-(trifluoromethyl)isoxazoles **3f–o** bearing a protected amino function in 40–95% yield (Table 1, Entries 6–15). It is important to outline that the target products **3** could be obtained on up to 150 g scale (checked for **3f**, 73% yield).

Interestingly, reaction of alkene **2** with dibromo derivative **4** in the presence of $NaHCO_3$ in less polar CH_2Cl_2 resulted in the formation of isoxazoline **5** (63% yield) (Scheme 3). Transformation of **5** into the product **6** required using $NaHCO_3$ in EtOAc (or K_2CO_3, CH_2Cl_2, rt, 1 week, 50% yield). Although formation of the intermediates of the type **5** bearing cyclic substituents or ester moiety was postulated for the [3+2] cycloadditions with nitrile oxides previously, but only a few examples of their isolation were reported to date.[55,56] Also, this transformation could be performed one-pot using 3-fold excess of $NaHCO_3$ in EtOAc (61% yield).



Scheme 3. Synthesis of 3-bromo-5-(trifluoromethyl)isoxazole (**6**)

It is important to outline that in all cases studied, only 3,5-disubstituted isomers **3a–o** and **6** were obtained. The structure of the products was confirmed proven by single crystal X-ray diffraction analysis of the compound **3h** (Figure 2).

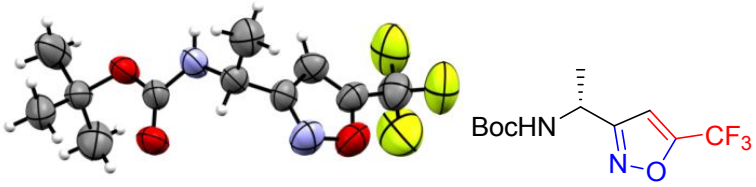
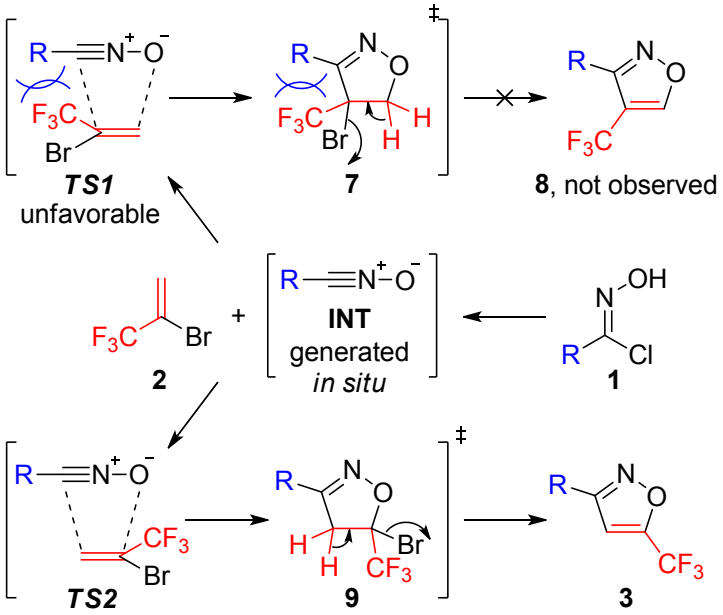


Figure 2. Molecular structure of **3h** (thermal ellipsoids are shown at 50% probability level)

The regioselectivity of the process might be governed by steric and/or electronic factors. In particular, the transition state **TS1** leading to the formation of 3,4-disubstituted isoxazolines **7** and corresponding isoxazoles **8** is unfavorable as compared to **TS2** (leading to **3** *via* isoxazolines **9**) due to steric repulsion between the R substituent, the trifluoromethyl group and the bromine atom (Scheme 4).



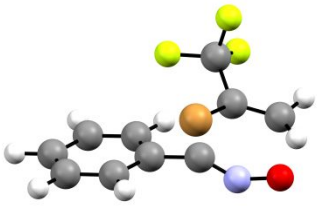
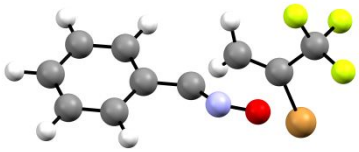
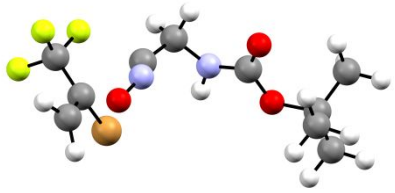
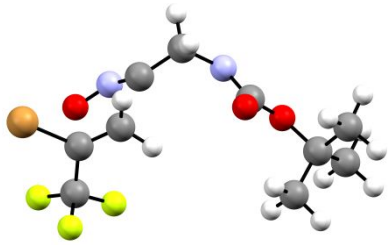
Scheme 4. A plausible mechanism of the reaction between **1** and **2**

In order to elucidate the observed regioselectivity, the reaction was studied using quantum chemical calculations (RI-BP86), modeling the preferable formation of derivatives **9b** and **9f** compared to the isomeric **7b** and **7f**. Since these structures contain sterically crowded *t*-Bu group (**9f**) or aromatic moiety (**9b**) disposed to interactions with large contributions of electron dispersion effects. This can significantly influence the ΔE and ΔG values computed using conventional DFT methods. Taking this fact into account, the structures corresponding to local minima were additionally optimized using Grimme's RI-B97-D approximation having a dispersion correction. The calculations predicted negative energies of formation (either ΔE or ΔG) for cyclic products of the both types. Nevertheless, formation **9b** and **9f** appeared to be more favorable as compared to isomeric **7b** and **7f** (see Supporting information, Tables S1, S2 for more details). Therefore, the calculations confirmed formation of the products of type **9b** and **9f** in the thermodynamically controlled cyclization reaction. Considering dispersion interactions using the RI-B97-D functional slightly reduces the ΔE and ΔG negative values (Tables 2 and S3).

Geometries of the transition states **TS2-b** and **TS2-f** are shown in Table 2. The corresponding activation energy values are by 3.9–4.3 kcal/mol lower than for the isomeric **TS1-b** and **TS1-f**. Hence almost exclusive formation of the cyclization products **9b** and **9f** is favorable, which is observed in the experiments. Moderate activation energy magnitudes estimated at the DFT level of approximation (ΔG = 25.6 and 23.0 kcal/mol for **9b** and **9f**, respectively) agree well with rather soft reaction conditions used. Thus, for the given set of the substituents, both thermodynamic and kinetic factors direct the process towards the same type of products in the studied reactions.

Relative stability of the products is driven by similar electronic and steric factors determining higher stability for **9b** and **9f** relative to their regioisomers **7b** and **7f**. The steric factor in the transition states is probably of high importance. This is best seen by comparing the conformations of **TS1-b** and **TS2-b** (Table 2).

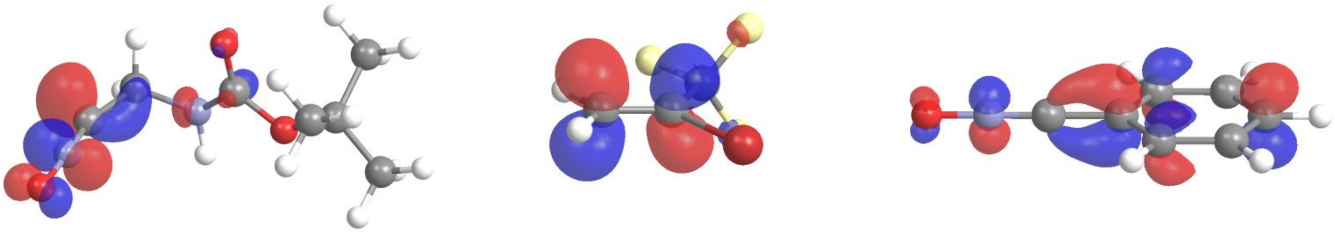
Table 2. Optimized (RI-BP86) structures of **TS1-b**, **TS2-b**, **TS1-f**, and **TS2-f**. The ΔG values are given in kcal/mol relative to the starting reactants.

Transition state	RI-B97-D optimized structure	$\Delta G^{\ddagger}$ (kcal/mol)
TS1-b		29.5
TS2-b		25.6
TS1-f		26.7
TS2-f		23.0

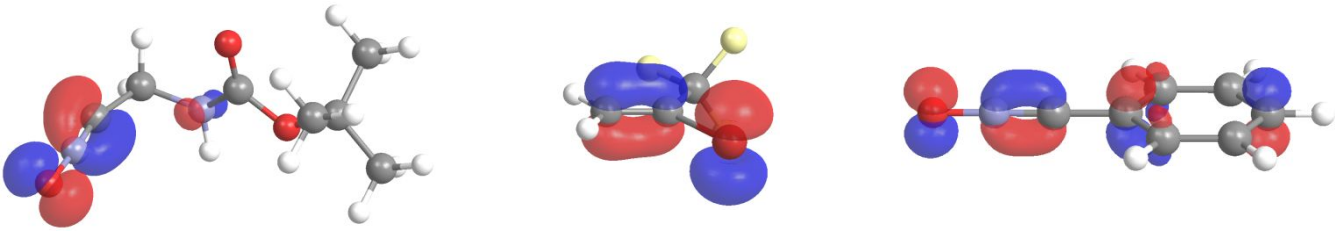
In **TS2-b**, the phenyl moiety is efficiently conjugated with the C–N–O fragment, whereas in **TS1-b**, the aromatic ring is orthogonal to it. Noteworthy, the located **TS2** structures evidence rather synchronous [3+2] cycloaddition: the C–C and C–O distances corresponding to the newly formed bonds are comparable (2.196 and 2.489 Å for **TS2-b**, and 2.176 and 2.525 Å for **TS2-f**).

Frontier molecular orbitals (FMO), *i.e.* the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) for the starting material **2** and corresponding intermediates **INT** with corresponding orbital energies are shown in Figure 3. Two types of [3+2] HOMO – LUMO interactions are possible: HOMO(**INT**) – LUMO(**2**) *vs* HOMO(**2**) – LUMO(**INT**). The smaller ΔE values were found for the combinations of molecular orbitals HOMO(**INT-b**)–

LUMO(**2**) and HOMO(**INT-f**)–LUMO(**2**) (13.53 and 12.10 eV, respectively), which corresponds to the FMO interaction between the highest occupied molecular orbital of the 1,3-dipole and the lowest unoccupied molecular orbital of the dipolarophile (the normal-electron demand). An alternative possibility for the 1,3-dipolar cycloaddition reactions, the interaction between the LUMO of the 1,3-dipole and the HOMO of the dipolarophile (the inverse-electron demand), is characterized here by higher ΔE values: 14.71 and 12.62 eV, respectively. Thus, the first type of interaction is expected in the considered cases.



LUMO(**INT-b**), E = 4.166 eV LUMO(**2**), E = 3.140 eV LUMO(**INT-f**), E = 2.084 eV



HOMO(**INT-b**), E = –10.39 eV HOMO(**2**), E = –10.545 eV HOMO(**INT-f**), E = –8.964 eV

Figure 3. Chemissian[57] plots of FMOs for the 1,3-dipole molecules (**INT-b** and **INT-f**) and for the dipolarophile **2** calculated at the RHF/6-31G*//RI-B97-D/TZVP level of theory.

As can be seen from the FMO graphical representation, contributions from the corresponding atoms into HOMO(**INT-b,f**) and LUMO(**2**) participating in the reaction are very similar and hence, the orbital overlapping extent cannot explain the observed regioselectivity of the process. Additional information can be derived analyzing the natural bond orbital (NBO) atomic charges[58,59] in the reacting species (Figure 4). The shown transition states demonstrate favored C–C interaction (attraction of positive and

negative charges) and less pronounced C–O repulsion than in the alternative structures. Thus, the charge distribution favors the product structures identical to those found experimentally.

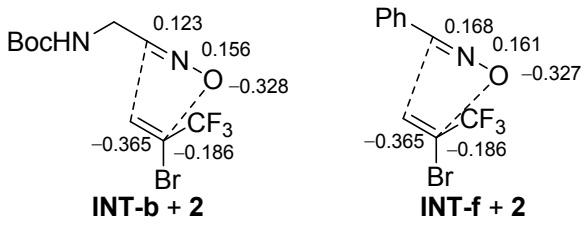
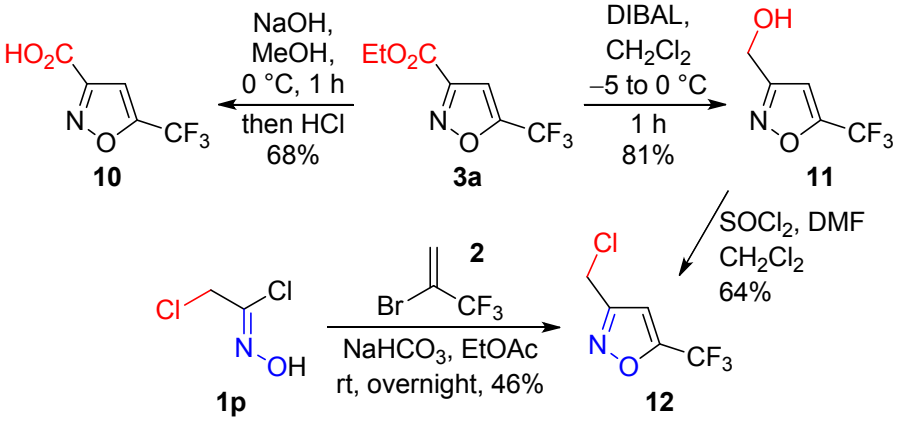


Figure 4. NBO atomic charges in the reagents (BP86/TZVP//RI-B97-D/TZVP level of theory).

Further studies of 5-trifluoromethyl derivatives obtained above included preparation of bulding blocks relevant to drug discovery, *i.e.* carboxylic acid **10**, alcohol **11**, chloride **12**, and amines **13**. Synthesis of the corresponding carboxylic acid **10** from ester **3a** was found to be challenging (Scheme 5). Reactions of **3a** with TMSBr or TMSI in HOAc, as well as KHMDS or TMSOK were unfruitful due to low yields of **10** and/or long reaction times (up to 72 h).



Scheme 5. Synthesis of building blocks **10–12**

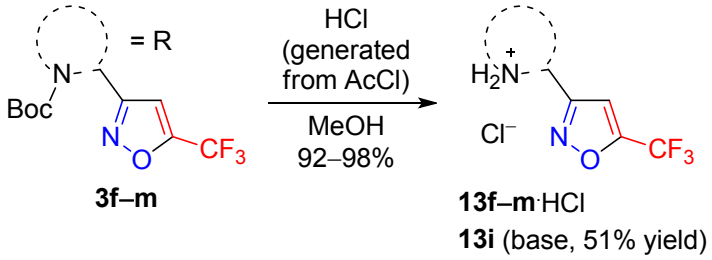
Thus, compound **10** was obtained in 68% yield *via* slow dropwise addition of **3a** solution in MeOH to the homogenous solution of NaOH in MeOH at 0 °C. It should be noted that the aforementioned reaction was highly exothermic.

Reduction of **3a** with $LiAlH_4$ was unfruitful in all attempts; thus, the corresponding alcohol **11** was smoothly synthesized from **3a** in 81% yield *via* reaction with DIBAL in CH_2Cl_2 at –5 to 0 °C for 1 h, followed by aq HCl work-up.

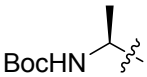
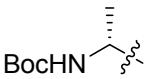
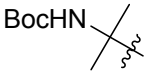
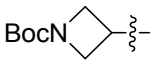
In turn, preparation of alkylating agent **12** relied on the reaction of hydroxymethyl derivative **11** with $SOCl_2$. The yield of the product **12** was moderate (64%; 30% overall yield from **1a**); the use of other reagents such as $(COCl)_2$ or NCS – PPh_3 did not improve the reaction outcome. More efficient approach to **12** relied on direct [3+2] cycloaddition reaction of chloroxime **1p** and 3-fold excess of **2** (600 g), which led to the target derivative **12** in 46% yield on 100 g scale.

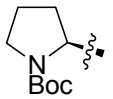
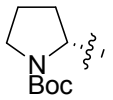
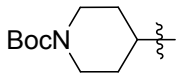
In turn, deprotection of the Boc derivatives **3f–m** upon action of generated *in situ* methanolic HCl led to aliphatic amines **13f–m** (92–98% yield, isolated as hydrochlorides except **13i**, which was obtained and purified as a free base in 51% yield) (Table 3). It is important to stress out that the building blocks **13f·HCl**, **13i, 13k–l·HCl** could be obtained at multigram scale (up to 30 g).

Table 3. Synthesis of amines **13f–m**



3f–m **13f–m**·HCl
13i (base, 51% yield)

Entry	Boc derivative	R	Product	Yield, %[a]
1	**3f**		**13f**·HCl	95
2	**3g**		**13g**·HCl	93
3	**3h**		**13h**·HCl	92
4	**3i**		**13i**	51[b]
5	**3j**		**13j**·HCl	95

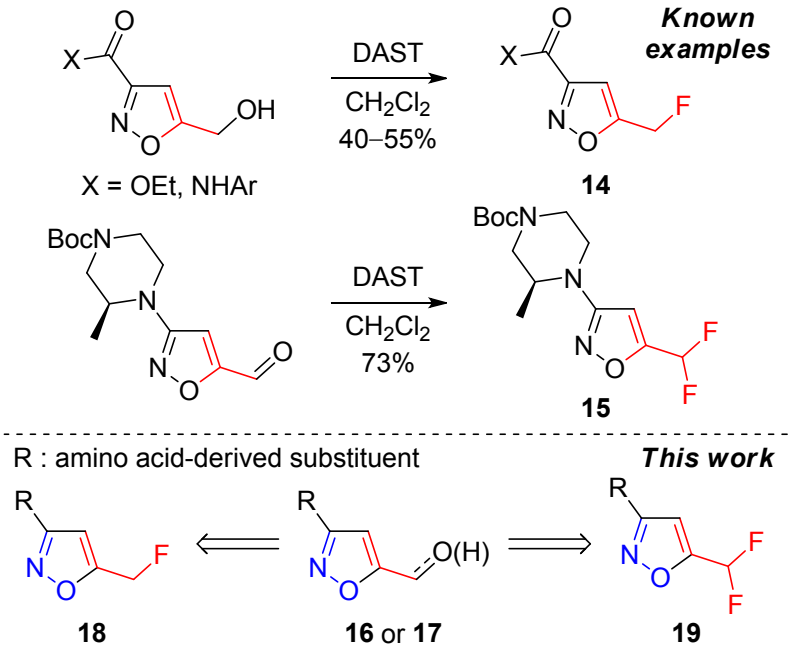
6	**3k**		**13k**·HCl	97
7	**3l**		**13l**·HCl	98
8	**3m**		**13m**·HCl	92

[a] Yields of isolated products [b] Purified and isolated as a free base

Synthesis of other 5-(fluoroalkyl)isoxazoles. Since unlike 2-bromo-3,3,3-trifluoroprop-1-ene (**2**), the corresponding mono- and difluorinated alkenes are not readily available, we have switched to the deoxofluorination strategy for the preparation of the 5-(fluoromethyl)- and 5-(difluoromethyl)isoxazoles. Only a few examples of similar transformations were reported in the literature, including synthesis of the compounds **14** and **15** (Scheme 6).[25,26]

We anticipated that alcohols **16** and the corresponding aldehydes **17** (obtained by oxidation of **16**) might be proper key intermediates for the preparation of the target products **18** and **19**, respectively. In turn, synthesis of hydroxymethyl derivatives **16** might rely on [3+2] cycloaddition of functionalized halogenoximes **1** and propargylic alcohol. To the best of our knowledge, only a single example of analogous transformation which involved metal catalysis was mentioned in the literature to date.[60]

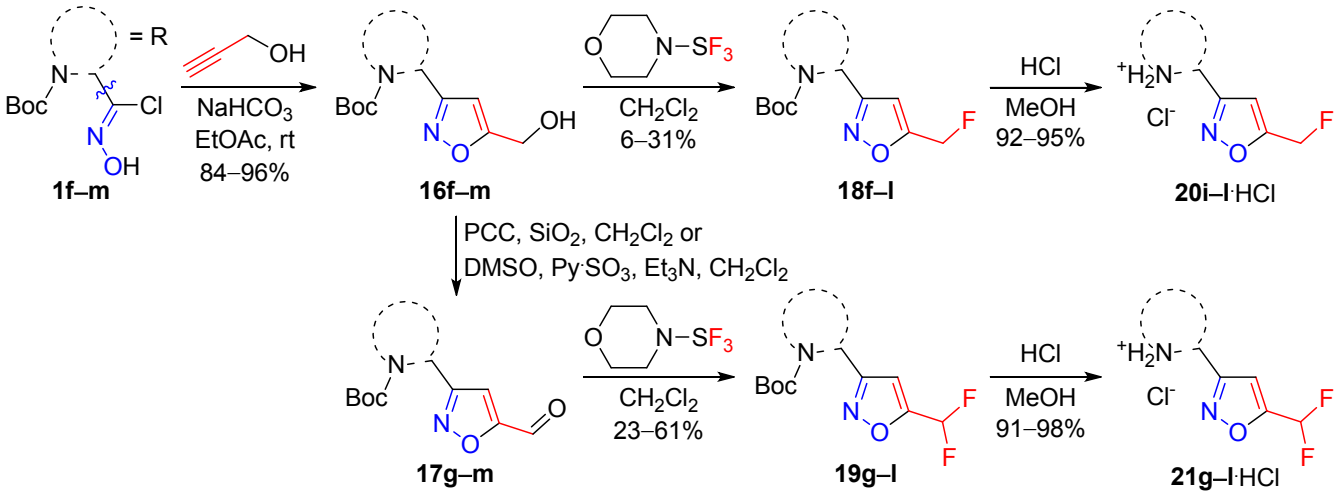
In this work, a transition metal-free version of this reaction was used. In particular, it was found that chloroximes **1f–m** smoothly reacted with propargyl alcohol under the standard conditions ($NaHCO_3$, EtOAc, rt) to give the target products **16f–m** in 84–96% yield (Table 4). Deoxofluorination of **16f–l** with morph-DAST in CH_2Cl_2 at –10 °C gave the title isoxazoles **18f–l** in low to moderate yields (6–31% after chromatographic purification).



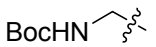
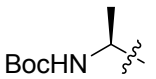
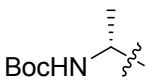
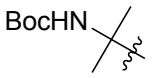
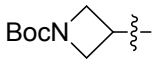
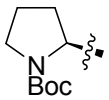
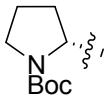
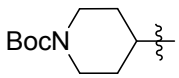
Scheme 6. Synthesis of 5-((di)fluoromethyl)isoxazoles **18** and **19** *via* deoxofluorination

To obtain the difluoromethyl-substituted products **19**, alcohols **16f–m** were first oxidized the corresponding aldehydes **17g–m** with PCC (43–80% yield). Oxidation with the Parikh – Doering reagent gave better reaction outcome (69–83% yield, except **17j** obtained in 14% yield); meanwhile, using the Dess – Martin reagent was unfruitful due to low yields of the products. Aldehyde **17f** appeared

Table 4. Synthesis of 5-((di)fluoromethyl)isoxazoles **18**–**21**



R	Alcohol **16** (yield, %[a])	Product **18** (yield, %)	Product **20**·HCl (yield, %[a])	Aldehyde **17** (yield, %)	Product **19** (yield, %[a])	Product **21**·HCl (yield, %[a])

1		**16f** (94)	**18f** (6[b], 93[c])	N/A[d]	N/A[d]	N/A[d]	N/A[d]
2		**16g** (96)	**18g** (10[b], 97[c])	N/A[d]	**17g** (66[e], 78[f])	**19g** (23)	**21g**·HCl (96)
3		**16h** (95)	**18h** (12[b], 98[c])	N/A[d]	**17h** (67[e], 76[f])	**19h** (25)	**21h**·HCl (95)
4		**16i** (91)	**18i** (30[b], 93[c])	**20i**·HCl (92)	**17i** (80[e], 83[f])	**19i** (28)	**21i**·HCl (93)
5		**16j** (84)	**18j** (16[b], 96[c])	N/A[d]	**17j** (43[e], 14[f])	**19j** (35)	**21j**·HCl (91)
6		**16k** (90)	**18k** (31[b])	**20k**·HCl (94)	**17k** (78[e], 81[f])	**19k** (53)	**21k**·HCl (96)
7		**16l** (92)	**18l** (25[b])	**20l**·HCl (95)	**17l** (75[e], 80[f])	**19l** (61)	**21l**·HCl (98)
8		**16m** (85)	**18m** (N/A[d])	N/A[d]	**17m** (55[e], 69[f])	N/A[d]	N/A[d]

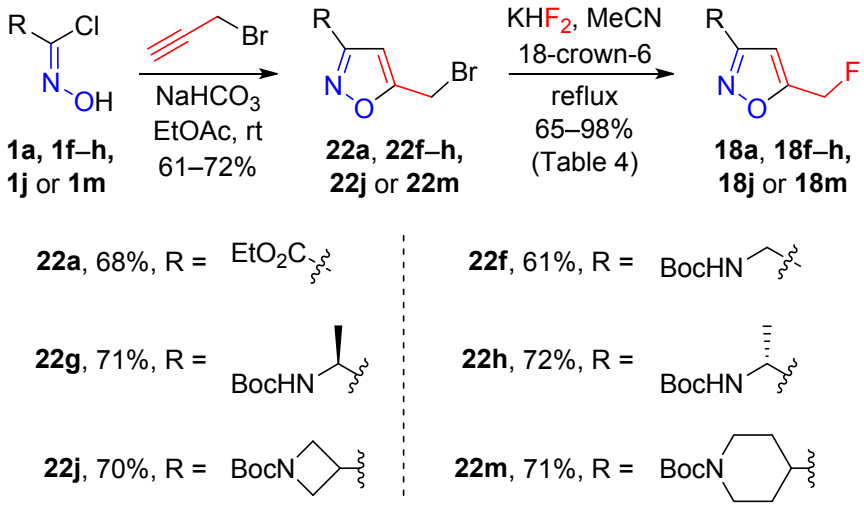
[a] Yield of isolated products [b] Yield of isolated products given for the deoxofluorination reaction (Morph-DAST, CH_2Cl_2, –35 °C to –10 °C, 1.5 h) [c] Yield of isolated products given for the Finkelstein reaction (KHF_2, MeCN, 18-crown-6, reflux, overnight) [d] The compound was not prepared due to the low yield of the starting material on the previous step of the reaction sequence [e] Yield of isolated products of oxidation performed with PCC, SiO_2, CH_2Cl_2 [f] Yield of isolated products of oxidation *via* using of DMSO, Py·SO_3, Et_3N.

to be too unstable to be isolated, whereas other compounds of this series could be isolated and stored at +4 °C. Deoxofluorination of **17g–l** under the aforementioned conditions led to the formation of **19g–l** in moderate yields (23–61%). Deprotection of **18** and **19** with methanolic HCl proceeded smoothly and gave building blocks **20** and **21**, respectively, in 91–98% yield.

Due to the low yields of the deoxofluorination of alcohols **16f–h**, **16j** and **16m**, the Finkelstein reaction was successfully applied for preparation of CH_2F-derivatives **18** (Scheme 7). The bromide substitution of **22f–h**, **22j** and **22m** proceeded in 93–98% yield by refluxing of the substrate, KHF_2 and 18-crown-6 as catalyst in MeCN. Applying dibenzo-18-crown-6 as a phase-transfer catalyst did not improve the yields of **18**.

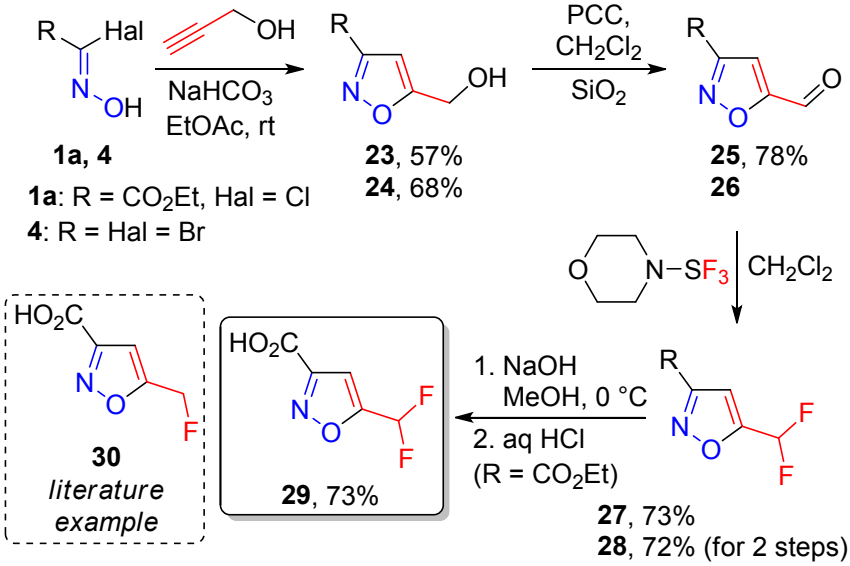
In turn, bromides **22** were obtained in 61–72% yield by cycloaddition reaction of chloroxime **1f–h**, **1j** and **1m** and freshly distilled propargyl bromide in the presence of 1.1-fold excess of $NaHCO_3$ in EtOAc.

