

# Ethyl Difluoro(trimethylsilyl)acetate and Difluoro(trimethylsilyl)acetamides – Precursors of 3,3-Difluoroazetidinones<sup>[‡]</sup>

Michel Bordeau,<sup>\*,[a]</sup> Frédéric Frébault,<sup>[a]</sup> Mallory Gobet,<sup>[a]</sup> and Jean-Paul Picard<sup>\*,[a]</sup>

**Keywords:** Fluorine / Silicon / Amino acids / Amides / Lactams / Electrosynthesis

Difluoro(trimethylsilyl)acetamides **7** have been prepared from chlorodifluoroacetamides **5** by electrochemical silylation. When condensed with carbonyl compounds, they were shown to be precursors of 2,2-difluoro-3-hydroxyacetamides **8**. *N*-(*p*-Methoxyphenyl)-2,2-difluoro-3-hydroxy-4-methylvaleramide (**8a**) has been converted into the corre-

sponding 3,3-difluoroazetidinone **9a**. This new route to 3,3-difluoroazetidinones is shown to be an alternative to the one utilizing the condensation of ethyl difluoro(trimethylsilyl)acetate with imines.

(© Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2006)

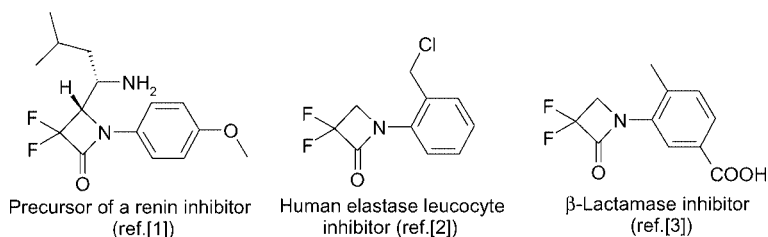
## Introduction

Azetidin-2-one structures (“ $\beta$ -lactams”) are present in many natural and nonnatural compounds that have proven to be of interest as antibiotics. Although they have been extracted from natural sources, great efforts have been dedicated to their synthesis both at academic and at industrial levels. The continuous need for new types of  $\beta$ -lactams emerged when bacterial resistance to some of these drugs appeared.

Among the possible means to address this problem, the preparation of fluorinated azetidinones has been proposed as one good response because the substitution of a methylene group by a difluoromethylene one induces changes in physical and chemical, and consequently biological, behavior. 3,3-Difluoro- $\beta$ -lactams have been already synthesized, and some of them are bioactive<sup>[1–3]</sup> (Scheme 1).

Several general strategies have been used to synthesize the 3,3-difluoroazetidinone skeleton (Scheme 2); they mainly involve internal cyclization<sup>[4]</sup> either of  $\beta$ -amino- $\alpha,\alpha$ -difluoro esters **A**, with elimination of the corresponding alcohols,<sup>[5–7]</sup> or of 2,2-difluoro-3-hydroxy amides **B**, with elimination of water.<sup>[1,8,9]</sup> Access to the starting materials has been achieved through the condensation of the appropriate Reformatsky reagents derived from an ethyl halodifluoroacetate with either imines (to form **A**) or aldehydes or ketones to form 2,2-difluoro-3-hydroxy esters **A'**, which were converted into the desired amides **B**.

In both cases, Reformatsky reagents were produced from bromo- or iododifluoroacetates, which are very expensive materials. Ethyl chlorodifluoroacetate constitutes a more attractive starting reagent, as it is commercially available and relatively cheap. We anticipated that ethyl difluoro(trimethylsilyl)acetate (**1**), a recently described modified

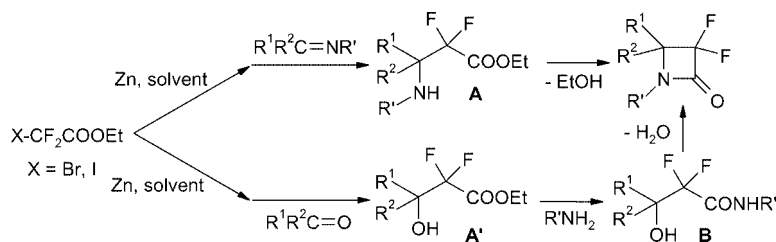


Scheme 1. Bioactive 3,3-difluoroazetidin-2-ones.

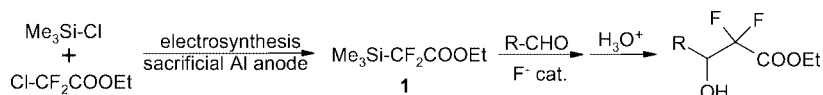
[‡] Functionalized Ruppert Reagents, 3. Part 2: in preparation. Part 1: Ref.<sup>[10]</sup>

[a] Laboratoire de chimie organique et organométallique, Université Bordeaux I, 33405 Talence Cedex, France  
E-mail: m.bordeau@lcoo.u-bordeaux1.fr  
j-p.picard@lcoo.u-bordeaux1.fr

Ruppert reagent,<sup>[10,11]</sup> might be used advantageously as it is easily prepared from ethyl chlorodifluoroacetate and is storable. Moreover, **1** had been demonstrated to react efficiently with aldehydes and ketones to form 2,2-difluoro-3-hydroxyacetates in good to excellent yields (Scheme 3).<sup>[10,11]</sup>



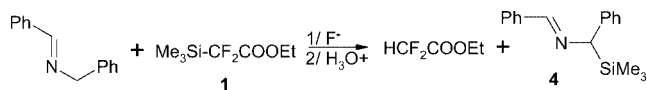
Scheme 2. Reformatsky routes to 3,3-difluoroazetidin-2-ones.

Scheme 3. Access to 2,2-difluoro-3-hydroxyacetates from **1**.

## Results

We extended this study to the condensation of **1** with an imine (namely a Schiff base) and obtained the corresponding ethyl 3-amino-2,2-difluoroacetate **2**.<sup>[12]</sup> The reaction required the use of 1 equiv. of fluoride ion, however, imines being less nucleophilic in character than carbonyl compounds. This  $\beta$ -amino ester was easily transformed into the already known<sup>[5]</sup> azetidinone **3** on treatment with a base as shown in Scheme 4.

However, we have not yet been able to extend the scope of this reaction to other types of imines. Use of *N*-benzylidenbenzylamine, for instance, resulted in desilylation of **1** (forming ethyl difluoroacetate) and silylation of the starting imine at the benzylic position (compound **4**).<sup>[13]</sup> This could be indicative of a relatively basic character of the intermediate anionic species (Scheme 5).

Scheme 5. Attempted addition of **1**.

We thus turned to a reversed strategy in which the azetidinone precursors were 2,2-difluoro-3-hydroxyacetamides, which required the prior synthesis of a series of difluoro(trimethylsilyl)acetamides **7**, a new class of functionalized Rupprecht reagents. The amides were prepared by condensation of the appropriate primary amines with either chlorodi-

fluoroacetic acid or its sodium salt by described methods.<sup>[14,15]</sup> Yields were slightly higher from the salt than from the free acid, because of the volatility of the acid (Scheme 6).

Method A<sup>[14]</sup>  $R-NH_2 + Cl-CF_2COO^- Na^+ \xrightarrow{Ph_3P/I_2} Cl-CF_2CONHR$  **5**

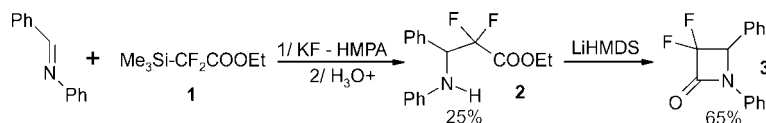
Method B<sup>[15]</sup>  $R-NH_2 + Cl-CF_2COOH \xrightarrow{Ph_3P/CCl_4} Cl-CF_2CONHR$  **5**

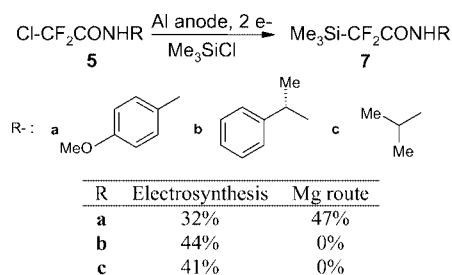
| R-NH <sub>2</sub> | Method | Chloroamide <b>5</b> | Yield (%) |
|-------------------|--------|----------------------|-----------|
|                   | A      | <b>5a</b>            | 60        |
|                   | B      | <b>5a</b>            | 56        |
|                   | A      | <b>5b</b>            | 64        |
|                   | B      | <b>5b</b>            | 41        |
|                   | A      | <b>5c</b>            | 62        |
|                   | B      | <b>5c</b>            | 47        |

Scheme 6. Syntheses of chlorodifluoroacetamides **5**.

