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Multigram Synthesis of C_4/C_5 3,3-Difluorocyclobutyl-Substituted Building Blocks

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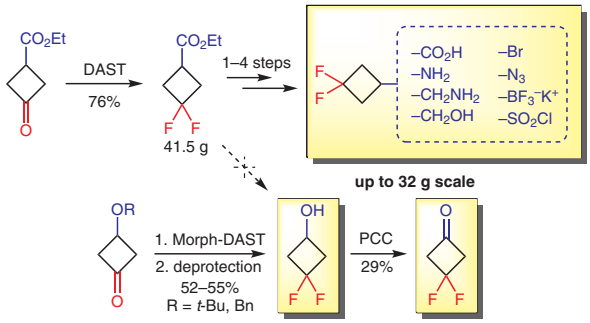

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Abstract An approach for the multigram synthesis of 3,3-difluorocyclobutyl-substituted building blocks (including carboxylic acid, amines, alcohols, azide, trifluoroborate ketone) is described. It is shown that, in most cases, ethyl 3,3-difluorocyclobutanecarboxylate is a convenient common synthetic intermediate to obtain the target derivatives. For preparation of 3,3-difluorocyclobutanol or -cyclobutanone, an alternative pathway via reaction of dichloroketene and *tert*-butyl or benzyl vinyl ether should be applied.

Key words cycloalkanes, organofluorine compounds, fluorination, conformational restriction, lead-oriented synthesis

Cycloalkanes are important structural fragments often found in natural compounds and widely used in drug discovery.[1] Of these cyclic cores, cyclobutane is the smallest structural motif that allows for conformational restriction without significant change in the chemical properties of the parent molecule (which is not true for the smallest representative, cyclopropane).[2] Fluorinated cyclobutanes have attracted interest as building blocks for the synthesis of various biologically relevant molecules. In particular, 3,3-difluorocyclobutanes feature in the structure of many potential drugs, such as $Na_V1.1$ channel blockers (**1**),[3] mitogen-activated protein kinase 1 (MAPK1) inhibitors (**2**),[4] heat shock protein 90 (Hsp90) inhibitors (**3**),[5] CCR5 antagonists (**4**),[6] isocitric dehydrogenase 1 (IDH1) inhibitors (**5**),[7] or cholesteryl ester transfer protein (CETP) inhibitors (**6**) (Figure 1).[8] Like other fluorinated (cyclo)alkyl groups, the 3,3-difluorocyclobutyl substituent can participate in protein binding through hydrophobic interactions; moreover, the fluorine atoms can act as weak hydrogen bond acceptors.[9]

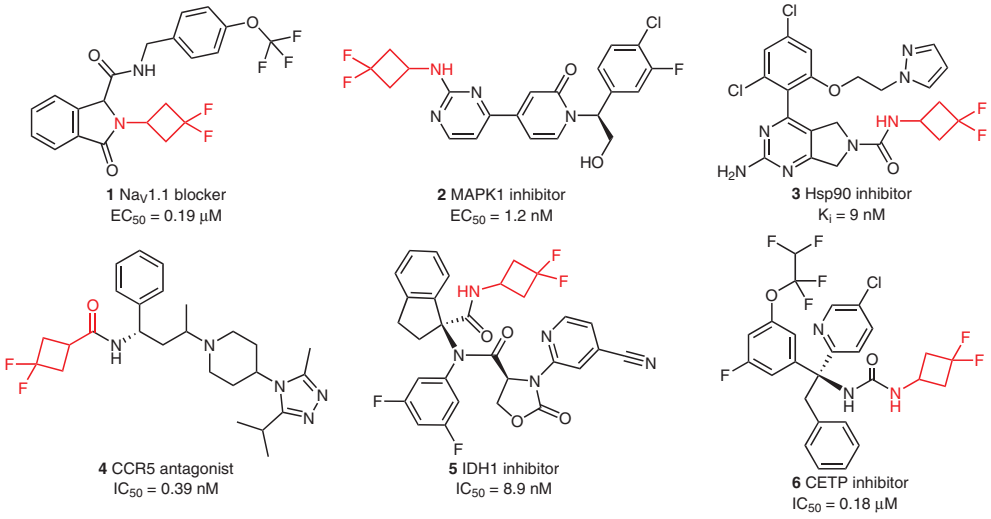


Figure 1 Some biologically active 3,3-difluorocyclopropane derivatives

The 3,3-difluorocycloalkyl group adds little to molecular weight and size and can even improve hydrophilicity of the molecule as compared to the parent cyclobutyl or other common fluorinated groups such as trifluoromethyl (Figure 2).[10] Therefore, building blocks having the 3,3-difluorocycloalkyl moiety are fully compatible with the requirements of lead-oriented synthesis, which imposes strict molecular weight (MW) and LogP limitations.[11] Moreover, the 3,3-difluorocycloalkyl group might improve metabolic stability of the compounds–a feature which is characteristic for the fluorinated substituents.[9] Finally, due to its symmetry, this moiety has the advantage of not introducing any new stereocenters into a potential drug molecule.

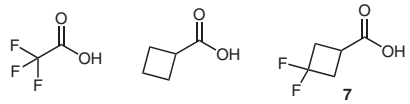


Figure 2 3,3-Difluorocyclobutyl substituent–an attractive structural element for drug design (TSA = total solvent-accessible surface area of the molecule)

3,3-Difluorocyclobutyl-substituted building block are known in the literature. Carboxylic acid **7** or its derivatives are quite obvious key intermediates which have been involved in most known syntheses of 3,3-difluorocyclobutanes. Two main approaches have been described for the preparation of the compound **7** (Scheme 1). In 1987, Dolbier and Al-Fekri reported the synthesis of **7** by hydrogenation of compound **8**, in turn obtained via thermal [2+2] cycloaddition of 1,1-dichloro-2,2-difluoroethylene (**9**) and acrylonitrile.[12] An alternative approach was described by the group of Fray in 2005;[13] it commenced from 3-methylenecyclobutanecarbonitrile (**10**), which is not readily available from common chemical suppliers on a large scale. In turn, preparation of **10** involves thermal [2+2] cycloaddition of acrylonitrile and allene. Although, in both cases, the authors reported the preparation of the target compound **7** on 20–30 g scale, these syntheses cannot be considered as convenient for multigram laboratory preparations, due to handling of highly toxic acrylonitrile, which is also potentially explosive at elevated temperatures, as well as the use of high pressure equipment and relatively expensive transition metal reagents/catalysts.

