

A Ring-Closing Metathesis Pathway to Fluorovinyl-Containing Nitrogen Heterocycles

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The synthesis of highly functionalized fluorinated piperidines is described. The key step in this synthesis is a ring-closing metathesis reaction involving fluoride-substituted olefins, which leads to the corresponding cyclic vinyl fluo-

rides. Several sequences to arrive at differently substituted piperidines have been evaluated.

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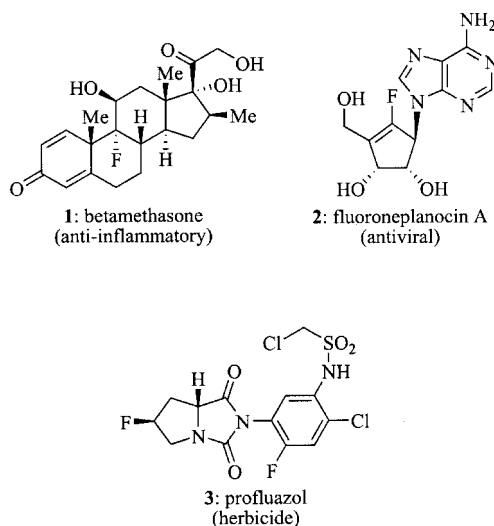
Introduction

During the past decades, the pharmaceutical and agrochemical industry have shown a growing interest in fluorinated organic compounds due to their specific chemical, biological and physical properties.^[1] For example, in the medicinal chemistry field, 9 out of the 31 new chemical entities approved in 2002 contained at least one fluorine atom.^[2] The first successful fluorinated drugs were introduced on the market as early as in the 1950s being anaesthetic and *anti-inflammatory* agents.^[3] Subsequently, the interest of the pharmaceutical industry in such a fluorination approach has grown substantially, and a variety of new fluorine-containing products have become available in different areas.^[4] Besides in the pharmaceutical industry, a similar expansion in the use of fluorinated compounds was encountered in the field of agrochemical research and development. For example, recent market studies have shown that the share of fluorine-containing ingredients for crop protection has grown from 9% in 1988 to 17% in 1999.^[5] Today, there are successfully utilized fluorinated compounds in all major areas of crop protection.^[6]

Generally, the term 'fluorinated' refers to the presence of either a fluoride or a trifluoromethyl substituent. More particularly, most of the biologically active fluorinated compounds up to date possess either a fluoride- or trifluoromethyl-substituted aromatic system because of the relative facile access to these structural units. Such (hetero)aromatics are either commercially available or can be readily prepared by well-established synthetic methodologies. Inversely, until now the synthesis of fluorinated non-aromatic (hetero)cycles is much less established.^[7] In our group, part

of the research focuses on the development of such methodologies. In this contribution recent progress in the area of fluoride-substituted heterocycles will be detailed.

The relevance of the latter class of compounds is exemplified in Scheme 1. As an example, betamethasone (**1**) is a representative of a class of *anti-inflammatory* drugs, in which useful modification of the biological activity was achieved by the introduction of a carbon–fluorine instead of a carbon–hydrogen bond.^[8] Fluoroneplanocin A (**2**) acts as an antiviral drug by inhibiting (*S*)-adenosylhomocysteine hydrolase (SAN).^[9] Finally, proflumazone (**3**) is a herbicide that inhibits protoporphyrinogen oxidase.^[10]



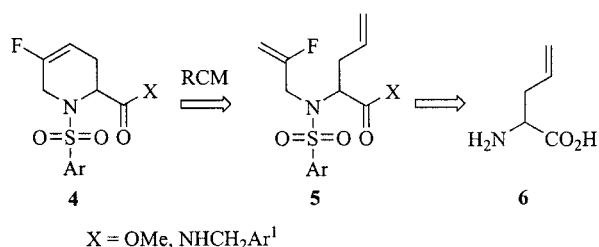
Scheme 1.

Considering the general relevance of (partially) saturated fluorinated heterocycles and the poor accessibility to such structural units, we set out to explore new synthetic methodology in order to gain access to these molecules. In conjunction with a continuing program on ring-closing metathesis in our group,^[11] we decided to study the possibility to

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obtain the fluoride-containing heterocycles **4** through ring-closing metathesis of the vinyl fluorides **5**, which in turn should be readily accessible from allylglycine (**6**, Scheme 2). Besides the study of this key reaction, we also aimed to develop suitable pathways to functionalize these scaffolds with biologically relevant pharmacophores (Ar = 4-MeC₆H₄, 2-Cl-5-MeOC₆H₃, Ar¹ = Ph, 2,3-F₂C₆H₃, 2-ClC₆H₄, 2-CF₃-3-ClC₆H₃).



Scheme 2. RCM approach to fluorinated (hetero)cyclic systems.

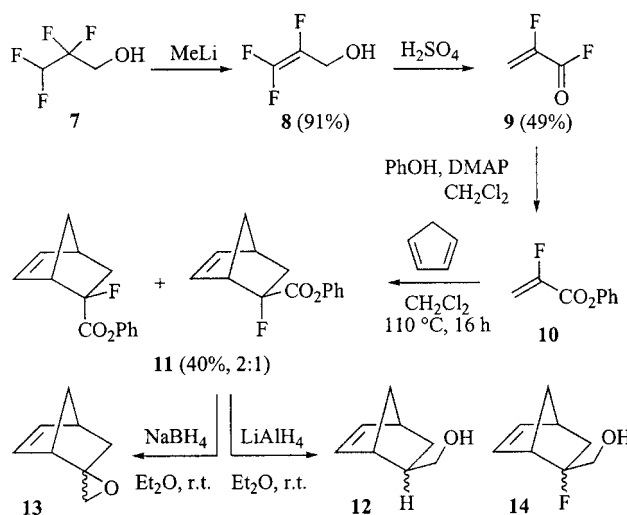
Over the years, ring-closing olefin metathesis has become a reliable approach for the construction of (hetero)cyclic systems.^[12] Initially, applications were restricted to terminal olefins, but gradually – stimulated by the emergence of more reactive Ru-carbene and Mo-catalysts – a wide variety of different substituents located at one of the participating olefins was reported to successfully undergo a ring-closing metathesis process. Substituents other than alkyl include heteroatoms such as nitrogen,^[11g,13] oxygen,^[14] phosphorus,^[15] silicon,^[16] and boron.^[17] Until recently, however, there were no examples in which halides were tolerated in this conversion. Considering the generally low reactivity of vinyl fluorides in transition-metal-mediated reactions, we reasoned that such functionalities might well undergo a metathesis process in the desired fashion. Although Grubbs had shown previously that 1,1-difluoroethylene forms a stable complex with ruthenium carbenes,^[18] several other groups were working along the same lines. In fact, during the course of our work RCM of vinyl fluorides and trifluoromethylated olefins,^[19] the Weinreb group published the first successful examples of vinyl chloride metathesis^[20] and soon thereafter, the Brown group reported the first examples of vinyl fluoride ring-closing metathesis.^[21] More recently, the Haufe group published examples of fluoroacrylate ring-closing metathesis.^[22] These examples once more emphasize the versatility of the RCM technique, giving facile access to potentially useful cyclic vinyl fluoride-containing heterocycles.

In this contribution, we wish to provide a detailed account of recent research in this area from our group, including studies towards the preparation of vinyl fluoride-containing reagents, a series of successful metathesis examples and elaboration of the resulting products into highly functionalized biologically relevant heterocycles.

Results and Discussion

The synthesis of precursor molecules for vinyl fluoride metathesis requires the availability of suitable acylating or

alkylating reagents, which allow the introduction of the fluoroalkene moiety. In order to introduce a fluoroacrylate moiety, we initially relied on the acid fluoride **9**, which has been described previously in the literature (Scheme 3).^[23] This sequence commences with 2,2,3,3-tetrafluoropropanol (**7**), which upon elimination of HF, followed by acid-mediated isomerization can be transformed into the desired acylating agent **9**. Besides a reagent that can be used to introduce a fluoroacrylate moiety, we used commercially available 1-chloro-2-fluoro-2-propene to introduce the 2-fluoroallyl substituent. A drawback of this latter reagent is that it is rather expensive, which prompted us to search for pathways to an alternative fluoroallylating reagent. Such a reagent might be accessible by the reduction of **9** into 2-fluoro-2-propenol. However, because direct reductive methods in our hands failed to convert the acyl fluoride **9** into the 2-fluoro-2-propenol, we envisioned that temporary masking of the double bond might solve this problem. This approach was chosen in analogy with our own synthesis of the corresponding trifluoromethyl-substituted propenol, where such a masking strategy was applied successfully.^[19] Thus, esterification of **9**, followed by Diels–Alder reaction with cyclopentadiene provided the adduct **11** as a 2:1 mixture of *endo*- and *exo*-products in 40% yield.^[24] Again, however, reductive methods failed to produce the intended product **14**, which was planned to undergo a *retro*-Diels–Alder reaction using Flash Vacuum Thermolysis (FVT). This failure may be due to intramolecular displacement of the fluoride with the generated alkoxide to form an epoxide. Proof for such a mechanism was obtained from the reaction of **11** with NaBH₄, where we were indeed able to isolate small amounts of the epoxide **13**. Whereas using the stronger reducing agent LiAlH₄, the same reaction may occur, followed by nucleophilic opening of the epoxide to form the alcohol **12**. More definite proof for loss of the fluoride was obtained by the tosylation of **11** (TsCl, pyridine, room temp.), followed by FVT (oven temperature 600 °C, 0.04 mbar), which only yielded the tosylated allyl alcohol. A series of other reducing agents applied under a variety of conditions (e.g.

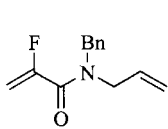
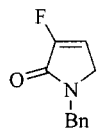
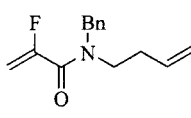
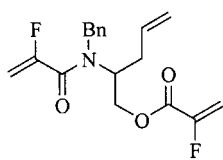
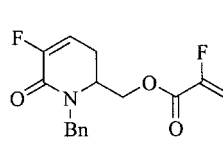


Scheme 3.

same reagents at lower temperatures, use of DIBALH at low temperatures) also failed to give the target compound **14**, and generally showed loss of the fluoride substituent. Because we were not able to come up with alternative pathways, we decided to abandon these alternative pathways.