Direct condensation of chlorodifluoroacetyl chloride (**6**) with these amines by described procedures<sup>[16–18]</sup> gave the corresponding amides, but in low yields, probably because of the low boiling point of the acyl chloride (bp. 26–28 °C at atmospheric pressure).

The chloro amides were therefore electrochemically silylated by the aluminium sacrificial anode technique<sup>[10]</sup> as in the case of the chloro ester to yield the corresponding trimethylsilyl amides **7** (Scheme 7).

Scheme 4. Synthesis of azetidinone **3**.

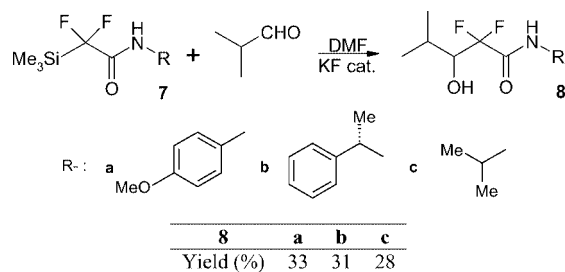
Scheme 7. Synthesis of difluoro(trimethylsilyl)acetamides **7**.

We also treated **5** with chlorotrimethylsilane and magnesium in THF according to Uneyama's procedure for aryl esters.<sup>[11b]</sup> Only **7a** was obtained in comparable yield. This result parallels Uneyama's observation that aliphatic esters could not be silylated in this way.

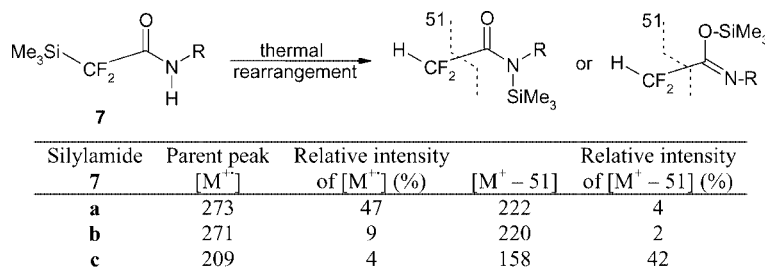
The GC/MS data of amides **7a–c** each present an  $m/z$  peak at  $[M - 51]$ , indicating the loss of the  $[\text{HCF}_2]$  fragment (Scheme 8). This could be the result of a  $\text{C} \rightarrow \text{N}$  or a  $\text{C} \rightarrow \text{O}$  silyl migration induced by heat on the GC column or in the injection chamber to form either the *N*-silyldifluoroacetamide or the *O*-silyliminodifluoroacetate.

The relative intensities of these  $[M^+ - 51]$  peaks vary with the nature of the R group and can be related to the electronic density on the nitrogen or oxygen atom.

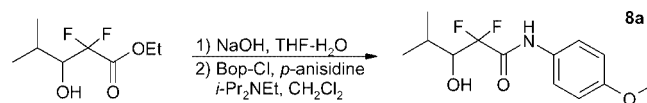
As in the case of the silyl esters, compounds **7** were condensed with an aldehyde, namely isobutyraldehyde, in the presence of a catalytic amount of fluoride anion to form the desired 2,2-difluoro-3-hydroxyacetamides **8** (Scheme 9).

Scheme 9. Synthesis of 2,2-difluoro-3-hydroxyacetamides **8**.

No asymmetric induction had occurred, as hydroxy ester **8b** was obtained as a 1:1 mixture of two diastereomers.

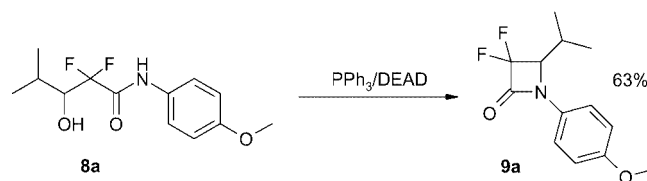
Scheme 8. Thermal behavior of **7** and relative magnitude of the loss of the  $\text{CHF}_2$  fragment.

An alternate synthesis of **8a** by direct amidation of the corresponding hydroxy ester (Scheme 10) has been reported.<sup>[8,19]</sup>

Scheme 10. Synthesis of **8a** from the corresponding 3-hydroxy ester.

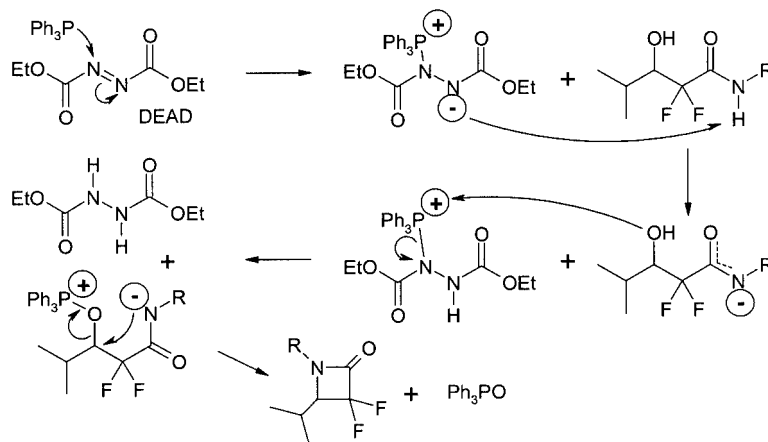
Hydroxy amides **8** were subjected to cyclization reaction in the presence of the Mitsunobu reagent [diethyl azodicarboxylate (DEAD)/triphenylphosphane] to yield the expected azetidinones **9**. It should be pointed out that cyclization of 3-hydroxy amides as a synthetic route to  $\beta$ -lactams is not very popular.<sup>[18,20–23]</sup>

This strategy was actually efficient only in the case of **8a** (Scheme 11), whereas **8b** and **8c** were recovered unchanged. Use of diisopropyl diazodicarboxylate (DIAD),<sup>[24]</sup> reported to be more active in Mitsunobu reactions, did not give better results.

Scheme 11. Synthesis of 3,3-difluoroazetidinone **9a** from amide **8a**.

The mechanism of this transformation is based on the formation of an ylide between triphenylphosphane and DEAD and on deprotonation of NH of the amide function by the ylide in preference to OH. Finally, the oxygen atom of the hydroxy group attacks the phosphorus atom to form diethyl hydrazodicarboxylate and the azetidinone (Scheme 12). The failure to cyclize **8b** or **8c** is probably due to the proton on the nitrogen atom being less acidic than the one of the hydroxy group.

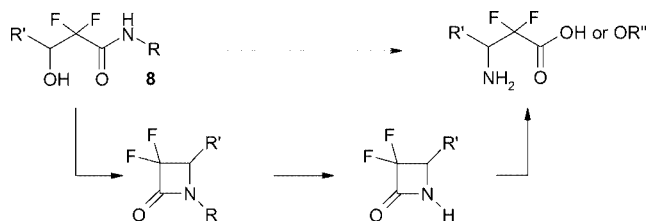
Although a previous synthesis of **9a** had already been reported,<sup>[18,23]</sup> no physicochemical data for this azetidinone had been given, so its full structural description was established in this work by  $^1\text{H}$ ,  $^{13}\text{C}$ , and  $^{19}\text{F}$  NMR spectroscopy, complemented by partial simulation of the spectra to ascertain coupling constants.