This approach was also extended to chloroxime **1a** to obtain isoxazole **22a** (68% yield), which was used for the preparation of fluoromethyl derivative **18a** bearing an ester moiety (65% yield).



Scheme 7. Synthesis of **18** *via* the Finkelstein reaction of **22**

Analogous synthetic strategy was also implemented for the preparation of difluoromethyl-substituted building blocks bearing ester of bromine at C-3 position (Scheme 8).

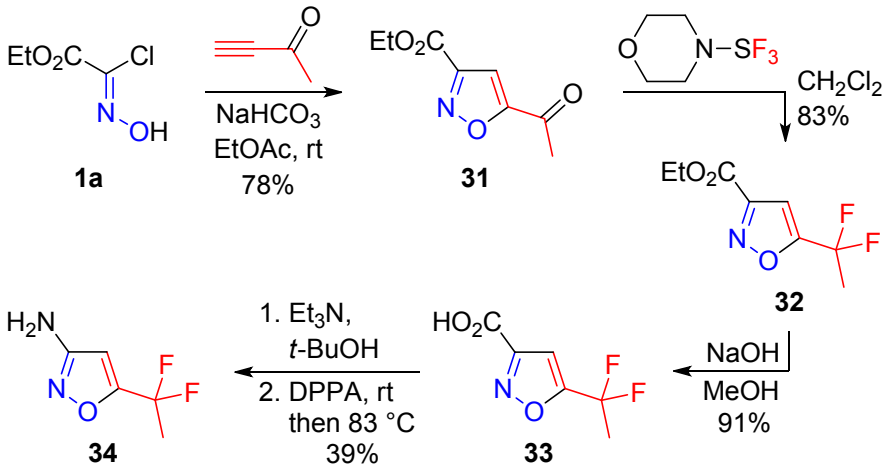


Scheme 8. Preparation of building blocks **28** and **29**

The reaction sequence commenced with the reaction of halogenoxymes **1a** or **4** with propargyl alcohol resulted in the hydroxymethyl isoxazoles **23** or **24** in 57% and 68% yield, respectively. Oxidation of **23**

and **24** to the corresponding aldehydes **25** and **26** was more efficient with PCC, while the Parikh – Doering reagent led to extremely low yields (13% yield for **25**). It is interesting to outline that deoxofluorination of aldehydes **25** and **26** proceeded smoothly, and the products **27** and **28** were obtained in 73% yield and 72% yield (for two steps), respectively. Mild alkaline hydrolysis of ester **27** using the method applied for the synthesis of **10** provided the carboxylic acid **29** in 73% yield. Building blocks **28** and **29** were obtained at up to 40 g scale. It should be noted that very similar approach was described in the literature for the preparation of **30**.[26]

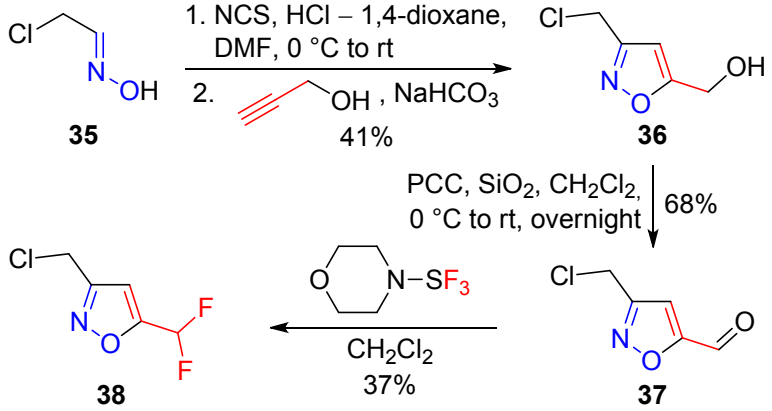
The aforementioned method was further applied for the preparation of a homologue of **29**, *i.e.* 1,1-difluoroethyl derivative. The reaction sequence included the cycloaddition of **1a** and methyl ethynyl ketone (resulted in 5-acetylisoxazole-3-carboxylate **31**), deoxofluorination to the derivative **32** (1 week, 83% yield) and its mild alkaline hydrolysis, which gave **33** in 91% (Scheme 9). Modified Curtius rearrangement of **33** using DPPA, *t*-BuOH, Et_3N gave the corresponding amine **34** in 39% yield after Boc-protection group cleavage.



Scheme 9. Preparation of 1,1-difluoroethyl carboxylic acid **33** and amine **34**

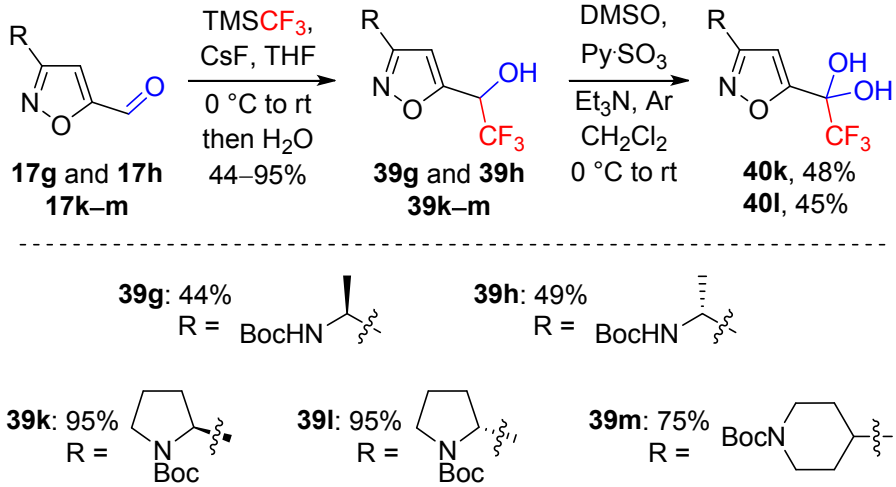
Next, similar strategy was used for the preparation of the F_2HC-containing analogue of the alkylating agent **12**. Thus, the corresponding oxime **35** was transformed to isoxazole **36** by treatment with NCS, HCl in DMF at 0 °C to rt, followed by addition of propargyl alcohol and $NaHCO_3$ (Scheme 10). The reaction proceeded for 48 h and led to isoxazole **36** in 41% yield on up to 150 g scale. Subsequent

oxidation of the chloromethyl derivative **36** to the corresponding aldehyde **37** was performed with PCC in the presence of SiO_2 in CH_2Cl_2 at 0 °C to rt. The intermediate **37** was isolated in 68% yield after distillation and then subjected to the deoxofluorination step providing the target building block **38** in 37% yield.



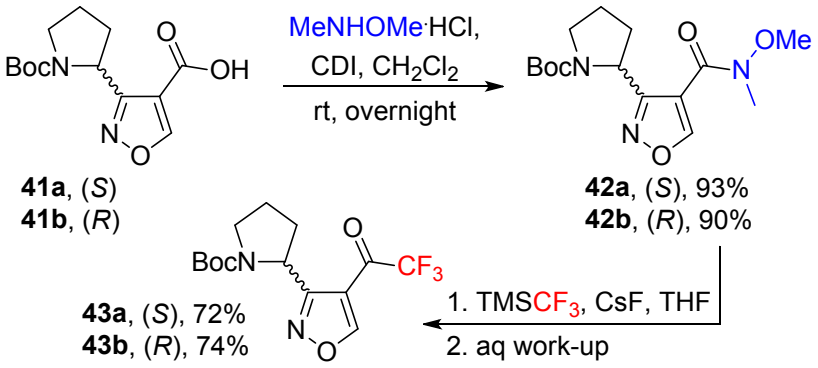
Scheme 10. Synthesis of difluoromethyl-containing alkylating agent **38**

Alternatively, aldehydes of the type **17** were transformed into 5-(fluoroalkyl)isoxazoles **39** *via* reaction with the Ruppert – Prakash reagent ($TMSCF_3$) (Scheme 11). In this case, *N*-Boc-protected amino alcohols **39g**, **39h** and **39k–m** were obtained in 44–95% yield. Subsequent oxidation of **39k** and **39l** with the Parikh – Doering reagent led to corresponding ketones isolated as a hydrates **40k** and **40l** (45–48% yield), while the Swern reagent led to **40** only in 13% in the most successful case.



Scheme 11. Preparation of fluorinated isoxazoles **39** and **40**

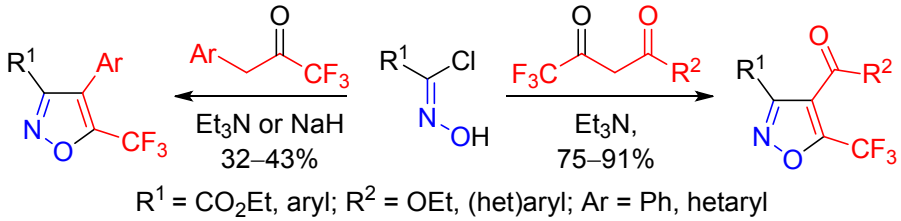
Moreover, we have tested an approach to the isomers of **40k** and **40l** from previously described carboxylic acids **41** (Scheme 12).[54] In turn, carboxylic acids **41** were transformed to Weinreb amides **42** (90–93% yield), which were used in the aforementioned reaction with $TMSCF_3$ and CsF in THF, resulted in **43** in 72–74% yield.



Scheme 12. Synthesis of trifluoromethyl ketone **43**

It should be noted that in the case of isomeric trifluoromethyl ketones **43a** and **43b**, no hydrate formation was observed.

Reaction of chloroximes with aliphatic di- and trifluoromethyl ketones. As it was mentioned above, fluoroalkyl-substituted isoxazoles can be obtained by reaction of chloroximes and fluorinated ketones.[38–40] The scope of the method studied so far was limited by aryl- or CO_2Et-substituted chloroximes (Scheme 13).

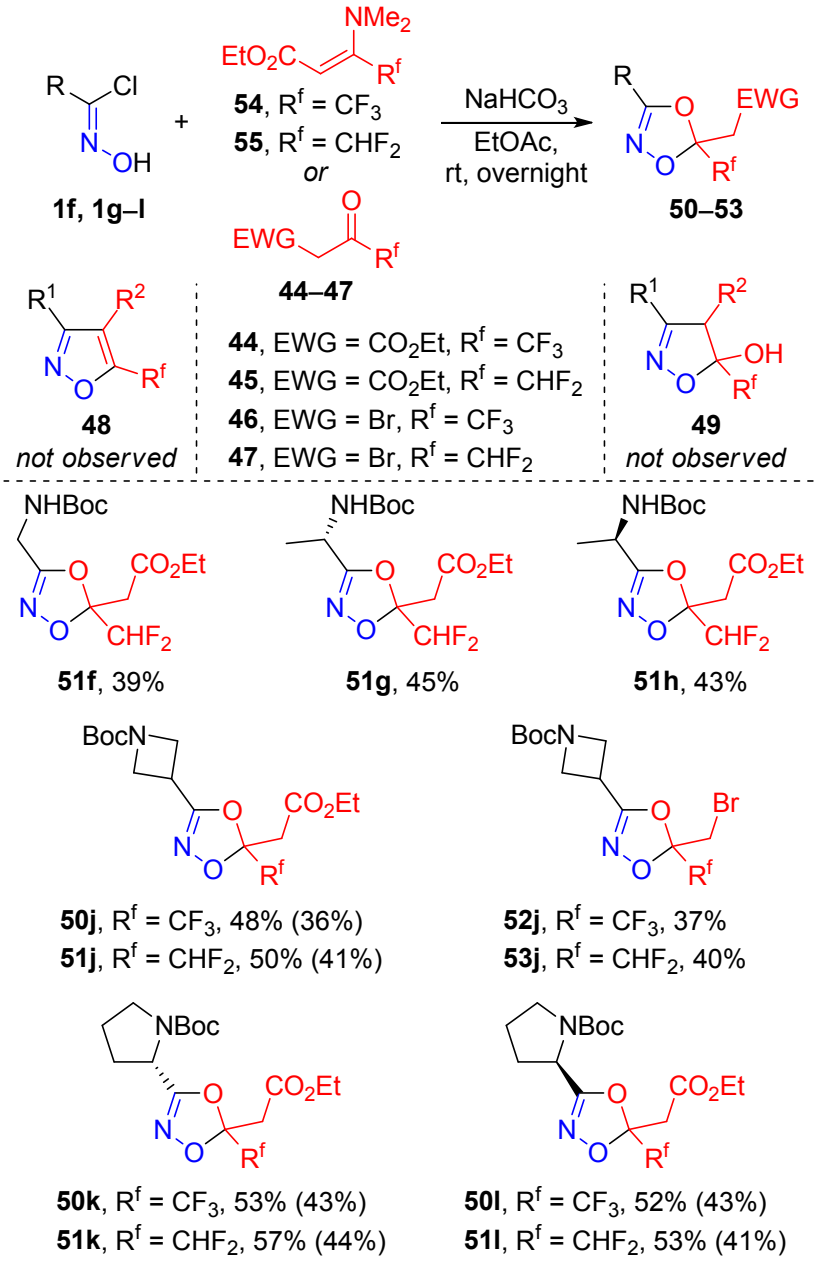


Scheme 13. Known reactions of chloroximes and fluorinated ketones

Therefore, we have studied base-mediated reaction of fluorinated β-ketoesters **44** and **45** or α-bromoketones **46** and **47** with chloroximes **1f** and **1h–j** (Scheme 14). Surprisingly, neither target

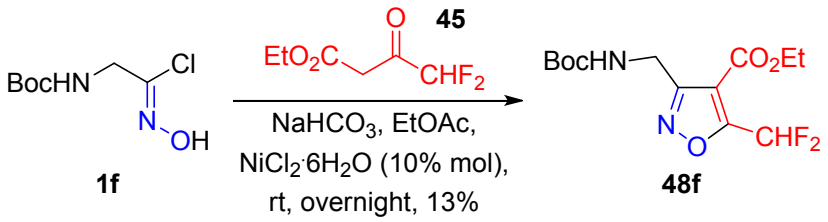
isoxazoles **48** nor isoxazolines **49** were detected in the reaction mixture; instead, 1,4,2-dioxazole derivatives **50** and **51** were obtained from **44** and **45**, respectively, in 39–57% yield. Replacing the starting ketones **44** and **45** with the corresponding enamines **54** and **55** gave the same products **50** and **51**, but with lower yields (36–44%).

Analogously, 1,4,2-dioxazoles **52j** and **53j** were synthesized *via* reaction of α-bromoketones **46** and **47** with chloroxime **1j** in 37% and 40% yields, respectively. Although similar transformations leading to the formation of 1,4,2-dioxazoles were described in the literature recently: they were obtained as minor products in reactions of chloroximes and α-keto esters.[38]



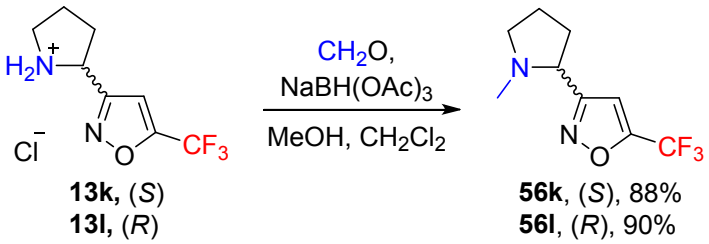
Scheme 14. Formation of 1,4,2-dioxazoles **50–53** (yields from **54** and **55** are given in brackets)

Nevertheless, the product of the type **48**, *i.e.* difluoromethyl isoxazole **48f**, could be obtained in low yield (13%) by reaction of **45** and **1f** in the presence of $NiCl_2 \cdot 6H_2O$ (10% mol.) (Scheme 15).[61] Other catalysts like $CuSO_4$, $Cu(OAc)_2 \cdot H_2O$, $Cu(OAc)_2 \cdot H_2O$ – TMEDA, or $NiCl_2 \cdot 6H_2O$ – TMEDA did not improve the reaction outcome.



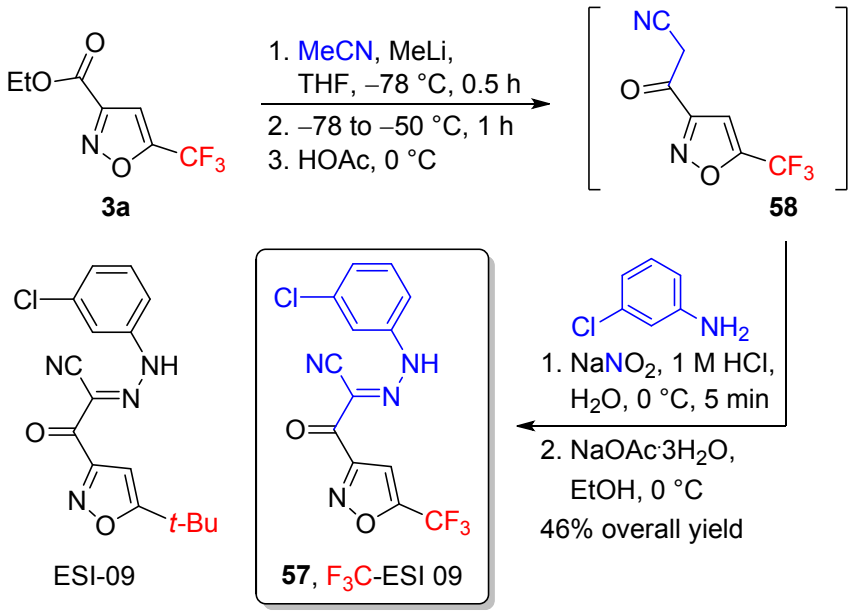
Scheme 15. Preparation of trisubstituted isoxazole **48f**

Synthesis of ABT-418 and ESI-09 analogues. In the above sections, a number of fluorinated heterocyclic building blocks were obtained at multigram scale. To demonstrate their utility for medicinal chemistry, several fluorinated isosteric analogues of known biologically active compounds were prepared. In particular, trifluoromethyl-substituted analogues of ABT-418 – (*R*)- and (*S*)-enantiomers of the compound **56** – were obtained from amines **13k** and **13l** in 88% and 90% yield, respectively (Scheme 16).



Scheme 16. Fluorinated analogues of ABT-418

In turn, F_3C-containing analogue **57** of exchange factor directly activated by cAMP (EPAC) inhibitor ESI-09 was synthesized from ester **3a** (Scheme 17). The compound **3a** reacted with generated *in situ* (cyanomethyl)lithium to give β-ketonitrile **58**, which was used in subsequent step without additional purification. F_3C-ESI 09 **57** was obtained from **58** by azo coupling with *M*–chlorophenyldiazonium[62] in 46% overall yield.



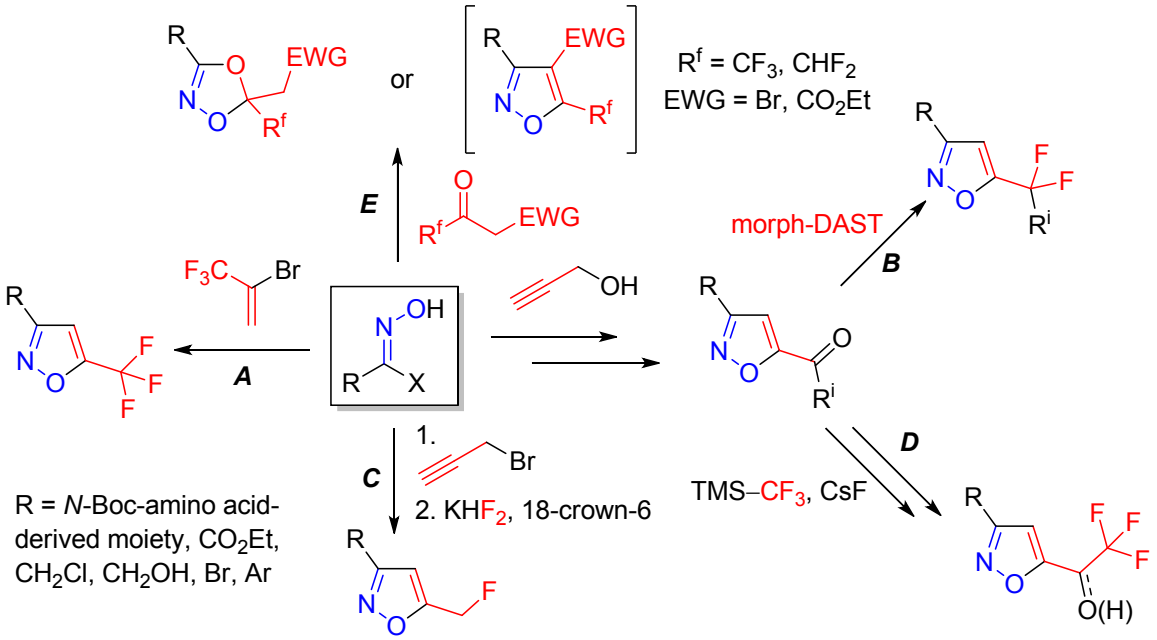
Scheme 17. Fluorinated analogue **57** of EPAC inhibitor ESI-09

Conclusions

Synthetic potential of functionalized halogenoximes for the preparation of fluorinated isoxazole derivatives has been studied thoroughly. As a result, several different approaches were identified (Scheme 18). In particular, one-pot metal-free [3+2] cycloaddition of 2-bromo-3,3,3-trifluoropropene and *in situ* generated nitrile oxides bearing ester, bromine, chloromethyl, aryl and protected amino groups is general and regioselective approach to 3-functionalized 5-(trifluoromethyl)isoxazoles (40–95% yield) (method **A**).

Base-promoted reaction of halogenoximes and propargilic alcohol was used for the preparation of 3-substituted 5-((di)fluoromethyl)isoxazoles. Deoxyfluorination of the resulting 5-(hydroxymethyl)isoxazoles morph-DAST gave the corresponding fluoromethyl derivatives in low yields (6–31%). Meanwhile, deoxofluorination of the corresponding aldehydes (obtained by oxidation of the CH_2OH derivatives with the Parikh – Doering reagent or PCC) was more efficient and gave 5-(difluoromethyl)isoxazoles in 23–61% overall yield (method **B**).

More efficient method for the synthesis of 5-fluoromethyl-substituted derivatives included nucleophilic substitution in the corresponding 5-bromomethyl derivatives (91–98% yield), in turn prepared by [3+2] cycloaddition of halogenoximes and propargyl bromide (61–71% yield) (method **C**). 5-(β,β,β-Trifluoro-α-hydroxyethyl)isoxazoles were prepared by reaction of isoxazole-5-carbaldehydes with the Ruppert – Prakash reagent (44–95% yield) (method **D**). Oxidation of the resulting *N*-Boc-protected amino alcohols led to the corresponding 5-(trifluoroacetyl)isoxazoles, which were obtained as hydrates.



Scheme 18. Summary of methods for the preparation of 5-(fluoroalkyl)isoxazoles developed in this work

Experimental part

The solvents were purified according to the standard procedures.[63] The starting materials **1a–p**, **2**, **4**, **44–47**, **54** and **55** were purchased from commercial sources. Melting points were measured on an automated melting point system. Analytical TLC was performed using silica gel plates. Column chromatography was performed using silica gel (230–400 mesh) as the stationary phase. ^{1}H and ^{13}C NMR spectra were recorded on a NMR spectrometer at 500 MHz for Protons and 126 MHz for Carbon-13 or at 400 MHz for protons and 101 MHz for Carbon-13. Chemical shifts are reported in ppm downfield from TMS as an internal standard. Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, National Taras Shevchenko University of Kyiv. Mass spectra were recorded on an LCMS instrument (chemical ionization (CI)) and GCMS instrument (electron impact ionization (EI)). Preparative flash chromatography was performed on chromatograph using 40 g columns. Optical rotations were measured on polarimeter in MeOH (for amine hydrochlorides) or $CHCl_3$ (in all other cases) using 1-dm cell; optical rotation values are given in 10^{-1} deg cm^2 g^{-1}; concentrations (c) are given in mmol/L, wavelength 589 nm at 20 °C. The enantiomeric excess and retention time (t_R) was determined for major signal by HPLCs. CCDC 1945950 (**3h**) 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.

Calculation methods. All calculations were carried out using TURBOMOLE program package (versions 6.4).[64,65] Geometry optimization and calculation of total energy values were made using DFT (RI-BP86) approximation with the TZVP basis sets, the implemented into the TURBOMOLE set of programs polarized Ahlrich's "triple-zeta" TZV basis sets.[66] The structures corresponding to local minima were re-optimized using Grimme's RI-B97-D, having a dispersion correction.[67–69] For structure 5a a manual conformational analysis was performed searching the most favorable conformation. The found total energy variation for the four conformational isomers was quite small (within few tenths kcal/mol, see the SI for more detail). For locating transition state structures, force constants were calculated and the standard procedure for location of the transition state structures, implemented into the

TURBOMOLE set of program, were used. Vibration frequencies and corrections for calculation of relative energies and relative free Gibbs energies were derived analytically (RI-BP86) or numerically (RI-B97-D). For the structures corresponding to local energy minima no imaginary frequencies were found, whereas for every TS structure only one imaginary frequency was detected. For computing relative energies, the corresponding corrections on vibrations at 0 K (ZPE) were added to the total energies. For deriving relative free Gibbs energy values, chemical potential magnitudes calculated at the standard conditions (pressure: 0.1 MPa, temperature: 298.15 K) with the default scaling coefficient (0.9914) were used as corrections for the both DFT methods. Frontier molecular orbitals (FMO) were presented graphically using the Chemissian program.[57] Corresponding single-point density matrices and NBO atomic charges[58,59] were derived for the isolated molecules of 1,3-dipoles and dipolarophile using the GAUSSIAN-09 set of programs.[70]

General procedure for the preparation of isoxazoles 3a–o.

The corresponding halogenoxime **1a**–**o** (40.2 mmol, 1 eq) was dissolved in EtOAc (100 mL, 0.4 M solution of **1a**–**o**) (NOTE: in the case of **1j**, EtOAc – THF (100 mL, 1:1, v/v) was used), and 2-bromo-3,3,3-trifluoro-1-propene (**2**, 21.1 g, 121 mmol, 3 eq) and $NaHCO_3$ (11.1 g, 133 mmol, 3.3 eq) were added to the vigorously stirred homogeneous solution at rt. The resulting mixture was stirred overnight. The completion of the reaction was monitored by ^1H NMR spectroscopy. Then, the resulting mixture was filtered through a plug of silica gel and evaporated in *vacuo*.

Ethyl 5-(trifluoromethyl)isoxazole-3-carboxylate (3a).[53] The compound was purified by distillation in *vacuo*. Yield 5.81 g (69%, can be scaled up to 95.2 g by using **1a** (100 g, 0.660 mol) and **2** (346 g, 1.98 mol)); colorless oil; bp 39–40 °C / 8.5 mmHg. ^1H NMR (400 MHz, DMSO-d_6) δ 7.91 (d, J = 1.1 Hz, 1H), 4.40 (q, J = 7.1 Hz, 2H), 1.33 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 159.1 (q, J = 42.7 Hz), 158.3, 117.8 (q, J = 270 Hz), 108.0 (q, J = 2.3 Hz), 62.9, 14.1. $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6) δ –64.0. LC/MS (CI): m/z = 210 $[M+H]^+$. Anal. Calcd. for $C_7H_6F_3NO_3$: C, 40.20; H, 2.89; N, 6.70. Found: C, 40.59; H, 3.28; N, 6.84.

3-Phenyl-5-(trifluoromethyl)isoxazole (3b).[71,72] The compound was purified by distillation in *vacuo*. Yield 3.77 g (44%); colorless powder; mp 76–78 °C; sublimation 55–57 °C / 0.8 mmHg. ^1H NMR (400

MHz, DMSO-d_6) δ 8.07 (s, 1H), 7.99 – 7.93 (m, 2H), 7.60 – 7.53 (m, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 163.2, 157.9 (q, J = 41.7 Hz), 131.6, 129.7, 127.4, 127.2, 118.3 (q, J = 270 Hz), 105.9 (d, J = 2.4 Hz). $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6) δ –63.9. GC/MS (EI): m/z = 77 $[Ph]^+$, 144 $[M–CF_3]^+$, 194 $[M–F]^+$, 213 $[M]^+$.Anal. Calcd. for $C_{10}H_6F_3NO$: C, 56.35; H, 2.84; N, 6.57. Found: C, 56.57; H, 2.60; N, 6.29.