Carboxylic acid **7** and nitrile **11** have been used in the synthesis of amines **12** and **13** via Curtius rearrangement[14,15] and catalytic hydrogenation,[3] respectively. Alternatively, amine **12** has been obtained via deoxofluorination of ketone **14**.[15]

In this work, we have aimed at developing convenient protocols for the preparation of C_4/C_5 3,3-difluorocyclobutane building block series, i.e. compounds **7**, **12**, **13**, and **15**–**21** (Figure 3). Initially, we turned our attention to the possible use of 3-oxocyclobutanecarboxylic acid as an easily available synthetic precursor for these building blocks. This compound is commercially available on a kilogram scale;[16] it can also be prepared by double alkylation of diisopropyl malonate with 1,3-dibromo-2,2-dimethoxypropane, followed by acidic hydrolysis, in 51% overall yield.[17]

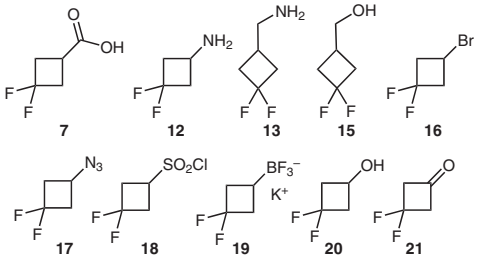
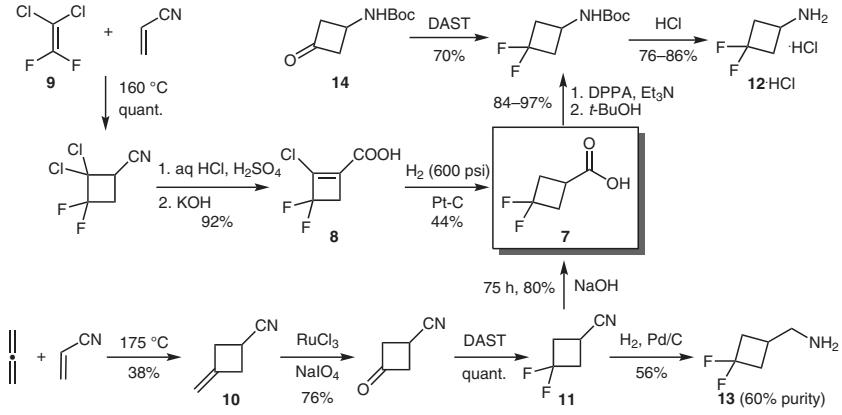
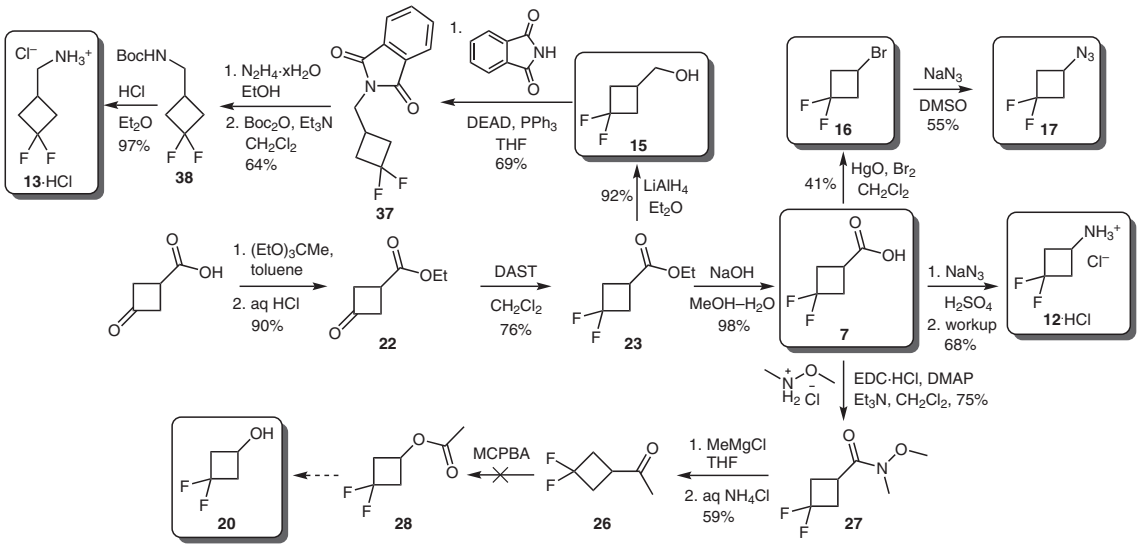


Figure 3 Target molecules of this study

It was found that ester **22** (obtained from 3-oxocyclobutanecarboxylic acid in 90% yield) smoothly reacted with DAST to give the target ethyl 3,3-difluorocyclobutanoate



Scheme 1 Syntheses of C_4/C_5 3,3-difluorocyclobutyl-substituted building blocks reported in literature



Scheme 2 Synthesis of building blocks **7**, **12**, **13**, and **15–17**, and attempted preparation of **19**

(**23**) in 76% yield (after vacuum distillation) (Scheme 2).[18] Notably, this synthetic scheme was effective even on a 40 gram scale without considerable changes in the product yields.

Compound **23** was a common synthetic intermediate in our further synthesis of several building blocks containing the 3,3-difluorocyclobutyl moiety (Scheme 2). First of all, standard reactions were studied; in particular, hydrolysis of **23** occurred under mild conditions (KOH, aq MeOH, r.t., 15 h) and gave carboxylic acid **7** in 98% (32 g) yield. Reduction of **23** with $LiAlH_4$ in Et_2O led to the formation of alcohol **15** (24.9 g, 92%).[18] Reaction of **15** with phthalimide under modified Mitsunobu conditions, followed by hydrazinolysis, allowed for the preparation of amine **13**, which was isolated as a hydrochloride after purification of its Boc derivative. It should be noted that a previously published method for the preparation of **13**[3] gave milligram quantities of the target product in 60% purity. Finally, we have optimized transformation of **7** into amine **12**. It was found that the literature method involving the use of DPPA[14,15] led to a considerable drop in the yield upon scale-up. In contrast, Schmidt reaction conditions (NaN_3/H_2SO_4, $CHCl_3$) were more effective and allowed for the preparation of up to 7.17 g of **12** (68% yield, isolated as hydrochloride).[19]