Scheme 12. Proposed Mitsunobu reaction mechanism.

## Conclusions

Modified Ruppert's reagents **1** and **7** provide original routes to 3-amino-2,2-difluoro ester **2** and 2,2-difluoro-3-hydroxy amides **8a–c** and to 3,3-difluoroazetidinones **3** and **9a**. Since these cyclic compounds are excellent precursors of  $\beta$ -amino acids,<sup>[23]</sup> after *N*-deprotection and basic hydrolysis, this strategy is very interesting, as fluorinated  $\beta$ -hydroxy amides can be converted through a two-step process into the corresponding fluorinated  $\beta$ -amino acids, ready to be incorporated into polypeptides chains (Scheme 13).

Scheme 13. Possible route to 3-amino-2,2-difluoroaliphatic acids (and esters) from 2,2-difluoro-3-hydroxyaliphatic amides **8** by well-known  $\beta$ -lactam chemistry transformations.

Moreover, zinc is not particularly recommended in biological media because it can cause undesired effects. In this context, our route to fluorinated  $\beta$ -lactam derivatives offers an interesting alternative. Further studies are in progress.

## Experimental Section

**General:**  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded with a Bruker AC 250 FT ( $^1\text{H}$  NMR: 250 MHz,  $^{13}\text{C}$  NMR: 62.9 MHz), a Bruker DPX 300 ( $^1\text{H}$  NMR: 300 MHz,  $^{13}\text{C}$  NMR: 75 MHz) or a Bruker DPX 400 ( $^1\text{H}$  NMR: 400 MHz,  $^{13}\text{C}$  NMR: 100 MHz) spectrometer with use of  $\text{CDCl}_3$  ( $\delta = 77.7$  ppm) or residual  $\text{CHCl}_3$  ( $\delta = 7.27$  ppm) as internal standards.  $^{19}\text{F}$  NMR spectra were obtained in  $\text{CDCl}_3$  with a Bruker AP 200 spectrometer (188 MHz), with  $\text{PhCF}_3$  as the internal standard ( $\delta = -63$  ppm versus  $\text{FCCl}_3$ ). IR spectra were recorded with a Perkin–Elmer Paragon 1000 FT/IR spectrometer. Coupled GC/MS analyses were performed with a Finnigan integrated spectrometer. Liquid chromatography was performed on silica gel (0.040–0.063 mm) and progress of the reactions was monitored by TLC on silica gel plates (thickness 0.2 mm with fluore-

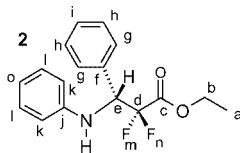
cence indicator 60 F<sub>254</sub>). Specific rotations of chiral compounds dissolved in chloroform were obtained at 20 °C with a P3001 Krüss Optronic automatic digital polarimeter and a 10 cm long tube. Slow additions were performed with a Razel A-99 automatic syringe. Dichloromethane and DMF were distilled from calcium hydride, THF and  $\text{Et}_2\text{O}$  from sodium/benzophenone ketyl, and  $\text{TMSCl}$  from magnesium turnings. Electrosyntheses were performed by use of the described equipment and procedures.<sup>[10]</sup>

**Synthesis of Ethyl 2,2-Difluoro-2-(trimethylsilyl)acetate (1):** This silyl ester was synthesized as in the literature.<sup>[10]</sup> Spectroscopic data are identical to those reported in the literature<sup>[10]</sup> and are supplemented as: B.p. 55 °C (20 Torr).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta = 0.16$  (s, 9 H, Si- $\text{CH}_3$ ), 1.27 (t, 3 H,  $^3J = 7$  Hz,  $\text{CH}_2\text{CH}_3$ ), 4.24 (q, 2 H,  $^3J = 7$  Hz,  $\text{CH}_2\text{CH}_3$ ) ppm.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta = -5.23$  (Si- $\text{CH}_3$ ), 13.92 ( $\text{CH}_2$ - $\text{CH}_3$ ), 62 ( $\text{CH}_2$ - $\text{CH}_3$ ), 120.95 (t,  $^1J_{\text{C,F}} = 268.9$  Hz,  $\text{CF}_2$ ), 166.24 (t,  $^2J_{\text{C,F}} = 25.7$  Hz,  $\text{C}=\text{O}$ ) ppm.  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ ):  $\delta = -123.5$  (s) ppm. IR (KBr):  $\tilde{\nu} = 2959, 1756$  ( $\text{C}=\text{O}$ ), 1255, 1114, 1052  $\text{cm}^{-1}$ . MS (EI):  $m/z$  (%) = 196 (1) [ $\text{M}^+$ ], 181 (5), 153 (7), 125 (8), 103 (10), 81 (17), 77 (38), 73 (100), 55 (15), 45 (21).

**Addition of 1 to a Schiff Base to Provide Amino Ester 2:** Under anhydrous nitrogen static pressure, *N*-benzylideneaniline (3.63 g, 20 mmol), KF (1.27 g, 21.5 mmol), and HMPA (20 mL) were introduced into a round-bottomed flask fitted with a condenser and a magnetic stirring bar. The mixture was stirred at 50 °C, **1** (3.92 g, 20 mmol) was added, and stirring was continued for 12 h. The organic phase was extracted with diethyl ether, the resulting ethereal solution was separated, and the diethyl ether was evaporated. The crude product was purified by chromatography on silica gel (pentane/ $\text{Et}_2\text{O}$ , 19:1). Amino ester **2** was recovered in 25% yield.

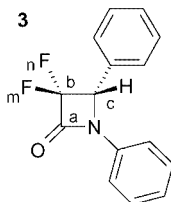
**Ethyl 2,2-Difluoro-3-phenyl-3-(phenylamino)propionate (2):** M.p. 104 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta = 1.26$  (t,  $^3J = 7.2$  Hz, 3 H,  $H_a$ ), 4.28 (q,  $^3J = 7.2$  Hz, 2 H,  $H_b$ ), 4.46 (d,  $^3J = 9.8$  Hz, 1 H,  $\text{NH}$ ), 5.10 (ddd,  $^3J_{\text{H,F}_n} = 7.7$  Hz,  $^3J_{\text{H,F}_m} = 18.8$  Hz,  $^3J_{\text{H,H}} = 9.8$  Hz,  $H_c$ ), 6.65 (d,  $^3J = 7.6$  Hz, 2 H,  $H_k$ ), 6.72 (t,  $^3J = 7.6$  Hz, 2 H,  $H_l$ ), 7.14 (t,  $^3J = 7.6$  Hz, 1 H,  $H_o$ ) and 7.60 (m, 5 H,  $H_{\text{arom}}$  in Ph-C) ppm.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta = 13.86$  ( $C_a$ ), 60.12 (dd,  $^2J_{\text{C,F}} = 26.9$  Hz,  $^2J_{\text{C,F}} = 22.5$  Hz,  $C_e$ ), 63.19 ( $C_b$ ), 114.29 (dd,  $^1J_{\text{C,F}} = 257.4$  Hz,  $^1J_{\text{C,F}} = 256.3$  Hz,  $C_d$ ), 115.18 ( $C_k$ ), 119.14 ( $C_o$ ), 128 ( $C_l$ ), 145.33 ( $C_j$ ), 128–129 ( $C_g$ ,  $C_h$  and  $C_i$ ), 133.84 ( $C_f$ ) and 163.54 (dd,  $^2J_{\text{C,F}} = 30.7$  Hz,  $^2J_{\text{C,F}} = 32.9$  Hz,  $C_c$ ) ppm.  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ ):  $\delta = -109.55$  (dd,  $F_m$  or  $F_n$ ) and  $-119.55$  (ddd,  $^3J_{\text{H,F}} = 7.7$  Hz,  $^3J_{\text{H,F}} = 18.8$  Hz,  $^2J_{\text{F,F}} = 258$  Hz,  $F_n$  or  $F_m$ ) ppm. From the  $^1\text{H}$  and  $^{19}\text{F}$  NMR spectra, fluorine atoms are observed to be diastereotopic, owing to the presence of a close chiral center. IR (KBr):  $\tilde{\nu} = 3354$  (NH), 3035, 2985, 1760

(C=O), 1603, 1497, 1455, 1442, 1372, 1298, 1266, 1255, 1212, 1194, 1107, 1076, 1062, 882, 833, 756, 724, 692 cm<sup>-1</sup>. MS (EI): *m/z* (%) = 305 (3) [M<sup>+</sup>], 259 (2), 195 (12), 182 (59), 180 (88), 105 (23), 104 (24), 77 (100), 51 (35). C<sub>17</sub>H<sub>17</sub>F<sub>2</sub>NO<sub>2</sub> (305.32): calcd. C 66.87, H 5.61, N 4.59; found C 66.94, H 5.58, N 4.60.