3-(4-Methoxyphenyl)-5-(trifluoromethyl)isoxazole (3c). The compound was purified by column chromatography on silica gel (40 g RediSep column; run length: 89.2 CV; flow rate: 60 mL / min; rack: 16 mm × 150 mm tubes) using hexanes – *t*-BuOMe (3:2) as eluent. Yield 7.23 g (74%); beige powder; mp 72–75 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 8.01 (s, 1H), 7.95 – 7.83 (m, 2H), 7.17 – 7.07 (m, 2H), 3.83 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 162.7, 161.9, 157.6 (q, J = 41.6 Hz), 129.0, 119.5, 118.4 (q, J = 270 Hz), 115.1, 105.6, 105.6, 55.7. $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6) δ –63.9. GC/MS (EI): m/z = 76 $[C_6H_4]^+$, 107 $[C_6H_4OMe]^+$, 174 $[M–CF_3]^+$, 224 $[M–F]^+$, 243 $[M]^+$. Anal. Calcd. for $C_{11}H_8F_3NO_2$: C, 54.33; H, 3.32; N, 5.76. Found: C, 54.25; H, 2.99; N, 5.81.

3-(4-Fluorophenyl)-5-(trifluoromethyl)isoxazole (3d). The compound was purified by column chromatography on silica gel (40 g RediSep column; run length: 63.0 CV; flow rate: 60 mL / min; rack: 16 mm × 150 mm tubes) using hexanes – *t*-BuOMe (7:3) as eluent. Yield 6.88 g (73%); colorless powder; mp 45–47 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 8.07 (s, 1H), 8.01 (dd, J = 8.9, 5.3 Hz, 2H), 7.40 (t, J = 8.9 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 164.2 (d, J = 249 Hz), 162.2, 157.9 (q, J = 41.8 Hz), 129.8 (d, J = 8.9 Hz), 123.7 (d, J = 3.3 Hz), 118.3 (q, J = 270 Hz), 116.7 (d, J = 22.1 Hz), 105.7 (q, J = 2.3 Hz). $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6) δ –64.1, –109.9 (tt, J = 8.9, 5.3 Hz). GC/MS (EI): m/z = 162 $[M–CF_3]^+$, 212 $[M–F]^+$, 231 $[M]^+$. Anal. Calcd. for $C_{10}H_5F_4NO$: C, 51.96; H, 2.18; N, 6.06. Found: C, 51.97; H, 2.31; N, 6.01.

3-(Thiophen-2-yl)-5-(trifluoromethyl)isoxazole (3e). The compound was purified by column chromatography on silica gel (40 g RediSep column; run length: 74.0 CV; flow rate: 60 mL / min; rack: 16 mm × 150 mm tubes) using hexanes – $CHCl_3$ (4:1) as eluent. Yield 3.52 g (40%); colorless powder; mp 112–113 °C; sublimation 50–52 °C / 0.4 mmHg. ^1H NMR (400 MHz, DMSO-d_6) δ 8.04 (s, 1H),

7.89 – 7.82 (m, 2H), 7.27 (dd, J = 5.1, 3.7 Hz, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 158.7, 157.6 (q, J = 41.5 Hz), 131.4, 130.7, 128.8, 128.1, 118.2 (q, J = 271 Hz), 105.9 (d, J = 2.4 Hz). $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6) δ –63.8. LC/MS (CI): m/z = 220 $[M+H]^+$. Anal. Calcd. for $C_8H_4F_3NOS$: C, 43.84; H, 1.84; N, 6.39; S, 14.63. Found: C, 43.56; H, 1.65; N, 6.09; S, 14.46.

***tert*-Butyl ((5-(trifluoromethyl)isoxazol-3-yl)methyl)carbamate (3f).** The compound was purified by column chromatography on silica gel using hexanes – $CHCl_3$ (4:1) as eluent. Yield 9.52 g (89%); colorless powder; mp 62–64 °C. In the case of using **1f** (160 g, 0.767 mol), the reaction was performed with **2** (335 g, 1.92 mol) and $NaHCO_3$ (128 g, 1.53 mol), which gave 148 g (73%) of **3f**. ^1H NMR (400 MHz, DMSO-d_6) δ 7.51 (t, J = 5.9 Hz, 1H), 7.24 (s, 1H), 4.27 (d, J = 5.6 Hz, 2H), 1.39 (s, 9H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 163.6, 156.8 (q, J = 41.6 Hz), 155.7, 117.9 (q, J = 270 Hz), 106.2, 78.5, 35.6, 28.1. $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6): δ –63.9. GC/MS (EI): m/z = 57 [t-Bu]$^+$, 150 [M–$NHCO_2t$-Bu]$^+$, 166 [M-CO_2–$H_2C{=}C(CH_3)_2$]$^+$, 193 [M–Ot-Bu]$^+$, 210 [M–$H_2C{=}C(CH_3)_2$]$^+$. Anal. Calcd. for $C_{10}H_{13}F_3N_2O_3$: C, 45.12; H, 4.92; N, 10.52. Found: C, 45.22; H, 4.69; N, 10.89.

(*S*)-*tert*-Butyl (1-(5-(trifluoromethyl)isoxazol-3-yl)ethyl)carbamate (3g). The compound was purified by column chromatography on silica gel (125 g RediSep column; run length: 14.2 CV; flow rate: 100 mL / min; rack: 16 mm × 150 mm tubes) using hexanes – t-BuOMe (7:3) as eluent. Yield 8.11 g (72%); colorless powder; mp 86–88 °C. $[\alpha]^{20}_D$ = –55.3 (c = 35.7, $CHCl_3$), 98% *ee*, t_R = 9.53 min. ^1H NMR (500 MHz, DMSO-d_6) δ 7.52 (d, J = 6.6 Hz, 1H), 7.28 (s, 1H), 4.89 – 4.78 (m, 1H), 1.40 (s, 3H), 1.38 (s, 9H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 167.4, 156.7 (q, J = 41.6 Hz), 154.9, 117.9 (q, J = 270 Hz), 105.4, 78.4, 42.9, 28.0, 19.7. $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6): δ –63.1. GC/MS (EI): m/z = 57 [t-Bu]$^+$, 164 [M–$NHCO_2t$-Bu]$^+$, 180 [M–CO_2–$H_2C{=}C(CH_3)_2$]$^+$, 207 [M–Ot-Bu]$^+$, 224 [M–$H_2C{=}C(CH_3)_2$]$^+$, 265 [M–CH_3]$^+$. Anal. Calcd. for $C_{11}H_{15}F_3N_2O_3$: C, 47.14; H, 5.40; N, 10.00. Found: C, 47.44; H, 5.57; N, 10.27.

(*R*)-*tert*-Butyl (1-(5-(trifluoromethyl)isoxazol-3-yl)ethyl)carbamate (3h). The compound was purified by column chromatography on silica gel using hexanes – t-BuOMe (7:3) as eluent. Yield 8.56 g (76%); colorless powder; mp 86–88 °C. $[\alpha]^{20}_D$ = +53.2 (c = 35.7, $CHCl_3$), 96% *ee*, t_R = 10.4 min. The spectral data are analogous to that of *S*-isomer **3g**. LC/MS (CI): m/z = 165 [M–$NHCO_2t$-Bu+H]$^+$, 181

$[M–CO_2–H_2C=C(CH_3)_2]^+$, 208 $[M–Ot\text{-}Bu+H]^+$, 225 $[M–H_2C=C(CH_3)_2+H]^+$. Anal. Calcd. for $C_{11}H_{15}F_3N_2O_3$: C, 47.14; H, 5.40; N, 10.00. Found: C, 46.85; H, 5.64; N, 10.11.

***tert*-Butyl (2-(5-(trifluoromethyl)isoxazol-3-yl)propan-2-yl)carbamate (3i).** The compound was purified by HPLC (SunFire C_{18} Column, 100 Å, 3.5 μm, 4.6 mm × 150 mm, 0–9.5 min; H_2O – MeCN; flow rate 30mL / min) or by column chromatography on silica gel using hexanes – *t*-BuOMe (7:3) as eluent. Yield 10.1 g (85%); colorless powder; mp 79–81 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.46 – 7.33 (m, 1H), 7.30 (s, 1H), 1.53 (s, 6H), 1.32 (s, 9H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (s, 1H), 4.96 (s, 1H), 1.66 (s, 6H), 1.37 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 169.8, 158.3 (q, J = 42.3 Hz), 154.3, 117.9 (q, J = 270 Hz), 103.8, 80.1, 51.4, 28.2, 27.9. ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ –64.2. GC/MS (EI): *m/z* = 57 $[t\text{-}Bu]^+$, 178 $[M–NHCO_2t\text{-}Bu]^+$, 194 $[M–CO_2–H_2C=C(CH_3)_2]^+$, 221 $[M–Ot\text{-}Bu]^+$, 238 $[M–H_2C=C(CH_3)_2]^+$. Anal. Calcd. for $C_{12}H_{17}F_3N_2O_3$: C, 48.98; H, 5.82; N, 9.52. Found: C, 49.01; H, 6.07; N, 9.52.

***tert*-Butyl 3-(5-(trifluoromethyl)isoxazol-3-yl)azetidine-1-carboxylate (3j).** The compound was purified by column chromatography on silica gel (80 g RediSep column; run length: 20.7 CV; flow rate: 60 mL / min; rack: 16 mm × 150 mm tubes) using hexanes – *t*-BuOMe (7:3) as eluent. Yield 4.93 g (42% if the reaction was performed in EtOAc) or 9.51 g (81% if the reaction was performed in EtOAc – THF); colorless powder; mp 57–58 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.64 (s, 1H), 4.23 (d, J = 6.8 Hz, 2H), 4.04 – 3.93 (m, 3H), 1.39 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 166.0, 157.5 (d, J = 41.5 Hz), 155.9, 117.0 (q, J = 276 Hz), 106.9, 54.1, 28.5, 25.3. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6): δ –63.7. GC/MS (EI): *m/z* = 57 $[t\text{-}Bu]^+$, 192 $[M–CO_2–H_2C=C(CH_3)_2]^+$, 219 $[M–Ot\text{-}Bu]^+$, 236 $[M–H_2C=C(CH_3)_2]^+$. Anal. Calcd. for $C_{12}H_{15}F_3N_2O_3$: C, 49.32; H, 5.17; N, 9.59. Found: C, 49.62; H, 5.43; N, 9.46.

(*S*)-*tert*-Butyl 2-(5-(trifluoromethyl)isoxazol-3-yl)pyrrolidine-1-carboxylate (3k). The compound; purified by column chromatography on silica gel (125 g RediSep column; run length: 18.2 CV; flow rate: 100 mL / min; rack: 16 mm × 150 mm tubes) using hexanes – *t*-BuOMe (3:2) as eluent; existed as *ca*. 5:4 mixture of rotamers. Yield 11.6 g (94%); white crystals; mp 55–58 °C; bp 82–84 °C / 1 mmHg.

$[\alpha]^{20}_D$ = –60.3 (*c* = 32.7, $CHCl_3$), 99% *ee*, t_R =6.93 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.43 (d, *J* = 44.6 Hz, 1H), 5.02 – 4.86 (m, 1H), 3.53 – 3.37 (m, 2H), 2.33 (s, 1H), 1.90 (d, *J* = 5.2 Hz, 3H), 1.39 (s, 4H), 1.20 (s, 5H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 168.2 and 167.5, 157.0 (q, *J* = 41.5 Hz), 154.1 and 153.3, 118.4 (q, *J* = 270 Hz), 106.2 and 105.9, 79.5 and 79.3, 53.4, 46.9 and 46.7, 33.2 and 31.9, 28.5 and 28.2, 24.0 and 23.4. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6): *δ* –63.6 and –63.8. GC/MS (EI): *m/z* = 57 [*t*-Bu]$^+$, 206 [M–CO_2–H_2C=$C(CH_3)_2$]$^+$, 233 [M–O*t*-Bu]$^+$, 250 [M–H_2C=$C(CH_3)_2$]$^+$. Anal. Calcd. for $C_{13}H_{17}F_3N_2O_3$: C, 50.98; H, 5.59; N, 9.15. Found: C, 50.67; H, 5.86; N, 8.86.

(*R*)-*tert*-Butyl 2-(5-(trifluoromethyl)isoxazol-3-yl)pyrrolidine-1-carboxylate (3l). The compound; purified by column chromatography on silica gel (125 g RediSep column; run length: 18.2 CV; flow rate: 100 mL / min; rack: 16 mm × 150 mm tubes) using hexanes – *t*-BuOMe (3:2) as eluent; existed as *ca*. 5:4 mixture of rotamers. Yield 11.7 g (95%); white crystals; mp 56–58 °C. $[\alpha]^{20}_D$ = +61.6 (*c* = 32.7, $CHCl_3$), 100% *ee*, t_R = 6.18 min. The spectral data are analogous to that of *S*-isomer **3k**. LC/MS (CI): *m/z* = 207 [M–CO_2–H_2C=$C(CH_3)_2$+H]$^+$, 251 [M–H_2C=$C(CH_3)_2$+H]$^+$. Anal. Calcd. for $C_{13}H_{17}F_3N_2O_3$: C, 50.98; H, 5.59; N, 9.15. Found: C, 51.16; H, 5.51; N, 8.83.

***tert*-Butyl 4-(5-(trifluoromethyl)isoxazol-3-yl)piperidine-1-carboxylate (3m).** The compound; purified by column chromatography on silica gel (40 g RediSep column; run length: 47.0 CV; flow rate: 55 mL / min; rack: 16 mm × 150 mm tubes) using gradient CH_2Cl_2 – MeCN or hexanes – *t*-BuOMe (7:3) as eluent. Yield 7.34 g (57%); colorless powder; mp 78–79 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.51 (d, *J* = 2.8 Hz, 1H), 3.98 (d, *J* = 11.0 Hz, 2H), 3.10 – 2.99 (m, 1H), 2.88 (s, 2H), 1.89 (d, *J* = 12.8 Hz, 2H), 1.61 – 1.47 (m, 2H), 1.40 (d, *J* = 3.7 Hz, 9H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 168.1, 157.0 (q, *J* = 41.4 Hz), 154.3, 118.4 (q, *J* = 270 Hz), 106.3, 79.1, 43.3, 33.7, 30.3, 28.5. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ –63.8. GC/MS (EI): *m/z* = 57 [*t*-Bu]$^+$, 220 [M–CO_2–H_2C=$C(CH_3)_2$]$^+$, 247 [M–O*t*-Bu]$^+$, 264 [M–H_2C=$C(CH_3)_2$]$^+$. Anal. Calcd. for $C_{14}H_{19}F_3N_2O_3$: C, 52.50; H, 5.98; N, 8.75. Found: C, 52.16; H, 6.18; N, 8.54.

***tert*-Butyl (*S*)-2,2-dimethyl-4-(5-(trifluoromethyl)isoxazol-3-yl)oxazolidine-3-carboxylate (3n).** The compound was purified by HPLC (SunFire C18 Column, 100 Å, 3.5 μm, 4.6 mm×150 mm, 0–6.5

min; H_2O – MeOH; flow rate 30mL / min); existed as *ca*. 5:4 mixture of rotamers. Yield 5.41 g (40%); colorless solid; mp 43–45 °C. $[\alpha]^{20}_D$ = –66.2 (*c* = 29.7, $CHCl_3$), 99% *ee*, t_R = 7.33 min. ^1H NMR (400 MHz, $CDCl_3$) δ 6.65 (s, 1H), 5.22 – 4.97 (m, 1H), 4.26 (d, *J* = 13.5 Hz, 2H), 1.69 (s, 1H), 1.57 (s, 5H), 1.48 (s, 4H), 1.33 (s, 5H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 165.2 and 164.6, 158.8 (q, *J* = 46.2, 44.6 Hz), 152.1 and 151.2, 117.7 (q, *J* = 270 Hz), 104.4 and 103.5, 94.8 and 94.3, 81.3 and 80.8, 67.9 and 67.1, 53.6 and 53.3, 28.1 and 28.1, 27.0 and 26.1, 24.2 and 23.2. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ –64.8 and –64.9. LC/MS (CI): *m/z* = 223 $[M–CH_3–CO_2–H_2C=C(CH_3)_2+H]^+$, 237 $[M–CO_2–H_2C=C(CH_3)_2+H]^+$, 322 $[M–CH_3+H]^+$. Anal. Calcd. for $C_{14}H_{19}F_3N_2O_4$: C, 50.00; H, 5.69; N, 8.33. Found: C, 50.01; H, 5.43; N, 8.11.

***tert*-Butyl (*R*)-2,2-dimethyl-4-(5-(trifluoromethyl)isoxazol-3-yl)oxazolidine-3-carboxylate (3o).** The compound was purified by HPLC (SunFire C_{18} Column, 100 Å, 3.5 μm, 4.6 mm × 150 mm, 0–6.5 min; H_2O – MeOH; flow rate 30mL / min); existed as *ca*. 5:4 mixture of rotamers. Yield 5.68 g (42%); colorless solid; mp 43–45 °C. $[\alpha]^{20}_D$ = +70.8 (*c* = 29.7, $CHCl_3$), 100% *ee*, t_R = 6.45 min. The spectral data are analogous to that of *S*-isomer **3n**. Anal. Calcd. for $C_{14}H_{19}F_3N_2O_4$: C, 50.00; H, 5.69; N, 8.33. Found: C, 50.22; H, 5.64; N, 8.59.

3,5-Dibromo-5-(trifluoromethyl)-4,5-dihydroisoxazole (5). Hydroxycarbonimidic dibromide (**4**, 8.15 g, 40.2 mmol) was dissolved in CH_2Cl_2 (100 mL), and 2-bromo-3,3,3-trifluoro-1-propene (**2**, 21.1 g, 121 mmol) and $NaHCO_3$ (11.1 g, 133 mmol) were added to the vigorously stirred homogeneous solution at rt. The resulting mixture was stirred overnight. The completion of the reaction was monitored by ^1H NMR spectroscopy. Then, the resulting mixture was filtered through a plug of silica gel and evaporated in *vacuo*. The compound was purified by distillation in *vacuo*. Yield 7.52 g (63%); yellowish oil; bp 57–59 °C / 17 mmHg. ^1H NMR (400 MHz, $CDCl_3$) δ 4.08 (d, *J* = 19.3 Hz, 1H), 3.83 (d, *J* = 19.3 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 140.3, 120.6 (q, *J* = 281 Hz), 92.3 (q, *J* = 37.3 Hz), 56.2. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ –78.3. GC/MS (EI): *m/z* = 216/218 $[M–Br]^+$, 295/297/299 $[M]^+$. Anal. Calcd. for $C_4H_2Br_2F_3NO$: C, 16.18; H, 0.68; N, 4.72; Br, 53.83. Found: C, 16.30; H, 0.69; N, 4.77; Br, 53.92.

3-Bromo-5-(trifluoromethyl)isoxazole (6). Method A: Hydroxycarbonimidic dibromide (**4**, 8.15 g, 40.2 mmol) was dissolved in EtOAc (100 mL), and 2-bromo-3,3,3-trifluoro-1-propene (**2**, 21.1 g, 121 mmol) and $NaHCO_3$ (30.3 g, 363 mmol) were added to the vigorously stirred homogeneous solution at rt. The resulting mixture was stirred overnight. The completion of the reaction was monitored by ^1H NMR spectroscopy. Then, the mixture was filtered through a plug of silica gel and evaporated in *vacuo*. **Method B:** The corresponding dihydroisoxazole **5** (7.00 g, 23.6 mmol) was dissolved in EtOAc (100 mL) and $NaHCO_3$ (5.94 g, 70.8 mol) was added. The resulting mixture was stirred at rt overnight, the solvent was evaporated in *vacuo*. The compound was purified by distillation in *vacuo*. Yield 5.29 g (61% from **4** *via* Method **A**) or 2.91 g (57% from **5** *via* Method **B**); colorless oil; bp 33–35 °C / 94 mmHg. ^1H NMR (400 MHz, $CDCl_3$) δ 6.78 (s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 160.0 (q, J = 43.6 Hz), 140.5, 116.9 (q, J = 271 Hz), 108.9 (q, J = 2.2 Hz). $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ –65.3. GC/MS (EI): *m/z* = 146/148 $[M–CF_3]^+$, 215/217 $[M]^+$. Anal. Calcd. for C_4HBrF_3NO: C, 22.25; H, 0.47; N, 6.49; Br, 37.00. Found: C, 22.24; H, 0.38; N, 6.49; Br, 36.92.

General procedure for the preparation of carboxylic acid 10 and 29

A solution of the corresponding ester **3a** or **28** (0.335 mol, 1 eq) in MeOH (700 mL, 0.5 M solution of ester) was cooled to 0 °C, and pre-cooled absolute solution of NaOH (14.0.g, 0.351 mol, 1.05 eq) in MeOH (61 mL, 5.75 M solution of NaOH) was added dropwise (NOTE: the reaction is highly exothermic). After addition, the mixture was stirred for 1 h at 0 °C to rt, and evaporated in *vacuo* to dryness. Then, 6 M aq HCl (50 mL) was added in portions, and the reaction mixture was stirred for 10 min at rt (NOTE: MeOH traces led to formation of the corresponding methyl esters *via* the trans-esterification reaction). Most of solvents was evaporated in *vacuo*, the residue was diluted with CH_2Cl_2 (500 mL), dried over Na_2SO_4, and evaporated in *vacuo*.

5-(Trifluoromethyl)isoxazole-3-carboxylic acid (10). The compound; purified by column chromatography on silica gel (330 g RediSep column; run length: 14.7 CV; flow rate: 100 mL / min; rack: 16 mm × 150 mm tubes) using gradient hexanes – *t*-BuOMe. Yield 41.2 g (68%); white crystals; mp 109–111 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 9.59 (br s, 1H), 7.17 (s, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 162.6, 160.9 (q, J = 43.8 Hz), 155.8, 117.2 (q, J = 271 Hz), 106.2 (q, J = 2.2 Hz). $^{19}F\{^1H\}$

NMR (376 MHz, $CDCl_3$) δ –64.5. LC/MS: *m/z* = 136 $[M–CO_2–H]^-$. Anal. Calcd. for $C_5H_2F_3NO_3$: C, 33.17; H, 1.11; N, 7.74. Found: C, 33.30; H, 0.86; N, 7.52.

5-(Difluoromethyl)isoxazole-3-carboxylic acid (29). Yield 39.9 g (73%); gray powder; mp 121–122 °C. ^1H NMR (400 MHz, D_2O) δ 6.97 (s, 1H), 6.87 (t, *J* = 52.0 Hz, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, D_2O) δ 165.0 (t, *J* = 30.4 Hz), 161.9, 157.4, 107.1 (t, *J* = 238 Hz), 105.1 (t, *J* = 2.7 Hz). $^{19}F\{^1H\}$ NMR (376 MHz, D_2O) δ –119.5. LC/MS: *m/z* = 118 $[M–CO_2–H]^-$. Anal. Calcd. for $C_5H_3F_2NO_3$: C, 36.83; H, 1.85; N, 8.59. Found: C, 37.20; H, 1.95; N, 8.43.

(5-(Trifluoromethyl)isoxazol-3-yl)methanol (11).[73] A solution of ester **3a** (10.0 g, 47.8 mmol) in CH_2Cl_2 (150 mL) was cooled to –5 °C, and DIBAL (17.8 mL, 14.2 g, 0.100 mol) was added dropwise. After addition, the resulting mixture was stirred at 0 °C for 1 h, and 6 M aq HCl (*ca.* 50 mL) was added in small portions until pH = 4 was reached (NOTE: extensive gas evolution was observed). The precipitate formed was filtered off, the filtrate was evaporated in *vacuo*. Yield 6.47 g (81%); colorless liquid. ^1H NMR (400 MHz, DMSO-d_6) δ 7.36 (s, 1H), 5.69 (t, *J* = 5.9 Hz, 1H), 4.59 (d, *J* = 6.0 Hz, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 165.6, 156.8 (q, *J* = 41.7 Hz), 118.1 (q, *J* = 270 Hz), 106.2, 54.7. $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6) δ –64.2. GC/MS (EI): *m/z* = 167 $[M]^+$. Anal. Calcd. for $C_5H_4F_3NO_2$: C, 35.94; H, 2.41; N, 8.38. Found: C, 35.91; H, 2.49; N, 8.26.

3-(Chloromethyl)-5-(trifluoromethyl)isoxazole (12). Method A: The halogenoxime **1p** (146 g; 1.14 mol) was dissolved in EtOAc (3000 mL), and 2-bromo-3,3,3-trifluoro-1-propene (**2**, 600 g; 3.43 mol) and $NaHCO_3$ (316 g, 3.76 mol) were added to the vigorously stirred homogeneous solution at rt. The resulting mixture was stirred overnight. The completion of the reaction was monitored by ^1H NMR spectroscopy. The, the reaction mixture was filtered through a plug of silica gel and evaporated in *vacuo*. **Method B:** A solution of alcohol **11** (4.60 g, 27.5 mmol) in CH_2Cl_2 was cooled to –5 °C, and a drop of DMF (5.00 μL, 4.74 mg) was added. Then, $SOCl_2$ (2.29 mL, 3.76 g, 31.6 mmol) was added dropwise. The completion of reaction was monitored by ^1H NMR (*ca.* 10 h). Then, the reaction mixture was evaporated in *vacuo.* The compound was purified by distillation in *vacuo*. Yield 97.3 g (46% from **1p** *via* Method **A**) or 3.28 g (64% from **11** *via* Method **B**); colorless liquid; bp 39–41 C / 60 mmHg. ^1H NMR (400 MHz, $CDCl_3$) δ 6.83 (s, 1H), 4.63 (s, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 161.4, 159.6

(q, J = 42.9 Hz), 117.7 (q, J = 270 Hz), 105.2, 34.8. $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ –65.4. GC/MS (EI): *m/z* = 185/187 $[M]^+$. Anal. Calcd. for $C_5H_3ClF_3NO$: C, 32.37; H, 1.63; N, 7.55; Cl, 19.11. Found: C, 32.35; H, 1.42; N, 7.70; Cl, 18.96.

General procedure for the preparation of amines 13f–m·HCl, 13i, 20i–l·HCl and 21g–l·HCl.

The corresponding *N*-Boc-amine **3f**–**m**, **18i–l** or **19g–l** (4.80 mmol, 1 eq) was dissolved in MeOH (9 mL, 0.53 M solution of **3**, **18** or **19**) and the solution was cooled to –1 °C. Acetyl chloride (412 μL, 455 mg, 5.80 mmol, 1.2 eq) was added dropwise at –1 °C. The completion of the reaction was monitored by NMR. Then, most of MeOH was evaporated in *vacuo* (NOTE: if necessary, the resulting solid was recrystallized from MeCN (*ca.* 1 mL) unless other is specified).

(5-(Trifluoromethyl)isoxazol-3-yl)methanamine hydrochloride (13f·HCl). Yield 924 mg (95%); colorless powder; mp 95–97 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.87 (br s, 3H), 7.63 (s, 1H), 4.28 (s, 2H). $^{13}C\{^{1}H\}$ NMR (126 MHz, DMSO-d_6) δ 159.6, 156.9 (q, J = 42.0 Hz), 117.7 (q, J = 270 Hz), 107.4, 34.1. $^{19}F\{^{1}H\}$ NMR (376 MHz, DMSO-d_6): δ –64.2. LC/MS (CI): *m/z* = 167 $[M–HCl+H]^+$. Anal. Calcd. for $C_5H_6ClF_3N_2O$: C, 29.65; H, 2.99; N, 13.83; Cl, 17.50. Found: C, 29.43; H, 2.99; N, 13.76; Cl, 17.39.

(*S*)-1-(5-(Trifluoromethyl)isoxazol-3-yl)ethan-1-amine hydrochloride (13g·HCl). Yield 936 mg (93%); beige powder; mp 93–96 °C. $[\alpha]^{20}_D$ = -4.02 (*c* = 46.2, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.11 (br.s, 3H), 7.79 (s, 1H), 4.71 (dd, J = 13.2, 6.5 Hz, 1H), 1.61 (d, J = 6.8 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (126 MHz, DMSO-d_6) δ 163.7, 157.2 (q, J = 42.4 Hz), 117.7 (q, J = 270 Hz), 106.5, 42.9, 17.9. $^{19}F\{^{1}H\}$ NMR (376 MHz, DMSO-d_6): δ –63.8. LC/MS (CI): *m/z* = 181 $[M–HCl+H]^+$. Anal. Calcd. for $C_6H_8ClF_3N_2O$: C, 33.27; H, 3.72; N, 12.93; Cl, 16.37. Found: C, 32.95; H, 3.98; N, 12.59; Cl, 16.60.