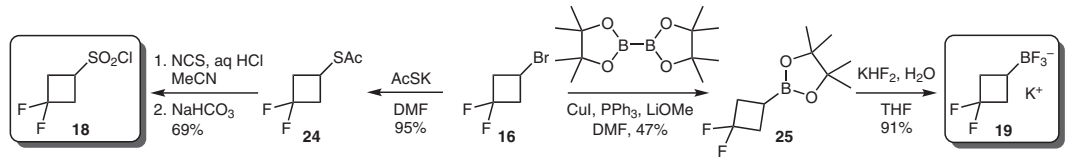
Less common transformations of **7** included the modified Hunsdiecker–Borodin reaction (Br_2/HgO), which allowed for the preparation of bromide **16** (Scheme 2). It should be noted that isolation of the product **16** appeared to be rather tedious, so that the choice of the solvent for the reaction was critical. In particular, when the reaction was carried out in CCl_4[20] or 1,2-dibromoethane as the solvent, bromide **16** was formed, but could not be isolated due to its volatility. An optimized procedure included performing the reaction in CH_2Cl_2, followed by removal of inorganic components and fractional distillation of the resulting solution at atmospheric pressure. On a 1 gram scale of **7**, product **16** was obtained in 45% yield as a ca. 67% (w/w) solution in CH_2Cl_2. Nevertheless, the outcome of the reaction did not change significantly upon scale-up (20 g of **7**), and, in this case, pure **16** was isolated in 41% yield.

Bromide **16** was the key intermediate in the synthesis of azide **17**, sulfonyl chloride **18**, and trifluoroborate **19** (Schemes 2 and 3). In particular, reaction of **16** with NaN_3 gave the building block **17** in 55% yield. Compound **18** was prepared via nucleophilic substitution with AcSK, which gave thioacetate **24** in 95% yield. Oxidative chlorination of **24** resulted in the formation of the target sulfonyl chloride **18** (69% yield).

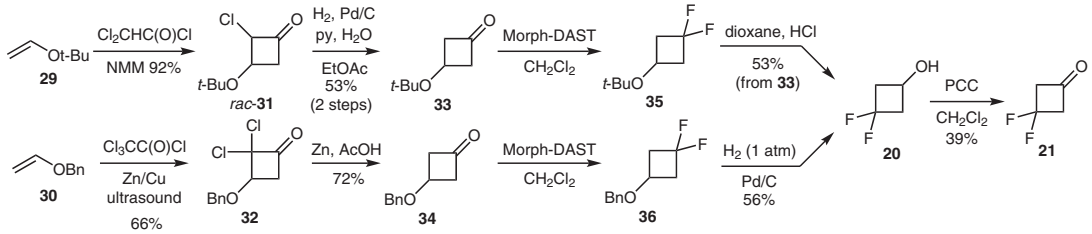
To obtain trifluoroborate **19**, bromide **16** was allowed to react with bis(pinacolato)diboron in the presence of $Cu(PPh_3)I$ (Scheme 3).[21] The corresponding pinacolate **25** thus obtained (47% yield) was transformed into **19** by treatment with KHF_2 (91% yield).

For the preparation of 3,3-difluorocyclobutanol (**20**), we initially considered Bayer–Villiger oxidation of ketone **26**, which was in turn prepared from **7** via the corresponding Weinreb amide **27** in 59% yield (Scheme 2). Unfortunately, only trace amounts of ester **28** were detected by LCMS in the crude reaction mixture obtained by treatment of **26** with MCPBA or H_2O_2/AcOH. In addition to that, we have also tried diazotization of amine **12** using $NaNO_2$/aq $HClO_4$; unfortunately, this resulted only in trace amounts of the target product **20**.

Therefore, we switched to the alternative approach to the synthesis of **20** shown in Scheme 4. In particular, [2+2] cycloaddition of (di)chloroketene and vinyl ethers **29** or **30** using modified literature methods[22,23] gave cyclobutanones **31** and **32,** respectively. These products were subjected to



Scheme 3 Synthesis of building blocks **18** and **19**



Scheme 4 Synthesis of building blocks **20** and **21**

reductive dechlorination to give O-protected hydroxy ketones **33** and **34** (53% and 48% yield for two steps, respectively). Deoxofluorination of **33** and **34** with morpholinosulfur trifluoride (Morph-DAST) proceeded smoothly and gave the corresponding products **35** and **36**, respectively. Deprotection of **35** with HCl in dioxane gave the target alcohol **20** (52% yield from **33**). Catalytic debenzylation of **36** also proceeded without any complications and gave **20** in 56% yield (from **34**). Therefore, both the reaction sequences shown in the Scheme 4 gave comparable overall yields, although, in our opinion, using benzyl ether **30** as the starting material was slightly more convenient. Finally, oxidation of **20** with pyridinium chlorochromate (PCC) led to the formation of 3,3-difluorocyclobutanone (**21**) in 39% yield. Moderate yield was observed due to the high volatility of the product, hence it is recommended to obtain and handle compound **21** in the form of solution.

In conclusion, a series of 3,3-difluorocyclobutyl-substituted low-molecular-weight building blocks, including carboxylic acid **7**, primary amines **12** and **13**, bromide **16**, azide **17**, sulfonyl chloride **18**, trifluorocyclobutylborate **19**, and ketone **26** can be prepared via deoxofluorination of the readily available ethyl 3-oxocyclobutanecarboxylate. For the synthesis of 3,3-difluorocyclobutanol (**20**) and 3,3-difluorocyclobutanone (**21**), an alternative synthetic pathway relying on [2+2] cycloaddition of (di)chloroketene and the appropriate vinyl ethers is more convenient. The target C_4/C_5 building blocks are important advanced reagents for early drug discovery programs which are compatible with the guidelines for lead-oriented synthesis; they can also be useful for agricultural chemistry[24] and other areas of applied science.

The solvents were purified according to standard procedures.[25] All the starting materials were purchased from commercial sources. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 2000 spectrometer (at 400 MHz for ^{1}H and 101 MHz for ^{13}C). Chemical shifts are reported in ppm downfield from TMS (^{1}H and ^{13}C NMR); the residual solvent signal was used as an internal standard. For ^{19}F NMR spectra, C_6F_6 was used as an internal standard. Elemental analyses were performed at the Laboratory of Organic Analysis, Institute of Organic Chemistry, National Academy of Sciences of Ukraine; the results were found to be in good agreement (±0.4%) with the calculated values. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization; APCI).