**Cyclization of 2 to Azetidinone 3:** A lithium hexamethyldisilylamide (LiHMDS) solution was prepared under anhydrous conditions in a 250 mL Grignard flask. Butyllithium (*n*-BuLi, 1.64 mmol) was added with stirring to hexamethyldisilazane (264 mg, 1.64 mmol), diluted in anhydrous THF (10 mL). Separately, amino ester **2** (500 mg, 1.64 mmol) and dried THF (15 mL) were introduced into a 100 mL Grignard flask. The LiHMDS solution was then slowly added at -20 °C with stirring. Stirring was continued for 5 min, and the reaction mixture was quenched with HCl (4 M, 25 mL) and extracted three times with dichloromethane (3 × 15 mL). The organic layer was separated and dried with magnesium sulfate. Organic solvents were evaporated and the residue was subjected to column chromatography on silica gel (pentane/Et<sub>2</sub>O, 9:1). Pure **3** was obtained in 65% yield.

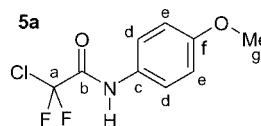
**3,3-Difluoro-1,4-diphenylazetidin-2-one (3):** M.p. 135 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ = 5.42 (dd, <sup>3</sup>J<sub>H,F</sub> = 2.1 Hz, <sup>3</sup>J<sub>H,F</sub> = 7.6 Hz, 1 H, H<sub>c</sub>), 7.10–7.50 (m, 10 H, H<sub>arom</sub>) ppm. <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 69.05 (dd, <sup>2</sup>J<sub>C,F<sub>m</sub></sub> = 26.9 Hz, <sup>2</sup>J<sub>C,F<sub>n</sub></sub> = 24.7 Hz, C<sub>e</sub>), 119.48 (dd, <sup>1</sup>J<sub>C,F</sub> = 284.5 Hz, <sup>1</sup>J<sub>C,F</sub> = 287.5 Hz, C<sub>b</sub>), 118–137 (C<sub>arom</sub>), 157.87 (t, <sup>2</sup>J<sub>C,F</sub> = 31.6 Hz, C<sub>a</sub>) ppm. <sup>19</sup>F NMR (CDCl<sub>3</sub>): δ = -114.13 (dd, <sup>3</sup>J<sub>H<sub>c</sub>,F<sub>m</sub></sub> = 7.6 Hz, <sup>2</sup>J<sub>F<sub>m</sub>,F<sub>n</sub></sub> = 226.2 Hz, F<sub>m</sub>), -119.90 (dd, <sup>3</sup>J<sub>H<sub>c</sub>,F<sub>n</sub></sub> = 2.1 Hz, <sup>2</sup>J<sub>F<sub>n</sub>,F<sub>m</sub></sub> = 226.2 Hz, F<sub>n</sub>) ppm.<sup>[25]</sup> IR (KBr): ν̄ = 1765 (C=O), 1494, 1458, 1392, 1316, 1207, 1157, 1108, 1003, 825, 753 cm<sup>-1</sup>. MS (EI): *m/z* (%) = 259 (5.6) [M<sup>+</sup>], 140 (100) [Ph-CH=CF<sub>2</sub><sup>+</sup>], 119 (15.7), 104 (8.6), 91 (12.4), 78 (7.2) [O=C=CF<sub>2</sub><sup>+</sup>], 77 (32.5), 51 (17.3). The base peak at *m/z* = 140 is indicative of the preferred fragmentation pattern of the azetidinone ring, affording isocyanate and olefin fragments over ketene and imine fragments. This phenomenon has already been observed.<sup>[26]</sup> C<sub>15</sub>H<sub>11</sub>F<sub>2</sub>NO (259.25): calcd. C 69.49, H 4.28, N 5.40; found C 69.47, H 4.30, N 5.37.



**Attempted Addition of 1 to *N*-Benzylidenbenzylamine:** *N*-Benzylidenbenzylamine (3.81 g, 20 mmol) was treated with **1** under the same conditions as had been used for the Schiff base. However, GC and NMR analysis of the crude product showed that ethyl difluoroacetate and *N*-benzylidene-α-(trimethylsilyl)benzylamine (**4**) were formed. Ester: <sup>19</sup>F NMR (CDCl<sub>3</sub>): δ = -127 (d, <sup>2</sup>J<sub>H,F</sub> = 52.8 Hz) ppm. Imine **4**: M.p. 142 °C (ref.<sup>[13a]</sup> 143–145.3 °C). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ = 4.16 (s, 1 H, SiCHPh) ppm. C<sub>17</sub>H<sub>21</sub>NSi (267.44): calcd. C 76.35, H 7.91, N 5.24; found C 76.38, H 7.85, N 5.23.

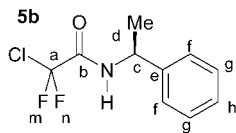
**Syntheses of Chlorodifluoroacetamides 5:** Three methods were used. **Method A (from the Sodium Salt):**<sup>[14]</sup> PPh<sub>3</sub> (3.93 g, 15 mmol, 1 equiv.) and iodine (3.81 g, 15 mmol, 1 equiv.), dissolved in anhydrous dichloromethane (150 mL), were introduced into a two-necked 250 mL flask fitted with a dropping funnel and a condenser. After homogenization of the mixture, sodium chlorodifluoroacetate (2.29 g, 15 mmol, 1 equiv.) was added and the mixture was stirred for 1 h. A mixture of *p*-anisidine (1.50 mL, 16.5 mmol, 1.1 equiv.), NEt<sub>3</sub> (2.3 mL, 16.5 mmol, 1.1 equiv.), and anhydrous CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added dropwise. Stirring was maintained for 30 min and the formed sodium salts were then separated by filtration through a fritted glass filter (porosity 3). The solid residue was washed with a saturated aqueous sodium thiosulfate solution (2 × 20 mL), a HCl (10%) solution, a saturated aqueous sodium hydrogencarbonate solution (10 mL), and finally with brine (20 mL). The final organic phase was separated by decantation and dried with MgSO<sub>4</sub>, and the solvent (CH<sub>2</sub>Cl<sub>2</sub>) was removed under vacuum. The crude product was purified by column chromatography (light petroleum ether/EtOAc, 2:1). **Method B (from the Acid):**<sup>[15]</sup> The same amides were obtained, albeit in lower yield, from the corresponding amines by the above procedure. **Method C (via the Acyl Chloride):** PCl<sub>5</sub> (2.626 g, 12.6 mmol, 1.25 equiv.) was introduced into a 50 mL Grignard flask, fitted with a distillation column, a condenser, and a cold trap, and placed in an oil bath maintained at 35–40 °C. Chlorodifluoroacetic acid (1.313 g, 10.1 mmol, 1 equiv.) was added dropwise by syringe and the temperature of the bath was then raised to 60 °C in order to recover the final traces of the acyl chloride **6**, which appeared as a colorless, clear liquid (390 mg, 26%); b.p. 26–28 °C. <sup>19</sup>F NMR (CDCl<sub>3</sub>): δ = -65.0 (s) ppm. Compound **6** was then treated with the appropriate primary amine to give the desired amides **5**, albeit in lower yields.

