A New Tandem Cross Metathesis–Intramolecular Aza-Michael Reaction for the Synthesis of α,α-Difluorinated Lactams

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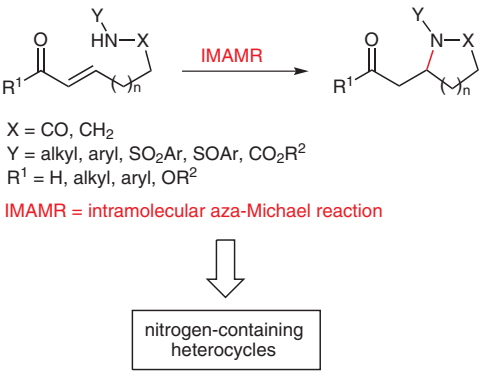
Abstract: A new tandem cross metathesis–intramolecular aza-Michael reaction in which an α,α-difluorinated amide serves as a source of nucleophilic nitrogen is described. This process gives rise to a new family of fluorinated γ- and δ-lactams. The tandem protocol is catalyzed by the Hoveyda–Grubbs second-generation ruthenium catalyst with titanium(IV) tetraisopropoxide as a co-catalyst and it is highly efficient when conjugated ketones are used as the Michael acceptors. With conjugated esters, however, it is necessary to perform a step-by-step procedure in which the cyclization event is activated by the addition of a base. An asymmetric version of the process is also evaluated.

Key words: Michael additions, tandem reactions, catalysis, heterocycles, fluorine, amides, asymmetric catalysis

Tandem processes usually generate high levels of molecular complexity in a single chemical operation thereby minimizing the use of solvents and reagents and reducing the time and number of steps involved in purification. These advantages make tandem transformations extremely appealing from both academic and industrial points of view. Indeed, tandem protocols have been extensively developed in recent decades, and they have found a wide variety of applications in natural-product synthesis.[1] Moreover, asymmetric versions greatly enhance the usefulness and relevance of tandem reactions and these have become extremely powerful and popular tools for synthetic organic chemists.[2]

The conjugated addition of nitrogen-centered nucleophiles to the β-carbon of electron-deficient olefins, the so-called aza-Michael reaction (AMR), is a particularly interesting transformation because it probably represents the shortest route to β-amino carbonyl derivatives, such as β-amino acids. Furthermore, a wide variety of nitrogen nucleophiles and Michael acceptors can participate in this process, which is also simple and displays significant atom economy.[3] The intramolecular version of the AMR is especially relevant because it permits the direct generation of nitrogen-containing heterocycles, yielding natural products and pharmaceutically relevant molecules in a relatively simple manner (Scheme 1).[4]

Olefin metathesis is one of the most powerful methods for the formation of carbon–carbon double bonds.[5] In comparison with the ring-closing metathesis reaction, the cross metathesis (CM) variant was initially underdeveloped because of a lack of predictability in the product distribution and the stereoselectivity of the reaction. However, the development of new ruthenium-based complexes that exhibit improved efficiency and tolerance to various functional groups changed the situation and it is now possible to achieve perfect control of *E*/*Z* selectivity in CM reactions.[6]



Scheme 1 Intramolecular aza-Michael reactions

In terms of their selectivities and yields, both aza-Michael[3c,7] and olefin metathesis reactions[8] exhibit suitable properties for participation in effective tandem protocols. In fact, each of these reactions has been combined with other types of transformations in many tandem sequences. However, only a few examples of combinations of CM and AMR have been reported, probably because of the poor compatibility of ruthenium catalysts with the basic nitrogen-containing functionalities that are necessary to effect the hetero-Michael addition. This difficulty can, however, be overcome by the use of weak nucleophiles, such as amides, carbamates, or nitrogen heterocycles, in conjunction with Lewis acids as co-catalysts. For instance, appropriately substituted pyrroles[9] and indoles[10] have been shown to be good partners in tandem CM–intramolecular aza-Michael reaction (IMAMR) sequences. Our previous studies have shown that carbamates[11] or *N*-sulfinyl amines[12] as nitrogen sources in the presence of boron trifluoride etherate or titanium(IV) tetraisopropoxide, respectively, can also participate in highly efficient CM–IMAMR protocols.

Among heterocyclic compounds, fluorinated lactams occupy a prominent position in organofluorine chemistry. These are interesting cyclic systems that are present in a

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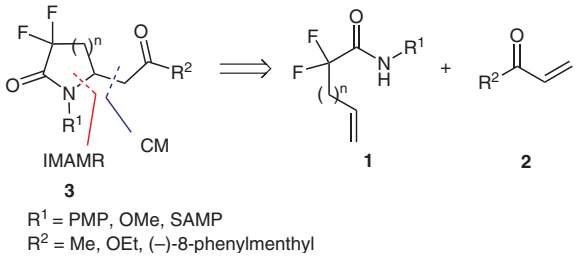
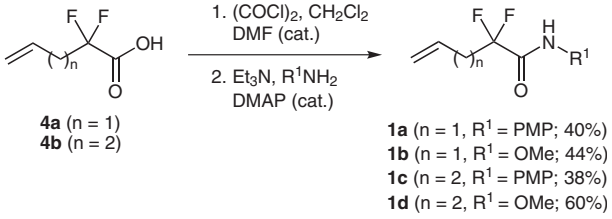
wide range of natural and synthetic biologically active molecules and drug candidates.[13] In pursuit of our ongoing interest in the development of methods for the preparation of fluorine-containing heterocycles,[14] we hypothesized that it might be possible to perform a tandem CM–IMAMR protocol that would provide a route for the synthesis of a new family of fluorinated γ- and δ-lactams **3** (Scheme 2). In this process, an α,α-difluorinated amide **1** would be employed as the source of a nitrogen nucleophile. Here, we report our attempts to carry out this synthetic sequence and to extend it in an asymmetric form.



Scheme 2 Synthetic strategy

First, we assembled a series of fluorinated amides **1** by condensation of various primary amines with *gem*-difluorinated carboxylic acids **4**,[15] via the corresponding acid chlorides, to give difluoro amides **1** in moderate yields (Scheme 3).

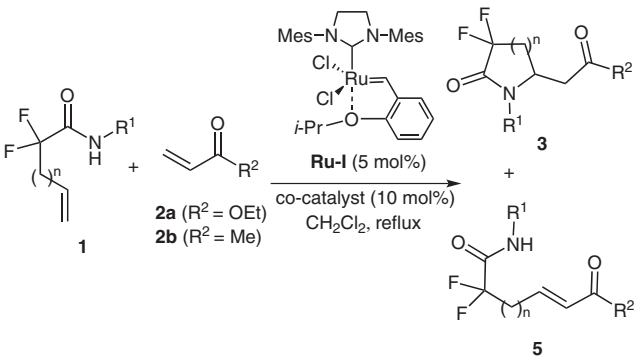


Scheme 3 Preparation of starting fluorinated amides **1a–d**

On the basis of our previous findings,[11,12] we decided to study the tandem process in the presence of a Lewis acid to establish the feasibility of our new tandem CM–IMAMR with fluorinated amides. The reaction of fluorinated amide **1a** with ethyl acrylate (**2a**) in the presence of the Hoveyda–Grubbs second-generation catalyst **Ru-I** and titanium(IV) tetraisopropoxide as a co-catalyst in refluxing dichloromethane gave the CM product **5a** in excellent yield after five hours (Table 1, entry 1). Similar results were obtained when boron trifluoride etherate was used as the co-catalyst (Table 1, entry 2). Likewise, amides **1b–d** reacted under the same conditions to give good yields of the corresponding CM products **5b–d** (Table 1, entries 3–6).

We had previously observed a similar behavior in the reaction of α,β-unsaturated esters with *N*-sulfinyl amines bearing a remote olefin moiety; that is, no tandem process occurred, but the reaction stopped at the CM step. On the other hand, with conjugated ketones, which are better Michael acceptors than esters, as the reaction partners, metathesis was followed by cyclization through IMAMR in a highly efficient manner to give the fluorinated lactams in a single step. When amides **1** were subjected to the conditions discussed above in the presence of methyl vinyl ketone (**2b**), a tandem reaction led to the desired products **3** in moderate yields (Table 1, entries 7–10).

Table 1 Results for the Tandem CM–IMAMR Sequence



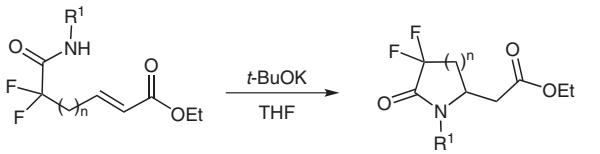
Entry	Reactants		Co-catalyst	Time (h)	Product **3** [yield[a] (%)]	Product **5** [yield[a] (%)]
1	**1a**	**2a**	$Ti(Oi\text{-}Pr)_4$	5	–	**5a** (90)
2	**1a**	**2a**	$BF_3{\cdot}OEt_2$	5	–	**5a** (80)
3	**1b**	**2a**	$Ti(Oi\text{-}Pr)_4$	5	–	**5b** (71)
4	**1b**	**2a**	$BF_3{\cdot}OEt_2$	2	–	**5b** (76)
5	**1c**	**2a**	$Ti(Oi\text{-}Pr)_4$	5	–	**5c** (89)
6	**1d**	**2a**	$Ti(Oi\text{-}Pr)_4$	6	–	**5d** (75)
7	**1a**	**2b**	$Ti(Oi\text{-}Pr)_4$	8	**3e** (61)	–
8	**1b**	**2b**	$Ti(Oi\text{-}Pr)_4$	10	**3f** (58)	–
9	**1c**	**2b**	$Ti(Oi\text{-}Pr)_4$	8	**3g** (51)	–
10	**1d**	**2b**	$Ti(Oi\text{-}Pr)_4$	10	**3h** (49)	–

[a] Isolated yield after flash column chromatography.

Having prepared α,β-unsaturated esters **5** by the CM reaction of amides **1** with ethyl acrylate (**2a**), we attempted to perform the IMAMR under basic conditions, since the conjugate addition of amides as Michael donors is often activated by the presence of bases as catalysts. In this manner, we hoped to obtain fluorinated lactams **3** corresponding to cyclic derivatives of β-amino acids.

Amides **5a** and **5c**, each bearing a *p*-methoxyphenyl (PMP) group on the nitrogen atom, cyclized efficiently at room temperature in the presence of potassium *tert*-butoxide to give high yields of the corresponding lactams **3a** and **3c**. On the other hand, compounds **5b** and **5d**, which have a methoxy group attached to the nitrogen, required refluxing of the reaction mixture for 72 hours to give good yields of the final products (Scheme 4). These results

show that the nucleophilicity of the potassium amides from substrates **5a** and **5c** bearing a PMP group is higher than that of their counterparts containing a methoxy group (**5b** and **5d**).