We set out to prepare the fluoroacrylates **15–17** since we had the desired reagents available (Table 1). The yields of **15–17** refer to the acylation of the corresponding benzylamines with 1.0 equiv. of 2-fluoroacryloyl fluoride (**9**) at -78°C in diethyl ether. After stirring overnight at room temp., the acylated products were isolated in satisfactory yields considering the volatility of acyl fluoride **9**. Whereas the first two benzylamines were readily available (Entries 1 and 2), the preparation of the third benzylamine required a few steps. This involved condensation of methyl 2-amino-4-pentenoate with benzaldehyde and subsequent reduction with NaBH_4 . The precursors **15–17** were treated with the 2nd generation Grubbs catalyst at 100°C in toluene for the indicated time. In all cases, the catalyst was added in small portions during the reaction, because at these elevated temperatures the catalyst decomposition would lead to incomplete conversions. The ring-closing metathesis process also proceeded at lower temperatures (70 or 80°C), but again the catalyst had to be added in small portions due to decomposition and the reaction rate was significantly lower. Additionally, several experiments were conducted in a microwave without better results. Thus, the products **18–20** were obtained in good to excellent yields in these RCM reactions, giving rise to fluoro-substituted five- and six-membered α,β -unsaturated lactams. Interestingly, the corresponding seven-membered ring precursor (not shown) failed to give any cyclization product under these conditions.

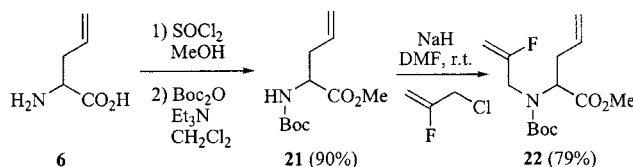
Table 1. RCM of vinyl fluorides.

Entry	Precursor (yield)	cat. (mol-%)	Time (h)	Product (yield)
1	 15 (41%)	7	4	 18 (99%)
2	 16 (30%)	7	4	 19 (80%)
3	 17 (20%)	4	4	 20 (99%)

At this point, because we had realized successful examples of fluoroacrylate metathesis, we adjusted our strategy

and aimed for new classes of heterocycles, that would allow straightforward variation of substituents at multiple positions. In the new strategy, we intended to start from commercially available 2-amino-4-pentenoic acid, a so-called trifunctional amino acid,^[25] which allows the use of the nitrogen and ester substituent as an attachment point for the introduction of new substituents in a later stage, and thus generate series of potentially biologically active cyclic fluorinated amino acid derivatives.

The first vinyl fluoride-containing metathesis precursor **22** was obtained by standard protection of 2-amino-4-pentenoic acid (**6**, allylglycine) as the corresponding Boc-protected methyl ester (**21**), followed by alkylation with 1-chloro-2-fluoro-2-propene using NaH in DMF in 79% overall yield (Scheme 4).



Scheme 4.

Other specifically functionalized metathesis precursors were also synthesized (Table 2). This sequence also commenced with allylglycine (**6**), which was first transformed into the sulfonamides **23–25** (TMSCl, CH_2Cl_2 reflux, then sulfonyl chloride, Et_3N) in good yields, followed by introduction of differently substituted benzylamines at the carboxylic acid position (HOBt, EDCI, CH_2Cl_2 , room temp., 1 h, then benzylamine, room temp., 12 h) to give the amides **26–28**. The amide formation also proceeded in very good to excellent yields. Finally, the 2-fluoro-2-propenyl substituent was introduced at the sulfonamide nitrogen. As can be seen from Table 2, this resulted in rather disappointing yields of the target products **29** and **30** (Entries 1 and 2). A different solvent (THF) or base (NaHMDS) and variable amounts of 3-chloro-2-fluoropropene (up to 2 equiv.) did not give better results. The addition of NaI also did not improve the reaction, but only the raise of the temperature to 50°C gave a significant increase in the yield to 30% for product **31** (Entry 3). The lower alkylation yields compared to **22** might be explained by the lower nucleophilicity of the sulfonamides, but these problems could also be due to the presence of the amide nitrogen, which may give rise to side products.

Gratifyingly, all four precursors **21** and **29–31** underwent facile cyclization under the previously optimized conditions (2nd generation Grubbs catalyst, added in portions during the reaction, toluene, 100°C , Table 3). Compound **21** gave a somewhat faster cyclization reaction, with a lower amount of catalyst. This may have to do with the nature of the side chain, where the methyl ester interferes less with the cyclization than the amide substituents in the precursors **29–31**. A variety of other conditions [lower temperatures, lower and higher catalyst loading (added both in portions and at once), different solvents] was also screened. However, no clear difference in yields was observed, the cyclizations pro-

Table 2. Synthesis of RCM precursors.^[a]

Entry	PG	Yield	X	Yield	Yield
1	Ts	23 (86%)		26 (80%)	29 (9%)
2		24 (80%)		27 (87%)	30 (10%)
3		25 (80%)		28 (99%)	31 (30%)

[a] Reagents and conditions. (a) i) Me_3SiCl , CH_2Cl_2 , reflux, 2 h, ii) ArSO_2Cl , Et_3N , CH_2Cl_2 , room temp., 1 h; (b) HOBt, EDCI, CH_2Cl_2 , room temp., 1 h, then benzylamine, room temp., 12 h; (c) NaH, DMF, 3-chloro-2-fluoropropene (1 equiv.), room temp. or 50°C , 12 h.

ceeded smoothly in very good to excellent yields. The cyclization of **29** (Entry 2) was also carried out in a microwave (toluene, 100°C , 300 W, 5 mol-% catalyst, 50 min) to see if this would lead to a faster reaction and/or a higher yield of the reaction. However, this did not really lead to an increase of the yield. In conclusion, a series of functionalized cyclic vinyl fluoride-containing amino acids was obtained in a straightforward manner.

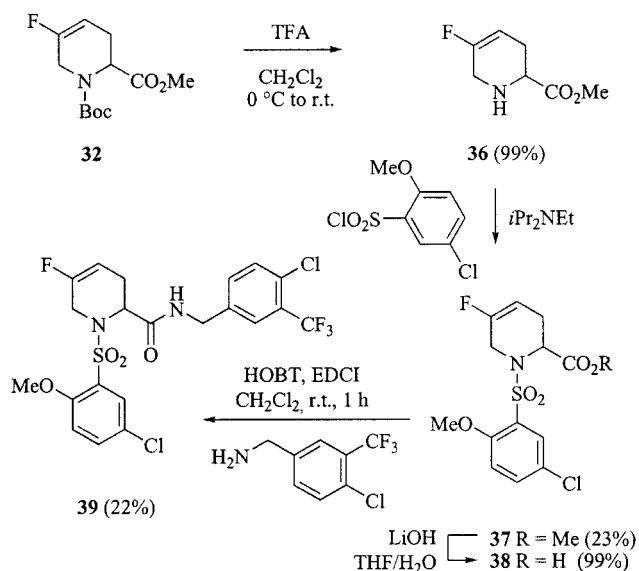
Clearly, the previously detailed sequence contains one low-yielding step, which makes the pathway less suitable for the production of large libraries of compounds. Therefore, we investigated whether building block **32** – readily accessible in good yields – could be used as a useful starting point for further functionalization. Initially, we focused on a pathway consisting of Boc-deprotection/functionalization, followed by ester hydrolysis/amide formation, which is outlined in Scheme 5. TFA-mediated Boc-deprotection proceeded in excellent yield, but sulfonylation of the nitrogen (Hünig's base, sulfonyl chloride, CH_2Cl_2) gave a rather disappointing 23% yield of the sulfonamide **37**. Then, ester hydrolysis (LiOH , $\text{THF}/\text{H}_2\text{O}$) followed by amide formation resulted in the target compound **39**. However, the low yield in the amide formation, combined with the poor sulfonylation reaction prompted us to reverse the order of events.

Thus, ester hydrolysis under similar conditions was again followed by amide formation with appropriate benzylamines to give the compounds **41** and **42** in good overall yields (Scheme 6). Boc-deprotection using TFA and subsequent sulfonylation (Hünig's base, sulfonyl chloride, CH_2Cl_2) provided the target piperidine derivatives **45** and **39**. Although the final step gave a relatively low yield, this

Table 3. RCM to functionalized cyclic amino acid derivatives.

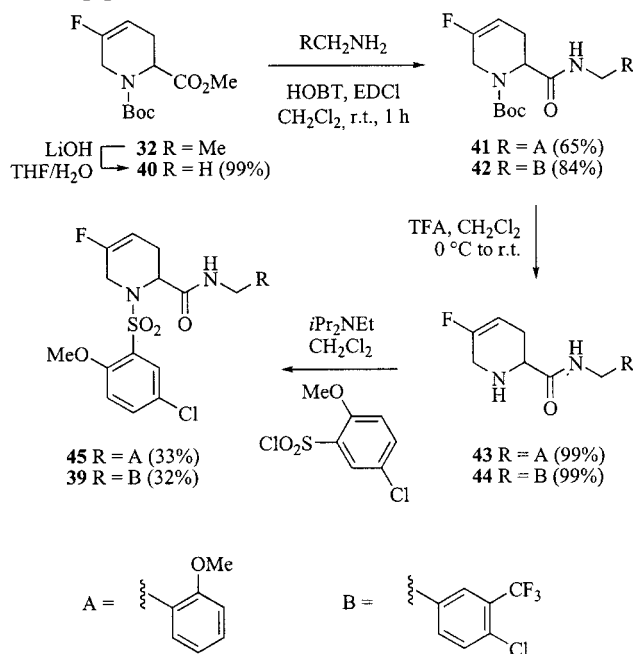
Entry	Precursor	cat. (mol-%)	Time (min)	Product (yield)
1		2.5	30	32 (99%)
2		5	50	33 (74%) ^[a]
3		5	60	34 (99%)
4		5	60	35 (90%)

[a] The reaction was carried out in a microwave oven: toluene, 100°C , 300 W, 5 mol-% 2nd generation Grubbs catalyst, 50 min.