**2-Chloro-2,2-difluoro-*N*-(*p*-methoxyphenyl)acetamide (5a):** This amide was obtained as a yellowish oil, which was purified on a silica gel column and recovered as white crystals (1.41 g, 60%); m.p. 111 °C. TLC: R<sub>f</sub> = 0.80. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ = 3.81 (s, 3 H, H<sub>g</sub>), 6.90 and 7.45 (AA'BB', 2 × 2 H, H<sub>d,e</sub>), 7.77 (s, NH) ppm. <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 55.5 (C<sub>g</sub>), 114.4 (C<sub>d</sub>), 119.5 (t, <sup>1</sup>J<sub>C,F</sub> = 300 Hz, C<sub>a</sub>), 122.2 (C<sub>e</sub>), 128.2 (C<sub>c</sub>), 157.0 (t, <sup>2</sup>J<sub>C,F</sub> = 30 Hz, C<sub>b</sub>), 157.7 (C<sub>f</sub>) ppm. <sup>19</sup>F NMR (CDCl<sub>3</sub>): δ = -64.24 (s) ppm. IR (KBr): ν̄ = 3414 (N-H), 1701 (C=O), 2836, 1512, 1248, 1038, 831, 620 cm<sup>-1</sup>. MS (EI): *m/z* (%) = 237 (24), 235 (80), 200 (13), 149 (16), 122 (100), 95 (14), 52 (8). C<sub>9</sub>H<sub>8</sub>ClF<sub>2</sub>NO<sub>2</sub> (235.61): calcd. C 45.88, H 3.42, N 5.94; found C 45.85, H 3.41, N 5.89.

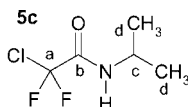


**2-Chloro-2,2-difluoro-*N*-[(*S*)-1-phenylethyl]acetamide (5b):** This compound was obtained from (–)-(*S*)-1-phenylethylamine ([α]<sub>D</sub> = -30 ± 1, *c* = 10, ethanol; -8 ± 1, *c* = 10, CHCl<sub>3</sub>) as a yellowish oil, which was purified on a silica gel column and recovered in 64% yield as white crystals (m.p. 70 °C). TLC: R<sub>f</sub> = 0.85. [α]<sub>D</sub> = +55 ± 1 (*c* = 10, CHCl<sub>3</sub>). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ = 1.60 (d, <sup>3</sup>J = 2.1 Hz, 3 H, H<sub>d</sub>), 5.12 (m, 1 H, H<sub>c</sub>), 6.42 (s, 1 H, NH), 7.30 (m, 5 H, H<sub>f,g,h</sub>) ppm. <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 21.4 (C<sub>d</sub>), 48.7 (C<sub>c</sub>), 119.5 (t, <sup>1</sup>J<sub>C,F</sub> = 300 Hz, C<sub>a</sub>), 126.5 (C<sub>g</sub>), 128.5 (C<sub>h</sub>), 129.3 (C<sub>f</sub>), 141.4 (C<sub>e</sub>), 158.8 (t, <sup>2</sup>J<sub>C,F</sub> = 30.0 Hz, C<sub>b</sub>) ppm. <sup>19</sup>F NMR (CDCl<sub>3</sub>): δ = -64.51 (s) ppm. IR (KBr): ν̄ = 3414 (N-H), 1700 (C=O), 1536, 1138, 984,

700, 630  $\text{cm}^{-1}$ . MS (EI):  $m/z$  (%) = 235 (14), 233 (41), 218 (37), 198 (19), 148 (22), 105 (100), 77 (36), 51 (16).  $\text{C}_{10}\text{H}_{10}\text{ClF}_2\text{NO}$  (233.61): calcd. C 51.41, H 4.31, N 5.99; found C 51.44, H 4.38, N 5.91.

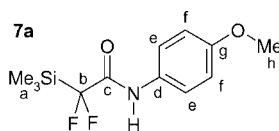


**2-Chloro-2,2-difluoro-N-isopropylacetamide (5c):** This compound was obtained as a white, crystalline powder (62% yield). TLC:  $R_f$  = 0.91.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  = 1.24 (d,  $^3J$  = 8.1 Hz, 6 H,  $H_d$ ), 4.10 (sept,  $^3J$  = 8.1 Hz, 1 H,  $H_c$ ), 6.10 (s, NH) ppm.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  = 22.0 ( $C_d$ ), 42.9 ( $C_c$ ), 119.1 (t,  $^1J_{\text{C,F}}$  = 300 Hz,  $C_a$ ), 158.4 (t,  $^2J_{\text{C,F}}$  = 30 Hz,  $C_b$ ) ppm.  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  = -64.56 (s) ppm. IR (KBr):  $\tilde{\nu}$  = 3413 (N-H), 1700 (C=O), 1135, 990, 623  $\text{cm}^{-1}$ . MS (EI):  $m/z$  (%) = 158 (30), 156 (90), 108 (9), 87 (12), 86 (100), 85 (26), 70 (14), 43 (80).  $\text{C}_5\text{H}_8\text{ClF}_2\text{NO}$  (171.57): calcd. C 35.00, H 4.70, N 8.16; found C 34.94, H 4.78, N 8.11.



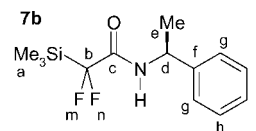
**Synthesis of Silylamides 7. Electrosilylation of Chloroamides 5:** Electrodes (aluminium anode and stainless steel cathode) were washed with a hydrochloric acid solution (10%) for 10 min, then rinsed with pure water and then acetone, and were finally dried at 120  $^{\circ}\text{C}$  for 30 min. Tetrabutylammonium bromide (0.25 g, 0.25 mmol, 0.05 equiv.) and a magnetic stirring bar were introduced into the electrolysis cell fitted with the electrodes. HMPA (10 mL) was introduced under dry nitrogen and the mixture was stirred until the salt was dissolved. Finally, dried THF (40 mL) and TMSCl (distilled from magnesium turnings, 3.2 mL, 25 mmol, 5 equiv.) were added. Preelectrolysis (45 min) was carried out first, and the chloroamide **5** (1.178 g, 5 mmol, 1 equiv., diluted in 5 mL anhydrous THF) was then added to the mixture at the rate of the electrolysis ( $i$  = 100 mA) by automatic syringe over 3 h 45 min (1350 C,  $2.5 \text{ F}\cdot\text{mol}^{-1}$ ). The solvents were evaporated under vacuum and the raw material was purified on a column of silica gel (petroleum ether/EtOAc, 2:1) to provide the pure silyl amide **7**.

**2,2-Difluoro-N-(*p*-methoxyphenyl)-2-(trimethylsilyl)acetamide (7a):** This compound was obtained as a white, crystalline solid (442 mg, 32% yield). TLC:  $R_f$  = 0.87.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  = 0.29 (s, 9 H,  $H_a$ ), 3.80 (s, 3 H,  $H_b$ ), 6.90 and 7.45 (AA'BB',  $2 \times 2$  H,  $H_{c,f}$ ), 7.80 (s, NH) ppm.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  = -4.7 ( $C_a$ ), 55.5 ( $C_b$ ), 114.3 ( $C_c$ ), 122.3 ( $C_f$ ), 122.6 (t,  $^1J_{\text{C,F}}$  = 300 Hz,  $C_b$ ), 129.2 ( $C_d$ ), 157.1 ( $C_g$ ), 164.3 (t,  $^2J_{\text{C,F}}$  = 30 Hz,  $C_e$ ) ppm.  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  = -122.10 (s) ppm. IR (KBr):  $\tilde{\nu}$  = 3338 (N-H), 1675 (C=O), 1538, 1257, 1031, 855  $\text{cm}^{-1}$ . MS (EI):  $m/z$  (%) = 273 (47), 258 (13), 222 (4), 180 (12), 122 (51), 77 (23), 73 (100).  $\text{C}_{12}\text{H}_{17}\text{F}_2\text{NO}_2\text{Si}$  (273.35): calcd. C 52.73, H 6.27, N 5.12; found C 52.68, H 6.20, N 5.15.