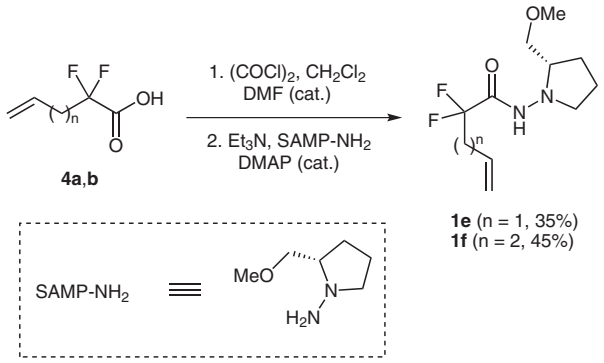
5a (n = 1, R^1 = PMP)
5b (n = 1, R^1 = OMe)
5c (n = 2, R^1 = PMP)
5d (n = 2, R^1 = OMe)

3a (4 h, r.t., 97%)
3b (72 h, reflux, 80%)
3c (6 h, r.t., 79%)
3d (72 h, reflux, 60%)

Scheme 4 IMAMR of fluorinated unsaturated amides **5a**–**d**

Next, we examined the asymmetric synthesis of fluorinated lactams. In our first approach, our strategy involved the use of a chiral auxiliary attached to the amide nitrogen. Enders' hydrazones were the auxiliaries of choice, because they had previously been employed, with satisfactory results, in Michael-type additions,[16] despite the fact that they are rarely used as chiral sources of nucleophilic nitrogen. Furthermore, the presence of a second nitrogen atom should enhance the nucleophilicity of the amide nitrogen in the cyclization step.

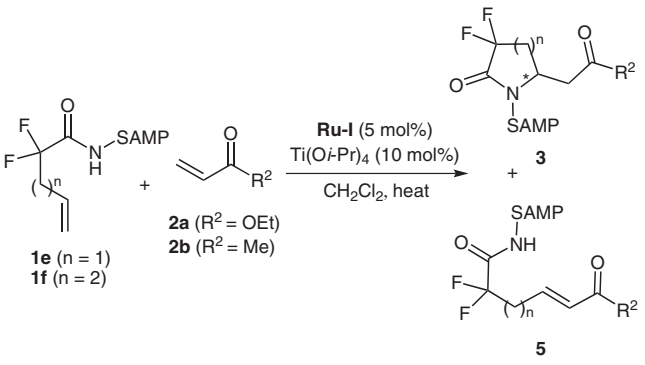
The starting amides **1e** and **1f**, with the (2*S*)-2-(methoxymethyl)pyrrolidine-1-amino (SAMP) moiety as a chiral auxiliary, were prepared by following an analogous procedure to that used to prepare the non-chiral compounds (Scheme 5).



Scheme 5 Preparation of (2*S*)-2-(methoxymethyl)pyrrolidine-1-amine (SAMP)-derived starting amides **1e** and **1f**

Substrates **1e** and **1f** were subjected to tandem reaction with the appropriate α,β-unsaturated derivative **2** in the presence of catalyst **Ru-I** and titanium(IV) tetraisopropoxide as a co-catalyst in refluxing dichloromethane. As in the case of the racemic substrates, when ethyl acrylate (**2a**) was used to generate the Michael acceptor, the CM products **5e** and **5f** were obtained in good yields (Table 2, entries 1, 2). Again, the use of methyl vinyl ketone (**2b**) as the conjugated partner allowed us to perform a tandem CM–IMAMR process to give the corresponding nitrogen heterocycles **3k** and **3l** in moderate yields but with poor stereoselectivity at the newly created stereocenter (Table 2, entries 3, 4). Unfortunately, it was not possible to separate the resulting mixtures of diastereoisomers.

Table 2 Asymmetric Tandem CM–IMAMR with SAMP-Derived Amides **1e** and **1f**



Entry	Reactants		Time (h)	Product **3** [yield[a,b] (%)]	Product **5** [yield[a] (%)]	dr[c]
1	**1e**	**2a**	3	–	**5e** (75)	–
2	**1f**	**2a**	4	–	**5f** (64)	–
3	**1e**	**2b**	8	**3k** (58)	–	51:49
4	**1f**	**2b**	8	**3l** (62)	–	59:41

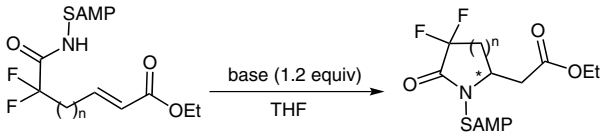
[a] Isolated yields after flash column chromatography.
[b] Combined yields of two diastereoisomers.
[c] Determined by GC/MS.

Because compounds **5e** and **5f** did not cyclize under acidic conditions, we decided to activate the amide deprotonation with a base. The results are summarized in Table 3.

Initially, we treated **5e** (n = 1) with either potassium *tert*-butoxide or lithium hexamethyldisilazide (LiHMDS) at 0 °C, but we found it to be totally inert under these conditions (Table 3, entries 1 and 2). At room temperature, the cyclized product **3i** was obtained in 18% yield as a 59:41 mixture of diastereoisomers (entry 3). It was necessary to heat the reaction mixture at 70 °C to obtain **3i** in good yield and with a slightly improved selectivity (entry 4). When tetrabutylammonium fluoride (TBAF) was used as a base, the reactivity of **5e** changed markedly.[17] Even at –78 °C, cyclization occurred in 64% yield to give a nearly 1:1 mixture of diastereoisomers (entry 5). The same IMAMR at room temperature gave a 71:29 mixture of the diastereoisomeric pyrrolidinones **3i** (entry 6), and the best result in terms of selectivity (dr = 75:25) was achieved at 70 °C (entry 7). When these conditions were applied to the formation of fluorinated piperidinones **3j** (entries 8–10), the best result was obtained at 70 °C, when **3j** was isolated in 77% yield as a 80:20 mixture of diastereoisomers (entry 10).

These results suggest that cyclization through the IMAMR is reversible, and at higher temperatures the formation of the thermodynamic product is favored (longer reaction times led to decomposition products). Unfortu-

Table 3 Base-Promoted Cyclization of Substrates **5e** and **5f**



5e (n = 1)
5f (n = 2)

3i (n = 1)
3j (n = 2)

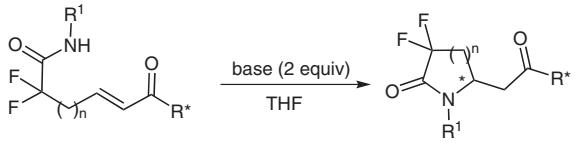
Entry	Substrate	Base	Temp (°C)	Time (h)	Product **3** [yield[a] (%)]	dr[b]
1	**5e**	*t*-BuOK	0	4	–	–
2	**5e**	LiHMDS	0	6	–	–
3	**5e**	LiHMDS	r.t.	5	**3i** (18)	59:41
4	**5e**	LiHMDS	70	4	**3i** (84)	62:38
5	**5e**	TBAF	–78	8	**3i** (67)	52:48
6	**5e**	TBAF	r.t.	5	**3i** (70)	71:29
7	**5e**	TBAF	70	1	**3i** (70)	75:25
8	**5f**	TBAF	0	8	**3j** (64)	70:30
9	**5f**	TBAF	r.t.	4	**3j** (70)	76:24
10	**5f**	TBAF	70	1	**3j** (77)	80:20

[a] Combined yields of two diastereoisomers.
[b] Determined by GC/MS.

nately, we were unable to separate the diastereoisomeric mixtures of compounds **3i** or **3j**.

In the next step of our study, we introduced a chiral auxiliary into the Michael acceptor. We decided to use 8-phenylmenthyl acrylate as the conjugated partner, since 8-phenylmenthol-derived crotonates have been efficiently employed in other intermolecular aza-Michael additions.[18] Thus, the starting fluorinated amides **1** were treated with the chiral acrylate **2c** in the presence of ruthenium catalyst **Ru-I** and titanium(IV) tetraisopropoxide as a co-catalyst. As expected, because the Michael acceptors were α,β-unsaturated esters, the IMAMR did not occur spontaneously, and the CM products **5g–j** were formed in moderate-to-good yields after refluxing for five hours in dichloromethane (Scheme 6).

Table 4 Base-Promoted Cyclization of Substrates **5g–j**

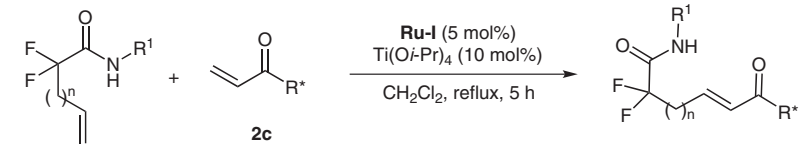


5g–j **3m–p**

R* = (1*R*,2*S*,5*R*)-(–)-8-phenylmenthyl

Entry	Substrate	Base	Temp (°C)	Time (h)	Product [yield[a] (%)]	dr[b]
1	**5g**	*t*-BuOK	r.t.	6	**3m** (51)	62:38
2	**5g**	LiHMDS	r.t.	6	**3m** (70)	67:33
3	**5g**	TBAF	r.t.	12	**3m** (87)	70:30
4	**5g**	*t*-BuOK	–78	6	**3m** (65)	75:25
5	**5g**	LiHMDS	–78	10	**3m** (23)	78:32
6	**5g**	TBAF	–78	24	**3m** (85)	83:17
7	**5h**	*t*-BuOK	r.t.	10	**3n** (46)	51:49
8	**5h**	LiHMDS	r.t.	10	**3n** (30)	57:43
9	**5h**	TBAF	r.t.	10	**3n** (85)	53:47
10	**5h**	*t*-BuOK	–78	24	**3n** (34)	63:37
11	**5h**	LiHMDS	–78	24	**3n** (14)	61:39
12	**5h**	TBAF	–78	48	**3n** (64)	57:43
13	**5i**	TBAF	0	48	**3o** (67)	65:35
14	**5j**	TBAF	0	48	**3p** (69)	67:33

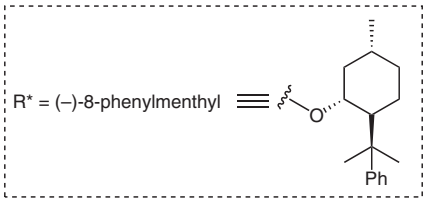
[a] Combined yields of two diastereoisomers.
[b] Determined by ^{19}F NMR integration.



1a (n = 1, R^1 = PMP)
1c (n = 2, R^1 = PMP)
1b (n = 1, R^1 = OMe)
1d (n = 2, R^1 = OMe)

2c

5g (87%)
5h (89%)
5i (46%)
5j (38%)

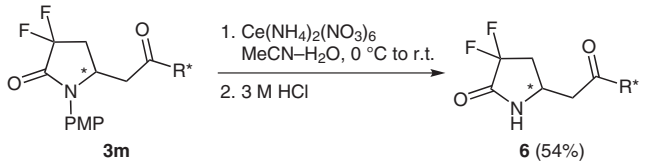


Scheme 6 Preparation of 8-phenylmenthol-derived unsaturated amides **5g–j**

Next, we completed the base-mediated cyclization of compounds **5g–j**; the results are summarized in Table 4.