Ethyl 3-Oxocyclobutanecarboxylate (22)

A solution of 3-oxo-cyclobutanecarboxylic acid (60.0 g, 0.524 mol) and triethyl orthoacetate (288 mL, 1.57 mol) in toluene (1.2 L) was heated at 110 °C for 5 h. The reaction mixture was cooled to r.t. and quenched with 1 M aq HCl (1 L). The organic phase was separated, washed with sat. aq $NaHCO_3$ (3 × 350 mL) and brine (3 × 250 mL), dried over Na_2SO_4, filtered, and evaporated in vacuo to give ester **22**.

Yield: 67.4 g (90%); clear colorless oil.

Spectral and physical data have been reported previously.[26]

Ethyl 3,3-Difluorocyclobutane-1-carboxylate (23)

DAST (139 g, 0.867 mol) was dissolved in CH_2Cl_2 (635 mL) at –10 °C under an argon atmosphere, and a solution of ester **22** (47.1 g, 0.332 mol) in CH_2Cl_2 (212 mL) was added over 40 min. The mixture was allowed to warm to r.t. and stirred for 15 h. H_2O (108 mL, 5.99 mol) was added dropwise with stirring at 0 °C; then, sat. aq $NaHCO_3$ (1.2 L) was added slowly over 3 h. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 300 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo to give the crude product, which was purified by distillation in vacuo.

Yield: 41.5 g (76%); clear yellowish oil; bp 73–75 °C/60 mbar.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.15 (q, *J* = 7.1 Hz, 2 H), 2.97–2.86 (m, 1 H), 2.87–2.68 (m, 4 H), 1.24 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.7 (t, *J* = 2.4 Hz), 118.2 (dd, *J* = 284, 271 Hz), 60.6, 38.2 (t, *J* = 24.4 Hz), 26.0 (dd, *J* = 14.3, 5.3 Hz), 13.5.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –84.1 (d, *J* = 194 Hz), –98.3 (d, *J* = 194 Hz).

GCMS (EI): *m*/*z* = 164 $[M]^+$.

Anal. Calcd for $C_7H_{10}F_2O_2$: C, 51.22; H, 6.14. Found: C, 50.85; H, 5.83.

3,3-Difluorocyclobutane-1-carboxylic Acid (7)

NaOH (10.7 g, 0.268 mol) was dissolved in MeOH (100 mL) and H_2O (100 mL). Ester **23** (40.0 g, 0.244 mol) was added at r.t., and the resulting mixture was stirred at r.t. for 15 h, then evaporated in vacuo to half of the volume, acidified with concd aq HCl to pH 1, and extracted with CH_2Cl_2 (3 × 350 mL). The combined organic extracts were evaporated in vacuo.

Yield: 32.4 g (98%); white solid; mp 49–52 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 12.11 (br s, 1 H), 3.06–2.96 (m, 1 H), 2.94–2.79 (m, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 179.6, 118.0 (dd, *J* = 284, 271 Hz), 38.1 (t, *J* = 24.8 Hz), 26.0 (dd, *J* = 14.0, 5.7 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –84.5 (d, *J* = 194 Hz), –97.8 (d, *J* = 194 Hz).

GCMS (EI): *m*/*z* = 119 $[M – OH]^+$, 97 $[M – CO_2H]^+$.

Anal. Calcd for $C_5H_6F_2O_2$: C, 44.13; H, 4.44. Found: C, 43.86; H, 4.42.

(3,3-Difluorocyclobutyl)methanol (15)

$LiAlH_4$ (16.8 g) was suspended in Et_2O (800 mL), and a solution of **23** (36.6 g) in Et_2O (100 mL) was added dropwise over 30 min (temperature increased to 34 °C upon addition process). The resulting mixture was stirred at r.t. overnight, then quenched by dropwise addition of H_2O until H_2 evolution ceased. Then 10% aq H_2SO_4 was added until the precipitate dissolved (ca. 300 mL). The organic phase was separated, and the aqueous layer was extracted again with Et_2O (2 × 300 mL). The combined organic extracts were dried over K_2CO_3 and evaporated at atmospheric pressure. The residue was distilled in vacuo.

Yield: 24.9 g (92%); clear colorless oil; bp 92–95 °C/65 mbar.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.64 (br s, 2 H), 2.69–2.52 (m, 2 H), 2.46–2.18 (m, 3 H), 1.99–1.87 (m, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 119.6 (dd, *J* = 283, 275 Hz), 64.9 (dd, *J* = 3.7, 1.3 Hz), 36.8 (dd, *J* = 23.4, 22.0 Hz), 24.2 (dd, *J* = 11.3, 7.1 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –84.7 (d, *J* = 193 Hz), –94.3 (d, *J* = 193 Hz).

GCMS (EI): *m*/*z* = 104 $[M – H_2O]^+$, 57 $[C_3H_2F]^+$.

Anal. Calcd for $C_5H_8F_2O$: C, 49.18; H, 6.60. Found: C, 49.58; H, 6.66.

2-[(3,3-Difluorocyclobutyl)methyl]-1*H*-isoindole-1,3(2*H*)-dione (37)

A solution of PPh_3 (61.2 g, 0.233 mol) in THF (1.4 L) was cooled to 0 °C, and DEAD (40.6 g, 0.233 mol) was added dropwise. The reaction mixture was stirred at 0 °C for 30 min. (Note: If the reaction mixture is cooled below –5 °C at this step, a precipitate is formed, which is not dissolved even upon further addition of **15**.) A solution of **15** (28.5 g, 0.233 mol) in THF (50 mL) was added dropwise, and the reaction mixture was stirred at 0 °C for an additional 15 min. Phthalimide (34.2 g, 0.233 mol) was added in portions below 0 °C (the precipitate mentioned above dissolved at this step). The reaction mixture was stirred at r.t. for 72 h. The solution was evaporated in vacuo, and the residue was suspended in Et_2O (1 L), stirred for 15 min, and filtered. The filtrates were evaporated in vacuo. The crude product was purified by column chromatography (silica gel, hexanes–EtOAc, 4:1).

Yield: 40.1 g (69%); white solid; mp 106–108 °C; R_f = 0.54 (hexanes–EtOAc, 4:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.85 (dd, *J* = 5.3, 3.1 Hz, 2 H), 7.73 (dd, *J* = 5.3, 3.1 Hz, 2 H), 3.82 (d, *J* = 6.9 Hz, 2 H), 2.73–2.60 (m, 2 H), 2.61–2.50 (m, 1 H), 2.49–2.36 (m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 167.9, 133.7, 131.4, 122.9, 118.9 (dd, *J* = 283, 274 Hz), 41.6, 38.4 (t, *J* = 22.9 Hz), 22.2 (dd, *J* = 12.5, 6.5 Hz).