(*R*)-1-(5-(Trifluoromethyl)isoxazol-3-yl)ethan-1-amine hydrochloride (13h·HCl). Yield 956 mg (92%); beige powder; mp 94–96 °C. $[\alpha]^{20}_D$ = +4.61 (*c* = 46.2, MeOH). The spectral data are analogous to that of *S*-isomer **13g·HCl**. LC/MS (CI): *m/z* = 181 $[M–HCl+H]^+$. Anal. Calcd. for $C_6H_8ClF_3N_2O$: C, 33.27; H, 3.72; N, 12.93; Cl, 16.37. Found: C, 33.04; H, 4.10; N, 12.80; Cl, 16.32.

2-(5-(Trifluoromethyl)isoxazol-3-yl)propan-2-amine (13i). The resulting **13i·HCl** (864 mg, 78% yield) was dissolved in MeOH (5 mL), and NaOH (196 mg, 4.90 mmol) in MeOH (1 mL) was added at rt. The resulting mixture was stirred for 2 h, the filtered and evaporated in *vacuo*. The compound was purified by distillation in *vacuo*. Yield 475 mg (51%); beige powder; mp 146–149 °C (as a hydrochloride); bp 54–56 °C / 9 mmHg (as a base). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.51 (s, 1H), 2.24 (s, 2H), 1.40 (s, 6H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 173.2, 156.3 (q, J = 41.4 Hz), 118.0 (q, J = 270 Hz), 105.3, 49.4, 29.5. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6): δ –64.4. LC/MS (CI): *m/z* = 195 $[M+H]^+$. Anal. Calcd. for $C_7H_9F_3N_2O$: C, 43.30; H, 4.67; N, 14.43. Found: C, 43.26; H, 4.84; N, 14.52

3-(Azetidin-3-yl)-5-(trifluoromethyl)isoxazole hydrochloride (13j·HCl). Yield 1.04 g (95%); beige powder; mp 106–109 °C ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.58 (br. s, 2H), 7.79 (s, 1H), 4.34 – 4.26 (m, 5H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 164.5, 157.4 (q, J = 41.9 Hz), 118.3 (q, J = 270 Hz), 107.2, 49.4, 28.2. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6): δ –63.9. LC/MS (CI): *m/z* = 193 $[M–HCl+H]^+$. Anal. Calcd. for $C_7H_8ClF_3N_2O$: C, 36.78; H, 3.53; N, 12.25; Cl, 15.51. Found: C, 36.94; H, 3.61; N, 12.28; Cl, 15.15.

(*S*)-3-(Pyrrolidin-2-yl)-5-(trifluoromethyl)isoxazole hydrochloride (13k·HCl). Yield 1.13 g (97%); beige powder; mp 96–98 °C. $[\alpha]^{20}_D$ = -16.2 (c = 41.2, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.24 (d, J = 281 Hz, 2H), 7.80 (s, 1H), 4.88 (t, J = 7.5 Hz, 1H), 3.40 – 3.26 (m, 2H), 2.47 – 2.39 (m, 1H), 2.24 – 1.95 (m, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 161.7, 157.6 (q, J = 42.0 Hz), 118.1 (q, J = 270 Hz), 107.6 (d, J = 2.1 Hz), 53.9, 45.1, 29.6, 23.3. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6): δ –63.9. LC/MS (CI): *m/z* = 207 $[M–HCl+H]^+$. Anal. Calcd. for $C_8H_{10}ClF_3N_2O$: C, 39.60; H, 4.15; N, 11.55; Cl, 14.61. Found: C, 39.52; H, 3.86; N, 11.36; Cl, 14.84.

(*R*)-3-(Pyrrolidin-2-yl)-5-(trifluoromethyl)isoxazole hydrochloride (13l·HCl). Yield 1.14 g (98%); beige powder; mp 97–99 °C. $[\alpha]^{20}_D$ = +16.7 (c = 41.2, MeOH). The spectral data are analogous to that of *S*-isomer **13k·HCl**. LC/MS (CI): *m/z* = 207 $[M–HCl+H]^+$. Anal. Calcd. for $C_8H_{10}ClF_3N_2O$: C, 39.60; H, 4.15; N, 11.55; Cl, 14.61. Found: C, 39.92; H, 4.52; N, 11.27; Cl, 14.42.

3-(Piperidin-4-yl)-5-(trifluoromethyl)isoxazole hydrochloride (13m·HCl). Yield 1.14 g (92%); colorless powder; mp 153–155 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.03 (s, 2H), 7.49 (s, 1H), 3.29 (s, 2H), 3.19 (t, J = 11.4 Hz, 1H), 3.01 (t, J = 12.3 Hz, 2H), 2.14 (d, J = 13.3 Hz, 2H), 1.87 (qd, J = 15.1, 3.8 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 167.2, 157.2 (q, J = 41.5 Hz), 118.4 (q, J = 270 Hz), 106.5 (d, J = 2.0 Hz), 42.7, 31.5, 26.8. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ –63.8. LC/MS (CI): m/z = 221 [M–HCl+H]$^{+}$. Anal. Calcd. for $C_9H_{12}ClF_3N_2O$: C, 42.12; H, 4.71; N, 10.92; Cl, 13.81. Found: C, 41.74; H, 4.37; N, 10.59; Cl, 13.49.

2-(5-(Fluoromethyl)isoxazol-3-yl)propan-2-amine hydrochloride (20i·HCl). Yield 859 mg (92%); yellow powder, mp 154–155 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.99 (br.s, 3H), 7.08 (d, J = 3.2 Hz, 1H), 5.61 (d, J = 47.0 Hz, 2H), 1.65 (s, J = 37.0 Hz, 6H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 167.2 (d, J = 18.8 Hz), 166.2 (d, J = 2.6 Hz), 103.6 (d, J = 4.5 Hz), 74.0 (d, J = 163 Hz), 51.7, 25.7. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6): δ –215.0 (td, J = 47.0, 3.3 Hz). LC/MS (CI): m/z = 159 [M–HCl+H]$^{+}$. Anal. Calcd. for $C_7H_{12}ClFN_2O$: C, 43.20; H, 6.21; N, 14.39; Cl, 18.21. Found: C, 42.85; H, 5.85; N, 14.54; Cl, 18.54.

(*S*)-5-(Fluoromethyl)-3-(pyrrolidin-2-yl)isoxazole hydrochloride (20k·HCl). Yield 768 mg (94%); yellow powder; mp 166–167 °C. $[\alpha]^{20}_{D}$ = –21.2 (c = 48.4, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.13 (d, J = 353 Hz, 2H), 7.05 (d, J = 3.2 Hz, 1H), 5.63 (d, J = 47.0 Hz, 2H), 4.82 – 4.69 (m, 1H), 3.34 – 3.24 (m, 2H), 2.40 (dt, J = 14.4, 5.8 Hz, 1H), 2.09 – 2.02 (m, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 167.6 (d, J = 18.7 Hz), 160.7 (d, J = 2.7 Hz), 105.4 (d, J = 4.5 Hz), 74.4 (d, J = 164 Hz), 54.4, 45.0, 29.7, 23.2. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6): δ –215.0 (t, J = 47.0 Hz). LC/MS (CI): m/z = 171 [M–HCl+H]$^{+}$. Anal. Calcd. for $C_8H_{12}ClFN_2O$: C, 46.50; H, 5.85; N, 13.56; Cl, 17.15. Found: C, 46.20; H, 6.18; N, 13.54; Cl, 17.20.

(*R*)-5-(Fluoromethyl)-3-(pyrrolidin-2-yl)isoxazole hydrochloride (20l·HCl). Yield 760 mg (95%); yellow powder; mp 166–167 °C. $[\alpha]^{20}_{D}$ = +24.3 (c = 48.4, MeOH). The spectral data are analogous to that of *S*-isomer **20k·HCl**. LC/MS (CI): m/z = 171 [M–HCl+H]$^{+}$. Anal. Calcd. for $C_8H_{12}ClFN_2O$: C, 46.50; H, 5.85; N, 13.56; Cl, 17.15. Found: C, 46.54; H, 5.68; N, 13.47; Cl, 17.22.

(*S*)-1-(5-(Difluoromethyl)isoxazol-3-yl)ethanamine hydrochloride (21g·HCl). Yield 915 mg (96%); beige powder; mp 99–101 °C. $[\alpha]^{20}_{D} = -7.59$ (*c* = 50.4, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.01 (s, 3H), 7.44 (t, *J* = 52.5 Hz, 1H), 7.33 (s, 1H), 4.66 (dd, *J* = 13.3, 6.5 Hz, 1H), 1.58 (d, *J* = 6.7 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 163.8 (t, *J* = 28.7 Hz), 163.5, 108.0 (t, *J* = 237 Hz), 105.0, 43.5, 18.6. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6): δ –118.7 (d, *J* = 52.5 Hz). LC/MS (CI): *m/z* = 163 [M–HCl+H]$^+$. Anal. Calcd. for $C_6H_9ClF_2N_2O$: C, 36.29; H, 4.57; N, 14.11; Cl, 17.85. Found: C, 36.42; H, 4.65; N, 13.97; Cl, 17.89.

(*R*)-1-(5-(Difluoromethyl)isoxazol-3-yl)ethanamine hydrochloride (21h·HCl). Yield 906 mg (95%); beige powder; mp 99–101 °C. $[\alpha]^{20}_{D} = +8.23$ (*c* = 50.4, MeOH). The spectral data are analogous to that of *S*-isomer **21g·HCl**. LC/MS (CI): *m/z* = 163 [M–HCl+H]$^+$. Anal. Calcd. for $C_6H_9ClF_2N_2O$: C, 36.29; H, 4.57; N, 14.11; Cl, 17.85. Found: C, 36.04; H, 4.27; N, 14.27; Cl, 18.20.

2-(5-(Difluoromethyl)isoxazol-3-yl)propan-2-amine hydrochloride (21i·HCl). Yield 949 mg (93%); colorless powder; mp 107-109 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.05 (br.s, 3H), 7.43 (t, *J* = 52.6 Hz, 1H), 7.40 (s, 1H), 1.67 (s, 6H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 166.3, 163.5 (t, *J* = 29.0 Hz), 107.6 (t, *J* = 237 Hz), 103.7, 51.8, 25.6. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6): δ –118.8. LC/MS (CI): *m/z* = 177 [M–HCl+H]$^+$. Anal. Calcd. for $C_7H_{11}ClF_2N_2O$: C, 39.54; H, 5.21; N, 13.18; Cl, 16.67. Found: C, 39.25; H, 4.92; N, 13.58; Cl, 16.52.

3-(Azetidin-3-yl)-5-(difluoromethyl)isoxazole hydrochloride (21j·HCl). Yield 920 mg (91%); orange powder; mp 83–86 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.68 (s, 2H), 7.42 (t, *J* = 52.6 Hz, 1H), 7.33 (s, 1H), 4.43 – 4.19 (m, 3H), 4.14 – 4.03 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 163.4, 163.3 (t, *J* = 28.8 Hz), 107.7 (t, *J* = 236 Hz), 104.7 (t, *J* = 3.4 Hz), 49.2, 27.8. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6): δ –118.6 (d, *J* = 52.6 Hz). LC/MS (CI): *m/z* = 175 [M–HCl+H]$^+$. Anal. Calcd. for $C_7H_9ClF_2N_2O$: C, 39.92; H, 4.31; N, 13.30; Cl, 16.83. Found: C, 40.25; H, 4.12; N, 13.60; Cl, 16.55.

(*S*)-5-(Difluoromethyl)-3-(pyrrolidin-2-yl)isoxazole hydrochloride (21k·HCl). Yield 1.04 g (96%); beige powder; mp 133–135 °C. $[\alpha]^{20}_{D} = -18.6$ (*c* = 44.5, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.00 (d, *J* = 298 Hz, 2H), 7.44 (t, *J* = 52.5 Hz, 1H), 7.32 (s, 1H), 4.91 – 4.77 (m, 1H), 2.49 – 2.30 (m,

2H), 2.19 – 1.97 (m, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) δ 163.9 (t, J = 28.9 Hz), 161.1, 108.0 (t, J = 237 Hz), 105.6 (d, J = 3.2 Hz), 54.1, 45.1, 29.6, 23.3. $^{19}F\{^{1}H\}$ NMR (376 MHz, DMSO-d_6) δ -118.7 (dd, J = 52.4, 1.2 Hz). LC/MS (CI): m/z = 189 $[M–HCl+H]^+$. Anal. Calcd. for $C_8H_{11}ClF_2N_2O$: C, 42.77; H, 4.94; N, 12.47; Cl, 15.78. Found: C, 42.86; H, 5.25; N, 12.82; Cl, 15.95.

(*R*)-5-(Difluoromethyl)-3-(pyrrolidin-2-yl)isoxazole hydrochloride (21l·HCl). Yield 1.06 g (98%); beige powder; mp 133–135 °C. $[\alpha]^{20}_D$ = +18.9 (c = 44.5, MeOH). The spectral data are analogous to that of *S*-isomer **21k**·HCl. LC/MS (CI): m/z = 189 $[M–HCl+H]^+$. Anal. Calcd. for $C_8H_{11}ClF_2N_2O$: C, 42.77; H, 4.94; N, 12.47; Cl, 15.78. Found: C, 42.71; H, 5.27; N, 12.13; Cl, 15.65.

General procedure for the preparation of alcohols 16f–m, 23, and 24.

The corresponding halogenoxime **1a**, **1f**–**m**, or **4** (40.2 mmol, 1 eq) was dissolved in EtOAc (100 mL, 0.4 M solution of **1** or **4**). Propargyl alcohol (2.93 g, 52.3 mmol, 1.3 eq) and $NaHCO_3$ (5.74 g, 68.3 mmol, 1.7 eq) were added to the vigorously stirred homogeneous solution at rt. The resulting mixture was stirred overnight; the completion of reaction was monitored by ^{1}H NMR spectroscopy. Next, the solution was filtered through a plug of silica gel and evaporated in *vacuo*.

***tert*-Butyl ((5-(hydroxymethyl)isoxazol-3-yl)methyl)carbamate (16f).** The compound; purified by column chromatography on silica gel (24 g RediSep column; run length: 33.5 CV; flow rate: 100 mL / min; rack: 16 mm × 150 mm tubes) using gradient hexanes – *t*-BuOMe as eluent**.** Yield 8.63 g (94%); yellowish powder; mp 58–60 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.50 – 7.33 (m, 1H), 6.21 (s, 1H), 5.61 (t, J = 6.4 Hz, 1H), 4.52 (d, J = 3.3 Hz, 2H), 4.12 (d, J = 4.4 Hz, 2H), 1.38 (s, 9H). $^{13}C\{^{1}H\}$ NMR (126 MHz, DMSO-d_6): δ 173.0, 162.4, 155.8, 100.8, 78.3, 54.8, 35.6, 28.2. GC/MS (EI): m/z = 57 $[t\text{-Bu}]^+$, 112 $[M–NHCO_2t\text{-Bu}]^+$, 128 $[M–CO_2–H_2C{=}C(CH_3)_2]^+$, 155 $[M–Ot\text{-Bu}]^+$, 172 $[M–H_2C{=}C(CH_3)_2]^+$. Anal. Calcd. for $C_{10}H_{16}N_2O_4$: C, 52.62; H, 7.07; N, 12.27. Found: C, 53.01; H, 6.82; N, 12.50.

(*S*)-*tert*-Butyl (1-(5-(hydroxymethyl)isoxazol-3-yl)ethyl)carbamate (16g). The compound; purified by column chromatography on silica gel (220 g RediSep column; run length: 26.0 CV; flow rate: 100 mL / min; rack: 16 mm × 150 mm tubes) using gradient hexanes – *t*-BuOMe as eluent. Yield 9.35 g

(96%); colorless powder; mp 83–85 °C. $[\alpha]^{20}_D$ = –72.3 (*c* = 41.3, $CHCl_3$), 96% *ee*, t_R = 12.21 min. ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 7.41 (d, *J* = 7.8 Hz, 1H), 6.26 (s, 1H), 5.60 (t, *J* = 6.0 Hz, 1H), 4.78 – 4.67 (m, 1H), 4.52 (d, *J* = 5.9 Hz, 2H), 1.38 (s, 9H), 1.34 (d, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-*d*$_6$): δ 172.7, 166.3, 154.9, 99.8, 78.1, 54.8, 42.8, 28.2, 20.2. GC/MS (EI): *m/z* = 57 [*t*-Bu]$^+$, 126 [M–NHCO$_2$*t*-Bu]$^+$, 142 [M–CO$_2$–H$_2$C=C(CH$_3$)$_2$]$^+$, 169 [M–O*t*-Bu]$^+$, 186 [M–H$_2$C=C(CH$_3$)$_2$]$^+$. Anal. Calcd. for $C_{11}H_{18}N_2O_4$: C, 54.53; H, 7.49; N, 11.56. Found: C, 54.51; H, 7.42; N, 11.82.

(*R*)-*tert*-Butyl (1-(5-(hydroxymethyl)isoxazol-3-yl)ethyl)carbamate (16h). The compound; purified by column chromatography on silica gel (220 g RediSep column; run length: 26.0 CV; flow rate: 100 mL / min; rack: 16 mm × 150 mm tubes) using gradient hexanes – *t*-BuOMe as eluent. Yield 9.25 g (95%); colorless powder; mp 82–84 °C. $[\alpha]^{20}_D$ = +66.1 (*c* = 41.3, $CHCl_3$), 93% *ee*, t_R = 8.29 min. The spectral data are analogous to that of *S*-isomer **16g**. GC/MS (EI): *m/z* = 57 [*t*-Bu]$^+$, 126 [M–NHCO$_2$*t*-Bu]$^+$, 142 [M–CO$_2$–H$_2$C=C(CH$_3$)$_2$]$^+$, 169 [M–O*t*-Bu]$^+$, 186 [M–H$_2$C=C(CH$_3$)$_2$]$^+$. Anal. Calcd. for $C_{11}H_{18}N_2O_4$: C, 54.53; H, 7.49; N, 11.56. Found: C, 54.79; H, 7.21; N, 11.44.

***tert*-Butyl (2-(5-(hydroxymethyl)isoxazol-3-yl)propan-2-yl)carbamate (16i).** Yield 9.79 g (91%); colorless powder; mp 84–86 °C. ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 7.20 (s, 1H), 6.18 (s, 1H), 5.59 (t, *J* = 6.0 Hz, 1H), 4.51 (d, *J* = 5.9 Hz, 2H), 1.48 (s, 6H), 1.34 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-*d*$_6$): δ 172.5, 170.2, 154.7, 100.1, 78.3, 55.2, 51.1, 28.6, 28.2. GC/MS (EI): *m/z* = 57 [*t*-Bu]$^+$, 140 [M–NHCO$_2$*t*-Bu]$^+$, 200 [M–H$_2$C=C(CH$_3$)$_2$]$^+$. Anal. Calcd. for $C_{12}H_{20}N_2O_4$: C, 56.24; H, 7.87; N, 10.93. Found: C, 55.98; H, 8.23; N, 10.58.

***tert*-Butyl 3-(5-(hydroxymethyl)isoxazol-3-yl)azetidine-1-carboxylate (16j).** The compound; purified by column chromatography on silica gel (40 g RediSep column; run length: 27.6 CV; flow rate: 40 mL / min; rack: 16 mm × 150 mm tubes) using gradient hexanes – *t*-BuOMe as eluent. Yield 8.59 g (84%); yellowish oil. ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 6.45 (s, 1H), 5.61 (d, *J* = 5.7 Hz, 1H), 4.54 (d, *J* = 5.4 Hz, 2H), 4.21 (s, 2H), 3.87 (s, 3H), 1.38 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-*d*$_6$): δ 174.0, 164.6, 156.0, 100.8, 79.3, 55.3, 54.4, 28.5, 25.5. GC/MS (EI): *m/z* = 57 [*t*-Bu]$^+$, 154 [M–CO$_2$–

$H_2C=C(CH_3)_2]^+$, 181 [M–O*t*-Bu]$^+$, 197 [M–$H_2C=C(CH_3)_2]^+$. Anal. Calcd. for $C_{12}H_{18}N_2O_4$: C, 56.68; H, 7.14; N, 11.02. Found: C, 56.66; H, 7.49; N, 10.86.

(*S*)-*tert*-Butyl 2-(5-(hydroxymethyl)isoxazol-3-yl)pyrrolidine-1-carboxylate (16k). The compound existed as *ca*. 5:4 mixture of rotamers .Yield 9.71 g (90%); colorless oil. $[\alpha]^{20}_D$ = -80.2 (*c* = 37.3, $CHCl_3$), 98% *ee*, t_R = 18.8 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.24 (s, 1H), 5.60 (t, *J* = 6.0 Hz, 1H), 4.89 – 4.81 (m, 1H), 4.52 (d, *J* = 5.2 Hz, 2H), 3.46 – 3.37 (m, 2H), 2.25 – 2.17 (m, 1H), 1.91 – 1.84 (m, 3H), 1.40 (s, 4H) and 1.25 (s, 5H). ^{13}C{^{1}H} NMR (126 MHz, DMSO) δ 172.8, 166.1 and 165.7, 153.6 and 153.2, 100.3 and 99.7, 78.8 and 78.7, 54.8, 53.3 and 53.2, 46.4 and 46.1, 32.6 and 31.4, 28.2 and 28.0, 23.7 and 23.0. GC/MS (EI): *m/z* = 57 [*t*-Bu]$^+$, [M–CO_2–$H_2C=C(CH_3)_2]^+$. Anal. Calcd. for $C_{13}H_{20}N_2O_4$: C, 58.19; H, 7.51; N, 10.44. Found: C, 58.36; H, 7.86; N, 10.59.

(*R*)-*tert*-Butyl 2-(5-(hydroxymethyl)isoxazol-3-yl)pyrrolidine-1-carbo-xylate (16l). The compound existed as *ca*. 5:4 mixture of rotamers. Yield 9.92 g (92%); colorless oil. $[\alpha]^{20}_D$ = +65.9 (*c* = 37.3, $CHCl_3$), 98% *ee*, t_R = 11.5 min. The spectral data are analogous to that of *S*-isomer **16k**. GC/MS (EI): *m/z* = 57 [*t*-Bu]$^+$, [M–CO_2–$H_2C=C(CH_3)_2]^+$. Anal. Calcd. for $C_{13}H_{20}N_2O_4$: C, 58.19; H, 7.51; N, 10.44. Found: C, 58.34; H, 7.56; N, 10.65.

***tert*-Butyl 4-(5-(hydroxymethyl)isoxazol-3-yl)piperidine-1-carboxy-late (16m).** The compound; purified by column chromatography on silica gel (80 g RediSep column; run length: 24.2 CV; flow rate: 60 mL / min; rack: 16 mm × 150 mm tubes) using gradient $CHCl_3$ – *t*-BuOMe as eluent. Yield 7.15 g (85%); colorless powder; mp 57–59 °C. ^{1}H NMR (400 MHz, DMSO-d_6): *δ* 6.35 (s, 1H), 5.58 (t, *J* = 6.0 Hz, 1H), 4.51 (d, *J* = 5.9 Hz, 2H), 3.97 (d, *J* = 12.0 Hz, 2H), 2.96 – 2.75 (m, 3H), 1.85 (d, *J* = 12.5 Hz, 2H), 1.57 – 1.44 (m, 2H), 1.41 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): *δ* 172.7, 166.5, 154.0, 100.2, 78.7, 54.9, 43.3, 33.3, 30.4, 28.1. LC/MS (CI): *m/z* = 183 [M–CO_2–$H_2C=C(CH_3)_2$+H]$^+$, 227 [M–$H_2C=C(CH_3)_2$+H]$^+$. Anal. Calcd. for $C_{14}H_{22}N_2O_4$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.24; H, 8.20; N, 10.04.

Ethyl 5-(hydroxymethyl)isoxazole-3-carboxylate (23). The compound was purified by column chromatography on silica gel using hexanes – EtOAc (1:1) as eluent. Yield 3.92 g (57%); colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.63 (s, 1H), 4.79 (s, 2H), 4.40 (q, *J* = 7.1 Hz, 2H), 2.96 (s, 1H),

1.37 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 173.5, 159.9, 156.3, 102.5, 62.3, 56.3, 14.1. LC/MS (CI): m/z = 172 $[M+H]^+$. Anal. Calcd. for $C_7H_9NO_4$: C, 49.12; H, 5.30; N, 8.18. Found: C, 49.00; H, 5.60; N, 7.99.

(3-Bromoisoxazol-5-yl)methanol (24). The compound was purified by distillation in *vacuo*. Yield 4.87 g (68%); colorless liquid; bp 53–55 °C / 1 mmHg. ^1H NMR (400 MHz, $CDCl_3$) δ 6.33 (s, 1H), 4.73 (s, 2H), 2.87 (s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 173.4, 140.5, 105.6, 56.3. GC/MS (EI): m/z = 177/179 $[M]^+$. Anal. Calcd. for $C_4H_4BrNO_2$: C, 26.99; H, 2.27; N, 7.87; Br, 44.89. Found: C, 26.73; H, 2.01; N, 8.02; Br, 44.85.

General procedure for the preparation of aldehydes 17g–m, and 25.

Method A: Pyridinium chlorochromate (12.1 g, 55.9 mmol, 1.5 eq), SiO_2 (*ca*. 20 g) were suspended in CH_2Cl_2 (100 mL, 0.56 M solution of PCC). The resulting mechanically stirred solution was cooled to –10 °C and the corresponding alcohol **16g–m** or **23** (37.3 mmol, 1 eq) in CH_2Cl_2 (100 mL, 0.37 M solution of **16** or **23**) was added dropwise at –10 °C (NOTE: the temperature should not exceed –5 °C). The resulting mixture was stirred overnight at rt, then filtered through a plug of silica gel, and the filtrate was evaporated in *vacuo*.

Method B: The corresponding alcohol **16g–m** or **23** (37.3 mmol, 1 eq) was dissolved in CH_2Cl_2 (100 mL, 0.37 M solution of **16** or **23**), then Et_3N (16.4 mL, 11.9 g, 0.117 mol, 3.15 eq) and DMSO (HPLC grade, 13.2 mL, 14.6 g, 0.187 mol, 5 eq) were added under argon atmosphere. The resulting solution was cooled to 0 °C, and Py·SO_3 (17.8 g, 0.112 mol, 3 eq) was added (NOTE: in the case of **23**, 6-fold excess Py·SO_3 (35.6 g, 0.224 mol, 6 eq) was used). The resulting mixture was warmed up to rt, stirred for 1 h; the completion of the reaction was monitored by ^1H NMR. The mixture was poured onto ice (125 g), organic phase was separated and most of CH_2Cl_2 evaporated in *vacuo*. The aqueous phase was extracted with EtOAc (3×100 mL), combined extracts were added to the residue obtained after CH_2Cl_2 evaporation. The resulting solution was washed with saturated aq $NaHSO_3$ (3×100 mL), brine (3×75 mL), dried over Na_2SO_4, and evaporated in *vacuo*.

(*S*)-*tert*-Butyl (1-(5-formylisoxazol-3-yl)ethyl)carbamate (17g). The compound was purified by column chromatography on silica gel (330 g RediSep column; run length: 20.0 CV; flow rate: 100 mL / min; rack: 16 mm × 150 mm tubes) using hexanes – *t*-BuOMe (3:2) as eluent. Yield 5.91 g (66% from **22j** *via* method **A**) or 6.98 g (78% *via* method **B**); colorless powder; mp 77–79 °C. $[\alpha]^{20}_{D} = -61.6$ ($c = 41.6$, $CHCl_3$). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.89 (s, 1H), 7.54 (d, $J = 7.0$ Hz, 1H), 7.26 (s, 1H), 4.83 (dt, $J = 14.9$, 7.5 Hz, 1H), 1.40 (s, 3H), 1.39 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 179.9, 167.6, 165.3, 155.0, 109.8, 78.4, 43.0, 28.2, 20.0. GC/MS (EI): *m/z* = 57 [*t*-Bu]$^+$, 124 [M–$NHCO_2$*t*-Bu]$^+$, 167 [M–O*t*-Bu]$^+$, 184 [M–$H_2C{=}C(CH_3)_2$]$^+$, 225 [M–CH_3]$^+$. Anal. Calcd. for $C_{11}H_{16}N_2O_4$: C, 54.99; H, 6.71; N, 11.66. Found: C, 54.71; H, 7.09; N, 12.04.