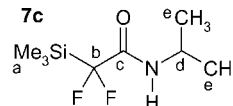


**2,2-Difluoro-N-[(*S*)-1-phenylethyl]-2-(trimethylsilyl)acetamide (7b):** This compound was obtained in 44% yield as a white, crystalline solid (m.p. 75  $^{\circ}\text{C}$ ). TLC:  $R_f$  = 0.45.  $[a]_D^{25}$  = -21  $\pm$  1 ( $c$  = 10,  $\text{CHCl}_3$ ).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  = 0.21 (s, 9 H,  $H_a$ ), 1.54 (d,  $^3J$  = 1.7 Hz, 3 H,  $H_e$ ), 5.15 (m, 1 H,  $H_d$ ), 6.44 (s, 1 H, NH), 7.30 (m, 5 H,  $H_{g,h,i}$ ) ppm.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  = -4.7 ( $C_a$ ), 20.7 ( $C_e$ ), 48.6 ( $C_d$ ), 122.5 (t,  $^1J_{\text{C,F}}$  = 300 Hz,  $C_b$ ), 126.2 ( $C_h$ ), 127.7 ( $C_i$ ), 128.8 ( $C_g$ ), 142.1 ( $C_f$ ), 165.1 (t,  $^2J_{\text{C,F}}$  = 30.0 Hz,  $C_c$ ) ppm.  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  = -122.82 (s) ppm. IR (KBr):  $\tilde{\nu}$  = 3414 (N-H), 1669 (C=O), 1539, 1111, 852  $\text{cm}^{-1}$ . MS (EI):  $m/z$  (%) = 271 (9), 256 (3), 220 (2), 152 (10), 105 (100), 77 (15), 73 (11).  $\text{C}_{13}\text{H}_{19}\text{F}_2\text{NOSi}$  (271.38): calcd. C 57.54, H 7.06, N 5.16; found C 57.50, H 6.97, N 5.21.



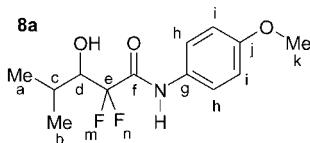
**2,2-Difluoro-N-isopropyl-2-(trimethylsilyl)acetamide (7c):** This compound was obtained as a white, crystalline solid in 41% yield. TLC:  $R_f$  = 0.48.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  = 0.23 (s, 9 H,  $H_a$ ), 1.20 (d,  $^3J$  = 7.7 Hz, 6 H,  $H_e$ ), 4.11 (m,  $^3J$  = 7.7 Hz, 1 H,  $H_d$ ), 6.0 (s, NH) ppm.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  = -4.8 ( $C_a$ ), 22.5 ( $C_e$ ), 42.4 ( $C_d$ ), 122.5 (t,  $^1J_{\text{C,F}}$  = 300 Hz,  $C_b$ ), 165.4 (t,  $^2J_{\text{C,F}}$  = 30 Hz,  $C_c$ ) ppm.  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  = -123.0 (s) ppm. IR (KBr):  $\tilde{\nu}$  = 3414 (N-H), 1662 (C=O), 1552, 1256, 1109, 1026, 852, 628  $\text{cm}^{-1}$ . MS (EI):  $m/z$  (%) = 209 (4), 194 (40), 158 (41), 116 (14), 81 (20), 77 (38), 73 (100), 43 (56).  $\text{C}_8\text{H}_{17}\text{F}_2\text{NOSi}$  (271.38): calcd. C 45.91, H 8.19, N 6.69; found C 45.86, H 8.18, N 6.75.



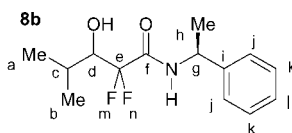
**Synthesis of  $\beta$ -Hydroxy Amides 8:** Dried potassium fluoride (2.9 mg, 0.05 mmol, 0.05 equiv.), isobutyraldehyde (144.2 mg, 2 mmol, 2 equiv.), and distilled DMF (5 mL) were introduced under anhydrous nitrogen into a two-necked, round-bottomed flask. (Trimethylsilyl)acetamide (**7**, 273.4 mg, 1 mmol, 1 equiv.), dissolved in DMF (3 mL), was added slowly with stirring at -10  $^{\circ}\text{C}$ , the reaction mixture was allowed to return to ambient temperature and stirred for 2 h, and the mixture was poured into dilute HCl (2 mL, 1% solution in water) and extracted with diethyl ether ( $3 \times 5$  mL). The organic phases were washed with a cold saturated aqueous solution of sodium hydrogencarbonate (1 mL) and brine (10 mL) and dried with magnesium sulfate, and the solvent was evaporated under vacuum. The raw material was obtained as a colorless, viscous liquid and products **8** were purified by column chromatography on silica gel (petroleum ether/EtOAc, 2:1), yielding compounds **8** as white, crystalline solids.

**2,2-Difluoro-3-hydroxy-N-(*p*-methoxyphenyl)-4-methylpentanamide (8a):** This compound was obtained in 33% yield. TLC (petroleum ether/EtOAc, 2:1):  $R_f$  = 0.33.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  = 1.05 and 1.07 (d,  $^3J$  = 7.2 Hz,  $2 \times 3$  H,  $H_a$  and  $H_b$ ), 2.1 (m,  $^3J$  = 7.2 and 7.0 Hz, 1 H,  $H_c$ ), 2.6 (d,  $^3J$  = 6.4 Hz, 1 H, OH), 3.8 (s, 3 H,  $H_b$ ), 4.00 (sept,  $^3J$  = 6.4 and 7.0 Hz, 1 H,  $H_d$ ), 6.9 and 7.4 (AA'BB',  $2 \times 2$  H,  $H_{h,i}$ ), 8 (s, NH) ppm.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  = 17.3 ( $C_a$ ), 19.6 ( $C_b$ ), 28.8 ( $C_c$ ), 55.5 ( $C_k$ ), 75.4 (t,  $^2J_{\text{C,F}}$  = 24.9 Hz,  $C_d$ ), 121.1 ( $C_i$ ), 122.07 ( $C_h$ ), 127.5 ( $C_g$ ), 128.8 (dd,  $^1J_{\text{C,F}_m}$  = 249 Hz,  $^1J_{\text{C,F}_n}$  = 256 Hz,  $C_e$ ), 157.9 ( $C_j$ ), 165.1 (t,  $^2J_{\text{C,F}}$  = 32 Hz,  $C_f$ ) ppm.  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  = -110.11 (dd,  $^3J_{\text{F}_m,\text{H}}$  = 18.8,  $^2J_{\text{F}_m,\text{F}_n}$  = 261.8 Hz),

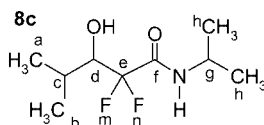
–120.72 (dd,  $^3J_{F_n,H} = 7.5$ ,  $^2J_{F_n,F_m} = 261.8$  Hz) ppm.  $C_{13}H_{17}F_2NO_2$  (273.28): calcd. C 57.14, H 6.27, N 5.13; found C 57.19, H 6.30, N 5.11.