Scheme 5.

sequence gives by far the highest overall yield of all the sequences that have been evaluated. Also in terms of ease of functionalization, the latter pathway is preferred: the versatile scaffold **32** was prepared in a scalable manner and appeared a useful starting point to synthesize series of the desired piperidines.



Scheme 6.

Conclusions

Generally applicable routes were developed for the synthesis of vinyl fluoride-containing building blocks, which may be relevant for the agrochemical and pharmaceutical industry. Key step in this sequence is the ring-closing metathesis of vinyl fluorides, which were shown to readily undergo a ruthenium-mediated cyclization process in very good yields. Furthermore, different pathways were evaluated to probe combinatorial approaches resulting in series of highly functionalized, fluorinated and potentially bioactive cyclic amino acid derivatives.

Experimental Section

General Information: All reactions were carried out under dry nitrogen. Solvents were distilled from the appropriate drying agents immediately prior to use. Infrared (IR) spectra were recorded with an ATI Mattson Genesis Series FTIR spectrometer and absorptions are reported in cm^{-1} . NMR spectra were recorded with a Bruker DMX300 (300 MHz) spectrometer from CDCl_3 solutions (unless otherwise reported) using TMS as internal standard. Mass spectra and accurate mass measurements were carried out with a Fisons (VG) Micromass 7070E or a Finnigan MAT900S instrument. R_f values were obtained by thin layer chromatography (TLC) on silica gel-coated plates (Merck silica gel 60 F₂₅₄) with the indicated solvent (mixture). Flash chromatography was performed with Acros Organics silica gel (0.035–0.070 nm). Melting points were deter-

mined with a Büchi melting point B-545 apparatus. The microwave reactions were carried out in a CEM Discover microwave.

Phenyl 2-Fluorobicyclo[2.2.1]hept-5-ene-2-carboxylate (11): To a solution of 2-fluoroacryloyl fluoride^[26] (300 mg, 3.26 mmol) and 4-(dimethylamino)pyridine (DMAP, 398 mg, 3.26 mmol) in dry CH_2Cl_2 (80 mL) was added phenol (307 mg, 3.26 mmol). The mixture was stirred at room temp. until the reaction was complete (TLC). To this crude reaction mixture was added cyclopentadiene (4.5 mL, 6.52 mmol) in CH_2Cl_2 (80 mL) at 110 °C in a sealed-glass vial for 10 h.^[22] After the mixture was cooled to room temp., CH_2Cl_2 and the excess of cyclopentadiene were removed under reduced pressure and the residue was purified by column chromatography (heptane/EtOAc, 6:1) to give **11** (413 mg, 40%) as a colorless oil (2:1 mixture of *endo/exo*-isomers). ^1H NMR (300 MHz, CDCl_3 , both diastereoisomers): δ = 6.52–6.38 (m, 1 H, $\text{CH}=\text{CH}$), 6.17–6.02 (m, 1 H, $\text{CH}=\text{CH}$), 3.39–3.20 (m, 1 H, CFCCCH), 3.04–2.97 (m, 1 H, CFCCCH_2CH), 2.58–1.51 (m, 4 H, CF_3CCH_2 , $\text{CH}_{2\text{bridge}}$) ppm. ^{13}C NMR (75 MHz, CDCl_3 , two diastereoisomers, signals separated by slashes): δ = 171.06 (d, J = 29.3 Hz, $\text{C}=\text{OCF}$), 168.5 (d, J = 28.1 Hz, $\text{C}=\text{OCF}$), 150.4, 142.1/140.3, 132.3/130.9, 129.4, 126.1, 121.3, 101.1 (d, J = 196.1 Hz, CF), 52.07, 49.8/48.6, 48.8, 42.5/41.6, 40.6/40.3 ppm.

(Bicyclo[2.2.1]-5-heptene-2-yl)methanol (12) and Subsequent Flash Vacuum Thermolysis: A solution of **11** (413 mg, 1.28 mmol) in anhydrous diethyl ether (1 mL) was added to a suspension of LiAlH_4 (48.5 mg, 1.28 mmol) in anhydrous diethyl ether (1 mL) over 30 min at room temp., and the mixture was stirred for 5 h. EtOAc (1 mL) was added slowly, followed by saturated aqueous Na_2SO_4 (a few drops) and solid Na_2SO_4 . After stirring for a few min, the mixture was filtered. The solvent was evaporated and the residue was purified by column chromatography (heptane/EtOAc, 6:1) to give **12** (133 mg, 73%) as a colorless oil (2:1 mixture of *endo/exo*-isomers). ^1H NMR (300 MHz, CDCl_3 , both diastereoisomers, signals separated by slashes): δ = 6.13–5.92 (m, 2 H, $\text{CH}=\text{CH}$), 3.72–3.49/3.41–3.21 (m, 2 H, CH_2OH), 2.92–2.80 (m, 2 H, $\text{C}=\text{CCH}$, $\text{C}=\text{CCH}$), 1.85–1.56 (m, 2 H, $\text{C}=\text{CCHCH}_2$), 1.48–1.36 (m, 2 H, $\text{CH}_{2\text{bridge}}$) ppm. This product was directly subjected to the tosylation reaction. As solution of **12** (133 mg, 0.94 mmol) and tosyl chloride (193 mg, 1.012 mmol) in dry pyridine (0.8 mL) was stirred at room temp. for 24 h. The reaction mixture was poured into cold 1 N HCl and extracted with diethyl ether. The extract was washed with dilute aqueous HCl, aqueous NaHCO_3 , brine and dried (MgSO_4). After evaporation of the solvent, the corresponding tosylate (216 mg, 77%) was obtained as a yellow oil. Subjection of the tosylate (148 mg, 0.5 mmol) to flash vacuum thermolysis (600 °C, 0.04 mbar) provided allyl tosylate (102 mg, 79%) as a colorless oil. ^1H NMR (400 MHz, $[\text{D}_8]\text{THF}$): δ = 7.78 (d, J = 8.5 Hz, 2 H, ArH), 7.40 (d, J = 8.2 Hz, 2 H, ArH), 5.87–5.78 (m, 1 H, $\text{H}_2\text{C}=\text{CH}$), 5.29 (d, J = 17.2 Hz, 1 H, $\text{CH}=\text{CH}$), 5.18 (d, J = 11.5 Hz, 1 H, $\text{CH}=\text{CH}$), 4.49 (d, J = 5.8 Hz, 2 H, CH_2O), 2.42 (s, 3 H, CH_3) ppm.

Epoxide 13: To a solution of **11** (300 mg, 1.29 mmol) in MeOH (2 mL), at 0 °C, NaBH_4 (59 mg, 1.55 mmol) was added in small portions. The reaction mixture was stirred for 3 h, quenched with saturated aqueous NaHCO_3 (2 mL) and extracted with diethyl ether (3 $\times$ 2 mL). The combined organic layers were washed with saturated aqueous NaHCO_3 and brine, dried (MgSO_4) and the solvents evaporated. The residue was purified by column chromatography (heptane/EtOAc, 10:1) to give **13** (19 mg, 12%) as a colorless oil. This product also contained several other minor impurities. ^1H NMR (200 MHz, CDCl_3): δ = 6.37–6.33 (m, 1 H, $\text{CH}=\text{CH}$), 6.05–6.02 (m, 1 H, $\text{CH}=\text{CH}$), 3.88–3.70 (m, 3 H, CH_2O , COCH), 3.05

(br. s, 1 H, COCH₂CH), 2.81 (br. s, 2 H, COCH₂), 1.58–1.51 (m, 2 H, CH₂bridge) ppm. GC-LRMS: calcd. for C₈H₁₀O [M⁺] 122, found 122.

***N*-Allyl-*N*-benzyl-2-fluoroacrylamide (15):** A solution of *N*-benzylamine^[27] (240 mg, 1.63 mmol) and triethylamine (0.227 mL, 1.63 mmol) in Et₂O (1 mL) was added dropwise at –78 °C to a solution of 2-fluoroacryloyl fluoride (**9**, 150 mg, 1.63 mmol) in Et₂O (1 mL). The reaction mixture was stirred overnight thereby slowly reaching room temp. The mixture was concentrated and the residue was purified using column chromatography (heptane/EtOAc, 6:1) to give the fluoride **15** (145 mg, 41%) as a colorless oil. IR (neat, cm^{–1}): $\tilde{\nu}$ = 3062, 2987, 2887, 2800, 1726, 1443, 1261, 1174, 1080, 1016, 800. ¹H NMR (300 MHz, CDCl₃): δ = 7.35–7.23 (m, 5 H, ArH), 5.83–5.70 (m, 1 H, CH₂=CH), 5.32 (dd, *J* = 3.5, 47.3 Hz, 1 H, FC=CH_{trans}), 5.21 (dd, *J* = 3.4, 16.8 Hz, 1 H, FC=CH_{cis}), 5.28–5.04 (m, 2 H, CH₂=CH), 4.57 (s, 2 H, CH₂Ph), 3.88 (br. s, 2 H, CHCH₂) ppm. ¹³C NMR (75 MHz, CDCl₃, some signals refer to rotamers, C=O signal is lacking): δ = 157.5 (d, *J* = 271.7 Hz, CF), 132.8, 128.7, 127.6, 118.5, 99.8 (d, *J* = 14.4 Hz, CCF), 50.8/50.1, 48.4/47.9 ppm. HRMS (EI): calcd. for C₁₃H₁₄FNO [M⁺] 219.1059, found 219.1059.