Initially, we attempted to cyclize amide **5g** (n = 1; R^1 = PMP) with various bases at room temperature (Table 4, entries 1–3). TBAF was found to be the best of these bases, giving pyrrolidinone **3m** in 87% yield as a 70:30 mixture of inseparable diastereoisomers (entry 3). The same reactions were then carried out at –78 °C with similar results (entries 4–6); again the best yield and diastereoselectivity were achieved with TBAF (Table 4, entry 6). Compound **5h** (n = 2; R^1 = PMP) also gave inseparable mixtures of diastereoisomeric piperidinones **3n** with low selectivities, regardless of the temperature or the base employed (entries 7–12). With substrate **5i** (n = 1; R^1 = OMe) or **5j** (n = 2; R^1 = OMe), the IMAMR did not take place at –78 °C, highlighting the lower reactivity of these fluorinated amides compared with **5g** and **5h**, which contain a PMP protecting group. For compound **5i** and **5j**, cyclization occurred at 0 °C to give the corresponding N-heterocycles **3o** and **3p** in good yields but low diastereoselectivities (entries 13 and 14).

Finally, we removed the nitrogen-protecting group from compound **3m** by treating the mixture of diastereoisomeric pyrrolidinones with an excess of cerium(IV) ammonium nitrate for five days in order to produce total conversion. After the reaction had been quenched with hydrochloric acid, the difluorinated pyrrolidinones **6** were obtained in moderate yield, again as an inseparable mixture of diastereoisomers (Scheme 7).



3m **6** (54%)

R* = (1*R*,2*S*,5*R*)-(–)-8-phenylmenthyl

Scheme 7 N-Deprotection of pyrrolidinone **3m**

In summary, we synthesized a new family of fluorinated γ- and δ-lactams by means of a CM–IMAMR sequence. With conjugated ketones as the Michael acceptors, the process can be performed in a tandem fashion, showing that weak nucleophiles such as amides can participate in such processes in the presence of a Lewis acid. When esters were used as the conjugated partners, a step-by-step protocol with a base-promoted IMAMR was necessary. The asymmetric version of this sequence was also performed by introducing a chiral auxiliary on either at the nitrogen nucleophile or the Michael acceptor. The asymmetric reaction generally provided good yields and, in the best cases, moderate diastereoselectivities.

Reactions were carried out under argon unless otherwise indicated. The solvents were purified before use: THF was distilled from Na/benzophenone; CH_2Cl_2 and MeCN were distilled from CaH_2. The reactions were monitored by TLC on 0.25-mm precoated silica gel plates. Visualization was carried out with UV radiation and aqueous ceric ammonium molybdate solution or $KMnO_4$ stain. Flash column chromatography was performed with the indicated solvents on silica gel 60 (particle size 0.040–0.063 mm). ^1H, ^{13}C and ^{19}F NMR spectra were recorded on Bruker AC-300 MHz and AC-500 MHz spectrometers. Chemical shifts are given in ppm (δ) with reference to the residual proton resonances of the solvents. Coupling constants (*J*) are given in hertz (Hz). High-resolution mass spectra were recorded on an ABSciex TRIPLETOF-5600 spectrometer in the ESI or EI mode.

Fluorinated Amides 1; General Procedure

A catalytic amount of DMF and a 2.0 M soln of oxalyl chloride in CH_2Cl_2 (0.74 mL, 1.47 mmol) were added dropwise to a soln of carboxylic acid **4a** or **4b** (1.47 mmol) in CH_2Cl_2 (8 mL) at 0 °C. The mixture was then stirred at r.t. for 1 h then cooled to 0 °C. A soln of Et_3N (1.62 mmol), the appropriate amine (1.62 mmol), and a catalytic amount of DMAP in CH_2Cl_2 (3 mL) was added. The resulting mixture was stirred at r.t. for 5 h before the reaction was quenched with 3 M aq HCl (10 mL). The mixture was extracted with CH_2Cl_2 (3 × 10 mL) and the extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure to give a crude product that was purified by flash column chromatography.

2,2-Difluoro-*N*-(4-methoxyphenyl)pent-4-enamide (1a)

White solid; yield: 142 mg (40%); mp 76–78 °C.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.95 (tdt, $^3J_{HF}$ = 31.5 Hz, $^3J_{HF}$ = 16.9 Hz, $^4J_{HF}$ = 2.4 Hz, 2 H), 3.01 (s, 3 H), 5.26–5.34 (m, 2 H), 5.78 (tdd, ^3J = 31.5 Hz, ^3J = 17.3 Hz, ^3J = 10.2 Hz, 1 H), 6.89 (td, ^2J = 15.9 Hz, ^3J = 9.0 Hz, ^3J = 4.5 Hz, 2 H), 7.46 (td, ^2J = 15.9 Hz, ^3J = 9.0 Hz, ^3J = 4.5 Hz, 2 H), 7.87 (br s, 1 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 38.9 (t, $^2J_{CF}$ = 23.0 Hz), 55.9, 114.7, 117.6 (t, $^1J_{CF}$ = 254.5 Hz), 122.4, 127.5 (t, $^3J_{CF}$ = 5.6 Hz), 129.3, 157.7, 161.5 (t, $^2J_{CF}$ = 28.3 Hz).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –105.9 (td, $^3J_{HF}$ = 34.7 Hz, $^3J_{HF}$ = 16.9 Hz, $^4J_{HF}$ = 2.9 Hz 2 F).

HRMS (ESI): *m*/*z* [M + H^+] calcd for $C_{12}H_{14}F_2NO_2$: 242.0993; found: 242.0998.

2,2-Difluoro-*N*-methoxypent-4-enamide (1b)

Brown oil; yield: 107 mg (44%).

^1H NMR (300 MHz, $CDCl_3$): δ = 2.86 (tdt, ^3J = 33.6 Hz, $^3J_{HF}$ = 16.8 Hz, ^3J = 2.4 Hz, 2 H), 3.81 (s, 3 H), 5.25–5.31 (m, 2 H), 5.72 (m, 1 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 38.9 (t, $^2J_{CF}$ = 23.5 Hz), 65.0, 117.4 (t, $^1J_{CF}$ = 253.7 Hz), 122.7, 127.0 (t, $^3J_{CF}$ = 5.5 Hz), 161.4 (t, $^2J_{CF}$ = 28.6 Hz).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –106.8 (dt, $^2J_{FF}$ = 242.9 Hz, $^3J_{HF}$ = 16.8 Hz, 2 F).

HRMS (ESI): *m*/*z* [M + $Na]^+$ calcd for $C_6H_9F_2NNaO_2$: 188.0499; found: 188.0500.

2,2-Difluoro-*N*-(4-methoxyphenyl)hex-5-enamide (1c)

Brown solid; yield: 143 mg (38%); mp 70–74 °C.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.29 (m, 4 H), 3.80 (s, 3 H), 5.50 (m, 2 H), 5.81 (m, 1 H), 6.89 (td, ^2J = 15.9 Hz, ^3J = 9.3 Hz, ^3J = 4.5 Hz, 2 H), 7.47 (td, ^2J = 15.9 Hz, ^3J = 9.0 Hz, ^3J = 4.5 Hz, 2 H), 7.89 (br s, 1 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 26.3 (t, $^3J_{CF}$ = 4.7 Hz), 33.5 (t, $^2J_{CF}$ = 23.3 Hz), 55.9, 114.7, 118.5 (t, $^1J_{CF}$ = 253.4 Hz), 116.2, 122.3, 129.3, 136.3, 157.6, 161.9 (t, $^2J_{CF}$ = 28.6 Hz).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –106.0 (td, $^3J_{HF}$ = 32.0 Hz, $^3J_{HF}$ = 15.5 Hz, $^4J_{HF}$ = 2.9 Hz, 2 F).

HRMS (EI): *m*/*z* [M^+] calcd for $C_{13}H_{15}F_2NO_2$: 255.1071; found: 255.1060.

2,2-Difluoro-*N*-methoxyhex-5-enamide (1d)
Brown oil; yield: 158 mg (brown oil).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.21 (m, 5 H), 3.83 (s, 3 H), 5.05 (m, 2 H), 5.78 (m, 1 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 25.9 (t, $^3J_{CF}$ = 4.8 Hz), 33.6 (t, $^2J_{CF}$ = 22.9 Hz), 65.0, 118.1 (t, $^1J_{CF}$ = 252.4 Hz), 116.1, 136.1, 161.7 (t, $^2J_{CF}$ = 28.9 Hz).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –107.2 (t, *J* = 14.9 Hz, 2 F).

HRMS (ESI): *m*/*z* [M^+] calcd for $C_7H_{11}F_2NO_2$: 179.0758; found: 179.0773.

2,2-Difluoro-*N*-[(2*S*)-2-(methoxymethyl)pyrrolidin-1-yl]pent-4-enamide (1e)
Brown oil: yield: 128 mg (35%); $[\alpha]_D^{25}$ –14.3 (*c* 1.0, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.38–1.50 (m, 1 H), 1.60–1.70 (m, 2 H), 1.75–1.87 (m, 1 H), 2.59–2.73 (m, 3 H), 2.92–3.09 (m, 2 H), 3.13 (s, 3 H), 3.20–3.27 (m, 2 H), 5.04–5.10 (m, 2 H), 5.48–5.62 (m, 1 H), 7.80 (br s, 1 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 21.1, 26.1, 38.5 (t, $^2J_{CF}$ = 24.1 Hz), 54.9, 58.9, 63.8, 74.8, 117.0 (t, $^1J_{CF}$ = 253.7 Hz), 121.5, 127.2 (t, $^3J_{CF}$ = 5.5 Hz), 162.2 (t, $^2J_{CF}$ = 27.3 Hz).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –106.5 (dt, $^1J_{FF}$ = 252.7 Hz, $^3J_{HF}$ = 15.5 Hz, 1 F), –107.4 (dt, $^1J_{FF}$ = 253.7 Hz, $^3J_{HF}$ = 17.8 Hz, 1 F).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{19}F_2N_2O_2$: 249.1415; found: 249.1412.

2,2-Difluoro-*N*-[(2*S*)-2-(methoxymethyl)pyrrolidin-1-yl]hex-5-enamide (1f)
Brown oil: yield: 174 mg (45%); $[\alpha]_D^{25}$ –20.6 (*c* 1.0, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.62 (ddd, *J* = 21.6 Hz, *J* = 12.0 Hz, *J* = 3.3 Hz, 1 H), 1.86 (ddd, *J* = 17.7 Hz, *J* = 9.6 Hz, *J* = 4.8 Hz, 2 H), 1.96–2.03 (m, 1 H), 2.13–2.28 (m, 4 H), 2.88 (dd, ^3J = 10.2 Hz, ^3J = 5.1 Hz, 1 H), 3.13–3.46 (m, 4 H), 3.31 (s, 3 H), 5.02 (quint, 2 H), 5.74–5.84 (m, 1 H).