**2,2-Difluoro-3-hydroxy-4-methyl-N-[(S)-1-phenylethyl]pentanamide (8b):** This compound was recovered in 31% yield. TLC (petroleum ether/EtOAc, 7:1):  $R_f = 0.17$ .  $^{13}C$  NMR ( $CDCl_3$ ):  $\delta = 17.0$  ( $C_a$  and  $C_b$ ), 20 ( $C_h$ ), 28.5 ( $C_c$ ), 49 ( $C_g$ ), 75 ( $C_d$ ), 112.3 (dd,  $^1J_{C,F_m} = 255$  Hz,  $^1J_{C,F_n} = 256.5$  Hz,  $C_e$ ), 126.1 ( $C_i$ ), 127.8 ( $C_j$ ), 128.6 ( $C_k$ ), 141.5 ( $C_l$ ), 163 (t,  $^2J_{C,F} = 31$  Hz,  $C_f$ ) ppm. Careful examination of the  $^1H$  and  $^{19}F$  NMR spectra of the crude material revealed the presence of two diastereomers in a 1:1 ratio.  $^1H$  NMR ( $CDCl_3$ ): one diastereomer:  $\delta = 1.0$  (d,  $^3J = 8.1$  Hz, 3 H,  $H_a$ ), 1.015 (d,  $^3J = 8.6$  Hz, 3 H,  $H_b$ ), 1.50 (d,  $^3J = 6.8$  Hz, 3 H,  $H_h$ ), 1.91 (m, 1 H,  $H_c$ ), 2.60 (s, OH), 3.85 (ddd,  $^3J_{H,F_m} = 18.1$  Hz,  $^3J_{H,F_n} = 7.2$  Hz,  $^3J_{H,H} = 5.3$  Hz, 1 H,  $H_d$ ), 5.07 (quint,  $^3J = 7.1$  Hz, 1 H,  $H_g$ ), 6.60 (s, NH), 7.30–7.40 (m, 5 H,  $H_{j,k,l}$ ) ppm; other diastereomer:  $\delta = 0.99$  (d,  $^3J = 8.5$  Hz, 3 H,  $H_a$ ), 1.02 (d,  $^3J = 8.4$  Hz, 3 H,  $H_b$ ), 1.56 (d,  $^3J = 7.3$  Hz, 3 H,  $H_h$ ), 2.01 (m, 1 H,  $H_c$ ), 2.65 (s, OH), 3.88 (td,  $^3J_{H,F_m} = 22.7$  Hz,  $^3J_{H,F_n} = 7.35$  Hz,  $^3J_{H,H} = 7.35$  Hz, 1 H,  $H_d$ ), 5.15 (quint,  $^3J = 8.4$  Hz, 1 H,  $H_g$ ), 6.80 (s, NH), 7.35–7.45 (m, 5 H,  $H_{arom}$ ) ppm.  $^{19}F$  NMR ( $CDCl_3$ ): one diastereomer:  $\delta = -110.7$  (dd,  $^3J_{F_m,H} = 18.8$  Hz,  $^2J_{F_m,F_n} = 263.7$  Hz), –120.8 (dd,  $^3J_{F_n,H} = 7.5$  Hz,  $^2J_{F_m,F_n} = 263.7$  Hz) ppm; other diastereomer:  $\delta = -110.1$  (dd,  $^3J_{F_m,H} = 18.8$  Hz,  $^2J_{F_m,F_n} = 263.7$  Hz), –121.9 (dd,  $^3J_{F_n,H} = 7.5$  Hz,  $^2J_{F_m,F_n} = 267.1$  Hz) ppm.  $C_{14}H_{19}F_2NO_2$  (271.30): calcd. C 61.98, H 7.06, N 5.16; found C 62.08, H 7.01, N 5.18.



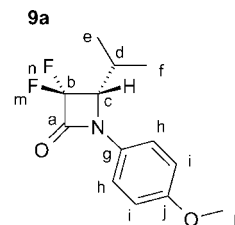
**2,2-Difluoro-3-hydroxy-N-isopropyl-4-methylpentanamide (8c):** This compound was obtained in 28% yield. TLC:  $R_f = 0.86$ .  $^1H$  NMR ( $CDCl_3$ ):  $\delta = 1.02$  (d,  $^3J = 7.5$  Hz, 3 H,  $H_a$ ), 1.04 (d,  $^3J = 7.1$  Hz, 3 H,  $H_b$ ), 1.22 (d,  $^3J = 6.4$  Hz, 6 H,  $H_h$ ), 2.00 (m, 1 H,  $H_c$ ), 2.72 (d,  $^3J = 6.4$  Hz, 1 H, OH), 3.91 (m, 1 H,  $H_d$ ), 4.11 (m, 1 H,  $H_g$ ), 6.25 (s, 1 H, NH) ppm.  $^{13}C$  NMR ( $CDCl_3$ ):  $\delta = 17.1$  ( $C_a$ ), 19.3 ( $C_b$ ), 22.4 ( $C_h$ ), 28.6 ( $C_c$ ), 42.0 ( $C_g$ ), 75.5 (t,  $^2J_{C,F} = 25$  Hz,  $C_d$ ), 116.0 (dd,  $^1J_{C,F_m} = 255$  Hz,  $^1J_{C,F_n} = 257$  Hz,  $C_e$ ), 165.0 (t,  $^2J_{C,F} = 31$  Hz,  $C_f$ ) ppm.  $^{19}F$  NMR ( $CDCl_3$ ):  $\delta = -110.7$  (dd,  $^3J_{F_m,H} = 18.7$  Hz,  $^2J_{F_m,F_n} = 267.5$  Hz), –120.9 (dd,  $^3J_{F_n,H} = 7.5$  Hz,  $^2J_{F_m,F_n} = 267.5$  Hz) ppm.  $C_9H_{17}F_2NO_2$  (271.30): calcd. C 51.66, H 8.19, N 6.69; found C 51.61, H 8.25, N 6.65.



**Cyclization of 8a Into Azetidinone 9a:** Triphenylphosphane (104.3 mg, 0.4 mmol, 2 equiv.) and **8a** (54.8 mg, 0.2 mmol, 1 equiv.), dissolved in dry THF (3 mL), were introduced under dry nitrogen into a 10 mL round-bottomed flask. The resulting solution was stirred at 20 °C for 15 min and DEAD (61  $\mu$ L, 0.4 mmol, 2 equiv.) was added dropwise at 0 °C. The mixture was stirred for

an additional 24 h. Evaporation of the solvent under vacuum left a viscous, orange liquid, which was purified by column chromatography on silica gel (petroleum ether/EtOAc, 4:1) to provide **9a** as a white, crystalline solid.

**3,3-Difluoro-4-isopropyl-N-(p-methoxyphenyl)azetidin-2-one (9a):** This compound was obtained in 63% yield. TLC (petroleum ether/EtOAc):  $R_f = 0.55$ .  $^1H$  NMR ( $CDCl_3$ ):  $\delta = 1.02$  (d,  $^3J = 7.0$  Hz, 3 H,  $H_e$ ), 1.09 (d,  $^3J = 7.0$  Hz, 3 H,  $H_f$ ), 2.36 (m, 1 H,  $H_d$ ), 3.82 (s, 3 H,  $H_k$ ), 4.30 (m, 1 H,  $H_c$ ), 6.92 and 7.50 (AA'BB' d,  $^3J = 9.0$  Hz, 2 H,  $H_i$  and d,  $^3J = 9.0$  Hz, 2 H,  $H_n$ , respectively) ppm.  $^{13}C$  NMR ( $CDCl_3$ ):  $\delta = 16.9$  ( $C_e$ ), 18.4 ( $C_f$ ), 27.4 ( $C_d$ ), 55.5 ( $C_k$ ), 70.5 (t,  $^2J_{C,F} = 23$  Hz,  $C_a$ ), 114.6 ( $C_i$ ), 117.0 (t,  $^1J_{C,F} = 300$  Hz,  $C_b$ ), 120.4 ( $C_h$ ), 120.8 ( $C_g$ ), 129.0 ( $C_j$ ), 157.6 (t,  $^2J_{C,F} = 30$  Hz,  $C_a$ ) ppm.  $^{19}F$  NMR ( $CDCl_3$ ):  $\delta = -112.18$  (dd,  $^3J_{F_m,H} = 8.8$  Hz,  $^2J_{F_m,F_n} = 234.4$  Hz,  $F_m$ ), –120.72 (dd,  $^3J_{F_n,H} = 1.9$  Hz,  $^2J_{F_m,F_n} = 234.4$  Hz,  $F_n$ ) ppm. Coupling constants were obtained through calculations carried out with a simulation program.<sup>[27]</sup> Owing to the asymmetric nature of  $C_c$ , the two fluorine atoms are magnetically inequivalent and have different chemical shifts and coupling constants  $^3J_{H,F}$ . The larger  $^3J_{H,F}$  value (8.8 Hz) was attributed to  $F_m$  *cis* to  $H_c$  and the lower (1.9 Hz) to  $F_n$  *trans* to  $H_c$ .<sup>[25]</sup> Apparently, protons of one methyl group ( $Me_e$ , for instance) are coupled with  $H_c$  ( $^4J_{H_c,H_e} = 0.5$  Hz) whilst those of  $Me_f$  are not. This would result from the diastereotopy of these methyl groups. A COSY H–H experiment showed  $Me_e$  and  $Me_f$  to be coupled and  $^4J_{H_c,H_e}$  relating to  $Me_f$  to be less than 0.5 Hz, a value too small to show up in a 400 MHz spectrum. Similarly,  $F_n,H_c$  coupling is not visible, although simulation indicates a 1.9 Hz value. MS (EI):  $m/z$  (%) = 255 (42), 240 (7), 149 (100), 134 (51). The presence of the ion  $m/z = 149$  as the base peak is indicative of a pattern of a preferred fragmentation of the azetidinone ring to afford isocyanate and olefin fragments over a fragmentation giving ketene and imine fragments. This phenomenon had already been observed previously.<sup>[26]</sup>  $C_{13}H_{15}F_2NO_2$  (255.26): calcd. C 61.17, H 5.92, N 5.49; found C 61.19, H 5.90, N 5.53.