***N*-Benzyl-*N*-(but-3-enyl)-2-fluoroacrylamide (16):** A solution of *N*-benzyl-*N*-(but-3-enyl)amine^[27] (322 mg, 2.01 mmol) and triethylamine (0.31 mL, 2.23 mmol) in Et₂O (2 mL) was added dropwise at –78 °C to a solution of 2-fluoroacryloyl fluoride (**9**, 205 mg, 2.23 mmol) in Et₂O (2 mL). The reaction mixture was stirred overnight thereby slowly reaching room temp. The mixture was concentrated and the residue was purified using column chromatography (heptane/EtOAc, 6:1) to give **16** (140 mg, 30%) as a colorless oil. IR (neat, cm^{–1}): $\tilde{\nu}$ = 3062, 3036, 2924, 2843, 1640, 1424, 1359, 1178, 996, 919, 884, 728, 689. ¹H NMR (300 MHz, CDCl₃): δ = 7.32–7.22 (m, 5 H, ArH), 5.74–5.65 (m, 1 H, CH₂=CH), 5.38 (br. s, 1 H, FC=CH), 5.21 (br. s, 1 H, FC=CH), 5.13–5.0 (m, 2 H, CH₂=CH), 4.61 (s, 2 H CH₂Ph), 3.36 (t, *J* = 7.5 Hz, 2 H, NCH₂CH₂), 2.32 (q, *J* = 7.3 Hz, 2 H, NCH₂CH₂) ppm. ¹³C NMR (75 MHz, CDCl₃, some signals refer to rotamers): δ = 162.3 (d, *J* = 30.1 Hz, FCC=O), 157.6 (d, *J* = 269.2 Hz, CF=C), 136.3, 134.7/134.0, 128.6, 127.6, 126.9, 117.6–116.9 (m, CH₂=CH), 99.8–99.1 (m, CH₂=CF), 52.2–52.0/49.2–49.1 (m, NCH₂CH₂), 47.3–47.2/45.5–45.3 (m, CH₂Ph), 33.5–33.3/31.7–31.5 (m, NCH₂CH₂) ppm. HRMS (EI): calcd. for C₁₄H₁₆FNO [M⁺] 233.1216, found 233.1209.

2-[Benzyl(2-fluoroacryloyl)amino]pent-4-enyl 2-Fluoroacrylate (17): A solution of *N*-benzyl-2-amino-4-pentenol^[27] (425 mg, 2.23 mmol) and triethylamine (0.31 mL, 2.23 mmol) in Et₂O (2 mL) was added dropwise at –78 °C to a solution of 2-fluoroacryloyl fluoride (**9**, 205 mg, 2.23 mmol) in diethyl ether (2 mL). The reaction mixture was stirred overnight reaching slowly the room temp. The mixture was concentrated and the residue was purified using column chromatography (heptane/EtOAc, 6:1) to give **17** (149 mg, 20%) as a colorless oil. IR (neat, cm^{–1}): $\tilde{\nu}$ = 3010, 2919, 1744, 1643, 1446, 1424, 1317, 1163, 988, 926, 780, 720, 689. ¹H NMR (300 MHz, CDCl₃): δ = 7.28–7.23 (m, 5 H, ArH), 5.70–5.56 (m, 1 H, CH₂=CH), 5.56 (dd, *J* = 3.3, 42.9 Hz, 1 H, NCFC=CH_{trans}), 5.29 (dd, *J* = 3.3, 13.0 Hz, 1 H, NCFC=CH_{cis}), 5.34–5.05 (m, 4 H, CH₂=CF, CH₂=CH), 4.68 (br. s, 2 H, CH₂Ph), 4.43 (br. s, 2 H, CHCH₂O), 4.25 (br. s, 1 H, CHCH₂O), 2.44 (br. s, 2 H, NCHCH₂) ppm. ¹³C NMR (75 MHz, CDCl₃, some signals refer to rotamers, signals of the quaternary carbons are not visible): δ = 135.0, 128.6, 128.0, 127.4, 118.6/118.6, 102.8–102.4 (m, FC=CH₂), 99.2–99.8 (m, FC=CH₂), 64.8/64.8, 57.1/56.9, 56.7/56.6, 34.14 ppm. HRMS (EI): calcd. for C₁₈H₁₉F₂NO₃ [M⁺] 335.1333, found 335.1332.

General Procedure for the RCM Reactions: To a 0.01 M solution of the diene in dry toluene under an inert atmosphere, the 2nd generation Grubbs catalyst was added at 100 °C. Stirring was continued until the reaction was complete (indicated by TLC or GC), followed by concentration of the reaction mixture and subsequent purification with column chromatography.

1-Benzyl-3-fluoro-1,5-dihydropyrrol-2-one (18): To a solution of *N*-allyl-*N*-benzyl-2-fluoroacrylamide (**15**, 50 mg, 0.23 mmol) in dry toluene (20 mL) the 2nd generation Grubbs catalyst (7 mol-%) was added at 100 °C in small portions. The reaction was complete in 4 h. The mixture was evaporated and the product was purified using column chromatography (heptane/EtOAc, 3:1) to give **18** (44 mg, 99%) as a white solid.^[28] M.p. 37–41 °C. IR (neat, cm^{–1}): $\tilde{\nu}$ = 3058, 2920, 2854, 1697, 1664, 1452, 1232, 1219, 988, 926, 780, 720, 689. ¹H NMR (300 MHz, CDCl₃): δ = 7.35–7.20 (m, 5 H, ArH), 6.24–6.21 (m, 1 H, FC=CH), 4.63 (s, 2 H, CH₂Ph), 3.74–3.72 (m, 2 H, CHCH₂) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 162.7 (d, *J* = 31.2 Hz, FCC=O), 152.7 (d, *J* = 275.7 Hz, CF), 136.2, 128.8, 128.1, 127.8, 112.7 (d, *J* = 7.4 Hz, HC=CF), 47.1, 45.5 (d, *J* = 5.4 Hz, CH₂CH=CF) ppm. HRMS (EI): calcd. for C₁₁H₁₀FNO [M⁺] 191.0764, found 191.0740.

1-Benzyl-3-fluoro-5,6-dihydro-1*H*-pyridin-2-one (19): To a solution of *N*-benzyl-*N*-(3-butenyl)-2-fluoroacrylamide (**16**, 34 mg, 0.15 mmol) in dry toluene (10 mL) the 2nd generation Grubbs catalyst (7 mol-%) was added at 100 °C in small portions. The reaction was complete in 4 h. The mixture was evaporated and the product was purified using column chromatography (heptane/EtOAc, 3:1) to give **19** (25 mg, 80%) as an amorphous solid. IR (neat, cm^{–1}): $\tilde{\nu}$ = 3058, 2920, 1640, 1428, 1318, 1155, 910, 730, 690. ¹H NMR (300 MHz, CDCl₃): δ = 7.34–7.25 (m, 5 H, ArH), 5.97 (dt, *J* = 4.5, 10.5 Hz, 1 H, FC=CH), 4.61 (s, 2 H CH₂Ph), 3.32 (t, *J* = 7.3 Hz, 2 H, NCH₂CH₂), 2.39–2.35 (m, 2 H, NCH₂CH₂) ppm. ¹³C NMR (75 MHz, CDCl₃, some signals refer to rotamers): δ = 159.6 (d, *J* = 30.6 Hz, FCC=O), 149.7 (d, *J* = 253.3 Hz, CF), 136.6, 128.6, 128.0, 127.6, 112.7 (d, *J* = 14.5 Hz, HC=CF), 50.0/49.9, 44.8, 21.6 (d, *J* = 5.6 Hz, CH₂CH=CF) ppm. HRMS (EI): calcd. for C₁₂H₁₂FNO [M⁺] 205.0903, found 205.0910.

[1-Benzyl-5-fluoro-6-oxo-1,2,3,6-tetrahydropyridin-2-yl]methyl 2-Fluoroacrylate (20): To a solution of 2-fluoroacrylic acid 2-[benzyl-(2-fluoroacryloyl)amino]pent-4-enyl ester (**17**, 102 mg, 0.30 mmol) in dry toluene (40 mL) the 2nd generation Grubbs catalyst (4 mol-%) was added at 100 °C in small portions. The reaction was complete in 4 h. The mixture was evaporated and the residue was purified using column chromatography (heptane/EtOAc, 3:1) to give **20** (91 mg, 99%) as an amorphous white solid. IR (neat, cm^{–1}): $\tilde{\nu}$ = 3050, 2915, 2850, 1744, 1658, 1450, 1260, 1156, 1022, 798, 698. ¹H NMR (300 MHz, CDCl₃): δ = 7.33–7.13 (m, 5 H, ArH), 5.87–5.83 (m, 1 H, NCFC=CH), 5.65 (dd, *J* = 3.6, 42.9 Hz, 1 H, FC=CH), 5.38–5.30 (m, 2 H, FC=CH, CH₂Ph), 4.35–4.21 (m, 2 H, CHCH₂O), 4.06 (d, *J* = 14.4, 1 H, CH₂Ph), 3.73–3.67 (m, 1 H, NCH), 2.33 (s, 2 H, NCHCH₂) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 159.5 (d, *J* = 36.5 Hz, FCC=ON), 158.2 (d, *J* = 30.6 Hz, FCC=OO), 152.2 (d, *J* = 268.8 Hz, CH₂=CF), 148.8 (d, *J* = 260.8 Hz, CH=CF), 136.5, 128.6, 127.7, 125.0, 110.0 (d, *J* = 15.0 Hz, CH=CF), 103.6 (d, *J* = 14.6 Hz, CH₂=CF), 63.8, 52.3, 48.5, 23.4 ppm. HRMS (EI): calcd. for C₁₆H₁₅F₂NO₃ [M⁺] 307.1020, found 307.1021.