^{19}F NMR (470 MHz, $CDCl_3$): δ = –83.7 to –85.1 (m), –95.7 to –96.9 (m).

GCMS (EI): *m*/*z* = 251 $[M]^+$.

Anal. Calcd for $C_{13}H_{11}F_2NO_2$: C, 62.15; H, 4.41; N, 5.58. Found: C, 62.36; H, 4.26; N, 5.97.

tert-Butyl [(3,3-Difluorocyclobutyl)methyl]carbamate (38)

Compound **37** (40.1 g, 0.160 mol) was dissolved in EtOH (1.5 L) upon heating. The resulting solution was cooled to r.t., and hydrazine hydrate (63%, 8.50 mL, 0.160 mol) was added dropwise upon stirring. The reaction mixture was stirred at 50 °C for 12 h, then cooled to r.t.; the precipitate was filtered and washed with Et_2O (200 mL). The filtrate was cooled at –24 °C for 30 min, and an additional amount of precipitate was removed by filtration. The filtrates were acidified with HCl/E_2O until strongly acidic, and the solvent was removed in vacuo.

The resulting crude product **38** (25.2 g) was suspended in CH_2Cl_2 (350 mL), and Et_3N (69.0 mL, 0.495 mol) was added; then the mixture was stirred at r.t. for 10 min and cooled to 0 °C, before a solution of Boc_2O (52.3 g, 0.240 mol) in CH_2Cl_2 (150 mL) was added. The reaction mixture was additionally stirred at r.t. overnight, then washed with 10% aq citric acid (150 mL), H_2O (50 mL), sat. aq $NaHCO_3$ (150 mL), and brine (150 mL). The organic layer was separated, dried over Na_2SO_4, and evaporated in vacuo. The crude product was purified by column chromatography (silica gel, hexanes–EtOAc, 5:1).

Yield: 22.4 g (64% over two steps); white solid; mp 74–76 °C; R_f = 0.45 (hexanes–EtOAc, 5:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.62 (s, 1 H), 3.24 (s, 2 H), 2.69–2.58 (m, 2 H), 2.36–2.18 (m, 3 H), 1.45 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.0, 119.8 (dd, *J* = 283, 275 Hz), 79.5, 44.6, 38.4 (dd, *J* = 23.4, 21.9 Hz), 28.3, 23.3.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –84.4 (d, *J* = 193 Hz), –95.1 (d, *J* = 193 Hz).

GCMS (EI): *m*/*z* = 221 $[M]^+$.

Anal. Calcd for $C_{10}H_{17}F_2NO_2$: C, 54.29; H, 7.75; N, 6.33. Found: C, 54.68; H, 7.39; N, 6.36.

(3,3-Difluorocyclobutyl)methanamine Hydrochloride (13·HCl)

Compound **38** (22.4 g, 0.101 mol) was dissolved in 10% HCl in Et_2O (500 mL), and the mixture was stirred at r.t. overnight. The precipitate was filtered and washed with Et_2O (2 × 150 mL).

Yield: 15.5 g (97%); white solid; mp 202–204 °C.

^{1}H NMR (400 MHz, D_2O): δ = 3.06 (d, *J* = 7.3 Hz, 2 H), 2.82–2.60 (m, 2 H), 2.48–2.22 (m, 3 H).

^{13}C NMR (100 MHz, D_2O): δ = 119.9 (dd, *J* = 281, 274 Hz), 43.5, 38.1 (t, *J* = 23.1 Hz), 20.7 (dd, *J* = 12.9, 7.1 Hz).

^{19}F NMR (376 MHz, D_2O): δ = –82.2 (d, *J* = 191 Hz), –92.9 (d, *J* = 191 Hz).

GCMS (EI): *m*/*z* = 121 $[M]^+$.

Anal. Calcd for $C_5H_{10}ClF_2N$: C, 38.11; H, 6.4; N, 8.89; Cl, 22.50. Found: C, 38.06; H, 6.52; N, 9.17; Cl, 22.69.

3,3-Difluorocyclobutanamine Hydrochloride (12·HCl)

To a solution of carboxylic acid **7** (10.0 g, 73.4 mmol) in $CHCl_3$ (400 mL), 98% H_2SO_4 (21.8 mL) was added. The mixture was heated to 50 °C, and NaN_3 (9.54 g, 147 mmol) was added portionwise over 3 h. The reaction mixture was stirred at 50 °C for an additional 3 h, then cooled to r.t. and stirred for 48 h. The mixture was poured into ice (500 g) and the organic layer was separated. The aqueous phase was adjusted to pH 12 with 15% aq NaOH (200 mL) and extracted with CH_2Cl_2 (4 × 300 mL). The organic phase was acidified with sat. HCl in Et_2O (40 mL) until the precipitate started to form, and then evaporated in vacuo to dryness.

Yield: 7.17 g (68%); white solid; mp 276–278 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.76 (br s, 3 H), 3.62 (sept, *J* = 7.6 Hz, 1 H), 2.97–2.81 (m, 4 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 118.7 (dd, *J* = 280, 271 Hz), 38.1 (t, *J* = 24.3 Hz), 33.4 (dd, *J* = 17.8, 7.8 Hz).

^{19}F NMR (376 MHz, DMSO-d_6): δ = –82.0 (d, *J* = 196 Hz), –97.9 (d, *J* = 196 Hz).

LCMS (CI): *m*/*z* = 108 $[M + 1]^+$.

Anal. Calcd for $C_4H_8ClF_2N$: C, 33.47; H, 5.62; N, 9.76; Cl, 24.69. Found: C, 33.58; H, 5.81; N, 9.96; Cl, 24.76.

3-Bromo-1,1-difluorocyclobutane (16)

A mixture of HgO (32.0 g, 0.147 mol) and carboxylic acid **7** (20.0 g, 0.147 mol) in CH_2Cl_2 (800 mL) was refluxed under an argon atmosphere for 20 min. Note: the reaction flask was covered with aluminum foil to avoid access of light. Bromine (29.2 g, 9.40 mL, 0.183 mol) in CH_2Cl_2 (100 mL) was slowly added dropwise to the resulting mixture at reflux upon stirring over 75 min. Then, the reaction mixture was refluxed for an additional 5 h. The solution was cooled in a cold water bath, and insoluble precipitates were filtered off. The filtrates were washed with sat. aq $NaHCO_3$ (2 × 250 mL) and brine (200 mL) and dried over Na_2SO_4. ^{19}F NMR analysis of the solution showed that a single fluorine-containing product (**16**) was obtained. The solution was subjected to fractional distillation at atmospheric pressure.