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 21.4, 25.9 (t, $^3J_{CF}$ = 4.7 Hz), 26.2, 33.4 (t, $^2J_{CF}$ = 23.1), 55.3, 59.3, 64.0, 74.8, 115.7, 118.6 (t, $^1J_{CF}$ = 252.9 Hz), 136.2, 162.7 (t, $^2J_{CF}$ = 27.6 Hz).

^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –100.54 (*J* = 16.6 Hz), –106.9 to –107.1 (m, 2 F).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{21}F_2N_2O_2$: 263.1566; found: 263.1558.

Difluoropyrrolidones 3 and Difluoro Amides 5 (Tandem Protocol); General Procedure
$Ti(O\textit{i}\text{-}Pr)_4$ (0.38 mmol) or $BF_3{\cdot}OEt_2$ (0.38 mmol) was added to a soln of amide **1** (0.38 mmol) in CH_2Cl_2 (3.8 mL) in a sealed tube and the mixture was stirred for 5 min at r.t. The α,β-unsaturated compound **2** (3 equiv) and Hoveyda–Grubbs second-generation ruthenium catalyst **Ru-I** (0.038 mmol, 10 mol%) were added and the mixture was heated at 60 °C until all the starting material was consumed (TLC; 5–10 h). The crude mixture was cooled to r.t., concentrated, and purified by flash column chromatography.

Base-Promoted Cyclization of Difluoro Amides 5; General Procedure
The appropriate base (1.2–3.0 equiv) was added to a soln of amide **5** (0.1 mmol) in THF (2 mL) and the mixture was stirred at the appropriate temperature until the starting material was consumed. The reaction was quenched with sat. aq NH_4Cl (5 mL) and the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The extracts were concentrated and the resulting crude mixture was purified by flash column chromatography.

Ethyl [4,4-Difluoro-1-(4-methoxyphenyl)-5-oxopyrrolidin-2-yl]acetate (3a)
Yellow solid: yield: 30 mg (97%); mp 70–85 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19 (t, ^3J = 7.1 Hz, 3 H), 2.35–2.50 (m, 2 H), 2.70 (dd, ^2J = 18.0 Hz, ^3J = 3.0 Hz, 1 H), 2.88 (dtd, *J* = 31.0, *J* = 22.3 Hz, *J* = 10.5 Hz, 1 H), 3.81 (s, 3 H), 4.05 (d, ^3J = 7.1 Hz, 2 H), 4.47–4.57 (m, 1 H), 6.94 (ddd, ^1J = 15.9 Hz, ^2J = 9.0 Hz, ^3J = 4.5 Hz, 2 H), 7.29 (ddd, ^1J = 15.9 Hz, ^2J = 9.0 Hz, ^3J = 4.5 Hz, 2 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.4, 36.9 (t, $^2J_{CF}$ = 22.4 Hz), 38.5, 51.9 (q, $^3J_{CF}$ = 5.2 Hz), 55.9, 61.5, 115.1, 117.7 (t, $^1J_{CF}$ = 249.6 Hz), 126.1, 128.1, 159.2, 162.9 (t, $^2J_{CF}$ = 30.9 Hz), 170.0.

^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –100.8 (dtd, $^2J_{FF}$ = 271.8 Hz, $^3J_{HF}$ = 32.6 Hz, $^4J_{HF}$ = 4.5 Hz, 1 F), –105.80 (dq, $^2J_{FF}$ = 271.6 Hz, $^3J_{HF}$ = 16.5 Hz, $^4J_{HF}$ = 10.4 Hz, 1 F).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{17}F_2NNaO_4$: 336.1023; found: 336.1023.

Ethyl (4,4-Difluoro-1-methoxy-5-oxopyrrolidin-2-yl)acetate (3b)
Brown oil: yield: 19 mg (80%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.2 (t, ^3J = 7.2 Hz, 3 H), 2.18–2.35 (m, 1 H), 2.45 (dd, $^3J_{HF}$ = 16.2 Hz, ^3J = 8.1 Hz, 1 H), 2.66–2.88 (m, 2 H), 63.80 (s, 3 H), 4.08–4.17 (m, 2 H), 4.21–4.31 (m, 1 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.5, 35.3 (t, $^2J_{CF}$ = 23.5 Hz), 37.6 (t, $^4J_{CF}$ = 1.6 Hz), 48.1, 49.9 (t, $^3J_{CF}$ = 2.7 Hz), 61.8, 63.4, 115.8 (t, $^1J_{CF}$ = 253.0 Hz), 169.9.

^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –102.1 (dddd, $^2J_{FF}$ = 270.6 Hz, $^3J_{HF}$ = 16.6 Hz, $^4J_{HF}$ = 4.2 Hz, 1 F), –104.8 (ddd, $^2J_{FF}$ = 270.6 Hz, $^3J_{HF}$ = 14.9 Hz, $^3J_{HF}$ = 12.9 Hz, 1 F).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_9H_{14}F_2NO_4$: 238.0885; found: 238.0882.

Ethyl [5,5-Difluoro-1-(4-methoxyphenyl)-6-oxopiperidin-2-yl]acetate (3c)
Brown solid: yield: 26 mg (79%); mp 105–108 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19 (t, ^3J = 7.2 Hz, 3 H), 1.99–2.12 (m, 1 H), 2.28–2.61 (m, 5 H), 3.81 (s, 3 H), 4.02 (ddd, $^3J_{HF}$ = 14.2 Hz, *J* = 7.2 Hz, *J* = 1 Hz, 2 H), 4.24–4.32 (m, 1 H), 6.90–6.96 (m, 2 H), 7.09–7.14 (m, 2 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.4, 24.1 (t, $^3J_{CF}$ = 5.2 Hz), 29.3 (t, $^2J_{CF}$ = 23.2 Hz), 38.3, 55.8, 57.2, 61.4, 112.6 (t, $^1J_{CF}$ = 244.5 Hz), 115.2, 129.0, 131.5, 159.5, 162.2 (t, $^2J_{CF}$ = 30.0 Hz), 170.3.

^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –100.7 (dt, $^2J_{FF}$ = 282.4 Hz, $^3J_{HF}$ = 14.1 Hz, 1 F), –101.8 (dt, $^2J_{FF}$ = 280.1 Hz, $^3J_{HF}$ = 11.3 Hz, 1 F).

HRMS (ESI): *m*/*z* [M^+] calcd for $C_{16}H_{19}F_2NO_4$: 327.1282; found: 327.1295.

Ethyl (5,5-Difluoro-1-methoxy-6-oxopiperidin-2-yl)acetate (3d)
Brown oil: yield: 15 mg (60%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28 (t, ^3J = 7.2 Hz, 3 H), 1.88–2.02 (m, 1 H), 2.15–2.36 (m, 3 H), 2.49 (dd, ^2J = 15.9 Hz, ^3J = 7.5 Hz, 1 H), 2.92 (dd, ^2J = 15.9 Hz, ^3J = 5.4 Hz, 1 H), 3.78 (s, 3 H), 4.78 (ddd, *J* = 21.3 Hz, *J* = 7.2 Hz, *J* = 1.8 Hz, 2 H), 4.26–4.35 (m, 1 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.5, 23.7 (t, $^3J_{CF}$ = 4.8 Hz), 26.9 (t, $^2J_{CF}$ = 23.1 Hz), 37.7, 56.5, 61.6, 62.4, 113.3 (t, $^1J_{CF}$ = 252.9 Hz), 155.2 ($^2J_{CF}$ = 31.3 Hz), 170.6.

^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –101.7 (t, *J* = 26.8 Hz, 2 F).

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{16}F_2NO_4$: 252.1042; found: 252.1043.

3,3-Difluoro-1-(4-methoxyphenyl)-5-(2-oxopropyl)pyrrolidin-2-one (3e)
Brown oil; yield: 66 mg (61%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.09 (s, 3 H), 2.19–2.34 (m, 1 H), 2.52–2.61 (m, 1 H), 2.81–2.99 (m, 1 H), 2.94 (dd, *J* = 16.6 Hz, *J* = 7.5 Hz, 1 H), 3.81 (s, 3 H), 4.52–4.62 (m, 1 H), 6.92 (ddd, ^3J = 15.9 Hz, ^4J = 9.0 Hz, ^5J = 4.5 Hz, 2 H), 7.26 (ddd, ^3J = 15.9 Hz, ^4J = 9.0 Hz, ^5J = 4.5 Hz, 2 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 30.8, 35.9 (t, $^2J_{CF}$ = 22.3 Hz), 47.0, 51.1 (d, $^3J_{CF}$ = 2.8 Hz), 55.9, 115.2, 117.8 (t, $^1J_{CF}$ = 248.0 Hz), 125.8, 128.8, 128.0, 159.1, 162.4 (t, $^2J_{CF}$ = 28.5 Hz), 205.5.

^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –100.34 (dtd, $^2J_{FF}$ = 271.6 Hz, $^3J_{HF}$ = 38.7 Hz, $^4J_{HF}$ = 4.2 Hz, 1 F), –106.38 (dq, $^2J_{HF}$ = 269.2 Hz, $^3J_{HF}$ = 16.3 Hz, $^4J_{HF}$ = 9.6 Hz, 1 F).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{16}F_2NO_3$: 284.1093; found: 284.1085.

3,3-Difluoro-1-methoxy-5-(2-oxopropyl)pyrrolidin-2-one (3f)
Brown oil; yield: 46 mg (58%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.12–2.18 (m, 1 H), 2.22 (s, 3 H), (s, 3 H), 2.58 (dd, $^3J_{HF}$ = 18.0 Hz, $^4J_{HF}$ = 8.1 Hz, 1 H), 2.73–2.73 (m, 1 H), 3.12 (dd,^2J = 17.8 Hz, ^3J = 4.8 Hz, 1 H), 3.82 (s, 3 H), 4.34–4.43 (m, 1 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 30.8, 35.5 (t, $^2J_{CF}$ = 23.3 Hz), 46.3, 46.3, 48.9 (t, $^3J_{CF}$ = 2.9 Hz), 63.0, 115.5 (t, $^1J_{CF}$ = 252.4 Hz), 205.1.

^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –100.34 (dtd, $^2J_{FF}$ = 271.6 Hz, $^3J_{HF}$ = 34.4 Hz, $^4J_{HF}$ = 4.2 Hz, 1 F), –106.36 (dq, $^2J_{FF}$ = 271.5 Hz, $^3J_{HF}$ = 18.9 Hz, $^4J_{HF}$ = 9.6 Hz, 1 F).

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_8H_{11}F_2NNaO_3$: 230.0605; found: 230.0607.

3,3-Difluoro-1-(4-methoxyphenyl)-6-(2-oxopropyl)piperidin-2-one (3g)
Brown oil; yield: 58 mg (51%) .