Methyl 2-[*tert*-Butoxycarbonyl-(2-fluoroallyl)amino]pent-4-enoate (22): To a suspension of NaH (155 mg, 6.5 mmol) in DMF (10 mL) was added the Boc-protected allylglycine methyl ester (**21**,^[29] 740 mg, 3.20 mmol) at room temp. After stirring for 15 min, 3-chloro-2-fluoropropene (301 mg, 3.20 mmol) was added. The reac-

tion was stirred for 12 h, quenched with water (7 mL) and extracted with Et₂O (3 × 10 mL). The ether layer was dried MgSO₄, the solvent evaporated and the residue purified using column chromatography (heptane/EtOAc, 10:1) to give **22** (726 mg, 79%) as a colorless oil. IR (neat, cm⁻¹): $\tilde{\nu}$ = 2976, 1744, 1701, 1450, 1368, 1243, 1165, 1001, 932, 862, 780. ¹H NMR (300 MHz, CDCl₃): δ = 5.84–5.70 (m, 1 H, CH₂=CH), 5.14–5.05 (m, 2 H, HC=CH, FC=CH), 4.69–4.39 (m, 3 H, HC=CH, FC=CH, COCH), 4.12–3.71 (m, 2 H, FCCH₂), 3.70 (s, 3 H, CH₃), 2.77–2.66 (m, 1 H, HCCH=CH₂), 2.65–2.53 (m, 1 H, HCCH=CH₂), 1.44 (s, 9 H, 3CH₃) ppm. ¹³C NMR (75 MHz, CDCl₃, some signals refer to rotamers): δ = 171.1/170.9, 162.1 (d, J = 259 Hz, CF)/159.5 (d, J = 255 Hz, CF), 154.8/154.3, 133.9/131.9, 119.2/117.8, 92.6 (d, J = 16.1 Hz, FC=C), 91.4 (d, J = 17.8 Hz, FC=C), 81.2/81.0, 60.1/58.9, 53.0/52.1, 48.1 (d, J = 33.0 Hz, FCCH₂)/46.6 (d, J = 35.6 Hz, FCCH₂), 35.0/34.0, 28.4 ppm. HRMS (EI): calcd. for C₁₄H₂₂FNO₄ [M⁺] 287.1533, found 287.1534.

N-Benzyl-2-[(2-fluoroallyl)(*p*-tosyl)amino]-4-pentenamide (29): To a suspension of allylglycine (0.57 g, 5.00 mmol) in CH₂Cl₂ (10 mL) was added Me₃SiCl (0.54 g, 5.00 mmol). The mixture was heated at reflux for 2 h, Et₃N (1.4 mL, 10.0 mmol) was added, followed by addition of a solution of *p*-toluenesulfonyl chloride (0.95 g, 5.00 mmol) in CH₂Cl₂ (5 mL).^[30] The resulting mixture was vigorously stirred for 1 h at room temp., MeOH (0.81 mL, 20.0 mmol) was added, and the mixture was evaporated. The residue was dissolved in water and brought to pH 8 using aqueous K₂CO₃. The aqueous layer was washed with diethyl ether (3 × 10 mL), acidified to pH 1 using 1 N hydrochloric acid (1 N) and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (MgSO₄) and the solvent was evaporated to afford **23** (1.15 g, 86%) as a white solid. The crude acid **23** (1.15 g, 4.29 mmol) was dissolved in CH₂Cl₂ (86 mL) and stirred for 1 h with 1-hydroxybenzotriazole (HOBt, 0.637 g, 4.72 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI, 0.903 g, 4.72 mmol). Benzylamine (1.4 mL, 12.9 mmol) was added and the mixture was stirred for 12 h. The solvent was evaporated and the residue was purified using column chromatography (heptane/EtOAc, 3:1 to 1:1) to give **26** (1.18 g, 80%) as a white solid. M.p. 141–144 °C, IR (neat, cm⁻¹): $\tilde{\nu}$ = 3322, 3235, 3067, 3036, 2920, 1645, 1554, 1455, 1338, 1161, 1070, 927, 815, 698. ¹H NMR (300 MHz, CDCl₃, 25 °C, TMS): δ = 7.69 (d, J = 8.4 Hz, 2 H, Ph), 7.32–7.17 (m, 7 H, Ph), 6.72 (br. s, 1 H, C=ONH), 5.44–5.30 (m, 1 H, CH₂=CH), 5.06–4.95 (m, 3 H, TsNH, H₂C=CH), 4.43–4.30 (m, 2 H, NCH₂Ph), 3.78–3.71 (m, 1 H, COCH), 2.54–2.43 (m, 1 H, HCCH=CH₂), 2.43 (s, 3 H, CH₃), 2.29–2.20 (m, 1 H, HCCH=CH₂) ppm. ¹³C NMR (75 MHz, CDCl₃, 25 °C): δ = 170.2, 144.2, 137.7, 136.3, 132.2, 129.9, 128.7, 127.7, 127.6, 127.4, 120.3, 56.1, 43.7, 37.0, 21. ppm. HRMS (EI): calcd. for C₁₉H₂₂N₂O₃S [M⁺] 358.1351, found 358.1348. To a solution of **26** (468 mg, 1.31 mmol) in DMF (3.5 mL) was added NaHMDS (135 μ L of a 1 M solution in THF, 1.36 mmol), 3-chloro-2-fluoropropene (123 mg, 1.36 mmol) and NaI (8.5 mg, 0.055 mmol). After stirring at room temp. for 10 h, water (5 mL) was added and the mixture it was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with water (3 × 5 mL), brine (3 × 5 mL), dried (Na₂SO₄) and the solvents evaporated. The residue was purified using column chromatography (heptane/EtOAc from, 3:1 to 1:1) to give **29** (55 mg, 9%) as a yellow oil. IR (neat, cm⁻¹): $\tilde{\nu}$ = 3378, 3317, 3062, 3032, 2980, 2924, 1675, 1528, 1338, 1156, 1087, 923, 815, 698, 664, 543. ¹H NMR (300 MHz, CDCl₃): δ = 7.67–7.64 (m, 2 H, Ph), 7.32–7.22 (m, 7 H, Ph), 6.78 (br. s, 1 H, NH), 5.37–5.23 (m, 1 H, CH₂=CH), 4.93–4.78 (m, 2 H, H₂C=CH), 4.66–4.25 (m, 5 H, FC=CH₂, NCH₂Ph, COCH), 4.15–3.90 (m, 2 H, FCCH₂), 2.79–2.70 (m, 1

H, HCCH=CH₂), 2.40 (s, 3 H, CH₃), 2.23–2.13 (m, 1 H, HCCH=CH₂) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 168.7, 163.7 (d, J = 249 Hz, CF), 144.0, 137.6, 136.4, 133.5, 129.6, 128.5, 127.7, 127.4, 118.0, 94.7 (d, J = 17.5 Hz, FC=C), 60.1, 44.7 (d, J = 30.2 Hz, FCCH₂), 44.1, 33.1, 21.9 ppm. HRMS (EI): calcd. for C₂₂H₂₅FN₂O₃S [M⁺] 416.157, found 416.1572.

2-[(5-Chloro-2-methoxyphenyl)sulfonyl(2-fluoroallyl)amino]-N-(3,4-difluorobenzyl)-4-pentenamide (30): To a suspension of allylglycine (2.00 g, 17.4 mmol) in CH₂Cl₂ (35 mL) was added Me₃SiCl (2.2 mL, 17.4 mmol). The mixture was heated at reflux for 2 h, Et₃N (4.87 mL, 34.8 mmol) was added, followed by a solution of 5-chloro-2-methoxybenzenesulfonyl chloride (4.2 g, 17.4 mmol) in CH₂Cl₂ (17.5 mL). The resulting mixture was vigorously stirred for 1 h, MeOH (2.78 mL, 20.0 mmol) was added and the mixture was evaporated. The residue was dissolved in water and brought to pH 8 using aqueous K₂CO₃. The aqueous layer was washed with diethyl ether (3 × 10 mL), acidified to pH 1 using 1 N hydrochloric acid (1 N) and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (MgSO₄) and to afford **24** (4.41 g, 80%) as a yellow solid. A solution of the crude acid **24** (1.00 g, 3.13 mmol) in CH₂Cl₂ (65 mL) was stirred for 1 h at with HOBt (466 mg, 3.45 mmol) and EDCI (662 mg, 3.45 mmol). 3,4-Difluorobenzylamine (1.1 mL, 9.39 mmol) was added, the mixture was stirred for 12 h and the solvent was evaporated. The residue was dissolved in EtOAc (20 mL), washed with brine (10 mL) and aqueous NaHCO₃ (10 mL). The combined water phases were reextracted with EtOAc (3 × 10 mL), and the combined organic layers were dried (MgSO₄) and the solvents evaporated. The residue was crystallized (heptane/Et₂O, 3:1) to give **27** (1.21 g, 87%) as a white solid. M.p. 115–118 °C. IR (neat, cm⁻¹): $\tilde{\nu}$ = 3309, 3261, 3097, 3075, 2980, 2894, 1653, 1515, 1437, 1329, 1282, 1156, 1113, 1070, 1014, 897, 815, 646. ¹H NMR (400 MHz, CDCl₃): δ = 7.85 (d, J = 3.2 Hz, 1 H, ArH), 7.55–7.52 (m, 1 H, ArH), 7.15–6.92 (m, 4 H, 1 H, ArH), 6.85 (br. s, 1 H, C=ONH), 5.57–5.44 (m, 2 H, CH₂=CH, TsNH), 5.15–5.05 (m, 2 H, H₂C=CH), 4.39–4.25 (m, 2 H, NCH₂), 3.95 (s, 3 H, OCH₃), 3.74 (t, J = 8.0 Hz, 1 H, COCH), 2.61–2.53 (m, 1 H, HCCH=CH₂), 2.34–2.24 (m, 1 H, HCCH=CH₂) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 170.3, 154.9, 150.1 (dd, J = 47.1, 247.0 Hz, ArF), 149.9 (dd, J = 47.1, 247.0 Hz, ArF), 135.0–134.9 (m, ArF), 134.8, 132.0, 129.8, 127.8, 125.8, 123.6–123.4 (m, ArF), 119.9, 117.0 (dd, J = 17.2, 61.7 Hz, ArF), 116.9 (dd, J = 17.2, 61.7 Hz, ArF), 113.6, 56.6, 56.5, 42.5, 37.1 ppm. HRMS (EI): calcd. for C₁₉H₁₉ClF₂N₂O₄S [M⁺] 444.0722, found 444.0718. To a suspension of NaH (70 mg, 2.88 mmol) in DMF (6 mL) was added at 10 °C **27** (640 mg, 1.44 mmol). After stirring for 15 min, 3-chloro-2-fluoropropene (135 mg, 1.44 mmol) was added dropwise at room temp. The reaction was stirred for 12 h, quenched with water (6 mL) and extracted with Et₂O (3 × 6 mL). The ether layers were dried (MgSO₄), evaporated and the residue was purified using column chromatography (heptane/EtOAc, 3:1 to 1:1) to give **30** (30 mg, 10%) as a colorless oil. IR (neat, cm⁻¹): $\tilde{\nu}$ = 3379, 3087, 2950, 2846, 1679, 1607, 1585, 1519, 1478, 1434, 1390, 1333, 1273, 1155, 1111, 1067, 1015, 913, 877, 817, 735, 647, 584. ¹H NMR (400 MHz, CDCl₃): δ = 7.89 (d, J = 2.4 Hz, 1 H, ArH), 7.53–7.50 (m, 1 H, ArH), 7.15–7.00 (m, 4 H, ArH, NH), 6.92 (d, J = 8.8 Hz, 1 H, ArH), 5.37–5.27 (m, 1 H, CH₂=CH), 4.99 (dd, J = 1.2, 16.8 Hz, 1 H, HHC=CH), 4.88 (dd, J = 0.8, 10.0 Hz, 1 H, HHC=CH), 4.62–4.57 (m, 1.5 H, FC=CH₂), 4.46–4.25 (m, 4.5 H, FC=CH₂, NCH₂, NCH₂CF), 3.88 (s, 4 H, CH₃, COCH), 2.89–2.82 (m, 1 H, HCCH=CH₂), 2.35–2.27 (m, 1 H, HCCH=CH₂) ppm. ¹³C NMR (100 MHz, CDCl₃, some signals refer to rotamers): δ = 169.2, 160.1 (d, J = 259.2 Hz, C=CF), 155.3, 150.0 (dd, J = 58.4, 247.1 Hz, ArF), 149.9 (dd, J = 58.1 Hz, 247.2 Hz, ArF), 134.9–