(*R*)-*tert*-Butyl (1-(5-formylisoxazol-3-yl)ethyl)carbamate (17h). The compound was purified by column chromatography on silica gel gel (330 g RediSep column; run length: 20.0 CV; flow rate: 100 mL / min; rack: 16 mm × 150 mm tubes) using hexanes – *t*-BuOMe (3:2) as eluent. Yield 6.00 g (67% *via* method **A**) or 6.81 g (76% *via* method **B**); colorless powder; mp 77–79 °C. $[\alpha]^{20}_{D} = +58.7$ ($c = 41.6$, $CHCl_3$). The spectral data are analogous to that of *S*-isomer **17g**. GC/MS (EI): *m/z* = 57 [*t*-Bu]$^+$, 124 [M–$NHCO_2$*t*-Bu]$^+$, 167 [M–O*t*-Bu]$^+$, 184 [M–$H_2C{=}C(CH_3)_2$]$^+$, 225 [M–CH_3]$^+$. Anal. Calcd. for $C_{11}H_{16}N_2O_4$: C, 54.99; H, 6.71; N, 11.66. Found: C, 55.07; H, 6.34; N, 11.84.

***tert*-Butyl (2-(5-formylisoxazol-3-yl)propan-2-yl)carbamate (17i).** Yield 7.59 g (80% *via* method **A**) or 7.87 g (83% *via* method **B**); gray powder; mp 85–86 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.89 (s, 1H), 7.38 (br.s, 1H), 7.25 (s, 1H), 1.53 (s, 6H), 1.33 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 179.9, 171.1, 164.9, 154.4, 110.0, 78.2, 50.7, 28.2, 27.6. GC/MS (EI): *m/z* = 57 [*t*-Bu]$^+$, 138 [M–$NHCO_2$*t*-Bu]$^+$, 154 [M–CO_2–$H_2C{=}C(CH_3)_2$]$^+$, 181 [M–O*t*-Bu]$^+$, 198 [M–$H_2C{=}C(CH_3)_2$]$^+$, 239 [M–CH_3]$^+$. Anal. Calcd. for $C_{12}H_{18}N_2O_4$: C, 56.68; H, 7.14; N, 11.02. Found: C, 56.65; H, 7.49; N, 11.32.

***tert*-Butyl 3-(5-formylisoxazol-3-yl)azetidine-1-carboxylate (17j).** Yield 4.05 g (43% *via* method **A**) or 1.41 g (14% *via* method **B**); yellowish oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.91 (s, $J = 26.1$ Hz, 1H), 7.55 (s, 1H), 4.26 (t, $J = 7.4$ Hz, 2H), 4.06 – 3.91 (m, 3H), 1.40 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): δ 180.1, 166.2, 165.9, 156.0, 110.7, 79.3, 54.5, 28.5, 25.5. GC/MS (EI): *m/z* = 57 [*t*-Bu]$^+$,

152 [M–CO_2–H_2C=$C(CH_3)_2$]$^+$, 179 [M–O*t*-Bu]$^+$, 196 [M–H_2C=$C(CH_3)_2$]$^+$, 237 [M–CH_3]$^+$. Anal. Calcd. for $C_{12}H_{16}N_2O_4$: C, 57.13; H, 6.39; N, 11.10. Found: C, 57.31; H, 6.60; N, 11.27.

(*S*)-*tert*-Butyl 2-(5-formylisoxazol-3-yl)pyrrolidine-1-carboxylate (17k). The compound was purified by column chromatography on silica gel (330 g RediSep column; run length: 20.0 CV; flow rate: 125 mL / min; rack: 16 mm × 150 mm tubes) using hexanes – *t*-BuOMe (3:2) as eluent; existed as *ca*. 5:4 mixture of rotamers. Yield 7.75 g (78% *via* method **A**) or 8.05 g (81% *via* method **B**); colorless oil. $[\alpha]^{20}_D$ = -78.7 (*c* = 37.6, $CHCl_3$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 7.33 (d, *J* = 27.3 Hz, 1H), 4.96 (d, *J* = 11.5 Hz, 1H), 3.59 – 3.43 (m, 1H), 3.43 – 3.35 (m, 1H), 2.37 – 2.20 (m, 1H), 2.00 – 1.78 (m, 3H), 1.40 (s, 4H) and 1.23 (s, 5H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): *δ* 179.6, 167.6 and 167.0, 165.2, 153.7 and 153.0, 110.1 and 109.7, 79.0 and 78.9, 53.2, 46.5 and 46.2, 32.7 and 31.4, 28.5 and 27.9, 23.7 and 23.0. GC/MS (EI): *m/z* = 57 [*t*-Bu]$^+$, 166 [M–CO_2–H_2C=$C(CH_3)_2$]$^+$, 193 [M–O*t*-Bu]$^+$. Anal. Calcd. for $C_{13}H_{18}N_2O_4$: C, 58.63; H, 6.81; N, 10.52. Found: C, 58.88; H, 6.68; N, 10.20.

(*R*)-*tert*-Butyl 2-(5-formylisoxazol-3-yl)pyrrolidine-1-carboxylate (17l). The compound existed as *ca*. 5:4 mixture of rotamers. The compound was purified by column chromatography on silica gel using hexanes – *t*-BuOMe (3:2) as eluent. Yield 6.33 g (75% *via* method **A**) or 6.75 g (80% *via* method **B**); colorless oil. $[\alpha]^{20}_D$ = +74.9 (*c* = 37.6, $CHCl_3$). The spectral data are analogous to that of *S*-isomer **17k**. GC/MS (EI): *m/z* = 57 [*t*-Bu]$^+$, 166 [M–CO_2–H_2C=$C(CH_3)_2$]$^+$, 193 [M–O*t*-Bu]$^+$. Anal. Calcd. for $C_{13}H_{18}N_2O_4$: C, 58.63; H, 6.81; N, 10.52. Found: C, 58.94; H, 7.21; N, 10.40.

***tert*-Butyl 4-(5-formylisoxazol-3-yl)piperidine-1-carboxylate (17m).** Yield 5.75 g (55% *via* method **A**) or 7.21 g (69% *via* method **B**); colorless powder; mp 55–57 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 7.44 (s, 1H), 3.99 (d, *J* = 11.9 Hz, 2H), 3.08 – 3.01 (m, 1H), 2.89 (s, 2H), 1.91 (d, *J* = 11.5 Hz, 2H), 1.54 (qd, *J* = 12.3, 4.1 Hz, 2H), 1.41 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): *δ* 180.1, 168.1, 165.6, 154.3, 110.3, 79.1, 43.7, 33.7, 30.6, 28.5. GC/MS (EI): *m/z* = 57 [*t*-Bu]$^+$, 180 [M–CO_2–H_2C=$C(CH_3)_2$]$^+$, 207 [M–O*t*-Bu]$^+$, 224 [M–H_2C=$C(CH_3)_2$]$^+$. Anal. Calcd. for $C_{14}H_{20}N_2O_4$: C, 59.99; H, 7.19; N, 9.99. Found: C, 59.95; H, 7.42; N, 9.92.

Ethyl 5-formylisoxazole-3-carboxylate (25). Yield 4.92 g (78% *via* method **A**) or 820 mg (13% *via* method **B**); pinkish solid; mp 24–27 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.99 (s, 1H), 7.32 (s, 1H), 4.45

(q, J = 7.2 Hz, 2H), 1.40 (t, J = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 177.6, 166.8, 158.7, 157.1, 108.9, 62.8, 14.1. GC/MS (EI): *m/z* = 169 $[M]^+$. Anal. Calcd. for $C_7H_7NO_4$: C, 49.71; H, 4.17; N, 8.28. Found: C, 49.93; H, 3.86; N, 8.55.

General procedure for the preparation of fluoromethyl oxazoles 18a, 18f–l.

Method A: The corresponding alcohol **16f–l** (18.6 mmol, 1 eq) was dissolved in CH_2Cl_2 (50 mL, 0.37 M solution of **16f–l**) and the solution was cooled to –15 °C under argon atmosphere. Morpholinosulfur trifluoride (3.49 g, 19.9 mmol, 1.07 eq) in CH_2Cl_2 (15 mL) was added dropwise (NOTE: the temperature shouldn't exceed –10 °C.). Reaction mixture was stirred at -10 °C for 1.5 h. Then, the reaction mixture was poured into brine – ice (2 mL – 2 g, 1/1, v/m) and $NaHCO_3$ was added to *ca.* pH = 7–8. Most of CH_2Cl_2 was evaporated in *vacuo* and water phase was extracted with EtOAc (3×15 mL). Combined organic phases were washed with brine (2×10 mL) dried over Na_2SO_4 and evaporated in *vacuo.*

Method B: KHF_2 (176 mg, 22.5 mmol, 1.5 eq) and 18-crown-6 (19.6 mg, 75.0 μmol, 0.005 eq) were added to a solution of the corresponding bromide **22a**, **22f–l**, **22j** or **22m** (15.0 mmol, 1 eq) in MeCN (10 mL, 1.5 M solution of bromide **22**) at rt. The completion of reaction was monitored by ^1H NMR (*ca.* 10 h). Then, the reaction mixture was evaporated in *vacuo*, the residue was dissolved in EtOAc (10 mL), the precipitate was filtered off, washed with EtOAc (5 mL) and the combined filtrates were evaporated in *vacuo*.

Ethyl 5-(fluoromethyl)isoxazole-3-carboxylate (18a). The compound was purified by column chromatography on silica gel using heptane – EtOAc (3:2) or CH_2Cl_2 – hexanes (9:1) as eluent. Yield 169 mg (65% from **22a** *via* method **B**); colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 6.81 (d, J = 2.8 Hz, 1H), 5.46 (d, J = 47.1 Hz, 2H), 4.44 (q, J = 7.1 Hz, 2H), 1.41 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 167.5 (d, J = 21.2 Hz), 158.8, 156.0 (d, J = 2.7 Hz), 104.5 (d, J = 4.0 Hz), 73.2 (d, J = 170 Hz), 61.8, 13.5. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -217.4. GC/MS (EI): *m/z* = 173 $[M]^+$. Anal. Calcd. for $C_7H_8FNO_3$: C, 48.56; H, 4.66; N, 8.09. Found: C, 48.72; H, 4.26; N, 8.04.

***tert*-Butyl ((5-(fluoromethyl)isoxazol-3-yl)methyl)carbamate (18f).** The compound; purified by column chromatography on silica gel (24 g RediSep column; run length: 27.6 CV; flow rate: 100 mL / min; rack: 16 mm × 150 mm tubes) using hexanes – *t*-BuOMe (7:3) and then $CHCl_3$ – MeCN (4:1) as eluent. Yield 257 mg (6% from **16f** *via* method **A**) or 3.21 (93% from **22f** *via* method **B**); yellowish oil. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.49 – 7.42 (m, 1H), 6.57 (s, 1H), 5.52 (d, J = 47.3 Hz, 2H), 4.18 (d, J = 5.5 Hz, 2H), 1.39 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 166.3 (d, J = 18.3 Hz), 162.9, 155.8, 104.7 (d, J = 4.1 Hz), 78.4, 73.9 (d, J = 163 Hz), 35.6, 28.2. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6): δ –214.0 (td, J = 47.1, 2.6 Hz). GC/MS (EI): *m/z* = 57 [*t*-Bu]$^+$, 114 [M–NHCO$_2$*t*-Bu]$^+$, 130 [M–CO$_2$–H$_2$C=C(CH$_3$)$_2$]$^+$, 157 [M–O*t*-Bu]$^+$, 174 [M–H$_2$C=C(CH$_3$)$_2$]$^+$. Anal. Calcd. for $C_{10}H_{15}FN_2O_3$: C, 52.17; H, 6.57; N, 12.17. Found: C, 51.78; H, 6.80; N, 12.45.

(*S*)-*tert*-Butyl (1-(5-(fluoromethyl)isoxazol-3-yl)ethyl)carbamate (18g). The compound; purified by column chromatography on silica gel (125 g RediSep column; run length: 24.5 CV; flow rate: 100 mL / min; rack: 16 mm × 150 mm tubes) using gradient hexanes – *t*-BuOMe as eluent. The compound was purified by column chromatography on silica gel using hexanes – *t*-BuOMe (7:3) as eluent; existed as *ca*. 2:1 mixture of rotamers. Yield 454 mg (10% from **16g** *via* method **A**) or 3.55 (97% from **22g** *via* method **B**); colorless powder; mp 81–83 °C. $[\alpha]^{20}_D$ = –82.2 (*c* = 40.9, $CHCl_3$), 96% *ee*, t_R = 13.0 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.48 (d, J = 8.5 Hz, 1H), 6.61 (d, J = 3.5 Hz, 1H), 5.54 (d, J = 47.3 Hz, 2H), 4.79 – 4.74 (m, 1H), 1.39 (s, 6H), 1.37 (s, 3H), 1.35 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 166.9, 166.2 (d, J = 18.4 Hz), 155.0, 103.8, 78.2, 74.0 (d, J = 163 Hz), 42.9, 28.2, 20.0. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6): δ –213.0 (t, J = 47.3 Hz). GC/MS (EI): *m/z* = 57 [*t*-Bu]$^+$, 128 [M–NHCO$_2$*t*-Bu]$^+$, 144 [M–CO$_2$–H$_2$C=C(CH$_3$)$_2$]$^+$, 171 [M–O*t*-Bu]$^+$, 188 [M–H$_2$C=C(CH$_3$)$_2$]$^+$, 229 [M–CH$_3$]$^+$. Anal. Calcd. for $C_{11}H_{17}FN_2O_3$: C, 54.09; H, 7.02; N, 11.47. Found: C, 53.77; H, 6.87; N, 11.31.

(*R*)-*tert*-Butyl (1-(5-(fluoromethyl)isoxazol-3-yl)ethyl)carbamate (18h). The compound; purified by column chromatography on silica gel (80 g RediSep column; run length: 19.6 CV; flow rate: 100 mL / min; rack: 16 mm × 150 mm tubes) using hexanes – *t*-BuOMe (7:3) as eluent; existed as *ca*. 2:1 mixture of rotamers. Yield 545 mg (12% method **A**; from **16h** *via* method **A**) or 3.59 (98% from **22h** *via*

method **B**); colorless powder; mp 81–83 °C. $[\alpha]^{20}_{D}$ = +47.1 (*c* = 40.9, $CHCl_3$), 86% *ee*, t_R = 12.3 min. The spectral data are analogous to that of *S*-isomer **18g**. GC/MS (EI): *m/z* = 57 [*t*-Bu]$^+$, 128 [M–$NHCO_2$*t*-Bu]$^+$, 144 [M–CO_2–H_2C=$C(CH_3)_2$]$^+$, 171 [M–O*t*-Bu]$^+$, 188 [M–H_2C=$C(CH_3)_2$]$^+$, 229 [M–CH_3]$^+$. LC/MS (CI): *m/z* = 145 [M–CO_2–H_2C=$C(CH_3)_2$+H]$^+$. Anal. Calcd. for $C_{11}H_{17}FN_2O_3$: C, 54.09; H, 7.02; N, 11.47. Found: C, 54.16; H, 6.78; N, 11.65.

***tert*-Butyl (2-(5-(fluoromethyl)isoxazol-3-yl)propan-2-yl)carbamate (18i).** The compound; purified by column chromatography on silica gel (220 g RediSep column; run length: 20.0 CV; flow rate: 100 mL / min; rack: 16 mm × 150 mm tubes) using hexanes – *t*-BuOMe (3:2) as eluent. Yield 1.44 g (30% from **16i** *via* method **A**) or 3.60 (93% from **22i** *via* method **B**); colorless powder; mp 82–84 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.27 (br.s, 1H), 6.55 (d, *J* = 3.1 Hz, 1H), 5.52 (d, *J* = 47.4 Hz, 2H), 1.50 (s, 6H), 1.33 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 170.7, 165.9 (d, *J* = 18.2 Hz), 154.7, 104.1 (d, *J* = 4.9 Hz), 78.4, 74.3 (d, *J* = 163 Hz), 51.1, 28.6, 28.0. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6): δ –213.5 (t, *J* = 46.5 Hz). GC/MS (EI): *m/z* = 57 [*t*-Bu]$^+$, 158 [M–CO_2-H_2C=$C(CH_3)_2$]$^+$, 185 [M–O*t*-Bu]$^+$, 202 [M–H_2C=$C(CH_3)_2$]$^+$. LC/MS (CI): *m/z* = 143 [M–$NHCO_2$*t*-Bu+H]$^+$, 203 [M–H_2C=$C(CH_3)_2$+H]$^+$. Anal. Calcd. for $C_{12}H_{19}FN_2O_3$: C, 55.80; H, 7.41; N, 10.85. Found: C, 55.54; H, 7.79; N, 11.04.

***tert*-Butyl 3-(5-(fluoromethyl)isoxazol-3-yl)azetidine-1-carboxylate (18j).** The compound; purified by column chromatography on silica gel (80 g RediSep column; run length: 44.0 CV; flow rate: 100 mL / min; rack: 16 mm × 150 mm tubes) using hexanes – *t*-BuOMe (3:2) as eluent. Yield 727 mg (16% from **16j** *via* method **A**) or 3.69 (96% from **22j** *via* method **B**); yellowish oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.84 (d, *J* = 3.4 Hz, 1H), 5.54 (d, *J* = 47.2 Hz, 2H), 4.23 (s, 2H), 3.91 (s, 3H), 1.38 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 166.8 (d, *J* = 18.5 Hz), 164.7 (d, *J* = 2.9 Hz), 155.6, 104.4 (d, *J* = 4.6 Hz), 78.9, 74.0 (d, *J* = 163 Hz), 53.7, 28.1 and 25.0. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6): δ –214.4 (td, *J* = 47.2, 3.3 Hz). GC/MS (EI): *m/z* = 57 [*t*-Bu]$^+$, 156 [M–CO_2–H_2C=$C(CH_3)_2$]$^+$, 183 [M–O*t*-Bu]$^+$, 200 [M–H_2C=$C(CH_3)_2$]$^+$. LC/MS (CI): *m/z* = 157 [M–CO_2–H_2C=$C(CH_3)_2$+H]$^+$, 201 [M–H_2C=$C(CH_3)_2$+H]$^+$, 255 [M–H]$^+$. Anal. Calcd. for $C_{12}H_{17}FN_2O_3$: C, 56.24; H, 6.69; N, 10.93. Found: C, 56.48; H, 6.37; N, 10.64.

(*S*)-*tert*-Butyl 2-(5-(fluoromethyl)isoxazol-3-yl)pyrrolidine-1-carboxylate (18k). The compound; purified by column chromatography on silica gel (80 g RediSep column; run length: 20.6 CV; flow rate: 50 mL / min; rack: 16 mm × 150 mm tubes) using hexanes – *t*-BuOMe (3:2) as eluent; existed as *ca*. 5:4 mixture of rotamers. Yield 1.56 g (31% from **16k** *via* method **A**); colorless powder; mp 71–73 °C. $[\alpha]^{20}_{D}$ = –79.6 (*c* = 37.0, $CHCl_3$), 99% *ee*, t_R = 8.33 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.63 (d, *J* = 13.9 Hz, 1H), 5.53 (d, *J* = 47.2 Hz, 2H), 4.95 – 4.84 (m, 1H), 3.47 – 3.35 (m, 2H), 2.32 – 2.20 (m, 1H), 1.96 – 1.80 (m, 3H), 1.39 (s, 4H), 1.23 (s, 5H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 166.8, 166.1 (d, *J* = 18.3 Hz), 153.6 and 153.2, 104.2 and 103.7, 78.9 and 78.77, 73.9 (d, *J* = 163 Hz), 53.2, 46.5 and 46.2, 32.7 and 31.4, 28.2 and 27.9, 23.7 and 23.0. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ -213.5 (t, *J* = 46.9 Hz), -213.9 (t, *J* = 48.1 Hz). GC/MS (EI): *m/z* = 57 [*t*-Bu]$^+$, 170 [M–CO_2-H_2C=$C(CH_3)_2$]$^+$, 197 [M–O*t*-Bu]$^+$, 214 [M–H_2C=$C(CH_3)_2$]$^+$. Anal. Calcd. for $C_{13}H_{19}FN_2O_3$: C, 57.77; H, 7.09; N, 10.36. Found: C, 58.06; H, 7.23; N, 10.71.

(*R*)-*tert*-Butyl 2-(5-(fluoromethyl)isoxazol-3-yl)pyrrolidine-1-carboxy-late (18l). The compound; purified by column chromatography on silica gel (125 g RediSep column; run length: 35.8 CV; flow rate: 85 mL / min; rack: 16 mm × 150 mm tubes) using hexanes – *t*-BuOMe (3:2) as eluent; existed as *ca*. 5:4 mixture of rotamers. Yield 1.26 g (25% from **16l** *via* method **A**); colorless powder; mp 72–73 °C. $[\alpha]^{20}_{D}$ = +77.9 (*c* = 37.0, $CHCl_3$), 100% *ee*, t_R = 6.98 min. The spectral data are analogous to that of *S*-isomer **18k**. GC/MS (EI): *m/z* = 57 [*t*-Bu]$^+$, 170 [M–CO_2–H_2C=$C(CH_3)_2$]$^+$, 197 [M–O*t*-Bu]$^+$, 214 [M–H_2C=$C(CH_3)_2$]$^+$. Anal. Calcd. for $C_{13}H_{19}FN_2O_3$: C, 57.77; H, 7.09; N, 10.36. Found: C, 58.10; H, 6.84; N, 10.22.

General procedure for the preparation of difluoromethyl oxazoles 19g–l, 27, and 38.

The corresponding aldehyde **17a**, **17g–l**, **25** or **37** (26.3 mmol, 1 eq) was dissolved in CH_2Cl_2 (70 mL, 0.38 M solution of aldehyde) and the solution was cooled to –4 °C under argon atmosphere. Morpholinosulfur trifluoride (5.06 g, 28.9 mmol, 1.1 eq) in CH_2Cl_2 (25 mL) was added dropwise (internal temperature was between –40 to –35 °C.). The resulting mixture was stirred at –10 °C for 1.5 h. Then, the reaction mixture was poured into brine–ice (*ca.* 4 mL – 4 g, 1/1, v/m) and $NaHCO_3$ was

added until pH = 7–8. Most of CH_2Cl_2 was evaporated in *vacuo*, and aqueous phase was extracted with EtOAc (3×30 mL). Combined organic phases were washed with brine (2×50 mL) and dried over Na_2SO_4 and the solvent was evaporated in *vacuo*.

(*S*)-*tert*-Butyl (1-(5-(difluoromethyl)isoxazol-3-yl)ethyl)carbamate (19g). The compound was purified by column chromatography on silica gel using hexanes – *t*-BuOMe (3:2) and then using $CHCl_3$ – MeCN (19:1) as eluent. Yield 1.74 g (23%); colorless powder; mp 86–88 °C. $[\alpha]^{20}_D$ = -61.0 (*c* = 38.1, $CHCl_3$), 97% *ee*, t_R = 14.6 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.59 – 7.46 (m, 1H), 7.32 (t, *J* = 52.9 Hz, 1H), 6.86 (s, 1H), 4.80 (s, 1H), 1.39 (s, 9H), 1.35 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 166.9, 162.6 (t, *J* = 28.3 Hz), 155.0, 107.6 (t, *J* = 236 Hz), 103.8, 78.4, 42.9, 28.2, 19.9. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6): δ –118.43 (d, *J* = 52.7 Hz). GC/MS (EI): *m/z* = 57 [*t*-Bu]$^+$, 146 [M–NHCO$_2$*t*-Bu]$^+$, 162 [M–CO$_2$–H$_2$C=C(CH$_3$)$_2$]$^+$, 189 [M–O*t*-Bu]$^+$, 206 [M–H$_2$C=C(CH$_3$)$_2$]$^+$. Anal. Calcd. for $C_{11}H_{16}F_2N_2O_3$: C, 50.38; H, 6.15; N, 10.68. Found: C, 50.55; H, 6.39; N, 10.52.

(*R*)-*tert*-Butyl (1-(5-(difluoromethyl)isoxazol-3-yl)ethyl)carbamate (19h). The compound was purified by column chromatography on silica gel using hexanes – *t*-BuOMe (3:2) and then using $CHCl_3$ – MeCN (19:1) as eluent. Yield 1.89 g (25%); colorless powder; mp 86–88 °C. $[\alpha]^{20}_D$ = +43.4 (*c* = 38.1, $CHCl_3$), 81% *ee*, t_R = 13.6 min. The spectral data are analogous to that of *S*-isomer **19g**. GC/MS (EI): *m/z* = 57 [*t*-Bu]$^+$, 146 [M–NHCO$_2$*t*-Bu]$^+$, 162 [M–CO$_2$–H$_2$C=C(CH$_3$)$_2$]$^+$, 189 [M–O*t*-Bu]$^+$, 206 [M–H$_2$C=C(CH$_3$)$_2$]$^+$. Anal. Calcd. for $C_{11}H_{16}F_2N_2O_3$: C, 50.38; H, 6.15; N, 10.68. Found: C, 50.28; H, 6.14; N, 10.41.

***tert*-Butyl (2-(5-(difluoromethyl)isoxazol-3-yl)propan-2-yl)carbamate (19i).** The compound was purified by column chromatography on silica gel using hexanes – *t*-BuOMe (7:3) as eluent. Yield 2.24 g (28%); colorless powder; mp 88–89 °C. ^{1}H NMR (400 MHz, DMSO-d_6): *δ* 7.32 (br.s, 1H), 7.31 (t, *J* = 52.8 Hz, 1H), 6.80 (s, 1H), 1.51 (s, 6H), 1.32 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 170.4, 162.0 (t, *J* = 28.2 Hz), 154.3, 107.7 (t, *J* = 236 Hz), 103.7, 78.2, 50.7, 28.1, 27.5. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6): *δ* –118.2 (d, *J* = 52.8 Hz). GC/MS (EI): *m/z* = 57 [*t*-Bu]$^+$, 160 [M–NHCO$_2$*t*-Bu]$^+$, 176 [M–CO$_2$–H$_2$C=C(CH$_3$)$_2$]$^+$, 203 [M–O*t*-Bu]$^+$, 220 [M–H$_2$C=C(CH$_3$)$_2$]$^+$, 261 [M–CH$_3$]$^+$. Anal. Calcd. for $C_{12}H_{18}F_2N_2O_3$: C, 52.17; H, 6.57; N, 10.14. Found: C, 52.37; H, 6.58; N, 9.93.

***tert*-Butyl 3-(5-(difluoromethyl)isoxazol-3-yl)azetidine-1-carboxylate (19j).** The compound was purified by column chromatography on silica gel using $CHCl_3$ – *t*-BuOMe (4:1) as eluent. Yield 2.77 g (35%); yellowish crystals; mp 53–55 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.34 (t, J = 52.7 Hz, 1H), 7.16 (s, 1H), 4.24 (t, J = 7.6 Hz, 2H), 3.95 (q, J = 6.4, 6.0 Hz, 3H), 1.39 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 165.2, 163.7 (t, J = 28.8 Hz), 156.0, 108.1 (t, J = 236 Hz), 104.7, 79.3, 54.3, 28.4, 25.4. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6): δ –118.6 (dd, J = 53.0, 1.2 Hz). GC/MS (EI): *m/z* = 57 [*t*-Bu]$^+$, 174 [M–CO_2–H_2C=$C(CH_3)_2$]$^+$, 201 [M–O*t*-Bu]$^+$, 218 [M–H_2C=$C(CH_3)_2$]$^+$, 259 [M–CH_3]$^+$. Anal. Calcd. for $C_{12}H_{16}F_2N_2O_3$: C, 52.55; H, 5.88; N, 10.21. Found: C, 52.68; H, 5.63; N, 10.61.

(*S*)-*tert*-Butyl 2-(5-(difluoromethyl)isoxazol-3-yl)pyrrolidine-1-carboxylate (19k). The compound existed as *ca*. 5:4 mixture of rotamers. The compound was purified by column chromatography on silica gel using hexanes – *t*-BuOMe (7:3) as eluent. Yield 4.42 g (53%); colorless powder; mp 30–33 °C. $[\alpha]^{20}_D$ = –70.5 (c = 34.7, $CHCl_3$), 82% *ee*, t_R =7.59 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.33 (t, J = 52.9 Hz, 1H), 6.93 (d, J = 23.0 Hz, 1H), 4.98 – 4.86 (m, 1H), 3.49 – 3.44 (m, 1H), 3.41 – 3.36 (m, 1H), 2.35 – 2.22 (m, 1H), 1.96 – 1.84 (m, 3H), 1.39 (s, 4H), 1.22 (s, 5H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 167.4 and 166.8, 163.0 (t, J = 28.6 Hz), 154.1 and 153.5, 108.1 (t, J = 236 Hz), 104.4 and 104.0, 79.3, 53.5, 46.9 and 46.7, 33.1 and 31.8, 28.5 and 28.3, 24.1 and 23.4. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6): δ -118.3 (dd, J = 52.4, 8.4 Hz), –118.4 (d, J = 52.7 Hz). GC/MS (EI): *m/z* = 57 [*t*-Bu]$^+$, 188 [M–CO_2–H_2C=$C(CH_3)_2$]$^+$, 215 [M–O*t*-Bu]$^+$. Anal. Calcd. for $C_{13}H_{18}F_2N_2O_3$: C, 54.16; H, 6.29; .N, 9.72. Found: C, 54.02; H, 6.40; N, 9.52.