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.91–2.00 (m, 4 H), 2.29–2.46 (m, 3 H), 2.55–2.71 (m, 2 H), 3.81 (s, 3 H), 4.32–4.40 (m, 1 H), 6.92 (ddd, ^3J = 15.3 Hz, ^4J = 9.0 Hz, ^5J = 4.5 Hz, 2 H), 7.09 (ddd, ^3J = 15.3 Hz, ^4J = 9.0 Hz, ^5J = 4.5 Hz, 2 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 24.4 (t, $^3J_{CF}$ = 5.2 Hz), 29.5 (t, $^2J_{CF}$ = 23.1 Hz), 30.9, 46.7, 55.9, 56.3, 112.7 (t, $^1J_{CF}$ = 244.3 Hz), 115.2, 129.0, 131.6, 159.5, 162.4 (t, $^2J_{CF}$ = 29.9 Hz), 205.5.

^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –101.1 (t, ^3J = 14.7 Hz, 2 F).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{18}F_2NO_3$: 298.1249; found: 298.1253.

3,3-Difluoro-1-methoxy-6-(2-oxopropyl)piperidin-2-one (3h)
Brown oil; yield: 41 mg (49%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.79–1.90 (m, 1 H), 2.09–2.15 (m, 1 H), 2.17–2.22 (m, 4 H), 2.23–2.29 (m, 1 H), 2.52 (dd, ^2J = 17.4 Hz, ^3J = 6.9 Hz, 1 H), 3.06 (dd, ^2J = 17.4 Hz, ^3J = 5.4 Hz, 1 H), 3.71 (s, 3 H), 4.36–4.45 (m, 1 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 23.7 (t, $^3J_{CF}$ = 5.0 Hz), 29.5 (t, $^2J_{CF}$ = 23.0 Hz), 30.7, 45.8, 55.2, 61.7, 113.3 (t, $^1J_{CF}$ = 246.5 Hz), 159.0 (t, $^3J_{CF}$ = 30.4 Hz), 205.3.

^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –101.7 (t, *J* = 12.7 Hz, 2 F).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_9H_{14}F_2NO_3$: 222.0936; found: 222.0928.

Ethyl [(2′*S*)-4,4-Difluoro-2′-(methoxymethyl)-5-oxo-1,1′-bipyrrolidin-2-yl]acetate (3i)
Brown oil: yield: 22 mg (70%; 75:25 mixture of diastereoisomers).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (t, ^3J = 7.2 Hz, 3 H), 1.32–1.53 (s, 1 H), 1.60–1.75 (m, 1 H), 1.81–2.27 (m, 3 H), 2.40 (td, ^3J = 32.5 Hz, $^3J_{HF}$ = 16.5 Hz, ^4J = 8.1 Hz, 1 H), 2.59–2.78 (m, 1 H), 2.89 (dd,^2J = 15.9 Hz, ^3J = 5.1 Hz, 1 H), 3.15–3.33 (m, 6 H), 5.53 (dd, ^2J = 16.5 Hz, ^3J = 8.1 Hz, 1 H), 3.90 (dq, ^2J = 16.8 Hz, ^3J = 4.2 Hz, 1 H), 4.02–4.18 (m, 3 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.4, 14.5, 22.5, 22.5, 26.8, 26.9, 35.6 (t, $^2J_{CF}$ = 22.6 Hz), 35.8 (t, $^2J_{CF}$ = 21.8 Hz), 38.2 (d, $^2J_{CF}$ = 1.1 Hz), 38.6 (d, $^2J_{CF}$ = 1.5 Hz), 51.6 (t, $^3J_{CF}$ = 2.5 Hz), 51.7, 53.1, 53.6 (t, $^3J_{CF}$ = 2.6 Hz), 58.7, 58.9, 59.0, 59.7, 61.1, 61.2, 75.4, 75.8, 116.4 (t, $^1J_{CF}$ = 252.8 Hz), 116.6 (t, $^1J_{CF}$ = 250.5 Hz), 161.7 (t, $^2J_{CF}$ = 30.7 Hz), 161.9 (t, $^2J_{CF}$ = 30.2 Hz), 170.6, 170.9.

^{19}F NMR (282.4 MHz, $CDCl_3$): δ (major) = –103.1 (dddd, $^2J_{FF}$ = 268.2 Hz, $^3J_{HF}$ = 28.2 Hz, $^4J_{HF}$ = 4.2 Hz, 1 F), –106.9 (dt, $^2J_{FF}$ = 268.9 Hz, $^3J_{HF}$ = 16.9 Hz, 1 F); δ (minor) = –104.0 (dddd, $^2J_{FF}$ = 265.6 Hz, $^3J_{HF}$ = 25.4 Hz, $^4J_{HF}$ = 3.7 Hz, 1 F), –106.3 (ddd, $^2J_{FF}$ = 268.6 Hz, $^3J_{HF}$ = 17.8 Hz, $^4J_{HF}$ = 14.7 Hz, 1 F).

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{14}H_{22}F_2N_2O_4$: 320.1548; found: 320.1561.

Ethyl {5,5-Difluoro-1-[(2*S*)-2-(methoxymethyl)pyrrolidin-1-yl]-6-oxopiperidin-2-yl}acetate (3j)
Brown oil; yield: 26 mg (77%; 80:20 mixture of diastereoisomers).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22–1.44 (m, 1 H), 1.29 (t, ^3J = 7.2 Hz, 3 H), 1.58–2.34 (m, 5 H), 2.43 (dd, *J* = 15.6 Hz, *J* = 7.5 Hz, 1 H), 2.96 (dd, *J* = 15.6 Hz, *J* = 5.5 Hz, 1 H), 3.06–3.43 (m, 4 H), 3.31 (s, 3 H), 3.51 (q, *J* = 7.7 Hz, 1 H), 3.85–3.94 (m, 1 H), 4.12–4.27 (m, 2 H), 4.16 (q, *J* = 7.2 Hz, 2 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.6, 23.1, 24.1, 27.5, 29.4 (t, $^2J_{CF}$ = 22.9 Hz), 39.1, 53.1, 59.1, 59.5, 59.8, 61.2, 75.9, 113.2 (t, $^1J_{CF}$ = 248.6 Hz), 161.1 (t, $^2J_{CF}$ = 29.6 Hz), 171.4.

^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –101.8 (dd, $^3J_{HF}$ = 29.1 Hz, $^4J_{HF}$ = 13.6 Hz, 2 F).

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{25}F_2N_2O_4$: 335.1777; found: 335.1785.

(2′*S*)-3,3-Difluoro-2′-(methoxymethyl)-5-(2-oxopropyl)-1,1′-bipyrrolidin-2-one (3k)
Brown oil; yield: 64 mg (58%; 51:49 mixture of diastereoisomers).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37–1.44 (m, 1 H), 1.51–1.59 (m, 1 H), 1.67–1.77 (m, 2 H), 1.84–1.91 (m, 1 H), 1.92–1.98 (m, 1 H), 1.99–2.12 (m, 4 H), 2.18 (d, *J* = 4.0 Hz, 6 H), 2.49 (td, ^2J = 37.5 Hz,^{3} *J* = 8.5 Hz, 2 H), 2.67–2.78 (m, 2 H), 3.05 (td, ^2J = 16.0 Hz, ^3J = 3.5 Hz, 1 H), 3.13–3.18 (m, 3 H), 3.21–3.24 (m, 1 H), 3.28 (s, 4 H), 3.29–3.30 (m, 2 H), 3.32 (s, 4 H), 3.57 (dd, ^2J = 16.5 Hz, ^3J = 8.5 Hz, 1 H), 3.89 (ddd, *J* = 23.3 Hz, *J* = 7.75 Hz, *J* = 3.5 Hz, 1 H), 4.08–4.17 (m, 3 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 22.4, 22.7, 26.5, 26.7, 30.5, 30.5, 35.7 (t, $^2J_{CF}$ = 22.2 Hz), 35.9 (t, $^2J_{CF}$ = 21.6 Hz), 46.7 (d, $^3J_{CF}$ = 1.1 Hz), 47.4 (d, $^3J_{CF}$ = 1.5 Hz), 50.9 (t, $^3J_{CF}$ = 2.6 Hz), 51.6, 52.9 (t, $^3J_{CF}$ = 2.5 Hz), 53.1, 58.8, 58.8, 58.9, 58.9, 74.8, 76.3, 116.5 (t, $^1J_{CF}$ = 250.4 Hz), 116.6 (t, $^1J_{CF}$ = 254.2 Hz), 161.6 (t, $^2J_{CF}$ = 30.5 Hz), 161.8 (t, $^2J_{CF}$ = 29.6 Hz), 205.8, 205.8.

^{19}F NMR (282.4 MHz, $CDCl_3$): δ (first isomer) = –102.6 (dtd, $^2J_{FF}$ = 268.3 Hz, $^3J_{HF}$ = 29.9 Hz, $^4J_{HF}$ = 4.5 Hz, 1 F), –106.6 ($^2J_{FF}$ = 268.3 Hz, $^3J_{HF}$ = 31.1 Hz, $^4J_{HF}$ = 15.5, 2 F); δ (second isomer) = –103.2 (dtd, $^2J_{FF}$ = 268.7 Hz, $^3J_{HF}$ = 27.4 Hz, $^4J_{HF}$ = 4.0 Hz, 1 F), –107.2 ($^2J_{FF}$ = 268.7 Hz, $^3J_{HF}$ = 32.8 Hz, $^4J_{HF}$ = 16.7, 2 F).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{21}F_2N_2O_3$: 291.1514; found: 291.1512.

3,3-Difluoro-1-[(2*S*)-2-(methoxymethyl)pyrrolidin-1-yl]-6-(2-oxopropyl)piperidin-2-one (3l)
Brown oil; yield: 72 mg (62%; 59:41 mixture of diastereoisomers).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33–1.39 (m, 1 H), 1.45–1.53 (m, 1 H), 1.55–1.61 (m, 1 H), 1.64–1.74 (m, 2 H), 1.81–1.87 (m, 2 H), 1.94–2.05 (m, 4 H), 2.10–2.16 (m, 2 H), 2.18 (m, 5 H), 2.28 (dd,

J = 10.4 Hz, J = 3.3 Hz, 1 H), 2.49 (dd, J = 10.2 Hz, J = 4.8 Hz, 1 H), 3.03 (td, J = 9.5 Hz, J = 4.5 Hz, 1 H), 3.16 (dd, J = 10.2 Hz, J = 2.4 Hz, 1 H), 3.24–3.26 (m, 2 H), 3.28 (s, 3 H), 3.29–3.10 (m, 1 H), 3.32 (s, 2 H), 3.41–3.45 (m, 1 H), 3.50 (dd, J = 14.9 Hz, J = 4.8 Hz, 1, H), 3.82–3.87 (m, 1 H), 4.14–4.20 (m, 1 H), 4.22–4.28 (m, 1 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 22.5, 22.9, 24.0 (t, $^4J_{CF}$ = 5.2 Hz), 25.1 (t, $^4J_{CF}$ = 4.1 Hz), 26.5, 27.3, 29.2 (t, $^2J_{CF}$ = 22.8 Hz), 30.3 (t, $^2J_{CF}$ = 22.9 Hz), 30.4, 30.6, 46.5, 47.2, 50.3, 53.1, 56.6, 56.6, 58.6 (d, $^3J_{CF}$ = 11.3 Hz), 58.9 (d, $^3J_{CF}$ = 9.4 Hz), 59.6, 59.6, 74.8, 76.7, 113.1 (t, $^1J_{CF}$ = 245.0 Hz), 113.2 (t, $^1J_{CF}$ = 245.5 Hz), 161.1 (t, $^2J_{CF}$ = 30.3 Hz), 161.8 (t, $^2J_{CF}$ = 29.8 Hz), 205.5, 206.0.