134.8 (m, ArF), 134.7, 133.5, 131.0, 128.7, 125.7, 123.7 (m, ArF), 118.0, 117.3 (d, $J = 18.1$ Hz, ArF), 116.8 (d, $J = 17.7$ Hz, ArF), 113.6, 94.9 (d, $J = 17.7$ Hz, C=CF), 59.3, 56.4, 44.9 (d, $J = 29.9$ Hz, CH₂CF), 42.9, 32.6 ppm. HRMS (EI): calcd. for C₂₂H₂₃ClF₃N₂O₄S [M⁺ + H] 503.0965, found 503.1019.

***N*-(2-Chlorobenzyl)-2-[(5-chloro-2-methoxyphenylsulfonyl)(2-fluoroallyl)aminol]-4-pentenamide (31):** To a suspension of allylglycine (2.00 g, 17.4 mmol) in dichloromethane (35 mL) was added Me₃SiCl (2.2 mL, 17.4 mmol). The mixture was heated at reflux for 2 h, Et₃N (4.87 mL, 34.8 mmol) was added, followed by a solution of 5-chloro-2-methoxybenzenesulfonyl chloride (4.20 g, 17.4 mmol) in CH₂Cl₂ (17.5 mL). The resulting mixture was vigorously stirred for 1 h, MeOH (2.78 mL, 20.0 mmol) was added and the mixture was evaporated. The residue was dissolved in water and brought to pH 8 using aqueous K₂CO₃. The aqueous layer was washed with diethyl ether (3 × 10 mL), acidified to pH 1 with 1 N hydrochloric acid (1 N) and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (MgSO₄), and the solvent was evaporated to afford **25** (4.41 g, 80%) as a yellow solid. A solution of the crude acid **25** in CH₂Cl₂ (35 mL) was stirred for 1 h with HOBt (233 mg, 1.75 mmol) and EDCI (331 mg, 1.75 mmol). 2-Chlorobenzylamine (250 μL, 1.75 mmol) was added, the mixture was stirred for 12 h and the solvent was evaporated. The residue was dissolved in EtOAc (20 mL), washed with brine (10 mL) and aqueous NaHCO₃ (10 mL). The water layer was reextracted with EtOAc (3 × 10 mL), and the combined organic layers were dried (MgSO₄) and the solvents evaporated. The residue was crystallized (heptane/Et₂O, 3:1) to give **28** (700 mg, 99%) as a white solid. M.p. 90–100 °C. IR (neat, cm⁻¹): $\tilde{\nu} = 3404, 3114, 3075, 2967, 2933, 2846, 1653, 1528, 1480, 1437, 1325, 1277, 1156, 1018, 914, 750$. ¹H NMR (400 MHz, CDCl₃, 25 °C, TMS): $\delta = 7.85$ (d, $J = 2.4$ Hz, 1 H, SO₂Ph), 7.49–7.46 (m, 1 H, SO₂Ph), 7.38–7.35 (m, 1 H, Ph), 7.30–7.23 (m, 3 H Ph), 6.90 (d, $J = 8.8$ Hz, 1 H, SO₂Ph), 6.66 (br. s, 1 H, C=ONH), 5.58–5.48 (m, 2 H, CH₂=CH, TsNH), 5.11–5.04 (m, 2 H, H₂C=CH), 4.48–4.37 (m, 2 H, CH₂Ph), 3.93 (s, 3 H, OCH₃), 3.77–3.73 (m, 1 H, C=OCH), 2.61–2.54 (m, 1 H, HCCH=CH₂), 2.33–2.26 (m, 1 H, HCCH=CH₂) ppm. ¹³C NMR (75 MHz, CDCl₃, 25 °C): $\delta = 170.1, 154.9, 134.9, 134.6, 133.6, 133.4, 132.1, 129.7, 129.6, 129.5, 128.9, 127.9, 127.1, 125.7, 119.7, 113.5, 56.6, 56.5, 41.5, 37.4$ ppm. HRMS (EI): calcd. for C₁₉H₂₀Cl₂N₂O₄S [M⁺] 442.0521, found 442.0514.

To a suspension of NaH (34 mg, 1.43 mmol) in DMF (3 mL) was added **28** (310 mg, 0.714 mmol). After stirring for 15 min, 3-chloro-2-fluoro-2-propene (67 mg, 0.714 mmol) was added slowly at 50 °C. The reaction was stirred for 12 h at 50 °C, quenched with water (3 mL) and extracted with Et₂O (3 × 3 mL). The ether layers were dried (MgSO₄), evaporated and the residue was purified using column chromatography (heptane/EtOAc, 3:1 to 1:1) to give **31** (90 mg, 30%) as a colorless oil. IR (neat, cm⁻¹): $\tilde{\nu} = 3379, 2961, 2851, 2758, 2642, 2543, 1747, 1720, 1670, 1533, 1478, 1440, 1390, 1333, 1270, 1198, 1174, 1138, 1070, 1015, 1006, 919, 875, 836, 798, 721, 644, 589$. ¹H NMR (400 MHz, CDCl₃): $\delta = 7.88$ (d, $J = 2.4$ Hz, 1 H, ArH), 7.49–7.46 (m, 1 H, ArH), 7.37–7.35 (m, 2 H, Ph), 7.27–7.22 (m, 2 H, ArH), 6.98 (br. s, 1 H, NH), 6.88 (d, $J = 8.8$ Hz, 1 H, ArH), 5.44–5.34 (m, 1 H, CH₂=CH), 4.99 (dd, $J = 1.6, 17.2$ Hz, 1 H, FC=CH), 4.89 (dd, $J = 1.2, 10.4$ Hz, 1 H, FC=CH), 4.57–4.51 (m, 3 H, H₂C=CH, COCH), 4.43–4.34 (m, 4 H, CH₂Ph, FCCH₂), 3.85 (s, 3 H, OCH₃), 2.87–2.79 (m, 1 H, HCCH=CH₂), 2.37–2.29 (m, 1 H, HCCH=CH₂) ppm. ¹³C NMR (100 MHz, CDCl₃): $\delta = 168.9, 160.3$ (d, $J = 259.3$ Hz, CF), 155.2, 135.1, 134.6, 133.6, 133.4, 130.9, 129.9, 129.4, 128.85, 128.8, 126.9, 125.5, 117.9, 113.5, 94.8 (d, $J = 17.9$ Hz, CH₂=CF), 59.4, 56.3, 44.9 (d, $J = 30.5$ Hz, NCH₂CF), 41.5, 32.9 ppm. HRMS (EI):

calcd. for C₂₂H₂₉Cl₂FN₂O₄S [M⁺ + H] 501.0786, found 501.0818.

1-*tert*-Butyl 2-Methyl 5-Fluoro-3,6-dihydropyridine-1(2H),2-dicarboxylate (32): To a solution of **21** (412 mg, 1.44 mmol) in dry toluene (160 mL) the 2nd generation Grubbs catalyst (2.5 mol-%) was added at 100 °C in small portions. The reaction was finished in 30 min. The solvent was evaporated and the product purified using column chromatography (heptane/EtOAc, 10:1) to give **32** (369 mg, 99%) as a colorless oil. IR (neat, cm⁻¹): $\tilde{\nu} = 2971, 2863, 1740, 1697, 1407, 1368, 1329, 1156, 1104, 1022, 888, 811$. ¹H NMR (300 MHz, CDCl₃): $\delta = 5.27$ – 5.22 (m, 1 H, FC=CH), 5.00–4.98 (m, 1 H, COCH), 4.09 (d, $J = 17.4$ Hz, 1 H, FCCH), 3.84 (d, $J = 18.6$ Hz, 1 H, FCCH), 3.71 (s, 3 H, CH₃), 2.69–2.50 (m, 2 H, H₂CCH=CF), 1.49/1.46 (s, 9 H, 3CH₃) ppm. ¹³C NMR (75 MHz, CDCl₃): $\delta = 171.3, 155.0, 154.9$ (d, $J = 248.7$ Hz, CF), 98.4 (d, $J = 13.5$ Hz, FC=C), 81.2, 52.7, 51.1, 41.6 (d, $J = 39.6$ Hz, FCCH₂), 28.6, 24.3 ppm. HRMS (technique): calcd. for C₁₂H₁₈FN₂O₄ [M⁺] 259.1220, found 259.1220.