(*R*)-*tert*-Butyl 2-(5-(difluoromethyl)isoxazol-3-yl)pyrrolidine-1-arboxylate (19l). The compound existed as *ca*. 5:4 mixture of rotamers. The compound was purified by column chromatography on silica gel using hexanes – *t*-BuOMe (7:3) as eluent. Yield 5.08 g (61%); colorless powder; mp 30–33 °C. $[\alpha]^{20}_D$ = +69.9 (c = 34.7, $CHCl_3$), 99% *ee*, t_R = 6.59 min. The spectral data are analogous to that of *S*-isomer **19k**. GC/MS (EI): *m/z* = 57 [*t*-Bu]$^+$, 188 [M–CO_2–H_2C=$C(CH_3)_2$]$^+$, 215 [M–O*t*-Bu]$^+$. Anal. Calcd. for $C_{13}H_{18}F_2N_2O_3$: C, 54.16; H, 6.29; N, 9.72. Found: C, 54.03; H, 6.63; N, 9.37.

Ethyl 5-(difluoromethyl)isoxazole-3-carboxylate (27). The compound was purified by distillation in *vacuo*. Yield 3.67 g (73%); colorless oil; mp 46–49 °C / 0.68 mmHg. ^{1}H NMR (400 MHz, DMSO-d_6) δ

7.41 (s, 1H), 7.40 (t, J = 53.8 Hz, 1H), 4.39 (q, J = 6.9, 2H), 1.33 (t, J = 6.9 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 165.0 (t, J = 29.1 Hz), 158.9, 156.8, 107.6 (t, J = 237 Hz), 106.0 (t, J = 3.6 Hz), 62.6, 14.0. $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6) δ –119.2. GC/MS (EI): m/z = 191 $[M]^+$. Anal. Calcd. for $C_7H_7F_2NO_3$: C, 43.99; H, 3.69; N, 7.33. Found: C, 43.80; H, 3.44; N, 7.20.

3-(Chloromethyl)-5-(difluoromethyl)isoxazole (38). The compound was purified by distillation in *vacuo* or by column chromatography on silica gel (220 g RediSep column; run length: 21.8 CV; flow rate: 100 mL / min; rack: 16 mm × 150 mm tubes) using gradient hexanes – *t*-BuOMe as eluent. Yield 1.63 g (37%); colorless liquid; bp 24–26 °C / 1 mmHg;. bp 47–49 °C / 17 mmHg.^1H NMR (500 MHz, $CDCl_3$) δ 6.72 (t, J = 53.5 Hz, 1H), 6.67 (s, 1H), 4.59 (s, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 164.3 (t, J = 30.9 Hz), 161.1, 107.1 (t, J = 239 Hz), 103.8 (t, J = 2.6 Hz), 35.0. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ –118.7. GC/MS (EI): m/z = 167/169 $[M]^+$. Anal. Calcd. for $C_5H_4ClF_2NO$: C, 35.85; H, 2.41; N, 8.36; Cl, 21.16. Found: C, 35.83; H, 2.75; N, 8.52; Cl, 21.21.

General procedure for the preparation of bromomethyl isoxazoles 22a, 22f–h, 22j and 22m.

The corresponding chloroxime **1a**, **1f–h**, **1j** or **1m** (2.23 mmol) was dissolved in EtOAc (10 mL), then freshly distilled propargyl bromide (343 mg, 2.90 mmol) and $NaHCO_3$ (318 mg, 3.71 mmol) were added to the solution at rt. The resulting mixture was stirred overnight; the completion of reaction was monitored by ^1H NMR spectroscopy. Next, the solution was filtered through a plug of silica gel and evaporated in *vacuo*.

Ethyl 5-(bromomethyl)isoxazole-3-carboxylate (22a). The compound was purified by column chromatography on silica gel using heptane – EtOAc (3:2) as eluent. Yield 355 mg (68%); yellow crystals; mp 37–40 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 6.73 (d, J = 2.3 Hz, 1H), 4.51 – 4.49 (m, 2H), 4.44 (dd, J = 6.8, 1.8 Hz, 2H), 1.41 (dd, J = 8.8, 6.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 168.9, 158.9, 156.2, 103.8, 61.8, 17.5, 13.6. GC/MS (EI): m/z = 233/235 $[M]^+$. Anal. Calcd. for $C_7H_8BrNO_3$: C, 35.92; H, 3.45; N, 5.98; Br, 34.14. Found: C, 36.03; H, 3.65; N, 6.25; Br, 34.32.

***tert*-Butyl ((5-(bromomethyl)isoxazol-3-yl)methyl)carbamate (22f).** The compound was purified by HPLC (SunFire C18 Column, 100 Å, 3.5 μm, 4.6 mm×150 mm, 0–6.5 min; H_2O – MeCN; flow rate

30mL / min). Yield 396 mg (61%); beige powder; mp 50–53 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.30 (s, 1H), 4.99 (s, 1H), 4.41 (s, 2H), 4.35 (d, *J* = 6.0 Hz, 2H), 1.44 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 167.8, 162.3, 155.8, 103.1, 80.1, 36.4, 28.3, 18.5. LC/MS (CI): *m/z* = 191/193 [M–CO_2–H_2C=$C(CH_3)_2$+H]$^+$, 235/237 [M–H_2C=$C(CH_3)_2$+H]$^+$, 314/316 [M+Na]$^+$. Anal. Calcd. for $C_{10}H_{15}BrN_2O_3$: C, 41.25; H, 5.19; N, 9.62; Br, 27.44. Found: C, 41.34; H, 5.21; N, 9.53; Br, 27.72.

(*S*)-*tert*-Butyl (1-(5-(bromomethyl)isoxazol-3-yl)ethyl)carbamate (22g). The compound was purified by HPLC (SunFire C_{18} Column, 100 Å, 3.5 µm, 4.6 mm × 150 mm, 0–6.5 min; H_2O – MeCN; flow rate 30mL / min). Yield 483 mg (71%); beige powder; mp 73–76 °C. $[\alpha]^{20}_D$ = –41.4 (*c* = 32.8, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.25 (s, 1H), 4.97 – 4.86 (m, 2H), 4.41 (s, 2H), 1.50 (d, *J* = 6.7 Hz, 3H), 1.43 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 167.6, 166.2, 155.0, 102.5, 79.9, 43.8, 28.3, 20.3, 18.5. LC/MS (CI): *m/z* = 205/207 [M–CO_2–H_2C=$C(CH_3)_2$+H]$^+$, 328/330 [M+Na]$^+$. Anal. Calcd. for $C_{11}H_{17}BrN_2O_3$: C, 43.29; H, 5.62; N, 9.18; Br, 26.18. Found: C, 43.68; H, 5.85; N, 9.30; Br, 26.27.

(*R*)-*tert*-Butyl (1-(5-(bromomethyl)isoxazol-3-yl)ethyl)carbamate (22h). The compound was purified by HPLC (SunFire C_{18} Column, 100 Å, 3.5 µm, 4.6 mm × 150 mm, 0–6.5 min; H_2O – MeCN; flow rate 30mL / min). Yield 491 mg (72%); colorless powder; mp 74–77 °C. $[\alpha]^{20}_D$ = 41.5 (*c* = 32.8, $CHCl_3$). The spectral data are analogous to that of *S*-isomer **22g**. LC/MS (CI): *m/z* = 205/207 [M–CO_2–H_2C=$C(CH_3)_2$+H]$^+$, 328/330 [M+Na]$^+$. Anal. Calcd. for $C_{11}H_{17}BrN_2O_3$: C, 43.29; H, 5.62; N, 9.18; Br, 26.18. Found: C, 43.22; H, 5.66; N, 8.81; Br, 26.06.

***tert*-Butyl 3-(5-(bromomethyl)isoxazol-3-yl)azetidine-1-carboxylate (22j).** The compound was purified by HPLC (SunFire C_{18} Column, 100 Å, 3.5 µm, 4.6 mm × 150 mm, 0–6.5 min; H_2O – MeCN; flow rate 30mL / min). Yield 495 mg (70%); colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.35 (s, 1H), 4.43 (s, 2H), 4.29 (t, *J* = 8.6 Hz, 2H), 4.00 (dd, *J* = 8.6, 5.8 Hz, 2H), 3.85 – 3.77 (m, 1H), 1.43 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 168.3, 164.7, 156.0, 102.1, 79.7, 54.1, 28.3, 25.5, 18.6. LC/MS (CI): *m/z* = 217/219 [M–CO_2–H_2C=$C(CH_3)_2$+H]$^+$, 243/245 [M–O*t*-Bu]$^+$, 261/263 [M–H_2C=$C(CH_3)_2$+H]$^+$. Anal. Calcd. for $C_{12}H_{17}BrN_2O_3$: C, 45.44; H, 5.40; N, 8.83; Br, 25.19. Found: C, 45.48; H, 5.59; N, 8.79; Br, 25.55.

***tert*-Butyl 4-(5-(bromomethyl)isoxazol-3-yl)piperidine-1-carboxylate (22m).** The compound was purified by HPLC (SunFire C_{18} Column, 100 Å, 3.5 μm, 4.6 mm × 150 mm, 0–6.5 min; H_2O – MeCN; flow rate 30mL / min). Yield 547 mg (71%); beige powder; mp 68–70 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.16 (s, 1H), 4.41 (s, 2H), 4.14 (d, *J* = 13.4 Hz, 2H), 2.86 (q, *J* = 12.8, 12.2 Hz, 3H), 1.91 (d, *J* = 12.8 Hz, 2H), 1.61 (qd, *J* = 12.2, 4.2 Hz, 2H), 1.45 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 167.3, 167.1, 154.7, 102.0, 79.6, 43.4, 34.1, 30.7, 28.4, 18.7. LC/MS (CI): *m/z* = 245/247 [M–CO_2–H_2C=$C(CH_3)_2$+H]$^+$, 289/291 [M–H_2C=$C(CH_3)_2$+H]$^+$. Anal. Calcd. for $C_{14}H_{21}BrN_2O_3$: C, 48.71; H, 6.13; N, 8.11; Br, 23.14. Found: C, 48.49; H, 5.74; N, 8.51; Br, 23.34.

3-Bromo-5-(difluoromethyl)isoxazole (28). Pyridinium chlorochromate (16.2 g, 75.0 mmol), SiO_2 (*ca*. 25 g) were suspended in CH_2Cl_2 (150 mL). The resulting mechanically stirred solution was cooled to –10 °C and alcohol **24** (8.90 g, 50.0 mmol) in CH_2Cl_2 (150 mL) was added dropwise at –10 (NOTE: the temperature should not exceed –5 °C.). The resulting mixture was stirred overnight at rt, then filtered through a plug of silica gel, and the filtrate was evaporated in *vacuo*. The corresponding aldehyde **26** was dissolved in CH_2Cl_2 (100 mL) and the solution was cooled to –4 °C under argon atmosphere. Morpholinosulfur trifluoride (9.63 g, 55.0 mmol) in CH_2Cl_2 (50 mL) was added dropwise (internal temperature was between –40 to –35 °C.). The resulting mixture was stirred at –10 °C for 1.5 h. Then, the reaction mixture was poured into brine–ice (*ca.* 4 mL – 4 g, 1/1, v/m) and $NaHCO_3$ was added until pH = 7–8. Most of CH_2Cl_2 was evaporated in *vacuo*, and aqueous phase was extracted with EtOAc (3×45 mL). Combined organic phases were washed with brine (3×50 mL) and dried over Na_2SO_4 and the solvent was evaporated in *vacuo*. The compound was purified by column chromatography on silica gel (125 g RediSep column; run length: 16.9 CV; flow rate: 85 mL / min; rack: 16 mm × 150 mm tubes) using gradient hexanes – *t*-BuOMe as eluent. Yield 7.13 g (72% for two steps); colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.74 (t, *J* = 53.4 Hz, 1H), 6.68 (t, *J* = 1.7 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 164.8 (t, *J* = 31.5 Hz), 140.5 (t, *J* = 1.7 Hz), 107.6 (t, *J* = 2.6 Hz), 106.5 (t, *J* = 240 Hz). ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –119.2. GC/MS (EI): *m/z* = 197/199 [M]$^+$.

Anal. Calcd. for $C_4H_2BrF_2NO$: C, 24.27; H, 1.02; N, 7.08; Br, 40.36. Found: C, 24.13; H, 1.19; N, 6.73; Br, 40.62.

Ethyl 5-acetylisoxazole-3-carboxylate (31). Chloroxime **1a** (1.27 g, 8.39 mmol) was dissolved in EtOAc (15 mL), then methyl ethynyl ketone (600 mg, 8.81 mmol) and $NaHCO_3$ (775 mg, 9.23 mmol) were added to the solution at rt. The resulting mixture was stirred overnight; the completion of reaction was monitored by ^{1}H NMR spectroscopy. Next, the solution was dried over Na_2SO_4, filtered through a plug of silica gel and evaporated in *vacuo*. Yield 1.20 (78%); colorless liquid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.73 (s, 1H), 4.40 (q, J = 7.1 Hz, 2H), 2.60 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 186.3, 167.4, 159.0, 157.3, 109.3, 62.6, 27.8, 14.2. LC/MS (CI): *m/z* = 184 $[M+H]^+$. Anal. Calcd. for $C_8H_9NO_4$: C, 52.46; H, 4.95; N, 7.65. Found: C, 52.53; H, 5.17; N, 7.51.

Ethyl 5-(1,1-difluoroethyl)isoxazole-3-carboxylate (32). Ethyl 5-acetylisoxazole-3-carboxylate (**31**, 40.0 g, 0.218 mol) was dissolved in CH_2Cl_2 (400 mL) and the solution was cooled to –4 °C under argon atmosphere. Morpholinosulfur trifluoride (40.1 g, 0.229 mol) in CH_2Cl_2 (400 mL) was added dropwise (internal temperature was between –40 to –35 °C.). The resulting mixture was stirred at rt for 1 week. Then, the reaction mixture was poured into brine–ice (*ca.* 4 mL – 4 g, 1/1, v/m) and $NaHCO_3$ was added until pH = 7–8. Most of CH_2Cl_2 was evaporated in *vacuo*, and aqueous phase was extracted with EtOAc (3×300 mL). Combined organic phases were washed with brine (2×100 mL) and dried over Na_2SO_4 and the solvent was evaporated in *vacuo*. The compound was purified but distillation in *vacuo*. Yield 37.1 g (83%); colorless liquid; bp 31–33 °C / 3.75 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (s, 1H), 4.44 (q, J = 7.1 Hz, 2H), 2.02 (t, J = 18.4 Hz, 3H), 1.40 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7 (t, J = 37.4 Hz), 159.0, 156.4, 115.6 (t, J = 238 Hz), 103.3, 62.6, 23.3 (t, J = 26.4 Hz), 14.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ –89.5. LC/MS (CI): *m/z* = 206 $[M+H]^+$. Anal. Calcd. for $C_8H_9F_2NO_3$: C, 46.84; H, 4.42; N, 6.83. Found: C, 46.94; H, 4.74; N, 6.73.

5-(1,1-Difluoroethyl)isoxazole-3-carboxylic acid (33). A solution of the ester **32** (36.5 g, 0.180 mol) in MeOH (400 mL) was cooled to 0 °C, and pre-cooled absolute solution of NaOH (7.83 g, 0.196 mol) in MeOH (33.2 mL) was added dropwise (NOTE: the reaction is highly exothermic). After addition, the mixture was stirred for 1 h at 0 °C to rt, and evaporated in *vacuo* to dryness. Then, 6 M aq HCl (35 mL)

was added in portions, and the reaction mixture was stirred for 10 min at rt (NOTE: MeOH traces led to formation of the corresponding methyl esters *via* the tranesterification reaction). Most of solvents was evaporated in *vacuo*, the residue was diluted with CH_2Cl_2 (400 mL), dried over Na_2SO_4, and evaporated in *vacuo*. The compound; purified by column chromatography on silica gel using gradient $CHCl_3$ – THF. Yield 29.0 g (91% from the ester **31**); beige crystals; mp 85–86 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.25 (s, 1H), 6.95 (s, 1H), 2.05 (t, J = 18.5 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 168.4 (t, J = 37.5 Hz), 163.4, 155.7, 115.5 (t, J = 238 Hz), 103.5 (t, J = 2.2 Hz), 23.3 (t, J = 26.3 Hz). ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –89.5. LC/MS (CI): *m/z* = 178 $[M+H]^+$. Anal. Calcd. for $C_6H_5F_2NO_3$: C, 40.69; H, 2.85; N, 7.91. Found: C, 40.96; H, 2.89; N, 8.07.

5-(1,1-Difluoroethyl)isoxazol-3-amine (34). Carboxylic acid **33** (16.8 g, 95.0 mmol) was suspended in *t*-BuOH (150 mL), then Et_3N (15.2 mL,11.1 g, 0.109 mol) and DPPA (22.5 mL, 28.8 g, 0.105 mol) were added at rt. The resulting mixture was stirred at 83 °C overnight, then evaporated in *vacuo* to dryness. The residue was dissolved in EtOAc (250 mL), washed with pre-cooled to 5 °C 10% aq NaOH (3×50 mL), brine (3×50 mL), dried over Na_2SO_4, filtered through a plug of silica gel, and evaporated in *vacuo*. The residue was suspended in *t*-BuOMe (75 mL) and filtered through a plug of silica gel, and evaporated in *vacuo*. The obtained residue was dissolved in MeOH (75 mL), the solution was cooled to cooled to –1 °C and acetyl chloride (7.09 mL, 7.83 g, 99.8 mmol) was added dropwise at –1 °C. The resulting mixture was warmed up to rt, stirred for 1 h, then cooled to 0 °C and NaOH (4.79 g, 0.120 mol) in MeOH (20.3 mL) was added in portions at 0 °C. The solvent was evaporated in *vacuo*, the residue was dissolved in CH_2Cl_2 (100 mL), filtered through a pad of Na_2SO_4 and evaporated in *vacuo*. Yield 5.49 g (39%); beige crystals; mp 69–71 °C ^{1}H NMR (400 MHz, Benzene-d_6) δ 5.35 (s, 1H), 3.43 (s, 2H), 1.48 (t, J = 18.5 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, Benzene-d_6) δ 165.4 (t, J = 36.0 Hz), 163.1, 116.3 (t, J = 237 Hz), 95.1, 22.4 (t, J = 26.6 Hz). ^{19}F{^{1}H} NMR (376 MHz, Benzene-d_6) δ –89.6. GC/MS (EI): *m/z* = 148 $[M]^+$. Anal. Calcd. for $C_5H_6F_2N_2O$: C, 40.55; H, 4.08; N, 18.91. Found: C, 40.27; H, 3.85; N, 18.87.

(3-(Chloromethyl)isoxazol-5-yl)methanol (36). 2-Chloroacetaldehyde oxime (**35**, 207 g, 2.21 mol) was dissolved in DMF (2000 mL) and the solution was cooled to 0 °C. NCS (310 g, 2.32 mol) and then

4 M HCl – 1,4-dioxane (55.3 mL, 0.221 mol) were added to the solution. The resulting mixture was warmed up to rt and stirred overnight. Then, propargylic alcohol (153 mL, 149 g, 2.65 mol) and $NaHCO_3$ (316 g, 3.76 mol) were added. The resulting mixture was stirred at rt for 48 h, then most of solvents was evaporated in *vacuo*. The residue was diluted with *t*-BuOMe (1500 mL), the precipitate was filtered off, and the mother liquor was evaporated in *vacuo*. The compound was purified but distillation in *vacuo*. Yield 134 g (41%); colorless liquid; bp 81–83 °C / 0.1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.36 (s, 1H), 4.76 (s, 2H), 4.56 (s, 2H), 2.14 (s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 172.7, 160.9, 101.7, 56.0, 35.4. GC/MS (EI): *m/z* = 147/149 $[M]^+$. Anal. Calcd. for $C_5H_6ClNO_2$: C, 40.70; H, 4.10; N, 9.49; Cl, 24.02. Found: C, 40.98; H, 4.39; N, 9.77; Cl, 23.89.

3-(Chloromethyl)isoxazole-5-carbaldehyde (37). Alcohol **36** (119 g, 0.807 mol) was dissolved in CH_2Cl_2 (1000 mL) and the solution was cooled to 0 C. Then, PCC (261 g, 1.21 mol) and silica gel (261 g) were added. The resulting mixture was warmed up to rt and stirred overnight, the precipitate was filtered through silica gel, and the mother liquor was evaporated in vacuo. The compound was purified by distillation in vacuo. Yield.79.9 g (68%); colorless liquid; bp 35–36 °C / 0.1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.99 (s, 1H), 7.10 (s, 1H), 4.68 (s, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 177.9, 166.4, 161.7, 108.4, 35.0. GC/MS (EI): *m/z* = 145/147 $[M]^+$. Anal. Calcd. for $C_5H_4ClNO_2$: C, 41.26; H, 2.77; N, 9.62; Cl, 24.36. Found: C, 41.04; H, 2.39; N, 9.91; Cl, 24.68.

General procedure for the preparation of (2,2,2-trifluoro-1-hydroxyethyl)isoxazoles 39 or ketones 43.

The corresponding aldehyde **17g**, **17h** or **17k–m** or Weinreb amides **42a** or **42b** (40.0 mmol) was dissolved in THF 0.4 M solution of **17** or **42**) under argon atmosphere, and the solution was cooled to 0 °C. Then, $TMSCF_3$ (6.26 g, 44.0 mmol, 1.1 eq) and CsF (608 mg, 4.00 mmol, 0.1 eq) were added, and the resulting mixture was stirred overnight at rt. Then H_2O (15 mL) was added at rt, and the resulting mixture was stirred for 2 h, then evaporated in *vacuo*. The aqueous residue was extracted with EtOAc (3×25 mL), dried over Na_2SO_4, filtered through a plug of silica gel, and evaporated in *vacuo*.

***tert*-Butyl ((1*S*)-1-(5-(2,2,2-trifluoro-1-hydroxyethyl)isoxazol-3-yl)ethyl)carbamate (39g).** The compound was purified by distillation in *vacuo* or by column chromatography on silica gel (220 g

RediSep column; run length: 41.7 CV; flow rate: 95 mL / min; rack: 16 mm × 150 mm tubes) using hexanes – *t*-BuOMe as eluent, or by HPLC (SunFire C18 Column, 100 Å, 3.5 μm, 4.6 mm×150 mm, 0–6.5 min; H_2O – MeCN; flow rate 30mL / min). Yield 5.59 g (44%); colorless powder; mp 88–91 °C. $[\alpha]^{20}_D$ = –37.9 (*c* = 34.9, $CHCl_3$). ^1H NMR (400 MHz, DMSO-d_6) δ 7.45 (d, *J* = 8.5 Hz, 1H), 7.39 (dd, *J* = 6.7, 2.0 Hz, 1H), 6.53 (s, 1H), 5.54 (p, *J* = 6.4 Hz, 1H), 4.80 – 4.69 (m, 1H), 1.38 (s, 9H), 1.34 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 166.5 (d, *J* = 33.2 Hz), 155.0, 123.8 (q, *J* = 283 Hz), 102.6, 79.2, 78.3, 64.8 (q, *J* = 33.0 Hz), 42.9, 28.2, 20.0. $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6) δ -76.9 (d, *J* = 7.1 Hz). GC/MS (EI): *m/z* = 57 [*t*-Bu]$^+$, 194 [M–$NHCO_2$*t*-Bu]$^+$, 211 [M–CO_2–$H_2C{=}C(CH_3)_2$]$^+$, 237 [M–O*t*-Bu]$^+$, 254 [M–$H_2C{=}C(CH_3)_2$]$^+$, 310 [M]$^+$. Anal. Calcd. for $C_{12}H_{17}F_3N_2O_4$: C, 46.45; H, 5.52; N, 9.03. Found: C, 46.33; H, 5.28; N, 8.90.

***tert*-Butyl ((1*R*)-1-(5-(2,2,2-trifluoro-1-hydroxyethyl)isoxazol-3-yl)ethyl)carbamate (39h).** The compound was purified by HPLC (SunFire C_{18} Column, 100 Å, 3.5 μm, 4.6 mm×150 mm, 0–6.5 min; H_2O – MeCN; flow rate 30mL / min). Yield 6.08 g (49%); yellowish oil. $[\alpha]^{20}_D$ = +38.8 (*c* = 34.9, $CHCl_3$). The spectral data are analogous to that of *S*-isomer **39g**. GC/MS (EI): *m/z* = 211 [M–CO_2–$H_2C{=}C(CH_3)_2$]$^+$, 237 [M–O*t*-Bu]$^+$, 254 [M–$H_2C{=}C(CH_3)_2$]$^+$. Anal. Calcd. for $C_{12}H_{17}F_3N_2O_4$: C, 46.45; H, 5.52; N, 9.03. Found: C, 46.35; H, 5.33; N, 8.64.

(2*S*)-*tert*-Butyl 2-(5-(2,2,2-trifluoro-1-hydroxyethyl)isoxazol-3-yl)pyrrolidine-1-carboxylate (39k). The compound was purified by HPLC (SunFire C_{18} Column, 100 Å, 3.5 μm, 4.6 mm×150 mm, 0–6.5 min; H_2O – MeCN; flow rate 30mL / min). Yield 12.8 g (95%); colorless powder; mp 84–87 °C. $[\alpha]^{20}_D$ = -63.7 (*c* = 14.9, $CHCl_3$). ^1H NMR (400 MHz, DMSO-d_6) δ 7.40 (s, 1H), 6.52 (s, 1H), 5.52 (s, 1H), 4.95 – 4.80 (m, 1H), 3.44 – 3.32 (m, 2H), 2.31 – 2.18 (m, 1H), 1.93 – 1.83 (m, 3H), 1.39 (s, 3H) and 1.20 (s, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 167.1 and 167.0 and 166.9, 166.6 and 166.5 and 166.4, 154.1 and 153.5, 124.1 (q, *J* = 283 Hz), 103.4 and 103.0 and 102.7, 79.3 and 79.1, 65.2 (qd, *J* = 33.8, 33.3, 11.8 Hz), 53.56, 49.1, 46.8 and 46.6, 33.2 and 31.7, 28.5 and 28.1, 27.2, 24.1 and 23.5. $^{19}F\{^1H\}$ NMR (470 MHz, DMSO-d_6) δ --76.30 – -76.40 (m), -76.5 (dd, *J* = 77.7, 7.1 Hz). GC/MS (EI):

m/z = 57 [*t*-Bu]$^+$, 237 [M–CO_2–H_2C=$C(CH_3)_2$]$^+$, 263 [M–O*t*-Bu]$^+$, 280 [M–H_2C=$C(CH_3)_2$]$^+$, 336 [M]$^+$. Anal. Calcd. for $C_{14}H_{19}F_3N_2O_4$: C, 50.00; H, 5.69; N, 8.33. Found: C, 50.09; H, 5.79; N, 8.08.

(2*R*)-*tert*-Butyl 2-(5-(2,2,2-trifluoro-1-hydroxyethyl)isoxazol-3-yl)pyrrolidine-1-carboxylate (39l). The compound was purified by HPLC (SunFire C_{18} Column, 100 Å, 3.5 μm, 4.6 mm×150 mm, 0–6.5 min; H_2O – MeCN; flow rate 30mL / min). Yield 12.8 g (95%); colorless powder; mp 84–87 °C. $[\alpha]^{20}_D$ = +63.9 (*c* = 14.9, $CHCl_3$). The spectral data are analogous to that of *S*-isomer **39k**. GC/MS (EI): *m/z* = 57 [*t*-Bu]$^+$, 237 [M–CO_2–H_2C=$C(CH_3)_2$]$^+$, 263 [M–O*t*-Bu]$^+$, 280 [M–H_2C=$C(CH_3)_2$]$^+$, 336 [M]$^+$. Anal. Calcd. for $C_{14}H_{19}F_3N_2O_4$: C, 50.00; H, 5.69; N, 8.33. Found: C, 49.90; H, 6.09; N, 8.14.