^{19}F NMR (282.4 MHz, $CDCl_3$): δ (major) = –101.1 (dtd, $^2J_{FF}$ = 271.7 Hz, $^3J_{HF}$ = 33.3 Hz, $^4J_{HF}$ = 4.2 Hz, 1 F), –106.2 ($^2J_{FF}$ = 271.7 Hz, $^3J_{HF}$ = 16.6 Hz, $^4J_{HF}$ = 10.7, 1 F); δ (minor) = –101.4 (dtd, $^2J_{FF}$ = 271.5 Hz, $^3J_{HF}$ = 31.9 Hz, $^4J_{HF}$ = 4.2 Hz, 1 F), –105.7 ($^2J_{FF}$ = 271.7 Hz, $^3J_{HF}$ = 16.8 Hz, $^4J_{HF}$ = 11.6, 1 F).

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{14}H_{23}F_2N_2O_3$: 305.1671; found: 305.1662.

(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl [4,4-Difluoro-1-(4-methoxyphenyl)-5-oxopyrrolidin-2-yl]acetate (3m)

Brown oil: yield: 43 mg (85%; 83:17 mixture of diastereoisomers).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.80–0.97 (m, 7 H), 1.12 (s, 3 H), 1.15–1.18 (m, 1 H), 1.21 (s, 3 H), 1.25 (d, J = 3.3 Hz, 2 H), 1.62–1.71 (m, 4 H), 1.81–1.91 (m, 2 H), 1.98–2.07 (m, 1 H), 2.11–2.28 (m, 1 H), 2.76 (ddd, J = 31.8 Hz, J = 15.3 Hz, J = 7.8 Hz, 1 H), 3.85 (s, 3 H), 4.13–4.23 (m, 1 H), 4.76 (td, J = 11.3 Hz, J = 4.5 Hz, 1 H), 6.79 (t, ^3J = 7.2 Hz, 1 H), 6.92–7-05 (m, 4 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 22.1, 22.6, 23.1, 23.4, 26.5, 26.6, 30.1, 30.5, 31.6, 32.3, 34.8, 34.9, 35.6 (t, $^2J_{CF}$ = 22.3 Hz), 35.7 (t, $^2J_{CF}$ = 23.3 Hz), 38.2, 38.3, 39.6, 39.8, 41.9, 42.0, 50.2, 50.3, 55.9, 55.9, 75.2, 75.4, 115.1, 117.7 (t, $^1J_{CF}$ = 249.2 Hz), 115.2, 117.7 (t, $^1J_{CF}$ = 249.2 Hz), 125.3, 125.4, 125.5, 126.6, 126.5, 128.1, 128.3, 128.4, 128.8, 128.9, 132.4, 132.5, 152.2, 152.2, 159.3, 159.4, 162.9 (t, $^2J_{CF}$ = 33.4 Hz), 163.0 (t, $^2J_{CF}$ = 30.9 Hz), 169.2, 169.4.

^{19}F NMR (282.4 MHz: δ (major) = –100.1 (dtd, $^2J_{FF}$ = 271.4 Hz, $^3J_{HF}$ = 16.3 Hz, $^4J_{HF}$ = 3.4 Hz, 1 F), –105.9 (ddd, $^2J_{FF}$ = 271.4 Hz, $^3J_{HF}$ = 16.6 Hz, $^4J_{HF}$ = 10.7 Hz, 1 F); δ (minor) = –101.4 (dtd, $^2J_{FF}$ = 271.4 Hz, $^3J_{HF}$ = 15.3 Hz, $^4J_{HF}$ = 3.9 Hz, 1 F), –105.2 (ddd, $^2J_{FF}$ = 271.2 Hz, $^3J_{HF}$ = 17.4 Hz, $^4J_{HF}$ = 12.7 Hz, 1 F).

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{29}H_{36}F_2NO_4$: 500.2612; found: 500.2617.

(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl [5,5-Difluoro-1-(4-methoxyphenyl)-6-oxopiperidin-2-yl]acetate (3n)

Brown oil: yield: 33 mg (64%; 57:43 mixture of diastereoisomers).

^{1}H NMR ($CDCl_3$, 300 MHz, $CDCl_3$): δ = 0.85–0.99 (m, 10 H), 1.17–1.34 (m, 15 H), 1.41–1.56 (m, 3 H), 1.61–1.80 (m, 7 H), 1.83–1.97 (m, 5 H), 2.01–2.11 (m, 2 H), 2.24–2.41 (m, 7 H), 3.86 (s, 2 H), 3.90 (s, 3 H), 4.00–4.14 (m, 2 H), 4.71–4.82 (m, 2 H), 6.96–7.15 (m, 10 H), 7.20–7.28 (m, 6 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 22.0, 22.1, 22.9, 23.8 (t, $^3J_{CF}$ = 5.4 Hz), 23.9, 24.1 (t, $^3J_{CF}$ = 5.1 Hz), 26.5, 26.7, 29.1 (t, $^2J_{CF}$ = 23.1 Hz), 29.4 (t, $^2J_{CF}$ = 20.4 Hz), 29.6, 29.6, 30.1, 30.7, 31.6, 31.6, 37.8, 37.9, 39.7, 39.8, 41.8, 42.0, 50.4, 50.4, 55.9, 55.9, 56.7, 57.1, 75.1, 75.2, 112.6 (t, $^1J_{CF}$ = 244.3 Hz), 114.6 (t, $^1J_{CF}$ = 247.2 Hz), 115.2, 115.2, 125.3, 125.4, 125.5, 125.6, 128.2, 128.3, 129.7, 129.8, 131.5, 131.6, 152.0, 152.2, 159.5, 159.6, 162.2 (t, $^3J_{CF}$ = 29.8 Hz), 162.3 (t, $^2J_{CF}$ = 30.2 Hz), 169.7, 169.8.

^{19}F NMR (282.4 MHz, $CDCl_3$): δ (major) = –100.2 (dt, $^2J_{CF}$ = 281.1 Hz, $^3J_{HF}$ = 16.1 Hz, 1 F), –101.8 (ddd, $^2J_{CF}$ = 281.1 Hz, $^3J_{CF}$ = 17.4 Hz, 1 F); δ (minor) = –100.5 (dt, $^2J_{CF}$ = 281.1 Hz, $^3J_{HF}$ = 15.0 Hz, 1 F), –101.7 (dt, $^2J_{CF}$ = 281.7 Hz, $^3J_{HF}$ = 19.6 Hz, 1 F).

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{30}H_{38}F_2NO_4$: 514.2691; found: 514.2717.

(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (4,4-Difluoro-1-methoxy-5-oxopyrrolidin-2-yl)acetate (3o)

Brown oil: yield: 28 mg (67%; 65:35 mixture of diastereoisomers).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (d, J = 6.6 Hz, 3 H), 0.94–1.01 (m, 1 H), 1.12–1.26 (m, 4 H), 1.28 (s, 3 H), 1.41–1.55 (m, 1 H), 1.60–1.85 (m, 3 H), 1.88–2.29 (m, 4 H), 2.56–2.72 (m, 1 H), 3.78 (s, 1 H), 3.81 (s, 3 H), 3.83–3.90 (m, 1 H), 4.78–4.88 (m, 1 H), 7.08–7.17 (m, 1 H), 7.25–7.31 (m, 4 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 22.2, 22.4, 22.5, 22.9, 26.5, 26.5, 30.5, 30.6, 31.6, 31.7, 34.7, 34.8, 35.2 (t, $^2J_{CF}$ = 23.7 Hz), 35.3 (t, $^2J_{CF}$ = 23.1 Hz), 37.6 (d, $^4J_{CF}$ = 1.5 Hz), 37.9 (d, $^4J_{CF}$ = 1.2 Hz), 39.6, 39.7, 41.9, 41.9, 49.5, (t, $^3J_{CF}$ = 2.8 Hz), 49.7 (t, $^3J_{CF}$ = 2.7 Hz), 50.2, 50.4, 63.2, 63.3, 75.4, 75.4, 115.3 (t, $^1J_{CF}$ = 249.2 Hz), 115.4 (t, $^1J_{CF}$ = 252.5 Hz), 125.4, 125.6, 125.6, 125.7, 128.3, 128.4, 152.5, 152.6, 158.6 (t, $^2J_{CF}$ = 31.4 Hz), 158.7 (t, $^2J_{CF}$ = 31.4 Hz), 169.1, 169.3.

^{19}F NMR (282.4 MHz, $CDCl_3$): δ (major) = –102.4 (dddd, ^2J = 270.2 Hz, $^3J_{HF}$ = 27.6 Hz, $^4J_{HF}$ = 10.4 Hz, 1 F), –105.0 (ddd, $^2J_{FF}$ = 270.2 Hz, $^3J_{HF}$ = 17.9 Hz, $^4J_{HF}$ = 13.8 Hz, 1 F); δ (minor) = –102.1 (dddd, $^2J_{FF}$ = 270.1 Hz, $^3J_{HF}$ = 27.8 Hz, $^4J_{HF}$ = 4.2 Hz, 1 F), –104.5 (ddd, $^2J_{FF}$ = 270.1 Hz, $^3J_{HF}$ = 17.7 Hz, $^4J_{HF}$ = 13.8 Hz, 1 F).

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{23}H_{31}F_2NNaO_4$: 446.2123; found: 446.2104.

(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (5,5-Difluoro-1-methoxy-6-oxopiperidin-2-yl)acetate (3p)

Brown oil: yield: 30 mg (69%; 67:33 mixture of diastereoisomers).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85 (d, J = 6.6 Hz, 3 H), 0.90–0.98 (m, 1 H), 1.08–1.18 (m, 4 H), 1.25 (s, 3 H), 1.42–1.46 (m, 1 H), 1.59–1.73 (m, 4 H), 1.76–1.87 (m, 2 H), 1.92–2.24 (m, 5 H), 3.68 (s, 3 H), 3.75–3.82 (m, 1 H), 4.71–4.81 (m, 1 H), 7.05–7.12 (m, 1 H), 7.21–7.28 (m, 4 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 22.1, 22.2, 22.8, 22.9, 23.5 (t, $^3J_{CF}$ = 5.7 Hz), 23.7 (t, $^3J_{CF}$ = 5.2 Hz), 26.6, 26.6, 29.6 (t, $^2J_{CF}$ = 23.1 Hz), 29.8 (t, $^2J_{CF}$ = 23.0 Hz), 30.3, 30.3, 31.4, 31.6, 34.8, 34.9, 37.3, 37.8, 39.7, 39.8, 41.8, 41.9, 50.2, 50.4, 56.1, 56.6, 62.2, 62.5, 75.2, 75.5, 113.1 (t, $^1J_{CF}$ = 246.8 Hz), 113.3 (t, $^1J_{CF}$ = 246.8 Hz), 125.4, 125.5, 125.7, 125.7, 128.3, 128.4, 152.3, 152.6, 159.6 (t, $^2J_{CF}$ = 29.8 Hz), 159.8 (t, $^2J_{CF}$ = 28.2 Hz), 169.6, 169.9.