***N*-Benzyl-5-fluoro-1-(*p*-tosyl)-1,2,3,6-tetrahydropyridine-2-carboxamide (33):** To a solution of **29** (41 mg, 98 μmol) in dry toluene (4 mL) in a resealable vial was added the 2nd generation Grubbs catalyst (2.4 mg, 2 mol-%). The mixture was heated in a microwave for 20 min at 300 W. The reaction was followed by GC and new portions of catalyst were added, followed by heating until the reaction was complete (at total of 5 mol-% of catalyst, 50 min heating). The mixture was evaporated and the residue was purified using column chromatography (heptane/EtOAc, 3:1) to give **33** (35 mg, 74%) as a white solid. M.p. 90–93 °C. IR (neat, cm⁻¹): $\tilde{\nu} = 3378, 3356, 3317, 3062, 3028, 2924, 2863, 1671, 1524, 1342, 1165, 1091, 962, 815, 698, 569$. ¹H NMR (300 MHz, CDCl₃): $\delta = 7.66$ – 7.63 (m, 2 H, Ph), 7.33–7.20 (m, 7 H, Ph), 6.90 (br. s, 1 H, NH), 5.16–5.08 (m, 1 H, FC=CH), 4.58–4.34 (m, 3 H, NCH₂Ph, COCH), 4.17 (d, $J = 17.4$ Hz, 1 H, FCCH), 3.76 (d, $J = 18$ Hz, 1 H, FCCH), 2.84–2.76 (m, 1 H, HCCH=CF), 2.41 (s, 3 H, CH₃), 1.87–1.80 (m, 1 H, HCCH=CF) ppm. ¹³C NMR (75 MHz, CDCl₃): $\delta = 168.1, 152.5$ (d, $J = 252.2$ Hz, CF), 144.4, 137.7, 135.5, 130.0, 128.7, 127.5, 127.4, 127.0, 100.0 (d, $J = 13.5$ Hz, FC=C), 54.0, 44.2, 41.1 (d, $J = 39.3$ Hz, FCCH₂), 21.9, 21.4 ppm. HRMS (technique) calcd. for C₂₀H₂₁FN₂O₃S [M⁺] 388.1257, found 388.1258.

1-(5-Chloro-2-methoxyphenylsulfonyl)-*N*-(3,4-difluorobenzyl)-5-fluoro-1,2,3,6-tetrahydropyridine-2-carboxamide (34): To a solution of **30** (30 mg, 0.06 mmol) in dry toluene (12 mL) the 2nd generation Grubbs catalyst (5 mol-%) was added at 100 °C in small portions. The reaction was complete in 60 min. The solvent was evaporated and the residue purified using column chromatography (heptane/EtOAc from, 3:1 to 1:1) to give **34** (28 mg, 99%) as slightly colored solid. M.p. 165–167 °C. IR (neat, cm⁻¹): $\tilde{\nu} = 3329, 3109, 2956, 2923, 2846, 1714, 1648, 1519, 1484, 1429, 1390, 1333, 1273, 1209, 1155, 1111, 1015, 949, 814, 647, 592$. ¹H NMR (400 MHz, CDCl₃): $\delta = 7.92$ (d, $J = 2.8$ Hz, 1 H, ArH), 7.54–7.51 (m, 1 H, ArH), 7.16–6.93 (m, 5 H, ArH, NH), 5.32–5.26 (m, 1 H, FC=CH), 4.44–4.40 (m, 4 H, NCH₂Ph, FCCH₂N), 3.86 (s, 4 H, OCH₃, COCH), 3.78–3.72 (m, 1 H, HCCH=CF), 1.87–1.81 (m, 1 H, HCCH=CF) ppm. ¹³C NMR (100 MHz, CDCl₃): $\delta = 168.5, 153.7$ (d, $J = 324.6$ Hz, C=CF), 154.6, 150.9, 141.2, 140.1, 135.1, 131.2, 127.6, 125.9, 123.5–123.4 (m, ArH), 117.7, 113.6, 99.5 (d, $J = 13.7$ Hz, C=CF), 56.5, 53.6, 43.1, 41.1 (d, $J = 41.1$ Hz, CH₂CF), 21.2 ppm. HRMS (EI): calcd. for C₂₀H₁₉ClF₃N₂O₄S [M⁺ + H] 475.0660, found 475.0706.

***N*-(2-Chlorobenzyl)-1-(5-chloro-2-methoxyphenylsulfonyl)-5-fluoro-1,2,3,6-tetrahydropyridine-2-carboxamide (35):** To a solution of **31** (33 mg, 66 μmol) in dry toluene (15 mL) the 2nd generation Grubbs catalyst (5 mol-%) was added at 100 °C in small portions. The reac-

tion was complete in 60 min. The solvent was evaporated and the residue was purified using column chromatography (heptane/EtOAc, 3:1 to 1:1) to give **35** (28 mg, 90%) as a light yellow solid. M.p. 145–148 °C. IR (neat, cm^{-1}): $\tilde{\nu}$ = 3307, 3104, 2906, 1917, 1714, 1665, 1514, 1478, 1437, 1388, 1338, 1273, 1245, 1163, 1017, 960, 812, 738, 587. ^1H NMR (400 MHz, CDCl_3): δ = 7.92 (d, J = 3.6 Hz, 1 H, SO_2Ph), 7.52–7.48 (m, 1 H, ArH), 7.40–7.23 (m, 4 H, ArH), 7.03 (br. s, 1 H, NH), 6.91 (d, J = 12.4 Hz, 1 H, ArH), 5.31–5.23 (m, 1 H, $\text{FC}=\text{CH}$), 4.61–4.38 (m, 4 H, NCH_2Ph , FCCH_2N), 3.82 (s, 3 H, OCH_3), 3.74 (s, 1 H, COCH), 2.86–2.79 (m, 1 H, $\text{HCCH}=\text{CF}$), 1.91–1.84 (m, 1 H, $\text{HCCH}=\text{CF}$) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 168.2, 155.2, 153.4 (d, J = 253.2 Hz, CF), 135.0, 133.6, 131.1, 130.0, 129.7, 129.1, 127.9, 127.1, 125.9, 113.5, 99.7 (d, J = 13.9 Hz, $\text{C}=\text{CF}$), 56.4, 53.5, 42.1, 41.0 (d, J = 40.4 Hz, NCH_2CF), 21.3 (d, J = 6.1 Hz, $\text{CH}_2\text{CH}=\text{CF}$) ppm. HRMS: calcd. for $\text{C}_{20}\text{H}_{20}\text{Cl}_2\text{FN}_2\text{O}_4\text{S}$ [$\text{M}^+ + \text{H}$] 473.0550, found 473.0505.

1-(5-Chloro-2-methoxyphenylsulfonyl)-N-(4-chloro-3-trifluoromethylbenzyl)-5-fluoro-1,2,3,6-tetrahydropyridine-2-carboxamide (39): As shown in Scheme 3. Trifluoroacetic acid (5.0 mL, 6.45 mmol) was added to a solution of **32** (730 mg, 2.81 mmol) in CH_2Cl_2 (20 mL) at 0 °C. The resulting mixture was stirred at room temp. for 6 h and the solvent was evaporated. Residual traces of trifluoroacetic acid were azeotropically removed using CH_2Cl_2 (3×10 mL). The crude compound **36** was redissolved in CH_2Cl_2 (8 mL) and Hünig's base (0.98 mL, 5.62 mmol) was added. After 15 min, 5-chloro-2-methoxybenzenesulfonyl chloride (668 mg, 2.81 mmol) was added and the reaction mixture was stirred overnight. The solvent was evaporated and the residue was filtered through silica gel (heptane/EtOAc, 3:1 to 1:1) to give crude **37** (235 mg, 23%) as a yellow oil. Crude **37** (60 mg, 0.17 mmol) was dissolved in THF/ H_2O (4:1 v/v, 1 mL), LiOH (8.2 mg, 0.34 mmol) was added and the reaction mixture was stirred at room temp. Upon completion, the solution was acidified to pH 1 with 1 N hydrochloric acid and extracted with EtOAc (3×5 mL). The combined organic phases were dried (MgSO_4) and the solvent evaporated to afford **38** (59 mg, 99%) as a yellow oil. This product was directly dissolved in CH_2Cl_2 (5 mL) and treated with HOBt (26 mg, 0.189 mmol) and EDCI (36 mg, 0.189 mmol). Then, 4-chloro-3-trifluoromethylbenzylamine (108 mg, 0.516 mmol) was added and the mixture was stirred for 12 h. The solvent was evaporated and the residue was purified using column chromatography (heptane/EtOAc, 3:1 to 1:1) to give **39** (20 mg, 22%) as a white solid. M.p. 180–182 °C. IR (neat, cm^{-1}): $\tilde{\nu}$ = 3324, 3104, 3054, 2945, 2906, 1717, 1657, 1528, 1478, 1322, 1273, 1163, 1144, 1015, 960, 817. ^1H NMR (400 MHz, CDCl_3): δ = 7.87 (d, J = 3.5 Hz, 1 H, SO_2Ph), 7.53–7.41 (m, 3 H, ArH), 7.33 (d, J = 10.7 Hz, 1 H, ArH), 7.09 (br. s, 1 H, NH), 6.90 (d, J = 12 Hz, 1 H, ArH), 5.29–5.21 (m, 1 H, $\text{FC}=\text{CH}$), 4.46–4.36 (m, 5 H, NCH_2Ph , COCH, FCCH_2N), 3.83 (s, 3 H, OCH_3), 3.73 (d, J = 23.2 Hz, 1 H, $\text{HCCH}=\text{CF}$), 2.77 (br. d, J = 22.7 Hz, 1 H, $\text{HCCH}=\text{CF}$) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 169.2, 155.6, 153.6 (d, J = 337.6 Hz, CF), 137.5, 135.2, 131.9, 131.8, 131.6–131.4 (m, $\text{ClC}=\text{CCF}_3$), 131.2, 130.8, 129.3 (q, J = 92.4 Hz, CCF_3), 127.5, 126.6 (q, J = 6.7 Hz, $\text{C}=\text{CCF}_3$), 125.9, 122.9 (q, J = 362.8 Hz, CF_3), 113.9, 99.7 (d, J = 18.3 Hz, $\text{C}=\text{CF}$), 56.7, 53.8, 43.2, 41.4 (d, J = 54.5 Hz, $\text{CH}_2\text{FC}=\text{C}$), 21.4 ppm. HRMS (EI): calcd. for $\text{C}_{21}\text{H}_{18}\text{Cl}_2\text{F}_4\text{N}_2\text{O}_4\text{S}$ [$\text{M}^+ + \text{H}$] 541.0450, found 541.0379.