Yield: 20.4 g (41%); colorless liquid; bp 95–98 °C/1 atm.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.28–4.09 (m, 1 H), 3.30–3.18 (m, 2 H), 3.02–2.89 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 119.1 (dd, *J* = 286, 273 Hz), 47.8 (t, *J* = 23.4 Hz), 27.7 (dd, *J* = 18.0, 8.8 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –84.7 (d, *J* = 198 Hz), –99.1 (d, *J* = 198 Hz).

GCMS (EI): *m*/*z* = 170/172 $[M]^+$.

Anal. Calcd for $C_4H_5BrF_2$: C, 28.10; H, 2.95; Br, 46.73. Found: C, 28.49; H, 3.23; Br, 47.11.

3-Azido-1,1-difluorocyclobutane (17)

To a solution of bromide **16** (0.500 g, 2.92 mmol) in DMSO (5 mL), NaN_3 (0.569 g, 8.76 mmol) was added. The reaction mixture was stirred at 75 °C overnight, cooled to r.t., diluted with H_2O (10 mL), and extracted with Et_2O (2 × 5 mL). The organic layer was washed with H_2O (4 × 5 mL), dried over Na_2SO_4, and evaporated at atmospheric pressure.

Yield: 0.215 g (55%); colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.02–3.90 (m, 1 H), 3.03–2.89 (m, 2 H), 2.72–2.58 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 117.5 (dd, *J* = 284, 270 Hz), 44.7 (dd, *J* = 17.7, 6.7 Hz), 42.4 (t, *J* = 23.5 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –83.6 (d, *J* = 193 Hz), –97.03 (d, *J* = 193 Hz).

Anal. Calcd for $C_4H_5F_2N_3$: C, 36.10; H, 3.79; F, 28.55; N, 31.57. Found: C, 36.46; H, 4.02; F, 28.30; N, 31.19.

S-(3,3-Difluorocyclobutyl) Ethanethioate (24)

Potassium thioacetate (2.20 g, 19.3 mmol) and bromide **16** (1.71 g, 10.0 mmol) were dissolved in DMF (50.0 mL) and the solution was stirred at 60 °C for 4 h. Then, the resulting mixture was dissolved in EtOAc (250 mL) and washed with brine (3 × 75 mL). The organic phase was separated, dried over Na_2SO_4, and evaporated in vacuo. The crude product was purified by column chromatography (silica gel, hexanes–EtOAc, gradient 9:1 to 4:1).

Yield: 1.57 g (95%); yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.84–3.69 (m, 1 H), 3.13–3.00 (m, 2 H), 2.59–2.45 (m, 2 H), 2.27 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 195.1, 119.3 (dd, *J* = 283, 274 Hz), 42.8 (t, *J* = 23.5 Hz), 30.3, 25.1 (dd, *J* = 15.4, 8.0 Hz).

^{19}F NMR (470 MHz, $CDCl_3$): δ = –83.3 to –84.1 (m), –95.9 to –96.7 (m).

GCMS (EI): *m*/*z* = 166 $[M]^+$.

Anal. Calcd for $C_6H_8F_2OS$: C, 43.36; H, 4.85; S, 19.29. Found: C, 43.21; H, 5.12; S, 19.24.

3,3-Difluorocyclobutane-1-sulfonyl Chloride (18)

A mixture of NCS (1.60 g, 12.0 mmol), MeCN (12 mL), and concd aq HCl (3.00 mL) was stirred at r.t. for 10 min. Then, a solution of **24** (1.66 g, 10.0 mmol) in MeCN (3 mL) was added at 0 °C. The reaction mixture was stirred for an additional 10 min and then diluted with sat. aq $NaHCO_3$ (50 mL). The resulting mixture was extracted with *t*-BuOMe (3 × 50 mL). The combined organic phases were dried over Na_2SO_4 and evaporated in vacuo. The crude product was purified by column chromatography (silica gel, gradient hexanes to hexanes–EtOAc, 1:1).

Yield: 1.32 g (69%); yellowish liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.33–4.21 (m, 1 H), 3.32–3.24 (m, 2 H), 3.19–3.12 (m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$: δ = 115.4 (dd, *J* = 286, 271 Hz), 55.9 (dd, *J* = 15.9, 6.5 Hz), 39.4 (t, *J* = 26.7 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –84.5 (d, *J* = 197 Hz), –96.5 (d, *J* = 197 Hz).

GCMS (EI): *m*/*z* = 154 $[M – HCl]^+$.

Anal. Calcd for $C_4H_5ClF_2O_2S$: C, 25.21; H, 2.64; S, 16.82; Cl, 18.60. Found: C, 25.41; H, 2.97; S, 16.48; Cl, 18.34.

2-(3,3-Difluorocyclobutyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (25)

Alkyl bromide **16** (3.00 g, 17.5 mmol) was added dropwise through a syringe to a mixture of CuI (330 mg, 1.73 mmol), PPh_3 (600 mg, 2.29 mmol), LiOMe (1.41 g, 37.1 mmol), bis(pinacolato)diboron (6.78 g, 26.7 mmol), and DMF (36 mL) under an argon atmosphere. The resulting mixture was stirred vigorously at 35 °C for 24 h, then diluted

with EtOAc (50 mL) and filtered through a silica gel pad (ca. 3.0 g). The filtrates were evaporated in vacuo, and the residue was purified by column chromatography (silica gel, hexanes–EtOAc, 10:1).

Yield: 1.81 g (47%); white solid; mp 58–60 °C; R_f = 0.42 (hexanes–EtOAc, 10:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.64–2.42 (m, 4 H), 1.56 (quin, *J* = 9.4 Hz, 1 H), 1.22 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 121.3 (dd, *J* = 284, 277 Hz), 83.7, 36.7 (t, *J* = 22.8 Hz), 24.7, 4.5 (br s).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –84.4 (d, *J* = 187 Hz), –95.9 (d, *J* = 187 Hz).

GCMS (EI): *m*/*z* = 218 $[M]^+$, 203 $[M - CH_3]^+$, 131, 107.