## Acknowledgments

The authors wish to thank Aquitaine Regional Government for funding part of this work through an Aquitaine-Euskadi Cooperation Program, P. B. Gonzalez Perez (Aquitaine-Euskadi fellow) for some preliminary experiments, and D. Nuñez Villanueva (Erasmus fellow from the University of Malaga, Spain) for complementary work. They are also indebted to M. Petraud and J. C. Lartigue (CESAMO, University Bordeaux I) for their very kind and efficient assistance in NMR studies. They also acknowledge the assistance of M.-H. Lescure for the recording of GC/MS data.

- [1] S. Thaisrivongs, H. J. Schostarez, D. T. Pals, S. R. Turner, *J. Med. Chem.* **1987**, *30*, 1837.
- [2] J.-L. Maillard, C. Favreau, M. Reboud-Ravaux, R. Kobaiter, R. Joyeau, M. Wakselman, *Eur. J. Cell Biol.* **1990**, *52*, 213.

- [3] R. Joyeau, H. Molines, R. Labia, M. Wakselman, *J. Med. Chem.* **1988**, *31*, 370.
- [4] See also the dehydrohalogenation route from  $\beta$ -bromo-3,3-difluoroamides, ref.<sup>[3]</sup>
- [5] T. Taguchi, O. Kitagawa, Y. Suda, S. Ohkawa, A. Hashimoto, Y. Iitaka, Y. Kobayashi, *Tetrahedron Lett.* **1988**, *29*, 5291; O. Kitagawa, T. Taguchi, Y. Kobayashi, *Tetrahedron Lett.* **1988**, *29*, 1803.
- [6] S. Marcotte, X. Pannecoucke, C. Feasson, J.-C. Quirion, *J. Org. Chem.* **1999**, *64*, 8461.
- [7] K. Sato, A. Tarui, S. Matsuda, M. Omote, A. Ando, I. Kumadaki, *Tetrahedron Lett.* **2005**, *46*, 7679.
- [8] A. Otaka, H. Watanabe, E. Mitsuyama, A. Yukimasa, H. Tamamura, N. Fujii, *Tetrahedron Lett.* **2001**, *42*, 285.
- [9] S. Lacroix, A. Cheguillaume, S. Gérard, J. Marchand-Brynaert, *Synthesis* **2003**, 2483.
- [10] P. Clavel, C. Biran, M. Bordeau, N. Roques, S. Trevin, *Tetrahedron Lett.* **2000**, *41*, 8763.
- [11] For alternative syntheses of **1** starting from trifluoroacetates see: a) K. Uneyama, G. Mizutani, K. Maeda, T. Kato, *J. Org. Chem.* **1999**, *64*, 6717; b) H. Amii, T. Kobayashi, K. Uneyama, *Synthesis* **2000**, 2001.
- [12] For a previously reported example, see ref.<sup>[11a]</sup>
- [13] a) E. Popowsky, *Z. Chem.* **1974**, *14*, 289; b) E. Popowsky, *Z. Chem.* **1975**, *15*, 275; c) M. Komatsu, M. Ohno, S. Tsuno, Y. Ohshiro, *Chem. Lett.* **1990**, 575.
- [14] Q. Z. Zhou, Z. C. Chen, *Synth. Commun.* **2000**, *30*, 3189.
- [15] L. E. Barstow, V. J. Hruby, *J. Org. Chem.* **1971**, *36*, 1305.
- [16] R. S. Corley, S. G. Cohen, M. S. Simon, H. T. Wolosinski, *J. Am. Chem. Soc.* **1956**, *78*, 2608.
- [17] J. H. Saunders, R. I. Slocombe, I. I. Hardy, *J. Am. Chem. Soc.* **1949**, *71*, 752.
- [18] H. Oberhammer, K. I. Gobbatto, C. Leibold, S. Centeno, C. O. Delle Vedona, H. G. Mack, *J. Mol. Struct.* **1996**, *380*, 55.
- [19] E. J. Thomas, C. T. Brain, A. Chen, A. Nelson, N. Tanikkul, *Tetrahedron Lett.* **2001**, *42*, 1247.
- [20] C. A. Townsen, L. T. Nguyen, *J. Am. Chem. Soc.* **1981**, *103*, 4582.
- [21] C. A. Townsen, L. T. Nguyen, *Tetrahedron Lett.* **1982**, *23*, 4859.
- [22] C. T. Brain, A. Chen, A. Nelson, N. Tanikkul, E. J. Thomas, *Tetrahedron Lett.* **2001**, *42*, 1247.
- [23] A. Otaka, J. Watanaba, A. Yukimasa, Y. Sasaki, H. Watanabe, T. Kinoshita, S. Oishi, H. Tamamura, N. Fujii, *J. Org. Chem.* **2004**, *69*, 1634.
- [24] See for instance: D. L. Hughes, R. A. Reamer, J. J. Bergan, E. J. J. Grabowski, *J. Am. Chem. Soc.* **1988**, *110*, 6487; J. P. Coleman, F. X. Felpin, W. Chen, *J. Org. Chem.* **2004**, *69*, 7309.
- [25] It has been reported that  $J_{\text{H,H}}$  (*cis*) is larger than  $J_{\text{H,H}}$  (*trans*) in small rings such as cyclobutane, oxetane, and azetidine derivatives. See, for example: R. M. Silverstein, G. C. Bassler, T. C. Morill, *Spectrometric Identification of Organic Compounds*, 5th ed., J. Wiley, New York, **1991**, p. 221; D. L. Pavia, G. M. Lampman, G. S. Kriz Jr, *Introduction to Spectroscopy*, Saunders College Publishing, Orlando, Florida, USA, **1979**, p. 117. The same phenomenon was also observed for  $J_{\text{H,F}}$  in monofluorinated oxirane; see, for example: E. Pretsch, P. Bühlmann, C. Affolter, *Structure Determination of Organic Compounds*, 3rd ed., Springer, Berlin, **2000**, p. 196.
- [26] B. E. Autier, M. Fétizon, H. B. Kagan, J. L. Luche, *Bull. Soc. Chim. Fr.* **1967**, 2297; V. S. Georgiev, D. C. Coonber, G. B. Mullen, *Org. Mass Spectrom.* **1988**, *23*, 283; G. Bourgeois, J. P. Picard, F. P. Cossio, C. Palomo, *Adv. Mass Spectrom.* **1989**, *11*, 876.
- [27] Simulation performed with the MestreC 23 program. Fluorine, having a spin of 1/2, like the proton, was integrated into the calculations without difficulty.

Received: February 20, 2006  
Published Online: July 12, 2006