1-(5-Chloro-2-methoxyphenylsulfonyl)-5-fluoro-N-(2-methoxybenzyl)-1,2,3,6-tetrahydropyridine-2-carboxamide (45): Compound **32** (500 mg, 1.93 mmol) was dissolved in THF/ H_2O (3:1 v/v, 12 mL), LiOH (93 mg, 3.86 mmol) was added and the reaction mixture was stirred at until the reaction was complete. The solution was acidified to pH 1 with 1 N hydrochloric acid and extracted with EtOAc (3×10 mL). The combined organic phases were dried (MgSO_4) and

the solvent evaporated to afford **40** (200 mg, 0.82 mmol, 99%) as a yellow oil. The crude product was dissolved in CH_2Cl_2 (7 mL) and reacted for 1 h with HOBt (122 mg, 0.90 mmol) and EDCI (173 mg, 0.90 mmol). 2-Methoxybenzylamine (0.32 mL, 2.46 mmol) was added and the mixture was stirred for 12 h at room temp. The solvent was evaporated and the residue was purified using column chromatography (heptane/EtOAc, 4:1 to 4:2) to give **41** (190 mg, 65%) as a colorless oil. IR (neat, cm^{-1}): $\tilde{\nu}$ = 3439, 3329, 3065, 2972, 2928, 1692, 1602, 1519, 1492, 1459, 1410, 1363, 1242, 1166, 1105, 1026, 973, 888, 809, 751. ^1H NMR (400 MHz, CDCl_3): δ = 7.29–7.19 (m, 2 H, ArH), 6.92–6.83 (m, 2 H, ArH), 6.53 (br. s, 1 H, NH), 5.34–5.28 (m, 1 H, $\text{FC}=\text{CH}$), 4.89–4.74 (br. m, 1 H, COCH), 4.51–4.15 (m, 3 H, NCH_2Ph , FCCH_2N), 3.83 (s, 3 H, OCH_3), 3.65–3.59 (br. m, 1 H, FCCH_2N), 2.79–2.73 (m, 1 H, $\text{HCCH}=\text{CF}$), 2.39–2.32 (m, 1 H, $\text{HCCH}=\text{CF}$) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 169.5, 157.3, 155.4, 153.3 (d, J = 246.1 Hz, CF), 129.4, 128.8, 125.7, 120.5, 110.1, 99.1–98.9 (m, $\text{CH}=\text{CF}$), 81.3, 55.0, 51.1, 39.6–39.5 (m, $\text{CH}_2\text{CH}=\text{CF}$), 31.6, 28.0, 22.5 ppm. HRMS calcd. for $\text{C}_{19}\text{H}_{26}\text{FN}_2\text{O}_4$ [$\text{M}^+ + \text{H}$] $^+$, 365.1803, found 365.1877. To a solution of compound **41** (190 mg, 0.52 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added trifluoroacetic acid (0.48 mL, 6.3 mmol). The resulting mixture was stirred at room temp. for 6 h, the solvent was evaporated and residual traces of trifluoroacetic acid were azeotropically removed with dichloromethane (3×10 mL). The crude mixture was redissolved in CH_2Cl_2 (4 mL) and Hünig's base (0.29 mL, 1.56 mmol) was added at room temp. After 15 min, 5-chloro-2-methoxybenzenesulfonyl chloride (125 mg, 0.52 mmol) was added and the reaction mixture was stirred overnight. The solvent was evaporated and the residue was purified using column chromatography (heptane/EtOAc, 3:1 to 1:1) to give **45** (80 mg, 33%) as a white solid. M.p. 102–105 °C. IR (neat, cm^{-1}): $\tilde{\nu}$ = 3401, 324, 3071, 3005, 2934, 2840, 1717, 1676, 1588, 1519, 1481, 1440, 1390, 1338, 1270, 1245, 1160, 1113, 1015, 960, 812, 735. ^1H NMR (400 MHz, CDCl_3): δ = 7.91 (d, J = 3.5 Hz, 1 H, ArH), 7.51–7.47 (m, 1 H, ArH), 7.32–7.20 (m, 3 H, ArH, NH), 6.94–6.88 (m, 3 H, ArH), 5.28–5.20 (m, 1 H, $\text{FC}=\text{CH}$), 4.54–4.11 (m, 5 H, NCH_2Ph , OCH, FCCH_2N), 3.87 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 3.73–3.67 (m, 1 H, $\text{HCCH}=\text{CF}$), 2.85–2.78 (m, 1 H, $\text{HCCH}=\text{CF}$) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 167.9, 157.8, 155.2, 153.6 (d, J = 347.1 Hz, CF), 135.0, 131.1, 129.8, 128.2, 125.8, 125.7, 120.7, 113.5, 110.4, 99.5 (d, J = 18.0 Hz, $\text{C}=\text{CF}$), 56.3, 55.3, 53.7, 40.7, 31.9, 22.7 ppm. HRMS (EI): calcd. for $\text{C}_{21}\text{H}_{21}\text{ClFN}_2\text{O}_5\text{S}$ [$\text{M}^+ - \text{H}$] 467.0876, found 467.0844.

1-(5-Chloro-2-methoxyphenylsulfonyl)-N-(4-chloro-3-trifluoromethylbenzyl)-5-fluoro-1,2,3,6-tetrahydropyridine-2-carboxamide (39): According to Scheme 4. A solution of compound **32** (500 mg, 1.93 mmol) in THF/ H_2O (3:1 v/v, 12 mL), was treated with LiOH (93 mg, 3.86 mmol), and the mixture was stirred at room temp. until the reaction was complete (TLC). The solution was acidified to pH 1 with 1 N hydrochloric acid and extracted with EtOAc (3×10 mL).

The combined organic phases were dried (MgSO_4) and the solvent evaporated to afford **40** (200 mg, 0.82 mmol, 99%) as a yellow oil. The crude product was dissolved in CH_2Cl_2 (7 mL) and reacted for 1 h with HOBt (122 mg, 0.90 mmol) and EDCI (173 mg, 0.90 mmol). 2-Methoxybenzylamine (0.32 mL, 2.46 mmol) was added and the mixture was stirred for 12 h at room temp. The solvent was evaporated and the residue was purified using column chromatography (heptane/EtOAc, 4:1 to 4:2) to give **42** (390 mg, 84%) as a colorless oil. IR (neat, cm^{-1}): $\tilde{\nu}$ = 3324, 3071, 2972, 2934, 2862, 1695, 1665, 1525, 1478, 1366, 1316, 1256, 1168, 1135, 1111, 1037, 984, 888. ^1H NMR (400 MHz, CDCl_3): δ = 7.54–7.35 (m, 3

H, ArH), 6.4 (br. s, 1 H, NH), 5.44–5.37 (m, 1 H, FC=CH), 4.91 (br. s, 1 H, COCH), 4.52–4.13 (m, 3 H, NCH₂Ph, FCCHHN), 3.66–3.62 (m, 1 H, FCCHHN), 2.78–2.73 (m, 1 H, HHCCH=CF), 2.46–2.33 (m, 1 H, HHCCH=CF) ppm. ¹³C NMR (100 MHz, CDCl₃) some signals are not visible: δ = 170.9, 137.8, 132.1, 126.7, 122.9 (q, *J* = 362.8 Hz, CF₃), 99.5 (d, *J* = 18.3 Hz, C=CF), 82.3, 47.4, 42.8, 32.1, 28.5, 22.9 ppm. HRMS (EI): calcd. for C₁₉H₂₀ClF₄N₂O₃ [M – H][–] 435.1030, found 435.1099. To a solution of compound **42** (320 mg, 0.74 mmol) in CH₂Cl₂ (5 mL) at 0 °C was added trifluoroacetic acid (0.11 mL, 1.48 mmol). The resulting mixture was stirred at room temp. for 6 h, the solvent was evaporated and residual traces of trifluoroacetic acid were azeotropically removed with dichloromethane (3 × 10 mL). The crude mixture was redissolved in CH₂Cl₂ (3 mL) and Hünig's base (0.3 mL, 1.43 mmol) was added at room temp. After 15 min, 5-chloro-2-methoxybenzenesulfonyl chloride (178 mg, 0.74 mmol) was added and the reaction mixture was stirred overnight. The solvent was evaporated and the residue was purified using column chromatography (heptane/EtOAc, 3:1 to 1:1) to give **39** (127.9 mg, 32%) as a white solid. M.p. 180–182 °C. IR (neat, cm^{–1}): ν̄ = 3324, 3104, 3054, 2945, 2906, 1717, 1657, 1528, 1478, 1322, 1273, 1163, 1144, 1015, 960, 817. ¹H NMR (400 MHz, CDCl₃): δ = 7.87 (d, *J* = 3.5 Hz, 1 H, SO₂Ph), 7.53–7.41 (m, 3 H, ArH), 7.33 (d, *J* = 10.7 Hz, 1 H, ArH), 7.09 (br. s, 1 H, NH), 6.90 (d, *J* = 12 Hz, 1 H, ArH), 5.29–5.21 (m, 1 H, FC=CH), 4.46–4.36 (m, 5 H, NCH₂Ph, COCH, FCCH₂N), 3.83 (s, 3 H, OCH₃), 3.73 (d, *J* = 23.5 Hz, 1 H, HCCH=CF), 2.80–2.75 (m, 1 H, HCCH=CF) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 169.2, 155.6, 153.6 (d, *J* = 337 Hz, CF), 137.5, 135.2, 131.9, 131.8, 131.6–131.4 (m, ClC=CCF₃), 131.2, 130.8, 129.3 (q, *J* = 92.4 Hz, CCF₃), 127.5, 126.6 (q, *J* = 6.7 Hz, C=CCF₃), 125.9, 122.9 (q, *J* = 362 Hz, CF₃), 113.9, 99.7 (d, *J* = 18.3 Hz, C=CF), 56.7, 53.8, 43.2, 41.4 (d, *J* = 54.5 Hz, CH₂FC=C), 21.4 ppm. HRMS (EI): calcd. for C₂₁H₁₈Cl₂F₄N₂O₄S [M⁺ + H] 541.0450, found 541.0379.

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