Anal. Calcd for $C_{10}H_{17}BF_2O_2$: C, 55.08; H, 7.86. Found: C, 55.27; H, 7.68.

Potassium (3,3-Difluorocyclobutyl)trifluoroborate (19)

KHF_2 (0.450 g, 5.76 mmol) in H_2O (3 mL) was added to a solution of **25** (0.500 g, 2.29 mmol) in THF (5 mL); the reaction mixture was stirred at r.t. overnight, and then evaporated in vacuo to dryness and diluted with MeCN (50 mL). The insoluble precipitate was filtered off and washed with MeCN (3 × 25 mL). The filtrate was evaporated in vacuo, and the residue was diluted with Et_2O (25 mL). The precipitate was filtered and dried in vacuo.

Yield: 0.408 g (91 %); white powder; mp 204–206 °C.

^{1}H NMR (400 MHz, D_2O): δ = 2.25–2.00 (m, 4 H), 0.79 (br s, 1 H).

^{13}C NMR (125 MHz, D_2O): δ = 123.5 (dd, *J* = 288, 278 Hz), 35.1 (t, *J* = 20.2 Hz), 8.8 (br s).

^{19}F NMR (376 MHz, D_2O): δ = –75.9 (d, *J* = 179 Hz), –96.2 (d, *J* = 179 Hz), –144.8 to –149.7 (m).

Anal. Calcd for $C_4H_5BF_5K$: C, 24.27; H, 2.55. Found: C, 24.55; H, 2.92.

3,3-Difluoro-*N*-methoxy-*N*-methylcyclobutane-1-carboxamide (27)

To a solution of carboxylic acid **7** (3.10 g, 22.8 mmol) in CH_2Cl_2 (85 mL), *N*,*O*-dimethylhydroxylamine hydrochloride (2.58 g, 26.4 mmol), EDC·HCl (5.06 g, 26.4 mmol), DMAP (0.135 g, 1.11 mmol), and Et_3N (6.84 g, 9.42 mL, 67.5 mmol) were added, and the reaction mixture was stirred overnight at r.t.. Then, H_2O (50 mL) was added, and the organic phase was separated and washed with 10% aq citric acid (75 mL), sat. aq $NaHCO_3$ (75 mL), and brine (50 mL). The organic layer was dried over Na_2SO_4 and evaporated in vacuo to give the crude product, which was used in the next step without further purification.

Yield: 2.97 g (75%); yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.68 (s, 3 H), 3.32–3.23 (m, 1 H), 3.20 (s, 3 H), 2.93–2.80 (m, 2 H), 2.76–2.65 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.2, 119.1 (dd, *J* = 286, 268 Hz), 61.4, 38.2 (t, *J* = 24.1 Hz), 32.4, 24.3 (d, *J* = 13.8 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –83.1 (d, *J* = 193 Hz), –99.6 (d, *J* = 193 Hz).

GCMS (EI): *m*/*z* = 179 $[M]^+$.

1-(3,3-Difluorocyclobutyl)ethan-1-one (26)

MeMgCl (3 M in THF, 37.2 mL, 112 mmol) was added to a solution of Weinreb amide **27** (10.0 g, 55.8 mmol) in THF (100 mL) at 0 °C. The reaction mixture was slowly warmed to r.t. and stirred overnight. Sat. aq NH_4Cl (50.0 mL) was added in portions, and the obtained mixture was extracted with EtOAc (2 × 20 mL). The organic layer was separated, dried over Na_2SO_4, and evaporated in vacuo. The crude product was purified by distillation in vacuo.

Yield: 4.41 g (59%); colorless oil; bp 62–65 °C/30 mbar.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.08–2.96 (m, 1 H), 2.80–2.60 (m, 4 H), 2.14 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 206.3, 118.4 (dd, *J* = 285, 271 Hz), 37.5 (t, *J* = 24.3 Hz), 33.6 (dd, *J* = 12.9, 5.2 Hz), 27.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –84.2 (d, *J* = 193 Hz), –97.6 (d, *J* = 193 Hz).

GCMS (EI): *m*/*z* = 134 $[M]^+$.

Anal. Calcd for $C_6H_8F_2O$: C, 53.73; H, 6.01. Found: C, 54.01; H, 6.13.

3-(*tert*-Butoxy)-2-chlorocyclobutanone (31)

tert-Butyl vinyl ether (38.1 g, 0.380 mol) and chloroacetyl chloride (45.0 g, 0.399 mol) were dissolved in hexanes (300 mL) under an argon atmosphere, and the mixture was heated to 45 °C. *N*-Methylmorpholine (46.0 g, 0.456 mol) was added dropwise while stirring for 45 min; the resulting mixture was heated at 45 °C for 1 h, then cooled to r.t. and washed with H_2O (3 × 150 mL). The organic layer was separated, dried over Na_2SO_4, and evaporated in vacuo. The crude product was used in the next step without purification.

Yield: 61.8 g; yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.77–4.69 (m, 1 H), 4.26 (td, *J* = 7.5, 5.4 Hz, 1 H), 3.24 (ddd, *J* = 17.9, 8.0, 2.3 Hz, 1 H), 3.10 (ddd, *J* = 17.9, 7.0, 3.5 Hz, 1 H), 1.26 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 69.6, 40.8, 34.4, 31.1, 28.3, 27.9.

GCMS (EI): *m*/*z* = 120/122 $[M - C_4H_8]^+$.

3-(*tert*-Butoxy)cyclobutanone (33)[22]

Pyridine (236 mL, 2.91 mol), H_2O (1 L), and 10% Pd/C (14.7 g) were added to a stirred solution of **31** (147 g, 0.832 mol) in EtOAc (1.6 L). The mixture was hydrogenated with H_2 (5 bar) at r.t. while stirring overnight, then filtered through Celite. The organic layer was washed with 6 M aq HCl (3 × 75 mL), H_2O (3 × 150 mL), and brine (3 × 100 mL), dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by distillation in vacuo.

Yield: 67.3 g (53% for two steps); colorless liquid; bp 75–78 °C/20 mmHg (Lit.[27] 67–69 °C/14 mmHg).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.40 (quin, *J* = 6.2 Hz, 1 H), 3.23–3.17 (m, 2 H), 3.13–3.07 (m, 2 H), 1.23 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.2, 74.5, 56.9, 56.6, 28.2.

GCMS (EI): *m*/*z* = 142 $[M]^+$.

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.58; H, 10.06.