^{19}F NMR (282.4 MHz, $CDCl_3$): δ (major) = –102.3 (ddd, $^2J_{FF}$ = 281.1 Hz, $^3J_{HF}$ = 22.1 Hz, $^4J_{HF}$ = 11.9 Hz, 1 F), –107.4 (t, $^3J_{HF}$ = 16.1 Hz, 1 F); δ (minor) = –100.9 (ddd, $^2J_{FF}$ = 277.0 Hz, $^3J_{HF}$ = 18.2 Hz, $^4J_{HF}$ = 12.1 Hz, 1 F), –107.1 (t, $^3J_{HF}$ = 16.3 Hz, 1 F).

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{24}H_{34}F_2NO_4$: 438.2450; found: 438.2446.

Ethyl (2*E*)-5,5-Difluoro-6-[(4-methoxyphenyl)amino]-6-oxohex-2-enoate (5a)

Brown solid; yield: 107 mg (90%); mp 94–97 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28 (t, ^3J = 7.2 Hz, 3 H), 3.10 (tdd, $^3J_{HF}$ = 16.8 Hz, ^3J = 7.5 Hz, ^4J = 1.5 Hz, 2 H), 3.80 (s, 3 H), 4.19 (q, J = 7.2 Hz, 2 H), 6.04 (dt, ^3J = 15.7 Hz, ^4J = 1.3 Hz, 1 H), 6.83–6.93 (m, 3 H), 7.45 (dm, J = 9.0 Hz, 2 H), 7.95 (br s, 1 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.6, 24.7 (t, $^3J_{CF}$ = 4.9 Hz), 32.5 (t, $^2J_{CF}$ = 23.7 Hz), 55.7, 60.7, 114.5, 117.9 (t, $^1J_{CF}$ = 254.2 Hz), 122.4, 122.8, 129.2, 146.1, 157.5, 161.8 (t, $^2J_{CF}$ = 28.4 Hz), 166.5.

^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –106.13 (dt, $^3J_{HF}$ = 16.3 Hz, $^4J_{HF}$ = 2.5 Hz, 2 F).

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{15}H_{17}F_2NNaO_4$: 336.1023; found: 336.1024.

Ethyl (2*E*)-5,5-Difluoro-6-(methoxyamino)-6-oxohex-2-enoate (5b)
Brown oil; yield: 64 mg (71%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28 (t, ^3J = 6.9 Hz, 3 H), 3.03 (tdd, $^3J_{HF}$ = 33.6 Hz, $^3J_{HF}$ = 16.8 Hz, ^3J = 1.2 Hz, 2 H), 3.81 (s, 3 H), 4.19 (dd, ^2J = 12.3 Hz, ^3J = 7.2 Hz, 2 H), 6.01 (d, ^3J = 15.9 Hz, 1 H), 6.80 (quint, 1 H), 9.26 (br s, 1 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.6, 37.0 (t, $^2J_{CF}$ = 24.5 Hz), 61.1, 65.0, 116.9 (t, $^1J_{CF}$ = 255.9 Hz), 128.0, 136.7 (t, $^3J_{CF}$ = 5.3 Hz), 160.8 (t, $^2J_{CF}$ = 27.9 Hz), 165.9.

^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –106.4 (t, $^3J_{HF}$ = 16.7 Hz, 2 F).

HRMS (EI): *m*/*z* $[M + Na]^+$ calcd $C_9H_{13}F_2NNaO_4$: 260.0710; found: 260.0717.

Ethyl (2*E*)-6,6-Difluoro-7-[(4-methoxyphenyl)amino]-7-oxohept-2-enoate (5c)
Brown solid; yield: 111 mg (89%); mp 67–70 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (t, ^3J = 6.9 Hz, 3 H), 2.36 (m, 4 H), 3.78 (s, 3 H), 4.16 (dd, ^2J = 14.1 Hz, ^3J = 7.2 Hz, 2 H), 5.85 (dt, ^3J = 15.9 Hz, ^3J = 1.5 Hz, 1 H), 6.90 (m, 3 H), 7.46 (^3J = 15.9 Hz, ^4J = 9.3 Hz, ^5J = 4.5 Hz, 2 H), 8.06 (br s, 1 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.6, 24.7 (t, $^3J_{CF}$ = 4.9 Hz), 32.5 (t, $^2J_{CF}$ = 23.7 Hz), 55.7, 60.7, 114.5, 117.9 (t, $^1J_{CF}$ = 254.2 Hz), 122.4, 122.8, 129.2, 146.1, 157.5, 161.8 (t, $^2J_{CF}$ = 28.4 Hz), 166.5.

^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –106.13 (dt, $^3J_{HF}$ = 16.3 Hz, $^4J_{HF}$ = 2.5 Hz, 2 F).

HRMS (EI): *m*/*z* $[M]^+$ calcd $C_{16}H_{19}F_2NO_4$: 327.1282; found: 327.1291.

Ethyl (2*E*)-6,6-Difluoro-7-(methoxyamino)-7-oxohept-2-enoate (5d)
Brown oil; yield: 72 mg (75%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (t, ^3J = 7.2 Hz, 3 H), 2.17–2.47 (m, 4 H), 3.79 (s, 3 H), 4.16 (dd, $^2J_{HF}$ = 14.4 Hz, $^3J_{HF}$ = 7.2 Hz, 2 H), 5.84 (dt, ^2J = 15.6 Hz, ^3J = 1.5 Hz, 1 H), 6.89 (td, ^3J = 15.7 Hz, ^3J = 6.6 Hz, 1 H), 9.76 (br s, 1 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.5, 24.5 (t, $^3J_{CF}$ = 4.9 Hz), 32.2 (t, $^2J_{CF}$ = 23.3 Hz), 60.8, 64.8, 117.8 (t, $^1J_{CF}$ = 253.3 Hz), 122.9, 146.0, 161.4 (t, $^2J_{CF}$ = 28.6 Hz), 166.7.

^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –107.4 (t, $^3J_{HF}$ = 16.3 Hz, 2 F).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{10}H_{16}F_2NO_4$: 252.1030; found: 252.1037.

Ethyl (2*E*)-5,5-Difluoro-6-{[(2*S*)-2-(methoxymethyl)pyrrolidin-1-yl]amino}-6-oxohex-2-enoate (5e)
Yellow oil; yield: 91 mg (75%); $[\alpha]_D^{25}$ –15.0 (*c* 1.0, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (t, ^3J = 7.1 Hz, 3 H), 1.57–1.68 (m, 1 H), 1.81–2.05 (m, 3 H), 2.82 (q, *J* = 8.5 Hz, 1 H), 3.00 (td, *J* = 16.7 Hz, *J* = 7.4 Hz, *J* = 1.3 Hz, 2 H), 3.08–3.13 (m, 1 H), 3.21–3.30 (m, 1 H), 3.31 (s, 3 H), 3.37–3.46 (m, 2 H), 4.17 (q, *J* = 7.2 Hz, 2 H), 5.98 (d, ^3J = 15.7 Hz, 1 H), 6.81 (dt, ^3J = 15.7 Hz, *J* = 7.2 Hz, 1 H), 7.61 (br s, 1 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.2, 21.1, 25.9, 36.8 (t, $^2J_{CF}$ = 24.5 Hz), 55.2, 59.1, 60.6, 64.1, 74.7, 116.5 (t, $^1J_{CF}$ = 255.2 Hz), 127.4, 136.4 (t, $^3J_{CF}$ = 5.3 Hz), 161.6 (t, $^2J_{CF}$ = 21.1 Hz), 165.4.

^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –106.2 (dt, $^4J_{HF}$ = 5.1 Hz, $^3J_{HF}$ = 16.7 Hz, 2 F).

HMRS (ESI): *m*/*z* $[M + H^+]$ calcd for $C_{14}H_{23}F_2N_2O_4$: 321.1538; found: 321.1534.

Ethyl (2*E*)-6,6-Difluoro-7-[(2*S*)-2-(methoxymethyl)pyrrolidin-1-yl]amino}-7-oxohex-2-enoate (5f)
Yellow oil; yield: 81 mg (64%); $[\alpha]_D^{25}$ –15.8 (*c* 1.0, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (t, ^3J = 7.2 Hz, 3 H), 1.57–1.64 (m, 1 H), 1.83–1.89 (m, 2 H), 1.95–2.03 (m, 2 H), 2.20–2.30 (m, 2 H), 2.38–2.43 (m, 2 H), 2.84 (q, *J* = 8.4 Hz, 1 H), 3.08–3.14 (m, 1 H), 3.31 (s, 3 H), 3.37–3.48 (m, 2 H), 4.17 (q, *J* = 7.2 Hz, 2 H), 5.84 (dt, ^3J = 16.0 Hz, ^4J = 1.5 Hz, 1 H), 6.91 (dt, *J* = 15.6 Hz, *J* = 7.0 Hz, 1 H), 7.53 (br s, 1 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.4, 21.4, 24.5 (t, $^3J_{CF}$ = 4.8 Hz), 26.1, 32.6 (t, $^2J_{CF}$ = 23.4 Hz), 55.4, 59.3, 60.5, 64.3, 75.3, 117.9 (t, $^1J_{CF}$ = 253.5 Hz), 122.7, 146.0, 162.2 (t, $^2J_{CF}$ = 24.8 Hz), 166.4.

^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –106.7 (dt, $^2J_{FF}$ = 259.8 Hz, $^3J_{HF}$ = 16.7 Hz, 1 F), –107.6 (dt, $^2J_{FF}$ = 258.8 Hz, $^3J_{HF}$ = 16.4 Hz, 1 F).

HMRS (ESI): *m*/*z* $[M + H^+]$ calcd for $C_{15}H_{25}F_2NO_4$: 335.1777; found: 335.1758.