***tert*-Butyl 4-(5-(2,2,2-trifluoro-1-hydroxyethyl)isoxazol-3-yl)piperi-dine-1-carboxylate (39m).** The compound was purified by HPLC (SunFire C_{18} Column, 100 Å, 3.5 μm, 4.6 mm × 150 mm, 0–6.5 min; H_2O – MeCN; flow rate 30mL / min). Yield 10.5 g (75%); yellowish oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.43 – 7.33 (m, 1H), 6.65 (d, *J* = 4.6 Hz, 1H), 5.50 (p, *J* = 6.4 Hz, 1H), 3.97 (d, *J* = 13.1 Hz, 2H), 2.97 – 2.80 (m, 3H), 1.86 (d, *J* = 13.0 Hz, 2H), 1.55 – 1.46 (m, 2H), 1.40 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 167.2, 166.7, 154.3, 124.1 (q, *J* = 283 Hz), 103.3, 79.1, 65.2 (q, *J* = 32.9 Hz), 43.4, 33.7, 30.6, 28.5. ^{19}F{^{1}H} NMR (470 MHz, DMSO-d_6) δ -76.5 (d, *J* = 7.2 Hz). LC/MS (CI): *m/z* = 251 [M–CO_2-H_2C=$C(CH_3)_2$+H]$^+$, 277 [M–O*t*-Bu+H]$^+$, 295 [M–H_2C=$C(CH_3)_2$+H]$^+$. Anal. Calcd. for $C_{15}H_{21}F_3N_2O_4$: C, 51.43; H, 6.04; N, 8.00. Found: C, 51.22; H, 6.42; N, 7.70.

(*S*)-*tert*-Butyl 2-(4-(2,2,2-trifluoroacetyl)isoxazol-3-yl)pyrrolidine-1-carboxylate (43a). The compound was purified by HPLC (SunFire C_{18} Column, 100 Å, 3.5 μm, 4.6 mm × 150 mm, 0–6.5 min; H_2O – MeCN; flow rate 30mL / min); existed as a mixture of *ca.* 11:9 of rotamers. Yield 9.63 g (72%); yellowish liquid. $[\alpha]^{21}_D$ = -33.4 (*c* = 35.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.07 (s, 0.45H) and 9.03 (s, 0.55H), 5.41 (dd, *J* = 8.1, 2.0 Hz, 0.55H) and 5.33 (dd, *J* = 7.7, 2.9 Hz, 0.45H), 3.67 – 3.60 (m, 0.9H) and 3.52 – 3.40 (m, 1.1H), 2.40 – 2.30 (m, 1H), 2.00 – 1.79 (m, 3H), 1.41 (s, 4.95H) and 1.22 (s, 4.05H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 174.1 (q, *J* = 38.3 Hz), 165.3 and 164.5, 165.0 (q, *J* = 4.9 Hz) and 164.8 (q, *J* = 4.9 Hz), 154.1 and 153.5, 115.7 (q, *J* = 290 Hz), 112.9 and 112.7, 79.9 and 79.7, 53.8 and 53.4, 46.7 and 46.4, 32.2 and 31.2, 28.4 and 28.1, 23.4 and 22.9. ^{19}F{^{1}H} NMR (376 MHz,

$CDCl_3$) δ –75.8 and –75.9. LC/MS (CI): *m/z* = 235 $[M–CO_2–H_2C=C(CH_3)_2+H]^+$. Anal. Calcd. for $C_{14}H_{17}F_3N_2O_4$: C, 50.30; H, 5.13; N, 8.38. Found: C, 50.32; H, 5.49; N, 8.44.

(*R*)-*tert*-Butyl 2-(4-(2,2,2-trifluoroacetyl)isoxazol-3-yl)pyrrolidine-1-carboxylate (43b). The compound was purified by HPLC (SunFire C18 Column, 100 Å, 3.5 μm, 4.6 mm×150 mm, 0–6.5 min; H_2O – MeCN; flow rate 30mL / min); existed as a mixture of *ca.* 11:9 of rotamers. Yield 9.89 g (74%); yellowish liquid. $[\alpha]^{21}_D$ = +34.3 (*c* = 35.5, $CHCl_3$). The spectral data are analogous to that of *S*-isomer **43a**. Anal. Calcd. for $C_{14}H_{17}F_3N_2O_4$: C, 50.30; H, 5.13; N, 8.38. Found: C, 50.28; H, 5.03; N, 8.72.

General procedure for the preparation of trifluoromethyl ketones 40.

The corresponding alcohol **39k** or **39l** (3.36 g, 10.0 mmol, 1 eq) was dissolved in CH_2Cl_2 (35 mL, 0.29 M solution of **39**), then Et_3N (4.39 mL, 3.18 g, 31.5 mmol, 3.15 eq) and DMSO (HPLC grade, 3.55 mL, 3.91 g, 50.0 mmol, 5 eq) were added under argon atmosphere. The resulting solution was cooled to 0 °C, and Py·SO_3 (4.77 g, 30.0 mmol, 3 eq) was added. The resulting mixture was stirred overnight at rt, the completion of the reaction was monitored by ^{1}H NMR. The mixture was poured onto ice (40 g), organic phase was separated and most of CH_2Cl_2 evaporated in *vacuo*. The aqueous phase was extracted with EtOAc (3×40 mL), combined extracts were added to the residue obtained after CH_2Cl_2 evaporation. The resulting solution was washed with saturated aq $NaHSO_3$ (3×30 mL), brine (3×30 mL), dried over Na_2SO_4, and evaporated in *vacuo*.

(*S*)-*tert*-Butyl 2-(5-(2,2,2-trifluoro-1,1-dihydroxyethyl)isoxazol-3-yl)pyrrolidine-1-carboxylate (40k). The compound was purified by distillation in *vacuo* or by column chromatography on silica gel using $CHCl_3$ – MeCN as eluent; existed as a mixture of *ca.* 2:1 of rotamers. Yield 1.69 g (48%); colorless powder; mp 72–75 °C. $[\alpha]^{20}_D$ = –38.6 (*c* = 41.4, $CHCl_3$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 (d, *J* = 10.9 Hz, 1H), 6.51 (s, 1H), 4.93 – 4.81 (m, 1H), 3.57 – 3.39 (m, 2H), 2.46 – 2.10 (m, 2H), 1.94 – 1.81 (m, 3H), 1.39 (s, 3H), 1.21 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 168.7 and 170.0, 154.1 and 153.5, 122.8 (q, *J* = 289 Hz), 103.8 and 103.2, 90.2 (q, *J* = 32.4 Hz), 79.2, 53.6, 46.9 and 46.7, 33.2 and 31.7, 28.5 and 28.2, 24.1 and 23.5. ^{19}F{^{1}H} NMR (376 MHz, DMSO) δ –83.5, –83.6.

LC/MS (CI): *m/z* = 253 $[M–CO_2–H_2C=C(CH_3)_2+H]^+$. Anal. Calcd. for $C_{14}H_{19}F_3N_2O_5$: C, 47.73; H, 5.44; N, 7.95. Found: C, 47.66; H, 5.25; N, 7.97.

(*R*)-*tert*-Butyl 2-(5-(2,2,2-trifluoro-1,1-dihydroxyethyl)isoxazol-3-yl)pyrrolidine-1-carboxylate (40l). The compound was purified by distillation in *vacuo* or by column chromatography on silica gel using $CHCl_3$ – MeCN as eluent; existed as a mixture of *ca.* 2:1 of rotamers. Yield 1.59 g (45%); colorless powder; mp 72–75 °C. $[\alpha]^{20}_D$ = +39.5 (*c* = 41.4, $CHCl_3$). The spectral data are analogous to that of *S*-isomer **40k**. LC/MS (CI): *m/z* = 253 $[M–CO_2–H_2C=C(CH_3)_2+H]^+$. Anal. Calcd. for $C_{14}H_{19}F_3N_2O_5$: C, 47.73; H, 5.44; N, 7.95. Found: C, 47.46; H, 5.51; N, 7.61.

General procedure for the preparation of Weinreb amides 42

The corresponding carboxylic acid **41a** or **41b** (10.0 g; 35.4 mmol, 1 eq) was dissolved in CH_2Cl_2 (100 mL, 0.35 M solution of carboxylic acid **41**), and CDI (6.86 g; 42.5 mmol, 1.2 eq) was added in portions at rt. The resulting mixture was stirred at rt for 1 h, and *N*,*O*-dimethylhydroxylamine hydrochloride (3.80 g; 38.9 mmol, 1.1 eq) was added in portions at rt. The reaction mixture was stirred overnight, then pre-cooled to 10 °C H_2O (7 mL) was added, and the solution was stirred for 10 min. Organic phase was separated, washed with saturated aq $NaHSO_3$ (3×30 mL), brine (3×30 mL), dried over Na_2SO_4, and evaporated in *vacuo*.

(*S*)-*tert*-Butyl 2-(4-(methoxy(methyl)carbamoyl)isoxazol-3-yl)pyrroli-dine-1-carboxylate (42a). The compound was purified by HPLC (SunFire C18 Column, 100 Å, 3.5 μm, 4.6 mm×150 mm, 0–6.5 min; MeCN; flow rate 30mL / min). The compound existed as a mixture of *ca.* 11:9 of rotamers. Yield 10.7 g (93%); yellowish liquid. $[\alpha]^{21}_D$ = –30.1 (*c* = 30.7, $CHCl_3$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.37 (s, 0.55H) and 9.34 (s, 0.45H), 5.37 – 5.35 (m, 0.45H) and 5.34 – 5.32 (m, 0.55H), 3.69 (s, 1.35H) and 3.68 (s, 1.65H), 3.48 – 3.41 (m, 1.1H) and 3.40 – 3.34 (m, 0.9H), 3.24 (s, 3H), 2.30 – 2.19 (m, 1H), 1.88 – 1.78 (m, 3H), 1.37 (s, 4.05H) and 1.18 (s, 4.95H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 165.9 and 165.2, 162.2, 160.9, 153.6 and 153.3, 111.1 and 111.0, 78.9 and 78.6, 61.6, 53.9 and 53.8, 46.8 and 46.5, 32.6, 31.8, 28.5 and 28.2, 23.3 and 22.6. LC/MS (CI): *m/z* = 226 $[M–CO_2–H_2C=C(CH_3)_2+H]^+$. Anal. Calcd. for $C_{15}H_{23}N_3O_5$: C, 55.37; H, 7.13; N, 12.92. Found: C, 55.60; H, 7.38; N, 12.63.

(*R*)-*tert*-Butyl 2-(4-(methoxy(methyl)carbamoyl)isoxazol-3-yl)pyrroli-dine-1-carboxylate (42b). The compound was purified by HPLC (SunFire C18 Column, 100 Å, 3.5 μm, 4.6 mm×150 mm, 0–6.5 min; MeCN; flow rate 30mL / min). Yield 10.4 (90%); yellowish liquid. $[\alpha]^{21}_{D}$ = +35.8 (*c* = 30.7, $CHCl_3$). The spectral data are analogous to that of *S*-isomer **42a**. LC/MS (CI): *m/z* = 226 [M–CO_2–$H_2C{=}C(CH_3)_2$+H]$^+$. Anal. Calcd. for $C_{15}H_{23}N_3O_5$: C, 55.37; H, 7.13; N, 12.92. Found: C, 55.41; H, 7.27; N, 13.28.

General procedure for the preparation of 1,4,2-oxadioazoles 50–53.

The corresponding chloroxime **1f**, **1h–j** (24.0 mmol, 1 eq) was dissolved in EtOAc (50 mL, 0.48 M solution of chloroxime **1**), then the corresponding fluoromethyl ketone **44–47** (25.2 mmol, 1.05 eq) or enamine **54** or **55** (25.2 mmol, 1.05 eq), and $NaHCO_3$ (6.04 g, 72.0 mmol, 3 eq) were added to the vigorously stirred solution at rt. The resulting mixture was stirred overnight. The resulting mixture was dried over Na_2SO_4, filtered through a plug of silica gel and evaporated in *vacuo*.

***tert*-Butyl 3-(5-(2-ethoxy-2-oxoethyl)-5-(trifluoromethyl)-1,4,2-dioxazol-3-yl)azetidine-1-carboxylate (50j).** The compound was purified by HPLC (SunFire C18 Column, 100 Å, 3.5 μm, 4.6 mm×150 mm, 0–6.5 min; H_2O – MeCN; flow rate 30mL / min). Yield 4.40 g (48% from **44**) or 3.30 g (36% from **54**); yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23 – 4.13 (m, 4H), 4.13 – 4.04 (m, 2H), 3.63 – 3.43 (m, 1H), 3.10 (dd, *J* = 8.3, 2.6 Hz, 2H), 1.41 (s, 9H), 1.24 (td, *J* = 7.2, 2.4 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 165.3, 160.4, 155.7, 120.5 (q, *J* = 289 Hz), 108.2 (q, *J* = 34.2 Hz), 80.1, 61.5, 51.2, 34.9, 28.2, 22.8, 13.9. ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ –135.2 (dd, *J* = 293, 54.1 Hz), -137.1 (dd, *J* = 293, 49.3 Hz). LC/MS (CI): *m/z* = 283 [M–CO_2–$H_2C{=}C(CH_3)_2$+H]$^+$. Anal. Calcd. for $C_{15}H_{21}F_3N_2O_6$: C, 47.12; H, 5.54; N, 7.33. Found: C, 47.07; H, 5.51; N, 7.03.

(2*S*)-*tert*-Butyl 2-(5-(2-ethoxy-2-oxoethyl)-5-(trifluoromethyl)-1,4,2-dioxazol-3-yl)pyrrolidine-1-carboxylate (50k). The compound was purified by HPLC (SunFire C18 Column, 100 Å, 3.5 μm, 4.6 mm×150 mm, 0–6.5 min; H_2O – MeCN; flow rate 30mL / min). The compound existed as a mixture of *ca.* 2:1 of diastereomers and rotamers. Yield 5.04 g (53% from **44**) or 4.09 g (43% from **54**); yellow oil. $[\alpha]^{20}_{D}$ = -42.5 (*c* = 50.6, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.76 – 4.67 (m, 0.33H) and 4.67 – 4.56

(m, 0.67H), 4.16 (s, 2H), 3.54 – 3.41 (m, 1.33H) and 3.42 – 3.31 (m, 0.67H), 3.05 (s, 2H), 2.24 – 2.10 (m, 2H), 2.06 – 1.88 (m, 2H), 1.42 (s, 3H) and 1.42 (s, 6H), 1.27 – 1.21 (m, 3H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 165.2 (d, J = 21.9 Hz), 161.1 (d, J = 6.9 Hz), 153.6 (d, J = 18.8 Hz), 120.5 (q, J = 289 Hz) and 120.5 (q, J = 289 Hz), 108.0 (q, J = 33.9 Hz), 80.5 (d, J = 20.4 Hz), 80.1, 61.4 (d, J = 3.5 Hz), 51.4 and 50.8, 46.2 and 45.8, 35.4 and 35.1, 30.2 (d, J = 68.6 Hz) and 29.3 (d, J = 24.8 Hz), 28.3 and 28.1, 24.0 (d, J = 17.6 Hz) and 23.1 (d, J = 65.0 Hz), 14.0. $^{19}F\{^{1}H\}$ NMR (470 MHz, $CDCl_3$) δ -85.6 (d, J = 8.4 Hz), -85.7 (d, J = 99.9 Hz). LC/MS (CI): *m/z* = 297 $[M–CO_2–H_2C=C(CH_3)_2+H]^+$. Anal. Calcd. for $C_{16}H_{23}F_3N_2O_6$: C, 48.48; H, 5.85; N, 7.07. Found: C, 48.26; H, 6.21; N, 7.44.

(2*R*)-*tert*-Butyl 2-(5-(2-ethoxy-2-oxoethyl)-5-(trifluoromethyl)-1,4,2-dioxazol-3-yl)pyrrolidine-1-carboxylate (50l). The compound was purified by HPLC (SunFire C18 Column, 100 Å, 3.5 µm, 4.6 mm×150 mm, 0–6.5 min; H_2O – MeCN; flow rate 30mL / min). Yield 4.95 g (52% from **44**) or 4.09 g (43% from **54**); yellow oil. $[\alpha]^{20}_D$ = +41.3 (*c* = 50.6, MeOH). The spectral data are analogous to that of *S*-isomer **50k**. LC/MS (CI): *m/z* = 297 $[M–CO_2–H_2C=C(CH_3)_2+H]^+$. Anal. Calcd. for $C_{16}H_{23}F_3N_2O_6$: C, 48.48; H, 5.85; N, 7.07. Found: C, 48,83; H, 6,14; N, 7,39.

Ethyl 2-(3-(((*tert*-butoxycarbonyl)amino)methyl)-5-(difluoromethyl)-1,4,2-dioxazol-5-yl)acetate (51f). The compound was purified by HPLC (SunFire C18 Column, 100 Å, 3.5 µm, 4.6 mm×150 mm, 0–6.5 min; H_2O – MeCN; flow rate 30mL / min). Yield 3.17 g (39%); brownish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96 (t, J = 54.3 Hz, 1H), 4.86 (s, 1H), 4.17 (q, J = 7.2 Hz, 2H), 4.10 (s, 2H), 3.04 (s, 2H), 1.43 (s, 9H), 1.26 (t, J = 7.1 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 166.6, 158.3, 155.3, 110.9 (t, J = 252 Hz), 109.7 (t, J = 24.9 Hz), 80.5, 61.5, 36.4, 34.2, 28.2, 14.0. $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ –135.7 (d, J = 294 Hz), –137.2 (d, J = 294 Hz). LC/MS (CI): *m/z* = 239 $[M–CO_2–H_2C=C(CH_3)_2+H]^+$. Anal. Calcd. for $C_{13}H_{20}F_2N_2O_6$: C, 46.15; H, 5.96; N, 8.28. Found: C, 46.25; H, 5.62; N, 8.40.

Ethyl 2-(3-((*S*)-1-((tert-butoxycarbonyl)amino)ethyl)-5-(difluoromethyl)-1,4,2-dioxazol-5-yl)acetate (51g). The compound was purified by HPLC (SunFire C18 Column, 100 Å, 3.5 µm, 4.6 mm×150 mm, 0–6.5 min; H_2O – MeCN; flow rate 30mL / min). Yield 3.81 g (45%); yellow oil.

$[\alpha]^{20}_D$ = -31.2 (*c* = 45.6, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95 (td, *J* = 54.4, 2.2 Hz, 1H), 4.72 (d, *J* = 85.7 Hz, 2H), 4.17 (qd, *J* = 7.2, 2.5 Hz, 2H), 3.03 (s, 2H), 1.44 (s, 3H), 1.42 (s, 9H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 166.6 (d, *J* = 11.3 Hz), 161.3 (d, *J* = 16.4 Hz), 154.6, 110.9 (t, *J* = 252 Hz), 109.6 (t, *J* = 24.8 Hz), 80.3, 61.5 (d, *J* = 5.2 Hz), 41.7, 36.4, 28.2, 18.4 (d, *J* = 8.1 Hz), 14.0. ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ –134.9 (dd, *J* = 110, 54.2 Hz), –135.5 (dd, *J* = 110, 54.2 Hz), –136.6 (dd, *J* = 54.7, 40.2 Hz), –137.2 (dd, *J* = 54.7, 40.2 Hz). LC/MS (CI): *m/z* = 351 $[M–H]^–$. Anal. Calcd. for $C_{14}H_{22}F_2N_2O_6$: C, 47.73; H, 6.29; N, 7.95. Found: C, 47.40; H, 6.06; N, 7.57.

Ethyl 2-(3-((*R*)-1-((tert-butoxycarbonyl)amino)ethyl)-5-(difluoromethyl)-1,4,2-dioxazol-5-yl)acetate (51h). The compound was purified by HPLC (SunFire C18 Column, 100 Å, 3.5 μm, 4.6 mm×150 mm, 0–6.5 min; H_2O – MeCN; flow rate 30mL / min). Yield 3.64 g (43%); yellow oil $[\alpha]^{20}_D$ = +30.4 (*c* = 45.6, MeOH). The spectral data are analogous to that of *S*-isomer **51g**. LC/MS (CI): *m/z* = 351 $[M–H]^–$. Anal. Calcd. for $C_{14}H_{22}F_2N_2O_6$: C, 47.73; H, 6.29; N, 7.95. Found: C, 48.12; H, 6.13; N, 8.03.

***tert*-Butyl 3-(5-(difluoromethyl)-5-(2-ethoxy-2-oxoethyl)-1,4,2-dioxazol-3-yl)azetidine-1-carboxylate (51j).** The compound was purified by HPLC (SunFire C18 Column, 100 Å, 3.5 μm, 4.6 mm×150 mm, 0–6.5 min; H_2O – MeCN; flow rate 30mL / min). Yield 4.37 g (50% from **45**) or 3.58 g (41% from **55**); yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94 (t, *J* = 54.2 Hz, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 4.16 – 4.13 (m, 2H), 4.09 (ddd, *J* = 8.8, 6.1, 3.0 Hz, 2H), 3.51 (tt, *J* = 8.8, 6.0 Hz, 1H), 3.05 (s, 2H), 1.42 (s, 9H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 166.4, 160.2, 155.7, 111.0 (t, *J* = 252 Hz), 109.6 (t, *J* = 24.5 Hz), 80.1, 61.5, 51.4, 36.5, 28.3, 22.9, 14.0. ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ –135.2 (ddd, *J* = 294, 54.2, 5.8 Hz), –137.1 (dd, *J* = 294, 54.2 Hz). LC/MS (CI): *m/z* = 265 $[M–CO_2–H_2C=C(CH_3)_2+H]^+$, 309 $[M–H_2C=C(CH_3)_2+H]^+$. Anal. Calcd. for $C_{15}H_{22}F_2N_2O_6$: C, 49.45; H, 6.09; N, 7.69. Found: C, 49.41; H, 6.45; N, 7.70.

***tert*-Butyl (2*S*)-2-(5-(difluoromethyl)-5-(2-ethoxy-2-oxoethyl)-1,4,2-dioxazol-3-yl)pyrrolidine-1-carboxylate (51k).** The compound was purified by HPLC (SunFire C18 Column, 100 Å, 3.5 μm, 4.6 mm×150 mm, 0–6.5 min; H_2O – MeCN; flow rate 30mL / min). The compound existed as a mixture of

ca. 2:1 of diastereomers and rotamers. Yield 5.18 g (57% from **45**) or 4.00 g (44% from **55**); yellow oil. $[\alpha]^{20}_{D}$ = -81.7 (*c* = 48.5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96 (dt, *J* = 54.6, 7.7 Hz, 1H), 4.58 (dd, *J* = 8.0, 4.1 Hz, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 3.40 (d, *J* = 30.4 Hz, 2H), 3.10 – 2.95 (m, 2H), 2.12 (d, *J* = 21.3 Hz, 2H), 2.02 (dt, *J* = 12.7, 7.3 Hz, 1H), 1.95 – 1.86 (m, 1H), 1.43 (d, *J* = 2.7 Hz, 9H)+, 1.24 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 166.7 and 166.5 and 166.4 and 166.4, 161.2 and 161.0 and 160.9, 153.9 and 153.6 and 153.5 and 153.5, 113.2 – 112.4 (m), 111.1 – 110.4 (m), 109.6 – 108.4 (m), 80.5 – 80.3 (m), 80.5 and 80.4 and 80.2 and 80.1, 61.4 and 61.4 and 61.3, 51.1 and 51.0 and 50.9, 46.5 and 46.4 and 46.1 and 46.0, 37.3 and 36.6 and 36.4 and 34.8, 30.6 and 30.4 and 29.7, 28.2, 24.1 and 23.3 and 23.2, 14.0 and 13.9. ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ -134.6 – -138.5 (m) LC/MS (CI): *m/z* = 279 $[M–CO_2–H_2C=C(CH_3)_2+H]^+$. Anal. Calcd. for $C_{16}H_{24}F_2N_2O_6$: C, 50.79; H, 6.39; N, 7.40. Found: C, 50.94; H, 6.04; N, 7.12.

***tert*-Butyl (2*R*)-2-(5-(difluoromethyl)-5-(2-ethoxy-2-oxoethyl)-1,4,2-dioxazol-3-yl)pyrrolidine-1-carboxylate (51l).** The compound was purified by HPLC (SunFire C18 Column, 100 Å, 3.5 μm, 4.6 mm×150 mm, 0–6.5 min; H_2O – MeCN; flow rate 30mL / min). Yield 4.81 g (53% from **45**) or 3.72 g (41% from **55**); yellow oil. $[\alpha]^{20}_{D}$ = 80.4 (*c* = 48.5, MeOH). The spectral data are analogous to that of *S*-isomer **51k**. LC/MS (CI): *m/z* = 279 $[M–CO_2–H_2C=C(CH_3)_2+H]^+$. Anal. Calcd. for $C_{16}H_{24}F_2N_2O_6$: C, 50.79; H, 6.39; N, 7.40. Found: C, 50.92; H, 6.04; N, 7.72.

***tert*-Butyl 3-(5-(bromomethyl)-5-(trifluoromethyl)-1,4,2-dioxazol-3-yl)azetidine-1-carboxylate (52j).** The compound was purified by HPLC (SunFire C18 Column, 100 Å, 3.5 μm, 4.6 mm×150 mm, 0–6.5 min; H_2O – MeCN; flow rate 30mL / min). Yield 3.46 g (37%); brownish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 (t, *J* = 9.0 Hz, 3H), 4.12 (t, *J* = 8.0 Hz, 1H), 3.86 (d, *J* = 12.5 Hz, 1H), 3.78 (d, *J* = 12.5 Hz, 1H), 3.59 (d, *J* = 8.5 Hz, 1H), 1.45 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 160.5, 155.7, 119.8 (q, *J* = 290 Hz), 108.0 (q, *J* = 33.7 Hz), 80.2, 51.2, 28.2, 27.9, 22.7. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -83.4. LC/MS (CI): *m/z* = 289/291 $[M–CO_2–H_2C=C(CH_3)_2+H]^+$, 297 $[M–CH_2Br]^+$, 333/335 $[M–H_2C=C(CH_3)_2+H]^+$. Anal. Calcd. for $C_{12}H_{16}BrF_3N_2O_4$: C, 37.04; H, 4.14; N, 7.20; Br, 20.53. Found: C, 37.12; H, 4.01; N, 6.86; Br, 20.45.

***tert*-Butyl 3-(5-(bromomethyl)-5-(difluoromethyl)-1,4,2-dioxazol-3-yl)azetidine-1-carboxylate (53j).** The compound was purified by HPLC (SunFire C18 Column, 100 Å, 3.5 µm, 4.6 mm×150 mm, 0–6.5 min; H_2O – MeCN; flow rate 30mL / min). Yield 3.56 g (40%); yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 5.93 (t, J = 53.8 Hz, 1H), 4.24 – 4.17 (m, 2H), 4.15 – 4.12 (m, 1H), 3.76 – 3.70 (m, 1H), 3.56 (s, 1H), 1.57 (s, 2H), 1.44 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 160.37 (d, J = 5.5 Hz), 155.70, 110.37 (td, J = 252.4, 16.1 Hz), 109.17 (d, J = 24.8 Hz), 80.17, 51.35, 41.22, 28.19 (d, J = 8.8 Hz), 22.87 (d, J = 3.4 Hz). ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -135.2 (d, J = 62.0 Hz), -136.0 (d, J = 41.5 Hz). LC/MS (CI): m/z = 271/271 $[M–CO_2–H_2C=C(CH_3)_2+H]^+$, 315/317 $[M–H_2C=C(CH_3)_2+H]^+$. Anal. Calcd. for $C_{12}H_{17}BrF_2N_2O_4$: C, 38.83; H, 4.62; N, 7.55; Br, 21.53. Found: C, 38.46; H, 4.38; N, 7.55; Br, 21.39.

Ethyl 3-(((*tert*-butoxycarbonyl)amino)methyl)-5-(difluoromethyl)-isoxazole-4-carboxylate (48f). The chloroxime **1f** (5.00 g, 24.0 mmol) was dissolved in EtOAc (50 mL), then ethyl 4,4-difluoro-3-oxobutanoate (**45**, 4.19 g, 25.2 mmol), $NiCl_2·6H_2O$ (570 mg, 2.40 mmol), and $NaHCO_3$ (6.04 g, 72.0 mmol) were added to the vigorously stirred solution at rt. The resulting mixture was stirred overnight. The resulting mixture was dried over Na_2SO_4, filtered through a plug of silica gel and evaporated in *vacuo*. The compound was purified by HPLC (SunFire C18 Column, 100 Å, 3.5 µm, 4.6 mm×150 mm, 0–6.5 min; H_2O – MeCN; flow rate 30mL / min). Yield 999 mg (13%); yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, J = 45.2 Hz, 1H), 5.29 (s, 1H), 4.61 (s, 2H), 4.38 (q, J = 7.2 Hz, 2H), 1.43 (s, 9H), 1.38 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 160.7, 160.0, 159.0, 155.4, 111.6, 105.7 (t, J = 241 Hz), 80.1, 62.2, 36.7, 28.3, 14.1. ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ -120.0, -120.1. LC/MS (CI): m/z = 221 $[M–CO_2+H_2C=C(CH_3)_2+H]^+$, 265 $[M–H_2C=C(CH_3)_2+H]^+$, 343 $[M+Na]^+$. Anal. Calcd. for $C_{13}H_{18}F_2N_2O_5$: C, 48.75; H, 5.66; N, 8.75. Found: C, 48.68; H, 5.44; N, 9.12.