3-(Benzyloxy)-2,2-dichlorocyclobutanone (32)[23]

To a solution of benzyl vinyl ether (**30**) (25.0 g. 0.186 mol) in anhyd Et_2O (1500 mL), the Zn/Cu couple (61.0 g, 0.930 mol) was added at r.t.. The reaction mixture was sonicated while trichloroacetyl chloride (53.0 mL, 0.465 mol) was added dropwise carefully over 3 h, while the temperature of the cooling bath was kept between 15 and 20 °C. The mixture was sonicated for an additional 1 h and then filtered through a pad of Celite; the pad was washed with Et_2O (500 mL). The filtrates were concentrated to about one half of the original volume, and the organic phase was washed with H_2O (2 × 800 mL) and sat aq

$NaHC0_3$ (800 mL). The organic phase was dried over $MgS0_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography (silica gel, gradient hexanes to hexanes–EtOAc, 95:5).

Yield: 30.2 g (66%); yellowish liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.35 (m, 5 H), 4.93 (d, *J* = 11.3 Hz, 1 H), 4.64 (d, *J* = 11.4 Hz, 1 H), 4.49 (dd, *J* = 8.2, 7.2 Hz, 1 H), 3.46 (dd, *J* = 18.5, 8.2 Hz, 1 H), 3.36 (dd, *J* = 18.5, 7.2 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 190.9, 135.6, 128.2, 128.0, 127.8, 87.8, 76.4, 72.8, 48.7.

LCMS (CI): *m*/*z* = 245/247 $[MH]^+$, 106 $[C_6H_5CHO]^+$.

Anal. Calcd for $C_{11}H_{10}Cl_2O_2$: C, 53.90; H, 4.11; Cl, 28.93. Found: C, 53.52; H, 4.43; Cl, 28.83.

3-(Benzyloxy)cyclobutanone (34)[23,28]

Compound **32** (24.5 g, 0.100 mol) was dissolved in AcOH (300 mL). Zinc dust (32.3 g, 0.500 mol) was added, and the reaction mixture was stirred at r.t. for 2 h and then reflux for 4 h. The mixture was diluted with H_2O (1.5 L), neutralized with solid $NaHCO_3$, and extracted with EtOAc (3 × 500 mL). The organic layer was washed with brine (500 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by vacuum distillation.

Yield: 12.7 g (72%); yellowish liquid; bp 72–74 °C/0.1 mmHg (Lit.[29] 97–102 °C/0.3 mmHg).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.28 (m, 5 H), 4.53 (s, 2 H), 4.41–4.33 (m, 1 H), 3.28–3.10 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.8, 137.3, 128.6, 128.0, 127.9, 71.7, 63.7, 54.2.

GCMS (EI): *m*/*z* = 176 $[M]^+$.

Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.79; H, 7.20.

3,3-Difluorocyclobutanol (20)

*Method A (from **33**):* Morpholin-4-ylsulfur trifluoride (Morph-DAST; 31.4 g, 0.179 mol) was added to a stirred solution of ketone **33** (20.0 g, 0.140 mol) in CH_2Cl_2 (200 mL) at 0 °C for 20 min; then, the resulting mixture was additionally stirred at r.t. for 3 d. The reaction mixture was poured into sat. aq $NaHCO_3$ (200 mL) and extracted with CH_2Cl_2 (3 × 200 mL). The combined organic extracts were dried over Na_2SO_4 and evaporated in vacuo to give crude product **35**, which was used in the subsequent step without further spectral characterization. Product **35** was dissolved in dioxane (160 mL), and 10% HCl in dioxane (16 mL) was added. The resulting mixture was heated at 60 °C overnight, then diluted with CH_2Cl_2 (200 mL), dried over Na_2SO_4, and subjected to fractional distillation in vacuo.

Yield: 7.97 g (53% from **33**); yellowish liquid; bp 84–86 °C/300 mmHg.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.33 (dquin, *J* = 13.1, 7.3 Hz, 1 H), 2.90 (tt, *J* = 12.6, 6.7 Hz, 2 H), 2.52 (qd, *J* = 15.6, 5.7 Hz, 2 H), 2.40 (br s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 117.9 (dd, *J* = 283, 269 Hz), 57.1 (dd, *J* = 18.8, 6.7 Hz), 45.4 (dd, *J* = 23.2, 21.1 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –84.7 (d, *J* = 200 Hz), –98.7 (d, *J* = 200 Hz).

GCMS (EI): *m*/*z* = 71 $[M - H_2O–F]^+$, 43 $[C_2H_3O]^+$.

Anal. Calcd for $C_4H_6F_2O$: C, 44.45; H, 5.60. Found: C, 44.31; H, 5.20.

*Method B (from **34**):* To a stirred solution of **34** (9.80 g, 55.7 mmol) in CH_2Cl_2 (100 mL), Morph-DAST (15.4 g, 88.0 mol) was added slowly at 0 °C. The resulting reaction mixture was warmed to r.t. and stirred for 3 d, then poured into sat aq $NaHCO_3$ (300 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to give crude product **36**, which was used in the next step without characterization. Product **36** was dissolved in MeOH (30 mL), 10% Pd/C (1.30 g) was added under an argon atmosphere, and the mixture was hydrogenated with H_2 (1 atm) at r.t. overnight. The catalyst was filtered off, and the filtrates were subjected to fractional distillation in vacuo.

Yield: 3.37 g (56% from **35**).

Spectral and physical data were identical to those described above.

3,3-Difluorocyclobutanone (21)

Alcohol **20** (1.66 g, 15.6 mmol) was added to a suspension of PCC (4.37 g, 20.2 mmol) in CH_2Cl_2 (30 mL). The reaction mixture was stirred at r.t. overnight, then Et_2O (60 mL) was added, and the resulting mixture was passed through a silica gel pad to remove the chromium salts. The filtrates were subjected to fractional distillation at atmospheric pressure.

Yield: 0.632 g (39%); colorless liquid; bp 87–90°C/1 atm.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.60 (t, *J* = 10.1 Hz, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.7 (t, *J* = 18.2 Hz), 115.9 (t, *J* = 271 Hz), 58.1 (t, *J* = 26.5 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –101.7.

GSMS (EI): *m*/*z* = 91 $[CF_2{=}CHC(O)]^+$, 64 $[CF_2CH_2]^+$, 57 $[C_3H_2F]^+$.

Anal. Calcd for $C_4H_4F_2O$: C, 45.29; H, 3.80. Found: C, 45.45; H, 3.71.

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Supporting Information

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