(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (2*E*)-5,5-Difluoro-6-[(4-methoxyphenyl)amino]-6-oxohex-2-enoate (5g)
Brown oil; yield: 165 mg (87%); $[\alpha]_D^{25}$ +49.9 (*c* 1.0, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (d, ^3J = 6.6 Hz, 3 H), 0.96 (t, *J* = 12.0 Hz, 1 H), 1.04–1.16 (m, 1 H), 1.22 (s, 3 H), 1.29 (s, 3 H), 1.42–1.58 (m, 1 H) 1.64–1.79 (m, 2 H), 1.86–1.93 (m, 1 H), 2.07 (ddd, *J* = 22.7 Hz, *J* = 10.5 Hz, *J* = 3.6 Hz, 1 H), 2.97 (tdd, $^3J_{HF}$ = 33.8 Hz, *J* = 7.2 Hz, *J* = 1.2 Hz, 2 H), 3.82 (m, 3 H), 4.11–4.19 (m, 1 H), 4.86 (td, *J* = 21.4 Hz, *J* = 4.2 Hz, 1 H), 5.43 (d, ^3J = 15.6 Hz, 1 H), 6.45 (dt, ^3J = 15.6 Hz, ^3J = 7.5 Hz, 1 H), 6.87–6.94 (m, 2 H), 7.09–7.18 (m, 1 H), 7.22–7.28 (m, 4 H), 7.46–7.51 (m, 2 H), 7.94 (br s, 1 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 22.2, 24.9, 26.9, 28.6, 31.7, 34.5, 36.9 (t, $^2J_{CF}$ = 24.5 Hz), 39.9, 41.9, 50.8, 55.7, 74.9, 114.7, 116.9 (t, $^1J_{CF}$ = 255.7 Hz), 122.5, 125.2, 127.7, 128.2, 128.3, 129.1, 135.8 (t, $^3J_{CF}$ = 4.9 Hz), 151.9, 157.7, 161.3 (t, $^2J_{CF}$ = 27.8 Hz), 164.9.

^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –105.1 (dt, $^3J_{HF}$ = 33.8 Hz, $^4J_{HF}$ = 2.8 Hz, 2 F).

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{29}H_{35}F_2NNaO_4$: 522.2429; found: 522.2426.

(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (2*E*)-6,6-Difluoro-7-[(4-methoxyphenyl)amino]-7-oxohept-2-enoate (5h)
Brown oil; yield: 174 mg (89%); $[\alpha]_D^{25}$ +12.8 (*c* 1.0, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.86 (d, ^3J = 6.3 Hz, 3 H), 0.96 (t, *J* = 12.3 Hz, 1 H), 1.06–1.14 (m, 1 H), 1.19 (s, 3 H), 1.28 (s, 3 H), 1.62–1.77 (m, 2 H) 1.83–1.91 (m, 2 H), 2.01–2.09 (m, 1 H), 2.27–2.31 (m, 2 H), 3.74 (t, *J* = 6.6 Hz, 1 H), 3.80 (s, 3 H), 4.82 (ddd, *J* = 21.3 Hz, *J* = 10.8 Hz, *J* = 4.2 Hz, 1 H), 5.57 (d, ^3J = 15.9 Hz, 1 H), 6.39 (dt, ^3J = 15.3 Hz, ^3J = 6.0 Hz, 1 H), 6.87–6.91 (m, 2 H), 7.06–7.15 (m, 1 H), 7.22–7.25 (m, 2 H), 7.25–7.26 (m, 1 H), 7.45–7.55 (m, 4 H), 7.69–7.74 (m, 1 H), 7.96 (br s, 1 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 22.2, 24.5 (t, $^3J_{CF}$ = 4.9 Hz), 24.9, 26.9, 28.6, 31.7, 32.5 (t, $^2J_{CF}$ = 23.5 Hz), 34.9, 39.9, 42.9, 50.8, 55.8, 74.7, 114.7, 118.1 (t, $^1J_{CF}$ = 253.8 Hz), 122.3, 125.1, 125.7, 128.3, 129.2, 129.3, 132.6, 152.1, 157.7, 161.7 (t, $^2J_{CF}$ = 28.2 Hz), 165.7.

^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –106.1 (t, $^3J_{HF}$ = 16.3 Hz, 2 F).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{30}H_{38}F_2NO_4$: 514.2763; found: 514.2755.

(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (2*E*)-5,5-Difluoro-6-(methoxyamino)-6-oxohex-2-enoate (5i)
Brown oil; yield: 74 mg (46%); $[\alpha]_D^{25}$ +4.3 (*c* 1.0, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (d, ^3J = 6.6 Hz, 3 H), 0.89–1.01 (m, 1 H), 1.10 (td, *J* = 12.6 Hz, *J* = 3.3 Hz, 1 H), 1.18–1.28 (m, 1 H), 1.19 (s, 3 H), 1.28 (s, 3 H), 1.34–1.53 (m, 1 H), 1.63–1.78 (m, 2 H), 1.85–1.92 (m, 1 H), 2.01–2.06 (m, 1 H), 2.87 (dtd, *J* = 7.4 Hz, *J* = 16.9 Hz, *J* = 1.3 Hz, 2 H), 3.82 (s, 3 H), 4.83 (td, *J* = 10.7 Hz, *J* = 4.5 Hz, 1 H), 5.37 (d, *J* = 15.7 Hz, 1 H), 6.36 (dt, ^3J = 15.6 Hz,

^3J = 5.7 Hz, 1 H), 7.08–7.15 (m, 1 H), 7.18–7.29 (m, 4 H), 9.03 (br s, 1 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 22.1, 24.9, 26.9, 28.6, 31.7, 34.9, 36.9 (t, $^2J_{CF}$ = 24.0 Hz), 39.9, 41.9, 50.9, 65.0, 75.1, 116.8, 117.7 (t, $^1J_{CF}$ = 266.4 Hz), 122.7, 125.2, 125.4, 125.7, 128.3, 135.4 (t, $^3J_{CF}$ = 10.3 Hz), 151.9, 160.9 (t, $^2J_{CF}$ = 28.4 Hz), 165.0.

^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –106.4 (d, J = 8.5 Hz, 2 F).

HRMS (ESI): m/z $[M + NH_4]^+$ calcd for $C_{23}H_{35}F_2N_2O_4$: 441.2559; found: 441.2558.

(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (2*E*)-6,6-Difluoro-7-(methoxyamino)-7-oxohept-2-enoate (5j)

Brown oil; yield: 66 mg (38%); $[\alpha]_D^{25}$ +19.3 (*c* 1.0, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84 (d, ^3J = 6.6 Hz, 3 H), 0.87–0.99 (m, 2 H), 1.07 (td, J = 12.8 Hz, J = 3.0 Hz, 1 H), 1.17 (s, 3 H), 1.26 (s, 3 H), 1.59–1.74 (m, 3 H), 1.83–1.89 (m, 1 H), 1.99–2.17 (m, 3 H), 2.19–2.28 (m, 2 H), 3.71 (s, 3 H), 4.79 (td, J = 10.8 Hz, J = 4.2 Hz, 1 H), 5.23 (dt, J = 17.1 Hz, J = 1.5 Hz, 1 H), 5.75 (br s, 1 H), 6.36 (dt, ^3J = 15.8 Hz, ^3J = 6.0 Hz, 1 H), 7.05–7.13 (m, 1 H), 7.18–7.25 (m, 4 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 22.2, 24.4 (t, $^3J_{CF}$ = 4.9 Hz), 24.9, 26.9, 28.7, 31.7, 32.4 (t, $^2J_{CF}$ = 23.3 Hz), 35.0, 40.0, 42.1, 50.9, 74.7, 117.7 (t, $^1J_{CF}$ = 257.4 Hz), 123.1, 125.2, 125.4, 125.7, 125.8, 128.3, 128.4, 142.2, 152.2, 160.2 (t, $^2J_{CF}$ = 27.1 Hz), 165.7.

^{19}F NMR (282.4 MHz, $CDCl_3$): δ = –107.4 (t, J = 16.1 Hz, 2 F).

HRMS (ESI): m/z $[M + NH_4]^+$ calcd for $C_{23}H_{35}F_2N_2O_4$: 441.2565; found: 441.2558.

(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (4,4-Difluoro-5-oxopyrrolidin-2-yl)acetate (6)

A soln of CAN (8 mmol) in H_2O (2 mL) was added dropwise to a soln of ester **3m** (40 mg, 0.08 mmol; 83:17 mixture of diastereoisomers) in MeCN (2 mL) at 0 °C. The ice bath was removed and the mixture was stirred for 5 d at r.t. until the starting material was consumed (TLC). 3 M aq HCl (5 mL) was then added and the mixture was stirred for 1 h to give a yellow soln. The soln was basified with sat. aq $NaHCO_3$ until it became almost transparent then extracted with EtOAc (4 × 10 mL). The combined organic layers were washed with 20% aq Na_2SO_3 (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography [hexanes–EtOAc (1:1)] to give a slightly yellow oil: yield: 17 mg (54%; 83:17 mixture of diastereoisomers).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.83–0.99 (m, 6 H), 1.13 (s, 3 H), 1.14–1.22 (m, 2 H), 1.25 (s, 3 H), 1.47 (dd, J = 17.1 Hz, J = 10.8 Hz, 2 H), 1.66–1.79 (m, 3 H), 1.82–1.96 (m, 3 H), 2.03–2.11 (m, 1 H), 2.46–2.63 (m, 1 H), 3.47–3.58 (m, 1 H), 4.83 (td, J = 21.3 Hz, J = 10.5 Hz, J = 4.5 Hz, 1 H), 6.45 (br s, 1 H), 7.04–7.11 (m, 1 H), 7.14–7.20 (m, 1 H), 7.23–7.25 (m, 4 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ (first isomer) = 22.2, 26.5, 31.7, 318, 34.8, 36.7 (t, $^2J_{CF}$ = 22.7 Hz), 39.7, 40.4, 42.2, 44.9 (t, $^3J_{CF}$ = 3.6 Hz), 50.3, 75.3, 117.1 (t, $^1J_{CF}$ = 250.7 Hz), 125.5, 125.7, 128.4, 128.5, 152.4, 165.2 (t, $^3J_{CF}$ = 31.0 Hz), 170.1; δ (second isomer) = 22.4, 27.4, 30.9, 31.6, 34.8, 35.6, 36.8 (t, $^2J_{CF}$ = 21.9 Hz), 39.7, 40.3, 42.1, 44.9 (t, $^3J_{CF}$ = 3.6 Hz), 50.4, 75.1, 122.0 (t, $^1J_{CF}$ = 251.8 Hz), 125.6, 125.7, 128.1, 128.2, 152.6, 165.1 (t, $^3J_{CF}$ = 29.2 Hz), 168.9.

^{19}F NMR (282.4 MHz, $CDCl_3$): δ (first isomer) = –104.3 (dtt, $^2J_{FF}$ = 272.8 Hz, $^3J_{HF}$ = 28.2 Hz, $^4J_{HF}$ = 3.1 Hz, 1 F), –107.5 (ddd, $^2J_{FF}$ = 272.5 Hz, $^3J_{HF}$ = 15.3 Hz, $^4J_{HF}$ = 2.5 Hz, 1 F); δ (second isomer) = –105.2 (dtt, $^2J_{FF}$ = 271.4 Hz, $^3J_{HF}$ = 29.1 Hz, $^4J_{HF}$ = 3.1 Hz, 1 F), –107.6 (ddd, $^2J_{FF}$ = 271.5 Hz, $^3J_{HF}$ = 16.2 Hz, $^4J_{HF}$ = 2.3 Hz, 1 F).

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{22}H_{30}F_2NO_3$: 394.2188; found: 394.2190.

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