General procedure for the preparation of F_3C-ABT-418 analogues 56

The corresponding amine **13k** or **13l** (5.14 g, 21.2 mmol) was suspended in dichloroethane (400 mL). Then, MeOH (100 mL), 30% aq CH_2O (20 mL) and $NaBH(OAc)_3$ (14.0 g, 66.1 mmol) were added. The resulting mixture was stirred overnight at rt, then evaporated in *vacuo*. The residue was diluted with

EtOAc (400 mL), and K_2CO_3 was added until pH = 10 (CAUTION: extensive CO_2 evolution). The reaction mixture was stirred over Na_2SO_4 for *ca.* 10 min, the precipitate was filtered off, and the filtrate was evaporated in *vacuo*.

(*S*)-3-(1-Methylpyrrolidin-2-yl)-5-(trifluoromethyl)isoxazole (56k). The compound was purified by distillation in *vacuo*. Yield 4.11 g (88%); colorless powder; mp 56–58 °C; bp 71–73 °C / 0.7 mmHg. $[\alpha]^{20}_D$ = –63.3 (*c* = 45.4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (s, 1H), 3.47 (t, *J* = 8.1 Hz, 1H), 3.19 (t, *J* = 8.3 Hz, 1H), 2.35 (d, *J* = 8.9 Hz, 1H), 2.26 (s, 4H), 2.22 (d, *J* = 8.9 Hz, 2H), 2.00 – 1.93 (m, 1H), 1.85 (td, *J* = 15.0, 12.8, 5.5 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.0, 158.6 (q, *J* = 42.4 Hz), 117.9 (q, *J* = 270 Hz), 103.6, 61.4, 56.6, 40.3, 32.3, 23.0. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): *δ* –64.9. LC/MS (CI): *m/z* = 221 $[M+H]^+$. Anal. Calcd. for $C_9H_{11}F_3N_2O$: C, 49.09; H, 5.04; N, 12.72. Found: C, 48.92; H, 5.36; N, 12.46.

(*R*)-3-(1-Methylpyrrolidin-2-yl)-5-(trifluoromethyl)isoxazole (56l). The compound was purified by distillation in *vacuo*. Yield 4.20 g (90%); colorless powder; mp 56–58 °C; bp 71–73 °C / 0.7 mmHg. $[\alpha]^{20}_D$ = 63.1 (*c* = 45.4). The spectral data are analogous to that of *S*-isomer **56k**. LC/MS (CI): *m/z* = 221 $[M+H]^+$. Anal. Calcd. for $C_9H_{11}F_3N_2O$: C, 49.09; H, 5.04; N, 12.72. Found: C, 48.94; H, 4.79; N, 12.49.

***N′*-(3-Chlorophenyl)-2-oxo-2-(5-(trifluoromethyl)isoxazol-3-yl)aceto-hydrazonoyl cyanide (57).** 1.6 M hexanes solution of MeLi (8.96 mL) was added dropwise to the solution of MeCN (1.50 mL) in THF (30 mL) at –78 °C under argon atmosphere. The resulting solution was stirred for –78 to –50 °C for 0.5 h. Then, ester **3a** (1.50 g, 7.17 mmol) was added at –78 to –50 °C, and the solution was warmed up to 0 °C for 1 h. After, HOAc (0.82 mL) was added, the reaction mixture was poured into H_2O (25 mL), extracted with EtOAc (50 mL), dried over Na_2SO_4, and evaporated in *vacuo*. The crude compound **56** was used in the next step without further purification. Next, 1 M aq HCl (1.05 mL) and $NaNO_2$ (592 mg, 8.58 mmol) in H_2O (2.5 mL) were added to the solution of *M*–chloroaniline (1.10 g, 8.63 mmol) in H_2O (15 mL) at –5 °C (NOTE: the solution should be homogenous after HCl addition; if the precipitate is formed, additional amount of H_2O should be added). After 30 min, NaOAc·3H_2O (1.94 g, 14.3 mmol) was added, followed by addition of solution of **58** (*ca.* 1.46 g) in EtOH (15 mL) at 0 °C. After 5 min, the resulting mixture was poured into H_2O (30 mL) at 0 °C, and then extracted with EtOAc (60 mL). The

compound was purified by HPLC (SunFire C18 Column, 100 Å, 3.5 µm, 4.6 mm×150 mm, 0–6.5 min; MeCN; flow rate 30mL / min). Yield 2.45 g (46%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.44 (m, 1H), 7.43 – 7.26 (m, 3H), 7.19 (d, *J* = 7.1 Hz, 2H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 176.4 and 175.9, 160.1 and 159.9, 159.7 and 159.4, 141.2 and 141.1, 136.2 and 136.0, 131.0, 128.3, 117.5 and 115.6, 116.1 (q, *J* = 260 Hz) 110.6 and 108.9, 106.3 and105.5. $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ -64.4. LC/MS (CI): *m/z* = 343 $[M+H]^+$. Anal. Calcd. for $C_{13}H_6ClF_3N_4O_2$: C, 45.57; H, 1.77; N, 16.35; Cl, 10.35. Found: C, 45.61; H, 1.41; N, 16.46; Cl, 10.64.

Supporting Information included copies of ^{1}H, ^{13}C and ^{19}F NMR spectra, crystallographic information files and computational data. This material is available free of charge at http://pubs.acs.org.

Acknowledgements

The work was funded by Enamine Ltd and NIH grant No. GM133836 (to Prof. John J. Irwin and Y.S.M.). O.O.G. and B.A.V. were also funded by Ministry of Education and Science of Ukraine (Grants No. 19BF037-03 and 19BF037-06, respectively). A.B.R. thanks to the Alexander von Humboldt Foundation (Bonn, Germany) for the financial support by purchasing computer equipment and the license for the *Turbomole* program used in the current investigation. The authors thank Prof. Dr. Andrey A. Tolmachev for his encouragement and support, Mr. Vasyl V. Skyba for column chromatography purification, and Mr. Oleksandr Liashuk for his help with manuscript preparation.

References

(1) Hamper, B. C.; Leschinsky, K. L. Reaction of Benzohydroximinoyl Chlorides and β -(Trifluoromethyl)-Acetylenic Esters: Synthesis of Regioisomeric (Trifluoromethyl)-Isoxazolecarboxylate Esters and Oxime Addition Products. *J. Heterocycl. Chem.* **2003**, *40* (4), 575–583.

(2) Sysak, A.; Obmińska-Mrukowicz, B. Isoxazole Ring as a Useful Scaffold in a Search for New Therapeutic Agents. *Eur. J. Med. Chem.* **2017**, *137*, 292–309.

(3) Taylor, R. D.; MacCoss, M.; Lawson, A. D. G. Rings in Drugs. *J. Med. Chem.* **2014**, *57* (14), 5845–5859.

(4) Greenwood, D. *Antimicrobial Drugs: Chronicle of a Twentieth Century Medical Triumph*; Oxford University Press, **2008**, 368 pp.

(5) Fischer, J.; Robin Ganellin, C.; *Analogue-Based Drug Discovery*; WILEY-VCH Verlag GmbH & Co.KGaA: Weinheim, **2006**, 606 pp.

(6) Goodman, L. S.; Brunton, L. L.; Chabner, B.; Knollmann, B. C. *The Pharmacological Basis of Therapeutics*, 12th ed.; The McGraw-Hill Companies, Inc., **2011**, 1808 pp.

(7) Fagervall, I.; Ross, S. B. Inhibition of Mono Amine Oxidase in Monoaminergic Neurones in the Rat Brain by Irreversible Inhibitors. *Biochem. Pharmacol.* **1986**, *35* (8), 1381–1387.

(8) Sanders, S.; Harisdangkul, V. Leflunomide for the Treatment of Rheumatoid Arthritis and Autoimmunity. *Am. J. Med. Sci.* **2002**, *323* (4), 190–193.

(9) Zhang, J.; Ding, E. L.; Song, Y. Adverse Effects of Cyclooxygenase 2 Inhibitors on Renal and Arrhythmia Events. Meta-Analysis of Randomized Trials. *JAMA* **2006**, *296* (13), 1619.

(10) Pevear, D. C.; Tull, T. M.; Seipel, M. E.; Groarke, J. M. Activity of Pleconaril against Enteroviruses. *Antimicrob. Agents Chemother.* **1999**, *43* (9), 2109–2115.

(11) Loubatières, A.; Ribes, G.; Mariani, M.-M.; Alric, R. Pharmacological Comparison between Tolbutamide and Two Second Generation Hypoglycemic Sulfonylureas (Glibenclamide and Glisoxepide). *Acta Diabetol. Lat.* **1973**, *10* (2), 261–282.

(12) Cohen, Y. The Novel Oomycide Oxathiapiprolin Inhibits All Stages in the Asexual Life Cycle of Pseudoperonospora Cubensis - Causal Agent of Cucurbit Downy Mildew. *PLoS One* **2015**, *10* (10), e0140015.

(13) Dallanoce, C.; Magrone, P.; Matera, C.; Lo Presti, L.; De Amici, M.; Riganti, L.; Clementi, F.; Gotti, C.; De Micheli, C. Synthesis of Novel Chiral Δ2-Isoxazoline Derivatives Related to ABT-418 and Estimation of Their Affinity at Neuronal Nicotinic Acetylcholine Receptor Subtypes.

Eur. J. Med. Chem. **2010**, *45* (12), 5594–5601.

(14) Dong, K.; Qin, H.; Bao, X.; Liu, F.; Zhu, C. Oxime-Mediated Facile Access to 5-Methylisoxazoles and Applications in the Synthesis of Valdecoxib and Oxacillin. *Org. Lett.* **2014**, *16* (20), 5266–5268.

(15) Meanwell, N. A. Fluorine and Fluorinated Motifs in the Design and Application of Bioisosteres for Drug Design. *J. Med. Chem.* **2018**, *61* (14), 5822–5880.

(16) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Acenã, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. Next Generation of Fluorine-Containing Pharmaceuticals, Compounds Currently in Phase II-III Clinical Trials of Major Pharmaceutical Companies: New Structural Trends and Therapeutic Areas. *Chem. Rev.* **2016**, *116* (2), 422–518.

(17) Bonacorso, H. G.; Ketzer, A.; Garcia, F. D.; Rosa, W. C.; Calheiro, T. P.; Feitosa, S. C.; Dal Forno, G. M.; Zanatta, N.; Martins, M. A. P.; Frizzo, C. P. Efficient Approach for Regioselective Synthesis of New Trifluoromethyl-Substituted Spirotetracyclic Isoxazolines and Isoxazoles. *J. Fluor. Chem.* **2017**, *197*, 6–14.

(18) Okada, E.; Hatakenaka, M.; Sakaemura, T. Facile and Convenient Syntheses for Fluorine-Containing Pyrazolo[4,3-c]Quinolines, Isoxazoloquinolines, and 1,4-Diazepino[6,5-c]Quinolines. *Heterocycles* **2015**, *90* (2), 1072–1081.

(19) Yang, X.; Fang, X.; Zhang, D.; Yu, Y.; Zhang, Z.; Wu, F. Regioselective Nucleophilic Addition of 3-Aryl-5-Difluoromethyl-Isoxazoles to Aldehydes. *J. Fluor. Chem.* **2013**, *145*, 1–7.

(20) Aggarwal, R.; Bansal, A.; Mittal, A. Synthesis and Antimicrobial Activity of 3-(2-Thienyl)-4-Arylazo-5-Hydroxy-5-Trifluoromethyl-Δ2-Isoxazolines and 3-(2-Thienyl)-4-Arylazo-5-Trifluoromethylisoxazoles. *J. Fluor. Chem.* **2013**, *145* (2010), 95–101.

(21) Sosnovskikh, V. Y.; Moshkin, V. S.; Kodess, M. I. Reactions of 3-(Polyfluoroacyl)Chromones with Hydroxylamine: Synthesis of Novel RF-Containing Isoxazole and Chromone Derivatives. *Tetrahedron* **2008**, *64* (34), 7877–7889.

(22) Martins, M. A. P.; Machado, P.; Piovesan, L. A.; Flores, A. F. C.; de Campos, M. M. A.; Scheidt, C.; Bonacorso, H. G.; Zanatta, N. Microwave-Assisted Synthesis and Antimicrobial Activity of

5-Trihalomethyl-3-Arylisoxazoles. *Monatsh. Chem.* **2008**, *139* (8), 985–990.

(23) Nenajdenko, V. G.; Pronin, S. V; Balenkova, E. S. Synthesis of Aminoalkylpyrazoles And-Isoxazoles from Cyclic β-(Trifluoroacetyl) Enamines. *Russ. Chem. Bull.* **2007**, *56* (2), 336–344.

(24) Ngo, T. N.; Ejaz, S. A.; Hung, T. Q.; Dang, T. T.; Iqbal, J.; Lecka, J.; Sévigny, J.; Langer, P. Efficient One-Pot Synthesis of 5-Perfluoroalkylpyrazoles by Cyclization of Hydrazone Dianions. *Org. Biomol. Chem.* **2015**, *13* (30), 8277–8290.

(25) Shiozaki, M.; Maeda, K.; Miura, T.; Kotoku, M.; Yamasaki, T.; Matsuda, I.; Aoki, K.; Yasue, K.; Imai, H.; Ubukata, M.; Akira Suma, A.; Yokota, M.; Hotta, T.; Tanaka, M.; Hase, Y.; Haas, J.; Fryer, A. M.; Laird, E. R.; Littmann, N. M.; Andrews., S. W.; Josey, J. A.; Mimura, T.; Shinozaki, Y.; Yoshiuchi, H. Inaba, T. Discovery of (1*S*,2*R*,3*R*)-2,3-Dimethyl-2-Phenyl-1-Sulfamidocyclopropanecarboxylates: Novel and Highly Selective Aggrecanase Inhibitors. *J. Med. Chem.* **2011**, *54* (8), 2839–2863.

(26) Lepage, F.; Tombret, F.; Cuvier, G.; Marivain, A.; Gillardin, J. New N-Aryl Isoxazolecarboxamides and N-Isoxazolylbenzamides as Anticonvulsant Agents. *Eur. J. Med. Chem.* **1992**, *27* (6), 581–593.

(27) Hu, F.; Szostak, M. Recent Developments in the Synthesis and Reactivity of Isoxazoles: Metal Catalysis and Beyond. *Adv. Synth. Catal.* **2015**, *357* (12), 2583–2614.

(28) Vishwanatha, T. M.; Sureshbabu, V. V. Copper(0) Nanoparticles in Click Chemistry: Synthesis of 3,5-Disubstituted Isoxazoles. *J. Heterocycl. Chem.* **2015**, *52* (6), 1823–1833.

(29) Dubrovskiy, A. V; Jain, P.; Shi, F.; Lushington, G. H.; Santini, C.; Porubsky, P.; Larock, R. C. Solution-Phase Synthesis of a Diverse Library of Benzisoxazoles Utilizing the [3 + 2] Cycloaddition of in Situ-Generated Nitrile Oxides and Arynes. *ACS Comb. Sci.* **2013**, *15* (4), 193–201.

(30) Hansen, T. V; Wu, P.; Fokin, V. V. One-Pot Copper(I)-Catalyzed Synthesis of 3,5-Disubstituted Isoxazoles. *J. Org. Chem.* **2005**, *70* (19), 7761–7764.

(31) Grecian, S.; Fokin, V. V. Ruthenium-Catalyzed Cycloaddition of Nitrile Oxides and Alkynes: Practical Synthesis of Isoxazoles. *Angew. Chem. Int. Ed.* **2008**, *47* (43), 8285–8287.

(32) Mohamed Ahmed, M. S.; Kobayashi, K.; Mori, A. One-Pot Construction of Pyrazoles and Isoxazoles with Palladium-Catalyzed Four-Component Coupling. *Org. Lett.* **2005**, *7* (20), 4487–4489.

(33) Schmidt, M. A.; Katipally, K.; Ramirez, A.; Soltani, O.; Hou, X.; Zhang, H.; Chen, B.-C.; Qian, X.; Deshpande, R. P. Synthesis of Ethyl 3-Phenyl-4-(Trifluoromethyl)Isoxazole-5-Carboxylate via Regioselective Dipolar Cycloaddition. *Tetrahedron Lett.* **2012**, *53* (31), 3994–3997.

(34) Weimin, P.; Shizheng, Z.; Guifang, J. Convenient Synthesis of 5-Perfluoroalkylsubstituted Isoxazoles. *Tetrahedron* **2001**, *57* (27), 5781–5784.

(35) Hou, X.; Zhu, J.; Chen, B. C.; Watterson, S. H.; Pitts, W. J.; Dyckman, A. J.; Carter, P. H.; Mathur, A.; Zhang, H. An Efficient Scale-Up Synthesis of BMS-520, a Potent and Selective Isoxazole-Containing S1P1Receptor Agonist. *Org. Process Res. Dev.* **2016**, *20* (5), 989–995.

(36) Roscales, S.; Bechmann, N.; Weiss, D. H.; Köckerling, M.; Pietzsch, J.; Kniess, T. Novel Valdecoxib Derivatives by Ruthenium(II)-Promoted 1,3-Dipolar Cycloaddition of Nitrile Oxides with Alkynes – Synthesis and COX-2 Inhibition Activity. *Medchemcomm* **2018**, *9* (3), 534–544.

(37) Hanamoto, T.; Hakoshima, Y.; Egashira, M. Tributyl(3,3,3-Trifluoro-1-Propynyl)Stannane as an Efficient Reagent for the Preparation of Various Trifluoromethylated Heterocyclic Compounds. *Tetrahedron Lett.* **2004**, *45* (41), 7573–7576.

(38) Zhang, X.; Cai, C.; Winters, M.; Wells, M.; Wall, M.; Lanter, J.; Sui, Z.; Ma, J.; Novack, A.; Nashashibi, I.; Wang, Y.; Yan, W.; Suckow, A.; Hua, H.; Bell, A.; Haug, P.; Clapper, W.; Jenkinson, C.; Gunnet, J.; Leonard, J.; Murray, W. V. Design, Synthesis and SAR of a Novel Series of Heterocyclic Phenylpropanoic Acids as GPR120 Agonists. *Bioorg. Med. Chem. Lett.* **2017**, *27* (15), 3272–3278.

(39) Vitale, P.; Perrone, M. G.; Malerba, P.; Lavecchia, A.; Scilimati, A. Selective COX-1 Inhibition as a Target of Theranostic Novel Diarylisoxazoles. *Eur. J. Med. Chem.* **2014**, *74*, 606–618.

(40) Tummalapalli, S. R.; Bhat, R.; Chojnowski, A.; Prorok, M.; Kreiss, T.; Goldberg, R.; Canan, S.; Hawryluk, N.; Mortensen, D.; Khetani, V.; Zeldis, J.; Siekierka, J. J.; Rotella, D. P. Discovery of a Stress-Activated Protein Kinase Inhibitor for Lymphatic Filariasis. *ACS Med. Chem. Lett.* **2018**,

9 (3), 210–214.

(41) Schaumann, E. *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations Vol. 11: Five-Membered Hetarenes with One Chalcogen and One Additional Heteroatom*; Georg Thieme Verlag, **2014**, 1160 pp.

(42) Feuer, H. *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis: Novel Strategies in Synthesis*; John Wiley & Sons, **2008**, 768 pp.

(43) Hassner, A. *Synthesis of Heterocycles via Cycloadditions I*; Springer, **2008**, 218 pp.

(44) Mandal, D. K. *Pericyclic Chemistry: Orbital Mechanisms and Stereochemistry*; Elsevier, **2018**, 532 pp.

(45) Padwa, A.; Pearson, W. H. *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; John Wiley & Sons, **2003**, 952 pp.

(46) Roscales, S.; Bechmann, N.; Holger Weiss, D.; Köckerling, M.; Pietzsch, J.; Kniess, T. Novel Valdecoxib Derivatives by Ruthenium(II)-Promoted 1, 3-Dipolar Cycloaddition of Nitrile Oxides with Alkynes - Synthesis and COX-2 Inhibition Activity. *Medchemcomm* **2018**, *9* (3), 534–544.

(47) Khutorianskyi, A.; Chalyk, B.; Borysko, P.; Kondratiuk, A.; Mykhailiuk, P. K. Difluoromethyl Nitrile Oxide (CF_2HCNO): A Neglected Chemical Reagent. *Eur. J. Org. Chem.* **2017**, *2017* (27), 3935–3940.

(48) Chalyk, B. A.; Sosedko, A. S.; Volochnyuk, D. M.; Tolmachev, A. A.; Gavrilenko, K. S.; Liashuk, O. S.; Grygorenko, O. O. Regioselective Synthesis of Isoxazole and 1,2,4-Oxadiazole-Derived Phosphonates: Via [3 + 2] Cycloaddition. *Org. Biomol. Chem.* **2018**, *16* (47), 9152–9164.

(49) Slobodyanyuk, E. Y.; Andriienko, A. A.; Vashchenko, B. V.; Volochnyuk, D. M.; Ryabukhin, S. V.; Grygorenko, O. O. Expanding the Chemical Space of Sp 3-Enriched 4,5-Disubstituted Oxazoles via Synthesis of Novel Building Blocks. *Chem. Heterocycl. Compd.* **2019**, *55* (4–5), 421–434.

(50) Solomin, V. V.; Radchenko, D. S.; Slobodyanyuk, E. Y.; Geraschenko, O. V.; Vashchenko, B. V.; Grygorenko, O. O. Widely Exploited, Yet Unreported: Regiocontrolled Synthesis and the

Suzuki-Miyaura Reactions of Bromooxazole Building Blocks. *Eur. J. Org. Chem.* **2019**, *2019* (18), 2884–2898.

(51) Chalyk, B. A.; Hrebeniuk, K. V.; Gavrilenko, K. S.; Shablykin, O. V.; Yanshyna, O. O.; Bash, D.; Mykhailiuk, P. K.; Liashuk, O. S.; Grygorenko, O. O. Synthesis of Bi- and Polyfunctional Isoxazoles from Amino Acid Derived Halogenoximes and Active Methylene Nitriles. *Eur. J. Org. Chem.* **2018**, *2018* (22), 2753–2761.

(52) Hou, X.; Zhu, J.; Chen, B.-C.; Watterson, S. H.; Pitts, W. J.; Dyckman, A. J.; Carter, P. H.; Mathur, A.; Zhang, H. An Efficient Scale-Up Synthesis of BMS-520, a Potent and Selective Isoxazole-Containing S1P 1 Receptor Agonist. *Org. Process Res. Dev.* **2016**, *20* (5), 989–995.

(53) Piotrowski, D. W.; Rogers, B. N.; McWhorter JR., W. W.; Walker, D. P.; Corbett, J. W.; Groppi JR., V. E.; Rudmann, D. G. US2003/236287, 2003.

(54) Chalyk, B. A.; Kandaurova, I. Y.; Hrebeniuk, K. V.; Manoilenko, O. V.; Kulik, I. B.; Iminov, R. T.; Kubyshkin, V.; Tverdokhlebov, A. V.; Ablialimov, O. K.; Mykhailiuk, P. K. A Base Promoted Multigram Synthesis of Aminoisoxazoles: Valuable Building Blocks for Drug Discovery and Peptidomimetics. *RSC Adv.* **2016**, *6* (31), 25713–25723.

(55) T. Hamme, A.; Xu, J.; Wang, J.; Cook, T.; Ellis, E. Synthesis of Functionalized 5,5-Disubstituted Isoxazolines via 1,3-Dipolar Cycloaddition Reactions of Geminal Disubstituted Alkenes. *Heterocycles* **2005**, *65* (12), 2885.

(56) Arjona, O.; de Dios, A.; la Pradilla, R. F. de; Mallo, A.; Plumet, J. Polar vs Steric Effects in the 1,3-Dipolar Cycloaddition Reactions of Acetonitrile Oxide and 2-Endo-Acetoxy-5-Halo-7-Oxabicyclo[2.2.1]Hept-5-En-2-Exo-Carbonitrile. *Tetrahedron* **1990**, *46* (24), 8179–8186.

(57) L. Skripnikov, *Chemissian Program, v. 4.60, www.chemissian.com*, **2018**.

(58) Foster, J. P.; Weinhold, F. Natural Hybrid Orbitals. *J. Am. Chem. Soc.* **1980**, *102* (24), 7211–7218.

(59) Reed, A. E.; Weinstock, R. B.; Weinhold, F. Natural Population Analysis. *J. Chem. Phys.* **1985**, *83* (2), 735–746.

(60) Vishwanatha, T. M.; Sureshbabu, V. V. Copper (0) Nanoparticles in Click Chemistry : Synthesis

Of. *J. Heterocycl. Chem.* **2014**, *52* (6), 1823–1833.

(61) Bartlett, S. L.; Sohtome, Y.; Hashizume, D.; White, P. S.; Sawamura, M.; Johnson, J. S.; Sodeoka, M. Catalytic Enantioselective [3 + 2] Cycloaddition of α-Keto Ester Enolates and Nitrile Oxides. *J. Am. Chem. Soc.* **2017**, *139* (25), 8661–8666.

(62) Chen, H.; Ding, C.; Wild, C.; Liu, H.; Wang, T.; White, M. A.; Cheng, X.; Zhou, J. Efficient Synthesis of ESI-09, a Novel Non-Cyclic Nucleotide EPAC Antagonist. *Tetrahedron Lett.* **2013**, *54* (12), 1546–1549.

(63) Armarego, W. L. F.; Chai, C. *Purification of Laboratory Chemicals*, 5th ed.; Elsevier: Oxford, **2003**, 608 pp.

(64) *TURBOMOLE V6.4 2012, a Development of University of Karlsruhe and Forschungszentrum Karlsruhe GmbH, 1989-2007, TURBOMOLE GmbH, since 2007; www.turbomole.com,* **2012**.

(65) Furche, F.; Ahlrichs, R.; Hättig, C.; Klopper, W.; Sierka, M.; Weigend, F. Turbomole. *Wiley Interdiscip. Rev. Comput. Mol. Sci.* **2014**, *4* (2), 91–100.

(66) Schäfer, A.; Huber, C.; Ahlrichs, R. Fully Optimized Contracted Gaussian Basis Sets of Triple Zeta Valence Quality for Atoms Li to Kr. *J. Chem. Phys.* **1994**, *100* (8), 5829–5835.

(67) Schwabe, T.; Grimme, S. Towards Chemical Accuracy for the Thermodynamics of Large Molecules: New Hybrid Density Functionals Including Non-Local Correlation Effects. *Phys. Chem. Chem. Phys.* **2006**, *8* (38), 4398–4401.

(68) Grimme, S.; Antony, J.; Schwabe, T.; Mück-Lichtenfeld, C. Density Functional Theory with Dispersion Corrections for Supramolecular Structures, Aggregates, and Complexes of (Bio)Organic Molecules. *Org. Biomol. Chem.* **2007**, *5* (5), 741–758.

(69) Grimme, S. Density Functional Theory with London Dispersion Corrections. *Wiley Interdiscip. Rev. Comput. Mol. Sci.* **2011**, *1* (2), 211–228.

(70) M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A.

Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, *Gaussian 09, Revision D.01*, Wallingford CT, **2013**

(71) Sosnovskikh, V. Y.; Barabanov, M. A. The First Synthesis of 8-Aza-2-Polyfluoroalkylchromones. *J. Fluor. Chem.* **2003**, *120* (1), 25–28.

(72) Kumar, V.; Aggarwal, R.; Singh, S. P. The Reaction of Hydroxylamine with Aryl Trifluoromethyl-β-Diketones: Synthesis of 5-Hydroxy-5-Trifluoromethyl-Δ2-Isoxazolines and Their Dehydration to 5-Trifluoromethylisoxazoles. *J. Fluor. Chem.* **2006**, *127* (7), 880–888.

(73) Tang, X. Q.; Hu, C. M. A New and Concise Method for the Synthesis of 5-Trifluoromethylisoxazoles. *J. Fluor. Chem.* **1995**, *73* (2), 133–135.